RSC Sustainability

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Sustainability*, 2025, **3**, 4098

Mechano-enzymatic and deep eutectic solvent (DES) mediated sulfoxidation reactions: a comparison study†

Amina Cheraitia,[ab] Chuhan Li,[a] Michele Crotti,[a] Naima Merabet[b] and Daniele Castagnolo *[a]

Received 23rd June 2025
Accepted 9th July 2025

DOI: 10.1039/d5su00467e

rsc.li/rscsus

The oxidation of sulfide substrates into sulfoxides is a common reaction in organic chemistry, and it has found broad applications in the synthesis of drugs, chemicals and materials. Many sulfoxidation catalytic methods, including photo-, organo- and biocatalytic methods, have been developed to date with the aim to make such transformation more sustainable and in line with the principles of green chemistry. This work describes the development and green assessment of three sulfoxidation methodologies that combine biocatalysis with mechanochemistry and the use of deep eutectic solvents (DESs). A new mechano-enzymatic method where sulfoxides are prepared under mechanochemical conditions with CALB biocatalyst, UHP and AcOEt was first developed, followed by a mechanochemical method requiring only lactic acid (LacOH) and UHP. Finally, a DES-mediated method where sulfoxides are generated by the reaction of UHP with LacOH-based DES media was developed. All three methodologies afforded sulfoxide products selectively with high yields. A comparison of the green metrics revealed that the mechano and the mechano-enzymatic methods show the best green profile in terms of *E*-factor and RME parameters.

Sustainability spotlight

Green technologies such as biocatalysis, mechanochemistry, and the use of green solvents are vital to enabling safer, more efficient, and environmentally sustainable chemical processes across both academia and industry. This work contributes to the advancement of sustainable chemical manufacturing through the development and comparison of three innovative sulfoxidation methodologies that integrate biocatalysis, mechanochemistry, and deep eutectic solvents (DESs). These methods significantly reduce chemical waste, enhance reaction efficiency, and avoid hazardous reagents, fully aligning with the principles of green chemistry. By minimizing environmental impact and promoting resource efficiency, this research aligns with the UN Sustainable Development Goals (SDGs), in particular with SDG 9 (Industry, Innovation and Infrastructure), SDG 12 (Responsible Consumption and Production), and SDG 13 (Climate Action), offering scalable and greener alternatives for the synthesis of sulfoxides used in pharmaceutical and fine chemical production.

Introduction

The selective oxidation of sulfides into sulfoxides is a key transformation in organic synthesis, and it finds broad application in the pharmaceutical, chemical and agrochemical industries.[1] Drugs such as omeprazole,[2] armodafinil[3] or sulindac[4] contain a sulfoxide moiety, which is crucial for their pharmaceutical activity. The sulfoxide motif can also be found in natural products such as the garlic components allicin,[5] ajoene[6] and garlicnins B-2 and L-1 (ref. 7) as well as in chiral ligands used in asymmetric organic syntheses, such as Skarzewsky's ligand[8] Fig. 1.

Traditionally, the oxidation of sulfides into sulfoxides has been performed using stoichiometric amounts of oxidant reagents such as *meta*-chloroperbenzoic acid (*m*-CPBA),[9] oxone,[10] H_2O_2,[11] NaOCl,[12] or hypervalent iodine reagents.[13] Such methods generally require harsh reaction conditions, generate hazardous waste, and the overoxidation of sulfides into sulfone by-products may represent a drawback. In the last few decades, several catalytic sulfoxidation methods, especially organocatalytic,[14] photocatalytic[15] and biocatalytic,[16] have been developed, making this transformation greener and more in line with the principles of green chemistry. Our group recently described the preparation of chiral sulfoxide derivatives through different biocatalytic methodologies using lipase,[17] monooxygenase (BVMO and FMO)[18] and reductase (MsrA)[19] enzymes.

[a]*Department of Chemistry, University College London, Manufacturing Futures Lab, Marshgate Building, 7 Sidings Street, E20 2AE, London, UK. E-mail: d.castagnolo@ucl.ac.uk*

[b]*Laboratoire de Pharmacologie et de Phytochimie, Faculté des Sciences Exactes et Informatique, Université de Jijel, 18000 Jijel, Algeria*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d5su00467e

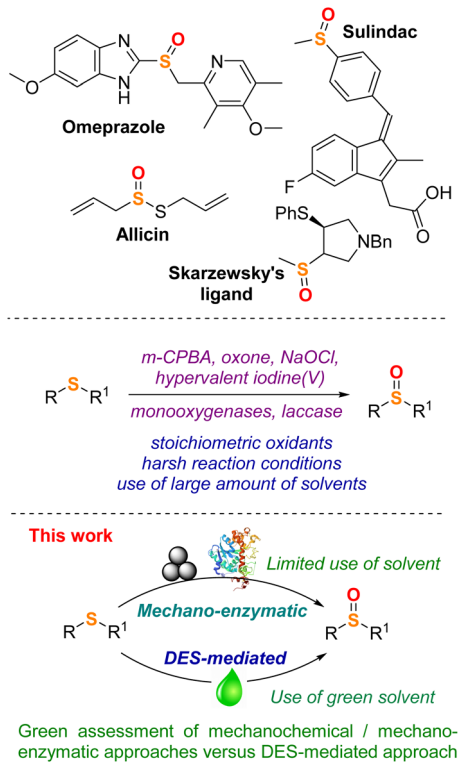


Fig. 1 Examples of sulfoxidation methods and aim of the work.

In an effort to further explore greener and more sustainable synthetic approaches that minimize the production of chemical waste and reduce the use of strong oxidant reagents and petroleum-based solvents, while maintaining high efficiency and selectivity, herein we report the development and evaluation of new sulfoxidation methodologies that integrate biocatalysis with mechanochemistry and deep eutectic solvents (DESs).

Mechanochemistry is a green and low-cost technology that uses mechanical energy to initiate chemical reactions, and it has gained increasing attention as a solvent-free and energy-efficient alternative to conventional synthetic methods.[20]

Ball milling and other mechanochemical techniques offer enhanced reaction rates and selectivity while reducing or eliminating the need for volatile organic solvents. However, despite its potential, mechanochemical sulfoxidation reactions remain poorly explored. A few attempts to combine mechanochemistry with biocatalysis into greener mechano-enzymatic reactions have been recently described for the deracemization of alcohols and amines, the synthesis of the drug ketorolac, the cleavage of sugars and lignin, or polyester polymerization,[21] and they have demonstrated the possibility to carry out enzymatic transformations also in the absence or with minimal amounts of solvents.

In parallel, DESs have also emerged as attractive green reaction media due to their low toxicity and high biodegradability.[22] DESs represent cheap and environmentally friendly alternatives to conventional organic solvents and ionic liquids, and they have recently found wide application in organic synthesis. Examples of biocatalytic reactions carried out in DESs have also been recently described,[23,16b] demonstrating the versatility of such solvents and their compatibility with enzymes.

Following up our recent work on the oxidation of sulfides employing CALB and urea hydrogen peroxide (UHP) in AcOEt solution,[17] herein we present a novel approach that introduces a completely different energy source driven by mechanochemistry, while enhancing sustainability through the use of the CALB biocatalyst and deep eutectic solvent (DES) in sulfoxidation reactions. In particular, the possibility to perform CALB biocatalysed reactions using minimal amounts of AcOEt as organic solvent or to replace AcOEt with DESs was investigated.

Results and discussion

Development and optimization of mechanochemical sulfoxidation reactions

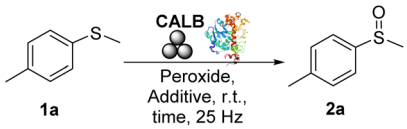
In our previous work, we described the synthesis of sulfoxides using CALB and UHP in AcOEt, which played the dual role of solvent and substrate for CALB to be converted *in situ* into the oxidant peroxyacid AcOOH (Table 1, entry 1).[17] First, the possibility to carry out the same CALB-mediated sulfoxidation reaction using a minimal amount of AcOEt under mechanochemical conditions was investigated. The model substrate methyl *p*-tolyl sulfide **1a** was placed in a 10 mL jar containing 3 × 5 mm balls and reacted in a mill mixer at 25 Hz with 1 eq. of UHP, 10 eq. of AcOEt and 20% w/w CALB. After 2 hours, the desired sulfoxide product **2a** was formed in 98% conversion as detected by GC-MS analysis (Table 1, entry 2). A $\eta = 9.1$ parameter was calculated for the reaction, indicating that under such conditions (10 eq. of AcOEt), the transformation must still be considered a solution rather than a mechanochemical reaction.[24] The same reaction was then carried out using a lower amount of AcOEt. When 5 eq. of AcOEt were used, the sulfoxide **2a** was formed with high 95% conversion, while in the presence of only 1 eq. of AcOEt, **2a** was obtained with 83% conversion (Table 1, entries 4 and 5).

With 5 eq. of AcOEt, the reaction resulted in a slurry mixture ($\eta = 5.1$), similar to that with 1 eq. of AcOEt, even though with a lower $\eta = 1.9$. The increase in milling time was found to be beneficial, and the ideal reaction conditions were found at 4 hours using 1 eq. UHP and 5 eq. of AcOEt (Table 1, entries 6–8). When the reaction was carried out using a lower shaking frequency (15 Hz), lower conversion (94%) was obtained (Table 1, entry 9). Thus, we selected the frequency of 25 Hz as it provided a balance between reaction reproducibility while avoiding higher milling intensities on the CALB enzyme.

Blank experiments without UHP, AcOEt and CALB were carried out, confirming that the reaction was promoted by CALB, which catalysed the conversion of AcOEt into the peroxyacid AcOOH (Scheme 1a and Table 1, entries 10–12). When used alone, the oxidant UHP was in fact able to form the sulfoxide **2a** only in low conversion (9%).

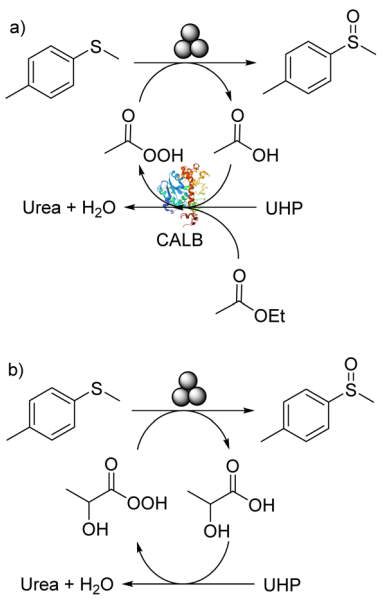
Since organic carboxylic acids are also known to be substrates of CALB, we decided to explore the possibility of replacing AcOEt with D,L-lactic acid (LacOH). Lactic acid can be

Table 1 Optimization of the reaction conditions for the mechanoenzymatic and mechanochemical synthesis of sulfoxide **2a**



Entry	CAL-B (%W/W)	Peroxide (1 equiv.)	Additive (equiv.)	Time	Conv.[a] (%)	Ball milling conditions[b] (η)
1	20	UHP	AcOEt (46 eq.)	2 h	99	Solution
2	20	UHP	AcOEt (10 eq.)	2 h	98	Solution ($\eta = 9.1$)
3	—	UHP	AcOEt (10 eq.)	2 h	2	Solution ($\eta = 11.8$)
4	20	UHP	AcOEt (5 eq.)	2 h	95	Slurry ($\eta = 5.1$)
5	20	UHP	AcOEt (1 eq.)	2 h	83	Slurry ($\eta = 1.9$)
6	20	UHP	AcOEt (5 eq.)	3 h	96	Slurry ($\eta = 5.1$)
7	20	UHP	AcOEt (1 eq.)	3 h	85	Slurry ($\eta = 1.9$)
8	**20**	**UHP**	**AcOEt (5 eq.)**	**4 h**	**98**	**Slurry ($\eta = 5.1$)**
9	20	UHP	AcOEt (5 eq.)	4 h	94[c]	Slurry ($\eta = 5.1$)
10	20	—	AcOEt (5 eq.)	4 h	ND[d]	ND[d]
11	—	UHP	—	4 h	9	ND[d]
12	—	—	AcOEt (5 eq.)	4 h	ND[d]	ND[d]
13	20	UHP	Lactic acid[e] (5 eq.)	4 h	>99	Slurry ($\eta = 4.1$)
14	—	UHP	Lactic acid[e] (5 eq.)	4 h	>99	Slurry ($\eta = 5.3$)
15	—	**UHP**	**Lactic acid[e](1 eq.)**	**4 h**	**>99**	Slurry ($\eta = 2.2$)
16	—	—	Lactic acid[e] (1 eq.)	4 h	ND[d]	—

[a] Determined by GC-MS analysis of the crude mixture. [b] Calculated as μL of liquid per mg of solid used. The sulfide **1a** is a liquid, and thus it has been considered as such in the calculation of the η value. [c] The reaction was carried out at 15 Hz frequency. [d] ND: sulfoxide product was not detected by GC-MS analysis. [e] Racemic D,L-lactic acid (LacOH) was used. D,L-LacOH is liquid at room temperature and thus it has been considered as such in the calculation of the η value.



Scheme 1 Reaction mechanisms for the mechano-enzymatic (a) and mechanochemical (b) sulfoxidation of **1a**.

obtained from renewable resources such as glucose or biomass through fermentation. It is considered a green bio-based solvent, and thus it was selected as a more sustainable and greener alternative to AcOEt.[25]

The sulfide **1a** was then reacted with 5 eq. of LacOH, 1 eq. of UHP and CALB 20% w/w under mechanochemical milling, affording **2a** with excellent >99% conversion after 4 h (Table 1, entry 13). Interestingly, the same conversion was observed when the reaction was carried out without CALB under identical mechanochemical conditions as well as with only 1 eq. of LacOH (slurry conditions) and no CALB (Table 1, entries 14 and 15). However, a blank experiment confirmed that LacOH alone was unable to promote the oxidation of **1a** and that the formation of **2a** was due to the combined action of both LacOH and UHP (Table 1, entry 16). It is evident that, differently from AcOEt, LacOH reacted with UHP and was converted into the oxidant peroxyacid LacOOH without the need of the CALB catalyst (Scheme 1b). Titration experiments confirmed the conversion of LacOH into LacOOH when reacted with UHP (Fig. S1†).

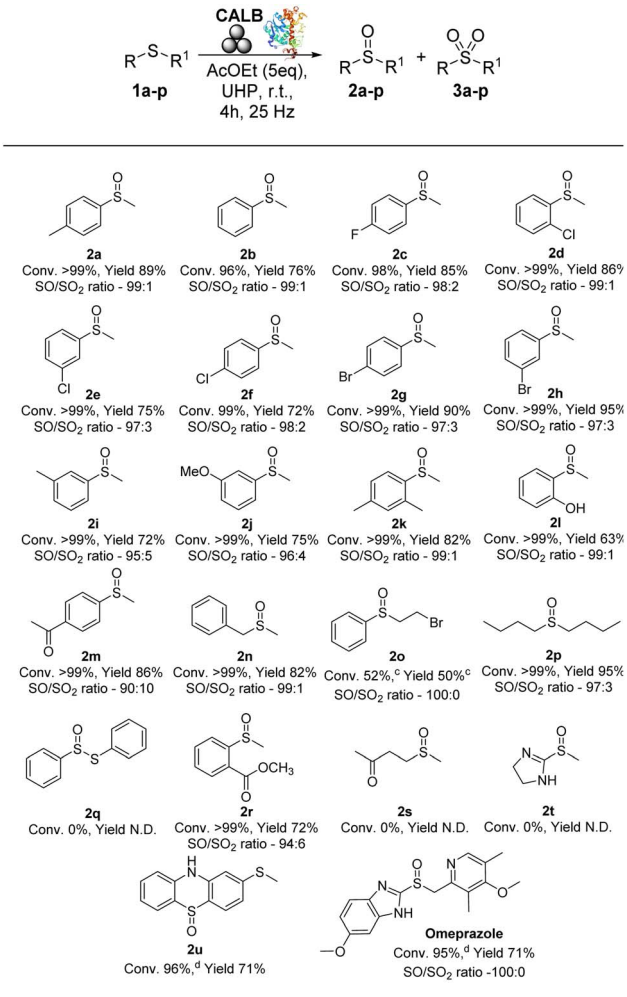
Two approaches for the sulfoxidation **1a** were thus identified, namely the mechano-enzymatic sulfoxidation using UHP, CALB and AcOEt, and the mechanochemical sulfoxidation using LacOH and UHP (Scheme 1). It should be noted that the data in Table 1 are based on single measurements without experimental repeats. Therefore, the small differences in conversion and yield observed between several entries should be interpreted as indicative rather than statistically significant. The selection of optimal conditions was guided by overall high conversions, minimal reagent use, mixing regime (η), and the mechanistic and catalytic role of CALB or LacOH in generating the active oxidant species.

The substrate scope of both methods was then explored.

Mechano-enzymatic sulfoxidation reactions

When the sulfoxidation reaction was carried out under mechano-enzymatic conditions, excellent conversions and high isolated yields were observed for most of the sulfide substrates **1a–p** (Table 2). The phenyl-methylsulfoxide **2b** was obtained with high 76% yield, and, remarkably, only a minimal amount of the sulfone by-product **3b** was observed by GC-MS analysis. The aryl-methylsulfoxides **2c–h**, bearing a halogen on the aromatic ring, were all formed with excellent conversion and high yields. In particular, the bromine derivatives **2g** and **2h** were obtained with 90% and 95% isolated yields, respectively. In all cases, low amounts of sulfone by-products **3c–h** were observed. A similar trend was observed for the derivatives **2i–k**, which were isolated in high yields (72% to 82%), as well as for sulfoxide **2n** bearing a benzyl group attached to the sulfur atom. The *o*-OH-substituted sulfoxide **2l** was formed with excellent conversion (>99%), as monitored by GC-MS, but it was isolated with low 63% yield, due to work-up extraction problems. The acetyl-phenyl sulfoxide **2m** was obtained in high yields, but together with a higher amount of the sulfone by-product **3m**. While a slightly lower conversion was observed for **2o** (92%), the di-butyl sulfoxide **2p** was obtained with remarkably high isolated yield (95%) and high sulfoxide/sulfone ratio. The bulkier sulfoxide **2r**, bearing an ester group at the phenyl *ortho* position, was obtained with excellent conversion (99%) and yield (72%) but with a lower 94 : 6 sulfoxide/sulfone ratio. Interestingly, no formation of sulfoxides **2q**, **2s** and **2t** was observed, while the 2-methylthiophenothiazine sulfoxide **2u** was obtained with high conversion (96%) and yield (71%). The analysis of the ^{13}C NMR spectrum of **2u** showed a peak at 14.5 ppm, indicating that the oxidation occurred at the sulfur on the phenothiazine ring rather than on the thiomethyl group at position 2. Finally, the mechano-enzymatic method was used for the synthesis of omeprazole from the corresponding sulfide precursor.

Table 2 Substrate scope of the mechanoenzymatic sulfoxidation of **1a–p**[a,b]



[a] Determined by GC-MS analysis of the crude mixture. [b] Isolated yields are reported. Isolated yields refer to the purified sulfoxides. [c] The phenyl vinyl sulfoxide side product arising from the elimination of bromine was formed with 39% conversion, together with **2o** (conv. 52%) and unreacted **1o** (9%). [d] Calculated by ^{1}H-NMR analysis.

Omeprazole was obtained with high conversion (95%) and isolated yields (71%) and, remarkably, no sulfone by-product was observed by GC-MS analysis. The mechano-enzymatic method clearly proved to be very efficient in the preparation of sulfoxides, and, even if slurry conditions were used, the method allows saving a large amount of AcOEt solvent when compared to the classic methodology in solution.

With a view to further expand the scope of the mechano-enzymatic reaction, the Baeyer–Villiger oxidation of cyclic ketones **4a–c** and the epoxidation of alkene substrates **6a–f** were also investigated (Table 3).[26,27] Under the ideal mechano-enzymatic conditions, only cyclobutanone was oxidised into the corresponding γ-lactone **5a**, while low conversions of δ-lactone **5b** and ε-caprolactone **5c** were observed. On the other hand, better conversions were obtained when the menchano-enzymatic methodology was employed for the epoxidation of alkenes **6a–f**.

While styrene was poorly converted into the corresponding epoxide **7a**, good conversions were observed for the di-substituted alkene substrates **7b** and **7c**. The cyclic alkenes **6e** and **6f** were also found to be reactive under the mechano-enzymatic conditions, and they were converted into the epoxides **7e** and **7f** with good isolated yields.

Mechanochemical sulfoxidation reactions

When the sulfoxidation reaction was carried out under mechanochemical conditions using the LacOH/UHP system, slightly lower conversions were observed than those observed on the same sulfides **1** using the mechano-enzymatic method (Table 4).

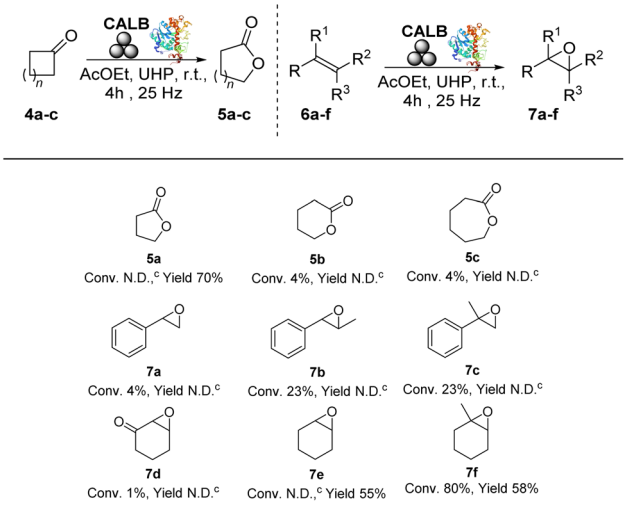
All sulfoxides were formed with similar high conversions (91–98%) and isolated yields (72–85%). The fluoro derivative **2c** showed the best yield, as well as full selectivity in the formation of the sulfoxide *versus* the sulfone by-product **3c**. Excellent sulfoxide/sulfone selectivity was also observed for the compounds **2d** and **2j**. The aliphatic di-butyl-sulfoxide **2p** was also formed with excellent conversion (>99%), yield (91%) and no formation of sulfone by-product **3p**.

Sulfoxidation reactions in DES media

Following up on the results obtained under mechanochemical conditions, we decided to investigate the sulfoxidation of sulfide **1a** in LacOH-based DES media (Table 5). The sulfide **1a** was first dissolved in a 1 : 2 choline chloride (ChCl)/LacOH DES, and treated with UHP and CALB (20% w/w). The mixture was heated at 37 °C for 16 hours, affording the desired sulfoxide **2a** with excellent conversion (>99%, Table 5, entry 1).

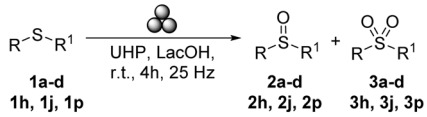
Unsurprisingly, the same conversion (>99%) was also obtained without CALB (Table 5, entry 2). As observed with mechanochemical reactions, LacOH, other than being one of the DES components, can react with UHP to provide the oxidant peroxyacid LacOOH, as confirmed by titration experiments (Scheme 1b and Fig. S2†). When the DES-mediated reaction was carried out at room temperature, the sulfoxide **2a** was obtained with a slightly lower conversion (95%, Table 5, entry 4). Interestingly, when the DES was replaced with Et_2O as the solvent, no formation of **2a** was observed, confirming that UHP alone is unable to promote the sulfoxidation of **1a** (Table 5, entry 5). In contrast, when LacOH was added to a solution of **1a** and UHP (1 eq.) in Et_2O at 37 °C, with or without CALB, the sulfoxide **2a** was obtained in variable amounts (Table 5, entries 6–11). When 10 eq. of LacOH were used, high conversions of **2a** were observed (80%), even if lower than those obtained in DES (entry 7). The presence of CALB slightly improved the reaction conversion to 88%, but it was not essential in the formation of **2a** (entry 6). Moreover, reducing the amount of LacOH to 1 eq., led to the formation of **2a** with lower conversions (20% without CALB, and

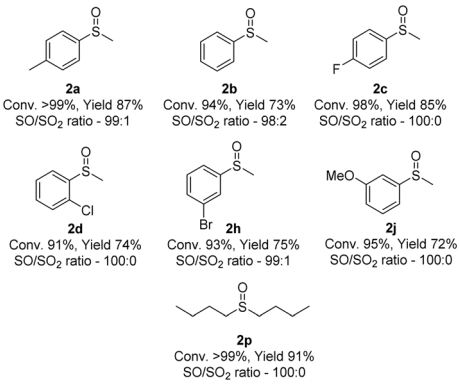
Table 3 Mechano-enzymatic oxidation of ketones **4a–c** and alkenes **6a–f**[a,b]



[a] Determined by GC-MS analysis of the crude mixture. [b] Isolated yields are reported. Isolated yields refer to the purified sulfoxides. [c] Not determined.

Table 4 Mechanochemical synthesis of sulfoxides **2** mediated by LacOH[a,b]



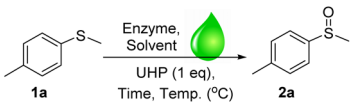


[a] Determined by GC-MS analysis of the crude mixture. [b] Isolated yields are reported. Isolated yields refer to the purified sulfoxides.

40% with CALB, entries 8 and 9). The reduction of the reaction temperature also proved to be detrimental for the reaction (entries 10 and 11). Finally, the sulfoxidation of **1a** in different DES media was investigated. Low conversions of **2a** were observed (20% and 16%, with and without CALB, respectively), in a 2 : 1 ChCl/citric acid (CitOH) DES (Table 5, entries 12 and 13), while no formation of **2a** was detected when a 1 : 3 ChCl/octanoic acid (OctOH) DES was used (Table 5, entries 14 and 15). Interestingly, when a 2 : 1 DES of O-methyl-lactic acid (MeO-LacOH)/ChCl was used, **1a** was fully converted into **2a** at 37 °C after 16 hours (Table 5, entry 16), while low conversion (30%) was observed when 1 eq. of MeO-LacOH was reacted with UHP in Et_2O solution (Table 5, entry 17).

Once the ideal conditions for the DES-mediated sulfoxidation were found (1 eq. UHP, 1 : 2 ChCl : LacOH DES, 37 °C, 16 hours), the substrate scope of the reaction was investigated (Table 6). Excellent conversions were obtained for all the

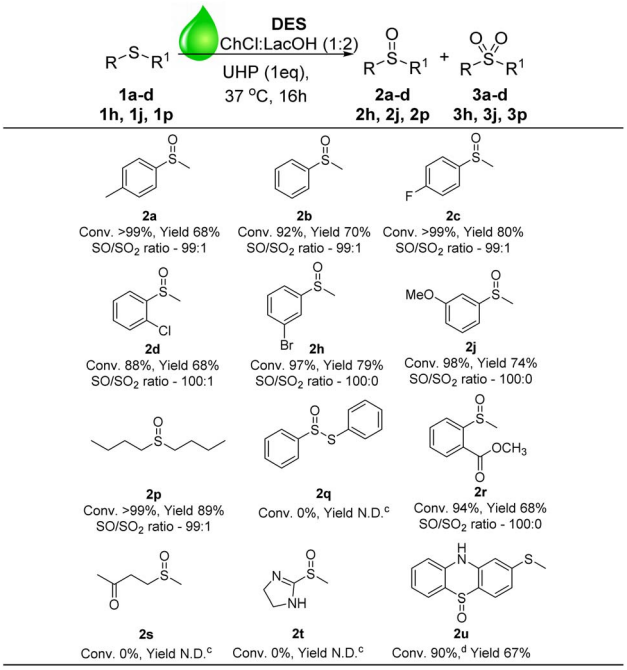
Table 5 Optimization of the DES-mediated sulfoxidation of **1a**



Entry	CALB (%W/W)	Solvent	Temp.	Time	Conv.[a] (%)
1	20	ChCl : LacOH 1 : 2	37 °C	16 h	>99
2	**—**	**ChCl : LacOH 1 : 2**	**37 °C**	**16 h**	**>99**
3[c]	—	ChCl : LacOH 1 : 2	37 °C	16 h	ND[b]
4	—	ChCl : LacOH 1 : 2	rt	16 h	95
5	—	Et_2O	37 °C	16 h	ND[b]
6	20	LacOH (10 eq.) in Et_2O	37 °C	16 h	88
7	—	LacOH (10 eq.) in Et_2O	37 °C	16 h	80
8	20	LacOH (1 eq.) in Et_2O	37 °C	16 h	40
9	—	LacOH (1 eq.) in Et_2O	37 °C	16 h	20
10	20	LacOH (1 eq.) in Et_2O	rt	2 h	5
11	—	LacOH (1 eq.) in Et_2O	rt	2 h	5
12	20	ChCl : CitOH 2 : 1	37 °C	16 h	20
13	—	ChCl : CitOH 2 : 1	37 °C	16 h	16
14	20	ChCl : OctOH 1 : 3	37 °C	16 h	ND[b]
15	—	ChCl : OctOH 1 : 3	37 °C	16 h	ND[b]
16	—	ChCl : MeO-LacOH 1 : 2	37 °C	16 h	>99
17	—	MeO-LacOH (1 eq.) in Et_2O	37 °C	16 h	30

[a] Determined by GC-MS analysis of the crude mixture after work-up. [b] Not determined. [c] No UHP was used.

Table 6 Substrate scope of the oxidation of sulfides **1** mediated by DES (ChCl : LacOH)[a,b]



[a] Determined by GC-MS analysis of the crude mixture. [b] Isolated yields are reported. Isolated yields refer to the pure sulfoxides. [c] Not determined. [d] Calculated by ^{1}H-NMR analysis.

substrates, and sulfoxides **2a–d**, **2g**, **2j** and **2p** were formed in good to high yields.

In general, the isolated yields observed in DES were lower than those obtained under mechanochemical conditions. This is partly due to the difficulties associated with the extraction of the sulfoxide products from the DES during the work-up of the reaction. This was confirmed by the GC-MS analysis of the DES recovered from the reaction of **1a**, which revealed the presence of **2a** in the DES also after several extractions with AcOEt (Fig. S5†). Remarkably, all the sulfoxides were formed as the only oxidation products or with negligible amounts of the sulfone side products **3**.

Finally, the DES-mediated oxidation of cyclohexanone and styrene was also attempted, but in both cases, the oxidation products were not formed (Tables S6 and S7†).

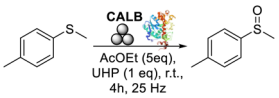
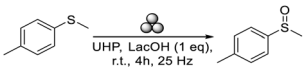
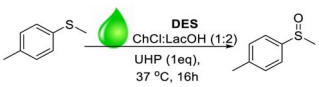
Green assessment

The green metrics of **2a** with the three sulfoxidation methodologies developed in this study were finally analysed (Table 7).[28] Since the work-up protocols and purification of the crude mixtures by column chromatography were identical across all three methods, the mass of chemicals and solvents used in these steps was omitted from the calculation of the *E*-factor and the generalised RME. This decision reflects the objective of the study, which was to develop and compare synthetic methodologies under controlled conditions, rather than to optimise full process-scale workflows. However, the purification process, particularly silica gel chromatography and associated solvent use, can have a significant impact on green metrics, especially the *E*-factor. Preliminary estimations show that inclusion of this step in the calculation of green metrics can increase the *E*-factor by up to two orders of magnitude. This highlights the importance of purification strategy optimisation for future scale-up, where greener alternatives such as crystallisation, supercritical fluid chromatography or solvent-free techniques could substantially reduce the environmental footprint. Nonetheless, for the purpose of methodology comparison, excluding these identical purification steps allows for a clearer and more meaningful evaluation of the reaction conditions themselves.

As previously discussed, the lower yield observed for **2a** in the DES-mediated method may be ascribable to the difficulties associated with the extraction of the sulfoxide products from the DES media. While parameters such as the reaction mass efficiency, both Curzons RME (RME_c) and Kernel RME (RME_k), are similar for the mechano-enzymatic and mechanochemical methods, a larger difference emerges from the generalised RME (RME_g) value. This is strictly related to the amount of AcOEt used in the mechano-enzymatic procedure (5 eq.), significantly higher than the LacOH (1 eq.) used in the mechanochemical method. This also reflects the higher *E*-factor observed for the mechano-enzymatic reaction (4.1) *versus* the excellent value (1.4) observed with the mechanochemical one. In general, the metrics calculated for the DES-mediated transformations were lower than those of the mechanochemistry reactions, due to the use of the solvent (the DES).

Attempts to recycle the DES were carried out. The sulfide **1a** (152 mg) was reacted with UHP in 5 mL of 1 : 2 ChCl : LacOH DES, affording **2a** with >99% conversion. At the end of the

Table 7 Green metrics for the mechano-enzymatic, mechanochemical and DES-mediated sulfoxidation reactions

	Mechanoenzymatic	Mechanochemical	DES-mediated
			
Sulfide **1a**	30.4 mg (0.22 mmol)	30.4 mg (0.22 mmol)	30.4 mg (0.22 mmol)
Sulfoxide **2a**	30.2 mg (0.20 mmol)	29.3 mg (0.19 mmol)	23.1 mg (0.15 mmol)
UHP	20.7 mg (0.22 mmol)	20.7 mg (0.22 mmol)	20.7 mg (0.22 mmol)
AcOEt	96.9 mg (1.1 mmol)	—	—
CALB	6 mg	—	—
D,L-LacOH	—	19.8 mg	
DES[a]	—	—	1 mL = 1.16 g
Yield	0.89	0.87	0.68
Atom economy	0.66	0.66	0.66
E-Factor[b]	4.1 (3.9)[e]	1.4	51.4 (4.1)[f]
RME_c	0.59	0.57	0.45
RME_k	0.59	0.57	0.45
RME_g[c]	0.20	0.41	0.019
1/SF	1	1	1
MRP	0.33	0.72	0.042
EcoScale[d]	71	69	50

[a] The mass of 1 mL of DES was empirically measured. [b] No mass from the work-up and the purification steps were included in the calculation of the *E*-factor. [c] No mass from the work-up and the purification steps were included in the calculation of the RME_g. [d] Calculated using the online calculator available at **https://ecoscale.cheminfo.org/**. [e] CALB was not included in the calculation of the *E*-factor. [f] Calculated taking into account the recycling of DES solvent.

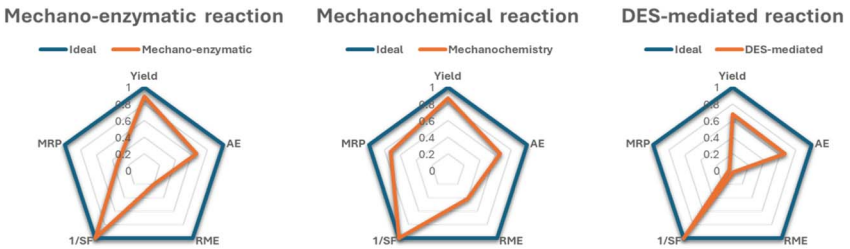


Fig. 2 Radial pentagon representations of the green profiles for the three sulfoxidation methods.

reaction, 4 mL of DES were recovered in the work-up through solvent extraction and reused in a new sulfoxidation reaction. The *E*-factor of the DES-mediated reaction was recalculated taking into account the recycled DES and was found to be 4.1, close to that calculated for the mechano-enzymatic reaction. However, in general, the DES-mediated reaction shows lower green metrics for **2a** than the mechanochemical approaches. The green profile of each method is presented in the radial pentagons in Fig. 2.

Finally, the EcoScale parameter of **2a** was calculated for the three methodologies, showing high similarity for the mechanochemical approaches.[29]

Additional green metrics for a representative range of substrates (**2b**, **2c**, **2d**, **2h**, **2j**, and **2p**) under all three methods are also provided in the ESI (Tables S1–S3),† confirming the generality of the observed trends for **2a**.

Overall, the mechano-enzymatic and the mechanochemical approaches show the best green profile, with the latter presenting the best parameters in terms of mass consumption and waste production.

Conclusions

In conclusion, this work describes three complementary approaches for the selective oxidation of sulfide substrates into sulfoxides under green chemistry conditions. Building upon our previously reported solution-phase method using AcOEt as solvent,[17] we developed a mechano-enzymatic protocol showing that the CALB biocatalysed transformations can be performed under mechanochemical conditions using only limited amounts of AcOEt. This approach results in an *E*-factor of 4.1, tenfold lower than our earlier method, highlighting its improved sustainability.

A second method using LacOH and UHP under solvent-free mechanochemical conditions revealed that LacOH can generate the oxidant species LacOOH *in situ* without the need

for an enzyme catalyst. Finally, a third sulfoxidation protocol was developed using a recyclable LacOH-based deep eutectic solvent (2 : 1 LacOH : ChCl). The analysis of the green metrics indicates that these new methods, particularly the LacOH/UHP mechanochemical approach, demonstrate notable improvements in *E*-factor and RME compared to our previous solution-based protocol (Table S4†).[17] These results underscore the potential of integrating mechanochemistry, biocatalysis, and green solvents to advance more sustainable sulfoxidation strategies and represent promising options that offer potential for future study and improvement.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

AC: synthesis of substrates, methodology development, compound characterization, data curation, writing and review; CL: methodology development, analysis and characterization of compounds; MC: analysis of compounds, GC-MS method development, supervision; NM: supervision, resources, review; DC: conceptualization, project administration, supervision, resources, writing and review

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the China Scholarship Council (CSC, scholarship no. 202108310078) for the PhD studentship to CL. AC and NM acknowledge the Ministry of Higher Education and Scientific Research of Algeria (grant number 49/2023) for financial support to AC during her stay at UCL.

Notes and references

1 (*a*) J. Han, V. A. Soloshonok, K. D. Klika, J. Drabowicz and A. Wzorek, *Chem. Soc. Rev.*, 2018, **47**, 1307–1350; (*b*) S. Anselmi, N. Aggarwal, T. S. Moody and D. Castagnolo, *ChemBioChem*, 2021, **22**, 298–307; (*c*) D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**, 8701–8780; (*d*) E. Wojaczyńska and J. Wojaczyński, *Curr. Opin. Chem. Biol.*, 2023, **76**, 102340; (*e*) X. Yu, Y. Liu, Y. Li and Q. Wang, *J. Agric. Food Chem.*, 2016, **64**(15), 3034–3040.
2 M. J. Kendall, *Aliment. Pharmacol. Ther.*, 2003, **17**, 1–4.
3 C. J. Loland, M. Mereu, O. M. Okunola, J. Cao, T. E. Prisinzano, S. Mazier, T. Kopajtic, L. Shi, J. L. Katz, G. Tanda and A. Hauck Newman, *Biol. Psychiatry*, 2012, **72**, 405–413.
4 D. Y. Graham, J. L. Smith, G. I. Holmes and R. O. Davies, *Clin. Pharmacol. Ther.*, 1985, **38**, 65–70.
5 A. Harunobu, *J. Nutr.*, 2006, **136**, 716S–725S.
6 E. Block, S. Ahmad, M. K. Jain, R. W. Crecely, R. Apitz-Castro and M. R. Cruz, *J. Am. Chem. Soc.*, 1984, **106**, 8295–8296.
7 T. Nohara, Y. Fujiwara, T. Ikeda, K. Murakami, M. Ono, D. Nakano and J. Kinjo, *Chem. Pharm. Bull.*, 2013, **61**, 695–699.
8 G. Sipos, E. E. Drinkel and R. Dorta, *Chem. Soc. Rev.*, 2015, **44**, 3834–3860.
9 (*a*) F. Silva, A. Baker, J. Stansall, W. Michalska, M. Yusubov, M. Graz, R. Saunders, G. J. S. Evans and T. Wirth, *Eur. J. Org Chem.*, 2018, **18**, 2134–2137; (*b*) J. Berry, T. K. Lindhorst and G. Despras, *Chem.–Eur. J.*, 2022, **28**, e202200354.
10 B. Yu, A.-H. Liu, L.-N. He, B. Li, Z.-F. Diao and Y.-N. Li, *Green Chem.*, 2012, **14**, 957–962.
11 (*a*) M. M. Khodaei, K. Bahrami and A. Karimi, *Synthesis*, 2008, 1682–1684; (*b*) M. Matteucci, G. Bhalay and M. Bradley, *Org. Lett.*, 2003, **5**, 235–237; (*c*) M. Mba, L. J. Prins and G. Licini, *Org. Lett.*, 2007, **9**, 21–24; (*d*) H. Egami and T. Katsuki, *J. Am. Chem. Soc.*, 2007, **129**, 8940–8941.
12 T. Okada, H. Matsumuro, S. Kitagawa, T. Iwai, K. Yamazaki, Y. Kinoshita, Y. Kimura and M. Kirihara, *Synlett*, 2015, **26**, 2547–2552.
13 (*a*) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 282–284; (*b*) W. Qian and L. Pei, *Synlett*, 2006, 709–712; (*c*) H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa and Y. Kita, *J. Org. Chem.*, 1999, **64**, 3519–3523; (*d*) E. Avramidou, A. K. Triandafyllou, S. A. Zisopoulou, N. A. Stini, V. P. Demertzidou, C. G. Kokotos, P. L. Gkizis and J. K. Gallos, *Eur. J. Org Chem.*, 2024, **27**, e202400596.
14 (*a*) E. Voutyritsa, I. Triandafillidi and C. G. Kokotos, *Synthesis*, 2017, **49**, 917–924; (*b*) F. Gelat, J. Jayashankaran, J.-F. Lohier, A.-C. Gaumont and S. Perrio, *Org. Lett.*, 2011, **13**, 3170–3173; (*c*) S. C. Davidson, G. dos Passos Gomes, L. R. Kuhn, I. V. Alabugin, A. R. Kennedy and N. C. O. Tomkinson, *Tetrahedron*, 2021, **78**, 131784.
15 (*a*) E. Skolia, P. L. Gkizis, N. F. Nikitasa and C. G. Kokotos, *Green Chem.*, 2022, **24**, 4108–4118; (*b*) J. Park, S. H. Kim, J.-Y. Cho, S. R. Atriardi, J.-Y. Kim, H. Mardhiyah, B. Y. Park and S. K. Woo, *Green Chem.*, 2025, **27**, 3284–3292; (*c*) S. Bierbaumer, L. Schmermund, A. List, C. K. Winkler, S. M. Glueck and W. Kroutil, *Angew. Chem., Int. Ed.*, 2022, **61**, e202117103; (*d*) C. K. Spyropoulou, E. Skolia, D. F. Flesariu, G. A. Zissimou, P. L. Gkizis, I. Triandafillidi, M. Athanasiou, G. Itskos, P. A. Koutentis and C. G. Kokotos, *Adv. Synth. Catal.*, 2023, **365**, 2643–2650.
16 (*a*) Y. Song, Y. Wang, B. Pan, X. Cheng, J. Yang and Y. Chen, *Asian J. Org. Chem.*, 2025, e202400708; (*b*) G. de Gonzalo, *Sustainable Chem.*, 2020, **1**, 290–297; (*c*) G. de Gonzalo and A. Franconetti, *Enzyme Microb. Technol.*, 2018, **113**, 24–28; (*d*) G. de Gonzalo, M. J. L. J. Fürst and M. W. Fraaije, *Catalysts*, 2017, **7**, 1–10; (*e*) T. Gul, M. Krzek, H. P. Permentier, M. W. Fraaije and R. Bischoff, *Drug Metab. Dispos.*, 2016, **44**, 1270–1276; (*f*) A. Rioz-Martínez, G. de Gonzalo, D. E. T. Pazmiño, M. W. Fraaije and V. Gotor, *Eur. J. Org Chem.*, 2010, 6409–6416; (*g*) M. J. L. J. Fürst, A. Gran-Scheuch, F. S. Aalbers and

M. W. Fraaije, *ACS Catal.*, 2019, **9**, 11207–11241; (*h*) T. Heine, A. Scholtissek, A. Hofmann, R. Koch and D. Tischler, *ChemCatChem*, 2020, **12**, 199–209; (*i*) I. Bassanini, E. E. Ferrandi, M. Vanoni, G. Ottolina, S. Riva, M. Crotti, E. Brenna and D. Monti, *Eur. J. Org Chem.*, 2017, 7186–7189; (*j*) Y. Li, Y. Ma, P. Li, X. Zhang, D. Ribitsch, M. Alcalde, F. Hollmann and Y. Wang, *ChemPlusChem*, 2020, **85**, 254–257.

17 S. Anselmi, S. Liu, S.-H. Kim, S. M. Barry, T. S. Moody and D. Castagnolo, *Org. Biomol. Chem.*, 2021, **19**, 156–161.

18 J. Wu, S. Anselmi, A. T. P. Carvalho, J. Caswell, D. J. Quinn, T. S. Moody and D. Castagnolo, *Green Chem.*, 2024, **26**, 8685–8693.

19 S. Anselmi, A. T. P. Carvalho, A. Serrano-Sanchez, J. L. Ortega-Roldan, J. Caswell, I. Omar, G. Perez-Ortiz, S. M. Barry, T. S. Moody and D. Castagnolo, *ACS Catal.*, 2023, **23**, 4742–4751.

20 (*a*) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094; (*b*) K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145–2162; (*c*) N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García and E. Colacino, *Chem. Soc. Rev.*, 2023, **52**, 6680–6714; (*d*) F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocci and A. Porcheddu, *ChemSusChem*, 2022, **15**, e202200362; (*e*) F. Basoccu, L. De Luca and A. Porcheddu, *Eur. J. Org Chem.*, 2024, **27**, e202400425.

21 (*a*) M. Pérez-Venegas and E. Juaristi, *ACS Sustainable Chem. Eng.*, 2020, **8**, 8881–8893; (*b*) E. M. Carter, E. Ambrose-Dempster, J. M. Ward, T. D. Sheppard and H. C. Hailes, *Green Chem.*, 2022, **24**, 3662–3666; (*c*) J. G. Hernández, M. Frings and C. Bolm, *ChemCatChem*, 2016, **8**, 1769–1772; (*d*) M. Pérez-Venegas, A. M. Rodríguez-Treviño and E. Juaristi, *ChemCatChem*, 2020, **12**, 1782–1788; (*e*) F. Hammerer, S. Ostadjoo, T. Friščić and K. Auclair, *ChemSusChem*, 2020, **13**, 106–110; (*f*) U. Weißbach, S. Dabral, L. Konnert, C. Bolm and J. G. Hernández, *Beilstein J. Org. Chem.*, 2017, **13**, 1788–1795; (*g*) A. Rios-Echeverri, C. E. Puerto Galvis, K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2025, e202402446; (*h*) S. Spinella, M. Ganesh, G. Lo Re, S. Zhang, J.-M. Raquez, P. Dubois and R. A. Gross, *Green Chem.*, 2015, **17**, 4146–4150.

22 (*a*) B. B. Hansen, S. Spittle, B. Chen, D. Poe, Y. Zhang, J. M. Klein, A. Horton, L. Adhikari, T. Zelovich, B. W. Doherty, B. Gurkan, E. J. Maginn, A. Ragauskas, M. Dadmun, T. A. Zawodzinski, G. A. Baker, M. E. Tuckerman, R. F. Savinell and J. R. Sangoro, *Chem. Rev.*, 2021, **121**, 1232–1285; (*b*) Q. Zaib, M. J. Eckelman, Y. Yang and D. Kyung, *Green Chem.*, 2022, **24**, 7924–7930; (*c*) E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 11060–11082.

23 (*a*) M. Pätzold, S. Siebenhaller, S. Kara, A. Liese, C. Syldatk and D. Holtmann, *Trends Biotechnol.*, 2019, **37**, 943–959; (*b*) C. E. Paul and V. Gotor-Fernández, Applied biocatalysis in deep eutectic solvents, in *Biocatalysis in Green Solvents*, ed. P. Lozano, Academic Press, 2022, ch. 16, pp. 467–510; (*c*) N. Zhang, P. Domínguez de María and S. Kara, *Catalysts*, 2024, **14**, 84.

24 L. E. Wenger and T. P. Hanusa, *Chem. Commun.*, 2023, **59**, 14210–14222.

25 Y. Jie, J. N. Tan and Y. Gu, *Green Chem.*, 2012, **14**, 3304–3317.

26 P. Zhou, X. Wang, B. Yang, F. Hollmann and Y. Wang, *RSC Adv.*, 2017, **7**, 12518–12523.

27 A. Drożdż, K. Erfurt, R. Bielas and A. Chrobok, *New J. Chem.*, 2015, **39**, 1315–1321.

28 A. Bardow, J. Pérez-Ramírez, S. Sala and L. Vaccaro, *Green Chem.*, 2024, **26**, 11016–11018.

29 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3.