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Vinylogous Mannich-Type Reaction Catalyzed by an Iodine-Substituted Chiral Phosphoric Acid

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Abstract: 2-Trimethylsiloxyfuran underwent a vinylogous Mannich-type reaction with aldimines under the action of a new chiral phosphoric acid, bearing iodine on the 6,6′-positions of the binaphthyl group, as a chiral Brønsted acid to give γ-butenolide derivatives bearing an amino functionality with high diastereo- and enantioselectivity.

Keywords: addition to imines; amines; asymmetric catalysis; asymmetric synthesis; C–C bond formation; organic catalysis

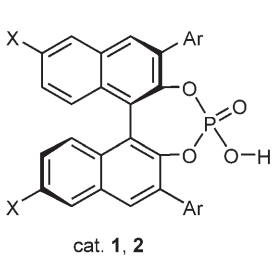
The γ-butenolide skeleton is one of the most ubiquitous structures found in natural products. Thus, the development of novel methods for the stereoselective synthesis of butenolide derivatives has continuously attracted the attention of synthetic organic chemists.[1,2]

The vinylogous Mannich-type reaction of trimethylsiloxyfuran with aldimine is a useful means to prepare γ-butenolide derivatives bearing an amine functionality. A wide range of Lewis acids has been developed as catalysts for the reaction.[3,4]

In contrast, the enantioselective, catalyzed-version of the vinylogous Mannich-type reaction has been little explored. Martin and co-workers reported the enantioselective synthesis of γ-butenolide derivatives catalyzed by the Ti(O-*i*-Pr)$_4$/(*S*)-BINOL system,[3f] but the enantioselectivities and the chemical yields were moderate. In this regard, the development of an efficient catalyst for the synthesis of γ-butenolide derivatives in terms of both yields and optical purity is still desired. Recently, Hoveyda and co-workers reported a highly enantioselective vinylogous Mannich-type reaction catalyzed by a silver salt, in which only aromatic aldimines were employed.[5] Organocatalyzed vinylogous Mannich-type reactions have been also reported lately.[6]

Chiral Brønsted acid catalysts have recently emerged as a new class of environmentally benign chiral catalysts.[7] We have reported that chiral phosphoric acid **1** (Figure 1) is a useful chiral Brønsted acid catalyst for the electrophilic activation of aldimines.[8] The phosphoric acid has recently been recognized to be an efficient chiral catalyst for a number of enantioselective reactions.[9,10] We focused our attention on the application of chiral Brønsted acid catalysts to the vinylogous Mannich-type reaction. We report herein the use of the novel phosphoric acid **2b** (Figure 1), bearing iodine groups on the 6,6′-positions in the vinylogous Mannich-type reaction, producing γ-butenolides with high enantioselectivities.[11] Aliphatic aldimines as well as aromatic aldimines proved to be good substrates.

At the outset, we examined the catalytic activity of chiral phosphoric acids **1a–c**. Aldimine **3a** underwent a vinylogous Mannich-type reaction with trimethylsiloxyfuran **4** in the presence of 5 mol% of **1a** to afford γ-butenolide derivative **5a** in 98% yield in favor of the *anti* isomer (*anti*/*syn* 79/21). Chiral HPLC analysis revealed that the *anti* isomer was obtained preferentially in 48% *ee* (Table 1, entry 1). The introduction of a bulky aryl group to 3,3′-positions improved the enantioselectivity, while use of 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$-substituted phosphoric acid **1c** gave **5a** in 74% *ee* (entry 3). Interestingly, the introduction of halogen atoms onto the 6,6′-positions of the binaphthyl rings

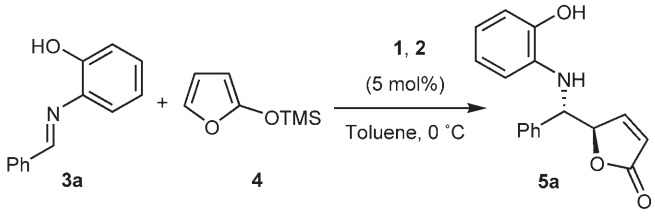


cat. **1**, **2**

1a: Ar = Ph, X = H
1b: Ar = 2,4,6-Me$_3$C$_6$H$_2$, X = H
1c: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, X = H
2a: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, X = Br
2b: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, X = I

Figure 1.

Table 1. Effect of the 6,6′-substituents of the chiral Brønsted acid.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*anti*/*syn*	*ee* [%][c]
1	**1a**	7	98	79/21	48
2	**1b**	15	100	77/23	38
3	**1c**	13	100	93/7	74
4	**2a**	19	69	84/16	79
5	**2b**	19	100	91/9	82

[a] 3.0 equiv. of trimethylsiloxyfuran were employed.
[b] Isolated yield.
[c] The *ee* of the *anti* isomer.

had a beneficial effect on the enantioselectivity (entry 4) and use of **2b** bearing iodine groups on the 6,6′-positions resulted in the formation of **5a** in 82% *ee* (entry 5).

These conditions were applicable to the synthesis of γ-butenolide derivatives using various aldimines as substrates (Table 2). The use of aldimines derived from aromatic aldehydes gave addition products in high yields, good to high diastereoselectivities, and excellent *ee* (up to 99% *ee*) (entries 2–8). Furthermore, we found that **2b** is effective for the reaction with aldimine **3i** bearing a basic pyridine moiety (entry 9). An aldimine derived from a heteroaromatic aldehyde also gave an adduct with high enantioselectivity (entry 10). It is noted that aliphatic aldimines **3k–l** gave γ-butenolide derivatives with high enantioselectivities (entries 11 and 12). The absolute stereochemistry of **5c** (R = *p*-BrC_6H_4; entry 3) was determined by X-ray crystallographic analysis, while those of the other γ-butenolide derivatives were assigned by analogy.[12]

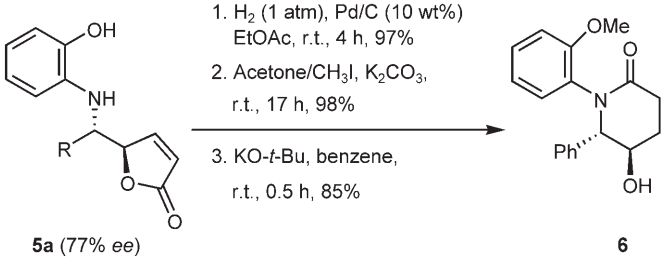
γ-Butenolide **5a** was readily transformed into δ-lactam **6** *via* three successive reactions: reduction of the olefinic double bond, protection of the phenolic hydroxy group, and treatment with a base. A good yield was obtained without sacrificing the enantiomeric purity (Scheme 1).

We surmise that the present vinylogous Mannich-type reaction proceeded *via* a 9-membered transition state (Figure 2) similar to the Mannich-type reaction previously proposed by us based on theoretical calculations.[8a,g] In order to gain an insight into the effect of the iodine substituents of **2b**, the dihedral angles of **1c** and **2b** were calculated with Spartan (HF 3-21G*)[13] to be 52.9° and 52.8°, respectively. Based on these results, we suppose that an electronic effect exerted by the iodine substituents on the phosphoric acid moiety might played a role rather than a steric effect.

Table 2. Enantioselective synthesis of γ-butenolide derivatives catalyzed by chiral Brønsted acid.[a]

Entry	R	Time [h]	Yield [%][b]	*anti*/*syn*	*ee* [%][c]
1	Ph (**3a**)	19	100	91/9	82
2	*p*-FC_6H_4 (**3b**)	24	100	95/5	87
3[d]	*p*-BrC_6H_4 (**3c**)	31	82	92/8 (99/1)[e]	55 (>99)[e]
4[d]	*p*-$NO_2C_6H_4$ (**3d**)	22	85	97/3	96
5	*m*-$NO_2C_6H_4$ (**3e**)	15	86	68/32	96
6[d]	*o*-$NO_2C_6H_4$ (**3f**)	24	100	98/2	92
7	*p*-$CF_3C_6H_4$ (**3g**)	20	95	69/31	99
8	*p*-NCC_6H_4 (**3h**)	28	89	83/17	90
9	4-pyridyl (**3i**)	23	30	94/6	98
10	2-furyl (**3j**)	15	77	68/32	89
11[f]	*c*-C_6H_{11} (**3k**)	15	77	88/12	90
12[f]	*i*-Pr (**3l**)	18	84	88/12	92

[a] 3.0 equiv. of trimethylsiloxyfuran were employed.
[b] Isolated yield.
[c] The *ee* of the *anti* isomer.
[d] **1c** was used instead of **2b**.
[e] After two recrystallization from benzene.
[f] Aldimine was generated *in situ* in the presence of Na_2SO_4 and treated with siloxyfuran and **2b**.



Scheme 1. Transformation of the adduct.

In summary, we have developed a method for the enantioselective synthesis of γ-butenolide derivatives, which involves the vinylogous Mannich-type reaction catalyzed by a novel chiral phosphoric acid bearing iodine groups at the 6,6′-positions. Aliphatic as well as aromatic aldimines turned out to be good substrates and γ-butenolide derivatives were obtained in high yields, with good to high diastereo-and enantioselectivities.

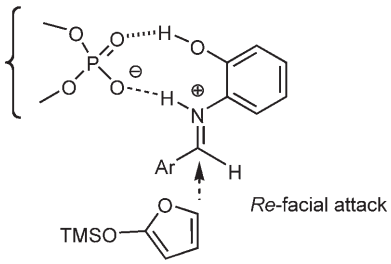


Figure 2. Plausible transition state model.

Experimental Section

Typical Procedure for the Enantioselective Synthesis of Butenolide Derivatives (Entry 7, Table 2)

To a solution of aldimine **3g** (45.2 mg, 0.170 mmol) and (*R*)-6,6′-diiodo-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl phosphate **2b** (8.9 mg, 0.00886 mmol) in toluene (1 mL) was added trimethylsiloxyfuran **4** (88 μL, 0.507 mmol) at 0 °C. Aftereing stirred at the temperature for 20 h and confirming the disappearance of the aldimine by TLC, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution, saturated KF solution, THF and MeOH. The solution was extracted with ethyl acetate. The combined organic layers were successively washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to give the product **5g**; yield: 56.1 mg 0.163 mmol, 95%) and with 99% *ee*, which was determined by chiral HPLC analysis on a Daicel Chiralcel OD-H column.

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