ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Interfacial Catalysis of Aldol Reactions by Prolinamide Surfactants in Reverse Micelles

Premkumar Rathinam Arivalagan and Yan Zhao*

Received
First published on the web
DOI: 10.1039/b000000x

L-Proline and their derivatives are one of the most important class of organic catalysts. Three prolinamide surfactants were designed and synthesized. Although the surfactants carried identical catalytic groups, their headgroups contained different functionalities that affected their ability to self-assemble under reverse micelle conditions and hydrogen-bond with the reactants. The surfactant with a zwitterionic headgroup capable of strong aggregation was found to have the highest activity. The self-association of the surfactants played critical roles in the enhanced activity. The location of the catalytic groups at the surfactant/polar solvent interface also endowed unusual selectivity in the aldol reactions catalyzed.

Introduction

Chemical reactions depend on not only inherent reactivity of the reactants but also their surrounding environments.[1] In the simplest case, a change of solvent can speed up a sluggish reaction, sometimes thousands of times or more. In biology, enzymes are powerful catalysts capable of promoting reactions that are otherwise impossible. Many times, not only the various functional groups in the active site play critical roles in the catalysis, the unique environment of the active site is also vital. In an effort to understand or mimic enzymatic catalysts, chemists have created molecular capsules to control both the reactivity and the selectivity of reactions.[2] Other promising platforms include dendrimers,[3] star polymers,[4] organic and metal-organic nanocapsules,[2] multifunctional mesoporous materials,[5] and metal-organic frameworks.[6]

Reverse micelles (RMs) are assemblies of surfactants in nonpolar solvents. A nanometer-sized pool of a polar solvent (often water) in the center of a RM solvates the headgroups of the surfactants to help them self-assemble into spherical structures typically.[7] Because the water molecules in the RM core differ from bulk water in many aspects, chemists have examined many reactions in RM solutions.[7-8] Another usage of RMs is in template synthesis of inorganic nanomaterials.[9] Metal salts can be dissolved in the water pools of RMs, followed by desired chemical reactions that are modulated by the surfactant assemblies. Alternatively, inorganic precursors such as tetraethoxysilane can be dissolved in the organic phase and subsequently undergo sol–gel reactions to afford the final inorganic materials.

Our group has a long interest in the environmental control of catalysts. Amphiphilic baskets,[10] foldamers,[11] surface-cross-linked micelles,[12] and interfacially cross-linked reverse micelles[13] have been used to tune the polarity and other properties of the local environments around catalysts to influence their activity and selectivity. In this work, we synthesized several L-prolinamide-derived surfactants and examined their catalysis of aldol reactions in the RM configuration. The catalytic groups located at the surfactant/polar solvent interface were found to have unusual activity and selectivity. The surfactant with the strongest aggregation was the best catalyst, suggesting that the self-assembling of the surfactants was directly responsible for the enhanced catalytic activity.

Results and discussion

Catalyst Design and Synthesis

L-Proline and their derivatives are one of the most important class of organic catalysts. Having both an acid and a base catalytic group, proline can catalyze a number of important reactions including aldol, Mannich, and Michael reactions.[14] Its carboxylic acid is crucial to the catalysis. Converting the carboxyl into amide lowers its catalytic activity for aldol reactions[15] but, with a higher concentration of reactants (e.g., 0.5 M 4-nitrobenzaldehyde in neat acetone), prolinamides could catalyze aldol reactions effectively. Excellent ee could be obtained with prolinamides carrying vicinal hydrogen-bonding groups such as hydroxyl.[16]

Chemists have studied proline-catalyzed aldol reactions in surfactant assemblies very early on, interested in whether the surfactant phases could provide special benefits.[17] Although L-proline itself is catalytically ineffective in water, its derivatives with micelle-forming hydrophobic tails work well.[18] Polymeric micelles similarly were found to promote the reaction.[19] However, to our knowledge, proline-derived catalysts in the RM configuration, particularly at the interface of surfactant/polar solvent, have not been studied. Because reactivity at the interface can be profoundly different from that in a bulk solution, we decided to synthesize surfactants with proline-derived headgroups so that their organization will place

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111, USA. Fax: +1-515-294-0105; Tel: +1-515-294-5845; E-mail: zhaoy@iastate.edu

† Electronic Supplementary Information (ESI) available: syntheses of compounds. See http://dx.doi.org/10.1039/b000000x/

the proline group at the surfactant/polar solvent interface.

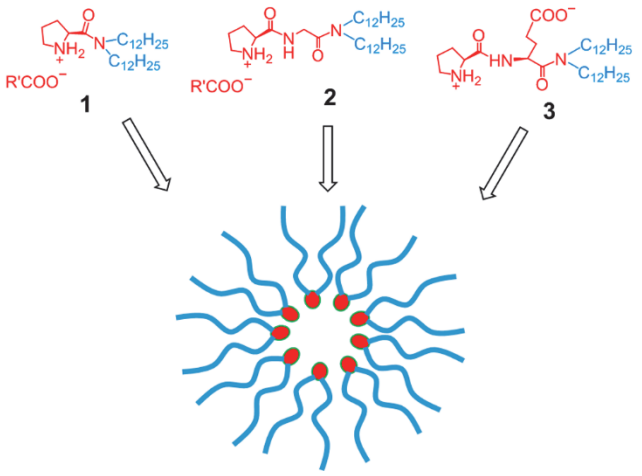
Three amphiphiles (**1**–**3**) were synthesized for this purpose, all with two dodecyl tails, resembling the common RM-forming surfactant AOT.[7] Self-assembly of a surfactant strongly depends on its critical packing parameter ($Q = v/a_0 l_c$), in which v is the volume of the hydrophobic tail, a_0 the area of the hydrophilic headgroup, and l_c the average critical length of the amphiphile.[20] Two long hydrocarbon chains in **1**–**3** increase their hydrophobic volume and make them pack more easily in the RM configuration. (The long tails are also important to the solubility of the catalysts in nonpolar solvents.)

Surfactant **1** was prepared by coupling the carboxylic acid group of L-proline to didodecylamine. The synthesis involved standard protection/deprotection chemistry, with the amino group of proline protected by Boc initially and deprotected using trifluoroacetic acid after amide coupling. For the catalysis, the surfactant was used as an ammonium salt, with either acetate or benzoate as the counterion. Surfactants **2** and **3** were synthesized similarly, with **2** having a glycine and **3** having a glutamate in between proline and the didodecyl amide.

All three surfactants share the L-prolinamide catalytic functionality. Their difference lies in the potential hydrogen-bonding and electrostatic interactions among the headgroups of the surfactants. Whereas both **1** and **2** have the ammonium and carboxylate (acetate or benzoate) as counterions, surfactant **3** is a zwitterion with the counteranion in the same molecule. Unlike surfactant **1** that has a tertiary amide in the headgroup, surfactants **2** and **3** have secondary amides in the headgroup. For the latter two, the abundance of hydrogen-bond donors and acceptors in the headgroup should provide additional driving force (in addition to solvation or hydrophobic effect) to the self-assembly of the surfactants in nonpolar solvents.[21]

Aldol reactions catalyzed by prolinamide surfactants

Aldol reactions catalyzed by proline and their derivatives are typically performed in DMSO or DMF. Nonpolar solvents such as benzene are rarely used possibly due to insolubility of the catalysts. To perform the reactions under RM conditions, however, we need a small amount of a polar solvent such as water or DMSO in a largely nonpolar mixture.[7] The polar solvent molecules solvate the headgroups of the surfactants to assist their self-assembly, with the hydrophobic tails point outward to be compatible with the nonpolar environment (Scheme 1).



Scheme 1 Structures of prolinamide surfactants and schematic representation of their aggregation in a nonpolar solvent.

To our delight, all three surfactants were readily soluble in benzene with the help of a tiny amount of polar solvent (e.g., w_0 = [DSMO or water]/[surfactant] = 5). The solution was completely transparent, suggesting any aggregates formed must be small enough not to cause significant scattering of visible light.

Our model aldol reaction was between acetone and *p*-nitrobenzaldehyde. The reaction is commonly used by researchers in proline-catalyzed reactions.[14–16] As will be shown below, another benefit of the reactant pair is that the simplicity of their ^{1}H NMR peaks makes it straightforward to monitor the reaction progress. In the literature, a high concentration of *p*-nitrobenzaldehyde (e.g., 0.5 M) and a large excess of ketone (sometimes using the ketone as the solvent) are often used in prolinamide-catalyzed aldol reactions,[16] due to the low activity of prolinamide in comparison to proline. In our case, the concentration of the aldehyde was 70 mM and a ratio of [acetone]/[*p*-nitrobenzaldehyde] ≈ 12/1 was employed. The catalyst was used at 10 mol % to the aldehyde, which is also lower than many literature examples.

We did not use a huge amount of acetone for two primary reasons. First, acetone is quite polar; a large amount of it could disrupt the self-assembly of the surfactants. Second, this study was mainly aimed to identify whether catalytic groups located at the surfactant/polar solvent interface could behave differently from those in the homogeneous solution. Since the three surfactants have identical catalytic groups, we wanted to put the catalysts under challenging conditions to see their differences. A large excess of acetone (as in typical literature reactions) might overshadow the subtle differences in the catalysts' activity.

The solubility of the surfactants in deuterated DMSO/benzene mixture at w_0 = 5 allowed us to monitor the reactions by ^{1}H NMR spectroscopy. Figure 1 showed the progress of the aldol reaction catalyzed by surfactant **1** and **3**. (Kinetics for surfactant **2** was intermediate between those of **1** and **3** and thus not shown.) Despite the identical catalytic functionality, the three surfactants behaved very differently. Surfactant **1** showed negligible activity under our reaction condition; the product peaks (H_c and H_d) were barely visible even at the end. With **3**, however, the product peaks quickly became major after several hours at room temperature. The activity was quite high, considering the low concentrations of the reactants and (anticipated) low activity of typical prolinamides.[16]

An internal standard added (i.e., bistrimethylsilylethane) allowed us to quantify the amount of product formed by integration. Figure 2 shows the yields of the three reactions as a function of time. Because the reaction was performed under pseudo-first-order conditions, good linearity was observed over

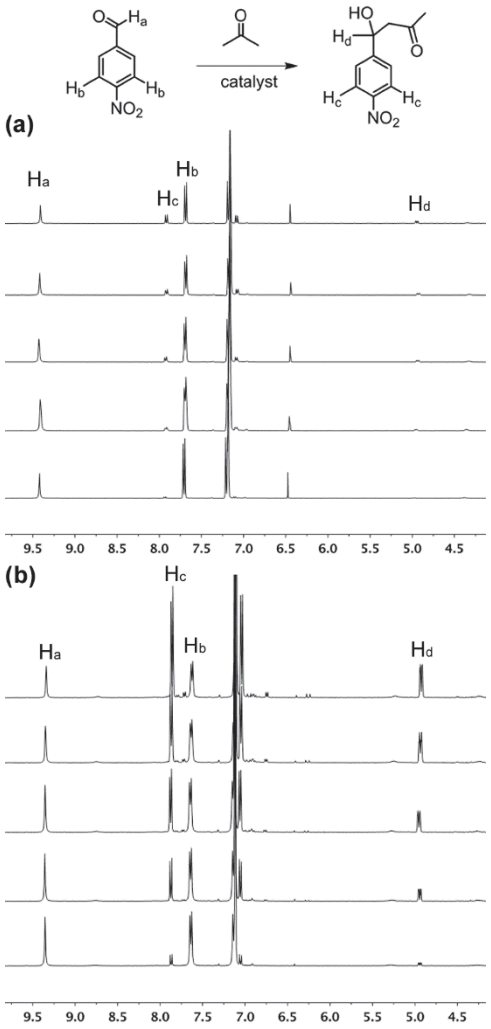


Fig. 1 ^{1}H NMR spectra of the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by **1** (a) and **3** (b) in DMSO-d_6/benzene-d_6 at ambient temperature. Reaction conditions: *p*-nitrobenzaldehyde (0.07 mmol), acetone (0.86 mmol), catalyst (0.007 mmol), benzene-d_6 (1.0 mL), DMSO-d_6 (2.0 μL). The spectra from bottom to top were taken at 0, 45, 100, 145 and 205 for catalysts **1** and at 10, 60, 100, 145 and 190 for catalyst **3**.

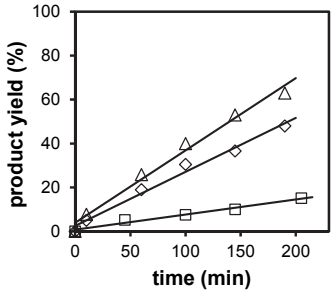


Fig. 2 Reaction yields of the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by **1** (□), **2** (◇), and **3** (△) in DMSO-d_6/benzene-d_6 at ambient temperature. Reaction conditions: *p*-nitrobenzaldehyde (0.07 mmol), acetone (0.86 mmol), catalyst (0.007 mmol), benzene-d_6 (1.0 mL), DMSO-d_6 (2.0 μL).

much of the course of the reaction. These curves clearly show catalyst **3** as the most active and **1** as the least active catalyst.

Surfactant **2** was significantly more efficient than **1** as a catalyst for the aldol reaction. Thus, the extra glycine must have helped the catalysis, directly or indirectly. The reason for the higher activity of **2** could be mechanistic. It is known that aldol reactions catalyzed by prolinamides go through an enamine intermediate and the hydrogen bond between the amide proton and the aldehyde is important to the reactivity and enantioselectivity of the reaction.[14] Since catalyst **1** had no amide proton being a tertiary amide, the higher activity of **2** could just be normal.

Prolinamide **3** was more active than **2**. Even though the difference in their reaction rates in Figure 2 was not huge, the results suggest that having the carboxylate in the same molecule instead of as a counteranion is beneficial. To further understand the differences in these catalysts and identify the cause for their different activity, we performed our model aldol condensation under a number of different conditions. For these studies, we generally let the reaction proceed at ambient temperature for 9 h and used the product yield as a measure for the efficiency of a catalyst.

The results were illuminating. As shown in Table 1 (entries 1–2 and 4–5), the change of the counterion from acetate to benzoate in the case of **1** and **2** increased the catalytic activity slightly when the reaction was performed in DMSO/benzene at w_0 = 5. Regardless of the counteranion, **1** and **2** had lower activity than zwitterionic **3** (entry 3). Without the prolinamide surfactants, the reaction did not occur at all, as we had anticipated (entry 6).

Table 1. Reaction yields at 9 h for the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by the prolinamide surfactants under different conditions.[a]

entry	solvent composition	catalyst	counterion	yield
1	w_0 = 5 (DMSO)[b]	**1**	acetate	18
2	w_0 = 5 (DMSO)[b]	**2**	acetate	72
3	w_0 = 5 (DMSO)[b]	**3**	none	88
4	w_0 = 5 (DMSO)[b]	**1**	benzoate	33
5	w_0 = 5 (DMSO)[b]	**2**	benzoate	78
6	w_0 = 5 (DMSO)[b]	none	none	0
7	w_0 = 5 (water)[c]	**1**	benzoate	20
8	w_0 = 5 (water)[c]	**2**	benzoate	33
9	w_0 = 5 (water)[c]	**3**	none	78
10	DMSO/benzene = 1:9	**1**	benzoate	0
11	DMSO/benzene = 1:9	**2**	benzoate	0
12	DMSO/benzene = 1:9	**3**	none	20
13	DMSO/benzene = 9:1	**3**	none	0
14	benzene (no DMSO)	**3**	none	85

[a] Reaction conditions: catalyst (0.007 mmol), *p*-nitrobenzaldehyde (0.07 mmol), acetone (0.86 mmol). [b] Solvent = 2.0 μL DMSO + 1.0 mL benzene. [c] Solvent = 0.5 μL water + 1.0 mL benzene.

A small amount of water in the proline-catalyzed aldol reaction is known to help the reactivity but a large amount of water is detrimental.[14] Since, under the RM conditions (i.e., DMSO/benzene at w_0 = 5), the polar solvent should be concentrated near the headgroups of the surfactants in the nonpolar solvent, we were interested to know whether replacing DMSO with water would affect the activity to any significant degree. It is possible that the high local concentration of the polar solvent could "magnify" the solvent effect near the catalytic headgroups. Indeed, as shown in entries 7–9 of Table 1, the product yields decreased for all three catalysts: from 33 to 20% for **1**, from 78 to 33% for **2**, and from 88 to 78% for **3**. As far as "water resistance" is concerned, it seems prolinamide **3** was the most robust among the three.

DMSO is often the preferred solvent for proline- or prolinamide-catalyzed aldol reactions.[14] The conventional thinking, thus, predicts that an increase in DMSO in our reaction mixture at least should not cause problems. On the other hand, if the formation of RM or similarly aggregated states (vide infra) for the catalytic surfactants is important to the observed activity, then the addition of the polar solvent (DMSO) would destabilize the aggregates and reduce the catalytic activity as a result.[22]

The latter turned out to be true. When the amount of DMSO was increased from 2.0 μL (i.e., w_0 = 5) to 100 μL (i.e., DMSO/benzene = 1/9), catalysts **1** and **2** became completely inactive (entries 10 and 11) and catalyst **3** lost significant activity, with the yield going down from 88% (entry 3) to 20% (entry 12). A further increase of DMSO to DMSO/benzene = 9/1 shut down the activity of **3** entirely (entry 13).

We also found that the polar solvent DMSO was not necessary for the enhanced activity. Without any DMSO, catalyst **3** afforded 85% of the aldol product (entry 14). The yield was experimentally the same as what was observed at w_0 = 5 (entry 3). The results indicate that DMSO itself was not playing any particular roles in the reaction and most likely it was the aggregation of the surfactants that was responsible for the enhanced activity.[23] The postulation is supported by the work of Escuder, Maravet, and co-workers, who demonstrated a bisprolinamide derivative was far more catalytically active for the Henry nitroaldol reaction in the gel state than in solution.[24] The authors attributed the enhanced activity (in the gel) to the higher basicity of the proline amine in the aggregates. It is likely that a similar mechanism was enhancing the catalytic efficiency in our case. The electrostatic and hydrogen-bonding interactions among the headgroups should be the strongest in the zwitterionic **3**, making the surfactant most capable of aggregating and its amine the most basic.

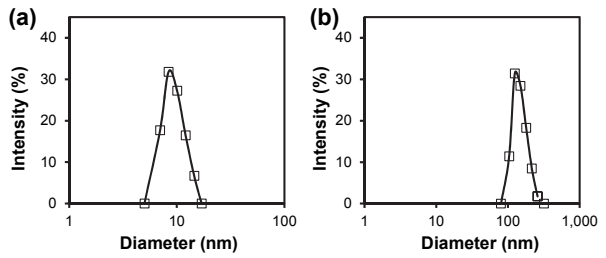


Fig. 3 Dynamic light scattering by the aggregates of **3** in (a) DMSO/heptane and (b) DMSO/benzene at w_0 = [DSMO]/[surfactant] = 5.

Dynamic light scattering (DLS) could detect surfactant aggregates easily while an individual surfactant is generally too small to be observed. To understand the aggregation of these prolinamide surfactants, we first used heptane instead of benzene as the nonpolar solvent because its nonpolarity facilitates the RM formation.[7] The amount of DMSO was chosen to be w_0 = 5, exactly as that in our typical reactions. DLS under this condition gave poor correlation curves for surfactant **1** and **2** and no stable particles were observed. In contrast, surfactant **3** gave nanoparticles ca. 10 nm in diameter (Figure 3a), reasonable in size for typical RMs.[7] Changing the nonpolar solvent from heptane to benzene (i.e., the reaction solvent system) is expected to make RM formation more difficult. This is because, the miscibility of DMSO and benzene would make phase separation of DMSO into the central core of a RM more costly in free energy. Indeed, instead of small-sized RMs, larger particles ca. 150 nm in size were observed by DLS (Figure 3b). In 1:9 DMSO/benzene, where the activity of the catalyst was severely compromised (Table 1, entry 12), no stable particles could be identified by DLS. In benzene alone, surfactant **3** did aggregate to afford large aggregates > 500 nm in size.

The DLS study thus confirmed surfactant **3** as the one having the strongest aggregation propensity in nonpolar-dominant solvents. The aggregates apparently do not need to be exactly RMs, as the (aggregated) surfactant in benzene (Table 1, entry 14) and in DMSO/benzene at w_0 = 5 (Table 1, entry 3; Figure 3b) both showed good activity.

In addition to catalytic activity, we were interested in the effects of aggregation on other properties such as enantiomeric and substrate selectivity. Chiral HPLC showed low ee for these surfactants (~15%). The number was comparable to those reported for unactivated prolinamides in the literature.[16b] Thus, no special effects were exerted by the aggregation on the enantioselectivity of the catalysts.

On the other hand, interesting substrate selectivity was clearly observed for surfactant **3**, our best catalyst (Table 2). Acetone, cyclopentanone, and cyclohexanone were all reactive, with subtle differences in reactivity. The anti/syn ratio of the products was 25/75 and 76/24 for cyclopentanone and cyclohexanone, respectively. These numbers were comparable to those reported in the literature for other prolinamide catalysts.[25] Thus, neither enantio- nor diastereoselectivty of the reaction was significantly affected by the aggregation.[26] Cycloheptanone and the acyclic 3-pentanone were completely unreactive under the typical reaction conditions (i.e., DMSO in benzene at w_0 = 5). It is not completely clear why such a dramatic substrate effect was present. We suspect that it derives from the location of the catalytic groups at the surfactant/polar solvent interface. Both the initial iminium ion and the enamine

intermediates between the ketone and the proline amine need to be formed on the surfactant headgroup in our case. It is possible that the stability of these intermediates may be quite sensitive to the size, hydrophobicity, and/or flexibility of the substrate in the tight space around the aggregated headgroups.

Table 2. Reaction yields at 9 h for the aldol reaction between different ketones and *p*-nitrobenzaldehyde catalyzed by surfactant **3** under reverse micelle conditions.[a]

entry	ketone	catalyst	counterion	yield
1	acetone	**3**	none	88
2	cyclopentanone	**3**	none	>95[b]
3	cyclohexanone	**3**	none	75[c]
4	cycloheptanone	**3**	none	0
5	3-pentanone	**3**	none	0

[a] Reaction conditions: catalyst (0.007 mmol), *p*-nitrobenzaldehyde (0.07 mmol), acetone (0.86 mmol), benzene-d_6 (1.0 mL), DMSO-d_6 (2.0 μL). [b] The anti/syn ratio was determined by ^{1}H NMR spectroscopy to be 25/75. [c] The anti/syn ratio was determined by ^{1}H NMR spectroscopy to be 76/24.

Conclusions

Aggregation of prolinamide surfactants enhanced their catalytic activity dramatically and allowed the reaction to proceed in nonpolar solvents such as benzene (with or without a small amount of DMSO). The observed catalytic activity correlated with the aggregation propensity of the surfactants in DMSO/benzene mixtures. Traditionally, chemists improve the performance of catalysts by manipulating their structures directly, whether the active metal center or the organic catalytic functionality. Nature frequently employs a different approach, by controlling the microenvironment of the catalysts. This work demonstrates that even relatively simple aggregation could enhance the activity of prolinamide dramatically and unusual selectivity could be obtained at the same time. Chemists have already recognized the importance of environmental control on the catalysis. As shown by others[1-2, 27] and our recent work,[10–13] there are numerous ways to manipulate the microenvironment around a catalyst and the effect can be profound. We believe that, as chemists further develop their skills in the environmental control in catalysis, unusual reactivity and selectivity seen in enzymatic catalysis can also be realized with synthetic systems.

Experimental

General

All reagents and solvents were of ACS-certified grade or higher and used as received from commercial suppliers. Routine ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or on a Varian VXR-400 spectrometer. HR-MS mass was recorded on Shimadzu LCMS-2010 mass spectrometer. Dynamic light scattering (DLS) was performed on a PD2000DLS+ dynamic light scattering detector. Syntheses of the compounds are reported in the Electronic Supplementary Information (ESI).

General procedure for the aldol reaction under RM conditions

DMSO (2.0 μL) was added to a solution of the appropriate prolinamide catalyst (0.007 mmol) in deuterated benzene (1.0 mL) in a vial. The mixture was ultrasonicated until a clear solution was obtained. Bistrimethylsilylethane (10 μL) was added as an internal standard, followed by *p*-nitrobenzaldehyde (10 mg, 0.07 mmol) and acetone (50 μL, 0.86 mmol). The mixture was then transferred to a NMR tube and the reaction was monitored by ^{1}H NMR spectroscopy.

Acknowledgments

We thank the NSF (CHE-1303764) for supporting this research.

Notes and references

[a] *Department of Chemistry, Iowa State University, Ames, Iowa 50011, USA. Fax: +1-515-294-0105; Tel: +1-515-294-5845; E-mail: zhaoy@iastate.edu*

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