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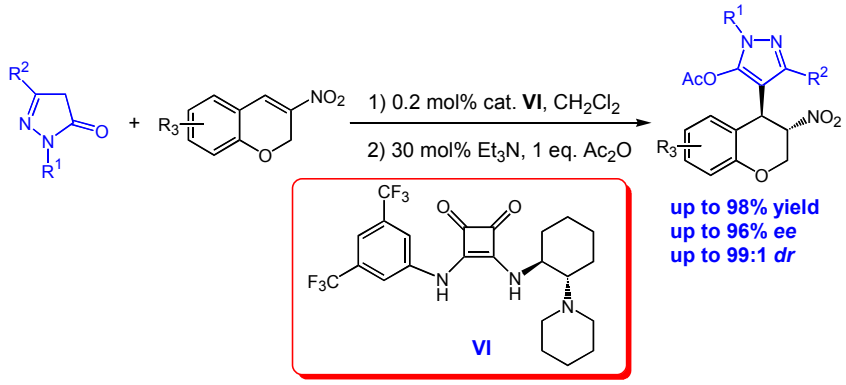
Graphic Abstract

An efficient chiral squaramide-catalysed enantioselective Michael addition of pyrazolin-5-ones to 3-nitro-2*H*-chromenes afforded chiral heterocycles containing both chroman and pyrazolone derivatives in high to excellent yields (up to 98%) with high enantioselectivities (up to 96%) and excellent diastereoselectivities (up to 99:1) under very low catalyst loading (0.2 mol%).



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Enantioselective synthesis of chiral heterocycles containing both chroman and pyrazolone derivatives catalysed by an efficient chiral squaramide

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An efficient chiral squaramide-catalysed enantioselective Michael addition of pyrazolin-5-ones to 3-nitro-2*H*-chromenes for the synthesis of chiral heterocyclic systems containing both chroman and pyrazolone derivatives has been developed. This reaction afforded the desired products in high to excellent yields (up to 98%) with high enantioselectivities (up to 96%) and excellent diastereoselectivities (up to 99:1) under very low catalyst loading (0.2 mol%). This catalytic asymmetric reaction provides an efficient route toward the synthesis of chiral heterocyclic systems containing both chroman and pyrazolone derivatives, which possess potential pharmaceutical activities.

Introduction

Chroman derivatives are present in a number of natural and pharmaceutical products, possessing diverse biological activities.[1] For example, they have been identified as apoptosis-inducing agents, anti-HIV agents, modulators of the estrogen receptors, antibacterials, antioxidants and anticonvulsants.[2] (Fig. 1). In view of their great significance, Chroman derivatives have become attractive synthetic targets, and many efficient approaches have been established,[3] Particularly many significant chiral chroman derivatives have been synthesized use the chromenes as substrates.[4] Likewise, pyrazolone skeletons are important structural units, many of the pyrazolone derivatives have approved antiinflammatory, antiviral, antitumor, and antibacterial properties,[5] and the pyrazolone derivatives was also widely used in organic synthesis and pharmaceutical chemistry (Fig. 1).[6] So the synthesis of chiral heterocyclic compounds containing both chroman and pyrazolone derivative should be significant work. However, we are not aware of any reports about the chiral heterocyclic compounds containing both chroman and pyrazolone derivative.

In the past few years, great progresses in asymmetric organocatalysis have been achieved. In this area, phosphoric acid catalysts[7], proline or pyrrolidine catalysts[8], bifunctional thiourea catalysts[9] and squaramide catalysts[10] all have been proved to be effective in asymmetric catalysis. In recent years the squaramide catalysts derived from (1*S*,2*S*)-cyclohexane-1,2-diamine has been synthesized by several groups.[11] Our group has devoted great efforts to this kind of squaramide catalysts and several highly efficient asymmetric reactions have been developed.[10g,11c,11e,12] In all of the cases, less than 1 mol% catalyst loading was enough for the asymmetric reactions. Most of the catalyst loading were 0.2 mol%, or 0.25 mol%. Through a series of experiments, we believe that the squaramide catalysts derived from (1*S*,2*S*)-cyclohexane-1,2-diamine is a kind of highly efficient organocatalysts, and we will proved it by our further work.

Herein, we would like to present an highly efficient squaramide catalysts derived from (1*S*,2*S*)-cyclohexane-1,2-diamine catalysed enantioselective Michael addition reaction

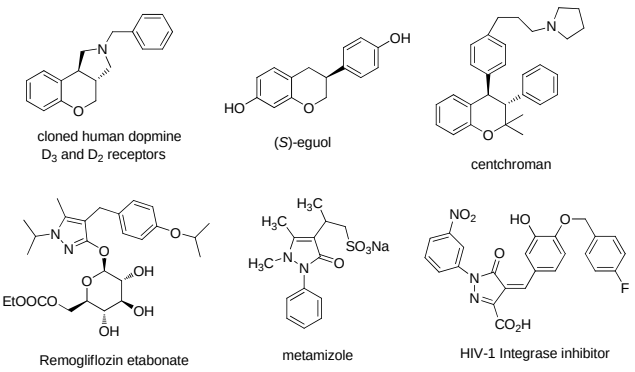

Fig. 1. Representative examples of biologically active chroman derivatives and pyrazolone derivatives.

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between pyrazolones and 3-nitro-2*H*-chromenes for the first synthesis of chiral heterocyclic compounds containing both chromans and pyrazolone derivatives. The corresponding products can be obtained in high to excellent yields (up to 98%), with high enantioselectivities (up to 96% ee) and excellent diastereoselectivity (up to 99:1).

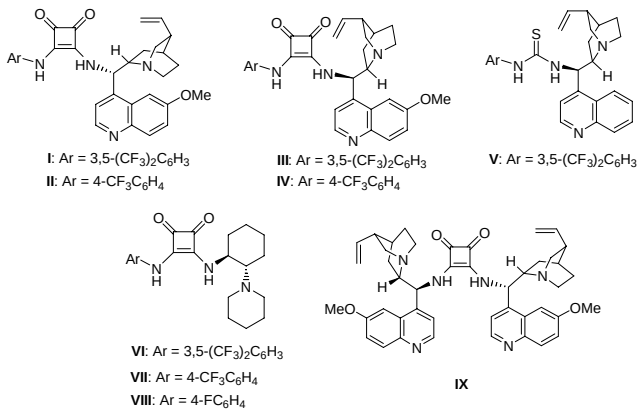
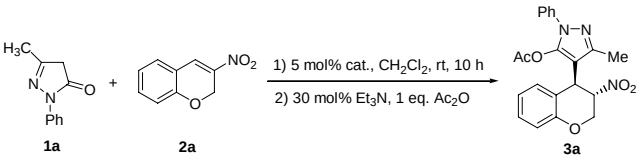


Fig. 2 The structures of screened organocatalysts.

Results and discussion

To begin our initial investigation, quinine-derived squaramide **I** was firstly screened to promote the model reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one (**1a**) with 3-nitro-2*H*-chromene (**2a**) in the presence of 5 mol% catalyst at room temperature in dichloromethane (Table 1, entry 1). Indeed, the model reaction ran smoothly to give the corresponding conjugate addition product. However, the analysis of NMR spectroscopy indicated that the conjugate addition product was a mixture of tautomers. Fortunately, this mixture could be further acylated by the acetic anhydride to afford the desired product **3a** in excellent yield (97%) with high diastereoselectivity (97:3) and good enantioselectivity (88% ee). Then several other bifunctional squaramide organocatalysts (Fig. 2) were screened to evaluate their ability to promote the model reaction. The squaramide **II** gave the desired product **3a** in excellent yield (96%) with high diastereoselectivity (96:4 dr) and moderate enantioselectivity (62% ee). The squaramides **III** and **IV** derived from quinidine were utilized, the opposite enantiomers of **3a** were obtained with the same excellent stereoselectivities and yields, but lower enantioselectivities were obtained (85% ee and 50% ee). We then turned our attention to squaramide catalysts **VI**, **VII** and **VIII** derived from (1*S*,2*S*)-cyclohexane-1,2-diamine (Table 1, entries 6 to 8). Satisfactorily, catalysts **VI** afforded the desired product in excellent yield (99% yield) and diastereostereoselectivity (97:3 dr) with high enantioselectivity (90% ee). C_2-Symmetrical quinine-derived squaramide **IX** and one kind of thiourea catalyst **V** were also examined, but no better result were observed. Consequently squaramide **VI** derived from (1*S*,2*S*)-cyclohexane-1,2-diamine once again was proved to be the optimal catalyst and was used for further optimization.

Table 1 Screening of organocatalysts for the asymmetric Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one to 3-nitro-2*H*-chromene[a]



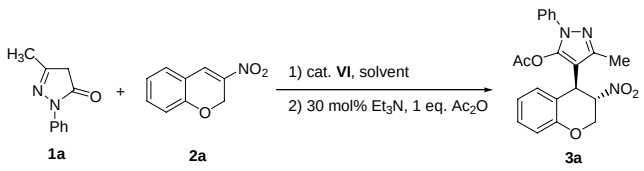
1a **2a** **3a**

Entry	Catalyst	Yield[b] (%)	dr[c] (%)	ee[c] (%)
1	**I**	97	97:3	88
2	**II**	96	96:4	62
3[d]	**III**	99	96:4	85
4[d]	**IV**	98	96:4	50
5[d]	**V**	99	96:4	45
6	**VI**	99	97:3	90
7	**VII**	98	96:4	50
8	**VIII**	98	96:4	84
9	**IX**	98	96:4	54

[a] Reactions were carried out with 3-methyl-1-phenyl-2-pyrazolin-5-one **1a** (0.10 mmol) and 3-nitro-2*H*-chromene **2a** (0.10 mmol) in CH_2Cl_2 (0.5 mL) at room temperature for 10 h. [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] The opposite enantiomer.

With squaramide **VI** as the best catalyst, we further screened the effect of solvents, catalyst loading, and temperature for the optimal reaction conditions. The results are shown in Table 2. After a variety of solvents were surveyed (Table 2, entries 1–7), dichloromethane appeared to be the most suitable reaction media. Then the catalyst loading was screened, and we found that increasing the catalyst loading could lead to the decrease of the enantioselectivity (Table 2, entry 8), while the high enantioselectivities were still maintained with a reduced catalyst loading from 2.5 to 0.2 mol%, and excellent yields were obtained at the same time (Table 2, entries 9–12). But slightly decrease in enantioselectivity (86% ee) and yield (87%) was appeared with 0.1 mol% catalyst loading (Table 2, entry 13). So the 0.2 mol% catalyst loading was selected for further optimization. Then, the temperature was decreased from room temperature to −15 °C, the enantioseletivity was increased to 96% ee while the excellent yield was still maintained. The temperature was further decreased to −30 °C, and to avoid the reaction take too long time, 5 mol% catalyst loading was used, but only the similar result was obtained. Furthermore, when the molecular sieves or anhydrous magnesium was used as additive, the excellent yields and diastereoselectivities were obtained, but the enantioselectivities were slightly lower. As a consequence the optimal condition for this Michael addition was obtained as using 0.2 mol% of catalyst **VI** in dichloromethane at −15 °C.

Table 2 Optimization of reaction conditions for the asymmetric Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one to 3-nitro-2*H*-chromene[a]



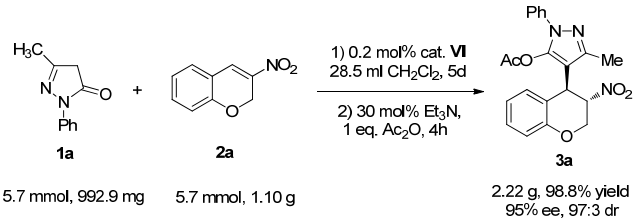
Entry	Solvent	*T* (°C)	Loading (mol%)	*t*(h)	Yield[b] (%)	dr[c] (%)	ee[c] (%)
1	CH_2Cl_2	rt	5	10	99	97:3	90
2	$CHCl_3$	rt	5	10	97	96:4	90
3	$ClCH_2CH_2Cl$	rt	5	10	99	96:4	90
4	Et_2O	rt	5	10	91	97:3	74
5	CH_3CN	rt	5	10	97	96:4	97
6	$PhCH_3$	rt	5	10	99	96:4	86
7	THF	rt	5	10	94	97:3	86
8	CH_2Cl_2	rt	10	10	99	97:3	87
9	CH_2Cl_2	rt	2.5	10	97	97:3	90
10	CH_2Cl_2	rt	1	16	99	97:3	90
11	CH_2Cl_2	rt	0.5	24	98	96:4	91
12	CH_2Cl_2	rt	0.2	32	97	96:4	90
13	CH_2Cl_2	rt	0.1	48	87	96:4	86
14	CH_2Cl_2	–15	0.2	96	95	96:4	96
15	CH_2Cl_2	–30	5	14	86	96:4	95
16[d]	CH_2Cl_2	–15	0.2	72	99	96:4	92
17[e]	CH_2Cl_2	–15	0.2	96	99	97:3	93

[a] Reactions were carried out with 3-methyl-1-phenyl-2-pyrazolin-5-one **1a** (0.10 mmol) and 3-nitro-2*H*-chromene **2a** (0.10 mmol) in solvent (0.5 mL). [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] 20 mg molecular sieves were added. [e] 12 mg anhydrous magnesium was added.

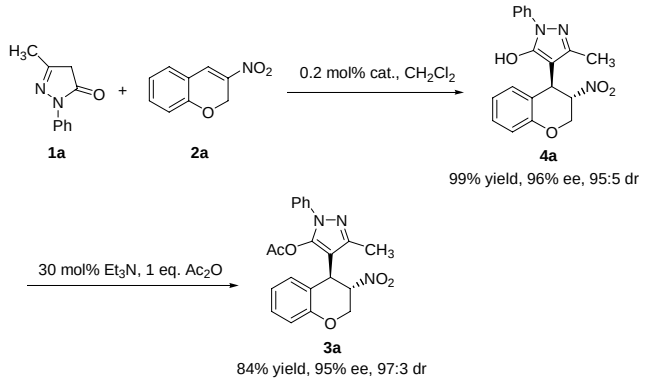
With the optimized reaction conditions established, the scope of the reaction was explored with respect to both the nucleophile and the electrophile and the representative results are listed in Table 3. The nucleophile substitutes on R^1 and R^2 groups were first explored, and the good to excellent yields and enantioselectivities, and with excellent diastereoselectivities were obtained (Table 3, entries 1–6). The electon-withdrawing group (CF_3) in 3-position of pyrazolinone ring result in lower yield of corresponding product **3f**. Then a variety of 3-nitro-2*H*-chromenes bearing different substituent on R^3 group were surveyed (Table 3, entries 7–13). Generally, the products with substitutions on the phenyl ring of chromene were obtained in excellent yields and diastereoselectivities. As for enantioselectivities, the products with electron-withdrawing groups (Table 3, entries 7–9 and 13), good to excellent enantioselectivities were obtained. On the other hand, the enantioselectivities of products with electron-donating substituents were slightly lower (Table 3, entries 10 and 11). A polycyclic 3-nitro-2*H*-chromene, 3-nitro-1,2-dihydrophenanthrene was also used as a substrate, affording the desired product **3l** in excellent yield and diastereoselectivity, and with good enantioselectivity (Table 3, entries 12). Moreover, when the oxygen atom of 3-nitro-2*H*-chromene was replaced by a methylene or a sulfur atom, the reactions using these two substrates also proceeded smoothly, and affording the corresponding products **3n** and **3o** in good yield with excellent diastereoselectivity and good enantioselectivity (Table 3, entries 14 and 15). In addition to various 3-nitro-2*H*-chromenes, acyclic nitroalkene (β-methyl-β-nitrostyrene) was also used as the substrate, and the reactivity of this substrate was lower, because no reaction was detected when 0.2 mol% catalyst loading was used. But this substrate could also be successfully employed in this transformation with 2.0 mol% catalyst loading and afforded the desired product **3p** in 83% yield with 83:17 d.r. and 91% ee (Table 3, entries 16).

To evaluate the synthetic potential of this catalytic system, the gram-scale preparation of product **3a** was also performed in the presence of 0.2 mol% of catalyst **VI**, and the reaction time was appropriately prolonged as shown in Scheme 1 to guarantee the complete of the reaction, and the corresponding product **3a** (2.22 g) was obtained in 98.8% yield with 97:3 d.r. and 95% ee.

In addition, the intermediate product **4a** was also isolated in almost quantitative yield with excellent diastereoselectivity and enantioselectivity. Then intermediate **4a** was acylated, and the corresponding product **3a** was obtained in similar diastereoselectivity and enantioselectivity as compared with the one-pot sequential reaction, but the yield was slightly lower. The lower yield was mainly due to the addition intermediate **4a** was a mixture of tautomers, which lead to the unstability of the intermediate **4a**. The loss of yield was unavoidable even brief storage time before the acylated process.

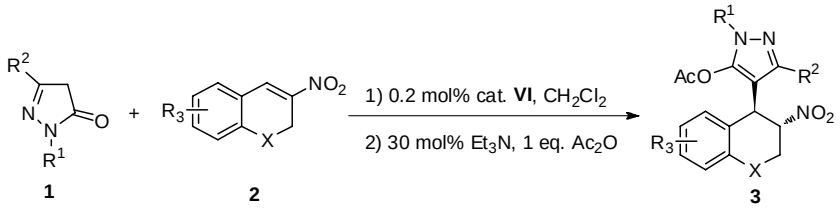


Scheme 1. Gram-scale preparation of **3a**.



Scheme 2. The isolation of the addition intermediate product and its further acetylation.

Table 3 Scope of the asymmetric Michael addition of pyrazolin-5-ones to 3-nitro-2*H*-chromenes[a]



Entry	R^1	R^2	R^3	X	Product	Yield[b] (%)	dr[c] (%)	ee[d] (%)
1	Ph	Me	H	O	**3a**	95	96:4	96
2	4-ClC_6H_4	Me	H	O	**3b**	98	96:4	96
3	4-MeC_6H_4	Me	H	O	**3c**	98	96:4	95
4	Ph	Et	H	O	**3d**	87	97:3	92
5	Ph	Ph	H	O	**3e**	98	99:1	92
6	Ph	CF_3	H	O	**3f**	75	97:3	92
7	Ph	Me	6-Br	O	**3g**	97	97:3	93
8	Ph	Me	6-Cl	O	**3h**	96	97:3	93
9	Ph	Me	6-NO_2	O	**3i**	96	>25:1	96
10	Ph	Me	8-OEt	O	**3j**	98	97:3	72
11	Ph	Me	8-OMe	O	**3k**	92	97:3	84
12	Ph	Me	5,6-benzo	O	**3l**	98	99:1	93
13	Ph	Me	6,8-Br_2	O	**3m**	97	96:4	83
14	Ph	Me	H	CH_2	**3n**	89	99:1	73
15	Ph	Me	H	S	**3o**	89	96:4	88
16[e]	Ph	Me	H	–	**3p**	83	83:17	91

[a] Unless noted otherwise, reactions were carried out with pyrazolin-5-one **1** (0.1 mmol), 3-nitro-2*H*-chromene **2** (0.10 mmol) and catalyst **VI** (0.2 mol%) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis or NMR spectroscopy analysis [d] Determined by chiral HPLC analysis. [e] 2.0 mol% catalysts were used.

The absolute configuration of **3m** was unambiguously established to be (3*S*, 4*S*) by X-ray crystal structure analysis (Fig. 3), and those of other adducts were assigned by analogy.[13] On the basis of the absolute configuration of **3a** and the theoretical study on the mechanism of squaramide-catalysed Michael addition,[14] a possible reaction mechanism is outlined in Figure 4. We envisioned that the chiral squaramide **VI** may acts as a bifunctional catalyst. The 3-nitro-2*H*-chromene is activated by the squaramide moiety through double hydrogen bonding between the NH groups and the nitro group. Meanwhile, the pyrazolone substrate, in its enol form, interacts with the tertiary amine unit of the chiral catalyst through hydrogen bonding. The deprotonated pyrazolinone attacks the activated nitroalkene from the *Re*-face to afford the nitronate intermediate, and the final product **3a** with (3*S*, 4*S*)-configured stereocenter is formed after the following nitronate protonation, enolization and acylation reaction with anhydride, which is consistent with the observed results.Presumably under the reaction conditions the chiral centre next to the nitro group is epimerisable (by deprotonation/ reprotonation) and thus the origin of high levels of *anti* diastereoselectivity arise from thermodynamic control rather than

requiring kinetic control in the nitronate protonation step. It's worth noting that, in this catalytic system, each molecule of the squaramide catalyst can efficiently work for 500 cycles.

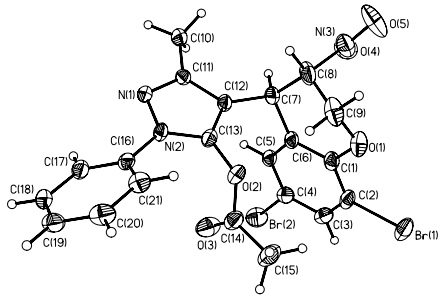


Figure 3. X-ray crystal structure of **3m**.

Conclusions

In summary, we have successfully developed a squaramide-catalysed diastereoselective and enantioselective Michael addition of pyrazolin-5-ones to 3-nitro-2*H*-chromenes. This transformation is catalyzed by an efficient chiral squaramide with very low catalyst loading (0.2 mol%). The corresponding Michael adducts were obtained in high to excellent yields (up to 98%) with high enantioselectivities (up to 96% ee) and excellent diastereoselectivities (up to 99:1 dr). This catalytic asymmetric reaction provides an easy access to chiral heterocyclic compounds containing both chroman and pyrazolone derivative motifs, which possess potential pharmaceutical activity. Further studies about chiral squaramide catalysed reactions are underway in our group to broaden their applications in asymmetric catalysis.

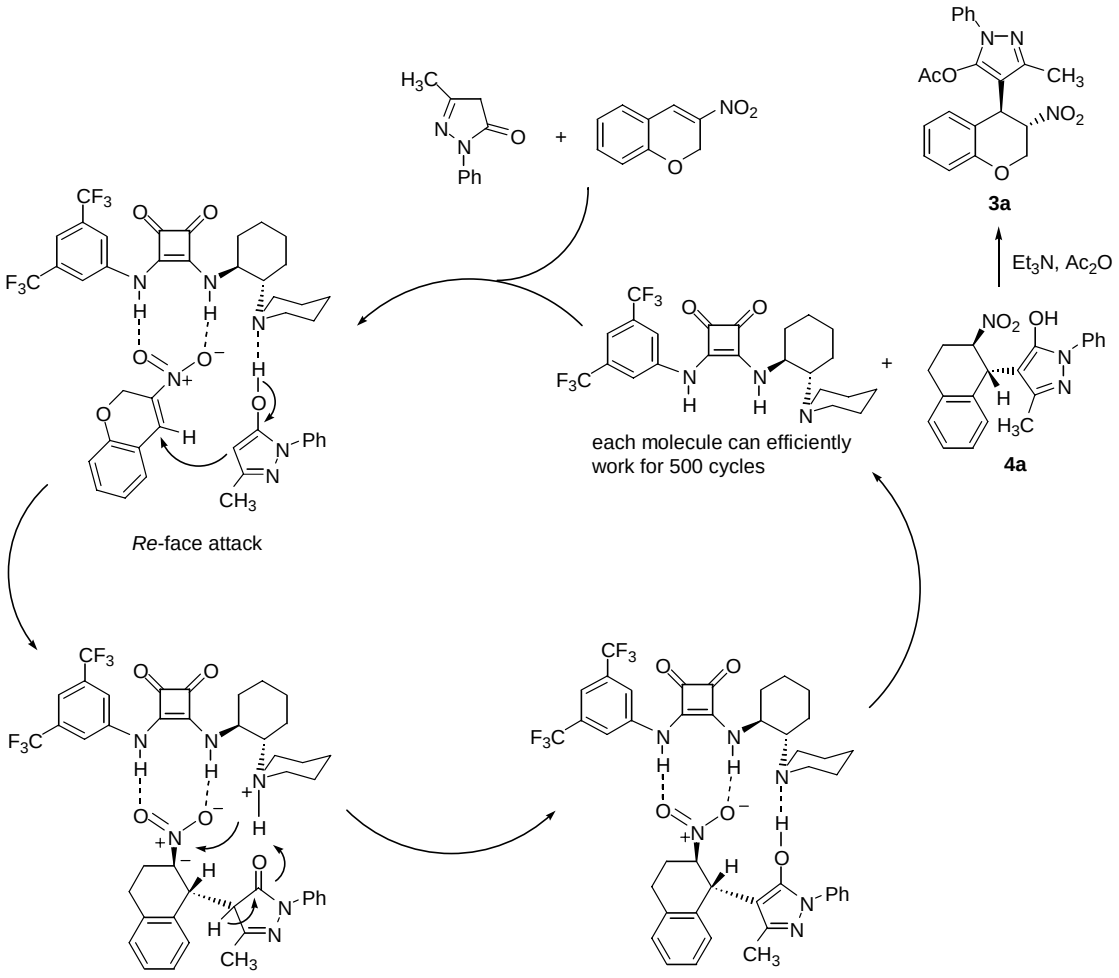


Figure 4. Proposed reaction mechanism

Experimental

General information

Commercially available compounds were used without further purification. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus without correction. The ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz or a Bruker Avance 400 MHz spectrometer, while ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained with a Perkin Elmer Spectrum One FT-IR spectrometer. The high resolution ESI-MS spectra were obtained with Bruker APEX IV Fourier transform mass spectrometer. Optical rotations were

measured with a Krüss P8000 polarimeter at the indicated concentration with unit g per 100 mL. The enantiomeric excesses of the products were determined by chiral HPLC using Agilent 1200 LC instrument on Daicel Chiralpak AD-H or IB columns.

Materials

The squaramide organocatalysts were prepared following the reported procedures.[10d,11a,11c] The racemic products of **3** were obtained using Et_3N as catalyst.

General procedure for the enantioselective Michael addition reaction

Organocatalyst **VI** (2.0 mg) was added to dichloromethane to afford a solution of catalyst **VI** (10 mL). A mixture of 3-nitro-2*H*-chromene **2** (0.10 mmol) and 0.5 mL of the above catalyst **VI** solution (0.0002 mmol) was stirred at −15 °C for 10 min, then pyrazolin-5-one (0.10 mmol) was added in one portion. After stirring for 96 h at −15 °C, the reaction mixture was warmed to room temperature. Then acetic anhydride (0.1 mmol) and triethylamine (0.03 mmol) were added successively. After stirring for another 30 min at room temperature, the reaction mixture was concentrated and directly purified by silica gel column chromatography (with ethyl acetate–petroleum ether as eluent) to afford the desired products **3**.

3-Methyl-4-((3*S*,4*S*)-3-nitrochroman-4-yl)-1-phenyl-1*H*-pyrazol-5-yl acetate (3a). Compound **3a** was obtained according to the general procedure as a white solid (37.3 mg, 95% yield); m.p. 53–55 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 9.8 min, minor enantiomer t_R = 11.3 min, 96% ee; $[\alpha]_D^{25}$ = +136.2 (*c* = 1.67, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.38 (m, 4H, ArH), 7.33–7.28 (m, 1H, ArH), 7.19–7.15 (m, 1H, ArH), 7.12 (d, *J* = 7.6 Hz, 1H, ArH), 6.96–6.89 (m, 2H, ArH), 4.95–4.91 (m, 1H, CH), 4.84 (d, *J* = 6.0 Hz, 1H, CH), 4.61–4.57 (m, 1H, CH), 4.52 (dd, J_1 = 3.2 Hz, J_2 = 11.6 Hz, 1H, CH), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 153.1, 147.0, 142.6, 137.5, 130.1, 129.2, 128.6, 127.6, 122.7, 122.1, 119.0, 116.7, 106.9, 82.7, 64.5, 34.4, 19.6, 13.2 ppm. IR (KBr): $\tilde{\nu}$ 2925, 1790, 1596, 1584, 1553, 1506, 1489, 1370, 1263, 1227, 1167, 1046, 757, 694 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{20}N_3O_5$ $[M + H]^+$ 394.13975, found 394.13973.

1-(4-Chlorophenyl)-3-methyl-4-((3*S*,4*S*)-3-nitrochroman-4-yl)-1*H*-pyrazol-5-yl acetate (3b). Compound **3b** was obtained according to the general procedure as a white solid (42.0 mg, 98% yield); m.p. 45–48 °C. HPLC (Daicel Chiralpak AD-H column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 11.9 min, minor enantiomer t_R = 10.7 min, 96% ee; $[\alpha]_D^{25}$ = +137.9 (*c* = 1.60, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.37 (m, 4H, ArH), 7.19 (t, *J* = 7.6 Hz, 1H, ArH), 7.10 (d, *J* = 7.6 Hz, 1H, ArH), 6.97–6.91 (m, 2H, ArH), 4.95–4.91 (m, 1H, CH), 4.84 (d, *J* = 6.4 Hz, 1H, CH), 4.61–4.52 (m, 2H, CH_2), 2.11 (s, 3H, CH_3), 1.90 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 153.1, 147.5, 142.7, 136.1, 133.3, 130.1, 129.4, 128.7, 123.9, 122.3, 119.0, 116.8, 107.3, 82.6, 64.6, 34.4, 19.7, 13.2 ppm. IR (KBr): $\tilde{\nu}$ 2926, 1791, 1596, 1585, 1552, 1502, 1490, 1462, 1369, 1227, 1166, 1092, 1041, 1013, 892, 833, 757 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{19}ClN_3O_5$ $[M + H]^+$ 428.10077, found 428.10144.

3-Methyl-4-((3*S*,4*S*)-3-nitrochroman-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl acetate (3c). Compound **3c** was obtained according to the general procedure as a white solid (40.0 mg, 98% yield); m.p. 57–60 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 9.5 min, minor enantiomer t_R = 11.1 min, 95% ee; $[\alpha]_D^{25}$ = +140.7 (*c* 1.23, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.4 Hz, 2H, ArH), 7.21–7.16 (m, 3H, ArH), 7.12 (d, *J* = 7.6 Hz, 1H, ArH), 6.96–6.89 (m, 2H, ArH), 4.94–4.91(m, 1H, CH), 4.83 (d, *J* = 6.0 Hz, 1H, CH), 4.60 (dd, J_1 = 6.4 Hz, J_2 = 11.6 Hz, 1H, CH), 4.53 (dd, J_1 = 2.8 Hz, J_2 = 11.4 Hz, 1H, CH), 2.36 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 153.2, 146.8, 142.6, 137.6, 135.1, 130.2, 129.8, 128.6, 122.8, 122.2, 119.1, 116.7, 106.7, 82.8, 64.5, 34.4, 21.0, 19.7, 13.2 ppm. IR (KBr): $\tilde{\nu}$ 2925, 1789, 1584, 1551, 1518, 1489, 1452, 1386, 1369, 1265, 1227, 1168, 1043, 822, 757, 736, 503 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{22}N_3O_5$ $[M + H]^+$ 408.15540, found 408.15632. calcd. for $C_{22}H_{21}N_3NaO_5$ $[M + Na]^+$ 430.13734, found 430.13835.

3-Ethyl-4-((3*S*,4*S*)-3-nitrochroman-4-yl)-1-phenyl-1*H*-pyrazol-5-yl acetate (3d). Compound **3d** was obtained according to the general procedure as a white solid (35.6 mg, 87% yield); m.p. 41–44 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R= 15.7 min, minor enantiomer t_R = 17.2 min, 92% ee; $[\alpha]_D^{25}$ = +132.1 (*c* 1.64, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H, ArH), 7.42–7.38 (m, 2H, ArH), 7.32–7.28 (m, 1H, ArH), 7.19–7.15 (m, 1H, ArH), 7.11 (d, *J* = 7.6 Hz, 2H, ArH), 6.95–6.89 (m, 2H, ArH), 4.96–4.93 (m, 1H, CH), 4.85 (d, *J* = 6.0 Hz, 1H, CH), 4.63–4.59 (m, 1H, CH), 4.56 (dd, J_1 = 3.2 Hz, J_2 = 11.6 Hz, 1H, CH), 2.62–2.42 (m, 2H, CH_2), 1.82 (s, 3H, CH_3), 1.26 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 153.1, 152.1, 142.5, 137.8, 130.3, 129.2, 128.6, 127.6, 122.8, 122.2, 119.4, 116.7, 106.4, 83.0, 64.6, 34.3, 20.8, 19.6, 12.7 ppm. IR (KBr): $\tilde{\nu}$ 2973, 2934, 1791, 1596, 1585, 1553, 1506, 1489, 1449, 1392, 1369, 1360, 1263, 1227, 1166, 1057, 887, 857, 757, 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{22}N_3O_5$ $[M + H]^+$ 408.15540, found 408.15631.

4-((3*S*,4*S*)-3-Nitrochroman-4-yl)-1,3-diphenyl-1*H*-pyrazol-5-yl acetate (3e). Compound **3e** was obtained according to the general procedure as a white solid (45.0 mg, 98% yield); m.p. 129–131°C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R= 9.7 min, minor enantiomer t_R = 9.0 min, 92% ee; $[\alpha]_D^{25}$ = +149.7 (*c* = 1.91, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 4H, ArH), 7.45–7.40 (m, 5H, ArH), 7.34 (t, *J* = 7.2 Hz, 1H, ArH), 7.22 (d, *J* = 8.4 Hz, 1H, ArH), 7.17 (d, *J* = 8.0 Hz, 1H, ArH), 6.96 (t, *J* = 7.2 Hz, 1H, ArH), 6.88 (d, *J* = 8.4 Hz, 1H, ArH), 5.16 (d, *J* = 5.2 Hz, 1H, CH), 4.86–4.83 (m, 1H, CH), 4.60 (d, J_1 = 5.6 Hz, J_2 = 11.6 Hz, 1H, CH), 4.47 (dd, J_1 = 2.4 Hz, J_2 = 12.0 Hz, 1H, CH), 1.75 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 152.9, 150.1, 143.1, 137.5, 132.5, 130.7, 129.2, 128.8, 128.74, 128.71, 128.01, 127.96, 123.0, 122.1, 119.2, 116.7, 106.7, 82.0, 64.1, 34.2, 19.5 ppm. IR (KBr): $\tilde{\nu}$ 3059, 1793, 1586, 1551, 1501, 1490, 1452, 1369, 1267, 1226, 1165, 1007, 880, 858, 758, 696, 508 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{22}N_3O_5$ $[M + H]^+$ 456.15540, found 456.15581.

4-((3*S*,4*S*)-3-Nitrochroman-4-yl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl acetate (3f). Compound **3f** was obtained according to the general procedure as a white solid

(33.4 mg, 75% yield); m.p. 49–52 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.4 min, minor enantiomer t_R = 6.7 min, 92% ee; $[\alpha]_D^{25}$ = +100.3 (*c* 1.19, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.39 (m, 5H, ArH), 7.20 (t, *J* = 7.6 Hz, 1H, ArH), 7.08 (d, *J* = 7.6 Hz, 1H, ArH), 6.95 (t, *J* = 7.4 Hz, 1H, ArH), 6.91 (d, *J* = 8.4 Hz, 1H, ArH), 5.12 (d, *J* = 4.4 Hz, 1H, CH), 5.00–4.98 (m, 1H, CH), 4.73 (dd, J_1 = 5.2 Hz, J_2 = 12.0 Hz, 1H, CH), 4.52 (dd, J_1 = 2.4 Hz, J_2 = 12.0 Hz, 1H, CH), 1.70 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 153.0, 143.8, 139.5 (q, $J_{C\text{-}F}$ = 37.5 Hz), 136.7, 130.5, 129.5, 129.1, 129.0, 123.5, 122.3, 119.6, 118.0, 116.8, 107.9, 82.5, 63.9, 33.2, 19.3 ppm. IR (KBr): $\tilde{\nu}$ 2926, 1796, 1587, 1553, 1490, 1450, 1393, 1360, 1286, 1227, 1151, 1128, 1010, 858, 756, 697 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{16}F_3N_3NaO_5$ $[M + Na]^+$ 470.09343, found 470.09403.

4-((3*S*,4*S*)-6-Bromo-3-nitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3g). Compound **3g** was obtained according to the general procedure as a white solid (46 mg, 97% yield); m.p. 51–54 °C. HPLC (Daicel Chiralpak AD-H + IB column, *n*-hexane–isopropanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 15.2 min, minor enantiomer t_R = 15.9 min, 93% ee; $[\alpha]_D^{25}$ = +42.8 (*c* 1.93, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.41 (m, 4H, ArH), 7.36–7.26 (m, 3H, ArH), 6.81 (d, *J* = 8.8 Hz, 1H, ArH), 4.92–4.88 (m, 1H, CH), 4.81 (d, *J* = 5.6 Hz, 1H, CH), 4.63 (dd, J_1 = 6.0 Hz, J_2 = 11.6 Hz, 1H, ArH), 4.50 (dd, J_1 = 2.6 Hz, J_2 = 11.8 Hz, 1H, CH), 2.14 (s, 3H, CH_3), 1.93 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 152.3, 146.9, 142.6, 137.4, 132.6, 131.7, 129.3, 127.8, 123.0, 121.2, 118.6, 114.3, 106.4, 82.2, 64.4, 34.0, 19.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2925, 1791, 1597, 1551, 1505, 1481, 1437, 1370, 1262, 1229, 1166, 1050, 819, 759, 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{19}BrN_3O_5$ $[M + H]^+$ 472.05026, found 472.05092.

4-((3*S*,4*S*)-6-Chloro-3-nitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3h). Compound **3h** was obtained according to the general procedure as a white solid (41 mg, 96% yield); m.p. 49–52 °C. HPLC (Daicel Chiralpak AD-H + IB column, *n*-hexane–isopropanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 14.6 min, minor enantiomer t_R = 15.3 min, 93% ee; $[\alpha]_D^{25}$ = +72.9 (*c* 1.68, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.41 (m, 4H, ArH), 7.34 (t, *J* = 6.8 Hz, 1H, ArH), 7.17–7.12 (m, 2H, ArH), 6.86 (d, *J* = 8.4 Hz, 1H, ArH), 4.93–4.89 (m, 1H, CH), 4.80 (d, *J* = 5.6 Hz, 1H, CH), 4.62 (dd, J_1 = 6.0 Hz, J_2 = 12.0 Hz, 1H, CH), 4.51 (dd, J_1 = 2.8 Hz, J_2 = 11.6 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.94 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 151.8, 146.9, 142.6, 137.4, 129.7, 129.2, 128.8, 127.8, 127.1, 122.9, 120.7, 118.2, 106.4, 82.2, 64.5, 34.1, 19.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2930, 1791, 1598, 1553, 1506, 1485, 1386, 1371, 1262, 1231, 1167, 1049, 821, 759, 696 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{19}ClN_3O_5$ $[M + H]^+$ 428.10077, found 428.10143.

4-((3*S*,4*S*)-3,6-Dinitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3i). Compound **3i** was obtained according to the general procedure as a white solid (42.0 mg, 96% yield); m.p. 66–69 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R= 29.2 min, minor enantiomer t_R= 38.6 min, 96% ee; $[\alpha]_D^{25}$ = +50.5 (*c* 1.59, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.07 (m, 2H, ArH), 7.46–7.40 (m, 4H, ArH), 7.37–7.31 (m, 1H, ArH), 7.02 (d, *J* = 8.8 Hz, 1H, ArH), 4.97–4.94 (m, 1H, CH), 4.89 (d, *J* = 4.8 Hz, 1H, CH), 4.83–4.78 (m, 1H, CH), 4.59 (dd, J_1 = 2.8 Hz, J_2 = 12.0 Hz, 1H, CH), 2.15 (s, 3H, CH_3), 1.91 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 158.0, 146.6, 142.5, 142.4, 137.2, 129.3, 128.0, 126.6, 124.5, 123.1, 119.8, 117.6, 106.1, 81.4, 64.4, 33.9, 19.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2926, 1790, 1587, 1555, 1522, 1505, 1371, 1342, 1260, 1238, 1165, 1092, 1049, 851, 761, 749, 738, 696 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{19}N_4O_7$ $[M + H]^+$ 439.12483, found 439.12515.

4-((3*S*,4*S*)-8-Ethoxy-3-nitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3j): Compound **3j** was obtained according to the general procedure as a white solid (43.0 mg, 98% yield); m.p. 58–61 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 10.8 min, minor enantiomer t_R = 15.2 min, 72% ee; $[\alpha]_D^{25}$ = +116.9 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.40 (m, 4H, ArH), 7.32 (t, *J* = 7.0 Hz, 1H, ArH), 6.88 (t, *J* = 7.8 Hz, 1H, ArH), 6.79 (d, *J* = 8.0 Hz, 1H, ArH), 6.71 (d, *J* = 7.6 Hz, 1H, ArH), 4.98–4.94 (m, 1H, CH), 4.83 (d, *J* = 6.4 Hz, 1H, CH), 4.67–4.60 (m, 2H, CH_2), 4.10 (q, *J* = 7.2 Hz, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.48 (t, *J* = 7.2 Hz, 3H, CH_3) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 147.4, 147.1, 143.0, 142.7, 137.5, 129.2, 127.6, 122.8, 121.8, 121.4, 120.2, 111.5, 106.8, 82.7, 65.2, 64.4, 34.5, 19.8, 14.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2979, 2928, 1791, 1598, 1587, 1553, 1506, 1486, 1473, 1388, 1369, 1266, 1200, 1168, 1128, 1070, 1039, 856, 763, 696, 671 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{23}H_{24}N_3O_6$ $[M + H]^+$ 438.16596, found 438.16660.

4-((3*S*,4*S*)-8-Methoxy-3-nitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3k): Compound **3k** was obtained according to the general procedure as a white solid (38.9 mg, 92% yield); m.p. 58–62 °C. HPLC (Daicel Chiralpak AD-H column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 17.8 min, minor enantiomer t_R = 14.4 min, 84% ee; $[\alpha]_D^{25}$ = +123.8 (*c* 1.48, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.39 (m, 4H, ArH), 7.34–7.29 (m, 1H, ArH), 6.90 (t, *J* = 8.0 Hz, 1H, ArH), 6.79 (d, *J* = 7.2 Hz, 1H, ArH), 6.73 (d, *J* = 7.6 Hz, 1H, ArH), 4.97–4.93 (m, 1H, CH), 4.83 (d, *J* = 6.4 Hz, 1H, CH), 4.68–4.61 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 2.08 (s, 3H, CH_3), 1.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 148.1, 147.1, 142.8, 142.6, 137.6, 129.2, 127.6, 122.8, 121.9, 121.6, 120.1, 110.2, 106.8, 82.6, 65.0, 56.0, 34.4, 19.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2934, 1791, 1596, 1588, 1551, 1506, 1487, 1439, 1387, 1370, 1266, 1220, 1168, 1129, 1075, 1037, 879, 763, 734, 695, 671, 502 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{21}N_3NaO_6$ $[M + Na]^+$ 446.13226, found 446.13260.

3-Methyl-4-((1*S*,2*S*)-2-nitro-2,3-dihydro-1H-benzo[*f*]chromen-1-yl)-1-phenyl-1*H*-pyrazol-5-yl acetate (3l): Compound **3l** was obtained according to the general procedure as a white solid (43.4 mg, 98% yield); m.p. 80–83 °C. HPLC (Daicel Chiralpak AD-H column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 11.3 min, minor enantiomer t_R = 14.7 min, 93% ee; $[\alpha]_D^{25}$ = +164.6 (*c* = 1.67, CH_2Cl_2). ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.71 (d, *J* = 9.2 Hz, 1H, ArH), 7.62 (d, *J* = 8.4 Hz, 1H, ArH), 7.45 (t, *J* = 7.6 Hz, 1H, ArH), 7.38–7.34 (m, 5H, ArH), 7.31–7.27 (m, 1H, ArH), 7.10 (d, *J* = 8.8 Hz, 1H, ArH), 5.35 (s, 1H, CH), 4.98 (d, *J* = 12.8 Hz, 1H, CH), 4.90 (s, 1H, CH),

4.51 (d, J = 12.4 Hz, 1H, CH), 2.24 (s, 3H, CH_3), 1.64 (3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 150.8, 146.7, 142.3, 137.3, 132.2, 129.7, 129.4, 129.2, 128.5, 127.7, 127.2, 124.1, 122.9, 122.1, 118.1, 109.0, 107.2, 81.6, 61.9, 30.6, 19.4, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2926, 1789, 1625, 1598, 1551, 1504, 1472, 1435, 1369, 1265, 1238, 1226, 1165, 1095, 1050, 1002, 882, 815, 745, 695 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{25}H_{22}N_3O_5$ $[M + H]^+$ 444.15540, found 444.15601.

4-((3*S*,4*S*)-6,8-Dibromo-3-nitrochroman-4-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3m): Compound **3m** was obtained according to the general procedure as a white solid (53.0 mg, 97 % yield); m.p. 68–71 °C. HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 13.5 min, minor enantiomer t_R = 19.1 min, 83% ee; $[\alpha]_D^{25}$ = +93.5 (c = 2.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H, ArH), 7.44–7.41 (m, 4H, ArH), 7.38–7.33 (m, 1H, ArH), 7.24 (s, 1H, ArH), 4.92–4.88 (m, 1H, CH), 4.82 (d, J = 5.2 Hz, 1H, CH), 4.77 (dd, J_1 = 5.6 Hz, J_2 = 12.0 Hz, 1H, CH), 4.60 (dd, J_1 = 2.4 Hz, J_2 = 12.0 Hz, 1H, CH), 2.16 (s, 3H, CH_3), 1.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 149.1, 146.6, 142.6, 137.3, 134.6, 132.0, 129.3, 127.9, 122.9, 122.3, 114.2, 111.6, 106.2, 81.7, 64.9, 34.1, 19.7, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2926, 1790, 1597, 1555, 1506, 1465, 1444, 1384, 1369, 1240, 1169, 1049, 854, 759, 736, 695, 679, cm^{-1}. HRMS (ESI): m/z calcd. for $C_{21}H_{18}Br_2N_3O_5$ $[M + H]^+$ 549.96077, found 549.95991.

4-((1*S*,2*R*)-2-Nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methyl-1-phenyl-1H-pyrazol-5-yl acetate (3n): Compound **3n** was obtained according to the general procedure as a white solid (34.8 mg, 89% yield); m.p. 48–51 °C. HPLC (Daicel Chiralpak AD-H column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 9.7 min, minor enantiomer t_R = 8.7 min, 73% ee; $[\alpha]_D^{25}$ = +82.2 (c = 1.53, CH_2Cl_2). ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.49–7.46 (m, 2H, ArH), 7.42–7.38 (m, 2H, ArH), 7.32–7.25 (m, 1H, ArH), 7.19–7.11 (m, 4H, ArH), 4.96–4.90 (m, 1H, CH), 4.71 (d, J = 9.2 Hz, 1H, CH), 3.04 (dd, J_1 = 5.2 Hz, J_2 = 8.0 Hz, 2H, CH_2), 2.55–2.40 (m, 2H, CH_2), 2.00 (s, 3H, CH_3), 1.99 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 147.3, 142.7, 137.8, 134.1, 133.8, 129.3, 129.1, 128.3, 127.4, 127.0, 126.9, 122.7, 108.0, 87.6, 38.3, 28.0, 27.4, 19.9, 13.3 ppm. IR (KBr): $\tilde{\nu}$ 2924, 2848, 1789, 1597, 1546, 1504, 1434, 1369, 1164, 1073, 1046, 879, 750, 694, 670, 575, 501 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{22}H_{22}N_3O_4$ $[M + H]^+$ 392.16048, found 392.16097; m/z calcd. for $C_{22}H_{21}N_3NaO_4$ $[M + Na]^+$ 414.14243, found 414.14177.

4-((3*S*,4*R*)-3-Nitrothiochroman-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-yl acetate (3o): Compound **3o** was obtained according to the general procedure as a white solid (36.6 mg, 89 % yield); m.p. 138–141 °C. HPLC (Daicel Chiralpak AD-H column, *n*-hexane–isopropanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 12.8 min, minor enantiomer t_R = 10.9 min, 88% ee; $[\alpha]_D^{25}$ = +148.9 (c = 1.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.39 (m, 4H, ArH), 7.33–7.29 (m, 1H, ArH), 7.18–7.04 (m, 4H, ArH), 5.18–5.13 (m, 1H, CH), 4.79 (d, J = 8.4 Hz, 1H, CH), 3.58 (dd, J_1 = 9.2 Hz, J_2 = 12.8 Hz, 1H, CH), 3.40 (dd, J_1 = 3.0 Hz, J_2 = 12.8 Hz, 1H, CH) 2.07 (s, 3H, CH_3), 2.04 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 147.2, 142.7, 137.7, 131.9, 131.1, 130.6, 129.2, 127.6, 127.3, 126.4, 125.8, 122.8, 107.8, 85.4, 37.8, 29.3, 19.9, 13.1 ppm. IR (KBr): $\tilde{\nu}$ 2917, 1787, 1724, 1596, 1538, 1504, 1422, 1366, 1164, 1071, 1049, 1003, 880, 801, 756, 699, 589, 484 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{21}H_{20}N_3O_4S$ $[M + H]^+$ 410.11690, found 410.11752; m/z calcd. for $C_{21}H_{19}N_3NaO_4S$ $[M + Na]^+$ 432.09885, found 432.09944; m/z calcd. for $C_{21}H_{19}KN_3O_4S$ $[M + K]^+$ 448.07279, found 448.07361.

4-((1*S*,2*R*)-2-Nitro-1-phenylpropyl)-3-methyl-1-phenyl-1H-pyrazol-5-yl acetate (3p): Compound **3p** was obtained according to the general procedure as a white solid (31.3 mg, 83 % yield); m.p. 39–41 °C. HPLC (Daicel Chiralpak OJ-H column, *n*-hexane–isopropanol 60:40, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 36.8 min, minor enantiomer t_R = 19.2 min, 91% ee; $[\alpha]_D^{25}$ = –50.2 (c = 1.22, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.38 (m, 3H, ArH), 7.32 (d, J = 7.2 Hz, 2H, ArH), 7.29–7.24 (m, 5H, ArH), 5.41–5.28 (m, 1H, CH), 4.37 (d, J = 11.6 Hz, 1H, CH), 2.23 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.51 (d, J = 6.8 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 147.5, 141.2, 138.0, 137.9, 129.1, 129.0, 128.3, 127.6, 127.4, 123.0, 107.2, 84.6, 45.9, 20.4, 19.7, 13.4 ppm. IR (KBr): $\tilde{\nu}$ 2923, 1790, 1596, 1549, 1504, 1435, 1368, 1161, 1040, 868, 756, 695, 670, 497 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{21}H_{21}N_3NaO_4$ $[M + Na]^+$ 402.14243, found 402.14179; m/z calcd. for $C_{21}H_{21}KN_3O_4$ $[M + Na]^+$ 418.11636, found 418.11494.

The isolation of the addition intermediate product 4a and its further acetylation.

Organocatalyst **VI** (2.0 mg) was added to dichloromethane to afford a solution of catalyst **VI** (10 mL). A mixture of 3-nitro-2*H*-chromene **2a** (0.10 mmol) and 0.5 mL of the above catalyst **VI** solution (0.0002 mmol) was stirred at –15 °C for 10 min, then pyrazolin-5-one **1a** (0.10 mmol) was added in one portion. After stirring for 96 h at –15 °C, the reaction mixture was concentrated and directly purified by silica gel column chromatography (ethyl acetate–petroleum ether 1:2) to afford the intermediate product **4a** (35.0 mg, 99% yield, 96% ee, 95:5 dr). m.p. 93–97 °C. HPLC (Daicel Chiralpak AS-H column, *n*-hexane–isopropanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 12.2 min, minor enantiomer t_R = 22.0 min, 96% ee; $[\alpha]_D^{25}$ = +135.6 (c = 1.08, CH_2Cl_2). The product **4a** was a mixture of tautomers, and the NMR spectroscopy was a complex of mess. IR (KBr): $\tilde{\nu}$ 2797, 1614, 1574, 1545, 1488, 1409, 1352, 1309, 1279, 1229, 1063, 809, 746, 717, 688, 582, 500 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{19}H_{18}N_3O_4$ $[M + H]^+$ 352.12918, found 352.12944; m/z calcd. for $C_{19}H_{17}N_3NaO_4$ $[M + Na]^+$ 374.11113, found 374.11159; m/z calcd. for $C_{19}H_{17}KN_3O_4$ $[M + K]^+$ 390.08506, found 390.08553. **4a** was dissolved in 0.5 mL dichloromethane, then acetic anhydride (0.1 mmol) and triethylamine (0.03 mmol) were added successively. After stirring for 30 min at room temperature, the reaction mixture was concentrated and directly purified by silica gel column chromatography (ethyl acetate–petroleum ether 1:5) to afford the desired products **3a** (33.1 mg, 84% yield, 95% ee, 97:3 dr).

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