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General switch in regioselectivity in the Mukaiyama aldol reaction of silyloxyfuran with aldehydes in aqueous solvents†

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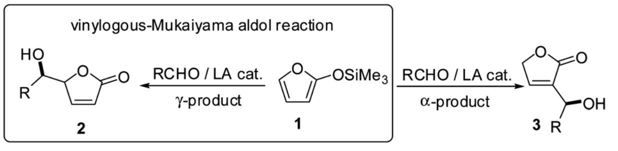
An unexpected yet disciplined course of catalytic Mukaiyama-aldol reaction instead of the expected vinylogous Mukaiyama-aldol reaction has been observed for the reaction of silyloxyfuran with various aldehydes under Lewis acid catalytic control in water-containing solvents.

The Mukaiyama aldol reaction is an important and valuable carbon–carbon bond-forming reaction controlling regio- and stereochemistry during the addition of simple carbonyl partners[1] and even *en route* to the complex polyketides.[2] By using chiral Lewis acids, enantiomerically enriched alcohols are accessible with stereogenic centers at the β-position or the α- and β-positions of the aldol adducts. The Mukaiyama aldol reaction can be extended in vinylogous terms by employing an α,β-unsaturated carbonyl compound pre-activated as conjugated silicon dienolate resulting in the formation of a complimentary δ-hydroxy α,β-unsaturated carbonyl compound.[3]

Various types of butadiene-based silyl dienol ethers cleverly served to implement butenoate fragments into diverse, structurally complex polyketide frameworks and targets *via* vinylogous Mukaiyama aldol reaction (VMAR) with nicely controlled regio- and stereoselectivity.[4] Cyclic dienoxy silane, including the widely exploited furan-based substrate **1**, has been also largely explored in VMAR processes to enter a variety of highly functionalized γ-substituted chiral butenolide type frameworks **2** (Scheme 1).[5]

In fact, the Lewis-acid promoted nucleophilic reactivity of silyloxyfurans is believed to be highly restricted to the C-5 site and all presented synthetic strategies have been based on this type of fundamental chemical behaviour of conjugated systems. In contrast to this disciplined reaction course, only non-catalytic examples of unselective VMAR have been recorded where the main product was the α-substituted ketone (**3**) resulting from Sn-enolate-based carbon–carbon bond formation at the C-3 position of **1**, followed by double bond isomerisation.[6,7] However, to our knowledge there is no complete study on the catalytic Mukaiyama reaction of **1** with aldehydes that offers a full account of the issue of the regio- and stereoselectivity of the aldol process with the focus on competitive VMAR *vs.* Mukaiyama processes. In a broader context, there is also a general lack *of a catalytic method* that produce an α-substituted furan-based moiety either in direct[8] or Mukaiyama methodology. In general, a controlled and predictable access to C-3 substituted cyclic butenolides of type **3** is still unknown.



Scheme 1 1,2- *vs.* 1,4-Addition of aldehydes to silyloxyfuran **1**.

Here we would like to reduce this gap and show that regioselectivity of addition of various aldehydes to silyloxyfuran **1** can be easily controlled by simple solvent tuning. Moreover, elusive reaction product **3** can be accessed, even in an asymmetric manner under water-compatible Lewis acid catalytic control. Our observation can also be seen as general switch in regioselectivity of Mukaiyama aldol reaction in a conjugated butenolide system.

Although several interesting reactions with unique reactivity and selectivity have been developed in water or water–organic solvents,[9] development of an asymmetric aqua aldol-type reaction is still ongoing and needs broad investigation.[10] Earlier we[11] and others[12] reported few examples of aqueous Mukaiyama aldol reaction efficiently promoted by water-compatible chiral Lewis acids. Previous findings in the field of aqueous Mukaiyama aldol reaction forced us also to explore such unusual aqueous conditions for the vinylogous Mukaiyama aldol reaction of siloxyfuran **1**.

First, we decided to screen which Lewis acid, if any, can promote reaction of silyloxyfurans with various aldehydes in water-containing solvents. Thus, treatment of 2-(trimethylsilyloxy)furan (**1**) with benzaldehyde (Scheme 2) in the presence of 10 mol% of various Lewis acids in dry THF afforded the corresponding α,β-unsaturated-γ-lactone **2a** in high yield, strictly according to our expectation (Table 1, entries 1–4). To our surprise however, addition of only 10% of water to the reaction solvent changed the reaction course leading to unexpected predominant formation of a carbon–carbon bond at C-3 of the furan ring (product **3a**, Table 1, entries 5–8).

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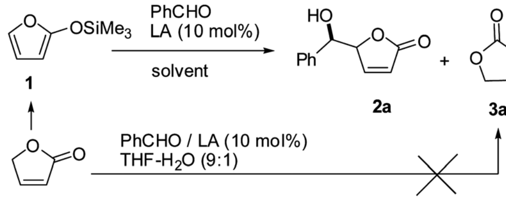
† Electronic supplementary information (ESI) available: Experimental procedures, NMR of compounds in Table 2, HPLC of compounds in Table 3 and determination of absolute configuration of products. See DOI: 10.1039/c2cc36656h



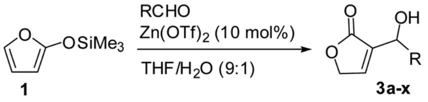
Scheme 2 Reaction of silyloxyfuran with benzaldehyde: catalyst and solvent study.

Table 1 Reaction of siloxy furan **1** with benzaldehyde. Catalyst and solvent study[a]

Entry	Cat. (LA)	Solvent	**2a**[b] [%]	**3a**[b] [%]
1	$Cu(OTf)_2$	THF	80	—
2	$Zn(OTf)_2$	THF	90	—
3	$Yb(OTf)_3$	THF	94	—
4	$Sc(OTf)_3$	THF	69	—
5	$Cu(OTf)_2$	THF/H_2O (9 : 1)	14	71
6	$Zn(OTf)_2$	THF/H_2O (9 : 1)	15	76
7	$Yb(OTf)_3$	THF/H_2O (9 : 1)	5	81
8	$Sc(OTf)_3$	THF/H_2O (9 : 1)	8	30
9	$Zn(OTf)_2$	$EtOH/H_2O$ (9 : 1)	12	74
10	$Zn(OTf)_2$	EtOH	Trace	—
11	$Zn(OTf)_2$	*i*-PrOH	Trace	—

[a] Reactions were performed with **1** (0.85 mmol), PhCHO (0.71 mmol), catalyst (10 mol%) in solvent (2 mL) at RT for 12 h. [b] Isolated yield after column chromatography.

Table 2 Scope of α-selective reaction of silyloxyfuran **1** with various aldehydes[a]



Entry	Product	R	Yield[b] [%]
1	**3a**	Ph	88
2	**3a**	Ph	85[c]
3	**3b**	$4\text{-MeO-}C_6H_4$	65
4	**3c**	$4\text{-Me-}C_6H_4$	75[d]
5	**3d**	$2\text{-Me-}C_6H_4$	59[d]
6	**3e**	Me	84
7	**3f**	Et	86
8	**3g**	*i*-Pr	76
9	**3h**	Bu	80
10	**3i**	Pent	84
11	**3j**	Hex	86
12	**3k**	Hept	81
13	**3l**	Undec	84

[a] Reactions were performed with **1** (0.85 mmol), aldehyde (0.71 mmol), $Zn(OTf)_2$ (10 mol%) in THF–H_2O (9 : 1, 2 mL) at 0 °C for 4 h. [b] Isolated yield after column chromatography. [c] Reaction was performed with **1** (0.85 mmol), aldehyde (0.71 mmol), $Zn(OTf)_2$ (10 mol%) in EtOH–H_2O (9 : 1, 2 mL) at 0 °C for 4 h. [d] Reaction time 12 h.

Although stability of silyloxyfuran in the tested aqueous solvent was sufficient enough for Mukaiyama aldol reaction, we also checked possible competitive reaction of α,β-unsaturated-γ-lactone with the conclusion that this substrate is unreactive towards formation of product **3a** under elaborated reaction conditions (Scheme 2).

Many water compatible Lewis acids including Zn^{II}, Cu^{II}, Yb^{III}, and Sc^{III} showed the same feature promoting formation of **3a** in water containing solvents (entries 5–8 *vs.* 1–4).

This finding was interesting as all previously published reports mentioned only the formation of γ-substituted VMAR-type products even in the presence of water. Katsuki and co-workers exploited a Cr(salen) complex and investigated the effect of water and alcohol on the enantioselectivity of the reaction product, but also exclusive formation of γ-substituted product **2a** was reported without any comments on exception from this rule.[13] We found that application of alcoholic solvents to elaborated reaction was unsuccessful (Table 1, entries 9 and 10) showing that addition of water is essential for observed reactivity and selectivity. Reaction carried out in a EtOH–water mixture delivered only little worse results when compared with THF–water solvent (entry 6 *vs.* 9).

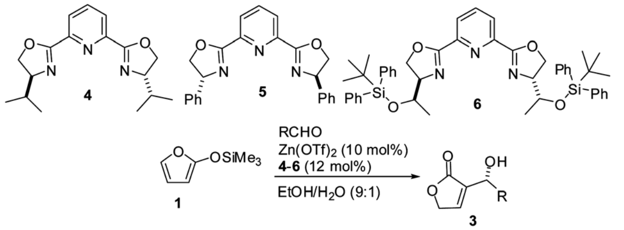
To optimize this unique reaction further we selected the best solvent, Lewis acid, and reaction conditions. Zinc triflate was confirmed as the most promising Lewis acid for this Mukaiyama aldol reaction (Table 2). A variety of aromatic (entries 1–5) and aliphatic (entries 6–13) aldehydes were found to be suitable coupling partners, which always formed α-substituted furan ring **3a-l**. Thus the reaction is not highly sensitive towards various structures and electronic nature of aldehydes.

It is important to mention that under optimised reaction conditions we did not observe formation of the side γ-substituted products and the reaction could be a synthetically useful tool for the synthesis of the butenolide moiety substituted at the α-position by a chain bearing hydroxyl group. To check further this hypothesis we decided to test an asymmetric variant of the reaction under water compatible chiral Lewis-acid control, which conspicuously have never been elaborated previously.

While discovery of water-compatible Lewis acids has greatly expanded its application to asymmetric aqueous Mukaiyama reactions,[14] the asymmetric version of the reaction is still difficult to achieve and limited to few examples mostly restricted to aromatic aldehydes.[12] An interesting breakthrough was published only recently by Ollevier, where the catalytic enantioselective Mukaiyama aldol reaction of various aromatic and aliphatic aldehydes with silyl enol ethers in aqueous media has been achieved by using benzoic acid-assisted iron perchlorate and a chiral bipyridine ligand.[15]

We have recently discovered zinc-based chiral Lewis acids as cheap, non-toxic, and environmentally benign catalysts for the asymmetric Mukaiyama carbon–carbon bond forming process.[11] Now, a series of *pybox* ligands was evaluated in association with Zn salt to identify the most enantioselective and reliable system (Table 3). Although in all cases the reaction proceeded smoothly to give the α-aldol product **3a** in good yields, the enantioselectivities depended on the structure of *pybox* ligands. While commercial ligands **4** and **5** were not promising, we decided to test more hindered analogue **6**.[11b] Thus application of lipophilic TBDPS-hydroxyethyl-*pybox* increased selectivity as reflected in the higher ee (50%, entry 3). For the asymmetric variant aqueous ethanol solvent turned out to be the best, and when the reaction was performed in EtOH–water, the enantioselectivity of **3** was good and ranges 70% ee for aromatic (entries 4–7) and *ca.* 55% ee for aliphatic aldehydes (entries 8 and 9) at −30 °C. When 10 mol% of the zinc based-catalyst was used in the presence of a catalytic amount of benzoic acid, the reaction of aromatic aldehydes afforded aldols in higher yield and higher

Table 3 Initial study of asymmetric Mukaiyama aldol reaction of silyloxyfuran **1** with aldehydes[a]



Entry	R	Ligand	Yield[b] [%]	ee[c] [%]
1	Ph	**4**	59	20
2	Ph	**5**	46	Rac
3	Ph	**6**	63	50
4	Ph	**6**	83	70[d]
5	4-Me–C_6H_4	**6**	69	66[d]
6	2-Me–C_6H_4	**6**	52	64[d]
7	4-MeO–C_6H_4	**6**	42	68[d]
8	Bu	**6**	63	53
9	Oct	**6**	73	56

[a] Reactions were performed with **1** (0.85 mmol), aldehyde (0.71 mmol), $Zn(OTf)_2$ (10 mol%), ligand (12 mol%) in EtOH–H_2O (9 : 1, 2 mL) at −30 °C for 4 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC analysis on chiral phase (Chiralpak AD-H) columns. [d] Reactions were performed with **1** (0.85 mmol), aldehyde (0.71 mmol), $Zn(OTf)_2$ (10 mol%), ligand (12 mol%), PhCOOH (0.07 mmol, 10 mol%) in EtOH–H_2O (9 : 1, 2 mL) at −30 °C for 12 h.

enantioselectivities (entries 4–7). This tendency was not general, and a Brønsted acid additive was unwelcome for the reaction of aliphatic substrates.[16]

In conclusion, we observed unprecedented formation of α-substituted α,β-unsaturated-γ-lactone in the catalytic aqueous Mukaiyama aldol reaction of 2-(trimethylsiloxy)-furan and aldehydes. A wide range of chiral α-butenolides could be obtained from the broad scope of aldehydes in good yield and in good enantioselectivities. This is also the first example of asymmetric Mukaiyama aldol reaction of 2-(trimethylsiloxy)-furan and aldehydes controlled by a chiral zinc-based Lewis acid. Although, enantioselectivities need further improvement, the concept we have developed might be an efficient and missing methodology for the construction of the enantioselective α-butenolides that exist in many biologically active natural products.

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