A Chiral Sulfoxide-Based C–H Acid

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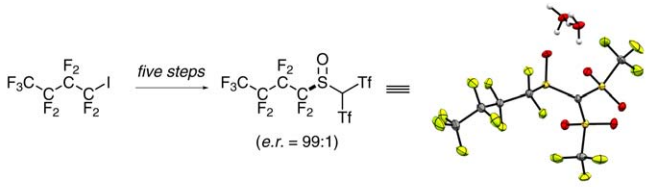

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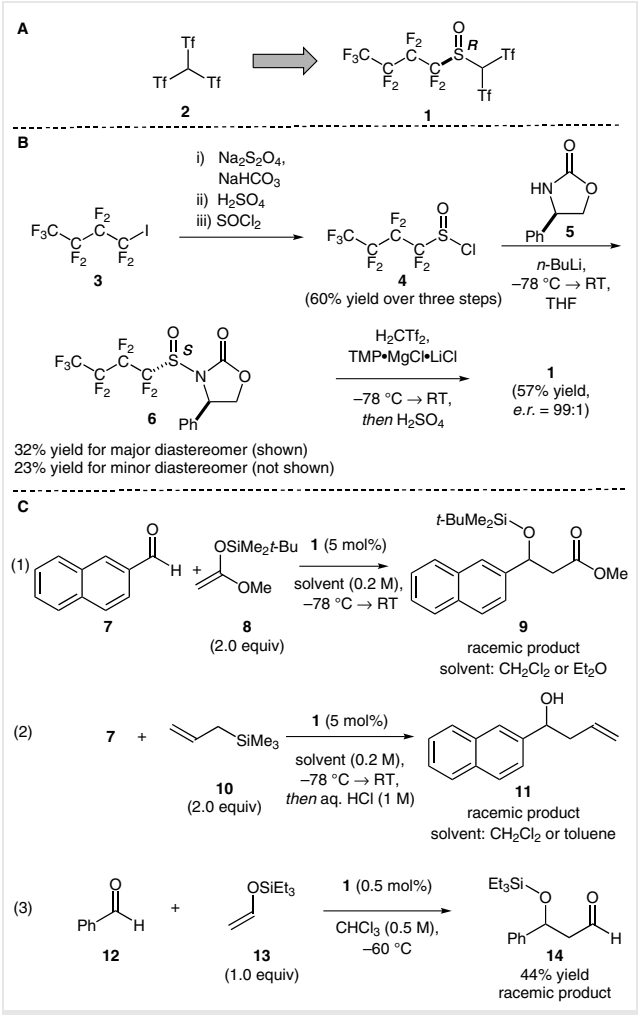
Abstract We report the design and synthesis of a strong, chiral, enantiopure sulfoxide-based C–H acid. Single-crystal X-ray analysis confirms the proposed structure and its absolute configuration. The new motif shows a high acidity and activity in Brønsted and Lewis acid catalyzed transformations. So far, only little to no enantioselectivities were achieved.

Key words sulfoxide C–H acids, stereogenic sulfur, triflyl groups, strong acids, noncoordinating anions, Brønsted acids

Chiral binaphthyl-derived acids have shown great success in asymmetric Lewis and Brønsted acid catalysis,[1] especially confined variants.[2] However, their catalytic activity is inherently limited by the electron-rich binaphthyl system, which also limits their acidity and catalytic reactivity. With both enantiomers readily available, chiral sulfur-stereogenic sulfoxides are attractive ligands in transition-metal catalysis.[3] In organocatalysis, a stereogenic sulfur has been either a contributing factor or exclusively responsible for high enantioselectivities when using weakly acidic chiral urea- or thiourea-derived catalysts.[3,4] We envisioned a new, tris(triflyl)methane (**2**)[5]-inspired motif with the acidic proton very close to the stereogenic sulfur atom, which we hypothesized could lead to efficient asymmetric induction. These considerations led to the design of **1**, expected to be a very strong C–H acid, with two triflyl (SO_2CF_3) groups[6] and one chiral sulfoxide moiety (Scheme 1A). Indeed, a synthesis was developed, from commercially available iodide **3**,



Scheme 1 Design (A), synthesis (B), and application (C) of the chiral, enantiopure sulfoxide C–H acid. TMP = 2,2,6,6-tetramethylpiperidine.

which was converted into a diastereomeric mixture of two oxazolidinones **6** by following reported procedures.[7] The major diastereomer (**6a**) was separated by flash chromatography and converted into the desired enantiopure sulfoxide acid **1** by treatment with bis(triflyl)methane in the presence of a strong base followed by H_2SO_4 acidification.[8] With the desired C–H acid **1** in hand, we were able to assign its absolute configuration by X-ray single-crystal structure analysis of its hydroxonium hydrate (see Supporting Information).[9]

Further, an experimental pK_{ip} value of –12.5 ± 0.5 (in 1,2-dichloroethane, relative to picric acid) was determined for **1**. The corresponding free-ion pK_a value for a molecule of this size is expected to be essentially the same.[10] This acidity corresponds to a pK_a of around 0 in acetonitrile.[11] Therefore, to the best of our knowledge, sulfoxide **1** can be considered to be the strongest enantiopure Brønsted acid that has been prepared so far. We applied acid **1** as a catalyst in a variety of different reactions including two Mukaiyama aldolizations and a Hosomi–Sakurai allylation (Scheme 1C). Although the catalytic activity was promising, little to no enantioselectivity was observed in all cases. In the future, further modifications of this easily accessible motif to increase its enantiodiscrimination are envisioned as well as its potential applications as an anionic ligand in transition-metal catalysis.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1695-4516.

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(8) **1-{[Bis(triflyl)methyl]}sulfinylnonafluorobutane (1)**
A Schlenk flask was charged with bis(triflyl)methane (0.46 g, 1.6 mmol, 1.0 equiv) and THF (3.5 mL) to give a colorless clear solution that was cooled to −78 °C. A 1.2 M solution of TMP·MgCl·LiCl in THF (3.1 mL, 3.8 mmol, 2.3 equiv) was added dropwise, followed by the diastereomerically pure sulfinyl oxazolidinone **6a** (4.3 g, 14 mmol, 1.0 equiv; dr >99:1) in THF (3.5 mL). The mixture was allowed to reach RT overnight. All volatiles were then removed under reduced pressure to give an orange solid that was dissolved in CH_2Cl_2 (30 mL) and washed with sat. aq. $NaHCO_3$ (3 × 10 mL). The pooled aqueous phases were extracted with CH_2Cl_2 (2 × 10 mL). The pooled organic phases were washed with concd aq HCl (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellowish viscous oil was dissolved in CH_2Cl_2 (30 mL), washed with concd H_2SO_4 (3 × 10 mL), stirred over dried $BaCl_2$ for 80 min, and filtered. All volatiles were removed under reduced pressure until 7 mL of liquid remained. This solution was stored at –29 °C overnight, which led to the formation of a precipitate. The mother liquor was removed to give a colorless solid; yield: 0.51 g (57%, 0.93 mmol).
LC/MS (chiral): (150 mm Chiralpak IC-3, 4.6 mm i.d., 30:70 MeCN–0.2% TFA, 1.0 mL/min, 20.8 MPa, 298 K): $t_{R\text{-}(S)\text{-enantiomer}}$ = 21.06 min, $t_{R\text{-}(R)\text{-enantiomer}}$ = 22.69 min; *e.r.* = 1:99. ^{13}C NMR (151 MHz, acetone-d_6): δ = 123.74 (t, *J* = 23.1 Hz, C_6), 120.22 (q, *J* = ~322.0 Hz, $C_{7,8}$), 117.14 (tt, *J* = 322.7, 36.6 Hz, C_1), 114.51 (qt, *J* = 287.0, 32.5 Hz, C_4), 111.21 (tp, *J* = 266.2, 34.0 Hz, C_2), 108.76 (th, *J* = 271.0, ~35 Hz, C_3). ^{19}F NMR (471 MHz, acetone-d_6): δ = –179.16 (br, 3 F, $F_{7,8}$), –80.68 (br, 3 F, $F_{7,8}$), –81.37 to –82.51 (td, *J* = 9.6, 5.1 Hz, 3 F, F_4), –103.82 (br d, *J* = 220.6 Hz, 1 F, $F_{1'}$), –121.02 (dt, *J* = 221.8, 10.3 Hz, 1 F, $F_{1''}$), –123.63 [br d (AB system), *J* = ~300.0 Hz, 1 F, $F_{2'}$], –124.33 [br d (AB system), *J* = ~300.0 Hz, 1 F, $F_{2'}$], –126.39 [br d (AB system), *J* = 293.0 Hz, 1 F, $F_{3'}$], –127.19 [br d (AB system), *J* = 293.0 Hz, 1F, $F_{3''}$]. MS (ESI–): *m/z* = 545 [M –H].

HRMS (ESI–): *m/z* [M –H] calcd for $C_7F_{15}O_5S_3$: 544.8674; found: 544.8674. Anal.: Calcd for $C_7HF_{15}O_5S_3$ (546.24 g/mol): C, 15.39; H, 0.18; F, 52.17; S, 17.61; Found: C, 15.42; H, 0.17; F, 52.14; S, 17.60.

(9) CCDC 2106642 and 2106643 contain the supplementary crystallographic data for **1** hydroxonium hydrate and **6a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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