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Chiral VAPOL Imidodiphosphoric Acid-Catalyzed Asymmetric Vinylogous Mannich Reaction for the Synthesis of Butenolides

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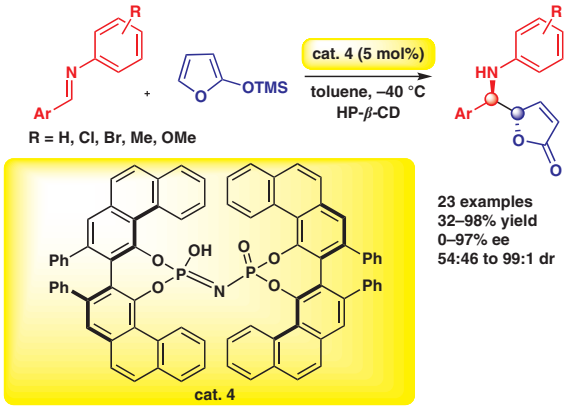

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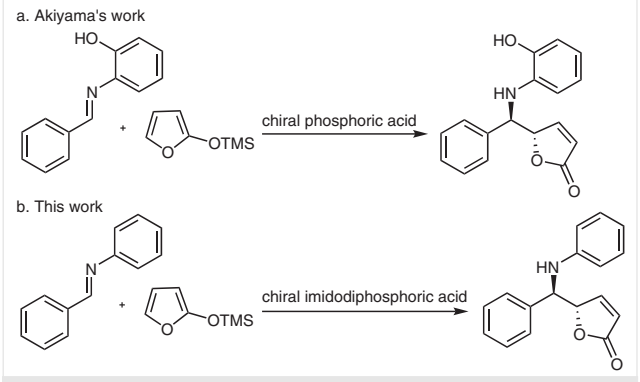
Abstract Chiral butenolides were synthesized by the enantioselective vinylogous Mannich reaction. Chiral (VAPOL)-type imidodiphosphoric acids are efficient catalysts for the asymmetric vinylogous Mannich (AVM) reaction of aldimines and trimethylsiloxyfuran in toluene. Under the optimized conditions, a series of butenolides were obtained with high yields (up to 98%) and enantioselectivities (up to 97% ee) as well as excellent diastereoselectivities (up to 99:1 dr).

Key words butenolides, trimethylsiloxyfuran, organocatalysis, enantioselectivity, asymmetric vinylogous Mannich reaction

γ-Butenolides[1] are common structures widely present in natural products, medicinal and biological chemistry. Functional and chiral γ-butenolides exhibit various biological activities.[2–4] The asymmetric vinylogous Mannich reaction is an important approach to synthesize γ-butenolides bearing amine groups and two stereocenters.[5–13] The first AVM reaction between aldimine and 2-(trimethylsilyloxy)furan was reported by Martin's group in 1999.[7] Subsequent studies focused on Lewis acid catalysis of this reaction.[8] In 2006, Hoveyda's group reported an AVM reaction catalyzed by a silver complex with excellent diastereo- and enantioselectivity.[9] In 2009 and 2013, Shi's and Xu's groups applied chiral phosphine silver(I) to catalyze an AVM reaction.[10–12] Organocatalysis has also attracted considerable attention in AVM reactions. In 2008, Akiyama et al. first reported chiral phosphoric acid as a catalyst to synthesize chiral γ-butenolides with good yields and stereoselectivities. The aldimine [2-(benzylideneamino)phenol] containing a 2-hydroxyphenyl moiety was used as an electrophile, and the authors proposed that the AVM reaction proceeded via a cyclic transition state between the aldimine and the catalyst (Scheme 1, a).[13] However, it is hard to control the selectivity of the reaction without the help of a neighboring hydroxy group; the stereoselectivity of the reaction is difficult to control without a dual hydrogen-bonding interaction between the catalyst and 2-hydroxyphenyl aldimine. Hence, the scope of substrates was limited. Recent reports are focused on solving this problem in related Mannich reactions.[14]



Scheme 1 Chiral Brønsted acid-catalyzed asymmetric vinylogous Mannich reaction

Chiral imidodiphosphoric acids are another kind of chiral Brønsted acid catalysts. In 2012, imidodiphosphoric acids were first reported by List and co-workers in asymmetric spiroacetalization. Since then, those catalysts have been efficient in many enantioselective reactions, such as asymmetric Mannich reaction, asymmetric Friedel–Crafts reaction, and asymmetric Pictet–Spengler reaction.[15,16] Inspired by previous works, we believe that chiral Brønsted acids may be suitable catalysts for AVM reactions and pro-

vide special chiral environments for the substrates. In this report, we used chiral imidodiphosphoric acids as the catalysts and chose 2-(trimethylsilyloxy)furan as the nucleophile to attack aldimines without a neighboring hydroxy group (Scheme 1, b). To begin the study, we investigated the activity of catalysts **1**–**5** (Figure 1) in the reaction of aldimine **6a** and 2-(trimethylsilyloxy)furan **7**.

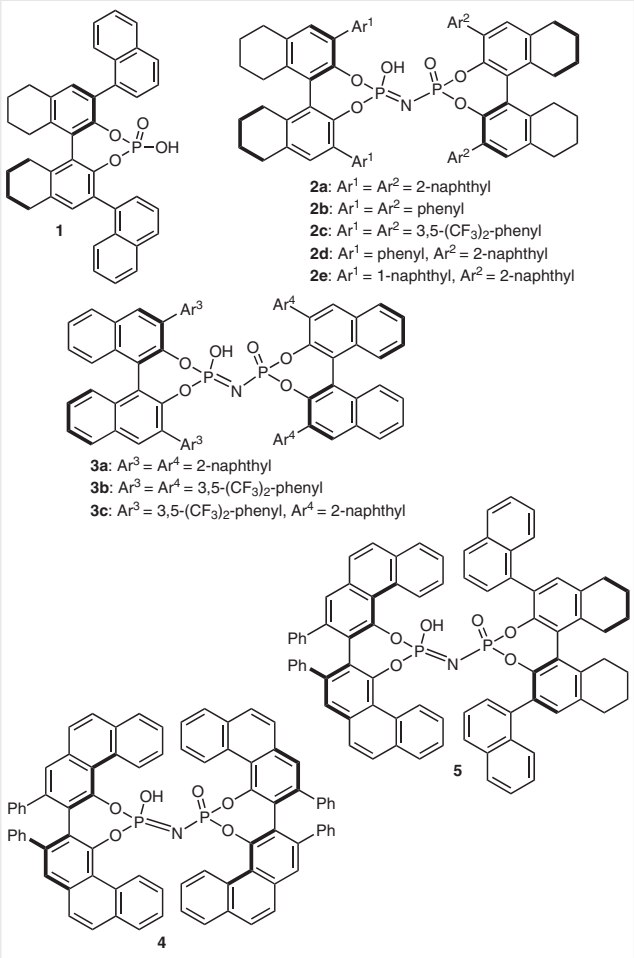
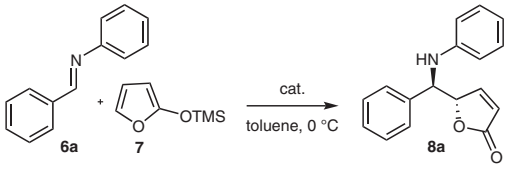


Figure 1 Chiral phosphoric acids and imidodiphosphoric acids screened in the AVM reaction

As shown in Table 1, the yields increase from entry 1 to 5, but the enantioselectivities are still low. BINOL-type catalysts **3a** and **3b** with similar substituents as those in **2a** and **2c**, provided better yields (74 and 58%) and enantioselectivities (51 and –60% ee; Table 1, entries 7 and 8). Interestingly, when using catalysts **2c** and **3b** the sense of product enantioselectivity could be switched. It was supposed that the strong electron-withdrawing ability of the trifluoromethyl group leads to different directions of the chiral control of the catalyst to the substrate. Catalyst **3c**, however, gave only 70% yield and 27% ee (Table 1, entry 9). As a whole, compared with chiral phosphoric acids, chiral imidodiphosphoric acids were more suitable to control the stereoselectivity in this reaction. For this reason, we selected other types imidodiphosphoric catalysts for further study. As shown in Table 1, entry 10, we found VAPOL-derived bisphosphorylated catalyst **4** to be the most effective for this reaction. It provided the adduct with 92% yield in 65% ee. VAPOL bisphosphorylated **5** could also give 92% yield, but with a lower ee value (61% ee; Table 1, entry 11).

Table 1 Screening of Chiral Phosphoric Acids and Imidodiphosphoric Acid Catalysts[a]



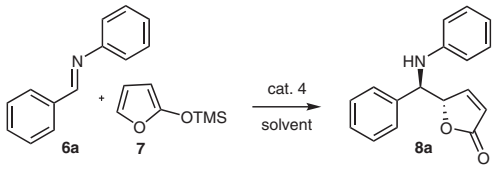
Entry	Catalyst	t (h)	Yield (%)[b]	ee (%)[c]	dr[c]
1	**1**	24	52	10	54:46
2	**2a**	60	63	rac	54:46
3	**2b**	48	70	11	56:44
4	**2c**	6	75	–48	77:23
5	**2d**	10	61	rac	53:47
6	**2e**	10	41	11	90:10
7	**3a**	16	74	51	91:9
8	**3b**	12	58	–60	80:20
9	**3c**	10	70	27	74:26
10	**4**	13	92	65	92:8
11	**5**	13	92	61	87:13

[a] *Reaction conditions*: aldimine **6a** (0.1 mmol,1.0 equiv), 2-(trimethylsilyloxy)-furan **7** (0.3 mmol, 3 equiv), catalyst (5 mol%), toluene (1 mL), 0 °C.
[b] Isolated yield.
[c] Enantiomeric excess of the major diastereomer; determined by high-performance liquid chromatography (HPLC) analysis on a chiralcel OJ-H column.

Having identified the optimal catalyst **4** (Table 1, entry 10), we studied the effect of different solvents on the reaction (Table 2, entries 1–8). As shown in Table 2, toluene gave a better result (Table 2, entry 1). After raising the temperature to 10 °C, the yield increased to 95%, but the ee value decreased to 62% (Table 2, entry 9). When lowering the temperature to –40 °C, an improved yield of 94% and 80% ee were observed (Table 2, entry 11).

Under the optimized conditions (Table 3, entry 6), we examined a broad scope of aldimines with various kinds of substituents. In Table 4, aldimines derived from aromatic aldehydes, bearing a halogen group in *para* position of the phenyl ring (Table 4, entries 2–4), such as **6b** and **6c** bearing a fluorine and a chlorine group, respectively, gave the products **8b** and **8c** in high yields (98 and 97%) and enantioselectivities (85 and 80% ee). Contrarily, 4-bromoaldimine **6d** led to lower enantioselectivity (62% ee; Table 4, entry 4).

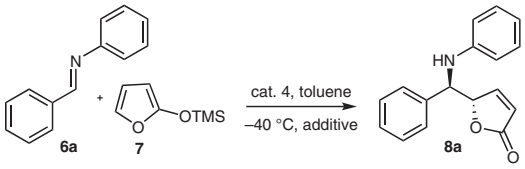
Table 2 Optimization of the Solvent and Temperature for the AVM Reaction of Aldimines with 2-(Trimethylsilyloxy)furan[a]



Entry	Solvent	T (°C)	t (h)	Yield (%)[b]	ee (%)[c]	dr[c]
1	toluene	0	13	92	65	92:8
2	*o*-xylene	0	5	92	60	90:10
3	*m*-xylene	0	10	88	57	90:10
4	mesitylene	0	12	92	60	91:9
5	ethylbenzene	0	12	57	47	86:14
6	anisole	0	7	89	45	88:12
7	THF	0	14	62	31	78:22
8	acetone	0	14	45	8	56:44
9	toluene	10	7	95	62	89:11
10	toluene	−20	15	92	74	94:6
11	toluene	−40	17	94	80	95:5
12	toluene	−60	21	94	79	94:6
13	toluene	−78	25	57	31	59:41

[a] *Reaction conditions*: aldimine **6a** (0.1 mmol, 1.0 equiv), 2-(trimethylsilyloxy)-furan **7** (0.3 mmol, 3 equiv), catalyst **4** (5 mol%), solvent (1 mL).
[b] Isolated yield.
[c] Enantiomeric excess of the major diastereomer; determined by HPLC analysis on a chiralcel OJ-H column.

Table 3 Optimization of the Catalyst Loading and Additive for the AVM Reaction of Aldimines with 2-(Trimethylsilyloxy)furan[a]



Entry	Additive (mg/mmol)	t (h)	Yield (%)[b]	ee (%)[c]	dr[c]
1[d]	none	15	89	75	89:11
2[e]	none	15	87	72	91:9
3	3 Å MS (40)	15	86	70	90:10
4	4 Å MS (40)	15	86	71	90:10
5	5 Å MS (40)	15	86	72	91:9
6	HP-β-CD (40)	10	97	80	95:5

[a] *Reaction conditions*: aldimine **6a** (0.1 mmol, 1.0 equiv), 2-(trimethylsilyloxy)-furan **7** (0.3 mmol, 3 equiv), toluene (1 mL), catalyst **4** (5 mol%), −40 °C.
[b] Isolated yield.
[c] Enantiomeric excess of the major diastereomer; determined by HPLC analysis on a chiralcel OJ-H column.
[d] Catalyst **4** (10 mol%).
[e] Catalyst **4** (3 mol%).

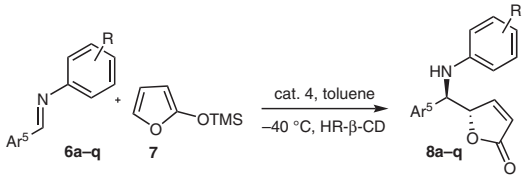
Substrate **6e** with a 4-methyl group afforded the product in 87% yield with 84% ee (Table 4, entry 5). Changing the substituent to a 4-methoxy group, however, decreased the yield to 67% and the ee value to 55% (Table 4, entry 6). In summary, a stronger electron-donating capability of the substrates involved much poorer yields and enantioselectivities. *Meta*-methyl phenyl substrate **6h** gave **8h** with 64% yield and 63% ee (Table 4, entry 8). Compound **6g** with an isopropyl group in *para* position gave only 55% yield and 82% ee (Table 4, entry 7). When a phenyl ring was changed into a naphthyl ring, the corresponding products **8i** and **8j** were obtained in poor enantioselectivities (Table 4, entries 9–10). Substrate **6k** combined 4-fluoroaldehyde with 4-methylaniline, and gave **8k** with high enantioselectivity and moderate diastereoselectivity (84% ee, 74:26 dr; Table 4, entry 11).

Compounds **6l**, **6m**, and **6n**, substituted with chlorine atoms at different positions on the aniline's phenyl ring were separately studied (Table 4, entries 12–14). *Meta*-chloro **6m** gave **8m** with a high yield (98%), 79% ee, and 84:16 dr (Table 4, entry 13). Contrarily, with use of *ortho*-chloro **6l**, the lowest ee was observed for **8l** (Table 4, entry 12). Product **8o** was obtained in 61% yield but no enantioselectivity was observed (Table 4, entry 15). Furthermore, two substituents on the aldehyde's phenyl ring were examined: 2,4-dichloro **6p** gave **8p** in excellent yield (97%) and diasteroselectivity (99:1 dr; Table 4, entry 16). For 3,4-dichloro **6q**, product **8q** was obtained in good enantioselectivity (90% ee), yield (90%), and diasteroselectivity (85:15 dr; Table 4, entry 17).

With 3,4-dichlorobenzaldehyde as a suitable moiety in the substrates (Table 4, entry 17), different substituents on the aniline were further studied (see results in Table 5). Substrates **6r** and **6s**, substituted with bromo and methyl at the *para* position, all gave good yields, excellent enantioselectivities, and good diastereoselectivities (Table 5, entries 1–2). In particular, **8s** was obtained in 97% yield, 96% ee, and 85:15 dr (Table 5, entry 2). When substituted in *meta* position, aldimines **6t–v** gave the products in high yields (90–98%) with excellent enantioselectivities and good diastereoselectivities (96–97% ee, 81:19 dr, 80:20 dr, 84:16 dr; Table 5, entries 3–5). In addition, when the phenyl group was changed to naphthyl, the corresponding adduct **8w** was obtained with poor diastereoselectivity (55:45 dr) and yield (Table 5, entry 6). We determined the absolute configuration of **8s** as (*R*,*S*)-configuration by X-ray crystallographic analysis (Figure 2).[17] The transition state of the reaction was suggested on the basis of the product configuration (see Supporting Information).

In conclusion, we have developed an AVM reaction for aldimine and 2-(trimethylsilyloxy)furan using a VAPOL-type chiral imidodiphosphoric acid as the catalyst.[18] Under the optimal reaction conditions, a variety of γ-butenolides were prepared in high yields with excellent enantioselec-

Table 4 Scope of Aldimines Having Different Substituents (Ar^5 and R) in the AVM Reaction[a]



Entry	Product	Ar^5	R	t (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	**8a**	C_6H_5	H	10	97	80	93:7
2	**8b**	4-FC_6H_4	H	6	98	85	89:11
3	**8c**	4-ClC_6H_4	H	7	97	80	89:11
4	**8d**	4-BrC_6H_4	H	9	91	62	88:12
5	**8e**	4-MeC_6H_4	H	8	87	84	55:45
6	**8f**	4-$MeOC_6H_4$	H	10	67	55	71:29
7	**8g**	4-*i*-PrC_6H_4	H	10	55	82	90:10
8	**8h**	3-MeC_6H_4	H	9	64	63	82:18
9	**8i**	2-naphthyl	H	10	72	66	65:35
10	**8j**	1-naphthyl	H	10	87	64	66:34
11	**8k**	4-FC_6H_4	4-Me	10	85	84	74:26
12	**8l**	C_6H_5	2-Cl	12	74	15	54:46
13	**8m**	C_6H_5	3-Cl	8	98	79	84:16
14	**8n**	C_6H_5	4-Cl	11	87	60	89:11
15	**8o**	C_6H_5	2-OMe	10	61	rac	70:30
16	**8p**	2,4-$Cl_2C_6H_3$	H	7	97	64	99:1
17	**8q**	3,4-$Cl_2C_6H_3$	H	10	90	90	85:15

[a] *Reaction conditions*: aldimine **6a**–**q** (0.1 mmol, 1.0 equiv), 2-(trimethylsilyloxy)-furan **7** (0.3 mmol, 3 equiv), toluene (1 mL), catalyst **4** (5 mol%), HP-β-CD (4 mg), –40 °C.
[b] Isolated yield.
[c] Enantiomeric excess of the major diastereomer; determined by HPLC analysis on OD-H, OJ-H, and AD-H chiralcel columns.
[d] Determined by ^{1}H NMR spectroscopy.

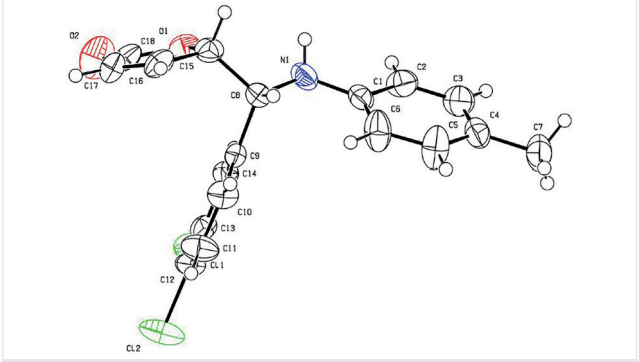
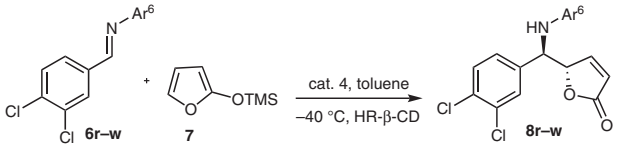


Figure 2 X-ray crystal structure of product **8s**

Table 5 Scope of Aldimines Having Different Substituents (Ar^6) in the AVM Reaction[a]



Entry	Product	Ar^6	t (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	**8r**	4-BrC_6H_4	8	93	91	77:23
2	**8s**	4-MeC_6H_4	8	97	96	85:15
3	**8t**	3-ClC_6H_4	7	98	96	81:19
4	**8u**	3-BrC_6H_4	7	98	97	80:20
5	**8v**	3-MeC_6H_4	8	90	97	84:16
6	**8w**	1-naphthyl	12	32	–	55:45

[a] *Reaction conditions*: aldimine **6r**–**w** (0.1 mmol,1.0 equiv), 2-(trimethylsilyloxy)-furan **7** (0.3 mmol, 3 equiv), toluene (1 mL), catalyst **4** (5 mol%), HP-β-CD (4 mg), –40 °C.
[b] Isolated yield.
[c] Enantiomeric excess of the major diastereomer; determined by HPLC analysis on OD-H and AD-H chiralcel columns.
[d] Determined by ^{1}H NMR spectroscopy.

tivities and diastereoselectivities. Notably, in our work, the scope of substrates without a neighboring hydroxy group was broadened, which is generally regarded as necessary for good stereoselectivity. Further investigation of this reaction and the application of those catalysts are under way in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610232.

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(18) **General Procedure for the Asymmetric Vinylogous Mannich Reaction of Aldimines with 2-(Trimethylsilyloxy)furan**
A mixture of aldimine **6** (0.1 mmol), VAPOL imidodiphosphoric acid **4** (5 mol%) HP-β-CD (4 mg), toluene (1 mL) was stirred at –40 °C for 15 min. Then, 2-(trimethylsilyloxy)furan **7** (0.3 mmol) was added under an argon atmosphere at –40 °C. After the reaction was completed (monitored by TLC), the mixture was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:6) to directly afford product **8**.
(*S*)-5-[(*R*)-Phenyl(phenylamino)methyl]furan-2(5H)-one (8a)
Colorless oil, 97% yield, $[\alpha]_D^{20}$ = –124.2 (*c* = 1.5, $CHCl_3$), 80% ee, 93:7 dr [DaicelChiralcel OJ-H column, *n*-hexane/ethanol 80:20, 1.0 mL/min, λ = 254 nm, t(major) = 27.865 min, t(minor) = 32.746 min]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (d, *J* = 8.0 Hz, 1 H),7.43 (d, *J* = 4.0 Hz, 2 H), 7.30 (t, *J* = 8.0 Hz, 2 H), 7.24–7.21 (m, 1 H), 7.02 (t, *J* = 8.0 Hz, 2 H), 6.68 (d, *J* = 8.0 Hz, 2 H), 6.53 (t, *J* = 8.0 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 6.17–6.15 (m, 1 H), 5.50 (d, *J* = 4.0 Hz, 1 H), 4.90–4.87 (m, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.1, 156.5, 147.7, 138.8, 129.2, 128.4, 128.3, 127.9, 122.2, 117.0, 113.7, 85.5, 58.6 ppm. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{15}NO_2$: 266.1103; found: 266.1188.