Oxazoline–Thiourea as a Bifunctional Organocatalyst: Enantioselective aza-Henry Reactions

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Abstract: Bifunctional oxazoline–thiourea-based organocatalysts were synthesized and applied to the aza-Henry reactions between *N*-Boc aryl imines and nitromethane in high ee and chemical yields at room temperature.

Key words: oxazoline, thiourea, aza-Henry reactions, organocatalyst

The addition of a nitroalkane across the C=N bond of an imine (known as aza-Henry reaction) has attracted much attention because it is an important C–C bond-forming process.[1] The resulting 1,2-nitroamine adducts can be transformed into 1,2-diamines[2] by reduction[3] as well as to α-amino acids by a Nef oxidation.[4]

Recently, the development of catalytic asymmetric versions of the nitro-Mannich reaction has become a topic of interest. Shibasaki reported the reaction of nitro compounds with *N*-phosphinoyl imines derived from aromatic aldehydes using binaphthoxide-based heterobimetallic complexes of ytterbium and aluminum as catalysts.[5] Jørgensen reported the reaction of silyl nitronates with amino esters catalyzed by copper bis(oxazoline) complexes.[6] Palomo also described the use of complexes of Zn^{II} and *N*-methylephedrine as catalysts of the reaction of nitromethane and *N*-Boc aryl imines,[7] thus providing a new entry to enantioenriched diamines and aryl glycines.

In the last decade, asymmetric organocatalysis has proven to be a robust and valid alternative to traditional metal-based catalysis for a number of reactions.[8] High enantiomeric excesses have been achieved in the reaction between nitroalkanes and imines (aza-Henry reaction) using chiral, enantiopure organic catalysts. Remarkable results were obtained in particular by Takemoto[9] and Jacobsen,[10] who employed thioureas as organocatalysts.

Encouraged by these results, we explored the structure of the above organocatalysts and found that they contained a thiourea moiety and a neighboring tertiary amino group in their structure (Figure 1). We envisaged that the combination of oxazoline with thiourea may promote the asymmetric aza-Henry reaction, since the thiourea moiety can activate the nitroalkane to produce the corresponding nitronate, followed by deprotonation by the neighboring tertiary amino group (Scheme 1).[11] In addition, the oxazoline N is a much stronger base than a tertiary N due to the resonance effect of the neighboring O, which favors the deprotonation of the nitronate.

In this communication, we present a successful application of such new chiral bifunctional organocatalysts towards the enantioselective aza-Henry reaction. To the best of our knowledge, this is the first example of enantioselective organocatalytic Henry reaction catalyzed by oxazoline–thiourea bifunctional catalyst.

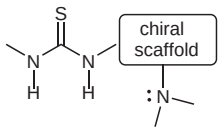
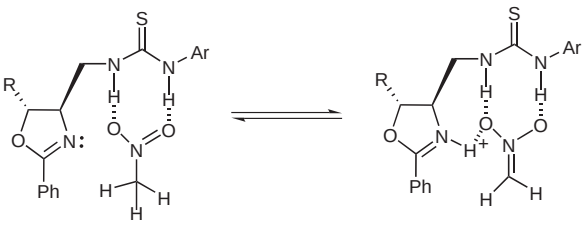
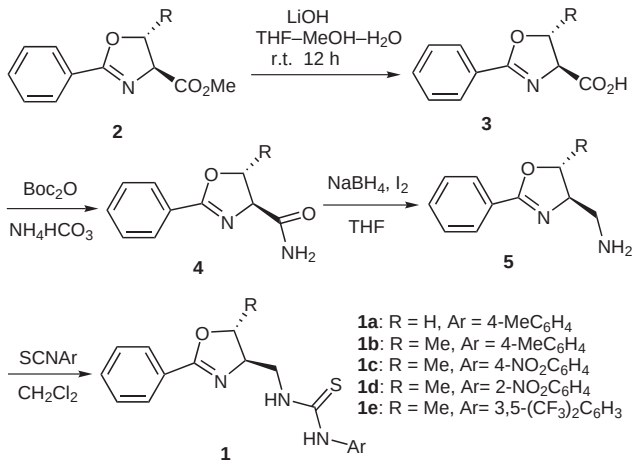


Figure 1



Scheme 1



Scheme 2

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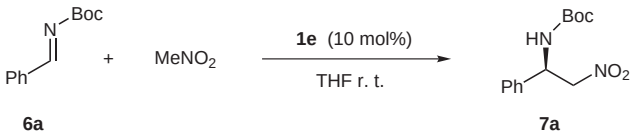
The desired organic catalysts were successfully synthesized according to Scheme 2. Initially, compound **2**[12] was hydrolyzed in the presence of lithium hydroxide to provide the carboxylic acid **3** in 96% yield. Compound **3** was then reacted with ammonium hydrogen carbonate in the presence of Boc_2O to afford **4** in 80% yield.[13] A subsequent reduction was performed using $NaBH_4$ and I_2 in THF to obtain compound **5** in 70% yield. The target compounds were easily generated through the reaction of compound **5** with different aryl isothiocyanates in 96–97% ee and 78–92% yield.

The organocatalysts were screened for their efficiency in the aza-Henry reaction (Table 1). The reaction between *N*-Boc phenyl imines and nitromethane was carried out in THF at room temperature in the presence of 10 mol% of the catalyst. It was found that catalysts **1a** and **1b** exhibited poor activity (Table 1, entries 1 and 2). In contrast, compounds **1c**–**e** afforded promising results (entries 3–5). Under the same reaction conditions, catalyst **1e** gave the corresponding adduct in high enantioselectivity (88% ee). It was noted that the substituent of the isothiocyanate part played an important role in the catalytic process. All reactions were completed in 48 hours at room temperature. Further investigation on catalyst **1e** in different solvents such as DMF, methanol, and chloroform revealed that more polar solvents gave lower product enantioselectivity. This finding suggested a destruction of hydrogen-bonding interactions between the thiourea and the nitro group in the substrate in strongly H-bonding-acceptor solvents. Similar reaction runs in nitromethane, toluene, and dichloromethane essentially gave no better enantioselectivity. It was also noted that lowering the temperature did not provide higher enantioselectivity (Table 1, entry 12).

With optimized reaction conditions in hand, the scope of the reaction was explored (Table 2). The aza-Henry reaction of nitromethane with a variety of *N*-Boc aryl imines was probed.[14] The results showed that, in general, the reactions took place efficiently (68–97% yield) with high levels of enantioselectivity (73–92% ee) for *N*-Boc phenyl imines bearing either electron-donating or electron-withdrawing substituents. In order to examine the diastereoselectivity of this reaction, we investigated the reaction of other nucleophiles such as 1-nitropropane and nitroethane with *N*-Boc phenyl imines. Interestingly, under the same reaction conditions, the reactions proceeded smoothly to afford the corresponding products **7j** in 2.5:1 dr and 87% ee and **7k** in 3.2:1 dr and 90% ee, respectively (Table 2, entries 11 and 12). There was no observable effect of the substituted groups on nitroalkanes on the efficiency of the aza-Henry reactions.

In summary, we have developed a new class of bifunctional oxazoline–thioureas **1**, which serve as efficient organocatalysts for the asymmetric aza-Henry reaction of nitromethane to *N*-Boc phenyl imines. To the best of our knowledge, this is the first example of a highly enantioselective aza-Henry reaction catalyzed by oxazoline–thiourea organocatalysts. We believe this kind of organocatalyst constitutes an important step towards the design of new catalysts in this field. Further investigations aimed at the understanding of the mechanism and scopes of this reaction are currently under way.

Table 1 Aza-Henry Reaction Catalyzed by Bifunctional Organocatalysts[a]



6a **7a**

Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	THF	48	89	44
2	**1b**	THF	48	92	38
3	**1c**	THF	48	86	70
4	**1d**	THF	48	90	82
5	**1e**	THF	48	93	88
6	**1e**	DMF	12	86	14
7	**1e**	MeOH	48	64	31
8	**1e**	$CHCl_3$	12	80	10
9	**1e**	$MeNO_2$	12	90	5
10	**1e**	CH_2Cl_2	12	83	9
11	**1e**	Toluene	12	88	4
12	**1e**	THF[d]	48	72	89
13	**1e**	THF[e]	48	80	87

[a] Reactions were carried out with **6a** (1 mmol), $MeNO_2$ (10 mmol), and catalyst (0.1 mmol) in 2 mL of solvent.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] Reactions were performed at 0 °C.
[e] Amount of catalyst was 5 mol%.

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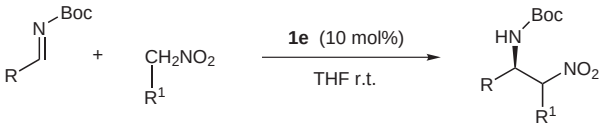
Table 2 Aza-Henry Reaction of *N*-Boc Imines with Nitroalkanes Catalyzed by Bifunctional Organocatalyst[a]



6a–k **7a–k**

Entry	Substrate	R	R^1	Time (h)	Yield (%)[b]	ee[c] (%, dr)[d]
1	**6a**	Ph	H	48	93	88
2	**6b**	2-MeC_6H_4	H	48	84	90
3	**6c**	4-MeC_6H_4	H	48	93	74
4	**6c**	4-MeC_6H_4	H	63	94	73
5	**6d**	3-$MeOC_6H_4$	H	48	86	78
6	**6e**	4-$MeOC_6H_4$	H	48	92	88
7	**6f**	4-ClC_6H_4	H	48	95	92
8	**6g**	4-$F_3CC_6H_4$	H	48	97	83
9	**6h**	3-$NO_2C_6H_4$	H	48	75	89
10	**6i**	4-$NO_2C_6H_4$	H	48	68	80
11	**6j**	Ph	Me	48	94	87 (2.5:1[d])
12	**6k**	Ph	Et	48	93	90 (3.2:1[d])

[a] Reactions were carried out with **6a–k** (1 mmol), $MeNO_2$ (10 mmol), and **1e** (0.1 mmol) in 2 mL of THF at r.t.
[b] Isolated yield.
[c] The ee was determined by HPLC.
[d] The dr was determined by ^1H NMR.

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(14) **Representative Procedure**
To a stirred solution of *N*-Boc phenyl imines (1 mmol) and the catalyst (0.1 mmol) in THF (2 mL) was added $MeNO_2$ (10 mmol), and the mixture was stirred for 24 h at r.t. Then the reaction mixture was condensed under reduced pressure, and the obtained residue was purified by column chromatography on silica gel to afford desired product **6a** (93% yield).