RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Highly enantioselective direct vinylogous Michael addition of γ-substituted deconjugated butenolides to maleimides catalyzed by chiral squaramides†

Cite this: *RSC Advances*, 2013, **3**, 16973

Received 1st July 2013,
Accepted 23rd July 2013

DOI: 10.1039/c3ra43344g

www.rsc.org/advances

Yun-Long Guo,[ab] Li-Na Jia,[ab] Lin Peng,[a] Liang-Wen Qi,[ab] Jing Zhou,[ab] Fang Tian,[a] Xiao-Ying Xu*[a] and Li-Xin Wang*[a]

Highly enantioselective direct vinylogous Michael reactions of γ-aryl-substituted deconjugated butenolides with maleimides, catalyzed by only 1 mol% bifunctional squaramides derived from cinchona alkaloids, were achieved with excellent yields (up to 96%) and enantioselectivities (up to 97% ee). This protocol features a very low catalyst loading, mild reaction conditions and provides a potential and effective method for the construction of optically active chiral butenolides with adjacent quaternary and tertiary stereocenters.

Introduction

Chiral butenolides, bearing quaternary stereocenters,[1] are the core structural motifs in a number of natural compounds[2] (Fig. 1) which exhibit biological activities. There are two generally applied and feasible strategies used for the construction of these interesting molecules: the reaction of γ-substituted butenolides or substituted silyloxy furans with various acceptors.[3] Among them, the direct asymmetric vinylogous Michael reaction of γ-substituted butenolides provides a straightforward route. Recently, the reactions of γ-substituted butenolides with enals,[4] nitroolefins[5] and (*E*)-4-oxo-4-arylbutenamides[6] have been studied, while similar additions of γ-substituted butenolides to maleimides (which are extensively used to construct chiral succinimides[7]) have not been documented. Very recently, and during the preparation of this manuscript, Mukherjee and Manna have reported the first catalytic asymmetric direct vinylogous Michael addition of deconjugated butenolides to maleimides.[8] However, only aliphatic substituents of butenolides were investigated. To expand and gain deeper understanding of this useful and asymmetric transformation, it is still desirable to develop new efficient catalytic systems.

Over the past few years, chiral thioureas have been proved to be effective tools for asymmetric catalysis.[9] However, it was discovered that chiral squaramide catalysts were superior in activity and stereoinduction and have been successfully implemented in various important asymmetric transformations.[10] Based on this background, we recognized that tertiary amine squaramides could be efficient catalysts in the reaction of γ-substituted butenolides with maleimides, in which the tertiary amine group would activate the γ-substituted butenolides and the H-bond of the squaramide would activate the maleimides. Thus the synergistic interactions would ensure high stereoselectivity in such a transformation, affording the corresponding optically active products *via* a postulated transition state (TS) as shown in Scheme 1. As part of our continuing interests in asymmetric syntheses,[11] herein, we wish to report the highly effective direct vinylogous Michael reaction of γ-substituted butenolides with maleimides, which was catalyzed by only 1 mol% of bifunctional squaramides derived from cinchona alkaloids under mild conditions.

Results and discussion

Initial investigations were carried out using a series of squaramide catalysts (Fig. 2) for the model reaction of *N*-phenyl maleimide **1a**

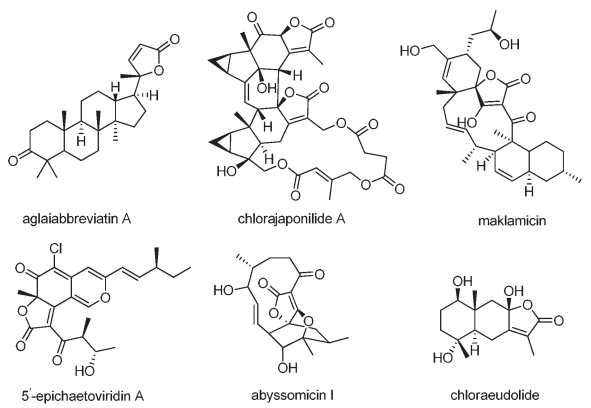
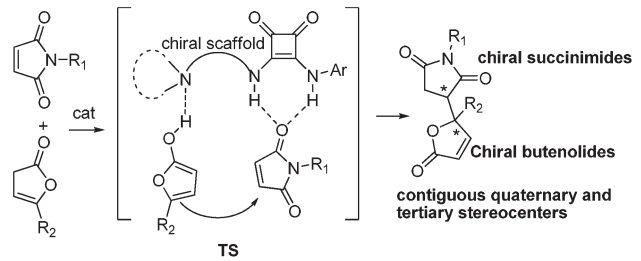


Fig. 1 Several natural compounds containing butenolides.

[a]*Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, People's Republic of China. E-mail: wlxioc@cioc.ac.cn; xuxy@cioc.ac.cn; Fax: +86-028-8525-5208*

[b]*University of Chinese Academy of Sciences, Beijing 10039, People's Republic of China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra43344g



Scheme 1 Strategy for the direct vinylogous Michael reaction.

with γ-phenyl-substituted butenolide **2a** in 1,2-dichloroethane at 30 °C. As shown in Table 1, when 10 mol% catalyst **4a** was used, the reaction afforded **3a** in 85% yield and 95% ee (Table 1, entry 1). Bifunctional squaramides **4b–f** were then screened and good yields, moderate diastereoselectivities and excellent enantioselectivities were obtained (90–94% yield, 75/25–91/9 dr and 86–95% ee, Table 1, entries 2–6). Cinchona alkaloid derived squaramides **4a–d** gave better enantioselectivities than cyclohexane-1,2-diamine derived squaramides **4e** and **4f** (Table 1, entries 1–4 *vs.* entries 5–6). Through the catalyst screening, catalyst **4b** was the better catalyst and was chosen for further optimization. When the catalyst loading was decreased to 1 mol%, the desired product **3a** was obtained in excellent yield and enantioselectivity (96% yield, 83/17 dr and 97% ee, Table 1, entry 7) over a longer reaction time (65 h). By increasing the concentration of the substrates, the reaction time was reduced to 5 h with almost the same yield and enantioselectivity (Table 1, entry 8 *vs.* entry 7). Solvents slightly affected the enantioselectivities and yields. In terms of reaction time and results, DCM was chosen as the suitable solvent (Table 1, entry 9). Based on the above results, 0.22 mmol **1a** and 0.2 mmol **2a** in 0.3 mL DCM with 1 mol% catalyst **4b** at 30 °C were established as the optimal reaction conditions.

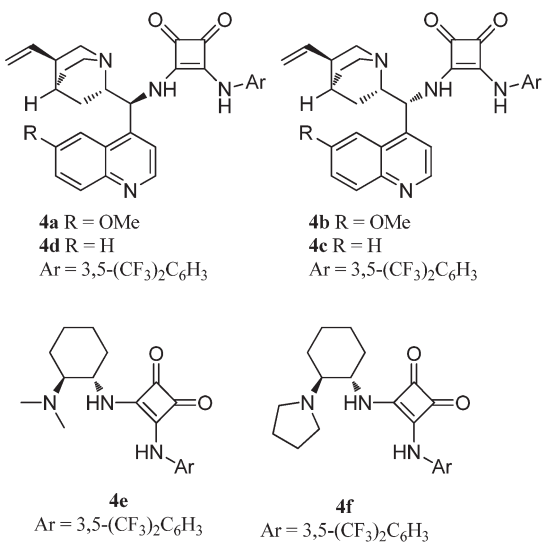
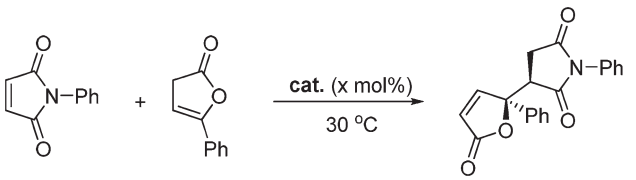


Fig. 2 Squaramide catalysts used for the asymmetric vinylogous Michael addition reactions.

Table 1 Screening of conditions for the asymmetric vinylogous Michael addition of **1a** to **2a**[a]



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

Entry	Cat.	*x*	Solvent	*t* (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	10	DCE	12	85	77/23	95[f]
2	**4b**	10	DCE	12	90	75/25	95
3	**4c**	10	DCE	12	93	80/20	95
4	**4d**	10	DCE	12	92	80/20	94[f]
5	**4e**	10	DCE	12	94	91/9	86[f]
6	**4f**	10	DCE	12	90	87/13	90[f]
7	**4b**	1	DCE	65	96	83/17	97
8[e]	**4b**	1	DCE	5	97	81/19	96
9[e]	**4b**	1	DCM	5	96	82/18	97
10[e]	**4b**	1	$CHCl_3$	7	95	79/21	97
11[e]	**4b**	1	THF	24	95	67/33	92
12[e]	**4b**	1	*m*-Xylene	24	96	78/22	96

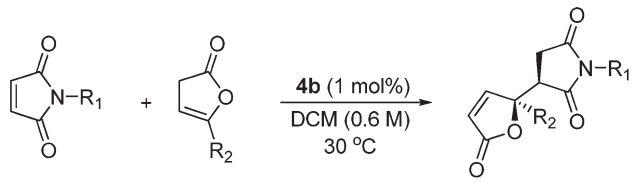
[a] Reactions carried out using 0.11 mmol **1a** and 0.1mmol **2a** in 1.0 mL DCM at 30 °C. [b] Isolated yield of the products after column chromatography. [c] Determined by HPLC analysis. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. [e] Reactions carried out using 0.22 mmol **1a** and 0.2 mmol **2a** in 0.3 mL DCM. [f] Contrary configuration.

Under the optimized reaction conditions, the scope of the asymmetric vinylogous Michael reaction was surveyed with respect to both maleimides and γ-substituted butenolides. The results are summarized in Table 2. For all cases, high yields (up to 96%), excellent enantioselectivities (up to 97%) and acceptable diastereoselectivities were obtained. The effects of *N*-aryl maleimides were screened first. It was found that the reaction worked well with various *N*-aryl maleimides bearing either electron-donating or electron-withdrawing substituents in the aromatic ring, regardless of the substituents at *ortho*- (Table 2, entry 12), *meta*- (Table 2, entries 8–11) or *para*-positions (Table 2, entries 2–7), and excellent yields and enantioselectivities were obtained (88%–96% yield, 94%–97% ee, Table 2, entries 2–12). *N*-Methyl maleimide was also studied and **3m** was obtained in 82% yield and 95% ee (Table 2, entry 13). γ-Aryl-substituted butenolides were evaluated and afforded products **3n–s** with good yields and excellent enantioselectivities (80–96% yield, 94–97% ee, Table 2, entries 14–19). γ-Methyl-substituted butenolide was used and led to **3t** with 83% ee because of the smaller steric interaction of the methyl group compared with aryl substitutes.

Conclusions

In conclusion, a highly effective direct vinylogous Michael addition of γ-aryl-substituted butenolides to maleimides, catalyzed by cinchona alkaloid derived squaramides, with a low catalyst loading (1 mol%) has been reported. This protocol features a very

Table 2 The scope of the asymmetric vinylogous Michael addition[a]



1 2 3

Entry	R_1	R_2	t (h)	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	Ph	5	**3a**	96	82/18	97
2	4-F-C_6H_4	Ph	5	**3b**	95	74/26	96
3	4-Cl-C_6H_4	Ph	7	**3c**	96	78/22	96
4	4-NO_2-C_6H_4	Ph	10	**3d**	94	81/19	95
5	4-OMe-C_6H_4	Ph	5	**3e**	96	77/23	96
6	4-Br-C_6H_4	Ph	5	**3f**	93	77/23	96
7	4-Me-C_6H_4	Ph	5	**3g**	95	81/19	97
8	3-NO_2-C_6H_4	Ph	4	**3h**	93	82/18	92
9	3-F-C_6H_4	Ph	4	**3i**	95	81/19	96
10	3-Br-C_6H_4	Ph	4	**3j**	91	78/22	94
11	3-Me-C_6H_4	Ph	20	**3k**	93	80/20	97
12	2-F-C_6H_4	Ph	4	**3l**	88	79/21	95
13	Me	Ph	96	**3m**	82	44/56	95/70
14	Ph	4-F-C_6H_4	30	**3n**	80	75/25	95
15	Ph	4-Cl-C_6H_4	6	**3o**	86	77/23	94
16	Ph	4-Br-C_6H_4	6	**3p**	83	78/22	95
17	Ph	4-Me-C_6H_4	3	**3q**	87	79/21	97
18	Ph	2,5-$(Me)_2$-C_6H_3	24	**3r**	96	77/23	97
19	Ph	2-naphthyl	4	**3s**	95	78/22	97
20	3-Me-C_6H_4	Me	12	**3t**	92	68/32	83[e]

[a] Reactions carried out using 0.22 mmol **1** and 0.2 mmol **2** in 0.3 mL DCM. [b] Isolated yield of the products after column chromatography. [c] Determined by HPLC analysis. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. [e] determined by comparing the retention times of the two enantiomers on a chiral HPLC with the literature.[8]

low catalyst loading, mild conditions and excellent results (up to 96% yield, 97% ee), which provides a potential and effective method for the construction of optically active chiral butenolides with adjacent quaternary and tertiary stereocenters.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21272230) and Western Light Talent Culture Project.

References

1 For selected reviews see: (*a*) J. Christoffers and A. Mann, *Angew. Chem.*, 2001, **113**, 4725, (*Angew. Chem., Int. Ed.*, 2001, **40**, 4591); for a recent book see: (*b*) *Quaternary Stereocenters*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, 2005.

2 (*a*) Y. Igarashi, L. K. Yu, S. Miyanaga, T. Fukuda, N. Saitoh, H. Sakurai, I. Saiki, P. Alonso Vega and M. E. Trujillo, *J. Nat. Prod.*, 2010, **73**, 1943; (*b*) F. Zhang, J. S. Wang, Y. C. Gu and L. Y. Kong, *J. Nat. Prod.*, 2010, **73**, 2042; (*c*) W. S. Borges, G. Mancilla, D. O. Guimarães, R. Durán Patrón, I. G. Collado and M. T. Pupo, *J. Nat. Prod.*, 2011, **74**, 1182; (*d*) P. L. Fang, Y. L. Cao, H. Yan, L. L. Pan, S. C. Liu, N. B. Gong, Y. Lü, C. X. Chen, H. M. Zhong, Y. Guo and H. Y. Liu, *J. Nat. Prod.*, 2011, **74**, 1408; (*e*) Y. Igarashi, H. Ogura, K. Furihata, N. Oku, C. Indananda and A. Thamchaipenet, *J. Nat. Prod.*, 2011, **74**, 670; (*f*) Q. H. Wang, H. X. Kuang, B. Y. Yang, Y. G. Xia, J. S. Wang and L. Y. Kong, *J. Nat. Prod.*, 2011, **74**, 16.

3 For selected examples see: (*a*) S. P. Brown, N. C. Goodwin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 1192; (*b*) H. Suga, T. Kitamura, A. Kakehi and T. Baba, *Chem. Commun.*, 2004, 1414; (*c*) H. L. Cui, J. R. Huang, J. Lei, Z. F. Wang, S. Chen, L. Wu and Y. C. Chen, *Org. Lett.*, 2010, **12**, 720; (*d*) R. P. Singh, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 9558; (*e*) A. Yanagisawa, N. Kushihara and K. Yoshida, *Org. Lett.*, 2011, **13**, 1576; (*f*) L. Zhou, L. L. Lin, J. Ji, M. S. Xie, X. H. Liu and X. M. Feng, *Org. Lett.*, 2011, **13**, 3056; (*g*) X. Huang, J. Peng, L. Dong and Y. C. Chen, *Chem. Commun.*, 2012, **48**, 2439; (*h*) E. K. Kemppainen, G. Sahoo, A. Valkonen and P. M. Pihko, *Org. Lett.*, 2012, **14**, 1086.

4 A. Quintard, A. Lefranc and A. Alexakis, *Org. Lett.*, 2011, **13**, 1540.

5 (*a*) M. Manna, V. Kumar and S. Mukherjee, *Chem. Commun.*, 2012, **48**, 5193; (*b*) V. Kumar, B. Ray, P. Rathi and S. Mukherjee, *Synthesis*, 2013, **45**, 1641.

6 W. Zhang, D. Tan, R. Lee, G. H. Tong, W. C. Chen, B. J. Qi, K. W. Huang, C. H. Tan and Z. Y. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 10069.

7 For reviews see: (*a*) P. Chauhan, J. Kaur and S. S. Chimni, *Chem.–Asian J.*, 2013, **8**, 328; for selected examples on cycloaddition reaction using maleimides see: (*b*) X. F. Xiong, Q. Zhou, J. Gu, L. Dong, T. Y. Liu and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2012, **51**, 4401; (*c*) Q. Y. Zhao, X. Y. Han, Y. Wei, M. Shi and Y. X. Lu, *Chem. Commun.*, 2012, **48**, 970; (*d*) F. R. Zhong, G. Y. Chen, X. Y. Han, W. J. Yao and Y. X. Lu, *Org. Lett.*, 2012, **14**, 3764; (*e*) Y. Wang, L. Liu, T. Zhang, N. J. Zhong, D. Wang and Y. J. Chen, *J. Org. Chem.*, 2012, **77**, 4143; for selected examples on the Michael addition reaction see: (*f*) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2006, **45**, 4966; (*g*) L. S. Zu, H. X. Xie, H. Li, J. Wang, W. Jiang and Wei Wang, *Adv. Synth. Catal.*, 2007, **349**, 1882; (*h*) Z. Y. Jiang, W. P. Ye, Y. Y. Yang and C. H. Tan, *Adv. Synth. Catal.*, 2008, **350**, 2345; (*i*) Z. Y. Jiang, Y. H. Pan, Y. J. Zhao, T. Ma, R. Lee, Y. Y. Yang, K. W. Huang, M. Wong and C. H. Tan, *Angew. Chem., Int. Ed.*, 2009, **48**, 3627; (*j*) F. Yu, X. M. Sun, Z. C. Jin, S. G. Wen, X. M. Liang and J. X. Ye, *Chem. Commun.*, 2010, **46**, 4589; (*k*) F. Xue, L. Liu, S. L. Zhang, W. H. Duan and W. Wang, *Chem.–Eur. J.*, 2010, **16**, 7979; (*l*) Y. H. Liao, X. L. Liu, Z. J. Wu, L. F. Cun, X. M. Zhang and W. C. Yuan, *Org. Lett.*, 2010, **12**, 2896; (*m*) G. Eduardo, A. Diego, A. G. Enrique and N. Carmen, *Org. Lett.*, 2011, **13**, 6106; (*n*) Y. H. Liao, X. L. Liu, Z. J. Wu, X. L. Du, X. M. Zhang and W. C. Yuan, *Adv. Synth. Catal.*, 2011, **353**, 1720; (*o*) S. Shirakawa, S. J. Terao, R. J. He and K. Maruoka, *Chem. Commun.*, 2011, **47**, 10557; (*p*) Q. Y. Zhao, C. K. Pei, X. Y. Guan and M. Shi, *Adv. Synth. Catal.*, 2011, **353**, 1973; (*q*) T. C. Nugent, A. Sadiq, A. Bibi, T. Heine, L. L. Zeonjuk, N. Vankova and B. S. Bassil, *Chem.–Eur. J.*, 2012, **18**, 4088; (*r*) L. X. Li, W. C. Chen, W. G. Yang, Y. H. Pan, H. J. Liu, C. H. Tan and Z. Y. Jiang, *Chem. Commun.*, 2012, **48**, 5124; for the direct vinylogous Michael addition of dicyanoolefins to maleimide see: (*s*) J. Lu, W. J. Zhou, F. Liu and T. P. Loh, *Adv. Synth. Catal.*, 2008, **350**, 1796.

8 M. Manna and S. Mukherjee, *Chem.–Eur. J.*, 2012, **18**, 15277.
9 For selected reviews see: (*a*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*b*) S. Schenker, A. Zamfir, M. Freund and S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2011, 2209.
10 For reviews see: (*a*) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem.–Eur. J.*, 2011, **17**, 6890, and references therein; for selected examples see: (*b*) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416; (*c*) W. Yang and D. M. Du, *Org. Lett.*, 2010, **12**, 5450; (*d*) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**, 1850; (*e*) F. Manoni, C. Cornaggia, J. Murray, S. Tallon and S. J. Connon, *Chem. Commun.*, 2012, **48**, 6502; (*f*) S. W. Duan, Y. Li, Y. Y. Liu, Y. Q. Zou, D. Q. Shi and W. J. Xiao, *Chem. Commun.*, 2012, **48**, 5160; (*g*) W. S. Sun, G. M. Zhu, C. Y. Wu, L. Hong and R. Wang, *Chem.–Eur. J.*, 2012, **18**, 6737; (*h*) P. Kasaplar, P. Riente, C. Hartmann and M. A. Pericàs, *Adv. Synth. Catal.*, 2012, **354**, 2905; (*i*) J. B. Ling, Y. Su, H. L. Zhu, G. Y. Wang and P. F. Xu, *Org. Lett.*, 2012, **14**, 1090.
11 (*a*) L. L. Wang, J. F. Bai, L. Peng, L. W. Qi, L. N. Jia, Y. L. Guo, X. Y. Luo, X. Y. Xu and L. X. Wang, *Chem. Commun.*, 2012, **48**, 5175; (*b*) Y. L. Guo, J. F. Bai, L. Peng, L. L. Wang, L. N. Jia, X. Y. Luo, F. Tian, X. Y. Xu and L. X. Wang, *J. Org. Chem.*, 2012, **77**, 8338; (*c*) L. L. Wang, L. Peng, J. F. Bai, L. N. Jia, X. Y. Luo, Q. C. Huang, X. Y. Xu and L. X. Wang, *Chem. Commun.*, 2011, **47**, 5593; (*d*) L. L. Wang, L. Peng, J. F. Bai, Q. C. Huang, X. Y. Xu and L. X. Wang, *Chem. Commun.*, 2010, **46**, 8064.

