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Biocatalytic Promiscuity of Lipase in Chemoselective Oxidation of Aryl Alcohols/Acetates: A Unique Synergism of CAL-B and [hmim]Br for the Metal-Free H_2O_2 Activation†

Upendra K. Sharma, Nandini Sharma, Rakesh Kumar, Rajesh Kumar, and Arun K. Sinha*

Natural Plant Products Division, Institute of Himalayan Bioresource Technology, CSIR, Palampur-176061 (H.P.), India

aksinha08@rediffmail.com

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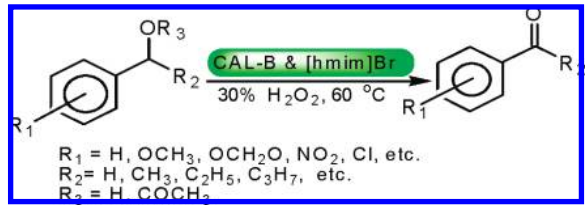
ABSTRACT



A unique synergistic combination of lipase and ionic liquid [hmim]Br is reported for metal-free H_2O_2 activation, which is the first example of biocatalytic promiscuity of CAL-B for chemoselective oxidation of aryl alcohols/acetates. The catalytic system exhibits excellent functional group compatibility under neutral conditions besides reusability up to ten cycles thereby making the process economically and environmentally viable.

The recent development in the biocatalytic promiscuity[1] of enzymes has greatly extended their application in organic syntheses such as various lipase catalyzed C−C, C−N, and C−S bond formations.[2] In this Letter, we have assessed the catalytic activity of lipase for oxidation.

Oxidation of alcohols to corresponding carbonyl compounds is an important and challenging transformation both at laboratory and industrial scales.[3] Conventionally, oxidation is brought up by utilizing stoichiometric/superstoichiometric amounts of inorganic oxidants[4] which are incongruous to the principles of Green Chemistry.

Currently, the use of H_2O_2 as a terminal oxidant has received great attention from both economic and environmental viewpoints. This reagent has, however, high activation energy, making catalysis necessary,[5] and thus many systems have been developed for H_2O_2 activation using either

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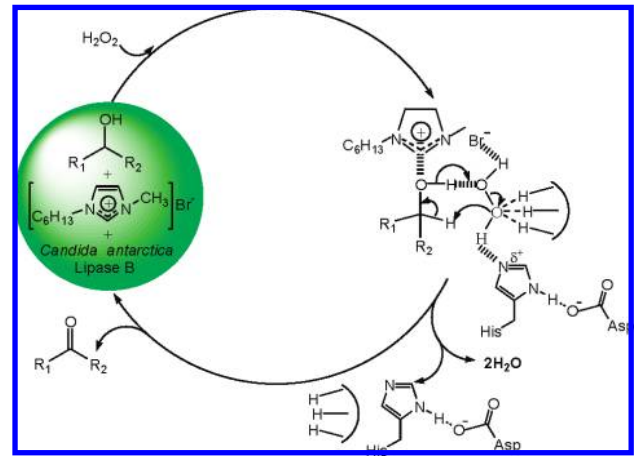
transition metals or organocatalysts.[6] However, most of these methods suffer from limitations such as use of strong acidic/basic conditions, lower yields, and laborious workup procedures besides poor recovery of expensive metal catalysts. Consequently, in an endeavor to develop more efficient processes, much attention has been paid by chemists to design new metal based ligands[6b] while the inherent advantages of enzymes as catalysts has remained largely overlooked except for a few reports.[7] For the past few years, the use of room temperature ionic liquids (ILs) for transformations with enzymes is gaining attraction due to their versatility, stability, and environmental credentials compared to conventional solvents.[8]

Recently, our group has reported the use of neutral ILs for expediting various organic reactions.[9] Encouraged by the results we were particularly interested in exploring the potential of IL and a biocatalyst for alcohol oxidations with H_2O_2. Herein, we report a highly efficient and recyclable combination of *Candida antarctica* lipase B (CAL-B) and neutral ionic liquid [hmim]Br for metal-free H_2O_2 activation in the chemoselective oxidation of aryl alcohols/acetates into carbonyls.

Initial investigation of CAL-B and [hmim]Br catalyzed oxidation was carried out with 4-methoxyphenylpropanol (**1a**) as substrate with 30% H_2O_2 at 40 °C for 16 h thereby providing 4-methoxyphenylpropanone (**1b**) in 90% yield. Increasing the temperature from 40 to 60 °C significantly brought down the reaction time from 16 to 8 h. After systematic optimization of reaction temperature, the amount of oxidant, and effect of different solvents, lipases, ILs, and oxidants were established for the oxidation of **1a** (see the Supporting Information, Tables S1 and S2). The different lipases (immobilized or lyophilized powder) furnished almost a similar effect on yield, but with respect to stability and reusability; CAL-B is markedly preferred. Interestingly, replacement of [hmim]Br with acidic, basic, or even other neutral ILs provided **1b** in low yield wherein the type of anion (Br^- vs. Cl^-) in the IL plays a decisive role. A very trace conversion was observed in the presence of lipase or IL alone even if the reaction mixture was stirred for 5 days at 60 °C. Also, control experiments with inactivated enzymes,[2c] solid support, and bovine serum albumin did not show appriciable yields (see the Supporting Information, Table S1), clearly indicating the role of a lipase−IL combination as an H_2O_2 activator.

Mechanistically, it is presumed that the hydroxy group of alcohol interacts with the imidazolium cation of IL (Scheme 1) resulting in polarization of the C−O bond[9c] followed by

Scheme 1. A Plausible Mechanism for Lipase−IL Catalyzed Oxidation of Aryl Alcohols with H_2O_2



attack of H_2O_2. Subsequent charge stabilization by an oxyanion hole of lipase[2a−c,7a,10] results in the formation of product along with the release of water.

Under the following conditions—0.25 mmol of alcohol, 50 mg of CAL-B, 1 mL of [hmim]Br, 4 equiv of 30% H_2O_2, 60 °C—various 1° and 2° benzylic alcohols, without deactivation by halogen- and nitrogen- substituents, were converted into their corresponding carbonyls in high to moderate yields within 8 to 12 h (Tables 1 and 2). In the case of 2° alcohols the oxidation proceeded without discrimination between *R* and *S* forms (Supporting Information, Figure S3).

Compared to benzylic and allylic alcohols, aliphatic alcohols showed no conversion—wherein oxidation of an equimolar mixture of **1a** and octanol provided only **1b**, with octanol being unreacted—demonstrating the remarkable chemoselectivity for the oxidation of benzyl alcohols over aliphatic analogues (see the Supporting Information, Table S3).

Subjecting acetylated derivatives of 1° and 2° alcohols to oxidation resulted in simultaneous hydrolysis and oxidation which is an additional benefit of the developed protocol (Table 1, entries 12−15; Table 2, entry 7).

In the case of 1° benzylic alcohols, formation of acid (5−10%) was also observed in some cases. To address this, we conveniently replaced H_2O_2 with a urea−H_2O_2 adduct (UHP) without affecting the efficiency of the process, although urea was generated as an additional byproduct.

As a demonstration of the utility of this catalytic protocol for the complex organic compounds and natural products, we investigated the oxidation of podophyllotoxin, a well-known natural anticancer drug, and achieved podophyllo-

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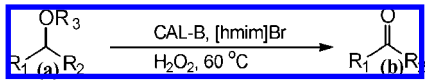
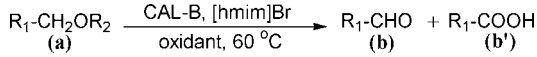
Table 1. CAL-B/[hmim]Br Catalyzed Oxidation of 2° Alcohols and Their Derivatives with H_2O_2[a]



entry	R_1	R_2	R_3	time (h)	yield (%)[b]
1	4-$MeOC_6H_4$	C_2H_5	H	8	96 (93)[c]
2	3,4-$(MeO)_2C_6H_3$	CH_3	H	8	94 (89)[c]
3	3,4,5-$(MeO)_3C_6H_2$	C_2H_5	H	12	80
4	C_6H_5	C_2H_5	H	8	85
5	C_6H_5	CH_3	H	8	90
6	4-ClC_6H_4	CH_3	H	8	84
7	4-$NO_2C_6H_4$	CH_3	H	8	75
8	4-$MeOC_6H_4$	C_3H_7	H	10	80 (76)[c]
9	4-$MeOC_6H_4$	C_4H_9	H	10	72
10	2-(6-$MeOC_{10}H_6$)	C_2H_5	H	12	65
11	3,4-$OCH_2OC_6H_3$	CH_3	H	8	86
12	3,4-$(MeO)_2C_6H_3$	CH_3	$COCH_3$	8	74
13	4-$MeOC_6H_4$	C_2H_5	$COCH_3$	8	86
14	4-ClC_6H_4	CH_3	$COCH_3$	10	72
15	4-$NO_2C_6H_4$	CH_3	$COCH_3$	10	68
16		-	-	8	65[d]
17	Cyclohexanol	-	-	24	nd

[a] Reaction conditions: 0.25 mmol of substrate, 50 mg of CAL-B, 1 mL of IL, 4 equiv of H_2O_2, at 60 °C. [b] Yield based on HPLC with comparison to standard and product identification by GC-MS. [c] Isolated yield in parentheses. [d] 6 equiv of H_2O_2.

Table 2. Lipase−IL Catalyzed Oxidation[a] of 1° Alcohols by H_2O_2 or by UHP



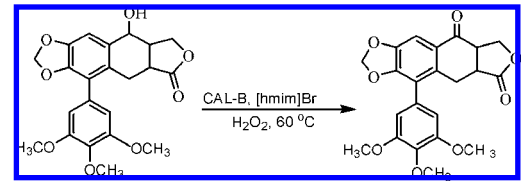
				yield (%)[b]	
entry	R_1	R_2	time (h)	H_2O_2	UHP
1	3,4-$(MeO)_2C_6H_3$	H	8	80(10)[c]	84(t)[c]
2	4-$MeOC_6H_4$	H	8	75(8)[c]	77(t)[c]
3	2-ClC_6H_4	H	8	78(5)[c]	81(t)[c]
4	2-MeC_6H_4	H	8	68(5)[c]	70
5	4-$MeOC_6H_4CH_2$	H	24	nd	nd
6	3,4-$OCH_2OC_6H_3$	H	8	76	78 [71][d]
7	3,4-$OCH_2OC_6H_3$	$COCH_3$	8	65	65
8	$C_6H_5CH{=}CH_2$	H	8	55	50
9	*n*-octanol		24	nd	nd

[a] Reaction conditions: 0.25 mmol of substrate, 50 mg of CAL-B, 1 mL of IL, 4 equiv of H_2O_2 or UHP, at 60 °C. [b] Yield on the basis of HPLC conversion. [c] Yield of acid (**1b′**−**3b′**) in parentheses. [d] isolated yield in sqaure brackets; t = traces.

toxon[11] in 60% yield with high product selectivity (more than 90%; Scheme 2).

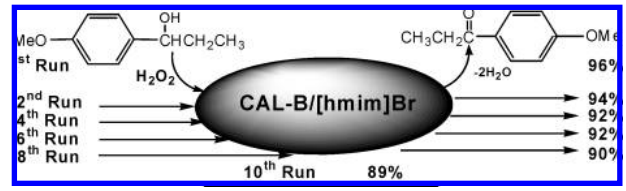
Having established the optimum conditions and scope for the reaction, we proceeded to assess the recyclability of the

Scheme 2. Oxidation of Podophyllotoxin to Podophyllotoxon



catalytic system (CAL-B and [hmim]Br). While the recovered catalysts retained high activity for ten cycles, yield decreased below 85% afterward with certain minor side products, which was compensated by adding a few milligrams of fresh lipase and 2−3 drops of IL (Scheme 3).

Scheme 3. Recyclability Study of Catalytic System



In conclusion, we have successfully developed a highly efficient process for the chemoselective oxidation of a wide range of aryl alcohols/acetates using CAL-B and cheaper IL [hmim]Br whose significant features are the following: (i) metal-free activation of H_2O_2, (ii) catalyst recyclability, (iii) waste-free process, (iii) easy isolation of the product, (iv) high efficiency under relatively mild conditions, (v) and compatibility with base- and acid-sensitive substrates. To the best of our knowledge, this is the first report on lipase−IL catalyzed oxidation with H_2O_2.

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Supporting Information Available: Complete experimental details and HPLC and spectroscopic data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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