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PII: S0040-4039(14)00782-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.05.006
Reference: TETL 44596

To appear in: *Tetrahedron Letters*

Received Date: 14 March 2014
Revised Date: 29 April 2014
Accepted Date: 5 May 2014

Please cite this article as: Yu, L., Li, P., New simple primary amine-thiourea organocatalysts and their application in asymmetric conjugate addition, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.05.006

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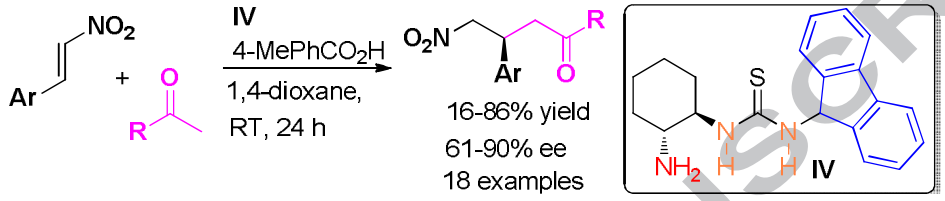

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New simple primary amine-thiourea organocatalysts and their application in asymmetric conjugate addition

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Organocatalysis
Conjugate addition
Primary amine
thiourea
nitroalkene

ABSTRACT

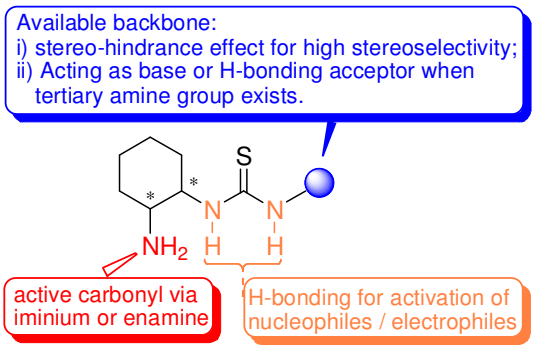
A kind of simple primary amine-thiourea organocatalysts was developed. And their application in asymmetric conjugate addition of ketone to nitroalkene was investigated. In the presence of the new primary amine-thiourea, the conjugate addition of ketone to nitroalkene proceeded smoothly to afford the 1,4-adducts in high yields with good enantioselectivities.

Asymmetric organocatalysis has emerged as an alternative and/or complementary approach to currently developed organometallic and enzymatic catalysis, which offers an efficient access to highly enantioenriched natural products, chiral drugs, building-blocks, and interesting molecules.[1] Since pioneering examples from Jacobsen,[2] Schreiner[3] and Takemoto,[4] employing thiourea derivatives as catalyst has become a subject of considerable interest in asymmetric organocatalysis.[5]

We have successfully developed a new type of multifunctional organocatalysts consisting of 1,2-diaminocyclohexane and 9-amino(9-deoxy)epicinchona alkaloid for the enantioselective Michael addition of α,β-unsaturated ketone.[6] This type of primary amine-thioureas provides multifunctional groups: a primary amine activating and arranging α,β-unsaturated ketone via iminium ion, and tertiary amine and thiourea helping to active and arrange the nucleophile via hydrogen bond. These functional groups exhibit synergistic cooperation and affect organic reaction, which was confirmed by the results with excellent yields and enantioselectivities.

As a result of the demonstrated potential of thiourea as attractive organocatalyst, many research groups focus their interest on developing new thiourea as organocatalyst and its application in the useful asymmetric transformation. However, most of these amine-thioureas contain three or more than three stereocenters, which caused some difficulties in terms of optical purity and yield in the preparations of these complex structures.[7]

Therefore, we have a high motivation to develop a simple amine-thiourea as organocatalyst to affect the reaction with excellent efficiency and asymmetric induction.



Scheme 1. General structure of new primary amine-thiourea

Here, we describe a new primary amine-thiourea organocatalyst consisting of chiral 1,2-diaminocyclohexane and available achiral backbone (Scheme 1). The primary amine is expected to activate carbonyl compound (enone, enal, ketone, aldehyde, et al.) via iminium ion or enamine formed *in situ*. And the hydrogen of thiourea is expected to activate nucleophile / electrophile via hydrogen bonding. The available backbone provides sterically hindered interaction and helps to construct a chiral pocket. When a tertiary amine group exists on available

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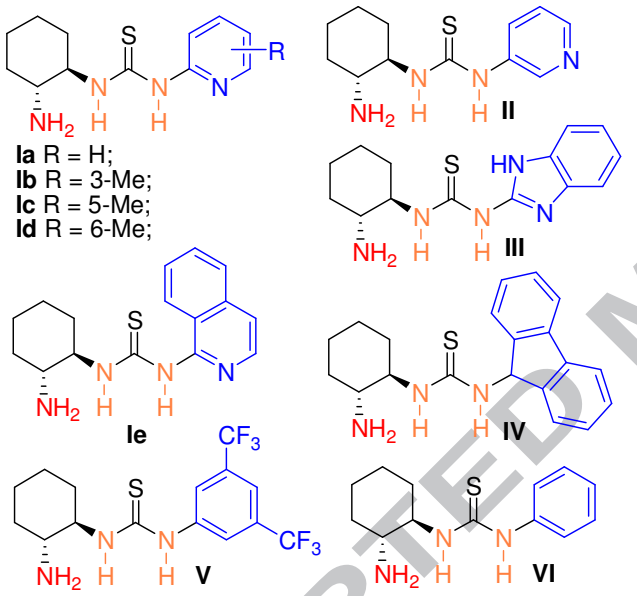
backbone, it can act as base to activate nucleophile or act as hydrogen acceptor to activate nucleophile / electrophile.

Based on our design of the primary amine-thiourea organocatalyst, a series of primary amine-thioureas are synthesized (Scheme 2). Compared with our former developed primary amine-thiourea organocatalyst,[6] the complex chiral cinchona alkaloid skeleton was replaced with simple achiral available backbones, such as pyridine ring (organocatalysts **Ia-d**, **II**), isoquinoline ring (organocatalyst **Ie**), 1*H*-benzoimidazole ring (organocatalyst **III**), 9*H*-fluorene ring (organocatalyst **IV**) and et al. There is a tertiary amine group on each of pyridine ring and isoquinoline ring, which can act as base and/or hydrogen bonding acceptor as well as providing stereo-hindrance effect. The 1*H*-benzoimidazole ring in catalyst III contains two nitrogen atoms, which may offer the stronger basicity and hydrogen bonding interaction. The 9*H*-fluorene ring in catalyst IV has a bigger bulk, which could be better to shield a face of the intermediate formed from substrates and catalyst to construct chiral environment. For comparison, the reported efficient organocatalysts V and VI were also prepared.

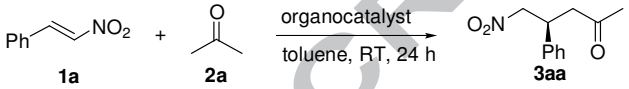


Scheme 2. Structures of new primary amine-thioureas

To evaluate the catalytic potential of the new primary-thiourea organocatalysts, the enantioselective conjugate addition of ketone to nitroalkene is chosen as a test reaction. The conjugate addition of ketone to nitroalkene offers an efficient access to γ-nitroketone, which is a valuable and diversified building block in organic synthesis and medicinal chemistry.[8-12] As a result, much effort has been devoted to the development of more efficient catalytic systems for this important transformation.[13]

Initial experiments were performed with the reaction between β-nitrostyrene **1a** and acetone **2a** in toluene to identify the most active organocatalyst. And the results were listed in Table 1. It was confirmed that the new primary amine-thiourea could successfully catalyze the conjugate addition of acetone to β-nitrostyrene. The primary amine-thioureas containing pyridine ring furnished adducts with quite different enantioselectivities. Both the size and position of substituent on pyridine ring affected the asymmetric induction obviously (Table 1, entries 1-4). Replacing pyridine ring with isoquinoline ring resulted in a slight higher ee value (Table 1, entry 5). An essential enhancement of enantioselectivity was achieved when the reaction was catalyzed by 3-aminopyridine derived the primary amine-thiourea **II** (Table 1, entry 6). Using the primary amine-thiourea **III** afforded 1,4-adduct with similar yield and ee value (Table 1, entry 7). To our delight, up to 73% ee and 11% yield were obtained in the presence of the primary amine-thiourea **IV** derived from 9*H*-fluoren-9-amine, which indicated that the new simple primary amine-thiourea was effective for the conjugate addition of ketone to nitroalkene (Table 1, entry 8). In contrast, the primary amine-thiourea **V** catalyzed conjugate addition of acetone to β-nitrostyrene furnished adduct in 45% yield with 65% ee under the same conditions (Table 1, entry 9). The primary amine-thiourea **VI** was found to hardly catalyze the conjugate addition and yield trace of the desired product (Table 1, entry 10).

Table 1. Identification of the organocatalyst [a]



Entry	Organocatalyst	Yield (%)[b]	ee (%)[c]
1	**Ia**	21	4
2	**Ib**	27	1
3	**Ic**	14	6
4	**Id**	16	-16
5	**Ie**	18	16
6	**II**	29	60
7	**III**	31	53
8	**IV**	11	73
9	**V**	45	65
10	**VI**	trace	N.D.[d]

[a] Unless noted, the reaction was carried out as following: The mixture of **1a** (0.5 mmol), **2a** (2.5 mmol) and organocatalyst (15 mol%) was stirred in toluene (0.5 mL) for 24 h.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (Chiralpak AS-H, *n*-hexane/2-propanol = 70/30).

[d] N.D. = Not determined.

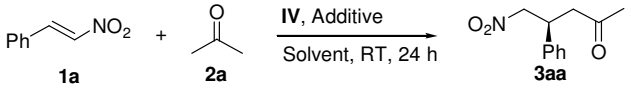
With the promising organocatalyst **IV** in hand, optimization of reaction conditions was then investigated. An overview of the representative results is summarized in Table 2.

After careful screening of solvent, it was found that reaction media affected the conjugate addition severely, especially in terms of reaction rate. The conjugate addition proceeded hardly in CH_2Cl_2, MeCN, THF, Et_2O, *t*-BuOMe, respectively (Table 2, entries 2-6). The reaction in EtOAc furnished **3aa** in 8% yield with 60% ee (Table 2, entry 7). Using 1,2-dimethoxyethane as solvent resulted in 25% yield and 60% ee (Table 2, entry 8). 1,4-Dioxane was found to be more suitable for this transformation to afford **3aa** in 36% yield with 71% ee (Table 2, entry 9).

A survey of additives revealed that they play an important role in governing reaction yields and have a small effect on the enantioselectivities. Remarkable enhancements of yield were achieved when different acidic additive was added to the reaction system, respectively. In the presence of catalyst **IV** combined with benzoic acid, adduct **3aa** was obtained in 80% yield with 75% ee (Table 2, entry 10). Notably, **IV**/4-methylbenzoic acid catalytic system furnished adduct **3aa** in up to 86% yield with

75% ee (Table 2, entry 12). The use of 2-methoxybenzoic acid as additive also afforded satisfactory results, 85% yield and 72% ee (Table 2, entry 13). Both 2-nitrobenzoic acid and 4-nitrobenzoic acid were found to affect the yield slightly (Table 2, entries 16-17). The chiral acidic additives were also investigated and moderate yields were obtained (Table 2, entries 20-21). It should be noted that all the probed acidic additives affected asymmetric induction slightly and the ee values vibrated around the level of 75%.

Table 2. Optimization of reaction conditions [a]



Entry	Solvent	Additive	Yield (%)[b]	ee (%)[c]
1	toluene	-	11	73
2	CH_2Cl_2	-	trace	N.D.[d]
3	MeCN	-	trace	N.D.
4	THF	-	trace	N.D.
5	Et_2O	-	trace	N.D.
6	*t*-BuOMe	-	trace	N.D.
7	EtOAc	-	8	60
8	$(CH_2OMe)_2$	-	25	60
9	1,4-dioxane	-	36	71
10	1,4-dioxane	$PhCO_2H$	80	75
11	1,4-dioxane	2-$MePhCO_2H$	77	74
12	1,4-dioxane	4-$MePhCO_2H$	86	75
13	1,4-dioxane	2-$MeOPhCO_2H$	85	72
14	1,4-dioxane	4-$MeOPhCO_2H$	81	73
15	1,4-dioxane	4-$FPhCO_2H$	67	76
16	1,4-dioxane	2-NO_2PhCO_2H	35	79
17	1,4-dioxane	4-NO_2PhCO_2H	34	77
18	1,4-dioxane	1-naphthoic acid	64	76
19	1,4-dioxane	2-naphthoic acid	68	78
20	1,4-dioxane	(*R*)-PhCH(OH)CO_2H	52	77
21	1,4-dioxane	*L*-*N*-Boc-tyrosine	58	75

[a] Unless noted, the reaction was carried out as following: The mixture of **1a** (0.5 mmol), **2a** (2.5 mmol), **IV** (15 mol%) and additive (15 mol%) was stirred in the solvent (0.5 mL) for 24 h.

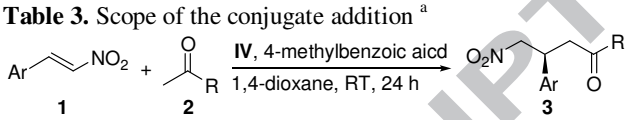
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (Chiralpak AS-H, *n*-hexane/2-propanol = 70/30).

[d] N.D. = Not determined.

To further test the effectiveness of the **IV**/4-methylbenzoic acid system, the conjugate additions of acetone to a series of nitroalkenes were examined (Table 3). In the presence of primary amine-thiourea **IV** together with 4-methylbenzoic acid, adducts **3** were isolated in moderate to good yield with 61-78% ee from the reactions between nitroalkenes and acetone. One exception was 2-methoxynitrostyrene, which was found to react slowly with acetone to afford adduct **3ea** in 38% yield with 80% ee (Table 3, entry 5). Both electron-withdrawing (F, Cl, Br, NO_2, CF_3) and eletron-donating substituents (Me, MeO) can be introduced on the aromatic ring with a small effect on the yield and asymmetric induction of the conjugate addition (Table 3, entries 2-16). Particularly, the heteroaromatic nitroalkene (**1q**) could also be successfully employed under these reaction conditions to afford addust **3qa** in 72% yield with 77% ee (Table 3, entry 17). The conjugate addition between β-nitrostyrene (**1a**) and acetophenone (**2b**) was also surveyed and adduct **3ab** with about 90% ee was obtained in 16% yield (Table 3, entry 18).

Table 3. Scope of the conjugate addition [a]



Entry	Ar	R	Adduct	Yield (%)[b]	ee (%)[c]
1	Ph	Me	**3aa**	86	75
2	2-FPh	Me	**3ba**	80	73
3	2-ClPh	Me	**3ca**	57	74
4	2-NO_2Ph	Me	**3da**	74	61
5	2-MeOPh	Me	**3ea**	38	80
6	2,3-$(MeO)_2$Ph	Me	**3fa**	70	73
7	3-BrPh	Me	**3ga**	60	67
8	3-NO_2Ph	Me	**3ha**	51	63
9	3-MePh	Me	**3ia**	54	70
10	3-MeOPh	Me	**3ja**	57	72
11	4-FPh	Me	**3ka**	56	74
12	4-ClPh	Me	**3la**	76	71
13	4-BrPh	Me	**3ma**	64	71
14	4-CF_3Ph	Me	**3na**	58	67
15	4-MePh	Me	**3oa**	68	77
16	4-MeOPh	Me	**3pa**	59	78
17	2-thienyl	Me	**3qa**	72	77
18	Ph	Ph	**3ab**	16	90

[a] Unless noted, the reaction was carried out as following: The mixture of **1** (0.5 mmol), **2** (2.5 mmol), **IV** (15 mol%) and 4-methylbenzoic acid (15 mol%) was stirred in 1,4-dioxane (0.5 mL) for 24 h.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (see Supporting Information).

The absolute configuration of **IV**-catalytic conjugate addition adduct 5-nitro-4-phenylpentan-2-one was *S*, which was determined by comparison of the chiral HPLC analysis method according to the literature.[7]

In conclusion, we have developed a new simple primary amine-thiourea derived from chiral 1,2-diaminocyclohexane and achiral available backbone. And we have successfully extended the new organocatalyst to catalyze asymmetric conjugate addition of ketone to nitroalkene with good to high yields and asymmetric induction. Further efforts on the application of the primary amine-thiourea organocatalyst to other valuable transformation are under active investigation.

Acknowledgments

We gratefully thank the Startup Fund from South University of Science and Technology of China (SUSTC) and National

Natural Science Foundation of China (NSFC 21302089) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://

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