JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00888 • Publication Date (Web): 22 May 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Class of Amide Ligands Enable Cu-Catalyzed Coupling of (Hetero)aryl Halides with Sulfinic Acid Salts under Mild Conditions

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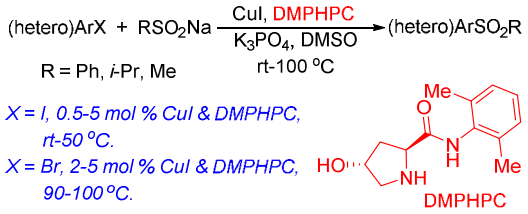


Abstract

The amide derived from 4-hydroxy-L-proline and 2,6-dimethylaniline is a powerful ligand for Cu-catalyzed coupling of (hetero)aryl halides with sulfinic acid salts, allowing the formation of a wide range of (hetero)aryl sulfones from the corresponding (hetero)aryl halides at considerably low catalytic loadings. The coupling of (hetero)aryl iodides and sodium methanesulfinate proceeds at room temperature with only 0.5 mol % CuI and ligand, representing the first example for Cu-catalyzed arylation at both low catalytic loading and room temperature.

Introduction

Aryl sulfone has been one of the top 5 most frequently used scaffolds in drug structure on the basis of 6932 FDA-approved drugs and experimental drugs.[1] The prominent drugs containing aryl sulfone unit include two recently approved anti-tumor drugs Ceritinib[2] (Figure 1) and Vismodegib;[3] antipsychotic drug Amisulpride,[4] Intepirdine[5] in phase III clinical trials for treatment Alzheimer's disease, and Xiidra[6] for the treatment of signs and symptoms of dry eye disease.

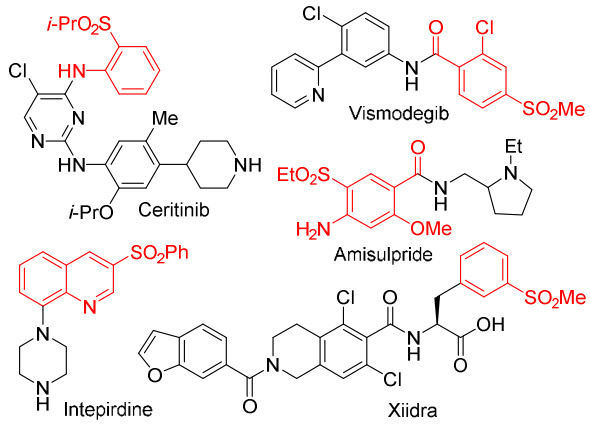


Figure 1. Structures of some pharmaceutically important (hetero)aryl sulfones

The classical method for preparing aryl sulfones is direct sulfonylation of arenes. This approach is not favorable for late-stage manipulation in medicinal chemistry because of its unsatisfactory regioselectivity and poor functional group tolerance.[7] During the past decades, considerable efforts have been attempted to develop new methods for preparing aryl sulfones.[7-13] Among emerging methods, Cu or Pd-catalyzed arylation of sulfinic acid salts has received more and more attention and has been applied in the assembly of designed aryl sulfones.[6-12] Several aromatic electrophiles have been demonstrated as suitable substrates in this transformation,

which include (hetero)aryl halides,[8,9] aryl boronic acids,[10] arenediazonium salts[11] and nitroarenes.[12] Although the progress in this area is significant, further improvements are still needed. For example, aryl chlorides as the cheapest and most abundant aromatic electrophiles are difficult substrates for either Cu- or Pd-catalyzed coupling reaction,[7-9] while higher catalytic loadings (>10 mol % for both copper salt and ligand) are required for Cu-catalyzed coupling with aryl iodides and bromides.[8] Additionally, limited reaction scope was seen in case of aryl bromides as the coupling partners.

Recently, we reported the first metal-catalyzed coupling reaction of (hetero)aryl chlorides with sodium methanesulfinate by combining CuI and a new class of amide ligands with hybrid structures of 4-hydroxy-*L*-proline and oxalic diamides (Figure 2).[14] During our studies on copper salts/oxalic diamides catalyzed coupling reactions,[15] we found that when ligands that were suitable for Cu-catalyzed coupling reactions with (hetero)aryl chlorides, were applied for coupling reactions with more reactive (hetero)aryl bromides and iodides, both catalytic loadings and reaction temperatures could be greatly reduced. Accordingly, we explored the possibility if a more practical method for preparing aryl sulfones could be discovered by using these newly-developed amide ligands.

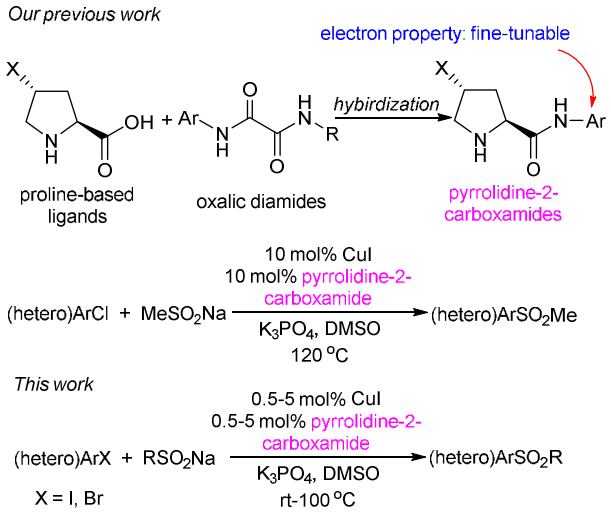


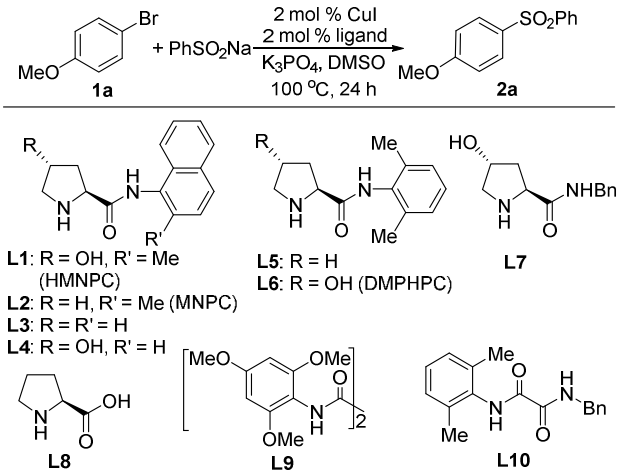
Figure 2. CuI/pyrrolidine-2-carboxamide-catalyzed coupling reactions of (hetero)aryl halides with sulfinic acid salts

Results and Discussions

Because CuI/*L*-proline could not efficiently catalyze the coupling of (hetero)aryl bromides and relatively bulky sodium benzenesulfinate,[8c] we chose the coupling of 4-bromoanisole with sodium benzenesulfinate as a model reaction to screen suitable ligands, and the results are summarized in Table 1. Initially, we examined (2*S*,4*R*)-4-hydroxy-*N*-(2-methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (**L1**, HMNPC),[14] the best ligand for Cu-catalyzed coupling reaction of (hetero)aryl chlorides and sodium methanesulfinate. It was found that under the action of 2 mol % CuI and **L1**, the reaction completed after 24 h at 100 °C to afford 1-methoxy-4-(phenylsulfonyl)benzene (**2a**) in 99% yield (entry 1). The hydroxyl group in this ligand seemed to play an important role, as evident from that the yield decreased dramatically in case of **L2** as the ligand (entry 2). The similar trend was

seen when aniline part was changed to naphthalene-1-yl or 2,6-dimethylphenyl (entries 3-6). When benzylamine-derived ligand **L7** was used, a poor yield was observed (entry 7), indicating that the aromatic amides are better ligands than aliphatic ones. Almost no conversion was observed in case of *L*-proline, implying that the amido moiety in the ligands is essential for this transformation. We also examined two oxalic diamides that showed excellent activity in Cu-catalyzed amination of aryl chlorides,[15a,15c] and found that they are less powerful than proline-derived mono-amides (entries 9 and 10). Since **L1** and **L6** ((2*S*,4*R*)-*N*-(2,6-dimethylphenyl)-4-hydroxypyrrolidine-2-carboxamide, DMPHPC) gave the almost same results and 2,6-dimethylaniline is much cheaper than (2-methylnaphthalen-1-yl)amine, we decided to use **L6** as the ligand for subsequent reaction scope study. The excellent performance displayed by **L1** and **L6** might partially result from the better solubility of the corresponding copper salts. Among the solvents examined, DMSO gave the best result, *t*-BuOH or 2-methoxyethanol could serve as the alternative solvents (entries 11 and 12), while DMF or dioxane gave no conversion (entries 13 and 14).

Table 1. CuI/Ligand-Catalyzed Coupling of 4-Bromoanisole and Sodium Benzenesulfinate[a]

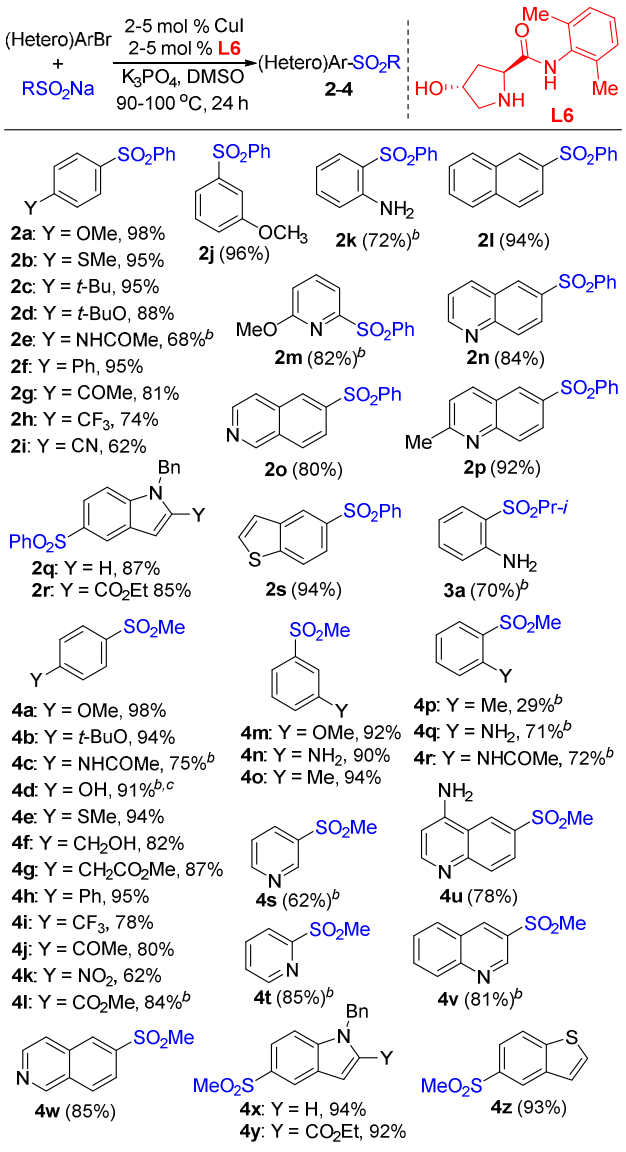


Entry	Ligand	Yield (%)[b]	Entry	Ligand	Yield (%)[b]
1	**L1**	99	8	**L8**	trace
2	**L2**	48	9	**L9**	18
3	**L3**	36	10	**L10**	13
4	**L4**	94	11	**L6**	82[c]
5	**L5**	42	12	**L6**	74[d]
6	**L6**	99	13	**L6**	0[e]
7	**L7**	27	14	**L6**	0[f]

[a]Reaction conditions: **1a** (5 mmol), $PhSO_2Na$ (6.5 mmol), CuI (0.1 mmol), ligand (0.1 mmol), K_3PO_4 (5 mmol), DMSO (2.5 mL), 100 °C, 24 h. [b]Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]In *t*-BuOH. [d]In 2-methoxyethanol. [e]In DMF. [f]In 1,4-dioxane.

By employing **L6** as the ligands, we examined the coupling reaction with a series of (hetero)aryl bromides and sulfinic acid salts. As illustrated in Table 2, under the catalysis of 2 mol % CuI and **L6**, coupling reaction completed at 100 ^{o}C in most cases to afford the corresponding diaryl sulfones **2a**-**2l** in 62-98% yields. The substrates with coordination ability such as amino (**2k**) and amido (**2e**) moieties required higher catalytic loadings (5 mol %) to ensure a complete conversion. Additionally, a variety of heteroaryl bromides were applicable under these conditions to afford the corresponding heteroaryl sulfones **2m**-**2s**. Using sodium isopropylsulfinate as a coupling partner, 2-(isopropylsulfonyl)aniline **3a** was obtained in 70% yield. In this case complete conversion was observed at 90 ^{o}C. Similarly, a large number of substituted aryl and heteroaryl bromides coupled smoothly with sodium methanesulfinate at 90 ^{o}C, delivering (hetero)aryl methylsulfones **4a**-**4o** and **4q**-**4z** in good to excellent yields. However, coupling reaction of 2-methylbromobenzene was quite sluggish, and only 29% yield of **4p** was obtained even using 5 mol % CuI and **L6**. This result indicated that the present coupling was very sensitive to steric hindrance.

Table 2. CuI/**L6** Catalyzed Coupling of (Hetero)aryl Bromides with Sulfinic Acid Salts[a]



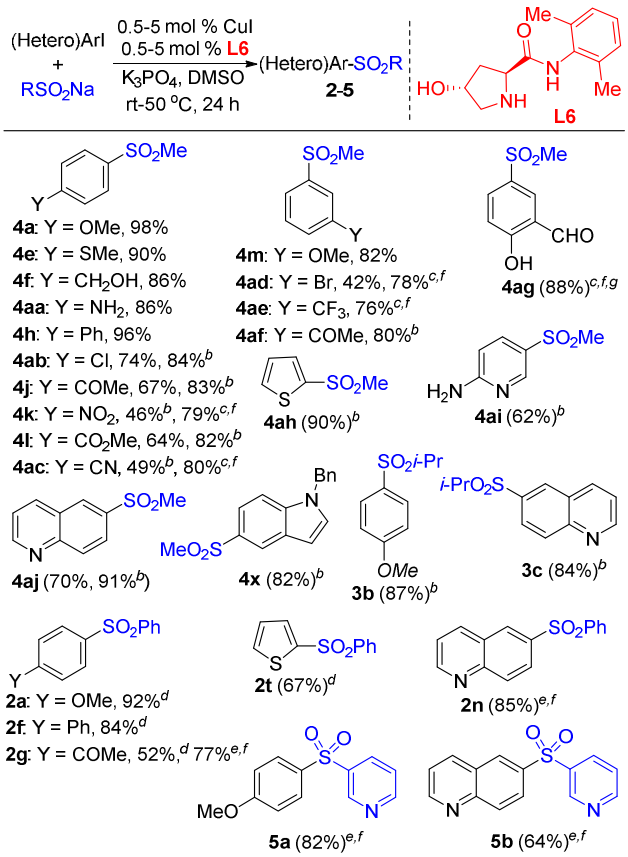
[a]Raection condition: (hetero)aryl bromide (5 mmol), RSO_2Na (6.5 mmol), K_3PO_4 (5 mmol), CuI (0.1 mmol), **L6** (0.1 mmol), DMSO (3 mL), 100 °C (for producing **2**), or 90 °C (for producing **3** and **4**), 24 h. [b]5 mol % CuI and **L6** were used. [c]10 mmol of K_3PO_4 was used.

Since earlier report on Cu/ligand-catalyzed coupling reactions of aryl iodides and sulfinic acid salts required more than 10 mol % copper salts and ligands with reaction temperature at 90-110 ^{o}C,[8] we next investigated whether the catalytic system of CuI/**L6** could lead to milder reaction conditions. To our delight, under the catalysis of 0.5 mol % CuI and **L6**, the coupling reaction of 4-iodoanisole with sodium methanesulfinate proceeded at room temperature to afford **4a** in 98% yield (Table 3). Further studies illustrated that a wide range of 4-substituted aryl iodides are compatible with these reaction conditions, providing the corresponding aryl methylsulfones in good to excellent yields. Generally, electron-poor aryl iodides are less reactive than electron-rich ones, and therefore in some cases increased catalytic loadings and reaction temperatures were required to get complete conversion (**4ab, 4j-4l, 4ac**). Some 3-substituted aryl iodides also worked well at rt-50 ^{o}C to give the related coupling products in good yields. The coupling of several heteroaryl iodides could also run at room temperature, leading to the formation of **4ah**-**4aj** and **4x** in 62-91% yields. The 2-amino-5-iodopyridine was less reactive than other heteroaryl iodides, presumably because the aminopyridine moiety could coordinate with Cu and therefore reduce the activity of the present catalytic system.

When more bulky sulfinic acid salts were used, the coupling reaction turned out to be slow. But they gave satisfactory results when the coupling reaction was conducted at rt-50 ^{o}C with the employment of 1-5 mol % CuI and **L6** as the catalysts. Noteworthy is that sodium benzenesulfinate and sodium pyridine-3-sulfinate were

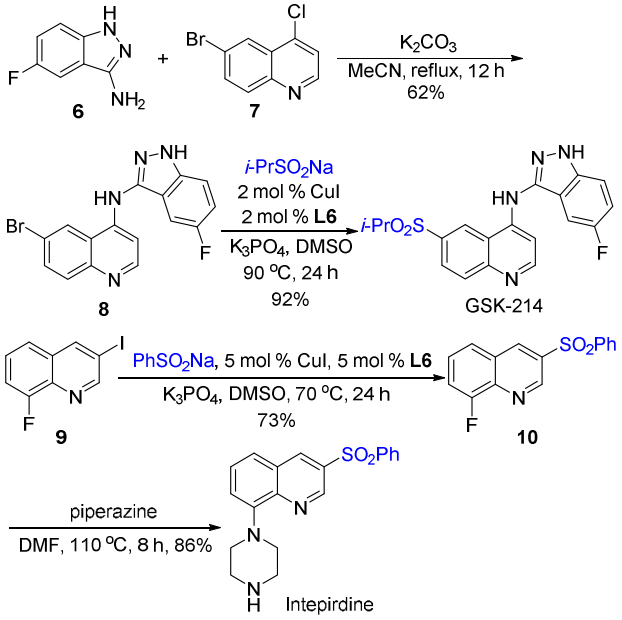
workable under these conditions, providing a variety of diaryl (**2a**, **2f** and **2g**), aryl-heteroaryl (**2n**, **2t** and **5a**) and diheteroaryl sulfones (**5b**).

Table 3. CuI/**L6** Catalyzed Coupling of (Hetero)aryl Iodides with Sulfinic Acid Salts[a]



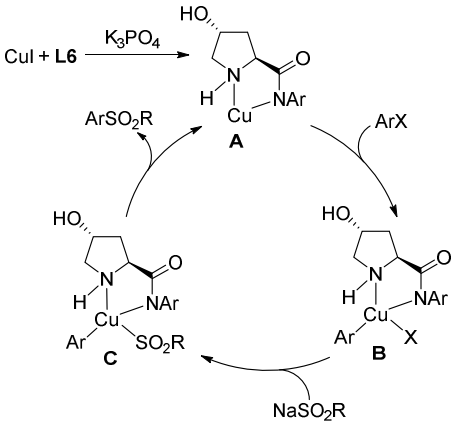
[a]Reaction condition: (hetero)aryl iodide (5 mmol), RSO_2Na (6.5 mmol), K_3PO_4 (5 mmol), CuI (0.025 mmol), **L6** (0.025 mmol), DMSO (4 mL), rt, 24 h. [b]1 mol % CuI and **L6** were used. [c]2 mol % CuI and **L6** were used. [d]3 mol % CuI and **L6** were used. [e]5 mol % CuI and **L6** were used. [f]At 50 °C. [g]10 mmol of K_3PO_4 was used.

It is notable that several coupling products in the present study are valuable building blocks for assembling bioactive agents. For example, **4g**[16] and **4j**[17] have been used for preparing COX-2 inhibitors, respectively, while **3a** is a key intermediate for the synthesis of antitumor drug Ceritinib.[2] To further demonstrate the usage of this method, we attempted to prepare RIP2 kinase inhibitor GSK214[18] and anti-Alzheimer's disease drug Intepirdine.[5] As shown in Scheme 1, nucleophilic replacement of 6-bromo-4-chloroquinoline **7** with 5-fluoro-1*H*-indazol-3-amine **6** in refluxed MeCN provided bromide **8**, which was coupled with sodium *i*-propane-2-sulfinate under the catalysis of 2 mol % CuI and **L6** to deliver GSK 214 in 92% yield. In a parallel procedure, CuI/**L6**-catalyzed coupling of 8-fluoro-3-iodoquinoline **9** with sodium benzenesulfinate proceeded smoothly at 70 ^{o}C to afford sulfone **10** in 73% yield, which was subjected to a nucleophilic replacement reaction with piperazine to furnish Intepirdine in 86% yield.



Scheme 1. Synthesis of GSK-214 and Intepirdine

A possible mechanism for our reaction is depicted in Scheme 2. After reaction with K_3PO_4, ligand **L6** could give a deprotonated salt, which would react with CuI to deliver Cu(I) complex **A**. Oxidative addition of **A** to (hetero)aryl halides could provide Cu(III) complex **B,** which would undergo ligand exchange to afford complex **C**. Reductive elimination of **C** would produce (hetero)aryl sulfones and regenerate the catalytic species **A**.



Scheme 2. Possible catalytic cycle

In conclusion, we have demonstrated a superior method for promoting the coupling of (hetero)aryl halides and sulfinic acid salts by employing the combination of CuI and DMPHPC as the catalytic system, which allows the coupling with (hetero)aryl iodides and bromides to proceed at low catalytic loadings. Notably, the coupling of (hetero)aryl iodides occurs at room temperature with a broad reaction scope. This applicability for preparing various aryl or alkyl sulfones from aryl bromides and iodides, together with that the extraordinary broad range of functional group compatibility (such as alcohol, amine, aldehyde, ketone, ester, nitro, nitrile, chloro and bromo) make the present method very attractive for a diverse set of aryl/heteroaryl sulfones. Additionally, the excellent performance displayed by

pyrrolidine-2-carboxamide ligands will stimulate further ligand design for greater applicability of Cu-catalyzed coupling reactions.

Experimental

General procedure for ligand preparation. To a solution of *N*-(*tert*-butoxycarbonyl)-*L*-proline (6.456 g, 30 mmol) or (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (6.933 g, 30 mmol) in CH_2Cl_2 (100 mL) were sequentially added Et_3N (3.939 g, 39 mmol, 1.3 equiv) and *iso*-butyl chloroformate (4.914 g, 36 mmol, 1.2 equiv) at 0 ^oC. The resulting mixture was stirred at room temperature for 1 h before aryl amine (36 mmol, 1.2 equiv) added. The solution was stirred overnight at room temperature, and then trifluoroacetic acid (20 g) was added. After the mixture was stirred at room temperature for another 5 h, it was concentrated *in vacuo*. The residue was added into saturated sodium bicarbonate (30 mL) and the mixture was stirred to give a precipitate, which was collected and purified by flash chromatography (eluting with 25:1-20:1 dichloromethane/methanol) to afford the ligand.

(2S,4R)-4-Hydroxy-N-(2-methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (**L1**).[14] White solid (6.244 g, 77% yield); mp 163-165 ^oC; ^1H NMR (500 MHz, CD_3OD) δ 7.84 (dd, *J* = 8.3, 2.7 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 4.49 (t, *J* = 4.4 Hz, 1H), 4.27 (t, *J* = 8.4 Hz, 1H), 3.20 (dd, *J* = 12.0, 4.1 Hz, 1H), 3.03 (dt, *J* = 12.0, 1.6 Hz, 1H), 2.41-2.37 (m, 1H), 2.36 (s, 3H), 2.13-2.06 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.1, 134.2,

134.2, 131.9, 131.0, 129.7, 129.0, 128.5, 127.5, 126.3, 123.3, 73.5, 61.0, 56.2, 41.3, 18.6; ESI-MS *m/z* 271 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{19}O_2N_2$ $[M + H]^+$ 271.1441, found 271.1440.

(S)-N-(2-Methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (**L2**).[14] White solid (5.951 g, 78% yield); mp 94-95 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1), 7.75 (d, *J* = 8.5 Hz, 1H), 7.53-7.47 (m, 1H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 4.68 (t, *J* = 7.8 Hz, 1H), 3.38-3.30 (m, 2H), 2.70-2.59 (m, 1H), 2.35 (s, 3H), 2.31-2.21 (m, 1H), 2.15-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 132.8, 132.5, 130.4, 130.1, 128.9, 128.1, 127.0, 126.4, 125.2, 122.3, 61.0, 47.6, 31.2, 26.5, 18.8; ESI-MS *m/z* 255 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{19}ON_2$ $[M + H]^+$ 255.1492, found 255.1492.

(S)-N-(Naphthalen-1-yl)pyrrolidine-2-carboxamide (**L3**).[14] White solid (5.983 g, 83% yield); mp 117-119 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 10.62 (s, 1H), 8.10-8.04 (m, 1H), 8.00-7.95 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.62-7.50 (m, 3H), 4.63 (t, *J* = 7.8 Hz, 1H), 3.38 (s, 1H), 3.37-3.27 (m, 2H), 2.58-2.51 (m, 1H), 2.18-2.10 (m, 1H), 2.04-1.98 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 168.3, 134.2, 132.8, 128.7, 128.2, 126.7, 126.6, 126.6, 126.0, 123.0, 122.6, 60.1, 46.2, 30.3, 24.1; ESI-MS *m/z* 241 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{15}H_{17}ON_2$ $[M + H]^+$ 241.1335, found 241.1335.

(2S,4R)-4-Hydroxy-N-(naphthalen-1-yl)pyrrolidine-2-carboxamide (**L4**).[14] White solid (5.459 g, 71% yield); mp 151-153 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.93 (d, *J* = 8.3 Hz, 1H), 7.91-7.85 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.58-7.51 (m, 2H),

7.51-7.45 (m, 1H), 4.45 (s, 1H), 4.22 (t, J = 8.4 Hz, 1H), 3.15-3.04 (m, 2H), 2.39-2.32 (m, 1H), 2.08-2.01 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.0, 135.6, 133.5, 129.6, 128.8, 127.4, 127.1, 126.9, 126.6, 122.2, 121.5, 73.8, 61.5, 56.0, 40.8; ESI-MS *m/z* 257 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{15}H_{17}O_2N_2$ $[M + H]^+$ 257.1285, found 257.1282.

(S)-N-(2,6-Dimethylphenyl)pyrrolidine-2-carboxamide (**L5**).[14] White solid (5.370 g, 82% yield); mp 126-127 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.39 (s, 1H), 7.05 (s, 3H), 3.73 (dd, J = 8.8 Hz, 5.4 Hz, 1H), 2.92 (t, J = 6.6 Hz, 2H), 2.12 (s, 6H), 2.09-2.01 (m, 1H), 1.87-1.78 (m, 1H), 1.74-1.65 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 172.9, 135.1, 134.9, 127.6, 126.1, 60.4, 46.8, 30.7, 25.8, 18.0; ESI-MS *m/z* 219 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{13}H_{19}ON_2$ $[M + H]^+$ 219.1492, found 219.1491.

(2S,4R)-N-(2,6-dimethylphenyl)-4-hydroxypyrrolidine-2-carboxamide (**L6**). White solid (6.255 g, 89% yield); mp 164-166 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.92 (s, 1H), 9.01 (s, 1H), 7.14-7.07 (m, 3H), 5.55 (s, 1H), 4.55-4.46 (m, 2H), 3.36 (dd, J = 12.1, 3.9, 1H), 3.11 (d, J = 12.1, 1H), 2.43 (dd, J = 13.0, 7.1, 1H), 2.14 (s, 6H), 2.07-2.00 (m, 1H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 166.5, 135.0, 133.8, 127.8, 126.9, 69.1, 58.1, 53.2, 39.0, 18.0; ESI-MS *m/z* 235 $[M + H]^+$ HRMS (ESI-TOF) Calcd. for $C_{13}H_{19}O_2N_2$ $[M + H]^+$ 235.1441, found 235.1445.

(2S,4R)-N-Benzyl-4-hydroxypyrrolidine-2-carboxamide (**L7**). Yellow solid (5.155 g, 78% yield); mp 105-107 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.37-7.24 (m, 5H), 4.41 (s, 2H), 4.39-4.36 (m, 1H), 3.95 (t, J = 8.3, 1H), 3.02 (dd, J = 12.0, 4.1, 1H), 2.91 (dt,

J = 12.0, 1.8, 1H), 2.22-2.16 (m, 1H), 1.91-1.84 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.9, 139.9, 129.5, 128.4, 128.2, 73.5, 60.7, 56.0, 43.7, 41.0; ESI-MS *m/z* 221 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{12}H_{17}O_2N_2$ $[M + H]^+$ 221.1285, found 221.1285.

General procedure for the CuI-catalyzed coupling of (hetero)aryl bromides with sulfinic acid salts. A 25 mL resealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with CuI (0.1-0.25 mmol), **L6** (0.1-0.25 mmol), (hetero)aryl bromide (if solid) (5.0 mmol), RSO_2Na (6.5 mmol) and K_3PO_4 (5 mmol). The tube was then evacuated and backfilled with argon, and (hetero)aryl bromide (if liquid) (5.0 mmol) and solvent (3 mL, DMSO) were then added into the tube via syringe. The reaction mixture was stirred at 90-100°C in an oil bath for 24 h. After cooling to room temperature, the crude product was diluted with ethyl acetate, and filtrated through silica gel and kieselguhr. Then the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (eluting with ethyl acetate/hexanes or dichloromethane/methanol) to afford the corresponding aryl sulfone.

General procedure for the CuI-catalyzed coupling of (hetero)aryl iodides with sulfinic acid salts. A 25 mL resealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with CuI (0.025-0.25 mmol), **L6** (0.025-0.25 mmol), (hetero)aryl iodide (if solid) (5.0 mmol), RSO_2Na (6.5 mmol) and K_3PO_4 (5 mmol). The tube was then evacuated and backfilled with argon, and (hetero)aryl iodide (if liquid) (5.0 mmol) and solvent (4 mL, DMSO) were then added

into the tube via syringe. The reaction mixture was stirred at rt-50 °C in an oil bath for 24 h. After cooling to room temperature, the crude product was diluted with ethyl acetate, and filtrated through silica gel and kieselguhr. Then the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (eluting with 1:10-1:3 ethyl acetate/hexanes) to afford the corresponding aryl sulfone.

1-Methoxy-4-(phenylsulfonyl)benzene (**2a**).[8c] Yield (1.214 g, 98% for aryl bromide; 1.140 g, 92% for aryl iodide); Physical appearance: White solid; mp 90-91 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.88 (d, J = 9.0 Hz, 2H), 7.56-7.51 (m, 1H), 7.51-7.46 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 142.5, 133.3, 133.0, 130.0, 129.3, 127.4, 114.6, 55.8; EI-MS *m/z* 248 (M^+).

Methyl(4-(phenylsulfonyl)phenyl)sulfane (**2b**).[19a] Yield (1.250 g, 95% for aryl bromide); Physical appearance: White solid; mp 106-108 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.93 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 146.6, 141.4, 136.5, 133.5, 129.7, 127.7, 127.1, 125.6, 13.8; ESI-MS *m/z* 265 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{13}H_{12}NaO_2S_2[M + H]^+$ 287.0171, found 287.0179.

1-(tert-Butyl)-4-(phenylsulfonyl)benzene (**2c**).[19b] Yield (1.301 g, 95% for aryl bromide); Physical appearance: White solid; mp 129-131 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2, 2H), 7.86 (d, J = 8.4, 2H), 7.56-7.52 (m, 1H), 7.52-7.47 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 142.1, 138.7, 133.1, 129.3,

127.7, 127.6, 126.4, 35.3, 31.6, 31.1; ESI-MS *m/z* 275 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{19}O_2S$ $[M + H]^+$ 275.1100, found 275.1103.

1-(tert-Butoxy)-4-(phenylsulfonyl)benzene (**2d**). Yield (1.276 g, 88% for aryl bromide); Physical appearance: White solid; mp 78-79 ^oC; ^1H NMR (500 MHz, DMSO-*d6*) δ 7.95-7.92 (m, 2H), 7.87-7.83 (m, 2H), 7.69-7.64 (m, 1H), 7.63-7.58 (m, 2H), 7.18-7.14 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 160.0, 141.7, 133.8, 133.4, 129.7, 129.1, 127.1, 122.0, 79.8, 28.3; ESI-MS *m/z* 291 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{19}O_3S$ $[M + H]^+$ 291.1049, found 291.1048.

N-(4-(Phenylsulfonyl)phenyl)acetamide (**2e**).[8c] Yield (0.935 g, 68% for aryl bromide); Physical appearance: Yellow solid; mp 191-193 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 (d, *J* = 7.2, 2H), 7.83 (d, *J* = 8.8, 2H), 7.65 (d, *J* = 8.8, 2H), 7.55 (t, *J* = 7.4, 1H), 7.48 (t, *J* = 7.5, 2H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 142.7, 141.7, 135.8, 133.2, 129.3, 128.9, 127.4, 119.6, 24.6; ESI-MS *m/z* 274 $[M - H]^+$; HRMS (ESI-TOF) Calcd. for $C_{14}H_{14}O_3NS$ $[M + H]^+$ 276.0689, found 276.0691.

4-(Phenylsulfonyl)-1,1'-biphenyl (**2f**).[8f] Yield (1.398 g, 95% for aryl bromide; 1.230 g, 84% for aryl iodide); Physical appearance: White solid; mp 150-151 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03-7.97 (m, 4H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.60-7.55 (m, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.43-7.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 141.9, 140.2, 139.3, 133.3, 129.4, 129.2, 128.7, 128.3, 128.1, 127.8, 127.5; EI-MS *m/z* 294 (M^+); HRMS (EI-TOF) Calcd. for $C_{18}H_{14}O_2S$ (M^+) 294.0715, found 294.0718.

1-(4-(Phenylsulfonyl)phenyl)ethan-1-one (**2g**).[8c] Yield (1.060 g, 81% for aryl bromide; 0.997 g, 77% for aryl iodide); Physical appearance: White solid; mp 132-134 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.01 (m, 4H), 7.95 (d, *J* = 7.8 Hz, 2H), 7.61-7.57 (m, 1H), 7.54-7.50 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 145.5, 140.9, 140.4, 133.8, 129.6, 129.2, 128.1, 128.0, 27.0; EI-MS *m/z* 260 (M^+); HRMS (EI-TOF) Calcd. for $C_{14}H_{12}O_3S$ (M^+) 260.0507, found 260.0513.

1-(Phenylsulfonyl)-4-(trifluoromethyl)benzene (**2h**).[19a] Yield (1.139, 74% for aryl bromide); Physical appearance: White solid; mp 90-92 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2, 2H), 7.96 (d, *J* = 7.5, 2H), 7.76 (d, *J* = 8.4, 2H), 7.60 (t, *J* = 7.4, 1H), 7.53 (t, *J* = 7.6, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.33 (s), 140.7 (s), 134.9 (q, *J* = 33.1), 133.9 (s), 129.6 (s), 128.3 (s), 128.0 (s), 126.6 (q, *J* = 3.7), 123.2 (q, *J* = 273.1); ESI-MS *m/z* 309 $[M + Na]^+$; HRMS (ESI-TOF) Calcd. for $C_{13}H_9O_2F_3SNa$ $[M + Na]^+$ 309.0168, found 309.0169.

4-(Phenylsulfonyl)benzonitrile (**2i**).[8d] Yield (0.821 g, 62% for aryl bromide); Physical appearance: Yellow solid; mp 125-127 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6, 2H), 7.94 (d, *J* = 7.3, 2H), 7.79 (d, *J* = 8.7, 2H), 7.64-7.59 (m, 1H), 7.53 (t, *J* = 7.7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 140.2, 134.1, 133.2, 129.7, 128.3, 128.0, 117.2, 117.0; ESI-MS *m/z* 266 $[M + Na]^+$; HRMS (ESI-TOF) Calcd. for $C_{13}H_9O_2NSNa$ $[M + H]^+$ 266.0246, found 266.0252.

1-Methoxy-3-(phenylsulfonyl)benzene (**2j**).[19a] Yield (1.190 g, 96% for aryl bromide); Physical appearance: White solid; mp 89-91 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.02-7.96 (m, 2H), 7.71-7.65 (m, 1H), 7.64-7.59 (m, 2H), 7.56-7.48 (m, 2H),

7.45-7.43 (m, 1H), 7.27-7.21 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 159.7, 142.3, 141.0, 133.7, 131.0, 129.7, 127.4, 119.5, 119.4, 112.1, 55.7; EI-MS *m/z* 248 (M^+).

2-(Phenylsulfonyl)aniline (**2k**).[19c] Yield (0.839 g, 72% for aryl bromide); Physical appearance: Yellow solid; mp 117-118 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7, 2H), 7.84 (dd, *J* = 8.0, 1.0, 1H), 7.56 (t, *J* = 7.4, 1H), 7.48 (t, *J* = 7.7, 2H), 7.31-7.27 (m, 1H), 6.79 (t, *J* = 7.6, 1H), 6.65 (d, *J* = 8.2, 1H), 5.13 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 142.0, 135.1, 133.2, 130.1, 129.1, 127.0, 122.0, 118.0, 117.8; ESI-MS *m/z* 234 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{12}H_{12}O_2NS$ $[M + H]^+$ 234.0583, found 234.0584.

2-(Phenylsulfonyl)naphthalene (**2l**).[19a] Yield (1.261 g, 94% for aryl bromide); Physical appearance: White solid; mp 119-121 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.03-7.99 (m, 2H), 7.97 (d, *J* = 7.9, 1H), 7.92 (d, *J* = 8.7, 1H), 7.88-7.83 (m, 2H), 7.64-7.57 (m, 2H), 7.54 (t, *J* = 7.3, 1H), 7.49 (t, *J* = 7.4, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 138.5, 135.1, 133.3, 132.3, 129.8, 129.5, 129.4, 129.2, 129.2, 128.0, 127.8, 127.7, 122.8; ESI-MS *m/z* 269 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{13}O_2S$ $[M + H]^+$ 269.0631, found 269.0636.

2-Methoxy-6-(phenylsulfonyl)pyridine (**2m**).[19d] Yield (1.011 g, 82% for aryl bromide); Physical appearance: Yellow solid; mp 74-76 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.03-7.95 (m, 3H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ

163.5, 154.9, 141.2, 138.4, 134.1, 129.4, 128.5, 115.6, 115.1, 53.7; ESI-MS *m/z* 250 $[M + H]^+$.

6-(Phenylsulfonyl)quinolone (**2n**). Yield (1.124 g, 84% for aryl bromide; 1.141 g, 85% for aryl iodide); Physical appearance: Yellow solid; mp 125-127 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 9.04 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 8.09 (dd, *J* = 8.9, 2.1 Hz, 1H), 8.03-8.00 (m, 2H), 7.59-7.56 (m, 1H), 7.54-7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 149.6, 141.2, 139.4, 137.5, 133.6, 131.5, 129.6, 129.2, 128.0, 127.5, 126.6, 122.8; EI-MS *m/z* 269 (M^+); HRMS (EI-TOF) Calcd. for $C_{15}H_{11}NO_2S$ (M^+) 269.0511, found 269.0521.

6-(Phenylsulfonyl)isoquinoline (**2o**). Yield (1.070 g, 80% for aryl bromide); Physical appearance: Yellow solid; mp 184-186 ^oC; ^1H NMR (500 MHz, DMSO-*d6*) δ 9.42 (s, 1H), 8.77 (s, 1H), 8.64 (d, *J* = 5.7 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.12-8.01 (m, 4H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 152.6, 144.5, 142.2, 140.3, 134.3, 134.0, 130.0, 129.8, 128.9, 127.6, 127.3, 123.9, 121.3; ESI-MS *m/z* 270 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{15}H_{12}O_2SN$ $[M + H]^+$ 270.0583, found 270.0581.

2-Methyl-6-(phenylsulfonyl)quinoline (**2p**). Yield (1.3 g, 92% for aryl bromide); Physical appearance: Yellow solid; mp 157-158 ^oC; ^1H NMR (500 MHz, DMSO-*d6*) δ 8.73 (d, *J* = 1.7 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 1H), 8.11-8.05 (m, 2H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.69 (t, *J* = 6.8 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H); 2.68 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 162.7, 148.6, 140.9, 137.6, 137.5,

133.8, 130.2, 129.8, 129.1, 127.4, 126.1, 125.4, 123.8, 25.1; ESI-MS *m/z* 284 [M + H]$^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{14}O_2SN$ [M + H]$^+$ 284.0740, found 284.0738.

1-Benzyl-5-(phenylsulfonyl)-1H-indole (**2q**). Yield (1.507 g, 87% for aryl bromide); Physical appearance: Yellow solid; mp 105-106 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.29 (d, *J* = 1.2 Hz, 1H), 7.96-7.91 (m, 2H), 7.72 (d, *J* = 3.2 Hz, 1H), 7.70-7.63 (m, 2H), 7.61-7.50 (m, 3H), 7.29-7.25 (m, 2H), 7.24-7.16 (m, 3H), 6.74 (d, *J* = 3.7 Hz, 1H), 5.47 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 142.6, 137.6, 137.5, 132.9, 132.1, 131.6, 129.5, 128.6, 127.8, 127.5, 127.0, 126.9, 121.4, 119.8, 111.2, 103.0, 49.3; ESI-MS *m/z* 348 [M + H]$^+$; HRMS (ESI-TOF) Calcd. for $C_{21}H_{18}O_2SN$ [M + H]$^+$ 348.1053, found 348.1052.

Ethyl 1-benzyl-5-(phenylsulfonyl)-1H-indole-2-carboxylate (**2r**). Yield (1.782 g, 85% for aryl bromide); Physical appearance: Yellow solid; mp 123-125 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 1.5, 1H), 7.97 (d, *J* = 7.1, 2H), 7.78 (dd, *J* = 8.9, 1.7, 1H), 7.53-7.44 (m, 4H), 7.42 (d, *J* = 8.9, 1H), 7.26-7.18 (m, 3H), 7.02 (d, *J* = 7.1, 2H), 5.84 (s, 2H), 4.35 (q, *J* = 7.1, 2H), 1.36 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 142.5, 141.0, 137.3, 133.9, 132.9, 130.4, 129.2, 128.8, 127.6, 127.5, 126.3, 125.6, 124.1, 123.6, 112.1, 111.9, 61.2, 48.3, 14.3; ESI-MS *m/z* 420 [M + H]$^+$; HRMS (ESI-TOF) Calcd. for $C_{24}H_{22}O_4NS$ [M + H]$^+$ 420.1264, found 420.1267.

5-(Phenylsulfonyl)benzo[b]thiophene (**2s**). Yield (1.284 g, 94% for aryl bromide); Physical appearance: White solid; mp 126-128 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.60 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.96 (d, *J* = 5.5 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.68-7.61 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR

(125 MHz, DMSO-*d6*) δ 143.9, 141.5, 139.4, 137.3, 133.5, 130.7, 129.6, 127.2, 124.5, 124.1, 123.3, 121.8; ESI-MS *m/z* 275 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{14}H_{11}O_2S_2$ $[M + H]^+$ 275.0195, found 275.0193.

2-(Phenylsulfonyl)thiophene (**2t**).[8c] Yield (0.705 g, 67% for aryl iodide); Physical appearance: White solid; mp 119-121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 4.9 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 142.2, 134.0, 133.5, 133.4, 129.4, 128.0, 127.4; EI-MS *m/z* 224 (M^+); HRMS (EI-TOF) Calcd. for $C_{10}H_8O_2S_2$ (M^+) 223.9966, found 223.9967.

2-(iso-Propylsulfonyl)aniline (**3a**).[19e] Yield (0.701 g, 70% for aryl bromide); Physical appearance: Yellow solid; mp 83-84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.34-7.30 (m, 1H), 6.78-6.74 (m, 1H), 6.71 (dd, *J* = 8.3 Hz, 0.8, 1H), 5.09 (br s, 2H), 3.31 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 135.1, 131.3, 118.1, 117.6, 117.5, 54.2, 15.3; ESI-MS *m/z* 200 $[M + H]^+$.

1-(iso-Propylsulfonyl)-4-methoxybenzene (**3b**).[19f] Yield (0.926 g, 87% for aryl iodide); Physical appearance: White solid; mp 125-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.19-3.11 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 131.3, 128.5, 114.4, 55.9, 55.8. 16.0; EI-MS *m/z* 214 (M^+); HRMS (EI-TOF) Calcd. for $C_{10}H_{14}O_3S$ (M^+) 214.0664, found 214.0657.

6-(iso-Propylsulfonyl)quinolone (**3c**). Yield (0.986 g, 84% for aryl iodide); Physical appearance: Yellow solid; mp 115-117 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06-9.01 (m, 1H), 8.43 (d, *J* = 1.7 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.05 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.33-3.21 (m, 1H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 149.7, 137.0, 134.8, 131.0, 131.0, 127.4, 127.2, 122.7, 55.7, 15.7; EI-MS *m/z* 235 (M^+); HRMS (EI-TOF) Calcd. for $C_{12}H_{13}NO_2S(M^+)$ 235.0667, found 235.0663.

1-Methoxy-4-(methylsulfonyl)benzene (**4a**).[8c] Yield (0.911 g, 98% for aryl bromide; 0.914 g, 98% for aryl iodide); Physical appearance: White solid; mp 118-120 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 132.3, 129.5, 114.5, 55.7, 44.8; EI-MS *m/z* 186 (M^+).

1-(tert-Butoxy)-4-(methylsulfonyl)benzene (**4b**). Yield (1.073 g, 94% for aryl bromide); Physical appearance: White solid; mp 93-95 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.8, 2H), 7.09 (d, *J* = 8.8, 2H), 3.03 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 133.9, 128.9, 122.8, 80.3, 77.4, 77.2, 76.9, 44.8, 28.9; ESI-MS *m/z* 251 $[M + Na]^+$; HRMS (ESI-TOF) Calcd. for $C_{11}H_{17}O_3S$ $[M + H]^+$ 229.0893, found 229.0899.

N-(4-(Methylsulfonyl)phenyl)acetamide (**4c**).[8c] Yield (0.801 g, 75% for aryl bromide); Physical appearance: White solid; mp 185-187 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 10.37 (s, 1H), 7.86-7.79 (m, 4H), 3.15 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 169.1, 143.8, 134.4, 128.2, 118.6, 43.8, 24.2; EI-MS *m/z* 213 $[M + H]^+$.

4-(Methylsulfonyl)phenol (**4d**).[8c] Yield (0.783 g, 91% for aryl bromide); Physical appearance: White solid; mp 94-96 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.56 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.10 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.9, 130.9, 129.4, 115.7, 44.1; EI-MS *m/z* 172 $[M + H]^{+}$.

Methyl (4-(methylsulfonyl)phenyl)sulfane (**4e**).[8b] Yield (0.950 g, 94% for aryl bromide; 0.946 g, 90% for aryl iodide); Physical appearance: White solid; mp 97-99 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 3.03 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 136.4, 127.8, 125.6, 44.8, 14.9; EI-MS *m/z* 202 (M^{+}).

(4-(Methylsulfonyl)phenyl)methanol (**4f**).[14] Yield (0.761 g, 82% for aryl bromide; 0.801 g, 86% for aryl iodide); Physical appearance: White solid; mp 82-84 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.77 (s, 2H), 3.01 (s, 3H), 2.64 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 139.4, 127.7, 127.3, 64.2, 44.7; EI-MS *m/z* 186 (M^{+}); HRMS (EI-TOF) Calcd. for $C_8H_{10}O_3S$ (M^{+}) 186.0351, found 186.0347.

Methyl 2-(4-(methylsulfonyl)phenyl)acetate (**4g**).[19g] Yield (0.992 g, 87% for aryl bromide); Physical appearance: White solid; 84-85 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 2H), 3.63 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 171.4, 140.8, 139.9, 130.9, 127.4, 52.4, 44.0, 40.2; ESI-MS *m/z* 228 $[M + H]^{+}$.

4-(Methylsulfonyl)-1,1'-biphenyl (**4h**).[8c] Yield (1.105 g, 95% for aryl bromide; 1.116 g, 96% for aryl iodide); Physical appearance: White solid; mp 139-141 ^{o}C; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 139.3, 139.2, 129.2, 128.8, 128.1, 128.0, 127.5, 44.8; EI-MS *m/z* 232 (M^+).

1-(Methylsulfonyl)-4-(trifluoromethyl)benzene (**4i**).[8b] Yield (0.873 g, 78% for aryl bromide); Physical appearance: Yellow solid; mp 109-110 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.17 (d, *J* = 8.2 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 144.6, 133.2 (q, *J* = 32.3 Hz), 128.1, 126.6 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 273.0 Hz), 43.1; EI-MS *m/z* 224 (M^+).

1-(4-(Methylsulfonyl)phenyl)ethan-1-one (**4j**).[8c] Yield (0.793 g, 80% for aryl bromide; 0.823 g, 83% for aryl iodide); Physical appearance: White solid; mp 125-127 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 3.08 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 144.3, 141.0, 129.3, 128.0, 44.5, 27.1; EI-MS *m/z* 198 (M^+).

1-(Methylsulfonyl)-4-nitrobenzene (**4k**).[8b] Yield (0.624 g, 62% for aryl bromide; 0.792 g, 79% for aryl iodide); Physical appearance: Yellow solid; mp 125-126 ^{o}C; ^{1}H NMR (500 MHz, CDCl3) δ 8.41 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 146.1, 129.1, 124.8, 44.4; EI-MS *m/z* 201 (M^+).

Methyl 4-(methylsulfonyl)benzoate (**4l**).[8c] Yield (0.900 g, 84% for aryl bromide; 0.877 g, 82% for aryl iodide); Physical appearance: White solid; mp 120-121 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H), 3.98 (s, 3H),

3.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 144.4, 135.0, 130.7, 127.6, 52.9, 44.4; EI-MS *m/z* 214 (M^+).

1-Methoxy-3-(methylsulfonyl)benzene (**4m**).[10d] Yield (0.0.856 g, 92% for aryl bromide; 0.763 g, 82% for aryl iodide); Physical appearance: White solid; mp 47-48 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.44-7.43 (m, 1H), 7.18-7.15 (m, 1H), 3.87 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 141.9, 130.6, 120.3, 119.6, 112.0, 55.9, 44.6; EI-MS *m/z* 186 (M^+); HRMS (EI-TOF) Calcd. for $C_8H_{10}O_3S$ $(M)^+$ 186.0351, found 186.0347.

3-(Methylsulfonyl)aniline (**4n**).[19h] Yield (0.770 g, 90% for aryl bromide); Physical appearance: Yellow solid; mp 165-167 ^oC; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.25 (t, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 2.0 Hz, 1H), 7.02-6.96 (m, 1H), 6.87-6.81 (m, 1H), 5.65 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 150.0, 141.8, 130.3, 118.6, 113.8, 111.4, 44.1; ESI-MS *m/z* 171 $[M + H]^+$.

1-Methyl-3-(methylsulfonyl)benzene (**4o**).[19i] Yield (0.798 g, 94% for aryl bromide); Physical appearance: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 2H), 7.41-7.39 (m, 2H), 2.99 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.6, 134.4, 129.2, 127.6, 124.4, 44.4, 21.3; ESI-MS *m/z* 171 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_8H_{10}O_2SNa$ $[M + Na]^+$ 193.0294, found 193.0293.

1-Methyl-2-(methylsulfonyl)benzene (**4p**).[8c] Yield (0.246 g, 29% for aryl bromide); Physical appearance: Yellow oil; ^{1}H NMR (500 MHz, CDCl3) δ 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.6 Hz,

1H), 3.06 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.6, 133.8, 132.8, 129.3, 126.8, 43.8, 20.4; EI-MS *m/z* 170 (M^+).

2-(Methylsulfonyl)aniline (**4q**).[19j] Yield (0.608 g, 71% for aryl bromide); Physical appearance: Yellow solid; mp 84-85 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.53 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.37-7.32 (m, 1H), 6.89 (dd, *J* = 8.3 Hz, 0.9 Hz, 1H), 6.72-6.67 (m, 1H), 6.03 (s, 2H), 3.09 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 147.2, 134.7, 128.6, 120.4, 117.2, 115.8, 41.9; ESI-MS *m/z* 172 $[M + H]^+$.

N-(2-(Methylsulfonyl)phenyl)acetamide (**4r**).[19j] Yield (0.770 g, 72% for aryl bromide); Physical appearance: Yellow solid; mp 145-147 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.57 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 7.74-7.68 (m, 1H), 7.44-7.38 (m, 1H), 3.26 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 168.9, 136.5, 134.7, 130.9, 129.2, 125.6, 125.2, 43.4, 24.1; ESI-MS *m/z* 214 $[M + H]^+$.

3-(Methylsulfonyl)pyridine (**4s**).[8c] Yield (0.487 g, 62% for aryl bromide); Physical appearance: Yellow solid; mp 52-54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.12 (d, *J* = 1.2, 1H), 8.85 (d, *J* = 4.1, 1H), 8.21 (td, *J* = 8.0, 1.8, 1H), 7.51 (dd, *J* = 8.0, 4.9, 1H), 3.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 148.6, 137.0, 135.3, 124.0, 44.9; ESI-MS *m/z* 158 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_6H_8O_2NS$ $[M + H]^+$ 158.0270, found 158.0274.

2-(Methylsulfonyl)pyridine (**4t**).[19h] Yield (0.667 g, 85% for aryl bromide); Physical appearance: Yellow solid; mp 120-121 oC; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.80-8.77 (m, 1H), 8.16 (td, *J* = 7.7 Hz, 1.7 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H),

7.78-7.70 (m, 1H), 3.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 157.7, 150.1, 139.1, 127.9, 120.7, 39.8; ESI-MS *m/z* 157 $[M + H]^+$.

6-(Methylsulfonyl)quinolin-4-amine (**4u**).[19k] Yield (0.866 g, 78% for aryl bromide); Physical appearance: Yellow solid; mp 238-240 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.83 (d, *J* = 2.0, 1H), 8.38 (d, *J* = 5.7, 1H), 8.10 (dd, *J* = 8.9, 2.0, 1H), 7.95 (d, *J* = 8.9, 1H), 6.74 (d, *J* = 5.7, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.3, 152.4, 150.4, 137.4, 129.4, 128.0, 125.2, 118.7, 104.8, 44.5; ESI-MS *m/z* 223 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{10}H_{11}O_2N_2S$ $[M + H]^+$ 223.0536, found 223.0537.

3-(Methylsulfonyl)quinoline (**4v**).[19l] Yield (0.838 g, 81% for aryl bromide); Physical appearance: Yellow solid; mp 139-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 2.2, 1H), 8.76 (d, *J* = 1.9, 1H), 8.17 (d, *J* = 8.5, 1H), 7.95 (d, *J* = 8.1, 1H), 7.90-7.85 (m, 1H), 7.70-7.64 (m, 1H), 3.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 146.6, 137.3, 133.5, 133.0, 129.7, 129.3, 128.6, 126.2, 77.4, 45.1; ESI-MS *m/z* 208 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{10}H_{10}O_2NS$ $[M + H]^+$ 208.0427, found 208.0426.

6-(Methylsulfonyl)isoquinoline (**4w**). Yield (0.880 g, 85% for aryl bromide); Physical appearance: White solid; mp 134-136 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.47 (s, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 8.65 (s, 1H), 8.36 (d, *J* = 8.6 Hz, 1H), 8.13 (dd, *J* = 8.6 Hz, 1.6 Hz, 1H), 8.07 (d, *J* = 5.7 Hz, 1H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 152.6, 144.4, 142.0, 134.2, 129.6, 129.1, 126.8, 123.8, 121.4, 43.2; ESI-MS *m/z* 208 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{10}H_{10}NO_2S[M + H]^+$ 208.0427, found 208.0425.

1-Benzyl-5-(methylsulfonyl)-1H-indole (**4x**).[14] Yield (1.339 g, 94% for aryl bromide); Physical appearance: Yellow solid; mp 110-112 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.78 (d, *J* = 2.1 Hz, 1H), 8.56 (d, *J* = 2.1 Hz, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.34-7.28 (m, 2H), 7.28-7.22 (m, 3H), 6.77 (d, *J* = 3.5 Hz, 1H), 5.57 (s, 2H), 3.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 136.5, 131.6, 131.1, 129.0, 128.3, 128.0, 126.8, 121.8, 120.2, 110.5, 103.5, 50.5, 45.2; ESI-MS *m/z* 286 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{16}NO_2S$ $[M + H]^+$ 286.0896, found 286.0895.

Ethyl 1-benzyl-5-(methylsulfonyl)-1H-indole-2-carboxylate (**4y**).[14] Yield (1.642 g, 92% for aryl bromide); Physical appearance: Yellow solid; mp 145-147 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.40 (d, *J* = 0.9 Hz, 1H), 7.89-7.78 (m, 2H), 7.61 (s, 1H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 5.93 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.21 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 160.7, 140.6, 137.8, 133.4, 129.7, 128.6, 127.2, 126.2, 124.8, 123.2, 122.9, 112.4, 112.0, 60.9, 47.5, 44.1, 14.0; ESI-MS *m/z* 358 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{19}H_{20}NO_4S$ $[M + H]^+$ 358.1108, found 358.1110.

5-(Methylsulfonyl)benzo[b]thiophene (**4z**).[14] Yield (0.980 g, 93% for aryl bromide); Physical appearance: White solid; mp 105-107 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.50 (d, *J* = 1.5, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 5.4 Hz, 1H), 7.87 (dd, *J* = 8.5 Hz, 1.6 Hz, 1H), 7.69 (d, *J* = 5.4 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 144.3, 139.6, 137.6, 131.0, 125.0, 124.2, 123.4, 122.0, 44.4; ESI-MS *m/z* 212 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_9H_8NaO_2S_2$ $[M + H]^+$ 234.9858, found 234.9860.

4-(Methylsulfonyl)aniline (**4aa**).[8c] Yield (0.735 g, 86% for aryl iodide); Physical appearance: Yellow solid; mp 135-137 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 4.19 (br s, 2H), 3.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 129.5, 129.8, 114.2, 45.1; EI-MS *m/z* 171 (M^+).

1-Chloro-4-(methylsulfonyl)benzene (**4ab**).[8b] Yield (0.798 g, 84% for aryl iodide); Physical appearance: White solid; mp 91-93 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.1, 129.7, 129.0, 44.6; EI-MS *m/z* 190 (M^+).

4-(Methylsulfonyl)benzonitrile (**4ac**).[8c] Yield (0.727 g, 80% for aryl iodide); Physical appearance: White solid; mp 143-145 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H), 3.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 133.3, 128.2, 117.6, 117.1, 44.2; EI-MS *m/z* 181 (M^+).

1-Bromo-3-(methylsulfonyl)benzene (**4ad**).[10a] Yield (0.912 g, 78% for aryl iodide); Physical appearance: White solid; mp 100-102 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (t, J = 1.9 Hz, 1H), 7.88-7.86 (m, 1H), 7.79-7.77 (m, 1H), 7.45 (t, J = 7.9 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 136.9, 131.1, 130.5, 126.1, 123.5, 44.6; EI-MS *m/z* 234, 236 (M^+); HRMS (EI-TOF) Calcd. for $C_7H_7O_2SBr$ (M^+) 233.9350, found 233.9344.

1-(Methylsulfonyl)-3-(trifluoromethyl)benzene (**4ae**).[8c] Yield (0.850 g, 76% for aryl iodide); Physical appearance: White solid; mp 58-60 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 3.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 132.2 (q, J = 33.6 Hz), 130.9

(q, J = 0.8 Hz), 130.5 (q, J = 3.5 Hz), 130.4, 124.7 (q, J = 3.8 Hz), 123.2 (q, J = 272.9 Hz), 44.5; EI-MS *m/z* 225 $[M + H]^+$.

1-(3-(Methylsulfonyl)phenyl)ethan-1-one (**4af**).[19m] Yield (0.793 g, 80% for aryl iodide); Physical appearance: White solid; mp 103-105 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.21 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 3.08 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 141.5, 138.2, 133.2, 131.5, 130.1, 127.3, 44.5, 26.9; EI-MS *m/z* 198 (M^+).

2-Hydroxy-5-(methylsulfonyl)benzaldehyde (**4ag**). Yield (0.882 g, 88% for aryl iodide); Physical appearance: Yellow solid; mp 121-123 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 11.48 (s, 1H), 9.96 (s, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 8.8, 2.3 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 165.4, 135.3, 134.1, 132.3, 120.1, 119.4, 44.8; EI-MS *m/z* 200 (M^+); HRMS (EI-TOF) Calcd. for $C_8H_8O_4S$ (M^+) 200.0143, found 200.0146.

2-(Methylsulfonyl)thiophene (**4ah**).[8c] Yield (0.729 g, 90% for aryl iodide); Physical appearance: Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.68 (m, 2H), 7.15-7.12 (m, 1H), 3.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 133.8, 133.6, 128.0, 46.2; EI-MS *m/z* 162 (M^+); HRMS (EI-TOF) Calcd. for $C_5H_6O_2S_2$(M^+) 161.9809, found 161.9806.

5-(Methylsulfonyl)pyridin-2-amine (**4ai**). Yield (0.533 g, 62% for aryl iodide); Physical appearance: Yellow solid; mp 132-134 ^oC; ^1H NMR (500 MHz, DMSO-*d*6) δ 8.35 (s, 1H), 7.75 (d, J = 8.7 Hz, 1H), 6.99 (s, 2H), 6.52 (d, J = 8.9 Hz, 1H), 3.11 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 162.5, 148.7, 135.8, 123.8, 107.2, 44.5;

EI-MS *m/z* 172 (M^+); HRMS (EI-TOF) Calcd. for $C_6H_8N_2O_2S$ (M^+) 172.0306, found 172.0312.

6-(Methylsulfonyl)quinoline **(4aj)**.[19h] Yield (0.942 g, 91% for aryl iodide); Physical appearance: White solid; mp 128-130 ^oC; ^1H NMR (500 MHz, DMSO-*d*6) δ 9.08 (dd, *J* = 4.2 Hz, 1.6 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H), 8.64 (dd, *J* = 8.3 Hz, 1.0 Hz, 1H), 8.24 (d, *J* = 8.9 Hz, 1H), 8.20 (dd, *J* = 8.9 Hz, 2.0 Hz, 1H), 7.70 (dd, *J* = 8.3 Hz, 4.2 Hz, 1H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.9, 138.3, 137.5, 131.6, 129.4, 127.4, 126.0, 122.9, 44.6; EI-MS *m/z* 207 $[M + H]^+$.

3-((4-Methoxyphenyl)sulfonyl)pyridine (**5a**). Yield (1.020 g, 82% for aryl bromide); mp 135-137 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, J = 1.9, 1H), 8.73 (dd, J = 4.8, 1.6, 1H), 8.18-8.14 (m, 1H), 7.9-7.85 (m, 2H), 7.43-7.39 (m, 1H), 7.00-6.95 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 153.4, 148.5, 139.1, 135.0, 132.2, 130.1, 123.9, 114.9, 55.83; ESI-MS *m/z* 250 $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{12}H_{12}O_3NS$ $[M + H]^+$ 250.0532, found 250.0536.

6-(Pyridin-3-ylsulfonyl)quinolone (**5b**). Yield (0.864 g, 64% for aryl iodide); Physical appearance: Yellow solid; mp 166-168 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 2.3 Hz, 1H), 9.03 (d, *J* = 2.8 Hz, 1H), 8.76 (d, *J* = 3.8 Hz, 1H), 8.58 (d, *J* = 1.3 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 8.07 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.44 (dd, *J* = 8.1, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 153.8, 149.7, 148.9, 138.4, 137.9, 137.4, 135.5, 131.8, 129.6, 127.4, 126.2, 124.0, 122.9; EI-MS *m/z* 270 (M^+); HRMS (EI-TOF) Calcd. for $C_{14}H_{10}N_2O_2S$ (M^+) 270.0463, found 270.0466.

6-Bromo-N-(5-fluoro-1H-indazol-3-yl)quinolin-4-amine (**8**). To a solution of 6-bromo-4-chloroquinoline (5 mmol) in MeCN (10 mL) were added 5-fluoro-1H-indazol-3-amine (5.5 mmol) and K_3PO_4 (6.5 mmol). The mixture was stirred and refluxed overnight. After cooling to room temperature the residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (eluting with 1:2 ethyl acetate/hexanes) to afford 1.104 g of **8** (62%) as brown solid. mp 232-234 ^oC; ^1H NMR (500 MHz, DMSO-*d*6) δ 8.93 (d, *J* = 4.8 Hz, 1H), 8.74 (d, *J* = 2.2 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.92 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.64 (d, *J* = 4.8 Hz, 1H), 7.62 (dd, *J* = 9.1, 4.0 Hz, 1H), 7.34 (td, *J* = 9.0, 2.5 Hz, 1H), 6.28 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 156.9 (d, *J* = 236.6 Hz), 152.2 (d, *J* = 4.5 Hz), 151.3, 148.4, 142.4, 137.6, 132.8, 131.5, 127.5, 123.6, 119.4, 118.0 (d, *J* = 9.7 Hz), 117.0 (d, *J* = 26.7 Hz), 114.3, 112.2 (d, *J* = 9.3 Hz), 105.9 (d, *J* = 24.2 Hz); ESI-MS *m/z* 357 (^{79}Br), 359 (^{81}Br) $[M + H]^+$; HRMS (ESI-TOF) Calcd. for $C_{16}H_{11}N_4FBr$ (M^+) 357.0146, found 357.0150.

N-(5-Fluoro-1H-indazol-3-yl)-6-(iso-propylsulfonyl) quinolin-4-amine (GSK214).[18] A 25 mL resealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with CuI (9.5 mg, 0.05 mmol), **L6** (11.7 mg, 0,05 mmol), **8** (892.5 mg, 2.5 mmol), $(CH_3)_2CHSO_2Na$ (429.0 mg, 3.3 mmol) and K_3PO_4 (530.6 mg, 2.5 mmol). The tube was evacuated and back filled with argon, and DMSO (3 mL) was then added into the tube via syringe. The reaction mixture was stirred at 90 °C in an oil bath for 24

h. After cooling to room temperature, the crude product was diluted with ethyl acetate, and filtrated through silica gel and kieselguhr. Then the filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (eluting with 40:1 dichloromethane/methanol) to afford 0.882 g (92%) of GSK-214 as yellow solid. mp 268-270 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.11 (d, *J* = 1.9 Hz, 1H), 9.07 (d, *J* = 4.9 Hz, 1H), 8.29 (d, *J* = 8.9 Hz, 1H), 8.14 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.75 (d, *J* = 4.9 Hz, 1H), 7.64 (dd, *J* = 9.1, 4.0 Hz, 1H), 7.35 (td, *J* = 9.0, 2.5 Hz, 1H), 6.29 (s, 2H), 3.55-3.45 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 157.1 (d, *J* = 237.2 Hz), 153.9, 152.6 (d, *J* = 4.4 Hz), 151.2, 144.5, 137.7, 134.0, 130.8, 128.6, 127.4, 121.4, 118.5 (d, *J* = 9.8 Hz), 117.0 (d, *J* = 26.5 Hz), 114.6, 112.5 (d, *J* = 9.3 Hz), 106.0 (d, *J* = 24.2 Hz), 54.3, 15.2; ESI-MS *m/z* 385 [M + H]$^{+}$.

8-Fluoro-3-(phenylsulfonyl)quinolone (**10**).[19n] A 25 mL resealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with CuI (19.0 mg, 0.1 mmol), **L6** (23.4 mg, 0.1 mmol), 8-fluoro-3-iodoquinoline (0.546 g, 2.0 mmol), $PhSO_2Na$ (0.427 g, 2.6 mmol) and K_3PO_4 (0.424 g, 2 mmol). The tube was evacuated and back filled with argon, and DMSO (2 mL) was then added into the tube via syringe. After the reaction mixture was stirred at 70 °C in an oil bath for 24 h, it was cooled to room temperature, and diluted with ethyl acetate. The mixture was filtrated through silica gel and kieselguhr, and then the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (eluting with 1:3 ethyl acetate/hexanes) to afford 0.419 g of **10** (73%) as yellow solid. mp 166-168 ^{o}C; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 9.30 (d, *J* = 2.1 Hz, 1H), 8.87-8.83 (m, 1H), 8.05-8.01 (m, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.59-7.53 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0 (d, *J* = 259.4 Hz), 147.5 (d, *J* = 1.5 Hz), 140.7, 139.5 (d, *J* = 11.8 Hz), 136.7 (d, *J* = 2.8 Hz), 136.1, 134.1, 129.8, 128.6 (d, *J* = 7.9 Hz), 128.1 (d, *J* = 1.7 Hz), 128.0, 125.0 (d, *J* = 4.9 Hz), 117.0 (d, *J* = 18.9 Hz); ESI-MS *m/z* 288 $[M + H]^+$.

3-(Phenylsulfonyl)-8-(piperazin-1-yl)quinoline (Intepirdine, SB-742457).[9b] To a solution of **12** (0.287 g, 1 mmol) in DMF (5 mL) were added piperazine (0.258 g, 3 mmol) and K_3PO_4 (0.276 g, 1.3 mmol). The resultant mixture was stirred at 110 °C for 8 h. After the cooled solution was partitioned between methylene chloride and water, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (eluting with 50:1 dichloromethane/methanol) to afford 0.304 g of Intepirdine (86%) as yellow solid. mp 183-185 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.23 (d, *J* = 2.3 Hz, 1H), 9.05 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.0 Hz, 1H), 7.67-7.59 (m, 3H), 7.30 (d, *J* = 7.7 Hz, 1H), 4.41 (br s, 1H), 3.29 (s, 4H), 3.01 (s, 4H); ^{13}C NMR (125 MHz, DMSO-*d*6) δ 149.0, 143.8, 142.6, 140.7, 137.6, 134.1, 133.8, 129.9, 128.9, 127.6, 127.6, 122.3, 119.2, 51.5, 45.0; ESI-MS *m/z* 354 $[M + H]^+$.

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT. The authors are grateful to Chinese Academy of Sciences (sup-ported by the Strategic Priority Research Program, grant XDB20020200 & QYZDJ-SSW-SLH029) and the National Natural Science Foundation of China (grant 21621002) for their financial support.

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