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Solvent-free enantioselective conjugate addition and bioactivities of nitromethane to Chalcone containing pyridine

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ABSTRACT

A series of chiral thioureas derived from quinine were tested as catalysts in the enantioselective Michael additions of nitromethane to α,β-unsaturated ketones containing pyridine. The best results were obtained with the bifunctional catalyst prepared from 3,5-di(trifluoromethyl)-aniline under solvent-free conditions. This thiourea promoted the reaction with high enantioselectivities and chemical yields for aryl ketones. The origins of enantioselectivity were further investigated *via* experiment and computation. Meanwhile, the products from our reaction showed potent antibacterial activities against rice bacterial leaf blight, with the *S*-enantiomer performing much better than the *R*-enantiomer. Given the promising bioactivity of this class of molecules, our work is expected to offer important applications in developing future generations for drug design.

1. Introduction

Chalcone was one of the most useful molecular frameworks in medicinal chemistry and its derivatives exhibited a broad spectrum of biological activities.[1] Especially 1,4-addition products of chalcone were reported to possess promising biological activities such as anticancer,[2] antiplant-viral,[3] antimicrobial,[4] anti-HIV,[5] and anti-urease[6] properties. The biological activity of 1,4-addition compounds depends on their absolute configuration. Therefore, the synthesis of enantiomerically pure 1,4-addition compounds has received considerable attentions.[7] At present, the enantioselective addition of different nucleophiles to chalcone were obtained successfully.[8–12] Among them, the conjugate addition of nitroalkanes to chalcone (nitro-Michael reaction) has attracted enormous attention because the nitro group can be converted to other functional groups,[13] such as pyrrolidines,[14] lactones,[15] carbocycles,[16] and amino acids.[17]

So far, there are many asymmetric approaches involving organocatalysis,[18] heterogeneous catalysis,[19] phase-transfer catalysis,[20] aqueous-phase catalysis,[21] and metal-catalysis,[22] to synthesize enantioselective compounds. However, highly selectivities are generally restricted to chalcone substrates without heterocyclic moieties that are necessary for good bioactivities.[23] In 2013, Blay and co-workers[24] first reported La^{III}-pyBOX complexes-catalyzed conjugate addition to chalcones containing pyridine to nitroalkanes, but only moderate yield and ee were obtained. In addition, there are few studies in synthesizing highly enantiomerically pure γ-nitroketones containing heterocycle that exhibit high biological activities.

It is well known that there are pronounced advantages in solvent-free synthetic approach include easy work-up procedures, short reaction time, and simple apparatus requirements, which has attracted considerable attention in recent years.[25] Herein, we report the efficient conjugate additions of nitromethane to chalcone containing pyridine *via* thiourea organic catalyst under solvent-free conditions. The origins of enantioselectivity were further investigated via experimental and computational studies. Meanwhile, the antibacterial activities against rice bacterial leaf blight of 1,4-addition chiral products were evaluated.

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2. Results and discussion

Thiourea catalysts with the cinchona motif via hydrogen-bonding interactions were successfully applied in different types of Michael reactions.[26] These findings prompted us to synthesize bifunctional thiourea derivatives of quinine **Q1**~**Q6** that are capable of dual activation through two H bonding (Fig. 1) and apply them in the conjugate addition of nitromethane (**2**) to 2-enoylpyridines (**1a**) (Table 1). These catalysts were then studied for their ability to mediate enantioselective 1,4-addition. Among them, **Q1**, **Q3**, and **Q4** turned out to be poor catalysts, and **Q2** failed to accelerate this transformation. However, catalysts **Q5** and **Q6** afforded promising results (Table 1, entries 5, 6). The change trend in the catalytic activity with the introduction of the different substituent on aromatic ring, indicating that the electron withdrawing property contributed to higher reactivity for 1,4-addition. In addition, quinine on the catalyst is crucial for the reaction enantioselectivity. Next, the influence of solvents on the enantioselective 1,4-addition was studied using the most efficient catalyst **Q5** (Table 1, entry 7–10), toluene performed better than alternative solvents (Table 1, entry 7). Most notably, when the model reaction was performed in neat nitromethane, a nearly complete conversion was achieved (Table 1, entry 11). Almost no change in enantioselectivity and reactivity was observed when the loading of **Q5** was reduced from 20 mol% to 10 mol% (Table 1, entry 12); however, a little decrease of reactivity and no significant loss of enantioselectivity were observed when a catalyst load was reduced from 10 mol% to 5 mol% (Table 1, entry 13). Under this reaction condition, the chemical yield was not improved when the reaction time was increased from 12 h to 24 h (Table 1, entry 14). It should be noted that the other enantiomer of the reaction could be obtained by using **Q6** as the catalyst (Table 1, entry 16). Based on the above results, the optimized reaction conditions (entries 12, 16) were used for the model reaction. In contrast to the conventional process (Table 1, entry 15), solvent-free synthetic approach reduced the reaction time dramatically, raised the yield and simplified the post-treatment.

Under these optimized reaction conditions (Table 1, entry 12), a series of enones were investigated in the asymmetric Michael addition reaction. As illustrated in Table 2, consistently excellent enantioselectivity was observed for a broad range of enones. β-Aryl substituted enones with various substituents afforded 1,4-adducts with excellent enantioselectivities (Table 2, entries 1–11). β-Heteroaromatic enones were also excellent substrates for the present transformation (Table 2, entries 12–13). β-Aryl and β-heteroaromatic enones underwent the Michael addition reaction smoothly to give the corresponding products in high yields. By comparison, enones with a *para*-substituted phenyl (Table 2, entry 9) or heteroaromatic (Table 2, entries 12–13) showed a slightly reduced reactivity.

To understand the reaction mechanism, we applied both theoretical and experimental approaches to clarify how the catalyst (Cat) activates the nucleophilic (Nu) and the electrophilic (EI) groups. *Via* the experiments, the key factors for the enantioselective

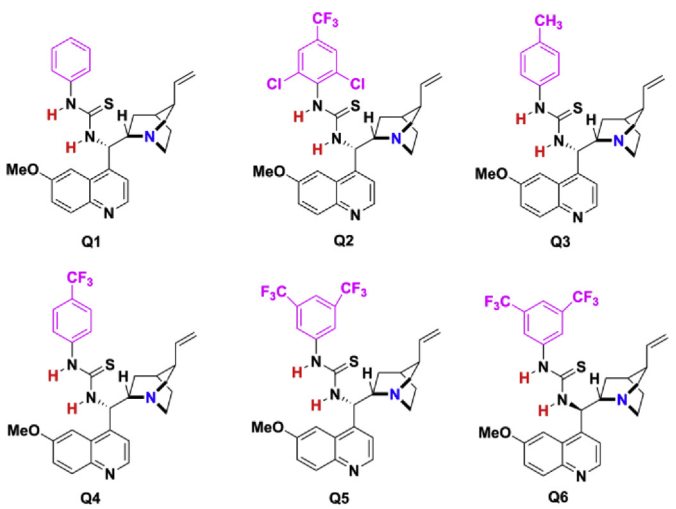
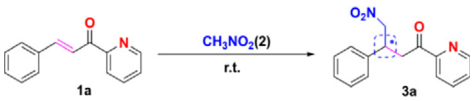


Fig. 1. Thiourea-quinine organocatalysts (**Q1**–**Q6**).

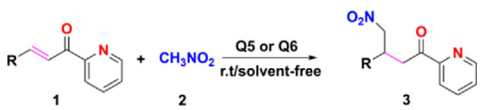
Table 1
Optimization of reaction conditions for conjugate addition of nitromethane (**2**) with trans-chalcone (**1a**).



Entry[a]	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**Q1** (20)	xylene	48	13	90
2	**Q2** (20)	xylene	48	0	0
3	**Q3** (20)	xylene	48	5	81
4	**Q4** (20)	xylene	48	37	95
5	**Q5** (20)	xylene	48	74	96
6	**Q6** (20)	xylene	48	73	−95
7	**Q5** (20)	toluene	48	79	95
8	**Q5** (20)	THF	48	69	93
9	**Q5** (20)	CH_2Cl_2	48	72	92
10	**Q5** (20)	neat	48	95	98
11	**Q5** (20)	neat	12	94	98
12	**Q5** (10)	neat	12	94	97
13	**Q5** (5)	neat	12	80	95
14	**Q5** (5)	neat	24	81	95
15	**Q5** (10)	toluene	12	32	94
16	**Q6** (10)	neat	12	93	−96

[a] Reactions were carried out with **1a** (0.2 mmol), 10 equiv of **2** (2 mmol) in capped vials at R.T.
[b] Isolated yields.
[c] The ee was determined by chiral HPLC analysis.

Table 2
Enantioselective conjugate addition of nitromethane to a series of β-substituted 2-enoylpyridines (**3a**~**3m**).



Entry	R	Product	Yield (%)[a]	Ee (%)[b]
1	Ph	**3a** (*R*)/(*S*)	93/94	96/97
2	2-FC_6H_4	**3b** (*R*)/(*S*)	95/97	96/98
3	2-$CF_3C_6H_4$	**3c** (*R*)/(*S*)	96/97	94/95
4	2-BrC_6H_4	**3d** (*R*)/(*S*)	96/98	96/97
5	2-$CH_3C_6H_4$	**3e** (*R*)/(*S*)	91/93	95/96
6	3-$CH_3OC_6H_4$	**3f** (*R*)/(*S*)	92/94	95/97
7	3-BrC_6H_4	**3g** (*R*)/(*S*)	93/92	97/98
8	4-ClC_6H_4	**3h** (*R*)/(*S*)	94/93	96/97
9	4-BrC_6H_4	**3i** (*R*)/(*S*)	93/92	96/97
10	4-$CH_3C_6H_4$	**3j** (*R*)/(*S*)	92/91	98/99
11	4-$CH_3OC_6H_4$	**3k** (*R*)/(*S*)	83/85	95/96
12	2-furan	**3l** (*R*)/(*S*)	76/79	98/99
13	2-thienyl	**3m** (*R*)/(*S*)	81/82	96/97

[a] Isolated yield after silica gel chromatography.
[b] The ee was determined by chiral HPLC analysis; and absolute configuration of the product 3a obtained using **Q5** catalyst was determined by X-ray analysis of *S* (CCDC:1457122) and the absolute configuration of all other product 3 were assigned by analogy.

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