Synthesis of a New Chiral Sulfonic Acid A New Chiral Sulfonic Acid

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Synthesis of a New Chiral Sulfonic Acid

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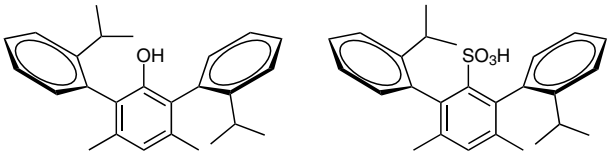
Abstract: A convenient route to an original chiral sulfonic acid is disclosed. The synthesis is based on an optimized and regioselective direct bis-orthoarylation of a commercially available phenol, followed by a Newman–Kwart rearrangement. Resolution by preparative chiral HPLC and oxidative cleavage give the targeted Brønsted acid in >99% ee.

Key words: Brønsted acid, sulfonic acid, Pinhey–Barton reaction, Newman–Kwart rearrangement, synthesis

The research field dedicated to chiral Brønsted acid catalysis has grown enormously during the last few years. BINOL derived chiral phosphoric acids have emerged as effective catalysts for various enantioselective transformations.[1] Even if numerous applications have appeared, the uses of these Brønsted acids are generally restricted to the electrophilic activation of imines with a proper basic character. As a consequence, many efforts are devoted to improve the acidity of the catalyst in order to widen the scope of activation to functionalities such as carbonyl, hydroxy, or double bonds.[2] Mostly, modifications of the phosphoric acid moiety by the appropriate introduction of electron-withdrawing group (triflyl) or substitution of oxygen atoms with more stabilizing ones (sulfur or selenium) are reported.[3] Interestingly, the design of chiral strong sulfonic acids has been less investigated. For example, the bis-sulfonic acids based on a chiral binaphthyl backbone (BINSA) have failed to deliver any useful selectivity.[4] However, DFT calculations have shown that sulfonic acids behaved as bifunctional catalysts similarly to phosphoric acids.[5] In this context, there is still a need for new chiral sulfonic acids with suitable chiral environment and appropriate acidity to activate a broad range of functionalities.

A few years ago, Yamamoto reported phenol **1** bearing C_2 symmetry elements as an efficient chiral auxiliary for aldol and Mannich reactions (Figure 1).[6] As a consequence, the sulfonic acid **2** based on this chiral scaffold was envisioned as a candidate for the development of a new catalyst. In this contribution, we report on the synthesis and the resolution of this new Brønsted acid.

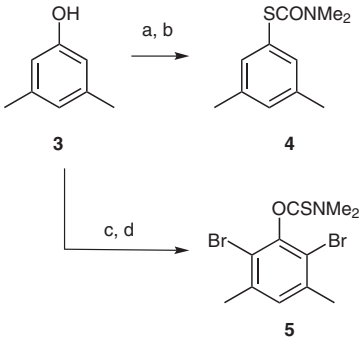
Several strategies were investigated for the synthesis of the sulfonic acid **2**. All synthetic approaches shared the cheap commercially available 3,5-dimethylphenol (**3**) as



1 2

Figure 1 Structure of phenol **1**

the starting material and relied on a Newman–Kwart rearrangement of an *O*-aryl thiocarbamate to introduce the sulfur moiety.[7] Initially, it was thought to introduce aryl *ortho*-substituents by using a suitably halogenated thiocarbamate. Accordingly, the *S*-aryl thiocarbamate **4** was easily synthesized from 3,5-dimethylphenol (**3**) (Scheme 1), but its regioselective 2,6-dibromination proved to be unsuccessful.



Scheme 1 Unsuccessful attempts for the preparation of **2**. *Reagents and conditions*: a) $ClCSNMe_2$, K_2CO_3, acetone, 65 °C; b) neat, 250 °C, 66% from **3**; c) Br_2, *t*-$BuNH_2$, toluene, –78 °C; d) $ClCSNMe_2$, K_2CO_3, acetone, 65 °C, 46% from **3**.

Then, an electrophilic bromination was carried out earlier in the synthesis, and *O*-aryl thiocarbamate **5** was prepared in two steps from phenol **3** (Scheme 1).[6b] Unfortunately, no conversion was observed for the Suzuki–Miyaura coupling of **5** with 2-isopropylbenzeneboronic acid, probably due to the increased steric hindrance developed by the bulky thiocarbamate group.

As the late introduction of aryl substituents was ineffective, the biarylphenol **1** was prepared from phenol **3** following two methods (Scheme 2). According to reaction conditions developed previously,[3b] the Suzuki–Miyaura coupling of dibromophenol **6** with 2-isopropylbenzeneboronic acid afforded an excellent 91% yield of an inseparable 5:1 mixture of racemic and *meso*-phenol **1**.

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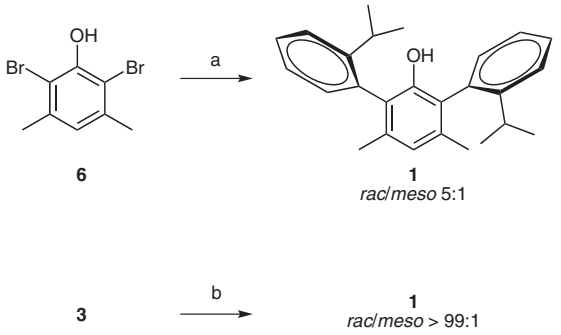


Scheme 2 Regioselective bis-orthoarylation of phenol **3**. *Reagents and conditions*: a) $Pd(dba)_2$, *S*-Phos, 2-(*i*-Pr)$C_6H_4B(OH)_2$, K_3PO_4, toluene, 100 °C, 20 h, 91%; b) 2-(*i*-Pr)$C_6H_4Pb(OAc)_3$, DABCO, toluene, r.t., 82%.

The second strategy involved a Pinhey–Barton arylation using (2-isopropyl)phenyllead triacetate in the presence of DABCO. This reaction afforded stereoselectively the racemic phenol **1** in 82% yield (Scheme 2).[8] The required 2-isopropylphenyllead(IV) triacetate was easily prepared on large scale through a mercury-catalyzed boron–lead exchange.[9] Finally, racemic phenol **1** was treated with dimethylaminothiocarbamoyl chloride under vigorous conditions to afford the *O*-aryl thiocarbamate **7** in 75% yield (Scheme 3).

The Newman–Kwart rearrangement[7] of **7** was carried out under microwave irradiation at different temperatures.[10] The formation of a 1:1 mixture of easily separable *rac*-**8** and *meso*-**9** *S*-aryl thiocarbamates was systematically observed (Scheme 3). When the conversion was incomplete, isomerization of racemic **7** was observed by ^{1}H NMR spectroscopy, thus suggesting that the latter occurred prior to the rearrangement. Attempts to decrease the temperature in order to avoid the formation of *meso*-isomer **9** using the recently published Pd-catalyzed rearrangement[11] were unsuccessful.

After optimization, the sulfonic acid precursor **8** was isolated in 45% yield (Scheme 3). The moderate yield of the reaction could be improved by equilibrating the isolated *meso*-**9** at 285 °C under microwave irradiation. The relative configuration of **9** was undoubtedly determined by X-ray diffraction study of a single crystal (Figure 2). Then, racemic acid **2** was easily obtained through the oxidative cleavage of **8** with hydrogen peroxide in formic acid.[12]

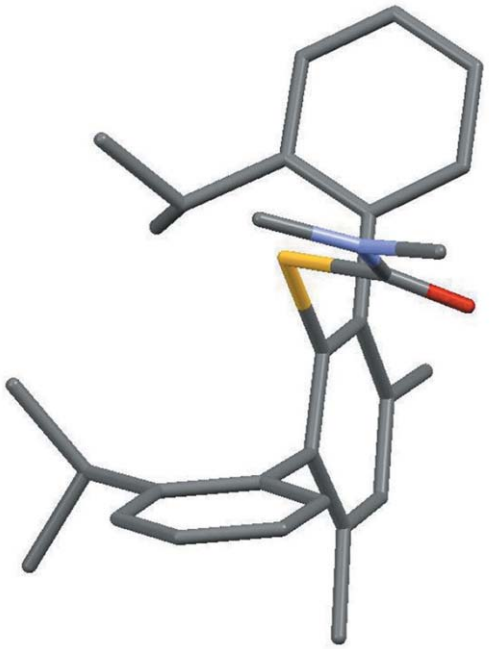
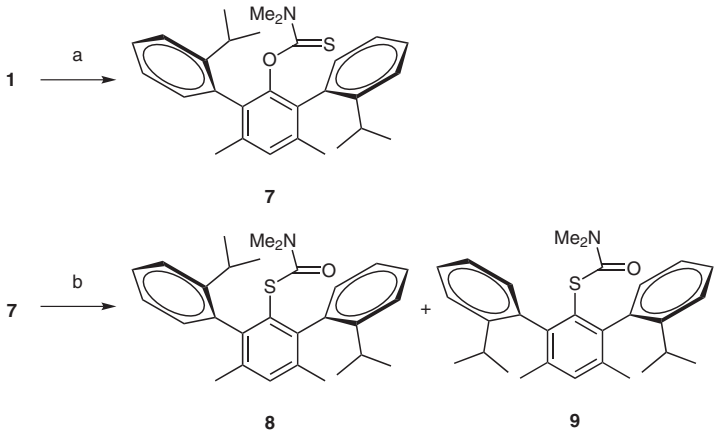


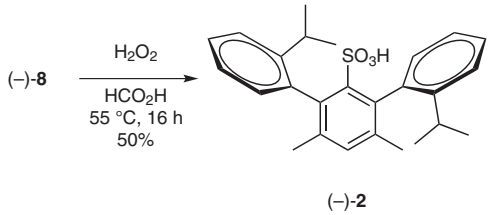
Figure 2 X-ray diffraction structure of *meso*-thiocarbamate **9**

The resolution of sulfonic acid **2** was attempted following several approaches. In the presence of chiral α-methylbenzylamine, no suitable crystallization was observed. Derivatization of the corresponding sulfonyl chloride to sulfonate or sulfonamide diastereomers failed due to lack of reactivity, even in the presence of lithium (*R*)-2-ethylphenylamide. These unsuccessful results suggested a very high steric hindrance around the sulfur moiety. Finally, the resolution of *S*-aryl thiocarbamates **8** was achieved by preparative chiral HPLC.[13] Using simple conditions [Daicel Chiralpak® IA, *n*-heptane–*i*-PrOH (98:2), 20 °C, 1 mL/min] both enantiomers of **8** were obtained in enantiopure form in gram quantities. The (–)-*S*-thiocarbamate **8** was oxi-



Scheme 3 Newman–Kwart rearrangement. *Reagents and conditions*: a) $ClCSNMe_2$, NaH, THF, 70 °C, 75%; b) neat, MW 220 °C, 45%.

dized using in situ generated performic acid to afford the desired sulfonic acid (–)-**2** in 50% yield (Scheme 4).



Scheme 4 Oxidation of thiocarbamate into sulfonic acid

In conclusion, a new chiral sulfonic acid (–)-**2** based on a benzene scaffold was synthesized in 5 steps (overall yield: 5.5%) from the cheap commercially available 3,5-dimethylphenol (**3**). This opens new opportunities to investigate the catalytic activities of this original chiral sulfonic acid as organocatalyst for several asymmetric transformations. Several asymmetric chemical reactions are currently under investigation in our laboratory.

Commercially available compounds were used without further purification. Solvents were obtained from a Pure-Solv™ 400 Solvent Purification System. Melting points were determined on a Electrothermal digital apparatus IA9100 series. NMR spectra were recorded on a Bruker Avance DPX 500 or DPX 400 spectrometers. Chemical shifts are relative to TMS or to solvent as the internal standard. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck). MS and HRMS were obtained on a Waters-Micromass Q-Tof micro instrument. IR spectra were recorded on a Perkin-Elmer 16 PC FTIR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 LC polarimeter.

_O_-[2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl] _N_,_N_-Dimethylthiocarbamate (7)

To a solution of phenol **1** (960 mg, 2.68 mmol, 1 equiv) in anhyd THF (60 mL) was added NaH (60% oil dispersed, 268 mg, 6.7 mmol, 2.5 equiv) at r.t. The suspension was stirred for 5 min, treated with $ClCSNMe_2$ (989 mg, 8.04 mmol, 3 equiv), and the mixture was further stirred for 48 h at 70 °C. H_2O (5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were evaporated and the residue was washed with MeCN (1 mL) to afford **7** as a colorless solid (890 mg, 74%); mp 193 °C.

IR (neat): 2961, 2929, 1526, 1391, 1250, 1160 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.6 Hz, 1 H, ArH), 7.37 (dd, *J* = 7.6, 1.2 Hz, 1 H, ArH), 7.32–7.27 (m, 3 H, ArH), 7.18–7.12 (m, 3 H, ArH), 7.18–7.12 (m, 3 H, ArH), 6.94 (dd, *J* = 8.2, 1.2 Hz, 1 H, ArH), 3.05–2.98 [m, 1 H, C*H*$(CH_3)_2$], 2.91 (s, 3 H, NCH_3), 2.64–2.58 [m, 3 H, C*H*$(CH_3)_2$], 2.48 (s, 3 H, NCH_3), 2.12 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 1.26 [d, *J* = 6.8 Hz, 3 H, CH(CH_3)$_2$], 1.22 [d, *J* = 6.8 Hz, 6 H, CH(CH_3)$_2$], 1.07 [d, *J* = 6.8 Hz, 3 H, CH(CH_3)$_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.1 (C),149.7 (C),148.7 (C), 146.8 (C), 137.0 (C), 136.8 (C), 134.9 (C), 134.8 (C), 132.8 (C), 132.8 (C), 131.8 (CH), 131.4 (CH), 129.2 (CH), 127.7 (CH), 126.4 (CH), 124.8 (CH), 124.7 (CH), 124.4 (CH), 42.7 (NCH_3), 37.8 (NCH_3), 30.4 (CH), 30.0 (CH), 26.7 (CH_3), 24.8 (CH_3), 24.2 (CH_3), 23.6 (CH_3), 20.5 (CH_3), 20.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{36}NOS$ $(M + H)^+$: 446.2518; found: 446.2498.

(+)-_S_-[2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl] _N_,_N_-Dimethylthiocarbamate [(+)-8]

O-Aryl thiocarbamate **7** (200 mg, 0.46 mmol) was introduced in a microwave quartz tube and placed in a Discover® microwave oven at 220 °C for 20 min. ^1H NMR spectrum showed complete conversion of the starting material. The crude product was purified by flash chromatography using cyclohexane–EtOAc (98:2 to 95:5) as eluent to afford racemic and *meso* products in a 1.13:1 ratio [*rac*-**8**; yield: 90 mg (45%) and *meso*-**9**; yield: 80 mg (40%)]. The enantiomers were separated by preparative chiral HPLC on Daicel Chiralpak IA using 98% *n*-heptane, 2% *i*-PrOH, 1 mL/min, 20 °C, 210.0 nm, t_1 = 4.21 min (+), t_2 = 4.67 min (–).

Yield: 90 mg (45%); colorless solid; mp 57 °C; $[\alpha]_D^{20}$ + 9.7 (*c* = 1.0, $CHCl_3$); ee = 100%.

IR (neat): 2959, 2924, 2866, 1665, 1444, 1359, 1261 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4 H, ArH), 7.23 (s, 1 H, ArH), 7.14 (t, *J* = 6.8 Hz, 2 H, ArH), 7.03 (br s, 2 H, ArH), 2.70 [br s, 2 H, C*H*$(CH_3)_2$], 2.51 (br s, 6 H, NCH_3), 2.02 (s, 6 H, CH_3), 1.13–1.08 [br m, *J* = 6.8 Hz, 12 H, CH(CH_3)$_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.5 (C), 139.1 (C), 136.2 (C), 133.0 (CH), 130.3 (CH), 129.3 (C), 127.5 (CH), 125.3 (CH), 124.8 (CH), 43.6 (CH_3), 30.3 (CH), 30.1 (CH), 24.6 (CH_3), 23.8 (CH_3), 21.2 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{36}NOS$ $(M + H)^+$: 446.2518; found: 446.2497.

(–)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenylsulfonic Acid [(–)-2]

To a solution of (–)-*S*-aryl thiocarbamate **8** (335 mg, 0.75 mmol) in HCO_2H (5 mL) was added H_2O_2 (1.8 mL, 18 mmol, 18 equiv) at r.t. and the reaction mixture was stirred for 16 h at 55 °C. H_2O (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). Evaporation of the combined organic layers gave a brownish crude product (300 mg). The crude product was purified by flash chromatography using CH_2Cl_2–MeOH (95:5 to 9:1) to afford (–)-**2** as a colorless solid (156 mg, 50%); mp 274 °C; $[\alpha]_D^{20}$ –17.2 (*c* = 1, $CHCl_3$).

IR (neat): 2960, 2928, 2868, 2790, 2476, 1735, 1625, 1463, 1442, 1384 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 6 H, ArH), 7.14–7.06 (m, 3 H, ArH), 6.32 (br s, 1 H, OH), 2.60–2.53 [m, 2 H, C*H*$(CH_3)_2$], 1.89 (s, 6 H, CH_3), 1.12 [d, *J* = 6.8 Hz, 6 H, CH(CH_3)$_2$], 1.08 [d, *J* = 6.8 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 146.9 (C), 139.1 (C), 137.7 (C), 137.4 (C), 136.8 (C), 134.3 (CH), 130.1 (CH), 127.4 (CH), 125.4 (CH), 124.8 (CH), 34.9 (CH), 30.5 (CH), 24.4 (CH_3), 23.9 (CH_3), 21.3 (CH_3).

HRMS (ENI): *m*/*z* calcd for $C_{26}H_{29}O_3S$ $(M - H)^+$: 421.1837; found: 421.1832.

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