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Biologically Inspired Multi-Step One-Pot Reactions

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Biologically Inspired Multi-Step One-Pot Reactions

by

Steven Thomas Scroggins

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Committee in charge:

Professor Jean M. J. Fréchet, Chair
Professor Richmond Sarpong
Professor Jhih-Wei Chu

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Abstract

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The development of one-pot reactions is an approach to chemistry that seeks to address shortcomings of traditional, sequential multi-step synthetic strategies. One-pot reactions reduce the number of set-up and purification steps in a synthesis and thereby shorten the process and save on the resources needed to reach the final desired compound. Moreover, one-pot reactions can utilize intermediates that cannot be isolated and used with a multi-pot strategy. In contrast to traditional synthetic approaches, Nature uses "one-pot reactions" almost exclusively; in other words, biological reaction pathways occur in an open, complex and dynamic environment in which multiple reactions are performed in the same vessel (i.e. cell) en route to final products. Nature's approach has inspired us to develop new materials and systems to enable one-pot reactions in the lab. In particular, we have invented and utilized means of site-isolating reactive components to enable complex reaction cascades and demonstrated a unique method to direct a one-pot reaction without relying on traditional functional group chemoselectivity.

Chapter 1 presents a summary of research into the implementation of one-pot reactions, primarily using materials-based approaches. The strategies that researchers have used to combine incompatible reagents in one-pot reactions through site isolation are summarized, as well as research into various types of selectivity in systems that utilize substrate size and shape to direct chemical reactions.

Chapter 2 describes the development of a two-step, asymmetric one-pot reaction that is enabled by the site isolation of a strong acid and a base in separate star polymers. This reaction couples three substrates using a combination of four organocatalytic entities and cannot be done using small molecule or linear polymer catalysts. Any one of the four diastereomers of the final product can be made, depending on the choice of the catalytic functionalities. The chapter describes the synthesis of the polymers used in this reaction, as well as the design and optimization of the reaction.

Chapter 3 shows how incompatible chemical and biological catalysts can be used in a one-pot reaction through site isolation of the chemical catalyst in a star polymer. The two-step reaction involves an acid-catalyzed deacetalization reaction followed by a yeast-catalyzed asymmetric hydrogenation. The strong acid star polymer catalyst has superior site isolation to small molecule and linear polymer catalysts as well as insoluble polymer bead supports.

Chapter 4 discusses the development of a new strategy for making core-functionalized star polymers that can be used in one-pot reactions. The synthesis of these star polymers is both very modular and mild, allowing for the synthesis of a wide variety of catalytic stars. A family of stars

with functional, hydrophobic cores and hydrophilic shells are synthesized and characterized. These stars have several interesting catalytic properties, including "nanoenvironment" effects from the non-polar core and site isolation of two catalysts in a one-pot reaction.

Chapters 5 and 6 describe the development of the novel concept of polarity-directed one-pot reactions. Chapter 5 introduces the concept of combining aqueous-phase catalysis with hydrophobic substrates to induce unusual selectivity in a one-step reaction. Chapter 6 shows how these concepts were utilized and expanded to develop a reaction in which substrates with identical chemical reactivity are distinguished on the basis of their polarity and water solubility.

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Dedications

To the friends and family who helped get me through graduate school, in particular my labmates Derek and Tom, my wife Lina, and my parents and grandparents.

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I acknowledge with gratitude the contributions of my advisor, Prof. Jean Fréchet, to this research.

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Chapter 1
Materials-Based Approaches to Site-Isolation and Selectivity in One-Pot Reactions

Abstract

Traditional organic synthesis routes require several reactions to be performed in sequence with the purification of intermediate compounds after each reaction. One-pot reactions, which involve multiple transformations in a single step, save both time and resources and are very attractive synthetic strategies. For example, biology utilizes complex reaction cascades which inspire the development of similar synthetic reactions. This chapter introduces and summarizes the research into areas of catalyst site-isolation and selectivity in the context of one-pot reactions. These properties are utilized heavily in nature and are required for the design of complex multi-step one-pot reactions in the lab.

1. Introduction

One-pot multistep reactions are attractive synthetic tools that save on time and resources required to perform multiple reactions sequentially and give products that cannot be obtained in a multi-pot strategy.[1] An archetypal one-pot reaction is shown in Figure 1. The major challenge to developing one-pot reactions is catalyst selectivity. Chemists have made great strides towards certain kinds of catalytic selectivity, such as stereoselectivity and functional-group chemoselectivity. However, the kinds of selectivity that would assist in the design of one-pot reactions have not been nearly as well-developed. For example, synthetic reactions are performed in isolation because they usually contain a highly sensitive component – reagent, catalyst or solvent – that is not compatible with other reactions. There are only a few reliable methods to prevent, for example, two highly reactive catalysts from reacting with each other.[2] Selectivity helps to drive reactivity in one-pot reactions in more subtle ways, for unless a reaction cascade is designed very specifically, dictating the order of substrate transformations can be impossible without sufficiently selective catalysts.[3] Solving the dual challenges of compatibility and reaction sequence is critical to developing useful one-pot reactions and inspires the development of strategies for enhancing catalyst selectivity.

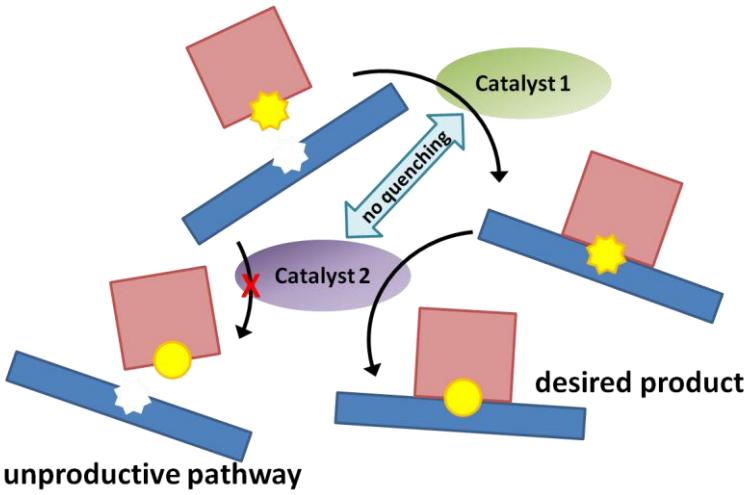

Figure 1. Both catalyst site isolation and substrate selectivity are requirements for a well-controlled one-pot reaction. If the second reaction step occurs prior to the first, the desired final product cannot be formed.

As challenging as one-pot reactions are synthetically, biology relies on them almost exclusively. Nature owes the ability to execute complex one-pot reaction cascades to the unique properties of biological catalysts, which are primarily enzymes. Because their active sites are protected and unlikely to interact, a huge number of enzymes can be present in the same system at the same time. This site isolation effect allows biochemical reaction pathways to include several steps in a one-pot reaction and has inspired chemists to utilize similar strategies. Compatibility alone does not ensure fidelity to the lengthy and complex reaction pathways observed in biology. Nature also uses enzymes to dictate the order of reactivity in ways that are unique to biological systems. Without control over the sequence of a reaction pathway, it is often impossible to obtain a desired product. Among enzymes' many desirable properties is an

extraordinarily high selectivity, and, to a great extent, enzymes will not interact with undesired substrates.[4] In order to achieve this selectivity, enzymes go beyond the functional group differentiation strategy that is central to chemical catalysis. Instead, the size and shape of substrates dictates access to the active site at the core of an enzyme. Achieving some semblance of this kind of selectivity will be critical if chemists hope to design one-pot reactions consisting of more than two or three steps.

Naturally-occurring enzymes can be very useful to synthetic chemists, and there are several examples of one-pot reactions that combine enzymes and chemical catalysts. These chemoenzymatic reactions often take advantage of the excellent selectivity of enzymes, as in some types of dynamic kinetic resolution.[5] However, chemists are interested in many reactions for which there are no enzymatic catalysts. There are high hurdles to the *de novo* creation of the complex three-dimensional structures of enzymes; therefore, alternative strategies must be developed to bring some of the concepts of biological chemistry into the lab. There are several routes to site isolation that can be used to combine incompatible catalysts in one pot. Usually involving encapsulation or immobilization of a catalytic functionality, these systems are fairly modular and are often more general than enzymes. There are fewer examples of selectivity that are not based on functional-group differentiation, and the lack of fundamental progress in this area is a major obstacle to the development of one-pot reactions.

2. Site-Isolation in One-Pot Reactions

Many synthetic catalysts lend themselves well to site-isolation strategies involving attachment to insoluble polymers. If the catalysts cannot leach off of the polymer, it becomes impossible for them to interact in solution. The first example of this principle was the concept of a "Wolf and Lamb" reaction, indroduced by Cohen et al. to describe a system in which two incompatible functionalities, in this case a strongly basic reagent[6] and an acylating group, were compatibilized by immobilization on separate insoluble polymer supports (Figure 2).[7]

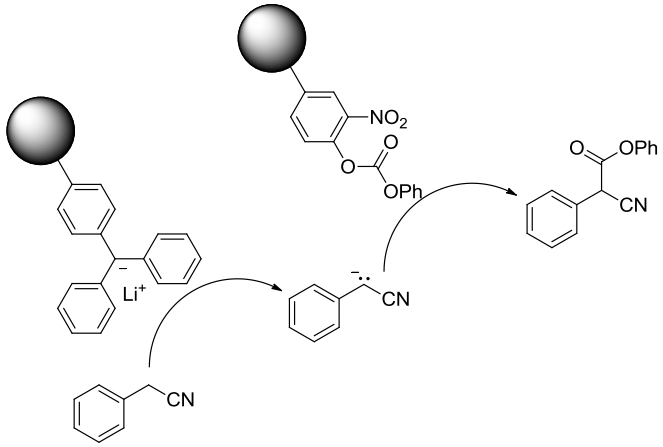

Figure 2. The prototypical "Wolf and Lamb" reaction utilizing polymer-immobilized substrates. In this case, the alkyl anion on one bead cannot be alkylated by the activated carbonate on the other polymer, preventing the formation of a complex product mixture.[7]

This strategy was rapidly extended to supported catalysis, particularly in the area of acid/base catalysis. In an early example shown in Figure 3, Kozikowski et al. synthesized cyclopentenones using resins with immobilized sulfonic acid and ammonium hydroxide to perform a one-pot deacetalation/intramolecular cyclic condensation reaction.[8]

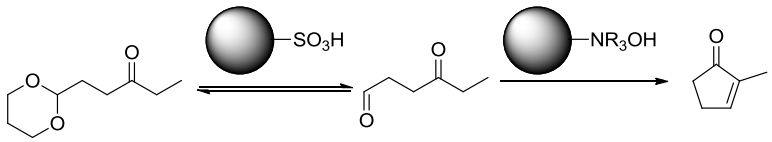

Figure 3. Acids and bases immobilized on separate resins can be used to catalyze a one-pot reaction without quenching each other.[8]

Helms et al. pioneered the use of soluble star polymers with acidic and basic cores to perform a tandem deprotection/Baylis-Hillman reaction in one pot. The analogous linear polymers were shown to quench each other.[9] This concept has been applied to biorefinery concepts, such as in Fraile et al.'s use of the strong acid resin Nafion NR-50 in conjunction with styrene-bound triazabicyclodecene (TBD) for the multi-step conversion of triglycerides into solketal in one pot (Figure 4).[10]

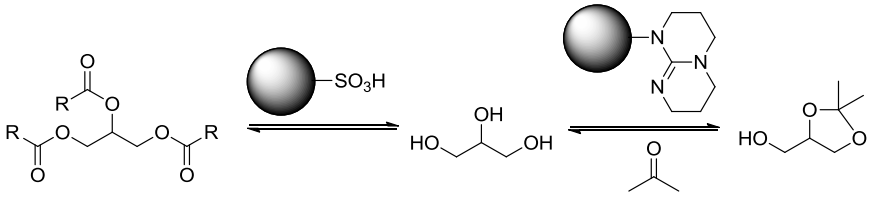

Figure 4. The combination of acidic and basic resins allows for the formation of solketal in one pot from glycerides. The equilibrium reaction is driven to completion by evaporation of soketal.[10]

As shown in Figure 5, Gembus et al. demonstrated a more complex example that used the same TBD polymer with Amberlyst to synthesize pyrazolines by a combination of a base-catalyzed aza-Michael reaction and a transimination reaction using stoichiometric acid in one pot.[11]

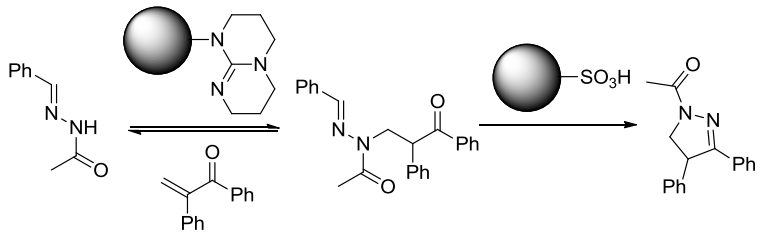

Figure 5. An base-catalyzed can be combined with an aza-Michael reaction in one-pot using a bead-based base catalyst and stoichiometric amounts of Amberlyst resin.[11]

Asymmetric reactions are also possible using this strategy. Akagawa et al. combined Amberlite with a short proline-terminated peptide attached to a PEG-polystyrene resin to perform a combined deacetalization/enantioselective aldol reaction in one-pot.[12] Without site isolation, proline was irreversibly protonated by the sulfonic acid on Amberlite or *p*TSA.

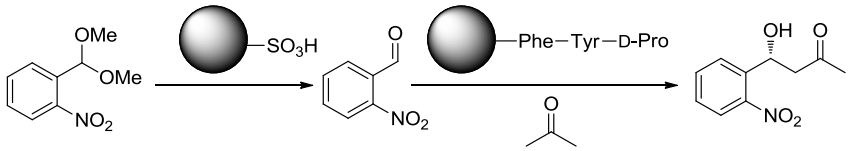

Figure 6. Short bead-bound oligopeptides can be used in conjunction with Amberlite to promote two-step, one-pot asymmetric reactions.[12]

This concept was readily extended to heterogeneous supports other than polymers that could be used for various one-pot reactions requiring site isolation. Huang et al. used mesoporous silica nanoparticles for the reaction shown in Figure 7 combining an acid-catalyzed acetal deprotection and an amine-catalyzed Henry condensation.[13]

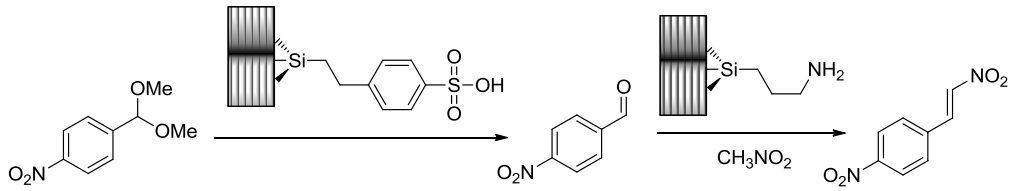

Figure 7. Mesoporous silica nanoparticles with immobilized acid and amine functionalities can also be used for one-pot reactions requiring site isolation.[13]

Pilling et al. used polymer-supported 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as a base in conjunction with acidic Amberlyst A-15 or acidic silica for one-pot azaspirocyclization cascades (Figure 8).[14]

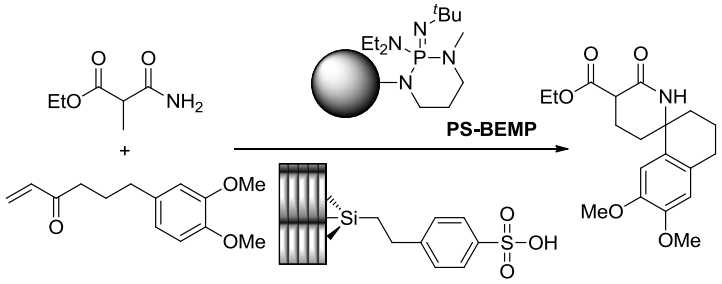

Figure 8. The combination of a basic polymer with various strongly acidic heterogeneous catalysts promotes the one-pot spirocyclization reaction. The use of small molecule catalysts changes the reaction outcome due to quenching.[14b]

Takagaki et al. have utilized Amberlyst in conjunction with basic hydrotalcite to convert sugars into 5-hydroxymethylfurfural using a combination of base-catalyzed isomerization and acid-catalyzed dehydration reactions.[15] This reaction, shown in Figure 9, has potential benefits for the production of synthetically useful chemicals from biological feedstocks.

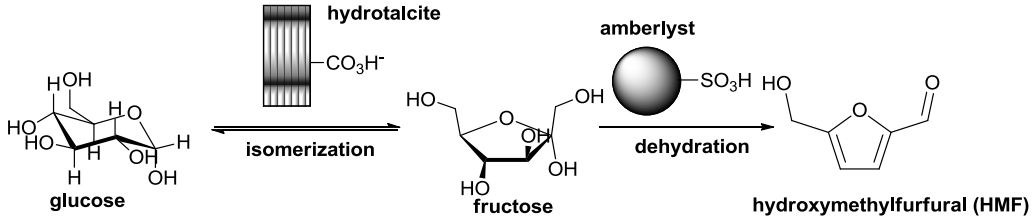

Figure 9. The combination of hydrotalcite and an a acidic resin allows for the one-pot refining of glucose into HMF.[15]

Phan et al. demonstrated multi-step reactions by combining various types of supported catalysts (Figure 10). An acidic resin, amine-functionalized silica, and Pt/Al_2O_3 particles were combined to perform one-pot deacetalization/condensation and condensation/hydrogenation cascade reactions.[16]

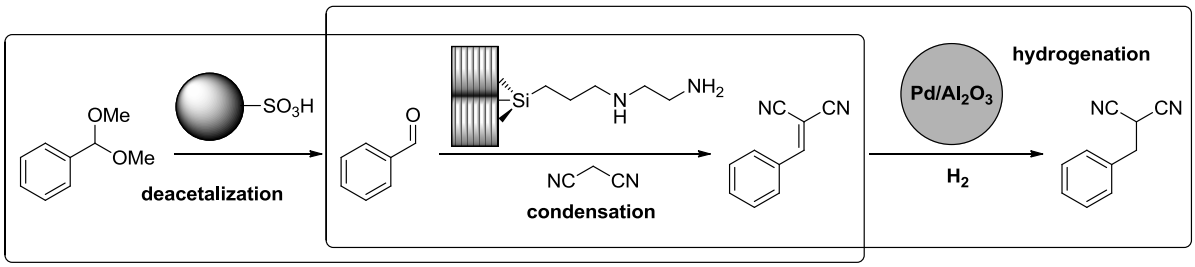

Figure 10. Some examples of the one-pot site-isolated catalysis achieved using a variety of heterogeneous catalysts.[16]

The Avnir group has utilized silica sol-gel's extensively to isolate incompatible catalysts and enable one-pot reactions. A variety of catalysts used by the group are shown in Figure 11.

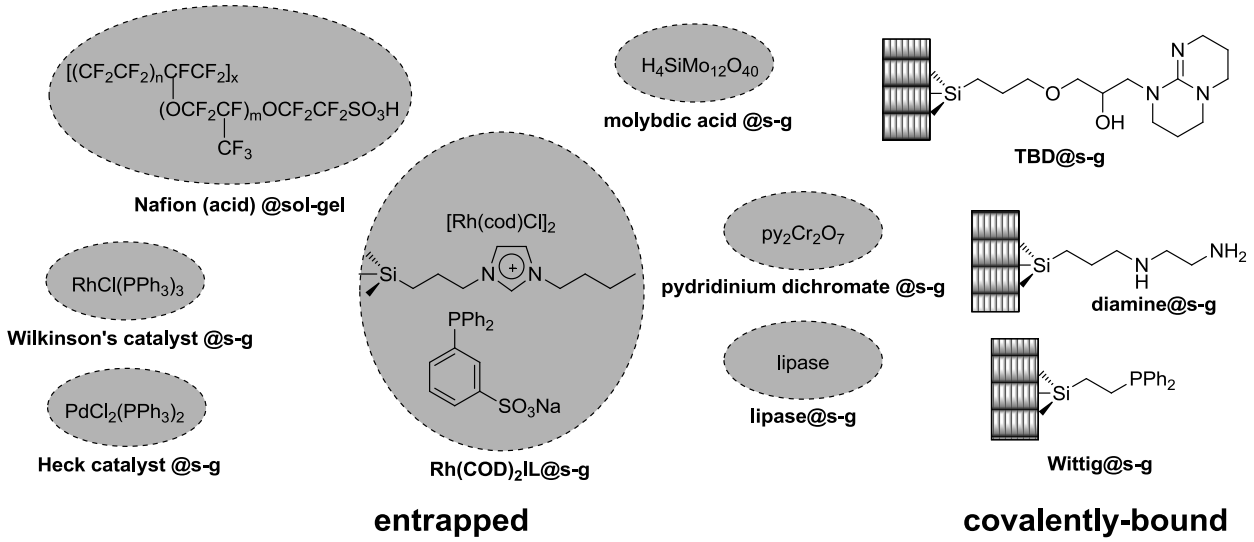

Figure 11. A sampling of silica sol-gel catalysts utilized to demonstrate site-isolation in one-pot reactions. Both physically entrapped and covalently bound catalysts and reagents can be utilized.

As summarized in Figure 12, a variety of unique one-pot reactions can be performed using these catalysts. Acid/base pairs can be used to catalyze both rearrangement/condensation and dehydrohalogenation/aromatic alkylation cascades.[17] Uniquely, the researchers combined a Heck reaction with a photocyclization and observed stabilization of the entrapped palladium catalyst, which they attributed to site isolation from byproducts of the irradiation of iodobenzene over the course of the reaction.[18] Rhodium-based hydrogenation catalysts have proven particularly useful. An amine sol-gel was combined with an encapsulated form of Wilkinson's catalyst to perform a dehydrohalogenation/hydrogenation cascade.[19] The hydrogenation sol-gel could also be combined with a pyridinium dichromate sol-gel for a variety of oxidation/hydrogenation cascades.[20] The Wilkinson's catalyst could even be combined with lipases encapsulated in the sol-gels to facilitate a tandem esterification/hydrogenation reaction.[21] Hamza et al. also utilized sol-gels to achieve three step reactions in one pot, including a combined hydroformylation/condensation/hydrogenation reaction[22] and an oxidation/Wittig/hydrogenation sequence.[23] These sol-gel-catalyzed one-pot reactions are summarized in Figure 12.

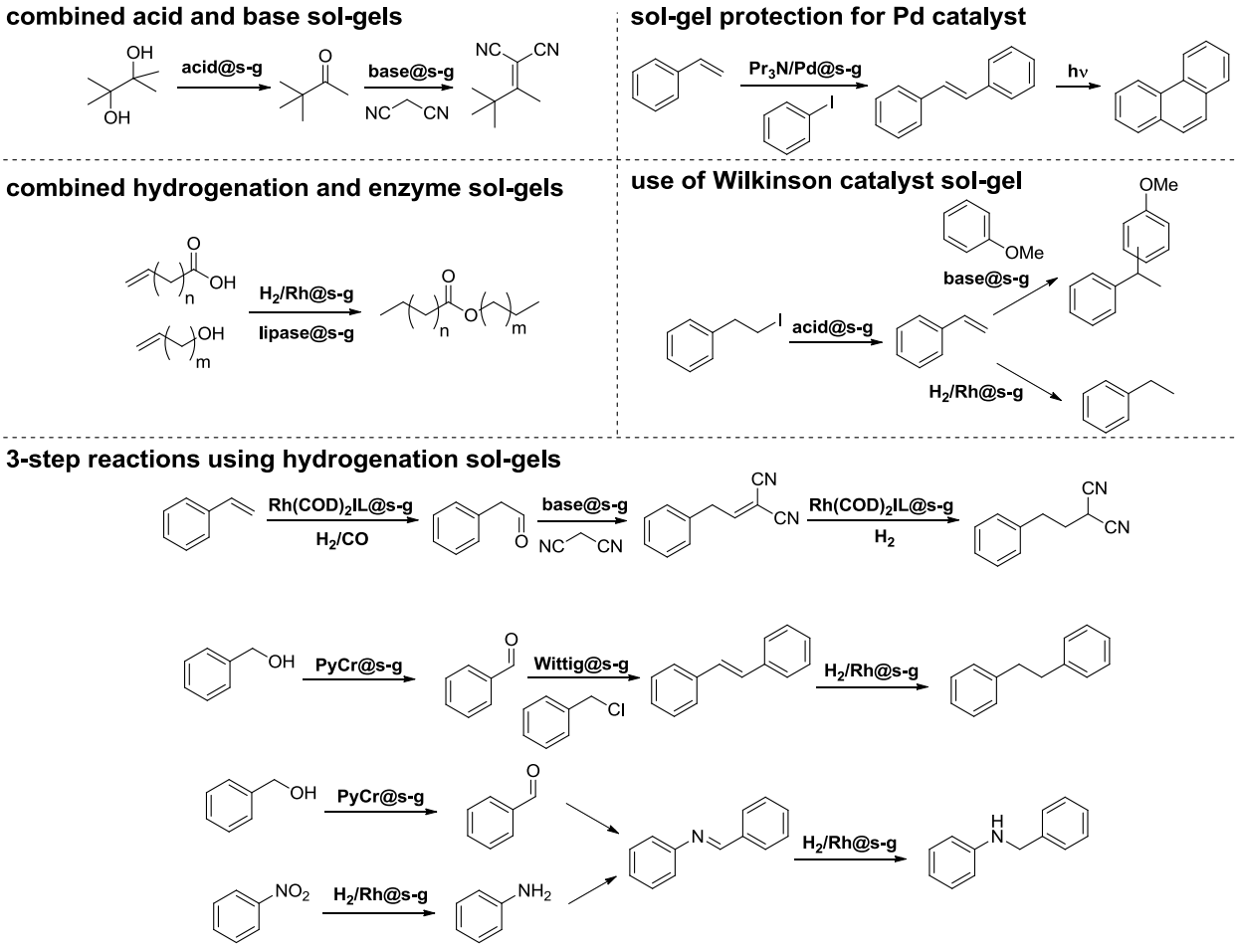

Figure 12. Sol-gel encapsulated catalysts and reagents enable a wide range of one-pot reactions requiring catalyst site isolation.[17-23]

The Bowden group has made extensive use of PDMS thimbles to site isolate various catalysts and reagents through physical separation in one-pot reactions. The PDMS thimbles have varying permeability to different small molecules. A small molecule Grubbs catalyst was separated from *m*CPBA[24] and AD-mix-α/β[25] in one-pot metathesis/oxidation reactions (Figure 13). In these examples, the interior and exterior of the thimbles contain different solvents which prevent catalyst mixing, while the substrates readily move between the phases. These thimbles can even be used to site-isolate catalysts from solvents such as water, allowing reactions with Grignard reagents and $LiAlH_4$ to happen in the same vessel as aqueous catalysis.[26] Low permeability to high molecular weight compounds allowed the thimbles to site-isolate linear polymer catalysts in single-solvent systems.[27]

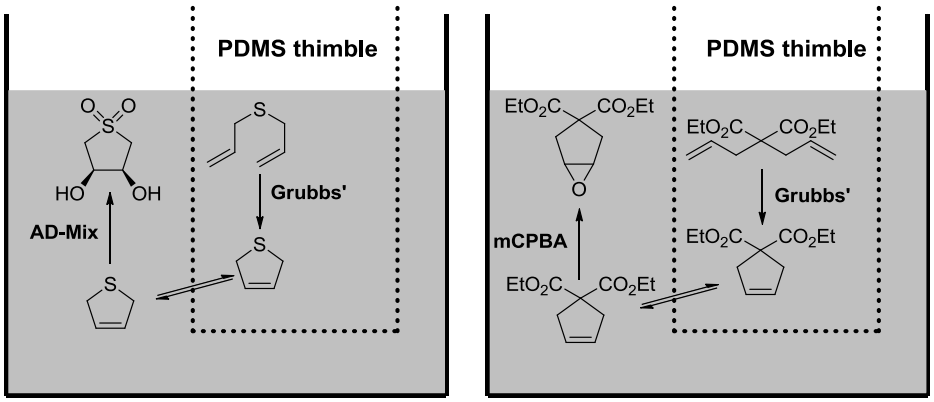

Figure 13. Combinations of Grubbs' catalysts and oxidative reactions in one-pot are enabled by site isolation in semipermeable PDMS membranes.[24-25]

Similarly, the McQuade group has utilized microcapsules to encapsulate polymeric catalysts, allowing for cascade reactions involving an amine-catalyzed Henry condensation followed by a nickel-catalyzed Michael addition.[28] Interestingly, this reaction utilizes a nitroalkene intermediate that cannot be used in the analogous two-pot reaction due to its tendency to react with a second equivalent of nitromethane (Figure 14).

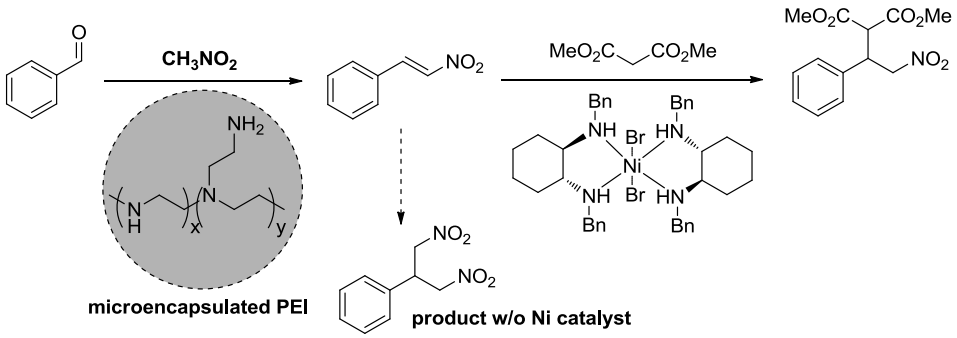

Figure 14. McQuade's microencapsulated catalyst enables a one-pot condensation/Michael addition reaction that is not possible in a two-pot process with PEI as the amine catalyst.[28]

Several groups have shown that materials can be made containing both strong acidic and basic residues that do not quench each other (Figure 15). These types of materials have been applied to

cooperative catalysis,[29] but are also useful in one-pot reactions. Motokura et al. used separate acidic and basic layered clays to perform combined acid-catalyzed deacetalization and base-catalyzed condensation reactions[30] but also showed that this technique could be applied to catalysts on the same clay.[31] Shylesh et al. showed that acidic and basic functionalities could be immobilized on the same mesoporous silica nanoparticles and still enable a deacetalization/condensation reaction that required both catalysts.[29a, 32]

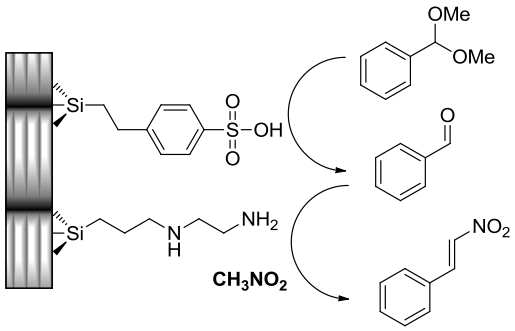

Figure 15. Acid and base functionalities can be combined on the same particle (e.g. mesoporous silica) and still be effective catalysts for one-pot reactions.[32]

There are some shortcomings of these site-isolation strategies that may help direct future research. Firstly, many of these examples require catalyst immobilization via covalent attachment strategies, which nearly always requires some modification of a catalytic functional group. This modification can often be difficult, and covalent attachment has been shown to have a detrimental impact on various aspects of catalytic behavior.[33] Explorations using noncovalent catalyst immobilization for recycling purposes may be useful in site isolation applications and overcome some of these problems.[34] Furthermore, heterogeneous catalysis is often associated with lower reaction rates due to the kinetic barrier of phase transfer; however, the examples of soluble star polymers that can be used for catalyst site isolation are promising for future work in this direction.[9] Finally, current immobilization strategies provide only weak benefits to a variety of catalysts – most notably organometallics – that have a tendency to leach off their supports and thereby decrease site isolation,[35] although the discovery of more reliable supports may ameliorate this problem.[36] Overall, research in the area of catalyst site isolation is entering a mature phase where it will be interesting to find applications to more complex systems and solve some of the more persistent problems described above.

3. Catalyst Selectivity in One-Pot Reactions

In contrast to the advances using site-isolation in one-pot reactions, there are very few examples of non-enzymatic systems in which reaction pathway control is achieved without traditional functional group chemoselectivity. Most notably, Wei et al. recently reported the use of layered catalytic PDMS particles to direct the order of reactivity in reactions involving alkyne coupling followed by hydrogenation. As shown in Figure 16, if hydrogenation occurs before the copper-catalyzed coupling reaction, the final coupled product will not be formed. Since switching the order of reactivity does not result in the desired product, the order of reactivity

must be regulated. The researchers performed the one-pot reaction using a PDMS particle with a core/shell structure. The hydrogenation catalyst is placed at the core of the particle, and this reaction occurs only after the substrates have traversed and reacted in the peripheral layer containing the coupling catalyst.[37] There are also many reports of synthetic catalysts with size- and shape-based substrate selectivity, however, few if any of these systems have been applied to multi-step one-pot reactions that are not achievable without enzyme-like selectivity.

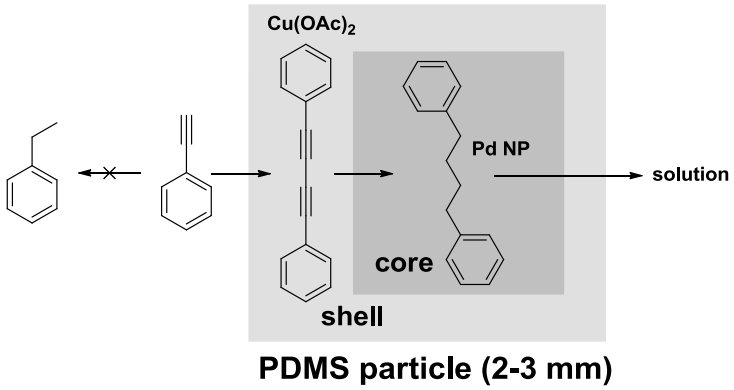

Figure 16. Copper-catalyzed alkyne coupling must precede the hydrogenation reaction catalyzed by palladium nanoparticles in the one-pot reaction shown above. Reaction order is dictated by the spatial arrangement of the catalysts in a PDMS particle with a core/shell architecture.[37]

The use of molecular sieves as shape- and size-selective catalyst platforms was pioneered in 1960 by the Weisz group and subsequent research has described a wide variety of catalysts and reactions.[38] Apart from these ordered inorganic structures, the Bowden group has shown that the low solubility of polar and ionic compounds in PDMS could be used to isolate Grubbs catalysts from water and ionic substrates.[39] This encapsulation was also shown to have unique effects on the reactivity of a wide variety of metathesis substrates.[40] Several groups have also used dendrimers with functionalized cores for selective reactions on the basis of substrate size or polarity (Figure 17). For example, in a competition experiment, the Kaneda group observed significantly faster hydrogenation of 3-cyclohexene-1-methanol than cyclohexene with a dendrimeric palladium catalyst.[41] The Chow group used a Lewis-acid functionalized dendrimer to gain size-based substrate selectivity in a competitive Diels-Alder reaction. The Crooks group has done a significant amount of research in this area, using the steric crowding of dendrimers for substrate selectivity in palladium-catalyzed hydrogenations.[42] Both dendrimer generation and peripheral functionalization were found to have an effect on selectivity.[43]

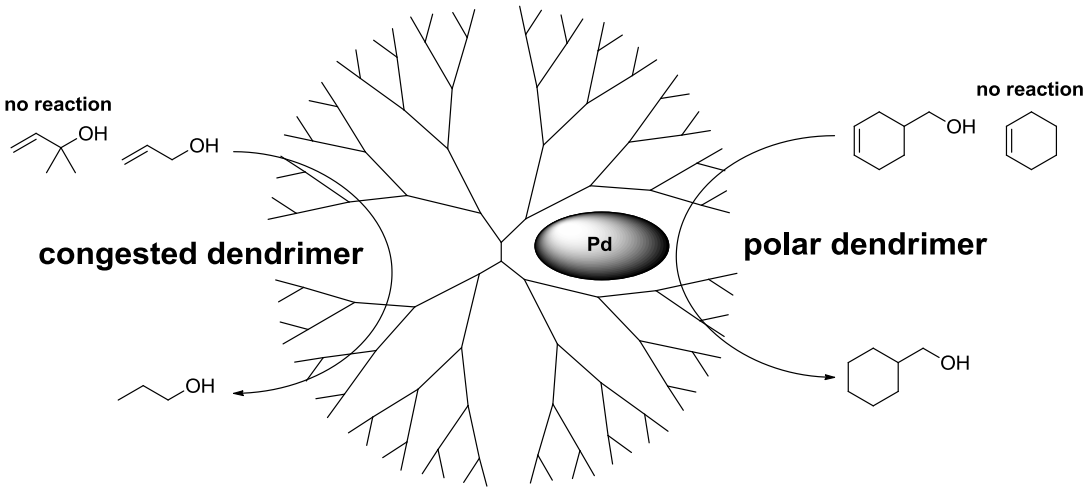

Figure 17. Depending on their peripheral and interior properties, dendrimers encapsulating palladium nanoparticles can be used for the selective hydrogenation of polar[41] and less bulky[42] substrates.

Extensive use has been made of self-assembled supramolecular containers as reaction vessels with interesting substrate selectivity.[44] Rebek's pioneering example of a self-assembled nanocapsule as a Diels-Alder catalyst included an experiment demonstrating size-selective reactivity.[45] The Bergman and Raymond groups have developed a supramolecular cluster that can be used for a variety of acid-catalyzed reactions and demonstrates excellent selectivity for appropriately-sized substrates.[46] As shown in Figure 18, complete deacetalization of heptyl aldehyde was observed using the clusters in a basic solution, while there was no reaction of nonyl aldehyde.[47] The acceleration of aza-Cope rearrangements by these clusters was highly and uniquely dependent on the substrate shape.[48] The clusters could also be combined with a second catalyst via encapsulation of a rhodium complex which could then distinguish substrates with as little as one carbon difference in an isomerization reaction.[49]

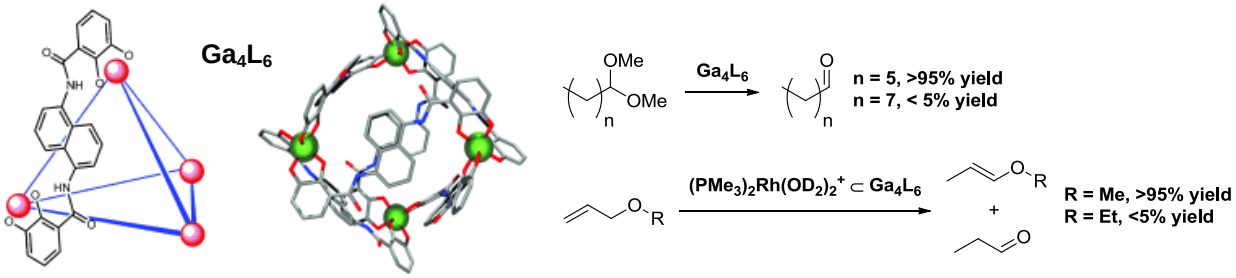

Figure 18. The supramolecular clusters (Ga_4L_6) developed by Raymond and Bergman have demonstrated remarkable size selectivities for substrates with as little as one carbon difference in various reactions.[47, 49]

Liu et al. demonstrated that the differential binding of constitutionally isomeric esters within deep-cavity cavitands could be used to preferentially "protect" substrates from hydrolysis in the bulk solution (Figure 19).[50]

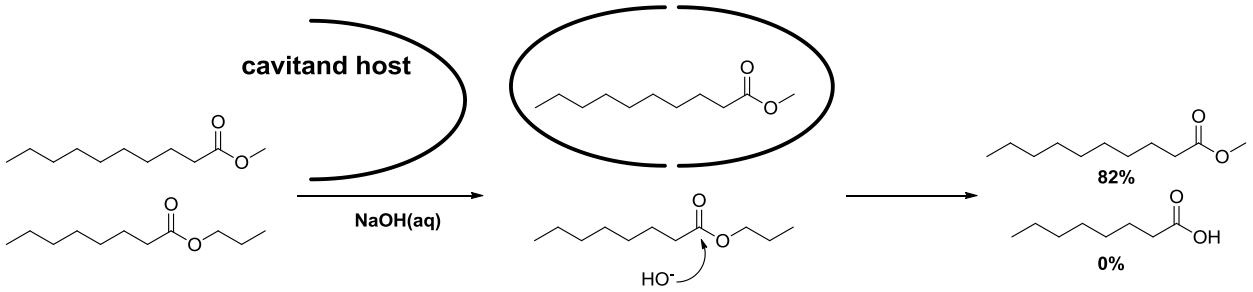

Figure 19. A cavitand forms a supramolecular capsule that can selectively encapsulate one of two esters that are constitutional isomers. The propyl ester is selectively hydrolyzed in basic solution.[50]

The earliest examples of catalysts with enzyme-like selectivity primarily concerned reactions with relatively limited scope for application to one-pot processes. However, increasing research and insight into this area has greatly expanded the scope of reactions and the complexity of shape and size effects in enzyme mimics. Before these concepts can be applied broadly to the control of one-pot reactions, further work must be performed to enforce site isolation in these systems and incorporate synthetically versatile catalysts. Overall, the strides made in catalytic site isolation and selectivity should encourage exciting new research in the development of synthetic multi-step one-pot reactions.

4. References

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Chapter 2
One-Pot Multi-Component Asymmetric Cascade Reactions Catalyzed by Soluble Star Polymers with Highly Branched Non-Interpenetrating Catalytic Cores

Abstract

Non-interpenetrating star polymer catalysts designed to mimic the site isolation characteristics of enzymes enable the one-pot combination of multiple otherwise incompatible catalysts for asymmetric cascade reactions that involve iminium, enamine, and hydrogen-bonding catalysis. Control experiments replacing star polymer catalysts with the corresponding small molecule or linear polymer analogs lead to little or no cascade reaction. This strategy gives straightforward access to all possible stereoisomers of the cascade product individually. This work represents a unique example of soluble polymers as site-isolated, enzyme-like catalysis that generate cascade products with multiple chiral centers.

1. Introduction

Living cells often concurrently make many complex molecules via multi-step cascade reactions. For these multiple simultaneous enzymatic reactions to work well, one key concept nature adopts is 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] Soluble hyperbranched polymers have been used to combine the normally incompatible acid and base catalysts in one-pot for a simple two-step sequential reaction.[6] This chapter describes the design of non-interpenetrating star polymer catalysts that allow the combination of iminium,[7] enamine,[8] and hydrogen-bonding[9] catalysts in one-pot for asymmetric reactions that generate cascade products with more than one chiral center. The combination of catalysts with appropriate chirality allows for straightforward access to all possible stereoisomers of the cascade products individually. This work represents the a unique example of soluble polymers as site-isolated, enzyme-like catalysis that generate cascade products with multiple chiral centers.

Previous research has established that the pairing of an imidazolidinone with a strong acid forms an optimal iminium ion catalyst[10] and that chiral pyrrolidines are excellent enamine catalysts.[11] In some cases a single type of catalyst has 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 and inferior for other reactions. Additionally, using a single asymmetric catalyst for one-pot multiple catalytic cycles gives access to a limited set of diastereomers of the cascade products. Instead, we aimed to develop a general system for one-pot multi-step reactions combining optimal enamine and iminium catalysts.

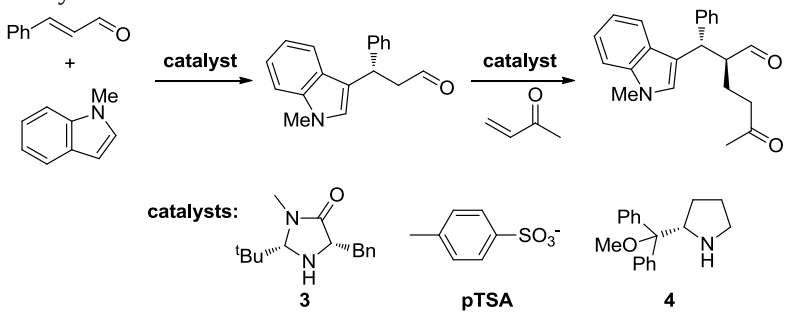
2. Results and Discussion

2.1 Small molecule model reaction. Our work began with the careful investigation of an imidazolidinone-mediated nucleophilic addition of N-methyl indole to 2-hexenal to give **1** (Table 1, entry 1) previously developed by MacMillan and co-workers,[12] and a chiral pyrrolidine-catalyzed Michael addition of **1** to methyl vinyl ketone (MVK) (Table 1, entry 5)[8, 13] using small molecule catalysts. No combination of the three catalysts and co-catalysts (**3**, pTSA and **4**) can mediate both reaction steps (Table 1). In particular, the presence of strong acid pTSA (alone or paired with imidazolidinone **3**) diminished the ability of **4** to effect enamine catalysis (Table 1, entry 4). Consequently, a simple combination of these catalysts in one-pot cannot mediate a cascade reaction involving both reaction steps.

We therefore proposed to encapsulate analogs of pTSA and **4** in the core of separate star polymers to give **5** and **7** respectively (Figure 1). The cores of star polymers **5** and **7** cannot interact 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**[14] added to the one-pot reaction is expected to activate the relatively non-reactive Michael acceptor (MVK) in the enamine catalysis cycle.

Table 1. Experimental results indicating that the model cascade reaction cannot be performed with any combination of the small molecule catalysts **3** and **4**.



entry	catalyst(s)[a]	reaction (a) yield%[b]	reaction (b) yield%[b]
1	**3** + **pTSA**	> 95 (90% ee[c])	0
2	**3**	0	0
3	**pTSA**	0	0
4	**4** + **pTSA**	n.r.[d]	0
5	**4**	n.r.[d]	60 (93:7 d.r.[b])
6	**3** + **4** + **pTSA**	34	0

[a]Reaction conditions: 20 mol% of each catalyst, 1.2 eq N-methylindole, 3 eq vinylmethyl ketone. [b]Measured by ^{1}H NMR of the crude reaction mixture. [c]Determined by chiral phase HPLC using the corresponding alcohol of 1. [d]No desired reaction; Michael product from the addition of catalyst 4 to 2-hexenal was observed.

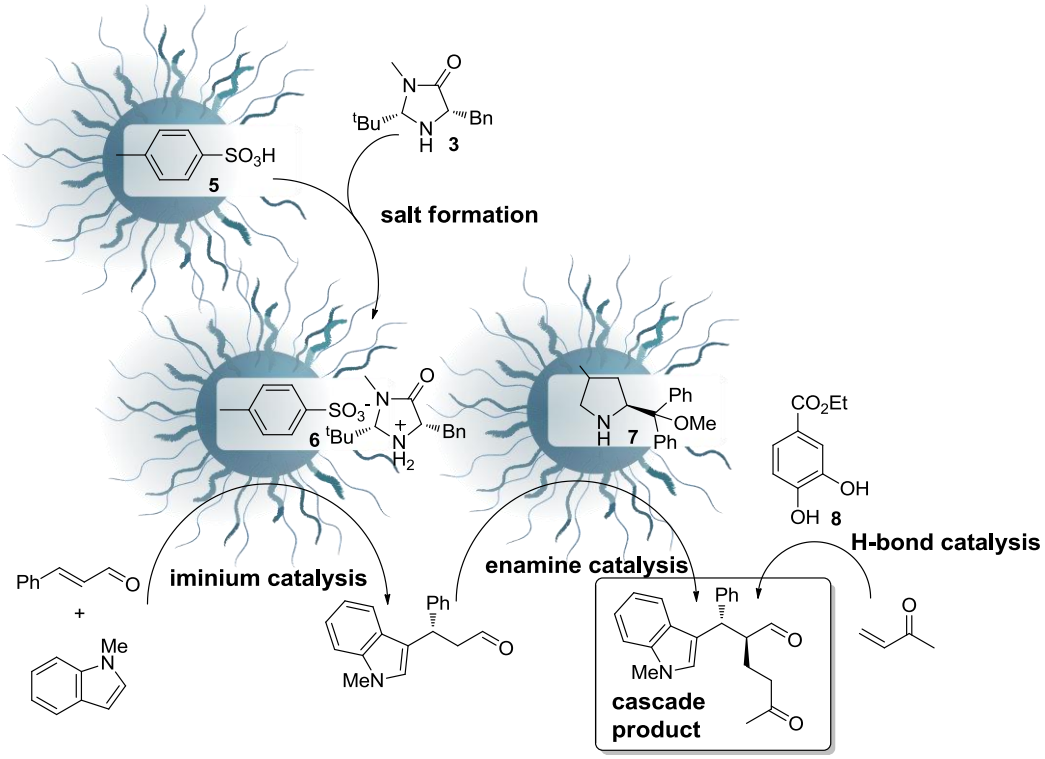
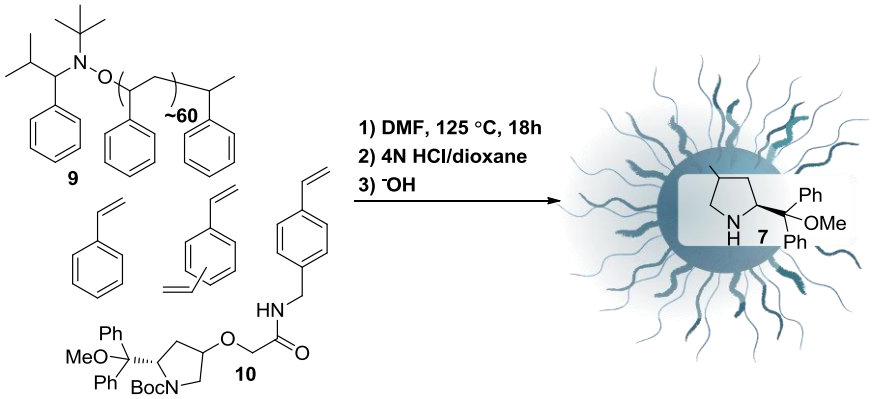


Figure 1. Illustration of our design: non-interpenetrating star polymers for one-pot cascade catalysis

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 mmol 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 = 6 577, M_w = 7 301, PDI = 1.11), divinylbenzene cross linker and functional monomer **10** (Scheme 1). ^{1}H NMR analysis of **7** indicated approximately 0.30 mmol amine catalyst per gram of polymer.



Scheme 1. The star containing the site-isolated amine catalyst is synthesized via the arm-first method from a functional monomer and a poly(styrene) polymer synthesized by nitroxide-mediated radical polymerization.

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 catalyzed reaction. While the catalytic efficiency of star **7** is somewhat lower than that of its corresponding small molecule analogs for the enamine reaction, a good reaction yield could still be obtained by extending the reaction time.

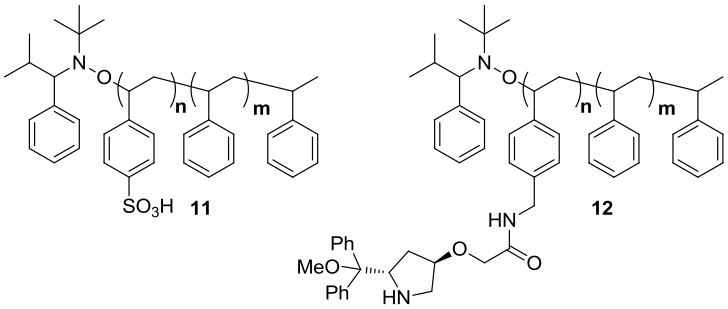
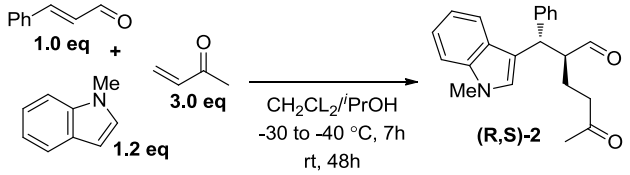


Figure 2. Linear polymer analogues to star polymer catalysts employed in control reactions.

We then employed the star polymer catalysts for the one-pot multiple-component cascade reaction shown in Table 2. 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 simultaneously, and approximately 30% cascade product was observed after 5 days. Control experiments using small molecule catalysts (**3**, pTSA, **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 2, entry 1). This is likely because **7** is partially consumed by Michael addition to 2-hexenal. The overall reaction efficiency was further enhanced when hydrogen-bonding catalyst **8** was used to activate MVK (100 mol% relative to 2-hexenal; Table 2, entry 2). This result showed that hydrogen bonding activation could be combined in one-pot with iminium and enamine catalysis. An excellent yield (89%) and stereoselectivity (100: 7 d.r., > 99% ee for the major diastereomer) of the cascade product could be achieved in two days when the non-interpenetrating star polymer catalysts were employed for the one-pot reaction. When acid star polymer **5** was replaced with pTSA or amine star polymer **7** with **4**, no cascade product was observed (Table 2, entries 3-5). Additionally, replacing either of the star polymers (**5** and **7**) with their linear polymer analogs (**11** and **12**) resulted in little cascade product formation (Table 2, entry 6-7). 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 2, entry 8).

Table 2. The one-pot multicomponent asymmetric tandem reaction is uniquely enabled by the combination of star polymer catalysts **5** and **7**.



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

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

3. Conclusions

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

4. Methods

4.1 Materials. Commercial chemicals were purchased from Sigma-Aldrich and used as received. Phenyl p-styrenesulfonate (for the synthesis of acid polymers) was prepared according to literature procedures.[16] Methylene chloride, THF, toluene, DMF, and triethylamine were purchased from Fisher and vigorously purged with nitrogen for 1 h. The solvents were further purified by passing them under nitrogen pressure through two packed columns (Glass Contour) of neutral alumina (for THF and methylene chloride), neutral alumina and copper(II) oxide (for toluene), or activated molecular sieves (for DMF). Silica gel column chromatography was performed on a Biotage flash column chromatography system. High Resolution Mass Spectometry (HRMS) using Electron Impact (EI) was done with ProSpec magnetic sector mass spectrometer equipped with electron impact ion source (Micromass). Elemental analysis was performed on a Perkin Elmer 2400 Series II combustion analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AV-300, AVQ 400, or AVB-400 instruments using CDCl3 as the solvent. SEC with THF was carried out at 1.0 mL/min. Three PLgel columns (7.5 x 300 mm) were used. The columns had a pore size of 105, 103, and 500 Å, respectively. The particle size was 5 mm. The SEC system consisted of a Waters 510 pump, a Waters 717 auto sampler, a Waters 486 UV-Vis detector, a Wyatt DAWN EOS light scattering detector, and a Wyatt Optilab DSP differential refractive index detector. The columns were thermostatted at 35 °C. Chromatographic enantiomeric excess (ee) determinations were performed on a Waters 2695 HPLC using a Chiralcel OD-H or Chiralpak AS-H analytical column (detection at 254 nm).

4.2 Studies on reaction steps using small molecule catalysts. General procedure for the reaction shown in Table 1, entry 1:[12] to a small vial equipped with a magnetic stir bar, was added 50 mg **3** (0.2 mmol), 38 mg pTSA (as monohydrate; 0.2 mmol) and 2 ml CH_2Cl_2/^{i}PrOH (95/5; v/v). The mixture was stirred for about 5 minutes at rt, and then cooled to -40 ºC. Substrate 2-hexenal (116 μL, 1 mmol) was added. The mixture was stirred for about 5 minutes, and 1-methyl indole (150 μL, 1.2 mmol) was added. The reaction mixture was stirred at -30 to -40 ºC for 7 h. Yield of the reaction was determined by ^{1}H NMR analysis of the crude reaction mixture. Product **1** was isolated using a Biotage Flash Chromatography System. For enantiomeric excess (*ee*) determination, aldehyde **1** was reduced to the corresponding alcohol with excess $NaBH_4$.[1] The *ee* of the alcohol was determined on a Waters 2695 HPLC using a Chiralcel ODH column [mobile phase: hexane/MeOH (v/v: 98/2; premixed); flow rate: 1 mL/min; retention time: 35.1 min (*R*-enantiomer); 40.0 min (*S*-enantiomer)]. Absolute configuration of compound **1** was assigned according to MacMillan's work.

General procedure for reaction the reaction shown in Table 1, entry 5 (enamine catalysis): aldehyde **1** (230 mg, 1 mmol; ~90% ee) and catalyst **4** (54 mg; 0.2 mmol) were dissolved in 2 mL CH_2Cl_2/^{i}PrOH (95/5; v/v) in a small vial. The mixture was stirred at rt for about 5 minutes,

and methyl vinyl ketone (243 μL, 3 mmol) was added. The resulting solution was stirred at rt for 48 h. The yield and diastereomeric ratio of the product was determined by ^{1}H NMR analysis of the crude reaction mixture. The reaction mixture was directly subjected to silica gel column chromatography to isolate Michael product **2** (major diastereomer as shown) as a viscous oil. Absolute configuration of the newly generated chiral center in **2** was assigned according to previous reports on analogous reactions mediated by the same catalyst.[17] Product **2**: ^{1}H NMR (300 Hz, $CDCl_3$): 9.56 (d, J = 3.9 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 6.81 (s, 1H), 3.65 (s, 3H), 3.23-3.15 (m, 1H), 2.63-2.54 (m, 1H), 2.372.15 (m, 2H), 1.92 (s, 3H), 1.80-1.53 (m, 4H), 1.24-1.01 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H). 13C HMR (75 Hz, CDCl3): 207.9, 205.5, 137.1, 127.4, 126.9, 121.5, 119.2, 118.8, 114.1, 109.4, 56.5, 40.9, 37.1, 35.9, 32.6, 29.8, 21.1, 20.8, 13.9. HRMS-EI: $[M]^+$ calculated: 299.1815, found 299.1880.

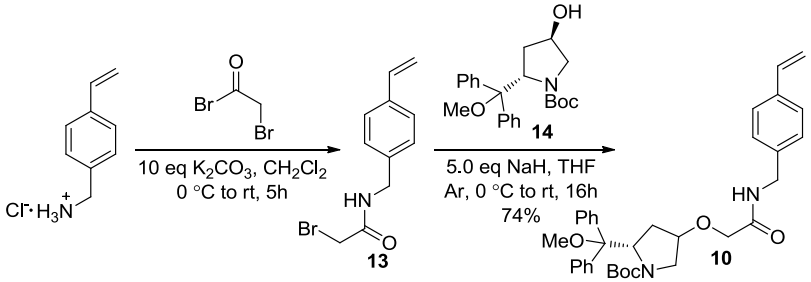
4.3 Studies on reactions using polymer catalysts. Catalyst **3** (12 mg, 0.05 mmol) and **5** (125 mg, about 0.07 mmol) were dissolved in 500 μL CH_2Cl_2/^{i}PrOH (95/5; v/v) in a small vial. The solution was stirred for about 30 min at rt, and cooled to – 40 ºC. Substrate 2-hexenal (30 μL, 0.25 mmol) and N-methyl indole (40 μL, 0.30 mmol) were added, and the mixture was stirred at -40 to -30 ºC for 7 h. ^{1}H NMR analysis of a aliquot of the crude reaction mixture indicated nearly complete conversion of 2-hexenal. Catalyst **7** (200 mg, 0.06 mmol) and **10** (46 mg, 0.25 mmol) were added, followed by the addition of 500 μL CH_2Cl_2/^{i}PrOH (95/5; v/v) to give a clear solution. The reaction solution was warmed to rt and stirred for about 5 minutes. Methyl vinyl ketone (62 μL; 0.75 mmol) was added. The mixture was stirred for 48 h at rt. The reaction yield (89%) and diastereomeric ratio (100: 8) of the cascade product *(R,S)*-**2** were determined by ^{1}H NMR analysis of the crude reaction mixture. The reaction mixture was directly subjected to column chromatography, giving about 35 mg of **2** as the major diastereomer. To determine its enantiomeric excess, compound **2** was converted to the corresponding acetal using a literature procedure.[13] Acetal of **2**: ^{1}H NMR (300 MHz, $CDCl_3$), 7.64 (d, J = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 6.9 Hz, 1H), 6.85 (s, 1H), 4.23 (d, J = 6.0 Hz, 1H), 4.13 (dd, J = 4.8, 11.4 Hz, 1H), 4.01 (dd, J = 5.1, 11.4 Hz, 1H), 3.76 (s, 3H), 3.54 (dt, J = 2.1, 11.4 Hz, 1H), 3.53 (dt, J = 2.7, 11.4 Hz, 1H), 3.35-3.28 (m, 1H), 2.73-2.63 (m, 1H), 2.52-2.41 (m, 1H), 2.04 (s, 3H), 2.12-1.98 (m, 1H), 1.87-1.64 (m, 4H), 1.57-1.44 (m, 1H), 1.28-1.15(m, 3H), 0.85 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, CDCl3): 210.0, 136.7, 128.9, 126.8, 121.3, 119.7, 118.6, 115.8, 109.1, 104.7, 66.9, 66.8, 47.1, 43.9, 36.4, 35.5, 32.9, 30.0, 26.1, 21.3, 14.4. HRMS-EI: $[M]^+$ calculated: 357.2304, found 357.2312. The ee was determined on a Waters 2695 HPLC using a Chiralpak ASH column [mobile phase: pump A (75% hexane, by volume), pump B (25% hexane/MeOH, 98/2, v/v); flow rate: 0.4 mL/min; retention time: 41.4 min (*R,S*, as shown*)*; 44.8 min (*S.R*-enantiomer)]. Because of the very high ee of the cascade product, we prepared each of the four stereo-isomers of the cascade product separately using the stepwise reaction (Scheme 1) in order to develop the HPLC ee assays. For the sample in Entries 2 and 8 (Table 2), the minor enantiomer was barely observed in the HPLC assay.

The other set of diastereomers (Table 2, Entry 8) was prepared by following the general procedures. *(S,S)*-2: ^{1}H NMR (300 Hz, $CDCl_3$): 9.48 (d, J = 3.0 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.26-7.12 (m, 2H), 7.08-7.02 (m, 1H), 6.77 (s, 1H), 3.68 (s, 3H), 3.28-3.21 (m, 1H), 2.59-2.51 (m, 1H), 2.45-2.39 (m, 1H), 2.33-2.22 (m, 1H), 2.02 (s, 3H), 1.91-1.83 (m, 2H), 1.76-1.65 (m, 2H), 1.30-1.09 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H). 13C HMR (75 Hz, CDCl3): 208.3, 205.4, 137.2, 127.7, 127.0, 121.8, 119.2, 119.1, 114.9, 109.5, 56.1, 41.3, 37.0, 35.0, 32.9, 30.2, 21.0,

20.7, 14.2. The ee determination for (*S*,*S*)-**2** was realized by using its acetal derivative . ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (d, J = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 6.9 Hz, 1H), 6.81 (s, 1H), 4.32 (d, J = 3.6 Hz, 1H), 4.08-3.97 (m, 1H), 3.76 (s, 3H), 3.68-3.53 (m, 1H), 3.47 (dt, J = 2.4, 9.0 Hz, 1H), 3.17-3.11 (m, 1H), 2.72-2.60 (m, 1H), 2.51-2.53 (m, 1H), 2.08 (s, 3H), 2.08-1.96 (m, 1H), 1.86-1.65 (m, 5H), 1.31-1.06 (m, 3H), 0.84 (t, J = 7.6 Hz, 3H). 13C HMR (100 Hz, CDCl3): 210.1, 137.1, 128.3, 126.5, 121.4, 119.9, 118.5, 117.2, 109.1, 104.5, 67.0, 6.9, 47.5, 43.4, 36.4, 33.6, 32.9, 30.0, 26.1, 21.2, 20.8, 14.4. HPLC ee determination: Waters 2695 HPLC using a Chiralpak ASH column [mobile phase: pump A (75% hexane, by volume), pump B (25% hexane/MeOH, 98/2, v/v); flow rate: 0.4 mL/min; retention time: 48.7 min (S,*S*, as shown*)*; 34.5 min (*R*,*R*-enantiomer)].

4.4 Synthetic details

(13). Amide formation between p-vinyl benzylamine and 2-bromoacetyl bromide gave compound **13** in quantitative yield. Reaction of **13** (1.2 eq) with **14** (1.0 eq) (derived from trans-4-hydroxy-L-proline)[2] in the presence of excess NaH in THF gave functional monomer **10** as a viscous gel after column chromatography (74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 7.42-7.20 (m, 14H), 6.78-6.69 (m, 1H), 6.68 (dd, J = 17.4, 10.8 Hz, 1H), 5.72 (d, J = 17.4, 1H); 5.23 (d, J = 10.8 Hz, 1H), 5.17-4.80 (br, 1H), 4.42 (dq, J = 6.3, 12.6 Hz, 2H), 3.90-3.41 (m, br, 2H), 3.83 (s, 2H), 2.95 (s, 3H), 2.83-2.65 & 2.53-2.30 (br, 1H), 2.26-2.10 (br, 1H), 2.02-1.78 (br, 1H), 1.47-0.99 (br, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 169.5, 156.0, 137.8, 137.1, 136.6, 130.0, 129.6, 128.3, 127.9, 127.6, 126.8, 114.2, 87.0, 79.9, 77.3, 68.5, 64.9, 61.4, 53, 42.8, 35.0, 28.4, 22.9; HRMS-EI: $[M]^+$ calculated: 557.3015, found 557.3024.



Scheme 3. The synthesis of the amine functional monomer **10**.

Poly(styrene) macroinitiator (9).[18] **S**tyrene (21.2 g, 204 mmol) was purified by passing through basic alumina and added to a Schlenk tube along with 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane initiator (0.78 g, 2.40 mmol)[4]. After 5 freeze/pump/thaw cycles to degas the solution, the reaction was stirred at 125 °C for 6 h under Ar. The viscous mixture was then diluted with 20 mL of dichloromethane and the resulting solution was added dropwise to 800 mL of rapidly stirring methanol. The resulting white precipitate was collected by filtration to yield macroinitiator **9** as a white powder (16.2 g; 76% yield). SEC with THF: M_n = 6 577, M_w = 7 301, PDI = 1.11.

Acid star polymer (5).[6] The polystyrene macroinitiator **9** (4.58 g, 0.696 mmol; SEC with THF: M_n = 6 577, M_w = 7 301, PDI = 1.11), phenyl *p*-styrenesulfonate (0.725 g, 2.79 mmol), styrene (0.435 g, 4.18 mmol), and technical grade divinylbenzene (mixture containing 55% 3-, and 4-

divinylbenzene and 45% 3- and 4-ethylvinylbenzene) (0.363 g solution, 2.79 mmol divinylbenzene) were combined with 15.5 mL DMF in a Schlenk tube. After 5 freeze/pump/thaw cycles to degas the solution, the solution was stirred at 125 °C for 16 h under Ar. The solution was then added dropwise to 400 mL rapidly stirring isopropyl alcohol. The resulting white precipitate was collected by filtration and dissolved in 400 mL of benzene. Fractionation using approximately 200 mL of methanol produced a gel that was collected by dissolving in 10 mL of dichloromethane. This dichloromethane solution was added to 200 mL of stirring isopropyl alcohol. The resulting white precipitate was collected by filtration to produce a white powder as star polymer (1.82 g; 30% yield). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.5-6.8 (b, Ar-H), 6.7-6.3 (b, Ar-H), 2.3-1.7 (b, -C(Ar)*H*-), 1.7-1.2 (b, -CH_2-). (SEC with THF: M_n = 36 490, M_w = 43 950, PDI = 1.20. MALLS: M_w = 74 000).

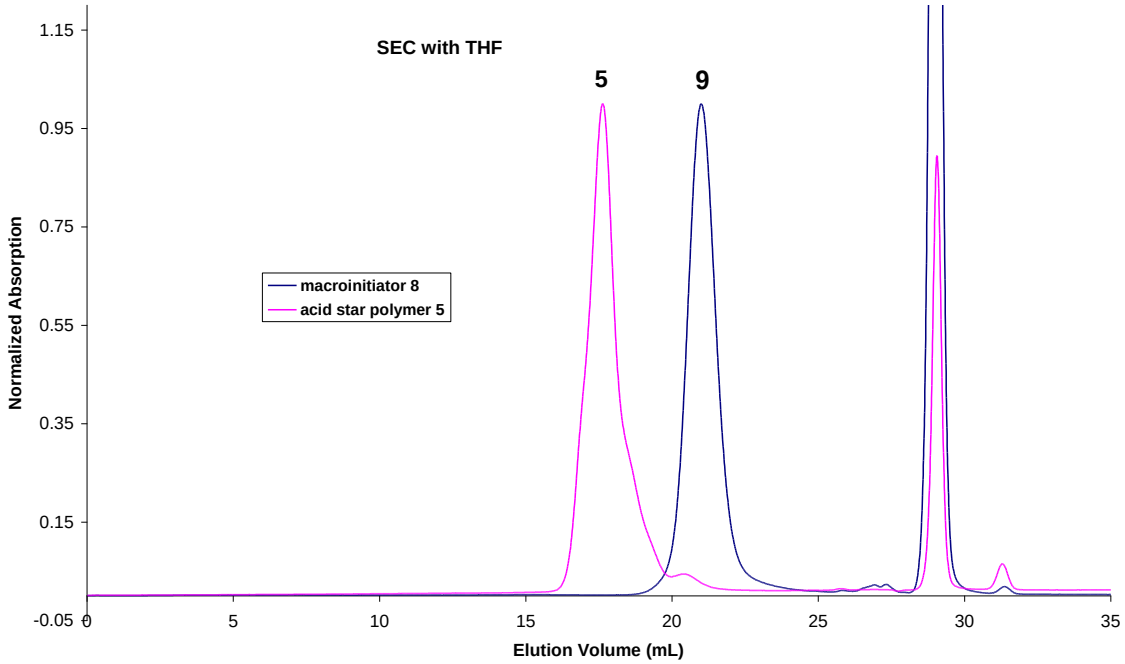


Figure 3. Comparison of SEC traces of the poly(styrene) macroinitiator "arm" **9** and the acid star polymer **5**.

This star polymer containing phenyl sulfonate (500 mg) was mixed with KOH (100 mg), THF (10 ml), MeOH (2 ml) and H_2O (0.2 ml) to give a clear solution. The reaction solution was heated to 50 ºC for 15 h under Ar. The solution was cooled to rt, and an excess amount of water was added dropwise to produce a white precipitate. The white precipitate was collected by filtration, washed with water, and then MeOH. The solid was dissolved in CH_2Cl_2 (50 ml), to which a solution containing 2 g H_2SO_4, 1 ml MeOH and 1 ml CH_2Cl_2 was added dropwise. The resulting mixture was stirred at rt for 5 h and then precipitate into ^{i}PrOH. The white precipitate was filtered, washed with MeOH extensively, dried and collected. The precipitate was dissolved in CH_2Cl_2 to give a solution with a small amount of solid. The mixture was filtered through a filter paper (to remove the solid), and the resulting clear solution was added dropwise to rapidly-stirring ^{i}PrOH. The resulting precipitate was filtered, washed with MeOH, and dried to give the desired acid star polymer **5** (380 mg, 76% yield). Elemental analysis of the sulfur content (C: 86.43; H: 7.34; N: < 0.2; S: 1.89) revealed 0.60 to 0.67 mmol acid per gram of the polymer (duplicated analysis of the same sample).

Amine star polymer (7). The polystyrene macroinitiator **9** (2.50 g, 0.38 mmol; SEC with THF: M_n = 6 577, M_w = 7 301, PDI = 1.11), functional monomer **10** (1.06 g, 1.90 mmol), styrene (219 uL, 1.90 mmol), and technical grade divinylbenzene (mixture containing 55% 3-, and 4-divinylbenzene and 45% 3- and 4-ethylvinylbenzene) (361 uL solution, 1.52 mmol divinylbenzene) were combined with 6.0 mL of DMF in a Schlenk tube. After 5 freeze/pump/thaw cycles to degas the solution, the solution was stirred at 125 °C for 18 h under Ar. The DMF reaction solution was mixed with about 6 mL benzene, to which MeOH was slowly added until a sticky gel was formed. The solvent was poured out, and the remaining gel was further fractionationed using DMF/benzene (1:1; v/v) as good solvents and MeOH as a bad solvent. After several fractionation cycles (monitored by SEC analysis), star polymer with a narrow PDI was obtained (1.05 g, ~ 25% yield) as a white solid (SEC with THF: M_n = 70 014, M_w = 92 151, PDI = 1.32; MALLS: M_w = 216 900). This polymer (650 mg) was dissolved in about 4 ml THF at 0 ºC, to which 10 ml 4N HCl/dioxane was added. The mixture was stirred overnight (about 16 h), during which time it warmed to rt. The solvents (THF and dioxane) were removed by a stream of N_2. The resulting residue was dissolved in 5 ml DMF and precipitate into ^{i}PrOH to give a white solid (as HCl salt). The white solid was dissolved in 5 ml DMF, followed by the addition of 3 ml triethylamine to give a clear solution. The mixture was stirred for 3 h, and then precipitated into ^{i}PrOH. The white solid was filtered, washed extensively with MeOH, and dried to give 550 mg (85% yield) white solid as the desired amine star polymer catalyst **7**. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.6-6.9 (br, Ar-H), 6.8-6.3 (br, Ar-H), 3.2-2.9 (br, -OCH_3 on chiral pyrrolidine, integrated as ~0.093 when Ar-H is integrated as 5 H). 2.1-1.7 (br, -C(Ar)*H*-), 1.6-1.1 (br, -CH_2-). Integration of the -O*C*H_3 on the catalytic entity of 7 indicated approximately 0.30 mmol of chiral pyrrolidine catalyst per gram of polymer.

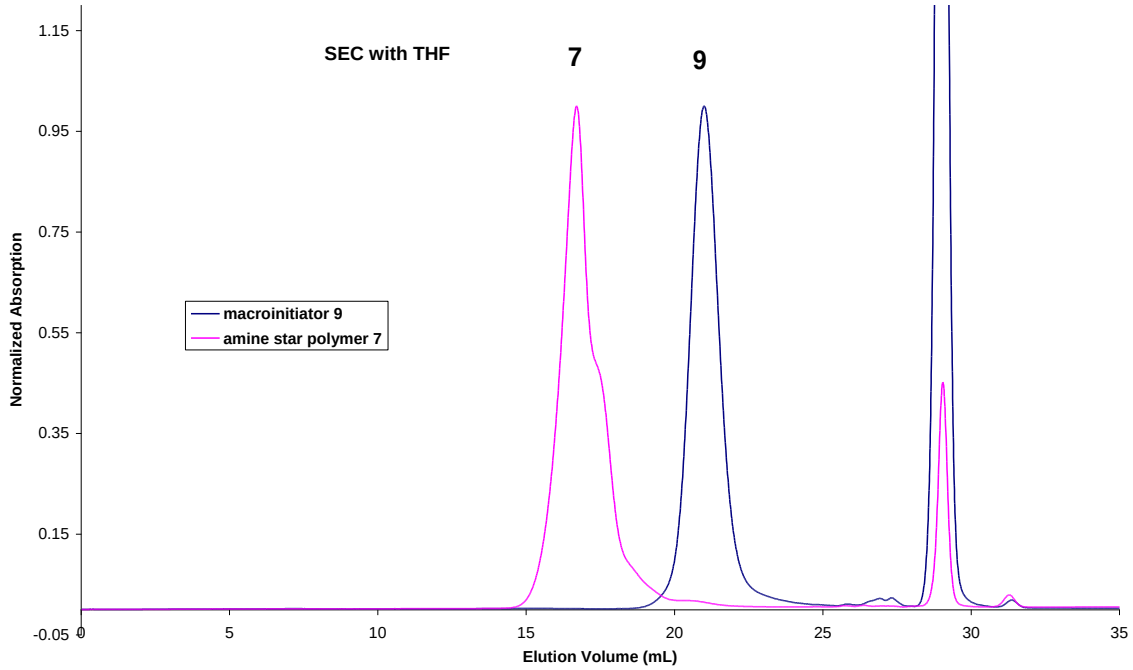


Figure 4. Comparison of SEC traces of the poly(styrene) macroinitiator "arm" **9** and the amine star polymer **7**.

Linear acid copolymer (11). A polystyrene macroinitiator (3.00 g, 0.698 mmol; SEC with THF: M_n = 4 300, M_w = 4 890, PDI = 1.14), phenyl *p*-styrenesulfonate (0.726 g, 2.79 mmol), and styrene (0.727 g, 6.98 mmol) were combined with 15.2 mL of DMF in a Schlenk tube. After 5 freeze/pump/thaw cycles to degas the solution, the reaction was stirred at 125 °C for 16 h under Ar. The solution was then poured into 400 mL of stirring isopropyl alcohol. The resulting precipitate was collected by filtration to yield a white powder 1.82 g (92%). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.3-6.8 (b, Ar-H), 6.7-6.3 (b, Ar-H), 2.3-1.7 (b, -C(Ar)*H*-), 1.7-1.2 (b, -CH_2-). SEC with THF: M_n = 6 560, M_w = 7 530, PDI = 1.15. Linear acid copolymer **11** was prepared using a hydrolysis and acidification procedure similar to star polymer **5**. Elemental analysis of the sulfur content revealed 0.67 mmol of acid per gram of polymer.

Linear amine copolymer (12). The polystyrene macroinitiator **9** (0.50 g, 0.076 mmol; SEC with THF: M_n = 6 577, M_w = 7 301, PDI = 1.11), functional monomer 10 (0.21 g, 0.38 mmol), and styrene (78 uL, 0.68 mmol) were combined with 1.0 mL of DMF in a Schlenk tube. After 5 freeze/pump/thaw cycles to degas the solution, the solution was stirred at 125 °C for 18 h under Ar. The solution was then added dropwise to a rapidly stirring isopropyl alcohol. The resulting precipitate was collected by filtration to yield a white powder (450 mg, 57% yield). Linear polymer **12** was prepared according to the deprotection procedure utilized on star polymer **7**. The amine catalyst content of **12** was estimated to be 0.34 mmol per gram of polymer via ^{1}H NMR analysis.

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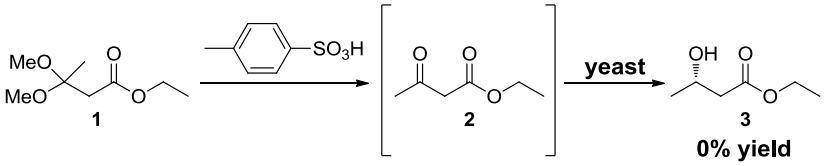
Chapter 3
Enzyme-Like Star Polymers in Combination with Yeast: Exploring the Compatibility of Biological and Chemical Catalysts in a One-Pot Reaction

Abstract

There are few examples of combined chemical and biological catalysis in a one-pot reaction. Here, we show that site isolation of a strong acid at the core of a star polymer is necessary for compatibility with a biocatalyst in the context of a two-step, one-pot reaction.

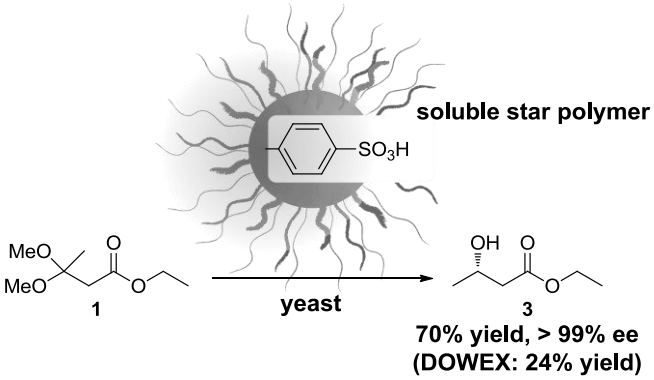
1. Introduction

One-pot reactions are used extensively by nature in the form of biochemical reaction pathways, which can synthesize complex molecules without the need for the isolation or purification of intermediates.[1] A strategy of combining biological and chemical catalysts in one pot could enhance access to synthetically and industrially useful products that are not accessible by one-pot strategies using a single type of catalyst alone.[2] However, there are only a few examples of combined chemical and biological catalysts in one pot.[3] A major challenge to the design of one-pot reactions is compatibility between reactive species in solution. For catalysts, Nature uses enzymes, whose macromolecular structure helps to prevent undesired reactions at the active site. Small molecule species lack this encapsulation effect and are often incompatible with enzymes in solution. Although incompatibility can sometimes be circumvented through the careful choice of reagents and order of addition,[3a, b] a site isolation strategy provides a more general route to catalyst compatibilization and would allow for greater freedom in the design of one-pot reactions combining chemical and biological catalysts.[4]



Scheme 1. Proposed chemical-biological cascade reaction cannot be performed using a small molecule acid catalyst.

Several tools have been developed to prevent incompatible catalytic moieties from interacting, including catalyst immobilization[5] and semipermeable physical barriers.[6] We have developed enzyme-like star polymers with core-confined functional moieties to be used as soluble, site-isolated catalysts for one-pot reactions.[7] The structure of these polymers prevents mutual quenching between catalytic functionalities on different stars, while their solubility and the small size of the polymer cores allows for the easy access of small molecule substrates. We were interested in seeing whether the designed site isolation of these stars could be combined with the native site isolation of biological catalysts to facilitate one-pot reactions. Herein, we use a combination of a star polymer acid and yeast to perform a one-pot, two-step reaction that is not possible using a small molecule acid (Scheme 1) and is much less efficient in the presence of an insoluble-polymer supported catalyst (Scheme 2).



Scheme 2 Chemical-biological reaction cascade facilitated by catalyst site isolation.

2. Results and Discussion

Our choice of a one-pot reaction was designed to demonstrate this principle by requiring the presence of incompatible chemical and biological catalysts. As shown in Scheme 1, this reaction involves the strong-acid catalyzed acetal deprotection of ethyl 3,3-dimethoxybutyrate **1** to form ethyl acetoacetate **2** followed by a yeast-catalyzed reaction to asymmetrically reduce **2** to (S)-ethyl 3-hydroxybutyrate **3**. While these reactions work well in isolation, the one-pot combination of the small molecule acid catalyst *para*-toluene sulfonic acid (*p*TSA) with yeast results in no formation of **3** and, indeed, no conversion of **1** to **2**.

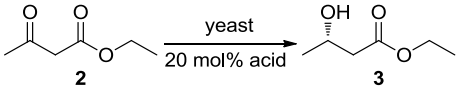
Table 1. Results for the combined chemical biological cascade reaction **1** → **2** → **3**.

			% yield[a]		
Entry[b]	Acid (mol%)	Yeast	**1**	**2**	**3**
1	pTSA (20%)	none	0	>99	0
2	pTSA (20%)	1.0 g	>99	0	0
3	PSS-H^+	none	0	>99	0
4	PSS-H^+	1.0 g	>99	0	0
5	DOWEX-H^+ (20%)[c]	none	0	>99	0
6	DOWEX-H^+ (20%)[c]	1.0 g	1	92	7
7	star (20%)[d]	none	0	>99	0
8	star (20%)[d]	1.0 g	0	68	32

[a]Determined using GC/MS with dodecane as an internal standard. [b]Reaction conditions: 30 μmol **1**, 1 mL toluene, 24 μL water, rt, 24h. [c]Acid loading determined based on 1.0 meq/g. [d]Acid loading determined based on 0.53 meq/g (see SI).

This result indicated that yeast is incompatible with the deprotection reaction catalyzed by *p*TSA. As shown in Table 1, entry 1, in the absence of yeast, this reaction goes to completion. However, the addition of yeast completely quenches the deprotection step (Table 1, entry 2). We also tested the linear polymeric analogue of *p*TSA (PSS-H^+) as an acid catalyst for the reaction. As shown by a comparison of entries 3 and 4 in Table 1, this catalyst was also deactivated by yeast. This indicates that a macromolecular architecture alone is not sufficient to isolate the acid. Because our star polymers share some properties with macroscopic bead-based catalysts, we also tested a commercially available acidic DOWEX resin in the cascade reaction. The DOWEX retained its activity in the presence of yeast, but there was very low conversion of **2** to **3** (Table 1, entries 5 and 6). The star acid catalyst also produced excellent conversion of **1** to **2** in the presence of yeast, and, under the initial conditions tested, the biological reagent also converted **2** into **3** in moderate yield (Table 1, entries 7 and 8).[8]

Table 2. Effect of sulfonic acid on the yeast-catalyzed reduction of ethyl acetoacetate **2**.



Entry[a]	Acid	% yield **3**[b]
1	none	50%
2	*p*TSA	4%
3	PSS-H^+	5%
4	DOWEX-H^+[c]	8%
5	star[d]	59%

[a]Reaction conditions: 30 μmol **2**, 30 mg yeast, 6.0 μmol acid, 1.0 mL toluene, 24 μL water, rt, 24h. [b]Conversion was determined using GC/MS with dodecane as an internal standard. [c]Acid loading determined based on 1.0 meq/g. [d]Acid loading determined based on 0.53 meq/g (see SI).

These tests of the deprotection reaction did not allow us to probe the effect of acid on the conversion of **2** to **3**. In order to further elucidate the role of site isolation in this reaction we also investigated the effect of the various sulfonic acids on the second step of our reaction cascade (Table 2). Comparisons of the conversion of **2** to **3** in the presence of yeast and various acids showed that only the star polymer had no negative effect on the biocatalytic reaction. These results confirmed that DOWEX would be a poor catalyst for the full one-pot cascade.

Table 3. Optimization of the chemical-biological reaction cascade reaction **1** → **2** → **3**.

			% yield[a]		
Entry[b]	Acid (mol%)	Yeast	**1**	**2**	**3**
1	star (10%)[c]	1 g	6	59	35
2	star (40%)[c]	1 g	0	69	31
3	star (20%)[c]	2 g	1	42	57
4	**star (20%)[c]**	**3 g**	**1**	**29**	**70**
5	DOWEX-H^+ (20%)[d]	3 g	60	16	24
6	DOWEX-H^+ (40%)[d]	3 g	7	70	22

[a]Determined using GC/MS with dodecane as an internal standard. [b]Reaction conditions: 30 μmol **1**, 1.0 mL toluene, 0.80 mL water per g yeast, rt, 24h. [c]Acid loading determined based on 0.53 meq/g (see SI). [d]Acid loading determined based on 1 meq/g.

Reaction optimization was a relatively simple operation, given the unique compatibility of the star polymer with yeast. Changing the amount of star polymer used had little effect on the yield (Table 3, entries 1 and 2), but added yeast predictably increased the reaction yield (Table 3, entries 3 and 4). This is in line with literature reports that require yeast/substrate ratios of 3.0-5.0 g/mmol for optimal yields. The best yield of **3** of 70% was achieved with 3.0 g of yeast and 20 mol% of star polymer acid equivalents. By contrast, it was difficult to optimize the use of DOWEX because adding more of either catalyst had a detrimental effect on the other part of the cascade (Table 3, entries 5 and 6).

3. Conclusions

In conclusion, we have shown that a strong acid catalyst is compatible with a biological catalyst when placed at the core of a poly(styrene) star polymer. The structure of the polymer, which contains no acid sites exposed at the surface, provides clear advantages over both small molecule and bead-based sulfonic acids. We are in the process of designing new reaction cascades with the expectation that this strategy will be generally applicable to one-pot reactions containing incompatible biological and chemical catalysts.

4. Methods

4.1 Materials. Commercial chemicals were purchased from Sigma-Aldrich. Fleischmann's active dry Baker's yeast was purchased from Safeway and stored at room temperature. Toluene and DMF were purchased from Fisher and vigorously purged with nitrogen for 1 h. The solvents were further purified by passing them under nitrogen pressure through two packed columns (Glass Contour) of neutral alumina copper(II) oxide (for toluene) or activated molecular sieves (for DMF). SEC with THF was carried out at 1.0 mL/min. Three PLgel columns (7.5 x 300 mm) were used. The columns had a pore size of 105, 103, and 500 Å, respectively. The particle size was 5 mm. The SEC system consisted of a Waters 510 pump, a Waters 717 auto sampler, a Waters 486 UV-Vis detector, a Wyatt DAWN EOS light scattering detector, and a Wyatt Optilab DSP differential refractive index detector. The columns were thermostatted at 35 °C. All polymer samples were quantified using a calibration curve of linear poly(styrene) samples. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AVQ 400 or AVB 400 instruments.

4.2 General analytical reaction procedure. A stock solution of either **1** or **2** (0.03M) and dodecane (0.01M as an internal reference) was prepared in toluene. These solutions were analyzed by GC/MS in single-ion detection mode. Yeast and water were added to a vial and then 1 mL of the stock solution was added, immediately followed by the sulfonic acid. After stirring for 24h at room temperature, the reaction mixture was analyzed by GC/MS.

4.3 Purification of ethyl 3-hydroxybutyrate (3) from cascade reaction and measurement of ee. Into a vial was weighed **1** (42.3 mg, 0.24 mmol). Yeast (0.720 g) and water (0.576 mL) were added, followed by toluene (8 mL) and **4** (89.8 mg). The reaction was stirred for 24h before being poured into 50 mL of diethyl ether. The yeast and precipitated polymer were filtered off and the solvents were removed *in vacuo*. The residue was subjected to column chromatography to isolate **3** (12.7 mg, 40% yield) as a volatile liquid (b.p. 170 °C). The identity of **3** was confirmed by spectroscopic comparison with a commercial sample. Chiral GC/FID was used to determine an ee of >99% by comparison with the racemic commercial sample. GC condition: Supelco beta Dex 225 column, N_2 1.0mL/min, programmed for 70 °C (hold 25 min.) to 80 °C (hold 20 min.) at 0.25 °C/min; t_R = 44.0 (major) and t_R = 45.6 (minor). The absolute configuration of **3(S)** was assigned based on literature reports.[8b]

4.4 Synthetic details.

Synthesis of ethyl 3,3-dimethoxybutanoate 1. Trimethyl orthoformate (8.75 mL, 8.49 g, 80.0 mmol), montmorillonite clay K10 (700 mg), *para*-toluene sulfonic acid monohydrate (38.0 mg, 0.2 mmol, 0.01 eq) were dissolved in a flame-dried flask containing methanol (20 mL, dried by distillation over CaH_2). After stirring for 5 min, ethyl acetoacetate (2.53 mL, 2.60 g, 20.0 mmol) was added. The mixture was stirred for 24h at rt. The mixture was filtered and the retentate washed with dichloromethane. The filtrate was washed with saturated sodium carbonate and water and dried over magnesium sulfate. After concentration of the crude material, **1** was purified via column chromatography on silica (10% ethyl acetate in hexanes; TLC conditions: 10% ethyl acetate in hexanes, R_f(product) 0.23 (anisaldehyde stain)) to give 2.13 g (12.1 mmol, 60% yield) of **1** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (q, J = 6.7 Hz, 2H), 3.19 (s, 6H), 2.63 (s, 2H), 1.44 (s, 3H), 1.24 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR δ = 169.61, 99.75, 60.45, 48.34, 42.25, 21.74, 14.09 ppm.

Synthesis of acid star polymer 4.[7a] A poly(styrene) macroinitiator[9] (M_n 5588, PDI 1.11, 2.79 g, 0.5 mmol), phenyl 4-styrene sulfonate[10] (0.521 g, 2 mmol), technical grade divinyl benzene (55wt% mixture of para and meta isomers, 0.519 mL, 2 mmol), and styrene (0.345 mL, 0.312 g, 3 mmol) were added to DMF (11.1 mL) in a Schlenk tube. After 5 freeze-pump-thaw cycles the tube was sealed under N_2 and heated to 125 °C with stirring for 16h. After cooling to room temperature, the mixture was diluted with a small amount of methylene chloride and precipitated in 500 mL of isopropyl alcohol. The solid polymer was dissolved in 300 mL of benzene and fractionally precipitated using approximately 100 mL of methanol. After collecting the gel and precipitating in isopropyl alcohol, the final star polymer (2.00 g, 52% recovery) with protected sulfonic acid was collected via filtration as a white solid (M_n = 38 645, M_w = 62 399, PDI = 1.61). Note that the absolute molecular weight for this star polymer can be significantly higher than that found by comparison with linear standards.[7b]

The protected polymer was dissolved in 15 mL of tetrahydrofuran and added to a solution of potassium hydroxide (0.375 g) dissolved in methanol (7.5 mL) and tetrahydrofuran (7.5 mL). More tetrahydrofuran (15 mL) was added, followed by water (0.750 mL). The mixture was stirred at 50 °C overnight. The polymer was precipitated via dropwise addition of water. The polymer was filtered and washed with methanol and water. The polymer was dissolved in 175 mL of dichloromethane. A mixture of 7.5 g sulfuric acid, 7.5 mL dichloromethane, and 7.5 mL methanol was added to the polymer solution. After stirring at rt for 3.5h, the mixture was precipitated in isopropyl alcohol. The polymer was filtered and washed with methanol. The polymer was dissolved in dichloromethane, filtered, and concentrated. The polymer was dissolved in benzene and precipitated in isopropyl alcohol. The polymer was filtered and washed with methanol. The polymer was recovered as a white solid (1.34 g, 35% over both steps).

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Chapter 4
Easy Access to A Family of Polymer Catalysts from Modular Star Polymers

Abstract

We report a versatile and scalable synthesis of a water-dispersible modular star polymer platform with an enzyme-inspired hydrophobic interior. The cores of the stars can be functionalized at will, independently from the modification of the polymer structure. We explore the use of this material for the creation of local hydrophobic solvent environment in water, and for site-isolation of incompatible catalytic entities.

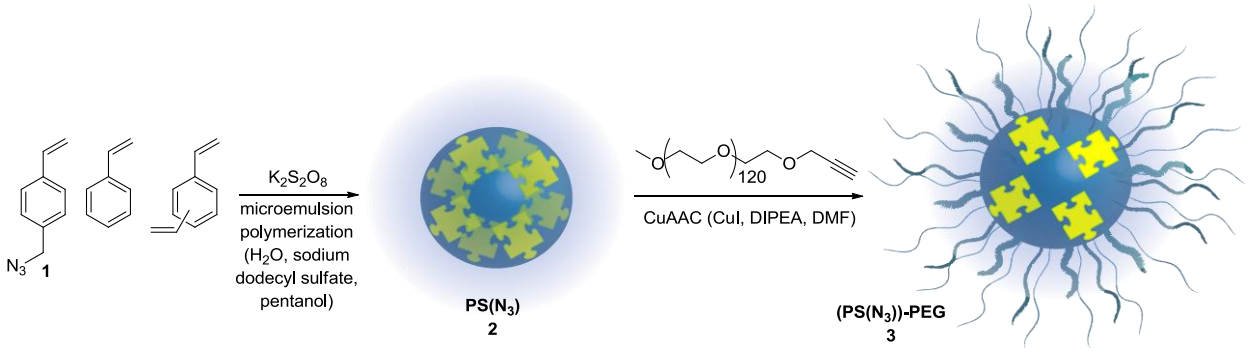
1. Introduction

Enzymes, Nature's polymer catalysts, are capable of carrying out thousands of competing and often incompatible reactions in crowded cellular milieu with perfect fidelity and selectivity. These functional linear polyamides create a favorable solvent environment around the catalytic site, isolate it from the action of other enzymes, and are capable of recognizing specific substrates. Enzymes achieve this exquisite level of functionality by folding into intricate tertiary structures.[1]

Ab initio rational design of linear polymers capable of protein-like programmed self-assembly remains an elusive goal. Materials with fractal or highly branched topologies are more amenable to molecular engineering due to their globular shape, core-shell microstructure, and multiple functionalization points.[2] At the same time, these materials can be expected to approximate many of the desirable features of natural biopolymers. Recent publications[3] have described the use of branched constructs for the site isolation of catalytic entities, and enzyme-like mediation of local solvent environment. In particular, this strategy allows for the combination of normally incompatible catalysts in one-pot sequential reaction cascades[4] without the use of solid supports.[5]

Star polymers, in which several linear polymer chains (arms) are attached to a central core, represent a readily accessed class of branched materials.[6] These polymers are an attractive target in materials design, since their topological and chemical complexity, which can approach that of dendrimers, is generated in a single key step. To date, few general methods are available for the topologically precise introduction of reactive or catalytic functional groups into star polymers. In the reported syntheses of catalytic star polymers, either the unimolecular core is catalytic,[7] or the catalytic moieties are incorporated via functional monomers in an arm-first process.[4, 8] The unimolecular core approach yields materials with just a few arms, which limits the degree of core isolation and shielding of local environment.[9] Furthermore, the functional diversity of the resulting materials is limited, and only a single catalytic moiety is incorporated into each macromolecule. The arm-first polymerization strategy provides access to polymers bearing a wide range of functional groups. However, the morphology of the materials prepared by this process is significantly influenced by the nature of the functional groups being incorporated. A more rapid and general route to star polymers with tunable functionalities and controlled microstructure is desired. Here we describe the coupling-onto synthesis of star polymers with "clickable"[10] cores. The highly efficient and tolerant copper(I) catalyzed alkyne-azide cycloaddition (CuAAC) reaction[11] allowed us to incorporate a wide range of functionalities into the resulting materials.

2. Results and Discussion



Scheme 1. Synthesis of (PS(N_3))-PEG star polymer **3.**

2.1 Star polymer synthesis. Microemulsion polymerization of styrene, divinylbenzene, and 4-azidomethylstyrene **1** yielded functionalized polystyrene nanoparticles PS(N_3) **2** with narrow size distribution (Scheme 1). The size of the particles could be controlled between 15 and 50 nm through variations in the ratio of polymerization mixture to surfactant. After purification by precipitation, **2** was reacted with propargylated poly(ethylene glycol) (PEG- alkyne, M_n ~ 5 kg/mol) under standard CuAAC conditions as described by Meldal *et al.*[11c] As shown in Figure 1, reaction progress was monitored by the disappearance of the characteristic azide band (2097 cm^{-1}) in the IR spectrum of the polymer. The resulting star polymers, (PS(N_3))-PEG **3**, were fully dispersible in water.

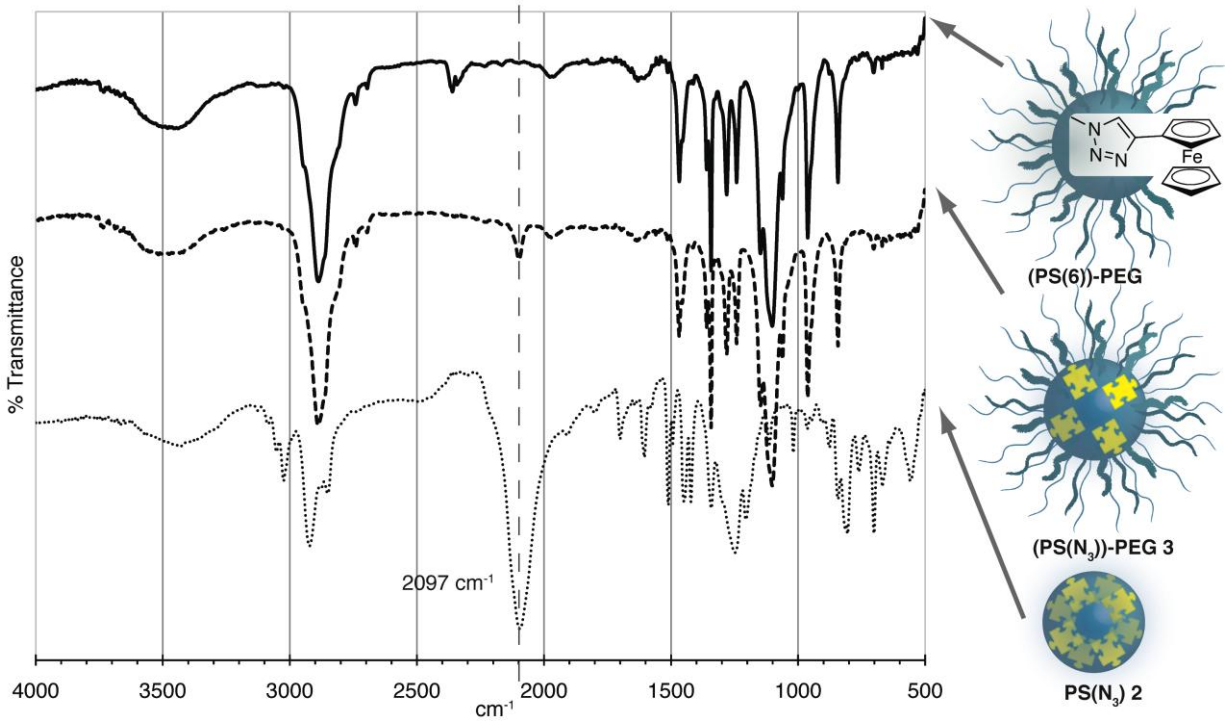


Figure 1. Infrared spectra of PS(N_3) **2** (bottom), (PS(N_3))-PEG **3** (middle), and (PS(**6**))-PEG (top). The characteristic signal of azide groups is the sharp peak at 2097 cm^{-1}.

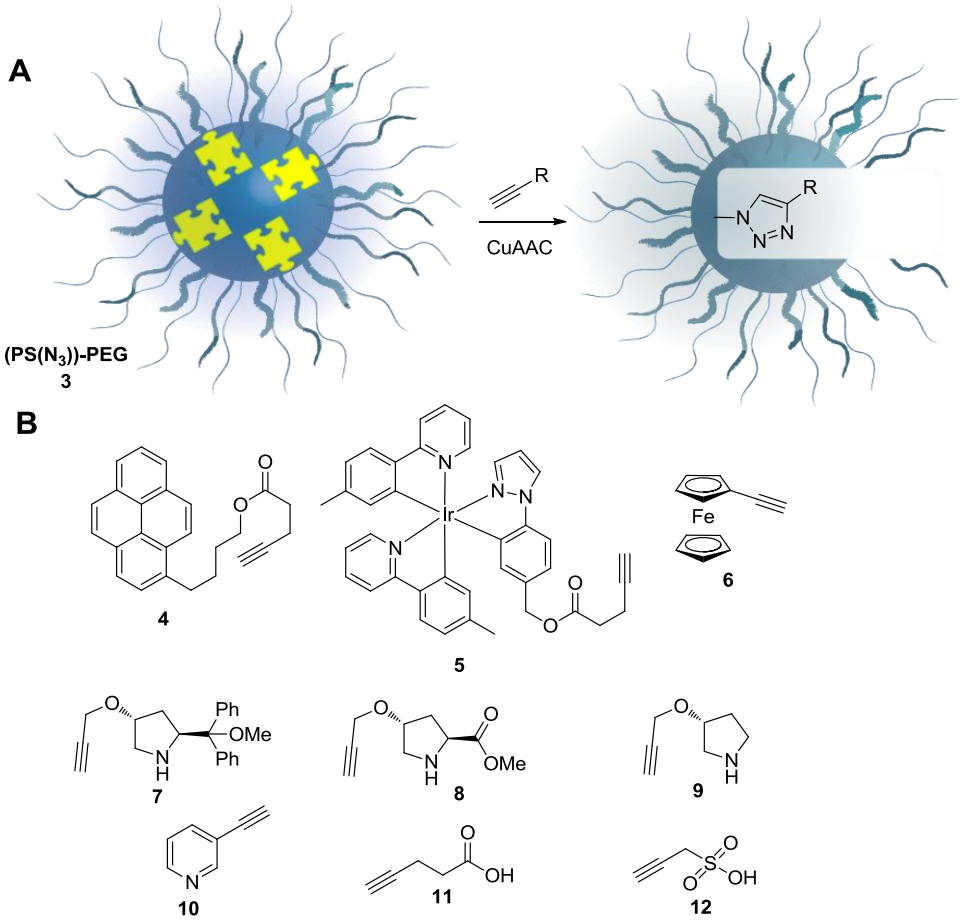


Figure 2. Functional payloads incorporated into (PS(N_3))-PEG star polymers. (A) Coupling of functional alkyne payloads to (PS(N_3))-PEG. (B) Alkynes that were successfully incorporated into (PS(N_3))-PEG. For convenience, the functionalized stars are designated by an abbreviation (PS(**X**))-PEG, where **X** is the number of the alkyne payload.

We found that the ratio of divinylbenzene crosslinker to monomers used in the microemulsion polymerization step had a profound effect on the reactivity of PS(N_3) nanoparticles. When 2.5 wt. % or less of divinylbenzene was added, all of the core azide groups were capable of reacting with the PEG-alkyne. Some azide groups could be left unreacted by purposely using substoichiometric amount of PEG-alkyne during reaction with PS(N_3). However, subsequent functionalization with polar (**8**, **10**), or highly hydrophobic (**5**, **7**) alkyne payloads (Figure 2B) resulted in materials that formed intractable aggregates in water. When the ratio of divinylbenzene in the polymerization mixture was increased to 5 wt. %, only one third of the azide groups in the cores of the resulting nanoparticles was consumed after a prolonged (96 hours) CuAAC catalyzed reaction with excess PEG-alkyne, indicating that not all azide groups in the PS(N_3) core were accessible to the relatively large linear PEG chains. This is indicated by the residual azide peak in the IR spectrum of (PS(N_3))-PEG shown in Figure 1. Fortunately, smaller molecules do not share this limitation and, following installation of the PEG arms, a wide variety of lower molecular weight payloads were successfully incorporated into the core of (PS(N_3))-PEG via reaction with the remaining azide groups (Figure 2). None of the resulting materials possessed the characteristic signal of the N_3 group in their IR spectra, and their dispersibility in

water was unaffected by either hydrophobic or highly polar payloads. As shown in Figure 3, the amount of reactive azide groups was determined to be 0.18 mmol/g by measuring the UV absorbance of (PS(N_3))-PEG functionalized with pyrene derivative **4**. We used a feed ratio of 5 wt. % of divinylbenzene for synthesizing all of the PS(N_3) nanoparticles in this study.

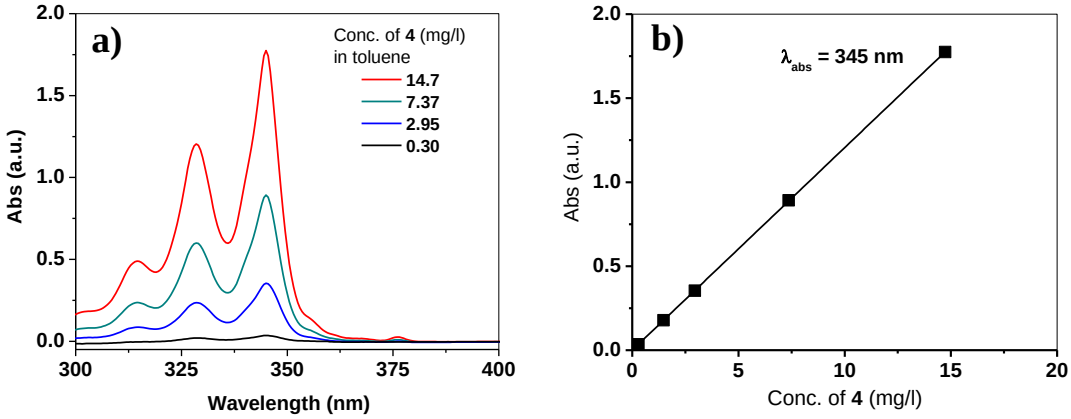


Figure 3. Quantifying the reactive azide groups on (PS(N_3))-PEG using pyrene derivative **4** as a UV-active probe: a) UV-vis spectra of **4** in toluene at different concentrations and b) The calibration curve for **4** in toluene at λ_{abs} = 345 nm.

Dynamic light scattering (DLS) analysis indicated that the hydrodynamic diameter of particles increased from 20 nm to *ca*. 70 nm after PEG-alkyne coupling (Figure 4). The size of polymer particles observed in the atomic force microscopy (AFM) phase image (Figure 5B) agrees well with the DLS data. The phase image reveals nanoscale material contrast between the cores of the particles and their outer regions. When overlaid, the line profiles of the AFM topography (Figure 5A) and phase images show a 20-25 nm central core that comprises much of the significant height of the polymer (Figure 5C). The core appears to be surrounded by a *ca.* 10 nm band of material. The same architecture with well-defined corona and core regions was observed in a transmission electron microscopy image of (PS(N_3))-PEG stained with sodium phosphotungstate (Figure 6). The TEM and AFM images in Figures 5 and 6 correspond to the same sample. We attribute the larger core size observed in the TEM experiment (Figure 6) to the staining of the denser part of the PEG corona with sodium phosphotungstate. On the TEM image of the star polymer labeled with electron-dense iridium complex **5** 25-30 nm cores are readily visible (Figure 7). Unlike sodium phosphotungstate, the alkyne label **5** has no affinity for the PEG corona. Thus, only the cores of the polymer stars are visible in this last image.

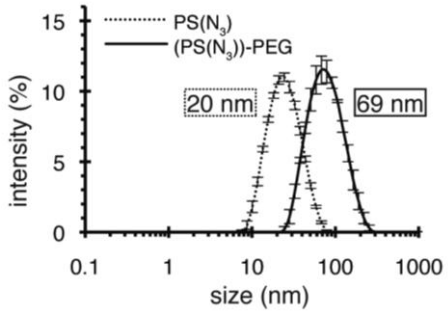


Figure 4. DLS data for PS(N_3) and (PS(N_3))-PEG in water.

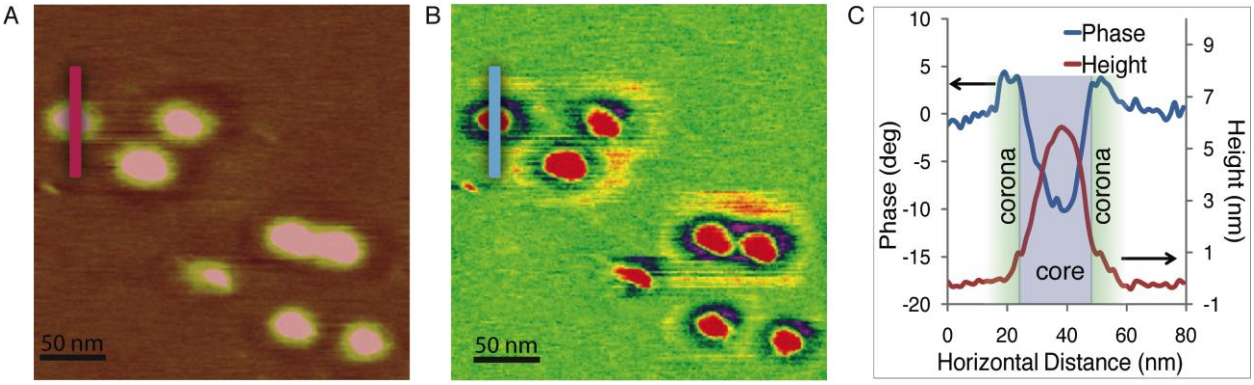


Figure 5. AFM image of a (PS(N_3))-PEG sample: (A) topography image; (B) phase image that was acquired simultaneously with topography; (C) superimposed plots of phase and height values (cross-sections are highlighted on the phase and topography images).

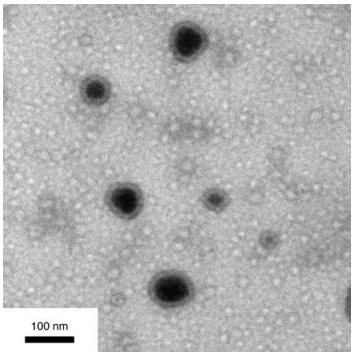


Figure 6. TEM image of a (PS(N_3))-PEG sample stained with sodium phosphotungstate. The PEG shell and the more densely stained core region are clearly discernible.

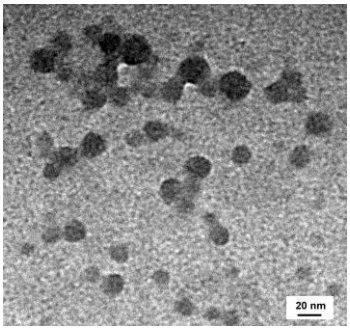


Figure 7. TEM image of a (PS(**5**))-PEG sample. Only the ca. 20 nm polystyrene cores are visible, since they are the only region of the polymer reactive towards electron-dense "clickable" iridium complex **5**

2.2 Properties of core nanoenvironment. We envision the use of (PS(N_3))-PEG **3** as a water-soluble support for hydrophobic, or water-incompatible catalysts. We examined the ability of **3** and its derivatives to transport hydrophobic materials by using Nile Red **13** (Figure 8A), a hydrophobic solvatochromic dye.[13] Nile Red has a very low solubility in water (Figure 8B, vial 1). The solubility of Nile Red was unaffected by adding 1 wt. % of linear PEG (M_n ~ 5000

kg/mol) to the solution (Figure 8B, vial 2). In contrast, (PS(N_3))-PEG **3** (1 wt. %) was able to efficiently solubilize Nile Red (Figure 8B, vial 3) affording a solution that exhibited a strong emission at λ_{max}=592 nm (λ_{exc}=515 nm), suggesting that the environment of the core had a remarkably low polarity comparable to that of dichloromethane (Figures 8C, 8D). Incorporation of polar heterocyclic cargos such as ethynylated proline **8**, or pyridine **10**, into the star core resulted in a red shift of the emission wavelength of Nile Red to λ_{max}=615 nm, suggesting a polarity comparable to that of methanol.

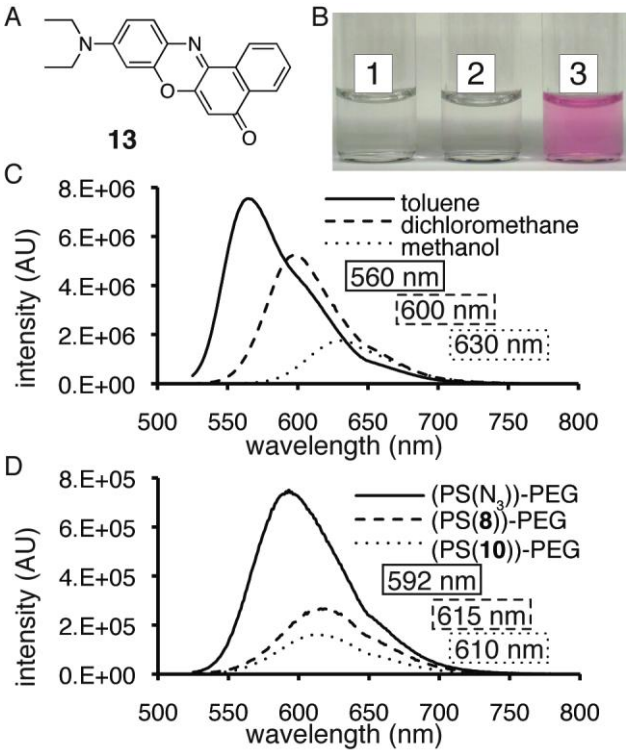
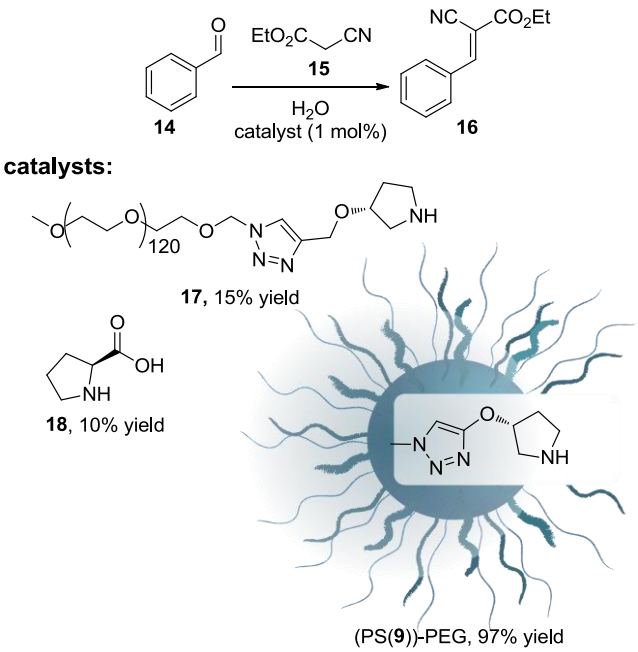


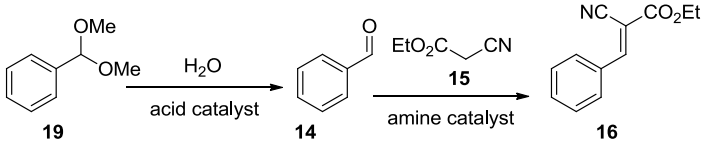
Figure 8. Fluorescence experiments with solvatochromic dye Nile Red **13**. (A) Nile Red **13**. (B) Transport of **13**: vial 1 contains **13** in water; vial 2 contains **13** in 1 wt. % aqueous solution of linear PEG (M_n ~ 5 kg/mol); vial 3 contains **13** in 1 wt. % aqueous solution of (PS(N_3))-PEG. (C) Fluorescence emission spectra of **13** in toluene, dichloromethane, and methanol (λ_{exc}=515 nm). (D) Fluorescence emission spectra of **13** solubilized in water by (PS(N_3))-PEG, (PS(**8**))-PEG, and (PS(**10**))-PEG (λ_{exc}=515 nm).

2.3 Catalyst attachment and site isolation experiments. To probe the viability of our material as a catalyst support, we used a model Knoevenagel condensation between benzaldehyde **14** and ethyl cyanoacetate **15** in water (Scheme 2). The rate of the uncatalyzed reaction is negligible at room temperature. (PS(**9**))-PEG demonstrated activity superior to that of L-proline **18**, or the functional PEG **17**. (PS(**9**))-PEG could be recycled multiple times with no loss of activity. The superior catalytic activity of our material may be due to the placement of catalytic amine moieties within the hydrophobic environment of the core.[14]



Scheme 2. Model Knoevenagel condensation. Yields are for reactions run for 24 hours at 20±2ºC in H_2O, with [**14**]=[**15**]=0.94 M. Yields are based on GC-MS measurements.

Table 1. Catalytic results for a one-pot reaction cascade using acid and amine catalysts.[a]



Entry	Amine catalyst	Acid catalyst	Conversion of **19** [%][c]	Yield of **16** [%][c]
1	pyrrolidine	PTSA	0	0
2	(PS(**9**))-PEG	PTSA	0	0
3	pyrrolidine	(PS(**12**))-PEG	0	0
4	(PS(**9**))-PEG	(PS(**12**))-PEG[b]	100	95

[a]Reactions were run for 24 hours at 20±2ºC in H_2O/methanol (4:1), [**19**]=60 mM, [**15**]=440 mM. 10 mol. % of amine and acid catalysts (relative to **19)** were used. [b]Loading of ca. 2 mol. % of (PS(**12**))-PEG and 10 mol % of (PS(**9**))-PEG results in 85% yield of **16** after 3 hours, indicating that the star acid is not inactivated even by a large excess of amine star [c]Yields are based on GC-MS measurements.

We used the one-pot cascade transformation of benzaldehyde dimethyl acetal **19** into the Knoevenagel condensation product **16** to evaluate the utility of the new materials for site isolation applications (Table 1).[4b] We chose (PS(**9**))-PEG as the amine catalyst for the Knoevenagel condensation step of the cascade and star acid (PS(**12**))-PEG for the acetal hydrolysis step. Control reactions with *p*-toluenesulfonic acid (PTSA) and pyrrolidine (Entry 1), as well as PTSA and (PS(**9**))-PEG (Entry 2) and pyrrolidine and (PS(**12**))-PEG (Entry 3), resulted in no acetal hydrolysis and no cascade product **16** being formed. Complete and rapid conversion of acetal **14** to cascade product **16** was observed for the combination of amine catalyst (PS(**9**))-PEG with acid star (PS(**12**))-PEG. These results support our assumption that the

star cores are sufficiently isolated from each other to prevent mutual deactivation of incompatible core-bound catalytic groups.

3. Conclusions

We have developed a versatile and scalable synthesis of a water-dispersible modular star polymer platform with enzyme-inspired hydrophobic interior, and explored the use of this material for the creation of local hydrophobic solvent environment in water. We have demonstrated that the core of the materials can be functionalized at will, independently from the modification of the polymer structure. These "clickable" stars may be employed in the synthesis of a library of enzyme-inspired site isolated catalysts that may be used in aqueous medium.

4. Methods

4.1 Materials. Commercial reagents were purchased from VWR or Aldrich and used without any further purification. Poly(ethylene glycol) methyl ether (M_n ~ 5000) was purchased from Nektar (Huntsville, AL). THF, dichloromethane, and toluene were dried by passing through activated alumina columns. The following solutions have been used to stain TLC plates: ammonium molybdate/H_2O, anisaldehyde/ethanol, and $KMnO_4/H_2O$. Preparative TLC was performed on 2000 μm silica gel plates (Analtech, Newark, DE). The bands were visualized with UV light, and products were extracted with 20% v/v methanol/dichloromethane. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh) silica. Reactions requiring anhydrous conditions were performed under nitrogen using standard Schlenk line techniques.

4.2 Instrumental methods. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AVQ 400 or AVB 400 instruments. GC-MS analyses have been performed on an Agilent 7890A gas chromatograph equipped with a 30 m HP-5 capillary column and an Agilent 5975C mass-selective detector. Elemental analyses were performed by UC Berkeley Microanalysis Facility. Infrared spectra were recorded on a Varian 3100 FT-IR spectrometer in KBr pellets. Ground-state UV/visible absorption spectra were measured on a Shimadzu UV-3600 UV-VIS-NIR spectrophotometer. Optical emission and excitation spectra were obtained using an ISA/SPEX Fluorolog 3.22 equipped with a 450W Xe lamp, double excitation and double emission monochromators, and a digital photoncounting photomultiplier. Slit widths were set to a 3-nm bandpass on both excitation and emission monochromators. The size distribution of the star polymers was determined by dynamic light scattering (DLS) using a Zetasizer Nano-ZS instrument (Malvern Instruments, Malvern, UK). Samples for absorbance and emission experiments were measured in standard 1 cm quartz cells. All measurements were performed at room temperature. Transmission electron microscopy (TEM) images were obtained on a FEI Tecnai 12 microscope operated at 100 kV. For TEM imaging, samples were dispersed in water and deposited on carbon-coated copper grids. For negative staining, the sample-deposited grid was immersed in 1 wt. % sodium phosphotungstate aqueous solution for 5 sec before drying in air. Atomic force microscopy (AFM) images were obtained on a Digital Instruments Multimode atomic force microscope operated in tapping mode with a Nanoscope V controller. Silicon

cantilevers (k= 40 N/m) with integrated tips (r<10nm) from Veecoprobes (Tap 300) were used. The samples were prepared by spin coating the polymer at 4000 rpm for 30 seconds from a 0.5 μg/ml solution in chloroform onto freshly cleaved mica.

4.3 Catalytic reaction protocols. The reaction catalyzed by (PS(**9**))-PEG was performed using 50 mg of (PS(**9**))-PEG (~0.18 mmol/g, ~0.009 mmol pyrrolidine groups, 0.094 eq.) dissolved in 1 mL of deionized water. 97 μL of benzaldehyde (101 mg, 0.95 mmol, 1 eq.) and 101 μL of ethyl cyanoacetate (107 mg, 0.95 mmol, 1 eq.) was added, and the reaction was stirred vigorously for 24 hours. The reaction was heterogeneous (opaque). No phase separation occurred after the stirring was stopped. After 24 hours of vigorous stirring, a 50 μL aliquot was taken from the reaction, diluted with 500 μL of methanol, and analyzed by GC-MS. Only traces of starting materials could be seen in the chromatogram. The aqueous phase was extracted with three 1 mL aliquots of diethyl ether (phase separation was facile). The ether fractions were combined, dried over anhydrous $MgSO_4$, and the solvent was removed yielding 184 mg (97%) of the condensation product free of contamination by starting materials (determined by GC-MS analysis). The remaining aqueous phase containing (PS(**9**))-PEG could be used to perform additional Knoevenagel condensations in the way described above by adding more starting materials. We performed this catalyst recycling experiment four times.

Control reactions (uncatalyzed, or catalyzed by proline and functional PEG **17**) have been performed in the same way as the reactions catalyzed by (PS(**9**))-PEG. The loading of catalysts and the starting materials was as follows: *Uncatalyzed reaction*: 0.96 mL (9.4 mmol, 1 eq.) benzaldehyde, 1.00 mL (9.4 mmol, 1 eq.) ethyl cyanoacetate in 10 mL water; *Reaction catalyzed by proline*: 0.96 mL (9.4 mmol, 1 eq.) benzaldehyde, 1.00 mL (9.4 mmol, 1 eq.) ethyl cyanoacetate, 10.8 mg (0.094 mmol, 0.01 eq.) proline in 10 mL water; *Reaction catalyzed by **17***: 0.48 mL (4.7 mmol, 1 eq.) benzaldehyde, 0.50 mL (4.7 mmol, 1 eq.) ethyl cyanoacetate, and 85 mg (0.043 mmol, 0.009 eq.) 17 in 5 mL water.

The reaction catalyzed by **17** had the same opaque/stable emulsion appearance as the reaction catalyzed by (PS(**9**))-PEG. Neither the uncatalyzed reaction nor the reaction catalyzed by proline did formed stable emulsions: phase separation occurred after stirring was stopped. 50 μL aliquots were taken out of the reactions after 24 hours, diluted by 500 μL of methanol, and analyzed by GC-MS to determine the extent of conversion (peaks corresponding to benzaldehyde and the condensation product were used). Only traces of condensation product were detected in the uncatalyzed reaction. The reaction catalyzed by proline reached ~10% conversion, and the reaction catalyzed by functional PEG **17** reached ~15% conversion.

4.4 Synthetic details.

Propargylated poly(ethylene glycol) methyl ether (PEG-alkyne). Poly(ethylene glycol) methyl ether (MPEG) (50 g, 10 mmol, 1 eq) was placed in a 500 ml round bottom flask fitted with a Dean-Stark azeotropic distillation adapter and a magnetic stir bar, and 250 ml of benzene was added. The apparatus was flushed with N_2, and 200 ml of benzene was distilled off the MPEG. Most of the remaining benzene was removed on a rotary evaporator, the flask was flushed with N_2, fitted with a rubber septum, and 250 ml of dry DMF was added.

A thoroughly dried three-neck round bottom flask was fitted with a rubber septum, inert gas inlet, magnetic stirring bar, and charged with 2 g of 60% wt. dispersion of NaH in mineral oil (50 mmol, 5 equiv.). The flask was flushed with N_2, and then the MPEG solution was quickly added

via a cannula while stirring. The reaction was stirred for 2 hours at room temperature, at which point 4.3 ml of 80 wt. % solution of propargyl bromide in toluene (40 mmol, 4 equiv.) was added via a syringe. The light gray suspension turned dark brown over the course of the next 2 hours. The reaction was left to stir at room temperature for 72 hours. At that point, 5 ml of methanol was added via syringe. Upon end of hydrogen evolution, the reaction mass is filtered through a coarse fritted glass filter, and the filtrate is quickly poured into 1.6 l of diethyl ether with vigorous stirring. The resulting amorphous brown precipitate was collected on a 45 μm Nylon filter membrane, washed with three 100 ml portions of diethyl ether, and air-dried. The brown powder was re-suspended in 500 ml of ethyl acetate, and washed with five 100 ml portions of 2% aqueous solution of NH_4Cl. The ethyl acetate fraction was discarded. Viscous, dark brown aqueous fractions were collected, and extracted with five 100 ml portions of dichloromethane. Dichloromethane fractions were combined, dried over anhydrous $MgSO_4$, and the solvent was removed on the rotary evaporator to yield dark brown, amorphous solid. The material thus obtained was taken up into 250 ml of chloroform. The solution was heated to 40°C, and 1.2 l of diethyl ether (20°C) was added to the flask with vigorous stirring. Addition of the last 50-100 ml of ether has to be done with great care: once the solution becomes visibly cloudy, it has to be very promptly filtered trough a 45 μm Nylon membrane. PEG-alkyne spontaneously precipitated from the mostly colorless filtrate upon cooling to room temperature (this can be helped by cooling the filter flask in the refrigerator, or by adding a few more ml of cold ether). The precipitate was collected and dried in a vacuum dessicator to yield 40 g of pure product as an off-white, moderately hygroscopic, slightly waxy powder, that has a strong tendency to foam in water solutions. The compound stains yellow with basic $KMnO_4$ on silica gel TLC plates (no heat applied). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.20 (broad d, 2H, propargyl CH_2), 3.80-3.50 (broad s, ~490H, main PEG chain), 3.37 (s, 3H, terminal CH_3O), 2.44 (broad t, 1H, propargyl CH).

Star polymer PS(N_3) (2). Sodium dodecyl sulfate (1.50 g) and pentanol (0.15 mL) were dissolved in 40 mL of deionized water. The polymerization mixture containing 4-azidomethylstyrene 1 (600 mg), styrene (600 mg), and divinylbenzene (60 mg of 80 wt. %) was added to the aqueous surfactant solution dropwise. A steady stream of N_2 was passed through the solution for 10 min. before 20 mg $K_2S_2O_8$ in 0.5 mL of deionized water was added. The reaction mixture was heated to 60°C, and stirred with a magnetic stirrer (400 rpm) for 6 hours. The mixture was dialyzed against deionized water (dialysis membrane molecular weight cutoff 50 kDa). The polymer was precipitated by adding a trace amount of $CaCl_2$. The material was re-suspended in THF, and precipitated with methanol to give PS(N_3) as a white solid (800 mg, 64%).

Star polymer (PS(N_3))-PEG (3). 120 mg of PS(N_3) **2** was suspended in 3 mL of THF in a 20 mL screw cap vial. 5 mL of DMF was added. Most of the THF was removed on a rotary evaporator (it was important to avoid heating the suspension). Following that, 1.10 g of PEG-alkyne, 1 mL of diisopropylethylamine, and 15 mg of CuI were added in the order indicated. The vial was capped, sonicated for 5 min., and left to stand for 24 hours with no stirring. The viscosity of the reaction mass was observed to increase dramatically as the reaction progressed. The product was precipitated by pouring the reaction mixture into 100 mL of diethyl ether. The solid was washed with two 50 mL portions of ether, and suspended in 20 mL of water. 500 mg of disodium salt of EDTA was added, the resulting bluish-green solution was filtered through a 0.45

μm Nylon membrane, and dialyzed against deionized water (dialysis membrane molecular weight cutoff 100 kDa). Water was removed by lyophilization to yield 970 mg of **3** as a flaky, light white solid.

Star polymer (PS(9))-PEG. 400 mg of (PS(N_3))-PEG **3** was suspended in 5 mL of DMF. 20 mg of (S)-3-(prop-2-ynyloxy)pyrrolidine **9** was added, followed by 1 mL of diisopropylethylamine and 15 mg of CuI. The vial was capped, sonicated for 5 min., and left for 24 hours with no stirring. The product was isolated and purified using the same procedure used for (PS(N_3))-PEG **3** to yield 400 mg of (PS(**9**))-PEG as an off-white solid.

Other catalytic star polymers. Other functionalized star polymers have been prepared in the same way as (PS(**9**))-PEG. (PS(**12**))-PEG was prepared in a 10% water/DMSO mixture (sodium salt of **12** is insoluble in DMF). It was necessary to add the accelerating tris((benzimidazol-2-yl)methyl)amine ligand[15] (1 eq. relative to CuI) under those conditions. The resulting polymer was washed with multiple portions of 2.0M solution of HCl in ether, dried, and kept under vacuum for 14 days. At that point, no AgCl precipitate formed when concentrated solution of $AgNO_3$ was added to the aqueous dispersion of the polymer, indicating that most of the HCl bound to the polymer has been removed. The 1,2,3-triazole moiety is a very weak base (pK_a of conjugated acid is ~1.2).

4-(pyren-1-yl)butyl pent-4-ynoate (4). 4-(pyren-1-yl)butan-1-ol (1.08 g, 3.94 mmol), 4-pentynoic acid (0.386 g, 3.94 mmol, 1 eq), dicyclohexylcarbodiimide (0.812 g, 3.94 mmol, 1 eq), and a catalytic amount of DMAP (98.1 mg, 0.394 mmol, 0.1 eq) were dissolved in 20 mL of dichloromethane and allowed to react overnight. The reaction mixture was filtered from dicyclohexylurea, the solvent was removed on a rotary evaporator, and the product was purified by flash chromatography (1:10 ethyl acetate/hexanes). Yield 1.00 g (72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, 1H), 8.22 (d, 1H), 8.20 (d, 1H), 8.17 (s, 1H), 8.15 (d, 1H), 8.07 (d, 2H), 8.06 (t, 1H), 7.91 (d, 1H), 4.23 (t, 2H, CH_2O), 3.42 (t, 2H, ArCH_2), 2.60-2.50 (m, 4H, $CO_2CH_2CH_2$), 2.1-1.9 (m, 2H, $CH_2CH_2CH_2O$), 1.98 (t, 1H, C*H*), 1.9-1.8 (m, 2H, $CH_2CH_2CH_2O$).

(2*S*,4*R*)-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (7). A thoroughly dried three-neck round bottom flask was fitted with a rubber septum, inert gas inlet, magnetic stirring bar, and charged with 1.75 g of 60% wt. dispersion of NaH in mineral oil (44 mmol, 5 eq). The flask was flushed with N_2, and sodium hydride was washed with three 20 mL portions of dry hexanes. 12 mL of dry DMF was added, and the flask was cooled to -15°C. Solution of (2S,4R)-tert-butyl 4-hydroxy-2-(methoxydiphenylmethyl)pyrrolidine-1-carboxylate (3.39 g, 8.83 mmol) in 50 mL of dry DMF was quickly added via a cannula while stirring. The reaction was left to stir under N_2 for 30 min., at which point the evolution of H_2 has largely ceased. Propargyl bromide (80 wt. % solution in toluene, 2.85 mL, 26.5 mmol, 3 eq) was promptly added. The color of the reaction mixture immediately turned brown. The reaction was allowed to warm up to ca. -5°C, and stirred for 6 hours. Progress was monitored by TLC (3:7 ethyl acetate/hexanes). 5 mL of methanol was slowly added to the flask. After gas evolution stopped, the reaction mixture was diluted with 200 mL of water, and extracted with five 30 mL portions of dichloromethane. The organic fractions were combined, dried over anhydrous $MgSO_4$, and the solvent was removed on a rotary evaporator. The product, (2*S*,4*R*)-*tert*-butyl-2-(methoxydiphenylmethyl)-4-

(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate, was purified by preparative TLC. Yield 2.4 g, 64% as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.29 (m, 10H, aromatic), 5.2-4.9 (broad, 1H), 4.0-3.4 (4 broad, 2H), 3.97 (broad, 2H, propargyl CH_2), 2.97 (s, 3H, OCH_3), 2.36 (broad, 1H, propargyl CH), 2.23 (broad, 1H), 2.18 (s, 1H), 2.05-1.90 (broad, 1H), 1.4-1.2 (two broad s, 9H, Boc CH_3).

(2*S*,4*R*)-*tert*-butyl-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (590 mg, 1.4 mmol) was dissolved in 50 mL of 4M solution of HCl in dioxane. After two hours the solvent was removed on a rotary evaporator. The oily residue was dissolved in 20 mL dichloromethane, and extracted with three 10 mL portions of 20 wt. % aqueous NaOH and 20 mL water. The organic fraction was dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 385 mg (86%) of product as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.40 (b, 10H, *Ar*), 4.80-4.90 (br, 1H, -CH_2C*H*(O)CH_2-), 4.15 (s, 2H, -OC*H*$_2$C≡), 3.85-9.90 (br, H, -CH_2C*H*NH-), 3.20 (s, 3H, -OC*H*$_3$), 3.30-3.40&2.80-2.90 (dd, 2H, -CHC*H*$_2$NH-), 2.38 (s, 1H, -C≡C*H*), 1.95-2.10 (m, 2H, -CHC*H*$_2$CH-).

(*S*)-3-(prop-2-yn-1-yloxy)pyrrolidine (9). The boc-protected intermediate was prepared from (*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (560 mg, 2.99 mmol) using the same protocol as for the precursor to **7** (see above). The yield was 545 mg (81%) of (*S*)-*tert*-butyl 3-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate as a viscous light yellow oil. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 4.25-4.30 (b, 1H, -CH_2C*H*(O)CH_2-), 4.18 (s, 2H, -OC*H*$_2$C≡), 3.35-3.46 (m, 4H, -CH_2C*H*$_2$N- and -CHC*H*$_2$N-), 2.51 (s, 1H, -C≡C*H*), 1.93-2.05 (m, 2H, CH_2C*H*$_2$CH), 1.53 (s, 9H, -C(C*H*$_3$)$_3$).

(*S*)-*tert*-butyl 3-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (500 mg, 2.2 mmol) was dissolved in 5 mL dichloromethane, and 2 mL trifluoroacetic acid was added while stirring. The color of the solution immediately turned dark brown. The reaction was left to stir for 17 hours. After that, it was diluted with 20 mL dichloromethane, and extracted with four 10 mL portions of 20 wt. % aqueous NaOH and 20 mL water. The organic fraction was dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 190 mg (70%) of product as brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.25-4.30 (br, 1H, -CH_2C*H*(O)CH_2-), 4.15 (s, 2H, -OC*H*$_2$C≡), 3.05-3.15 (m, 2H, -CHC*H*$_2$N-), 2.85-2.90 (m, 2H, -CH_2C*H*$_2$N-), 2.42 (s, 1H, -C≡C*H*), 1.90-2.00 (m, 2H, -CH_2C*H*$_2$CH-).

Sodium prop-2-yne-1-sulfonate (12). An 80 wt% solution of propargyl bromide in toluene 13.6 mL (126 mmol) was added to 28.8 g (252 mmol) of potassium thioacetate in 450 mL of acetonitrile. The mixture was stirred for 2 days, at which point it was diluted with 100 mL of water and extracted three times with 200 mL of diethyl ether. The organic extracts were combined and dried over magnesium sulfate to give crude S-prop-2-ynyl ethanethioate. The intermediate has been purified by short-path distillation. Acetic acid (200 mL) was added to S-prop-2-ynyl ethanethioate and the reaction mixture was heated to 60°C while hydrogen peroxide (64 mL of a 30 wt. % aqueous solution) was added dropwise. After 3h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude material was dissolved in water and neutralized with 10% NaOH. Concentration under vacuum gave 9.8 g of a white powder which contained the product as an approximately 65 wt% mixture with sodium acetate (analysis of mixture by ^{1}H NMR, ~53% overall yield). ^{1}H NMR, ~53% overall yield). ^{1}H NMR (D_2O, 400 MHz): δ 3.78 (s, 2H, -SC*H*$_2$C≡), 2.65 (s, 1H, -C≡C*H*).

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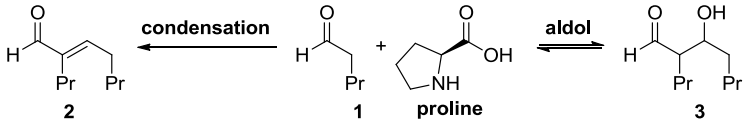
Chapter 5
Control of Aldol Reaction Pathways of Enolizable Aldehydes in an Aqueous Environment with Proline and a Hyperbranched Polymer

Abstract

A fundamental chemoselectivity challenge that remains intrinsically unsolved in aldol-type reactions is the suppression of self-aldol reactions with enolizable aldehydes in reactions such as cross-aldol processes. Contrasting with the usual practice of using large excesses of one component to compete with the undesired self aldehyde condensation reactions, we have developed catalyst system consisting of a hyperbranched polyethyleneimine derivative and proline that can eliminate the self-aldol reactions by suppressing an irreversible aldol condensation pathway. Control experiments and mechanistic studies suggest the aqueous environment containing the polymer and proline provides an optimal condition for the aldol reaction to proceed selectively in water. The catalytic conditions provided by the polymer are difficult to duplicate with typical small molecule analogs. This polymer catalyst system or its modified version have potential applications in developing new or more efficient synthesis, as demonstrated in a dynamic catalytic process for the preparation of α,β-unsaturated ketones using cross ketone/aldehyde reactions without the need for excess substrates.

1. Introduction

A central challenge of organic chemistry resides in the control of reaction pathways to avoid undesired reactions and develop new or more efficient syntheses. Nature uses precise control to amplify kinetically or thermodynamically unfavorable transformations with the assistance of enzymes, catalytic biopolymers that fold into sophisticated tertiary structure in water.[1] A number of important advances have been made in approximating enzymes with synthetic materials. These include for example Miller's synthetic peptide catalysts,[2] Breslow's polymer/pyridoxamine enzyme mimics,[3] Reymond's peptide dendrimer catalysts,[4] Moore's catalytic phenylene ethynylene foldamer,[5] the metal complex self-assemblies of Bergman and Raymond,[6] and the unimolecular free energy pump reactor of Fréchet and Hawker.[7] However, it is still extremely difficult to mimic the complex and precise functional make-up of an enzyme. In this study we attempted to replicate an enzyme's ability to control competing reaction pathways by using synthetic polymers that promote reactions in aqueous environment. We anticipated that this environment effect might be used to direct the reaction pathways in a way not readily achievable with small molecule catalysts alone.



Scheme 1. Proline can catalyze the "self" reaction of an enolizable aldehyde to form either the condensation product (irreversibly) or the aldol product (reversibly).

A class of reactions that attracted our attention are aldehyde transformations, such as cross ketone/aldehyde aldol condensations. These reactions are of fundamental importance in organic chemistry and have broad application from the manufacture of basic chemicals to the preparation of fine pharmaceuticals.[8] Indeed, aldehydes are the most common substrates in the recent explosive development of enamine[9], iminium[10] and SOMO[11] catalysis. However, since enolizable aldehydes are often very reactive as both nucleophiles and electrophiles, controlling the competing pathways to avoid self-aldol reactions is an intrinsically unsolved chemoselectivity challenge. Usually, a large excess of one reagent is used to ensure high yielding reactions. For example, cross ketone/aldehyde reactions are typically carried out using the ketone substrates as solvent in the presence of either inorganic bases such as NaOH or amines such as proline as the catalyst.[12] Here we report aqueous conditions that eliminate the self-aldol reactions by suppressing an irreversible aldol pathway, thereby allowing for the amplification of otherwise unfavorable reactions without the need for excess reactants.

2. Results and Discussion

2.1 Small molecule model reactions. Our investigation began with a careful re-examination of the widely studied proline-catalyzed aldol reaction[9,13] with enolizable aldehydes as the substrates. A typical model reaction of butanal (**1**) shows two major competing pathways at room temperature (rt) (Scheme 1). One is the irreversible condensation of α,β-unsaturated aldehyde **2**, presumably through a Mannich-type pathway involving an iminium intermediate formed between aldehyde **1** and proline; the other is the reversible formation of β-hydroxy-aldehyde **3** via an enamine intermediate. These results were consistent with observations and postulations in

the literature.[9, 13] Our aim was to eliminate the irreversible pathway leading to the formation of **2**. Thus the reversible formation of **3** can be turned into dynamic catalysis in developing new or more efficient syntheses. We speculated that the undesired pathway might be disrupted by controlling the charged iminium species involved in the Mannich-type reaction leading to **2**. Initial studies indicated that the use of typical small molecule amine catalysts (e.g., proline, pyrrolidine), changes in solvent polarity, or the use of water[14] as solvent or co-solvent failed to suppress the formation of **2**. Here we are interested in the development of soluble synthetic polymers to address this chemoselectivity problem.

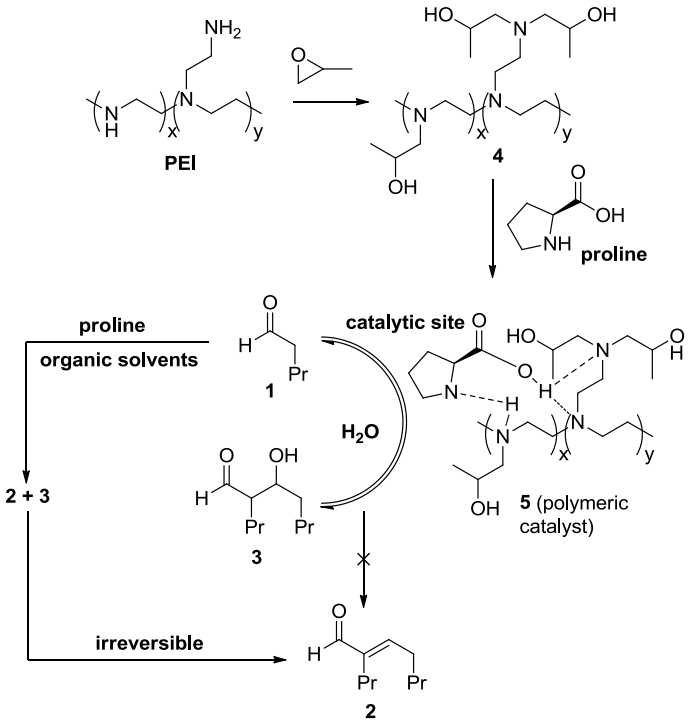


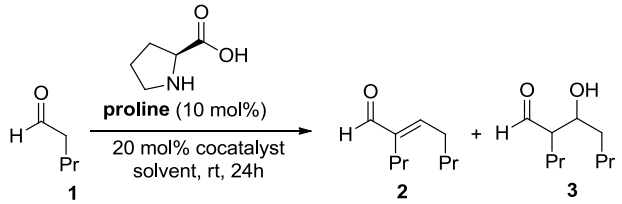
Figure 1. The hyperbranched polymer catalyst gives unique selectivity for the reversible aldol pathway in an aqueous environment. Unlike when organic solvents or typical small molecule catalysts are used, no condensation product is formed.

Results, including pH values of some of the catalyst solutions and the reaction mixture, for the reaction of pentanal at 24 and 48 hours are summarized in Table 1. Similar results were observed when other enolizable aldehydes were used as the substrates. The reversibility of the aldol reaction shown in Scheme 1 and Figure 1 was verified by using the isolated aldol products (**2**, **3**) as substrates under the same catalytic conditions.

2.2 Polymer catalyst synthesis. We chose a commercial hyperbranched polyethyleneimine (PEI) to create a unique aqueous environment. In contrast to the use of PEI and related amine polymers and dendrimers[15] as catalyst supports[16] (e.g., for metal nanoparticles), we aimed to use this type of water-soluble highly branched polymer to facilitate catalytic reactions in an aqueous environment.[3, 17] Pristine commercial PEI contains primary and secondary amine groups, and is thus not suitable for our purpose because these amino groups catalyze the aldol reaction without any control over the competing pathways shown in Scheme 1. However, simple chemical modification of PEI readily affords polymers of tunable structures and properties; for example,

reaction of PEI with propylene oxide gave a water-soluble polymer (a possible structure is illustrated by **4**) that met our requirements (Figure 1). Instead of introducing catalytically active sites via covalent linkages, we took advantage of the tertiary amino groups in **4** as non-covalent handles to attract proline catalysts via electrostatic interactions,[18] affording the desired polymer catalyst (**5**). Proline and **4** were used in 1:2 molar ratio (based on amino groups) to prepare **5**. Increasing the amount of polymer **4** leads to faster aldol reaction. The catalyst loading refers to proline, unless otherwise indicated.

Table 1. Self-aldol reaction of enolizable aldehyde.



					24 hours		48 hours	
entry[a]	cocatalyst	solvent	pH[b]	pH[c]	conversion (%)[d]	Selectivity (**3**:**2**)	Conversion (%)[d]	Selectivity (**3**:**2**)
1	-	DMF			82	1.4	88	0.6
2	-	H_2O			< 1	-	<1	--
3	4	H_2O	9.2	7.7	56	63	70	22
4	4	DMF			86	0.6	91	0.3
5	TEA	H_2O	11.1	10.5	80	1.0	85	0.4
7	MDEA[e]	H_2O	10.1	9.7	82	5.3	82	2.4
8	MDEA + SDS[f]	H_2O			77	3.3	80	1.6
9	$N(EtOH)_3$	H_2O	9.5	8.9	86	15	81	4.9
10	TEA[g]	H_2O	10.2	9.8	90	0.1	--	--
11	TEA + HOAc[h]	H_2O	9.7	8.7	82	8.5	--	--
12	TEA + HOAc[h]	H_2O	9.5	6.3	2	--		
13	TEA + HOAc[h]	H_2O	9.3	6.1	2	--		
14	TEA	DMF			97	0.05	99	0.017
15	MDEA	DMF			95	0.06	97	0.024
16	$N(EtOH)_3$	DMF			94	0.10	97	0.035

[a]See text for experimental details. [b]pH values of the catalyst solution in water, as measured by a pH meter. [c]pH values after the addition of aldehyde substrate. [d]Measured by ^{1}H NMR (**2** + **3**) of the crude reaction mixture; diastereoselectivity of aldol product **3** is around 1.2:1, enantioselectivity was not determined. [e]N-methyldiethanolamine. [f]sodium dodecyl sulfate (a surfactant; 10 mg; above critical micelle concentration) was added. [g]The pH of the catalyst solution was titrated to 10.2 by the addition of 2,2,2-trifluoroethanol (the catalyst solution contains 1.0 mmol proline, 2.0 mol TEA, 5.0 mL water, and 2.5 mL trifluoroethanol). [h]The pH of catalyst solution was titrated to the values shown in the table by the addition of HOAc (0.14-0.17 equivalent relative to the aldehyde substrate).

2.3 Polymer-catalyzed self-aldol reaction. Unique control over the aldehye reaction was observed when the reaction was performed using the aqueous polymer solution as a catalytic environment (Figure 1). The formation of β-hydroxy aldehyde **3** is facile and reversible. Very little (typically less than 1%) unsaturated aldehyde **2** was detected even at long reaction times (two days or longer). Significantly, **5** did not provide any control over the two competing pathways when the reaction is carried out in organic solvents such as DMF, dimethyl sulfoxide, or CH_2Cl_2. For example, a typical self-aldol reaction of **1** with 10 mol% catalyst **5** in water reached equilibrium with reversible formation of 50-70% β-hydroxy aldehyde **3**. The remainder was starting aldehyde **1** while essentially no unsaturated aldehyde **2** was observed after 24 hours (chemoselectivity, the ratio between **3** and **2**, is greater than 60; Table 1, entry 3). The same reaction (with **5** as the catalyst) carried out in organic solvents such as DMF under otherwise identical conditions led to poor chemoselectivity with the irreversible formation of **2** as the major product (Table 1, entry 4).. In initial studies, triethylamine (TEA) tested as the small molecule analog of polymer **4** under otherwise identical conditions showed poor reaction control (Table 1, entry 5). Further experiments using tertiary amines containing alcohol groups (N-methyldiethanolamine, triethanolamine) in aqueous medium gave results better than that with TEA (Table 1, entries 6-9). The pH values of the reaction medium were measured. It appears that pH has an effect on the reaction selectivity, and reactions in aqueous media with pH around 9.0 gave optimal results. A conclusive relation between pH and reaction selectivity cannot be drawn at this moment and other parameters such as solvent properties can have profound effects on the reaction outcome too.[19] Overall, the conditions provided by the polymer can be approximated, but are difficult to duplicate, therefore significant formation of the undesired self aldol product **2** was still observed with the small molecule tertiary amines tested under various conditions, including different pHs. The use of alcohols, such as methanol, 2-propanol and 2,2,2-trifluoroethanol as additives or co-solvents, has no desired effect on reaction selectivity. In all cases, polymer catalyst **5** performs best in controlling the aldol reaction pathways (Figure 1).

2.4 Polymer-catalyzed cross-aldol reaction of aldehydes with acetone. In view of the numerous chemical transformations involving enolizable aldehydes as substrates, the catalyst system with polymer complexes such as **5** might prove useful in the development of more efficient syntheses. In particular, a dynamic catalytic process might be developed for the amplification of desired products by reactions involving either the aldehyde substrate or the reversibly formed β-hydroxy aldehyde adduct. The aldol product **3** may undergo further aldol reactions, especially at elongated reaction time,[20] suggesting that useful reaction may be developed by reacting with this aldol product. Initially, we chose to study the cross-aldol condensation between butanal and acetone to demonstrate this concept and highlight the potential of this catalytic system. The product of this condensation, an α,β-unsaturated ketone, is a key intermediate in the commercial production of methyl amyl ketone, a FDA listed food additive.[21] In general, α,β-unsaturated ketones are both important commercial chemicals and common functional groups found in complex molecules such as natural products. Previous methods used to prepare these compounds typically require the use of a large excess of ketone to compete with the generally more rapid aldehyde self-condensation.

In a model cross aldol reaction between acetone and butanal using catalytic complex **5** in water (Figure 2), the self-aldol reaction of **6** to form β-hydroxy aldehyde **7** proceeded much faster than the cross-aldol reaction, reaching maximum conversion in about 30 minutes. However, the facile reversibility of the self-aldol reaction in our catalytic system led to the eventual formation of the kinetically disfavored cross-aldol product **8** in more than 90% yield in 22 hours. In this instance,

a slight excess of ketone was used to facilitate monitoring of reaction progress but it is not necessary in preparative scale syntheses. Surprisingly, little β-hydroxy ketone **9** was detected in the reaction. A sample of **9** prepared using a literature procedure did not yield any dehydration product (the unsaturated ketone) when subjected to the same catalytic condition,[12b] suggesting that the condensation proceeds exclusively via a Mannich-type mechanism. The Mannich-type pathway is proposed to involve the reaction of an enamine intermediate formed between acetone and proline, and an iminium ion derived from aldehyde and a second molecule of proline. It remains unclear exactly why the same iminium intermediate does not react with the enamine derived from aldehyde and proline to yield the aldehyde self-condensation product under the aqueous catalytic conditions with polymer complex **5**.

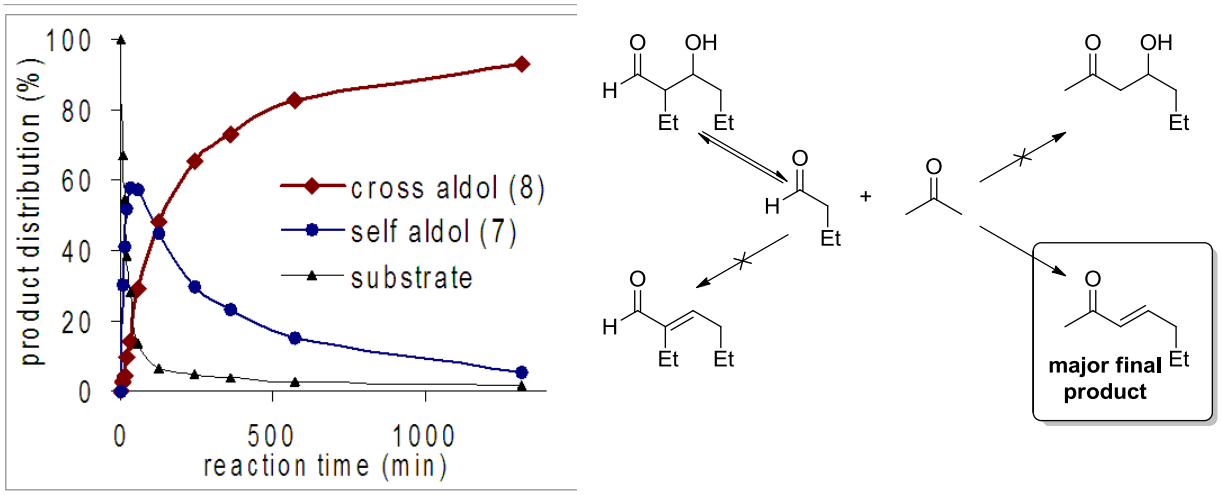
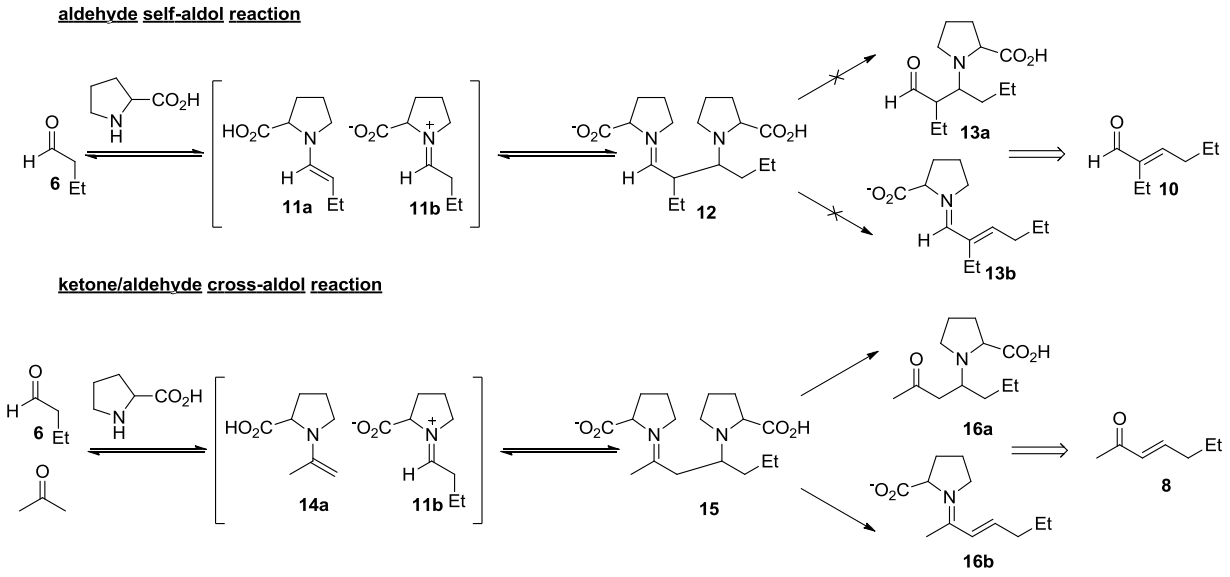


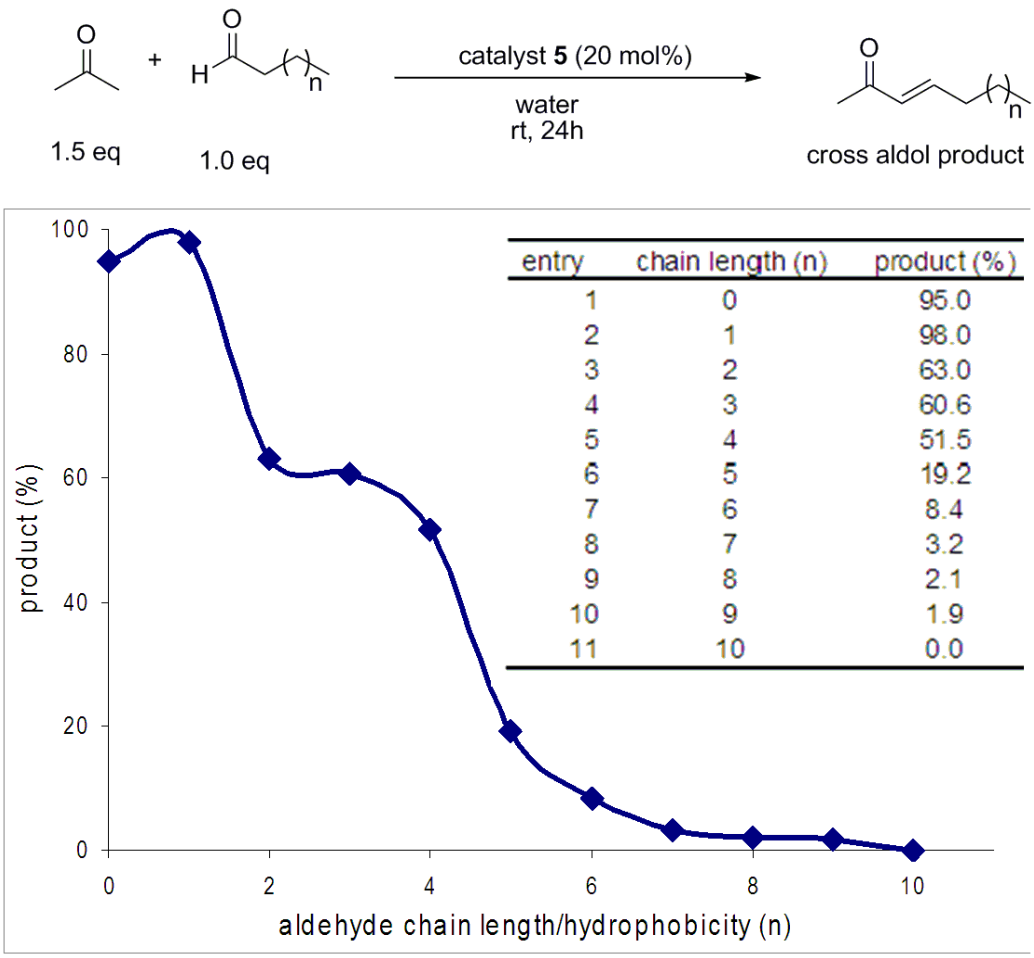
Figure 2. The dynamic catalytic cross ketone/aldehyde reaction only irreversibly produces the cross aldol condensation product. The self-aldol product is formed, but reversibly, while the other potential aldol products are not formed at all.

The observed selectivity suggests the possible mechanism shown in Scheme 2. The experimental observations suggest that the unique aqueous environment alters the energetic requirements of key reaction steps. In the ketone/aldehyde cross condensation, the pathways leading to cross-condensation proceed effectively. In the aldehyde self-aldol reaction under catalytic conditions with polymer complex **5**, the initial Mannich-type addition adduct (**12**) formed from enamine **11a** and iminium **11b** is prevented from undergoing further reaction to give **13a** or **13b**, two possible intermediates responsible for the formation of self-condensation product **10**. Instead, adduct **12** reverts to **11a** and **11b**. Both **11a** and **11b** are then effectively hydrolyzed to the aldehyde substrate **6**. In contrast, under conditions with conventional organocatalysts, the pathways for the conversion of **12** to **13a** or **13b** cannot be avoided. The special catalytic environment induced by polymer complex **5** alters the reaction kinetics and favors the decomposition of **12** back to the starting materials and disfavors pathways leading to self-condensation product **10.** In the ketone/aldehyde cross aldol reaction, all pathways required for the facile formation of cross condensation product **8** proceed effectively.



Scheme 2. Possible aldol reaction pathways under aqueous catalytic conditions with polymer complex **5**.

To gain further mechanistic insight and probe the substrate scope of these catalytic reactions, we first examined cross acetone/aldehyde condensations with unhindered straight-chain aliphatic aldehydes of different size and hydrophobicity. As shown in Figure 3, increasing aldehyde hydrophobicity leads to a large decrease in reaction efficiency. After 24 hours at room temperature, the cross-aldol reaction gave excellent yield with propanal and butanal, moderate yield with pentanal, hexanal, and heptanal, and less than 20 % yield with octanal or its longer linear aldehyde analogs. This specificity determined by substrate hydrophobicity – a characteristic often seen in enzymatic catalysis – is not observed in typical small molecule catalysis in organic solvents. This selectivity determined by substrate hydrophobicity may be used to design polymer-assisted polarity gradient-directed chemo-selective reactions, such as aldehyde/aldehyde cross-aldol reactions.[22]



entry	chain length (n)	product (%)
1	0	95.0
2	1	98.0
3	2	63.0
4	3	60.6
5	4	51.5
6	5	19.2
7	6	8.4
8	7	3.2
9	8	2.1
10	9	1.9
11	10	0.0

Figure 3. Yield of cross-aldol reaction using aldehydes of different size and hydrophobicity

The mild catalytic conditions that prevail with **5** should enable the use of this catalyst with substrates containing functional groups such as esters, which are not compatible with the use of strong bases (e.g., NaOH) as catalysts. A small set of cross-aldol condensation products, including variations in ketone substrates, is illustrated in Scheme 4. Reaction conditions were not optimized, and conversion was determined by NMR analysis of the crude reaction mixture. Isolated yields after column chromatography are in the range of 50-80% for **17c** and **17h**. Our method provides access to α,β-unsaturated ketones in a efficient manner without the need for excess reagents. While our polymer catalyst was solely designed to control reaction pathways, a side benefit of such polymer catalyst systems is the relative ease of catalyst recycling. For example, in a scalable preparation of **17c** and **17h** (Figure 4), distillation yielded a mixture with two separate layers: an organic layer containing the desired product in high purity and a water layer. The white solid residue remaining after distillation contains the catalyst, which was directly reused without purification, showing only a slight loss in catalytic activity.

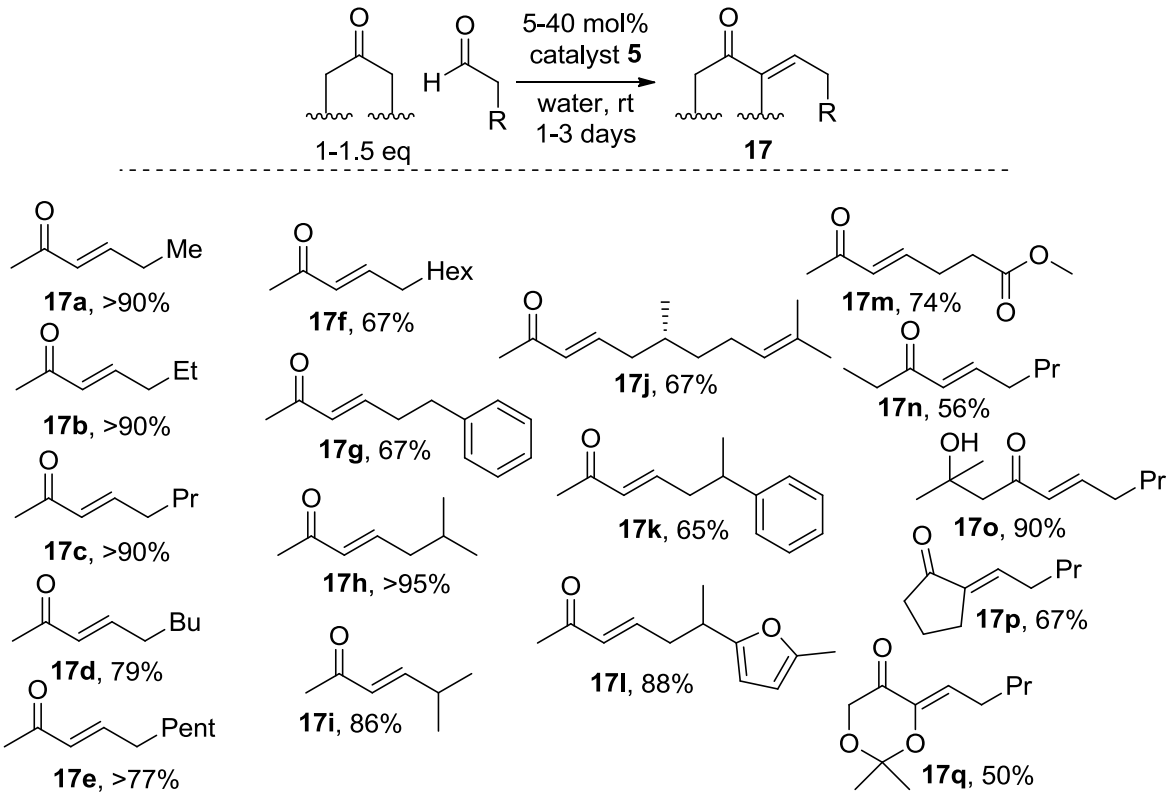


Figure 4. Catalytic cross ketone/aldehyde condensation

3. Conclusions

In summary, we have developed an aqueous polymer catalyst system that controls the challenging aldol reaction pathways of enolizable aldehydes, a problem that had remained intrinsically unsolved previously. Such control of reaction pathways allows dynamic catalytic processes for the amplification of otherwise unfavorable reactions. Although we have primarily focused on addressing the chemoselectivity problems at this point, studies in progress indicate that stereoselective reactions are achievable using this catalyst system. Given the large number of transformations that involve enolizable aldehydes as substrates, this catalyst and its polymer or small molecule analogues may be useful in a broad range of new or more efficient syntheses.

4. Methods

4.1 Catalytic self-aldol reaction of enolizable aldehydes. Catalyst **5** containing PEI derivative **4** and L-proline in 2:1 molar ratio (based on amino groups) was prepared as a gel or stock solution of the desired concentration by mixing the proper amounts of the two components. For example, a 1 M catalyst stock solution was prepared by dissolving 2.30 g (20 mmol) L-proline and 4.05 g of **4** (40 mmol amino groups) in water and adjusting the total solution volume to 20 mL. The following discussion concerning loading or concentration of catalyst **5** refers to the amount of proline, unless otherwise specified.

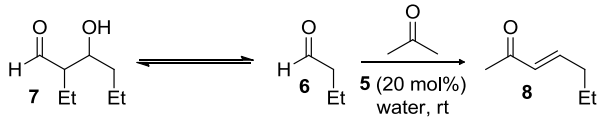
To a small vial equipped with a magnetic stir bar, was added 500 μL catalyst solution containing 0.1 mmol catalyst and the appropriate proper amount of additives (Table 2), followed

by the addition of pentanal (106 μL, 1.0 mmol) or butanal (90 μL, 1.0 mmol). The mixture quickly turned milky upon stirring when polymer catalyst **5** was used, or stayed as a heterogeneous mixture under other conditions with small molecule catalysts. The reaction mixture was stirred at rt, and progress of the reaction was monitored by ^{1}H NMR analysis.

For the catalytic aldol reaction in water, 100 μL of the aqueous reaction mixture was mixed with 1 mL benzene-d_6 in a vial. The vial was vigorously shaken for a few seconds, and anhydrous Na_2SO_4 was added to absorb the water. The dried benzene-d_6 solution containing both reactants and products of the catalytic reaction was filtered into an NMR tube and used for ^{1}H NMR analysis. For the catalytic reaction in organic solvents (e.g., DMF), 100 μL of the reaction mixture was mixed with 600 μL benzene-d_6 or $CDCl_3$ for ^{1}H NMR analysis. The calculations were based on ^{1}H NMR integration of the relatively clean spectrum region (8-11 ppm for self aldol reaction; 6-11 ppm for cross-aldol reaction).

4.2 Dynamic catalytic cross ketone/aldehyde reaction. To a small vial equipped with a magnetic stir bar was added 2 mL aqueous solution containing 0.8 mmol catalyst **5** (from a stock solution), followed by a pre-mixed solution of acetone (440 μL, 6.0 mmol) and butanal (360 μL, 4.0 mmol). The reaction mixture turned milky quickly upon stirring. The reaction mixture was then stirred at rt, and progress of the reaction was monitored by ^{1}H NMR analysis at different reaction times. Table 2 contains the data showing the reaction progress in Figure 2.

Table 2. Product distribution of the dynamic catalytic acetone/butanal reaction *vs.* reaction time



entry	time (min)	cross aldol **8** (%)	self-aldol **7** (%)	remained substrate **6** (%)
1	0	0	0	100
2	5	3	30	67
3	10	4	41	55
4	20	10	52	38
5	30	14	58	28
6	55	29	57	14
7	123	48	45	7
8	243	66	30	5
9	362	73	23	4
10	572	82	15	3
11	1320	93	6	1

Other cross-aldol reactions were performed in a similar manner: acetone (110 μL, 1.5 mmol) and aldehyde (1.0 mmol) were added to 0.5 mL aqueous solution containing 0.2 mmol catalyst **5** (from a stock solution) in a small vial equipped with a magnetic stir bar. The reaction mixture was stirred at rt for 24 hours, and yield of the cross-aldol product was determined via ^{1}H NMR analysis. The reaction with propanal as a substrate used 5 mol% L-proline and 40 mol% **4** as the catalyst. For **17a**, 5 mol% proline and 40 mol% **4** (relative to aldehyde) were used as the catalyst and a good yield was obtained after two days. For **17b**, **17c**, **17d**, **17e**, **17g**, **17h**, **17k**, **17l**, and **17m**, 0.2 mmol catalyst **5** was used and the reaction took one to two days. For **17f**, **17i**, **17j**, **17n**, **17o**, **17p**, and **17q**, 0.4 mmol catalyst **5** was used and the reaction took about three days.

Preparative scale syntheses and catalyst recycling were conducted using **17c** and **17h** as examples on a 20 mmol scale (aldehyde substrate), and it is reasonable to anticipate that these reactions can be easily scaled up due to the very mild reaction conditions. Product isolation was achieved with either distillation or extractive work-up (with diethyl ether) followed by silica gel column chromatography, giving non-optimized yield in the 50-80% range. Catalyst **5** could be recycled either by using the aqueous layer from the extractive work-up or by addition of water to the white residue remaining after distillation.

4.3 Synthetic details.

Modified poly(ethylene imine) polymer catalyst (5). Commercially available hyperbranched PEI (BASF, Mw = 25 KD, Mn = 10 KD) contains 39 mol% primary amine, 32 mol% secondary amine and 29 mol% tertiary amine with a 69% degree of branching as determined by ^{13}C NMR ($CDCl_3$) analysis.[23] In a general procedure for PEI modification, the commercial PEI (6.6 g, 153 mmol amino groups) was mixed with propylene oxide (30 mL, 428 mmol) in a pressure tube. A small amount of methanol (MeOH, up to 5 mL) was added to assist in dissolving the unmodified PEI in propylene oxide to give a clear solution. The solution was heated to 80 ºC for three days. Excess propylene oxide and MeOH solvent were removed under high vacuum at about 50 ºC to yield a pale brown viscous gel as the desired PEI derivative **4** in quantitative yield.

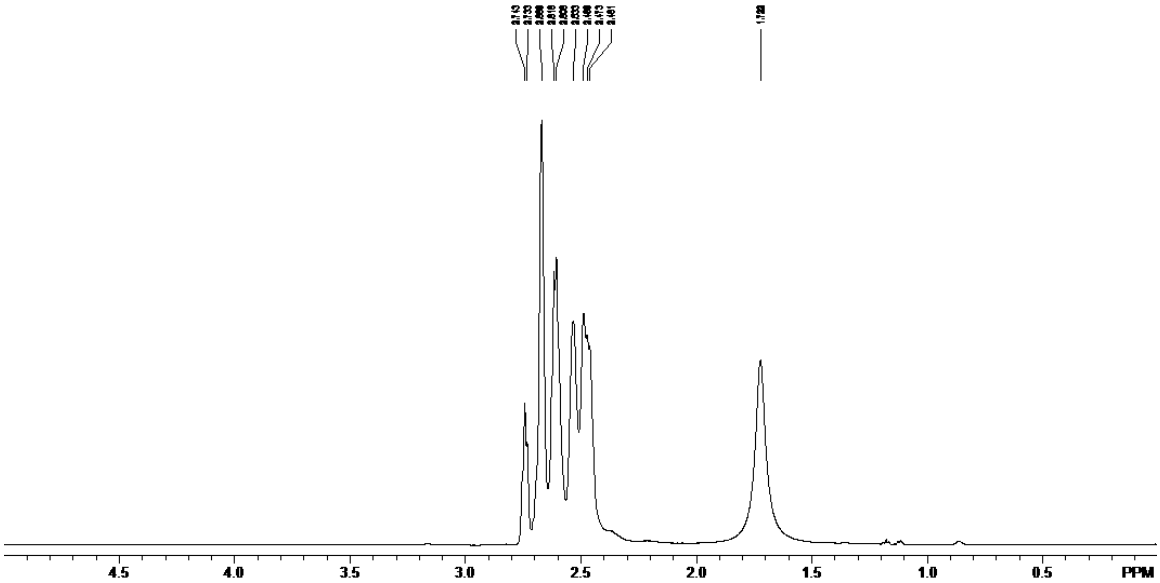


Figure 5. ^{1}H NMR spectrum of unmodified PEI in $CDCl_3$ obtained on a Bruker DRX 500 NMR.

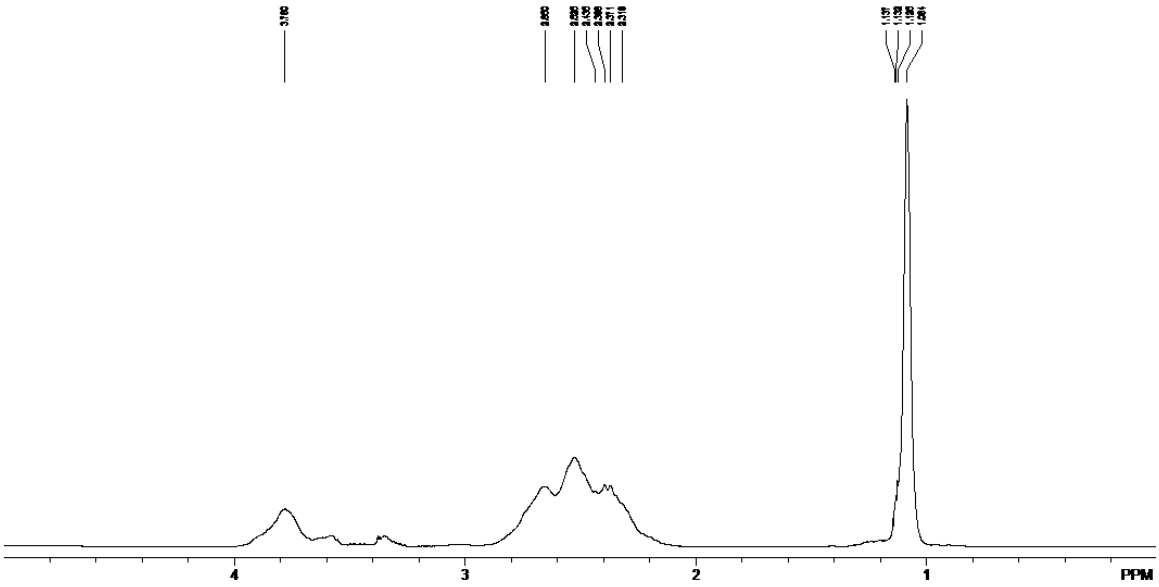


Figure 6. ^{1}H NMR spectrum of modified PEI (**4**) in $CDCl_3$ obtained on a Bruker DRX 500 NMR.

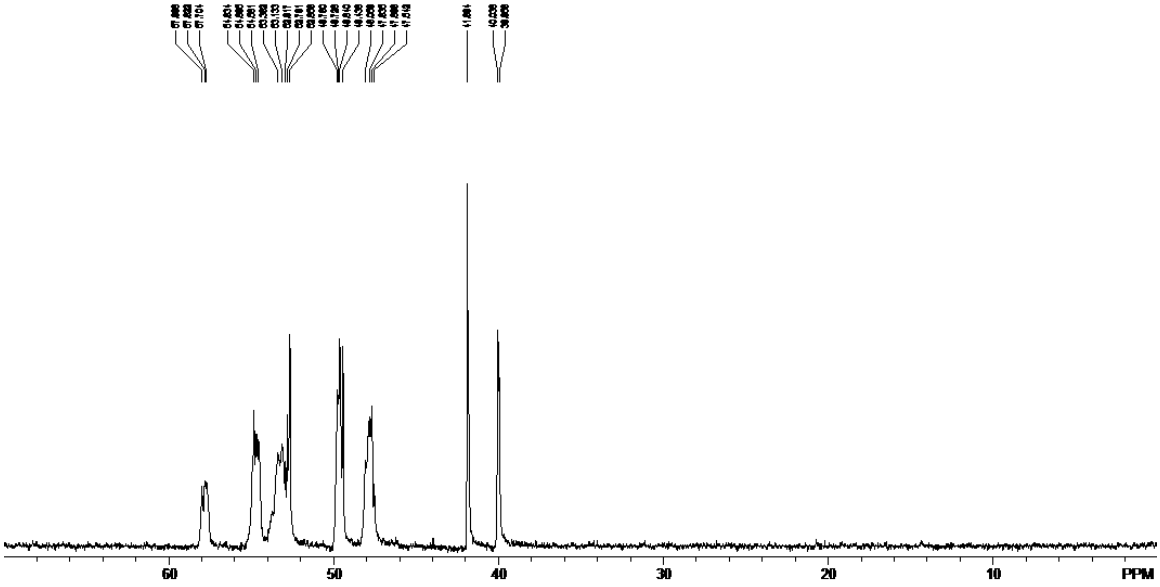


Figure 7. ^{13}C NMR spectrum of PEI in $CDCl_3$ obtained on a Bruker DRX 500 NMR.

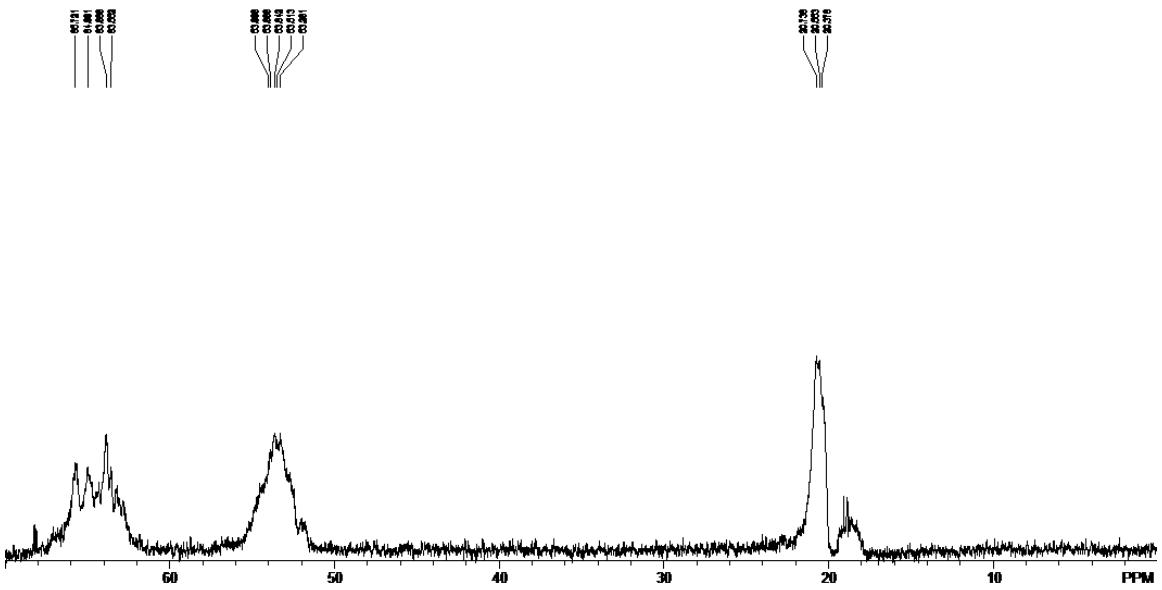


Figure 8. ^{13}C NMR spectrum of modified PEI in $CDCl_3$ obtained on a Bruker DRX 500 NMR.

Spectroscopic analysis (^1H NMR, ^{13}C NMR, FT-IR; Figures 5-9) indicated complete conversion of all primary and secondary amines to tertiary amino groups. Figure 9 shows the comparison of IR spectra for PEI and modified PEI (**4**). In the top spectrum (PEI), several characteristic IR peaks are observed. The strong broad peak at 3600-3000 cm^{-1} corresponds to the N-H stretching vibrations of amines; the sharp peak at 1570 cm^{-1} corresponds to the N-H bending vibrations characteristic of primary amines. Peaks at 2939 and 2829 cm^{-1} correspond to CH_2 stretching vibrations; the strong, sharp peak at 1473 cm^{-1} corresponds to CH_2 in plane bending vibrations (scissoring). In the bottom spectrum (**4**), several characteristic changes are observed relative to unmodified PEI. The disappearance of the peak at 1570 cm^{-1} corresponds to the removal of primary amines from the modified PEI structure. The appearance of a strong peak at 1064 cm^{-1} corresponds to the C-O stretching vibration of an alcohol resulting from epoxides opening. The appearance of peaks at 2966 cm^{-1} and 1371 cm^{-1} confirm the presence of methyl groups, derived from propylene oxide, as they correspond to the asymmetric stretch and the symmetric bend of a methyl, respectively. The IR peak at 3600-3000 cm^{-1} is still observed, and now corresponds to the O-H stretch of an alcohol.

Additionally, catalytic self-aldol reactions of pentanal in water or DMF were used to confirm that complete conversion is achieved in the PEI modification process. In a typical experiment, a mixture of pentanal (106 μL, 1 mmol), PEI derivative **4** (303 mg, 3 mmol amino group) and 1 mL solvent (water or DMF) were stirred at rt for 24 hours. ^1H NMR analysis (of the crude reaction mixture showed no detectable aldol reaction, confirming complete conversion of primary and secondary amines in PEI to tertiary amino groups. In contrast, unmodified PEI and PEI with partial modification catalyzed the self-aldol reaction in non-selective fashion.

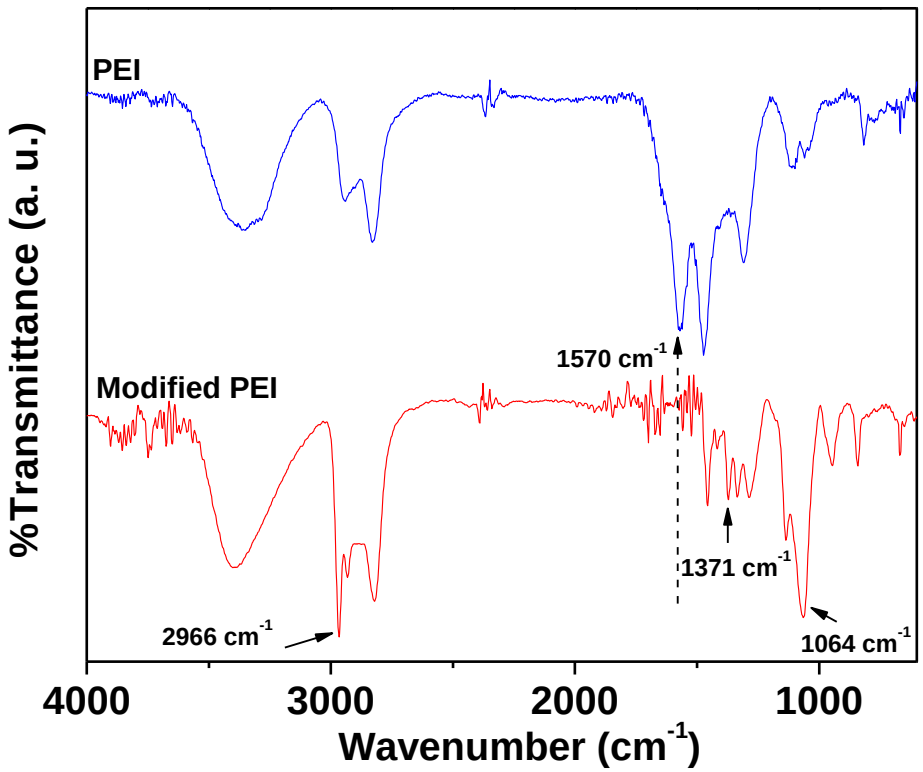


Figure 9. IR spectrum of PEI and modified PEI collected on a Varian 3100 FT-IR spectrometer from a thin film on a KBr disc.

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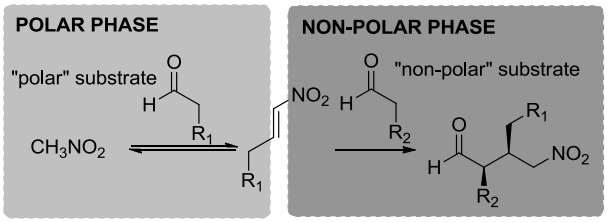
Chapter 6
Polarity-Directed One-Pot Asymmetric Cascade Reactions Mediated by Two Catalysts in an Aqueous Buffer

Abstract

Polarity makes a big difference in distinguishing substrates of otherwise nearly identical chemical reactivities. A one-pot cascade reaction (condensation followed by conjugate addition) involving nitromethane and two aliphatic aldehydes with similar reactivities is developed. The use of a biphasic reaction medium with two different organic catalysts is shown to result in the controlled incorporation of both aldehyde substrates in a major "cross" product rather than a statistical mixture of the four possible cascade products.

1. Introduction

Modern organic synthesis predominately relies on functional group reactivity differences in order to achieve the chemoselective formation of desired products.[1] Here we report a one-pot multi-step asymmetric catalytic reaction in which substrates with similar chemical reactivities are differentiated based on polarity. The one-pot reaction involves two catalysts and three substrates in the presence of water. The reaction mixture consists of two phases: a polar aqueous phase and a hydrophobic organic phase. The biphasic nature of the reaction medium and the polarity properties of the substrates and catalysts enable the selective formation of a major product instead of a statistical mixture of four possible cascade products.



Scheme 1. Polarity-directed chemoselective incorporation of two different aldehydes to form a major cross cascade product in a one-pot reaction involving two aldehydes with similar reactivity but different polarity.

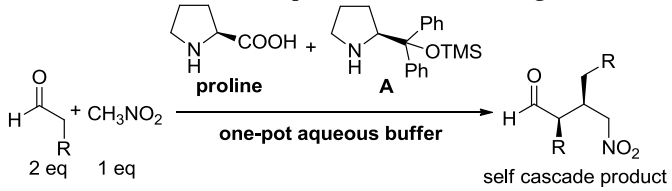
We chose a two-step reaction involving condensation[2,3] followed by conjugate addition as a model to develop a polarity-directed cascade reaction. Both reaction steps can involve linear aliphatic aldehydes as substrates (Scheme 1).[4,5] Our aim was to combine the two reaction steps to develop a one-pot reaction in which two different aldehyde substrates react in a controlled manner to generate the desired *cross* product. We use the term "self" to refer to cascade reactions incorporating the same aldehyde in both steps. The term "cross" refers to reactions incorporating different aldehydes in each step. A typical homogeneous (one-phase) version of such one-pot reactions in organic solvents results in a statistical mixture of all four possible cascade products in an approximately 1:1:1:1 ratio, as confirmed in our preliminary studies. Therefore, we decided to focus on a water/organic biphasic system that might allow for the use of substrate polarity differences to control the reaction pathways (Scheme 1).

2. Results and Discussion

2.1 Two-step, one-pot aldehyde "self" reaction. We first examined the condensation reaction of nitromethane and pentanal mediated by proline in an aqueous buffer (Table 1). The condensation reaction is reversible.[2b, 2d] Subsequently, the α,β-unsaturated nitroalkene formed in this step was consumed in a conjugate addition reaction to generate a self cascade product with 45% yield and little enantioselectivity (Table 1, entry 1). The low yield was due to many side reactions, such as aldol reactions and the addition of nitromethane to the nitroalkene intermediate. The condensation reaction mediated by proline is a facile process, and the conjugate addition catalyzed by proline[6] appeared to be slow under the aqueous conditions.[7] Therefore, we reasoned that the formation of the cascade product could be improved by accelerating the conjugate addition step. This may be achieved through the addition of a second catalyst such as diphenylprolinol TMS ether (**A**),[5a, 8] an efficient and stereoselective catalyst for the conjugate addition of aldehydes to nitroalkenes.[5] As shown in entry 2 of Table 1, when a combination of

proline and **A** (20 mol% each) was used, the reaction yield was significantly improved. The cascade reaction performed in this manner had good enantioselectivity (~93:7). This indicates that the rate of the competitive, non-stereoselective conjugate addition mediated by proline was negligible under these conditions. Previous reports by others[5c, 9] and our own studies have indicated that the conjugate addition reaction mediated by **A** in the presence of water mainly takes place in a concentrated organic phase and not in water. When only **A** was used, there was little formation of either the nitroalkene intermediate or the final cascade product (Table 1, entry 3), which suggested that **A** was not effective in mediating the condensation step. When decanal (more hydrophobic than pentanal) was used as the substrate with proline or a combination of proline and **A** as the catalyst(s), only a small amount of the nitroalkene intermediate and/or the cascade product was observed (Table 1, entries 4 and 5). These results indicate that the condensation reaction requires some miscibility of the aldehyde with the aqueous solution containing proline and nitromethane. The hydrophobic nature of decanal explains its poor reactivity in contrast to the less hydrophobic pentanal.

Table 1. Studies on the reaction of nitromethane with pentanal or decanal to generate a self cascade product. [a]

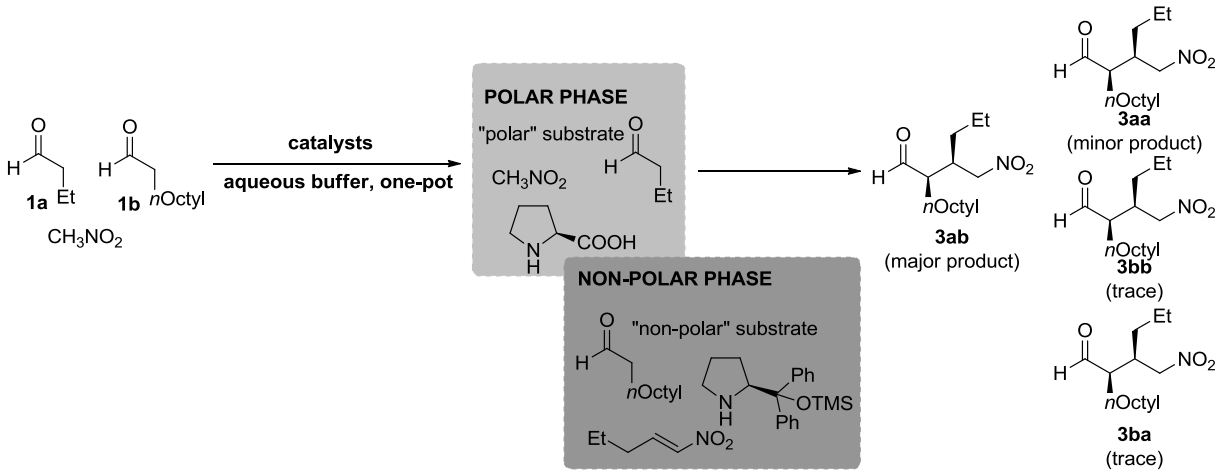


Entry[a]	R	mol% proline	mol% **A**	% yield	e.r.[b]
1	*n*Pr	20	0	45[c]	~50:50
2	*n*Pr	20	20	70[c]	93:7
3[d]	*n*Pr	0	20	trace[e]	-
4[d]	*n*Octyl	20	20	trace[e]	-
5	*n*Octyl	20	0	none[e]	-

[a]Reaction conditions: 2 mmol aldehyde, 1 mmol nitromethane, 1 mL pH 7.5 PBS, rt, 16h. [b]Determined by ^{1}H NMR assay.[10] Absolute and relative stereochemistry established by analogy to literature precedent.[5] [c]Isolated yield after column chromatography. [d]Attempted with and without added lauric acid, a co-catalyst used to promote the reactions mediated by amine **A**. [e]Estimated from ^{1}H NMR of crude reaction mixture.

2.2 Two-step, one-pot aldehyde "cross" reaction. The solubility properties of the reacting components and the results summarized in Table 1 suggest that the condensation reaction mainly occurs in the aqueous phase of the one-pot system. The conjugate addition catalyzed by **A** predominately takes place in the organic phase constituted by the aldehyde substrate and the nitroalkene intermediate. We next sought to perform a controlled one-pot reaction involving two different aldehydes to produce a single "cross" product. We anticipated that aldehydes with different polarities, such as butanal **1a** and decanal **1b**, could be distinguished and react in a programmed manner. While both butanal and decanal are hydrophobic molecules, butanal should have a significantly greater miscibility with the aqueous phase than decanal. For example, in water/octanol systems butanal partitions into the aqueous phase approximately 1000 times more favorably than decanal.[11] The condensation reaction step occurring in water mainly involves butanal and nitromethane as the substrates to produce nitroalkene **2a** as the intermediate. This hydrophobic intermediate diffuses into the organic phase consisting of catalyst **A** and the other organic components of the reaction. Under these heterogeneous conditions with 20 mol% proline and 20 mol% **A**, the desired cross product **3ab** was formed as the major product (Scheme 2)

when the aldehydes were used in equimolar amounts and added to the reaction mixture simultaneously. The main side product was **3aa** (the ratio **3ab**:**3aa** being approximately 4:1), formed between aldehyde **1a** and nitroalkene **2a**. Products **3bb** and **3ba**, which would require a nitroalkene intermediate (not shown in Scheme 2) generated from decanal, were observed in only trace amounts. This is because decanal is too hydrophobic to participate in the aqueous phase condensation reaction to form the corresponding nitroalkene intermediate.



Scheme 2. A polarity-directed one-pot reaction for the selective formation of a major cascade product. The reaction mixture consists of oily droplets (organic phase) in an aqueous medium. The relatively polar butanal is converted to nitroalkene intermediate **2a** by a reaction in the aqueous phase. This intermediate is converted to the final product by reaction with decanal in the organic substrate phase.

2.3 Reaction optimization. Having demonstrated the possibility of selectively forming the "cross" product **3ab**, we then adjusted several parameters to further improve the reaction selectivity. The "cross" cascade reactions were optimized extensively with respect to temperature, order of reagent addition, reagent and catalyst concentrations/loadings, and buffer pH. Reactions were monitored for selectivity by ^{1}H NMR and yields estimated by comparison of the NMR integration of the product and starting material relative to that of nitromethane. We first attempted to achieve an aldehyde concentration bias by the slow addition of one aldehyde component.[1a] However, undesired side reactions consumed whichever aldehyde was in excess, indicating that the simultaneous addition of the aldehydes may be the best method. The consumption of intermediate **2a** in the absence of aldehyde **1b** indicates that stepwise reactions under these conditions are not suitable for the synthesis of **3ab**, which further demonstrates the advantages of our one-pot reaction approach.[3]

We found that the most productive optimization approach was to accelerate the formation of nitroalkene intermediate **2a**. Our methods for selectively accelerating the formation of **2a** included raising the pH of the aqueous layer,[12] increasing the concentration of nitromethane used, and lowering the ratio of catalyst **A** to proline. Accelerating **2a** formation increases nitroalkene concentration and decreases the presence of butanal in the organic phase. This minimizes the conjugate addition reaction leading to **3aa** and avoids other significant side reactions in the organic phase. Therefore, accelerating the condensation reaction between nitromethane and butanal favors the ultimate formation of desired product **3ab**.

Increasing the amount of nitromethane resulted in greater selectivity for the formation of the desired "cross" cascade product, but other side reactions, such as conjugate addition of the

nitromethane to the nitroalkene intermediate, also increased. The use of 3 eq of nitromethane was found to be optimal for reaction yield. A similar pattern was observed when increasing the amount of proline, and/or decreasing the amount of catalyst **A** or lauric acid. A very small amount of catalyst **A** (e.g., 1 mol%) in combination with an acid co-catalyst[4c, d, 13] was optimal to perform the conjugate addition in the organic phase. Lauric (dodecanoic) acid is sufficiently hydrophobic to remain exclusively in the organic layer and was chosen as the acid co-catalyst.

Decreasing the pH of the buffer from 8.0 to 7.0 resulted in greater selectivity for the desired "cross" cascade product over the undesired "self" products, but other side reactions increased. Some examples of these side reactions are aldol-type reactions of the aldehydes and the conjugate addition of nitromethane to the nitroalkene intermediate. A pH of 7.5 was found to be optimal for reaction yield. As the buffer pH dropped below 7.0, the rate, selectivity and yield of the reaction decreased along with pH. Below a pH of approximately 6.5 (near the isoelectric point of proline), the first step of the reaction was strongly inhibited, most likely because the free amine site on proline is essential to its catalytic activity. For this reason, the reaction conditions were carefully controlled to exclude water-miscible organic acids derived from the aldehyde substrates, which lead to undesirable lowering of the pH of the aqueous phase.

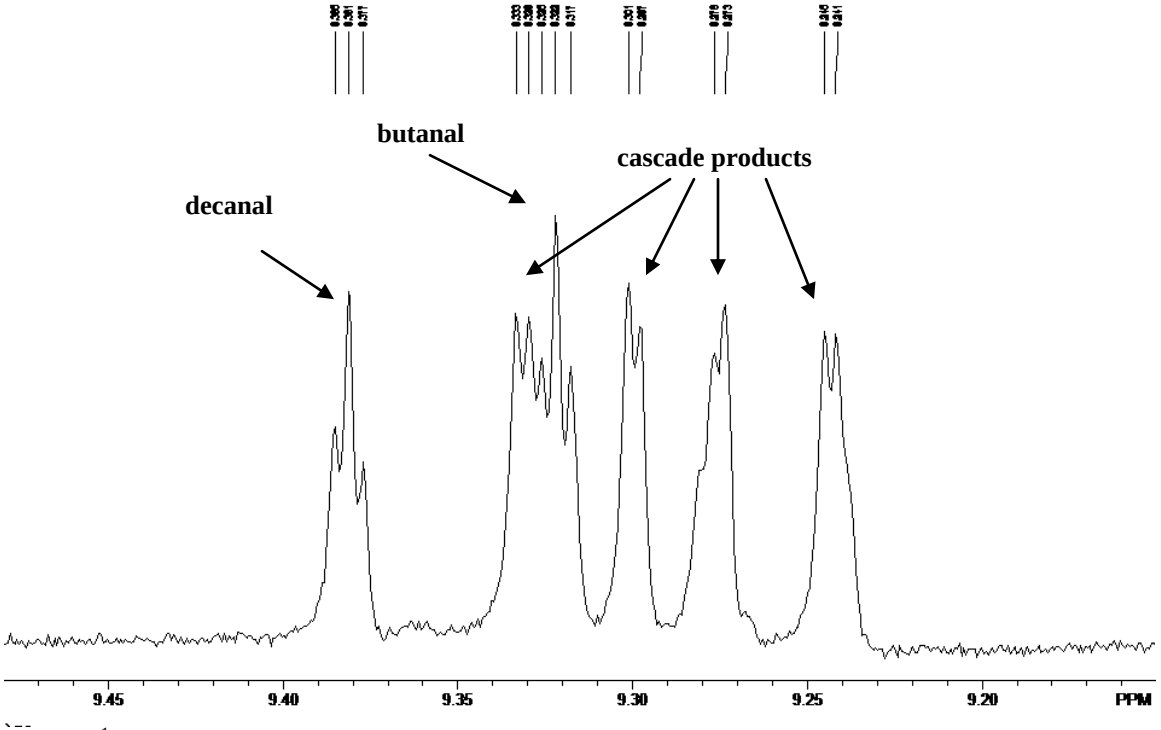


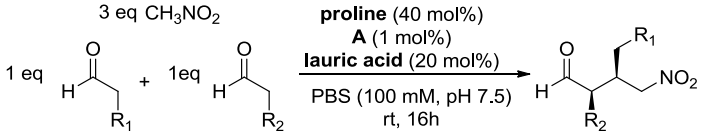
Figure 1. A ^{1}H NMR spectrum of the crude reaction mixture from the cascade reaction using DMF as a solvent shows that under homogeneous reaction conditions all four of the products are formed in roughly equal amounts.

We settled on conditions employing three equivalents of nitromethane, a 0.4 M concentration of proline (40 mol%), 1 mol% **A**, and 20 mol% lauric acid. The ratio of products **3ab** and **3aa** observed by ^{1}H NMR at full conversion of both aldehydes was around 6:1 in favor of **3ab**, and few side reaction products were observed. Under these conditions, **3ab** could be isolated in 67% yield (82% for each step) and around 9:1 d.r; and the major diastereomer was formed with excellent enantioselectivity. The beneficial feature of the biphasic mixture was further confirmed by a control reaction in a homogeneous solution (DMF as the solvent) under otherwise similar conditions. Multiple side products (including those other than the cascade products) were formed,

and NMR analysis of the crude reaction mixture showed that **3aa**, **3ab**, **3ba**, and **3bb** were formed in roughly equal molar amounts. Under homogeneous conditions there was no significant chemical reactivity difference between these aldehydes (Figure 1). This is a further confirmation that the controlled formation of a single cascade product in our system is achieved using polarity differences.

2.4 Substrate scope. Using the one-pot, two-phase system containing multiple catalysts and substrates, aldehyde pairs with a small size difference can be differentiated and react in a controlled manner to selectively form a single cross product. The yield of the reaction is most sensitive to the identity of the "more polar" aldehyde component, for which a certain degree of miscibility with water is required for the condensation reaction to occur efficiently. Therefore, butanal and pentanal are much more effective as the more polar reacting partners than is hexanal. Aldehyde pairs with as little as one carbon difference (such as butanal and pentanal) can react selectively. A small set of examples involving several aldehyde pairs are summarized in Table 2. The highest yield is obtained with 3-methylbutanal as the more polar aldehyde component because it effectively undergoes the condensation reaction but participates very little in the conjugate addition reaction due to its steric bulk (Table 2, entry 12).

Table 2. Polarity-directed one-pot cascade reaction involving two different aliphatic aldehydes



Entry	Compound	R^1	R^2	Yield (%)[a]	e.r. (major)[b]	d.r.[c]
1	**3ab**	Et	*n*Octyl	67	>95:5	10:1
2	**3ab**[d]	Et	*n*Octyl	77	-	9:1
3	**3ab**[e]	Et	*n*Octyl	75	-	13:1
4	**6**	Me	*n*Octyl	45	>95:5	9:1
5	**7**	*n*Pr	*n*Octyl	63	>95:5	10:1
6	**8**[f]	*n*Bu	*n*Octyl	40	-	-[g]
7	**9**[f]	Et	*n*Pr	>25	-	-
8	**10**[f]	Et	*n*Bu	64	-	-
9	**11**[f]	*n*Pr	*n*Bu	>25	-	-
10	**12**	Et	*n*Hexyl	62	>95:5	13:1
11	**13**	Et	*n*Decyl	65	>95:5	19:1
12	**14**	*i*Pr	*n*Octyl	77	99:1[h]	16:1

[a]Isolated yield after column chromatography. [b]Determined for major diastereomer by ^{1}H NMR assay.[10] [c]Measured by ^{1}H NMR of isolated products. [d]2 eq of decanal were used. [e]2 eq of butanal were used. [f]Estimated yield based on ^{1}H NMR analysis of incompletely separated products. [g]Diastereomeric ratio was not determined for incompletely isolated products; [h]Enantiomeric ratio confirmed by HPLC.

3. Conclusion

In summary, we have developed a polarity-directed one-pot cascade reaction. Substrates with different hydrophobicities but similar reactivities can be differentiated to react in a programmed manner. Two catalysts were used, and each catalyst mediates an individual reaction step in either the aqueous or organic phase. The system highlights an often-ignored approach to developing

chemoselective reactions by using properties other than chemical reactivity (such as polarity) inherent to the substrates and/or catalysts. We anticipate that these results should inspire the design of new catalytic systems, including those using enzyme-like polymer catalysts, which can achieve unusual control of reactions.[14]

4. Methods

4.1 Materials. Commercial chemicals were purchased from Sigma-Aldrich except: lauric acid which was from Mathewson, Coleman and Bell; (S)-(+)-1-methoxy-2-propylamine, which was from Alfa Aesar; monobasic sodium phosphate monohydrate, which was from EMD Chemicals; and dibasic sodium phosphate heptahydrate, which was from EM Sciences. L-Proline, DL-proline, pyrrolidine (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**A)**, lauric acid, and nitromethane were used as received from commercial sources. It was found that for the reactions to proceed efficiently, it was essential to minimize the presence of acid in the aldehydes as a result of oxidation. Therefore, immediately prior to use, all aldehydes (with the exception of propionaldehyde) were washed successively with 10% sodium carbonate, saturated sodium sulfite, and water, and dried over magnesium sulfate. Subsequently, the aldehydes were distilled and approximately 1 mol% hydroquinone was added to inhibit oxidation. The aldehyde/hydroquinone mixtures were used directly in the reactions as soon as possible after distillation. DMF was purchased from Fisher and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AVQ 400 or AVB 400 instruments. High resolution mass spectra were obtained by the mass spectrometry facility at UC Berkeley using electron impact (EI) ionization. Infra-red spectra were recorded on a Varian 3100 FT-IR spectrometer. The pH values were measured using a Fischer Accumet AB15 pH meter.

4.2 General procedure for the monitoring of the one-pot reactions using ^{1}H NMR. Reaction optimization experiments and several other reactions were monitored by ^{1}H NMR analysis of the crude reaction mixture. For the analysis of reactions in the aqueous mixture, 100 μL of the reaction mixture was mixed with 700 μL benzene-d_6 in a vial. The vial was vigorously shaken for a few seconds, and anhydrous Na_2SO_4 was added to absorb the water. The dried benzene-d_6 solution containing both reactants and products of the catalytic reaction was filtered into an NMR tube and used for ^{1}H NMR analysis. For the catalytic reaction in DMF, 100 μL of the reaction mixture was mixed with 600 μL benzene-d_6 for ^{1}H NMR analysis. An approximate estimation of the ratios of the reaction products was made using ^{1}H NMR analysis.

4.3 Homogeneous reaction using DMF. The one-pot reaction of decanal and butanal was performed using various catalyst combinations in DMF. ^{1}H NMR analysis of the crude reaction mixtures showed that in all cases the four possible cascade products shown in Scheme 2 were formed in roughly equal molar amounts. For example, the spectrum shown below is from a reaction in which all catalyst and substrate ratios correspond to those used in the one-pot reaction conditions. In addition to the triplet peaks corresponding to the two aldehyde starting materials, four doublets from the various cascade products are observed with roughly equal magnitudes. Under these homogeneous conditions the reactivity of the two aldehydes is nearly indistinguishable.

4.4 General procedure for measuring the ee of the cascade product by a ^{1}H NMR ee assay. According to the method of Chi et al.,[11] the enantiomeric excess of the products could be estimated by treating the product with the chiral amine (S)-(+)-1-methoxy-2-propylamine and measuring the diastereomeric ratio of the resulting imine by ^{1}H NMR. Immediately before the ^{1}H NMR experiment, 15 μL of the chiral amine was added to the NMR tube containing about 9 mg of the sample and 1 mg of acetic acid in 670 μL of $CDCl_3$. The imine protons of all four diastereomeric products were clearly visible as separated doublets in the region of 7.6-7.4 ppm and were assigned by comparison with the corresponding racemic samples. The absolute and relative stereochemistry of the products was assumed to be (R,R) by analogy to literature examples employing similar substrates and catalysts. Figure 2 shows the sample ^{1}H NMR spectra of the in situ formed imine species containing the protons of interest for compound **14** in the ee assay. On the left is the racemic form of product **14** prepared using DL-proline and substituting chiral catalyst **A** with pyrrolidine. The two largest doublets are from the major enantiomers of the cascade product. The integrations of the minor peaks are consistent with the diastereomeric ratio observed in the spectrum of the corresponding cascade products (aldehyde samples). On the right is compound **14** synthesized in the one-pot reaction with a combined use of proline and catalyst **A**.

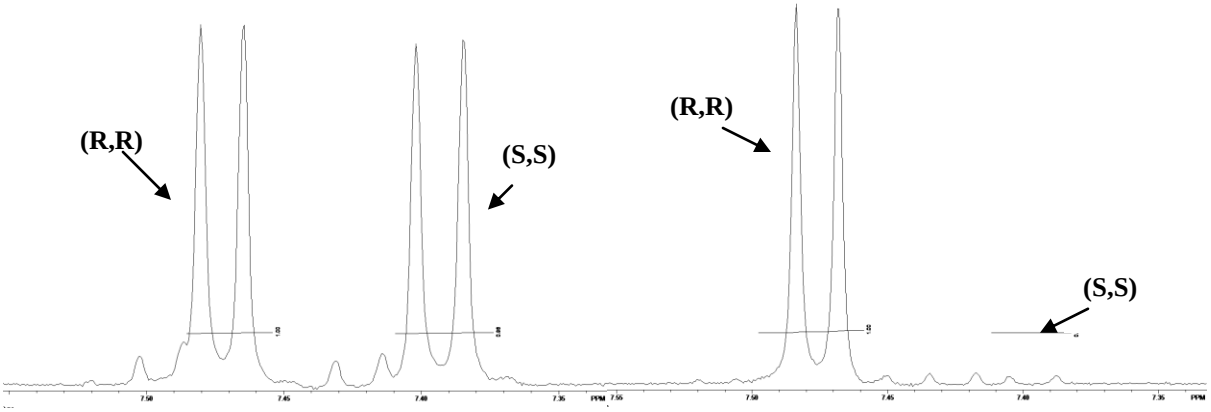


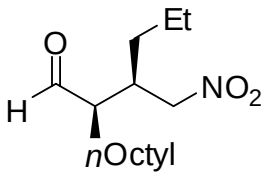
Figure 2. ^{1}H NMR spectra used to determine the approximate enantioselectivity of the conjugate addition reaction catalyzed by **A**. On the left is a sample of racemic compound treated with (S)-(+)-1-methoxy-2-propylamine revealing the presence of two enantiomers in equal amounts in the initial product mixture. The right-hand spectrum shows that the purified reaction product produces a single major peak, indicating that a single product enantiomer is formed in excess.

In order to verify these data, compound **14** was used as a model compound to verify the enantiomeric ratio by chiral HPLC. After purification, 10 mg of both the racemic and enantiomerically enriched samples of **14** were converted to the corresponding alcohol by treatment with 10 mg of $NaBH_4$ in 1 mL of MeOH for a few minutes. The reactions were quenched with 2 mL of ice-cold saturated NH_4Cl solution and extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtering and evaporation of the solvent, the identity of the material was confirmed by ^{1}H NMR and the samples were redissolved in hexanes. The enantiomeric ratio was determined by HPLC using a Chiracel OD-H column, λ=210 nm, hexane/isopropanol (v/v: 99.75:0.25, premixed), flow rate = 0.6 mL/min; t_R = 134.5 min (major), 146.7 min (minor) (99:1 e.r.).

4.5 Sample one-pot reaction procedure. All one-pot reactions for the synthesis of the "cross" cascade products (shown in Table 2) followed a similar procedure for the synthesis of **3ab** from butyraldehyde and decyl aldehyde: To a small vial equipped with a magnetic stir bar, was added 3.3 mg (0.010 mmol) of **A**, 46.1 mg (0.400 mmol) of L-proline, and 40.1 mg (0.200 mmol) of lauric acid. A 100 mM phosphate buffer solution (1 mL, pH 7.5) was added. The resulting cloudy mixture was stirred for a few minutes at rt and then 162 μL (183 mg, 3 mmol) of nitromethane was added via a syringe. After stirring at rt for another few minutes, the two aldehyde substrates were added via a syringe: 188 μL (156 mg, 1 mmol) of decanal was added, followed immediately by 89.6 μL (72.1 mg, 1 mmol) of butanal. The reaction mixture was stirred vigorously at rt for 16h, at which point complete consumption of decanal was observed through ^{1}H NMR and GC/MS analysis. The reaction mixture was then extracted three times with approximately 20 mL of dichloromethane. The collected organic fractions were dried over sodium sulfate and concentrated. Purification via flash chromatography (gradient of 2-4% ethyl acetate in hexanes) yielded the product (181 mg, 67% yield) as a pale yellow oil. The ^{1}H and ^{13}C NMR spectra of the compound were identical to a compound synthesized from the conjugate addition of decanal to nitroalkene **2a**.[5c]

In all of the reactions tested, the four cascade products (i.e. **3aa**, **3ab**, **3ba**, and **3bb**) could be easily isolated together as a mixture. In all cases under the optimized reaction conditions, approximately 80% of the theoretical mass of the final products was contained within this product mixture. For the most part, the desired product (i.e. **3ab**) could be isolated at approximately 65% of the theoretical mass. The remainder of the product mixture contained primarily self adduct (i.e. **3aa**) and trace amounts of the other two cascade products (i.e. **3bb**, **3ba**). In the case of the reactions to form products **8**, **9**, **10**, and **11** it was difficult to completely separate the desired major cascade products from the other products without significant loss of material. In cases where complete product isolation via flash chromatography was difficult, the yield of the major products was estimated based on ^{1}H NMR and GC/MS analysis of an isolated mixture of several cascade products.

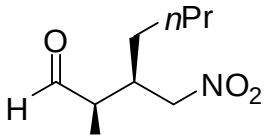
4.6 Characterization data.



3ab

2-(1-nitropentan-2-yl)decanal.

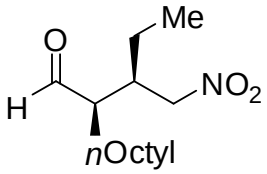
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.15 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 6.8, 12.8 Hz, 1H), 3.74 (dd, *J* = 6.9 Hz, 12.5, 1H), 2.37-2.34 (m, 1H), 1.96-1.92 (m, 1H), 1.37-1.10 (m, 13H), 1.02-0.87 (m, 5H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.64 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR *d* = 201.55, 76.58, 52.12, 36.55, 31.91, 31.00, 29.64, 29.38, 29.30, 27.62, 24.90, 22.75, 19.77, 14.02, 13.56 ppm; IR (neat) 2960, 2928, 2857, 2727, 1725, 1554, 1466, 1381, 723; HRMS (EI) *m/z* calculated for [M^++1] 272.2226, found 272.2230.



4

3-(nitromethyl)-2-propylheptanal.[16]

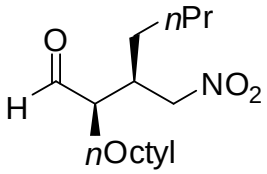
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.12 (d, *J* = 1.4 Hz, 1H), 3.82 (dd, *J* = 6.9, 12.8 Hz, 1H), 3.72 (dd, *J* = 6.9, 12.5 Hz, 1H), 2.32-2.27 (m, 1H), 1.92-1.90 (m, 1H), 1.32-0.78 (m, 10H), 0.74 (t, *J* = 7.0 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR *d* = 201.53, 76.59, 51.82, 36.68, 28.71, 28.55, 26.90, 22.41, 20.72, 13.79, 13.61 ppm; IR (neat) 2961, 2935, 2874, 2729, 1724, 1553, 1467, 1382, 731; HRMS (EI) *m/z* calculated for [M^++1] 216.1600, found 216.1597.



6

2-(1-nitrobutan-2-yl)decanal.

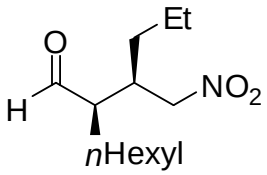
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.13 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 7.1, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.8, 12.7 Hz, 1H), 2.25-2.06 (m, 1H), 1.94-1.87 (m, 1H), 1.40-0.70 (m, 16H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.50 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR *d* = 201.59, 76.25, 51.81, 38.16, 31.91, 29.63, 29.37, 29.31, 27.50, 24.95, 22.75, 21.68, 14.02, 10.75 ppm; IR (neat) 2957, 2928, 2857, 2725, 1725, 1554, 1465, 1383, 723; HRMS (EI) *m/z* calculated for [M^++1] 258.2069, found 258.2074.



7

2-(1-nitrohexan-2-yl)decanal.

^{1}H NMR (400 MHz, C_6D_6) *d* = 9.16 (d, *J* = 1.3 Hz, 1H), 3.84 (dd, *J* = 7.2, 12.6 Hz, 1H), 3.77 (dd, *J* = 6.7, 12.5 Hz, 1H), 2.42-2.20 (m, 1H), 2.02-1.92 (m, 1H), 1.40-0.70 (m, 20H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J*= 7.6 Hz, 3H) ppm; ^{13}C NMR *d* = 201.57, 76.60, 52.10, 36.74, 31.91, 29.63, 29.37, 29.32, 28.71, 28.56, 27.61, 24.91, 22.75, 22.42, 14.02, 13.62 ppm; IR (neat) 2958, 2928, 2857, 2725, 1725, 1553, 1467, 1381, 724; HRMS (EI) *m/z* calculated for [M^++1] 286.2382, found 286.2381.

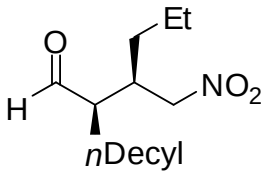


12

2-(1-nitropentan-2-yl)octanal.

^{1}H NMR (400 MHz, C_6D_6) *d* = 9.14 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 6.9, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.7, 12.7 Hz, 1H), 2.38-2.19 (m, 1H), 1.95-1.89 (m, 1H), 1.30-0.80 (m, 14H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.63 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR *d* = 201.54, 76.58, 52.11, 36.54, 31.53, 30.99,

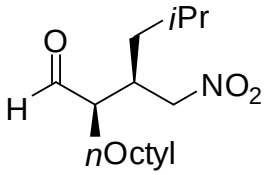
29.28, 27.56, 24.88, 22.62, 19.77, 13.94, 13.56 ppm; IR (neat) 2960, 2931, 2860, 2723, 1723, 1554, 1466, 1382, 725; HRMS (EI) *m/z* calculated for [M^++1] 300.2539, found 300.2539.



13

2-(1-nitropentan-2-yl)dodecanal.

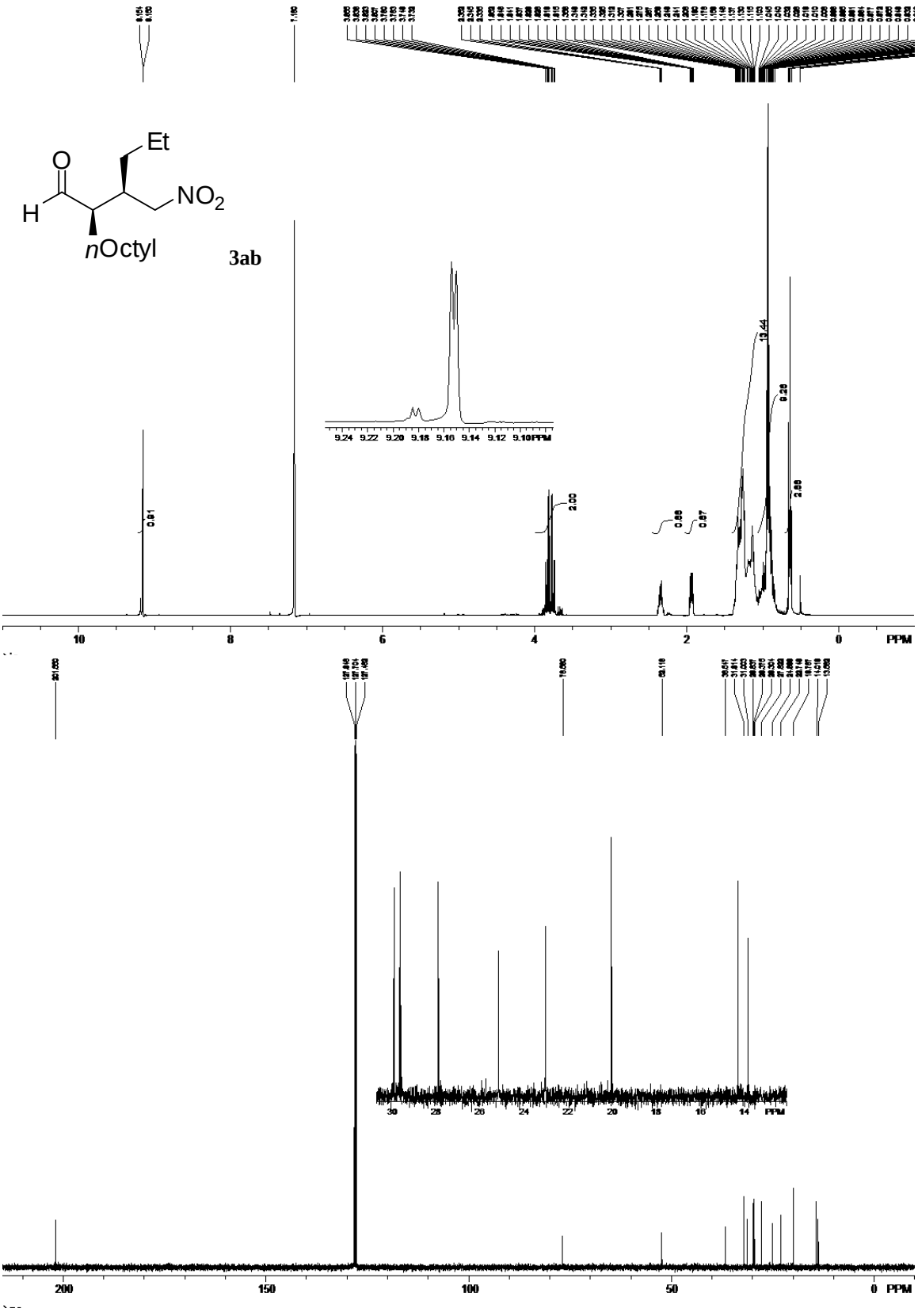
^{1}H NMR (400 MHz, C_6D_6) *d* = 9.14 (d, *J* = 1.4 Hz, 1H), 3.82 (dd, *J* = 7.2, 12.5 Hz, 1H), 3.74 (dd, *J* = 6.8, 12.4 Hz, 1H), 2.39-2.20 (m, 1H), 1.97-1.90 (m, 1H), 1.40-0.80 (m, 25H), 0.63 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR *d* = 201.53, 76.57, 52.12, 36.54, 31.99, 30.99, 29.72, 29.67, 29.66, 29.45, 29.44, 27.64, 24.89, 22.78, 19.77, 14.03, 13.58 ppm; IR (neat) 2959, 2927, 2856, 2722, 1725, 1554, 1466, 1381, 722; HRMS (EI) *m/z* calculated for [M^++1] 244.1913, found 244.1913.



14

2-(4-methyl-1-nitropentan-2-yl)decanal.

^{1}H NMR (400 MHz, C_6D_6) *d* = 9.16 (d, *J* = 1.3 Hz, 1H), 3.85 (dd, *J* = 6.7, 12.5 Hz, 1H), 3.76 (dd, *J* = 7.1, 12.5 Hz, 1H), 2.55-2.34 (m, 1H), 2.04-1.95 (m, 1H), 1.42-0.78 (m, 17H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR *d* = 201.49, 76.66, 52.23, 37.95, 34.63, 31.91, 29.64, 29.38, 29.32, 27.71, 24.87, 24.79, 22.75, 22.24, 21.65, 14.03 ppm; IR (neat) 2959, 2929, 2723, 1725, 1555, 1467, 1382, 723; HRMS (EI) *m/z* calculated for [M^++1] 286.2382, found 286.2383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NO2
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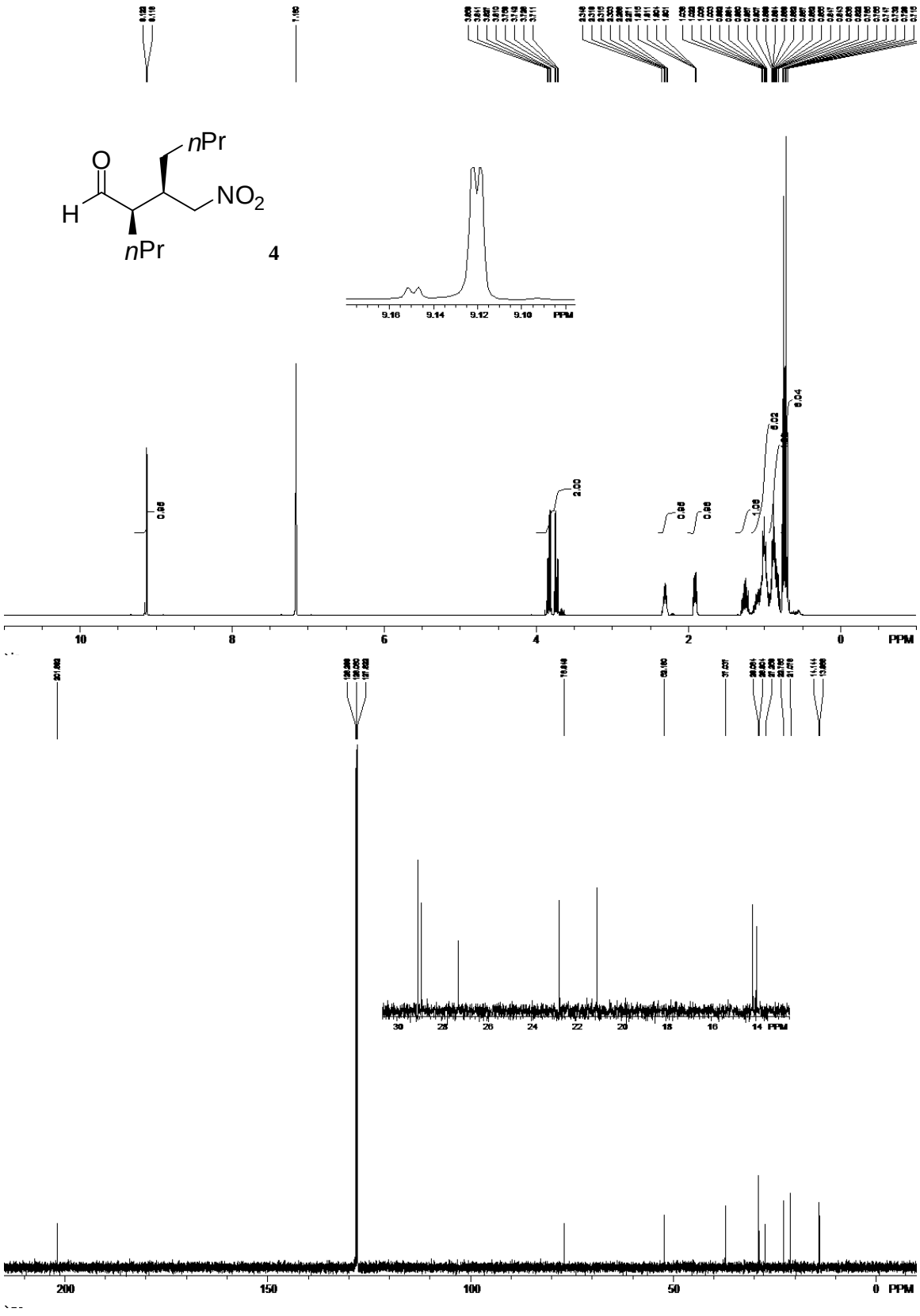
3ab
PPM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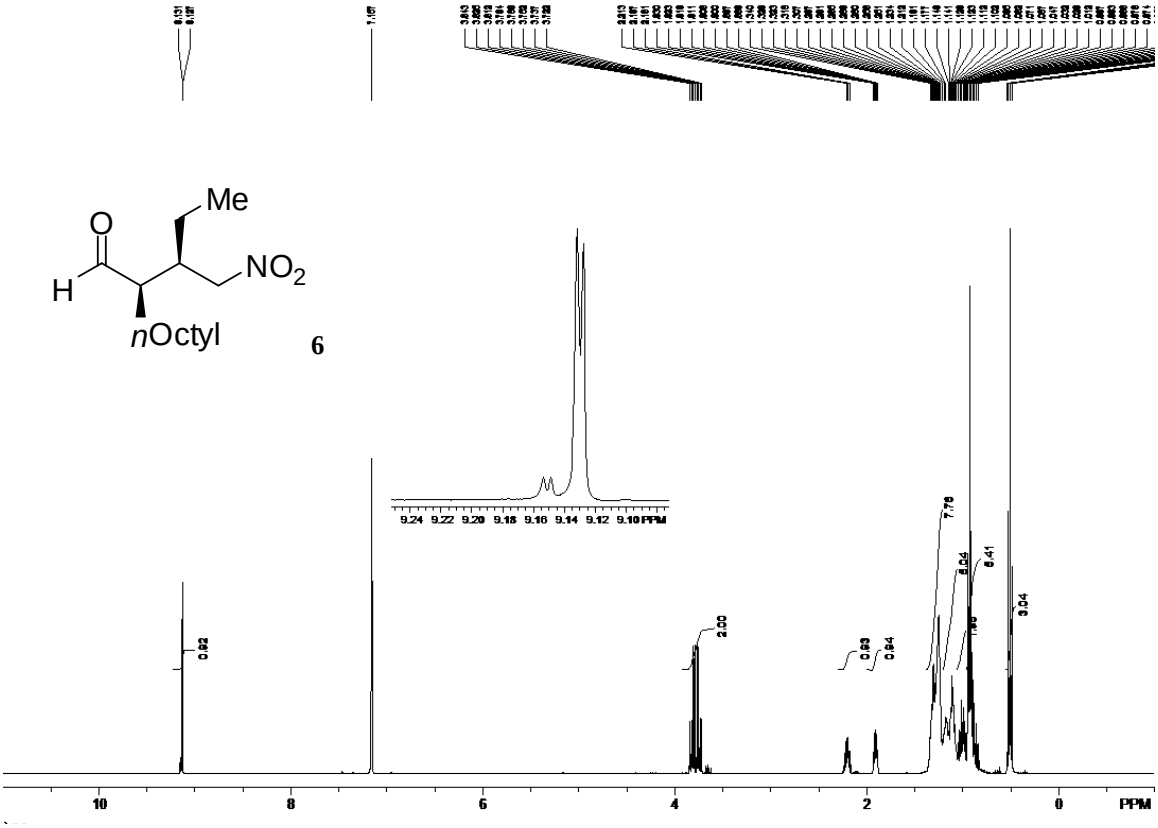
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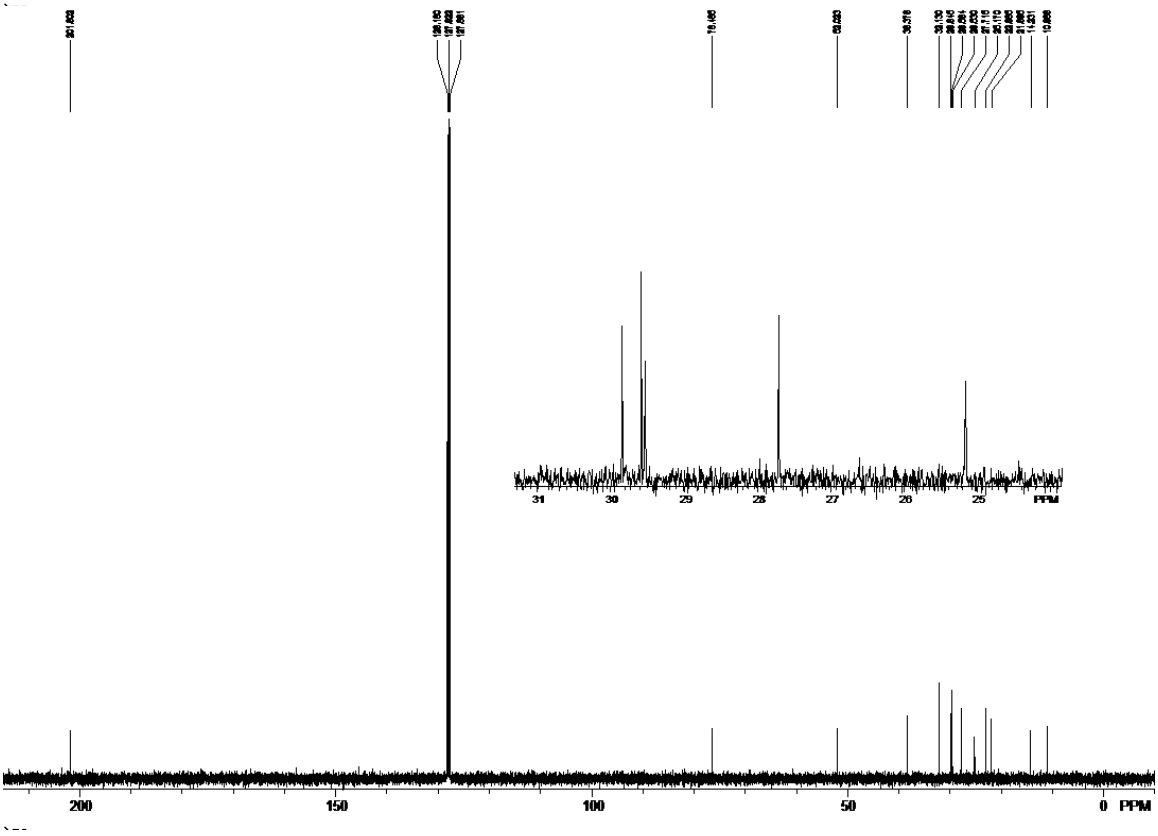
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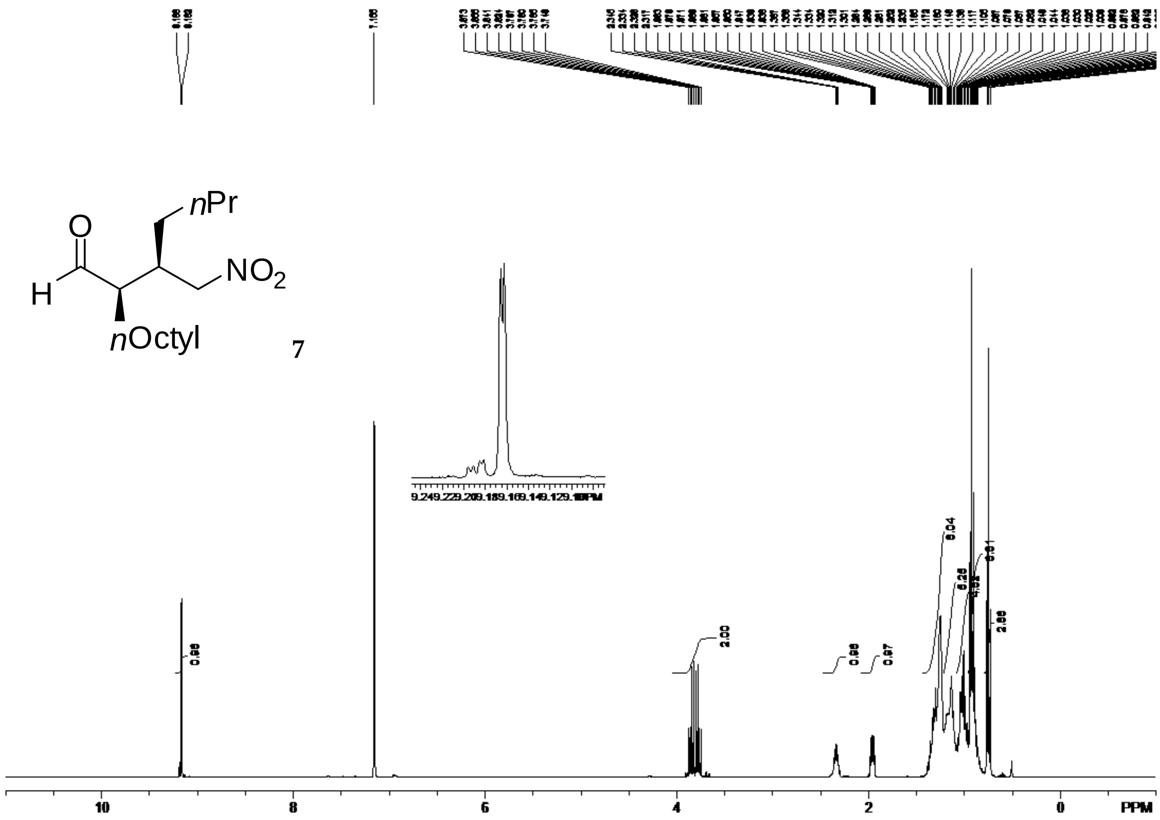

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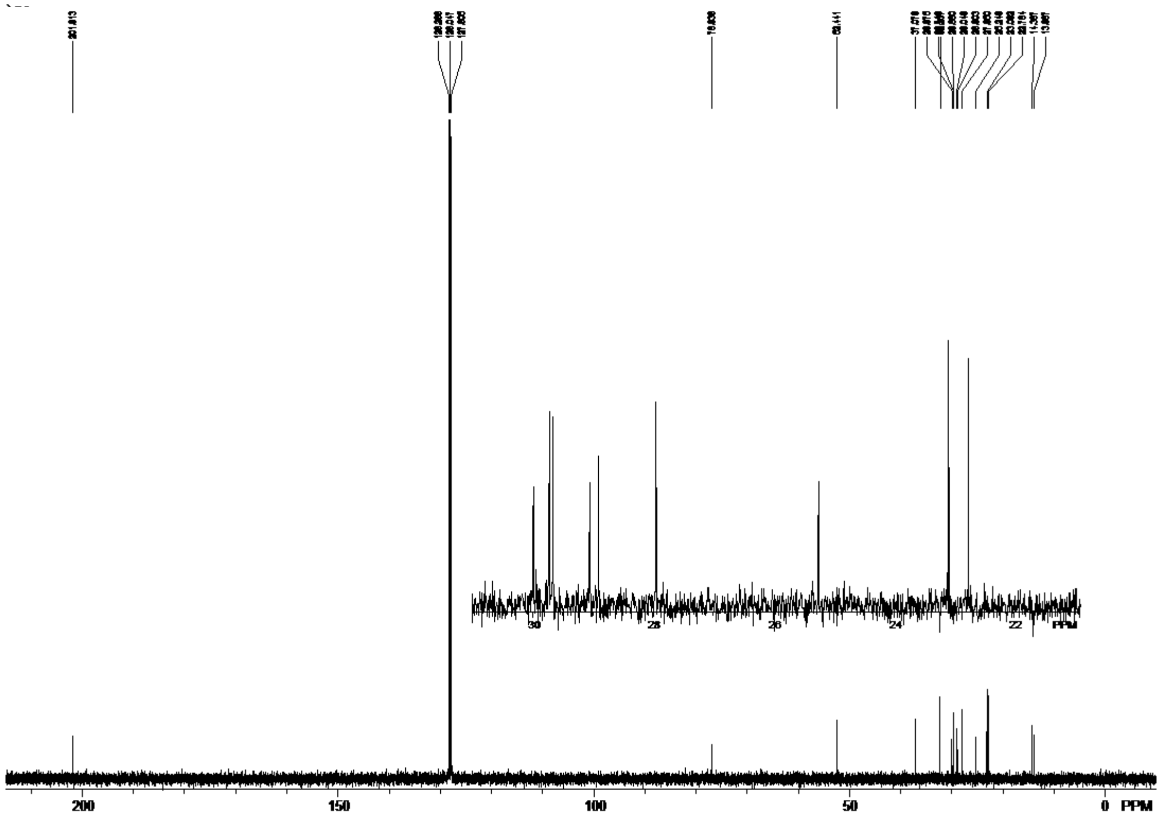

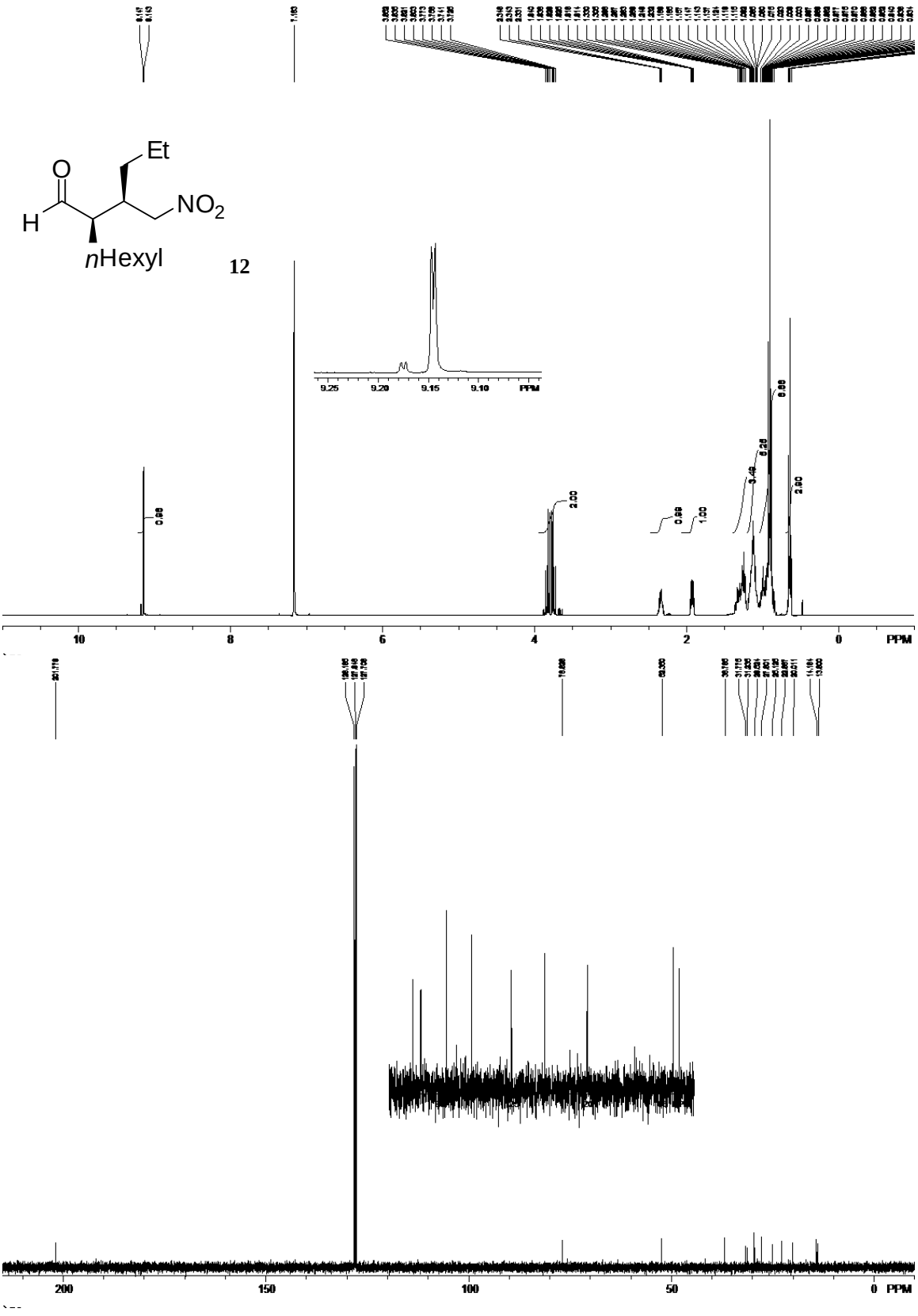
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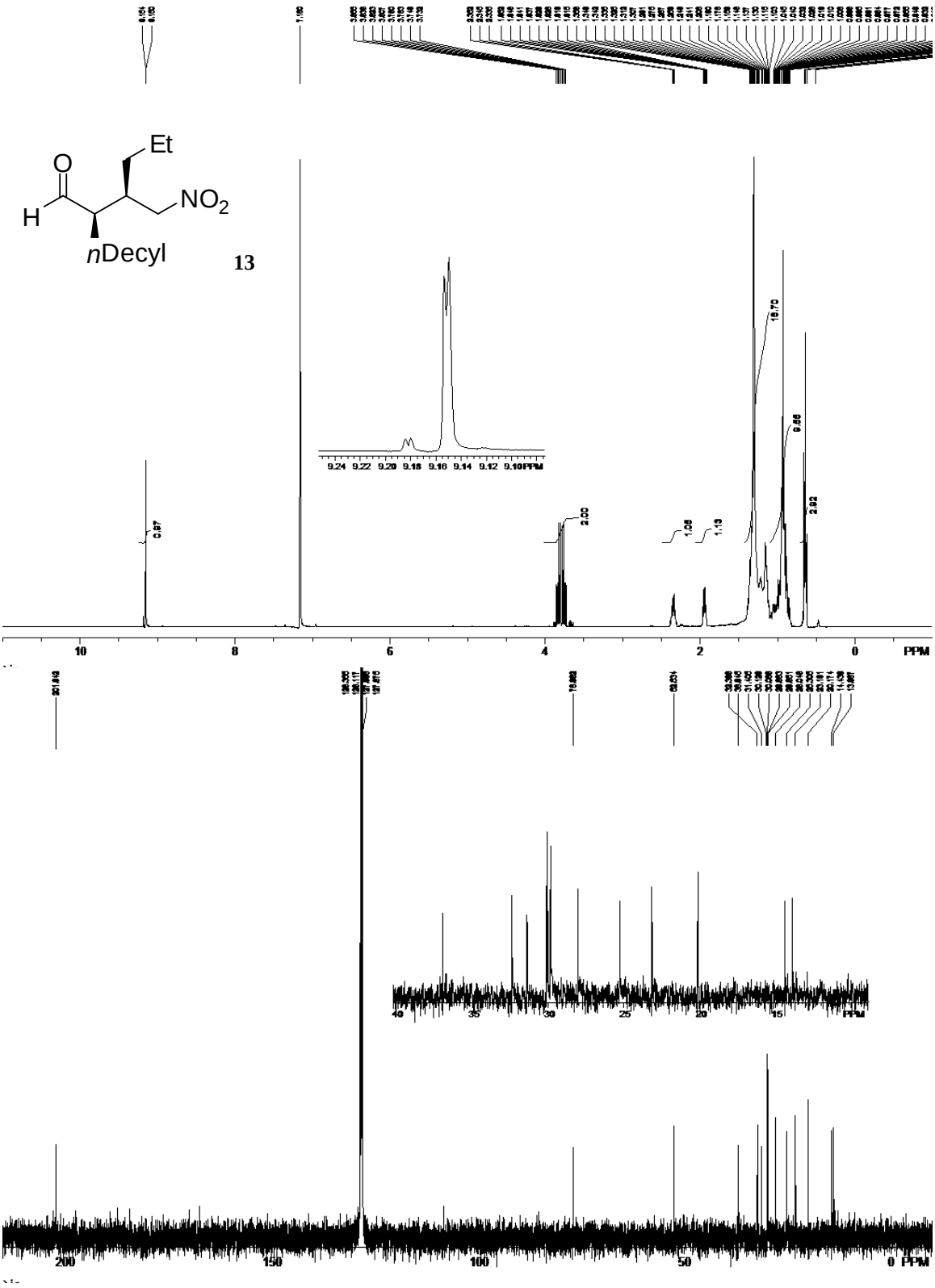
PPM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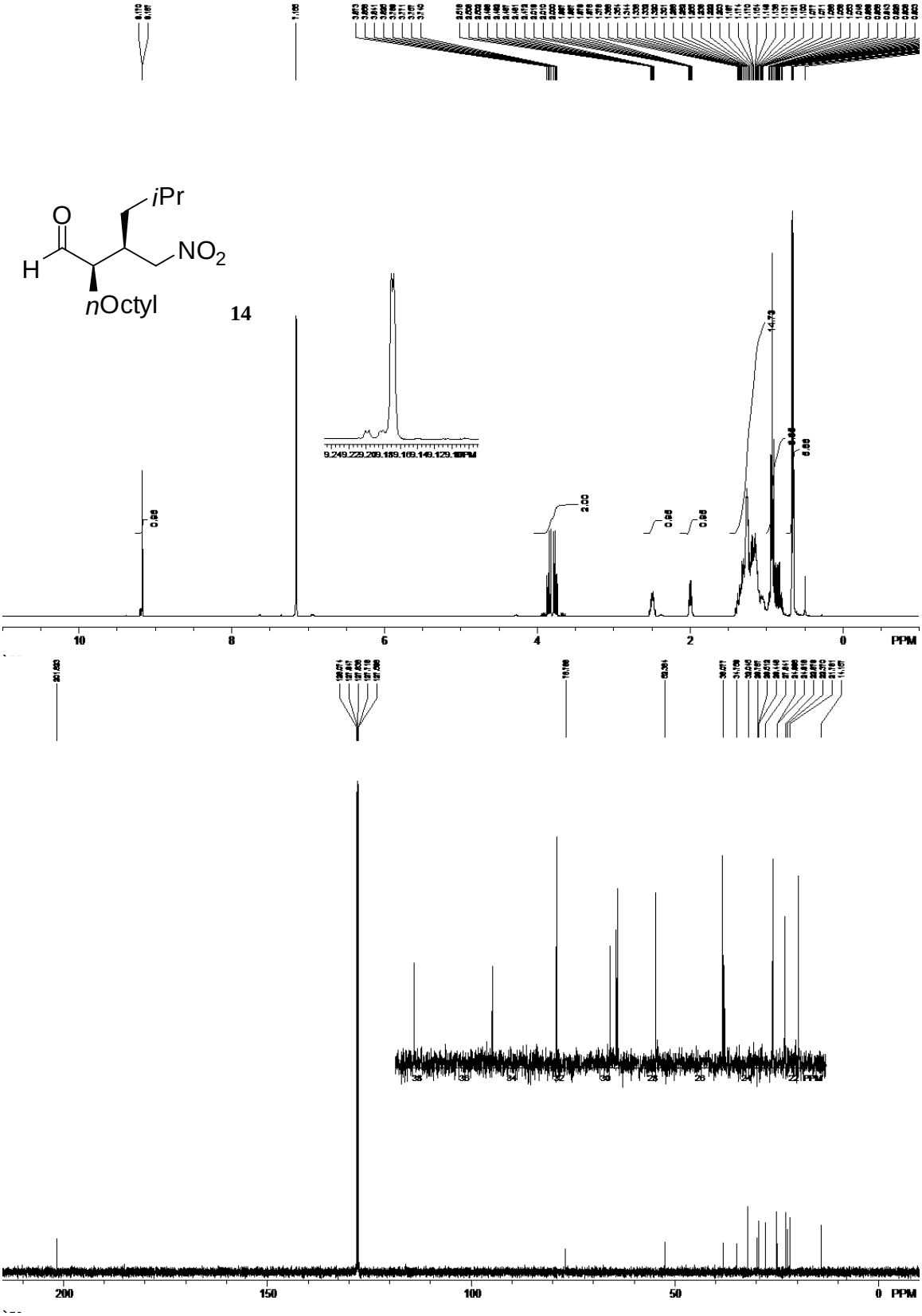
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