Tetrahedron Letters 51 (2010) 2803–2805

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly asymmetric Michael additions of α,α-disubstituted aldehydes to β-nitroalkenes promoted by chiral pyrrolidine–thiourea bifunctional catalysts

Jian-Fei Bai [a,b], Xiao-Ying Xu [a], Qing-Chun Huang [a], Lin Peng [a,b], Li-Xin Wang [a,*]

[a] Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China
[b] Graduate School of Chinese Academy of Sciences, Beijing 100039, PR China

ARTICLE INFO

Article history:
Received 31 December 2009
Revised 9 March 2010
Accepted 12 March 2010
Available online 15 March 2010

ABSTRACT

A series of secondary amine–thiourea catalysts derived from L-proline and chiral diamine were prepared and first applied to the Michael addition of α,α-disubstituted aldehydes to *trans*-β-nitroalkenes. Moderate yields (47–75%) and excellent enantioselectivities (up to 96% ee) were obtained for a variety of aryl and heteroaryl nitroalkenes.

Asymmetric organocatalysis has become a powerful tool for the preparation of optically active compounds recently.[1,2] The Michael reaction is one of the most efficient carbon–carbon bond formation reactions in organic chemistry, much recent attentions have focused on this organocatalytic reaction.[3] Many methods have been developed for the direct asymmetric Michael addition of unmodified aldehydes and ketones with nitroalkenes to produce enantiomerically enriched nitroalkanes.[4] There has been only a few reports on the use of α,α-disubstituted aldehydes as donors for asymmetric Michael reactions.[5]

Bifunctional activations, which simultaneously activate both acceptors and donors, have recently emerged as an important strategy in asymmetric small molecular catalysis. Generally, thiourea-based catalysts have been widely used due to their strong activation of carbonyl and nitro groups through efficient double-hydrogen-bonding interactions.[6] Secondary amine, typically represented by L-proline and its structural analogues, is a powerful tool to activate aldehydes and ketones via enamine or imine transition state.[7,8] The secondary amine–thiourea catalysts **1a**-**1d** synergistically combining chiral thiourea and chiral pyrrolidine with two catalytic sites of chiral thiourea and L-prolic amide skeleton have not drawn enough attentions except one analogous catalyst applied to catalyze the aldol reaction of acetophenone with aldehyde in very low enantioselectivity.[9] We expected that these bifunctional catalysts could be used to catalyze the asymmetric Michael addition, and the reactivity and enantioselectivity may be enhanced by double activation, mutual stereo-compatibility, and chiral recognition.

As a part of our everlasting interests in asymmetric synthesis,[10] herein we wish to report the first example of asymmetric conjugate addition of α,α-disubstituted aldehyde to *trans*-β-nitroalkenes promoted by these chiral thiourea–secondary amine bifunctional catalysts. The strategies of the catalysts are illustrated in Figure 1.

Chiral catalysts **1a–d** were prepared via simple procedures.[9] The direct Michael reaction of isobutyraldehyde with *trans*-β-nitrostyrene was used as a model case to determine the asymmetric reaction conditions and the results are summarized in Table 1. Moderate to excellent enantioselectivities (55–91% ee) and moderate yields

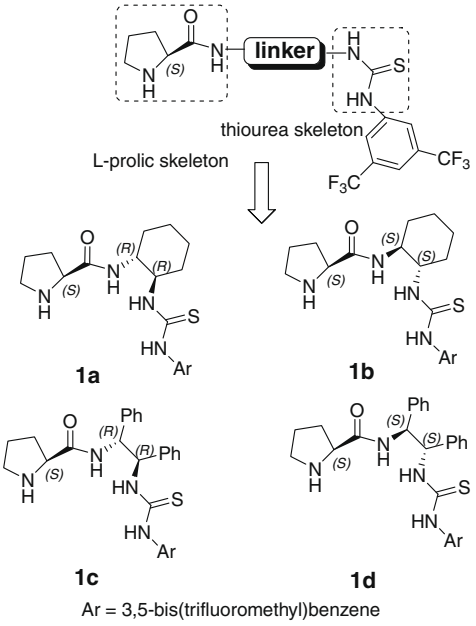

Figure 1. Secondary amine–thiourea catalysts.

* Corresponding author. Tel./fax: +86 28 85255208.
E-mail address: wlxioc@cioc.ac.cn (L.-X. Wang).

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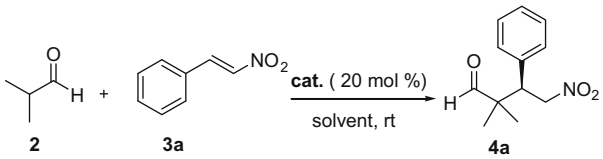
doi:10.1016/j.tetlet.2010.03.039

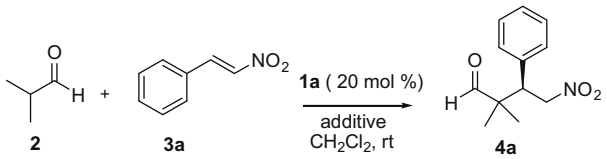
Table 1
Addition of isobutyraldehyde to *trans*-β-nitrostyrene catalyzed by thiourea **1a–d**[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**1a**	CH_2Cl_2	48	55	91
2	**1b**	CH_2Cl_2	48	43	69
3	**1c**	CH_2Cl_2	48	49	89
4	**1d**	CH_2Cl_2	48	49	55
5	**1a**	Et_2O	72	46	86
6	**1a**	$CHCl_3$	72	41	79
7	**1a**	Cyclohexane	72	50	86
8	**1a**	*n*-Hexane	72	49	77
9	**1a**	Xylene	72	49	88
10	**1a**	THF	72	45	77
11	**1a**	MeOH	72	43	13
12	**1a**	DMF	72	47	−0.9
13	**1a**	DMSO	72	38	−65
14	**1a**	CH_3CN	72	n.d.	n.d
15	**1a**	H_2O	72	n.d.	n.d.

[a] Unless otherwise specified, all reactions were carried out with isobutyraldehyde (**2**, 0.40 mmol), *trans*-β-nitrostyrene (**3a**, 0.20 mmol), and the catalyst (0.04 mmol) in the specified solvent (0.5 mL) at room temperature.
[b] Isolated yield after column chromatography.
[c] ee values were determined by HPLC with a Chiralpak-OD column.
[d] The absolute configuration of the product was determined as R by comparing with reported data.[5a]

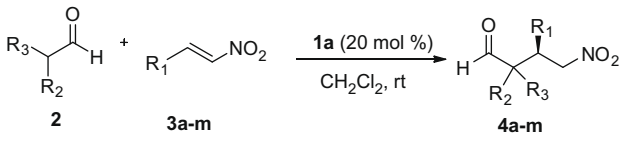
Table 2
Effect of additives on the reaction[a]



Entry	Additive	Time (h)	Yield[b] (%)	ee (%)
1	—	72	58	91
2	PhCOOH	72	50	82
3	AcOH	72	55	89
4	CF_3COOH	72	49	82
5	DIPEA	72	61	57
6	TEA	72	43	81
7	DMAP	72	52	80
8	DABCO	72	41	81

[a] Reactions were carried out with isobutyraldehyde (**2**, 0.40 mmol), nitrostyrene (**3a**, 0.20 mmol), additive (0.04 mmol, 20 mol %), and the catalyst (**1a,** 0.04 mmol) in CH_2Cl_2 (0.5 mL) at rt.
[b] Isolated yields.

Table 3
Asymmetric Michael addition of aldehyde to β-nitrostyrenes[a]



Entry	R_2	R_3	R_1	Prodcut	Yield[b] (%)	ee[c,d] (%)
1	CH_3	CH_3	C_6H_5 **3a**	**4a**	58	91
2	CH_3	CH_3	4-FC_6H_4 **3b**	**4b**	58	77
3	CH_3	CH_3	4-ClC_6H_4 **3c**	**4c**	51	86
4	CH_3	CH_3	4-BrC_6H_4 **3d**	**4d**	52	91
5	CH_3	CH_3	4-$NO_2C_6H_4$ **3e**	**4e**	47	90
6	CH_3	CH_3	4-$CH_3C_6H_4$ **3f**	**4f**	49	77
7	CH_3	CH_3	4-$CH_3OC_6H_4$ **3g**	**4g**	56	85
8	CH_3	CH_3	2-ClC_6H_4 **3h**	**4h**	75	91
9	CH_3	CH_3	3-$NO_2C_6H_4$ **3i**	**4i**	68	82
10	CH_3	CH_3	3-$CH_3C_6H_4$ **3j**	**4j**	55	86
11	CH_3	CH_3	2-Thienyl **3k**	**4k**	57	86
12	CH_3	CH_3	2-Furyl **3l**	**4l**	71	74
13	CH_3	CH_3	2-Naphthyl **3m**	**4m**	60	96
14	$CH_2(CH_2)_3CH_2$		C_6H_5 **3n**	**4n**	51	80

[a] Reactions were carried out with aldehyde (**2**, 0.40 mmol), nitroalkenes (**3a**, 0.20 mmol), and the catalyst (0.04 mmol) in CH_2Cl_2 (0.5 mL) at rt for 72 h.
[b] Isolated yields.
[c] ee values were determined via HPLC with a Chiralpak-OD column.
[d] The absolute configuration of the product was determined as R by comparing with reported data.[5]

(49–55%) were achieved catalyzed by **1a–d** (Table 1, entries 1–4) in CH_2Cl_2 at room temperature. The enantioselectivity seems to be controlled by the chiral linker unit and the compatibility of the two catalytic chiral centers. The incompatible chiral centers in **1b** and **1d** exert no synergic effects on the enantioselectivities. Catalyst **1a** afforded a higher enantioselectivity compared with **1b** and **1d** (Table 1, entries 1 vs 2–4).

A range of solvents was screened for the addition of isobutyraldehyde to *trans*-β-nitrostyrene catalyzed by **1a**. The yields and enantioselectivities were highly variable in different solvents. Polar solvents such as CH_3OH, DMF, and DMSO showed negative effects on the yields and enantioselectivities (Table 1, entries 11–13). Particularly, when the reaction was carried out in CH_3CN and H_2O, no desired products were observed (Table 1, entries 14, 15). Less polar solvents such as CH_2Cl_2 and Et_2O gave moderate yields and good enantioselectivities (Table 1, entries 1, 5). These results indicated that CH_2Cl_2 is a suitable candidate solvent for this reaction (Table 1, entry 1).

To improve the reaction rate, a series of acid and base additives were also investigated and the results are listed in Table 2. However, no significant improvement in the results was observed. Through extensive screening, the optimized reaction conditions were found to be 20 mol % of catalyst **1a** and CH_2Cl_2 as solvent at room temperature.

Under the optimized conditions, we also studied the generality of this catalytic system with a variety of *trans*-β-nitroalkenes and the results are listed in Table 3, and all the substituted β-nitrostyrenes bearing either electron-donating substituents or electron-withdrawing substituents on the aromatic ring gave the desired Michael adducts in acceptable yields (47–75%) and high enantioselectivities (up to 96% ee). More significantly, all the substituents in *para*- (Table 3, entries 2-7), *ortho*- (Table 3, entry 8) and *meta*-position (Table 3, entries 9 and 10) gave moderate yields and good enantioselectivities.

Further extending the optimized protocol to heteroaromatic nitroalkenes such as 2-furanyl-nitroethene and 2-thienyl-nitroethene, all the substrates gave good yields and enantioselectivities (Table 3, entries 11 and 12). Significantly, 1-naphthyl-nitroethene provided the highest enantioselectivity and acceptable yield (96% ee, 60% yield; Table 3, entry 13). Cyclohexanecarbaldehyde was also investigated and gave moderate yield (51%) and good enantioselectivity (81% ee, Table 3, entry 14).

Based on the observed reactivity and experimental results, we suggested a plausible bifunctional catalytic mechanism involving hydrogen binding and enamine formation as shown in Figure 2. A joint experimental-theoretical study showed that only one oxygen atom of the nitro group was bonded to the thiourea moiety,[11] which could enhance the electrophilic property of nitroolefin. The basic pyrrolidine group reacts with isobutyraldehyde to form an activated enamine intermediate.

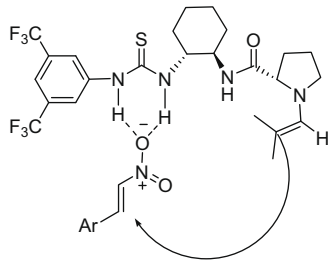


Figure 2. Proposed transition state model.

In conclusion, we first successfully applied the secondary amine–thiourea bifunctional catalysts with two catalytic sites of chiral thiourea and L-prolic amide skeleton to catalyze the Michael addition of isobutyraldehyde to nitroalkenes with good yields (up to 75%) and excellent enantioselectivities (up to 96% ee) for a variety of aryl and heteroaryl nitroalkenes. Further studies of the newly developed catalyst model and related catalysts in other catalytic reactions are currently underway.

Acknowledgments

We are grateful for the financial support from National Natural Science Foundation of China (20802075) and the Chinese Academy of Sciences.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.039.

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