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Rh-catalyzed intramolecular aromatic C–H insertion of α-diazo β-ketoesters: synthesis of 4-carbonyl chroman derivatives

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ABSTRACT

A Rh-catalyzed intramolecular aromatic C–H insertion of α-diazo β-ketoesters was developed. This protocol offers a practical strategy for the synthesis of 4-carbonyl chroman derivatives with high yield and is compatible with a wide variety of substituents. Synthetic applications of the 4-carbonyl chroman were also demonstrated.

1. Introduction

As one of the most prevalent polycyclic heterocycle in natural products benzopyran derivatives, especially displayed in numerous kinds of flavonoids, are widely distributed in plant secondary metabolites, fulfilling a series of significant functions.[1,2] The benzopyran derivatives are also found to be responsible for observed biological activities in medicinal chemistry. For example, as one of the benzopyran sub-category, several privileged structures of 4-carbonyl chroman have been extensively studied, such as deguelin,[3] stachyoidin,[4] and brazilide A[5] (Fig. 1). The major synthetic efforts to this 4-carbonyl chroman category previously focused on Robinsen cyclization,[6] Bucherer–Bergs reaction,[7] and Favorskii type rearrangement.[8] Until very recently, Nicolaou and co-workers proposed an organo-SOMO catalytic enantioselective intramolecular Friedel–Crafts arylation to carry out the structure with electronic-rich analogs.[9] However, lengthy procedures, poor yields, and access to limited substitution patterns make these methodologies unsuitable for high-throughput synthesis and library generation.

The aromatic C–H insertion is a valuable and powerful synthetic approach for the efficient construction of structurally unique frameworks and the wide adaptability of this robust method have been proved to tolerate diverse functional groups, allowing to reach a number of elaborative heterocycles. For example, Padwa and Sa first introduced the method in 1999.[10] As a part of our synthetic method development toward exquisite heterocycles in the context of diazo precursors, we recently described a tunable aromatic C–H insertion and Wolff rearrangement of α-diazo-β-ketoesters to

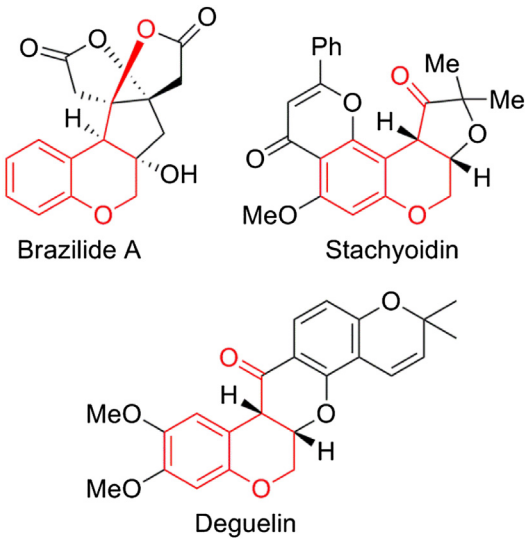

Fig. 1. Representative 4-carbonyl chroman derivatives.

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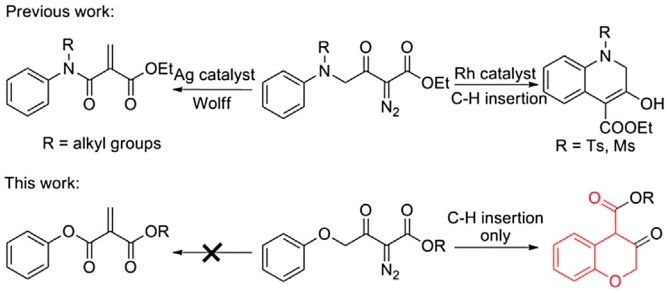
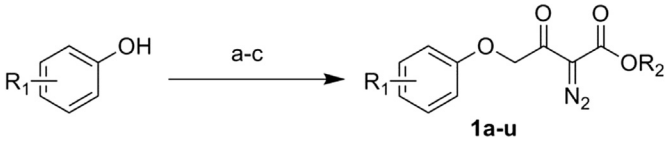
multiple nitrogen-containing heterocycles (Scheme 1).[11] Here we wish to expand this method to oxygen (sulfur)-containing structures, which is capable of producing a range of 4-carbonyl chromans exactly.



Scheme 1. Intramolecular aromatic C–H insertion to heterocycles.

2. Results and discussion

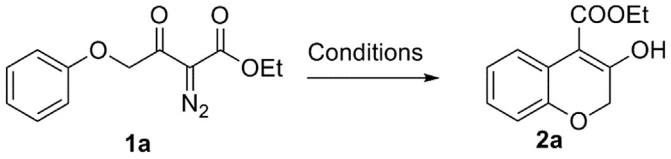
To test our rational design, we prepared α-diazo-β-ketoesters precursors **1a**–**u** in three steps, which were started from the nucleophilic substitution of bromoacetate to phenoxyacetate, followed by Claisen condensation[12] and Regitz diazo transfer[13] (Scheme 2). To our delight, initial survey of the aromatic C–H insertion between **1a** and $Rh_2(OAc)_4$ in dichloromethane gave the desired product in moderate yield, suggesting the rhodium catalyst allowed the intramolecular reaction under the neutral conditions, albeit to a limited extent (Table 1, entry 1). According to our previous research,[11] Du Bois' catalyst bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] that possess two chelating bis-carboxylate ligand can enhance the yield of cyclization with sulfonamide substrate, thus we found the treatment of $Rh_2(esp)_2$ to **1a** also remarkably improved the yield, even lower the loading amount to 0.1 mol % (Table 1, entries 4–7). Further screen of solvents and transition metal catalysts revealed dichloromethane and $Rh_2(esp)_2$ were the best solvent and catalyst for this catalytic system (Table 1, entries 2 and 3, 8–10). However, substrate **1a** could not undergo Wolff rearrangement reaction either with Ag_2O or under self-thermal initiation condition, as its tertiary amine counterpart did (Table 1, entries 11 and 12). We reasoned that the less nucleophilic oxygen was unable to attack the Wolff ketene intermediate so that it cannot transfer to the subsequent carboxylacrylate.



Scheme 2. Preparation of α-diazo-β-ketoesters **1a**–**u** (a) K_2CO_3, bromoacetate, KI, DMF, 50 °C, 16 h; (b) LiHDMS, EtOAc, THF, −78 °C, 2 h; (c) TsN_3, TEA, CH_3CN, room temperature, 2 h.

Next we investigated the scope of this aromatic C–H insertion to construct 4-carbonyl chroman analogs under the optimized conditions. Firstly, we found that the electron properties of the aromatic ring did not affect the reaction: both electron-donating and electron-withdrawing groups on the phenyl rings worked well (Table 2, entries 1–6). Subsequently, regarding to the positions of substitution, the reaction can tolerate not only *ortho*- and *meta*-substitutions but also the di-substitution and poly-aromatic ring system, such as naphthalene and biphenyl (Table 2, entries 7–16). It was also worth to note that the C–H insertion exclusively occurred at the *para*-position of methoxyl substitution instead of *ortho*-position probably due to the combine effect of the electron density and hindrance effect (Table 2, entry 11). However, the insertion could not happen to sp^3 C–H bond when employing the substrate that has both sp^2 *ortho*-positions blocked (entry 17, Table 2). Comparing with the aromatic C–H insertion containing nitrogen atom, the oxygen substrates showed better yields and broader tolerance to sensitive functional groups, suggesting it would be a sufficiently mild platform to build 4-carbonyl chroman-based natural products.

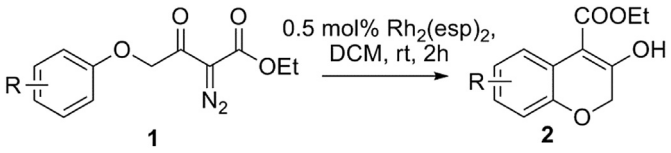
Table 1
Condition screening of C–H insertion[a]



Entry	Catalyst	Solvent	T (°C)/t (h)	Yield[b] (%)
1	$Rh_2(OAc)_4$	CH_2Cl_2	25/2	62
2	$Rh_2(OAc)_4$	$CHCl_3$	25/2	0
3	$Rh_2(OAc)_4$	DCE	25/2	10
4	$Rh_2(esp)_2$	CH_2Cl_2	25/2	90
5[c]	$Rh_2(esp)_2$	CH_2Cl_2	25/2	87
6[d]	$Rh_2(esp)_2$	CH_2Cl_2	25/2	87
7[e]	$Rh_2(esp)_2$	CH_2Cl_2	25/4	67
8	Ag_2O	DCM	25/2	0
9	CuI	DCM	25/2	0
10	None[f]	DCM	25/2	0
11	Ag_2O	Tol	100/3	0
12	None[f]	Tol	100/3	0

[a] Reactions were carried out with 0.2 mmol **1a** and 0.5 mol % catalyst unless specified at room temperature with stirring.
[b] Isolated yield.
[c] Catalyst loading (0.1 mol %).
[d] Catalyst loading (0.1 mol %).
[e] Catalyst loading (0.05 mol %).
[f] No catalyst was added.

Table 2
The reaction scope of the C–H insertion to form 4-carbonyl chroman[a]



Entry	R	Yield[b] (%)
1	H	90 (**2a**)
2	4-Cl	86 (**2b**)
3	4-I	82 (**2c**)
4	4-F	81 (**2d**)
5	4-OMe	97 (**2e**)
6	4-^{t}Bu	92 (**2f**)
7	4-Ph	90 (**2g**)
8	2-Cl	85 (**2h**)
9	2-I	83 (**2i**)
10	2-OMe	95 (**2j**)
11	3-OMe	96 (**2k**)
12	2-Me	93 (**2l**)
13	2,3-DiMe	88 (**2m**)
14	3,4-DiMe	91 (**2n**)
15	3,4-[1,3]Dioxole	94 (**2o**)
16	1-Naphthal	91 (**2p**)
17	2,6-DiMe	0[c]

[a] Reactions were carried out with 0.2 mmol **1a** and 0.5 mol % catalyst unless specified at room temperature with stirring.
[b] Isolated yield.
[c] All starting materials left.

We then explored the reaction scope of the ester group and the possibility to other heterocyclic scaffolds (Fig. 2). For a variety of ester substituents, the reaction afforded chroman ring in high yields comparable to the ethyl ester. However, the

seven-membered ring precursor **1t** produced only a trace amount of benzooxepane (LC–MS detected, but too low to isolate). Additionally, in our attempt to include the sulfur substrate in the catalytic system, we found that the rhodium catalyst lose its activity instantly after treating with the first drops of thioether substrate **1u**. The reason can probably be ascribed to the displacement of acetate ligand to thioether one that was commonly occurred on rhodium and other transition metal complexes.[14]

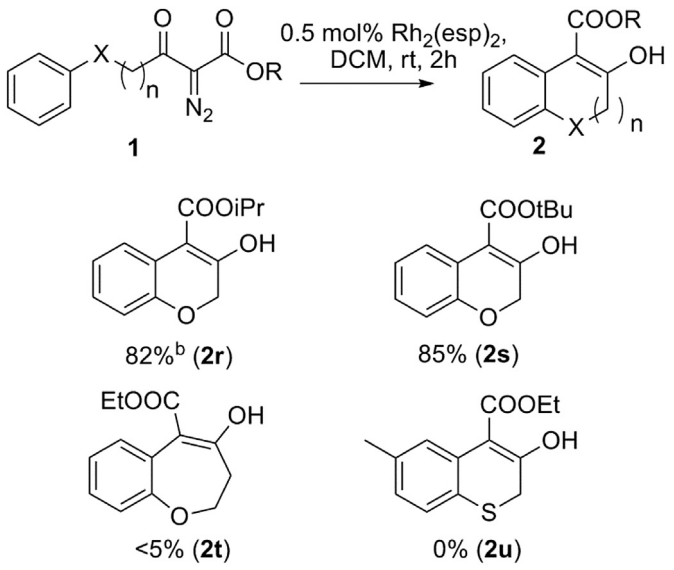
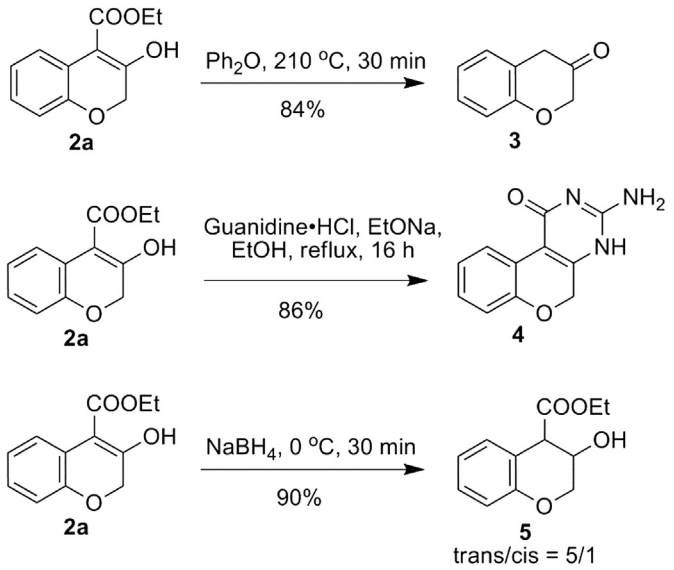


Fig. 2. Further scope of the C–H insertion reaction.[a] [a]Reactions were carried out with 0.2 mmol **1a** and 0.5 mol % catalyst at room temperature with stirring. [b]Isolated yield.

To demonstrate the reliability and practicability of this C–H insertion method, we also commented on the synthetic transformations of the 1-carbonyl chroman product. The C–H insertion product **2a** was readily converted into the chroman-3-one **3** through the decarboxylation at high temperature. The ketoester motif of **2a** can also be served as the building block of various heterocycles, such as the cytosine derivative **4**. And the successive reduction of the ketoester with sodium borohydride delivered the trans/cis mixture of alcohol **5** in a 5:1 ratio, which was demonstrated by the 2D NMR analysis. All the transformations proceeded in good yields under non-optimized conditions (Scheme 3).



Scheme 3. Synthetic transformations of **2a**.

3. Conclusions

In summary, we have developed a direct aromatic C–H insertion for efficient construction of 4-carbonyl chromans that are privilege in many biologically active compounds. Starting from the simple materials, high yields were obtained with different substitution patterns on the aromatic ring. And the following synthetic conversion indicates the potential application of the C–H insertion product as a versatile and straightforward building block. We are exploring the total synthesis of the related 4-carbonyl chroman natural products by using this method.

4. Experimental section

4.1. General

All reagents were purchased from commercial suppliers unless otherwise stated. Dichloromethane was distilled from CaH_2 under argon. THF was distilled from Na/benzophenone under argon. All moisture-sensitive reactions were carried out in oven-dried glassware under argon atmosphere. ^{1}H NMR spectra were recorded on a Bruker AVIII-400 spectrometer. ^{13}C NMR spectra were obtained by using the same NMR spectrometers. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, br s: broad singlet for proton spectra. Chemical shifts are reported in parts per million with the solvent signals as reference, coupling constants (*J*) are reported in Hertz (Hz). MS (ESI) was run on a Bruker Esquire 3000 plus spectrometer in MeOH. HRMS (ESI) were determined on a Micromass Q-Tof Global mass spectrometer. Flash column chromatography was performed using silica gel (200–300 mesh). Visualization was achieved under a UV lamp (254 nm and 365 nm).

4.2. General procedure for preparing starting material 1a–u

To a solution of β-ketoester (2.0 mmol) in acetonitrile (10 mL) were added *p*-methylbenzenesulfonyl azide (0.414 g, 2.1 mmol) and triethylamine (0.5 mL, 3.6 mmol). The resulting orange slurry was stirred for 2 h at room temperature. After evaporating all the volatiles, the residue was purified by flash column chromatography eluting with the mixture of petroleum ether and ethyl acetate (20:1).

*4.2.1. Ethyl 2-diazo-3-oxo-4-phenoxybutanoate (**1a**).* Yellow solid; isolated yield 81% (402 mg). R_f 0.33 (PE/EtOAc, 6:1); mp 52–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.31 (m, 2H), 6.92–6.99 (m, 3H), 5.14 (s, 2H), 4.32 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H) ppm. The date of the compound is identical with the described date of the reference.[15]

*4.2.2. Ethyl 4-(4-chlorophenoxy)-2-diazo-3-oxobutanoate (**1b**).* Colorless solid; isolated yield 80% (451 mg). R_f 0.31 (PE/EtOAc, 6:1); mp 68–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H), 6.83–6.87 (m, 2H), 5.12 (s, 2H), 4.34 (q, *J*=7.1 Hz, 2H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.80, 161.28, 156.78, 129.53, 126.68, 116.32, 71.42, 62.11, 14.49 ppm; MS (ESI): *m*/*z* 346 $[M+Na+CH_3CN]^+$; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{12}ClN_2O_4$ 283.0480, found 283.0483.

*4.2.3. Ethyl 2-diazo-4-(4-iodophenoxy)-3-oxobutanoate (**1c**).* Light yellow solid; isolated yield 83% (620 mg). R_f 0.35 (PE/EtOAc, 6:1); mp 68–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.57 (m, 2H), 6.68–6.71 (m, 2H), 5.11 (s, 2H), 4.33 (q, *J*=7.8 Hz, 2H), 1.35 (t, *J*=7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.71, 161.27, 158.04, 138.41, 117.32, 84.03, 71.12, 62.12, 14.49 ppm; MS (ESI): *m*/*z* 397

$[M+Na]^+$; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{12}IN_2O_4$ 374.9836, found 374.9828.

*4.2.4. Ethyl 2-diazo-4-(4-fluorophenoxy)-3-oxobutanoate (**1d**).* Colorless solid; isolated yield 78% (415 mg). R_f 0.37 (PE/EtOAc, 6:1); mp 68.9–69.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93–6.98 (m, 2H), 6.85–6.88 (m, 2H), 5.10 (s, 2H), 4.33 (q, J=8.0 Hz, 2H), 1.35 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.10, 161.28, 157.83 (d, $^1J_{C-F}$=239.2 Hz), 154.28 (d, $^4J_{C-F}$=4.0 Hz), 116.19 (d, $^2J_{C-F}$=23.1 Hz), 116.01 (d, $^3J_{C-F}$=8.2 Hz), 75.42, 71.92, 62.07, 14.47 ppm; MS (ESI): m/z 330 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}FN_2O_4$ 267.0776, found 267.0772.

*4.2.5. Ethyl 2-diazo-4-(4-methoxyphenoxy)-3-oxobutanoate (**1e**).* Colorless solid; isolated yield 76% (422 mg). R_f 0.32 (PE/EtOAc, 5:1); mp 73.1–74.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 5.09 (s, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.76 (s, 3H), 1.35 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.50, 161.33, 154.56, 152.33, 116.17, 114.76, 75.37, 72.21, 62.01, 55.83, 14.49 ppm; MS (ESI): m/z 342 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_5$ 279.0975, found 279.0972.

*4.2.6. Ethyl 4-(4-(tert-butyl)phenoxy)-2-diazo-3-oxobutanoate (**1f**).* Yellow solid; isolated yield 87% (529 mg). R_f 0.41 (PE/EtOAc, 6:1); mp 67.1–67.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.31 (m, 2H), 6.84–6.88 (m, 2H), 5.12 (s, 2H), 4.34 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.38, 161.34, 155.87, 144.39, 126.42, 114.41, 71.38, 62.01, 34.24, 31.62, 14.48 ppm; MS (ESI): m/z 368 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_4$ 305.1496, found 305.1491.

*4.2.7. Ethyl 4-([1,1′-biphenyl]-4-yloxy)-2-diazo-3-oxobutanoate (**1g**).* Light yellow solid; isolated yield 84% (544 mg). R_f 0.35 (PE/EtOAc, 5:1); mp 110.1–110.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.55 (m, 4H), 7.41 (t, J=8.0 Hz, 2H), 7.31 (t, J=6.0 Hz, 1H), 7.00 (d, J=8.0 Hz, 2H), 5.19 (s, 2H), 4.35 (q, J=8.0 Hz, 2H), 1.37 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.07, 161.29, 157.60, 140.75, 134.76, 128.80, 128.80, 128.30, 126.88, 126.87, 115.15, 71.22, 62.04, 14.45 ppm; MS (ESI): m/z 388 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_4$ 325.1183, found 325.1187.

*4.2.8. Ethyl 4-(2-chlorophenoxy)-2-diazo-3-oxobutanoate (**1h**).* Colorless solid; isolated yield 87% (490 mg). R_f 0.34 (PE/EtOAc, 5:1); mp 82.1–82.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 6.92 (t, J=8.0 Hz, 1H), 6.81 (d, J=8.0 Hz, 1H), 5.21 (s, 2H), 4.32 (q, J=8.0 Hz, 2H), 1.34 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.47, 161.25, 153.80, 130.65, 127.68, 123.34, 122.50, 114.23, 75.43, 71.99, 62.08, 14.43 ppm; MS (ESI) m/z: 346 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}ClN_2O_4$ 283.0480, found 283.0482.

*4.2.9. Ethyl 2-diazo-4-(2-iodophenoxy)-3-oxobutanoate (**1i**).* Light yellow solid; isolated yield 85% (636 mg). R_f 0.32 (PE/EtOAc, 6:1); mp 84.0–84.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, J=7.7, 1.5 Hz, 1H), 7.25 (td, J=8.2, 1.5 Hz, 1H), 6.66–6.78 (m, 2H), 5.20 (s, 2H), 4.33 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.21, 161.13, 156.86, 139.72, 129.39, 123.42, 112.72, 86.52, 75.38, 72.06, 62.02, 14.47 ppm; MS (ESI): m/z 397 $[M+Na]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}IN_2O_4$ 374.9836, found 374.9830.

*4.2.10. Ethyl 2-diazo-4-(2-methoxyphenoxy)-3-oxobutanoate (**1j**).* Yellow solid; isolated yield 87% (484 mg). R_f 0.30 (PE/EtOAc, 5:1); mp 92.2–92.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78–6.97 (m, 4H), 5.19 (s, 2H), 4.31 (q, J=8.0 Hz, 2H), 3.87 (s, 3H), 1.33 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.05, 161.31, 149.63, 147.47, 122.35, 120.72, 114.42, 112.13, 75.23, 72.17, 61.93, 55.96, 14.41 ppm; MS (ESI): m/z 301 $[M+Na]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_5$ 279.0975, found 279.0972.

*4.2.11. Ethyl 2-diazo-4-(3-methoxyphenoxy)-3-oxobutanoate (**1k**).* Yellow solid; isolated yield 82% (456 mg). R_f 0.31 (PE/EtOAc, 5:1); mp 59.0–59.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, J=8.0 Hz, 1H), 6.47–6.58 (m, 3H), 5.12 (s, 2H), 4.33 (q, J=7.1 Hz, 2H), 3.78 (s, 3H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.00, 161.29, 160.95, 159.32, 130.03, 107.42, 106.73, 101.65, 76.90, 71.18, 62.03, 55.44, 14.48 ppm; MS (ESI): m/z 342 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_5$ 279.0975, found 279.0980.

*4.2.12. Ethyl 2-diazo-3-oxo-4-(o-tolyloxy)butanoate(**1l**).* Light yellow solid; isolated yield 82% (430 mg). R_f 0.45 (PE/EtOAc, 6:1); mp 77.0–77.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J=7.7 Hz, 1H), 7.11 (t, J=8.0, 8.0 Hz, 1H), 6.89 (t, J=8.0, 7.7 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 5.16 (s, 2H), 4.34 (q, J=8.0 Hz, 2H), 2.31 (s, 3H), 1.35 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.40, 161.34, 156.35, 131.11, 127.41, 126.77, 121.43, 111.65, 71.53, 62.01, 16.39, 14.48 ppm; MS (ESI): m/z 326 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_4$ 263.1026, found 263.1021.

*4.2.13. Ethyl2-diazo-4-(2,3-dimethylphenoxy)-3-oxobutanoate (**1m**).* Yellow solid; isolated yield 85% (469 mg). R_f 0.35 (PE/EtOAc, 7:1); mp 71.0–71.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 (t, J=8.0, 8.0 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.59 (d, J=8.0 Hz, 1H), 5.14 (s, 2H), 4.33 (q, J=8.0 Hz, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.35 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.51, 161.34, 156.14, 138.41, 125.90, 125.78, 123.30, 109.61, 71.85, 61.98, 20.22, 14.47, 11.89 ppm; MS (ESI): m/z 340 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4$ 277.1183, found 277.1188.

*4.2.14. Ethyl 2-diazo-4-(3,4-dimethylphenoxy)-3-oxobutanoate (**1n**).* Yellow solid; isolated yield 84% (464 mg). R_f 0.32 (PE/EtOAc, 7:1); mp 72.0–72.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, J=12.0 Hz, 1H), 6.75 (d, J=4.0 Hz, 1H), 6.65 (dd, J=12.0, 4.0 Hz, 1H), 5.10 (s, 2H), 4.34 (q, J=8.0 Hz, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 1.36 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.41, 161.37, 156.23, 137.96, 130.42, 129.74, 116.53, 111.79, 71.39, 62.00, 20.18, 18.97, 14.48 ppm; MS (ESI): m/z 340 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4$ 277.1183, found 277.1189.

*4.2.15. Ethyl 4-(benzo[d][1,3]dioxol-5-yloxy)-2-diazo-3-oxobutanoate (**1o**).* Light yellow solid; isolated yield 88% (514 mg). R_f 0.30 (PE/EtOAc, 5:1); mp 93.1–93.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (d, J=8.5 Hz, 1H), 6.54 (d, J=2.5 Hz, 1H), 6.33 (dd, J=8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 5.06 (s, 2H), 4.32 (q, J=8.5 Hz, 2H), 1.35 (t, J=8.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.23, 161.26, 153.65, 148.38, 142.45, 107.99, 106.39, 101.39, 98.77, 76.91, 72.29, 62.01, 14.46 ppm; MS (ESI): m/z 315 $[M+Na]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_2O_6$ 293.0768, found 293.0763.

*4.2.16. Ethyl 2-diazo-4-(naphthalen-1-yloxy)-3-oxobutanoate (**1p**).* Purple solid; isolated yield 83% (494 mg). R_f 0.32 (PE/EtOAc, 5:1); mp 131.1–131.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38–8.42 (m, 1H), 7.78–7.82 (m, 1H), 7.45–7.52 (m, 3H), 7.34 (t, J=8.8 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 5.33 (s, 2H), 4.35 (q, J=8.0 Hz, 2H), 1.36 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.88, 161.38, 153.99, 134.74, 127.51, 126.69, 125.80, 125.64, 125.59, 122.41, 121.40, 105.57, 71.57, 62.07, 14.50 ppm; MS (ESI): m/z 362 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_4$ 299.1026, found 299.1022.

*4.2.17. Ethyl 2-diazo-4-(2,6-dimethylphenoxy)-3-oxobutanoate (**1q**).* Colorless solid; isolated yield 82% (452 mg). R_f 0.35 (PE/EtOAc, 6:1); mp 72–72.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91–7.00

(m, 3H), 4.92 (s, 2H), 4.27 (q, J=8.0 Hz, 2H), 2.28 (s, 6H), 1.31 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.31, 161.24, 155.59, 130.86, 129.00, 124.42, 75.14, 74.90, 61.79, 16.37, 14.44 ppm; MS (ESI): m/z 340 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4$ 277.1183, found 277.1185.

*4.2.18. Isopropyl 2-diazo-3-oxo-4-phenoxybutanoate (**1r**).* Yellow solid; isolated yield 75% (393 mg). R_f 0.36 (PE/EtOAc, 6:1); mp 72.3–72.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J=8.0 Hz, 2H), 6.97 (t, J=8.0 Hz, 1H), 6.93 (d, J=8.0 Hz, 2H), 5.15–5.23 (m, 1H), 5.14 (s, 2H), 1.34 (d, J=4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.22, 160.91, 158.11, 129.62, 121.70, 114.94, 75.67, 71.21, 70.21, 22.09 ppm; MS (ESI): m/z 326 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_4$ 263.1026, found 263.1031.

*4.2.19. tert-Butyl 2-diazo-3-oxo-4-phenoxybutanoate (**1s**).* Yellow solid; isolated yield 71% (392 mg). R_f 0.39 (PE/EtOAc, 6:1); mp 78.1–78.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J=8.0 Hz, 2H), 6.97 (t, J=8.0 Hz, 1H), 6.93 (d, J=8.0 Hz, 2H), 5.11 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.42, 160.52, 158.15, 129.61, 121.67, 114.99, 84.10, 76.26, 71.23, 28.45 ppm; MS (ESI): m/z 340 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4$ 277.1183, found 277.1180.

*4.2.20. Ethyl 2-diazo-3-oxo-5-phenoxypentanoate (**1t**).* Yellow solid; isolated yield 84% (440 mg). R_f 0.41 (PE/EtOAc, 6:1); mp 68.1–68.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.33 (m, 2H), 6.86–6.99 (m, 3H), 4.32–4.37 (m, 4H), 3.39 (t, J=7.0 Hz, 2H), 1.37 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.15, 161.38, 158.74, 129.54, 121.02, 114.76, 76.91, 62.84, 61.71, 40.02, 14.48 ppm; MS (ESI): m/z 326 $[M+Na+CH_3CN]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_4$ 263.1026, found 263.1028.

*4.2.21. Ethyl 2-diazo-3-oxo-4-(p-tolylthio)butanoate (**1u**).* Light yellow liquid; isolated yield 94% (520 mg); R_f 0.33 (PE/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, J=1.6, 6.4 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 4.30 (q, J=6.4 Hz, 2H), 4.08 (s, 2H), 2.31 (s, 3H), 1.33 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.17, 161.06, 137.28, 131.10, 130.91, 129.76, 61.69, 42.14, 21.06, 14.28 ppm; MS (ESI): m/z 279 $[M+H]^+$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_3S$ 279.0803, found 279.0800.

4.3. General procedure for the $Rh_2(esp)_2$-catalyzed aromatic C–H insertion

A solution of α-diazo-β-ketoester (0.5 mmol) in CH_2Cl_2 (5 mL) is added via syringe pump at a rate of 5–10 mL/h to a stirred solution of $Rh_2(esp)_2$ (2 mg, 0.5 mol %) in anhydrous CH_2Cl_2 (5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was continued stirring for another hour upon the completion of addition. After evaporating all the volatiles, the residue was purified by flash column chromatography eluting with the mixture of petroleum ether and ethyl acetate (50:1).

*4.3.1. Ethyl 3-hydroxy-2H-chromene-4-carboxylate (**2a**).* Light yellow solid; isolated yield 90% (100 mg). R_f 0.55 (PE/EtOAc, 10:1); mp 57.6–57.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H), 7.78 (dd, J=7.9, 1.6 Hz, 1H), 7.07 (dt, J=7.9, 1.6 Hz, 1H), 6.98 (dt, J=7.9, 1.4 Hz, 1H), 6.91 (dd, J=7.9, 1.4 Hz, 1H), 4.65 (s, 2H), 4.43 (q, J=7.1 Hz, 2H), 1.44 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.01, 169.45, 151.40, 126.60, 125.85, 122.34, 120.12, 116.50, 97.20, 66.07, 61.65, 14.39 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}O_4$ 221.0808, found 221.0805.

*4.3.2. Ethyl 6-chloro-3-hydroxy-2H-chromene-4-carboxylate (**2b**).* Yellow solid; isolated yield 86% (109 mg). R_f 0.51 (PE/EtOAc, 10:1); mp 103.0–103.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.07 (s, 1H), 7.77 (d, J=2.4 Hz, 1H), 7.01 (dd, J=8.5, 2.4 Hz, 1H), 6.82 (d, J=8.5 Hz, 1H), 4.64 (s, 2H), 4.44 (q, J=7.1 Hz, 2H), 1.45 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.60, 170.05, 149.81, 127.31, 126.16, 125.68, 121.57, 117.56, 96.65, 66.09, 61.95, 14.32 ppm; MS (ESI): m/z 253 $[M-H]^-$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}ClO_4$ 255.0419, found 255.0420.

*4.3.3. Ethyl 3-hydroxy-6-iodo-2H-chromene-4-carboxylate (**2c**).* Colorless solid; isolated yield 82% (142 mg). R_f 0.60 (PE/EtOAc, 10:1); mp 78.2–78.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (s, 1H), 8.10 (d, J=2.1 Hz, 1H), 7.33 (dd, J=8.4, 2.1 Hz, 1H), 6.65 (d, J=8.4 Hz, 1H), 4.64 (s, 2H), 4.43 (q, J=7.1 Hz, 2H), 1.45 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.54, 169.75, 151.14, 135.18, 134.52, 122.50, 118.57, 96.33, 85.14, 66.00, 61.96, 14.25 ppm; MS (ESI) m/z 345 $[M-H]^-$; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{12}IO_4$ 346.9775, found 346.9779.

*4.3.4. Ethyl 6-fluoro-3-hydroxy-2H-chromene-4-carboxylate (**2d**).* Colorless solid; isolated yield 81% (96 mg). R_f 0.62 (PE/EtOAc, 10:1); mp 75.1–75.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.08 (s, 1H), 7.49–7.53 (m, 1H), 6.81–6.85 (m, 1H), 6.72–6.77 (m, 1H), 4.62 (s, 2H), 4.44 (q, J=7.1 Hz, 2H), 1.45 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.66, 170.44, 158.14 (d, $^1J_{C-F}$=237.0 Hz), 147.18 (d, $^4J_{C-F}$=1.5 Hz), 121.41 (d, $^3J_{C-F}$=9.5 Hz), 117.06 (d, $^3J_{C-F}$=8.9 Hz), 112.67 (d, $^2J_{C-F}$=13.7 Hz), 112.47 (d, $^2J_{C-F}$=10.3 Hz), 96.89 (d, $^4J_{C-F}$=1.0 Hz), 66.19, 61.89, 14.35 ppm; MS (ESI): m/z 237 $[M-H]^-$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}FO_4$ 239.0714 found 239.0717.

*4.3.5. Ethyl 3-hydroxy-6-methoxy-2H-chromene-4-carboxylate (**2e**).* Gray solid; isolated yield 97% (121 mg). R_f 0.45 (PE/EtOAc, 10:1); mp 58.2–59.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.02 (s, 1H), 7.39 (d, J=4.0 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 6.61 (dd, J=8.0, 4.0 Hz, 1H), 4.59 (s, 2H), 4.42 (q, J=6.0 Hz, 2H), 3.78 (s, 3H), 1.44 (t, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 170.41, 154.78, 145.34, 120.98, 116.73, 111.80, 111.32, 97.24, 66.29, 61.64, 55.73, 14.37 ppm; MS (ESI): m/z 249 $[M-H]^-$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}O_5$ 251.0914, found 251.0915.

*4.3.6. Ethyl 6-(tert-butyl)-3-hydroxy-2H-chromene-4-carboxylate (**2f**).* Yellow solid; isolated yield 92% (127 mg). R_f 0.61 (PE/EtOAc, 10:1); mp 59.2–59.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.93 (s, 1H), 7.87 (d, J=2.4 Hz, 1H), 7.10 (dd, J=8.4, 2.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 4.63 (s, 2H), 4.41 (q, J=7.2 Hz, 2H), 1.46 (t, J=7.2 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.11, 169.37, 149.50, 128.30, 125.83, 123.58, 121.66, 119.70, 97.34, 65.99, 61.57, 16.10, 14.37 ppm; MS (ESI): m/z 275 $[M-H]^-$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{21}O_4$ 277.1434, found 277.1438.

*4.3.7. Ethyl 3-hydroxy-6-phenyl-2H-chromene-4-carboxylate (**2g**).* Colorless solid; isolated yield 90% (133 mg). R_f 0.45 (PE/EtOAc, 10:1); mp 69.0–69.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.04 (s, 1H), 8.09 (d, J=2.1 Hz, 1H), 7.56–7.58 (m, 2H), 7.45 (t, J=7.6 Hz, 2H), 7.31–7.36 (m, 2H), 6.99 (d, J=8.3 Hz, 1H), 4.70 (s, 2H), 4.45 (q, J=7.1 Hz, 2H), 1.47 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 169.59, 150.93, 141.37, 135.32, 128.86, 126.90, 126.86, 125.26, 124.76, 120.25, 116.71, 97.15, 66.14, 61.70, 14.36 ppm; MS (ESI): m/z 295 $[M-H]^-$; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{17}O_4$ 297.1121, found 297.1123.

*4.3.8. Ethyl 8-chloro-3-hydroxy-2H-chromene-4-carboxylate (**2h**).* Colorless solid; isolated yield 85% (108 mg). R_f 0.54 (PE/EtOAc, 10:1); mp 73.3–73.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.05 (s, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.13 (d, J=8.0 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 4.74 (s, 2H), 4.43 (q, J=7.1 Hz, 2H), 1.43 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.70, 169.55, 147.05, 127.30, 124.25,

122.53, 121.78, 121.72, 96.97, 66.34, 61.88, 14.35 ppm; MS (ESI): *m/z* 253 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}ClO_4$ 255.0419, found 255.0420.

*4.3.9. Ethyl 3-hydroxy-8-iodo-2H-chromene-4-carboxylate (**2i**).* Colorless solid; isolated yield 83% (143 mg). R_f 0.43 (PE/EtOAc, 10:1); mp 82.1–82.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (s, 1H), 7.75 (dd, *J*=7.9, 1.4 Hz, 1H), 7.51 (dd, *J*=7.9, 1.4 Hz, 1H), 6.73 (t, *J*=7.9 Hz, 1H), 4.73 (s, 2H), 4.42 (q, *J*=7.1 Hz, 2H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.62, 169.58, 150.38, 136.18, 126.02, 123.94, 120.82, 96.92, 84.33, 66.54, 61.87, 14.36 ppm; MS (ESI): *m/z* 344.9 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}IO_4$ 346.9775, found 346.9778.

*4.3.10. Ethyl 3-hydroxy-8-methoxy-2H-chromene-4-carboxylate (**2j**).* Light yellow solid; isolated yield 95% (118 mg). R_f 0.46 (PE/EtOAc, 10:1); mp 77.3–77.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.01 (s, 1H), 7.41 (d, *J*=8.1 Hz, 1H), 6.93 (t, *J*=8.1 Hz, 1H), 6.75 (d, *J*=8.1 Hz, 1H), 4.70 (s, 2H), 4.41 (q, *J*=7.1 Hz, 2H), 3.87 (s, 3H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 169.59, 148.33, 140.28, 121.93, 121.13, 118.13, 109.67, 97.15, 66.30, 61.64, 56.13, 14.33 ppm; MS (ESI): *m/z* 249 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}O_5$ 251.0914, found 251.0910.

*4.3.11. Ethyl 3-hydroxy-7-methoxy-2H-chromene-4-carboxylate (**2k**).* Colorless solid; isolated yield 96% (120 mg). R_f 0.47 (PE/EtOAc, 10:1); mp 56.1–56.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.76 (s, 1H), 7.69 (d, *J*=8.0 Hz, 1H), 6.56 (dd, *J*=8.0, 4.0 Hz, 1H), 6.49 (d, *J*=4.0 Hz, 1H), 4.63 (s, 2H), 4.41 (q, *J*=8.0 Hz, 2H), 3.78 (s, 3H), 1.43 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 167.38, 158.52, 152.59, 126.49, 112.73, 108.07, 102.41, 97.10, 66.19, 61.54, 55.49, 14.39 ppm; MS (ESI): *m/z* 249 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}O_5$ 251.0914, found 251.0916.

*4.3.12. Ethyl 3-hydroxy-8-methyl-2H-chromene-4-carboxylate (**2l**).* Colorless solid; isolated yield 93% (108 mg). R_f 0.6 (PE/EtOAc, 10:1); mp 71.2–71.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.95 (s, 1H), 7.62 (d, *J*=7.8 Hz, 1H), 6.96 (d, *J*=7.8 Hz, 1H), 6.89 (t, *J*=7.8 Hz, 1H), 4.65 (s, 2H), 4.42 (q, *J*=7.1 Hz, 2H), 2.22 (s, 3H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.11, 169.37, 149.50, 128.30, 125.83, 123.58, 121.66, 119.70, 97.34, 65.99, 61.57, 16.10, 14.37 ppm; MS (ESI): *m/z* 233 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}O_4$ 235.0965, found 235.0969.

*4.3.13. Ethyl 3-hydroxy-7,8-dimethyl-2H-chromene-4-carboxylate (**2m**).* Colorless solid; isolated yield 88% (109 mg). R_f 0.6 (PE/EtOAc, 10:1); mp 57.2–57.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.82 (s, 1H), 7.51 (d, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 4.62 (s, 2H), 4.41 (q, *J*=8.0 Hz, 2H), 2.25 (s, 3H), 2.15 (s, 3H), 1.42 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.12, 168.79, 149.42, 135.64, 124.47, 123.20, 122.73, 117.41, 97.50, 66.10, 61.48, 19.89, 14.37, 11.90 ppm; MS (ESI) *m/z* 247 $[M-H]^-$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_4$ 249.1121, found 249.1125.

*4.3.14. Ethyl 3-hydroxy-6,7-dimethyl-2H-chromene-4-carboxylate (**2n**).* Colorless solid; isolated yield 91% (113 mg). R_f 0.63 (PE/EtOAc, 10:1); mp 68.2–68.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.82 (s, 1H), 7.54 (s, 1H), 6.70 (s, 1H), 4.59 (s, 2H), 4.42 (q, *J*=7.1 Hz, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.44 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.98, 168.82, 149.39, 135.04, 130.09, 126.82, 117.43, 117.32, 97.13, 66.18, 61.53, 19.65, 19.62, 14.35 ppm; MS (ESI): *m/z* 247 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_4$ 249.1121, found 249.1125.

*4.3.15. Ethyl 7-hydroxy-6H-[1,3]dioxolo[4,5-g]chromene-8-carboxylate (**2o**).* Light yellow solid; isolated yield 94% (124 mg). R_f 0.52 (PE/EtOAc, 10:1); mp 79.0–79.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.80 (s, 1H), 7.29 (s, 1H), 6.49 (s, 1H), 5.91 (s, 2H), 4.56 (s, 2H), 4.41 (q, *J*=8.0 Hz, 2H), 1.42 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.71, 168.14, 146.51, 145.45, 142.72, 112.88, 105.87, 101.25, 99.00, 97.35, 66.41, 61.65, 14.39 ppm; MS (ESI): *m/z* 263 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{13}O_6$ 265.0707, found 265.0710.

*4.3.16. Ethyl 3-hydroxy-2H-benzo[h]chromene-4-carboxylate (**2p**).* Light yellow solid; isolated yield 91% (123 mg). R_f 0.55 (PE/EtOAc, 10:1); mp 69.1–69.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.98 (s, 1H), 8.13–8.16 (m, 1H), 7.94 (d, *J*=8.8 Hz, 1H), 7.75–7.77 (m, 1H), 7.40–7.49 (m, 3H), 4.83 (s, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 1.46 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.94, 168.93, 146.21, 132.63, 127.44, 125.94, 125.77, 124.70, 123.88, 121.76, 121.38, 115.05, 97.63, 66.49, 61.67, 14.42 ppm; MS (ESI): *m/z* 269 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_4$ 271.0965, found 271.0969.

*4.3.17. Isopropyl 3-hydroxy-2H-chromene-4-carboxylate (**2r**).* Colorless solid; isolated yield 82% (96 mg). R_f 0.6 (PE/EtOAc, 10:1); mp 65.1–65.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (s, 1H), 7.78 (dd, *J*=7.9, 1.6 Hz, 1H), 7.07 (dt, *J*=7.9, 1.6 Hz, 1H), 6.98 (dt, *J*=7.9, 1.4 Hz, 1H), 6.90 (dd, *J*=7.9, 1.4 Hz, 1H), 5.26–5.35 (m, 1H), 4.64 (s, 2H), 1.41 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.58, 169.40, 151.37, 126.50, 125.82, 122.32, 120.29, 116.48, 97.32, 69.76, 66.08, 22.09 ppm; MS (ESI): *m/z* 235 $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}O_4$ 235.0965, found 235.0961.

*4.3.18. tert-Butyl 3-hydroxy-2H-chromene-4-carboxylate (**2s**).* Colorless solid: isolated yield 85% (105 mg). R_f 0.62 (PE/EtOAc, 10:1); mp 81.2–81.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.19 (s, 1H), 7.77 (d, *J*=7.9 Hz, 1H), 7.06 (t, *J*=7.9 Hz, 1H), 6.96 (t, *J*=7.9 Hz, 1H), 6.90 (d, *J*=7.9 Hz, 1H), 4.62 (s, 2H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.58, 169.11, 151.44, 126.35, 125.82, 122.19, 120.59, 116.44, 97.99, 83.75, 66.12, 28.52 ppm; MS (ESI): *m/z* 247 $[M-H]^-$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_4$ 249.1121, found 249.1119.

4.4. Preparation of compounds 3–5

*4.4.1. chroman-3-one (**3**).* The mixture of **2a** (44 mg, 0.2 mmol) and Ph_2O (400 mg) was heated to 210 °C under argon for 30 min. After cooling to the room temperature, the residue was purified on silica gel (PE/EtOAc, 30:1) to get the product as a colorless oil (25 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.22 (m, 1H), 7.14–7.12 (m, 1H), 7.06 (d, *J*=7.6 Hz, 2H), 4.41 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.74, 154.65, 129.08, 128.58, 123.45, 121.63, 117.80, 73.08, 41.03 ppm. The date of the compound is identical with the described date of the reference.[16]

*4.4.2. 3-Amino-4,5-dihydro-1H-chromeno[3,4-d]pyrimidin-1-one (**4**).* The sodium metal (10 mg, 0.4 mmol) was added to absolute EtOH (400 μL) at room temperature and stirred for 30 min until the solid was dissolved. Guanidine hydrochloride (28.5 mg, 0.3 mmol) and **2a** (44 mg, 0.2 mmol) were added to the solution and raise the temperature to 80 °C with stirring overnight. Saturated aqueous NH_4Cl solution (1 mL) was added to neutralize the reaction. The resulting mixture was extracted with EtOAc (10 mL×2), washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (CH_2Cl_2/MeOH, 30:1) to get the product as a colorless solid (37 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H), 8.38 (dd, *J*=1.6, 7.6 Hz, 1H), 7.05–7.02 (m, 1H), 6.94–6.90 (m, 1H), 6.84–6.82 (m, 2H), 4.75 (s, 2H), 3.17 (d, *J*=5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.47, 158.96, 155.29, 151.39, 126.31, 124.72, 121.48, 120.70, 115.55, 101.70, 67.92 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_2$ 216.0773, found 216.0767.

*4.4.3. trans-Ethyl 3-hydroxychroman-4-carboxylate (**5**).* To a solution of **2a** (66 mg, 0.3 mmol) in methanol (1 mL) was added sodium borohydride (35 mg, 0.9 mmol) at 0 °C. After stirring for 30 min, the reaction was stopped by the addition of water (1 mL). The resulting mixture was extracted with EtOAc (10 mL×2), washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (PE/EtOAc, 5:1) to get the product as a colorless oil (60 mg, 90%). The crude proton NMR showed a 5:1 ratio of a trans/cis mixture. The *trans*-product was demonstrated by the HSQC/HMBC assignment and further cross peaks identification of NOESY (see Supplementary data). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.18 (m, 2H), 6.93–6.87 (m, 2H), 4.34–4.28 (m, 1H), 4.22 (q, J=7.2 Hz, 2H), 4.15–4.13 (m, 1H), 4.03 (d, J=4.4 Hz, 1H), 3.28 (d, J=7.2 Hz, 1H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.39, 153.73, 130.29, 129.05, 121.02, 117.12, 117.00, 67.40, 64.22, 61.65, 46.13, 14.26 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{15}O_4$ 223.0970, found 223.0960.

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Supplementary data

These data include all the NMR data of compounds **1a**–**u**, **2a**–**r**, and **3**–**5** described in this article. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.093.

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