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Organocatalytic Enantioselective Vinylogous Michael Reaction of Vinylketene Silyl-*N,O*-Acetals

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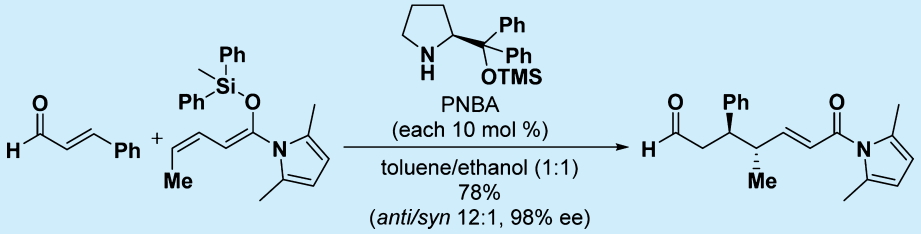
Supporting Information



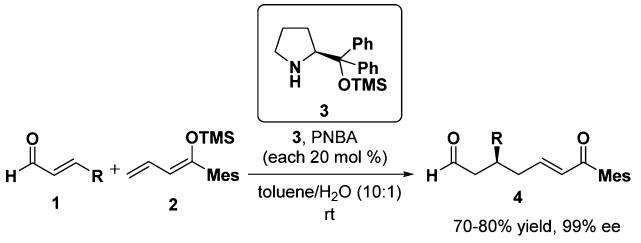
ABSTRACT: The enantioselective vinylogous Michael reaction of vinylketene silyl *N,O*-acetals derived from α,β-unsaturated *N*-acyl pyrroles and a broad range of α,β-unsaturated aldehydes proceeds with good regio-, diastereo-, and enantioselectivity when the Hayashi–Jørgensen diphenylprolinolsilylether was employed as a chiral organocatalyst. Products were obtained in generally good yields and as single stereoisomers after chromatographic purification with very high optical purity. They were easily derivatized into a set of useful synthetic building blocks.

Vinylogous carbon–carbon bond forming reactions of dienolates provide a valuable platform for the rapid construction of complex organic molecules and have emerged as powerful tools in the synthesis of complex molecules.[1] In contrast to vinylogous aldol and Mannich reactions, which have been studied in great detail, only a limited number of enantioselective vinylogous Michael processes are currently available to synthetic chemists, and the majority of them are restricted to the use of specific electron-rich five-membered heterocycles or 1,1-dicyanoalkenes as latent dienolates.[2]

Only recently, other electron-rich dienes have successfully been employed in vinylogous Michael reactions. Thus, β-alkyl-substituted cyclohexenones were employed by Melchiorre and co-workers in reactions with β-nitrostyrenes and alkylidene cyanoesters in which they reacted selectively at the exocyclic γ-position to deliver products with excellent enantioselectivity.[3] Reactions of 3-alkylidene oxindoles and nitroalkenes under thiourea catalysis, as reported by Curti and Casiraghi, proceeded with exceptional regio- and enantioselectivity.[4] More recently, Wang et al. established a magnesium-salen-catalyzed, formal [4 + 2]-cycloaddition reaction of β-alkylated chalcones and nitro alkenes based upon a selective, in situ, γ-deprotonation of enones which furnished highly substituted nitro cyclohexenols in one synthetic operation and typically excellent enantio- and good diastereoselectivity.[5] A conceptually different synthesis of vinylogous Michael products was reported by Johnson and co-workers who took advantage of a sequential vinylation-[1.2]-Brook rearrangement of silyl glyoxylates.[6]

We have recently reported the first catalytic, asymmetric vinylogous Mukaiyama–Michael reaction of acyclic silyl dienol ethers **2** derived from α,β-unsaturated ketones and α,β-unsaturated aldehydes **1**. It proceeds with exceptional regio- and enantioselectivity (Scheme 1).[7] Using γ-substituted dienol silyl ethers, products with two asymmetric stereogenic centers were formed with good diastereoselectivity. As the chiral catalyst, we employed the Hayashi–Jørgensen diphenylprolinolsilylether **3**, which activated the enals in an iminium ion catalysis mode, and delivered the Michael products **4** as single stereoisomers in good yield.[8]

Scheme 1. Vinylogous Mukaiyama–Michael Reaction of Dienol Silyl Ether 2 (Mes = Mesityl)[7]



There were some limitations in this process. The rather high catalyst loading typically required for this reaction (20 mol % of **3**) was impractical for large-scale applications. More importantly however, the subsequent synthetic manipulation of the Michael products **4** proved problematic and could only be achieved under forcing conditions. Accordingly, we envisaged a modified dienolate substrate which should ideally both be more reactive and, at the same time, produce a Michael

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adduct that would be more readily derivatized later on. We have now found that vinylketene silyl *N,O*-acetals **5** derived from *α,β*-unsaturated *N*-acyl-2,5-dimethylpyrroles fulfill both requirements and deliver the corresponding vinylogous Michael products **6** and **8**, respectively, with good-to-excellent levels of regio-, diastereo-, and enantioselectivity.

Silylketene *N,O*-acetals derived from *N*-acyl pyrroles have previously been employed in transition metal-catalyzed and organocatalytic carbon−carbon bond forming reactions with great success.[9] On the basis of the similar electronic properties of *N*-acyl pyrroles and ketones, we speculated that the corresponding vinylketene silyl *N,O*-acetals derived from *α,β*-unsaturated *N*-acyl-2,5-dimethylpyrroles might be successfully employed in our vinylogous Michael reaction.[10] If successful, the *N*-acyl pyrroles formed in these reactions could be expected to be highly reactive carboxylic derivatives that could easily be converted into a range of other useful substrate classes. The two methyl substituents within the pyrrole heterocycle were incorporated to provide additional steric shielding of the *α*-site within the dienolate, and enhance the desired *γ*-regioselectivity.

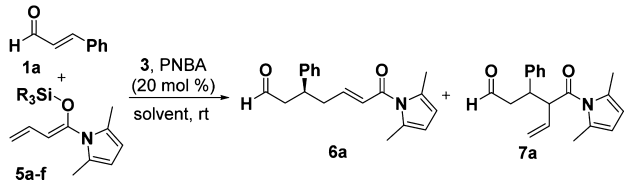
Vinylketene silyl *N,O*-acetals **5** were prepared through enolization and silylation of the corresponding *α,β*-unsaturated *N*-acyl-2,5-dimethyl pyrroles with NaHMDS and DMPU in THF at −78 °C followed by trapping of the enolate with the requisite chlorosilane. The products **5a−f** were typically obtained in good yield and predominatly as *Z*-stereoisomers; one product **5d** could be further purified by recrystallization as a homogeneous *Z*-isomer. The crystal structure of **5d** nicely reveals that the dienolate moiety is twisted out of conjugation with the pyrrole ring due to the additional steric constraints imposed by the methyl substituents (see the Supporting Information (SI)).

When vinylketene silyl *N,O*-acetals **5a−f** were treated with cinnamaldehyde (**1a**) under previously optimized reaction conditions varying amounts of *γ*- and *α*-regioisomers **6a** and **7a**, respectively, were formed in typically good overall yields (Table 1). Solvent mixtures of THF or toluene with ethanol proved optimal for both the conversion and enantioselectivity, and the *γ*-regioisomer was consistently obtained in >95% ee.

The regioselectivity, however, was dependent on the steric bulk of the silyl group. Thus, **5a** carrying a TMS-group delivered 55% of *γ*-regiosiomer **6a** along with 35% of *α*-regioisomer **7a** (entry 1). Slowly increasing the steric demand of the silyl group further increased the proportion of the desired *γ*-regioisomer. With the TES-dienolate **5b** the *γ*/*α*-ratio increased to ca. 5:1 in 80% overall yield similar to the dimethylphenylsilyl-substituted dienolate **5c** (entries 2 and 3). The best regioselectivity was obtained for the diphenylmethylsilyl (DPMS)-substituted dienolate **5d** which produced pure *γ*-regioisomer **6a** in 80% isolated yield and 98% ee along with only 11% of *α*-regioisomer **7a**, which was easily removed by SiO_2 flash chromatography (entry 4). More importantly, almost the same result was obtained when the catalyst loading was reduced to 10 mol % (entry 5), and even with 5 mol % of catalyst, the product was still obtained with 97% ee albeit in a reduced yield of 61% (entry 6). Interestingly, reactions with TBS- and TIPS-dienolates **5e** and **5f**, respectively, did not give rise to any product (entries 7 and 8).

With these optimized conditions in hand vinylogous Michael reactions of DPMS-substituted dienolate **5d** were studied with a broad range of enals to obtain the desired vinylogous Michael products **6a−l** in generally excellent enantioselectivity and 55−95% yield after chromatographic purification (Table 2).

Table 1. Optimization of the Vinylogous Michael Reaction[a]

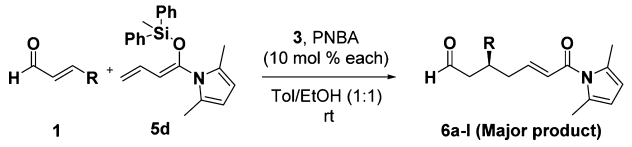


no.	dienolate **5** (SiR_3)	solvent	*γ*-1,4 **6a** [%][d]	*α*-1,4 **7a** [%][d]	ee [%][e]
1	**5a** (TMS)	Tol/H_2O (11:1)	55	35	95
2	**5b** (TES)	Tol/EtOH (1:1)	67	13	97
3	**5c** (DMPS)	THF/EtOH (1:1)	70	16	>97
4	**5d** (DPMS)	Tol/EtOH (1:1)	80	11	98
5[b]	**5d** (DPMS)	Tol/EtOH (1:1)	80	10	97
6[c]	**5d** (DPMS)	Tol/EtOH (1:1)	61	7	97
7	**5e** (TBS)	Tol/EtOH (1:1)	–	–	–
8	**5f** (TIPS)	Tol/EtOH (1:1)	–	–	–

[a]Standard conditions: 0.50 mmol (2.0 equiv) of vinylketene silyl *N,O*-acetal **5**, 0.25 mmol (1.0 equiv) of aldehyde **1**, 20 mol % of **3** and *p*-nitrobenzoic acid (PNBA) each, 1.25 mL of solvent, rt. [b]10 mol % of **3**. [c]5 mol % of **3**. [d]Yield of chromatographically purified product. [e]Determined by HPLC on a chiral stationary phase (see the SI).

Aromatic, heteroaromatic, and *β*-silyl-substituted enals all gave rise to full conversions whereas aliphatic aldehydes failed to react.

Table 2. Organocatalytic Vinylogous Michael Reactions of DPMS-Substituted Dienolate 5d[a]



no.	R	product	yield [%][b,c]	ee [%][d]
1	Ph	**6a**	80(10)	97
2	2-$NO_2C_6H_4$	**6b**	55(23)	95
3	3-$MeOC_6H_4$	**6c**	81(0)	98
4	4-$MeOC_6H_4$	**6d**	80(trace)	98
5	$PhMe_2Si$	**6e**	75(0)	99
6	3-MeC_6H_4	**6f**	74(14)	97
7	4-MeC_6H_4	**eg**	68(15)	97
8	1-Nap	**6h**	83(trace)	97
9	2-Nap	**6i**	69(7)	95
10	2-Furyl	**6j**	95(trace)	90
11	2-Thienyl	**6k**	75(15)	95
12	3-Thienyl	**61**	61(13)	95

[a]Standard conditions: 0.37 mmol (1.5 equiv) of vinylketene silyl *N,O*-acetal **5d**, 0.25 mmol (1.0 equiv) of aldehyde **1**, 10 mol % of **3** and *p*-nitrobenzoic acid (PNBA) each, 1.25 mL of ethanol/toluene (1:1), rt, 24−60 h. [b]Yield of chromatographically purified *γ*-1,4 product. [c]Yield of chromatographically purified *α*-1,4 product in brackets. [d]Determined by HPLC on a chiral stationary phase (see the SI).

Varying amounts of the undesired *α*-regioisomer were formed in up to 23% yield with the highest proportion observed for electron-withdrawing cinnamaldehydes (entry 2). On the other hand, electron-rich cinnamaldehydes and the *β*-silyl-substituted enal produced only trace amounts of the *α*-

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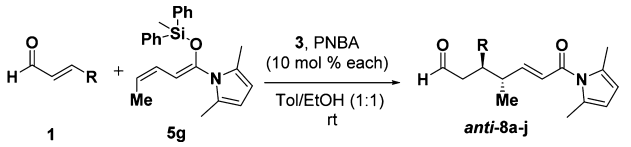
regioisomer and gave up to 95% yield of the desired vinylogous Michael products.

To explore the full potential of this transformation we next studied reactions of γ-methyl-substituted dienolate **5g** with enals according to the general protocol (Table 3). The products

Table 3. Organocatalytic Vinylogous Michael Reactions of γ-Methyl-Substituted Dienolate 5g[a]



no.	R	product	yield[%][b,c]	*anti/syn*[d]	ee [%][e]
1	Ph	**8a**	78(6)	12:1	98
2	4-MeOC$_6$H$_4$	**8b**	82(2)	14:1	99
3	3- MeC$_6$H$_4$	**8c**	54(14)	7:1	96
4	4-MeC$_6$H$_4$	**8d**	68(11)	9:1	99
5	1-Nap	**8e**	76(trace)	14:1	98
6	2-Nap	**8f**	56(22)	9:1	99
7	2-Furyl	**8g**	78(3)	9:1	99
8	2-Thienyl	**8h**	54(16)	9:1	98
9	2-MeC$_6$H$_4$	**8i**	69(14)	7:1	97
10	4-ClC$_6$H$_4$	**8j**	70(12)	7:1	98

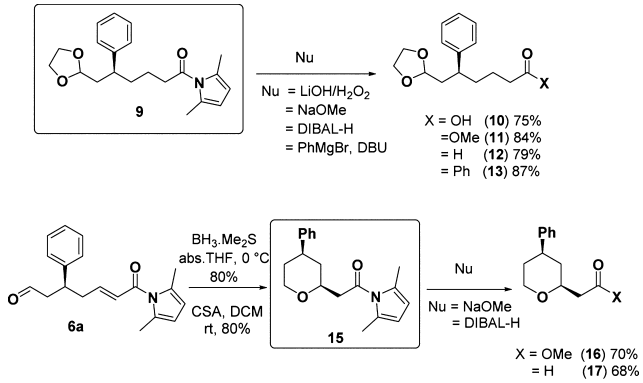
[a]Standard conditions: 0.50 mmol (2.0 equiv) of vinylketene silyl *N,O*-acetal **5g**, 0.25 mmol (1.0 equiv) of aldehyde **1**, 10 mol % of **3** and *p*-nitrobenzoic acid (PNBA) each, 1.25 mL of ethanol/toluene (1:1), rt, 40−60 h. [b]Yield of chromatographically purified *anti*-diastereomer γ-1,4 product. [c]Yield of chromatographically purified α-1,4 product in brackets. [d]*anti:syn* ratio determined by ^{1}H NMR spectroscopy on crude product mixture. [e]Determined by HPLC on a chiral stationary phase (see the SI).

8a−j were formed in good overall yields and typically excellent enantioselectivity with the desired γ-regioisomers as either the major or even the sole product. The diastereoselectivity in favor of the *anti*-stereoisomer ranged between 7:1 and 14:1, and the diastereomers were separated through SiO_2 flash chromatography. We assume that an extended open-chain transition state is involved in this reaction in which minimized gauche interactions between the methyl group and the β-substituent within the enal account for this diastereoselectivity.

Finally, the conversion of the products into other useful synthetic building blocks was investigated. For this purpose, the acetal-protected, saturated *N*-acyl pyrrole **9** was employed as a test substrate. As expected, hydrolysis, transesterification, reduction, and alkylation all proceeded well on this substrate and furnished the corresponding acid, ester, aldehyde, and ketone **10−13**, respectively, in good yields (Scheme 2).[11] In addition, taking advantage of the conjugate double bond aldehyde **6a** was converted into tetrahydropyran **15** as a single diastereomer through reduction and subsequent oxa-Michael addition, which thereafter was converted into the tetrahydropyran-containing ester and aldehyde **16−17**, respectively, in good yield.[12]

In conclusion, we have reported a highly enantioselective, organocatalyzed, vinylogous Michael reaction of acyclic vinylketene silyl *N,O*-acetals with α,β-unsaturated aldehydes. It furnishes highly functionalized 1,7-dioxo compounds with good diastereoselectivity and excellent optical purity. Previous limitations with respect to nucleophile reactivity, catalyst loading, and subsequent product manipulation have now been readily overcome by employing a new dienolate. Studies toward the extension of this methodology to other Michael acceptors are currently ongoing and will be reported in due course.

Scheme 2. Conversion of *N*-Acyl Pyrrole 6a into Other Building Blocks



■ ASSOCIATED CONTENT

Supporting Information

Single crystal X-ray crystallography data for nucleophile **5d** (CCDC 970124) and **5g** (CCDC 970125) are available free of charge at http://www.ccdc.cam.ac.uk. Experimental procedures and full spectroscopic and analytical data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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