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Copper-catalyzed oxidative cross-dehydrogenative coupling of 2*H*-chromenes and terminal alkynes†

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An efficient copper-catalyzed cross-dehydrogenative coupling of 2*H*-chromenes and terminal alkynes mediated by DDQ has been established. Protic additive EtOH proved to be crucial to harmonizing the oxidation with subsequent alkynylation step by retaining the oxidation state of oxocarbenium ion in the form of acetal. The CDC reaction exhibits good substrate scope, with a range of terminal aryl- and alkyl alkynes well tolerated. The copper-catalyzed alkynylation of 2*H*-chromene acetals with terminal alkynes were also explored.

Introduction

α-Substituted 2*H*-chromenes and their analogs represent common structural motifs in numerous biologically active natural products and synthetic pharmaceuticals exhibiting antipsychotic, antibacterial, antifungal, antiviral, anticancer, antioxidative, antidepressive, antihypertensive, and antidiabetic activities.[1] Given the significance of this privileged motif in modern pharmacology, developing an efficient, economic, and modular method to its synthesis is of paramount importance.[2] Nucleophilic substitution of 2*H*-chromene acetals has been recognized as one of the most versatile protocols to access the substructures bearing diverse α-substituent patterns.[3-7] Elegant methods have been established to install diversely hybridized carbon-centered moieties into the α-position of the skeleton. For examples, Schaus disclosed a chiral Brønsted acid-catalyzed enantioselective vinylation and arylation of 2*H*-chromene acetals with corresponding boronate esters with excellent enantiocontrol.[3] Moreover, the Doyle group developed a nickel-catalyzed coupling of chromene acetals with aryl boronic acids in high efficiency.[4] Watson reported the catalytic enantioselective alkynylation of 2*H*-chromene acetals with a variety of terminal alkynes in the presence of a combination of $BF_3{\cdot}OEt_2$ and dicyclohexyl methyl amine.[5] Rueping and co-workers reported an asymmetric alkylation of 2*H*-chromene acetals with aldehydes by adopting a synergistic catalytic strategy.[6]

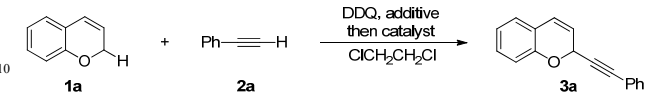
Albeit great innovations, at least one of the two coupling components requires prefunctionalizations.[8] The direct cross-dehydrogenative coupling (CDC) of 2*H*-chromenes with readily available C–H components represents an ideal synthetic strategy with a minimal amount of intermediary refunctionalizations and with high atom economy.[9,10] In this context, we have reported CDC reactions of 2*H*-chromenes with 1,3-dicarbonyl compounds[11] and electron-rich arenes,[12] providing respective alkylation and arylation compounds. However, the corresponding CDC of 2*H*-chromenes with terminal alkynes has never been established to date, which might be ascribed to their relatively weak nucleophilicity compared to 1,3-dicarbonyl compounds and electron-rich arenes.[13] In addition, alkyne moieties are pervasive structural elements in chemistry, biology, material science, and medicine, and serve as versatile handles for a variety of functional groups. Particularly, replacing the complicated α-substitutions of anticancer alkaloids with simple alkyne moieties has recently been demonstrated as a practical strategy to maintain the intrinsic biological activity while simplifying the whole synthesis.[14] Therefore, a practical and efficient CDC of 2*H*-chromenes with terminal alkynes to rapidly access a multitude of α-substituted chromene analogs remains highly desired.

Results and discussion

Initially, the CDC of 2*H*-chromene **1a** and phenylacetylene **2a** using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as the oxidant was selected as the model reaction for optimization (Table 1). No expected alkynylation product **3a** was observed when CuBr was employed as the catalyst (entry 1, Table 1). Since DDQ has been demonstrated to effect the oxidation of **1a**,[11] such observation might be ascribed to the low stability of oxidized oxocarbenium intermediate towards the subsequent capture by **2a**. We envisioned that a protic additive might be beneficial to harmonize the oxidation with subsequent alkynylation.[15] When one equiv of EtOH was introduced, desired **3a** was isolated in 8% yield (entry 2, Table 1). The reaction at 80 °C afforded an improved yield of 21% (entry 3, Table 1). Next, an extensive investigation of different copper catalysts revealed $Cu(CN)_4PF_6$ as the ideal choice, furnishing **3a** in 60% yield (entries 4-10, Table 1). Other protic additives like MeOH and ^{i}PrOH did not provide better results (entries 10-12, Table 1). The reaction proved to be highly dependent on the solvent choice; performing the oxidation in CH_2Cl_2 and subsequent coupling in toluene gave

the expected **3a** in 80% yield (entry 13, Table 1). The use of K_2CO_3 as the additive was found to be beneficial for improving the yield to 82% (entry 14, Table 1). Inferior results were obtained when other common oxidants for CDC reactions including $PhI(OAc)_2$, $Na_2S_2O_8$, MnO_2, and *tert*-butyl hydroperoxide (TBHP) were used (entry 15, Table 1).

Table 1. Reaction condition optimization.[a]



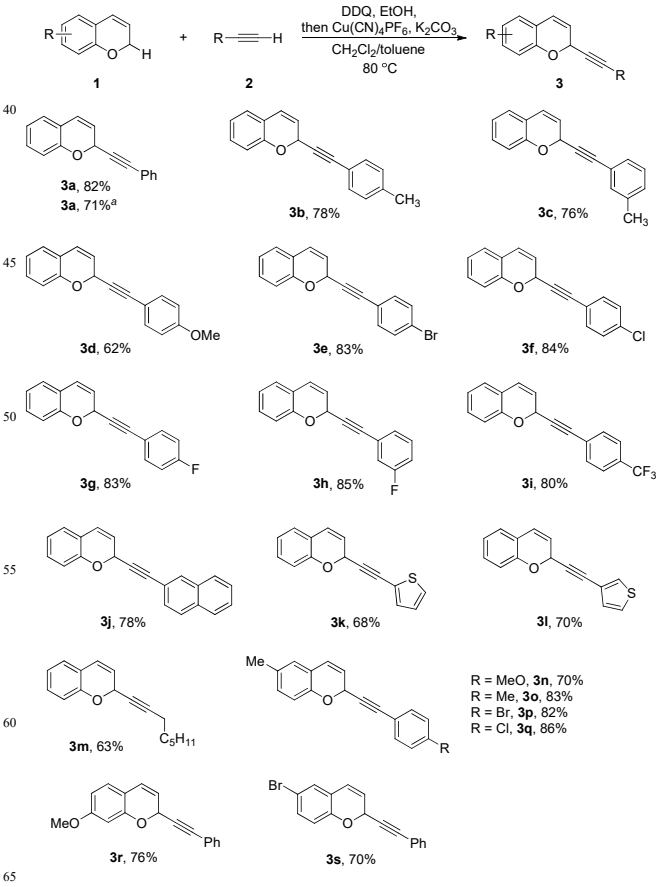
1a **2a** **3a**

Entry	Catalyst	Additive	Yield[b] (%)
1	CuBr	—	< 5
2	CuBr	EtOH	8
3[c]	CuBr	EtOH	21
4[c]	$CuBr_2$	EtOH	< 5
5[c]	CuCl	EtOH	23
6[c]	$CuCl_2$	EtOH	< 5
7[c]	CuI	EtOH	15
8[c]	CuOAc	EtOH	< 5
9[c]	CuCN	EtOH	10
10[c]	$Cu(CN)_4PF_6$	EtOH	60
11[c]	$Cu(CN)_4PF_6$	MeOH	58
12[c]	$Cu(CN)_4PF_6$	^{i}PrOH	41
13[d]	$Cu(CN)_4PF_6$	EtOH	80
14[d,e]	$Cu(CN)_4PF_6$	EtOH	82
15[f]	$Cu(CN)_4PF_6$	EtOH	< 20

[a]General conditions: **1a** (0.1 mmol), DDQ (0.11 mmol), and additive (0.11 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) at rt for 1 h, followed by **2a** (0.15 mmol), and catalyst (10 mol%) at rt for 5 h. [b]Isolated yield. [c]Performing the oxidation in $ClCH_2CH_2Cl$ at rt, and coupling in at 80 °C. [d]Performing the oxidation in CH_2Cl_2 (0.5 mL) at rt, followed by alkynylation in toluene (1.2 mL) at 80 °C. [e]Rection with 0.3 equiv of K_2CO_3. [f]$PhI(OAc)_2$, $Na_2S_2O_8$, MnO_2, or TBHP as the oxidant.

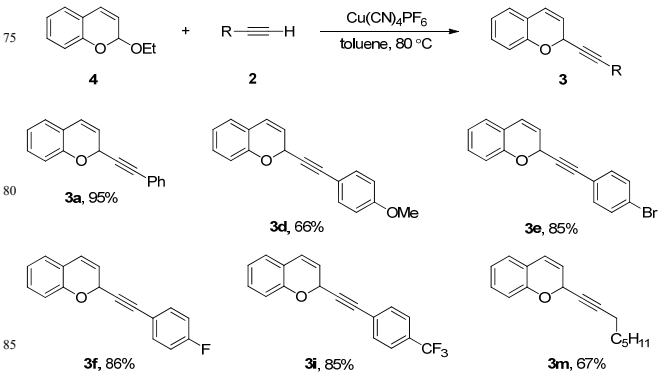
With the optimized reaction condition in hand, we investigated the scope of the CDC of 2*H*-chromenes with terminal alkynes (Scheme 1). The reaction proved to be fairly general for a variety of electronically varied aryl acetylenes with different substituent patterns (**3a**-**3i**). Electron-donating moieties (**3b**-**3d**) together with electron-withdrawing halides (**3e**-**3h**) and trifluoromethyl (**3i**) ones were well tolerated with up to 85% yield. 2-Naphthyl acetylene (**3j**) and heteroaryl acetylenes (**3k** and **3l**) were viable coupling components. Besides arylacetylenes, alkyl acetylene was also found to be compatible with the CDC reaction, as demonstrated by the generation of **3m** in 63% yield. The CDC of electronically varied 2*H*-chromenes with different substituent patterns with and diverse aryl acetylenes proceeded smoothly, providing **3n**-**3s** in high efficiency. The mild CDC reaction exhibits good functional group compatibility for further manipulations.

During the standard CDC reaction of **1a** with **2a**, a considerable amount of an intermediate was observed by TLC



Scheme 1. The CDC reaction scope. [a]Reaction in 1.0 g scale.

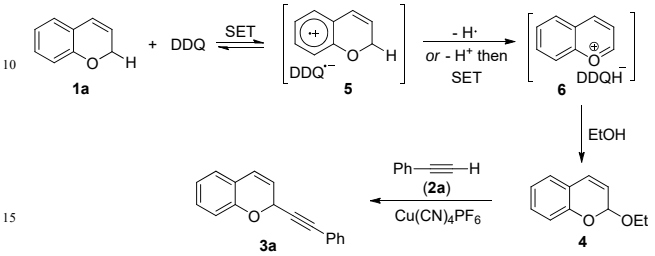
analysis, which was identified as EtOH adduct acetal **4** (Scheme 2). Accordingly, a control experiment was performed to explore the role of EtOH by subjecting **4** to the standard CDC conditions (Scheme 2). Comparable yields to those of CDC processes were obtained, suggesting that acetal **4** might be an intermediate for the CDC process.



Scheme 2. Alkynylation of 2*H*-chromene acetals.

The DDQ-mediated oxidation of 2*H*-chromenes was significantly suppressed by adding stoichiometric amount of radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) or TEMPO, thus indicating that a radical intermediate might be involved. Based on these preliminary studies, a plausible mechanism was proposed (Scheme 3). 2*H*-chromene **1a** might

undergo a single electron transfer (SET) to DDQ giving radical cation **5**, which then proceeds through a hydrogen atom abstraction or proton abstraction followed by a SET to generate α,β-unsaturated oxocarbenium intermediate **6**.[16] A stoichiometric protic additive EtOH rapidly capture **6** to give 2*H*-chromene acetal **4** for subsequent alkynylation.



Scheme 3. A proposed mechanism.

Conclusions

In conclusion, an efficient copper-catalyzed CDC of 2*H*-chromenes and terminal alkynes using DDQ as the oxidant is described. Protic additive EtOH proved to be crucial to harmonizing the oxidation with subsequent alkynylation step by retaining the oxidation state of oxocarbenium ion in the form of acetal. The copper-catalyzed alkynylation of 2*H*-chromene acetals with terminal alkynes were also explored. Ongoing studies focus on the developing the catalytic asymmetric variant of on the discovery of biologically important small molecules.

Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 500 MHz and 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23 ppm. Analytical TLC was performed on precoated silica gel GF254 plates. HRMS were carried out using an Orbitrap analyzer.

General procedure for the oxidative C–H alkynylation of 2*H*-chromenes (Scheme 1)

To a solution of 2*H*-chromene **1a** (0.1 mmol, 1.0 eq) in CH_2Cl_2 (0.5 mL) was added EtOH (0.14 mmol, 1.4 eq) and DDQ (0.12 mmol, 1.2 eq) successively at rt. The mixture was stirred at that temperature under N_2 atmosphere until all the **1a** disappeared monitored by TLC. Then toluene (1.2 mL) was added and volatiles were removed under reduced pressure. After that, $Cu(CN)_4PF_6$ (0.01 mmol, 10 mol%), K_2CO_3 (0.03 mmol, 0.3 eq), and terminal alkyne (0.15 mmol, 1.5 eq) were added, and the mixture was stirred at 80 °C for 5 h. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (5 : 95) as an eluent to give the desired product.

2-(Phenylethynyl)-2*H*-chromene (3a)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3a** as a light yellow oil (19.0 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.33–7.27 (m, 3H), 7.17 (td, *J* = 7.9, 1.2 Hz, 1H), 7.07–7.02 (m, 1H), 6.97–6.88 (m, 2H), 6.53 (d, *J* = 9.4 Hz, 1H), 5.85 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.83–5.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 132.1, 129.7, 128.8, 128.4, 126.9, 124.8, 122.3, 122.2, 122.0, 121.6, 116.6, 86.2, 85.9, 65.2; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{17}H_{13}O$: 233.0961, found 233.0976.

2-(*p*-Tolylethynyl)-2*H*-chromene (3b)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3b** as a yellow oil (19.2 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.20–7.15 (m, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 2H), 6.52 (d, *J* = 9.5 Hz, 1H), 5.86 (dd, *J* = 9.5, 3.9 Hz, 1H), 5.83–5.79 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 139.0, 132.0, 129.6, 129.1, 126.9, 124.7, 122.4, 121.9, 121.6, 119.2, 116.6, 86.0, 85.5, 65.3, 21.6; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{18}H_{15}O$: 247.1117, found 247.1110.

2-(*m*-Tolylethynyl)-2*H*-chromene (3c)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3c** as a light yellow oil (18.6 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.20–7.14 (m, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.95–6.89 (m, 2H), 6.52 (dd, *J* = 9.5, 0.8 Hz, 1H), 5.85 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.80 (dd, *J* = 4.0, 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 138.0, 132.6, 129.7, 129.6, 129.1, 128.2, 126.9, 124.7, 122.3, 122.1, 121.9, 121.6, 116.6, 86.0, 85.8, 65.2, 21.3; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{18}H_{15}O$: 247.1117, found 247.1122.

2-((4-Methoxyphenyl)ethynyl)-2*H*-chromene (3d)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3d** as a light yellow oil (16.2 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2H), 7.15 (td, *J* = 7.8, 1.6 Hz, 1H), 7.03 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.95–6.87 (m, 2H), 6.84–6.77 (m, 2H), 6.51 (d, *J* = 9.5 Hz, 1H), 5.84 (dd, *J* = 9.5, 3.9 Hz, 1H), 5.79 (dd, *J* = 3.9, 1.5 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 152.7, 133.6, 129.6, 126.9, 124.7, 122.5, 121.9, 121.6, 116.6, 114.0, 113.3, 85.9, 84.9, 65.4, 55.4; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{18}H_{15}O_2$: 263.1067, found 263.1059.

2-((4-Bromophenyl)ethynyl)-2*H*-chromene (3e)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3e** as a light yellow oil (25.6 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.3 Hz, 2H), 7.31–7.27 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.97–6.86 (m, 2H), 6.52 (d, *J* = 9.5 Hz, 1H), 5.88–5.76 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 133.5, 132.1, 131.7, 129.7, 128.4, 127.0, 124.9, 123.2, 122.0, 121.4, 116.6,

87.3, 84.8, 65.1; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{17}H_{12}BrO$: 311.0066, found 311.0061.

2-((4-Chlorophenyl)ethynyl)-2*H*-chromene (3f)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3f** as a light yellow oil (22.2 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.23 (m, 2H), 7.16 (td, *J* = 7.8, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.95–6.88 (m, 2H), 6.52 (d, *J* = 9.4 Hz, 1H), 5.83 (dd, *J* = 9.4, 4.0 Hz, 1H), 5.79 (dd, *J* = 4.0, 1.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 134.9, 133.3, 129.7, 128.7, 127.0, 124.9, 122.0, 121.9, 121.5, 120.8, 116.6, 87.2, 84.7, 65.1; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{17}H_{12}ClO$: 267.0571, found 267.0578.

2-((4-Fluorophenyl)ethynyl)-2*H*-chromene (3g)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3g** as a light yellow oil (20.7 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2H), 7.17 (td, *J* = 7.8, 1.6 Hz, 1H), 7.05 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.01–6.96 (m, 2H), 6.95–6.89 (m, 2H), 6.53 (d, *J* = 9.5 Hz, 1H), 5.84 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.80 (dd, *J* = 4.0, 1.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 161.9, 152.5, 134.0, 129.7, 127.0, 124.8, 122.0, 121.5, 118.4, 116.6, 115.7, 85.9, 84.8, 65.1; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{17}H_{12}FO$: 251.0867, found 251.0875.

2-((3-Fluorophenyl)ethynyl)-2*H*-chromene (3h)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3h** as a light yellow oil (21.2 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.22 (m, 1H), 7.22–7.15 (m, 2H), 7.12 (ddd, *J* = 9.4, 2.4, 1.3 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.04–6.99 (m, 1H), 6.97–6.89 (m, 2H), 6.53 (d, *J* = 9.5 Hz, 1H), 5.84 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.80 (dd, *J* = 4.0, 1.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 161.4, 152.4, 130.0, 129.7, 127.9, 127.0, 125.0, 124.1, 122.0, 121.5, 118.9, 116.6, 116.2, 87.1, 84.5, 65.0; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{17}H_{12}FO$: 251.0867, found 251.0870.

2-((4-(Trifluoromethyl)phenyl)ethynyl)-2*H*-chromene (3i)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3i** as a light yellow oil (24.0 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (q, *J* = 8.5 Hz, 4H), 7.19 (td, *J* = 7.9, 1.4 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.94 (dd, *J* = 14.1, 7.7 Hz, 2H), 6.55 (d, *J* = 9.2 Hz, 1H), 5.84 (dt, *J* = 8.0, 4.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 132.3, 130.5, 129.8, 127.0, 126.1, 125.3, 125.1, 122.9, 122.1, 121.6, 121.4, 116.6, 88.6, 84.4, 65.0; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{18}H_{12}F_3O$: 301.0835, found 301.0832.

2-(Naphthalen-2-ylethynyl)-2*H*-chromene (3j)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3j** as a light yellow oil (22.0 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.82–7.76 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.52–7.45 (m, 3H), 7.19 (td, *J* = 7.8, 1.6 Hz, 1H), 7.07 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.99–6.92 (m, 2H), 6.56 (d, *J* = 9.1 Hz, 1H), 5.93–5.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 133.1, 132.9, 132.2, 129.7, 128.6, 128.0, 127.9, 127.9, 127.0, 126.7, 124.8, 122.2, 122.0, 121.6, 119.6, 116.7, 86.5, 86.2, 65.3; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{21}H_{15}O$: 283.1117, found 283.1110.

2-(Thiophen-2-ylethynyl)-2*H*-chromene (3k)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3k** as a light yellow oil (16.2 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 4.5 Hz, 1H), 7.22 (d, *J* = 3.5 Hz, 1H), 7.17 (td, *J* = 7.9, 1.4 Hz, 1H), 7.05 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.93 (dt, *J* = 15.8, 6.6 Hz, 3H), 6.56–6.50 (m, 1H), 5.87–5.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 133.1, 129.7, 127.9, 127.1, 127.0, 124.9, 122.2, 122.0, 121.7, 121.4, 116.6, 90.1, 79.2, 65.3; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{15}H_{11}OS$: 239.0525, found 239.0520.

2-(Thiophen-3-ylethynyl)-2*H*-chromene (3l)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3l** as a light yellow oil (16.6 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 2.9, 0.9 Hz, 1H), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (td, *J* = 7.8, 1.5 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.05 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.96–6.88 (m, 2H), 6.52 (d, *J* = 9.4 Hz, 1H), 5.84 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.80 (dd, *J* = 4.0, 1.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 130.1, 129.9, 129.7, 126.9, 125.4, 124.8, 122.1, 122.0, 121.5, 121.3, 116.6, 85.8, 81.0, 65.2; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{15}H_{11}OS$: 239.0525, found 239.0536.

2-(Oct -1-yn-1-yl)-2*H*-chromene (3m)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3m** as a light yellow oil (15.1 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.9, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.93–6.85 (m, 2H), 6.45 (dd, *J* = 9.6, 0.9 Hz, 1H), 5.75 (dd, *J* = 9.6, 3.8 Hz, 1H), 5.58–5.53 (m, 1H), 2.20 (td, *J* = 7.2, 2.0 Hz, 2H), 1.52–1.44 (m, 2H), 1.38–1.18 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 129.5, 126.8, 124.3, 123.1, 121.8, 121.7, 116.6, 87.3, 65.1, 31.4, 28.6, 28.5, 22.6, 18.9, 14.2; HRMS (EI) *m*/*z* [M + H]$^+$ calculated for $C_{17}H_{21}O$: 241.1587, found 241.1596.

2-((4-Methoxyphenyl)ethynyl)-6-methyl-2*H*-chromene (3n)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3n** as a light yellow oil (19.3 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.97 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.86 (d, *J* = 1.4 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 9.5 Hz, 1H), 5.84 (dd, *J* = 9.5, 3.9 Hz, 1H), 5.77 (dd, *J* = 3.9, 1.5 Hz, 1H), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 138.9, 132.0, 131.1, 130.0, 129.1, 127.4, 124.8, 122.4,

121.4, 119.3, 116.3, 85.9, 85.6, 65.2, 21.6, 20.7; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{19}H_{17}O_2$: 277.1223, found 277.1231.

6-Methyl-2-(*p*-tolylethynyl)-2*H*-chromene (3o)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3o** as a light yellow oil (21.5 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 6.96 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.83–6.78 (m, 3H), 6.47 (dd, *J* = 9.5, 1.1 Hz, 1H), 5.83 (dd, *J* = 9.5, 3.9 Hz, 1H), 5.75 (dd, *J* = 3.9, 1.6 Hz, 1H), 3.79 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 150.5, 133.6, 131.1, 130.0, 127.4, 124.8, 122.5, 121.4, 116.3, 114.4, 114.0, 85.8, 85.0, 65.3, 55.4, 20.7; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{19}H_{17}O$: 261.1274, found 261.1270.

2-((4-Bromophenyl)ethynyl)-6-methyl-2*H*-chromene (3p)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3p** as a light yellow oil (26.6 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.31–7.28 (m, 2H), 6.96 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.86 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 9.5 Hz, 1H), 5.84 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.77 (dd, *J* = 3.9, 1.5 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 132.1, 131.2, 130.1, 128.8, 128.3, 127.4, 124.9, 122.4, 122.3, 121.4, 116.4, 86.3, 85.7, 65.2, 20.7; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{18}H_{14}BrO$: 325.0223, found 325.0216.

2-((4-Chlorophenyl)ethynyl)-6-methyl-2*H*-chromene (3q)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3q** as a light yellow oil (24.0 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2H), 7.27–7.22 (m, 2H), 6.96 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.85 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 9.5 Hz, 1H), 5.82 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.75 (dd, *J* = 3.9, 1.2 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 134.9, 133.3, 131.3, 130.2, 128.7, 127.4, 125.1, 122.0, 121.3, 120.8, 116.3, 87.3, 84.5, 65.1, 20.7; HRMS (EI) *m/z* $[M + H]^+$ calculated for $C_{18}H_{14}ClO$: 281.0728, found 281.0720.

7-Methoxy-2-(phenylethynyl)-2*H*-chromene (3r)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3r** as a light yellow oil (19.8 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2H), 7.35–7.27 (m, 3H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.57–6.42 (m, 3H), 5.79 (dd, *J* = 3.9, 1.5 Hz, 1H), 5.72 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 154.0, 132.2, 128.9, 128.4, 127.7, 124.6, 122.5, 119.3, 115.0, 108.0, 102.5, 86.5, 85.8, 65.5, 55.6; HRMS (EI) m/z $[M + H]^+$ calculated for $C_{18}H_{15}O_2$: 263.1067, found 263.1057.

6-Bromo-2-(phenylethynyl)-2*H*-chromene (3s)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford **3s** as a light yellow oil (21.6 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.39 (m, 2H), 7.36–7.27 (m, 3H), 7.27–7.24 (m, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.90 (dd, *J* = 9.6, 4.1 Hz, 1H), 5.80 (dd, *J* = 4.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 132.3, 132.2, 129.5, 129.0, 128.5, 123.8, 123.5, 123.5, 122.2, 118.5, 114.1, 86.4, 85.6, 65.4; HRMS (EI) m/z $[M + H]^+$ calculated for $C_{17}H_{12}BrO$: 311.0066, found 311.0075.

General procedure for the alkynylation of 2*H*-chromenes (Scheme 2)

To a solution of 2*H*-chromene **4** (0.1 mmol, 1.0 eq) in toluene (1.0 mL) was added $Cu(CN)_4PF_6$ (0.01 mmol, 10 mol%) and terminal alkyne (0.15 mmol, 1.5 eq). The mixture was stirred at 80 °C for 3 h before the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (5 : 95) as an eluent to give the desired product.

Conflicts of interest

There are no conflicts to declare.

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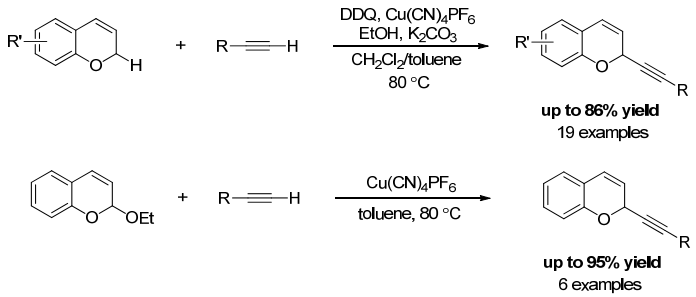

A practical cross-dehydrogenative coupling of 2*H*-chromenes with terminal alkynes is described.