Supporting Information

The First Route for Efficient Synthesis of ¹⁸O labled Alcohols using the HOF·CH₃CN Complex

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<u>1. Experimental section</u>

¹H NMR spectra were recorded using a 400 MHz spectrometer with CDCl₃ or DMSO-*d*₆ as a solvent and Me₄Si as an internal standard. The proton broad-band decoupled ¹³C NMR spectra were recorded at 100.5 MHz. Flash chromatography was performed using Merck silica gel 60 H. Thin layer chromatography was carried on pre-coated plates (Merck, silica gel 60 PF254). MS of phenols were measured under APPI conditions. In case of alkyl alcohols this method could not detect the molecular ion, but we have successfully employed a methanol cluster-based chemical ionization method that produces protonated molecular ions from molecules introduced through a supersonic molecular beam interface developed in our department by Amirav.¹ The main feature of this method is to provide electron ionization, while the sample is vibrationally cooled in a supersonic molecular beam. The presence of MeOH reduces the chances for water elimination from the alkyl alcohols. As a result the abundance of the molecular ions is considerably enhances.² Commercially available reagents (all Boronic acids) were used without further purification.

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and corrosive material. In organic chemistry, it is mostly used after dilution with nitrogen or helium. Such dilution can be achieved by using either an appropriate cooper or monel vacuum line constructed in a well-ventilated area or by purchasing pre-diluted fluorine. A detailed description for simple setup had appeared in the past.³ The reactions themselves are carried out in regular glassware. If elementary precautions are taken, work with F₂ is simple and we have had no bad experience working with it.

General Procedure for Producing HOF·CH₃CN. A mixture of 10 - 20% F₂ in nitrogen was used throughout this work and passed at a rate of about 400 mL per minute through a cold (-15 °C) mixture of 50 mL of CH₃CN and 5 mL of H₂O in a regular glass reactor. H¹⁸OF·CH₃CN was similarly prepared by mixing 10 ml dry CH₃CN and one ml H₂¹⁸O. The development of the oxidizing solution was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were about 0.4 - 0.6 molar.

General Procedure for Working with HOF·CH₃CN. About 2.5 mmols of a boronic acid derivative was dissolved in 10 - 20 mL CH₂Cl₂. The solution containing the oxidizing agent was than added slowly to the reaction vessel. The reaction was stopped after a few minutes by evaporation the solvent. When necessary, the crude product was usually purified by vacuum flash chromatography (P.E/EtOAc serving as eluent) or by recrystallization. The outcome of the reaction was analyzed by NMR (¹H and ¹³C), IR, and GCMS. The physical and spectral data of the products (all known for the ¹⁶O alcohols) were compared with the literature, and in every case an excellent agreement was found. The ¹⁸O containing alcohols were identified mainly through their mass spectrum.

Phenol $(2a)^4$ was prepared from 1a (0.32 g) as described in the general procedure in 95% yield: 0.24 g, white solid; mp 41 – 42 °C; ¹H NMR 7.24 – 7.20 (m, 2H), 6.93 – 6.88 (m, 1H), 6.84 – 6.81 (m, 2H) ppm. ¹³C NMR 155.5, 129.6, 120.5, 115.4 ppm.

4-Methylphenol (2b)⁵ was prepared from **1b** (0.38 g) as described in the general procedure in quantitative yield: 0.29 g, white solid; mp 32 - 34 °C; ¹H NMR 7.01 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 2.26 (s, 3H) ppm. ¹³C NMR 153.0, 130.2, 130.1, 115.3, 20.5 ppm.

4-t-Butylphenol $(2c)^6$ was prepared from **1c** (0.43 g) as described in the general procedure in quantitative yield: 0.36 g, white solid; mp 97 – 99 °C; ¹H NMR 7.31 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 1.36 (s, 9H) ppm. ¹³C NMR 153.2, 143.7, 126.6, 114.9, 34.2, 31.7 ppm.

2,6-Dimethylphenol $(2d)^4$ was prepared from **1d** (0.33 g) as described in the general procedure in 92% yield: 0.24 g, white solid; mp 43 – 44 °C; ¹H NMR 6.99 (d, J = 7.2 Hz, 2H), 6.78 (t, J = 7.2 Hz, 1H), 4.63 (s. 1H), 2.26 (s, 6H) ppm. ¹³C NMR 152.2, 128.6 (2C) 123.2, 120.2 (2C), 15.9 (2C) ppm.

2-Naphthalenol (**2e**)⁷ was prepared from **1e** (0.43 g) as described in the general procedure in 90% yield: 0.32 g, beige solid; mp 122 – 124 °C; ¹H NMR 7.74 (t, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.33 – 7.29 (m, 1H), 7.12 – 7.06 (m, 2H), 5.10 (s, 1H) ppm. ¹³C NMR 153.4, 134.6, 130.0, 129.1, 127.9, 126.7, 126.5, 123.8, 117.8, 109.6 ppm.

4-Methoxyphenol $(2f)^7$ was prepared from **1f** (0.24 g) as described in the general procedure in 93% yield: 0.18 g, white solid; mp 57 – 58 °C; ¹H NMR 6.76 (d, J = 1.8 Hz, 4H), 5.81 (s, 1H), 3.74 (s, 3H) ppm. ¹³C NMR 153.6, 149.6, 116.3 (2C), 115.1 (2C), 56.0 ppm.

4-Hydroxyacetophenone $(2g)^7$ was prepared from 1g (0.57 g) as described in the general procedure in quantitative yield: 0.45 g, beige solid; mp 108 – 110 °C; ¹H NMR 7.99 (s, 1H), 7.91 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 2.60 (s, 3H) ppm. ¹³C NMR 198.6, 161.6, 131.3, 129.6, 115.6, 26.4 ppm.

3-Hydroxyacetophenone (**2h**)⁸ was prepared from **1h** (0.25 g) as described in the general procedure in quantitative yield: 0.20 g, white solid; mp 92 – 95 °C; ¹H NMR 7.49 – 7.46 (m, 2H), 7.32 – 7.28 (m, 1H), 7.10 – 7.07 (m, 1H), 2.58 (s, 3H) ppm. ¹³C NMR 199.3, 156.7, 138.4, 129.9, 120.9, 120.8, 114.8, 26.8 ppm.

4-Chlorophenol (2i)⁴ was prepared from **1i** (0.55 g) as described in the general procedure in quantitative yield: 0.43 g, white solid; mp 44 – 45 °C; ¹H NMR 7.16 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.41 (br-s, 1H) ppm. ¹³C NMR 154.2, 129.4 (2C), 125.3, 116.7 (2C) ppm.

2-Fluorobiphenyl-4-ol (2j)⁹ was prepared from **1j** (0.76 g) as described in the general procedure in 90% yield: 0.59 g, white solid; mp 136 – 137 °C; ¹H NMR (DMSO-*d*₆) 9.99 (d, J = 1.05 Hz, 1H), 7.50 – 7.42 (m, 5H), 7.36 – 7.31 (m, 2H), 6.74 – 6.63 (m, 2H) ppm. ¹⁹F NMR (DMSO-*d*₆): –117.4 ppm.

Isobutanol $(4a)^{10}$ was prepared from **3a** (0.31 g) as described in the general procedure in 80% yield: 0.17 g, colorless liquid; ¹H NMR 3.53 (s, 1H), 3.25 (m, 2H), 1.64 (m, 1H), 0.80 (d, J = 6.70 Hz, 6H) ppm. ¹³C NMR 69.3, 30.7, 18.9 (2C) ppm.

Cyclohexanol (**4b**)¹¹ was prepared from **3b** (0.46 g) as described in the general procedure in 90% yield: 0.32 g, pale-yellow oil; ¹H NMR 3.61-3.57 (m, 1H), 1.89 – 1.84 (m, 2H), 1.67 – 1.75 (m, 2H), 1.55 – 1.50 (m, 1H) 1.32 – 1.12 (m, 5H) ppm. ¹³C NMR 70.3, 35.4 (2C), 25.5, 24.2 (2C) ppm.

2-Phenylethanol (4c) was prepared from **3c** (0.33 g) as described in the general procedure in 92% yield: 0.25 g, colorless oil; ¹H NMR 7.44 – 7.09 (m, 5H), 3.80 (t, J = 6.8 Hz, 2H), 2.84 (t, J = 6.8 Hz, 2H) ppm.

6-Bromohexanol (4d) was prepared from 4c (0.54 g) as described in the general procedure in 93% yield: 0.44 g, colorless oil; ¹H NMR 3.53 (t, J = 6.81 Hz, 2H), 3.32 (t, J = 6.81 Hz, 2H), 1.78 (quin, J = 7.38 Hz, 2H), 1.48 (quin, J = 7.38 Hz, 2H), 1.40 – 1.25 (m, 4H) ppm. ¹³C NMR 62.5, 33.9, 32.6, 32.1, 27.9, 24.9 ppm.

2. NMR spectra

Phenol (2a) ¹H NMR (400 MHz) in CDCl₃



Phenol (2a) ¹³C NMR (400 MHz) in CDCl₃

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4-Methylphenol (2b) ¹H NMR (400 MHz) in CDCl₃



4-Methylphenol (2b) ¹³C NMR (400 MHz) in CDCl₃

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4-t-Butylphenol (2c) ¹H NMR (400 MHz) in CDCl₃



4-t-Butylphenol (2c) ¹³C NMR (400 MHz) in CDCl₃

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2,6-Dimethylphenol (2d) ¹³C NMR (400 MHz) in CDCl₃

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2-Naphthalenol (2e) ¹H NMR (400 MHz) in CDCl₃





2-Naphthalenol (2e) ¹³C NMR (400 MHz) in CDCl₃

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4-Methoxyphenol (2f) ¹H NMR (400 MHz) in CDCl₃



4-Methoxyphenol (2f) ¹³C NMR (400 MHz) in CDCl₃



4-Hydroxyacetophenone (2g) ¹H NMR (400 MHz) in CDCl₃



4-Hydroxyacetophenone (2g) 13 C NMR (400 MHz) in CDCl₃

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3-Hydroxyacetophenone (2h) ¹³C NMR (400 MHz) in CDCl₃

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4-Chlorophenol (2i) ¹H NMR (400 MHz) in CDCl₃



4-Chlorophenol (2i) ¹³C NMR (400 MHz) in CDCl₃



2-Fluorobiphenyl-4-ol (2j) ¹H NMR (400 MHz) in CDCl₃











Isobutanol (4a) ¹³C NMR (400 MHz) in CDCl₃



Cyclohexanol (4b) ¹H NMR (400 MHz) in CDCl₃



Cyclohexanol (4b) ¹³C NMR (400 MHz) in CDCl₃

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6-Bromohexanol (4d) ¹H NMR (400 MHz) in CDCl₃



6-Bromohexanol (4d) ¹³C NMR (400 MHz) in CDCl₃

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3. Elemental composition reports



 O^{18} – Phenol (5a)

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Elemental Composition Report

Single Mass Analysis

Tolerance = 10.0 PPM 7 DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 9 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 0-10 H: 0-10 160: 0-2 180: 0-2 104Pd: 0-1

JL-89 Julia Luria ROZEN172E3 106 (5.351) Cm (104:110)



18

O¹⁸ - 4-Hydroxyacetophenone (5b)

3.0.



Elemental Composition Report

Single Mass Analysis Tolerance = 5.0 PPM 7 DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 5-12 H: 5-15 16O: 0-2 18O: 0-2 P: 0-2 JL97X Julia Luria ROZEN173 339 (17.074) Cm (329:340)



O¹⁸ - 4-Hydroxy-3-methylbenzonitrile (5c)

Elemental Composition Report



Single Mass Analysis

Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions 4 formula(e) evaluated with 3 results within limits (up to 50 closest results for each mass) Elements Used: C: 6-10 H: 4-10 N: 0-2 18O: 0-1 JL 107*JULIA GATENYO ROZEN190B 90 (4.545) Cm (90)





O¹⁸ - Isobutanol (5d)

O¹⁸ - Cyclohexanol (5e)



O¹⁸ - Phenylethanol (5f)



O¹⁸ - 6-Bromohexanol (5g)



References

- (1) For more information on this unique method see Aviv Analytical Ltd, Tel Aviv Israel: www.avivanalytical.com
- (2) (a) Amirav, A.; Gordin, A.; Poliak, M.; Fialkov, A. B. J. Mass. Spectrom. 2008, 43, 141-163. (b) Fialkov, A. B.; Amirav, A. Rapid. Com.
 Mass. Spectrom. 2003, 17, 1326-1338.
- (3) Dayan, S.; Kol, M.; Rozen, S. Synthesis **1999**, 1427-1430.
- (4) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. Org. Lett. 2010, 12, 1964-1967.
- (5) Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. Chem. Eur. J. 2011, 17, 5652-5660.
- (6) Lohre, C.; Droge, T.; Wang, C.; Glorius, F. Chem. Eur. J. 2011, 17, 6052-6055.
- (7) Zhu, C.; Wang, R.; Falck, J. R. Org. Lett. 2012, 14, 3494-3497.
- (8) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. J. Am. Chem. Soc. 2006, 128, 10694–10695.
- (9) Edsall, R. J.; Harris, H. A.; Manas, E. S.; Mewshaw, R. E. Bioorg. Med. Chem. 2003, 11, 3457-3474.
- (10) Jones, I. C.; Sharman, G. J.; Pidgeon, J. Magn. Reson. Chem. 2005, 43, 497–509.
- (11) Dieskau, A. P.; Begouin, J. M.; Plietker, B. Eur. J. Org. Chem. 2011, 5291–5296.