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of sulfoxides were prepared in moderate to excellent yields.

A general and selective zinc-catalyzed oxidation of sulfides to sulfoxides

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ABSTRACT

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'Green chemistry' has become one of the hottest terms in chemistry during recent years. And if we related oxidation reaction in relation with the 12 principles of green chemistry,¹ it's apparently to have conclusions like increasing the reaction efficiency; using green oxidant and non-toxic catalyst are the most obvious aspects we can start. Concerning the green oxidant, hydrogen peroxide is one of the most powerful candidates besides oxygen, because it's cheap, readily available, high atom efficiency, and water is expected as the only by-product to be generated from the reaction.² Regarding the green catalyst, zinc salts hold the features like inexpensive, non-toxic, abundant and environmental benign.³ To explore zinc-catalyzed organic reactions are both interesting in academic and also in industrial.

Sulfoxides are an important class of compounds in organic chemistry with wide applications in chemical synthesis and in the preparation of biologically active compounds, even applied in the activation of enzymes.⁴ Traditionally, sulfoxides were oxidized from the corresponding sulfides with stoichiometric amount of organic or inorganic oxidant such as NaOCl and H₅IO₆ which produced a large amount of wastes. However, numerous methodologies have been developed during last decades for the selective oxidation of sulfides. Good yields of sulfoxides could be obtained from different catalytic systems based on acid,⁵ iron,⁶ vanadium,⁷ tungsten,⁸ manganese,⁹ copper,¹⁰ titanium,¹¹ platinum,¹² magnesium,¹³ cobalt,¹⁴ and silver.¹⁵ Interestingly, the group of Beller found even the hydrogen peroxide itself can promote the reaction

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0040-4039/\$ - see front matter © 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tetlet.2012.06.003 as well.¹⁶ Sulfoxides were obtained in excellent yields with good selectivity at 70 °C under solvent free conditions. As our continual interest in zinc-catalyzed oxidation reactions,¹⁷ taking the importance of sulfoxides into consideration, and it is more ideal to perform the oxidation reactions at room temperature in an open flask, we developed a general zinc-catalyzed oxidation of sulfides to sulfoxides. All the reactions were carried out at room temperature, by using hydrogen peroxide as the oxidant combined with catalytic amount of zinc catalyst; sulfoxides were produced in good yields and with excellent selectivity. Remarkably, the ligands applied are commercially available no tedious preparation process are needed.

A general zinc-catalyzed oxidation of sulfides to sulfoxides has been developed. All the reactions pro-

ceeded at room temperature. Hydrogen peroxide was used as a green oxidant. Twenty-one examples

Initially, the reaction was carried out with 1 mmol of phenyl sulfide in 2 mL of dioxane, 50% of conversion was obtained in the presence of 10 mol % of ZnBr₂ using H₂O₂ (4 mmol) as the oxidant at room temperature (Table 1, entry 1). Then nine types of nitrogen ligands were tested (Table 1, entries 2-10). 80-84% Yields of the sulfoxide with excellent conversions were observed using pyridine-2,6-dicarboxylic acid as the ligand (Table 1, entries 2-4). To our surprise, only 19% of conversion was observed with phthalic acid as the ligand (Table 1, entry 5). These results illustrate the importance of the ligands structure. The other tested ligands gave decreased conversions and yields (Table 1, entries 6-10). The effects of ligand and catalyst were also checked; only 5-15% conversion and 2-4% yields were detected if we carried out the reaction in the absence of catalyst (Table 1, entries 11-12). No starting material was converted in the absence of H_2O_2 (Table 1, entry 13). After these testing, we chose pyridine-2,6-dicarboxylic acid as the ligand to test the influence of zinc salts in dioxane at room temperature (Table 1, entries





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Table 1 Zinc catalyzed ovidation of

Zinc-catalyzed oxidation of phenyl sulfide^a



Entry	[Zn] (10 mol %)	Solvent (2 mL)	L (10 mol %)	Conv. ^b (%)	Y 1 ^b (%)	Y 2 ^b (%)
1	ZnBr ₂	Dioxane	1	50	32	14
2	ZnBr ₂	Dioxane	L 1	95	80	7
3	ZnBr ₂	Dioxane	L 2	>99	84	8
4	ZnBr ₂	Dioxane	L 3	96	80	10
5	ZnBr ₂	Dioxane	L 4	19	10	4
6	ZnBr ₂	Dioxane	L 5	80	66	5
7	ZnBr ₂	Dioxane	L 6	55	35	13
8	ZnBr ₂	Dioxane	L 7	62	39	9
9	ZnBr ₂	Dioxane	L 8	21	12	3
10	ZnBr ₂	Dioxane	L 9	15	8	2
11	1	Dioxane	L 2	5	2	2
12	1	Dioxane	_	15	4	9
13	ZnBr ₂	Dioxane	L 2	0	0	0 ^c
14	ZnCl ₂	Dioxane	L 2	70	47	20
15	ZnI ₂	Dioxane	L 2	15	3	8
16	ZnF ₂	Dioxane	L 2	29	10	15
17	$Zn(OAc)_2$	Dioxane	L 2	22	9	11
18	ZnSO ₄ ·7H ₂ O	Dioxane	L 2	50	30	11
19	Zn(NO ₃) ₂ ·6H ₂ O	Dioxane	L 2	85	53	21
20	$Zn(acac)_2 \times H_2O$	Dioxane	L 2	15	3	7
21	ZnBr ₂	Dioxane	L 2	82	61	8 ^d
22	ZnBr ₂	MeOH	L 2	>99	90	5
23	ZnBr ₂	EtOH	L 2	>99	70	21
24	ZnBr ₂	MeCN	L 2	>99	80	18
25	ZnBr ₂	THF	L 2	69	50	10
26	ZnBr ₂	H ₂ O	L 2	10	8	1
27	ZnBr ₂	Acetone	L 2	90	60	28

^a Zinc salt (10 mol %), ligand (10 mol %), solvent (2 mL), H₂O₂ (4 mmol, 30% in water), phenyl sulfide (1 mmol), rt, 6 h, air.

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

^c Without additional H₂O₂.

^d ZnBr₂ (5 mol %), **L** 2 (5 mol %).

 $2 \operatorname{Hor}_2(3 \operatorname{Hor}_2), \mathbf{E} \mathcal{E}(3 \operatorname{Hor}_2).$

14–20). No better results were achieved in all the cases. With decreased loading of catalyst, lower conversion and yield were observed (Table 1, entry 21). The solvents testing were carried out afterwards (Table 1, entries 22–27). To our delight, 90% of sulfoxide was produced in methanol with total conversion of starting material and only 5 mol % of sulfone as the over oxidized product was formed (Table 1, entry 22). In most of the cases, the decomposition of the substrate could also be detected, which also can explain the difference between yields and conversion.

With the best reaction conditions in our hand (Table 1, entry 22), we started to check the generality and efficiency of this methodology (Table 2).¹⁸ Various (methylsulfinyl)benzenes were produced in good to excellent yields with excellent selectivity (Table 2, entries 2–12). In addition to methoxy-, methyl-, bromo-, and nitrile-substituted sulfides, (4-(methylsulfinyl)phenyl)meth-anol was also produced from the corresponding sulfide and only a small amount of 4-(methylsulfinyl)benzaldehyde was observed as the oxidation of the benzyl alcohols (Table 2, entry 7). No amide

was formed by the hydration of the nitrile functional group (Table 2, entry 9). Amine can be tolerated as well, 93% of 4-(methylsulfinyl)aniline was formed without the formation of nitro byproduct (Table 2, entry 10). In the cases of using (4-(bromomethyl) phenyl)(methyl)sulfane, 4-(methylthio)benzaldehyde, (chloromethyl)(phenyl)sulfane and (2-chloroethyl)(phenyl)sulfane as substrates, the reactions were performed in dioxane in order to avoid the reaction of substrates with solvent and moderate to good yields of the corresponding products were produced (Table 2, entries 8, 11, 14 and 15).

Besides the substituents on the arene part, vinyl-, benzyl-decorated phenylsulfides were also applied as substrates and gave 53–80% yields (Table 2, entries 16–17). No oxidation of the double bond was identified (Table 2, entry 16), and in the case of benzyl substituent, the decomposition of starting material was detected (Table 2, entry 17). Moreover, heterocyclic and alkyl sulfide were successfully applied as substrates as well and gave the corresponding sulfoxides in good yields (Table 2, entries 19–21).

Table 2 (continued)

Table 2

Zinc-catalyzed oxidation of sulfides^a



Entry	Product	Conv.	Yield ^b (%)	Select ^b (%)
15	O S Cl	>99	66 ^d	66
16	O S S	>99	80	80
17	O S Ph	>99	53	53
18	о В ОН	>99	88	88
19	S S O	>99	45	45
20	ſŢ S S S	>99	89	89
21	0	>00	80 ^c	01
21	∕~ ^s √∕	- 33	01	01

 a ZnBr_2 (10 mol %), L 2 (10 mol %), MeOH (2 mL), H_2O_2 (4 mmol, 30% in water), sulfides (1 mmol), rt, 6 h, air.

 $^{\rm b}$ Conversions and yields were determined by GC using hexadecane as the internal standard based on sulfides.

^c Isolated yields.

^d Dioxane (2 mL) as the solvent.

In conclusion, a general zinc-catalyzed oxidation of sulfides to sulfoxides has been developed. The reactions proceeded at room temperature, and use hydrogen peroxide as the green oxidant. Twenty-one examples of sulfoxides have been prepared in moderate to excellent yields.

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- General comments: All reactions were carried out under air. ZnBr2, pyridine-2,3-dicarboxylic acid, 1,4-dioxane, THF, MeOH, H₂O₂ (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 id, 0.25 µm film thickness) using argon as the 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 id, 0.25 µm film thickness) using helium carrier gas. General procedure for the oxidation of sulfides to sulfoxides: In a 25 mL reaction tube, ZnBr₂ (10 mol %), pyridine-2,6-dicarboxylic acid (10 mol %) and a stirring bar were added, followed by the addition of sulfides (1 mmol) and MeOH (2 mL) with syringe. At the end H₂O₂ (4 mmol; 30% aq) was added in one pot to the solution. The resulting solution was kept at room temperature for 6 h. Then 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 mixed. All the products are commercially available. The GC yields were calculated based on the calibration with commercially available products, and GC-MS spectroscopies were also compared.