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Enantioselective Synthesis of β-Amino Esters Bearing a Benzothiazole Moiety via a Mannich-Type Reaction Catalyzed by a Cinchona Alkaloid Derivative

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Novel β-amino esters bearing a bioactive benzothiazole moiety were obtained with high enantioselectivities (up to 95 % *ee*) through a Mannich-type reaction of different imines with malonate in the presence of a new chiral cinchona alkaloid thiourea catalyst. Imines derived from both aromatic and heterocyclic aldehydes were found useful in this conversion.

Introduction

The importance for the enrichment of a single enantiomer, often as the bioactive chiral component, has grown sharply in recent years, driven not only by the demands of the pharmaceutical industry, but also by other applications in the field of agriculture and materials science.[1] Optically active enantiopure β-amino acids and their derivatives have extensive biological, pharmacological and plant-regulatory activities. They are encountered in numerous compounds and are part of crucial building blocks of many natural products.[2] Because of their role in various key industries, enantioselective synthesis of these compounds has attracted considerable attention in recent times.[3] On the other hand, benzothiazole derivatives have been studied extensively and found to have a broad spectrum of biological activities which include antiviral,[4] antiallergic,[5] antimicrobial,[6] and anticancer.[7] So, based on our technical competence in the field of plant virology,[1d] we prepared herein a series of novel asymmetric β-amino esters incorporating a benzothiazole moiety to obtain potent environmentally friendly antiviral agents for plants. Enantioenriched β-amino esters from achiral precursors of imines and different nucleophilic donor components were obtained in the past through asymmetric Mannich reactions in the presence of chiral bifunctional organocatalysts. Unlike many other efficient chiral catalysts in the literature, asymmetric organocatalysis[8] benefits from purely organic materials and is free from metal ions. This makes them easy to synthesize, easy to handle, cheap, and less toxic than their metal-ion counterparts. In addition to employing proline and its derivatives in direct three-component Mannich reactions for preparing chiral β-amino carbonyl compounds,[9] some other metal-free bifunctional organocatalysts such as Brønsted acids,[10] chiral thioureas,[11] and cinchona alkaloids[12] may also be employed in asymmetric Mannich reactions. These asymmetric catalysts, by virtue of their intrinsic chemical nature, often affiliate with flat substrates and prevent or promote, to some extent, an addition reaction of a reagent to one or to other faces of the double bond. These transformations are usually targeted to reach high levels of efficiencies and widen the substrate scope in the Mannich reaction.

Similar to enzyme catalysis characterized by selective substrate recognition and activation, hydrogen bonding induced by synthetic chiral bifunctional organocatalysts plays an important role in asymmetric catalysis.[13] The weak interactions of small, metal-free compounds with electron-rich binding sites have been investigated in detail and further extended by other researchers to study the hydrogen-bonding ability of various chiral thiourea derivatives in asymmetric Mannich reactions. These purely organic compounds effectively accelerate simple organic reactions, behave like weak Lewis acid catalysts, but act through explicit double hydrogen bonding instead of covalent binding known for traditional-metal-ion-mediated catalysis.

It is generally believed that appropriate positioning of a typical bifunctional organocatalyst containing a thiourea (capable of providing activation through hydrogen bonding) and a basic amine in a chiral scaffold could result in a new type of organocatalyst. Based on this idea, the organocatalytic asymmetric Mannich addition of malonates to *N*-Boc-protected aromatic aldimines was developed in the presence of base-compatible cinchona-based chiral bifunctional organocatalysts (Figure 1, **a**) to access β-amino acid ester derivatives in high yield with high *ee* (up to 99 %).[12a] It was

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proposed that the thiourea group of the bifunctional catalyst activates and directs the electrophilic imine through H-bonding, whereas the tertiary nitrogen atom of the quinine moiety activates the nucleophile. Upon hydrogenation, the benzyl ester was deprotected and subsequent decarboxylation provided the *N*-protected β-amino acid (Scheme 1).

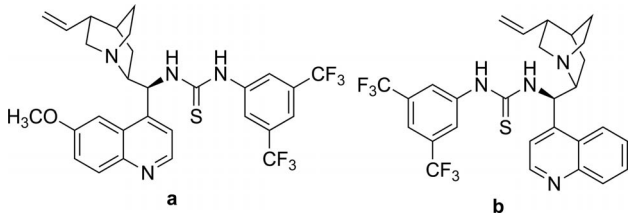
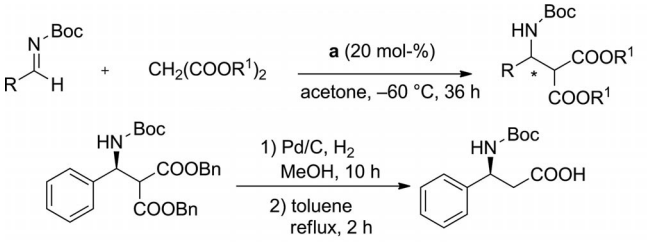
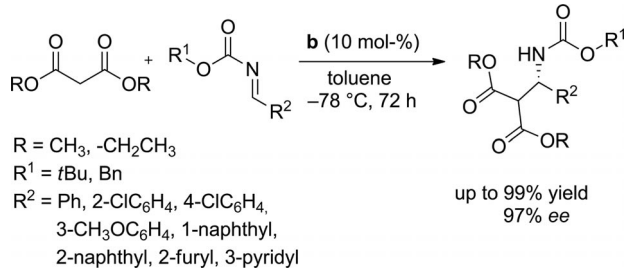


Figure 1. Some potential cinchona alkaloid thiourea catalysts for asymmetric transformations.



Scheme 1. Asymmetric Mannich addition of malonate to *N*-Boc-protected aromatic aldimines catalyzed by **a**.



Scheme 2. Asymmetric Mannich addition using chiral catalyst **b**.

A similar thiourea–cinchonine alkaloid catalyst (Figure 1, **b**) was also successfully used for the asymmetric addition of malonates to *N*-Boc- and *N*-Cbz-protected aldimines.[12b] The β-amino esters were obtained as Mannich adducts of dimethyl malonate and the protected aromatic aldimines with high *ee* values (Scheme 2).

Fascinated by these reports, we prepared new cinchona-based thiourea **Q-1** from 2,6-dichloro-4-(trifluoromethyl)-aniline. The selection of this amine, which serves as a useful precursor to some commercial insecticides[14] and pesticides, was governed by several factors such as its low price and easy availability. The asymmetric Mannich reaction of malonate with different imines in the presence of **Q-1** afforded β-amino esters with good to high enantioselectivities (80–95%*ee*) under mild conditions. Under similar conditions, catalyst **a**, prepared from more-expensive 3,5-bis(trifluoromethyl)aniline, afforded similar result in terms of enantioselectivity and yield. To the best of our knowledge, this is the first report on the preparation of asymmetric β-amino esters bearing a bioactive benzothiazole moiety.

Results and Discussion

New cinchona-based thiourea **Q-1** was prepared as outlined in Scheme 3. *N*-(2-Fluorobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (**1a**) and diethyl malonate (**2a**) were adopted as the starting materials for the initial explo-

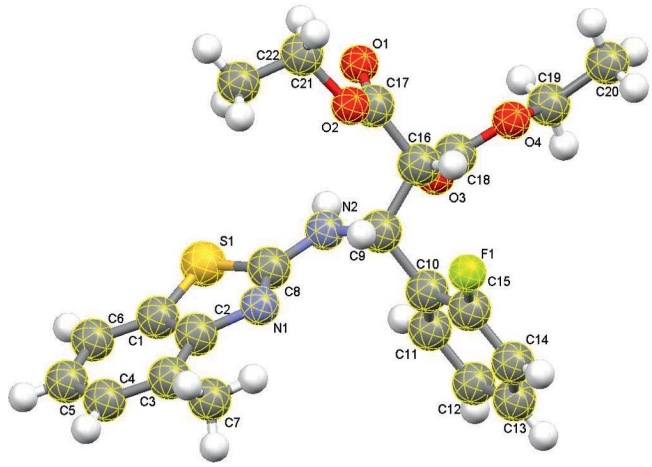
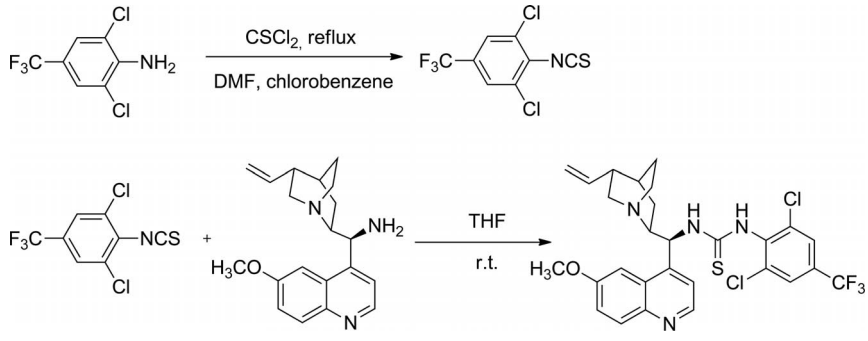


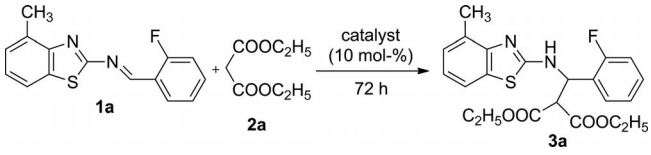
Figure 2. X-ray crystal structure of adduct **3a**.



Scheme 3. Synthesis of **Q-1**.

ration of the asymmetric Mannich reaction. The reaction was carried out in various solvents in the presence of the catalyst (10 mol-%) at room temperature for 72 h. In DCM, product **3a** (Figure 2) was obtained in 84%*ee* (Table 1, Entry 1). Another catalyst, quinine, although it appeared superior in terms of yield (85%), afforded the product with lower enantioselectivity (79%*ee*; Table 1, Entry 2) in the same solvent. Higher *ee* values were obtained in chloroform and toluene (87 and 89%*ee*; Table 1, Entries 3 and 6, respectively); however, the yields were lower. Both yields and enantioselectivities were found to be poor in acetone and THF (Table 1, Entries 4 and 5). Of all the five solvents selected for the screening (Table 1), xylene gave a better yield and enantioselectivity (91%*ee*) of product **3a** (Table 1, Entry 7). As mentioned earlier, similar results were obtained with catalyst **a** (Table 1, Entry 8).

Table 1. Optimization studies.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**Q-1**	DCM	77	84
2	quinine	DCM	85	79[d]
3	**Q-1**	$CHCl_3$	58	87
4	**Q-1**	acetone	70	67
5	**Q-1**	THF	73	17
6	**Q-1**	toluene	75	89
7	**Q-1**	xylene	88	91
8	**a**	xylene	87	90

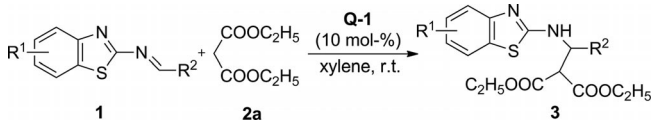
[a] Unless otherwise indicated, all reactions were conducted with **1a** (0.3 mmol), **2a** (0.36 mmol), and the catalyst (10 mol-%, 0.03 mmol) in the specified solvent (3 mL) at room temperature for 72 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC analysis (Chiralpak IA). [d] The configuration of the Mannich adduct is different from those of the other adducts obtained in other entries.

Various imines and diethyl malonate were then reacted under the optimized conditions, and the results are collected in Table 2. All the synthesized imines afforded the desired β-amino esters with good to high *ee* values (80–93%).

Substituent effects usually have a significant impact of the yield and enantioselectivity. Almost all of the desired products derived from 2-amino-4-methylbenzothiazole were obtained in higher yields and with higher *ee* values compared to those derived from 2-amino-6-methoxybenzothiazole. With R^1 = 4-CH_3, better enantioselectivities were achieved with an *ortho* substituent in the aryl ring (Table 2, Entries 1–4), whereas a *para* substituent usually gave better results with R^1 = 6-OCH_3 (Table 2, Entries 8–11).

Selected imines were treated with dimethyl malonate to broaden the scope of the Mannich reaction, and the results are listed in Table 3. All of the desired products were obtained with high *ee* values; the most promising result was

Table 2. Asymmetric Mannich reaction of diethyl malonate (**2a**) with imines catalyzed by **Q-1**.[a]

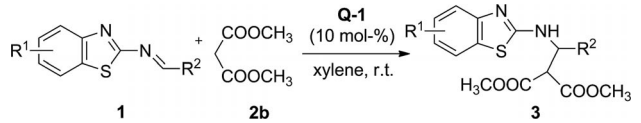


Entry	R^1	R^2	Time [h]	Yield [%][b]	*ee* [%][c]
1	4-CH_3	2-FC_6H_4	72	**3a**[d], 88	91
2	4-CH_3	4-FC_6H_4	72	**3b**, 85	90
3	4-CH_3	2-ClC_6H_4	72	**3c**, 88	93
4	4-CH_3	4-ClC_6H_4	72	**3d**, 78	90
5	4-CH_3	C_6H_5	72	**3e**, 75	89
6	4-CH_3	thiophen-2-yl	96	**3f**, 56	80
7	4-CH_3	naphthalen-1-yl	96	**3g**, 67	88
8	6-OCH_3	2-FC_6H_4	96	**3h**, 73	82
9	6-OCH_3	4-FC_6H_4	96	**3i**, 65	85
10	6-OCH_3	2-ClC_6H_4	96	**3j**, 77	84
11	6-OCH_3	4-ClC_6H_4	96	**3k**, 67	84
12	6-OCH_3	C_6H_5	96	**3l**, 63	86
13	6-OCH_3	4-$CH_3C_6H_4$	96	**3m**, 60	85
14	6-OCH_3	thiophen-2-yl	96	**3n**, 57	89

[a] Unless otherwise indicated, all reactions were conducted with imine (0.3 mmol), **2a** (0.36 mmol), and catalyst **Q-1** (10 mol-%, 0.03 mmol) in xylene (3 mL) at room temperature for 72–96 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC analysis (Chiralpak IA). [d] Absolute configuration of **3a** obtained in the presence of **Q-1** was determined to be (*R*) by single-crystal X-ray structure analysis (Figure 2).[15]

achieved with *N*-(furan-2-ylmethylene)-6-methoxybenzo[*d*]-thiazol-2-amine and dimethyl malonate in the presence of 10 mol-% of catalyst **Q-1** (95%*ee*; Table 3, Entry 10).

Table 3. Asymmetric Mannich reaction of diethyl malonate (**2b**) with imines catalyzed by **Q-1**.[a]



Entry	R^1	R^2	Time [h]	Yield [%][b]	*ee* [%][c]
1	4-CH_3	2-FC_6H_4	72	**3o**, 80	89
2	4-CH_3	2-ClC_6H_4	72	**3p**, 77	92
3	4-CH_3	C_6H_5	72	**3q**, 73	90
4	4-CH_3	furan-2-yl	72	**3r**, 50	91
5	4-CH_3	thiophen-2-yl	72	**3s**, 49	86
6	4-CH_3	naphthalen-1-yl	96	**3t**, 65	91
7	6-OCH_3	4-FC_6H_4	96	**3u**, 75	86
8	6-OCH_3	4-ClC_6H_4	96	**3v**, 70	87
9	6-OCH_3	4-$CH_3C_6H_4$	96	**3w**, 73	85
10	6-OCH_3	furan-2-yl	96	**3x**, 50	95
11	6-OCH_3	thiophen-2-yl	96	**3y**, 47	88

[a] Unless otherwise noted, all reactions were conducted with imine (0.3 mmol), **2b** (0.36 mmol), and catalyst **Q-1**(10 mol-%, 0.03 mmol) in xylene (3 mL) at room temperature for 72–96 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC analysis (Chiralpak IA).

Conclusions

In summary, we have developed for the first time an enantioselective synthesis of β-amino esters bearing a

benzothiazole moiety by employing a Mannich reaction catalyzed by a new and cheap quinine-derived thiourea catalyst. The desired products were obtained with high enantioselectivities (80–95%).

Experimental Section

Typical Procedure for the Organocatalytic Asymmetric Mannich-Type Reaction: To a solution of imine **1a** (0.3 mol) and chiral catalyst (10 mol-%) in dimethylbenzene (3.0 mL) at room temperature was added diethyl malonate (**2b**, 0.36 mmol) in one portion. After stirring for 72–96 h, the mixture was concentrated, and the residue was purified directly by preparative thin-layer chromatography (hexane/diethyl ether, 9:1–3:1) to afford products **3a**. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane/ethanol = 70:30; 1.0 mL/min; λ = 270 nm): t_R = 4.29 (major), 4.82 (minor) min.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, characterization data of the prepared compounds, ^{1}H and ^{13}C NMR spectra, and HPLC analysis data.

Acknowledgments

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[15] Crystal data of **3a**: $C_{22}H_{23}FN_2O_4S$, M_r = 430.48, triclinic, space group *P1*, a = 9.1694(12) Å, b = 9.2368(11) Å, c = 13.6139(17) Å, α = 79.486(5)°, β = 72.968 (5)°, γ = 79.460(5)°, V = 1073.6(2) Å3, $D_{calcd.}$ = 1.329 Mg/m^3, T = 293(2) K, Z = 2, 11437 reflections collected, 3717 independent (R_{int} = 0.0426), final R indices [$I > 2\sigma(I)$]: R_1 = 0.0775, wR_2 = 0.1031, R indices (all data): R_1 = 0.1031, wR_2 = 0.2541, absolute structure parameter: 0.008(4), GOF = 0.974. CCDC-781779 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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