ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 5880–5882

www.rsc.org/chemcomm

COMMUNICATION

Highly efficient enantioselective three-component synthesis of 2-amino-4*H*-chromenes catalysed by chiral tertiary amine-thioureas†

Gaosheng Yang,* Chongrong Luo, Xiaolong Mu, Tingting Wang and Xin-Yuan Liu*

Received 2nd February 2012, Accepted 17th April 2012
DOI: 10.1039/c2cc30731f

A three-component cascade reaction of salicylaldehyde, malononitrile/cyanoacetate and nitromethane catalysed by chiral tertiary amino-thioureas was developed, which leads to the production of highly functionalized 2-amino-4*H*-chromenes in good yields with good to excellent enantioselectivities.

2-Amino-4*H*-chromenes are common structural motifs in a number of both biologically active and natural compounds.[1] In particular, 4-aryl/alkyl-2-amino-4*H*-chromene derivatives bearing a nitrile or ester group at the 3-position show pro-apoptotic activity against a range of cancer cells as a single agent or in combination with chemo radiotherapy.[2] Given the fact that within a chiral surrounding two enantiomers often show distinct biological activity, the development of effective protocols to access optically pure 2-amino-4*H*-chromenes would be extremely desirable to further study the correlation between the chirality of these compounds and their propensities for biological activities to search for more potent and/or appropriate pharmaceutical candidates. In contrast to the numerous reports on the synthesis of racemic 2-amino-4*H*-chromenes,[3] examples on the construction of these structures in catalytic asymmetric ways are rather limited, while asymmetric organocatalysis has proved to be an efficient way for this purpose.[4] For examples, by using the cooperative catalysis composed of 9-amino-9-deoxyepiquinine and (*R*)-1,1′-binaphth-2,2′-diyl hydrogen phosphate, Xie and co-workers have shown asymmetric reactions of α,β-unsaturated ketones with malononitrile to give chiral 2-amino-4*H*-chromenes with high enantioselectivities;[4a] Wang and co-workers have utilized indane-amine-thiourea organocatalysts to promote the asymmetric reaction of *tert*-butyl(2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate with malononitrile to afford 2-amino-4*H*-chromenes with good enantioselectivities in the presence of Li_2CO_3.[4b] However, these current asymmetric processes often suffer from several drawbacks such as rather complex starting materials requiring tedious prior preparation, external additives (such as inorganic bases or other cooperative catalysts) or a specialized product scope with the substituent on the 3-position strictly restricted to the nitrile group.

Organocatalytic asymmetric multi-component cascade reactions are powerful tools for the fast construction of optically active molecules from simple starting materials with excellent selectivity and high atom- and step-economy.[5] In this regard, compared to other common organocatalysts like chiral secondary or primary amines and phosphoric acids,[5] examples of such reactions catalysed by chiral tertiary amine-thioureas are sparse.[6] As part of our continuing efforts toward the synthesis of chiral heterocyclic compounds using chiral tertiary amine-thiourea organocatalysts,[6b] we described herein an application of this type of catalysts to the asymmetric one-pot three-component cascade reaction of salicylaldehyde and malononitrile/cyanoacetate with nitromethane. A variety of chiral 2-amino-4*H*-chromenes were obtained in good to excellent yields (up to 92%) with excellent enantioselectivities (up to 96% ee). Noteworthy is that this is a general and efficient protocol for the rapid synthesis of chiral 2-amino-4*H*-chromenes from readily accessible starting materials utilizing only tertiary amine-thiourea organocatalysts with no need for any additional additives.[7] Furthermore, an exceptional and very intriguing inversion of the absolute configuration of the major products was also revealed when changing the substrate from malononitrile to cyanoacetate.

We first examined the solvent effect in the three-component reaction of salicylaldehyde (**1a**), malononitrile (**2a**) and nitromethane (**3a**) with catalyst **C1** (Fig. 1). The reaction proceeded smoothly in CH_2Cl_2 in the presence of 4 Å MS at rt to form the desired product **4a** in 78% yield and 68% ee (Table 1, entry 1). However, the use of other solvents such as toluene, *n*-hexane, THF, DCE, and isopropanol did not give better results (entries 2–6). A panel of catalysts (Fig. 1) were also screened in this reaction (entries 8–10). To our delight, the use of Takemoto catalyst

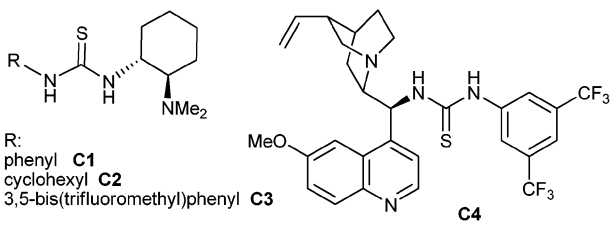
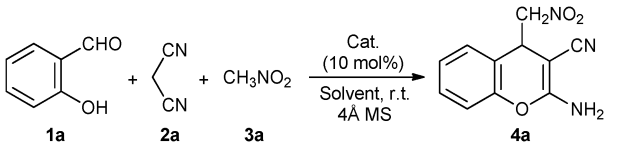


Fig. 1 Chiral tertiary amine-thiourea catalysts used in this study.

Anhui Key Laboratory of Functional Molecular Solids, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China. E-mail: gshyang@mail.ahnu.edu.cn, xyliu79@gmail.com; Fax: +86-553-3883517; Tel: +86-553-3869310

† Electronic supplementary information (ESI) available: Experimental procedures, product characterizations for new compounds, Scheme S1, and Fig. S1. CCDC 860045 (**4b**), 860044 (**5b**), and 860046 (**Ia**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc30731f

Table 1 Optimization of reaction conditions[a]



1a 2a 3a 4a

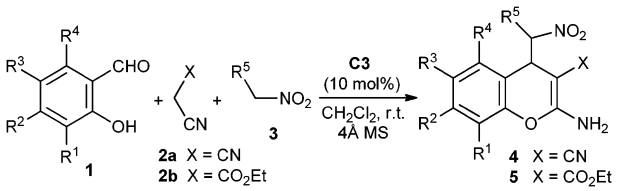
Entry	Catalyst	Solvent	Molar ratio of **1a**/**2a**/**3a**	Yield[b] (%)	ee[c] (%)
1	**C1**	CH_2Cl_2	1.0/1.0/1.0	78	68
2	**C1**	Toluene	1.0/1.0/1.0	76	14
3	**C1**	*n*-Hexane	1.0/1.0/1.0	82	21
4	**C1**	THF	1.0/1.0/1.0	49	36
5	**C1**	DCE	1.0/1.0/1.0	84	53
6	**C1**	Isopropanol	1.0/1.0/1.0	74	26
7	No catalyst	CH_2Cl_2	1.0/1.0/1.0	NR	—
8	**C2**	CH_2Cl_2	1.0/1.0/1.0	61	69
9	**C3**	CH_2Cl_2	1.0/1.0/1.0	84	82
10	**C4**	CH_2Cl_2	1.0/1.0/1.0	95	−34
11[d]	**C3**	CH_2Cl_2	1.0/1.0/1.0	67	78
12[e]	**C3**	CH_2Cl_2	1.0/1.0/1.0	74	71
13	**C3**	CH_2Cl_2	1.0/1.2/1.5	88	84
14	**C3**	CH_2Cl_2	1.0/1.5/1.2	85	76
15	**C3**	CH_2Cl_2	1.0/1.5/1.5	93	79
16	**C3**	CH_2Cl_2	1.0/1.5/2.0	94	80
17	**C3**	CH_2Cl_2	1.0/2.0/1.5	90	74
18[f]	**C3**	CH_2Cl_2	1.0/1.2/1.5	60	71

[a] Unless otherwise noted, the reaction was conducted with 0.3 mmol of salicylaldehyde (**1a**), 50 mg of 4 Å MS and catalyst (10 mol%) in 1.5 mL of solvent at room temperature for 30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis on a chiral OJ-H column. [d] The loading of catalyst was 5 mol%. [e] 4 Å MS was not added. [f] The reaction was conducted at 0 °C for 48 h.

C3[8] resulted in a significantly improved enantioselectivity (82%) (entry 9). Notably, no reaction took place in the absence of the catalyst (entry 7). Next, the molar ratio of the reactants was screened. We found the presence of an optimum ratio of **2a** to **3a** in this system (entry 13), whereas decreasing or increasing this ratio all led to inferior results (entries 14–17). Both the yield and ee values were decreased by lowering the catalytic loading from 10 mol% to 5 mol%, with no use of 4 Å MS or by lowering the reaction temperature to 0 °C (entries 11, 12, 18). Therefore, the three-component reaction of **1a**, **2a** and **3a** with the molar ratio of 1 : 1.2 : 1.5 was best carried out using 10 mol% of catalyst **C3** in the presence of 4 Å MS in CH_2Cl_2 at room temperature (entry 13).

Under the optimized reaction conditions, we examined the substrate scope of this three-component reaction. A variety of salicylaldehydes were similarly treated with malononitrile (**2a**) and nitromethane (**3a**). As depicted in Table 2, salicylaldehydes having one or two electron-withdrawing or electron-donating substituent(s) on different positions of the phenyl ring could be successfully employed to afford the corresponding chiral 2-amino-4*H*-chromenes in good yields and high ee (Table 2, entries 2–7). Functional groups, such as chloride, bromide, methoxy, and even nitro groups were well tolerated. When nitroethane (**3b**) was used as the substrate, high yield could still be obtained albeit with diminished ee value and poor diastereoselectivity (entry 8). The absolute configuration of product **4b** was determined to be (*R*) by X-ray crystallographic analysis (Fig. 2, Flack χ = 0.03(3)). The absolute configuration of products **4a** and **4c–4g** were assigned in reference to **4b**.

Table 2 Scope study[a]



1 2a X = CN 2b X = CO_2Et 3 4 X = CN 5 X = CO_2Et

Entry	**1** (R^1, R^2, R^3, R^4)	**3** (R^5)	Product	Yield[b] (%)	ee[c] (%)
1	**1a** (H, H, H, H)	**3a** (H)	**4a**	88	84
2	**1b** (H, H, Br, H)	**3a** (H)	**4b**	92	87
3	**1c** (H, H, Cl, H)	**3a** (H)	**4c**	85	82
4	**1d** (H, H, NO_2, H)	**3a** (H)	**4d**	80	81
5	**1e** (Br, H, Br, H)	**3a** (H)	**4e**	78	96
6	**1f** (Cl, H, Cl, H)	**3a** (H)	**4f**	75	80
7	**1g** (H, H, H, MeO)	**3a** (H)	**4g**	64	83
8	**1a** (H, H, H, H)	**3b** (Me)	**4h**	88[d]	58, 75
9	**1a** (H, H, H, H)	**3a** (H)	**5a**	76	87
10	**1b** (H, H, Br, H)	**3a** (H)	**5b**	83	91
11	**1c** (H, H, Cl, H)	**3a** (H)	**5c**	76	84
12	**1e** (Br, H, Br, H)	**3a** (H)	**5d**	78	89
13	**1f** (Cl, H, Cl, H)	**3a** (H)	**5e**	81	77 (>99)[e]
14	**1h** (H, H, MeO, H)	**3a** (H)	**5f**	86	77 (97)[e]
15	**1i** (H, Cl, H, Cl)	**3a** (H)	**5g**	76	87
16	**1g** (H, H, H, MeO)	**3a** (H)	**5h**	41	61

[a] Unless otherwise noted, the reaction was conducted with 0.3 mmol of salicylaldehyde (**1**), 0.36 mmol of malononitrile (**2a**)/ethyl cyanoacetate **2b**, 0.45 mmol of nitroalkane (**3**), 50 mg of 4 Å MS and catalyst **C3** (10 mol%) in 1.5 mL CH_2Cl_2 at room temperature for 30 h/48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Ratio of diastereomers is 43 : 57. [e] After recrystallization from dichloromethane/*n*-hexane.

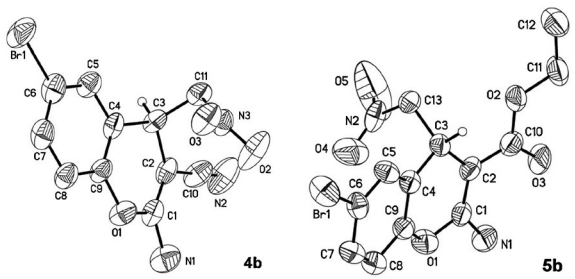
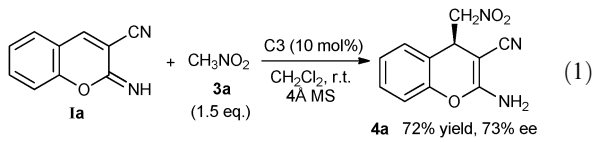


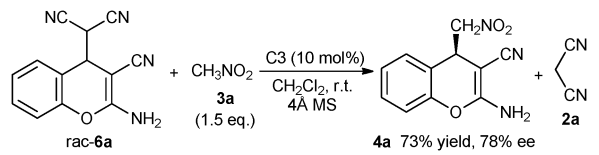
Fig. 2 X-Ray crystal structure of **4b** and **5b**.

To further investigate the scope of this reaction, we then tested the use of cyanoacetate (**2b**) as substrate instead of malononitrile (**2a**). In general, cyanoacetate demonstrated reactivity similar to that of malononitrile (Table 2). Under similar reaction conditions, besides salicylaldehyde (**1a**), other differently substituted salicylaldehydes with electron-withdrawing or electron-donating substituents on the phenyl ring were also well tolerated in the reaction to afford the corresponding products **5** in good yields and with good to excellent enantioselectivities (entries 9–16). An electron-donating MeO group on the *meta* position of aldehyde could still give comparably good results, while its presence on the *ortho* position gave considerably diminished yield and ee value (entries 14 and 16). Notably, the ee value of these products could be improved upon simple recrystallization (entries 13 and 14). The absolute configuration of (*S*)-**5b** was also established by X-ray crystallographic analysis (Fig. 2, Flack χ = 0.016(17)) and the stereochemistry of other products **5a** and **5c–5h** were assigned correspondingly. It should

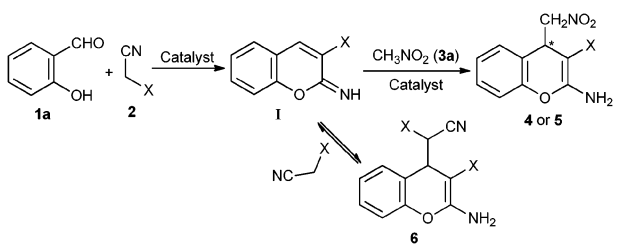
be noted that the absolute configuration of the major products obtained here is inversed compared to those derived from malononitrile (**2a**) while in the presence of the same chiral tertiary amine-thiourea catalyst **C3** under otherwise same conditions.

Several control experiments were conducted to gain some insight into the mechanism of this three-component cascade reaction (Scheme S1 in the ESI†). In the presence of the racemic catalyst (±)-**C1**, no reaction occurred between salicylaldehyde (**1a**) and nitromethane (**3a**) (Scheme S1 (ESI†), eqn (1)). In contrast, the reaction of **1a** with malononitrile (**2a**) took place smoothly under the same reaction conditions to give **6a** and **Ia**, respectively, clearly indicating that the reaction of **1a** with **2a** should be involved as the first step in this three-component cascade sequence (Scheme S1 (ESI†), eqn (2)). The reaction of **Ia** with **3a** catalysed by **C3** afforded chiral product **4a** in 72% yield with 73% ee (eqn (1)). Under the same conditions, the reaction of racemic **6a** with **3a** also resulted in comparable result (eqn (2)).[9] These results suggested that **6a** might be in equilibrium with **Ia** in the reaction system, and a nucleophilic attack by **3a** would pull the equilibrium to generate the final product **4a**, which is also consistent with previous findings.[3b,c]





On the basis of the above observations and previous studies,[3] a possible mechanism for the present tertiary amino-thiourea-catalysed three-component cascade reaction was proposed (Scheme 1). First, a tandem Knoevenagel condensation–cyclization reaction of **1** with **2** would generate an intermediate **I**, which might be in fast equilibrium with **6**. Then the addition of **3** to **I** giving the desired final product **4** or **5** should be the main stereodifferentiating step. However, the exact mechanism for the stereoselective control process, especially the unexpected reversal of the product absolute configuration resulting from the use of **2a** and **2b**, remains unclear at present and deserves further detailed study.



Scheme 1 Proposed mechanism of the three-component reaction.

In summary, a general and efficient three-component cascade asymmetric reaction of salicylaldehyde, malononitrile/cyanoacetate and nitromethane has been developed using a simple chiral tertiary amino-thiourea as catalyst without the need for additional additives. This protocol provides an atom-economic and straightforward method for the synthesis of chiral highly functionalized 2-amino-4*H*-chromenes in good yields with high enantioselectivities from simple starting materials. Furthermore, the absolute configuration of the major products was found to be switchable *via* a simple change in one of the reactants while still using the same catalyst system. Further studies to expand the substrate scope and to probe the origin of stereocontrol are currently in progress.

We thank Prof. Hongtao Zhang, Yun Wei and Shuangliu Zhou for their help with X-ray crystallographic analyses. This work was supported by the National Natural Science Foundation of China (20972001, 21172002) and Anhui Provincial Natural Science Foundation (090416236).

Notes and references

1 (*a*) M. Kidwai, S. Saxena, M. K. R. Khan and S. S. Thukral, *Bioorg. Med. Chem. Lett*., 2005, **15**, 4295; (*b*) N. J. Thumar and M. P. Patel, *ARKIVOC*, 2009, **13**, 363; (*c*) N. M. Sabry, H. M. Mohamed, E. S. A. E. H. Khattab, S. S. Motlaq and A. M. El-Agrody, *Eur. J. Med. Chem*., 2011, **46**, 765.

2 For selected examples, see: (*a*) J. M. Doshi, D. Tian and C. Xing, *J. Med. Chem*., 2006, **49**, 7731; (*b*) W. Kemnitzer, S. Jiang, Y. Wang, S. Kasibhatla, C. Crogan-Grundy, M. Bubenik, D. Labrecque, R. Denis, S. Lamothe, G. Attardo, H. Gourdeau, B. Tseng, J. Drewea and S. X. Cai, *Bioorg. Med. Chem. Lett*., 2008, **18**, 603; (*c*) S. G. Das, J. M. Doshi, D. Tian, S. N. Addo, B. Srinivasan, D. L. Hermanson and C. Xing, *J. Med. Chem*., 2009, **52**, 5937.

3 For selected examples, see: (*a*) D. Grée, S. Vorin, V. L. Manthati, F. Caijo, G. Viault, F. Manero, P. Juin and R. Grée, *Tetrahedron Lett*., 2008, **49**, 3276; (*b*) M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov, A. I. Ilovaisky, S. K. Feducovich, P. A. Belyakov and G. I. Nikishina, *Adv. Synth. Catal*., 2008, **350**, 591; (*c*) M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, P. A. Belyakov, A. O. Chizhov and G. I. Nikishin, *Tetrahedron*, 2010, **66**, 4043; (*d*) K. Kumaravel and G. Vasuki, *Green Chem*., 2009, **11**, 1945; (*e*) S. N. Murthy, B. Madhav, V. P. Reddy and Y. V. D. Nageswar, *Tetrahedron Lett*., 2010, **51**, 3649.

4 (*a*) J. W. Xie, X. Huang, L. P. Fan, D. C. Xu, X. S. Li, H. Su and Y. H. Wen, *Adv. Synth. Catal*., 2009, **351**, 3077; (*b*) Q. Ren, W. Y. Siau, Z. Du, K. Zhang and J. Wang, *Chem.–Eur. J*., 2011, **17**, 7781.

5 For selected recent reviews, see: (*a*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed*., 2005, **44**, 1602; (*b*) C. F. Barbas III, *Angew. Chem., Int. Ed*., 2008, **47**, 42; (*c*) Ł. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem., Int. Ed*., 2011, **50**, 8492; (*d*) A. Moyano and R. Rios, *Chem. Rev*., 2011, **111**, 4703.

6 (*a*) Y. Yamaoka, H. Miyabe and Y. Takemoto, *J. Am. Chem. Soc*., 2007, **129**, 6686; (*b*) X. S. Wang, G. S. Yang and G. Zhao, *Tetrahedron: Asymmetry*, 2008, **19**, 709; (*c*) S. Bai, X. Liang, B. Song, P. S. Bhadury, D. Hu and S. Yang, *Tetrahedron: Asymmetry*, 2011, **22**, 518.

7 During the preparation of this manuscript, a paper describing chiral thiourea-catalysed asymmetric three-component reactions among aromatic aldehyde, malononitrile, and coumarin/cyclohexane-1,3-dione to give pyranocoumarins and 2-amino-4*H*-pyran appeared: G. Zhang, Y. Zhang, J. Yan, R. Chen, S. Wang, Y. Ma and R. Wang, *J. Org. Chem*., 2012, **77**, 878.

8 T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc*., 2003, **125**, 12672.

9 The good chemical yield obtained here makes less probable a process involving a direct S_N2 substitution of **6a** with **3a** to give the chiral product **4a**.