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Self-assembly of organocatalysts for the enantioselective Michael addition of aldehydes to nitroalkenes

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ABSTRACT

A proline–thiourea self-assembled organocatalyst is described as a good catalyst for the enantioselective nitro-Michael addition of aldehydes to nitroalkenes. The reaction is efficient with 5% of the thiourea, to give moderate to good enantioselectivity (up to 76% ee). High *syn*-selectivity was obtained with both branched and unbranched aliphatic aldehydes. This is the first example of self-assembly of organocatalysts with an achiral additive in a Michael addition wherein aldehydes are utilized as donors.

1. Introduction

In recent years, organocatalysis, which in organic reactions are catalyzed by small organic molecules, has expanded rapidly.[1] The Michael reaction of carbon-centered nucleophiles to nitroalkenes is one such reaction that is catalyzed by organocatalysts.[2] Nitroalkanes are crucial intermediates in organic synthesis due to their ability to transform the nitro group into other useful functionalities.[3] After the first organocatalytic asymmetric Michael addition of aldehydes to nitroalkenes was reported by Betancort and Barbas,[4] extraordinary progress has been sought in order to find more selective and efficient catalytic systems for these Michael reactions.[5] Even though L-proline, which is a widely distributed amino acid, has been described as a catalyst for asymmetric Michael reactions with aldehydes as the donor, only poor enantioselectivity is typically observed.[6,4b] The enolates of aldehydes have reactions that are more difficult to manage, with polymerization and aldolization processes competing. Proline-derived or pyrrolidine-based catalytic systems have been shown to be successful for this transformation in both ketones and aldehydes. Nonetheless, they are generally more complex and, therefore, have to be prepared by a multistep synthesis. Thus, the development of more-effective asymmetric catalysts in terms of both enantioselectivity and a substrate scope is still desirable.

In 2007, Clarke and Funtes reported the first example of the self-assembly of organocatalysts for the Michael addition of ketones to nitroalkenes, wherein the addition of achiral additives to a chiral organocatalyst host can transform an unselective catalyst into a highly effective one through hydrogen-bonding interactions.[7] Zhao and Mandal reported that organocatalysts that were formed through the self-assembly of simple α-amino acids and alkaloid thiourea derivatives could be used as efficient catalysts for the nitro-Michael addition of ketones and nitroalkenes.[8] This approach is not only beneficial in avoiding chemical synthesis but it is also useful for constructing libraries of structurally diverse catalysts. To the best of our knowledge, there has been no report on the application of these types of self-assembly of organocatalysts with an achiral additive in a Michael addition wherein aldehydes are utilized as donors.

We have previously shown the proof-of-principle results of proline-catalyzed direct aldol reactions between cyclic ketones and aldehydes using 1,3-bis[3,5-bis(trifluoromethyl)phenyl] thiourea **A** as the additive.[9] We proposed that the reaction would proceed according to a modified Houk–List model,[10] in which the carboxylate moiety of the proline forms an assembly with the thiourea, in turn enhancing the reactivity and selectivity of the catalyst. Furthermore, the thiourea is treated as a non-polar counterpart to proline, amplifying its solubility limits in non-polar solvents, such as hexane or toluene (Fig. 1).

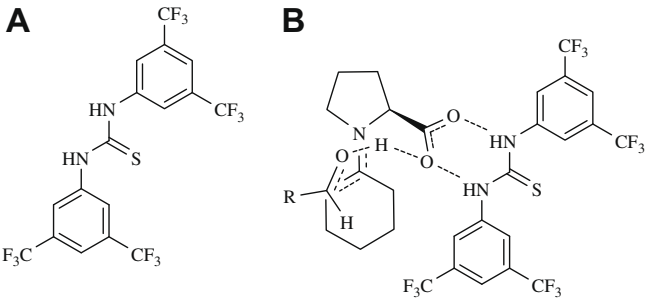

Figure 1. Our previous study.

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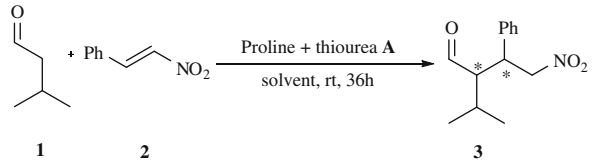
The possibility of fine-tuning these proline–thiourea interactions also presents a possible strategy for asymmetric catalyst development.

2. Result and discussion

Herein, we report the results of the enantioselective Michael addition of aldehydes to nitroalkenes catalyzed by a proline–thiourea host–guest complex. To optimize the reaction conditions, the reaction of isovaleraldehyde and *trans*-β-nitrostyrene was investigated as a model (Scheme 1).



Scheme 1.

The reaction was performed at rt for 36 h in the presence of L-proline and 1,3-bis[3,5-bis(trifluoromethyl)phenyl] thiourea. During the studies, some representative illustrative solvents were screened; the screening results are summarized in Table 1.

As can be seen, our first attempt in hexane gave a good conversion but low enantioselectivity (entry 1). Under the same reaction conditions, a similar trend was observed for the other solvents, such as dioxane and chloroform. Examination of the solvents showed that the best enantioselectivity was obtained when the solvent benzene was used as the solvent (entries 9 and 11). For further optimization of the reaction condition, we screened the effect of an equivalent of the donor, and catalyst loading. From a practical point of view, the Michael addition of aldehydes to β-nitrostyrene usually requires a large (10-fold) excess of the donor, due to competing aldol pathways. However, in the present study, the reaction worked with only 3 equiv of the donor. Further investigation showed that by using only 5% thiourea, the reaction produced a good conversion without a decrease in enantioselectivity. When the reaction was carried out without the thiourea additive, the reaction was very slow, with a low stereoselectivity (Table 1, entry 12). These results obviously demonstrate the influential effect of the thiourea on the reactivity and selectivity.

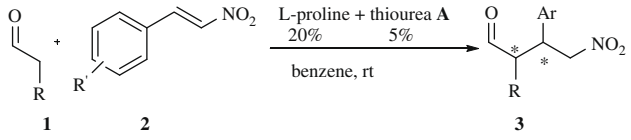
With the optimized conditions in hand, the generality of the reaction was then examined. Various nitroalkenes and aldehydes were tested under the optimized reaction conditions, in which the results are shown in Table 2.

Unbranched aldehydes, such as propionaldehyde **1a**, butanal **1b**, and pentanal **1c**, gave the 1,4-addition in good yields and moderate to good enantioselectivities with excellent diastereoselectivities. We then continued to evaluate the scope of the reaction by testing the Michael addition of isovaleraldehyde **1d** to various nitroalkenes, in which a good yield and moderate to good enantioselectivities were observed. On the other hand, α-branched aldehydes, isobutyraldehyde **1e**, led to a good isolated yield (66%) and good enantioselectivity (72%) (Table 2, entry 11). The reactions with nitroalkenes bearing not only phenyl, but also electron-rich and electron-deficient aryl groups on the nitroalkene proceeded efficiently, with a high diastereoselectivity. In all the cases, as little as 5% thiourea was adequate to obtain the best ee values.

To explain the higher *syn*-diastereoselectivities and the enantioselectivities with respect to proline, we propose a TS based on Seebach's model[11] as can be seen in Figure 2. In this model, the preferential formation of the *anti*-enamine with the double bond was oriented away from the bulky substituent at the 2-position of the pyrrolidine ring. Subsequently, the enamine reacts with

Table 2
The enantioselective Michael addition of aldehydes to nitroalkenes

Entry	Aldehyde **1** R	R′	Yield (%)	*syn*/*anti*	ee (%)
1	$-CH_3$ **a**	H	85	12:1	76 **3a**
2	$-CH_3$ **a**	4-OMe	79	11:1	60 **3b**
3	CH_3 **a**	4-Br	80	10:1	60 **3c**
4	$-CH_2CH_3$ **b**	H	77	20:1	67 **3d**
5	$-CH_2CH_3$ **b**	4-Br	79	17:1	69 **3e**
6	$-CH_2CH_2CH_3$ **c**	H	86	15:1	76 **3f**
7	$-CH_2CH_2CH_3$ **c**	4-OMe	50	14:1	44 **3g**
8	$-CH_2CH_2CH_3$ **c**	4-Br	65	15:1	50 **3h**
9	$-CH(CH_3)_2$ **d**	H	88	38:1	75 **3i**
10	$-CH(CH_3)_2$ **d**	4-Br	80	35:1	60 **3j**
11[a]	$-CH_3$, $-CH_3$ **e**	H	66	—	72 **3k**
12[b]	$-CH_3$, $-CH_3$ **e**	H	87	—	23 **3k**



[a] 20:20% Proline–thiourea was used.
[b] DMSO was used as a solvent, 20:0% Proline–thiourea was used, see Ref. 5d.

Table 1
Solvent screening for the enantioselective Michael reaction of **1** and **2**

Entry	Cat. (%) proline:urea	Solvent	Equiv of aldehyde	Conv. (%)	*syn*/*anti*	ee (%)
1	20:20	Hexane	10	94	36:1	25
2	20:20	Toluene	10	83	65:1	29
3	20:20	Chloroform	10	87	41:1	35
4	20:20	Chloroform	3	86	40:1	32
5	20:10	Chloroform	3	85	40:1	32
6	20:20	Dioxane	3	95	38:1	35
7	20:20	Cyclohexane	3	94	36:1	53
8	20:20	Benzene	3	99	30:1	76
9	20:10	Benzene	3	99	41:1	72
10	20:5	Benzene	3	98	39:1	76
11	5:5	Benzene	3	90	41:1	72
12	20:0	Benzene	3	⩽6	15:1	nd

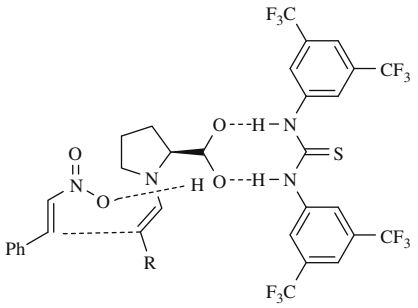


Figure 2. Possible transition state.

the nitro olefin via an acyclic synclinal transition state. A bulky substituent at the 2-position of the pyrrolidine ring plays two important roles: it favors the selective formation of the *anti*-enamine and also shields its *Re*-face.

3. Conclusion

In conclusion, the results from our investigations show that the additon of achiral thiourea to an L-proline have an enormous effect on solubility reactivity and selectivity, even in an unconventional non-polar reaction medium, thus eliminating the need to use low temperatures. These self-assembled organocatalysts are good catalysts for the enantioselective nitro-Michael addition of aldehydes to nitroalkenes. The reaction is efficient with just 5% thiourea, in which moderate to good enantioselectivity and high *syn*-selectivity was obtained in both branched and unbranched aliphatic aldehydes. This is the first example of self-assembly of organocatalysts with an achiral additive in a Michael addition wherein aldehydes are utilized as donors.

4. Experimental section

4.1. General

All commercially available reagents were used without further purification. Purification of products was carried out by flash column chromatography using Silica Gel 60. Analytical thin layer chromatography was performed on aluminum sheets precoated with Silica Gel 60F254. Visualization was accomplished with UV light and anisaldehyde followed by heating.

4.2. General procedure for the enantioselective Michael addition of aldehydes to nitroalkenes

Proline (0.1 mmol, 11.5 mg), thiourea **A** (0.025 mmol, 12.5 mg), and 3.2 ml of benzene were placed in a screw-capped vial. Then aldehyde (1.5 mmol) was added, in which the resulting mixture was stirred for 30 min at ambient temperature followed by the addition of nitroalkene (0.50 mmol), wherein stirring was continued until the completion of the reaction (TLC monitoring). After completion of the reaction, the reaction mixture was treated with a saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a crude residue, which was purified by column chromatography over silica gel using hexane–ethyl acetate as an eluent to afford a pure product. Diastereoselectivity and conversion were determined by ^{1}H NMR analysis of the crude product. The enantiomeric excess (ee) of **3** was determined by chiral-phase HPLC analysis. The absolute configuration of the products was determined by comparing the values with those previously reported in the literature.

4.2.1. 2-Methyl-4 nitro-3-phenylbutyraldehyde 3a

From propionaldehyde **1a** and nitrostyrene **2a** at rt according to the general procedure; *syn*/*anti* = 12/1; ee = 76%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 80:20, UV 220 nm, 0.8 ml/min, *syn*: t_R = 17.7 (minor) and t_R = 22.6 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (d, J = 1.7, 1H), 7.33–7.21 (m, 3H), 7.14–7.10 (m, 2H), 4.76 (dd, J = 5.5, 12.7, 1H), 4.65 (dd, J = 9.3, 12.7, 1H), 3.76 (td, J = 5.5, 9.2, 1H), 2.78–2.70 (m, 1H), 1.01 (d, J = 7.3, 3H).

4.2.2. 3-(4-Methoxyphenyl)-2-methyl-4-nitrobutyraldehyde 3b

From propionaldehyde **1a** and *trans*-4-methoxy-β-nitrostyrene **2b** at rt according to the general procedure; *syn*/*anti* = 11/1; ee = 60%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 85:15, UV 254 nm, 1.0 ml/min, *syn*: t_R = 19.8 (minor) and t_R = 22.2 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (d, J = 1.7, 1H), 7.12–7.03 (m, 3H), 6.85–6.80 (m, 2H), 4.78–4.67 (m, 1H), 4.60 (dd, J = 9.4, 12.5, 1H), 3.76 (s, 3H), 2.81–2.64 (m, 1H), 1.18 (d, J = 7.2, 1H), 1.01 (d, J = 7.3, 3H).

4.2.3. 3-(4-Bromophenyl)-2-methyl-4-nitro-butyraldehyde 3c

From propionaldehyde **1a** and *trans*-4-bromo-β-nitrostyrene **2c** at rt according to the general procedure; *syn*/*anti* = 10/1; ee = 60%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 8:2, UV 254 nm, 0.8 ml/min, *syn*: t_R = 17.7 (minor) and t_R = 22.6 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, J = 1.5, 1H), 7.52–7.45 (m, 2H), 7.13–7.03 (m, 2H), 4.80 (dd, J = 5.2, 12.8, 1H), 4.65 (dd, J = 9.6, 12.8, 1H), 3.91–3.67 (m, 1H), 2.93–2.62 (m, 1H), 1.01 (d, J = 7.3, 3H).

4.2.4. 2-Ethyl-4-nitro-3-phenyl butyraldehyde 3d

From butanal **1b** and nitrostyrene **2a** at rt according to the general procedure; *syn*/*anti* = 20/1; ee = 67%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 80:20, UV 237 nm, 0.8 ml/min, *syn*: t_R = 16.2 (minor) and t_R = 17.5 (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, J = 2.6 Hz, 1H), 7.30–7.19 (m, 3H), 7.10–7.12 (m, 2H), 4.65 (dd, J = 12.8, 4.9 Hz, 1H), 4.56 (dd, J = 12.8, 9.7 Hz, 1H), 3.72 (ddd, J = 9.7, 9.7, 4.9 Hz, 1H), 2.66–2.58 (m, 1H), 1.48–1.38 (m, 2H), 0.76 (dd, J = 7.5, 7.5 Hz, 3H).

4.2.5. 3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal 3e

From butanal **1b** and *trans*-4-bromo-β-nitrostyrene **2c** at rt according to the general procedure; *syn*/*anti* = 17/1; ee = 69%; the enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hex: *i*PrOH 98.5:1.5, UV 237 nm, 1.0 ml/min, *syn*: t_R = 33.5 (major) and t_R = 59.4 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, J = 2.3 Hz, 1H;), 7.43 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 4.67 (dd, J = 4.8 Hz, 12.8 Hz, 1H), 4.56 (dd, J = 9.9 Hz, 12.8 Hz, 1H), 3.72 (dt, J = 4.8 Hz, 9.9 Hz, 1H), 2.62 (m, 1H), 1.53–1.46 (m, 2H), 0.77 (t, J = 7.5 Hz, 3H).

4.2.6. 2-(2-Nitro-1-phenylethyl)pentanal 3f

From pentanal **1c** and nitrostyrene **2a** at rt according to the general procedure; *syn*/*anti* = 15/1; ee = 76%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 90:10, UV 220 nm, 1.0 ml/min, *syn*: t_R = 16.2 (minor) and t_R = 18.7 (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (d, J = 2.8, 1H), 7.34–7.24 (m, 3H), 7.16–7.11 (m, 2H), 4.70–4.56 (m, 2H), 3.73 (td, J = 5.3, 9.5, 1H), 2.67 (tt, J = 3.2, 9.5, 1H), 1.50–1.40 (m, 1H), 1.37–1.21 (m, 2H), 1.20–1.06 (m, 1H), 0.77 (t, J = 7.1, 3H).

4.2.7. 2-(1-(4-Methoxyphenyl)-2-nitroethyl)pentanal 3g

From pentanal **1c** and *trans*-4-methoxy-β-nitrostyrene **2b** at rt according to the general procedure; *syn*/*anti* = 14/1; ee = 44%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 90:10, UV 237 nm, 1.0 ml/min, *syn*: t_R = 20.4 (minor)

and t_R = 22.9 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, J = 3.3 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 9.0, 2H), 4.62 (dd, J = 5.4, 12.6 Hz, 1H), 4.52 (dd, J = 9.3, 12.3 Hz, 1H), 3.71 (s, 3H), 3.65 (dt, J = 5.7, 9.9 Hz, 1H), 2.60 (dt, J = 3.0, 9.3 Hz, 1H), 1.49–1.10 (m, 4H), 0.75 (t, J = 6.9 Hz, 3H).

4.2.8. 2-(1-(4-Bromophenyl)-2-nitroethyl)pentanal 3h

From pentanal **1c** and *trans*-4-bromo-β-nitrostyrene **2c** at rt according to the general procedure; *syn*/*anti* = 15/1; ee = 50%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 90:10, UV 220 nm, 1.0 ml/min, *syn*: t_R = 20.5 (minor) and t_R = 21.7 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 4.63 (dd, J = 5.1, 12.9 Hz, 1H), 4.54 (dd, J = 9.9, 13.2 Hz, 1H), 3.68 (dt, J = 4.8, 9.6 Hz, 1H), 2.62 (dt, J = 3.3, 9.3 Hz, 1H), 1.46–1.05 (m, 4H), 0.75 (t, J = 7.2 Hz, 3H).

4.2.9. 2-Isopropyl-4-nitro-3-phenylbutanal 3i

From isovaleraldehyde **1d** and nitrostyrene **2a** at rt according to the general procedure; *syn*/*anti* = 38/1; ee = 75%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 97:03, UV 220 nm, 0.7 ml/min, *syn*: t_R = 28.1 (minor) and t_R = 30.4 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (d, J = 2.4, 1H), 7.28–7.17 (m, 3H), 7.12–7.07 (m, 2H), 4.58 (dd, J = 4.4, 12.5, 1H), 4.48 (dd, J = 10.0, 12.5, 1H), 3.81 (td, J = 4.4, 10.4, 1H), 2.69 (ddd, J = 2.4, 4.1, 10.8, 1H), 1.70–1.57 (m, 1H), 1.01 (d, J = 7.2, 3H), 0.79 (d, J = 7.0, 3H).

4.2.10. 3-(4-Bromophenyl)-2-isopropyl-4-nitrobutanal 3j

From isovaleraldehyde **1d** and *trans*-4-bromo-β-nitrostyrene **2c** at rt according to the general procedure; *syn*/*anti* = 35/1; ee = 60%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 90:10, UV 220 nm, 1.0 ml/min, *syn*: t_R = 15.7 (minor) and t_R = 17.2 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.4 Hz, 1.5 Hz, 2H), 7.01 (dd, J = 8.4 Hz, 1.5 Hz, 2H), 4.65–4.59 (m, 1H), 4.52–4.44 (m, 1H), 3.82 (m, 1H), 2.71–2.67 (m, 1H), 1.64 (m, 1H), 1.04 (d, J = 7.2 Hz, 3H), 0.80 (d, J = 7.2 Hz, 3H).

4.2.11. 3-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal 3k

From isobutyraldehyde **1e** and nitrostyrene **2a** at rt according to the general procedure; ee = 72%; the enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex: *i*PrOH 80:20, UV 220 nm, 1.0 ml/min, *syn*: t_R = 11.5 (minor) and t_R = 16.6 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 7.30–7.19 (m, 5H), 4.86 (t, J = 12.9 Hz, 1H), 4.70 (d, J = 12.9 Hz, 1H), 3.80 (d, J = 11.7 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H).

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