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Expeditious Assembly of a 2-Amino-4*H*-chromene Skeleton by Using an Enantioselective Mannich Intramolecular Ring Cyclization–Tautomerization Cascade Sequence

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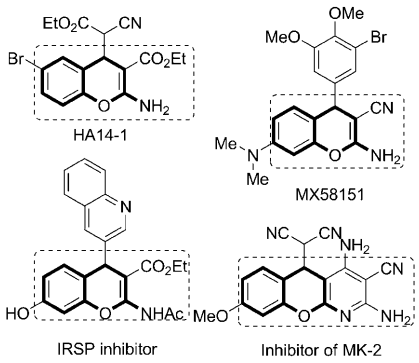
The concept of a "privileged medicinal scaffold" has emerged as one of the most guiding principles in the process of drug discovery.[1] The privileged scaffold commonly consists of a rigid hetero-ring system that assigns a well-defined orientation of appended functionalities for target recognition.[2] In the light of this, the accessibility of convenient methods for the diversification of privileged scaffold functionalities impacts on the success in seeking potential drugs. Undoubtedly, the discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point in modern medicinal chemistry.[3]

Chromene, as one of the privileged scaffolds, often appears as an important structural component in both biologically active and natural compounds. It has widely appeared in natural alkaloids, tocopherols, flavonoids, and anthocyanins.[4] Moreover, in recent years functionalized chromenes have played an ever-increasing role in the field of synthetic and medicinal chemistry.[5] Among the diverse chromene systems, 2-amino-4*H*-chromenes are particularly privileged medicinal scaffolds for the generation of small-molecule-based ligands with highly pronounced spasmolytic, diuretic, anticoagulant, and antianaphylactic activities.[6] In particular, the current interest in 2-amino-4*H*-chromene derivatives with a nitrile functionality arises from their potential application in the treatment of human inflammatory tumor necrosis factor (TNF)α-mediated diseases, such as rheumatoid and psoriatic arthritis.[7]

The corresponding cyano-functionalized benzopyranopyridine (inhibitor of MK-2) originating from the 2-amino-4*H*-chromene scaffold was found to inhibit mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK-2) and suppress the expression of TNFα in U937 cells.[7a] In the case of cancer therapy, the tumor antagonist HA14-1 and a



family of related alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of the cancer-implicated Bcl-2 protein and induce apoptosis or programmed cell death in follicular lymphoma B cells and leukemia HL-60 cells.[7b] The 2-amino-3-cyano-4*H*-chromene MX58151, with a 3-bromo-4,5-dimethoxyphenyl substituent at the 4-position, represents a promising class of proapoptotic small-molecule agents with multiple action modes against the breast cancer cell line T47D, the lung cancer cell line H1299, and the colorectal cancer cell line DLD-1.[7c,f] It induces caspase-mediated apoptosis in tumor cells and is about as potent as or slightly more potent than the commonly prescribed anticancer alkaloids Vinblastine and Paclitaxel in the caspase activation assay.[7f] Furthermore, compound MX58151 might have an advantage for the treatment of the drug-resistant cancers as it retains activity in tumor cells resistant towards current antimitotic agents, taxanes (including Taxol and Taxotere), and the Vinca alkaloids.[7c,f] The inhibition of tubuline polymerization and disruption of preformed endothelial cell capillary tubules constitute other significant activities of 2-amino-3-cyano-4-aryl-4*H*-chromenes of type 3 that can place them in the row of effective anticancer therapeutics with an analogous mode of action.[7c,f] Most recently, another 2-amino-4-aryl-4*H*-chromene compound (IRSP inhibitor) has been discovered as an insulin-regulated aminopeptidase inhibitor. In particular, this inhibitor is maybe useful in therapeutic application including enhancing memory and learning functions.[7g]

In view of the significance of this framework, efficient syntheses of 2-amino-4*H*-chromenes are of great interest.

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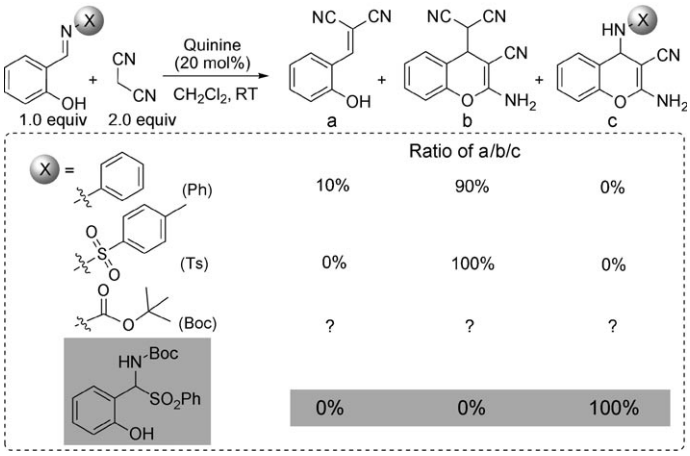
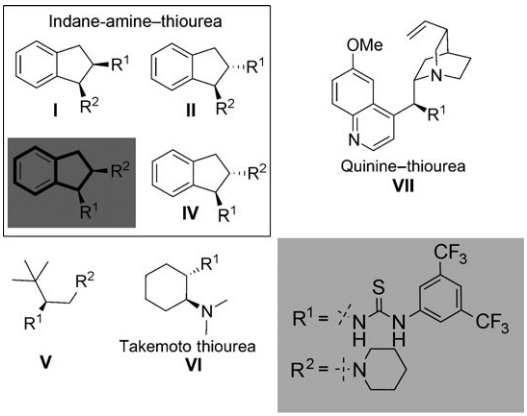
Despite the fact that asymmetric organocatalysis has evolved as a powerful tool for the preparation of enantiomerically enriched compound,[8] organocatalytic methods to generate optically pure 2-amino-4*H*-chromenes are still absent. Recently, hydrogen-bonding-mediated catalysis for C–C bond formation has been discovered as a powerful new tool and synthetic method for the efficient construction of molecular architectures.[9] In particular, there was a remarkable development and application on chiral bifunctional thiourea catalysis.[10] The utilization of inexpensive and readily synthesized chiral thiourea catalysts has attracted considerable interest and proved to be effective in several asymmetric transformations. Herein, we document a novel strategy for the preparation of chiral 2-amino-4*H*-chromenes through a hydrogen-bonding-mediated enantioselective cascade process. To date, such a progress has not been described. Significantly, this strategy allowed a quick construction of diversely functionalized 2-amino-4*H*-chromenes under mild reaction conditions and with good to high enantioselectivities (74–89% enantiomeric excess (*ee*)) and high to excellent yields (81–94%) could be achieved. In this context, we sought to extent the usage of the indane catalytic system for the construction of novel and useful complexes based on the several successful examples disclosed by our research group.

We began our investigation by examining the organic base catalyzed reaction of α-substituted ketones with β,γ-unsaturated ketoesters. The initial experiment results showed that the use of a catalytic amount of quinine enabled a reaction between 2-hydroxy imine and malononitrile. Surprisingly, if a phenyl group was introduced to 2-hydroxy imine, a mixture of undesired compounds **a** and **b** were generated in 10 min (Scheme 1, **a**/**b** = 10:90). Then, we tried a stronger electron-withdrawing group involved 2-hydroxy *N*-Ts imine (Scheme 1, X = tosyl, (Ts)). However, only compound **b** was finally produced (Scheme 1, **a**/**b** = 0:100). Based on above experimental results, we deduced that both strong electron-withdrawing groups and good leaving groups on the 2-hydroxyl imine might assist the Knoevenagel-type reaction to form intermediate **a**. Then, intermediate **a** trigged the sequential reactions to generate the undesired compound **b**. To avoid these side reactions, we decided to introduce a poor leaving group (X = *tert*-butoxycarbonyl (Boc)) with a less electron-withdrawing character into the imine structure. To our knowledge, *N*-Boc protected imine is an ideal choice. Unfortunately, we failed to seek a successful method to synthesize 2-hydroxyl *N*-Boc imine (Scheme 1). Instead, a *N*-Boc α-amido sulfone,[11] one of the precursors of *N*-Boc imine, was used to react with malononitrile. Gratifyingly, the investigation showed only desired compound **c** was afforded (Scheme 1, **a**/**b**/**c** = 0:0:100).



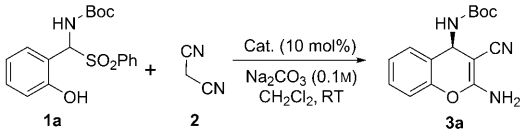
Scheme 1. Investigation of 2-hydroxyimines.

With the initial experiments in hand, we then went on to probe the asymmetric catalytic feasibility of this reaction. *tert*-Butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate (**1a**) was treated with malononitrile **2** in the presence of catalyst **VII** (quinine–thiourea), which was developed by the Soós, Dixon, and Connon groups, respectively (Scheme 2).[12] As shown in Table 1, catalyst **VII** gave a 43% yield in 10 min with a 16% *ee* (Table 1, entry 7). The Takemoto thiourea catalyst **VI** also only offered a 46% yield with a 42% *ee* (Table 1, entry 6). Consequently, the



Scheme 2. Bifunctional chiral organocatalysts.

Table 1. Evaluation of different bifunctional chiral organocatalysts.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**I**	38	29
2	**II**	43	9
3	**III**	50	77
4	**IV**	48	30
5	**V**	61	44
6	**VI**	46	42
7	**VII**	43	16

[a] Reaction conditions: CH_2Cl_2 (0.2 mL), *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate (**1a**, 0.1 mmol, 1.0 equiv), malononitrile **2** (0.11 mmol, 1.1 equiv), Na_2CO_3 solution (0.1 M, 0.12 mmol, 1.2 equiv), and catalyst (10 mol%) at RT. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

discovery of a novel and active chiral catalyst that could promote this reaction with both high efficiency and excellent stereocontrol became our main focus. In this context, we sought to extent the usage of the indane-amine–thiourea catalytic system based on several successful examples disclosed by our research group.[13] Undoubtedly, bifunctional indane-amine–thiourea organocatalysts demonstrated some unique aspects, such as higher activity, excellent stereocontrol, and a flexible skeleton. Catalyst **I**, **II**, and **IV** (Scheme 2) exhibited high stereoselectivity in several Michael addition reaction-triggered cascade processes. Unfortunately, catalyst **I** gave a poor result in this catalytic process (Table 1, 38% yield, 29% *ee*). Catalyst **III**, a similar analogue of catalyst **I** but with a switch of amine and thiourea functional groups, showed good enantioselectivity (Table 1, 50% yield, 77% *ee*). While the further improvements were ongoing, we noticed that the dihedral angle between the two functional groups on the catalyst was a critical factor in controlling the stereochemistry. Consequently, catalysts **II** and **IV** (Scheme 2) were synthesized with the amine and thiourea group *anti* to each other. In contrast to the structure of catalysts **I** and **III**, catalysts **II** and **IV** just have a chiral inversion on the amine part, respectively, but maintain all the other features. Results showed that catalysts **II** and **IV** were not the best catalysts (Table 1, entries 2 and 4, 9 and 30% *ee*, respectively). Meanwhile, we examined catalyst **V**, a L-*tert*-leucine derivative; however, only a moderate result was generated (Table 1, entry 5, 61% yield, 44% *ee*). Having failed to find a catalyst more promising than **III**, a base screen was then performed.

Optimization studies highlighted the ability of a range of bases, either solid or an aqueous solution (Table 2), to generate the *N*-Boc imine in situ. Stronger aqueous bases K_2CO_3, Cs_2CO_3, LiOH, or KOH, did increase the conversion to the desired product, but did not increase the *ee* value (Table 2, entries, 4, 5, 7, and 8). Use of solid Na_2CO_3 (no water) decreased the reaction rate and *ee* value (Table 2, entry 2, 720 min, 52% *ee*). A slightly weaker base Li_2CO_3 improved the reaction conversion and maintained the *ee* value (Table 2, entry 3, 88% yield, 77% *ee*). A slow conversion was observed when $NaHCO_3$ was used (Table 2, entry 9). This evidence prompted us to select aqueous Li_2CO_3 as the base media of choice and the further optimization of the standard reaction parameters was carried out.

For further optimization, solvent, as well as reaction temperature, were examined (Table 3). The initial solvent screen was performed at room temperature. In general, less polar solvents are crucial for obtaining good enantioselectivities at room temperature (Table 3, entries 1–5, 71–78% *ee*). For high polar solvents, relatively lower enantioselectivities were obtained due to the potential removal of the hydrogen-bonding interaction between the substrates and the catalyst (Table 3, entries 6 and 7, 20 and 45% *ee*, respectively). Finally, CH_2Cl_2 gave the best results with respect to reaction rate, yield and *ee* value (Table 3, entry 1). To further optimize the reaction, we varied the reaction temperature and the concentration of Li_2CO_3. The results showed that the enantioselectivity can be enhanced by an appropriate temperature and base concentration (Table 3, entry 10, 30 min, 94% yield, 88% *ee*).

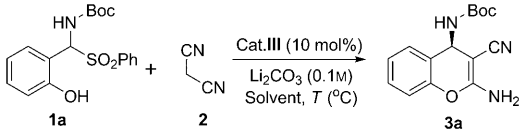
Under the optimized reaction conditions, the generality of our cascade process was examined by using various in situ generated aromatic *N*-carbamoyl α-imino ethyl glyoxylates **1a–i** (Scheme 3). Aromatic *N*-carbamoyl α-imino ethyl glyoxylates having both electron-withdrawing (Scheme 3, **3b–d**, 82–87% yield, 83–85% *ee*) and electron-donating sub-

Table 2. Base effect.[a]

Entry[a]	Base	*t* [min]	Yield [%][b]	*ee* [%][c]
1	Na_2CO_3	10	50	77
2[d]	Na_2CO_3	720	74	52
3	Li_2CO_3	10	88	77
4	K_2CO_3	10	70	76
5	Cs_2CO_3	10	77	74
6	$(NH_4)_2CO_3$	30	86	74
7	LiOH	2	71	73
8	NaOH	2	82	71
9	$NaHCO_3$	180	85	68

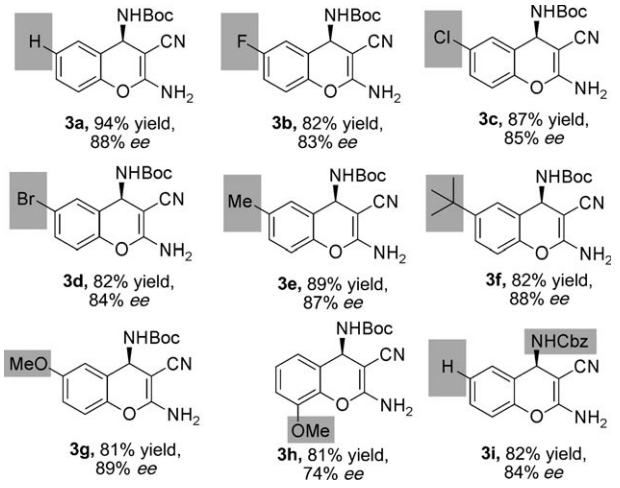
[a] Reaction conditions: *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate (**1a**, 0.1 mmol, 1.0 equiv), malononitrile **2** (0.11 mmol, 1.1 equiv), base (0.1 M, 0.12 mmol, 1.2 equiv), and catalyst **III** (10 mol%) in CH_2Cl_2 (0.2 mL) at RT. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC. [d] 0.12 mmol of dry Na_2CO_3 was used.

Table 3. Evaluation of other parameters.[a]



Entry	Solvent	*T* [°C]	*c* [mol L^{-1}][b]	*t* [min]	Yield [%][c]	*ee* [%][d]
1	CH_2Cl_2	RT	0.5	10	88	77
2	$C_2H_2Cl_2$	RT	0.5	10	78	71
3	Toluene	RT	0.5	60	72	76
4	$PhCF_3$	RT	0.5	60	80	72
5	Anisole	RT	0.5	60	67	78
6	*i*PrOH	RT	0.5	60	67	27
7	DMSO	RT	0.5	60	77	3
8	CH_2Cl_2	0	0.5	10	89	79
9	CH_2Cl_2	0	0.1	10	90	83
10	CH_2Cl_2	0	0.05	30	94	88
11	CH_2Cl_2	0	0.025	120	94	83
12	CH_2Cl_2	−10	0.05	180	92	83

[a] Reaction conditions: *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate (**1a**, 0.1 mmol, 1.0 equiv), malononitrile **2** (0.11 mmol, 1.1 equiv), Li_2CO_3 (0.1 M, 0.12 mmol, 1.2 equiv), and catalyst **III** (10 mol%). [b] Concentration. [c] Yield of isolated product after column chromatography. [d] Enantiomeric excess (*ee*) was determined by HPLC.



Scheme 3. Substrate scope under the optimized conditions; see Table 3, entry 10.

stituents (Scheme 3, **3e–h**, 81–89% yield, 74–89% *ee*) could be applied to this transformation; the substitution pattern of the arene had limited influence on the enantioselectivity of the reaction. In addition, it was possible to use carbobenzyloxy (Cbz) as protecting group in this reaction (Scheme 3, **3i**, 82% yield, 84% *ee*). The absolute configuration of the products was determined by single-crystal X-ray analysis of **3d** (Figure 1).[14]

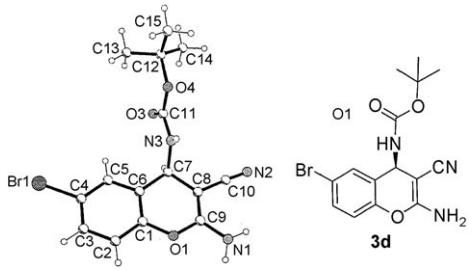
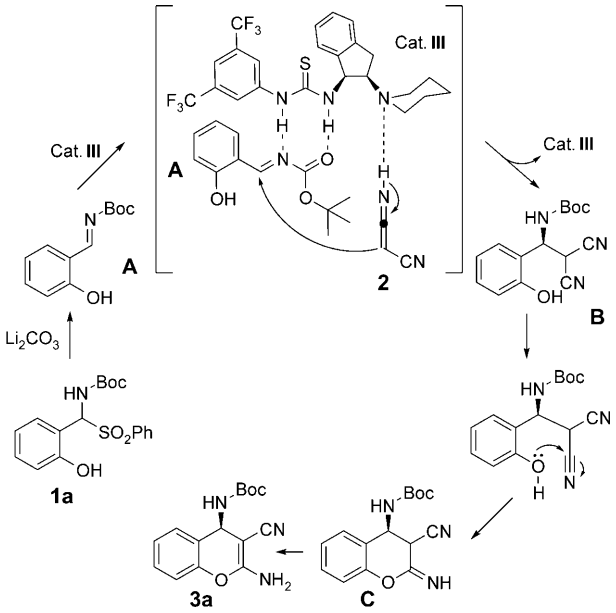


Figure 1. X-ray crystal structure of **3d**.

Our postulated reaction pathways are summarized in Scheme 4. In the initial step, an elimination of compound **1a** causes formation of the intermediate imine **A** under the presence of Li_2CO_3. The subsequent Mannich reaction of intermediate **A** with malononitrile **2** forms the intermediate **B** catalyzed by indane-amine–thiourea **III**. Then, the intramolecular oxa-nucleophilic addition of nitrile group leads to the intermediate **C**. Finally, intermediate **C** undergoes a tautomerization to offer the desired compound **3a**.

In summary, we have developed an efficient and convenient cascade process for the synthesis of 2-amino-4*H*-chromenes in high to excellent yields (81–94%) and with good to high enantioselectivities (74–89% *ee*). This protocol proceeded through a Mannich cyclization–tautomerization cascade sequence. We hope that the catalytic system and strategy demonstrated here could be applied to other asymmetric transformations to efficiently assemble chiral materials with complex structures. Further elaboration of the products to other types of biologically active compounds and the potential application of the catalytic system are now ongoing in our group.



Scheme 4. Proposed catalytic cycle.

Experimental Section

General procedure: To a solution of *tert*-butyl (2-hydroxyphenyl) (phenylsulfonyl)methylcarbamate **1a** (0.1 mmol, 1.0 equiv), malononitrile **2** (0.11 mmol, 1.1 equiv) and catalyst **III** (0.01 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C, was added chilled lithium carbonate aqueous solution (0.1 M, 0.12 mmol, 1.2 equiv) in one portion. The resulting biphasic reaction mixture was kept stirring at 0 °C for 0.5 h. Then the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (5 mL, three times). Organic layers were combined, washed with brine (6 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 3:1 to afford the desired product **3a** as white solid (27.0 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.33–7.22 (m, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 5.64 (d, J = 7.9 Hz, 1H), 4.94 (d, J = 7.9 Hz, 1H), 4.87 (m, 2H), 1.46 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.57, 155.07, 148.38, 129.18, 129.11, 125.35, 121.35, 118.96, 116.13, 80.00, 58.56, 43.90, 28.30 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{17}N_3O_3Na$: 310.1162 [M+Na$^+$]; found 310.1169. HPLC (Chiralpak IA, isopropanol/hexane = 20:80, flow rate: 1.0 mL min^{-1}, λ = 254 nm): R_t (major) = 7.7 min, R_t (minor) = 14.7 min; *ee* = 88%; $[\alpha]_D^{25} = -63.2$ (c = 0.79 in acetone).

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Keywords: asymmetric catalysis · cascade reaction · chromene · indane · organocatalysis · thiourea

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[14] CCDC-818689 (**3d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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