

Organocatalytic oxy-Michael addition of alcohols to α,β -unsaturated aldehydes

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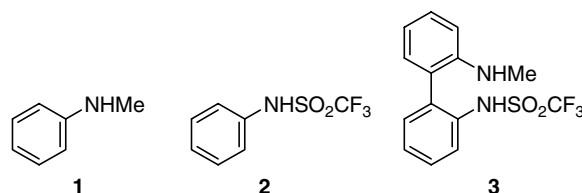
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Abstract—1,4-Addition of alcohols to α,β -unsaturated aldehydes was found to be efficiently promoted by biphenyldiamine-based catalyst **3** without formation of the acetals.

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β -Hydroxy carbonyl compounds and their alkoxy analogues are very important as valuable building blocks and structural motifs in a variety of natural products,¹ and these compounds are usually prepared by the aldol reaction² and the subsequent alkylation of the resulting hydroxyl group. Alternatively, intermolecular 1,4-addition of alcohols to α,β -unsaturated carbonyl compounds also represents an attractive method for the direct synthesis of β -alkoxy carbonyl compounds. Such oxy-Michael additions of alcohols to α,β -unsaturated ketones or esters have recently been reported to be promoted by several catalysts such as PMe_3 ,³ DBU,⁴ Tf_2NH ⁵ and transition metal complexes;⁶ however, the oxy-Michael addition of alcohols to α,β -unsaturated aldehydes remains a challenge, mainly because of the competitive acetal formation. On the other hand, 1,4-addition reactions of other heteroatom nucleophiles such as thiols⁷ and amides⁸ to α,β -unsaturated aldehydes via iminium ion intermediates have recently been realized by secondary amine–acid salt catalysts. In this context, we are interested in developing a novel secondary amine-type catalyst for the 1,4-addition reaction of alcohols to α,β -unsaturated aldehydes. Herein, we wish to report that biphenyldiamine-based organocatalyst can be successfully utilized to realize the first intermolecular oxy-Michael addition reaction of alcohols to α,β -unsaturated aldehydes without the acetal formation.



We chose *N*-alkyl aromatic amines as a catalyst for the oxy-Michael addition due to its having enough nucleophilicity to form the iminium salts of α,β -unsaturated aldehydes as a reactive intermediate,⁹ in addition to the ease of structural and electronical modifications. Thus, the oxy-Michael reactions of methanol to 2-heptenal were carried out in $\text{MeOH}/\text{H}_2\text{O}$ (95:5) in the presence of 5 mol % of *N*-methylaniline derivatives at 0 °C, and the results are summarized in Table 1. While the reaction with *N*-methylaniline (**1**) gave only trace amounts of the desired oxy-Michael adduct **4** (entry 2), the addition of HCl co-catalyst accelerated both the oxy-Michael addition and the acetalization (entry 3). Use of a weaker acid such as TFA led to an increased ratio of oxy-Michael adduct **4** to acetal **5** (entry 4). Moreover, in the case of the weakly acidic additive **2**, the oxy-Michael addition occurred exclusively to give **4** in moderate yield (entry 5), while it was found that **2** itself could not catalyze the oxy-Michael addition (entry 6). Based on these observations, we then prepared the biphenyldiamine-based catalyst **3**,¹⁰ which has both secondary amine and acidic moieties in the molecule, and consequently, it was found that the reaction using **3** proceeded smoothly to give oxy-Michael adduct **4** in good yield (entry 7).

Keywords: Oxy-Michael addition; α,β -Unsaturated aldehyde; Organocatalyst.

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Table 1. Oxy-Michael addition of methanol to 2-heptenal with aromatic amine-based catalysts^a

Entry	Catalyst	Time (h)	% Yield ^b	
			4	5
1	—	10	0	4
2	1	10	5	0
3	1 + HCl	4	23	29
4	1 + TFA	4	42	15
5	1 + 2	10	51	0
6	2	10	0	10
7	3	10	87	0

^a The reaction of 2-heptenal (0.25 mmol) was carried out in the presence of 5 mol % of the catalyst in MeOH (950 μ L) and H₂O (50 μ L) at 0 °C.

^b Isolated yield.

We next examined the scope of the oxy-Michael addition between various α,β -unsaturated aldehydes and alcohols catalyzed by **3**, and the representative results are summarized in Table 2.¹¹ The oxy-Michael addition of methanol to α,β -unsaturated aldehydes, which have a primary alkyl or a secondary alkyl group at the β -position, gave the corresponding oxy-Michael adducts in moderate to good yields (entries 1–4), while the reaction of sterically hindered *tert*-butyl-substituted analogue resulted in a decrease in yield (entry 5). In addition, catalyst **3** was also shown to be effective for the oxy-Michael addition of ethanol, allyl alcohol and benzyl alcohol, and the corresponding oxy-Michael adducts were obtained in moderate to good yields (entries 6–8). Since benzyl and allyl groups can be easily removed from the products formed, both oxy-Michael adducts of benzyl alcohol and allyl alcohol serve as synthetic equivalents to oxy-Michael adducts of H₂O. In each case, the addition of a proper amount of H₂O to the alcohol solvent is necessary to attain good chemical yields.

Table 2. Oxy-Michael addition of alcohols to α,β -unsaturated aldehydes catalyzed by biphenyldiamine-based catalyst **3**^a

Entry	R ¹	R ²	Time (h)	% Yield ^{b,c}
1	<i>n</i> -Bu	Me	10	87
2	<i>n</i> -Pr	Me	8	83
3	BnCH ₂	Me	10	80
4	<i>i</i> -Pr	Me	10	72
5	<i>t</i> -Bu	Me	36	41
6 ^d	<i>n</i> -Bu	Et	22	81
7 ^e	<i>n</i> -Bu	Allyl	40	72
8 ^e	<i>n</i> -Bu	Bn	24	64

^a Unless otherwise noted, the reaction of an α,β -unsaturated aldehyde (0.25 mmol) was carried out in the presence of 5 mol % of **3** in an alcohol (950 μ L) and H₂O (50 μ L) at 0 °C.

^b Isolated yield.

^c Acetal was not detected.

^d EtOH (970 μ L), H₂O (30 μ L).

^e Alcohol (990 μ L), H₂O (10 μ L).

In summary, we have shown the efficiency of the biphenyldiamine-based organocatalyst **3** for oxy-Michael addition reactions of alcohols to α,β -unsaturated aldehydes under mild conditions. Under these conditions, acetalization of α,β -unsaturated aldehydes was not observed. Further work aimed at the development of an asymmetric variant of this process is currently underway.

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- Since the reaction using either anhydrous methanol as a solvent or *N,N*-dimethylaniline–2 salt as a catalyst was significantly retarded, we believe that the present reaction proceeds via the iminium intermediate.
- 2-Trifluoromethanesulfonylamino-2'-methylamino-1,1'-biphenyl (**3**): To a stirred solution of 2-methylamino-2'-amino-1,1'-biphenyl¹² (198 mg, 1.0 mmol) and ^tPr₂NEt (174 μ L, 1.0 mmol) in CH₂Cl₂ (10 mL) was added Tf₂O (168 μ L, 1.0 mmol) dropwise at –78 °C. After 3 h of stirring at –78 °C, the reaction mixture was poured into water and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/CH₂Cl₂ = 1:1) to afford **3** (182 mg, 0.55 mmol, 55% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.60 (1H, d, *J* = 7.6 Hz, Ar-H), 7.37–7.46 (4H, m, Ar-H), 7.17 (1H, dd, *J* = 1.2, 7.6 Hz, Ar-H), 6.98 (1H, appt, Ar-H), 6.89 (1H, d, *J* = 8.4 Hz, Ar-H), 2.83 (3H, s, NHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 144.6, 133.7, 132.5, 131.5, 131.4, 129.8, 129.0.

- 127.9, 125.9, 125.3, 120.1, 119.4 (q, $J_{C-F} = 324$ Hz), 112.7, 31.3; IR (neat) 3340, 2360, 1364, 1271, 1225, 1196, 1140, 959, 822, 741, 597 cm^{-1} ; HRMS (ESI-TOF) Calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2\text{S}$: 331.0723 ($[\text{M}+\text{H}]^+$); Found: 331.0722 ($[\text{M}+\text{H}]^+$).
11. Typical procedure for the oxy-Michael addition of an alcohol to an α,β -unsaturated aldehyde: To a solution of catalyst **3** (4.1 mg, 0.0125 mmol) in MeOH/H₂O (95:5 v/v, 0.25 M) was added (*E*)-2-heptenal (33 μL , 0.25 mmol) at 0 °C. Upon consumption of the starting material, the reaction mixture was directly purified by flash column chromatography on silica gel (pentane/diethyl ether = 4:1 as eluent) to afford 3-methoxyheptanal (31.4 mg, 0.218 mmol, 87% yield): ¹H NMR (400 MHz, CDCl₃) δ 9.81 (1H, t, $J = 2.4$ Hz, CHO), 3.71 (1H, m, CHOMe), 3.35 (3H, s, OMe), 2.60 (1H, ddd, $J = 2.4, 7.2, 16.4$ Hz, CHHCHO), 2.52 (1H, ddd, $J = 2.0, 5.2, 16.4$ Hz, CHHCHO), 1.25–1.65 (6H, m, CH₂CH₂CH₂), 0.91 (3H, t, $J = 7.2$ Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 201.4, 76.3, 56.8, 48.0, 33.6, 27.3, 22.8, 14.1; IR (neat) 2957, 2930, 2860, 2826, 2725, 2342, 1724, 1466, 1094, 1032, 748 cm^{-1} ; HRMS (ESI-TOF) Calcd for $\text{C}_8\text{H}_{16}\text{O}_2\text{Na}$: 167.1043 ($[\text{M}+\text{Na}]^+$); Found: 167.1048 ($[\text{M}+\text{Na}]^+$).
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