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Communication

Bismuth trichloride-catalyzed oxy-Michael addition of water and alcohol to α,β-unsaturated ketones

Zhen Wu[a,b], Xue-Xin Feng[a,b], Qing-Dong Wang[b], Jin-Jin Yun[a], Weidong Rao[c], Jin-Ming Yang[a,b,*], Zhi-Liang Shen[a,*]

[a] School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China
[b] School of Pharmacy, Yancheng Teachers University, Yancheng 224007, China
[c] Jiangsu Key Laboratory of Biomass-based Green Fuels and Chemicals, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China

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ABSTRACT

An efficient method was developed for the conjugate addition of water to various α,β-unsaturated ketones by using bismuth(III) chloride as a catalyst. The reactions proceeded smoothly in the presence of a catalytic amount of $BiCl_3$ (20 mol%) in aqueous media to furnish a variety of synthetically useful β-hydroxyl ketones in moderate to good yields. Apart from water molecule, various alcohols could also be employed as nucleophiles to react with α,β-unsaturated ketones, leading to β-alkoxyl ketones in modest to high yields. In addition, the mild reaction conditions also entailed the conjugate addition reactions to proceed with the tolerance to a range of functional groups.

β-Hydroxyl carbonyl compounds, which are structural motif widely found in numerous natural products, play an important role in organic chemistry as versatile synthetic intermediates [1,2]. Besides the well-known Aldol reaction between aldehyde and ketone which serves as a practical method for the synthesis of β-hydroxyl carbonyl compounds [2], β-hydroxyl carbonyl compounds could also be constructed by a two-step reaction sequence [3]. However, these methods suffered either from the production of undesired products due to the relatively strong basic reaction conditions or from the comparatively low efficiency of multi-step synthesis. In this context, the direct addition of water to α,β-unsaturated carbonyl compounds, a commonly occurred reaction which widely exists in living organism, provides an easy and direct entry to β-hydroxyl carbonyl compounds *via* a Michael-type reaction pathway, along with the inhibition of undesired side reactions. However, the reaction of water with α,β-unsaturated carbonyl compounds constitutes a big challenge because the reaction is an equilibrium and the formed β-hydroxyl carbonyl compound has a strong tendency to undergo β-hydroxyl elimination to regenerate the original substrate of more stable α,β-unsaturated carbonyl compound [4]. It was not until 2003 that Bergman and Toste had reported an efficient phosphine-catalyzed reaction of alcohol/water with α,β-unsaturated carbonyl compound by means of *in situ* forming a strong base as reaction catalyst [5]. However, only one case using water as a reaction nucleophile was reported in their protocol. Thereafter, Feringa and Roelfes reported an enantioselective Michael-type reaction of water with specific α,β-unsaturated 2-acyl imidazole/pyridine by employing DNA-supported copper catalyst or artificial metalloenzymes as reaction promoter [6]. More recent studies from the Hanefeld group have revealed that amino acid or enzyme is also able to catalyze the oxy-Michael reaction of water with cyclic enones or lactones with moderate success (mostly in low to modest yields), further implying the difficulty of realizing the transformation [7,8]. Very recently, our group described that a catalytic amount of In$(OTf)_3$ or $CrCl_3$ are capable of catalyzing the reaction between water and α,β-unsaturated ketones in aqueous media, providing an effective method for the synthesis of β-hydroxyl ketones [9].

In recent decades, bismuth(III) salts have been demonstrated to be efficient catalysts for effecting various organic transformations due to their powerful Lewis acidity [10]. As a continued task of our group to develop organic reactions in aqueous media [11–13], herein we report an efficient method for the synthesis of β-hydroxyl carbonyl compounds *via* a bismuth(III)-catalyzed direct addition of water to α,β-unsaturated carbonyl compound. The reactions proceeded smoothly in aqueous media to furnish a

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[*] Corresponding authors at: School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China.
E-mail addresses: yangjm@yctu.edu.cn (J.-M. Yang), ias_zlshen@njtech.edu.cn (Z.-L. Shen).

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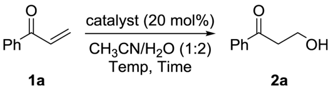
variety of synthetically useful β-hydroxyl ketones in moderate to good yields, along with the tolerance to a range of functional groups. Aside from water, alcohols could also be employed as nucleophiles to react with a wide range of α,β-unsaturated ketones, leading to β-alkoxyl ketones in modest to high yields.

In the beginning, an array of bismuth(III) salts were employed to investigate their catalytic activity in the Michael-type reaction of 1-phenylprop-2-en-1-one (**1a**) with water. The reactions were carried out at 80 °C for 24 h in aqueous acetonitrile in the presence of 20 mol% bismuth(III) salts. As shown in Table 1, among the various bismuth(III) salts surveyed (entries 1–9), $BiCl_3$ exhibited the best catalytic performance to afford the corresponding product **2a** in 72% yield (entry 1). In contrast, the use of bismuth(III) salts containing other anions led to decreased product yields (entries 2–9). Further studies of other reaction parameters, including reaction temperature and reaction time (entries 10–14), showed that the reaction worked with best performance when it was performed at 80 °C for 24 h by employing $BiCl_3$ as reaction catalyst.

Subsequently, the substrate scope of the reaction was surveyed by using a variety of structurally diverse α,β-unsaturated ketones as starting materials. As summarized in Table 2, different types of electron-deficient alkenes were applicable to the present conjugate addition, affording the corresponding products in modest to good yields. Not only aryl enones containing electron-withdrawing groups (including CN, COOMe, F, Cl, and Br) in the benzene ring, but also aryl enones containing electron-donating substituents (including Me, OMe, and OCH_2O) in the benzene ring were capable of efficiently participating in the 1,4-addition reaction to furnish the expected product **2b-k** in 34%-84% yields (entries 1-10). In addition to aryl substituted enones, enones **1l-n** possessing heteroaryl substituents were amenable to the mild reaction conditions, giving rise to the anticipated products **2l-n** in moderate to good yields (46%-89% yields, entries 11-13). Moreover, alkyl substituted enones **1o-p** reacted in the same manner to afford the desired β-hydroxyl carbonyl compounds **2o-p** in acceptable yields (42%-54% yields, entries 14 and 15). When (*E*)-1-phenylbut-2-en-1-one (**1q**)

Table 1
Optimization of reaction conditions.[a]



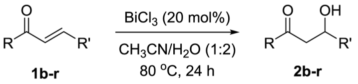
Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]
1	$BiCl_3$	80	24	72 (70)[c]
2	$BiBr_3$	80	24	2
3	BiI_3	80	24	58
4	BiF_3	80	24	17
5	$BiONO_3$	80	24	41
6	$Bi(OTf)_3$	80	24	66
7	$Bi(NO_3)_3$	80	24	54
8	$Bi(OAc)_3$	80	24	22
9	$Bi_2(SO_4)_3$	80	24	57
10	$BiCl_3$	r.t.	24	14
11	$BiCl_3$	50	24	47
12	$BiCl_3$	100	24	10
13	$BiCl_3$	80	12	59
14	$BiCl_3$	80	36	64

[a] Unless otherwise noted, the reactions were performed at 80 °C for 24 h by using 1-phenyl-prop-2-en-1-one (**1a**, 1 mmol) and bismuth(III) salt (0.20 mmol) in CH_3CN/H_2O (1 mL/2 mL).

[b] Yield was determined by NMR analysis of the crude reaction mixture by using 1,4-dimethoxy-benzene as an internal standard.

[c] Isolated yield.

Table 2
Substrate scope study by using various enones.[a]



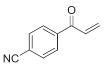
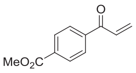
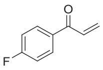
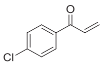
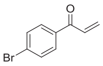
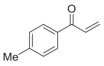
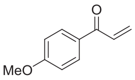
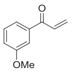
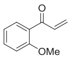
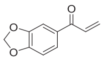
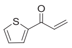
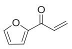
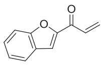
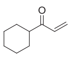
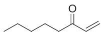
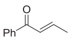
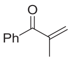
Entry	Substrate	Product	Yield (%)[b]
1		**2b**	59
2		**2c**	34
3		**2d**	83
4		**2e**	53
5		**2f**	64
6		**2g**	66
7		**2h**	84
8		**2i**	75
9		**2j**	58
10		**2k**	71
11		**2l**	89
12		**2m**	82
13		**2n**	46
14		**2o**	54
15		**2p**	42
16		**2q**	40

Table 2 (*Continued*)

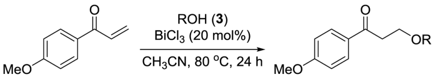
Entry	Substrate	Product	Yield (%)[b]
17		**2r**	0

[a] The reactions were performed at 80 °C for 24 h by using enone **1** (1 mmol) and $BiCl_3$ (0.20 mmol) in CH_3CN/H_2O (1 mL/2 mL).
[b] Isolated yield.

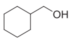
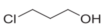
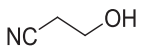
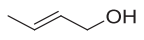
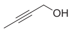
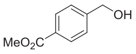
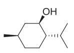
containing a methyl group at its *β* position was used as substrate, the addition reaction proceeded with reduced efficiency to give the product **2q** in 40% yield (entry 16), presumably due to steric hindrance. In sharp contrast, no reaction occurred when enone **1r** bearing a methyl group at its *α* position was utilized as reactant (entry 17).

Next, the substrate scope of the reaction was further surveyed by using various alcohols as nucleophiles [14]. As shown in Table 3, the conjugate addition involving enone **1h** and various alcohols **3** proceeded smoothly to give the corresponding products **4a-l** in moderate to good yields. Besides alkyl alcohols (entries 1-6), allylic alcohol (entry 7), propargylic alcohol (entry 8), and benzyl alcohols (entries 9 and 10) were also demonstrated to be efficient substrates for the transformation, leading to the anticipated products **4g-j** in moderate to good yields. In addition to primary alcohols, secondary alcohols (entries 2 and 11) also efficiently participated in the addition reactions to produce the products **4b** and **4k** in moderate yields. In the same fashion, chiral alcohol of menthol could also be smoothly converted into the corresponding *β*-alkoxyl ketone **4l** in an acceptable yield (entry 12). However, when relatively acidic phenol was employed as a nucleophile to react with enone **1h** under the optimized reaction conditions, only a trace amount of the desired product could be detected, probably owing to the poorer nucleophilicity of phenol when compared to aliphatic alcohols. It is worth mentioning that the mild reaction conditions entailed the presence of various important functional groups or substituents embedded in the starting materials, including chloro, cyano, ethoxycarbonyl, C = C, and C≡C.

Table 3
Substrate scope study by using various alcohols.[a]

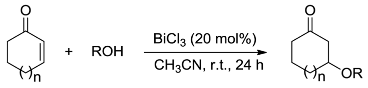


1h **4a-l**

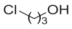
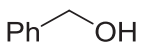
Entry	ROH	Product	Yield (%)[b]
1	EtOH[c]	**4a**	96
2	*i*-PrOH[c]	**4b**	91
3	*n*-BuOH[c]	**4c**	91
4		**4d**	93
5		**4e**	90
6		**4f**	96
7		**4g**	72
8		**4h**	81
9	$PhCH_2OH$	**4i**	93
10		**4j**	81
11	$PhCH(CH_3)OH$	**4k**	42
12		**4l**	46

[a] Unless otherwise noted, the reactions were performed at 80 °C for 24 h by using 1-(4-methoxyphenyl)prop-2-en-1-one (**1 h**, 1 mmol), alcohol **3** (6 mmol) and $BiCl_3$ (0.20 mmol) in CH_3CN (1 mL).
[b] Isolated yield.
[c] The reaction was directly performed in alcohol (ROH, 3 mL) instead of in CH_3CN.

Table 4
Substrate scope study by using cyclic enones and various alcohols.[a]



1s (n = 1)
1t (n = 2)
3
4m-q

Entry	Substrate	ROH	Product	Yield (%)[b]
1	**1s**	EtOH[c]	**4 m**	15
2	**1t**	EtOH[c]	**4n**	91
3	**1t**	*i*-PrOH[c]	**4o**	43
4	**1t**		**4p**	85
5	**1t**		**4q**	50

[a] Unless otherwise noted, the reactions were performed at room temperature for 24 h by using cyclic enones **1s/1t** (1 mmol), alcohol **3** (6 mmol), and $BiCl_3$ (0.20 mmol) in CH_3CN (1 mL).
[b] Isolated yield.
[c] The reaction was directly performed in alcohol (ROH, 3 mL) instead of in CH_3CN.

Besides linear enones, cyclic enones could also be employed as substrates. As listed in Table 4, six-membered enone **1s** reacted with ethanol with usual poor performance, leading to the desired product **4m** only in 15% yield (entry 1). In sharp contrast, the reactions involving seven-membered enone **1t** and some typical alcohols **3** proceeded with enhanced efficiency to give the target products **4n-q** in moderate to high yields (entries 2-5). However, the reaction of cyclopentenone with ethanol could not afford the desired product, presumably because of the instability of the *in situ* formed *β*-hydroxyl ketone which has the strong tendency to undergo *β*-elimination.

In a nutshell, an efficient method for achieving the conjugate addition of water with various *α*,*β*-unsaturated ketones was developed. The reactions proceeded smoothly in the presence of a catalytic amount of $BiCl_3$ (20 mol%) in aqueous media to furnish a variety of synthetically useful *β*-hydroxyl ketones in moderate to good yields. Apart from water, various alcohols could also be employed as nucleophiles to react with a wide range of *α*,*β*-unsaturated ketones, leading to *β*-alkoxyl ketones in modest to high yields. In addition, the mild reaction conditions also allowed the conjugate addition reactions to proceed with the tolerance to a range of functional groups.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.017.

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