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Note

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Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Chlorobenzenesulfonamides with Alkyl Grignard Reagents: Entry to Alkylated Aromatics

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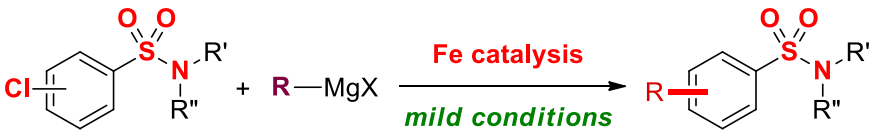
Abstract



■ *biologically-relevant sulfonamide scaffold (sulfa drugs)*
■ *the most reactive activating group for Fe-catalyzed cross-coupling*
■ *operationally-simple conditions* ■ *challenging alkyl nucleophiles*
■ *sustainable iron catalysis* ■ *broad scope* ■ *high selectivity*

Alkylated benzosulfonamides are compounds of high importance in organic synthesis, including the production of pharmaceuticals, agrochemicals and plasticizers. We report the iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of chlorobenzosulfonamides with alkyl Grignard reagents under mild and sustainable conditions. Electronically- and sterically-varied benzosulfonamides as well as challenging alkyl organometallics containing β-hydrogen afford alkylated benzosulfonamides in high to excellent yields. Sulfonamide represents the most reactive activating group for iron-catalyzed cross-coupling. The process affords alkylated benzenesulfonamides poised for medicinal chemistry applications and traceless reductive cleavage.

The iron-catalyzed cross-coupling has emerged as an increasingly powerful method for organic synthesis.[1,2] The high interest of the organic community in iron catalysis is driven by the abundance of iron in the Earth's crust leading to a sustained catalyst economy.[3] Equally importantly, iron-catalysis allows to execute traditionally challenging cross-coupling disconnections,[4] including alkylative cross-couplings which are notoriously difficult because of the propensity of alkyl organometallic reagents to undergo β-hydride elimination and homo-coupling.[5] In recent years, iron-catalyzed cross-couplings have attracted a major attention of researchers in pharmaceutical industry.[6]

Sulfonamides are among the most important molecules in drug discovery.[7] In particular, the discovery of sulfa drugs have led to the construction of the dominant concepts in modern medicinal chemistry,[7,8] and resulted in the development of a wide range of antibacterial, hypoglycaemic, diuretic and antihypertensive drugs (Figure 1). In modern drug discovery alkylated benzenesulfonamides are further used as lead molecules for the treatment of cancer, as fatty acid amide hydrolase inhibitors, N-myristoyl transferase inhibitors and calcium-sensing receptor antagonists (Figure 1), among other applications.[9] Furthermore, alkylated benzenesulfonamides are prevalent in industries beyond drug discovery, including as agrochemical agents and plasticizers.[10] As a consequence of the key importance of sulfonamides in organic chemistry, new methods for the synthesis of sulfonamides continue to have a major impact on organic synthesis and medicinal chemistry.[11]

Inspired by our interest in amide bonds[12] and iron-catalyzed cross-couplings,[13] herein, we report the iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling of chlorobenzenesulfonamides with alkyl Grignard reagents (Figure 2). The reaction proceeds under exceedingly mild conditions using sustainable iron-catalysis. We demonstrate that a broad range of electronically- and sterically-varied benzosulfonamides as well as challenging alkyl organometallics containing β-hydrogen are compatible with these conditions. Mechanistic studies reveal that sulfonamide acts as one of the most reactive activating groups for iron-catalyzed alkylative cross-coupling with Grignard reagents,[14,15] which may have implications for the future design of iron-catalyzed cross-coupling methods mediated by O-coordinating

additives. Collectively, the process affords alkylated benzosulfonamides poised for applications in medicinal chemistry as well as traceless reductive cleavage processes.

Notable features of our findings include: (1) the synthesis of alkylated benzenesulfonamides of medicinal interest that would be difficult to access by other methods, (2) the discovery of sulfonamide as the strongest activating group for iron-catalyzed cross-couplings, (3) the potential for using tertiary sulfonamides as traceless activating groups.

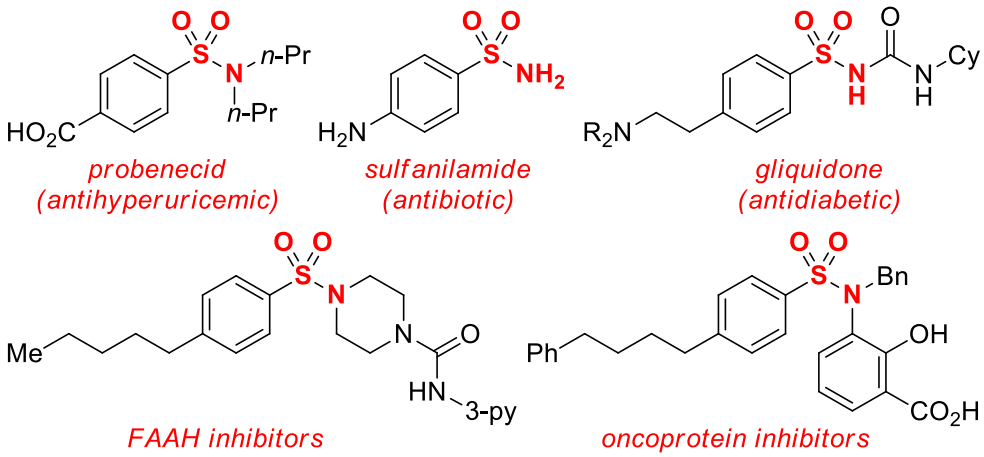


Figure 1. Biologically-active sulfonamides: (a) Classic sulfa drugs (top), and (b) pharmaceutically-active alkylated sulfonamides (bottom).

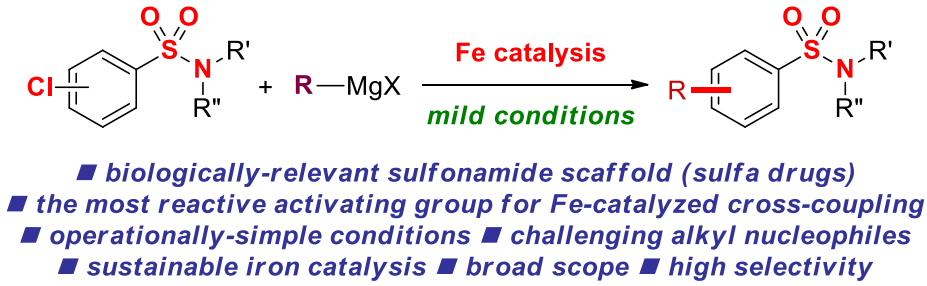


Figure 2. Iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling of chloro-benzosulfonamides with alkyl Grignard reagents (this study).

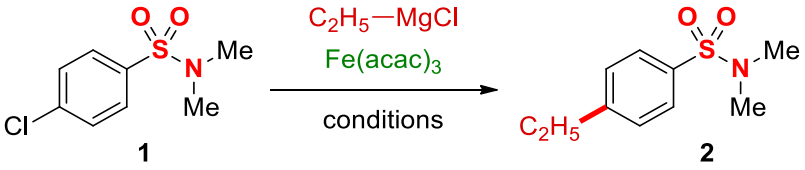
Our studies began with an investigation of the cross-coupling of N,N-dimethyl-4-chlorobenzenesulfonamide with *n*-alkyl Grignard reagent containing β-hydrogens (Table 1). An important precedent in the cross-coupling of sterically-hindered sulfonamides should be noted.[14a,b] In contrast to the amide bond, the nitrogen atom in the sulfonamide grouping tends to be pyramidalized,[16] which in turn may influence the coordination. Furthermore, the weak N–SO_2 bond is prone to reductive cleavage under cross-coupling conditions.[17] Hence, at the outset it was unclear if non-sterically demanding sulfonamides can be used as cross-coupling partners. Since we are focused on developing operationally-practical methods of broad synthetic appeal, we selected rapid addition of organometallic reagent and the use of cheap, readily accessible O-coordinating additives.[14a,b] As shown, no reaction was observed in the absence of iron (Table 1, entry 1). The reaction was inefficient in the absence of additives (entry 2). Pleasingly, we found that the combined use of iron and NMP (NMP = N-methyl-2-pyrrolidone) afforded the coupling product in excellent yield (Table 1, entries 3-6). Importantly, while efficient coupling was observed with as little as 50 mol% of NMP (entry 4), the use of excess of NMP afforded the cleanest reactions. We further note that the use of TMEDA (61% yield) or HMTA (hexamethylenetetramine) (70% yield) under the optimized conditions is less efficient; however, DMI (98%) and DMPU (97%) can be used as NMP replacements in this cross-coupling. NMP was selected for the study to enable comparison with the benchmark method. At present, cross-coupling at lower catalyst loading is less efficient. Ongoing studies in our laboratories are focused on the development of iron-catalyzed cross-couplings at low catalyst loadings. Importantly, under these reaction conditions, the cleavage of SO_2–N bond, or side reactions from the Grignard reagents, including β-hydride elimination and homo-coupling were not observed, indicating a significant activating effect of the sulfonamide moiety.

Having determined that sterically-non-hindered N,N-dimethyl-4-chlorobenzenesulfonamide serves as an efficient cross-coupling partner, the substrate scope of this reaction was next explored (Table 2). Pleasingly, the reaction was found to tolerate electronically- and sterically-varied benzosulfonamides as well as challenging alkyl organometallics containing β-hydrogen (Table 2, entries 1-12). Importantly,

sulfonamides with varied steric hindrance at the nitrogen atom are readily tolerated, including NMe_2 (entry 1), NEt_2 (entry 2) and N-*i*Pr_2 (entry 3) with no deleterious effect on the coupling. Furthermore, highly medicinally-relevant N-cyclic sulfonamides are readily tolerated (entry 4). The reaction is also compatible with N-Ar sulfonamides (entry 5), which are used in sulfonamide exchange reactions[18] to increase the diverse modifications of the sulfonamide bond, as well as N-Bn sulfonamides, which are used as synthetic equivalent of secondary sulfonamides after hydrogenolysis[19] (entry 6). Intriguingly, very high efficiency without any modification of the reaction conditions was observed in the cross-coupling of a meta-substituted benzosulfonamide (entry 7), indicating that conjugation with the sulfonamide moiety is not required for the coupling. Furthermore, even the ortho-substituted benzenesulfonamide afforded the desired coupling product, albeit in a modest yield (entry 8). The two latter findings sharply contrast with the cross-coupling of the analogous chloro-benzamides,[13d] which (1) require extensive optimization for the cross-coupling at the non-conjugated position, (2) are completely unreactive in cross-coupling at the sterically-hindered ortho-position.

The scope of the reaction also encompasses challenging secondary alkyl Grignard reagents, such as cyclohexyl (entry 9) and isopropyl (entry 10). Again, these Grignard reagents afford cross-coupling products using the analogous chloro-benzamides in significantly lower yields,[13d] showing the superior propensity of sulfonamide as the activating group for cross-coupling. Furthermore, isomerization to *n*-alkyl product, which is the major side reaction using other iron-catalyst systems[20] was not observed under these mild conditions. Finally, we were pleased to find that other representative Grignard reagents, such as prone to β-hydride elimination phenethyl Grignard reagent (entry 11) and sensitive dioxolane Grignard (entry 12), which serves as a synthetic carbonyl equivalent are readily tolerated in the cross-coupling. It is worthwhile to note that Grignard addition to the electrophilic sulfonamide bond was not observed in any of the tested examples, attesting to the mild conditions and facility of the coupling. Several of the synthesized products map very well onto the structures of bioactive alkylbenzenesulfonamides.[8,9] Thus, these reactions should find wide application in the preparation of medicinally-relevant scaffolds.

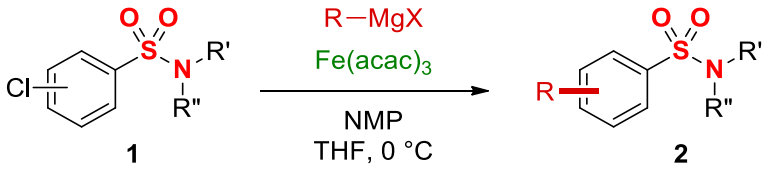
Table 1. Optimization of Fe-Catalyzed Cross-Coupling[a]

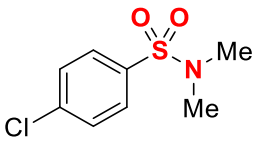
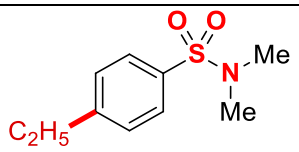
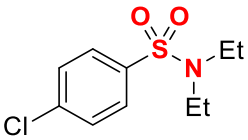
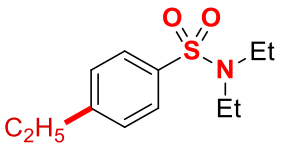
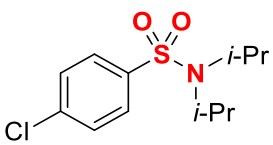
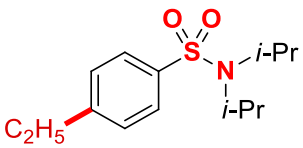


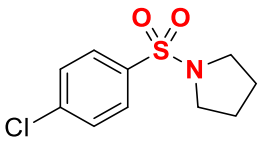
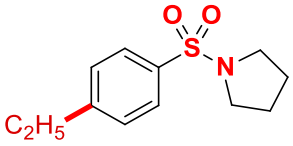
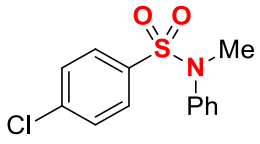
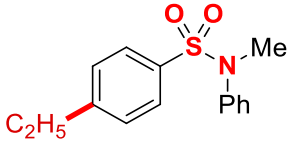
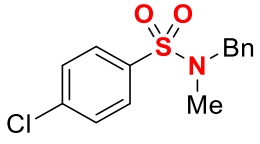
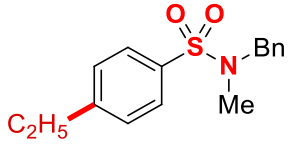
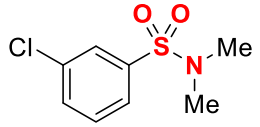
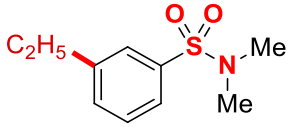
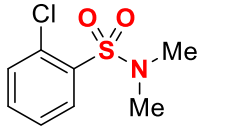
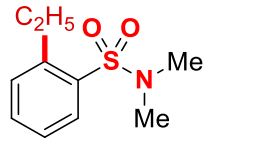
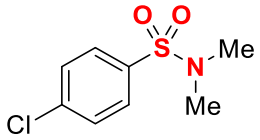
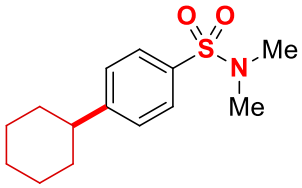
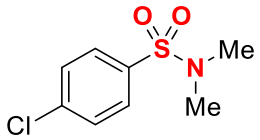
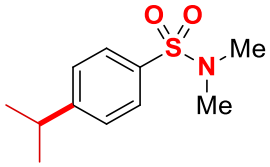
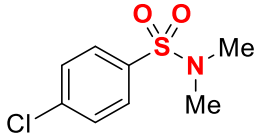
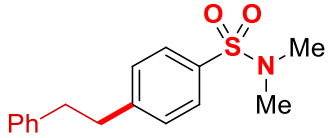
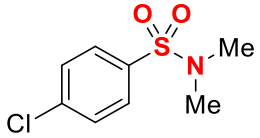
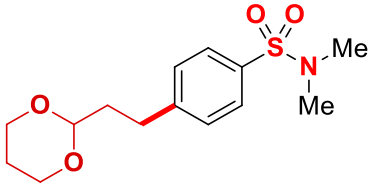
Entry	Fe(acac)$_3$ (mol%)	Ligand	mol%	Time	Yield (%)[b]
1	-	-	-	10 min	0
2	5	-	-	10 min	75
3	5	NMP	20	10 min	88
4	5	NMP	50	10 min	96
5	5	NMP	200	10 min	>98
6	5	NMP	600	10 min	>98

[a]**1** (0.50 mmol), Fe(acac)$_3$ (5 mol%), THF (0.15 M), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), 0 °C, 10 min. RMgCl added dropwise over 1-2 s. [b] Determined by ^{1}H NMR and/or GC-MS.

Table 2. Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Sulfonamides with Alkyl Grignard Reagents[a]



Entry	Substrate	**2**	Product	Yield (%)
1		**2a**		97
2		**2b**		96
3		**2c**		97

4		**2d**		95
5		**2e**		98
6		**2f**		97
7		**2g**		93
8[b]		**2h**		50
9[c]		**2i**		84
10[c]		**2j**		74
11[c]		**2k**		83
12[d]		**2l**		96

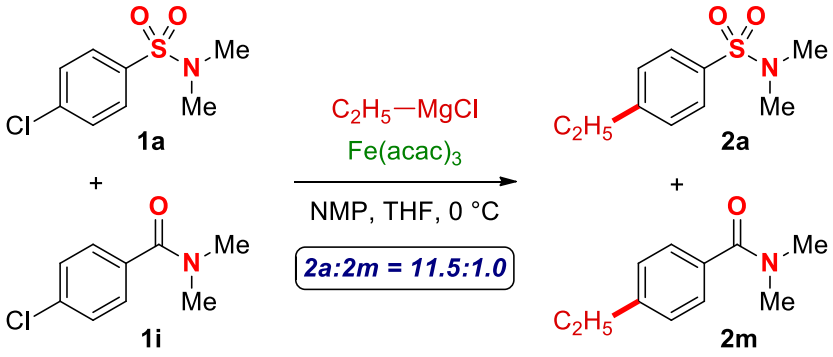
[a]**1** (0.50 mmol), $Fe(acac)_3$ (5 mol%), THF (0.15 M), NMP, RMgX (1.20 equiv, THF), 0 °C, 10 min. [b]15 h, 0 °C. [c]1 h, 0 °C. [d]15 h, 23 °C, RMgX (3.0 equiv). See the Supporting Information for details.

Intermolecular competition experiments were conducted to gain insight into the unique reactivity of benzenesulfonamides in the cross-coupling (Schemes 1-2). Intriguingly, we identified sulfonamide as a significantly more potent activating group than the amide bond (Scheme 1, sulfonamide:amide = 11.5:1).[13d] The excellent activating profile of sulfonamide was further confirmed in the competition with

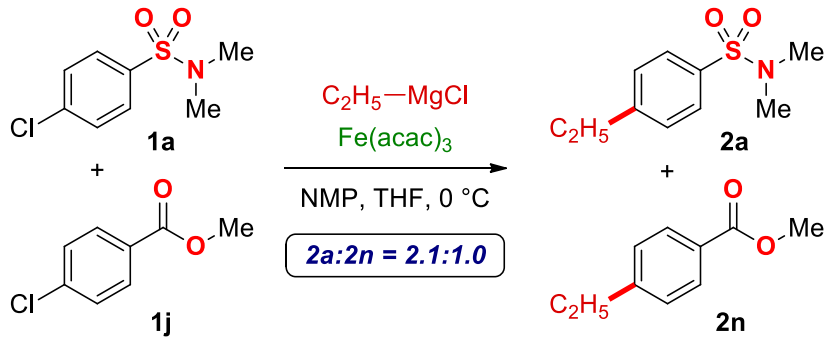
the ester bond (Scheme 2, sulfonamide:ester = 2.1:1). Hence, to our knowledge, sulfonamide has been identified as the most activating group for iron-catalyzed cross-couplings,[1,13d,14] which may find wide application in future studies of iron-catalyzed cross-coupling methods. Future work is focused on mechanistic analysis evaluating broad classes of activating groups in iron-catalyzed cross-coupling.

The utility of the sulfonamide bond is not limited to medicinal chemistry applications. For example, a recent manuscript describes reductive cleavage of *n*-alkylbenzosulfonamides catalyzed by Ni.[21] Thus, in combination with our facile way of preparing diverse *n*-alkylbenzenesulfonamides by iron-catalysis, this method represents a traceless sulfonamide-based approach to *n*-alkylated aromatics (Scheme 3). Furthermore, owing to the utility of SO_2NR_2 moiety, other methods for manipulation of tertiary sulfonamides are well-established, further enhancing the utility of our method.[22]

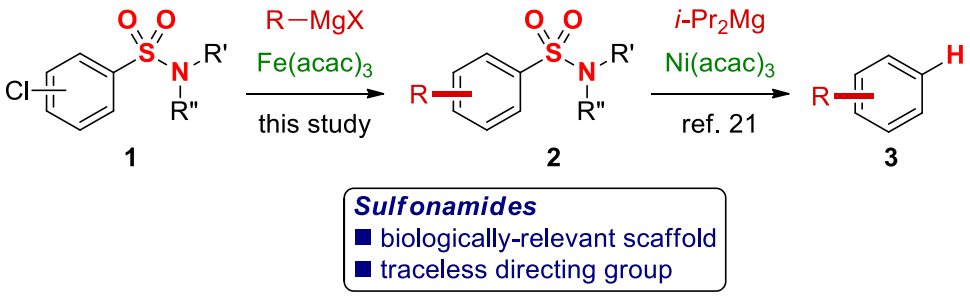
Scheme 1. Intermolecular Competition Experiments: Amides



Scheme 2. Intermolecular Competition Experiments: Esters



Scheme 3. Sulfonamide as Traceless Activating Group



In conclusion, we have reported the iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling of chlorobenzenesulfonamides with alkyl Grignard reagents. The method represents a convenient access to alkylated benzenesulfonamides that are widely used in the synthesis of pharmaceuticals, agrochemicals and plasticizers. A broad range of electronically- and sterically-varied benzenesulfonamides and challenging alkyl organometallics containing β-hydrogen undergo cross-coupling under exceedingly mild reaction conditions that tolerate the presence of an electrophilic sulfonamide moiety in the presence of readily-accessible and cheap Grignard organometallics. Importantly, our study demonstrates that sulfonamide acts as the one of most reactive activating groups for iron-catalyzed alkylative cross-couplings, a class of reactions that is broadly used in pharmaceutical settings. Further, the sulfonamide group is poised for applications as traceless activating group. Studies to facilitate further reaction development using sustainable iron-catalysis are in progress and will be reported in due course.

Experimental Section

General Methods. All compounds reported in the manuscript are commercially available or have been previously described in literature unless indicated otherwise. All experiments involving iron were performed using standard Schlenk techniques under argon or nitrogen atmosphere unless stated otherwise. All sulfonamides have been prepared by standard methods.[23] ^{1}H NMR and ^{13}C NMR data are given for all compounds in the Experimental Section for characterization purposes. ^{1}H NMR, ^{13}C NMR

and HRMS data are reported for all new compounds. All products have been previously reported, unless stated otherwise. Spectroscopic data matched literature values. General methods have been published.[13a]

General Procedure for Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling. An oven-dried vial equipped with a stir bar was charged with an sulfonamide substrate (neat, typically, 0.50 mmol, 1.0 equiv) and $Fe(acac)_3$ (typically, 5 mol%), placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under vacuum. Tetrahydrofuran (0.15 M) and NMP were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of Grignard reagent (typically, 1.2 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for the indicated time at 0 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 *N*, 1.0 mL) and Et_2O (1 x 30 mL), the organic layer was extracted with HCl (1.0 *N*, 2 x 10 mL), dried and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes = 1/3) afforded the title product.

General Procedure for Determination of Relative Reactivity. According to the general procedure, an oven-dried vial equipped with a stir bar was charged with two chloride substrates (each 0.50 mmol, 1.0 equiv) and $Fe(acac)_3$ (5 mol%), placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under vacuum. Tetrahydrofuran (0.15 M) and NMP (neat, 600 mol%) were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of C_2H_5MgCl (2.0 M in THF, 0.25 mmol, 0.50 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for 10 min at 0 °C. Following the standard work-up, the sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples.

Characterization Data for Starting Materials

4-Chloro-*N*,*N*-dimethylbenzenesulfonamide (1a).[24] Yield 95% (2.09 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 2.72 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 139.4, 134.1, 129.5, 129.2, 38.9.

4-Chloro-*N*,*N*-diethylbenzenesulfonamide (1b).[25] Yield 97% (2.41 g). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 3.24 (q, *J* = 7.1 Hz, 4H), 1.13 (t, *J* = 7.1 Hz, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 138.9, 138.5, 129.2, 128.3, 42.0, 14.1.

4-Chloro-*N*,*N*-diisopropylbenzenesulfonamide (1c).[14a] Yield 88% (2.44 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 3.76-3.65 (m, 2 H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 141.4, 138.3, 129.2, 128.8, 48.9, 22.1.

1-((4-Chlorophenyl)sulfonyl)pyrrolidine (1d).[26] Yield 96% (2.35 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 3.24 (ddd, *J* = 6.8, 4.4, 2.7 Hz, 4H), 1.80-1.76 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 139.2, 135.6, 129.5, 129.0, 48.1, 25.4.

4-Chloro-*N*-methyl-*N*-phenylbenzenesulfonamide (1e).[27] Yield 97% (2.73 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (q, *J* = 8.8 Hz, 4H), 7.35-7.27 (m, 3H), 7.12-7.07 (m, 2H), 3.18 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 141.3, 139.5, 135.0, 129.4, 129.2, 129.2, 127.8, 126.8, 38.3.

***N*-Benzyl-4-chloro-*N*-methylbenzenesulfonamide (1f)**.[28] Yield 95% (2.82 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.37-7.27 (m, 5H), 4.14 (s, 2H), 2.60 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 139.3, 136.0, 135.4, 129.6, 129.0, 128.8, 128.5, 128.2, 54.2, 34.44.

3-Chloro-*N*,*N*-dimethylbenzenesulfonamide (1g).[29] Yield 96% (2.11 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 1.9 Hz, 1H), 7.69-7.65 (m, 1H), 7.61-7.57 (m, 1H), 7.53-7.48 (m, 1H), 2.74 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 137.5, 135.5, 133.0, 130.5, 127.8, 125.9, 38.0.

2-Chloro-*N*,*N*-dimethylbenzenesulfonamide (1h).[11b] Yield 95% (2.09 g). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9 Hz, 1H), 7.56-7.47 (m, 2H), 7.44-7.38 (m, 1H), 2.89 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 136.1, 133.7, 132.2, 127.1, 37.5.

Characterization Data for Cross-Coupling Products

4-Ethyl-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2a). *New compound.* Prepared according to the general procedure using 4-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 97% (103.0 mg). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 2.73 (q, *J* = 7.7 Hz, 2H), 2.69 (s, 6H), 1.27 (t, *J* = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 132.4, 128.5, 127.9, 38.0, 28.8, 15.2. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{15}NO_2SNa$ 236.0721 found 236.0724.

***N*,*N*,4-Triethylbenzenesulfonamide (Table 2, 2b).**[25] Prepared according to the general procedure using *N*,*N*,4-triethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 96% (115.6 mg). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 3.23 (q, *J* = 7.1 Hz, 4H), 2.71(q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 6H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.1, 137.4, 128.5, 127.1, 42.1, 28.8, 15.2, 14.2.

4-Ethyl-*N*,*N*-diisopropylbenzenesulfonamide (Table 2, 2c). *New compound.* Prepared according to the general procedure using 4-chloro-*N*,*N*-diisopropylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 97% (130.4 mg). White solid. Mp = 63-64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 3.75-3.64 (m, 2H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.26 (d, *J* = 6.8 Hz, 12H), 1.25 (t, *J* = 7.7 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.7, 139.9, 128.3, 127.3, 48.6, 28.8, 22.0, 15.2. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{23}NO_2SNa$ 292.1347 found 292.1344.

1-((4-Ethylphenyl)sulfonyl)pyrrolidine (Table 2, 2d). *New compound.* Prepared according to the general procedure using 1-((4-chlorophenyl)sulfonyl)pyrrolidine (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 95% (113.8 mg). White solid. Mp = 73-74 °C. ^1H NMR (400 MHz,

$CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 3.23 (t, *J* = 6.6 Hz, 4H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.75 (t, *J* = 6.6 Hz, 4H), 1.27 (t, *J* = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.5, 134.0, 128.5, 127.7, 47.9, 28.8, 25.2, 15.1. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_2SNa$ 262.0878 found 262.0876.

4-Ethyl-*N*-methyl-*N*-phenylbenzenesulfonamide (Table 2, 2e). *New compound*. Prepared according to the general procedure using 4-chloro-*N*-methyl-*N*-phenylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 98% (134.5 mg). White solid. Mp = 78-79 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.32-7.21 (m, 5H), 7.12-7.07 (m, 2H), 3.15 (s, 3H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 141.6, 133.6, 128.9, 128.2, 128.0, 127.3, 126.6, 38.1, 28.8, 15.1. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{17}NO_2SNa$ 298.0878 found 298.0876.

***N*-Benzyl-4-ethyl-*N*-methylbenzenesulfonamide (Table 2, 2f).** *New compound.* Prepared according to the general procedure using *N*-benzyl-4-chloro-*N*-methylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 98% (141.0 mg). White solid. Mp = 71-72 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.33-7.24 (m, 5H), 4.12 (s, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 135.7, 134.4, 128.6, 128.6, 128.4, 127.8, 127.6, 54.1, 34.4, 28.8, 15.1. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_2SNa$ 312.1034 found 312.1035.

3-Ethyl-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2g). *New compound.* Prepared according to the general procedure using 3-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 93% (99.4 mg). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 2H), 7.49-7.43 (m, 2H), 2.74 (q, *J* = 7.7 Hz, 2H), 2.71 (s, 6H), 1.27 (t, *J* = 7.6 Hz, 3H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.6, 135.3, 132.5, 129.1, 127.0, 125.2, 38.1, 28.8, 15.5. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{15}NO_2SNa$ 236.0721 found 236.0720.

2-Ethyl-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2h). *New compound.* Prepared according to the general procedure using 2-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and C_2H_5MgCl (2.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 15 h at 0 °C. Yield 50% (53.0 mg). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.31 (td, *J* = 7.9, 1.4 Hz, 1H), 3.04 (q, *J* = 7.5 Hz, 2H), 2.80 (s, 6H), 1.28 (t, *J* = 7.5 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.4, 135.5, 133.0, 131.3, 130.1, 126.0, 37.2, 26.3, 15.8. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{15}NO_2SNa$ 236.0721 found 236.0717.

4-Cyclohexyl-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2i). *New compound.* Prepared according to the general procedure using 4-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and *c*-$C_6H_{11}MgCl$ (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 60 min at 0 °C. Yield 84% (112.4 mg). White solid. Mp = 102-103 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 2.70 (s, 6H), 2.64-2.53 (m, 1H), 1.92-1.82 (m, 4H), 1.81-1.73 (m, 1H), 1.48-1.35 (m, 4H), 1.31-1.21 (m, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.4, 132.7, 128.0, 127.6, 44.6, 38.1, 34.2, 26.8, 26.1. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{21}NO_2SNa$ 290.1191 found 290.1187.

4-Isopropyl-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2j). *New compound.* Prepared according to the general procedure using 4-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and *i*-PrMgBr (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 60 min at 0 °C. Yield 74% (84.3 mg). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 3.05-2.94 (m, 1H), 2.70 (s, 6H), 1.28 (d, *J* = 6.9 Hz, 6H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.2, 132.8, 128.0, 127.2, 38.1, 34.3, 23.8. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{17}NO_2SNa$ 250.0878 found 250.0880.

***N*,*N*-Dimethyl-4-phenethylbenzenesulfonamide (Table 2, 2k).**[30] Prepared according to the general procedure using 4-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and $PhCH_2CH_2MgCl$ (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 60 min at 0 °C. Yield 83% (119.8 mg). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 7.15-7.12 (m, 2H), 3.03-2.97 (m, 2H), 2.96-2.91 (m, 2H), 2.68 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 147.2, 140.9, 132.9, 129.3, 128.6, 128.0, 126.4, 38.1, 37.9, 37.5.

4-(2-(1,3-Dioxan-2-yl)ethyl)-*N*,*N*-dimethylbenzenesulfonamide (Table 2, 2l). *New compound*. Prepared according to the general procedure using 4-chloro-*N*,*N*-dimethylbenzenesulfonamide (0.50 mmol), $Fe(acac)_3$ (5 mol%), NMP (600 mol%), THF (0.15 M), and (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (0.5 M in THF, 3.00 equiv). The reaction mixture was stirred for 15 h at 23 °C. Yield 96% (143.7 mg). White solid. Mp = 112-113 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 4.52 (t, *J* = 5.1 Hz, 1H), 4.12 (dd, *J* = 10.7, 5.0 Hz, 2H), 3.80-3.72 (m, 2H), 2.84-2.78 (m, 2H), 2.70 (s, 6H), 2.15-2.02 (m, 1H), 1.96-1.89 (m, 2H), 1.40-1.33 (m, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 147.4, 132.9, 129.1, 128.0, 101.0, 66.9, 38.0, 36.2, 30.0, 25.8. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{21}NO_4SNa$ 322.1089 found 322.1085.

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

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