Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.


# Convenient and Accurate Insight into Solution-Phase Equilibria from FlowNMR Titrations

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## Supplementary Information

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## 2. NMR Titration Apparatus

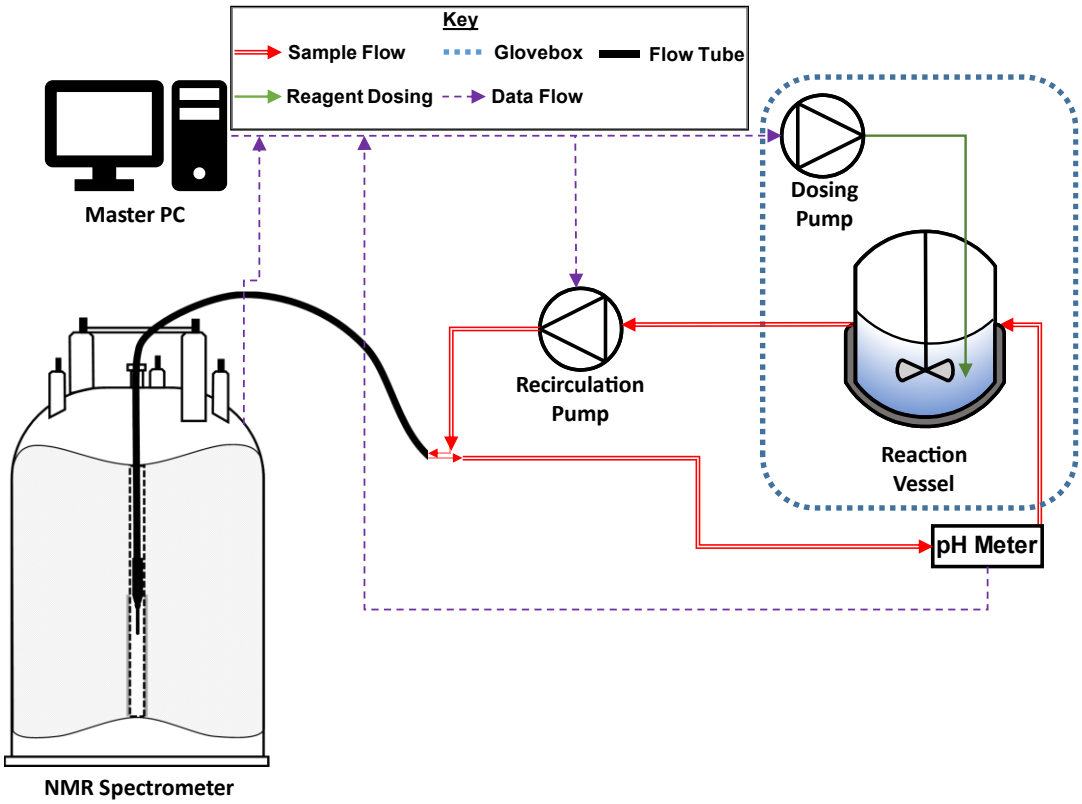



*Figure S1: Schematic of the recirculating flow set-up.*

Titrations were performed in round-bottomed flasks with a magnetic stirrer bar. A peristaltic pump (Vapourtec SF-10) circulated reaction mixture through a Bruker InsightMR flow tube (5 mm tube, glass tip internal volume = 0.5 mL) inserted into an NMR spectrometer (Bruker Ultrashield 500 MHz Avance II+ or Avance III HD equipped with either a room temperature broadband (BBO) probe or a nitrogen-cooled Prodigy Cryoprobe). All spectra were acquired under flow conditions except for variable temperature, DOSY, COSY, and reagent characterisation spectra, which were acquired either in a static sample tube, or with recirculation and dosing flow stopped.

The flow path and transfer lines were composed of fluorinated polyethylene-propylene tubing (Teflon FEP, I.D = 0.76 mm, O.D = 1/16”) and were supported on a plastic trolley (Rubbermaid) which allowed the flow setup to be transported as required. Transfer lines were connected to the reaction vessel via a rubber septum. Reagent dosing under atmospheric conditions was done at 6.6 mL/hr with a Cole-Parmer 78-9100C single-syringe pump connected to a 20 cm length of FEP tubing (O.D 1/16”, I.D 0.51 mm) with PEEK fittings (Upchurch Scientific).

Air-sensitive reactions were carried out from inside a glovebox with an argon atmosphere, connected to the flow tube via feed-through ports made from zero-volume 1/16” PEEK unions. Reagent dosing was done at 6.66 mL/hr with a Harvard Apparatus 22 dual syringe pump housed within the glovebox connected to a 20 cm length of FEP tubing (O.D 1/16”, I.D 0.76 mm) with PEEK fittings (Upchurch Scientific).

Dosing tubing was connected to the titration vessel via a rubber septum and submerged in the analyte to ensure gradual dosing. Dosed reagent concentrations were calculated from the syringe pump dosing rate. Reagent dosing was confirmed to be uniform without leaching or inefficient mixing by periodically stopping the dosing and creating a time-adjusted titration profile to observe any tailing or inconsistencies (Figure S2). Performing an experiment without any acid addition confirmed that flowing base through the flow path without acid resulted in no background drift of chemical shift (Figure S3).

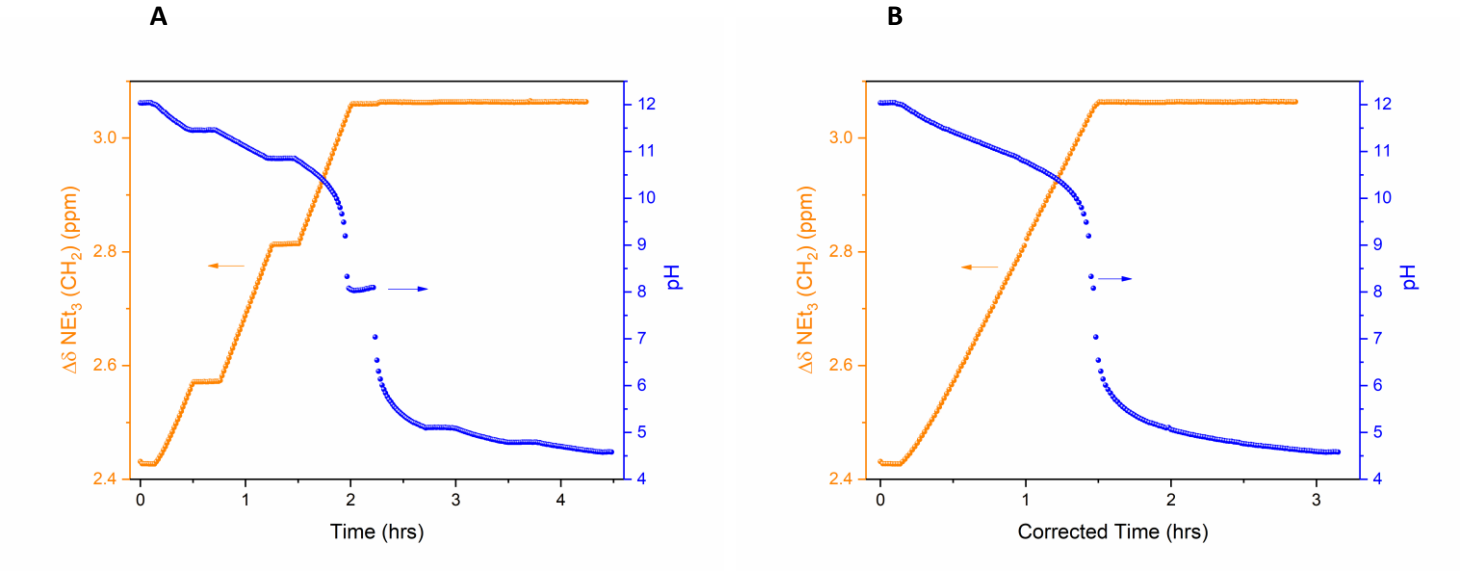



*Figure S2: Chemical shift and pH of triethylamine (100 mM) titrated with pivalic acid (100 mM) in $H_2O$ at 293K with periodic pausing of acid dosing (A) and the time adjusted profile (B).*

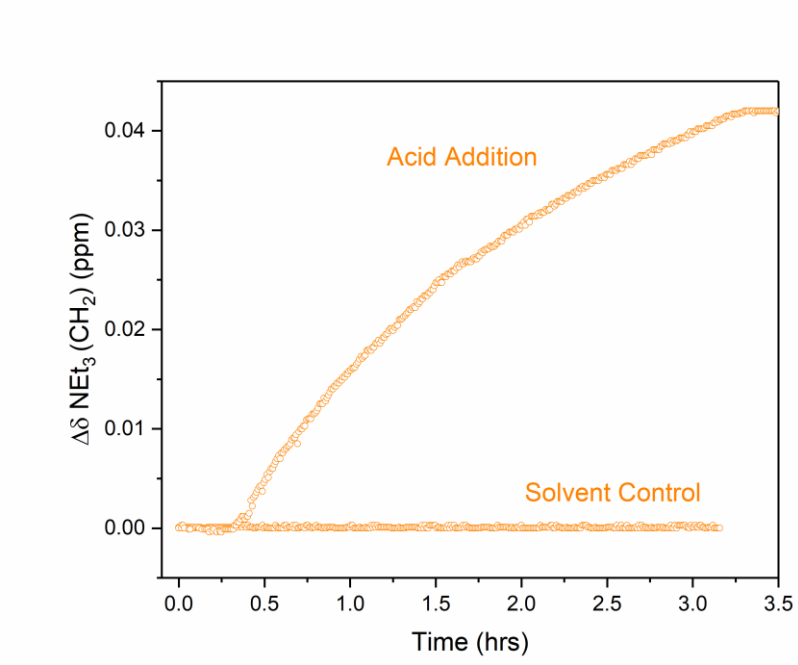



*Figure S3: Chemical shift evolution of triethylamine (100 mM) when flowed with and without the addition of pivalic acid (100 mM) in THF at 293K.*

## 3. pH Titration Apparatus

pH data in the flow path was acquired using Unisense flow pH probes (pH 500 and ref-100 mounted in stainless steel flow cells) inserted sequentially at the end of the flow path using a combination of PEEK HPLC-type fittings and 1/8" Swagelok connections (Figure S4).

pH data in the vessel was acquired with a Metrohm Unitrode pH probe (6.0258.000) which was submerged in the bulk analyte (Figure S5). This setup was used for the acquisition of pH data for the titration of triethylamine (100 mM) with pivalic acid (100 mM) in $H_2O$ (Figure S2) and the titration of protonated Leu-Ala (63 mM) with NaOH (200 mM) in $H_2O$ (Figure S26).

All data was recorded using a Metrohm 913 pH meter at time intervals of 10 or 60 seconds. All probes were thoroughly rinsed with deionised water prior to and after use and stored in appropriate buffer solutions. Data acquisition was completed within a month of a three-point probe calibration using standardised solutions from the manufacturer.

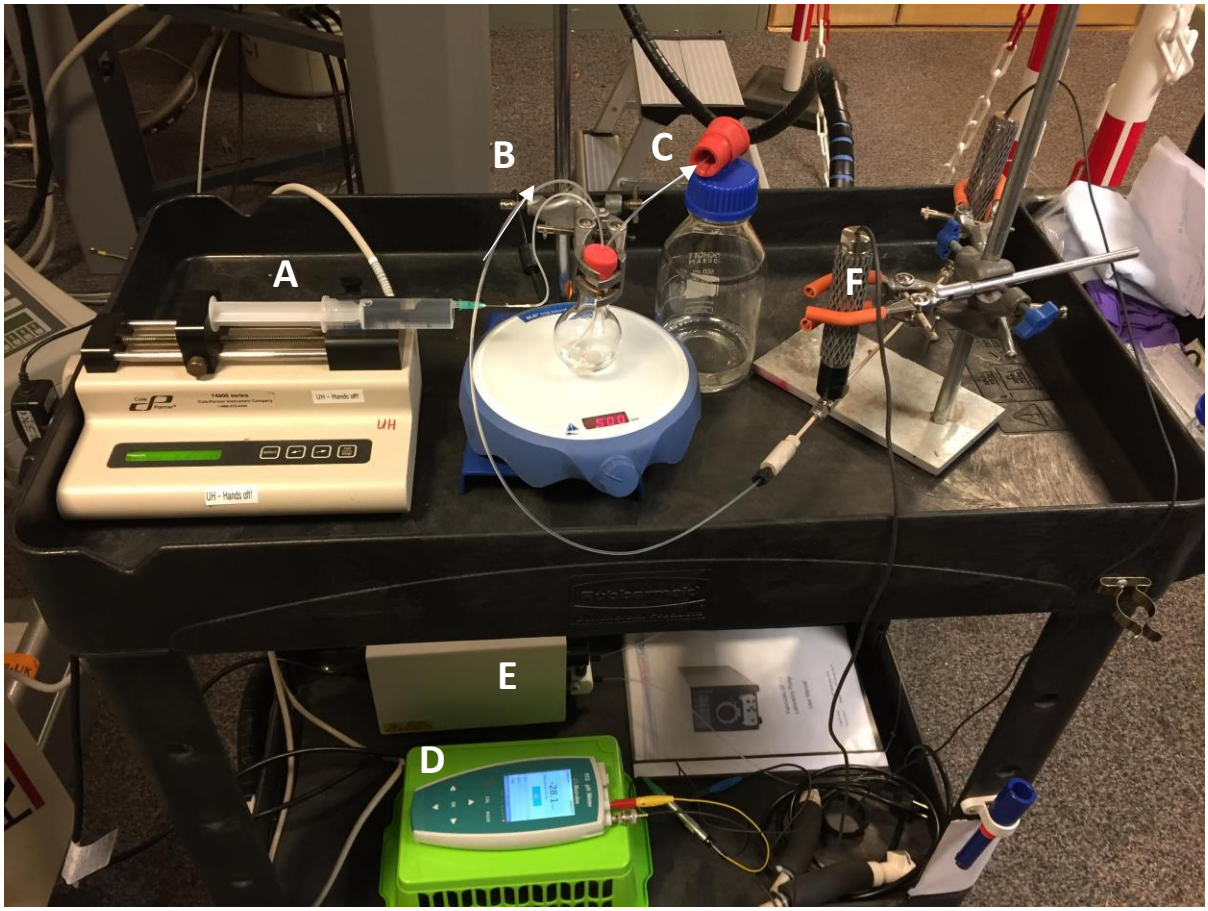



*Figure S4: A labelled image of the FlowNMR titration apparatus with the inclusion of Unisense flow pH probes. A – dosing pump, B – reaction vessel inlet, C – reaction vessel outlet, D – pH meter, E – recirculation pump, F – flow pH probe.*

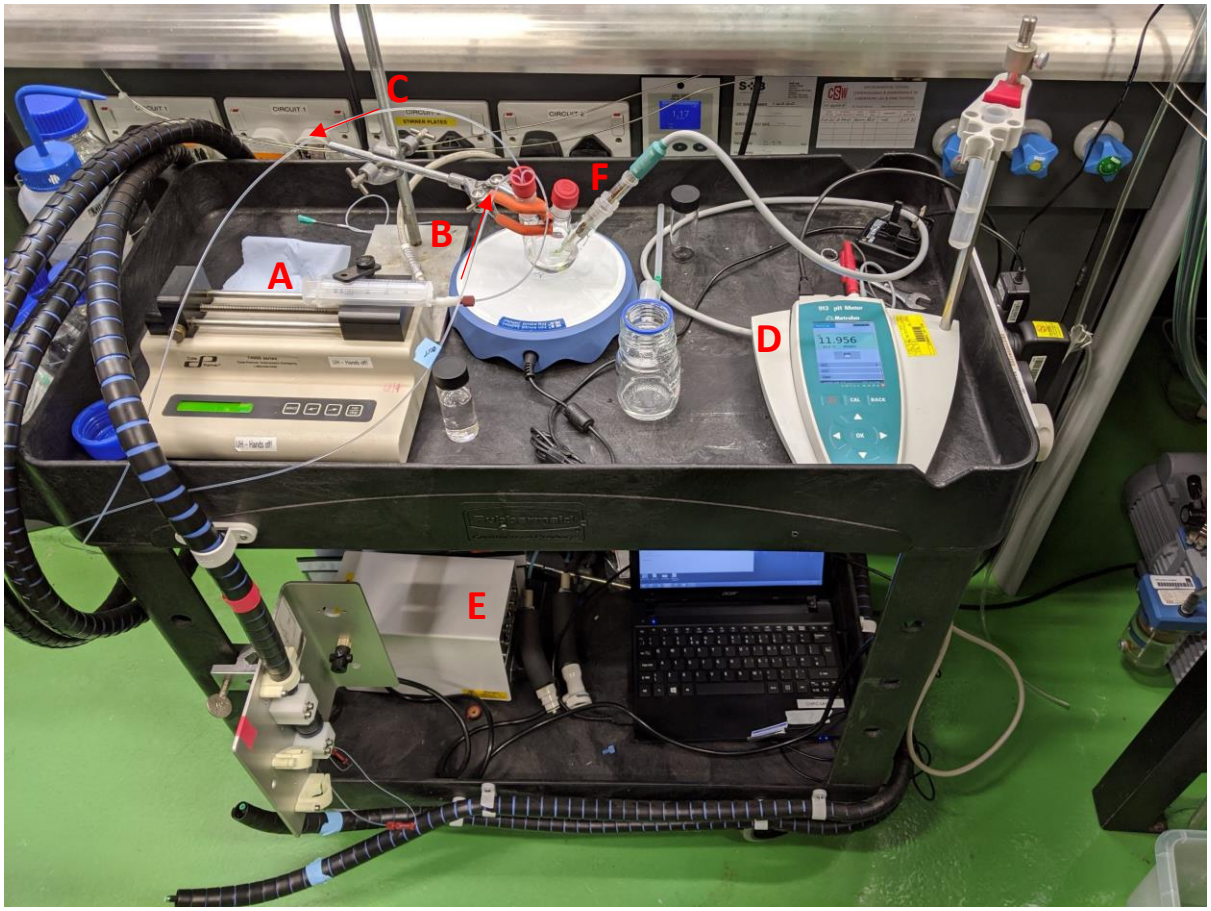



*Figure S5: A labelled image of the FlowNMR titration apparatus with the inclusion of a Metrohm Unitrode pH probe. A – dosing pump, B – reaction vessel inlet, C – reaction vessel outlet, D – pH meter, E – recirculation pump, F – pH probe.*

# 4. General

All reagents and solvents were sourced from major commercial suppliers and used as received unless otherwise stated. Chemistry sensitive to atmospheric conditions was carried out in flame-dried glassware under an atmosphere of dry argon inside a glovebox or using Schlenk techniques.

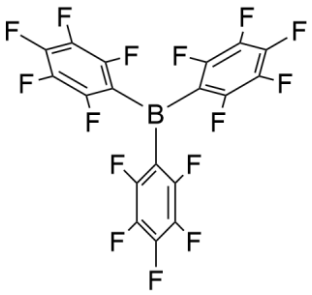
Tetrahydrofuran (THF) and Toluene (Tol) were freshly distilled from potassium and sodium/benzophenone, respectively. Dry stock solutions and solvents were vacuum degassed, stored over 3Å molecular sieves under argon and kept for no longer than a week. Acetonitrile (MeCN) 99.9% extra dry over molecular sieves was purchased from Acros Organics and further dried over freshly activated 3 Å molecular sieves prior to use.

Reagent grade 2,6-lutidine (Lut) was refluxed over calcium hydride for 3 hours before being fractionally distilled from calcium hydride at 175 °C, with the first fraction being discarded. Anhydrous pyridine was purchased from Acros Organics, stored over $CaH_2$ and syringe filtered before use.

Bromopentafluorobenzene was pre-dried over phosphorous pentoxide for 2 hours before being fractionally distilled from fresh phosphorous pentoxide at 150 °C.

# 5. Synthesis

## Tris(pentafluorophenyl)borane



tris(pentafluorophenyl)borane

Tris(pentafluorophenyl)borane etherate was synthesised according to literature.[1] The etherate (yellow cubic crystals) was thoroughly dried in *vacuo* and then purified by two-fold sublimation. The sublimate of the first sublimation (70-75 °C) was discarded and the remaining off-white solid was sublimed at 100 °C yielding $B(C_6F_5)_3$ as an amorphous white powder as confirmed by NMR analysis.

$^{11}$B NMR (500 MHz, 293 K, toluene) δ = 61.5.

$^{19}$F NMR (500 MHz, 293 K, toluene) δ = -130.0 (o-F), -142.7 (p-F), -161.1 (m-F).

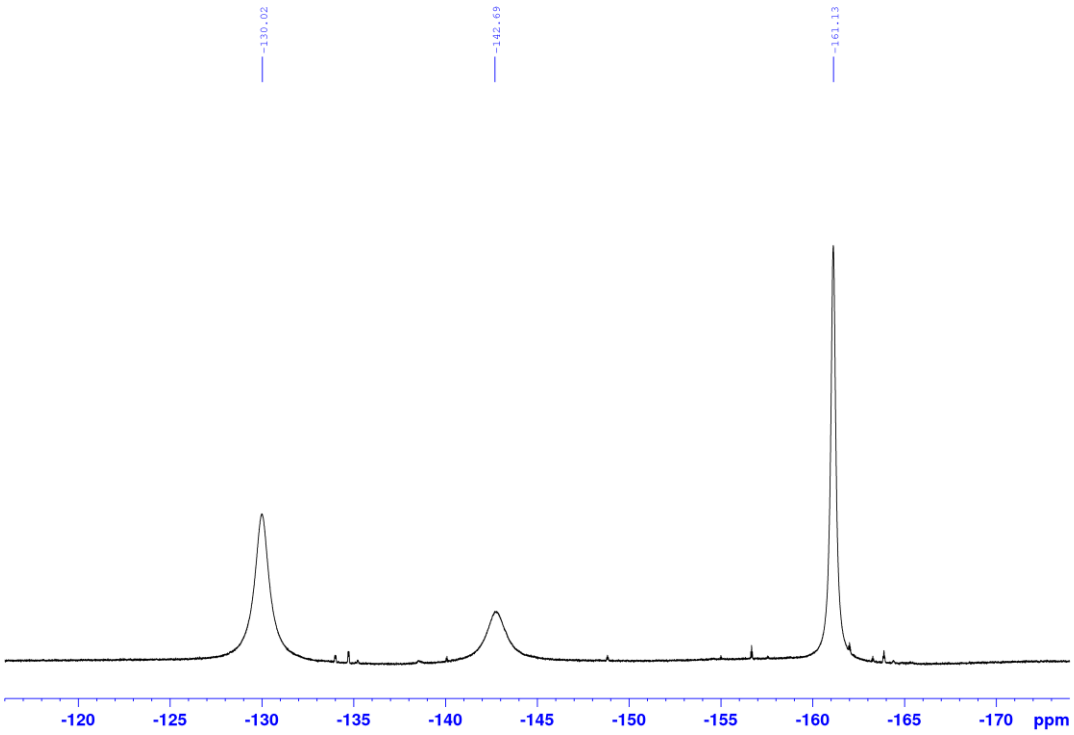
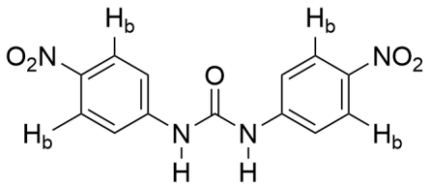



*Figure S6: $^{19}$F NMR spectrum of doubly sublimed tris(pentafluorophenyl) borane in toluene-H8 at 293 K.*

## 1,3-bis(4-nitrophenyl)urea




1,3-bis(4-nitrophenyl)urea was synthesised according to literature.[2] 4-nitrophenylisocyanate (0.32 g, 2 mmol) and 4-nitroaniline (0.27g, 2 mmol) were charged to a round bottom flask and the atmosphere exchanged for dry argon. Anhydrous dioxane (100 mL) was added and the mixture was heated at 100 °C for 18 hours. The reaction volume was reduced to about half by reduced pressure, and the yellow precipitate formed was filtered, washed with water, and dried in *vacuo*.

$^1$H NMR (500 MHz, 293 K, DMSO) δ = 8.22 (d, 4H, $H_b$), 7.73 (d, 4H, $H_a$), 9.66 (s, 2H, NH).

*minor impurities: 1,4 dioxane, water, 4-nitroaniline.

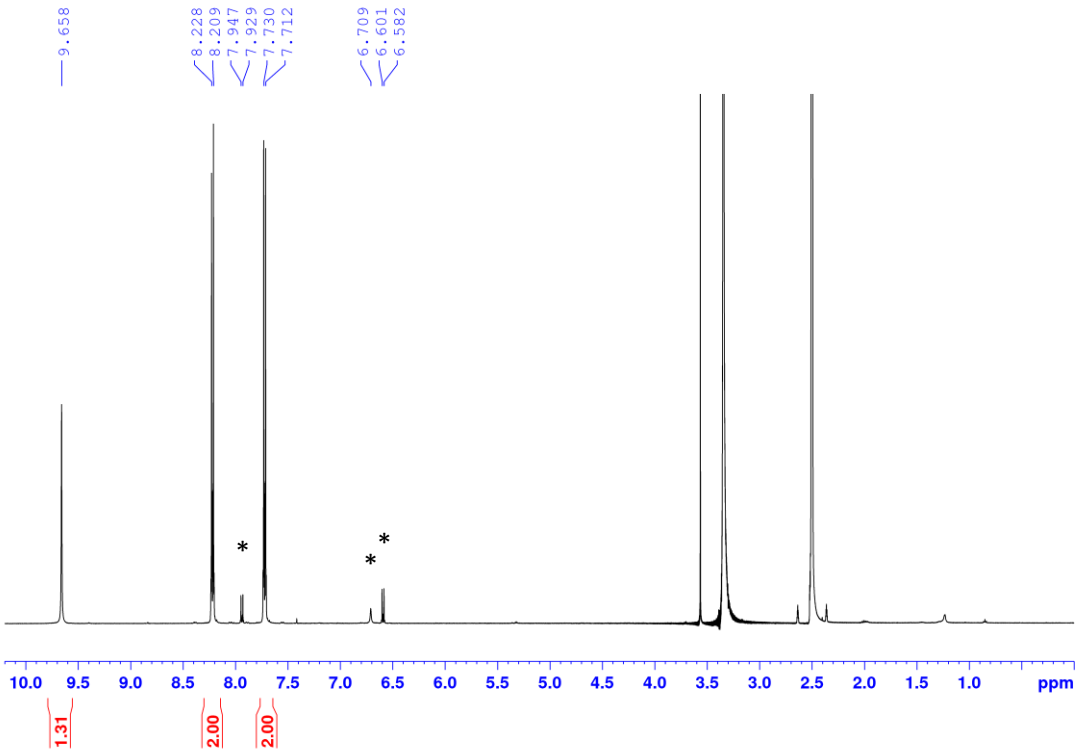



*Figure S7: $^1$H NMR spectrum of 1,3-bis(4-nitrophenyl) urea in DMSO-H6 at 293 K.*

# 6. Brønsted Acid/Base Titrations

## General procedure

The flow tube and flow path were emptied of any residual solvent and thoroughly rinsed with titration solvent for a minimum of 20 minutes at 4 mL/min. Solvent miscibility was checked before changing solvents within the flow path to ensure that immiscible solvents were not mixed in the flow path.

A base stock solution (10 mL) was charged to a 50 mL round bottom flask with a stirrer bar. Inlet and outlet of the flow setup were connected to the flask via a rubber septum, the stock solution was circulated around the flow path and acquisition was started. An acid stock solution (20 mL) was charged to a 24 mL Luer lock syringe, connected to fluoropolymer tubing (FEP, O.D 1/16”, I.D 0.51 mm) and mounted onto the syringe pump. The dosing tubing was inserted into the reaction vessel via rubber septum and submerged in the analyte to prevent stepwise additions caused by droplets. NMR (and pH where used) acquisition were started, titration progress was monitored by NMR and the reaction was stopped 10 minutes after complete reagent addition.

This methodology was used for all Brønsted acid-base titrations unless stated otherwise. Variables such as reagent concentration and acquisition parameters are noted in the captions of spectral plots.

## Spectral Stack Plots

### Triethylamine vs Acetic acid in $D_2O$

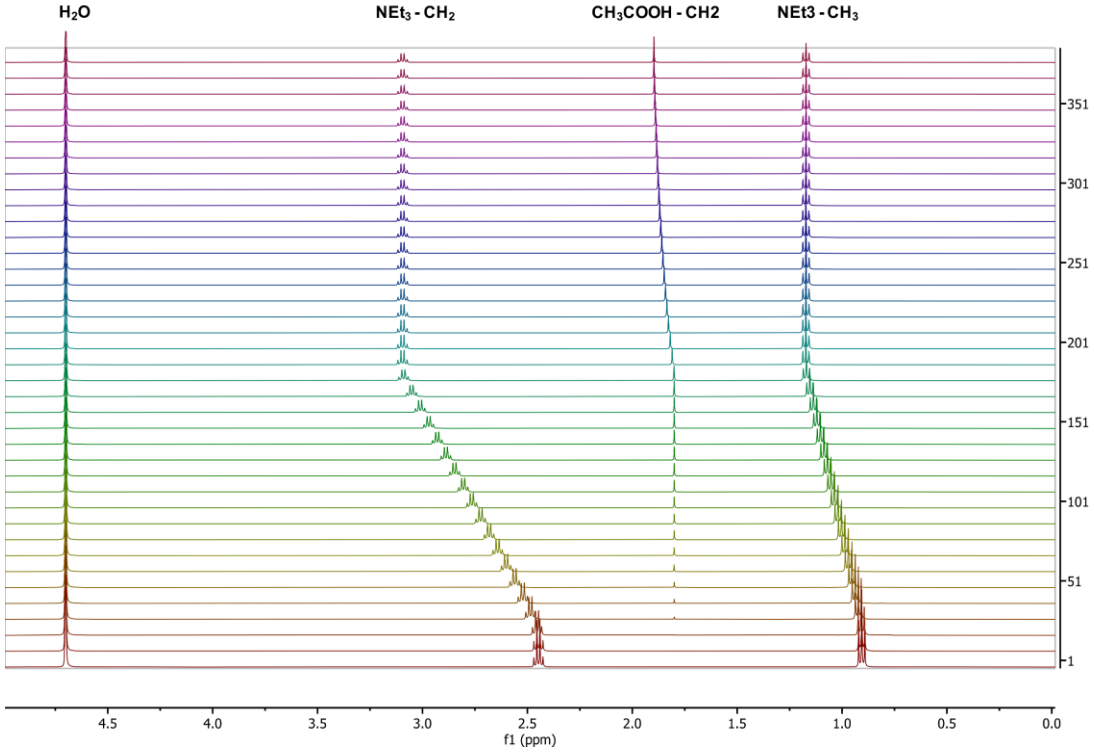



*Figure S8: Stacked $^1$H NMR spectra from the titration of triethylamine (100 mM) with acetic acid (100 mM) in $D_2O$ at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

Triethylamine vs Pivalic acid in $H_2O$

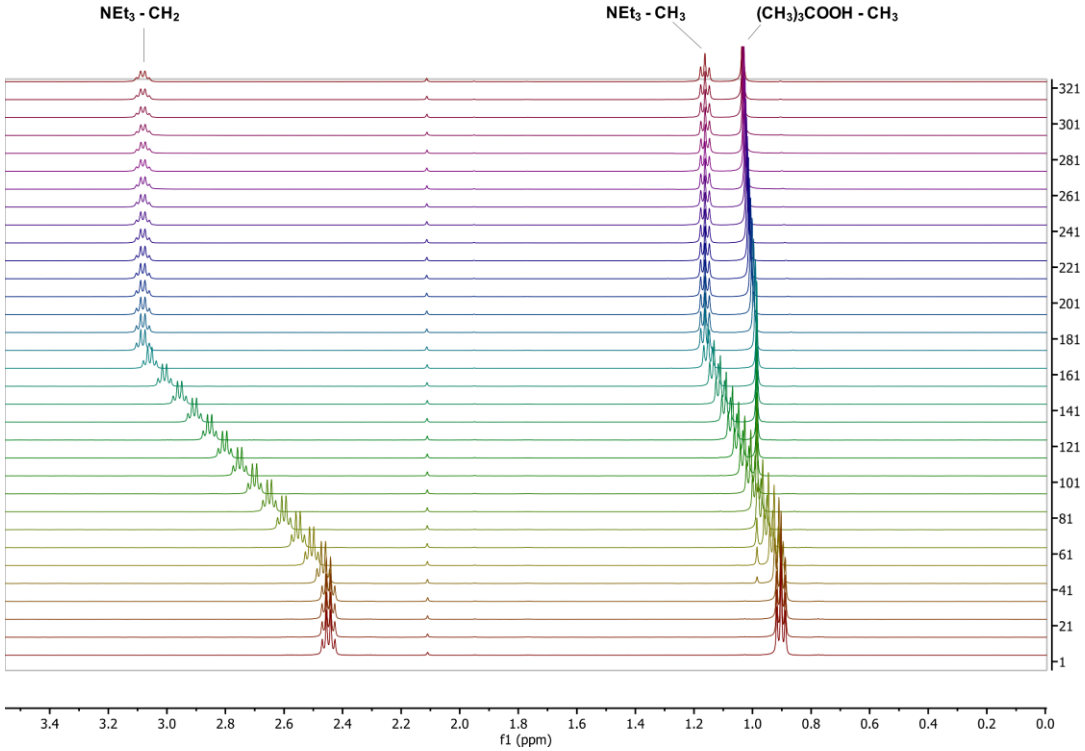



*Figure S9: Stacked $^1H$ NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in $H_2O$ at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG wet, 2 scans, 3s delay.*

Triethylamine vs Pivalic acid in MeCN

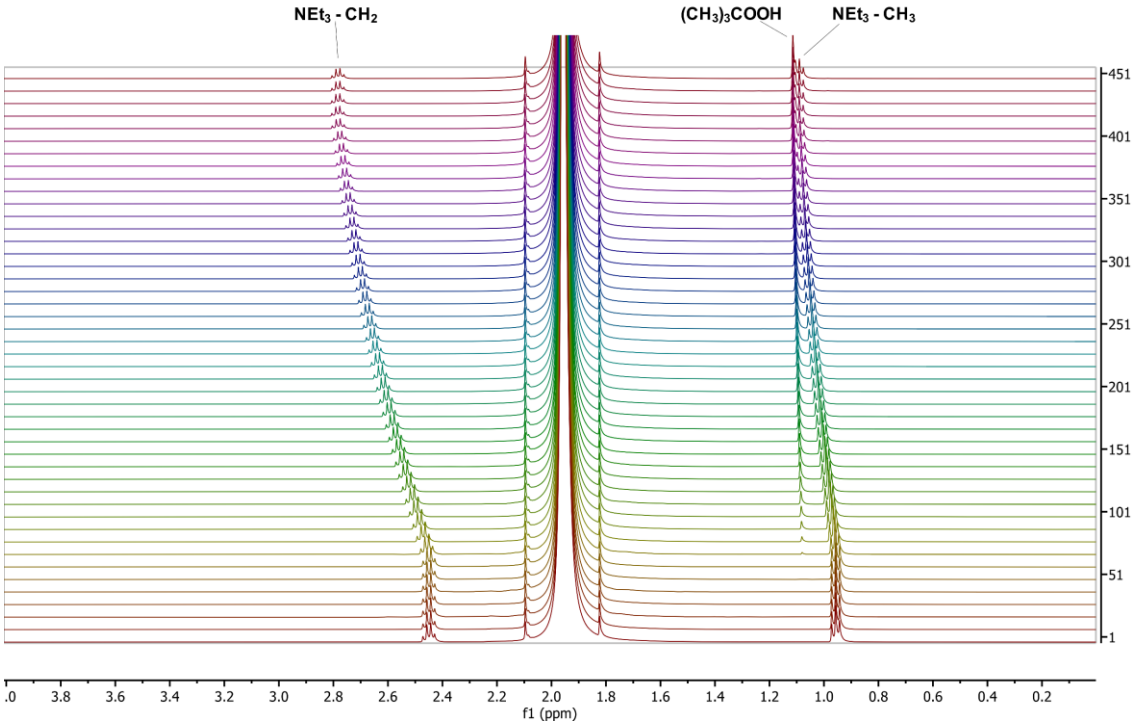



*Figure S10: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in acetonitrile at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

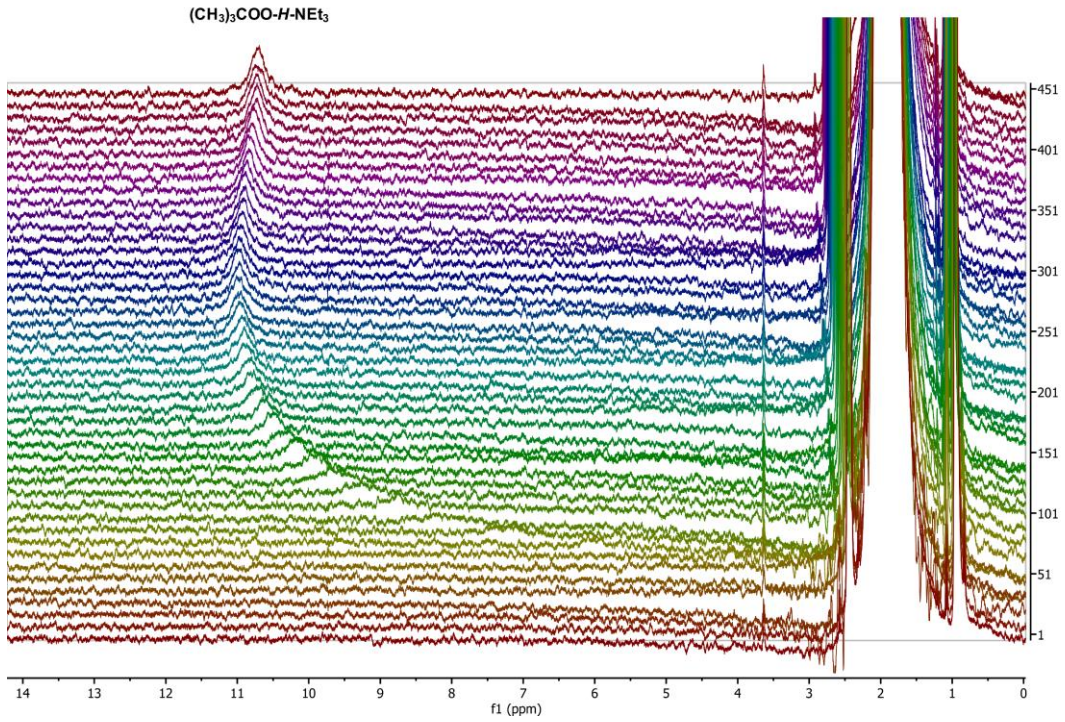



*Figure S11: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in acetonitrile at 293 K focused on a broad resonance at 8-12 ppm. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

Triethylamine vs Pivalic acid in THF

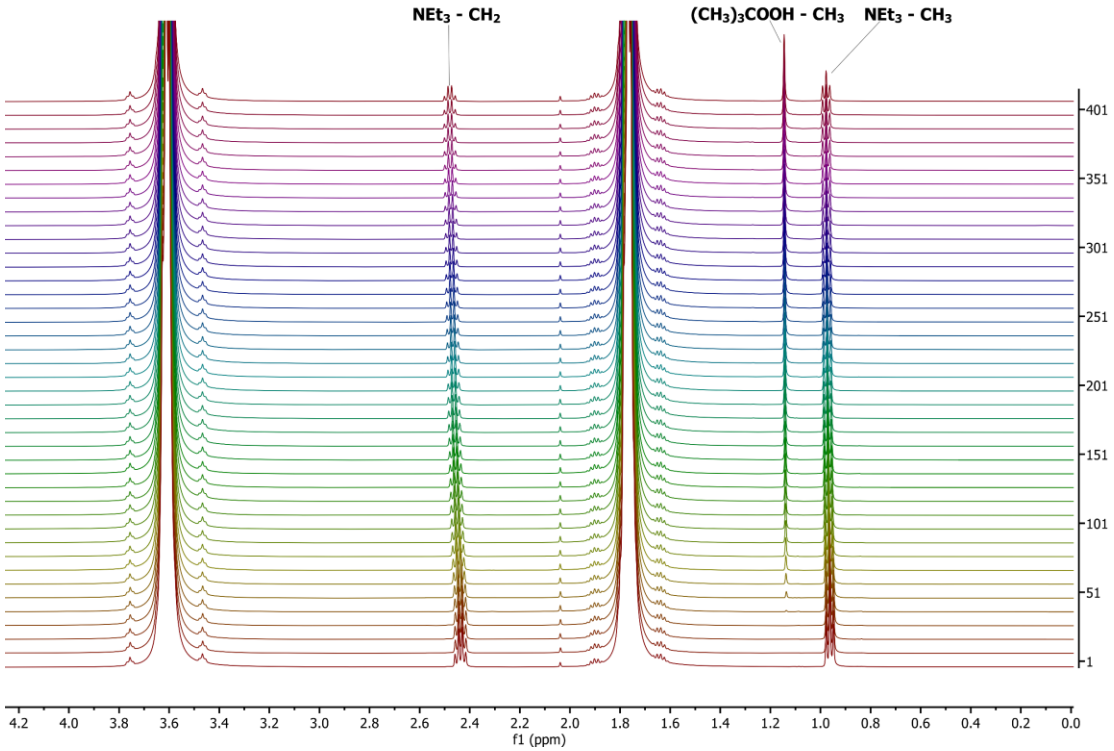



*Figure S12: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in tetrahydrofuran at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

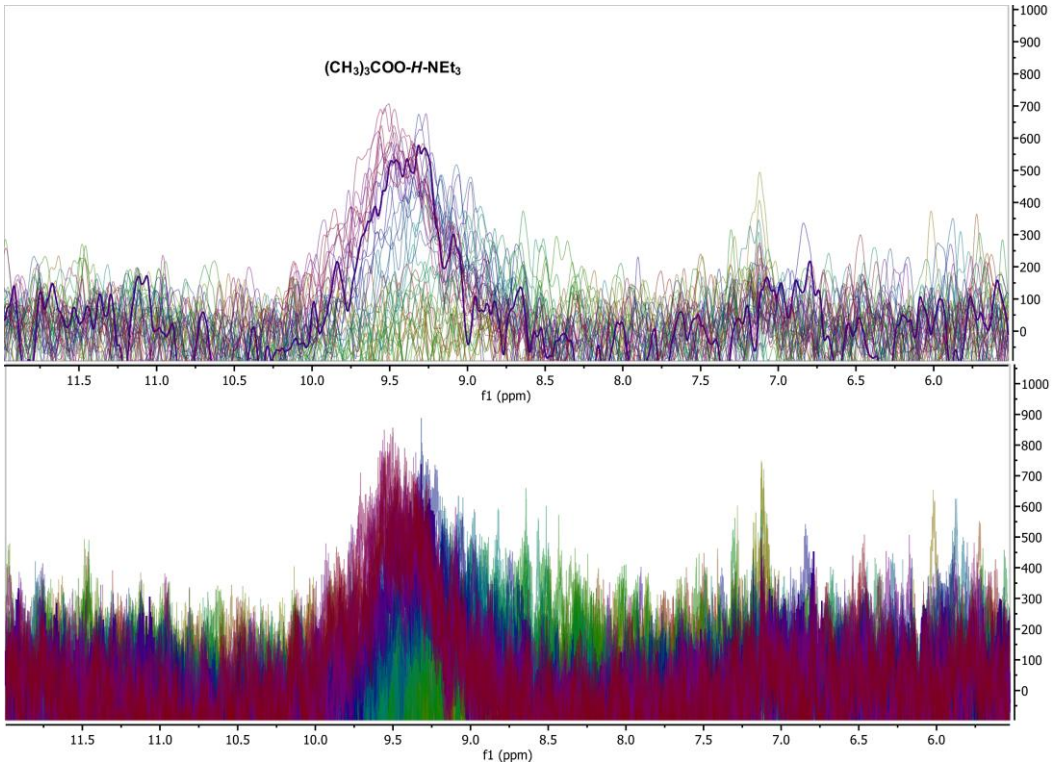



*Figure S13: Superimposed $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in acetonitrile at 293 K with added line broadening (top) to highlight the broad resonance at 9-10 ppm. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

Triethylamine vs Pivalic acid in Toluene

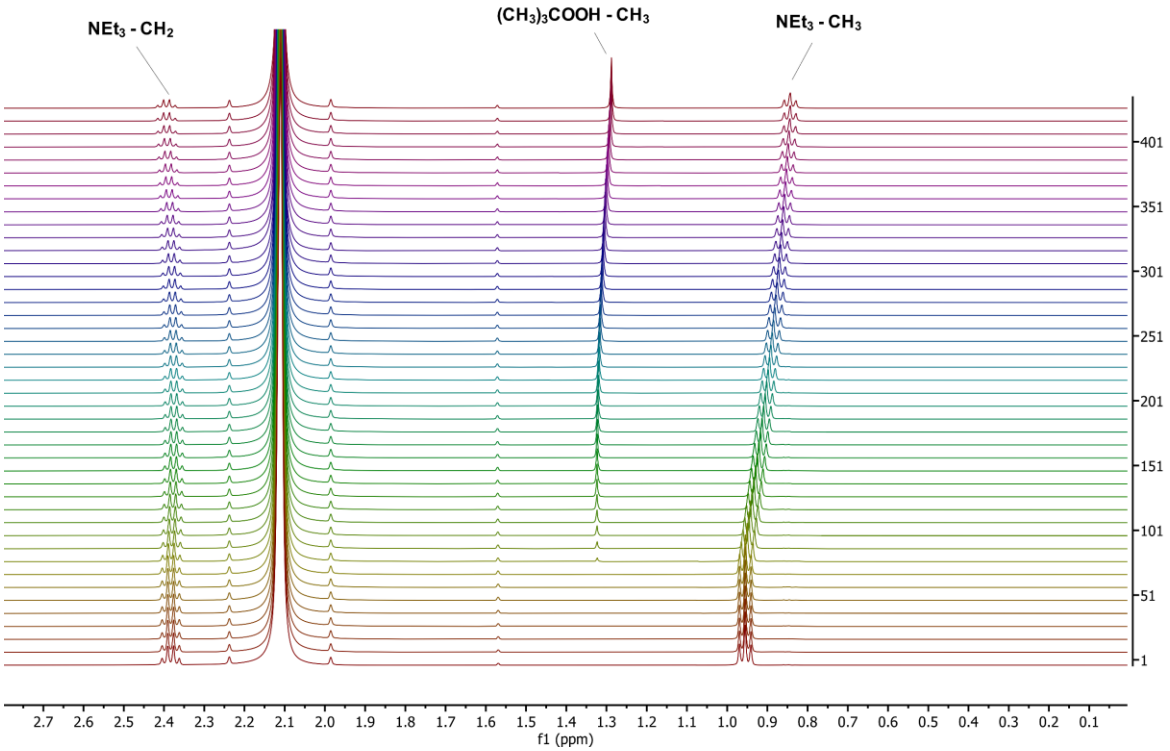



*Figure S14: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in toluene at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

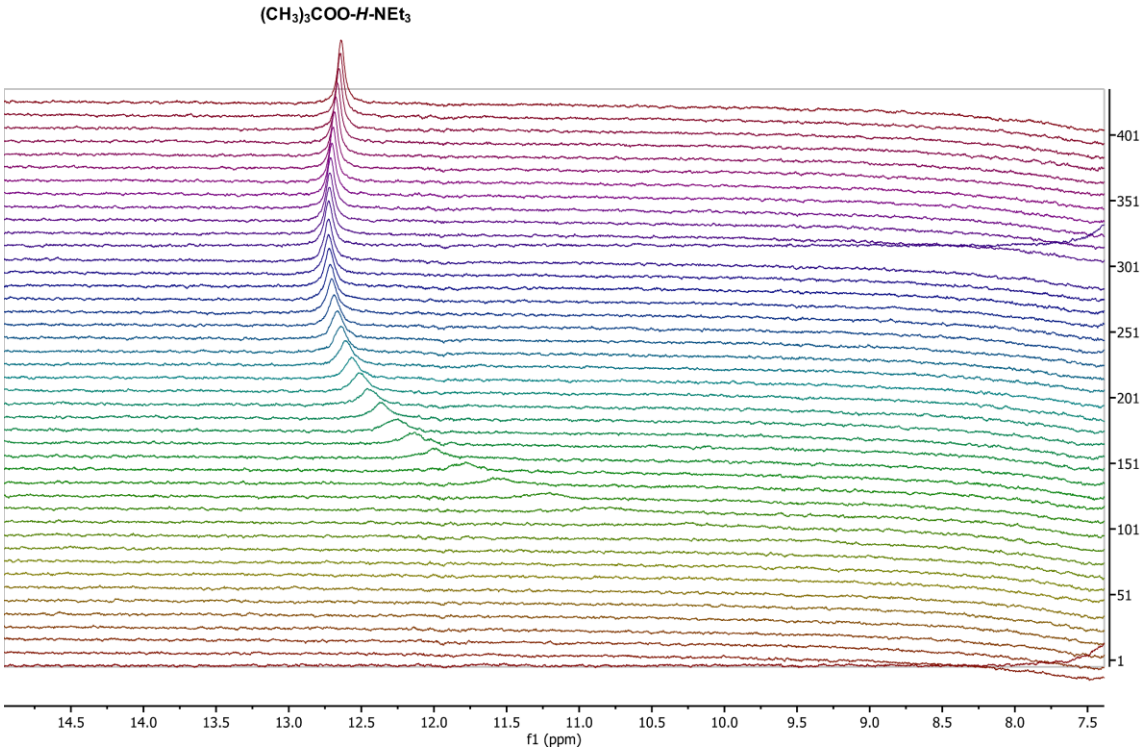



*Figure S15: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with pivalic acid (100 mM) in toluene at 293 K focused on the broad resonance at 10-13 ppm. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay.*

Triethylamine vs Acetic acid in wet THF

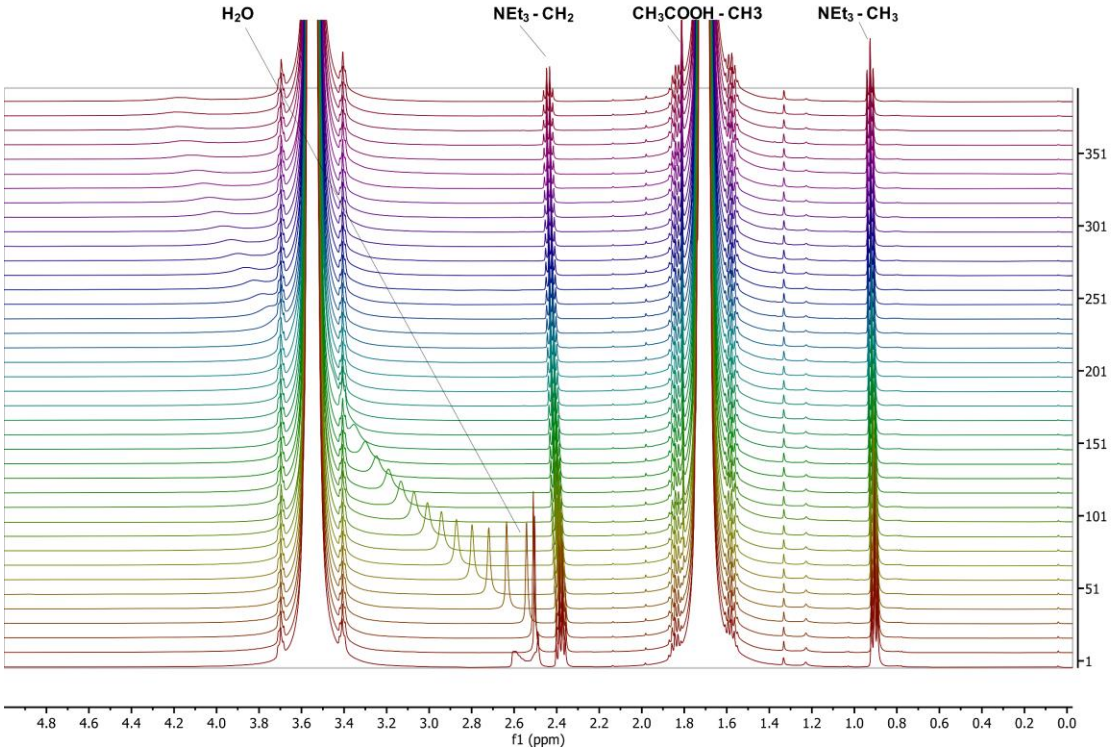



*Figure S16: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) with acetic acid (100 mM) in wet THF at 293 K. Data density was reduced by a factor of 10 for clarity. Acquisition parameters: PULPROG zg30, 8 scans, 1s delay*

Triethylamine and Pyridine vs p-Toluene sulfonic acid in MeCN

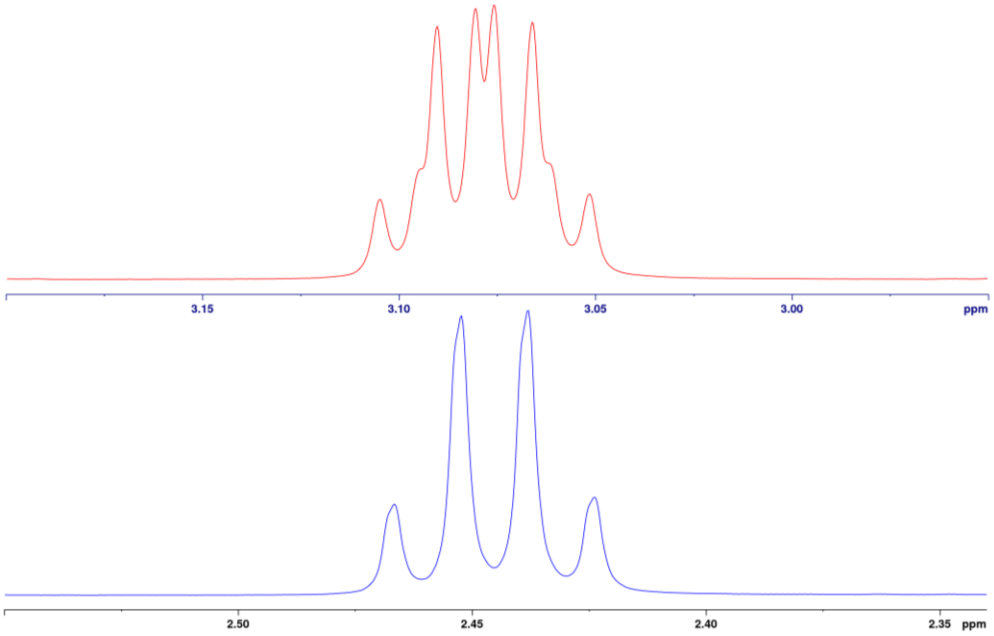



*Figure S17: $^{1}$H NMR spectra of triethylamine methylene resonance taken at 0 equivalents (quartet, $^{3}J_{HH}$ = 7.2 Hz, blue) and 4 equivalents (doublet of quartets, $^{3}J_{HH}$ = 7.2, 5 Hz, red) of p-toluene sulfonic acid. Chemical shift difference observed because of protonation. Acquisition parameters: PULPROG zg30, 32 scans, 1s delay*

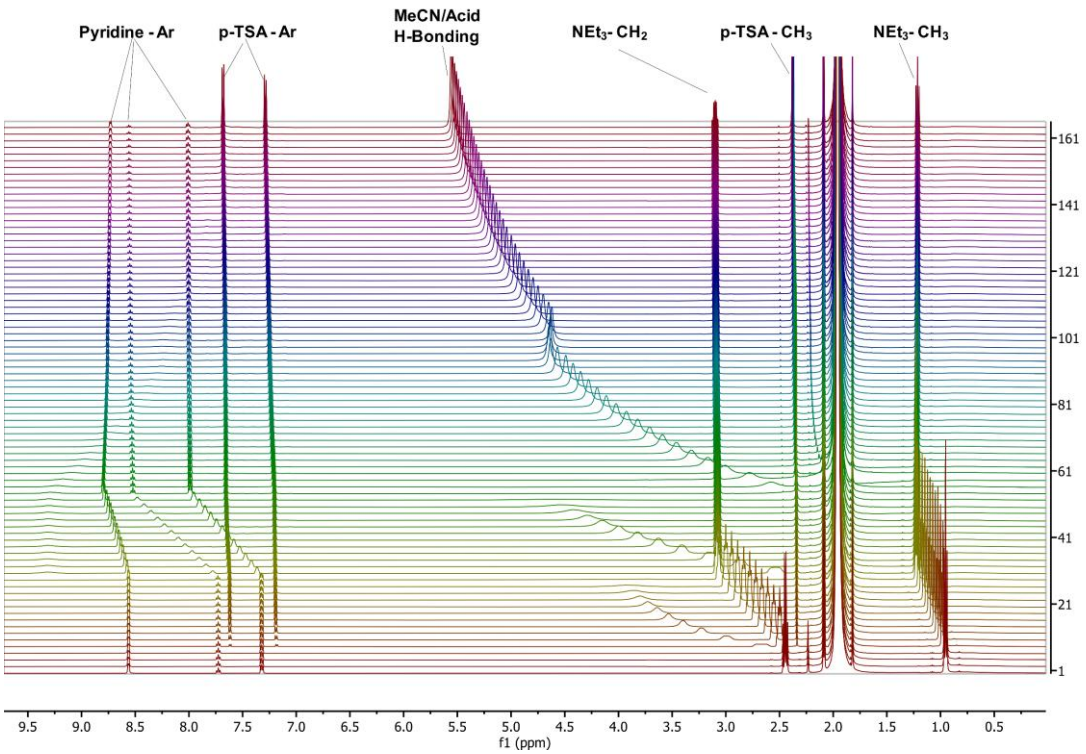



*Figure S18: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) and pyridine (100 mM) with p-toluene sulfonic acid (200 mM, 2 x 20 mL) in dry acetonitrile at 293 K. Data density was reduced by a factor of 2 for clarity. Acquisition parameters: PULPROG zg30, 32 scans, 1s delay*

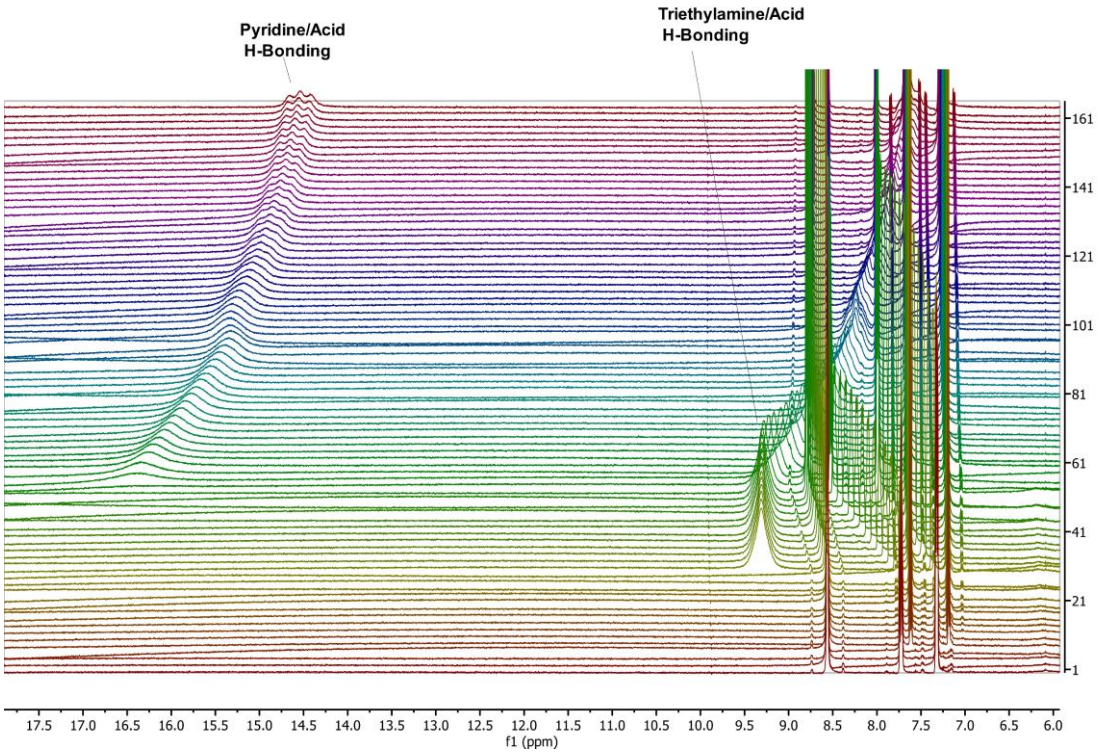



*Figure S19: Stacked $^{1}$H NMR spectra from the titration of triethylamine (100 mM) and pyridine (100 mM) with p-toluene sulfonic acid (200 mM, 2 x 20 mL) in dry acetonitrile at 293 K with a focus on 6-17 ppm. Data density was reduced by a factor of 2 for clarity. Acquisition parameters: PULPROG zg30, 32 scans, 1s delay.*

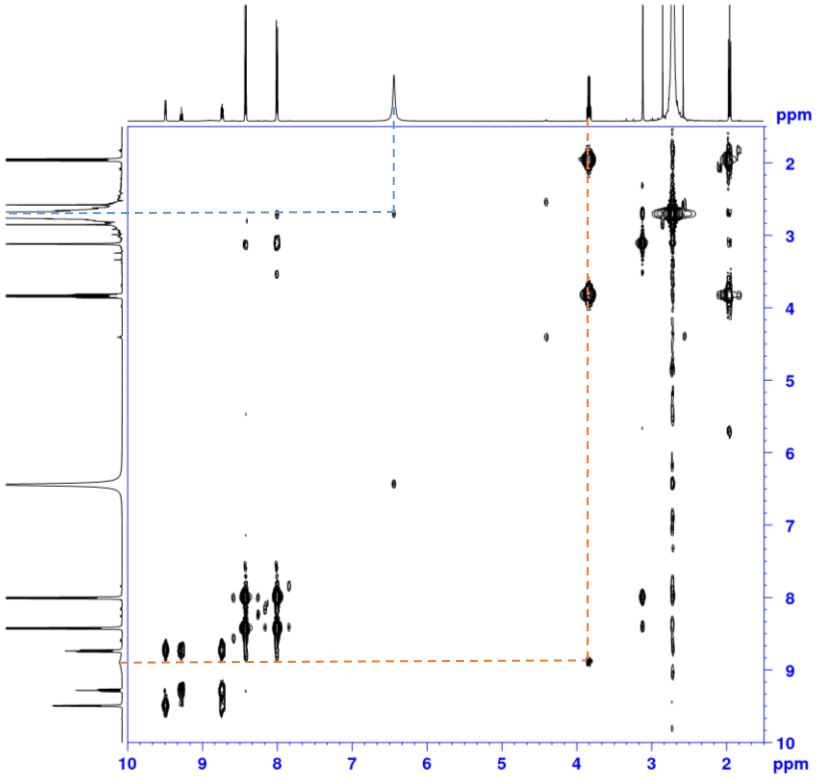



*Figure S20: $^{1}$H COSY NMR spectrum of triethylamine (100 mM), pyridine (100 mM) and p-toluene sulfonic acid (400 mM). Cross peaks with broad resonances for acetonitrile (blue) and triethylamine (orange) are highlighted. Acquisition parameters: PULPROG cosygpmfqf, 16 dummy scans, 4 scans, 1.88s delay*

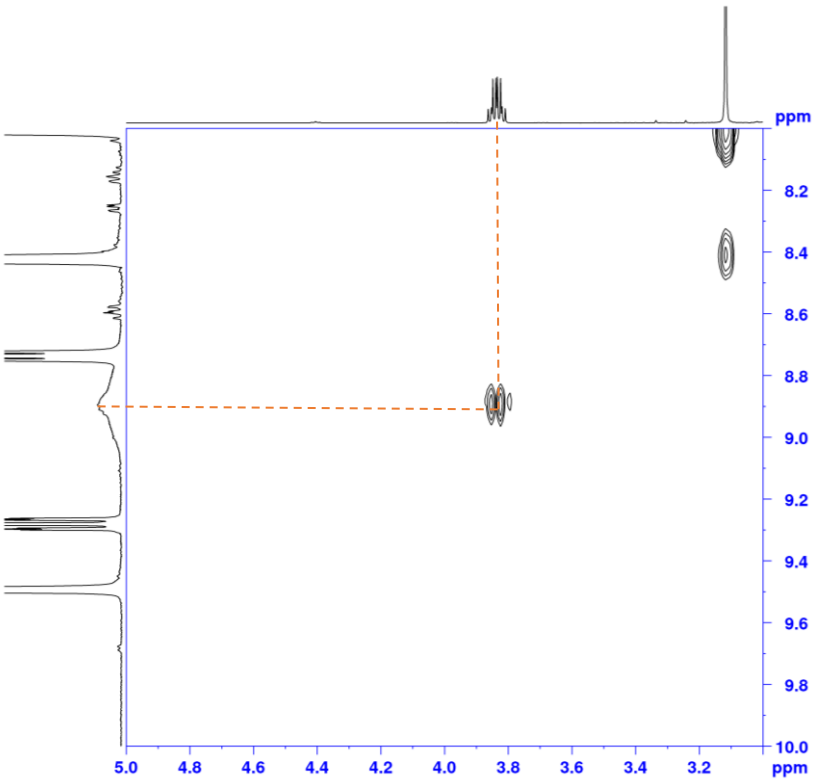



*Figure S21: $^{1}$H COSY NMR spectrum triethylamine (100 mM), pyridine (100 mM) and p-toluene sulfonic acid (400 mM) with focus on cross peak between a broad resonance (8.9 ppm) and triethylamine (3.8 ppm, orange). Acquisition parameters: PULPROG cosygpmfqf, 16 dummy scans, 4 scans, 1.88s delay*

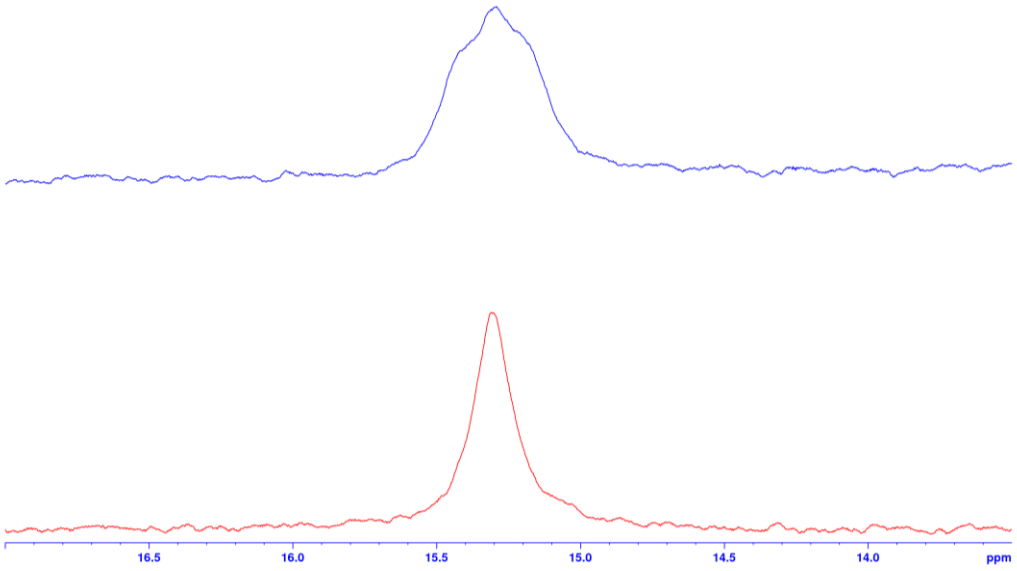
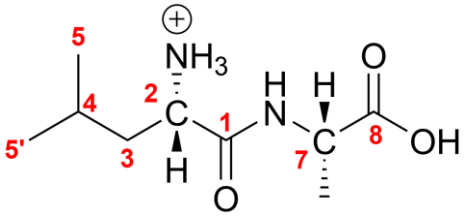



*Figure S22: $^{1}H$ (top, blue) and $^{1}H\{^{14}N\}$ (bottom, red) NMR spectra of pyridine (200 mM) and p-toluene sulfonic acid (1000 mM) in acetonitrile focused on the observed H-bonding peak. $^{14}N$ coupling to the broad singlet is observed. Acquisition parameters: $^{1}H$ - PULPROG zg30, 16 scans, 1s delay. $^{1}H\{^{14}N\}$ – PULPROG zgig30, 16 scans, 1s delay.*

L-Leucyl-L-alanine (protonated) vs Sodium Hydroxide in $H_2O$



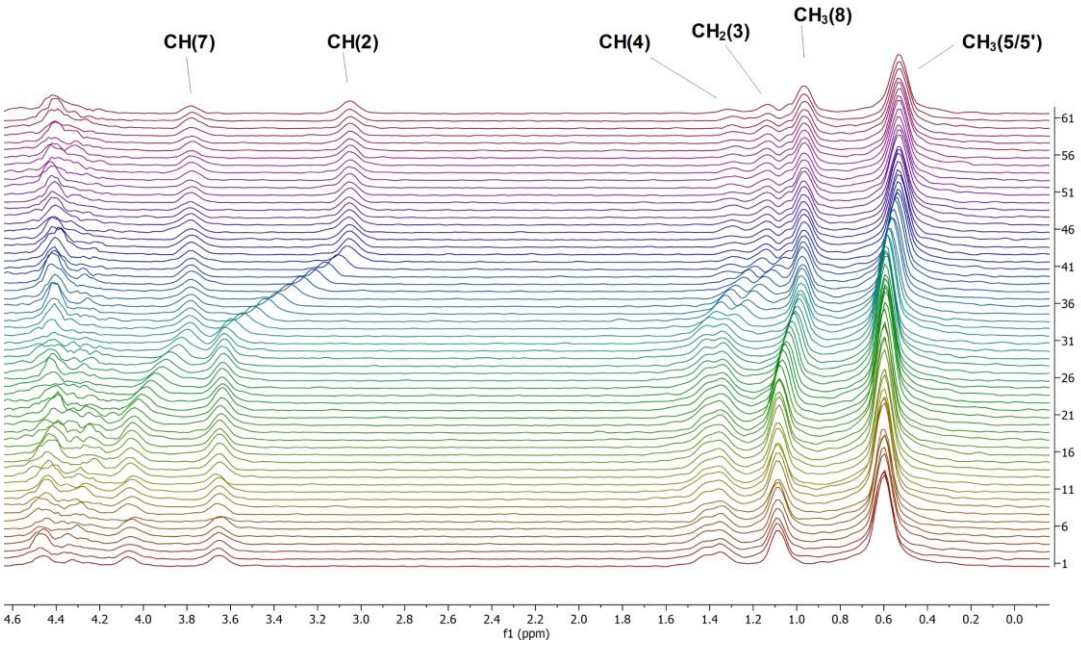




*Figure S23: 1D $^{1}H$ NMR projection stack plot from the deprotonation of protonated Leu-Ala (63 mM) with NaOH (200 mM) in $H_2O$ at 293 K. Acquisition parameters: PULPROG asaphmqc_dipsi.be, 16 dummy scans, 4 scans, 0.25 s delay.*

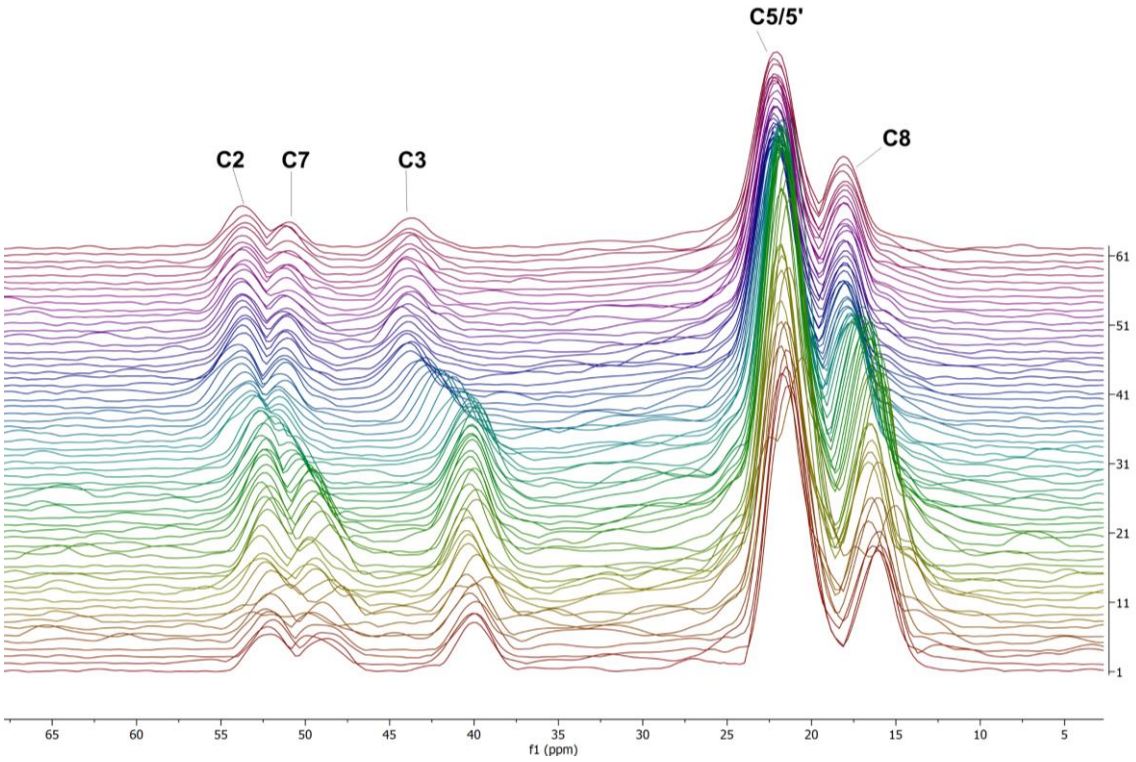



*Figure S24: 1D $^{13}C$ NMR projection stack plot from the deprotonation of protonated Leu-Ala (63 mM) with NaOH (200 mM) in $H_2O$ at 293 K. Acquisition parameters: PULPROG asaphmqc_dipsi.be, 16 dummy scans, 4 scans, 0.25 s delay.*

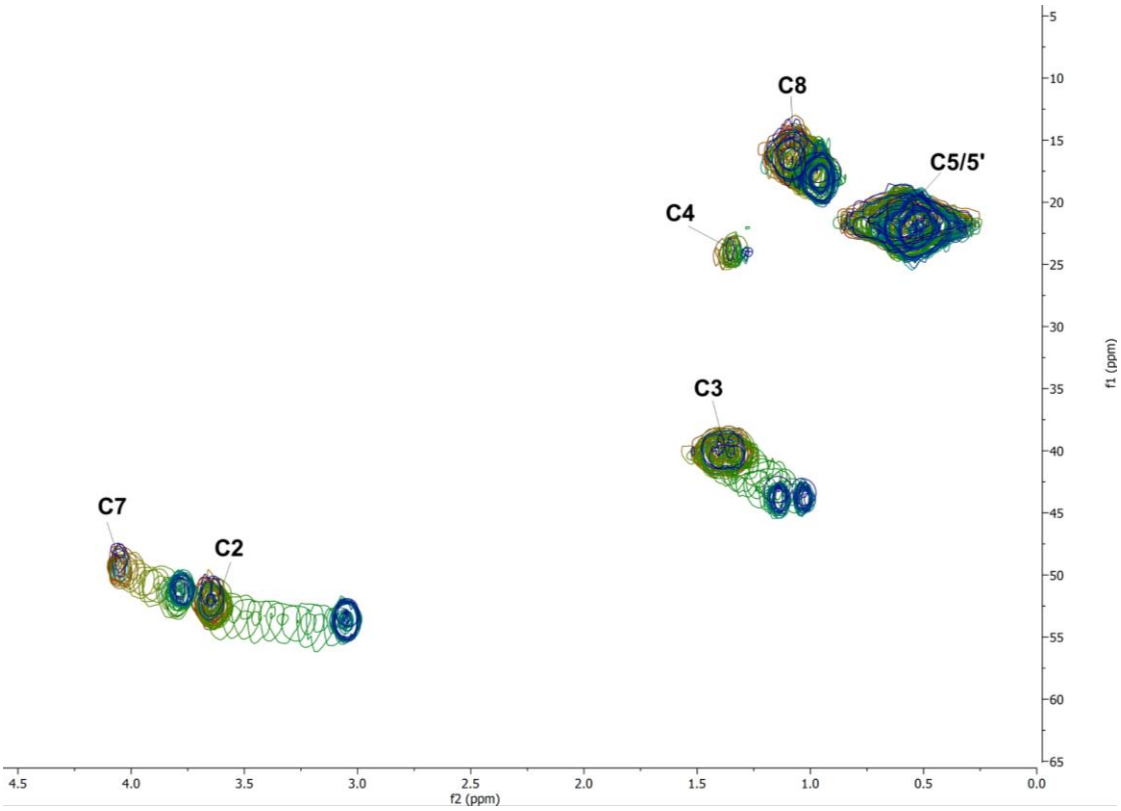



*Figure S25: 2D ASAP HMBC NMR stack plot from the deprotonation of protonated Leu-Ala (63 mM) with NaOH (200 mM) in $H_2O$ at 293 K. Start point (protonated Leu-Ala) indicated by red/green, end point (deprotonated Leu-Ala) indicated by blue. Acquisition parameters: PULPROG asaphmqc_dipsi.be, 16 dummy scans, 4 scans, 0.25 s delay*

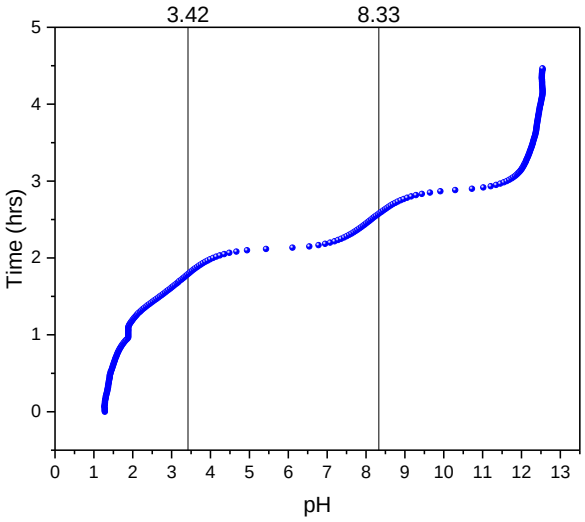



*Figure S26: pH data over time for the deprotonation of protonated Leu-Ala (63 mM) with NaOH (200 mM) in $H_2O$ at 293 K. Data acquired every 60 seconds using a Metrohm Unitrode pH probe.*

# 7. Guest-Host Titration

## General procedure

The flow tube and flow path were emptied of storage solvent and thoroughly rinsed with dimethyl sulfoxide (DMSO) for a minimum of 20 minutes. Solvent miscibility was checked before changing solvents within the flow path to ensure that immiscible solvents were not mixed in the flow path.

A host (1,3-bis(4-nitrophenyl) urea, 15.1 mg) stock solution in DMSO (10 mL, 5 mM) was charged to a 50 mL round bottom flask with a stirrer bar. The stock solution was circulated around the flow path and acquisition was started. A guest (tetrabutylammonium fluoride trihydrate (TBAF), 63.1 mg) stock solution in DMSO (20 mL, 10 mM) was charged to a 24 mL Luer lock syringe. The syringe was connected to fluoropolymer tubing (FEP, O.D 1/16”, I.D 0.51 mm) and mounted onto a syringe pump. The tubing was inserted into the reaction vessel via rubber septum, the tubing was submerged in the analyte to prevent stepwise additions caused by droplets. NMR acquisition was started, titration progress was measured by $^{1}H$ and $^{19}F$ NMR and the reaction was stopped 10 minutes after complete reagent addition. Host-guest data was corrected post-run to account for starting material (4-nitroaniline) present in the urea (denoted by * in Figure S7) as well as residual $HF_2$ present in the TBAF.

## Spectral Plots

### 1,3-Bis(4-nitrophenyl) urea vs Tetra-n-butylammonium fluoride in DMSO

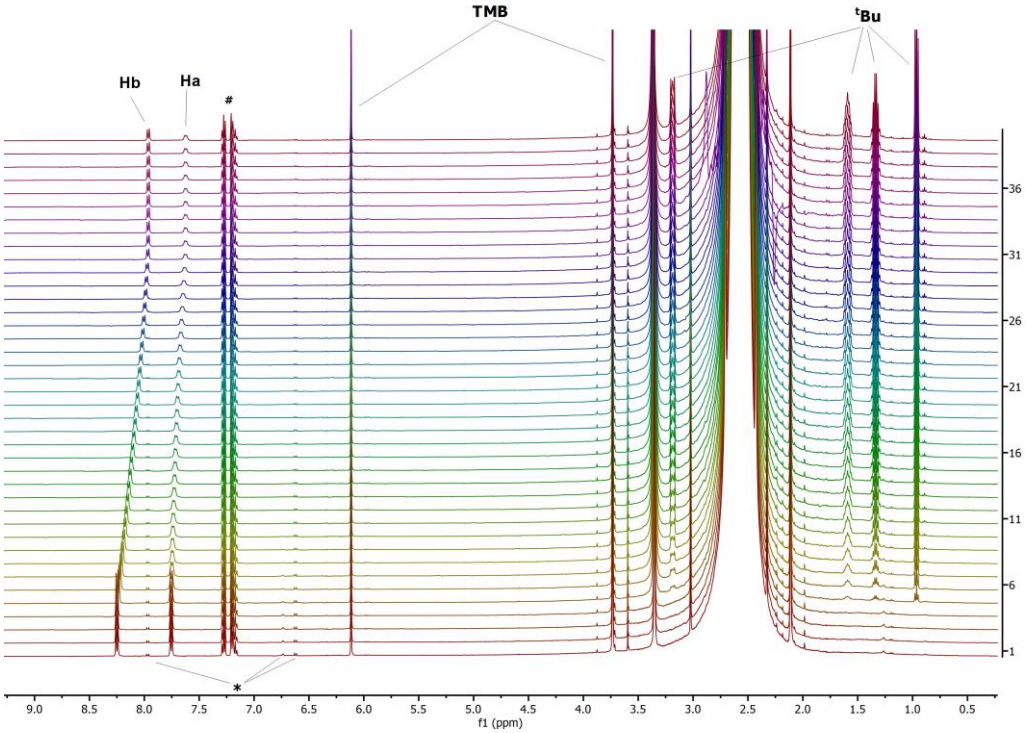



*Figure S27: Stacked $^{1}H$ NMR spectra from the titration of 1,3-bis(4-nitrophenyl) urea (5 mM) with tetrabutylammonium fluoride (10 mM) in dimethyl sulfoxide at 293 K. 1,3,5 trimethoxy benzene (TMB) was added to the reaction mixture as an internal standard. Residual toluene (#) and 4-nitroaniline (*) were observed as impurities which remained unaffected by the titration. Acquisition parameters : PULPROG zg30, 32 scans, 1 s delay.*

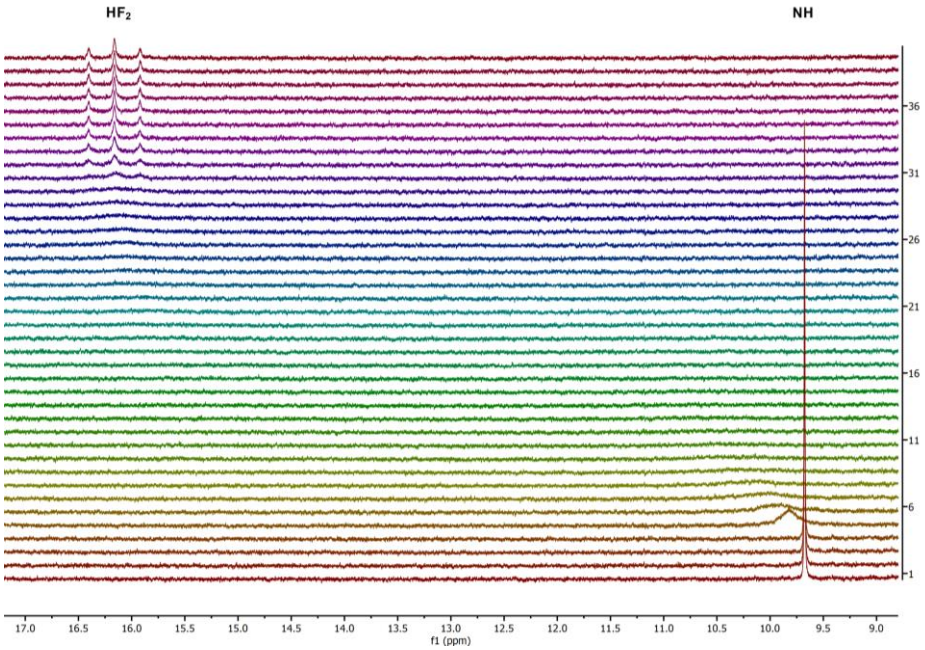



*Figure S28: Stacked $^{1}H$ NMR spectra from the titration of 1,3-bis(4-nitrophenyl) urea (5 mM) with tetrabutylammonium fluoride (10 mM) in dimethyl sulfoxide at 293 K. Plot focused on 9-17 ppm where the NH resonance for the urea and the $HF_2^-$ resonance (J = 120.4 Hz) are observed. Acquisition parameters: PULPROG zg30, 32 scans, 1 s delay.*

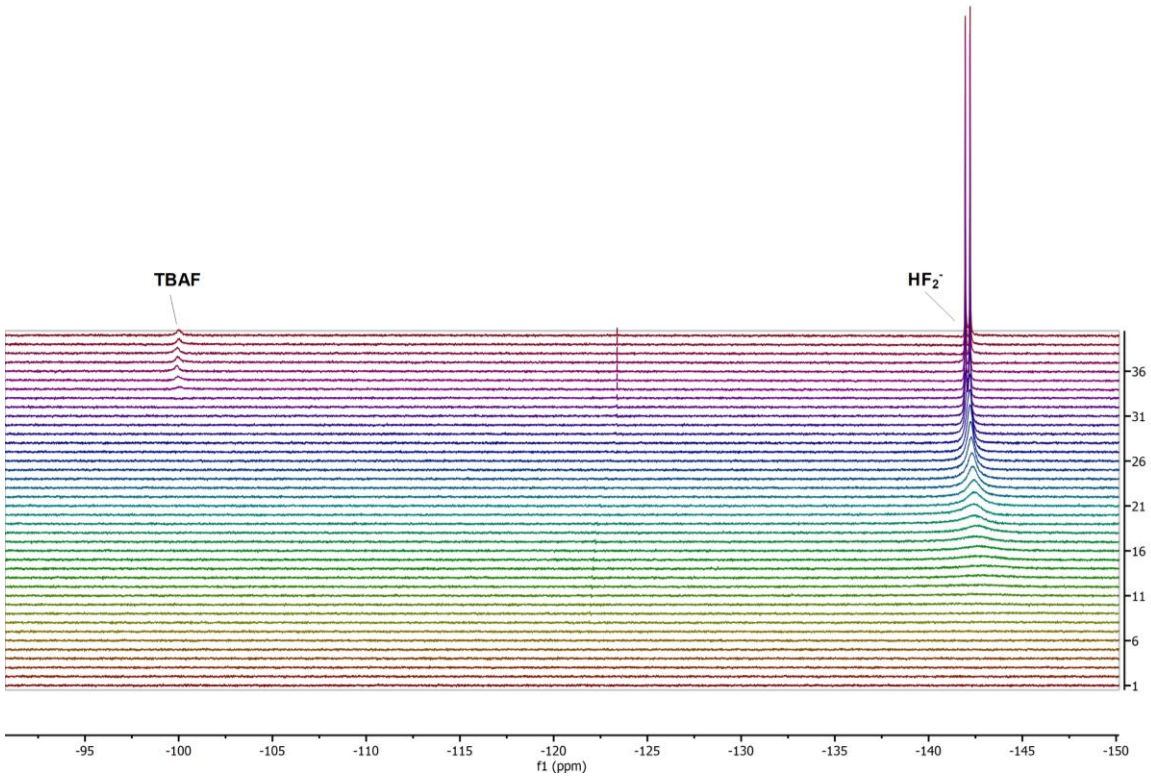



*Figure S29: Stacked $^{19}F$ NMR spectra from the titration of 1,3-bis(4-nitrophenyl) urea (5 mM) with tetrabutylammonium fluoride (10 mM) in dimethyl sulfoxide at 293 K. Excess TBAF and $HF_2^-$ (J = 120.4 Hz) are observed. Acquisition parameters: PULPROG zgflqn, 4 dummy scans, 32 scans, 1 s delay.*

# 8. Lewis Acid/Base Titrations

## General procedure

Titration apparatus (dosing pump, reaction vessel and required chemicals) were all handled in a glovebox under an argon atmosphere after purification as mentioned in section 4. Toluene was thoroughly vacuum degassed before being introduced to the glovebox.

The flow tube and flow path were emptied of any residual solvent and thoroughly rinsed with HPLC grade Toluene with at least two 15-minute washes at 4 mL/min. Solvent miscibility was checked before changing solvents within the flow path to ensure that immiscible solvents were not mixed in the flow path. The flow path inlet was connected to a Schlenk line and purged with argon for a minimum of 15 minutes to ensure an inert atmosphere, the pump was stopped and the inlet to the flow path was connected to a double feed-through port made of PEEK HPLC unions (1/16 “), the pump was turned on and the flow tube was flushed with argon for a further 5 minutes. The inlet tubing housed within the glovebox was then pushed through the rubber seal of a Cajon flask containing dry toluene and the flow system was flushed with dry solvent for a minimum of 15 minutes at 4 mL/min (waste outside the glovebox). The flow tube was then emptied and dried with argon from the glovebox for 5 minutes, and the outlet of the flow path was reconnected to the glovebox. As the Lewis acid was the most sensitive compound being used and the $^{19}F/^{11}B$ resonances were used for monitoring, a BCF solution (8 mM, 10 mL) was used as a wash solution to ensure no trace compounds that might react with the Lewis acid during the titration were present.** The wash solution was flowed around the apparatus and monitored by $^{19}F$ NMR until no spectral change was observed. The flow apparatus was then emptied, rinsed with dry toluene inside the glovebox for 5 minutes and emptied with argon.

Lewis acid (BCF) stock solution (20 mM, 10 mL) was charged to a 50 mL round bottom flask with a stirrer bar. The inlet and outlet of the flow apparatus were connected to the flask via rubber septum and the stock solution was circulated around the flow path and NMR acquisition was started. A base stock solution (40 mM, 20 mL) was charged to a 24 mL Luer lock syringe. The syringe was connected to fluoropolymer tubing (FEP, O.D 1/16”, I.D 0.51 mm) and mounted onto the syringe pump. The tubing was inserted into the reaction vessel via rubber septum, the tubing was submerged in the analyte to prevent stepwise additions caused by droplets. NMR acquisition was started, titration progress was measured by $^{1}H$, $^{19}F$ and $^{11}B$ NMR and the reaction was stopped 10 minutes after complete reagent addition. This methodology was used for all Lewis acid-base titrations unless stated otherwise. Variables such as reagent concentration and acquisition parameters are noted in the captions of spectral plots.

**It was observed that if polyetheretherketone (PEEK) tubing was used that residual acetone may leach from the tubing and form an adduct with the Lewis acid.

Integral values termed "normalised" were corrected for dilution based on the volume of reagent dosed as measured by the syringe pump according to the following equation:

$$Int_{(normalised)} = Int_{(measured)} \times [(V_{initial} + V_{added})/V_{initial})]$$

## Spectral plots

### Tris(pentafluorophenyl)borane vs Pyridine in Toluene

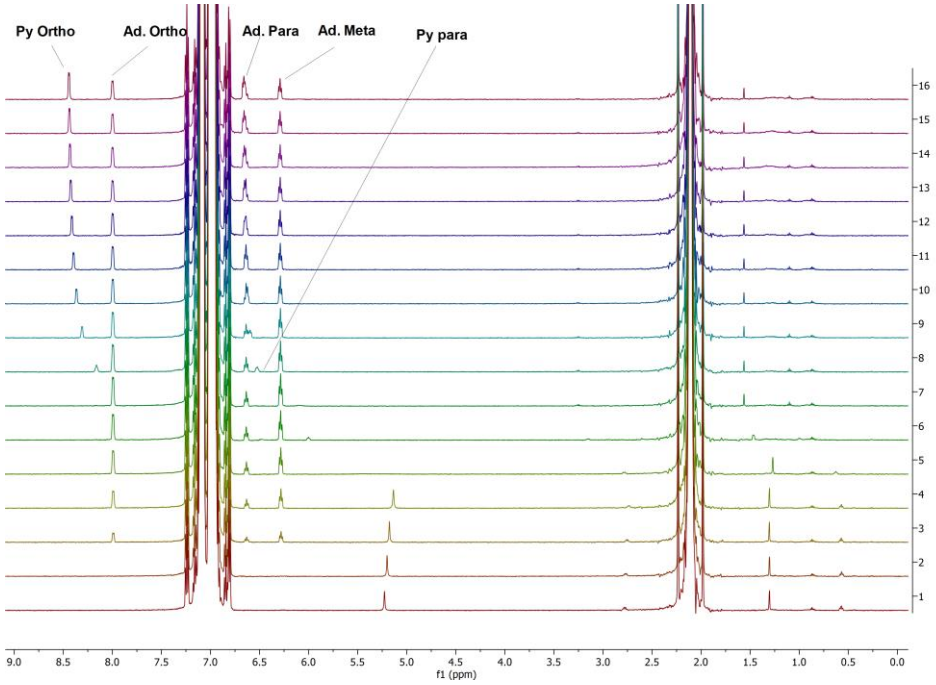



*Figure S30: Stacked $^{1}H$ spectra for the titration of BCF (20 mM) with pyridine (40 mM) in toluene at 293 K. Parameters: PULPROG zg30, 16 scans, 1 s delay.*

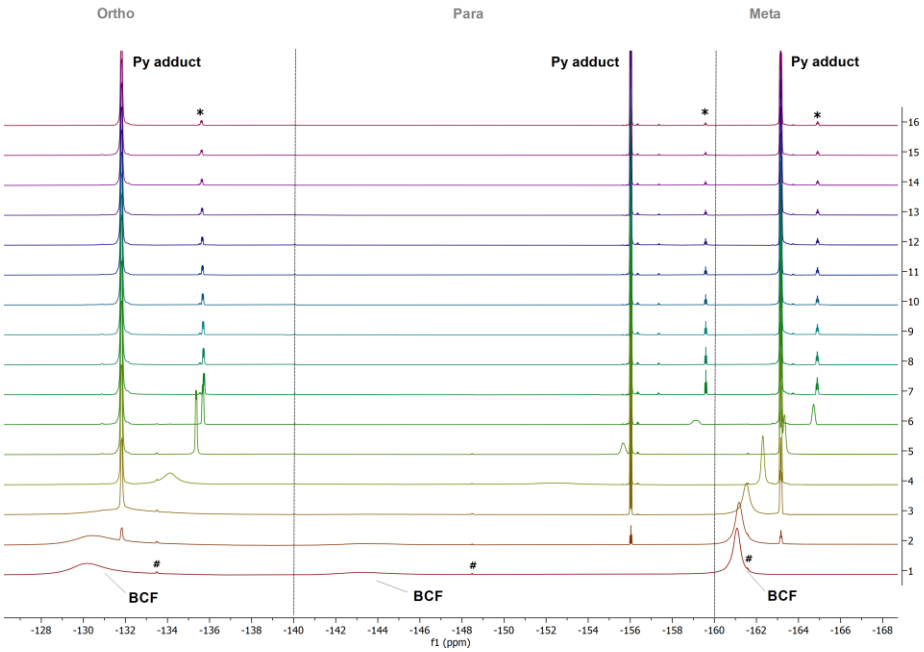



*Figure S31: Stacked $^{19}F$ spectra for the titration of BCF (20 mM) with pyridine (40 mM) in toluene at 293 K. Parameters: PULPROG zgflqn, 4 dummy scans, 32 scans, 1 s delay. Processed using linear prediction to remove background $^{19}F$ signals: ME_mod – LPbc, NCOEF – 32, TDoff – 16. # is attributed to $B(C_6F_5)_2OH$ as a trace impurity from the BCF synthesis.[3] * is attributed to the pyridine adduct of the $B(C_6F_5)_2OH$ impurity.*

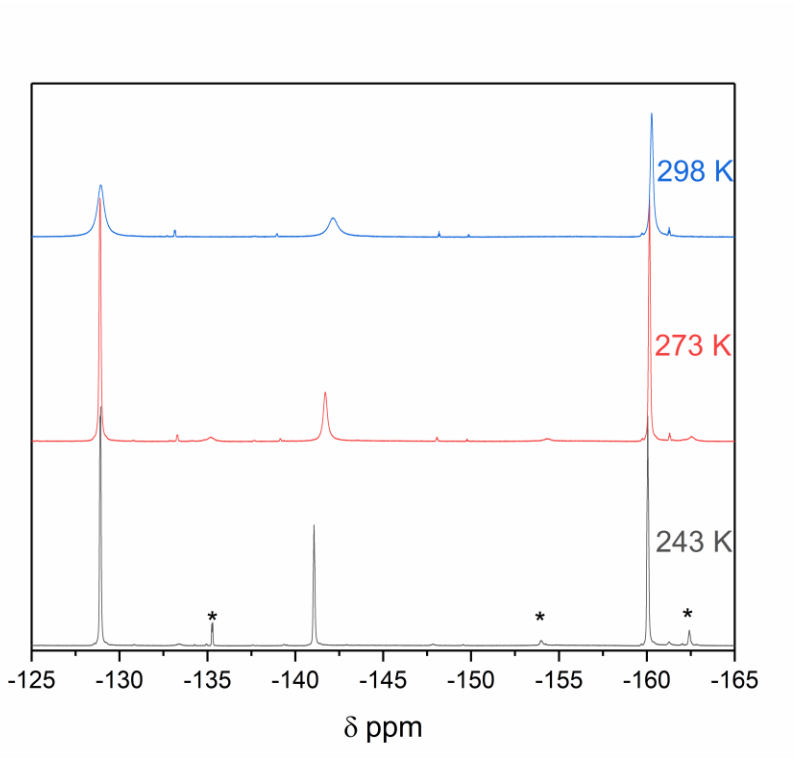



*Figure S32:Variable temperature spectra of BCF (10.2 mg) in toluene (0.55 mL). The resolution of $B(C_6F_5)_3(OH_2)$ (noted as *) at lower temperature is observed with shifts concurrent with literature.[4] Parameters: PULPROG zgflqn, 4 dummy scans, 32 scans, 1 s delay.*

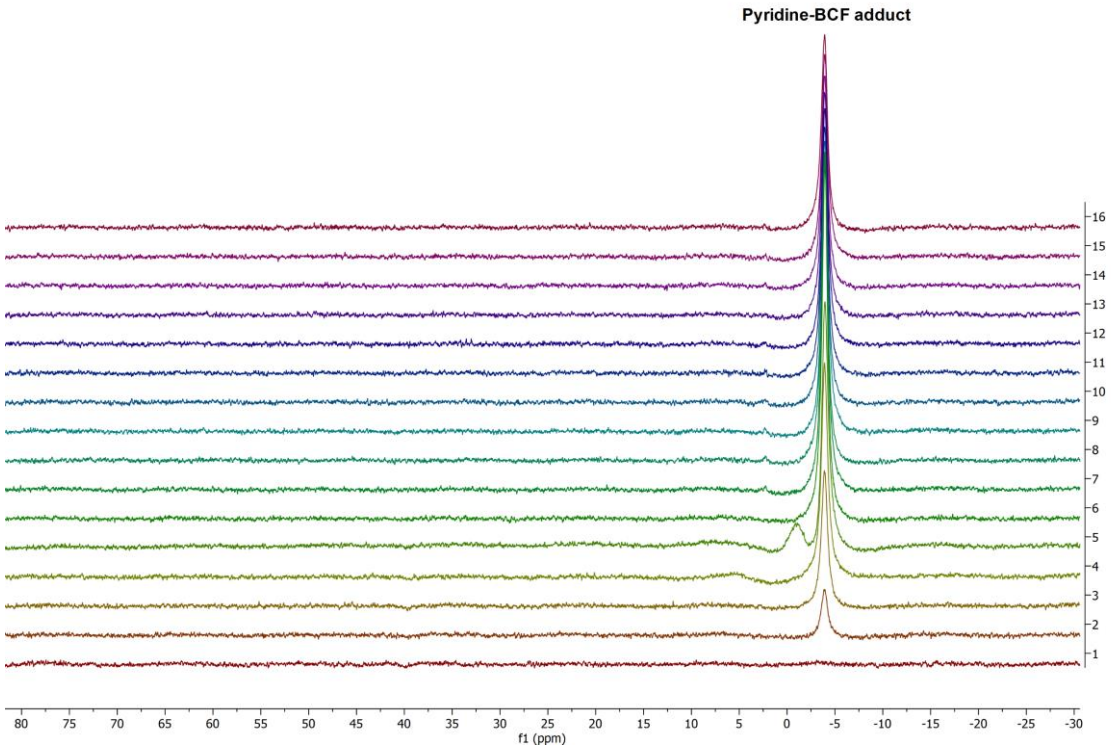



*Figure S33: Stacked $^{11}B$ spectra for the titration of BCF (20 mM) with pyridine (40 mM) in toluene at 293 K. Parameters: PULPROG zg, 4 dummy scans, 128 scans, 0.5 s delay. Processed using linear prediction to remove background $^{19}F$ signals: ME_mod – LPbc, NCOEF – 32, TDoff – 32.*

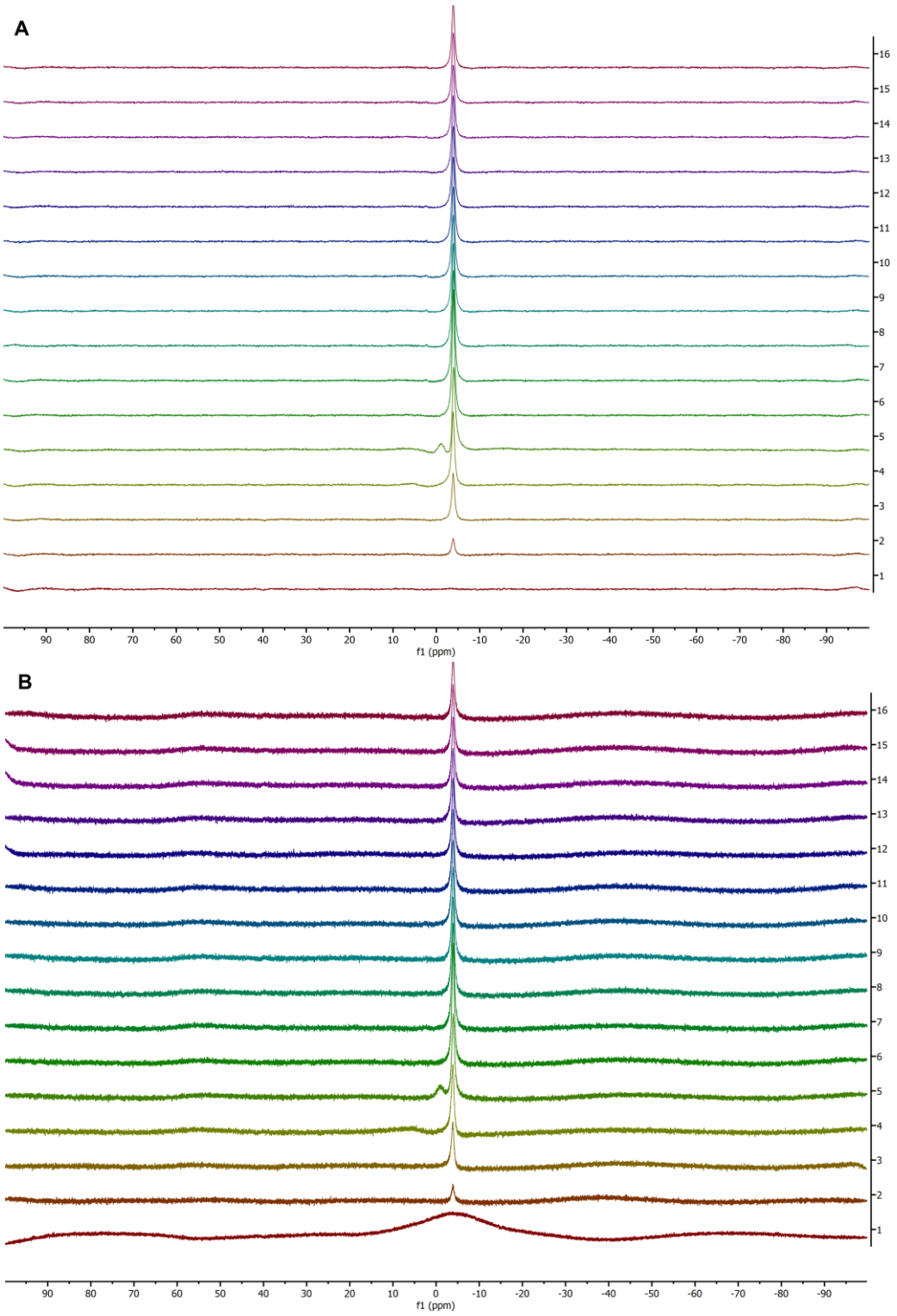



*Figure S34: Stacked $^{11}B$ spectra for the titration of BCF (20 mM) with pyridine (40 mM) in toluene at 293 K. Spectra with (A) and without (B) background removal using topspin command adsu/'accumulate'. Both plots are matched in scale. Parameters: PULPROG zg, 4 dummy scans, 128 scans, 0.5 s delay*

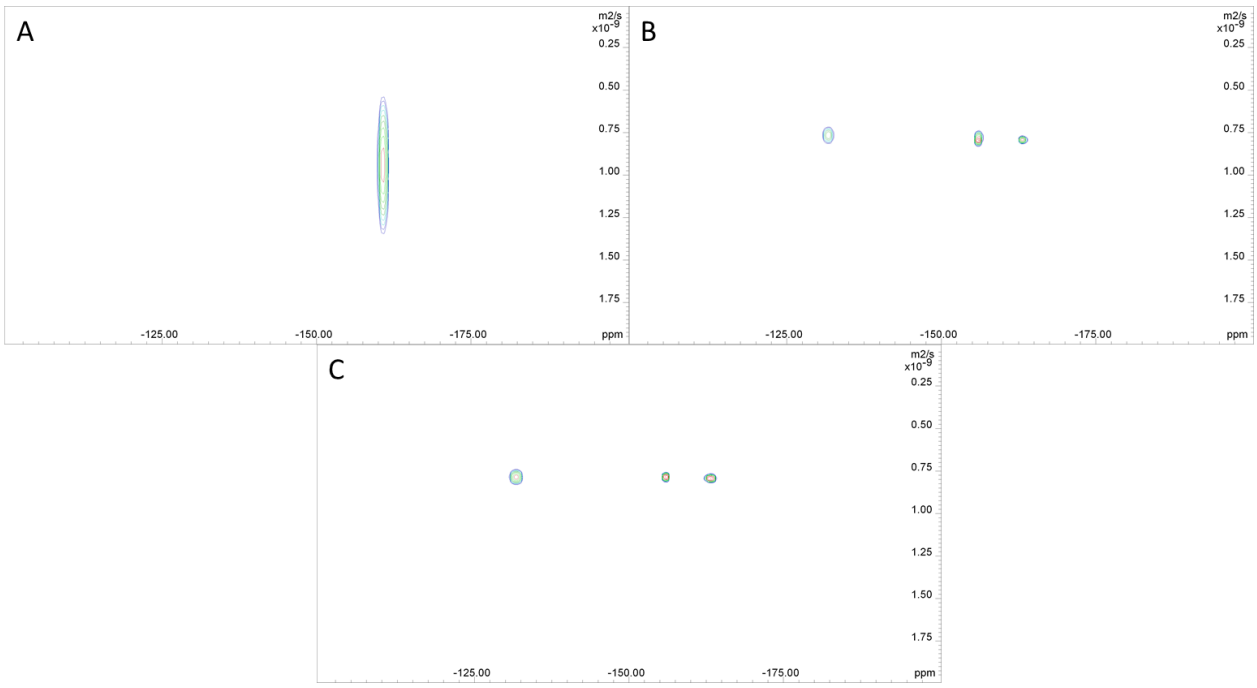



*Figure S35: DOSY spectra at 0 (A), 0.5 (B) and 3 (C) equivalents of pyridine for the titration of BCF (20 mM) with pyridine (40 mM) in toluene at 293 K. Parameters PULPROG dstebpgp3s, 16 dummy scans, 16 scans, 2 s delay, 0.025 s d20, 1250 µs p30.*

Tris(pentafluorophenyl)borane vs 2,6-Lutidine in Toluene

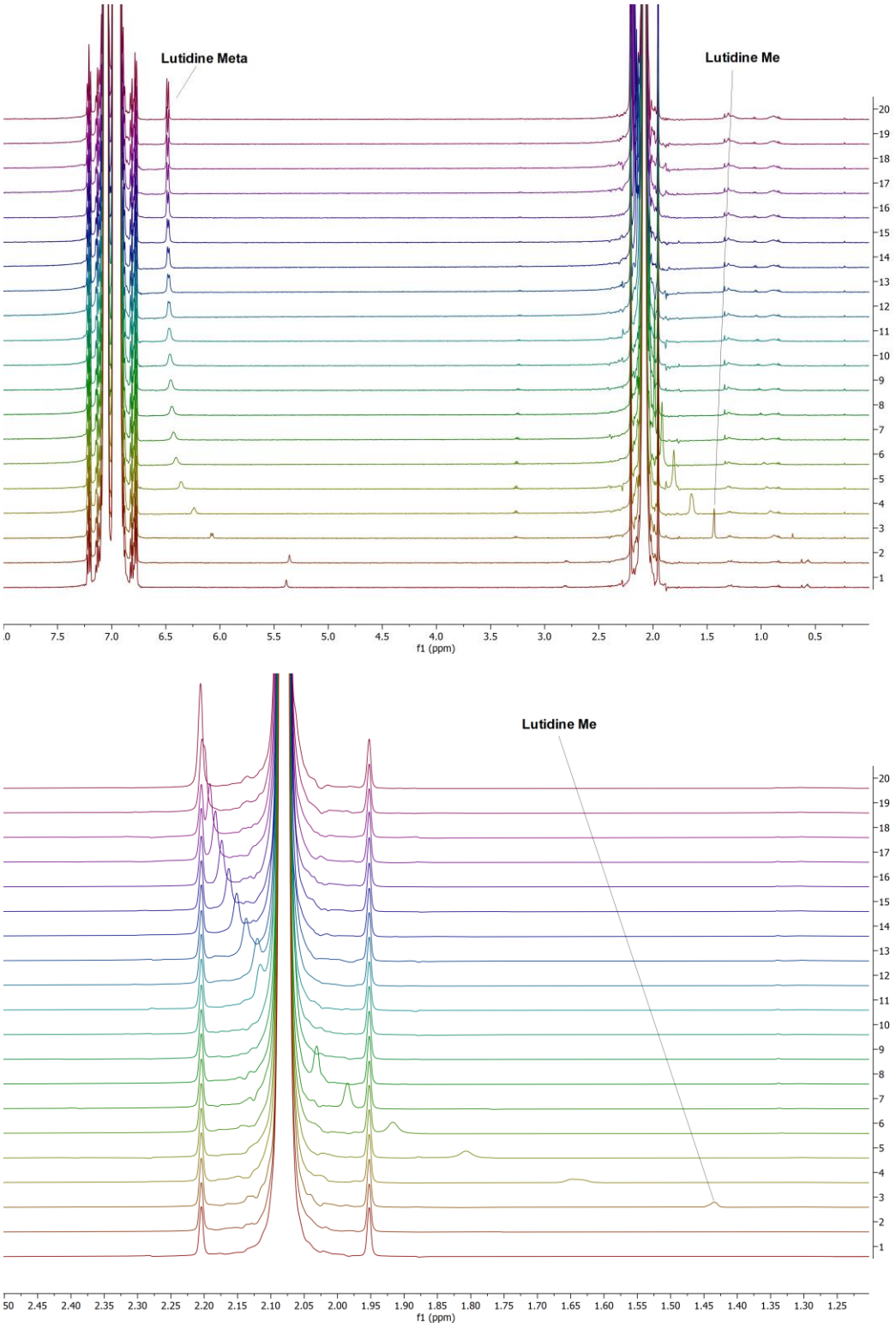



*Figure S36: Stacked $^{1}H$ spectra for the titration of BCF (20 mM) with 2,6-lutidine (40 mM) in toluene at 293 K. Parameters: PULPROG zg30, 16 scans, 1 s delay*

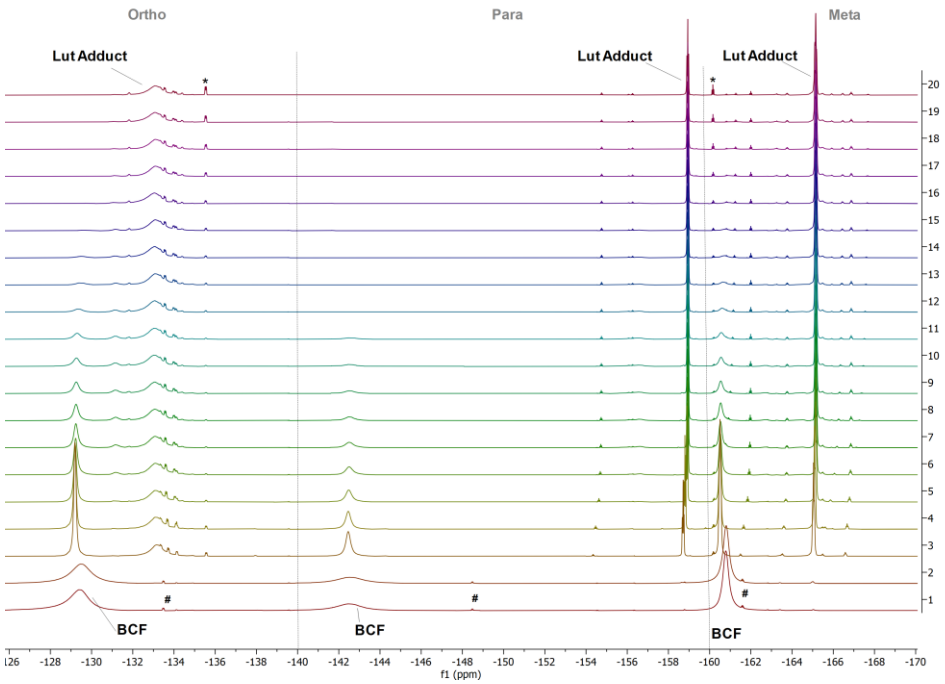



*Figure S37: Stacked $^{19}F$ spectra for the titration of BCF (20 mM) with Lutidine (40 mM) in toluene at 293 K. Parameters: PULPROG zgflqn, 4 dummy scans, 32 scans, 1 s delay. Processed using linear prediction to remove background $^{19}F$ signals: ME_mod – LPbc, NCOEF – 32, TDoff – 16. # is attributed to $B(C_6F_5)_2OH$ as a trace impurity from the BCF synthesis.[3] * is attributed to the lutidine adduct of $B(C_6F_5)_3(OH_2)$ which is an observable impurity in the BCF at low temperature (See Figure S32).*

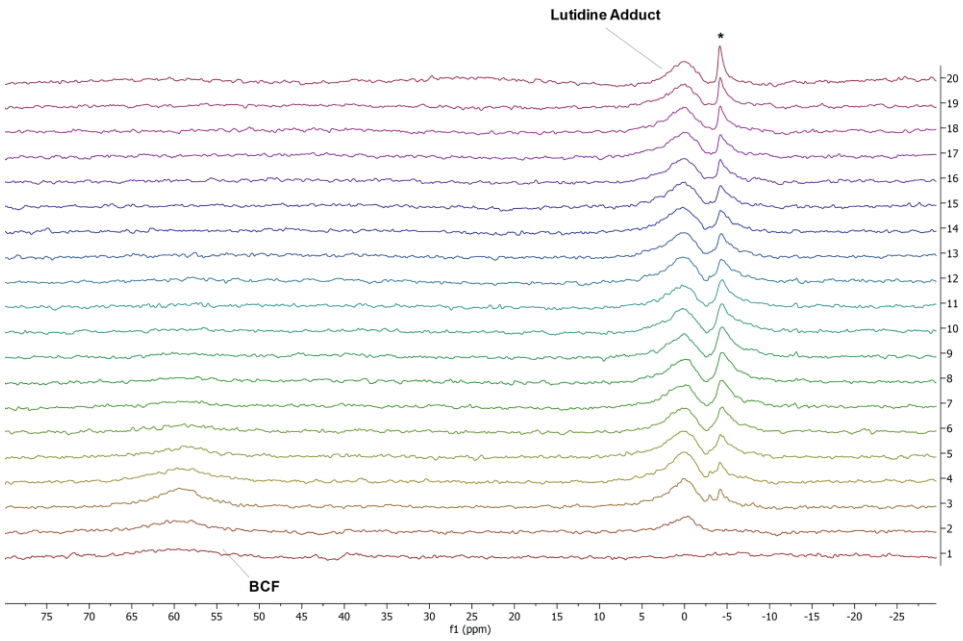



*Figure S38: Stacked $^{19}F$ spectra for the titration of BCF (20 mM) with Lutidine (40 mM) in toluene at 293 K. Parameters: PULPROG zg, 4 dummy scans, 128 scans, 0.5 s delay. Processed using linear prediction to remove background $^{19}F$ signals: ME_mod – LPbc, NCOEF – 32, TDoff – 32, LB – 20 Hz. * is attributed to the lutidine adduct of $B(C_6F_5)_3(OH_2)$ which is an observable impurity in the BCF at low temperature (See Figure S32).*

## Rate of exchange ($k_{ex}$) and equilibrium constant ($K_{eq}$) calculations

The equilibrium constant ($K_{eq}$) at a given time point during a titration was calculated from the integral of the adduct divided by the sum of the individual species (equation 1). Concentration was determined by integrals as a fraction of total known $^{19}F$ speciation and the concentration of 2,6-lutidine was calculated from dosing.

$$K_{eq} = \frac{[Adduct]}{[LA][LB]}$$

*Equation 1 – Equation for the calculation of equilibrium constant for 1:1 binding equilibria.*

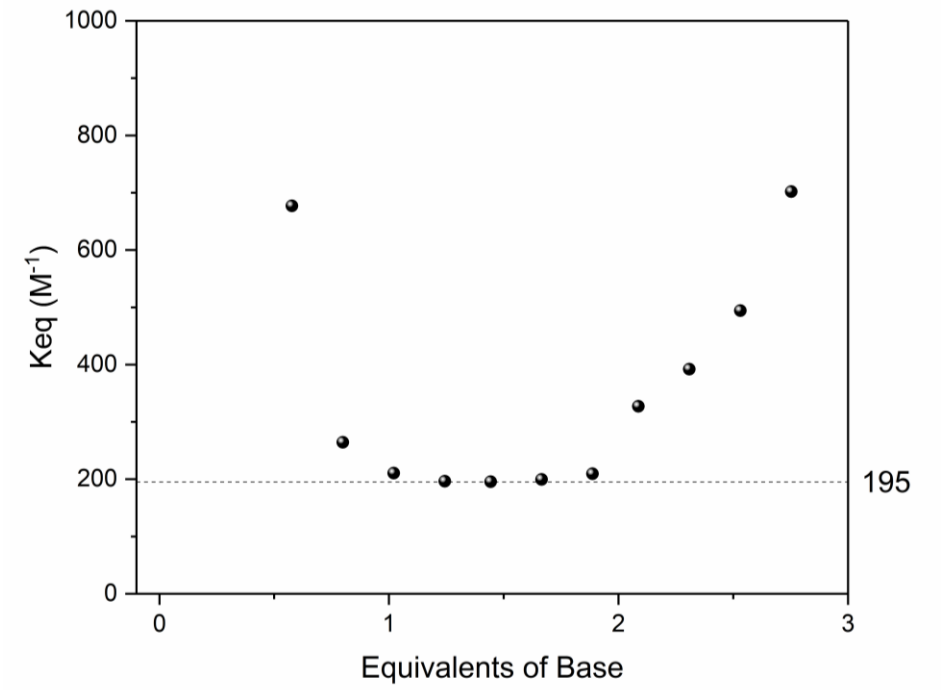



*Figure S39: A plot of the equilibrium ($K_{eq}$) constant against equivalents of base for the titration of BCF (20 mM) with 2,6-lutidine (40 mM). Values between 1 and two equivalents were deemed to be at equilibrium where appreciable concentrations of all species could be observed.*

$K_{eq}$ was also calculated using $^{1}H$ chemical shift perturbation as previously described in literature.[5, 6] As the titration started with Lewis acid the curve was extrapolated to give a zero point for chemical shift.

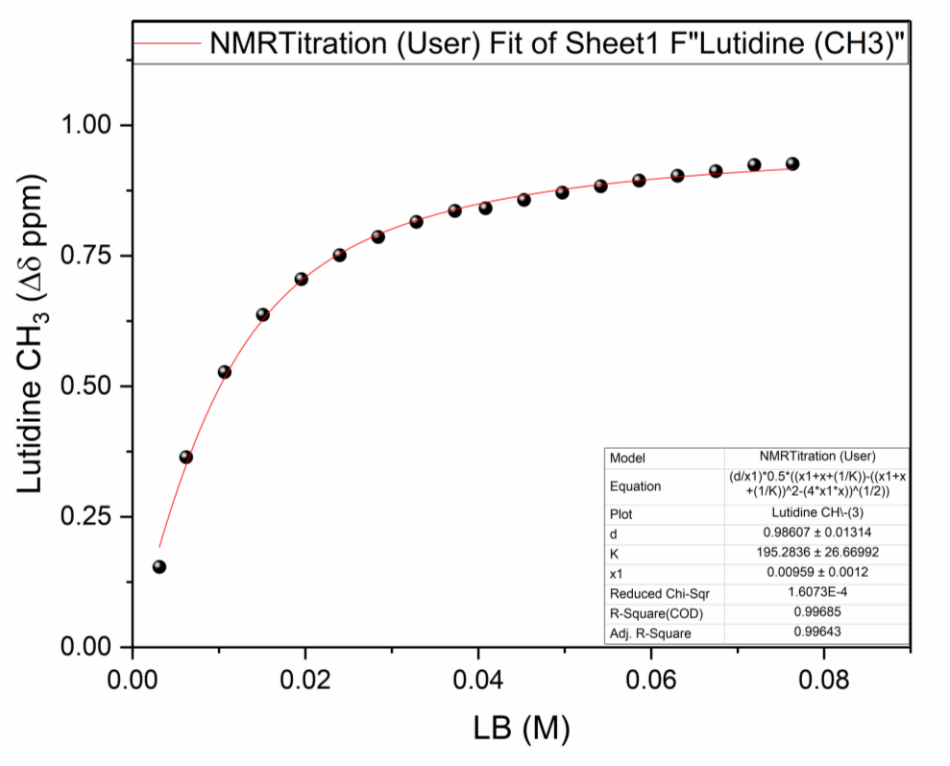



*Figure S40: A plot of lutidine methyl chemical shift (Δδ ppm) against base concentration for the titration of BCF (20 mM) with 2,6-lutidine (40 mM). The value of x1 was allowed to vary in the equation as previously done in literature.*[5]

The rate of exchange ($k_{ex}$) was estimated based on absolute peak shifts observed in $^{1}H$ and $^{19}F$ spectra according to equation 2 below where $k_c$ is the rate of exchange at the coalescence point and $\Delta\nu_{AB}$ is the frequency difference between two observed species, in this case the free Lewis acid/base and the adduct.

$$k_c \approx 2.22\ \Delta\nu_{AB}$$

*Equation 2: The equation relating the rate of exchange at the coalescence point ($k_c$) to the frequency separation of two resonances ($\nu_{AB}$).*

As we observe a sum of both species in the $^{1}H$ NMR (a single, consistently shifting peak) we can say that the rate of exchange must be faster than that observed at the coalescence point under these conditions relative to the $^{1}H$ NMR timescale. $^{19}F$ NMR showed separate peaks for each species, therefore the rate of exchange must be slower than that at the coalescence point under these conditions relative to the $^{19}F$ NMR timescale.

In the $^{1}H$ NMR spectrum the maximum shift is approximately 1 ppm (at 500 Hz) and this can be assumed to be the separation between the two peaks. Therefore, at coalescence $k_c = 1110\ s^{-1}$, the reciprocal of which gives a lifetime of $\tau = 9.0 \times 10^{-4}$ s.

In the $^{19}F$ NMR spectrum the smallest peak separation is observed is approximately 5 ppm for the ortho resonances. Multiplying this by the frequency of $^{19}F$ acquisition (470 Hz) and the 2.2 factor in equation 2 gives $k_c = 5170\ s^{-1}$, the reciprocal of which yields $\tau = 1.9 \times 10^{-4}$ s.

# 9. Metal-Ligand Binding

## General procedure

Titration apparatus (dosing pump, reaction vessel and required chemicals) were all handled housed in a glovebox under an argon atmosphere after purification as mentioned in section 4. Acetonitrile was thoroughly vacuum degassed before being pumped into the glovebox. All reagent flow within the flow apparatus was done at 4 mL/min. Reagent dosing for these titrations was done at 5.00 mL/hr.

The flow tube and flow path were emptied of any residual solvent and thoroughly rinsed with HPLC grade acetonitrile with at least two 15-minute washes at 4 mL/min. Solvent miscibility was checked before changing solvents within the flow path to ensure that immiscible solvents were not mixed in the flow path. The flow path inlet was connected to a Schlenk line and purged with argon for a minimum of 15 minutes to ensure an inert atmosphere, the pump was stopped and the inlet to the flow path was connected to a double feed-through port made of PEEK HPLC-type unions (1/16 “), the pump was turned on and the flow tube was flushed with argon for a further 5 minutes. The inlet tubing housed within the glovebox was then pushed through the rubber seal of a Cajon flask containing dry acetonitrile and the flow system was flushed with dry solvent for a minimum of 15 minutes (waste outside the glovebox). The flow tube was then pumped dry with argon from the glovebox for 5 minutes and with argon flowing, the outlet of the flow path was connected to the second glovebox port.

Complex $(Pd(MeCN)_4(BF_4)_2$ stock solution (20 mM, 10 mL) was charged to a 50 mL round bottom flask with a stirrer bar. The inlet and outlet of the flow apparatus were connected to the flask via rubber septum and the stock solution was circulated around the flow path and NMR acquisition was started. A ligand stock solution (160 mM, 20 mL) was charged to a 24 mL Luer lock syringe. The syringe was connected to fluoropolymer tubing (FEP, O.D 1/16”, I.D 0.51 mm) and mounted onto a syringe pump. The tubing was inserted into the reaction vessel via rubber septum, the tubing was submerged in the analyte to prevent large additions caused by droplets. NMR acquisition was started, titration progress was measured by $^{31}P$ NMR and the reaction was stopped 10 minutes after complete reagent addition. Variables such as reagent concentration and acquisition parameters are noted in the captions of spectral plots.

## Spectral plots

### Tetrakis(acetonitrile)palladium(II) tetrafluoroborate vs triphenylphosphine in acetonitrile

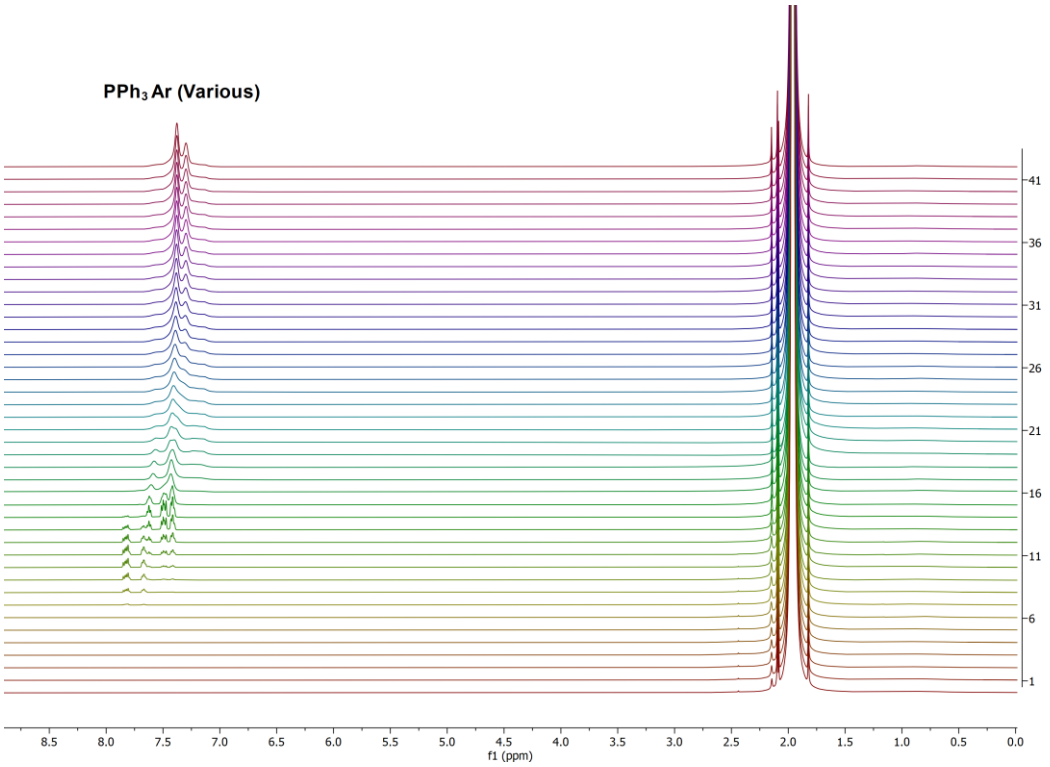



*Figure S41: Stacked $^{1}H$ NMR spectra from the titration of $Pd(MeCN)_4(BF_4)_2$ (20 mM) with triphenylphosphine (160 mM) in acetonitrile at 293 K. Acquisition parameters: PULPROG zg30, 16 scans, 1 s delay.*

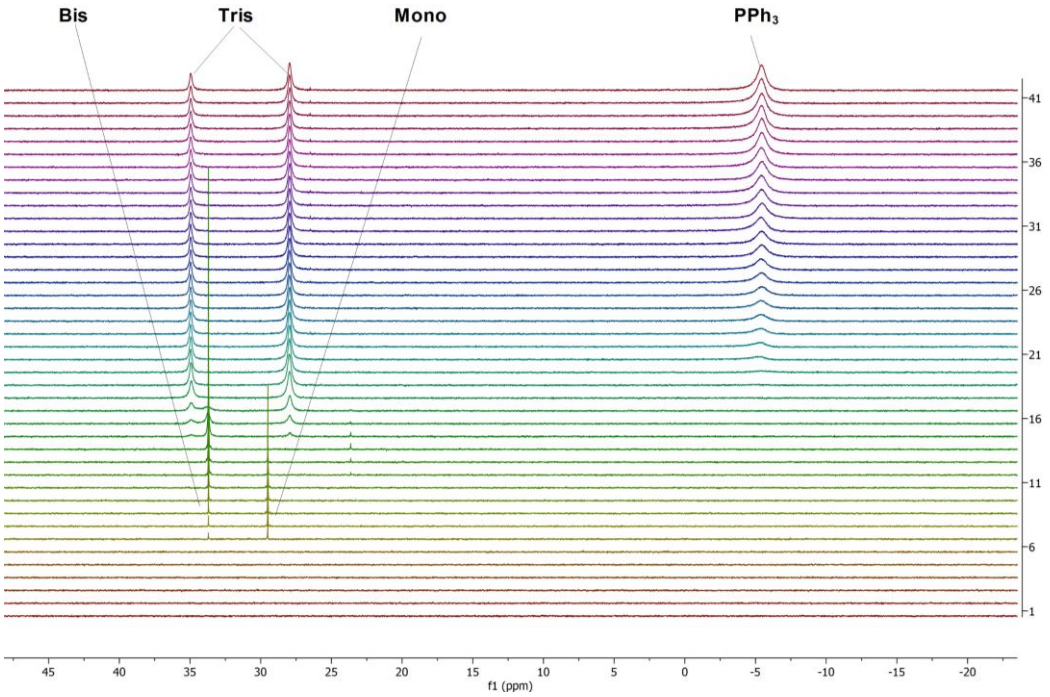



*Figure S42: Stacked $^{31}P$ NMR spectra from the titration of $Pd(MeCN)_4(BF_4)_2$ (20 mM) with triphenylphosphine (160 mM) in acetonitrile at 293 K. Acquisition parameters: PULPROG zgpg60, 128 scans, 0.5 s delay.*

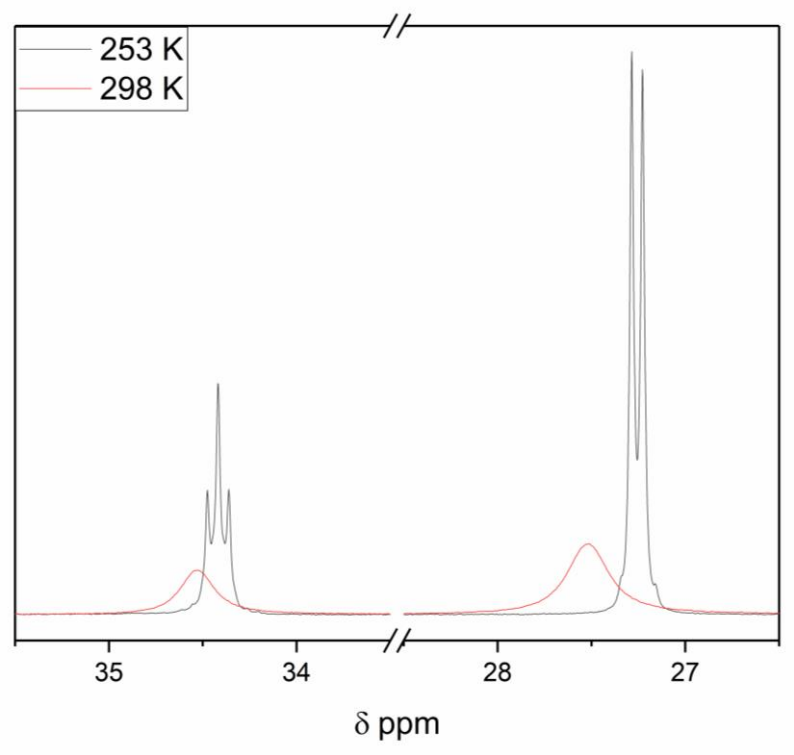



*Figure S43: Variable temperature $^{31}P$ spectra of a sample of $Pd(MeCN)_4(BF_4)_2$ (20 mM) with triphenylphosphine (100 mM) in acetonitrile. Parameters: PULPROG zgpg60, 128 scans, 0.5 s delay. Peak integrals were 1.0 (34.5 ppm) and 2.0 (27.3 ppm) for both spectra.*

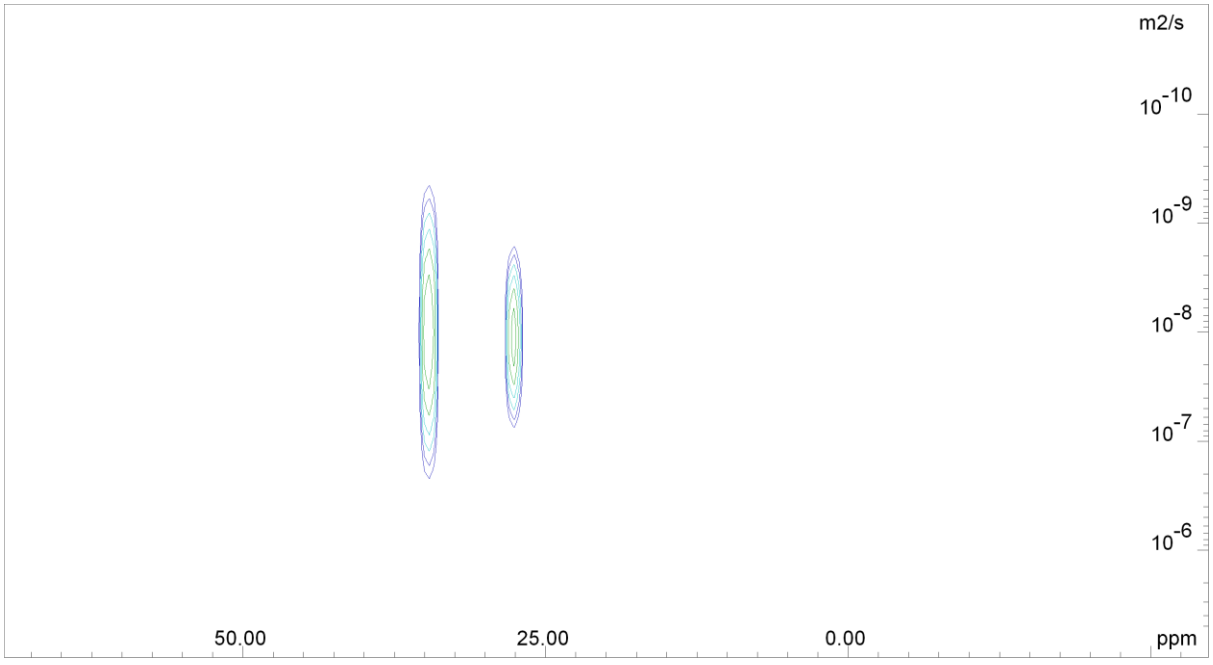



*Figure S44: $^{31}P$ DOSY NMR spectrum of a sample of $Pd(MeCN)_4(BF_4)_2$ (20 mM) with triphenylphosphine (100 mM) in acetonitrile at 293 K. Acquisition parameters: PULPROG ledbpgp2s, 16 dummy scans, 128 scans, 1 s d1, 0.06 s d20, 1250 µs p30.*

# 10. References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2. M. Boiocchi, L. Del Boca, D. E. Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Journal of the American Chemical Society*, 2004, **126**, 16507-16514.
3. N. Miyamoto, Y. Ikeda and T. Tsukahara, *Inorganic Chemistry*, 2020, **59**, 11347-11356.
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6. P. Thordarson, *Chemical Society Reviews*, 2011, **40**, 1305-1323.