Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

# Supporting information

# Revisiting the Role of Acids and Hydrogen Bond Acceptors in Enamine Formation

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# 1. General

$^1$H NMR spectra were recorded at 400 MHz, using $CDCl_3$, *d*-Benzene, *d*- DMSO, or d-THF as a solvent. Chemical shifts are given in ppm with the residual signal of the corresponding solvent as the internal reference ($CD_3SOCD_2H$ δ 2.50 ppm, $CD_2HC_6D_5$ δ 2.11 ppm, $CHCl_3$ δ 7.26 ppm, $C_4D_7HO$ δ 7.26 ppm 1.79); All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. Other chemicals were purchased from Aldrich, Alfa Aesar, or Strem. *All the products formed in these reactions have been reported in the literature (references are found in the manuscript).*

# 2. NMR technics for kinetic measurements

In situ NMR spectroscopy was used to monitor the progress of a reaction. The reactions were monitored with $^1$H NMR (single pulse or 1 scan for fast reactions). Some NMR measurements were conducted using the NMR experiment array (a series of spectra measured at predetermined time intervals over a period of time by adjusting the pre-acquisition delay). NMR experiment array gives better precision for both concentration (via integrations) and reaction time because each measurement is conducted at almost identical shimming and temperature conditions.

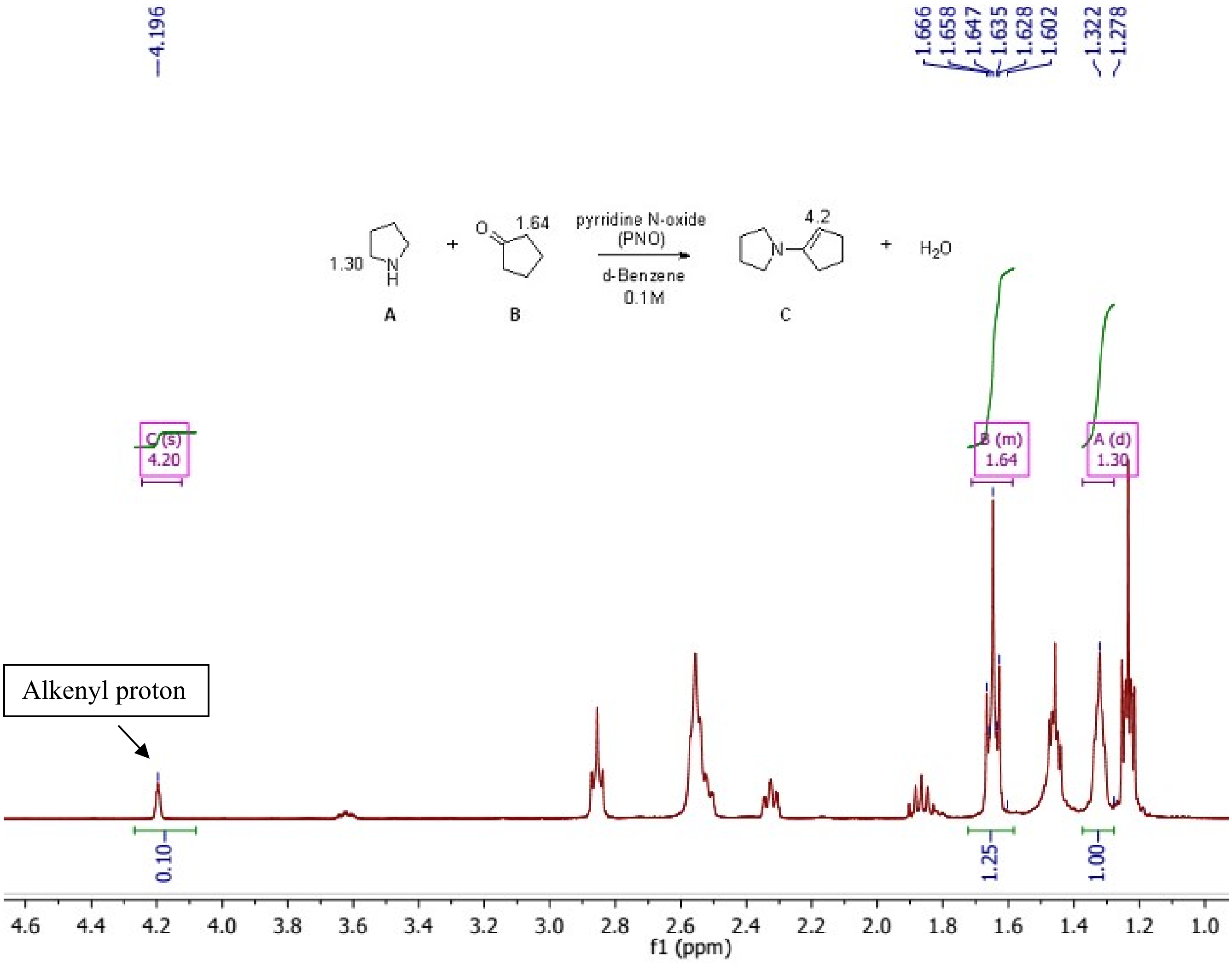
# 3. Determination of the absolute equilibrium constants

We used the same method developed by the Vilarrasa group.[1] In practice, A NMR tube was charged with pyrrolidine (0.1mmol), Pyridine N-oxide, and 0.5 mL *d*-benzene. Cyclopentanone (0.1mmol) was then introduced. After shaking the resulting mixture, the spectrum was registered immediately and repeatedly until the reaction reach the equilibrium (a consistent ratio of the corresponding areas). The accuracy of our measurements, under these conditions, is limited by the accuracy of the $^1$H NMR integrations.

$$\text{Carbonyl compound} \quad + \quad \text{secondary amine} \quad \overset{K\text{eq}}{\rightleftharpoons} \quad \text{Enamine} \quad + \quad H_2O$$

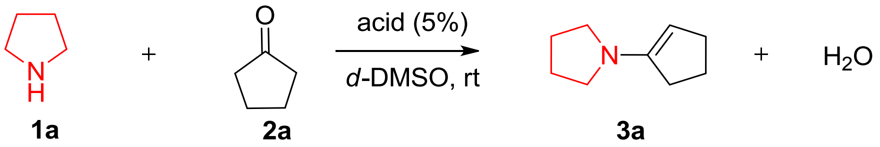
Example:

$$k_{\text{eq}} = \frac{[\text{C}]\ [\text{H}_2\text{O}]}{[\text{A}]\ [\text{B}]} = \frac{[\text{C}]^2}{[\text{A}] \cdot [\text{B}]} = \frac{[0.1]^2}{[1.0 / 4] \ \cdot \ [1.25 / 4]} = 1.28$$

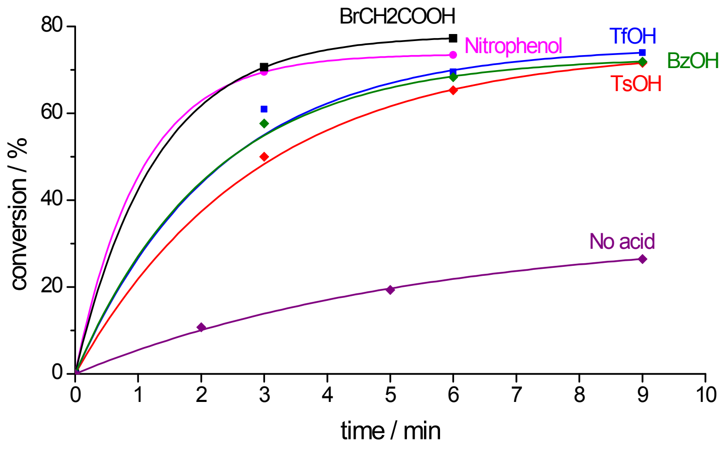


# 4. Reaction procedures and conversion versus time graphs for enamine formation

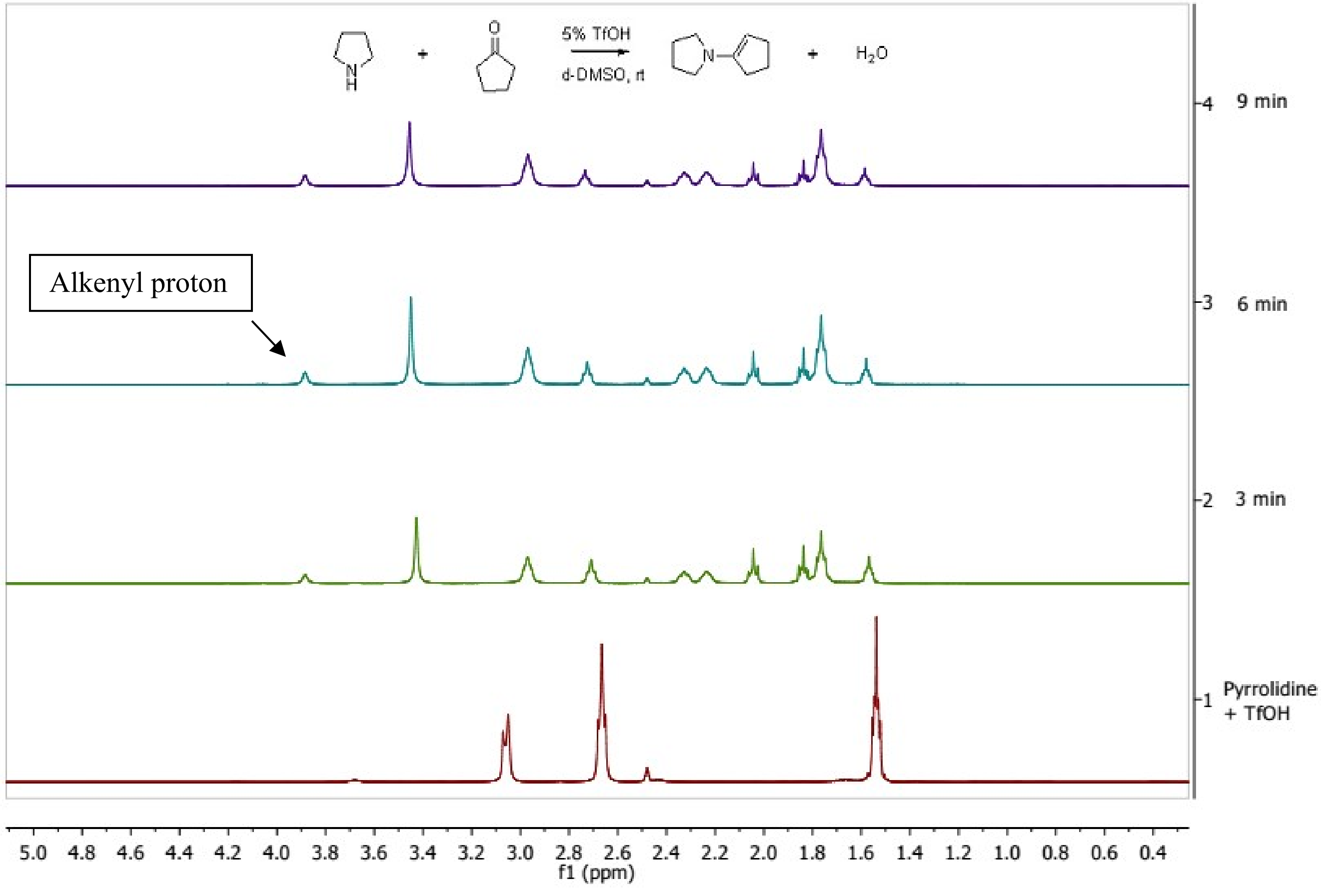
## 4.1. Different acids effect on enamine 3a formation reaction rate and equilibrium[2]



An NMR tube was charged with pyrrolidine (0.2mmol), *d*-DMSO (0.5 mL), and 5% acid. Cyclopentanone (0.2mmol) was then introduced. After shaking the resulting mixture, the spectrum was registered immediately and repeatedly until the reaction reach the equilibrium (a consistent ratio of the corresponding areas).

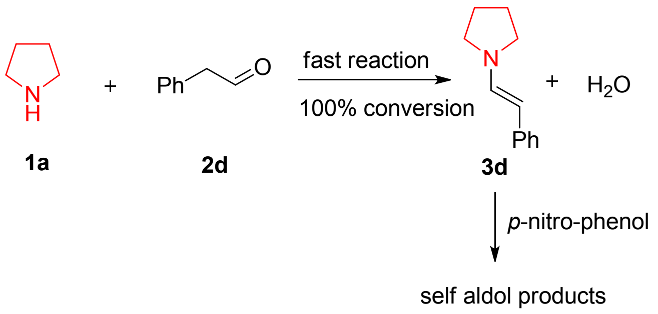


One example with TfOH:

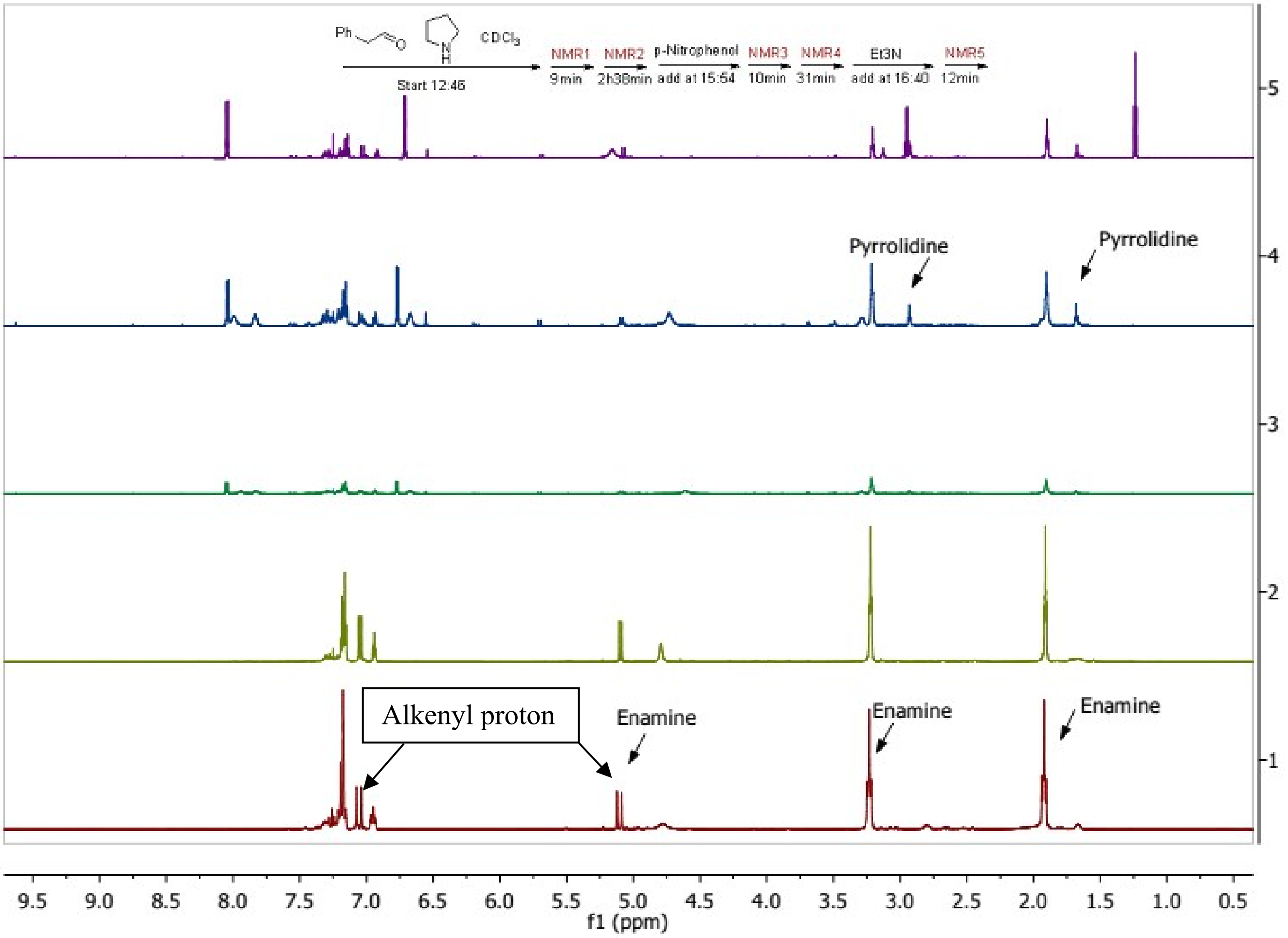


## 4.2. $^1$H NMR spectra of acid effect on the stability of enamine formation

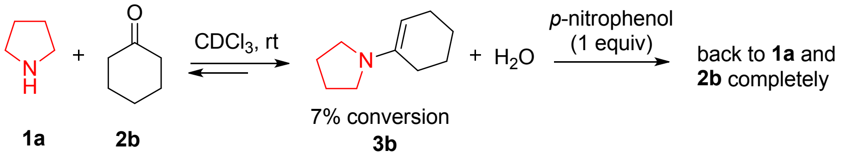
### 4.2.1 Enamine 3d formation by pyrrolidine with phenylacetaldehyde[3]



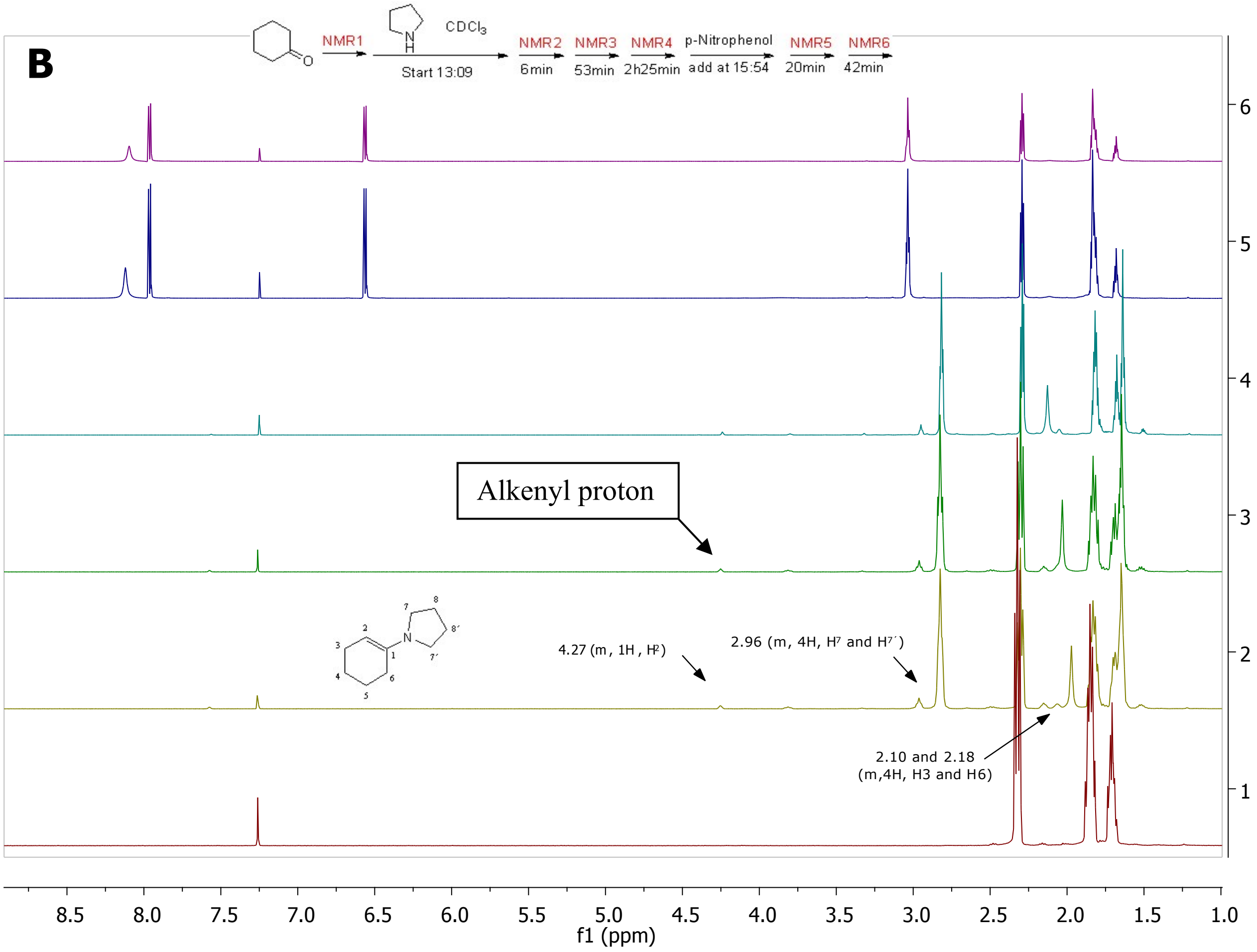
An NMR tube was charged with pyrrolidine (0.1mmol), $CDCl_3$ (0.5 mL) and phenylacetaldehyde (0.1mmol). After shaking the resulting mixture, the spectrum was registered repeatedly (NMR1 and NMR2) until the reaction reach the equilibrium (a consistent ratio of the corresponding areas). Nitrophenol (0.1mmol) was then introduced and NMR was registered repeatedly (NMR1 and NMR2) until the reaction reaches the equilibrium. Trimethylamine was then added and NMR was registered (NMR5).



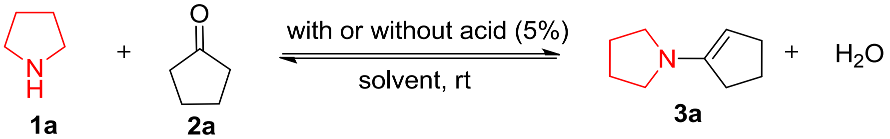
### 4.2.2. Enamine 3b formation by pyrrolidine with cyclohexanone[2]



An NMR tube was charged with cyclohexanone (0.1mmol), CDCl$_3$ (0.5 mL), and a $^1$H NMR was registered (NMR1). Pyrrolidine (0.1mmol) was then introduced and the resulting mixture was shaken and $^1$H NMR was registered immediately (NMR2). 2 more $^1$H NMRs were registered after 53 mins (NMR3), and 145 mins (NMR4). The reaction reached equilibrium as a consistent ratio of the corresponding areas was formed. Nitrophenol (0.1mmol) was then introduced and NMR was registered after 20 mins (NMR5), and 42 mins (NMR6) and the reaction reached the equilibrium.



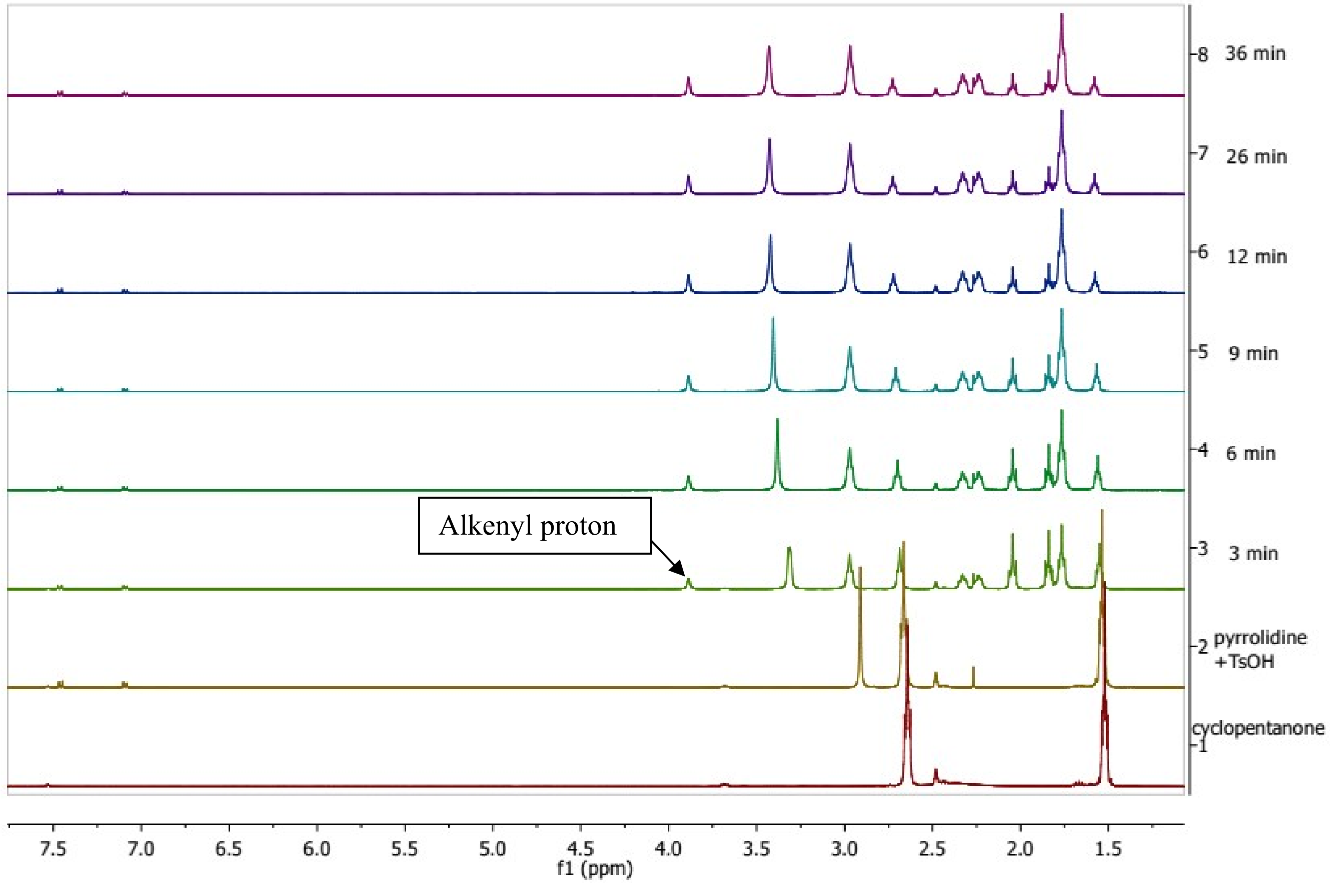
### 4.3. Acid and solvent effect on enamine 3a formation reaction rate and equilibrium[2]



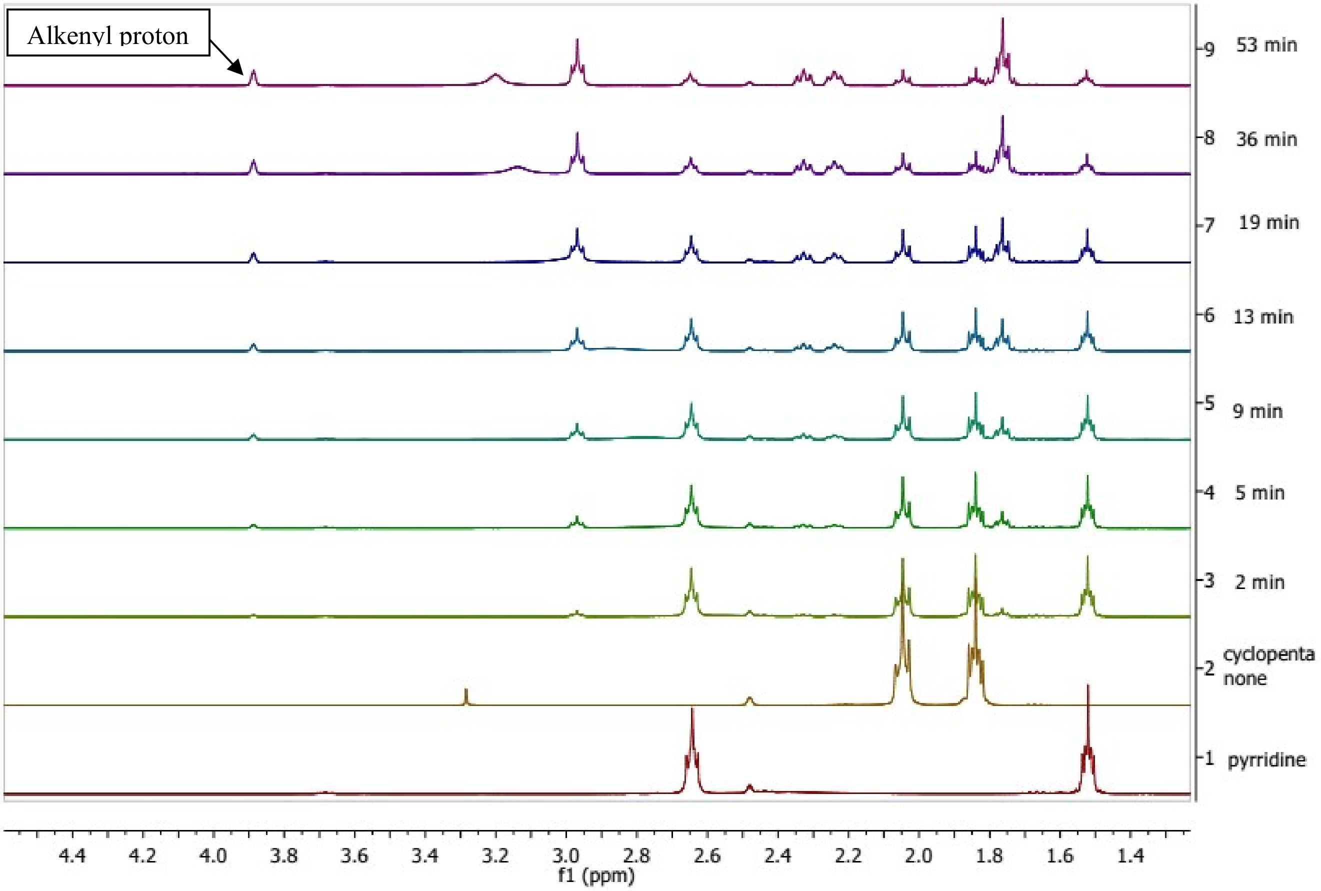
One example with *d*-DMSO as solvent and TsOH:

An NMR tube was charged with pyrrolidine (0.2mmol), *d*-DMSO (0.5 mL), and 5% TsOH. Cyclopentanone (0.2mmol) was then introduced. After shaking the resulting mixture, the spectrum was registered immediately and repeatedly until the reaction reach the equilibrium (a consistent ratio of the corresponding areas).

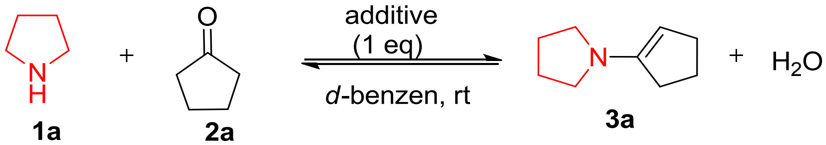
With 5% TsOH:



Without 5% TsOH:

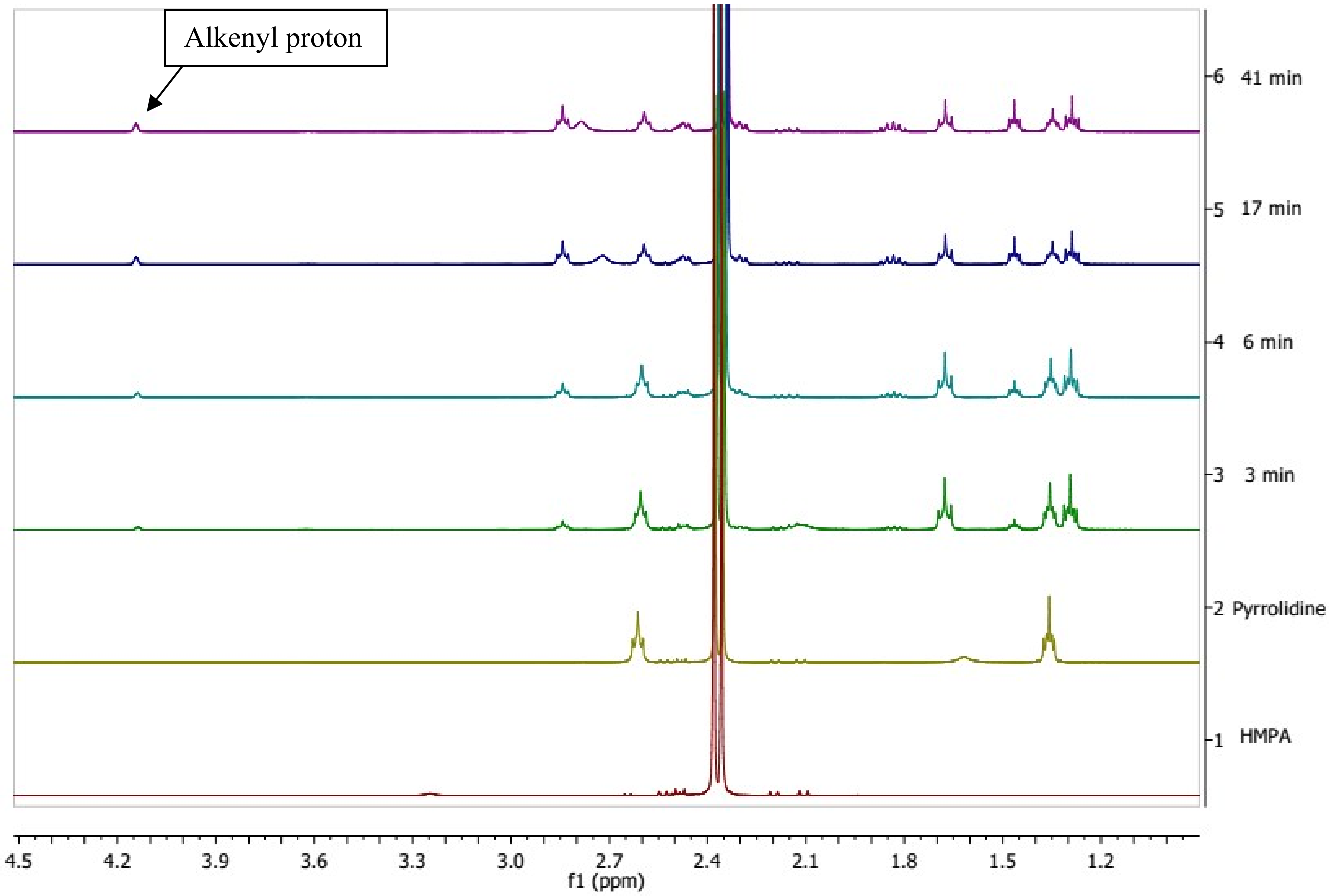


## 4.4. Different hydrogen bond acceptors' effect on enamine 3a formation reaction rate and equilibrium[2]

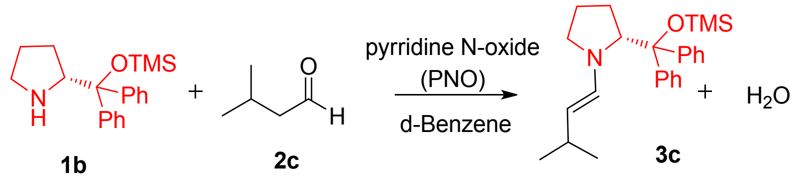


<u>One example with HMPA:</u>

An NMR tube was charged with pyrrolidine (0.2 mmol), *d*-benzene (0.5 mL) and HMPA (0.2 mmol). Cyclopentanone (0.2 mmol) was then introduced. After shaking the resulting mixture, the spectrum was registered immediately and repeatedly until the reaction reach the equilibrium (a consistent ratio of the corresponding areas).



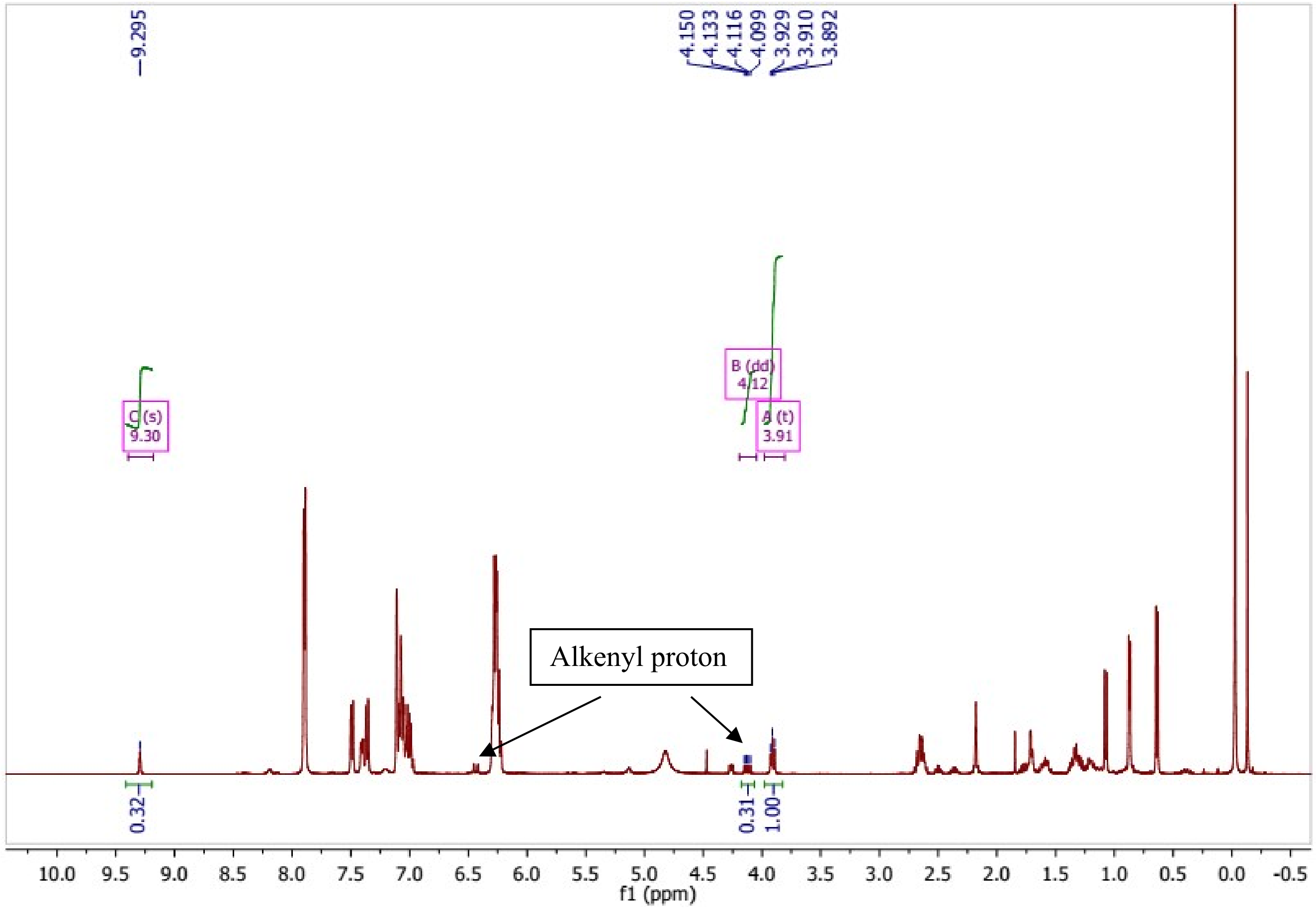
### 4.5. Correlation of different amount of Pyridine N-oxide (PNO) and reaction equilibrium constant of Diarylprolinol silyl ether chiral enamine 3c formation[1a]



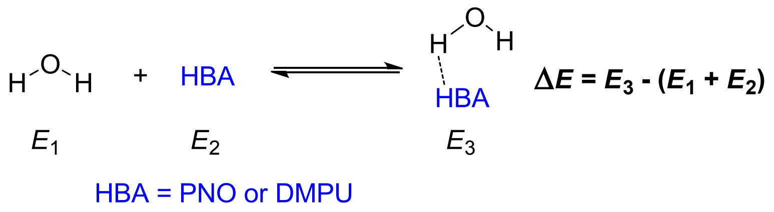
(2mg/10μL) Pyridine N-Oxide stock solution preparation: 40 mg of Pyridine N-Oxide was dissolved in 200 uL d-benzene.

An NMR tube was charged with Diarylprolinol silyl ether (0.1mmol), *d*-benzene (0.5 mL), and NMR was registered 10 μL PNO stock solution was then introduced and another NMR was registered. Isovaleraldehyde (0.1mmol) was added and the mixture monitored by NMR until reaction got equilibrium. More PNO stock solution was introduced and the mixture was monitored with NMR each time until reaction got equilibrium. Absolute equilibrium constants were calculated with the previous method. The correlation chart with PNO and the absolute equilibrium constants was formed with Excel.

One example NMR with 4eq of PNO:



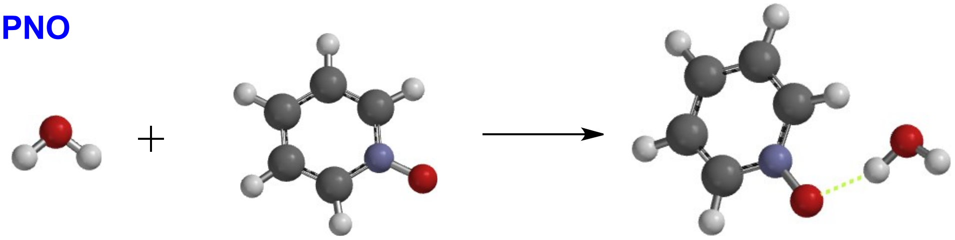
## 5. DFT calculation for hydrogen bonding between hydrogen bonding acceptors and water



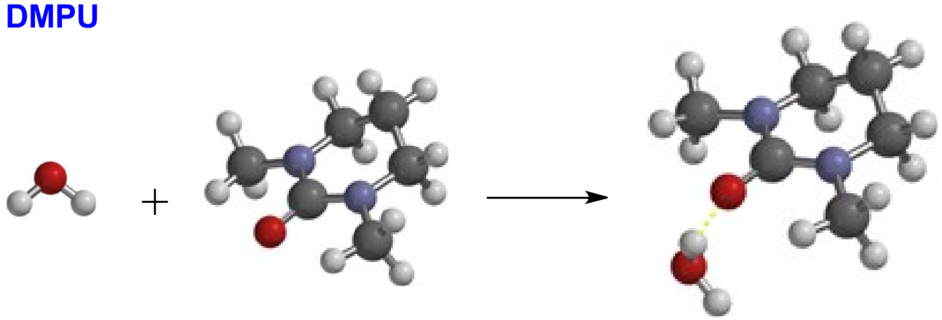
| Complex | $E_3$ | $E_1$ | $E_2$ | $\Delta E$ (kJ/mol) |
|---|---|---|---|---|
| PNO-H2O | -399.756029 | -76.3979035 | -323.340736 | -45.656132 |
| DMPU-H2O | -496.915977 | -76.3979035 | -420.502566 | -40.714941 |

Theoretical DFT calculation with ωB97X-D (6-31G**) in a vacuum.; The energies are in a.u. (atomic unit), except otherwise stated.

**HBA = PNO**



**HBA = DMPU**



## 6. References

1. (a) Carneros, H.; Sánchez, D.; Vilarrasa, J. *Org. Lett.* **2014,** *16*, 2900-2903; (b) Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012,** *14*, 536-539.
2. Zhao, X.; Liu, D.; Xie, F.; Zhang, W. *Tetrahedron* **2009,** *65*, 512-517.
3. Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.* **2006,** *71*, 7481-7484.