Study on guanidine-based task-specific ionic liquids as catalysts for direct aldol reactions without solvent†

Anlian Zhu, Tao Jiang,* Buxing Han,* Jun Huang, Jicheng Zhang and Xiumin Ma

Received (in Montpellier, France) 9th January 2006, Accepted 3rd March 2006
First published as an Advance Article on the web 16th March 2006
DOI: 10.1039/b600277c

In this work, the effect of the anions of tetramethylguanidine-based ionic liquids on the catalytic activity in direct aldol reactions was studied. In solvent-free conditions at room temperature, [TMG][Ac] (1,1,3,3-tetramethylguanidinium acetate) was found to have the highest activity among the ionic liquids including [TMG][Pr] (1,1,3,3-tetramethylguanidinium propionate), [TMG][*n*-Bu] (1,1,3,3-tetramethylguanidinium *n*-butyrate), [TMG][*i*-Bu] (1,1,3,3-tetramethylguanidinium isobutyrate), [TMG][Lac] (1,1,3,3-tetramethylguanidinium lactate) and [TMG][TFA] (1,1,3,3-tetramethylguanidinium trifluoroacetate). On the basis of this preliminary result, a series of direct aldol reactions was performed using [TMG][Ac] as the catalyst, and satisfactory results with high yields and good chemo- and regioselectivity were obtained. From combination of the reaction results with UV–Vis spectroscopy studies, it was deduced that the reactions proceeded through an enamine intermediate. The anion effect was believed to operate though its interaction with the cation and the special structure of the enamine based on tetramethylguanidine may be the reason for the unusual regioselectivity, which is different from that of aldol reactions catalyzed by proline and its derivatives in organic solvents.

1. Introduction

Aldol reactions are very powerful C–C bond forming reactions and the products are important reaction intermediates in organic synthesis. These reactions have been studied extensively.[1,2] Classical aldol reactions are highly atom efficient but suffer from poor selectivity. Stoichiometric or larger amounts of reagents such as trimethylchlorosilane (TMSCl) have been introduced into aldol reactions in the presence of a Lewis acid (Mukaiyama aldol reaction) in order to overcome limitations in the scope and improve the selectivity of these catalytic reactions.[3] However, these methods to some extent reduce the atom efficiency of aldol reactions and at the same time produce a great deal of waste. In recent years, green methods for aldol reactions have been developed mainly by a return to the direct catalytic procedures in searching for higher selectivity and atom efficiency, and in a number of instances they may open up routes for highly efficient and environmentally friendly C–C bond forming processes.[4] However, the reaction rate is still very low for some ketones such as butanone and cyclopentanone, which have high steric hindrance, and will need one to two days to get moderate yields.[5] Most of the direct aldol reactions are proved to proceed through an enamine or enolate intermediate based on multiple-step acid–base catalysis with proline or diamine together with an acid additive as a superior bifunctional catalyst system.[6]

Ionic liquids (ILs) are organic salts and have been extensively investigated in organic synthesis;[7] they possess many different properties compared with traditional organic solvents. Ionic liquids have also been introduced into direct aldol reactions mainly as green solvents to replace organic solvents such as DMF or DMSO.[8,9] In recent years, a great number of task-specific functional ionic liquids were synthesized for different purposes.[10] 1,1,3,3-Tetramethylguanidine-based (TMG) ionic liquid synthesized in our previous work through simple neutralizing of equimolar TMG with acids[10*b*] has been found to be useful in preparing an immobilized catalyst for hydrogenation of olefins[11] and absorbing SO_2 from simulated flue gases.[12] Both of these uses are based on the electron lone pair of the guanidine cation. Recently, we reported a green method for direct aldol reactions catalyzed by [TMG][Lac] (1,1,3,3-tetramethylguanidinium lactate) at room temperature without solvents.[13] However, the reaction mechanism is still not clear and ketones having higher steric hindrance still suffer from low conversions even though good chemo- and regioselectivities have been obtained. We know that ionic liquids have been called "designer solvents" because their properties can be easily tailored through changing the anions or cations, but the relationship between the structure and the properties, especially their effects on reactions, have not been well studied.[14]

As a continuation of our work in the direct aldol reaction and applications of ILs, we synthesized a series of basic ILs and studied the effects of anions of ILs on their catalytic performance in these reactions. Herein we wish to report our progress. The results showed that the anions significantly affect the catalytic properties of ILs. A reaction mechanism based on an enamine was suggested and, from the viewpoint of

---

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100080, China. E-mail: Jiangt@iccas.ac.cn; Hanbx@iccas.ac.cn; Fax: +86-10-62562821

† Electronic supplementary information (ESI) available: ^{1}H-NMR data for compounds in Table 2. See DOI: 10.1039/b600277c

intermolecular interactions, the difference in catalytic activity of the ILs was interpreted. The special structure of the enamine based on tetramethylguanidine was thought to be the origin of the special regioselectivity.

2. Experimental

The ionic liquids were prepared by neutralizing 1,1,3,3-tetramethylguanidine and the corresponding acids in ethanol according to the literature procedures.[10b] The other starting materials (A. R. grade) were purchased from Beijing Chemical Reagents Company. The solid aldehydes were recrystallized from a mixture of ethanol and water. Acetone was distilled after being dried over anhydrous $CaSO_4$ overnight. Other chemicals were used as received. ^{1}H-NMR spectra of aldol products were recorded as solutions in $CDCl_3$ at room temperature on a Bruker spectrometer at 300 MHz (the NMR data are available as ESI†).

Typical procedures for direct aldol reactions catalyzed by ionic liquids

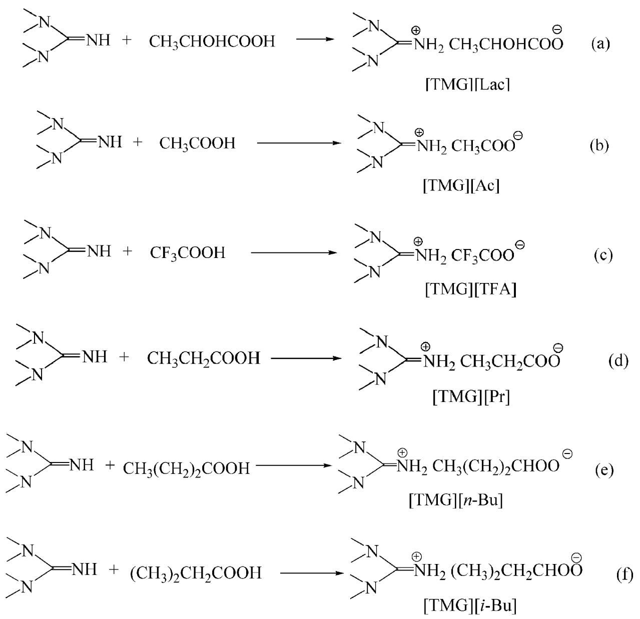
1 mmol aldehyde, 0.3 mmol ionic liquid, and 20 mmol ketone were mixed in a flask and stirred for the desired time at room temperature. The reactions were monitored by TLC. At the end of the reaction, diethyl ether was added to the reaction mixture to extract the products. The crude hydroxyl ketone obtained from diethyl ether was purified by flash chromatography on silica gel (eluent: ethyl acetate–petroleum ether). The product and the *syn* : *anti* ratio were analyzed by ^{1}H-NMR spectroscopy.

UV–Vis experiments

Mixtures of the ionic liquids and cyclopentanone were prepared by mass on the same molar ratio as in the reaction mixtures (~1 : 66). The mixtures were stirred using a magnetic stirrer at room temperature for 24 h to reach equilibrium. The UV–Vis spectra were recorded using a TU-1021 UV–Vis spectrometer produced by Beijing Instrument Company (the wavenumber accuracy is ±0.5 nm). Cyclopentanone was chosen as the blank.

3. Results and discussion

Six ionic liquids based on tetramethylguanidine (Scheme 1) were used to catalyze aldol reactions of 4-nitrobenzaldehyde with cyclopentanone and 2-butanone. The results are listed in Table 1. The reaction of 4-nitrobenzaldehyde with cyclopentanone catalyzed by [TMG][Ac] can be completed in two hours. The isolated yield of the target aldol adducts is 85% (Entry 2) because a by-product was produced. Mass spectroscopy (ESI) measurement showed that the molecular weight of the by-product was 386.14, indicating that the by-product was an adduct of two 4-nitrobenzaldehyde molecules with one cyclopentanone molecule. In our previous work, the same reaction catalyzed by [TMG][Lac] could achieve 96% yield for the target aldol adducts in a prolonged reaction time of about 24 h (Entry 1). The reactions catalyzed by [TMG][Pr], [TMG][*n*-Bu], or [TMG][*i*-Bu] were little slower than that catalyzed by [TMG][Ac] and more by-products were produced (Entries 3–5). The reaction catalyzed by [TMG][TFA] was the most sluggish, and the total conversion of the reaction is less than 50% even after five days (Entry 6).



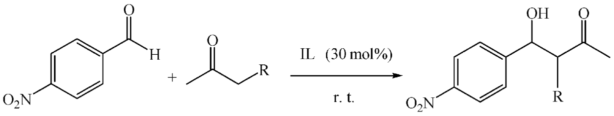
Scheme 1 Synthesis of the 1,1,3,3-tetramethylguanidine-based ionic liquids.

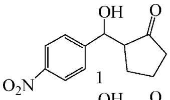
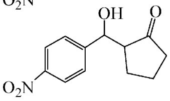
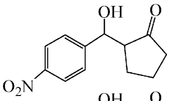
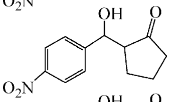
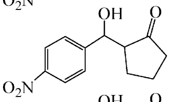
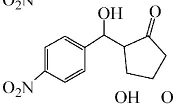
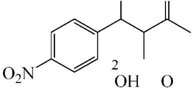
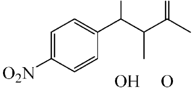
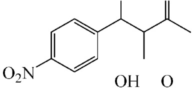
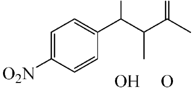
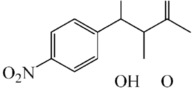
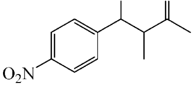
For the reaction of 4-nitrobenzaldehyde with 2-butanone using [TMG][Ac] as the catalyst, the isolated yield can reach 92% in 24 h (Entry 8), which is much superior to 25% yields in 72 h using [TMG][Lac] as the catalyst (Entry 7).[13] The isolated yields of the reactions catalyzed by [TMG][Pr], [TMG][*n*-Bu], or [TMG][*i*-Bu] (Entries 9–11) can also exceed 90% with a prolonged reaction time. But the reaction catalyzed by [TMG][TFA] can only proceed to less than 10% after five days (Entry 12). We have also found that all reactions of 4-nitrobenzaldehyde with 2-butanone catalyzed by all six ionic liquids give the same regioselectivity at methylene, which is the same as in the antibody-mediated aldol addition[15] but quite different from direct aldol reactions catalyzed by proline and its derivatives in organic solvents.[16] Barbas and coworkers[17] have also developed a direct aldol reaction in buffered aqueous media catalyzed by cyclic secondary amines, but can only achieve moderate regioselectivity at methylene with equivalent yield.

The above results indicate that [TMG][Ac] has the highest catalytic activity for the direct aldol reactions among the six ionic liquids, and the six ionic liquid catalyzed reactions have the same excellent regioselectivity at methylene. Therefore, we conducted a series of aldol reactions using [TMG][Ac] and the successful results are collected in Table 2. All of the reactions involving electron deficient aromatic aldehydes can be carried out and completed in shorter times and comparable or even better yields compared with the corresponding reactions catalyzed by [TMG][Lac] in our previous work. However the reactions cannot occur when benzaldehyde or an aliphatic aldehyde were used as the acceptor.

For the reactions of 4-nitrobenzaldehyde with acetone, cyclohexanone and acetophenone (Entries 1, 3, 4), good yields can be obtained in less than 7 h while 24 h were required when [TMG][Lac] was used as the catalyst. For those ketones with

Table 1 Direct aldol reaction of 4-nitrobenzaldehyde with cyclopentanone or 2-butanone catalyzed by the six different ionic liquids



Entry	Ketones	Ionic liquids	Products	Reaction time/h	Yield (%) (*syn*/*anti*)
1	Cyclopentanone	[TMG][Lac]	 1	24	96[a] (68/32)[b]
2	Cyclopentanone	[TMG][Ac]		2	85 (75/25)[b]
3	Cyclopentanone	[TMG][Pr]		3	74 (71/29)[b]
4	Cyclopentanone	[TMG][*n*-Bu]		3.5	68 (72/28)[b]
5	Cyclopentanone	[TMG][*i*-Bu]		4	65 (70/30)[b]
6	Cyclopentanone	[TMG][TFA]		120	$<$50 (65/35)[b]
7	2-Butanone	[TMG][Lac]	 2	72	25[a] (68/32)[b]
8	2-Butanone	[TMG][Ac]		24	92 (63/37)[b]
9	2-Butanone	[TMG][PrA]		36	92 (65/35)[b]
10	2-Butanone	[TMG][*n*-BuA]		36	92 (53/47)[b]
11	2-Butanone	[TMG][*i*-BuA]		48	90 (63/37)[b]
12	2-Butanone	[TMG][TFA]		120	$<$10 (not detected)

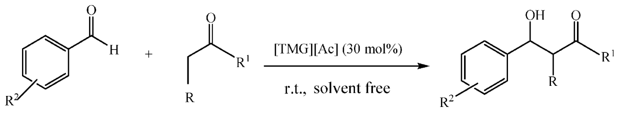
[a] Ref. 13. [b] Determined by ^{1}H-NMR.

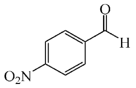
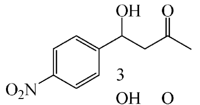
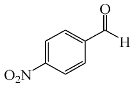
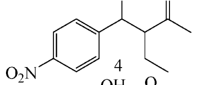
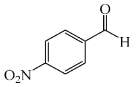
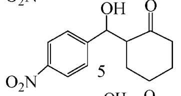
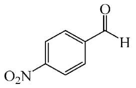
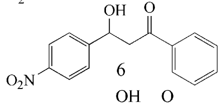
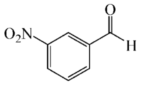
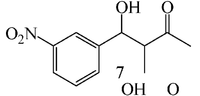
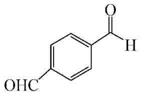
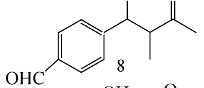
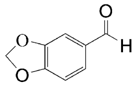
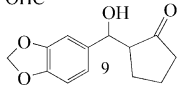
non-equivalent α-hydrogens, the regioselectivity was further studied using the reaction of 4-nitrobenzaldehyde with 2-pentanone (Entry 2), 3-nitrobenzaldehyde with 2-butanone (Entry 5), and terephthalic aldehyde with 2-butanone (Entry 6). The same regioselectivity and high yields can be obtained for all of the three reactions. Moreover, when terephthalic aldehyde was used, the reaction had good chemoselectivity and only one product illustrated in Entry 6 was produced in good yield, leaving the other aldehyde group unreacted. For the reaction of heliotropin with cyclopentanone (Entry 7), the sole product was obtained with good selectivity but the same reaction does not occur using [TMG][Lac] or [TMG][TFA] as the catalyst.

The other important selectivity for the reactions of ketones possessing an alkyl-substituted group at the α-position is *syn*/*anti* diastereoselectivity. As shown in Tables 1 and 2, the corresponding aldol adducts are more *syn*-diastereoselective when the present six ILs are used as catalysts, which suggests that perhaps the same transition state exists in the reactions for different ILs with the same cations.

As for the reaction mechanism, we believe that all of the aldol reactions catalyzed by the six tetramethylguanidine-based ILs followed the same reaction mechanism because they possess the same chemo-, regio- and diastereoselectivity, perhaps proceeding through a thermodynamically-controlled process with enamine as an intermediate. To get evidence for

Table 2 The direct aldol reactions catalyzed by [TMG] [Ac]



Entry	Aldehyde	Ketone	Product	Time/h	Yields (%) (*syn*/*anti*)
1		Acetone	 3	7	92
2		2-Pentanone	 4	36	75 (60/40)
3		Cyclohexanone	 5	6	85 (65/35)
4		Acetophenone	 6	6	92
5		2-Butanone	 7	24	90 (58/42)
6		2-Butanone	 8	24	90 (64/36)
7		Cyclopentanone	 9	48	60 (65/35)

our hypothesis, a UV–Vis method was used to detect the new conjugate system based on guanidine and enamine (the wavelength of the maximum absorbance of the ionic liquids in *n*-hexane is about 220 nm). We found that there were new maximum absorbances at a wavelength of about 346 nm after cyclopentanone was mixed with the six ionic liquids (Fig. 1) separately at room temperature, which was believed to be the conjugated absorbance of the tetramethylguanidine and the enamine double bonds, suggesting that all six ionic liquids can form the same intermediates.

When the regioselectivity of asymmetric ketones such as 2-butanone was considered, the enamine double bond and the guanidine double bond must be inclined to adopt an (*E*)-configuration in order to minimize 1,3-diolefin strain. The possible structures for the enamine of 2-butanone are illustrated in Scheme 2. There is no doubt that the structure "b" has higher steric energy due to higher hindrance, so structure "a" is the more stable intermediate for the enamine, which perhaps indicates why the regioselectivity is at the much more substituted α-hydrogen. In Scheme 3, we illustrate a possible process for how a direct aldol reaction is performed using 2-butanone as a model.

It has been suggested by Saito and Yamamoto that reactions catalyzed by proline and diamine with acid additives showed a higher catalytic activity through the electronic tuning of the acid function.[16b] In this work, we believe that the difference in catalytic activity for the six ILs with different anions might also come from the effect of the anions on the

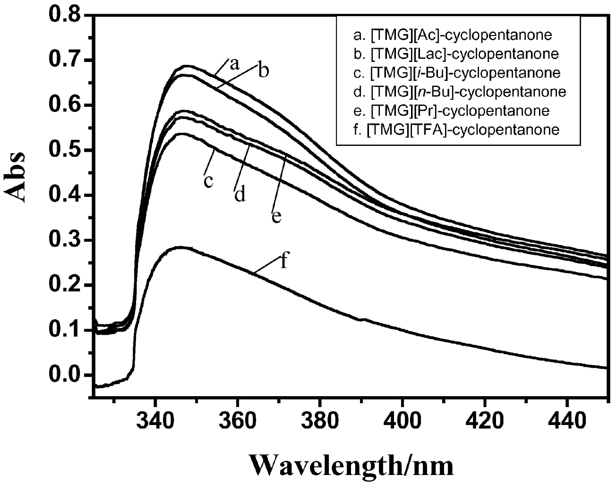
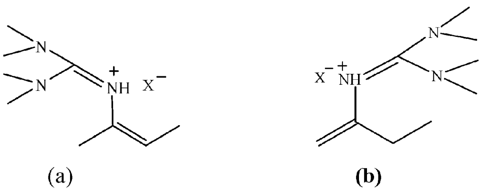
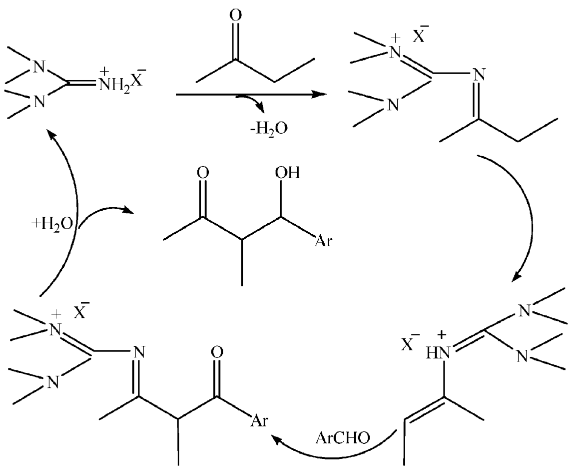


Fig. 1 The UV–Vis spectroscopy of the six ionic liquids mixed with cyclopentanone using cyclopentanone as the blank.



Scheme 2 The possible structure for the enamine intermediate.



Scheme 3 The possible reaction mechanism for the aldol reaction catalyzed by 1,1,3,3-tetramethylguanidine-based ionic liquids.

electronic distribution of the cations; and the difference in electronic distribution of the cations might then lead to the different intensity of interactions between the cation and the substrates. From the UV–Vis spectra for the six ILs mixed with cyclopentanone, we can see that following the sequence of [TMG][Ac], [TMG][Lac] to [TMG][TFA] (Fig. 1), the intensity of the conjugated maximum absorbance decreased gradually, which suggests that following the same order, the equilibrium concentration of enamine intermediates decreased, resulting in a decrease of reaction rate. From the intermolecular interaction we can see that, following the same order, the acidity of the conjugated acid of the anions increased because of the increase in the atom electron negativity, which in other words led to an increase in the interaction between the cation and anion in the ILs and a decrease in the electron density of the cation. The decrease in the electronic density of guanidine then led to a decrease in the intensity of the interaction of the guanidine cation with the substrates, so the stability of the enamine intermediate in the corresponding system was decreased and the equilibrium concentration was reduced. Therefore, on this point, we deduce that the effect of the anions on the catalytic activity is brought about through their ability to modulate the electronic distribution of the cations. When [TMG][Pr], [TMG][*n*-Bu] and [TMG][*i*-Bu] were used, although the conjugated acids of these anions are stronger than that of [TMG][Ac], their catalytic activity and the absorbance intensity of the conjugate systems in the UV–Vis are weaker than those of [TMG][Ac]. The results might come from the much higher hindrance of the anions especially for [TMG][*i*-Bu], which makes it difficult for the substrate to approach the catalyst. However, the reason why [TMG][Lac] has a higher absorbance intensity in the UV–Vis but its catalytic activity is lower than the other four ionic liquids is not clear at this stage. One possible reason might be the hydroxyl group at the α-position of the carboxyl.

4. Conclusions

In this work, we have studied the effect of anions of 1,1,3,3-tetramethylguanidine-based ILs on their catalytic activity in direct aldol reactions, and found that the guanidine-based IL with $[Ac]^-$ as the anion ([TMG][Ac]) has the highest catalytic activity among these ionic liquids including [TMG][Lac], [TMG][Pr], [TMG][*n*-Bu], [TMG][*i*-Bu] and [TMG][TFA]. A series of direct aldol reactions catalyzed by [TMG][Ac] can be carried out, and even the ketones with high hindrance such as 2-butanone and 2-pentanone can give good yields in a reasonable reaction time. The regioselectivity of the reactions is different from the direct aldol reactions catalyzed by proline and its derivatives. Combining these results with the spectroscopy studies, we suggest that: (1) the effect of anion on the reaction operates through its interaction with the cation and this study might provide a successful example for designing ionic liquids for a specific reaction; (2) the reaction perhaps proceeds through an enamine intermediate, and the special structure of the guanidine-based enamine is the origin of the special regioselectivity.

Acknowledgements

We wish to thank the National Natural Science Foundation of China (20332030, 20473105) for financial support.

References

1 C. H. Heathcock, in *Comperehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Perganon, Oxford, 1991, Vol. 2.
2 (*a*) S. D. Rychonvsky, *Chem. Rev.*, 1995, **95**, 2021; (*b*) K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44.
3 For Mukaiyama aldol reactions: (*a*) T. K. Hollis and B. J. Bosnich, *J. Am. Chem. Soc.*, 1995, **117**, 4570; (*b*) S. E. Denmark and W. Lee, *J. Org. Chem.*, 1994, **59**, 707; (*c*) J. Mlynarski and J. Jankowska, *Adv. Synth. Catal.*, 2005, **347**, 521.
4 R. Mestres, *Green Chem.*, 2004, **6**, 583, and literatures cited therein.
5 Z. Tang, Z. Yang, X. Chen, L. Cun, A. Mi, Y. Jiang and L. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285.
6 W. Motz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580.
7 For reviews for the utilization of ionic liquid in organic synthesis, see: (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*b*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; (*c*) R. Sheldon, *Chem. Commun.*, 2001, 2399; (*d*) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667.
8 A. Cordova, *Tetrahedron Lett.*, 2004, **45**, 3949.
9 H. Guo, L. Cun, L. Gong, A. Mi and Y. Jiang, *Chem. Commun.*, 2005, 1450.
10 (*a*) D. Zhao, Z. Fei, T. J. Geldbach, R. Scopelliti and P. J. Dyson, *J. Am. Chem. Soc.*, 2004, **126**, 15876; (*b*) H. Gao, B. Han, J. Li, T. Jiang, Z. Liu, W. Wu, Y. Chang and J. Zhang, *Synth. Commun.*, 2004, **34**, 3083.
11 J. Huang, T. Jiang, H. Gao, B. Han, Z. Liu, W. Wu, Y. Chang and G. Zhao, *Angew. Chem., Int. Ed.*, 2004, **43**, 1397.
12 W. Wu, B. Han, H. Gao, Z. Liu, T. Jiang and J. Huang, *Angew. Chem., Int. Ed.*, 2004, **43**, 2415.
13 A. Zhu, T. Jiang, D. Wang, B. Han, L. Liu, J. Huang, J. Zhang and D. Sun, *Green Chem.*, 2005, **7**, 514.
14 (*a*) A. Aggarwal, N. L. Lancaster, A. R. Sethi and T. Welton, *Green Chem.*, 2002, **4**, 517; (*b*) J. Wang, A. Zhu, Y. Zhao and K. Zhuo, *J. Solution Chem.*, 2005, **34**, 585.
15 V. Maggiotti, S. Bahmanyar, M. Reiter, M. Resmini, K. N. Houk and V. Gouverneur, *Tetrahedron*, 2004, **60**, 619.
16 (*a*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260; (*b*) S. Saito and H. Yamamoto, *Acc. Chem. Res.*, 2004, **37**, 570.
17 A. Córdova, W. Notz and C. F. Barbas III, *Chem. Commun.*, 2002, 3024.