Scope of the Desulfinylative Palladium-Catalyzed Cross-Coupling of Aryl Sulfinates with Aryl Bromides

Dirk H. Ortgies, Alexandre Barthelme, Sara Aly, Brigitte Desharnais, Steven Rioux, Pat Forgione*

Concordia University, Department of Chemistry and Biochemistry, 7141 rue Sherbrooke O., Montréal, QC, H4B 1R6, Canada and Centre for Green Chemistry and Catalysis, CP 6128, succursale Centre-ville, Montréal, QC, H3C 3J7, Canada
Fax +1(514)8482868; E-mail: pat.forgione@concordia.ca

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Dedicated to the memory of Keith Fagnou

Abstract: Herein is described the full scope of a desulfinylative cross-coupling of aryl sulfinates with aryl bromides. Optimized conditions were established and a bidentate phosphine ligand was found to be the key in obtaining good cross-coupling yields. Preliminary efforts to elucidate the reaction mechanism suggest that a Pd(0)-catalyzed mechanism is operative.

Key words: palladium, sulfur, cross-coupling, catalysis, biaryls

Palladium-catalyzed cross-coupling reactions in biaryl synthesis[1] are frequently limited to the commercial availability of organometallic coupling partners. The organometallic reagents required for the transformations can often be expensive, sensitive to water and/or oxygen and produce stoichiometric amounts of potentially toxic, metallic by-products. The importance of the biaryl motif in drug-discovery,[2] material science,[3] and as part of ligands[4] (illustrated in Figure 1) inspires researchers to continue developing novel methods for their preparation that aim to improve the afore-mentioned issues.

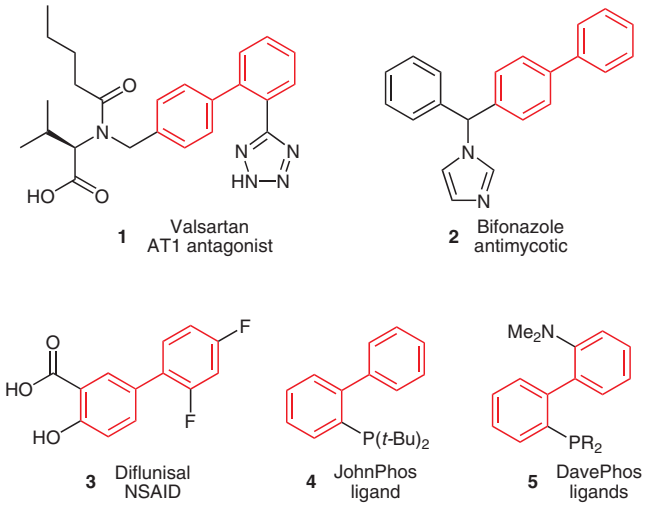
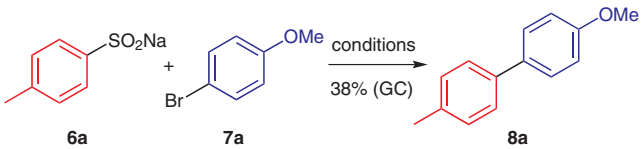


Figure 1 Important structures containing the biphenyl motif

Recently, alternative methods for the preparation of biaryls have emerged that circumvent the need for the organometallic coupling partners. The efforts to directly activate a C–H aryl bond for the preparation of biaryls are perhaps the simplest solution, and indeed have yielded numerous elegant examples demonstrating the transformation.[5] This overcomes a limitation by reducing the number of functional group manipulations required to prepare the organometallic coupling partner. Additionally, the reduction in the number of steps in a synthetic sequence can have dramatic economic and environmental advantages. Alternatively, decarboxylative couplings have also demonstrated great utility in the formation of biaryls.[6,7] Previously, we had reported the palladium-mediated decarboxylative cross-coupling of heteroaromatics.[8] In a further extension of these efforts, we were interested in extending the scope to desulfinylative couplings. Oxidative additions into sulfonyl chlorides and their use as electrophilic species in Heck-like reactions are known.[9] Additionally, the use of sulfinates directly as coupling partners in related reactions has also been reported.[10] The use of aryl sulfinates as the nucleophilic coupling partner in a palladium-catalyzed coupling has, to the best of our knowledge, only been reported sparsely.[11] In order to fully evaluate the scope of this useful transformation, the commercially available *p*-toluenesulfinate **6a** was at first treated with 4-bromoanisole (**7a**) under our previously reported conditions for decarboxylative cross-couplings using microwave heating. Rewardingly, the desired product **8a** was obtained in 38% yield as determined by GC (Scheme 1).



Scheme 1 *Reagents and conditions*: sodium *p*-toluenesulfinate (**6a**; 0.8 mmol, 2.0 equiv), 4-bromoanisole (**7a**; 0.4 mmol, 1.0 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol%), $n\text{-}Bu_4NCl{\cdot}H_2O$ (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.6 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min.

Initial evaluation of the conditions for the cross-coupling involved the screening of the catalyst, temperature, and heating source. Modifying the reaction temperature, while employing microwave irradiation (Table 1, entries 1–3), exhibited a minor impact on yield. Generation of the Pd(0)

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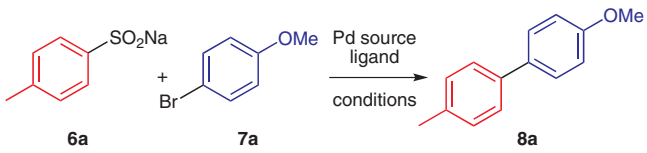
Table 1 Screening of Ligands and Reaction Conditions[a]



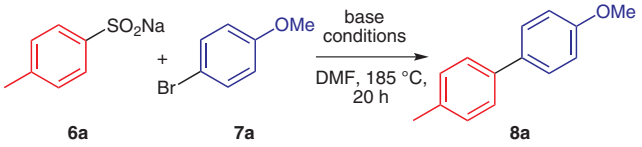
Entry	Pd source	Ligand	T (°C), Time	Yield (%)[b]
1[c]	$[Pd(PPh_3)_4]$		µw, 170, 8 min	32
2[c]	$[Pd(PPh_3)_4]$		µw, 160, 2 h	14
3[c]	$[Pd(PPh_3)_4]$		µw, 190, 2 h	29[d]
4	$PdCl_2$	$[PH(t\text{-}Bu)_3]BF_4$	µw, 170, 8 min	20
5	$PdCl_2$	$[PH(t\text{-}Bu)_2CH_3]BF_4$	µw, 170, 8 min	19
6	$PdCl_2$	JohnPhos	µw, 170, 8 min	19
7	$PdCl_2$	$[PH(Cy)_3]BF_4$	µw, 170, 8 min	15
8[c]	$[Pd(PPh_3)_4]$		Δ, 130, 15 h	44
9[c]	$[Pd(PPh_3)_4]$		Δ, 160, 10 h	14
10	$PdCl_2$	PhDavePhos **5a**	µw, 170, 48 min	27
11[e]	$PdCl_2$	PhDavePhos **5a**	Δ, 185, 19 h	57
12[f]	$PdCl_2$	PhDavePhos **5a**	Δ, 185, 19 h	60
13[g]	$PdCl_2$	PhDavePhos **5a**	Δ, 185, 19 h	60[d]
14[g]	$PdCl_2$	PhDavePhos **5a**	Δ, 170, 17 h	62
15[g]	$PdCl_2$	*t*-BuDavePhos **5b**	Δ, 170, 17 h	55
16[g]	$PdCl_2$	DavePhos **5c**	Δ, 170, 17 h	46
17[g]	$PdCl_2$	dppf	Δ, 170, 17 h	74

[a] Reaction conditions: sodium *p*-toluenesulfinate (**6a**; 0.8 mmol, 2 equiv), 4-bromoanisole (**7a**; 0.4 mmol, 1 equiv), Pd source (5 mol%), ligand (5 mol%), Cs_2CO_3 (0.6 mmol, 1.5 equiv), DMF (4 mL).
[b] Yields were determined by GC-MS.
[c] *n*-Bu_4NBr (0.4 mmol, 1.0 equiv) was used as additive.
[d] Complete conversion of 4-bromoanisole (**7a**).
[e] Sulfinate **6a** used: 3 equiv.
[f] Sulfinate **6a** used: 4 equiv.
[g] Sulfinate **6a** used: 5 equiv.

catalyst in situ employing a selection of phosphine ligands led to markedly reduced cross-coupling yields (entries 4–7). Transferring to thermal heating conditions while employing the $Pd(PPh_3)_4$ catalyst led to increased yields (entry 8); however, further increase in reaction temperature proved detrimental (entry 9). Since thermal heating provided superior results, further evaluations were conducted with this heating method while generating the catalyst in situ. An increase in the amount of sulfinate **6a** employed from two (entry 10) to three (entry 11) equivalents and a higher temperature of 185 °C led to a substantial increase in product yield observed by GC-MS (27% to 57%), when the voluminous ligand 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl (**5a**) (PhDavePhos) was used. However, further increases in the amount of sulfinate **6a** proved ineffective (entries 12, 13), but the temperature could be reduced to 170 °C and the reaction time reduced to 17 hours with no effect on the yield (entry 14). Subsequently, selected variations of DavePhos **5** were evaluated only to produce reduced yields (entries 15, 16). The bidentate 1,1′-bis(diphenylphosphino)ferrocene ligand (dppf) provided a substantial increase in cross-coupling yield and was consequently used for further screenings employing an excess of aryl sulfinate (entry 17). It has been reported that sulfinates undergo homocoupling when employing a stoichiometric amount of a Pd(II) source.[12] Employing the bidentate dppf ligand likely suppresses homocoupling products that are derived from a Pd(II)-mediated process.

The nature of the base employed was subsequently evaluated. Initial efforts focused on the use of the relatively organic-soluble Cs_2CO_3 (Table 2, entry 1). The use of less soluble lithium, sodium, and potassium carbonate bases substantially reduced yields (entries 2–4). The base proved to be critical for cross-coupling to occur as no product was obtained in its absence (entry 5). The use of the soluble organic base triethylamine did not yield any coupling product (entry 6).

Table 2 Base Screening[a]



Entry	Base	GC Yield (%)
1	Cs_2CO_3	79
2	Li_2CO_3	29
3	Na_2CO_3	24
4	K_2CO_3	2
5	none	0
6	Et_3N	0

[a] Reaction conditions: sodium *p*-toluenesulfinate (**6a**; 2 mmol, 5.0 equiv), 4-bromoanisole (**7a**; 0.4 mmol, 1.0 equiv), $PdCl_2$ (5 mol%), dppf (5 mol%), base (0.6 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.

An aryl bromide **7** screening was performed while employing the developed optimized conditions utilizing a $PdCl_2$ precatalyst, dppf ligand, Cs_2CO_3 base, and 4 equivalents of *p*-toluenesulfinate. The isolated yields are shown in Table 3. Varying the methoxy group from the C-4 in **7a** to the C-3 position in **7b** (Table 3, entry 1 vs 2) produced an increased yield. However, the more sterically hindered 2-bromoanisole (**7c**) provided the desired product in slightly lower yield (entry 3). Switching to the more reac-

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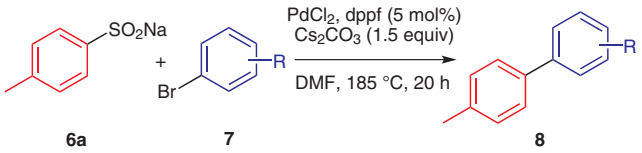
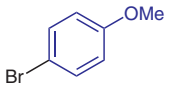
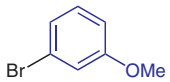
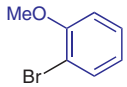
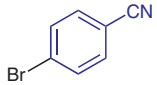
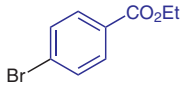
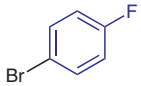
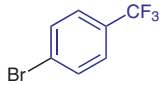
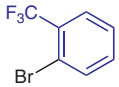
Table 3 Scope for Aryl Bromides[a]



6a 7 8

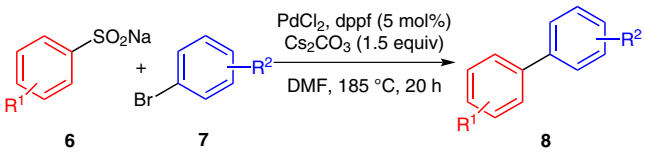
Entry	Aryl bromide	Yield (%)[b]
1	 **7a**	53
2	 **7b**	66
3	 **7c**	50[c]
4	 **7d**	74
5	 **7e**	77[d]
6	 **7f**	76
7	 **7g**	82
8	 **7h**	73[c]

[a] Reaction conditions: sodium *p*-toluenesulfinate (**6a**; 2 mmol, 4.0 equiv), aryl bromide **7** (0.5 mmol, 1.0 equiv), $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.
[b] Isolated yields.
[c] 48 h.
[d] $PdCl_2$ (10 mol%).

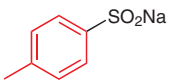
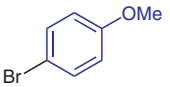
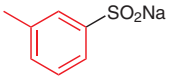
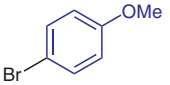
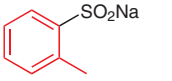
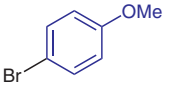
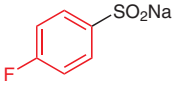
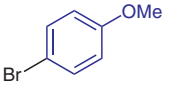
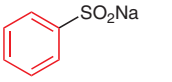
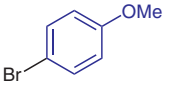
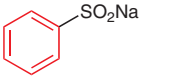
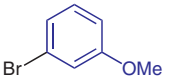
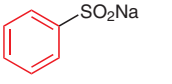
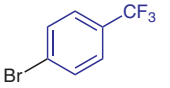
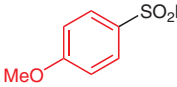
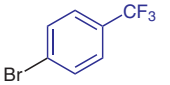
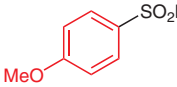
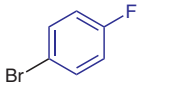
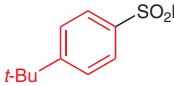
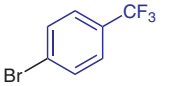
tive electron-poor aryl bromides **7d–h** provided the product in high yields (entries 4–7). Interestingly, the sterically hindered but noncoordinating trifluoromethyl group at the 2-position in **7h** also provided the desired product in good yield (entry 10), which was in contrast to the electron-donating and potentially coordinating 2-bromoanisole (**7c**) (entry 3). Overall, good to very good yields are obtained with a range of aryl bromides.

Subsequently, the scope of the reaction with aryl sulfinates **6** was performed (Table 4). The use of both 4-Me **6a** and 3-Me **6b** substituents (Table 4, entries 1 and 2) had

Table 4 Scope of Aryl Sulfinates[a]



6 7 8

Entry	Aryl sulfinate	Aryl bromide	Yield (%)[b]
1	 **6a**	 **7a**	53
2	 **6b**	 **7a**	50
3	 **6c**	 **7a**	67
4	 **6d**	 **7a**	19
5	 **6e**	 **7a**	74
6	 **6e**	 **7b**	66
7	 **6e**	 **7g**	78
8	 **6f**	 **7g**	82
9	 **6f**	 **7f**	62
10	 **6g**	 **7g**	80

[a] Reaction conditions: sodium aryl sulfinate **6** (2 mmol, 4.0 equiv), aryl bromide **7** (0.5 mmol, 1.0 equiv), $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.
[b] Isolated yields.

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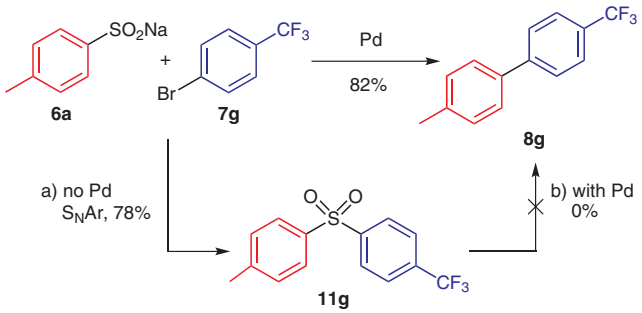
little impact on the yield. Interestingly, the use of the more sterically hindered 2-Me **6c** led to an increased yield (entry 3). The use of electron-poor sulfinate **6d** when coupling with an electron-rich aryl bromide **7a** leads to a low yield (entry 4). Phenyl sulfinate **6e** provides a good yield in comparison to *p*-toluenesulfinate **6a** when coupling to 4-bromoanisole (**7a**) (entry 5) and proceeds in comparable yields with aryl bromides **7b** and **7g** (entries 6 and 7). Electron-rich sulfinates **6f** and **6g** also produce good yields of the desired coupling product **8** (entries 8–10). Overall, a broad range of aryl sulfinates can undergo this cross-coupling reaction; however, electron-rich and -neutral sulfinates seem to be more reactive than electron-poor sulfinates.

In order to determine if the reaction was proceeding via a Pd(0) mediated coupling, a range of control experiments were performed. During the initial screenings of the reaction conditions, a number of by-products were observed (Scheme 2, R = OMe), namely, 4,4′-dimethylbiphenyl (**9**) through homocoupling of the sulfinate **6a**, the formation of a biaryl thioether **10**, and a biaryl sulfone **11a**. Intrigued by the presence of trace amounts of sulfone **11a** and with precedence that sulfinates can act as sulfur nucleophiles,[13] that also react with less-reactive aryl bromides,[13a] the reaction with electron-poor aryl bromide **7g** (4-bromobenzotrifluoride) was further investigated. This led to drastic improvement in the yield of the cross-coupling product **8g** and simultaneously increased the amount of sulfone **11g** produced, likely via an S_NAr reaction (Scheme 2, R = CF_3).

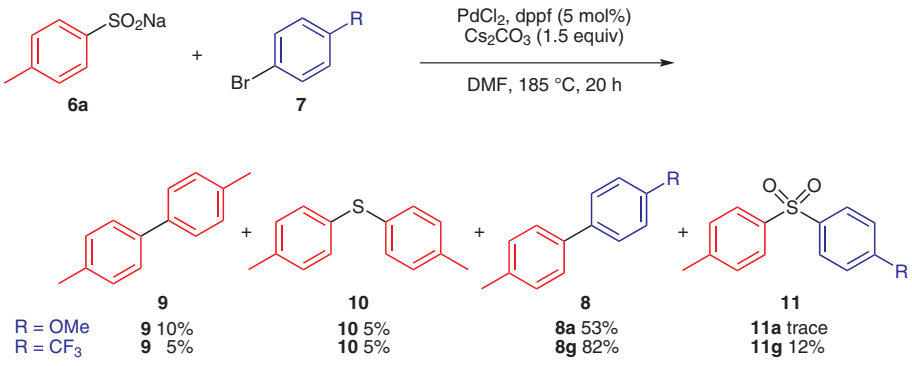
To exclude the possibility of a palladium-catalyzed S_NAr reaction, the coupling was performed in the absence of both the Pd(II) source and the dppf ligand (Scheme 3). In this case, the S_NAr product **11g** was generated in very good yield and only trace amounts of the cross-coupling product **8g** were observed (Scheme 3, conditions a). The sulfone **11g** was then evaluated as a potential intermediate in the cross-coupling reaction; however, when it was treated to the optimized cross-coupling reaction conditions only starting material **11g** was recovered (Scheme 3, conditions b) and no cross-coupling product **8g** was observed.



Scheme 3 The sulfone **11g** is not an intermediate in the reaction. *Reagents and conditions*: sodium *p*-toluenesulfinate (**6a**; 2 mmol), aryl bromide **7g** (0.5 mmol): a) Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h; b) $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h.

The reaction of sulfinate **6a** with 4-bromobenzotrifluoride (**7g**) and 4-fluorobenzotrifluoride (**12**) in the presence and absence of catalyst was evaluated (Scheme 4). In the absence of catalyst (conditions a) the major product of the reaction with the bromoarene **7g** is the S_NAr-derived sulfone **11g**. In the presence of a Pd(0)-catalyst the amount of S_NAr product **11g** is substantially reduced (12%) and the cross-coupling product **8g** is obtained in good yield (82%, conditions b). Fluoroarene **12** is a superior S_NAr substrate than the bromoarene **7g**, but a poor substrate for the cross-coupling reaction. In the absence of catalyst (conditions a) the S_NAr product **11g** was again produced in good yield (73%). When the reaction was attempted with the palladium catalyst (conditions b), no cross-coupling with the fluoroarene **12** was observed. Combined, these results suggest that the cross-coupling of aryl sulfinates **6** with aryl bromides **7** is indeed a palladium-catalyzed reaction and sulfone by-products **11** are produced via a competing S_NAr reaction.

Overall, these experiments support that the transformation is a Pd(0)-mediated coupling, and that the homocoupling by-products **9** and **10** are mediated by palladium while the S_NAr by-product is not. The presence of thioether **10** as a by-product also demonstrates the reducing environment that is created by the liberation of SO_2.[14] Further mecha-



Scheme 2 Observed products for cross-coupling reactions

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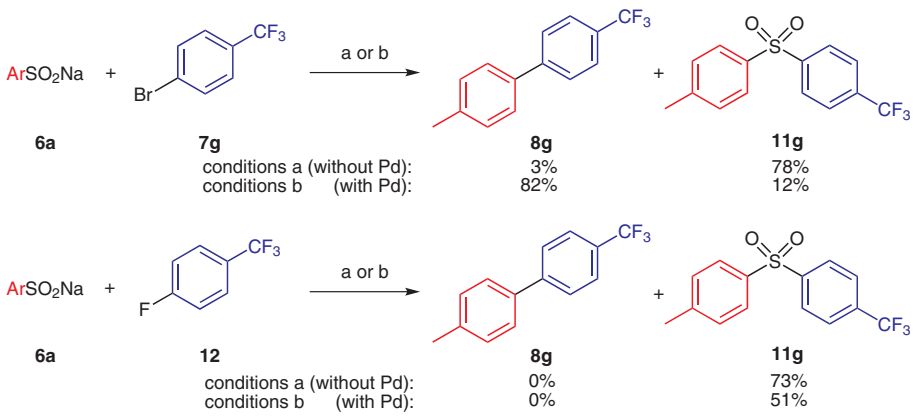
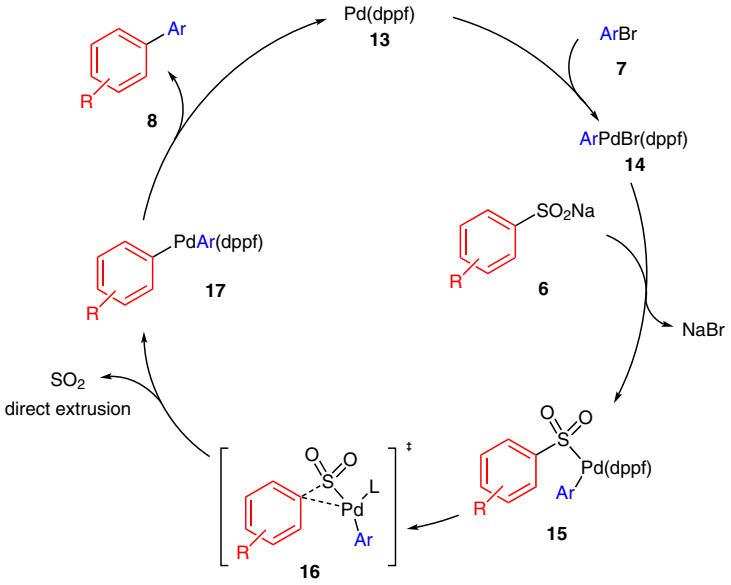


Scheme 4 Investigation of palladium-assisted S_NAr-reaction. *Reagents and conditions*: a) sodium *p*-toluenesulfinate (**6a**; 2 mmol), aryl halide (0.5 mmol), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h; b) sodium *p*-toluenesulfinate (**6a**; 2 mmol), aryl halide (0.5 mmol), $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h.

nistic investigations are required to fully elucidate the details of this transformation; however, these observations lead us to propose a Pd(0)-catalyzed direct extrusion mechanism (Scheme 5), analogous to previous observations for decarboxylative cross-couplings.[7,8] Initial oxidative addition of the palladium-ligand complex **13** into the aryl bromide bond followed by a ligand exchange from bromide to sulfinate **6** produces sulfinato-complex **15**. Due to the tetrahedral character of the sulfinate anion, the phenyl group does not lie in the same plane as palladium and sulfur but is rather prepositioned in closer proximity to the palladium than in a comparable benzoate. The reaction then proceeds via the direct extrusion of SO_2 to yield bis-arylated species **17**, which is the main driving force of the reaction. The bis-arylated intermediate **17**, then undergoes reductive elimination yielding the biphenyl product **8** while regenerating the catalytic Pd(0) complex **13**.

To gain further mechanistic insights and to better understand the role of sulfur dioxide, additional control experiments were envisioned favoring its capture and neutralization. $CaCO_3$ and other calcium bases are commonly used in industrial scrubbing processes of SO_2.[15] Therefore, we investigated the use of $CaCO_3$ as both a carbonate base and SO_2 scrubber. A slight decline in yield was observed when using $CaCO_3$ (Table 5, entry 2) compared to the optimized Cs_2CO_3 (entry 1); however, CaO (entry 3) demonstrated a drastic reduction in sulfinate-derived by-product formation when used in excess (entry 4). Hence, further investigations are required to reduce the excess use of sodium sulfinate **6** while maintaining high yields. Promising preliminary results demonstrate only a minor reduction in yield when reducing sulfinate loading to one equivalent (entry 5 vs 1). Current efforts in our lab are aimed at exploiting this for further optimization of the reaction.



Scheme 5 Proposed Pd(0) mechanism for desulfinylative coupling

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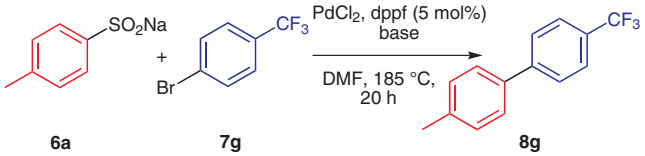
Table 5 Investigation of the Removal of SO_2[a]



6a 7g 8g

Entry	Base	Yield (%)
1	Cs_2CO_3	82
2	$CaCO_3$[b]	72
3	CaO	67
4	CaO (6 equiv)[c]	64
5	CaO (6 equiv)[d]	72

[a] Reaction conditions: sodium *p*-toluenesulfinate (**6a**; 2 mmol), 4-bromobenzotrifluoride (**7g**; 0.5 mmol), $PdCl_2$ (5 mol%), dppf (5 mol%), base (0.75 mmol), DMF (4 mL), 185 °C, 20 h.
[b] $CaCO_3$ used: 4 equiv (2 mmol).
[c] CaO used: 3 mmol.
[d] *p*-Toluenesulfinate and CaO used: 0.5 and 3 mmol, respectively.

In conclusion, we have demonstrated that the desulfinylative cross-coupling reaction between aryl sulfinates **6** and aryl bromides **7** can be performed with a range of substrates. We have also shown that the choice of base is critical to the success of the reaction. Importantly, the transformation could be performed using Pd(0) catalysts formed in situ. Bidentate ligands proved to have an important effect on the activity of the palladium complex. Efforts were also made to further understand the operative mechanism, and preliminary results lead us to propose a Pd(0)-mediated transformation. Initial results indicate that SO_2 scavengers will play an important role in the future optimization of this reaction.

All reactions were performed in oven-dried (110 °C) microwave glassware (10 mL) under an argon atmosphere containing a Teflon-coated stir bar and dry septum unless more specific conditions are stated. Chemicals were purchased from Aldrich and Alfa Aesar and if not stated otherwise used as purchased without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and were dried over activated molecular sieves (3 Å). Distilled water was obtained from an in-house water distillery prior to use. Column chromatography was done on silica gel (Zeoprep 60 Eco, 40–63 µm, Zeochem AG), the eluents are indicated for each compound.

^1H, ^{13}C, and ^{19}F spectra were recorded on a Varian VNMRS-500 NMR (500 MHz ^1H NMR, 125 MHz ^{13}C NMR, and 470 MHz ^{19}F NMR) or a Varian INOVA-300 NMR (300 MHz ^1H NMR, 75 MHz ^{13}C NMR). TMS was used as a reference for the ^1H and ^{13}C spectra. Microwave assisted reactions were performed using the Biotage Initiator™ Microwave System with a 400 W magnetron. The masses of the compounds were obtained on a GCMS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV).

Desulfinylative Palladium-Catalyzed Cross-Coupling of Aryl Sulfinates with Aryl Bromides; General Procedure

An oven dried microwave-vessel under argon was charged with sodium sulfinate **6** (2.0 mmol), anhyd Cs_2CO_3 (244 mg, 0.75 mmol), $PdCl_2$ (4.5 mg, 0.025 mmol), dppf (13.9 mg, 0.025 mmol), bromoarene **7** (0.5 mmol), and DMF (4 mL). The vial was capped with a septum and heated for 20 h in a wax-bath at 185 °C. After cooling to 23 °C, the mixture was filtered through Celite and the vessel was rinsed with EtOAc (4 × 7 mL) and H_2O (2 × 7 mL). The layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (2 × 15 mL), sat. aq $NaHCO_3$ (2 × 15 mL) and again with brine (2 × 15 mL). After drying (Na_2SO_4), the organic layer was concentrated under reduced pressure. The crude, colored product was purified by column chromatography to yield a colorless solid.

4-Methoxy-4′-methyl-1,1′-biphenyl (8a)
[CAS Reg. No. 53040-92-9]

Compound **8a** was prepared from 4-bromoanisole (**7a**; 63 µL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol). Purification by column chromatography (pure hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (52 mg, 0.26 mmol, 53%); mp 104–106 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8a**.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 6.96 (m, ^3J = 9 Hz, 2 H, H-3, H-5), 7.22 (d, ^3J = 8 Hz, 2 H, H-3′,5′), 7.44 (m, ^3J = 8 Hz, 2 H, H-2′,6′), 7.51 (m, ^3J = 9 Hz, 2 H, H-2,6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0 (CH_3), 55.3 (OCH_3), 114.2, 126.6, 127.9, 129.4, 133.8, 136.3, 138.0, 158.9.

MS (EI, 70 eV): *m/z* (%) = 155.1 (40), 183.0 (60), 198.1 (100, $[M]^+$).

3-Methoxy-4′-methyl-1,1′-biphenyl (8b)
[CAS Reg. No. 24423-07-2]

Compound **8b** was prepared from 3-bromoanisole (**7b**; 63.3 µL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol). Purification by column chromatography (pure hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (65 mg, 0.32 mmol, 66%); mp 74–76 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8b**.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.87 (d, ^3J = 8 Hz, 1 H, H-4), 7.16 (m, 2 H, H-2,6), 7.24 (d, ^3J = 8 Hz, 2 H, H-3′,5′), 7.34 (t, ^3J = 8 Hz, 1 H, H-5), 7.49 (d, ^3J = 8 Hz, 2 H, H-2′,6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 55.3 (OCH_3), 112.4, 112.7, 119.5, 127.0, 129.4, 129.7, 130.1, 132.6, 137.2, 138.2, 142.7, 159.9.

MS (EI, 70 eV): *m/z* (%) = 198.1 (100, $[M]^+$).

2-Methoxy-4′-methyl-1,1′-biphenyl (8c)
[CAS Reg. No. 92495-53-9]

Compound **8c** was prepared from 2-bromoanisole (**7c**; 62.3 µL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol) in 48 h reaction time. Purification by column chromatography (pure hexanes, followed by 2% Et_2O–hexanes) gave 49 mg (50%) of a colorless solid; mp 78–81 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8c**.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 6.99 (m, 2 H, H-3,5), 7.21 (d, ^3J = 8 Hz, 2 H, H-3′,5′), 7.30 (m, 2 H, H-6,4), 7.42 (d, ^3J = 8 Hz, 2 H, H-2′,6′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 55.5 (OCH_3), 111.2, 120.8, 128.3, 128.7, 129.4, 130.8, 135.6, 136.6, 156.5.

MS (EI, 70 eV): *m/z* (%) = 168.0 (50), 183.0 (50), 198.1 (100, $[M]^+$).

4-Cyano-4′-methyl-1,1′-biphenyl (8d)
[CAS Reg. No. 50670-50-3]

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Compound **8d** was prepared from 4-bromobenzonitrile (**7d**; 91 mg, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol). Purification by column chromatography (5–10% Et_2O–hexanes) gave a colorless solid (72 mg, 0.37 mmol, 74%); mp 103–105 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8d**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.29 (dm, ^3J = 8 Hz, 2 H, H-3′,5′), 7.49 (dm, ^3J = 8 Hz, 2 H, H-2′,6′), 7.67 (dm, ^3J = 9 Hz, 2 H, H-3,5), 7.71 (dm, ^3J = 9 Hz, 2 H, H-2,6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.0, 127.4, 129.8, 132.5, 136.3, 138.7, 145.6.

MS (EI, 70 eV): *m*/*z* (%) = 165.1 (20), 193.1 (100, $[M]^+$).

Ethyl 4′-Methylbiphenyl-4-carboxylate (8e)
[CAS Reg. No. 106508-97-8]

Compound **8e** was prepared from ethyl 4-bromobenzoate (**7e**; 114 mg, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol) using 10 mol% $PdCl_2$ (9 mg, 0.05 mmol) and dppf (27.8 mg, 0.05 mmol). Purification by column chromatography (5% to 10% Et_2O–hexanes) gave a colorless solid (94 mg, 0.39 mmol, 78%); mp 76–78 °C. The spectroscopic data (NMR) matched those reported in the literature for **8e**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7 Hz, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 4.40 (q, ^3J = 7 Hz, 2 H, OCH_2), 7.27 (d, ^3J = 8 Hz, 2 H, H-3′,5′), 7.53 (dm, ^3J = 8 Hz, 2 H, H-2′,6′), 7.64 (dm, ^3J = 9 Hz, 2 H, H-3,5), 8.09 (dm, ^3J = 9 Hz, 2 H, H-2,6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 (CH_3), 21.1 (CH_3), 60.9 (OCH_3), 126.7, 127.0, 128.0, 128.7, 129.0, 129.6, 130.0, 131.2, 137.2, 138.1, 141.4, 145.5, 166.6 (CO_2Et).

4-Fluoro-4′-methyl-1,1′-biphenyl (8f)
[CAS Reg. No. 72093-43-7]

Compound **8f** was prepared from 1-bromo-4-fluorobenzene (**7f**; 54.5 μL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol). Purification by column chromatography (hexanes) gave a colorless solid (71 mg, 0.38 mmol, 76%); mp 72–74 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8f**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 7.10 (m, 2 H), 7.23 (m, 2 H), 7.43 (m, 2 H) 7.51 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 115.4, 115.6, 126.9, 128.4, 128.5, 129.5, 137.0, 137.3, 137.4, 161.3, 163.3.

MS (EI, 70 eV): *m*/*z* (%) = 186.1 (100, $[M]^+$).

4-Methyl-4′-(trifluoromethyl)-1,1′-biphenyl (8g)
[CAS Reg. No. 97067-18-0]

Compound **8g** was prepared from 4-bromobenzotrifluoride (**7g**; 70 μL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol). Purification by column chromatography (hexanes) gave a colorless solid (97 mg, 0.41 mmol, 82%); mp 119–121 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8g**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.28 (dm, ^3J = 8, 0.5 Hz, 2 H, H-3′,5′), 7.50 (dm, ^3J = 8, 0.5 Hz, 2 H, H-2′,6′), 7.67 (s, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 125.5, 125.8, 127.0, 127.3, 129.2, 129.8, 136.9, 138.1, 144.6.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.4.

MS (EI, 70 eV): *m*/*z* (%) = 167.1 (33), 236.1 (100, $[M]^+$).

4-Methyl-2′-(trifluoromethyl)-1,1′-biphenyl (8h)
[CAS Reg. No. 145486-55-1]

Compound **8h** was prepared from 2-bromobenzotrifluoride (**7h**; 68.1 μL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol) in 48 h reaction time. Purification by column chromatography (hexanes) gave a clear liquid (86 mg, 0.36 mmol, 73%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8h**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.22 (s, 4 H), 7.32 (d, ^3J = 8 Hz, 1 H), 7.44 (t, ^3J = 8 Hz, 1 H), 7.54 (t, ^3J = 8 Hz, 1 H), 7.73 (d, ^3J = 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 126.1, 126.2, 127.3, 128.6, 129.0, 131.4, 132.3, 137.3, 137.5.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –56.9.

MS (EI, 70 eV): *m*/*z* (%) = 236.1 (100, $[M]^+$).

4-Methoxy-3′-methyl-1,1′-biphenyl (8i)
[CAS Reg. No. 17171-17-4]

Compound **8i** was prepared from 4-bromoanisole (**7a**; 63 μL, 0.5 mmol) and sodium *m*-toluenesulfinate (**6b**; 356 mg, 2 mmol). Purification by column chromatography (pure hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (49 mg, 0.25 mmol, 50%); mp 51–52 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8i**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.97 (d, ^3J = 9 Hz, 2 H, H-3,5), 7.12 (d, ^3J = 7.5 Hz, 1 H), 7.30 (d, ^3J = 7.5 Hz, 1 H), 7.35 (m, 2 H), 7.52 (d, ^3J = 9 Hz, 2 H, H-2,6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 55.3 (OCH_3), 114.1, 123.9, 127.4, 127.6, 128.2, 128.6, 133.9, 138.3, 140.8, 159.1.

MS (EI, 70 eV): *m*/*z* (%) = 198.1 (100, $[M]^+$).

4-Methoxy-2′-methyl-1,1′-biphenyl (8j)
[CAS Reg. No. 92495-54-0]

Compound **8j** was prepared from 4-bromoanisole (**7a**; 63 μL, 0.5 mmol) and sodium *o*-toluenesulfinate (**6c**; 356 mg, 2 mmol). Purification by column chromatography (hexanes, followed by 2% Et_2O–hexanes) gave a light yellow liquid (66 mg, 0.33 mmol, 67%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8j**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.95 (d, ^3J = 8 Hz, 2 H, H-3,5), 7.24 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5 (CH_3), 55.3 (OCH_3), 113.5, 125.7, 127.0, 129.9, 130.2, 130.3, 134.4, 135.5, 141.5, 158.5.

MS (EI, 70 eV): *m*/*z* (%) = 198.1 (100, $[M]^+$).

4′-Fluoro-4-methoxy-1,1′-biphenyl (8k)
[CAS Reg. No. 450-39-5]

Compound **8k** was prepared from 4-bromoanisole (**7a**; 63 μL, 0.5 mmol) and sodium 4-flurobenzenesulfinate (**6d**; 364 mg, 2 mmol). Purification by column chromatography (hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (19 mg, 0.09 mmol, 19%); mp 81–83 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8k**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.96 (d, ^3J = 8.5 Hz, 2 H, H-3,5), 7.09 (t, ^3J = 9 Hz, 2 H, H-3,5), 7.49 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.2, 114.3, 115.0, 115.4, 115.6, 126.7, 128.0, 128.1, 128.2, 128.2, 128.7, 132.8, 134.5, 137.0, 159.1, 162.0 (d, 244 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 133.0 (25), 159.1 (50), 187.1 (50), 202.1 (100, $[M]^+$).

4-Methoxy-1,1′-biphenyl (8l)
[CAS Reg. No. 613-37-6]

Compound **8l** was prepared from 4-bromoanisole (**7a**; 63 μL, 0.5 mmol) and sodium benzenesulfinate (**6e**; 364 mg, 2 mmol). Purification by column chromatography (pure hexanes, followed by 2%

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Et_2O–hexanes) gave a colorless solid (49 mg, 0.27 mmol, 53%); mp 83–84 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8l**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.98 (d, ^3J = 7.5 Hz, 2 H, H-3,5), 7.30 (t, ^3J = 7.5 Hz, 1 H, H-4′), 7.41 (t, ^3J = 7.5 Hz, 2 H), 7.54 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 114.2, 126.6, 128.2, 128.7, 133.8, 140.8, 159.1.

MS (EI, 70 eV): *m*/*z* (%) = 184.1 (100, $[M]^+$).

3-Methoxy-1,1′-biphenyl (8m)
[CAS Reg. No. 2113-56-6]

Compound **8m** was prepared from 3-bromoanisole (**7b**; 63.3 μL, 0.5 mmol) and sodium benzenesulfinate (**6e**; 364 mg, 2 mmol). Purification by column chromatography (pure hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (61 mg, 0.33 mmol, 66%); mp 88–90 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8m**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.88 (d, ^3J = 8 Hz, 1 H, H-4), 7.12 (m, 1 H, H-6), 7.17 (d, ^3J = 7.5 Hz, 1 H), 7.34 (m, 2 H), 7.42 (t, ^3J = 7.5 Hz, 2 H), 7.58 (d, ^3J = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 112.7, 112.9, 119.7 127.2, 127.4, 128.7, 129.7, 141.1, 142.8, 159.9.

MS (EI, 70 eV): *m*/*z* (%) = 184.1 (100, $[M]^+$).

4-(Trifluoromethyl)-1,1′-biphenyl (8n)
[CAS Reg. No. 398-36-7]

Compound **8n** was prepared from 4-bromobenzotrifluoride (**7g**; 70.0 μL, 0.5 mmol) and sodium benzenesulfinate (**6e**; 364 mg, 2 mmol). Purification by column chromatography (hexanes) gave a colorless solid (86 mg, 0.39 mmol, 78%); mp 70–72 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8n**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, ^3J = 7.5 Hz, 1 H, H-4′), 7.47 (d, ^3J = 7.5 Hz, 2 H, H-3,5), 7.6 (d, ^3J = 7.5 Hz, 2 H, H-2,6), 7.65 (s, 4 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 123.3, 125.4, 125.7, 127.3, 127.4, 127.6, 128.2, 129.0, 129.2, 129.5, 139.8, 144.7.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.4.

4-Methoxy-4′-(trifluoromethyl)-1,1′-biphenyl (8o)
[CAS Reg. No. 10355-12-1]

Compound **8o** was prepared from 4-bromobenzotrifluoride (**7g**; 70.0 μL, 0.5 mmol) and sodium *p*-methoxybenzenesulfinate (**6f**; 388 mg, 2 mmol). Purification by column chromatography (hexanes, followed by 2% Et_2O–hexanes) gave a colorless solid (104 mg, 0.41 mmol, 82%); mp 122–124 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8o**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 7.01 (d, ^3J = 8 Hz, 2 H, H-3,5), 7.54 (d, ^3J = 8 Hz, 2 H, H-2,6), 7.65 (s, 4 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.4, 123.3, 125.6, 126.9, 128.4, 128.6, 128.8, 144.3, 159.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.4.

MS (EI, 70 eV): *m*/*z* (%) = 209.0 (50), 237.0 (30), 252.0 (100, $[M]^+$).

4-Fluoro-4′-Methoxy-1,1′-biphenyl (8p)
[CAS Reg. No. 450-39-5]

Compound **8p** was prepared from 1-bromo-4-fluorobenzene (**7f**; 54.5 μL, 0.5 mmol) and sodium 4-methoxybenzenesulfinate (**6f**; 388 mg, 2 mmol). Purification by column chromatography (hexanes, followed by 2% EtOAc–hexanes) gave a colorless solid (63 mg, 0.31 mmol, 62%); mp 81–83 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8p**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.96 (d, ^3J = 8.5 Hz, 2 H, H-3/H-5), 7.09 (t, ^3J = 9 Hz, 2 H, H-3/H-5), 7.49 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.2, 114.3, 115.0, 115.4, 115.6, 126.7, 128.0, 128.1, 128.2, 128.2, 128.7, 132.8, 134.5, 137.0, 159.1, 162.0 (d, 244 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 133.0 (25), 159.1 (50), 187.1 (50), 202.1 (100) $[M]^+$.

4-*tert*-Butyl-4′-(trifluoromethyl)-1,1′-biphenyl (8q)
[CAS Reg. No. 386742-85-4]

Compound **8p** was prepared from 4-bromobenzotrifluoride (**7g**; 70 μL, 0.5 mmol) and sodium 4-*tert*-butylbenzenesulfinate (**6g**; 440 mg, 2 mmol). Purification by column chromatography (hexanes) gave a colorless solid (111 mg, 0.40 mmol, 80%); mp 104–106 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **8q**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, t-C_4H_9), 7.50 (d, ^3J = 8.5 Hz, 2 H, H-3′,5′), 7.55 (d, ^3J = 8.5 Hz, 2 H, H-2′,6′), 7.68 (s, 4 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.2 (CH_3), 34.6, 123.3, 125.3, 125.5, 125.8, 126.2, 126.5, 126.8, 127.1, 127.3, 128.9, 129.2, 136.8, 144.6, 151.4.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.3.

MS (EI, 70 eV): *m*/*z* (%) = 235.1 (25), 263.1 (100), 278.1 (25, $[M]^+$).

4,4′-Dimethyl-1,1′-biphenyl (9)
[CAS Reg. No. 613-33-2]

Compound **9** was obtained as by-product as described in Scheme 2. Purification by column chromatography (hexanes) gave a colorless solid; mp 116–118 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **9**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 7.24 (d, ^3J = 8 Hz, 2 H), 7.48 (d, ^3J = 8 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 126.8, 129.4, 136.69, 138.28.

MS (EI, 70 eV): *m*/*z* (%) = 167.1 (45), 182.1 (100, $[M]^+$).

4,4′-Dimethyldiphenyl Sulfide (10)
[CAS Reg. No. 620-94-0]

Compound **10** was obtained as a by-product as described in Scheme 2. Purification by column chromatography (hexanes) gave a colorless solid; mp 54–55 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **10**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 7.10 (d, ^3J = 8.5 Hz, 2 H), 7.23 (d, ^3J = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 129.9, 131.1, 132.7, 136.9.

MS (EI, 70 eV): *m*/*z* (%) = 199.0 (33), 214.1 (100, $[M]^+$).

1-Trifluoromethyl-4-(toluene-4-sulfonyl)benzene (11g)
[CAS Reg. No. 947185-15-1]

Compound **11g** was prepared from 4-bromobenzotrifluoride (**7g**; 70.0 μL, 0.5 mmol) and sodium *p*-toluenesulfinate (**6a**; 388 mg, 2 mmol) following the general procedure but without $PdCl_2$ and dppf. Purification by column chromatography (10% EtOAc–hexanes) gave a colorless solid (117 mg, 0.39 mmol, 78%); mp 125–128 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for **11g**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.33 (d, ^3J = 8.4 Hz, 2 H), 7.75 (d, ^3J = 8.4 Hz, 2 H) 7.84 (d, ^3J = 8.4 Hz, 2 H), 8.06 (d, ^3J = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 126.6, 128.2, 130.5, 145.2.

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MS (EI, 70 eV): *m*/*z* (%) = 91.0 (70), 107.0 (70), 139.0 (100), 300.1 (75, $[M]^+$).

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