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Thiourea-catalyzed asymmetric formal [3+2] cycloaddition of azomethine ylides with nitroolefins

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ABSTRACT

A chiral thiourea catalyst possessing an amine function catalyzes an asymmetric [3+2] cycloaddition of azomethine ylides to nitroolefins to provide highly functionalized pyrrolidines with high diastereo- and enantioselectivities (up to 98:1:1 dr, 92% ee). The reaction proceeds in a stepwise manner consisting of Michael addition and subsequent intramolecular aza-Henry reaction. Both reactions are promoted by the thiourea catalyst, and the reaction rate of the latter step is efficiently enhanced by the addition of 2,2,2-trifluoroethanol.

The [3+2] cycloaddition reactions have been employed as one of the most powerful synthetic tools to provide a variety of five-membered carbocycles as well as heterocycles.[1] For example, the [3+2] cycloaddition of azomethine ylides with olefins affords highly functionalized pyrrolidines, which are structural motifs of biologically active naturally occurring substances as well as pharmaceuticals.[2] Development of the catalytic enantioselective variants with high stereoselectivity is currently of interest.[3] There are several studies on the asymmetric [3+2] cycloaddition of azomethine ylides using metal salts, such as silver,[4] copper,[5] zinc,[6] and nickel,[7] with a variety of chiral ligands. Quite recently, the highly enantioselective catalytic [3+2] cycloaddition of azomethine ylides with α,β-unsaturated aldehydes and maleates by chiral proline derivatives[8] and a chiral phosphonic acid,[9] respectively, were reported. To the best of our knowledge, there is only one report on the enantioselective organocatalytic [3+2] cycloaddition with nitroolefins.[10] However, in this case, the level of asymmetric induction is still moderate (up to 63% ee). Herein, we describe a thiourea-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides with nitroolefins, reaching ee values up to 92% with high diastereoselectivity.

It is widely accepted that [3+2] cycloaddition proceeds through either a concerted [$_{\pi}2_{s}+_{\pi}4_{s}$] 1,3-dipolar cycloaddition pathway or a non-concerted stepwise addition pathway. Almost all of the enantioselective catalytic [3+2] cycloaddition of azomethine ylides were designed on the basis of the concerted mechanism.[10] We considered that good stereoselectivity in [3+2] cycloaddition of azomethine ylides with nitroolefins could be achieved through a stepwise mechanism. Namely, we have recently developed chiral thiourea catalyst **1**,[11] which demonstrated highly asymmetric induction in a variety of reactions, such as Michael addition of malonates to nitroolefins[11d,e] and aza-Henry reaction of imines with nitroalkanes.[11f,g] Taking into account our recent results, we envisaged that the thiourea **1** can catalyze a formal [3+2] cycloaddition of azomethine ylides with nitroolefins (Scheme 1). Thus, both the azomethine ylide, which is generated from α-amino malonate imine **2** and nitroolefin **3** would be anchored and activated through hydrogen-bonding system with the amine and thiourea moieties of the catalyst **1**, respectively. As a result, enantioselective Michael addition of **2**–**3** would proceed to furnish a zwitterionic intermediate **4**, and then a subsequent intramolecular aza-Henry reaction of **4** affords the desired pyrrolidine **5**.

In an initial study, we investigated the thiourea-catalyzed reaction between **2a** and **3a** in a series of organic solvents (Table 1). When the reaction was carried out in the presence of **1** (10 mol %) in CH_2Cl_2 at ambient temperature, no [3+2] cycloadduct was observed but only Michael adduct **4aa** was obtained in 55% yield with good enantioselectivity (86% ee, entry 1). The reaction in a polar aprotic solvent such as THF and CH_3CN afforded only **4aa** with somewhat lower enantioselectivities (entries 2 and 3). On the contrary, the desired pyrrolidine **5aa** was formed in 59% yield along with **4aa** (19% yield), when the reaction was carried out in a protic solvent, EtOH. However, both the enantiomeric excesses of the products **4aa** and **5aa** were quite low (21% ee, 11% ee; entry 4). Among the solvents examined, use of toluene gave the best asymmetric induction, affording the Michael adduct **4aa** (81%, 86% ee; entry 5). Furthermore, both the chemical yield and

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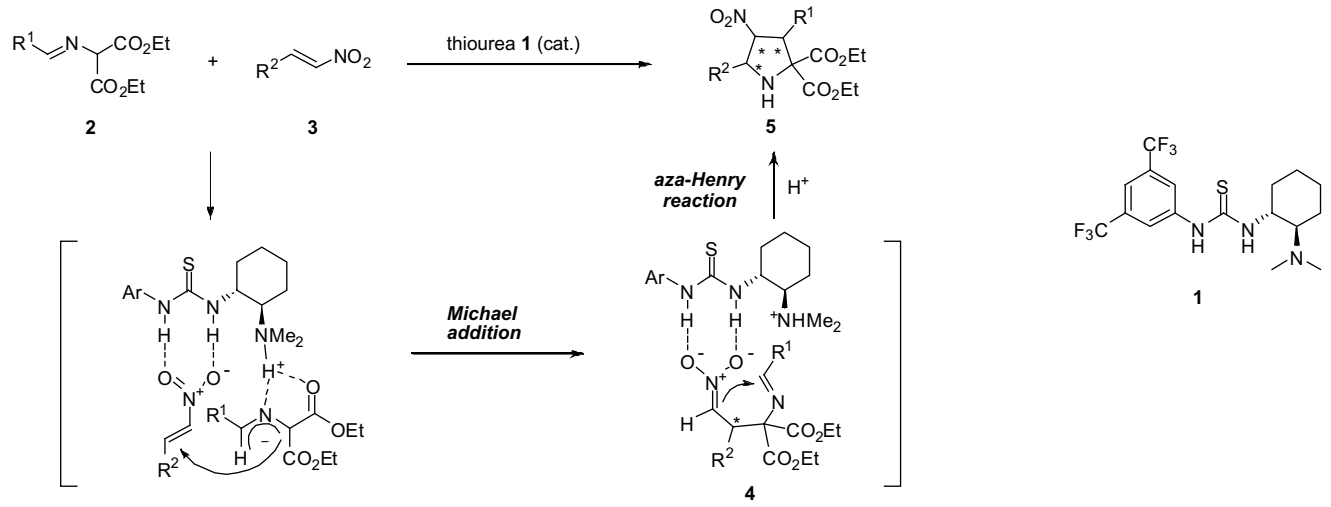
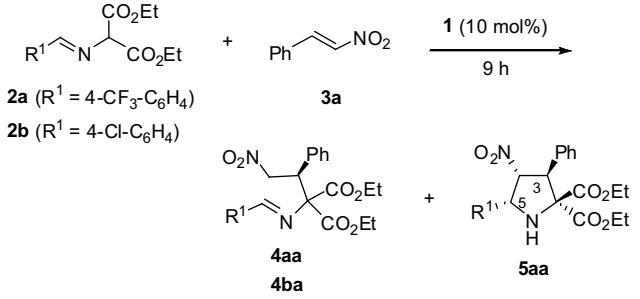


Scheme 1. A proposed mechanism for the formal [3+2] cycloaddition catalyzed by **1**.

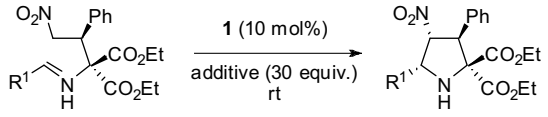
Table 1
Enantioselective Michael addition of **2a** and **2b** with **3a** catalyzed by **1**[a]



Entry	Solvent	Temp.	**4aa** (**5aa**)	
			% Yield[b]	% ee[c]
1	CH_2Cl_2	rt	55	86
2	THF	rt	51	74
3	CH_3CN	rt	77	33
4	EtOH	rt	19 (59)[d]	21 (11)[d]
5	Toluene	rt	81	86
6	Toluene	0 °C	90	90
7[e]	Toluene	0 °C	0	—
8[f]	Toluene	0 °C	82	90

[a] The reactions were carried out with **2a** (0.30 mmol), **3a** (0.30 mmol), and **1** (0.030 mmol).
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.
[d] The value in parentheses means the chemical yield of **5aa** and its enantiomeric excess.
[e] The reaction was carried out in the absence of **1** for 12 h.
[f] The reaction was carried out with **2b** and **3a** to give **4ba**.

Table 2
Thiourea-catalyzed intramolecular aza-Henry reaction[a]



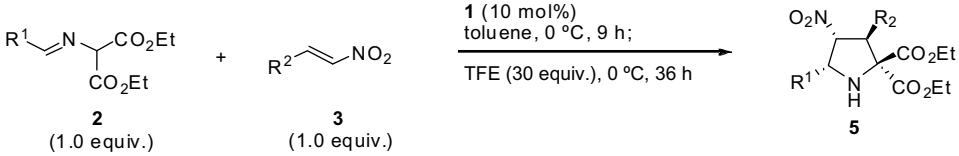
Entry	Solvent	Additive	Time (h)	**5aa**	
				% conv.[b]	dr[c,d]
1	Toluene	—	48	0	—
2	CH_2Cl_2	—	48	0	—
3	Dioxane	—	48	0	—
4	EtOH	—	48	95	92:7: Trace
5	Toluene	EtOH	24	6	99: Trace
6	Toluene	TFE	24	99	89:10:1
7[e]	Toluene	TFE	24	85	97:2: Trace
8[f]	Toluene	TFE	24	0	—

[a] The reactions were carried out with **4aa** (0.10 mmol) in the absence or in the presence of an additive (30 equiv) at ambient temperature.
[b] The conversion yields were determined by ^{1}H NMR.
[c] The stereochemistry of the minor diastereomers was not determined.
[d] The diastereomeric ratios were determined by ^{1}H NMR.
[e] The reaction was carried out at 0 °C.
[f] The reaction was carried out in the absence of **1**.

enantioselectivity of **4aa** were improved to 90% yield and 90% ee by conducting the reaction at 0 °C (entry 6). The catalyst is essential for the Michael addition; no formation of **4aa** was observed in the absence of thiourea **1** (entry 7). Under the optimum conditions in hand, Michael addition of **2b** with **3a** afforded **4ba** in 82% yield with 90% ee (entry 8). The absolute configuration of the Michael adduct was unambiguously determined to be *R* by an X-ray crystallography of **4ba**.[12] The enantioselection is consistent with the previous asymmetric reactions reported by us.[11d]

We next investigated the catalytic intramolecular aza-Henry reaction of **4aa** into **5aa** in the presence of **1** (Table 2). Although several aprotic solvents, such as toluene, CH_2Cl_2, and 1,4-dioxane, were tested, no reaction occurred at all at ambient temperature (entries 1–3). On the contrary, pyrrolidine **5aa** was formed in an excellent yield with high diastereoselectivity without loss of the enantiomeric excess in EtOH as a protic solvent (entry 4). As toluene is the optimum solvent in the above asymmetric Michael addition, reactions in toluene in the presence of protic compounds as an additive were investigated. Although EtOH (30 equiv) was added to the reaction, the cyclization slightly proceeded to give **5aa** in 6% yield (entry 5). On the other hand, use of 2,2,2-trifluoroethanol (TFE) having a more acidic proton than EtOH resulted in the better results, affording **5aa** in a diastereomeric ratio of 89:10:1 (entry 6). Lowering the temperature to 0 °C further enhanced the diastereoselectivity of **5aa** without any loss of its enantiomeric excess (entry 7). It was clear that no reaction occurred by the addition of TFE without thiourea catalyst **1** (entry 8). Thus, it is noteworthy that the cooperation of both thiourea and TFE is crucial to accelerate the intramolecular aza-Henry reaction. The stereochemistry of the major diastereomer of **5aa** was fully assigned by an X-ray crystallographic analysis to be (3*R*,4*R*,5*R*) configuration.[13]

Table 3
Reaction of various α-amino malonate imines and nitroolefins[a]



2 (1.0 equiv.) **3** (1.0 equiv.) **5**

Entry	**2** (R^1)	**3** (R^2)	Product	% Yield[b]	dr[c,d]	% ee[e]
1	**2a** (4-CF_3–C_6H_4)	**3a** (C_6H_5)	**5aa**	84	98:1:1	92
2	**2a** (4-CF_3–C_6H_4)	**3b** (4-MeO–C_6H_4)	**5ab**	81	95:4:1	91
3	**2a** (4-CF_3–C_6H_4)	**3c** (4-Cl–C_6H_4)	**5ac**	72	98:1:1	90
4	**2a** (4-CF_3–C_6H_4)	**3d** (3-Cl–C_6H_4)	**5ad**	75	98:1:1	90
5	**2a** (4-CF_3–C_6H_4)	**3e** (2-Cl–C_6H_4)	**5ae**	52	94:4:2	92
6	**2a** (4-CF_3–C_6H_4)	**3f** (2-thienyl)	**5af**	86	91:5:4	84
7	**2a** (4-CF_3–C_6H_4)	**3g** (1-naphthyl)	**5ag**	75	96:3:1	88
8	**2b** (4-Cl–C_6H_4)	**3a** (C_6H_5)	**5ba**	80	98:1:1	91
9	**2c** (C_6H_5)	**3a** (C_6H_5)	**5ca**	78	96:3:1	80
10	**2d** (4-CH_3–C_6H_4)	**3a** (C_6H_5)	**5da**	83	96:2:2	54

[a] The reactions were carried out with **2** (0.30 mmol), **3** (0.30 mmol), and **1** (0.030 mmol).
[b] Isolated yield.
[c] The stereochemistry of the minor diastereomers was not determined.
[d] Diastereomeric ratios were determined by ^{1}H NMR.
[e] Enantiomeric excess was determined by HPLC analysis using a chiral column.

With the optimum conditions for both enantioselective Michael addition and stereoselective intramolecular aza-Henry reaction in hand, we next examined the formal [3+2] cycloaddition in one-pot sequence to give pyrrolidine **5** from imines **2** and nitroolefins **3**. The results are summarized in Table 3. After the reaction of **2a** (1.0 equiv) with **3a** (1.0 equiv) in the presence of thiourea **1** (10 mol %) was carried out at 0 °C for 9 h, TFE (30 equiv) was added to the mixture at the same temperature and then stirring was continued for additional 36 h to give the [3+2] cycloadduct **5aa** in 84% yield with high diastereo- and enantioselectivities (98:1:1 dr, 92% ee; entry 1).[14] Similarly, high diastereo- and enantioselectivities were achieved in the reaction of **2a** with various nitroolefins **3b**–**3g** having an electron-rich, electron-deficient aromatic group or heteroaromatic group (entries 2–7). On the other hand, an electronic nature on the aromatic moiety of **2** affects the asymmetric induction of the cycloaddition. Imine **2b,** having *p*-chloro substituent on the aromatic moiety, afforded **5ba** with high enantioselectivity in good yield (entry 8). In contrast, removal of an electron-withdrawing substituent or introduction of electron-donating group led to a decrease in enantioselectivity (entries 9 and 10).[15]

The stereochemical outcome in the sequential [3+2] cycloaddition can be rationalized by the following plausible mechanism (Fig. 1). According to our previous literature,[11d] (*R*)-**4** would be produced predominantly through a ternary complex of **1**, **2**, and **3**. The resulting nitroalkane **4** would be deprotonated by the amino group of **1**, furnishing the corresponding nitronate anion, which is stabilized by the assistance of the thiourea moiety of **1**. Moreover, an external acidic proton of TFE might activate the imine moiety of **4** and stabilize a transition state by the hydrogen bond. Consequently, a good diastereoselectivity is observed in the cyclization step.

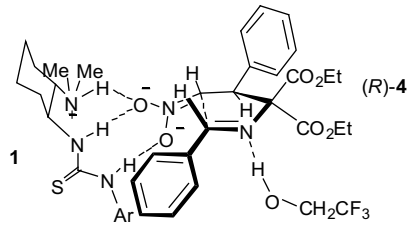


Figure 1. A plausible transition state model of the thiourea-catalyzed intramolecular aza-Henry reaction in the presence of TFE.

In summary, we have developed a formal enantioselective [3+2] cycloaddition of azomethine ylides with nitroolefins by the collaboration of thiourea **1** and trifluoroethanol, giving the optically active multi-functional pyrrolidines in up to 92% ee and 96% de.

Acknowledgments

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12. Crystal data for **4ba** (enantiomer). $C_{22}H_{23}ClN_2O_5$, monoclinic. Space group $P2_1$. $a = 9.8653(8)$ Å, $b = 9.2121(6)$ Å, $c = 11.9418(8)$ Å, $\beta = 91.355(2)^\circ$, $V = 1085.0(1)$ Å^3, $Z = 2$, $D_{calc} = 1.319$ g/cm^3, $R = 0.034$, $R_w = 0.057$, GOF = 0.66, Flack parameter = 0.00(3). The absolute structure was determined to be (*R*)-configuration with a high degree of certainty from the Flack parameter $\chi = 0.00(3)$. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. CCDC 696671 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
13. Crystal data for **5aa** (enantiomer). $C_{23}H_{23}F_3N_2O_6$, monoclinic. Space group $P2_12_12_1$. $a = 6.914(3)$ Å, $b = 15.714(7)$ Å, $c = 21.718(9)$ Å, $V = 2359.5(17)$ Å^3, $Z = 4$, $D_{calc} = 1.352$ g/cm^3, $R = 0.042$, $R_w = 0.051$, GOF = 0.78. CCDC 696672 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. *Typical experimental procedure for [3+2] cycloaddition of* **2** *with* **3**. To a solution of imine **2** (0.30 mmol) in toluene (3.0 mL) were added nitroolefin **3** (0.30 mmol) and **1** (12.4 mg, 0.030 mmol) at 0 °C. After being stirred at the same temperature for 9 h, trifluoroethanol (0.66 mL, 9.0 mmol) was added to the reaction mixture at the same temperature. The mixture was stirred at 0 °C for additional 36 h, and then was concentrated. The resulting residue was purified by silica gel chromatography (hexane/ethyl acetate = 9:1) to give pyrrolidine **5**. *Compound* **5aa**: Colorless prisms. Mp 128–130 °C (ethanol). IR (KBr) 3367, 1725, 1555 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.60 (d, $J = 8.1$ Hz, 2H), 7.55 (d, $J = 8.1$ Hz, 2H), 7.34–7.29 (m, 5 H), 5.64 (dd, $J = 8.0$, 7.0 Hz, 1H), 5.55 (dd, $J = 8.0$, 5.7 Hz, 1H), 5.14 (d, $J = 7.0$ Hz, 1H), 4.38 (qd, $J = 10.9$, 7.4 Hz, 1H), 4.30 (qd, $J = 10.9$, 7.4 Hz, 1H), 3.91 (qd, $J = 10.9$, 7.4 Hz, 1H), 3.54 (qd, $J = 10.9$, 7.4 Hz, 1H), 3.25 (d, $J = 5.7$ Hz, 1H), 1.30 (t, $J = 7.4$ Hz, 3H), 0.79 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.1, 168.3, 140.8, 134.7, 130.9 (q, $^2J_{(C,F)} = 33.6$ Hz), 128.7, 128.5, 128.4, 127.7, 125.4 (q, $^3J_{(C,F)} = 3.6$ Hz), 123.9 (q, $^1J_{(C,F)} = 274$ Hz), 93.5, 75.9, 63.8, 62.3, 62.1, 51.9, 14.0, 13.3. MS (FAB$^+$) *m*/*z*: 481 (M+H$^+$, 100). Anal. Calcd for $C_{23}H_{23}F_3N_2O_6$: C, 57.50; H, 4.83; N, 5.83. Found: C, 57.50; H, 4.91; N, 5.84. HPLC (CHIRALCEL AD-H, hexane/2-propanol = 85/15, flow rate 1.0 mL/min, 254 nm), t_r(minor) = 11.9 min, t_r(major) = 24.1 min. A sample with 92% ee by HPLC analysis gave $[\alpha]_D^{32}$ 43.80 (*c* 1.00, $CHCl_3$).
15. Crystal data for **5ca** (racemate). $C_{22}H_{24}N_2O_6$, monoclinic. Space group $P2_1/c$; $a = 10.8269(7)$ Å, $b = 17.907(1)$ Å, $c = 11.1352(8)$ Å, $\beta = 100.958(2)^\circ$, $V = 2119.5(3)$ Å^3, $Z = 4$, $D_{calc} = 1.292$ g/cm^3, $R = 0.039$, $R_w = 0.045$, GOF = 1.74. CCDC 696673 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.