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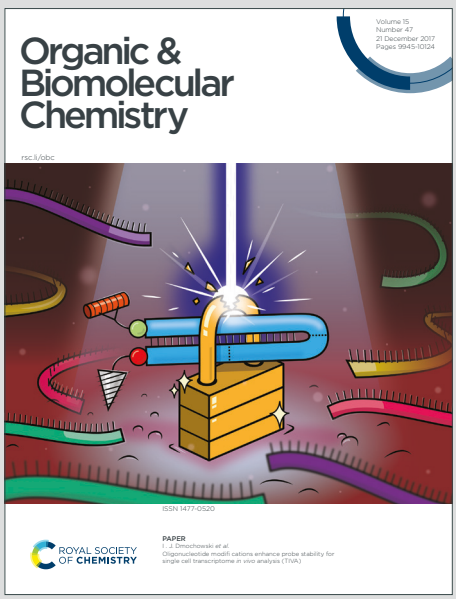

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COMMUNICATION

A mild and chemoselective CALB biocatalysed synthesis of sulfoxides exploiting the dual role of AcOEt as solvent and reagent

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A mild, chemoselective and sustainable biocatalysed synthesis of sulfoxides has been developed exploiting CALB and using AcOEt with a dual role of more environmentally friendly reaction solvent and enzyme substrate. A series of sulfoxides, including the drug omeprazole, has been synthesised in high yields and with excellent E-factors.

Sulfoxides are an ubiquitous class of organic compounds that play pivotal roles in organic synthesis as chiral auxiliaries,[1] synthons for C–C bond forming reactions,[2] directing groups in C–H bond functionalisation[3] and can partake in numerous other functionalisation reactions.[4] The sulfoxide moiety is also widely found in many pharmaceutical agents, including the blockbuster antacid agent omeprazole **1** and the dopamine reuptake inhibitor modafinil **2**,[5] as well as in nature, for example in the garlic components alliin **4** and ajoene **5** which is crucial for their antimicrobial and antifungal activity (Figure 1).[6] Sulfoxides can be easily obtained through oxidation of the corresponding sulfides using nitric acid,[7] hypohalites such as $NaIO_4$ and NaOCl,[8] peroxides such as *tert*-butyl hydroperoxide (TBHP),[9] *meta*-chloroperbenzoic acid (*m*CPBA)[10] and oxone.[9c,11] However these methods have limited industrial use as they require potentially shock sensitive or explosive reagents or expensive metal-based catalysts making them unsuitable for large scale production. Recently, several protocols exploiting borax,[12] 2,2,2-trifluoroacetophenone[13] and enzymes like cytochromes P450, monooxygenases, chloroperoxidases, laccase, and reductive enzymes[14] have been proposed to provide more sustainable, cheaper and ultimately safer methodologies to access sulfoxide compounds.[15,14b] However, despite the excellent conversions, these approaches still have poor industrial applicability because of the low recyclability, high costs and stability of the enzymes. In addition, some enzymatic oxidations also require toxic and flammable additives and effective aeration of the system, all of which represent drawbacks in industry.[16]

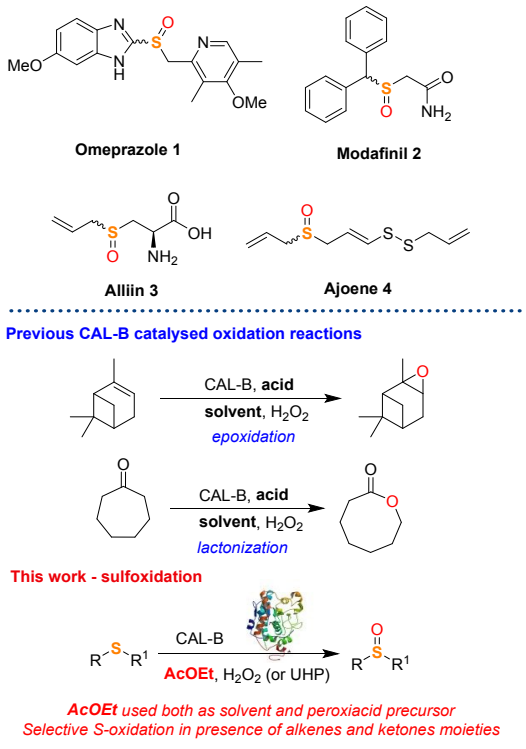

Figure 1. Sulfoxide containing drugs and natural products and an overview of the work

Immobilised *Candida antarctica lipase B* (CALB) is a robust and versatile enzyme which retains its activity in aqueous and

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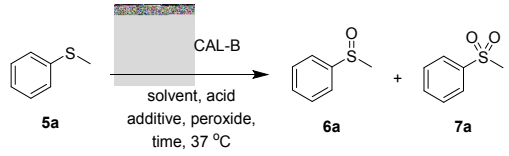
Electronic Supplementary Information (ESI) available: Full characterization of sulfoxide compounds and copies of ^{1}H-NMR and ^{13}C-NMR spectra. See DOI: 10.1039/x0xx00000x

organic solvents and it is already widely used in industry for both hydrolytic and acylation reactions of esters, alcohols and amines.[17] Currently, CALB is one of the few enzymes that finds application and offers a real sustainable alternative to chemocatalysis in industry.[17b] In addition to its natural hydrolytic activity, CALB has been recently used as a biocatalyst in oxidative reactions, including epoxidations,[18] Baeyer-Villiger lactonizations/esterifications[19] and amine oxidation.[20] These reactions exploit the CALB ability to catalyse the *in situ* generation of peroxyacid oxidants from carboxylic acids under mild reaction conditions (Figure 1). Surprisingly, to the best of our knowledge, the use of CALB as a biocatalyst in the oxidation of sulfide substrates into sulfoxides has never been investigated. Following our interest in the development of new and industrially applicable green methodologies for the synthesis of drugs and drug-like synthons, herein we report a facile, chemoselective and scalable biocatalytic protocol for the synthesis of sulfoxides using CALB. The method proves to be cost effective, robust and selective showing little side-reactions (epoxidation and esterification). Furthermore, we exploit AcOEt in the dual role of solvent and CALB substrate, thus avoiding the use of extra acid additives. The choice of AcOEt as solvent/reagent improves the industrial sustainability of the method. In fact, when considering all factors in choosing a solvent for a chemical process such as the health, environment and safety scores,[21] AcOEt is considered a safer and more economical alternative to other widely used solvents, such as halogenated or high boiling point solvents or even ionic liquids. Thus, AcOEt is ideal for the development of this sulfoxidation methodology, where it can serve as a solvent and CALB substrate, in turn contributing to the atom economy of the process.

The commercially available methyl phenyl sulfide **5a** was selected as substrate to develop the CALB biocatalysed sulfoxidation methodology. Sulfide **5a** was initially treated with CALB (20% w/w) and 1.1 equivalents of H_2O_2 in EtOAc (400 mM) leading to an 83:17 mixture of the desired sulfoxide **6a** and the over-oxidation sulfone by-product **7a** within 24h (*entry 1*, Table 1). Replacement of H_2O_2 with urea hydrogen peroxide (UHP),[22] which is often used as a more stable alternative to H_2O_2, led to the full oxidation of **5a** in only 2h and to the formation of the sulfoxide **6a** as the major product in improved 93:7 ratio against **7a** (*entry 2*). Reducing the concentration of **5a** to 200 mM (*entry 3*) led to a small improvement in the sulfoxide/sulphone ratio (94:6), while a lower ratio (92:8) was observed in more concentrated conditions (*entry 4*). Thus, the optimal reaction concentration of **5a** was kept at 400mM. All the reactions were carried out under open air conditions. In order to confirm that the oxidation of sulfide **5a** was biocatalysed by CALB rather than being promoted by UHP only or by air, a series of control experiments (*entries 5-7*) was performed. Upon the removal of the CALB and in the presence of UHP only, both in stoichiometric amount and in excess (5.0 eq.), negligible formation of **6a** was observed, clearly accounting for the key role of CALB for the *in situ* generation of the peroxyacid oxidant intermediate **8a** (Scheme 1).[19a,23] Similarly, when UHP was omitted from the reaction, only a small amount of **6a** was obtained and 96% of **5a** was recovered. Finally, no sulfoxidation was observed when DCM or toluene (*entries 8-9*) were used as solvents, further corroborating the key dual role of AcOEt as solvent and CALB substrate and precursor of peroxyacid **8a**. Remarkably, compared to traditional methods based on the use of a peroxyacid such as the industrially unappealing *m*CPBA,[10b] very little over-oxidation to the undesired sulfone was observed by proton NMR, clearly showing that the peroxyacid formed *in situ* rapidly oxidises the more reactive sulfide to sulfoxide and is converted back to the corresponding acid for a new oxidation cycle.

Table 1. Optimization of the CALB biocatalysed sulfoxidation of **5a**



Entry	5a (mM)	CALB (%w/w)	Perox-ide[a]	Solv-ent	Acid additive[a]	Time (h)	Conv. (%)[b]	Ratio 6a/7a[c]
1	400	20	H_2O_2	AcOEt	-	24	99	83:17
2	**400**	**20**	**UHP**	**AcOEt**	**-**	**2**	**>99[d]**	**93:7**
3	200	20	UHP	AcOEt	-	2	>99	94:6
4	600	20	UHP	AcOEt	-	2	>99	92:8
5	400	-	UHP	AcOEt	-	2	8	ND
6	100	-	UHP (5.0 eq.)	AcOEt	-	24	30	ND
7	400	20	-	AcOEt	-	2	4	ND
8	400	20	UHP	DCM	-	2	1	ND
9	400	20	UHP	Toluene	-	2	4	ND
10	400	20	H_2O_2	DCM		20	44	ND
11	400	20	UHP	Toluene		2	17	ND
12	160	20	UHP	Toluene		20	81	66:34
13	160	20	UHP	Toluene		2	16	ND

[a]1.1 eq. of H_2O_2 or UHP were used unless indicated differently; [b]Determined by analysis of the ^{1}H-NMR crude mixture and referred to the conversion of **5a** into **6a-7a** together; [c]Determined by ^{1}H-NMR; [d]Compound **6a** was obtained with 89% isolated yield

As a further confirmation of the key dual functionality of AcOEt over the use of inert solvents such as DCM and toluene, a series of experiments using acid additives as precursors of the peroxyacid oxidant was carried out. The treatment of **5a** with

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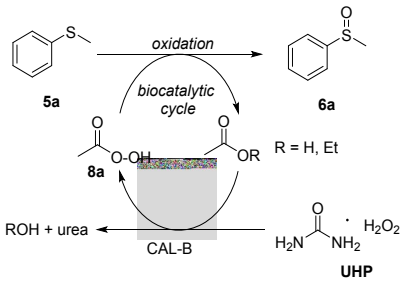
CALB in DCM or toluene in presence of stoichiometric hexanoic acid and 2-ethylhexanoic acid (*entries 10-11*) led to **6a** with poor conversion after 2h. Interestingly, in the presence of 2-methylbutyric acid, **5a** was converted at 81%, but with poor 66:34 sulfoxide/sulphone ratio (*entry 12*), while in the presence of the ester additive ethyl (2-ethyl)-hexanoate in toluene, **6a** was obtained in low amount (*entry 13*).

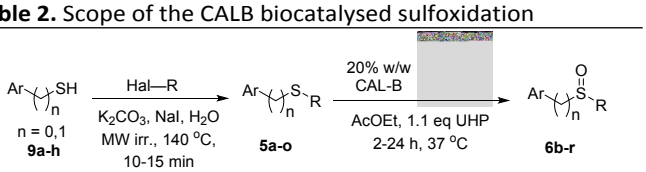


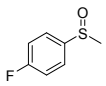
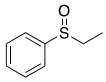
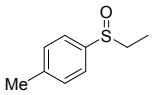
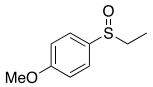
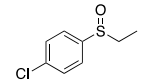
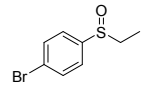
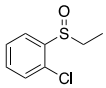
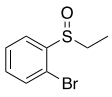
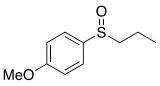
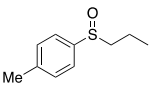
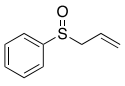
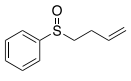
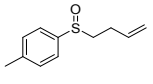
Scheme 1. Proposed mechanism for the CALB biocatalysed sulfoxidation

Following identification of the best reaction conditions, the scope of the CALB biocatalysed sulfoxidation was investigated. A series of alkyl-aryl(benzyl) sulfides **5a-o** was synthesised from the appropriate thiophenol or benzylthiol precursors **9a-h** through the reaction of the appropriate alkyl halide in water under microwave irradiation. All substrates **5** were converted into the corresponding sulfoxides **6** with high yields as shown in Table 2. In most cases, only a low amount of the sulphone by-product was formed and high isolated yields were obtained regardless the size of the alkyl substituent (Me, Et, Pr) on the sulfoxide moiety. Remarkably, derivatives **6l-n** bearing a double bond were also obtained selectively with high yields (*entries 11-13*). It is widely reported that CALB can catalyse the epoxidation of double bonds when in presence of peroxides and acid substrates.[18] However, no traces of epoxide (by)-products were detected from the reaction of **5l-n**, highlighting the chemoselectivity of this reaction and the preferred oxidation of sulfur over the alkenes. Finally, excellent conversions and high yields were obtained also for the benzyl sulfoxides **6o-p** (*entries 14-15*), the chiral nitrile **6q** (*entry 16*) and the dialkyl derivative **6r** (*entry 17*).

It is documented that CALB can also catalyse the Baeyer-Villiger oxidation of ketone substrates when in the presence of peroxides.[19] Thus, with the aim to further investigate the chemoselectivity of our transformation, namely the S-oxidation versus the C=O oxidation/esterification, a series of sulfide substrates **12a-f** bearing a carbonyl moiety was synthesised as described in Table 3. All the carbonyl containing substrates **12a-f** were selectively oxidised at the sulphur atom, as determined by NMR, affording the corresponding sulfoxides **13a-f** with excellent conversions (up to 99%) and high yields after 24h. The only exception was represented by the aldehyde substrate **12c** (*entry 3*) which degraded during the reaction and no sulfoxide or other oxidation by-products were obtained from the reaction mixture. In all cases, the oxidation was highly selective towards the formation of the sulfoxide over the sulphone. Remarkably, no Baeyer-Villiger oxidation side products were observed in any reaction, further proving the high chemoselectivity of the methodology.

Table 2. Scope of the CALB biocatalysed sulfoxidation



Entry		Compound	Conv. (%)[a]	Yield (%)[b,c,d]	Ratio SO/SO$_2$
1	**6b**		>99[e]	85	88.12
2	**6c**		99	63	66:34
3	**6d**		90	71	80:20
4	**6e**		97[e]	60	70:30
5	**6f**		90	67	80:20
6	**6g**		97	67	76:24
7	**6h**		99	81	83:17
8	**6i**		99	80	90:10
9	**6j**		98	79	80:20
10	**6k**		88	68	80:20
11	**6l**		90	68	100:0
12	**6m**		67	58	100:0
13	**6n**		85	73	100:0

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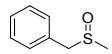
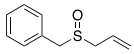
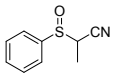
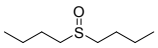
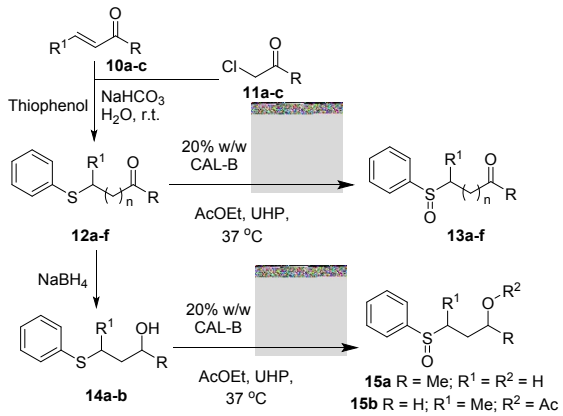
14	**6o**		90	82	83:17
15	**6p**		96	86	92:8
16	**6q**		94	78[f]	95:5
17	**6r**		>99[e]	89	94:6

[a]Determined by analysis of the ^{1}H-NMR crude mixture and referred to the conversion of **5** in **6-7** together. [b]All the reactions were carried out for 24h, unless completed before as revealed by TLC. [c]Isolated yields are reported; isolated yields refer to the pure sulfoxides. [d]Isolated yields refer to the biocatalytic step only. [e]The reaction was completed in 2h. [f]Obtained as a 3:2 mixture of diastereoisomers

Finally, the alcohol derivatives **14a-b**, in turn obtained from **12a** and **12c**, were oxidised leading to products **15a-b** with excellent conversions and yields (*entries 7-8*).[24] Interestingly, in the case of **15b**, CALB also catalysed the acetylation of the primary hydroxyl group in addition to the S-oxidation.

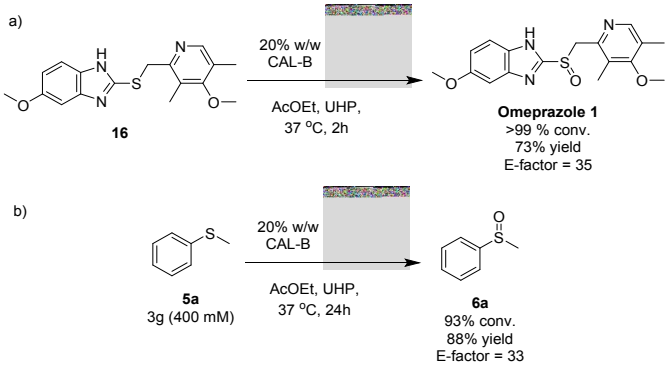
Table 3. CALB biocatalysed synthesis of sulfoxides bearing carbonyl groups



Entry	Cmpd	R	R^1	n	Conv. (%)[a]	Yield (%)[b,c]	Ratio SO/SO_2
1	**13a**	Me	H	1	89	71	100:0
2	**13b**	Me	Me	1	68[d]	42	100:0
3	**13c**	H	Me	1	0	0	100:0
4	**13d**	Me	H	0	99	67	80:20
5	**13e**	Et	H	0	96	81	85:15
6	**13f**	*i*Pr	H	0	93	68	89:11
7	**15a**	Me	H	1	99	67	76:24
8	**15b**	H	Me	1	99	74	76:24

[a]Determined by analysis of the ^{1}H-NMR crude mixture and referred to the conversion of **12** in SO/SO_2 products together; [b]Isolated yields are reported; isolated yields refer to the pure sulfoxides. [c]Isolated yields refer to the biocatalytic step only. [d]30% w/v H_2O_2 used as peroxide.

In order to prove the applicability of the methodology to pharmaceutical ingredients, the synthesis of omeprazole **1** was carried out (Scheme 2a). The substrate **16** was treated with CALB and UHP under standard conditions[25] and the selective oxidation of the sulphur to sulfoxide was accomplished within 2 hours, leading to omeprazole **1** with 73% isolated yield. No trace of the sulphone by-product were observed. Gratifyingly, the E-factor of the transformation was found to be 35, confirming the high industrial applicability of the CALB oxidation method. Interestingly, most of the current approaches reported in literature for the synthesis of omeprazole **1** are carried out under harsher reaction conditions and longer reaction times,[26,12,13,15] highlighting the potential impact of this method on the synthesis of sulfoxide containing pharmaceutical ingredients at industrial level.



Scheme 2. a) Synthesis of omeprazole **1** *via* CALB biocatalysed oxidation; b) Gram-scale synthesis of sulfoxide **6a**

One of the main drawbacks of the synthetic methodologies developed within an academic environment is that they often fail to perform at an industrial scale level. The scalability of the CALB S-oxidation was thus investigated through the oxidation at multi-gram scale of **5a**[27] (Scheme 2b). The sulfoxide **6a** was obtained with 93% conversion and 88% isolated yield with an excellent E-factor of 33.

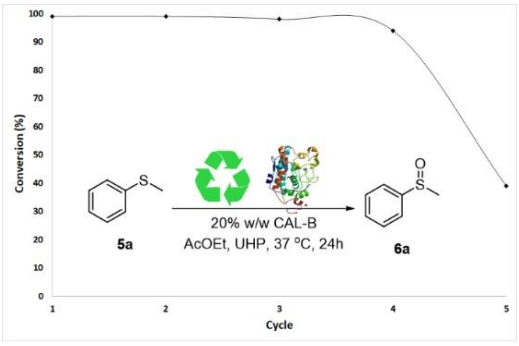


Figure 2. Recycling experiments of CALB

Finally, a series of recyclability experiments were performed to further confirm the industrial potentiality of the methodology. Sulfide **5a** was dissolved in AcOEt (400 mM) with 20% *w/w* CALB and 1.1 equivalents of UHP and stirred for 24h. At the end of the reaction, CALB was filtered off and washed with a 9:1 mixture of CH_3CN/water (9:1) to remove leftover urea from UHP. CALB, obtained with a recovery rate of 75-96%, was then re-used in a subsequent sulfoxidation reaction of **5a**. The

catalytic activity of CALB was maintained through four reaction cycles without significant loss in oxidation activity (99-94% conversions of **5a**, Figure 2). A drop to 39% of activity was observed in the fifth cycle.[28]

Conclusions

In conclusion, a novel, mild and selective methodology for the synthesis of sulfoxide compounds in high yields was developed using CALB biocatalyst and UHP. The oxidation of sulfide substrates occurs exploiting AcOEt with a dual role of solvent and CALB substrate in the generation of the peroxyacid reactive intermediate **8a**. Sulfide substrates bearing different functional groups such as alkenes and carbonyls were also selectively oxidised at the sulfur atom, proving the chemoselectivity of the methodology over side reactions like epoxidations and Baeyer-Villiger oxidations. The methodology was applied to the synthesis of the drug omeprazole and investigated at gram scale on the substrate **5a**, showing excellent yields and E-factors. These data, in addition to the robustness and the recyclability of CALB biocatalyst, demonstrate the high translation potential of this methodology for industrial applications.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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