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Asymmetric synthesis and antiviral activity of novel chiral amino-pyrimidine derivatives

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ABSTRACT

By using a chiral cinchona alkaloid-squaramide catalyst, a series of both enantiomers of novel amino-pyrimidine derivatives can be obtained in an enantioselective three-component one-pot Mannich reaction with high yields and excellent enantioselectivities. In addition, these chiral derivatives were found to exhibit higher antiviral activities against tobacco mosaic virus (TMV) *in vivo* than the commercial agent ningnanmycin. In particular, chiral compounds **(R)-4b** and **(R)-4e** showed excellent antiviral activity against TMV at a concentration of 500 μg/mL, with a curative activity of 56.8% and 55.2%, respectively, a protection activity of 69.1% and 67.1%, respectively, and an inactivation activity of 91.5% and 94.3%, respectively. These values are superior to those of the agent ningnanmycin (which has curative, protective, and inactivation activities of 52.9%, 62.8%, and 90.4%, respectively). The antiviral mechanisms and enhanced antiviral activities of these chiral derivatives are interesting subjects for future investigation.

The objective of organic agricultural chemistry is the design and synthesis of molecules having value in agriculture. Over the past decade, the number of non-racemic chiral pesticides has rapidly grown in the agrochemical market. Chiral agrochemicals that have greater efficacy can be used in smaller quantities and cause less environmental damage [1–5]. Hence, it is important to prepare agrochemicals using asymmetric synthetic methods to minimize losses. Using chiral organocatalysis is one effective measure. As a result of its convenience and economic advantages, asymmetric organocatalysis has had a significant influence on drug synthesis and has gradually developed into a pragmatic synthetic strategy in medicine and in the pesticide industry [6–11].

Owing to their broad spectrum of biological and pharmacological activity, heterocyclic compounds have received special attention in recent years [12–17]. There are many biologically active compounds containing six-membered rings with two heteroatoms, and the pyrimidine heterocyclic ring is an important skeleton associated with several active compounds [18–23]. For example, several molecules with a pyrimidine moiety are known to possess significant anticancer [24], anti-HIV [25], antimalarial [26], and antifungal protein kinase inhibitor [27] properties. In addition, the amino-pyrimidine ring system has been used to develop insecticides [28], fungicides [29], herbicides [30–31], and acaricides [32]. However, to our knowledge, research on modified amino-pyrimidine derivatives has mainly focused on racemates. Therefore, the development of new and highly efficient asymmetric synthesis methods to prepare optically active amino-pyrimidine derivatives is important for agrochemical synthesis.

Chiral cinchona alkaloid-derived bifunctional catalysts that function via H-bonding interactions have been successfully applied in various asymmetric reactions [33–38]. Deng et al. reported the synthesis of chiral β-amino acids through a Mannich-type reaction catalyzed by cinchona alkaloid-based thiourea organocatalysts [39]. Subsequently, these catalysts have been utilized in Mannich-type reactions for the *in situ* generation of carbamate-protected imines [40]. Rawal and coworkers developed an asymmetric Michael addition reaction of 1,3-dicarbonyl compounds to nitroolefins using the cinchonine-squaramide organocatalyst [41]. Du et al. also reported an enantioselective Mannich reaction of imines bearing a benzothiazole or isoxazole with malonates catalyzed by a cinchona-based squaramide organocatalyst [42]. Jacobsen and coworkers reported that chiral selenium derivatives can be obtained through the enantioselective selenocyclization using chiral squaramide as the catalyst [43]. Our group previously described the asymmetric addition of malonate with benzothiazolyl imine [44], and showed that the thiourea-cinchonine alkaloid derivatives were highly efficient catalysts in the synthesis of chiral β-amino esters bearing a benzothiazole moiety.

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Based on these reports, to find new types of highly efficient chiral antiviral agents, we used the cinchona alkaloid catalyst system in the Mannich reaction to investigate the synthesis of masked amino-pyrimidine derivatives. We then evaluated the antiviral activities against tobacco mosaic virus (TMV) of both enantiomers from our asymmetric Mannich reactions.

To determine suitable experimental conditions, we initially employed commercial quinine and cinchona alkaloid derivatives **C1**–**C5** (Figure 1) in a one-pot asymmetric catalytic Mannich-type reaction of 4-methoxy-6-methylpyrimidin-2-amine, benzaldehyde, and dimethyl malonate. Quinine without the thiourea moiety or squaramide moiety turned out to be a poor catalyst (entry 1, Table 1), whereas cinchona alkaloid-squaramide catalysts **C4** and **C5** afforded an especially promising result at 40 °C for 48 h (yield 53%, 65% ee; yield 50%, 62% ee; entries 5 and 6, Table 1). Of note, the acidity of the hydrogen-bond donor motifs had a certain effect on their catalytic activity. Organic catalysts without 3,5-$(CF_3)_2$ substitution (strong electron-withdrawing group) on the aromatic ring gave lesser yields and enantioselectivity, such as 4-CF_3 and 4-OMe substitutions. The cinchona alkaloid-squaramide catalysts **C4** and **C5**, which are trifluoromethyl-modified squaramide bifunctional organocatalysts, were the most effective catalysts for this enantioselective Mannich reaction.

To improve reaction selectivity, different experimental parameters (reaction temperature, and solvent and catalyst loading) were studied using the optimal cinchona alkaloid catalysts **C4** and **C5** (Table 2). The effects of solvents were evaluated by using **C4** as the catalyst, and *p*-xylene was found to be an optimal solvent, while obvious decreases in yield and enantioselectivities were observed when chloroform, ethyl acetate, tetrahydrofuran, acetone, or ethanol were used as the solvent (entries 1–5, Table 2). The catalytic ability of the chiral catalyst was favored by raising the temperature within a specific range, while the activity was inhibited if the reaction temperature was over that range. An obvious increase in enantioselectivity and yield were observed when the reaction temperature was increased from 40 °C to 50 °C (entry 6–7, Table 2). However, a sharp decrease of enantioselectivity was observed when the reaction temperature was increased from 50 °C to 70 °C (entry 7–9, Table 2). Notably, almost no changes in enantioselectivity and yield were observed when the loading of **C4** was decreased from 20 mol% to 10 mol% (entries 7 and 10, Table 2). It should be noted that the other enantiomer of the reaction could be obtained by using **C5** as the catalyst (entry 11, Table 2). The best result was achieved at 50 °C with 10 mol% catalyst loading in *p*-xylene.

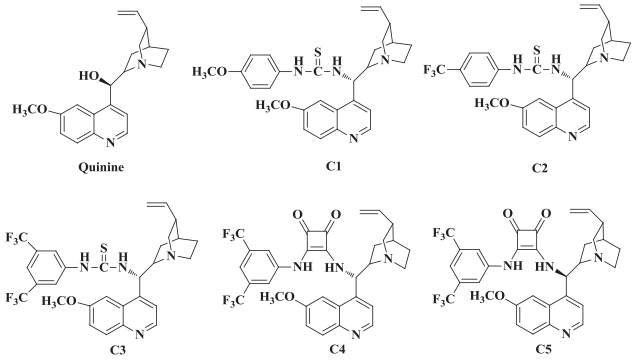
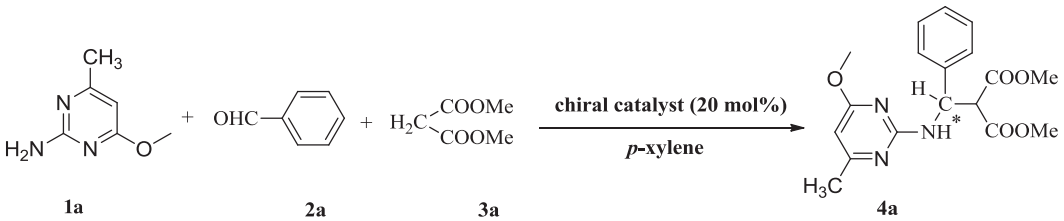


Fig. 1. Structure of quinine and cinchona alkaloid catalysts **C1–C5**.

With the optimized Mannich-reaction conditions in hand, the scope of various aldehydes and malonates were investigated to demonstrate the generality of these asymmetric Mannich reactions. Aromatic, aliphatic, or heterocyclic substituted aldehydes, using the chiral catalysts **C4** or **C5,** underwent this Mannich reaction smoothly, leading to the desired non-racemic products with good to excellent enantioselectivities and yields. Notably, the electronic properties of the substituted aldehydes did not significantly affect the experimental outcomes. High yields and excellent enantioselectivities were obtained for aromatic aldehydes bearing a substituent at the para-position of either electron-withdrawing groups, such as Cl- (entries 3 and 4, Table 3), and electron-donating groups, such as methyl (entries 5 and 6, Table 3) and methoxyl (entries 7 and 8, Table 3). In addition, furfural (entries 9 and 10, Table 3) and hexahydrobenzaldehyde (entries 11–14, Table 3) were also good substrates with high yield and excellent enantiomeric excess. Finally, we examined the generality of the reaction with other heterocyclic amines (entries 17–22, Table 3). Unsurprisingly, 2-amino pyridine (**1b**), 4-chloro-6-methoxypyrimidin-2-amine (**1c**) and 2-methoxypyridin-3-amine (**1d**) had high to excellent yields (84–90%) and excellent enantioselectivities (89–98% ee) (entries 17–22, Table 3). Unfortunately, the reaction of 3-methoxyaniline failed to provide any product (entries 23, Table 3),

Table 1
Screening of various catalysts.[a]



Entry	Catalyst	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	quinine	40	22	13
2	C1	40	31	29
3	C2	40	42	37
4	C3	40	45	52
5	C4	40	53	65
6	C5	40	50	62

[a] Reactions were carried out with 1.0 mmol of **1a**, 1.0 mmol of **2a**, and 1.0 mmol of **3a** in 4.0 mL of *p*-xylene using 20 mol% of catalyst at 40 °C for 48 h.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis (Chiralpak IA).