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Asymmetric Direct Vinylogous Aldol Reaction of Unactivated γ-Butenolide to Aldehydes

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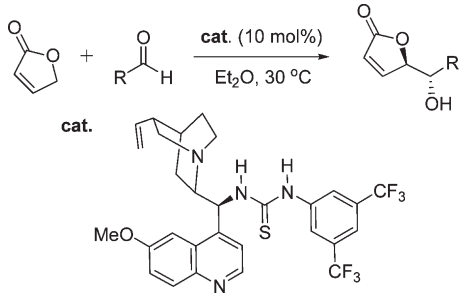
Received May 14, 2010



The asymmetric direct vinylogous aldol reaction of unactivated γ-butenolide with aldehydes has been developed, giving the corresponding 5-(1′-hydroxy)butenolide derivatives in high yields (up to 93%) and enantioselectivities (up to 83% ee) under mild conditions.

The 5-(1′-hydroxy)-γ-butenolide subunits are frequently found in biologically active natural products, such as Nafuredin-γ[1] and Lembertellols A and B.[2] Many protocols have been developed successfully for the formation of this linchpin.[3] Thus the synthesis of such compounds has attracted significant attention. Recently, catalytic vinylogous aldol (VA) reactions were described to be one of the most efficient methods for the construction of 5-membered furanone derivatives.[4] 2-Silyoxyfuran, which was synthesized from γ-butenolides, was the general nucleophilic reagent in the reactions (Scheme 1, eq 1). But it was hard to store and also not atom-economic, which limited its use. The VA reaction of γ-butenolides[5,6] could overcome such shortcoming and directly afford hydroxyl-γ-butenolides (Scheme 1, eq 2). However, γ-butenolides were infrequently investigated owing to their low reactivity. Most recently, Terada et al. reported the enantioselective VA reaction of aldehydes.[6e] Halo substituent(s) of 2(5*H*)-furanone were used to improve nucleophilicity at the γ-position and prevent the reaction at the α-position. When nonsubstituted furanone was used, the reaction only provided complex mixtures. To the best of our knowledge, the enantioselective direct VA reaction of unactivated γ-butenolides has not yet been reported. Herein, we wish to describe the asymmetric VA reaction of γ-butenolides catalyzed by a quinine-derived thiourea organocatalyst, affording the corresponding products in up to 93% yield, 85:15 *anti*/*syn*, and 83% ee.

Chiral bifuctional thioureas[7] are a type of organocatalysts that combine a basic nitrogen with a readily tunable hydrogen-bonding group, which have emerged as powerful tools for asymmetric construction of chiral molecules. Accordingly, our initial investigation began with screening chiral diamine derived thioureas **1a**−**d** (Figure 1). In the presence of **1a**, the reaction of γ-butenolide **2** and benzaldehyde **3a** in Et_2O at 30 °C afforded only a trace amount of **4a** (Table 1, entry 1). Then we synthesized thiourea **1b** from cyclohexane diamine, which promoted the reaction with 30% yield, 63:37 *anti*/*syn*, and 76% ee of the *anti* product (Table 1, entry 2).[8] However, when **1c**, possessing two bulky ethyl groups at the

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(8) Absolute configurations were determined by conversion to known compound. See the Supporting Information for details.

Published on Web 06/30/2010 DOI: 10.1021/jo100946d

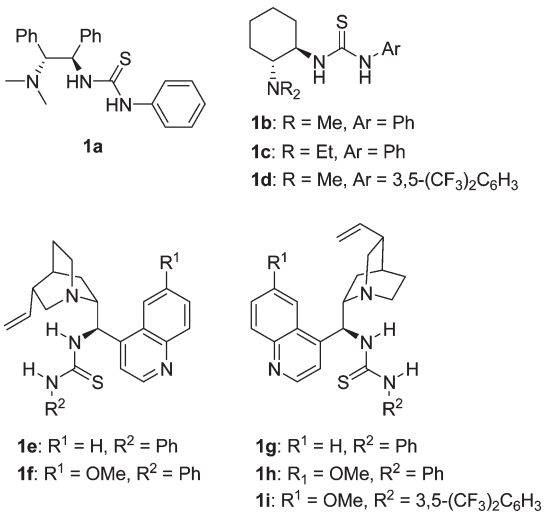


FIGURE 1. Thiourea catalysts evaluated.

SCHEME 1. Asymmetric VA Reactions for the Synthesis of Chiral Hydroxyl-γ-butenolides

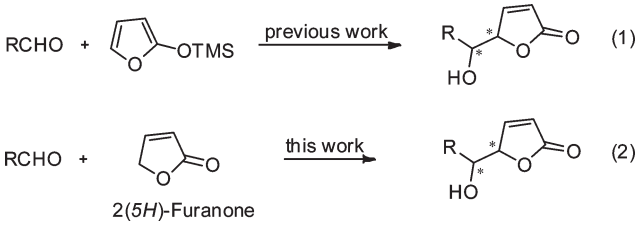
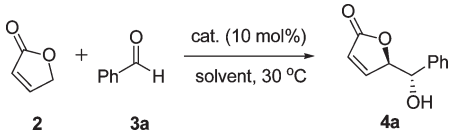


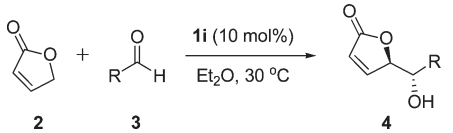
TABLE 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	yield (%)[b]	dr[c] (*anti*/*syn*)	ee of *anti* (%)[c,d]
1	**1a**	Et_2O	trace		
2	**1b**	Et_2O	30	63:37	−76 (−35)
3	**1c**	Et_2O	trace		
4	**1d**	Et_2O	50	80:20	−81 (−60)
5	**1e**	Et_2O	26	80:20	−71 (−18)
6	**1f**	Et_2O	10	85:15	−76 (−39)
7	**1g**	Et_2O	18	85:15	70 (35)
8	**1h**	Et_2O	41	83:17	76 (7)
9	**1i**	Et_2O	62	85:15	82 (54)
10	**1i**	THF	15	87:13	77 (80)
11	**1i**	PhOMe	44	81:19	74 (53)
12	**1i**	*t*-BuOMe	38	89:11	83 (65)
13	**1i**	CH_2Cl_2	31	76:24	64 (32)
14	**1i**	$CHCl_3$	40	83:17	75 (36)
15	**1i**	toluene	75	76:24	71 (10)
16	**1i**	MeCN	trace		
17[e]	**1i**	Et_2O	87	85:15	82 (43)
18[f]	**1d**	Et_2O	75	80:20	−81 (−60)

[a]Unless otherwise noted, all reactions were carried out with **1** (10 mol %), 2(5*H*)-furanone **2** (0.2 mmol), and benzaldehyde **3a** (0.1 mmol) in solvent (0.5 mL) at 30 °C for 40 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. Relative configurations of the product were assigned according to ref 4a. [d]The results in parentheses are ee of *syn* products. [e]Reaction was performed with 0.4 mmol of **2** for 50 h. [f]Reaction was performed with 0.4 mmol of **2** for 70 h.

TABLE 2. Substrate Scope for the Catalytic Enantioselective VA Reaction of γ-Butenolide 2 to Aldehydes 3[a]



entry	R	*t* (h)	yield (%)[b]	dr[c] (*anti*/*syn*)	ee of *anti* (%)[c,d]
1	Ph	50	87 (**4a**)	85:15	82 (43)
2	4-FC_6H_4	48	90 (**4b**)	84:16	82 (18)
3	4-ClC_6H_4	40	83 (**4c**)	81:19	81 (27)
4	4-BrC_6H_4	40	83 (**4d**)	82:18	79 (13)
5	2-FC_6H_4	40	80 (**4e**)	85:15	82 (36)
6	2-MeC_6H_4	52	76 (**4f**)	81:19	82 (46)
7	3-MeC_6H_4	48	91 (**4g**)	81:19	83 (4)
8	4-MeC_6H_4	52	75 (**4h**)	82:18	81 (20)
9	2-$MeOC_6H_4$	52	93 (**4i**)	82:18	81 (60)
10	3-$MeOC_6H_4$	52	89 (**4j**)	79:21	79 (22)
11	4-$MeOC_6H_4$	72	73 (**4k**)	83:17	78 (15)
12	2-thienyl	48	91 (**4l**)	85:15	81 (7)
13	2-naphthyl	48	82 (**4m**)	79:21	79 (4)
14	*c*-hexyl	48	40 (**4n**)	80:20	78 (17)

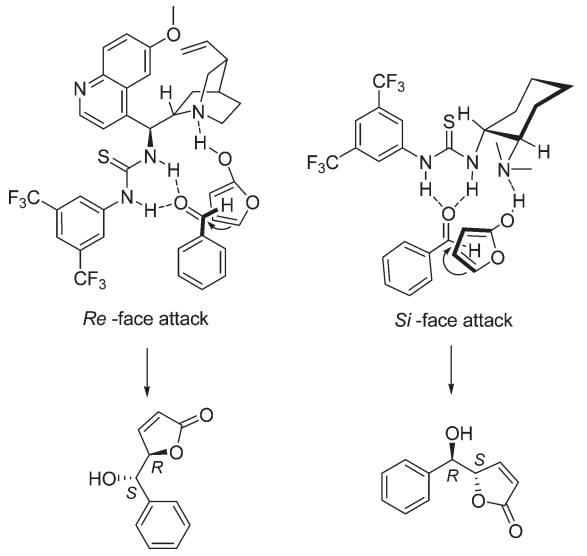
[a]All reactions were carried out with **1i** (10 mol %), 2(5*H*)-furanone **2** (0.4 mmol), and aldehyde **3** (0.1 mmol) in Et_2O (0.5 mL) at 30 °C for 40−72 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. Relative configurations of the product were assigned according to ref 4a. [d]The results in parentheses are ee of *syn* products.

amine moiety, was used, the reaction rate decreased dramatically (Table 1, entry 3 vs 2). It seemed that the steric hindrance at tertiary nitrogen hampered the deprotonation of γ-butenolide to generate the active dienolate. The electron-withdrawing trifluoromethyl group at the thiourea moiety could enhance the acidity of the hydrogen bond donor, and catalyst **1d** promoted the reaction with improved yield and enantioselectivity (50% yield, 81% ee, 80:20 *anti*/*syn*; Table 1, entry 4 vs 2). To further improve the results of the reaction, several chiral cinchona-alkaloid-derived thioureas were investigated. The results suggested that thiourea **1h** was superior to the other three ones **1e**−**g** in both yields and enantioselectivities (Table 1, entry 8 vs entries 5−7). With regards to the thiourea moiety, compound **1i**, which has a bulky 3,5-bis-(trifluoromethyl)phenyl group attached, gave a promising ee value of 82% (Table 1, entry 9 vs 8).

To improve the outcomes, other reaction conditions were explored. The solvent was found to be an important parameter on reactivity and enantioselectivity. The ether solvents such as THF, PhOMe, and *t*-BuOMe gave either low yield or poor enantioselectivity (Table 1, entries 10−12 vs entry 9). The screening of other solvents showed that Et_2O was the best solvent for the VA reaction (Table 1, entry 9 vs entries 13−16). By increasing the amount of γ-butenolide **2** to 4 equiv and prolonging the reaction time to 50 h a 87% yield was obtained with the selectivities maintained (Table 1, entry 17 vs 9). Therefore, the optimal reaction conditions were identified as 0.1 mmol of benzaldehyde, 10 mol % of **1i**, and 0.4 mmol of 2(5*H*)-furanone in 0.5 mL of Et_2O at 30 °C. Notably, the product with opposite configuration was also obtained in 75% yield with 81% ee and 80:20 dr by using catalyst **1d** under the optimal condition (Table 1, entry 18) (see the Supporting Information).

With the optimized conditions in hand, substrate scope was investigated and the results were summarized in Table 2. High enantioselectivities and good diastereoseletivities were obtained

SCHEME 2. Proposed Transition State for VA Reaction Catalyzed by 1i and 1d



with a series of aromatic aldehydes (78−83% ee, up to 85:15 dr; Table 2, entries 1−13). Substrates with electron-withdrawing groups exhibited higher reactivity than those with electron-donating groups. Moreover, the position of the substituents at aromatic ring had no obvious effect on the enantioselectivity (78−83% ee; Table 2, entries 2−11). Furthermore, the hetero-aromatic aldehyde could be smoothly converted to the desired product in 91% yield with 81% ee (Table 2, entry 12), while the condensed-ring aldehyde also succeeded with 82% yield and 79% ee (Table 2, entry 13). Significantly, the aliphatic aldehyde **3n** gave the corresponding product in 40% yield with 78% ee (Table 2, entry 14).

On the basis of the absolute configurations of (5*R*,1′*S*)-**4a** catalyzed by **1i** and (5*S*,1′*R*)-**4a**[8] catalyzed by **1d**, two transition state models for the reaction of **2** and **3a** have been proposed (Scheme 2). The aldehyde **3a** was activated by the thiourea moiety through double hydrogen bonding formed from the interaction between the NH group of **1i** or **1d** and the carbonyl group of **3a**,[9−11] while the basic nitrogen in the catalyst may deprotonate γ-butenolide **2** to generate dienolate. Then, for catalyst **1i**, the desired product (5*R*,1′*S*)-**4a** could be produced by the *Re*-face attack to the activated aldehyde, as well as (5*S*,1′*R*)-**4a** by the *Si*-face attack for catalyst **1d**.

In conclusion, we have developed the first enantioselective direct aldol reaction of unactivated γ-butenolide with aldehydes, using a cinchona alkaloid-based thiourea. Various aldehydes were converted into the corresponding products in high yields (up to 93%) and enantioseletivities (up to 83% ee) under mild conditions. This contribution provides a simple, practical, and atom-economy synthetic strategy for direct formation of 5-(1′-hydroxy)-γ-butenolides, which are the linchpin for further transformations. Further efforts are devoted to the study of γ-butenolides as direct starting materials in asymmetric reactions and its applications in natural product synthesis.

Experimental Section

General Procedure for the Catalytic Enantioselective VA Reaction between Aldehyde 3b and 2(5*H*)-Furanone 2. Aldehyde **3b** (11 μL, 0.1 mmol) and catalyst **1i** (5.9 mg, 0.01 mmol) were stirred in Et_2O (0.5 mL) for 20 min at ambient temperature, and the 2(5*H*)-furanone **2** (28 μL, 0.4 mmol) was added. The mixture was stirred at 30 °C for 48 h. After that, the reaction mixture was purified directly by flash chromatography to give the desired product **4b**: 90% yield; 82% ee, 84:16 dr (determined by HPLC analysis with a Chiral AD-H column, hexane/2-propanol 95: 5, 1.0 mL/min, UV = 210 nm; t_1 = 24.2 min, t_2 = 27.4 min, t_3 = 31.6 min, t_4 = 33.0 min); $[\alpha]^{25}_D$ +94.3 (*c* 0.212, in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 3H), 7.18 (dd, *J* = 8.0, 4.0 Hz, 1H, *syn*), 7.13−7.06 (m, 2H, *anti*, *syn*), 6.19 (dd, *J* = 6.0, 2.0 Hz, 1H, *anti*), 6.18 (dd, *J* = 6.0, 2.0 Hz, 1H, *syn*), 5.16−5.14 (m, 2H, *syn*, *anti*), 5.05 (m, 1H, *anti*), 4.74 (dd, *J* = 9.6, 3.2 Hz, 1H, *syn*), 2.85 (d, *J* = 3.2 Hz, 1H, *syn*), 2.63 (d, *J* = 3.6 Hz, 1H, *anti*) ppm; ^{13}C NMR δ (100 MHz, $CDCl_3$) δ 152.60, 134.01, 127.84 (d, *J* = 5.3 Hz), 123.38, 115.83, 115.69, 86.26, 72.68; HRMS (ESI) calcd for $C_{11}H_9FO_3$ [M + NH_4^+] 226.0874, found 226.0872.

Acknowledgment. We appreciate the financial support from the National Natural Science Foundation of China (Nos. 20732003 and 20902060), PCSIRT (No. IRT0846), and the National Basic Research Program of China (973 Program No. 2010CB833300). We also thank Sichuan University Analytical & Testing Center for NMR analysis.

Supporting Information Available: Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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