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A General and Efficient Zinc-Catalyzed Oxidation of Benzyl Alcohols to Aldehydes and Esters

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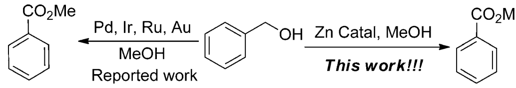
The development of environmental benign methodologies has become one of the main targets for organic chemists.[1] To fulfill the needs of green chemistry, certain challenges remain, such as the replacement of noble metals with cheap catalysts, increasing of reaction efficiency, using green reagents etc. For example, H_2O_2, as one of the green oxidants in oxidation reactions, generates water as the only by-product: thus, it should be used to replace other toxic oxidants.[2] Zinc catalysts are cheap, abundant, and nontoxic. Therefore, the use of zinc catalysts instead of catalysts based on noble metals (Pd, Ir, Ru, etc.) is interesting and important from academic, industrial, and sustainability aspects.[3]

Esters are an important moiety in organic synthesis, which hold broad applications in bulk chemicals, fine chemicals, natural products, and polymers.[4] Traditionally, esters are prepared by the reaction of activated acid derivatives with alcohols. Alternatively, the palladium-catalyzed carbonylation of aryl halides with alcohols offers an interesting and convenient procedure for their preparation.[5] Additionally, the oxidative esterification of aldehydes with alcohols is also reported for the synthesis of esters.[6] More recently, the groups of Beller and Lei reported a synthetically interesting oxidative cross-esterification of benzylic and aliphatic alcohols, respectively.[7] In their methods, palladium was used as catalyst and by using oxygen as the terminal oxidant various esters were prepared in good yields.

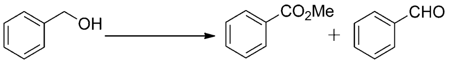
Herein, we wish to report a general and efficient methodology for the oxidation of benzyl alcohols to the corresponding aldehydes and esters by using zinc bromide as catalyst. H_2O_2 was used as a green oxidant, and all the reactions were carried out at room temperature under air. To the best of our knowledge, this is the first zinc-catalyzed oxidative cross-esterification of alcohols (Scheme 1).



Scheme 1. Transition-metal-catalyzed oxidative esterification of alcohols.

Initially, the reaction was carried out with one equivalent of $ZnBr_2$. Thereby, the corresponding ester and benzaldehyde were formed from benzyl alcohol (1 mmol) in 12 and 14 % yield, respectively, with 64 % conversion in MeOH (2 mL) by using H_2O_2 (4 mmol) as oxidant at room temperature (Table 1, entry 1). The addition of AcOH (2 mmol) improved the conversion to 94 % with improved yield of the ester (Table 2, entry 2). To our delight, similar results were also observed with 10 mol % of $ZnBr_2$ (Table 1, entry 3). When using 10 mol % of $CuBr_2$, $MnCl_2$, or $FeCl_3$ to replace $ZnBr_2$ under the conditions, only traces of benzaldehyde were formed with less than 5 % of benzyl alcohol converted. Then, other zinc salts were tested, but, in all the cases, no better results were observed and only moderate conversion was achieved (Table 1, entries 4–9). After the testing of different zinc salts, $ZnBr_2$ was chosen as catalyst to examine some other acid additives. Pivalic acid (2 mmol) did not further improve the yields of the desired products, and the best results were obtained by using trifluoroacetic acid (TFA) as additive (Table 1, entries 10–13). In all the experiments, ben-

Table 1. Zinc-catalyzed oxidation of benzyl alcohol.[a]



Entry	[Zn]	Additive	Conv. [%][b]	Yield of ester [%][b]	Yield of aldehyde [%][b]
1	$ZnBr_2$ (1 mmol)	–	64	12	14
2	$ZnBr_2$ (1 mmol)	AcOH (2 mmol)	94	23	16
3	$ZnBr_2$ (10 mol %)	AcOH (2 mmol)	61	15	8
4	ZnI_2 (10 mol %)	AcOH (2 mmol)	50	0	7
5	ZnF_2 (10 mol %)	AcOH (2 mmol)	50	0	15
6	$Zn(OTf)_2$ (10 mol %)	AcOH (2 mmol)	42	0	18
7	$Zn(OAc)_2$ (10 mol %)	AcOH (2 mmol)	46	0	17
8	$Zn(TFA)_2$ (10 mol %)	AcOH (2 mmol)	52	0	17
9	$Zn(CN)_2$ (10 mol %)	AcOH (2 mmol)	56	0	16
10	$ZnBr_2$ (10 mol %)	PivOH (2 mmol)	53	2	16
11	$ZnBr_2$ (10 mol %)	TFA (0.2 mL)	98	24	41
12	$ZnBr_2$ (10 mol %)	TFA (0.1 mL)	97	29	41
13	$ZnBr_2$ (10 mol %)	TFA (0.05 mL)	100	30	32
14	–	–	<3	0	0

[a] Zinc catalyst, benzyl alcohol (1 mmol), MeOH (2 mL), H_2O_2 (4 mmol), additive, RT, 16 h. [b] Conversion and yield were determined by GC using hexadecane as internal standard, based on benzyl alcohol.

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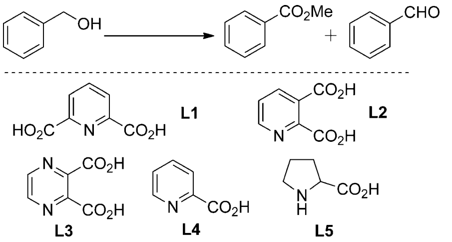
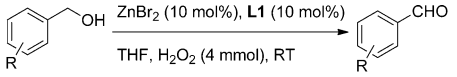
Table 2. Zinc-catalyzed oxidation of benzyl alcohol.[a]

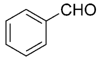
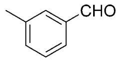
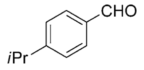
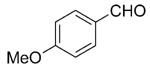
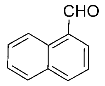
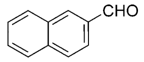
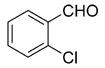
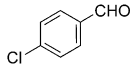
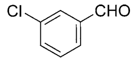


Entry	Ligand	Solvent	Conv. [%][b]	Yield of ester [%][b]	Yield of aldehyde [%][b]
1	**L1**	MeOH	100	23	61
2	**L2**	MeOH	100	16	50
3	**L3**	MeOH	100	14	43
4	**L4**	MeOH	100	18	53
5	**L5**	MeOH	100	21	47
6	**L1**	MeOH	100	89[c]	0
7	**L1**	THF	100	0	91
8	**L1**	1,4-dioxane	100	0	60
9	**L1**	MeCN	100	0	80
10	**L1**	H_2O	100	0	49
11	**L1**	*t*BuOH	100	0	82

[a] $ZnBr_2$ (10 mol%), ligand (10 mol%), benzyl alcohol (1 mmol), TFA (0.1 mL), solvent (2 mL), H_2O_2 (4 mmol), RT, 16 h. [b] Conversion and yield were determined by GC using hexadecane as internal standard, based on benzyl alcohol. [c] H_2O_2 (6 mmol) was added in three portions.

Table 3. Zinc-catalyzed oxidation of benzyl alcohols to aldehydes.[a]



Entry	Aldehyde	Yield [%][b]
1		91 85[c]
2		93
3		95
4		65
5		95 90[c]
6		97 90[c]
7		77
8		89
9		81
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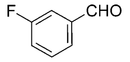
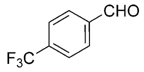
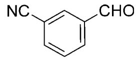
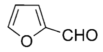
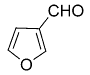
11		90
12		81
13		85
14		53
15		62

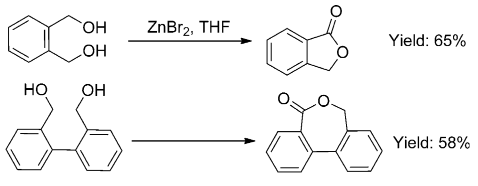
[a] $ZnBr_2$ (10 mol%), pyridine-2,6-dicarboxylic acid (10 mol%), benzyl alcohol (1 mmol), THF (2 mL), H_2O_2 (4 mmol), TFA (0.1 mL), RT, 16 h. [b] Yield was determined by GC using hexadecane as internal standard, based on benzyl alcohol. [c] Isolated yield.

zoic acid and some over-oxidized products were formed and detected. At the end, a blank experiment was carried out, which verified the importance of the zinc catalyst in this reaction system (Table 1, entry 14).

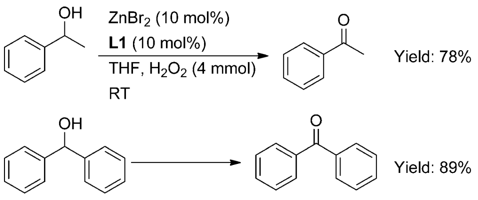
Then, $ZnBr_2$ was used as catalyst and trifluoroacetic acid as additive to test the influence of ligands on this transformation (Table 2). The five ligands chosen are commonly applied in transition-metal-catalyzed oxidation reactions, because of their resistance to oxidants.[8] To our delight, benzaldehyde and methyl benzoate were formed in 61 and 23% yield, respectively, by using pyridine-2,6-dicarboxylic acid as ligand (Table 2, entry 1). The selectivity between the aldehyde and ester could be modified by adding 6 mmol of hydrogen peroxide in three portions and changing the solvent (Table 2, entry 6). By simply changing the reaction media, the aldehyde could be produced as the only product of this transformation (Table 2, entries 7–11), and benzaldehyde was formed in 91% yield in THF (Table 2, entry 7).

With the best reaction conditions in hand (Table 2, entries 6 and 7), we started to test the generality of this methodology (Table 3 and 4). Excellent yields of methyl- and isopropyl-substituted aldehydes were produced from the corresponding benzyl alcohols (Table 3, entries 2 and 3). 4-Methoxybenzaldehyde was formed from 4-methoxybenzyl alcohol in 65% yield, together with 16% of 4-bromoanisol (Table 3, entry 4).[9] Naphthyl aldehydes were also produced in excellent yields from the corresponding alcohols (Table 3, entries 5 and 6). In addition, electron-withdrawing groups substituted at the *para*-, *meta*-, or *ortho*-position were also tolerable and gave good yields of the corresponding aldehydes (Table 3, entries 7–13). Two examples of furancarbaldehydes were also prepared in moderate yields without further modification (Table 3, entries 14 and 15). The reaction with aliphatic alcohols, such as 2-phenylethanol and heptan-1-ol, was also tested under our standard conditions, but no desired products were formed and only the starting materials were detected by GC and GC-MS. Moreover, secondary benzylic alcohols were oxidized to the corresponding ketones under the same conditions (Scheme 3).

Moreover, 15 examples of methyl benzoates were prepared in moderate to excellent yields (Table 4). The reactions were carried out in methanol, and H_2O_2 (6 mmol) was divided into three portions. Both electron-donating and electron-withdrawing functional groups were tolerable in this methodology. In addition, heterocycles could also be tolerated and gave moderate yields of the corresponding



Scheme 2. Zinc-catalyzed oxidation of diols.



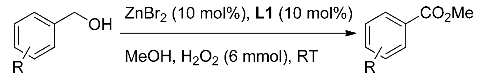
Scheme 3. Zinc-catalyzed synthesis of ketones.

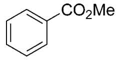
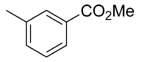
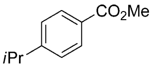
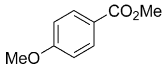
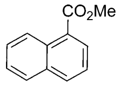
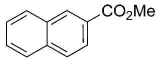
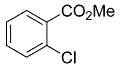
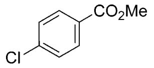
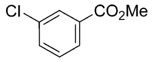
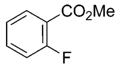
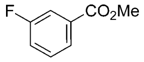
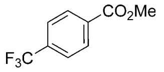
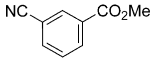
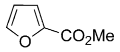
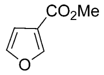
esters (Table 4, entries 14 and 15). The formation of esters proceeds through the corresponding aldehydes as intermediates. An excess of H_2O_2 is necessary for the oxidative esterification of these in situ formed aldehydes with methanol. H_2O_2 was divided into three portions to keep its concentration during the oxidation down and avoid decomposition.

Additionally, two heterocycles were produced in moderate yields under the standard conditions (Scheme 2). Besides the shown heterocycles, phthalaldehyde and [1,1′-biphenyl]-2,2′-dicarbaldehyde were also formed in 15–20 % yield as the expected products.

In conclusion, a general and efficient zinc-catalyzed oxidation of benzyl alcohols has been developed. All the reactions were carried out under air at room temperature by using H_2O_2 as green oxidant. As the first zinc-catalyzed oxidation of benzyl alcohols, various aldehydes and esters were prepared in moderate to excellent yields. In addition, two heterocycles were also synthesized from the corresponding diols under our standard conditions.

Table 4. Zinc-catalyzed oxidation of benzyl alcohols to esters.[a]



Entry	Ester	Yield [%][b]
1		89
2		84
3		90 82[c]
4		63
5		89 86[c]
6		91 85[c]
7		73
8		85
9		84
10		88
11		89
12		75
13		70
14		45
15		56

[a] $ZnBr_2$ (10 mol %), pyridine-2,6-dicarboxylic acid (10 mol %), benzyl alcohol (1 mmol), MeOH (2 mL), H_2O_2 (6 mmol) in three portions, TFA (0.1 mL), RT, 16 h. [b] Yield was determined by GC using hexadecane as internal standard, based on benzyl alcohol. [c] Isolated yield.

Experimental Section

General comments: All reactions were carried out under air. $ZnBr_2$, trifluoroacetic acid, THF, MeOH, H_2O_2 (30 % in water), and all the substrates were purchased from Aldrich and used as received. Gas chromatography analysis was performed on an Agilent HP-5890 instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5 % phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) by using argon as carrier gas. Gas chromatography–mass analysis was carried out on an Agilent HP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column (polydimethylsiloxane with 5 % phenyl groups, 30 m, 0.25 mm i.d., 0.25 μm film thickness) by using helium carrier gas.

General procedure for the oxidation of benzyl alcohols to aldehydes and ketones: $ZnBr_2$ (10 mol %), pyridine-2,6-dicarboxylic acid (10 mol %), and a stirring bar were added to a 50 mL pressure tube. Then, benzyl alcohol (1 mmol), trifluoroacetic acid (0.1 mL), and THF (2 mL) were added by using a syringe. At the end, H_2O_2 (4 mmol; 30 % aqueous) was added in one portion and the final solution was kept at room temperature for 16 h. Hexadecane (100 mg) and ethyl acetate (3 mL) were injected and a part of the solution was taken for GC and GC-MS analysis after being properly mixed. All the products are commercially available. The GC yields were calculated based on the calibration with commercially available products, and GC-MS spectra were also compared.

General procedure for the oxidation of benzyl alcohols to esters: $ZnBr_2$ (10 mol %), pyridine-2,6-dicarboxylic acid (10 mol %), and a stirring bar were added to a 50 mL pressure tube. Then, benzyl alcohol (1 mmol), trifluoroacetic acid (0.1 mL), and MeOH (2 mL) were added by using a syringe. At the end, H_2O_2 (6 mmol; 30 % aqueous) was added in three portions (every 2 mmol of H_2O_2 per 4 h) and the final solution was kept at room temperature for 8 h. Hexadecane (100 mg) and ethyl acetate (3 mL) were injected and a part of the solution was taken for GC and GC-MS analysis after being properly mixed. All the products are commercially available. The GC yields were calculated based on the calibration with commercially available products, and GC-MS spectra were also compared. This procedure was also applied for the oxidation of diols to heterocycles.

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Keywords: aldehydes · benzyl alcohols · esters · oxidation · zinc

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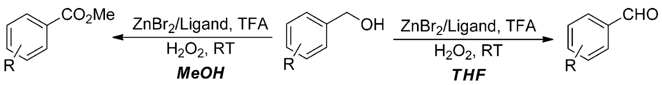

Go green: A general and efficient zinc-catalyzed oxidation of benzyl alcohols has been developed. In the presence of a zinc catalyst, various aldehydes and esters have been prepared in good to excellent yields under mild conditions (see scheme).

Zinc Catalysis

*X.-F. Wu** .... ■■■■–■■■■

A General and Efficient Zinc-Catalyzed Oxidation of Benzyl Alcohols to Aldehydes and Esters