Practical Synthesis of 5-Aryl-3-alkylsulfonyl-phenol and 5-Aryl-3-arylsulfonyl-phenol Libraries

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A straightforward and cost-effective synthesis of 5-aryl-3-alkylsulfonyl-phenols by a sequential scaffold derivatization strategy has been developed. The procedure is suitable for parallel synthesis of small libraries around the biphenyl privileged core having an unusual 1,3,5-substitution pattern. The synthesis is exemplified by a pilot library of 30 compounds.

Introduction

The biaryl (particularly biphenyl) ring system is a common, so-called privileged substructure in recent drug discovery; 4.3% of registered drugs contain such hydrophobic moieties, including some best selling drugs such as Losartan and Valsartan.[1] Although the emergence of transition metal-catalyzed coupling reactions has made such privileged substructures readily available for research, the typical biphenyl framework contains substituents mostly in the para position and, to a lesser extent, in the ortho position.

In contrast, meta-substituted sulfur-containing aryl-phenols or phenol ethers are particularly unexploited chemotypes in pharmaceutical research, although a few examples have been reported as having biological activities as MMP inhibitors[2] or for treatment of "complement-mediated" immune diseases.[3−5] In the course of a lead generation effort, we required a flexible method, amenable to the high-throughput parallel synthesis of 3-aryl-5-alkylsulfonyl-phenols. Only a few synthetic routes have been reported toward such structures. Thus, cyclization of 4-bis(methylthio)-3-buten-2-one with acetophenone (Scheme 1) affords 5-hydroxy-3-(methylthio)-biphenyl (**I**, R = Ph, R^1 = Me) yielding entities with S-substitution limited to methyl derivatives (**I**, R^1 = Me).[6] An alternative route involving Suzuki−Miyaura coupling requires the corresponding 3-halogen substituted 5-(methylsulfinyl)anisoles **II** as precursors. The major reason for the under-representation of this type of chemistry is a poor synthetic availability of such meta-halogen-substituted intermediates. The only known example is the synthesis of 3,5-dibromoanisole from the corresponding brominated anilines through deamination, monobromolithium exchange with *sec*-butyllithium, and reaction of the resultant aryllithium with sulfur followed by S-alkylation.[7]

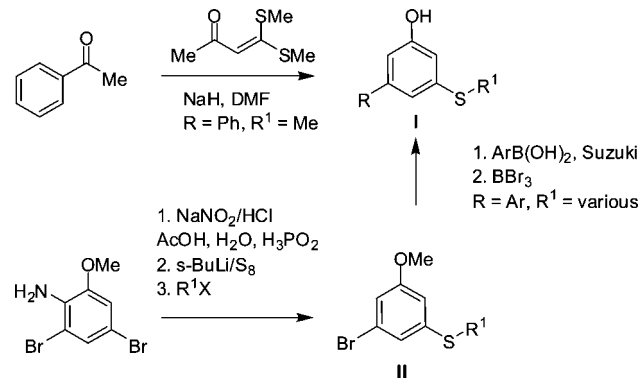
Another approach utilizes *O*-aryl thiocarbamates to yield the corresponding *S*-aryl thiocarbamates via the Newman−Kwart rearrangement[8] (Scheme 2).

Here, we report the development of a straightforward, advantageous and cost-effective synthesis of 5-aryl-3-alkylsulfonyl-phenols and the parallel library synthesis of such compounds by a sequential scaffold derivatization strategy.

Results and Discussion

Starting with *m*-dihalobenzene derivatives, several well-described procedures can be considered[9] for the exchange of one aromatic halogen for an *S*-alkyl (especially *S*-Me) group, while keeping the other intact for further introduction of the aryl ring. In the case of such deactivated aryl halides, the application of catalysts (Pd^0)[10] has been reported to improve reaction yields. Alternatively, *t*-BuLi[11] was required under inert atmosphere to initialize the proper reaction. These reactions needed fine-tuning of the conditions and are usually accompanied by side-product formation. On the basis of this, we began our work with direct nucleophilic substitution of dibromide **1** using sodium thiomethoxide. Thus, the methylsulfanyl-benzene derivative (**2a**) was synthesized in moderate yield (50%) in DMF using sodium thiomethoxide, followed by a subsequent oxidation to afford alkyl-sulfone (**3a**) (Scheme 3).

Scheme 1



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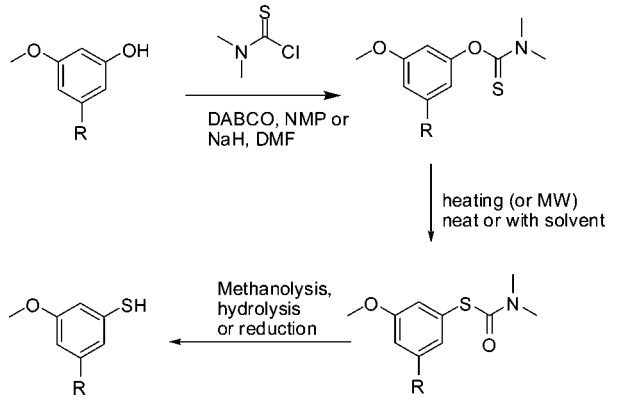
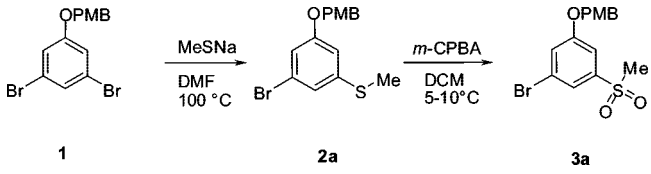
Scheme 2



Scheme 3



This procedure was also tested with other alkyl thiolates, but poor conversion was obtained, particularly when thiols with branched alkyl groups were used as starting materials. Another option was to replace one halogen atom by an *S*-alkyl group using palladium(0) catalysis. However, this route is still limited by the number of commercially available alkyl thiols.

Ideally, we envisioned that alkylsulfanyl-benzene derivatives can be obtained by the introduction of the thiol moiety on the *meta*-dibromo-benzene scaffold as a first step, followed by alkylation of the intermediate aryl thiol with diverse, commercially available alkyl bromides. Thus, we turned our attention to the recently reported Pd-catalyzed S-thiolation protocol,[12] which involves intermediate *S*-aryl thioacetates, and their subsequent hydrolysis yielding the corresponding thiols. We extended the scope of this reaction to protected 3-bromo-5-alkylsulfanyl-phenols as precursors of our target molecule. We were pleased to find that this sequential scaffold derivatization method results in a short, convenient, and cost-effective synthesis of a 5-aryl-3-alkylsulfonyl-phenols from 1,3,5-tribromobenzene in 6 steps, and its application in parallel synthesis gives the required products in 5−20% overall yields.

Starting from 1,3,5-tribromobenzene, the PMB-protected 3,5-dibromophenol **1** was obtained by nucleophilic displacement with *para*-methoxybenzyl alcohol. (Scheme 4). This step was followed by a microwave-assisted Pd-catalyzed thiolation. The intermediate acetate **7** was rather unstable; thus, it was used immediately in the subsequent hydrolysis step without purification.

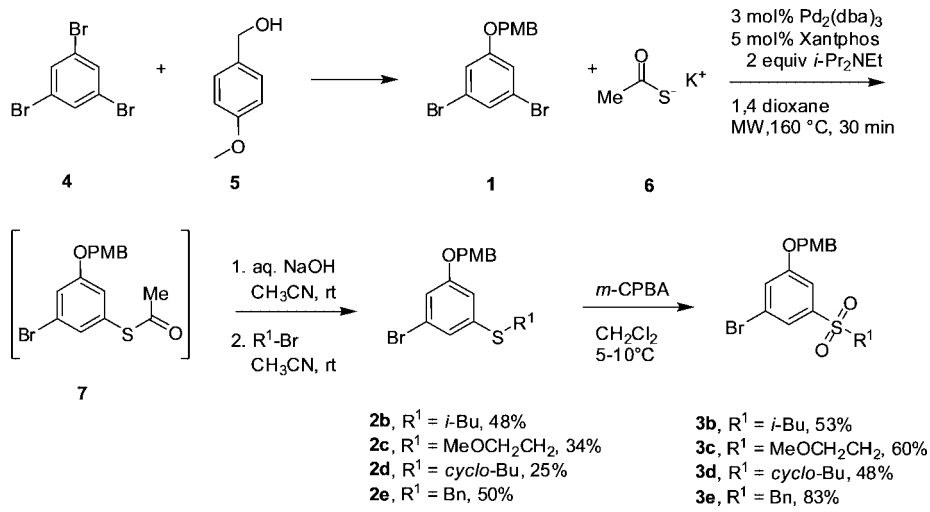
The corresponding PMB-protected 3-bromo-5-hydroxy-benzene-thiolate sodium salt was further alkylated with a variety of alkyl bromides, as well as benzyl bromide, to produce a set of thioethers **2** in moderate yields. The thioethers were then oxidized using *m*-chloro-perbenzoic acid in DCM to afford the corresponding sulfones **3b**−**e** in 48−83% yield. The representative procedures and analytical data for compounds **3** are presented in the Experimental Section.

The above procedure was not suitable to produce the 3-aryl-5-alkylsulfonyl-phenols in the case of R_1 = Ph and *t*-Bu. The appropriate sulfides were synthesized in a coupling reaction using the corresponding thiols in the presence of palladium catalyst (Scheme 5).

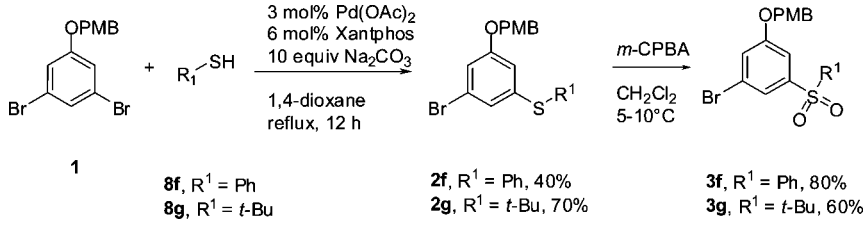
Further generation of the desired 5-aryl-3-alkylsulfonyl-phenol library included a Suzuki C−C bond formation and subsequent PMB-deprotection. Optimization of this chemistry was required to avoid partial PMB-deprotection and the formation of side-products in the Suzuki coupling step. The optimized reaction conditions (Scheme 6) were applied to methyl sulfone **3a** with various boronic acids, and an 18-membered library of 3-aryl-5-methylsulfonyl-phenols was generated. Scheme 5 contains the structures of the boronic acids, the synthetic methods applied, and the numbering of the products, and Table 1 shows the yields obtained for the Suzuki coupling reaction and subsequent deprotection step. Substituted arylboronic acids (**9**) were reacted in the presence of $Pd(PPh_3)_4$ and a catalytic amount of KI in DME under microwave irradiation at 160 °C for 60 min (Method A). Heterocyclic boronic acids were less reactive and full conversion could not be achieved under these conditions. Nevertheless, using $Pd(PPh_3)_4$ and catalytic amounts of CsF in acetonitrile at 160 °C for 45 min (Method B), the heterocyclic derivatives can be synthesized in moderate yields. The PMB-cleavage step was also carried out with two alternative methods. In the case of derivatives that are sensitive to strong acidic media the regular BBr_3 deprotection conditions (Method C) were complemented with mild reduction using H_2 in the presence of Pd/C catalyst (Method D). The crude purity of the final compounds was 60−85%, and they were further purified by HPLC. Synthetic results and the conditions used are summarized in Table 1 for compounds derived from **3a** and boronic acids **9a**−**r**.

To extend the diversity beyond methyl-sulfonyl derivatives, sulfones **3b**−**g** were examined in the Suzuki coupling reaction with two boronic acids, affording in good yields another 12 compound representatives in the 5-aryl-3-alkyl- and 5-aryl-3-aryl-sulfonyl-phenol library (Scheme 7, Tables 2 and 3). Method A for the Suzuki coupling step proved to be efficient, while the subsequent deprotection needed further optimization because most of the entities in this set were sensitive to strong Lewis acidic treatment or hydrogenation conditions. We were glad to discover that acidic conditions are sufficient and superior for PMB cleavage. Thus, the deprotection occurred smoothly by heating intermediates **10** in neat Glacial acetic acid at 100 °C for 1 h (Method E). Moreover, when these reactions were performed under microwave irradiation conditions, the reaction time could be drastically shortened to one hour to afford the targets in good yields. The 2-methoxyethyl-sulfonyl derivative **3c** behaved differently from the other R^1-series. Interestingly, 2-methoxyethyl-sulfonyl derivative **3c** did not afford the target compounds by Method A, while Method B resulted Suzuki

Scheme 4



Scheme 5



reaction and sequential deprotection to yield 3-aryl-5-(2-methoxy-ethane-sulfonyl-phenols **11c**,**a** and **11c**,**b** in one pot.

Conclusion and Summary

We have developed a short and cost-effective synthesis procedure of 3-aryl-5-alkylsulfonyl-phenols from 1,3,5-tribromobenzene, which is suitable for the parallel synthesis of small molecule libraries around the biphenyl privileged core with an unusual 1,3,5-substitution pattern.

Reaction conditions for Suzuki coupling and deprotection steps were optimized depending on reactivity and the substitution pattern of the building blocks. A total of 30 compounds were synthesized as a pilot library to demonstrate the versatility of the procedure reported here.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 or 400 MHz on a Bruker DRX 300 or Bruker Avance II 400 instruments, respectively. The measurements were done at room temperature with $CDCl_3$ and dimethylsulfoxide-d_6 as solvents. For the calibration of the spectra, the solvent peak and TMS signal were used in the case of choroform-*d*, and the solvent peak was used in the case of DMSO-d_6. All chemical reagents were obtained from commercial sources and were used without further purification.

Mass spectra and LC-MS mass data were obtained on (i) HPLC system comprising Waters 1525 high pressure binary HPLC pump integrated with splitter, MUX-UV 2488 detector (Waters Corp.) and in-house developed autosampler based on a Cavro RSP 9452 (Cavro Scientific Inst., Inc.) robotic workstation or (ii) ZQ2000 MS instrument (Waters Corp.) with ESI interface integrated with MUX (Waters Corp.). LC-MS analyses were obtained using a LiChroCART 30-4 Purospher STAR RP-18, end capped, 3 μm column (Merck) with UV detection at 220 or 254 nm using a standard solvent gradient program.

Synthesis of 1,3-Dibromo-5-(4-methoxybenzyloxy)benzene (1). In a 250-mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser, sodium hydride (60%, 6.67 g; 167 mmol) was added portionwise to a solution of (4-methoxy)-benzyl alcohol (14.0 g; 101 mmol) in dry DMF (40 mL), keeping the temperature below 60 °C (vigorous gas evolution!), and the mixture was stirred at 55 °C for 10 min. 1,3,5-Tribromobenzene (20.9 g; 66.5 mmol) was added portionwise while stirring and keeping the inner temperature below 60 °C, and the color of the mixture turned deep brown. The resulting mixture was heated to 120 °C and stirred for 4 h. The reaction was monitored by TLC using hexanes/ethyl-acetate 20:1. The mixture was cooled to room temperature and partitioned between diethyl ether (500 mL) and water (200 mL). The organic layer was separated, washed with water (2 × 100 mL), 5% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified on silica using a hexanes/ethyl-acetate (20:1) mixture as eluent to afford the product (15.9 g, 64%) as a pale yellow solid.

1,3-Dibromo-5-(4-methoxybenzyloxy)benzene (1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 7.25 (t, J = 1.6 Hz, 1H), 7.06 (d, J = 1.6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.94 (s, 2H), 3.82 (s, 3H).

Synthesis of (3-(4-Methoxybenzyloxy)-5-bromophenyl)-(methyl)sulfane (2a). NaSMe (1.97 g, 1 equiv.; 28.1 mmol) was added to a solution of 1,3-dibromo-(5-(4-methoxy-

Scheme 6

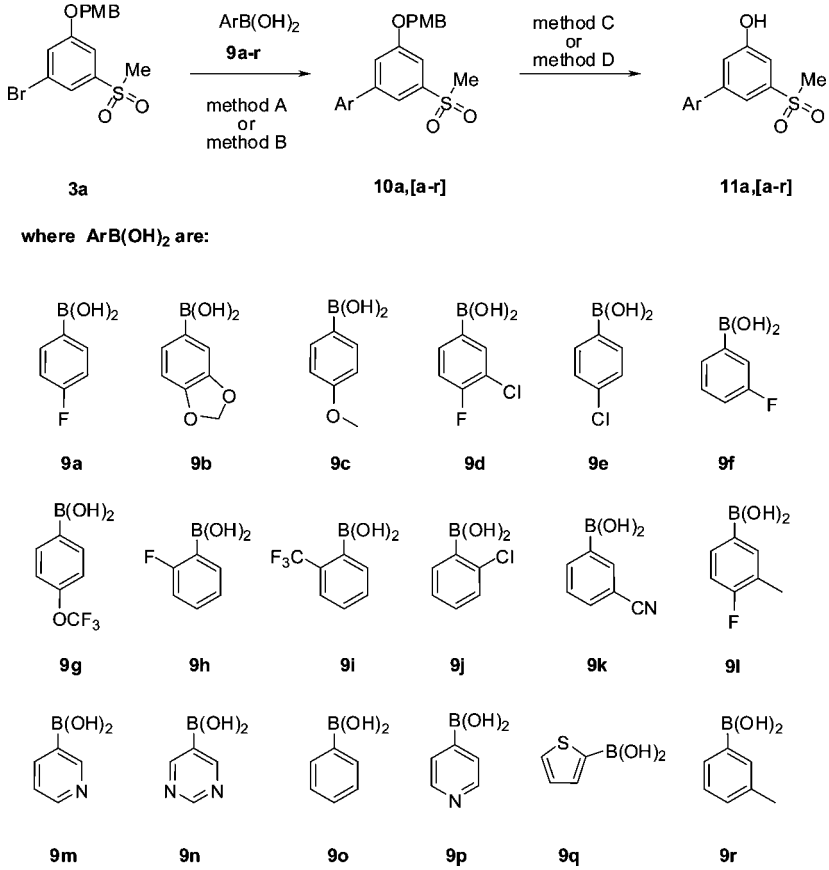


Table 1. Yields of Suzuki and PMB-Deprotection Reactions for **10a** and **11a** Series [**a**−**r**][a]

	compounds **10**		compounds **11**	
entry	no.	yield %	no.	yield %
1	**10a,a**	80[b]	**11a,a**	49[d]
2	**10a,b**	79[b]	**11a,b**	66[e]
3	**10a,c**	98[b]	**11a,c**	49[e]
4	**10a,d**	87[b]	**11a,d**	84[d]
5	**10a,e**	52[b]	**11a,e**	94[d]
6	**10a,f**	90[b]	**11a,f**	79[d]
7	**10a,g**	67[b]	**11a,g**	74[e]
8	**10a,h**	89[b]	**11a,h**	17[d]
9	**10a,i**	53[b]	**11a,i**	69[d]
10	**10a,j**	90[b]	**11a,j**	32[d]
11	**10a,k**	60[b]	**11a,k**	23[d]
12	**10a,l**	89[b]	**11a,l**	77[d]
13	**10a,m**	54[c]	**11a,m**	54[d]
14	**10a,n**	32[c]	**11a,n**	24[d]
15	**10a,o**	88[b]	**11a,o**	82[d]
16	**10a,p**	43[c]	**11a,p**	57[d]
17	**10a,q**	50[b]	**11a,q**	52[d]
18	**10a,r**	90[b]	**11a,r**	58[d]

[a] The representative procedures and analytical data for compounds **10** and **11** are presented in Experimental Section. [b] Method A: $Pd(PPh_3)_4$, KI, 1,2-dimethoxyethane, microwave irradiation, 160 °C, 60 min. [c] Method B: $Pd(PPh_3)_4$, CsF, acetonitrile, microwave irradiation, 160 °C, 45 min. [d] Method C: 4 equiv BBr_3, methylene chloride, RT. [e] Method D: H_2 10% Pd/C, ambient conditions.

benzyloxy)benzene (10.48 g, 28.1 mmol) in dry DMF (5.5 mL), and the mixture was stirred at 100 °C for an hour. After it was cooled to room temperature, the reaction mixture was partitioned between diethyl ether (50 mL) and water (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified on silica gel to afford the product (3.68 g, 39%) as yellow oil.

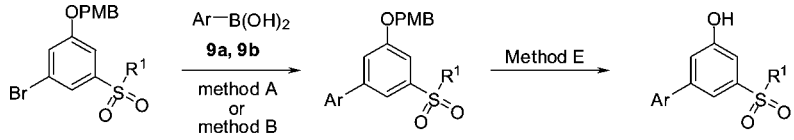
(3-(4-Methoxybenzyloxy)-5-bromophenyl)(methyl)sulfane (2a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 6.96 (t, J = 1.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.89 (dd, J = 2.1, 1.7 Hz, 1H), 6.76 (dd, J = 2.1, 1.7 Hz, 1H), 4.94 (s, 2H), 3.82 (s, 3H), 2.44 (s, 3H).

Synthesis of Compounds 2f and 2g. A 100-mL round-bottom flask equipped with a magnetic stir bar and reflux condenser, was charged with a solution of 1,3-dibromo-5-(4-methoxy-benzyloxy)-benzene (3.72 g, 10 mmol) in dry 1,4-dioxane (20 mL) followed by the appropriate thiol (0.5 equiv), 3 mol % palladium(II) acetate, 6 mol % 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, and 10 equiv sodium carbonate (10.6 g, 100 mmol). The mixture was stirred at 100 °C under nitrogen for 4 h. Additional thiol (0.5 equiv) was added to the mixture, and the solution was stirred at 100 °C under nitrogen overnight.

The reaction mixture was partitioned between methylene chloride (150 mL) and water (100 mL). The organic layer was separated, washed with water (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified on silica gel to afford the products.

(3-Bromo-5-(4-methoxybenzyloxy)phenyl)(phenyl)sulfane (2f): yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.42 (m, 2H), 7.30−7.36 (m, 3H), 7.27 (d, J = 8.5 Hz, 2H), 6.98 (t, J = 1.5 Hz, 1H), 6.95 (dd, J = 2.4, 1.6 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 6.76 (dd, J = 2.3, 1.5 Hz, 1H), 4.89 (s, 2H), 3.81 (s, 3H).

Scheme 7



3[b-g] **10[b-g],[a-b]** **11[b-g],[a-b]**

3b, R^1 = *i*-Bu
3c, R^1 = $MeOCH_2CH_2$
3d, R^1 = *cyclo*-Bu
3e, R^1 = Bn
3f, R^1 = Ph
3g, R^1 = *tert*-Bu

10 & 11b, R^1 = *i*-Bu, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl
10 & 11c, R^1 = $MeOCH_2CH_2$, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl
10 & 11d, R^1 = *cyclo*-Bu, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl
10 & 11e, R^1 = Bn, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl
10 & 11f, R^1 = Ph, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl
10 & 11g, R^1 = *t*-Bu, **a**, Ar=*p*-F-C_6H_4, **b**, Ar= benzo[1,3]dioxol-5-yl

Table 2. Yields of Suzuki- reactions for 10[b-g],[a-b] series[a]

	Ar = *p*-F-C_6H_4		Ar = benzo[1,3]dioxol-5-yl	
R^1	compound no.	yield %	compound no.	yield %
i-Bu	**10b**,**a**	71[b]	**10b**,**b**	66[b]
CH_2CH_2OMe	**10c**,**a**		**10c**,**b**	
cyclo-Bu	**10d**,**a**	72[b]	**10d**,**b**	76[b]
Bn	**10e**,**a**	72[b]	**10e**,**b**	56[b]
Ph	**10f**,**a**	80[b]	**10f**,**b**	65[b]
tert-Bu	**10g**,**a**	70[b]	**10g**,**b**	73[b]

[a] The representative procedures and analytical data for compounds **10** and **11** are presented in the Experimental Section. [b] Method A: $Pd(PPh_3)_4$, KI, 1,2-dimethoxyethane, microwave irradiation, 160 °C, 60 min.

Table 3. Yields of PMB-deprotection reactions for 11[b-g],[a-b] series[a]

	Ar = *p*-F-C_6H_4		Ar = benzo[1,3]dioxol-5-yl	
R^1	compound no.	yield %	compound no.	yield %
i-Bu	**11b**,**a**	89[b]	**11b**,**b**	91[b]
CH_2CH_2OMe	**11c**,**a**	44[c]	**11c**,**b**	42[c]
cyclo-Bu	**11d**,**a**	69[b]	**11d**,**b**	77[b]
Bn	**11e**,**a**	76[b]	**11e**,**b**	74[b]
Ph	**11f**,**a**	78[b]	**11f**,**b**	88[b]
tert-Bu	**11g**,**a**	77[b]	**11g**,**b**	65[b]

[a] The representative procedures and analytical data for compounds **10** and **11** are presented in the Experimental Section. [b] Method E: AcOH, 100 °C, microwave irradiation, 60 min. [c] Conditions of method B leading directly to the phenol.

(3-Bromo-5-(4-methoxybenzyloxy)phenyl)(t-butyl)sulfane (2g): yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 1.5 Hz, 1H), 7.13 (t, J = 1.5 Hz, 1H), 7.06 (t, J = 1.5 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 4.97 (s, 2H), 3.81 (s, 3H), 1.28 (s, 9H).

Synthesis of Compounds 2b, 2c, 2d, 2e, and 7. A mixture of 1,3-dibromo-5-(4-methoxy-benzyloxy)-benzene (3.72 g, 10 mmol), potassium thioacetate (1.71 g, 15 mmol), tris-(dibenzylideneacetone)dipalladium (228 mg, 3 mol%) 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (289 mg, 6 mol%) *N*,*N*-diisopropylethylamine and dry 1,4-dioxane (36 mL) was irradiated in microwave glass vessel at 160 °C for 35 min using a CEM Explorer Labmate Microwave instrument.

The reaction mixture was concentrated under reduced pressure and the residue was purified on silica gel−$MgSO_4$−Hyflo Super Cel pad and washed with hexanes/EtOAc as a gradient eluent from 100:1 to 50:1.

3-Bromo-5-(4-methoxybenzyloxy)phenyl ethanethioate (7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 7.12−7.20 (m, 2H), 6.96−7.00 (m, 1H), 6.92 (d, J = 8.8 Hz, 2H), 4.96 (s, 2H), 3.82 (s, 3H), 2.42 (s, 3H).

Synthesis of Compounds 2b−e. To a solution of intermediate **7** (~1.1 g, obtained in the previous step) in acetonitrile (9 mL) was added NaOH (150 mg, 3.75 mmol) and water (100 μL). The mixture was stirred at room temperature for 3−4 h; the corresponding alkyl bromide (3.3 mmol) was added, and the mixture was stirred at room temperature overnight.

The reaction mixture was poured into a mixture of methylene chloride (100 mL) and water (50 mL). The organic layer was separated, washed with water (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on silica gel to afford the products.

(3-Bromo-5-(4-methoxybenzyloxy)phenyl)(isobutyl)sulfane (2b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 7.01 (t, J = 1.5 Hz, 1H), 6.89−6.95 (m, 3H), 6.82 (t, J = 2.0 Hz, 1H), 4.94 (s, 2H), 3.82 (s, 3H), 2.77 (d, J = 6.9 Hz, 2H), 1.75−1.95 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H).

(3-Bromo-5-(4-methoxybenzyloxy)phenyl)(2-methoxyethyl)sulfane (2c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 7.06 (t, J = 1.6 Hz, 1H), 6.88−6.95 (m, 3H), 6.87 (dd, J = 2.2, 1.6 Hz, 1H), 4.94 (s, 2H), 3.82 (s, 3H), 3.57 (t, J = 6.7 Hz, 2H), 3.36 (s, 3H), 3.09 (t, J = 6.7 Hz, 2H).

Benzyl(3-bromo-5-(4-methoxybenzyloxy)phenyl)sulfane (2e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.34 (m, 7H), 7.03 (t, J = 1.5 Hz, 1H), 6.88−6.94 (m, 3H), 6.79 (dd, J = 2.2, 1.6 Hz, 1H), 4.88 (s, 2H), 4.09 (s, 2H), 3.81 (s, 3H).

Synthesis of Compounds 3a−g. A round-bottom flask equipped with a magnetic stir bar was charged with the corresponding 1-bromo-3-(4-methoxy-benzyloxy)-5-R^1-sulfanyl-benzene **2a−g** (2 mmol) dissolved in methylene chloride (20 mL). The mixture was cooled to between 0 and −5 °C, and 3-chloroperbenzoic acid (1.1 equiv) was added portionwise. The mixture was stirred at 0−5 °C for 3 h. The precipitated solid was filtered off and washed with methylene chloride. If no precipitation occurred, then additional methylene chloride (20 mL) was added to the solution. The methylene chloride solution was washed sequentially with a 10% aq solution of Na_2SO_3 (20 mL), saturated aq $NaHCO_3$ solution (20 mL), and water (20 mL), and the solution was dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was purified on silica gel using hexanes/EtOAc 4:1 to afford the products in 48−83% yields.

1-Bromo-3-(isobutylsulfonyl)-5-(4-methoxybenzyloxy)-benzene (3b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, J = 1.5 Hz, 1H), 7.40 (dd, J = 2.0, 1.4 Hz, 1H), 7.36 (t, J = 1.7 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.04 (s, 2H), 3.82 (s, 3H), 2.96 (d, J = 6.5 Hz, 2H), 2.15−2.28 (m, 1H), 1.06 (d, J = 6.6 Hz, 6H).

1-Bromo-3-(4-methoxybenzyloxy)-5-(2-methoxyethylsulfonyl)benzene (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (t, J = 1.5 Hz, 1H), 7.42 (dd, J = 1.9, 1.5 Hz, 1H), 7.36 (t, J = 1.9 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.03 (s, 2H), 3.82 (s, 3H), 3.72 (t, J = 6.2 Hz, 2H), 3.36 (t, J = 6.2 Hz, 2H), 3.25 (s, 3H).

1-Bromo-3-(cyclobutylsulfonyl)-5-(4-methoxybenzyloxy)-benzene (3d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (t, J = 1.5 Hz, 1H), 7.29−7.37 (m, 4H), 6.92 (d, J = 8.8 Hz, 2H), 5.03 (s, 2H), 3.82 (s, 3H), 3.72−3.83 (m, 1H), 2.46−2.61 (m, 2H), 2.11−2.24 (m, 2H), 1.92−2.06 (m, 2H).

1-(Benzylsulfonyl)-3-bromo-5-(4-methoxybenzyloxy)-benzene (3e): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.57 (dd, J = 2.3, 1.7 Hz, 1H), 7.27−7.40 (m, 7H), 7.15−7.22 (m, 2H), 6.96 (d, J = 8.8 Hz, 2H), 5.08 (s, 2H), 4.74 (s, 2H), 3.76 (s, 3H).

1-Bromo-3-(4-methoxybenzyloxy)-5-(phenylsulfonyl)-benzene (3f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.7 Hz, 2H), 7.63 (t, J = 1.5 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.43 (dd, J = 2.3, 1.5 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 2.2 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.00 (s, 2H), 3.82 (s, 3H).

1-Bromo-3-(*tert*-butylsulfonyl)-5-(4-methoxybenzyloxy)-benzene (3g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 1.5 Hz, 1H), 7.30−7.40 (m, 4H), 6.92 (d, J = 8.7 Hz, 2H), 5.05 (s, 2H), 3.81 (s, 3H), 1.29−1.34 (m, 9H).

Synthesis of Compounds 10a,a, 10a,b, 10a,c, 10a,d, 10a,e, 10a,f, 10a,g, 10a,h, 10a,i, 10a,j, 10a,k, 10a,l, 10a,o, 10a,q, 10a,r, 10b,a, 10b,b, 10d,a, 10d,b, 10e,a, 10e,b, 10f,a, 10f,b, 10g,a, 10g,b. Method A. A mixture of the corresponding 1-bromo-3-(4-methoxy-benzyloxy)-5-(R^1-1-sulfonyl)-benzene (0.5 mmol), the appropriate boronic acid (1.4 equiv), Na_2CO_3 (2.2 mL, 20% aqueous solution), a catalytic amount of KI, tetrakis-(triphenylphosphine)palladium(0) catalyst (29 mg, 5 mol%, 0.025 mmol) and DME (2.2 mL) was irradiated with 80 W power at 160 °C for 45 min. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (50 mL) and water (25 mL). The organic layer were separated, washed with water (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel using hexanes/EtOAc 4:1 to afford 60−80% yields of the products.

Synthesis of Compounds 10a,m, 10a,n, 10a,p, 11c,a, 11c,b. Method B. A mixture of the corresponding 1-bromo-3-(4-methoxy-benzyloxy)-5-(R^1-1-sulfonyl)-benzene (0.5 mmol), the appropriate boronic acid (1.4 equiv), cesium fluoride (2.5 equiv), tetrakis-(triphenylphosphine)palladium(0) catalyst (29 mg, 5 mol %, 0.025 mmol), and dry acetonitrile (5 mL) was transferred into a 8-mL microwave glass vessel. The vessel was capped, and the reaction mixture was irradiated with 80 W power at 160 °C for 15−30 min. The vessel was cooled to room temperature and uncapped. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column using Biotage purification station with hexanes/EtOAc 4:1 to afford 40−50% yields of the product.

Synthesis of Compounds 11a,a, 11a,d, 11a,e, 11a,f, 11a,h, 11a,i, 11a,j, 11a,k, 11a,l, 11a,m, 11a,n, 11a,o, 11a,p, 11a,q, 11a,r. Method C. The flask was charged with the corresponding R^2-3-(4-methoxy-benzyloxy)-5-(methyl-1-sulfonyl)-biphenyl (0.5 mmol) and methylene chloride (5 mL), flushed with dry nitrogen gas, and capped with a rubber septum. The solution was cooled to −60 to −70 °C and boron tribromide solution (8 M solution in methylene chloride, 4 equiv dissolved in 250 μL of methylene chloride) was injected carefully through the septum. The mixture was stirred at room temperature overnight. Crushed ice and methylene chloride (3 mL) were added to the mixture. If precipitation occurred, the solid was filtered off, and the crystals were washed with hexanes. Otherwise the organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized from hexanes, filtered off, and washed further with hexanes to afford 17−94% of the product.

4′-Fluoro-5-(methylsulfonyl)biphenyl-3-ol (11a,a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (br. s., 1H), 7.74 (dd, J = 8.4, 5.6 Hz, 1H), 7.56 (s, 1H), 7.26−7.35 (m, 5H), 3.24 (s, 3H).

3′-Chloro-4′-fluoro-5-(methylsulfonyl)biphenyl-3-ol (11a,d): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 7.97 (dd, J = 7.1, 2.3 Hz, 1H), 7.69−7.76 (m, 1H), 7.61 (t, J = 1.5 Hz, 1H), 7.53 (t, J = 8.9 Hz, 1H), 7.34 (t, J = 1.6 Hz, 1H), 7.30 (t, J = 1.5 Hz, 1H), 3.26 (s, 3H).

4′-Chloro-5-(methylsulfonyl)biphenyl-3-ol (11a,e): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.38 (br. s., 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.58 (s, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.33 (s, 1H), 7.29 (s, 1H), 3.25 (s, 3H).

3′-Fluoro-5-(methylsulfonyl)biphenyl-3-ol (11a,f): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.38 (br. s., 1H), 7.62 (t, J = 1.6 Hz, 1H), 7.60−7.49 (m, 3H), 7.36 (t, J = 1.6 Hz, 1H), 7.30 (t, J = 1.6 Hz, 1H), 7.29−7.22 (m, 1H), 3.26 (s, 3H).

5-(Methylsulfonyl)-2′-(trifluoromethyl)biphenyl-3-ol (11a,i): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (br. s., 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.33 (dd, J = 2.3, 1.8 Hz, 1H), 7.25 (t, J = 1.8 Hz, 1H), 7.02 (t, J = 2.3 Hz, 1H), 3.21 (s, 3H).

3′-Hydroxy-5′-(methylsulfonyl)biphenyl-3-carbonitrile (11a,k): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br. s., 1H), 8.24 (t, J = 1.5 Hz, 1H), 8.05 (ddd, J = 8.0, 1.9, 1.1 Hz, 1H), 7.89 (dt, J = 8.0, 1.0 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.68 (t, J = 1.5 Hz, 1H), 7.41 (dd, J = 2.3, 1.8 Hz, 1H), 7.33 (dd, J = 2.3, 1.5 Hz, 1H), 3.27 (s, 3H).

4′-Fluoro-3′-methyl-5-(methylsulfonyl)biphenyl-3-ol (11a,l): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.34 (br. s., 1H), 7.64

(d, $J = 7.3$ Hz, 1H), 7.50−7.59 (m, 2H), 7.30 (t, $J = 1.6$ Hz, 1H), 7.20−7.29 (m, 2H), 3.24 (s, 3H), 2.32 (d, $J = 1.3$ Hz, 3H).

3-(Methylsulfonyl)-5-(pyridin-3-yl)phenol (11a,m): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (br. s., 1H), 9.24 (d, $J = 1.9$ Hz, 1H), 8.88 (d, $J = 5.4$ Hz, 1H), 8.77 (d, $J = 8.4$ Hz, 1H), 8.03 (dd, $J = 8.2, 5.6$ Hz, 1H), 7.78 (t, $J = 1.5$ Hz, 1H), 7.52 (t, $J = 1.9$ Hz, 1H), 7.42 (t, $J = 1.9$ Hz, 1H), 3.27 (s, 3H).

3-(Methylsulfonyl)-5-(pyrimidin-5-yl)phenol (11a,n): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.56 (br. s., 1H), 9.23 (s, 1H), 9.17 (s, 2H), 7.73 (t, $J = 1.8$ Hz, 1H), 7.47 (t, $J = 1.8$ Hz, 1H), 7.38 (t, $J = 1.8$ Hz, 1H), 3.27 (s, 3H).

3-(Methylsulfonyl)-5-(pyridin-4-yl)phenol (11a,p): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (br. s., 1H), 8.77 (d, $J = 6.0$ Hz, 2H), 7.92 (d, $J = 6.3$ Hz, 2H), 7.76 (t, $J = 1.8$ Hz, 1H), 7.51 (t, $J = 1.8$ Hz, 1H), 7.42 (t, $J = 1.8$ Hz, 1H), 3.27 (s, 3H).

3-(Methylsulfonyl)-5-(thiophen-2-yl)phenol (11a,q): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.59 (dd, $J = 3.5, 1.3$ Hz, 1H), 7.53 (t, $J = 1.6$ Hz, 1H), 7.36 (dd, $J = 2.3, 1.5$ Hz, 1H), 7.21 (dd, $J = 2.1, 1.6$ Hz, 1H), 7.17 (dd, $J = 5.0, 3.8$ Hz, 1H), 3.23 (s, 3H).

Synthesis of Compounds 11a,b, 11a,c, 11a,g. Method D. The corresponding R^2-3-(4-methoxy-benzyloxy)-5-(methyl-1-sulfonyl)-biphenyl (0.5 mmol) was dissolved in a 1:1 mixture of MeOH/methylene chloride (3 mL) and 10% Pd/C catalyst (20 weight % to the starting material) was added. The mixture was hydrogenated at room temperature under atmospheric pressure, while the H_2 consumption was measured by a gas burette. The reaction time varied between 1.5 h and 1 day. The mixture was filtered through a Hyflo Super Cel pad, which was then washed with MeOH/methylene chloride. The filtrates were combined and concentrated under reduced pressure. The residue was crystallized from hexanes, filtered, and washed with hexanes to afford 49−74% of the products.

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(methylsulfonyl)phenol (11a,b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (br. s.,1H), 7.48 (t, $J = 1.7$ Hz, 1H), 7.28 (d, $J = 1.6$ Hz, 1H), 7.25 (t, $J = 1.7$ Hz, 1H), 7.21 (t, $J = 1.7$ Hz, 1H), 7.17 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.01 (d, $J = 8.1$ Hz, 1H), 6.08 (s, 2H), 3.22 (s, 3H).

4′-Methoxy-5-(methylsulfonyl)biphenyl-3-ol (11a,c): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (br. s., 1H), 7.63 (d, $J = 7.4$ Hz, 2H), 7.53 (s, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 7.05 (d, $J = 7.4$ Hz, 2H), 3.81 (s, 3H), 3.23 (s, 3H).

5-(Methylsulfonyl)-4′-(trifluoromethoxy)biphenyl-3-ol (11a,g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.77 (br. s., 1H), 7.83 (d, $J = 8.3$ Hz, 2H), 7.59 (t, $J = 1.5$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.36 (t, $J = 1.8$ Hz, 1H), 7.31 (t, $J = 1.8$ Hz, 1H), 3.25 (s, 3H).

Synthesis of Compounds 11b,a, 11b,b, 11d,a, 11d,b, 11e,a, 11e,b, 11f,a, 11f,b, 11g,a, 11g,b. Method E. The solution of the corresponding R^2-3-(4-methoxy-benzyloxy)-5-(R^1-1-sulfonyl)-biphenyl (0.5 mmol) in glacial acetic acid (5 mL) was irradiated with 80 W power at 100 °C for 60 min, and the reaction was monitored by TLC using chloroform/MeOH 20:1. Acetic acid was removed under reduced pressure. The residue was purified on a Biotage SP4 four-column sequential flash purification station equipped with a FLASH 12+M cartridge using dichlorethane/MeOH 50:1 to afford 65−91% of the products.

4′-Fluoro-5-(isobutylsulfonyl)biphenyl-3-ol (11b,a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (t, $J = 1.5$ Hz, 1H), 7.55 (dd, $J = 8.7, 5.2$ Hz, 2H), 7.41 (dd, $J = 2.2, 1.6$ Hz, 1H), 7.29 (dd, $J = 2.2, 1.6$ Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 6.49 (br. s., 1H), 3.04 (d, $J = 6.5$ Hz, 2H), 2.22−2.36 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 6H).

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(isobutylsulfonyl)phenol (11b,b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, $J = 1.5$ Hz, 1H), 7.35 (dd, $J = 2.3, 1.6$ Hz, 1H), 7.25 (dd, $J = 2.3, 1.6$ Hz, 1H), 7.03−7.11 (m, 2H), 6.88 (d, $J = 8.8$ Hz, 1H), 6.33 (br. s., 1H), 6.02 (s, 2H), 3.03 (d, $J = 6.5$ Hz, 2H), 2.19−2.35 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 6H).

5-(Cyclobutylsulfonyl)-4′-fluorobiphenyl-3-ol (11d,a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.72 (dd, $J = 8.9, 5.4$ Hz, 2H), 7.45 (t, $J = 1.5$ Hz, 1H), 7.26−7.36 (m, 3H), 7.20 (t, $J = 1.9$ Hz, 1H), 4.04−4.23 (m, 1H), 2.26−2.43 (m, 2H), 2.07−2.21 (m, 2H), 1.83−2.01 (m, 2H).

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(cyclobutylsulfonyl)phenol (11d,b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.40 (t, $J = 1.6$ Hz, 1H), 7.24−7.28 (m, 2H), 7.13−7.18 (m, 2H), 7.01 (d, $J = 8.1$ Hz, 1H), 6.08 (s, 2H), 4.09−4.23 (m, 1H), 2.26−2.42 (m, 2H), 2.02−2.20 (m, 2H), 1.83−2.01 (m, 2H).

5-(Benzylsulfonyl)-4′-fluorobiphenyl-3-ol (11e,a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.64 (dd, $J = 8.8, 5.4$ Hz, 2H), 7.27−7.35 (m, 7H), 7.17−7.24 (m, 2H), 7.07 (dd, $J = 2.2, 1.6$ Hz, 1H), 4.69 (s, 2H).

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(phenylsulfonyl)phenol (11f,b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (br. s., 1H), 8.00 (d, $J = 7.2$ Hz, 2H), 7.70 (t, $J = 7.2$ Hz, 1H), 7.63 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 1.4$ Hz, 1H), 7.20−7.24 (m, 3H), 7.12 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.00 (d, $J = 8.1$ Hz, 1H), 6.07 (s, 2H).

5-(*tert*-Butylsulfonyl)-4′-fluorobiphenyl-3-ol (11g,a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (br. s., 1H), 7.70 (dd, $J = 8.8, 5.4$ Hz, 2H), 7.37−7.40 (m, 1H), 7.35−7.37 (m, 1H), 7.32 (t, $J = 8.9$ Hz, 2H), 7.16−7.22 (m, 1H), 1.28 (s, 9H).

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(tert-butylsulfonyl)phenol (11g,b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.34 (br. s., 1H), 7.33 (t, $J = 1.3$ Hz, 1H), 7.30 (t, $J = 1.8$ Hz, 1H), 7.22 (d, $J = 1.8$ Hz, 1H), 7.10−7.16 (m, 2H), 7.01 (d, $J = 8.1$ Hz, 1H), 6.08 (s, 2H), 1.27 (s, 9H).

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Supporting Information Available. A pdf file containing additonal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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