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Efficient and practical catalytic vinylogous aldol reaction of dioxinone-derived silyl dienol ethers with aromatic aldehydes

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Abstract—Vinylogous Mukaiyama-aldol reaction was realized by use of dioxinone-derived silyl dienol ethers and various aldehydes in the presence of highly catalytic amounts of bismuth triflate. The reaction proceeds rapidly and affords the corresponding β-hydroxy-1,3-dioxin-4-ones in very good to excellent yields (up to 98%).

β-Hydroxy ketones and esters are extremely important compounds as biologically active molecules.[1] The development of new methods for the preparation of aldols is therefore an important area of synthetic efforts. The vinylogous Mukaiyama-aldol reaction provides a rapid route of such compounds by fast connection of a carbonyl framework to the γ carbon of a dienolate.[2] Over the past years, many elegant enantioselective versions of this reaction have been described, using high catalytic amount of various chiral mediators.[3] However, to our knowledge, all non enantioselective examples up to now have employed Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$ or $SiCl_4$.[4] Yet, moisture sensitivity and the high cost of these catalysts restrict their use. In addition, all reported racemic reactions used the Lewis acid in stoichiometric amount or even in excess.[4] In view of the versatile synthetic utility of β-hydroxy-1,3-dioxin-4-ones, for example, for the synthesis of 4-hydroxy-2-pyrones via the oxidation of the hydroxyl group,[4c] there is clearly a need for practical, and efficient conditions that involve a bench-stable catalyst, used in very low loading.

Bismuth compounds provide a good alternative due to low toxicity, low cost, and good stability.[5] Bismuth(III) salts have been reported as effective catalysts for an array of synthetic transformations: opening of epoxides,[6] Mannich-type reactions,[7] formation of acetals,[8] Friedel–Crafts reactions,[9] Fries and Claisen rearrangements,[10] and Sakurai reactions.[11] Bismuth triflate [$Bi(OTf)_3$] is particularly attractive due to its commercial availability or ease of preparation from commercial cheap starting materials.[12] Bismuth triflate was reported by Dubac as very efficient for the Mukaiyama-aldol reaction with silyl enol ethers.[13] However, the vinylogous Mukaiyama-aldol has never been investigated with $Bi(OTf)_3{\cdot}4H_2O$ as a catalyst.

As a part of our ongoing interest in bismuth(III)-catalyzed condensation reactions,[14] we report herein a bismuth(III)-catalyzed vinylogous Mukaiyama-aldol reaction with 2,2-dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-diox-4-ene **2b**. Aldols are obtained efficiently in the presence of 1 mol % of $Bi(OTf)_3{\cdot}4H_2O$.

The $Bi(OTf)_3{\cdot}4H_2O$ (3 mol %) catalyzed reaction of silyl ketene acetal **2a** with benzaldehyde led to the expected product as a mixture of silylated aldol **3** and aldol **4** in moderate to good yields (Scheme 1, entries 1 and 2). The need for fluoride-mediated deprotection of silylated aldol **3** in aldol **4** motivated us to use TMS derivative **2b** instead of **2a** for easier work-up of the reaction mixture (aq HCl, THF, 22 °C, 2 h). As shown in Table 1, the formation of the corresponding aldol **4** from readily available ketene acetal **2b** was achieved in good yield and complete γ-regioselectivity (entries 3–9). Because of the better yield obtained for our model reaction, diethylether was selected as the solvent of choice with 1 mol % $Bi(OTf)_3{\cdot}4H_2O$ (compare entries 7–8 with 4–5). Only 1.5 equiv of the reagent were required to ensure complete conversion (Table 1, compare entries 5–8 with

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Keywords: Bismuth; Bismuth(III) triflate; Aldol; Lewis acid; Silyl dienolate; Vinylogous.

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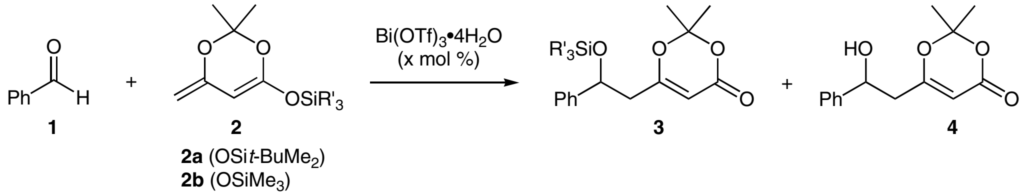
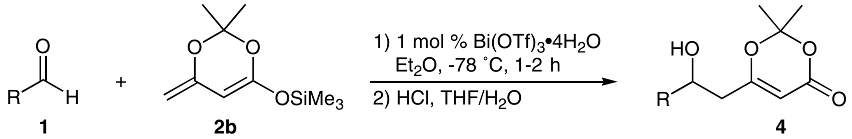


Scheme 1.

Table 1. Bi(OTf)$_3$ catalyzed vinylogous Mukaiyama-aldol reaction of benzaldehyde[a]

Entry	**2** (equiv)	*x*	Conditions	Yield **3**[a] (%)	Yield **4**[b] (%)
1	**2a** (1.2)	3	Et_2O, −78 °C, 8 h	43	21
2	**2a** (1.5)	3	CH_2Cl_2, −78 °C, 7.5 h	75	6
3	**2b** (1.2)	3	Et_2O, −78 °C, 5.5 h	—	75
4	**2b** (1.2)	3	CH_2Cl_2, −78 °C, 3 h	—	82
5	**2b** (1.5)	3	CH_2Cl_2, −78 °C, 4 h	—	98
6	**2b** (1.5)	3	THF, −78 °C, 4 h	—	75
7	**2b** (1.5)	3	Et_2O, −78 °C, 4 h	—	89
8	**2b** (1.5)	1	Et_2O, −78 °C, 4 h	—	95
9	**2b** (1.5)	0.5	Et_2O, −78 °C, 4 h	—	93

[a] Conditions: *x* mol % Bi(OTf)$_3$·4H$_2$O, −78 °C, then 10% aq HCl, THF, 22 °C, 2 h.
[b] Isolated yield.



Scheme 2.

3–4). More interestingly, from a preparative point of view, the drastic reduction of the catalyst loading (down to 0.5 mol %) did not cause any appreciable decrease of yield (Table 1, entry 9).

The addition of silyl ketene acetal **2b** to various aldehydes **1** proceeded readily employing Bi(OTf)$_3$·4H$_2$O as the Lewis acid (Scheme 2, Table 2).[15] Generally, excellent yields of β-hydroxy-1,3-dioxin-4-ones were obtained with 1.5 equiv of TMS-derived silyl ketene acetal **2b** and 0.01 equiv of Bi(OTf)$_3$·4H$_2$O at −78 °C in Et$_2$O. Aromatic aldehydes as well as an α,β-unsaturated aldehyde reacted smoothly to give the corresponding β-hydroxy-1,3-dioxin-4-ones **4** in high yield (Table 2, entries 1–10). Electron-rich *p*-, *m*-, or *o*-methoxybenzaldehyde led to the desired product in excellent yield (Table 2, entries 3–5). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the expected product **4** was obtained with excellent yields (Table 2, entries 6–8). In addition, heteroaromatic aldehyde such as furfural can also serve as a substrate in this reaction, giving the corresponding aldol in a moderate yield (Table 2, entry 9). Conjugated aldehydes were good substrates as well (Table 2, entry 10). Aliphatic aldehydes lead to a poor yield of the aldol due to incomplete conversion (Table 2, entries 11 and 12).

In summary, we have found that the vinylogous Mukaiyama-aldol reaction proceeds smoothly with

Table 2. Bi(OTf)$_3$ catalyzed vinylogous Mukaiyama-aldol reaction of various aldehydes[a]

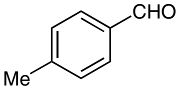
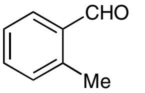
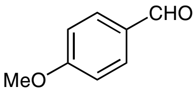
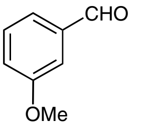
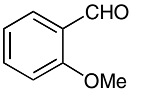
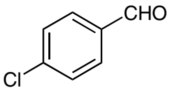
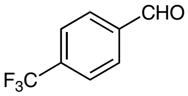
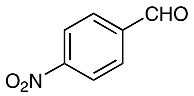
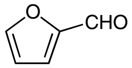
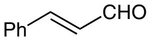
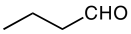
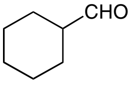
Entry	**1**	Compound	Yield **4**[b] (%)
1		**4b**	86
2		**4c**	90
3		**4d**	91
4		**4e**	96
5		**4f**	93
6		**4g**	98
7		**4h**	97

Table 2 (*continued*)

Entry	**1**	Compound	Yield **4**[b] (%)
8		**4i**	74[c]
9		**4j**	73
10		**4k**	80
11		**4l**	35[d]
12		**4m**	28[d]

[a] Conditions: 1.5 equiv silyl ketene acetal **2b**, 1 mol % $Bi(OTf)_3{\cdot}4H_2O$, Et_2O, −78 °C, then 10% aq HCl, THF, 22 °C, 2 h.

[b] Isolated yield.

[c] 2 h, −78 °C then 2 h, 22 °C.

[d] Unoptimized conditions.

dioxinone-derived silyl ketene acetal and a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$. This method offers several advantages including mild reaction conditions, highly catalytic (1%) process, and no formation of by-products. Because of its numerous benefits, the $Bi(OTf)_3{\cdot}4H_2O$ protocol should find utility in the synthesis of biologically active compounds.

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15. *General procedure for the bismuth-catalyzed vinylogous Mukaiyama-aldol reaction.* Under an inert atmosphere of argon, the aldehyde (0.5 mmol) was stirred with $Bi(OTf)_3{\cdot}4H_2O$ (0.005 mmol) in 0.5 mL of dry Et_2O at 22 °C for 0.5 h. After cooling down to −78 °C, the silyl ketene acetal (0.75 mmol) in 0.5 mL of dry Et_2O was added dropwise to the solution. The mixture was stirred at −78 °C until the reaction was completed as indicated by TLC. The reaction was diluted with THF (1 mL), quenched with 10% aqueous HCl and stirred for 2 h.

The crude reaction mixture was then extracted with 3 × 10 mL of diethyl ether. The organic phase was washed with water, then with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under vacuum (rotatory evaporator). The crude product was purified by column chromatography (eluent hexane/ethyl acetate). The spectral data of the aldols match with those reported in the literature.[3e,4c,d]