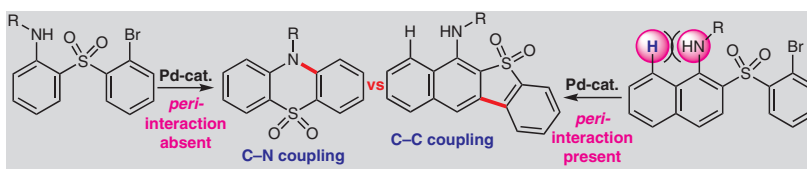


# Palladium-Catalysed Intramolecular C–N versus C–C Coupling: The Effect of 1,8-*peri*-Interaction in the Naphthalene System

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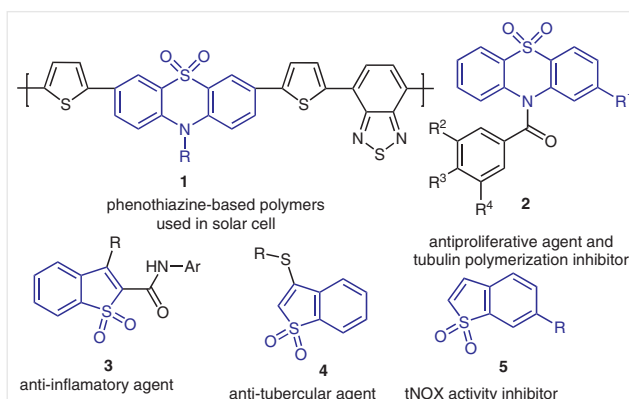
**Abstract** Palladium-catalysed competitive intramolecular C–N and C–C coupling of 2-amino-2'-bromodiphenylsulfones has been carried out based on 1,8-*peri*-interactions for the synthesis of phenothiazinedioxide and benzonaphthathiophenedioxide derivatives. A DFT study has been performed that provides support for the influence of the 1,8-*peri*-interaction.

**Key words** naphthalene, 1,8-*peri*-interaction, cyclization, fused-ring, heterocycles

Due to the rigidity of the naphthalene skeleton, the substituents on 1- and 8-positions are forced to be relatively close, at 2.5 Å, which is within the van der Waals radius for many atoms. In contrast, *ortho*-substituents on a benzene ring are separated by 3.3 Å.<sup>1</sup> This 1,8-*peri*-interaction of naphthalenes, also known as a *peri*-interaction, results in some unique reactivity compared with substituted benzene derivatives.

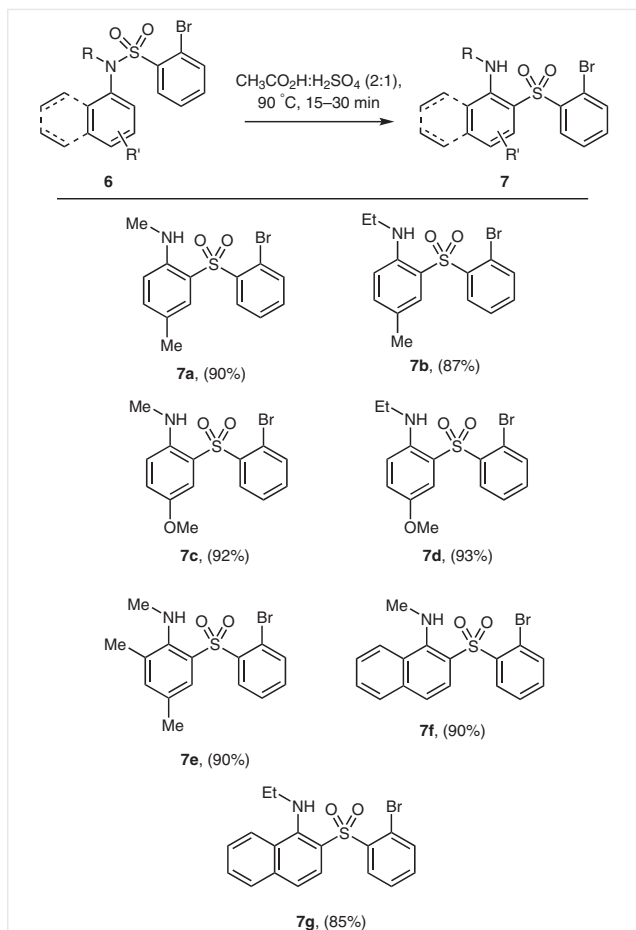
During our continuing studies on developing novel synthetic routes to heterocycles,<sup>2</sup> we have prepared phenothiazine dioxides and benzonaphthathiophene dioxides via Pd-catalysed intramolecular C–N and C–C coupling and we have studied the effect of the 1,8-*peri*-interaction on the

reactivity of the naphthalene moiety. Arylthiazine dioxides and arylthiophene dioxides are important classes of heterocycles because of their applications in medicinal and materials chemistry (Figure 1).<sup>3</sup> Moreover thiazine and thiophene cores are also found in various biologically active natural products and synthetic drugs.<sup>4</sup>



**Figure 1** Examples of some useful arylthiazinedioxides and arylthiophenedioxides

We began this work with 2-amino-2'-bromodiphenylsulfones **7**, which were prepared from the corresponding 2-bromo-*N*-alkyl-*N*-arylbenzenesulfonamide derivatives **6** according to our reported procedure (Scheme 1).<sup>5</sup>



**Scheme 1** Regioselective Fries type rearrangement for 2-amino-2'-bromodiarylsulfones synthesis

2-Amino-2'-bromodiarylsulfone **7a** was treated with  $\text{Pd}(\text{OAc})_2$  catalyst in DMF using  $\text{Cs}_2\text{CO}_3$  as base at 100 °C for 1 h to effect intramolecular C–N coupling, leading to phenothiazine dioxide **8a** in 78% yield. We then optimised the reaction conditions by varying the Pd catalyst, base, solvent, additive, temperature and time. The summarised results are presented in Table 1. Among the three Pd catalysts examined,  $\text{Pd}(\text{OAc})_2$  provided the best result. Changing base from  $\text{Cs}_2\text{CO}_3$  to  $\text{K}_2\text{CO}_3$  led to a notable decrease in yield; whereas KOAc proved more effective. Among different solvents, DMF showed the best results compared with toluene and DMA. The addition of TBAB did not show any improvement in yield. Increasing time or temperature led to little or a slight lowering of reaction yields. At low temperatures (50–70 °C), the reaction did not proceed even with extended reaction periods (entries 15 and 16). Increasing the temperature to 85 °C led to a 30% yield of product. The effect of catalyst loading was also studied and we observed the best result using 5 mol%  $\text{Pd}(\text{OAc})_2$  as catalyst, 2.5 equivalents KOAc as base, DMF as solvent at 100 °C for 1 h, obtaining phenothiazine dioxide in 96% yield (entry 10).

**Table 1** Optimisation of Reaction Conditions for Pd-Catalysed Intramolecular C–N coupling<sup>a</sup>

Entry	Cat. System (mol%)	Base <sup>b</sup>	Solvent	Additive	Time (h)	Temp. (°C)	Yield (%) <sup>c</sup>
1	$\text{Pd}(\text{OAc})_2$ (10)	$\text{Cs}_2\text{CO}_3$	DMF	–	1	100	78
2	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (10)	$\text{Cs}_2\text{CO}_3$	DMF	–	1	100	67
3	$\text{Pd}_2\text{dba}_3$ (10)	$\text{Cs}_2\text{CO}_3$	DMF	–	1	100	65
4	$\text{Pd}(\text{OAc})_2$ (10)	$\text{Cs}_2\text{CO}_3$	DMF	TBAB	1	100	75
5	$\text{Pd}(\text{OAc})_2$ (10)	$\text{Cs}_2\text{CO}_3$	toluene	–	1	100	52
6	$\text{Pd}(\text{OAc})_2$ (10)	$\text{K}_2\text{CO}_3$	DMF	–	1	100	55
7	$\text{Pd}(\text{OAc})_2$ (10)	KOAc	DMF	–	1	100	92
8	$\text{Pd}(\text{OAc})_2$ (10)	KOAc	DMF	–	2	100	81
9	$\text{Pd}(\text{OAc})_2$ (10)	KOAc	DMF	–	1	120	79
10	<b><math>\text{Pd}(\text{OAc})_2</math> (5)</b>	<b>KOAc</b>	<b>DMF</b>	–	<b>1</b>	<b>100</b>	<b>96</b>
11	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMF	TBAB	1	100	92
12	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMA	–	2	100	78
13	$\text{Pd}(\text{OAc})_2$ (3)	KOAc	DMF	–	1	120	64
14	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMF	–	0.5	100	70
15	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMF	–	4	50	np
16	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMF	–	4	70	np
17	$\text{Pd}(\text{OAc})_2$ (5)	KOAc	DMF	–	4	85	30

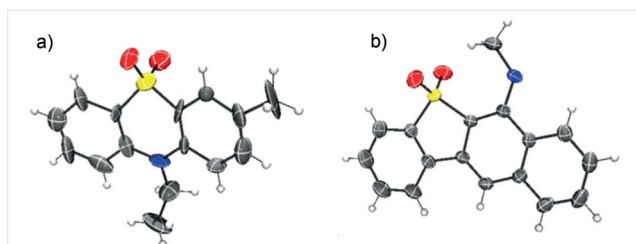
<sup>a</sup> All reactions were carried out in a sealed tube under nitrogen.

<sup>b</sup> In every case 2.5 equivalents of base were used.

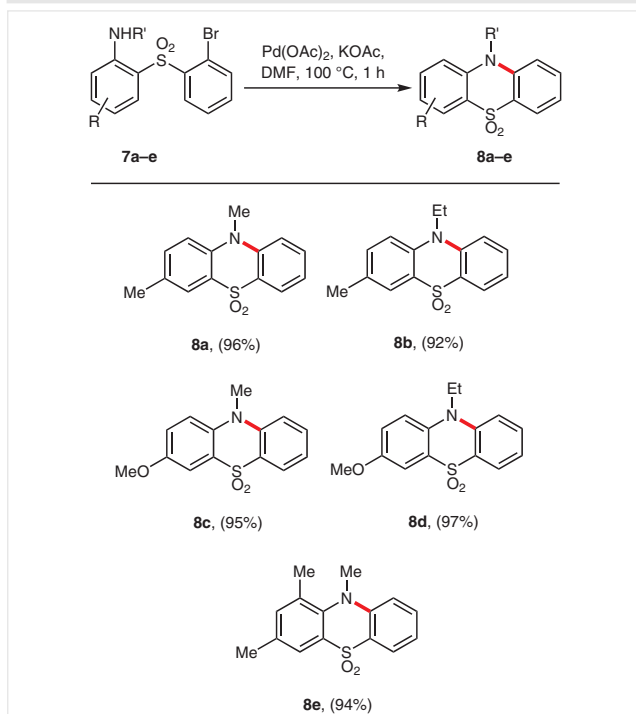
<sup>c</sup> np = no product

After optimising the reaction conditions, 2-amino-2'-bromodiarylsulfone derivatives **7b–g** were used for the preparation of the corresponding phenothiazine dioxide derivatives **8b–g**. For compounds **7b–e** the corresponding phenothiazine dioxides **8b–e** were formed in excellent yields under the optimised reaction conditions (Scheme 2); however, for substrates **7f** and **7g** a different reaction course took place. The <sup>1</sup>H NMR spectra of the products obtained from precursors **7f** and **7g** showed the N–H proton to be present and one aromatic proton was absent; whilst the <sup>13</sup>C NMR spectra revealed the presence of two additional fully substituted aromatic carbon atoms. These data indicate that, for precursors **7f** and **7g**, intramolecular C–C coupling had occurred instead of intramolecular C–N cou-

pling, leading to the corresponding benzonaphthathio-  
phene dioxide derivatives **8f** and **8g**. Finally we confirmed  
the structures of compound **8a**<sup>6</sup> and **8f**<sup>7</sup> by single-crystal  
X-ray analysis (Figure 2).



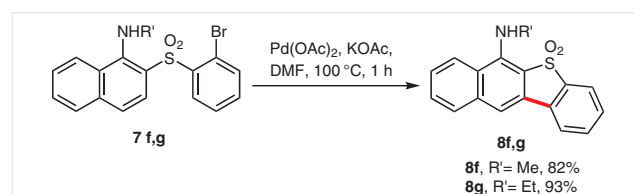
**Figure 2** ORTEP diagrams of (a) phenothiazine dioxide **8a** and  
(b) benzonaphthathio-phene dioxide **8f** (the thermal ellipsoids are  
drawn at the 50% probability level).



**Scheme 2** Synthesis of phenothiazine dioxide derivatives

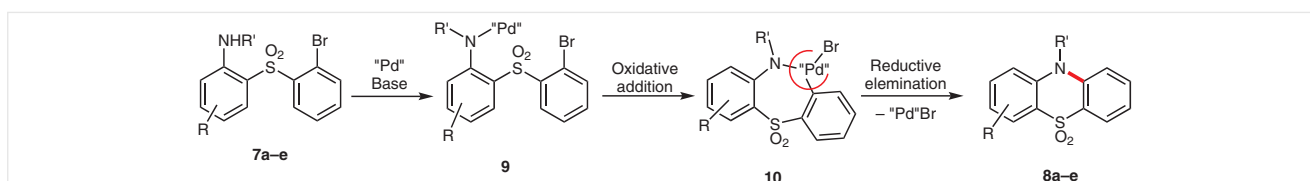
During cyclisation of compounds **7a–f**, two different  
modes of cyclisation, C–N and C–C, are possible. However,  
between these two possibilities, C–N coupling is preferred  
for compounds **7a–e**. A plausible mechanism for the forma-  
tion of compounds **8a–e** is shown in Scheme 3. Initially,  
Pd(OAc)<sub>2</sub> is reduced to give the active Pd(0) species,<sup>8</sup> which  
complexes with **7a–e** via coordination with nitrogen to form  
aryl palladium intermediates **9a–e**. The intermediate then  
leads to the phenothiazine dioxide derivatives **8a–e** via oxi-  
dative addition followed by reductive elimination.

When compounds **7f** and **7g** were treated under the  
same reaction conditions, C–C coupling was observed in-  
stead of C–N coupling, leading to benzonaphthathio-  
phene dioxide derivatives **8f** and **8g** (Scheme 4). A plausible mech-  
anism for the formation of **8f** and **8g** is shown in Scheme 5.  
Here N–Pd complex **11** is not formed, which may be due to  
the *peri*-interaction between H-8 and the 1-alkyl-NPd group.  
Instead, Pd(0) first undergoes oxidative addition to form  
intermediates **12f** and **12g**, which then lead to the  
benzonaphthathio-phene dioxide derivatives **8f** and **8g** via  
carbopalladation followed by elimination of PdBr.

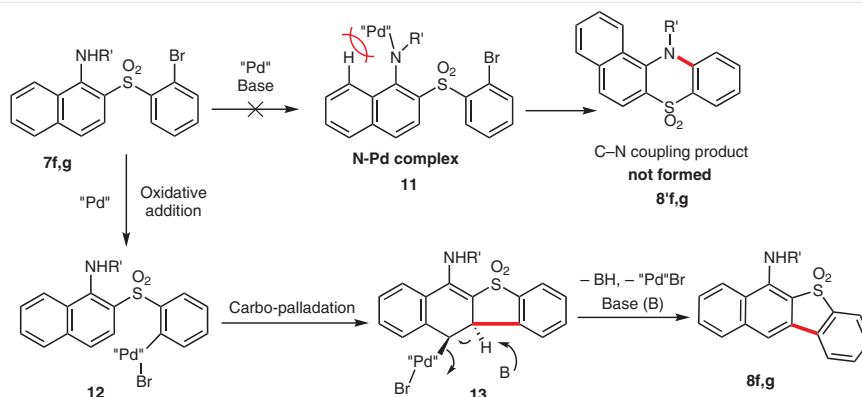


**Scheme 4** Synthesis of benzonaphthathio-phene dioxide derivatives

We performed DFT calculations to investigate the 1,8-  
*peri*-interaction in naphthalene systems and the results  
support the mechanism depicted in Scheme 5 for C–C cou-  
pling. All calculations were performed with the Gaussian09  
program package<sup>9</sup> using hybrid density functional (B3LYP)  
theory and the 6-31G(d) basis set. For Pd, the LanL2DZ basis  
set was used with LanL2 effective core potential. This DFT  
study shows that the formation energy of complex **11** from  
the anion of **7f** is  $-420.48$  kcal mol<sup>-1</sup>; whereas the forma-  
tion energy of intermediate **12** is  $-490.33$  kcal mol<sup>-1</sup>. This  
indicates that the formation of intermediate **12** is more en-  
ergetically favourable than that of complex **11** by 69.85 kcal  
mol<sup>-1</sup>. This could explain why the reaction passes through  
the successive oxidative addition of Pd(0) to the C–Br bond,



**Scheme 3** Plausible mechanism for Pd-catalysed C–N coupling



**Scheme 5** Plausible mechanism for Pd-catalysed C–C coupling.

carbopalladation and elimination of PdBr to give the corresponding benzonaphthathiophene dioxides **8f** and **8g** instead of phenothiazine dioxides **8'f** and **8'g**.

In conclusion we have synthesised phenothiazine dioxides **8a–e** and benzonaphthathiophene dioxides **8f** and **8g** by Pd-catalysed intramolecular C–N and C–C coupling reactions, respectively. The effect of the 1,8-*peri*-interaction in the naphthalene system was investigated by DFT calculations and the results support the observed outcomes.

### Synthesis of 7e

Compound **7e** was prepared according to the previously reported procedure.<sup>5</sup>

IR (KBr): 3420, 2915, 1617, 1531, 1302, 1135, 708, 580 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.13 (d, *J* = 7.8 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.38–7.34 (m, 1 H), 6.45 (s, 1 H), 5.99 (br s, 1 H), 2.80 (s, 3 H), 2.23 (s, 3 H), 2.13 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 146.9, 145.5, 140.6, 135.6, 133.8, 132.1, 127.3, 123.8, 120.7, 115.7, 112.8, 30.1, 20.6, 18.5.

LCMS (ES<sup>+</sup>): *m/z* [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>17</sub>BrNO<sub>2</sub>S<sup>+</sup>: 354.02; found: 354.

### Synthesis of Phenothiazine Dioxides 8a–e and Benzonaphthathiophene Dioxides 8f and 8g; General Procedure

#### 3,10-Dimethyl-10H-phenothiazine 5,5-dioxide (8a)

A solution of **7a** (200 mg, 0.59 mmol) in anhydrous DMF (2 mL) and KOAc (115 mg, 1.17 mmol) was purged with nitrogen for 10 min. Pd(OAc)<sub>2</sub> (7 mg, 5 mol%) was then added and the mixture was heated to 100 °C for 1 h in a sealed tube. The reaction mixture was cooled, H<sub>2</sub>O (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with H<sub>2</sub>O (10 mL), brine (10 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was distilled off to furnish a viscous residue that was purified by column chromatography (EtOAc/petroleum ether, 1:4) on silica gel to yield compound **8a** (146 mg, 96%) as a white solid; mp 149–151 °C.

IR (KBr): 2975, 1597, 1477, 1273, 1154, 748, 577 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.12 (d, *J* = 7.8 Hz, 1 H), 7.94 (s, 1 H), 7.66–7.60 (m, 1 H), 7.44 (d, *J* = 8.6 Hz, 1 H), 7.33–7.20 (m, 3 H), 3.67 (s, 3 H), 2.46 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 142.1, 139.9, 134.2, 133.1, 131.9, 124.2, 123.4, 123.0, 121.5, 115.6, 115.5, 35.7, 20.5.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>2</sub>S<sup>+</sup>: 260.0740; found: 260.0743.

#### 10-Ethyl-3-methyl-10H-phenothiazine 5,5-dioxide (8b)

Yield: 92%; white solid; mp 136–138 °C.

IR (KBr): 2979, 1584, 1471, 1273, 1155, 746, 560 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.09 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.92–7.89 (m, 1 H), 7.59–7.54 (m, 1 H), 7.39 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.32 (d, *J* = 8.6 Hz, 1 H), 7.27–7.17 (m, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.39 (s, 3 H), 1.49 (t, *J* = 7.1 Hz, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 140.6, 138.3, 134.4, 133.3, 131.8, 123.8, 123.7, 123.2, 121.4, 115.8, 115.6, 43.1, 20.5, 12.6.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>2</sub>S<sup>+</sup>: 274.0896; found: 274.0898.

#### 3-Methoxy-10-methyl-10H-phenothiazine 5,5-dioxide (8c)

Yield: 95%; white solid; mp 168–170 °C.

IR (KBr): 2929, 1584, 1479, 1275, 1150, 835, 746, 579 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.11 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.65–7.58 (m, 2 H), 7.30–7.24 (m, 3 H), 7.24–7.20 (m, 1 H), 3.91 (s, 3 H), 3.70 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 154.8, 142.3, 136.4, 133.2, 124.8, 123.6, 123.5, 121.8, 121.5, 117.4, 115.3, 105.4, 56.1, 35.8.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>3</sub>S<sup>+</sup>: 276.0689; found: 276.0690.

#### 10-Ethyl-3-methoxy-10H-phenothiazine 5,5-dioxide (8d)

Yield: 97%; white solid; mp 158–160 °C.

IR (KBr): 2934, 1578, 1478, 1269, 1145, 832, 752, 568 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.09 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.61–7.54 (m, 2 H), 7.34–7.29 (m, 2 H), 7.24–7.17 (m, 2 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 3.86 (s, 3 H), 1.50 (t, *J* = 7.0 Hz, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 154.6, 140.7, 134.7, 133.2, 124.3, 123.7, 122.9, 122.1, 121.3, 117.6, 115.4, 105.2, 56.1, 43.1, 12.7.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>3</sub>S<sup>+</sup>: 290.0845; found: 290.0849.

#### 2,4,10-Trimethyl-10H-phenothiazine 5,5-dioxide (8e)

Yield: 94%; white solid; mp 152–154 °C.

IR (KBr): 2973, 1594, 1465, 1273, 1148, 745, 570 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.08 (d, *J* = 7.7 Hz, 1 H), 7.83 (s, 1 H), 7.60–7.56 (m, 1 H), 7.25–7.21 (m, 2 H), 7.05 (s, 1 H), 3.66 (s, 3 H), 2.37 (s, 3 H), 2.31 (s, 3 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 142.9, 142.1, 140.1, 132.9, 130.9, 124.3, 123.4, 123.3, 121.8, 121.4, 116.4, 115.3, 35.6, 20.7, 18.9$ .

LCMS (ES+):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_2\text{S}^+$ : 274.09; found: 274.1.

**N-Methylbenzo[d]naphtho[2,3-b]thiophen-6-amine-5,5-dioxide (8f)**

Yield: 82%; white solid; mp 183–185 °C.

IR (KBr): 3404, 2967, 1554, 1280, 1135, 758, 542  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 7.92$  (d,  $J = 8.4$  Hz, 1 H), 7.87–7.80 (m, 2 H), 7.77 (d,  $J = 7.9$  Hz, 1 H), 7.60 (td,  $J = 7.5, 0.9$  Hz, 1 H), 7.56–7.41 (m, 4 H), 5.25 (m, 1 H), 3.58 (d,  $J = 5.2$  Hz, 3 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 144.6, 138.4, 136.5, 133.4, 132.3, 130.0, 129.6, 129.2, 129.0, 126.7, 126.1, 122.6, 121.6, 121.6, 114.7, 110.9, 34.9$ .

DEPT-135 ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 133.4, 130.0, 129.6, 129.0, 126.7, 122.6, 121.6, 121.6, 110.9, 34.9$ .

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{14}\text{NO}_2\text{S}^+$ : 296.0740; found: 296.0742.

**N-Ethylbenzo[d]naphtho[2,3-b]thiophen-6-amine-5,5-dioxide (8g)**

Yield: 93%; white solid; mp 177–179 °C.

IR (KBr): 3407, 2968, 1549, 1272, 1136, 750, 537  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 7.93$  (d,  $J = 8.4$  Hz, 1 H), 7.81 (t,  $J = 7.7$  Hz, 2 H), 7.74 (d,  $J = 8.0$  Hz, 1 H), 7.58 (td,  $J = 7.6, 0.8$  Hz, 1 H), 7.54–7.38 (m, 4 H), 4.81 (br s, 1 H), 3.89 (q,  $J = 7.1$  Hz, 2 H), 1.45 (t,  $J = 7.1$  Hz, 3 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 143.9, 138.5, 136.7, 133.5, 132.3, 130.0, 129.6, 129.0, 126.7, 123.2, 121.6, 116.4, 111.6, 43.2, 16.2$ .

DEPT-135 ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 133.5, 130.0, 129.6, 129.0, 126.7, 123.2, 121.7, 121.6, 111.6, 43.2, 16.2$ .

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_2\text{S}^+$ : 310.0896; found: 310.0899.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611667>.

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