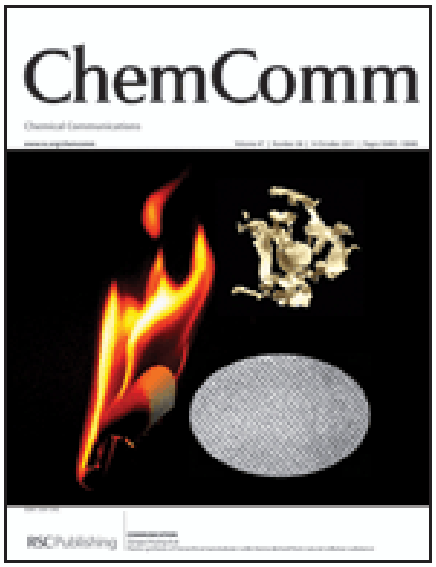
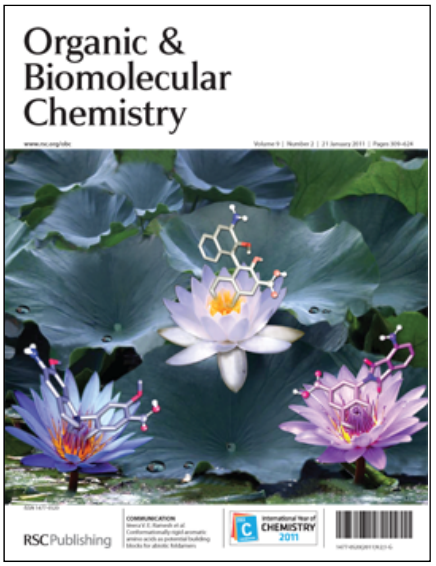




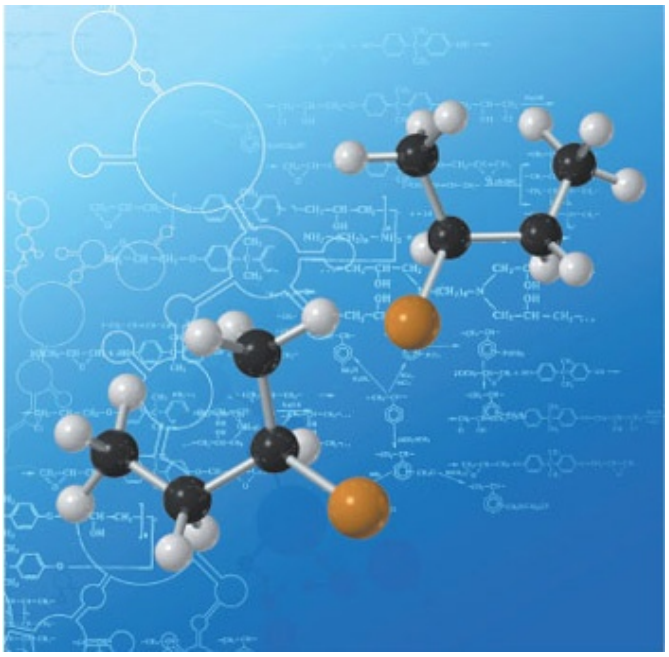
This article is part of the

Organocatalysis

web themed issue

Guest editors: Professors Keiji Maruoka, Hisashi Yamamoto, Liu-Zhu Gong and Benjamin List

All articles in this issue will be gathered together online at www.rsc.org/organocatalysis



ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2012, **48**, 5040–5042

www.rsc.org/chemcomm

COMMUNICATION

Chiral guanidine-catalyzed asymmetric direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates†‡

Yang Yang, Shunxi Dong, Xiaohua Liu,* Lili Lin and Xiaoming Feng*

Received 28th February 2012, Accepted 21st March 2012
DOI: 10.1039/c2cc31470c

The asymmetric direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates has been developed. Various 5-substituted 3-pyrrolidin-2-ones were obtained in high yields (up to 93%) with excellent stereoselectivities (up to 94% ee, 95:5 dr), using a novel bifunctional C_1-symmetric guanidine organocatalyst embodied a secondary amine subunit.

Chiral butyrolactams are common and crucial fragments in natural products and biologically active compounds,[1] such as (+)-lactacystin[1d] and haplophytine.[1e] Owing to their synthetic significance, various methods for the preparation of optically active 5-substituted butyrolactam derivatives have been established.[2] In recent years, α,β-unsaturated γ-butyrolactams[3] and 2-siloxypyrrole[4] have been employed as donors for the construction of 5-substituted 3-pyrrolidin-2-one derivatives. Considering atom-economy, it is no doubt that direct vinylogous addition of α,β-unsaturated γ-butyrolactams is worthy of development.[5] The Shibasaki group have employed their dinuclear nickel catalytic system for the efficient vinylogous Mannich reaction and Michael reaction of nitroolefins.[5a] Later, asymmetric vinylogous Michael (VM) reactions with α,β-unsaturated aldehydes[5b] and enones[5c–e] were well developed. However, the direct organocatalytic asymmetric VM reaction of activated olefins has not yet been reported. Herein, we describe our efforts devoted to the asymmetric VM reaction between α,β-unsaturated γ-butyrolactams and alkylidene malonates by the use of a new bifunctional chiral guanidine–amine organocatalyst.

Recently, we have successfully developed a new type of chiral guanidines and bisguanidines[6] derived from α-amino acids as efficient bifunctional organocatalysts.[7] Inspired by prior work, we hypothesized that guanidine moieties might be favorable to the deprotonation of α,β-unsaturated γ-butyrolactams, and then might activate the generated dienolate to perform the VM reaction smoothly.

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: liuxh@scu.edu.cn, xmfeng@scu.edu.cn; Fax: +86-28-85418249; Tel: +86-28-85418249

† This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available. CCDC 869057 (**7i**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31470c

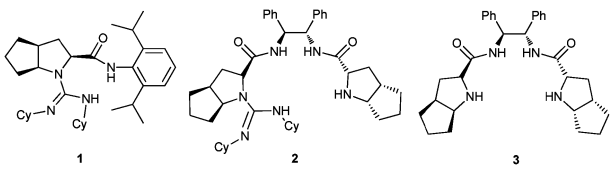
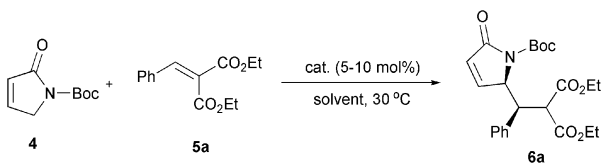


Fig. 1 Chiral organocatalyst evaluated.

Initially, the reaction between α,β-unsaturated γ-butyrolactam **4** and diethyl benzylidenemalonate **5a** was carried out in the presence of chiral guanidine catalyst **1** at 30 °C in toluene (Fig. 1). To our disappointment, the desired product **6a** was afforded in only a trace amount even after 4 days (Table 1, entry 1). Therefore, organocatalysts with multisite activation functional groups were designed, which could promote the reaction *via* acid–base cooperative activation. C_2-Symmetric bisguanidine catalysts, previously used in the catalytic asymmetric reactions,[7b,c] afforded complex mixtures. Interestingly, the untargeted guanidine–secondary amine **2**, obtained in the preparation of the corresponding bisguanidine catalyst, was found to be efficient for the reaction. The desired product **6a** was generated in 82% yield, 90% ee and 95:5 dr (Table 1, entry 2). It seemed

Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Solvent	*t*/h	Yield[b] (%)	dr[c]	ee[c] (%)
1	**1**	PhMe	96	Trace	—	—
2	**2**	PhMe	36	82	95:5	90
3	**3**	PhMe	96	0	—	—
4	**2**	THF	36	72	95:5	91
5	**2**	CH_2Cl_2	96	16	95:5	86
6	**2**	AcOEt	36	70	94:6	85
7	**2**	CH_3CN	96	32	77:23	82
8	**2**	$PhCF_3$	24	82	90:10	93
9[d]	**2**	$PhCF_3$	24	82	95:5	94
10[d,e]	**2**	$PhCF_3$	18	82	95:5	94

[a] Unless otherwise noted, all reactions were carried out with **1–3** (10 mol%), **4** (0.05 mmol) and **5a** (0.1 mmol) in solvent (0.5 mL) at 30 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 10 mg of 4 Å molecular sieves. [e] 5 mol% of **2** in 0.25 mL of $PhCF_3$.

that the secondary amine moiety was crucial for the occurrence of the process. Then catalyst **3**, the precursor of the guanidine catalyst **2**, was evaluated. However, it failed to promote the reaction at all (Table 1, entry 3 *vs.* 2). These results suggested that guanidine and secondary amino group of the catalyst **2** worked cooperatively. Next, screening of solvent revealed that the best one was $PhCF_3$ in reactivity and enantioselectivity (82% yield with 93% ee; Table 1, entry 8 *vs.* 4–7). The diastereoselectivity was increased to 95 : 5 when 4 Å molecular sieves (MS) were added (Table 1, entry 9 *vs.* 8). To our delight, the catalyst loading could be decreased from 10 mol% to 5 mol% without decreasing the yield and stereoselectivity of the reaction (Table 1, entry 10 *vs.* 9). Therefore, the optimal reaction conditions were established using 5 mol% of **2** and 4 Å MS as additives in $PhCF_3$ at 30 °C.

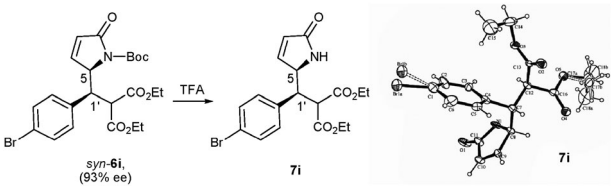
Under the optimized conditions, the ester group of benzylidenemalonate was first evaluated. Similar results on the yields, diastereo- and enantioselectivities were obtained with dimethyl-, diethyl-, or dibenzyl benzylidenemalonate (Table 2, entries 1–3). Then a series of diethyl alkylidene malonates was investigated, giving the corresponding products with excellent enantioselectivities (up to 94% ee). As shown in Table 2, alkylidene malonates with either an electron-withdrawing or

Table 2 Substrate scope for the catalytic asymmetric VM reaction of α,β-unsaturated γ-butyrolactam **4** to alkylidene malonates **5**[a]

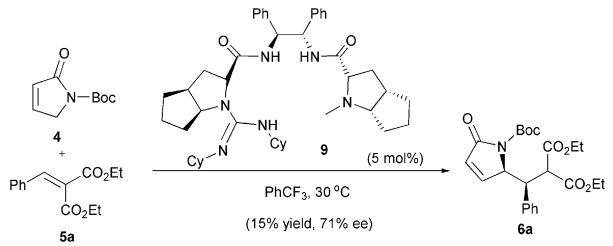
4 5 6

Entry	R^1	R^2	*t*/h	Yield[b] (%)	dr[c]	ee[c] (%)
1	Ph	Et	18	**6a**, 82 (86)[d]	95 : 5	94 (93)[d]
2	Ph	Me	18	**6b**, 85	95 : 5	93
3	Ph	Bn	18	**6c**, 83	95 : 5	91
4	4-FC_6H_4	Et	12	**6d**, 78	95 : 5	94
5	2-ClC_6H_4	Et	12	**6e**, 75	95 : 5	93
6	3-ClC_6H_4	Et	12	**6f**, 80	94 : 6	90
7	4-ClC_6H_4	Et	12	**6g**, 85	95 : 5	92
8	3-BrC_6H_4	Et	12	**6h**, 85	94 : 6	93
9	4-BrC_6H_4	Et	12	**6i**, 86	95 : 5	93[e]
10	3-MeC_6H_4	Et	18	**6j**, 76	95 : 5	93
11	4-MeC_6H_4	Et	18	**6k**, 82	95 : 5	93
12	3-$MeOC_6H_4$	Et	18	**6l**, 93	95 : 5	93
13	4-$MeOC_6H_4$	Et	24	**6m**, 72	95 : 5	93
14		Et	36	**6n**, 64	90 : 10	91
15	4-PhC_6H_4	Et	18	**6o**, 83	95 : 5	90
16	3-$PhOC_6H_4$	Et	18	**6p**, 89	95 : 5	89
17	2-Thienyl	Et	18	**6q**, 72	95 : 5	90
18	3-Thienyl	Et	18	**6r**, 70	93 : 7	91
19	2-Naphthyl	Et	18	**6s**, 82	93 : 7	91
20		Et	12	**6t**, 75	81 : 19	78
21	*c*-Hexyl	Et	18	**6u**, 70	95 : 5	90

[a] Unless otherwise noted, all reactions were carried out with **2** (5 mol%), **4** (0.05 mmol), **5** (0.1 mmol) and 10 mg of 4 Å MS in $PhCF_3$ (0.25 mL) at 30 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The data in parentheses are results when the reaction was carried out with **2** (5 mol%), **4** (0.5 mmol), **5** (1.0 mmol) and 100 mg of 4 Å MS in $PhCF_3$ (2.5 mL) at 30 °C for 18 hours. [e] The absolute configuration of **6i** has been determined by X-ray crystallographic analysis after conversion to **7i**.



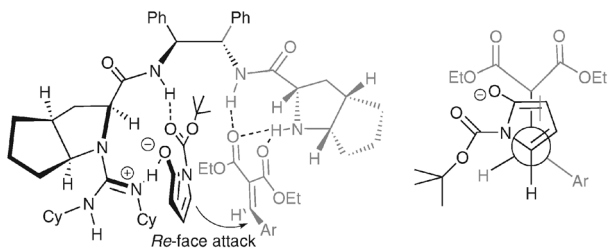
Scheme 1 Determination of the absolute configuration of the product.



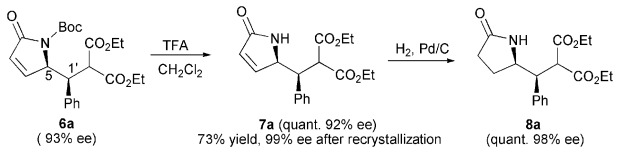
Scheme 2 Comparative experiment.

an electron-donating substituent on the aromatic ring in the R^1 group could be converted to the corresponding 5-substituted 3-pyrrolidin-2-ones in high yields, excellent ee values, and diastereoselectivities (up to 93% yield, 89–94% ee; Table 2, entries 4–16). It was notable that the system demonstrated good tolerance to fused-ring and hetero-aromatic substrates (Table 2, entries 17–19). However, the cinnamonic substrate **5t** showed lower stereoselectivities (78% ee and 81 : 19 dr; Table 2, entry 20). Additionally, the cyclohexylmethylene malonate **5u** was also a suitable substrate for the direct vinylogous Michael reaction with 70% yield and 90% ee (Table 2, entry 21). The absolute configuration of the product **6i** was concluded as (5*R*, 1′*S*) by X-ray crystallography of **7i** (Scheme 1).[8]

To further investigate the role of the secondary amino group in the catalyst **2**, a comparative experiment was carried out with *N*-Me protected guanidine–tertiary amine derivative **9** (Scheme 2). Under the optimized conditions, both the reactivity and stereoselectivity decreased sharply, and the product **6a** was obtained only in 15% yield and 71% ee in 18 hours. It showed that the proton of the secondary amino group played a vital role in the direct vinylogous Michael reactions. Based on the experiments and our previous work,[7] the possible activation model of the reaction was proposed[6h,9] as shown in Scheme 3. The basic guanidine in the catalyst could accelerate γ-deprotonation of α,β-unsaturated γ-butyrolactam **4** to generate dienolate. The *N*-Boc protection group of **4** was favorable to the contribution of the dual hydrogen bonding between the formed intermediate and the guanidine moiety as well as the amide on the same side of the catalyst **2**. Meanwhile, the alkylidene malonate **5** was activated through a



Scheme 3 Proposed activation model for asymmetric VM reaction catalyzed by **2**.



6a (93% ee) **7a** (quant. 92% ee) 73% yield, 99% ee after recrystallization **8a** (quant. 98% ee)

Scheme 4 Transformations of the corresponding Michael products.

network of hydrogen bonds of NH groups of both the secondary amine and amide on the other side of the catalyst. Therefore, the desired product could be obtained by the *Re*-face attack of the activated alkylidene malonate **5**.

The highly enantiomerically enriched compounds **6** obtained by this method can be easily converted into 5-substituted pyrrolidin-2-ones, which are important intermediate skeletons in many natural drug molecular structures.[1a–c] For example, the optically pure 5-substituted pyrrolidin-2-one **8a**, containing two adjacent chiral centers, was easily obtained by two steps from the product **6a** (Scheme 4).

In conclusion, we have developed a novel guanidine combining with secondary amine as a highly efficient bifunctional catalyst in asymmetric direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates. High yields (up to 93%) and excellent selectivities (up to 94% ee, 95 : 5 dr) were generally obtained for a range of substrates using 5 mol% catalyst loading under mild reaction conditions. A possible catalytic model was proposed to explain the observed high enantioselectivities. The successful application of C_1-symmetric guanidine–amine organocatalysts helps to design a new kind of catalysts. Further studies on the mechanism of the reaction and the application of this catalyst are underway.

We appreciate the National Natural Science Foundation of China (No. 21021001 and 21072133), the Ministry of Education of China (NCET-11-0345), and the Basic Research Program of China (973 Program: 2010CB833300) for financial support.

Notes and references

1 (*a*) G. Casiraghi, F. Zanardi, L. Battistini and G. Rassu, *Synlett*, 2009, 1525; (*b*) G. Casiraghi and F. Zanardi, *Chem. Rev.*, 2000, **100**, 1929; (*c*) A. Gheorghe, M. Schulte and O. Reiser, *J. Org. Chem.*, 2006, **71**, 2173; For selected examples, see: (*d*) H. Uno, J. E. Baldwin and A. T. Russell, *J. Am. Chem. Soc.*, 1994, **116**, 2139; (*e*) K. C. Nicolaou, S. M. Dalby and U. Majumder, *J. Am. Chem. Soc.*, 2008, **130**, 14942.

2 (*a*) D. M. Iula and R. E. Gawley, *J. Org. Chem.*, 2000, **65**, 6196; (*b*) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; (*c*) L. Duc, J. F. McGarrity, T. Meul and A. Warm, *Synthesis*, 1992, 391; (*d*) S. Louwrier, M. Ostendorf, A. Boom, H. Hiemstra and W. N. Speckamp, *Tetrahedron*, 1996, **52**, 2603.

3 For direct use of α,β-unsaturated γ-butyrolactams in racemic vinylogous reactions, see: (*a*) A. Sartori, C. Curti, L. Battistini, P. Burreddu, G. Rassu, G. Pelosi, G. Casiraghi and F. Zanardi, *Tetrahedron*, 2008, **64**, 11697; (*b*) C. Curti, A. Sartori, L. Battistini, G. Rassu, P. Burreddu, F. Zanardi and G. Casiraghi, *J. Org. Chem.*, 2008, **73**, 5446.

4 For recent examples of enantioselective catalyzed reactions of 2-siloxypyrroles, see: (*a*) H. Suga, H. Takemoto and A. Kakehi, *Heterocycles*, 2007, **71**, 361; (*b*) C. Curti, A. Sartori, L. Battistini, G. Rassu, F. Zanardi and G. Casiraghi, *Tetrahedron Lett.*, 2009, **50**, 3428; (*c*) C. Curti, L. Battistini, B. Ranieri, G. Pelosi, G. Rassu, G. Casiraghi and F. Zanardi, *J. Org. Chem.*, 2011, **76**, 2248. For selected asymmetric induction in total synthesis, see: (*d*) D. A. DeGoey, H.-J. Chen, W. J. Flosi, D. J. Grampovnik, C. M. Yeung, L. L. Klein and D. J. Kempf, *J. Org. Chem.*, 2002, **67**, 5445.

5 For limited examples, see: (*a*) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666; (*b*) X. Feng, H.-L. Cui, S. Xu, L. Wu and Y.-C. Chen, *Chem.–Eur. J.*, 2010, **16**, 10309; (*c*) Y. Zhang, Y.-L. Shao, H.-S. Xu and W. Wang, *J. Org. Chem.*, 2011, **76**, 1472; (*d*) H. Huang, Z. Jin, K. Zhu, X. Liang and J. Ye, *Angew. Chem., Int. Ed.*, 2011, **50**, 3232; (*e*) L. Lin, J. Zhang, X. Ma, X. Fu and R. Wang, *Org. Lett.*, 2011, **13**, 6410.

6 For reviews on chiral guanidine catalysts, see: (*a*) T. Ishikawa and T. Isobe, *Chem.–Eur. J.*, 2002, **8**, 552; (*b*) D. Leow and C.-H. Tan, *Chem.–Asian J.*, 2009, **4**, 488. For selected examples, see: (*c*) E. J. Corey and M. J. Grogan, *Org. Lett.*, 1999, **1**, 157; (*d*) T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda and T. Isobe, *Chem. Commun.*, 2001, 245; (*e*) H. Liu, D. Leow, K.-W. Huang and C.-H. Tan, *J. Am. Chem. Soc.*, 2009, **131**, 7212; (*f*) T. Misaki, K. Kawano and T. Sugimura, *J. Am. Chem. Soc.*, 2011, **133**, 5695; (*g*) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2002, **41**, 2832; (*h*) M. Terada and K. Ando, *Org. Lett.*, 2011, **13**, 2026.

7 (*a*) Z. P. Yu, X. H. Liu, L. Zhou, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2009, **48**, 5195; (*b*) S. X. Dong, X. H. Liu, X. H. Chen, F. Mei, Y. L. Zhang, B. Gao, L. L. Lin and X. M. Feng, *J. Am. Chem. Soc.*, 2010, **132**, 10650; (*c*) X. H. Chen, S. X. Dong, Z. Qiao, Y. Zhu, M. S. Xie, L. L. Lin, X. H. Liu and X. M. Feng, *Chem.–Eur. J.*, 2011, **17**, 2583; (*d*) S. X. Dong, X. H. Liu, Y. L. Zhang, L. L. Lin and X. M. Feng, *Org. Lett.*, 2011, **13**, 5060; (*e*) X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Commun.*, 2009, 6145.

8 CCDC 869057 (**7i**)†.

9 (*a*) H. Ube, N. Shimada and M. Terada, *Angew. Chem., Int. Ed.*, 2010, **49**, 1858; (*b*) X. Fu and C.-H. Tan, *Chem. Commun.*, 2011, **47**, 8210 and references therein.

