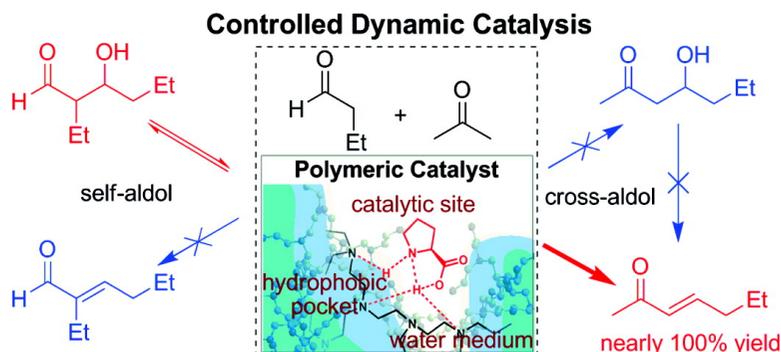


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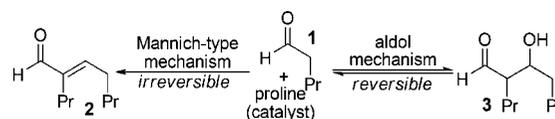
A central challenge of organic chemistry resides in the control of reaction pathways to avoid undesired reactions and develop new or more efficient syntheses. Nature uses precise control to amplify kinetically or thermodynamically unfavorable transformations with the assistance of enzymes, catalytic biopolymers that fold into sophisticated tertiary structures 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,^{2a} Breslow's polymer/pyridoxamine enzyme mimics,^{2b} Raymond's peptide dendrimer catalysts,^{2c} Moore's catalytic phenylene ethynylene foldamer,^{2d} the metal complex self-assemblies of Bergman and Raymond,^{2e} and the unimolecular free energy pump reactor of Fréchet and Hawker.^{2f} However, it is still extremely difficult to mimic the complex and precise functional makeup 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 an aqueous environment. We anticipated that such macromolecule catalysts might be used to direct the reaction pathways in a way not readily achievable with typical small molecule catalysts.

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 applications from the manufacture of basic chemicals to the preparation of fine pharmaceuticals.³ Indeed, aldehydes are the most common substrates in the recent explosive development of enamine,⁴ iminium,⁵ and SOMO⁶ 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.⁷ Here we report a soluble polymer catalyst that can eliminate the self-aldol reactions in an aqueous environment by suppressing an irreversible aldol pathway, thereby allowing for the amplification of otherwise unfavorable reactions without the need for excess reactants.

Our investigation began with a careful re-examination of the widely studied proline-catalyzed aldol reaction^{4,8} with enolizable aldehydes as the substrates. A typical model self-aldol of butanal (**1**) shows two major competing pathways at room temperature (rt) (Scheme 1). One is the *irreversible* formation 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 (see Supporting Information [SI]) were consistent with observations and postulations in the literature.^{4,8} Our aim was to eliminate the irreversible pathway

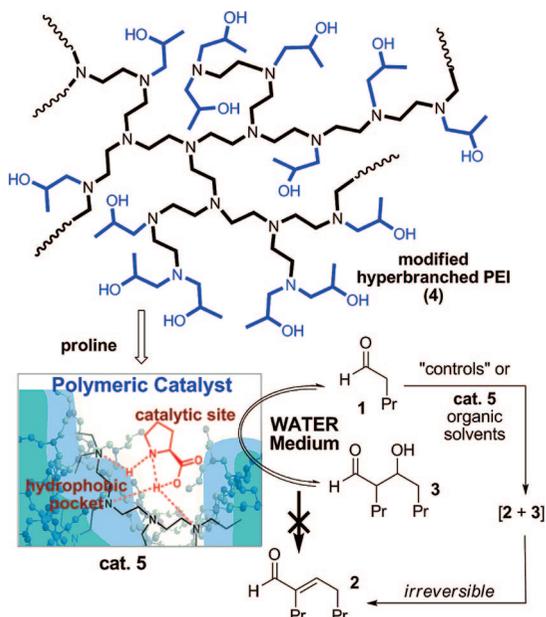
leading to the formation of **2**. Thus the reversible formation of **3** can be turned into dynamic catalysis in developing new or more efficient syntheses. We speculated that the undesired pathway might be disrupted by controlling the charged iminium species involved in the Mannich-type reaction leading 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 water⁹ as solvent or cosolvent failed to suppress the formation of **2**. Here we are interested in the development of soluble synthetic polymers to address this chemoselectivity problem.

Scheme 1. Competing Pathways of Enolizable Aldehyde Self-Aldol Reactions



We chose a commercial hyperbranched polyethyleneimine (PEI) as the scaffold to develop our polymer catalyst. In contrast to the use of PEI and related amine polymers and dendrimers¹⁰ as catalyst supports¹¹ (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.¹² 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 (Scheme 2). Instead of introducing catalytically active sites via covalent linkages, we took advantage of the tertiary amino groups in **4** as noncovalent handles to attract proline catalysts¹³ via electrostatic interactions,¹⁴ affording the desired polymer catalyst (**5**). This polymer catalyst **5** provided nearly complete control over the two reaction pathways when the aldol reaction was carried out in water (Scheme 2).

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 (2 days or longer). Very interestingly, **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%¹³ 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 h (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

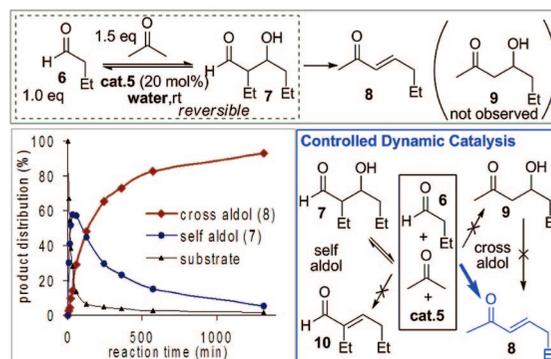
Scheme 2. Control of Aldol Reaction Pathways with a Hyperbranched Polymer Catalyst in Aqueous Environment

Table 1. Self-Aldol Reaction of Enolizable Aldehyde^a

entry	cocatalyst	solvent	conv. (2+3)% ^b	selectivity (3:2)	pH ^c
1	—	DMF	82	1.4	—
2	—	H ₂ O	<1	—	—
3	polymer 4	H ₂ O	56	63	9.2
4	polymer 4	DMF	86	0.6	—
5	Et ₃ N	H ₂ O	80	1.0	11.1
7	CH ₃ N(EtOH) ₂ ^d	H ₂ O	82	5.3	10.1
8	CH ₃ N(EtOH) ₂ ^e	H ₂ O	77	3.3	—
9	N(EtOH) ₃	H ₂ O	86	15	9.5

^a See SI for experimental details. ^b Measured by ¹H NMR of the crude reaction mixture; diastereoselectivity of aldol product **3** is ~1.2:1; enantioselectivity was not determined. ^c pH of the catalyst solution in water (before the addition of aldehyde substrate). ^d *N*-Methyldiethanolamine. ^e Sodium dodecyl sulfate (a surfactant) was added (see SI).

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 analogue of polymer **4** under otherwise identical conditions showed poor reaction control (Table 1, entry 5). Further experiments using tertiary amines containing alcohol groups (*N*-methyl-diethanolamine, triethanolamine) in an aqueous medium gave results better than that with TEA (Table 1, entry 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 ~9.0 gave optimal results.¹⁵ The catalytic 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 pH's (see SI). The use of alcohols, such as methanol, 2-propanol, and 2,2,2-trifluoroethanol as additives or cosolvents, does not improve reaction selectivity. In all cases,

polymer catalyst **5** performs best in controlling the aldol reaction pathways (Scheme 2).

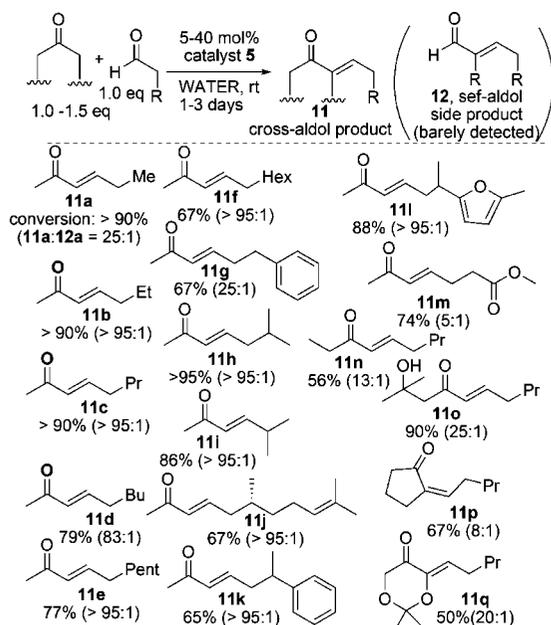
Scheme 3. Dynamic Catalytic Cross Ketone/Aldehyde Reaction


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.¹⁶ 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, an FDA listed food additive.¹⁷ 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 (Scheme 3), the self-aldol reaction of **6** to form β -hydroxy aldehyde **7** proceeded much faster than the cross-aldol reaction, reaching maximum conversion in ~30 min. 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 h. 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,^{7b} suggesting that the cross 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 as well as 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** (see the SI).

To probe the substrate scope, we first examined cross acetone/aldehyde condensations with unhindered straight-chain aliphatic aldehydes of different size and hydrophobicity. Increasing aldehyde hydrophobicity leads to a large decrease in reaction efficiency due to the polar nature of the aqueous polymer catalytic phase (see SI). This selectivity determined by substrate hydrophobicity may be used to design polymer-assisted polarity gradient-directed chemoselective

Scheme 4. Catalytic Cross Ketone/Aldehyde Condensation



reactions, such as aldehyde/aldehyde cross-aldol reactions.¹⁸ 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 4.¹⁹ Our method provides access to α,β -unsaturated ketones in an 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 without further proline addition.²⁰

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. Ongoing work also suggest that very challenging reactions, such as those involving hindered and unreactive substrates with the generation of quaternary carbon centers, can be developed. Given the large number of transformations that involve enolizable aldehydes as substrates, we anticipate that this catalyst and its polymer or small molecule analogues may be useful in a broad range of new or more efficient syntheses. Overall, the design of macromolecule catalysts that can address fundamental challenges is of both conceptual and practical importance in chemistry.

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Supporting Information Available: Experimental details and additional discussions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (20) For example, in a scalable preparation of **11c** and **11h** (Scheme 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.

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