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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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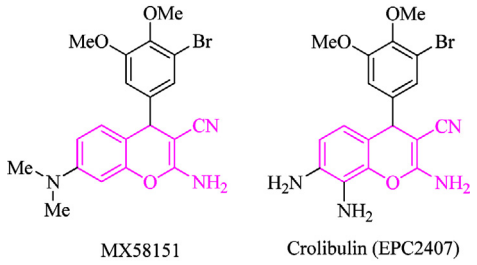

Fig. 1. Structures of corresponding biologically active molecules.

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

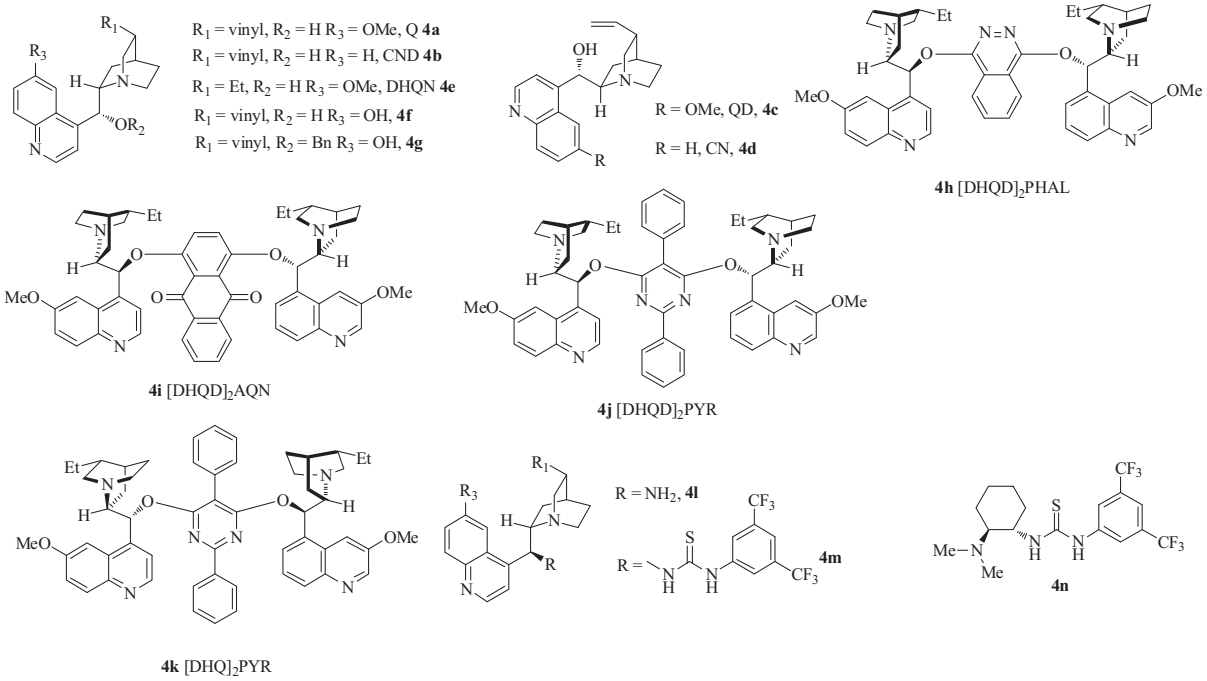

Fig. 2. Structures of corresponding organocatalysts.

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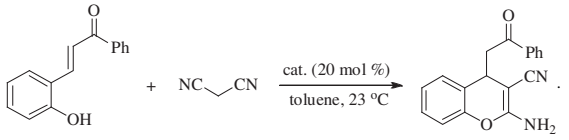
Table 1
Screening reaction conditions for the domino reaction of **1a** with **2**.[a]



1a **2** **3a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	**4a**	Toluene	24	>99	68
2	**4b**	Toluene	49	>99	34
3	**4c**	Toluene	28	>99	−46
4	**4d**	Toluene	144	94	−21
5	**4e**	Toluene	36	99	67
6	**4f**	Toluene	72	87	0
7	**4g**	Toluene	72	39	−11
8	**4h**	Toluene	168	49	32
9	**4i**	Toluene	168	76	−13
10	**4j**	Toluene	168	66	49
11	**4k**	Toluene	168	43	−15
12	**4l**	Toluene	168	46	−22
13	**4m**	Toluene	80	89	13
14	**4n**	Toluene	80	88	36
15	**4a**	DCM	28	>99	48
16	**4a**	$CHCl_3$	21	98	56
17	**4a**	Ether	30	77	58
18	**4a**	$PhCF_3$	24	>99	49
19	**4a**	THF	30	73	6
20	**4a**	MeOH	28	96	<5
21[d]	**4a**	Toluene	48	94	68

[a] Unless otherwise noted, all of the reactions were performed with 0.1 mmol of **3a**, 0.12 mmol of malononitrile **2**, and 20 mol% of catalyst in 1 mL of solvent at 23 °C. DCM = dichloromethane, THF = Tetrahydrofuran.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on a chiral AS-H column.
[d] The reaction was performed at 0 °C.

Table 2
Additives screening for the domino reaction of **1a** with **2**.[a]

Entry	Additive	Time (h)	Yield (%)[i]	*ee* (%)[j]
1	M. S. (20 mg)	48	99	68
2	M. S. (40 mg)	96	75	70
3[b]	$PhCO_2H$	75	97	72
4[b]	2,4-$(NO_2)_2PhCO_2H$	114	>99	76
5[b]	*p*-$MeOPhCO_2H$	66	>99	67
6[b]	*o*-$OHPhCO_2H$	114	>99	71
7[b]	HOAc	120	>99	76
8[b]	TFA	120	>99	71
9[b]	TsOH	72	>99	69
10[c]	PhOH	37	67	73
11[c]	*p*-MePhOH	144	85	75
12[c]	*p*-MeOPhOH	144	96	71
13[c]	*p*-NO_2PhOH	144	32	73
14[c]	2,4,6-$(NO_2)_3PhOH$	168	99	78
15[c]	α-Naphthol	144	43	81
16[c]	β-Naphthol	144	81	74
17[d]	α-Naphthol	48	>99	72
18[e]	α-Naphthol	72	93	78
19[f]	α-Naphthol	168	99	79
20[g]	α-Naphthol	168	>99	81
21[g,h]	α-Naphthol	168	>99	76
22[g]	*R*-BINOL	168	>99	73
23[g]	*S*-BINOL	120	>99	69
24[c]	^tBuOH	37	96	71
25[c]	CF_3CH_2OH	78	>99	73

[a] Unless otherwise noted, all the reactions were performed with 0.1 mmol of **1a**, 0.12 mmol of malononitrile **2**, 20 mol% of quinine **4a,** and the corresponding additive in 1 mL of solvent at 23 °C. HOAc = CH_3CO_2H, TFA = Trifluoroacetic acid, TsOH = *p*-Toluenesulfonic acid.
[b] 5 mol% of additive.
[c] One equivalent of additive.
[d] 20 mol% of additive.
[e] 30 mol% of additive.
[f] 40 mol% of additive.
[g] 50 mol% of additive.
[h] 20 mg of M.S. was added.
[i] Isolated yield after flash chromatography on silica gel.
[j] Determined by HPLC on a chiral AS-H column.

carboxylic acids and sulfonic acids were also examined (entries 7–9) and acetic acid enhanced the ee value from an original value of 68–76% (entry 7). Considering the strong acidity of carboxylic acids, in the following study we performed the tandem reaction of **1a** with malononitrile in the presence of less acidic phenolic compounds (entries 10–23) [12e,h]. When one equivalent of phenol and its analogues were added in the cascade reaction, a significant decrease in reactivity was observed and prolonged reaction time was required in almost all cases. The use of phenolic compounds improved the enantioselectivity to a greater extent when compared to carboxylic and sulfonic acids (entries 10–23 *vs.* 3–9). The electronic effect on the aromatic ring of phenol was not apparent (entries 11–14 *vs.* 10). The electron-rich *para*-methyl substituted phenol afforded 75% *ee* (entry 11) while the electron-poor 2,4,6-trinitrophenol delivered 78% *ee* (entry 14). Further studies indicated that α-naphthol greatly improved the enantioselectivity and 81% *ee* was detected (entry 15). However, β-naphthol only generated the desired compound with 74% *ee* (entry 16). Considering the poor conversion of α-naphthol, the subsequent investigation focused on the loading of additive. A decrease in loading led to a significant conversion enhancement (entries 17–20). The transformation completed within 72 h in the presence of 20 or 30 mol% α-naphthol, however, the enantioselectivity also reduced (entries 17 and 18). Fortunately, the enantioselectivity remained in the presence of 50 mol% α-naphthol and almost quantitative yield was obtained after one week (entry 20). Next, we added α-naphthol together with the molecular sieves to the reaction. This resulted in an inferior enantioselectivity (76% *ee*) (entry 21). The chiral additive 1,1′-bi-2-naphthol (BINOL) was also evaluated [12g] (entries 22 and 23) and poorer stereo control was observed for both additives. Both (*R*)-BINOL and (*S*)-BINOL afforded the desired heterocycles with the same configuration. It further confirmed that it's the quinine rather than the additives that played a crucial role during the course of asymmetric induction. Finally, alcohols were found to slightly enhance the enantioselectivity (entries 24 and 25).

Having established the optimal reaction conditions, we subsequently examined the substrate scope of the domino reaction of functionalized chalcone **1** and malononitrile **2**. As summarized in Table 3, all the reaction proceeded smoothly in the presence of 20 mol% quinine and 50 mol% α-naphthol in toluene and the desired chromenes were generated in high yields (75%–99%) and moderate to good enantioselectivity (49%–84% *ee*). The substrate scope study revealed that electron-donating and electron-withdrawing groups, locating at the phenyl group adjacent to the carbonyl group, were all well tolerated. All the substrates **1b–g** underwent efficient cascade reactions with malononitrile, affording the desired heterocycles in high yields (entries 2–7). Generally speaking, the substrates containing electron-withdrawing groups afforded comparable *ee* values with the substrates containing electron-donating groups (entries 5–7 *vs.* 3–4). An *ortho*-substituted chalcone **1b** produced the corresponding product with poorer enantioselectivity (49% *ee*), probably caused by the steric effect of the methyl group (entry 2). Moreover, reactions with heteroaryl-containing substrates **1h–i** proceeded well and the desired products were obtained with moderate stereoselectivity (entries 8 and 9). Notably, a pronounced positive additive effect was observed again in **1b–i** when the α-naphthol was involved under otherwise identical conditions (entries 2–9, data outside brackets *vs.* data in brackets). Up to 37% enantioselectivity improvement was observed in the case of **1i** with a thienyl group (entry 9). We next investigated the effect of another phenyl group

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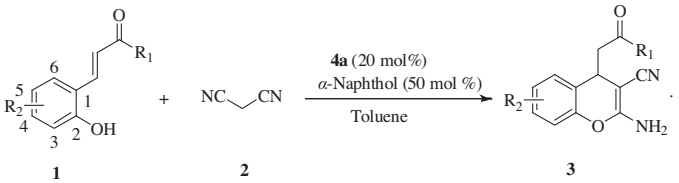
Table 3
Substrate spectrum investigation of the domino reaction of **1** and **2**.[a]



1 **2** **3**

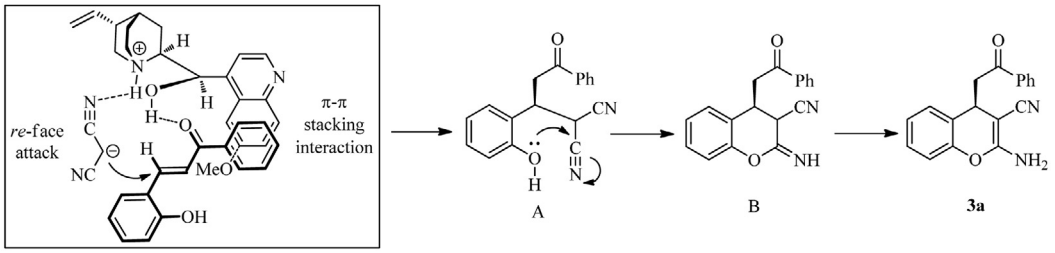
Entry	R_1	R_2	Temp. (°C)	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	H	H (**1a**)	23	168	>99	81 (*R*)[d]
2	*o*-$CH_3C_6H_4$	H (**1b**)	23	120	99 (85)[e]	49 (37)[e]
3	*p*-$CH_3C_6H_4$	H (**1c**)	23	120	99 (99)[e]	68 (43)[e]
4	*p*-$CH_3OC_6H_4$	H (**1d**)	23	120	98 (95)[e]	72 (68)[e]
5	*p*-FC_6H_4	H (**1e**)	23	120	93 (98)[e]	72 (63)[e]
6	*p*-ClC_6H_4	H (**1f**)	23	120	99 (99)[e]	67 (45)[e]
7	*p*-BrC_6H_4	H (**1g**)	23	120	91 (99)[e]	70 (53)[e]
8	2-Furyl	H (**1h**)	23	120	94 (96)[e]	57 (39)[e]
9	2-Thienyl	H (**1i**)	23	120	93 (99)[e]	49 (12)[e]
10	C_6H_5	3-CH_3O (**1j**)	10	168	99	74
11	C_6H_5	5-Cl (**1k**)	10	168	99	71
12	C_6H_5	3,5-Br_2 (**1l**)	10	168	99	84
13	*p*-$CH_3C_6H_4$	3,5-Br_2 (**1m**)	10	120	82	80
14	*p*-$CH_3OC_6H_4$	3,5-Br_2 (**1n**)	10	168	75	83
15	*p*-FC_6H_4	3,5-Br_2 (**1o**)	10	120	99	82
16	*p*-ClC_6H_4	3,5-Br_2 (**1p**)	10	168	93	81
17	*p*-BrC_6H_4	3,5-Br_2 (**1q**)	10	120	99	81

[a] Unless otherwise noted, all of the reactions were performed with 0.1 mmol of **1**, 0.12 mmol of malononitrile **2**, 20 mol% of quinine **4a,** and 50 mol% of α-naphthol in 1 mL of toluene at 23 °C.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on a chiral column.
[d] The configuration of the product.
[e] The data in parentheses is for the transformations conducted without α-naphthol under otherwise identical conditions.

on the terminal double bond in the functionalized chalcones (entries 10–12). Compounds **1j–l** successfully converted into the desired chromenes. Almost quantitative yields and better enantioselectivity could be achieved at 10 °C when compared to reactions conducted at 23 °C. Gratifyingly, up to 84% *ee* was achieved for substrate **1l** with two bromine atoms on the phenyl group (entry 12). Further studies indicated that good enantioselectivity remained for dibromo-substituted chalcones **1m–q** when electron-donating and electron-withdrawing groups were introduced to the phenyl group adjacent to the carbonyl group (entries 13–17). The configuration of the products was determined to be *R* on the basis of the reported optical rotation. [7]

The postulated reaction pathway is summarized in Scheme 1. Our domino process might share a similar transition state as Lattanzi's enantioselective Michael reaction [15] due to the similar configuration of the product. In the initial step, malononitrile was deprotonated by the tertiary amine moiety of quinine and orientated *via* a hydrogen bond. Meanwhile, the hydroxy group was involved in a hydrogen-bonding interaction with the oxygen in the carbonyl moiety in chalcone **1a**. The formation of a ternary complex of quinine, chalcone **1a**, and malononitrile would stereoselectively afford intermediate **A**. Subsequently, the intermolecular oxo-nucleophilic addition of the nitrile group led to intermediate **B**. Finally, intermediate **C** underwent tautomerization to give the desired compound **3a**. The preferential attack of malononitrile towards the *re*-face of the enone might likely be assisted by a favorable π–π stacking interaction between the quinoline residue of the catalyst and the aromatic moiety linked to the carbonyl group. This resulted in an *R*-configured product.

To further investigate the role of additive, the Michael addition of an *ortho*-methoxy substituted chalcone **5** with malononitrile was conducted under the identical conditions mentioned above (Scheme 2). Notably, the beneficial effect was observed again. The process generated the desired adduct with 79% *ee* in the absence of α-naphthol; however, up to 82% *ee* was obtained once 50 mol% α-naphthol was introduced. This confirmed that the additive effect was general. The participation of α-naphthol resulted in a decrease in the reaction rate and an improvement in enantioselectivity (Table 1, entry 1 *vs.* Table 2, entry 20; Table 3, entries 2–9). We postulated that the acidic α-naphthol could attach to quinine *via* the protonation of the tertiary amine moiety of quinine. This would disturb the deprotonation of malononitrile and slow down the reaction rate. At the same time, the resulting complex of quinine and α-naphthol might possess catalytic activity and afforded



Scheme 1. Proposed mechanism for the domino reaction.

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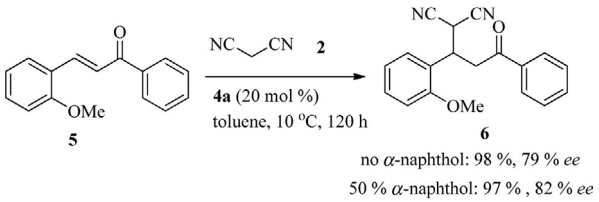

Scheme 2. Michael addition of an *ortho*-methoxy substituted chalcone 5 with malononitrile.

better enantioselectivity when compared to the process solely catalyzed by quinine [16]. As a result, a significant enhancement of enantioselectivity was observed. Nevertheless, the real catalytic mechanism still needs further investigation.

4. Conclusion

We have developed an efficient strategy to construct 2-amino-3-nitrile-chromenes, with potential antitumor activity, from readily accessible functionalized chalcones and malononitrile. The natural cinchona alkaloids such as quinine could efficiently promote the tandem conversion to produce the desired heterocycles in high yields (75%–99%) and moderate to good enantioselectivity (49%–84% *ee*). In particular, achiral α-naphthol exerted a positive impact to the stereoselectivity and a significant improvement in enantioselectivity. The beneficial additive effect was frequently observed in the case of primary and secondary amine-promoted transformations; however, it was seldom found in the process catalyzed by tertiary amines. Although an enhancement of reactivity and enantioselectivity was observed in the case of the heterogeneous catalytic enantioselective hydrogenation of ethyl pyruvate after achiral tertiary amines were utilized, the cinchona alkaloids were employed in the reaction as the ligand and not the organocatalyst [18]. Further research actively performed in our lab concentrates on clarifying the definite role of α-naphthol and the synthetic utilizations of the attained product.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.08.013.

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