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Electrocatalytic Dehydrogenative Cyclization of 2-Vinylanilides for the Synthesis of Indoles

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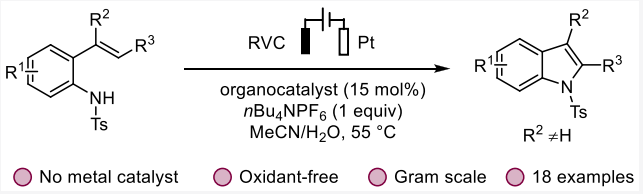
ABSTRACT: Indole is prevalent in bioactive compounds and natural products. The development of efficient and sustainable methods to access this privileged structural scaffold has been a long-standing interest of synthetic chemists. Herein, we report an electrocatalytic method for the synthesis of indoles through dehydrogenative cyclization of 2-vinylanilides. The reactions employ an organic redox catalyst and do not require any external chemical oxidant, providing speedy and efficient access to 3-substituted and 2,3-disubstituted indoles.

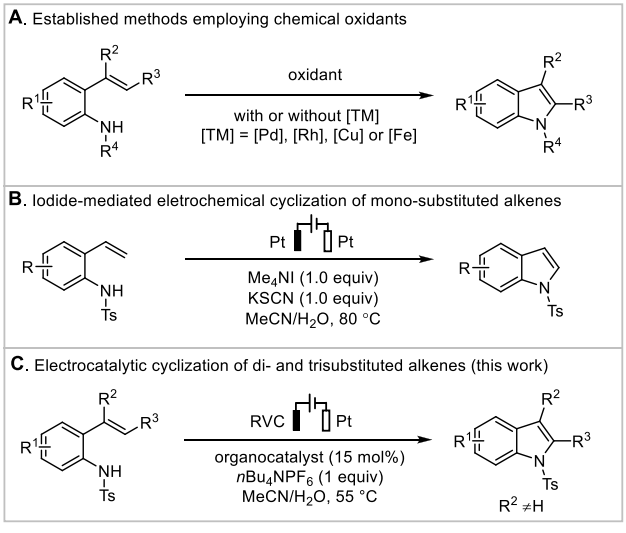


INTRODUCTION

The development of efficient and sustainable synthetic methods to access indoles has been constantly pursued by organic chemists because of the prevalence of the indole moiety in bioactive compounds and natural products.[1,2] Among various methods for the synthesis of indoles, the oxidative cyclization of 2-vinylanilines provides regio-specific access to functionalized indoles from easily available materials. These reactions are commonly achieved using chemical oxidants with[3−7] or without[8−11] transition metal catalysts (Scheme 1A). The use of chemical oxidants in organic solvents not only pose significant safety and environmental concerns, but also produce stoichiometric waste products that may complicate product isolation and interfere with the desired transformation.[12] It is thus highly desirable to develop alternative technologies to reduce the use and manufacture of chemical oxidants.

Organic electrochemistry can achieve oxidation and reduction reactions without using common chemical oxidants or reductants and is enjoying a renaissance.[13−29] Under electrochemical conditions, dehydrogenative transformations can proceed through H_2 evolution, obviating the need for any chemical oxidants. This feature makes electrochemistry a highly attractive tool to address the "oxidant problem".[30] In this context, many electrochemical methods have been developed for the synthesis of heterocycles through dehydrogenative processes.[31−33] Related to this work, Wang and co-workers have reported iodide mediated electrochemical cyclization of 2-vinylanilides for the synthesis of indoles that bear no substituents at positions 2 and 3 (Scheme 1B).[34] With our continued interests in electrochemically driven radical reactions,[35−39] we report herein an electrocatalytic method for the synthesis of 3-substituted and 2,3-disubstituted indoles (Scheme 1C). The reactions employ an organic redox catalyst and provides metal- and oxidant-free access to functionalized indoles.

Scheme 1. Synthesis of Indoles via Oxidative Cyclization of 2-Vinylanilines



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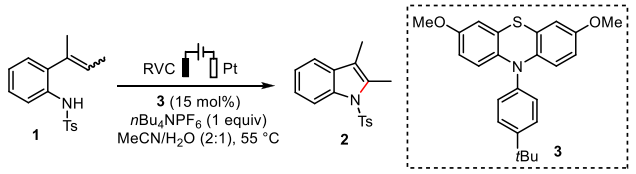
RESULTS AND DISCUSSION

Our studies began by optimizing the electrolysis conditions for the cyclization of sulfonamide **1** (Table 1). The electrolysis was carried out with a Schlenk tube equipped with a reticulated vitreous carbon anode (RVC) and a Pt plate cathode. These experiments revealed that the desired 2,3-disubstituted indole **2** could be isolated in 83% yield when the reaction was conducted in MeCN/H_2O (2:1) at 55 °C employing phenothiazine **3** as the molecular catalyst (entry 1). Phenothiazine-based redox catalysts had been previously studied by us and others for the electrocatalytic generation of carbon- and nitrogen-centered radicals.[40,41] Electricity (entry 2) and catalyst **3** (entry 3) were critical in obtaining a synthetically useful yield of **2**. Conducting the reaction at 45 °C (entry 4) or rt (entry 5) resulted in reduced yields of 58% and 25%, respectively. Ferrocene was much less effective than **3** in promoting the formation of **2** despite its extensive application in electrocatalytic generation of nitrogen- and carbon-centered radicals (entry 6).[42−46] The yield of **2** was also diminished by changing the solvent to either pure MeCN (entry 7) or MeCN/H_2O (1:1) (entry 8), using a higher current of 10 mA to increase productivity (entry 9), or addition of Cs2CO3 as a base (entry 10). Scaling up the electrochemical reaction by 40-fold to 8.0 mmol produced indole **2** in 71% yield (entry 11).

Table 1. Optimization of Reaction Conditions[a]

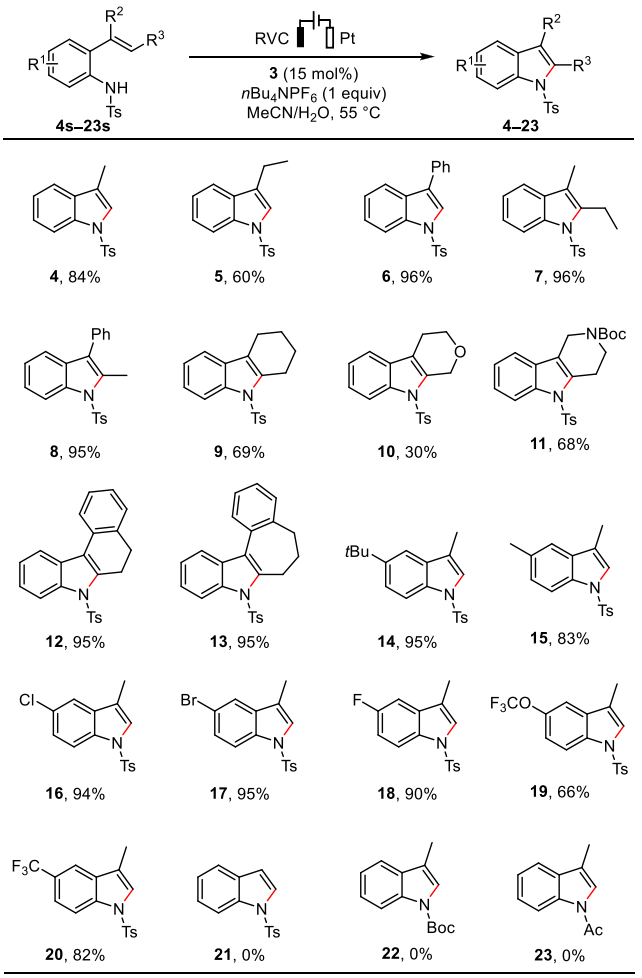


entry	deviation from standard conditions	yield, %[b]
1	none	83[c]
2	no electricity	0 (90)
3	no catalyst **3**	12 (41)
4	45 °C	58
5	rt	25 (8)
6	ferrocene as catalyst	34 (32)
7	MeCN as solvent	42 (23)
8	MeCN/H_2O (1:1) as solvent	42 (14)
9[d]	10 mA	25 (47)
10	Cs_2CO_3 (0.1 equiv) as base	58
11[e]	2.4 g (8.0 mmol) of **1**	71

[a]Reaction conditions: RVC anode (100 PPI), Pt cathode, **1** (0.2 mmol), solvent (6 mL), argon, 7.5 mA, 1.7 h (2.3 F mol^{-1}). [b]Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Recovery of unreacted **1** shown within parentheses. [c]Yield of isolated product. [d]Reaction for 1.3 h. [e]Reaction with a constant current of 300 mA for 1.8 h.

The scope of the electrosynthesis of indoles was probed by changing the substituents on the alkene and the benzene ring (Scheme 2). Terminal alkenes bearing an alkyl or phenyl group at the R^2 position cyclized smoothly to generate 3-substituted indoles (**4**−**6**). Trisubstituted alkenes, both acyclic (**7**, **8**) and cyclic ones (**9**−**13**), all reacted successfully to afford 2,3-disubstituted indoles. The benzene ring tolerated substituents of various electronic properties such as alkyl groups (**14**, **15**), halides (**16**−**18**), CF_3O (**19**), and CF_3 (**20**). Limitations of the method included the failure in the cyclization of monosubstituted alkenes (**21**) and anilides bearing a Boc (**22**) or Ac (**23**) group on the aniline nitrogen atom. For the latter two cases, most of the starting anilides remained unreacted.

Scheme 2. Scope of the Electrocatalytic Synthesis of Indoles[a]



[a]Reactions were conducted at 0.2 mmol scale. Boc = *tert*-butyloxycarbonyl. Ac = acetyl.

The catalytic role of phenothiazine **3** in oxidizing the anilide substrates was confirmed by observing a catalytic current when its voltammogram was taken in the presence of anilide **1** and a base, Cs_2CO_3 (Scheme 3A). The voltammogram of **3** did not change in the presence of **1** without a base. These results suggested that the deprotonation of the anilide was critical in its oxidation by the catalyst.[40,42] This observation was consistent with the dramatic decrease in oxidation potential of **1** from its neutral form ($E_{p/2}$ = 1.41 V) to its conjugate base ($E_{p/2}$ = 0.49 V vs SCE). The oxidation of the latter occurred at a potential close to that of the catalyst **3** ($E_{p/2}$ = 0.37 V vs SCE).

Based on the results of this study and our previous work,[40,42] a possible mechanism was proposed for electrocatalytic synthesis of indoles (Scheme 3B). The electrochemical processes commenced with the anodic oxidation of the catalyst **3** to its radical cation $\mathbf{3}^{\cdot+}$ and cathodic reduction of solvent H_2O to generate H_2 and HO^-. The cathodically generated HO^- deprotonates the anilide **1** [pK_a (TsNHPh) = 8.46 in H_2O] to its conjugate base **24**, which is oxidized by radical

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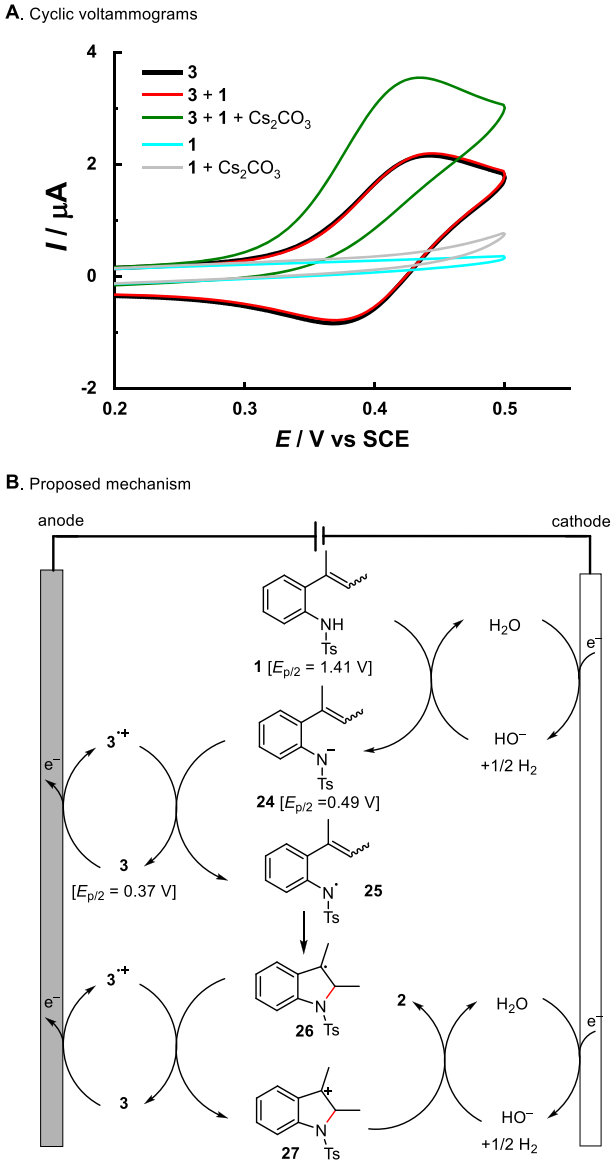
Scheme 3. Mechanistic Studies and Proposal



cation $3^{\cdot+}$ to form radical **25**. Cyclization of **25** followed by further oxidation by $3^{\cdot+}$ and deprotonation affords the final indole product **2**. The failure to form **21** was probably caused by the more difficult radical cyclization to form a secondary C-radical. Although no base is added for the preparative electrolysis, the cathodic reduction can generate continuously the requisite base to promote the oxidation of the substrate, showcasing the unique features of electrochemistry.

In summary, we have developed an electrocatalytic method to accomplish the cyclization of 2-vinylanilides for the synthesis of functionalized indoles. The reactions employ an organic redox catalyst and proceed through H_2 evolution without using any external chemical oxidants. The reactions provide speedy and scalable access to 3-substituted and 2,3-disubstituted indoles.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were commercially available and used as received. Flash column chromatography was performed with silica gel (200−300 mesh). NMR spectra were recorded on Bruker AV-400, Bruker AV-500, or Bruker AV-600 instruments. Data were reported as chemical shifts in ppm relative to TMS (0.00 ppm) for ^{1}H and $CDCl_3$ (77.2 ppm) for ^{13}C. High-resolution mass spectra (ESI) were recorded on an Agilent 6500 series Q-TOF. Sulfonamide substrates **1**,[47] **4s**,[47] **6s**,[11] **8s**,[48] **9s**,[49] **15s**,[50] **16s**,[51] **17s**,[52] **18s**,[51] **21s**,[11] **22s**,[53] **23s**[54] are known compounds and prepared according the reported procedures.

General Procedures for the Electrolysis. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with the sulfonamide substrate (0.2 mmol, 1 equiv), **3** (0.03 mmol, 15 mol %), and nBu$_4$NPF$_6$ (0.2 mmol, 1 equiv). The Schlenk tube was equipped with a reticulated vitreous carbon (100 PPI) anode (0.6 cm × 1.0 cm × 1.2 cm) and a platinum plate (1 cm × 1 cm) cathode (Figure S1). The resulting mixture was sealed and degassed via vacuum evacuation and backfilled with argon three times. MeCN (4 mL) and H_2O (2 mL) were added. The constant current (7.5 mA) electrolysis was carried out at 55 °C (oil bath temperature) until complete consumption of the substrate (monitored by TLC or ^{1}H NMR). The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/petroleum ether to give the product.

Procedure for Gram Scale Synthesis of 2. A beaker-type cell was charged with **1** (2.4 g, 8.0 mmol), **3** (0.48 g, 1.2 mmol), and nBu$_4$NPF$_6$ (3.2 g, 8.2 mmol). The flask was equipped with a rubber stopper, two pieces of reticulated vitreous carbon (100 PPI, 1.2 cm × 4.0 cm × 6.0 cm) as anode, and a platinum plate (5.0 cm × 5.0 cm) cathode (Figure S2). The flask was flushed with argon. MeCN (160 mL) and H_2O (80 mL) were added. The constant current (300 mA) electrolysis was carried out at 55 °C (oil bath temperature) under argon for 1.8 h (2.5 F mol^{-1}). The reaction mixture was concentrated under reduced pressure and then extracted by CH_2Cl_2. The combined organic solution was concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/petroleum ether to give **2** in 71% yield (1.7 g) of 2,3-dimethyl-1-tosyl-1*H*-indole (**2**).[8] Pale blue solid (51 mg, 83%) (petroleum ether/EtOAc = 15:1), electricity = 2.3 F mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.30−7.17 (m, 2H), 7.14 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.29 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.5, 136.6, 136.4, 132.4, 131.4, 129.9, 126.4, 124.0, 123.3, 118.4, 116.1, 114.7, 21.6, 12.8, 9.0.

3-Methyl-1-tosyl-1*H*-indole (4).[8] White solid (50 mg, 84%) (petroleum ether/EtOAc = 25:1), electricity = 2.3 F mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.26−7.20 (m, 2H), 7.19−7.13 (m, 1H), 7.09 (d, J = 8.1 Hz, 2H), 2.22 (s, 3H), 2.16 (d, J = 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.8, 135.6, 135.4, 131.9, 129.9, 126.9, 124.7, 123.2, 123.1, 119.5, 118.7, 113.8, 21.7, 9.8.

3-Ethyl-1-tosyl-1*H*-indole (5). White solid (37 mg, 60%) (petroleum ether/EtOAc = 15:1), electricity = 2.3 F mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.32−7.26 (m, 2H), 7.24−7.15 (m, 3H), 2.67 (qd, J = 7.5, 1.3 Hz, 2H), 2.30 (s, 3H), 1.30 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.7, 135.5, 131.2, 129.9, 126.8, 125.4, 124.7, 123.0, 122.1, 119.5, 113.8, 21.6, 18.3, 13.4. IR (neat, cm^{-1}): 2965, 1596, 1447, 1364, 1170, 664, 576. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{17}H_{17}NO_2SNa$: 322.0872. Found: 322.0872.

3-Phenyl-1-tosyl-1*H*-indole (6).[8] White solid (71 mg, 96%) (petroleum ether/EtOAc = 20:1), electricity = 2.4 F mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.3 Hz, 1H), 7.82−7.72 (m, 3H), 7.70 (d, J = 1.8 Hz, 1H), 7.61−7.56 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37−7.31 (m, 2H), 7.29−7.23 (m, 1H), 7.17 (d, J = 8.1 Hz, 2H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.1, 135.7, 135.4, 133.2, 130.0, 129.4, 129.0, 128.0, 127.7, 127.0, 125.0, 124.1, 123.7, 123.1, 120.6, 114.0, 21.7.

2-Ethyl-3-methyl-1-tosyl-1*H*-indole (7).[55] Pale blue oil (62 mg, 96%) (petroleum ether/EtOAc = 20:1), electricity = 2.3 F mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21−8.13 (m, 1H), 7.60−7.52 (m, 2H), 7.37−7.33 (m, 1H), 7.27−7.19 (m, 2H), 7.11 (d, J = 8.0 Hz, 2H),

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3.00 (q, J = 7.4 Hz, 2H), 2.28 (s, 3H), 2.13 (s, 3H), 1.26 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.4, 139.0, 136.7, 136.4, 131.7, 129.8, 126.3, 124.1, 123.4, 118.4, 116.2, 115.2, 21.6, 19.9, 15.1, 8.9.

2-Methyl-3-phenyl-1-tosyl-1*H*-indole (8).[8] White solid (73 mg, 95%) (petroleum ether/EtOAc = 20:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.48−7.36 (m, 3H), 7.37−7.25 (m, 4H), 7.25−7.16 (m, 3H), 2.59 (s, 3H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.8, 136.5, 136.4, 133.2 (2C), 130.2, 130.1, 130.0, 128.7, 127.4, 126.5, 124.3, 123.6, 122.7, 119.3, 114.6, 21.7, 13.6.

9-Tosyl-2,3,4,9-tetrahydro-1*H*-carbazole (9).[8] Colorless oil (45 mg, 69%) (petroleum ether/EtOAc = 30:1), electricity = 2.4 F mol^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.27−7.22 (m, 1H), 7.22−7.18 (m, 1H), 7.15 (d, J = 8.1 Hz, 2H), 3.00 (tt, J = 6.5, 2.0 Hz, 2H), 2.57 (tt, J = 6.0, 2.0 Hz, 2H), 2.30 (s, 3H), 1.90−1.83 (m, 2H), 1.80−1.73 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.5, 136.5, 136.4, 135.5, 130.5, 129.9, 126.5, 124.0, 123.3, 118.7, 118.1, 114.5, 24.8, 23.4, 22.2, 21.6, 21.2.

9-Tosyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (10). White solid (20 mg, 30%) (petroleum ether/EtOAc = 10:1), electricity = 2.6 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.40−7.36 (m, 1H), 7.33−7.27 (m, 1H), 7.26−7.21 (m, 1H), 7.19 (d, J = 8.1 Hz, 2H), 5.05 (t, J = 2.0 Hz, 2H), 3.96 (t, J = 5.5 Hz, 2H), 2.73 (tt, J = 5.5, 2.1 Hz, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.1, 135.9, 135.6, 132.7, 130.1, 129.9, 126.6, 124.6, 123.6, 118.5, 116.2, 114.2, 65.0, 64.6, 22.3, 21.7. IR (neat, cm^{-1}): 2922, 1655, 1451, 1364, 1173, 587. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{18}H_{17}NO_3SNa$: 350.0821. Found: 350.0821.

***tert*-Butyl 5-Tosyl-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (11).** Colorless oil (59 mg, 68%) (petroleum ether/EtOAc = 5:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.34−7.27 (m, 2H), 7.25−7.20 (m, 1H), 7.18 (d, J = 8.1 Hz, 2H), 4.51 (s, 2H), 3.75 (t, J = 5.8 Hz, 2H), 3.13 (t, J = 5.9 Hz, 2H), 2.32 (s, 3H), 1.49 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 155.0, 145.0, 136.4, 136.0, 130.0, 126.5, 124.6, 123.6, 118.0, 114.6, 80.3, 28.6, 21.7. IR (neat, cm^{-1}): 2975, 1698, 1597, 1367, 1172, 661, 571. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{23}H_{26}N_2O_4SNa$: 449.1505. Found: 449.1505.

7-Tosyl-6,7-dihydro-5*H*-benzo[*c*]carbazole (12).[56] White solid (74 mg, 95%) (petroleum ether/EtOAc = 15:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33−8.25 (m, 1H), 7.99−7.91 (m, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.36−7.20 (m, 4H), 7.18−7.09 (m, 3H), 3.33 (t, J = 7.8 Hz, 2H), 2.98 (t, J = 7.8 Hz, 2H), 2.25 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.0, 137.7, 137.3, 135.9, 134.7, 131.7, 130.0, 128.0, 127.4, 126.9, 126.5, 126.4, 124.2, 124.1, 123.4, 120.0, 118.1, 115.1, 29.5, 22.7, 21.6.

8-Tosyl-5,6,7,8-tetrahydrobenzo[3,4]cyclohepta[1,2-*b*]indole (13). Pale blue oil (75 mg, 95%) (petroleum ether/EtOAc = 20:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.3 Hz, 1H), 7.72−7.64 (m, 3H), 7.58 (d, J = 7.5 Hz, 1H), 7.37−7.20 (m, 5H), 7.17 (d, J = 8.1 Hz, 2H), 3.06 (t, J = 7.1 Hz, 2H), 2.48 (t, J = 6.9 Hz, 2H), 2.30 (s, 3H), 2.25 (p, J = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.9, 141.2, 138.1, 137.0, 136.3, 133.8, 129.9, 129.7, 128.6, 128.1, 127.1, 126.4 (2C), 124.2, 123.8, 121.5, 119.0, 115.2, 34.4, 32.4, 23.6, 21.6. IR (neat, cm^{-1}): 2928, 1597, 1447, 1367, 1188, 1141, 577. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{24}H_{21}NO_2SNa$: 410.1185. Found: 410.1184.

5-(*tert*-Butyl)-3-methyl-1-tosyl-1*H*-indole (14). Yellow oil (71 mg, 95%) (petroleum ether/EtOAc = 20:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 1.9 Hz, 1H), 7.37 (dd, J = 8.8, 1.9 Hz, 1H), 7.26 (s, 1H), 7.15 (d, J = 8.1 Hz, 2H), 2.28 (s, 3H), 2.23 (d, J = 1.3 Hz, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 146.2, 144.6, 135.7, 133.4, 131.6, 129.8, 126.9, 123.1, 122.7, 118.8, 115.5, 113.2, 34.8, 31.8, 21.6, 9.8. IR (neat, cm^{-1}): 2921, 1596, 1452, 1368, 1171, 671. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{20}H_{23}NO_2SNa$: 364.1342. Found: 364.1341.

3,5-Dimethyl-1-tosyl-1*H*-indole (15).[57] Colorless oil (51 mg, 83%) (petroleum ether/EtOAc = 30:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 7.7 Hz, 2H), 7.24 (s, 1H), 7.20 (s, 1H), 7.17−7.07 (m, 3H), 2.39 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.6, 135.6, 133.7, 132.7, 132.2, 129.8, 126.8, 126.0, 123.3, 119.4, 118.6, 113.5, 21.6, 21.4, 9.8.

5-Chloro-3-methyl-1-tosyl-1*H*-indole (16).[8] Colorless oil (62 mg, 94%) (petroleum ether/EtOAc = 25:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 2.1 Hz, 1H), 7.32−7.30 (m, 1H), 7.24 (dd, J = 8.8, 2.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 2H), 2.30 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.1, 135.3, 133.7, 133.2, 130.0, 129.1, 126.8, 124.9, 124.6, 119.3, 118.2, 114.9, 21.7, 9.7.

5-Bromo-3-methyl-1-tosyl-1*H*-indole (17).[57] Pale blue solid (76 mg, 95%) (petroleum ether/EtOAc = 25:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 1.9 Hz, 1H), 7.38 (dd, J = 8.8, 1.9 Hz, 1H), 7.31−7.28 (m, 1H), 7.18 (d, J = 8.2 Hz, 2H), 2.30 (s, 3H), 2.17 (d, J = 1.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.1, 135.2, 134.1, 133.7, 130.0, 127.5, 126.8, 124.4, 122.4, 118.1, 116.7, 115.2, 21.7, 9.7.

5-Fluoro-3-methyl-1-tosyl-1*H*-indole (18).[8] White solid (59 mg, 90%) (petroleum ether/EtOAc = 25:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J = 9.0, 4.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.06 (dd, J = 8.8, 2.5 Hz, 1H), 7.01 (td, J = 9.0, 2.6 Hz, 1H), 2.30 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.7 (d, J_{C-F} = 240.3 Hz), 145.0, 135.3, 133.0 (d, J_{C-F} = 9.3 Hz), 131.7, 123.0, 126.9, 124.9, 118.6 (d, J_{C-F} = 4.1 Hz), 114.8 (d, J_{C-F} = 9.3 Hz), 112.6 (d, J_{C-F} = 25.5 Hz), 105.2 (d, J_{C-F} = 23.8 Hz), 21.7, 9.8.

3-Methyl-1-tosyl-5-(trifluoromethoxy)-1*H*-indole (19). White solid (51 mg, 66%) (petroleum ether/EtOAc = 40:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.39−7.35 (m, 1H), 7.29−7.26 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.18−7.14 (m, 1H), 2.33 (s, 3H), 2.21 (d, J = 1.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.4 (q, J_{C-F} = 1.9 Hz), 145.2, 135.3, 133.5, 132.7, 130.1, 126.9, 125.0, 120.8 (q, J_{C-F} = 256.5 Hz). 118.5, 118.2, 114.7, 112.1, 21.7, 9.7. ^{19}F NMR (471 MHz, $CDCl_3$): δ −58.01. IR (neat, cm^{-1}): 2924, 1597, 1452, 1372, 1256, 1171, 587. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{17}H_{14}F_3NO_3SNa$: 392.0539. Found: 392.0538.

3-Methyl-1-tosyl-5-(trifluoromethyl)-1*H*-indole (20).[57] White solid (58 mg, 82%) (petroleum ether/EtOAc = 30:1), electricity = 2.3 F mol^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.6 Hz, 1H), 7.79−7.70 (m, 3H), 7.54 (d, J = 8.8 Hz, 1H), 7.42 (s, 1H), 7.21 (d, J = 7.7 Hz, 2H), 2.32 (s, 3H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.4, 136.8, 135.2, 131.6, 130.1, 126.9, 125.5 (q, J_{C-F} = 32.3 Hz), 124.8, 124.8 (q, J_{C-F} = 277.2 Hz), 121.5 (q, J_{C-F} = 3.6 Hz), 118.7, 117.2 (q, J_{C-F} = 4.2 Hz), 114.0, 21.7, 9.7.

***N*-(2-(But-1-en-2-yl)phenyl)-4-methylbenzenesulfonamide (5s).** To a solution of 2-(but-1-en-2-yl)aniline (0.68 g, 4.6 mmol) and pyridine (1.2 mL, 15 mmol) in CH_2Cl_2 (30 mL) was added TsCl (1.0 g, 5.2 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred for 12 h. The reaction was quenched with H_2O and extracted by CH_2Cl_2. The combined organic phase was washed with brine and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **5s** as a white solid (0.60 g, 44%) (petroleum ether/EtOAc = 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.68−7.60 (m, 3H), 7.24−7.18 (m, 3H), 7.03 (t, J = 7.6 Hz, 1H), 7.00−6.94 (m, 2H), 5.23 (s, 1H), 4.68 (s, 1H), 2.36 (s, 3H), 1.96 (q, J = 7.5 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.8, 144.0, 136.4, 134.1, 133.4, 129.7, 128.4, 128.1, 127.3, 124.2, 120.0, 115.1, 30.7, 21.6, 12.0. IR (neat, cm^{-1}): 3260, 2921, 1743, 1488, 1339, 1167, 670, 569. HRMS (ESI), m/z: (M + Na)$^+$ Calcd for $C_{17}H_{19}NO_2SNa$: 324.1029. Found: 324.1028.

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4-Methyl-*N*-(2-(pent-2-en-2-yl)phenyl)benzenesulfonamide (7s). To a solution of 2-(pent-2-en-2-yl)aniline (0.72 g, 4.1 mmol) and pyridine (1.0 mL, 12 mmol) in CH_2Cl_2 (30 mL) was added TsCl (0.91 g, 4.8 mmol) at 0 °C. The reaction mixture was warmed up to rt slowly and stirred for 12 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic phase was washed with brine and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **7s** as yellow oil (0.63 g, 49%) (petroleum ether/EtOAc = 20:1). *Z*/*E* = 2.5/1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75−7.60 (m, 4.2H), 7.26−7.17 (m, 4.2H), 7.08−7.01 (m, 1.4H), 7.00−6.92 (m, 1.8H), 6.78 (s, 1H), 5.62 (tq, *J* = 7.5, 1.6 Hz, 1H), 5.05 (tq, *J* = 7.1, 1.5 Hz, 0.4H), 2.41−2.32 (m, 4.2H), 2.13 (p, *J* = 7.2 Hz, 0.8H), 1.73−1.53 (m, 6.2H), 1.02 (t, *J* = 7.5 Hz, 1.2H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.9, 136.5, 133.4, 133.3, 132.1, 131.3, 129.6, 128.6, 127.8, 127.2, 124.2, 118.5, 24.8, 22.3, 21.5, 13.9. IR (neat, cm^{-1}): 3276, 2963, 1599, 1490, 1338, 1169, 664, 560. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{18}H_{21}NO_2SNa$: 338.1185. Found: 338.1185.

***N*-(2-(3,6-Dihydro-2*H*-pyran-4-yl)phenyl)-4-methylbenzenesulfonamide (10s).** To a mixture of 4-methyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (1.1 g, 2.9 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (50 mg, 0.061 mmol) in 15 mL of 1,4-dioxane was added 5 mL of a 3 N solution of NaOH followed by 3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (1.0 g, 4.3 mmol). The resulting mixture was heated to 80 °C. After 12 h, the mixture was cooled to rt and filtered through a pad of Celite. The filtrate was diluted with saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2. The combined organic phase was washed with brine and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **10s** as a white solid (0.52 g, 52%) (petroleum ether/EtOAc = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−7.59 (m, 3H), 7.26−7.19 (m, 3H), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H), 7.02−6.96 (m, 2H), 5.42−5.37 (m, 1H), 4.19 (q, *J* = 2.8 Hz, 2H), 3.78 (t, *J* = 5.4 Hz, 2H), 2.36 (s, 3H), 1.92−1.86 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.0, 136.5, 134.2, 133.2, 132.7, 129.7, 128.5, 128.2, 127.3, 127.2, 124.9, 121.6, 65.2, 64.2, 29.8, 21.6. IR (neat, cm^{-1}): 3269, 2924, 1596, 1488, 1336, 1163, 542. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{18}H_{19}NO_3SNa$: 352.0978. Found: 352.0978.

***tert*-Butyl 5-(2-((4-methylphenyl)sulfonamido)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (11s).** To a mixture of *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (1.0 g, 2.7 mmol), *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.2 g, 3.9 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.14 mmol) and K_2CO_3 (1.1 g, 8.0 mmol) was added a 1:1:2 (v/v/v) mixture of EtOH/H_2O/toluene (20 mL). The resulting mixture was heated to 80 °C. After 12 h, water was added and the mixture was extracted with ethyl acetate. The combined organic solution was evaporated under reduced pressure. The residue was chromatographed through silica gel to afford **11s** as a white solid (0.36 g, 31%) (petroleum ether/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.56 (m, 3H), 7.27−7.19 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.40 (tt, *J* = 4.0, 2.0 Hz, 1H), 3.68−3.44 (m, 4H), 2.37 (s, 3H), 2.21 (tq, *J* = 5.8, 2.9 Hz, 2H), 1.50 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 155.1, 144.2, 136.4, 133.9, 132.2, 129.8, 129.2, 128.7, 127.3, 124.9, 80.3, 28.6, 25.2, 21.7. IR (neat, cm^{-1}): 3275, 2927, 1694, 1598, 1416, 1166, 664, 572. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{23}H_{28}N_2O_4SNa$: 451.1662. Found: 451.1660.

***N*-(2-(3,4-Dihydronaphthalen-1-yl)phenyl)-4-methylbenzenesulfonamide (12s).** To a mixture of 4-methyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (1.2 g, 3.2 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (49 mg, 0.060 mmol) in 15 mL of 1,4-dioxane was added 5 mL of a 3 N solution of NaOH followed by 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (1.1 g, 4.0 mmol). The resulting mixture was heated to 80 °C. After 12 h, the mixture was cooled to rt and filtered through a pad of Celite. The filtrate was diluted with saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2. The combined organic phase was washed with brine and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **12s** as yellow solid (0.46 g, 38%) (petroleum ether/EtOAc = 25:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.33 (td, *J* = 7.8, 1.7 Hz, 1H), 7.19−7.05 (m, 5H), 7.03 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.90 (td, *J* = 7.7, 2.1 Hz, 1H), 6.45 (s, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 5.45 (t, *J* = 4.5 Hz, 1H), 2.81 (t, *J* = 8.1 Hz, 2H), 2.35 (s, 3H), 2.33−2.25 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.7, 136.1, 135.6, 134.9, 134.5, 133.4, 132.3, 130.7, 130.3, 129.5, 128.6, 128.0, 127.9, 127.3, 126.9, 125.2, 124.4, 121.8, 27.7, 23.3, 21.6. IR (neat, cm^{-1}): 3330, 2933, 1598, 1488, 1166, 671, 564. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{23}H_{21}NO_2SNa$: 398.1185. Found: 398.1183.

***N*-(2-(6,7-Dihydro-5*H*-benzo[7]annulen-9-yl)phenyl)-4-methylbenzenesulfonamide (13s).** To a mixture of 4-methyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-benzenesulfonamide (0.93 g, 2.5 mmol), 6,7-dihydro-5*H*-benzo[7]-annulen-9-yl trifluoromethanesulfonate (1.2 g, 4.1 mmol), $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol), and K_2CO_3 (1.1 g, 8.0 mmol) was added a 1:1:2 (v/v/v) mixture of EtOH/H_2O/toluene (12 mL). The resulting mixture was heated to 80 °C. After 12 h, water was added and the mixture was extracted with ethyl acetate. The combined organic solution was evaporated under reduced pressure. The residue was chromatographed through silica gel to afford **13s** as a white solid (0.55 g, 57%) (petroleum ether/EtOAc = 25:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.1 Hz, 1H), 7.43−7.39 (m, 2H), 7.29−7.22 (m, 2H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.09−7.01 (m, 2H), 6.97 (td, *J* = 7.5, 1.4 Hz, 1H), 6.51 (s, 1H), 6.37 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.87 (t, *J* = 6.8 Hz, 1H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.36 (s, 3H), 2.16 (p, *J* = 7.0 Hz, 2H), 1.99 (q, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.7, 141.5, 138.8 (2C), 136.2, 134.8, 134.4, 133.1, 131.1, 129.6, 129.4, 128.5, 128.4, 127.8, 127.3, 126.5, 124.6, 120.6, 34.5, 33.1, 26.2, 21.6. IR (neat, cm^{-1}): 3334, 2927, 1598, 1429, 1337, 1165, 764, 564. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{24}H_{23}NO_2SNa$: 412.1342. Found: 412.1341.

***N*-(4-(*tert*-Butyl)-2-(prop-1-en-2-yl)phenyl)-4-methylbenzenesulfonamide (14s).** To a mixture of potassium trifluoro(prop-1-en-2-yl)borate (0.92 g, 6.2 mmol), Cs_2CO_3 (5.4 g, 17 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (0.23 g, 0.27 mmol) and *N*-(2-bromo-4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (1.9 g, 5.0 mmol) was added a 10:1 (v/v) mixture of THF/H_2O (66 mL). The reaction mixture was stirred at reflux for 16 h. The mixture was cooled to room temperature and diluted with H_2O, followed by extraction with ether. The organic layer was washed with 1 N HCl and brine successively, and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **14s** as a white solid (1.2 g, 71%) (petroleum ether/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.59 (m, 2H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.24−7.19 (m, 3H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.95 (s, 1H), 5.23 (p, *J* = 1.6 Hz, 1H), 4.68−4.66 (m, 1H), 2.37 (s, 3H), 1.71 (t, *J* = 1.3 Hz, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.4, 143.8, 142.7, 136.7, 134.5, 130.2, 129.6, 127.3, 125.2, 124.8, 120.4, 116.9, 34.4, 31.4, 24.6, 21.6. IR (neat, cm^{-1}): 3287, 2952, 1597, 1496, 1167, 654, 553. HRMS (ESI), *m*/*z*: (M + Na)$^+$ Calcd for $C_{20}H_{25}NO_2SNa$: 366.1498. Found: 366.1498.

4-Methyl-*N*-(2-(prop-1-en-2-yl)-4-(trifluoromethoxy)-phenyl)benzenesulfonamide (19s). To a mixture of potassium trifluoro(prop-1-en-2-yl)borate (0.87 g, 5.9 mmol), Cs_2CO_3 (4.4 g, 14 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (0.22 g, 0.27 mmol), and *N*-(2-bromo-4-(trifluoromethoxy)phenyl)-4-methylbenzenesulfonamide (1.8 g, 4.5 mmol) was added a 10:1 (v/v) mixture of THF/H_2O (66 mL). The reaction mixture was stirred at reflux for 16 h. The mixture was cooled to room temperature and diluted with H_2O, followed by extraction with ether. The organic layer was washed with 1 N HCl and brine successively, and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **19s** as yellow solid (1.1 g, 70%) (petroleum ether/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 9.0 Hz, 1H), 7.66−7.59 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.10−7.05 (m, 1H), 7.02 (s, 1H), 6.89−6.86 (m, 1H), 5.30 (p, *J* = 1.6 Hz, 1H), 4.71 (t, *J* = 1.3 Hz, 1H), 2.38 (s, 3H), 1.69 (t, *J* = 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.7 (q,

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J_{C-F} = 1.9 Hz), 144.4, 140.9, 136.6, 136.2, 131.7, 129.9, 127.3, 122.1, 120.8, 120.7, 120.5 (q, J_{C-F} = 257.2 Hz), 118.3, 24.2, 21.7. ^{19}F NMR (471 MHz, $CDCl_3$): δ −58.07. IR (neat, cm^{-1}): 3279, 2922, 1597, 1496, 1256, 1163, 664, 551. HRMS (ESI), *m*/*z*: $(M + Na)^+$ Calcd for $C_{17}H_{16}F_3NO_3SNa$: 394.0695. Found: 394.0698.

4-Methyl-*N*-(2-(prop-1-en-2-yl)-4-(trifluoromethyl)phenyl)-benzenesulfonamide (20s). To a mixture of potassium trifluoro-(prop-1-en-2-yl)borate (0.64 g, 4.3 mmol), Cs_2CO_3 (3.5 g, 11 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (0.23 g, 0.27 mmol), and *N*-(2-bromo-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (1.4 g, 3.6 mmol) was added a 10:1 (v/v) mixture of THF/H_2O (66 mL). The reaction mixture was stirred at reflux for 16 h. The mixture was cooled to room temperature and diluted with H_2O, followed by extraction with ether. The organic layer was washed with 1 N HCl and brine successively and concentrated under reduced pressure. The residue was chromatographed through silica gel to afford **20s** as a white solid (0.25 g, 20%) (petroleum ether/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.71−7.64 (m, 2H), 7.45 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.30−7.22 (m, 3H), 7.15 (s, 1H), 5.37 (p, *J* = 1.6 Hz, 1H), 4.81−4.77 (m, 1H), 2.39 (s, 3H), 1.80 (t, *J* = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 144.7, 141.0, 136.3, 136.1, 134.3, 130.0, 127.4, 126.2 (q, J_{C-F} = 32.7 Hz), 125.3 (q, J_{C-F} = 3.9 Hz), 124.0 (q, J_{C-F} = 271.8 Hz). 119.4, 118.7, 24.4, 21.7. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.24. IR (neat, cm^{-1}): 3266, 2925, 1497, 1335, 1166, 1083, 747. HRMS (ESI), *m*/*z*: $(M + Na)^+$ Calcd for $C_{17}H_{16}F_3NO_2SNa$: 378.0746. Found: 378.0745.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00988.

Description of reaction setups, cyclic voltammograms, and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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