ELECTRONIC SUPPLEMENTARY INFORMATION

Deciphering the Roles of Multiple Additives in Organocatalyzed Michael Additions**

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1. General

All the reagents were purchased from Aldrich or TCI and used without any further purification. The solvents were directly used from bottle unless otherwise is indicated. Anhydrous solvents were obtained from a Solvent Purification System. TLC chromatography was performed on silica gel 60 F_{254} aluminum sheets. Flash chromatography was performed using silica gel P60 (200-500 mesh). HPLC analyses were performed using a Shimadzu Prominence modular equipment with autosampler and UV-Vis detector. The characterization of products by NMR was performed on an automated Varian VNMRS 400 MHz equipped with a One NMR Probe. $^1$H NMR kinetic experiments were recorded on Bruker DRX-400 MHz equipped with a BBFO 5 mm Prove or Bruker 500 MHz equipped with a cryoprobe.
2. Preparation and NMR spectra of catalyst I

Catalyst I was prepared according to a described procedure and matches literature data.[1] Unprotected (1S,2S)-diaminocyclohexane was used instead of the mono Boc-protected diamine to avoid potential acid contamination during the deprotection step.

(400 MHz, DMSO-d$_6$)

(100 MHz, DMSO-d$_6$)

3. Enantioselective Michael addition of acetone to nitrostyrene

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{NO}_2 & + \quad \text{2} \\
\text{I} & \quad \text{10 mol\%} \\
\text{AcOH} & \quad \text{5 mol\%} \\
\text{1 equiv. water, toluene, RT} & \quad \rightarrow \quad \text{Ph} \\
\text{3a} & \quad \text{O} \\
\end{align*}
\]

In a vial, catalyst I (0.1 equiv., 0.0335 mmol, 9.3 mg) and nitrostyrene 1 (1 equiv., 0.335 mmol, 50 mg) were weighed and dissolved in 1.9 mL of toluene. To this clear solution, 0.05 equiv. of AcOH was added (using 100 µL of a stock solution of 0.168 mmol, 10 µL AcOH in 1 mL toluene). Finally, 1 equiv. of water and 10 equiv. of acetone were added (using 0.25 mL of a stock solution of 0.335 mmol, 24 µL water in 1 mL acetone). The reaction was stirred at room temperature for 24 hours. To quench the reaction, water was added to the reaction vial and the organic phase was extracted with EtOAc(x3). The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated and the crude mixture was directly analyzed by ¹H NMR to determine the conversion. Purification by flash chromatography (EtOAc:Hexane= 1:4) afforded the product 3a. Enantiomeric excess was determined by HPLC by comparison with the authentic racemic compounds (Phenomenex Lux 5u-Amylose-2 column, Hexane:iPrOH= 90:10, 1 mL/min, 209 nm). HPLC samples were directly prepared from the crude reaction mixture.

3.1. ¹H NMR spectrum of Michael adduct 3a

(400 MHz, CDCl₃)
3.2. HPLC chromatograms of Michael adduct 3a

The ee value was measured along the reaction. It stays constant over time.

<table>
<thead>
<tr>
<th>time (h)</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>90</td>
</tr>
</tbody>
</table>
4. Quantitative $^1$H NMR kinetic analysis

4.1. Materials and general procedure for NMR kinetic experiments

D$_8$-toluene (D % 99.6 ampoules of 1 mL) was purchased from Sigma-Aldrich. NMR spectra were recorded on Bruker DRX-400 MHz equipped with a BBFO 5 mm Proxe. A capillary with pyrazine (δ= 7.90 ppm) was used as an external standard to quantify the concentration of the different species. To achieve quantitative data for all the species we measured the 90 degree flip angle (P1/4) and the longitudinal relaxation time (T1) for pyrazine as 7.5 s (all the species had a relaxation time lower than pyrazine). Relaxation delay (D1) was calculated as 37.5 s (7.5 s x 5) and used in all kinetic experiments.

4.2. Calibration curve for qNMR

To calibrate the pyrazine capillary five different solutions of known concentration of nitrostyrene 1 (NS) were prepared. $^1$H NMR of each solution with the capillary of pyrazine was recorded with ns= 8. The signals of pyrazine and NS (δ= d, 7.74 ppm) were integrated and the ratios of areas were plotted vs. the concentration of nitrostyrene.

<table>
<thead>
<tr>
<th>Concentration of NS [M]</th>
<th>(AreaNS/Area pyrazine)×100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0998</td>
<td>21.18</td>
</tr>
<tr>
<td>0.2018</td>
<td>41.47</td>
</tr>
<tr>
<td>0.3004</td>
<td>62.40</td>
</tr>
<tr>
<td>0.4003</td>
<td>86.54</td>
</tr>
<tr>
<td>0.5008</td>
<td>100.62</td>
</tr>
</tbody>
</table>

![Graph showing the calibration curve for qNMR](image.png)
4.3. General procedure for kinetic experiments

7.5 mg (0.027 mmol) of catalyst I was weighed directly into NMR tube. The other reagents were added from common stock solutions in the indicated order below in function of experiment required. The reaction starting time was recorded just after the addition of the nitrostyrene (last reagent added). The shimming was done as fast as possible using the same reaction tube once the reaction was setted up (4 min approximately).

- **Stock solution A (nitrostyrene):** 201.4 mg (1.35 mmol) nitrostyrene in 1 mL d₈-toluene
- Stock solution B (AcOH):
  - for 10 mol% AcOH: 162.4 mg (155.5 µL, 2.7mmol) of acetic acid in 1 mL d₈-toluene. 0.1 mL of this solution was diluted to 1 mL d₈-toluene.  
    Final solution: 0.27 mmol AcOH / mL solution
  - for 5 mol% AcOH: 81.2 mg (77.4 µL, 1.35mmol) of acetic acid in 1 mL d₈-toluene. 0.1 mL of this solution was diluted to 1 mL d₈-toluene.  
    Final solution: 0.135 mmol AcOH / mL solution
  - for 2.5mol% AcOH: 40.5 mg (38.7 µL, 0.675 mmol) of acetic acid in 1 mL d₈-toluene. 0.1 mL of this solution was diluted to 1 mL d₈-toluene.  
    Final solution: 0.0675 mmol AcOH / mL solution
- **Stock solution C (H₂O):**
  - for 1 equiv. H₂O: 24.3 µL H₂O (1.35 mmol) in 1 mL acetone.  
  - for 0.5 equiv. H₂O: 24.3 µL H₂O (1.35 mmol) in 2 mL acetone.

Reagent addition order for the different experiments

![Reaction diagram]

i. “no extra water added” reactions (conditions B):
   + 100 µL toluene- d₈
   + 200 µL acetone
   + 100 µL stock soln. B
   + 200 µL stock soln. A

ii. “added water” reactions (conditions C):
   + 100 µL toluene- d₈
   + 200 µL stock soln. C
   + 100 µL stock soln. B
   + 200 µL stock soln. A
4.4. Concentration vs time plots at different AcOH and water amounts

The same colors and different symbols are used for the same acid and different water amount sets.

**Figure 1.** Consumption of nitrostyrene 1 over time under different conditions
**Figure 2.** Formation of addition product 3a over time under different conditions.
Figure 3. Formation of double addition side product 3b over time under different conditions.
4.5 Catalytic species profile over the reaction course (Conditions A):

*Figure 4.* Reaction profile under “no extra water added, no AcOH” conditions (Conditions A), [1]₀=0.45 M, 10 equiv. acetone, 10 mol% I. Nitrostyrene concentration is shown in the left Y axis. Catalytic species and the addition product 3a concentrations are shown in the right Y axis. Recorded on a Bruker Avance 600 MHz equipment.
4.6 Catalytic species profile over the reaction course (Conditions B):

Figure 5. Catalytic species profile determined by $^1$H NMR during the reaction under “no extra water added” conditions (Conditions B). $[\text{I}]=0.45$ M, 5 equiv. acetone, 10 mol% I, 5 mol% AcOH. {I-2}, green; {I-3a}, blue; {I-3b}, red; unknown species, yellow; total concentration of detected catalytic species, black hyphen. Recorded on a Bruker 500 MHz spectrometer equipped with a cryoprobe.

The concentration of catalyst-acetone imine {I-2} decreases fast from the beginning of the reaction and then stays at a very low level (green squares). Catalyst-product imine {I-3a} concentration (blue triangles) also decreases at the beginning but after the reaction is ca. 50% conversion its concentration increases again slowly and remains constant thereafter. In contrast, concentration of the catalyst-double addition product imine {I-3b} increases along the reaction up to a maximum at ca. 0.009 M, and then decreases down to very low concentrations at the end of the reaction (red circles). This behavior suggests an equilibrium between {I-3a} and {I-3b}. $^1$H NMR signals corresponding to unknown species that we attribute to catalyst decomposition products (yellow crosses) are initially at very low intensity, but the concentration of these species increases constantly with time. The total concentration of detected catalytic species decreases constantly along the reaction, from 0.014 M to 0.006 M (black hyphens).
4.7 Catalytic species profile over the reaction course (Conditions C):

Figure 6. Catalytic species profile determined by $^1H$ NMR during the reaction under acid and water added (Conditions C). $[1]=0.45$ M, 5 equiv. acetone, 10 mol% I, 5 mol% AcOH, 1 equiv. water. {I-2}, green; {I-3a}, blue; {I-3b}, red; unknown species, yellow; total concentration of detected catalytic species, black hyphen. Recorded on a Bruker 500 MHz spectrometer equipped with a cryoprobe.

The concentration of catalyst-acetone imine {I-2} decreases fast from the beginning of the reaction and then stays at a very low but appreciable level (ca. 0.001 M, green squares). Catalyst-product imine {I-3a} concentration (blue triangles) decreases fast at the beginning but afterwards stabilizes at ca. 0.001 M, and after 10 hours its concentration increases again slowly. In contrast, concentration of the catalyst-double addition product imine {I-3b} increases fast at the beginning up to a maximum at ca. 0.003 M, and then decreases down slowly to very low concentrations at the end of the reaction (red circles). This behavior suggests an equilibrium between {I-3a} and {I-3b}. $^1H$ NMR signals corresponding to unknown species that we attribute to catalyst decomposition products (yellow crosses) are initially at very low intensity, but the concentration of these species increases up to 0.001 M and stays constant after 6 hours. The total concentration of detected catalytic species decreases constantly along the reaction, from 0.005 M to 0.003 M, at around 8-10 hours. Afterwards the total concentration increases slowly to the original level (black hyphens).
4.8. Characterization of intermediate species

\[
\begin{align*}
\text{Ph} & \quad \text{NO}_2 \\
\text{1} \quad & \quad \text{O} \quad & \quad \text{10 mol\% I} \quad \text{(R-NH}_2) \quad & \quad \text{O} \\
\quad & \quad \text{Ph} \quad & \quad \text{NO}_2 \\
\quad & \quad \text{3a} \\
\quad \text{10 mol\% I} \quad \text{(R-NH}_2) \quad & \quad \text{to} & \quad \text{RT} \quad & \quad \text{3a} \\
\quad & \quad \text{Ph} \quad & \quad \text{NO}_2 \\
\quad & \quad \text{O} \quad & \quad \text{Ph} \quad & \quad \text{N}^R \quad \text{R} \quad \text{Ph} \\
\quad & \quad \text{to} & \quad \text{Ph} \quad & \quad \text{NO}_2 \\
\quad \text{I-3b} \quad & \quad \text{I-3b} \\
\end{align*}
\]

In the absence of added water and AcOH (Conditions A, [1]_0=0.45 M, 10 equiv. acetone, 10 mol\% I), the catalyst-double addition imine intermediate \{I-3b\} and the product 3a formed cleanly and could be fully characterized by NMR.

![Figure 7](image_url)

**Figure 7.** $^1$H NMR characterization of the catalytic species \{I-3b\} and product 3a. Performed in the absence of added water and AcOH (Conditions A).
Figure 8. Expansion of $^1$H NMR spectrum range 3.50-4.75 ppm

Figure 9. Expansion of $^1$H NMR spectrum range 1.0-3.4 ppm
Figure 10. Full COSY NMR Spectrum in the absence of added water and AcOH (Conditions A).
Figure 11. COSY cross peaks on the range 1.5-4.5 ppm
Figure 12. COSY cross peak between protons 1 and 2 of compound {I-3b}
Figure 13. COSY cross peaks on the range 1.5-4.5 ppm
Figure 14. \(^{13}\text{C}\) NMR characterization of the catalytic species \{I-3b\} and product 3a. Performed in the absence of added water and AcOH (Conditions A).

Figure 15. Expansion of \(^{13}\text{C}\) NMR spectrum range 20-90 ppm
Figure 16. Full HSQC Spectrum in the absence of added water and AcOH (Conditions A).
Figure 17. Expansion of HSQC spectrum range 0.0-6.5 ppm
Figure 18. Full HMBC Spectrum in the absence of added water and AcOH (Conditions A).
Figure 19. Expansion of HMBC Spectrum range 0.0-5.5 ppm
When the Michael addition was performed in the presence of 10 mol% AcOH and no added water (Conditions B, $[1]_0=0.45$ M, 10 equiv. acetone, 10 mol% I, 10 mol% AcOH), in the beginning of the reaction (up to 30 min), catalyst-product imine intermediate {I-3a} could be characterized by NMR.

**Figure 20.** $^1$H NMR characterization of the catalytic species {I-3a} and product 3a (Conditions B).

**Figure 21.** Expansion of $^1$H NMR spectrum range 2.7-4.6 ppm.
Figure 22. Expansion of $^1$H NMR spectrum range 1.0-3.5 ppm.
Figure 23. COSY cross peaks on the range 0.5-6.0 ppm
**Figure 24.** COSY cross peaks on the range 3.5-4.8 ppm
Figure 25. $^{13}$C NMR characterization of the catalytic species \{I-3a\} and product 3a under Conditions B. $[1]_0=0.45$ M, 10 equiv. acetone, 10 mol% I, 10 mol% AcOH.

Figure 26. Expansion of $^{13}$C NMR spectrum range 20-90 ppm
**Figure 27.** Full HSQC Spectrum under Conditions B. $[\text{1}]_0=0.45$ M, 10 equiv. acetone, 10 mol% I, 10 mol% AcOH.
Figure 28. Expansion of HSQC Spectrum range 0.0-6.5 ppm.
4.9. $^1$H NMR spectra for the reaction run with 1 equivalent of water added but no AcOH

Under acid-free conditions but adding 1 equiv. of water ($[1]_0=0.45$ M, 10 equiv. acetone, 10 mol% I, 1 equiv. water) double addition product imine {I-3b} and product 3a were formed (See Section 7.6). After 24 hours the concentration of the two species remained constant.
4.10. Effect of the amount of AcOH

Effect of AcOH amount in the Michael addition of acetone to nitrostyrene was tested under Conditions C. \([1]_0=0.45 \text{ M}, 10 \text{ equiv. acetone}, 10 \text{ mol\% catalyst I}, x \text{ mol\% AcOH}, 0.5 \text{ equiv. water in toluene at rt.}\)
4.11. Disappearance of nitrostyrene due to the formation of products, intermediates and side-products

**Figure 29.** Conversion vs. time under “added water” conditions (Conditions C). \([1]_0 = 0.45 \text{ M}, 10 \text{ equiv. acetone}, 10 \text{ mol\% catalyst I}, 5 \text{ mol \% AcOH}, 1 \text{ equiv. water.}

**Figure 30.** Conversion vs. time under “no extra water added” conditions (Conditions B). \([1]_0 = 0.45 \text{ M}, 10 \text{ mol\% catalyst I}, 5 \text{ mol \% AcOH.}

*Red squares:* conversion calculated based on product 3a formation

\[
\text{conversion } \% = \left( \frac{[3a]}{[1]_0} \right) \times 100
\]

*Blue triangles:* conversion based on product 3a plus double-addition side product 3b formation

\[
\text{conversion } \% = \left( \frac{[3a] + [3b]}{[1]_0} \right) \times 100
\]

*Yellow circles:* conversion based on nitrostyrene disappearance

\[
\text{conversion } \% = \left( \frac{[1]_0 - [1]_t}{[1]_0} \right) \times 100
\]
4.12. Proof of the “free catalyst” does not deactivate

The reactions were carried out under three different sets of reaction conditions (Conditions A-C). For all three sets of reactions, [1]₀ = 0.45 M, 10 equiv. acetone and 10 mol% catalyst I were used. First, the catalyst (7.5 mg, 0.027 mmol) was weighed directly into the NMR tube, and then the reagents were added from common stock solutions in the indicated order. The catalyst was exposed to nitrostyrene for 3 hours prior to acetone addition. The reaction was then recorded continuously by NMR.

- **Stock solution A (nitrostyrene):** 201.4 mg (1.35 mmol) nitrostyrene in 1 mL d₈-toluene
- **Stock solution B (AcOH):** 81.2 mg (77.4 µL, 1.35 mmol) of acetic acid in 1 mL d₈-toluene. 0.1 mL of this solution was diluted to 1 mL d₈-toluene.  
  
  *Final solution: 0.135 mmolAcOH / mL solution*

**Conditions A, in the absence of added water and AcOH:**

+ 200 µL d₈-toluene  
+ 200 µL stock soln. A  
Wait 3 hours  
+ 200 µL acetone  
Wait 1 hour  
+ 100 mL stock soln. B

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Before AcOH addition

![NMR spectrum before AcOH addition](image_url)

After AcOH addition

![NMR spectrum after AcOH addition](image_url)
Conditions B, with 5 mol% AcOH and no extra water added:
  +100 µL toluene-d₈
  + 100 µL stock soln. B
  + 200 µL Stock soln. A
  Wait 3 hours
  + 200 µL acetone
Formation of product 3a was observed similarly to a reference reaction without catalyst pre-mixing with NS.

Conditions C, with 5 mol% AcOH and water added (1 equiv.):
  +100 µL d₈-toluene
  + 100 µL Stock soln B
  + 200 µL Stock soln A
  + 4.86 µL H₂O
  Wait 3 hours
  + 200 µL acetone
Formation of product 3a was observed identical to a reference reaction without catalyst pre-mixing with nitrostyrene.
4.13. Proof of no product inhibition

An initial kinetic experiment by $^1$H NMR (red squares) was repeated under identical conditions (Conditions B, $[1]_0=0.45$ M, 10 equiv. acetone, 10 mol% catalyst I and 5 mol% AcOH) and recorded continuously by NMR. The amount of product formed during the first 2.5 hours (yellow circles) was calculated as 0.114 M (15 mg, 0.0684 mmol). Another experiment was carried out under identical conditions adding the calculated amount of product at the beginning of the reaction. The overlay of these two traces (product added experiment and the reference experiment) concludes there is no product inhibition responsible for this reaction.

![Graph showing proof of no product inhibition](image)

**Figure 31.** Proof of no product inhibition by carrying out reaction with and without addition of product at $t_0$. 