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Highly Enantioselective Synthesis of γ-Nitro Heteroaromatic Ketones in a Doubly Stereocontrolled Manner Catalyzed by Bifunctional Thiourea Catalysts Based on Dehydroabietic Amine: A Doubly Stereocontrolled Approach to Pyrrolidine Carboxylic Acids

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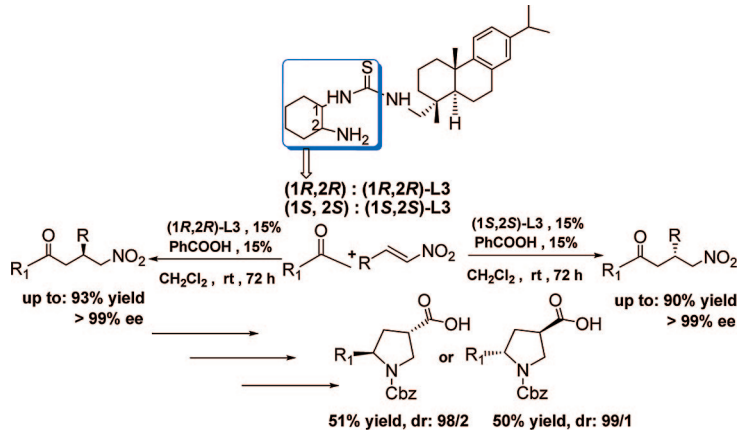
ABSTRACT



A new class of dehydroabietic amine-substituted primary amine-thiourea bifunctional catalysts were designed and synthesized. The doubly stereocontrolled organocatalytic conjugate addition of a variety of heterocycles-bearing ketones to nitroalkenes was investigated for the first time, affording (*S*)- or (*R*)-γ-nitro heteroaromatic ketones with excellent enantioselectivities (up to ee >99%). Furthermore, the nearly optically pure γ-nitro heteroaromatic ketones can be readily transformed into chiral pyrrolidine carboxylic acids.

From a synthetic perspective, both enantiomers of a chiral compound are often useful and versatile in organic synthesis and in the pharmaceutical industry. However, the doubly stereocontrolled synthesis of chiral organic molecules is a challenging task,[1,2] and to the best of our knowledge, effective metal-free organocatalytic methods using a double asymmetric induction have rarely been reported to date. Thus,

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developing an effective organocatalytic method is a highly desirable goal. In the past few years, a series of thiourea-based catalysts have been designed, synthesized, and used to effectively catalyze various types of asymmetric reactions.[3,4] Great progress has been achieved in this field as a result of seminal contributions from the groups of Jacobsen,[5] Takemoto,[6] Connon,[7] Wang,[8] and Deng.[9] Nevertheless, the potential application of these thiourea catalysts in doubly stereocontrolled asymmetric reactions remains a much less developed field, and there is still great demand for novel bifunctional thiourea catalysts for this purpose. We first report herein a new class of dehydroabietic amine-substituted primary amine-thiourea bifunctional catalysts and their application in a highly enantioselective and doubly stereocontrolled synthesis of (*S*)- or (*R*)-γ-nitro heteroaromatic ketones with excellent enantioselectivities.[10,11] Our attention was especially drawn to γ-nitro heteroaromatic ketones because they could be readily converted to chiral pyrrolidine carboxylic acids. In particular, β^2-pyrrolidine carboxylic acids are important building blocks in the synthesis of β-peptides, bioactive molecules, and pharmaceuticals or are of other potential biomedical utilities.[12]

Inspired by the excellent structural backbone and well-defined stereocenters of dehydroabietic amine, we designed and synthesized a new class of primary amine-thiourea bifunctional catalysts (1*S*,2*S*)-**L3** and (1*R*,2*R*)-**L3** (see Supporting Information). With these novel catalysts in hand, the effects of the thiourea catalysts were investigated in comparison with other thiourea catalysts. A model reaction of acetophenone to *trans*-β-nitrostyrene was performed in CH_2Cl_2 at room temperature in the presence of 15 mol % of thiourea catalysts (Table 1).

These results indicate that the stereochemical control of the reaction is mainly provided by the 1,2-diaminocyclohexane moiety of thiourea (switching the configuration of 1,2- diaminocyclohexane moiety from (*R*,*R*) to (*S*,*S*) exhibited an opposite sense of asymmetric induction) and that the catalytic activity depends mainly on the remaining chiral scaffold moiety of thiourea (the inherent property of stereochemical structure of the remaining chiral scaffold moiety of thiourea) and also on the suitable matching of the configuration of the 1,2-diaminocyclohexane moiety with the remaining chiral scaffold moiety. In addition, this remaining chiral amine moiety of thiourea also has an important effect on the stereoselectivity for the formation of adduct. These results also reveal that the catalytic activity increased in the order of **L3** > **L2** > **L1**, which corresponds to thiourea catalysts bearing a dehydroabietic amine scaffold, a saccharide scaffold, and a phenylethanamine scaffold. Although Ma's catalyst **L2**[13] with an (*R*,*R*)-1,2-diaminocyclohexane moiety can induce high enantioselectivity (97% ee, entry 3) and afford the (*S*)-adduct with a moderate yield of 60%, the catalytic activity of **L2** can be inhibited drastically when replacing the (*R*,*R*) configuration with an (*S*,*S*) configuration (in other words, the (*S*,*S*) configuration of the 1,2-diaminocyclohexane moiety could not match the β-D-glucopyranose scaffold of thiourea), resulting in relatively low enantioselectivity

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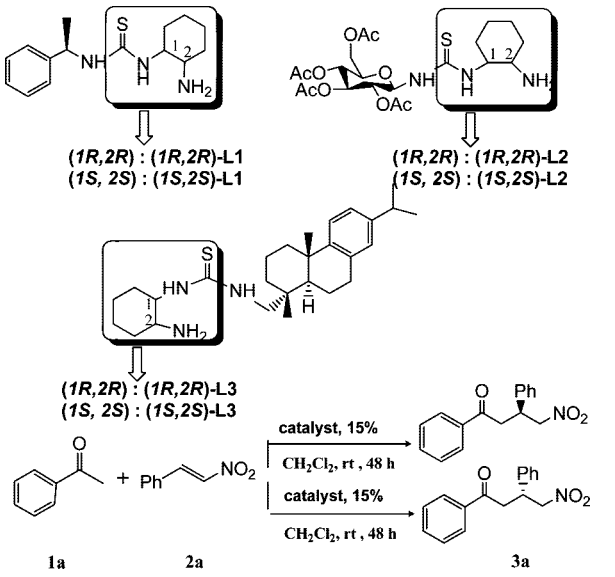
Table 1. Enantioselective Michael Addition of Acetophenone to *trans*-β-Nitrostyrene[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	(1*R*,2*R*)-**L1**	10	76 (*S*)
2	(1*S*,2*S*)-**L1**	6	72 (*R*)
3[d]	(1*R*,2*R*)-**L2**	60	97 (*S*)
4[d]	(1*S*,2*S*)-**L2**	46	87 (*R*)
5	(1*R*,2*R*)-**L3**	79	99 (*S*)
6	(1*S*,2*S*)-**L3**	78	98 (*R*)
7[e]	(1*R*,2*R*)-**L3**	96	>99 (*S*)
8[e]	(1*S*,2*S*)-**L3**	93	98 (*R*)

[a] The reaction was conducted with *trans*-β-nitrostyrene (0.2 mmol) and acetophenone (0.6 mmol). [b] Isolated yield. [c] The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data. [d] See ref 13. [e] PhCOOH (0.15 equiv) was added to the reaction for 72 h.

(87% ee, entry 4) and the (*R*)-adduct with a poor yield of 46%. In contrast, the (*R*,*R*) configuration of 1,2-diaminocyclohexane moiety or the (*S*,*S*) configuration can well-match the dehydroabietic amine scaffold of **L3** due to its excellent structural backbone and well-defined stereocenters, resulting in excellent enantioselectivities ((*S*)-adducts, 99% ee; (*R*)-adducts, 98% ee) and good yields ((*S*)-adducts, 79%; (*R*)-adducts, 78%; entries 5 and 6). It was realized that the two chiral moieties of thiourea are mutually reinforcing for the high efficacy of catalyst, and primary amine-thiourea **L3** is found to be the best one for the doubly stereocontrolled organocatalytic process. Gratifyingly, the addition of catalytic amounts of benzoic acid could lead to further improvement of the yield in CH_2Cl_2 (entries 7 and 8).

In addition, we attempted to decrease the loading of thiourea ligands (Table 2). To our surprise, the decrease of the loading of thiourea ligands did not affect the stereoselectivity of the doubly stereocontrolled catalytic conjugate addition, but a decrease in yield was observed (entries 1−6). To test the power of the thiourea ligands, we further lowered

Table 2. Enantioselective Michael Addition of Acetophenone to *trans*-β-Nitrostyrene with Lower Loading[a]

entry	catalyst	loading (%)	yield (%)[b]	ee (%)[c]
1	(1*R*,2*R*)-**L3**	10	82	99 (*S*)
2	(1*S*,2*S*)-**L3**	10	80	98 (*R*)
3	(1*R*,2*R*)-**L3**	5	68	98 (*S*)
4	(1*S*,2*S*)-**L3**	5	64	98 (*R*)
5	(1*R*,2*R*)-**L3**	1	58	98 (*S*)
6	(1*S*,2*S*)-**L3**	1	59	98 (*R*)
7	(1*R*,2*R*)-**L3**	0.5	42	97 (*S*)

[a] The reaction was conducted with *trans*-β-nitrostyrene (0.2 mmol), acetophenone (0.6 mmol), and PhCOOH (0.15 equiv) in CH_2Cl_2. [b] Isolated yield. [c] The ee values were determined by HPLC.

the loading of thiourea to 0.5 mol % and 97% ee was still obtained but with a low yield of 42% (entry 7).

Heterocycles are among the most common substructures found in organic active compounds. Although the asymmetric Michael reactions of simple ketones to nitroalkenes have been investigated intensely,[14] the reaction of heterocycles-bearing ketones has not been developed so far. Results of experiments under the optimized conditions that probe the scope of the reaction are summarized in Table 3. First, the doubly stereocontrolled catalytic conjugate addition of a variety of heterocycles-bearing ketones to nitroalkenes was examined considering their usefulness and versatility in organic synthesis (entries 1−11). All reactions underwent clean reactions affording the desired products of the (*S*) or (*R*) configuration with excellent enantioselectivities ((*S*)-adducts, 98−99% ee; (*R*)-adducts, 98−99% ee) and moderate to high yields. In view of the utility of γ-nitro heteroaromatic ketones in the synthesis of β^2-pyrrolidine carboxylic acids, the doubly stereocontrolled catalytic conjugate addition of a variety of ketones to furyl- and thienyl-substituted nitroalkenes was probed next (Table 3). As expected, the reaction proceeded not only with heterocycles-bearing and aromatic ketones but also with aliphatic ketones to give nearly optically pure (*S*)- or (*R*)-adducts with high to excellent yields (entries 12−21). The excellent performance of our doubly stereocontrolled catalytic system also encouraged us to check

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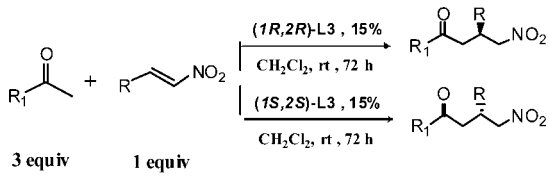
Table 3. Enantioselective and Double Sterecontrolled Synthesis of (*S*)- or (*R*)-γ-Nitro Heteroaromatic Ketones[a]



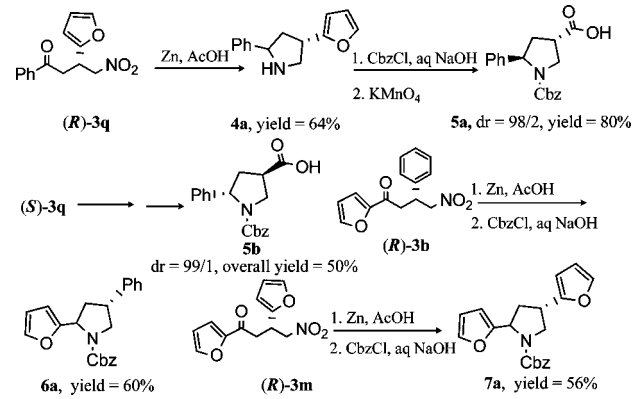
entry	adduct	R_1	R	yield (%)[b] (*S*/*R*)	ee (%)[c] (*S*/*R*)
1	**3b**	2-furyl	Ph	83/82	98/98
2	**3c**	2-furyl	4-FPh	85/82	98/98
3	**3d**	2-furyl	2-ClPh	81/84	>99/>99
4	**3e**	2-furyl	3-ClPh	85/83	>99/>99
5	**3f**	2-furyl	4-MeOPh	71/73	>99/98
6	**3g**	2-furyl	4-MePh	75/70	98/98
7	**3h**	2-furyl	2-MeOPh	72/71	>99/98
8	**3i**	5-methylfuryl	Ph	61/59	98/99
9	**3j**	2,5-dimethylfuryl	Ph	56/54	>99/98
10	**3k**	2-thienyl	Ph	68/66	>99/98
11	**3l**	2-thiazoleyl	Ph	57/55	>99/>99
12	**3m**	2-furyl	2-furyl	83/81	98/98
13	**3n**	2-furyl	2-thienyl	80/80	98/98
14	**3o**	5-methylfuryl	2-furyl	66/70	98/98
15	**3p**	2-thienyl	2-furyl	71/68	>99/>99
16[d]	**3q**	Ph	2-furyl	83/81	98/98
17	**3r**	4-ClPh	2-furyl	87/85	>99/98
18	**3s**	4-FPh	2-furyl	89/89	99/98
19	**3t**	3-BrPh	2-furyl	92/90	>99/98
20	**3u**	3-MePh	2-furyl	85/89	>99/98
21	**3v**	Me	2-furyl	93/85	96/95

[a] The reaction was conducted with nitroalkenes (0.2 mmol), ketones (0.6 mmol), and PhCOOH (0.15 equiv). [b] Isolated yield. [c] The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data. [d] The reaction was conducted with *trans*-2-(2-nitrovinyl)furan (5.0 mmol).

if it could suit multigramscale synthesis, and the catalytic conjugate addition of acetophenone to *trans*-2-(2-nitrovinyl)-furan (5 mmol) was conducted under the optimized conditions. In general, we obtained a satisfactory result, although the yield was slightly diminished (entry 16).

Conversion of the conjugate addition products to pyrrolidine carboxylic acids proved straightforward. As an illustration, the adduct (*R*)-**3q** was transformed into β^2-pyrrolidine carboxylic acid **5a** by means of a three-step procedure (Scheme 1). Adduct **3q** was caused to undergo reduction and cyclization to pyrrolidine **4a** with 64% yield, followed by protection with benzyl chloroformate and oxidation, which provided the Cbz-protected β^2-pyrrolidine carboxylic acid **5a** (dr = 98/2, 80% yield). In the same manner, starting from (*S*)-**3q**, **5b** was attained with an overall

Scheme 1. Synthesis of Chiral Pyrrolidine Derivatives and β^2-Pyrrolidine Carboxylic Acids



yield of 50% (Scheme 1). In the same way, we could attain **6a** (60% yield) and **7a** (56% yield), which correspond to (*R*)-**3b** and (*R*)-**3m** (Scheme 1). This representative example demonstrates the inherent synthetic potential of this methodology, our route being shorter and more convenient, which will be of immense benefit for biomedical utilities and industrial applications.

In conclusion, we have developed a new class of bifunctional primary amine-thiourea catalysts based on dehydroabietic amine, which has been successfully applied to the doubly stereocontrolled synthesis of γ-nitro heteroaromatic ketones. Furthermore, the adducts can be readily transformed into chiral pyrrolidine carboxylic acids, and the synthetic route is more convenient for practical use. Further investigation of the efficacy of these organocatalysts in other doubly stereocontrolled asymmetric reactions and mechanistic studies are ongoing in our laboratories.

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Supporting Information Available: Experimental details on the syntheses and analyses of the presented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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