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Original article

Enantioselective synthesis of 2-amino-3-nitrile-chromenes catalyzed by cinchona alkaloids: A remarkable additive effect

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ABSTRACT

2-Amino-3-nitrile-chromenes with potential antitumor activity were constructed by a novel catalytic system. In combination with α-naphthol, quinine could effectively promote the Michael-cyclization process of malononitrile with functionalized chalcones in high yields and moderate to good enantioselectivity (up to 84% *ee*). It is notable that the enantioselectivity could be greatly improved when α-naphthol was employed as additive.

1. Introduction

2-Amino-3-nitrile-chromene is an important medicinal scaffold and displays a wide range of biological properties. In addition to *in vitro* antibacterial activity [1], its derivatives might be employed to treat drug-resistant cancer. For example, compound MX58151 (Fig. 1) retained activity in tumor cells resistant towards current antimitotic agents, taxanes (including Taxol and Taxotere), and Vinca alkaloids [2]. Furthermore, these heterocycles were identified as vascular-disrupting agents (VDA), and one of the leading compounds, Crolibulin (EPC2407) (Fig. 1) [3], is currently in phase II clinical trials.

Considering its attractive biological activities, the development of efficient synthetic approaches for this structure is of significant interest. Although there are numerous reports on the construction of its racemic form [4], examples of the catalytic asymmetric syntheses of these scaffolds were relatively less explored. Notably, the *R*-isomer of Crolibulin exhibited stronger antitumor activity (50–100 times more active) than the corresponding *S*-isomer [5]. Yang and Zhao successfully obtained 2-amino-3-nitrile-chromene derivatives possessing a naphthene group *via* an addition–cyclization reaction of 2-naphthol with α,α-dicyanoolefins [6]. Later Xie *et al.* [7] and other groups [8] synthesized these heterocycles through the nucleophilic addition of malononitrile to a functional acceptor, followed by an intramolecular cyclization. Recently Yang and other groups developed a valuable catalytic process to synthesize enantiomerically pure 2-amino-4*H*-chromenes utilizing a Michael addition of 2-iminochromenes [9]. Although high yields and excellent enantioselectivity have been achieved in these published examples, it was the modified organocatalysts rather than the natural products that exhibited optimal catalytic reactivity and stereoselectivity almost in all cases [10].

The synthesis of a suitable organocatalyst requires many redesigning sessions and long or expensive synthetic procedures. On the other hand, many enzymes, which are highly efficient biological catalysts, only displayed high activity and enantioselectivity when coenzymes were involved [11]. Motivated by the enzymatic systems, many readily available achiral additives were involved in the catalytic asymmetric transformations and an impressive improvement, in terms of reactivity and stereoselectivity was observed when compared with the use of organocatalysts alone [12]. This approach was beneficial in avoiding tedious chemical syntheses and would ultimately allow the highly efficient construction of libraries of catalyst systems by simply changing the additives. Based on our continuous efforts on asymmetric Michael reaction [13], herein we describe a domino process to construct 2-amino-3-nitrile-chromenes *via* a Michael-cyclization sequence of functionalized chalcones and malononitriles promoted by naturally occurring cinchona alkaloids. Notably, a remarkable enantioselectivity

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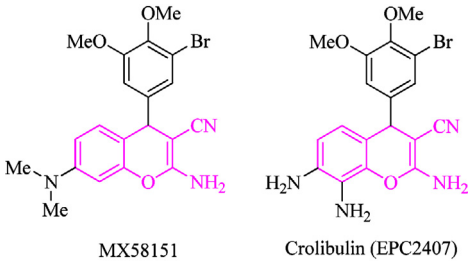

Fig. 1. Structures of corresponding biologically active molecules.

improvement was observed once additives were introduced to the catalyst system.

2. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz spectrometers. ESI-HRMS spectra were recorded on a BioTOF instrument (Bruker Daltonics). Enantiomeric excess (*ee*) was determined by HPLC analysis on Chiralpak AS-H, AD-H, and OD-H columns. Optical rotation data were recorded on an SGW-1 automatic polarimeter. The spectral data and spectra of all the compounds are presented in the Supporting information.

The functionalized chalcones **1a–q** were prepared according to the procedures reported in literature [14]. Commercial grade solvents were dried and redistilled before use. All other reagents were purchased from commercial sources and used without further purification.

3. Results and discussion

Initially, we examined the catalytic effect of a series of natural cinchona alkaloids. The designed cascade reaction of functional chalcone **1a** and malononitrile proceeded smoothly in toluene and afforded the desired 2-amino-3-nitrile-chromene **3a,** with quinine **4a** (Fig. 2) giving an almost quantitative yield [15] (Table 1, entry 1). Cinchonidine **4b** (Fig. 2) displayed lower catalytic activity and poorer enantioselectivity (entry 2). Quinidine **4c** and cinchonine **4d** (Fig. 2) delivered adducts with an opposite configuration and inferior optical purity than those delivered by quinine **4a** (entries 3 and 4). We next studied the effect of the modified cinchona alkaloids. As we could see, the dihydroquinine **4e** (Fig. 2) exhibited slightly higher enantioselectivity and poorer reactivity than quinine (entry 5). The C6′-OH cinchona alkaloids **4f** and **4g** (Fig. 2) were examined and unsatisfactory stereoselectivity was detected in both cases (entries 6 and 7). A range of biscinchona alkaloids **4h–4k** (Fig. 2) failed to complete the domino reaction even after one week, and less than 50% *ee* values were observed (entries 8–11). Furthermore, the 9-*epi*-amino cinchona alkaloid **4l** and the corresponding thiourea **4m** (Fig. 2) were investigated, and the desired products were obtained with marginal optical purity (entries 12 and 13). Moreover, when the Takemoto catalyst **4n** (Fig. 2) was employed, only 36% *ee* was achieved (entry 14). The subsequent solvent screening revealed that polarity has a remarkable impact on the enantioselectivity (entries 15–20). Only marginal stereoselectivity was obtained when the more polar solvents, THF and MeOH, were used (entries 19 and 20). Unfortunately, no enantioselective improvement was observed when this transformation was performed at 0 °C (entry 21).

Using the identified quinine **4a** as the optimal catalyst and toluene as the solvent of choice, we next focused on effects of the additives on the enantioselectivity and catalytic activity. The addition of molecular sieves (M.S., 4 Å) led to an impairment of the reaction rate but negligible improvement of *ee* values (Table 2, entries 1 and 2). It has been documented that the structural modifications of cinchona alkaloids exerted a direct impact on their asymmetric induction [16]. As previously reported, acids might protonate the *N*-quinuclidine moiety and induce conformational changes of cinchona alkaloids, resulting in different catalytic behaviors [17]. Inspired by Baiker's observations on the heterogeneous hydrogenation of ethyl pyruvate [17b,c], we attempted to introduce readily available acidic additives to the catalytic system. As summarized in Table 2, when 5 mol% of aromatic carboxylic acid was added, a slight enantioselectivity increase was attained at the cost of a decrease in reactivity (entries 3–6). Aliphatic

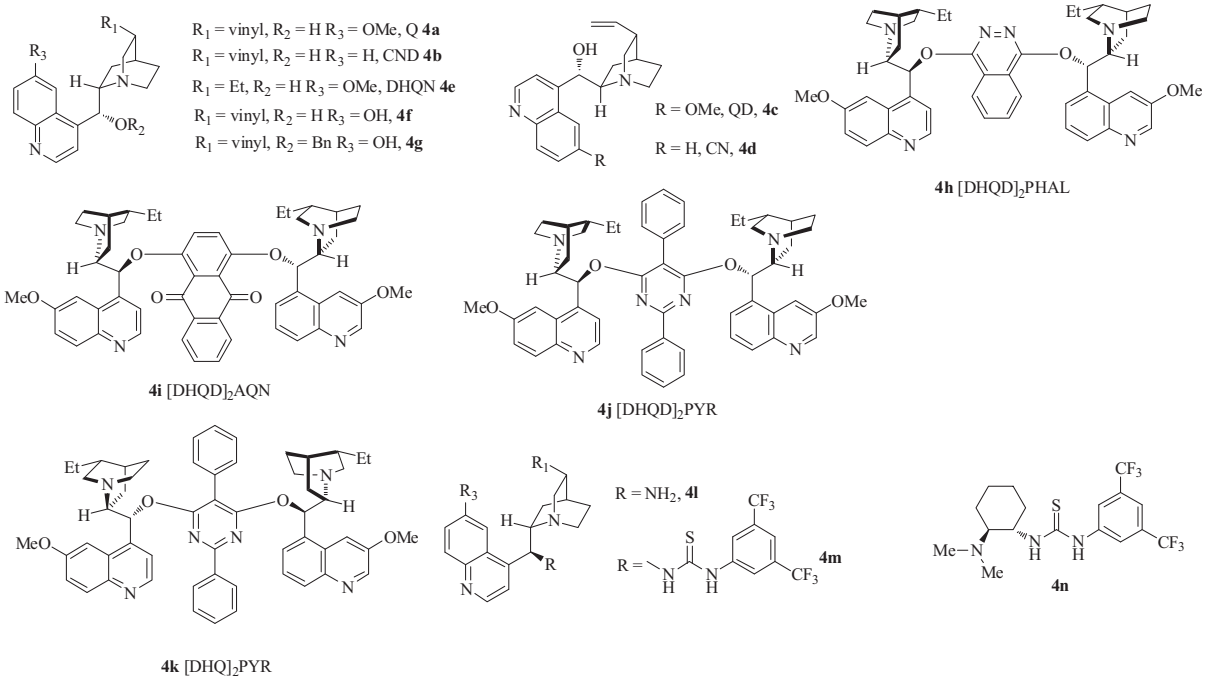

Fig. 2. Structures of corresponding organocatalysts.