Synthetic Autocatalysts show Organocatalysis of other Reactions

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Supporting Information

General Experimental

All reagents were obtained from commercial suppliers and used without further purification. NMR spectra were recorded on a Bruker DRX-600 spectrometer at 300 K. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification. Reverse Phase High Performance Liquid Chromatography (HPLC) for analysis was performed on Hewlett Packard HP-1100 series system with following gradient: 5 to 40% over 7 min, 40 to 100% over 25 min and then 100% over 5 min CH$_3$CN in H$_2$O (0.1% TFA), with the flow rate of 0.5 mL/min on a GL Sciences Inc. Inertsil-ODS-1HO, 4.6 x 150 mm column. Peak areas were integrated with 254 nm. MALDI-FTMS experiments were performed on an IonSpec FTMS mass spectrometer.

Experimental Procedures and Characterization

Scheme S1. Synthesis of the amine 3b
Boc-Protected Amine 7

1) NaBH(CN)$_3$ (446 mg, 7.10 mmol) and AcOH (812 μL, 14.2 mmol) was added to the aldehyde 6 (580 mg, 1.42 mmol) and trans-N-Boc-1,2-diaminocyclohexane (608 mg, 2.84 mmol) in DMF (14 mL) at 0 °C. After 24 h of stirring at 50 °C, the mixture was quenched with aqueous solution of the saturated NH$_4$Cl, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was used for the next reaction without further purification.

2) Benzyl bromide (338 μL, 2.84 mmol) and Cs$_2$CO$_3$ (1.39 g, 4.26 mmol) was added to the residue in CH$_3$CN (14 mL) at 0 °C. After 6 h of stirring at room temperature, the mixture was quenched with saturated aqueous NH$_4$Cl, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 15% ethyl acetate in hexane to afford ester 7 (752 mg, 1.08 mmol, 76% in 2 steps) as a colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.76 (d, J = 2.4 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.38 – 7.22 (m, 7H), 5.32 (s, 1H), 4.29 (d, J = 13.6 Hz, 1H), 4.03 (s, 3H), 3.93 – 3.85 (m, 1H), 3.58 – 3.52 (m, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.43 – 3.35 (m, 1H), 2.48 – 2.42 (m, 1H), 2.37 (td, J = 3.0, 11.4 Hz, 1H), 2.32 – 2.25 (m, 1H), 1.84 – 1.80 (m, 1H), 1.76 – 1.57 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.48 (s, 9H), 1.45 – 1.33 (m, 1H), 1.38 (s, 9H), 1.37 (s, 9H), 1.29 – 1.26 (m, 1H), 1.18 – 1.07 (m, 1H), 0.97 – 0.91 (m, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 167.0, 156.4, 148.6, 147.1, 145.0, 131.7, 129.3 x 2, 129.2, 128.3, 128.1, 127.1, 126.9, 126.8, 126.5, 125.7, 120.6, 118.6, 78.8, 62.0, 53.0, 52.3, 51.8, 46.8, 35.1, 34.7, 33.6, 32.0, 31.9, 31.6, 31.4, 28.8, 25.9, 24.8, 24.0, 23.8; HRMS (MALDI-FTMS: MH$^+$) calcd. for C$_{44}$H$_{61}$N$_2$O$_5$ $^+$ 697.4581, found 697.4581.

Amine 3b

1) HCl gas was bubbled through a solution of the ester 7 (752 mg, 1.08 mmol) in
ethyl acetate (11 mL) for 2 min. at 0 °C. After being stirred at room temperature for 12 h, the mixture was concentrated in vacuo. The residue was diluted with diethyl ether and filtered. The filtrate was dried in vacuo to afford amine 3b (526 mg, 0.83 mmol, 77%) as a white solid.

**1H NMR** (600 MHz, DMSO-d$_6$, mixture of rotamers) δ 9.02 (s, 0.5H), 8.86 (s, 1H), 8.21 (d, $J = 1.9$ Hz, 0.5H), 7.87 – 7.65 (m, 3.5H), 7.61 (d, $J = 2.1$ Hz, 0.5H), 7.60 (d, $J = 2.1$ Hz, 0.5H), 7.44 – 7.36 (m, 2H), 7.35 (d, $J = 2.1$ Hz, 0.5H), 7.26 (t, $J = 7.3$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 4.91 (d, $J = 10.6$ Hz, 0.5H), 4.78 (dd, $J = 8.8$, 12.5 Hz, 0.5H), 4.64 (dd, $J = 7.9$, 13.6 Hz, 0.5H), 4.29 (dd, $J = 2.3$, 13.0 Hz, 0.5H), 4.08 – 3.74 (m, 5H), 3.56 (d, $J = 13.9$ Hz, 1H), 3.27 (t, $J = 9.8$ Hz, 0.5H), 3.10 – 3.02 (s, 0.5H), 2.63 (td, $J = 2.8$, 11.1 Hz, 0.5H), 2.45 (d, $J = 10.3$ Hz, 0.5H), 2.20 – 2.13 (m, 0.5H), 2.07 – 1.90 (m, 1H), 1.86 – 1.80 (m, 0.5H), 1.77 – 1.50 (m, 7H), 1.50 – 1.24 (m, 19H), 1.23 – 1.09 (m, 1H), 1.09 – 0.88 (m, 2H);

**13C NMR** (151 MHz, DMSO-d$_6$, mixture of rotamers) δ 166.0, 165.4, 147.0, 146.4, 146.1, 145.6, 145.4, 145.2, 144.8, 139.3, 131.8, 131.2, 131.1, 130.7, 129.5, 129.4, 128.9, 128.8, 128.5, 128.2, 127.9, 126.9, 125.5, 125.4, 125.3, 125.0, 121.1, 118.3, 117.6, 115.4, 62.6, 62.1, 59.7, 53.4, 52.4, 52.2, 50.1, 48.0, 47.0, 40.1, 34.6, 34.4, 34.3, 34.2, 32.9, 32.2, 32.1, 31.3, 31.2, 31.1, 31.0, 30.3, 29.8, 24.7, 23.6, 23.3, 23.3, 22.6, 22.4, 20.7;

**HRMS** (MALDI-FTMS: MH$^+$) calcd. for C$_{39}$H$_{53}$N$_2$O$_3$ 597.4055, found 597.4053.

**Scheme S2.** Synthesis of amine 3a
**Boc-Protected Amine 12**

1) KOH (806 mg, 14.3 mmol) was added to a solution of the ester 7 (1.00 g, 1.43 mmol) in MeOH (14 mL) at 0 °C. After 12 h of stirring at reflux, the mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

2) To a stirred solution of the residue in CH₂Cl₂ (28 mL) was added Phenol (403 mg, 4.29 mmol), DCC (443 mg, 2.15 mmol) and DMAP (263 mg, 2.15 mmol) at 0 °C. After 6 h of stirring at room temperature, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexane to afford semi-pure phenyl ester 8. The residue was used for the next reaction without further purification.

3) Biguanide•2HCl (979 mg, 7.15 mmol) and triethylamine (1.4 mL) was added to the residue in EtOH (14 mL) at room temperature. After 2 days of stirring at reflux, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 20% acetone in CH₂Cl₂ to afford triazine 12 (576 mg, 0.78 mmol, 54% in 3 steps) as a white solid.

**1H NMR** (600 MHz, DMSO- 𝑑₆) δ 8.31 (s, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.20 – 7.13 (m, 3H), 6.85 – 6.65 (m, 4H), 5.45 (s, 1H), 3.97 (d, J = 13.6 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.25 – 3.20 (m, 1H), 3.22 (d, J = 13.6 Hz, 1H), 2.12 (td, J = 3.0, 11.4 Hz, 1H), 2.08 – 2.04 (m, 1H), 1.82 – 1.76 (m, 1H), 1.71 – 1.65 (m, 1H), 1.60 (s, 3H), 1.55 (s, 3H), 1.51 – 1.44 (m, 1H), 1.36 (s, 9H), 1.31 (s, 9H), 1.25 (s, 9H), 1.20 – 1.09 (m, 2H), 0.96 – 0.79 (m, 2H);

**13C NMR** (151 MHz, DMSO- 𝑑₆) δ 172.3, 167.2, 155.1, 146.5, 145.9, 144.6, 144.2, 140.6, 130.4, 128.9, 128.6, 127.8, 127.0, 126.5, 126.4, 124.7, 124.5, 123.1, 120.3, 79.2, 77.5, 62.1, 52.5, 50.7, 46.9, 34.5, 34.2, 34.1, 33.0, 31.6, 31.4, 31.3, 28.2, 25.3, 24.3, 23.0;

**HRMS** (MALDI-FTMS: MH⁺) calcd. for C₄₅H₆₂N₇O₃⁺ 748.4908, found 748.4904.

**Amine 3a**

1) HCl gas was bubbled through a solution of the diaminotriazine 12 (250 mg,
335 μmol) in ethyl acetate (3.4 mL) for 2 min. at 0 °C. After 6 h of stirring at room temperature, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and filtered. The filtrate was dried in vacuo to afford amine 3a (181 mg, 265 μmol, 79%) as a white solid.

\[ 1^H \text{NMR} \quad (600 \text{ MHz, DMSO-}d_6) \delta 8.88 – 8.35 (m, 4H), 7.80 (s, 1H), 7.78 (s, 1H), 7.62 – 7.58 (m, 3H), 7.58 (s, 1H), 7.38 – 7.34 (m, 2H), 7.36 (s, 1H), 7.27 – 7.20 (m, 3H), 4.89 (d, \text{J} = 11.9 \text{ Hz, 1H}), 4.60 (d, \text{J} = 11.9 \text{ Hz, 1H}), 3.77 – 3.72 (m, 2H), 3.40 – 3.35 (m, 1H), 3.15 – 3.05 (m, 1H), 2.49 – 2.40 (m, 1H), 2.05 – 1.98 (m, 1H), 1.80 – 1.72 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.38 – 1.33 (m, 1H), 1.34 (s, 9H), 1.30 (s, 9H), 1.23 – 1.16 (m, 1H), 1.02 – 0.91 (m, 1H), 0.89 – 0.75 (m, 1H).

\[ 1^C \text{NMR} \quad (151 \text{ MHz, DMSO-}d_6) \delta 172.0, 162.0, 145.7, 145.7, 145.3, 144.9, 138.9, 130.6, 128.9, 128.7, 128.2, 128.1, 127.9, 126.9, 125.4, 125.2, 121.2, 118.3, 79.3, 49.8, 34.5, 34.4, 34.3, 32.8, 31.6, 31.3, 31.3, 31.1, 29.7, 24.6, 23.5, 22.3, 21.1.

HRMS (MALDI-FTMS: MH\(^+\)) calcd. for C\(_{40}\)H\(_{54}\)N\(_7\)O\(^+\) 648.4384, found 648.4386.

**Scheme S3.** Synthesis of thymine derived thioisocyanate 4a

Thymine Derived Thioisocyanate 4a

1) HCl gas was bubbled through a solution of the 13 (1.50 g, 5.57 mmol) in ethyl acetate (60 mL) for 2 min. at 0 °C. After 12 h of stirring at room temperature, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and filtered. The filtrate was dried in vacuo to afford amine as a white solid. The amine was used for the next reaction without further purification.
2) Thiophosgene (849 μL, 11.2 mmol) was added to a solution of the amine in CH₂Cl₂ (50 mL) and saturated aqueous sodium bicarbonate (5 mL) at 0 °C. After 6 h of stirring at same temperature, the mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 3% methanol in CH₂Cl₂ to afford thioisocyanate 4a (952 mg, 4.51 mmol, 81% in 2 steps) as a pale yellow solid.

**1H NMR** (600 MHz, DMSO-d₆) δ 11.40 (s, 1H), 7.56 (s, 1H), 3.99 – 3.88 (m, 4H), 1.76 (s, 3H).

**13C NMR** (151 MHz, DMSO-d₆) δ 164.2, 150.8, 141.2, 129.8, 108.8, 46.4, 43.7, 11.9.

**HRMS** (MALDI-FTMS: MH⁺) calcd. for C₈H₁₀N₃O₂S⁺ 212.0488, found 212.0485.

**Scheme S4.** Synthesis of thymine derived thioisocyanate 4b

**Thymine Derived Boc-Protected Amine 14**

1) Methyl iodide (691 mL, 11.2 mmol) and K₂CO₃ (2.31 g, 16.7 mmol) was added to a solution of 13 (1.50 g, 5.57 mmol) in DMF (60 mL) at 0 °C. After 6 h of stirring at room temperature, the mixture was quenched with 1M HCl and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate, H₂O and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 2% methanol in chloroform to afford 14 (1.28 g, 4.51 mmol, 81%) as pale yellow oil.
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.93 (s, 1H), 5.17 (s, 1H), 3.80 (t, $J = 5.7$ Hz, 2H), 3.36 – 3.29 (m, 2H), 3.26 (s, 3H), 2.13 – 2.07 (m, 1H), 1.84 (s, 3H), 1.34 (s, 9H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 162.7, 156.2, 151.9, 139.2, 109.4, 79.8, 49.1, 39.4, 28.4, 28.0, 13.1.

HRMS (MALDI-FTMS: MH$^+$) calcd. for C$_{13}$H$_{22}$N$_3$O$_4$ $^+$ 284.1605, found 284.1602.

**Thymine Derived Thioisocyanate 4b**

1) HCl gas was bubbled through a solution of 14 (1.28 g, 4.51 mmol) in ethyl acetate (45 mL) for 2 min. at 0 °C. After 10 h of stirring at room temperature, the mixture was concentrated *in vacuo*. The residue was used for the next reaction without further purification.

2) Thiophosgene (688 μL, 9.02 mmol) was added to a solution of the residue in CH$_2$Cl$_2$ (50 mL) and saturated aqueous sodium bicarbonate (5 mL) at 0 °C. After 6 h of stirring at same temperature, the mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 1% methanol in CH$_2$Cl$_2$ to afford thioisocyanate 4b (568 mg, 2.52 mmol, 56% in 2 steps) as a pale yellow solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 7.63 (s, 1H), 4.01 (t, $J = 5.8$ Hz, 2H), 3.95 (t, $J = 5.8$ Hz, 2H), 3.19 (s, 3H), 1.82 (s, 3H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 164.1, 151.9, 140.6, 130.8, 108.7, 48.4, 44.6, 28.4, 13.4.

HRMS (MALDI-FTMS: MH$^+$) calcd. for C$_9$H$_{12}$N$_3$O$_2$S$^+$ 226.0645, found 226.0648.
General procedure for coupling reaction of amine 3a or 3b with thymine derived thioisocyanate 4a or 4b:

Thymine derived thioisocyanate 4a or 4b (1.2 equiv.) was treated with a solution of amine 3a or 3b (1.0 equiv.) in CH$_2$Cl$_2$ (7.6 mM) and triethylamine (0.4 mM) at -78 °C in an acetone dry ice bath. After 24 h of stirring at -78 °C, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 20% acetone in chloroform to afford the thiourea.

Scheme S5. Coupling reaction of amine 3a and thymine derived thioisocyanate 4a

Thiourea 2a

$^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.70 (d, $J = 2.4$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.35 – 7.26 (m, 3H), 7.25 – 7.18 (m, 3H), 7.13 (t, $J = 7.3$ Hz, 1H), 7.03 (s, 1H), 6.60 – 6.48 (m, 2H), 4.06 – 3.90 (m, 3H), 3.94 (s, 3H), 3.91 – 3.68 (m, 4H), 3.72 (d, $J = 13.9$ Hz, 1H), 3.60 (d, $J = 13.7$ Hz, 1H), 3.27 (s, 3H), 2.56 (t, $J = 9.8$ Hz, 1H), 2.25 (s, 1H), 2.06 (d, $J = 9.9$ Hz, 1H), 1.85 – 1.73 (m, 1H), 1.79 (s, 3H), 1.73 – 1.65 (m, 1H), 1.58 (s, 6H), 1.51 – 1.38 (m, 1H), 1.38 – 1.16 (m, 1H), 1.32 (s, 9H), 1.30 (s, 9H), 1.14 – 1.01 (m, 1H), 1.02 – 0.90 (m, 1H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 182.4, 167.4, 164.2, 152.7, 149.1, 147.3, 146.4, 145.4, 141.0, 139.2, 132.2, 129.5, 129.3, 128.6, 127.4, 127.2, 127.0, 126.6, 126.6, 120.9, 118.3, 110.3, 62.8, 55.5, 53.4, 52.6, 48.7, 44.2, 35.3, 35.0, 34.9, 33.5, 32.00, 31.9, 31.8,

**HRMS** (MALDI-FTMS: MH⁺) calcd. for C₄₈H₆₃N₁₀O₃S⁺ 859.4805, found 859.4792.

**Scheme S6.** Coupling reaction of amine 3a and thymine derived thioisocyanate 4b

![Scheme S6](image)

**Thiourea 2b**

**¹H NMR** (600 MHz, DMSO-<d₆>) δ 11.25 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.38 (s, 1H), 7.30 – 7.24 (m, 3H), 7.20 – 7.13 (m, 4H), 6.83 (s, 1H), 4.05 – 3.88 (m, 1H), 3.93 (s, 3H), 3.86 – 3.77 (m, 1H), 3.76 – 3.69 (s, 2H), 3.65 – 3.45 (m, 3H), 3.32 (s, 2H), 2.56 – 2.46 (m, 1H), 2.16 – 2.00 (m, 2H), 1.76 – 1.69 (m, 1H), 1.63(s, 3H), 1.62 – 1.57 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.30 (s, 9H), 1.29 – 1.15 (m, 2H), 1.28 (s, 9H), 1.10 – 0.85 (m, 2H).

**¹³C NMR** (151 MHz, DMSO-<d₆>) δ 166.4, 164.3, 151.0, 146.9, 145.5, 145.2, 144.6, 141.5, 140.0, 131.1, 128.4, 128.2, 128.0, 127.0, 126.5, 126.3, 125.6, 125.2, 120.5, 118.4, 108.1, 62.3, 52.9, 52.3, 46.9, 46.1, 42.2, 40.1, 34.3, 34.2, 32.9, 32.3 31.3, 31.2, 31.1, 25.1, 24.5, 11.8.

**HRMS** (MALDI-FTMS: MH⁺) calcd. for C₄₉H₆₅N₁₀O₃S⁺ 873.4961, found 873.4950.
Scheme S7. Coupling reaction of amine 3b and thymine derived thioisocyanate 4a was done as described above.

Thiourea 5

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.24 (s, 1H), 7.64 – 7.57 (m, 1H), 7.51 (d, $J = 2.2$ Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.35 – 7.27 (m, 1H), 7.24 (d, $J = 2.2$ Hz, 1H), 7.23 – 7.11 (m, 6H), 6.93 – 6.74 (m, 4H), 6.59 (s, 1H), 3.83 – 3.77 (m, 1H), 3.81 (d, $J = 12.9$ Hz, 1H), 3.77 – 3.68 (m, 2H), 3.62 – 3.43 (m, 2H), 3.38 – 3.32 (m, 2H), 3.21 (d, $J = 14.1$ Hz, 1H), 2.31 – 2.21 (m, 1H), 2.07 – 2.01 (m, 1H) 1.95 – 1.89 (m, 1H), 1.81 – 1.70 (m, 1H), 1.62 (s, 6H), 1.54 – 1.47 (m, 1H), 1.50 (s, 3H), 1.30 (s, 9H), 1.27 (s, 9H), 1.24 – 1.13 (m, 2H), 0.95 – 0.80 (m, 2H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 173.3, 168.1, 165.3, 151.9, 147.5, 146.9, 145.6, 145.1, 142.4, 141.0, 131.4, 129.6, 129.3, 128.9, 128.0, 127.3, 127.1, 126.8, 125.1, 123.8, 121.0, 120.9, 109.0, 63.0, 54.2, 53.5, 47.8, 46.4, 43.2, 35.4, 35.1, 33.7, 33.2, 32.3, 32.2, 30.9, 26.0, 25.5, 23.7, 12.7.

HRMS (MALDI-FTMS: MH$^+$) calcd. for C$_{48}$H$_{64}$N$_{5}$O$_{5}$S$^+$ 822.4628, found 822.4620.
Scheme S8. Coupling reaction of amine 3b and thymine derived thioisocyanate 4b was done as described above.

**Thiourea 15**

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.63 – 7.54 (s, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 7.33 – 7.29 (m, 1H), 7.28 – 7.01 (m, 7H), 6.94 – 6.73 (s, 4H), 6.60 (s, 1H), 3.92 – 3.76 (m, 4H), 3.60 – 3.52 (m, 1H), 3.46 (d, $J$ = 12.4 Hz, 1H), 3.40 – 3.32 (s, 2H), 3.21 (d, $J$ = 14.1 Hz, 1H), 3.15 (s, 3H), 2.30 – 2.22 (s, 1H), 2.10 – 1.97 (m, 1H), 1.97 – 1.88 (m, 1H), 1.82 – 1.71 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.59 – 1.51 (m, 1H), 1.50 (s, 3H), 1.30 (s, 9H), 1.26 (s, 9H), 1.22 – 1.09 (m, 2H), 0.98 – 0.76 (m, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 172.4, 167.2, 163.4, 151.1, 146.6, 146.0, 144.7, 144.2, 140.1, 139.9, 130.6, 128.7, 128.4, 127.9, 127.1, 126.4, 126.2, 125.9, 124.2, 122.9, 120.1, 107.2, 62.1, 53.3, 52.6, 48.1, 45.5, 42.2, 40.1, 34.4, 34.2, 34.2, 32.8, 32.3, 31.4, 31.3, 30.0, 27.4, 25.1, 24.6, 22.9, 12.5.

HRMS (MALDI-FTMS: MH$^+$) calcd. for C$_{47}$H$_{62}$N$_5$O$_5$S$^+$ 808.4471, found 808.4470.
General procedure of competition studies for coupling reaction of amine 3a or 3b with thymine derived thioisocyanates 4a and 4b

Thymine derived thioisocyanates 4a and 4b (8.0 mM) were mixed with a solution of amine 3a or 3b (8.0 mM) in Et₃N/CH₂Cl₂ (5/95) at -78 °C as described above. After 24 h of stirring at -78 °C, the mixture was analyzed by HPLC using the peak areas [254 nm].

**Scheme S9.** Coupling reaction of amine 3a and thymine derived thioisocyanates 4a and 4b was done as described above.

**Scheme S10.** Coupling reaction of amine 3b and thymine derived thioisocyanates 4a and 4b was done as described above.
General procedure of competition studies in the presence of thiourea 2a for coupling reaction of amine 3a with thymine derived thioisocyanates 4a and 4b

A solution of amine 3a (8.0 mM) and thymine derived thioisocyanates 4a and 4b (8.0 mM) in Et3N/CH2Cl2 (5/95) was treated with thiourea 2a (2.0 mM or 4.0 mM) at -78 °C. After 24 h of stirring at -78 °C, the mixture was analyzed by HPLC using the peak areas [254 nm].

**Scheme S11.** Coupling reaction of amine 3a and thymine derived thioisocyanates 4a and 4b in the presence of 25% thiourea 2a

![Scheme S11](attachment:image1.png)

Yield of 2a + 2b (%) = 94%
Ratio (2a : 2b = 74 : 26)

**Scheme S12.** Coupling reaction of amine 3a and thymine derived thioisocyanate 4a and 4b in the presence of 50% thiourea 2a

![Scheme S12](attachment:image2.png)

Yield of 2a + 2b (%) = 92%
Ratio (2a : 2b = 74 : 26)
General procedure of competition studies in the presence of thiourea 2a for coupling reaction of amine 3a with thymine derived thioisocyanates 4a and 4b utilizing high dilution condition

Thymine derived thioisocyanates 4a and 4b (8.0 mM) were added very slowly to a solution of amine 3a (8.0 mM) and thiourea 2a (2.0 mM or 4.0 mM) in Et3N/CH2Cl2 (5/95) at -78 °C over 6 h. After 24 h of stirring at -78 °C, the mixture was analyzed by HPLC using the peak areas [254 nm].

Scheme S13. Coupling reactions of amine 3a and thymine derived thioisocyanates 4a and 4b in the presence of 25% thiourea 2a under high dilution

Scheme S14. Coupling reactions of amine 3a and thymine derived thioisocyanates 4a and 4b in the presence of 50% thiourea 2a under high dilution.
General procedure for Organocatalytic Hydride Reduction

The trans-β-nitrostyrene 16 (1.0 equiv.) was added to a solution of thiourea 2a (0.5 equiv.), and Hantzch ester 17 (10.0 equiv.) in CDCl₃ (5.0 mM) at 0 °C. The bath was removed and the solution was allowed to come to room temperature. The mixture was analyzed by ¹H NMR as shown in Figure S1 below.

Scheme S15. Organocatalytic Hydride Reduction

Figure S1. ¹H NMR spectra of the reaction in the presence of 50% 2a
**Table S1.** Concentrations of 18 in the Organocatalytic Hydride Reduction

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Concentration of 18 (50% 3a)</th>
<th>Concentration of 18 (50% 3a)</th>
<th>Concentration of 18 (50% 3a)</th>
<th>Concentration of 18 (50% 3a)</th>
<th>Concentration of 18 (50% 3a)</th>
<th>Concentration of 18 (50% 3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 d</td>
<td>0.77</td>
<td>0.01</td>
<td>1.79</td>
<td>2.07</td>
<td>-</td>
<td>0.18</td>
</tr>
<tr>
<td>2 d</td>
<td>1.76</td>
<td>0.03</td>
<td>2.79</td>
<td>3.38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 d</td>
<td>2.86</td>
<td>0.05</td>
<td>3.60</td>
<td>4.30</td>
<td>0.24</td>
<td>0.35</td>
</tr>
<tr>
<td>4 d</td>
<td>3.90</td>
<td>0.05</td>
<td>4.05</td>
<td>4.74</td>
<td>0.27</td>
<td>0.45</td>
</tr>
<tr>
<td>5 d</td>
<td>3.96</td>
<td>0.08</td>
<td>4.69</td>
<td>4.88</td>
<td>0.32</td>
<td>0.49</td>
</tr>
<tr>
<td>6 d</td>
<td>4.70</td>
<td>0.10</td>
<td>4.86</td>
<td>4.90</td>
<td>0.43</td>
<td>0.54</td>
</tr>
</tbody>
</table>
General procedure of Organocatalytic Michael addition

The trans-β-nitrostyrene 16 (1.0 equiv.) was added to a solution of thiourea 2a (0.5 equiv.), 2,5-pentanedione 19 (5.0 equiv.) and Et₃N (5 equiv) in CDCl₃ (5.0 mM) at 0 °C. The bath was removed and the solution was allowed to come to room temperature. The mixture was analyzed by ¹H NMR as shown in Figure S2 below.

Scheme S16. Organocatalytic Michael addition

Figure S2. ¹H NMR spectrum of the reaction, in the presence of 50% 2a
**Table S2.** Concentrations of 20 in the Organocatalytic Michael addition

<table>
<thead>
<tr>
<th>Concentration of 20 (50% 2a)</th>
<th>Concentration of 20 (no 2a)</th>
<th>Concentration of 20 (50% 3a + 50% 4b)</th>
<th>Concentration of 20 (50% 2b)</th>
<th>Concentration of 20 (50% 3a)</th>
<th>Concentration of 20 (50% 4a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1h</td>
<td>0.724</td>
<td>0.229</td>
<td>0.91</td>
<td>0.86</td>
<td>0.383</td>
</tr>
<tr>
<td>3h</td>
<td>1.377</td>
<td>0.532</td>
<td>1.441</td>
<td>1.77</td>
<td>0.745</td>
</tr>
<tr>
<td>5h</td>
<td>1.731</td>
<td>0.791</td>
<td>1.881</td>
<td>2.37</td>
<td>1.078</td>
</tr>
<tr>
<td>8h</td>
<td>2.52</td>
<td>1.206</td>
<td>2.56</td>
<td>3.16</td>
<td>1.466</td>
</tr>
<tr>
<td>18h</td>
<td>3.97</td>
<td>2.549</td>
<td>4.00</td>
<td>4.50</td>
<td>2.392</td>
</tr>
<tr>
<td>29h</td>
<td>4.481</td>
<td>3.316</td>
<td>4.51</td>
<td>4.94</td>
<td>3.099</td>
</tr>
</tbody>
</table>
General procedure of Organocatalytic Michael addition using thiophenol

The trans-β-nitrostyrene 16 (1.0 equiv.) was added to a solution of thiourea 2a (0.2 equiv.) and thiophenol 21 (2.0 equiv.) in CD$_2$Cl$_2$ (5.0 mM) at 0 °C. The bath was removed and the solution was allowed to come to room temperature. The mixture was analyzed by $^1$H NMR as shown in Figure S3 below.

**Scheme S17.** Organocatalytic Michael addition using thiophenol

![Scheme S17](image)

**Figure S3.** Organocatalytic Michael addition