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碘化亚铜/4-羟基吡啶酰肼催化的(杂)芳基氯代物和苯基亚磺酸钠的偶联反应

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摘要 采用一种新型的 4-羟基吡啶甲酰胺配体, 成功地完成了之前难以反应的芳基氯化物和苯基亚磺酸钠的铜催化偶联, 这代表着这两类底物的第一次金属催化的偶联反应. 反应在 130 ℃下进行, 生成二芳基砜, 收率在 53%～96%. 底物可以兼容各种电性的芳基氯和杂芳基氯.
关键词 偶联反应; 铜催化; 配体; 芳基氯代物; 二芳基砜

CuI/4-Hydroxy Picolinohydrazide Catalyzed Coupling Reaction of (Hetero)aryl Chlorides with Sodium Aryl Sulfinates

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Abstract By using a newly developed 4-hydroxy picolinohydrazide as the ligand, Cu-catalyzed coupling of (hetero)aryl chlorides with sodium aryl sulfonates proceeded smoothly at 130 ℃ to give a series of biarylsulfones in 53%～96% yields. This represents the first metal-catalyzed coupling reaction of (hetero)aryl chlorides with sodium aryl sulfonates. Aryl and heteroaryl chlorides bearing either electron-donating or electron-withdrawing groups were applicable for this coupling reaction.
Keywords coupling reaction; copper catalysis; ligand; (hetero)aryl chloride; biarylsulfone

1 Introduction

Many biarylsulfone-containing compounds have displayed interesting biological activities. Examples include antibacterial drug dapsone (**1**),[1] CX-157 [**2**, a reversible inhibitor of monoamine oxidase-A that has being developed for the treatment of major depressive disorder (MDD)],[2] intepirdine (**3**, a highly selective 5-HT_6 receptor antagonist that has entered phase III clinical trials for treatment Alzheimer's disease),[3] as well as mycobacterium tuberculosis-thio-redoxin reductase inhibitor **4** (Figure 1).[4] Consequently development of more practical methods for diverse synthesis of biarylsulfones is highly warranted.[5] Traditionally, direct sulfonylation of arenes has been frequently used for preparing biarylsulfones, which suffered from unsatisfactory regioselectivity and poor functional group tolerance if more complex substrates were used.[5-8] Accordingly, it is not surprised that considerable interest has been directed to metal-catalyzed arylation of sulfinic acid salts during the past decades.[6-8] While a number of aromatic electrophiles were successfully applied as the suitable coupling partners, the cheapest and most abundant (hetero)aryl chlorides were still recognized as the difficult substrates for metal-catalyzed coupling reaction.[6-8] In 2017, our group[6f] reported that ((2*S*,4*R*)-4-hydroxy-*N*-(2-methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (HMNPC), an amide derived from 4-hydroxy-*L*-proline and 2-methyl naphthalen-1-amine, was able to promote Cu-catalyzed coupling of (hetero)aryl chlorides and $NaSO_2Me$ (Scheme 1). However, very poor conversions were observed if less reactive sodium aryl sulfinates were used, whose reaction scope was marrow in constrast

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with Cu-catalyzed coupling of (hetero)aryl bromides with sodium sulfinates.[6g] To overcome this drawback, we re-investigated the Cu-catalyzed coupling of (hetero)aryl chlorides and sodium aryl sulfinates with some newly developed ligands, and found that using 4-hydroxy picolinohydrazide as the ligand could give good to excellent conversions. Therefore, it provides an alternative method for assembling biarylsulfones.

2 Results and discussion

Using the coupling of 4-chloroanisole and sodium benzenesulfinate as a model reaction, reaction conditions were examined by varying ligands, bases, solvents and reaction temperatures (as summarized in Table 1,). Initially, two 4-hydroxy-*L*-proline derived amides **L1** and **L2** were checked, which led to the formation of the desired coupling product **7a** in only 11%～12% yields after heating at 120 ℃ for 24 h in the presence of 10 mol% CuI and ligand using K_3PO_4 as the base (Entries 1 and 2). Interestingly, 4-hydroxypicolinamide **L3**,[9] an analogue of **L2**, performed well in promoting Cu-catalyzed coupling of (hetero)aryl chlorides with primary sulfonamides and gave a better result (Entry 3). Further improvement was seen when 2-(5-methyl-1,3,4-oxadiazol-2-yl)aniline derived amide **L4** was employed (Entry 4). With **L4** as a ligand, the base and solvent effects of this coupling reaction were next explored. It was disappointedly found that the combination of K_3PO_4 and dimethylsulfoxide (DMSO) was still the best choice (compare Entries 4～9). After further ligand screening, it was pleased that the yield of **7a** was increased to 57% if 4-hydroxy picolinohydrazide **L5** was utilized (Entry 10). The orientation of the hydroxy group in **L5** plays an important role, as evident from the excellent reactivity of 6-hydroxy picolinohydrazide **L6** in Cu-catalyzed hydroxylation of (hetero)aryl halides,[10] and **7a** was obtained in only 23% yield (Entry 11). Using **L5** as a ligand and attempting to increase reaction temperature, it was found that 72% and 79% yields were obtained at 130 ℃ for 24 and 48 h, respectively (Entry 12). Changing the copper source to CuBr and Cu_2O led to decrease yields, but if CuTC was employed, the yields were increase. Further attempts revealed that yield was reached to 93% if increasing the amount of sodium benzenesulfonate to 1.5 equiv. Thus, it was concluded that the optimized conditions were using 10 mol% CuTC and **L5** as the catalytic system, 1.5 equiv. of sodium benzenesulfonate as the coupling partner, and carrying out the reaction in DMSO at 130 ℃ in the presence of K_3PO_4.

The established optimal reaction conditions were checked by varying (hetero)aryl chlorides. As demonstrated in Table 2, a series of *para*-substituted aryl chlorides bearing either electron-donating groups (**7a～7d**) or electron-withdrawing groups (**7e～7i**) worked well, producing the corresponding biarylsulfones in 58%～96% yields. The similar results were observed when four aryl chlorides had heterocycles at the *para*-position (**7j～7m**). In case of ethyl 4-chlorobenzoate as a substrate, using 2 equiv. of K_3PO_4 gave a low yield of **7i** owing to partial hydroxylation of the ester moiety, while reducing the amount of K_3PO_4 to 1 equiv. afforded **7i** in 70% yield. Additionally, coupling with 2-chloronaphthalene provided **7n** in a nearly quantitative yield, while other three *meta*-substituted aryl

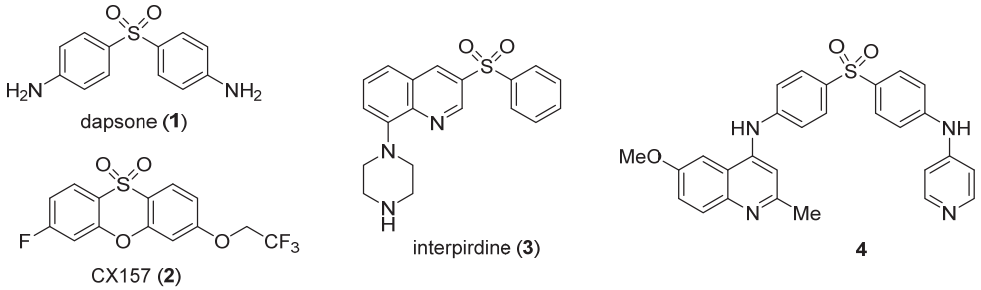
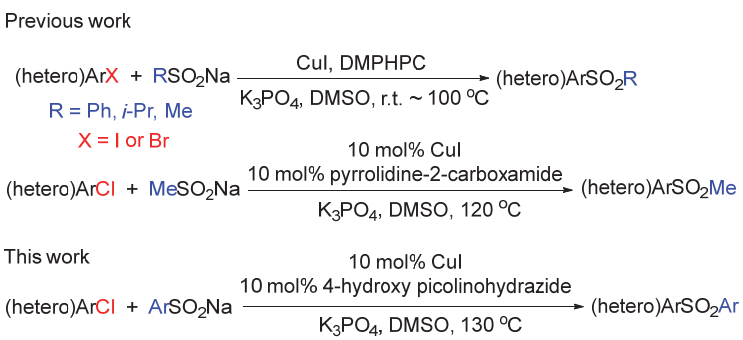
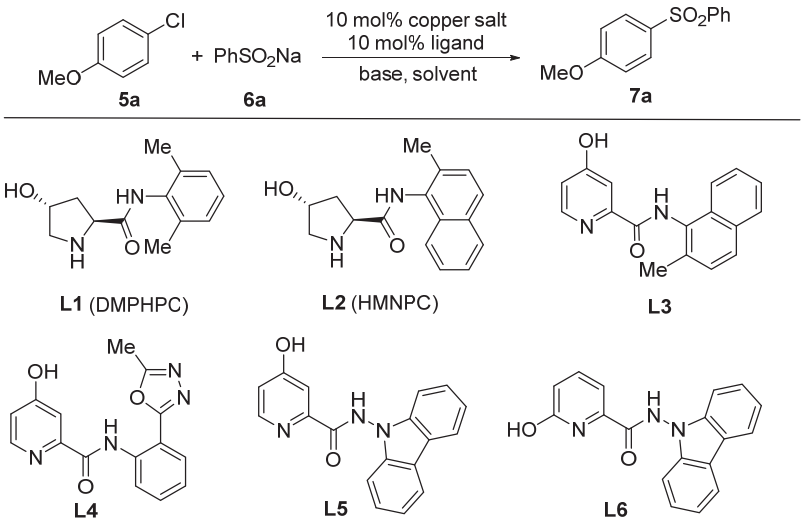


Figure 1 Structures of some bioactive biarylsulfones



Scheme 1 Assembly of biarylsulfones via different ligand-promoted Cu-catalyzed coupling reactions

Table 1 Condition screening for Cu-catalyzed coupling of 4-chloroanisole with sodium benzenesulfonate[a]



Entry	Copper salt	Ligand	Base	Solvent	Temp./℃	Yield[b]/%
1	CuI	**L1**	K_3PO_4	DMSO	120	11
2	CuI	**L2**	K_3PO_4	DMSO	120	12
3	CuI	**L3**	K_3PO_4	DMSO	120	33
4	CuI	**L4**	K_3PO_4	DMSO	120	45
5	CuI	**L4**	K_2CO_3	DMSO	120	25
6	CuI	**L4**	Cs_2CO_3	DMSO	120	42
7	CuI	**L4**	K_3PO_4	DMAc	120	18
8	CuI	**L4**	K_3PO_4	Sulfolane	120	41
9	CuI	**L4**	K_3PO_4	NMP	120	39
10	CuI	**L5**	K_3PO_4	DMSO	120	57
11	CuI	**L6**	K_3PO_4	DMSO	120	23
12	CuI	**L5**	K_3PO_4	DMSO	130	72 (79)[c]
13	CuBr	**L5**	K_3PO_4	DMSO	130	63
14	Cu_2O	**L5**	K_3PO_4	DMSO	130	15
15	CuTC	**L5**	K_3PO_4	DMSO	130	77 (83)[c]
16	CuTC	**L5**	K_3PO_4	DMSO	130	93[d]

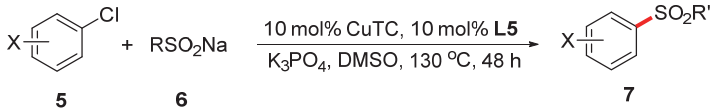
[a] Reaction conditions: **5a** (1.0 mmol), **6a** (1.3 mmol), copper salt (0.1 mmol), ligand (0.1 mmol), base (2.0 mmol), solvent (0.5 mL), 24 h. [b] Determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard, in most case complete conversions were observed because the reaction was quite slow. [c] 48 h. [d] 1.5 mmol of **6a** was used.

chlorides also successfully coupled with sodium benzenesulfinate to provide **7o**～**7q**. It is worth noting that **7q** was isolated in only 53% yield, presumably because nucleophilic replacement of **7q** with nucleophiles occurred under the present conditions. Furthermore, several heteroaryl chlorides were examined, which led to the formation of thiophene-, pyridine-, benzothiophene-, quinoline- and imidazo[1,2-*a*]pyridine-embodied biarylsulfones **7r**～**7v**. This fact, together with a number of functional groups tolerated under these conditions, such as amine (**7c**, **7k** and **7p**), thioether (**7d**), nitrile (**7f**), ketone (**7g**), sulfone (**7h**), ester (**7i**), and ketal (**7l**), makes our coupling reaction attractive for assembling biarylsulfones in a diverse manner. Finally, we briefly evaluated other sodium sulfinates, and found that coupling of sodium 4-methylbenzene sulfinate with two (hetero)aryl chlorides proceeded smoothly to deliver **7w** and **7aa**, similar result was observed when another electron-rich sodium aryl sulfinate was utilized (**7x**), but two electron-poor sodium aryl sulfinates failed to give coupling products **7y** and **7z**. These results indicated that electronic nature of the sodium aryl sulfinates played an essential role for effective coupling. However, this drawback has limited influence on the reaction scope of the present coupling, mainly because more conveniently available (hetero)aryl chlorides can be chosen as alternative coupling partners for this cross coupling to obtain the desired products. Additionally, we were pleased that excellent yields were gained when 4-chloroanisole was coupled with $NaSO_2Me$ (**7ab**) and $NaSO_2Et$ (**7ac**) even at a reduced catalytic loading (5 mol% CuI and **L5**).

3 Conclusions

In conclusion, we have revealed that 4-hydroxy picolinohydrazide **L5** was a more effective ligand, leading to the effective coupling between CuI catalyzed (hetero)aryl

Table 2 CuI/4-hydroxy picolinohydrazide-catalyzed coupling of (hetero)aryl chlorides with sodium sulfinates[a]



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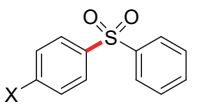
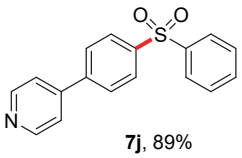
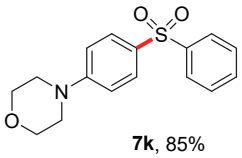


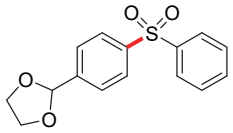
7a: X = OMe, 91%
7b: X = *t*-Bu, 96%
7c: X = NMe2, 76%
7d: X = SMe, 94%
7e: X = Ph, 91%
7f: X = CN, 80%
7g: X = COPh, 81%
7h: X = SO_2Me, 58%
7i: X = CO_2Et, 70%[b]



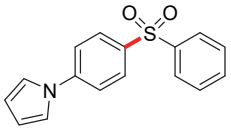
7j, 89%



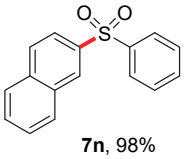
7k, 85%



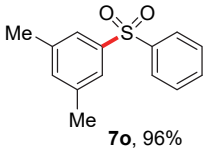
7l, 81%



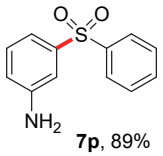
7m, 65%



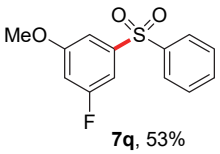
7n, 98%



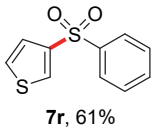
7o, 96%



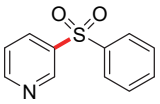
7p, 89%



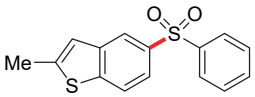
7q, 53%



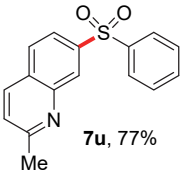
7r, 61%



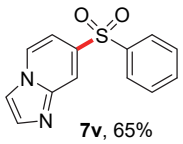
7s, 63%



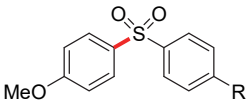
7t, 93%



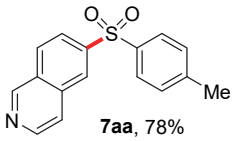
7u, 77%



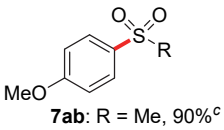
7v, 65%



7w: R = Me, 95%
7x: R = OMe, 76%
7y: R = CN, 0%
7z: R = NO_2, 0%



7aa, 78%



7ab: R = Me, 90%[c]
7ac: R = Et, 91%[c]

[a] Reaction conditions: **5** (1.0 mmol), **6** (1.5 mmol), CuTC (0.1 mmol), **L5** (0.1 mmol), K_3PO_4 (2.0 mmol), DMSO (0.5 mL), 130 ℃, 48 h, isolated yield. [b] Reaction was conducted with 1 mmol of K_3PO_4. [c] 5 mol% CuI and 5 mol% **L5** were used, 24 h.

chlorides and sodium arylsulfinates at 130 ℃, providing a variety of biaryl sulfones. Since both coupling partners are inexpensive and conveniently available, this method provides a facile approach for preparing biologically important biaryl sulfones.

4 Experimental section

4.1 Instruments and reagents

All commercial materials were used as received unless otherwise noted. Base including K_2CO_3 (reagent grade, ⩾ 99%, TCI), K_3PO_4 (reagent grade, ⩾99%, Sigma Aldrich)), Cs_2CO_3 (reagent grade, ⩾99%, Sigma Aldrich) and solvents, such as dimethylacetamide (DMAc), sulfolane, *N*-methylpyrrolidone (NMP) and DMSO from J&K Scientific were used in the Cu-catalyzed reactions. CuI, CuBr, Cu_2O and CuTc were used as supplied by Alfa Aesar and TCI. All reactions for the Cu-catalyzed coupling were carried out in a glass sample bottle with a magnetic stir bar in the glovebox. Unless otherwise noted, the reaction test tubes were cooled to room temperature prior to other operations. Reaction temperatures refer to heat block temperature. Thin layer chromatography (TLC) was performed using silica gel 60 F-254 precoated glass plates (0.25 mm) and visualized by UV irradiation. Flash chromatography was performed using 230～400 mesh SiliaFlash® P60 (Silicycle Inc.). Melting points were recorded on a digital melting point apparatus. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer and an Agilent DD2 500 MHz NMR spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR). High resolution mass spectra (HRMS) were operated on a Bruker Daltonics APEXIII 7.0 TESLA FTMS instrument and a Thermo Fisher Scientific LTQ FT Ultra instrument. Specific rotation of the chiral products has been recorded on an Anton Paar MCP 5500 polarimeter.

4.2 Experimental method

(Hetero)aryl chloride **5** (1.0 mmol) [Note: for liquid substrates, they were added after DMSO], CuTC (0.1 mmol, 19.1 mg), **L5** (0.1 mmol, 30.3 mg) RSO_2Na (1.5 mmol) and K_3PO_4 (2.0 mmol, 424 mg) were placed into a glass sample bottle (4 mL) with a magnetic stir bar in the glovebox. DMSO (0.5 mL) was added afterwards. The bottle was heated at 130 ℃ for 48 h in the glovebox. Upon completion of reaction, the cooled mixture was diluted with ethyl acetate, washed with water and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate/hexane) to afford the corresponding sulfones.

1-Methoxy-4-(phenylsulfonyl)benzene (**7a**): White solid, 226 mg, yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, J=7.1 Hz, 2H), 7.87 (d, J=9.0 Hz, 2H), 7.52 (t, J=7.3 Hz, 1H), 7.47 (t, J=7.4 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:

163.47, 142.44, 133.17, 132.94, 129.96, 129.30, 127.38, 114.61, 55.74; HRMS (ESI) calcd for $C_{13}H_{13}O_3S$ $[M+H]^+$ 249.0580, found 249.0586.

1-(*tert*-Butyl)-4-(phenylsulfonyl)benzene (**7b**): White solid, 263 mg, yield 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J=7.4 Hz, 2H), 7.86 (d, J=8.6 Hz, 2H), 7.54 (t, J=7.3 Hz, 1H), 7.52～7.45 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.2, 142.1, 138.7, 133.1, 129.3, 127.7, 127.6, 126.4, 35.3, 31.1; HRMS (ESI) calcd for $C_{16}H_{19}O_2S$ $[M+H]^+$ 275.1100, found 275.1106.

N,*N*-Dimethyl-4-(phenylsulfonyl)aniline (**7c**): White solid, 198 mg, yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (d, J=6.8 Hz, 2H), 7.75 (d, J=9.1 Hz, 2H), 7.50～7.46 (m, 1H), 7.44 (t, J=7.2 Hz, 2H), 6.65 (d, J=9.1 Hz, 2H), 3.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 153.17, 143.49, 132.37, 129.58, 129.12, 127.03, 126.56, 111.25, 40.17; HRMS (ESI) calcd for $C_{14}H_{16}NO_2S$ $[M+H]^+$ 262.0896, found 262.0901.

Methyl(4-(phenylsulfonyl)phenyl)sulfane (**7d**): White solid, 248 mg, yield 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, J=7.7 Hz, 2H), 7.81 (d, J=7.1 Hz, 2H), 7.53 (t, J=7.1 Hz, 1H), 7.48 (t, J=7.1 Hz, 2H), 7.26 (d, J=7.1 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 146.75, 141.98, 137.26, 133.16, 129.37, 128.05, 127.52, 125.57, 14.80; HRMS (ESI) calcd for $C_{13}H_{13}O_2S_2$ $[M+H]^+$ 265.0351, found 265.0351.

4-(Phenylsulfonyl)-1,1'-biphenyl (**7e**): White solid, 268 mg, yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (t, J=8.4 Hz, 4H), 7.70 (d, J=8.6 Hz, 2H), 7.60～7.54 (m, 3H), 7.52 (t, J=7.4 Hz, 2H), 7.46 (t, J=7.4 Hz, 2H), 7.40 (t, J=7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 146.29, 141.85, 140.23, 139.26, 133.31, 129.44, 129.17, 128.70, 128.31, 128.05, 127.76, 127.46; HRMS (ESI) calcd for $C_{18}H_{15}O_2S$ $[M+H]^+$ 295.0787, found 295.0787.

4-(Phenylsulfonyl)benzonitrile (**7f**): White solid, 195 mg, yield 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06, 8.04, 7.95, 7.94, 7.80, 7.79, 7.64, 7.62, 7.61, 7.56, 7.54, 7.53; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 145.98, 140.24, 134.15, 133.20, 129.77, 128.40, 128.10, 117.27, 117.04; HRMS (ESI) calcd for $C_{13}H_9NNaO_2S$ $[M+Na]^+$ 266.0246, found 266.0245.

Phenyl(4-(phenylsulfonyl)phenyl)methanone (**7g**): Light yellow solid, 260 mg, yield 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (d, J=8.5 Hz, 2H), 7.99 (d, J=7.3 Hz, 2H), 7.87 (d, J=8.5 Hz, 2H), 7.76 (d, J=7.2 Hz, 2H), 7.66～7.58 (m, 2H), 7.54 (t, J=7.6 Hz, 2H), 7.49 (t, J=7.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 195.33, 144.84, 141.86, 140.99, 136.50, 133.78, 133.45, 130.62, 130.25, 129.62, 128.73, 128.04, 127.79; HRMS (ESI) calcd for $C_{19}H_{15}O_3S$ $[M+H]^+$ 323.0736, found 323.0732.

1-(Methylsulfonyl)-4-(phenylsulfonyl)benzene (**7h**): Light yellow solid, 171 mg, yield 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, J=8.4 Hz, 2H), 8.07 (d, J=8.3 Hz, 2H), 7.95 (d, J=7.5 Hz, 2H), 7.62 (t, J=7.4 Hz, 1H), 7.54 (t, J=7.8 Hz, 2H), 3.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 146.87, 144.84, 140.22, 134.14, 129.76, 128.80, 128.61, 128.10, 44.33; HRMS (ESI) calcd for $C_{13}H_{12}NaO_4S_2$ $[M+Na]^+$ 319.0069, found 319.0066.

Ethyl 4-(phenylsulfonyl)benzoate (**7i**): White solid, 204 mg, yield 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.12 (d, J=8.3 Hz, 2H), 7.98 (d, J=8.3 Hz, 2H), 7.93 (d, J=7.6 Hz, 2H), 7.55 (t, J=7.3 Hz, 1H), 7.48 (t, J=7.6 Hz, 2H), 4.35 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.98, 145.36, 140.84, 134.67, 133.65, 130.43, 129.48, 127.83, 127.67, 61.74, 14.24; HRMS (ESI) calcd for $C_{15}H_{15}O_4S$ $[M+H]^+$ 291.0686, found 291.0691.

4-(4-(Phenylsulfonyl)phenyl)pyridine (**7j**): Light yellow solid, 264 mg, yield 89%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.69 (s, 2H), 8.09 (d, J=8.4 Hz, 2H), 8.06～7.96 (m, 4H), 7.75～7.67 (m, 3H), 7.64 (t, J=7.6 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 150.40, 145.17, 142.26, 141.43, 140.87, 133.88, 129.83, 128.33, 128.18, 127.47, 121.67; HRMS (ESI) calcd for $C_{17}H_{14}NO_2S$ $[M+H]^+$ 296.0740, found 269.0742.

4-(4-(Phenylsulfonyl)phenyl)morpholine (**7k**): Light yellow solid, 258 mg, yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (d, J=6.5 Hz, 2H), 7.79 (d, J=7.1 Hz, 2H), 7.54～7.41 (m, 3H), 6.87 (d, J=7.1 Hz, 2H), 3.81 (s, 4H), 3.25 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.12, 142.87, 132.67, 130.05, 129.55, 129.20, 127.18, 113.90, 66.50, 47.42; HRMS (ESI) calcd for $C_{16}H_{18}NO_3S$ $[M+H]^+$ 304.1002, found 304.1007.

2-(4-(Phenylsulfonyl)phenyl)-1,3-dioxolane (**7l**): Yellow solid, 235 mg, yield 81%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.00 (d, J=8.3 Hz, 2H), 7.97 (d, J=8.3 Hz, 2H), 7.72～7.65 (m, 3H), 7.62 (t, J=7.5 Hz, 2H), 5.82 (s, 1H), 4.05～3.89 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 143.82, 141.60, 140.93, 133.78, 129.78, 127.77, 127.53, 127.36, 101.54, 64.98; HRMS (ESI) calcd for $C_{15}H_{15}O_4S$ $[M+H]^+$ 291.0686, found 294.0687.

1-(4-(Phenylsulfonyl)phenyl)-1*H*-pyrrole (**7m**): White solid, 185 mg, yield 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, J=8.9 Hz, 2H), 7.96 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.52 (t, J=7.5 Hz, 2H), 7.49 (d, J=8.8 Hz, 2H), 7.13～7.06 (m, 2H), 6.41～6.34 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.29, 141.79, 137.97, 133.38, 129.71, 129.50, 127.69, 120.14, 119.15, 112.17; HRMS (ESI) calcd for $C_{16}H_{14}NO_2S$ $[M+H]^+$ 284.0740, found 284.0741.

2-(Phenylsulfonyl)naphthalene (**7n**): White solid, 263 mg, yield 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (s, 1H), 8.01 (d, J=7.1 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.91 (d, J=8.7 Hz, 1H), 7.89～7.82 (m, 2H), 7.65～7.56 (m, 2H), 7.54 (t, J=7.3 Hz, 1H), 7.49 (t, J=7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 141.68, 138.44, 135.04, 133.26, 132.25, 129.74, 129.44, 129.37, 129.23, 129.14, 127.99, 127.76, 127.71, 122.71; HRMS (ESI) calcd for $C_{16}H_{13}O_2S$ $[M+H]^+$ 269.0631, found 269.0635.

1,3-Dimethyl-5-(phenylsulfonyl)benzene (**7o**): 237 mg, white yellow solid, yield 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J=7.2 Hz, 2H), 7.54 (d, J=7.4 Hz, 3H), 7.49 (t, J=7.4 Hz, 2H), 7.16 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 141.98, 141.33, 139.47,

135.04, 133.12, 129.32, 127.68, 125.28, 21.32; HRMS (ESI) calcd for $C_{14}H_{15}O_2S$ $[M+H]^+$ 247.0787, found 247.0787.

3-(Phenylsulfonyl)aniline (**7p**): Yellow solid, 208 mg, yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, J=8.4 Hz, 2H), 7.53 (t, J=6.8 Hz, 1H), 7.47 (t, J=7.4 Hz, 2H), 7.23 (dt, J=15.4, 7.0 Hz, 3H), 6.78 (d, J=7.8 Hz, 1H), 3.91 (br, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 147.52, 142.24, 141.78, 133.16, 130.28, 129.28, 127.63, 119.47, 117.22, 113.22; HRMS (ESI) calcd for $C_{12}H_{12}NO_2S$ $[M+H]^+$234.0583, found 234.0587.

1-Fluoro-3-methoxy-5-(phenylsulfonyl)benzene (**7q**): White solid, 141 mg, yield 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, J=7.6 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.51 (t, J=7.6 Hz, 2H), 7.26 (s, 1H), 7.20 (dt, J=7.5, 1.8 Hz, 1H), 6.76 (dt, J=10.1, 2.3 Hz, 1H), 3.82 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −107.63. ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.36 (d, J=251.8 Hz), 161.56 (d, J=10.8 Hz), 144.16 (d, J=8.8 Hz), 140.93, 133.67, 129.51, 127.85, 109.12 (d, J=3.0 Hz), 107.28 (d, J=25.0 Hz), 106.77 (d, J=24.9 Hz), 56.20; HRMS (ESI) calcd for $C_{13}H_{12}FO_3S$ $[M+H]^+$ 267.0486, found 267.0486.

3-(Phenylsulfonyl)thiophene (**7r**): White solid, 137 mg, yield 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (d, J=2.4 Hz, 1H), 7.96 (d, J=7.6 Hz, 2H), 7.58 (t, J=7.3 Hz, 1H), 7.51 (t, J=7.6 Hz, 2H), 7.41～7.36 (m, 1H), 7.33 (d, J=5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 142.08, 141.69, 133.40, 131.69, 129.41, 128.51, 127.55, 125.95; HRMS (ESI) calcd for $C_{10}H_8NaO_2S_2$ $[M+Na]^+$ 246.9858, found 246.9860.

3-(Phenylsulfonyl)pyridine (**7s**): White solid, 137 mg, yield 63%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.14 (s, 1H), 8.78 (d, J=4.3 Hz, 1H), 8.21 (d, J=8.1 Hz, 1H), 7.97 (d, J=7.7 Hz, 2H), 7.61 (t, J=7.4 Hz, 1H), 7.54 (t, J=7.6 Hz, 2H), 7.45 (dd, J=8.0, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 153.75, 148.78, 140.83, 138.43, 135.38, 133.96, 129.71, 127.91, 124.00; HRMS (ESI) calcd for $C_{11}H_{10}NO_2S$ $[M+H]^+$ 220.0427, found 220.0472.

2-Methyl-5-(phenylsulfonyl)benzo[b]thiophene (**7t**): Yellow solid, 269 mg, yield 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.99 (d, J=8.1 Hz, 2H), 7.91 (d, J=8.5 Hz, 1H), 7.82 (d, J=8.5 Hz, 1H), 7.57～7.49 (m, 1H), 7.48 (t, J=7.2 Hz, 2H), 7.19 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 145.03, 142.08, 139.63, 137.35, 133.10, 132.94, 129.33, 127.57, 124.41, 123.80, 122.31, 121.74, 13.90; HRMS (ESI) calcd for $C_{15}H_{13}O_2S_2$ $[M+H]^+$ 289.0351, found 289.0354.

2-Methyl-7-(phenylsulfonyl)quinoline (**7u**): Light yellow solid, 217 mg, yield 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 8.06 (d, J=8.5 Hz, 1H), 8.00 (d, J=7.2 Hz, 2H), 7.93 (dd, J=8.5, 1.7 Hz, 1H), 7.86 (d, J=8.5 Hz, 1H), 7.54 (t, J=7.4 Hz, 1H), 7.48 (t, J=7.5 Hz, 2H), 7.39 (d, J=8.5 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 161.37, 146.92, 142.29, 141.31, 136.10, 133.49, 129.56, 129.46, 129.35, 128.80, 128.04, 124.78, 122.69, 25.51; HRMS (ESI) calcd for $C_{16}H_{14}NO_2S$ $[M+H]^+$ 284.0740, found 284.0746.

7-(Phenylsulfonyl)imidazo[1,2-a]pyridine (**7v**): 167 mg, White solid, yield 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 8.20 (d, J=7.1 Hz, 1H), 7.96 (d, J=7.5 Hz, 2H), 7.81 (s, 1H), 7.70 (s, 1H), 7.58 (t, J=7.4 Hz, 1H), 7.51 (t, J=7.7 Hz, 2H), 7.18 (dd, J=7.1, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 143.27, 140.52, 137.12, 136.79, 133.78, 129.56, 127.86, 126.74, 119.01, 114.45, 109.20; HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2S$ $[M+H]^+$ 259.0536, found 259.0536.

1-Methoxy-4-tosylbenzene (**7w**): White solid, 248 mg, yield 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (d, J=8.9 Hz, 2H), 7.79 (d, J=8.3 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 6.94 (d, J=8.9 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.34, 143.85, 139.55, 133.66, 129.94, 129.82, 127.48, 114.56, 55.74, 21.64; HRMS (ESI) calcd for $C_{14}H_{15}O_3S$ $[M+H]^+$ 263.0736, found 263.0739.

4,4'-Sulfonylbis(methoxybenzene) (**7x**): White solid, 212 mg, yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (d, J=8.9 Hz, 4H), 6.94 (d, J=8.9 Hz, 4H), 3.83 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.21, 134.09, 129.63, 114.54, 55.75.

6-Tosylisoquinoline (**7aa**): Yellow solid, 220 mg, yield 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 8.65 (d, J=5.7 Hz, 1H), 8.52 (s, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.97 (dd, J=8.6, 1.5 Hz, 1H), 7.88 (d, J=8.3 Hz, 2H), 7.77 (d, J=5.7 Hz, 1H), 7.31 (d, J=8.3 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 152.63, 144.93, 144.74, 143.53, 137.78, 135.01, 130.24, 129.56, 129.41, 128.11, 127.25, 124.34, 121.43, 21.70; HRMS (ESI) calcd for $C_{16}H_{14}NO_2S$ $[M+H]^+$ 284.0740, found 284.0742.

1-Methoxy-4-(methylsulfonyl)benzene (**7ab**): White solid, 168 mg, yield 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (d, J=8.9 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 3.86 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.77, 132.35, 129.61, 114.59, 55.80, 44.92; HRMS (ESI) calcd for $C_8H_{11}O_3S$ $[M+H]^+$ 187.0423, found 187.0423.

1-(Ethylsulfonyl)-4-methoxybenzene (**7ac**): White solid, 183 mg, yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, J=9.0 Hz, 2H), 6.98 (d, J=8.9 Hz, 2H), 3.83 (s, 3H), 3.04 (q, J=7.4 Hz, 2H), 1.20 (t, J=7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.71, 130.31, 129.99, 114.44, 55.71, 50.82, 7.57; HRMS (ESI) calcd for $C_9H_{13}O_3S$ $[M+H]^+$ 201.0580, found 201.0585.

Supporting Information The analytical data for all coupling products and copies of NMR spectra for all products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] Repichet, S.; Roux, C. L.; Dubac, J. *J. Org. Chem.* **1999**, *64*, 6429.
[2] Fowler, J.; Logan, J.; Azzaro, A. *Neuropsychopharmacol* **2010**, *35*, 623.
[3] Codony, X.; Vela, J. M.; Ramirez, M. J. *Curr. Opin. Pharmacol.* **2011**, *11*, 94.
[4] Koch, O.; Bering, L. *US 2020/0123130*, **2020**.

[5] for a review, see: Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis* **2016**, *48*, 1939.
[6] for Cu-catalyzed coupling reactions with aryl halides, see:
(a) Suzuki, H.; Abe, H. *Tetrahedron Lett*. **1995**, *36*, 6239.
(b) Baskin, J. M.; Wang, Z. *Org. Lett*. **2002**, *4*, 4423.
(c) Zhu, W.; Ma, D. *J. Org. Chem*. **2005**, *70*, 2696.
(d) Bian, M.; Xu, F.; Ma, C. *Synthesis* **2007**, *19*, 2951.
(e) Yuan, Y. Q.; Guo, S. R. *Synlett* **2011**, *18*, 2750.
(f) Ma, D.; Niu, S.; Zhao, J.; Jiang, X.; Jiang, Y.; Zhang, X.; Sun, T. *Chin. J. Chem*. **2017**, *35*, 1661.
(g) Zhao, J.; Niu, S.; Jiang, X.; Jiang, Y.; Zhang, X.; Sun, T.; Ma, D. *J. Org. Chem*. **2018**, *83*, 6589.
(h) for a review, see: Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136.
[7] for Pd-catalyzed coupling reactions with aryl halides and triflates, see: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett*. **2002**, *4*, 4719.
(b) Smyth, L.; Phillips, E.; Chen, V.; Napolitana, J.; Henry, R.; Shekhar, S. *J. Org. Chem*. **2016**, *81*, 1285.
[8] for Cu-catalyzed coupling reactions with other electrophiles, see:
(a) Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D. A. *Tetrahedron Lett*. **2004**, *45*, 3233.
(b) Kir, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett*. **2007**, *9*, 3405.
(c) Huang, F.; Batey, R. A. *Tetrahedron* **2007**, *63*, 7667.
(d) Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem.-Eur. J.* **2011**, *17*, 5652.
(e) Gund, S. H.; Shelkar, R. S.; Nagarkar, J. M. *RSC Adv.* **2015**, *5*, 62926.
(f) Zhang, K.; Xu, X. H.; Qing, F. L. *J. Org. Chem*. **2015**, *80*, 7658.
[9] Li, Q.; Xu. L.; Ma, D. *Angew. Chem., Int. Ed*. **2022**, *62*, e202210483.
[10] Xu, L.; Zhou, J.; Shen, X.; Chai, J.; Shi, L.; Wu, B.; Li, W.; Ma, D. *Angew. Chem., Int. Ed*. **2024**, *64*, e202412552.

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