Efficient conjugate addition of carbonyl compounds to 3-nitro-2*H*-chromenes in the presence of bases

Zhi-peng Hu, Jun-min Zhang, Chun-liang Lou, Jin-jia Wang, Shao-zhen Nie, and Ming Yan*

Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
E-mail: yanming@mail.sysu.edu.cn

Abstract
The conjugate addition of aldehydes and ketones to 3-nitro-2*H*-chromenes under basic conditions has been explored. A series of inorganic and organic bases were examined. Proline combined with NaOAc was found to act as an efficient catalyst for the reaction. A number of substituted 3-nitro-2*H*-chromenes, aldehydes, and ketones are applicable for this transformation. *trans*-3-Nitro-4-substituted chromanes were sometimes obtained in good yields and with excellent diastereoselectivities. *trans*-2-Methyl-2-(3-nitrochroman-4-yl)propanal could be transformed into *cis*-2,3-dihydro-1,1-dimethyl-1*H*-chroman[3,4-*b*]pyrrole in one step.

Keywords: Conjugate addition, carbonyl compounds, 3-nitro-2*H*-chromenes, organocatalysis, proline

Introduction

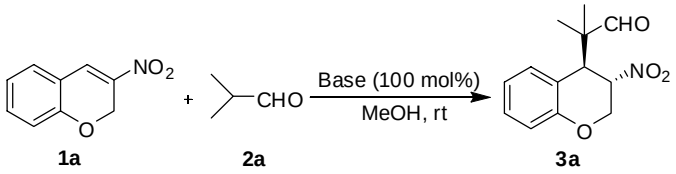
Chromans are important structural units of many natural products and drugs.[1] Chroman derivatives exhibit a variety of useful biological activities,[2] such as antioxidation,[3] antiestrogen,[4] anticonvulsion,[5] and neuroprotection.[6] Their synthetic methods have been the subject of a number of publications.[7] 3-Nitro-2*H*-chromenes, readily available from the reaction of salicylaldehyde and nitroethylene, are valuable intermediates for the synthesis of chroman derivatives.[8] Their conjugate addition reactions with nucleophiles,[9] reduction,[1a] and 1,3-dipolar cycloaddition with azomethine, azide, and diazo compounds,[10] have been developed for the synthesis of many chroman derivatives. We speculate that the conjugate addition of unmodified carbonyl compounds to 3-nitro-2*H*-chromenes can provide a simple and direct route for chroman derivatives. To the best of our knowledge, such a transformation has never been explored. In this paper, we report highly efficient conjugate addition of aldehydes and ketones to 3-nitro-2*H*-chromenes in the presence of bases. Proline combined with NaOAc was found to be a good

catalyst for this reaction. A series of 3-nitrochromans was prepared, sometimes in good yields and with excellent diastereoselectivities.

Results and Discussion

Initially the reaction of 3-nitro-2*H*-chromene **1a** and isobutyraldehyde **2a** was studied. A number of inorganic and organic bases were examined as the catalyst. The results are summarized in Table 1. NaOAc and K_2CO_3 were found to be inefficient and no reaction was observed (Table 1, entries 1-2). Strong inorganic bases, such as LiOH and KOH provided low yield of product **3a** together with many side products (Table 1, entries 3-4). Organic bases, such as triethylamine (TEA), *N,N*-diisopropylethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), and *N*-methylpyrrolidine (NMP) gave **3a** in poor yields (Table 1, entries 5-10). On the other hand, piperidine provided product **3a** in significantly improved yield (Table 1, entry 11). Further study indicated that pyrrolidine is even a better base for the reaction (Table 1, entry 12). The results strongly imply that secondary amines exhibit beneficial effect for the transformation. Special base catalytic mechanism may not be involved in this case and the enamine activation mechanism is highly possible. In recent years, proline and its derivatives have been found to be efficient catalysts for many reactions of aldehydes and ketones via the enamine activation mechanism.[11] Thus, proline was examined as the catalyst for the reaction of **1a** and **2a**. Unfortunately, the reaction only provided **3a** in low yield (Table 1, entry 13). Further study uncovered that the combination of 20 mol % proline and 100 mol % NaOAc produces an extremely efficient catalyst system. Product **3a** was obtained in excellent yield (98%) (Table 1, entry 14). In addition the reaction occurred with excellent diastereoselectivity and only *trans*-**3a** was observed. The *trans*-configuration of **3a** was assigned by $^{3}J_{(3\text{-H},\ 4\text{-H})} \approx 0$ Hz and further confirmed by NOESY spectrum. Homochiral (*S*)-proline was also examined, but the enantioselectivity of the reaction was low (23% ee, determined by chiral HPLC analysis).[12] Proline methyl ester combined with NaOAc gave **3a** in lower yield (Table 1, entry 15). The result suggests that the free carboxylic group of proline is important for the catalytic activity. The hypothesis was further supported by the fact that pyrrolidine combined with NaOAc gave moderated yield of **3a** (Table 1, entry 16).

Table 1. Reaction of **1a** and **2a** in the presence of bases[a]



1a **2a** **3a**

Entry	Base	Yield (%)[b,c]
1	NaOAc	0
2	K_2CO_3	0
3	LiOH	14
4	KOH	13
5	TEA	19
6	DIPEA	17
7	DABCO	14
8	DBU	38
9	DMAP	12
10	NMP	28
11	Piperidine	76
12	Pyrrolidine	84
13	Proline	28
14	Proline (20 mol%)/NaOAc (100 mol%)	98
15	Proline methyl ester (20 mol%)/NaOAc (100 mol%)	52
16	Pyrrolidine (20 mol%)/NaOAc (100 mol%)	68

[a]The reactions were carried out with **1a** (0.10 mmol), **2a** (1.00 mmol) and base (0.10 mmol) in MeOH (1.0 mL) at room temperature for 5 h.
[b]GC yields determined with dodecane as the internal standard.
[c]Only *trans*-**3a** was observed by NMR analysis.

Using proline/NaOAc as the catalyst, a number of reaction solvents were screened and the results are summarized in Table 2. Significant effect of the solvent on the yield was observed. Low yields of **3a** were obtained in hexane, toluene, dichloromethane, THF, and diethyl ether (Table 2, entries 1-5). Only traces of product were obtained in 1,4-dioxane and acetonitrile (Table 2, entries 6-7). Methanol was found to be the optimum solvent and excellent yield was achieved (Table 2, entry 8). The result implicates that protic solvents may be necessary for the reaction.

Table 2. Effect of reaction solvents[a]

Entry	Solvent	Yield (%)
1	Hexane	23
2	Toluene	12
3	CH_2Cl_2	17
4	THF	12
5	Et_2O	17
6	1,4-Dioxane	3
7	CH_3CN	5
8	MeOH	98

[a] The reactions were carried out with **1a** (0.10 mmol), **2a** (1.00 mmol), NaOAc (0.10 mmol) and (*R*/*S*)-proline (0.02 mmol) in the solvent (1.0 mL) at room temperature for 5 h.

The effect of the loading of proline and NaOAc was also studied and the results are summarized in Table 3. The loading of proline and NaOAc exerted significant effect on the yield. Using 5 mol % and 10 mol % proline and NaOAc provided poor yields of **3a** (Table 3, entries 1-2). Increasing the loading of proline/AcONa to 20 mol % improved the yield (Table 3, entry 3). In addition, increasing the loading of NaOAc also resulted in better yield (Table 3, entry 4). Excellent yield was achieved using 20 mol % proline and 100 mol % NaOAc (Table 3, entry 5).

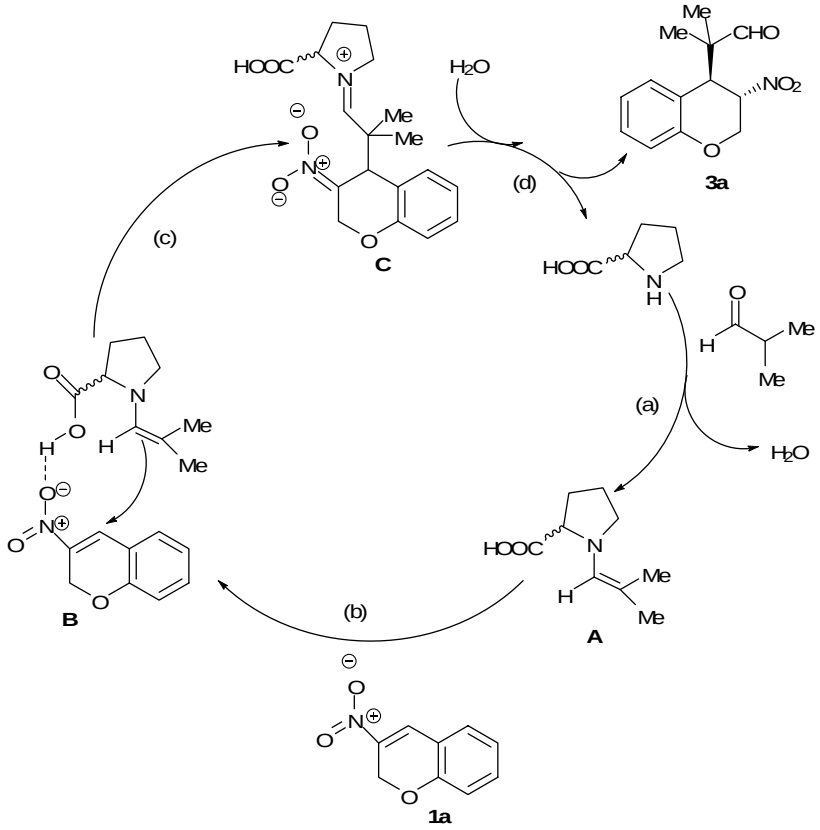
Table 3. Effect of the loading of proline and NaOAc[a]

Entry	Proline (mol%)	NaOAc (mol%)	Yield (%)
1	5	5	8
2	10	10	17
3	20	20	53
4	20	50	82
5	20	100	98

[a]The reactions were carried out with **1a** (0.1 mmol), **2a** (1.0 mmol) in MeOH (1.0 mL) at room temperature for 5 h.

A mechanism of proline/NaOAc catalysis is suggested (Scheme 1). Enamine intermediate **A** is generated from the reaction of proline and isobutyraldehyde. 3-Nitro-2*H*-chromene **1a** is activated via the hydrogen-bonding interaction with the carboxylic group of proline and the transition state **B** is provided. The consequent conjugate addition affords the intermediate **C**, which is hydrolyzed to provide product **3a** and to regenerate proline. The hydrogen-bonding interaction in the transition state **B** seems to be important for the activation of 3-nitro-2*H*-chromene **3a**, since the pyrrolidine and proline methyl ester gave much lower yield than proline.

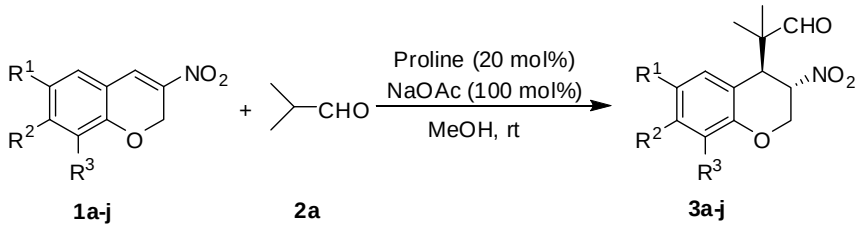
Although AcONa was found to be very important for achieving good yield, its exact function in the reaction is not clear. It may work as a base to promote the formation of enamine intermediate **A**.



Scheme 1

A variety of 3-nitro-2*H*-chromenes **1a-1j** were examined in the reaction with isobutyraldehyde **2a**. The results are summarized in Table 4. The substitutionof the aromatic ring by a methoxy group at the C7 or C8 position was tolerated very well (Table 4, entries 2-3). Substitution of the aromatic ring at C6 with methoxy, methyl, or a halogen also provided the products in good yields (Table 4, entries 4-7). However the substitution at C6 with a nitro group or the disubstitution at C6 and C8 with an halogen resulted in low yields (Table 4, entries 8-10). In these cases, some unidentified side products were observed.

Table 4. Reactions of isobutyraldehyde **2a** with a variety of 3-nitro-2*H*-chromenes **1a-1j**[a]



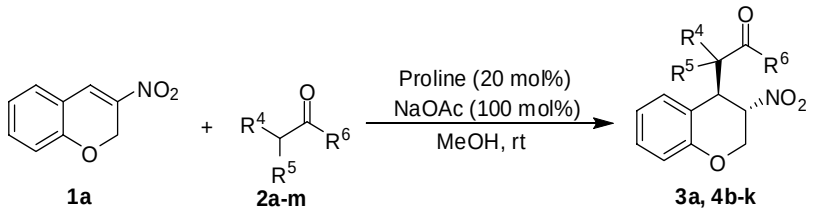
1a-j **2a** **3a-j**

Entry	Substrate			Product	Time (h)	Yield (%)[b,c]
	R^1	R^2	R^3			
1	H	H	H	**3a**	5	96
2	H	H	CH_3O	**3b**	6	92
3	H	CH_3O	H	**3c**	6	89
4	CH_3O	H	H	**3d**	6	85
5	CH_3	H	H	**3e**	8	71
6	Cl	H	H	**3f**	3	77
7	Br	H	H	**3g**	2	81
8	NO_2	H	H	**3h**	3.5	20
9	Cl	H	Cl	**3i**	2.5	40
10	Br	H	Br	**3j**	4	31

[a]The reactions were carried out with **1a-1j** (0.10 mmol), **2a** (1.00 mmol), (*R/S*)-proline (0.02 mmol) and NaOAc (0.10 mmol) in MeOH (1.0 mL) at room temperature.
[b]Isolated yields.
[c]Only *trans*-products were observed by NMR analysis.

A number of aldehydes and ketones were also examined and the results are summarized in Table 5. Acetaldehyde provided the product in low yield after extended reaction time (Table 5, entry 2). Propanal and butanal were highly reactive substrates and the reactions could be completed in less than 5 min. The corresponding adducts were obtained in good yields, but with low diastereoselectivities (Table 5, entries 3-4). Cyclopentane carbaldehyde also provided product **4e** in good yield (Table 5, entry 5). Cyclopentanone was found to be a good substrate for the transformation and good yield could be achieved (Table 5, entry 6). Cyclohexanone gave lower yield than cyclopentanone, probably due to bigger steric hindrance (Table 5, entry 7). Acetone and acetophenone provided products **4h** and **4i** respectively in moderate yields (Table 5, entries 8-9). 1-Methoxyl acetone gave product **4j** in good yield and with complete regioselectivity, but the diastereoselectivity was low (Table 5, entry 10). Hydroxylacetone also afforded the corresponding products, but in moderate yield (Table 5, entry 11).

Table 5. Reaction of **1a** with aldehydes and ketones **2**[a]

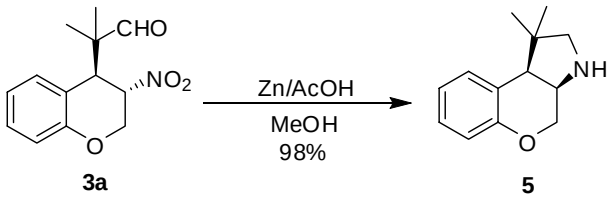


1a **2a-m** **3a, 4b-k**

Entry	Carbonyl compounds **2**			Product	Time (h)	Yield (%)[b]	Dr[c]
	R^4	R^5	R^6				
1	CH_3	CH_3	H	**3a**	5	96	-
2	H	H	H	**4b**	18	20	-
3	CH_3	H	H	**4c**	0.1	90	71:29
4	CH_3CH_2	H	H	**4d**	0.1	97	60:40
5	$(CH_2)_4$		H	**4e**	5	88	-
6	H	$(CH_2)_3$		**4f**	5	92	84:16
7	H	$(CH_2)_4$		**4g**	5	78	57:43
8	H	H	CH_3	**4h**	5	56	-
9	H	H	Ph	**4i**	5	60	-
10	H	OCH_3	CH_3	**4j**	5	83	55:45
11	H	OH	CH_3	**4k**	5	63	60:40

[a]The reactions were carried out with **1a** (0.10 mmol), **2a-2m** (1.00 mmol), (*R/S*)-proline (0.02 mmol) and NaOAc (0.10 mmol) in MeOH (1.0 mL) at room temperature.
[b]Isolated yields.
[c]Determined by NMR analysis.

Product **3a** could be reduced with zinc powder under acid conditions and chroman[3,4-*b*]pyrrole **5** was obtained in excellent yield (Scheme 2). The 3,4-*cis*-configuration was established by NOE analysis as well as the coupling constant $^3J_{(3\text{-H},\ 4\text{-H})}$ = 11.8 Hz. The racemization at C_3 of **3a** occurred under the reaction conditions and thus the thermodynamically favoured **5** showing the *cis*-fusion was obtained.



3a **5**

Scheme 2

Conclusions

In conclusion, we have developed an efficient conjugate addition of aldehydes and ketones to 3-nitro-2*H*-chromenes. Proline associated with NaOAc was found to be the best catalyst. An enamine activation mechanism was proposed. The reaction provided a number of 4-substituted 3-nitrochromans, sometimes in good yields and with excellent diastereoselectivities. The reduction of *trans*-2-methyl-2-(3-nitrochroman-4-yl)propanal **3a** with zinc/AcOH gave the chroman[3,4-*b*]pyrrole **5** in one step. Further studies are currently underway to apply the method for the synthesis of valuable chromane derivatives and to develop an enantioselective version of the reaction.

Experimental Section

General. All solvents were used as commercial anhydrous grade without further purification. Nitroethylene was purchased from Taiyang Chemical Company of China. The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Company. Melting points were recorded on an electrothermal digital melting-point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer as solutions in $CDCl_3$ unless otherwise stated. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ = 0.00 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ = 77.0 ppm). High-resolution mass spectra were obtained with the Thermo MAT 95XP mass spectrometer. The low resolution mass spectra were obtained with the Thermo Trace GC Ultra – DSQ II and Agilent 6120 (Quadrupole LC-MS) mass spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as frequency of absorption (cm^{-1}). Enantiomeric excesses of compound **3a** were determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 95/5, λ = 210 nm, 0.5 mL/min). GC yields were determined by GC (Agilent 6890N) with a Agilent capillary column HP-5 (30m × 0.32mm, 0.25μm) and dodecane was used as the internal standard.

Typical experimental procedure for the synthesis of 3-nitro-2*H*-chromenes 1a-1j[8a,b]
A solution of salicylaldehyde (1.22 g, 10 mmol) and Bu_2NH (0.65 g, 5 mmol) in dry chloroform (80 mL) was placed in a round-bottomed flask fitted with a Dean-Stark apparatus. At the room temperature, nitroethylene (0.73 g, 10 mmol) was added slowly with a syringe pump over 24 h. Then the reaction mixture was refluxed for 24 h and the water formed during the reaction was removed by the Dean-Stark apparatus. A second portion of nitroethylene (0.73 g, 10 mmol) was added according to the above procedure and the reaction solution was refluxed for further 24 h. After cooling down, the reaction solution was filtered through a layer of silica gel and washed with CH_2C1_2/petroleum ether (*V*/*V* = 1/1). The filtrate was washed with 1% aqueous sodium

hydroxide to remove unreacted salicylaldehyde, and then with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was recrystallized from hexane to give 3-nitro-2*H*-chromene **1a**.

3-Nitro-2*H*-chromene (1a).[8a,e] Yield: 45%. yellow solid, Mp 77.0-78.0 °C (lit.[8a] Mp 79.5-80.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (s, 1H), 7.34 (m, 1H), 7.25 (dd, J = 7.6, 1.6 Hz, 1H), 7.00 (m, 1H), 6.91 (d, J = 8.2 Hz, 1H), 5.25 (d, J = 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.95, 139.15, 133.96, 130.53, 129.21, 122.70, 118.27, 116.58, 62.93; IR (KBr): 1651, 1601, 1570, 1481, 1320, 1226, 1198, 1123, 1072, 764, 713 cm^{-1}; MS (ESI): m/z = 176.0 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_6NO_3^-$ [M - H]$^-$: 176.0348, found: 176.0360.

8-Methoxy-3-nitro-2*H*-chromene (1b).[8a,b,e] Yield: 55%. Yellow solid, Mp 125.6-127.1 °C (lit.[8a] Mp 128-129 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (s, 1H), 6.98 (m, 2H), 6.89 (dd, J = 6.5, 2.6 Hz, 1H), 5.31 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.22, 143.92, 139.29, 129.24, 122.60, 122.24, 119.03, 116.40, 63.20, 56.26; IR (KBr): 1577, 1559, 1541, 1508, 1480, 1338, 1272, 1015, 784, 719 cm^{-1}; MS (ESI): m/z = 206.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{10}H_8NO_4^-$ [M - H]$^-$: 206.0453, found: 206.0462.

7-Methoxy-3-nitro-2*H*-chromene (1c).[8a,b,e] Yield: 50%. Yellow solid, Mp 117.6-118.8 ° C (lit.[8a] Mp 120-121 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.57 (dd, J = 8.5, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.24 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.84, 156.95, 136.18, 131.80, 129.76, 111.34, 109.64, 101.80, 63.14, 55.68; IR (KBr): 1618, 1559, 1508, 1490, 1459, 1437, 1337, 1257, 1077, 954, 870, 715 cm^{-1}; MS (ESI): m/z = 206.0 [M - H]$^-$; HRMS (ESI) calcd for $C_{10}H_8NO_4^-$ [M - H]$^-$: 206.0453, found: 206.0460.

6-Methoxy-3-nitro-2*H*-chromene (1d).[8a,b,e] Yield: 56%; Yellow solid, Mp 88.7-89.8 ° C (lit.[8a] Mp 90-91 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.71 (s, 1H), 6.90 (q, J = 8.9, 2.9 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 6.75 (d, J = 2.9 Hz, 1H), 5.16 (d, J = 0.8 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.91, 148.90, 139.81, 129.22, 120.04, 118.84, 117.29, 114.02, 62.88, 55.80; IR (KBr): 3060, 1652, 1576, 1507, 1489, 1458, 1320, 1255, 1135, 842 cm^{-1}; MS (ESI): m/z = 206.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{10}H_8NO_4^-$ [M - H]$^-$: 206.0453, found: 206.0459.

6-Methyl-3-nitro-2*H*-chromene (1e).[8b,e] Yield: 42%. Yellow solid, Mp 74.1-75.6 °C (lit.[8b] Mp 75-76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.14 (dd, J = 8.3, 1.9 Hz, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.82 (dd, J = 8.3, 3.8 Hz, 1H), 5.22 (d, J = 0.9 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.89, 139.18, 134.70, 132.21, 130.63, 129.45, 118.13, 116.30, 62.93, 20.36; IR (KBr): 2920, 1576, 1508, 1340, 1158, 1076, 945, 860 cm^{-1}; MS (ESI): m/z = 190.0 [M - H]$^-$; HRMS (ESI) calcd for $C_{10}H_8NO_3^-$ [M - H]$^-$: 190.0504, found: 190.0507.

6-Chloro-3-nitro-2*H*-chromene (1f).[8a] Yield: 46%. Yellow solid, Mp 109.5-110.4 °C (lit.[8a] Mp 115-116 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.70 (s, 1H), 7.28 (dd, J = 8.6, 2.5 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 5.25 (d, J = 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 153.33, 140.07, 133.41, 129.53, 127.84, 127.59, 119.51, 117.92, 63.05; IR (KBr): 3080, 1655, 1517, 1479, 1338, 1163, 1070, 951, 861, 840, 646 cm^{-1}; MS (ESI): m/z = 210.0 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_5ClNO_3^-$ [M - H]$^-$: 209.9958, found: 210.0002.

6-Bromo-3-nitro-2*H*-chromene(1g).[8a,b] Yield: 40%. Yellow solid, Mp 120.1-121.5 ° C (lit.[8a] Mp 121-122 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.70 (s, 1H), 7.42 (dd, J = 8.6, 2.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 5.26 (d, J = 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.86, 139.98, 136.33, 132.49, 127.74, 120.03, 118.33, 114.62, 63.03; IR (KBr): 1513, 1474, 1331, 1013, 901, 836, 709 cm^{-1}; MS (ESI): m/z = 253.8 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_5BrNO_3^-$ [M - H]$^-$: 253.9453, found: 253.9460.

3,6-Dinitro-2*H*-chromene(1h).[8a] Yield: 58%. Yellow solid, Mp 157.0-158.0 °C (lit.[8a] Mp 160-161 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.19-8.24 (m, 2H), 7.81 (s, 1H), 7.02 (d, J = 8.9 Hz, 1H), 5.41 (d, J = 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.36, 142.78, 140.39, 129.03, 126.95, 125.91, 118.02, 117.17, 63.79; IR (KBr): 3068, 1660, 1661, 1509, 1480, 1456, 1332, 1237, 1209, 1101, 837, 752 cm^{-1}; MS (ESI): m/z = 221.0 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_5N_2O_5^-$ [M - H]$^-$: 221.0198, found: 221.0202.

6,8-Dichloro-3-nitro-2*H*-chromene (1i). Yield: 54%. Yellow solid, Mp 130.2-131.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (s, 1H), 7.39 (t, J = 2.7 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.13, 140.57, 133.44, 128.07, 127.46, 127.15, 122.85, 120.35, 63.58; IR (KBr): 1558, 1508, 1457, 1326, 1163, 1071, 867, 710 cm^{-1}; MS (ESI): m/z = 243.8 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_4Cl_2NO_3^-$ [M - H]$^-$: 243.9568, found: 243.9555.

6,8-Dibromo-3-nitro-2*H*-chromene (1j).[8a] Yield: 64%. Yellow solid, Mp 142.6-143.8 °C(lit.[8a] Mp 146.5-147.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (m, 2H), 7.33 (d, J = 2.3 Hz, 1H), 5.36 (d, J = 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.65, 140.40, 138.88, 131.65, 127.03, 120.66, 114.55, 111.50, 63.65; IR (KBr): 1541, 1507, 1458, 1330, 1190 cm^{-1}; MS (ESI): m/z = 331.8 [M - H]$^-$; HRMS (ESI) calcd for $C_9H_4Br_2NO_3^-$ [M - H]$^-$: 331.8558, found: 331.8415.

Typical experimental procedure for the conjugate addition of carbonyl compounds to 3-nitro-2*H*-chromenes

A mixture of proline (2.30 mg, 0.02 mmol), NaOAc (8.20 mg, 0.10 mmol) and 3-nitro-2H-chromene **1a** (17.72 mg, 0.10 mmol) in MeOH (1.0 mL) was stirred for 5 min at room temperature. Then isobutyraldehyde **2a** (72.11 mg, 1.00 mmol) was added and the reaction mixture was stirred for 5 h at room temperature. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide **3a**.

***trans*-2-(3-Nitrochroman-4-yl)-2-methylpropanal (3a).** Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.53 (s, 1H), 7.20 (m, 1H), 7.06 (dd, J = 7.7, 1.4 Hz, 1H), 6.93 (m, 2H), 4.97 (m, 1H), 4.64 (ddd, J = 12.8, 4.33, 1.53 Hz, 1H), 4.45 (dd, J = 12.8, 5.0 Hz, 1H), 4.03 (s, 1H), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.93, 154.43, 130.45, 129.35, 121.88, 118.45, 117.44, 80.88, 64.99, 49.71, 43.16, 20.50, 20.32; IR (KBr): 2968, 2918, 2850, 1719, 1608, 1585, 1556, 1508, 1490, 1397, 1361, 1230, 1120, 1042, 758 cm^{-1}; MS (ESI): m/z = 248.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{13}H_{14}NO_4^-$ [M - H]$^-$: 248.0923, found: 248.0912.

***trans*-2-(8-Methoxy-3-nitrochroman-4-yl)-2-methylpropanal (3b).** Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.55 (s, 1H), 6.90 (t, J = 8.1 Hz, 1H), 6.82 (dd, J = 8.1, 1.0 Hz, 1H), 6.66 (dd, J

= 7.8, 0.9 Hz, 1H), 4.99 (m, 1H), 4.72 (ddd, *J* = 12.8, 4.4, 1.4 Hz, 1H), 4.53 (dd, J = 12.8, 5.1 Hz, 1H), 4.06 (s, 1H), 3.86 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.77, 148.60, 143.79, 121.98, 121.52, 119.50, 111.13, 80.75, 65.42, 55.93, 49.71, 42.82, 20.47, 20.26; IR (KBr): 2921, 2851, 1717, 1587, 1553, 1458, 1361, 1264, 1224, 1102, 1028, 734 cm^{-1}; MS (ESI): *m*/*z* = 278.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{14}H_{16}NO_5^-$ [M - H]$^-$: 278.1028, found: 278.1034.

***trans*-2-(7-Methoxy-3-nitrochroman-4-yl)-2-methylpropanal (3c).** Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.52 (s, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.52 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.44 (d, *J* = 2.6 Hz, 2H), 4.93 (m, 1H), 4.68 (ddd, *J* = 13.0, 3.9, 1.7 Hz, 1H), 4.39 (dd, J = 13.0, 4.7 Hz, 1H), 3.95 (s, 1H), 3.76 (s, 1H),1.15 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.22, 160.41, 155.10, 131.02, 109.93, 108.73, 102.07, 80.70, 64.63, 55.30, 49.70, 42.70, 20.49, 20.28; IR (KBr): 2920, 2850, 2718, 1718, 1619, 1555, 1506, 1464, 1361, 1202, 1163, 1031, 752 cm^{-1}; MS (ESI): *m*/*z* = 278.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{14}H_{16}NO_5^-$ [M - H]$^-$: 278.1028, found: 278.1032.

***trans*-2-(6-Methoxy-3-nitrochroman-4-yl)-2-methylpropanal (3d).** Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.54 (s, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.59 (d, *J* = 2.9 Hz, 1H), 4.97 (m, 1H), 4.42-4.53 (m, 2H), 4.02 (d, *J* = 2.6 Hz, 1H), 3.75 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.87, 154.30, 148.63, 119.89, 118.15, 115.12, 115.03, 81.21, 65.66, 55.69, 49.86, 43.46, 20.50, 20.21; IR (KBr): 2920, 2851, 1719, 1555, 1499, 1472, 1361, 1212, 1048, 725 cm^{-1}; MS (ESI): *m*/*z* = 278.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{14}H_{16}NO_5^-$ [M - H]$^-$: 278.1028, found: 278.1035.

***trans*-2-(6-Methyl-3-nitrochroman-4-yl)-2-methylpropanal (3e).** Pale yellow solid, Mp 121.2-123.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.54 (s, 1H), 7.00 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.84 (d, *J* = 1.5 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.96 (m, 1H), 4.59 (ddd, *J* = 12.7, 4.52, 1.5 Hz, 1H), 4.43 (dd, J = 12.7, 5.1 Hz, 1H), 3.97 (s, 1H), 2.26 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.02, 152.33, 131.27, 130.63, 130.05, 118.29, 117.15, 81.08, 65.14, 49.70, 43.34, 20.69, 20.55, 20.24; IR (KBr): 2924, 2854, 1720, 1553, 1499, 1459, 1359, 1216, 1032, 882, 817 cm^{-1}; MS (ESI): *m*/*z* = 262.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{14}H_{16}NO_4^-$ [M - H]$^-$: 262.1079, found: 262.1083.

***trans*-2-(6-Chloro-3-nitrochroman-4-yl)-2-methylpropanal (3f).** White solid, Mp 86.6-88.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.50 (s, 1H), 7.17 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 4.95 (m, 1H), 4.70 (ddd, *J* = 13.0, 3.8, 1.7 Hz, 1H), 4.43 (dd, *J* = 13.0, 4.9 Hz, 1H), 4.00 (d, *J* = 1.9 Hz, 1H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.40, 152.87, 130.06, 129.49, 126.67, 119.90, 118.82, 80.36, 64.92, 49.49, 42.76, 20.70, 20.48; IR (KBr): 3116, 3039, 2919, 1722, 1556, 1486, 1231, 1024, 735 cm^{-1}; MS (ESI): *m*/*z* = 282.0 [M - H]$^-$; HRMS (ESI) calcd for $C_{13}H_{13}ClNO_4^-$ [M - H]$^-$: 282.0533, found: 282.0539.

***trans*-2-(6-Bromo-3-nitrochroman-4-yl)-2-methylpropanal (3g).** Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.50 (s, 1H), 7.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 4.94 (m, 1H), 4.71 (ddd, *J* = 13.0, 3.8, 1.7 Hz, 1H), 4.42 (dd, J = 13.0, 4.8 Hz, 1H), 3.99 (s, 1H), 1.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.38, 153.38, 132.98, 132.41,

120.37, 119.24, 113.92, 80.32, 64.83, 49.48, 42.72, 20.74, 20.48 ; IR (KBr): 2921, 2851, 1719, 1552, 1474, 1360, 1230, 1179, 1126, 1026, 816 cm^{-1}; MS (ESI): *m*/*z* = 325.9 $[M - H]^-$; HRMS (ESI) calcd for $C_{13}H_{13}BrNO_4^-$ $[M - H]^-$: 326.0028, found: 326.0033.

***trans*-2-(3,6-Dinitrochroman-4-yl)-2-methylpropanal (3h).** White solid, Mp 125.0-127.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ=9.51 (s, 1H), 8.07-8.14 (m, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 4.94-5.02 (m, 2H,), 4.50 (dd, J = 14.0, 4.6 Hz, 1H), 4.10 (s, 1H), 1.23 (s, 3H), 1.22 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.69, 158.81, 141.86, 126.85, 125.32, 118.10, 117.90, 79.29, 64.70, 49.21, 42.30, 21.14, 20.48; IR (KBr): 2920, 2851, 1717, 1584, 1553, 1515, 1472, 1339, 1237, 1096, 748 cm^{-1}; MS (ESI): *m*/*z* = 293.1 $[M - H]^-$; HRMS (ESI) calcd for $C_{13}H_{13}NO_6^-$ $[M - H]^-$: 293.0774, found: 293.0771.

***trans*-2-(6,8-Dichloro-3-nitrochroman-4-yl)-2-methylpropanal (3i).** Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=9.49 (s, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 4.1 Hz, 1H), 4.99 (m, 1H), 4.85 (dd, *J* = 13.2, 1.4 Hz, 1H), 4.54 (dd, J = 13.2, 4.9 Hz, 1H), 4.04 (s, 1H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.90, 148.70, 129.86, 128.67, 126.45, 123.42, 121.25, 80.04, 65.50, 49.45, 42.62, 20.85, 20.40; IR (KBr): 2920, 2851, 1719, 1553, 1468, 1246, 1184, 1026, 866 cm^{-1}; MS (ESI): *m*/*z* = 316.0 $[M - H]^-$; HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NO_4^-$ $[M - H]^-$: 316.0143, found: 316.0150.

***trans*-2-(6,8-Dibromo-3-nitrochroman-4-yl)-2-methylpropanal (3j).** Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=9.48 (s, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 4.98 (m, 1H), 4.84 (ddd, *J* = 13.2, 4.3, 1.5 Hz, 1H), 4.54 (dd, J = 13.2, 5.0 Hz, 1H), 4.03 (s, 1H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.88, 150.13, 135.37, 132.26, 121.66, 113.79, 112.45, 80.09, 65.60, 49.46, 42.72, 20.85, 20.35; IR (KBr): 2920, 2851, 1718, 1551, 1464, 1356, 1242, 1170, 722 cm^{-1}; MS (ESI): *m*/*z* = 403.9 $[M - H]^-$; HRMS (ESI) calcd for $C_{13}H_{12}Br_2NO_4^-$ $[M - H]^-$: 403.9133, found: 403.9135.

***trans*-2-(3-Nitrochroman-4-yl)acetaldehyde (4b).** Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=9.83 (s, 1H), 7.20 – 7.14 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.97 (td, *J* = 7.6, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.84 – 4.80 (m, 1H), 4.77 (ddd, *J* = 12.1, 4.2, 1.5 Hz, 1H), 4.32 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.28 – 4.22 (m, 1H), 3.10 (dd, *J* = 18.9, 4.4 Hz, 1H), 2.90 (ddd, *J* = 18.9, 9.0, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.41, 153.01, 128.65, 128.59, 122.27, 120.88, 117.37, 81.31, 63.41, 49.45, 31.24; IR (KBr): 2961, 2851, 1716, 1609, 1585, 1541, 1489, 1459, 1363, 1222, 1042, 756 cm^{-1}; MS (ESI): *m*/*z* = 220.1 $[M - H]^-$; HRMS (ESI) calcd for $C_{11}H_{10}NO_4^-$ $[M - H]^-$: 220.0610, found: 220.0617.

2-(3-Nitrochroman-4-yl)propanal (4c). Colorless oil. Dr = 71:29, signals corresponding to the major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=9.77 (d, *J* = 1.0 Hz, 1H), 7.23 – 6.85 (m, 4H), 4.90 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.72 (ddd, *J* = 12.4, 4.8, 1.3 Hz, 1H), 4.42 (dd, J = 12.4, 3.5 Hz, 1H), 4.13 (t, *J* = 5.5 Hz, 1H), 2.85 – 2.75 (m, 1H), 1.18 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.43, 154.06, 129.60, 128.78, 121.81, 118.45, 117.47, 80.80, 64.01, 49.96, 37.88, 11.25; signals corresponding to the minor diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=9.79 (d, *J* = 0.8 Hz, 1H), 7.23 – 6.85 (m, 4H), 4.77 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.73 (ddd, *J* = 12.4, 4.8, 1.3 Hz, 1H), 4.55 (dd, J = 12.4, 3.5 Hz, 1H), 4.28 (t, *J* = 5.5 Hz, 1H), 3.11 – 2.97 (m,

1H), 1.16 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=201.86, 153.50, 129.02, 128.38, 122.38, 119.46, 117.62, 80.39, 64.91, 50.57, 36.17, 10.12; IR (KBr): 2923, 2852, 1718, 1609, 1585, 1551, 1490, 1458, 1361, 1225, 1121, 1043, 858, 757 cm^{-1}; MS (ESI): *m*/*z* = 234.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{12}H_{12}NO_4^-$ [M - H]$^-$: 234.0766, found: 234.0769.

2-(3-Nitrochroman-4-yl)butanal (4d). Colorless oil. Dr = 60:40, signals corresponding to the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=9.73 (d, *J* = 2.1 Hz, 1H), 7.24 – 6.82 (m, 4H), 4.86 (q, *J* = 3.7 Hz, 1H), 4.74 (ddd, *J* = 10.4, 4.1, 1.6 Hz, 1H), 4.36 (dd, J = 12.6, 3.5 Hz, 1H), 4.06 (dd, *J* = 7.3, 3.4 Hz, 1H), 2.66 (dddd, *J* = 9.0, 7.3, 4.9, 2.1 Hz, 1H), 1.64 -1.49 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=203.28, 153.41, 128.09, 128.63, 121.77, 118.63, 117.52, 80.54, 63.77, 56.91, 37.06, 19.97, 11.92; signals corresponding to the minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (d, *J* = 2.3 Hz, 1H), 7.24 – 6.82 (m, 4H), 4.80 (q, *J* = 3.4 Hz, 1H), 4.77 (ddd, *J* = 12.4, 4.8, 1.3 Hz, 1H), 4.32 (dd, J = 12.3, 3.2 Hz, 1H), 4.20 (dd, *J* = 7.3, 3.4 Hz, 1H), 2.76 (dddd, *J* = 9.0, 7.3, 4.9, 2.1 Hz, 1H), 1.91 -1.74 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.25, 153.80, 129.59, 128.90, 122.25, 119.17, 117.59, 80.54, 64.45, 57.50, 36.53, 19.52, 12.32; IR (KBr): 2965, 1717, 1609, 1585, 1556, 1491, 1462, 1388, 1361, 1232, 1122, 1044, 857, 758 cm^{-1}; MS (ESI): *m*/*z* = 248.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{13}H_{14}NO_4^-$ [M - H]$^-$: 248.0923, found: 248.0929.

***trans*-1-(3-Nitrochroman-4-yl)cyclopentanecarbaldehyde (4e).** White solid, Mp 95.1-96.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=9.39 (s, 1 H), 7.25 – 7.16 (m, 2 H), 7.06 – 6.92 (m, 1 H), 6.88 (d, *J* = 8.5, 1 H), 4.85 (dt, *J* = 4.2, 2.7, 1 H), 4.81 – 4.71 (m, 1 H), 4.32 (dd, *J* = 13.3, 4.3, 1 H), 3.96 (s, 1 H), 2.25 (t, *J* = 7.9, 1 H), 2.11 (dd, *J* = 12.7, 7.4, 1 H), 1.86 – 1.34 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=203.75, 153.75, 130.24, 129.55, 121.70, 117.67, 117.37, 81.26, 63.83, 61.58, 43.79, 32.45, 30.86, 24.28, 23.76; IR (KBr): 2923, 2853, 1718, 1608, 1584, 1553, 1489, 1457, 1392, 1361, 1228, 1122, 1044, 756 cm^{-1}; MS (ESI): *m*/*z* = 274.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{15}H_{16}NO_4^-$ [M - H]$^-$: 274.1079, found: 274.1081.

2-(3-Nitrochroman-4-yl)cyclopentanone (4f). Brown oil. Dr = 84:16, signals corresponding to the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.24 – 6.81 (m, 3H), 6.96 (dd, *J* = 7.8, 1.6 Hz, 1H), 5.34 (q, *J* = 3.7 Hz, 1H), 4.89 (ddd, *J* = 12.8, 3.3, 1.8 Hz, 1H), 4.43 (dd, J = 12.8, 3.1 Hz, 1H), 4.13 - 4.04 (m, 1H), 2.48 – 2.37 (m, 1H), 2.34 – 2.25 (m, 1H), 2.24 – 2.12 (m, 1H), 2.09 – 1.98 (m, 2H), 1.84 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=218.30, 153.27, 129.62, 129.10, 121.73, 119.41, 117.44, 81.07, 63.62, 53.15, 38.87, 37.73, 27.97, 20.51; signals corresponding to the minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.24 – 6.81 (m, 3H), 7.00 (dd, *J* = 7.5, 1.2 Hz, 1H). 4.72 – 4.67 (m, 1H), 4.61 (ddd, *J* = 11.7, 5.3, 1.1 Hz, 1H), 4.32 (dd, J = 11.8, 3.0 Hz, 1H), 4.27 (t, *J* = 4.5 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.34 – 2.25 (m, 1H), 2.24 – 2.12 (m, 1H), 2.09 – 1.98 (m, 2H), 1.84 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=216.72, 154.03, 128.56, 128.17, 122.50, 121.14, 117.63, 81.07, 65.68, 54.76, 38.03, 35.48, 26.08, 20.59; IR (KBr): 2923, 2853, 1734, 1583, 1544, 1460, 1362, 1223, 756 cm^{-1}; MS (ESI): *m*/*z* = 260.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{14}H_{14}NO_4^-$ [M - H]$^-$: 260.0923, found: 260.0927.

2-(3-Nitrochroman-4-yl)cyclohexanone (4g). White solid, Mp 92.6-93.8 °C. Dr = 57:43, signals corresponding to the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.21 – 6.83

(m, 4H), 4.99 (q, *J* = 3.6 Hz, 1H), 4.80 (ddd, *J* = 12.6, 3.6, 1.5 Hz, 1H), 4.41 (dd, J = 12.6, 3.5 Hz, 1H), 4.10 (dd, *J* = 8.7, 3.7 Hz, 1H), 3.04 – 2.47 (m, 2H), 2.38 (dtd, *J* = 21.7, 13.2, 5.8 Hz, 1H), 2.13 (tdd, *J* = 12.5, 5.9, 2.9 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.81 – 1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.14, 154.79, 130.83, 128.89, 122.61, 121.35, 117.34, 81.30, 63.79, 54.18, 42.89, 37.26, 32.27, 28.15, 25.33; signals corresponding to the minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.21 – 6.83 (m, 4H), 4.89 (dd, *J* = 5.3 3.3 Hz, 1H), 4.70 (ddd, *J* = 12.3, 3.6, 1.4 Hz, 1H), 4.35 (s, 1H), 4.14 (dd, J = 12.4, 3.1 Hz, 1H), 3.04 – 2.47 (m, 2H), 2.38 (dtd, *J* = 21.7, 13.2, 5.8 Hz, 1H), 2.13 (tdd, *J* = 12.5, 5.9, 2.9 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.81 – 1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=210.59, 153.44, 128.10, 128.33, 121.03, 119.28, 117.64, 81.91, 66.42, 55.45, 42.30, 34.38, 29.49, 27.57, 25.72; IR (KBr): 2925, 2855, 1703, 1584, 1549, 1489, 1451, 1358, 1309, 1224, 1124, 757 cm^{-1}; MS (ESI): *m*/*z* = 274.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{15}H_{16}NO_4^-$ [M - H]$^-$: 274.1079, found: 274.1084.

***trans*-1-(3-Nitrochroman-4-yl)propan-2-one (4h).** Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.19 – 7.12 (m, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.96 (td, *J* = 7.6, 1.2 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.85 (dd, *J* = 6.1, 3.5 Hz, 1H), 4.77 (ddd, *J* = 12.3, 3.9, 1.6 Hz, 1H), 4.29 (dd, *J* = 12.3, 2.4 Hz, 1H), 4.20 – 4.12 (m, 1H), 3.02 (dd, *J* = 18.5, 4.2 Hz, 1H), 2.81 (dd, *J* = 18.5, 9.3 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.13, 153.00, 128.63, 128.44, 122.14, 121.47, 117.26, 81.38, 63.37, 49.18, 32.29, 30.27; IR (KBr): 2921, 2851, 1716, 1609, 1585, 1542, 1489, 1459, 1361, 1222, 1041, 756 cm^{-1}; MS (ESI): *m*/*z* = 234.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{12}H_{12}NO_4^-$ [M - H]$^-$: 234.0766, found: 234.0769.

***trans*-2-(3-Nitrochroman-4-yl)-1-phenylethanone (4i).** White solid, Mp 86.4-88.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.68 – 7.57 (m, 1H), 7.49 (dd, *J* = 10.7, 4.7 Hz, 2H), 7.22 – 7.13 (m, 2H), 7.01 – 6.93 (m, 1H), 6.88 (dd, *J* = 8.6, 1.0 Hz, 1H), 4.96 (dd, *J* = 6.0, 2.7 Hz, 1H), 4.84 (ddd, *J* = 12.4, 3.6, 1.6 Hz, 1H), 4.39 (d, *J* = 10.3 Hz, 1H), 4.35 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.59 (dd, *J* = 18.4, 3.8 Hz, 1H), 3.33 (dd, *J* = 18.4, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.69, 153.32, 136.25, 134.11, 129.09, 129.06, 128.65, 128.27, 122.37, 121.92, 117.49, 81.66, 63.52, 44.90, 32.60; IR (KBr): 2921, 2851, 1678, 1583, 1549, 1489, 1448, 1355, 1222, 1103, 754, 689 cm^{-1}; MS (ESI): *m*/*z* = 296.1 [M - H]$^-$; HRMS (ESI) calcd for $C_{17}H_{14}NO_4^-$ [M - H]$^-$: 296.0923, found: 296.0913.

1-Methoxy-1-(3-nitrochroman-4-yl)propan-2-one (4j). Brown oil. Dr = 55:45, signals corresponding to the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 – 6.84 (m, 4H), 4.92 (dd, *J* = 6.3, 3.7 Hz, 1H), 4.77 (ddd, *J* = 11.7, 3.3, 1.6 Hz, 1H), 4.34 (dd, J = 12.5, 3.0 Hz, 1H), 4.16 – 4.13 (m, 1H), 3.91 (d, *J* = 6.1 Hz, 1H), 3.38 (s, 3H). 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=209.51, 153.56, 129.10, 128.87, 121.67, 117.55, 117.47, 88.20, 79.52, 64.11, 59.76, 38.97, 27.98; signals corresponding to the minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 – 6.84 (m, 4H), 4.86 (dd, *J* = 5.5, 2.8 Hz, 1H), 4.80 (ddd, *J* = 11.3, 3.4, 1.8 Hz, 1H), 4.46 (dd, J = 12.2, 2.7 Hz, 1H), 4.16 – 4.13 (m, 1H), 4.07 (d, *J* = 4.1 Hz, 1H), 3.27 (s, 3H). 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.86, 154.05, 129.73, 128.49, 121.96, 118.21, 116.73, 89.07, 79.27, 66.91, 59.16, 37.99, 27.47; IR (KBr): 2921, 2851, 1717, 1542, 1508, 1458,

1362, 1100, 753 cm^{-1}; MS (ESI): *m*/*z* = 264.1 $[M - H]^-$; HRMS (ESI) calcd for $C_{13}H_{14}NO_5^-$ $[M - H]^-$: 264.0872, found: 264.0877.

1-Hydroxy-1-(3-nitrochroman-4-yl)propan-2-one (4k). Pale yellow oil. Dr = 60:40, signals corresponding to the major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 – 6.87 (m, 4H), 4.82 (ddd, *J* = 12.3, 2.9, 1.6 Hz, 1H), 4.67 (t, *J* = 2.9 Hz, 1H), 4.57 (dd, *J* = 5.1, 2.8 Hz, 1H). 4.47 (dd, *J* = 12.3, 2.8 Hz, 1H), 4.16 (s, 1H), 3.50 (s, 1H). 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.98, 154.28, 128.99, 128.27, 122.25, 117.77, 117.67, 79.81, 79.20, 64.99, 39.07, 26.43; signals corresponding to the minor diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 – 6.87 (m, 4H), 4.93 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.77 (ddd, *J* = 12.3, 3.7, 1.6 Hz, 1H), 4.52 (dd, J = 12.4, 2.8 Hz, 1H), 4.51 (t, *J* = 2.9 Hz, 1H), 4.29 (s, 1H), 3.51 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.38, 154.17, 129.34, 128.46, 121.82, 117.86, 115.66, 80.98, 79.28, 64.35, 40.05, 26.76; IR (KBr): 3448, 2925, 2853, 1716, 1609, 1586, 1552, 1491, 1461, 1225, 1103, 1041, 758 cm^{-1}; MS (ESI): *m*/*z* = 250.0 $[M - H]^-$; HRMS (ESI) calcd for $C_{12}H_{12}NO_5^-$ $[M - H]^-$: 250.0715, found: 250.0720.

Reduction of *trans*-2-(3-nitrochroman-4-yl)-2-methylpropanal (3a) with zinc/AcOH[13]

To a solution of the **3a** (62 mg, 0.25 mmol) in MeOH/AcOH (*V*/*V* = 1/1, 5 mL) at 0 °C was added zinc powder (400 mg, 6.25 mmol) in small portions over a period of 5 min. The reaction mixture was stirred for 2 h at room temperature and was then filtered. The filtrate was adjusted to pH 12 with aqueous NaOH (4 M). The aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (CH_2Cl_2/MeOH = 20/1) to provide c*is*-1,1-dimethyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*b*]pyrrole (**5**) as a colorless oil. ^1H NMR (400 MHz, MeOD): δ=7.24 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.5, 4.6 Hz, 1H), 6.85 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.48 (dd, *J* = 9.4, 4.1 Hz, 1H), 4.10 (dd, *J* = 10.8, 9.5 Hz, 1H), 3.50 (td, *J* = 11.6, 3.7 Hz, 1H), 3.30 (dd, *J* = 1.6, 3.2 Hz, 1H), 3.10 (d, *J* = 11.2 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.71 (d, *J* = 11.6 Hz, 1H), 1.47 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ=155.69, 128.91, 127.27, 123.35, 121.24, 117.49, 70.96, 62.52, 58.12, 51.87, 40.68, 28.78, 22.52; IR (KBr): 3444, 2961, 2929, 2878, 1609, 1486, 1452, 1230, 1160, 1074, 953, 860, 754 cm^{-1}; MS (ESI): *m*/*z* = 204.1 $[M + H]^-$; HRMS (ESI) calcd for $C_{13}H_{18}NO^+$ $[M + H]^+$: 204.1388, found: 204.1378.

Acknowledgements

We thank National Natural Science Foundation of China (No. 20772160, 20972195), Ministry of Science and Technology of China (No. 2009ZX09501-017) for the financial support of this study.

References

1. (a) Mellin, C.; Vallgaarda, J.; Nelson, D. L.; Bjoerk, L.; Yu, H.; Anden, N. E.; Csoeregh, I.; Arvidsson, L. E.; Hacksell, U. *J. Med. Chem.* **1991**, *34*, 497. (b) Podona, T.; Guardiola-Lemaitre, B.; Caignard, D. H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779. (c) Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D. H.; Renard, P.; Rettori, M. C.; Adam, G.; Guardiola-Lemaitre, B. *J. Med. Chem*. **1996**, *39*, 4285. (d) Dubuffet, T.; Newman-Tancredi, A.; Cussac, D.; Audinot, V.; Loutz, A.; Millan, M. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2059. (e) Cueva, J. P.; Giorgioni, G.; Grubbs, R. A.; Chemel, B. R.; Watts, V. J.; Nichols, D. E. *J. Med. Chem*. **2006**, *49*, 6848. (f) Furuta, T.; Hirooka, Y.; Abe, A.; Sugata, Y.; Ueda, M.; Murakami, K.; Suzuki, T.; Tanaka, K.; Kan, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3095. (g) Kolokythas, G.; Kostakis, I. K.; Pouli, N.; Marakos, P.; Kousidou, O. C.; Tzanakakis, G. N.; Karamanos, N. K. *Eur. J. Med. Chem.* **2007**, *42*, 307.
2. For a recent review of chroman derivatives with biological activity, see: Wang, G. X.; Wang, N. X.; Shi, T.; Yu, J. L.; Tang, X. L. *Progress in Chemistry* **2008**, *20*, 518.
3. Kwak, J. H.; Kang, H. E.; Jung, J. K.; Kim, H.; Cho, J.; Lee, H. *Arch. Pharm. Res.* **2006**, *29*, 934.
4. Kanbe, Y.; Kim, M. H.; Nishimoto, M.; Ohtake, Y.; Kato, N.; Tsunenari, T.; Taniguchi, K.; Ohizumi, I.; Kaiho, S.; Morikawa, K.; Jo, J. C.; Lim, H. S.; Kim, H. Y. *Bioorg. Med. Chem.* **2006**, *14*, 4803.
5. Emami, S.; Kebriaeezadeh, A.; Zamani, M. J.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1803.
6. Koufaki, M.; Kiziridi, C.; Alexi, X.; Alexis, M. N. *Bioorg. Med. Chem.* **2009**, *17*, 6432.
7. (a) Wise, L. D.; Dewald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. *J. Med. Chem*. **1988**, *31*, 688. (b)Yao, C. F.; Jang, Y. J.; Yan, M. C. *Tetrahedron Lett.* **2003**, *44*, 3813. (c) Xu, D. Q.; Wang, Y. F.; Luo, S. P.; Zhang, S.; Zhong, A. G.; Chen, H.; Xu, Z. Y. *Adv. Synth. Catal.* **2008**, *350*, 2610. (d) Rao, H. S. P.; Geetha, K. *Tetrahedron Lett.* **2009**, *50*, 3836. (e) Wang, Y. F.; Zhang, W.; Luo, S. P.; Li, B. L.; Xia, A. B.; Zhong, A. G.; Xu, D. Q. *Chem. Asian J.* **2009**, *4*, 1834.
8. (a) Dauzonne, D.; Royer, R. S*ynthesis* **1984**, 348. (b) Neirabeyeh, M. A.; Koussini, R.; Guillaumet, G. *Synth. Commun.* **1990**, *20*, 783. (c) Yan, M. C.; Jang, Y. J.; Yao, C. F. *Tetrahedron Lett.* **2001**, *42,* 2717. (d) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Green Chem.* **2005**, *7*, 825. (e) Koussini, R.; Al-Shihri, A. S. *J. Saudi Chem. Soc.* **2008**, *12*, 531.
9. (a) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Lett. Org. Chem.* **2005**, *2*, 616. (b) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Russ. Chem. Bull.* **2006**, *55*, 2020. (c) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B. *Russ. Chem. Bull.* **2007**, *56*, 2054. (d) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Shklyaev, Y. V. *Tetrahedron Lett.* **2008**, *49*, 5376. (e) Granados-Covarrubias,

E. H.; Maldonado, L. A. *J. Org. Chem.* **2009**, *74*, 5097. (f) Habib, P. M.; Kavala, V.; Raju, B. R.; Kuo, C. W.; Huang, W. C.; Yao, C. F. *Eur. J. Org. Chem.* **2009**, 4503.

10. (a) Nyerges, M.; Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Tőke, L. *Synlett* **2004**, 2761. (b) Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Toke, L.; Nyerges, M. *Tetrahedron* **2006**, *62*, 8720. (c) Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125. (d) Habib, P. M.; Raju, B. R.; Kavala, V.; Kuo, C. W.; Yao, C. F. *Tetrahedron* **2009**, *65*, 5799. (e) Korotaev, V. Y.; Sosnovskikh, V. Y.; Barabanov, M. A.; Yasnova, E. S.; Ezhikova, M. A.; Kodess, M. I.; Slepukhin, P. A. *Tetrahedron* **2010**, *66*, 1404.
11. For the reviews of proline and its derivatives as organocatalysts, see: (a) Cheng, C. L.; Hao, E. J.; Li, W.; Xu, G. Q. *HuaxueShiji* **2007**, *29*, 147. (b) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493. (c) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757.
12. Recently an organocatalytic asymmetric synthesis of 3-nitro-chromans from *o*-hydroxy cinamldehyde and nitroalkenes was reported. See: Zu, L. S.; Zhang, S. L.; Xie, H. X.; Wang, W. *Org. Lett.* **2009**, *11*, 1627.
13. Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357.