Supporting Information

for Designer Chiral Quaternary Ammonium Bifluorides as an Efficient Catalyst for Asymmetric Nitroaldol Reaction of Silyl Nitronates with Aromatic Aldehydes

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Preparation of C₂-Symmetric Chiral Quaternary Ammonium Bifluoride 1.¹ Chiral quaternary ammonium bifluoride **1** was prepared by passage of a methanolic solution of the corresponding bromide through a column of ion exchange resin Amberlyst A-26 (OH⁻) to afford the corresponding quaternary ammonium hydroxide, followed by neutralizing with 2 equiv of 1 N HF solution. The solvent was removed under reduced pressure, and the residue was co-evaporated with dichloromethane-hexane (1:1), then dried under vacuum. The requisite ammonium bifluoride was obtained quantitatively as fine powder and used for the asymmetric nitroaldol reaction without further purification. Recrystallization of these quaternary ammonium bifluorides, **1a** and **1b** were unsuccessful. **1a** and **1b** can be kept in a desiccator at room temperature for a month with gradual decrease of the catalytic activity, which, however, does not affect the enantioselectivity of the nitroaldol reaction.

C₂-Symmetric Chiral Quaternary Ammonium Bifluoride 1a: [α]_D²⁷ 78.0° (*c* 0.50, CH₃OH); ¹H NMR (400 MHz, CD₂Cl₂) δ 8.39 (2H, s, Ar-H), 8.30 (2H, s, Ar-H), 8.20 (2H, d, *J* = 7.9 Hz, Ar-H), 7.88 (2H, d, *J* = 8.3 Hz, Ar-H), 7.70 (2H, ddd, *J* = 1.2, 6.7, 7.9 Hz, Ar-H), 7.53 (2H, ddd, *J* = 1.2, 6.7, 8.3 Hz, Ar-H), 7.40 (2H, ddd, *J* = 1.2, 6.7, 8.3 Hz, Ar-H), 7.31 (2H, d, *J* = 8.7 Hz, Ar-H), 7.24 (2H, ddd, *J* = 1.2, 6.7, 8.3 Hz, Ar-H), 7.18 (2H, d, *J* = 8.3 Hz, Ar-H), 7.11 (2H, d, *J* = 8.7 Hz, Ar-H), 8.40-7.10 (6H, br, Ar-H) 6.27 (2H, d, *J* = 8.3 Hz, Ar-H), 4.64 (2H, d, *J* = 13.9 Hz, Ar-CH₂), 4.49 (2H, d, *J* = 13.9 Hz, Ar-CH₂), 4.26 (2H, d, *J* = 13.1 Hz, Ar-CH₂), 3.69 (2H, d, *J* = 13.1 Hz, Ar-CH₂); ¹³C NMR (100 MHz, CDCl₃, at 50 °C) δ 142.07, 139.59, 136.49, 136.37, 133.87, 133.78, 133.64, 133.26 (q, *J*_{C-F} = 36.9 Hz), 131.78, 131.15, 131.02, 128.67, 128.57, 128.38, 128.19, 128.12, 127.51, 127.40, 126.92, 126.19, 124.89, 124.47, 122.34, 122.14, 122.09, 62.37, 57.41; ¹⁹F NMR (376 MHz, CD₂Cl₂) δ -62.80, -152.20; IR (KBr) 3393, 1524, 1470, 1377, 1311, 1281, 1177, 1138, 1030, 897, 847, 750, 714, 681 cm⁻¹; HRMS (ESI-TOF) calcd for C₆₀H₃₆F₁₂N ([M]⁺): 998.2651. Found: 998.2655 ([M]⁺). Upon measuring melting point, the light yellow solid started changing to dark red at 210 °C and it finally melted at 239 °C. However, ¹H NMR analysis after the measurement showed almost total decomposition.

C₂-Symmetric Chiral Quaternary Ammonium Bifluoride 1b: $[\alpha]_D^{27}$ 62.3° (*c* 1.00, CH₃OH); ¹H NMR (400 MHz, CD₂Cl₂) δ 8.87 (2H, br, Ar-H), 8.59 (4H, br, Ar-H), 8.54 (2H, s, Ar-H), 8.26 (2H, s, Ar-H), 8.23 (2H, d, *J* = 8.3 Hz, Ar-H), 8.12 (2H, br, Ar-H), 8.10-7.90 (4H, br, Ar-H), 7.84 (4H, d, *J* = 8.3 Hz, Ar-H), 7.73 (2H, dd, *J* = 7.1, 7.9 Hz, Ar-H), 7.63 (2H, br, Ar-H), 7.49 (2H, ddd, *J* = 0.4, 7.1, 7.9 Hz, Ar-H), 7.44 (2H, ddd, *J* = 0.4, 7.1, 7.9 Hz, Ar-H), 7.35 (2H, d, *J* = 8.7 Hz, Ar-H), 7.27 (2H, d, *J* = 8.3 Hz, Ar-H), 7.18 (2H, ddd, *J* = 1.2, 6.7, 8.7 Hz; Ar-H), 7.07 (2H, d, *J* = 8.7 Hz, Ar-H), 6.58 (2H, d, *J* = 8.7 Hz, Ar-H), 4.93 (2H, d, *J* = 13.5 Hz, Ar-CH₂), 4.47 (2H, d, *J* = 13.5 Hz, Ar-CH₂), 4.36 (2H, d, *J* = 13.5 Hz, Ar-CH₂), 3.69 (2H, d, *J* = 13.5 Hz, Ar-CH₂); ¹³C NMR (100 MHz, CDCl₃, at 50 °C) δ 142.25, 141.97, 141.49, 139.65, 137.84, 136.75, 133.99, 133.83, 133.30, 132.75 (q, *J*_{C-F} = 40.2 Hz), 131.69, 131.18, 130.34, 128.60, 128.49, 128.24, 127.91, 127.82, 127.65, 127.49, 127.07, 126.61, 126.44, 125.05, 124.50, 122.62, 122.09, 122.05, 121.76, 62.27, 57.59; ¹⁹F NMR (376 MHz, CD₂Cl₂) δ -62.85, -151.16; IR (KBr) 3437, 3059, 1620, 1595, 1526, 1466, 1391, 1367, 1331, 1281, 1178, 1136, 901, 883, 845, 752, 706, 685 cm⁻¹; HRMS (ESI-TOF) calcd for C₈₈H₄₈F₂₄N ([M]⁺): 1574.3398. Found: 1574.3388 ([M]⁺). Melted at 241 °C with decomposition.

General Procedure for the Preparation of Silyl Nitronate 2.² To a stirred solution of diisopropylamine (7.1 mL, 51 mmol) in THF (100 mL) was added a 1.5 M hexane solution of *n*-BuLi (33 mL, 50 mmol) at 0 °C under argon atmosphere. After stirring for 30 min, this solution of lithium diisopropylamide was quickly transferred via cannular to the solution of nitroalkane (50 mmol) in THF (30 mL) at -78 °C. The resulting jelly was kept at -78 °C for 15 min and then trimethylsilyl chloride (6.2 mL, 50 mmol) was added. After stirring for 15 min at the temperature, cooling bath was removed and stirring was continued for additional 2 h. The resulting mixture was evaporated and the residual semi-solid was suspended in pentane (200 mL), which was filtered through a *Celite* pad on a glass filter followed by rapid washing with pentane (20 mL x 2). Fractional distillation of the residue gave the corresponding pure silyl nitronate in 50–80% yield.

Silyl Nitronate 2d: ¹H NMR (400 MHz, CD₂Cl₂) δ 7.31-7.19 (5H, m, Ph), 6.12 (1H, t, *J* = 6.1 Hz, N=CH), 4.43 (2H, s, PhCH₂), 3.53 (2H, t, *J* = 6.1 Hz, OCH₂CH₂), 2.49 (2H, dt, *J* = 6.1, 6.1 Hz, OCH₂CH₂), 0.23 (9H, s, SiCH₃); ¹³C NMR (100 MHz, CD₂Cl₂) 138.58, 128.54, 127.86, 127.80, 114.57, 73.19, 66.55, 27.88, 0.08; b.p. 112 °C/0.003 mmHg.

General Procedure for Asymmetric Nitroaldol Reaction Catalyzed by 1b. To a solution of chiral quaternary ammonium bifluoride **1b** (9.6 mg, 0.006 mmol) in distilled THF (3 mL) was added aldehyde (0.3 mmol) at room temperature and the mixture was cooled to -98 °C with methanol-liq. N₂ bath under argon atmosphere. Then, a solution of silyl nitronate **2** (0.36 mmol) in distilled THF (1 mL) was introduced over a period of 5 min. The mixture was maintained at -98 °C for 1 h and the stirring was continued at -78 °C for an additional 1–5 h. After the addition of 1 N HCl at -78 °C, it was warmed to 0 °C followed by vigorous stirring

for 20 min and the whole mixture was extracted with ether. The combined organic extracts were washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated and the residual oil was purified by column chromatography on silica gel (ether/hexane as eluant) to afford the corresponding nitroaldol adduct **3**.³ The optical purities of the nitroaldol adducts were determined by HPLC analysis using DAICEL Chiralpak AS. Table 2 shows the retention times of *anti* isomers.

Table 2. The Retention Time of *anti* Isomer

nitroaldol adduct	eluants (hexane/alcohol)	flow rate (mL/min)	retention time (min)	
			minor isomer	major isomer
3a (R ¹ = Me, R ² = Ph)	50:1 (<i>i</i> -PrOH)	1.0	26.2 (1 <i>S</i> ,2 <i>R</i>)	32.2 (1 <i>R</i> ,2 <i>S</i>)
3b (R ¹ = Me, R ² = <i>p</i> -Me-Ph)	30:1 (EtOH)	1.0	11.2	12.5
3c (R ¹ = Me, R ² = <i>p</i> -F-Ph)	30:1 (EtOH)	1.0	16.9	18.3
3d (R ¹ = Me, R ² = β -Np)	30:1 (EtOH)	1.0	18.1	19.9
3e (R ¹ = Et, R ² = Ph)	50:1 (<i>i</i> -PrOH)	1.0	20.0	23.0
3f [R ¹ = BnO(CH ₂) ₂ , R ² = Ph]	10:1 (<i>i</i> -PrOH)	0.5	27.2	29.7

Characterization of the Nitroaldols.

4-Benzyloxy-2-nitro-1-phenylbutan-1-ol (3f): ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.21 (10H, m, Ph), 5.20 (0.83H, dd, *J* = 3.6, 4.7 Hz, CHOH, *anti* isomer), 5.00-4.94 (0.34H, m, CHOH and CHNO₂, *syn* isomer), 4.88 (0.83H, ddd, *J* = 3.6, 4.7, 5.1 Hz, CHNO₂, *anti* isomer), 4.38 (1.66H, s, PhCH₂, *anti* isomer), 4.36 (0.34H, s, PhCH₂, *syn* isomer), 3.52 (0.83H, m, OCHCH₂, *anti* isomer), 3.42 (0.83H, ddd, *J* = 4.4, 8.7, 10.3 Hz, OCHCH₂, *anti* isomer), 3.38-3.28 (0.34H, m, OCH₂CH₂, *syn* isomer), 3.18 (0.83H, d, *J* = 4.0 Hz, OH, *anti* isomer), 2.80 (0.17H, d, *J* = 4.4 Hz, OH, *syn* isomer), 2.44-2.35 (0.83H, m, OCH₂CH, *anti* isomer), 2.28-2.25 (0.17H, m, OCH₂CH, *syn* isomer), 2.21-2.10 (1H, m, OCH₂CH); ¹³C NMR (100 MHz, CDCl₃) δ 138.23, 137.44, 137.36, 129.01, 128.87, 128.57, 128.48, 128.29, 127.67, 127.54, 126.72, 126.02, 90.57, 89.99, 75.50, 74.14, 73.22, 73.09, 65.97, 65.70, 30.71, 28.20, four signals of *syn* isomer were missing; IR (liquid film) 3423, 1653, 1549, 1454, 1367, 1094, 768, 741, 700 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₇H₁₉NNaO₄: 324.1206 ([M+Na]⁺). Found: 324.1208 ([M+Na]⁺); HPLC conditions DAICEL Chiralpak AS, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 27.2 min, 29.7 min (*anti*); 33.0 min, 43.0 min (*syn*); [70%, *anti*/*syn* = 87:13, 91% ee (*anti* isomer), 35% ee (*syn* isomer)].

Assignment of the Absolute Configuration of Nitroaldol 3a. Treatment of **3a** with a

catalytic amount of Raney nickel under a hydrogen atmosphere in methanol at room temperature followed by the reaction with di-*tert*-butyl dicarbonate (3 equiv) and a catalytic amount of DMAP (20 mol%) gave 2-*N*-Boc-amino-1-phenyl-1-propanol (**4**).⁴ The comparison of its HPLC retention time with that of (1*R*,2*S*)-2-*N*-Boc-amino-1-phenyl-1-propanol independently prepared from commercially available (1*R*,2*S*)-(-)-norephedrine confirmed that the absolute configuration of the nitroaldol product **3a** was (1*R*,2*S*). **4**: HPLC conditions: DAICEL Chiralpak AS, hexane/ethanol = 10:1, flow rate = 0.5 mL/min, retention time; 9.5 min [minor isomer (1*S*,2*R*)], 10.0 min [major isomer (1*R*,2*S*)].

NMR Study. The ¹⁹F-NMR spectra of a solution of chiral quaternary ammonium bifluoride **1b** (80 mg, 0.05 mmol) in THF-*d*₈ (600 μL) was measured at -78 °C, which showed broad resonance centered at δ -149.8 ppm. With the addition of trimethylsilyl nitronate (2.4 equiv, 20 μL, 0.12 mmol) at -78 °C, the signal of trimethylsilyl fluoride appeared at δ -157.61 ppm, supporting generation of the corresponding chiral ammonium nitronate. [Chemical shifts are reported from fluorobenzene resonance (-113.0 ppm) as the external standard.]

References

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¹H and ¹³C NMRs of New Compounds.

2d-1H

2d-13C

3f-1H

3f-13C