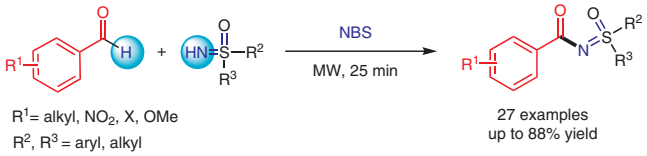
Synthesis K. K. Rajbongshi et al. Paper

Microwave-Accelerated *N*-Acylation of Sulfoximines with Aldehydes under Catalyst-Free Conditions

Kamal K. Rajbongshi[a]
Srinivas Ambala[a]
Thavendran Govender[b]
Hendrik G. Kruger[a]
Per I. Arvidsson[*a,c]
Tricia Naicker[*a]

[a] Catalysis and Peptide Research Unit, University of KwaZuluNatal, Durban, 4001, South Africa
naickert1@ukzn.ac.za
[b] Department of Chemistry, University of Zululand, Private Bag X1001, KwaDlangezwa 3886, South Africa
[c] Science for Life Laboratory, Drug Discovery & Development Platform & Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
Per.Arvidsson@scilifelab.se



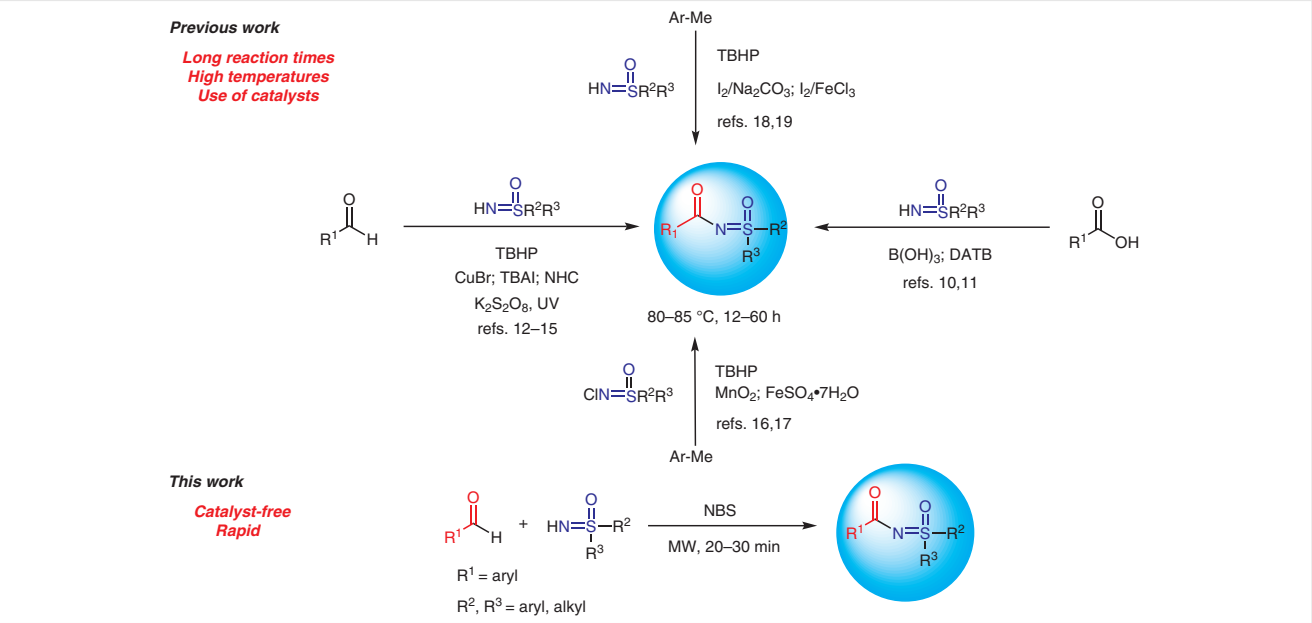
Received: 19.11.2019
Accepted after revision: 20.12.2019
Published online: 29.01.2020
DOI: 10.1055/s-0039-1691589; Art ID: ss-2019-t0643-op

Abstract An efficient catalyst-free radical cross-coupling reaction between aromatic aldehydes and sulfoximines was developed. The reaction took place in the presence of *N*-bromosuccinimide as the radical initiator under microwave irradiation to afford the corresponding acylated sulfoximines in moderate to excellent yields (27 examples). This protocol proved to be rapid, easy to handle, and applicable to a broad scope of substrates.

Key words acylation, radical reactions, sulfoximines, *N*-bromosuccinimide, microwave irradiation

Direct carbon–nitrogen bond formation reactions have been considered as one of the most effective ways to construct nitrogen-containing natural products as well as several biologically active molecules.[1] The chemistry of sulfoximines is gaining significant attention due to their wide application in the pharmaceutical and agricultural fields.[2] In addition, sulfoximines have been exploited as chiral ligands,[3] chiral auxiliaries,[4] and organocatalysts[5] in asymmetric synthesis, and as essential reagents[6] for the construction of heterocyclic molecules. Several research groups are continually working to develop practical synthetic methods for the synthesis of sulfoximines and derivatives.[7] *N*-Acylated sulfoximines belong to an important class of sulfoximines.[8] *N*-Acylsulfoximines are usually prepared by the treatment of sulfoximines with some activated carboxylic derivative such as an acyl chloride or anhydride in the presence of a base.[9] They can also be synthesized directly from carboxylic acids in the presence of strong carboxyl activating agents, such as *N*,*N*′-dicyclohexylcarbodiimide (DCC) or 3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropane-1-amine (EDC), in the presence of a suitable base such as DMAP.[8b,9b] In 2011, a boric acid mediated *N*-acylation of sulfoximine protocol was reported, using aliphatic carboxylic acids as the acyl donor (Scheme 1).[10] Recently, Kumagai et al. developed the direct acylation of sulfoximines with carboxylic acids using 1,3-dioxa-5-aza-2,4,6-triborinane (DATB) as a catalyst (Scheme 1).[11]

Bolm and co-workers reported a copper-catalyzed oxidative *N*-acylation of sulfoximines with aldehydes as the acyl donors (Scheme 1).[12] Similarly, Deng's group used a TBAI/TBHP catalytic system for the acylation with aldehydes (Scheme 1).[13] *N*-Heterocyclic carbenes are also suitable catalysts for the direct *N*-acylation of sulfoximines with aldehydes under oxidative conditions (Scheme 1).[14] Very recently, visible-light-promoted acylation of sulfoximines was reported in the presence of an oxidant (Scheme 1).[15] Reports on the *N*-acylation with methylarene as acyl donors are also known (Scheme 1).[16–19] However, in such cases, pre-activation of the sulfoximines are essential for the transformation. For example, Bolm and his team reported the synthesis of *N*-acylated sulfoximines by treating *N*-chlorosulfoximines with methylarenes when using MnO_2 as the catalyst.[16] Later, Kotha et al. performed another *N*-acylation reaction from *N*-chlorosulfoximines and methylarene by using iron as the catalyst.[17] Interestingly, Dong et al. disclosed iodine-catalyzed direct oxidative *N*-acylation with methylarenes without activating the sulfoximine.[18] Zhao and co-workers used I_2/$FeCl_3$/TBHP as the catalyst/oxidant system for direct oxidative *N*-acylation with methylarenes.[19] However, the most reported methods require catalysts and longer reaction time with high temperature. Consequently, the development of new, more efficient



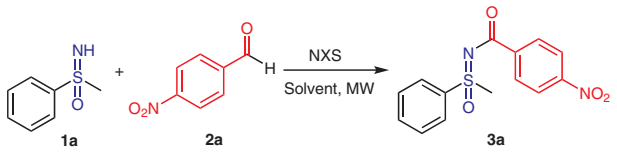
Scheme 1 Previous and current approaches for the synthesis of *N*-acylsulfoximines

methodologies with broad substrate scope is still highly desirable. Microwave-assisted organic synthesis has been considered as an essential tool to accelerate rapid transformation in all areas of organic synthesis.[20] It has some advantages over conventional heating, such as the reduction in reaction times, lower side reactions, and selectivity.[21] Recently, we have reported the synthesis of 1,2,4-thiadiazinanes from β-aminoethanesulfonamides with different methylene donors under MW conditions.[20e]

N-Bromosuccinimide (NBS) is a well-known reagent in organic synthesis, and is safe and easy to handle.[22] It has been extensively used for different organic transformations. Herein, we envisaged the *N*-acylation of sulfoximine derivatives from aldehydes using readily available and inexpensive NBS as the oxidant under microwave-irradiation conditions (Scheme 1). To the best of our knowledge, it is the first report of the rapid microwave-assisted synthesis of *N*-acylsulfoximines from aldehydes without the use of a catalyst.

Initially, we investigated the reaction by choosing *S*-methyl-*S*-phenylsulfoximine (**1a**) and 4-nitrobenzaldehyde (**2a**) as the model substrates and NBS as oxidant (Table 1). To a solution of *S*-methyl-*S*-phenylsulfoximine (**1a**) in ethyl acetate (1 mL), 4-nitrobenzaldehyde (**2a**; 1.1 equiv) and NBS (1.2 equiv) were added, and the reaction was performed under microwave irradiation for 25 minutes at 80 °C. To our delight, the desired product *N*-(4-nitrobenzoyl)sulfoximine **3a** was obtained in 76% yield (entry 1). Then other halogen sources were investigated; interestingly, NCS gave only 25% of the desired product, and no product was observed with I_2 (entries 2 and 3). Next, the reaction was performed in various solvents, such as CH_2Cl_2, MeCN, THF, 1,4-dioxane, and DCE (entries 4–8). It was found that DCE

Table 1 Optimization of the *N*-Acylation of Sulfoximine **1a** with Aldehyde **2a**[a]



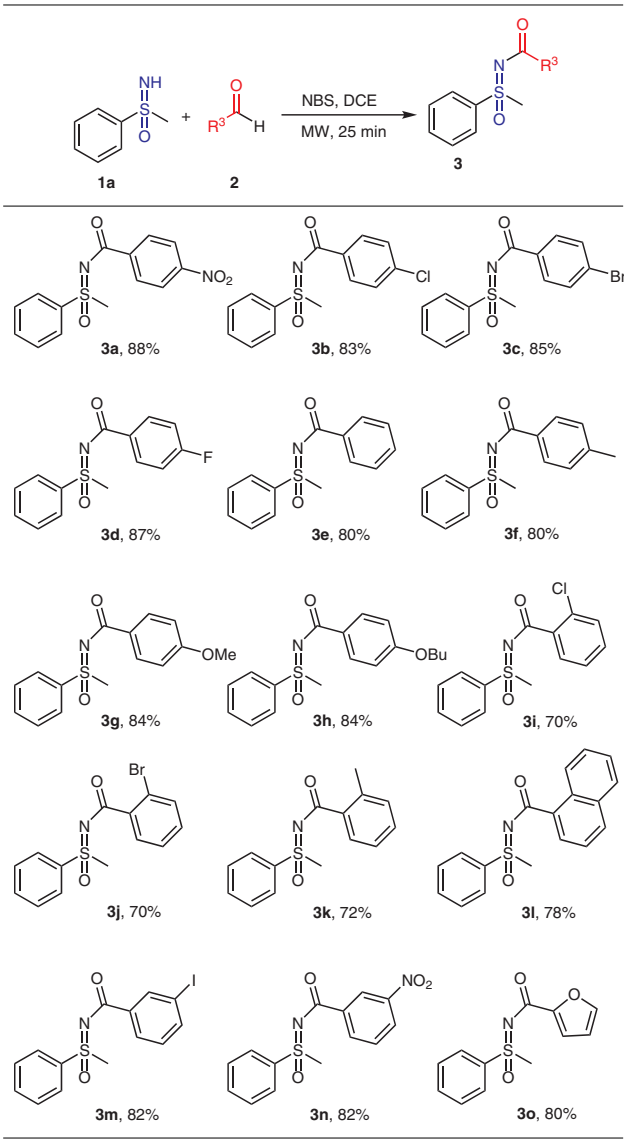
Entry	Oxidant	Solvent	Time	Yield (%)[b]
1	NBS	EtOAc	25 min	76
2	NCS	EtOAc	30 min	25
3	I_2	EtOAc	30 min	–
4	NBS	CH_2Cl_2	25 min	68
5	NBS	MeCN	25 min	55
6	NBS	THF	25 min	–
7	NBS	1,4-dioxane	25 min	85
8	**NBS**	**DCE**	**25 min**	**88**
9[c]	NBS	DCE	30 min	65
10[d]	NBS	DCE	12 h	–
11[e]	NBS	DCE	6 h	85

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.22 mol, 1.1 equiv), oxidant (0.24 mmol, 1.2 equiv), solvent (1 mL), 80 °C, MW, unless stated otherwise.
[b] Isolated yield.
[c] MW, 50 °C.
[d] At r.t., 12 h.
[e] At 80 °C, 6 h, conventional heating.

was the solvent of choice, furnishing the product in 88% yield. Further, performing the reaction at 50 °C under MW conditions resulted in a lower yield of 65% (entry 9). Also, when the reaction was carried out at room temperature for 12 hours, we did not observe any product (entry 10); instead, we could isolate *N*-bromosulfoximine as the main product under these conditions. However, conventional heating of the reaction mixture at 80 °C for 6 hours gave the desired product in 85% yield (entry 11). Thus, the results were optimal when using aldehyde (1.1 equiv), NBS (1.2 equiv), and DCE as the solvent under microwave irradiation (entry 8).

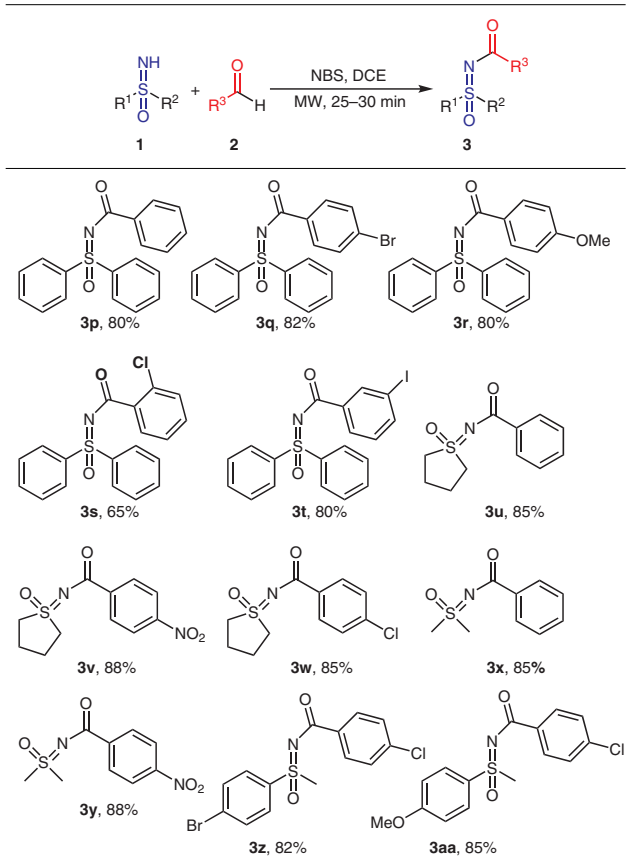
Having established the optimized conditions, we extended the reaction to different commercially available aldehydes to investigate the scope of the reaction (Table 2). Aldehydes bearing electron-withdrawing groups such as F, Cl, Br, and NO_2 or electron-donating groups (Me, OMe, and OBu) on the aromatic ring underwent smooth coupling and afforded the corresponding product in good to excellent yields (Table 2, 3a–h, 80–88%). However, aldehydes with an electron-withdrawing substituent showed slightly better results. The reaction was equally compatible with *ortho*- and *meta*-substituted aryl aldehydes. The reaction was showed to be effective with bulky 1-naphthaldehydes as well (**3l**). Notably, this procedure did not work well with aliphatic aldehydes, which only gave minor amounts of product as seen by LCMS; this is in consonance with the proposed radical mechanism (*vide infra*).

Table 2 Scope of the *N*-Acylation of Sulfoximine **1a** with Different Aldehydes **2**[a]

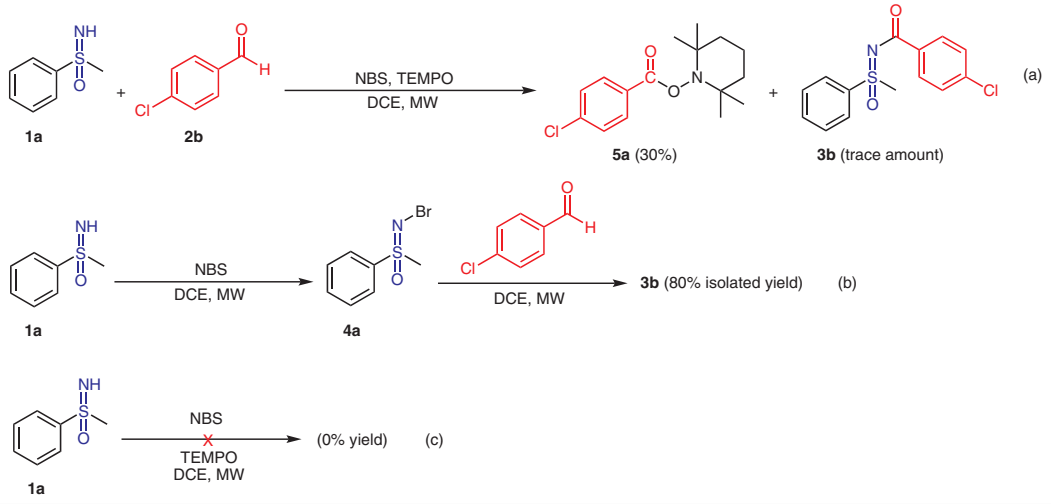


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mol), NBS (0.24 mmol), DCE (1 mL), MW, 80 °C, 25 min; yields shown of isolated products after chromatographic purification.

Table 3 Scope of the *N*-Acylation of Different Sulfoximines **1** with Aldehydes **2**[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mol), NBS (0.24 mmol), DCE (1 mL), MW, 80 °C, 25–30 min; yields shown of isolated products after chromatographic purification.



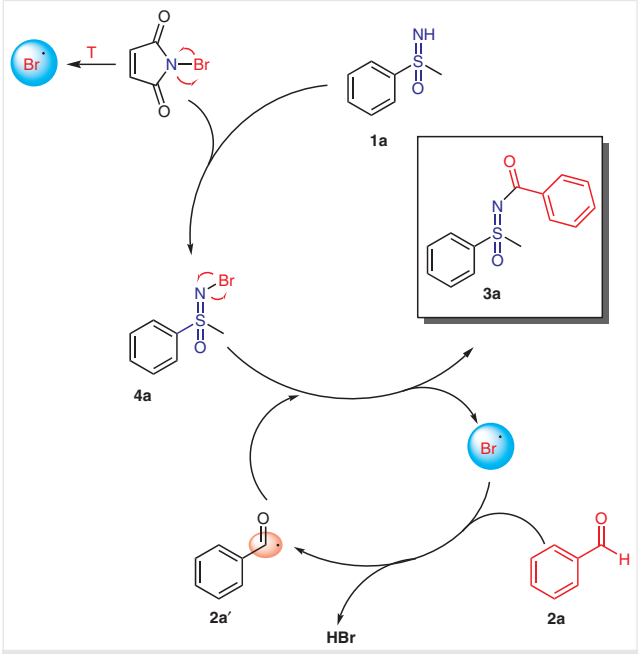
Scheme 2 Control experiments to demonstrate the involvement of a radical mechanism. The collected data suggest that the Br radical required for formation of the acyl radical may initiate from both NBS and *N*-bromosulfoximine intermediate **4a**.

Further, we investigated the *N*-acylation reactions with different sulfoximines under the optimized conditions with some of the aldehydes. The results are shown in Table 3. To our delight, the reaction proceeded smoothly with various *NH*-sulfoximines with reasonable to good efficiency. The formation of products with electron-rich as well as electron-deficient substituents on *S*-arylsulfoximines enhances the scope of this protocol (**3z**, **3aa**).

To understand the actual reaction pathway, we conducted a series of control experiments. Initially, we performed the reaction in the presence of a radical scavenger, i.e. TEMPO under the optimized conditions. The reaction produced the acyl–TEMPO adduct **5a** as the major product along with trace amounts of the acylated product **3b** (Scheme 2a). The formation of the TEMPO adduct **5a** established that the reaction likely follows a radical pathway.

Furthermore, in order to investigate formation of the *N*-bromosulfoximine intermediate, we conducted the reaction in a stepwise manner (Scheme 2b). As expected, we isolated *N*-bromosulfoximine **4a** (90%)[23] in the first step, which led to product **3b** (80%) in the following step (Scheme 2b). Isolation of **4a** established that the reaction proceeded via the *N*-bromosulfoximine intermediate. The observation that isolated **4a** can be converted into product **3b** in the absence of NBS suggests that **4a** can undergo homolytic N–Br cleavage upon heating, as a Br radical is needed to generate the required acyl radical. An additional experiment with **1a** and NBS in the presence of TEMPO did not afford the desired *N*-bromosulfoximine (Scheme 2c), again suggesting a radical step under our reaction conditions.

Based on these observations and existing literature,[17,24] a plausible mechanism for this catalyst-free protocol is depicted in Scheme 3. Initially, NBS reacts with sulfoximine **1a** to give *N*-bromosulfoximine **4a**; although this process is known to be possible through an ionic mechanism, our data suggest that a radical process is involved under our optimized reaction conditions. Acyl radical **2a′** is formed by reaction of the bromine radical with aldehyde **2a**. The Br radical may be initiated from either NBS or the *N*-bromosulfoximine intermediate **4a**. Finally, the desired product **3a** is formed through attack of the acyl radical **2a′** on **4a** with generation of a new Br radical, or termination by combination of the radicals.



Scheme 3 Proposed reaction mechanism. Under the reported conditions, a Br radical may be initiated from either NBS or *N*-bromosulfoximine intermediate **4a**. The Br radical in turn generates acyl radical **2a′** (by hydrogen abstraction), which may attack **4a** to generate the product and a new Br radical.

In summary, we have developed a complementary approach for the synthesis of *N*-acylsulfoximines, a functional group that is rapidly receiving interest for the design of biologically active compounds. The procedure uses readily available aldehydes with *N*-bromosuccinimide under microwave irradiation and proceeds without any catalyst. The new radical-mediated methodology offers a practical route towards a mild and convenient synthesis of *N*-acylsulfoximines. It is characterized by catalyst-free conditions, insensitivity to atmospheric moisture, applicability to a wide range of substrates, rapid transformation times, no preactivation of reagents, and avoidance of excess oxidant.

Starting materials (sulfoximines **1**) were prepared by using literature procedures. Aldehydes, *N*-bromosuccinimide (NBS), and solvents were purchased from Aldrich and other commercial suppliers. Gravity column chromatography utilizing silica gel (60–120 mesh) as the stationary phase and EtOAc/hexane as eluting solvents was used for purification. All chemical reactions were monitored by either LC/MS (Shimadzu 2020 UFLC-MS) or TLC (aluminum sheet coated with silica gel 60, visible at 254 nm) viewed under UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance III 400 MHz instrument of samples in $CDCl_3$ and by using the residual signals from $CDCl_3$ as the reference. HRMS was carried out by using a Bruker micro TOF-Q II instrument operating at ambient temperatures by using a sample concentration of approximately 1.0 ppm. All microwave-assisted reactions were carried out with a CEM Discover SP system.

N-Acylation of Sulfoximines 1 with Aldehydes 2; General Procedure

Aldehyde **2** (0.22 mmol) and NBS (0.24 mmol) were added to a solution of sulfoximine **1** (0.2 mmol) in DCE (1 mL). The reaction mixture was stirred under MW at 80 °C, 200 W for the appropriate time (tracked by TLC). The excess solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, EtOAc/hexane); this provided pure product **3**.

S-Methyl-*N*-(4-nitrobenzoyl)-*S*-phenylsulfoximine (3a)[18]

Yield: 54 mg (88%); yellow solid; mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 9.2 Hz, 2 H), 8.24 (d, *J* = 8.8 Hz, 2 H), 8.05 (d, *J* = 7.2 Hz, 2 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 2 H), 3.50 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 150.1, 141.0, 138.4, 134.2, 130.4, 129.8, 127.1, 123.2, 44.4).

N-(4-Chlorobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3b)[18]

Yield: 49 mg (83%); white solid; mp 115–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.8 Hz, 2 H), 8.04–8.02 (m, 2 H), 7.71–7.67 (m, 1 H), 7.63–7.59 (m, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 138.8, 138.5, 134.1, 133.9, 130.8, 129.7, 128.3, 127.1, 44.3.

N-(4-Bromobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3c)[18]

Yield: 58 mg (85%); white solid; mp 100–102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.01 (m, 4 H), 7.72–7.68 (m, 1 H), 7.64–7.60 (m, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 3.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 138.8, 134.5, 133.9, 131.3, 131.1, 129.7, 127.1, 44.4.

N-(4-Fluorobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3d)[12]

Yield: 48 mg (87%); white solid; mp 112–114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.14 (m, 2 H), 8.05–8.02 (m, 2 H), 7.68 (t, J = 7.2 Hz,1 H), 7.60 (t, *J* = 7.6 Hz, 2 H), 7.05 (t, *J* = 8.8 Hz, 2 H), 3.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 166.6, 164.2, 138.9, 133.8, 131.9, 131.8, 129.7, 129.4, 127.1, 115.1, 114.8, 44.3.

N-Benzoyl-*S*-methyl-*S*-phenylsulfoximine (3e)[18]

Yield: 42 mg (80%); white solid; mp 103–105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.16 (m, 2 H), 8.05 (d, *J* = 7.2 Hz, 2 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 8.4 Hz, 2 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 3.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 139.0, 135.6, 133.8, 132.1, 129.6, 129.4, 128.0, 127.1, 44.4.

S-Methyl-*N*-(4-methylbenzoyl)-*S*-phenylsulfoximine (3f)[18]

Yield: 44 mg (80%); white solid; mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.03 (m, 4 H), 7.69–7.65 (m, 1 H), 7.63–7.58 (m, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 3.45 (s, 3 H), 2.39 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 142.7, 139.1, 133.7, 132.9, 129.6, 129.5, 128.7, 127.1, 44.4, 21.6.

N-(4-Methoxybenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3g)[12]

Yield: 49 mg (84%); white solid; mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12. (d, *J* = 8.8 Hz, 2 H), 8.07–8.04 (m, 2 H), 7.69–7.65 (m, 1 H), 7.63–7.58 (m, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 3.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 162.9, 139.3, 133.7, 131.5, 129.6, 128.3, 127.2, 113.2, 55.9, 44.4.

N-(4-Butoxybenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3h)

Yield: 53 mg (84%); yellow solid; mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.8 Hz, 2 H), 8.06–8.03 (m, 2 H), 7.69–7.65 (m, 1 H), 7.62–7.58 (m, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.00 (t, *J* = 6.8 Hz, 2 H), 3.45 (s, 3 H), 1.81–1.74 (m, 2 H), 1.54–1.46 (m, 2 H), 0.97 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 162.9, 139.3, 133.7, 131.5, 129.6, 128.3, 127.2, 113.2, 67.8, 44.4, 31.2, 19.2, 13.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}NO_3S$: 332.1320; found: 332.1344.

N-(2-Chlorobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3i)[17]

Yield: 41 mg (70%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2 H), 7.76 (dd, *J* = 1.6, 7.2 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.57–7.52 (m, 2 H), 7.32 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.28–7.18 (m, 2 H), 3.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 138.5, 136.3, 134.0, 132.2, 131.2, 130.8, 130.6, 129.7, 127.3, 126.5, 44.3.

***N*-(2-Bromobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3j)**[17]

Yield: 47 mg (70%); yellow solid; mp 82–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 2 H), 7.72 (dd, *J* = 2 Hz, 7.2 Hz, 1 H), 7.63–7.59 (m, 1 H), 7.55–7.51 (m, 3 H), 7.27–7.23 (m, 1 H), 7.19–7.14 (m, 1 H), 3.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 138.5, 138.4, 134.0, 133.7, 131.2, 130.5, 129.5, 127.3, 127.1, 120.3, 44.3.

***S*-Methyl-*N*-(2-methylbenzoyl)-*S*-phenylsulfoximine (3k)**[17]

Yield: 40 mg (72%); white solid; mp 88–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 3 H), 7.70–7.66 (m,1 H), 7.63–7.59 (m, 2 H), 7.35–7.31 (m, 1 H), 7.24–7.19 (m, 2 H), 3.40 (s, 3 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 139.3, 139.0, 135.3, 133.7, 131.5, 130.9, 130.3, 129.7, 127.2, 125.4, 44.5. 21.7.

***S*-Methyl-*N*-(1-naphthylcarbonyl)-*S*-phenylsulfoximine (3l)**[12]

Yield: 48 mg (78%); yellow sticky solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (d, *J* = 8.4 Hz, 1 H), 8.35 (dd, *J* = 1.6, 7.6 Hz, 1 H), 8.11–8.08 (m, 2 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.89–7.82 (m, 1 H), 7.72- 7.66 (m, 1 H), 7.65–7.59 (m, 2 H), 7.57–7.46 (m, 3 H), 3.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 139.0, 133.9, 133.8, 132.9, 132.3, 131.3, 129.8, 129.7, 128.3, 127.1, 126.4, 125.8, 124.5, 44.5.

***N*-(3-Iodobenzoyl)-*S*-methyl-*S*-phenylsulfoximine (3m)**[18]

Yield: 63 mg (82%); white solid; mp 109–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (t, *J* = 1.6 Hz, 1 H), 8.11–8.09 (m, 1 H), 8.03 (d, *J* = 7.2 Hz, 2 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 8.0 Hz, 2 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 3.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 140.9, 138.7, 138.4, 137.6, 133.9, 129.8, 129.7, 128.5, 127.1, 93.7, 44.4.

***S*-Methyl-*N*-(3-nitrobenzoyl)-*S*-phenylsulfoximine (3n)**[18]

Yield: 50 mg (82%); white solid; mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (t, *J* = 2 Hz, 1 H), 8.45–8.43 (m, 1 H), 8.35–8.32 (m, 1 H), 8.05–8.03 (m, 2 H), 7.73–7.69 (m, 1 H), 7.66–7.56 (m, 3 H), 3.49 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 148.1, 138.4, 137.4, 135.1, 134.2, 129.8, 129.2, 127.1, 126.5, 124.4, 44.4.

***N*-(2-Furylcarbonyl)-*S*-methyl-*S*-phenylsulfoximine (3o)**[15]

Yield: 40 mg (80%); white sticky solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8 Hz, 2 H), 7.67 (t, *J* = 7.2 Hz, 1 H), 7.60 (t, *J* = 8 Hz, 2 H), 7.53 (br s, 1 H), 7.16 (d, *J* = 3.2 Hz, 1 H), 6.46 (br s, 1 H), 3.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 150.0, 145.5, 138.7, 133.9, 129.7, 127.2, 116.8, 111.8, 44.6.

***N*-Benzoyl-*S*,*S*-diphenylsulfoximine (3p)**[18]

Yield: 52 mg (80%); white solid; mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.2 Hz, 2 H), 8.10–8.04 (m, 4 H), 7.59 – 7.50 (m, 7 H), 7.44 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 139.8, 135.8, 133.3, 132.2, 129.6, 129.5, 128.1, 127.7.

***N*-(4-Bromobenzoyl)-*S*,*S*-diphenylsulfoximine (3q)**[25]

Yield: 63mg (82%); white solid; mp 115–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.95 (m, 6 H), 7.51–7.46 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 139.7, 134.7, 133.4, 131.3, 131.1, 129.6, 127.6, 127.2.

***N*-(4-Methoxybenzoyl)-*S*,*S*-diphenylsulfoximine (3r)**[25]

Yield: 56 mg (80%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 8.08–8.03 (m, 4 H), 7.59–7.50 (m, 6 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 162.9, 140.1, 133.2, 132.5, 131.5, 129.5, 129.1, 128.5, 127.9, 127.6, 113.1, 55.4.

***N*-(2-Chlorobenzoyl)-*S*,*S*-diphenylsulfoximine (3s)**

Yield: 46 mg (65%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 4 H), 7.83 (dd, *J* = 2, 7.6 Hz, 1 H), 7.54–7.42 (m, 6 H), 7.34 (dd, *J* = 1.6, 8 Hz, 1 H), 7.29–7.18 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 139.5, 136.4, 133.4, 132.4, 131.3, 130.6, 129.6, 127.7, 126.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}ClNO_2S$: 356.0512; found: 356.0484.

***N*-(3-Iodobenzoyl)-*S*,*S*-diphenylsulfoximine (3t)**

Yield: 71 mg (80%); white solid; mp 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 8.05 (d, *J* = 7.6 Hz, 4 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.63–7.53 (m, 6 H), 7.17 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 142.3, 141.0, 139.5, 138.9, 138.4, 137.7, 133.5, 129.8, 129.3, 128.7, 127.6, 93.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}INO_2S$: 447.9868; found: 447.9834.

***N*-(Benzoyl)-*S*,*S*-tetramethylenesulfoximine (3u)**[18]

Yield: 38 mg (85%); white solid; mp 94–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.4 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8 Hz, 2 H), 3.74–3.67 (m, 2 H), 3.37–3.30 (m, 2 H), 2.42–2.28 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 135.2, 132.2, 129.3, 128.0, 52.7, 23.8.

***N*-(4-Nitrobenzoyl)-*S*,*S*-tetramethylenesulfoximine (3v)**[12]

Yield: 47 mg (88%); white solid; mp 168–170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.22 (m, 4 H), 3.74–3.69 (m, 2 H), 3.40–3.35 (m, 2 H), 2.45–2.30 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 150.0, 140.7, 130.3, 123.2, 52.7, 23.7.

***N*-(4-Chlorobenzoyl)-*S*,*S*-tetramethylenesulfoximine (3w)**

Yield: 44 mg (85%); white solid; mp 94–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.73–3.66 (m, 2 H), 3.37–3.30 (m, 2 H), 2.41–2.21 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 138.5, 133.7, 130.8, 128.3, 52.7, 23.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}ClNO_2S$: 258.0356; found: 258.0350.

N-Benzoyl-S,S-dimethylsulfoximine (3x)[25]

Yield: 34 mg (85%); white solid; mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.10 (m, 2 H), 7.52–7.47 (m, 1 H), 7.39 (t, *J* = 8 Hz, 2 H), 3.37 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 135.4, 132.2, 129.2, 128.0, 41.8.

S,S-Dimethyl-N-(4-nitrobenzoyl)sulfoximine (3y)[12]

Yield: 43 mg (88%); white solid; mp 170–173 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.22 (m, 4 H), 3.42 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 150.1, 140.9, 130.3, 123.2, 41.9.

S-(4-Bromophenyl)-N-(4-chlorobenzoyl)-S-methylsulfoximine (3z)[26]

Yield: 61 mg (82%); white solid; mp 110–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 2 H), 7.89 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 3.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 138.6, 137.9, 133.8, 133.1, 130.8, 129.4, 128.7, 128.3, 44.4.

N-(4-Chlorobenzoyl)-S-(4-methoxyphenyl)-S-methylsulfoximine (3aa)

Yield: 55 mg (85%); yellow solid; mp 120–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 2 H), 7.96 (d, *J* = 9.2 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 3.89 (s, 3 H), 3.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 163.9, 138.3, 134.3, 130.8, 129.8, 129.3, 128.2, 114.9, 55.8, 44.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}ClNO_3S$: 324.0461; found: 324.0454

Control Experiment with TEMPO

To a solution of **1a** (0.2 mmol) in DCE (1 mL), **2b** (0.22 mmol), NBS (0.24 mmol), and TEMPO (2 equiv) were added and the reaction mixture was stirred under MW heating at 80 °C, 200 Watt for the appropriate time (tracked by TLC). The excess solvent was removed *in vacuo* and the crude product was purified by chromatography (silica gel, EtOAc/hexane).

2,2,6,6-Tetramethylpiperidin-1-yl 4-Chlorobenzoate (5a)[24a]

Yield: 18 mg (30%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 1.81–1.57 (m, 5 H), 1.48–1.45 (m, 1 H), 1.26 (s, 6 H), 1.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 139.3, 130.9, 128.8, 128.1, 60.5, 39.1, 31.9, 20.8, 16.9.

Funding Information

The authors would like to thank the South African National Research Foundation (grant numbers 105213 and 105236), Aspen Pharmacare, and the South African Medical Research Council for their support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691589.

References

(1) (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. *Chem. Asian J.* **2008**, *3*, 810. (c) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (d) Rajbongshi, K. K.; Saikia, I.; Chanu, L. D.; Roy, S.; Phukan, P. *J. Org. Chem.* **2016**, *81*, 5423. (e) Rit, R. K.; Shankar, M.; Sahoo, A. K. *Org. Biomol. Chem.* **2017**, *15*, 1282.

(2) (a) Bizet, V.; Hendriks, C. M. M.; Bolm, C. *Chem. Soc. Rev.* **2015**, *44*, 3378. (b) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (c) Lücking, U. *Angew. Chem. Int. Ed.* **2013**, *52*, 9399. (d) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. *Eur. J. Med. Chem.* **2017**, *126*, 225. (e) Bizet, V.; Kowalczyk, R.; Bolm, C. *Chem. Soc. Rev.* **2014**, *43*, 2426. (f) Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem.* **2011**, *59*, 2950. (g) Chen, X. Y.; Park, S. J.; Buschmann, H.; De Rosa, M.; Bolm, C. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4307. (h) Park, S. J.; Baars, H.; Mersmann, S.; Buschmann, H.; Baron, J. M.; Amann, P. M.; Czaja, K.; Hollert, H.; Bluhm, K.; Redelstein, R.; Bolm, C. *ChemMedChem* **2013**, *8*, 217. (i) Thota, N.; Makam, P.; Rajbongshi, K. K.; Nagiah, S.; Abdul, N. S.; Chuturgoon, A. A.; Kaushik, A.; Lamichhane, G.; Somboro, A. M.; Kruger, H. G.; Govender, T.; Naicker, T.; Arvidsson, P. I. *ACS Med. Chem. Lett.* **2019**, *10*, 1457.

(3) (a) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (b) Bolm, C.; Simić, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830. (c) Frings, M.; Thomé, I.; Schiffers, I.; Pan, F.; Bolm, C. *Chem. Eur. J.* **2014**, *20*, 1691.

(4) (a) Harmata, M.; Hong, X. *Org. Lett.* **2007**, *9*, 2701. (b) Peraino, N. J.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2015**, *17*, 1735.

(5) Frings, M.; Thomé, I.; Bolm, C. *Beilstein J. Org. Chem.* **2012**, *8*, 1443.

(6) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341.

(7) (a) Yu, H.; Li, Z.; Bolm, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 324. (b) Tota, A.; Zenzola, M.; Chawner, S. J.; John-Campbell, S. S.; Carlucci, C.; Romanazzi, G.; Degennaro, L.; Bull, J. A.; Luisi, R. *Chem. Commun.* **2017**, *53*, 348. (c) Zhu, H.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2016**, *52*, 11908. (d) Gupta, S.; Chaudhary, P.; Muniyappan, N.; Sabiah, S.; Kandasamy, J. *Org. Biomol. Chem.* **2017**, *15*, 8493. (e) Gupta, S.; Baranwal, S.; Muniyappan, N.; Sabiah, S.; Kandasamy, J. *Synthesis* **2019**, *51*, 2171.

(8) (a) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (b) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Org. Lett.* **2013**, *15*, 1638. (c) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258. (d) Yadav, M. R.; Shankar, M.; Ramesh, E.; Ghosh, K.; Sahoo, A. K. *Org. Lett.* **2015**, *17*, 1886.

(9) (a) Bolm, C.; Hackenberger, C. P. R.; Simić, O.; Verrucci, M.; Müller, D.; Bienewald, F. *Synthesis* **2002**, 879. (b) Hackenberger, C. P. R.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2004**, *10*, 2942.

(10) Garimallaprabhakaran, A.; Harmata, M. *Synlett* **2011**, 361.

(11) Noda, H.; Asada, Y.; Shibasaki, M.; Kumagai, N. *Chem. Commun.* **2017**, *53*, 7447.

(12) Wang, L.; Priebbenow, D. L.; Zou, L.-H.; Bolm, C. *Adv. Synth. Catal.* **2013**, *355*, 1490.

(13) Qin, W.-J.; Li, Y.; Yu, X.; Deng, W.-P. *Tetrahedron* **2015**, *71*, 1182.

(14) Porey, A.; Santra, S.; Guin, J. *Asian J. Org. Chem.* **2016**, *5*, 870.
(15) Jiang, W.; Huang, Y.; Zhou, L.; Zeng, Q. *Sci. China: Chem.* **2019**, *62*, 1213.
(16) Priebbenow, D. L.; Bolm, C. *Org. Lett.* **2014**, *16*, 1650.
(17) Muneeswara, M.; Kotha, S. S.; Sekar, G. *Synthesis* **2016**, *48*, 1541.
(18) Zou, Y.; Xiao, J.; Peng, Z.; Dong, W.; An, D. *Chem. Commun.* **2015**, *51*, 14889.
(19) Zhao, Z.; Wang, T.; Yuan, L.; Jia, X.; Zhao, J. *RSC Adv.* **2015**, *5*, 75386.
(20) (a) Gawande, M. B.; Shelke, S. N.; Zboril, R.; Varma, R. S. *Acc. Chem. Res.* **2014**, *47*, 1338. (b) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629. (c) de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (d) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (e) Khumalo, M. F.; Akpan, E. D.; Chinthakindi, P. K.; Brasil Edikarlos, M.; Rajbongshi, K. K.; Makatini, M. M.; Govender, T.; Kruger, H. G.; Naicker, T.; Arvidsson, P. I. *RSC Adv.* **2018**, *8*, 37503.
(21) Deka, N.; Sarma, J. C. *J. Org. Chem.* **2001**, *66*, 1947.
(22) (a) Saikia, I.; Borah, A. J.; Phukan, P. *Chem. Rev.* **2016**, *116*, 6873. (b) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (c) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861. (d) Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2008**, *10*, 1863.
(23) Bohnen, C.; Bolm, C. *Org. Lett.* **2015**, *17*, 3011.
(24) (a) Achar, T. K.; Mal, P. *J. Org. Chem.* **2015**, *80*, 666. (b) Minisci, F. *Synthesis* **1973**, 1.
(25) Pimpasri, C.; Sumunnee, L.; Yotphan, S. *Org. Biomol. Chem.* **2017**, *15*, 4320.
(26) Bala, B. D.; Sharma, N.; Sekar, G. *RSC Adv.* **2016**, *6*, 97152.