ACS Combinatorial Science

Letter

pubs.acs.org/acscombsci

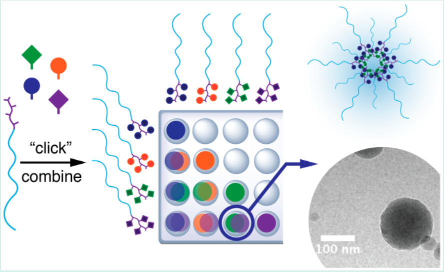
Cooperative Catalysis With Block Copolymer Micelles: A Combinatorial Approach

Konstantin V. Bukhryakov,[†] Victor G. Desyatkin,[‡] John-Paul O'Shea,[†] Sarah R. Almahdali,[†] Vera Solovyeva,[†] and Valentin O. Rodionov*[,†]

[†]KAUST Catalysis Center and Division of Physical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal, 23955-6900, Kingdom of Saudi Arabia

[‡]Chemistry Department, M.V. Lomonosov Moscow State University, Leninskye Gory, 119992 Moscow, Russia

Supporting Information



ABSTRACT: A rapid approach to identifying complementary catalytic groups using combinations of functional polymers is presented. Amphiphilic polymers with "clickable" hydrophobic blocks were used to create a library of functional polymers, each bearing a single functionality. The polymers were combined in water, yielding mixed micelles. As the functional groups were colocalized in the hydrophobic microphase, they could act cooperatively, giving rise to new modes of catalysis. The multipolymer "clumps" were screened for catalytic activity, both in the presence and absence of metal ions. A number of catalyst candidates were identified across a wide range of model reaction types. One of the catalytic systems discovered was used to perform a number of preparative-scale syntheses. Our approach provides easy access to a range of enzyme-inspired cooperative catalysts.

KEYWORDS: *cooperative catalysis, block-copolymer micelles, combinatorial approach, amphiphilic polymers*

The precise, tailored structures attained by proteins allow them to achieve an unparalleled degree of functional perfection. Enzymes in particular achieve their catalytic competency through precise positioning of multiple functional groups around the active sites and close participation of cofactors, prosthetic groups, and metal ions.[1]

These "perfect" catalysts are a product of a random search process known as biological evolution. Over the course of billions of years, Nature sampled a vast combinatorial space of potential catalytic macromolecules, continuously selecting the useful ones. While chemists have been quite successful in developing efficient and practical catalysts through rational design, the number of reasonable-guess structures that can be synthesized and evaluated within a practical time frame is necessarily limited by the difficulties inherent to multistep synthesis. To address this challenge, a variety of evolution-inspired, combinatorial methods have been applied to catalyst discovery.[2] One of the more elegant strategies, first devised by Menger, involves random/uncontrolled derivatization of simple, soluble polymer supports using reliable coupling reactions.[3] A large number of functional polymers differing in the degree of functionalization and the specific combinations of functional groups can thus be prepared and screened rapidly. Through this simple approach, a number of remarkably competent multifunctional catalysts were identified. Since the derivatization is performed in a single step even with multiple functional moieties, very large combinatorial spaces are easily accessible. Unfortunately, this also complicates the identification of specific functional group interactions responsible for catalytic activity.

Here, we present a rapid approach to identifying complementary catalytic groups using combinations of functional polymers.[4,5] We use amphiphilic polymer supports[6] with "clickable"[7] hydrophobic blocks to create a small library of functional polymers, each bearing a single functionality. The functional group tolerance of "click" reactions allows easy access to a wide variety of functional polymers. When these polymers are combined in water, they form mixed micelles. As the functional groups are colocalized in the hydrophobic microphase, they can act cooperatively, giving rise to new modes of catalysis. Due to the hydrophobic character of the interior of the micelles, even hydrogen-bonding electrophile activators, normally ineffective in pure water, could be competent in our design. The resulting multipolymer "clumps"[4] are then screened for catalytic activity, both in the presence and absence of metal ions. To explore the limits of our discovery strategy, we chose to target a number of challenging, bond-making reactions of import to organic chemists (Figure 1).

We prepared the amphiphilic "clickable" supports by polymerizing 4-azidomethylstyrene (N_3St) using methoxypoly(ethylene glycol) (MPEG) ($M_w \approx 5000$) derivatized with a reversible addition−fragmentation chain transfer (RAFT) initiator.[8] When choosing the specific polymerization conditions (section 3, Supporting Information), we aimed to produce extremely short N_3St blocks to ensure the "clicked" functional copolymers retain excellent solubility in water. The

Received: November 2, 2014
Published: December 29, 2014

DOI: 10.1021/co5001713
ACS Comb. Sci. 2015, 17, 76−80

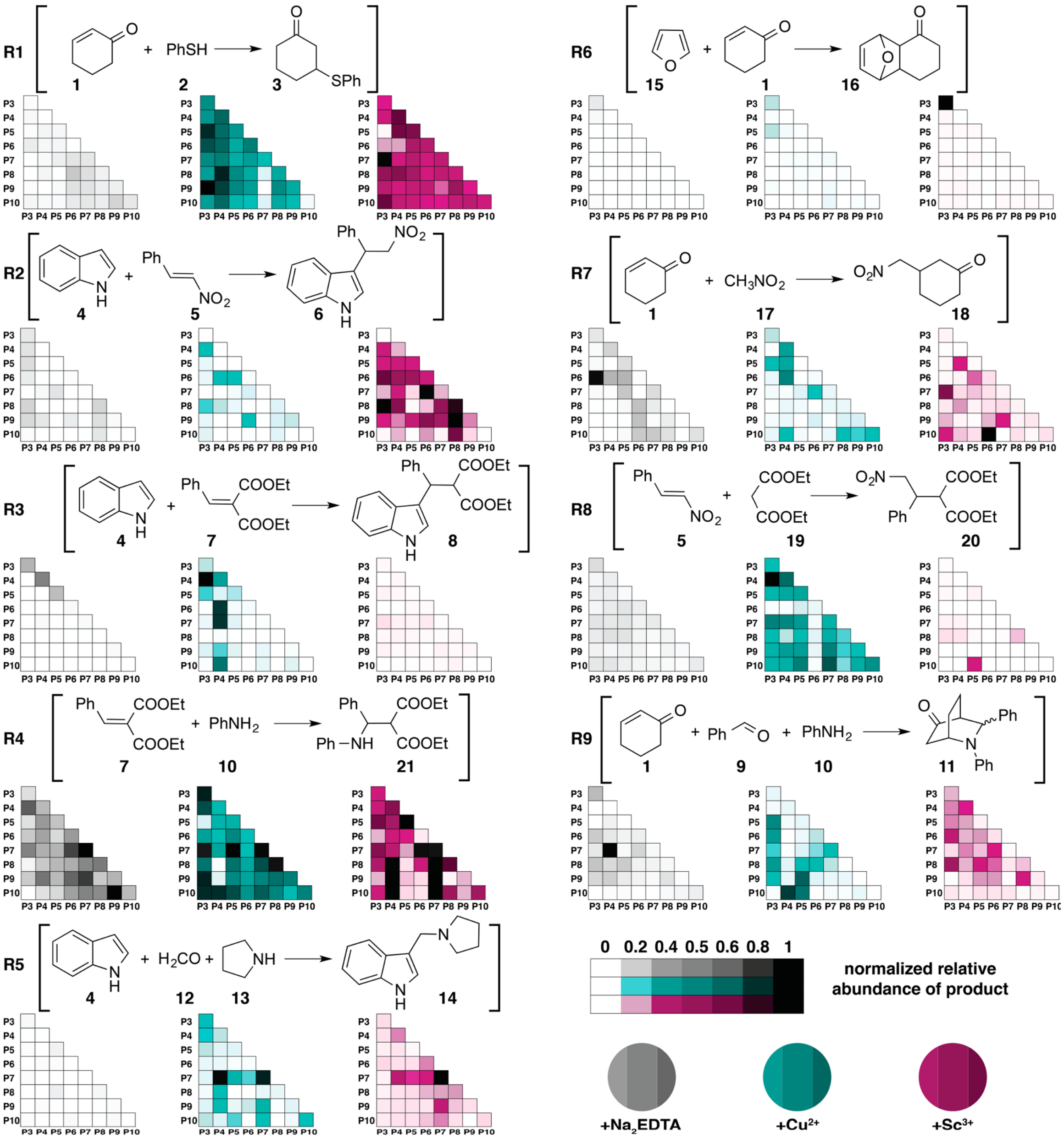


Figure 1. Combinatorial screening of a range of organic reactions catalyzed by binary combinations of block copolymers **P3**−**P10**. Darker shading indicates a higher relative abundance of the expected reaction product. Blocks of different color correspond to reactions performed in the presence of Na_2EDTA (gray), Cu^{2+} (green), and Sc^{3+} (purple). Reactions **R1**−**R8** were analyzed by LC-MS, and **R9** was analyzed by NMR.

two polymers we used throughout the study are MPEG(5000)-*b*-$(N_3St)_5$ (**P1**) and MPEG(5000)-*b*-$(N_3St)_3$ (**P2**). A part of polymer **P1** was reduced with triphenylphosphine to yield the amine-functionalized polymer **P1A**. Some loss of dithioester end group,[9] and subsequent dimerization through disulfide bond was observed for all three "clickable" polymers, especially for **P1A** because of the nucleophilicity of its amine groups. While thiols could participate in some of our chosen reactions, this interference will be negligible for the low loadings of polymer catalysts we used (5 mol % or less on functional group basis). As the solubility of the polymers was not affected, we did not take any specific measures to prevent the end-group loss.

The copolymers were then functionalized with "clickable" payloads (Scheme 1 and section 4, Supporting Information). An established copper-catalyzed azide−alkyne cycloaddition (CuAAC)[10] protocol was used with azide-bearing **P1** and **P2**, yielding functional copolymers **P3**−**P9**. In the case of polymers **P3** and **P9**, some cross-linking with the bifunctional alkyne payloads was inevitable, yet the polymers remained soluble. The amine-bearing **P1A** was treated with 3,5-bis(trifluoromethyl)phenylisothiocyanate, yielding the thiourea-functionalized copolymer **P10**. All the functional polymers showed strong tendency to aggregate, even in good solvents such as chloroform and DMSO (section 6, Supporting Information).

For the screening of catalytic activity, dilute aqueous solutions of the polymers (1 wt %) were dispensed into 96-well polypropylene plates, either alone or pairwise. Reagents were added as aqueous or dimethylformamide solutions to start the experiment. Three sets of conditions were explored for each of the reactions (Figure 1). To evaluate the organocatalytic competence of the polymer "clumps", any effect of trace Cu

Scheme 1. Synthesis of Functional Amphiphilic Block-Copolymers

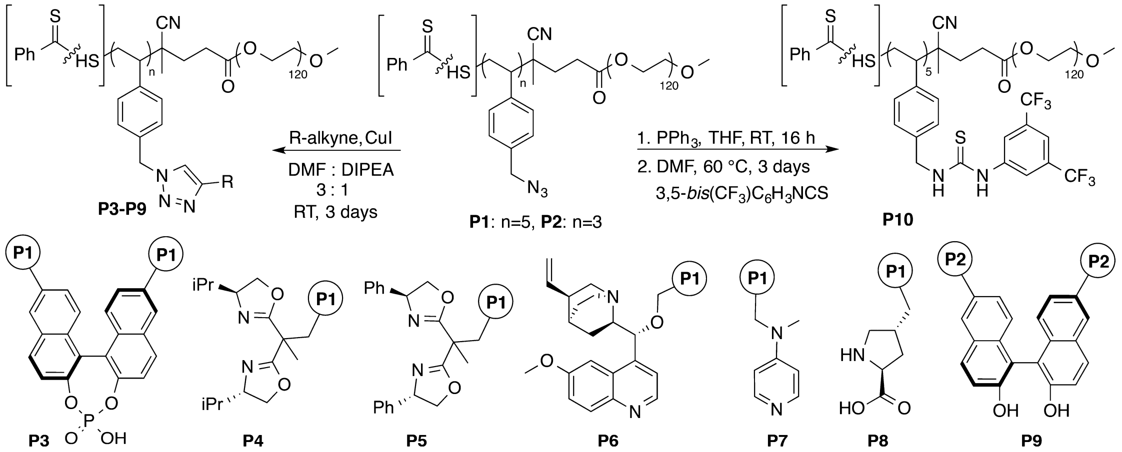


Table 1. Most Effective Combinations of Functional Polymers/Metal Ions Identified in Combinatorial Screening

ID	+Na_2EDTA	+Cu^{2+}	+Sc^{3+}	reported in H_2O
R1		**P3** + **P5**; **P3** + **P9**; **P4** + **P8**; **P4** + **P9**	**P3** + **P7**	[12–17]
R2			**P8**; **P6** + **P7**; **P3** + **P8**; **P8** + **P9**	[19–21]
R3		**P3** + **P4**; **P4** + **P6**; **P4** + **P7**		NR[a]
R4*	**P7**; **P9** + **P10**	**P3**; **P7**; **P8**; **P3** + **P7**; **P5** + **P7**	**P5**; **P7**; **P4** + **P8**; **P4** + **P9**; **P4** + **P10**; **P7** + **P6**; **P7** + **P8**; **P7** + **P9**; **P7** + **P10**	NR[a]
R5		**P7**; **P4** + **P7**	**P7**	NR[a]
R6			**P3**	NR[a]
R7	**P3** + **P6**		**P6** + **P10**	NR[a]
R8		**P3** + **P4**		NR[a]
R9	**P4** + **P7**	**P4** + **P10**		[23]

[a] Not reported.

remaining from the CuAAC reactions had to be eliminated. To this end, Na_2EDTA was added to each well. We also performed reactions in the presence of added $Cu(OTf)_2$ and $Sc(OTf)_3$ as Lewis acid cocatalysts.[11] Thus, for each of the reactions **R1**–**R9**, 108 catalyst/cocatalyst combinations were screened, for an overall 972 reactions. Each reaction was also performed in the absence of metal ions and polymers. No product formation was observed in any of the control experiments.

The reactions were allowed to run overnight before being analyzed by liquid chromatography–mass spectrometry (LC-MS). The intensity of the signal of each of the expected products was compared to the signal of (4-aminophenyl)-diethylamine hydrochloride, a convenient internal standard. The standard was introduced immediately prior to analysis, to avoid any undesirable side reactions. In the case of Michael reaction **R4**, this internal standard was unsuitable, as it was reactive toward one of the substrates (**7**). Thus, the outcome of **R4** was analyzed by NMR.

The results of the screening are summarized in Figure 1, where the relative abundance of each expected product at the end of the experiment is represented as shades of color. It is important to note that the abundance values have been normalized individually for each reaction, and are thus not directly comparable across the entire **R1**–**R9** set. It is immediately evident that different combinations of functional polymers and metal ions lead to dramatically different reaction outcomes. The most effective combinations are listed in Table 1.

R1 is the conjugate addition of thiophenol **2** to cyclo-2-hexenone **1**. Chakraborti and co-workers have previously shown that this reaction could work without a catalyst in water under ambient conditions.[12] Other groups found that poly(*N*-vinyl-imidazole),[13] serum albumin,[14] squaric acid,[15] borax,[16] or sodium acetate[17] is necessary. In the present study, the reaction did not proceed without a catalyst. However, it did proceed well in the presence of both of binol derivatives (**P3, P9**), proline (**P8**), DMAP (**P7**), or oxazolines (**P4, P5**). In all cases, combinations of polymers were necessary to produce reasonable conversions.

The Friedel–Crafts reaction of indole **4** with *β*-nitrostyrene **5** (**R2**) has previously been shown to proceed without a catalyst neat[18] or in water,[19] albeit at high temperatures. *β*-Cyclodextrin and zinc alkylsulfonates are effective catalysts.[20] Results here show that in the presence of $Sc(OTf)_3$, the proline derivative (**P8**) was effective alone and in combination with either binaphthylphosphoric acid (**P3**) or binol (**P9**) derivatives. This finding agrees partially with Xie et al., who found that $Sc(OTf)_3$ alone could be a good catalyst for this reaction in water.[21]

The Friedel–Crafts reaction of indole **4** with diethyl-2-benzylidenemalonate **7** (**R3**) has not previously been reported to proceed in water. Here, we identified the combination of $Cu(OTf)_2$ with binaphthylphosphoric acid (**P3**) and oxazoline (**P4**) derivatives as promising catalytic systems.

For **R4**, the Michael reaction of diethyl 2-benzylidenemalonate **7** with aniline, a wide variety of polymers and their combinations were effective. DMAP (**P7**) was active both alone, and in combination with a range of other polymers and metal ions. iPr-oxazoline (**P4**) was active in combination with proline (**P8**), binol (**P9**), or thiourea (**P10**) or in the presence of Sc^{3+}. Interestingly, the Ph-oxazoline (**P5**) was most efficient in a binary combination with Sc^{3+}: there was no benefit from adding polymeric cocatalysts. Although we did not find previous examples of this reaction in water, there is at least one report of a moderate yield attained under neat conditions in the presence of 50 mol % of $LiClO_4$.[22] This catalyst loading is an order of magnitude higher than was necessary in any of our reactions.

We could not find any previous reports of reactions **R5**−**R8** in water. In our hands, the Mannich reaction **R5** between indole, formaldehyde and pyrrolidine proceeded in the presence of Cu^{2+} or Sc^{3+} and DMAP (**P7**). The Diels−Alder reaction **R6** of furan with cyclo-2-hexenone was found to require two Lewis acid catalysts, the binaphthylphosphoric acid (**P3**) and $Sc(OTf)_3$. The conjugate addition **R7** of cyclo-2-hexenenone **1** with nitromethane was found to proceed in the presence of quinine (**P6**) and either binaphthylphosphoric acid (**P3**), or $Sc(OTf)_3$ and thiourea (**P10**). The addition **R8** of β-nitrostyrene with diethyl malonate required a combination of $Cu(OTf)_2$, binaphthylphosphoric acid (**P3**) and oxazoline (**P4**).

Reaction **R9** is the aza-Diels−Alder reaction of benzaldehyde with aniline and cyclo-2-hexenone. Previously, Huang et al. demonstrated this type of reaction in aqueous media with moderate yields using 20 mol % of α-Zr-phosphate in the presence of sodium calix[4]arene sulfonate surfactant.[23] In our case, reasonable yields were achieved with only 5 mol % of two amphiphilic cocatalysts (**P4** and **P10**, calculated on a functional group basis) and 5 mol % of Cu^{2+}. We scaled this reaction up and established the exo/endo ratio for the products (Table S10, Supporting Information). Under optimal conditions (37 °C, 96 h), we obtained a 66% product yield with a 72:28 endo:exo ratio. Interestingly, the endo:exo ratio is significantly affected by the temperature. At 100 °C, a 50% yield could be obtained after 16 h with an endo:exo ratio of 54:46. As the stereoselectivity of the parent reaction is not normally as affected by temperature, we attribute the change in the endo:exo ratio to the change in the structure of catalytic "clumps". Both **P4** and **P10** were necessary for the reaction to proceed: in the presence of Cu^{2+} but not the polymers, only a 3% yield with a 61:39 endo:exo ratio was realized overnight.

Next, we characterized the **P4**, **P10**, **P4** + **P10**, and **P4** + **P10** + Cu^{2+} polymer "clumps" by cryo-transmission electron microscopy (CryoTEM) (Figure 2). **P4** and alone forms small, spherical micellar aggregates (Figure 2A), while **P10**'s aggregates were disordered and wormlike (Figure 2B). A combination of **P4** + **P10** resulted in somewhat larger spherical aggregates (Figure 2C). The structure of the aggregates changed dramatically in the presence of Cu^{2+} ions (Figure 2D). Large (100−200 nm), electron-dense spherical "clumps" were the most representative structures. It is reasonable to assume that the interactions that guide the formation of these striking assemblies also have bearing on the observed catalytic competency. Cryo-TEM images of other functional polymers are summarized in section 7, Supporting Information.

Using an empirical, yet rapid and flexible approach, we have been able to identify promising catalyst candidates and reaction conditions in water across a wide range of model reaction types. One of the catalytic systems discovered was used to perform a number of preparative-scale syntheses. Our approach provides easy access to a range of enzyme-inspired multifunctional catalysts. Efforts are underway in our laboratories to extend the results to other classes of reactions, as well as to gain mechanistic insights.

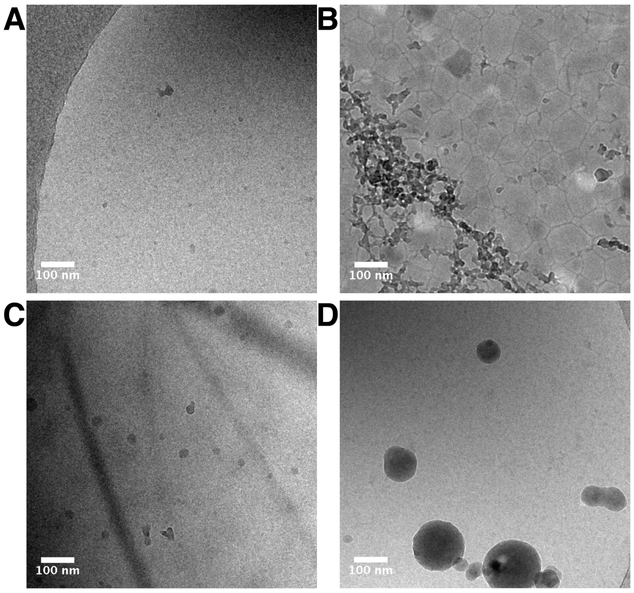


Figure 2. Cryo-TEM images of aqueous solutions of (A) **P4**, (B) **P10**, (C) combination of **P4** and **P10**, and (D) combination of **P4** and **P10** in the presence of Cu^{2+}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details of organic synthesis, spectroscopic characterization, additional cryo-TEM images. and a list of abbreviations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: valentin.rodionov@kaust.edu.sa. Tel: +966-12-8084592.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Rachid Sougrat for his assistance with cryo-TEM. Funding from KAUST OCRF (award project "Catalysis with Soft Materials") is acknowledged with thanks.

■ REFERENCES

(1) Fersht, A. *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding*; W. H. Freeman: New York, 1999.

(2) (a) Brümmer, O.; Hall, K. A.; Leclerc, M.; Lee, S. E.; Murphy, V. Combinatorial Methods in Catalysis and Materials Science. *Ullmann's Encycl. Ind. Chem.* **2000**, 585−625. (b) Revell, J. D.; Wennemers, H. Peptidic Catalysts Developed by Combinatorial Screening Methods. *Curr. Opin. Chem. Biol.* **2007**, *11*, 269−278.

(3) (a) Menger, F. M.; Eliseev, A. V.; Migulin, V. A. Phosphatase Catalysis Developed Via Combinatorial Organic Chemistry. *J. Org. Chem.* **1995**, *60*, 6666−6667. (b) Menger, F. M.; Ding, J.; Barragan, V. Combinatorial Catalysis of an Elimination Reaction. *J. Org. Chem.* **1998**, *63*, 7578−7579.

(4) Menger, F. M.; Fei, Z. X. Fast Amide Cleavage Under Mild Conditions: An Evolutionary Approach to Bioorganic Catalysis. *Angew. Chem., Int. Ed.* **1994**, *33*, 346−348.

(5) Chung, C. W. Y.; Toy, P. H. Multipolymer Reaction System for Selective Aerobic Alcohol Oxidation: Simultaneous Use of Multiple

Different Polymer-Supported Ligands. *J. Comb. Chem.* **2007**, *9*, 115–120.

(6) Nuyken, O.; Weberskirch, R.; Kotre, T.; Schönfelder, D. Polymers for Micellar Catalysis. *Polym. Mater. Org. Synth. Catal.* **2003**, 277–304.

(7) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function From a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

(8) Boyer, C.; Stenzel, M. H.; Davis, T. P. Building Nanostructures Using RAFT Polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 551–595.

(9) (a) Harvison, M. A.; Roth, P. J.; Davis, T. P.; Lowe, A. B. End Group Reactions of RAFT-Prepared (Co)Polymers. *Aust. J. Chem.* **2011**, *64*, 992–1006. (b) Willcock, H.; O'Reilly, R. K. End Group Removal and Modification of RAFT Polymers. *Polym. Chem.* **2010**, *1*, 149–157.

(10) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective Ligation of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles By Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(11) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. Organic Synthesis Inside Particles in Water: Lewis Acid-Surfactant-Combined Catalysts for Organic Reactions in Water Using Colloidal Dispersions as Reaction Media. *J. Am. Chem. Soc.* **2000**, *122*, 7202–7207.

(12) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. Catalyst-Free Conjugated Addition of Thiols to α,β-Unsaturated Carbonyl Compounds in Water. *Org. Lett.* **2006**, *8*, 2433–2436.

(13) Beletskaya, I. P.; Tarasenko, E. A.; Khokhlov, A. R.; Tyurin, V. S. Poly(*N*-Vinylimidazole) as Efficient and Recyclable Catalyst for the Addition of Thiols to Michael Acceptors in Aqueous Medium. *Russ. J. Org. Chem.* **2007**, *43*, 1733–1736.

(14) Gaggero, N.; Albanese, D. C. M.; Celentano, G.; Banfi, S.; Aresi, A. Stereoselective Thio-Michael Addition to Chalcones in Water Catalyzed By Bovine Serum Albumin. *Tetrahedron: Asymmetry* **2011**, *22*, 1231–1233.

(15) Azizi, N.; Saki, E.; Edrisi, M. Squaric Acid as an Impressive Organocatalyst for Michael Addition in Water. *C. R. Chim.* **2011**, *14*, 973–977.

(16) Hussain, S.; Bharadwaj, S. K.; Chaudhuri, M. K.; Kalita, H. Borax as an Efficient Metal-Free Catalyst for Hetero-Michael Reactions in an Aqueous Medium. *Eur. J. Org. Chem.* **2007**, *2007*, 374–378.

(17) Ranu, B. C.; Mandal, T. A Simple, Efficient, and Green Procedure for the 1,4-Addition of Thiols to Conjugated Alkenes and Alkynes Catalyzed By Sodium Acetate in Aqueous Medium. *Aust. J. Chem.* **2007**, *60*, 223–227.

(18) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. The Reaction of Nitroölefins With Indole. *J. Am. Chem. Soc.* **1955**, *77*, 456–457.

(19) (a) De Rosa, M.; Soriente, A. A Combination of Water and Microwave Irradiation Promotes the Catalyst-Free Addition of Pyrroles and Indoles to Nitroalkenes. *Tetrahedron* **2010**, *66*, 2981–2986. (b) Habib, P. M.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. Catalyst-Free Aqueous-Mediated Conjugative Addition of Indoles to B-Nitrostyrenes. *Tetrahedron Lett.* **2008**, *49*, 7005–7007.

(20) (a) Kumar, V. P.; Sridhar, R.; Srinivas, B.; Narender, M.; Rao, K. R. Friedel-Crafts Alkylation of Indoles With Nitroolefins in the Presence of Beta-Cyclodextrin in Water Under Neutral Conditions. *Can. J. Chem.* **2008**, *86*, 907–911. (b) Jafarpour, M.; Rezaeifard, A.; Aliabadi, M. Zirconium Tetrakis(Dodecylsulfate) as an Efficient and Recyclable Lewis Acid-Surfactant-combined Catalyzed C–C and C–N Bond Forming Under Mild and Environmentally Benign Conditions. *Lett. Org. Chem.* **2009**, *6*, 94–99.

(21) Xie, J. W.; Zhu, X. H.; Huang, M. N.; Meng, F.; Wang, M.; Wan, Y. Q. Sc(OTf)$_3$: A Highly Efficient and Renewable Catalyst for Michael Addition of Indoles to Nitroolefins in Water. *Synth. Commun.* **2010**, *40*, 3259–3267.

(22) Aryanasab, F.; Saidi, M. R. LiClO$_4$-Accelerated Three-Component Mannich-Type Reaction of Diethyl Malonate with Imines: An Efficient Synthesis of β-Amino Esters Under Solvent-Free Conditions. *Synth. Commun.* **2008**, *38*, 4036–4044.

(23) Huang, L.; Chen, J.-P.; Jin, C.; Su, W.-K. An Efficient Synthesis of 2,3-Diaryl-2-azabicyclo[2.2.2]octan-5-ones and Their Acetylcholinesterase Inhibitory Activity. *Chin. Chem. Lett.* **2013**, *24*, 347–350.