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Asymmetric Organocatalytic Synthesis of 4-Aminoisochromanones via a Direct One-Pot Intramolecular Mannich Reaction

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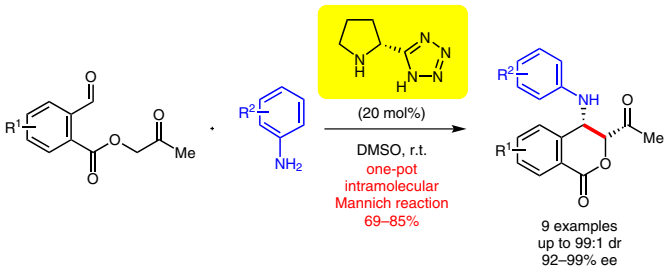

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Abstract A highly stereoselective one-pot intramolecular Mannich reaction using 2-oxopropyl-2-formylbenzoates and anilines as substrates, catalyzed by a secondary amine, has been developed. The procedure leads to a new class of 4-aminoisochromanones bearing two adjacent stereocentres in good yields (up to 85%) with excellent *cis*-stereoselectivities (dr up to 99:1) and ee values of 92–99%.

Key words organocatalysis, one-pot reaction, asymmetric synthesis, isochromanones, Mannich reaction

The isochroman-1-one framework is a common scaffold of a variety of natural and synthetic compounds showing notable biological activities, such as ochtratoxin A (**I**),[1] a powerful mycotoxin isolated from *Aspergillus ochraceus*, the antidiabetic (–)-hydrangenol (**II**),[2] the aldosterone synthase inhibitor (**III**),[3] and fusarentin (**IV**),[4] a natural insecticide (Figure 1). Due to their interesting chemical and medicinal properties, these compounds have been widely studied in recent years.[5]

Asymmetric organocatalytic methodologies are becoming an increasingly efficient alternative to the well-established metal-based and enzymatic procedures for the construction of new stereogenic centers.[6] In the vast field of asymmetric synthesis, organocatalytic Mannich reactions have proven to be a powerful and highly selective tool for the synthesis of β-aminocarbonyl compounds under mild conditions.[7] Particularly, after the pioneering work of List in 2000,[8] the direct Mannich reaction between unmodified ketones and in situ generated imines has been widely investigated, because basically this one-pot sequence avoids the time-consuming and costly preparation/purification of the

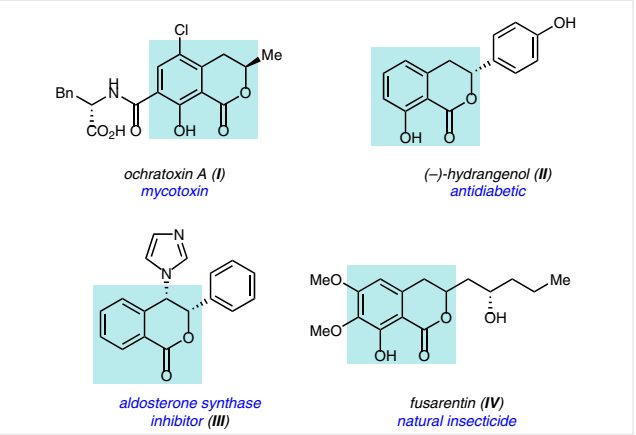


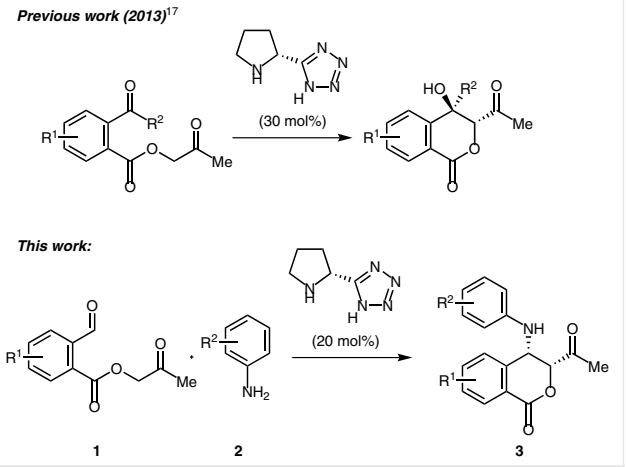
Figure 1 Natural 3,4-disubstituted isochromanones with remarkable biological activities

imine intermediate and represents an outstanding resource in total synthesis.[6a,h,7b,c,9] However, the application of this protocol has been mainly focused on intermolecular approaches and less attention has been given to intramolecular direct Mannich reaction.[7b,9a,b,10]

Mannich-type cyclizations have been involved as key step in numerous total syntheses of complex natural products, but it often required functional group protections as well as the isolation/purification of the intermediates.[11] Nevertheless, in the last decade some examples of organocatalytic intramolecular Mannich and aza-Mannich methodologies have been reported, employing pyrrolidine derivatives,[12] cinchona alkaloids,[13] amino acids,[14] and cyclodextrins as catalysts,[15] as well as under an oxidative coupling.[16]

In 2013, we reported a secondary amine-catalyzed aldol addition reaction for the *trans*-selective synthesis of 3,4-difunctionalized isochroman-1-one derivatives (Scheme 1).[17] We envisaged the possibility to employ the 2-oxopropyl-2-

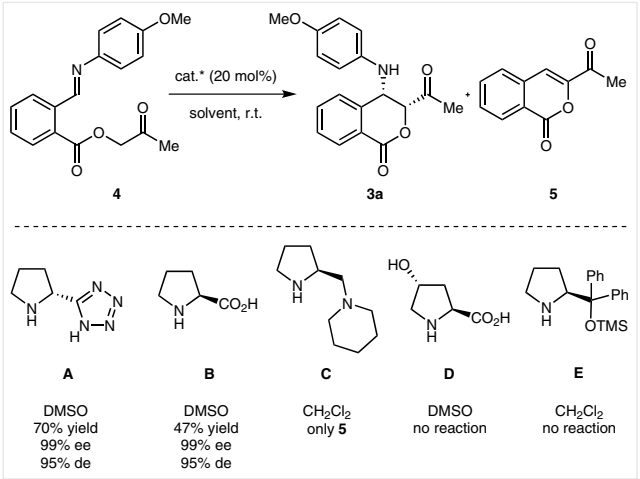
formylbenzoate substrates **1** in an intramolecular direct Mannich reaction to achieve a new class of 3-acetyl-4-aminoisochroman-1-ones bearing two contiguous stereogenic centers. This particular 4-aminoisochromanone scaffold has never been achieved nor studied, although related 3,4-diaminoisochromen-1-ones have been synthesized utilizing multicomponent Strecker or Ugi reactions.[18] In view of the previously discussed importance of this particular class of heterocycles, the development of a facile access to a variety of these molecules is of high interest.



Scheme 1 Asymmetric organocatalytic syntheses of 3,4-disubstituted isochromanones

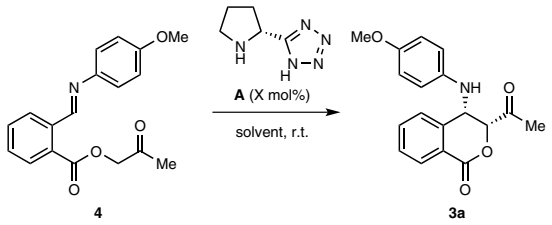
By taking advantage of the well-demonstrated application of pyrrolidine derivatives in organocatalytic asymmetric Mannich reactions, a number of differently substituted prolines were first tested, which can interact with the preformed imine **4** (Scheme 2). Considering that Mannich and aldol reactions are competing transformations, it was not surprising to isolate the isocumarin **5** as a single product when catalyst **C** was applied. This outcome could be rationalized by hydrolysis of the imine **4** to form the 2-oxopropyl-2-formylbenzoate **1**, which reacts with the catalyst to give **5** or by *p*-methoxyaniline elimination from **3a**. In contrast, no products could be detected when the Jørgensen–Hayashi catalyst **E** as well as the hydroxyproline **D** were employed. However, (*S*)-proline (**B**) and the tetrazole-substituted catalyst **A** showed moderate to good reactivity (47% and 70% yield, respectively) accompanied with an excellent stereoselectivity (dr 97:3 and 99% ee in both cases).

Further optimization involving catalyst **A** has been carried out by analyzing the effect of both solvents and catalyst loading on the reaction outcome (Table 1). By changing from the initially used DMSO to DMF, no significant changes in the stereoselectivity were observed (dr 96:4, 99% ee). However, the reaction time was prolonged from 24 to 72 hours (Table 1, entry 2). Subsequently we tested the effects of less polar solvents, but in almost all cases product formation could not be observed (entries 3–7). Further screening of the catalyst loading led to the identification of the best reaction conditions using 20 mol% of **A** to provide 72% yield, 97:3 dr, and 99% ee (entries 8–10).



Scheme 2 Catalyst screening for the direct intramolecular Mannich reaction

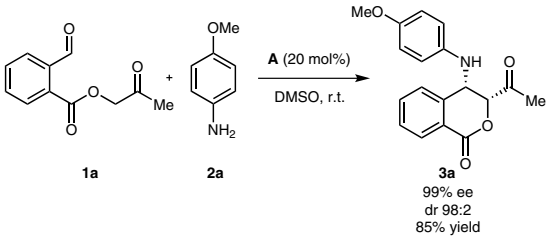
Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Catalyst **A** (mol%)	Time (d)	Yield (%)[b]	dr[c]	ee (%)[d]
1	DMSO	20	1	70	97:3	99
2	DMF	20	3	70	96:4	99
3	CH_2Cl_2	20	3	nr	–	–
4	$CHCl_3$	20	3	12	nd	nd
5	MeCN	20	3	22	nd	nd
6	Et_2O	20	3	nr	–	–
7	THF	20	3	nr	–	–
8	DMSO	5	1	35	97:3	99
9	DMSO	10	1	50	97:3	99
10	DMSO	30	1	72	97:3	99

[a] Unless otherwise stated, the reaction conditions were: 0.2 mmol of **4** and 0.4 mL of solvent (0.5 M); nr = no reaction, nd = not determined.
[b] Yield of the isolated product **3a** after flash chromatography.
[c] Determined via HPLC analysis on a chiral stationary phase.
[d] Determined via HPLC analysis on a chiral stationary phase.

In all the above-mentioned cases, the condensation product **5** has been detected in non-negligible amounts, caused by the previously discussed side reaction. In order to avoid this complication, we subsequently tested unmodified 2-oxopropyl-2-formylbenzoate (**1a**) and *p*-anisidine (**2a**) as substrates under the optimized reaction conditions to perform a one-pot intramolecular Mannich reaction. To our delight, the isochroman-1-one **3a** was obtained in better yield (85%) as compared to the former procedure (70% yield), with no loss in either diastereo- or enantioselectivity (dr 98:2, 99% ee) (Scheme 3).



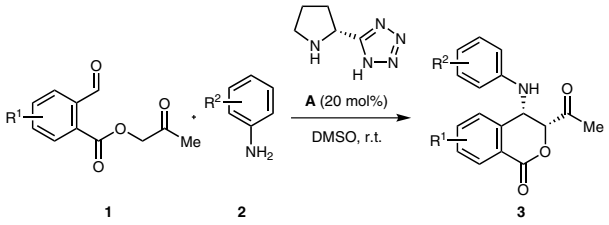
Scheme 3 Asymmetric organocatalytic synthesis of **3a**

Due to the intramolecular character of our transformation and to avoid the possible condensation product under the one-pot condition, it was necessary to push the equilibrium towards the imine formation by using 1.5 equivalents of aniline, as well as a more concentrated solution. Indeed the condensation product **5** could then be detected in only trace amount.

With the optimized reaction conditions in hand, we focused on the general applicability of the developed new protocol by using variously substituted substrates (Table 2). A broad scope of anilines **2a–f** was tested and the corresponding isochromanones **3a–f** were obtained in good yields (70–85%) and with very high diatereo- and enantioselectivities (dr up to 99:1 and 99 ee in almost all cases), irrespective of the steric and electronic nature of the substituents. Similar results have been observed after the introduction of different functional groups on the substrates **1**. However, the presence of a bulky substituent R^1 on the 6-position of the aromatic ring led to a decrease of the diastereoselectivity to 79:21 (**3g**). The presence of strongly electron-donating groups on positions 7 and 8 [7,8-$(OMe)_2$] did not influence the reaction outcome and the corresponding product **3h** was obtained with high stereoselectivity (dr 94:6, 98% ee).

The absolute configuration was unambiguously determined by X-ray crystal structure analysis of compound **3b**,[19] and by analogy the configuration of all other products was assigned accordingly (Figure 2). The *cis*-configuration of the 3,4-disubstituted δ-lactone ring, different as compared to our previously developed *trans*-selective 6-*enolexo* aldolization on the same substrates, is in accordance with literature reports.[9c] Indeed, it has been demonstrated that

Table 2 Investigation of the Substrate Scope[a]



3	R^1	R^2	Time (d)	Yield (%)[b]	dr[c]	ee (%)[d]
a	H	4-OMe	1	85	98:2	99
b	H	4-Cl	1.7	70	99:1	99
c	H	4-F	1.7	81	98:2	99
d	H	4-CF_3	1.7	81	95:5	99
e	H	4-Me	1.7	72	99:1	99
f	H	4-Br	1.7	84	97:3	92
g	6-Br	4-OMe	1	69	79:21	99
h	7,8-$(OMe)_2$	4-Cl	1	83	94:6	98
i	6-Cl	4-Cl	1	75	98:2	99

[a] Unless otherwise stated, the reaction conditions were: 0.2 mmol of **1**, 0.3 mmol of **2** (1.5 equiv) in 0.4 mL of solvent (0.5 M), and 0.04 mmol of catalyst **A** (20 mol%).
[b] Yield of the isolated product **3** after flash chromatography.
[c] Determined via HPLC analysis on a chiral stationary phase.
[d] Determined via HPLC analysis on a chiral stationary phase.

aldol and Mannich reaction usually show an opposite relative topicity in intermolecular reactions, and this stereochemical outcome may also be reflected in intramolecular reactions.

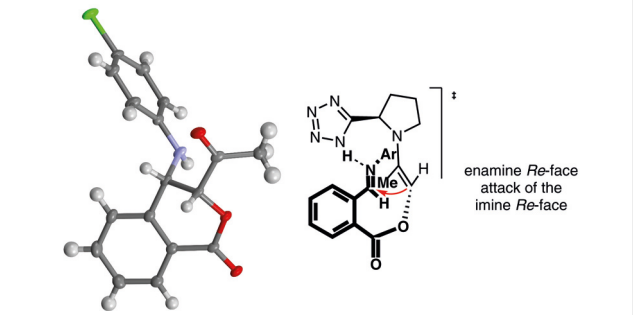


Figure 2 X-ray crystal structure of compound **3b**[19] and proposed transition state for the intramolecular direct one-pot Mannich reaction

The proposed reaction mechanism for the direct one-pot intramolecular Mannich reaction involves the formation of the corresponding imine **4**, which is attacked on its *Re*-face by the *Re*-face of the *E*-enamine, formed from the organocatalyst **A** and the ketone moiety, explaining the observed *cis*-diastereo- and enantioselectivity.

In summary, we have developed an efficient asymmetric synthesis for the new class of 4-aminoisochromanones via an organocatalytic direct intramolecular Mannich reaction. The one-pot sequence involves an initial imine formation followed by a *cis*-selective 6-*enolexo-exo-trig* Mannich reaction catalyzed by a tetrazole analogue of proline to provide the potentially bioactive title heterocycles in good yields (up to 85%) with excellent stereoselectivities (dr up to 99:1, up to 99% ee).

Unless otherwise noted, all commercially available compounds were used without further purification. For preparative column chromatography SIL G-25 UV252 from Macherey-Nagel, particle size 0.040–0.063 nm (230–240 mesh. flash) was used. Visualization of the developed TLC plates was performed with UV irradiation (254 nm) or by staining with ninhydrin stain (0.5% EtOH solution); P = *n*-pentane. Optical rotations were measured on a PerkinElmer 241 polarimeter. Mass spectra were recorded on a Finnigan SSQ7000 (EI 70 eV) spectrometer and high-resolution mass spectra on a Thermo Fisher Scientific Orbitrap XL spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 using ATR-Unit. ^{1}H and ^{13}C spectra were recorded at ambient temperature on Varian Mercury 300, Inova 400, Varian VNMRS-400, or Varian VNMRS-600 spectrometers with TMS as an internal standard. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases (Daicel AD, Daicel AS, Daicel IA, Daicel OD, Daicel OJ, Chiralpak IC, or Whelk M columns).

The catalyst **A** was prepared according to the previously described procedure.[20]

2-Oxopropyl 2-Formylbenzoates 1; General Procedure

Under argon atmosphere, the respective phthalide (7 mmol, 1.0 equiv) was dissolved in CCl_4 (35 mL, 0.2 M). NBS (7.7 mmol, 1.1 equiv) and AIBN (0.7 mmol, 0.1 equiv) were added and the reaction mixture was refluxed for 3 h. After stirring for another 1 h at 0 °C, the mixture was filtered, and the filtrate was concentrated under reduced pressure. H_2O (25 mL) was then added and the suspension was refluxed 2 h. After cooling to r.t., EtOAc was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were dried (anhyd $MgSO_4$), filtered, and concentrated under reduced pressure to give the crude corresponding 2-formylbenzoic acid. The crude product was dissolved in acetone (14 mL, 0.5 M) and Et_3N (7 mmol, 1.0 equiv), and chloroacetone (7.35 mmol, 1.5 equiv) was added to the suspension. The mixture was refluxed for 2 h, then H_2O was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (anhyd $MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired 2-oxopropyl 2-formylbenzoate **1**.

2-Oxopropyl 2-Formylbenzoate (1a)

Prepared from commercially available 2-formylbenzoic acid; yield: 1.227 g (85%); yellow oil; R_f = 0.26 (P/Et_2O, 1:1).

IR (ATR): 3450, 2933, 1788, 1725, 1593, 1420, 1367, 1280, 1191, 1128, 1086, 1011, 961, 920, 828, 793, 753, 698, 641 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.63 (s, 1 H, CHO), 8.07–8.04 (m, 1 H, CH_{ar}), 7.98–7.95 (m, 1 H, CH_{ar}), 7.71–7.65 (m, 2 H, CH_{ar}), 4.97 (s, 2 H, CH_2), 2.25 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 200.52, 192.18, 165.67, 137.28, 133.17, 132.93, 131.34, 130.76, 128.62, 69.37, 26.23.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 206.0 (4, $[M]^+ = [C_{11}H_{10}O_4]^+$), 205.1 (27), 149.1 (97), 133.0 (51), 120.1 (14), 104.1 (100), 93.1 (12), 83.0 (18), 76.1 (98).

MS (CI$^+$, methane): *m*/*z* (%) = 207 (28, $[M + H]^+ = [C_{11}H_{11}O_4]^+$).

HRMS (ESI$^+$): *m*/*z* $[M + Na]^+$ calcd for $[C_{11}H_{10}O_4Na]^+$: 229.0471; found: 229.0471.

2-Oxopropyl 4-Bromo-2-formylbenzoate (1b)

Yield: 280 mg (20%, after 3 reaction steps); pale yellow solid; mp 58–59 °C; R_f = 0.23 (P/Et_2O, 4:6).

IR (ATR): 3436, 3345, 3100, 3036, 2980, 2942, 2851, 1716, 1680, 1580, 1562, 1473, 1426, 1377, 1271, 1179, 1136, 1088, 1010, 957, 878 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.60 (s, 1 H, CHO), 8.08 (d, *J* = 2.0 Hz, 1 H, CH_{ar}), 7.94 (d, *J* = 8.3 Hz, 1 H, CH_{ar}), 7.79 (dd, *J* = 8.3, 2.1 Hz, 1 H, CH_{ar}), 4.97 (s, 2 H, CH_2), 2.25 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.10, 190.74, 164.92, 138.66, 136.04, 132.42, 131.61, 129.81, 128.31, 69.44, 26.16.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 386.1 (6, $[M + H]^+ = [C_{11}H_{10}BrO_4]^+$), 229.1 (19), 227.1 (22), 213.0 (17), 210.9 (11), 184.0 (11), 183.1 (9), 75 (41), 58 (100).

MS (CI$^+$, methane): *m*/*z* (%) = 315.1 (3, $[M + C_2H_5, {}^{81}Br]^+ = [C_{13}H_{14}BrO_4]^+$), 313.1 (3, $[M + C_2H_5, {}^{79}Br]^+ = [C_{13}H_{14}BrO_4]^+$), 287.0 (12, $[M, {}^{81}Br]^+ = [C_{11}H_9BrO_4]^+$), 284.9 (13, $[M, {}^{79}Br]^+ = [C_{11}H_9BrO_4]^+$), 228.9 (18), 226.9 (21), 213.9 (12), 212.9 (95), 211.9 (13), 210.9 (100).

HRMS (ESI$^+$): *m*/*z* $[M + Na]^+$ calcd for $[C_{11}H_9BrO_4Na]^+$: 306.9574; found: 306.9576.

2-Oxopropyl 6-Formyl-2,3-dimethoxybenzoate (1c)

Prepared from commercially available 2,3-dimethoxy-6-formylbenzoic acid; yield: 2.369 g (89%); colorless solid; mp 93–95 °C; R_f = 0.5 (P/EtOAc, 4:6).

IR (ATR): 2930, 2853, 1722, 1679, 1572, 1458, 1429, 1372, 1273, 1150, 1049, 962, 908, 828, 791, 743 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.90 (s, 1 H, CHO), 7.64 (d, *J* = 8.5 Hz, 1 H, CH_{ar}), 7.09 (d, *J* = 8.5 Hz, 1 H, CH_{ar}), 4.92 (s, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 2.27 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 202.38, 189.29, 165.91, 157.99, 146.83, 129.50, 128.32, 126.98, 112.81, 69.72, 62.06, 56.39, 26.63.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 266.3 (1, $[M]^+ = [C_{13}H_{14}O_6]^+$), 209.1 (23), 194.1 (12), 193.1 (100), 165.1 (32), 163.1 (12), 150.1 (12), 149.1 (12), 135.1 (14), 122.1 (23), 121.1 (14), 119.1 (13), 107.2 (27), 106.1 (12), 105.1 (16), 104.1 (16), 79.2 (31), 78.2 (19), 77.2 (36), 76.2 (17), 65.3 (13), 63.3 (18), 58.4 (14), 53.4 (12), 51.3 (35), 50.3 (18).

HRMS (ESI$^+$): *m*/*z* $[M + Na]^+$ calcd for $[C_{13}H_{14}O_6Na]^+$: 289.0683; found: 289.0683.

2-Oxopropyl 4-Chloro-2-formylbenzoate (1d)

Prepared from commercially available 4-chloro-2-formylbenzoic acid; yield: 430 mg (44%); yellow oil; R_f = 0.51 (P/Et_2O, 1:2).

IR (ATR): 3851, 3743, 3673, 3451, 3081, 2928, 1727, 1587, 1420, 1371, 1276, 1187, 1105, 899, 844, 774 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.59 (s, 1 H, CHO), 8.03 (d, *J* = 2.1 Hz, 1 H, CH_{ar}), 7.94 (d, *J* = 8.3 Hz, 1 H, CH_{ar}), 7.65 (d, *J* = 10.4 Hz, 1 H, CH_{ar}), 4.98 (s, 2 H, CH_2), 2.26 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 199.97, 190.86, 164.52, 139.81, 135.38, 133.06, 132.82, 130.88, 130.13, 69.55, 26.17.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 241.0 (3, $[M + H]^+ = [C_{11}H_{10}ClO_4]^+$), 182.9 (53), 166.9 (63), 138.9 (31), 111.0 (24), 75.1 (38), 58.1 (100).

HRMS (ESI$^+$): *m*/*z* $[M + Na]^+$ calcd for $[C_{11}H_9ClO_4Na]^+$: 263.0082; found: 263.0082.

Direct Organocatalytic Mannich Reaction; General Procedure

To a solution of the appropriate 2-oxopropyl 2-formylbenzoate **1** (0.2 mmol, 1.0 equiv) in DMSO (0.4 mL, 0.5 M) was added the respective aniline **2** (0.3 mmol, 1.5 equiv) and the mixture was stirred for 2 h. Then the catalyst **A** was added to the solution (5.6 mg, 0.04 mmol, 20 mol%) and the reaction mixture was stirred at r.t. After completion of the reaction, H_2O (3 mL) was added, and the mixture was extracted with Et_2O (3 × 2 mL). The combined organic phases were dried (anhyd $MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired *cis*-(3*R*,4*S*)-3-acetyl-4-aminoisochromanone **3a–i**.

(3*R*,4*S*)-3-Acetyl-4-[(4-methoxyphenyl)amino]isochroman-1-one (3a)

Yield: 53 mg (85%); colorless solid; mp 158–159 °C; R_f = 0.46 (P/Et_2O, 1:2); $[\alpha]_D^{20}$ +88.2 (*c* 1.00, $CHCl_3$, 99% ee).

HPLC: Whelk M, *n*-heptane/EtOH (8:2), 0.5 mL/min, λ = 230.4 nm; major diastereomer: t_R = 43.0 min (minor), t_R = 21.4 min (major); minor diastereomer: t_R = 28.2 min (minor), t_R = 24.0 min (major); 98:2 dr, 99% ee.

IR (ATR): 3364, 2956, 2833, 2289, 2185, 2063, 1887, 1717, 1603, 1513, 1457, 1357, 1243, 1113, 1033, 824, 766, 696 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.7, 1.1 Hz, 1 H, CH_{ar}), 7.51 (dtd, *J* = 30.7, 7.5, 1.2 Hz, 2 H, CH_{ar}), 7.20 (d, *J* = 7.5 Hz, 1 H, CH_{ar}), 6.77 [d, *J* = 8.9 Hz, 2 H, CH_{ar} (aniline)], 6.66 [d, *J* = 8.9 Hz, 2 H, CH_{ar} (aniline)], 5.00 (d, *J* = 3.2 Hz, 1 H, CH), 4.97 (dd, *J* = 10.5, 3.2 Hz, 1 H, NHC*H*), 3.75 (s, 3 H, OCH_3), 3.56 (d, *J* = 10.4 Hz, 1 H, NH), 2.42 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.44, 163.77, 154.09, 139.77, 139.54, 134.94, 131.04, 129.43, 126.73, 123.05, 117.61, 115.02, 84.20, 55.77, 55.11, 28.76.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 312.1 (23, $[M + H]^+ = [C_{18}H_{18}NO_4]^+$), 311.1 ($[M]^+$, 100), 239.1 (15), 138.2 (67), 211.1 (40), 210.1 (12), 196.1 (38), 167.1 (19), 147.1 (9), 123.1 (22), 122.1 (40), 118.1 (12), 108.1 (26), 90.2 (12), 89.2 (23), 77.2 (11), 48.5 (61).

MS (CI$^+$, methane): *m*/*z* (%) = 340.1 (16, $[M + C_2H_5]^+ = [C_{20}H_{22}NO_4]^+$), 313.1 (33), 312.0 (100, $[M + H]^+ = [C_{18}H_{18}NO_4]^+$), 311.0 ($[M]^+$, 58.3), 328.0 (9).

HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $[C_{18}H_{18}NO_4]^+$: 312.1230; found: 312.1230.

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.13; H, 5.42; N, 4.42.

(3*R*,4*S*)-3-Acetyl-4-[(4-chlorophenyl)amino]isochroman-1-one (3b)

Yield: 44 mg (70%); colorless solid; after measuring the HPLC data, the product was recrystallized from a mixture of PE/Et_2O (1:1); the crystals were filtered and washed with the same solvent mixture; mp 150–151 °C; R_f = 0.46 (P/Et_2O 4:6); $[\alpha]_D^{20}$ +162.4 (*c* 0.50, $CHCl_3$, 99% ee).

HPLC: Whelk M, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, λ = 254.4 nm, t_R = 28.7 min (minor), t_R = 11.9 min (major); 99:1 dr, 99% ee.

IR (ATR): 3374, 3057, 2925, 2312m 2089, 1870, 1712, 1596, 1495, 1246, 1093, 765, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.5 Hz, 1 H, CH_{ar}), 7.57 (t, *J* = 7.5 Hz, 1 H, CH_{ar}), 7.50 (t, *J* = 7.6 Hz, 1 H, CH_{ar}), 7.28 (d, *J* = 7.6 Hz, 1 H, CH_{ar}), 7.15 [d, *J* = 8.7 Hz, 2 H, CH_{ar} (aniline)], 6.67 [d, *J* = 8.8 Hz, 2 H, CH_{ar} (aniline)], 5.10 (dd, *J* = 10.1, 3.0 Hz, 1 H, NHC*H*), 5.00 (d, *J* = 3.2 Hz, 1 H, CH), 4.00 (d, *J* = 10.4 Hz, 1 H, NH), 2.39 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.17, 163.35, 144.30, 139.25, 135.03, 130.92, 129.48, 129.39, 126.41, 124.57, 123.00, 116.07, 83.56, 53.18, 28.53.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 317.0 (14, [M, $^{37}Cl]^+ = [C_{17}H_{14}ClNO_3]^+$), 315.0 (44, [M, $^{35}Cl]^+ = [C_{17}H_{14}ClNO_3]^+$), 244.0 (32), 242.0 (100), 217.0 (20), 216.0 (24), 215.0 (65), 214.0 (49), 147.0 (12), 127.0 (27), 118.0 (12), 111.0 (14), 90.2 (11), 89.1 (16), 77.2 (11), 75.1 (11).

MS (CI$^+$, methane): *m*/*z* (%) = 344.0 (7, $[M + C_2H_5, {}^{35}Cl]^+ = [C_{19}H_{19}ClNO_3]^+$), 317.9 (23, [M + H, $^{37}Cl]^+ = [C_{17}H_{15}ClNO_3]^+$), 317.0 (13, [M, $^{37}Cl]^+ = [C_{17}H_{14}ClNO_3]^+$), 316.0 (67), 314.9 (35, [M, $^{35}Cl]^+ = [C_{17}H_{14}ClNO_3]^+$), 271.9 (12), 258.2 (14), 257.4 (18), 242.0 (24), 216.3 (11), 214.0 (15), 190.1 (11), 188.9 (99), 187.9 (36), 156.0 (17), 149.0 (16), 147.1 (2), 145.4 (13), 130.1 (28), 129.1 (33), 128.0 (100), 127.0 (81), 75.2, (12).

HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{15}ClNO_3]^+$: 316.0735; found: 316.0735.

(3*R*,4*S*)-3-Acetyl-4-[(4-fluorophenyl)amino]isochroman-1-one (3c)

Yield: 48 mg (81%); colorless solid; mp 166–167 °C; R_f = 0.66 (P/Et_2O, 4:6); $[\alpha]_D^{20}$ +151.3 (*c* 0.40, $CHCl_3$, 99% ee).

HPLC: IB, *n*-heptane/EtOH (9:1), 0.7 mL/min, λ = 230.16 nm; major diastereomer: t_R = 18.8 min (minor), t_R = 17.1 min (major); minor diastereomer: t_R = 22.1 min (minor), t_R = 19.8 min (major); 98:2 dr, 99% ee.

IR (ATR): 3782, 3360, 3047, 2870, 2635, 2454, 2285, 2167, 2050, 1863, 1717, 1603, 1511, 1415, 1362, 1272, 1216, 1109, 811, 696 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.8, 1.4 Hz, 1 H, CH_{ar}), 7.56 (td, *J* = 7.5, 1.4 Hz, 1 H, CH_{ar}), 7.49 (td, *J* = 7.6, 1.2 Hz, 1 H, CH_{ar}), 7.24–7.21 (m, 1 H, CH_{ar}), 6.93–6.87 [m, 2 H, CH_{ar} (aniline)], 6.69–6.63 [m, 2 H, CH_{ar} (aniline)], 5.02 (dd, *J* = 10.3, 3.2 Hz, 1 H, NHC*H*), 5.00 (d, *J* = 3.3 Hz, 1 H, CH), 3.78 (d, *J* = 10.3 Hz, 1 H, NH), 2.42 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.28, 163.48, 157.97, 156.39, 141.93, 139.35, 134.93, 130.94, 129.44, 126.48, 122.94, 116.73, 116.68, 116.11, 115.96, 83.83, 54.33, 30.94.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 300.1 (17), 299.1 (73, $[M]^+ = [C_{17}H_{14}FNO_3]^+$), 227.1 (23), 226.1 (100), 200.1 (9), 199.1 (69), 198.1 (67), 111.1 (12).

MS (CI$^+$, methane): *m*/*z* (%) = 378.2 (4, $[M + C_2H_5]^+ = [C_{20}H_{19}F_3NO_3]^+$), 350.1 (48), 349.1 (35, $[M]^+ = [C_{18}H_{14}F_3NO_3]^+$), 331.1 (13), 330 (61), 277.1 (23), 276.1 (100), 249.1 (24).

HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $[C_{18}H_{15}F_3NO_3]^+$: 350.0999; found: 350.0999.

(3*R*,4*S*)-3-Acetyl-4-{[4-(trifluoromethyl)phenyl]amino}isochroman-1-one (3d)

Yield: 49 mg (81%); colorless solid; mp 168–169 °C; R_f = 0.46 (P/Et_2O 4:6); $[\alpha]_D^{20}$ +150.3 (*c* 0.40, $CHCl_3$, 99% ee).

HPLC: OD, *n*-heptane/*i*-PrOH (9:1), 1.0 mL/min, λ = 254.16 nm; major diastereomer: t_R = 20.7 min (minor), t_R = 17.4 min (major); minor diastereomer: t_R = 10.4 min (minor), t_R = 14.8 min (major); 95:5 dr, 99% ee.

IR (ATR): 3390, 3069, 2925, 2851, 2159, 2077, 2044, 1981, 2894, 1718, 1611, 1535, 1461, 1417, 1323, 1263, 1215, 1157, 1093, 1061, 911, 854, 820, 767, 729, 695 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.8, 1.0 Hz, 1 H, CH_{ar}), 7.60 (td, *J* = 7.6, 1.3 Hz, 1 H, CH_{ar}), 7.51 (td, *J* = 7.7, 1.1 Hz, 1 H, CH_{ar}), 7.45 [d, *J* = 8.6 Hz, 2 H, CH_{ar} (aniline)], 7.34 (d, *J* = 7.6 Hz, 1 H, CH_{ar}), 6.79 [d, *J* = 8.6 Hz, 2 H, CH_{ar} (aniline)], 5.26 (dd, *J* = 10.2, 3.3 Hz, 1 H, NHC*H*), 5.02 (d, *J* = 3.3 Hz, 1 H, CH), 4.48 (d, *J* = 10.1 Hz, 1 H, NH), 2.39 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.32, 163.43, 148.53, 139.16, 135.39, 131.11, 129.80, 127.09 (q, $J_{C,F}$ = 3.7 Hz), 126.57, 123.25, 121.38 (q, $J_{C,F}$ = 32.8 Hz), 113.65, 83.48, 52.02, 28.71.

MS (EI^+, 70 eV): *m*/*z* (%) = 349.1 (8, $[M]^+ = [C_{18}H_{14}F_3NO_3]^+$), 277.1 (19), 276.1 (100), 250.1 (13), 249.1 (84), 248.1 (85), 208.1 (11), 180.1 (9), 145.0 (25), 118.1 (10), 89.1 (12), 69.2 (11), 48.4 (28).

HRMS (ESI^+): *m*/*z* $[M + Na]^+$ calcd for $[C_{17}H_{14}FNO_3Na]^+$: 322.0850; found: 322.0846.

(3*R*,4*S*)-3-Acetyl-4-(*p*-tolylamino)isochroman-1-one (3e)

Yield: 43 mg (72%); pale yellow solid; mp 139–140 °C; R_f = 0.51 (P/Et_2O, 4:6); $[\alpha]_D^{20}$ +156.6 (*c* 0.35, $CHCl_3$, 99% ee).

HPLC: IA, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, λ = 230.4 nm, t_R = 17.2 min (minor), t_R = 18.7 min (major); 99:1 dr, 99% ee.

IR (ATR): 3352, 2925, 2302, 2084, 1881, 1717, 1614, 1514, 1359, 1260, 1096, 804, 696 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 7.8, 1.3 Hz, 1 H, CH_{arom}), 7.55 (td, *J* = 7.5, 1.4 Hz, 1 H, CH_{arom}), 7.48 (td, *J* = 7.6, 1.2 Hz, 1 H, CH_{arom}), 7.30–7.27 (m, 1 H, CH_{arom}), 7.01 [d, *J* = 8.0 Hz, 2 H, CH_{arom} (aniline)], 6.63 [d, *J* = 8.4 Hz, 2 H, CH_{arom} (aniline)], 5.12–5.08 (m, 1 H, C*H*NH), 5.00 (d, *J* = 3.3 Hz, 1 H, CH), 3.77 (d, *J* = 8.0 Hz, 1 H, NH), 2.40 (s, 3 H, CH_3), 2.25 (s, 3 H, ArCH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.36, 163.74, 143.40, 139.86, 135.06, 130.98, 130.16, 129.50, 129.42, 126.65, 123.12, 115.43, 84.02, 53.71, 28.74, 20.61.

MS (EI^+, 70 eV): *m*/*z* (%) = 295.0 (12, $[M]^+ = [C_{18}H_{17}NO_3]^+$), 223.1 (18), 222.1 (93), 196.1 (15), 195.1 (100), 194.1 (69), 118.1 (12), 107.2 (23), 106.1 (20), 91.2 (24), 89.2 (13), 77.2 (12), 65.3 (10).

MS (CI^+, methane): *m*/*z* (%) = 297.2 (8), 296.2 (46, $[M + H]^+ = [C_{18}H_{18}NO_3]^+$), 295.1 (8, $[M]^+ = [C_{18}H_{17}NO_3]^+$), 189.0 (84), 149.1 (22), 108.2 (100), 107.3 (14).

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $[C_{18}H_{18}NO_3]^+$: 296.1281; found: 296.1279.

(3*R*,4*S*)-3-Acetyl-4-[(4-bromophenyl)amino]isochroman-1-one (3f)

Yield: 43 mg (84%); colorless solid; mp 175–176 °C; R_f = 0.66 (P/Et_2O, 4:6); $[\alpha]_D^{20}$ +164.1 (*c* 0.50, $CHCl_3$, 92% ee).

HPLC: AD, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 230.16 nm; major diastereomer: t_R = 11.7 min (minor), t_R = 9.3 min (major); minor diastereomer: t_R = 8.5 min (minor), t_R = 5.1 min (major); 97:3 dr, 92% ee.

IR (ATR): 3379, 3050, 2319, 2083, 1885, 1713, 1592, 1497, 1254, 1081, 778 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 7.8, 1.1 Hz, 1 H, CH_{ar}), 7.58 (td, *J* = 7.6, 1.4 Hz, 1 H, CH_{ar}), 7.50 (td, *J* = 7.6, 1.1 Hz, 1 H, CH_{ar}), 7.31–7.26 [m, 3 H, CH_{arom} and 2 × CH_{ar} (aniline)], 6.64–6.59 [m, 2 H, CH_{ar} (aniline)], 5.11 (br s, 1 H, NHC*H*), 5.00 (d, *J* = 3.3 Hz, 1 H, CH), 4.01 (br s, 1 H, NH), 2.39 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.36, 163.51, 144.92, 1f39.38, 135.24, 132.47, 131.11, 129.68, 126.59, 123.16, 116.60, 111.84, 83.70, 53.15, 28.73.

MS (EI^+, 70 eV): *m*/*z* (%) = 362.0 (4, $[M, ^{81}Br]^+ = [C_{17}H_{14}BrNO_3]^+$), 360.8 (4, $[M, ^{79}Br]^+ = [C_{17}H_{14}BrNO_3]^+$), 287.9 (29), 185.9 (29), 261 (39), 260.0 (35), 259.0 (42), 258.9 (43), 219.2 (10), 209.2 (23), 207.1 (27), 198.1 (11), 196.1 (12), 193.2 (14), 180.1 (52), 178.1 (27), 173.0 (58), 171.0 (58), 157.1 (31), 155.0 (30), 153.2 (15), 152.0 (30), 151.1 (16), 147.1 (100), 145.0 (30), 118.1 (57), 104.1 (20), 91.2 (32).

MS (CI^+, methane): *m*/*z* (%) = 362.0 (17, $[M, ^{81}Br]^+ = [C_{17}H_{14}BrNO_3]^+$), 360.0 (18, $[M, ^{79}Br]^+ = [C_{17}H_{14}BrNO_3]^+$), 267.1 (9), 207.1 (22), 190.1 (12), 189.0 (100), 174.0 (64), 173.0 (16), 172.0 (64), 171.0 (13), 147.1 (9), 121.1 (16), 93.1 (26), 79.1 (17), 75.2 (44).

HRMS (ESI^+): *m*/*z* $[M + Na]^+$ calcd for $[C_{17}H_{14}BrNO_3Na]^+$: 382.0049; found: 382.0047.

(3*R*,4*S*)-3-Acetyl-6-bromo-4-[(4-methoxyphenyl)amino]isochroman-1-one (3g)

Yield: 54 mg (69%); yellow solid; the two diastereomers were separated by preparative TLC with hexane/*i*-PrOH (8:2); mp 151–152 °C; R_f = 0.6 (P/Et_2O, 1:2); $[\alpha]_D^{20}$ +90.2 (*c* 0.25, $CHCl_3$, 99% ee).

HPLC: IC, *n*-heptane/EtOH (9:1), 1.0 mL/min, λ = 254.4 nm; major diastereomer: t_R = 13.0 min (minor) t_R = 11.4 min (major); minor diastereomer: t_R = 24.2 min (minor), t_R = 15.8 min (major); 79:21 dr, 99% ee.

IR (ATR): 3344, 3003, 2932, 2835, 2254, 2068, 1724, 1590, 1509, 1465, 1409, 1360, 1233, 1095, 1035, 907, 826, 782, 727, 690 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 0.3 H, CH_{ar}, minor), 7.99 (d, *J* = 8.3 Hz, 1 H, CH_{ar}, major), 7.65 (dd, *J* = 8.4, 1.9 Hz, 0.4 H, CH_{ar}, minor), 7.62 (dd, *J* = 8.4, 1.9 Hz, 1 H, CH_{ar}, major and 0.22 H, CH_{ar}, minor), 7.41 (d, *J* = 1.9 Hz, 1 H, CH_{ar}, major), 6.87–6.83 (m, 0.6 H, CH_{ar}, minor), 6.82–6.77 (m, 2 H, CH_{ar}, major), 6.76–6.72 (m, 1 H, CH_{ar}, minor), 6.70–6.63 (m, 2 H, CH_{ar}, major), 5.18 (d, *J* = 2.7 Hz, 0.5 H, CH, minor), 4.96 (m, 2 H 2 × CH, major and 0.5 H, CH, minor), 3.78 (d, *J* = 3.5 Hz, 1.5 H, OCH_3, minor), 3.77 (d, *J* = 3.5 Hz, 3 H, OCH_3, major), 3.70–3.61 (m, 1.4 H, 2 × NH), 2.39 (s, 3 H, CH_3, major), 2.22 (s, 1.3 H, CH_3, minor).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 205.87, 204.27, 162.89, 162.15, 154.09, 141.32, 138.96, 133.19, 132.68, 132.37, 131.81, 131.61, 130.05, 129.47, 121.82, 117.19, 116.39, 116.14, 115.26, 115.03, 114.19, 83.51, 83.29, 65.83, 55.63, 54.40, 53.39, 51.62, 34.11, 28.60.

MS (EI^+, 70 eV): *m*/*z* (%) = 391.0 (15, $[M, ^{81}Br]^+ = [C_{18}H_{16}BrNO_4]^+$), 389.0 (15, $[M, ^{79}Br]^+ = [C_{18}H_{16}BrNO_4]^+$), 335.0 (15), 334.0 (96), 333.0 (20), 332.0 (100), 318 (16), 316 (16), 255.1 (10), 247.0 (11), 246.0 (11), 245.0 (9), 244.0 (10), 210.0 (19), 207.9 (19), 166.0 (10).

MS (CI^+, methane): *m*/*z* (%) = 392.2 (5), 391.3 (5, $[M, ^{81}Br]^+ = [C_{18}H_{16}BrNO_4]^+$), 390.1 (6), 389.1 (6, $[M, ^{79}Br]^+ = [C_{18}H_{16}BrNO_4]^+$), 269.0 (29), 268.1 (13), 267.0 (19), 266.0 (6), 125.2 (7), 124.2 (89), 123.1 (100), 109.2 (10), 108.1 (44), 80.2 (6).

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $[C_{18}H_{17}BrNO_4]^+$: 390.0341; found: 390.0340.

(3*R*,4*S*)-3-Acetyl-4-[(4-chlorophenyl)amino]-7,8-dimethoxyisochroman-1-one (3h)

Yield: 62 mg (83%); pale yellow solid; mp 107–108 °C; R_f = 0.64 (P/EtOAc, 4:6); $[\alpha]_D^{20}$ +165.3 (*c* 0.50, $CHCl_3$, 98% ee).

HPLC: IC, *n*-heptane/EtOH (9:1), 1.0 mL/min, λ = 230.4 nm; major diastereomer: t_R = 14.8 min (minor) t_R = 15.9 min (major); minor diastereomer: t_R = 37.7 min (minor), t_R = 31.2 min (major); 94:6 dr, 98% ee.

IR (ATR): 3358, 2940, 2844, 2325, 2099, 1925, 1726, 1582, 1489, 1417, 1363, 1269, 1198, 1133, 1051, 956, 901, 821, 736, 675 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 12.3, 8.2 Hz, 2 H, CH_{ar}), 7.07 (dd, *J* = 16.0, 8.6 Hz, 2 H, CH_{ar}), 6.98 (d, *J* = 8.4 Hz, 1 H, CH_{ar}), 6.67 (dd, *J* = 13.4, 8.8 Hz, 2 H, CH_{ar}), 6.60 (d, *J* = 8.7 Hz, 1 H, CH_{ar}), 5.05 (d, *J* = 2.06 Hz, 0.21 H, NHC*H*, minor), 5.01–4.96 (m, 1 H, NHC*H*, major), 4.88–4.85 (m, 1.13 H, CH, major and minor), 4.14 (d, *J* = 9.5 Hz, 1.25 H, NH, major and minor), 3.96 (d, *J* = 4.8 Hz, 3.82 H, OCH_3, major and minor), 3.89 (s, 0,67 H, OCH_3, minor), 3.86 (s, 3 H, OCH_3, major), 2.36 (s, 3 H, CH_3, major), 2.19 (s, 0.72 H, CH_3, minor).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.80, 205.38, 160.25, 159.80, 154.22, 151.79, 144.63, 132.00, 129.68, 129.47, 129.22, 124.33, 124.08, 121.88, 118.01, 117.94, 117.35, 116.34, 116.07, 115.00, 83.27, 82.97, 61.76, 61.72, 56.35, 56.32, 53.50, 51.37, 28.76, 27.21.

MS (EI^+, 70 eV): *m*/*z* (%) = 377.5 (16, $[M, {}^{37}Cl]^+ = [C_{19}H_{18}ClNO_5]^+$), 376.5 (25), 375.5 (35, $[M, {}^{35}Cl]^+ = [C_{19}H_{18}ClNO_5]^+$), 320.5 (29), 319.5 (15), 318.5 (100), 304.5 (25), 303.5 (14), 302.5 (71), 258.4 (12), 207.5 (33), 192.4 (10), 150.7 (12), 149.3 (13), 127.3 (13), 111.2 (17).

MS (CI^+, methane): *m*/*z* (%) = 404.5 (11, $[M + C_2H_5, {}^{35}Cl]^+ = [C_{21}H_{23}ClNO_5]^+$), 378.5 (36, $[M + H, {}^{37}Cl]^+ = [C_{19}H_{19}ClNO_5]^+$), 377.5 (26, $[M, {}^{37}Cl]^+ = [C_{19}H_{18}ClNO_5]^+$), 376.5 (100, $[M + H, {}^{35}Cl]^+ = [C_{19}H_{19}ClNO_5]^+$), 375.5 (24, $[M, {}^{35}Cl]^+ = [C_{19}H_{18}ClNO_5]^+$), 304.4 (15), 302.4 (47).

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $[C_{19}H_{19}ClNO_5]^+$: 376.0946; found: 376.0954.

(3*R*,4*S*)-3-Acetyl-6-chloro-4-[(4-chlorophenyl)amino]isochroman-1-one (3i)

Yield: 53 mg (75%); colorless solid; mp 168–169 °C; R_f = 0.6 (P/Et_2O, 4:6); $[\alpha]_D^{20}$ +160.4 (*c* 0.50, $CHCl_3$, 99% ee).

HPLC: IA, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 254.4 nm, t_R = 19.8 min (minor), t_R = 13.4 min (major); 98:2 dr, 99% ee.

IR (ATR): 3366, 3080, 2962, 2852, 2261, 2086, 1993, 1887, 1729, 1597, 1488, 1414, 1362, 1241, 1188, 1087, 1013, 970, 823, 782, 728, 682 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.1 Hz, 1 H, CH_{ar}), 7.53 (dd, *J* = 8.2, 2.2 Hz, 1 H, CH_{ar}), 7.24 (d, *J* = 8.2 Hz, 1 H, CH_{ar}), 7.18–7.14 [m, 2 H, CH_{ar} (aniline)], 6.68–6.64 [m, 2 H, CH_{ar} (aniline)], 5.08 (s, 1 H, NHC*H*), 4.98 (d, *J* = 3.3 Hz, 1 H, CH), 3.96 (s, 1 H, NH), 2.39 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 205.89, 162.38, 144.17, 137.72, 135.87, 135.26, 130.87, 129.66, 128.09, 125.09, 124.64, 116.34, 83.61, 52.92, 28.72.

MS (EI^+, 70 eV): *m*/*z* (%) = 354.1 (1, $[M, 2 \times {}^{37}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 353.1 (7) 352.1 (9, $[M, {}^{37}Cl$ and $ {}^{35}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 351.0 (38), 350.1 (15, $[M, 2 \times {}^{35}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 349.0 (57), 294.0 (15), 292.0 (24), 280.0 (11), 279.0 (11), 278.0 (62), 277.0 (18), 275.9 (100), 51.0 (27), 250.0 (22), 249.0 (42), 248.0 (28), 181.0 (10), 127.0 (19), 111.0 (11).

MS (CI^+, methane): *m*/*z* (%) = 354.1 (2, $[M, 2 \times {}^{37}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 353.1 (3), 352.0 (15, $[M, {}^{37}Cl$ and $ {}^{35}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 351.1 (6), 350.0 (23, $[M, 2 \times {}^{35}Cl]^+ = [C_{17}H_{13}Cl_2NO_3]^+$), 241.0 (16), 225.0 (35), 224.0 (17), 223.0 (100), 222.0 (13), 168.9 (19), 166.9 (57), 130.0 (14), 129.0 (14), 128.0 (46), 127.0 (40), 85.0 (35), 83.0 (53).

HRMS (ESI^+): *m*/*z* $[M + Na]^+$ calcd for $[C_{17}H_{13}Cl_2NO_3Na]^+$: 372.0165; found: 372.0164.

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Supporting Information

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