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Zinc-catalyzed oxidative esterification of aromatic aldehydes

Xiao-Feng Wu*

Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou, Zhejiang Province 310018, People's Republic of China Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

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ABSTRACT

conditions.

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The application of zinc salts as catalysts in organic synthesis has attracted a lot of attention during the last decade.¹ Because of their inexpensiveness, abundance, and low toxicity, zinc salts have been tested and used in organic synthesis and also been used to take the place of expensive and toxic metals in some reactions. Thus the group of Enthaler has developed a series of novel methodologies for the transformation of primary amides into nitriles,^{10-t} which was reported with palladium catalyst before.²

Carboxylic acid derivatives constitute integral parts of polymers, pharmaceuticals, and agrochemicals, as well as building blocks for organic synthesis and natural products. Typically, they are prepared from the corresponding acid, activated ester, or acid halide in stoichiometric reactions with O nucleophiles.³ An interesting and more direct manner is the oxidative esterification of the readily available aldehydes with alcohols.⁴ But these potentially valuable procedures require the use of stoichiometric heavymetal oxidants or expensive transition metal catalysts.⁵ Recently, the group of Darcel reported a general and efficient iron-catalyzed oxidative esterification of aldehydes.⁶ Fe(ClO₄)₃·xH₂O was used as the pre-catalyst, both aromatic and aliphatic aldehydes can be transformed into esters in good to excellent yields. But the presence of perchlorate counterion is potentially explosive, especially in the case of lithium cation.⁷ Taking the development of environmental benign methodologies into consideration; it will be extremely interesting for synthetic chemists to develop a cheap metal-catalyzed oxidative esterification of aldehydes with green oxidants.

E-mail address: xiao-feng.wu@catalysis.de

Here, we wish to report an efficient zinc-catalyzed oxidative esterification of aromatic aldehydes. H_2O_2 as green oxidant was applied in this reaction which generates water as the only by-product. With 10 mol % of ZnBr₂ and 4 equiv of H_2O_2 , 21 examples of esters were produced in 60–95% of yields.

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A general and efficient protocol for the oxidative esterification of aldehydes has been developed. By using

10 mol % of ZnBr₂ and 4 equiv of H₂O₂, 21 examples of esters were produced in good to excellent yields.

Both electron-donating and electron-withdrawing functional groups are tolerable under our reaction

Initially, the reaction of benzaldehyde (1 mmol) in methanol (2 mL) was carried out with ZnCl₂ (10 mol %; anhydrous) as the pre-catalyst and H₂O₂ (2 mmol) as the oxidant. To our delight, 38% of the desired ester was formed with 50% conversion of benzaldehyde (Table 1, entry 1). Benzoic acid and (dimethoxymethyl)benzene were also detected as by-products in the reaction. Because of the low conversion, we decided to increase the amount of oxidant used. With 4 mmol of H₂O₂, the yield of the ester was improved to 60% with 82% conversion (Table 1, entry 2). Then we started to check the influence of different zinc salts, ZnBr₂ gave 70% of methyl benzoate and 43% of the product was produced with Zn(OTf)₂ as the pre-catalyst (Table 1, entries 3 and 4). But to our surprise, no ester was formed by using Zn(CN)₂ and Zn(OAc)₂ as the pre-catalysts (Table 1, entries 5 and 6). Some other cheap metals were also tested, such as, calcium salts, manganese salts, magnesium salts, and also lithium chloride. Their chloride salts resulted in 56-60% yields of the desired ester with good conversion, but non-chloride salts did not give any product (Table 1, entries 7-14). Based on these results, ZnBr₂ was chosen as the precatalyst for further optimization. The yield of the ester decreased to 35% by using 1 mL of methanol as the solvent (Table 1, entry 15). In contrast, 89% of methyl benzoate and 99% of conversion was achieved with 4 mL of methanol as the solvent (Table 1, entry 16). No ester was formed in the absence of catalyst, but only benzoic acid was detected (Table 1, entry 17). Because of the





^{*} Tel.: +49 381 1281 343.

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Table 1

Oxidative esterification of benzaldehyde^a



Entry	Metal salt (10 mol %)	H ₂ O ₂ (equiv)	Conv. ^b (%)	Yield ^b (%)	Select. (%)
1	ZnCl ₂	2	50	38	76
2	ZnCl ₂	4	82	60	73
3	ZnBr ₂	4	90	70	78
4	$Zn(OTf)_2$	4	77	43	56
5	$Zn(OAc)_2$	4	50	0	0
6	$Zn(CN)_2$	4	68	0	0
7	$Mn(OAc)_3$	4	48	0	0
8	$Ca(OH)_2$	4	30	0	0
9	$Ca(OAc)_2$	4	45	0	0
10	Mg(OAc) ₂ ·4H ₂ O	4	60	0	0
11	MgCl ₂	4	85	60	70
12	MnCl ₂	4	72	57	79
13	CaCl ₂	4	82	57	69
14	LiCl	4	80	56	70
15	ZnBr ₂	4	96	35°	36
16	ZnBr ₂	4	99	89 ^d	90
17	1	4	15	0	0

 a Catalyst (10 mol %), benzaldehyde (1 mmol), MeOH (2 mL), H_2O_2 (30 $\,\%$ in water), rt, air, 16 h.

^b Conversion and yield were determined by GC using hexadecane as the internal standard based on benzaldehyde.

^c MeOH (1 mL).

^d MeOH (4 mL).

Table 2

Zinc-catalyzed oxidative esterification of aldehydes^a

CHO $\frac{\text{ZnBr}_2 (10 \text{ mol}\%)}{\text{H}_2 \text{O}_2 (4 \text{ mmol})}$ R'OH (4 mL)
RT, 16 h $CO_2 \text{R'}$

Entry	Aldehyde	Esters	Yield ^b (%)
1	СНО	CO ₂ Me	89
2	СНО	CO ₂ Me	95 90 ^c
3	СНО	CO ₂ Me	90 81 ^c
4	СНО	CO ₂ Me	81
5	СНО	CO ₂ Me	88
6	Ph	Ph CO ₂ Me	85
7	Мео СНО	MeO CO ₂ Me	92 81 ^c
8	PhO	PhO CO ₂ Me	93 80 ^c
9	F CHO	F CO ₂ Me	80

Table 2 (continued)						
Entry	Aldehyde	Esters	Yield ^b (%)			
10	СІСНО	CICO2Me	83			
11	Br	Br CO ₂ Me	88			
12	O ₂ N CHO	O ₂ N CO ₂ Me	61			
13	СНО	CO ₂ Me	65			
14	СНО	CO ₂ Me	90			
15	СНО	CO ₂ Me	60			
16	СНО	CO ₂ Et	88			
17	СНО	CO ₂ Pr	84			
18	СНО	CO ₂ iPr	75			
19	СНО	CO ₂ CH ₂ CF ₃	80			
20	СНО	CO ₂ nBu	89 85 ^c			
21	СНО	CO ₂ nPent	86			

 $[^]a$ ZnBr_2 (10 mol %), aldehydes (1 mmol), ROH (4 mL), H_2O_2 (30 % in water, 4 mmol), rt, air, 16 h (reaction time is not optimized).

^b Yield was determined by GC using hexadecane as the internal standard based on aldehyde.

^c Isolated yield.

decomposition of H_2O_2 , we need an excess amount in order to have satisfied conversion. With 4 ml of MeOH to dilute the reaction solution, the direct oxidation of aldehyde can be suppressed in some distance. But the activation of aldehyde with zinc salt is still valid. We did not see the influence of air in our reaction system; the reaction can still happen if we do the reaction under argon atmosphere.

With the best reaction conditions in our hand,⁸ we decided to test the generality and efficiency of this methodology. As shown in Table 2, para-, meta-, and ortho-substituted benzaldehydes reacted with methanol under standard reaction conditions with 81-95% of yields (Table 2, entries 2-4). Naphthyl substitution can also be tolerated, and resulted in 88% of the corresponding ester (Table 2, entry 5). In addition, phenyl, methoxy-, and phenoxy-decorated benzaldehydes can be transformed into the desired esters in 85-93% of yields (Table 2, entries 6-8). Besides the mentioned electron-donating functional groups, electron-withdrawing substitutions can also be tolerated. F-, Cl-, Br-, and NO₂-substituted methyl esters were synthesized from their parent aldehydes in 61-88% of yields (Table 2, entries 9-12). Moreover, heterocyclic and α,β -unsaturated aldehydes can also be applied as substrates and gave the desired products in moderate to excellent yields (60-90%; Table 2, entries 13-15). But aliphatic aldehydes like cyclohexanecarbaldehyde and pentanal did not give any desired esters under our standard reaction conditions.

Besides methanol, the other low boiling point alcohols were also tested (Table 2, entries 16–21). Ethanol, propanol, and even pentanol were all successfully reacted with benzaldehyde and gave the corresponding esters in 75–88% of yields. When we carried out the reaction of benzaldehyde with phenol or *tert*-butanol, only benzoic acid was formed under our conditions.

In conclusion, a general and efficient protocol for oxidative esterification of aldehydes has been developed. By using 10 mol % of ZnBr₂ and 4 equiv of H₂O₂, 21 examples of different esters were produced in good to excellent yields. Both electron-donating and electron-withdrawing functional groups are all tolerable under our reaction conditions.

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- 8. General procedure for the ester synthesis: In a 50 mL tube, ZnBr₂ (10 mol %), and a stirring bar was added. Then H₂O₂ (4 mmol; 30% aq) was added slowly to the tube after the addition of aldehyde (1 mmol) and MeOH (4 mL) by syringe. Then keep the final solution at room temperature for 16 h. Hexadecane (100 mg) and ethyl acetate (3 mL) were injected, a part of the solution was taken for GC and GC–MS analysis after properly mixing. All the products are commercially available.