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Synthesis of Functionalized Coumarins and Quinolinones by NHC-Catalyzed Annulation of Modified Enals with Heterocyclic C−H Acids

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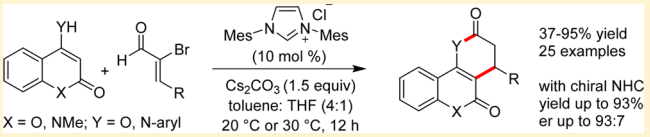
Supporting Information

ABSTRACT: N-Heterocyclic carbene (NHC) catalyzed lactonization and lactamization of 2-bromoenals with heterocyclic C−H acids proceeding via the α,β-unsaturated acyl azolium intermediates is reported. The reaction furnished coumarin- or quinolinone-fused lactone/lactam derivatives. In addition, results of the enantioselective version of this reaction using chiral NHC are presented.



The coumarin core is one of the characteristic structural motifs present in a variety of biologically active natural products and numerous pharmaceuticals.[1] Specifically, 4-hydroxycoumarin and their derivatives are valuable starting materials for the synthesis of natural products and drug molecules.[2] For instance, enantioselective organocatalytic conjugate addition of 4-hydroxycoumarin to α,β-unsaturated ketones is a straightforward method to access warfarin, which is a widely used anticoagulant (Figure 1).[3] Moreover, tioclomarol, a 4-hydroxycoumarin-derived second-generation drug, is employed as a rodenticide that is effective for the control of rodents.[4] Additionally, coumestan constitutes the essential core of a variety of natural compounds incorporating the coumarin moiety.[5] The possibility of wide range of biological properties make coumarins an interesting synthetic target. As a consequence, developing straightforward and flexible synthetic methods toward functionalized coumarins has attracted much attention from organic chemists.

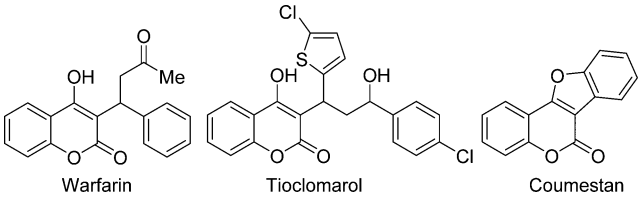
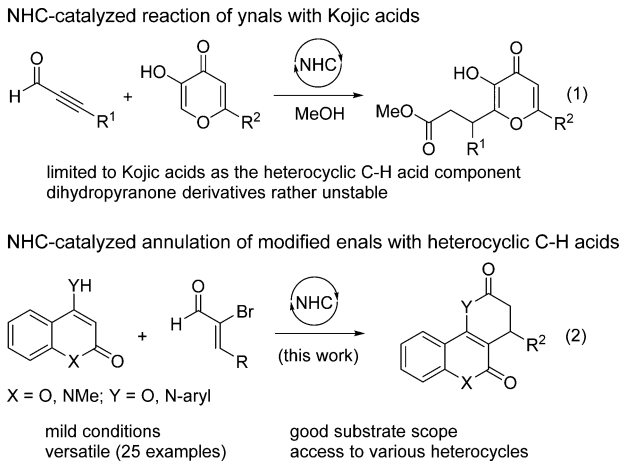


Figure 1. Selected drugs and natural product containing coumarin core.

Umpolung of aldehydes catalyzed by N-heterocyclic carbene (NHC) organocatalysis leading to the generation of nucleophilic acyl anion intermediates and homoenolate equivalents constitute an unconventional protocol for the construction of carbon−carbon and carbon−heteroatom bonds.[6] An important mode of action of NHCs that recently received immense attention is the generation of α,β-unsaturated acyl azoliums. NHC-catalyzed generation of α,β-unsaturated acyl azolium intermediates can be achieved from α,β-unsaturated enol esters or acyl fluorides,[7] enals under oxidative conditions,[8] ynals,[9] and 2-haloenals.[10] The nucleophilic coupling partners usually employed are alcohols, masked enolates, β-diketones, β-ketoesters, enamines, enolizable aldehydes, etc. Interestingly, however, the synthetic utility of heterocyclic C−H acids as nucleophile in α,β-unsaturated acyl azolium chemistry has received only scant attention.[8d,9b] In 2010, Bode and co-workers reported the enantioselective NHC-catalyzed reaction of ynals with Kojic acids, which proceeds via the Claisen rearrangement (Scheme 1, eq 1).[9b] However, the dihydropyranone products are rather unstable, and the stable ester product was obtained by the ring-opening of the dihydropyranones. Moreover, this reaction is limited only to Kojic acids as the heterocyclic C−H acid component.[11] Herein, we report the NHC-catalyzed reaction of 2-bromoenals with various heterocyclic C−H acids, and the reaction resulting in the practical

Scheme 1. NHC-Catalyzed Reaction of α,β-Unsaturated Aldehydes with Heterocyclic C−H Acids



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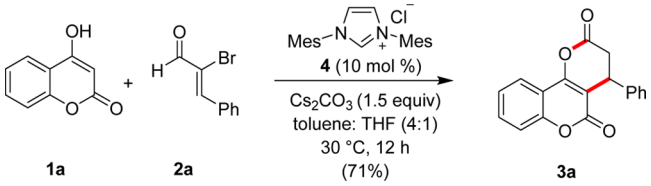
synthesis of coumarin/quinolinone fused dihydropyranones and dihydropyridinones (Scheme 1, eq 2).

Our present study commenced with the treatment of 4-hydroxycoumarin **1a** and α-bromo cinnamaldehyde **2a** with 10 mol % of imidazolium salt **4** and 1.1 equiv of the Cs_2CO_3. As anticipated, the reaction afforded the functionalized pyrano[3,2-*c*]chromene-2,5-dione derivative **3a** in 29% yield.[12] With this initial result, standard optimization studies were performed,[13] which revealed that the reaction carried out using a mixture of toluene and THF (4:1)[14] and an excess of Cs_2CO_3 (1.5 equiv) resulted in the formation of **3a** in 71% (Scheme 2).[15]

Scheme 2. NHC-Catalyzed Reaction of 4-Hydroxycoumarin with 2-Bromocinnamaldehyde

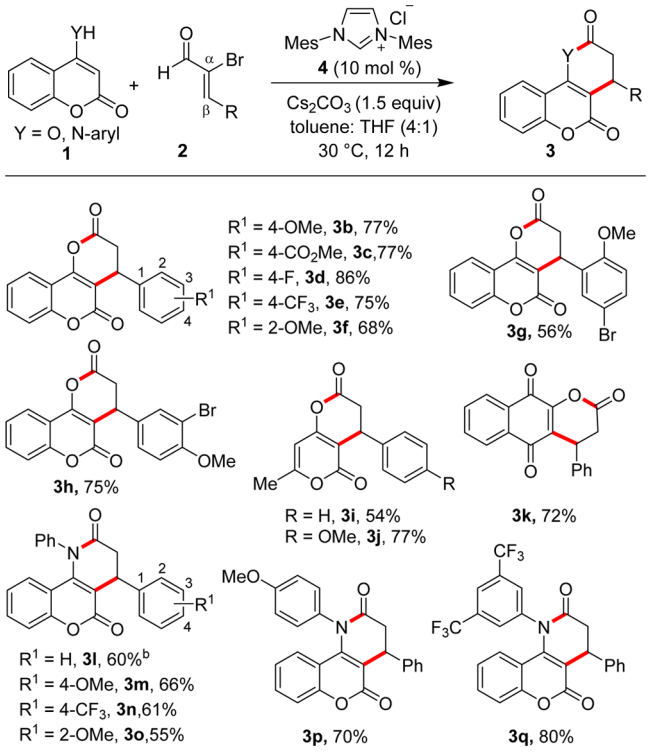


After optimizing the reaction conditions, we then studied the substrate scope of this interesting NHC-catalyzed annulation reaction (Table 1). In the beginning, we evaluated various 2-bromoenals. Various electron-donating or -withdrawing groups at the 4-position of the β-aryl ring of **2** were well tolerated, leading to coumarin-fused dihydropyranones in good yields (**3b**–**e**). Moreover, substitution at the 2-position of the β-aryl ring of **2** resulted in the smooth conversion to the product in good yield (**3f**). Additionally, 2-bromoenals with disubstitution on β-aryl ring furnished the desired product in moderate to good yields (**3g**, **3h**).[16] Furthermore, this novel annulation reaction is not limited to 4-hydroxycoumarin. Gratifyingly, 4-hydroxy-6-methyl-2-pyrone and 2-hydroxynaphthoquinone[17] were employed as the C–H acid component leading to the formation of the desired products (**3i**–**k**) in moderate to good yields, further expanding the scope of this annulation reaction.

Next, we focused our attention on various 4-(arylamino)-2*H*-chromen-2-one with a view to synthesize fused dihydropyridinones. As expected, the reaction of 4-(phenylamino)-chromenone **1l** with the parent bromoenal **2a** furnished the chromenone-fused dihydropyridinones **3l** in 60%. The reaction worked well with differently substituted 2-bromoenals furnishing the desired products in moderate to good yields (**3m**–**o**). In addition, electron releasing as well as electron-withdrawing group at the 4-(arylamino) moiety were well tolerated affording the fused dihydropyridinones in good yields (**3p**–**q**), thus considerably expanding the scope of this reaction.

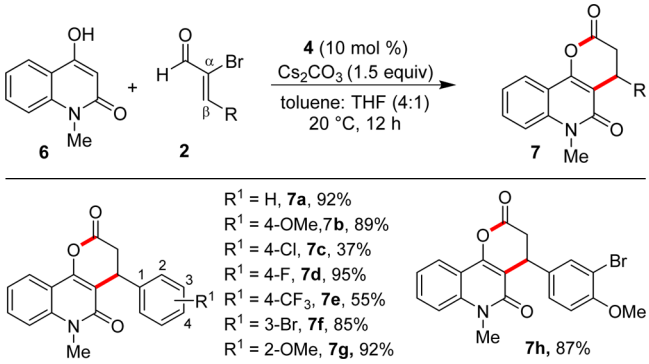
After examining the scope of the reaction with various coumarin-derived C–H acids, we then focused our attention on another class of heterocyclic C–H acids, namely 4-hydroxy-1-methylquinolin-2 (1*H*)-one **6**, with a view to construct quinolinone-fused dihydropyranones (Table 2). At the outset,

Table 1. Substrate Scope of the NHC-Catalyzed Annulation of Heterocyclic C–H Acids with 2-Bromoenals[a]



[a]General reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), **4** (10 mol %), Cs_2CO_3 (1.5 equiv), toluene/THF (4:1, 10 mL), 30 °C and 12 h. Yields of isolated products are given. [b]Reaction run using 15 mol % of **4**.

Table 2. Substrate Scope of the NHC-Catalyzed Annulation of Quinolinone-Derived C–H Acids with 2-Bromoenals[a]



[a]General reaction conditions: **6** (0.50 mmol), **2** (0.50 mmol), **4** (10 mol %), Cs_2CO_3 (1.5 equiv), toluene: THF (4:1, 10 mL), 20 °C, and 12 h. Yields of isolated products are provided.

treatment of 2-bromoenal **2a** with **6** in the presence of carbene generated from **4** using Cs_2CO_3 as base at 20 °C afforded the 2*H*-pyrano[3,2-*c*]quinoline-2,5(3*H*)-dione **7a** in 92% yield. Notably, this reaction worked at a lower temperature compared to the reaction of **2** with coumarin derivatives. Interestingly, the reaction worked well with a variety of electron-releasing and -withdrawing groups at various positions of the β-aryl ring of **2**. In all cases, the quinolinone-fused dihydropyranone derivatives were isolated in moderate to good yields (**7b**–**h**).[18]

Further insightful experiments have shed light on the mechanism of this new transformation. Competition experiments carried out using 4-hydroxycoumarin and differently substituted 2-bromoenals showed that the rate of the reaction increases in the order **2b** (4-OMe) < **2a** (4-H) < **2e** (4-CF_3), with **2e** reacting approximately 4 times faster than **2b** under optimized conditions (Scheme 3).[13] This finding suggests that the presence of electron-withdrawing group at the β-aryl group of **2** makes the α,β-unsaturated acyl azolium more electrophilic

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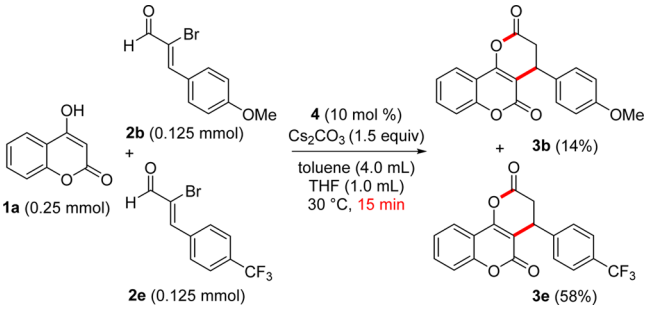
Scheme 3. Competition Experiment[a]

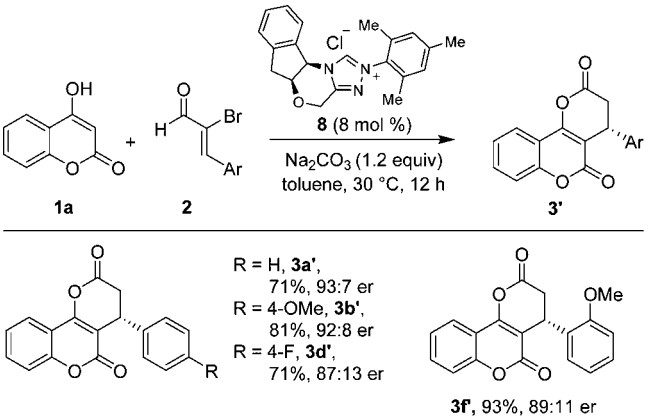


[a]The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard.

and facilitates efficient nucleophilic addition of **1a**. This also indicates the probable role of electronic nature of 2-bromoenals in the rate-determining step.

In addition, we have carried out experiments on the asymmetric version of this NHC-catalyzed annulation between 2-bromoenals and heterocyclic C−H acids. Treatment of 4-hydroxy coumarin **1a** and 2-bromoenal **2a** in the presence chiral triazolium salt **8**[19] and 1.2 equiv of Na_2CO_3 resulted in the formation of (*R*)-pyrano[3,2-*c*]chromene-2,5-dione derivative **3a′** in 75% yield and a promising 93:7 er (Table 3).[20]

Table 3. Enantioselective Synthesis of Functionalized Coumarins[a]



[a]General reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), **8** (8 mol %), Na_2CO_3 (1.2 equiv), toluene (1.0 mL), 30 °C, and 12 h.

Interestingly, electron-donating or -withdrawing groups at the 4-position of the *β*-aromatic ring of **2** were well tolerated, leading to fused-dihydropyranones in good yields and with moderate er values (**3b′**, **3d′**). Moreover, substitution at 2-position of *β*-aryl was also well tolerated (**3f′**).

In conclusion, we have developed the NHC-organocatalyzed reaction of 2-bromoenals with heterocyclic C−H acids leading to the formation of coumarin/quinolinone-fused dihydropyranone/dihydropyridinone derivatives. The reaction proceeds via the generation of *α,β*-unsaturated acylazolium intermediates.[21] Moreover, the results on the enantioselective version of this reaction are also presented.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. The 2-bromoenals were synthesized from the corresponding *α,β*-unsaturated aldehydes following the literature procedure.[22] The imidazolium salt **4** and triazolium salt **8** were synthesized following the literature procedure.[19a,23] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent. Chemical shifts (*δ*) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: *δ*H = 7.26 ppm, *δ*C = 77.16 ppm). HRMS measurements were carried out using ESI method and ion-trap mass analyzer.

General Procedure for the Synthesis of Functionalized Coumarins. To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken imidazolium salt **4** (17.5 mg, 0.05 mmol), Cs_2CO_3 (244 mg, 1.5 equiv), 2-bromoenal **2** (0.50 mmol), and coumarin derivative **1** (0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene/THF (4:1, 10.0 mL) under argon atmosphere, and mixture was stirred at 30 °C for 12 h. When the reaction was complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized coumarins (**3**).

*4-Phenyl-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (**3a**):*[20a] white solid (104.0 mg, 71%); R_f (petroleum ether/EtOAc = 70/30) 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (dd, J_1 = 1.7 Hz, J_2 = 8.2 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.39−7.24 (m, 7H), 4.53 (d, *J* = 7.3 Hz, 1H) 3.24−3.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.4, 160.9, 157.4, 153.3, 139.5, 133.1, 129.4, 128.2, 126.8, 124.8, 122.9, 117.0, 113.7, 106.5, 36.1, 36.0; HRMS calcd $[M + Na]^+$ for $C_{18}H_{12}O_4Na$ 315.0628, found 315.0624; FTIR (cm^{-1}) 3065, 3028, 2924, 1793, 1722, 1645, 1609, 1578, 1456, 1328, 1108, 906, 757, 699, 637.

*4-(4-Methoxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-c]-chromene-2,5-dione (**3b**):*[24] white solid (124.0 mg, 77%); R_f (petroleum ether/EtOAc = 70/30) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.91(dd, J_1 = 8.3 Hz, J_2 = 8.3 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.39−7.35 (m, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.48 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.21−3.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.6, 160.9, 159.4, 157.1, 153.3, 133.09, 131.5, 127.9, 124.77, 122.9, 117.0, 114.7, 113.7, 106.8, 55.4, 36.3, 35.3; HRMS calcd $[M + Na]^+$ for $C_{19}H_{14}O_5Na$ 345.0731, found 345.0729; FTIR (cm^{-1}) 2925, 2853, 1792, 1721, 1644, 1609, 1379, 1251, 1105, 1034, 983, 760, 637.

*Methyl 4-(2,5-dioxo-3,4-dihydro-2H,5H-pyrano[3,2-c]chromen-4-yl)benzoate (**3c**):* white solid (135.0 mg, 77%); R_f (petroleum ether/EtOAc = 70/30) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.98 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.40−7.37 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.58 (d, *J* = 7.5 Hz, 1H), 3.88 (s, 3H, CH_3), 3.24 (dd, J_1 = 7.8 Hz, J_2 = 16.3 Hz, 1H), 3.14 (d, *J* = 16.2 Hz,1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.6, 163.9, 160.8, 157.7, 153.4, 144.45, 133.3, 130.7, 130.1, 126.9, 124.9, 123.0, 117.1, 113.5, 105.7, 52.3, 36.0, 35.8; HRMS calcd $[M + Na]^+$ for $C_{20}H_{14}O_6Na$ 373.0683, found 373.0679; FTIR (cm^{-1}) 3869, 3823, 3728, 3232, 3181, 2854, 2379, 1638, 1524, 1287, 1058, 988.

*4-(4-Fluorophenyl)-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (**3d**):* white solid (133.0 mg, 86%); R_f (petroleum ether/EtOAc = 70/30) 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.59 (dd, J_1 = 1.9 Hz, J_2 = 10.2 Hz, 1H), 8.24−8.19 (m, 1H), 7.94−7.88 (m, 2H), 7.74−7.70 (m, 2H), 7.47−7.41 (m, 2H), 4.35 (dd, J_1 = 2.0 Hz, J_2 = 9.5 Hz, 1H), 2.74 (dd, J_1 = 9.5 Hz, J_2 = 20.0 Hz, 1H), 2.61 (dd, J_1 = 2.0 Hz, J_2 = 20.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 185.9, 185.23 (d, *J* = 310.2), 181.7, 177.4, 172.3, 149.7 (d, *J* = 4.26), 147.2, 141.3 (d, *J* = 9.8), 136.8, 134.4, 127.0, 126.2, 126.00, 122.6, 113.6, 26.0, 24.9; HRMS calcd $[M + Na]^+$ for $C_{18}H_{11}FO_4Na$ 333.0534, found 333.0527; FTIR (cm^{-1}) 3065, 3028, 2924, 1793, 1722, 1645, 1609, 1578, 1456, 1328, 1108, 906, 757, 699, 637.

*4-(4-(Trifluoromethyl)phenyl)-3,4-dihydropyrano[3,2-c]-chromene-2,5-dione (**3e**):* white solid (135.2 mg, 75%); R_f (petroleum ether/EtOAc = 70/30) 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.94 (dd, J_1= 1.5 Hz, J_2 = 8.2 Hz, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.42−7.38 (m, 4H), 4.60 (d, *J* = 7.3 Hz, 1H), 3.29 (dd, J_1= 7.8 Hz, J_2 = 16.3 Hz, 1H), 3.17 (dd, J_1= 1.5 Hz, J_2 = 16.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.9, 160.8, 157.8, 153.4, 143.5, 133.5,

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127.33, 126.5 (q, J = 3.7 Hz), 125.0, 123.0, 117.2, 113.5, 105.6, 35.9, 35.8; HRMS calcd $[M + Na]^+$ for $C_{19}H_{11}O_4F_3Na$ 383.0502, found 383.0498; FTIR (cm^{-1}) 3179, 2863, 1617, 1326, 1164, 1118, 1069, 979.

*4-(2-Methoxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-c]-chromene-2,5-dione (**3f**):* white solid (110.0 mg, 68%); R_f (petroleum ether/EtOAc = 70/30) 0.56; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 8.6 Hz, 1H), 7.39−7.31 (m, 3H), 7.28−7.24 (m, 1H), 6.93 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 4.52 (d, J = 8.5 Hz, 1H), 3.74 (s, 3H), 3.20−3.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.0, 157.1, 156.8, 153.1, 132.6, 129.3, 127.3, 124.5, 122.9, 120.9, 116.8, 113.9, 110.8, 104.0, 54.3, 34.5, 34.2; HRMS calcd $[M + Na]^+$ for $C_{19}H_{14}O_5Na$ 345.0733, found 345.0726; FTIR (cm^{-1}) 3070, 3014, 2926, 2841, 1792, 1722, 1645, 1609, 1490, 1456, 1378, 1248, 1108, 992, 906, 810, 758, 638.

*4-(5-Bromo-2-methoxyphenyl)-3,4-dihydropyrano[3,2-c]-chromene-2,5-dione (**3g**):*[20a] white solid (112.0 mg, 56%); R_f (petroleum ether/EtOAc = 70/30) 0.54; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.3, 1H), 7.60 (t, J = 8.1 Hz, 1H), 7.39−7.32 (m, 4H), 4.44 (d, J = 8.6 Hz, 1H), 3.71 (s, 3H), 3.16 (dd, J_1 = 9.1 Hz, J_2 = 17.0 Hz, 1H), 3.02 (d, J = 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 160.9, 157.3, 156.3, 153.3, 133.0, 132.9, 132.1, 129.5, 124.7, 123.0, 117.0, 113.8, 113.2, 112.6, 103.4, 54.8, 34.2, 34.0. HRMS calcd $[M + Na]^+$ for $C_{19}H_{13}O_5BrNa$ 422.9839, found 422.9836; FTIR (cm^{-1}) 3014, 2926, 2842, 1793, 1721, 1645, 1490, 1512, 1490, 1456, 1378, 1327, 1250, 1108, 1031, 992, 759, 699.

*4-(3-Bromo-4-methoxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-c]-chromene-2,5-dione (**3h**);* white solid (150.1 mg, 75%); R_f (petroleum ether/EtOAc = 70/30) 0.40; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J_1 = 8.1 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.43−7.37 (m, 3H), 7.15 (dd, J_1 = 2.2 Hz, J_2 = 8.5 Hz, 1H) 6.83 (d, J = 8.5 Hz, 1H), 4.46 (d, J = 7.4 Hz, 1H), 3.85 (s, 3H), 3.22−3.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 160.8, 157.5, 155.8, 153.4, 133.2, 132.9, 131.8, 126.8, 123.0, 117.1, 112.5, 106.1, 56.4, 36.3, 35.0; HRMS calcd $[M + Na]^+$ for $C_{19}H_{13}O_5BrNa$ 422.9839, found 422.9838; FTIR (cm^{-1}) 3570, 3016, 2855, 1686, 1588, 1492, 1380, 1260, 1179, 1105, 1052, 983, 759.

*7-Methyl-4-phenyl-3,4-dihydropyrano[4,3-b]pyran-2,5-dione (**3i**):* white solid (69.2 mg, 54%); R_f (petroleum ether/EtOAc = 70/30) 0.30; ^1H NMR (400 MHz, $CDCl_3$)) δ 7.32−7.29 (m, 2H), 7.26−7.23 (m, 1H), 7.19(d, J = 7.2 Hz, 2H), 5.99 (s, 1H), 4.35 (dd, J_1 = 2.2 Hz, J_2 = 6.9 Hz 1H), 3.10−3.01 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.6, 162.6, 161.8, 139.8, 129.3, 128.0, 126.7, 103.4, 98.9, 36.1, 35.3, 20.2; HRMS calcd $[M + Na]^+$ for $C_{15}H_{12}O_4Na$ 279.0628, found 279.0624; FTIR (cm^{-1}) 2924, 1794, 1719, 1648, 1597, 1512, 1492, 1217, 1104, 1033, 953, 667.

*4-(4-Methoxyphenyl)-7-methyl-3,4-dihydro-2H,5H-pyrano[4,3-b]pyran-2,5-dione (**3j**):* white solid (110.3 mg, 77%); R_f (petroleum ether/EtOAc = 70/30) 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.98 (s, 1H), 4.29 (d, J = 6.9 Hz, 1H) 3.74 (s, 3H), 3.07−2.97 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.4, 162.6, 161.6, 159.2, 131.8, 127.7, 114.6, 103.7, 98.9, 55.3, 36.3, 34.5, 20.2. HRMS calcd $[M + Na]^+$ for $C_{16}H_{14}O_5Na$ 309.0733, found 309.0732; FTIR (cm^{-1}) 3736, 3554, 3399, 2972, 2382, 2162, 1791, 1690, 1652, 1593, 1250, 1185, 1056, 1002, 832.

*4-Phenyl-3,4-dihydro-2H-benzo[g]chromene-2,5,10-trione (**3k**):* white solid (110.0 mg, 72%); R_f (petroleum ether/EtOAc = 70/30) 0.61; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19−8.17 (m, 1H), 8.08−8.06 (m, 1H), 7.77−7.75 (m, 2H), 7.34−7.31 (m, 2H), 7.27−7.25 (m, 3H), 4.67−4.65 (m, 1H), 3.15−3.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 177.4, 164.1, 151.5, 138.9, 134.7, 134.3, 131.5, 131.0, 129.6, 128.3, 127.0, 126.9, 126.8, 125.8, 35.4, 34.3; HRMS calcd $[M + Na]^+$ for $C_{19}H_{12}O_4Na$ 327.0628, found 327.0623; FTIR (cm^{-1}) 3068, 3027, 2924, 2853, 1791, 1722, 1645, 1608, 1378, 1108, 991, 834, 758, 638, 607.

*1,4-Diphenyl-3,4-dihydro-2H-chromeno[4,3-b]pyridine-2,5(1H)-dione (**3l**):* white solid (110.3 mg, 60%); R_f (petroleum ether/EtOAc = 70/30) 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 12H), 6.86 (t, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.65 (d, J = 5.9 Hz, 1H), 3.28−3.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 161.2, 153.8, 147.9, 139.3, 139.1, 131.4, 129.4, 129.2, 128.2, 127.7, 126.9, 126.1, 123.6, 117.7, 114.76, 114.4, 38.7, 35.5; HRMS calcd $[M + Na]^+$ for $C_{24}H_{17}O_3NNa$ 390.1101, found 390.1104; FTIR (cm^{-1}) 1699, 1609, 1563, 1490, 1451, 1376, 1283, 1187, 1135, 1071, 1000, 756,687.

*4-(4-Methoxyphenyl)-1-phenyl-3,4-dihydro-2H-chromeno[4,3-b]-pyridine-2,5(1H)-dione (**3m**):* white solid (131.0 mg, 66%); R_f (petroleum ether/EtOAc = 70/30) 0.41; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 9H), 6.89−6.81 (m, 4H), 4.62 (dd, J_1 = 1.9 Hz, J_2 = 6.4 Hz, 1H), 3.76 (s, 3H, CH_3), 3.28−3.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 161.2, 159.0, 153.7, 147.6, 139.1, 131.3, 129.4, 128.2, 128.0, 126.0, 123.5, 117.6, 114.8, 114.8, 114.5, 55.3, 38.8, 34.8; HRMS calcd $[M + Na]^+$ for $C_{25}H_{19}O_4NNa$ 420.1206, found 420.1205; FTIR (cm^{-1}) 1704, 1611, 1564, 1511, 1454, 1420, 1375, 1334, 1298, 1248, 1185, 1137, 1071, 1036, 1004, 954, 833, 755, 719, 689, 653.

*1-Phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-chromeno[4,3-b]pyridine-2,5(1H)-dione (**3n**):* white solid (133.0 mg, 61%); R_f (petroleum ether/EtOAc = 70/30) 0.51; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56−7.50 (m, 5H), 7.40−7.26 (m, 6H), 6.87 (t, J = 7.9 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.70 (d, J = 6.3 Hz, 1H), 3.30 (dd, J_1 = 7.1 Hz, J_2 = 15.6 Hz, 1H), 3.18 (d, J_1 = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 161.0, 153.8, 148.3, 143.4, 138.8, 131.6, 130.3−129.7 (m), 129.5, 128.4, 127.4, 126.1, 125.1, 123.7, 122.9, 117.7, 114.5, 113.3, 38.4, 35.4; HRMS calcd $[M + Na]^+$ for $C_{25}H_{16}O_3NF_3Na$ 458.0974, found 458.0974; FTIR (cm^{-1}) 1702, 1658, 1612, 1532, 1490, 1441, 1373, 1322, 1248, 1116, 1066, 1008, 946, 843, 750, 711, 685.

*4-(2-Methoxyphenyl)-1-phenyl-3,4-dihydro-2H-chromeno[4,3-b]-pyridine-2,5(1H)-dione (**3o**):* white solid (110.2 mg, 55%); R_f (petroleum ether/EtOAc = 70/30) 0.60; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.33 (m, 6H), 7.23−7.14 (m, 3H), 6.89−6.78 (m, 4H), 4.88 (d, J = 7.1 Hz, 1H), 3.24−3.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 160.9, 157.3, 153.9, 149.1, 139.2, 131.2, 129.3, 129.1, 128.1, 127.2, 126.3, 126.2, 123.4, 120.6, 117.7, 114.8, 112.7, 111.1, 55.4, 37.7, 31.8; HRMS calcd $[M + Na]^+$ for $C_{25}H_{19}O_4NNa$ 420.1206, found 420.1210; FTIR (cm^{-1}) 1707, 1610, 1566, 1459, 1370, 1278, 1247, 1127, 995, 725.

*1-(4-Methoxyphenyl)-4-phenyl-3,4-dihydro-2H-chromeno[4,3-b]-pyridine-2,5(1H)-dione (**3p**):* white solid (139.0 mg, 70%); R_f (petroleum ether/EtOAc = 70/30) 0.37; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05−6.83 (m, 9H), 6.53−6.52 (m, 4H), 4.26 (dd, J_1 = 2.2 Hz, J_2 = 6.4 Hz, 1H), 3.44 (s, 3H, CH_3), 2.90−2.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 161.3, 159.1, 153.8, 147.9, 139.3, 136.4, 131.6, 131.3, 129.1, 127.6, 126.9, 126.2, 123.6, 117.6, 114.8, 114.7, 113.9, 55.6, 38.6, 35.4; HRMS calcd $[M + Na]^+$ for $C_{25}H_{19}O_4NNa$: 420.1206, found: 420.1206; FTIR (cm^{-1}) 1699, 1659, 1611, 1534, 1489, 1442, 1372, 1296, 1248, 1181, 1133, 1070, 1032, 1001, 946, 881, 830, 750, 688, 652.

*1-(3,5-Bis(trifluoromethyl)phenyl)-4-phenyl-3,4-dihydro-2H-chromeno[4,3-b]pyridine-2,5(1H)-dione (**3q**):* white solid (202.3 mg, 80%); R_f (petroleum ether/EtOAc = 70/30): 0.48; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.47−7.40 (m, 3H), 7.32−7.24 (m, 6H), 6.94 (t, J = 8.3 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 4.74 (dd, J_1 = 3.7 Hz, J_2 = 7.7 Hz, 1H), 3.28 (t, J = 3.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 160.7, 153.9, 146.6, 140.4, 138.6, 132.0, 129.4, 128.1, 126.7, 125.1, 124.1, 118.3, 116.7, 113.9, 38.5, 35.3; HRMS calcd $[M + Na]^+$ for $C_{26}H_{15}O_3NF_6Na$: 526.0848, found: 526.0851; FTIR (cm^{-1}) 1707, 1609, 1566, 1459, 1370, 1328, 1278, 1247, 1176, 1124, 993, 892, 845, 799.

General Procedure for the Synthesis of Functionalized Quinolinones. To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken imidazolium salt **4** (17.5 mg, 0.05 mmol), Cs_2CO_3 (244 mg, 1.5 equiv), 2-bromoenal **2** (0.50 mmol), and 4-hydroxy-1-methylquinolin-2(1*H*)-one **6** (0.5 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene/THF (4:1, 10.0 mL) under argon atmosphere, and mixture was stirred at 20 °C (water bath) for 12 h. When the reaction was complete, the solvent was evaporated and the

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crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized quinolinones (7).

*6-Methyl-4-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-2,5(6H)-dione (**7a**):* white solid (140.0 mg, 92%); R_f (petroleum ether/EtOAc = 70/30) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H), 7.75−7.66 (m, 1H), 7.43 (t, J = 8.5 Hz, 2H), 7.35−7.26 (m, 5H), 4.73 (dd, J_1 = 3.7 Hz, J_2 = 5.6 Hz, 1 H), 3.76 (s, 3H), 3.19−3.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 182.3, 173.2, 156.2, 155.1, 145.5, 142.3, 140.4, 139.4, 134.0, 123.1, 120.1, 26.3, 26.0, 18.1; HRMS calcd [M + Na]$^+$ for $C_{19}H_{15}O_3NNa$ 328.0944, found 328.0938; FTIR (cm^{-1}) 3026, 2924, 2852, 1793, 1719, 1646, 1609, 1491, 1378, 1327, 1107, 905.99, 827.76, 758.07, 666.56

*4-(4-Methoxyphenyl)-6-methyl-4,6-dihydro-2H-pyrano[3,2-c]-quinoline-2,5(3H)-dione (**7b**):* white solid (150.0 mg, 89%); R_f (petroleum ether/EtOAc = 70/30) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.65 (dd, J_1 = 2.6 Hz, J_2 = 6.4 Hz,1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.12−3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 161.3, 159.1, 153.6, 139.5, 132.5, 131.8, 128.0, 123.2, 122.6, 114.6, 114.4, 113.9, 111.9, 55.4, 36.6, 35.5, 29.9; HRMS calcd [M + Na]$^+$ for $C_{20}H_{17}O_4NNa$ 358.1050, found 358.1046; FTIR (cm^{-1}) 3858, 3722, 3310, 2935, 2826, 2308, 1790, 1457, 1024.

*4-(4-Chlorophenyl)-6-methyl-4,6-dihydro-2H-pyrano[3,2-c]-quinoline-2,5(3H)-dione (**7c**):* white solid (63.0 mg, 37%); R_f (petroleum ether/EtOAc = 70/30) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.9 Hz, 1H), 7.69 (t, J = 8.3 Hz, 1H), 7.44 (d, J = 8.3, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.31−7.22 (m, 4H), 4.69(d, J= 6.8 Hz, 1H), 3.74 (s, 3H), 3.20−3.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.2, 154.1, 139.6, 138.9, 132.0, 128.4, 122.8, 114.5, 113.8, 111.0, 36.2, 35.7, 29.9; HRMS calcd [M + Na]$^+$ for $C_{19}H_{14}O_3NClNa$ 362.0554, found 362.0552; FTIR (cm^{-1}) 3856, 3727, 2865, 2382, 2307, 1636, 1544, 1498, 1461, 1369, 1315, 1168, 1057, 757.

*4-(4-Fluorophenyl)-6-methyl-3,4-dihydro-2H-pyrano[3,2-c]-quinoline-2,5(6H)-dione (**7d**):* white solid (153.3 mg, 95%); R_f (petroleum ether/EtOAc = 70/30) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.28−7.23 (m, 2H) 6.98 (t, J = 8.5 Hz, 2H), 4.68 (d, J = 6.1 Hz, 1H), 3.72 (s, 3H), 3.15−3.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.4, 161.2, 161.0, 153.9, 139.5, 136.2, 131.9, 128.6, 128.5, 123.1, 122.7, 116.2, 115.9, 114.4, 113.8, 111.3, 36.4, 35.5, 29.9; HRMS calcd [M + Na]$^+$ for $C_{19}H_{14}O_3NFNa$ 346.0850, found 346.0850; FTIR (cm^{-1}) 1788, 1653, 1601, 1508, 1465, 1417, 1385, 1316, 1280, 1226, 1149, 1113, 1042, 973.

*6-Methyl-4-(4-(trifluoromethyl)phenyl)-4,6-dihydro-2H-pyrano-[3,2-c]quinoline-2,5(3H)-dione (**7e**):* white solid (103.0 mg, 55%); R_f (petroleum ether/EtOAc = 70/30) 0.37; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz,1H), 7.68 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.43−7.34 (m, 4H), 4.74 (d, J = 7.4 Hz, 1H) 3.72 (s, 3H, CH_3), 3.19 (dd, J_1 = 7.8 Hz, J_2 = 16.2 Hz, 1H), 3.10 (d, J = 16.1 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 161.2, 154.3, 144,5, 139.6, 132.2, 130.5−129.7 (m), 127.5, 126.3−126.2 (m), 123.2, 123.0, 122.8, 114.5, 113.7, 110.6, 36.11, 36.0, 29.9; HRMS calcd [M + Na]$^+$ for $C_{20}H_{14}O_3NF_3Na$ 396.0818, found 396.0814; FTIR (cm^{-1}) 3736, 3393, 3180, 2852, 1651, 1325, 1116, 993.

*4-(3-Bromophenyl)-6-methyl-4,6-dihydro-2H-pyrano[3,2-c]-quinoline-2,5(3H)-dione (**7f**):* white solid (163.0 mg, 85%); R_f (petroleum ether/EtOAc = 70/30) 0.42; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz,1H), 7.68−7.65 (m, 1H), 7.42−7.33 (m, 4H), 7.18−7.13 (m, 2H), 4.64 (d, J = 7.3 Hz, 1H), 3.71 (s, 3H, CH_3), 3.15 (dd, J_1 = 7.4 Hz, J_2 = 16.3 Hz, 1H), 3.08 (d, J = 16.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 161.1, 154.3, 142.7, 139.7, 132.1, 131.0, 130.8, 130.1, 125.5, 121.3, 123.3, 122.7, 114.5, 113.7, 110.6, 36.3, 35.9, 29.9; HRMS calcd [M + Na]$^+$ for $C_{19}H_{14}O_3NBrNa$ 406.0049, found 406.0052; FTIR (cm^{-1}) 1786, 1651, 1600, 1498, 1463, 1413, 1383, 1313, 1282, 1249, 1146, 1022, 974, 817, 689.

*4-(2-Methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyrano[3,2-c]-quinoline-2,5(6H)-dione (**7g**):* white solid (155.0 mg, 92%); R_f (petroleum ether/EtOAc = 70/30) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.0 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.72 (d, J = 8.2 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.08−3.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.2, 153.8, 139.4, 131.5, 130.1, 129.0, 128.2, 123.1,122.4, 120.8, 114.2, 114.1, 110.8, 54.6, 34.6, 34.1, 29.8; HRMS calcd [M + Na]$^+$ for $C_{20}H_{17}O_4NNa$ 358.1050, found 358.1047; FTIR (cm^{-1}) 1782, 1648, 1597, 1495, 1463, 1382, 1282, 1025, 940, 756, 712, 681.

*4-(3-Bromo-4-methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyrano-[3,2-c]quinoline-2,5(6H)-dione (**7h**):* white solid (180.0 mg, 87%); R_f (petroleum ether/EtOAc = 70/30) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.42−7.40 (m, 2H), 7.34 (t, J = 8.3 Hz, 1H), 7.15 (dd, J_1 = 2.5 Hz, J_2 = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.12−3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.2, 155.5, 154.1, 139.6, 133.9, 132.0, 131.9, 126.9, 123.2, 122.7, 114.4,113.8, 112.4, 112.4, 111.0, 56.4, 36.5,35.2, 29.9; HRMS calcd [M + Na]$^+$ for $C_{20}H_{16}O_4NBrNa$ 436.0155, found 436.0155. FTIR (cm^{-1}) 1786, 1652, 1600, 1575, 1497, 1464, 1413, 1383, 1282, 1146, 1053, 974.

General Procedure for the Enantioselective Synthesis of Functionalized Coumarins. To a flame-dried screw-capped test tube equipped with a magnetic stir bar were taken triazolium salt **8** (7.4 mg, 0.02 mmol) and 2-bromoenal **2** (0.25 mmol), followed by 4-hydroxy-2*H*-chromen-2-one **1a** (0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere, and the mixture was allowed to stir at 30 °C. To this stirring solution was added the Na_2CO_3 (1.2 equiv). Then the reaction mixture was stirred at 30 °C for 12 h. When the reaction was complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized coumarins **3′**.

*(R)-4-Phenyl-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (**3a′**):*[20] white solid (55.1 mg, 75%); 93:7 er; $[\alpha]_D^{25}$ = −159.30 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 70:30 petroleum ether/EtOH, 1.0 mL/min) major 27.0 min, minor 35.4 min.

*(R)-4-(4-Methoxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-c]-chromene-2,5-dione (**3b′**):* white solid (65.0 mg, 81%); 92:8 er; $[\alpha]_D^{25}$ = −165.30 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 70:30 petroleum ether/EtOH, 0.7 mL/min) major 30.7 min, minor 46.0 min.

*(R)-4-(4-Fluorophenyl)-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (**3d′**):* white solid (55.0 mg, 71%); 87:13 er; $[\alpha]_D^{25}$ = −170.20 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 70:30 petroleum ether/EtOH, 1.0 mL/min) major 22.6 min, minor 30.10 min.

*(R)-4-(2-Methoxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-c]-chromene-2,5-dione (**3f′**):* white solid (75.0 mg, 93%); 89:11 er; $[\alpha]_D^{25}$ = −173.5 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 95:05 *n*-hexane/EtOH, 1.0 mL/min) minor 61.6 min, major 67.0 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all products, details on competition experiments, and HPLC data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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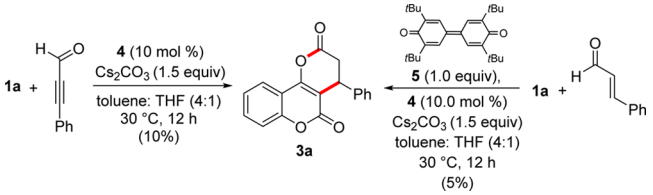
(14) The mixture of solvents was used to enhance the solubility of **1a**.

(15) Additional experiments were carried out to generate α,β-unsaturated acyl azolium from ynal and enal (under oxidative conditions). The reaction of ynal with **1a** furnished **3a** in 10%, and the reaction of enal with **1a** in the presence of oxidant **5** afforded **3a** in 5%. These results indicate that the generation of α,β-unsaturated acyl azolium from 2-bromoenal gave better results in the reaction with **1a**.



(16) It may be noted that β-alkyl-substituted bromoenals did not show any reactivity with 4-hydroxycoumarin under the optimized conditions.

(17) 2-Hydroxynaphthoquinone was also reported to be not participating in the reaction of α,β-unsaturated acyl azolium generated from ynals. For details, see ref 8d.

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Based on the [3,3] sigmatropic rearrangement mechanism suggested by Bode et al. for the addition of kojic acid derivatives to α,β-unsaturated acylazoliums (ref 9b), it is reasonable to believe that the same mechanism can be invoked in the addition of heterocyclic C-H acids to α,β-unsaturated acylazoliums.

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