

# Synthesis of arylbromides from arenes and *N*-bromosuccinimide (NBS) in acetonitrile — A convenient method for aromatic bromination

Eli Zysman-Colman, Karla Arias, and Jay S. Siegel

**Abstract:** Regioselective and chemoselective electrophilic bromination of a wide series of activated arenes using *N*-bromosuccinimide (NBS) in acetonitrile occurs readily. Environmentally friendly conditions, large substrate scope, and ease of synthesis enhance the utility of this method over other electrophilic bromination conditions.

**Key words:** arylbromides, electrophilic aromatic bromination, *N*-bromosuccinimide.

**Résumé :** La bromation électrophile chimiosélective et régiosélective d'une grande variété d'arènes activés, à l'aide de *N*-bromo-succinimide dans l'acétonitrile, se fait facilement. Des conditions expérimentales environnementalement correctes, un large éventail de substrats et la facilité de la synthèse augmentent l'utilité de cette méthode par comparaison avec celles nécessaires pour d'autres bromations électrophiles.

**Mots-clés :** bromures d'arènes, bromation aromatique, *N*-bromo-succinimide.

[Traduit par la Rédaction]

## Introduction

Bromoarenes are important intermediates for synthesis, specifically as useful substrates in metal-mediated aryl-coupling chemistry.<sup>1–3</sup> Since the late 1950s,<sup>4</sup> there has been considerable interest in *N*-bromosuccinimide (NBS) as an electrophilic aromatic brominating reagent. A major advantage in the use of inexpensive NBS is that the succinimide byproduct can be easily recovered and rebrominated.<sup>5</sup> A number of NBS-based aromatic bromination methods have been reported, each with their own scope and conditions (e.g., NBS/Brønsted acids,<sup>6</sup> NBS/Brønsted bases,<sup>7</sup> NBS plus alkyl amines,<sup>8</sup> NBS in chlorinated solvents,<sup>9</sup> NBS in CS<sub>2</sub>,<sup>10</sup> hexanes,<sup>11</sup> THF,<sup>12</sup> DMF,<sup>13,14</sup> propylene carbonate,<sup>4</sup> and MeOH,<sup>15</sup> NBS supported on silica gel,<sup>16,17</sup> NBS with Amberlyst® 15,<sup>18</sup> and NBS in ionic liquids<sup>19</sup>). Aromatic heterocycles can also be brominated by NBS in polar solvents.<sup>20</sup> Carreño and co-workers' reports using NBS in acetonitrile (ACN), for the efficient bromination of methoxy-substituted arenes<sup>21</sup> and naphthalenes,<sup>22</sup> drew our attention. Herein we document the substrate scope, regio-,<sup>10</sup> and chemo-selectivity of this relatively safe and user-friendly bromination procedure.

## Results and discussion

Bromination of arenes with 1 equiv. of NBS in ACN at 0 °C proceeded readily over a wide range of substrates (Table 1) and was found to be highly para-selective with respect to the most activating substituent; in instances where the para position is blocked, bromination occurred ortho to the most activating group.<sup>23</sup>

Work-ups were trivial, frequently requiring only a water quench to dissolve the succinimide and an extraction using hexanes.<sup>24</sup> Some products even precipitated once water was added and thus were easily filtered off (Table 1, entries 27–28).

The chemoselectivity was also excellent, monobromination occurring at a faster rate than dibromination, even for electron-rich anisidines (Table 1, entries 18–20); additionally, no benzylic bromination was detected. In the vast majority of cases, yields of monobrominated products were excellent, without the use of any additive. In particular, NBS monobromination was possible with phenols (Table 1, entries 10–14)<sup>25</sup> as well as unalkylated anilines (Table 1, entries 16–20). Bromination of arenes bearing deactivating groups occurred in the presence of a strong activating group (Table 1, entries 5, 12, 17); however, bromination of the weakly activated alkyl arenes, toluene (Table 1, entry 21) or *t*-butylbenzene, was not possible even at reflux.

Polyalkylbenzenes spanned the gamut of affinities toward bromination. Ortho- and *p*-xylene (Table 1, entries 23–24) proved to be poor substrates and the conversion to the corresponding monobrominated product was diminutive even using excess NBS and with longer reaction times. Efficient bromination of *m*-xylene (Table 1, entry 22) was possible; however, a reaction time of five days was required to obtain complete conversion. Isomers of trimethylbenzene provide some insight to the reactivity issue. Whereas mesitylene (Table 1, entry 25) readily monobrominates with quantita-

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**Table 1.** Scope of substrates for the bromination of arenes.



























































Entry	Educt	Product	Yield <sup>d</sup>	GC	Ortho	Para	Di
1			99	99	1	99	0
2			97	100	0	100	0
3			97	100	0	99	1
4			63	91	100	–	–
5			81	98	0	99	0
6			94	99	0	100	0
7			99	100	0	100	0
8			96	96	96	–	4
9 <sup>b</sup>			–	91	0	93	7
10			96	100	5	95	0
11			91	100	0	99	0
12			18	67	3	25	72
13			43	97	97	0	3
14			95	100	0	99	1
15			92	100	0	100	0

Table 1 (concluded).

Entry	Educt	Product	Yield <sup>a</sup>	GC	Ortho	Para	Di
16			94	98	2	96	2
17			97	100	0	100	0
18			71	62	16	68	16
19			47	92	0	86	14
20			20	100	69	0	31
21			0	–	–	–	–
22 <sup>c</sup>			98	100	0	85	0
23			–	<3	–	–	–
24			–	<3	–	–	–
25			93	100	0	100	0
26			43	67	0	100	0
27			92	97	98	0	2
28			94	100	0	100	0
29 <sup>b,d</sup>			–	99	3	74	0

**Note:** Conditions: 5 mmol NBS in 5 mL dry ACN was added to 5 mmol substrate in 5 mL dry ACN at 0 °C. Solution stirred for 18 h (0 °C – RT). The products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, Mp, and MS and quantified by GC. Brominations were repeated at least once per substrate and isolated yields and GC conversions were reproducible.

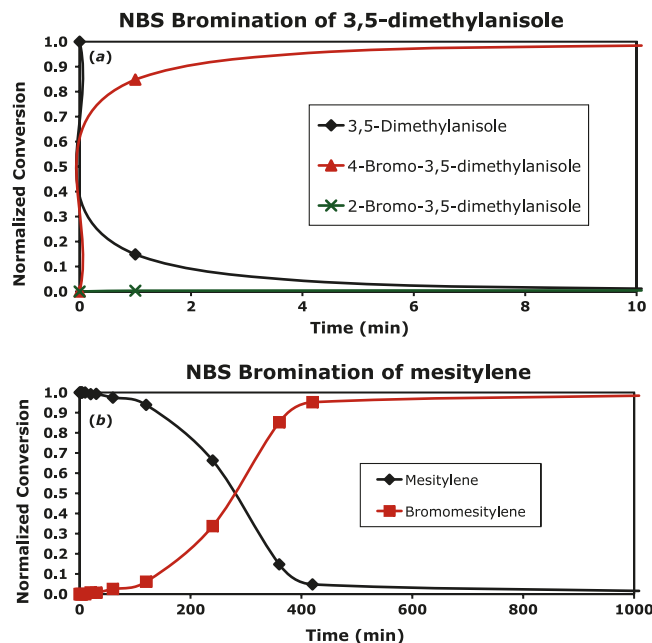
<sup>a</sup>Isolated yields (GC conversion).

<sup>b</sup>Product not isolated.

<sup>c</sup>Reaction stirred for five days.

<sup>d</sup>Side product: PhSSPh (see text).

**Fig. 1.** NBS bromination of (a) 0.41 mol/L 3,5-dimethylanisole in ACN and (b) 0.36 mol/L mesitylene in ACN. The progress of each of the reactions was monitored by GC-MS with *t*-butylbenzene as an internal standard.



tive conversion, monobromination of 1,2,3-trimethylbenzene (Table 1, entry 26) proceeded much less readily, affording only one regioisomeric product in moderate yield.

Effective bromination by this method appears to require site activation equivalent to at least two (better three) *o,p* alkyl groups. Treating this as a linear free energy issue, one sees that phenols and anilines activate roughly equivalent to three methyl groups. After monobromination, the remaining possible sites of bromination are deactivated by being meta to bromine, thus favoring monobromination.

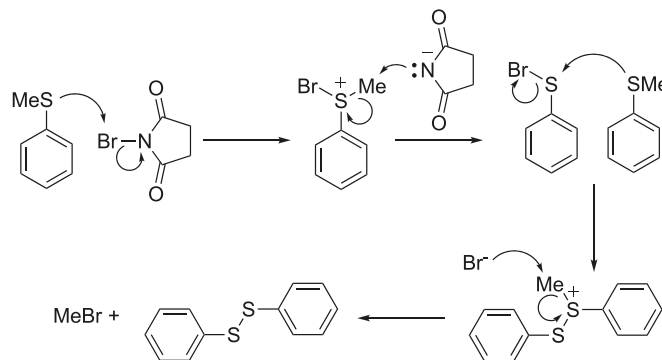
Though our standard protocol reflects a reaction time of 18 h, bromination can actually occur within minutes. For instance, the bromination of 3,5-dimethylanisole (Table 1, entry 1) proceeds smoothly, the reaction attaining completion in 20 min (Fig. 1a), as monitored by GC-MS. The bromination of isosteric mesitylene (Fig. 1b) is much slower, taking hours to go to completion. The rate of bromination is much faster than that observed in DMF (24 h) for similar substrates.<sup>13</sup>

Reactions are also easily amenable to scale-up; monobromination of 3,5-dimethylanisole, for instance, has been accomplished at a 200 g scale with no loss in yield or purity.

The bromination of thioanisole (Table 1, entry 29) did not proceed cleanly, with the observed formation of ca. 20% diphenyl disulfide as a byproduct, as observed by GC-MS and <sup>1</sup>H NMR and compared to an authentic sample. The oxidation of thiols with electrophilic bromine sources such as NBS is not unprecedented<sup>17,25</sup>; however, to our knowledge, the tandem demethylation–oxidation of thioanisoles to form disulfides is not known but can be rationalized (Scheme 1).

Bromination of deactivated aromatics such as halobenzenes and haloaldehydes did not occur under our conditions; bromination of 2-hydroxy-4-methylbenzoic acid also did not

**Scheme 1.** Formation of diphenyl disulfide.



proceed, perhaps because of the sparing solubility of the substrate in ACN.

Recently, Chhattise et al.<sup>26</sup> reported the photochemically induced aromatic bromination of phenols using NBS in acetonitrile. In that report, alkyl species were avoided due to free radical bromination at the benzylic positions (Table 2, entry 8 of their paper refers to the benzylic bromination of toluene). We find that light is not needed for the aromatic bromination and therefore our method is amenable to xylene and mesitylene bromination, whereas that of Chhattise et al.<sup>26</sup> is not. Indeed, even cresol derivatives, which undergo bromination rapidly and cleanly under our conditions, brominate less cleanly under their conditions, likely because of complications from light-induced free radical side reactions.

We have demonstrated the useful potential of NBS bromination of activated arenes in ACN. The advantages of our current procedure are simple work-ups, mild reaction conditions tolerant of diverse functionality, and high regio- and chemoselectivity, the products of which could usually be isolated by simple filtration or solvent extraction.

## Experimental

All experiments were carried out under nitrogen in reagent grade acetonitrile. Commercial chemicals were used as supplied. Column chromatography was performed using silica gel (Merck 60 0.040–0.063 mm). Analytical thin layer chromatography (TLC) was performed with Mecherey-Nagel SIL N-H/UV<sub>254</sub> plates with aluminum backings. Compounds were visualized under UV light. GC-MS samples were run through a Zebtron Zb5 column. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance (300 MHz) and a Bruker ARX 300 (75 MHz) spectrometer, respectively, with the solvent peak as an internal standard. The following abbreviations have been used for multiplicity assignments: “s” for singlet, “d” for doublet, “t” for triplet, “m” for multiplet, and “br” for broad.

The following is a sample procedure for the bromination of arenes using NBS in ACN.

### Bromomanisole

To a 0 °C solution of 3,5-dimethylanisole (685 mg, 5 mmol, 1 equiv.) in 5 mL ACN was added a solution of NBS (890 mg, 5 mmol, 1 equiv.) in 5 mL ACN via addition funnel. The solution was allowed to come to room temperature (RT) and stirred for an additional period, typically between 0.1 and 20 h, depending on the activity of the ring (cf. Fig. 1). The reac-

tion was quenched with H<sub>2</sub>O, hexanes were added, and the layers separated. The aqueous phase was extracted with 3 × hexanes. The organic phase was dried over MgSO<sub>4</sub>, filtered under reduced pressure, and the organic phase concentrated under reduced pressure then under vacuum. A clear liquid (1.09 g) was obtained. Yield: 99%. GC conversion: 100%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.63 (s, 2H), 3.74 (s, 3H), 2.37 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 158.0, 139.0, 118.1, 113.7, 55.2, 23.9. GC-MS (6.56) [M]<sup>+</sup>: 213.8. Anal. calcd. for C<sub>9</sub>H<sub>11</sub>BrO: C 50.26, H 5.15; found: C 50.37, H 4.95. This procedure could be scaled up to 100 g of 3,5-dimethylanisole with no measurable loss in yield or purity. <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>27,28</sup>

### 2-Bromo-5-methoxybenzaldehyde

White solid. Yield: 81%, mp 76–79 °C (lit.<sup>29</sup> mp 78–80 °C). GC conversion: 98%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.31 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 3.3 Hz, 1H), 7.02 (dd, *J* = 3.0, 9.0 Hz, 1H), 3.82 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 191.7, 159.3, 134.5, 134.0, 123.1, 117.9, 112.7, 55.7. GC-MS (6.87) [M]<sup>+</sup>: 216.0. Anal. calcd. for C<sub>8</sub>H<sub>9</sub>BrO<sub>3</sub>: C 44.68, H 3.28; found: C 44.85, H 3.51. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are in agreement with those previously reported.<sup>29</sup>

### 4-Bromo-3,5-dimethylaniline

White solid. The product was purified via flash chromatography (20% EtOAc/hexanes on silica, *R*<sub>f</sub>: 0.15). Yield: 94%, mp 73–75 °C (lit.<sup>29</sup> mp 75–76 °C). GC conversion: 98% with 2% dibrominated side product. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.39 (s, 2H), 3.55 (s, 2H), 2.30 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 144.9, 138.7, 115.8, 115.0, 23.7. GC-MS (7.40) [M]<sup>+</sup>: 198.8. Anal. calcd. for C<sub>8</sub>H<sub>10</sub>BrN: C 48.02, H 5.04, N 7.00; found: C 48.38, H 5.10, N 7.01. <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>30</sup>

### 1-Bromo-2,3,4,5,6-pentamethylbenzene

White solid. *R*<sub>f</sub>: 0.43 (hexanes on silica). Yield: 94%, mp 160–161 °C (lit.<sup>31,32</sup> mp 159–161 °C; lit.<sup>33</sup> mp 163.5–164.5 °C). GC conversion: 100%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 2.43 (s, 6H), 2.25 (s, 6H), 2.12 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 133.8, 133.3, 126.7, 21.4, 17.7, 16.8. GC-MS (8.27) [M]<sup>+</sup>: 225.9. Anal. calcd. for C<sub>11</sub>H<sub>15</sub>Br: C 58.17, H, 6.66; found: C 58.06, H 6.20.

### 2-Amino-5-bromobenzonitrile

White solid. *R*<sub>f</sub>: 0.06 (20% EtOAc/hexanes on silica). Yield: 97%, mp 97–99 °C (lit.<sup>34</sup> mp 98 °C). GC conversion: 100%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.46 (dd, *J* = 2.1, 13.0 Hz, 1H), 7.37 (dd, *J* = 2.4, 9.0 Hz, 1H), 6.61 (d, *J* = 13.0 Hz, 1H), 4.43 (s, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 148.6, 136.9, 134.0, 116.7, 116.2, 108.6, 97.5. GC-MS (7.78) [M]<sup>+</sup>: 196.0. <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>34</sup>

### Bromodurene

White solid. The product was purified via flash chromatography (hexanes on silica). *R*<sub>f</sub>: 0.39 (hexanes on silica). Yield: 92%, mp 60–61 °C (lit.<sup>35</sup> mp 59–60 °C). GC conversion: 97%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.88 (s, 1H), 2.35

(s, 6H), 2.27 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 134.7, 133.8, 130.2, 128.9, 20.8, 20.1. GC-MS (6.76) [M]<sup>+</sup>: 212.0. Anal. calcd. for C<sub>10</sub>H<sub>13</sub>Br: C 56.36, H 6.15; found: C 55.93, H 6.15. <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>35</sup>

### 2-Bromomesitylene

Pale yellowish liquid. Yield: 93%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.92 (s, 2H), 2.41 (s, 6H), 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 137.9, 136.2, 129.2, 124.4, 24.1, 20.8. GC-MS (5.24) [M]<sup>+</sup>: 197.8. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are in agreement with those previously reported.<sup>36</sup>

### 1-Bromo-2,3,4-trimethylbenzene

Clear oil. The product was purified via flash chromatography (hexanes on silica). *R*<sub>f</sub>: 0.40 (hexanes on silica). Yield: 43%. GC conversion: 66%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.30 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 2.41 (s, 3H), 2.47 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 136.9, 135.5, 129.3, 128.5, 122.8, 20.5, 19.9, 16.7. GC-MS (5.80) [M]<sup>+</sup>: 197.9. <sup>1</sup>H NMR spectrum is not in agreement with that previously reported.<sup>37</sup>

### Bromohydroquinone

White solid. The product was purified via flash chromatography (1:2:1 CH<sub>2</sub>Cl<sub>2</sub>/hexanes/Et<sub>2</sub>O on silica). *R*<sub>f</sub>: 0.19 (1:2:1 CH<sub>2</sub>Cl<sub>2</sub>/hexanes/Et<sub>2</sub>O on silica). Yield: 42%, mp 110–112 °C (lit.<sup>37</sup> mp 106–109 °C). GC Conversion: 97%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.97 (d, *J* = 3.0 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.70 (dd, *J* = 3.0, 9.0 Hz, 1H), 5.10 (s, 1H), 4.74 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>) δ: 151.8, 147.8, 119.9, 117.6, 116.3, 110.1. GC-MS (6.69) [M]<sup>+</sup>: 187.9. Anal. calcd. for C<sub>6</sub>H<sub>5</sub>BrO<sub>2</sub>: C 38.13, H 2.67; found: C 38.10, H 2.90. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are in agreement with those previously reported.<sup>38</sup>

### 4-Bromo-3,5-dimethylphenol

White solid. *R*<sub>f</sub>: 0.13 (10% EtOAc/hexanes on silica). The product was purified via flash chromatography (33% CH<sub>2</sub>Cl<sub>2</sub>/hexanes on silica, *R*<sub>f</sub>: 0.05). Yield: 96%, mp 116–117 °C (lit.<sup>38</sup> mp 114–115 °C). GC conversion: 100%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.57 (s, 2H), 4.99 (s, 1H), 2.34 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 153.7, 139.4, 118.3, 115.2, 23.7. GC-MS (7.20) [M]<sup>+</sup>: 199.8. Anal. calcd. for C<sub>8</sub>H<sub>9</sub>BrO: C 47.79, H 4.51; found: C 47.71, H 4.57. <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>39</sup>

### 4-Bromo-2,6-dimethylphenol

Yellow-orange solid. Yield: 96%, mp 78–79 °C (lit.<sup>40</sup> mp 79–80 °C). GC conversion: 99%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.10 (s, 2H), 4.55 (s, 1H), 2.22 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 151.2, 130.9, 125.3, 112.0, 15.6. GC-MS (6.64) [M]<sup>+</sup>: 199.8. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are in agreement with those previously reported.<sup>40</sup>

### 5-Bromobenzo[d][1,3]dioxole

Brown oil. *R*<sub>f</sub>: 0.10 (hexanes on silica). Yield: 94%. GC conversion: 99%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.91–6.88 (m, 2H), 6.63 (dd, *J* = 1.8, 8.1 Hz, 1H), 5.91 (d, *J* = 0.9 Hz,

2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.5, 146.9, 124.2, 113.0, 112.4, 109.4, 101.6. GC-MS (5.42)  $[\text{M}]^+$ : 200.0.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>41</sup> The compound was reported as a colorless oil.

#### 1-(4-Bromophenoxy)benzene

The reaction mixture was stirred for two days. Clear oil.  $R_f$ : 0.19 (hexanes on silica). GC conversion: 91% with 7% dibrominated side product.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.41 (d,  $J = 9.0$  Hz, 2H), 7.31 (t,  $J = 8.1$  Hz, 2H), 7.11 (tt,  $J = 0.9, 6.9$  Hz, 1H), 6.99 (dd,  $J = 1.2, 6.9$  Hz, 2H), 6.87 (d,  $J = 9.0$  Hz, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 156.6, 132.6, 129.8, 123.6, 120.5, 120.3, 118.9, 115.5. GC-MS (8.81)  $[\text{M}]^+$ : 247.9.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>42</sup>

#### 4-Bromoanisole

Clear oil.  $R_f$ : 0.18 (hexanes on silica). Yield: 97%. GC conversion: 100%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.36 (d,  $J = 8.4$  Hz, 2H), 6.76 (d,  $J = 8.4$  Hz, 2H), 3.77 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.6, 132.1, 115.6, 112.7, 55.3. GC-MS (4.61)  $[\text{M}]^+$ : 185.9.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>20,40</sup>

#### 1-Bromo-2,4-dimethylbenzene

The reaction mixture was stirred for five days. Clear oil.  $R_f$ : 0.19 (hexanes on silica). Yield: 98%. GC conversion: 100% with 3% benzyl and other monobrominated side products.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.36 (d,  $J = 8.1$  Hz, 1H), 7.03 (m, 1H), 6.84 (dd,  $J = 2.4, 8.1$  Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.0, 135.2, 132.0, 131.7, 127.7, 121.7, 22.8, 20.9. GC-MS (4.23)  $[\text{M}]^+$ : 183.7.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>36</sup>

#### 1-Bromo-4-methoxy-2-methylbenzene

Clear oil, which solidified to a white solid under vacuum.  $R_f$ : 0.16 (hexanes on silica). Yield: 97%.  $^1\text{H}$  NMR conversion: 100%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.40 (d,  $J = 8.7$  Hz, 1H), 6.79 (d,  $J = 3.0$  Hz, 1H), 6.61 (dd,  $J = 2.7, 8.7$  Hz, 1H), 3.76 (s, 3H), 2.38 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.8, 138.7, 132.7, 116.5, 115.3, 112.9, 55.2, 23.0. GC-MS (5.63)  $[\text{M}]^+$ : 200.0.  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>43,44</sup>

#### 2-Bromo-1-methoxy-4-methylbenzene

Clear oil.  $R_f$ : 0.30 (10% EtOAc/hexanes on silica). The product was purified via flash chromatography (10% EtOAc/hexanes on silica). Yield: 63%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34 (d,  $J = 2.1$  Hz, 1H), 7.04 (dd,  $J = 2.2, 8.1$  Hz, 1H), 6.77 (d,  $J = 8.4$  Hz, 1H), 3.84 (s, 3H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 153.7, 133.6, 131.4, 128.8, 111.8, 111.2, 56.2, 20.1. GC-MS (5.72)  $[\text{M}]^+$ : 200.0.  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>43,45</sup>

#### 1-Bromo-2,4-dimethoxybenzene

Clear oil.  $R_f$ : 0.19 (20% EtOAc/hexanes on silica). Yield: 99%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38 (d,  $J = 8.7$  Hz,

1H), 6.46 (d,  $J = 2.7$  Hz, 1H), 6.37 (dd,  $J = 2.7, 8.4$  Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.7, 155.0, 131.6, 104.4, 100.9, 98.5, 54.6, 54.0. GC-MS (7.10)  $[\text{M}]^+$ : 217.8. Anal. calcd. for  $\text{C}_8\text{H}_9\text{BrO}_2$ : C 44.27, H 4.18; found: C 44.18, H 4.25.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with that previously reported.<sup>46</sup>

#### 1-Bromo-2,5-dimethoxybenzene

Yellow oil.  $R_f$ : 0.06 (10% EtOAc/hexanes on silica). Yield: 99%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.10 (m, 1H), 6.82 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 154.0, 118.9, 114.6, 113.6, 112.9, 111.9, 56.9, 55.8. GC-MS (6.83)  $[\text{M}]^+$ : 217.8.  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>47</sup>

#### 4-Bromo-2-methoxybenzenamine

Red liquid.  $R_f$ : 0.07 (20% EtOAc/hexanes on silica). The product was purified via flash chromatography (20% EtOAc/hexanes on silica). Mp 59–60 °C (liquid) (lit.<sup>48</sup> mp 60–61 °C). Yield: 71%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.86 (m, 2H), 6.55 (dd,  $J = 2.1, 8.7$  Hz, 1H), 3.80 (s, 3H), 3.74 (s, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.8, 135.3, 123.6, 115.6, 113.7, 109.4, 55.6. GC-MS (7.17)  $[\text{M}]^+$ : 202.9.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>48</sup> The compound was reported as a brown solid.

#### 3,4-Dibromo-2-methoxybenzenamine

Red liquid, isolated as a side product in the monobromination reaction of *o*-anisidine.  $R_f$ : 0.25 (20% EtOAc/hexanes on silica). The product was purified via flash chromatography (20% EtOAc/hexanes on silica). Yield: 12%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.15 (d,  $J = 2.1$  Hz, 1H), 6.80 (d,  $J = 2.1$  Hz, 1H), 4.12 (s, 2H), 3.81 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.6, 134.1, 126.1, 112.5, 108.5, 108.1, 56.0. GC-MS (8.86)  $[\text{M}]^+$ : 278.9.  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>48</sup>

#### 4-Bromo-3-methoxybenzenamine

White solid.  $R_f$ : 0.05 (30% EtOAc/hexanes on silica). The product was purified via flash chromatography (30% EtOAc/hexanes on silica). Yield: 47%, mp 94–95.5 °C (lit.<sup>23,49</sup> mp 93–94 °C).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19 (d,  $J = 8.4$  Hz, 1H), 6.20 (d,  $J = 2.7$  Hz, 1H), 6.14 (dd,  $J = 2.4, 8.4$  Hz, 1H), 3.75 (s, 3H), 3.71 (s, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 156.3, 147.3, 133.2, 108.4, 99.6, 99.2, 55.9. GC-MS (7.92)  $[\text{M}]^+$ : 201.0. Anal. calcd. for  $\text{C}_7\text{H}_8\text{BrNO}$ : C 41.61, H 3.99, N 6.93; found: C 41.80, H 4.21, N 6.80.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>48</sup>

#### 2-Bromo-4-methoxybenzenamine

Red liquid.  $R_f$ : 0.13 (20% EtOAc/hexanes on silica). The product was purified via flash chromatography (20% EtOAc/hexanes on silica). Yield: 20%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.98 (dd,  $J = 0.9, 2.1$  Hz, 1H), 6.70 (m, 2H), 3.79 (s, 2H), 3.70 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 153.3, 138.6, 118.1, 117.2, 115.6, 110.1, 56.5. GC-MS (6.94)  $[\text{M}]^+$ : 201.0.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>48,49</sup>

### 5-Bromo-2-hydroxybenzaldehyde

White solid.  $R_f$ : 0.37 (20% EtOAc/hexanes on silica). The product was purified via flash chromatography (20% EtOAc/hexanes on silica). Yield: 18%, mp 102–105 °C (lit.<sup>50</sup> mp 104–105 °C).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.92 (s, 1H), 9.83 (s, 1H), 7.65 (d,  $J = 2.4$  Hz, 1H), 7.58 (dd,  $J = 2.7, 9.0$  Hz, 1H), 6.89 (d,  $J = 9.0$  Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 196.1, 161.3, 140.5, 136.4, 122.5, 120.6, 112.1. GC-MS (5.53)  $[\text{M}]^+$ : 200.0.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are in agreement with those previously reported.<sup>50,51</sup>

### 4-Bromo-3,5-dimethyl-*N,N*-dimethylaniline

Isolated as a thick colorless oil that solidified to a crystalline white substance after sitting under high vacuum for 16 h.  $R_f$ : 0.35 (50%  $\text{CH}_2\text{Cl}_2$ /hexanes on silica). The product was purified via flash chromatography (50%  $\text{CH}_2\text{Cl}_2$ /hexanes on silica). Yield: 95%, mp 25–26 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.51 (s, 2H), 2.81 (s, 6H), 2.41 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 149.2, 138.2, 114.5, 112.7, 40.6, 24.1. GC-MS (8.12)  $[\text{M}]^+$ : 227.0.  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>52</sup> The compound was reported as a colorless liquid.

### Bromojulolidine (referred to as 9-bromojulolidine in the reference)

The product was extracted with  $\text{CH}_2\text{Cl}_2$  to produce a dark red crystalline solid. Yield: 92%, mp 35–37 °C (lit.<sup>53</sup> mp 36.5 °C).  $R_f$ : 0.30 ( $\text{CH}_2\text{Cl}_2$  on silica). The product was purified via flash column chromatography ( $\text{CH}_2\text{Cl}_2$  on silica).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.93 (d,  $J = 0.6$  Hz, 2H), 3.17 (t,  $J = 6.5$  Hz, 4H), 2.76 (t,  $J = 5.7$  Hz, 4H), 2.01 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.3, 129.6, 124.0, 107.5, 50.3, 28.0, 22.3, 28.0. GC-MS (10.85)  $[\text{M}]^+$ : 251.1.

### 4-Bromothioanisole

Clear oil. GC conversion: 75%.  $R_f$ : 0.21 (hexanes on silica).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 (d,  $J = 8.7$  Hz, 2H), 7.10 (d,  $J = 8.7$  Hz, 2H), 2.46 (s, 3H). GC-MS (6.16)  $[\text{M}]^+$ : 201.9.

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