Reaction of Nitroorganic Compounds Using Thiourea Catalysts Anchored to Polymer Support

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Abstract: Immobilization of chiral thiourea catalyst was studied. The PEG-bound thiourea showed better catalytic activity than those of the carboxypolystyrene HL resin-bound and TentaGel carboxy resin-bound thioureas. In the presence of PEG-bound thiourea, Michael and tandem Michael reactions of *trans*-β-nitrostyrene proceeded enantioselectively.

Key words: organocatalyst, thiourea, enantioselective, polymer support, PEG

The use of organocatalyst in organic synthesis has generated considerable interest from both economical and environmental points of view. Recent progress in this area has resulted in the development of various chiral organocatalysts which do not require the strictly controlled reaction conditions compared to the metal-containing catalysts.[1]

Several groups have begun to explore the potential of ureas and thioureas to serve as Brønsted acid catalysts.[2–7] We have recently developed the chiral thiourea **1** as a bifunctional organocatalyst (Figure 1).[7] During our studies on thiourea catalysts, we found that thiourea **1** accelerates the aza-Henry reaction and the Michael reaction of nitro olefins or α,β-unsaturated imides as a result of dual activation of electrophile and nucleophile. However, these reactions suffered from the difficulty of recovering thiourea **1**. Immobilization of such catalyst is a challenging goal in advanced organic synthesis.[8] Immobilization facilitates the recovery and reuse of catalyst from the reaction mixture. Hence, we planned to develop a new and effective thiourea catalyst anchored to polymer support.

We planned to attach the thiourea to several polymer supports by using ester moiety. Prior to exploring issues of immobilization, we first investigated the catalytic activity of thiourea **2** having an ester group. Preparation of thiourea **2** is summarized in Scheme 1.[9]

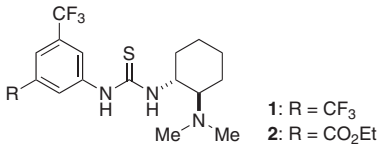

Figure 1 Chiral thiourea catalysts

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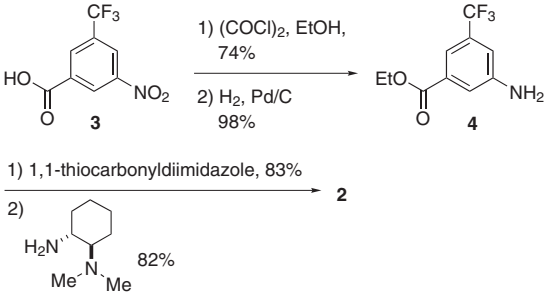
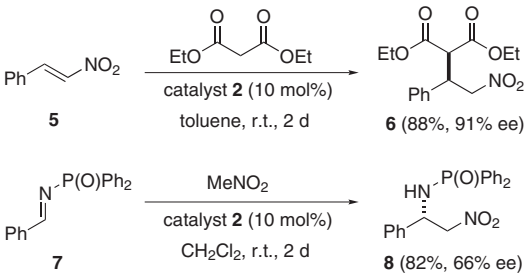


Scheme 1

To test the activity of catalyst **2**, the catalytic enantioselective Michael and aza-Henry reactions of nitroorganic compounds were investigated, since these reactions proceeded well by using original thiourea **1** (Scheme 2).[7] In the presence of **2** (10 mol%), the reaction of *trans*-β-nitrostyrene (**5**) with diethyl malonate in toluene afforded the Michael adduct (*S*)-**6** in 88% yield with 91% ee. In our previous study on reaction of **5** using original thiourea **1**, the Michael adduct (*S*)-**6** was obtained in 86% yield with 93% ee, after stirring at room temperature for 24 h.[7b] Next, we tried the aza-Henry reaction of *N*-phosphinoylimine **7**. In the presence of **2** (10 mol%), nitromethane was reacted with **7** to give the adduct **8** in 66% ee, comparable to that obtained by the reaction using catalyst **1**.[10] These observations suggest that thiourea **2** acts as a chiral catalyst with slightly less catalytic activity.



Scheme 2

On the basis of these results, we next explored the immobilization of catalyst. At first, the cross-linked polystyrene was used as a support for immobilizing the thiourea **2** (Figure 2). To enhance the catalytic activity of resin-bound thioureas, we introduced a spacer generated from pentane-1,5-diol. Preparation of resin-bound catalysts **9**

and **10** is shown in Scheme 3.[9] We used carboxypolystyrene HL resin and TentaGel carboxy resin purchased from Novabiochem. The thiourea **13** having the spacer moiety was attached to these resins by treatment with EDC in the presence of DMAP to give the resin-bound catalysts **9** and **10** in ca. 0.79 mmol/g and ca. 0.19 mmol/g loading levels, respectively. The loading levels of catalyst were determined by quantification of fluoride by elemental analysis.

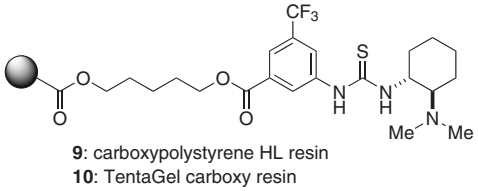
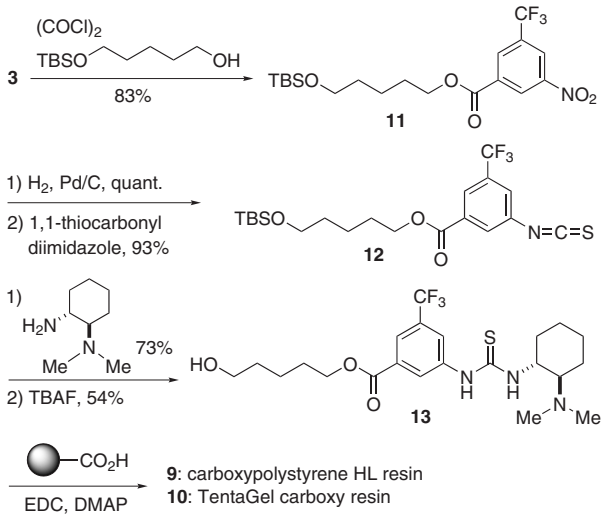


Figure 2 Resin-bound thiourea catalysts



Scheme 3

The viability of resin-bound thioureas **9** and **10** as catalysts was the next focus of our efforts (Table 1). The tedious workup to recover the catalyst was eliminated from the polymer-support methodology by washing the resin with solvents. Unfortunately, these catalysts showed lower catalytic activities as compared to the soluble catalyst **2**, leading to the low yields of the desired products **6** and **8**. It is assumed that the difference of activity between **9** and **10** was attributed to the difference in their loading levels. However, we were pleased to find that good enantioselectivities were observed in both Michael and aza-Henry reactions.

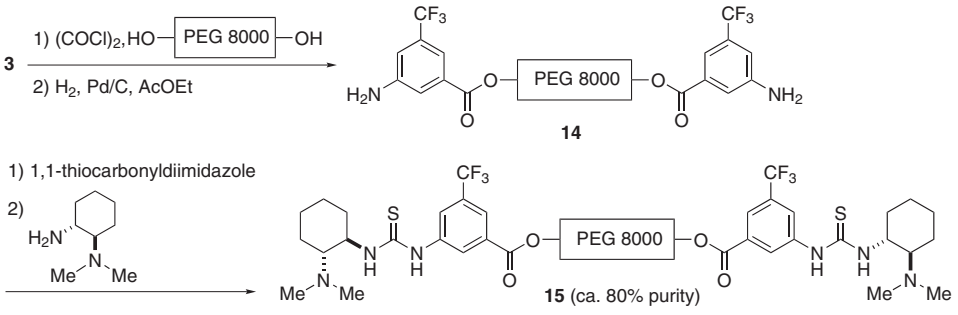
Table 1 Michael and Aza-Henry Reactions Using Catalysts **9** and **10**[a]

Entry	Substrate	Catalyst	Product (yield, %)[b]	ee (%)[c]
1	**5**	**9**	**6** (37)	87
2	**5**	**9** (recovered)	**6** (25)	85
3	**5**	**10**	**6** (4)	88
4	**7**	**9**	**8** (19)	67
5	**7**	**9** (recovered)	**8** (13)	68
6	**7**	**10**	**8** (3)	67

[a] Reactions were carried out in CH_2Cl_2 in the presence of catalyst **9** or **10** (10 mol%) at room temperature for 6 days.
[b] Isolated yields.
[c] Enantioselectivity was determined by HPLC analysis.

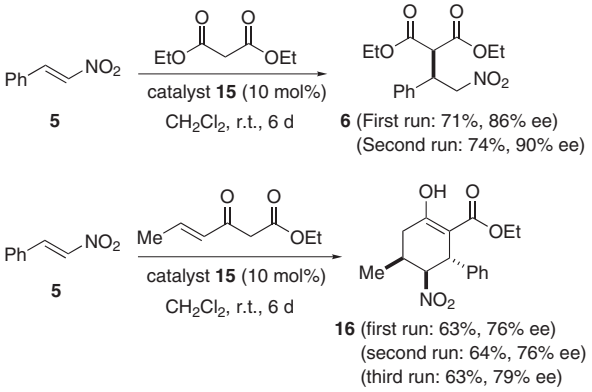
To overcome these drawbacks, we focused on a non-crosslinked polymer as a support for immobilizing the thiourea **2**. Particularly, soluble non-crosslinked polymer supports offer certain advantages over insoluble polymers in terms of ease of analysis and the establishment of homogeneous conditions.[11] Since poly(ethylene glycol) (PEG) has been wildly used as a soluble polymer support in combinatorial and general organic syntheses, we next prepared PEG-bound thiourea **15** as a homogeneous catalyst (Scheme 4).[12] The purity of catalyst **15** was determined to be ca. 80% by ^1H NMR analysis.

To survey the potency of PEG-bound thiourea **15** as a catalyst, we applied thiourea **15** to Michael and tandem Michael reactions of *trans*-β-nitrostyrene (**5**) (Scheme 5). As expected, the catalytic activity of **15** was enhanced under homogeneous conditions using CH_2Cl_2 as solvent. The Michael reaction of **5** with diethyl malonate afforded the Michael adduct (*S*)-**6** in 71% yield with 86% ee, after stirring at room temperature for six days. Furthermore, catalyst **15** was recoverable and reusable. The catalyst **15** was precipitated by the addition of diethyl ether and re-



Scheme 4

used without further treatment after recovery by filtration. In the repeated use of the recovered catalyst, (*S*)-**6** was obtained in 74% yield with 90% ee. Tandem Michael reaction of **5** also proceeded smoothly to give the cyclic product **16** in 63% yield with 76% ee.[7e,7g] The catalyst **15** was reused for the second and third reactions, affording **16** in 64% yield with 76% ee and in 63% yield with 79% ee, respectively.



Scheme 5

In summary, we have demonstrated the utility of PEG-bound thiourea as a homogeneous catalyst. To test the activity of the catalyst, the catalytic enantioselective reactions of nitroorganic compounds were investigated. Although the reaction rate was somewhat decreased with PEG-bound thiourea **15**, immobilization to a PEG support was proved to facilitate the recovery and reuse of thiourea catalyst without affecting the chemical yield and enantioselectivity.

Melting points were taken on a YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz, and at 125 MHz, respectively; TMS was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-410 Fourier-transfer infrared spectrometer. Low- and high-resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO DIP-360 polarimeter. Enantiomeric excess was determined by HPLC analysis.

Ethyl 5-(Trifluoromethyl)-3-nitrobenzoate

To a solution of 5-(trifluoromethyl)-3-nitrobenzoic acid (1.0 g, 4.3 mmol) in anhyd CH_2Cl_2 (50 mL) were added oxalyl chloride (1.61 mL, 18.8 mmol) and anhyd DMF (2 drops) under argon at 0 °C. After stirring for 18 h at room temperature, the mixture was concentrated under reduced pressure. The resulting oil was dissolved in anhyd THF (20 mL) under argon. To this solution was added anhyd EtOH (5 mL) under argon at 0 °C. After stirring for 3 h at r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, and then the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude solid was recrystallized from hexane–EtOAc to afford ethyl 5-(trifluoromethyl)-3-nitrobenzoate (832 mg, 74%) as colorless crystals; mp 53–55 °C (hexane–EtOAc).

IR ($CHCl_3$): 1729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.05 (1 H, s), 8.68 (1 H, s), 8.63 (1 H, s), 4.49 (2 H, q, *J* = 7.4 Hz), 1.46 (3 H, t, *J* = 7.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 148.5, 133.6, 132.8 (q, *J* = 34 Hz), 131.9, 127.5, 124.3, 122.5 (q, *J* = 271 Hz), 62.6, 14.1.

MS (EI$^+$): *m*/*z* (%) = 263 (19, M$^+$), 218 (100).

Anal. Calcd for $C_{10}H_8F_3NO_4$: C, 45.64; H, 3.06; N, 5.32. Found: C, 45.38; H, 2.97; N, 5.25.

Ethyl 3-Amino-5-(trifluoromethyl)benzoate (4)

To a solution of ethyl 5-(trifluoromethyl)-3-nitrobenzoate (1.0 g, 3.8 mmol) in anhyd EtOH (30 mL) was added 10% Pd/C (300 mg) at r.t. After stirring for 2 h under a H_2 atmosphere at r.t., the mixture was filtered through Celite pad and concentrated under reduced pressure. The crude solid was recrystallized from hexane–EtOAc providing amine **4** (870 mg, 98%) as colorless crystals; mp 72–74 °C (hexane–EtOAc).

IR ($CHCl_3$): 1717 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (1 H, s), 7.48 (1 H, s), 7.03 (1 H, s), 4.35 (2 H, q, *J* = 7.0 Hz), 4.08 (2 H, br s), 1.37 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 147.2, 132.2, 131.8 (q, *J* = 33 Hz), 123.7 (q, *J* = 273 Hz), 118.5, 115.7, 115.0, 61.3, 14.0.

MS (EI$^+$): *m*/*z* (%) = 233 (68, M$^+$), 188 (100).

Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.38; H, 4.24; N, 5.97.

Ethyl 3-Isothiocyanato-5-(trifluoromethyl)benzoate

To a solution of amine **4** (870 mg, 3.7 mmol) in anhyd MeCN (15 mL) were added imidazole (76 mg, 1.1 mmol) and 1,1-thiocarbonyldiimidazole (1.0 g, 5.6 mmol) under argon at 0 °C. After stirring for 1.5 h at r.t., the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane–EtOAc, 5:1) afforded ethyl 3-isothiocyanato-5-(trifluoromethyl)benzoate (850 mg, 83%) as a colorless oil.

IR ($CHCl_3$): 1726 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (1 H, s), 8.00 (1 H, s), 7.57 (1 H, s), 4.40 (2 H, q, *J* = 7.4 Hz), 1.39 (3 H, t, *J* = 7.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 139.6, 133.3, 133.2, 132.6 (q, *J* = 33 Hz), 129.7, 126.1, 124.5, 122.8 (q, *J* = 273 Hz), 62.0, 14.1.

MS (EI$^+$): *m*/*z* (%) = 275 (37, M$^+$), 230 (100).

HRMS (EI$^+$): *m*/*z* calcd for $C_{11}H_8F_3NO_2S$ (M$^+$): 275.0228; found: 275.0232.

Thiourea Catalyst 2

To a solution of ethyl 3-isothiocyanato-5-(trifluoromethyl)benzoate (85 mg, 0.31 mmol) in anhyd benzene (1.2 mL) was added (1*R*,2*R*)-*N*,*N*-dimethylcyclohexanediamine (88 mg, 0.62 mmol) under argon at 0 °C. After stirring for 3 h at r.t., the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH, 7:1) afforded thiourea **2** (106 mg, 82%) as colorless crystals; mp 118–120 °C (hexane–EtOAc); $[\alpha]_D^{27}$ –43.8 (*c* = 2.0, $CHCl_3$).

IR ($CHCl_3$): 1723 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (1 H, s), 8.06 (1 H, s), 7.89 (1 H, s), 4.40 (2 H, q, *J* = 7.0 Hz), 3.89 (1 H, br s), 2.61 (1 H, br s), 2.45 (1 H, dt, *J* = 11.0, 3.4 Hz), 2.27 (6 H, s), 1.94–1.67 (3 H, br m), 1.40 (3 H, t, *J* = 7.0 Hz), 1.40–1.05 (6 H, br m).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.6, 164.4, 139.3, 132.1, 131.3 (q, *J* = 32 Hz), 127.8, 124.4, 123.0 (q, *J* = 272 Hz), 122.4, 66.2, 61.3, 55.6, 39.5, 32.4, 24.5, 24.2, 21.1, 13.8.

MS (FAB$^+$): *m*/*z* (%) = 418 (100, M + H$^+$).

Anal. Calcd for $C_{19}H_{26}F_3N_3O_2S$: C, 54.66; H, 6.28; N, 10.06. Found: C, 54.87; H, 6.41; N, 9.81.

5-(*tert*-Butyldimethylsilyloxy)pent-1-yl 5-(Trifluoromethyl)-3-nitrobenzoate (11)

To a solution of 5-(trifluoromethyl)-3-nitrobenzoic acid (**3**; 2.0 g, 8.6 mmol) in anhyd CH_2Cl_2 (50 mL) were added oxalyl chloride (3.3 mL, 38 mmol) and anhyd DMF (4 drops) under argon at 0 °C. After stirring for 18 h at r.t., the mixture was concentrated under reduced pressure. The resulting oil was dissolved in anhyd THF (30 mL) under argon. To this solution were added 5-(*tert*-butyldimethylsilyloxy)pentan-1-ol (2.3 g, 11 mmol) and Et_3N (6 mL) under argon at 0 °C. After stirring for 12 h at r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, and then the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane–EtOAc, 12:1) afforded ester **11** (3.1 g, 83%) as a colorless oil.

IR ($CHCl_3$): 1729 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.03 (1 H, s), 8.68 (1 H, s), 8.61 (1 H, s), 4.44 (2 H, t, *J* = 6.7 Hz), 3.65 (2 H, t, *J* = 6.7 Hz), 1.85 (2 H, m), 1.60 (2 H, m), 1.54 (2 H, m), 0.88 (9 H, s), 0.05 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 148.6, 133.6, 132.8 (q, *J* = 34 Hz), 131.8, 127.4, 124.3, 122.4 (q, *J* = 273 Hz), 66.6, 62.7, 32.2, 28.3, 25.8, 22.3, 18.2, –5.5.

MS (FAB$^+$): *m*/*z* (%) = 436 (21, M + H$^+$), 69 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{19}H_{29}F_3NO_5Si$ (M + H$^+$): 436.1776; found: 436.1767.

5-(*tert*-Butyldimethylsilyloxy)pent-1-yl 3-Amino-5-(trifluoromethyl)benzoate

To a solution of ester **11** (4.0 g, 9.2 mmol) in EtOAc (200 mL) was added 10% Pd/C (500 mg) at r.t. After stirring for 5 h under a H_2 atmosphere at r.t., the mixture was filtered through a Celite pad and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane–EtOAc, 1:1) afforded 5-(*tert*-butyldimethylsilyloxy)pent-1-yl 3-amino-5-(trifluoromethyl)benzoate (3.7 g, quant) as a colorless oil.

IR ($CHCl_3$): 1717 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.60 (1 H, s), 7.46 (1 H, s), 7.02 (1 H, s), 4.30 (2 H, t, *J* = 6.7 Hz), 4.05 (2 H, br s), 3.61 (2 H, t, *J* = 6.4 Hz), 1.76 (2 H, m), 1.56 (2 H, m), 1.46 (2 H, m), 0.86 (9 H, s), 0.02 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 147.2, 132.3, 131.9 (q, *J* = 32 Hz), 123.7 (q, *J* = 272 Hz), 118.5, 115.8, 115.0, 65.4, 62.8, 32.3, 28.4, 25.8, 22.3, 18.2, –5.5.

MS (FAB$^+$): *m*/*z* (%) = 406 (30, M + H$^+$), 73 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{19}H_{31}F_3NO_3Si$ (M + H$^+$): 406.2026; found: 406.2016.

5-(*tert*-Butyldimethylsilyloxy)pent-1-yl 3-Isothiocyanato-5-(trifluoromethyl)benzoate (12)

To a solution of 5-(*tert*-butyldimethylsilyloxy)pent-1-yl 3-amino-5-(trifluoromethyl)benzoate (7.8 g, 19 mmol) in anhyd MeCN (74 mL) were added imidazole (375 mg, 5.5 mmol) and 1,1-thiocarbonyldiimidazole (4.9 g, 28 mmol) under argon at 0 °C. After stirring for 2 h at r.t. for 2 h, the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane–EtOAc, 10:1) afforded isothiocyanate **12** (8.0 g, 93%) as a colorless oil. IR ($CHCl_3$): 1724 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.16 (1 H, s), 8.03 (1 H, s), 7.63 (1 H, s), 4.38 (2 H, t, *J* = 6.7 Hz), 3.64 (2 H, t, *J* = 6.1 Hz), 1.81 (2 H, m), 1.58 (2 H, m), 1.51 (2 H, m), 0.88 (9 H, s), 0.05 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 139.6, 133.3, 133.2, 132.6 (q, *J* = 33 Hz), 129.6, 126.2, 124.5, 122.7 (q, *J* = 273 Hz), 66.1, 62.7, 32.2, 28.3, 25.8, 22.3, 18.2, –5.5.

MS (FAB$^+$): *m*/*z* (%) = 448 (8, M + H$^+$), 73 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{29}F_3NO_3SSi$ (M + H$^+$): 448.1590; found: 448.1585.

Thiourea 13

To a solution of isothiocyanate **12** (12.9 g, 28.9 mmol) in anhyd benzene (110 mL) was added (1*R*,2*R*)-*N*,*N*-dimethylcyclohexanediamine (6.1 g, 43.0 mmol) under argon at 0 °C. After stirring for 3 h at r.t., the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH, 20:1) afforded the silylated thiourea (12.3 g, 73%) as a colorless oil; $[\alpha]_D^{27}$ –9.2 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (1 H, s), 7.80 (1 H, s), 7.86 (1 H, s), 4.29 (2 H, t, *J* = 6.7 Hz), 3.90 (1 H, br s), 3.59 (2 H, t, *J* = 6.4 Hz), 2.57 (1 H, br s), 2.42 (1 H, dt, *J* = 11.0, 3.1 Hz), 2.22 (6 H, s), 1.88–1.05 (15 H, m), 0.84 (9 H, s), 0.00 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.7, 164.5, 139.3, 132.2, 131.4 (q, *J* = 33 Hz), 127.8, 124.5, 123.1 (q, *J* = 273 Hz), 122.5, 66.5, 65.5, 62.5, 55.8, 39.6, 32.5, 32.0, 28.1, 25.6, 24.6, 24.3, 22.0, 21.1, 17.9, –5.7.

MS (FAB$^+$): *m*/*z* (%) = 590 (100, M + H$^+$).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{28}H_{47}F_3N_3O_3SSi$ (M + H$^+$): 590.3060; found: 590.3063.

To a solution of the above silylated thiourea (3.2 g, 5.4 mmol) in THF (16 mL) was added Bu_4NF (1 mol/L in THF, 11 mL, 11 mmol) under argon at r.t. After stirring for 12 h at r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, and then the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH, 7:1) afforded the desilylated thiourea **13** (1.4 g, 54%); white solid; $[\alpha]_D^{26}$ –0.2 (*c* = 0.1, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (1 H, s), 8.04 (1 H, s), 7.89 (1 H, s), 4.34 (2 H, t, *J* = 6.7 Hz), 3.94 (1 H, br s), 3.67 (2 H, t, *J* = 6.4 Hz), 2.58 (1 H, br s), 2.46 (1 H, dt, *J* = 10.9, 3.0 Hz), 2.28 (6 H, s), 1.95–1.00 (16 H, m).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.5, 164.6, 139.5, 131.9, 131.2 (q, *J* = 32 Hz), 127.4, 124.1, 123.1 (q, *J* = 273 Hz), 122.2, 66.3, 65.4, 61.9, 55.6, 39.6, 32.4, 31.9, 28.0, 24.5, 24.2, 21.9, 20.9.

MS (FAB$^+$): *m*/*z* (%) = 476 (58, M + H$^+$), 125 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{22}H_{33}F_3N_3O_3S$ (M + H$^+$): 476.2195; found: 476.2202.

Attachment of Thiourea 13 to Resin

To a suspension of carboxypolystyrene HL resin (1.10 mmol/g, 1.0 g, 1.10 mmol) in CH_2Cl_2 (20 mL) were added thiourea **13** (1.36 g, 2.9 mmol), EDC (0.56 g, 2.9 mmol) and DMAP (0.21 mg, 1.7 mmol) under argon at r.t. After stirring for 1 h at r.t. for 1 h, the mixture was kept for 11 h. The resin was then filtered, washed well with CH_2Cl_2, EtOAc followed by MeOH and then dried in vacuo to give the catalyst **9**. Following the same procedure as for **9**, catalyst **10** was obtained from TentaGel carboxy resin (0.26 mmol/g). Loading level of catalyst **9**: ca. 0.79 mmol/g (Anal. Calcd: F, 4.17. Found: F, 3.00). Loading level of catalyst **10**: ca. 0.19 mmol/g (Anal. Calcd: F, 1.33. Found: F, 0.97).

PEG-Bound Ester

To a solution of 5-(trifluoromethyl)-3-nitrobenzoic acid (**3**; 1.0 g, 4.3 mmol) in anhyd CH_2Cl_2 (25 mL) were added oxalyl chloride (1.61 mL, 18.8 mmol) and anhyd DMF (2 drops) under argon at 0 °C. After stirring for 18 h at r.t., the mixture was concentrated under reduced pressure. The resulting oil was dissolved in anhyd CH_2Cl_2 (10 mL) under argon. To this solution was added, a solution of poly(ethylene glycol) (typical M_n 8000, 20 g, 2.5 mmol) and Et_3N (3 mL) in CH_2Cl_2 (100 mL) under argon at 0 °C. After stirring for 3 h at r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of H_2O and extracted with CH_2Cl_2. The organic layers were combined, and 95% of the resulting volume was removed under reduced pressure. A tenfold of Et_2O was slowly added to the residue with stirring. The crystalline polymer was collected by filtration and washed with ice-cold EtOH. The polymer was dissolved in CH_2Cl_2 and precipitated as above. This procedure was repeated twice. The PEG-bound ether was dried in vacuo; white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.06 (2 H, s), 8.69 (2 H, s), 8.64 (2 H, s).

Anal. Calcd for $C_{380}H_{736}F_6N_2O_{189}$: C, 53.87; H, 8.76; N, 0.33. Found: C, 53.51; H, 8.45; N, 0.53.

PEG-bound amine 14

To a solution of the above PEG-bound ester (10 g, 1.1 mmol) in EtOAc–CH_2Cl_2 (10:3, 300 mL) was added 10% Pd/C (1.0 g) at r.t. After stirring for 5 h under a H_2 atmosphere at r.t. for 5 h, the mixture was filtered through Celite pad and concentrated under reduced pressure. After the residue was dissolved in a minimum amount of CH_2Cl_2, a tenfold of Et_2O was slowly added with stirring. The crystalline polymer was collected by filtration and washed with ice-cold EtOH. The polymer was dissolved in CH_2Cl_2 and precipitated as above. This procedure was repeated twice. The PEG-bound amine **14** was dried in vacuo; white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (2 H, s), 7.50 (2 H, s), 7.06 (2 H, s).

PEG-Bound Isothiocyanate

To a solution of PEG-bound amine **14** (1.4 g, 0.16 mmol) in anhyd MeCN (20 mL) were added imidazole (6.8 mg, 0.1 mmol) and 1,1-thiocarbonyldiimidazole (200 mg, 1.1 mmol) under argon at 0 °C. After stirring for 2 h at r.t., 95% of the volume of the mixture was removed under reduced pressure. A tenfold of anhyd Et_2O was slowly added with stirring under argon and then solvent was removed by syringe. The crystalline polymer was washed with anhyd Et_2O as above to give PEG-bound isothiocyanate. Unstable isothiocyanate was immediately subjected to the next reaction; white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (2 H, s), 8.07 (2 H, s), 7.64 (2 H, s).

PEG-Bound Thiourea 15

To a solution of PEG-bound isothiocyanate (1.3 g, 0.15 mmol) in anhyd benzene–CH_2Cl_2 (1:1, 30 mL) was added (1*R*,2*R*)-*N*,*N*-dimethylcyclohexanediamine (0.14 g, 1.0 mmol) under argon at r.t. After stirring for 3 h at r.t., 95% of the volume of the mixture was removed under reduced pressure. A tenfold of Et_2O was slowly added to the residue with stirring. The crystalline polymer was collected by filtration and washed with ice-cold EtOH. The polymer was dissolved in CH_2Cl_2 and precipitated as above. This procedure was repeated twice. The PEG-bound thiourea **15** was dried in vacuo; white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (2 H, s), 8.10 (2 H, s), 8.03 (2 H, s).

Anal. Calcd for $C_{398}H_{772}F_6N_6O_{185}S_2$: N, 0.96; F, 1.30. Found: N, 0.77; F, 1.23.

Michael Reaction of 5; General Procedure

To a solution of *trans*-β-nitrostyrene (**5**; 29.8 mg, 0.20 mmol) and diethyl malonate or a γ,δ-unsaturated β-keto ester (0.40 mmol) in anhyd CH_2Cl_2 (5 mL) was added thiourea catalyst **9**, **10**, or **15** (0.02 mmol) under argon at r.t. The mixture was slowly stirred at r.t. In the case of **9** or **10**, the resin was filtered and washed well with CH_2Cl_2, and EtOAc followed by EtOH, and then the filtrate was concentrated under reduced pressure. In the case of **15**, 95% of the volume of the mixture was removed under reduced pressure, and then a tenfold of Et_2O was slowly added to the residue. The crystalline polymer was filtered and washed well with Et_2O, and then filtrate was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–Et_2O, 3:1) afforded Michael adduct **6** or **16**.[13]

Aza-Henry Reaction of 7; General Procedure

To a solution of *N*-phosphinoylimine **7** (61 mg, 0.20 mmol) and nitromethane (0.11 mL, 2.0 mmol) in anhyd CH_2Cl_2 (5 mL) was added thiourea catalyst **9** or **10** (0.02 mmol) under argon at r.t. After stirring slowly at r.t., the resin was filtered and washed well with CH_2Cl_2, and EtOAc followed by EtOH, and then the filtrate was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–EtOAc, 1:1) afford the adduct **8**.[13,14]

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