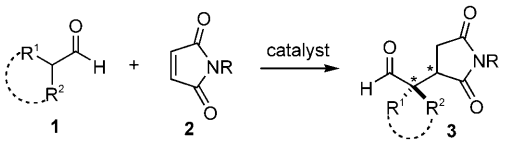
DOI: 10.1002/chem.201001207

A Simple Primary Amine Thiourea Catalyzed Highly Enantioselective Conjugate Addition of α,α-Disubstituted Aldehydes to Maleimides

Fei Xue,[a] Lu Liu,[a] Shilei Zhang,[a] Wenhu Duan,*[a, b] and Wei Wang*[a, b, c]

Conjugate addition reactions are powerful and versatile processes for the formation of C–C bonds in organic synthesis as a result of a wide variety of substances that can serve as electrophiles and nucleophiles and, consequently, a diverse array of products can be generated.[1,2] Notably, in recent years, organocatalytic, enantioselective conjugate reactions have been subject to intensive investigations. The general observation is that enals, enones, and nitroolefins are often used as Michael acceptors.[2] In sharp contrast, the use of maleimides **2**,[3–5] for C–C bond formation remains elusive, despite the broad synthetic and biological utilities of chiral α-branched succinimides **3** (Scheme 1).[6] To the best



Scheme 1. Catalytic enantioselective conjugate addition of aldehydes to maleimides.

of our knowledge, only a single study reported by Córdova and co-workers describes an enantioselective conjugate addition of aldehydes to maleimides catalyzed by a pyrrolidine silyl ether.[7] However, the reaction has a significant limitation. A low yield (40%) and poor enantioselectivity (51% enantiomeric excess (*ee*)) were obtained when α-branched isobutyraldehyde was used.

Because of significant steric hindrance and less reactivity, examples of α,α-disubstituted aldehydes **1** as potential nucleophilic partners in organocatalytic asymmetric conjugate reactions are very limited.[8] So far, the successful systems mainly rely on the use of highly active nitroolefins as effective Michael acceptors.[8] Notably, we,[8a,b] Barbas et al.,[8c,d] and others[8e–g] have reported chiral amine promoted, highly enantioselective conjugate additions of α,α-disubstituted aldehydes to nitroolefins. Moreover, the groups of Jacobsen[9a] and Yan[9b] disclosed elegant chiral primary amines as promoters for the process. Although the employment of maleimides for a direct, catalytic, asymmetric conjugate addition reaction with α,α-disubstituted aldehydes presents an appealing approach to valuable chiral α-branched succinimides, the realization of the process faces formidable challenges of generating contiguous quaternary and/or tertiary stereogenic centers with the highly hindered, less reactive substrates (Scheme 1). Herein, we report a simple primary amine thiourea promoted conjugate addition of aldehydes, including α,α-disubstituted substrates, to maleimides in high yields and with high enantioselectivities.

The unsatisfactory results (e.g., low enantioselectivity) of chiral secondary amine catalyzed conjugate addition of α,α-disubstituted aldehydes to maleimides[7,10] prompted us to seek new alternative catalytic systems. It is recognized that chiral primary amines have been demonstrated as unique promoters for the activation of enolizable carbonyl compounds to form enamines for nucleophilic additions.[11,12] Accordingly, we probed a model Michael reaction of isobutyraldehyde (**1a**) with maleimide (**2a**) in the presence of a bifunctional chiral primary amine (15 mol%) and H_2O (15 mol%) in $CHCl_3$ at RT (Table 1). Among the primary amine catalysts surveyed, catalysts **I** and **II**, which are similar to the Takamoto catalyst[13] were found to induce particularly high enantioselectivities (Table 1, entries 1 and 2). Furthermore, notably, they promoted the conjugate addition process very quickly and the reaction was accomplished in less than 1 h in high yields. We decided to select the simple

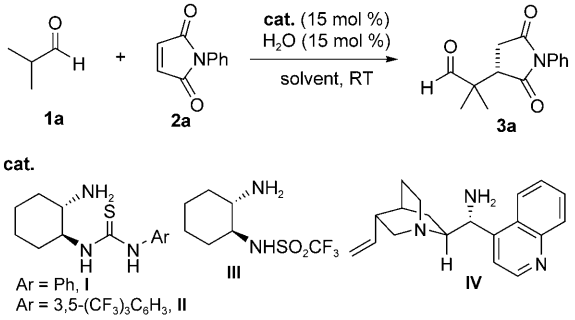
[a] F. Xue, L. Liu, Dr. S. Zhang, Prof. Dr. W. Duan, Prof. Dr. W. Wang
School of Pharmacy, East China University of Science
Shanghai 200237, China

[b] Prof. Dr. W. Duan, Prof. Dr. W. Wang
Shanghai Institute of Materia Medica, Chinese Academy of Sciences
555 Zuchongzhi Road, Shanghai 201203 (China)
Fax: (+86) 21-5080-6032
E-mail: whduan@mail.shcnc.ac.cn

[c] Prof. Dr. W. Wang
Department of Chemistry & Chemical Biology
University of New Mexico, MSC03 2060
Albuquerque, NM 87131-0001 (USA)
Fax: (+1) 505-277-2609
E-mail: wwang@unm.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001207.

Table 1. Optimization of reaction conditions for the catalytic enantioselective Michael reaction of isobutyraldehyde (**1a**) with maleimide (**2a**).[a]



Entry	Cat.	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	$CHCl_3$	0.67	93	97
2	**II**	$CHCl_3$	0.67	96	94
3	**III**	$CHCl_3$	1	96	77
4	**IV**	$CHCl_3$	24	66	88
5	**I**	THF	1.25	87	81
6	**I**	*i*PrOH	1.67	85	53
7	**I**	H_2O	0.5	89	62
8[d]	**I**	$CHCl_3$	0.67	89	91
9[e]	**I**	$CHCl_3$	2	98	96
10	**I**[f]	$CHCl_3$	2.5	93	97
11	**I**[g]	$CHCl_3$	22	87	97
12	**I**[h]	$CHCl_3$	70	87	97

[a] Unless specified, see the Experimental Section. [b] Isolated yields. [c] Determined by HPLC analysis (Chiralcel OD-H). [d] Without 15 mol% H_2O. [e] Reaction performed at 4°C. [f] 5 mol% used. [g] 1 mol% used. [h] 0.5 mol% used.

amine thiourea **I** for further optimization reaction conditions. While variation of solvents had a pronounced effect on enantioselectivity (Table 1, entries 1 and 5–7), high yields were obtained in all cases. Moreover, we observed that water as the additive was beneficial to the enantioselectivity of the reaction (Table 1, entry 1 vs. entry 8). It appeared that reaction temperature had a limited impact on both yield and enantioselectivity (Table 1, entry 9). Finally, the effect of catalyst loading on reaction efficiency was evaluated (Table 1, entries 10–12). Remarkably, the reaction proceeded smoothly even at catalyst with a loading as low as 0.5 mol% without loss of yield and enantioselectivity (87% yield and 97% *ee*, entry 12,). From operational convenience point of view, the use of 1 mol% **I** ensured a high level of reaction efficiency and enantioselectivity while maintaining reasonable reaction time (Table 1, entry 11).

Encouraged by these promising results, we next examined the scope and limitation of the **I**-promoted conjugate addition reactions with a variety of aldehydes and maleimides (Table 2). As demonstrated, the process served as a general approach to the formation of highly valuable, chiral disubstituted, α-branched succinimides **3** in high yields and with excellent enantioselectivities. The reactions of maleimides with electron-neutral, -donating and -withdrawing groups with isobutyraldehyde proceeded smoothly to give structurally diverse succinimides **3** (Table 2, entries 1–4) It was found that the electron-withdrawing group in **2** slowed down the reaction; however, the use of higher catalyst loading (15 mol%) dramatically enhanced the reaction rate (Table 2, entry 4). The reaction was also applicable to an aliphatic maleimide (Table 2, entry 5). The reactions of cyclopentanecarbaldehyde (Table 2, entry 6) or cyclohexanecarbaldehyde (Table 2, entry 7) with *N*-phenylmaleineimide displayed unexpected reaction behavior. Under the same reaction conditions, either low reaction yields or low enantioselectivities were observed. Therefore, we used 15 mol% of **I** for both cases and reactions occurred much faster. Furthermore, it was found that slow addition of the solution of *N*-phenylmaleineimide to cyclopentanecarbaldehyde was crucial to achieve high efficiency (Table 2, entry 6). It was essential to change the addition sequence of starting materials for the reaction of cyclohexanecarbaldehyde (Table 2, entry 7). Slow addition of the cyclohexanecarbaldehyde to the reaction solution of *N*-phenylmaleineimide and **I** resulted in a good yield and high enantioselectivity. The **I**-catalyzed conjugate addition reactions were also applicable to linear aldehydes without α-branch side chains. High enantioselectivities and good yields were obtained despite low diastereoselectivities (Table 2, entries 8 and 9). Finally, we probed unsymmetrical α,α-disubstituted aldehydes using 5 mol% of **I**. Notably, two contiguous quaternary and tertiary stereogenic centers were created in one step with excellent enantioselectivities in spite of relatively low diastereoselectivities (Table 2, entries 10–12).

It is noted that the nice feature of the **I**-catalyzed Michael reaction is that the process proceeded cleanly to give an adduct in high purity. For example, simple evaporation of the reaction solvents and volatile compounds gave product **3c** in more than 95% purity based on ^{1}H NMR spectroscopic analysis (Table 2, entry 3 and Figure S1 in the Supporting Information). The absolute configuration of the products was determined by single-crystal X-ray analysis of **3l** (Figure 1).[14]

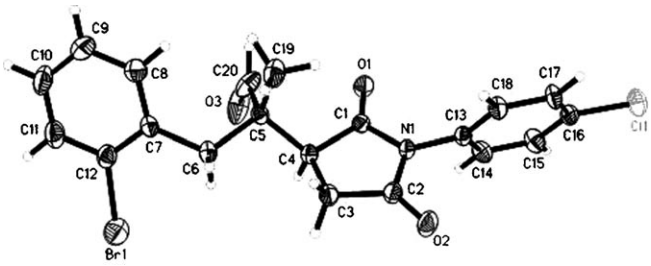
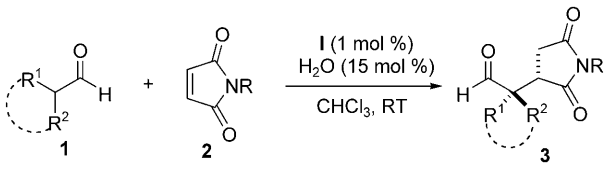
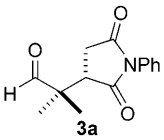
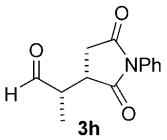
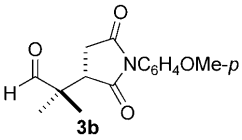
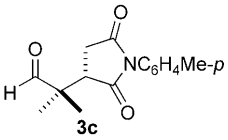
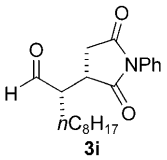
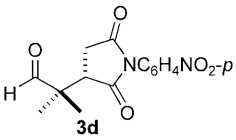
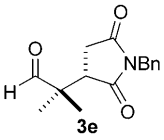
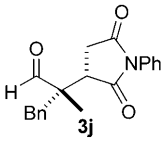
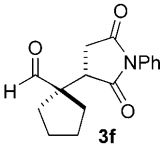
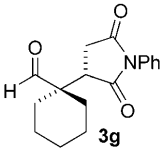
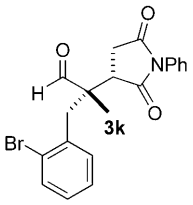
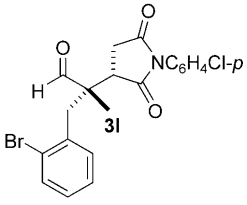


Figure 1. X-ray structure of compound **3l**.

In summary, an unprecedented primary amine thiourea promoted, direct, highly efficient conjugate addition reaction of α,α-disubstituted aldehydes and maleimides has been developed. The approach serves as a powerful tool for the preparation of synthetically and biologically important chiral disubstituted, α-branched succinimides. This structurally simple catalyst exhibits high catalytic activity and enantioselectivity towards a variety of aldehydes and maleimides with significant structural variations under mild reaction conditions. Furthermore, remarkably, two contiguous quater-

Table 2. Scope of **I** promoted enantioselective conjugate addition reactions of aldehydes **1** with maleimides **2**.[a,10]



Entry	Product	*t* [h]	Yield [%][b]	*ee* [%][c]	d.r.[d]	Entry	Product **3**	*t* [h]	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	 **3a**	22	87	97	–	8	 **3h**	48	79	96 (major)	
											1.3:1
2	 **3b**	20	93	95	–					98 (minor)	
3	 **3c**	18	86	98	–	9	 **3i**	48	68	95 (major)	
											1.2:1
4[e]	 **3d**	0.83	87	95	–					91 (minor)	
5	 **3e**	18	91	99	–	10[h]	 **3j**	70	79	98 (major)	
											2.3:1
6[f]	 **3f**	6	69	96	–					96 (minor)	
7[g]	 **3g**	12	72	95	–	11[h]	 **3k**	84	81	99 (major)	11:2
										96 (minor)	
						12[g]	 **3l**	84	91	99 (major)	5:1
										75 (minor)	

[a] Unless specified, see the Experimental Section. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD-H, OJ-H, Chiralcel AS-H, or AD-H). [d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] 15 mol % **I** used. [f] 15 mol % **I** and 10 equiv of cyclopentanecarbaldehyde used. [g] 15 mol % **I** and 8 equiv of cyclopentanecarbaldehyde used. [h] 5 mol % **I** used.

nary and/or tertiary stereogenic centers can be efficiently generated in one step with excellent enantioselectivities. Further efforts on exploration of new organic transformations using these types of catalysts and evaluation of the biological properties of the intriguing succinimides are underway in our laboratory.

Experimental Section

General procedure (Table 2 entry 1 as an example): Unless specifically stated, *N*-phenylmaleimide (**2a**, 0.2 mmol) was added to a solution of isobutyraldehyde (**1a**) (0.4 mmol) in the presence of catalyst **I** (0.002 mmol), water (0.15 equiv) and chloroform (0.5 mL), and the resulting solution was stirred at room temperature. The reaction mixture was directly purified by silica gel chromatography without workup and fractions were collected and concentrated in vacuo to provide the pure desired product **3a** used for compound characterization and chiral HPLC analysis.

Acknowledgements

Financial support of this research is supported by the China 111 Project (grant B07023) and the "thousands of talents" program (W.W.) is gratefully acknowledged.

Keywords: aldehydes · maleimides · Michael addition · organocatalysis

[1] For reviews of conjugate addition reactions, see: a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**; b) M. Sibi, S. Manyem, *Tetrahedron* **2001**, *57*, 8033; c) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2007**, *107*, 933.

[2] For recent reviews of organocatalyzed conjugate addition reactions, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; c) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; d) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; f) P. Melchiorre, M. Marigao, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*. 6138; g) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[3] Examples of chiral Lewis acid catalyzed Michael additions, see: a) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959; b) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2582; c) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425; d) R. Shintani, W.-L. Duan, T. Nagano, A. Okada, T. Hayashi, *Angew. Chem.* **2005**, *117*, 4687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4611; e) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628.

[4] For limited examples for using maleimides in organocatalysis, see: a) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem.* **2006**, *118*, 5088; Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem.* **2006**, *118*, 5088; *Angew. Chem. Int. Ed.* **2006**, *45*, 4966; b) W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454; c) Z. Jiang, W. Ye, Y. Yang, C.-H. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345; d) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong; C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681; C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627.

[5] We reported the first example of organocatalytic enantioselective cascade Michael–aldol reaction involving maleimides: L. Zu, H. Xie, H. Li, J. Wang, W. Jiang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 1882.

[6] a) S. Ahmed, *Drug Discovery* **1996**, *14*, 77; b) A.-S. S. Hamad Elgazwy, *Molecules* **2000**, *5*, 665; c) A. Mitchenson, A. Nadin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862; d) M. L. Curtin, R. B. Garland, H. R. Heyman, R. R. Frey, M. R. Michaelides, J. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, S. K. Davidsen, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919; e) R. Ballini, G. Bosica, G. Cioci, D. Fiorini, M. Petrini, *Tetrahedron* **2003**, *59*, 3603; f) J. Pohlmann, T. Lampe, M. Shimada, P. G. Nell, J. Pernerstorfer, N. Svenstrup, N. A. Brunner, G. Schiffer and C. Freiberg, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1189.

[7] G.-L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayah A. Córdova, *Chem. Commun.* **2007**, 734.

[8] For examples of α,α-disubstituted aldehydes in organocatalytic enantioselective conjugation addition to nitroolefins, see: a) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; b) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321; c) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527; d) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; e) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559; f) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901; g) Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50; h) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 6039; an example of aldol reaction: i) M. Markert, U. Scheffler, R. Mahrwald, *J. Am. Chem. Soc.* **2009**, *131*, 16642.

[9] a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; b) X.-J. Zhang, S.-P. Liu, J.-H. Lao, G.-J. Du, M. Yan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 1415.

[10] For a nonasymmetric approach, see: J. Nöth, K. J. Frankowski, B. Neuenswander, J. Aubé, O. Reiser, *J. Comb. Chem.* **2008**, *10*, 456.

[11] For recent reviews of primary amine catalyzed reactions, see: a) Y.-C. Chen, *Synlett* **2008**, 1919; b) L.-W. Xu, J. Luo, Y.-X. Lu, *Chem. Commun.* **2009**, 1807.

[12] For selected examples, see: a) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; b) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923; c) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; d) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413; e) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; f) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; g) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288; h) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49; i) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422; j) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; k) P. Li, Y. Wang, X. Liang, J, Ye, *Chem. Commun.* **2008**, 3302; l) Q. Zhu, L. Cheng, Y.-X. Lu, *Chem. Commun.* **2008**, 6315; m) K. Mei, M. Jin, S.-L. Zhang, P. Li, W.-J. Liu, X.-B. Chen, F. Xue, W.-H. Duan, W. Wang, *Org. Lett.* **2009**, *11*, 2864; n) Q. Zhu, Y.-X. Lu, *Chem. Commun.* **2010**, *46*, 2235.

[13] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[14] The structure of compound derived from molecule **31** was determined by X-ray crystal analysis. CCDC-772788 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: May 5, 2010
Published online: June 10, 2010

