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Efficient copper-catalyzed cross-coupling of nitrogen nucleophiles with *N,N*-dibenzyl-4-iodobenzenesulfonamide and its application in the synthesis of Celecoxib intermediate

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Graphical Abstract

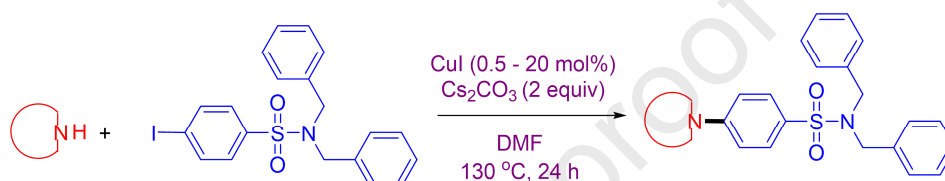
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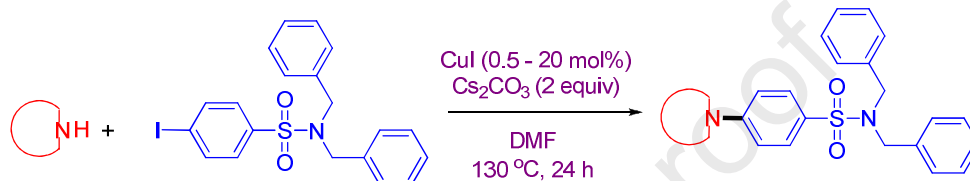
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ABSTRACT

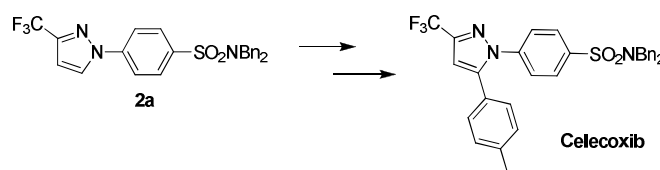
A practical and efficient strategy has been developed for the cross-coupling of *N,N*-dibenzyl-4-iodobenzenesulfonamide with nitrogen nucleophiles using 0.5–20 mol% of CuI under ligand-free conditions. A variety of nitrogen nucleophiles including nitrogen heterocycles, sulfonamides and amides afforded the corresponding products in moderate to good yields (up to 98%) under the optimized conditions. The application of this catalytic system to the synthesis of Celecoxib intermediate was also successfully demonstrated.

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The transition metal-catalysed formation of carbon and heteroatom bonds has emerged as a powerful tool in chemical synthesis. In particular, heteroaryl derivatives such as aryl pyrazoles are important building blocks in organic synthesis due to their biological properties.¹ An example is the 1, 3, 5-trisubstituted pyrazole structural motif found in numerous drug targets including the widely used COX-2 inhibitor Celecoxib (CELEBREXTM). Celecoxib (4-(5-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide) is a non-steroidal anti-inflammatory drug commonly used for the treatment of pain, fever and inflammation in numerous diseases and medical conditions such as osteoarthritis, rheumatoid arthritis, acute pain and primary dysmenorrhea.² The benefits of Celecoxib have led to increasing studies on the design and synthesis of novel Celecoxib derivatives as more potent anti-inflammatory agents with fewer side effects.³

The commercial route for the synthesis of Celecoxib involves a condensation reaction between 4-sulfamidophenylhydrazine with a diketone intermediate.⁴ This method lacks regioselectivity, affording a complex mixture of pyrazole regioisomers. Careful selection of solvents and conditions minimize the regiocontrol problems.⁵ To overcome the regioselective⁶ issue, Reddy described Michael addition of a hydrazine with a butynone and subsequently cyclization to afford the desired pyrazole.⁷ Oh demonstrated 1,3-dipolar cycloaddition reaction of a hydrozonoxy sulfonate with an enamine to generate Celecoxib.⁸ In most instances, time-consuming multistep procedures or structure-limited ring transformation reactions are required. Direct introduction of an aryl group onto the pyrazole nucleus via N-arylation for Celecoxib synthesis remains limited. In this context, the application of N-arylation for the synthesis of the key

intermediate **2a** has been reported by Gaulier and co-workers, using CuI and *N,N*-dimethylcyclohexylamine ligand at 115 °C for 50 h in a three linear step synthesis of Celecoxib.⁹



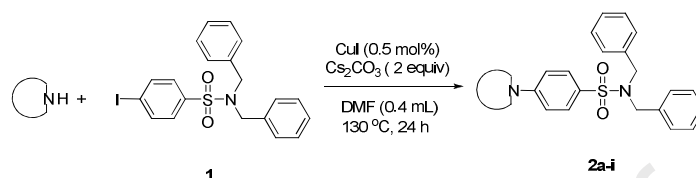
Cao and co-workers also reported a strategy for the N-arylation of 3-trifluoromethylpyrazole with aryl iodide using CuI in the presence of *N,N*-dimethylcyclohexylamine which can be applied to the synthesis of Celecoxib.¹⁰ Our group has developed protocols for the cross-coupling reactions of nitrogen nucleophiles with aryl iodides using ligand-free copper catalytic systems.¹¹ Encouraged by these precedents and to expand our interest in ligand-free copper catalysis, we envisage the application of the catalytic system for the synthesis of intermediate **2a** and to broaden the substrate scope to other classes of nitrogen nucleophiles such as nitrogen heterocycles, sulfonamides, benzamides and pyrrolidinone.

In our initial study, the C-N cross-coupling of commercially available 3-(trifluoromethyl)-1*H*-pyrazole and 4-iodobenzene-1-sulfonyl chloride was first carried out. Despite several efforts, the cross-coupling reaction afforded the desired product in poor yield. To facilitate the C-N cross-coupling, a protecting group strategy on the sulfonyl chloride functionality using a selected dibenzyl amine group was initiated.¹² The protected sulfonamide

N,N-dibenzyl-4-iodobenzenesulfonamide (1.5 equiv), 0.5 mol% CuI as catalyst, Cs₂CO₃ as base in DMF afforded *N,N*-dibenzyl-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide **2a**, an important intermediate for the synthesis of Celecoxib in excellent

the scope of ligand-free catalytic protocol was investigated with respect to *N,N*-dibenzyl-4-iodobenzenesulfonamide. As revealed in Table 1, pyrazole, imidazole, triazole and pyrrole afforded the corresponding derivatives in good to excellent yields (entries 1-2, 4-6). Good to excellent yields were afforded using 3-methylpyrazole, indole, indazole and 7-azaindole with an increase of catalyst loading to 1 or 2 mol% (entries 3, 7-9).

Table 1. CuI catalysed N-arylation of nitrogen heterocycles with *N,N*-dibenzyl-4-iodobenzenesulfonamide.^a



Entry	ArX	Product	Yield % ^b
1			99
2			92
3			55 80 ^c
4			81
5			77
6			70
7			58 88 ^d
8			58 85 ^c
9			55 ^c 75 ^d

^aUnless otherwise shown, the reaction was carried out with nitrogen heterocycles (0.80 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (1.20 mmol), Cs₂CO₃ (1.60 mmol), CuI (0.004 mmol) in DMF (0.4 ml) at 130 °C for 24 h. [

^bIsolated yield after column chromatography..

^cThe reaction was performed with CuI (0.008 mmol).

^dThe reaction was performed with CuI (0.016 mmol).

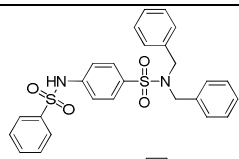
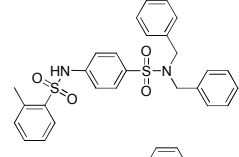
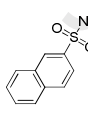
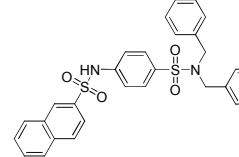

To further expand the scope of the ligand-free CuI-catalyzed amination, the reactions of a series of sulfonamides derivatives with *N,N*-dibenzyl-4-iodobenzenesulfonamide were then studied.

In general, the desired amination products were obtained in moderate to good yields (Table 2). The neutral and electron-donating substituted sulfonamides afforded the corresponding

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 effects and electronic effects on the reactions were limited as the increase of catalyst loading to 20 mol% (entries 2 and 5).
 reactions of *ortho*-substituted and electron-withdrawing

Table 2. CuI catalysed N-arylation of various sulfonamides with *N,N*-dibenzyl-4-iodobenzenesulfonamides.^a



Entry	ArX	Product	Yield % ^b
1			61
2			61 ^c
3			73
4			77
5			62 ^c
6			81
7			58

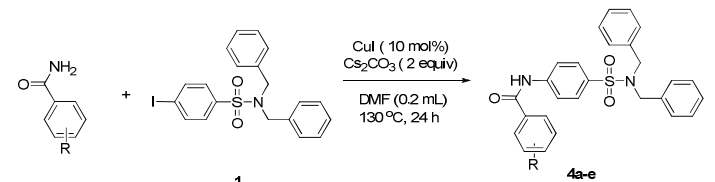
^aUnless otherwise shown, the reaction was carried out with sulfonamides (0.40 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.60 mmol), Cs₂CO₃ (0.8 mmol), CuI (0.04 mmol) in DMF (0.2 ml) at 130 °C for 24 h.


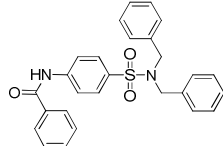
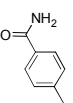
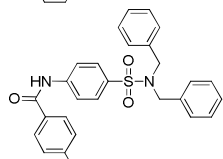
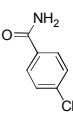
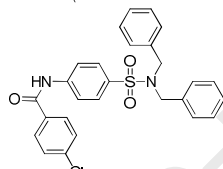
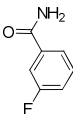
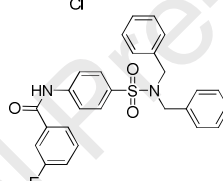

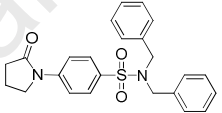
^bIsolated yield after column chromatography.

^cThe reaction was performed with CuI (0.08 mmol).

Encouraged by the applicability of the method to a broad substrate scope of both nitrogen heterocycles and sulfonamides, the protocol was tested on the N-arylation of amides. Benzamides with electron-withdrawing and electron-donating substituents gave

the respective arylated product in good yields (Table 3, entries 1-4). In addition, the N-arylation of a representative cyclic secondary amide, pyrrolidinone, afforded the product in good yield (entry 5).

Table 3. CuI catalysed N-arylation of various amides with *N,N*-dibenzyl-4-iodobenzenesulfonamide.^a


Entry	Amide	Product	Yield % ^b
1			64
2			62
3			60
4			65 ^c
5			68

^aUnless otherwise shown, the reaction was carried out with sulfonamides (0.40 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.60 mmol), Cs₂CO₃ (0.80 mmol), CuI (0.04 mmol) in DMF (0.2 mL) at 130 °C for 24 h.

^bIsolated yield after column chromatography.

^cThe reaction was performed with CuI (0.08 mmol).

In conclusion, we have developed a versatile and practical protocol for the synthesis of *N,N*-dibenzyl-4-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, a key intermediate for Celecoxib synthesis promoted by ligand-free CuI in DMF. In addition, the copper-catalytic system was extended to the N-arylation of various nitrogen nucleophiles including nitrogen heterocycles, benzamides and sulfonamides with *N,N*-dibenzyl-4-iodobenzenesulfonamide. In most instances, the N-arylated derivatives were obtained in good to excellent yields. This ligand-free catalytic system renders the current approach an attractive alternative to access various N-arylated moieties and will also provide a valuable platform for chemists who are interested in large-scale applications. Overall, we believe that the catalytic system could serve as a valuable tool for combinatorial chemistry involving the synthesis of biological and pharmaceutical products that contains N-arylated derivatives.

Experimental section

General Methods for the Cross Coupling Reaction. Chemicals and solvents were purchased from commercial suppliers. Analytical thin layer chromatography (TLC) was performed

using Merck 60 F254 precoated silica gel plate. (0.2 mm thickness). Subsequent to elution, plates were visualised using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254nm. Flash chromatography was performed using Merck silica gel 60 with AR grade solvents. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on a Bruker Avance DPX 400 spectrometer (CDCl₃ as solvent). Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). All reagents were purchased from commercial supplier and were used without any purification.

***N,N*-dibenzyl-4-iodobenzenesulfonamide (1).** Pipsyl chloride (1.11 g, 3.67 mmol) was dissolved in anhydrous dichloromethane (6.7 mL). Triethylamine (0.77 mL, 5.53 mmol) was added dropwise to the mixture. Followed by dibenzylamine (0.78 mL, 4.07 mmol) and the mixture was stirred at room temperature under N₂ for 24 h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (10 mL). The organic layer was washed with H₂O (10 mL) and aqueous HCl (1.0 M, 6.7 mL), dried over Na₂SO₄, filtered and solvent removed under reduced pressure to generate an off-white solid. Yield =

Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.24 (t, $J = 3.2$ Hz, 6H), 7.07-7.05 (m, 4H), 4.33 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 140.6, 138.3, 135.3, 128.5, 128.4, 128.3, 127.8, 99.6, 50.6. HRMS Calcd for $\text{C}_{20}\text{H}_{18}\text{INO}_2\text{S}$ [M^+]: 463.0103. Found: 462.6567.

General Procedure for the Cross Coupling Reaction. The N-nucleophile (0.4-0.8 mmol), CuI (0.004-0.04 mmol), Cs_2CO_3 (0.8-1.6 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.6-1.2 mmol) and dimethylformamide (DMF) (0.2-0.4 mL) were added to a reaction vial and a screw cap was fitted to it. The reaction mixture was stirred under air in a closed system at 130°C for 24 h. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered through a pad of Celite. The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography to afford the N-arylated product. The identity and purity of the products was confirmed by ^1H , ^{13}C NMR spectroscopic analysis and elemental analysis or mass spectroscopy.

***N,N*-dibenzyl-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (2a).**¹¹ Following the general procedure using *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) and 3-trifluoromethylpyrazole (0.109 g, 0.80 mmol) provided 372 mg (99%) of the coupling product as yellow powder after purification by flash chromatography (87: 13 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 8.05 (s, 1H), 7.92 (d, $J = 8.8$ Hz, 2H), 7.85 (d, $J = 8.9$ Hz, 2H), 7.26-7.20 (m, 7H), 7.10-7.08 (m, 4H), 6.80 (d, $J = 2.5$ Hz, 1H), 4.33 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 145.1, 144.8, 141.9, 139.6, 135.3, 128.8, 128.6, 128.5, 127.8, 119.6, 106.9, 106.8, 50.6. Anal. Calcd for $\text{C}_{24}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_2\text{S}$: C, 61.14; H, 4.28; N, 8.91; S, 6.80. Found: C, 60.28; H, 4.48; N, 8.29; S, 6.40. HRMS Calcd for $\text{C}_{24}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_2\text{S}$ [M^+]: 471.1228. Found: 471.0885.

***N,N*-dibenzyl-4-(1H-pyrazol-1-yl)benzenesulfonamide (2b).** Following the general procedure pyrazole (0.054 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 298 mg (92% yield) of the coupling product as yellow powder after purification by flash chromatography (75: 25 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 8.01 (d, $J = 2.5$ Hz, 1H), 7.92-7.85 (m, 2H), 7.84-7.82 (m, 2H), 7.79 (d, $J = 1.6$ Hz, 1H), 7.24-7.19 (m, 6H), 7.11-7.08 (m, 4H), 6.55 (t, $J = 2.2$ Hz, 1H), 4.35 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 142.9, 142.3, 138.1, 135.4, 128.8, 128.6, 128.6, 127.8, 126.9, 118.8, 108.8, 50.6. Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.50; H, 5.26; N, 10.28; S, 8.08. ^1H NMR (400 MHz, CDCl_3): δ 7.89-7.86 (m, 3H), 7.79-7.77 (m, 2H), 7.25-7.21 (m, 6H), 7.09-7.07 (m, 4H), 6.32 (s, 1H), 4.34 (s, 4H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.9, 142.7, 137.4, 135.5, 128.8, 128.6, 128.5, 127.8, 127.4, 118.3, 109.0, 50.5, 13.8. Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found: C, 69.07; H, 5.58; N, 9.89; S, 7.72.

***N,N*-dibenzyl-4-(3-methyl-1H-pyrazol-1-yl)benzenesulfonamide (2c).** Following the general procedure 3-methylpyrazole (0.064 mL, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 200 mg (55% yield) of the coupling product as yellow powder after purification by flash chromatography (84: 16 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 7.89-7.86 (m, 3H), 7.79-7.77 (m, 2H), 7.25-7.21 (m, 6H), 7.09-7.07 (m, 4H), 6.32 (s, 1H), 4.34 (s, 4H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.9, 142.7, 137.4, 135.5, 128.8, 128.6, 128.5, 127.8, 127.4, 118.3, 109.0, 50.5, 13.8. Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: C, 69.04; H,

7.72.

***N,N*-dibenzyl-4-(1H-imidazol-1-yl)benzenesulfonamide (2d).** Following the general procedure imidazole (0.054 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 261 mg (81% yield) of the coupling product as yellow powder after purification by flash chromatography (80: 20 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 7.94-7.90 (m, 3H), 7.51-7.48 (m, 2H), 7.35 (s, 1H), 7.27-7.23 (m, 7H), 7.11-7.09 (m, 4H), 4.38 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 140.2, 139.5, 135.3, 135.2, 131.3, 129.1, 128.6, 128.5, 127.8, 121.1, 117.7, 50.6. Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.25; H, 5.24; N, 10.44; S, 7.78.

***N,N*-dibenzyl-4-(1H-1,2,4-triazol-1-yl)benzenesulfonamide (2e).** Following the general procedure triazole (0.055 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 249 mg (77% yield) of the coupling product as yellow powder after purification by flash chromatography (70: 30 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 8.67 (s, 1H), 8.16 (s, 1H), 7.94 (d, $J = 8.7$ Hz, 2H), 7.83 (d, $J = 8.8$ Hz, 2H), 7.25-7.23 (m, 6H), 7.11-7.08 (m, 4H), 4.37 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 153.8, 153.2, 141.1, 140.3, 139.6, 135.2, 129.8, 128.7, 127.9, 119.9, 50.6. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$: C, 65.33; H, 4.98; N, 13.85; S, 7.93. Found: C, 65.17; H, 4.98; N, 13.41; S, 7.86.

***N,N*-dibenzyl-4-(1H-pyrrol-1-yl)benzenesulfonamide (2f).** Following the general procedure pyrrole (0.056 mL, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 224 mg (70% yield) of the coupling product as yellow powder after purification by flash chromatography (95: 5 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 7.86-7.84 (m, 2H), 7.47-7.45 (m, 2H), 7.22 (t, $J = 3.1$ Hz, 6H), 7.15 (t, $J = 2.2$ Hz, 2H), 7.09-7.06 (m, 4H), 6.41 (t, $J = 2.2$ Hz, 2H), 4.35 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.9, 137.1, 135.4, 128.9, 128.5, 128.4, 127.7, 119.8, 119.0, 111.9, 50.5. Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 71.62; H, 5.51; N, 6.96; S, 7.97. Found: C, 71.08; H, 5.36; N, 6.80; S, 7.40.

***N,N*-dibenzyl-4-(1H-indol-1-yl)benzenesulfonamide (2g).** Following the general procedure indole (0.094 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 320 mg (88% yield) of the coupling product as yellow powder after purification by flash chromatography (96: 4 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 7.92 (d, $J = 8.6$ Hz, 2H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.59 (t, $J = 7.7$ Hz, 3H), 7.34 (d, $J = 3.4$ Hz, 1H), 7.28-7.21 (m, 8H), 7.11-7.09 (m, 4H), 6.74 (d, $J = 3.3$ Hz, 1H), 4.40 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.2, 138.0, 135.4, 135.3, 129.8, 128.8, 128.6, 128.5, 127.8, 127.2, 123.7, 123.1, 121.5, 121.2, 110.3, 105.3, 50.6. Anal. Calcd for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: C, 74.31; H, 5.35; N, 6.19; S, 7.09. Found: C, 74.26; H, 5.38; N, 6.04; S, 6.98.

***N,N*-dibenzyl-4-(1H-indazol-1-yl)benzenesulfonamide (2h).** Following the general procedure indazole (0.095 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 211 mg (58% yield) of the coupling product as yellow powder after purification by flash chromatography (60: 40 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 8.26 (s, 1H), 7.98 (d, $J = 8.7$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 2H), 7.83 (t, $J = 9.0$ Hz, 2H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.25-7.22 (m, 6H), 7.12-7.10 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.6, 138.6, 137.9, 136.2, 134.6, 128.6, 128.5, 128.3, 128.0, 127.8, 126.0, 123.1, 121.9, 121.8, 110.4, 50.7. Anal. Calcd

***N,N*-dibenzyl-4-(1H-pyrrolo[2,3-b]pyridin-1-**

yl)benzenesulfonamide (2i). Following the general procedure 7-azaindole (0.095 g, 0.80 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556 g, 1.20 mmol) provided 200 mg (55% yield) of the coupling product as yellow powder after purification by flash chromatography (84:16 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 8.42 (d, *J* = 4.7 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.99 (t, *J* = 8.9 Hz, 3H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.24-7.18 (m, 7H), 7.12-7.10 (m, 4H), 6.72 (d, *J* = 3.8 Hz, 1H), 4.37 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 147.5, 143.7, 141.9, 137.0, 135.5, 129.4, 128.6, 128.4, 127.6, 126.7, 122.8, 122.1, 117.4, 110.9, 103.4, 50.6. Anal. Calcd for C₂₇H₂₃N₃O₂S: C, 71.50; H, 5.11; N, 9.26; S, 7.07. Found: C, 71.46; H, 5.21; N, 9.00; S, 6.97.

***N,N*-dibenzyl-4-(phenylsulfonamido)benzenesulfonamide**

(3a). Following the general procedure using benzenesulfonamide (63 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 116 mg (61% yield) of the coupling product as a yellow solid after purification by flash chromatography (75:25 hexane/ethyl acetate) of the crude oil. ¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45-7.49 (m, 2H), 7.15-7.23 (m, 8H), 7.01 (d, *J* = 9.1 Hz, 4H), 4.28 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 141.0, 138.9, 136.4, 135.7, 133.9, 129.7, 129.0, 128.8, 128.8, 128.0, 127.5, 119.7, 50.8. HRMS Calcd for C₂₆H₂₄N₂O₄S₂ [M⁺]: 492.1177. Found: 492.0862.

***N,N*-dibenzyl-4-(2-methylphenylsulfonamido)benzenesulfonamide (3b).**

Following the general procedure using *o*-toluenesulfonamide (68 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 123 mg (61% yield) of the coupling product as a yellow solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.21 – 7.17 (m, 7H), 7.11 – 7.09 (m, 3H), 7.03 – 7.00 (m, 4H), 4.34 (s, 4H), 2.68 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 140.3, 136.9, 136.6, 135.7, 135.1, 133.4, 132.6, 129.7, 128.5, 128.2, 128.1, 127.4, 126.3, 118.1, 50.2, 20.0. Anal. Calcd for C₂₇H₂₆N₂O₄S₂: C, 64.01; H, 5.17; N, 5.53; S, 12.66. Found: C, 64.63; H, 5.30; N, 5.42; S, 12.14.

***N,N*-dibenzyl-4-(4-methylphenylsulfonamido)benzenesulfonamide (3c).**

Following the general procedure using 4-methylbenzenesulfonamide (69 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 147 mg (73% yield) of the coupling product as a yellow solid after purification by flash chromatography (70:30 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.29 (s, 1H), 7.21-7.15 (m, 10H), 7.03-7.01 (m, 4H), 4.29 (s, 4H), 2.41 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 144.7, 140.8, 136.2, 135.6, 135.4, 130.0, 128.8, 128.5, 128.4, 127.8, 127.3, 119.3, 50.4, 21.6. Anal. Calcd for C₂₇H₂₆N₂O₄S₂: C, 64.01; H, 5.17; N, 5.53; S, 12.66. Found: C, 63.91; H, 5.22; N, 5.20; S, 11.55.

***N,N*-dibenzyl-4-(4-methoxyphenylsulfonamido)benzenesulfonamide (3d).**

methoxybenzenesulfonamide (75 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 162 mg (77% yield) of the coupling product as a off-white solid after purification by flash chromatography (70:30 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 7.80 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.18-7.20 (m, 8H), 7.00-7.03 (m, 4H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.28 (s, 4H), 3.84 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.6, 140.8, 136.2, 135.4, 130.0, 129.5, 128.8, 128.5, 128.4, 127.7, 119.2, 114.6, 55.7, 50.4. Anal. Calcd for C₂₇H₂₆N₂O₅S₂: C, 62.05; H, 5.01; N, 5.36; S, 12.27. Found: C, 62.12; H, 5.03; N, 5.33; S, 12.78.

***N,N*-dibenzyl-4-(4-(trifluoromethyl)phenylsulfonamido)benzenesulfonamide (3e).**

Following the general procedure using 4-(trifluoromethyl)benzenesulfonamide (90 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 140 mg (62% yield) of the coupling product as a yellow solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.18 (m, 8H), 7.04 – 7.02 (m, 4H), 4.31 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 159.8, 136.9, 135.3, 131.4, 128.9, 128.5, 127.8, 127.8, 127.0, 126.6, 124.2, 119.7, 118.7, 114.9, 50.4. HRMS Calcd for C₂₇H₂₃F₃N₂O₄S₂ [M⁺]: 560.1051. Found: 559.9877.

***N*-(4-(*N,N*-dibenzylsulfamoyl)phenyl)naphthalene-2-sulfonamide (3f).**

Following the general procedure using naphthalene (83 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 176 mg (81% yield) of the coupling product as a off-white solid after purification by flash chromatography (75:25 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 8.50 (s, 1H), 7.91-7.89 (m, 4H), 7.67-7.63 (m, 4H), 7.24 (d, *J* = 8.6 Hz, 3H), 7.11-7.08 (m, 6H), 6.98-6.96 (m, 4H), 4.24 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 140.8, 136.2, 135.5, 135.4, 135.1, 132.0, 129.9, 129.4, 129.2, 128.8, 128.5, 128.4, 128.0, 127.9, 127.7, 121.9, 119.3, 50.5. Anal. Calcd for C₃₀H₂₆N₂O₄S₂: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.88; H, 4.99; N, 4.95; S, 11.85.

***N,N*-dibenzyl-4-(methylsulfonamido)benzenesulfonamide**

(3g). Following the general procedure using methanesulfonamide (38 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 101 mg (58% yield) of the coupling product as a yellow solid after purification by flash chromatography (70:30 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.23-7.21 (m, 6H), 7.09-7.06 (m, 4H), 4.33 (s, 4H), 3.09 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 141.0, 136.3, 135.4, 129.1, 128.6, 128.5, 127.8, 118.8, 50.6, 40.0. Anal. Calcd for C₂₁H₂₂N₂O₄S₂: C, 58.58; H, 5.15; N, 6.51; S, 14.90. Found: C, 58.92; H, 5.06; N, 6.30; S, 14.88.

***N*-(4-(*N,N*-dibenzylsulfamoyl)phenyl)benzamide (4a).**

Following the general procedure using benzamide (49 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 117 mg (64% yield) of the coupling product as a yellow solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.80 (s, 4H), 7.59 (d, *J* = 6.4 Hz, 1H), 7.50 (t, *J* = 6.9 Hz, 2H), 7.23-7.22 (m, 6H), 7.09-7.07 (m, 4H), 4.32 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 165.9, 141.9, 135.6, 135.5, 134.2, 132.4, 129.0, 128.6, 128.5, 128.5, 127.7, 127.2, 119.9, 50.6. Anal. Calcd for C₂₇H₂₄N₂O₃S: C, 71.03; H, 5.30; N, 6.14; S, 7.02. Found: C, 71.58; H, 5.32; N, 5.91; S, 7.63.

N-(4-

(4b). Following the general procedure using *p*-toluamide (54 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 117 mg (62% yield) of the coupling product as a yellow solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 7.81 (t, *J* = 6.4 Hz, 5H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.24-7.21 (m, 7H), 7.09-7.07 (m, 4H), 4.33 (s, 4H), 2.45 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 143.1, 142.0, 135.6, 135.5, 131.3, 129.6, 129.0, 128.6, 128.5, 127.7, 127.2, 119.7, 50.6, 21.6. Anal. Calcd for C₂₈H₂₆N₂O₃S: C, 71.46; H, 5.57; N, 5.95; S, 6.81. Found: C, 71.47; H, 5.79; N, 5.65; S, 7.11.

4-chloro-*N*-(4-(*N,N*-dibenzylsulfamoyl)phenyl)benzamide

(4c). Following the general procedure using 4-chlorobenzamide (62 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 119 mg (60% yield) of the coupling product as a off-white solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.78 (s, 4H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 3.1 Hz, 6H), 7.08-7.06 (m, 4H), 4.31 (s, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 164.9, 141.7, 138.8, 135.8, 135.5, 132.6, 129.2, 128.7, 128.6, 128.5, 127.8, 120.0, 116.3, 50.6. Anal. Calcd for C₂₇H₂₃ClN₂O₃S: C, 66.05; H, 4.72; N, 5.71; S, 6.53. Found: C, 66.43; H, 4.85; N, 5.67; S, 6.71. HRMS Calcd for C₂₇H₂₃ClN₂O₃S [M+]: 490.1118. Found: 490.2506.

N-(4-(*N,N*-dibenzylsulfamoyl)phenyl)-3-fluorobenzamide

(4d). Following the general procedure using 3-fluorobenzamide (56 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 124 mg (65% yield) of the coupling product as a yellow solid after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.79 (s, 4H), 7.68-7.62 (m, 2H), 7.46-7.45 (m, 1H), 7.27-7.19 (m, 8H), 7.08-7.05 (m, 4H), 4.31 (s, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 168.4, 165.0, 164.4, 161.9, 141.9, 136.1, 135.8, 131.0, 128.9, 128.7, 128.1, 123.0, 120.4, 115.2, 114.9, 50.9. Anal. Calcd for C₂₇H₂₃FN₂O₃S: C, 68.34; H, 4.89; N, 5.90; S, 6.76. Found: C, 68.93; H, 4.87; N, 5.77; S, 7.36.

N,N-dibenzyl-4-(2-oxopyrrolidin-1-yl)benzenesulfonamide

(4e). Following the general procedure using pyrrolidione (31 mg, 0.40 mmol) and *N,N*-dibenzyl-4-iodobenzenesulfonamide (278 mg, 0.60 mmol) provided 114 mg (68% yield) of the coupling product as a yellow oil after purification by flash chromatography (80:20 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.79 (m, 4H), 7.23 – 7.20 (m, 6H), 7.08 – 7.06 (m, 4H), 4.31 (s, 4H), 3.93 – 3.90 (m, 2H), 2.70 – 2.66 (m, 2H), 2.27 – 2.17 (m, 2H). ¹³C NMR (100MHz, CDCl₃) δ 175.1, 143.3, 135.9, 135.6, 128.9, 128.7, 128.4, 128.0, 119.4, 50.92, 48.7, 33.1, 18.08. Anal. Calcd for C₂₄H₂₄N₂O₃S: C, 68.55; H, 5.75; N, 6.66; S, 7.63. Found: C, 69.13; H, 5.73; N, 6.43; S, 8.10.

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Supplementary Material

Experimental procedures and compound characterization data are available.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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