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Chiral Derivatives of 1,2-Benzenedisulfonimide as efficient Brønsted acid catalysts in Strecker reaction.

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Keywords: Sulfonimides**,** Brønsted acids, Asymmetric catalysis, Strecker reaction, Atropisomerism.

Abstract

Two chiral derivatives of 1,2-benzenedisulfonimide, namely 4-methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide and 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide have been easily synthetized in good overall yields (respectively 34% and 41%) by means of an eleven steps synthetic protocol from commercially available 2-methyl-6-nitroaniline or 2,3-dimethyl-6-nitroaniline. 4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide was also synthesized but the overall yield from 2,3-dimethyl-6-nitroaniline was lower (9%). The atropisomers of these compounds has been resolved and (-) atropisomers have been demonstrated to be efficient chiral catalysts in Strecker reaction .

Introduction

Asymmetric catalysis is still one of the major challenges in modern organic chemistry[1,2] and chiral Brønsted organic acid catalysis is, in particular, an emerging area.[3] In fact, the asymmetric Brønsted acid catalysis has proved itself to be a very efficient tool for the synthesis of chiral molecules as can boast of a number of impressive capabilities that contribute to obtaining the target products with very good enantioselectivity.

Currently, BINOL-derived phosphoric acids[3c,d] (first proposed by Akiyama *et al*.[4] and Terada *et al*.[5]) and the corresponding *N*-triflyl phosphoramides (first proposed by Yamamoto *et al.*[6]) are probably the most widely used chiral Brønsted acid catalysts and this well established class of chiral Brønsted acid catalysts has been applied to an ever-increasing number of useful transformations.

Two different research groups have very recently reported that chiral binaphthyl sulfonimides are very effective chiral Brønsted acid catalysts. A number of binaphthyl sulfonimides have been synthetized by Lee *et al.* and tested in the asymmetric Friedel-Crafts alkylation of indoles with imines.[7] List *et al.* developed chiral binaphthyl sulfonimide-catalyzed Mukaiyama aldol reactions, vinylogous and bisvinylogous Mukaiyama aldol reactions, hetero Diels–Alder reactions as well as Hosomi-Sakurai reactions.[8] Both groups obtained excellent enantioselectivity results, especially when sulfonimides bore bulky aryl groups with electron-withdrawing substituent.

We have recently reported the use of *o*-benzenedisulfonimide[9a] (OBS; **1**; Figure 1), in catalytic amounts, as a safe, nonvolatile and noncorrosive Brønsted acid in several acid-catalyzed organic reactions in very mild and selective conditions.[9b-m] The catalyst was easily recovered and purified, ready to be used in further reactions giving economic and ecological advantages.

The results and advantages of the use of **1** are very promising if one considers its applications in the field of asymmetric catalysis. We have, therefore, proposed the synthesis of a 1,2-benzenedisulfonimide chiral derivative, namely 4-methyl-3-(*o*-tolyl)-1,2-benzenedisulfonimide (**2;** Figure 1).[10a] Its chirality is due to the hindered rotation of the aryl group (atropisomerism). We used it as a chiral catalyst in the Strecker reaction and obtained unsatisfactory enantioselectivity results.[10b]

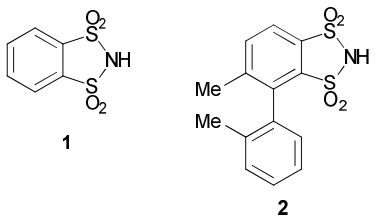


Figure 1 OBS **1** and its chiral derivative **2.**

Results and discussion

1. Synthesis of chiral derivatives of 1

Our goal was now to synthesize a chiral derivative of **1** which can be more efficient than **2** in asymmetric catalysis.

The key to achieving good enantioselectivity results in the presence of strong chiral Brønsted acids as catalysts, is the hydrogen bonding established between the protonated substrate and the conjugate chiral anion. Furthermore, a Brønsted acid should have the following attributes if it is to be considered a good chiral catalyst: adequate acidity[11a] in order *to catch up the substrate through hydrogen bonding without loose ion-pair formation*,[5b] type *C2* symmetry,[11b-c] and the presence of bulky substituents closer to the acidic function that *increase the stereochemical communication between catalyst and substrate*.[8a] Actually, **2** does not present type *C2* symmetry and has only one bulky group in the *ortho* position. In order to improve the chiral structure of **2**, we herein report the synthesis of 4-methyl- 3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **3a** (Figure 2) which has two bulky groups in the *ortho* positions but does not show *C2* symmetry, 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **3b** and 4,5-dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide **3c** (Figure 2) which have two bulky groups in *ortho* positions and *C2* symmetry. These new catalysts were tested in the Strecker reaction.

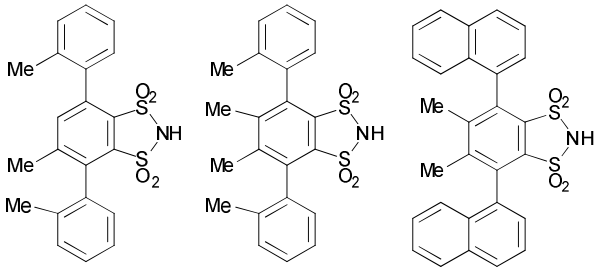
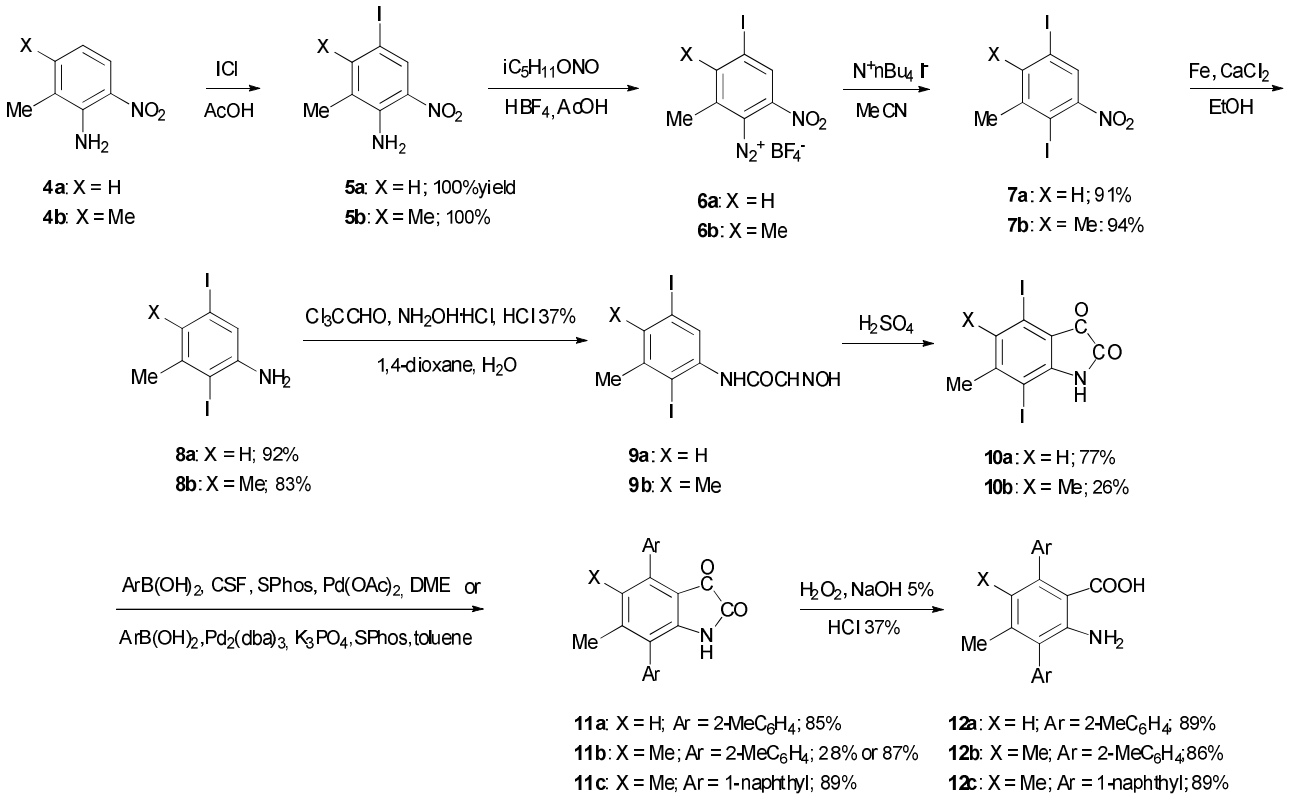


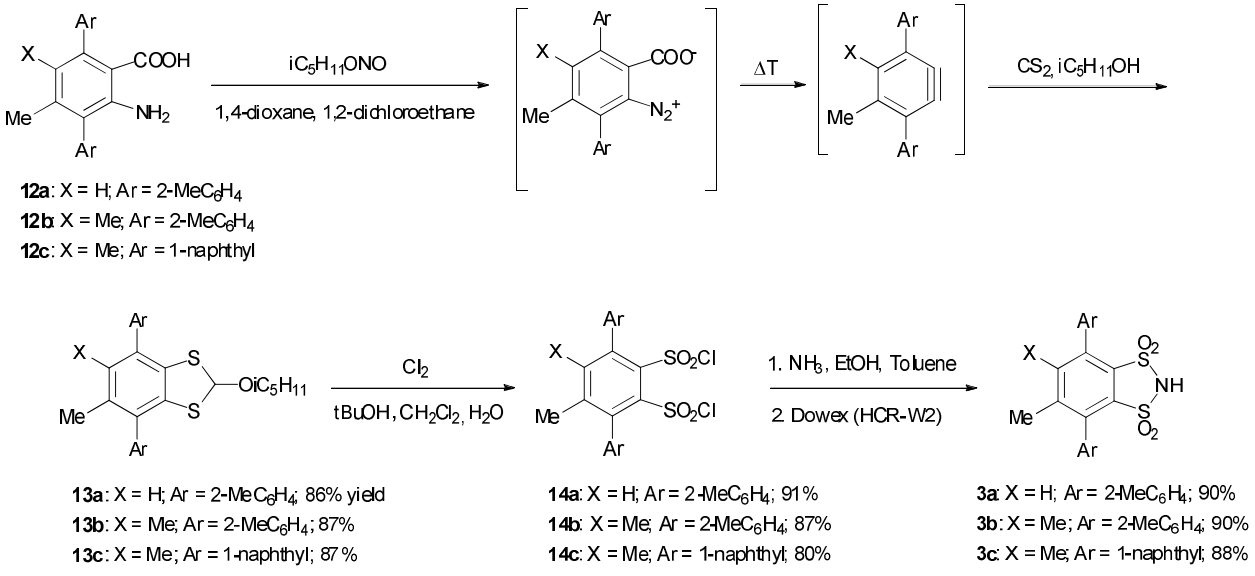
Figure 2 Chiral adducts **3a**, **3b**, **3c**.

The precursor to **3a** is the corresponding anthranilic acid **12a** which was obtained from commercially available 2-methyl-6-nitroaniline (**4a**) as reported in the Scheme 1.



Scheme 1 Synthetic protocol for anthranilic acids **12.**

12a was then converted into **3a**, using the same synthetic protocol[10a] employed in the preparation of **2** (Scheme 2). The overall yield of **3a**, obtained with this synthetic sequence from **4a**, was 34%.



Scheme 2 Synthetic protocol for sulfonimides **3.**

Conversely, the overall yield of immide **3b,** starting from 2,3-dimethyl-6-nitroaniline (**4b**)**,** was very low (only 3%). In fact, the acid cyclization of **9b** mainly afforded a monodeiodinated adduct. Moreover, the Suzuki coupling of **10b** afforded the adduct **11b** in a low yield (28%). It was possible to increase the Suzuki coupling yield (89%), by reacting **10b** with *o*-tolylboronic in the presence of $Pd_2(dba)_3$**,** Sphos and K_3PO_4 and toluene as a solvent[12] and the overall yield increased by up to 10%. Furthermore, we modified the synthetic protocol to further increase the overall yield as described below (Scheme 3).

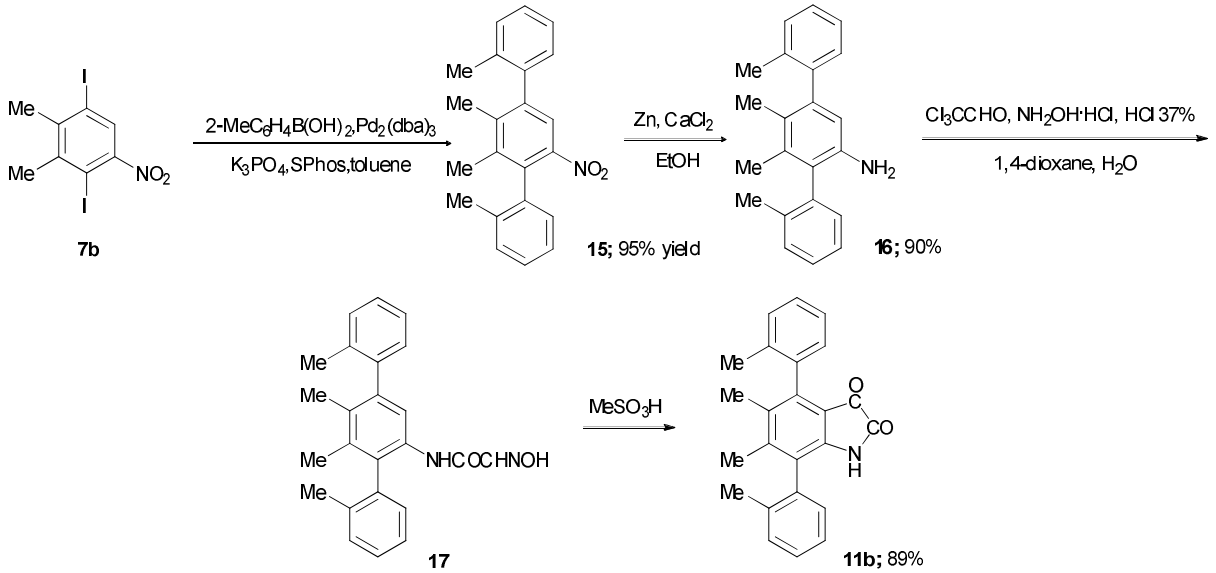
First of all, we carried out the Suzuki coupling on adduct **7b** and in the presence of $Pd_2(dba)_3$**,** Sphos and K_3PO_4**.** [12] In this way, we obtained the diarylated adduct **15** in a very good yield (95%).

The reduction of nitro group allowed us to obtain amine **16** which was transformed into the corresponding isatine **11b** in good yields (89%).

It is worth nothing that it was necessary to use $MeSO_3H$ instead of H_2SO_4 to transform intermediate **17** into **11b**. It was then converted into anthranilic acid **12b** which was converted into **3b** (Scheme 2)**.** The overall yield thus increased considerably (41%).

3c was also synthesized using the procedures reported in Scheme 1 and 2. The overall yield from **4b** was 9% when the Suzuki coupling was carryied out in the presence of $Pd_2(dba)_3$**,** Sphos and K_3PO_4**.**

Unfortunately**,** it was impossible to obtain the adduct derived from the Suzuki coupling of **7b** with adequate purity in this case (Scheme 3).



Scheme 3 Synthetic protocol for isatine **11b.**

2. Separation of atropisomers

After preparing chiral sulfonimides **3,** the next step was the resolution of their atropisomers. However, **3** are highly acidic (their pK_a value is most likely similar to that of parent OBS **1** which, measured, was 6.09 in butanone[13]) and polar compounds so their chromatographic separation can be considered extremely difficult. We preferred trying to separate the atropisomers of disulfonyl chlorides **14** that have the same chiral structure as **3**. Their separation was possible by semi-preparative chiral HPLC.

In particular, **14a** owns only one structural motif that leads to atropisomerism and this is due to the hindered rotation of the aryl group bonded to the 3 position carbon. It is worth noting that no hindered rotation of the aryl group bonded to the 6 position carbon takes place due to the lack of methyl group in the 5 position.[10a]

The racemic mixture of **14a** (40 mg) was chromatographed on a semipreparative Chiralpak IC column. The two atropisomers (-)**14a** and (+)**14a**, eluted as single peaks, were collected (respectively 19.2 mg and 20.8 mg; ratio 1: 1.08), after the solvents were removed under nitrogen flow (Figure 3).

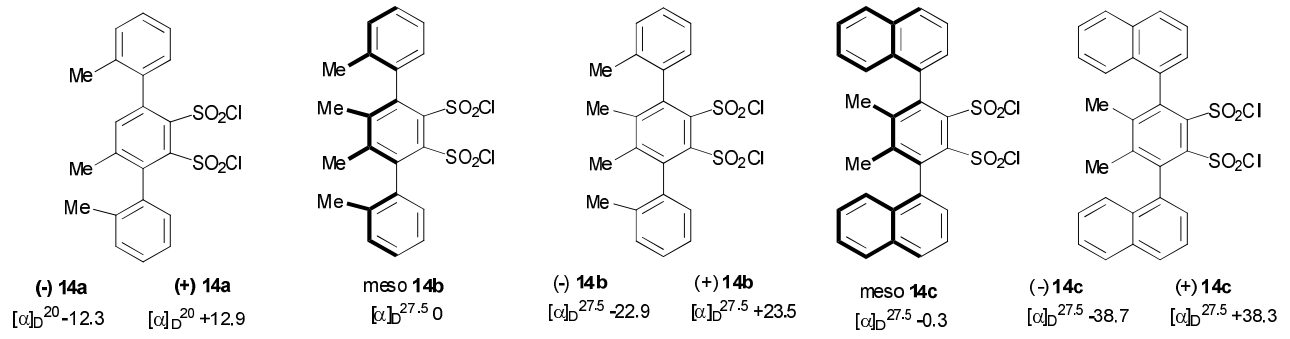


Figure 3 Atropisomers of **14.**

The situation is different for **14b** and **14c** for which there are two *identical* structural motifs that lead to the atropisomerism. For this reason, there is also *a meso form* in addition to the two atropisomers. Regarding **14b**, the mixture of atropisomers and meso form (40 mg) was chromatographed on a semipreparative Chiralpak IC column using an isocratic elution. We thus separated the meso form (the first eluted compound, 19.8 mg) from a racemic mixture of two atropisomers (the second eluted compound, 20.2 mg); ratio 1: 1.02.

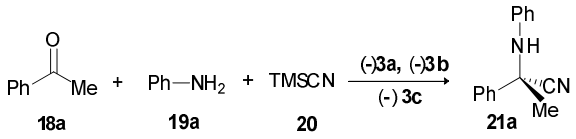
Then, another run (20 mg) allowed us to separate the atropisomer (-)**14b** (Figure 3; the first eluted compound, 9.5 mg), from the atropisomer (+)**14b** (Figure 3; the second eluted compound, 10.5 mg); ratio 1: 1.1. The same procedure was employed to separate the atropisomers of **14c** (40 mg). First, we separated the meso form (the first eluted compound, 20.4 mg) from a racemic mixture of two atropisomers (the second eluted compound, 19.6 mg); ratio 1.04: 1. Then, another run (19 mg) allowed us to separate the atropisomer (-)**14c** (Figure 3; the first eluted compound, 9.4 mg), from the atropisomer (+)**14c** (Figure 3; the second eluted compound, 9.6 mg); ratio 1: 1.02.

Finally, the separated atropisomers (-)**14a**-**c** were easily transformed into the corresponding (-) **3a-c** (Scheme 2).

3. Use of (-) atropisomers of 3 as catalysts

We reported that **2** catalyzed the Strecker reaction between acetophenone (**18a**), aniline (**19a**) and TMSCN (**20**) although it gave poor enantioselectivity (Table 1, entries 2 and 3).[10b]

In the light of this, we decided to test the (-) atropisomer of **3** in this model reaction (Scheme 4), in the same conditions as previously employed.[10b]



Scheme 4 Strecker reaction with chiral catalysts **3.**

The results were encouraging and are collected in Table 1. The use of (-) **3a** led to an increase in ee in 2-phenylaminopropanenitrile (**21a**; Table 1, entries 4 and 5). But the best results were obtained using (-) **3b.** The ee increased up to 84% when the reaction was carried out at 0° C (Table 1, entry 6) and further cooling to – 20° C increased it up to 94% (Table 1, entry 7). The yield however diminished as a small amount of the unreacted starting products was still present; **3c** was also a good chiral catalyst (Table 1, entries 8 and 9). From these data, it is evident that *C2* symmetry is essential to obtaining a good enantioselectivity.

Table 1 Three-component Strecker reaction between **18a**, **19a** and **20** catalyzed by chiral catalysts (-) **2** and (-) **3**

Entry	Catalyst	Temp. (°C)	Time (min)	Yield (%)[a,b] of **21a**	E.r. in **21a**	E.e. (%) in **21a**
1[10b]	**1**	rt	5	95	51:49	-
2[10b]	**2**	rt	5	92	66:34	32
3[10b]	**2**	0	180	88	78:22	56
4	**3a**	0	120	85	82:18	64
5	**3a**	-20	360	65	84:16	68
6	**3b**	0	120	86	92:8	84
7	**3b**	-20	360	70	97:3	94
8	**3c**	0	120	84	90:10	80
9	**3c**	-20	360	72	96:4	92

[a]All the reactions were performed with 5 mol% of **3** (10 mg); reactants **18a** and **19a** were in equimolar amounts (see experimental section). TMSCN (**20**) was in slight excess (1.1 eq). [b]Yields refer to the pure and isolated products.

Catalyst **3b** was easily recovered and used in another two consecutive catalytic cycles. The results are listed in Table 2. The enantiomeric excess was good in all cases.

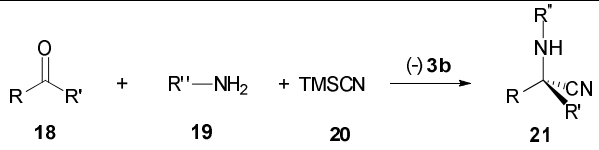
Table 2 Consecutive runs with recovered (-)**3b**.

Entry	Time (min)	Yield (%) of **21**[a,b]	Recovery (%) of **3b**	E.e. (%) in **21**
1	120	86	95, 9.5 mg[c]	84
2	120	85	86, 8.2 mg[d]	82
3	180	89	82, 6.7 mg	81

[a] Yields refer to the pure products. [b] The reaction was performed at 0 °C with 0.0468 mmol of **18a** and **19a,** 0.05148 mmol of **20** and 5 mol% of **3b** (10 mg, 0.0234 mmol). [c]Recovered **3b** was used as a catalyst in entry 2. [d] Recovered **3b** was used as a catalyst in entry 3.

The high enantiomeric excesses achieved encouraged us to further exploit catalyst **3b** in Strecker reactions. A selection (15 examples) of good results is collected in Table 3. The presence of electron-donating or electron-withdrawing groups on the aromatic ring of **18** or **19** did not affect the enantioselectivity of the reactions which generally provided excellent enantiomeric excecess. Even with aliphatic **18l** and aldehydes **18m-p** very good results were obtained.

Table 3 Three-component Strecker reaction catalyzed by (-)**3b**.

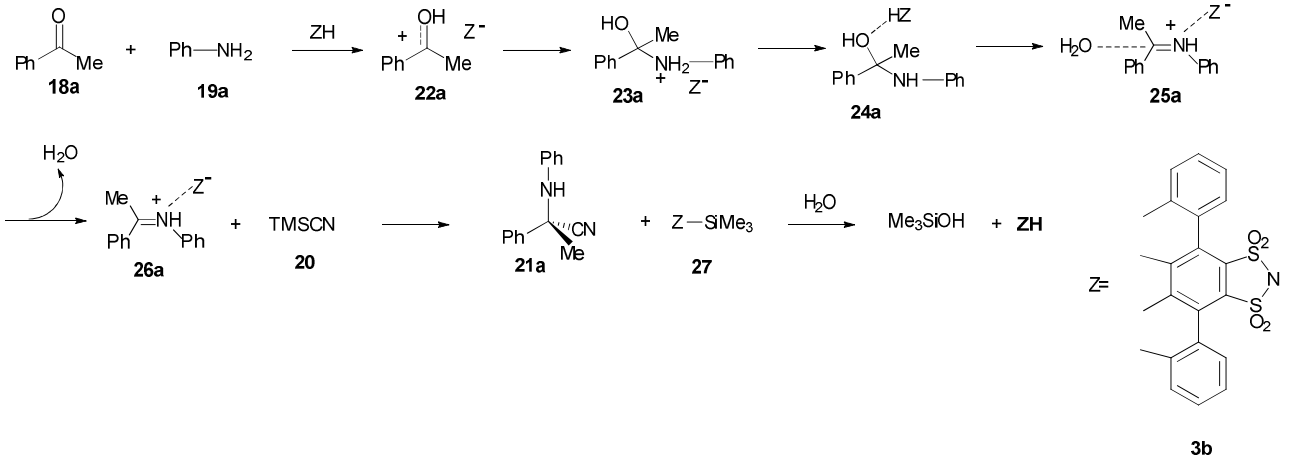


Entry	R	R'		R''		Products	Yield	Time	E.e
	in **18,21**	in **18,21**		in **19,21**		**21**	(%)[a,b]	(h)	in **21** (%)
1	Ph	Me	**18b**	4-$MeOC_6H_4$	**19b**	**21b**	69	6	95
2	Ph	Me	**18c**	4-$NO_2C_6H_4$	**19c**	**21c**	65	6	93
3	Ph	Me	**18d**	4-BrC_6H_4	**19d**	**21d**	61	7	92
4	Ph	Me	**18e**	4-FC_6H_4	**19e**	**21e**	64	5	93
5	Ph	Me	**18f**	2-$MeOC_6H_4$	**19f**	**21f**	68	6	82
6	Ph	Me	**18g**	3-$MeOC_6H_4$	**19g**	**21g**	70	6	89
7	4-MeC_6H_4	Me	**18h**	Ph	**19h**	**21h**	68	7	88
8	4-MeC_6H_4	Me	**18i**	4-$NO_2C_6H_4$	**19j**	**21i**	72	6	93
9	4-MeC_6H_4	Me	**18j**	4-$MeOC_6H_4$	**19k**	**21j**	68	5	97
10	4-$NO_2C_6H_4$	Me	**18k**	4-$MeOC_6H_4$	**19l**	**21k**	74	8	95
11	*n*Pr	Me	**18l**	Ph	**19m**	**211**	71	8	87

12	Ph	H	**18m**	Ph	**19n**	**21m**	80	2	88
13	4-$NO_2C_6H_4$	H	**18n**	Ph	**19o**	**21n**	85	2	95
14	4-MeC_6H_4	H	**18o**	Ph	**19p**	**21o**	88	2	89
15	2-Thienyl	H	**18p**	Ph	**19q**	**21p**	84	2	89

[a]All the reactions were performed at -20 °C with 5 mol% of **3b** (10 mg); the reactants **18** and **19** were in equimolar amounts (see experimental section). TMSCN (**20**) was in slight excess (1.1 eq). [b]Yields refer to the pure and isolated products.

Theoretical calculations have allowed us to explain the mechanism of the Strecker reaction catalyzed by **1**.[10b] The same mechanism should be used in the reactions catalyzed by **3b** (Scheme 5).



Scheme 5 Mechanism of three-component acid-catalysed Strecker reaction catalyzed by **3b.**

In particular, the intermediate **26a** should be crucial to carrying out this reaction in a highly enantioselective fashion. However, it must be stressed that this is only an hypothesis and in order to fully explain the role of **3b** as chiral catalyst, depth mechanistic studies are planned.

According to these data, this chiral Brønsted acid catalyzed reaction could be classified as ACDC.[2a] Infact, List[2a] has recently introduced the concept of asymmetric counteranion-directed catalysis (*ACDC*) in which the induction of enantioselectivity in a reaction *proceedees through a cationic intermediate by means of ion pairing with a chiral and enantiomerically pure anion provided by the catalyst.*

Conclusions

A protocol for the synthesis of three chiral derivatives of *o*-benzenedisulfonimide, namely **3a**, **3b** and **3c** was developed under easy and moderate reaction conditions and with good overall yields.

In particular, the atropisomers (-) **3b** showed a good enantioselectivity in Strecker reaction (16 examples, average ee 91%) and proved to be interesting chiral catalysts. In fact, *C2* simmetry[11a-b] and the presence of aryl substituents on the sulfonimidic ring (even without electron-withdrawing groups) created a chiral fashion allowing to have a high enantioselectivity. In order to confirm these good results, (-) **3b** will, of course, be tested in further reactions. Clearly, a shortcoming of this synthetic protocol is its lack of enantioselectivity. It is well known that chiral biaryl compounds have been easily synthesized in very good ee via catalytic asymmetric Suzuki coupling.[14] In order to obtain enantiomerically pure **15** (one of the precursors to **3b**; Scheme 3), we could carry out this coupling in the presence of a chiral ligand. However, in the step in which **12** was converted into **13,** the formation of a benzyne intermediate occurred (Scheme 2). Most likely, this benzyne is not enough hindered to prevent the rotation of the aryl group so that the previously achieved enantiomeric purity is lost.

Since (-) **3b** and (-) **3c** have proved to be (at least in the Strecker reaction) good chiral catalysts, we will dedicate future research to developing an effective enantioselective synthetic protocol that allows strictly chiral derivatives of **1** to be obtained, without having to separate the various atropisomers. In addition, we will also evaluate the possibility of synthesizing derivatives with more bulky aromatic groups which may also bear electron-withdrawing substituents.

Experimental

General

Analytical grade reagents and solvents were used and reactions were monitored 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 (rt)

is 20–25 °C. Mass spectra were recorded on an HP5989B mass selective detector connected to an HP 5890 GC with a cross-linked methyl silicone capillary column. ESI-MS spectra were obtained using a Waters micromass ZQ spectrometer equipped with an ESI ion source. Chiral analyses were performed on a Perkin-Elmer Autosystem GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-O-methyl-6-O-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Avance 200 spectrometer at 200 and 50 MHz respectively. IR spectra were recorded on a IR Perkin-Elmer UATR-two spectrometer. HPLC separations were performed on HPLC Waters 1525 connected to a column Chiralpack IA-SFC. For the determination of optical rotations, a Jasco P-2000 polarimeter was used. All reagents were purchased from Sigma-Aldrich. Satisfactory microanalyses were obtained for all new compounds. Syntheses, physical and spectral data of compounds **5, 7, 8, 10, 11, 12, 13, 15** and **16** precursors of **14a, 14b** and **14c** are reported in Electronic supplementary information (ESI).

Synthesis of 1,2-benzenedisulfonyl chlorides 14

1,3-Benzodithiole (**13**; 2 mmol) was dissolved in *t*-butyl alcohol (20 mL), CH_2Cl_2 (16 mL) and H_2O (3 mL).The resulting mixture was cooled to 0 °C. Chlorine was bubbled through while the temperature was maintained at 0 °C and the reaction mixture vigorously stirred. The reaction was monitored on TLC (PE/EtOAc 7:3). After 1 h, when the spot of **13** 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 (100 mL). The combined organic extracts were washed with a 5% NaOH solution (100 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue, purified in a chromatography column (PE/EtOAc 7:3) afforded pure **14.**

4-Methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (14a). Couple of atropisomers. White waxy solid (0.86 g, 91% yield). Found: C 53.76; H 3.92; Cl 15.07; S 13.71. $C_{21}H_{18}Cl_2O_4S_2$ requires: C 53.74; H 3.87; Cl 15.11; S 13.66%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.32–7.15 (m, 8H), 2.24 (s, 3H), 2.09 (s, 3H) 2.01 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.9, 147.5, 145.8, 145.2, 143.5, 141.2, 140.5, 138.2, 137.0, 136.0, 135.8, 130.9, 130.5, 129.7, 129.5, 128.7, 126.2, 125.6, 21.2, 21.1, 20.5. MS (ESI +) *m/z*: 469.12 $(M + H)^+$ .IR (neat) ν (cm^{-1}): 1383, 1175 (SO_2).

Compound **14a** (40 mg) was chromatographed on a semipreparative Chiralpak IC column (F 10 x 250 mm, Daicel, Osaka, Japan) using an isocratic elution with heptane/CH_2Cl_2 (4:1) at a flow rate of 3.0 mL/min. The compounds eluted from the column were monitored using a photodiode array detector. Two compounds

(respectively 19.2 mg and 20.8 mg), eluted as single peaks at 7.90 and 11.97 min, were collected, after removing the solvents under nitrogen flow.

The first was (-) 4-methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (**14a**; waxy white solid). $[a]_D^{20}$ -12.3 (c 0.18, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of two atropisomers.

The second was (+) 4-methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (**14a**; waxy white solid). $[a]_D^{20}$ + 12.9 (c 0.18, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of two atropisomers.

Circular dichroism studies are underway to determinate the absolute configuration of the atropisomers (-)**14a.**

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4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (14b). Mixture of diastereomers (*meso* isomer and a couple of atropisomers). Waxy white solid (0.84 g; 87% yield). Found: C 54.61; H 4.21; Cl 14.78; S 13.19. $C_{22}H_{20}Cl_2S_2O_4$ requires: C 54.66; H 4.17; Cl 14.67; S 13.26%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.10 (m, 8H), 2.09, 2.03, 1.98 and 1.96 (4s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.8, 144.6, 144.3, 137.8, 136.7, 136.3, 135.7, 130.7, 130.4, 130.2, 129.5, 129.4, 125.9, 125.8, 20.6, 20.4, 19.0, 18.6. MS (ESI +) *m/z*: 483.24 $(M + H)^+$ .IR (neat) ν (cm^{-1}): 1380, 1173 (SO_2).

Compound **14b** (40 mg) was chromatographed on a semipreparative Chiralpak IC column (F 10 x 250 mm, Daicel, Osaka, Japan) using an isocratic elution with heptane/CH_2Cl_2 (3:2) at a flow rate of 5.0 mL/min. The compounds eluted from the column were monitored using a photodiode array detector. Two compounds (respectively 19.8 mg and 20.2 mg), eluted as single peaks at 5.12 and 6.57 min, were collected, after removing the solvents under nitrogen flow.

The first was the meso isomer. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.10 (m, 8H), 2.09 (s, 3 H), 1.98 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.8, 144.6, 137.8, 136.7, 135.7, 130.7, 130.4, 129.5, 125.9, 20.6, 19.0. $[a]_D^{27.5}$ 0.0 (c 0.10, CH_2Cl_2). The second was a couple of atropisomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.10 (m, 8H), 2.03 (s, 3 H), 1.96 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.6, 144.3, 137.8, 136.3, 135.7, 130.7, 130.2, 129.4, 125.8, 20.4, 18.6). $[a]_D^{27.5}$ + 0.1 (c 0.10, CH_2Cl_2).

The second eluted compound (20 mg) was again chromatographed on a semipreparative Chiralpak IC column (F 10 x 250 mm, Daicel, Osaka, Japan) using an isocratic elution with heptane/CH_2Cl_2 (4:1) at a flow rate of 3.0 mL/min. The compounds eluted from the column were monitored with a photodiode array detector. Two compounds (respectively 9.5 mg and 10.5 mg), eluted as single peaks at 10.44 and 14.42 min, were collected, after removing the solvents under nitrogen flow.

The first one was (-) 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (**14b**; waxy white solid). $[a]_D^{27.5}$ -22.9 (c 0.15, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of atropisomers.

The second one was (+) 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonyl chloride (**14b**; waxy white solid). $[a]_D^{27.5}$ + 23.5 (c 0.15, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of atropisomers.

Circular dichroism studies are underway to determinate the absolute configuration of the atropisomers (-)**14b.**

4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonyl chloride (14c). Mixture of diastereomers (*meso* isomer and a couple of atropisomers). Waxy white solid (0.89 g; 80% yield). Found: C 60.51; H 3.67; Cl 12.80; S 11.52. $C_{28}H_{20}Cl_2S_2O_4$ requires: C 60.54; H 3.63; Cl 12.76; S 11.54%. ^{1}H NMR (200 MHz, CDCl3): δ = 7.68–7.44 (m, 10 H), 1.98 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.8, 137.6, 134.6, 134.2, 133.9, 133.8, 133.6, 132.5, 132.0, 131.8, 131.7, 128.4, 128.1, 127.5, 127.1, 126.9, 126.6, 126.2, 126.1, 125.2, 125.1, 19.2, 19.0. MS (ESI +) *m/z*: 555.31 $(M + H)^+$.IR (neat) ν (cm^{-1}): 1384, 1171 (SO_2).

Compound **14c** (40 mg) was chromatographed on a semipreparative Chiralpak IC column (F 10 x 250 mm, Daicel, Osaka, Japan) using an isocratic elution with heptane/CH_2Cl_2 (3:2) at a flow rate of 5.0 mL/min. The compounds eluted from the column were monitored with a photodiode array detector. Two compounds (respectively 20.4 mg and 19.6 mg), eluted as single peaks at 12.11 and 17.23 min, were collected, after removing the solvents under nitrogen flow.

The first one was the *meso* isomer. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.44 (m, 10 H), 1.98 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.8, 134.6, 134.2, 133.9, 133.6, 132.5, 131.7, 128.4, 127.5, 127.1, 126.6, 126.2, 125.2, 19.2. $[a]_D^{27.5}$ -0.3 (c 0.15, CH_2Cl_2). The second one was a couple of atropisomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.40 (m, 10H), 1.98 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.6, 134.6, 134.2, 133.8, 133.6, 132.0, 131.7, 128.1, 127.5, 126.9, 126.6, 126.1, 125.1, 19.0. $[a]_D^{27.5}$ -0.1 (c 0.15, CH_2Cl_2).

The second eluted compound (19 mg) was again chromatographed on a semipreparative Chiralpak IC column (F 10 x 250 mm, Daicel, Osaka, Japan) using an isocratic elution with heptane/MeOH (9:1) at a flow rate of 3.0 mL/min. The compounds eluted from the column were monitored with a photodiode array detector. Two compounds (respectively 9.4 mg and 9.6 mg), eluted as single peaks at 9.33 and 14.27 min, were collected, after removing the solvents under nitrogen flow.

The first was (-) 4,5-dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonyl chloride (**14c**; waxy white solid). $[a]_D^{21.5}$ -38.7 (c 0.10, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of atropisomers.

The second was (+) 4,5-dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonyl chloride (**14c**; waxy white solid). $[a]_D^{21.5}$ + 38.3 (c 0.10, CH_2Cl_2). Spectral data was identical to what had been reported for the couple of atropisomers.

Circular dichroism studies are underway to determinate the absolute configuration of the atropisomers (-)**14c.**

Synthesis of 1,2-benzenedisulfonimides 3

1,2-Benzenedisulfonyl chloride (**14**; 2 mmol) was dissolved in toluene (8 mL) and EtOH (12 mL). The resulting mixture was cooled to 0 °C. Ammonia was bubbled through while the temperature was mainteined at 0 °C and the reaction mixture vigorously stirred. The reaction was monitored by TLC (PE/EtOAc 7:3). After 30 min, the reaction was complete. 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 pure **3**.

4-Methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3a). Grey waxy solid (0.75 g, 90%). Found: C 61.02; H 4.68; N 3.33; S 15.54. $C_{21}H_{19}NO_4S_2$ requires: C 61.00; H 4.63; N 3.39; S 15.51%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.32–7.18 (m, 8H), 2.15 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.9, 145.7, 138.4, 138.0, 137.4, 136.7, 136.5, 136.3, 135.4, 134.2, 132.7, 130.5, 129.8, 129.6, 126.4, 126.3, 125.9, 125.8, 20.5, 20.4, 19.9. MS (ESI +) *m/z*: 414.63 $(M + H)^+$.IR (neat) ν (cm^{-1}): 3004 (NH),1362, 1151(SO_2).

(-) 4-Methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3a). The title compound (grey waxy solid; 32 mg, 77% yield) was obtained from (-) 4-methyl-3,6-bis(2-tolyl)-1,2-benzenedisulfonyl chloride (**14a**; 0.1 mmol, 47 mg) as reported above.

$[a]_D^{21}$ -14.8 (c 0.15, CH_2Cl_2). Spectral data was identical to what had been reported for the mixture of two atropisomers.

4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3b). Mixture of diastereomers (*meso* isomer and a couple of atropisomers). Grey waxy solid (0.77 g; 90% yield). Found: C 61.77; H 4.92; N 3.33; S 15.04. $C_{22}H_{21}NO_4S_2$ requires: C 61.81; H 4.95; N 3.28; S 15.00%. ^{1}H NMR (200 MHz, CDCl3): δ = 7.39–7.14 (m, 8H), 2.05 (s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 137.1, 136.9, 136.7, 135.4, 133.6, 130.5, 129.9, 129.8, 126.3, 126.2, 20.1, 19.9, 17.6. MS (ESI +) *m/z*: 428.01 $(M + H)^+$.IR (neat) ν (cm^{-1}): 3001 (NH),1360, 1156 (SO_2).

(-) 4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3b). The title compound (pale grey waxy solid; 35 mg, 82% yield) was obtained from (-) 4,5-dimethyl-3,6-(bis-2-tolyl)-1,2-benzenedisulfonyl chloride (**14b**, 0.1 mmol, 48 mg) as reported above.

$[a]_D^{27}$ -18.4 (c 0.12, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 8H), 2.05 (s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 137.1, 136.9, 136.7, 135.4, 133.6, 130.5, 129.8, 126.3, 19.9, 17.6.

4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide (3c). Mixture of diastereomers (*meso* isomer and a couple of atropisomers). Grey waxy solid (0.98 g; 88% yield). Found: C 67.40; H 4.21; N 2.74; S 12.84. $C_{28}H_{21}NO_4S_2$ requires: C 67.32; H 4.24; N 2.80; S 12.83%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.43–8.29 (m, 2H), 7.92–7.29 (m, 8H), 2.05 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.1, 140.0, 137.5, 137.4, 135.7, 135.5, 135.4, 135.1, 133.1, 130.2, 128.6, 128.2, 128.1, 128.0, 127.0, 126.3, 120.3, 120.2, 19.3, 19.2. MS (ESI +) *m/z*: 500.11 $(M + H)^+$.IR (neat) ν (cm^{-1}): 2998 (NH),1357, 1159 (SO_2)

(-) 4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide (3c). The title compound (pale grey waxy solid; 36 mg, 72% yield) was obtained from (-) 4,5-dimethyl-3,6-(bis-1-naphthyl)-1,2-benzenedisulfonyl chloride (0.1 mmol, 55 mg) as reported above.

$[a]_D^{21}$ -45.4 (c 0.15, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.36–8.29 (m, 2H), 8.36–8.29 (m, 2H), 7.92–7.29 (m, 8H), 2.05 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.0, 137.5, 135.7, 135.4, 135.1, 133.1, 130.2, 128.6, 128.2, 128.0, 127.0, 126.3, 120.2, 19.3.

Chiral sulfonimides 3 as catalysts in Strecker reaction

(-) 4-Methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3a) as a catalyst

1. TMSCN (**20**, 53 mg, 0.53 mmol) was added to a mixture of (-) 4-methyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**3a**; 5 mol%; 10 mg, 0.0242 mmol), acetophenone (**18a**, 58 mg, 0.484 mmol) and aniline (**19a**, 45 mg, 0.484 mmol) that had been cooled to 0 °C. The mixture was stirred at 0 °C for 3 hours until the GC and GC-MS analyses showed the complete disappearance of starting compounds and the complete formation of 2-phenyl-2-phenylaminopropanenitrile (**21a**). Cold H_2O (2 ml) was added to the reaction mixture, under vigorous stirring. The resulting solid was filtered on a Hirsch funnel and washed with additional cold H_2O (2 × 1 ml) and small amount of PE (1 ml). It was virtually pure (GC, GC-MS, ^{1}H NMR, ^{13}C NMR), 2-phenyl-2-phenylaminopropanenitrile (**21a;** white solid; 89 mg, 83% yield). Spectral and physical data was identical to what had been reported in the literature.[15] After analyzing **21a** on a GC with a chiral column, the presence of two enantiomers was found; enantiomeric ratio (er) was 82:18; enantiomeric excess (ee) was 64%.

2. The reaction was carried out at -20 °C and small amounts of **18a** and **19a** were detected by GC and GC-MS analyses after 6 hours. However, the reaction was stopped. The yield of **21a** was 65% (70 mg).

After analyzing **21a** on a GC with a chiral column, the presence of two enantiomers was found; er was 87:12; ee was 75%.

(-) 4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (3b) as a catalyst

1. (-) 4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**3b**; 5 mol%; 10 mg, 0.0234 mmol). The amounts of **18a**, **19a** and **20** were respectively 56 mg (0.0468 mmol), 43 mg (0.0468 mmol), 51 mg (0.0515 mmol) .At 0 °C the yield of **21a** was 86% (88 mg). After analyzing **21a** on a GC with a chiral column the presence of two enantiomers was found; er 92:8; ee was 84%. The aqueous washings were collected and evaporated under reduced pressure. After the removal of H_2O, virtually pure (^{1}H NMR) **3b** was recovered (9.5 mg, 95 % yield). The recovered **3b** was employed in another two catalytic cycles under the conditions described above. Table 2 reported the yields of **21a** and the yields of recovered **3b**.

2. The reactions was carried out at -20 °C and small amounts of **18a** and **19a** were detected by GC and GC-MS analyses after 6 hours. However, the reaction was stopped. The yield of **21a** was 70% (73 mg). After analyzing **21a** on a GC with a chiral column the presence of two enantiomers was found; er was 97:3; ee was 94%.

In the same conditions, 2-(4-methoxyphenyl)-2-phenylaminopropanenitrile (**21b**),[16] 2-(4-nitrophenyl)-2-phenylaminopropanenitrile (**21c**),[10b] 2-(4-bromophenylamino)-2-phenylpropanenitrile (**21d**),[10b] 2-(4-fluorophenylamino)-2-phenylpropanenitrile (**21e**),[10b] 2-(2-methoxyphenyl)-2-phenylaminopropanenitrile (**21f**),[10b] 2-(3-methoxyphenylamino)-2-phenylpropanenitrile (**21g**),[16] 2-phenylamino-2-(4-tolyl)propanenitrile (**21h**),[17] 2-(4-nitrophenylamino)-2-(4-tolyl)propanenitrile (**21i**),[10b] 2-(4-methoxyphenylamino)-2-(4-tolyl)propanenitrile (**21j**),[10b] 2-(4-methoxyphenylamino)-2-(4-nitrophenyl)propanenitrile (**21k**),[16] 2-methyl-2-phenylaminopentanenitrile (**21l**), 2-phenyl-2-phenylaminoacetonitrile (**21m**)[18], 2-(4-nitrophenyl)-2-phenylaminoacetonitrile (**21n**)[19], 2-(4-tolyl)-2-phenylaminoacetonitrile (**21o**)[20] and 2-(2-thienyl)-2-phenylaminoacetonitrile (**21e**)[21] were obtained. The yields and the ee of each of these compounds are reported in Table 3. Their spectral and physical data (reported in Electronic supplementary information) are identical to those reported in the literature, with the only ecception of **21l**, unknown in the literature.

2-Methyl-2-phenylaminopentanenitrile (21l). Viscous oil (65 mg, 71%). Found: C 76.51; H 8.55; N 14.92. $C_{12}H_{16}N_2$ requires: C 76.56; H 8.57; N 14.88%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.10 (m, 2H), 6.88–6.82 (m, 3H), 3.58 (br s, 1H), 1.97–1.75 (m, 2H), 1.64–1.44 (m, 2H), 1.58 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.1, 129.5, 121.9, 120.6, 117.4, 53.0, 42.7, 25.8, 17.7, 14.1. MS (EI) *m/z*: (%) 188 [M^+](5), 161 (35), 146 (45), 118 (100), 77 (55). IR ($CHCl_3$) ν (cm^{-1}): 3431 (NH), 2249 (CN).

(-) 4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide (3c) as a catalyst

1. 4,5-Dimethyl-3,6-bis(1-naphthyl)-1,2-benzenedisulfonimide (**3c**; 5 mol%; 10 mg, 0.02 mmol). The amounts of **18a**, **19a** and **20** were respectively 48 mg (0.04 mmol), 37 mg (0.04 mmol), 44 mg (0.044 mmol). At 0 °C the yield of **21a** was 84% (75 mg). After analyzing **21a** on a GC with a chiral column the presence of two enantiomers was found; er was 90:10; ee was 80%.

2. The reaction was carried out at -20 °C and small amounts of **18a** and **19a** were detected by GC and GC-MS analyses after 6 hours. However, the reaction was stopped. The yield of **21a** was 72% (64 mg). After analyzing **21a** on a GC with a chiral column the presence of two enantiomers was found; er was 96:4; ee was 92%.

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