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Solvent-free Mukaiyama and Mukaiyama–Michael vinylogous reactions of a dioxinone-derived silyl enol ether promoted by Lewis bases

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ABSTRACT

The vinylogous aldol-type addition of a dienolsilyl ether, derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, showed to occur with complete γ-selectivity by enolate activation promoted by neutral Lewis bases under solvent-free conditions. Moderate to high yields were obtained with aromatic, hetero-aromatic, and aliphatic aldehydes, as well as activated ketones. Under the same conditions and in the absence of catalyst, the first Mukaiyama–Michael addition of the masked acetoacetate ester to α,β-unsaturated aldehydes took place in satisfactory way.

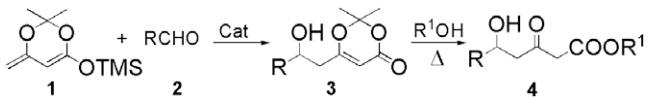
1. Introduction

The vinylogous aldol reaction[1] of the masked acetoacetate ester **1** is considered a valuable tool for the generation of a δ-hydroxy-β-ketoester core, which represents the main structural feature of the important key intermediates **4** in the synthesis of a variety of natural and unnatural bioactive compounds (Scheme 1).[2]

From the preparative point of view the typical approach is based on carbonyl activation (Scheme 2, Path **a**) usually by chiral and achiral Lewis acids (LA) such as Ti(IV),[3] B(III),[4] Eu(III),[5] Cu(II),[6] Si(IV),[7] and Bi(III)[8] compounds and complexes.

Furthermore, the use of some hydrogen bond donors has recently proven to be successful in the vinylogous Mukaiyama reaction of **1** with aldehydes.[9,10]

Conversely, in the past years rather comparable attention has not been paid to the alternative approach, involving enolate activation, presumably because of a competing α-addition leading to aldols of type **5** and/or **6** (Scheme 2, path **b**).



Scheme 1. Synthesis of **4** by vinylogous aldol reaction of silyloxydiene **1**.

In fact, the significant formation of products deriving from α-addition was observed in related processes for the vinylogous aldol reaction of dienolates.[11]

However, previous reports, concerning the aldol-type condensation of trimethylsilyl enolates (usually silyl ketene acetals) suitably activated by neutral Lewis bases (such as dimethyl sulfoxide,[12] N-oxides,[13] *N*-methyl imidazole,[14] and phosphine[15]) suggested an investigation on the reactivity of silyloxydiene **1** under conditions involving enolate activation.

2. Results and discussion

In a preliminary phase, aldehyde **2a** (Table 1, Fig. 1) was chosen as the representative substrate and was submitted to treatment with **1** in the presence of catalytic amount of a variety of Lewis bases under solvent-free conditions.

It has to be noted that, in the absence of activator the formation of the protected vinylogous aldol **7a** was found to occur in a not negligible way (Table 1, entry 1). The occurrence of the background reaction can be reasonably explained taking in mind a previous report[10] pointing out, through an experiment similar to the one reported in entry 1 (Table 1), that the formation of a TMSO-protected vinylogous aldol by reaction of **1** with benzaldehyde could be promoted by benzoic acid, usually present as auto-oxidation product in not freshly distilled starting material. Therefore acid-free aldehydes were always used in the following experiments.

The activation by dimethyl sulfoxide (DMSO) gave rather poor results, resulting in the formation of a mixture of protected and

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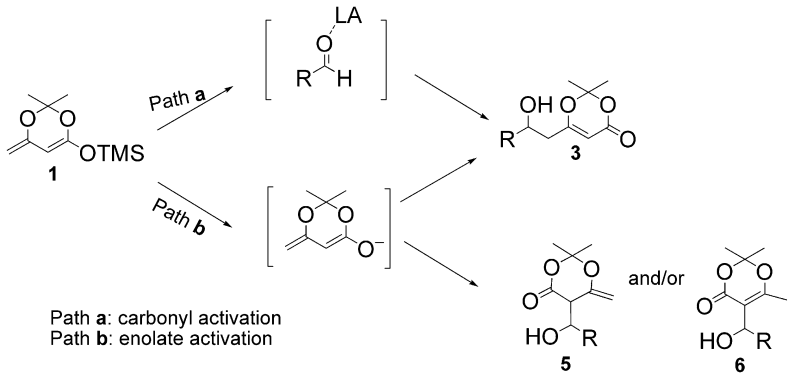
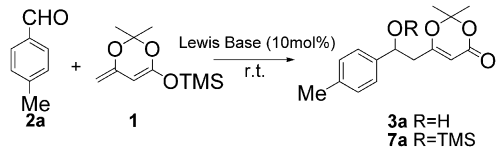


Scheme 2. Different activation pathways for vinylogous aldol reaction of dienol silyl ether **1**.

Table 1
Lewis base-catalyzed vinylogous aldol addition of **1** to **2a**



Entry[a]	Lewis base	Time (h)	**3a** yield[b] (%)	**7a** yield[b] (%)
1	—	3	—	33
2	DMSO	24	27	17
3	DMF	2	—	84
4	HMPA	2	—	84
5	PyN^+-O^-	2	—	87
6[c]	PyN^+-O^-	3	18	65

[a] In all entries 1/1.5/0.1 aldehyde **2a**/**1**/Lewis base ratio was used.
[b] All the yields refer to isolated chromatographically pure compound whose structure was confirmed by conversion into **3a** by Carreira procedure.[3f]
[c] In this entry PyN^+–O^- was used in 5 mol % amount.

free vinylogous aldols (respectively, **7a** and **3a**) in low overall yield after prolonged reaction times.

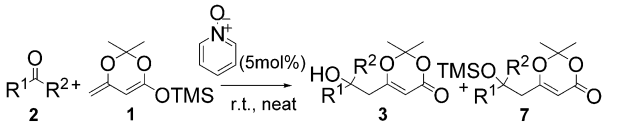
Conversely, very satisfactory results in terms of both efficiency and γ-selectivity were obtained by using dimethyl formamide (DMF) (entry 3), hexamethyl phosphoramide (HMPA) (entry 4), and pyridine N-oxide (PyN^+-O^-) (entry 5) under the conditions depicted in Table 1. In fact, the protected vinylogous aldol **7a** was usually isolated in rather good yields and no evidence of formation of a product deriving from α-addition of **1** to **2a** could be detected.

It is notable that in the presence of a lower PyN^+-O^- amount (5 mol %) the γ-vinylogous addition was again found to be the exclusive process affording in high overall yield the free aldol **3a** (16% yield) and the corresponding TMS-derivative **7a** (65% yield).

Furthermore, the use of a solvent seemed to cause a significant lowering of the efficiency and reaction rate: in fact, when the experiment of entry 6 was carried out in CH_2Cl_2 solution **7a** was isolated in 70% yields after 24 h. In view of a possible achievement of an asymmetric version of the reaction, the wide availability of procedures leading to chiral mono- and bidentate N-oxides suggested to check the scope of the protocol by using PyN^+-O^- as the activator (Table 2, Fig. 2). Therefore a broad variety of carbonyl compounds was submitted to reaction with **1** under the conditions used in entry 6, Table 1.

As reported in Table 2, entries 1–7, various substituted aromatic and hetero-aromatic aldehydes revealed a very satisfactory reactivity, resulting in the formation of the protected vinylogous aldols 7a–7g as only or most abundant products, contaminated occasionally by lower amounts of free vinylogous aldols of type **3**.

Table 2
PyN^+–O^--catalyzed vinylogous aldol addition of **1** to carbonyl compounds **2**



Entry[a]	R^1	R^2	Time (h)	**3** yield[b] (%)	**7** yield[b] (%)
1	4-MeC_6H_4 **2a**	H	3	**3a**: 18	**7a**: 65
2	4-$MeOC_6H_4$ **2b**	H	3	**3b**: —	**7b**: 88
3	4-ClC_6H_4 **2c**	H	3	**3c**: —	**7c**: 65
4	6-NO_2-Piperonal **2d**	H	1	**3d**: —	**7d**: 72
5	4-CNC_6H_4 **2e**	H	2	**3e**: 22	**7e**: 50
6	2-$MeOC_6H_4$ **2f**	H	2	**3f**: 16	**7f**: 64
7	5-NO_2-2-Furyl **2g**	H	1	**3g**: 19	**7g**: 56
8	$PhCH_2CH_2$ **2h**	H	24	**3h**: —	**7h**: 50
9	Me **2i**	COOEt	1	**3i**: —	**7i**: 48
10	Me **2j**	COMe	1	**3j**: —	**7j**: 56
11	4-$NO_2C_6H_4$ **2k**	Me	4	**3k**: —	**7k**: 40

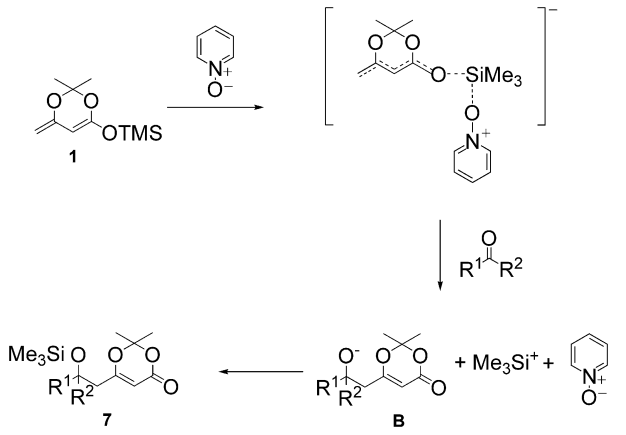
[a] In all entries 1/1.5/0.05 aldehyde **2a**/**1**/Lewis base ratio was used.
[b] All the yields refer to isolated chromatographically pure compounds whose structures were assigned by analytical and spectroscopic data. Particularly, the structure of products **7a**, **7b**, **7c**, **7e**, **7f**, **7h**, and **7i** refer to that of isolated chromatographically pure compounds which were further confirmed by comparison of desilylated known aldols[3c,9,10,16] **3a**, **3b**, **3c**, **3e**, **3f**, **3h,** and **3i** obtained through Carreira's protocol.[3f]

Less reactivity was exhibited by aliphatic aldehydes (entry 8) since the corresponding product **7h** could be isolated in moderate yield after 24 h.

Rather interestingly, the procedure proved to be successful with activated ketones (entries 9–11) affording rapidly the vinylogous TMS-derivatives **7i–7k** in 40–56% yield.

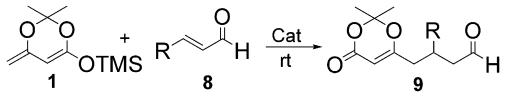
The presence of a vicinal (Table 2, entries 9 and 10) or remote electron-withdrawing group (Table 2, entry 11) seemed to be necessary for the efficiency of the reaction: in fact, when a non-activated ketone (such as acetophenone) was submitted to treatment with **1** under the conditions used in entry 7, Table 1, the reaction took place in only 16% yield after 24 h. No improvement was observed by performing the reaction in the presence of higher catalyst loading (20 mol %).

As regard to the mechanistic aspects, the enhancement of the nucleophilic properties of **1** by pyridine N-oxide (as well as the other Lewis bases) can be reasonably explained by its coordination to the silicon atom, resulting in the increase of the electron density on the silyloxydiene moiety as depicted in **A** (Scheme 3). Furthermore, shielding of C(α) atom by silicon ligands can be considered responsible for the observed γ-selectivity. The activated silyloxydiene **A** is then converted into the alkoxide intermediate **B** by



Scheme 3. Proposed catalytic cycle for PyN^{+}–O^{-}-catalyzed vinylogous aldol reaction of **1**.

Table 3
Addition of silyloxydiene **1** to α,β-unsaturated aldehydes **8**



Entry[a]	R	PyN^{+}-O^{-} (mol %)	Time (h)	**9** yield (%)[b,c]
1	C_6H_5 **8a**	5	6	**9a**: 34(36)
2	C_6H_5 **8a**	—	23	**9a**: 56(26)
3	C_6H_5 **8a**	—	6	**9a**: 20(9)
4	4-$NO_2C_6H_4$ **8b**	—	23	**9b**: 68(nd)
5	CH_3 **8c**	—	23	**9c**: 73(5)
6	C_2H_5 **8d**	—	23	**9d**: 57(7)
7	C_3H_7 **8e**	—	23	**9e**: 60(14)

[a] In all entries 1/1.5 aldehyde **2a**/**1** ratio was used.
[b] All the yields refer to isolated chromatographically pure compounds whose structures were assigned by analytical and spectroscopic data.
[c] Values in parentheses refer to isolated TMSO-protected vinylogous aldols.

reaction with the carbonyl compound with concomitant regeneration of pyridine N-oxide to establish a catalytic cycle, while trapping of Me_3Si^{+} cation by **B** leads to the final product **7**.

The attempt to extend the protocol to α,β-unsaturated aldehydes has allowed to disclose an unprecedented reactivity of the trimethylsilyl derivative **1** (Table 3, Fig. 3). In fact, when cinnamic aldehyde **8a** was reacted with **1** under the usual conditions (Table 1, entry 7), a γ-vinylogous Mukaiyama–Michael process was found to notably compete with the vinylogous aldol reaction (Table 3, entry 1).

As is in our habit, a control experiment was performed in the absence of catalyst and, to our delight, the formation of the vinylogous 1,4-adduct was found to be the far predominant process, leading to **9a**, contaminated by lower amount of the usual γ-vinylogous aldol, in 82% overall yield (entry 2). Although the mechanistic aspects are under investigation, the predominance of the vinylogous conjugate addition of **1**, in the absence of catalyst, after 24 h cannot be attributed to thermodynamic control conditions, since a similar ratio for 1,4/1,2-adducts was observed after 6 h (entries 2 and 3).

The superior properties of **1**, as Michael donor, were confirmed by further experiments carried out without catalyst on other α,β-unsaturated aldehydes bearing aromatic (Table 3, entry 4) and aliphatic substituents (Table 3, entries 5–7) in β-position. The corresponding adducts **9b–e** were isolated in rather satisfactory yields while the competing 1,2-addition was found to occur in a very reduced way.

It has to be noted that **1** has been rarely used in a vinylogous Mukaiyama–Michael additions and the poor available reports concern the employment of particularly activated Michael acceptors, such as 2-acyl-naphthoquinones.[17]

Furthermore, the easy access to polyfunctional compounds of type **9** can be considered of synthetic value because of the wide possibility of functional manipulation.

3. Conclusions

In conclusion, the vinylogous aldol-type addition of dienolsilylether **1** by enolate activation promoted by neutral Lewis bases under solvent-free conditions, proved to be a valid alternative to the classical carbonyl activation by Lewis acids. The procedure revealed to be successful with various substituted aromatic and hetero-aromatic aldehydes and ketones.

Moreover, the first vinylogous Mukaiyama–Michael addition of silyloxydiene **1** to α,β-unsaturated aldehydes was performed, proceeding in satisfactory yields and with chemoselectivity in the absence of any catalyst under solvent-free conditions.

The novelty, the operative simplicity, and the solvent-free conditions make this procedure synthetically useful and environmental friendly.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.016.

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