Asymmetric vinylogous Michael reaction of α,β-unsaturated ketones with γ-butenolide under multifunctional catalysis†

Huicai Huang, Feng Yu, Zhichao Jin, Wenjun Li, Wenbin Wu, Xinmiao Liang* and Jinxing Ye*

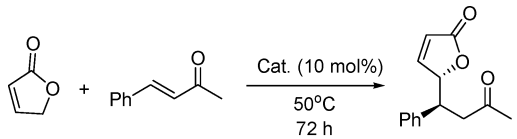
Received 21st April 2010, Accepted 7th June 2010
DOI: 10.1039/c0cc01054e

A general and direct organocatalytic asymmetric vinylogous Michael reaction of γ-butenolide with α,β-unsaturated ketones was investigated with a multifunctional primary amine salt as catalyst. The reaction enables straightforward access toward synthetically versatile γ-substituted butenolides from simple 2(5*H*)-furanone with satisfactory yields, diastereo- and enantioselectivities (up to 30 : 1 dr and 95–99% ee).

As one of the most powerful and useful carbon–carbon bond-forming reactions, the asymmetric Michael reaction enables access to a variety of optically active adducts combining abundant and various donors and acceptors. A variant of the reaction with a vinylogous nucleophile, known as the vinylogous Michael reaction, has attracted much interest.[1,2] It provides efficient access to functionalized γ-butenolides, which are ubiquitous building blocks for many natural products. Since γ-butenolides can easily isomerize into dienolates in the presence of a mild base, we envisioned that an asymmetric vinylogous Michael reaction could be achieved with 2(5*H*)-furanone with a chiral organocatalyst. Recently, a few excellent examples of catalytic asymmetric Mannich, aldol, Michael and allylation reactions have been reported with 2(5*H*)-furanone and related compounds as direct nucleophiles.[3] While this manuscript was in preparation, Li and co-workers reported a catalytic asymmetric vinylogous Michael addition of substituted γ-butenolides to chalcones catalyzed by vicinal primary-diamine salts.[4] But the substrate scope was limited to 3,4-diarylfuran-2(5*H*)-one and chalcones. For the simple 2(5*H*)-furanone, only 83% enantioselectivity and no diastereoselectivity were obtained. Herein we describe our efforts to address this reaction with much improved scope and efficiency, where a primary amine organocatalyst promoted the direct catalytic asymmetric vinylogous Michael reaction of simple 2(5*H*)-furanone with α,β-unsaturated ketones with high diastero- and enantioselectivities.[5]‡

Catalyst **1** developed in our group for the Michael reaction of α,β-unsaturated ketones was first examined in the reaction of benzalacetone and 2(5*H*)-furanone.[6] The reaction proceeded smoothly with 65% ee and 2.8 : 1 dr (Table 1, entry 1). Using 9-amino (9-deoxy) epiquinine as catalyst in the absence or presence of acidic additives, the reaction proceeded with 88% ee and 2.8 : 1 diastereoselectivity (Table 1, entry 2). Based on molecular modeling and conformational analysis of the iminium intermediate of the catalyst and benzalacetone, we hypothesized that a triamine might be a potential catalyst scaffold,[7] where a primary amine plays a role in activating the α,β-unsaturated ketone through an iminium mechanism,[8] and the secondary amine and hydrogen bond donor motif would

Table 1 Direct organocatalytic asymmetric vinylogous Michael reaction with γ-butenolide[a]



4 **5a** **6a**

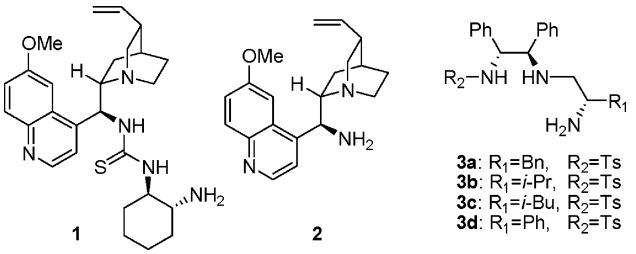
Entry	Catalyst	Solvent	Conversion (%)[b]	dr[c]	ee (%)[d]
1	**1**	$CHCl_3$	84	2.8 : 1	65
2	**2**	$CHCl_3$	85	2.8 : 1	88
3	**3a**	$CHCl_3$	90	3.5 : 1	39
4[e]	**3a**	$CHCl_3$	96	2.8 : 1	38
5[f]	**3a**	$CHCl_3$	95	4.8 : 1	75
6[g]	**3a**	$CHCl_3$	93	7 : 1	85
7[h]	**3a**	$CHCl_3$	95	11 : 1	95
8[h]	**3b**	$CHCl_3$	94	15 : 1	98
9[h]	**3c**	$CHCl_3$	97	10 : 1	97
10[h]	**3d**	$CHCl_3$	79	1 : 2.4	47
11[i]	**3b**	$CHCl_3$	86	15 : 1	97
12[j]	**3b**	$CHCl_3$	68	15 : 1	96
13[k]	**3b**	$CHCl_3$	90	12 : 1	97
14[l]	**3b**	$CHCl_3$	87	11 : 1	96
15[h]	**3b**	DCM	91	13 : 1	97
16[h]	**3b**	Toluene	93	13 : 1	96
17[h]	**3b**	THF	98	9 : 1	92
18[h]	**3b**	MeOH	92	2 : 1	77
19[h]	**3b**	DCE	94	11 : 1	97
20[h]	**3b**	EtOAc	93	11 : 1	96
21[h]	**3b**	MeCN	97	8 : 1	95
22[h]	**3b**	Et_2O	95	10 : 1	96
23[h]	**3b**	Dioxane	91	15 : 1	96
24[h]	**3b**	*n*-Hexane	99	9 : 1	95

[a] All reactions were carried out using 1.0 equiv. of **4** (0.10 mmol, 0.5 M), 2.0 equiv. of **5a** and 0.10 equiv. of catalyst. [b] Conversion was determined by GC. [c] Diastereoselectivity was determined by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC. [e] With 10 mol% of CH_3CO_2H. [f] With 10 mol% of CCl_3CO_2H. [g] With 10 mol% of $PhCO_2H$. [h] With 10 mol% of *N*-Boc-L-Phe (*N*-Boc-L-phenylalanine). [i] With 20 mol% of *N*-Boc-L-Phe. [j] With 30 mol% of *N*-Boc-L-Phe. [k] With 10 mol% of *N*-Boc-D-Phe. [l] With 10 mol% of *N*-Boc-L-Phg (*N*-Boc-L-phenylglycine).

Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China. E-mail: liangxm@ecust.edu.cn, yejx@ecust.edu.cn

† Electronic supplementary information (ESI) available: Experimental procedures and characterization of the Michael addition products. CCDC 774478. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc01054e

be beneficial to the reactivity and chiral assembly of 2(5*H*)-furanone.



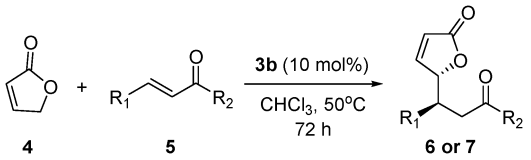
As such we designed another new type of catalyst **3** derived from L-amino acid and (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine, which had a primary amine, a vicinal secondary amine and a terminal hydrogen bond donor sulfonamide (catalysts **3a–3d**). The three functional groups constitute a chiral spatial pocket, which is responsible for both diastereo- and enantioselectivity. With catalyst **3a**, the reactivity and diastereoselectivity remained, while the enantioselectivity decreased (39% ee, entry 3). Screening found that the acidic additive had a profound effect both on the diastereoselectivity and enantioselectivity. Acetic acid produced similar results (entry 4). Trichloroacetic acid and benzoic acid as additives improved diastereo- and enantioselectivities (entries 5–6). Bulky *N*-Boc-L-Phe (*N*-Boc-L-phenylalanine) gave excellent results with 11 : 1 dr and 95% ee (entry 7). Screening of catalysts **3a–3d** revealed that **3b** from L-valine gave the highest diastereo- and enantioselectivities (entries 7–10). On increasing the amount of the bulky acidic additive, the reactivities decreased, while the stereoselectivities remained. (entries 7, 11–12). With other bulky acidic additives, *N*-Boc-D-Phe and *N*-Boc-L-Phg (*N*-Boc-L-phenylglycine), the reaction produced the desired chiral adducts only with slightly low diastereoselectivities (entries 13–14). This indicated that the chirality of the *N*-protected amino acid did not have a profound effect on the stereoselectivity of the reaction. Good to excellent stereoselectivities and conversions were observed in all the solvents screened except methanol (entries 15–24).

With these optimized conditions, the reactions of a variety of enones with γ-butenolide using **3b** were examined (Table 2). The reaction of benzalacetone with either an electron-withdrawing or electron-donating substituent—halogen, methoxy, methyl—at an *ortho*-, *meta*- or *para*-position afforded the desired products in high yield with high diastereo- and enantioselectivity (entries 2–15). The reactions between heteroaryl enones and γ-butenolide were quite successful (entries 17–18). It should be noted that chalcone was also applicable, affording the vinylogous product with 88 : 12 d.r. and 97% ee. Alkyl substituted enones were suitable substrates for the direct Michael reaction (entries 20–23). The reaction of 2-octen-4-one gave excellent enantioselectivity (99%) and good diastereoselectivity (7 : 1). With cyclic Michael acceptors, excellent enantioselectivity was observed using 20 mol% of catalyst **3b** with moderate to good yield and diastereoselectivity (entries 26–27).

Crystals of bromide product **6h** were obtained for an X-ray analysis, which established the *anti* stereochemical outcome and the absolute configuration.[9] A proposed transition state model that accounts for the observed stereoselectivity is given in Fig. 1. The enone formed an iminium salt with the primary amine of the catalyst, and the secondary amine and sulfonamide motifs may direct the γ-attack of the dienolate of 2(5*H*)-furanone toward one enantioface of the double bond. The G substituent and C anion simultaneously block the other enantioface of the double bond, which would also favor high enantioselectivity. TS B has less steric repulsion between the dienolate moiety and the C anion than TS A, leading to high diastereoselectivity. This hypothesis was supported by the excellent diastereo- and enantioselectivities when large G substituents (Bn, *i*-Pr, *i*-Bu *vs.* Ph) and bulky C anion motifs (*N*-Boc-L-Phe, *N*-Boc-D-Phe, *N*-Boc-L-Phg anion *vs.* $PhCO_2^-$, $CH_3CO_2^-$) were present.

In summary, a general and direct organocatalytic asymmetric vinylogous Michael reaction of γ-butenolide with α,β-unsaturated ketones was developed. The reaction enables straightforward access toward synthetically versatile γ-substituted butenolides from simple 2(5*H*)-furanone with satisfactory yields, diastereo- and enantioselectivities (2 : 1 → 30 : 1 dr and 95–99% ee).

Table 2 Organocatalytic asymmetric vinylogous Michael reaction of various α,β-unsaturated ketones[a]



Entry	R_1	R_2	Adduct	Yield[b] (%)	dr[c]	ee (%)[d]
1	Ph	Me	**6a**	84	15 : 1	98
2	*o*-FC_6H_4	Me	**6b**	80	10 : 1	97
3	*m*-FC_6H_4	Me	**6c**	75	15 : 1	96
4	*p*-FC_6H_4	Me	**6d**	79	15 : 1	98
5	*o*-ClC_6H_4	Me	**6e**	78	11 : 1	95
6	*m*-ClC_6H_4	Me	**6f**	81	10 : 1	97
7	*m*-BrC_6H_4	Me	**6g**	75	10 : 1	97
8	*p*-BrC_6H_4	Me	**6h**	78	8 : 1	95
9	*o*-$MeOC_6H_4$	Me	**6i**	85	13 : 1	98
10	*m*-$MeOC_6H_4$	Me	**6j**	73	19 : 1	97
11	*p*-$MeOC_6H_4$	Me	**6k**	84	10 : 1	96
12	*m*-MeC_6H_4	Me	**6l**	83	19 : 1	97
13	*p*-MeC_6H_4	Me	**6m**	85	19 : 1	96
14	2,3-$(MeO)_2C_6H_4$	Me	**6n**	86	11 : 1	97
15	2,4-$(MeO)_2C_6H_4$	Me	**6o**	85	11 : 1	98
16	2-Naphthyl	Me	**6p**	86	13 : 1	98
17	2-Furanyl	Me	**6q**	79	> 30 : 1	97
18	2-Thiophenyl	Me	**6r**	83	15 : 1	98
19	Ph	Ph	**6s**	79	7 : 1	97
20	Pr	Me	**6t**	75	> 20 : 1	98
21	Bu	Me	**6u**	74	> 20 : 1	96
22	Pen (pentyl)	Me	**6v**	82	> 20 : 1	97
23	Hex (hexyl)	Me	**6w**	78	> 20 : 1	97
24	Me	Bu	**6x**	65	7 : 1	99
25	$PhCH_2CH_2$	Me	**6y**	76	19 : 1	97
26[e]	$-(CH_2)_2-$		**7a**	51	2 : 1	97
27[e]	$-(CH_2)_4-$		**7b**	67	7 : 1	97

[a] All reactions were carried out using 1.0 equiv. of **4** (0.50 mmol, 0.5 M), 2.0 equiv. of **5**, 0.10 equiv. of catalyst **3b** and *N*-Boc-L-Phe in $CHCl_3$. [b] Isolated yield. [c] Diastereoselectivity was determined by ^1H NMR of the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC. [e] With 20 mol% catalyst.

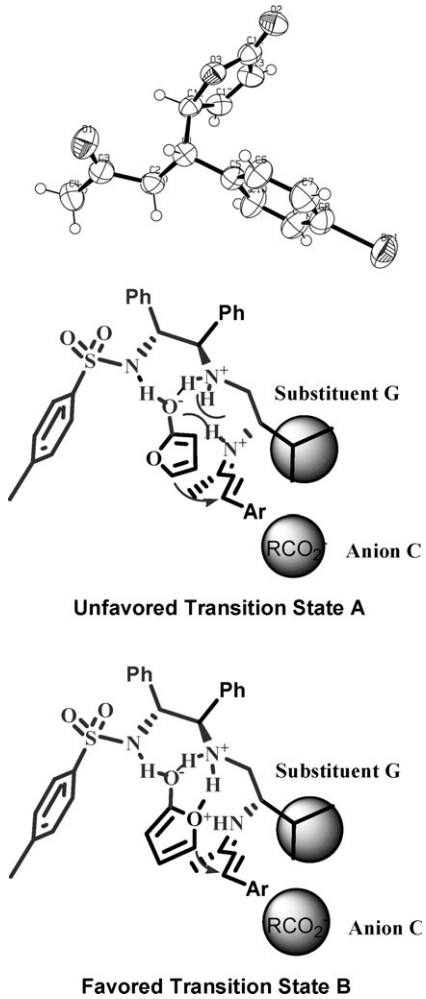


Fig. 1 X-Ray crystal structure of **6h** and proposed transition state in the vinylogous Michael reaction.

Expansion of the scope of this catalytic chemistry is currently underway.

We thank the Shanghai Pujiang Program (08PJ1403300), National Natural Science Foundation of China (20902018), the Fundamental Research Funds for the Central Universities and 111 project (B07023) for financial support.

Notes and references

‡ **General procedure for asymmetric Michael addition**: to a solution of α,β-unsaturated ketone **5** (1.0 mmol, 2.0 equiv.) in $CHCl_3$ (1.0 mL) was added catalyst **3b** (0.05 mmol, 0.1 equiv.) and *N*-Boc-L-Phe (0.05 mmol, 0.1 equiv.) followed by 2(5*H*)-furanone (0.5 mmol, 1.0 equiv.) The reaction mixture was stirred at 50 °C for 3 days and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired addition product.

Crystal structure determination of compound **6h**: $C_{14}H_{13}BrO_3$, M = 309.15; a block crystal (0.425 × 0.340 × 0.308 mm), T = 293(2) K, λ(Mo-Kα) = 0.71073 Å, orthorhombic, space group: $P2_12_12_1$, a = 6.5631(11) Å, b = 7.7659(12) Å, c = 27.286(4) Å, V = 1390.7(4) Å^3, 8391 total reflections, 3168 unique, R_{int} = 0.0517, R_1 = 0.0414 ($I > 2\sigma$), wR_2 = 0.0838, Flack parameter: 0.036(12).

1 For the reactions of silyloxy furan, see a recent review: (*a*) G. Casiraghi, F. Zanardi, L. Battistini and G. Rassu, *Synlett*, 2009, 1525. Selected examples: (*b*) H. Kitajima, K. Ito and T. Katsuki, *Tetrahedron*, 1997, **53**, 17015; (*c*) H. Kitajama and T. Katsuki, *Synlett*, 1997, 568; (*d*) H. Nishikori, K. Ito and T. Katsuki, *Tetrahedron: Asymmetry*, 1998, **9**, 1165; (*e*) G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zamponi and M. Zema, *Tetrahedron*, 2001, **57**, 10203; (*f*) S. P. Brown, N. C. Goodwin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 1192; (*g*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051; (*h*) H. Yang and S. Kim, *Synlett*, 2008, 555; (*i*) H. Suga, H. Takemoto and A. Kakehi, *Heterocycles*, 2007, **71**, 361.

2 For the reactions of α,α-dicyanoalkene, see a recent review: (*a*) H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 4479. Selected examples: (*b*) D. Xue, Y.-C. Chen, Q.-W. Wang, L.-F. Cun, J. Zhu and J.-G. Deng, *Org. Lett.*, 2005, **7**, 5293; (*c*) T. B. Poulsen, C. Alemparte and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 11614; (*d*) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Chem. Commun.*, 2006, 1563; (*e*) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Angew. Chem., Int. Ed.*, 2007, **46**, 389; (*f*) J. Alemán, C. B. Jacobsen, K. Frisch, J. Overgaard and K. A. Jørgensen, *Chem. Commun.*, 2008, 632.

3 (*a*) A. Yamaguchi, S. Matsunaga and M. Shibasaki, *Org. Lett.*, 2008, **10**, 2319; (*b*) B. M. Trost and J. Hitce, *J. Am. Chem. Soc.*, 2009, **131**, 4572; (*c*) H. Ube, N. Shimada and M. Terada, *Angew. Chem., Int. Ed.*, 2010, **49**, 1858; (*d*) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666; (*e*) H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu and Y.-C. Chen, *Org. Lett.*, 2010, **12**, 720.

4 J. Wang, C. Qi, Z. Ge, T. Cheng and R. Li, *Chem. Commun.*, 2010, **46**, 2124.

5 The asymmetric Michael reaction of chalcones and 2(5*H*)-furanone was catalyzed by Takemoto's bifunctional catalyst. Y. Zhang, C. Yu, Y. Ji and W. Wang, *Chem.–Asian J.*, 2010, DOI: 10.1002/asia.201000014.

6 (*a*) P. Li, Y. Wang, X. Liang and J. Ye, *Chem. Commun.*, 2008, 3302; (*b*) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang and J. Ye, *Org. Lett.*, 2009, **11**, 753.

7 (*a*) K. Ishihara and K. Nakano, *J. Am. Chem. Soc.*, 2005, **127**, 10504; (*b*) K. Ishihara and K. Nakano, *J. Am. Chem. Soc.*, 2007, **129**, 8930.

8 For primary amine catalyzed Michael reactions of unsaturated ketones through iminium mechanism, see the review: (*a*) G. Bartoli and P. Melchiorre, *Synlett*, 2008, 1759. Selected examples: (*b*) Y.-C. Chen, *Synlett*, 2008, 1919; (*c*) L.-W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, 2009, 1807; (*d*) H. Kim, C. Yen, P. Preston and J. Chin, *Org. Lett.*, 2006, **8**, 5239; (*e*) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri and P. Melchiorre, *Org. Lett.*, 2007, **9**, 1403; (*f*) X. Lu and L. Deng, *Angew. Chem., Int. Ed.*, 2008, **47**, 7710; (*g*) C. M. Reisinger, X. Wang and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 8112.

9 The absolute and relative configurations of **6h** were determined by X-ray crystallographic analysis.