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Iron-Catalyzed Arylsulfonylation of Activated Alkenes

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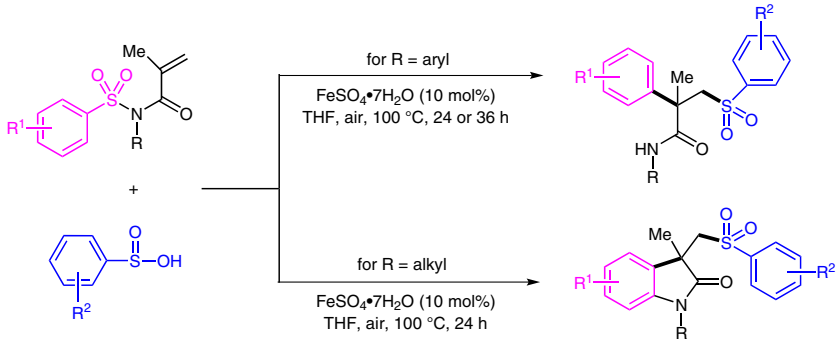

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Abstract An efficient iron-catalyzed arylsulfonylation of activated alkenes has been developed. The protocol uses readily available *N*-acryl-*N*-substituted benzenesulfonamides and arylsulfinic acids as the starting materials, inexpensive iron salt as the catalyst, and environmentally friendly oxygen in air as the oxidant. α-Aryl-β-sulfonyl amides containing a quarternary stereocenter were obtained using *N*-acryl-*N*-alkyl benzenesulfonamides as the substrates.

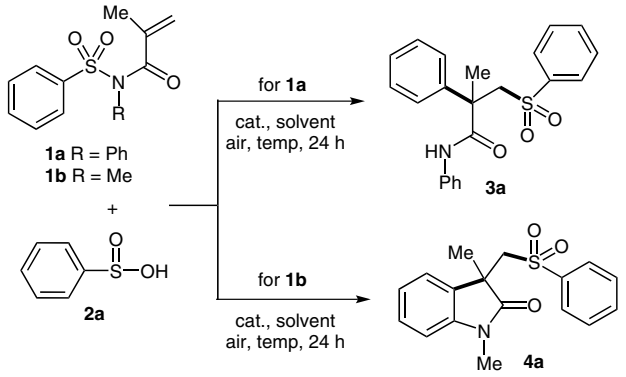
Key words iron, catalysis, arylsulfonylation, alkenes, domino reaction

Difunctionalization of alkenes has attracted wide attention.[1] Various transition-metal-mediated and metal-free diheterofunctionalization of alkenes have been developed including dioxygenation,[2] aminooxygenation,[3] diamination,[4] fluoroamination,[5] aminohalogenation,[6] azidooxygenation,[7] and amino- and oxotrifluoromethylation.[8] Recently, some carbo- and heterofunctionalization[9] and dicarbofunctionalization[10] of alkenes, mainly leading to oxindoles and related heterocycles, have been developed. Very recently, Nevado and co-workers have pioneered aryltrifluoromethylation, arylphosphonylation, and arylazidation of acryl sulfonamides.[11] On the other hand, synthesis of sulfones has received much attention for their wide biological functions.[12] For example, they show antifungal, antibacterial, and antitumor activities[13–15] some of them are applied as the inhibitors of thymidylate synthase[16] or HIV-1 reverse transcriptase.[17] In addition, sulfones are also valuable synthetic intermediates in organic synthesis.[18] Iron is one of the most abundant, cheap, and environmentally friendly metals on earth.[19] Herein, we have developed an iron-catalyzed arylsulfonylation of the activated alkenes with arylsulfinic acids.

As shown in Table 1, reaction of *N*-acryl-*N*-phenyl benzenesulfonamide (**1a**) with benzenesulfinic acid (**2a**) was used as the model to optimize reaction conditions including the catalysts, solvents, and temperature. In order to prevent homocoupling of benzenesulfinic acid (**2a**), **2a** was added in two portions (see note in Table 1). First, ten catalysts (10 mol% relative to amount of **1a**) were tested in acetonitrile at 100 °C in the presence of air (Table 1, entries 1–10), and $FeSO_4{\cdot}7H_2O$ provided the highest yield (Table 1, entry 6). Effect of solvents was investigated (compare entries Table 1, 6, 11–15), and THF gave the best result (Table 1, entry 12). The yields decreased when the reaction temperature was changed (Table 1, entries 16–18). Trace amount of target product was observed in the absence of catalyst (Table 1, entry 19). A lower yield was found under nitrogen atmosphere (Table 1, entry 20). In order to figure out whether other trace amount of transition metals involve this reaction, an extra 5 mol% $Cu(OAc)_2$ or $Pd(OAc)_2$ was added to the reaction system, and the result showed that addition of $Cu(OAc)_2$ or $Pd(OAc)_2$ decreased the yield (Table 1, entries 21 and 22). We applied the optimal conditions (Table 1, entry 12) to substrate **1b**, and a cyclic product **4a** was obtained in 44% yield (Table 1, entry 23).

Under the optimized conditions above, we investigated the scope for the iron-catalyzed synthesis of α-aryl-β-sulfonyl amides **3**.[20] As shown in Scheme 1, the tested *N*-acryl-*N*-aryl benzenesulfonamides provided moderate to good yields. For R^1 and the substituents on Ar of **1**, the substrates containing electron-donating groups provided higher reactivity than those containing electron-withdrawing groups. For example, the substrates containing acetyl and trifluoromethyl on phenyl needed longer reaction time (**3m** and **3n**). For arylsulfinic acids **2**, their reactivity also exhibited the similar electronic effect. The arylsulfonylation of *N*-acryl-*N*-aryl benzenesulfonamides **1** could tolerate some func-

Table 1 Reaction of *N*-Acryl-*N*-phenyl Benzenesulfonamide (**1a**) or *N*-Acryl-*N*-methyl Benzenesulfonamide (**1b**) with Benzenesulfinic Acid (**2a**): Optimization of Conditions[a]



Entry	1	Cat.	Solvent	Temp (°C)	Yield (%)[b]
1	**1a**	$Pd(OAc)_2$	MeCN	100	trace
2	**1a**	$Cu(OAc)_2$	MeCN	100	47
3	**1a**	CuBr	MeCN	100	39
4	**1a**	$AgNO_3$	MeCN	100	55
5	**1a**	$FeCl_2$	MeCN	100	21
6	**1a**	$FeSO_4{\cdot}7H_2O$	MeCN	100	61
7	**1a**	$FeCl_3$	MeCN	100	15
8	**1a**	$Fe(acac)_3$	MeCN	100	51
9	**1a**	$Fe_2(SO_4)_3$	MeCN	100	56
10	**1a**	$Fe(NO_3)_3{\cdot}9H_2O$	MeCN	100	45
11	**1a**	$FeSO_4{\cdot}7H_2O$	dioxane	100	31
12	**1a**	$FeSO_4{\cdot}7H_2O$	THF	100	71
13	**1a**	$FeSO_4{\cdot}7H_2O$	DMSO	100	trace
14	**1a**	$FeSO_4{\cdot}7H_2O$	toluene	100	19
15	**1a**	$FeSO_4{\cdot}7H_2O$	DCE	100	48
16	**1a**	$FeSO_4{\cdot}7H_2O$	THF	60	39
17	**1a**	$FeSO_4{\cdot}7H_2O$	THF	80	68
18	**1a**	$FeSO_4{\cdot}7H_2O$	THF	120	65
19	**1a**	–	THF	100	trace
20	**1a**	$FeSO_4{\cdot}7H_2O$	THF	100	27[c]
21	**1a**	$FeSO_4{\cdot}7H_2O$ + $Cu(OAc)_2$	THF	100	46
22	**1a**	$FeSO_4{\cdot}7H_2O$ + $Pd(OAc)_2$	THF	100	trace
23	**1b**	$FeSO_4{\cdot}7H_2O$	THF	100	44

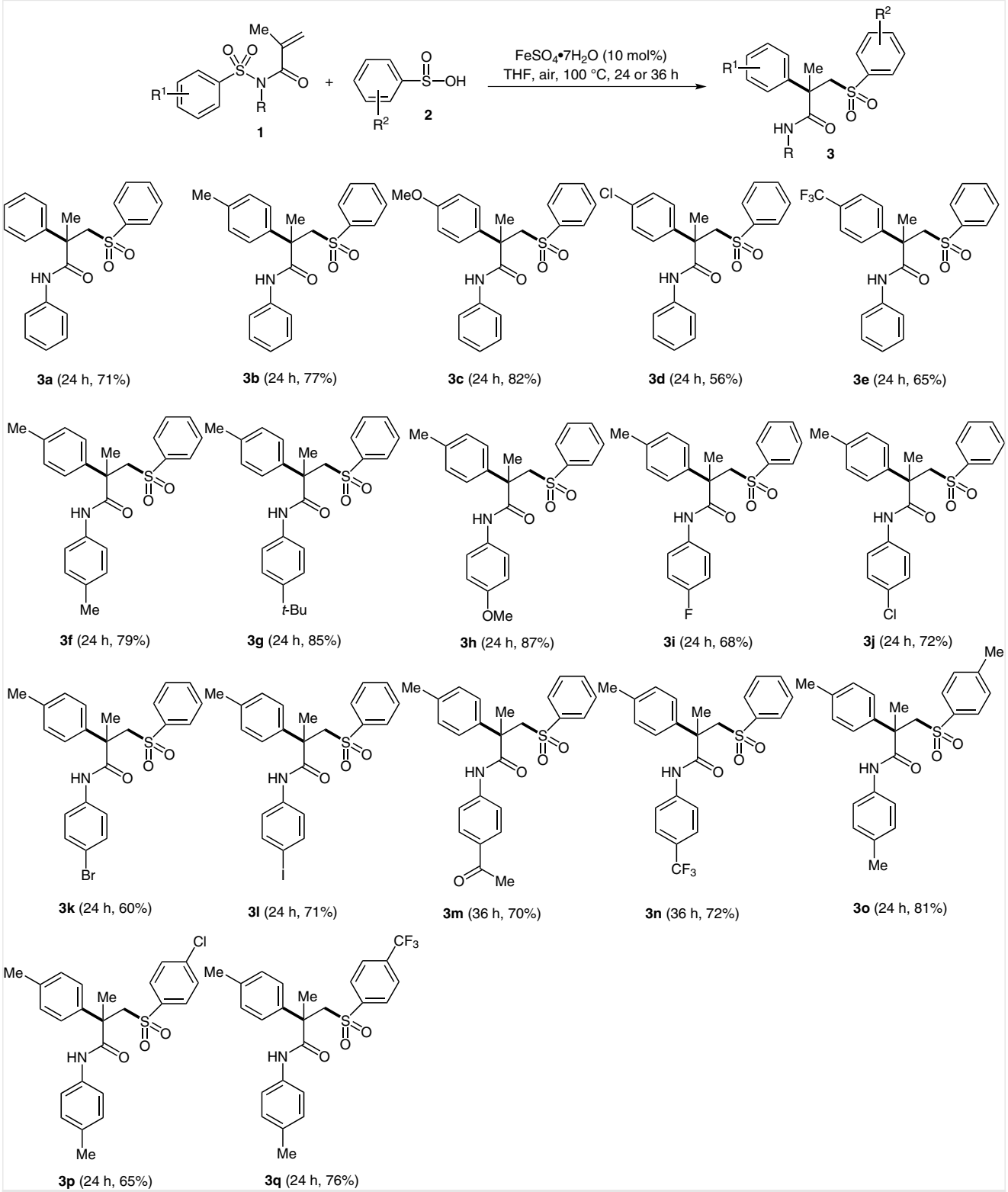
[a] Reaction conditions: air, *N*-acryl-*N*-phenyl benzenesulfonamide (**1a**) or *N*-acryl-*N*-methyl benzenesulfonamide (**1b**, 0.25 mmol), benzenesulfinic acid (**2a**, 0.75 mmol; 0.4 mmol of **2a** was added for the first time; after 12 h, 0.35 mmol of **2a** was added for the second time), catalyst (0.025 mmol), solvent (2.0 mL), 100 °C, 24 h, in a sealed Schlenk tube.
[b] Isolated yield.
[c] Under nitrogen atmosphere.

tional groups including ether (**3c** and **3h**), C–F bond (**3i**), C–Cl bond (**3d**, **3j**, and **3p**), C–Br bond (**3k**), C–I bond (**3l**), CF_3 (**3e**, **3n**, and **3q**), and acetyl (**3m**).

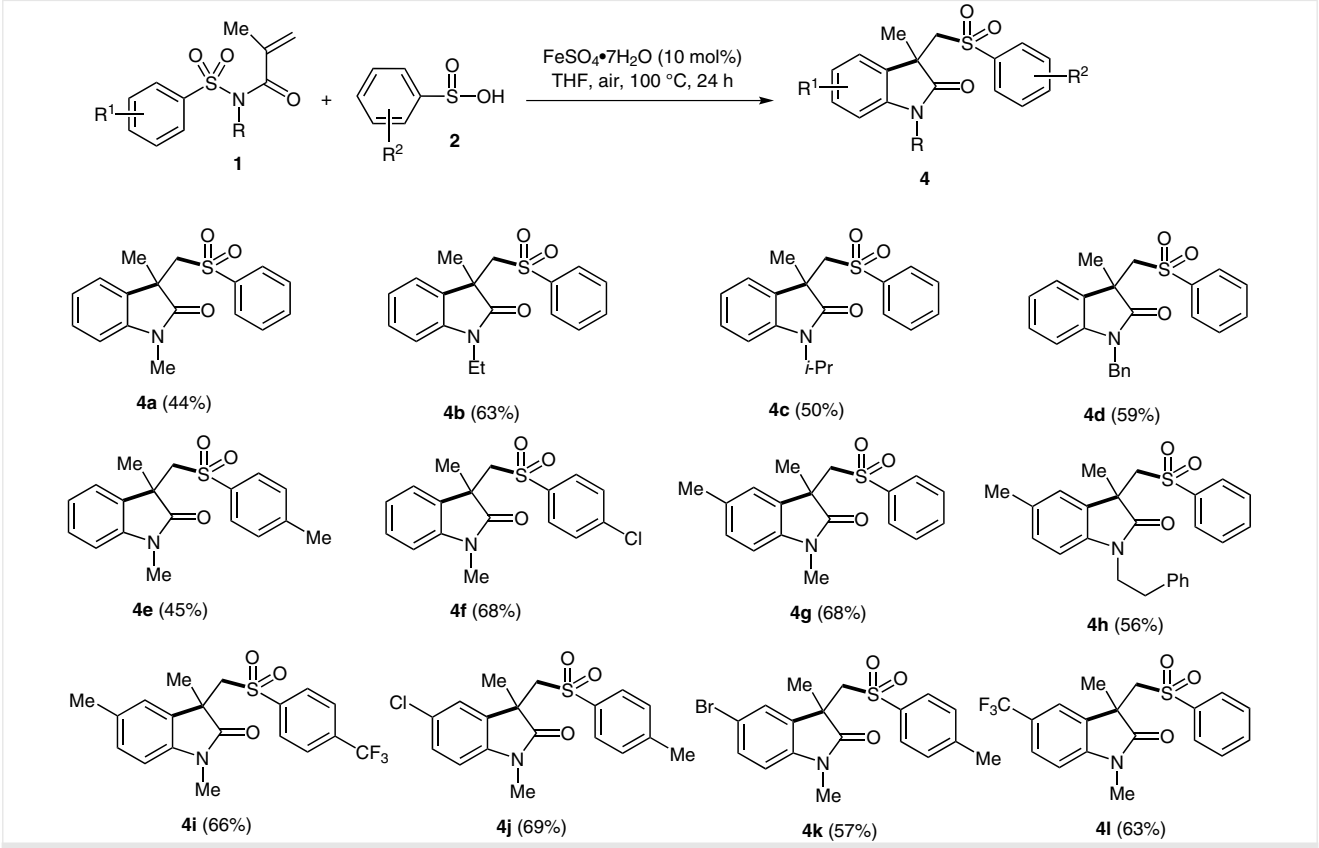
Further, we explored the scope for iron-catalyzed synthesis of sulfonylated oxindoles **4** under the optimized conditions.[20] As shown in Scheme 2, the tested *N*-acryl-*N*-alkyl benzenesulfonamides afforded moderate to good yields. The substrates containing R^1 = H gave lower yields than those containing other *para*-site substituents. For arylsulfinic acids **2**, their electronic effect did not show noticeable difference in reactivity. The arylsulfonylation of *N*-acryl-*N*-alkyl benzenesulfonamides **1** leading to oxindoles **4** also could tolerate some functional groups including C–Cl bond (**4f** and **4j**), C–Br bond (**4k**), and CF_3 (**4i** and **4l**).

Treatment of *N*-acryl-*N*-phenyl benzenesulfonamide (**1a**) or *N*-acryl-*N*-methyl benzenesulfonamide (**1b**) with benzenesulfinic acid (**2a**) was carried out in the presence of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) under the standard conditions, and only trace amount of products were observed (Scheme 3). The result showed that the iron-catalyzed arylsulfonylation could undergo a free-radical intermediate process. Therefore, a possible mechanism on the iron-catalyzed arylsulfonylation is suggested in Scheme 4 according to the results above and the previous reports.[11,21] First, oxidation of Fe(II) salt by oxygen in air gives Fe(III), arylsulfinic acid **2** transfers into the sulfonyl radical **I** in the presence of Fe(III), and treatment of **I** with alkene **2** provides **II**.[21] Cyclization of **II** and following desulfonylation produces nitrogen free radical **IV**.[11] For *N*-acryl-*N*-aryl benzenesulfonamides, reaction of **IV** with **2** affords **3** freeing **I**. For *N*-acryl-*N*-alkyl benzenesulfonamides, electrophilic addition of nitrogen free radical **IV** to phenyl gives carbon free radical **V**, and treatment of **V** with Fe(III) leads to the target product **4** leaving Fe(II) and proton. The possible reasons for the formation of two different products are as follows: the free radical **IV** with R^1 = aryl is more stable than one with R^1 = alkyl, and the former is not favored for electrophilic addition of nitrogen free radical **IV** to phenyl. However, the free radical **IV** with R^1 = alkyl is different, and electrophilic addition of the nitrogen free radical **IV** to phenyl provides **V**.

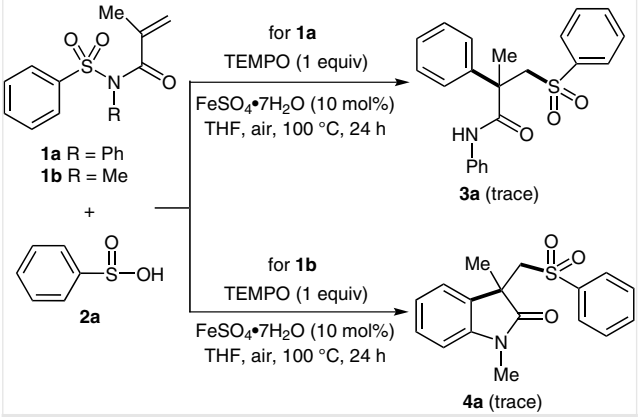
In summary, we have developed a simple and efficient iron-catalyzed arylsulfonylation of *N*-acryl-*N*-substituted benzenesulfonamides with arylsulfinic acids. The protocol uses readily available *N*-acryl-*N*-substituted benzenesulfonamides and arylsulfinic acids as the starting materials, inexpensive iron salt as the catalyst, and environmentally friendly oxygen in air as the oxidant. The procedure underwent sequential sulfonylation and desulfonylation process. For substrates *N*-acryl-*N*-aryl benzenesulfonamides, α-aryl-β-sulfonyl amides containing a quaternary stereocenter were obtained. When *N*-acryl-*N*-alkyl benzenesulfonamides were used as the substrates, the sulfonylated oxindoles were prepared after an extra intramolecular cyclization.



Scheme 1 Iron-catalyzed synthesis of α-aryl-β-sulfonyl amides **3**. *Reagents and conditions*: air, *N*-acryl-*N*-aryl benzenesulfonamide **1** (0.25 mmol), arylsulfinic acid **2** (0.75 mmol; 0.4 mmol of **2** was added for the first time; after 12 h, 0.35 mmol of **2** was added for the second time), 100 °C, 24 or 36 h, in a sealed Schlenk tube; isolated yield.



Scheme 2 Iron-catalyzed synthesis of sulfonylated oxindoles **4**. *Reagents and conditions*: air, *N*-acryl-*N*-alkyl benzenesulfonamide **1** (0.25 mmol), arylsulfinic acid **2** (0.75 mmol; 0.4 mmol of **2** was added for the first time; after 12 h, 0.35 mmol of **2** was added for the second time), 100 °C, 24 h, in a sealed Schlenk tube; isolated yield.



Scheme 3 Treatment of *N*-acryl-*N*-phenyl benzenesulfonamide (**1a**) or *N*-acryl-*N*-methyl benzenesulfonamide (**1b**) with benzenesulfinic acid (**2a**) in the presence of TEMPO under the standard conditions

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379940.

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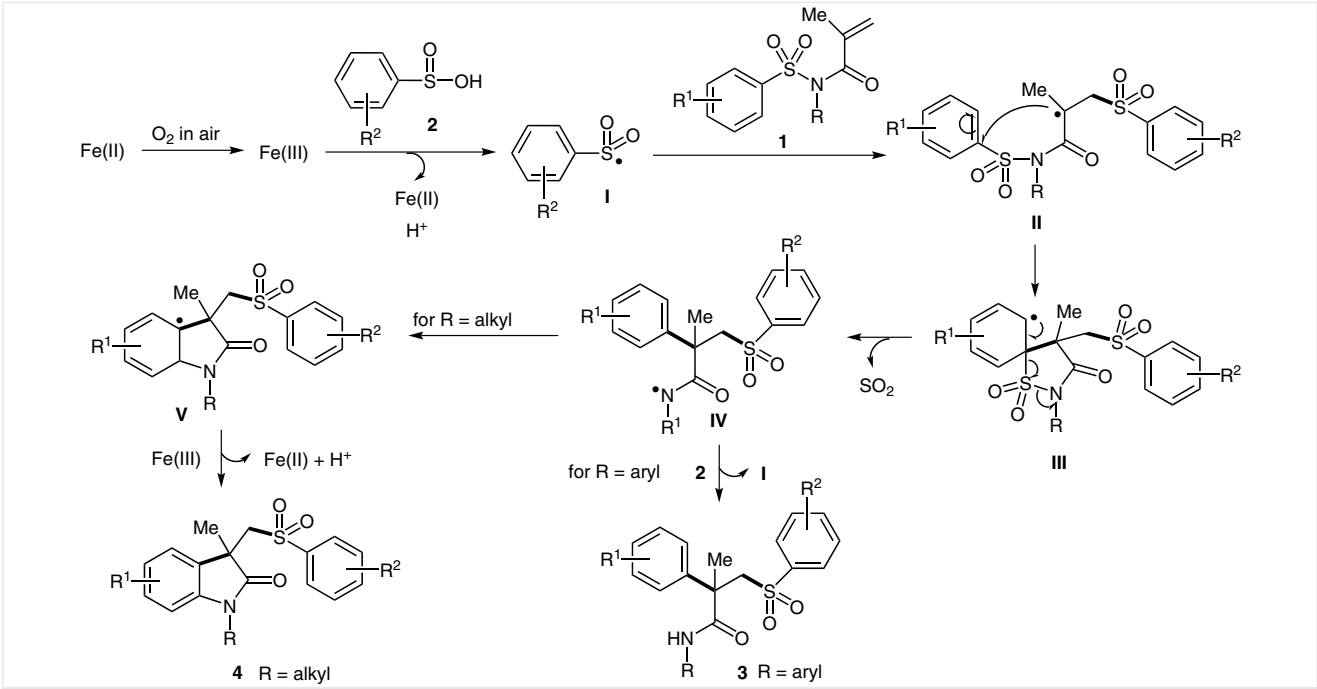

Scheme 4 Possible mechanism for iron-catalyzed arylsulfonylation of *N*-acryl-*N*-substituted benzenesulfonamides with arylsulfinic acids

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(20) **General Procedure for the Synthesis of α-aryl-β-Sulfonyl Amides 3a–q or Sulfonylated Oxindoles 4a–l**

A 25 mL Schlenk tube was charged with a magnetic stirrer and THF (2.5 mL). *N*-Acryl-*N*-aryl benzenesulfonamide (**1**, 0.25 mmol), arylsulfinic acid (**2**, 0.75 mmol; 0.4 mmol of **2** were added for the first time; after 12 h, 0.35 mmol of **2** were added for the second time), and $FeSO_4·7H_2O$ (0.025 mmol, 7 mg) were added to the tube. The tube was sealed, and the mixture was stirred at 100 °C for 24 or 36 h in the presence of air. The resulting mixture was cooled to r.t., the solvent was removed by a rotary evaporator, and the residue was purified by column chromatography on silica gel using PE–EtOAc as the eluent to give the desired target product **3** or **4**. Four representative examples are shown as follows:

2-Methyl-*N*,2-diphenyl-3-(phenylsulfonyl)propanamide (3a)

Eluent: PE–EtOAc (3:1); yield 67 mg (71%); white solid; mp 134–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, 2 H, *J* = 7.3 Hz), 7.52 (t, 1 H, *J* = 7.8 Hz), 7.41–7.25 (m, 11 H), 7.09 (t, 1 H, *J* = 7.3 Hz), 6.91 (s, 1 H), 4.02 (q, 2 H), 2.15 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 141.4, 139.6, 137.6, 133.4, 129.3, 129.2, 128.5, 127.8, 127.3, 124.9, 120.4, 64.3, 50.6, 22.9. ESI-MS: *m/z* = 380.2 $[M + H]^+$, 402.2 $[M + Na]^+$.

2-Methyl-3-(phenylsulfonyl)-2-(*p*-tolyl)-*N*-[4-(trifluoromethyl)phenyl]propanamide (3n)

Eluent: PE–EtOAc (5:1); yield 83 mg (72%); white solid; mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, 2 H, *J* = 8.2 Hz), 7.53–7.46 (m, 5 H), 7.37 (t, 2 H, *J* = 7.3 Hz), 7.21 (s, 1 H), 7.04 (d, 2 H, *J* = 8.2 Hz), 3.97 (q, 2 H), 2.29 (s, 3 H), 2.11 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 141.1, 140.7 138.4, 136.1,

133.3, 130.0, 129.9, 127.7, 126.9, 126.3 (q, *J* = 23.8 Hz), 124.1 (q, *J* = 273.2 Hz), 119.9, 64.3, 50.3, 22.7, 21.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.0. ESI-MS: *m/z* = 462.2 $[M + H]^+$.

1-Isopropyl-3-methyl-3-[(phenylsulfonyl)methyl]indolin-2-one (4c)

Eluent: PE–EtOAc (3:1); yield 43 mg (50%); light yellow solid; mp 181–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 3 H), 7.36 (t, 2 H, *J* = 6.9 Hz), 7.21 (t, 1 H, *J* = 7.8 Hz), 7.04 (d, 1 H, *J* = 8.2 Hz), 6.91 (d, 1 H, *J* = 7.3 Hz), 6.77 (t, 1 H, *J* = 7.8 Hz), 4.73–4.63 (m, 1 H), 3.76 (q, 2 H), 1.55 (d, 3 H, *J* = 6.4 Hz), 1.51 (d, 3 H, *J* = 6.4 Hz), 1.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 142.3, 140.7, 133.4, 130.2, 129.2, 128.5, 127.8, 124.2, 122.1, 110.4, 62.2, 45.6, 44.3, 25.8, 19.6, 19.1. ESI-MS: *m/z* = 344.1 $[M + H]^+$.

1,3,5-Trimethyl-3-({[4-(trifluoromethyl)phenyl]sulfonyl}methyl)indolin-2-one (4i)

Eluent: PE–EtOAc (3:1); yield 66 mg (66%); light yellow solid; mp 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 2 H, *J* = 8.6 Hz), 7.49 (d, 2 H, *J* = 8.3 Hz), 7.05 (d, 1 H, *J* = 7.9 Hz), 6.75 (d, 1 H, *J* = 7.9 Hz), 6.53 (s, 1 H), 3.84 (q, 2 H), 3.19 (s, 3 H), 2.06 (s, 3 H), 1.35 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 143.5, 141.4, 132.2, 129.4, 129.1, 128.6, 125.9 (q, *J* = 3.6 Hz), 124.7, 123.3 (q, *J* = 273.1 Hz), 108.5, 62.2, 45.7, 26.8, 25.6, 20.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.9. ESI-MS: *m/z* = 398.2 $[M + H]^+$.

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