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Metal-Free, Phosphonium Salt-Mediated Sulfoximination of Azine *N*-Oxides: Approach for the Synthesis of *N*-Azine Sulfoximines

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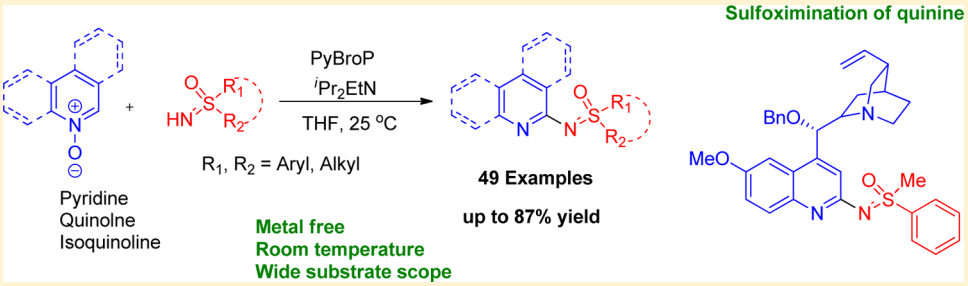
Supporting Information



ABSTRACT: Herein, we report a simple and metal-free method for the synthesis of *N*-azine sulfoximines by the nucleophilic substitution of azine *N*-oxides with *NH*-sulfoximines. The present method works at room temperature with wide functional group compatibility and gives several unprecedented *N*-azine sulfoximines. The reaction conditions were also found suitable with enantiopure substrates and furnished products without any racemization. It also finds an application in the sulfoximination of azine-based functional molecules such as 2,2′-bipyridine, 1,10-phenanthroline, and quinine.

INTRODUCTION

Sulfoximines are well-known for their application as chiral auxiliaries[1a−c] and ligands[1d−g] in asymmetric synthesis, as well as building blocks in pseudopeptides.[2] However, in recent years, their use in drug discovery have attracted the attention of medicinal chemists.[3] In drug discovery, this moiety has been used for improving specificity,[4] stability/oral bioavailability,[5] and reducing undesired toxicity.[6] In addition, sulfoximines have also been used as bioisosteres for several functional moieties such as heterocyclic amidine,[5,7] sulfones,[8] and secondary hydroxyl groups,[9] as well as stable transition-state analogue inhibitors.[10] Keeping in view the importance of sulfoximines in drug discovery and catalysis, several groups worldwide are interested in the synthesis of sulfoximines and their derivatives. There are several reports for the synthesis of *NH*-sulfoximines,[11,12] but only few reports are available for *N*-substituted derivatives,[1b,13] which involved either traditional transition-metal-catalyzed cross-coupling (Scheme 1, approach a)[1b,13a−d] or cross-dehydrogenative coupling methods (Scheme 1, approaches b and c).[13e,f]

Our constant interest in the functionalization of electron-deficient systems[14] motivated us to develop a simple method for the sulfoximination of electron-deficient heteroarenes. Initially, we tried the coupling of *iso*-quinoline with *N*-chlorosulfoximine in the presence of iron salt.[14a] Unfortunately, no reaction was observed (Scheme 1, approach e, path A). We rationalized that the attempted reactions generated sulfoximinyl radical cations from *N*-chlorosulfoximine,[15] which represents an electron-deficient system, and coupling between two electron-deficient systems might not be possible.[15] In this direction, Londregan et al. established a PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate)-mediated method for the functionalization of electron-deficient heteroarenes with various nucleophiles (amine, phenol, sulfonamide, malonate, pyridine, thiol, silyl ketene acetal)[16] which has become a remarkable strategy for constructing a variety of carbon−carbon or carbon−heteroatom bonds under metal-free conditions (Scheme 1, approach d).[16] Considering the nucleophilic nature of *NH*-sulfoximines, we envisioned that the same approach could be explored for the sulfoximination of electron-deficient heteroarenes. Here, we have successfully applied a precedented method for the sulfoximination of azines through azine *N*-oxides in the presence of the *N*-*O* activating agent, PyBroP (Scheme 1, approach e, path B). The method works well with substituted and unsubstituted quinolines, isoquinolines, and pyridines and gives the corresponding *N*-azine sulfoximines in good to excellent yields.

RESULTS AND DISCUSSION

Our investigation started with test substrates isoquinoline-*N*-oxide **1a** and racemic *S*-methyl-*S*-phenylsulfoximine **2a** in the presence of PyBroP as *N*-oxide activating agent using the conditions reported by Londregan et al.,[16b,c] which successfully gave desired coupled product **3aa** in a yield of 87%. After this success, the applicability of sulfoximines was examined, and all

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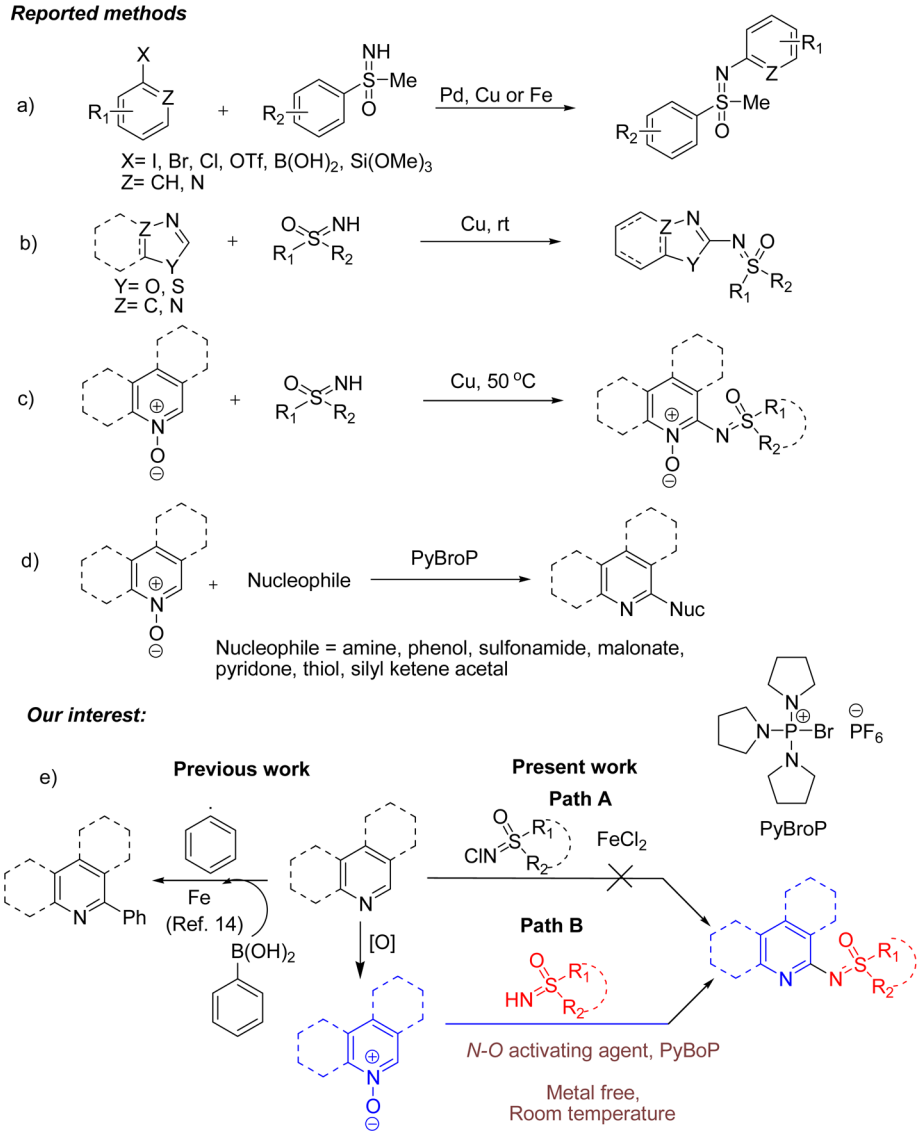
Scheme 1. Previous and Present Reports



the results are given in Scheme 2. Various sulfoximines efficiently coupled with isoquinoline-*N*-oxide **1a** and gave corresponding coupled products **3aa**–**ao** in good to excellent yields.

A series of alkyl aryl and diaryl sulfoximines containing electron-donating groups (OMe and Me) and electron-withdrawing groups (Br, Cl, F, and NO_2) on the aryl ring underwent smooth reaction with isoquinoline-*N*-oxide **1a** and gave the desired products (**3ab**–**3ah**) in good to high yields. The high C-1 regioselectivity as observed earlier[16c,17] might be directed by LUMO electron density of the azine *N*-oxide. Sulfoximines with electron-donating groups on the phenyl ring have shown slightly better yields than sulfoximines with electron-withdrawing groups. Cyclic and dialkyl sulfoximines, *S*,*S*-tetramethylene-sulfoximine, *S*,*S*-dimethylsulfoximine, and *S*,*S*-dibutyl-sulfoximine, also worked and afforded the corresponding products **3ai**, **3aj**, and **3ak** in good yields. Sterically hindered *S*-methyl-*S*-naphthyl sulfoximine did not give good results. To our delight, *S*-ethyl, *S*-propyl, and *S*-butyl phenyl sulfoximines also furnished high yields of corresponding products **3am**, **3an**, and **3ao**, respectively.

Further, this reaction was successfully extended to various pyridine- and quinoline-*N*-oxides (Scheme 3). Mostly, all substrates reacted smoothly and afforded the desired products in good yields. Pyridine-*N*-oxide gave a 1:1 mixture of separable 2- and 4-substituted products **4aa** and **4aa′** in an overall yield of 75%. Unfortunately, 2-methyl and 2,6-dimethylpyridine-*N*-oxides were not good substrates for this transformation (**4ab** and **4ac**). However, 3-methylpyridine-*N*-oxide gave corresponding 2-substituted products **4ad**–**4ae** with moderate to good yields. On the other hand, 3-bromopyridine-*N*-oxide gave a separable mixture of 2- and 6-substituted products **4af** and **4af′** in the ratio of 2:1 in an overall yield of 42%.[16c,17] The 2-phenylpyridine-*N*-oxide afforded corresponding single regiomers **4ag** and **4ah** in a yields of 65% and 35%, respectively. Further, 2-bromo-4-chloropyridine-*N*-oxide furnished low yields (**4ai** and **4aj**).

Pyridine-*N*-oxides having electron-donating (*t*Bu) and electron-withdrawing (CN, CF_3, NO_2) groups at the fourth position furnished the single regioisomeric respective products **4ak**–**4ao** in a yields of 75, 65, 75, 40, and 35%, respectively. Diazine-*N*-oxide such as pyrazine-*N*-oxide was not found to be a suitable substrate for this reaction. Gratifyingly, quinoline-*N*-oxides furnished single regioisomeric products with good to excellent yields. The quinoline-*N*-oxide, when subjected to a series of

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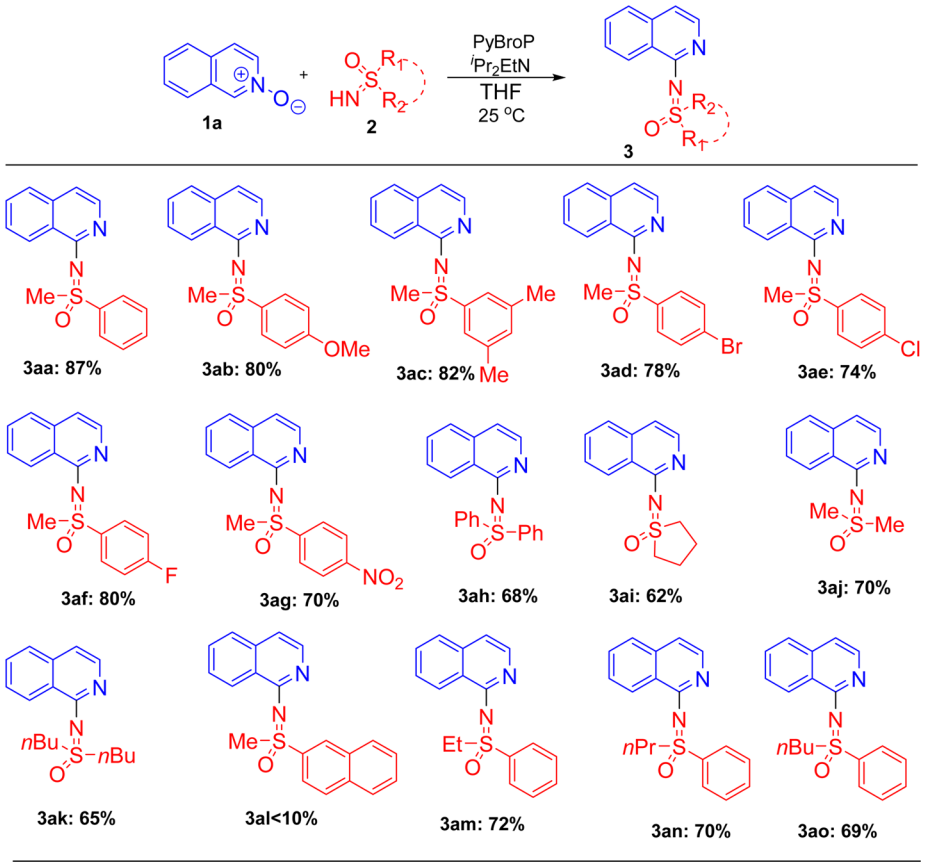
Scheme 2. Addition of Various Sulfoximines to Isoquinoline-*N*-oxide[a]



[a]Reaction conditions: All reactions were conducted at 0.2 M concentration with **1a** (0.2 mmol, 1.0 equiv), **2** (0.26 mmol, 1.3 equiv), $^{i}Pr_2EtN$ (0.6 mmol, 3.0 equiv), and PyBroP (0.22 mmol, 1.1 equiv) at 25 °C for 15 h.

different alkyl aryl and dialkyl sulfoximines, the corresponding coupled products **4ca**, **4cb**, **4cc**, and **4cd** were obtained in a yields of 80, 69, 65, and 53%, respectively. Similarly, 4-methylquinoline-*N*-oxide on coupling with various sulfoximines afforded coupled products **4ce**, **4cf**, and **4cg** in yields of 72, 60, and 65%, respectively. Furthermore, 5-bromoquinoline-*N*-oxide and 8-methoxyquinoline-*N*-oxide, when tried, also furnished coupled products **4ch** and **4ci** in 63% and 70% yields, respectively. When 6-bromoquinoline-*N*-oxide was employed in this reaction with *S*-methyl-*S*-phenylsulfoximine and *S*,*S*-dibutylsulfoximine, the corresponding products **4cj** and **4ck** were found in good yields of 70% and 60%, respectively. The *N*-methyl 7-aza indole-*N*-oxide did not undergo coupling.

Considering the mildness of the reaction conditions, isoquinoline-*N*-oxide **1a** was treated with enantiopure sulfoximine (*S*)-(+)-*S*-methyl-*S*-phenylsulfoximine (Scheme 4), and the corresponding product (***S***)-(−)-**3aa** was obtained in 85% yield with high enantiomeric excess (>99% ee, see the SI), respectively, which suggested that chiral substrates are also tolerated under reaction conditions.

After exploring the feasibility of the present method with various substrates, its application toward the diversification of azine-based functional molecules was also explored. Azine-based functional molecules, such as 1,10-phenanthroline and 2,2′-bipyridine, are well-known ligands, and in many instances, their substituted versions provide additional advantages in terms of reactivity and selectivity.[18] On the other hand, sulfoximines are also well-known for their application as chiral auxiliaries[1a−c] and ligands,[1d−g] and sulfoximination of the above-mentioned ligands may provide some advantages. Toward this end, sulfoximidoyl containing 1,10-phenanthroline **6aa** and 2,2′-bipyridine **6ab** were successfully synthesized on reaction with *S*-methyl-*S*-phenylsulfoximine (Scheme 5).

Furthermore, a notable example for the present method is the direct sulfoximination of quinine. The reaction of quinine analogue **7a** with racemic *S*-methyl-*S*-phenylsulfoximine **2a** (Scheme 6) provided the corresponding coupled product **8aa** as an unseparable diastereomeric mixture in a 1:1.2 ratio (predicted through NMR). The sulfoximination of azine-based functional molecules proved the utility of the present method in the functionalization and diversification.

■ CONCLUSIONS

In summary, we have developed a nucleophilic substitution reaction of azine *N*-oxides with sulfoximines. The present metal-free method provides a simple and mild approach for the synthesis of *N*-azine sulfoximines. This protocol works very well with various azines, such as substituted and unsubstituted isoquinoline, pyridine, and quinolines, and gives a diverse range of several novel and unprecedented *N*-azine sulfoximines. This reaction proceeds at room temperature, is operationally simple, and has broad functional group compatibility and substrate scope. Moreover, by utilizing the present method, direct sulfoximination of functional molecules, such as 1,10-phenanthroline, 2,2′-bipyridine, and quinine, was also achieved.

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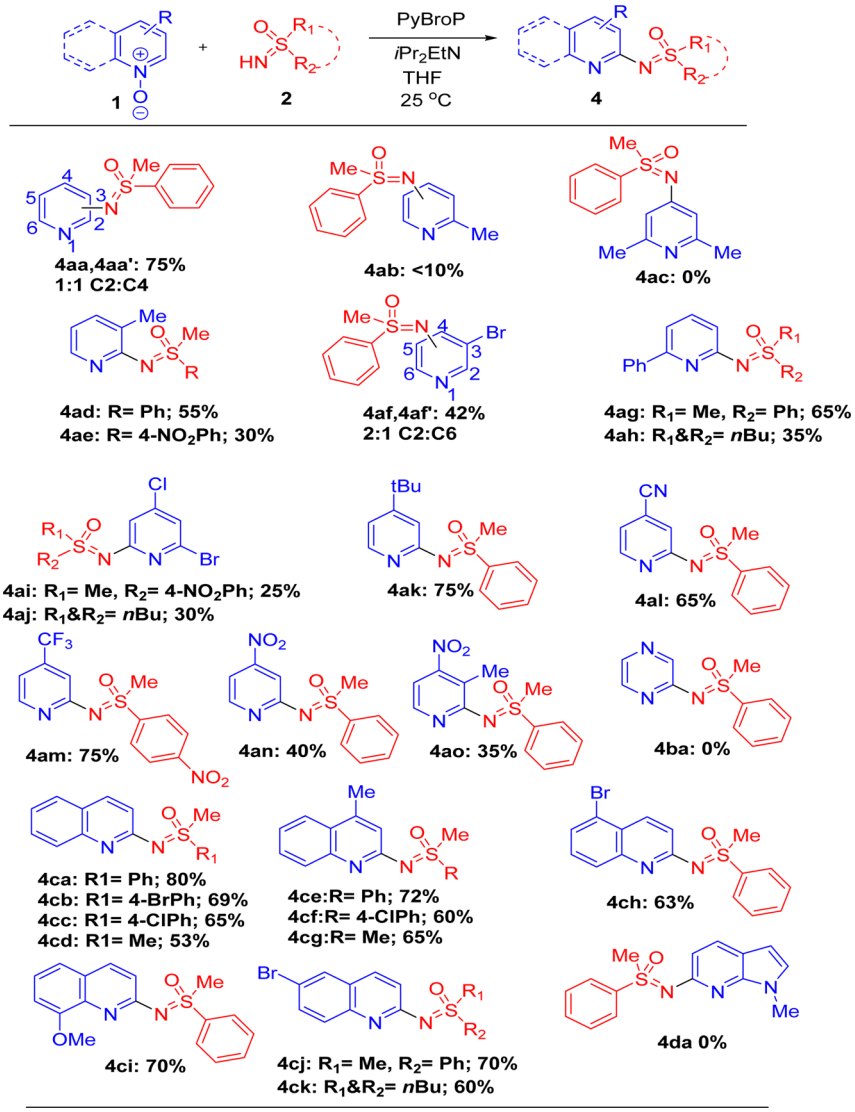
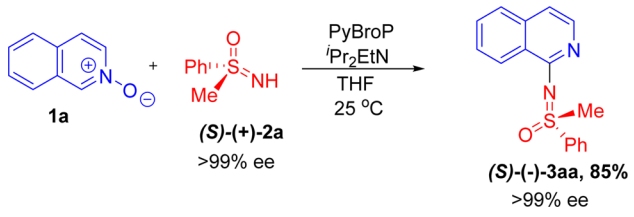
Scheme 3. Substrate Scope of Azine-*N*-oxides[a]



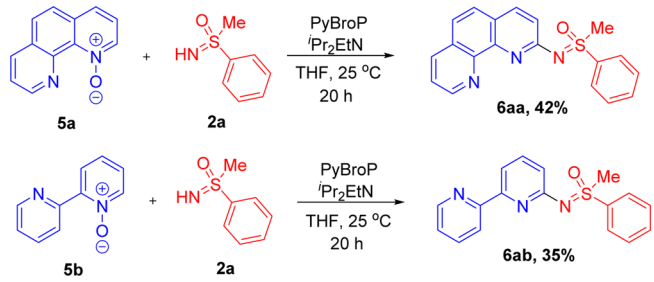
[a]Reaction conditions: All reactions were conducted at 0.2 M concentration with **1** (0.2 mmol, 1.0 equiv), **2** (0.26 mmol, 1.3 equiv), $^{i}Pr_2EtN$ (0.6 mmol, 3.0 equiv), and PyBroP (0.22 mmol, 1.1 equiv) at 25 °C for 15 h.

Scheme 4. Reaction with Enantiopure Sulfoximine[a]



[a]Reaction conditions: Reaction was conducted at 0.1 M concentration with **1a** (0.2 mmol, 1.0 equiv), **2a** 0.26 mmol, 1.3 equiv), $^{i}Pr_2EtN$ (0.6 mmol, 3.0 equiv), and PyBroP (0.22 mmol, 1.1 equiv) at 25 °C.

Scheme 5. Sulfoximination of Ligands[a]



[a]Reaction conditions: All reactions were conducted at 0.1 M concentration with **5a** or **5b** (0.2 mmol, 1.0 equiv), **2a** (0.26 mmol, 1.3 equiv), $^{i}Pr_2EtN$ (0.6 mmol, 3.0 equiv), and PyBroP (0.22 mmol, 1.1 equiv) at 25 °C.

EXPERIMENTAL SECTION

General Information. All the reactions were performed under a nitrogen atmosphere. Analytical thin layer chromatography was performed using TLC precoated silica gel 60 F_{254} (20 × 20 cm). TLC plates were visualized by exposing UV light. Organic solvents were concentrated by rotary evaporation. Column chromatography was performed on flash silica gel 230−400 mesh size, and an ethyl acetate/hexane mixture was used for elution. Melting points were recorded on a melting point instrument and are uncorrected. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (101 or 126 MHz) were recorded on FT-NMR

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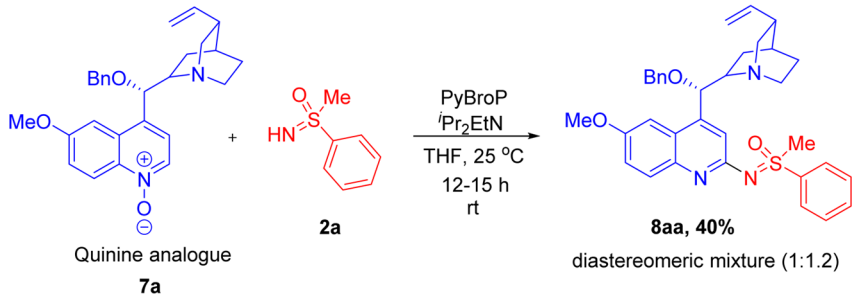
Scheme 6. Sulfoximination of Quinine[a]



[a]Reaction conditions: All reactions were conducted at 0.1 M concentration with **7a** (0.15 mmol, 1.0 equiv), **2a** (0.195 mmol, 1.3 equiv), $^{i}Pr_2EtN$ (0.45 mmol, 3.0 equiv), and PyBroP (0.165 mmol, 1.1 equiv) at 25 °C.

instruments. Chemical shift data for protons are reported in parts per million (ppm, scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26). The coupling constant (J) are in Hz. ESI-MS and HRMS spectra were recorded on LC-Q-TOF machines. FT-IR was recorded in chloroform using a NaCl plate. Optical rotations were measured at room temperature in 10 cm cells. Analytical HPLC was performed using a chiral stationary phase (flow rate: 1.0 mL/min, column type and eluent are given for the corresponding compound) and UV detection (λ = 210 or 254 nm) at 20 °C.

General Procedure for the Preparation of Sulfoximines.[19,20] *Step I. Oxidation of Sulfides to Sulfoxides.* To a stirred solution of $CuBr_2$ (0.05 equiv) and sulfide (1.0 equiv) in CH_3CN (2.0 mL/1 mmol) was added 70% *t*-BuOOH (in water, 5.0 equiv). The reaction mixture was heated to reflux, and the progress was monitored by TLC until all sulfide was found consumed. After completion, CH_3CN was evaporated and the crude mixture was washed with $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate was evaporated, and the crude sulfoxides were subsequently used for the imination reaction.

Step II. Imination of Sulfoxides. A solution of crude sulfoxide (1.0 equiv) and sodium azide (1.2 equiv) in $CHCl_3$ (~8−10 mL for 5 mmol of sulfoxide) was stirred in an oven-dried three-neck round-bottom flask equipped with a reflux condenser and an addition funnel. Concentrated sulfuric acid (~2.0 mL for 1.0 g of sulfoxide) was introduced over 5−10 min at 0 °C. The resulting mixture was slowly warmed up to 45 °C, and the same temperature was maintained until nitrogen gas evolution subsided. The reaction was continued for an additional 12 h at 45 °C. The reaction mixture was cooled, and the pasty-mass was dissolved with ice-water. The organic layer was decanted, and the aqueous layer was washed with a minimum amount of $CHCl_3$. The aqueous layer was made slightly alkaline using 20% NaOH solution and extracted with $CHCl_3$ (3 × 5 mL, for 5 mmol of sulfoxide). The combined organic extracts were dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel to afford the desired sulfoximines in good yields.

General Procedure for the Preparation of Azine *N*-Oxides.[21] To a 0 °C solution of the appropriate azine in CH_2Cl_2 (0.5 M) was added *m*-CPBA (2.0 equiv), and the reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with aq. KOH (6 N, 3×), the organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The azine *N*-oxides were obtained as white solids and used without further purification.

Synthesis of 1,10-Phenanthroline *N*-Oxide (5a).[22] Hydrogen peroxide (30%, 1.4 mL) was added into the solution of the phenanthroline (10 mmol) in acetic acid (10 mL). The reaction mixture was stirred at 70 °C for 72 h. The solvent was evaporated under vacuum, and the residue was basified with an aqueous solution of sodium carbonate until pH = 9. The resulting mixture was extracted with chloroform (3 × 20 mL). The organic phase was combined and dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc:methanol 8:1).

Synthesis of 2,2′-Bipyridyl *N*-Oxide (5b).[23] 2,2′-Bipyridine (1.248 g, 8.00 mmol) was added to a 50 mL round-bottom flask with a stir bar, followed by dissolution in trifluoroacetic acid (6.0 mL). This was cooled to room temperature, followed by slow addition of 30% H_2O_2 (1.2 mL, 12 mmol). Reaction was stirred at room temperature for 2 h, followed by addition of chloroform (25 mL). This was washed with 6 M aqueous NaOH (3 × 10 mL), followed by back extraction of the combined aqueous phase with dichloromethane (4 × 20 mL). The combined organic phase was dried over MgSO4, followed by evaporation *in vacuo* to give an oil. This was dried under vacuum overnight to obtain the required compound as a white solid.

Synthesis of *N*-Oxide Quinine Analogue (7a). *Step I: O-Benzylation.*[24] To a solution of quinine (4.0 g, 12.4 mmol) in DMF (40 mL) under a nitrogen atmosphere was added NaH (1.36 g, 57% suspension in mineral oil, 32.3 mmol), and the resulting mixture was stirred at room temperature for 2 h. Then, BnCl (1.56 mL, 13.6 mmol) was added dropwise via a syringe over 10 min. The resulting mixture was stirred overnight. After the starting material was completely consumed, brine was added carefully (40 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The organic phase was washed with H_2O (5 × 100 mL) and brine (100 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford a light yellow oil (5.1 g, 99%). This crude product was used for the next reaction without further purification.

Step II: Oxidation.[25] At 0 °C, *m*-chloroperoxybenzoic acid (77%, 9.20 g, 37.5 mmol) was added in portions to a solution of the above compound (4.89 g, 15.0 mmol) in chloroform (90 mL). The resulting suspension was allowed to warm to rt and stirred for 3 h at that temperature, during which time the reaction mixture became a clear yellow solution. The reaction was quenched with NaOH (aq) (10% in H_2O) until pH = 10. The resulting two-phase mixture was extracted with a mixed solvent of $CHCl_3$/MeOH (10/1, 50 mL × 6). The organic phase was collected, and the combined organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give the crude product as a light yellow foam (5.30 g, 99% yield). This crude product was used in the next step without further purification.

Step III: Deoxygenation.[25] To the solution of the above intermediate (5.30 g, 15.0 mmol) in acetone (60 mL) at 0 °C was added dropwise an aqueous solution of sulfurous acid (6 wt %, 24 mL, 18 mmol). The resulting mixture was warmed to rt. The resulting mixture was stirred overnight. Then, the acetone was removed under vacuum and ammonium hydroxide was added to make the solution alkaline. Chloroform (50 mL × 5) was used to extract the aqueous layer. The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH = 20/1 + 1% Et_3N) to afford **7a** as a viscous liquid (4.51 g, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 9.6 Hz, 1H), 8.37 (d, J = 6.3 Hz, 1H), 7.46−7.28 (m, 8H), 5.78 (ddd, J = 17.5, 10.3, 7.6 Hz, 1H), 5.00−4.91 (m, 2H), 4.44 (dd, J = 29.2, 11.5 Hz, 2H), 3.90 (s, 3H), 3.27 (s, 1H), 3.14 (d, J = 5.0 Hz,

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1H), 3.10−2.85 (m, 2H), 2.71−2.53 (m, 2H), 2.26 (s, 1H), 1.78 (dd, J = 33.4, 4.6 Hz, 3H), 1.49 (d, J = 7.8 Hz, 1H).

General Procedure for the Synthesis of *N*-Azine Sulfoximines. To a solution of sulfoximine (0.26 mmol, 1.3 equiv) in THF (1 mL) was added *i*-Pr_2EtN (0.6 mmol, 3 equiv) at room temperature. After stirring for 5 min, azine *N*-oxide (0.2 mmol, 1.0 equiv) and PyBroP (0.22 mmol, 1.1 equiv) were added sequentially. Then, the reaction mixture was stirred at room temperature. After completion of the reaction (by TLC analysis), the reaction mixture was diluted with $CHCl_3$ and washed with aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous $NaSO_4$, filtered, and concentrated *in vacuo*. The crude compounds were purified through column chromatography, and pure compounds were characterized by NMR and mass analysis.

N-[1-Isoquinolinyl]-S,S-methylphenylsulfoximine (**3aa**). TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 87% (49 mg); White solid; m.p.: 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 5.8 Hz, 1H), 7.66−7.56 (m, 6H), 7.11 (d, J = 5.8 Hz, 1H), 3.52 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.8, 141.0, 140.2, 137.4, 133.1, 130.0, 129.4, 127.7, 126.1, 126.0, 126.0, 123.7, 114.0, 45.0; HRMS (ESI-TOF) calc. for $C_{16}H_{14}N_2OS$ [M + H]$^+$ 283.0905; found 283.0900.

N-[1-Isoquinolinyl]-S,S-methyl(4-methoxyphenyl)sulfoximine (**3ab**). TLC (Hexane/EtOAc, 7:3) R_f = 0.25; Yield 80% (50 mg); White solid; m.p.: 121−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 5.8 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 3.49 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.3, 158.0, 141.1, 137.4, 131.5, 130.0, 129.9, 126.1, 126.0, 126.0, 123.8, 114.6, 113.9, 55.7, 45.2; HRMS (ESI-TOF) calc. for $C_{17}H_{17}N_2O_2S$ [M + H]$^+$ 313.1011; found 313.1019.

N-[1-Isoquinolinyl]-S,S-methyl(3,5-dimethylphenyl)sulfoximine (**3ac**). TLC (Hexane/EtOAc, 7:3) R_f = 0.50; Yield 82% (50 mg); White solid; m.p.: 102−105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 5.8 Hz, 1H), 7.72−7.65 (m, 3H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.23 (s, 1H), 7.11 (d, J = 5.8 Hz, 1H), 3.49 (s, 3H), 2.39 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.0, 141.1, 140.0, 139.5, 137.4, 134.8, 130.0, 126.1, 126.0, 125.9, 125.1, 123.8, 113.9, 45.0, 21.3; HRMS (ESI-TOF) calc. for $C_{18}H_{18}N_2OS$ [M + H]$^+$ 311.1218; found 311.1212.

N-[1-Isoquinolinyl]-S,S-methyl(4-bromophenyl)sulfoximine (**3ad**). TLC (Hexane/EtOAc, 7:3) R_f = 0.35; Yield 78% (56 mg); White solid; m.p.: 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 8.2 Hz, 1H), 7.95 (t, J = 5.5 Hz, 3H), 7.73−7.66 (m, 3H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 5.8 Hz, 1H), 3.49 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.5, 140.9, 139.3, 137.4, 132.7, 130.1, 129.4, 128.2, 126.2, 126.1, 125.9, 123.6, 114.3, 45.1; HRMS (ESI-TOF) calc. for $C_{16}H_{13}{}^{81}BrN_2OS$ [M + H]$^+$ 362.9990; found 362.9988.

N-[1-Isoquinolinyl]-S,S-methyl(4-chlorophenyl)sulfoximine (**3ae**). TLC (Hexane/EtOAc, 7:3) R_f = 0.50; Yield 74% (46 mg); White solid; m.p.: 139−142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 8.3 Hz, 1H), 8.03−7.99 (m, 2H), 7.96−7.92 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (dd, J = 7.5, 6.3 Hz, 3H), 7.12 (d, J = 5.8 Hz, 1H), 3.48 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.5, 140.9, 139.7, 138.8, 137.4, 130.1, 129.7, 129.3, 126.2, 126.1, 125.9, 123.6, 114.3, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{13}ClN_2OS$ [M + H]$^+$ 317.0515; found 317.0510.

N-[1-Isoquinolinyl]-S,S-methyl(4-fluorophenyl)sulfoximine (**3af**). TLC (Hexane/EtOAc, 7:3) R_f = 0.40; Yield 80% (48 mg); Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 11.1, 3.1 Hz, 1H), 8.08−7.93 (m, 2H), 7.86 (d, J = 5.9 Hz, 1H), 7.64−7.45 (m, 1H), 7.42 (ddd, J = 8.2, 6.8, 1.4 Hz, 2H), 7.16−7.05 (m, 2H), 7.02 (d, J = 5.9 Hz, 1H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.5 (d, J = 264.6 Hz), 157.6, 140.9, 137.4, 136.2 (d, J = 3.0 Hz), 130.5 (d, J = 9.4 Hz), 130.1, 126.2, 126.1, 125.9, 123.7, 116.70 (d, J = 22.7 Hz), 114.2, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{13}FN_2OS$ [M + H]$^+$ 301.0811; found 301.0803.

N-[1-Isoquinolinyl]-S,S-methyl(4-nitrophenyl)sulfoximine (**3ag**). TLC (Hexane/EtOAc, 6:4) R_f = 0.40; Yield 70% (46 mg); Yellow solid; m.p.: 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.2 Hz, 1H), 8.39−8.32 (m, 2H), 8.25−8.23 (m, 2H), 7.85−7.84 (m, 1H), 7.66−7.53 (m, 3H), 7.12 (t, J = 6.9 Hz, 1H), 3.50 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.96, 150.4, 146.6, 140.70, 137.5, 130.3, 129.2, 126.2, 126.3, 125.7, 124.5, 123.4, 114.7, 45.0; HRMS (ESI-TOF) calc. for $C_{16}H_{14}N_3O_3S$ [M + H]$^+$ 328.0756; found 328.0749.

N-[1-Isoquinolinyl]-S,S-Diphenylsulfoximine (**3ah**). TLC (Hexane/EtOAc, 7:3) R_f = 0.60; Yield 68% (46 mg); White solid; m.p.: 138−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 8.1 Hz, 1H), 8.13 (dd, J = 8.0, 1.3 Hz, 4H), 7.87 (d, J = 5.8 Hz, 1H), 7.66 (dt, J = 6.7, 4.4 Hz, 2H), 7.60−7.56 (m, 1H), 7.53−7.45 (m, 6H), 7.08 (d, J = 5.8 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 141.2, 141.2, 137.4, 132.5, 130.0, 129.3, 128.1, 126.2, 126.1, 125.9, 124.1, 114.1; HRMS (ESI-TOF) calc. for $C_{21}H_{16}N_2OS$ [M + H]$^+$ 345.1062; found 345.1058.

N-[1-Isoquinolinyl]-S,S-tetramethylenesulfoximine (**3ai**). TLC (Hexane/EtOAc, 7:3) R_f = 0.18; Yield 62% (30 mg); White solid; m.p.: 178−180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.63−7.58 (m, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 5.9 Hz, 1H), 3.81−3.74 (m, 2H), 3.45−3.39 (m, 2H), 2.42−2.33 (m, 2H), 2.29−2.22 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.5, 140.9, 137.4, 130.1, 126.0, 126.0, 125.9, 123.4, 113.8, 53.0, 23.8; HRMS (ESI-TOF) calc. for $C_{13}H_{14}N_2OS$ [M + H]$^+$ 247.0905; found 247.0898.

N-[1-Isoquinolinyl]-S,S-dimethylsulfoximine (**3aj**). TLC (Hexane/EtOAc, 1:1) R_f = 0.30; Yield 70% (30 mg); White solid; m.p.: 119−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.63−7.58 (m, 1H), 7.47 (dd, J = 11.5, 4.5 Hz, 1H), 7.14 (d, J = 5.8 Hz, 1H), 3.46 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.1, 140.8, 137.4, 130.1, 126.0, 126.0, 125.9, 123.5, 113.8, 42.3; HRMS (ESI-TOF) calc. for $C_{11}H_{12}N_2OS$ [M + H]$^+$ 221.0749; found 221.0725.

N-[1-Isoquinolinyl]-S,S-dibutylsulfoximine (**3ak**). TLC (Hexane/EtOAc, 9:1) R_f = 0.70; Yield 65% (40 mg); Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 5.9 Hz, 1H), 7.69−7.60 (m, 2H), 7.53−7.49 (m, 1H), 7.14 (d, J = 5.9 Hz, 1H), 3.68 (ddd, J = 13.8, 10.9, 5.5 Hz, 2H), 3.55 (ddd, J = 13.8, 10.8, 5.5 Hz, 2H), 2.01−1.83 (m, 4H), 1.56−1.47 (m, 4H), 1.09−0.96 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.1, 140.7, 137.4, 130.0, 127.0, 123.7, 113.5, 51.5, 24.3, 21.7, 13.6; HRMS (ESI-TOF) calc. for $C_{17}H_{25}N_2OS$ [M + H]$^+$ 305.1688; found 305.1682.

N-[1-Isoquinolinyl]-S,S-ethylphenylsulfoximine (**3am**). TLC (Hexane/EtOAc, 1:1) R_f = 0.55; Yield 72% (42 mg); White solid; m.p.: 107−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 8.2 Hz, 1H), 8.05−8.01 (m, 2H), 7.92 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.65−7.59 (m, 2H), 7.57−7.50 (m, 3H), 7.09 (d, J = 5.9 Hz, 1H), 3.76−3.59 (m, 2H), 1.31 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.8, 141.1, 137.7, 137.4, 133.0, 130.0, 129.3, 128.6, 126.1, 126.0, 125.9, 123.8, 113.9, 51.1, 7.9; HRMS (ESI-TOF) calc. for $C_{17}H_{17}N_2OS$ [M + H]$^+$ 297.1062; found 297.1031.

N-[1-Isoquinolinyl]-S,S-propylphenylsulfoximine (**3an**). TLC (Hexane/EtOAc, 7:3) R_f = 0.68; Yield 70% (43 mg); White solid; m.p.: 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.91 (d, J = 5.8 Hz, 1H), 7.66−7.56 (m, 3H), 7.51 (t, J = 7.5 Hz, 3H), 7.07 (d, J = 5.8 Hz, 1H), 3.64−3.57 (m, 2H), 1.88−1.72 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.8, 141.1, 138.4, 137.4, 132.9, 129.9, 129.3, 128.5, 126.1, 126.0, 125.9, 123.8, 113.8, 58.4, 16.8, 12.8; HRMS (ESI-TOF) calc. for $C_{18}H_{19}N_2OS$ [M + H]$^+$ 311.1218; found 311.1191.

N-[1-Isoquinolinyl]-S,S-butylphenylsulfoximine (**3ao**). TLC (Hexane/EtOAc, 8:2) R_f = 0.49; Yield 69% (44 mg); White solid; m.p.: 102−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 8.3 Hz, 1H), 8.05−8.01 (m, 2H), 7.92 (d, J = 5.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.64−7.58 (m, 2H), 7.54 (ddd, J = 12.0, 5.0, 3.1 Hz, 3H), 7.09 (d, J = 5.8 Hz, 1H), 3.69−3.58 (m, 2H), 1.85−1.67 (m, 2H), 1.43−1.35 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.8, 141.1, 138.4, 137.4, 132.9, 129.9, 129.3, 128.5, 126.1, 126.0, 125.9, 123.8, 113.8, 56.5, 24.9, 21.4, 13.5; HRMS (ESI-TOF) calc. for $C_{19}H_{21}N_2OS$ [M + H]$^+$ 325.1375; found 325.1389.

N-[2-Pyridinyl]-S,S-methylphenylsulfoximine (**4aa**).[26] TLC (Hexane/EtOAc, 1:1) R_f = 0.10; Yield 37% (17 mg); Yellow solid; m.p.: 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 8.05−8.01 (m, 2H), 7.58 (dt, J = 14.9, 7.2 Hz, 3H), 7.48 (td, J = 8.2, 1.9 Hz, 1H),

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6.87 (d, J = 8.2 Hz, 1H), 6.73 (dd, J = 6.4, 5.3 Hz, 1H), 3.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.9, 147.8, 140.1, 137.7, 133.0, 129.4, 127.8, 116.6, 116.1, 45.5; HRMS (ESI-TOF) calc. for $C_{12}H_{12}N_2OS$ $[M + H]^+$ 233.0749; found 233.0747.

*N-[4-Pyridinyl]-S,S-methylphenylsulfoximine (**4aa'**).* TLC (Hexane/EtOAc, 1:1) R_f = 0.25; Yield 37% (17 mg); White solid; m.p.: 105−106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.97 (t, J = 6.5 Hz, 3H), 7.66−7.61 (m, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 3.40 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.9, 138.6, 137.3, 134.1, 134.0, 132.1, 129.8, 129.5, 129.4, 127.5, 127.1, 44.4; HRMS (ESI-TOF) calc. for $C_{12}H_{12}N_2OS$ $[M + H]^+$ 233.0749; found 233.0743.

*N-[2-(3-Methyl)-pyridinyl]-S,S-methylphenylsulfoximine (**4ad**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 35% (17 mg); Yellow solid; m.p.: 98−102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−8.04 (m, 2H), 7.93 (dd, J = 3.1, 1.8 Hz, 1H), 7.62−7.59 (m, 1H), 7.56−7.53 (m, 2H), 7.35−7.33 (m, 1H), 6.67 (dd, J = 7.2, 5.0 Hz, 1H), 3.41 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.0, 145.0, 140.8, 137.7, 132.8, 129.3, 127.7, 125.3, 116.2, 45.0, 18.0; HRMS (ESI-TOF) calc. for $C_{13}H_{15}N_2OS$ $[M + H]^+$ 247.0905; found 247.0904.

*N-[2-(3-Methyl)-pyridinyl]-S,S-methyl(4-nitrophenyl)sulfoximine (**4ae**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 30% (18 mg); Gummy solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 4.5 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 6.70 (t, J = 15.5 Hz, 1H), 3.41 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.4, 150.2, 146.8, 144.2, 138.1, 129.2, 125.6, 124.2, 116.7, 44.9, 17.7; HRMS (ESI-TOF) calc. for $C_{13}H_{14}N_3O_3S$ $[M + H]^+$ 292.0756; found 292.0757.

*N-[2-(3-Bromo)-pyridinyl]-S,S-methylphenylsulfoximine (**4af**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.35; Yield 28% (17 mg); White solid; m.p.: 121−122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (m, 2H), 8.03−7.99 (m, 1H), 7.76 (dd, J = 7.7, 1.6 Hz, 1H), 7.66−7.61 (m, 1H), 7.57 (dd, J = 11.5, 4.1 Hz, 2H), 6.63 (dd, J = 7.7, 4.9 Hz, 1H), 3.43 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.7, 146.4, 140.9, 139.9, 133.2, 129.4, 127.8, 117.0, 113.0, 77.3, 77.0, 76.8, 44.8; HRMS (ESI-TOF) calc. for $C_{12}H_{11}BrN_2OS$ $[M + H]^+$ 310.9854 and 312.9833; found 310.9854 and 312.9834.

*N-[2-(5-Bromo)-pyridinyl]-S,S-methylphenylsulfoximine (**4af'**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 14% (8 mg); White solid; m.p.: 131−134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.58−7.54 (m, 3H), 6.77 (d, J = 8.7 Hz, 1H), 3.35 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6, 148.4, 140.2, 139.6, 133.2, 129.5, 127.8, 118.2, 111.7, 77.3, 77.0, 76.8, 45.5; HRMS (ESI-TOF) calc. for $C_{12}H_{11}{}^{81}BrN_2OS$ $[M + H]^+$ 312.9833; found 312.9834.

*N-[2-(6-Phenyl)-pyridinyl]-S,S-methylphenylsulfoximine (**4ag**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.40; Yield 65% (40 mg); White solid; m.p.: 117−119 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.4 Hz, 2H), 7.55−7.45 (m, 6H), 7.20 (t, J = 8.4 Hz, 3H), 7.13 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 3.31 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.4, 154.9, 140.7, 139.1, 138.5, 132.8, 129.5, 128.4, 128.2, 127.7, 126.6, 114.9, 112.5, 45.5; HRMS (ESI-TOF) calc. for $C_{18}H_{16}N_2OS$ $[M + H]^+$ 309.1062; found 309.1060.

*N-[2-(6-Phenyl)-pyridinyl]-S,S-dibutylsulfoximine (**4ah**).* TLC (Hexane/EtOAc, 9:1) R_f = 0.60; Yield 35% (23 mg); Yellow solid; m.p.: 115−118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−7.92 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.44 (dt, J = 13.3, 4.9 Hz, 2H), 7.44−7.41 (m, 1H), 7.27−7.18 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.53 (qdd, J = 13.8, 9.7, 6.4 Hz, 4H), 1.87−1.75 (m, 4H), 1.45 (dd, J = 14.9, 7.4 Hz, 4H), 0.96−0.86 (m, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.1, 155.0, 139.6, 138.4, 128.5, 126.6, 115.2, 112.2, 51.8, 24.3, 21.7, 13.6; HRMS (ESI-TOF) calc. for $C_{19}H_{27}N_2OS$ $[M + H]^+$ 331.1839; found 331.1836.

*N-[6-(2-Bromo-4-chloro)-pyridinyl]-S,S-methyl(4-nitrophenyl)-sulfoximine (**4ai**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 25% (19 mg); Brownish solid; m.p.: 124−126 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 7.0, 1.8 Hz, 2H), 8.19−8.18 (m, 2H), 6.95 (d, J = 1.5 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 3.42 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.5, 150.5, 146.0, 145.5, 139.2, 129.2, 124.6, 120.2, 115.1, 44.7; HRMS (ESI-TOF) calc. for $C_{12}H_{10}{}^{81}BrClN_3O_3S$ $[M + H]^+$ 391.9294; found 391.9273.

*N-[6-(2-Bromo-4-chloro)-pyridinyl]-S,S-dibutylsulfoximine (**4aj**).* TLC (Hexane/EtOAc, 9:1) R_f = 0.70; Yield 30% (22 mg); Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 1.5 Hz, 1H), 6.72 (d, J = 1.5 Hz, 1H), 3.49−3.38 (m, 4H), 1.87−1.73 (m, 4H), 1.52−1.42 (m, 4H), 0.96 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7, 145.7, 139.0, 118.8, 115.0, 51.7, 29.7, 24.0, 21.6, 13.5; HRMS (ESI-TOF) calc. for $C_{13}H_{21}{}^{81}BrClN_2OS$ $[M + H]^+$ 369.0226; found 369.0216.

*N-[2-(4-tert-Butyl)-pyridinyl]-S,S-methylphenylsulfoximine (**4ak**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.25; Yield 75% (43 mg); Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.7 Hz, 2H), 7.99 (d, J = 5.5 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 0.7 Hz, 1H), 6.76 (dd, J = 5.5, 1.1 Hz, 1H), 3.38 (s, 3H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.8, 159.0, 147.4, 140.4, 132.9, 129.4, 127.8, 113.6, 45.4, 34.6, 30.5; HRMS (ESI-TOF) calc. for $C_{16}H_{21}N_2OS$ $[M + H]^+$ 289.1375; found 289.1374.

*N-[2-(4-Cyano)-pyridinyl]-S,S-methylphenylsulfoximine (**4al**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 65% (34 mg); Pale yellow solid; m.p.: 105−108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 5.2, 0.7 Hz, 1H), 7.99 (dd, J = 5.2, 3.3 Hz, 2H), 7.65 (ddd, J = 6.6, 3.8, 1.2 Hz, 1H), 7.59−7.53 (m, 2H), 7.08−7.07 (m, 1H), 6.90 (dd, J = 5.2, 1.4 Hz, 1H), 3.37 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.8, 148.9, 139.3, 133.4, 129.6, 127.6, 121.6, 119.1, 116.8, 45.5; HRMS (ESI-TOF) calc. for $C_{13}H_{12}N_3OS$ $[M + H]^+$ 258.0701; found 258.0687.

*N-[2-(4-Trifluoromethyl)-pyridinyl]-S,S-methyl(4-nitrophenyl)-sulfoximine (**4am**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.35; Yield 75% (52 mg); Yellow solid; m.p.: 120−123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38−8.33 (m, 2H), 8.19−8.17 (m, 2H), 8.09 (d, J = 5.2 Hz, 1H), 7.07 (s, 1H), 6.92 (d, J = 5.1 Hz, 1H), 3.39 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.0, 150.5, 148.7, 145.9, 140.1 (q, J = 33.5 Hz), 129.2, 124.7, 122.8 (q, J = 273.4 Hz), 112.9 (d, J = 3.8 Hz) 112.0, 45.1; HRMS (ESI-TOF) calc. for $C_{13}H_{11}F_3N_3O_3S$ $[M + H]^+$ 346.0468; found 346.0463.

*N-[2-(4-Nitro)-pyridinyl]-S,S-methylphenylsulfoximine (**4an**).* TLC (Hexane/EtOAc, 1:1) R_f = 0.50; Yield 15% (8 mg); Yellow solid; m.p.: 145−147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 5.6 Hz, 1H), 8.04−8.00 (m, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.58 (dd, J = 13.1, 4.8 Hz, 3H), 7.41 (dd, J = 5.6, 2.0 Hz, 1H), 3.40 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.2, 155.4, 149.7, 139.2, 133.4, 129.6, 127.6, 109.8, 108.1, 45.5; HRMS (ESI-TOF) calc. for $C_{12}H_{11}N_3O_3S$ $[M + H]^+$ 278.0599; found 278.0594.

*Methyl((3-methyl-4-nitropyridin-2-yl)imino)(phenyl)-sulfanone (**4ao**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.20; Yield 35% (20 mg); Yellow solid; m.p.: 105−108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−7.98 (m, 3H), 7.68−7.62 (m, 1H), 7.62−7.56 (m, 2H), 7.02 (d, J = 5.5 Hz, 1H), 3.41 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 156.43, 145.6, 139.7, 133.3, 129.5, 127.6, 118.4, 109.0, 45.2, 13.34. HRMS (ESI-TOF) calc. for $C_{13}H_{14}N_3O_3S$ $[M + H]^+$ 292.0750; found 292.0750.

*N-[2-Quinolinyl]-S,S-methylphenylsulfoximine (**4ca**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.15; Yield 80% (45 mg); White solid; m.p.: 162−165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H), 7.68−7.47 (m, 6H), 7.29 (d, J = 7.1 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 3.51 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.1, 147.3, 140.2, 137.6, 133.1, 129.4, 128.9, 127.8, 127.5, 127.1, 124.5, 123.6, 118.1, 77.3, 77.0, 76.8, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{14}N_2OS$ $[M + H]^+$ 283.0905; found 283.0901.

*N-[2-Quinolinyl]-S,S-methyl(4-bromophenyl)sulfoximine (**4cb**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.20; Yield 69% (49 mg); White solid; m.p.: 117−119 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 12.3, 8.7 Hz, 3H), 7.70−7.61 (m, 4H), 7.53−7.47 (m, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 3.47 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.8, 147.1, 139.4, 137.7, 132.6, 129.4, 129.0, 128.2, 127.4, 127.1, 124.5, 123.8, 118.0, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{13}{}^{81}BrN_2OS$ $[M + H]^+$ 362.9990; found 362.9985.

*N-[2-Quinolinyl]-S,S-methyl(4-chlorophenyl)sulfoximine (**4cc**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.15; Yield 65% (41 mg); White solid; m.p.: 101−103 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.4, 3.6 Hz, 2H), 7.93 (dd, J = 8.7, 3.5 Hz, 1H), 7.63 (dd, J = 8.0, 4.3 Hz, 2H), 7.53−7.48 (m, 3H), 7.29 (dd, J = 13.3, 5.6 Hz, 1H), 7.04 (dd, J =

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8.7, 4.0 Hz, 1H), 3.48 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.8, 147.1, 139.7, 138.7, 137.7, 129.7, 129.3, 129.0, 127.4, 127.2, 124.5, 123.8, 118.0, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{13}ClN_2OS$ $[M + H]^+$ 317.0515; found 317.0511.

*N-[2-Quinolinyl]-S,S-dimethylsulfoximine (**4cd**).* TLC (Hexane/EtOAc, 1:1) R_f = 0.10; Yield 53% (24 mg); White solid; m.p.: 104−106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.50 (s, 1H), 7.25 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 3.40 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.5, 147.1, 137.8, 129.1, 127.3, 127.0, 124.3, 123.6, 118.4, 77.33, 77.0, 76.8, 42.4; HRMS (ESI-TOF) calc. for $C_{11}H_{12}N_2OS$ $[M + H]^+$ 221.0749; found 221.0738.

*N-[2-(4-Methyl)-quinolinyl]-S,S-methylphenylsulfoximine (**4ce**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.15; Yield 72% (42 mg); White solid; m.p.: 121−122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12−8.07 (m, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.61−7.47 (m, 4H), 7.30 (t, J = 7.5 Hz, 1H), 6.92 (s, 1H), 3.49 (s, 3H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.8, 147.2, 145.4, 140.4, 133.0, 129.3, 128.7, 128.0, 127.7, 124.8, 123.4, 123.3, 118.3, 45.3, 18.6; HRMS (ESI-TOF) calc. for $C_{17}H_{16}N_2OS$ $[M + H]^+$ 297.1062; found 297.1058.

*N-[2-(4-Methyl)-quinolinyl]-S,S-methyl(4-chlorophenyl)sulfoximine (**4cf**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.20; Yield 60% (39 mg); White solid; m.p.: 112−114 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 8.2 Hz, 3H), 7.31 (t, J = 7.5 Hz, 1H), 6.91 (s, 1H), 3.46 (s, 3H), 2.58 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.5, 147.1, 145.7, 139.6, 138.9, 129.6, 129.3, 128.8, 127.9, 124.8, 123.5, 123.3, 118.1, 45.3, 18.7; HRMS (ESI-TOF) calc. for $C_{17}H_{15}ClN_2OS$ $[M + H]^+$ 331.0672; found 331.0667.

*N-[2-(4-Methyl)-quinolinyl]-S,S-dimethylsulfoximine (**4cg**).* TLC (Hexane/EtOAc, 1:1) R_f = 0.15; Yield 65% (30 mg); White solid; m.p.: 102−104 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.2, 0.9 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.58−7.54 (m, 1H), 7.37−7.32 (m, 1H), 6.84 (s, 1H), 3.46 (s, 6H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.2, 147.0, 145.7, 128.9, 127.5, 124.6, 123.5, 123.4, 118.5, 42.5, 18.7; HRMS (ESI-TOF) calc. for $C_{12}H_{14}N_2OS$ $[M + H]^+$ 235.0905; found 235.0903.

*N-[2-(5-Bromo)-quinolinyl]-S,S-methylphenylsulfoximine (**4ch**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.20; Yield 63% (45 mg); White solid; m.p.: 119−120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 7.4 Hz, 2H), 7.63−7.52 (m, 5H), 7.32 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 3.50 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.8, 148.1, 139.9, 136.9, 133.2, 129.4, 129.2, 127.7, 127.3, 127.3, 123.8, 121.6, 119.3, 77.3, 77.0, 76.84, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{13}{}^{81}BrN_2OS$ $[M + H]+$ 362.9998; found 363.0014

*N-[2-(8-Methoxy)-quinolinyl]-S,S-methylphenylsulfoximine (**4ci**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.12; Yield 70% (43 mg); White solid; m.p.: 160−164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H), 7.63−7.52 (m, 3H), 7.24−7.17 (m, 2H), 7.05 (d, J = 8.7 Hz, 1H), 6.92 (dd, J = 6.6, 2.2 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.1, 154.3, 140.1, 138.9, 137.6, 133.0, 129.2, 127.9, 125.4, 123.5, 119.3, 118.1, 108.6, 56.0, 44.9; HRMS (ESI-TOF) calc. for $C_{17}H_{16}N_2O_2S$ $[M + H]+$ 313.1011; found 313.1005.

*N-[2-(6-Bromo)-quinolinyl]-S,S-methylphenylsulfoximine (**4cj**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.35; Yield 70% (51 mg); Yellow solid; m.p.: 105−107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (d, 1H), 8.10−8.01 (m, 2H), 7.54−7.39 (m, 5H), 7.29 (dd, J = 14.6, 7.0 Hz, 1H), 7.11 (dd, J = 8.9, 5.6 Hz, 1H), 3.47 (d, J = 5.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.8, 148.1, 139.9, 136.8, 133.2, 129.3, 127.5, 123.8, 121.6, 119.4, 45.2; HRMS (ESI-TOF) calc. for $C_{16}H_{14}{}^{81}BrN_2OS$ $[M + H]^+$ 362.9984; found 363.0014.

*N-[2-(6-Bromo)-quinolinyl]-S,S-dibutylsulfoximine (**4ck**).* TLC (Hexane/EtOAc, 9:1) R_f = 0.70; Yield 60% (45 mg); Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 7.68 (dd, J = 8.4, 0.6 Hz, 1H), 7.54 (dd, J = 7.5, 1.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 3.66−3.55 (m, 4H), 1.90−1.76 (m, 4H), 1.45 (dd, J = 14.9, 7.4 Hz, 4H), 0.92 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.2, 148.2, 136.6, 127.0, 126.9, 123.6, 121.8, 119.9, 23.9, 21.7, 13.5; HRMS (ESI-TOF) calc. for $C_{17}H_{24}{}^{81}BrN_2OS$ $[M + H]^+$ 385.0772; found 385.0766.

*(S)-(−)-N-[1-Isoquinolinyl]-S,S-methylphenylsulfoximine ((**S**)-(−)-**3aa**).* TLC (Hexane/EtOAc, 7:3) R_f = 0.30; Yield 85% (47 mg); White solid; m.p.: 200−202 °C; $[\alpha]_D$ −36.66° (c 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 5.8 Hz, 1H), 7.66−7.56 (m, 6H), 7.11 (d, J = 5.8 Hz, 1H), 3.52 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.8, 141.0, 140.2, 137.4, 133.1, 130.0, 129.4, 127.7, 126.1, 126.0, 126.0, 123.7, 114.0, 45.0; HRMS (ESI-TOF) calc. for $C_{16}H_{14}N_2OS$ $[M + H]^+$ 283.0905; found 283.0904; Chiral HPLC (ChiraSelect-AM, 250 × 4.6 mm, n-hexane/i-PrOH = 95:5, 1 mL/min, λ = 210 nm, 254 nm): t_R [(**S**)-(−)-**3aa**] = 23.82.

*N-[2-(1,10-Phenanthrolinyl)]-S,S-methylphenylsulfoximine (**6aa**).* TLC ($CHCl_3$/MeOH, 9:1) R_f = 0.20; Yield 42% (28 mg); White solid; m.p.: 155−158 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (dd, J = 4.3, 1.7 Hz, 1H), 8.33−8.29 (m, 2H), 8.18 (dd, J = 8.1, 1.7 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.64−7.60 (m, 1H), 7.57 (ddd, J = 12.5, 7.8, 2.2 Hz, 4H), 7.25 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.5, 149.4, 145.3, 145.0, 139.9, 137.6, 135.7, 133.1, 129.1, 128.8, 127.8, 126.2, 123.9, 123.0, 122.3, 118.7, 44.6; HRMS (ESI-TOF) calc. for $C_{19}H_{15}N_3OS$ $[M + H]^+$ 334.1014; found 334.1012.

*N-[2-(6-Bipyridyl)]-S,S-methylphenylsulfoximine (**6ab**).* TLC ($CHCl_3$/MeOH, 9.5:0.5) R_f = 0.20; Yield 35% (21 mg); Yellow solid; m.p.: 135−138 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 4.0 Hz, 1H), 8.09 (dd, J = 8.1, 1.4 Hz, 2H), 7.87 (d, J = 7.3 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65−7.56 (m, 5H), 7.18 (ddd, J = 7.4, 4.8, 1.1 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 3.39 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.8, 156.0, 153.6, 148.5, 140.3, 138.6, 136.2, 132.7, 129.3, 127.6, 123.0, 120.9, 116.5, 113.1, 45.4; HRMS (ESI-TOF) calc. for $C_{17}H_{15}N_3OS$ $[M + H]^+$ 310.1014; found 310.1019.

*Quinine Analogue (**8aa**).* TLC ($CHCl_3$/MeOH, 9:1) R_f = 0.5; Yield 40% (34 mg); White solid; IR ($CHCl_3$): ν_{max} = 3584, 3063, 2925, 2855, 1600, 1504, 1454, 1407, 1380, 1349, 1234, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, J = 7.1 Hz, 2H), 7.68 (d, J = 9.1 Hz, 1H), 7.63−7.48 (m, 3H), 7.34 (ddd, J = 21.6, 14.2, 7.7 Hz, 6H), 7.24−7.18 (m, 2H), 5.72 (ddd, J = 18.2, 13.9, 8.0 Hz, 1H), 5.01−4.89 (m, 2H), 4.55−4.32 (m, 2H), 3.86 (s, 3H), 3.51 (d, J = 5.7 Hz, 3H), 3.41 (bs, 1H), 3.17−3.01 (m, 2H), 2.62 (d, J = 10.7 Hz, 2H), 2.26 (bs, 1H), 1.88 (bs, 3H), 1.71 (d, J = 16.1 Hz, 2H), 1.48 (s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.0, 143.7, 142.0, 140.3, 138.2, 138.1, 133.0, 129.9, 129.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4, 123.2, 120.5, 114.2, 70.8, 59.9, 57.1, 55.7, 45.4, 43.3, 40.0, 29.6, 27.9, 27.7, 27.7; HRMS (ESI-TOF) calc. for $C_{34}H_{38}N_3O_3S$ $[M + H]^+$ 568.2634; found 568.2623.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00593.

Copies of NMR, HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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