Asymmetric Catalysis

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Organocatalytic, Highly Enantioselective Vinylogous Mukaiyama–Michael Reaction of Acyclic Dienol Silyl Ethers**

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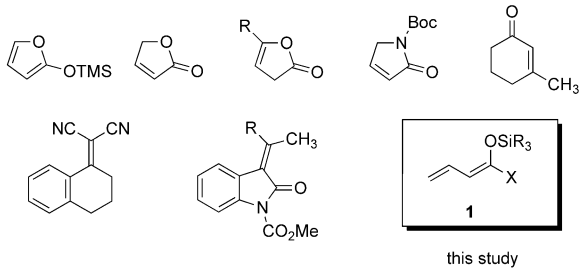
Dedicated to Prof. Herbert Mayr on the occasion of his 65th birthday

Vinylogous carbon–carbon bond forming processes of extended dienol derivatives, ideally proceeding with high regio- as well as enantioselectivity in the presence of a chiral catalyst, are among the most valuable transformations in synthetic organic chemistry on the basis of their carbon-backbone-generating character and the establishment of new stereogenic centers and functional groups. For the prototype of this class, the vinylogous Mukaiyama–aldol reaction,[1] a broad range of highly effective and selective methods exist since the ground-breaking work of Carreira, Evans, Denmark, Campagne, Kiyooka, Kalesse, and List. In the last few years, some very effective procedures for the execution of the vinylogous Mannich reaction have also been developed that rely either on chiral Lewis acids or on Brønsted acids, and these deliver the corresponding Mannich bases in very high optical purity.[2]

Vinylogous Michael reactions of dienol derivatives, however, proceeding both with high regio- and enantioselectivity, have been reported much less frequently (Scheme 1).[3] A major cause for this deficiency may be the existence of two reactive sites in both reaction partners principally giving rise to four regioisomeric products altogether, which may additionally be formed in various stereoisomeric forms. Therefore, most of the previously reported processes are limited to substrates which a priori have a strong preference for the γ-position in the nucleophile, such as silyloxyfurans,[4] the corresponding unsaturated butyrolactones[5] and -lactams,[6] and α,α-dicyanoalkenes.[7] Furthermore, two organocatalytic procedures were recently disclosed in reactions with nitroalkenes, which for the first time were suitable for other substrates as well. Thus, Melchiorre and co-workers revealed that β-alkyl-substituted cyclohexenones selectively engaged β-nitrostyrenes und alkylidene cyanoesters at the γ-position by way of dienamine catalysis and delivered products with excellent enantioselectivity.[8] More recently, Curti, Casiraghi, et al. reported thiourea-catalyzed reactions of 3-alkylidene oxindols with bifunctional cinchona alkaloid-based catalysts, which gave exceptional regio- and enantioselectivity in reactions with nitroalkenes.[9] A conceptually different and diastereoselective access to vinylogous Michael products has been devised by Johnson and co-workers based upon their previously developed sequential vinylation-[1.2]-Brook rearrangement of silyl glyoxylates.[10]



Scheme 1. Previously employed substrates in vinylogous Michael reactions in comparison to dienol silyl ether **1**.

We report herein the first catalytic, enantioselective, vinylogous Mukaiyama–Michael reactions of simple acyclic dienol silyl ethers **1** with α,β-unsaturated aldehydes, furnishing synthetically valuable, chiral 1,7-dioxo compounds as products. Regio- as well as enantioselectivity in these reactions are uniformly excellent, and in the case of γ-substituted dienol silyl ethers, products with two new stereogenic centers are obtained, which are furthermore formed with good diastereoselectivity. As the catalytic principle we utilize the iminium ion activation mode first established by MacMillan, which reversibly converts conjugated aldehydes into reactive, chiral α,β-unsaturated iminium salts.[11]

In orienting experiments, we had found that silyl dienolates of α,β-unsaturated ketones and thioesters proved to be the most suitable nucleophiles for this reaction. Thus, chiral imidazolidinone **3a**[12] in combination with 2,4-dinitrobenzenesulfonic acid catalyzed the vinylogous γ-1,4-regioselective Michael reaction of dienol silyl ethers **1a** and **1b** with crotonaldehyde in dichloromethane/water (10:1) and delivered the corresponding Michael products with 76% and 45% yield, respectively (Table 1, entries 1 and 2). The enantioselectivity, however, was unsatisfactory (40% *ee* and 37% *ee*, respectively). Likewise, vinylketene-*S*,*O*-silylacetals **1c** und **1d** were converted into products **4c** and **4d**, respectively, with only moderate yields and selectivities. As side products the γ-1,2-coupled regioisomers were formed additionally as vinyl-

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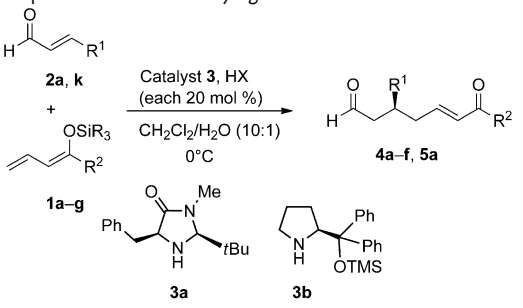
Table 1: Optimization of the vinylogous Michael reaction.[a]



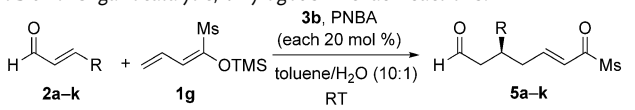
No.	Dienolate **1** (R^2, SiR_3)	R^1	Cat.	Product	Yield [%][b]	*ee* [%][c]
1	**1a** (Ph, TBS)	Me	**3a**	**4a**	76	40
2	**1b** (*t*Bu, TBS)	Me	**3a**	**4b**	45	37
3	**1c**[d] (S*t*Bu, TBS)	Me	**3a**	**4c**	55[e]	54
4	**1d**[d] (SPh, TBS)	Me	**3a**	**4d**	56[e]	50
5[f]	**1e** (Ph, TMS)	Ph	**3b**	**4e**	40[g]	95
6[f]	**1f**[d] (S*t*Bu, TMS)	Ph	**3b**	**4f**	40[g]	98
7[h]	**1g**[i] (Ms, TMS)	Ph	**3b**	**5a**	74	99

[a] Standard conditions: 0.50 mmol (2.0 equiv) dienol silyl ether **1**, 0.25 mmol (1.0 equiv) aldehyde **2**, 20 mol% **3** and 2,4-dinitro-benzenesulfonic acid (DNBSA), 1 mL CH_2Cl_2/H_2O (10:1), 0°C, 12–36 h. [b] Yield of chromatographically purified product. [c] Determined by HPLC on a chiral stationary phase. [d] 1*E*/1*Z* = 3:1. [e] 10% of the γ-1,2-product were isolated additionally. [f] *para*-Nitrobenzoic acid (PNBA) as cocatalyst in CH_2Cl_2/H_2O (10:1), RT. [g] 35% of the α-1,4-product were isolated additionally. [h] PNBA as cocatalyst in toluene/H_2O (10:1), RT. [i] 1*E*/1*Z* = 99:1. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, Ms = mesityl.

entry 7).[14] The absolute configuration of product **5a** was established after derivatization (see the Supporting Information) by comparison with literature data and is consistent with the transition-state model put forth for these reactions.

With this optimized procedure in hand, we successfully performed vinylogous Michael reactions of dienol silyl ether **1g** and a broad range of α,β-unsaturated aldehydes **2a–k**, delivering the corresponding vinylogous Michael products **5** as single regioisomers throughout and with typically 70–80% yield and 99% *ee* (Table 2). Of particular significance was the reaction of β-silyl-substituted aldehyde **2j**, which delivered

Table 2: Organocatalytic, vinylogous Michael reactions.[a]



No.	Aldehyde **2** (R)	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	**2a** (Ph)	48	**5a**	74	99
2	**2b** (4-ClC_6H_4)	33	**5b**	77	99
3	**2c** (4-BrC_6H_4)	38	**5c**	76	98
4	**2d** (4-NO_2C6H4]	36	**5d**	73	99
5	**2e** (4-$MeOC_6H_4$)	36	**5e**	70	99
6	**2f** (2-MeC_6H_4)	48	**5f**	72	99
7	**2g** (2-$NO_2C_6H_4$)	36	**5g**	72	99
8	**2h** (3-$MeOC_6H_4$)	38	**5h**	76	99
9	**2i** (2-Thienyl)	34	**5i**	72	99
10	**2j** ($PhMe_2Si$)	28	**5j**	90	> 99
11[d]	**2k** (Me)	48	**5k**	50	71

[a] Standard Conditions: 0.50 mmol (2.0 equiv) dienol silyl ether **1g**, 0.25 mmol (1.0 equiv) aldehyde **2**, 20 mol% of **3b** und *para*-nitrobenzoic acid (PNBA) each, 1 mL toluene/H_2O (10:1), RT, 24–48 h. [b] Yield of chromatographically purified product. [c] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [d] This reaction was conducted with 20 mol% benzoic acid as cocatalyst in ethanol. TMS = trimethylsilyl, Ms = mesityl.

ogous Mannich products, which contained the imidazolidinone in the product (Table 1, entries 3 and 4).

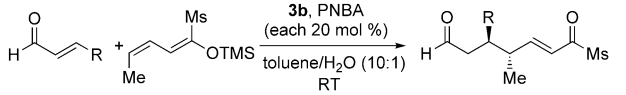
A breakthrough to a highly enantioselective reaction was realized by switching to the Jørgensen–Hayashi catalyst **3b**.[13] Using **3b** in combination with *para*-nitrobenzoic acid (PNBA) as cocatalyst (20 mol% each) converted dienol silyl ether **1e** and cinnamaldehyde (**2a**) into the desired vinylogous Michael product **4e** with 40% yield and 95% *ee* along with the undesired α-1,4-coupled regioisomer, which was formed in 35% yield (Table 1, entry 5). A very similar result was obtained in the reaction of thioester-based silyl dienolate **1f**, which again gave rise to significant amounts of the α-1,4-regioisomer, but the desired vinylogous Michael product **4f** was formed with excellent enantioselectivity (Table 1, entry 6). Eventually, the formation of the undesired α-1,4-regioisomer was completely suppressed by changing the phenyl group into a sterically more demanding mesityl group, which also shielded the α-position within the dienol moiety. Thus, the reaction of dienol silyl ether **1g** and cinnamaldehyde (**2a**) catalyzed by **3b** and PNBA (20 mol% each) delivered the desired vinylogous Michael product **5a** as a single regioisomer with 74% yield and 99% *ee* (Table 1, vinylogous Michael product **5j** with 90% yield and > 99% *ee* (Table 2, entry 10). In general, aromatic and heteroaromatic aldehydes proved to be suitable reaction partners in this reaction. Aliphatic and hence enolizable conjugated aldehydes, however, such as crotonaldehyde (**2k**), furnished products with diminished yields and enantioselectivities (Table 2, entry 11).

Furthermore, we wondered whether γ-substituted dienol silyl ethers may be employed in this process, as they would furnish Michael products with two new stereogenic centers. At the outset it was unclear whether the exceptional regioselectivity observed above would be deteriorated through the additional γ-substitution and with which degree of diastereoselectivity the products would form. To study the influence of the double-bond geometry, we prepared the γ-methyl-substituted dienol silyl ethers **6a** and **6b** as stereochemically pure 3*Z*- and 3*E*-isomers[15] and subjected them to reactions with various α,β-unsaturated aldehydes under the previously optimized conditions.

The 3*Z*-diastereomer **6a** reacted with cinnamaldehyde (**2a**) to yield a 92:8-diastereomeric mixture of vinylogous Michael product **7a** in 77% combined yield from which pure

anti-diastereomer *anti*-**7a** was separated chromatographically in 70% yield and with 99% *ee* (Table 3, entry 1).[16] Despite the additional steric hindrance at the γ-position imposed by the methyl group, the reaction remained highly regioselective, and no α-regioisomer was observed whatsoever.

Table 3: Vinylogous Michael reactions of the 3*Z*-dienol silyl ether **6a**.[a]



2a–i, l **6a** *anti*-**7a–j**

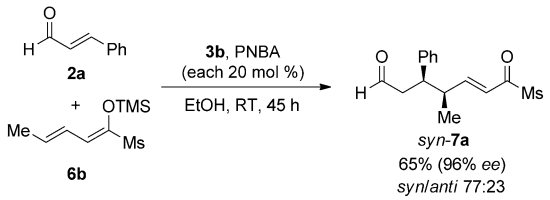
No.	Aldehyde **2** (R)	*t* [h]	Prod.	Yield [%][b,c]	*anti*/*syn* [d]	*ee* [%][e]
1	**2a** (Ph)	48	**7a**	77 (70)	92:8	99
2	**2b** (4-ClC_6H_4)	40	**7b**	73 (63)	86:14	99
3	**2c** (4-BrC_6H_4)	40	**7c**	74 (66)	89:11	99
4	**2d** (4-$NO_2C_6H_4$)	38	**7d**	80 (66)	82:18	96
5	**2e** (4-$OMeC_6H_4$)	38	**7e**	69 (61)	88:12	99
6	**2f** (2-MeC_6H_4)	48	**7f**	73 (64)	88:12	99
7	**2g** (2-$NO_2C_6H_4$)	40	**7g**	78 (64)	82:18	97
8	**2h** (3-$OMeC_6H_4$)	42	**7h**	74 (61)	84:16	98
9	**2i** (2-Thienyl)	40	**7i**	70 (62)	89:11	99
10	**2l** (3-MeC_6H_4)	48	**7j**	75 (64)	87:13	99

[a] Standard Conditions: 0.50 mmol (2.0 equiv) dienol silyl ether **6a** (1*E*/1*Z* = 6:1), 0.25 mmol (1.0 equiv) aldehyde **2**, 20 mol% of **3b** and PNBA each, 1 mL toluene/H_2O (10:1), RT, 24–48 h [b] Combined yield of both diastereomers. [c] Yield of chromatographically purified *anti*-diastereomer in brackets. [d] *anti*:*syn* Ratio determined by ^1H NMR-spectroscopy. [e] Determined by HPLC on a chiral stationary phase (see the Supporting Information). TMS = trimethylsilyl, Ms = mesityl, PNBA = *para*-nitrobenzoic acid.

Various more α,β-unsaturated aldehydes were successfully treated with **6a** delivering the desired vinylogous Michael products *anti*-**7b-j** in good yields and excellent enantioselectivity (Table 3). The diastereoselectivity in favor of the *anti*-diastereomer varied between 82:18 and 92:8, and in every case the major *anti*-diastereomer was obtained isomerically pure through chromatography in 60–70% yield and essentially complete optical purity.

In contrast, reactions of the 3*E*-stereoisomer **6b** proceeded much more slowly in the solvent mixture toluene/water and delivered products with only moderate yields. Thus, the reaction of **6b** and cinnamaldehyde (**2a**) furnished the vinylogous Michael product **7a** in only 45% combined yield and with 99% *ee* as 86:14 mixture of diastereomers. To accelerate the reaction, we switched to ethanol as solvent, which proved to be a good balance between enhanced reaction rates and slightly diminished stereoselectivity.[17] Under these conditions, **7a** was formed in 65% yield after 45 h at room temperature, and pure s*yn*-**7a** was isolated by chromatography in 50 yield and with 96% *ee* (Scheme 2).[18]

Apparently, reactions of γ-substituted dienol silyl ethers are for the most part stereoconservative processes in which the configuration of the nucleophile mainly determines the relative configuration of the major product diastereomer. We currently assume that open transition states are involved in which the diastereoselectivity of the reaction is governed by minimization of *gauche* interactions.[19]



Scheme 2. Vinylogous Michael reaction of 3*E*-dienol silyl ether **6b**.

In conclusion, we have established the first catalytic, enantioselective vinylogous Michael reaction of acyclic dienol silyl ethers, which furnished valuable chiral 1,7-dioxo compounds with good yields and excellent regio- as well as enantioselectivity. With γ-substituted nucleophiles, a second stereogenic center was formed additionally with typically good diastereoselectivity. In particular, reactions of the 3*Z*-configured dienol silyl ether **6a** delivered vinylogous Michael products *anti*-**7** as practically pure diastereo- and enantiomers in good yields after chromatographic purification. Studies to further improve this process and extend its scope are currently ongoing in our laboratory.

Experimental Section

General procedure (with **5a**; (Table 1, entry 7): α,α-Diphenylprolinolsilylether (**3b**, 16.3 mg, 0.05 mmol), *para*-nitrobenzoic acid (8.4 mg, 0.05 mmol), and cinnamaldehyde (**2a**, 31 μL, 0.25 mmol) were dissolved in toluene/water (10:1, 1 mL). Subsequently dienol silyl ether **1g** (130 mg, 0.50 mmol) was added and the solution was stirred at room temperature for 48 h. After removal of the solvent, the reaction mixture was directly purified by flash chromatography over silica gel (*n*-hexane/ethyl acetate 4:1), which furnished vinylogous Michael product **5a** (118 mg, 74%), the optical purity of which was determined by HPLC on a chiral AD-H-phase to be 99% *ee* (see the Supporting Information).

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Keywords: dienol silyl ethers · enantioselectivity · iminium ion catalysis · Michael reaction · organocatalysis

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[14] The analogous 3,5-bistrifluormethylphenyl-substituted prolinol silyl ether gave rise to identical enantioselectivity in the reaction with cinnamaldehyde; the yield, however, was only 21% owing to extensive decomposition of the sensitive dienol silyl ether **1g**.
[15] Based upon the different synthetic access, the 3*Z*-dienol silyl ether **6a** was obtained preferentially as the 1*E*-diastereomer (1*E*/1*Z* = 6:1), whereas the 3*E*-dienol silyl ether **6b** was predominantly formed as the 1*Z*-diastereomer (1*Z*/1*E* = 3:1; see the Supporting Information).
[16] For the assignment of the relative configuration, see the Supporting Information.
[17] Generally, reactions run in ethanol as solvent furnished products with slightly lower enantioselectivity (2–3% *ee*) as opposed to the toluene/water solvent mixture, as well as lower diastereoselectivity.
[18] Reaction of dienol silyl ether **6b** with other α,β-unsaturated aldehydes proceeded in comparable yields and selectivities.
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