Secondary Alcohol Hemiacetal Formation: an *in situ* Carbonyl Activation Strategy

Lei You and Eric V. Anslyn*

Supporting Information

Experimental Section

General. ^1H -NMR, ^{13}C -NMR and ^{19}F -NMR were recorded at a 300 MHz or 400 MHz Varian Mercury spectrometer. UV titration and kinetics were performed on a Beckman DU-640 UV-Vis spectrophotometer. The glassware for the synthesis was flame-dried and the compound **1** was stored under argon. Compounds **2-4** were commercially available. All the anhydrous solvents for the titration were stored with 3Å molecular sieves. All measurements were performed at 25 °C.

Synthesis of 2-difluoroacetylpyridine (1). To anhydrous Et_2O (10 mL) under argon cooled at -45 °C (dry ice-ethanol slurry), was added *n*-BuLi (1 M in hexanes, 5.7 mL) through an addition funnel. 2-Bromopyridine (1.27 g, 8.0 mmol) in Et_2O (5 mL) was then added to the mixture. The dark orange-red solution was stirred for 20 min and cooled to -70 °C by adding Et_2O and dry ice to the cooling bath. To 2-pyridyllithium in Et_2O cooled at -70 °C, was added ethyl difluoroacetate (1.29 g, 10.4 mmol) in Et_2O (10 mL) dropwise. The mixture was continued to stir at -70 °C for 2 h. After warming to room temperature, the yellow solution was poured into water: 2M sulfuric acid mixture (1:1, 80 mL) and transferred into a separatory funnel. The ether layer was extracted with 2 M sulfuric acid (2 × 30 mL). The aqueous layers were combined and adjusted to pH 10~11 by NaOH. The brown mixture formed was extracted with Et_2O (4 × 40 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (silica gel, hexane: EtOAc = 9:1 to 4:1) to afford a yellow oil (0.56 g, 44%). Both ketone and hydrate were observed in NMR. The mixture was dehydrated after stirring in CH_3CN in the presence of 3Å molecular sieves. ^1H -NMR (400 MHz, CD_3CN): δ 7.19 (1H, t, J = 54 Hz), δ 7.69 (1H, ddd, J = 7.6, 4.6, 1.4 Hz), δ 8.03 (1H, td, J = 7.6, 1.6 Hz), δ 8.12 (1H, dt, J = 7.6, 1.2 Hz), δ 8.74- 8.80 (1H, m). ^{19}F -NMR (400 MHz, CD_3CN): δ -131.4 (2F, d, J = 54 Hz). ^{13}C -NMR (300 MHz, CDCl_3): δ 107.6 (t), 123.9 (s), 128.7 (s), 137.6 (s), 149.7 (s), 150.6 (s), 187.4 (t). 98% purity by LC/MS: m/z 158.29 ($[\text{M} + \text{H}]^+$), 176.13 ($[\text{M} + \text{H}_2\text{O} + \text{H}]^+$).

NMR Titrations and Reactions Screen. For NMR titrations, a mixture of host **1**

(30- 40 mM), 2-propanol (5 equiv) and methanesulfonic acid (0- 2 equiv) in CD₃CN (0.85 mL) in the presence of 3Å molecular sieves, was stirred at room temperature for 2 h. The ¹H-NMR and ¹⁹F-NMR spectra were recorded after 4 h, 24 h and 48 h. For the control experiments, a mixture of host **1** or **4**, 2-propanol (5 eq.) and In(OTf)₃ (0- 1 eq.) in CD₃CN (0.85 mL) in the presence of 3Å molecular sieves was stirred at room temperature for 2 h. The ¹H-NMR and ¹⁹F-NMR spectra were recorded after 4 h, 24 h and 48 h. For screening of hosts and acids, the host, alcohol, and acid were stirred in CD₃CN for 2 h, and the NMR spectra were taken afterwards. The percentage of each component in the reaction mixture was calculated from the integrations of ¹H-NMR and ¹⁹F-NMR spectra.

UV Titrations and Kinetics Measurements. The stock solutions of host **1**, 2-propanol and acids in CH₃CN were stored in the presence of 3Å molecular sieves. For UV titrations, after addition of titrants the sample was sonicated for ~10 s and allowed to stand for ~5 min before measurement. For kinetics measurements with CH₃SO₃H or Zn(OTf)₂ as activators, all the reactants were mixed together in CH₃CN, and the absorbance at 255 nm or 269 nm was recorded. For kinetics measurements with In(OTf)₃, the host **1** and 2-propanol was mixed together in CH₃CN, and the absorbance spectra was recorded. The solution of In(OTf)₃ was then added quickly and time was recorded. The absorbance at 255 nm was followed immediately, and the starting time was also recorded. All the concentrations are listed in the captions of corresponding figures.

Table S1. Chemical shift changes (ppm) of host **2** upon binding of Brønsted and Lewis acids in CD₃CN.

Entry	Acid	H _a	H _b	H _c	H _d	H _e	Carbonyl C
1	no acid	8.80	7.62	7.97	7.94	10.02	195.1
2	CH ₃ SO ₃ H (5 equiv)	8.98	8.31	8.86	8.56	10.10	185.8
3	In(OTf) ₃ (1 equiv)	8.95	8.32	8.88	8.58	10.08	185.7
4	Zn(OTf) ₂ (1 equiv)	8.92	8.12	8.50	8.44	10.01	195.5

Table S2. Chemical shift changes (ppm) of host **1** upon binding of Lewis acid in CD₃CN.

Entry	Acid	H _a	H _b	H _c	H _d	H _e	F
1	no acid	8.77	7.69	8.03	8.12	7.19	-131.4
2	Zn(OTf) ₂ (1 equiv)	8.86	7.90	8.24	8.30	7.15	-130.1
3	CH ₃ SO ₃ H (5 equiv)	8.97	8.09	8.51	8.41	7.01	-129.7
4 ^a	In(OTf) ₃ (1 equiv)	/	/	/	/	6.97	/

a. The indium complex is so reactive that hydrate is the major component. All aromatic signals overlap with others.

Scheme S1. Addition of 2-propanol to hosts **1** and control **4** (30- 40 mM) in the presence of varied amount of indium triflate in CD₃CN.

Scheme S2. Addition of 2-propanol to host **1** (~ 36 mM) in the presence of varied amount of methanesulfonic acid in CD₃CN.

Scheme S3. Addition of 2-propanol to host **2** (~ 190 mM) in the presence of methanesulfonic acid.

Figure S1. Titration of MeSO₃H into host (0.17 mM) solution in CH₃CN. This is an acid-base reaction and the equilibrium is readily established.

Figure S2. Titration of 2-propanol into the solution of **1** (0.17 mM) and CH₃SO₃H (9.16 mM) in CH₃CN (left panel) and its binding isotherm (right panel).

Figure S3. Titration of In(OTf)₃ into host (0.17 mM) solution in CH₃CN. The complex of host with indium is so reactive that it will form hydrate immediately.

Figure S4. (Top panel) Time dependence of absorbance spectra of host **1** (0.17 mM), 2-propanol (19.25 mM) and CH₃SO₃H (9.40 mM) in CH₃CN and data points at two wavelengths. (Bottom panel) Linear fitting of data points at 255 nm and 269 nm.

Figure S5. Monitoring of the peak at 255 nm in the presence of host **1** (0.17 mM), MeSO₃H (9.41 mM) and 2-propanol (top panel: 19.25 mM; bottom panel: 3.08 mM) and data fitting.

Figure S6. ^1H -NMR of 1 with its hydrate in CD_3CN .

Figure S7. ^{19}F -NMR of **1** with its hydrate in CD_3CN .

Figure S8. ^{13}C -NMR of **1** with its hydrate in CDCl_3 .

Figure S9. ^1H -NMR of 1 after dehydration in CD_3CN .

Figure S10. ^{19}F -NMR of **1** after dehydration in CD_3CN .

Figure S11. LC/MS data of **1**.

Figure S13. ^{19}F -NMR of the reaction of **1** with 2-propanol (5 equiv) in the presence of $\text{In}(\text{OTf})_3$ (1 equiv) and 3Å MS in CD_3CN .

Figure S14. ^{19}F -NMR of the reaction of **1** with 2-propanol (5 equiv) in the presence of $\text{Zn}(\text{OTf})_2$ (1 equiv) in CD_3CN .

Figure S15. Region of ¹H-NMR of the reaction of **2** with 2-propanol (1 equiv) in the presence of In(OTf)₃ (0.5 equiv) in CD₃CN after 6 h.