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One-Pot Synthesis of Diaryl Sulfonamides using an Iron- and Copper-Catalyzed Aryl C–H Amidation Process

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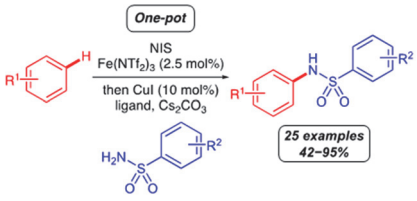

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Abstract A one-pot, two-stage synthesis of diaryl sulfonamides using sequential iron and copper catalysis is developed. Regioselective *para*-iodination of activated arenes by the super Lewis acid, iron triflimide and *N*-iodosuccinimide (NIS), is followed by a copper(I)-catalyzed *N*-arylation reaction. The process is found to be applicable for the coupling of a range of anisoles, anilines and acetanilides with primary sulfonamides and is used for the one-pot synthesis of biologically important compounds.

Key words sulfonamides, iron catalysis, copper catalysis, aryl substitution

Since the introduction of prontosil as an antibacterial agent in the early 20th century, sulfonamides have become an important motif for medicinal chemistry.[1,2] Within this compound class, diaryl sulfonamides have been exploited as therapeutic agents against a variety of diseases. Examples include GSK137647A (**1**), a selective agonist of the free fatty acid receptor 4 (FFA4/GPR120),[3] and diaryl sulfonamides such as **2** and **3**, which are cytotoxic and inhibit the growth of human cancer cell lines (Figure 1a).[4,5] Quinazolinone-derived sulfonamides **4** have been developed as small-molecule probes for the bromo and extra C-terminal domain (BET) family of bromodomains, which are protein modules implicated in a range of diseases.[6]

Due to the significant interest in diaryl sulfonamides, numerous methods have been developed for the synthesis of this class of compounds.[7,8] One of the main approaches involves the coupling of arylsulfonyl chlorides with anilines, under basic conditions. While this is highly effective, it requires the synthesis and handling of genotoxic sulfonyl chlorides.[9] To avoid the use of sulfonyl chlorides, recent methods have focused on the coupling of primary sulfonamides with suitably activated arenes. For example, diaryl sulfonamides have been prepared by the Pd(0)-catalyzed coupling of aryl halides (Figure 1b) or aryl nonaflates with primary sulfonamides.[9,10] Copper-catalyzed methods have also been developed using either aryl halides or boronic acids as the coupling partner.[11] To avoid prefunctionalized arenes, methods involving directed, chelation-controlled, transition-metal-catalyzed amidation have also been reported (Figure 1c).[12] Directing groups such as ketones, ketoximes, pyridines and oxazolines have been used in combi-

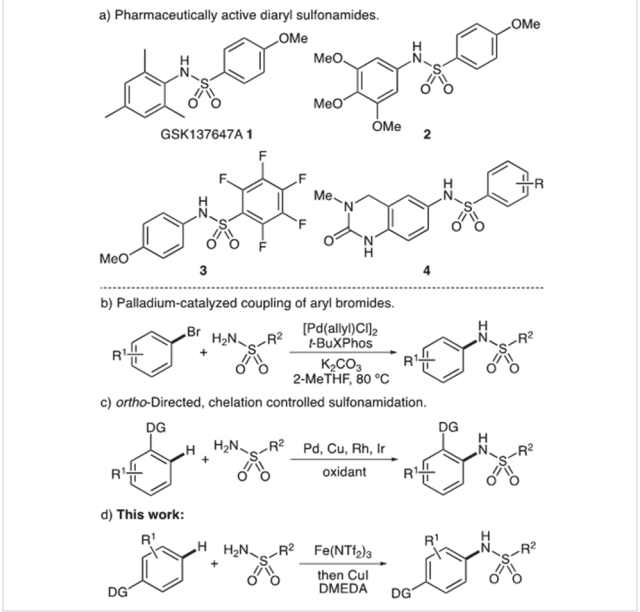


Figure 1 (a) Medicinally important diaryl sulfonamides. (b) Palladium-catalyzed coupling. (c) Directed, chelation-controlled, transition-metal-catalyzed amidation. (d) This work: Iron- and copper(I)-catalyzed amidation.

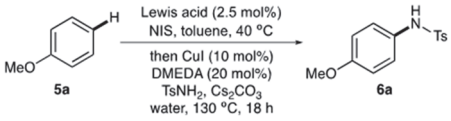
nation with various transition-metal catalysts and oxidants for regioselective *ortho*-amidation with primary sulfonamides.

In 2015, we reported a new approach for the regioselective iodination of arenes,[13] involving the activation of *N*-iodosuccinimide using the super Lewis acid, iron triflimide.[14] As well as extending this process for other halogenation reactions,[15] we demonstrated that the iron-catalyzed arene halogenation reaction could be coupled with a copper-catalyzed arylation process for the one-pot conversion of aryl C–H bonds into C–N and C–O bonds.[16] Although effective methods have been developed for the synthesis of diaryl sulfonamides, we proposed that a one-pot, iron-catalyzed, *para*-directed iodination reaction, followed by a copper(I)-catalyzed *N*-arylation reaction with sulfonamides would allow facile access to these compounds (Figure 1d). The use of this strategy would avoid prefunctionalized arenes and the use of precious transition-metal catalysts and strong oxidants. Furthermore, this one-pot process would be complementary to *ortho*-directed, chelation-controlled methods. We now report a one-pot, two-step synthesis of diaryl sulfonamides using iron(III)- and copper(I)-catalysis. As well as examining the scope of this *para*-directed method, we also describe the application of this process for the preparation of medicinally important targets.

The study began by investigating the one-pot coupling of anisole (**5a**) with *p*-toluenesulfonamide (Table 1). While the use of copper(I) iodide and DMEDA for the second-step Ullmann–Goldberg-type coupling was deemed optimal,[17] a screen of Lewis acids was conducted to determine the most effective activator of NIS during the first step. It was also important to identify a Lewis acid that was compatible with the second step. The first experiments assessed the standard electrophilic aromatic substitution catalysts $AlCl_3$ and $FeCl_3$ (entries 1 and 2). Once the iodination steps were deemed complete, the Cu(I)-catalyzed coupling was performed, which gave **6a** in 59% and 69% yields, respectively. While the overall two-step process was successful, the reaction times for the iodination reactions were deemed excessive for an activated arene. Therefore, other Lewis acid catalysts were considered. Next, the super Lewis acid, iron(III) triflimide, generated in situ from $FeCl_3$ and the commercially available ionic liquid [BMIM]NTf_2 was investigated (entry 3). In this case, the iodination step was complete after 4 hours and gave **6a** in 86% yield. Silver(I) triflimide,[18] a softer and more selective Lewis acid, also allowed a fast iodination step but gave a lower overall yield of 69% (entry 4). Finally, indium(III) triflate was investigated but resulted in no iodination product after a reaction time of 24 hours (entry 5).

Having developed an optimized one-pot synthesis of diaryl sulfonamide **6a**, the scope of the process was explored using anisole (**5a**) and a range of primary sulfonamide nucleophiles (Scheme 1). The one-pot *p*-iodination and *N*-arylation process was found to be general for a wide range of

Table 1 Optimization Studies on the Coupling of Anisole (**5a**) with *p*-Toluenesulfonamide

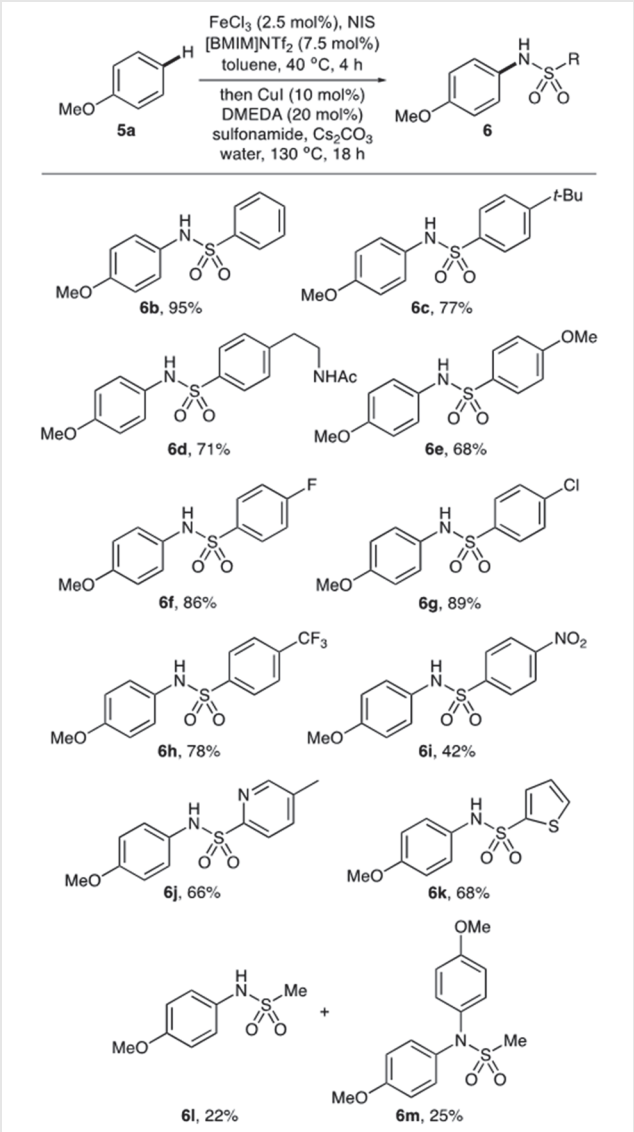


Entry	Lewis acid catalyst	Time (h)	Yield (%)[a]
1	$AlCl_3$	28	59
2	$FeCl_3$	22	69
3[b]	$FeCl_3$ + [BMIM]NTf_2	4	86
4	$AgNTf_2$	4	69
5	$In(OTf)_3$	24	0

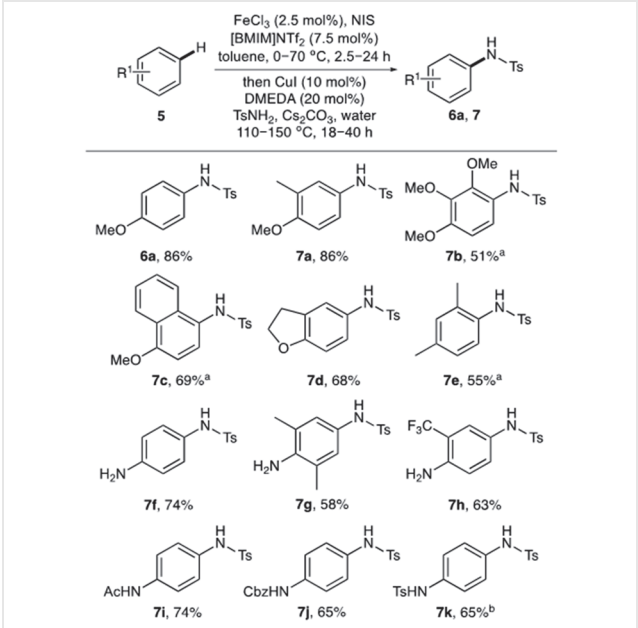
[a] Overall yield of isolated product **6a**.
[b] [BMIM]NTf_2 (7.5 mol%) was used.

aryl sulfonamides bearing either electron-rich or electron-deficient arene side chains, providing the coupled products **6a–i** in moderate to excellent yields (42–95%). Primary sulfonamides with heterocyclic side chains, such as 5-methylpyridine and thiophene, were also successfully coupled and gave diaryl sulfonamides **6j** and **6k** in 66% and 68% yields, respectively. The only limitation of the process was found using alkyl sulfonamides. Under the optimized conditions, selective mono-*N*-arylation was challenging to control. Although coupling with methanesulfonamide did generate coupled product **6l**, biaryl by-product **6m** was also isolated, likely formed via a second *N*-arylation reaction of **6l** with *p*-iodoanisole.

The scope of the arene was then investigated using *p*-toluenesulfonamide as a coupling partner (Scheme 2). Various analogues of anisole were converted into the coupled products **6a** and **7a–d**, as single regioisomers[19] in moderate to high yields. Arenes with *ortho*-substituents adjacent to the position of amidation (**5b** and **5c**) were found to couple with *p*-toluenesulfonamide more effectively using racemic *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as the ligand, instead of DMEDA. This more rigid cyclohexane-bidentate ligand is known to facilitate more demanding copper-catalyzed *N*-coupling reactions.[20] The one-pot amidation process was also successful with less activated arenes, such as *m*-xylene (**5e**).[21] While the iodination and coupling steps required higher temperatures (70 and 150 °C, respectively), this gave **7e** in 55% yield. Unprotected anilines **5f–h** were also coupled with *p*-toluenesulfonamide, which included the preparation of **7h**, a selective, potent agonist of the free fatty acid receptor 4 (FFA4).[22] It should be noted that despite the nucleophilic nature of these anilines, only *N*-substitution with *p*-toluenesulfonamide was observed. Acetyl-, Cbz- and tosyl-protected anilines **5i–k** were also found to be good substrates for this one-pot process. The only class of activated arene that was found to be problematic were



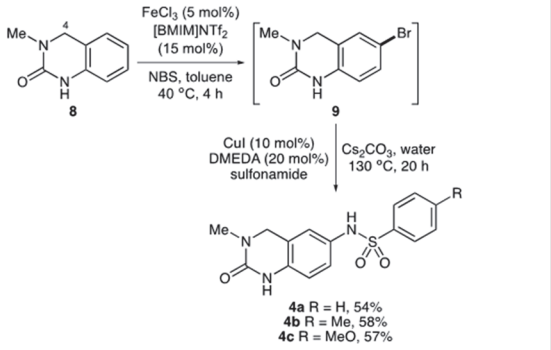
Scheme 1 Scope of the one-pot amidation process with anisole (**5a**)



Scheme 2 Scope of the one-pot process using various arenes. [a] The amidation step was performed using *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (20 mol%). [b] The iodination step was performed using $FeCl_3$ (5 mol%) and [BMIM]NTf_2 (15 mol%).

phenols. Iodination of phenol using $Fe(NTf_2)_3$ and NIS proceeded at room temperature and was complete after 2 hours. However, Ullmann-type coupling with *p*-toluenesulfonamide returned only phenol via a copper-mediated dehalogenation process. Buchwald and co-workers have reported phenols as problematic substrates during copper-catalyzed *N*-aryl coupling reactions, postulating the formation of a phenolate species under basic conditions, which coordinates to the copper and results in inactivation.[23]

Following the investigation of the scope and limitations of the one-pot diaryl sulfonamide synthesis, the project next investigated the synthetic utility of this method for rapid access to medicinally relevant compounds. Inhibitors of the BET family of bromodomains were chosen as targets as the C–H amidation of quinazolinones would represent another substrate class for the one-pot process (Scheme 3).[6] In addition, we were interested to discover whether the one-pot amidation process would allow more rapid access to these bromodomain inhibitors. The previously reported syntheses of these compounds involved separate bromination and metal-catalyzed cross-coupling reactions of 3-methyl-3,4-dihydroquinazolin-2(1*H*)-one (**8**), or a multistep route, which consisted of electrophilic aromatic nitration of **8**, nitro group reduction and coupling with arylsulfonyl chlorides.[6] Iodination of quinazolinone **8** was initially investigated with iron(III) triflimide (2.5 mol%) under standard conditions. However, the reaction was found to be unselective, with competing iodination at the C-4 position. Instead, halogenation was attempted using less reactive NBS, and while this gave selective bromination of the aromatic ring, using 2.5 mol% of iron(III) triflimide required a reaction time of 24 hours. Therefore, the catalyst loading was increased to 5 mol%, resulting in a significantly improved reaction time of 4 hours. Subsequent Ullmann–Goldberg coupling of various aryl sulfonamides using copper(I) iodide and DMEDA completed the one-pot synthesis of bromodomain inhibitors **4a–c** in 54–58% yields. The application of this method allowed the synthesis of these compounds using a one-pot method, while avoiding the use of genotoxic sulfonyl chlorides.



Scheme 3 One-pot synthesis of a BET family of bromodomain inhibitors

In conclusion, a one-pot method for the *para*-selective C–H amination of activated arenes using Earth-abundant transition-metal catalysis has been developed for the synthesis of diaryl sulfonamides. Activation of *N*-halosuccinimides with the super Lewis acid iron(III) triflimide for the regioselective halogenation of activated arenes, followed by a copper(I)-catalyzed Ullmann-Goldberg reaction with primary sulfonamides allowed facile access to a wide range of products. This method is complementary to *ortho*-directed, chelation-controlled, transition-metal-catalyzed amidation methods and provides rapid access to valuable synthetic intermediates and targets for medicinal chemistry. Work is currently underway to discover new applications employing metal-triflimide-catalyzed arene functionalization.

All reagents and starting materials were obtained from commercial sources and used as received. All reactions were performed under an atmosphere of air unless otherwise stated. All reactions requiring anhydrous conditions were performed using oven-dried glassware. All dry solvents were purified using a PureSolv 500 MD solvent purification system or obtained from commercial sources and used as received. Flash column chromatography was carried out using Fisher matrix silica 60 and Macherey-Nagel aluminum-backed plates precoated with silica gel 60 (UV_{254}) were used for thin-layer chromatography. ^{1}H NMR spectra were recorded on an NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the undeuterated solvent as the internal standard ($CHCl_3$, 7.26 ppm; MeOD, 3.31 ppm; DMSO, 2.50 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlapping non-equivalent resonances, integration). ^{13}C NMR spectra were recorded on an NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as the internal standard ($CDCl_3$, 77.16 ppm; CD_3OD, 49.00 ppm; DMSO-d_6, 39.52 ppm), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Assignment of ^{1}H and ^{13}C NMR signals are based on 2-dimensional COSY, HSQC and HMBC experiments. Infrared spectra were recorded using a Shimadzu IR Prestige-21 spectrometer or a Shimadzu 8400S spectrometer. Mass spectra were obtained using a JEOL JMS-700 spectrometer for EI, and Bruker Microtof-q or Agilent 6125B instruments for ESI. Melting points were determined on a Reichert platform melting point apparatus.

One-Pot Amidation; General Procedure

Iron(III) chloride (0.00203 g, 0.0125 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.0110 mL, 0.0375 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.113 g, 0.500 mmol) in toluene (0.5 mL). The arene (0.500 mmol) was added and the mixture was heated to 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and the primary sulfonamide (0.750 mmol), copper(I) iodide (0.00952 g, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (0.0108 mL, 0.100 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography.

N-(4-Methoxyphenyl)-4′-methylbenzenesulfonamide (6a)[24]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (20% ethyl acetate in petroleum ether) gave the title compound.

Yield: 0.119 g (86%); light yellow solid; mp 112–114 °C (Lit.[24] 113–114 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, 4′-CH_3), 3.75 (s, 3 H, OCH_3), 6.62 (br s, 1 H, NH), 6.72–6.79 (m, 2 H, 3-H and 5-H), 6.95–7.01 (m, 2 H, 2-H and 6-H), 7.21 (d, *J* = 8.0 Hz, 2 H, 3′-H and 5′-H), 7.59 (d, *J* = 8.0 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5 (CH_3), 55.4 (CH_3), 114.4 (2 × CH), 125.2 (2 × CH), 127.4 (2 × CH), 129.1 (C), 129.6 (2 × CH), 136.0 (C), 143.7 (C), 157.8 (C).

MS (EI): *m*/*z* = 277 (M^+) (35), 228 (11), 122 (100), 92 (12), 65 (8).

N-(4-Methoxyphenyl)benzenesulfonamide (6b)[25]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and benzenesulfonamide (0.118 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (10% ethyl acetate in petroleum ether) gave the title compound.

Yield: 0.125 g (95%); brown solid; mp 90–92 °C; spectroscopic data was consistent with the literature.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OCH_3), 6.71–6.78 (m, 3 H, 3-H, 5-H and NH), 6.95–7.01 (m, 2 H, 2-H and 6-H), 7.39–7.45 (m, 2 H, 3′-H and 5′-H), 7.53 (tt, *J* = 7.6, 1.2 Hz, 1 H, 4′-H), 7.70–7.74 (m, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.4 (CH_3), 114.5 (2 × CH), 125.3 (2 × CH), 127.3 (2 × CH), 129.0 (2 × CH and C), 132.9 (CH), 138.9 (C), 157.9 (C).

MS (ESI): *m*/*z* = 286 $[M + Na]^+$ (100).

4′-*tert*-Butyl-*N*-(4-methoxyphenyl)benzenesulfonamide (6c)

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-*tert*-butylbenzenesulfon-

amide (0.160 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40% diethyl ether in hexane) gave the title compound.

Yield: 0.123 g (77%); white solid; mp 126–129 °C.

IR (neat): 3248, 2962, 1508, 1400, 1327, 1157, 1130, 1065, 717 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9 H, $C(CH_3)_3$), 3.76 (s, 3 H, OCH_3), 6.61 (br s, 1 H, NH), 6.76 (d, *J* = 8.7 Hz, 2 H, 3-H and 5-H), 6.99 (d, *J* = 8.7 Hz, 2 H, 2-H and 6-H), 7.40–7.46 (m, 2 H, 3′-H and 5′-H), 7.63 (d, *J* = 8.8 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 31.2 (3 × CH_3), 35.3 (C), 55.6 (CH_3), 114.6 (2 × CH), 125.5 (2 × CH), 126.1 (2 × CH), 127.3 (2 × CH), 129.1 (C), 136.3 (C), 156.8 (C), 158.1 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}NO_3S$: 320.1315; found: 320.1310.

N-{2′-[4′-(4-Methoxyphenyl)sulfamoyl]phenylethyl}acetamide (6d)

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and *N*-[2′-(4-sulfamoylphenyl)ethyl]acetamide (0.182 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (1.5–4% methanol in dichloromethane) gave the title compound.

Yield: 0.124 g (71%); white solid; mp 129–131 °C.

IR (neat): 3379, 2974, 1643, 1543, 1504, 1153, 1092, 1030, 837 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.87 (s, 3 H, $COCH_3$), 2.83 (t, *J* = 7.2 Hz, 2 H, 2″-H_2), 3.39 (t, *J* = 7.2 Hz, 2 H, 1″-H_2), 3.71 (s, 3 H, OCH_3), 6.75 (d, *J* = 9.0 Hz, 2 H, 3-H and 5-H), 6.96 (d, *J* = 9.0 Hz, 2 H, 2-H and 6-H), 7.31 (d, *J* = 8.3 Hz, 2 H, 3′-H and 5′-H), 7.60 (d, *J* = 8.3 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, CD_3OD): δ = 21.1 (CH_3), 34.8 (CH_2), 40.0 (CH_2), 54.4 (CH_3), 113.9 (2 × CH), 124.3 (2 × CH), 127.1 (2 × CH), 129.0 (2 × CH), 129.9 (C), 137.5 (C), 144.6 (C), 157.6 (C), 171.9 (C).

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{17}H_{19}N_2O_4S$: 347.1071; found: 347.1071.

4′-Methoxy-*N*-(4-methoxyphenyl)benzenesulfonamide (6e)[26]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-methoxybenzenesulfonamide (0.140 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (10–25% ethyl acetate in hexane) gave the title compound.

Yield: 0.100 g (68%); white solid; mp 90–92 °C (Lit.[26] 93 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.63 (br s, 1 H, NH), 6.73–6.78 (m, 2 H, 3-H and 5-H), 6.85–6.90 (m, 2 H, 3′-H and 5′-H), 6.95–7.00 (m, 2 H, 2-H and 6-H), 7.61–7.67 (m, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.5 (CH_3), 55.7 (CH_3), 114.2 (2 × CH), 114.5 (2 × CH), 125.6 (2 × CH), 129.1 (C), 129.6 (2 × CH), 130.7 (C), 158.1 (C), 163.1 (C).

MS (ESI): *m*/*z* = 316 $[M + Na]^+$ (100).

4′-Fluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (6f)

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-fluorobenzenesulfonamide (0.131 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (20% ethyl acetate in petroleum ether) gave the title compound.

Yield: 0.120 g (86%); white solid; mp 102–104 °C.

IR (neat): 3262, 2937, 1592, 1508, 1495, 1247, 1241, 1165, 1153, 1090, 837, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.83–6.89 (m, 2 H, 3-H and 5-H), 7.06–7.12 (m, 3 H, 2-H, 6-H and NH), 7.15–7.22 (m, 2 H, 3′-H and 5′-H), 7.79–7.86 (m, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.4 (CH_3), 114.5 (2 × CH), 116.2 (d, $^2J_{CF}$ = 22.6 Hz, 2 × CH), 125.6 (2 × CH), 128.5 (C), 130.1 (d, $^3J_{CF}$ = 9.4 Hz, 2 × CH), 134.9 (d, $^4J_{CF}$ = 3.2 Hz, C), 158.1 (C), 165.2 (d, $^1J_{CF}$ = 255.1 Hz, C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{12}FNNaO_3S$: 304.0414; found: 304.0405.

4′-Chloro-*N*-(4-methoxyphenyl)benzenesulfonamide (6g)[27]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-chlorobenzenesulfonamide (0.144 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (5% ethyl acetate in petroleum ether) gave the title compound.

Yield: 0.133 g (89%); white solid; mp 138–140 °C (Lit.[27] 140–144 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 6.47 (br s, 1 H, NH), 6.74–6.81 (m, 2 H, 3-H and 5-H), 6.94–7.01 (m, 2 H, 2-H and 6-H), 7.37–7.42 (m, 2 H, 3′-H and 5′-H), 7.59–7.64 (m, 2 H, 2′-H and 6′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 55.4 (CH_3), 114.6 (2 × CH), 125.7 (2 × CH), 128.3 (C), 128.8 (2 × CH), 129.3 (2 × CH), 137.4 (C), 139.4 (C), 158.3 (C).

MS (EI): *m*/*z* = 297 (M^+) (73), 122 (100), 111 (23), 95 (34), 83 (27), 75 (17), 65 (7), 52 (13).

N-(4-Methoxyphenyl)-4′-(trifluoromethyl)benzenesulfonamide (6h)[28]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-(trifluoromethyl)benzenesulfonamide (0.169 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (30–40% diethyl ether in hexane) gave the title compound.

Yield: 0.130 g (78%); white solid; mp 137–140 °C (Lit.[28] 141–143 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OMe), 6.89 (br s, 1 H, NH), 6.75–6.82 (m, 2 H, 3-H and 5-H), 6.96–7.02 (m, 2 H, 2-H and 6-H), 7.70 (d, *J* = 8.3 Hz, 2 H, 3′-H and 5′-H), 7.83 (d, *J* = 8.3 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.6 (CH_3), 114.8 (2 × CH), 123.4 (q, $^1J_{CF}$ = 272.8 Hz, C), 126.0 (2 × CH), 126.3 (q, $^3J_{CF}$ = 3.7 Hz, 2 × CH), 128.0 (2 × CH), 128.0 (C), 134.7 (q, $^2J_{CF}$ = 33.0 Hz, C), 142.6 (C), 158.6 (C).

MS (ESI): *m*/*z* = 330 $[M - H]^-$ (100).

***N*-(4-Methoxyphenyl)-4′-nitrobenzenesulfonamide (6i)**[29]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 4-nitrobenzenesulfonamide (0.152 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (20–40% ethyl acetate in hexane) gave the title compound.

Yield: 0.0659 g (42%); pale-yellow solid; mp 174–176 °C (Lit.[29] 173–175 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OMe), 6.41 (br s, 1 H, NH), 6.80 (d, *J* = 9.0 Hz, 2 H, 3-H and 5-H), 6.97 (d, *J* = 9.0 Hz, 2 H, 2-H and 6-H), 7.86 (d, *J* = 9.0 Hz, 2 H, 2′-H and 6′-H), 8.28 (d, *J* = 9.0 Hz, 2 H, 3′-H and 5′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.6 (CH_3), 114.9 (2 × CH), 124.3 (2 × CH), 126.4 (2 × CH), 127.6 (C), 128.7 (2 × CH), 144.9 (C), 150.4 (C), 158.9 (C).

MS (ESI): *m*/*z* 309 $[M + H]^+$ (100).

***N*-(4-Methoxyphenyl)-5′-methyl-2′-pyridinesulfonamide (6j)**

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 5-methyl-2-pyridinesulfonamide (0.129 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40% ethyl acetate in hexane) gave the title compound.

Yield: 0.0917 g (66%); white solid; mp 186–189 °C.

IR (neat): 3256, 2924, 1508, 1339, 1250, 1169, 1107, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, 5′-CH_3), 3.71 (s, 3 H, OCH_3), 6.68–6.74 (m, 2 H, 3-H and 5-H), 7.13–7.18 (m, 2 H, 2-H and 6-H), 7.56 (dd, *J* = 8.0, 1.3 Hz, 1 H, 4′-H), 7.70 (d, *J* = 8.0 Hz, 1 H, 3′-H), 8.51–8.59 (m, 2 H, NH and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.7 (CH_3), 55.5 (CH_3), 114.4 (2 × CH), 123.1 (CH), 126.0 (2 × CH), 128.8 (C), 137.6 (C), 138.2 (CH) 150.6 (CH), 153.6 (C), 158.0 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{14}N_2NaO_3S$: 301.0617; found: 301.0620.

***N*-(4-Methoxyphenyl)-2′-thiophenesulfonamide (6k)**[30]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and 2-thiophenesulfonamide (0.122 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (10–25% ethyl acetate in hexane) gave the title compound.

Yield: 0.849 g (68%); white solid; mp 100–103 °C (Lit.[30] 104 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = (s, 3 H, OCH_3), 6.59 (br s, 1 H, NH), 6.77–6.83 (m, 2 H, 3-H and 5-H), 7.00 (dd, *J* = 5.0, 3.8 Hz, 1 H, 4′-H), 7.01–7.07 (m, 2 H, 2-H and 6-H), 7.42 (dd, *J* = 3.8, 1.3 Hz, 1 H, 5′-H), 7.53 (dd, *J* = 5.0, 1.3 Hz, 1 H, 3′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.6 (CH_3), 114.6 (2 × CH), 125.8 (2 × CH), 127.4 (CH), 128.6 (C), 132.4 (CH), 133.0 (CH), 139.4 (C), 158.4 (C).

MS (ESI): *m*/*z* = 270 $[M + H]^+$ (100).

***N*-(4-Methoxyphenyl)methanesulfonamide (6l)**[31]

The reaction was performed according to the general procedure using anisole (**5a**) (0.0543 mL, 0.500 mmol) and methanesulfonamide (0.0713 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (100% dichloromethane) gave the title compound.

Yield: 0.0224 g (22%); yellow solid; mp 109–112 °C (Lit.[31] 115 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (s, 3 H, SO_2CH_3), 3.80 (s, 3 H, OCH_3), 6.37 (br s, 1 H, NH), 6.86–6.93 (m, 2 H, 3-H and 5-H), 7.17–7.23 (m, 2 H, 2-H and 6-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 39.0 (CH_3), 55.6 (CH_3), 114.9 (2 × CH), 124.9 (2 × CH), 129.0 (C), 158.2 (C).

MS (ESI): *m*/*z* = 202 $[M + H]^+$ (100).

***N*-(3-Methyl-4-methoxyphenyl)-4′-methylbenzenesulfonamide (7a)**

The reaction was performed according to the general procedure using 2-methylanisole (0.122 mL, 1.00 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (25–50% diethyl ether in hexane) gave the title compound.

Yield: 0.250 g (86%); yellow solid; mp 77–79 °C.

IR (neat): 3256, 2951, 1598, 1501, 1224, 1154, 1091, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, 3-CH_3), 2.38 (s, 3 H, 4′-CH_3), 3.76 (s, 3 H, OCH_3), 6.38–6.62 (m, 1 H, NH), 6.65 (d, *J* = 9.4 Hz, 1 H, 5-H), 6.81–6.86 (m, 2 H, 2-H and 6-H), 7.21 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.61 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (CH_3), 21.7 (CH_3), 55.6 (CH_3), 110.3 (CH), 122.4 (CH), 126.7 (CH), 127.5 (2 × CH), 127.7 (C), 128.5 (C), 129.6 (2 × CH), 136.3 (C), 143.7 (C), 156.3 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NNaO_3S$: 314.0821; found 314.0817.

***N*-(2,3,4-Trimethoxyphenyl)-4′-methylbenzenesulfonamide (7b)**

The reaction was performed according to the general procedure using 1,2,3-trimethoxybenzene (0.0841 g, 0.500 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 2.5 h and the *N*-arylation step at 150 °C for 18 h, however, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (0.0158 mL, 0.100 mmol) was used. Purification by flash column chromatography (25% ethyl acetate in hexane) gave the title compound.

Yield: 0.0856 g (51%); white solid; mp 95–97 °C.

IR (neat): 3264, 2943, 1597, 1481, 1335, 1265, 1165, 1096 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, 4′-CH_3), 3.46 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.59 (d, *J* = 9.1 Hz, 1 H, 5-H), 6.78 (br s, 1 H, NH), 7.19 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.27 (d, *J* = 9.1 Hz, 1 H, 6-H), 7.59 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 56.2 (CH_3), 60.8 (CH_3), 61.0 (CH_3), 107.0 (CH), 116.9 (CH), 123.4 (C), 127.4 (2 × CH), 129.6 (2 × CH), 136.3 (C), 141.7 (C), 143.8 (C), 144.8 (C), 151.3 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{19}NNaO_5S$: 360.0876; found 360.0863.

***N*-(4-Methoxynaphthalen-1-yl)-4′-methylbenzenesulfonamide (7c)**

The reaction was performed according to the general procedure using 1-methoxynaphthalene (0.0726 mL, 0.500 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 50 °C for 5 h and the *N*-arylation step at 130 °C for 22 h, however,

trans-*N*,*N*′-dimethylcyclohexane-1,2-diamine (0.0158 mL, 0.100 mmol) was used. Purification by flash column chromatography (10–20% ethyl acetate in hexane) gave the title compound.

Yield: 0.113 g (69%); yellow solid; mp 143–144 °C.

IR (neat): 3261, 2936, 1596, 1465, 1304, 1272, 1185, 1091, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, 4′-CH_3), 3.98 (s, 3 H, OCH_3), 6.46 (br s, 1 H, NH), 6.68 (d, *J* = 8.2 Hz, 1 H, 3-H), 7.15 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.20 (d, *J* = 8.2 Hz, 1 H, 2-H), 7.38–7.46 (m, 2 H, 6-H and 7-H), 7.58 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H), 7.74 (d, *J* = 7.6 Hz, 1 H, 5-H), 8.22 (d, *J* = 7.6 Hz, 1 H, 8-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 55.8 (CH_3), 103.2 (CH), 122.0 (CH), 122.5 (CH), 123.9 (C), 125.7 (CH), 125.7 (CH), 126.1 (C), 127.2 (CH), 127.6 (2 × CH), 129.6 (2 × CH), 131.2 (C), 136.7 (C), 143.7 (C), 155.2 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_3S$: 350.0821; found 350.0817.

N-(2,3-Dihydrobenzofuran-5-yl)-4′-methylbenzenesulfonamide (7d)

The reaction was performed according to the general procedure using 2,3-dihydrobenzofuran (0.113 mL, 1.00 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (40% diethyl ether in hexane) gave the title compound.

Yield: 0.198 g (68%); yellow solid; mp 122–125 °C.

IR (neat): 3252, 2896, 1488, 1327, 1155, 1090, 905, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, 4′-CH_3), 3.13 (t, *J* = 8.7 Hz, 2 H, 3-H_2), 4.53 (t, *J* = 8.7 Hz, 2 H, 2-H_2), 6.57 (d, *J* = 8.4 Hz, 1 H, 7-H), 6.67 (dd, *J* = 8.4, 1.4 Hz, 1 H, 6-H), 6.81 (br s, 1 H, NH), 7.01 (br s, 1 H, 4-H), 7.21 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.60 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 29.8 (CH_2), 71.7 (CH_2), 109.4 (CH), 121.9 (CH), 124.3 (CH), 127.5 (2 × CH), 128.2 (C), 128.8 (C), 129.6 (2 × CH), 136.1 (C), 143.7 (C), 158.7 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NNaO_3S$: 312.0665; found 312.0666.

N-(2,4-Dimethylphenyl)-4′-methylbenzenesulfonamide (7e)[32]

The reaction was performed according to the general procedure using *m*-xylene (0.0612 mL, 0.500 mmol), *N*-iodosuccinimide (0.169 g, 0.750 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 70 °C for 24 h and the *N*-arylation step at 150 °C for 26 h, however, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (0.0158 mL, 0.100 mmol) was used. Purification by flash column chromatography (25–30% diethyl ether in hexane) gave the title compound.

Yield: 0.0760 g (55%); white solid; mp 89–91 (Lit.[32] 93–94 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, 2-CH_3), 2.26 (s, 3 H, 4-CH_3), 2.39 (s, 3 H, 4′-CH_3), 6.22 (br s, 1 H, NH), 6.90 (br s, 1 H, 3-H), 6.93 (br d, *J* = 8.1 Hz, 1 H, 5-H), 7.14 (d, *J* = 8.1 Hz, 1 H, 6-H), 7.21 (d, *J* = 8.2 Hz, 1 H, 3′-H and 5′-H), 7.59 (d, *J* = 8.2 Hz, 1 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.7 (CH_3), 21.0 (CH_3), 21.7 (CH_3), 125.2 (CH), 127.3 (2 × CH), 127.7 (CH), 129.7 (2 × CH), 131.6 (CH), 131.8 (C), 132.1 (C), 136.4 (C), 136.9 (C), 143.8 (C).

MS (ESI): *m*/*z* = 276 [M + H]$^+$ (100).

N-(4-Aminophenyl)-4′-methylbenzenesulfonamide (7f)[33]

The reaction was performed according to the general procedure using aniline (0.0456 mL, 0.500 mmol), *N*-iodosuccinimide (0.124 g, 0.550 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 0 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (35–40% ethyl acetate in hexane) gave the title compound.

Yield: 0.0969 g (74%); white solid; mp 182–184 °C (Lit.[33] 185–186 °C).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 3 H, 4′-CH_3), 4.93 (br s, 2 H, NH_2), 6.35–6.40 (m, 2 H, 3-H and 5-H), 6.64–6.69 (m, 2 H, 2-H and 6-H), 7.30 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H), 7.51 (d, *J* = 8.4 Hz, 2 H, 2′-H and 6′-H), 9.38 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 20.9 (CH_3), 114.0 (2 × CH), 124.5 (2 × CH), 125.4 (C), 126.8 (2 × CH), 129.3 (2 × CH), 136.9 (C), 142.6 (C), 146.4 (C).

MS (ESI): *m*/*z* = 263 [M +H]$^+$ (100).

N-(3,5-Dimethyl-4-aminophenyl)-4′-methylbenzenesulfonamide (7g)

The reaction was performed according to the general procedure using 2,6-dimethylaniline (0.0616 mL, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (60% diethyl ether in hexane) gave the title compound.

Yield: 0.0843 g (58%); light-brown solid; mp 120–123 °C.

IR (neat): 3252, 2924, 1601, 1485, 1319, 1153, 1092, 1030, 729 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 6 H, 3-CH_3 and 5-CH_3), 2.38 (s, 3 H, 4′-CH_3), 3.52 (br s, 2 H, NH_2), 6.36 (br s, 1 H, NH), 6.63 (s, 2 H, 2-H and 6-H), 7.20 (d, *J* = 8.1 Hz, 2 H, 3′-H and 5′-H), 7.59 (d, *J* = 8.1 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.7 (2 × CH_3), 21.6 (CH_3), 122.4 (2 × C), 124.7 (2 × CH), 126.1 (C), 127.5 (2 × CH), 129.5 (2 × CH), 136.6 (C), 141.5 (C), 143.5 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_2S$: 291.1162; found 291.1164.

N-(3-Trifluoromethyl-4-aminophenyl)-4′-methylbenzenesulfonamide (7h)[22]

The reaction was performed according to the general procedure using 2-(trifluoromethyl)aniline (0.126 mL, 1.00 mmol) and *p*-toluenesulfonamide (0.258 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (0.5% ethyl acetate in dichloromethane) gave the title compound.

Yield: 0.207 g (63%); white solid; mp 133–135 °C; spectroscopic data were consistent with the literature.[22]

^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, 4′-CH_3), 4.15 (br s, 2 H, NH_2), 6.37 (br s, 1 H, NH), 6.62 (d, *J* = 9.9 Hz, 1 H, 5-H), 6.99–7.05 (m, 2 H, 2-H and 6-H), 7.23 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.57 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 114.1 (q, $^2J_{CF}$ = 30.6 Hz, C), 118.0 (CH), 123.4 (q, $^3J_{CF}$ = 5.3 Hz, CH), 124.3 (q, $^1J_{CF}$ = 272.6 Hz, C), 126.1 (C), 127.5 (2 × CH), 129.8 (2 × CH), 130.0 (CH), 135.9 (C), 143.3 (q, $^3J_{CF}$ = 1.8 Hz, C), 144.1 (C).

MS (ESI): *m*/*z* = 353 [M + Na]$^+$ (100).

N-[4-(4′-Methylphenylsulfonamido)phenyl]acetamide (7i)[8c]

The reaction was performed according to the general procedure using acetanilide (0.135 g, 1.00 mmol) and *p*-toluenesulfonamide (0.256 g, 1.500 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40–100% ethyl acetate in hexane) gave the title compound.

Yield: 0.225 g (74%); white solid; mp 179–181 °C (Lit.[8c] 184–185 °C).

^{1}H NMR (400 MHz, CD_3OD): δ = 2.07 (s, 3 H, $COCH_3$), 2.36 (s, 3 H, 4′-CH_3), 7.00 (d, *J* = 9.0 Hz, 2 H, 3-H and 5-H), 7.26 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H), 7.38 (d, *J* = 9.0 Hz, 2 H, 2-H and 6-H), 7.59 (d, *J* = 8.4 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, CD_3OD): δ = 21.4 (CH_3), 23.7 (CH_3), 121.8 (2 × CH), 123.4 (2 × CH), 128.3 (2 × CH), 130.5 (2 × CH), 134.8 (C), 137.0 (C), 138.0 (C), 145.0 (C), 171.5 (C).

MS (ESI): *m*/*z* = 305 $[M + H]^+$ (100).

Benzyl [4-(4′-Methylphenylsulfonamido)phenyl]carbamate (7j)[34]

The reaction was performed according to the general procedure using benzyl (4-aminophenyl)carbamate (0.114 g, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 110 °C for 40 h. Purification by flash column chromatography (10% ethyl acetate in chloroform) gave the title compound.

Yield: 0.130 g (65%); white solid; mp 161–163 °C (Lit.[34] 162–163 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, 4′-CH_3), 5.18 (s, 2 H, OCH_2), 6.33 (br s, 1 H, NH), 6.62 (br s, 1 H, NH), 6.99 (d, *J* = 9.0 Hz, 2 H, 3-H and 5-H), 7.21 (d, *J* = 8.3 Hz, 2 H, 3′-H and 5′-H), 7.26 (d, *J* = 9.0 Hz, 2 H, 2-H and 6-H), 7.30–7.41 (m, 5 H, Ph), 7.58 (d, *J* = 8.3 Hz, 2 H, 2′-H and 6′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 67.3 (CH_2), 119.6 (2 × CH), 123.9 (2 × CH), 127.4 (2 × CH), 128.5 (2 × CH), 128.6 (CH), 128.8 (2 × CH), 129.8 (2 × CH), 131.8 (C), 135.9 (C), 136.0 (C), 136.0 (C), 144.0 (C), 153.4 (C).

MS (ESI): *m*/*z* = 397 $[M + H]^+$ (100).

N,*N*′-Ditosyl-1,4-diaminobenzene (7k)[35]

The reaction was performed according to the general procedure using iron(III) chloride (0.00406 g, 0.0250 mmol), 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.0220 mL, 0.0750 mmol), *N*-tosylaniline (0.124 g, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 24 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (80–100% diethyl ether in hexane and then 100% ethyl acetate) gave the title compound.

Yield: 0.134 g (65%); white solid; mp 260–262 °C (Lit.[35] 256–258 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 6 H, 4′-CH_3 and 4″-CH_3), 6.90 (s, 4 H, 2-H, 3-H, 5-H and 6-H), 7.29 (d, *J* = 8.1 Hz, 4 H, 3′-H, 5′-H, 3″-H and 5″-H), 7.53 (d, *J* = 8.1 Hz, 4 H, 2′-H, 6′-H, 2″-H and 6″-H), 10.01 (br s, 2 H, 2 × NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 20.9 (2 × CH_3), 121.5 (4 × CH), 126.6 (4 × CH), 129.5 (4 × CH), 134.0 (2 × C), 136.5 (2 × C), 143.1 (2 × C).

MS (ESI): *m*/*z* = 417 $[M + H]^+$ (100).

One-Pot Amidation of 3,4-Dihydro-3-methyl-2(1*H*)-quinazolinone (8); General Procedure

Iron(III) chloride (0.00406 g, 0.0250 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.0220 mL, 0.0750 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-bromosuccinimide (0.0979 g, 0.550 mmol) and 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (**8**) (0.0811 g, 0.500 mmol) in toluene (0.5 mL). The mixture was heated to 40 °C for 4 h. Upon completion of the bromination step, the reaction mixture was cooled to room temperature and the primary sulfonamide (0.750 mmol), copper(I) iodide (0.00952 g, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (0.0108 mL, 0.100 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography.

N-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)benzenesulfonamide (4a)[6]

The reaction was performed according to the general procedure using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (**8**) (0.0811 g, 0.500 mmol) and benzenesulfonamide (0.118 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave the title compound.

Yield: 0.0854 g (54%); white solid; mp 200–203 °C (decomposition); spectroscopic data were consistent with the literature.[6]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.80 (s, 3 H, NCH_3), 4.28 (s, 2 H, 4-H_2), 6.59 (d, *J* = 8.3 Hz, 1 H, 8-H), 6.77–6.83 (m, 2 H, 5-H and 7-H), 7.53 (t, *J* = 7.7 Hz, 2 H, 3′-H and 5′-H), 7.60 (t, *J* = 7.7 Hz, 1 H, 4′-H), 7.69 (d, *J* = 7.7 Hz, 2 H, 2′-H and 6′-H), 9.13 (s, 1 H, NH), 9.93 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 33.8 (CH_3), 49.6 (CH_2), 113.7 (CH), 118.4 (C), 119.3 (CH), 121.6 (CH), 126.7 (2 × CH), 129.1 (2 × CH), 130.5 (C), 132.7 (CH), 135.1 (C), 139.5 (C), 153.5 (C).

MS (ESI): *m*/*z* = 318 $[M + H]^+$ (100).

N-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4′-methylbenzenesulfonamide (4b)[6]

The reaction was performed according to the general procedure using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (**8**) (0.0811 g, 0.500 mmol) and 4-methoxybenzenesulfonamide (0.140 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave the title compound.

Yield: 0.0957 g (58%); white solid; mp 180–183 °C (decomposition); spectroscopic data were consistent with the literature.[6]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 3 H, 4′-CH_3), 2.80 (s, 3 H, NCH_3), 4.28 (s, 2 H, 4-H_2), 6.58 (d, *J* = 8.3 Hz, 1 H, 8-H), 6.76–6.82 (m, 2 H, 5-H and 7-H), 7.32 (d, *J* = 8.2 Hz, 2 H, 3′-H and 5′-H), 7.57 (d, *J* = 8.2 Hz, 2 H, 2′-H and 6′-H), 9.11 (s, 1 H, NH), 9.85 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 21.0 (CH_3), 33.8 (CH_3), 49.6 (CH_2), 113.7 (CH), 118.4 (C), 119.0 (CH), 121.3 (CH), 126.7 (2 × CH), 129.6 (2 × CH), 130.7 (C), 134.9 (C), 136.6 (C), 143.0 (C), 153.6 (C).

MS (ESI): *m*/*z* = 332 $[M + H]^+$ (100).

***N*-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4′-methoxybenzenesulfonamide (4c)**[6]

The reaction was performed according to the general procedure using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (**8**) (0.0811 g, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave the title compound.

Yield: 0.0985 g (57%); white solid; mp 165–168 °C (decomposition); spectroscopic data were consistent with the literature.[6]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.80 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 4.28 (s, 2 H, 4-H_2), 6.59 (d, *J* = 8.3 Hz, 1 H, 8-H), 6.76–6.82 (m, 2 H, 5-H and 7-H), 7.04 (d, *J* = 8.5 Hz, 2 H, 3′-H and 5′-H), 7.61 (d, *J* = 8.5 Hz, 2 H, 2′-H and 6′-H), 9.12 (s, 1 H, NH), 9.79 (br s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 33.8 (CH_3), 49.6 (CH_2), 55.6 (CH_3), 113.7 (CH), 114.3 (2 × CH), 118.4 (C), 119.1 (CH), 121.4 (CH), 128.9 (2 × CH), 130.9 (C), 131.1 (C), 134.9 (C), 153.6 (C), 162.3 (C).

MS (ESI): *m*/*z* = 348 $[M + H]^+$ (100).

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) (a) Drews, J. *Science* **2000**, *287*, 1960. (b) Smith, D. A.; Jones, R. M. *Curr. Opin. Drug. Discovery Dev.* **2008**, *11*, 72. (c) Bentley, R. *J. Ind. Microbiol. Biotechnol.* **2009**, *36*, 775.

(2) (a) Vicente-Blázquez, A.; González, M.; Álvarez, R.; del Mazo, S.; Medarde, M.; Peláez, R. *Med. Res. Rev.* **2019**, *39*, 775. (b) Elgemeie, G. H.; Azzam, R. A.; Elsayed, R. E. *Med. Chem. Res.* **2019**, *28*, 1099. (c) El-Gaby, M. S. A.; Ammar, Y. A.; El-Qaliei, M. I. H.; Ali, A. M.; Hussein, M. F.; Faraghally, F. A. *Egypt J. Chem.* **2020**, *63*, 5289.

(3) Sparks, S. M.; Chen, G.; Collins, J. L.; Danger, D.; Dock, S. T.; Jayawickreme, C.; Jenkinson, S.; Laudeman, C.; Leesnitzer, M. A.; Liang, X.; Maloney, P.; McCoy, D. C.; Moncol, D.; Rash, V.; Rimele, T.; Vulimiri, P.; Way, J. M.; Ross, S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3100.

(4) (a) Li, Q.; Sham, H.; Woods, K. W.; Steiner, B. A.; Gwaltney, S. L. II.; Barr, K. J.; Imade, H. M.; Rosenberg, S. US Patent 6521658, **2003**. (b) González, M.; Ovejero-Sánchez, M.; Vicente-Blázquez, A.; Medarde, M.; González-Sarmiento, R.; Peláez, R. *J. Enzyme Inhib. Med. Chem.* **2021**, *36*, 1029.

(5) Medina, J. C.; Shan, B.; Beckmann, H.; Farrell, R. P.; Clark, D. L.; Learned, R. M.; Roche, D.; Li, A.; Baichwal, V.; Case, C.; Baeuerle, P. A.; Rosen, T.; Jaen, J. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2653.

(6) (a) Fish, P. V.; Filippakopoulos, P.; Bish, G.; Brennan, P. E.; Bunnage, M. E.; Cook, A. S.; Federov, O.; Gerstenberger, B. S.; Jones, H.; Knapp, S.; Marsden, B.; Nocka, K.; Owen, D. R.; Philpott, M.; Picaud, S.; Primiano, M. J.; Ralph, M. J.; Sciammetta, N.; Trzupek, J. D. *J. Med. Chem.* **2012**, *55*, 9831. (b) Fish, P. V.; Cook, A. S.; Phillips, C.; Bent, A. F.; Mills, J. E. J.; Sciammetta, N. WO2013027168 A1, **2013**.

(7) For a review, see: Kolaczek, A.; Fusiarz, I.; Lawecka, J.; Branowska, D. *CHEMIK* **2014**, *68*, 620.

(8) For example, see: (a) Kim, J.-G.; Jang, D. O. *Synlett* **2007**, 2501. (b) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287. (c) Zhang, W.; Xie, J.; Rao, B.; Luo, M. *J. Org. Chem.* **2015**, *80*, 3504. (d) Flegeau, E. F.; Harrison, J. M.; Willis, M. C. *Synlett* **2016**, *27*, 101. (e) Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; Ende, C. W.; Ball, N. D. *Org. Lett.* **2018**, *20*, 3943. (f) Chen, Y.; Murray, R. D.; Davies, A. T.; Willis, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 8781. (g) Chen, K.; Chen, W.; Han, B.; Chen, W.; Liu, M.; Wu, H. *Org. Lett.* **2020**, *22*, 1841.

(9) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. *Org. Lett.* **2011**, *13*, 2564.

(10) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. *J. Org. Chem.* **2011**, *76*, 4552.

(11) (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (b) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295.

(12) (a) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (b) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (c) Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106. (d) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3554. (e) Maiden, T. M. M.; Swanson, S.; Procopiou, P. A.; Harrity, J. P. A. *J. Org. Chem.* **2016**, *81*, 10641. (f) Song, C.; Wang, T.; Yu, T.; Cui, D.-M.; Zhang, C. *Org. Biomol. Chem.* **2017**, *15*, 7212. (g) Zhang, W.; Yang, D.; Wang, W.; Wang, S.; Zhao, H. *Eur. J. Org. Chem.* **2018**, 2071. (h) Liu, L.; Wang, N.; Dai, C.; Han, Y.; Yang, S.; Huang, Z.; Zhao, Y. *Eur. J. Org. Chem.* **2019**, 7857.

(13) Racys, D. T.; Warrilow, C. E.; Pimlott, S. L.; Sutherland, A. *Org. Lett.* **2015**, *17*, 4782.

(14) (a) Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7860. (b) Earle, M. J.; Hakala, U.; McAuley, B. J.; Nieuwenhuyzen, M.; Ramani, A.; Seddon, K. R. *Chem. Commun.* **2004**, 1368.

(15) Mostafa, M. A. B.; Bowley, R. M.; Racys, D. T.; Henry, M. C.; Sutherland, A. *J. Org. Chem.* **2017**, *82*, 7529.

(16) (a) Mostafa, M. A. B.; Calder, E. D. D.; Racys, D. T.; Sutherland, A. *Chem. Eur. J.* **2017**, *23*, 1044. (b) Henry, M. C.; Senn, H. M.; Sutherland, A. *J. Org. Chem.* **2019**, *84*, 346. (c) Henry, M. C.; Sutherland, A. *Org. Lett.* **2020**, *22*, 2766.

(17) For reviews of copper-catalyzed aryl amination, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525. (d) Okano, K.; Tokuyama, H.; Fukuyama, T. *Chem. Commun.* **2014**, *50*, 13650.

(18) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. *J. Org. Chem.* **2016**, *81*, 772.

(19) It should be noted that in a previous study (see reference 16b), we performed DFT calculations using Fukui functions, which provided a molecular orbital rationale for the high *para* regioselectivity observed for iron triflimide catalyzed halogenation of arenes.
(20) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
(21) As previously reported (see references 13, 15 and 16), electron-rich arenes are required for the iron(III)-catalyzed halogenation step. Electron-deficient arenes are not substrates for this transformation.
(22) Xu, F.; Zhao, Y.; Zhou, H.; Li, C.; Zhang, X.; Hou, T.; Qu, L.; Wei, L.; Wang, J.; Liu, Y.; Liang, X. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127650.
(23) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.
(24) Nasrollahzadeh, M.; Ehsani, A.; Maham, M. *Synlett* **2014**, *25*, 505.
(25) Yang, K.; Ke, M.; Lin, Y.; Song, Q. *Green Chem.* **2015**, *17*, 1395.
(26) Kato, T.; Okamoto, I.; Tanatani, A.; Hatano, T.; Uchiyama, M.; Kagechika, H.; Masu, H.; Katagiri, K.; Tominaga, M.; Yamaguchi, K.; Azumaya, I. *Org. Lett.* **2006**, *8*, 5017.
(27) Nasrollahzadeh, M.; Rostami-Vartooni, A.; Ehsani, A.; Moghadam, M. *J. Mol. Catal. A: Chem.* **2014**, *387*, 123.
(28) Pan, C.; Cheng, J.; Wu, H.; Ding, J.; Liu, M. *Synth. Commun.* **2009**, *39*, 2082.
(29) Lawrence, H. R.; Kazi, A.; Luo, Y.; Kendig, R.; Ge, Y.; Jain, S.; Daniel, K.; Santiago, D.; Guida, W. C.; Sebti, S. M. *Bioorg. Med. Chem.* **2010**, *18*, 5576.
(30) Arcoria, A.; Maccarone, E.; Musumarra, G.; Tomaselli, G. A. *J. Org. Chem.* **1973**, *38*, 2457.
(31) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Synthesis* **2006**, 3316.
(32) Deruer, E.; Coulibali, S.; Boukercha, S.; Canesi, S. *J. Org. Chem.* **2017**, *82*, 11884.
(33) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 919.
(34) Ouyang, B.; Liu, D.; Xia, K.; Zheng, Y.; Mei, H.; Qiu, G. *Synlett* **2018**, *29*, 111.
(35) Jiang, Z. Y.; Xu, L.; Lu, M. C.; Chen, Z. Y.; Yuan, Z. W.; Xu, X. L.; Guo, X. K.; Zhang, X. J.; Sun, H. P.; You, Q. D. *J. Med. Chem.* **2015**, *58*, 6410.