

Brønsted Acid-Catalyzed, Enantioselective, Vinylogous Mannich Reaction of Vinylketene Silyl *N,O*-Acetals

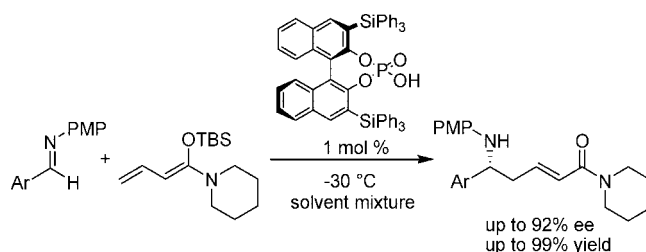
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ABSTRACT



Vinylketene silyl *N,O*-acetals undergo chiral phosphoric acid-catalyzed, vinylogous Mukaiyama–Mannich reactions with imines and afford δ -amino- α,β -unsaturated amides in typically good yields, complete γ -regioselectivity, and up to 92% ee with catalyst loadings of as low as 1 mol %. The Mannich products can be readily manipulated to furnish valuable synthetic intermediates.

Vinylogous carbon–carbon bond-forming reactions of metal dienolates are very important transformations in organic synthesis and deliver highly functionalized products of great utility. Asymmetric vinylogous aldol reactions furnishing δ -hydroxy α,β -unsaturated carboxylic acid derivatives have been widely studied in the context of the total synthesis of polyketide-derived natural products employing chiral auxiliaries as well as chiral catalysts.¹ The development of catalytic, enantioselective vinylogous Mannich reactions, however, lags behind, although this strategy holds great potential for natural product synthesis, in particular, alkaloid

synthesis.² Thus far, only a few protocols have been devised that furnish enantiomerically highly enriched products, and these methods are frequently restricted to special substrate patterns. Following precedence established by Martin,³ Hoveyda and Snapper et al. developed silver-catalyzed, vinylogous Mannich reactions of 2-silyloxy furans giving rise to highly enantiomerically enriched butenolides.⁴ A Brønsted acid-catalyzed approach to chiral γ -butenolides was described by Akiyama et al.⁵ Chen and co-workers recently established the first direct vinylogous asymmetric Mannich reaction of α,α -dicyano alkenes and Boc-protected imines with a bifunctional thiourea catalyst leading to the corresponding products in high yields and excellent enantioselectivity.

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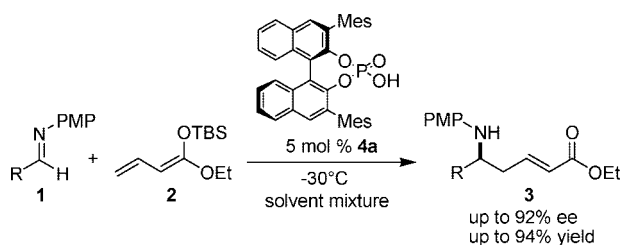
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lectivities as well as complete regioselectivity.⁶ Jørgensen and co-workers catalyzed the same reaction successfully under phase-transfer conditions with a chiral pyrrolidinium salt in up to 95% ee.⁷ Very recently, Shibasaki and co-workers disclosed a direct vinylogous Mannich reaction of γ -butenolides catalyzed through a chiral lanthanum complex.⁸

We have previously reported the first catalytic, enantioselective, vinylogous Mukaiyama–Mannich reaction of vinylketene silyl *O,O*-acetal **2** derived from an α,β -unsaturated ester and imines **1**.⁹ δ -Amino- α,β -unsaturated esters **3** were obtained in typically high yields, complete γ -regioselectivity, and good to very good enantioselectivities (Scheme 1). A

Scheme 1. Chiral Brønsted Acid-Catalyzed Vinylogous Mukaiyama–Mannich Reaction



BINOL-based phosphoric acid **4a** with 3,3'-mesityl groups was employed as chiral Brønsted acid catalyst which led to protonation of the imines and formed chiral contact ion pairs in situ. This general strategy had been established independently by the groups of Akiyama and Terada^{10,11} and was subsequently applied to a broad range of mainly imine addition reactions by various groups.^{12–16}

We have now extended this process to vinylogous Mukaiyama–Mannich reactions of vinylketene silyl *N,O*-

acetals **5** and imines. In a first step, we investigated various dienolates **5** differing in the amine component in reactions with imine **1a** (Table 1). As reaction conditions we employed our previously optimized protocol using 3 equiv of the respective vinylketene silyl *N,O*-acetal **5**, an alcoholic solvent system containing equal amounts of 2-propanol, 2-methyl-2-propanol, and 2-methyl-2-butanol with 1 equiv of water and 10 mol % of phosphoric acid **4a**. Whereas the *N,N*-dimethyl-, *N,N*-diisopropylamide-, and pyrrolidide-based silyl dienolates **5a–c**, respectively, did not perform to our expectations (entries 1–3), the piperidide- and morpholide-derived vinylketene silyl *N,O*-acetals **5d** and **5e** proved to be more suitable substrates and delivered the corresponding vinylogous Mannich products **9a** and **10a** in good yields and up to 78% ee within short reaction times of just 30 min at -30 °C (entries 4 and 5).

Changing the Brønsted acid catalyst from our previously optimized 3,3'-bismesityl-substituted phosphoric acid **4a** to the 3,3'-bistriphenylsilyl-substituted analogue **4b**^{12c} had a dramatic effect on the enantioselectivity of the reaction. The vinylogous Mannich product **9a** was now obtained in 91% yield and 90% ee whereas **10a** was isolated in 80% yield and 67% ee (entries 6 and 7). In both cases, the opposite enantiomers were formed using the identical *R*-BINOL-enantiomer as catalyst backbone. The same phenomenon had been observed earlier by You et al. in the asymmetric transfer hydrogenation of β,γ -alkynyl α -imino esters.¹⁷ On the basis of these results, we selected the piperidide-based vinylketene silyl *N,O*-acetal **5d** and phosphoric acid **4b** to study this reaction further.

The catalyst loading could be lowered to just 1 mol % by simply extending the reaction time with no detrimental effects on yield or enantioselectivity (Table 2). Thus, reaction of imine **1b** and vinylketene silyl *N,O*-acetal **5d** with 1 mol % of Brønsted acid **4b** furnished vinylogous Mannich product **9b** with 99% yield and 90% ee after 7 d at -30 °C even slightly exceeding the results obtained with higher catalyst loadings (compare entries 1 and 4).

Table 3 shows that the optimized protocol is broadly applicable to aromatic and heteroaromatic aldimines **1b–o** which were converted into the vinylogous Mannich products

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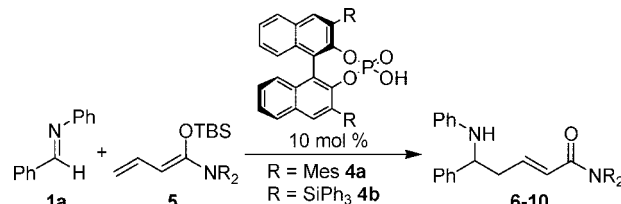
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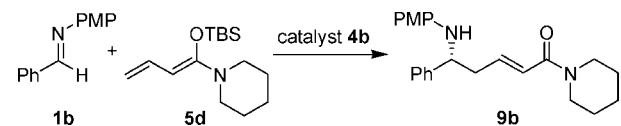
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Table 1. Nucleophile and Catalyst Screen^a


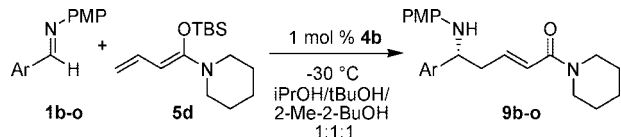
entry	vinylketene silyl <i>N,O</i> -acetal 5	cat.	time (h)	product	yield (%) ^c	ee (%) ^d
1	5a	4a	24	6a	34	41
2 ^b	5b	4a	90	7a	19	11
3	5c	4a	96	8a	67	17
4	5d	4a	0.5	9a	66	75
5	5e	4a	0.5	10a	97	78
6	5d	4b	40	9a	91	-90
7	5e	4b	24	10a	80	-67

^a Reactions were performed with imine **1a** (0.20 mmol) and vinylketene silyl *N,O*-acetals **5** (3.0 equiv) at $-30\text{ }^{\circ}\text{C}$ in a solvent mixture containing equal amounts of 2-propanol, 2-methyl-2-propanol, and 2-methyl-2-butanol with 1.0 equiv of water and 10 mol % of phosphoric acid **4** at 0.1 M concentration. ^b This reaction was conducted at $0\text{ }^{\circ}\text{C}$, *E/Z* ratio of 4/1. ^c Yields refer to chromatographically purified material. ^d Enantiomeric excesses were determined by HPLC using Chiralcel OD or OD-H columns (see the Supporting Information). The absolute configuration of the products was determined as described in the Supporting Information.

Table 2. Catalyst Loading^a


entry	catalyst loading (mol %)	reaction time (d)	yield ^b (%)	ee ^c (%)
1	10	5.5	85	87
2	5	5.5	86	89
3	2	6	91	90
4	1	7	99	90

^a Reactions conditions as given below Table 1. ^b Yields refer to chromatographically purified material. ^c Enantiomeric excesses were determined by HPLC using Chiralcel OD or OD-H columns (see the Supporting Information).

Table 3. Scope of the Vinylogous Mukaiyama–Mannich Reaction^a


entry	Ar	product	time (d)	yield ^b (%)	ee ^c (%)
1	Ph	9b	7	99	90
2	4-MeC ₆ H ₄	9c	10	85	79
3	4-EtC ₆ H ₄	9d	8	84	80
4	4- <i>t</i> BuC ₆ H ₄	9e	9	61	84
5	4-FC ₆ H ₄	9f	9	85	88
6	4-ClC ₆ H ₄	9g	9	73	80
7	4-CNC ₆ H ₄	9h	9	55	75
8	3-MeC ₆ H ₄	9i	3	82	92
9	3-ClC ₆ H ₄	9j	9	63	82
10	2-MeC ₆ H ₄	9k	9	66	80
11	2-ClC ₆ H ₄	9l	9	73	75
12	3-thiophenyl	9m	9	72	86
13	3-furyl	9n	9	72	84
14	2-naphthyl	9o	9	52	59

^a Reactions conditions as given below Table 1. ^b Yields refer to chromatographically purified material. ^c Enantiomeric excesses were determined by HPLC using Chiralcel OD or OD-H columns (see the Supporting Information). The absolute configuration of the products was determined as described in the Supporting Information.

9b–o in generally good yields, complete γ -regioselectivity, and up to 92% ee. Aromatic aldimines with ortho-substituents appear to react slightly less enantioselective than their meta- and para-substituted counterparts. As was already observed for the ester-based silyl dienolates,⁹ 3-thiophene- and 3-furyl-substituted aldimines were among the more selective substrates for the vinylogous Mannich reaction. Aliphatic aldimines decomposed under the reactions conditions and could not be employed as substrates.

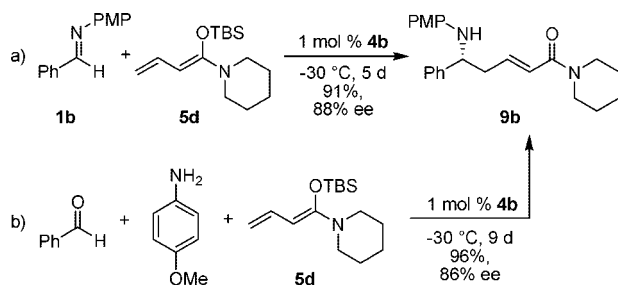
We assume that the catalytic cycle of this vinylogous Mannich reaction is similar to our previously discovered process in that water and/or alcohol present in the reaction medium serves to trap the TBS species as silanol or silyl ether, respectively, and reprotonates the phosphate counterion to regenerate the chiral Brønsted acid catalyst.⁹

To demonstrate the practicality of this process, the reaction of imine **1b** was performed at a 10-fold scale (2.0 mmol) with 1 mol % of phosphoric acid **4b** under otherwise identical reaction conditions. Vinylogous Mannich product **9b** was obtained in 91% yield and 88% ee after 5 d at $-30\text{ }^{\circ}\text{C}$ (Scheme 2, path a). The reaction may also be performed as a three-component Mannich reaction with aldehyde, amine, and silyl dienolate as starting materials, as was demonstrated for the same reaction (Scheme 2, path b). Mannich product **9b** was now isolated in 96% yield and 86% ee.

Vinylogous Mannich product **9b** was subsequently converted into synthetically useful building blocks with complete retention of configuration (Scheme 3).¹⁸ Treatment of amide

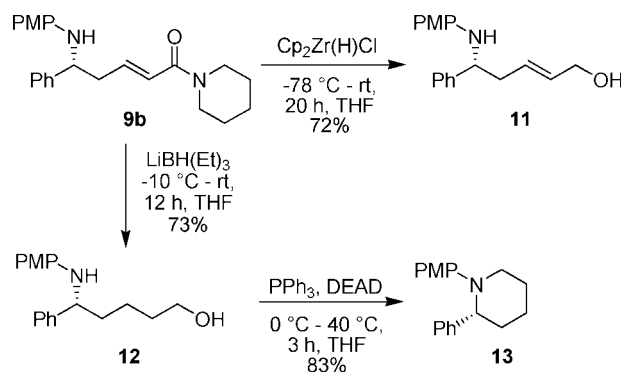
(18) For details see the Supporting Information.

Scheme 2



9b with the Schwartz reagent¹⁹ afforded allylic alcohol **11** in 72% yield, whereas reduction with lithium triethylborohydride²⁰ furnished the saturated alcohol **12** in 73% yield. The latter could be readily converted into piperidine **13** using a Mitsunobu reaction²¹ in good yield.

In conclusion, we have shown that vinylketene silyl *N,O*-acetals **5** readily participate in Brønsted acid-catalyzed vinyllogous Mukaiyama–Mannich reactions with aromatic and heteroaromatic aldimines and furnish δ -amino- α,β -unsaturated amides **9** in good yields and enantioselectivities. Direct three-component vinyllogous Mannich reactions deliver the products with almost identical yield and enantioselectivity,

Scheme 3. Elaboration of Vinyllogous Mannich Product **9b**

lectivity, thus avoiding the synthesis of the imines in a separate step. The utility of the vinyllogous Mannich products was demonstrated through conversion into various functional building blocks including a short synthesis of the enantiomerically highly enriched 2-phenylpiperidine **13**.

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Supporting Information Available: Detailed experimental procedures, characterization, and copies of spectra for the vinyllogous Mannich products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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