ORGANIC LETTERS

2011
Vol. 13, No. 18
4910–4913

# Enantioselective One-Pot Synthesis of 2-Amino-4-(indol-3-yl)-4*H*-Chromenes

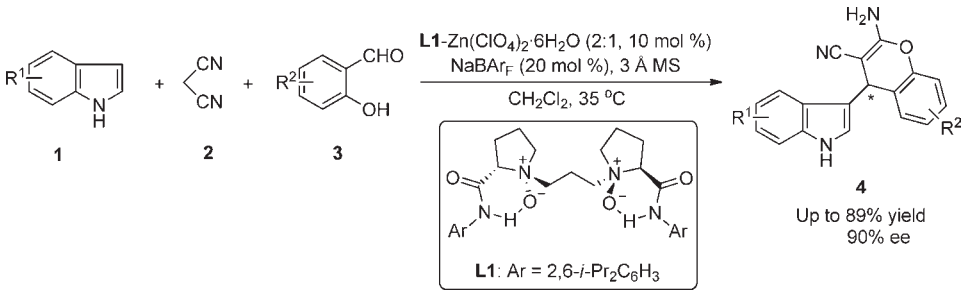
**Weiliang Chen, Yunfei Cai, Xuan Fu, Xiaohua Liu, Lili Lin, and Xiaoming Feng***

*Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China*

*xmfeng@scu.edu.cn*

**Received July 23, 2011**

## ABSTRACT




**An enantioselective one-pot synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromenes via a Knoevenagel/Pinner/Friedel–Crafts reaction of salicylaldehyde, malononitrile, and indole is presented. Moderate to good yields (up to 89%) and high enantioselectivities (up to 90% ee) were obtained with an *N,N'*-dioxide–Zn(II) complex as the catalyst. This strategy provides an efficient and convenient method to access enantiomerically enriched 2-amino-4*H*-chromene derivatives.**

Chromenes are the structural motifs frequently found in a number of natural products and biologically active molecules.[1] Their syntheses have attracted wide attention for their biological properties, such as anticancer, diuretic, spasmolytic, anticoagulant, and antianaphylactic activities.[2] Optically active 2-amino-4*H*-chromenes are particularly privileged pharmacological scaffolds among the chromene family members.[3] As such, the development of efficiently catalytic asymmetric approaches toward this structural class is of significant interest. One of the direct methods for the asymmetric synthesis of 2-amino-4*H*-chromene derivatives is through a Michael reaction of malononitrile to enones to generate a chiral center, following the intramolecular cyclization. Cinchona derivatives or thiourea were found to be efficient catalysts.[4] Very recently, a chiral thiourea-catalyzed Mannich/cyclization sequence was also applied to

(1) (a) Ellis, G. P.; Lockhart, I. M. In *The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 31, pp 1–1196. (b) Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II: Pyrans and Their Benzo Derivatives: Synthesis*; Katritzky, A. R., Rees, C. W., Scrien, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 351–468. (c) Geen, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II: Pyrans and Their Benzo Derivatives: Applications*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 469–500.

(2) (a) Foye, W. O. *Principi Di Chemico Farmaceutica*; Piccin: Padova, Italy, 1991; p 416. (b) Andreani, L. L.; Lapi, E. *Bull. Chim. Farm.* **1960**, *99*, 583. (c) Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H. *Yao Xue Xue Bao* **1982**, *17*, 17. *Chem. Abstr.* **1982**, *96*, 135383e. (d) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517. (e) Witte, E. C.; Neubert, P.; Roesch, A. *Ger. Offen DE. (Cl. C07D4052)* **1986**, 25. *Chem. Abstr.* **1986**, *104*, 224915f.

(3) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235. (b) Wang, J. L.; Liu, D. X.; Zhang, Z. J.; Shan, S. M.; Han, X. B.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124. (c) Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor, A. E. *Bioorg. Med. Chem.* **2006**, *14*, 4792. (d) Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. *Eur. J. Med. Chem.* **2009**, *44*, 3805. (e) Kemnitzer, W.; Jiang, S.; Wang, Y.; Kasibhatla, S.; Crogan-Grundy, C.; Bubenik, M.; Labrecque, D.; Denis, R.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 603. (f) Kemnitzer, W.; Drewe, J.; Jiang, S. C.; Zhang, H.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 417.

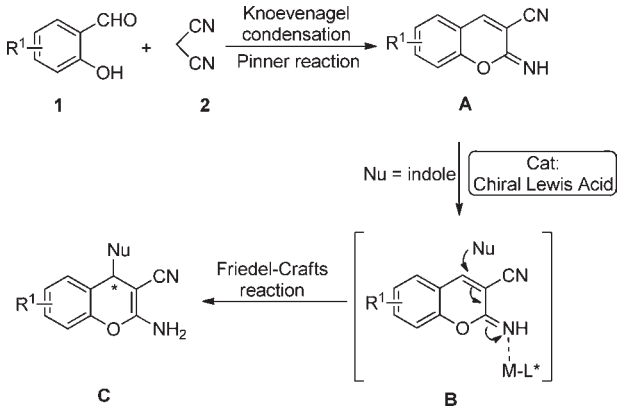
(4) (a) Xie, J. W.; Huang, X.; Fan, L. P.; Xu, D. C.; Li, X. S.; Su, H.; Wen, Y. H. *Adv. Synth. Catal.* **2009**, *351*, 3077. (b) Hu, Z. P.; Lou, C. L.; Wang, J. J.; Chen, C. X.; Yan, M. *J. Org. Chem.* **2011**, *76*, 3797. (c) Ren, Q.; Gao, Y. J.; Wang, J. *Chem.—Eur. J.* **2010**, *16*, 13594.

(5) Ren, Q.; Siau, W. Y.; Du, Z. Y.; Zhang, K.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 7781.

10.1021/ol2019949 
**Published on Web 08/22/2011**

the synthesis of optically active 2-amino-4*H*-chromene derivatives.[5]

**Scheme 1.** Strategy for the Asymmetric Synthesis of 2-Amino-4*H*-chromene Derivatives




It has been well-known that the iminochromene intermediates **A** can be generated from the Knoevenagel condensation of salicylaldehydes with malononitrile, followed by a Pinner reaction (Scheme 1).[6] $InCl_3$ has been proven to be efficient for such a domino reaction to access 2-amino-4*H*-chromenes.[6b] We envisioned that a suitable chiral Lewis acid might promote the enantioselective nucleophilic addition to this intermediate, thereby delivering a variety of novel enantiomerically pure 2-amino-4*H*-chromenes **C**. Herein, we report the successful application of such an approach in the one-pot domino reaction involving Knoevenagel condensation, Pinner reaction, and Friedel–Crafts alkylation processes. *N,N*′-Dioxide–Zn(II) complex[7] was developed to access optically active 2-amino-4-(indol-3-yl)-4*H*-chromene derivatives for the first time, in which another privileged moiety of indole[8] was combined.

Initially, the reaction of indole **1a**, malononitrile **2**, and salicylaldehyde **3a** was selected as the model substrates for the catalyst screening study. The primary metal screening was performed with *N,N*′-dioxide **L1** derived from L-proline, and the results are listed in Table 1. When $Sc(OTf)_3$, $Mg(OTf)_2$, and $Ni(ClO_4)_2 \cdot 6H_2O$ were examined, only very low enantioselectivities were obtained (Table 1, entries 1–3). Fortunately, $Zn(OTf)_2$ showed potential activity in this reaction, giving the product **4a** in 36% yield with 47% ee (Table 1, entry 4). Then the molar ratio of **L1** to $Zn(OTf)_2$ was investigated. When the molar ratio of **L1**/$Zn(OTf)_2$ was increased from 1:1 to 2:1, the enantioselectivity increased from 47 to 62% ee (Table 1, entries 4 and 5); further increasing the ratio to 3:1 was disfavorable for the reaction (8% ee, Table 1, entry 6). Thus the molar ratio of 2:1 (**L1**/$Zn(OTf)_2$) was the most efficient.

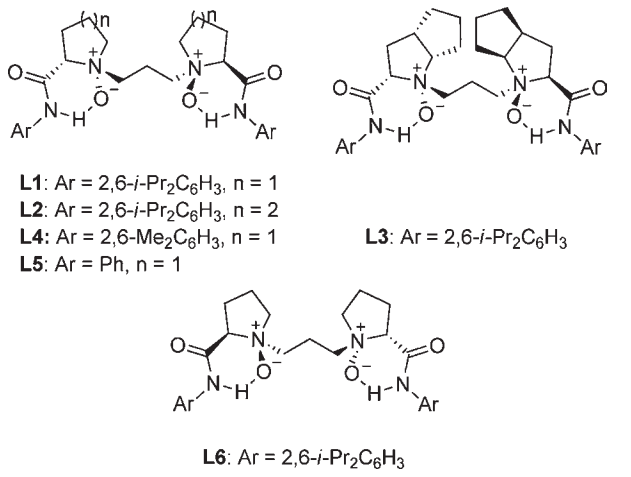



**Figure 1.** Chiral ligands used in this study.

Further optimization of the reaction conditions was aimed at exploring effective ligands (Figure 1). Both the chiral backbone and the steric hindrance of the amide moiety exhibited their considerable influence on the enantioselectivity of the reaction. L-Proline-derived **L1** was superior to that derived from (*S*)-pipecolic acid and L-ramipril (Table 1, entry 5 vs entries 7 and 8). If a less bulky substitute was introduced at the *ortho*-position of the aniline, the ee value decreased remarkably (Table 1, entry 5 vs entries 9 and 10). Thus, **L1** was chosen as the optimal ligand. The nature of the counterion of the central metal was found to be another factor significantly influencing the enantioselectivity and reactivity of the reaction. We envisioned that the larger and noncoordinating counterion might benefit the enantiocontrol of the reaction.[9] To our delight, when 20 mol % of $NaBAr_F$ was added,[10] the enantioselectivity of the reaction dramatically increased to 82% ee with 78% yield (Table 1, entry 11). In the presence of $NaBAr_F$, various Zn(II) salts were also studied. $Zn(ClO_4)_2 \cdot 6H_2O$ possessed more advantage over $ZnBr_2$ and $Zn(OTf)_2$ in enantioselectivity (Table 1, entry 13 vs entries 11 and 12). Further optimization for the reaction system revealed that 3 Å MS as an additive was the optimal choice. Therefore, the optimal conditions were

(6) (a) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, *46*, 6453. (b) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 6785.

(7) For selected examples of *N,N*′-dioxide–metal complexes in nucleophilic addition reactions, see: (a) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574. (b) Xie, M. S.; Chen, X. H.; Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799. (c) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (d) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2010**, *132*, 8532. (e) Wang, W. T.; Liu, X. H.; Cao, W. D.; Wang, J.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 1664. (f) Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Cai, Y. F.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290. (g) Zheng, K.; Yin, C. K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573.

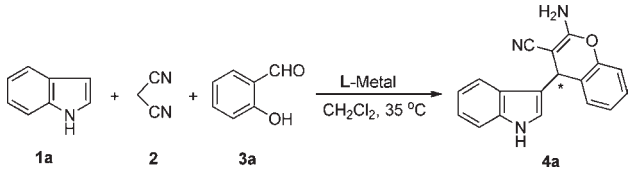
(8) (a) Saracoglua, N. *Bioactive Heterocycles V*; Springer: Berlin, 2007; pp 1–61. (b) Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles: Part I*; Wiley: New York, 1992.

(9) (a) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834. (b) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 932.

(10) $BArF^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

as follows: malononitrile (0.10 mmol), indole (0.11 mmol), salicylaldehyde (0.10 mmol), **L1**−$Zn(ClO_4)_2 \cdot 6H_2O$ (**L1**/$Zn(ClO_4)_2 \cdot 6H_2O$ = 2:1, 10 mol %), $NaBAr_F$ (20 mol %), and 3 Å MS (20 mg) in $CH_2Cl_2$ (0.5 mL) at 35 °C.

**Table 1.** Evaluation of Reaction Parameters[a]

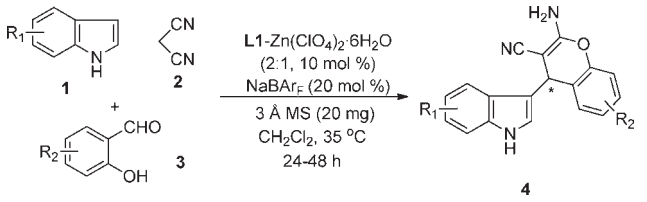



| entry | ligand | metal | **L**/metal | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **L1** | $Mg(OTf)_2$ | 1:1 | 51 | 3 |
| 2 | **L1** | $Sc(OTf)_3$ | 1:1 | trace | |
| 3 | **L1** | $Ni(ClO_4)_2 \cdot 6H_2O$ | 1:1 | 16 | 14 |
| 4 | **L1** | $Zn(OTf)_2$ | 1:1 | 36 | 47 |
| 5 | **L1** | $Zn(OTf)_2$ | 2:1 | 84 | 62 |
| 6 | **L1** | $Zn(OTf)_2$ | 3:1 | 87 | 8 |
| 7 | **L2** | $Zn(OTf)_2$ | 2:1 | 50 | 44 |
| 8 | **L3** | $Zn(OTf)_2$ | 2:1 | 56 | 54 |
| 9 | **L4** | $Zn(OTf)_2$ | 2:1 | 91 | 30 |
| 10 | **L5** | $Zn(OTf)_2$ | 2:1 | 96 | 5 |
| 11[d] | **L1** | $Zn(OTf)_2$ | 2:1 | 78 | 82 |
| 12[d] | **L1** | $ZnBr_2$ | 2:1 | 94 | 74 |
| 13[d] | **L1** | $Zn(ClO_4)_2 \cdot 6H_2O$ | 2:1 | 76 | 84 |
| 14[d,e] | **L1** | $Zn(ClO_4)_2 \cdot 6H_2O$ | 2:1 | 87 | 87 |

[a] Unless otherwise noted, reactions were carried out with 10 mol % of catalyst in $CH_2Cl_2$ (0.5 mL) at 35 °C for 26 h. [b] Isolated yield. [c] Determined by HPLC using chiral IB column. [d] 20 mol % of $NaBAr_F$ was added. [e] 3 Å MS (20 mg) was used.

To investigate the scope of the reaction, we first examined a range of indoles with malononitrile **2** and salicylaldehyde **3a** under the optimized conditions, and good results were obtained (Table 2, entries 1−9). The enantioselectivity and reactivity of the reaction were found to be sensitive to the electronic property of the indole. Generally, indoles containing electron-withdrawing groups on the aromatic ring gave higher enantioselectivities than those with electron-donating groups (Table 2, entries 1−5 vs 6−9). The 5-bromoindole **1d** gave the highest enantioselectivity (90% *ee*) among the indoles (Table 2, entry 4). Then, various salicylaldehydes were also examined, and good enantioselectivity were obtained. When 4-methoxyl-substituted salicylaldehyde was used, only 37% yield was obtained with 81% ee (Table 2, entry 10). 3,5-Di-*tert*-butyl-substituted salicylaldehyde gave lower yield with higher ee as a result of steric hindrance (41% yield, 90% ee, Table 2, entry 11). The 2-hydroxy-1-naphthaldehyde was found to be suitable in the reaction, delivering the corresponding product in 70% yield and 87% ee (Table 2, entry 12). Other salicylaldehyde derivatives proceeded well with **1a** to give the products **4m**, **4n**, and **4o** with 90%, 90%, and 84% ee, respectively[11] (Table 2, entries 13−15). Several substituted indoles and substituted salicylaldehydes were also tested, with good results obtained (88% and 87% ee, Table 2, entries 16 and 17). The oppositely configured

**Table 2.** Substrate Scope for the Domino Knoevenagel/Pinner/Friedel−Crafts Alkylation[a]




| entry | $R_1$ | $R_2$ | prod. | time (h) | yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 | H | H | **4a** | 26 | 87 | 87(*S*)[d] |
| 2 | 5-F | H | **4b** | 48 | 81 | 83 |
| 3 | 5-Cl | H | **4c** | 48 | 85 | 88 |
| 4 | 5-Br | H | **4d** | 48 | 75 | 90 |
| 5 | 6-Cl | H | **4e** | 48 | 82 | 85 |
| 6 | 5-Me | H | **4f** | 40 | 83 | 83 |
| 7 | 5-MeO | H | **4g** | 26 | 89 | 80 |
| 8 | 6-MeO | H | **4h** | 26 | 78 | 80 |
| 9 | 4-MeO | H | **4i** | 30 | 81 | 80 |
| 10 | H | 4-MeO | **4j** | 48 | 37 | 81 |
| 11 | H | 3,5-*t*Bu$_2$ | **4k** | 48 | 41 | 90 |
| 12 | H |  | **4l** | 48 | 70 | 87 |
| 13 | H | 5-MeO | **4m** | 48 | 85 | 90 |
| 14 | H | 5-Me | **4n** | 48 | 81 | 90 |
| 15 | H | 3-Me | **4o** | 48 | 78 | 84 |
| 16 | 6-Cl | 5-MeO | **4p** | 60 | 68 | 88 |
| 17 | 5-Br | 5-Me | **4q** | 60 | 67 | 87 |
| 18[e] | H | H | **4r** | 26 | 88 | 86(*R*) |
| 19[e] | 5-Cl | H | **4s** | 48 | 86 | 88 |
| 20[e] | 5-Br | H | **4t** | 48 | 79 | 89 |
| 21[e] | H | 5-MeO | **4u** | 48 | 82 | 89 |

[a] Unless otherwise noted, reactions were carried out with **L1** (20 mol %), $Zn(ClO_4)_2 \cdot 6H_2O$ (10 mol %), $NaBAr_F$ (20 mol %), 20 mg of 3 Å MS in $CH_2Cl_2$ (0.5 mL) at 35 °C. [b] Isolated yield. [c] Determined by HPLC using chiral IB or IC column. [d] The absolute configuration was determined to be *S* by X-ray crystallographic analysis. [e] **L6** was employed as the ligand instead of **L1**.

products were obtained in good enantioselectivities and yields by the use of **L6** derived from D-proline (Table 2, enrties 18−21).

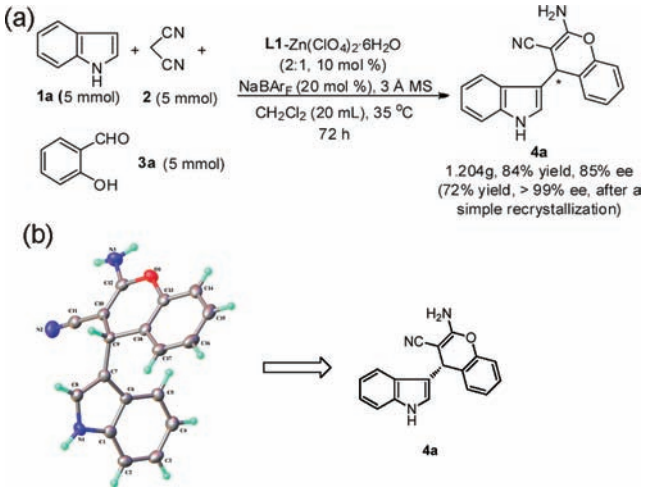
To show the potentially practical synthesis of the chiral chromene derivatives through the current method, a scaled-up version was performed. By treatment of 5 mmol of indole **1a** under the optimal reaction conditions, the desired product was produced without obvious loss of reactivity or enantioselectivity (Scheme 2a). The enantiopure product could be obtained by a simple recrystallization using petroleum ether and ethyl acetate. The absolute

(11) Salicylaldehydes with electron-withdrawing groups on the aromatic ring were also tested, only giving disappointing results.

(12) CCDC833191 (**4a**) contains the supplementary crystallographic date for this paper. These data can be obtained free from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

configuration of **4a** was determined to be *S* configuration by single-crystal X-ray analysis (Scheme 2b).[12]

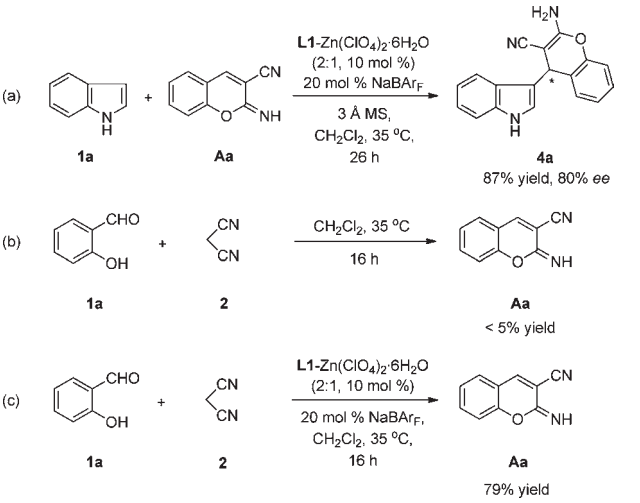
**Scheme 2.** (a) Scale-up Version of the Reaction and (b) Absolute Configuration of **4a** Determined by X-ray Crystallographic Analysis




For the purpose of illustrating the process of the reaction, some control experiments were carried out (Scheme 3). Under the optimized conditions, iminochromene **Aa** proceeds smoothly with indole **1a**, delivering the product **4a** in 87% yield with 80% ee (Scheme 3a). It indicated that **Aa** was probably the intermediate of the reaction. Additionally, the function of the catalyst in the formation of intermediate **Aa** was also investigated. Only trace amounts of **Aa** were detected from salicylaldehyde and malononitrile without the catalyst, while a 79% yield of **Aa** was obtained in the presence of the catalyst (Scheme 3c vs Scheme 3b). Thus, the catalyst was favorable for both the formation of the intermediate **Aa** and the enantioselective Friedel–Crafts alkylation process.

In summary, an efficient synthesis of enantioenriched 2-amino-4-(indol-3-yl)-4*H*-chromenes was presented by the use of 10 mol % of an *N*,*N*′-dioxide–Zn(II) complex

**Scheme 3.** Control Experiments




as the catalyst. Various indoles and salicylaldehydes were tested, giving the corresponding products in good yields with high enantioselectivities (up to 90% ee) under mild conditions. The reaction could be amplified to gram scales, which showed the potential value of the catalyst system. Further studies will be focused on cataytic asymmetric synthesis of other optically active chromenes.

**Acknowledgment.** The paper is dedicated to Professor Christian Bruneau on the occasion of his 60th birthday. We appreciate the National Natural Science Foundation of China (Nos. 20732003 and 21021001), and the Basic Research Program of China (973 Program: 2011CB808601) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR and X-ray analysis.

**Supporting Information Available.** Experimental procedures, spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.