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COMMUNICATION

Copper-Catalyzed Highly Efficient Ester Formation from Carboxylic acids /Esters and Formates

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A highly efficient copper-catalyzed protocol for the synthesis of esters has been developed from formates. This protocol is applicable to reactions with either esters or acids as the substrates, and shows broad substrate scopes and high yields.

The ester functionality represents one of the most common functional groups and is omnipresent in organic molecules.¹ Traditionally, esters can be synthesized via Fisher esterification with carboxylic acids and alcohols in the presence of acid catalysts or transesterification with esters and alcohols.² As both esterification and transesterification are equilibrium reactions, the use of an excess of one of the reagents or the removal of one of the products (normally water or alcohol) during the reaction are required to achieve desirable yields.³ Alternatively, esters can be prepared from alcohols and highly active acylating reagents such as acyl halides and acid anhydrides. These reactions require the addition of dehydration reagents or the preparation of acylating reagents, and generate a large amount of undesired by-products.⁴ In addition to these conventional methods, a variety of alternative methods are available for the synthesis of esters.²

Due to the ubiquity and importance of esters, developing new methods for the synthesis of esters is still of great interest and the subject of extensive studies. Over the past few years, various novel reactions have been discovered and some of them have become advantageous alternatives to traditional esterification methods.⁵ In this context, transition metal-catalyzed esterification gained considerable interests.⁶ It should be mentioned that these transition metal-catalyzed esterification often involve arylation of carboxylic acids, which is distinct from the formation of ester bonds in the traditional esterification reactions.

In the recent years, the use of nonnoble transition metals, such as Mn,⁷ Co,⁸ Fe,⁹ and Cu,¹⁰ and Ni,¹¹ as catalysts has gained extensive attention, and a rapidly growing number of the reactions enabled by these metals have been reported. Compared to their 4d and 5d analogues, these elements are relatively cheap and more abundant in the Earth's crust.¹² In addition, many of these metals, such as Fe and Cu, are less toxic, making them environmentally benign catalysts. It is noted that iron-catalyzed transesterification has been developed recently.¹³

Copper-catalyzed organic reactions have been the subject of extensive exploration, especially over the past decade, and a variety of reactions have been discovered, including C-N, C-O, and C-C bond formation reactions.¹⁴ However, copper-catalyzed reactions for the preparation of esters are rare.¹⁵ Although Cu(NO₃)₂¹⁶ and [Cu₂(O₂CPh)₄]¹⁷-catalyzed transesterification reactions have been reported, the substrates of these reactions were limited to acetate/formate or methanol, and one of the substrates (either acetate/formate or methanol) were used as the solvent. During the preparation of this manuscript, the Jiao group described an elegant Cu-catalyzed esterification reaction of 1,3-diones for the synthesis of α -ketoesters.¹⁸ Inspired by the great advantages of copper and the importance of esters, we herein report a novel copper-catalyzed reaction for the synthesis of esters from acetates and formates.

The research was initiated by the observation that pentyl benzoate was formed when benzoic acid was allowed to react with 4 equivalents of pentyl formate in the presence of 2 equivalents of K₂S₂O₈ and 10% Cu(OTf)₂ in 1,4-dioxane (Table 1). While polar solvents such as CH₃CN, DMA, and DMSO suppressed the formation of the ester, the yield was improved to 27% with nonpolar DCE as the solvent. Gratifyingly, the yield increased to 78% when K₂S₂O₈ was replaced with DCP, and was further improved to 91% and 94% in the presence of DTBP or TBHP. The use of 10% Cu(OTf)₂ proved to be necessary to achieve the excellent yield as the yield decreased significantly when the amount of the catalyst was reduced to 5% and 1% mol. 3 Equivalents of formate was enough and necessary for the reaction to give a high yield. Furthermore, the reactions gave desired products in low yields in the absence of TBHP or Cu(OTf)₂, and lowering the temperature to 110 °C decreased the yield to 67%.

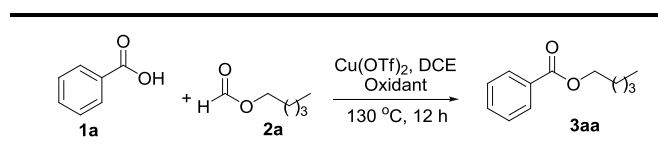
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Table 1 Survey of reaction conditions



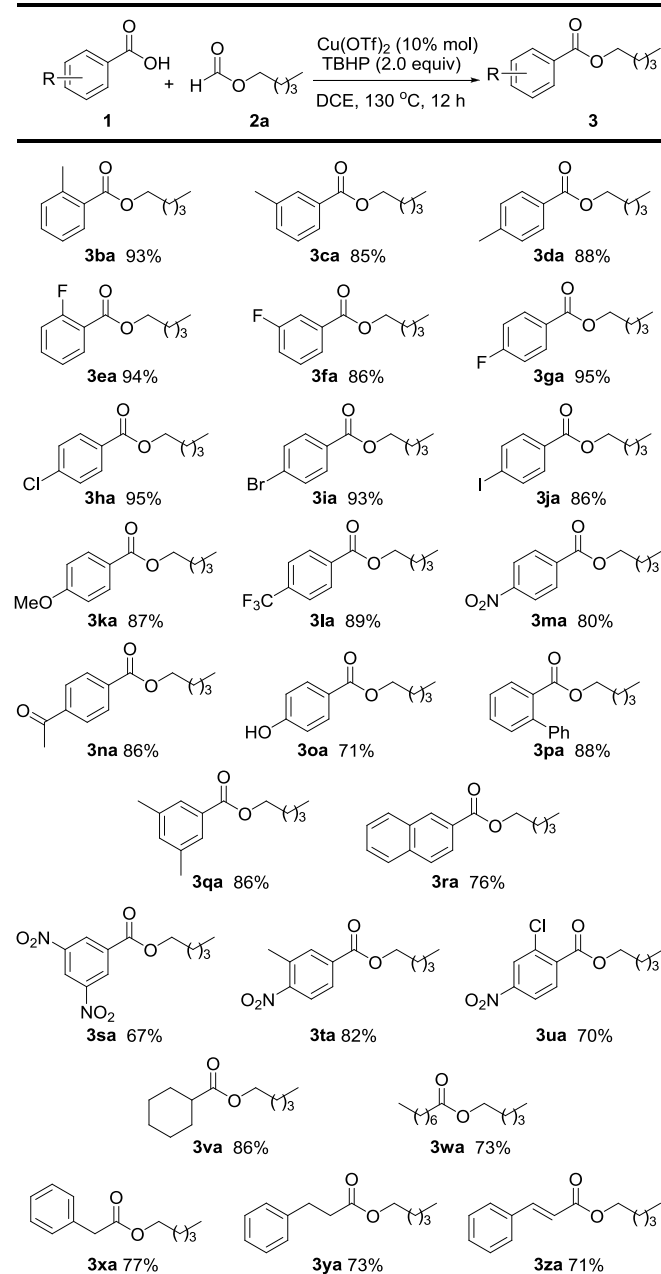
entry	2a	solvent	oxidant	yield %
1	4.0 equiv.	1,4-dioxane	K ₂ S ₂ O ₈	15
2	4.0 equiv.	CH ₃ CN	K ₂ S ₂ O ₈	NR
3	4.0 equiv.	DMA	K ₂ S ₂ O ₈	NR
4	4.0 equiv.	DMSO	K ₂ S ₂ O ₈	5
5	4.0 equiv.	DCE	K ₂ S ₂ O ₈	27
6	4.0 equiv.	DCE	(NH ₄) ₂ SO ₈	20
7	4.0 equiv.	DCE	oxone	<3
8	4.0 equiv.	DCE	AcOOH	17
9	4.0 equiv.	DCE	DCP	78
10	4.0 equiv.	DCE	DTBP	91
11	4.0 equiv.	DCE	TBHP	94
12	4.0 equiv.	DCE	TBHP	54 ^b
13	4.0 equiv.	DCE	TBHP	<3 ^c
14	3.0 equiv.	DCE	TBHP	93(85 ^d)
15	2.0 equiv.	DCE	TBHP	66
16	1.0 equiv.	DCE	TBHP	49
17	3.0 equiv.	DCE	----	24
18	3.0 equiv.	DCE	TBHP	23 ^e
19	3.0 equiv.	DCE	TBHP	67 ^f

^a The yields were determined by ¹H NMR analysis of crude products using CHCl₂CHCl₂ as the internal standard. DBPT = *tert*-Butyl peroxide, TBHP = *tert*-Butyl hydroperoxide, DCP = Dicumyl peroxide, DCE = 1,2-Dichloroethane. Reaction condition: **1a** (0.5 mmol), **2a** (3.0 equiv), Cu(OTf)₂ (10% mol), TBHP (2.0 equiv), 130 °C, 12 h, **all of the reactions were run under air**. ^b Cu(OTf)₂ = 5% mol, ^c Cu(OTf)₂ = 1% mol, ^d isolated yield. ^e No Cu(OTf)₂. ^f 110 °C.

Having identified the optimal protocol for the pentylation of benzoic acid, we explored the substrate scope with regard to aromatic carboxylic acids. The protocol proved to tolerate various functionalities and be compatible with a wide array of benzoic acids. As summarized in Scheme 1, *ortho*-, *meta*-, and *para*-methylbenzoic acids were all transformed into the corresponding esters in high yields under the reaction conditions. Halides, including fluoride, chloride, bromide, and iodide were all well-tolerated, and the reactions gave good yields. Methoxy and various electron-withdrawing groups including trifluoromethyl, nitro, and carbonyl were compatible with the reaction conditions. It is noted that hydroxyl group remained intact during the reaction, and the presence of a bulky phenyl group did not affect the yield. In addition, a range of disubstituted benzoic acids underwent the esterification reaction effectively. Notably, the esterification protocol also proved effective for aliphatic carboxylic acids. Finally, the benzyl group and the double bond were tolerated during the reaction.

Next, we probed the substrate scope of this protocol with respect to formates. In the conventional esterification reactions of carboxylic acids and alcohols, the reaction rates primarily depend on the steric hindrance of alcohols, and the reactivities of alcohols decrease with the increase of their sizes. This tendency was observed in this esterification reaction. As shown in Table 2, while the formate with a primary alcohol reacted with benzoic acid in high yield, the yields decreased substantially for the formates with secondary alcohols and no desired product was formed in the reaction of *tert*-butyl formate. It should be mentioned that an excessive amount of isopropyl formate had to be used to achieve an acceptable yield, presumably due to the low boiling point of isopropyl formate.

Scheme 1 Copper-catalyzed pentylation of various carboxylic acids.



^a reaction condition: **1** (0.5 mmol), **2a** (3.0 equiv), Cu(OTf)₂ (10% mol), TBHP (2.0 equiv), 130 °C, 12 h.

Notably, under the identical conditions, esters also reacted with formates to give transesterification products effectively. As shown in Table 3, a range of benzoates underwent transesterification reaction with pentyl formate to afford pentyl benzoate in good yields. Interestingly, the size of benzoates had no impact on the yields as the steric hindrance of the alkyl groups did not have negative effects on the yields. Benzyl, which is a common protecting group in organic synthesis, and vinyl benzoate were also transesterified in medium and good yields respectively. This phenomenon, the protocol is applicable to both acids and esters, is very intriguing and makes this reaction a versatile method for the synthesis of esters starting from both esters and acids.

Table 2 Copper-Catalyzed Esterification of Benzoic Acids with Various Formates

entry	substrate	product	yield
1			82%
2			51% ^b
3			47%
4			0%

^a reaction condition: **1a** (0.5 mmol), **2** (3.0 equiv), Cu(OTf)₂ (10% mol), TBHP (2.0 equiv), 130 °C, 12 h. ^b Isopropyl formate as solvent.

Table 3 Copper-Catalyzed Transesterification of Benzoates with Pentyl Formate

entry	substrate	yield	entry	substrate	yield
1		91%	4		86%
2		72%	5		74%
3		92%			

^a reaction condition: **3a** (0.5 mmol), **2a** (3.0 equiv), Cu(OTf)₂ (10% mol), TBHP (2.0 equiv), 130 °C, 12 h.

In summary, owing to the importance of esters and the existing drawbacks of the current reactions, developing efficient methods for the synthesis of esters is still the subject of extensive exploration. In

this report, we disclose a novel and highly efficient protocol for the synthesis of esters. In this protocol, cheap and less toxic copper was employed as the catalyst. Notably, both carboxylic acids and esters can react with formates and can be transformed into the desired esters effectively under the identical conditions. This reaction demonstrates broad substrate scopes and high yields. Mechanistic studies and further studies of this type of reaction are underway in our laboratory.

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