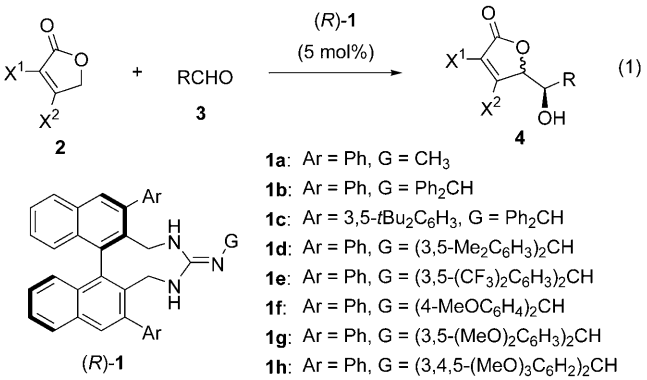
Organocatalysis

DOI: 10.1002/ange.200906647

Asymmetric Direct Vinylogous Aldol Reaction of Furanone Derivatives Catalyzed by an Axially Chiral Guanidine Base**

*Hitoshi Ube, Naoki Shimada, and Masahiro Terada**

The aldol reaction is one of the most ubiquitous in synthetic organic chemistry. The vinylogous extension of this fundamental C–C bond-forming reaction to nucleophilic components, namely the vinylogous aldol (VA) reaction, has also been intensively investigated,[1] as it provides efficient access to highly functionalized δ-hydroxy carbonyl compounds that contain a double bond. In particular, the utilization of 2-silyloxyfuran as the vinylogous nucleophile has attracted much attention[2] because the reaction affords γ-substituted butenolides,[3] an important structural motif in naturally occurring products and biologically active compounds. In this context, the development of the enantioselective catalysis of the VA reaction using 2-silyloxyfuran continues to be a substantial challenge in organic synthesis, and several excellent approaches have been reported to date.[1b,2] The direct use of 2-(5*H*)furanone derivatives, instead of 2-silyloxyfuran as the preformed nucleophile, provides a practical entry to γ-substituted butenolides, and has also been investigated using a stoichiometric amount of strong base.[1a] However, to the best of our knowledge, the enantioselective catalysis of direct VA reactions of furanone derivatives has yet to be reported,[4,5] despite their distinct advantage of being more atom economical and ecologically friendly. Recently, we reported the use of axially chiral guanidines (**1**)[6] as efficient enantioselective base catalysts.[7] Therefore, we aimed to develop the chiral guanidine-catalyzed direct VA reaction of furanone derivatives that afforded enantioenriched butenolides. For this purpose, (di)halofuran-2(5*H*)-ones (**2**) seemed attractive as vinylogous nucleophiles[8] because of their inherent multifunctionality and versatility as chiral building blocks.[9] Furthermore, the halo substituent(s) enhance the acidity of the furanones at the γ position and prevent bond formation at the α position, as with the normal aldol reaction. Herein, we report the first enantioselective catalysis of the direct VA reaction between dihalofuran-2(5*H*)-one (**2**) and aldehydes (**3**) using chiral guanidine catalysts (**1**) to give polyfunctionalized butenolides (**4**) in high enantioselectivities [Eq. (1)].



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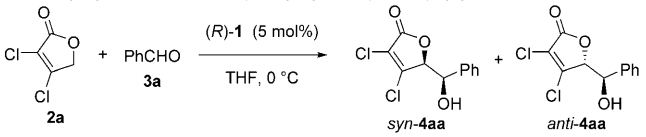
We began by exploring the use of a promising guanidine catalyst (**1**) in the reaction of benzaldehyde (**3a**) with 3,4-dichlorofuran-2(5*H*)-one (**2a**) (Table 1),[9] which can be readily prepared by the simple reduction of commercially available and inexpensive mucochloric acid.[9a,10] The catalyst was screened using 5 mol% of **1** in THF at 0°C whilst changing the Ar and G substituents at the 3,3′-position of the binaphthyl backbone and on the nitrogen atom of the guanidine moiety, respectively. The Ar and G substituents

Table 1: Enantioselective direct vinylogous aldol reaction of dichlorofuranone (**2a**) with benzaldehyde (**3a**) catalyzed by (*R*)-**1**.[a]



Entry	1	*t* [h]	Yield[b] [%]	d.r.[c] (*syn*/*anti*)	*ee* [%][d] *syn*	*anti*
1	**1a**	22	15	55:45	28	30
2	**1b**	22	54	27:73	50	69
3	**1c**	22	57	34:66	14	35
4	**1d**	24	47	24:76	64	80
5	**1e**	24	<10	ND[e]	ND[e]	ND[e]
6	**1f**	24	51	36:64	66	71
7	**1g**	7	72	65:35	84	62
8	**1h**	4	78	73:27	97	75
9[f]	**1h**	5	90	77:23	99	87

[a] All reactions were carried out using 0.005 mmol of (*R*)-**1** (5 mol%), 0.10 mmol of **2a**, and 0.12 mmol of **3a** (1.2 equiv) in 0.5 mL of THF at 0°C unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] ND = not determined. [f] At −40°C.

[*] Dr. H. Ube, N. Shimada, Prof. Dr. M. Terada
Department of Chemistry, Graduate School of Science
Tohoku University
Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
Fax: (+81) 22-795-6602
E-mail: mterada@mail.tains.tohoku.ac.jp
Homepage: http://www.orgreact.sakura.ne.jp/index.html

[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" (grant no. 19020006) from the MEXT (Japan). We also acknowledge the JSPS Research Fellowship for Young Scientists (H.U.) from the Japan Society for Promotion of Science.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906647.

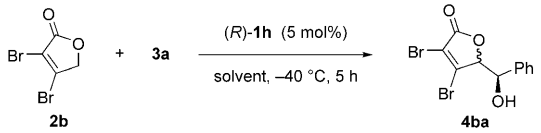
exhibited a marked influence not only on the enantio- and diastereoselectivity of the reaction but also on the catalytic activities (Table 1, entries 1–8). The introduction of a bulky benzhydryl substituent (**1b**) onto the guanidine nitrogen afforded an increase in the catalytic activities and enantioselectivities in comparison with those obtained with the sterically less-hindered methyl-substituted catalyst (**1a**; Table 1, entry 1 versus 2). Introduction of the sterically demanding *tert*-butyl substituents onto the phenyl rings lowered the enantioselectivity (Table 1, entry 3). Therefore, we focused our attention on the modification of benzhydryl substituents (Table 1, entries 4–8). The electron-withdrawing trifluoromethyl-substituted catalyst (**1e**) exhibited a low catalytic activity (Table 1, entry 5). In contrast, the enantiomeric excess was improved when the methyl-substituted catalyst (**1d**) was used (Table 1, entry 4). When the benzhydryl moiety was further modified by the introduction of electron-donating methoxy substituents, the enantiomeric excess of *syn*-**4aa** was found to increase in accordance with the number of methoxy groups introduced (Table 1, entries 6–8). Although the precise mechanism for this marked dependence of diastereo- and enantioselectivities on the G substituent is not yet clear, trimethoxy-substituted catalyst (**1h**) exhibited the best performance with respect to catalytic activity and enantioselectivity, albeit with moderate diastereoselectivity (Table 1, entry 8). As expected, the enantiomeric excess and diastereomeric ratio were improved by lowering the reaction temperature to −40 °C (Table 1, entry 9).

Although *syn*-**4aa** was obtained in almost optically pure form (Table 1, entry 9), the diastereoselectivity remained moderate. Therefore, we turned our attention to the dibrominated analogue of **2a**, 3,4-dibromofuran-2(5*H*)-one (**2b**).[8] To our delight, the diastereoselectivity was slightly improved (Table 2, entry 1), presumably owing to the additional steric demands of the bromine substituents. We further explored different solvents to increase the diastereoselectivities whilst maintaining a high level of enantioselectivity. However, other ethereal solvents such as acyclic ethers and DME (dimethoxyethane) compromised the diastereoselectivity and significantly retarded the reaction (Table 2, entries 2–4). Interestingly, the use of oxygenated organic solvents that have a carbonyl functionality, namely ethyl acetate and acetone, enhanced the diastereoselectivity, albeit at the expense of product yield (Table 2, entries 5 and 6). Of the solvents tested, acetone exhibited the highest diastereoselectivity whilst equally high enantioselectivity was also achieved. Therefore, we considered a mixed-solvent system composed of acetone and THF to improve the conversion to the aldol product (**4ba**) whilst retaining high stereoselectivities (Table 2, entries 7 and 8). As expected, under the acetone/THF mixed-solvent system, the chemical yield of **4ba** could be improved with higher diastereoselectivity than that obtained using only THF as the solvent (Table 2, entry 8 versus 1).

With a promising catalyst and optimal reaction conditions in hand, we next investigated the substrate scope of the reaction using dibromofuranone **2b** (Table 3).[11] Guanidine **1h** functions as an efficient catalyst, and the corresponding products (**4**) were obtained in good yield with the exception of the products arising from aldehydes that had an electron-donating methyl or methoxy substituent (**3b**,**d**,**e**). The low reactivity of **3d** and **3e** was circumvented by increasing the catalyst loading, prolonging the reaction time, and using THF as the solvent (Table 3, entries 3 and 4). In the reaction of substituted benzaldehydes, excellent enantioselectivities and high diastereoselectivities were observed for the major *syn* isomers, irrespective of the electronic properties and the steric demand of the aromatic rings (Table 3, entries 1–6). The heteroaromatic, 2-furyl, aldehyde was also a good reaction partner, affording the product in relatively high diastereoselectivity with excellent enantioselectivity for the major *syn* isomer (Table 3, entry 7).

Next, we investigated the reaction of an α-monobrominated furanone, 3-bromofuran-2(5*H*)-one (**2c**),[12] using catalyst **1h** [Eq. (2)].[13] The reaction of **2c** provided *syn*-**4ca** as the major product in equally high enantioselectivity. However, β,γ-unsaturated product **4ca′**[8] was also obtained as a single

Table 2: Enantioselective direct vinylogous aldol reaction of dibromofuranone (**2b**) with **3a** catalyzed by (*R*)-**1h**.[a]



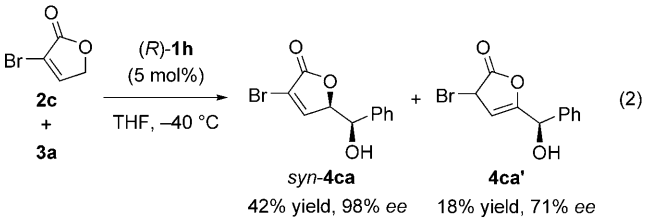
Entry	Solvent	Yield[b] [%]	d.r.[c] (*syn*/*anti*)	*ee* [%][d] *syn*	*anti*
1	THF	82	85:15	99	78
2	DME[e]	59	83:17	99	90
3	*t*BuOMe	30	81:19	97	62
4	CPME[f]	17	82:18	97	66
5	EtOAc	13	88:12	99	76
6	Acetone	52	92:8	99	89
7	acetone/THF (4:1)	65	90:10	99	84
8	acetone/THF (1:1)	77	90:10	98	84

[a] All reactions were carried out using 0.005 mmol of (*R*)-**1h** (5 mol%), 0.10 mmol of **2b**, and 0.12 mmol of **3a** (1.2 equiv) in 0.5 mL of solvent at −40 °C for 5 h unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase (for details, see the Supporting Information). [e] 1,2-Dimethoxyethane. [f] Cyclopentyl methyl ether.

Table 3: Enantioselective direct vinylogous aldol reaction of **2b** with various aldehydes (**3**) catalyzed by (*R*)-**1h**.[a]

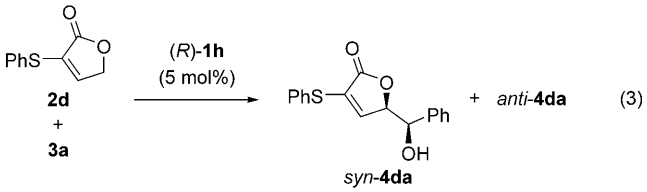
Entry	**3**, R	**4**	Yield[b] [%]	d.r.[c] (*syn*/*anti*)	*ee* [%][d] *syn*	*anti*
1[e]	**3b**, 2-MeC_6H_4	**4bb**	82	91:9	97	60
2	**3c**, 2-BrC_6H_4	**4bc**	91	88:12	96	58
3[e,f]	**3d**, 4-MeC_6H_4	**4bd**	95	86:14	99	80
4[e,f]	**3e**, 4-MeOC_6H_4	**4be**	58	87:13	97	80
5	**3f**, 4-BrC_6H_4	**4bf**	87	87:13	96	79
6	**3g**, 1-naphthyl	**4bg**	74	94:6	96	74
7	**3h**, 2-furyl	**4bh**	79	85:15	97	88

[a] All reactions were carried out using 0.01 mmol of (*R*)-**1h** (5 mol%), 0.20 mmol of **2b**, and 0.24 mmol of **3** (1.2 equiv) in 1.0 mL of 1:1 mixture of acetone and THF at −40 °C for 5 h unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral stationary phases HPLC analysis (for details, see the Supporting Information). [e] THF was employed as the only solvent. [f] 0.02 mmol of (*R*)-**1h** (10 mol%) for 12 h.



(2)

diastereomer with moderate enantioselectivity.[14] We then attempted the reaction of a furanone that had a phenylthio group, rather than a bromine atom, at the α position [Eq. (3)].



(3)

			syn-4da	anti-4da
THF	–40 °C, 5 h	98%	70 (99% *ee*)	: 30 (85% *ee*)
acetone/THF = 1:1	–80 °C, 24 h	>99%	85 (>99% *ee*)	: 15 (91% *ee*)

The reaction of 3-phenylthiofuran-2(5*H*)-one (**2d**) with **3a** exclusively afforded a diastereomeric mixture of VA products (**4da**) with moderate *syn* selectivity, albeit with excellent enantioselectivity. Thorough optimization of the reaction conditions, involving lowering of the reaction temperature and using an acetone/THF mixed-solvent system, improved the diastereomeric ratio of **4da** to 85% *syn* selectivity and provided *syn*-**4da** in nearly optically pure form.

In order to gain mechanistic insight into the stereoselectivities, we determined the absolute configuration of **4aa**, **4ba**, and **4da**. The stereochemistries of **4aa** and **4ba** were determined by X-ray crystallographic analysis or by transformation into the stereochemically known compounds to be 5*S*,1′*R* and 5*R*,1′*R* for the *syn* and *anti* isomers, respectively.[15] *syn*-**4da** was also determined to be 5*R*,1′*R* using a similar method to that used for the determination of **4ba**. For both **4aa** and **4ba**, the stereochemical outcome at the C1′ position, thus discriminating the enantiotopic faces of the prochiral aldehyde, was controlled more efficiently by the guanidine catalyst than by the interactions at the C5 position of the prochiral anionic furanone species (**2′**).[16] These results strongly suggest that a guanidinium ion, generated from the deprotonation of furanone derivative **2** by guanidine catalyst **1h**, would not only interact with the anionic **2′** but also with aldehyde **3** through hydrogen-bonding interactions between the N–H protons of the guanidinium ion and the Lewis basic sites of the anionic oxygen of **2′** and the carbonyl oxygen of **3**, respectively.[7] Furthermore, the diastereoselectivity is markedly dependent on the G substituent (benzhydryl moiety) that is introduced onto the nitrogen atom of the guanidine catalyst (Table 1, entries 2 and 4–8). More importantly, the stereochemical outcomes at the C1′ position are strictly controlled by the catalyst, giving the 1′*R* product predominantly in both *syn* and *anti* isomers, irrespective of the G substituent. In contrast, the stereochemical outcomes at the C5 position are significantly affected by the G substituent.[16,17] Consequently, an anionic furanone derivative (**2′**) would lie in the close vicinity of the G substituent in the transition state, thus suggesting a model such as is given in Figure 1. The observed

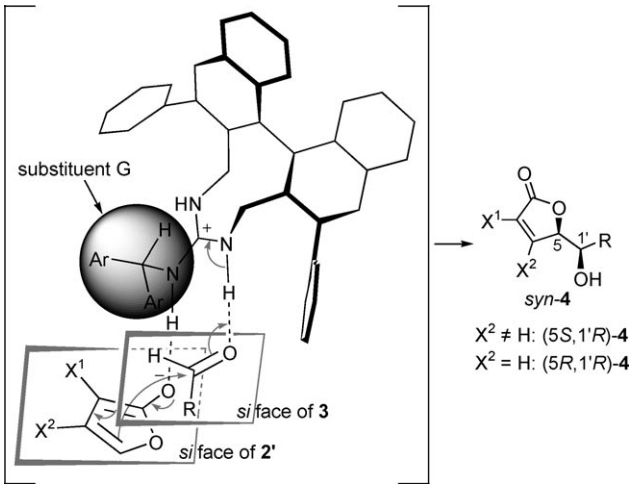


Figure 1. A proposed transition state in the *syn*-selective vinylogous aldol reaction.

stereoselectivity can be rationalized using this transition-state model, in which the aldehyde would approach **2′** from the far side of the G substituent whilst keeping away from the phenyl substituent at the 3,3′-position of the binaphthyl backbone. Here, **2′** would be oriented to avoid steric repulsion between the R moiety of the aldehyde and the X^2 substituent at the C4 position of the furan ring. In this arrangement, the *si* face of the aldehyde (**3**) is attacked by the *si* face of **2′**, giving the 1′*R*-configurational *syn* product **4**, which is consistent with the major stereoisomer obtained experimentally.

In conclusion, we have demonstrated the first enantioselective direct vinylogous aldol reaction of halogenated or α-thio-substituted furanones with aldehydes, catalyzed by an axially chiral guanidine base. This method enables efficient access to optically active polyfunctionalized butenolides, which can be utilized as versatile chiral synthons in synthetic organic chemistry. Further studies of direct transformations using the activation of furanone derivatives by chiral guanidine catalysts are currently underway in our laboratory.

Experimental Section

(*R*)-**1h** was added (4.2 mg, 0.005 mmol) to a solution of 3,4-dibromo-2-(5*H*)-furanone (**2b**; 24.2 mg, 0.10 mmol) and benzaldehyde (**3a**; 12.8 mg, 0.12 mmol) in acetone (0.25 mL) and THF (0.25 mL) solution at −40 °C, and the resulting mixture was stirred for 5 h. The reaction was quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and filtered. After removal of solvents, the residue was purified by flash column chromatography (hexane/AcOEt = 5:1 to 2:1 as eluent) to afford the

vinylogous aldol product **4ba** in 77% yield (*syn*/*anti* = 90:10, *syn* 98% *ee*, *anti* 84% *ee*).

Received: November 25, 2009
Published online: February 4, 2010

Keywords: aldol reaction · asymmetric catalysis · butenolides · guanidine · organocatalysis

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[14] The relative stereochemistry of **4ca′** is not determined.

[15] a) For the *syn* isomer, see: J. Hargreaves, J. Park, E. L. Ghisalberti, K. Sivasithamparam, B. W. Skelton, A. H. White, *Aust. J. Chem.* **2002**, *55*, 625–627; b) for the *anti* isomer, see: L. Emmanuvel, A. Sudalai, *Tetrahedron Lett.* **2008**, *49*, 5736–5738. See the Supporting Information for details of stereochemical determinations.

[16] For the (*R*)-**1h**-catalyzed reaction (Table 1, entry 8): (5*S*,1′*R*)-**4aa** *syn*/(5*R*,1′*S*)-**4aa** *syn*/(5*R*,1′*R*)-**4aa** *anti*/(5*S*,1′*S*)-**4aa** *anti* = 72:1:24:3. The stereochemical outcomes at the C1′ and C5 positions were controlled by (*R*)-**1h**: 1′*R*/1′*S* = 96:4; 5*S*/5*R* = 75:25.

[17] For the (*R*)-**1f**-catalyzed reaction (Table 1, entry 6): (5*S*,1′*R*)-**4aa** *syn*/(5*R*,1′*S*)-**4aa** *syn*/(5*R*,1′*R*)-**4aa** *anti*/(5*S*,1′*S*)-**4aa** *anti* = 30:6:55:9. The stereochemical outcomes at the C1′ and C5 positions were controlled by (*R*)-**1f**: 1′*R*/1′*S* = 85:15; 5*S*/5*R* = 39:61.

