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Oxidation of *N*-trifluoromethylthio sulfoximines using $NaOCl{\cdot}5H_2O$†

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N-Trifluoromethylthio sulfoximines are biologically interesting compounds, but their potential is still poorly understood. The oxidation of *N*-trifluoromethylthio sulfoximines led to their corresponding sulfoxide derivatives as a new class of compounds, when using sodium hypochlorite pentahydrate ($NaOCl{\cdot}5H_2O$) as a green and relatively unexplored reagent. The reactions took place with a small excess of oxidant under environmentally friendly conditions in EtOAc for 16 h at room temperature. Noteworthy distinctions of this transformation are the simplicity, high selectivity, energy and cost efficiency, minimal amounts of non-hazardous waste, isolation of most of the products without the additional need for chromatographic purification, and simple scalability to gram reactions without deterioration of the yield. The reaction exhibited excellent green chemistry metrics with high atom economy (82.0%), actual atom economy (79.5%), reaction mass efficiency (79.7%), *E*-factor (16.48) and a very high EcoScale score (84.5). Competitive experiments demonstrated that electron-rich substrates are more reactive than their electron-poor counterparts. Furthermore, the Suzuki–Miyaura functionalization of *N*-trifluoromethylsulfaneylidene sulfoximine could be achieved depending on the conditions, resulting in coupling products with or without an introduced sulfoxide moiety. Sonogashira coupling of *N*-trifluoromethylsulfaneylidene sulfoximine furnished the expected acetylene derivative in high yield, and the reaction conditions are compatible with the newly introduced sulfaneylidene functionality. Bromine and nickel catalysts were also shown to be deprotecting agents of the sulfoxide group. A selected *N*-trifluoromethylsulfaneylidene sulfoximine demonstrated its stability in water in the presence of air and in dilute hydrochloric acid, while it converted back to the parent sulfoximine under basic conditions.

Introduction

Sulfoximines and their derivatives have seen rapid development in recent years.[1] This effort is in no small part due to the biological activities that these compounds exhibit.[2] Some biologically active sulfoximines, trifluoromethylthio compounds, sulfoxides and trifluoromethyl sulfoxides (TFMSs) are presented in Fig. 1.[3]

Several pathways to synthesize sulfoximines have been reported. Some examples include *N*-alkylation of sulfides followed by oxidation,[4] iridium-catalyzed regio- and enantioselective C–H borylation of *N*-silyl diaryl sulfoximines using a chiral bidentate boryl ligand with a bulky side arm,[5] ruthenium-catalyzed synthesis of β-keto sulfoximines from *N*-tosyl-protected sulfoximidoyl chlorides and aryl alkynes under visible light,[6] and enantioenriched preparation of sulfonimidoyl fluorides and their stereospecific reaction on sulfur with Grignard reagents.[7] Various *N*-arylations have been developed, such as Ni/Ir photocatalyzed arylation of *N*-H sulfoximines

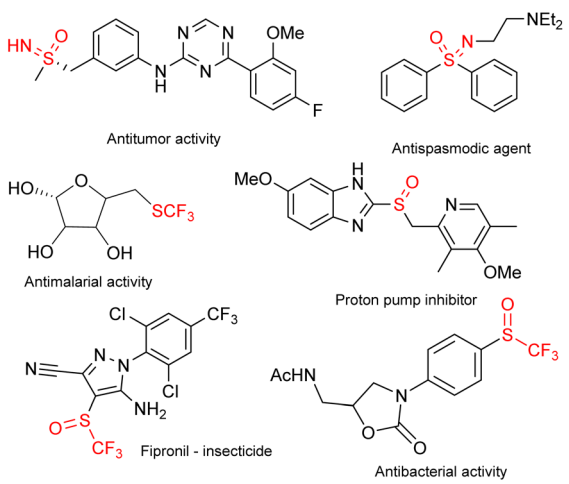

Fig. 1 A selection of biologically active sulfides, sulfoximines and sulfoxides.

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† Electronic supplementary information (ESI) available: Full experimental details and the copies of ^1H, ^{19}F and ^{13}C NMR spectra. See DOI: https://doi.org/10.1039/d3ob02033a

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with bromoarenes,[8] Ni-catalyzed *N*-arylation of *N*-H sulfoximines *via* paired electrolysis,[9] copper-catalyzed photoredox *N*-arylation of *N*-H sulfoximines with arylboronic acids,[10] a stereospecific S_NAr approach for the introduction of sulfonimidoyl functionalities into heterocyclic systems[11] and Pd-catalyzed arylation of *N*-H sulfoximines with aryl bromides in micellar media.[12] Pd-catalyzed introduction of lipophilic side chains into *N*-H sulfoximines using butadienes and alkyl bromides took place under blue light irradiation.[13] Stereospecific *S*-alkylation of chiral sulfinamides with alkyl halides and NaOH in DME gave products with high optical purity.[14] An Ir-catalyzed reaction of *N*-SCN with alkenes produced alkyl-substituted sulfoximines under photochemical conditions.[15] Functionalization of *N*-H sulfoximines with *gem*-difluoroalkenes and NBS under blue LED conditions led to the corresponding α-ketoacyl-substituted derivatives.[16] *N*-acylation of *N*-H-sulfoximines with thioacids in the presence of a photoredox catalyst could be accomplished under blue LED irradiation.[17] Similarly, the transformation of *N*-H sulfoximine with aryl aldehydes[18] or ketones[19] in the presence of NBS yielded the corresponding *N*-acyl derivatives. The introduction of a halogen atom[20] or a halogenated moiety[21] produced various interesting sulfoximines.

N-Trifluoromethylthio sulfoximines exhibit increased lipophilicity, which further increases their bioavailability.[21b] The addition of an oxygen atom to the trifluoromethylthio group would increase the polar character of the compound and potentially confer improved pharmacological properties to the products. The cLog *P* (calculated log *P*) decreased by about two points for most compounds, indicating that a higher amount of the compound would be found in the aqueous phase of an octanol/H_2O mixture, which is more in line with Lipinski's rules. An example of these values is shown in Fig. 2 for sulfoximine **1**, *N*-trifluoromethylthio sulfoximine **2** and *N*-trifluoromethylsulfaneylidene sulfoximine **3**.

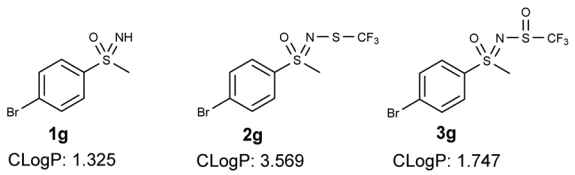

Fig. 2 cLog *P* values for **1g**, **2g** and **3g** obtained from ChemDraw.

The trifluoromethylsulfinyl moiety[22] (CF_3SO) is a vital part of several important biologically active molecules, such as the insecticide fipronil (Fig. 1) and its derivatives, as well as other pharmacologically active compounds.[23] TFMSs are reagents for metal-free C–H activation,[24] as well as precursors of Yagupolskii and Umemoto-type reagents.[23] Several synthetic approaches have been developed to introduce the trifluoromethylsulfinyl functionality. The functionalization of sulfite esters using $TMSCF_3$/CsF at elevated temperature led to TFMS derivatives.[25] Direct sulfinylation of common aromatic compounds by using triflinate salts in triflic acid led to TFMSs with preferential *para*-selectivity.[26] Sodium triflinate and phosphoryl chloride (2/1) are capable of transferring CF_3SO^+ into organic molecules, yielding trifluoromethanesulfinates or trifluoromethanesulfinamides.[27] Direct electrophilic trifluoromethylsulfinylation of activated indoles, pyrroles, anilines, and phenols took place with trifluoromethanesulfonyl chloride/tricyclohexyl phosphine.[28] A combination of sodium triflinate and $POCl_3$ afforded indole-derived TFMSs.[29] Recently, *N*-trifluoromethylsulfinylphthalimide was introduced, which was able to transfer the CF_3SO group into indoles, pyrroles and other electron-rich (hetero)aromatics. Alkyl, aromatic and heterocyclic amines were *N*-functionalized, while alcohols and phenols furnished the corresponding trifluoromethanesulfinate esters.[30] The most common methodology for the synthesis of TFMSs is probably the oxidation of parent trifluoromethyl sulfides. The main challenge with oxidation to sulfoxides is the potential overoxidation to sulfones, which in some cases is as rapid as oxidation to sulfoxides. While the oxidation of non-halogenated sulfides is very well known and has through the years become increasingly green,[31] the oxidation of the trifluoromethylthio functional group is mostly achieved using halogenated media[32] or halogenated agents such as *m*-CPBA[33] or TCCA,[34] generating considerable amounts of harmful waste, or using metal catalysts.[35] To this end, we have used solid sodium hypochlorite pentahydrate ($NaOCl{\cdot}5H_2O$) as a benign and selective oxidant.[36] Its crystals are easy to use in stoichiometric quantities and eliminate the need for titration and other methods for determining the concentration of sodium hypochlorite in solution. It contains about 44 wt% NaOCl as an active oxidizing agent and only up to 0.08 wt% NaOH and up to 0.5 wt% NaCl. Furthermore, the enhanced purity of these crystals is paramount to the success of the reactions described herein, as they generate products that require little to no purification, whereas using a commercial aqueous solution of NaOCl produces a large amount of impurities and is less selective towards sulfoxides. Since its introduction in 2013, it has been used in several interesting oxidations.[37]

To the best of our knowledge, no oxidations of *N*-trifluoromethylthio sulfoximines have been reported, and while it is known that reactions of *N*-alkyl, *N*-aryl, and *N*-H sulfoximines with *m*-chloroperbenzoic acid cleanly give the corresponding sulfones in high yield,[38] this was not the case for *N*-trifluoromethylthio sulfoximines. Herein we explore the optimization of the corresponding sulfoxide formation, the substrate scope, some mechanistic insights, some additional modifications and stability parameters for this novel functionalization of sulfoximines. The reaction proceeded at room temperature in ethyl acetate using a small excess of $NaOCl{\cdot}5H_2O$ (0.1 equiv.) with excellent selectivity, yielding products in high yield and a small amount of non-hazardous waste (NaCl). A remarkable advantage of the present method is that column chromatography could be avoided to a great extent due to the NMR purity of the vast majority of the crude products.

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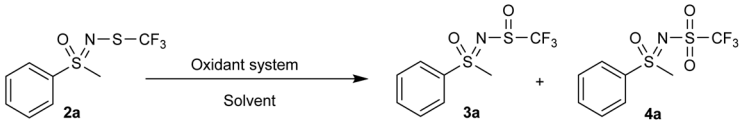
Results and discussion

We tested various oxidants and solvents with the goal of making the process as green and sustainable as possible. The first success in obtaining an adequate amount of sulfoxide was with the use of hydrogen peroxide and tungstic acid in water, which unfortunately required a stoichiometric amount of tungstic acid (Table 1, entry 1). Reducing this amount at the expense of increasing the amount of H_2O_2 (Table 1, entry 2) proved beneficial, but the method was still prone to overoxidation to sulfone **4a**. The reaction without tungstic acid (Table 1, entry 3) was more selective, but we observed a considerable amount of by-products that would require further purification. Substitution of tungsten with vanadium (Table 1, entry 4) resulted in a lower conversion, as 70% of the starting substrate **2a** remained unreacted. The combination of H_2O_2 and acetic acid (Table 1, entries 5 and 6) eliminated the need for metal catalysts, but still produced the undesirable sulfone **4a** in modest amounts. TBHP (Table 1, entry 7) did not yield any oxidized species in any of the tested solvents. Oxone (Table 1, entry 8) in water proved to be quite efficient, but there was always a non-negligible amount of **2a** and **4a** present, which would have required additional purification. Grinding neat **2a** with oxone without solvent (Table 1, entry 9) proved unsuccess-

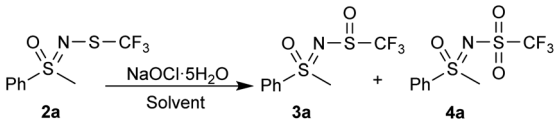
Table 1 Screening of oxidants and solvents[a]



Entry	Oxidant system	Temperature	Solvent	Relative ratio[b] (%) 2a	3a	4a
1	H_2O_2 (1.2 equiv.)/H_2WO_4 (1 equiv.)	60 °C	H_2O	—	79	21
2	H_2O_2 (6 equiv.)/H_2WO_4 (10 mol%)	60 °C	H_2O	—	75	25
3	H_2O_2 (6 equiv.)	60 °C	H_2O	—	91[c]	9
4	H_2O_2 (6 equiv.)/V_2O_5 (1 equiv.)	60 °C	H_2O	70	30	Trace
5	H_2O_2 (1.2 equiv.)	60 °C	AcOH	—	93	7
6	H_2O_2 (1.2 equiv.)	r.t.	AcOH	17	73	10
7	TBHP	r.t.	H_2O, MeOH, MeCN, EtOAc, AcOH, DMSO	100	—	—
8	Oxone (1.2 equiv.)	r.t.	H_2O	5	93	2
9	Oxone (1.2 equiv.)	r.t.	—	100	—	—
10	*m*-CPBA (1.1 equiv.)	r.t.	DCM	17	83	—

[a] Reaction conditions: a flask was charged with **2a** (0.1 mmol), solvent and an oxidant and the mixture was stirred for 16 h. [b] Determined by ^{1}H and ^{19}F NMR. [c] Other side-products were observed.

Table 2 Screening of solvents[a]



Entry	Temperature	Solvent	Relative ratio[b] (%) 2a	3a	4a
1	r.t.	H_2O	—	96[c]	1
2	0 °C	H_2O	—	96[c]	1
3	r.t.	DCM	64	36	Trace
4	r.t.	MeOH	100	Trace	Trace
5	r.t.	EtOH	100	—	—
6	r.t.	MeCN	33	56	11
7	r.t.	THF	Trace	100[c]	Trace
8	r.t.	Hexane	34	66	Trace
9	**r.t.**	**EtOAc**	—	**99**	**1**
10	r.t.	—	56	41	3
11	r.t.	NaOCl (aq.)[d]	34	48[c]	18

[a] Reaction conditions: a flask was charged with **2a** (0.1 mmol), solvent (0.3 mL) and an oxidant (1.1 equiv.) and the mixture was stirred for 16 h. [b] Determined by ^{1}H and ^{19}F NMR. [c] *N*-Chloro side-products were observed. [d] Commercial bleach solution (*ca.* 10%; 4 equiv.).

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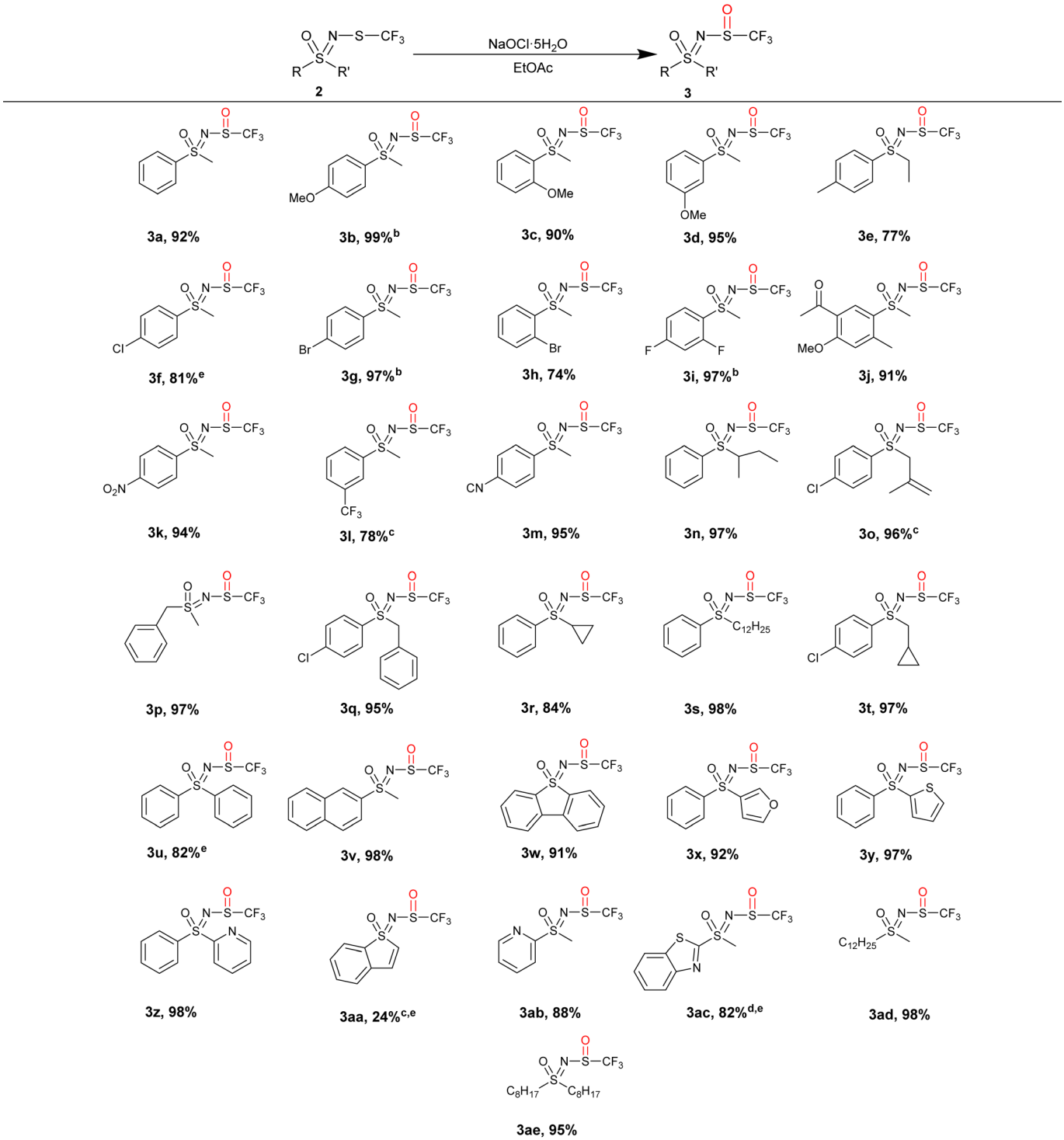
ful. Oxidation with *m*-CPBA in DCM produced a relatively good result (Table 1, entry 10), but we ultimately did not consider it due to our green criteria.

To our delight, NaOCl·5H_2O exhibited a most selective reaction profile. The reaction in water with 1.1 equiv. of NaOCl·5H_2O yielded the sulfoxide **3a**, whereby the sulfone **4a**

Table 3 Substrate scope[a]



[a] Reaction conditions: a flask was charged with **2** (0.3 mmol) and EtOAc (0.3 mL) and lastly NaOCl·5H_2O (1.1 equiv.) was added. The mixture was stirred for 16 h at r.t. After extraction from EtOAc/water, the organic phase was dried, and the solvent was removed. [b] 1.25 equiv. of NaOCl·5H_2O were needed. [c] 1.5 equiv. of NaOCl·5H_2O were needed. [d] 2 equiv. of NaOCl·5H_2O were needed. [e] Column chromatography was needed for additional purification.

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was present only in trace amounts (Table 2, entry 1). Lowering the temperature by means of an ice bath did not change the result (Table 2, entry 2). As can be judged from ^{1}H NMR spectra, about 3% of *N*-chloro sulfoximine was also present in the reaction; this by-product was only detected for **2a** and for none of the other substrates. Reducing the amount of NaOCl·5H_2O to 1.0 equiv. remedied this. The same reaction in DCM (Table 2, entry 3) afforded **3a** in about 36% yield, with traces of **4a**. In methanol, both oxidation products were found in traces, while no reaction was observed in ethanol (Table 2, entries 4 and 5). The same reaction in acetonitrile gave a mixture of sulfoxide **3a** and sulfone **4a**, with a portion of the starting material **2a** still present (Table 2, entry 6). The oxidation in THF proceeded selectively to provide sulfoxide **3a**, but there were many by-products that we assume were related to the oxidation/polymerization of THF itself (Table 2, entry 7). In hexane (Table 2, entry 8), two-thirds of **2a** were converted to **3a**, with traces of **4a**. The reaction in EtOAc was comparable to that in water, with all the starting materials consumed and minimal **4a** present, including traces of the corresponding *N*-chloro sulfoximine (Table 2, entry 9). Grinding NaOCl·5H_2O and neat **2a** without solvent (Table 2, entry 10) was found to be less effective and selective than using a solvent. Interestingly, the reaction in a commercial bleach solution was not selective and in addition produced unknown by-products (Table 2, entry 11). Although both water and EtOAc gave similar results, we ultimately decided in favour of EtOAc because it was significantly more selective towards sulfoxides for substituted phenyl substrates. This decision also allowed us to create a homogeneous reaction environment.

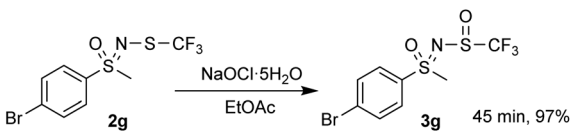
A number of *N*-trifluoromethylthio sulfoximines were prepared and oxidized in EtOAc with 1.1 equiv. of NaOCl·5H_2O (Table 3). Due to the weak absorption of the sulfoxide moiety **3**, TLC analysis was often inconclusive, so the reaction was stirred overnight (16 h) for convenience. Since only NaCl is formed during the reaction, the products could be purified by simple water/EtOAc extraction, which gave NMR-pure *N*-trifluoromethyl sulfoxides **3** in high yield without the need for additional purification.

The reaction worked well with aryl alkyl-substituted sulfoximines, regardless of whether they possessed an electron-rich or electron-poor aromatic ring, and gave the products **3a–3m** in 74–99% yields. The starting substrate **2n** furnished the expected **3n** in 97% yield despite its branched alkyl side chain. We were pleased to find that the alkene moiety in **2o** was compatible with the oxidizing reaction conditions, giving **3o** in 96% yield. Benzyl-, cyclopropyl- and dodecyl-substituted substrates **2p–2t** produced the corresponding sulfoxides **3p–3t** in excellent yields. Diaryl, naphthyl, dibenzothienyl, furyl, thienyl, pyridyl, benzothienyl and benzothiazolyl trifluoromethylthio sulfoximines **2u–2ac** produced the corresponding **3u–3ac** sulfoxide derivatives in notable yields of up to 98%, except for **3aa**. Substrates dodecyl methyl **2ad** and dioctyl **2ae** gave the corresponding sulfoxides **3ad** and **3ae** in 98% and 95% yields, respectively.

Most of the products were isolated in high yields. Products **3f**, **3u**, **3aa**, and **3ac** required additional purification *via* column chromatography to remove sulfones/starting materials or by-products, while in the case of **3a**, a small amount of *N*-Cl derivative was observed. In further experiments, the *N*-Cl derivative was only detected when an excess of NaOCl·5H_2O was added, suggesting that the sulfone **4a** was somehow responsible for its formation. Excess NaOCl·5H_2O should be avoided in the case of substrate **2a** to minimize the quantity of the *N*-Cl derivative. Product **3o** exhibited signs of decomposition since a fine white precipitate was found in the NMR sample tube. In fact, most of the product had already decomposed to many by-products at this point. This process appeared to be faster in deuterated chloroform, as undissolved **3o** showed less decomposition after 2 months. Complete conversion to the products **3b**, **3g** and **3i** was achieved with 1.25 equiv. of NaOCl·5H_2O, **3l**, **3o** and **3aa** with 1.5 equiv. of NaOCl·5H_2O, and **3ac** with 2 equiv. of NaOCl·5H_2O. Overall, this method proved to be effective for (het)aryl-alkyl as well as (het)aryl-aryl and alkyl-alkyl substrates. Notably, several functional groups such as the keto- **3j**, nitro- **3k**, cyano- **3m**, cyclopropyl- **3r** and alkenyl moieties do not interfere with the oxidation, making this method suitable for late-stage functionalization.

Sulfoximines **1** were synthesised according to standard procedures[39] and were racemic. Subsequent modification to *N*-trifluoromethylthio sulfoximines **2** and their oxidation to the corresponding sulfoxides **3** introduced an additional chiral center, leading to the formation of diastereoisomers, appearing as two sets of signals in the NMR spectra. For compound **3f**, we succeeded in separating and characterizing the diastereoisomers, while the other products were characterized as mixtures of both diastereoisomers. While the diastereoisomers are mostly formed in a 1 : 1 ratio, the reactions of some substrates (most notably **3h**) were more stereoselective, most likely due to their bulky substituents.

A gram-scale reaction experiment was also performed, in which aliquots were taken at 15 min intervals and analyzed by ^{1}H and ^{19}F NMR spectroscopy (Scheme 1). The reaction proceeded smoothly, with substrate **2g** no longer observable after 1 h. No by-products or degradation of **3g** were observed after a further 30 min. As with smaller scale reactions, ethyl acetate/water extraction was performed and the product **3g** was isolated in a nearly stoichiometric amount (97%). Most of the EtOAc was recovered during the evaporation process.



Scheme 1 Gram-scale reaction.

The gram-scale reaction was also used to determine the green chemistry metrics for this oxidation. The mass of the five moles of water in NaOCl·5H_2O was not included in the calcu-

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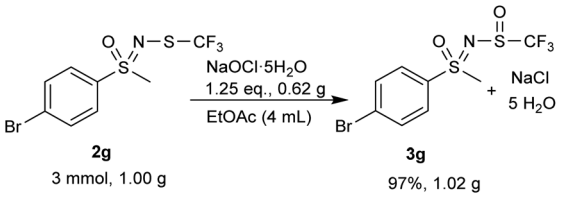
lations as it is not ecologically problematic. The atom economy was calculated to be 82%, while the actual atom economy and reaction mass efficiency were also high with 79.5% and 79.7%, respectively. The *E*-factor of 16.48 is mainly derived from water, EtOAc and salts (NaCl and Na_2SO_4), which are not particularly environmentally problematic. While the *E*-factor is still far from the ideal value of 0 or the acceptable value of 1–5, but at least the waste does not have to be specially disposed of. A result of 84.5 was achieved on the EcoScale,[40] which corresponds to a "great synthesis" according to the criteria of the method (Table 4). The calculations can be found in the ESI.†

Table 4 Green metrics

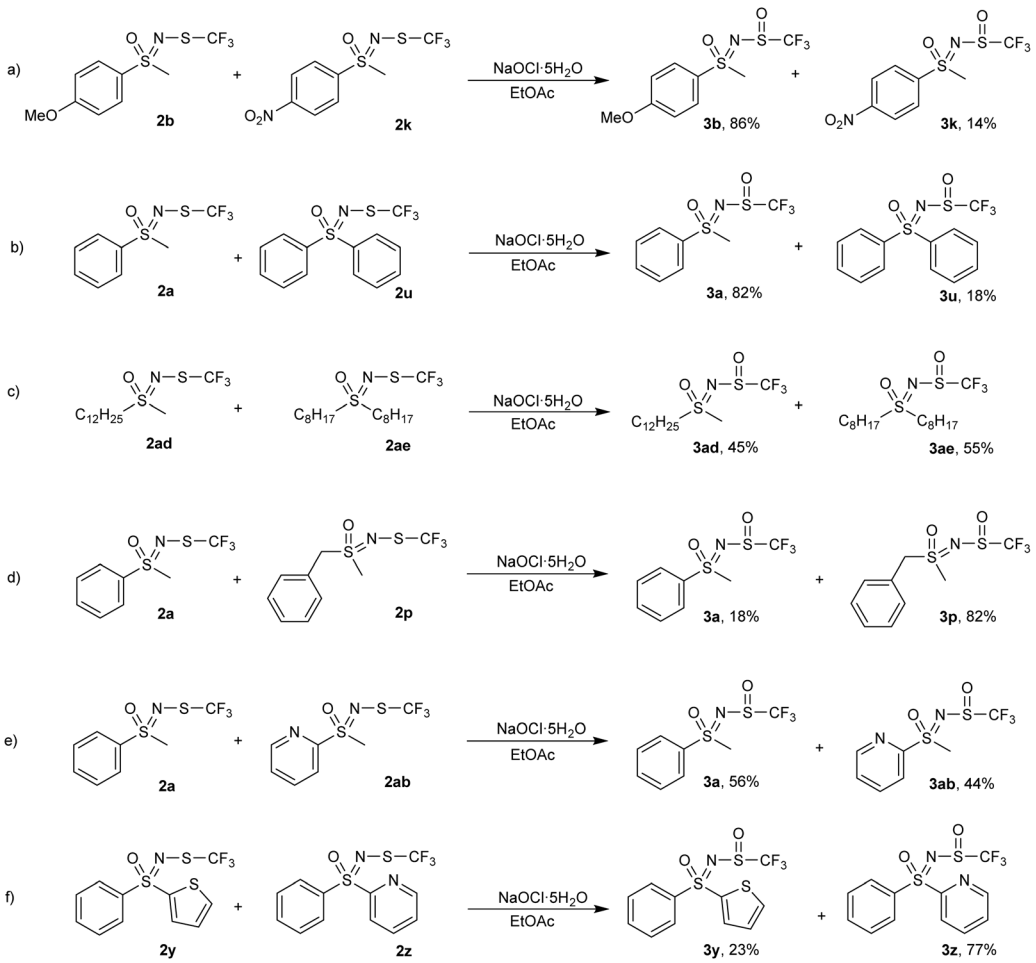


Atom economy	$\frac{\text{Molecular weight of product}}{\text{Molecular weight of reactants}}$	82%
Actual atom economy	Yield of product × atom economy	79.5%
Reaction mass efficiency	$\frac{\text{Mass of products}}{\text{Mass of reactants}}$	79.7%
E-Factor	$\frac{\text{Amount of waste}}{\text{Amount of product}}$	16.48
EcoScale	$100 - \sum$ Individul penalties	84.5

To gain a better understanding of the reactivity of our substrates, multiple competitive reactions were carried out in which two *N*-trifluoromethylthio sulfoximines **2** were mixed in a 1 : 1 ratio and 1 equiv. of oxidant was added. The reactions were stirred for 16 h, then an internal standard (1,3,5-trimethoxybenzene) was added and the mixture was analysed by ^{1}H and ^{19}F NMR spectroscopy. These reactions were repeated twice and only minimal deviations were observed.

In a competitive reaction between 4-methoxy-substituted **2b** and 4-nitro-substituted **2k** (Table 5, a), 86% of the oxidized species was attributed to the 4-methoxy product **3b**, indicating

Table 5 Competitive reactions[a]



[a] Reaction conditions: a flask was charged with both substrates **2** (0.1 mmol each) and EtOAc (0.2 mL) and lastly NaOCl·5H_2O (1 equiv.) was added. The mixture was stirred for 16 h at r.t. 1,3,5-Trimethoxy benzene was added and after extraction from EtOAc/water, the organic phase was dried and the solvent was removed under reduced pressure.

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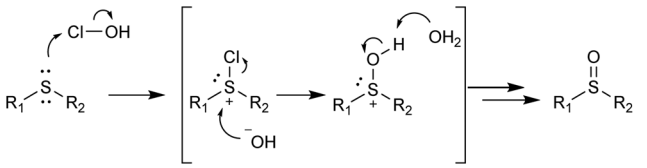
that electron-donating substituents on the phenyl ring promote this type of oxidation. The reaction between the phenyl methyl substrate **2a** and diphenyl **2u** (Table 5, b) favored the formation of **3a**, possibly due to steric hindrance or the electron-withdrawing effect of the second phenyl ring. Dodecyl methyl substrate **2ad** and dioctyl substrate **2ae** (Table 5, c) reacted similarly, both utilizing roughly half of the available oxidant, suggesting that the length of the alkyl chains is not an important factor in determining the reaction rate. Benzyl substrate **2p** was more reactive than its phenyl **2a** counterpart (Table 5, d), again indicating that the electron-withdrawing effect of the phenyl ring hinders oxidation. Phenyl-substituted **2a** and 2-pyridyl-substituted **2ab** (Table 5, entry e) produced similar amounts of oxidized products, although pyridine was thought to have a stronger electron-withdrawing effect. The substituted 2-pyridyl **3z** product was substantially favoured over the 2-thienyl **3y** product (Table 5, f), which again was somewhat surprising since the 2-thienyl moiety is more electron-donating and is less bulky than the 2-pyridyl group. The reaction mechanism for sulfide oxidations with $NaOCl{\cdot}5H_2O$ has been proposed previously[36] and involves the chlorination of the sulfide followed by nucleophilic attack by the hydroxide ion (Scheme 2). Our work supports this proposal as the electron-donating substituents were found to be more reactive and thus promote the nucleophilic attack of sulfur on the chloride atom.

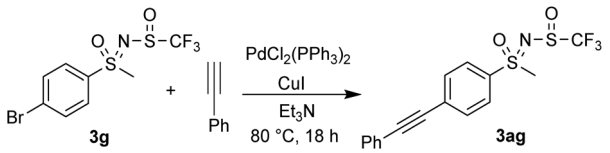


Scheme 2 Proposed mechanism for the oxidation of sulfides with $NaOCl{\cdot}5H_2O$.

The effect of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was also investigated. The reaction of 1 equiv. of TEMPO, 1 equiv. of **2a** and 1.1 equiv. of $NaOCl{\cdot}5H_2O$ gave product **3a** with 58% conversion, leaving 42% of the starting material **2a** unreacted. Upon reducing the amount of TEMPO to 0.2 equiv. the proportion of **3a** decreased to 43%. From this it can be concluded that the reaction between $NaOCl{\cdot}5H_2O$ and TEMPO takes place before the oxidation of the substrate and the oxidized species is then less reactive towards the substrate **2a**.

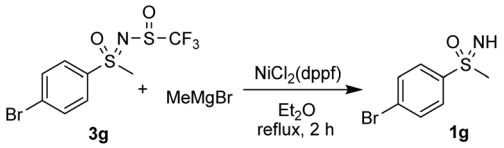
The newly formed sulfinyl moiety was tested in some post-modification transformations. The reaction of **3g** with 4-methylbenzeneboronic acid in boiling water in the presence of Pd/C led to Suzuki–Miyaura coupling with concomitant removal of the *N*-trifluoromethylsulfaneylidene moiety, yielding the sulfoximine **1ag** (Scheme 3). A similar reaction in 1,4-dioxane under milder conditions, which had already been used for sulfoximines,[41] furnished the coupling product **3af** with an intact *N*-trifluoromethylsulfaneylidene group (Scheme 3).

Sonogashira coupling of **3g** with phenylacetylene successfully furnished **3ag** using catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in Et_3N (Scheme 4).



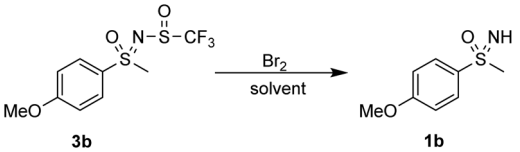
Scheme 4 Sonogashira coupling reaction.

Kumada-type coupling reactions with nickel and iron catalysts were also examined. The reaction of **3g** with $Fe(acac_3)$, HMTA, TMEDA and phenylmagnesium bromide in THF failed to produce any product and only the substrate **3g** was isolated. Reaction of **3g** with methylmagnesium bromide in the presence of $NiCl_2(dppf)$ in diethyl ether led to deprotection of the substrate and the sulfoximine **1g** was recovered (Scheme 5).

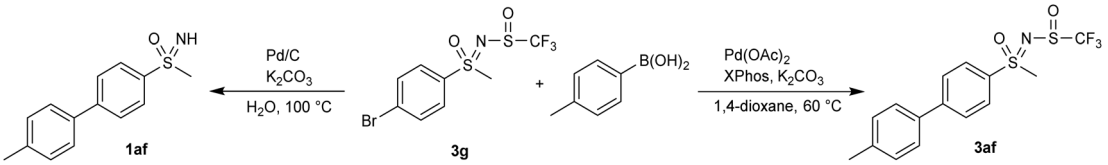


Scheme 5 Attempted nickel-catalysed Kumada-type reaction.

Next, electrophilic ring bromination was investigated. The use of NBS in hexafluoroisopropanol (HFIP) and MeCN did not lead to any reaction with **3b**. Using bromine in acetic acid and in chloroform produced the sulfoximine **1b**. Addition of $FeBr_3$ to further promote ring bromination also produced the sulfoximine **1b** (Scheme 6).



Scheme 6 Attempted ring bromination.



Scheme 3 Condition-dependent Suzuki–Miyaura coupling reactions.

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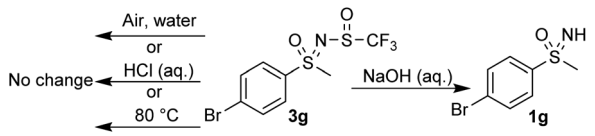
To further examine the stability of these compounds, which show no deterioration at room temperature or in air, compound **3g** was subjected to elevated temperature (80 °C) and no changes were observed after 3 h (Scheme 7). Stability at different pH values was tested by stirring **3g** in 2 M aqueous HCl and NaOH solutions for 3 h. Under basic conditions, degradation to sulfoximine **1g** was observed, while no change occurred in an acidic medium.



Scheme 7 Stability tests for compound **3g**.

Conclusion

In conclusion, we report a sustainable, practical, cost-effective and highly selective oxidation of various aryl-, heteroaryl- and alkyl-substituted *N*-trifluoromethythio sulfoximines to *N*-trifluoromethylsulfaneylidene sulfoximines. These novel functionalized sulfoximines were prepared in high yields and with almost no need for purification using $NaOCl{\cdot}5H_2O$ as a green oxidant, which produces ecologically benign waste. In competitive experiments, a general trend of reactivity that electron-rich substrates are more reactive than electron-poor substrates was observed. A scale-up experiment was performed with an atom economy of 82%, actual atom economy of 79.5%, a reaction mass efficiency of 79.7%, an *E*-factor of 16.48 and a total of 84.5 EcoScale points, denoting the method as a "great" synthesis from a green metric point of view. Further modifications of the functionalized sulfoximines are also possible and were demonstrated with Suzuki–Miyaura and Sonogashira coupling reactions. The stability of this new functional group was also investigated. While decomposition to sulfoximine **1** was observed under basic conditions, the compounds are stable in air, water, an acidic environment and at elevated temperatures.

Author contributions

Ž. T.: investigation, validation, data curation, writing – original draft and writing – review & editing. M. J.: conceptualization, resources, validation, supervision, writing – original draft and writing – review & editing.

Conflicts of interest

There are no conflicts of interest to declare.

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References

1 See for example: (*a*) H. Kour, A. Sharma, J. Kour, M. Ahmed and S. D. Sawant, *Eur. J. Org. Chem.*, 2022, e202201375; (*b*) D. Kong, D. Ma, P. Wu and C. Bolm, *ACS Sustainable Chem. Eng.*, 2022, **10**, 2863–2867; (*c*) A. L. Barthelemy, V. Certal, G. Dagousset, E. Anselmi, L. Bertin, L. Fabien, B. Salgues, P. Courtes, C. Poma, Y. El-Ahmad and E. Magnier, *Org. Process Res. Dev.*, 2020, **24**, 704–712; (*d*) R. Luisi and J. A. Bull, *Molecules*, 2023, **28**(3), 1120; (*e*) B. Wang, X. Liang and Q. Zeng, *Molecules*, 2023, **28**(3), 1367; (*f*) P. Zhao and Q. Zeng, *Chem. – Eur. J.*, 2023, **29**, e202302059.

2 See for example: (*a*) P. Mäder and L. Kattner, *J. Med. Chem.*, 2020, **63**, 14243–14275; (*b*) M. Frings, C. Bolm, A. Blum and C. Gnamm, *Eur. J. Med. Chem.*, 2017, **126**, 225–245; (*c*) N. Thota, P. Makam, K. K. Rajbongshi, S. Nagiah, N. S. Abdul, A. A. Chuturgoon, A. Kaushik, G. Lamichhane, A. M. Somboro, H. G. Kruger, T. Govender, T. Naicker and P. I. Arvidsson, *ACS Med. Chem. Lett.*, 2019, **10**, 1457–1461; (*d*) Y. Han, K. Xing, J. Zhang, T. Tong, Y. Shi, H. Cao, H. Yu, Y. Zhang, D. Liu and L. Zhao, *Eur. J. Med. Chem.*, 2021, **209**, 112885; (*e*) U. Lücking, *Chem. – Eur. J.*, 2022, **28**, e202201993; (*f*) N. A. Meanwell, *J. Agric. Food Chem.*, 2023, **71**, 18087–18122.

3 V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, **6**, 880–921.

4 C. A. Dannenberg, V. Bizet and C. Bolm, *Synthesis*, 2015, **47**, 1951–1959.

5 S. Y. Song, X. Zhou, Z. Ke and S. Xu, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217130.

6 P. Shi, Y. Tu, C. Wang, D. Ma and C. Bolm, *J. Org. Chem.*, 2022, **87**, 3817–3824.

7 S. Greed, O. Symes and J. A. Bull, *Chem. Commun.*, 2022, **58**, 5387–5390.

8 A. Wimmer and B. König, *Org. Lett.*, 2019, **21**, 2740–2744.

9 D. Liu, Z. R. Liu, C. Ma, K. J. Jiao, B. Sun, L. Wei, J. Lefranc, S. Herbert and T. S. Mei, *Angew. Chem., Int. Ed.*, 2021, **60**, 9444–9449.

10 C. Wang, H. Zhang, L. A. Wells, T. Liu, T. Meng, Q. Liu, P. J. Walsh, M. C. Kozlowski and T. Jia, *Nat. Commun.*, 2021, **12**, 1–11.

11 Z. P. Shultz, T. Scattolin, L. Wojtas and J. M. Lopchuk, *Nat. Synth.*, 2022, **1**, 170–179.

12 M. Song, L. Zhang, D. Wei, Y. He, J. Jia, H. Li and B. Yuan, *Green Chem.*, 2022, **24**, 6119–6124.

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13 D. Ma, D. Kong, P. Wu, Y. Tu, P. Shi, X. Wang and C. Bolm, *Org. Lett.*, 2022, **24**, 2238–2241.
14 Y. Maeda, S. Hamada, Y. Aota, K. Otsubo, T. Kano and K. Maruoka, *J. Org. Chem.*, 2022, **87**, 3652–3660.
15 D. Zhang, H. Wang, C. Bolm and R. Li, *Chem. Commun.*, 2018, **54**, 5772–5775.
16 Y. Tu, P. Shi and C. Bolm, *Org. Lett.*, 2022, **24**, 907–911.
17 P. Qiu, X. Duan, M. Li, Y. Zheng and W. Song, *Org. Lett.*, 2022, **24**, 2733–2737.
18 K. K. Rajbongshi, S. Ambala, T. Govender, H. G. Kruger, P. I. Arvidsson and T. Naicker, *Synthesis*, 2020, **52**, 1279–1286.
19 Y. Tu, D. Zhang, P. Shi, C. Wang, D. Ma and C. Bolm, *Org. Biomol. Chem.*, 2021, **19**, 8096–8101.
20 See for example: (*a*) H. Wang, M. Frings and C. Bolm, *Org. Lett.*, 2016, **18**, 2431–2434; (*b*) C. Wang, P. Shi and C. Bolm, *Org. Chem. Front.*, 2021, **8**, 2919–2923; (*c*) A. Zupanc and M. Jereb, *J. Org. Chem.*, 2021, **86**, 5991–6000.
21 (*a*) F. Teng, J. Cheng and C. Bolm, *Org. Lett.*, 2015, **17**, 3166–3169; (*b*) C. Bohnen and C. Bolm, *Org. Lett.*, 2015, **17**, 3011–3013; (*c*) V. Bizet, R. Kowalczyk and C. Bolm, *Chem. Soc. Rev.*, 2014, **43**, 2426–2438; (*d*) X. Shen and J. Hu, *Eur. J. Org. Chem.*, 2014, 4437–4451.
22 V. D. Romanenko, *Curr. Org. Chem.*, 2023, **27**, 411–434.
23 N. Shibata, A. Matsnev and D. Cahard, *Beilstein J. Org. Chem.*, 2010, **6**, 65.
24 D. Wang, C. G. Carlton, M. Tayu, J. J. W. McDouall, G. J. P. Perry and D. J. Procter, *Angew. Chem., Int. Ed.*, 2020, **59**, 15918–15922.
25 R. P. Singh, G. Cao, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1999, **64**, 2873–2876.
26 C. Wakselman, M. Tordeux, C. Freslon and L. Saint-Jalmes, *Synlett*, 2001, 550–552.
27 T. Billard, A. Greiner and B. R. Langlois, *Tetrahedron*, 1999, **55**, 7243–7250.
28 H. Chachignon and D. Cahard, *J. Fluorine Chem.*, 2017, **198**, 82–88.
29 D. W. Sun, X. Jiang, M. Jiang, Y. Lin and J. T. Liu, *Eur. J. Org. Chem.*, 2017, 3505–3511.
30 L. Yang, S. Wang, F. Liang, Y. Han, Y. Li, D. Shan, L. Liu, Q. Wang and D. Zhu, *Org. Chem. Front.*, 2023, **10**, 4368–4380.
31 See for example: (*a*) K. J. Liu, J. H. Deng, J. Yang, S. F. Gong, Y. W. Lin, J. Y. He, Z. Cao and W. M. He, *Green Chem.*, 2020, **22**, 433–438; (*b*) E. Skolia, P. L. Gkizis, N. F. Nikitas and C. G. Kokotos, *Green Chem.*, 2022, **24**, 4108–4118; (*c*) F. Shi, M. K. Tse, H. M. Kaiser and M. Beller, *Adv. Synth. Catal.*, 2007, **349**, 2425–2430; (*d*) M. Jereb, *Green Chem.*, 2012, **14**, 3047–3052.
32 See for example: (*a*) B. Zhao, G. B. Hammond and B. Xu, *Tetrahedron Lett.*, 2021, **82**, 153376; (*b*) S. Gan, J. Yin, Y. Yao, Y. Liu, D. Chang, D. Zhu and L. Shi, *Org. Biomol. Chem.*, 2017, **15**, 2647–2654; (*c*) L. V. Sokolenko, R. K. Orlova, A. A. Filatov, Y. L. Yagupolskii, E. Magnier, B. Pégot and P. Diter, *Molecules*, 2019, **24**(7), 1249; (*d*) M. Horvat, G. Kodrič, M. Jereb and J. Iskra, *RSC Adv.*, 2020, **10**, 34534–34540.
33 C. M. M. Hendriks, P. Lamers, J. Engel and C. Bolm, *Adv. Synth. Catal.*, 2013, **355**, 3363–3368.
34 R. Y. Tang, P. Zhong and Q. L. Lin, *J. Fluorine Chem.*, 2007, **128**, 636–640.
35 See for example: (*a*) H. Marom, S. Antonov, Y. Popowski and M. Gozin, *J. Org. Chem.*, 2011, **76**, 5240–5246; (*b*) E. Baciocchi, M. F. Gerini and A. Lapi, *J. Org. Chem.*, 2004, **69**, 3586–3589.
36 M. Kirihara, T. Okada, Y. Sugiyama, M. Akiyoshi, T. Matsunaga and Y. Kimura, *Org. Process Res. Dev.*, 2017, **21**, 1925–1937.
37 See for example: (*a*) M. Kirihara, R. Osugi, K. Saito, K. Adachi, K. Yamazaki, R. Matsushima and Y. Kimura, *J. Org. Chem.*, 2019, **84**, 8330–8336; (*b*) A. Watanabe, K. Miyamoto, T. Okada, T. Asawa and M. Uchiyama, *J. Org. Chem.*, 2018, **83**, 14262–14268; (*c*) S. Matsuki, H. Kayano, J. Takada, H. Kono, S. Fujisawa, T. Saito and A. Isogai, *ACS Sustainable Chem. Eng.*, 2020, **8**, 17800–17806.
38 J. Hachtel and H.-J. Gais, *Eur. J. Org. Chem.*, 2000, 1457–1465.
39 Y. Xie, B. Zhou, S. Zhou, S. Zhou, W. Wei, J. Liu, Y. Zhan, D. Cheng, M. Chen, Y. Li, B. Wang, X. S. Xue and Z. Li, *ChemistrySelect*, 2017, **2**, 1620–1624.
40 K. Van Aken, L. Strekowski, L. Patiny and L. Strekowski, *Beilstein J. Org. Chem.*, 2006, **2**, 3–17.
41 A. K. Bachon, A. D. Steinkamp and C. Bolm, *Adv. Synth. Catal.*, 2018, **360**, 1088–1093.

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