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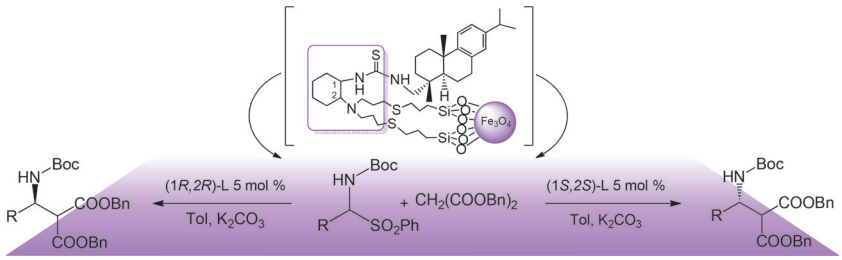

A rosin by any other name: Magnetic-nanoparticle-supported bifunctional rosin-derived tertiary amino thiourea catalysts are developed for the stereocontrolled synthesis of chiral β-amino acids. Boc = *tert*-butoxycarbonyl, Bn = benzyl.

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Highly Enantioselective Synthesis of N-Protected β-Amino Malonates Catalyzed by Magnetically Separable Heterogeneous Rosin-Derived Amino Thiourea Catalysts: A Stereocontrolled Approach to β-Amino Acids

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Highly Enantioselective Synthesis of N-Protected β-Amino Malonates Catalyzed by Magnetically Separable Heterogeneous Rosin-Derived Amino Thiourea Catalysts: A Stereocontrolled Approach to β-Amino Acids

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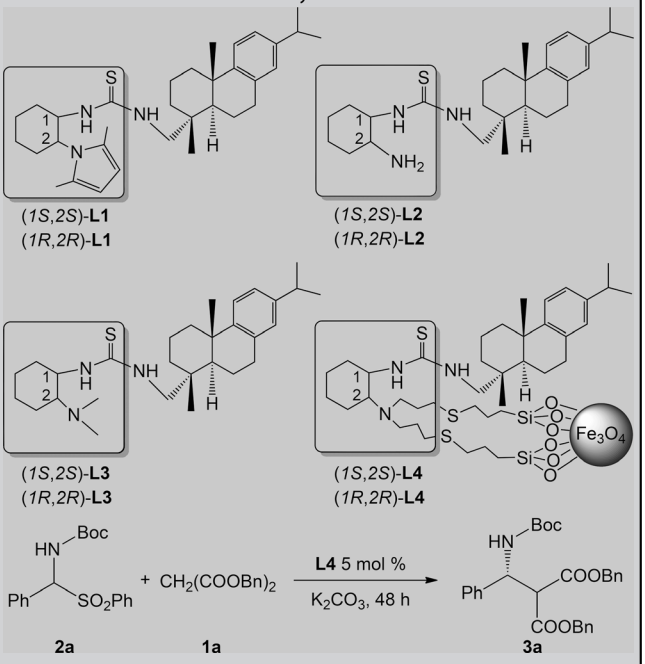
The Mannich reaction is one of the most versatile and attractive methods for the construction of nitrogen-containing compounds in organic synthesis.[1] In particular, β-amino-carbonyl derivatives constitute a class of compounds that can be readily converted into valuable synthetic building blocks or biologically active molecules.[2] Optically active β-amino acids have been found both in a series of biologically active natural peptides and as an important active structural element in synthetic peptides, which have shown potent biological and pharmaceutical activities, including clinically useful antibacterial activity, stability towards enzymatic degradation, and inhibition of lipid uptake.[3,4] Thus, the design and development of efficient asymmetric synthetic methods for the preparation of their enantioenriched forms is appealing. To date, many asymmetric catalytic procedures have been reported for the construction of β-amino acids through the Mannich-type reactions of enolizable carbonyl compounds with imines[5] or α-amido sulfones.[6] Although α-amido sulfones have been shown to be convenient and stable precursors for the in situ generation of carbamate-protected imine acceptors, apart from some recently reported examples,[7] cinchona-alkaloid derivatives are almost-exclusively employed in all of the related asymmetric Mannich-type reactions.[8] Therefore, the stereocontrolled synthesis of β-amino acids by using efficient organocatalysts through the in situ generation of carbamate-protected imines remains challenging and elusive.

Table 1. Screening of various solvents and temperatures in the reaction of α-amido sulfone **2a** with dibenzyl malonate.[a]



Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	(1*S*,2*S*)-**L4**	THF	RT	82	3 (*R*)
2	(1*S*,2*S*)-**L4**	MeCN	RT	90	17 (*R*)
3	(1*S*,2*S*)-**L4**	CH_2Cl_2	RT	88	73 (*R*)
4	(1*S*,2*S*)-**L4**	$CHCl_3$	RT	83	68 (*R*)
5	(1*S*,2*S*)-**L4**	toluene	RT	90	85 (*R*)
6	(1*S*,2*S*)-**L4**	toluene	0	90	84 (*R*)
7	(1*S*,2*S*)-**L4**	toluene	−15	88	95 (*R*)
8	(1*S*,2*S*)-**L4**	toluene	−30	85	86 (*R*)
9	(1*S*,2*S*)-**L4**	toluene	−78	56	77 (*R*)
10	(1*R*,2*R*)-**L4**	toluene	−15	85	91 (*S*)

[a] Unless otherwise stated, the reactions were performed with compound **2a** (0.1 mmol), dibenzyl malonate (**1a**, 0.2 mmol), and K_2CO_3 (1.0 equiv) in toluene (1.0 mL) and water (50 μL) for 48 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC and the configuration was assigned by comparison of the HPLC data and specific rotation with literature data.[5b] Bn = benzyl.

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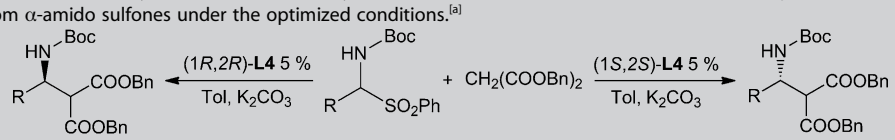
Compared with the wasteful and tedious isolation processes for homogeneous catalysis, immobilizd catalysts have attracted considerable attention owing to their recoverable and recyclable properties.[9] Magnetic nanoparticles (MNPs), as a new type of catalyst carrier, have several prominent advantages, such as high surface/area ratio, unique magnetic properties, outstanding dispersibility, chemical durability, and low toxicity.[10] In addition, magnetic separation renders the recovery of catalysts from a reaction media much easier than by filtration or centrifugation. For these reasons, MNPs, as burgeoning catalyst carriers, have tremendous potential for performing catalytic asymmetric synthetic transformations in an economical and environmentally friendly manner. Recently, we developed a series of rosin-derived amino thiourea catalysts to effectively organocatalyze aza-Henry reactions with the in situ generation of *N*-Boc imines Boc = *tert*-butoxycarbonyl).[11,12] In view of the current needs in peptide research and the different (or even opposite) pharmaceutical activities of individual enantiomers of the same compound,[13] herein, we report a new MNP-supported bifunctional rosin-derived tertiary amino thiourea catalyst for the stereocontrolled synthesis of β-amino acids through an asymmetric Mannich reaction with the in situ generation of *N*-Boc imines.

A model reaction of dibenzyl malonate (**1a**) with α-amido sulfone **2a** was performed in the presence of various thiourea catalysts at room temperature under different conditions (see the Supporting Information, Table S1). Our initial investigations began by screening a range of inorganic bases, either as solids or aqueous solutions, to evaluate their influence on this catalytic asymmetric process with rosin-derived tertiary amino thiourea catalyst (1*S*,2*S*)-**L3** (15 mol%) at room temperature in toluene (see the Supporting Information, Table S1, entries 1–9). We found that an inorganic base was crucial for obtaining high reaction efficiencies. We found that the best result was obtained when the reaction was conducted with 1.0 equivalent of K_2CO_3 in a biphasic solvent (90% yield, 85% *ee*; see the Supporting Information, Table S1, entry 6). Interestingly, when using the opposite configuration of tertiary amino thiourea **L3**, a pair of opposite optically active β-amino carbonyl adducts were obtained with similar yields and enantioselectivities (see the Supporting Information, Table S1, entry 7). Next, we tested the effects of other catalysts (see the Supporting Information, Table S1, entries 10–12). To further improve the recyclability of these catalysts, MNP-supported rosin-derived tertiary amino thiourea catalyst **L4** was fabricated and examined as a catalyst for this stereocontrolled organocatalytic asymmetric process during the elaboration of the optimal conditions.

Next, we further examined the optimal reaction conditions for this Mannich reaction (Table 1). These results indicated that changing the solvent had a significant effect on the enantioselectivity of this transformation and the use of, for example, THF and MeCN, significantly decreased the stereoselectivity (Table 1, entries 1 and 2). Of the solvents that were examined, toluene was the best in terms of chemical yield and enantioselectivity (Table 1, entry 5). With the purpose of improving the stereoselectivity, the reaction temperature was lowered further. The best result was obtained without a significantly decrease in yield (88% yield, 95% *ee*; Table 1, entry 7) for the reaction in the presence of thiourea (1*S*,2*S*)-**L4** at −15 °C; thiourea (1*R*,2*R*)-**L4** also exhibited superior catalytic activity, with an opposite sense of asymmetric induction (85% yield, 91% *ee*; Table 1, entry 10).

The results of experiments under the optimized conditions that probed the scope of this reaction are summarized in Table 2. Thus, the stereocontrolled catalytic Mannich reactions of dibenzyl malonate with various *N*-Boc-protected imines that were generated in situ from a variety of substituted α-amido sulfones were examined. Except for an aliphatic substrate (Table 2, entry 15), a variety of aromatic amido sulfones that contained various types of substituents underwent the reaction to afford the desired products with *S* or *R* configurations with excellent enantioselectivities and high yields (*R* adducts: 90–96% *ee*, 80–92% yield; *S* adducts: 90–96% *ee*, 81–90% yield; Table 2, entries 1–12). As expected, the reactions of heterocyclic amido sulfones also proceeded in excellent enantio-

Table 2. Mannich-type reactions of dibenzyl malonate with *N*-Boc-protected imines that are generated in situ from α-amido sulfones under the optimized conditions.[a]



3a-o **2a-o** **1a** **3a-o**

Entry	R	Product	Yield *R*/*S* [%][b]	*ee* *R*/*S* [%][c]
1	Ph	**3a**	88/85	95/91
2	2-naphthyl	**3b**	80/81	95/91
3	4-MePh	**3c**	80/83	90/90
4	4-MeOPh	**3d**	85/83	92/92
5	4-ClPh	**3e**	90/85	93/92
6	4-FPh	**3f**	83/86	95/91
7	4-BrPh	**3g**	90/86	96/94
8	3-ClPh	**3h**	85/90	93/94
9	3-MeOPh	**3**	81/81	91/90
10	2-FPh	**3**	92/86	95/96
11	2-BrPh	**3**	85/86	90/90
12	2-MeOPh	**3l**	80/82	93/92
13	2-thiophenyl	**3m**	88/90	92/90
14	2-furyl	**3n**	81/85	93/93
15	cyclohexyl	**3o**	05/08	n.d.

[a] Unless otherwise stated, the reactions were performed with an α-amido sulfone (0.1 mmol), dibenzyl malonate (**1a**, 0.2 mmol), and K_2CO_3 (1.0 equiv) in toluene (1.0 mL) and water (50 μL) at −15 °C for 48 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC and the configuration was assigned by comparison of the HPLC data and specific rotation with literature data.[5b]

selectivities and high yields (*R* adducts: 92% and 93% *ee*, 88% and 81% yield; *S* adducts: 90% and 93% *ee*, 90% and 85% yield; Table 2, entries 13 and 14, respectively).

TEM images showed that catalyst (1*S*,2*S*)-**L4** had an almost-spherical shape, with a mean diameter of 10 nm (Figure 1b). No remarkable change in the catalyst morphology was observed after 15 cycles, except for some slight aggregation (Figure 1c), thus confirming the robustness of this heterogeneous catalyst. The catalyst phase and crystallinity were determined by powder X-ray diffraction (Figure 1d). The magnetization curve verified that catalyst (1*S*,2*S*)-**L4** exhibited superparamagnetic behavior at 298 K, with a saturated magnetization value of 59.8 emu g^{-1} (cf. 38.7 emu g^{-1} for the Fe_3O_4 nanoparticles, Figure 1e). As shown in Figure 1e, inset, catalyst (1*S*,2*S*)-**L4** could be conveniently separated from the reaction mixture under an external magnetic field. FTIR analysis indicated that the thiourea catalyst had been successfully anchored onto the surfaces of the obtained MNPs (see the Supporting Information, Figure S1). Thermogravimetric (TG) analysis in N_2 showed a weight loss of 22.7 wt.% within the range 25–800 °C for the carriers and a weight loss of 29.3 wt.% for catalyst (1*S*,2*S*)-**L4**, thus implying that the loading of catalyst (1*S*,2*S*)-**L4**, approximately 6.6 wt.%, matched the ultimate analysis (0.13 mmol g^{-1}; see the Supporting Information, Figure S2).

To evaluate their recyclability, MNP-supported thiourea catalyst **L4** was employed in 15 successive cycles under the same reaction conditions (Table 3). These results indicated that the heterogeneous catalyst could be recycled up to 15 times with essentially no loss of yield and enantioselectivity.

According to a previously reported procedure,[14] these *N*-Boc-protected β-amino malonates were converted into their corresponding β-amino acids in a straightforward manner. Thus, the *N*-Boc-protected β-amino malonates (**3**) were transformed into their corresponding β-amino acids by heating at reflux with a 6 M aqueous solution of HCl (Scheme 1). The desirable β-amino acid hydro-

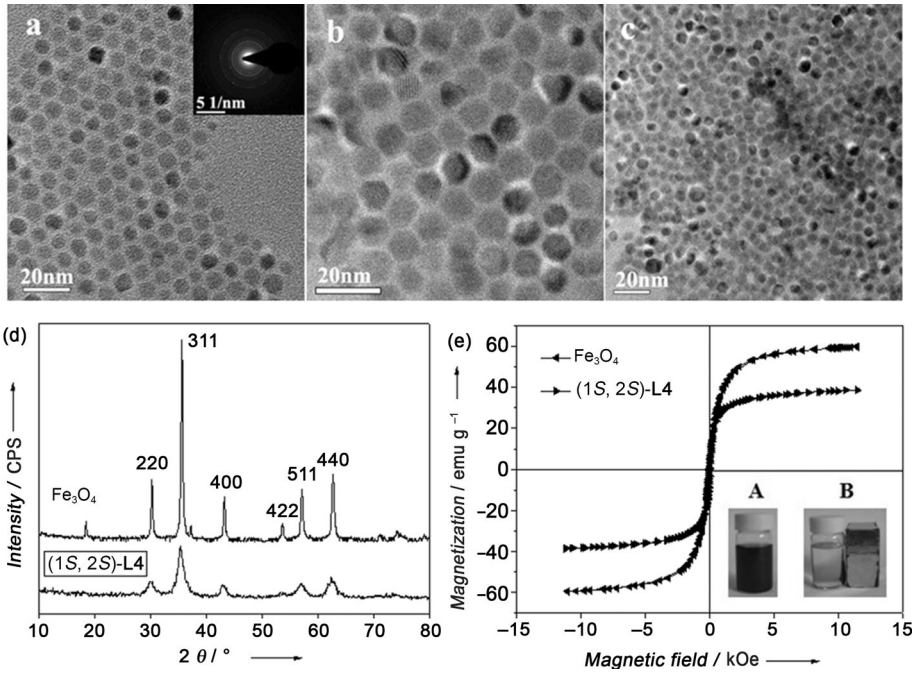
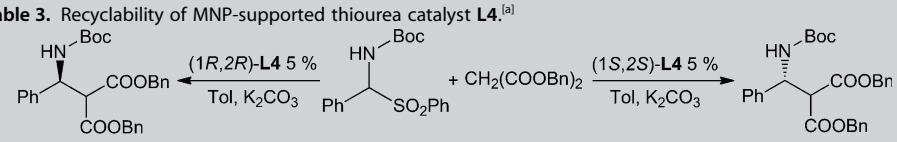


Figure 1. TEM images of a) Fe_3O_4, b) (1*S*,2*S*)-**L4**, and c) (1*S*,2*S*)-**L4** after 15 cycles. d) X-ray diffraction (XRD) patterns and e) vibrating sample magnetometry (VSM) plots of Fe_3O_4 and (1*S*,2*S*)-**L4**. CPS = counts per second.

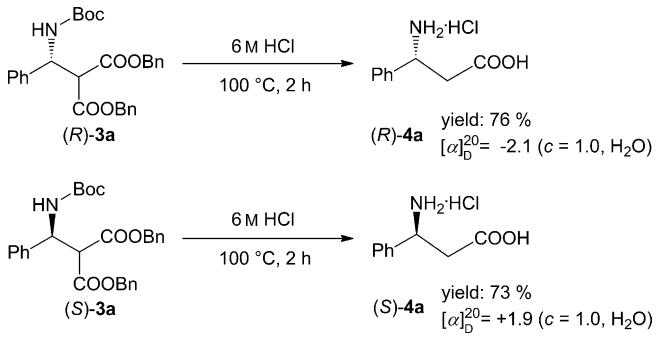
Table 3. Recyclability of MNP-supported thiourea catalyst **L4**.[a]



3a **2a** **1a** **3a**

Cycle number	Yield *R*/*S* [%][b]	*ee R*/*S* [%][c]
1	88/85	95/91
2	88/86	95/94
3	86/84	93/91
4	85/82	92/92
5	86/84	96/91
6	84/85	95/93
7	88/84	92/90
8	86/86	96/92
9	85/82	94/93
10	88/87	94/92
11	90/85	92/92
12	86/84	94/91
13	88/83	95/92
14	86/82	93/91
15	85/86	93/90

[a] Unless otherwise stated, the reactions were performed with compound **2a** (0.1 mmol), dibenzyl malonate **1a** (0.2 mmol), and K_2CO_3 (1.0 equiv) in toluene (1.0 mL) and water (50 μL) at −15 °C for 48 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC and the configuration was assigned by comparison of the HPLC data and specific rotation with literature data.[5b]



Scheme 1. Conversion of *N*-Boc-protected β-amino malonates into chiral β-amino acids.

chloride **4a** was obtained by evaporation of the solvent and washing of the residue with 6 M aqueous HCl.

In conclusion, an efficient stereocontrolled, organocatalytic method to access chiral β-amino acids through asymmetric Mannich reactions with the in situ generation of *N*-Boc imines by using new magnetic-nanoparticle-supported bifunctional rosin-derived tertiary amino thiourea catalysts has been established. These heterogeneous organocatalysts have been found to be very effective promoters for this kind of catalytic asymmetric process and this reaction provides a convenient, environmentally friendly, stereocontrolled synthesis of chiral β-amino acids with high optical purity.

Experimental Section

Asymmetric Mannich reaction of malonates with *N*-Boc-protected imines

Typically, a solution of dibenzyl malonate (**1a**, 0.2 mmol) in toluene (1.0 mL) and a 2 M aqueous solution of potassium carbonate (50 μL, 1.0 equiv) were added to a stirring solution of (1*R*,2*R*)-**L4** or (1*S*,2*S*)-**L4** (5.0 mol%) at −15 °C. Subsequently, α-amido sulfone **2a** (0.1 mmol) was added and the solution was stirred at −15 °C for 48 h. After the reaction had been completed (by TLC), the MNP-supported catalysts (**L4**) were separated from the reaction medium by using an external magnet. Then, the mixture was extracted with CH_2Cl_2 (4×10 mL) and dried with sodium sulfate. Concentration and purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:8) afforded the optically pure product. The enantiomeric purity of the product was determined by HPLC. The reactions with catalysts **L1**–**L3** were performed under similar procedures.

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Keywords: amino acids · enantioselectivity · heterogeneous catalysis · magnetic properties · nanoparticles

[1] a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; b) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102–112; c) M. Marques, *Angew. Chem.* **2006**, *118*, 356–360; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; d) J. Verkade, L. van Hemert, P. Quaedflieg, F. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41.

[2] a) J. A. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; b) J. A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630–636; c) B. Weiner, W. Szymanski, D. Janssen, A. Minnaarda, B. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656–1691.

[3] a) Y. Yu, X. Shao, C. Wang, H. Liu, Y. Cui, Y. Fan, J. Liu, R. Wang, *Peptides* **2007**, *28*, 859–870; b) C. Wang, J. Yao, Y. Yu, X. Shao, Y. Cui, H. Liu, L. Lai, R. Wang, *Bioorg. Med. Chem.* **2008**, *16*, 6415–6422.

[4] a) E. A. Porter, X. F. Wang, H. S. Lee, B. Weisblum, S. H. Gellman, *Nature* **2000**, *404*, 565–565; b) P. LePlae, J. Fisk, E. Porter, B. Weisblum, S. Gellman, *J. Am. Chem. Soc.* **2002**, *124*, 6820–6821.

[5] a) Y. Kang, D. Kim, *J. Org. Chem.* **2009**, *74*, 5734–5737; b) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; c) A. Tillman, J. Ye, D. Dixon, *Chem. Commun.* **2006**, 1191–1193.

[6] a) F. Fini, L. Bernadi, R. Herrera, D. Pettersen, A. Ricci, V. Sgarzani, *Adv. Synth. Catal.* **2006**, *348*, 2043–2046; b) J. Song, H. Shih, L. Deng, *Org. Lett.* **2007**, *9*, 603–606; c) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338–8351.

[7] C. Gianelli, L. Sambri, A. Carlone, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8828–8830; *Angew. Chem. Int. Ed.* **2008**, *47*, 8700–8702.

[8] a) E. Gomez-Bengoa, A. Linden, R. López, I. Mugica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966; b) S. Lou, P. Dai, S. Schauss, *J. Org. Chem.* **2007**, *72*, 9998–10008; c) B. Niess, K. Jørgensen, *Chem. Commun.* **2007**, 1620–1622.

[9] a) A. Trindade, P. Gois, C. Afonso, *Chem. Rev.* **2009**, *109*, 418–514; b) J. Lu, P. Toy, *Chem. Rev.* **2009**, *109*, 815–838; c) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688.

[10] a) S. Shylesh, V. Schünemann, W. Thiel, *Angew. Chem.* **2010**, *122*, 3504–3537; *Angew. Chem. Int. Ed.* **2010**, *49*, 3428–3459; b) A. Lu, E. Salabas, F. Schüth, *Angew. Chem.* **2007**, *119*, 1242–1266; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222–1244; c) P. Riente, C. Mendoza, M. Pericás, *J. Mater. Chem.* **2011**, *21*, 7350–7355; d) R. Luque, B. Baruwati, R. Varma, *Green Chem.* **2010**, *12*, 1540–1543.

[11] a) X. Jiang, Y. Zhang, A. Chan, R. Wang, *Org. Lett.* **2009**, *11*, 153–156; b) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562–5567; c) X. Jiang, Y. Zhang, L. Wu, G. Zhang, X. Liu, H. Zhang, D. Fu, R. Wang, *Adv. Synth. Catal.* **2009**, *351*, 2096–2100.

[12] a) A. Doyle, E. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; b) Y. Wang, H. Li, Y. Wang, Y. Liu, B. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365; c) M. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065; d) S. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618–620; *Angew. Chem. Int. Ed.* **2007**, *46*, 612–614.

[13] a) S. Debonis, J. Simorre, I. Crevel, L. Lebeau, D. Skoufias, A. Blangy, C. Ebel, P. Gans, R. Cross, D. Hackney, R. Wade, F. Kozielski, *Biochemistry* **2003**, *42*, 338–349; b) Z. Maliga, T. Kapoor, T. Mitchison, *Chem. Biol.* **2002**, *9*, 989–996; c) C. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.

[14] C. Ananthanawat, V. Banphavichit, T. Vilaivan, *Synth. Commun.* **2006**, *36*, 1845–1855.

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