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Selective Monoarylation of Benzenediols via Dianion Intermediates

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Selective Monoarylation of Benzenediols via Dianion Intermediates

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Abstract: Application of the S_NAr reaction on benzenediols with arylfluorides revealed an enhancement in monosubstitution selectivity over bis substitution when excess base was used. This trend was studied using symmetrical and nonsymmetrical benzenediols with various levels of steric hindrance. The effect of various bases was examined. A 100% monoselectivity was achieved in the presence of 2.5 equiv. of Cs_2CO_3. The methodology was employed in the synthesis of an important pharmaceutical product, **1**, an arylether.

Keywords: S_NAr, benzenediol, selective monoarylation, resorcinal

INTRODUCTION

The efficient preparation of monoarylethers of hydroquinone and resorcinols is important in the search for bioactive small molecules and advancing these molecules into clinical development.[1] In the course of an ongoing project, we required an expedient and practical method that would be readily adaptable to kilogram scales to produce monoarylated resorcinol derivatives, such as **2**. However, the monoarylation of resorcinol represents a problem for which no generally satisfactory procedure has yet been documented.

Traditional methods of differentiating the phenol moieties on hydroquinone or resorcinols have numerous drawbacks.[2] One tends to achieve

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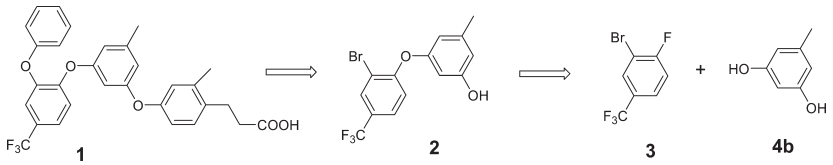


Scheme 1.

the selectivity of mono- vs. bis arylation via careful control of the stoichiometry of base and arylating agents. However, arylation of the monoanion with 1 equiv. of arylating agent generally gave poor selectivity.[1b,3] Adding a large excess of benzenediol may minimize the bisarylation,[4] but it is not economical and increases the burden of purification.

Further literature surveys revealed several other procedures for the preparation of monoarylated bisphenols, such as the condensation of haloaniline with phenol, followed by diazotization to afford the phenol derivative;[5] coupling of 3-iodophenylbenzyl ether with phenol, followed by deprotection of benzyl group;[6a] Bayer–Villager oxidation of phenoxybenzaldehyde; and S_NAr reactions via halobenzene–FeCp complexes.[6b] Herein, we report a general and practical method for the selective arylation of hydroquinones and resorcinols.

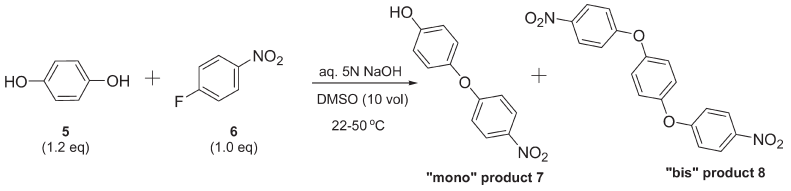
RESULTS AND DISCUSSION

Our initial work was inspired by Newman and Cella's studies[7] on monoalkylation of hydroquinone. By using the disodium salt of hydroquinone, Newman and Cella achieved moderate to good yields. The scope of their research was limited to hydroquinone alkylations, and the application was limited. We therefore intended to explore the dianion approach to produce a general, high-yielding, and selective synthesis of monoarylated benzenediols via the S_NAr reaction with arylfluoride.

Investigation of the monoselective arylation was first carried out using hydroquinone (**5**) and 4-fluoronitrobenzene (**6**) (Table 1). The dianion sodium salt of hydroquinone has relatively poor solubility in most organic solvents,[7] but it is soluble in the water–organic mix solvents. Aqueous 5 N NaOH solution in dimethyl sulfoxide (DMSO) was then chosen to accommodate the solubilities of both the dianion sodium salt of hydroquinone and organic substrates. 4-Fluoronitrobenzene was used as the electrophile in the initial studies mainly because of its strong electrophilicity in S_NAr reactions and ease of product isolation by direct crystallization from reaction mixtures.

Comparison of entries 1a–4a or 1b–4b (Table 1) clearly show the enhanced yields and mono/bis selectivities when excess NaOH was used. The mono/bis ratio increased from 1:1 to 6:1 when the NaOH amount was

Table 1. Effect of base stoichiometry and addition rate



Entry	5 N NaOH (equiv.)	Addition rate[a]	Yield[b] (%)	Mono:bis
1a	1.0	One portion	31	1:1
1b	1.0	Slowly	36	1:1
2a	2.0	One portion	62	3:1
2b	2.0	Slowly	77	8:1
3a	2.5	One portion	69	5:1
3b	2.5	Slowly	86	17:1
4a	3.0	One portion	72	6:1
4b	3.0	Slowly	87	22:1

[a]Entries 1a–4a: Electrophile added at once to rt solution of nucleophile, then heated to 50°C.

[b]Entries 1b–4b: Electrophile added slowly (over 30–60 min) to 50°C solution of nucleophile.

increased from 1.0 equiv. to 3.0 equiv. (entries 1a and 4a). Slow addition (30–60 min) of the electrophile to the preformed hydroquinone dianion solution was crucial to minimize the bis-product formation. The mono/bis ratio was elevated from 6:1 to 22:1 when applying the slow addition method in the case using 3 equiv. of 5 N NaOH (entries 4a, 4b).

The relationship of the yield increase of **7** vs. NaOH equiv. is illustrated in Fig. 1. Greater yield increase occurred when raising the NaOH amount from 1.0 to 2.0 equiv., but insignificant change was observed for the base equiv. between 2.5 and 3.0. We then chose 2.5 equiv., which was applied in all subsequent studies.

The mechanistic rational for excess base (>2 equiv.) was proposed on the basis of several literature precedents.[7,8] The aromatic substitution reaction rate of hydroquinone dianion with **6** (k_1) is greater than the rate of monoanion (k_2) (Scheme 2), and their relative reactivity determined the mono/bis selectivity. In detail, Breslow et al.[8] observed that the initial reaction rate of hydroquinone dianion alkylation was faster than that of the phenoxide anion.

To generalize the methodology with application to our ongoing project, we expanded the reaction scope to different benzenediols. Table 2 illustrates the results of resorcinol derivatives (**4**) with 4-fluoronitrobenzene (**6**). In general, monoselectivity on hydroquinone (Table 1, entry 4) is better than

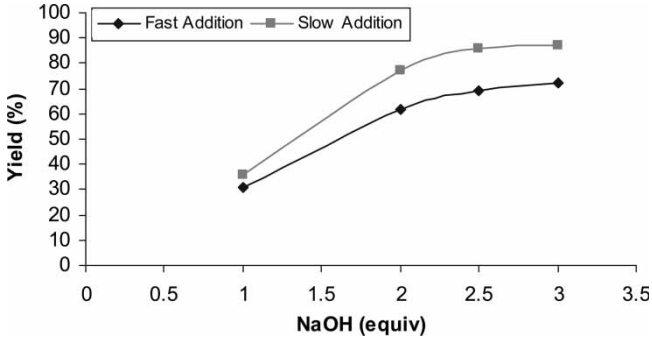
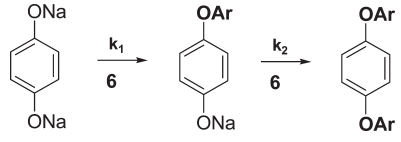


Figure 1. Yield vs. base stoichiometry.



Scheme 2.

that on resorcinol derivatives, which could be attributed to the pK_a differences of hydroquinone and resorcinol. ACD pK_a prediction: (a) hydroquinone; pK_a 1 = 9.68; pK_a 2 = 11.55; δ pK_a = 1.87; (b) resorcinol: pK_a 1 = 8.91; pK_a 2 = 10.38; δ pK_a = 1.47. Interestingly, when using 1.0 equiv. of NaOH, the mono/bis ratios for all resorcinol derivatives were the same (1:2), favoring the bis arylation, but the trend with excess of NaOH remained the same as that of hydroquinone (mono-product yields increased 40–50% when raising the base amount from 1.0 to 2.5 equiv.).

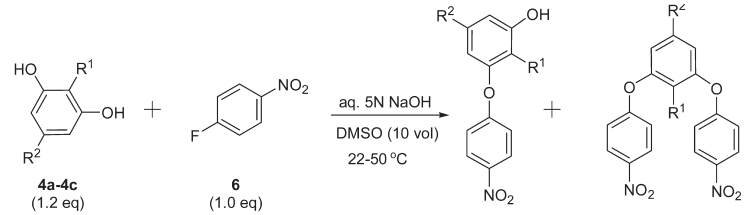
We have not extended our efforts to investigate a wide range of electrophiles. Besides 4-fluoronitrobenzene (**6**), we have only examined 2-fluoronitrobenzene, 3-bromo-4-fluorobenzotrifluoride, 2-fluoro-5-nitrobenzene, 4-fluorobenzotrifluororide, and 3-methyl-4-fluoronitrobenzene with resorcinol. All of these examples provided similar results to those of **6** (see the experimental section).

Base Screen

Aqueous NaOH solution is one of the cheapest bases available and is very easy to handle. However, the question is whether similar monoselectivities could be effected with other bases. With this in mind, we investigated Cs_2CO_3, K_2CO_3, and NaH in DMSO (Table 3).

The reactions using Cs_2CO_3 and K_2CO_3 in dry DMSO with prolonged stirring (entries 8c and 10c) caught our attention. Evidently, the initial rate

Table 2. Resorcinol derivatives as nucleophiles



4a R^1=H R^2=H
4b R^1=H R^2=Me
4c R^1=Me R^2=H

Entry	Nucleophile	5 N NaOH (equiv.)	Yield (mono)	Mono:bis
5a	Resorcinol	1.0	19%	1:2
5b	Resorcinol	2.5	63%	5:1
6a	2-Me Resorcinol	1.0	19%	1:2
6b	2-Me Resorcinol	2.5	72%	7:1
7a	Orcinol	1.0	27%	1:2
7b	Orcinol	2.5	77%	5:1

of the bis-product formation is equal to that of the mono-product, resulting in a moderate ratio of 1:1 (entries 8b and 10b). However, the bis-products slowly underwent nucleophilic cleavage[9] with resorcinol dianion to provide high yields of desired mono-products (Scheme 3). The nucleophilic cleavage reaction only occurred in the dry solvent system. Both K_2CO_3 and Cs_2CO_3 in aqueous DMSO system exhibited no selectivities (entries 8d and 10d).

Asymmetrical Benzenediol Nucleophiles

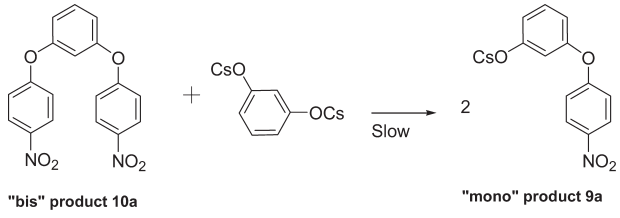
Hydroquinone, resorcinol, 2-substituted resorcinols, and 5-substituted resorcinols are symmetrical benzenediols. We then explored several unsymmetrical hydroquinone and resorcinol derivatives under the same reaction conditions. Experiments in Table 4 demonstrated that high selectivity of mono vs. bis was achieved as expected. The regioselectivity of both mono-products was determined by the steric bulkiness of the substituent. For example, changes of the alkyl group from methyl to ethyl to tert-butyl improved the regioisomer ratios from 1:1.5 to 1:4.1. 2,5-Dihydroxyacetophenone was the only substrate with a substituent other than an alkyl group (entry 14). Both regio- and monoselectivities were excellent, although the yield was moderate.

Table 3. Base screen on resorcinol with 4-fluoronitrobenzene[a]

Entry	Base	Base equiv.	Yield (mono)	Mono:bis
5a	5 N NaOH	1.0	19%	1:2
5b	5 N NaOH	2.5	63%	5:1
8a	Cs_2CO_3	1.0	12%	1:4
8b	Cs_2CO_3[b]	2.5	36% at 2 h	1:1
8c	Cs_2CO_3 (24 h)	2.5	93%	>100:1
8d	Cs_2CO_3 (aq.)	2.5	33%	1:1
9b	NaH	2.5	87%	6:1
10b	K_2CO_3 (5 h)	2.5	39%	1:1
10c	K_2CO_3 (7 days)	2.5	81%	12:1
10d	K_2CO_3 (aq.)	2.5	32%	1:1

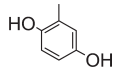
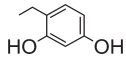
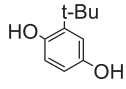
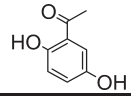
[a]All reactions were worked up after 24 h unless indicated.

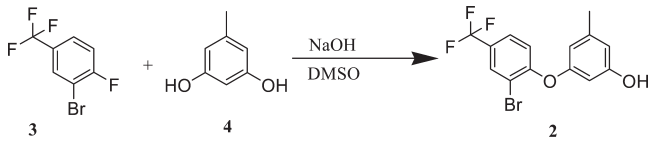
[b]Only acquired data at 5 min, 15 min, 1.5 h, and 2 h. All showed 1:1 ratio, but different conversion. The next data point is at 19 h, resulting in a ratio of 61:1.



Scheme 3.

Table 4. Asymmetrical benzenediol nucleophiles

Entry	Nucleophile	NaOH (equiv.)	Mono 1/ mono 2	Mono total/ bis
11a		1.0	1:1.5	1:1
11b		2.5	1:1	50:1
12a		1.0	1:2.4	1:2
12b		2.5	1:1.8	7:1
13		2.5	1:4.1	17:1
14		2.5	24:1	1:0



Scheme 4.

Synthesis of 2

Having successfully demonstrated this methodology, we decided to apply these conditions to our target molecule **2**. We chose 5 N NaOH because of its ease of handling and safety advantages over other bases during scaling. An efficient purification procedure via liquid–liquid extraction for removing the small amount of bisarylated product and the excess orcinol was developed, providing the clean product **2**.

CONCLUSION

In summary, we have achieved our goal of developing a general and practical method for high-yielding, monoselective S_NAr reactions of various symmetric and asymmetric benzenediols with aryl fluorides using excess base. The monoselectivity was influenced by base choice where the mono/bis ratio of 1:0 was attained by using 2.5 equiv. of Cs_2CO_3. When asymmetric benzenediols were used, the ratio of mono-products was influenced by steric hindrance. Finally, we employed the developed method to synthesize an important active pharmaceutical ingredient, **1**.

EXPERIMENTAL SECTION

General

All the reagents were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded at 400 MHz on a Varian Inova spectrometer with the solvents as internal standard. *J* values are given in hertz.

4-(4-Nitro-phenoxy)-phenol (7) and 1,4-Bis(4-nitrophenoxy) benzene (8)

A 250-mL reaction flask equipped with mechanical stirrer, thermocouple/probe, heating mantle, and nitrogen blanket was charged with dimethyl sulfoxide (40.0 mL) and aqueous 5 N NaOH (17.5 mL, 87.7 mmol, 2.50 eq.). The colorless biphasic solution was stirred at ambient temperature

for 5–10 min and charged with hydroquinone (4.68 g, 42.1 mmol, 1.20 eq.) as a solid in one portion.

The mixture was heated to 50°C and stirred for 10–15 min. A solution of 4-fluoronitrobenzene (5.00 g, 35.1 mmol) in dimethyl sulfoxide (10.0 mL) was prepared and added slowly (over 30–60 min) to the reaction mixture at 50°C. The reaction mixture was held at 50°C for 5 h, then cooled to ambient temperature and stirred overnight.

After cooling to 10–15°C, deionized water (100 mL) was charged, and the pH was adjusted to 6–7 with aqueous concentrated HCl, keeping the temperature colder than 30°C. The resulting product slurry was stirred at ambient temperature, filtered by suction, rinsed with 1:1/DMSO–H_2O and then water. The wet cake was dried in a vacuum oven at 50°C to constant weight to afford 7.01 g (86.4% yield) mono-compound **7** and 0.55 g (10.3% yield) bis-compound **8** (1,4-bis(4-nitrophenoxy)benzene). Known compound commercially available from Scientific Exchange Product List and Aurora Screening Library.

Preparation of 9a and 10a

Dimethyl sulfoxide (40.0 mL) and aqueous 5 N NaOH (17.5 mL, 87.7 mmol, 2.50 eq.) were added to a 250-mL reaction flask equipped with mechanical stirrer, thermocouple probe, heating mantle, and nitrogen blanket. The colorless biphasic solution was stirred at ambient temperature for 5–10 min. Resorcinol (4.68 g, 42.1 mmol, 1.20 eq.) was added as a solid in one portion.

The mixture was heated to 50°C and stirred for 10–15 min. A solution of 4-fluoronitrobenzene (5.00 g, 35.1 mmol) in dimethyl sulfoxide (10.0 mL) was prepared and added slowly (over 30–60 min) to the reaction mixture at 50°C. The reaction mixture was held at 50°C for 5–24 h (5 h here), then cooled to ambient temperature.

After cooling to 10–15°C, deionized water (50 mL) was charged, and the pH was adjusted to 6–7 with aqueous concentrated HCl, keeping the temperature colder than 30°C. EtOAc (50 mL) was added, and the reaction mixture was stirred until a complete biphasic solution resulted. The layers were separated, and the aqueous layer was extracted with additional EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered, the spent drying agent was rinsed with EtOAc, and the filtrate was concentrated in vacuo to give a crude mixture of products as an oil. The oil was purified by silica-gel chromatography (CH_2Cl_2 or 3:1 heptane–EtOAc) to afford 5.18 g (63.9% yield) of mono **9a** and 1.74 g (28.2% yield) of bis **10a** products.[11]

Compounds 9b and 10b

Following the procedure for the preparation of **9a** and **10a**, the reaction was run on a 5.00-g scale. The crude products were isolated by filtration and

purified as indicated to afford 6.65 g (77.3% yield) of mono **9b** and 1.79 g (14.0% yield) of bis **10b**[10] products.

Data for mono-compound **9b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (bs, 1H), 8.22 (m, 2H), 7.10 (m, 2H), 6.50 (s, 1H), 6.38 (s, 1H), 6.31 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 159.4, 155.6, 142.6, 141.4, 126.6, 117.9, 113.7, 111.7, 105.0, 21.5. HRMS m/z calcd. for $C_{13}H_{11}NO_4$ 246.0766 (M + 1); found 246.0765. Anal. calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.54; H, 4.47, N, 5.44.

Compounds 9c and 10c

Following the procedure for preparation of **9a** and **10a**, the reaction was run on a 5.00-g scale. The crude products were isolated and purified by silica-gel chromatography (4:1 heptane–EtOAc) to afford 6.16 g (71.6% yield) of mono **9c** and 1.24 g (19.2% yield) of bis **10c** products.

Data for mono-compound **9c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (bs, 1H), 8.20 (m, 2H), 7.08 (t, 1H, $J = 7.9$), 6.99 (m, 2H), 6.77 (d, 1H, $J = 7.9$), 6.53 (d, 1H, $J = 7.5$), 1.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 157.7, 153.2, 142.3, 127.7, 126.7, 17.1, 116.6, 112.8, 112.0, 9.3. HRMS m/z calcd. for $C_{13}H_{11}NO_4$ 246.0766 (M + 1); found 246.0771.

Data for bis-compound **10c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (m, 5H), 7.43 (t, 1H, $J = 8.2$), 7.12 (m, 5H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 154.0, 142.8, 129.2, 126.7, 119.0, 117.2, 9.7. HRMS m/z calcd. for $C_{19}H_{14}N_2O_6$ 367.0930 (M + 1); found 367.0934. Anal. calcd. for $C_{19}H_{14}N_2O_6$: C, 62.30; H, 3.85; N, 7.65. Found: C, 62.11; H, 3.86: N, 7.53.

Reaction of Resorcinol with 2-Fluoronitrobenzene

Followed the procedure for preparation of **9a** and **10a**, the reaction was ran on a 5.00-g scale. The crude products were isolated and purified by silica-gel chromatography (CH_2Cl_2 gradient to 98:2 CH_2Cl_2–MeOH) to afford 5.03 g (61.3% yield) of mono-product and 1.08 g (17.3% yield) of bis-product.

Data for mono-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (bs, 1H), 8.02 (m, 1H), 7.67 (m, 1H), 7.34 (m, 1H), 7.17 (m, 2H), 6.59 (m, 1H), 6.44 (m, 1H), 6.04 (t, 1H, $J = 2.4$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 157.3, 149.5, 141.8, 135.4, 131.1, 125.9, 124.7, 121.7, 112.0, 109.2, 105.9. HRMS m/z calcd. for $C_{12}H_9NO_4$ 232.0610 (M + 1); found 232.0584. Anal. calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06: Found: C, 62.22; H, 3.61; N, 5.86.

Data for bis-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, 2H, $J = 7.91$), 7.70 (t, 2H, $J = 7.47$), 7.43 (t, 1H, $J = 8.35$), 7.37 (dd, 2H, $J = 7.91, 7.47$), 7.23 (d, 2H, $J = 7.91$), 6.85 (d, 2H, $J = 8.35$), 6.79 (s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 149.0, 141.8, 135.6, 132.0, 126.2, 125.3, 122.0, 114.4, 109.3. HRMS m/z calcd. for $C_{18}H_{12}N_2O_6$ 353.0774 (M + 1); found 353.0797. Anal. calcd. for $C_{18}H_{12}N_2O_6$: C, 61.37; H, 3.43; N, 7.95. Found: C, 61.50; H, 3.26; N, 7.89.

Reaction of Resorcinol with 3-Bromo-4-fluorobenzotrifluoride

The same procedure was as before on 3.00-g scale. The crude products were isolated and purified by silica-gel chromatography (2:1 CH_2Cl_2–heptane gradient to CH_2Cl_2) to afford 2.12 g (52.6% yield) of mono- and 0.40 g (12.0% yield) of bis-products.

Data for mono-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.10 (app. split s, 1H), 7.72 (app. d, 1H, $J = 8.8$), 7.21 (t, 1H, $J = 8.35$), 7.09 (d, 1H, $J = 8.35$), 6.63 (m, 1H), 6.48 (m, 1H), 6.41 (t, 1H, $J = 2.20$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 157.14, 157.13, 156.6, 131.31, 131.20, 131.17, 127.12, 127.08, 120.0, 114.1, 112.4, 109.8, 106.4. HRMS m/z calcd. for $C_{13}H_8BrF_3O_2$ 330.9582 (M − 1); found 330.9592.

Data for bis-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 2H), 7.74 (app. d, 2H, $J = 8.8$), 7.48 (dd, 1H, $J = 7.9$ Hz, 8.3), 7.20 (d, 2H, $J = 8.3$), 6.92 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 156.6, 132.3, 131.5 (m), 127.2 (m), 120.5, 115.4, 114.4, 110.4. HRMS m/z calcd. for $C_{20}H_{10}Br_2F_2O_2$ 554.9030 (M + 1); found 554.9028. Anal. calcd. for $C_{20}H_{10}Br_2F_2O_2$: C, 43.20; H, 1.81. Found: C, 43.40; H, 1.98.

Reaction of Resorcinol with 2-Fluoro-5-nitrobenzene

The same procedure as before was used on a 3.00-g scale. The crude products were isolated and purified by silica-gel chromatography (CH_2Cl_2 gradient to 96:4 CH_2Cl_2–MeOH) to afford 2.92 g (62.2% yield) of mono- and 1.05 g (28.8% yield) of bis-products.

Data for mono-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.20 (m, 1H), 8.04 (m, 1H), 7.22 (dd, 1H, $J = 8.3$, 7.9), 6.87 (d, 1H, $J = 8.8$), 6.64 (m, 1H), 6.49 (m, 1H), 6.45 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 159.6, 156.5, 142.6, 131.3, 129.7, 126.9, 123.9, 117.0, 112.5, 110.4, 107.1, 16.2. HRMS m/z calcd. for $C_{13}H_{11}NO_4$ 246.0766 (M + 1), found 246.0777.

Data for bis-compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (app. split s, 2H), 8.05 (dd, 2H, $J = 8.8$, 9.2), 7.52 (dd, 1H, $J = 8.3$, 7.9), 6.97 (m, 4H), 6.90 (dd, 1H, $J = 2.6$, 2.2), 3.32 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 157.0, 143.0, 132.4, 130.1, 127.1, 123.9, 117.5, 116.2, 111.6, 16.2. HRMS m/z calcd. for $C_{20}H_{16}N_2O_6$ 403.0906 (M + Na); found 403.0925.

Reaction of 4-Fluoronitrobenzene with 2,5-Dihydroxyacetophenone

To a flask, 7 mL of NaOH and 5 N (2.5 eq., 35.4 mmol) and 20 mL of DMSO (10 vols.) were added and stirred for 10 min. 2,5-Dihydroxyacetophenone (2.57 g, 1.2 eq., 17 mmol) was added and stirred for 30 min. 4-Fluoronitrobenzene (2 g), LR, 14.1 mmol) was added. The reaction system was stirred at 50°C for 5 h. The reaction was cooled, and water (10 vols.) was added. pH was adjusted to 1.0 with 5 N HCl, and the reaction was extracted with EtOAc (3 × 20 vol. portions). The combined organics were washed with brine (10 vols.), dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica-gel chromatography (20 × SiO_2) with 25% EtOAc/hexanes. Yield 20% and purity 99.42% by GC. Mass spec: exact mass 273.06; ^{13}C NMR (400 MHz, DMSO-d_6) δ 203, 163, 158, 146, 142, 129, 126, 123, 122, 120, 117, 28.

Synthesis of 2

In a 22-L flask fitted with a thermocouple, temperature controller, and heating mantle, 2.4 L of DMSO and 620 mL of 5 N NaOH (3.1 mol, 3.1 eq.) were added. The temperature rose to approximately 40°C. Then 186.2 g of orcinol (1.5 mol, 1.5 eq.) were added. The resulting solution was stirred and heated to 80°C. Then 3-bromo-4-fluoro-benzotrifluoride (242.98 g, 1 mol, 1 eq.) was added over 20 to 45 min, with the temperature at 80–86°C. The reaction was stirred for 1.5 to 2 h after addition and cooled to 20–25°C, the transferred to a separation vessel and extracted with heptane.

The resulting aqueous layer was extracted three times with 2 L each of ethyl acetate. The combined ethyl acetate layers were combined and washed with a solution of 200 mL of 5 N HCl (1 mol) in 1 L of H_2O to convert the product to the free phenol. The ethyl acetate solution was washed with 1 L H_2O and then dried over sodium sulfate. The filtered ethyl acetate solution was evaporated to provide 250 g (72%) of **2** as a brown oil. Purity was >99% by ^{1}H NMR.

Data for **2**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.08 (d, 1H, $J = 2$), 7.71 (dd, 1H, $J = 8.5$), 7.08 (d, 1H, $J = 8.5$), 6.45 (s, 1H), 6.32 (s, 1H), 6.21 (dd, 1H, $J = 2.5, 2$), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 157.2, 156.4, 141.3, 131.1, 127.1, 122.7, 120.0, 114.0, 113.0, 110.5, 107.5, 103.7, 21.5.

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