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PAPER

Cascade reaction of β,γ-unsaturated α-ketoesters with phenols in trityl chloride/TFA system. Highly selective synthesis of 4-aryl-2*H*-chromenes and their applications†

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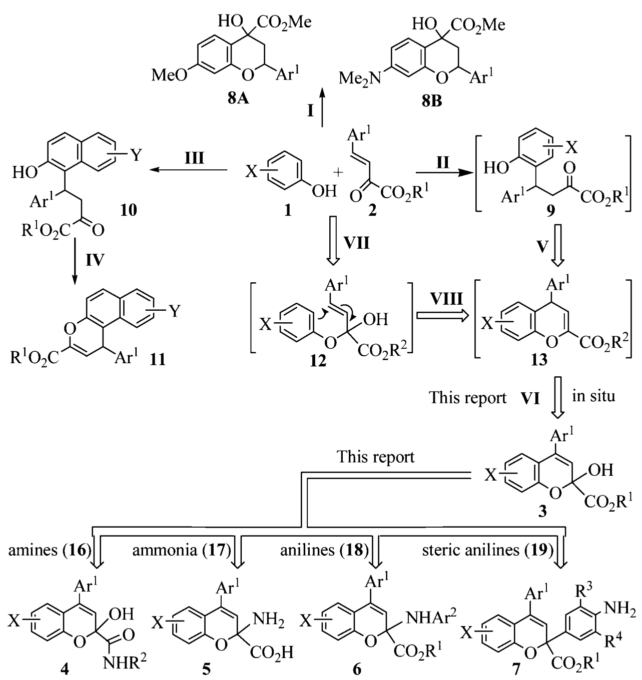
The treatment of β,γ-unsaturated α-ketoesters with phenols in the presence of trityl chloride and 4 Å molecular sieves in refluxing trifluoroacetic acid afforded 4-aryl-2*H*-chromenes in high yields, in which a reverse of the regiochemistry of Jørgensen–Rutjes chromane synthesis was observed. The isolation of 4*H*-chromene intermediates, confirmed by single-crystal X-ray analysis, indicates that the early stage of the reaction involves a Friedel–Crafts alkylation/cyclodehydration processes. Stirring of the 4*H*-chromene intermediate with trityl chloride in deuterotrifluoroacetic acid under reflux afforded the 2*H*-chromene and triphenylmethane in high yields, which implies the late stage of the reaction involves a hydrogen transfer process. Highly selective derivation of the hydroxyl esters to the corresponding hydroxyl amides, amino acids, amino esters and Friedel–Crafts adducts was further accomplished. Our endeavors will lead to a better understanding of the controlling elements behind their structural motifs. The products were confirmed unambiguously from their spectra and by single-crystal X-ray analysis.

Introduction

Selectivity continues to be a major area of focus in organic chemistry. The obtention of high selectivity in a cascade reaction is a long-standing challenge for organic chemists. Another challenge is to perform the reaction using substrates bearing multiple functional groups that could lead to many possible transformations. Thanks to their versatile functional groups of unsaturated double bonds, ketones and esters, β,γ-unsaturated α-ketoesters **2** (Scheme 1) are attractive substrates for the development of selective cascade reactions. **2** can react with phenols through Friedel–Crafts alkylation,[1,2] Friedel–Crafts hydroxyalkylation,[1a] oxa-Michael addition,[1a,3] transesterification,[4] hemiacetalization, acetalization and so on.[5,6] For example, Jørgensen and Rutjes reported an elegant Lewis acid-catalyzed [$Mg(OTf)_2$ or $Cu(OTf)_2$ in combination with bisoxazoline ligands in toluene] oxa-Michael addition/Friedel–Crafts hydroxyalkylation of β,γ-unsaturated α-ketoesters **2** with phenols **1** for the selective synthesis of optically active chromanes **8A–B** (Scheme 1, Route I).[1a] They noted that the above reaction and Friedel–Crafts alkylation of **2** with **1** concurrently occurred in some cases to result in side products **9** together with the desired products **8** (Scheme 1, Route II).[1a]



Scheme 1 Reaction of β,γ-unsaturated α-ketoesters **2** with phenols **1**.

Since the seminal work reported by Jørgensen and Rutjes, Luo (Scheme 1, Route II),[1c] Zhao and Yang (Scheme 1, Route III)[1b] have also developed selective Friedel–Crafts alkylation of β,γ-unsaturated α-ketoesters **2** with phenols **1** to afford Friedel–Crafts adducts **9–10**. Subsequent dehydration of **10** in dichloromethane

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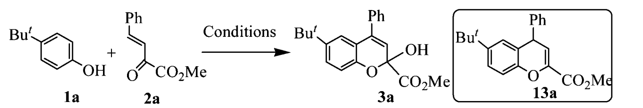
Table 1 A survey of the reaction conditions[a]



Entry	Conditions	Time	Yields
1	**2a** (2.0 equiv.), TFA, reflux	48 h	73%
2	**2a** (2.0 equiv.), 3 N HCl in MeOH, reflux	48 h	< 5%
3	**2a** (2.0 equiv.), AcOH, reflux	48 h	< 5%
4	**2a** (2.0 equiv.), HCO_2H, reflux	48 h	71%
5	**2a** (1.1 equiv.), TFA, reflux	48 h	36%
6	**2a** (2.0 equiv.), TFA, Na_2SO_4, reflux	12 h	77%
7	**2a** (2.0 equiv.), TFA, 4 Å MS, reflux	12 h	81%
8	**2a** (1.1 equiv.), TFA, $FeCl_3$, 4 Å MS, reflux	12 h	46%
9	**2a** (1.1 equiv.), TFA, DDQ, 4 Å MS, reflux	12 h	65%
10	**2a** (1.1 equiv.), TFA, chloranil, 4 Å MS, reflux	12 h	72%
11	**2a** (1.1 equiv.), TFA, Ph_3CBF_4, 4 Å MS, reflux	12 h	88%
12	**2a** (1.1 equiv.), TFA, Ph_3CCl, 4 Å MS, reflux	12 h	90%

[a] c = 0.1 M. MS = molecular sieves; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

with concentrated sulfuric acid afforded naphthopyran derivatives **11** (Scheme 1, Routes III–IV).[1b] In connection with our ongoing projects aiming for the development of selective strategies for the synthesis of various functional heterocycles,[7] herein we would like to report a cascade reaction of β,γ-unsaturated α-ketoesters **2** with phenols **1** for the selective synthesis of 4-aryl-2*H*-chromenes **3** in a one-pot fashion (Scheme 1). The tandem reaction likely involves processes of Friedel–Crafts alkylation (Route II), cyclodehydration (Route V), *in situ* oxidation and hydration (Route VI). As the ketone functionalities of **2** are activated by the ester groups, another possibility for the formation of potential intermediates **13** involves processes of hemiacetalization (Route VII), intramolecular Friedel–Crafts alkylation and cyclodehydration (Route VIII). This synthesis and Jørgensen–Rutjes chromane synthesis would complement each other to enrich the reaction diversity. Moreover, from the resulting hydroxyl esters **3** were derived, in a highly selective manner, the corresponding hydroxyl amides **4**, amino acids **5**, amino esters **6** and Friedel–Crafts adducts **7** (Scheme 1).

Results and discussion

The reaction of (3*E*)-2-oxo-4-phenylbut-3-enoate methyl ester (**2a**) with 4-*tert*-butylphenol (**1a**) was used as a probe for evaluating the reaction conditions, and several representative results are summarized in Table 1. Optimization of standard reaction parameters identified TFA as the most effective catalyst and solvent (entries 1–3).[8,9] Formic acid was also an effective solvent for this reaction (entry 4) and might be useful for a large scale process. However, TFA was chosen in our investigations because it led to the best yield.

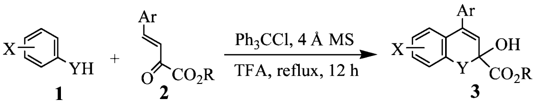
The desired 4-aryl-2*H*-chromene **3a** was isolated in only 36% yield when the molar ratio of **1a** to **2a** was changed from 1 : 2 to 1 : 1.1 under otherwise the same conditions (Table 1, entry 5), in which 4*H*-chromene intermediate **13a** (2% yield) and **1a** (43% of the starting material) were isolated. The isolation of **13a**, confirmed by single-crystal X-ray analysis (see the ESI†),[10,11] indicates that the early stage of the reaction involves a dehydration process. Therefore, the addition of a dehydrating agent to the reaction mixture would absorb the water produced, and thereby facilitate the reaction (entries 1 and 6–7). The yield of **3a** was increased up to 81% by simply adding 4 Å molecular sieves as dehydrating agent (entry 7).

The formation of **13a** (2% yield) and **3a** (Table 1, entry 5) also indicates that the transformation of **1a** and **2a** into 4*H*-chromene intermediate **13a** was not completely finished when the oxidation process of **13a** to **3a** took place. Herein, **2a** appeared to serve the dual role of the substrate and oxidation agent (entries 1–7). Thus, one equivalent of **2a** might be saved with another agent as the oxidant. On the other hand, the dual role of **2a** as the substrate and oxidation agent would affect the application scope of the protocol. Moreover, the potential reducing products were unstable under the harsh conditions and were not isolated from the reaction, which was not in accordance with the standpoint of atom economy. Therefore, a series of other oxidation agents was examined for the reaction (entries 8–12). Iron chloride ($FeCl_3$, 1.1 equiv.), DDQ (1.1 equiv.) and chloranil (1.1 equiv.) didn't provide any better results (entries 8–10). Gratifyingly, **3a** (90%) along with triphenylmethane (Ph_3CH, **14**, 81% yield) were isolated by simply adding trityl chloride (Ph_3CCl, 1.1 equiv.) as an oxidation agent (entries 7–12), in which nearly one equivalent of **2a** was saved. The formation of **14** indicates that the reaction involves a hydrogen transfer process.[12]

With the optimized reaction conditions in hand, the scope of the reaction with respect to β,γ-unsaturated α-ketoesters **2** and (thio)phenols **1** was subsequently investigated (Table 2). With weak electron-donating groups, *tert*-butyl, phenyl and methyl, at the *para* position of phenols, the cascade reaction of phenols **1a–c** with (3*E*)-2-oxo-4-phenylbut-3-enoate methyl ester (**2a**) under standard conditions afforded 2*H*-chromenes **3a–c** in high yields (entries 1–3). With the *para* position of phenols bearing electron-withdrawing groups such as fluoro, chloro and bromo, phenols **1d–f** reacted equally well with **2a** to afford 2*H*-chromenes **3d–f** in excellent yields (entries 4–6). With a strong electron-donating group such as a methoxy group at the *para* position of the phenol, phenol **1g** reacted with **2a** to afford 2*H*-chromene **3g** with a slightly decreased yield (78%, entry 7). Besides phenols, 1-naphthol (**1h**) and 2-naphthol (**1i**) were also reacted with **2a** to afford 2*H*-benzo[*h*]chromenes **3h–i** in 81% and 84% yields, respectively (entries 8–9). β,γ-Unsaturated α-ketoesters **2** with either electron-withdrawing or electron-donating groups have also been investigated, which reacted with phenols **1** uneventfully under standard conditions to afford the desired 2*H*-chromenes **3j–o** in 83–89% yields (entries 10–15). The cascade reaction of **2a** with thiophenol **1j** under standard conditions afforded 2*H*-thiochromene **3p** in 72% yield (entry 16), demonstrating similar selectivity as for 2*H*-chromenes. Highly deactivated 4-nitrophenol (**1k**) prevented any reaction (entry 17). β,γ-Unsaturated α-ketoesters **2f–h** were found to be quite unstable under the standard reaction conditions and therefore were incompatible substrates (entries 18–20). The structures of 2*H*-chromenes were confirmed from their spectra and supported by the X-ray crystallographic analysis of **3a** (see the ESI†).[13]

A proposed mechanistic model for this cascade reaction is outlined in Scheme 2. It is anticipated that the Friedel–Crafts alkylation/cyclodehydration of β,γ-unsaturated α-ketoesters **2** with phenols **1** formed the 4*H*-chromenes **13** (also see Scheme 1),

Table 2 Cascade reaction of β,γ-unsaturated α-ketoesters **2** with (thio)phenols **1**[a]



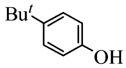
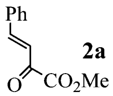
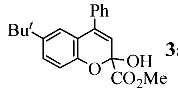
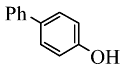
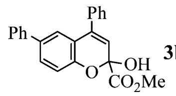
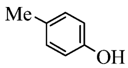
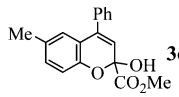
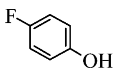
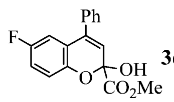
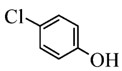
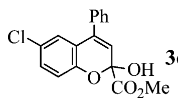
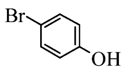
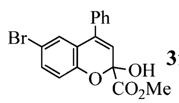
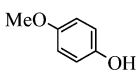
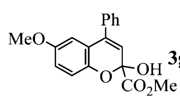
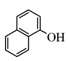
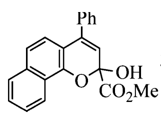
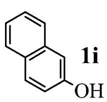
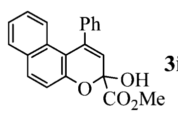
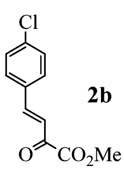
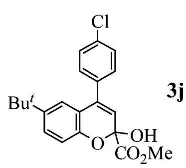
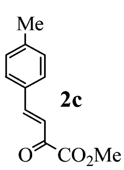
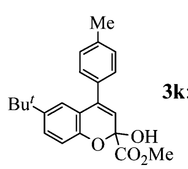
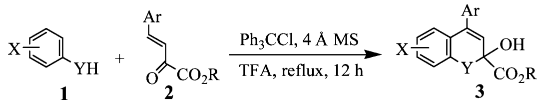
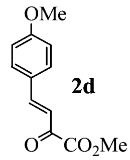
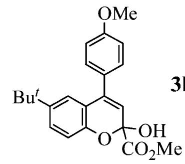
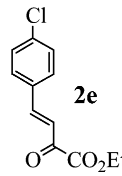
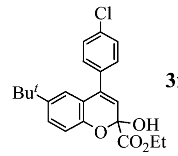
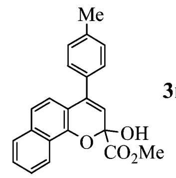
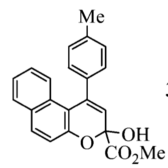
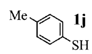
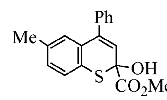
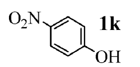
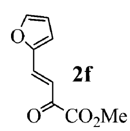
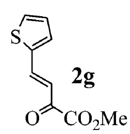
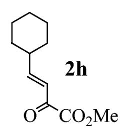
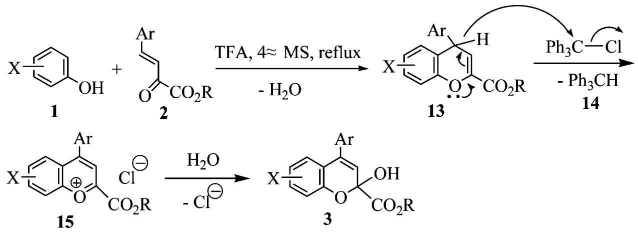
Entry	1	2	Yields of 3
1	 **1a**	 **2a**	 **3a**: 90%
2	 **1b**	**2a**	 **3b**: 87%
3	 **1c**	**2a**	 **3c**: 85%
4	 **1d**	**2a**	 **3d**: 83%
5	 **1e**	**2a**	 **3e**: 86%
6	 **1f**	**2a**	 **3f**: 88%
7	 **1g**	**2a**	 **3g**: 78%
8	 **1h**	**2a**	 **3h**: 81%
9	 **1i**	**2a**	 **3i**: 84%
10	**1a**	 **2b**	 **3j**: 86%
11	**1a**	 **2c**	 **3k**: 89%

Table 2 *(Contd.)*



Entry	1	2	Yields of 3
12	**1a**	 **2d**	 **3l**: 85%
13	**1a**	 **2e**	 **3m**: 86%
14	**1h**	**2c**	 **3n**: 83%
15	**1i**	**2c**	 **3o**: 84%
16	 **1j**	**2a**	 **3p**: 72%
17	 **1k**	**2a**	—
18	**1a**	 **2f**	—
19	**1a**	 **2g**	—
20	**1a**	 **2h**	—

[a] Conditions: **1** (1.0 equiv.), **2** (1.1 equiv.), Ph_3CCl (1.1 equiv.), c = 0.1 M, 4 Å MS.

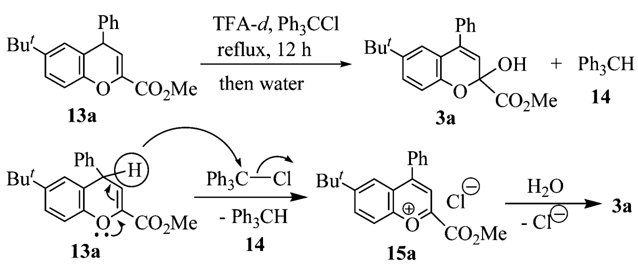


Scheme 2 Proposed mechanism for the cascade reaction of phenols **1** with β,γ-unsaturated α-ketoesters **2**.

and the intermolecular hydrogen transfer from **13** to trityl chloride formed triphenylmethane (**14**) and benzopyrylium ions **15**. Subsequent hydration of **15** with water afforded 4-aryl-2*H*-chromenes **3**.[14]

The reversible oxa-Michael addition of phenols **1** to β,γ-unsaturated α-ketoesters **2**, accomplished in Jørgensen–Rutjes chromane synthesis,[1a] was reported to be suppressed when some Brønsted acids were used.[1c] Accordingly, in our case, Brønsted acid TFA should also suppress the reversible process of oxa-Michael addition. Moreover, the facile and irreversible Friedel–Crafts alkylation of **2** with **1** in our reaction system should further obviate the reversible oxa-Michael addition, and thus cause a reverse of the regiochemistry of the Jørgensen–Rutjes chromane process.

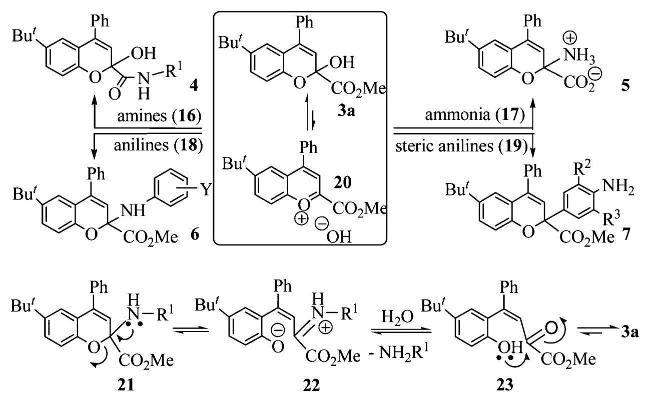
The intermolecular hydrogen transfer process was further confirmed by a hydrogen/deuterium exchange experiment (Scheme 3). In this case, the reaction of the isolated 4*H*-chromene intermediate **13a** with trityl chloride in deuterotrifluoroacetic acid (CF_3CO_2D, TFA-*d*) under reflux for 12 h, followed by hydration with water afforded 4-aryl-2*H*-chromene **3a** and triphenylmethane (**14**) in 91% and 83% yields, respectively. The transformation of trityl chloride to the non-deuterated **14** in a deuterated atmosphere implies a hydrogen transfer process, in which hydrogen is selectively transferred from the 4-position of **13a** to the quaternary carbon of trityl chloride.



Scheme 3 A hydrogen/deuterium exchange experiment.

2*H*-Chromenes have been a subject of consistent interest due to the presence of their structural motifs in a large number of natural products,[15] pharmaceuticals[16] and functional materials.[17] The multistate/multifunctional chemical system existing in 2-hydroxy-2*H*-chromenes has attracted increasing attention in molecular information processing, optical memories and logic gates.[18] The significance and prevalence of this class of compounds has served to stimulate continual interest in their diversity-oriented structural modification,[19] which triggered us to further study the derivation of our synthesized 2*H*-chromenes.

On the other hand, 2*H*-chromenes **3** are also among the challenging substrates for developing selective reactions due to their versatile functionalities of hemiacetal, hydroxyl and ester. The equilibrium between 2-hydroxy-2*H*-chromenes and benzopyrylium salts has long been a subject of extensive investigations in the overlapping areas of chemistry and biology due to their relevant importance in the plant kingdom and human beings.[20] In neutral or basic solutions, benzopyrylium salts are easily converted to the corresponding 2-hydroxy-2*H*-chromenes by hydration with water.[21] Accordingly, benzopyrylium species **20** in a neutral solution should be less stable than 2-hydroxy-2*H*-chromene **3a**, a normal representative of our synthesized 2*H*-chromenes **3** (Scheme 4). However, we believed that further reaction of **20** with some nucleophiles would drive the equilibrium toward the desired side. To our delight, by treating different types of amino-containing nucleophiles with hydroxyl ester **3a** in a dichloromethane refluxing system without the presence of any catalyst, various interesting functional compounds were obtained in high selectivity. Listed in Table 3 (entries 1–13) are representative results.

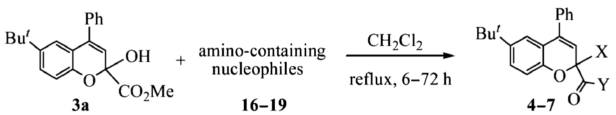


Scheme 4 Possible structural transformations.

By treating hydroxyl ester **3a** with heptylamine (**16a**) in dichloromethane under reflux for 24 h, hydroxyl amide **4a** was obtained in 83% yield (Table 3, entry 1). Decreasing yields were observed with primary amines **16b–c** in comparison to **16a** (entries 1–3), indicating that the steric factor affects the amide formation. Indeed, when sterically hindered amines such as cyclohexylamine (**16d**) and α-methylbenzylamine (**16e**) were used, no reaction took place and the starting materials were recovered (entries 4–5). It is noteworthy that the amination of the hemiacetal function of **3a** was not detected in these reactions (entries 1–5) even with an excess of amines **16** as nucleophiles. Indeed, the potential amino esters **21** (Scheme 4), supposed to be formed from the amination of hemiacetal **3a** with **16**, are probably unstable in the dichloromethane refluxing system. Nitrogen's lone pair of electrons, in aliphatic amines **21**, is likely to cause the transformation of *N*,*O*-acetals **21** into α-ketoesters **23**, which underwent intramolecular cyclization to convert back to the hemiacetal **3a**. The irreversible amidation of ester **3a** with active aliphatic amines **16** furthermore facilitated the reaction with a high selectivity.

Treatment of hydroxyl ester **3a** with aqueous ammonia (**17**) in dichloromethane under reflux for 6 h afforded amino acid **5** in 71% yield (Table 3, entry 6), in which conversion of a

Table 3 Highly selective reactions of hydroxyl ester **3a** with various amino-containing nucleophiles[a]



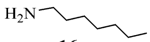
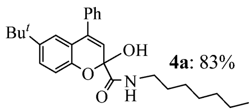
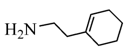
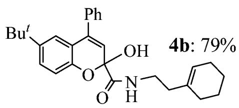
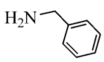
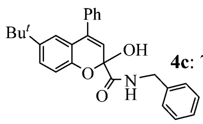
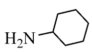
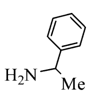
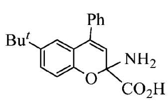
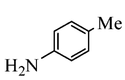
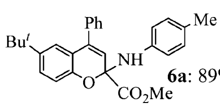
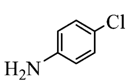
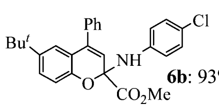
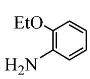
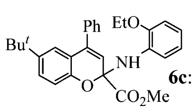
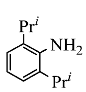
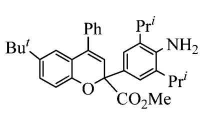
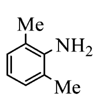
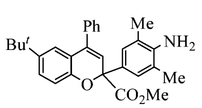
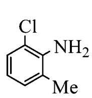
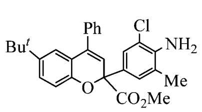
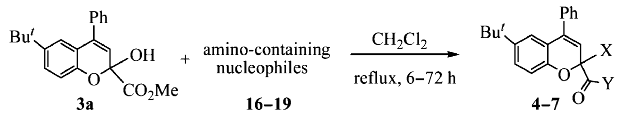
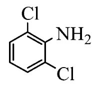
Entry	Nucleophiles	Time	Yields of products **4–7**
1	 **16a**	24 h	 **4a**: 83%
2	 **16b**	36 h	 **4b**: 79%
3	 **16c**	48 h	 **4c**: 77%
4	 **16d**	72 h	—[c]
5	 **16e**	72 h	—[c]
6	NH_3[b] (**17**)	6 h	 **5**: 71%
7	 **18a**	24 h	 **6a**: 89%
8	 **18b**	24 h	 **6b**: 93%
9	 **18c**	48 h	 **6c**: 71%
10	 **19a**	72 h	 **7a**: 82%
11	 **19b**	72 h	 **7b**: 80%
12	 **19c**	72 h	 **7c**: 51%

Table 3 *(Contd.)*



Entry	Nucleophiles	Time	Yields of products **4–7**
13	 **19d**	72 h	—[c]

[a] Conditions: **3a** (1.0 equiv.), nucleophiles (1.1 equiv.), CH_2Cl_2, reflux. [b] 5.0 M aqueous ammonia (5.0 equiv.) was used. [c] No reaction.

hydroxyl group to an amino group as well as the hydroxylation were efficiently achieved in a one-pot fashion. In contrast to the potential *N*,*O*-acetals **21** (Scheme 4), *N*,*O*-acetal **5** was stable because the intramolecular reaction between the amine and acid moiety, formed by aqueous hydrolysis, led to an ammonium salt (Scheme 4), supported by its ^{1}H NMR spectra (see the ESI†), which dispersed nitrogen's lone pair of electrons and thereby avoided the deamination process mentioned before.

Anilines **18a–c** are weaker nucleophiles than aliphatic amines **16a–c** since the orbital containing the nitrogen's lone pair of electrons overlaps with the π system of the aromatic ring. Accordingly, condensation of anilines **18a–c** with ester **3a** in dichloromethane under reflux did not afford the corresponding amides. Instead, amino esters **6a–c** were isolated in excellent yields (Table 3, entries 7–9). In contrast to *N*,*O*-acetals **21**, *N*,*O*-acetals **6a–c** were relatively stable because the nitrogen's lone pair of electrons was delocalized in the aromatic ring and thereby obviated the process of deamination mentioned previously, which was supported by the result that transamination of *N*,*O*-acetals **6** with another aromatic amine was not detected in refluxing dichloromethane. As in the case of **13a** and **3a**, the structure of **6a** was assigned from spectra and single crystal data (see the ESI†).[22]

In contrast to simple anilines **18a–c**, condensation of highly sterically hindered anilines with hydroxyl ester **3a** in dichloromethane under reflux did not afford amino esters. Instead, some Friedel–Crafts adducts were obtained (Table 3, entries 10–12). Treatment of 2,6-diisopropylaniline (**19a**) and 2,6-dimethylbenzenamine (**19b**) with **3a** in the dichloromethane refluxing system for 72 h afforded Friedel–Crafts adducts **7a–b** in 82% and 80% yields, respectively (entries 10–11). There was an obvious decrease in yields with the less activated 2-chloro-6-methylaniline (**19c**) in comparison to 2,6-dimethylbenzenamine (**19b**) (entries 11–12), reflecting the electronic factor effect on the Friedel–Crafts reaction. When 2,6-dichloroaniline (**19d**) was subjected to this procedure, the starting materials were recovered and no reaction took place (entry 13), confirming the importance of electronic effects in this catalyst-free Friedel–Crafts reaction.

Conclusions

In summary, we have detailed the cascade reaction of β,γ-unsaturated α-ketoesters with phenols, naphthols and thiophenols in a trityl chloride/TFA refluxing system to afford 4-aryl-2*H*-chromenes, 4-aryl-2*H*-benzo[*h*]chromenes and 4-aryl-2*H*-thiochromenes with excellent yields and high selectivity, in which a reverse of the regiochemistry of the Jørgensen–Rutjes chromane synthesis was observed. One representative of our synthesized 4-aryl-2*H*-chromenes, possessing hemiacetal, hydroxyl and ester functionalities, was selected to react with various amino-containing nucleophiles, which afforded hydroxyl amides, amino acids, amino esters and Friedel–Crafts adducts under catalyst-free conditions with high selectivity. Cytotoxicity tests (*in vitro*) indicated that hydroxyl amide **4b** is cytotoxic against a human colon tumor cell line HCT-116 (IC_{50} = 1.3 μM), which would widen the structural diversity of this antitumor target and confirm the perspectives of further investigations in this area. We believe that our controlling elements behind their structural motifs would be useful in the synthesis of complex molecules because of the significance and prevalence of these functionalities in modern organic synthesis.

Experimental

General procedure for the synthesis of 4-aryl-2*H*-chromenes

A mixture of (thio)phenol **1** (0.10 mmol), β,γ-unsaturated α-ketoester **2** (0.11 mmol), trityl chloride (0.11 mmol) and 4 Å molecular sieves (0.10 g) in TFA (1 mL) under a nitrogen atmosphere was stirred at reflux for 12 h, and concentrated. To the residue were added ethyl acetate (20 mL) and saturated aqueous sodium hydrogen carbonate (10 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography over silica gel to afford 4-aryl-2*H*-(thio)chromenes **3a–p** (Table 2).

4-Aryl-2*H*-chromene 3a. 90% yield; white solid; mp = 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (m, 5H), 7.35 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 1H), 4.48 (s, 1H), 3.92 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 148.2, 144.6, 139.4, 137.1, 128.8, 128.4, 128.3, 127.0, 123.1, 119.3, 117.0, 116.4, 93.2, 53.7, 34.3, 31.3; FTIR (KBr) 3467, 2960, 1743, 1489, 1287, 1236, 1149, 1026, 768, 698 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]+ $C_{21}H_{22}NaO_4$: 361.1410, Found: 361.1407; Anal. Calcd. For $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.77; H, 6.74.

4-Aryl-2*H*-chromene 3b. 87% yield; pale yellow solid; mp = 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.28 (m, 12H), 7.14 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 1H), 4.52 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 150.0, 140.6, 139.2, 136.9, 135.3, 128.9, 128.8, 128.7, 128.6, 128.5, 127.0, 126.9, 124.9, 120.4, 117.5, 117.4, 93.4, 53.9; FTIR (KBr) 3436, 1749, 1480, 1253, 1237, 1157, 1140, 1123, 1050, 1022, 826, 761, 700 cm^{-1}; Anal. Calcd. For $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.91; H, 5.18.

4-Aryl-2*H*-chromene 3c. 85% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 7.09 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 5.83 (s, 1H), 4.37 (s, 1H), 3.91 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 145.8, 136.8, 134.7, 128.9, 128.2, 126.5, 126.1, 125.9, 124.1, 117.5, 114.7, 114.4, 90.8, 51.5, 18.4; FTIR (KBr) 3443, 2954, 2928, 2855, 1753, 1489, 1242, 1124, 1046, 822, 761, 703 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]$^+$ $C_{18}H_{16}NaO_4$: 319.0941, Found: 319.0942; Anal. Calcd. For $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.89; H, 5.51.

4-Aryl-2*H*-chromene 3d. 83% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 5H), 7.04–6.94 (m, 2H), 6.89 (d, *J* = 9.0 Hz, 1H), 5.89 (s, 1H), 4.51 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 159.2, 156.1, 146.3, 146.3, 138.6, 138.6, 136.5, 128.7, 128.7, 128.7, 121.4, 121.3, 118.2, 118.1, 118.1, 116.6, 116.3, 112.7, 112.4, 93.3, 54.0; FTIR (KBr) 3060, 2955, 1754, 1484, 1248, 1193, 1044, 825, 765, 704 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]$^+$ $C_{17}H_{13}FNaO_4$: 323.0690, Found: 323.0692; Anal. Calcd. For $C_{17}H_{13}FO_4$: C, 68.00; H, 4.36. Found: C, 68.11; H, 4.53.

4-Aryl-2*H*-chromene 3e. 86% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.39 (m, 5H), 7.23 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 5.87 (s, 1H), 4.52 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 149.0, 138.4, 136.3, 129.7, 128.7, 128.7, 127.0, 125.9, 121.6, 118.4, 118.1, 93.3, 54.0; FTIR (KBr) 3446, 3029, 2954, 1755, 1475, 1253, 1046, 936, 821, 764, 702 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]$^+$ $C_{17}H_{13}ClNaO_4$: 339.0395, Found: 339.0397; Anal. Calcd. For $C_{17}H_{13}ClO_4$: C, 64.46; H, 4.14. Found: C, 64.34; H, 4.39.

4-Aryl-2*H*-chromene 3f. 88% yield; pale yellow solid; mp = 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.35 (m, 6H), 7.27 (dd, *J* = 6.3, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.7, 1.2 Hz, 1H), 5.86 (d, *J* = 0.9 Hz, 1H), 4.52 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 149.5, 138.3, 136.3, 132.6, 128.8, 128.7, 122.1, 118.9, 118.1, 114.4, 93.3, 77.2, 54.0; FTIR (KBr) 3411, 3057, 2958, 1757, 1475, 1259, 1165, 1123, 1026, 820, 762, 701 cm^{-1}; Anal. Calcd. For $C_{17}H_{13}BrO_4$: C, 56.53; H, 3.63. Found: C, 56.62; H, 3.73.

4-Aryl-2*H*-chromene 3g. 78% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.72 (d, *J* = 3.0 Hz, 1H), 5.88 (s, 1H), 4.33 (s, 1H), 3.91 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 154.4, 139.1, 137.0, 128.8, 128.7, 128.5, 128.5, 120.8, 117.8, 117.7, 115.5, 111.4, 93.2, 55.8, 53.9; FTIR (KBr) 3440, 2952, 1755, 1488, 1260, 1219, 1048, 829, 762, 703 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]$^+$ $C_{18}H_{16}NaO_5$: 335.0890, Found: 335.0886; Anal. Calcd. For $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.07; H, 5.39.

4-Aryl-2*H*-chromene 3h. 81% yield; pale yellow solid; mp = 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (t, *J* = 4.5 Hz, 1H), 7.76 (t, *J* = 4.5 Hz, 1H), 7.52–7.41 (m, 8H), 7.27 (dd, *J* = 4.5, 1.3 Hz, 1H), 5.91 (s, 1H), 4.55 (s, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 146.1, 139.6, 137.3, 134.5, 128.9, 128.5, 128.4, 127.6, 127.0, 125.9, 124.7, 123.2, 122.2, 121.2, 115.8, 114.6, 93.8, 53.9; FTIR (KBr) 3439, 3063, 2952, 1733, 1297, 1262, 1145, 1091, 985, 818, 753, 700 cm^{-1}; HRMS (FAB) Calcd. For [M+Na]$^+$ $C_{21}H_{16}NaO_4$: 355.0941, Found: 355.0942; Anal. Calcd. For $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.77; H, 4.98.

4-Aryl-2*H*-chromene 3i. 84% yield; pale yellow solid; mp = 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.40–7.38 (m, 5H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.26 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.06

(td, J = 7.6, 1.6 Hz, 1H), 6.02 (s, 1H), 4.30 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 149.7, 140.5, 139.4, 131.3, 130.7, 129.8, 128.5, 128.4, 128.0, 126.5, 125.4, 123.8, 118.5, 118.2, 114.4, 92.7, 53.8; FTIR (KBr) 3444, 3057, 2954, 1748, 1630, 1257, 1232, 1159, 1019, 821, 760, 700 cm^{-1}; HRMS (FAB) Calcd. For $[M+Na]^+$ $C_{21}H_{16}NaO_4$: 355.0941, Found: 355.0942; Anal. Calcd. For $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.79; H, 4.87.

4-Aryl-2*H*-chromene 3j. 86% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.82 (s, 1H), 4.40 (s, 1H), 3.91 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 148.1, 144.8, 138.5, 135.6, 134.4, 130.2, 128.7, 127.3, 122.9, 119.0, 117.2, 116.5, 93.1, 53.9, 34.3, 31.4; FTIR (KBr) 3439, 2961, 1751, 1489, 1243, 1130, 826, 754 cm^{-1}; Anal. Calcd. For $C_{21}H_{21}ClO_4$: C, 67.65; H, 5.68. Found: C, 67.52; H, 5.91.

4-Aryl-2*H*-chromene 3k. 89% yield; white solid; mp = 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 6H), 7.03 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 4.54 (s, br, 1H), 3.90 (s, 3H), 2.45 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 148.3, 144.6, 139.4, 138.2, 134.3, 129.2, 128.8, 126.9, 123.3, 119.5, 116.8, 116.5, 93.4, 53.8, 34.4, 31.5, 21.3; FTIR (KBr) 3468, 2959, 1739, 1489, 1285, 1258, 1237, 1145, 1032, 808 cm^{-1}; Anal. Calcd. For $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.85; H, 7.01.

4-Aryl-2*H*-chromene 3l. 85% yield; pale yellow solid; mp = 55–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.7, 2.1 Hz, 2H), 7.32 (dd, J = 8.7, 2.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.03–6.97 (m, 3H), 5.83 (s, 1H), 4.51 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 159.7, 148.3, 144.6, 139.0, 130.1, 129.5, 126.9, 123.2, 119.6, 116.5, 113.9, 93.4, 55.3, 53.7, 34.3, 31.4; FTIR (KBr) 3436, 2959, 1749, 1512, 1287, 1249, 1130, 1032, 830 cm^{-1}; Anal. Calcd. For $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.61; H, 6.58.

4-Aryl-2*H*-chromene 3m. 86% yield; foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.81 (s, 1H), 4.44 (s, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 148.2, 144.8, 138.4, 135.7, 134.4, 130.2, 128.7, 127.2, 122.9, 119.1, 117.3, 116.6, 93.0, 63.4, 34.3, 31.4, 14.1; FTIR (KBr) 3440, 2962, 1750, 1490, 1244, 1129, 1054, 827, 755 cm^{-1}; HRMS (FAB) Calcd. For $[M+Na]^+$ $C_{22}H_{23}ClNaO_4$: 409.1177, Found: 409.1173.

4-Aryl-2*H*-chromene 3n. 83% yield; white solid; mp = 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 1H), 7.78 (m, 1H), 7.52–7.26 (m, 8H), 5.91 (s, 1H), 4.56 (s, br, 1H), 3.95 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 146.1, 139.5, 138.3, 134.5, 129.2, 128.8, 127.6, 127.0, 125.9, 124.8, 123.3, 122.2, 121.1, 115.5, 114.7, 93.8, 53.9, 21.3; FTIR (KBr) 3440, 2956, 1733, 1378, 1295, 1262, 1146, 1090, 985, 815 cm^{-1}; Anal. Calcd. For $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.17; H, 5.38.

4-Aryl-2*H*-chromene 3o. 84% yield; white solid; mp = 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.73 (m, 2H), 7.35–7.19 (m, 8H), 6.01 (s, 1H), 4.29 (s, br, 1H), 3.93 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 149.7, 139.3, 138.0, 137.6, 131.2, 130.7, 129.9, 129.3, 128.5, 128.0, 126.7, 125.4, 123.8, 118.3, 118.1, 114.6, 92.8, 53.9, 21.3; FTIR (KBr) 3448, 2955, 1749, 1627, 1512, 1271, 1038, 821, 754 cm^{-1}; Anal. Calcd. For $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.21; H, 5.40.

4-Aryl-2*H*-thiochromene 3p. 72% yield; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.07 (m, 9H), 3.80 (s, 3H), 3.13 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 146.1, 137.3, 135.3, 129.5, 129.4, 129.1, 128.4, 128.4, 127.5, 125.7, 125.6, 123.8, 73.5, 52.9, 21.2; FTIR (film) 3478, 2951, 1724, 1483, 1440, 1256, 1228, 1068, 812, 744, 702 cm^{-1}; HRMS (FAB) Calcd. For $[M+Na]^+$ $C_{18}H_{16}NaO_3S$: 335.0712, Found: 335.0708; Anal. Calcd. For $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16. Found: C, 69.02; H, 5.39.

4-Aryl-4*H*-chromene 13a. white solid; mp = 176–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 6.8 Hz, 2H), 7.29 (d, J = 6.8 Hz, 1H), 7.26–7.20 (m, 4H), 7.09 (dd, J = 8.6, 1.31 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 4.5 Hz, 1H), 4.82 (d, J = 4.4 Hz, 1H), 3.85 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 148.3, 147.2, 145.0, 140.1, 128.8, 128.3, 127.0, 126.3, 125.3, 120.9, 116.5, 114.0, 52.4, 41.3, 34.3, 31.3; FTIR (KBr) 3028, 2961, 1738, 1665, 1497, 1286, 1233, 1137, 1083, 700 cm^{-1}; HRMS (FAB) Calcd. For $[M+H]^+$ $C_{21}H_{23}O_3$: 323.1642, Found: 323.1636; Anal. Calcd. For $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.14; H, 6.97.

The hydrogen/deuterium exchange experiment (Scheme 3)

A mixture of 4-aryl-4*H*-chromene **13a** (16.1 mg, 50.0 μmol) and trityl chloride (15.3 mg, 55.0 μmol) in deuterotrifluoroacetic acid (0.5 mL) under a nitrogen atmosphere was stirred at reflux for 12 h, and concentrated. To the residue were added ethyl acetate (20 mL) and saturated aqueous sodium hydrogen carbonate (10 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography over silica gel to afford 4-aryl-2*H*-chromene **3a** (15.4 mg, 91% yield) and triphenylmethane (**14**, 10.1 mg, 83% yield).

Triphenylmethane (14). Brown solid; mp = 93–94 °C; ^{1}H NMR (300 MHz, $CDClB_{3B}$) δ 7.23–7.03 (m, 15H), 5.47 (s, 1H); ^{13}C NMR (75 MHz, $CDClB_{3B}$) δ 143.9, 129.5, 128.3, 126.3, 56.8; FTIR (KBr) 3019, 1595, 1492, 1443, 1077, 1029, 914, 755, 731, 696, 658 cm^{-1}; Anal. Calcd. For $C_{19}H_{16}$: C, 93.40; H, 6.60. Found: C, 93.38; H, 6.69.

General procedure for reactions of 2*H*-chromene 3a with various amino-containing nucleophiles

A mixture of 4-aryl-2*H*-chromene **3a** (0.10 mmol) and amino-containing nucleophiles **16–19** (0.11 mmol) in dichloromethane (1 mL) under a nitrogen atmosphere was stirred at reflux for 6–72 h, and concentrated. The residue was purified by column chromatography over silica gel to afford the corresponding products **4–7** (Table 3).

Hydroxyl amide 4a. 83% yield; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (m, 5H), 7.34 (dd, J = 8.4, 2.4 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.27 (t, J = 5.1 Hz, 1H), 5.83 (s, 1H), 3.38–3.31 (m, 2H), 1.59–1.50 (m, 2H), 1.31–1.23 (m, 8H), 1.22 (s, 9H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 148.5, 144.9, 139.5, 137.0, 128.8, 128.5, 127.1, 123.2, 119.5, 118.5, 116.7, 93.3, 40.4, 34.3, 31.6, 31.4, 29.3, 28.8, 26.7, 22.5, 14.0; FTIR (KBr) 3321, 2956, 2928, 2858, 1669, 1538, 1491, 1466, 1446, 1365, 1243, 1130, 1037, 945, 895, 827, 701 cm^{-1}; Anal. Calcd. For $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.99; H, 8.42; N, 3.36.

Hydroxyl amide 4b. 79% yield; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 7.33 (dd, J = 8.4, 2.4 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.26 (t, J = 5.4 Hz, 1H), 5.79 (s, 1H), 5.41 (s, br, 1H), 3.43–3.38 (m, 2H), 2.19–2.13 (m, 2H), 1.91–1.83 (m, 4H), 1.61–1.43 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 148.5, 144.8, 139.6, 137.0, 134.0, 128.7, 128.5, 128.4, 127.1, 124.3, 123.1, 119.3, 118.6, 116.6, 93.4, 37.9, 37.3, 34.3, 31.4, 27.8, 25.1, 22.7, 22.2; FTIR (KBr) 3321, 2928, 1676, 1534, 1491, 1446, 1365, 1243, 1130, 1039, 828, 701 cm^{-1}; Anal. Calcd. For $C_{28}H_{33}NO_3$: C, 77.93; H, 7.71; N, 3.25. Found: C, 77.89; H, 7.70; N, 3.21.

Hydroxyl amide 4c. 77% yield; white solid; mp = 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.42 (m, 5H), 7.35–7.22 (m, 7H), 7.04 (d, J = 8.4 Hz, 1H), 6.65 (s, br, 1H), 5.89 (s, 1H), 4.55 (t, J = 6.9 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 148.4, 145.0, 139.8, 137.1, 137.0, 128.9, 128.8, 128.5, 127.8, 127.8, 127.2, 123.2, 119.5, 118.3, 116.7, 93.4, 44.3, 34.4, 31.4; FTIR (KBr) 3422, 1676, 1536, 1491, 1364, 1255, 700 cm^{-1}; Anal. Calcd. For $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.39; H, 6.72; N, 3.38.

Amino acid 5. 71% yield; white solid; mp = 53–54 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 7.34 (dd, J = 8.4, 2.4 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.04 (s, J = 8.4 Hz, 1H), 6.36 (s, br, 1H), 6.10 (s, br, 1H), 5.89 (s, 1H), 4.92 (s, br, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 148.3, 145.0, 139.7, 136.9, 128.8, 128.5, 127.2, 123.2, 119.5, 118.2, 116.7, 93.3, 77.2, 34.4, 31.4; FTIR (KBr) 3476, 3318, 2961, 1693, 1490, 1365, 1257, 1130, 1038, 759 cm^{-1}; HRMS (FAB) Calcd. For $[M+Na]^+$ $C_{20}H_{21}NNaO_3$: 346.1414, Found: 346.1410; Anal. Calcd. For $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.19; H, 6.71.

Amino ester 6a. 89% yield; white solid; mp = 175–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.25 (m, 7H), 7.15 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.84 (s, 1H), 4.73 (s, br, 1H), 3.79 (s, 3H), 2.24 (s, br, 3H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 149.7, 144.2, 141.0, 140.6, 137.2, 129. 8, 129.6, 128.7, 128.5, 127.2, 123.1, 120.2, 119.1, 117.1, 116.8, 86.9, 77.2, 53.4, 34.3, 31.4, 20.6; FTIR (KBr) 3384, 2956, 1743, 1521, 1491, 1254, 1135, 1048, 814 cm^{-1}; Anal. Calcd. For $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.52; H, 6.91; N, 3.20.

Amino ester 6b. 93% yield; white solid; mp = 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 7.29–7.27 (m, 1H), 7.16–7.12 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 5.80 (s, 1H), 4.86 (s, br 1H), 3.80 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 149.5, 144.5, 141.8, 141.4, 137.0, 129.0, 128.7, 128.6, 128.5, 127.4, 125.3, 123.2, 120.0, 118.6, 117.6, 116.9, 86.6, 53.6, 34.3, 31.4; FTIR (KBr) 3381, 2956, 1739, 1600, 1496, 1292, 1253, 1134, 1048, 824, 694 cm^{-1}; Anal. Calcd. For $C_{27}H_{26}ClNO_3$: C, 72.39; H, 5.85; N, 3.13. Found: C, 72.22; H, 5.90; N, 3.07.

Amino ester 6c. 71% yield; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.42 (m, 5H), 7.22–7.20 (m, 2H), 7.08–7.02 (m, 4H), 6.66 (d, J = 8.1 Hz, 1H), 6.29 (s, 1H), 4.06 (q, J = 6.9 Hz, 2H), 3.86 (s, 1H), 3.76 (s, 3H), 1.42 (t, J = 6.9 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 150.2, 146.3, 144.1, 138.0, 137.9, 136.7, 129.7, 128.8, 128.4, 128.1, 126.7, 123.0, 122.4, 121.2, 119.2, 116.6, 114.2, 109.5, 81.2, 63.8, 52.9, 34.2, 31.4, 14.9; FTIR (KBr) 3483, 3384, 3058, 2958, 1750, 1620, 1517, 1430, 1364, 1236, 1129, 1046, 828, 738, 703 cm^{-1}; Anal. Calcd. For $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 75.99; H, 6.89; N, 3.12.

Friedel–Crafts adduct 7a. 82% yield; white solid; mp = 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.41 (m, 5H), 7.29 (s, 2H), 7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.30 (s, 1H), 3.79 (s, 3H), 2.96–2.83 (m, 2H), 1.27 (d, J = 6.6 Hz, 12H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 150.3, 143.8, 140.6, 138.1, 137.4, 132.0, 129.3, 128.8, 128.3, 128.0, 126.6, 122.9, 121.12, 121.10, 116.5, 81.6, 52.7, 34.2, 31.3, 28.1, 22.32, 22.28; FTIR (KBr) 2962, 2870, 1745, 1624, 1490, 1465, 1445, 1365, 1290, 1270, 1235, 1175, 1128, 1051, 906, 824, 727, 700 cm^{-1}; Anal. Calcd. For $C_{33}H_{39}NO_3$: C, 79.64; H, 7.90; N, 2.81. Found: C, 79.76; H, 7.98; N, 2.89.

Friedel–Crafts adduct 7b. 80% yield; white solid; mp = 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (m, 5H), 7.25–7.19 (m, 3H), 7.06 (s, 2H), 6.25 (s, 1H), 3.76 (s, 3H), 3.61 (s, br, 2H), 2.17 (s, 6H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 150.4, 143.9, 143.2, 138.0, 137.5, 129.0, 128.8, 128.4, 128.1, 126.7, 126.3, 122.9, 122.5, 121.5, 120.9, 116.5, 81.2, 52.9, 34.2, 31.4, 17.9; FTIR (KBr) 3485, 3396, 3060, 3027, 1735, 1628, 1491, 1365, 1246, 907, 827, 733, 699 cm^{-1}; Anal. Calcd. For $C_{29}H_{31}NO_3$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.91; H, 7.22; N, 3.09.

Friedel–Crafts adduct 7c

51% yield; white solid; mp = 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 6H), 7.16 (s, 1H), 7.14 (dd, J = 8.4, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.13 (s, 1H), 3.96 (s, br, 2H), 3.68 (s, 3H), 2.09 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 150.0, 144.1, 141.4, 138.0, 137.7, 129.7, 128.7, 128.4, 128.2, 126.9, 126.6, 125.2, 123.2, 123.0, 121.7, 120.8, 118.8, 116.5, 80.6, 53.0, 34.2, 31.3, 18.1; FTIR (KBr) 3489, 3393, 3057, 2954, 1738, 1622, 1487, 1445, 1365, 1304, 1231, 1126, 1050, 1026, 899, 873, 802, 779, 731, 699 cm^{-1}; Anal. Calcd. For $C_{28}H_{28}ClNO_3$: C, 72.80; H, 6.11; N, 3.03. Found: C, 72.82; H, 6.10; N, 3.07.

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