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Development of Metal/Organo Catalytic Systems for Direct Vinylogous Michael Reactions to Build Chiral γ,γ-Disubstituted Butenolides

Dongxu Yang,[a] Linqing Wang,[a] Depeng Zhao,[a] Fengxia Han,[a] Bangzhi Zhang,[a] and Rui Wang*[a, b]

Cooperative catalysis is emerging as a valuable tool in asymmetric synthesis, fuelled by the identification of more efficient catalytic systems with increased substrate scopes.[1] Many endeavors have been devoted during the past few years toward developing the right catalyst pairs giving rise to powerful bifunctional systems, and many types of organic catalysts have been used in combination with appropriate metals to achieve unprecedented enantioselective processes.[2] In this field of research, cinchona-derived scaffolds have been recognized as one of the privileged structures for construction of new metal/organo binary catalytic systems,[3] given their extraordinary ability to induce stereocontrol and their commercial availability. Since Mukaiyama and co-workers developed the first example of combining cinchonine with $Sn(OTf)_2$ and applied it to the cyanation of aliphatic aldehydes,[4] several combinatorial catalytic strategies concerning cinchona alkaloid derivatives have been identified that promote addition reactions through dual activation of both substrates in nucleophilic–electrophilic additions.[5] These well-documented pioneering studies highlight the potential of this new research area and have brought us inspiration. Given these outstanding ideas and considering our continuous endeavors for designing metal/organo cooperative catalytic systems,[6] we believe that the design and operation of such systems with a high efficiency in promoting still challenging reactions plays a pivotal role in the discovery of useful synthetic pathways. Herein, we have tried to engage a series of Lewis acids to work together with the cinchona alkaloid and have developed two effective cooperative Brønsted base/Lewis acid catalytic systems that allow easy access to chiral γ,γ-disubstituted butenolides from γ-monosubstituted butenolides.

In recent years, the generation of optically active butenolides has attracted considerable attention owing to their synthetic significance in natural products and medicinally important agents.[7] In terms of atom economy and efficiency, tremendous excellent approaches have been accomplished toward developing direct stereocontrolled γ-functionalization of furanones and γ-butyrolactams to build the desired γ-monosubstituted adducts.[8] Despite these impressive contributions, however, the further use of such γ-monosubstituted butenolides to be rendered direct asymmetric transformations to γ,γ-disubstituted butenolides is still a dark side in this area of research. The first breakthrough in the direct enantioselective preparation of γ,γ-disubstituted butenolides derivatives was reported by Chen and co-workers[9] in 2010 with further contributions by the groups of Alexakis, Feng, and Mukherjee.[10] Very recently, a highly enantio- and diastereoselective asymmetric addition reaction between γ-substituted butenolides and electron-deficient olefins containing an oxazolidinone moiety has been reported by Huang, Tan, and Jiang et al. during the preparation of our manuscript.[11] In their work, the use of a *tert*-leucine-derived amine–thiourea catalyst could promote either γ-aryl- or alkyl-substituted butenolides as nucleophiles. Nevertheless, the direct asymmetric vinylogous conjugate addition of γ-substituted butenolides to the model substrate, such as enones, still represents a long-standing challenge. Moreover there is still a general deficiency of catalytic methods that tolerate variations of both the γ-aryl- and alkyl-substituted butenolides. Herein, we disclose our own solution to these problems by exploiting complementary activation modes of binary hybrid catalytic systems, which enabled a highly direct enantioselective vinylogous addition of both the γ-aryl- and alkyl-substituted butenolides to a series of aromatic and aliphatic enones.

To establish the method we investigated the addition of γ-phenyl-substituted butenolide **1a** with enone **2a** in detail. The initial trail under the catalysis of quinine (**B1**) failed to bring about bond formation after 24 h of stirring at room temperature (Table 1, entry 1). When the reaction was performed at 60 °C, the conversion improved a little and the product was obtained in 14 % yield with 72 % *ee* (*ee* = enantiomeric excess, entry 2). We hypothesized that the poor catalytic efficiency may be due to inefficient activation of the

[a] D. Yang, L. Wang, Dr. D. Zhao, F. Han, Dr. B. Zhang, Prof. Dr. R. Wang
Key Laboratory of Preclinical Study for New Drugs of Gansu Province, Institute of Biochemistry and Molecular Biology
School of Life Sciences and State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou, 730000 (P.R. China)

[b] Prof. Dr. R. Wang
State Key Laboratory of Chiroscience
Department of Applied Biology and Chemical Technology
The Hong Kong Polytechnic University, Kowloon (Hong Kong)
E-mail: wangrui@lzu.edu.cn
bcrwang@polyu.edu.hk

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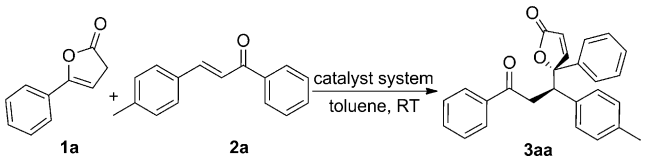
Table 1. Optimization of the direct vinylogous conjugate addition of γ-substituted butenolide **1a** to chalcone **2a**.[a]



Entry	B[b]	L[b]	M	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	B1	–	–	trace	–	–
2[f]	B1	–	–	14	7:1	72
3	B1	–	$M(OTf)_n$	–	–	–
4	B1	L1	$Ti(OiPr)_4$	22	>20:1	86
5[f]	B1	L1	$Ti(OiPr)_4$	45	16:1	69
6	**B1**	**L1**	**$Al(OiPr)_3$**	**81**	**>20:1**	**93**
7	B1	L1	$B(OnBu)_3$	25	>20:1	91
8	B1	L1	$In(OiPr)_3$	52	>20:1	88
9	B1	L1	$Sn(OiPr)_4$	34	>20:1	59
10	**B1**	**L1**	**$La(OiPr)_3$**	**88**	**>20:1**	**90**
11	B2	L1	$Al(OiPr)_3$	95	>20:1	−77
12	B3	L1	$Al(OiPr)_3$	63	>20:1	−74
13	B4	L1	$Al(OiPr)_3$	87	>20:1	88
14	B1	L2	$Al(OiPr)_3$	28	–	–
15	B1	L3	$Al(OiPr)_3$	21	–	–
16	B1	L4	$Al(OiPr)_3$	62	>20:1	88
17	B1	L5	$Al(OiPr)_3$	82	>20:1	75
18	B1	–	$Al(OiPr)_3$	72	>20:1	91

[a] Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), and B/M/L (10 mol%) in toluene (2.0 mL) at room temperature for 24 h. [b] B1 = quinine, B2 = quinidine, B3 = cinchonine, B4 = cinchonidine; L1 = (*R*)-Binol, L2 = 3,3′-Br,Br-(*R*)-Binol, L3 = 3,3′-I,I-(*R*)- Binol, L4 = 3,3′-(2-napthyl),(2-napthyl)-(*R*)-Binol; L5 = (*S*)-Binol. [c] Yield of isolated product. [d] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [e] Enantiomeric excess was determined by HPLC analysis. [f] Reactions were carried out at 60 °C.

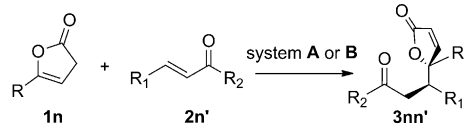
γ-substituted butenolide by a single Brønsted base. To improve the rate of the transformation, we explored the possibility of promoting a Lewis acid assisted Brønsted base system by incorporating an appropriate metal ion capable of activating the butenolide more effectively by enhancing the acidity of the α-C–H after the complexation. Meanwhile, the LUMO activation of the enone by the same Lewis acid could also smooth the bond-forming event. To test the concept, we initially examined a series of Lewis acids, such as $M(OTf)_n$[12] (entry 3), and much to our disappointment, the conjugate addition did not proceed as anticipated. We speculated that these strong metal ions may bind too tightly to the nitrogen atom, which could originally act as an organic base in the reaction. Considering the aforementioned hypothesis, we turned our attention to other metal ions that might be compatible with the precatalyst. Studies with well-developed titanium(IV) complexes[13] provided relatively higher reaction efficiency and better enantioselectivity (entries 4, 5). Given and encouraged by this finding, we deemed that we should broaden our views and look into potential cooperative catalytic systems that could better harness the reactivity of the substrates. After careful screening of a series of Lewis acids of this type, including $Al(OiPr)_3$,[14] $B(OnBu)_3$, $In(OiPr)_3$, $Sn(OiPr)_4$, and $La(OiPr)_3$,[15] we were pleased to observe a couple of binary Brønsted base/Lewis acid catalytic systems with perfect compatibility and that would produce the desired levels of stereoselectivity and catalytic efficiency (entries 6, 10). As illustrated in Table 1, the product **3a** could be obtained in 81% yield and 93% *ee* by using the B1/$Al(OiPr)_3$/L1 catalytic system, and a similar result (88%, 90% *ee*) could be achieved catalyzed by the B1/$La(OiPr)_3$/L1 system in a slightly higher yield with acceptable enantioselectivity. On the contrary, the other metal ions, such as boron(III), indium(III), and tin(IV) were not compatible to generate desirable catalytic systems in this asymmetric vinylogous conjugate addition. Additionally, we found that the catalytic systems needed properly compatible pairs between the Brønsted base and the ligand of the metal ions (entries 11–17),[5h] and the reaction performed without diphenol ligand could also generate the product **3aa** in relatively lower yield and with a slightly decreased *ee* value. (entry 6 vs. 18).

After establishing[16] the two optimized conditions for the efficient cooperative catalysis directed asymmetric vinylogous conjugate addition of γ-substituted butenolides to enones, we undertook an extensive survey of the scope of the reaction with respect to the substrate. As summarized in Table 2, aromatic enones **2** bearing various substituents and enones with condensed-ring or heteroaryl units were examined with **1a** (Table 2, entries 1–27). Excellent results were achieved except for **2c**, which produced a relatively lower yield (entry 5). The reaction was also conducted with aliphatic enones, such as **2t** and **2u**, and reasonable results were observed (entries 28, 29). Then the substrate scope of the vinylogous reaction of various γ-substituted butenolides **1** was examined. Excellent enantioselectivities and moderate to good yields (77–97%) were obtained for butenolides **1b–d** bearing different γ-aryl groups in the Michael reaction with enones **2** (entries 30–34), and it was pleasing that the reaction could be conducted with γ-alkyl butenolides **2e** despite 20% mol of the binary catalytic systems being required under a higher temperature (entries 35, 36). Finally, the data constructing the substrate scope in Table 1 suggests that using system **B** (B1/$La(OiPr)_3$/L1) resulted in higher yield with slightly lower enantioselectivity, whereas system **A** (B1/$Al(OiPr)_3$/L1) led to higher asymmetric induction. The absolute configuration of **3** was determined by X-ray crystallographic analysis of the product **3ah** (see the Supporting Information for details).[17]

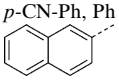
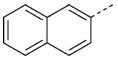
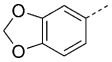
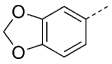
Finally, we have explored some concise synthetic transformations as shown in Scheme 1. The product **3ab** can be readily converted into γ,γ-disubstituted-lactone **5** in the presence of hydrogen gas and Pd/C. Then, lactone **5** can be easily transformed into the corresponding esters **6** by a Baeyer–Villiger oxidation. Alternatively, a highly stereoselective dihydroxylation of **3ab** furnished compound **4** when using $RuCl_3{\cdot}H_2O$ and $NaIO_4$. A single isomer of **4** was obtained and its relative configuration was confirmed by NOESY experiment (see the Supporting Information for details).

At the end of this work, an interesting phenomenon was observed. A retro-γ-functionalization was occasionally

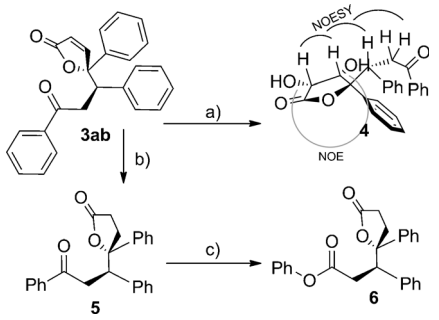
Table 2. Scope of the direct vinylogous Michael addition.



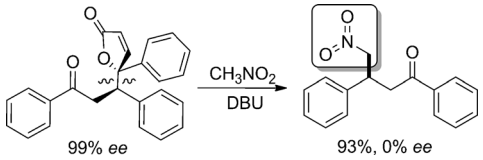
1a: R = Ph **1d**: R = *p*-MeO-Ph
1b: R = *p*-Me-Ph **1e**: R = Me
1c: R = *p*-Cl-Ph

Entry[a]	1	R_1, R_2	A/B[b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**1a**	*p*-Me-Ph, Ph (**2a**)	**A**	81	>20:1	93
2	**1a**	*p*-Me-Ph, Ph (**2a**)	**B**	88	>20:1	90
3	**1a**	Ph, Ph (**2b**)	**A**	82	>20:1	99
4	**1a**	Ph, Ph (**2b**)	**B**	91	>20:1	93
5	**1a**	*o*-Me-Phe, Ph (**2c**)	**A**	55	>20:1	99
6	**1a**	*m*-Me-Ph, Ph (**2d**)	**A**	77	>20:1	91
7	**1a**	*m*-Me-Ph, Ph (**2d**)	**B**	89	>20:1	91
8	**1a**	*p*-MeO-Ph, Ph (**2e**)	**A**	84	16:1	93
9	**1a**	*o*-MeO-Ph, Ph (**2f**)	**A**	72	11:1	95
10	**1a**	*o*-MeO-Ph, Ph (**2f**)	**B**	84	10:1	92
11	**1a**	*m*-MeO-Ph, Ph(**2g**)	**A**	85	>20:1	97
12	**1a**	*p*-Cl-Ph, Ph (**2h**)	**A**	92	>20:1	98
13	**1a**	*p*-Cl-Ph, Ph (**2h**)	**B**	94	>20:1	92
14	**1a**	*p*-Br-Ph, Ph (**2i**)	**A**	87	>20:1	97
15	**1a**	*p*-CN-Ph, Ph (**2j**)	**A**	99	>20:1	85
16	**1a**		**A**	90	>20:1	98
17	**1a**		**B**	95	>20:1	96
18	**1a**		**A**	69	>20:1	92
19	**1a**		**A**	83	17:1	91
20	**1a**		**B**	96	17:1	90
21	**1a**	2-furyl, Ph (**2n**)	**A**	82	>20:1	91
22	**1a**	2-thienyl, Ph (**2o**)	**A**	93	15:1	89
23	**1a**	2-thienyl, Ph (**2o**)	**B**	98	14:1	87
24	**1a**	Ph, *p*-Me-Ph (**2p**)	**A**	91	>20:1	95
25	**1a**	Ph, *p*-Cl-Ph (**2q**)	**A**	97	>20:1	90
26	**1a**	Ph, *p*-MeO-Ph (**2r**)	**A**	86	>20:1	93
27	**1a**	Ph, 2-furyl (**2s**)	**A**	92	>20:1	91
28	**1a**	*n*Hex, Ph (**2t**)	**A**	67	>20:1	86
29	**1a**	Ph, Me (**2u**)	**A**	85	>20:1	72
30	**1b**	Ph, *p*-Me-Ph (**2p**)	**A**	86	19:1	94
31	**1b**	Ph, Ph (**2b**)	**A**	86	17:1	92
32	**1c**	Ph, Ph (**2b**)	**A**	97	>20:1	98
33	**1d**	Ph, *p*-Me-Ph (**2p**)	**A**	77	18:1	97
34	**1d**	Ph, Ph (**2b**)	**A**	81	10:1	92
35[f]	**1e**	Ph, Ph (**2b**)	**A**	57	>20:1	82
36[f]	**1e**	Ph, Ph (**2b**)	**B**	68	>20:1	75

[a] Unless otherwise noted, reactions were carried out with **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), and the catalytic system **A** (B1/Al-(O*i*Pr)$_3$/L1) or **B** (B1/La(O*i*Pr)$_3$/L1) (10 mol%) in toluene (2 mL) at room temperature for 24 h. [b] This column indicates the catalytic system (**A** or **B**) used. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopic analysis of the isolated product. [e] Enantiomeric excess was determined by HPLC analysis. [f] The reactions were carried out by using 20 mol% of the catalytic system at 60°C for 48 h.



Scheme 1. Transformation of the vinylogous conjugate adducts. a) $RuCl_3{\cdot}H_2O$ (0.1 equiv), $NaIO_4$ (2.5 equiv), CH_3CN/H_2O (5:1, *v*/*v*), 0°C, 15 min, 52%; b) Pd/C, H_2 (balloon), MeOH, RT, overnight, 75%; c) KH_2PO_4, *meta*-chloroperoxybenzoic acid (*m*CPBA), dichloromethane, 60°C, 24 h, 72%.



Scheme 2. Observed reversibility of the γ-functionalization of the carbonyl group.

found, as shown in Scheme 2. When the adduct **3ab** was treated with a simple organic base, such as 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), the C–C bond cleavage at the γ-site of the carbonyl group of the γ,γ-disubstituted butenolides took place and a new bond was built up with another nucleophile.[18] A detailed study to expand the scope of the reaction to encompass additional nucleophilic reagents is currently underway in our laboratory.

In conclusion, we have developed two combinational catalytic systems that enable the efficient direct asymmetric vinylogous conjugate additions of γ-aryl-substituted butenolides to enones in good yields with high diastereoselectivities, and excellent enantioselectivities. In particular, the reversibility of γ-functionalization of carbonyl compounds was also discovered. Further research on the application of the combinatorial catalyst to other reactions and the synthetic utilities of the retrovinylogous additions are currently underway.

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Keywords: asymmetric synthesis · butenolides · catalysis · enones · organometallics

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