

Asymmetric Vinylogous Michael Reaction of α,β -Unsaturated Aldehyde with Buteno-4-lactone

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(Received February 14, 2011; CL-110123; E-mail: yejx@ecust.edu.cn)

The asymmetric vinylogous Michael reactions of α,β -unsaturated aldehydes with γ -butenolide (buteno-4-lactone) were efficiently catalyzed by the Jørgensen–Hayashi catalyst and LiOAc. The desired products were obtained in satisfactory yields with excellent enantioselectivities and moderate diastereoselectivities.

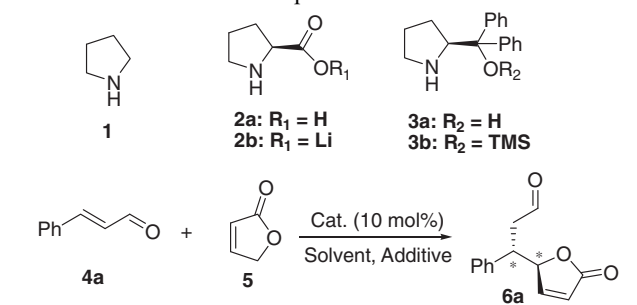
Compounds containing a γ -butyrolactone ring occur in many natural products, which are of broad biological activities such as antibacterial, anticancer, antiviral, and nonsteroidal anti-inflammatory drugs.¹ With the discovery of the potential bioactivities and other uses of those compounds, the preparation of them become a focus of attention.

Initially, intensive studies have been focused on the applications of silyloxyfuran.² Lewis acid-mediated asymmetric Mukaiyama Aldol and Mannich reactions employing silyloxyfuran and pyrrole have been well studied.^{2f,3} Furthermore, MacMillan developed an enantioselective Mukaiyama–Michael reaction of silyloxyfuran with aliphatic α,β -unsaturated aldehyde affording chiral γ -butenolide by MacMillan's amine catalyst.⁴ The direct reaction is highly valuable from the standpoint of atom economy. Therefore, in recent years, the intensive studies have been concentrated on the reactions of γ -butenolide and its derivatives.⁵ Moreover, Li and Wang realized diastereo- and enantioselective organocatalytic direct Michael addition of γ -butenolide or its derivatives to chalcones.⁶ Our group reported a general and direct organocatalytic asymmetric vinylogous Michael reaction of γ -butenolide with α,β -unsaturated ketones catalyzed by a multifunctional primary amine salt.⁷ Although great effort has been made for the vinylogous reactions of α,β -unsaturated system, the direct vinylogous Michael reactions of γ -butenolide to α,β -unsaturated aldehyde still remains a challenge due to the preference for 1,2-addition over 1,4-addition. Moreover, there has been no report of the direct vinylogous Michael reactions of γ -butenolide to α,β -unsaturated aldehydes. This stimulated us to screen various conditions to overcome the difficulties.

In this communication, we report the direct vinylogous Michael reactions of γ -butenolide to α,β -unsaturated aldehydes with high yields, excellent enantioselectivities, and moderate diastereoselectivities, which are catalyzed by the Jørgensen–Hayashi catalyst.⁸

We initially screened the conditions of direct vinylogous Michael reactions of γ -butenolide to α,β -unsaturated aldehydes. Since γ -butenolides can easily isomerize into dienolates in the presence of a mild base, we first conducted the reaction of cinnamaldehyde (**4a**) and γ -butenolide (**5**) in the presence of pyrrolidine. To our delight, the reaction proceeded to 85% of conversion (Table 1, Entry 1). This indicated that the direct

Table 1. Optimization studies



Entry ^a	Cat	Solvent	Additive	Conv. / % ^b	dr ^b	ee / % ^c
1 ^d	1	MeOH	None	85	1.6:1.0	0
2 ^d	2a	MeOH	None	38	1.6:1.0	nd
3 ^d	2b	MeOH	None	72	1.7:1.0	16
4 ^d	3a	MeOH	None	93	3.0:1.0	87
5 ^d	3b	MeOH	None	43	2.2:1.0	98
6 ^e	3b	MeOH	Boc-L-Phe	55	1.9:1.0	98
7 ^e	3b	MeOH	Boc-D-Phe	66	1.9:1.0	97
8 ^e	3b	MeOH	PhCOOH	51	2.1:1.0	97
9 ^e	3b	MeOH	PhCOOLi	70	2.4:1.0	97
10 ^e	3b	MeOH	LiOAc	82	2.4:1.0	99
11	3b	MeOH	LiOAc	91	2.5:1.0	>99
12	3b	EtOH	LiOAc	68	1.9:1.0	95
13	3b	DMF	LiOAc	85	2.1:1.0	74
14	3b	H ₂ O	LiOAc	47	2.2:1.0	99
15	3b	MeCN	LiOAc	21	2.2:1.0	nd
16	3b	Toluene	LiOAc	9	2.4:1.0	nd
17	3b	CHCl ₃	LiOAc	13	2.6:1.0	nd
18	3b	None	LiOAc	50	2.5:1.0	99
19	3b	MeOH ^f	LiOAc	93	2.3:1.0	99
20	3b	MeOH ^g	LiOAc	89	2.6:1.0	99

^aUnless otherwise noted, all reactions were performed with 3.0 mmol of **4a**, 1.0 mmol of **5**, 0.10 mmol of catalyst, and 0.20 mmol additive in 1.0 mL solvent at room temperature for 30 h. ^bDetermined by ¹H NMR of the crude product. ^cDetermined by chiral GC (the data are for the major isomer). ^d20 mol % of organic catalyst was used and the reaction time was 24 h. ^e20 mol % of organic catalyst and 20 mol % of additive were used and the reaction time was 24 h. ^fThe reaction was stirred in 0.5 mL MeOH. ^gThe reaction was stirred in 2.0 mL MeOH.

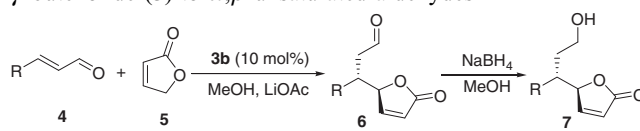
vinylogous Michael reactions could be efficiently promoted by the base. We next carried out the reaction in the presence of the chiral organocatalysts **2** and **3**. However, inferior results were

obtained catalyzed by **2** (Table 1, Entries 2 and 3). To our great delight, up to 93% conversion with 87% ee and 3.0:1.0 dr were obtained in the presence of **3a** (Table 1, Entry 4). Catalyzed by **3b**, excellent enantioselectivity (98%) with lower conversion (43%) was obtained (Table 1, Entry 5). We next used catalyst **3b** in the presence of acidic and basic additives. Screening results showed that the additives had a profound effect on the reaction rate but both the diastereo- and enantioselectivity were not remarkably effected (Table 1, Entries 6–10). For instance, Boc-D-phenylglycine, Boc-L-phenylglycine, and benzoic acid were introduced to produce the adducts with higher conversions and similar dr and ee values (Table 1, Entries 6–8). This revealed that acidic additive could not promote the reaction efficiently. Gratifyingly, the reaction would become fast in the presence of basic additive. The role of a mild base was proposed to shift the keto–enol tautomeric equilibrium to the enolic form, which is active for the nucleophilic reactions. With dr and ee values maintained, lithium benzoate and lithium acetate would give 70% and 82% conversion respectively (Table 1, Entries 9 and 10). Next, the catalyst loading was also taken into account. Reducing the catalyst loading to 10 mol %, up to 91% conversion with 2.5:1.0 dr and >99% ee were obtained after prolonged time (Table 1, Entry 11). A survey of different reaction solvents revealed that methanol was the most suitable solvent for this procedure. Performing the reaction in ethanol and DMF would induce a slight decrease of conversion (Table 1, Entries 12 and 13). However, the reaction in H₂O, MeCN, toluene, and CHCl₃ would become sluggish (Table 1, Entries 14–17). Interestingly, up to 50% conversion with 2.5:1.0 dr and 99% ee could still be observed when the reaction was carried out neat (Table 1, Entry 18). In addition, the amount of solvent was also examined. Unfortunately, this variation did not bring any improvement in the conversion and stereoselectivity (Table 1, Entries 19 and 20).

Having identified the best reaction conditions, we next explored the scope of the direct vinylogous Michael reactions of γ -butenolide to α,β -unsaturated aldehydes.⁹ Under the optimized conditions shown in Table 1, the reactions of a variety of α,β -unsaturated aldehydes **4** with γ -butenolide (**5**) were carried out.¹⁰ Representative results are shown in Table 2. The addition of γ -butenolide to aromatic α,β -unsaturated aldehydes gave products in good to excellent yields with good to excellent enantioselectivities and moderate diastereoselectivities (Table 2, Entries 1–13). Especially, the major diastereomers all formed with excellent enantioselectivities ranging from 93% to 98%. The results also indicated that the yields afforded by electron-donating groups were higher than those by electron-withdrawing groups, while the position of the substituent groups on the benzene ring have limited effect on stereoselectivity. Additionally, the large 3-(2-naphthyl)acrylaldehyde was also explored and the adduct was formed in 87% yield with 2.7:1.0 dr and 97/91% ee values (Table 2, Entry 14). Promising results were also achieved from the addition of γ -butenolide to aliphatic α,β -unsaturated aldehydes. Apart from (*E*)-pent-2-enal, the enantioselectivities of major diastereomers afforded by crotonaldehyde and hexenal, were excellent (Table 2, Entries 15–18).

Comparing proton nuclear magnetic resonance (¹H NMR) spectra and optical rotation of the minor diastereomer **6r** with the literature data^{4a} revealed that it was obtained as the (*S,R*)-diastereomer. Thus, according to the mechanism of catalyst **3b**

Table 2. Asymmetric vinylogous Michael reactions of γ -butenolide (**5**) to α,β -unsaturated aldehydes **4**



Entry ^a	R	Yield/% ^b	dr ^c	ee ^d /%
1	Ph	94, 7a	2.2:1.0	98 (83)
2 ^e	2-ClPh	71, 7b	1.6:1.0	93 (88)
3 ^e	4-ClPh	77, 7c	2.2:1.0	95 (89)
4 ^e	4-FPh	69, 7d	2.5:1.0	98 (88)
5 ^e	4-BrPh	74, 7e	2.3:1.0	96 (84)
6	2-MePh	90, 7f	1.6:1.0	98 (96)
7	3-MePh	88, 7g	2.2:1.0	98 (100)
8	4-MePh	92, 7h	2.5:1.0	98 (87)
9	2-MeOPh	81, 7i	2.2:1.0	97 (88)
10	3-MeOPh	75, 7j	2.1:1.0	94 (83)
11	4-MeOPh	93, 7k	2.5:1.0	96 (84)
12	2, 3-diMeOPh	93, 7l	2.3:1.0	94 (97)
13	2, 4-diMeOPh	92, 7m	2.8:1.0	98 (92)
14	2-Naphthyl	87, 7n	2.7:1.0	97 (91)
15 ^f	Me	56, 6o	2 ^g :1.0	94 ^h (77 ^h)
16 ^f	Et	43, 6p	2 ^g :1.0	82 ^h (84 ^h)
17 ^f	Pr	57, 6q	2 ^g :1.0	97 ^h (86 ^h)
18 ^f	<i>i</i> -Pr	68, 6r	2 ^g :1.0	>99 ^h (95 ^h)

^aUnless otherwise noted, all reactions were performed with 2.0 mmol of **4**, 1.0 mmol of **5**, 0.1 mmol of **3b**, and 0.20 mmol LiOAc in 1.0 mL MeOH at room temperature for 36 h.

^bIsolated yield of product after column chromatography.

^cDetermined by the crude ¹H NMR. ^dDetermined by chiral HPLC (the data in parentheses is related to the minor isomer).

^e20 mol % of **3b** and 30 mol % LiOAc were used. ^f1.0 mmol of **4** and 3.0 mmol of **5** were used. ^gDetermined by GC with area percentage. ^hDetermined by chiral GC with area percentage (the data in parentheses is related to the minor isomer).

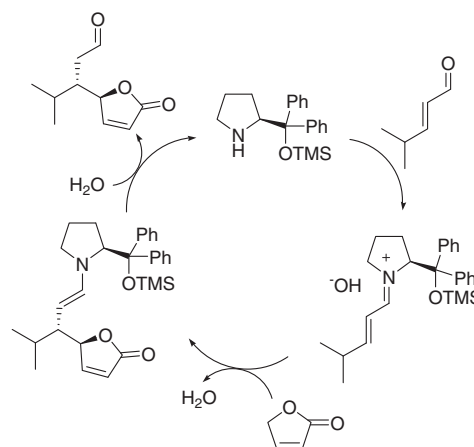


Figure 1. Proposed catalytic cycle.

(Figure 1), the major diastereomer **6r** is (*S,S*) absolute configuration.

In conclusion, an enantioselective vinylogous Michael reactions of α,β -unsaturated aldehydes with γ -butenolide was

efficiently developed. This approach serves as a powerful tool for the synthetically chiral γ -butenolide skeleton. The desired products were obtained in high yields with excellent enantioselectivities and moderate diastereoselectivities.

We thank Innovation Program of Shanghai Municipal Education Commission (No. 11ZZ56), Shanghai Pujiang Program (No. 08PJ1403300), National Natural Science Foundation of China (No. 20902018), and the Fundamental Research Funds for the Central Universities for financial support.

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- General procedure for asymmetric Michael addition of α,β -unsaturated aldehyde with γ -butenolide and reduction: To a solution of γ -butenolide (**5**) in solvent was added α,β -unsaturated aldehyde **4** and catalyst. The reaction mixture was stirred at room temperature for the time indicated in Table 2. Methanol was added to the mixture and then NaBH₄ was introduced. The resulting solution was stirred for an additional 1 h at rt. The crude was filtered using sintered discs with silica gel. The filtration was evaporated under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography to yield the desired product.
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