

# Supporting Information

## On the Fischer Indole Synthesis of 7-Ethyltryptophol - Mechanistic and Process Intensification Studies under Continuous Flow Conditions

Bernhard Gutmann,<sup>†</sup> Michael Gottsponer,<sup>‡</sup> Petteri Elsner,<sup>‡</sup> David Cantillo,<sup>†</sup>

Dominique M. Roberge,<sup>\*,‡</sup> and C. Oliver Kappe<sup>\*,†</sup>

*Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of  
Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-80010 Graz, Austria, and  
Microreactor Technology, Lonza AG, CH-3930 Visp, Switzerland*

## 1. Continuous Flow Reactions with Three Separate Feeds

**Table S1. Yields of 7-ET for flow reactions performed with increased residence volume for reactor module 2.<sup>a</sup>**

| Exp. | Flow Feed A<br>[g/min] | Flow Feed B<br>[g/min] | Flow Feed C<br>[mL/min] | RT module 1<br>[min] | RT module 2<br>[min] | total RT<br>[min] | Yield 7-ET (incl. HPLC assay) <sup>b</sup> |
|------|------------------------|------------------------|-------------------------|----------------------|----------------------|-------------------|--|
| 1    | 8.1                    | 8.2                    | 1.0                     | 0.31                 | 5.01                 | 5.63              | 35%  |
| 2    | 10.0                   | 10.1                   | 1.2                     | 0.26                 | 4.10                 | 4.61              | 36%  |
| 3    | 13.4                   | 13.6                   | 1.7                     | 0.19                 | 3.01                 | 3.38              | 35%  |
| 4    | 20.0                   | 20.2                   | 2.5                     | 0.13                 | 2.03                 | 2.28              | 38%  |

<sup>a</sup>Conditions: 1 equiv of DHF and 1.2 equiv of H<sub>2</sub>SO<sub>4</sub> at 115 °C reaction temperature; feed A: 0.8 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv NaOH in ethylene glycol/H<sub>2</sub>O; feed B: 0.8 M DHF, 0.008 equiv HCl in ethylene glycol/H<sub>2</sub>O; feed C: 50% H<sub>2</sub>SO<sub>4</sub>; RT module 1: Hastelloy C-22 flowplate<sup>TM</sup> and PFA coil (4.8 mL); RT module 2: Corning glass reactor and stainless steel coil (5.6 mL and 2 × 38mL). <sup>b</sup>Yields are based on quantitative HPLC analysis of samples after extraction and removing of solvent. RT = residence time.

**Table S2. Yields of 7-ET for flow reactions performed with increased residence volume for reactor module 1.<sup>a</sup>**

| Exp. | Flow Feed A<br>[g/min] | Flow Feed B<br>[g/min] | Flow Feed C<br>[mL/min] | RT module 1<br>[min] | RT module 2<br>[min] | total RT<br>[min] | Yield 7-ET (incl. HPLC assay) <sup>b</sup> |
|------|------------------------|------------------------|-------------------------|----------------------|----------------------|-------------------|--|
| 1    | 8.1                    | 8.2                    | 1.0                     | 0.58                 | 5.02                 | 5.91              | 44%  |
| 2    | 10.0                   | 10.1                   | 1.2                     | 0.47                 | 4.06                 | 4.78              | 39%  |

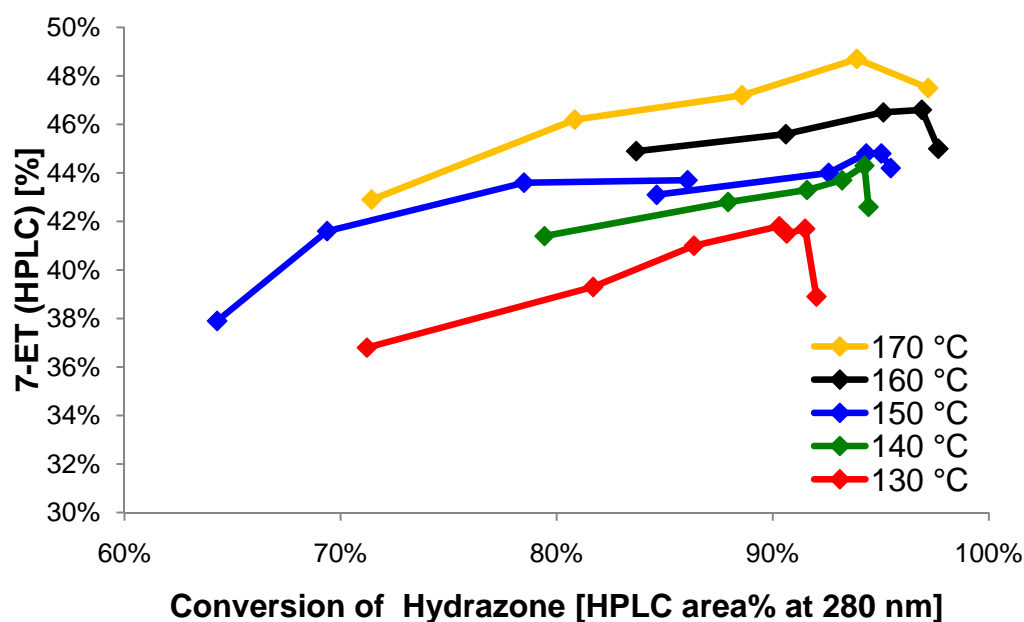
<sup>a</sup>Conditions: 1 equiv of DHF and 1.2 equiv of H<sub>2</sub>SO<sub>4</sub> at 115 °C reaction temperature; feed A: 0.8 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv NaOH in ethylene glycol/H<sub>2</sub>O; feed B: 0.8 M DHF, 0.008 equiv HCl in ethylene glycol/H<sub>2</sub>O; feed C: 50% H<sub>2</sub>SO<sub>4</sub>; RT module 1: Hastelloy C-22 flowplate<sup>TM</sup> and PFA coil (8.8 mL); RT module 2: Corning glass reactor and stainless steel coil (5.6 mL and 2 × 38mL). <sup>b</sup>Yields are based on quantitative HPLC analysis of samples after extraction and removing of solvent. RT = residence time.

**Table S3. Yields of 7-ET for flow reactions performed under stronger diluted conditions.<sup>a</sup>**

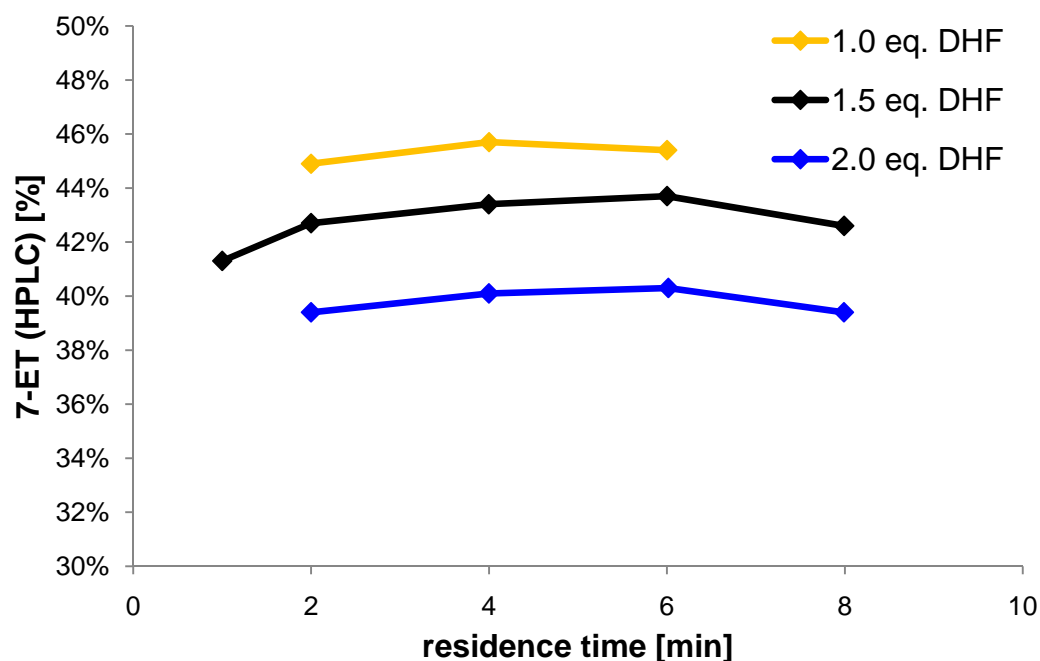
| Exp. | Flow Feed A<br>[g/min] | Flow Feed B<br>[g/min] | Flow Feed C<br>[mL/min] | RT module 1<br>[min] | RT module 2<br>[min] | total RT<br>[min] | Conv. of hydrazone (HPLC) <sup>b</sup><br>[area%] | Yield 7-ET (incl. HPLC assay) <sup>c</sup> |
|------|------------------------|------------------------|-------------------------|----------------------|----------------------|-------------------|---|--|
| 1.1  | 14.0                   | 13.5                   | 0.44                    | 0.33                 | 3.02                 | 3.54              | 46%   | -  |
| 1.2  | 14.0                   | 13.5                   | 0.44                    | 0.33                 | 3.02                 | 3.54              | 49%   | -  |
| 1.3  | 14.0                   | 13.5                   | 0.44                    | 0.33                 | 3.02                 | 3.54              | 31%   | 28%  |
| 2    | 21.5                   | 20.7                   | 0.64                    | 0.22                 | 2.04                 | 2.39              | 2%  | -  |

<sup>a</sup>Conditions: 1 equiv of DHF and 1.2 equiv of H<sub>2</sub>SO<sub>4</sub> at 115 °C reaction temperature; feed A: 0.2 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv NaOH in ethylene glycol/H<sub>2</sub>O; feed B: 0.2 M DHF, 0.003equiv HCl in ethylene glycol/H<sub>2</sub>O; feed C: 50% H<sub>2</sub>SO<sub>4</sub>; RT module 1: Hastelloy C-22 flowplate<sup>TM</sup> and PFA coil (8.8 mL); RT module 2: Corning glass reactor and stainless steel coil (5.6 mL and 2 × 38mL). <sup>b</sup>Conversion of hydrazone to 7-ET according to HPLC at 280 nm. <sup>c</sup>Yields are based on quantitative HPLC analysis of samples after extraction and removing of solvent. RT = residence time.

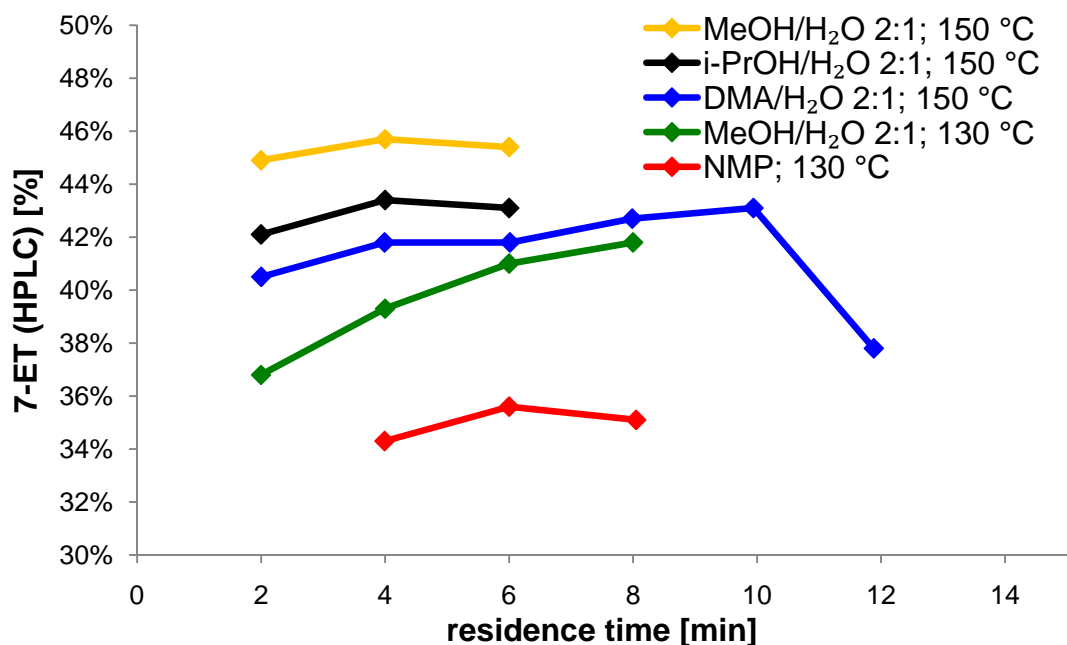
## 2. One Feed Continuous Flow Reactions



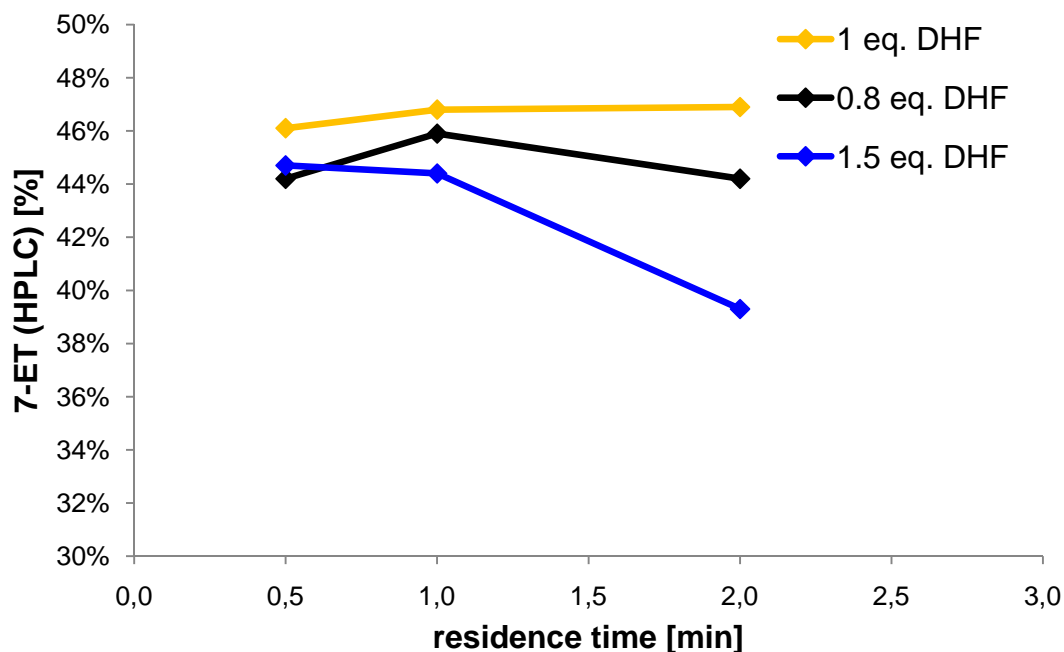
**Figure S1.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed without any catalyst. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF in MeOH/H<sub>2</sub>O 2:1. Yields of 7-ET are shown as a function of hydrazone conversion (HPLC at 280 nm). The accessible yields increased with increasing reaction temperature. 7-ET yields of ~40% were obtained after reaction times of just few minutes at a conversion of around 70% of the hydrazone. Longer residence time did not increase the yields of 7-ET significantly.



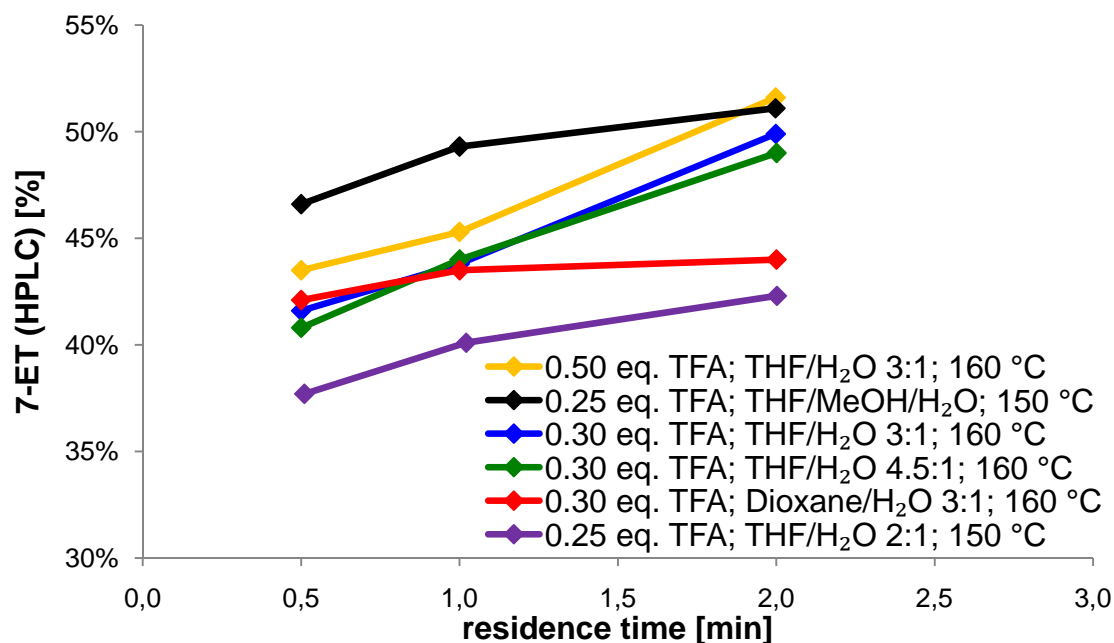
**Figure S2.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed with different amounts of DHF at 150 °C. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a** in MeOH/H<sub>2</sub>O 2:1.



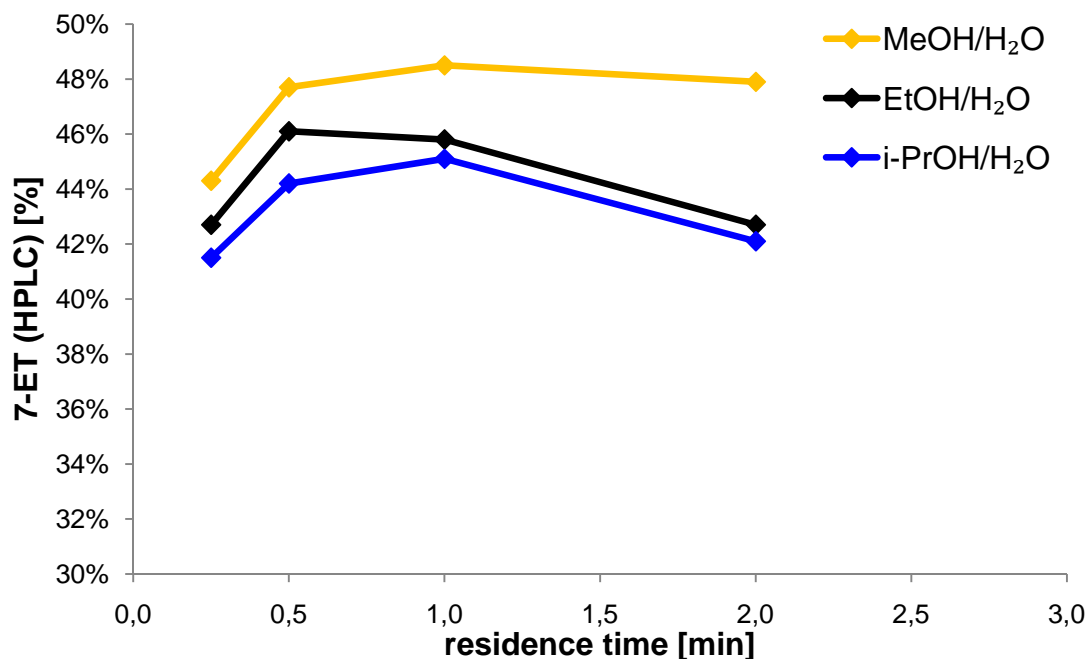
**Figure S3.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in different solvents at 130 or 150 °C. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a** and 1 equiv DHF.



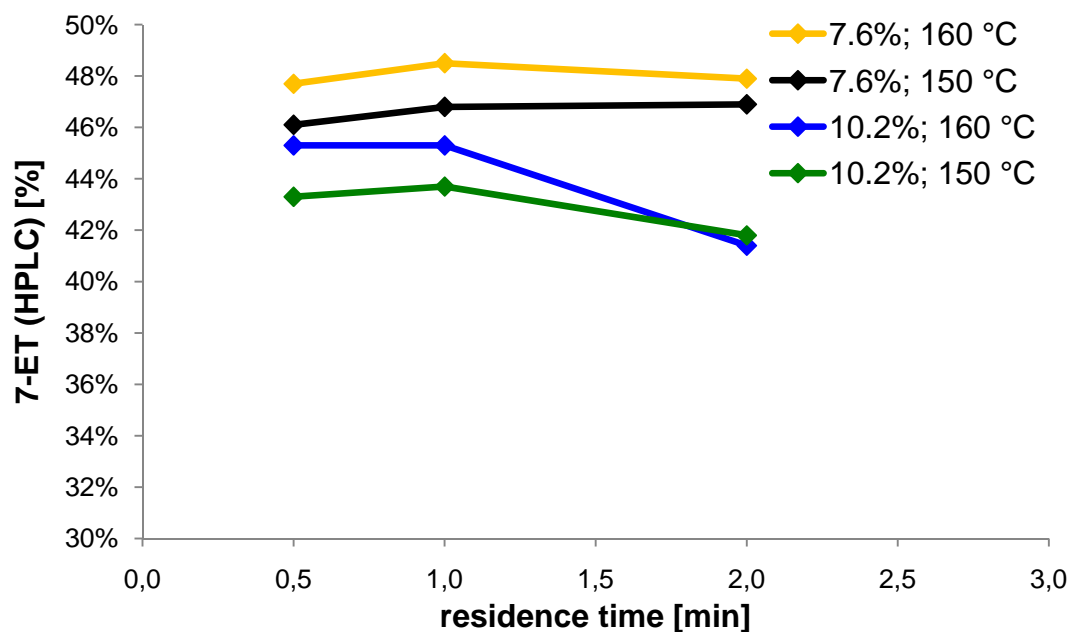
**Figure S4.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in the presence of TFA and different stoichiometries of DHF. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**, 25 mol% TFA in MeOH/H<sub>2</sub>O 2:1, 150 °C reaction temperature. Best results were obtained with 1 equiv of DHF. Higher and lower amounts of DHF gave inferior results.



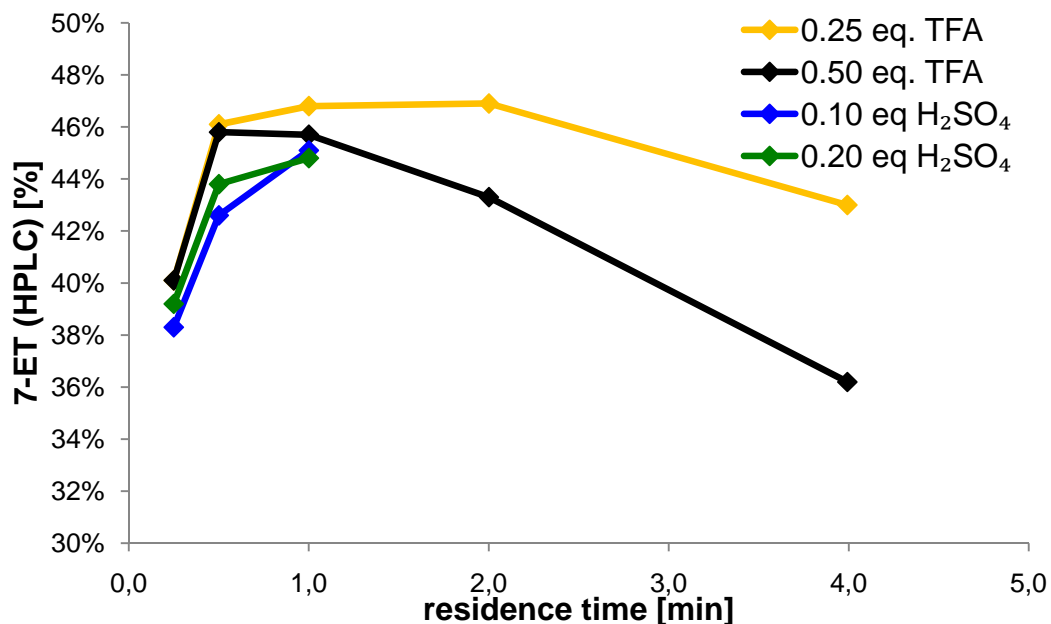
**Figure S5.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in the presence of TFA in different solvents. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**; 1 equiv DHF. The reaction in THF/H<sub>2</sub>O gave slightly better results than the reaction in MeOH/H<sub>2</sub>O as solvent.



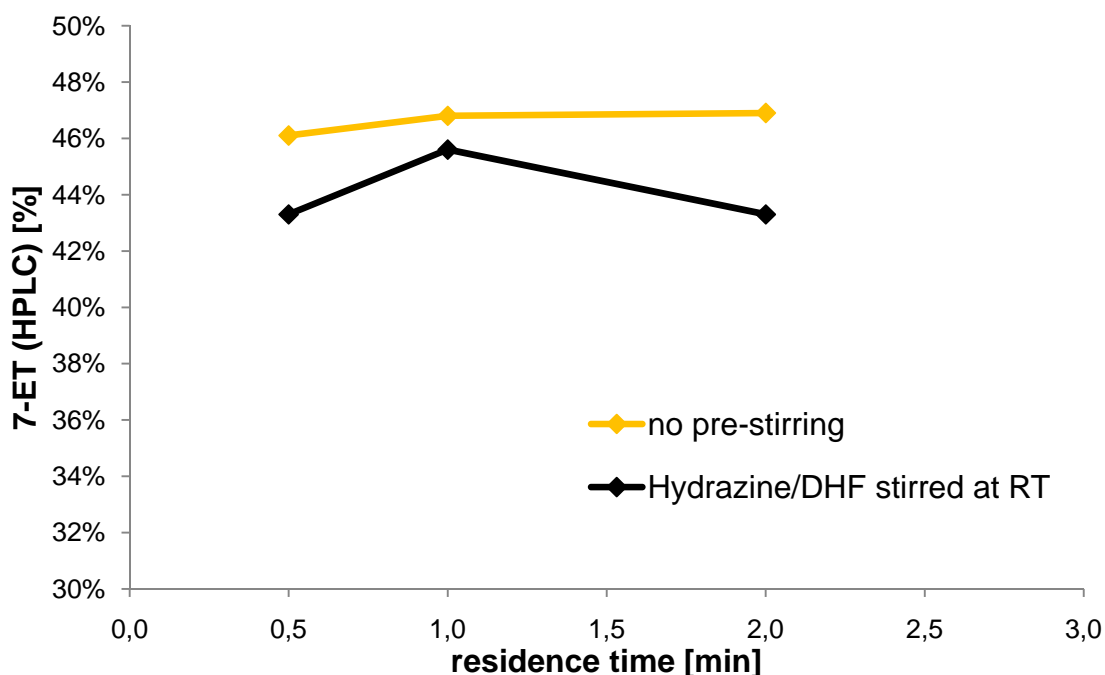
**Figure S6.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in the presence of TFA in different solvents at 160 °C reaction temperature. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**; 1 equiv DHF; 25 mol% TFA in solvent/H<sub>2</sub>O 2:1.



**Figure S7.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in the presence of TFA at different concentrations. Conditions: 0.41 M (7.6 wt%) or 0.55 M (10.2 wt%) 2-ethylphenylhydrazine hydrochloride **1a**; 1 equiv DHF; 25 mol% TFA in MeOH/H<sub>2</sub>O 2:1.



**Figure S8.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed in the presence of either TFA or H<sub>2</sub>SO<sub>4</sub> at 150 °C reaction temperature. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**; 1 equiv DHF in MeOH/H<sub>2</sub>O 2:1.



**Figure S9.** Yields of 7-ET **3a** based on quantitative HPLC analysis of the reaction mixture for flow reactions performed with and without stirring of the reaction mixture at room temperature before heating in the flow reactor. Conditions: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**; 1 equiv DHF, 0.25 equiv TFA in MeOH/H<sub>2</sub>O 2:1; 150 °C reaction temperature.

### 3. Batch Reactions

Tables S4-S6 show the results of preliminary batch experiments performed on  $\leq 1$  mmol scale. Consumption of the hydrazone and formation of side-products were determined by HPLC peak area integration. It should be mentioned, that owing to the formation of undetectable side-products (e.g. polymer and dienylymine **9a**), the HPLC peak areas do not necessarily relate to the content of 7-ET in the reaction mixtures and the results are shown only to demonstrate trends in dimer formation and hydrazone consumption.

**Table S4. HPLC purity (peak area integration at 215 nm) for batch reactions performed with different additives in DMA/H<sub>2</sub>O as solvent.<sup>a</sup>**

| Additive               | hydrazone<br><b>2a</b> | 7-ET<br><b>3a</b> | dimer<br><b>4a</b> |
|------------------------|------------------------|-------------------|--------------------|
| -                      | 4%                     | 82%               | 2%                 |
| 5% NaHCO <sub>3</sub>  | 6%                     | 83%               | 1%                 |
| 10% NaHCO <sub>3</sub> | 9%                     | 83%               | 0%                 |
| 20% NaHCO <sub>3</sub> | 15%                    | 76%               | 0%                 |
| 5% pyridine            | 4%                     | 84%               | 2%                 |
| 10% pyridine           | 5%                     | 83%               | 1%                 |
| 20% pyridine           | 7%                     | 85%               | 0%                 |

<sup>a</sup>Conditions: 1 mmol hydrazine hydrochloride **1a**, 1 equiv DHF in 1200  $\mu$ L DMA/H<sub>2</sub>O 2:1, 30 min at 130 °C.

**Table S5. HPLC purity (peak area integration at 215 nm) for batch reactions performed in the presence of different amounts of NaHCO<sub>3</sub> in MeOH/H<sub>2</sub>O as solvent.<sup>a</sup>**

| Additive               | hydrazone<br><b>2a</b> | 7-ET<br><b>3a</b> | dimer<br><b>4a</b> |
|------------------------|------------------------|-------------------|--------------------|
| -                      | 1%                     | 80%               | 7%                 |
| 10% NaHCO <sub>3</sub> | 5%                     | 83%               | 3%                 |
| 20% NaHCO <sub>3</sub> | 11%                    | 82%               | 2%                 |
| 50% NaHCO <sub>3</sub> | 38%                    | 58%               | 0%                 |

<sup>a</sup>Conditions: 0.5 mmol hydrazine hydrochloride **1a**, 1 equiv DHF in 600  $\mu$ L MeOH/H<sub>2</sub>O 2:1, 15 min at 130 °C.

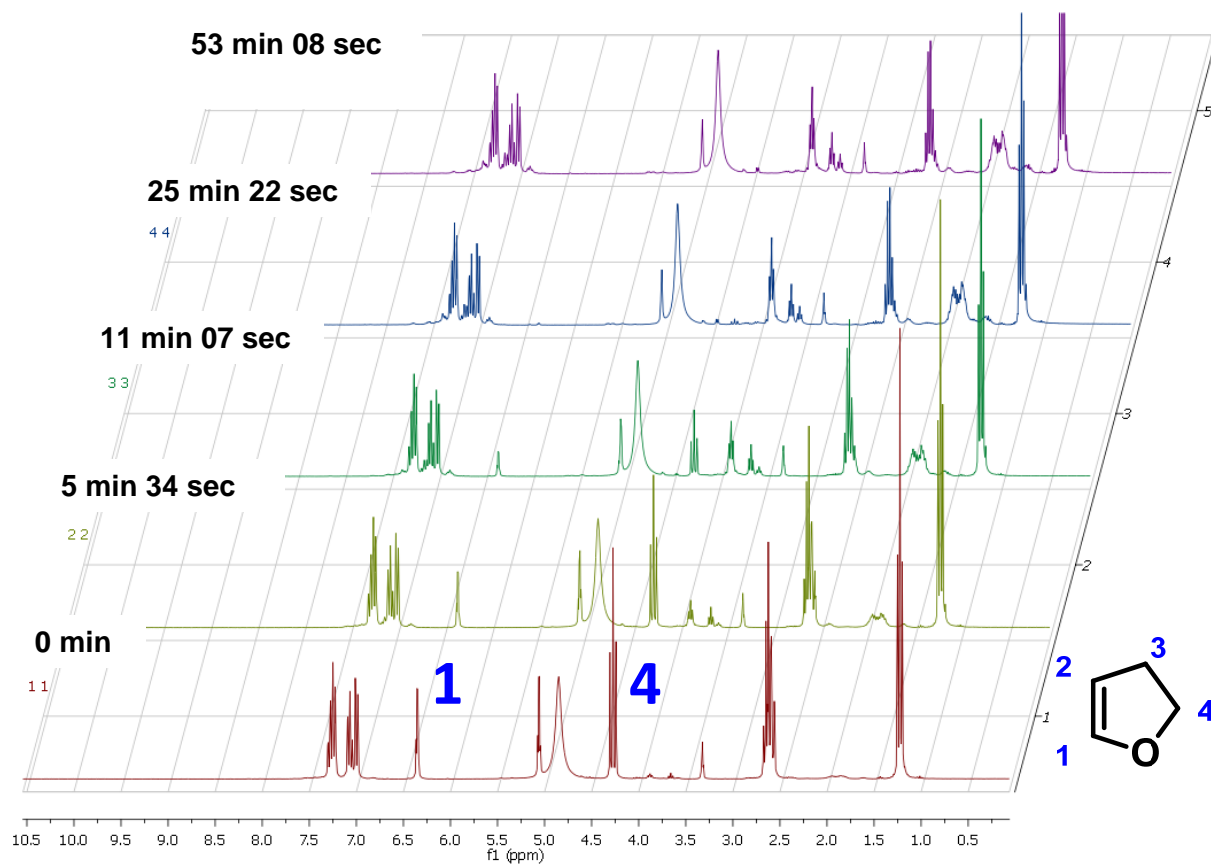
**Table S6. HPLC purity (peak area integration at 215 nm) for batch reactions performed in different solvents.<sup>a</sup>**

|                         | $\mu$ L/ $\mu$ L | hydrazone<br><b>2a</b> | 7-ET<br><b>3a</b> | dimer<br><b>4a</b> |
|-------------------------|------------------|------------------------|-------------------|--------------------|
| DMA/H <sub>2</sub> O    | 600/0            | 3%                     | 75%               | 0%                 |
|                         | 500/100          | 3%                     | 89%               | 0%                 |
|                         | 400/200          | 2%                     | 87%               | 2%                 |
|                         | 300/300          | 1%                     | 83%               | 3%                 |
|                         | 200/400          | 0%                     | 77%               | 6%                 |
| i-PrOH/H <sub>2</sub> O | 600/0            | 0%                     | 75%               | 21%                |
|                         | 500/100          | 0%                     | 71%               | 15%                |
|                         | 400/200          | 0%                     | 71%               | 12%                |
| MeOH/H <sub>2</sub> O   | 500/100          | 0%                     | 81%               | 10%                |
|                         | 400/200          | 0%                     | 81%               | 9%                 |
| EtOH/H <sub>2</sub> O   | 500/100          | 0%                     | 74%               | 12%                |
|                         | 400/200          | 0%                     | 76%               | 10%                |
| MeCN/H <sub>2</sub> O   | 500/100          | 0%                     | 58%               | 21%                |
|                         | 400/200          | 0%                     | 62%               | 16%                |
| DME/H <sub>2</sub> O    | 500/100          | 0%                     | 73%               | 16%                |
|                         | 400/200          | 0%                     | 79%               | 10%                |
| DMF/H <sub>2</sub> O    | 500/100          | 16%                    | 73%               | 1%                 |
|                         | 400/200          | 12%                    | 76%               | 1%                 |

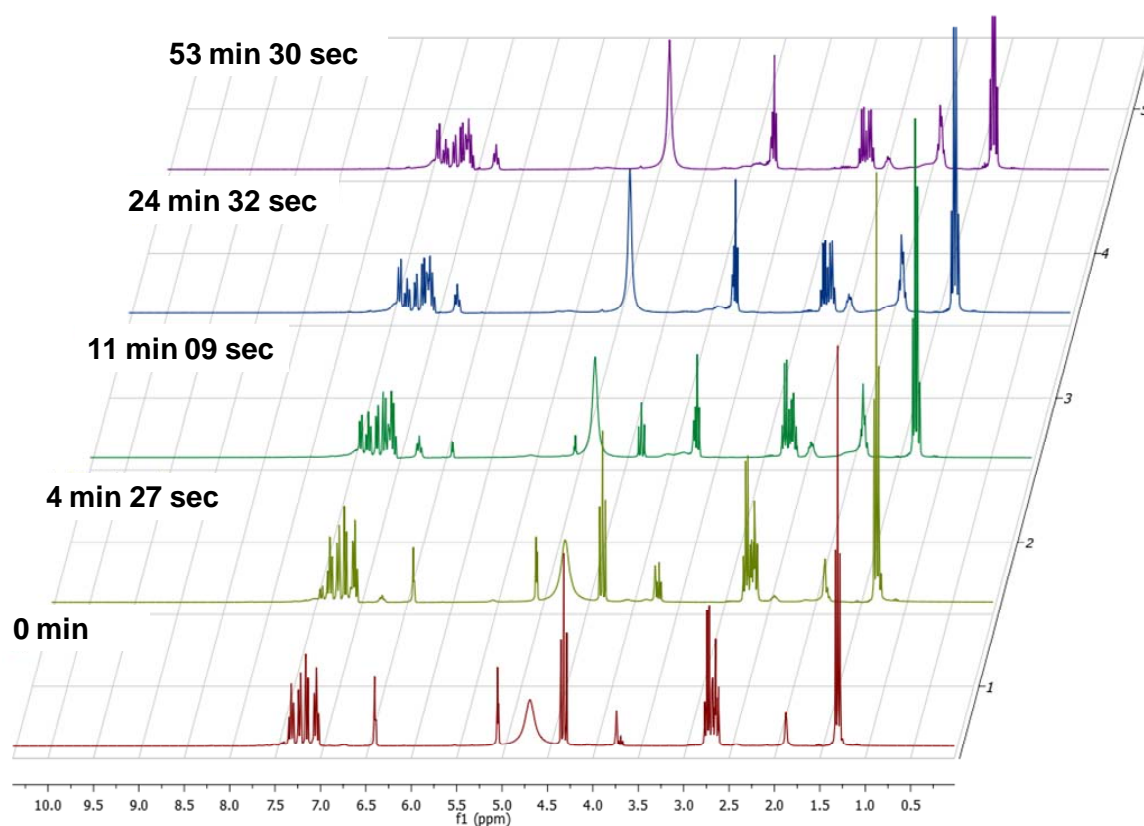
<sup>a</sup>Conditions: 0.5 mmol hydrazine hydrochloride **1a**, 1 equiv DHF in 600  $\mu$ L solvent/H<sub>2</sub>O, 30 min at 130 °C.



#### 4. Hydrazone formation

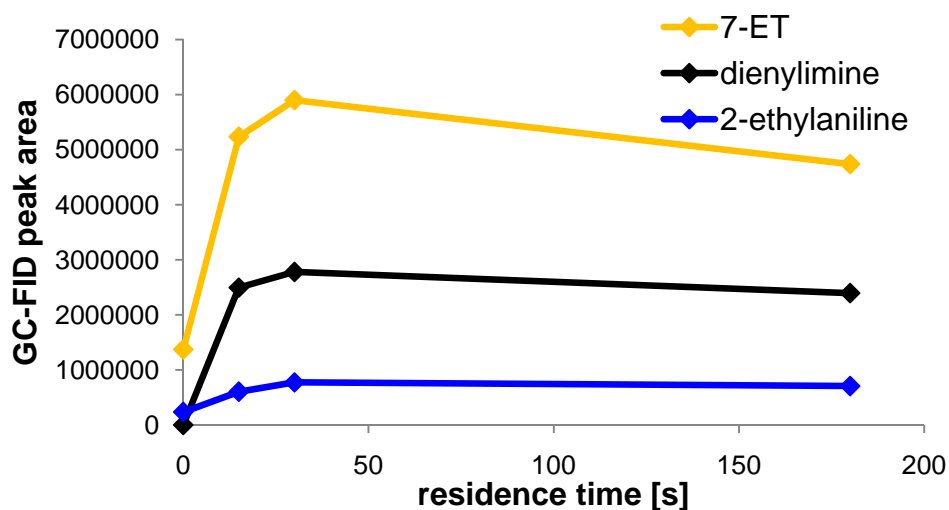


**Figure S10.** Hydrazone formation in MeOH/H<sub>2</sub>O at room temperature followed by <sup>1</sup>H-NMR. Conditions: 0.25 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF in 750 μL d-MeOH/d-H<sub>2</sub>O 2:1.

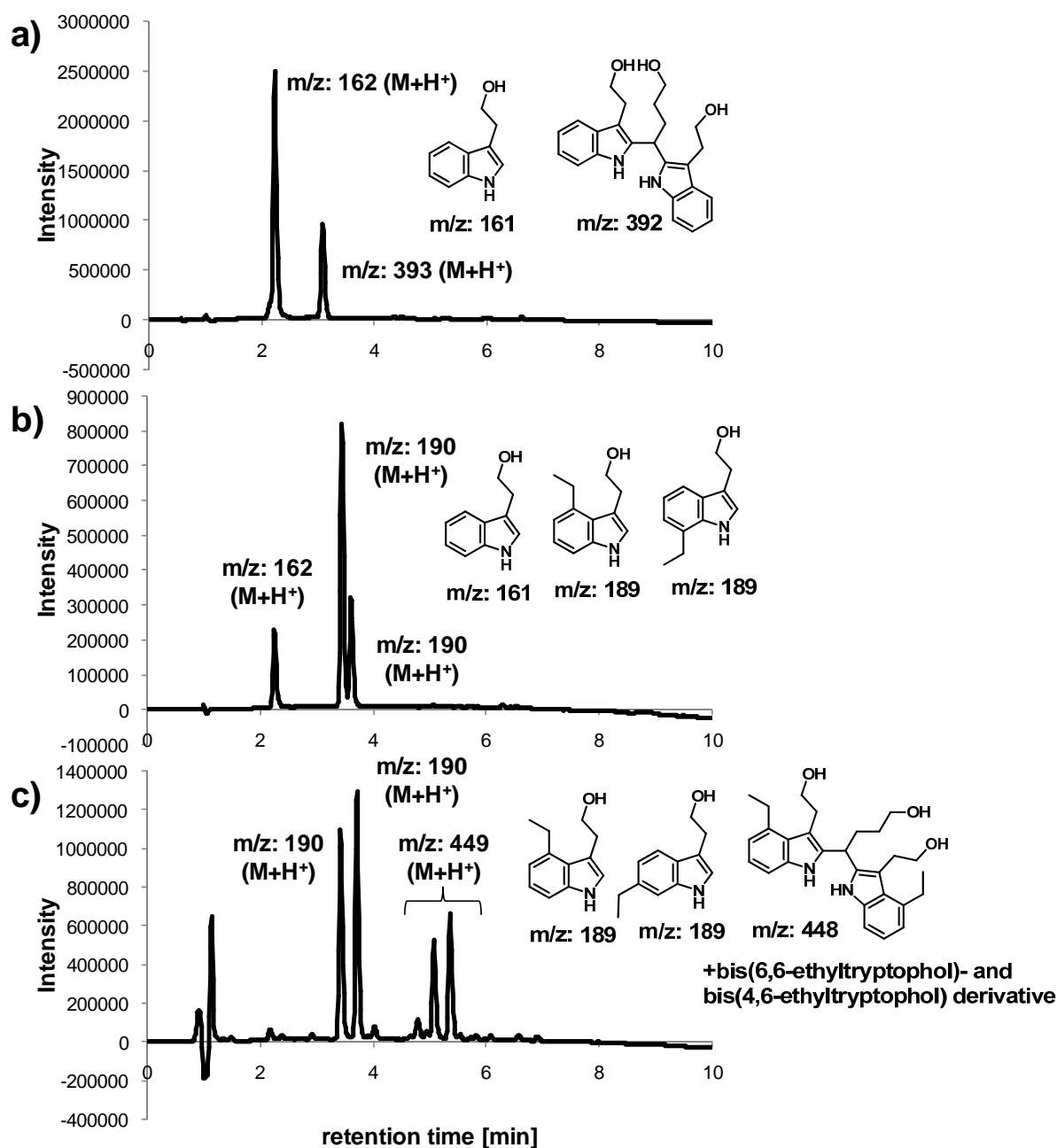


**Figure S11.** Hydrazone formation in THF/H<sub>2</sub>O at room temperature followed by <sup>1</sup>H-NMR. Conditions: 0.25 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF in 750  $\mu$ L d-THF/d-H<sub>2</sub>O 2:1.

## 5. [3,3]-Rearrangement



**Figure S12.** GC-FID analysis of samples after extraction of 50  $\mu$ L of the reaction mixture with sat. NaHCO<sub>3</sub>/EtOAc. Conditions: 1 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF, 1.5 mL MeOH/H<sub>2</sub>O 2:1, 20% H<sub>2</sub>SO<sub>4</sub>, 130  $^{\circ}$ C reaction temperature.



**Figure S13.** Comparison of HPLC traces of reaction mixtures (215 nm) of a) tryptophol synthesis: Conditions: 2 mmol phenylhydrazine hydrochloride, 1 equiv DHF, 25% TFA, 2 mL MeOH/H<sub>2</sub>O 2:1; 30 s reaction time at 150 °C (sealed vessel microwave heating); b) dienylymine **9a** after heating for 10 min at 150 °C in MeOH/H<sub>2</sub>O in the presence of 1 equiv of HCl (after column chromatography) and c) 4- and 6-ethyltryptophol synthesis: 1 mmol 3-ethylphenylhydrazine hydrochloride, 1 equiv DHF, 1.2 mL MeOH/H<sub>2</sub>O 2:1; 3 min reaction time at 150 °C.

## Computational details

All of the calculations reported in this work were carried out using the Gaussian 09 package. The ab initio MP2 method and the M06-2X density-functional were chosen for all the geometry optimizations and frequency analyses in conjunction with the 6-311+G(d,p) basis set. The geometries were optimized including solvation effects. For this purpose, the SMD solvation method was employed using methanol as solvent. Frequency calculations at 298.15 K on all the stationary points were carried out at the same level of theory as the geometry optimizations to ascertain the nature of the stationary points. Ground and transition states were characterized by none and one imaginary frequency, respectively. The relative energies presented in the manuscript are free energies at 298.15K with respect to the reactants, calculated at the MP2/6-311+G(d,p) level. Data obtained with the M06-2X density-functional are collected in the Table S7.

**Table S7.** Relative free energies for the intermediates and transition states involved in the [3,3]-rearrangement of **2b**, calculated at the MP2/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels of theory

| Structure  | Protonation state          | $\Delta G$ (kcal mol <sup>-1</sup> ) |                          |
|------------|----------------------------|--------------------------------------|--------------------------|
|            |                            | MP2/6-311+G(d,p)                     | M06-2X/6-311+G(d,p)      |
| <b>2b</b>  |                            | 0.0                                  | 0.00                     |
| <b>6b</b>  |                            | +9.1                                 | +9.2                     |
| <b>TS1</b> | free base                  | +27.7                                | +42.9                    |
| <b>TS2</b> |                            | +28.1                                | +45.7                    |
| <b>7b</b>  |                            | +2.4                                 | +7.4                     |
| <b>8b</b>  |                            | +5.3                                 | +10.6                    |
| <b>2b</b>  | N $\alpha$ -H <sup>+</sup> | +0.5                                 | +4.1                     |
|            | N $\beta$ -H <sup>+</sup>  | 0.0                                  | 0.0                      |
| <b>6b</b>  | N $\alpha$ -H <sup>+</sup> | +8.0                                 | +11.7                    |
|            | N $\beta$ -H <sup>+</sup>  | +8.1                                 | +11.9                    |
| <b>TS1</b> | N $\alpha$ -H <sup>+</sup> | +19.1                                | +26.7                    |
|            | N $\beta$ -H <sup>+</sup>  | +17.8                                | +28.1                    |
| <b>TS2</b> | N $\alpha$ -H <sup>+</sup> | +19.2                                | +25.9                    |
|            | N $\beta$ -H <sup>+</sup>  | +18.7                                | +26.3 +27.0 <sup>a</sup> |
| <b>7b</b>  | N $\alpha$ -H <sup>+</sup> | -7.9                                 | -5.5                     |
|            | N $\beta$ -H <sup>+</sup>  | -5.2                                 | -1.3                     |
| <b>8b</b>  | N $\alpha$ -H <sup>+</sup> | -2.9                                 | +0.3                     |
|            | N $\beta$ -H <sup>+</sup>  | -2.9                                 | +0.8                     |

<sup>a</sup>In this case two transition structures corresponding to a stepwise rearrangement were located.