Supporting Information

Enantioselective α-Amination of 1,3-Dicarbonyl Compounds in Batch and Flow with Immobilized Thiourea Organocatalysts

Pinar Kasaplar, Erhan Ozkal, Carles Rodríguez-Escrích and Miquel A. Pericàs

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1. General Information

All temperatures given for reaction conditions were externally measured. Organocatalytic reactions were performed without any precaution to exclude air but dry solvents were always used. Merrifield resin (1% DVB, \( f = 0.53 \text{ mmol Cl g}^{-1} \) resin) was obtained from Novabiochem. Commercial materials were used as received with the following exceptions: all solvents were taken from Solvent Purification System\(^1\) prior to use. All flash chromatographies were carried out using 60 mesh silica gel and dry-packed columns.\(^2\) The \(^1\)H and \(^13\)C NMR spectra were recorded at 400 MHz and 500 MHz for \(^1\)H or at 100 MHz and 125 MHz for \(^13\)C, respectively. TMS or (CD\(_3\))\(_2\)SO (2.50 ppm) was used as internal standard for \(^1\)H NMR and CDCl\(_3\) (77.16 ppm) or (CD\(_3\))\(_2\)SO (39.52 ppm) for \(^13\)C NMR. Chemical shifts are reported in ppm. FT-IR measurements were carried out on a FTIR spectrometer equipped with a DTGS detector, KBr beamsplitter at 4 cm\(^{-1}\) resolution. Elemental analyses were performed on a CHNS 932 micro-analyzer. The experiments under microwave irradiation were carried out in a CEM Discover microwave reactor. High performance liquid chromatography (HPLC) was performed by using commercial Chiralpak columns and guard columns. Racemic standard products were prepared using triethylamine or DABCO (20 mol\%) as catalyst in order to establish HPLC conditions. Compound 4 was synthesized according to a reported procedure.\(^3\) The degree of functionalization of a resin can be calculated from the results of elemental analysis with the formulas: \( f_N = (0.714/n_N)\%N \), where \( n_N \) is the number of nitrogen atoms in the functional unit and \%N is the percent of nitrogen provided by the elemental analysis.\(^4\)

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2. IR Spectra of Resins in the Synthesis of the PS-Thiourea Catalyst (PS-TU)

PS-NHFmoc resin

![Chemical Structures and IR Spectra](image)
PS-NH₂ resin (7)

```latex
\begin{tikzpicture}
  \node[anchor=west] at (0,0) {\includegraphics[width=0.4\textwidth]{ps_nh2_resin.png}};

  \node[anchor=east] at (9,0) {30\% piperidine in DMF (v/v) rt, 1 h};

  \node[anchor=west] at (0,-2) {\begin{align*}
    O & \quad CF_3 \\
    O & \quad \text{NHFmoc}
  \end{align*}};

  \node[anchor=east] at (9,-2) {O \quad CF_3}.

  \node[anchor=west] at (0,-4) {7}.

  \node[anchor=east] at (9,-4) {7}.
\end{tikzpicture}
```

Polystyrene-supported 4-isothiocyanato-2-(trifluoromethyl)benzoate (8)

```latex
\begin{tikzpicture}
  \node[anchor=west] at (0,0) {\includegraphics[width=0.4\textwidth]{polystyrene.png}};

  \node[anchor=east] at (9,0) {CH₂Cl₂, rt, 3 h};

  \node[anchor=west] at (0,-2) {\begin{align*}
    O & \quad CF_3 \\
    O & \quad \text{NHFmoc}
  \end{align*}};

  \node[anchor=east] at (9,-2) {O \quad CF_3}.

  \node[anchor=west] at (0,-4) {7}.

  \node[anchor=east] at (9,-4) {8}.
\end{tikzpicture}
```
PS-TU Catalyst

\[
\begin{array}{c}
\text{8} \\
\text{CH}_2\text{Cl}_2 \\
\text{rt, 16 h}
\end{array}
\]

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{PS-TU}
\end{array}
\]

Transmittance [%] vs. Wavenumber cm\(^{-1}\)

3500  3000  2500  2000  1500  1000  500

3903.98  3208.26  2924.46  1723.54  1505.38  1127.67  897.78
3. Description of the experimental set-up for the continuous-flow amination catalyzed by PS-TU

For the continuous flow experiments, the instrumental setup shown in Figure S1 was used. The packed bed reactor consisted of a vertical mounted and fritted low-pressure Omnifit glass chromatography column (10 mm bore size and up to maximal 70 mm of adjustable bed height) loaded with the polymer-supported thiourea resin PS-TU (300 mg, \( f = 0.426 \text{ mmol·g}^{-1} \)). The reactor inlet was connected to a three-way connector that allowed switching between two channels, connected to an Asia120® flow chemistry system developed by Syrris. At the start, toluene was flushed for 30 min at 200 \( \mu \text{L·min}^{-1} \) flow rate to swell the resin. After that, the solvent channel was switched to a solution of di-tert-butyl azodicarboxylate (1.52 g, 6.59 mmol, 1 equiv.) and ethyl 2-oxocyclopentanecarboxylate (1.46 mL, 9.89 mmol, 1.50 equiv.) in toluene (22 mL) (no reaction occurs in the absence of catalyst), which was pumped through the reactor at 50 \( \mu \text{L·min}^{-1} \) flow rate. The reactor outlet was connected to a receiving flask, where the product was collected. The other inlet channel was connected to a flask containing a triethylamine (700 \( \mu \text{L} \)) in toluene (25 mL) reservoir to clean the system (every 2 h, this solution was pumped through the reactor for 20 min at 200 \( \mu \text{L·min}^{-1} \) flow rate to restore catalytic activity and discarded without being collected). The formed product at any moment was characterized by \(^1\text{H} \text{NMR} \) (conversion) and HPLC (enantiomeric excess) measurements of periodically collected samples. After 7.5
h of flowing the reactants, the flow process was stopped and the catalytic resin was washed with toluene for 30 min. Then, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (cyclohexane-ethyl acetate, 95:5 to 90:10) to afford the final product as a thick colorless oil with 71% isolated yield (1.81 g, 4.68 mmol). Productivity: 4.88 mmol·mmol\textsubscript{cat}{-1}·h\textsuperscript{-1}; TON: 37 (from pure isolated product).

**Figure S2.** Data recorded for the continuous flow experiment over time.

**Figure S3.** Continuous flow apparatus during the flow reaction.
4. NMR Spectra

Carboxylic acid 6
α-Amination products

11a
11b
11cEt

SI-11
11d
5. HPLC Traces

11a

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### 11e

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### SI-16
6. Synthesis of the PS-thiourea catalyst involving a triazole linker (PS-Tr-TU)

Azidomethylpolystyrene resin (0.60 g, \( f = 0.521 \) mmol g\(^{-1} \)) was swollen for 10 min in 6 mL of dimethylformamide–tetrahydrofuran (1:1) inside a microwave vial. Then 4-ethynylbenzyl 4-amino-2-(trifluoromethyl)benzoate\(^5\) (0.40 mmol, 0.22 g) was added. Afterwards, TTM·CuCl\(^6\) (8 mol%) was added to the microwave tube and the reaction mixture was heated at 80 °C, 200 W for 3 h. The reaction was followed by IR spectroscopy, and after it was completed, the resin was filtered and washed with dimethylformamide (200 mL), water (200 mL), THF (200 mL), methanol (200 mL), and again THF (200 mL). The resin was dried overnight in vacuo at 40 °C.

Elemental analysis: (\%) = N 2.56, C 85.43, H 7.43, \( f = 0.457 \) mmol·g\(^{-1} \).

IR (ATR): \( \nu = 3387, 3025, 2921, 1725, 1625, 1492, 1450, 1342, 1249, 1162 \) cm\(^{-1} \).


PS-Tr-NCS (3)

PS-Tr-NH$_2$ (650 mg, 0.336 mmol, 1 equiv.) was swollen for 30 min in dichloromethane (13 mL); then, triethylamine (181 µL, 1.30 mmol, d = 0.726 g/mL, 4.00 equiv.) and thiophosgene (31 µL, 0.41 mmol, 1.2 equiv.) were added dropwise at rt. After 5 h, the dark brown reaction mixture was filtered and the resin was washed with dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), and finally, the dark brown resin 3 was vacuum dried for 30 min and used directly in the next step.

Elemental analysis: (%) = N 2.45, C 84.35, H 6.90, S 1.32; f = 0.437 mmol·g$^{-1}$.

IR (ATR): $\nu$ = 3025, 2921, 2014, 1737, 1601, 1492, 1450, 1372, 1284, 1148 cm$^{-1}$. 
PS-Tr-TU

**PS-Tr-NCS** 3 (600 mg, 0.30 mmol, 1 equiv.) was swollen for 30 min in THF (3 mL) and (1R,2R)-2-(piperidin-1-yl)cyclohexanamine 4 (55 mg, 0.30 mmol, 1 equiv.) in tetrahydrofuran (5 mL) was added to this suspension at rt. After shaking for 48 h, the dark brown reaction mixture was filtered and the resin was washed with dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), and finally, the dark brown resin **PS-TrTU** was dried under vacuum at 35 °C for 12 h. Elemental analysis: (%) = N 3.22, C 83.31, H 7.28, S 1.26 \( f = 0.383 \text{ mmol·g}^{-1} \).

IR (ATR): \( \nu = 3025, 2923, 1737, 1600, 1492, 1450, 1262, 1165 \text{ cm}^{-1} \).