Organocatalytic conjugate addition of nitroalkanes to 2H-chromene-3-carbaldehydes: synthesis of highly functionalized chroman derivatives

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Abstract

Conjugate addition of nitroalkanes to 2*H*-chromene-3-carbaldehydes has been studied using a number of amines as the catalysts. Prolinol triethylsilyl ether was found to be the best catalyst for the reaction. The use of protonic solvents was also important. The reaction of variously substituted 2*H*-chromene-3-carbaldehydes with nitromethane afforded the products with excellent yields and diastereoselectivities. Nitroethane and 1-nitropropane were also applicable, however in decreased yields. The enantioselectivities of the reaction were very low and almost racemic products (3~5% ee) were obtained in all cases. The reaction provides a new method for the preparation of highly functionalized chroman derivatives.

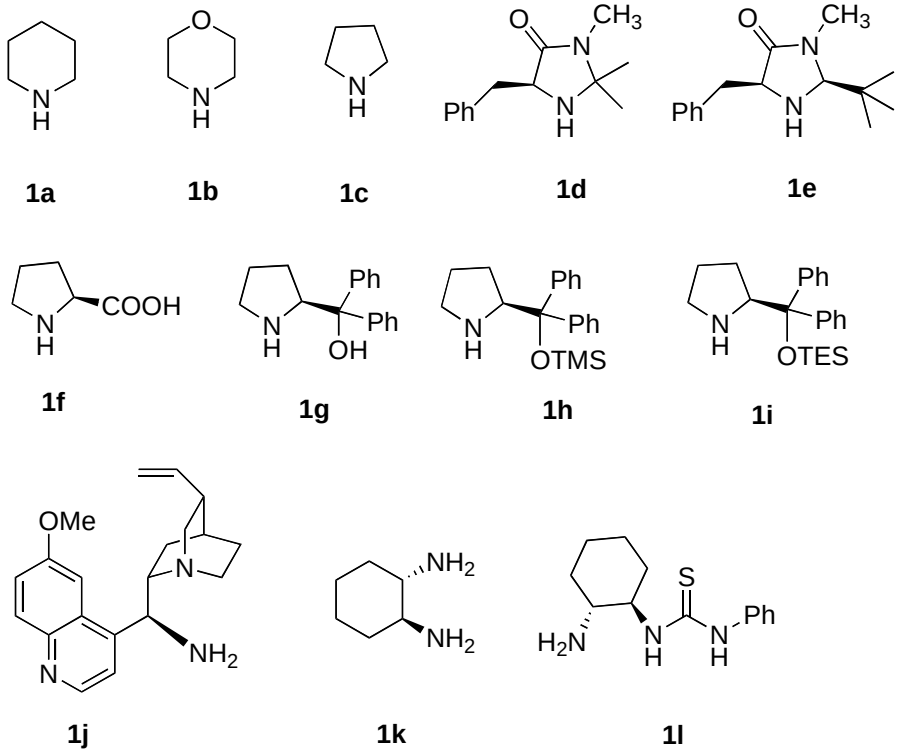
Keywords: 2*H*-Chromene-3-carbaldehyde, organocatalysis, conjugate addition, nitroalkane, chroman

Introduction

The chroman structural unit is found in a large number of drugs and natural products.[1] Chroman derivatives exhibit various useful biological activities,[2] such as antioxidant,[3] antiestrogen,[4] anticonvulsion,[5] and neuroprotection.[6] Many synthetic methods for chromans have been developed.[2,7] One of the efficient pathways is based on the transformation of 2*H*-chromenes, including oxidation,[7a,8] reduction[9] and conjugate addition.[10] In recent years, secondary amines and primary amines have been found to be efficient organocatalysts for the activation of α,β-unsaturated aldehydes and ketones via a LUMO lowering mechanism.[11] The conjugate addition of nitroalkanes to α,β-unsaturated aldehydes has been achieved using chiral amines as the catalysts. Good yields and excellent enantioselectivities were obtained in a couple of cases.[12] Recently, we and Córdova *et al*. found that the conjugate addition of bromonitroalkanes to α,β-unsaturated aldehydes can be catalyzed by prolinol silyl ethers efficiently.[13] To the best of our

knowledge, organocatalytic conjugate addition of nucleophiles to 2*H*-chromene-3-carbaldehydes had not been explored. Herein we report the first organocatalytic conjugate addition of nitroalkanes to 2*H*-chromene-3-carbaldehydes. Highly functionalized chroman derivatives were obtained in good yields and with excellent diastereoselectivities.

Results and Discussion

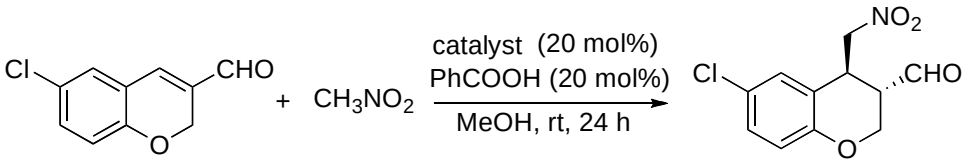


Scheme 1

A number of achiral and chiral amines **1a-1l** (Scheme 1) were examined as the catalysts for the reaction of 6-chloro-2*H*-chromene-3-carbaldehyde **2a** and nitromethane. Benzoic acid was used as the additive and the reaction was carried out in methanol at room temperature. The experimental results are summarized in Table 1. The reaction did not proceed in the absence of the catalyst. Both piperidine **1a** and morpholine **1b** are inefficient for the reaction, however pyrrolidine **1c** promoted the reaction to some extent. The product **3a** was obtained in low yield and with excellent diastereoselectivity (Table 1, entry 4). The relative configuration of **3a** was assigned as *trans* according to NOESY analysis (Scheme 2). MacMillan's imidazolidinone organocatalysts **1d** and **1e**, and proline **1f** were found to be inefficient (Table 1, entries 5-7). Diphenyl prolinol **1g** showed low catalytic activity, however prolinol TMS ether **1h** showed better catalytic activity. Good catalytic activity was achieved with diphenyl prolinol TES ether **1i**

and **3a** was obtained in good yield and with excellent diastereoselectivity. The result is rather surprising, since **1h** showed better catalytic activity than **1i** in previous studies. Although a full explanation can not be presented at the present, we speculate that the formation of the iminium cation between the catalyst and 2*H*-chromene-3-carbaldehyde benefits from using the more hydrophobic **1i**. For catalysts **1g**-**1i**, the enantioselctivities were very low (3~5% ee) as determined by chiral HPLC analysis. Chiral primary amine catalysts **1j**-**1l** were also examined and were found to be inefficient (Table 1, entries 11-13).

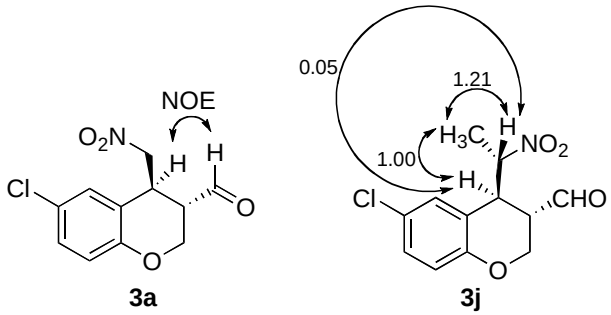
Table 1. Catalyst screening for the reaction of **2a** and nitromethane[a]



2a **3a**

Entry	Catalyst	Yield (%)[b]	Dr[c]	Ee (%)[d]
1	--	--	--	--
2	**1a**	trace	--	--
3	**1b**	trace	--	--
4	**1c**	23	96:4	--
5	**1d**	trace	--	--
6	**1e**	trace	--	--
7	**1f**	trace	--	--
8	**1g**	11	96:4	3
9	**1h**	52	97:3	3
10	**1i**	83	97:3	5
11	**1j**	trace	--	--
12	**1k**	trace	--	--
13	**1l**	trace	--	--

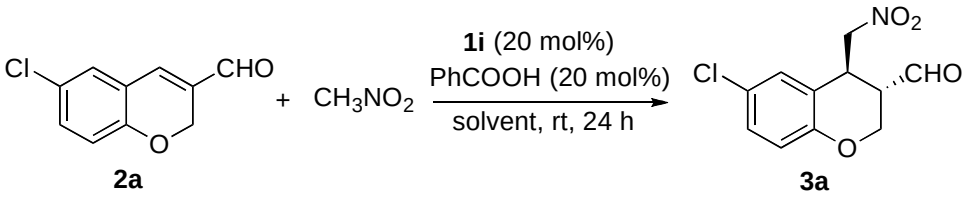
[a] The reactions were carried out with **2a** (0.2 mmol), nitromethane (0.6 mmol), **1a**-**1l** (0.04 mmol) and benzoic acid (0.04 mmol) in methanol (1 mL). [b] Isolated yields. [c] The diastereomeric ratios were determined by GC-MS analysis. [d] The ee values of **3a** were determined by chiral HPLC analysis.



Scheme 2

The optimization of reaction solvents was studied using **1i** as the catalyst and the results are listed in Table 2. EtOH and *i*-PrOH could also be used in the reaction, but with lower yields in comparison with MeOH (Table 2, entries 2-3 vs entry 1). The diastereoselectivities were generally excellent in these solvents, however the enantioselectivities were not improved. The use of other solvents, such as THF, dioxane, DMF, toluene, MeCN, CH_2Cl_2, Et_2O, and *n*-hexane gave no product (Table 2, entries 4-11). A protonic solvent seems to be necessary for the reaction.

Table 2. Screening of reaction solvents[a]

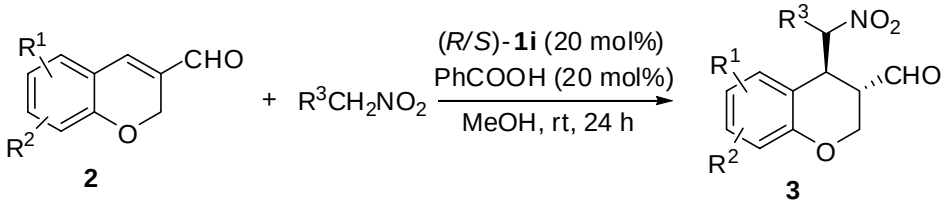


Entry	Solvent	Yield (%)[b]	Dr	Ee (%)
1	MeOH	83	97:3	5
2	EtOH	67	97:3	3
3	*i*-PrOH	56	98:2	6
4	THF	≈0	--	--
5	Dioxane	≈0	--	--
6	DMF	≈0	--	--
7	Toluene	≈0	--	--
8	MeCN	≈0	--	--
9	CH_2Cl_2	≈0	--	--
10	Et_2O	≈0	--	--
11	*n*-hexane	≈0	--	--

[a] The reactions were carried out with **2a** (0.2 mmol), nitromethane (0.6 mmol), **1i** (0.04 mmol), benzoic acid (0.04 mmol) in solvent (1 mL). [b] Isolated yields.

The reaction of a variety of 2*H*-chromene-3-carbaldehydes with nitromethane was investigated using racemic **1i** as the catalyst. The results are summarized in Table 3. The introduction of electron-withdrawing or electron-donating substituents on the phenyl ring of 2*H*-chromene-3-carbaldehydes did not exert significant influence on the yields (Table 3, entries 1-7). The position of the substituents on the phenyl ring influences the yields. 6-MeO-2*H*-chromene-3-carbaldehyde gave a better yield than 7-MeO- or 8-MeO- 2*H*-chromene-3-carbaldehyde (Table 3, entry 3 vs entries 6, 7). 6,8-Disubstituted 2*H*-chromene-3-carbaldehydes, such as 6,8-dichloro- and 6,8-dibromo- 2*H*-chromene-3-carbaldehydes, provided the products in lower yields (Table 3, entries 8-9).

Table 3. Reaction of 2*H*-chromene-3-carbaldehydes (**2**) with nitroalkanes catalyzed by (*R/S*)-**1i**[a]



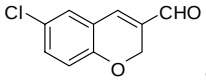
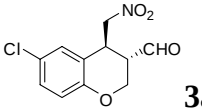
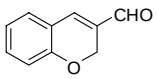
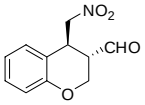
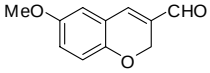
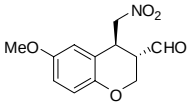
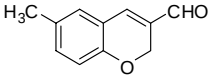
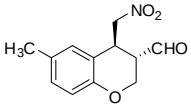
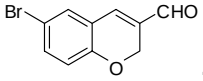
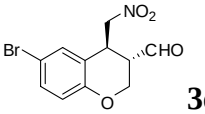
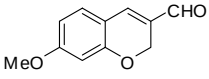
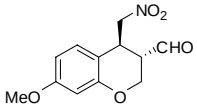
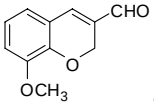
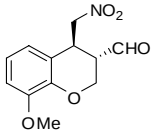
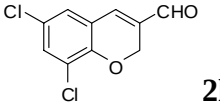
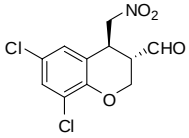
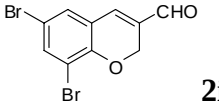
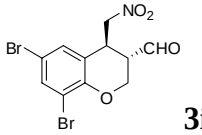
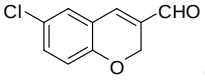
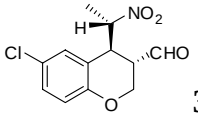
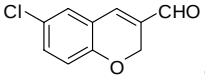
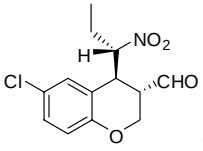
Entry	Substrate (**2**)	Nitroalkane	Product (**3**)	Yield (%)[b]	Dr[c]
1	 **2a**	CH_3NO_2	 **3a**	81	97:3
2	 **2b**	CH_3NO_2	 **3b**	84	94:6
3	 **2c**	CH_3NO_2	 **3c**	95	98:2
4	 **2d**	CH_3NO_2	 **3d**	94	96:4
5	 **2e**	CH_3NO_2	 **3e**	96	94:6
6	 **2f**	CH_3NO_2	 **3f**	81	95:5
7	 **2g**	CH_3NO_2	 **3g**	80	98:2

Table 3. Continued

Entry	Substrate (2)	Nitroalkane	Product (3)	Yield (%)b	Drc
8	 **2h**	CH_3NO_2	 **3h**	66	97:3
9	 **2i**	CH_3NO_2	 **3i**	62	95:5
10	 **2a**	$CH_3CH_2NO_2$	 **3j**	41	98:2
11	 **2a**	$CH_3CH_2CH_2NO_2$	 **3k**	31	99:1

[a] The reactions were carried out with **2** (0.2 mmol), nitroalkane (0.6 mmol), (*R/S*)-**1i** (0.04 mmol) and benzoic acid (0.04 mmol) in MeOH (1 mL). [b] Isolated yield. [c] The diastereomeric ratios were determined by GC-MS analysis.

Nitroethane and 1-nitropropane were also examined in the reaction with **2a.** The corresponding products were obtained with excellent diastereoselectivities, however in low yields (Table 3, entries 10-11). Their lower reactivities in comparison with nitromethane are ascribed to the bigger steric hindrance and weaker acidic α-methylene groups. The relative stereochemistry of **3j** was established by the NOESY analysis (Scheme 2, the values beside the curved arrows indicate the intensity of NOE signals). Compound **3k** was supposed to have similar relative configuration with **3j**.

Conclusions

In conclusion, organocatalytic conjugate addition of nitroalkanes to 2*H*-chromene-3-carbaldehydes has been developed. Diphenylprolinol triethylsilyl ether was identified as the best catalyst for the reaction. Excellent diastereoselectivities and good yields were achieved for the reaction of nitromethane with a number of substituted 2*H*-chromene-3-carbaldehydes. Nitroethane and 1-nitropropane were also applicable for this transformation, however in lower yields. The reaction provided a new method for the preparation of highly functionalized chroman derivatives.

Experimental Section

General. All solvents were used as commercial anhydrous grade without further purification. Flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. 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 $CDCl_3$. 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 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 SHIMADZU LCMS-IT-TOF mass spectrometer. The low resolution mass spectra were obtained with the Thermo Trace GC Ultra – DSQ II. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak). Enantiomeric excesses of chroman **3a** was determined by HPLC using a Daicel Chiralpak AS-H column (*n*-hexane/*i*-PrOH = 93/7, λ = 210 nm, 1.0 ml/min).

Typical experimental procedure for the synthesis of 2*H*-chromene-3-carbaldehydes[9a]
To a solution of salicylaldehyde (15 mmol) in dioxane (100 mL) was added K_2CO_3 (15 mmol) and acrolein (18 mmol). The mixture was refluxed for 2 h, then poured into water (100 mL). The solution was extracted with toluene (30 mL × 3). The combined organic layers was washed with NaOH (2 mmol/L, 30 mL) and water (30 mL) successively. Then the organic layer was dried over anhydrous Na_2SO_4. After the solvent was evaporated under vacuum, the residue was recrystallized from $CHCl_3$/*n*-hexane to give 2*H*-chromene-3-carbaldehyde as a yellow solid.
6-Chloro-2*H*-chromene-3-carbaldehyde (2a). Yellow solid, yield: 61%; m.p. 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (s, 1H, C<u>H</u>=O), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar-<u>H</u>), 7.19-7.17 (m, 2H, Ar-<u>H</u> and Ph-C<u>H</u>=C), 6.82 (d, *J* = 8.8 Hz, 1H, Ar-<u>H</u>), 5.03 (d, *J* = 1.3 Hz, 2H, Ph-O-C<u>H</u>$_2$-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5 (<u>C</u>H=O), 154.5 (Ar-<u>C</u>), 139.5 (Ph-<u>C</u>H=C), 132.6 (Ph-CH=<u>C</u>), 132.5 (Ar-<u>C</u>), 128.4 (Ar-<u>C</u>), 126.7 (Ar-<u>C</u>), 121.6 (Ar-<u>C</u>), 117.9 (Ar-<u>C</u>), 63.4 (Ph-O-<u>C</u>H$_2$-); IR (KBr, disc) *ν*/cm^{-1}: 1676 (s), 1633 (m), 1478 (m), 1337 (m), 1162 (m), 831 (m); MS (EI) *m/e* = 193.9 (M^+), 164.9, 130.9, 101.9, 74.9, 50.9; HRMS (ESI) calcd for $C_{10}H_7ClO_2$ [M + H]$^+$: 195.0213, found: 195.0210.
2*H*-Chromene-3-carbaldehyde (2b). Yellow solid, yield: 52%; m.p. 42-44 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H, C<u>H</u>=O), 7.30 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H, Ar-<u>H</u>), 7.25 (m, 1H, Ph-C<u>H</u>=C), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-<u>H</u>), 6.96 (dt, *J* = 7.5, 1.1 Hz, 1H, Ar-<u>H</u>), 6.87 (d, *J* = 8.2 Hz, 1H, Ar-<u>H</u>), 5.04 (d, *J* = 1.2 Hz, 2H, Ph-O-C<u>H</u>$_2$-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7 (<u>C</u>H=O), 156.1 (Ar-<u>C</u>), 141.1 (Ph-<u>C</u>H=C), 133.2 (Ph-CH=<u>C</u>), 131.7 (Ar-<u>C</u>), 129.3 (Ar-<u>C</u>), 121.9 (Ar-<u>C</u>), 120.5 (Ar-<u>C</u>), 116.5 (Ar-<u>C</u>), 63.3 (Ph-O-<u>C</u>H$_2$-); IR (KBr, disc) *ν*/cm^{-1}: 1671 (s), 1639 (m), 1603 (m), 1343 (m), 1163 (m), 757 (m); MS (EI) *m/e* = 159.9 (M^+), 130.8, 102.9, 76.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{10}H_8O_2$ [M + H]$^+$: 161.0603, found: 161.0599.

6-Methoxy-2*H*-chromene-3-carbaldehyde (2c). Yellow solid, yield: 63%; m.p. 51-52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (s, 1H, C<u>H</u>=O), 7.21 (s, 1H, Ph-C<u>H</u>=C), 6.87 (dd, *J* = 8.9, 2.9 Hz, 1H, Ar-<u>H</u>), 6.81 (d, *J* = 8.9 Hz, 1H, Ar-<u>H</u>), 6.74 (d, *J* = 2.9 Hz, 1H, Ar-<u>H</u>), 4.97 (d, *J* = 1.2 Hz, 2H, Ph-O-C<u>H$_2$</u>-), 3.78 (s, 3H, Ph-OC<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7 (<u>C</u>H=O), 154.4 (Ar-<u>C</u>), 150.1 (Ar-<u>C</u>), 141.2 (Ph-<u>C</u>H=C), 132.4 (Ph-CH=<u>C</u>), 121.0 (Ar-<u>C</u>), 119.2 (Ar-<u>C</u>), 117.3 (Ar-<u>C</u>), 113.2 (Ar-<u>C</u>), 63.1 (Ph-O-<u>C</u>H$_2$-), 55.8 (Ph-O-<u>C</u>H$_3$); IR (KBr, disc) ν/cm^{-1}: 1671 (s), 1636 (m), 1575 (m), 1489 (m), 1334 (m); 1219 (s), 1166 (m), 1039 (m), 707 (m); MS (EI) *m/e* = 189.9 (M^+), 160.9, 145.9, 117.9, 90.9, 76.9, 64.9, 50.9, 38.9, 28.9; HRMS (ESI) calcd for $C_{11}H_{10}O_3$ $[M + H]^+$: 191.0708, found: 191.0705.

6-Methyl-2*H*-chromene-3-carbaldehyde (2d). Yellow solid, yield: 59%; m.p. 66-68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1H, C<u>H</u>=O), 7.20 (s, 1H, Ph-C<u>H</u>=C), 7.09 (dd, *J* = 8.3, 2.2 Hz, 1H, Ar-<u>H</u>), 7.00 (d, *J* = 2.0 Hz, 1H, Ar-<u>H</u>), 6.77 (d, *J* = 8.3 Hz, 1H, Ar-<u>H</u>), 4.99 (d, *J* = 1.0 Hz, 2H, Ph-O-C<u>H$_2$</u>-), 2.28 (s, 3H, Ph-C<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7 (<u>C</u>H=O), 154.0 (Ar-<u>C</u>), 141.4 (Ph-<u>C</u>H=C), 133.9 (Ph-CH=<u>C</u>), 131.8 (Ar-<u>C</u>), 131.3 (Ar-<u>C</u>), 129.5 (Ar-<u>C</u>), 120.3 (Ar-<u>C</u>), 116.2 (Ar-<u>C</u>), 63.2 (Ph-O-<u>C</u>H$_2$-), 20.3 (Ph-<u>C</u>H$_3$); IR (KBr, disc) ν/cm^{-1}: 1672 (s), 1637 (m), 1575 (m), 1489 (m), 1399 (w); 1337 (m); 1226 (w), 1167 (m), 1121 (s), 909 (w), 831 (s); MS (EI) *m/e* = 173.9 (M^+), 144.9, 130.9, 114.9, 90.8, 62.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{11}H_{10}O_2$ $[M + H]^+$: 175.0759, found: 175.0754.

6-Bromo-2*H*-chromene-3-carbaldehyde (2e). Yellow solid, yield: 65%; m.p. 106-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (s, 1H, C<u>H</u>=O), 7.36 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-<u>H</u>), 7.31 (d, *J* = 2.4 Hz, 1H, Ar-<u>H</u>), 7.16 (m, 1H, Ph-C<u>H</u>=C), 6.75 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 5.02 (d, *J* = 1.3 Hz, 2H, Ph-O-C<u>H$_2$</u>-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5 (<u>C</u>H=O), 155.0 (Ar-<u>C</u>), 139.4 (Ph-<u>C</u>H=C), 135.5 (Ph-CH=<u>C</u>), 132.5 (Ar-<u>C</u>), 131.4 (Ar-<u>C</u>), 122.2 (Ar-<u>C</u>), 118.3 (Ar-<u>C</u>), 113.8 (Ar-<u>C</u>), 63.4 (Ph-O-<u>C</u>H$_2$-); IR (KBr, disc) ν/cm^{-1}: 1670 (s), 1633 (m), 1335 (m), 1161 (m), 888 (m); 836 (m); MS (EI) *m/e* = 237.8 and 239.8 (M^+), 208.8 and 210.8, 158.9, 129.9, 101.9, 76.9, 62.9, 50.9, 27.9; HRMS (ESI) calcd for $C_{10}H_7BrO_2$ $[M + H]^+$: 238.9708, 240.9687, found: 238.9703, 240.9682.

7-Methoxy-2*H*-chromene-3-carbaldehyde (2f). Yellow solid, yield: 61%; m.p. 85-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (s, 1H, C<u>H</u>=O), 7.20 (q, *J* = 1.0 Hz, 1H, Ph-C<u>H</u>=C), 7.12 (d, *J* = 8.5 Hz, 1H, Ar-<u>H</u>), 6.52 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-<u>H</u>), 6.41 (dd, *J* = 2.3, 1.0 Hz, 1H, Ar-<u>H</u>), 5.02 (d, *J* = 1.1 Hz, 2H, Ph-O-C<u>H$_2$</u>-), 3.81 (s, 3H, Ph-OC<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.4 (<u>C</u>H=O), 164.1 (Ar-<u>C</u>), 157.9 (Ar-<u>C</u>), 141.4 (Ph-<u>C</u>H=C), 130.6 (Ph-CH=<u>C</u>), 128.8 (Ar-<u>C</u>), 113.8 (Ar-<u>C</u>), 108.8 (Ar-<u>C</u>), 101.6 (Ar-<u>C</u>), 63.5 (Ph-O-<u>C</u>H$_2$-), 55.5 (Ph-O-<u>C</u>H$_3$); IR (KBr, disc) ν/cm^{-1}: 1670 (m), 1616 (s), 1561 (s), 1277 (s), 1159 (m); 867 (m), 808 (w); MS (EI) *m/e* = 189.9 (M^+), 160.9, 145.6, 117.8, 88.9, 76.9, 62.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{11}H_{10}O_3$ $[M + H]^+$: 191.0708, found: 191.0703.

8-Methoxy-2*H*-chromene-3-carbaldehyde (2g). Yellow solid, yield: 59%; m.p. 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1H, C<u>H</u>=O), 7.24 (t, *J* = 1.2 Hz, 1H, Ph-C<u>H</u>=C), 6.96-6.90 (m, 2H, Ar-<u>H</u>), 6.84 (dd, *J* = 6.7, 2.4 Hz, 1H, Ar-<u>H</u>), 5.09 (d, *J* = 1.2 Hz, 2H, Ph-O-C<u>H$_2$</u>-), 3.88 (s, 3H, Ph-OC<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6 (<u>C</u>H=O), 148.0 (Ar-<u>C</u>), 144.9 (Ar-<u>C</u>),

141.1 (Ph-CH=C), 131.6 (Ph-CH=C), 121.6 (Ar-C), 121.1 (Ar-C), 121.0 (Ar-C), 115.4 (Ar-C), 63.5 (Ph-O-CH_2-), 56.0 (Ph-O-CH_3); IR (KBr, disc) ν/cm^{-1}: 1667 (s), 1631 (m), 1483 (s), 1459 (s), 1262 (m); 1099 (s), 774 (m), 726 (s); MS (EI) *m/e* = 189.9 (M^+), 160.9, 145.9, 117.8, 90.9, 64.9, 50.9, 38.9, 28.0; HRMS (ESI) calcd for $C_{11}H_{10}O_3$ $[M + H]^+$: 191.0708, found: 191.0706.

6,8-Dichloro-2*H*-chromene-3-carbaldehyde (2h). Yellow solid, yield: 64%; m.p. 129-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H, CH=O), 7.34 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.16 (t, *J* = 1.3 Hz, 1H, Ph-CH=C), 7.10 (d, *J* = 2.4 Hz, 1H, Ar-H), 5.13 (d, *J* = 1.3 Hz, 2H, Ph-O-CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2 (CH=O), 150.2 (Ar-C), 138.5 (Ph-CH=C), 133.0 (Ph-CH=C), 132.6 (Ar-C), 127.0 (Ar-C), 126.5 (Ar-C), 122.5 (Ar-C), 122.4 (Ar-C), 64.2 (Ph-O-CH_2-); IR (KBr, disc) ν/cm^{-1}: 1674 (s), 1637 (m), 1338 (m), 1205 (m), 1153 (m); 698 (m); MS (EI) *m/e* = 227.8 (M^+), 198.8, 164.9, 135.9, 100.9, 74.9, 49.9, 28.0; HRMS (ESI) calcd for $C_{10}H_6Cl_2O_2$ $[M + H]^+$: 228.9823, found: 228.9820.

6,8-Dibromo-2*H*-chromene-3-carbaldehyde (2i). Yellow solid, yield: 66%; m.p. 149-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H, CH=O), 7.63 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.28 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.14 (t, *J* = 1.2 Hz, 1H, Ph-CH=C), 5.14 (d, *J* = 1.2 Hz, 2H, Ph-O-CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1 (CH=O), 151.8 (Ar-C), 138.5 (Ph-CH=C), 138.1 (Ar-C), 132.9 (Ph-CH=C), 130.6 (Ar-C), 122.8 (Ar-C), 113.7 (Ar-C), 111.4 (Ar-C), 64.3 (Ph-O-CH_2-); IR (KBr, disc) ν/cm^{-1}: 1672 (s), 1635 (m), 1338 (m), 1194 (m), 1153 (m); 721 (m); MS (EI) *m/e* = 317.7, 315.7 and 319.7 (M^+), 288.7, 208.9, 179.8, 128.9, 101.9, 74.9, 61.9, 50.9, 27.9; HRMS (ESI) calcd for $C_{10}H_6Br_2O_2$ $[M + H]^+$: 318.8792, found: 318.8787.

Typical experimental procedure for conjugate addition of nitroalkanes to 2H-chromene-3-carbaldehydes

A mixture of diphenylprolinol triethylsilyl ether **1i** (0.04 mmol), benzoic acid (0.04 mmol) and the 2*H*-chromone-3-carbaldehyde (**2a-i**) (0.2 mmol) in methanol (1.0 mL) was stirred for 5 minutes at room temperature. After nitromethane (0.6 mmol) was added, the reaction mixture was stirred for 24 h. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide the corresponding chroman-3-carbaldehyde (**3a-k**).

6-Chloro-4-(nitromethyl)chroman-3-carbaldehyde (3a). Yellow solid, m.p. 113-115 °C, dr = 97:3. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1H, CH=O), 7.19 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.13 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-H), 6.77 (d, *J* = 8.8 Hz, 1H, Ar-H), 4.78 (dd, *J* = 12.2, 1.1 Hz, 1H, Ph-O-CH_2-), 4.73 (dd, *J* = 13.1, 4.4 Hz, 1H, -CH_2-NO_2), 4.61 (dd, *J* = 13.0, 10.6 Hz, 1H, -CH_2-NO_2), 4.24 (dd, *J* = 12.2, 2.9 Hz, 1H, Ph-O-CH_2-), 4.14 (ddd, *J* = 10.4, 4.8, 4.4 Hz, 1H, -CH-CH_2-NO_2), 2.92-2.91 (m, 1H, -CH-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8 (CH=O), 152.8 (Ar-C), 129.6 (Ar-C), 129.0 (Ar-C), 126.6 (Ar-C), 119.2 (Ar-C), 118.8 (Ar-C), 78.8 (-CH_2-NO_2), 60.8 (Ph-O-CH_2-), 46.8 (-CH-CH=O), 31.8 (-CH-CH_2-NO_2); IR (KBr, disc) ν/cm^{-1}: 1732 (m), 1551 (s), 1485 (s), 1376 (m), 1225 (m), 817 (m); MS (EI) *m/e* = 254.9 (M^+), 207.9, 178.9, 164.9, 144.9, 124.8, 114.9, 101.9, 88.9, 76.9, 62.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{11}H_{10}ClNO_4$ $[M - H]^-$: 254.0220, found: 254.0221.

4-(Nitromethyl)chroman-3-carbaldehyde (3b). Yellow oil, dr = 94:6. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1H, C<u>H</u>=O), 7.19-7.15 (m, 2H, Ar-<u>H</u>), 6.96 (dt, *J* = 7.6, 1.2 Hz, 1H, Ar-<u>H</u>), 6.83 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar-<u>H</u>), 4.76 (ddd, *J* = 12.1, 2.8, 1.4 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.74 (dd, *J* = 12.8, 4.5 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.61 (dd, *J* = 12.9, 10.5 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.26 (dd, *J* = 12.1, 2.9 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.18-4.15 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 2.90-2.89 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3 (<u>C</u>H=O), 154.3 (Ar-<u>C</u>), 129.5 (Ar-<u>C</u>), 129.4 (Ar-<u>C</u>), 121.9 (Ar-<u>C</u>), 117.8 (Ar-<u>C</u>), 117.3 (Ar-<u>C</u>), 79.2 (-<u>C</u>H$_2$-NO$_2$), 60.7 (Ph-O-<u>C</u>H$_2$-), 47.1 (-<u>C</u>H-CH=O), 32.2 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1732 (m), 1550 (s), 1489 (s), 1377 (m), 1223 (m), 756 (m); MS (EI) *m/e* = 221.0 (M^+), 174.0, 160.0, 145.0, 130.9, 114.9, 107.0, 90.9, 76.9, 64.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{11}H_{11}NO_4$ [M - H]$^-$: 220.0610, found: 220.0606.

6-Methoxy-4-(nitromethyl)chroman-3-carbaldehyde (3c). Yellow solid, m.p. 99-101 °C, dr = 98:2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1H, C<u>H</u>=O), 6.76 (d, *J* = 1.6 Hz, 2H, Ar-<u>H</u>), 6.69-6.67 (m, 1H, Ar-<u>H</u>), 4.75 (dd, *J* = 12.9, 4.3 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.72 (ddd, *J* = 12.0, 3.0, 1.3 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.61 (dd, *J* = 12.9, 10.5 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.22 (dd, *J* = 12.0, 2.9 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.16-4.12 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 3.76 (s, 3H, Ph-OC<u>H$_3$</u>), 2.88-2.86 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4 (<u>C</u>H=O), 154.3 (Ar-<u>C</u>), 148.1 (Ar-<u>C</u>), 118.6 (Ar-<u>C</u>), 117.8 (Ar-<u>C</u>), 116.0 (Ar-<u>C</u>), 113.4 (Ar-<u>C</u>), 79.2 (-<u>C</u>H$_2$-NO$_2$), 60.8 (Ph-O-<u>C</u>H$_2$-), 55.7 (Ph-O-<u>C</u>H$_3$), 47.3 (-<u>C</u>H-CH=O), 32.4 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1727 (m), 1547 (s), 1497 (s), 1376 (m), 1205 (m), 1039 (m); MS (EI) *m/e* = 250.9 (M^+), 203.9, 176.0, 160.9, 149.0, 120.9, 114.9, 102.9, 90.9, 76.9, 64.9, 51.0; HRMS (ESI) calcd for $C_{12}H_{13}NO_5$ [M - H]$^-$: 250.0715, found: 250.0711.

6-Methyl-4-(nitromethyl)chroman-3-carbaldehyde (3d). Yellow solid, m.p. 70-73 °C, dr = 96:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1H, C<u>H</u>=O), 6.98-6.96 (m, 2H, Ar-<u>H</u>), 6.72 (d, *J* = 9.0 Hz, 1H, Ar-<u>H</u>), 4.76-4.75 (m, 1H, -C<u>H$_2$</u>-NO$_2$), 4.73-4.72 (m, 1H, Ph-O-C<u>H$_2$</u>-), 4.59 (dd, *J* = 12.8, 10.7 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.23 (dd, *J* = 12.1, 2.9 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.14-4.10 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 2.88-2.86 (m, 1H, -C<u>H</u>-CH=O), 2.26 (s, 3H, Ph-C<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (<u>C</u>H=O), 152.0 (Ar-<u>C</u>), 131.2 (Ar-<u>C</u>), 130.2 (Ar-<u>C</u>), 129.6 (Ar-<u>C</u>), 117.5 (Ar-<u>C</u>), 116.9 (Ar-<u>C</u>), 79.2 (-<u>C</u>H$_2$-NO$_2$), 60.6 (Ph-O-<u>C</u>H$_2$-), 47.2 (-<u>C</u>H-CH=O), 32.1 (-<u>C</u>H-CH$_2$-NO$_2$), 20.5 (Ph-<u>C</u>H$_3$); IR (KBr, disc) ν/cm^{-1}: 1733 (m), 1552 (s), 1501 (s), 1378 (m), 1227 (m), 820 (m); MS (EI) *m/e* = 234.9 (M^+), 187.9, 158.9, 144.9, 130.9, 114.9, 104.9, 90.8, 76.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{12}H_{13}NO_4$ [M - H]$^-$: 234.0766, found: 234.0761.

6-Bromo-4-(nitromethyl)chroman-3-carbaldehyde (3e). Yellow solid, m.p. 116-119 °C, dr = 94:6. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H, C<u>H</u>=O), 7.33 (d, *J* = 2.2 Hz, 1H, Ar-<u>H</u>), 7.27 (dd, *J* = 8.7, 2.4 Hz, 1H, Ar-<u>H</u>), 6.72 (d, *J* = 8.8 Hz, 1H, Ar-<u>H</u>), 4.78 (ddd, *J* = 12.3, 2.7, 1.4 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.73 (dd, *J* = 13.1, 4.4 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.60 (dd, *J* = 13.0, 10.6 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.24 (dd, *J* = 12.2, 3.0 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.16-4.12 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 2.92-2.90 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8 (<u>C</u>H=O), 153.3 (Ar-<u>C</u>), 132.4 (Ar-<u>C</u>), 132.0 (Ar-<u>C</u>), 119.6 (Ar-<u>C</u>), 119.4 (Ar-<u>C</u>), 113.8 (Ar-<u>C</u>), 78.8 (-<u>C</u>H$_2$-NO$_2$), 60.7 (Ph-O-<u>C</u>H$_2$-), 46.8 (-<u>C</u>H-CH=O), 31.7 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1730 (s), 1552 (s), 1482 (s), 1377 (m), 1222 (m), 817 (m); MS (EI) *m/e* = 300.8 and 298.9 (M^+), 253.8 and

251.8, 222.8, 210.8 and 208.8, 145.0, 130.9, 114.9, 88.9, 76.9, 62.9, 50.9, 39.0; HRMS (ESI) calcd for $C_{11}H_{10}BrNO_4$ [M - H]$^-$: 297.9715, 299.9694, found: 297.9710, 299.9688.

7-Methoxy-4-(nitromethyl)chroman-3-carbaldehyde (3f). Yellow solid, m.p. 99-112 °C, dr = 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H, C<u>H</u>=O), 7.07 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 6.55 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-<u>H</u>), 6.36 (d, *J* = 2.3 Hz, 1H, Ar-<u>H</u>), 4.77-4.74 (m, 1H, Ph-O-C<u>H$_2$</u>-), 4.70 (dd, *J* = 12.8, 4.5 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.58 (dd, *J* = 12.8, 10.6 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.24 (dd, *J* = 12.0, 2.7 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.12-4.08 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 3.74 (s, 3H, Ph-OC<u>H$_3$</u>), 2.86-2.85 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (<u>C</u>H=O), 160.4 (Ar-<u>C</u>), 155.2 (Ar-<u>C</u>), 130.2 (Ar-<u>C</u>), 109.4 (Ar-<u>C</u>), 109.2 (Ar-<u>C</u>), 102.0 (Ar-<u>C</u>), 79.2 (-<u>C</u>H$_2$-NO$_2$), 60.7 (Ph-O-<u>C</u>H$_2$-), 55.3 (Ph-O-<u>C</u>H$_3$), 47.0 (-<u>C</u>H-CH=O), 31.8 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1728 (m), 1619 (m), 1548 (s), 1504 (s), 1376 (m), 1161 (m), 1120 (m), 1028 (m); MS (EI) *m/e* = 250.9 (M$^+$), 213.0, 204.0, 174.9, 161.0, 146.9, 115.0, 103.0, 90.9, 77.1, 64.9, 50.9; HRMS (ESI) calcd for $C_{12}H_{13}NO_5$ [M - H]$^-$: 250.0715, found: 250.0710.

8-Methoxy-4-(nitromethyl)chroman-3-carbaldehyde (3g). Yellow solid, m.p. 118-120 °C, dr = 98:2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1H, C<u>H</u>=O), 6.94-6.90 (m, 1H, Ar-<u>H</u>), 6.81-6.77 (m, 2H, Ar-<u>H</u>), 4.90 (ddd, *J* = 12.1, 2.7, 1.3 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.76 (dd, *J* = 12.9, 4.3 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.61 (dd, *J* = 12.8, 10.6 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.31 (dd, *J* = 12.1, 2.9 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.20-4.16 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 3.84 (s, 3H, Ph-OC<u>H$_3$</u>), 2.92-2.91 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1 (<u>C</u>H=O), 148.6 (Ar-<u>C</u>), 143.8 (Ar-<u>C</u>), 121.5 (Ar-<u>C</u>), 120.9 (Ar-<u>C</u>), 118.1 (Ar-<u>C</u>), 110.7 (Ar-<u>C</u>), 79.1 (-<u>C</u>H$_2$-NO$_2$), 61.1 (Ph-O-<u>C</u>H$_2$-), 55.9 (Ph-O-<u>C</u>H$_3$), 47.1 (-<u>C</u>H-CH=O), 31.9 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1737 (m), 1586 (m), 1552 (s), 1486 (s), 1379 (m), 1265 (s), 1066 (m); MS (EI) *m/e* = 250.9 (M$^+$), 204.0, 174.9, 160.9, 145.0, 130.9, 117.0, 114.9, 103.0, 90.9, 76.9, 64.9, 50.9, 38.9; HRMS (ESI) calcd for $C_{12}H_{13}NO_5$ [M - H]$^-$: 250.0715, found: 250.0709.

6,8-Dichloro-4-(nitromethyl)chroman-3-carbaldehyde (3h). Yellow solid, m.p. 129-131 °C, dr = 97:3. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H, C<u>H</u>=O), 7.29 (d, *J* = 2.4 Hz, 1H, Ar-<u>H</u>), 7.12 (d, *J* = 2.4 Hz, 1H, Ar-<u>H</u>), 4.93 (ddd, *J* = 12.2, 2.6, 1.4 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.72 (dd, *J* = 13.1, 4.5 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.61 (dd, *J* = 13.1, 10.3 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.33 (dd, *J* = 12.3, 3.1 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.20-4.16 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 3.00-2.98 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2 (<u>C</u>H=O), 148.8 (Ar-<u>C</u>), 129.9 (Ar-<u>C</u>), 127.6 (Ar-<u>C</u>), 126.5 (Ar-<u>C</u>), 123.6 (Ar-<u>C</u>), 120.2 (Ar-<u>C</u>), 78.5 (-<u>C</u>H$_2$-NO$_2$), 61.5 (Ph-O-<u>C</u>H$_2$-), 46.9 (-<u>C</u>H-CH=O), 31.8 (-<u>C</u>H-CH$_2$-NO$_2$); IR (KBr, disc) ν/cm^{-1}: 1729 (m), 1549 (s), 1454 (s), 1375 (m), 1237 (m), 1181 (m), 866 (w); HRMS (ESI) calcd for $C_{11}H_9C_{l2}NO_4$ [M - H]$^-$: 287.9830, found: 287.9826.

6,8-Dibromo-4-(nitromethyl)chroman-3-carbaldehyde (3i). Yellow solid, m.p. 108-111 °C, dr = 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H, C<u>H</u>=O), 7.58 (d, *J* = 2.2 Hz, 1H, Ar-<u>H</u>), 7.31 (d, *J* = 1.8 Hz, 1H, Ar-<u>H</u>), 4.93 (ddd, *J* = 12.3, 2.6, 1.4 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.72 (dd, *J* = 13.1, 4.4 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.60 (dd, *J* = 13.1, 10.4 Hz, 1H, -C<u>H$_2$</u>-NO$_2$), 4.33 (dd, *J* = 12.3, 3.1 Hz, 1H, Ph-O-C<u>H$_2$</u>-), 4.20-4.16 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 2.99-2.97 (m, 1H, -C<u>H</u>-CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2 (<u>C</u>H=O), 150.1 (Ar-<u>C</u>), 135.4 (Ar-<u>C</u>), 131.3 (Ar-<u>C</u>), 120.7 (Ar-<u>C</u>), 113.7 (Ar-<u>C</u>), 112.7 (Ar-<u>C</u>), 78.6 (-<u>C</u>H$_2$-NO$_2$), 61.6 (Ph-O-<u>C</u>H$_2$-), 46.9 (-<u>C</u>H-CH=O),

31.8 (-CH-CH_2-NO_2); IR (KBr, disc) ν/cm^{-1}: 1732 (m), 1553 (s), 1470 (m), 1451 (s), 1376 (m), 1239 (m), 867 (w); HRMS (ESI) calcd for $C_{11}H_9Br_2NO_4$ $[M - H]^-$: 377.8800, found: 377.8796.

6-Chloro-4-(1-nitroethyl)chroman-3-carbaldehyde (3j). Yellow oil, dr = 98:2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (s, 1H, CH=O), 7.16-7.13 (m, 2H, Ar-H), 6.77-6.75 (m, 1H, Ar-H), 4.86-4.79 (m, 2H, Ph-O-CH_2- and -CH-CH-NO_2), 4.29 (dd, *J* = 12.3, 3.6 Hz, 1H, Ph-O-CH_2-), 3.76-3.74 (m, 1H, -CH-CH-NO_2), 2.73-2.71 (m, 1H, -CH-CH=O), 1.68 (d, *J* = 6.7 Hz, 3H, -CH-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9 (CH=O), 152.7 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 125.8 (Ar-C), 119.0 (Ar-C), 118.1 (Ar-C), 85.5 (-CH-NO_2), 61.1 (Ph-O-CH_2-), 46.2 (-CH-CH=O), 37.7 (-CH-CH-NO_2), 17.9 (-CH-CH_3); IR (KBr, thin film) ν/cm^{-1}: 1729 (s), 1548 (s), 1486 (s), 1387 (w), 1226 (m), 819 (m); MS (EI) *m/e* = 268.9 (M^+), 221.9, 194.9, 178.9, 164.9, 140.9, 131.0, 114.9, 102.9, 76.9, 66.9, 50.9, 42.9; HRMS (ESI) calcd for $C_{12}H_{12}ClNO_4$ $[M + H]^+$: 270.0533, found: 270.0528.

6-Chloro-4-(1-nitropropyl)chroman-3-carbaldehyde (3k). Yellow oil, dr = 99:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H, CH=O), 7.16-7.13 (m, 2H, Ar-H), 6.77-6.75 (m, 1H, Ar-H), 4.82 (dt, *J* = 12.2, 1.8 Hz, 1H, Ph-O-CH_2-), 4.64 (ddd, *J* = 11.0, 9.3, 3.5 Hz, 1H, -CH-CH-NO_2), 4.31 (dd, *J* = 12.2, 3.6 Hz, 1H, Ph-O-CH_2-), 3.77-3.74 (m, 1H, -CH-CH-NO_2), 2.70-2.68 (m, 1H, -CH-CH=O), 2.21-2.09 (m, 1H, -CH_2-CH_3), 1.98-1.88 (m, 1H, -CH_2-CH_3), 0.99 (t, *J* = 7.3 Hz, 3H, -CH_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9 (CH=O), 152.7 (Ar-C), 130.4 (Ar-C), 129.9 (Ar-C), 125.8 (Ar-C), 119.1 (Ar-C), 118.3 (Ar-C), 92.5 (-CH-NO_2), 61.2 (Ph-O-CH_2-), 46.3 (-CH-CH=O), 37.1 (-CH-CH_2-NO_2), 25.2 (-CH_2-CH_3), 10.4 (-CH_2-CH_3); IR (KBr, disc) ν/cm^{-1}: 1731 (m), 1548 (s), 1486 (s), 1370 (w), 1233 (w), 817 (m); MS (EI) *m/e* = 282.9 (M^+), 235.9, 220.9, 206.9, 192.9, 180.9, 164.9, 140.9, 132.0, 114.9, 102.9, 76.9, 50.9, 31.9; HRMS (ESI) calcd for $C_{13}H_{14}ClNO_4$ $[M + H]^+$: 284.0690, found: 284.0686.

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References and Notes

1. (a) Ellis, G. P. Chromenes, Chromanones, and Chromanones, and Chromones. In *The Chemisry of Heterocyclic Compounds*; Wiley: New York, 1977; Vol. 31, pp 11-139. (b) Hepworth, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon; Oxford, UK, 1984; Vol. 3, pp 737-883. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-

Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968. (f) Andrianasolo, E. H.; Haramaty, L.; Rosario-Passapera, R.; Bidle, K.; White, E.; Vetriani, C.; Falkowski, P.; Lutz, R. *J. Nat. Prod.* **2009**, *72*, 1216.

2. For the recent review of chroman derivatives with biological activity, see: Wang, G. X.; Wang, N. X.; Shi, T.; Yu, J. L.; Tang, X. L. *Prog. Chem.* **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) Wang, Q. L.; She, X. G.; Ren, X. F.; Ma, J. Y.; Pan, X. F. *Tetrahedron: Asymmetry* **2004**, *15*, 29. (b) Doi, F.; Ohara, T.; Ogamino, T.; Higashinakasu, K.; Hasegawa, K.; Nishiyama, S. *B. Chem. Soc. Jpn.* **2004**, *77*, 2257. (c) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672.
8. Lesch, B.; Bräse, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 115.
9. (a) Loiodice, F.; Longo, A.; Bianco, P.; Tortorella, V. *Tetrahedron: Asymmetry* **1995**, *6*, 1001. (b) Hatzenbuhler, N. T.; Baudy, R.; Evrard, D. A.; Failli, A.; Harrison, B. L.; Lenicek, S.; Mewshaw, R. E.; Saab, A.; Shah, U.; Sze, J.; Zhang, M.; Zhou, D.; Chlenov, M.; Kagan, M.; Golembieski, J.; Hornby, G.; Lai, M.; Smith, D. L.; Sullivan, K. M.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2008**, *51*, 6980.
10. (a) Nyerges, M.; Virányi, A.; Marth, G.; Dancsó, A.; Balaskó, G.; Tőke, L. *Synlett* **2004**, 2761. (b) Virányi, A.; Marth, G.; Dancsó, A.; Balaskó, G.; Tőke, L.; Nyerges, M. *Tetrahedron* **2006**, *62*, 8720.
11. For the reviews of activation of α,β-unsaturated aldehydes and ketones with secondary amines or primary amines, see: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (c) Walji, A. M.; Macmillan, D. W. C. *Synlett* **2007**, 1477. (d) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (e) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (f) Macmillan, D. W. C. *Nature* **2008**, *455*, 304. (g) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058. (h) Xu, L. W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807.
12. For the selected publications of organocatalytic conjugate addition of nitroalkanes to α,β-unsaturated aldehydes, see: (a) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431. (b) Zu, L.; Xie, H.; Li, Hao.; Wang, J.; Wang, W. *Adv. Synth. Catal*. **2007**, *349*, 2660. (c) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (d) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal*. **2007**, *349*, 740. (e) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.*

2008, 1232.
13. (a) Zhang, J. M.; Hu, Z. P.; Zhao, S. Q.; Yan, M. *Tetrahedron* **2009**, *65*, 802. (b) Zhang, J. M.; Hu, Z. P.; Dong, L. T.; Xuan, Y. N.; Lou, C. L.; Yan, M. *Tetrahedron: Asymmetry* **2009**, *20*, 355. (c) Vesely, J.; Zhao, G. -L.; Bartoszewicz, A.; Córdova, A. *Tetrahedron Lett*. **2008**, *49*, 4209.

