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Direct Organocatalytic Asymmetric Aldol Reaction of α-Isothiocyanato Imides to α-Ketoesters under Low Ligand Loading: A Doubly Stereocontrolled Approach to Cyclic Thiocarbamates Bearing Chiral Quaternary Stereocenters†

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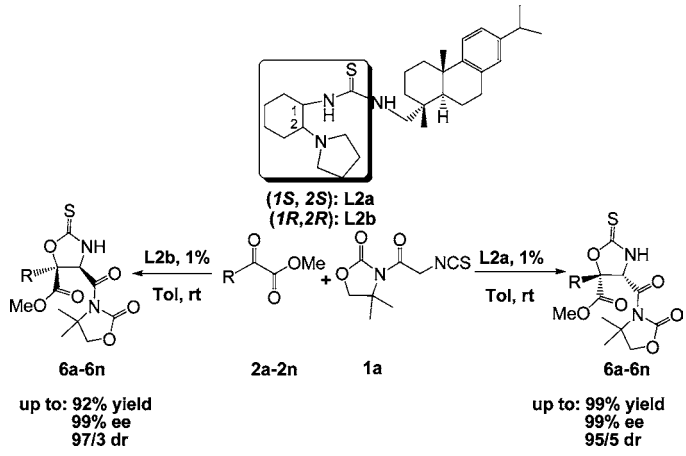
ABSTRACT



The first doubly stereocontrolled organocatalytic asymmetric aldol reaction of α-isothiocyanato imides with α-ketoesters by using rosin-derived tertiary amine-thiourea under low ligand loading to form cyclic thiocarbamates bearing quaternary stereogenic centers with high levels of enantio- and diastereoselectivity (up to 99% ee, and 97:3 dr) is presented. This reaction provides a convenient doubly stereocontrolled method to access synthetic useful multiply substituted cyclic thiocarbamates with high optical purity.

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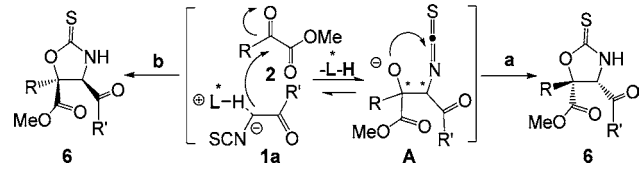
Cyclic thiocarbamates are important structural motifs in organic synthesis[1] and have been found as key structural elements commonly appearing in a series of biological assays that have shown potent biological and pharmaceutical activities, including fructose transport inhibition, antitumor, and clinically useful antibacterial activity.[2] Optically active cyclic thiocarbamates can not only be applied to the total synthesis of biologically and pharmaceutically active compounds or natural products,[3] but they can also be readily converted to valuable chiral β-hydroxy-α-amino acid,[4] therefore the development of highly efficient asymmetric synthetic methods to access these compounds is particularly appealing. To date, however, the asymmetric catalytic approaches to access chiral cyclic thiocarbamates are scarce,[4,5] and to our knowledge, only one report of their organocatalytic asymmetric synthesis via an intermolecular aldol reaction[6] of aldehyde electrophiles has been described.[5b] Thus, their organocatalytic chiral synthesis, especially of quaternary stereogenic centers, still remains challenging and elusive. Furthermore, an efficient catalytic method to access chiral cyclic thiocarbamates bearing quaternary stereogenic centers via a direct catalytic asymmetric intermolecular aldol reaction with α-ketoesters has not yet been established, and we believe this represents a considerable challenge.

During our recent efforts to develop rosin-derived amine thiourea catalyzed asymmetric addition reactions,[7,8] we have demonstrated that chiral tertiary amine-thiourea catalysts effectively furnish doubly stereocontrolled Michael reactions of 1,3-dicarbonyls with nitroalkenes,[8b] and aza-henry reactions with in situ generation of *N*-Boc imines.[8c] In view of the different or even opposite pharmaceutical activities for the individual enantiomers[9] and the challenging catalytic asymmetric construction of two contiguous stereogenetic centers containing an asymmetric quaternary carbon,[10] we hoped to build upon these chiral precedents bearing quaternary stereogenic centers in a doubly stereocontrolled manner via intermolecular aldol reaction of α-isothiocyanato imides[11] with α-ketoesters by using chiral tertiary amine-thiourea catalysts.

Scheme 1. Strategy for Doubly Stereocontrolled Synthesis of Chiral Cyclic Thiocarbamates by Chiral Tertiary Amines



We postulated that the asymmetric intermolecular aldol reaction of α-isothiocyanato imide **1a** to electron-deficient α-ketoesters might be initiated, in the presence of a chiral tertiary amine, by activating the acidic α-carbon atom of **1a** to generate intermediates **A**. Subsequent intramolecular cyclization reactions of intermediates **A** afforded cyclic thiocarbamates **6** (Scheme 1). Compared with simple ketones,

† Dedicated to Professor Albert S. C. Chan on the occasion of his 60th birthday.

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most of the α-ketoesters are too reactive, and background reactions always deteriorate the enantio- and diastereoselectivity under basic reaction conditions. Herein, we present the first doubly stereocontrolled organocatalytic asymmetric aldol reaction of α-isothiocyanato imides with α-ketoesters by using rosin-derived tertiary amine-thiourea under low ligand loading to form cyclic thiocarbamates bearing quaternary stereogenic centers with high levels of enantio- and diastereoselectivity (up to 99% ee, and 97:3 dr).

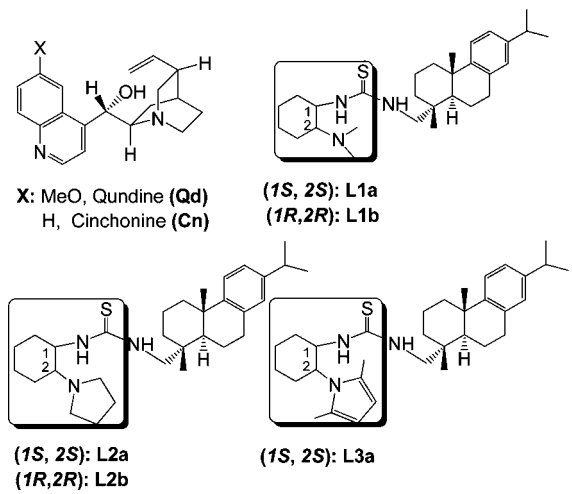
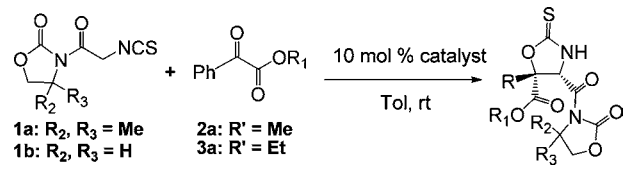


Figure 1. Organocatalysts Used in This Study

Our initial investigation began by screening tertiary amine organocatalysts (Figure 1) to evaluate their ability to promote the aldol reaction of α-isothiocyanato imide (**1a**) with α-ketoester (**2a**) in the presence of 10 mol % of ligand loading at room temperature in toluene (Table 1). Besides the chiral tertiary amine-thiourea catalysts **L1**−**L3**, naturally available quinidine (**Qd**) and cinchonine (**Cn**) were also tested. While the desirable product with good to excellent yields could be obtained in the presence of **Qd** or **Cn**, only moderate enantioselectivities (72% and 64% ee, entries 1 and 2) were observed in the reactions. Notably, tertiary amine-thiourea **L1** and **L2** gave the adducts with almost the same high yields and satisfactory diastereoselectivities, but **L2** furnished the products with slightly higher enantioselectivities (entries 3−6). In contrast, thiourea catalyst **L3** proved to be essentially inactive for this transformation (entry 7). Gratifyingly, we further lowered the loading of tertiary amine-thiourea **L2a** to 1.0 mol % and 96% ee and good diastereoselectivity was still obtained without a significantly decrease in yield (89% yield, and 80:20 dr, entry 11), and **L2b** also exhibited the superior catalytic activity with an opposite sense of asymmetric induction (90% yield, 94% ee, and 81:19 dr, entry 12). In addition, other substrates such as α-isothiocyanato imide (**1b**) and α-ketoester (**3a**) were also screened. Although those cases could provide the desirable adducts in high yields and enantioselectivities, poor diastereoselectivities were observed (entries 8 and 9).

Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]



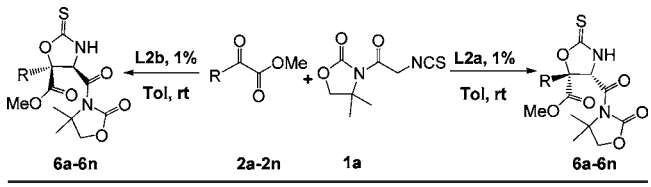
entry	catalyst	1	yield (%)[b]	dr[c]	ee (%)[d]
1	**Qd**	**1a**	(**6a**) 91	70:30	72
2	**Cn**	**1a**	(**6a**) 86	70:30	64
3	**L1a**	**1a**	(**6a**) 93	76:24	93
4	**L1b**	**1a**	(**6a**) 90	78:22	92
5	**L2a**	**1a**	(**6a**) 90	80:20	97
6	**L2b**	**1a**	(**6a**) 91	80:20	95
7	**L3a**	**1a**	trace	n.d.	n.d.
8	**L2a**	**1b**	(**4a**) 96	60:40	92
9[e]	**L2a**	**1a**	(**5a**) 82	65:35	89
10[f]	**L2a**	**1a**	(**6a**) 90	85:15	95
11[g]	**L2a**	**1a**	(**6a**) 89	80:20	96
12[g]	**L2b**	**1a**	(**6a**) 90	81:19	94

[a] Unless noted, the reaction was conducted with α-isothiocyanato imides (0.2 mmol) and **2a** (0.24 mmol) in Tol (1.0 mL) for 2 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The ee values were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **6e**. [e] The reaction was conducted with **3a** (0.24 mmol). [f] 5.0 mol % of ligand loading. [g] 1.0 mol % of ligand loading for 2.5 h.

Results of experiments under the optimized conditions that probe the scope of the reaction are summarized in Table 2. The doubly stereocontrolled catalytic aldol reaction of α-isothiocyanato imide (**1a**) with a variety of substituted α-ketoesters including those bearing electron-withdrawing and electron-donating substituents on the aryl ring, heterocyclic and aliphatic α-ketoesters under low ligand loading was examined. The results showed that all reactions with aromatic α-ketoesters underwent clean reactions affording the desired products that contain quaternary carbon centers (**L2a** afforded (4*S*,5*R*)-adducts, **L2b** afforded (4*R*,5*S*)-adducts) with good to excellent yields (78%−99% yields, entries 1−22) and high to excellent enantioselectivities (81%−99% ee, entries 1−22), and in all cases the *syn*-aldol adducts were obtained as the major diastereomer with selectivities of up to 97:3. Notably, the electron-withdrawing substituents at the ortho position provided more excellent diastereoselectivities (entries 15 and 16). As expected, heterocyclic and aliphatic α-ketoesters have also proven to be suitable substrates for this asymmetric process. Although the reactions afforded the *syn*-aldol adducts with low diastereoselectivities, high enantioselectivities and yields were still obtained (entries 23−25). The relative and absolute configurations of the products were determined by X-ray crystal structure analysis of **6e** (see the Supporting Information).

The proposed possible mechanism is shown in Figure 2. In light of the above results, we envisioned that the chiral

Table 2. Direct Catalytic Asymmetric Aldol Reactions of α-Isothiocyana to Imides to α-Ketoesters[a]



entry	R	ligand	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	**L2a**	(**6a**) 89	80:20	96
2	Ph	**L2b**	(**6a**) 90	81:19	94
3[e]	2-naphthyl	**L2a**	(**6b**) 79	88:12	97
4[e]	2-naphthyl	**L2b**	(**6b**) 78	90:10	96
5	4-FPh	**L2a**	(**6c**) 93	89:11	92
6	4-FPh	**L2b**	(**6c**) 88	90:10	90
7	4-ClPh	**L2a**	(**6d**) 92	80:20	98
8	4-ClPh	**L2b**	(**6d**) 91	83:17	92
9	4-BrPh	**L2a**	(**6e**) 81	90:10	95
10	4-BrPh	**L2b**	(**6e**) 84	85:15	98
11	3-BrPh	**L2a**	(**6f**) 82	86:14	96
12	3-BrPh	**L2b**	(**6f**) 83	85:15	93
13	3-ClPh	**L2a**	(**6g**) 88	85:15	99
14	3-ClPh	**L2b**	(**6g**) 87	90:10	96
15	2-ClPh	**L2a**	(**6h**) 99	95:05	81
16	2-BrPh	**L2a**	(**6i**) 92	97:03	85
17	4-MePh	**L2a**	(**6j**) 87	90:10	97
18	4-MePh	**L2b**	(**6j**) 85	88:12	97
19	3-MeOPh	**L2a**	(**6k**) 81	80:20	99
20	3-MeOPh	**L2b**	(**6k**) 86	83:17	99
21	3-MePh	**L2a**	(**6l**) 81	85:15	92
22	3-MePh	**L2b**	(**6l**) 80	87:13	93
23[f]	2-furyl	**L2a**	(**6m**) 82	75:25	86
24	Me	**L2a**	(**6n**) 92	72:28	84
25	Me	**L2b**	(**6n**) 90	70:30	83

[a] The reaction was conducted with α-isothiocyanato imides (0.2 mmol) and α-ketoesters (0.24 mmol) in Tol (1.0 mL) for 2.5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The ee values were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **6e**. [e] The reaction was stirred for 5 h. [f] 5.0 mol % of ligand loading.

tertiary amine-thiourea would act in a bifunctional fashion.[12] The electron-deficient α-ketoesters may be fixed and activated by the two thiourea hydrogen atoms through weak hydrogen bonds, alongside the acidic α-carbon atom of imides could be activated by an interaction between the tertiary amine moiety of the catalyst and α-isothiocyanato imides, directing the attack of the incoming nucleophiles on the α-ketoesters following a determined direction. Subsequent intramolecular cyclization reactions of intermediates afforded the chiral cyclic products.

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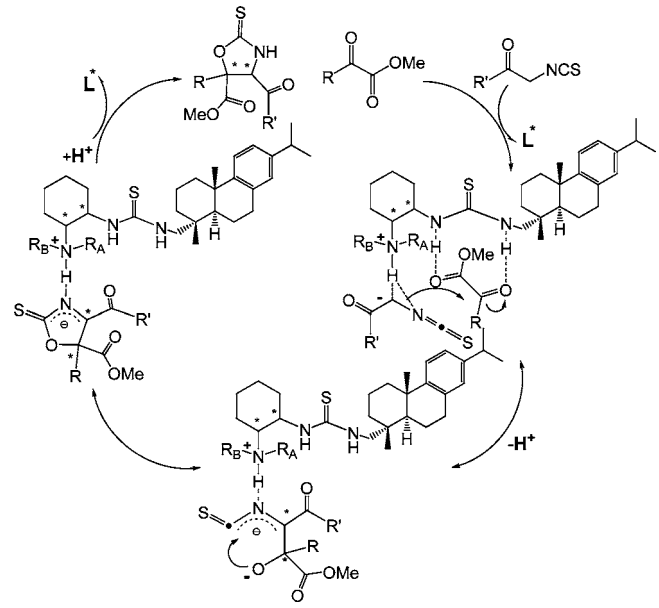

Figure 2. Proposed mechanism for the intermolecular Aldol reaction of α-isothiocyanato imides with α-ketoesters under the catalysis of a chiral tertiary amine-thiourea.

In conclusion, we have disclosed the first doubly stereocontrolled asymmetric intermolecular aldol reaction of α-isothiocyanato imides with α-ketoesters by rosin-derived tertiary amine-thiourea under low ligand loading to yield cyclic thiocarbamates bearing quaternary stereogenic centers with high levels of enantio- and diastereoselectivity (up to 99% ee, and 97:3 dr). This reaction provides a convenient doubly stereocontrolled method to access synthetic useful multiply substituted cyclic thiocarbamates with high optical purity. Further investigation is 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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