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Synthesis of 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 amounts, of 1,2-benzenedisulfonimide as a safe Brønsted acid in some acid-catalyzed organic reactions. 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). We resolved the atropisomers of one of these compounds.

1. Introduction

Organocatalysis has become a highly dynamic area in chemical research.[1] Recently, List[2] 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.[1,2]

We have recently reported the use of 1,2-benzenedisulfonimide (**1**, Fig. 1) in catalytic amounts as a safe, nonvolatile and non-corrosive Brønsted acid in some acid-catalyzed organic reactions, such as etherification,[3] esterification,[3,4] acetalization,[3] the Ritter reaction,[5] the Nazarov electrocyclization,[6] the disproportionation of dialkyl diarylmethyl ethers,[7] the Hosomi–Sakurai reaction,[8] the Friedländer annulation,[9] the Pictet–Spengler reaction[10] and the Mukaiyama–Aldol reaction.[11]

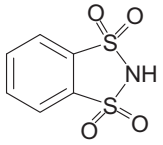

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Fig. 1. 1,2-Benzenedisulfonimide.

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 **1** 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 **1** 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 **1** becomes chiral, while leaving the acidic function responsible of the catalytic activity unaffected.

In this view, it was decided to bind a hindered aryl group to the 3-position of the aromatic ring of **1** in order to prevent the free

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rotation around the aryl-aryl bond and therefore generate atropisomerism[12a] (Fig. 2). In this paper we describe the synthesis of two hindered derivatives.

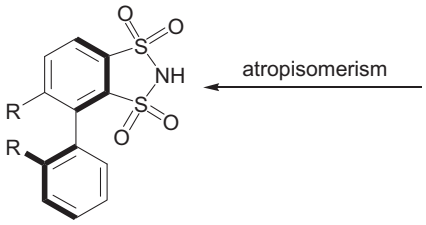


Fig. 2. Chiral derivatives of 1,2-benzenedisulfonimide.

To obtain these chiral derivatives, the rotational barrier of the chirality axis should be high enough to assure an atropisomer long life time. The role of common substituents in defining this barrier for biphenyls has already been well established.[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[13] describes the synthesis of BINBAM, namely (*R*)-2,2′-binaphthyldisulfonimide; List[14a] the synthesis of (*R*)-3,3′-bis[3,5-bis(trifluoromethyl)phenyl]-1,1′-binaphthyl-2,2′-disulfonimide (and other similar chiral derivatives[14b,c]), which is a highly active catalyst of the Mukaiyama–Aldol reaction with very good enantioselectivity and Lee[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.[16]

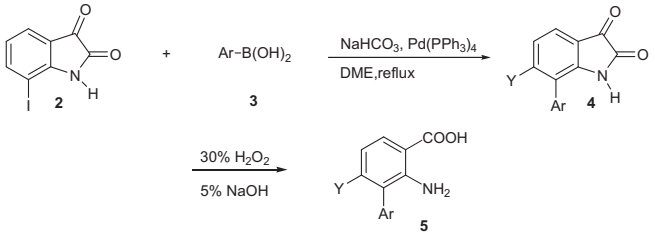
2. Results and discussion

2.1. Preparation of anthranilic acids 5

As reported in the literature,[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.

In the literature[19] a synthesis of 3-arylanthranilic acid is described. The process starts from 2-iodoaniline, passes through intermediates 7-iodoisatin **2** and 7-arylisatins **4**; the aryl group is inserted on isatin ring using the Suzuki protocol,[20] in the presence of $NaHCO_3$ as a base. Finally, 3-arylanthranilic acids **5** are easily obtained via the oxidative cleavage of 7-arylisatins **4** in a 5% sodium hydroxide and 30% hydrogen peroxide aqueous solutions (Scheme 1). We modified and improved this procedure using CsF in place of $NaHCO_3$ and palladium acetate as pre-catalyst in place of $Pd(PPh_3)_4$ (Table 1).



Scheme 1. Synthesis of 3-arylanthranilic acids.

The isatins are sensitive to alkaline environments. The Pfitzinger quinoline synthesis,[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 $NaHCO_3$ caused its total decomposition after 2 h (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).

However, under these conditions it was impossible to obtain hindered 7-arylisatins **4g**–**j** (Table 1, method A: entries 9, 11, 13 and 15). In fact the preparation of hindered biaryls via a Suzuki coupling has historically proven to be very difficult.[22] 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.[22] 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 and 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 and 8). Finally 3-arylanthranilic acids **5a**–**g**,**i**,**j** were easily obtained. The yields are reported in Table 2.

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.[23]

2.2. Theoretical studies

Discovering a method 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-benzendisulfonimides **6** endowed with a chiral element due to atropisomerism. Instead of synthesizing several sulfonimides **6** and then verifying their chiral stability, we decided to take advantage of theoretical methods to perform a screening of **6** 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^{-1}.[24]

The calculated value, obtained as described in the Theoretical methods section, is 26.7 kcal mol^{-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 **6** 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 note[25] and Supplementary data for more details).

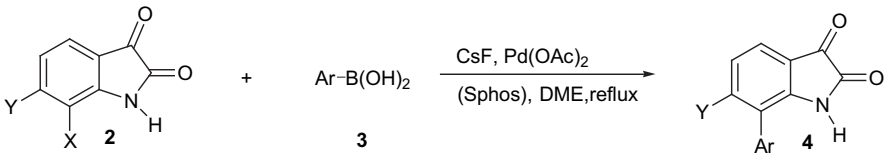
Comparing the isomers **6c** and **6e**, it is worthwhile noting that the methyl group is far more effective in increasing the rotational barrier (from 26 to 40 kcal mol^{-1}) when it is found in position 4 of the benzenedisulfonimide ring instead of position 8 of the naphthyl ring. A similar remarkable effect is also observed when the methyl group is added in position 4 of the benzenedisulfonimide in passing from **6a** to **6c**. Indeed, the rotational barrier rises from 19 to 40 kcal mol^{-1}.The steric effect is also evident from the great distorsion from planarity in the transition structures as shown, as an example, for **6c** in Fig. 3.

It is evident from the data that **6c** and **6d** 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^{-1} (25 °C). This corresponds to a life time for racemization of 10^8 years, which is significantly longer than the arbitrary threshold of 1000 s, considered by Oki[26] the minimum requirement for chemical separation of atropisomers.

2.3. Preparation of sulfonimides 6c and 6d

The starting 3-arylanthranilic acids **5** were firstly diazotized with 3-methylbutyl nitrite to form the internal diazonium salt,

Table 1
Synthesis of 7-arylisatines **4a–j**



2	X	Y
a	I	H
b	Br	Me

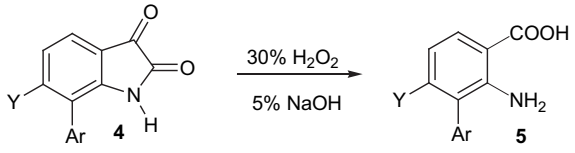
3	Ar
a	Ph
b	4-$MeOC_6H_4$
c	4-ClC_6H_4
d	2-MeC_6H_4
e	2-*i*-$PrOC_6H_4$
f	1-naphthyl
g	2-EtO-1-naphthyl
h	2,6-$Me_2C_6H_3$

4	Ar	Y	4	Ar	Y
a	Ph	H	**f**	1-naphthyl	H
b	4-$MeOC_6H_4$	H	**g**	2-EtO-1-naphthyl	H
c	4-ClC_6H_4	H	**h**	2,6-$Me_2C_6H_3$	H
d	2-MeC_6H_4	H	**i**	2-MeC_6H_4	Me
e	2-*i*-$PrOC_6H_4$	H	**j**	1-naphthyl	Me

Entry	Reactants		Products and yields[a] (%)	Method[b]	Time (h)
1	**2a**	**3a**	**4a**, 81	A	3
2	**2a**	**3b**	**4b**, 82	A	4
3	**2a**	**3c**	**4c**, 92	A	3
4	**2a**	**3d**	**4d**, 62	A	2.5
5	**2a**	**3d**	**4d**, 63	B	3
6	**2a**	**3e**	**4e**, 71	A	1
7	**2a**	**3f**	**4f**, 82	A	1.5
8	**2a**	**3f**	**4f**, 81	B	2
9	**2a**	**3g**	**4g**, —[c]	A	6
10	**2a**	**3g**	**4g**, 78	B	3
11	**2a**	**3h**	**4h**, —[c]	A	6
12	**2a**	**3h**	**4h**, traces[c,d]	B	6
13	**2b**	**3d**	**4i**, —[c]	A	6
14	**2b**	**3d**	**4i**, 76	B	1
15	**2b**	**3f**	**4j**, —[c]	A	6
16	**2b**	**3f**	**4j**, 82	B	3

[a] Yields refer to the pure and isolated products.
[b] Sphos was added as a ligand in the reactions carried out with the method B.
[c] After 6 h, we observed the total decomposition of **2a** or **2b**.
[d] On the GC–MS analysis of the crude residue traces of **4h** were detected, MS (*m*/*z*, EI)=251(M^+).

Table 2
Synthesis of 3-arylanthranilic acids **5a–j**

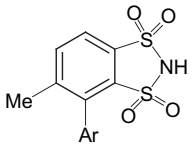


4,5	Ar	Y	4,5	Ar	Y
a	Ph	H	**f**	1-naphthyl	H
b	4-$MeOC_6H_4$	H	**g**	2-EtO-1-naphthyl	H
c	4-ClC_6H_4	H	**h**	2,6-$Me_2C_6H_3$	H
d	2-MeC_6H_4	H	**i**	2-MeC_6H_4	Me
e	2-*i*-$PrOC_6H_4$	H	**j**	1-naphthyl	Me

Entry	Reactants	Products and yields[a] (%)
1	**4a**	**5a**, 82
2	**4b**	**5b**, 66
3	**4c**	**5c**, 67
4	**4d**	**5d**, 72
5	**4e**	**5e**, 85
6	**4f**	**5f**, 89
7	**4g**	**5g**, 80
8	**4i**	**5i**, 87
9	**4j**	**5j**, 87

[a] Yields refer to the pure and isolated products.

Table 3
Calculated rotational free energy barriers (in kcal mol^{-1}) and life times of selected 3-aryl substituted 1,2-benzenedisulfonimides **6**



6 a-e

6	Ar	Y
a	2-MeC_6H_4	H
b	1-naphthyl	H
c	2-MeC_6H_4	Me
d	1-naphthyl	Me
e	8-Me-1-naphthyl	H

3-Aryl-1,2-benzenedisulfonimides **6**	ΔG_{att}	Life time	Optical purity (% after 24 h)
6a	19.4	26 s	0
6b	21.9	29 min	1
6c	39.5	10^8 year	100
6d	39.6	10^8 year	100
6e	26.2	710 h	94

which upon heating, tended to decompose losing nitrogen and carbon dioxide to give rise to the intermediate benzyne, which in the presence of carbon disulfide and 3-methylbutan-1-ol provided 2-(3-methylbutoxy)-1,3-benzodithioles **7**.[17a] The subsequent oxidative chlorination of these intermediates with chlorine–water furnished 1,2-benzenedisulfonyl chlorides **8**.[17b] These were then reacted with ammonia. The resulting ammonium salts were passed through a cation-exchange resin column to give **6** (Scheme 2).[18] The yields of these reactions are reported in Table 4.

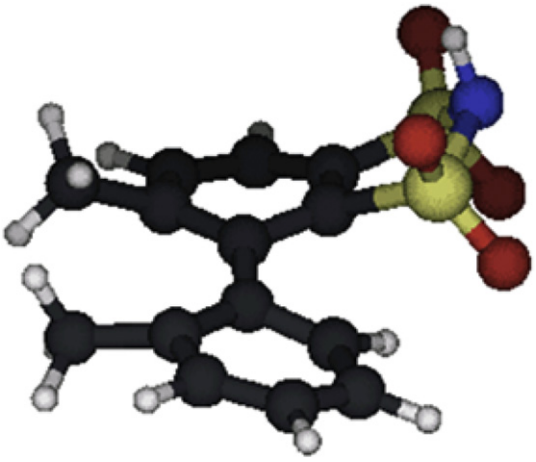
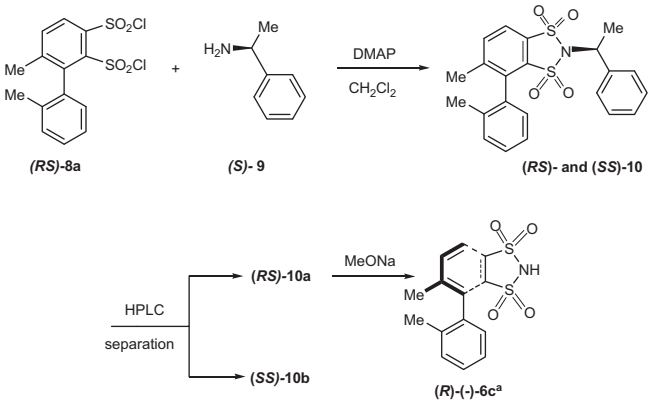
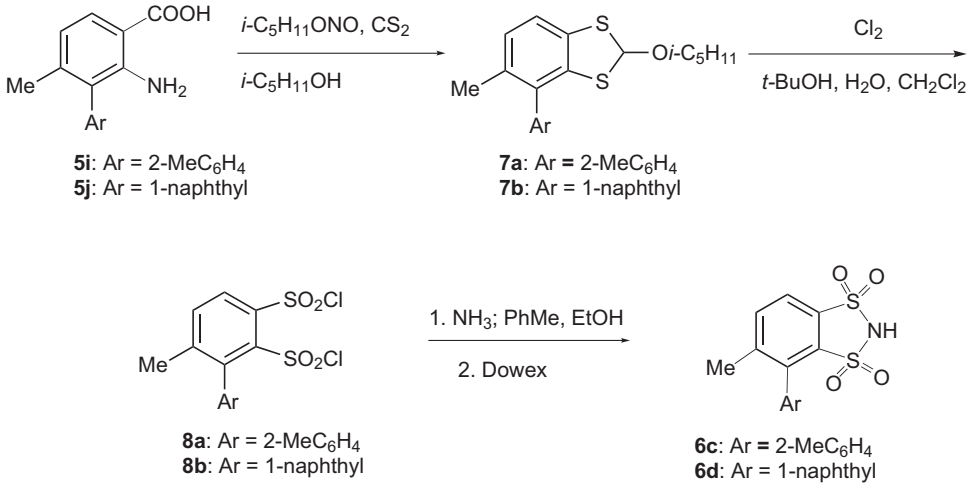


Fig. 3. Rotational transition structure for **6c**.



Scheme 3. Separation of atropisomers of **6c**.



Scheme 2. Synthesis of 3-aryl-1,2-benzenedisulfonimides **6**.

Table 4
Synthetic sequence for 3-aryl-1,2-benzenedisulfonimides **6**

Entry	Reactant	Products and yields[a] (%)	Products and yields[a] (%)	Products and yields[a] (%)
1	**5i**	**7a**, 79	**8a**, 74	**6c**, 74
2	**5j**	**7b**, 62	**8b**, 83	**6d**, 78

[a] Yields refer to the pure and isolated products.

Analyzing the ^{1}H and ^{13}C NMR spectra of compounds **7a** and 7**b**, which have a stereogenic carbon atom, it was possible to clearly see the presence of two diastereoisomers (and it can be inferred the presence of two pairs of enantiomers). The barriers for **7a** and **7b** are possibly around 40 kcal mol^{-1}, which when compared with those of **6c** and **6d**, should correspond to very long life times under any conditions. In fact, for **7a** and **7b** the two diastereoisomers were clearly detected on GC and GC–MS analyses as well. 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 6c

Having obtained the chiral compounds **6c** and **6d**, our next goal was to separate their atropisomers. Firstly, we planned to react them 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.

As reported by Lee[15] the reaction between **8a** and (*S*)-1-phenylethylamine (**9**; ee ≥99%), performed in the presence of DMAP, furnished the diastereomeric derivatives of **10**. It must be stressed that performing the same reaction starting from **8b** we obtained only a small amount of diastereomeric derivatives and was impossible to separate them from several by-products. We could not separate compounds **10** by silica gel column chromatography; however, their separation was possible by semi-preparative chiral HPLC. Two fractions containing the separated diastereomers **10a** and **10b** were collected and subsequently they were reinjected into the same column to check that they were diastereomerically pure.

These compounds provided the electronic Circular Dichroism (ECD) spectra of Fig. 4, which are almost a 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 flexible moieties made the quantitative analysis of ECD spectra of (*RS*)-**10** and (*SS*)-**10** by computational methods particularly involved and it will be the subject of a future report. A conformational analysis at MM level on both diastereomers revealed a large manifold of structures, differing for the 5-member ring conformation and the rotation of the single bonds in the amine moiety, together with a broad distribution of the dihedral angle between the two benzenes around 90°. This made the system hardly amenable to a complete analysis and we decided to dissect the amine moiety

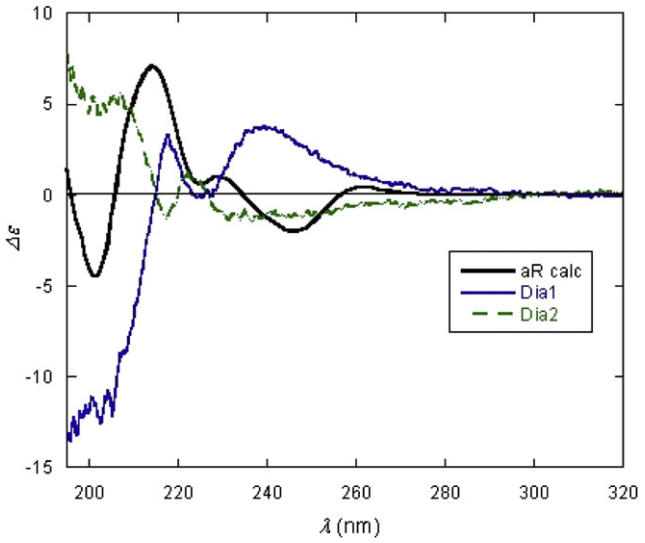


Fig. 4. Experimental and calculated electronic circular dichroism spectra for compounds **10a** and **10b**. The thin continuous and broken lines represent the first and the second eluted compounds, respectively. The bold continuous line represents the calculated Electronic Circular Dichroism spectrum for the *N*-methyl derivative of compound (*R*)-**6c**[a] (for computational details see Section 4.9).

and to formally substitute it with a methyl group, i.e., to limit our calculation to the *N*-methyl derivative of **6c**, **Me6c**. This choice appears justified by the fact that, as noted above, in this case the observed ECD appear dominated by axial chirality and they respond to the amine chiral centre only to a minor extent. Our model compound, (a*R*)-**Me6c**, displays two conformational minima corresponding to two different orientations of the methyl group, following inversion of the 5-member ring and a large manifold associated to the dihedral angle between the two benzene groups. Accordingly, we built 18 conformers of (a*R*)-**Me6c**, and optimized them by DFT, thereby calculating the Boltzmann averaged ECD spectrum by TDDFT as specified in Section 4.7 and shown Fig. 4. In spite of the approximation there is a fairly good agreement between this calculated spectrum and the experimental one relative to the first eluted diastereomer **10a**, which can then be assigned the (a*R*,*S*)-configuration. The only serious point of disagreement between the two spectra consists in the fact that we calculate a negative Cotton effect at about 240 nm, which is flanked by two positive ones at 260 and 230 nm. As we shall discuss in detail in a forthcoming publication, this may be due to our conformational average.

Finally, the reaction of the first separated diastereoisomer (*RS*)-**10a** with sodium methoxide[27] afforded the atropisomers (*R*)-(−) **6c**[a]. Because the starting material (*RS*)-**10a** resulted diastereomerically pure (see above) and on account of the high enantiomeric purity (ee: ≥99%) of the amine we used for this resolution, we can put forward that the atropisomer (*R*)-(−)**6c**[a] we obtained are highly enantiopure (ee ≥99%) although this was not further checked.

3. Conclusions

Our previous research showed that the potential applications of 1,2-benzenedisulfonimide **1** as a safe, noncorrosive, nonvolatile, recoverable and recyclable strong Brønsted acid-organocatalyst are in theory unlimited. For these reasons, to have synthesized the chiral compounds **6c** and **6d** and to have separated one of the atropisomers of **6c** 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. ^{1}H NMR and ^{13}C 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-methylaniline[28] 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-6-methylisatin (**2b**) was prepared, starting from 2-bromo-3-methylaniline (1.86 g, 10 mmol), as described in the literature[19a] for the synthesis of **2a**; pale brown solid; 1.82 g (yield 76%); mp 212 °C (EtOH); IR ($CHCl_3$) ν (cm^{-1}): 3419, 3026, 1766, 1743, 1618, 806; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.41 (d, 1H, J=7.2 Hz), 6.97 (d, 1H, J=7.2 Hz), 2.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_9H_6BrNO_2$: 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 H_2O (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_2Cl_2–EtOAc, 9.8:0.2), GC and GC–MS. Then, the reaction mixture was poured into CH_2Cl_2–H_2O (100 ml, 1:1). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with H_2O (2×50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue, purified in a chromatography column (CH_2Cl_2–EtOAc, 98:2), 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_2O (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_2O after 2 h we observed the total decomposition of **4a**.

*4.2.1. 7-Phenylisatin (**4a**).* Orange solid; 0.39 g (yield 81%); mp 185 °C (EtOH; lit.[19a] 185–186); R_f=0.59. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.59–7.33 (m, 7H), 7.22–7.11 (m, 1H); ^{1}H NMR data

identical to that reported in the literature;[19a] MS (*m*/*z*, EI)=223 (M^+).

*4.2.2. 7-(4-Methoxyphenyl)isatin (**4b**).* Orange solid; 0.42 g (yield 82%); mp 240 °C (EtOH; lit.[19a]>200); R_f=0.40. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (br s, 1H), 7.55–7.46 (m, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 7.25–7.21 (m, 1H), 7.09 (d, *J*=8.6 Hz, 2H), 3.82 (s, 3H); ^{1}H NMR data identical to that reported in the literature;[19a] MS (*m*/*z*, EI)=253 (M^+).

*4.2.3. 7-(4-Chlorophenyl)isatin (**4c**).* Orange solid; 0.47 g (yield 92%); mp 238–239 °C (EtOH); R_f=0.53. IR ($CHCl_3$) ν (cm^{-1}): 3424, 3036, 1750, 1743, 1608, 1210, 825; ^{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_3COCD_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)=259 (M^+), 257 (M^+); calcd for $C_{14}H_8ClNO_2$: 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%.

*4.2.4. 7-(2-Tolyl)isatin (**4d**).* Orange solid; 0.29 g (yield 62%); mp 145–146 °C (EtOH); R_f=0.60. IR ($CHCl_3$) ν (cm^{-1}): 3422, 3034, 1748, 1743, 1606, 1212, 789; ^{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%.

*4.2.5. 7-(2-Isopropoxyphenyl)isatin (**4e**).* Orange solid; 0.40 g (yield 71%); mp 120–121 °C (EtOH); R_f=0.41. IR ($CHCl_3$) ν (cm^{-1}): 3423, 3035, 1747, 1743, 1607, 1225, 1212, 785; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.57–7.47 (m, 2H), 7.39–7.33 (m, 1H), 7.30–7.29 (m, 1H), 7.25–7.24 (m, 1H), 7.21–6.98 (m, 2H), 4.52 (septuplet, *J*=6.2 Hz, 1H), 1.20 (d, *J*=6.2 Hz, 3H), 1.18 (d, *J*=6.2 Hz, 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%.

*4.2.6. 7-(1-Naphthyl)isatin (**4f**).* Orange solid; 0.45 g (yield 82%); mp 224–225 °C (EtOH); R_f=0.44. IR ($CHCl_3$) ν (cm^{-1}): 3422, 3033, 1748, 1742, 1609, 1225, 1212, 785, 771, 680; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99–7.95 (m, 2H), 7.75–7.43 (m, 7H), 7.38–7.24 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 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, 124.9, 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%.

*4.2.7. 7-(2-Ethoxy-1-naphthyl)isatin (**4g**).* Orange solid; 0.50 g (yield 78%); mp 152–153 °C (EtOH); R_f=0.35. IR ($CHCl_3$) ν (cm^{-1}): 3422, 3027, 1752, 1743, 1605, 1224, 795, 772, 678; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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), 7.44–7.29 (m, 4H), 7.22–7.15 (m, 2H), 4.14–4.05 (m, 2H), 1.24 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz): δ 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 $C_{20}H_{15}NO_3$ (317.34): C 75.70%; H 4.76%; N 4.41%; found: C 75.77%; H 4.78%; N 4.45%.

*4.2.8. 7-(2,6-Xylyl)isatin (**4h**).* Only few traces detected on GC–MS analysis (see Table 1, entry 12); MS (*m*/*z*, EI)=251 (M^+).

*4.2.9. 6-Methyl-7-(2-tolyl)isatin (**4i**).* Orange solid; 0.38 g (yield 76%); mp 207 °C (EtOH); R_f=0.61. IR ($CHCl_3$) ν (cm^{-1}): 3422, 3030, 1765, 1750, 1610, 1602, 1212, 785; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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%.

*4.2.10. 6-Methyl-7-(1-naphthyl)isatin (**4j**).* Orange solid; 0.47 g (yield 82%); mp 215–216 °C (EtOH); R_f=0.47. IR ($CHCl_3$) ν (cm^{-1}): 3419, 3027, 1758, 1754, 1618, 1600, 1428, 1316, 1229, 1212, 790, 775, 707, 667; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, *J*=3.6 Hz, 1H), 7.89 (d, *J*=3.6 Hz, 1H), 7.58–7.36 (m, 5H), 7.31 (d, *J*=7.6 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 1H), 6.90 (br s, 1H), 2.04 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 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 a 5% aqueous NaOH 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.

*4.3.1. 3-Phenylanthranilic acid (**5a**).* White solid; 0.35 g (yield 82%); mp 146 °C (EtOH; lit.[19a] 146 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94–7.89 (m, 1H), 7.49–7.38 (m, 5H), 7.23–7.19 (m, 1H), 6.73–6.65 (m, 1H); ^{1}H NMR data identical to that reported in the literature.[19a]

*4.3.2. 3-(4-Methoxyphenyl)anthranilic acid (**5b**).* White solid; 0.32 g (yield 66%); mp 214 °C (EtOH; lit.[19a] 158 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84–7.76 (m, 1H), 7.29 (d, *J*=8.6 Hz, 2H), 7.13–7.09 (m, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 6.63–6.56 (m, 1H), 3.78 (s, 3H); ^{1}H NMR data identical to that reported in the literature.[19a]

*4.3.3. 3-(4-Chlorophenyl)anthranilic acid (**5c**).* White solid; 0.33 g (yield 67%); mp 187–188 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3501, 3376, 3017, 1668, 1607, 1566, 1447, 1235, 1209, 840; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (dd, J_1=8.0 Hz, J_2=1.6 Hz, 1H), 7.40 (d, *J*=8.6 Hz, 2H), 7.30 (d, *J*=8.6 Hz, 2H), 7.17 (dd, J_1=8.0 Hz, J_2=1.6 Hz, 1H), 6.68 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 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%.

*4.3.4. 3-(2-Tolyl)anthranilic acid (**5d**).* White solid; 0.32 g (yield 72%); mp 137–138 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3505, 3373, 3012, 1667, 1605, 1566, 1445, 1233, 1211, 798; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ 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); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.8, 148.7, 137.3, 137.2, 135.7, 131.5, 130.5, 130.2, 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%.

*4.3.5. 3-(2-Isopropoxyphenyl)anthranilic acid (**5e**).* White solid; 0.46 g (yield 85%); mp 151 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3504, 3374, 3022, 1669, 1605, 1564, 1444, 1235, 1214, 1178, 1160, 791; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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), 4.36 (septuplet, *J*=6.2 Hz, 1H), 1.16 (d, *J*=6.2 Hz, 3H), 1.13 (d, *J*=6.2, 3H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 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%.

*4.3.6. 3-(1-Naphthyl)anthranilic acid (**5f**).* White solid; 0.47 g (yield 89%); mp 195 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3502, 3376, 3026, 2400, 1670, 1606, 1563, 1448, 1231, 929, 803, 708, 675; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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%.

*4.3.7. 3-(2-Ethoxy-1-naphthyl)anthranilic acid (**5g**).* White solid; 0.49 g (yield 80%); mp 159–160 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3501, 3380, 3015, 1668, 1607, 1561, 1448, 1237, 1211, 810, 772, 665; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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, $CDCl_3$ 25 °C): δ 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%.

*4.3.8. 4-Methyl-3-(2-tolyl)anthranilic acid (**5i**).* White solid; 0.42 g (yield 87%); mp 191 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3500, 3377, 3025, 1664, 1601, 1552, 1449, 1238, 1203, 804; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 173.2, 148.7, 143.5, 137.1, 135.9, 130.7, 130.6, 129.9, 128.0, 127.2, 126.8, 117.9, 106.7, 20.6, 18.9; calcd for $C_{15}H_{15}NO_2$ (241.29): C 74.67%; H 6.27%; N 5.80%; found: C 74.68%; H 6.31%; N 5.77%.

4.3.9. 4-Methyl-3-(1-naphthyl)anthranilic acid (5j). White solid; 0.48 g (yield 87%); mp 197–198 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3500, 3380, 3015, 1666, 1601, 1222, 1215, 790, 701, 670; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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-5-Methyl-2-(3-methylbutoxy)-1,3-benzodithioles 7. 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 heated to reflux 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_2O–H_2O (100 mL, 1:1). The aqueous layer was separated and extracted with Et_2O (2×50 mL). The combined organic extracts were washed with H_2O (2×50 mL) and saturated solution of Na_2CO_3 (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue, purified by column chromatography (PE–Et_2O 95:5), afforded the pure title compound **7**.

*4.4.1. 5-Methyl-4-(2-tolyl)-2-(3-methylbutoxy)-1,3-benzodithiole (**7a**).* Pale yellow waxy solid as a mixture (1:1) of two diastereomers; 0.55 g (yield: 79%). Having different retention times, the two diastereomers were clearly detected by GC and GC–MS analyses. The diastereomers ratio was determined by ^{1}H NMR analysis. In particular, the ratio was deduced by comparing the integration area of the signal centred at 6.69 ppm (pertinent to the H of the C bound to two S) of one diastereomer, with the signal centred at 6.68 ppm of the other diastereomer.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.22 (m, 4H), 7.07–7.03 (m, 2H), 6.69 (s, 1H), 6.68 (s, 1H), 3.48–3.44 (m, 2H), 2.15 (s, 3H), 2.06 (s, 3H), 1.98 (s, 3H), 1.75–1.22 (m, 1H), 1.47–1.41 (s, 2H), 0.90 (d, J=6.2 Hz, 6H), 0.88 (d, J=6.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.0, 139.9, 137.4, 137.3, 135.7, 135.4, 135.3, 135.1, 133.1, 133.0, 130.2, 128.5, 128.00, 127.9, 127.0, 126.2, 120.2, 120.1, 89.3, 89.1, 62.0, 61.8, 37.7, 37.6, 24.8, 24.7, 22.5, 22.4, 22.3 19.3, 19.2.

The two diastereomers were separated (0.30 g) by column chromatography (hexane/Et_2O 98:2).

Diastereomer **1**: viscous pale yellow oil; 0.16 g; R_f=0.78. IR ($CHCl_3$) ν (cm^{-1}): 3150, 2954, 2251, 1812, 1790, 1643, 1462, 1380, 1200, 1090, 812; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.20 (m, 4H), 7.08–7.04 (m, 2H), 6.68 (s, 1H), 3.47–3.42 (m, 2H), 2.15 (s, 3H), 1.97 (s, 3H), 1.70–1.21 (m, 1H), 1.46–1.41 (s, 2H), 0.91 (d, J=6.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.0, 137.5, 135.8, 135.3, 135.0, 133.2, 130.2, 128.6, 128.1, 126.9, 126.3, 120.1, 89.3, 62.0, 37.7, 24.8, 22.4, 22.2, 19.2; MS (*m*/*z*, EI)=344 (M^+); calcd for $C_{20}H_{24}OS_2$: C 69.72%; H 7.02%; S 18.61%; found: C 69.77%; H 6.98%; S 18.61%.

Diastereomer **2**: waxy solid: 0.14 g; R_f=0.72. IR ($CHCl_3$) ν (cm^{-1}): 3148, 2952, 2250, 1812, 1790, 1642, 1461, 1380, 1202, 1091, 812; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.21 (m, 4H), 7.08–7.04 (m, 2H), 6.66 (s, 1H), 3.47–3.43 (m, 2H), 2.07 (s, 3H), 1.97 (s, 3H), 1.73–1.21 (m, 1H), 1.46–1.40 (s, 2H), 0.88 (d, J=6.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.9, 137.4, 135.8, 135.3, 134.9, 133.0, 130.2, 128.5, 128.0, 127.0, 126.2, 120.0, 89.1, 61.9, 37.6, 24.7, 22.3, 22.2, 19.2; MS (*m*/*z*, EI)=344 (M^+); calcd for $C_{20}H_{24}OS_2$: C 69.72%; H 7.02%; S 18.61%; found: C 69.71%; H 7.03%; S 18.60%.

*4.4.2. 5-Methyl-4-(1-naphthyl)-2-(3-methylbutoxy)-1,3-benzodithiole (**7b**).* Pale yellow waxy solid as a mixture (1:1) of two diastereomer 0.47 g (yield: 62%). Having different retention times, the two diastereomer were clearly detected by GC analyses. The diastereomers ratio was determined by ^{1}H NMR analysis. In particular, the ratio was deduced by comparing the integration area of the signal centred at 6.61 ppm (pertinent to the H of the C bound to two S) of one diastereomer, with the signal centred at 6.58 ppm of the other diastereomer.

IR ($CHCl_3$) ν (cm^{-1}): 3156, 2957, 2255, 1817, 1794, 1644, 1466, 1382, 1210, 1096, 804, 705, 688; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91–7.86 (m, 2H), 7.54–7.28 (m, 6H), 7.11–7.06 (m, 1H), 6.61 (s, 1H), 6.58 (s, 1H), 3.44–3.27 (m, 2H), 1.92 (s, 3H), 1.90 (s, 3H) 1.71–1.22 (m, 3H), 0.91–0.87 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 134.3, 134.0, 133.7, 133.6, 133.4, 133.2, 130.8, 130.5, 128.4, 128.2, 128.1, 127.1, 127.0, 126.4, 126.3, 126.0, 125.9, 125.6, 125.5, 125.0, 124.8, 120.6, 89.4, 89.0, 62.3, 61.6, 37.6, 24.8, 24.7, 22.3, 19.4, 19.3; 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%.

Attempts to separate the two diastereomer by column chromatography failed.

4.5. 3-Aryl-4-methyl-1,2-benzenedisulfonyl chlorides 8. General procedure

4-Aryl-2-(3-methylbutoxy)-1,3-benzodithiole **8** (2 mmol) was dissolved in *tert*-butyl alcohol (20 mL), CH_2Cl_2 (16 mL) and H_2O (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 **7** disappeared and there was only one other spot, the reaction was complete. The reaction mixture was poured into CH_2Cl_2–H_2O

(100 mL, 1:1) The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with a 5% NaOH solution (2×50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue, purified in a chromatography column (PE–EtOAc 7:3) afforded the pure title compound **8**.

*4.5.1. 4-Methyl-3-(2-tolyl)-1,2-benzenedisulfonyl chloride (**8a**).* Pale brown solid; 0.58 g (yield: 74%); mp 148–149 °C (EtOH); R_f=0.35. IR ($CHCl_3$) ν (cm^{-1}): 3027, 3017, 1380, 1231, 1200, 803; ^1H NMR (200 MHz, CD_3CN): δ 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, $CDCl_3$): δ 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 $C_{14}H_{12}Cl_2O_4S_2$: 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%.

*4.5.2. 4-Methyl-3-(1-naphthyl)-1,2-benzenedisulfonyl chloride (**8b**).* Pale brown solid; 0.58 g (yield: 83%); mp 89–90 °C (EtOH); R_f=0.27. IR ($CHCl_3$) ν (cm^{-1}): 3030, 3015, 1380, 1231, 1201, 798, 701, 680; ^1H NMR (200 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ150.0, 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 $C_{17}H_{12}Cl_2O_4S_2$: 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-4-methyl-1,2-benzenedisulfonimides 6. General procedure

3-Aryl-1,2-benzenedisulfonyl chloride **8** (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 by TLC (PE–EtOAc 7:3). After 30 min, the reaction was completed. The mixture was first filtered in order to eliminate NH_4Cl and then solvent was evaporated under reduced pressure. The crude residue, dissolved in H_2O and passed through a Dowex (HCR–W2) column (H_2O), afforded the pure title compound **6**.

*4.6.1. 4-Methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (**6c**).* Pale brown waxy solid; 0.48 g (yield: 74%); IR ($CHCl_3$) ν (cm^{-1}): 3432, 3034, 1602, 1460, 1370, 1228, 797; ^1H 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, 135.9, 132.2, 130.3, 129.6, 129.0, 126.5, 126.0, 120.8, 19.9, 19.5; calcd for $C_{14}H_{13}NO_4S_2$: 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%.

*4.6.2. 4-Methyl-3-(1-naphthyl)-1,2-benzenedisulfonimide (**6d**).* Pale brown solid; 0.56 g (yield: 78%); mp 134–136 °C (EtOH). IR ($CHCl_3$) ν (cm^{-1}): 3432, 3032, 1602, 1370, 1231, 1228, 804, 704, 679; ^1H 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 $C_{17}H_{13}NO_4S_2$: 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_3N (0.20 g, 2.1 mmol) were added to a solution of **8a** (0.38 g, 1 mmol) in CH_2Cl_2 (100 mL). Then (*S*)-1-phenylethylamine (**9**, 0.12 g, 1.05 mmol; ee ≥99%) was slowly added dropwise. The reaction was monitored by TLC (PE–Et_2O 3:2). After 24 h, the reaction was completed. CH_2Cl_2 was removed under a nitrogen flow and the crude residue was purified in a chromatography column (PE–Et_2O 3:2) affording the pure title compound **10** (waxy solid; 0.32 g, 75%) as a mixture (1:1) of two diastereomers. The diastereomers ratio was determined by ^1H NMR analysis. In particular, the ratio was deduced by comparing the integration area of the signal centred at 1.99 ppm (pertinent to one of the Me group) of one diastereomer, with the signal centred at 1.97 ppm of the other diastereomer. ^1H NMR (200 MHz, $CDCl_3$): 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), 1.97 (s, 3H), 1.95 (d, J=7.2 Hz, 3H), 1.94 (d, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 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, 56.2, 19.6, 19.5, 19.1, 19.0.

Compound **10** (38 mg) was chromatographed on a semi-preparative Chiralpak IC column (Φ 10×250 mm, Daicel, Osaka, Japan) employing an isocratic elution with heptane–CH_2Cl_2 (1:1) at a flow rate of 4.7 mL/min. The compounds eluted from the column were monitored with a photodiode array detector. Compounds **10a** (18.8 mg) and **10b** (19.2 mg), eluted as single peaks at 8.9 and 12.8 min, were collected, after removing the solvents under nitrogen flow.

Compound (*RS*)-**10a**: waxy solid; $[\alpha]_D^{23}$ −12.1 (*c* 0.60, CH_2Cl_2); IR ($CHCl_3$) ν (cm^{-1}): 3025, 1603, 1457, 1349, 1167, 883, 709, 696; ^1H NMR (200 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{22}H_{21}NO_4S_2$: 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.

Compound (*SS*)-**10b**: waxy solid; $[\alpha]_D^{23}$ −2.4 (*c* 0.69, CH_2Cl_2); IR ($CHCl_3$) ν (cm^{-1}): 3025, 1603, 1457, 1349, 1167, 883, 709, 696; ^1H NMR (200 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{22}H_{21}NO_4S_2$: 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*)-(−)-6c[a] from (*RS*)-10a

Sodium methoxide 0.5 M in MeOH (14 mg, 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–Et_2O 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 CH_2Cl_2–H_2O (2 mL, 1:1). The aqueous layer was separated and passed through a Dowex (HCR–W2) column (H_2O), affording pure title compound (*R*)-(−)-**6c[a]**, (26 mg, 96% yield) after removing H_2O under nitrogen flow.

Compound (*R*)-(−)-**6c[a]**: pale brown waxy solid; $[\alpha]_D^{22.5}$ −14.1 (*c* 0.18, CH_2Cl_2); spectral data identical to that reported for **6c**.

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.[32] 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.[33] Finally, these data were combined with the gas-phase thermal and entropy corrections. All energy values are reported in the Supplementary data. Calculations were performed with the Gaussian 03 program.[34] Fig. 3 was prepared with program Molden.[35]

On the *N*-methyl derivative of compound (*R*)-**6c**[a] a conformational analysis and subsequent calculation of Electronic CD spectrum were performed. A first conformational search was conducted at Molecular Mechanics (MMFF force field) level by means of the procedure 'Systematic' implemented into Spartan 08.[36] 8 conformers within 2 kcal mol^{-1} above the total minimum were optimized DFT/B3LYP/6-31G(d) with Gaussian.[34] On the two lowest lying structures found above, the dihedral angle between the two aromatic rings was scanned in 5° steps and relative energies were calculated at DFT/CAM-B3LYP/SVP level. The Electronic CD spectra were calculated at TDDFT/CAM-B3LYP/SVP level. The final spectrum was obtained by Boltzmann averaging of 18 structures (eight dihedral angle steps on two conformers).

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Supplementary data

Total (in au) and relative (in kcal mol^{-1}) electronic energies and free energy corrections are reported. Nuclear coordinates (in Å) follows. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.127. These data include MOL files and InChIKeys of the most important compounds described in this article.

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