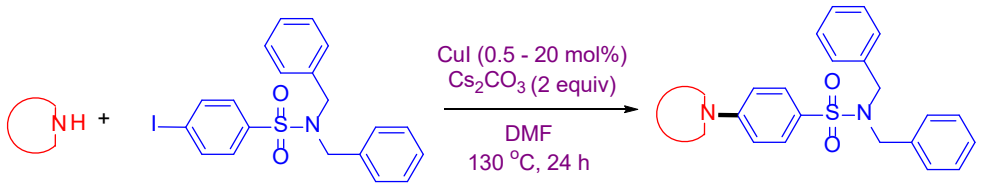
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

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

Leave this area blank for abstract info.

Fui-Fong Yong, Miskal Azri, Yong-En Darrell Lim and Yong-Chua Teo.



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.

Tetrahedron
journal homepage: www.elsevier.com

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

Fui-Fong Yong, Miskal Azri, Yong-En Darrell Lim and Yong-Chua Teo*

Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

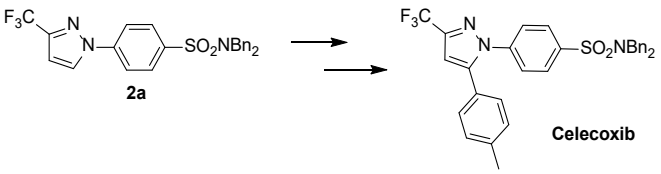
Keywords:
Cross coupling
Copper-catalyzed
Ligand-free
N-arylations
Celecoxib

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.

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 (CELEBREX™). 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 regioselective[6] 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 hydrozonoyl 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*-dimethylcylcohexylamine ligand at 115 °C for 50 h in a three linear step synthesis of Celecoxib.[9]

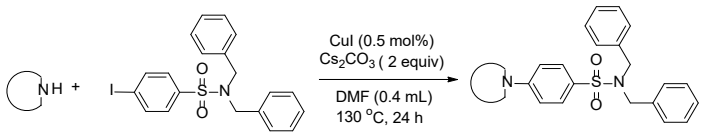


Cao and co-workers also reported a strategy for the N-arylation of 3-trifluoromethylpyrazole with aryl iodide using CuI in the presence of *N,N*-dimethylcylcohexylamine which can be applied to the synthesis of Celecoxib.[10] Our group has developed protocols for the cross-coupling reactions of nitrogen 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.

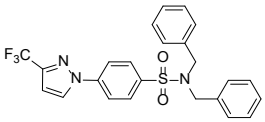
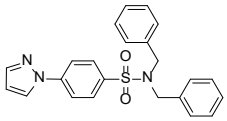
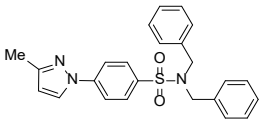
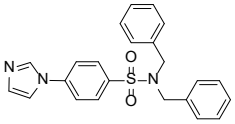
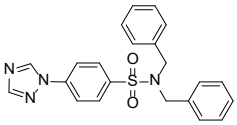
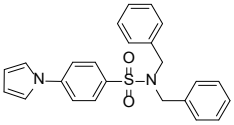
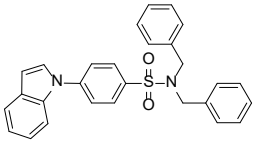
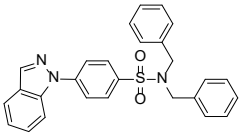
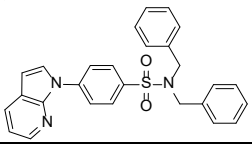
In our initial study, the C-N cross-coupling of commercially available 3-(trifluoromethyl)-1*H*-pyrazole and 4-iodobenzene-1-sulfonyl chloride was first carried out. Despite several efforts, the cross-coupling reaction afforded the desired product in poor yield. To facilitate the C-N cross-coupling, 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 was obtained in good yield without the need for column purification. Under ligand-free condition[11d], the cross-coupling of 3-(trifluoromethyl)-1*H*-pyrazole (1.0 equiv) with *N,N*-dibenzyl-4-iodobenzenesulfonamide (1.5 equiv), 0.5 mol% CuI as catalyst, Cs_2CO_3 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 yield of 99% (Table 1, entry 1). Encouraged by this result, 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-methyl-pyrazole, 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]



1 2a-i

Entry	ArX	Product		Yield %[b]
1			**2a**	99
2			**2b**	92
3			**2c**	55 80[c]
4			**2d**	81
5			**2e**	77
6			**2f**	70
7			**2g**	58 88[d]
8			**2h**	58 85[c]
9			**2i**	55[c] 75[d]

[a]Unless otherwise shown, the reaction was carried out with nitrogen heterocycles (0.80 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (1.20 mmol), Cs_2CO_3 (1.60 mmol), CuI (0.004 mmol) in DMF (0.4 ml) at 130 °C for 24 h. [

[b]Isolated yield after column chromatography..

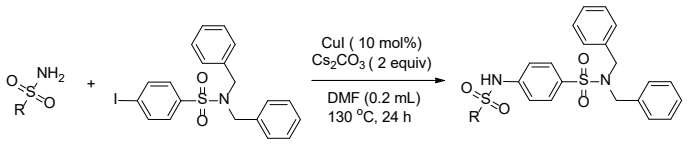
[c]The reaction was performed with CuI (0.008 mmol).

[d]The reaction was performed with CuI (0.016 mmol).

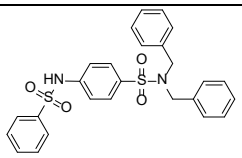
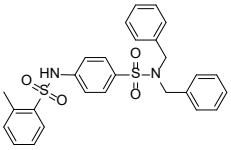
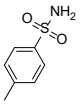
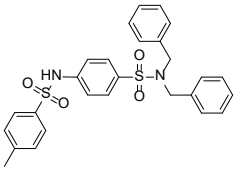
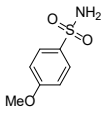
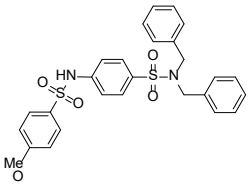
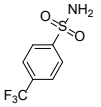
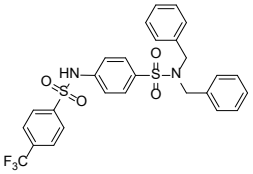
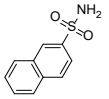
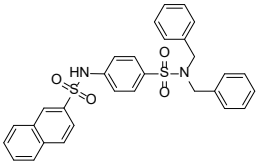
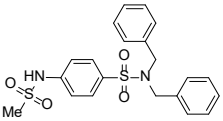
To further expand the scope of the ligand-free CuI-catalyzed amination, the reactions of a series of sulfonamides derivatives with *N,N*-dibenzyl-4-iodobenzenesulfonamide were then studied. In general, the desired amination products were obtained in moderate to good yields (Table 2). The neutral and electron-donating substituted sulfonamides afforded the corresponding

product in good to excellent yields (entries 1-4, 6-7). Steric effects and electronic effects on the reactions were limited as the reactions of *ortho*-substituted and electron-withdrawing substituted sulfonamides can achieve good yields with an increase of catalyst loading to 20 mol% (entries 2 and 5).

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



1 **3a-g**

Entry	ArX	Product		Yield %[b]
1			**3a**	61
2			**3b**	61[c]
3			**3c**	73
4			**3d**	77
5			**3e**	62[c]
6			**3f**	81
7			**3g**	58

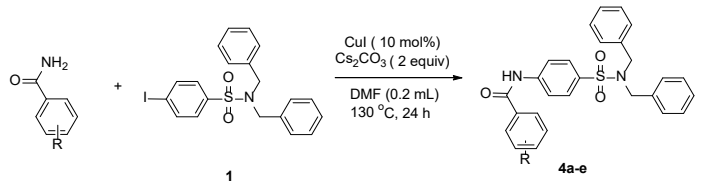
[a]Unless otherwise shown, the reaction was carried out with sulfonamides (0.40 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.60 mmol), Cs_2CO_3 (0.8 mmol), CuI (0.04 mmol) in DMF (0.2 ml) at 130 °C for 24 h.

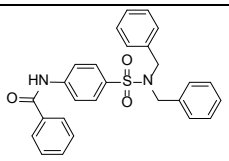
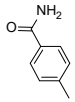
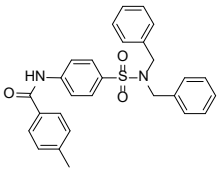
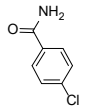
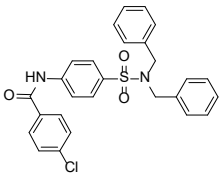
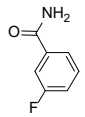
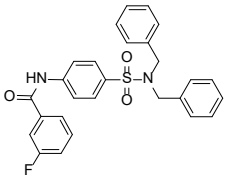
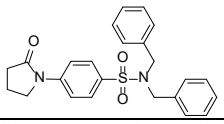
[b]Isolated yield after column chromatography.

[c]The 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 substitutes 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			**4a**	64
2			**4b**	62
3			**4c**	60
4			**4d**	65[c]
5			**4e**	68

[a]Unless otherwise shown, the reaction was carried out with sulfonamides (0.40 mmol), *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.60 mmol), Cs_2CO_3 (0.80 mmol), CuI (0.04 mmol) in DMF (0.2 ml) at 130 ºC for 24 h.

[b]Isolated yield after column chromatography.

[c]The 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 commerical 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 (^{1}H NMR) were recorded on a Bruker Avance DPX 400 spectrometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H 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 N_2 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 H_2O (10 mL) and aqueous HCl (1.0 M, 6.7 mL), dried over Na_2SO_4, filtered and solvent removed under reduced pressure to generate an off-white solid. Yield =

1520 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 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 $C_{20}H_{18}INO_2S$ [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 dimethylformami-de (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 ^{1}H, ^{13}C NMR spectroscopic analysis and elemental analysis or mass spectroscopy.

***N,N*-dibenzyl-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonami -de (2a).**[11] Following the general procedure using *N,N*-dibenzyl-4-iodobenzenesulfonamide (0.556g, 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). ^{1}H 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 $C_{24}H_{20}F_3N_3O_2S$: 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 $C_{24}H_{20}F_3N_3O_2S$ [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). ^{1}H 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 (100MHz, $CDCl^3$): 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 $C_{23}H_{21}N_3O_2S$: 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. ^{1}H 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 $C_{24}H_{23}N_3O_2S$: 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). ^{1}H 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 $C_{24}H_{23}N_3O_2S$: 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-(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). ^{1}H 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 $C_{23}H_{21}N_3O_2S$: 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). ^{1}H 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 $C_{22}H_{20}N_4O_2S$: 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). ^{1}H 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 $C_{24}H_{22}N_2O_2S$: 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). ^{1}H 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 $C_{28}H_{24}N_2O_2S$: 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). ^{1}H 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

for $C_{27}H_{23}N_3O_2S$: C, 71.5; H, 5.11; N, 9.26; S, 7.07. Found: C, 71.35; H, 5.22; N, 9.16; S, 7.09.

***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). ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{27}H_{23}N_3O_2S$: 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{24}N_2O_4S_2$ [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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{26}N_2O_4S_2$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{26}N_2O_4S_2$: 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).** Following the general procedure using 4-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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{26}N_2O_5S_2$: 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)benzenesulfon-amide (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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{27}H_{23}F_3N_2O_4S_2$ [M+]: 560.1051. Found: 559.9877.

***N*-(4-(N,N-dibenzylsulfamoyl)phenyl)naphthalene-2-sulfonamide (3f).** Following the general procedure using naphathalene (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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{30}H_{26}N_2O_4S_2$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 136.3, 135.4, 129.1, 128.6, 128.5, 127.8, 118.8, 50.6, 40.0. Anal. Calcd for $C_{21}H_{22}N_2O_4S_2$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{24}N_2O_3S$: 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-(*N,N*-dibenzylsulfamoyl)phenyl)-4-methylbenzamide (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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{28}H_{26}N_2O_3S$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{23}ClN_2O_3S$: 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 $C_{27}H_{23}ClN_2O_3S$ [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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{23}FN_2O_3S$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100MHz, $CDCl_3$) 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 $C_{24}H_{24}N_2O_3S$: 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.

Acknowledgments

The authors would like to thank the National Institute of Education and Nanyang Technological University (RI 5/17 TYC) for funding this work.

References and notes

1. For reviews, see: (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pergamon: Oxford, 1996; Vol. 5. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 5400. (c) Chegaev, K.; Lazzarato, L.; Tosco, P.; Cena, C.; Marini, E.; Rolando, B.; Carrupt, P. A.; Fruttero, R.; Gasco, A. *J. Med. Chem.* **2007**, *50*, 1449. (d) Wiglenda, T.; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475.
2. (a) Schoenthal, A. H.; Chen, T. C.; Hofman, F. M.; Louie, S. G.; Petasis, N. A. *Expert Opin. Investig. Drugs* **2008**, *17*, 197. (b) Battistone, M. J.; Sawitzke, A. D. *Clin. Med. Insights: Ther.* **2010**, *2*, 245.
3. (a) Szabó, G. ; Fischer, J. ; Kis-Varga, A.; Gyires, K. *J. Med. Chem.* **2008**, *51*, 142. (b) Ramalho, T. C.; Rocha, M.V. ; Cunha, da E.F.; Freitas, M.P. *Expert Opin. Ther. Pat.* **2009**, *19*, 1193. (c) Chakraborti, A.K.; Garg, S.K.; Kumar, R.; Motiwala, H.F. ; Jadhavar, P.S. *Curr. Med. Chem.* **2010**, *17*, 1563.
4. (a) Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Velazquez, C.; Das, D.; Suresh, M. R.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 9694. (b) Li, S. X.; Deng, X. D.; Jiang, F. L.; Zhao, Y. J.; Xiao, W. S.; Kuang, X. Z.; Sun, X. M. *Lett. Drug Design Discovery* **2008**, *5*, 127. (c) Anumula, R. R.; Gilla, G.; Alla, S.; Akki, T. R.; Bojja, Y. US20080234491 A1. *Chem. Abstr.* **2008**, *149*, 378735. (d) Ambati, V. R. R.; Garaga, S.; Mallela, S. P. S.; Meenakshisunderam, S. WO2010095024 A2. *Chem. Abstr*. **2010**, *153*, 334033.
5. Reddy, A. R.; Sampath, A.; Goverdhan, G.; Yakambaram, B.; Mukkanti, K.; Reddy, P. P. *Org. Process Res. Dev.* **2009**, *13*, 98.
6. Li, F.; Nie, J; Sun, L.; Zhenng, Y.; Ma, J,-A. *Angew. Chem. Int. Ed.* **2013**, *52*, 6255.
7. Reddy, R.; Ramana, V.; Bell, S. C. WO 2003024958 A2. *Chem. Abstr.* **2003**, *138*, 271677.
8. Oh, L. M. *Tetrahedron Lett.* **2006**, *47*, 7943.
9. Gaulier, S. M.; McKay, R.; Swain, N. A. *Tetrahedron Lett.* **2011**, *52*, 6000.
10. Wang, Y; Han, J.; Chen, J.; Cao, W. *Tetrahedron* **2015**, *71*, 8256.
11. (a) Yong, F.-F.; Teo, Y.-C. *Synlett* **2010**, *20*, 3068. (b) Yong, F.-F.; Teo, Y.-C.; Tay, S.-H.; Tan, B. Y.-H.; Lim, K.-H. *Tetrahedron Lett.* **2011**, *52*, 1161. (c) Yong, F.-F.; Teo, Y.-C.; Chua, G.-L.; Lim, G. S.; Lin, Y. *Tetrahedron Lett.* **2011**, *52*, 1169. (d) Teo, Y.-C.; Yong, F-F. *Synlett* **2011**, 837. (e) Teo, Y. C.; Yong, F. F.; Sim, S. *Tetrahedron* **2013**, *69*, 7279. (f) Tan, B. Y. H; Teo, Y. C; Seow, A. H. *Eur. J. Org. Chem*. **2014**, 1541. (g) Tan, B. Y. H., Teo, Y. C. *Tetrahedron* **2016**, *72*, 6646. (h) Tan, B. Y. H.; Teo. Y. C. *Synlett*, *29*, **2018**, 2056.
12. Tercel, M.; Atwell, G. J.; Yang, S.; Stevenson, R. J.; Botting, K. J.; Boyd, M.; Smith, E.; Anderson, R. F.; Denny, W. A.; Wilson, W. R.; Pruijn, F. B. *J. Med. Chem.* **2009**, *52*, 7258.

Supplementary Material

Experimental procedures and compound characterization data are available.