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A Fluorous Super Brønsted Acid Catalyst: Application to Fluorous Catalysis without Fluorous Solvents

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Abstract: The preparation of a fluorous super Brønsted acid catalyst, 4-(1H, 1H-perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**3d**), is described. The fluorous catalyst **3d** can be recycled by using liquid/solid phase separation without fluorous solvents. A perfluorocarbon solvent is not essential for fluorous biphasic catalysis.

Key words: Brønsted acid, fluorous catalyst, ponytail, fluorous biphasic catalysis, superacid

Fluorous biphasic catalysis has recently become an environmentally attractive alternative to traditional catalytic methods.¹ Fluorous techniques take advantage of the temperature-dependent miscibility of organic and perfluorocarbon solvents to provide easier isolation of products and the recovery of a fluorinated catalyst. The fluorous biphasic technique involves dissolving a catalyst with long fluorinated alkyl chains (Rf) in a perfluorocarbon. The reactants are added to an organic solvent that is immiscible with the perfluorocarbon at room temperature, which forms a second phase. On heating, the two phases mix and the reaction occurs; on cooling, the fluorinated and organic layers separate. The organic phase can be removed and the product isolated, while the fluorinated catalyst-solvent phase can be reused. However, the large-scale use of perfluorocarbon solvents has some drawbacks: cost and concern over environmental persistence.

Recently, our group² and Gladysz's group³ independently demonstrated that a perfluorocarbon solvent is not essential for fluorous biphasic catalysis: the perfluorocarbon solvent can be omitted by designing fluorinated catalysts that themselves show temperature-dependent phase miscibility, i.e., solubility, in ordinary organic solvents (Figure 1). We previously reported that 3,5-bis(perfluorodecyl)phenylboronic acid is a good amide condensation catalyst which is insoluble in organic solvents at room temperature but becomes soluble under reflux in *o*-xylene (reaction conditions).² Gladysz et al. also reported the temperature-dependent solubility of the solid phosphine catalyst $P[(CH_2)_2(CF_2)_7CF_3]_3$ in octane.³

Recently, we successfully synthesized a new super Brønsted acid, pentafluorophenylbis(trifluoromethane-

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Figure 1 Fluorous catalysts recycling based upon liquid/solid phase separation

sulfonyl)methane (1), and developed an organic-solventswellable resin-bound super Brønsted acid, polystyrenebound tetrafluorophenylbis(trifluoromethanesulfonyl)methane (2), by using the *para*-substitution reaction of 1 with alkyllithium as a key step (Scheme).⁴ In this Letter, we describe a fluorous super Brønsted acid catalyst which can be recycled by applying liquid/solid phase separation without fluorous solvents.





Pentafluorophenylbis(trifluoromethanesulfonyl)methane **1** (47 wt% F) is soluble in most organic and fluorous solvents. If the nucleophilic *para*-substitution reaction of **1** can be adapted to not only alkyl anions but also alkoxy anions, it may be possible to achieve high fluorous-phase affinity for 4-alkoxy-2,3,5,6-tetrafluorophenyl-bis(trifluoromethanesulfonyl)methane (**3**) by appending several 'ponytails' OCH₂(CF₂)_nCF₃ groups to **1**. In preliminary experiments, the preparation of 4-hexanoxy- and 4-trifluroroethanoxy-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methanes, **3a** and **3b**, was examined by reacting a lithium salt of **1** with the corresponding sodium

alkoxides in pyridine at room temperature (Equation 1).⁵ As expected, **3a** and **3b** were obtained in respective yields of 83% and 93%.



Equation 1

Their pK_a values in glacial acetic acid were measured by the ¹H NMR method of Schantl et al. (Table).^{4,6} The Brønsted acidity of **3a** was less than that of concd H₂SO₄, while **3b** was a superacid like **1**.

 Table
 Brønsted Acidities of Arylbis(trifluoromethanesulfonyl)methanes

	3a	Concd H_2SO_4	3b	1
¹ H NMR (ppm) ^a	6.19	-	6.23	6.21 ^b
pK _a in AcOH	11	7.5 ^b (7.0) ^c	6.6	1.5 ^b

^{a 1}H NMR chemical shift observed for an acidic proton of $ArCHTf_2$ in $CDCl_3$ is indicated.

^b Ref.^{4a}

^c Ref.⁶

Based on the above results, **3c** (59 wt% F) was prepared in 97% yield from a lithium salt of **1** and sodium 1*H*,1*H*perfluorodecanoxide in the similar manner (Equation 1). To obtain higher fluroinated Brønsted acid, **3d** (62 wt% F) was prepared in 84% yield by heating a lithium salt of **1** and sodium 1*H*,1*H*-perfluorotetradecanoxide in a 2:1 mixed solvent of pyridine and perfluorotributylamine at 70 °C (Equation 2). Perfluorotributylamine was added to partially dissolve sodium 1*H*,1*H*-perfluorotetradecanoxide.



Equation 2

The acetalization of benzaldehyde with 1,3-propanediol was examined in the presence of 1 mol% of a fluorous super Brønsted acid, **3c** or **3d**, at azeotropic reflux in cyclohexane with the removal of water for 3 h (Equation 3). Both solid acids were soluble in cyclohexane under reflux conditions, and promoted the reaction well to give the desired acetal in good yields. Postreaction, **3d** was recovered in 96% yield by precipitation at room temperature. However, **3c** could not be recovered in the same manner. Be-

sides this acetalization, **3d** was also effective as a fluorous catalyst for the acylation of L-menthol with benzoic anhydride (Equation 4) and esterification of 3-phenylpropionic acid in methanol (Equation 5).⁷



Equation 3



Equation 4



Equation 5

Fluorous solid catalyst **3d** was also used in the Mukaiyama aldol reaction (Equation 6) and Sakurai–Hosomi allylation reaction (Equation 7). These reactions were performed at -78 °C and r.t., respectively, under heterogeneous conditions. Postreaction, **3d** was recovered in high yield by decanting the liquids at room temperature.



Equation 6





We believe that one-solvent protocols of the type described above may be applicable to a wide variety of fluorous catalysts. In this Letter, we demonstrate that **1** offers a great advantage over other analogous super Brønsted acids such as tris(trifluoromethanesulfonyl)methane, bis(trifluoromethanesulfonyl)imide, and trifluoromethanesulfonic acid from the perspective of synthetic modification. Barrett's group⁸ and Mikami's group⁹ have

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independently reported metal tris(perfluoroalkanesulfonyl)methides as fluorous Lewis acids. Similarly, it may be possible to design pentafluorophenylbis(perfluoroalkanesulfonyl)methanes. However, it is synthetically more concise and practical to append 1H,1H-perfluoroalkoxy groups to **1** by a *para*-substitution reaction. In addition, solid acids **2** and **3d** are more active catalysts than perfluoresinsulfonic acids such as Nafion[®].⁴

Experimental Procedure for Preparing 3d: To a mixture of NaH (60% dispersion in mineral oil, 30 mg, 0.75 mmol) and 1H,1H-perfluorotetradecanol (0.53 g, 0.75 mmol) were added pyridine (4 mL) and perfluorotributylamine (2 mL) at room temperature. The resulting mixture was heated to 70 °C and stirred at the same temperature for 1 h. Lithium pentafluorophenylbis(trifluoromethanesulfonyl)methide4a (0.11 g, 0.25 mmol) was then added at 70 °C, and the resulting mixture was stirred for an additional 1 day at the same temperature. After cooling to 0 °C, the reaction was quenched with 4 M aqueous HCl (40 mL) at 0 °C. The resultant acidified mixture was extracted with diethyl ether (40 mL \times 2). The organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a brown solid. Furthermore excess 1H,1H-perfluorotetradecanol which was contained in the solid was removed by vacuum sublimation (120 °C, 0.06 torr). The residual dark-brown solid was dissolved in diethyl ether (20 mL) or perfluoromethylcyclohexane (20 mL), and some insoluble impurities were then removed by filtration. The filtrate was concentrated under reduced pressure to give 3d (0.238 g, 0.21 mmol, 84% yield) as a white solid. Mp. 95~96 °C; IR (KBr) 1503, 1406, 1397, 1213, 1154, 1111, 984, 646, 625, 550, 527 cm⁻¹; ¹H NMR (toluene- d_8 + perfluorotoluene, 80 °C, 300 MHz) δ 4.06 (t, J = 12.5 Hz, 2 H), 6.21 (s, 1 H). Anal. Calcd for C₂₃H₃O₅F₃₇S₂: C, 24.53; H, 0.27. Found: C, 24.51; H, 0.31.

Spectral and analytical data of 3a-c are indicated as follows:

3a: Liquid; IR (film) 2959, 2090, 1651, 1505, 1406, 1215, 1119, 1017, 980, 627, 577, 513 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (t, *J* = 7.1 Hz, 3 H), 1.32–1.37 (m, 4 H), 1.43–1.51 (m, 2 H), 1.83 (quintet, *J* = 6.8 Hz, 2 H); 4.44 (t, *J* = 6.8 Hz, 2 H), 6.19 (s, 1 H); ¹⁹F NMR (CDCl₃, 282 MHz, CF₃Ph δ –64.00) δ –75.35 (s, 6 F), –130.64 (dt, *J* = 9.9, 21.2 Hz, 1 F), –143.16 (br, 1 F), –154.07 (d, *J* = 21.2 Hz, 1 F), –155.31 (d, *J* = 21.2 Hz, 1 F). Anal. Calcd for C₁₅H₁₄O₅F₁₀S₂: C, 38.47; H, 3.01. Found: C, 38.54; H, 2.98.

3b: Mp. 81–82 °C; IR (KBr) 1653, 1505, 1401, 1347, 1200, 1119, 995, 656, 610, 515, 494 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.71 (q, *J* = 7.8 Hz, 2 H), 6.23 (s, 1 H); ¹⁹F NMR (CDCl₃, 282 MHz, CF₃Ph δ –64.00) δ –153.8 (dd, *J* = 7.6, 22.8 Hz, 1 F), –152.8 (dd, *J* = 8.3, 21.4 Hz, 1 F), –141.3 (br, 1 F), –128.8 (dt, *J* = 9.9, 21.2 Hz, 1 F), –76.1 (t, *J*_{FH} = 7.6 Hz, 3 F), –75.3 (s, 6 F). Anal. Calcd for C₁₁H₃O₃F₁₃S₂: C, 25.11; H, 0.57. Found: C, 25.12; H, 0.55.

3c: Mp. 74–75 °C; IR (KBr) 1653, 1502, 1406, 1393, 1220, 1159, 1117, 1057, 984, 623 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.84 (t, *J* = 12.5 Hz, 2 H), 6.20 (s, 1 H); ¹⁹F NMR (CDCl₃, 282 MHz, CF₃Ph

 δ –64.00) δ –153.7 (dd, J = 6.2, 21.4 Hz, 1 F), –152.7 (dd, J = 9.2, 21.3 Hz, 1 F), –141.3 (br, 1 F), –128.7 (dt, J = 9.0, 21.4 Hz, 1 F), –127.1 (s, 2 F), –124.0 (s, 2 F), –123.7 (s, 2 F), –122.8 (s, 8 F), –121.5 (s, 2 F), –81.9 (t, J = 18.3 Hz, 3 F), –75.3 (s, 6 F). Anal. Calcd for $C_{19}H_3O_5F_{29}S_2$: C, 24.64; H, 0.33. Found: C, 24.61; H, 0.36.

Experimental Procedure for the Acetalization of Benzaldehyde with 1,3-Propanediol: To a solution of **3d** (33.8 mg, 0.03 mmol) in cyclohexane (6 mL) were added benzaldehyde (0.30 mL, 3.0 mmol) and 1,3-propanediol (0.24 mL, 3.3 mmol), and the resulting mixture was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. While monitoring the disappearance of the starting materials by TLC (for 3 h), the reaction mixture was cooled to ambient temperature to precipitate **3d**, which was filtered and washed with cyclohexane (2 mL) to recover **3d** (32.4 mg, 0.029 mmol, 96% yield). The filtrate was concentrated under reduced pressure. The purity of the recovered catalyst was checked by ¹H and ¹⁹F NMR analyses. The crude oil was purified by column chromatography on silica gel (eluent:hexane-EtOAc = 20:1 to 5:1) to afford the corresponding acetal (0.425 g, 2.6 mmol, 86% yield).

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