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Synthesis of 3-aryl- and 3-aryl-4-methyl-1,2-benzenedisulfonimides, new chiral Brønsted acids. A combined experimental and theoretical study.

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Abstract

We have recently reported the use, in catalytic amount, of 1,2-benzenedisulfonimide as a safe, nonvolatile and noncorrosive Brønsted acid in some acid-catalyzed organic reactions. All the reactions studied required mild reaction conditions, short reaction times and catalytic amount of 1,2-benzenedisulfonimide. With the design of new and chiral acid organocatalysts with the structure of 1,2-benzenedisulfonimide in mind, we herein propose a synthesis of 1,2-benzenedisulfonimide derivatives bearing an aryl group in the 3-position with good overall yields. The chirality of these compounds is due to the hindered rotation of the aryl group (atropisomerism). Theoretical studies demonstrate that the rotational barrier responsible for this property is high enough to lead to stable atropisomers. We resolved the atropisomers of one of these compounds by derivatization with (S)-1-phenylethylamine and subsequent HPLC. The electronic Circular Dichroism spectra of the resolved diastereomers allowed us to assign the absolute configuration.
1. Introduction

Organocatalysis has become a highly dynamic area in chemical research. Recently, List introduced a system of classification of catalysts based on their action mechanism; thus, there are essentially four categories of organocatalysts: Lewis acids, Lewis bases, Brønsted bases and Brønsted acids. Of these, Brønsted acids emerge as powerful catalysts that present a range of benefits including: a lack of sensitivity to moisture and oxygen, ready availability, a low cost, and low toxicity. This combination confers large direct benefits in many synthetic protocols when compared with metal catalysts.

We have recently reported the use of 1,2-benzenedisulfonimide (I, figure 1) in catalytic amounts as a safe, nonvolatile and noncorrosive Brønsted acid in some acid-catalyzed organic reactions such as etherification, esterification, acetalization, the Ritter reaction, the Nazarov electrocyclization, the disproportionation of dialkyl diarylmethyl ethers, the Hosomi-Sakurai reaction, the Friedlander annulation, the Pictet-Spengler reaction and the Mukayama-aldol reaction.

![Figure 1. 1,2-Benzenedisulfonimide.](image)

In general, all synthetic methods require mild reaction conditions, short reaction times, good selectivity and the absence or minimal formation of by-products are observed. Moreover, it is worthwhile to highlight the further valuable aspect of all the above reactions. This is the fact that I can easily and almost completely be recovered from the reaction mixtures, in good to high yield, due to its complete solubility in water. This permits its reuse in catalytic amounts in other reactions, immediately or after a fast purification run on a cation-exchange resin, without the loss of catalytic activity. This obviously has economic and ecological advantages.

The results and advantages of the use of I are very promising in view of the applications of this catalyst in the field of asymmetric catalysis. Of course, structural modifications are needed so that I becomes chiral, while leaving the acidic function responsible of the catalytic activity unaffected.

In this view, it was decided to bind an hindered aryl group to the 3- position of the aromatic ring of I in order to prevent the free rotation around the aryl-aryl bond and therefore generate atropisomerism (figure 2). In this paper we describe the synthesis of a set of hindered derivatives.
Figure 2. Chiral derivatives of 1,2-benzenedisulfonimide.

To obtain these chiral derivatives, the rotational barrier of the inter-ring C-C bond should be high enough to assure a atropisomer long lifetime. The role of common substituents in defining this barrier on biphenyl has already been well established.\textsuperscript{12b} By contrast, the use of a rigid sulfonimide group is unknown. Therefore, the rotational barriers for a series of 1,2-benzenedisulfonimides derivatives and precursors have been calculated by the DFT method.

It must be stressed that, recently, three different research groups have identified a disulfonimide functional group as a powerful motif for asymmetric catalysis. In particular, Giernoth\textsuperscript{13} describes the synthesis of BINBAM, namely \((R)-2,2’\)-binaphthyldisulfonimide; List\textsuperscript{14a} the synthesis of \((R)-3,3’\)-bis[3,5-bis(trifluoromethyl)phenyl]-1,1’-binaphthyl-2,2’-disulfonimide (and other similar chiral derivatives\textsuperscript{14b-c}), which is a highly active catalyst of the Mukaiyama aldol reaction with very good enantioselectivity and A. W. M. Lee\textsuperscript{15} the synthesis of several 3,3’-diaryl derivatives of \((R)-2,2’\)-binaphthyldisulfonimide. Furthermore, we have, very recently, proposed an alternative and convenient route to prepare \((R)-2,2’\)-binaphthyldisulfonimide.\textsuperscript{16}

2. Results and discussion

2.1 Preparation of anthranilic acids 5

As reported in the literature,\textsuperscript{17,18} 1 was easily prepared starting from anthranilic acid. In the light of this, our first synthetic goal was the preparation of 3-arylanthranilic acids 5 (Scheme 1). In the literature\textsuperscript{19} a synthesis of 3-arylanthranilic acids 5 is described. The process starts from 2-iodoaniline, passes through intermediates 7-iodoisatin (2a) and 7-arylisatins 4; the aryl group is inserted on isatin ring using the Suzuki protocol,\textsuperscript{20} in the presence of NaHCO\textsubscript{3} as a base. We modified and improved this procedure using CsF in place of NaHCO\textsubscript{3} and palladium acetate as precatalyst in place of Pd(PPh\textsubscript{3})\textsubscript{4}. The isatins are sensitive to alkaline environments. The Pfitzinger quinoline synthesis,\textsuperscript{21} where the reaction of isatin with a base gives a keto-acid, is well-known. In fact, heating 2a in the presence of a 5% aqueous solution of NaHCO\textsubscript{3} caused its total decomposition
after 2 hours (see Experimental Section). Owing to these changes, we obtained good yields of 4a-f, as reported in Table 1 (Method A: entries 1-4,6,7).

![Scheme 1. Synthesis of 3-arylanthranilic acids](image)

**Table 1. 7-Arylisatines 4a-j.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactants</th>
<th>Products and Yields a (%)</th>
<th>Method b</th>
<th>Time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a 3a</td>
<td>4a, 81</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2a 3b</td>
<td>4b, 82</td>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2a 3c</td>
<td>4c, 92</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>2a 3d</td>
<td>4d, 62</td>
<td>A</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>2a 3d</td>
<td>4d, 63</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>2a 3e</td>
<td>4e, 71</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2a 3f</td>
<td>4f, 82</td>
<td>A</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>2a 3f</td>
<td>4f, 81</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2a 3g</td>
<td>4g, [c]</td>
<td>A</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>2a 3g</td>
<td>4g, 78</td>
<td>B</td>
<td>3</td>
</tr>
</tbody>
</table>
Yields refer to the pure and isolated products.

Sphos was added as a ligand in the reactions carried out with the Method B.

After 6 hours, we observed the total decomposition of 2a or 2b.

On the GC-MS analysis of the crude residue traces of 4h were detected, MS (m/z, EI) = 251(M+).

However, under these conditions it was impossible to obtain hindered 7-arylisatins 4g-j (Table 1, method A: entries 9,11,13,15). In fact the preparation of hindered biaryls via a Suzuki coupling has historically proven to be very difficult. Nevertheless, the recent literature shows that Suzuki reactions performed with hindered aryl boronic acids proceed in excellent yield with the use of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) as a ligand. On these grounds, performing the reactions in the presence of 10 mol % of Sphos we obtained the hindered isatins 4g,i,j in good yields (Table 1, method B: entries 10,14,16) with the only exception of 4h (Table 1, method B: entry 12). It can also be seen that the use of Sphos was unnecessary in the reactions carried out with less hindered aryl boronic acids (Table 1, method B: entries 5,8,10). Finally, as described in the literature, 3-arylanthranilic acids 5a-g,i,j were easily obtained via the oxidative cleavage of 4 in a 5% sodium hydroxide and 30% hydrogen peroxide aqueous solutions (Scheme 1). The yields are reported in Table 2.

**Table 2.** 3-Arylanthranilic acids 5a-j.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactants</th>
<th>Products and Yields&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>5a, 82</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>5b, 66</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>5c, 67</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>5d, 72</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>5e, 85</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>5f, 89</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>5g, 80</td>
</tr>
<tr>
<td>8</td>
<td>4i</td>
<td>5i, 87</td>
</tr>
<tr>
<td>9</td>
<td>4j</td>
<td>5j, 87</td>
</tr>
</tbody>
</table>
Yields refer to the pure and isolated products.

It must be stressed that anthranilic acids and their derivatives are widely utilized in the synthesis of heterocyclic natural products and biologically active molecules; they are also important intermediates in the preparation of quinazolines, quinolines or drugs which are useful in the treatment of cancer.\textsuperscript{23}

### 2.2 Theoretical studies

Discovering a way to prepare the compounds 5 is the first important synthetic result in this work. However, our main goal is to synthesize 3-aryl substituted 1,2-benzenedisulfonimides 8 endowed with a chiral element due to atropisomerism (Scheme 2). Instead of synthesizing several sulfonimides 8 and then verifying their chiral stability, we decided to take advantage of theoretical methods to perform a screening of 8 based on a calculated barrier. The computational method was first tested by calculating the rotational free energy barrier for binaphthyl whose experimental value (in benzene) is 24.3 kcal mol\textsuperscript{-1}.\textsuperscript{24}

![Scheme 2. Synthesis of 3-aryl-1,2-benzenedisulfonimides 8.](image)

The calculated value, obtained as described in the Theoretical Methods section, is 26.7 kcal mol\textsuperscript{-1}, which is in reasonable agreement with the experimental data. Therefore, the conformational free
energy barriers in water at room temperature have been calculated for some selected 8 taking into account the fundamental role of steric hindrance. Results are collected in Table 3. Only the values of the lower barrier are reported (see note25 and Supporting Information for more details).

Table 3. Calculated rotational free energy barriers (in kcal mol\(^{-1}\)) and life times.

<table>
<thead>
<tr>
<th>3-Aryl-1,2-benzenedisulfonimides 8</th>
<th>(\Delta G^\ddagger)</th>
<th>Life Time</th>
<th>Optical purity (% after 24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8b</td>
<td>19.4</td>
<td>26 sec.</td>
<td>0</td>
</tr>
<tr>
<td>8c</td>
<td>21.9</td>
<td>29 min.</td>
<td>1</td>
</tr>
<tr>
<td>8d</td>
<td>39.5</td>
<td>(10^8) year</td>
<td>100</td>
</tr>
<tr>
<td>8e</td>
<td>39.6</td>
<td>(10^8) year</td>
<td>100</td>
</tr>
<tr>
<td>8f</td>
<td>26.2</td>
<td>710 h</td>
<td>94</td>
</tr>
</tbody>
</table>

Comparing the isomers 8e and 8f, it is worthwhile noting that the methyl group is far more effective in rising the rotational barrier (from 26 to 40 kcal mol\(^{-1}\)) when it is found in position 4 of the benzenedisulfonimide ring instead of position 8 of the naphthyl ring. A similar remarkable effect is also observed when the methyl group is added in position 4 of the benzenedisulfonimide in passing from 8b to 8d. Indeed, the rotational barrier raises from 19 to 40 kcal mol\(^{-1}\). The steric effect is also evident from the great distortion from planarity in the transition structures as shown, as an example, for 8d in Figure 3.

Figure 3. Rotational transition structure for 8d.
It is evident from the data that $8d$ and $8e$ are the best candidates for the synthesis; in fact, for them, the rotational free energy barrier between the two atropisomers has been calculated to be about 40 kcal/mol ($25^\circ$C). This corresponds to a life time for racemization of $10^8$ years which is significantly longer than the arbitrary threshold of 1000 sec, considered by Oki $^{26}$ the minimum requirement for chemical separation of atropisomers.

However, in order to enhance the value of the synthetic method, we decided to prepare also compounds $8a$-$c$, using the same synthetic procedure developed for the synthesis of $1$ (Scheme 2).$^{17,18}$

### 2.3 Preparation of imides $8$

The starting 3-arylanthranilic acids $5$ were firstly diazotized with 3-methylbutyl nitrite to form the internal salt 2-carboxylatebenzenediazonium which, upon heating tended to decompose losing nitrogen and carbon dioxide to give rise to the intermediate benzine, which in the presence of carbon disulfide and 3-methylbutan-1-ol provided 2-(3-methylbutoxy)-1,3-benzodithioles $6$.$^{16a}$ The subsequent oxidative chlorination of these intermediates with chlorine/water furnished 1,2-benzenedisulfonyl chlorides $7$.$^{17b}$ These were then reacted with ammonia. The resulting ammonium salts were passed through a cation-exchange resin column to give $8$ (Scheme 2).$^{18}$ The yields of these reactions are reported in Table 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Products and Yields$^a$ (%)</th>
<th>Products and Yields$^a$ (%)</th>
<th>Products and Yields$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$5a$</td>
<td>$6a$, 76</td>
<td>$7a$, 83</td>
<td>$8a$, 92</td>
</tr>
<tr>
<td>2</td>
<td>$5f$</td>
<td>$6b$, 75</td>
<td>$7b$, 62</td>
<td>$8b$, 94</td>
</tr>
<tr>
<td>3</td>
<td>$5g$</td>
<td>$6c$, 77</td>
<td>$7c$, 66</td>
<td>$8c$, 91</td>
</tr>
<tr>
<td>4</td>
<td>$5i$</td>
<td>$6d$, 79</td>
<td>$7d$, 74</td>
<td>$8d$, 74</td>
</tr>
<tr>
<td>5</td>
<td>$5j$</td>
<td>$6e$, 62</td>
<td>$7e$, 83</td>
<td>$8e$, 78</td>
</tr>
</tbody>
</table>

$^a$Yields refer to the pure and isolated products

Analyzing the $^1$H and $^{13}$C NMR spectra of compounds $6c$-$e$ which have a stereogenic carbon atom, it was possible to clearly see the presence of two pairs of enantiomers; in fact each of them gives different NMR signals (see Experimental section). The calculated rotational free energy barrier (see
Supporting Information) for the model of 6c is 22.6 kcal mol\(^{-1}\) (to be compared with 21.9 kcal mol\(^{-1}\) for 8c). This barrier corresponds to a lifetime (103 min) which is long enough to allow the separation of the NMR signals of the two couples of enantiomers. The barriers for 6d and 6e are possibly around 40 kcal mol\(^{-1}\), which when compared with those of 8d and 8e, should correspond to very long lifetimes under any conditions. In fact, for 6d and 6e the two pairs of enantiomers were clearly detected on GC and GC-MS analyses as well. By contrast, for 6c, the high temperature involved in the GC injector (250 °C) prevents the separation of the two couples of enantiomers. In fact, the rotational barrier remains high at about 25.0 kcal mol\(^{-1}\) but the lifetime drops to \(10^{-3}\) sec. All this experimentally confirmed that the hindered aryl group prevents the free rotation around inter-ring CC bond, producing atropisomerism.

2.4 Resolution of atropisomers of 8d

Having obtained the chiral compounds 8d and 8e, our next goal was to separate the atropisomers of 8d. Firstly, we planned to react 8d with cinchonidine or cinchonine, in order to try to separate the resulting diastereomeric salts. Unfortunately, these attempts failed completely. Because of this, we decided to follow the route described in the Scheme 3.

Scheme 3. Separation of atropisomers of 8d
As reported by A. W. M. Lee$^{15}$ the reaction between 7d and (S)-1-phenylethylamine (9), performed in the presence of DMAP, furnished the diastereomeric derivatives of 10. We could not separate them by silica gel column chromatography; however, their separation was possible by semipreparative chiral HPLC. These compounds provided the electronic Circular Dichiroism (ECD) spectra of Figure 4, which are almost mirror image, in spite of the fact that one deals with a pair of diastereomers. Apparently, the biaryl moiety plays a major role in determining this chiroptical property and it is only weakly coupled with the phenyl group attached to the chiral carbon atom. The presence of several points of marked conformational flexibility made the quantitative analysis of their ECD spectra particularly involved and will be the subject of a future report. We can anticipate that the first eluted compound 10a can be assigned to the $\alpha R$ axial chirality and thus is the RS diastereomer. Finally, the reaction of the first separated diastereoisomer (RS)-10a with sodium methoxide$^{27}$ afforded the optically pure atropisomers (R)-(−)8d$^a$.

![Figure 4. Electronic Circular Dichroism spectra](image)

3. Conclusions
Our previous research showed that the potential applications of 1,2-benzenedisulfonimide 1 as a safe, non corrosive, non volatile, recoverable and recyclable strong Brønsted acid-organocatalyst are in theory unlimited. For these reasons, to have synthetized the chiral compounds 8d and 8e and to have separated one of the atropisomers of 8d could be very interesting indeed, since they should maintain the same attractive features of 1 in the field of asymmetric catalysis.

4. Experimental section

4.1. General

Analytical grade reagents and solvents were used and reactions were monitored, where possible, by GC, GC-MS and TLC. Column chromatography and TLC were performed on Merck silica gel 60 (70-230 mesh ASTM) and GF 254, respectively. Petroleum ether (PE) refers to the fraction boiling in the range 40–70 °C. Room temperature is 20–25 °C. Mass spectra were recorded on an HP 5989B mass selective detector connected to an HP 5890 GC, cross-linked methyl silicone capillary column. 1H NMR and 13C NMR spectra were recorded on a Brucker Avance 200 spectrometer at 200 and 50 MHz respectively. HPLC separations were performed on HPLC Waters 1525. For the determination of optical rotations a Jasco P-2000 polarimeter was used. CD spectra were recorded with a Jasco J-710 spectropolarimeter with the following measurement parameters: scan speed, 50 nm/min; bandwidth, 1 nm; response, 1 s; 16 accumulations.

7-Iodoisatin (2a)19a and 2-bromo-3-methylaniline28 were prepared as reported in the literature. All the other reagents were purchased by Sigma-Aldrich. Structures and purity of all the products obtained in this work were confirmed by their spectral (NMR and MS) data. Satisfactory microanalyses were obtained for all the new compounds.

7-Bromo-8-methylisatin (2b) was prepared, starting from 2-bromo-3-methylaniline (1.86 g, 10 mmol), as described in the literature19a for the synthesis of 2a; pale brown solid; 1.82 g (yield 76%); mp 212 °C (EtOH). 1H NMR (200 MHz, CDCl3): δ 8.12 (br s, 1H), 7.41 (d, 2H, J = 7.2 Hz), 6.97 (d, 2H, J = 7.2 Hz), 2.42 (s, 3H); 13C NMR (50 MHz, CDCl3): δ 181.9, 159.0, 149.7, 148.4, 125.5, 123.9, 117.3, 108.0, 23.5; MS (m/z, EI) = 239 (M+); calcd for C9H6BrNO2: C 45.03%; H 2.52%; Br 33.29%; N 5.83%; found: C 45.07%; H 2.58%; Br 33.30%; N 5.87%.

4.2. 7-Arylisatins 4. General procedures

Method A: Boronic acid 3 (2.4 mmol) and then CsF (2.5 mmol, 0.38 g) dissolved in H2O (5 mL) were added to a stirring mixture of 7-iodoisatin (2a, 2 mmol, 0.54 g) or 7-bromo-8-methylisatin
(2b, 2 mmol, 0.48 g) and Pd(OAc)$_2$ (0.2 mmol; 24 mg) in DME (6 mL), first. The mixture was stirred at reflux until the disappearance of 2a or 2b, monitoring the reactions by TLC (CH$_2$Cl$_2$-EtOAc, 9.8:0.2), GC and GC-MS. Then, the reaction mixture was poured into CH$_2$Cl$_2$-H$_2$O (100 ml, 1:1) The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined organic extracts were washed with H$_2$O (2 × 50 mL), dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The crude residue, purified in a chromatography column (CH$_2$Cl$_2$-EtOAc, 9.8:0.2), afforded pure 4.

**Method B:** The only difference in comparison with Method A consisted in the use of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) as a ligand (0.4 mmol; 0.16 g). In a collateral proof, using NaHCO$_3$ (4.0 mmol, 0.34 g) dissolved in H$_2$O (60 mL, as reported in the literature$^{18}$) instead of CsF, we obtained 4a in lower yield (0.24 g, 50%). In another collateral proof, heating at reflux 2a (2 mmol, 0.54 g) dissolved in DME (60 mL) in the presence of NaHCO$_3$ (4.0 mmol, 0.34 g) dissolved in 60 mL of H$_2$O after 2 hours we observed the total decomposition of 4a.

**7-Phenylisatin (4a):** orange solid; 0.39 g (yield 81%); mp 185 °C (EtOH). NMR data identical to that reported in the literature.$^{19a}$ MS (m/z, EI) = 223 (M$^+$).

**7-(4-Methoxyphenyl)isatin (4b):** orange solid; 0.42 g (yield 82%); mp 240 °C (EtOH). NMR data identical to that reported in the literature.$^{19a}$ MS (m/z, EI) = 253 (M$^+$).

**7-(4-Chlorophenyl)isatin (4c):** orange solid; 0.47 g (yield 92%); mp 238–239 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): δ 7.75 (br s, 1H), 7.59–7.42 (m, 4H), 7.33–7.25 (m, 2H), 7.11–7.05 (m, 1H); $^{13}$C NMR (50 MHz, CD$_2$COCD$_3$): δ 183.8, 159.0, 147.4, 138.2, 134.4, 133.5, 130.0, 129.0, 124.9, 123.7, 123.2, 118.6; MS (m/z, EI) = 257 (M$^+$); calcd for C$_{14}$H$_8$ClNO$_2$: C 65.26%; H 3.13%; Cl 13.76%; N 5.44%; found: C 65.27%; H 3.18%; Cl 13.70%; N 5.47%.

**7-(2-Tolyl)isatin (4d):** orange solid; 0.29 g (yield 62%); mp 145–146 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): δ 7.64–7.60 (m, 1H), 7.48 (br s, 1H), 7.47–7.44 (m, 1H), 7.37–7.27 (m, 3H), 7.23–7.18 (m, 2H), 2.23 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ 183.1, 158.7, 146.8, 139.2, 136.2, 133.9, 131.0, 129.4, 129.1, 126.6, 126.1, 124.5, 123.7, 118.1, 19.7; MS (m/z, EI) = 237 (M$^+$); calcd for C$_{15}$H$_{11}$NO$_2$: C 75.94%; H 4.67%; N 5.90%; found: C 75.97%; H 4.68%; N 5.87%.

**7-(2-Isopropoxyphenyl)isatin (4e):** orange solid; 0.40 g (yield 71%); mp 120–121 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): δ 7.76 (br s, 1H), 7.57–7.47 (m, 2H), 7.47–7.44 (m, 1H), 7.37–7.27 (m, 3H), 7.22–7.18 (m, 2H), 2.23 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ 184.0, 159.1, 154.4, 147.8, 140.1, 131.5, 130.5, 125.5, 124.3, 123.8, 121.9, 118.2, 115.0, 71.7, 22.14; MS (m/z, EI) = 281 (M$^+$); calcd for C$_{17}$H$_{15}$NO$_3$: C 72.58%; H 5.37%; N 4.98%; found: C 72.61%; H 5.42%; N 5.00%.
7-(1-Naphthyl)isatin (4f): orange solid; 0.45 g (yield 82%); mp 224–225 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.99–7.95 (m, 2H), 7.75–7.43 (m, 7 H), 7.38–7.24 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 183.2, 158.6, 147.5, 140.1, 134.1, 132.2, 130.8, 129.7, 129.1, 127.7, 127.6, 126.9, 125.9, 125.0, 124.8, 124.1, 118.3; MS (m/z, EI) = 273 (M$^+$); calcd for C$_{18}$H$_{11}$NO$_2$: C 79.11%; H 4.06%; N 5.13%; found: C 79.15%; H 4.08%; N 5.16%.

7-(2-Ethoxy-1-naphthyl)isatin (4g): orange solid; 0.50 g (yield 78%); mp 152–153 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.90 (d, $J = 9.0$ Hz, 1H), 7.84 – 7.80 (m, 1H), 7.63 (d, $J = 7.4$ Hz, 1H), 7.52 (dd $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H), 7.44–7.15 (m, 2H), 4.14–4.05 (m, 2H), 1.24 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (50 MHz): $\delta$ 183.2, 158.5, 153.3, 148.2, 141.3, 132.4, 131.0, 129.0, 128.3, 127.4, 124.4, 124.1, 123.7, 123.3, 120.8, 118.1, 116.4, 114.1, 64.8, 14.8; MS (m/z, EI) = 317 (M$^+$); calcd for C$_{20}$H$_{15}$NO$_3$: C 75.70%; H 4.76%; N 4.41%; found: C 75.77%; H 4.78%; N 4.45%.

6-Methyl-7-(2-tolyl)isatin (4i): orange solid; 0.38 g (yield 76%); mp 207 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.47 (d, $J = 7.6$ Hz, 1H), 7.34–7.24 (m, 3H), 7.06–6.93 (m, 3H), 2.06 (s, 3H), 2.04 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$, 25°C): $\delta$ 182.4, 159.1, 148.8, 147.2, 136.3, 132.5, 130.8 129.2, 128.9, 126.7, 125.4, 125.1, 124.3, 115.8, 20.7, 19.2; MS (m/z, EI) = 251(M$^+$); calcd for C$_{16}$H$_{13}$NO$_2$: C 76.48%; H 5.21%; N 5.57%; found: C 76.47%; H 5.27%; N 5.56%.

6-Methyl-7-(1-naphthyl)isatin (4j): orange solid; 0.47 g (yield 82%); mp 215–216 °C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 3.6$ Hz, 1H), 7.89 (d, $J = 3.6$ Hz, 1H), 7.58–7.36 (m, 5H), 7.07 (d, $J = 7.6$ Hz, 1H), 6.90 (br s, 1H), 2.04 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 182.4, 158.9, 149.7, 148.0, 133.8, 130.8, 130.5, 129.3, 128.7, 127.3, 127.1, 126.6, 125.6, 125.2, 124.7, 124.3, 124.0, 115.9, 20.9; MS (m/z, EI) = 287 (M$^+$); calcd for C$_{19}$H$_{13}$NO$_2$: C 79.43%; H 4.56%; N 4.87%; found: C 79.38%; H 4.53%; N 4.82%.

4.3. 3-Arylanthranilic acids 5. General procedure

As reported in the literature,$^{19a}$ 30% hydrogen peroxide aqueous solution (10 mL) was added dropwise to a stirred suspension of 7-arylisatin 4 (2 mmol) in 5% NaOH aqueous solution (10 mL). The reaction mixture was stirred at 50 °C for 30 min and then was taken to room temperature, stirring for other 30 min. The reaction mixture was filtered, and the resulting solution was acidified with 1M HCl until pH 3-4; the precipitated solid, 5 virtually pure, was collected by filtration on a buchner funnel.

3-Phenylanthranilic acid (5a): white solid; 0.35 g (yield 82%); mp 146 °C (EtOH). NMR data identical to that reported in the literature.$^{19a}$
3-(4-Methoxyphenyl)anthranilic acid (5b): white solid; 0.32 g (yield 66%); m.p. 214 °C (EtOH). NMR data identical to that reported in the literature.\(^{19a}\)

3-(4-Chlorophenyl)anthranilic acid (5c): white solid; 0.33 g (yield 67%); mp 187–188 °C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.93 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 1.6\) Hz, 1H), 7.35–7.17 (m, 5H), 6.74 (t, \(J = 7.6\) Hz, 1H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 173.7, 148.4, 136.4, 135.8, 133.6. 131.9, 130.5, 129.2, 127.4, 115.8, 109.4; calcd for C\(_{13}\)H\(_{10}\)ClNO\(_2\): C 63.04%; H 4.07%; Cl 14.31%; N 5.66%; found: C 63.00%; H 4.04%; Cl 14.35%; N 5.67%.

3-(2-Tolyl)anthranilic acid (5d): white solid; 0.32 g (yield 72%); mp 137–138 °C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\), 25 °C): \(\delta\) 8.00 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 1.6\) Hz, 1H), 7.35–7.17 (m, 5H), 6.74 (t, \(J = 7.6\) Hz, 1H), 2.17 (s, 3H) ppm; \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 173.8, 148.7, 137.3, 137.2, 135.7, 131.5, 130.5, 129.2, 128.6, 128.2, 126.5, 115.7. 109.1, 19.5; calcd for C\(_{14}\)H\(_{13}\)NO\(_2\): C 73.99%; H 5.77%; N 6.16%; found: C 74.02%; H 5.78%; N 6.19%.

3-(2-Isopropoxyphenyl)anthranilic acid (5e): white solid; 0.46 g (yield 85%); mp 151°C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.93 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 1.6\) Hz, 1H), 7.33–7.18 (m, 3H), 6.99 (t, \(J = 7.0\) Hz, 2H), 6.67 (t, \(J = 7.6\) Hz, 1H), 4.45–4.27 (m, 1H), 1.19–1.11 (m, 6H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 74.4, 155.7, 149.6, 137.0, 132.2, 131.6, 129.5, 128.8, 126.7, 121.7, 115.9, 115.7, 109.5, 71.6, 22.2; calcd for C\(_{16}\)H\(_{17}\)NO\(_3\): C 70.83%; H 6.32%; N 5.16%; found: C 70.87%; H 6.38%; N 5.18%.

3-(1-Naphthyl)anthranilic acid (5f): white solid; 0.47 g (yield 89%); mp 195 °C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.08, (dd, \(J_1 = 8.0\) Hz, \(J_2 = 1.6\) Hz, 1H), 7.94 (d, \(J = 8.0\) Hz, 2H), 7.64–7.35 (m, 5H), 7.30 (d, \(J = 8.0\) Hz, 1H), 6.80 (t, \(J = 7.6\) Hz, 1H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 173.9, 149.2, 136.7, 135.8, 134.0, 132.1, 131.8, 128.6, 128.5, 128.0, 127.2, 126.7, 126.4, 126.0, 125.9. 116.0 ; calcd for C\(_{17}\)H\(_{13}\)NO\(_2\): C 77.55%; H 4.98%; N 5.32%; found: C 77.58%; H 4.98%; N 5.35%.

3-(2-Ethoxy-1-naphthyl)anthranilic acid (5g): white solid; 0.49 g (yield 80%); mp 159–160 °C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.02–7.99 (m, 1H), 7.88–7.76 (m, 2H), 7.40–7.28 (m, 4H), 7.22–7.19 (m, 1H), 6.73 (t, \(J = 7.6\) Hz, 1H), 4.07 (q, \(J = 7.0\) Hz, 2H), 1.20 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 173.8, 153.9, 149.4, 137.4, 133.2, 131.5, 129.8, 129.2, 128.3, 127.8, 126.7, 124.7, 123.8, 123.0, 120.7, 115.6, 109.4, 65.2, 14.9; calcd for C\(_{19}\)H\(_{17}\)NO\(_3\): C 74.25%; H 5.58%; N 4.56%; found: C 74.26%; H 5.55%; N 4.59%.

4-Methyl-3-(2-tolyl)anthranilic acid (5i): white solid; 0.42 g (yield 87%); mp 191 °C (EtOH). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.82 (d, \(J = 8.2\) Hz, 1H), 7.28–7.22 (m, 3H), 7.05–7.01 (m, 1H), 6.57 (d, \(J = 8.2\) Hz, 1H), 2.00 (s, 3H), 1.87 (s, 3H) ppm; \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 173.2, 148.7,
4-Methyl-3-(1-naphthyl)anthranilic acid (5j): white solid; 0.48 g (yield 87%); mp 197–198 °C (EtOH). \(^1^H\) NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.89 (d, \(J = 8.2\) Hz, 1H), 7.85 (d, \(J = 8.2\) Hz, 1H), 7.57–7.29 (m, 6H), 6.62 (d, \(J = 8.2\) Hz, 1H), 1.82 (s, 3H) ppm; \(^13^C\) NMR (CDCl\(_3\), 50 MHz, 25 °C): \(\delta\) 173.3, 149.4, 144.6, 134.3, 133.9, 131.5, 131.2, 128.3, 128.0, 127.8, 126.5, 126.1, 126.0, 125.6, 124.8, 117.9, 107.1, 20.7 ppm; calcd for C\(_{18}\)H\(_{15}\)NO\(_2\): C 77.96%; H 5.45%; N 5.05%; found: C 77.97%; H 5.42%; N 5.07%.

4.4. 4-Aryl-2-(3-methylbutoxy)-1,3-benzodithioles 6. General procedure

3-methylbutyl nitrite (2.4 mmol, 0.28 g), 3-methylbutan-1-ol (2 mmol, 0.36 g) and CS\(_2\) (16.6 mmol, 1.26 g) were dissolved in 1,2-dichloroethane (30 mL) and refluxed at 82 °C. Anthranilic acid 5 (2 mmol) dissolved in 1,4-dioxane (12 mL) was added dropwise to the previously prepared mixture. The resulting mixture was stirred first at reflux for 45 min and then at room temperature for 1 h. The reaction mixture was poured into Et\(_2\)O–H\(_2\)O (100 ml, 1:1). The aqueous layer was separated and extracted with Et\(_2\)O (2 × 50 mL). The combined organic extracts were washed with H\(_2\)O (2 × 50 mL) and saturated solution of Na\(_2\)CO\(_3\) (50 mL), dried over Na\(_2\)SO\(_4\) and evaporated under reduced pressure. The crude residue, purified by column chromatography (PE–Et\(_2\)O 9.5:0.5), afforded the pure title compound 6.

4-Phenyl-2-(3-methylbutoxy)-1,3-benzodithiole (6a): pale yellow solid; 0.48 g (yield: 76%); mp 59–60°C (EtOH). \(^1^H\) NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.59–7.37 (m, 6H), 7.26–7.14 (m, 2H), 6.72 (s, 1H), 3.55–3.47 (m, 2H), 1.66–1.24 (m, 1H), 1.50–1.41 (m, 2H), 0.90 (d, \(J = 6.2\) Hz, 6H); \(^13^C\) NMR (50MHz): \(\delta\) 141.3, 136.9, 135.6, 128.5, 128.1, 127.9, 126.4, 125.7, 120.8, 88.67, 62.9, 37.7, 24.8, 22.4; MS (m/z, EI) = 316 (M\(^+\)); calcd for C\(_{18}\)H\(_{20}\)OS\(_2\): C 68.31%; H 6.37%; S 20.26%; found: C 68.33%; H 6.39%; S 20.28%.

4-(2-Tolyl)-2-(3-methylbutoxy)-1,3-benzodithiole (6b): pale yellow solid; 0.50 g (yield: 75%); mp 48°C (EtOH). \(^1^H\) NMR (200 MHz): \(\delta\) 7.42–7.17 (m, 6H), 7.00 (dd, \(J_1 = 7.4\) Hz, \(J_2 = 1.2\) Hz, 1H), 6.73 (s, 1H), 3.52–3.46 (m, 2H), 2.28 (s, 3H), 1.72–1.25 (m, 1H), 1.51–1.45 (m, 2H), 0.91 (d, \(J = 6.2\) Hz, 6H); \(^13^C\) NMR (50MHz): \(\delta\) 140.9, 136.9, 136.4, 135.4, 130.3, 128.9, 128.7, 128.2, 126.3, 125.9, 125.3, 120.6, 88.7, 62.5, 37.8, 25.0, 22.5, 19.7; MS (m/z, EI) = 330 (M\(^+\)); calcd for C\(_{19}\)H\(_{22}\)OS\(_2\): C 69.05%; H 6.71%; S 20.26%; found: C 69.03%; H 6.75%; S 19.38%.

4-(1-Naphthyl)-2-(3-methylbutoxy)-1,3-benzodithiole (6c): pale yellow solid as a mixture (about 1:1) of two pairs of enantiomers; 0.56 g (yield: 77%).
It was impossible to separate by GC and TLC the two pairs of enantiomers.

\[ ^1H\text{ NMR (200 MHz, CDCl}_3); \text{ pair 1: } \delta 7.94–7.90 (m, 2H), 7.66–7.39 (m, 6H), 7.28-7.10 (m, 2H), 6.66 (s, 1H), 3.55–3.39 (m, 2H), 1.73–1.23 (m, 1H), 1.52-1.42 (m, 2H), 0.91 (d, \text{ J} = 6.2 \text{ Hz}, \text{ 6H}); \text{ pair 2: } \delta 7.94–7.90 (m, 2H), 7.66–7.39 (m, 6H), 7.28-7.10 (m, 2H), 6.63 (s, 1H), 3.55–3.39 (m, 2H), 1.73–1.23 (m, 1H), 1.52-1.42 (m, 2H), 0.88 (d, \text{ J} = 6.2 \text{ Hz}, \text{ 6H}) \text{ ppm}; \text{ the differences between the two pairs are underlined; }^{13}C\text{ NMR (50MHz, CDCl}_3); \text{ pair 1: } \delta 139.19, 137.10, 135.35, 134.00, 131.20, 128.74, 128.63, 127.62, 126.77, 126.55, 126.36, 126.26, 125.98, 125.60, 125.52, 121.14, 89.31, 62.96, 37.94, 25.17, 22.69; \text{ pair 2: } \delta 139.19, 136.82, 135.22, 133.85, 131.05, 128.68, 128.57, 127.55, 126.50, 126.36, 126.23, 125.96, 125.45, 121.08, 88.82, 62.58, 37.94, 25.05, 22.64; \text{ the differences between the two pairs are underlined; MS (m/z, EI) = 344 (M+) for each couple; caleed for C_{22}H_{22}OS_{2}: C 72.09%; H 6.05%; S 17.49%.

5-Methyl-4-(2-Tolyl)-2-(3-methylbutoxy)-1,3-benzodithiole (6d): pale yellow waxy solid as a mixture (about 1:1) of two pairs of enantiomers; 0.55 g (yield: 79%). Having different retention times, the two pairs were clearly detected by GC and GC-MS analyses. \[ ^1H\text{ NMR (200 MHz, CDCl}_3); \text{ pair 1: } \delta 7.35–7.22 (m, 4H), 7.07–7.03 (m, 2H), 6.69 (s, 1H), 3.48–3.44 (m, 2H), 2.15 (s, 3H), 1.98 (s, 3H), 1.75–1.22 (m, 1H), 1.47–1.41 (s, 2H), 0.90 (d, \text{ J} = 6.2 \text{ Hz}, 6H); \text{ pair 2: } \delta 7.35–7.22 (m, 4H), 7.07–7.03 (m, 2H), 6.68 (s, 1H), 3.48–3.44 (m, 2H), 2.06 (s, 3H), 1.98 (s, 3H), 1.75–1.22 (m, 1H), 1.47–1.41 (s, 2H), 0.88 (d, \text{ J} = 6.2 \text{ Hz}, 6H); \text{ the differences between the two pairs are underlined; }^{13}C\text{ NMR (50 MHz, CDCl}_3); \text{ pair 1: } \delta 139.99, 137.37, 135.68, 135.40, 135.13, 133.12, 130.20, 128.50, 128.00, 126.98, 126.23, 120.24, 89.32, 61.99, 37.69, 24.81, 22.48, 22.37, 19.30; \text{ pair 2: } \delta 139.94, 137.34, 135.68, 135.34, 135.13, 133.08, 130.20, 128.50, 127.96, 126.98, 126.23, 120.17, 89.17, 61.86, 37.64, 24.69, 22.48, 22.34, 19.23; \text{ the differences between the two pairs are underlined; MS (m/z, EI) = 344 (M+) for each couple; caleed for C_{22}H_{22}OS_{2}: C 69.72%; H 7.02%; S 18.61%; found: C 69.74%; H 7.00%; S 18.66%.

5-Methyl-4-(1-Naphthyl)-2-(3-methylbutoxy)-1,3-benzodithiole (6e): pale yellow waxy solid as a mixture (1:1) of two pairs of enantiomers; 0.47 g (yield: 62%). Having different retention times, the two pairs were clearly detected by GC analyses. \[ ^1H\text{ NMR (200 MHz, CDCl}_3); \text{ pair 1: } \delta 7.91–7.86 (m, 2H), 7.54–7.28 (m, 6H), 7.11–7.06 (m, 1H), 6.61 (s, 1H), 3.44–3.27 (m, 2H), 1.92 (s, 3H), 1.71–1.22 (m, 3H), 0.91–0.87 (m, 6H); \text{ pair 2: } \delta 7.91–7.86 (m, 2H), 7.54–7.28 (m, 6H), 7.11–7.06 (m, 1H), 6.58 (s, 1H), 3.44–3.27 (m, 2H), 1.90 (s, 3H), 1.71–1.22 (m, 3H), 0.91–0.87 (m, 6H); \text{ the differences between the two pairs are underlined; }^{13}C\text{ NMR (50 MHz, CDCl}_3); \text{ pair 1: } \delta 138.25, 134.30, 134.02, 133.72, 133.38, 133.20, 130.81, 130.47, 128.38, 128.24, 127.09, 126.35, 126.02, 125.63, 124.96, 120.57, 89.38, 62.27, 37.60, 24.78, 22.34, 19.43; \text{ couple 2: } \delta 138.25, 134.30, 134.02, 133.65, 133.38, 133.20, 130.81, 130.47, 128.38, 128.16, 127.02, 126.25, 125.94, 125.55,
124.83, 120.57, 89.00, 61.56, 37.60, 24.69, 22.34, 19.31; the differences between the two pairs are underlined; calcd for C_{23}H_{24}OS_{2}: C 72.59%; H 6.36%; S 16.85%; found: C 72.54%; H 6.40%; S 16.86%.

4.5. 3-Aryl-1,2-benzenedisulfonyl chlorides 7. General procedure

4-Aryl-2-(3-methylbutoxy)-1,3-benzodithiole 6 (2 mmol) was dissolved in tbutyl alcohol (20ml), CH_{2}Cl_{2} (16 mL) and H_{2}O (3 mL). The resulting mixture was cooled to 0-5 °C. Chlorine was bubbled through while maintaining the temperature at 0-5 °C and vigorously stirring the reaction mixture. The reaction was monitored on TLC (PE: EtOAc 7: 3). After 1 h, when the spot of 6 disappeared and there was only one other spot, the reaction was complete. The reaction mixture was poured into CH_{2}Cl_{2}–H_{2}O (100 mL, 1:1) The aqueous layer was separated and extracted with CH_{2}Cl_{2} (2 × 50 mL). The combined organic extracts were washed with a NaOH 5% solution (2 × 50 mL), dried over Na_{2}SO_{4} and evaporated under reduced pressure. The crude residue, purified in a chromatography column (PE–EtOAc 7: 3) afforded the pure title compound 7.

3-Phenyl-1,2-benzenedisulfonyl chloride (7a): pale brown solid; 0.58 g (yield: 83%); mp 132–133°C (EtOH). \(^{1}H\) NMR (200 MHz, CDCl_{3}): \(\delta\) 8.47 (dd, \(J_{1} = 8.0\) Hz, \(J_{2} = 1.6\) Hz, 1H), 7.90 (t, \(J = 8.0\) Hz, 1H), 7.76 (dd, \(J_{1} = 8.0\) Hz, \(J_{2} = 1.6\) Hz, 1H), 7.46–7.35 (m, 5H); \(^{13}C\) NMR (50 MHz, CDCl_{3}): \(\delta\) 146.4, 143.9, 140.5, 139.7, 138.0, 134.3, 131.9, 128.9, 128.4, 128.2; calcd for C_{12}H_{8}Cl_{2}O_{4}S_{2}: C 41.05%; H 2.30%; Cl 20.19%; S 18.26%; found: C 41.01%; H 2.33%; Cl 20.21%; S 18.26%.

3-(2-Tolyl)-1,2-benzenedisulfonyl chloride (7b): pale brown solid; 0.58 g (yield: 62%); mp 145–146°C (EtOH). \(^{1}H\) NMR (200 MHz, CDCl_{3}): \(\delta\) 8.56 (dd, \(J_{1} = 8.0\) Hz, \(J_{2} = 1.6\) Hz, 1H), 7.97 (t, \(J = 8.0\) Hz, 1H), 7.74 (dd, \(J_{1} = 8.0\) Hz, \(J_{2} = 1.6\) Hz, 1H), 7.37–7.21 (m, 4H), 2.17 (s, 3H); \(^{13}C\) NMR (50 MHz, CDCl_{3}): \(\delta\) 146.4, 144.2, 140.7, 140.1, 137.7, 135.4, 134.6, 132.4, 130.6, 129.3, 128.6, 125.7, 20.8; calcd for C_{13}H_{10}Cl_{2}O_{4}S_{2}: C 42.75%; H 2.76%; Cl 19.41%; S 18.26%; found: C 42.72%; H 2.74%; Cl 19.45%; S 17.59%.

3-(1-Naphthyl)-1,2-benzenedisulfonyl chloride (7c): pale brown solid; 0.58 g (yield: 66%); mp 145–146°C (EtOH). \(^{1}H\) NMR (200 MHz, CDCl_{3}): \(\delta\) 8.64 (dd, \(J_{1} = 8.0\) Hz, \(J_{2} = 1.6\) Hz, 1H), 8.00 (t, \(J = 8.0\) Hz, 1H), 7.84–7.27 (m, 8H); \(^{13}C\) NMR (50 MHz, CDCl_{3}): \(\delta\) 144.3, 141.4, 140.7, 134.7, 133.7, 133.0, 132.7, 131.0, 130.0, 128.8, 127.8, 126.8, 126.4, 126.2, 125.3; calcd for C_{16}H_{10}Cl_{2}O_{4}S_{2}: C 47.89%; H 2.51%; Cl 17.67%; S 15.98%; found: C 47.93%; H 2.50%; Cl 17.69%; S 16.00%. 
4-Methyl-3-(2-tolyl)-1,2-benzenedisulfonyl chloride (7d): pale brown solid; 0.58 g (yield: 74%); mp 148–149°C (EtOH). $^1$H NMR (200 MHz, CD$_3$CN): $\delta$ 8.43 (d, $J$ = 8.0 Hz, 1H), 7.92 (d, $J$ = 8.0 Hz, 1H), 7.33–7.20 (m, 3H), 7.05 (d, $J$ = 7.2 Hz, 1H), 1.98 (s, 3H), 1.95 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 149.2, 145.0, 141.5, 140.0, 135.9, 135.5, 135.4, 131.7, 130.1, 128.9, 127.6, 125.9, 21.4, 19.9; calcd for C$_{14}$H$_{12}$Cl$_2$O$_4$S$_2$: C 44.34%; H 3.19%; Cl 18.70%; S 16.91%; found: C 44.33%; H 3.22%; Cl 18.65%; S 16.95%.

4-Methyl-3-(1-naphthyl)-1,2-benzenedisulfonyl chloride (7e): pale brown solid; 0.58 g (yield: 83%); mp 89–90°C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.47 (d, $J$ = 8.0 Hz, 1H), 8.33 (d, $J$ = 8.0 Hz, 1H), 7.85–7.12 (m, 7H), 1.91 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 150.0, 142.8, 141.7, 140.9, 136.2, 133.9, 133.3, 132.3, 130.6, 127.8, 127.4, 126.9, 126.7, 125.8, 125.5, 125.1, 21.5; calcd for C$_{17}$H$_{12}$Cl$_2$O$_4$S$_2$: C 49.17%; H 2.91%; Cl 17.07%; S 15.44%; found: C 49.12%; H 2.92%; Cl 17.09%; S 15.49%.

4.6. 3-Aryl-1,2-benzenedisulfonimides 8. General procedure

3-Aryl-1,2-benzenedisulfonimide 7 (2 mmol) was dissolved in toluene (8 mL) and EtOH (12 mL). The resulting mixture was cooled to 0-5°C. Ammonia was bubbled through while maintaining the temperature at 0-5°C and vigorously stirring the reaction mixture. The reaction was monitored on TLC (PE–EtOAc 7: 3). After 30 min, when the spot of 7 disappeared, the reaction was complete. The mixture was first filtered in order to eliminate NH$_4$Cl and then solvent was evaporated under reduced pressure. The crude residue, dissolved in H$_2$O and passed through a Dowex (HCR–W2) column (H$_2$O), afforded the pure title compound 8.

3-Phenyl-1,2-benzenedisulfonimide (8a): pale brown waxy solid; 0.54 g (yield: 92%). $^1$H NMR (200 MHz): $\delta$ 7.94–7.75 (m, 3H), 7.57–7.27 (m, 5H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 140.1, 140.0, 137.5, 136.5, 134.9, 129.9, 129.2, 129.0, 121.1; calcd for C$_{12}$H$_9$NO$_4$S$_2$: C 48.80%; H 3.07%; N 4.74%; S 21.71%; found: C 48.74%; H 3.00%; N 4.81%; S 21.75%.

3-(2-Tolyl)-1,2-benzenedisulfonimide (8b): pale brown waxy solid; 0.58 g (yield: 94%). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.92 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.82 (t, $J$ = 7.8 Hz, 1H), 7.57 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.36–7.18 (m, 4H), 2.12 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): 140.0, 139.2, 138.1, 136.3, 136.2, 134.5, 134.3, 130.4, 129.9, 129.7, 125.7, 121.1, 20.4; calcd for C$_{13}$H$_{11}$NO$_4$S$_2$: C 50.47%; H 3.58%; N 4.53%; S 20.73%; found: C 50.49%; H 3.55%; N 4.55%; S 20.70%.

3-(1-Naphthyl)-1,2-benzenedisulfonimide (8c): pale brown waxy solid; 0.58 g (yield: 91%). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.41–8.28 (m, 1H), 8.00–7.17 (m, 9H); $^{13}$C NMR (50 MHz, CDCl$_3$, 25
4-Methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (8d): pale brown waxy solid; 0.48 g (yield: 74%); 
$^1$H NMR (200 MHz, CDCl$_3$): δ 7.81 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H) 7.35–7.10 (m, 5H), 2.12 (s, 3H), 2.00 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ 145.9, 138.3, 136.4, 136.0, 132.2, 130.3, 129.6, 129.0, 126.5, 126.0, 120.8, 19.9, 19.5; calcd for C$_{14}$H$_{13}$NO$_4$S$_2$: C 52.00%; H 4.05%; N 4.33%; S 19.83%; found: C 52.05%; H 4.00%; N 4.37%; S 19.91%.

4-Methyl-3-(1-naphthyl)-1,2-benzenedisulfonimide (8e): pale brown solid; 0.56 g (yield: 78%); mp 134–136°C (EtOH). $^1$H NMR (200 MHz, CDCl$_3$): δ 8.36–8.29 (m, 1H), 7.92–7.06 (m, 8H), 2.05 (s, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ 145.9, 137.7, 136.7, 136.2, 134.9, 134.0, 133.1, 132.6, 132.1, 131.8, 130.7, 129.8, 127.8, 126.7, 125.5, 121.5, 19.7; calcd for C$_{17}$H$_{13}$NO$_4$S$_2$: C 56.81%; H 3.65%; N 3.90%; S 17.84%; found: C 56.84%; H 3.66%; N 3.70%; S 17.80%.

4.7. Synthesis of N-(2-phenylethyl)-1,2-benzenedisulfonimide (10) and separation of its diastereoisomers 10a and 10b

DMAP (122 mg, 0.1 mmol) and Et$_3$N (0.20 g, 2.1 mmol) were added to a solution of 7d (0.38 g, 1 mmol) in CH$_2$Cl$_2$ (100 ml). Then (S)-1-phenylethylamine (9, 0.12 g, 1.05 mmol) was slowly added dropwise. The reaction was monitored on TLC (PE–Et$_2$O 3: 2). After 24 h, when the spot of 7d disappeared and there was only one other spot, the reaction was complete. CH$_2$Cl$_2$ was removed under nitrogen flow and the crude residue was purified in a chromatography column (PE–Et$_2$O 3: 2) affording the pure title compound 10 (waxy solid; 0.32 g, 75%) as a mixture (about 1:1) of two diastereoisomers. $^1$H NMR (200 MHz, CDCl$_3$); diastereoisomer 1: δ 7.79 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.51–7.47 (m, 2H), 7.39–7.09 (m, 7H), 5.27 (q, $J = 7.2$ Hz, 1H), 2.09 (s, 3H), 1.99 (s, 3H), 1.95 (d, $J = 7.2$ Hz, 3H); diastereoisomer 2: δ 7.79 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.51–7.47 (m, 2H), 7.39–7.09 (m, 7H), 5.27 (q, $J = 7.2$ Hz, 1H), 2.09 (s, 3H), 1.97 (s, 3H), 1.94 (d, $J = 7.2$ Hz, 3H); the differences between the two diastereoisomers are underlined; $^{13}$C NMR (50 MHz, CDCl$_3$); diastereoisomer 1: δ 145.5, 137.7, 137.3, 136.1, 135.5, 133.9, 133.0, 132.3, 130.2, 129.5, 129.1, 128.5, 128.3, 127.9, 125.9, 120.3, 56.3, 19.6, 19.5, 19.1; diastereoisomer 2: δ 145.5, 137.7, 137.3, 136.1, 135.5, 133.9, 133.0, 132.3, 130.2, 129.5, 129.1, 128.5, 128.3, 127.9, 125.9, 120.3, 56.2, 19.6, 19.5, 19.0; the differences between the two diastereoisomers are underlined. 10 (38 mg) was chromatographed on a semi-preparative Chiralpak IC column (Φ 10 x 250 mm, Daicel, Osaka, Japan) employing an isocratic elution with heptane–CH$_2$Cl$_2$ (1:1) at a flow...
rate of 4.7 ml/min. The compounds eluted from the column were monitored with a photoiodide array detector. **10a** (18.8 mg) and **10b** (19.2 mg), eluted as a single peaks at 8.9 and 12.8 min, were collected, after removing the solvents under nitrogen flow.

**RS-10a**: waxy solid; [α]_D^23 = -12.1 (c = 0.60, CH₂Cl₂); ^1^H NMR (200 MHz, CDC₁₃): δ (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.51–7.46 (m, 2H), 7.39–7.07 (m, 7H), 5.27 (q, J = 7.2 Hz, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.95 (d, J = 7.2 Hz; ^13^C NMR (50 MHz, CDCl₃): 145.5, 137.7, 137.2, 136.1, 135.4, 133.9, 133.0, 132.2, 130.2, 129.5, 129.1, 128.5, 128.3, 127.9, 125.9, 120.2, 56.1, 19.6, 19.5, 19.0; calcd for C₂₂H₂₁NO₄S₂: C 61.81%; H 4.95%; N 3.28%; S 15.00; found: C 61.85%; H 4.90%; N 3.30%; S 14.98%. By preliminary electronic Circular Dichroism analyses, **10a** can be assigned to the aR axial chirality and thus is the RS diastereomer.

**SS-10b**: waxy solid; [α]_D^23 = -2.4 (c = 0.69, CH₂Cl₂); ^1^H NMR (200 MHz, CDC₁₃): δ (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.51–7.46 (m, 2H), 7.39–7.07 (m, 7H), 5.27 (q, J = 7.2 Hz, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.95 (d, J = 7.2 Hz; ^13^C NMR (50 MHz, CDCl₃): 145.5, 137.7, 137.2, 136.1, 135.4, 133.9, 133.0, 132.2, 130.2, 129.5, 129.1, 128.5, 128.3, 127.9, 125.9, 120.2, 56.2, 19.6, 19.5, 19.1; calcd for C₂₂H₂₁NO₄S₂: C 61.81%; H 4.95%; N 3.28%; S 15.00; found: C 61.87%; H 4.93%; N 3.25%; S 15.02%.

4.8. Preparation of (R)-(−)-8d^a from (RS)-10a

Sodium methoxide 0.5 M (0.061 g, 0.0843 mmol) was added to a solution of (RS)-10a (36 mg, 0.0843 mmol) in MeOH (1 mL). The reaction was monitored on TLC (PE–Et₂O 3: 2). After 24 h, when the spot of (RS)-10a disappeared, the reaction was complete. MeOH was removed under nitrogen flow; the crude residue was poured into CH₂Cl₂–H₂O (2 mL, 1:1). The aqueous layer was separated and passed through a Dowex (HCR–W2) column (H₂O), affording pure title compound (R)-(−)-8d^a, (26 mg, 96% yield) after removing H₂O under nitrogen flow.

(R)-(−)-8d^a: pale brown waxy solid; [α]_D^22.5 = -14.1 (c = 0.18, CH₂Cl₂); spectral data identical to that reported for 8d.

4.9. Theoretical method

The theoretical study was performed within the Density Functional Theory (DFT)^2⁹ making use of the M05-2x functional.^3⁰ All geometries were fully optimized with the basis set 6-31+G(d)^3¹a,b and characterized through vibrational frequency analysis. Then, single point energy calculations were performed with the basis set 6-311+(3df,2p)^3¹c,d including the electrostatic and non electrostatic
solvent effects with the Polarized Continuum Method. Finally, these data were combined with the gas-phase thermal and entropy corrections. All energy values are reported in the Supporting Information. Calculations were performed with the Gaussian 03 program. Figure 3 was prepared with program Molden.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi...:

Total (in au) and relative (in kcal mol⁻¹) electronic energies and free energy corrections are reported. Nuclear coordinates (in Angstrom) follows.

References and note


25. The stable structures of the compounds 8 are all skew with a dihedral angle between the two rings ranging from 90 to 120° while nearly planar structures are all transition structures. Because the aromatic ring (Ar in schemes) is substituted with a methyl or a second ring (Ar = naphthyl) we have two transition structures: one (TS<sub>anti</sub>) with the substituent on the opposite side of the sulphur atom; the second (TS<sub>syn</sub>) with the substituent on the same side.


Graphical abstract