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Highly enantioselective Michael addition of isobutyraldehyde to nitroalkenes

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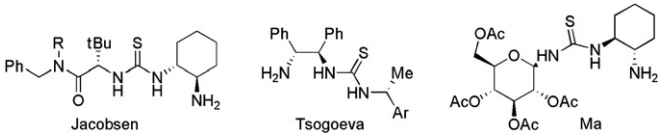
ABSTRACT

The asymmetric catalytic Michael reaction between isobutyraldehyde and nitroalkanes with chiral primary amine thiourea organocatalysts was described. In the presence of 10 mol % of 1-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-3-benzylthiourea, the desired products were achieved in excellent enantioselectivity (up to>99% ee) with up to 98% yield.

1. Introduction

As versatile synthetic intermediates, nitroalkanes are of significant interest in organic chemistry due to the various transformations of the nitro group into other useful functional groups.[1] The Michael addition of carbonyl compounds to nitroalkenes is a useful way in obtaining nitroalkanes. Since the pioneering works of asymmetric organocatalysis,[2] many catalytic systems have been developed for the asymmetric Michael addition between aldehydes/ketones and nitroalkenes to produce enantiomerically enriched nitroalkanes.[3] The synthesis of all-carbon quaternary stereogenic centers is considered a challenging topic in asymmetric synthesis. Although various chiral organocatalysts were highly efficient for the Michael addition of aldehydes to nitroolefins, only several organocatalysts provided excellent enantioselectivities for the Michael reaction between α,α-disubstitued aldehydes and nitroolefins.[4]

In recent years, considerable effort has been directed to the development of chiral primary amine thiourea catalysts (Scheme 1). Jacobsen's group[4c,5a] firstly reported cyclohexanediamine-derived chiral primary amine thioureas as organocatalyst for the highly enantioselective direct conjugate addition of both ketones and aldehydes to nitroalkenes. Tsogoeva et al.[5b–d] presented a successful application of the diphenylethyldiamine-derived bifunctional primary amine thioureas in the asymmetric Michael addition of ketones to nitroolefins. Ma et al.[6] developed a class of saccharide-based bifunctional primary amine thioureas, which were excellently enantioselective for Michael addition of aromatic ketones to nitroolefins. Later, cyclohexanediamine-derived chiral primary amine thioureas bearing cinchona alkaloid[7] or dehydroabietic amine[8] backbone were developed for the enantioselective Michael additions. As the loading of the catalyst is usually large amount (20–30 mol %) in the asymmetric organocatalysis, we are eager to develop the economical catalysts. Although Tsogoeva described the chiral arylethyl moiety adjacent to a thiourea was expected to shield one side of the activated nitroolefin, we found that the non-chiral benzyl moiety also can do it effectively. Herein, we report the asymmetric nitro-Michael additions of isobutyraldehyde to nitroolefins catalyzed by the chiral primary amine thiourea. The present research results provide an interesting comparison with the results obtained using Tsogoeva's catalysts.



Scheme 1. Examples of bifunctional primary amine thioureas.

2. Results and discussion

Initially, the addition of isobutyraldehyde to β-nitro-*p*-nitrostyrene was selected as a model reaction. We were pleased to find that all the primary amine thiourea derivatives could catalyze the Michael reaction with excellent enantioselectivities (Scheme 2). However, the catalytic activities of organic molecules **1a**–**h** were

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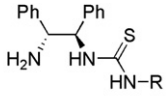
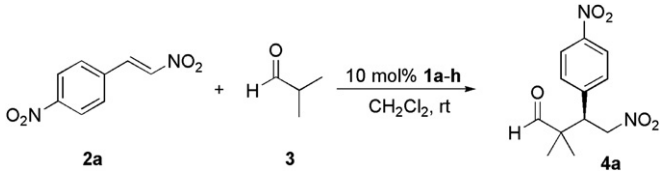
significantly different. The results summarized in Table 1 indicated thioureas **1d** and **1e** (entries 4 and 5) could catalyze the reaction smoothly in high yield. While their analogue **1f** gave poor yield (entry 6). Compared with thiourea **1d**, organocatalyst **1g** with methoxyl substitution at the *para*-position of phenyl also gave good yield, but the reaction took a long time (entry 7). Bearing an alkyl group, the catalyst **1h** afforded good yield and excellent enantioselectivity (entry 8). Surprisingly, the chemical yields became low when bearing aryl groups at the thiourea moieties (entries 1–3).



1a R = 3,5-$(CF_3)_2C_6H_3$; **1b** R = C_6H_5;
1c R = 4-$MeOC_6H_4$; **1d** R = $C_6H_5CH_2$;
1e R = (*R*)-CH(Me)C_6H_5; **1f** R = (*S*)-CH(Me)C_6H_5;
1g R = 4-$MeOC_6H_4CH_2$; **1h** R = *n*-Bu

Scheme 2. The screened chiral primary amine thioureas.

Table 1
Catalytic asymmetric Michael addition of isobutyraldehyde to β-nitro-*p*-nitrostyrene[a]



2a **3** **4a**

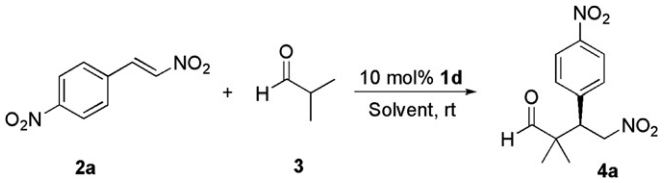
Entry	Catalyst	Time (d)	Yield[b] (%)	ee[c] (%)
1	**1a**	4	20	99
2	**1b**	4	15	96
3	**1c**	4	13	99
4	**1d**	1	75	99.3
5	**1e**	1	75	99.7
6	**1f**	1	28	95
7	**1g**	3	73	>99
8	**1h**	3	65	>99

[a] All reactions were conducted in CH_2Cl_2 (2 mL) using **2a** (0.2 mmol) and **3** (1 mmol, 5 equiv) in the presence of 10 mol % catalyst.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol=80/20).

The Michael reaction of isobutyraldehyde to β-nitro-*p*-nitrostyrene was next examined with thiourea **1d** under various reaction conditions (Table 2). The ratio of aldehyde to nitroolefin was investigated first. Using only threefold of aldehyde relative to nitrostyrene improved the chemical yield (entry 2). However, decreasing the amount of aldehyde to twofolds could not increase the yield further (entry 3). Then we explored the effects of the solvents. As shown in Table 2, the chemical yields varied significantly in the solvents tested. Polar solvents, such as EtOH and THF afforded poor yields (entries 4 and 5). Moderate yield was obtained when using chloroform as solvent (entry 7). Due to the poor solubility of substrate, rather low conversion was observed in ethyl ether, hexane and toluene (entries 8–10). The use of CH_2Cl_2 led to the highest yield and enantioselectivity (entry 2, 90% yield, 99.7% ee). In general, the reactions were displayed highly enantioselective in all the screened solvents (90–99.7% ee).

When the optimal reaction conditions were established, a variety of nitroolefins were then evaluated as substrates and the results are summarized in Table 3. The results indicated the reaction had a wide substrate scope with respect to nitroolefins. The Michael adducts were obtained in nearly optically pure form (>99% ee) in most of the cases examined (Table 3, entries 1–4, 7–19). Nitroolefins with electron-withdrawing aryl group were more reactive

Table 2
Effect of solvents and isobutyraldehyde loading on the asymmetric Michael addition of isobutyraldehyde to β-nitro-*p*-nitrostyrene[a]



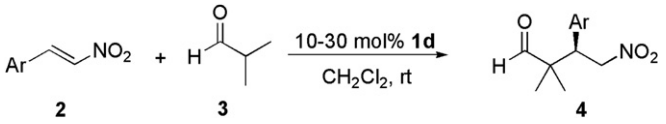
2a **3** **4a**

Entry	Solvent	**3**/**2a**	Time (d)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	5	1	75	>99
2	CH_2Cl_2	3	2	90	>99
3	CH_2Cl_2	2	3	85	>99
4	EtOH	3	2	10	97
5	THF	3	3	30	96
6	*i*-PrOH	3	2	80	98
7	$CHCl_3$	3	2	65	99
8	Ether	3	3	32	>99
9	*n*-Hexane	3	2	20	90
10	Toluene	3	2	38	96

[a] All reactions were conducted in solvent (2 mL) using **2a** (0.2 mmol) and **3** in the presence of 10 mol % **1d**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol=80/20).

than that with electron-donating aryl group or unsubstituted aryl group (entries 1–13 vs 14–19). The less reactive substrates could provide good chemical yields while increasing the catalyst loading to 30 mol % (entries 15, 17, and 19).

Table 3
Catalytic asymmetric Michael addition of isobutyraldehyde to different nitroolefins[a]



2 **3** **4**

Entry	Substrate	**1d** (mol %)	Time (d)	Yield[b] (%)	ee[c] (%)
1	4-$NO_2C_6H_4$	10	2	90	>99
2	4-$NO_2C_6H_4$	15	1	98	>99
3	3-$NO_2C_6H_4$	10	2	85	>99
4	3-$NO_2C_6H_4$	15	2	95	>99
5	2-$NO_2C_6H_4$	10	2	72	98
6	2-$NO_2C_6H_4$	15	2	80	98
7	4-CNC_6H_4	15	2	90	>99
8	4-FC_6H_4	15	2	72	>99
9	4-ClC_6H_4	10	2	65	>99
10	4-ClC_6H_4	15	2	85	>99
11	2-ClC_6H_4	15	2	85	>99
12	4-BrC_6H_4	15	2	75	>99
13	2-furyl	15	2	90	>99
14	C_6H_5	15	3	47	>99
15	C_6H_5	30	2	77	>99
16	4-MeC_6H_4	15	3	50	>99
17	4-MeC_6H_4	30	2	75	>99
18	4-$MeOC_6H_4$	15	3	50	>99
19	4-$MeOC_6H_4$	30	2	76	>99

[a] All reactions were conducted in CH_2Cl_2 (2 mL) using **2** (0.2 mmol) and **3** (0.6 mmol, 3 equiv) in the presence of **1d**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H or AS-H column).

3. Conclusion

In conclusion, we have developed a simple thiourea-based bifunctional organocatalysts for the highly enantioselective Michael reaction of isobutyraldehyde to nitroolefins in good yields. This