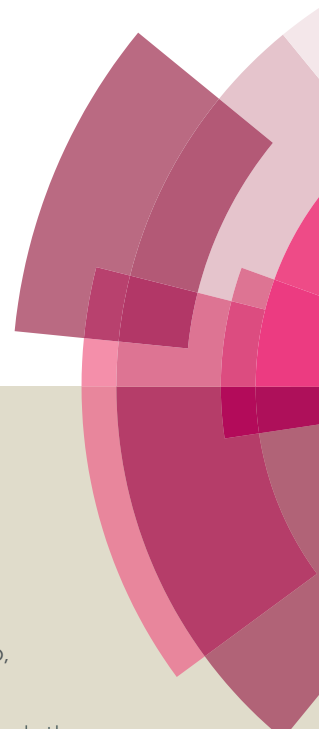
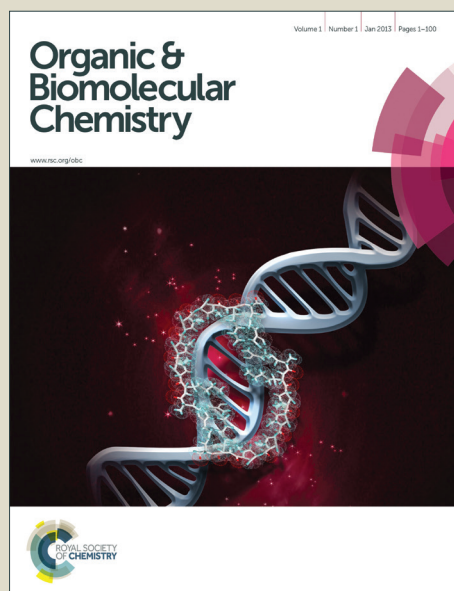


Organic & Biomolecular Chemistry

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: A. Adele, Z. Tao, D. Chen and Z. Han, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C4OB02602K.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

COMMUNICATION

Quinine-Catalyzed Highly Enantioselective
Cycloannulation of *o*-Quinone Methides with
Malononitrile

Cite this: DOI: 10.1039/x0xx000000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx000000x

www.rsc.org/

Alafate Adili, Zhonglin Tao, Dianfeng Chen and Zhiyong Han*

2-Amino-3-cyano-4*H*-chromenes hold great potential as novel anticancer agents. Here we report a quinine-catalyzed highly enantioselective formal 4+2 cycloaddition of ortho-quinone methides and malononitrile, providing a unique approach to 4-arylvinyl, 4-aryl and 4-vinyl 2-amino-3-cyano-4*H*-chromenes with excellent yields and enantioselectivities. Moreover, this reaction can be performed in up to 6 mmol scale without noticeable loss of yield and stereoselectivity.

2-Amino-3-cyano-4*H*-chromenes (Fig. 1) were found to exhibit strong cytotoxicity against human cancer cells.¹⁻³ Crolibulin, also known as EPC2407, is currently in phase I/II clinical trials as anticancer agent and apoptosis inducer for the treatment of anaplastic thyroid cancer.⁴ The stereo structure of 4*H*-chromene derivatives was reported to have significant effect on their antitumor activity. Roughly, the R-isomer of EPC2407 or 4*H*-chromene I, which was also found to have high antitumor activity, is about 50-100 times more active than the

corresponding S-isomer.^{5,6} Despite the importance for preparing these compounds in enantioenriched form, previous studies were mainly focused on racemic synthesis.⁷⁻¹⁴ Herein, we will report a quinine-catalyzed highly enantioselective formal [4+2] cycloaddition of ortho-quinone methides (*o*-QMs) with malononitrile, providing a series of 4*H*-chromenes that have similar structure to compound I.

o-QMs are significant intermediates in various transformations handled by nature. Many biologically molecules, such as anthracycline antibiotics, are able to bring us therapeutic benefits through their *o*-QMs variant, which can be targeted by enzymes in vivo.^{15,16} Moreover, the *o*-QMs are usually high active and hold unique synthetic potential in the construction of complex molecules (Figure 1), thus interesting chemists around the world.¹⁷⁻²¹

Mechanically, the inherent reactivity of *o*-QMs depends on their rapid rearomatisation propensity, mainly by two reaction pathways (Scheme 1): a) Michael addition of nucleophiles; b) cycloannulation reaction with 2π partners or dipoles.²² On account of the products' complexity and diversity, the cycloannulation reaction of *o*-QMs is now a hot topic that various reaction partners with *o*-QMs or other precursors have been discovered.^{23,24} However, as far as we know, there are only a few examples describing enantioselective cycloannulation processes (Scheme 1). In 2013, Ye's group and Scheidt's group independently reported similar chiral *N*-Heterocyclic carbene (NHC)-catalyzed highly enantioselective [4+3] annulations of enals with *o*-QMs (Scheme 1).^{25,26} Lectka and Ye chronologically demonstrated similar formal [4+2] cycloaddition reactions of prepared *o*-QMs with ketenes by using a chiral cinchona alkaloid-derived ammonium fluoride or an NHC catalyst [Scheme 1].²⁷ Very recently, Schneider and co-workers developed an enantioselective [4+2] annulations of in situ generated *o*-QMs

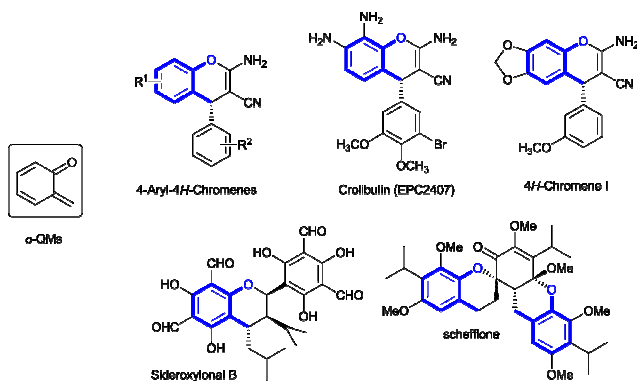
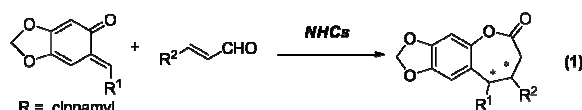


Figure 1 4*H*-chromenes and *o*-QMs-related Natural Products

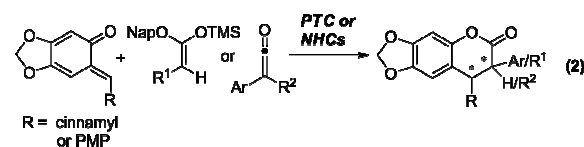
with β -diketones, providing an direct access to optically pure efficient synthesis of 4-aryl-4*H*-chromenes

(Scheme 1).²⁸ Inspired by these achievements of trapping active *o*-QMs intermediate in enantioselective manners, we envisioned that optically active 2-amino-3-cyano-4*H*-chromenes might be accessed through a formal [4+2] cycloaddition of *o*-QMs with malononitrile in the presence of a proper bifunctional catalyst.²⁹⁻³³

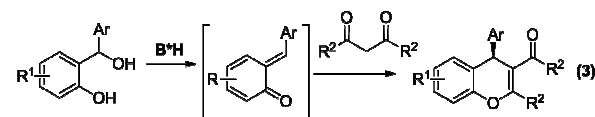
Ye's and Scheidt's work:



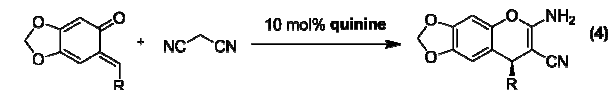
Lectka's and Ye's work:



Schneider's work:



This Work:

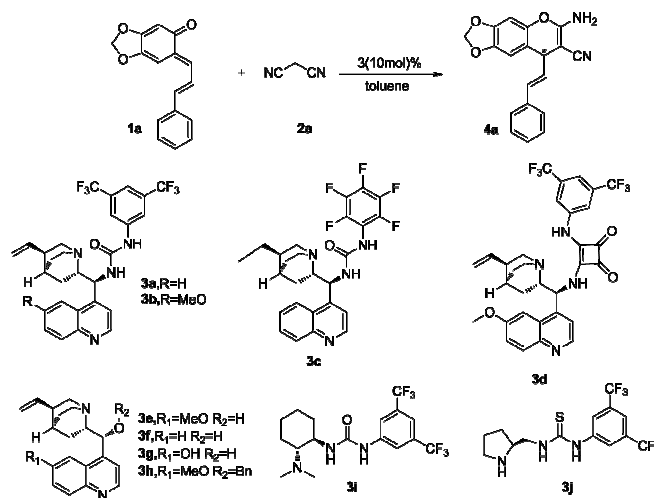


Scheme 1 Enantioselective Cycloannulation of *o*-QMs

Considering that the acidic α -H of malononitrile can be activated by Lewis base, and on the other hand, *o*-QMs might be activated by acidic H-bond donors, initially we chose quinine or cinchonine based chiral bifunctional-urea as the catalyst¹³⁻¹⁵ (Table 1). Our investigation began with the reaction of **1a** and **2a** catalyzed by 10 mol% of chiral bifunctional-urea (in toluene, 0 °C Table 1, entries 1 - 4). To our delight, the chiral bifunctional-ureas employed exhibited high reactivity and efficiency. Catalyst **3a** could render the reaction with 98% yield and 86% ee. In the case of catalyst **3b** - **4d**, the desired product could also be obtained in good yields and slightly lower enantioselectivities. Encouraged by these results we kept to our investigations to find more effective catalysts. Bearing both a tertiary amine and a hydroxyl group in one chiral scaffold, quinine is also an effective chiral bifunctional organocatalyst. We tried quinine and its derivatives as the catalyst (Table 1, entries 5 - 8). Despite that **3f** and **3g** showed poor enantioselectivity, **3e** (quinine) was able to bring about 98% yield and 88% ee (Table 1, entries 5 - 7). As expected, hydroxyl group protected quinine **3h** led to very poor enantioselectivity (Table 1, entry 8), implying that the hydroxyl group based hydrogen bond played a crucial role in controlling the stereoselectivity of the reaction. Chiral amine/ urea or thiourea bifunctional catalyst failed to improve the results (Table

1, entries 9 - 10). By reducing the reaction temperature to -40 °C

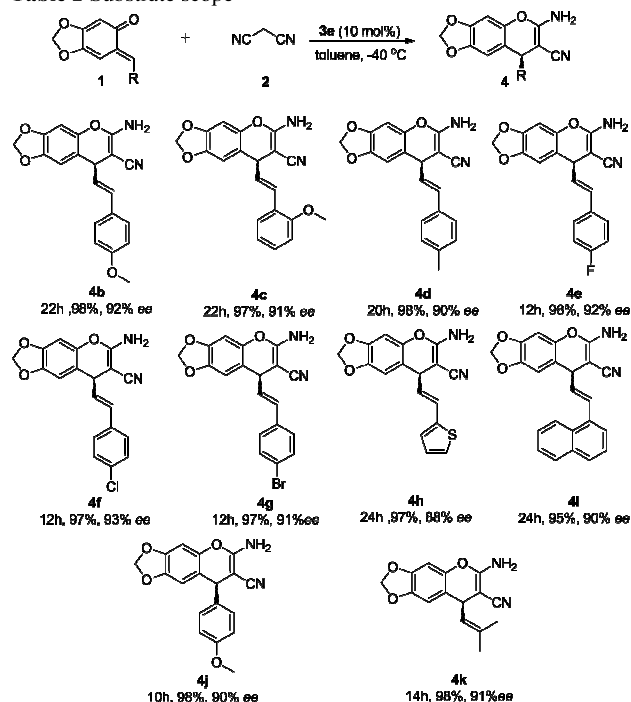
Table 1 Evaluation of catalysts and optimization of reaction Conditions^[a]



Entry	Catalyst	Solvent	Yield [%] ^[b]	ee [%] ^[c]
1	3a	toluene	98	86
2	3b	toluene	95	80
3	3c	toluene	93	86
4	3d	toluene	90	79
5	3e	toluene	98	88
6	3f	toluene	98	77
7	3g	toluene	84	-47
8 ^[d]	3h	toluene	95	34
9	3i	toluene	98	80
10 ^[d]	3j	toluene	30	10
11	3e	DCM	80	80
12 ^[e]	3e	toluene	99	92
13 ^[e]	3e	CHCl ₃	98	84
14 ^[e]	3e	Et ₂ O	98	50
15 ^[f]	3e	toluene	97	91
16 ^[g]	3e	toluene	95	90

^a Unless indicated otherwise, the reaction of **1a** (0.1 mmol) and **2a** (0.12 mmol) was carried out in 2 mL solvent at 0 °C in the presence of catalyst **3** (10 mol%) for 6-10 hours. ^b Isolated yield. ^c The ee value was determined by HPLC. ^d Reaction lasted for 48 hours. ^e Reaction performed at -40 °C for 18 - 24 hours. ^f Catalytic amount reduced to 5%; reaction performed at -40 °C for 18 - 24 hours. ^g Catalytic amount reduced to 2%; reaction performed at -40 °C for 18 - 24 hours.

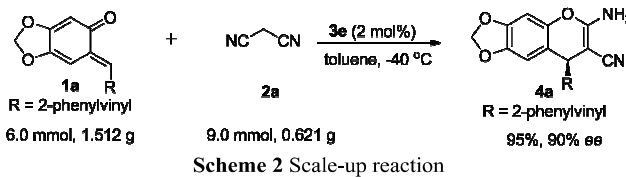
and extending the reaction time, a higher enantioselectivity could be achieved (92% ee) without any loss of the yield. Further, we examined the solvent effect of the reaction (Table 1, entries 12-14). Polar solvents such as diethyl ether gave poor enantioselectivity. DCM and Chloroform led to moderate yields and enantioselectivities. Toluene was found to be the ideal solvent for this reaction. Reducing catalyst loading to 5 mol% and 2 mol% led to only a slight loss of the enantioselectivity (Table 1, entries 15 - 16).

Table 2 Substrate scope^[a]

^a The reaction of **1** (0.1 mmol) and **2** (0.12 mmol) was carried out in 2 mL of toluene at -40 °C in the presence of catalyst **3e** (10 mol%).

With the optimized reaction condition in hand, we then examined the scope of the substrates (Table 2). Generally, for various substituted *o*-QMs tested, the reaction run smoothly and gave the desired product in very high yields. In terms of enantioselectivity, the electronic feature of substrates did not play an obvious part. Corresponding ortho-Quinone methides showed high reactivity and led to the product (**3a** - **3g**) in high enantioselectivity ranging from 90 to 94% ee. *o*-QMs bearing an electron-withdrawing group exhibited much higher reactivity (**3e**, **3g**). Thiophenyl and naphenyl substituted *o*-QMs also tolerated the reaction pretty well, giving the corresponding product with excellent yield and enantioselectivity (**4h**, **4i**). Importantly, 4*H*-4-aryl-chromene, which holds great potential as antitumor agent, could also be synthesized with excellent yield and enantioselectivity (**4j**). 4*H*-4-Vinyl chromene **4k** was obtained as well with 98% yield and 91% ee. The absolute configuration of **4b** was determined by X-ray analysis of its single crystal.

Due to the enantioenriched 2-amino-3-cyano-4*H*-chromenes synthesized via our methodology hold potential as antitumor agents, we tried to scale up the reaction (Scheme 2). To our delight, under 2 mol% catalytic amount, 6mmol **1a** (1.512g) and 9 mmol malononitrile (**2a**, 0.621g) was able to generate **4a** in 95% yield and 90% ee.



In conclusion, we have developed a chiral bifunctional-organocatalyzed formal 4+2 reaction of ortho-quinone methides and malononitrile, providing 2-amino-3-cyano-4*H*-chromenes, a class of potential anti-cancer agents, in excellent yields and enantioselectivities. Employed as catalyst, quinine is the best choice for our reaction, which represents excellent generality for a diversity of ortho-quinone methides, and leads to high yields and enantioselectivity. Significantly, we also managed to scale up the reaction with excellent results. Further studies will be continued on constructing complex molecules from ortho-quinone methides.

This work was supported by the Fundamental Research Funds for the Central Universities (WK2060190041).

Notes and references

Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China.

E-mail: hanzy2014@ustc.edu.cn; Fax: +86-551-3606266

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

- S. Kasibhatla, H. Gourdeau, K. Meerovitch, J. Drewe, S. Reddy, L. Oiu, H. Zhang, F. Bergeron, D. Bouffard, Q. Yang, J. Herich, S. Lamothe, S. X. Cai and B. Tseng, *Molecular Cancer Therapeutics*, 2004, **3**, 1365-1373.
- W. Kemnitzer, J. Drewe, S. C. Jiang, H. Zhang, Y. Wang, J. H. Zhao, S. J. Jia, J. Herich, D. Labreque, R. Storer, K. Meerovitch, D. Bouffard, R. Rej, R. Denis, C. Blais, S. Lamothe, G. Attardo, H. Gourdeau, B. Tseng, S. Kasibhatla and S. X. Cai, *J. Med. Chem.*, 2004, **47**, 6299-6310.
- W. Kemnitzer, S. Kasibhatla, S. C. Jiang, H. Zhang, J. H. Zhao, S. J. Jia, L. F. Xu, C. Crogan-Grundy, R. Denis, N. Barriault, L. Vaillancourt, S. Charron, J. Dodd, G. Attardo, D. Labrecque, S. Lamothe, H. Gourdeau, B. Tseng, J. Drewe and S. X. Cai, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4745-4751.
- ClinicalTrials.gov Identifier: NCT01240590.
- S. X. D. Cai, J. A.; Kasibhatla, S.; Kemnitzer, W. D.; Tseng, B. Y.; Blais, C.; Labreque, D.; Gourdeau, H., U.S. Patent 7,968,595 B2, 2011.
- A. M. Shestopalov, Y. M. Litvinov, L. A. Rodinovskaya, O. R. Malyshev, M. N. Semenova and V. V. Semenov, *ACS Comb Sci*, 2012, **14**, 484-490.
- A. G. A. Elagamey, S. Z. Sawllim, F. M. A. Eltaweel and M. H. Elnagdi, *Collect. Czech. Chem. Commun.*, 1988, **53**, 1534-1538.

8. C. P. Dell, J. Bloxham and C. W. Smith, *Heterocycles*, 1994, **38**, 399.
9. R. Ballini, G. Bosica, M. L. Conforti, R. Maggi, A. Mazzacani, P. Righi and G. Sartori, *Tetrahedron*, 2001, **57**, 1395-1398.
10. T. S. Jin, J. S. Zhang, L. B. Liu, A. Q. Wang and T. S. Li, *Synth. Commun.*, 2006, **36**, 2009-2015.
11. A. Q. Zhang, M. Zhang, H. H. Chen, J. Chen and H. Y. Chen, *Synth. Commun.*, 2007, **37**, 231-235.
12. X.-S. Wang, G.-S. Yang and G. Zhao, *Tetrahedron: Asymmetry*, 2008, **19**, 709-714.
13. K. Hu, A. Lu, Y. Wang, Z. Zhou and C. Tang, *Tetrahedron-Asymmetry*, 2013, **24**, 953-957.
14. Y. Gao and D.-M. Du, *Chem. Asian J.*, 2014, **9**, 2970-2974.
15. R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367-5405.
16. S. Bissada, C. K. Lau, M. A. Bernstein and C. Dufresne, *Can. J. Chem.*, 1994, **72**, 1866-1869.
17. N. J. Willis and C. D. Bray, *Chem. Eur. J.*, 2012, **18**, 9160-9173.
18. Y. Genisson, P. C. Tyler and R. N. Young, *J. Am. Chem. Soc.*, 1994, **116**, 759-760.
19. T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210-9215.
20. Y. Luan and S. E. Schaus, *J. Am. Chem. Soc.*, 2012, **134**, 19965-19968.
21. C. Selenski and T. R. Pettus, *J. Org. Chem.*, 2004, **69**, 9196-9203.
22. E. Alden-Danforth, M. T. Scerba and T. Lectka, *Org. Lett.*, 2008, **10**, 4951-4953.
23. T. Bekele, M. H. Shah, J. Wolfer, C. J. Abraham, A. Weatherwax and T. Lectka, *J. Am. Chem. Soc.*, 2006, **128**, 1810-1811.
24. T. P. Pathak and M. S. Sigman, *Org. Lett.*, 2011, **13**, 2774-2777.
25. J. Izquierdo, A. Orue and K. A. Scheidt, *J. Am. Chem. Soc.*, 2013, **135**, 10634-10637.
26. H. Lv, W. Q. Jia, L. H. Sun and S. Ye, *Angew. Chem. Int. Ed.*, 2013, **52**, 8607-8610.
27. H. Lv, L. You and S. Ye, *Adv. Synth. Catal.*, 2009, **351**, 2822-2826.
28. O. El-Sepelgy, S. Haseloff, S. K. Alamsetti and C. Schneider, *Angew. Chem. Int. Ed.*, 2014, **53**, 7923-7927.
29. M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901-4902.
30. T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672-12673.
31. A. Hamza, G. Schubert, T. Soos and I. Papai, *J. Am. Chem. Soc.*, 2006, **128**, 13151-13160.
32. Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299-4306.
33. S. J. Connon, *Chem. Eur. J.*, 2006, **12**, 5418-5427.