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Palladium-Catalyzed Cascade Cyclization−Oxidative Olefination of *tert*-Butyl 2-Alkynylbenozates

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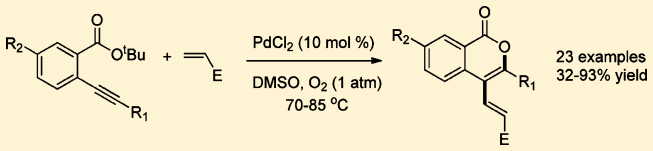
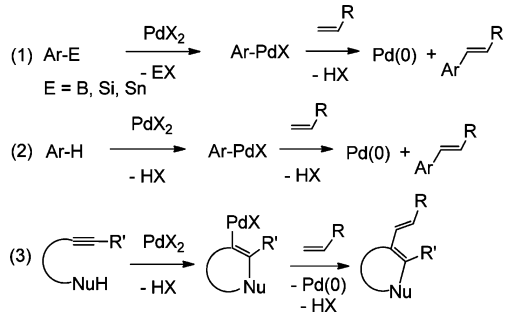
Supporting Information

ABSTRACT: Palladium(II) can catalyze the oxidative coupling of *tert*-butyl 2-alkynylbenzoates with olefins such as acrylates and styrenes, leading to isocoumarines. The reaction was carried out under simple aerobic conditions, and in most cases, high selectivity has been attained.



Palladium-catalyzed olefination reactions under oxidative conditions leading to C−C coupling have attracted increasing attention and have found widespread applications in the synthesis of complex structures.[1] In these systems, the intermediacy of an active organopalladium species is a prerequisite for subsequent olefination. In this context, three distinctive strategies for the construction of a Pd−C bond have been successfully utilized in catalytic systems (Scheme 1): (1) transmetalation using organo-main group reagents,[2] (2) palladium-catalyzed C−H activation,[1a,3] and (3) nucleopalladation.[4] While the former two methods enable ready construction of C−C bonds, the nucleopalladation-oxidative olefination pathway offers powerful and practical strategies for the construction of (hetero)cyclic ring structures because both C−E (E = C, N, and O) and C−C bonds are readily constructed in this tandem process. This strategy has found applications in the synthesis of complex heterocycles. These reactions are achieved owing to the unique dual role of palladium catalysts in promoting two or more intrinsically different reactions. They activate a C−C π-bond toward the addition of a tethered nucleophile to afford active organopalladium species, which then react with an olefin through carbopalladation and β-H elimination steps to yield the olefination product. The active palladium(II) species is then regenerated when the Pd(0) species is oxidized.

Scheme 1. Organopalladium Species in Oxidative Olefination



Various methods for the catalytic synthesis of useful (hetero)cycles have been developed by taking advantage of this tandem nucleopalladation−oxidative olefination.[5−7] In many cases, protic nucleophiles tethered to alkynes are used, including carbamate,[5a] sulfonamides,[5b] phenol,[5c,6d,7d] and anilines.[5b,7d] While the heterocyclization process can readily occur in these systems, the released HX byproduct (Scheme 1) may pose problems in that the resulting Pd−C bond is susceptible to protonolysis to give a C−H bond.[7d] While in principle this protonolysis would not have a detrimental effect when the resulting C−H bond is reversibly activated to give back the nucleopalladation species as in the palladation of electron-rich heterocycles such as benzofurans and indoles,[6d,7d] the olefination step will proceed in low efficiency if the protonolysis is irreversible and if the nucleopalladation species is too transient. To achieve high efficiency, the reaction conditions need to be optimized to reach a sufficiently high ratio of the rate of the subsequent olefination reaction (olefin insertions and β-hydrogen elimination) to that of protonolysis. Alternatively, aprotic nucleophiles functionalized with a removable protecting group such as a ^{t}Bu-protected nitrogen group (Scheme 2) can be used, and a stabilized cationic center in the incipient nucleopalladation intermediate is generated upon cyclization (Scheme 2).[7b,8] This organopalladium species is so stabilized that it is sufficiently stabilized for subsequent reactions with an olefin. While this key palladium species can still undergo the elimination of a proton, the proton here behaves in a buffered fashion. Thus, ideally the highest efficiency of this tandem reaction can be reached when deprotonation occurs only after the carbopalladation or subsequent steps. Indeed, this general strategy has been successfully demonstrated by Larock[7a] and Loh[7b] in the Pd(II)-catalyzed synthesis of isoquinolines and naphthalenes, respectively (Scheme 2).

Isocoumarins are an important class of heterocycles that are widely present in natural products and in synthetic pharmaceuticals.[9] Several synthetic methods have been reported.[10−12] Miura reported the synthesis of isocoumarins

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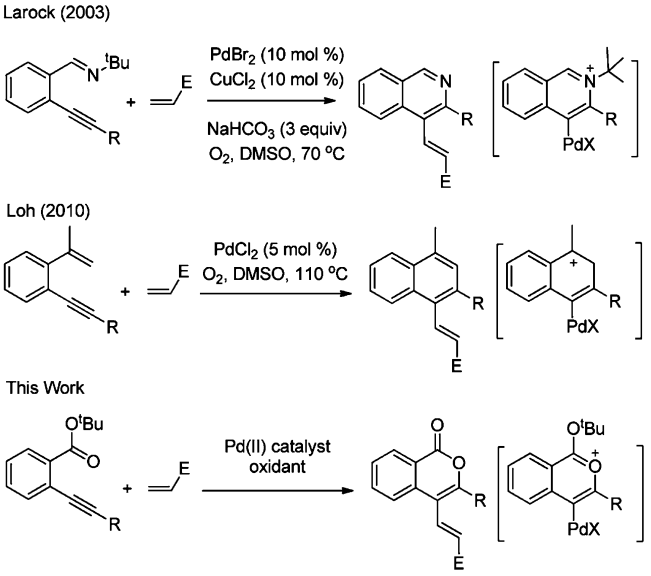
Scheme 2. Cyclization−Olefination via a Stabilized Cationic Intermediate

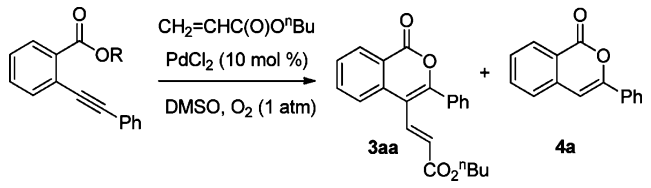


via rhodium(III)-catalyzed oxidative coupling of benzoic acids with alkynes.[11] However, products are often isolated as a mixture of isomers when unsymmetrical alkynes are used.[11a] Larock reported the synthesis of olefinated isocoumarins via a two-step sequence, in which formation of haloarenes and a subsequent Heck coupling is followed, but it has limited atom-economy.[12] We now report the synthesis of olefinated isocoumarins via a simple tandem cyclization−oxidative olefination strategy starting from alkenes and *tert*-butyl *ortho*-alkynylbenzoates.

We reasoned that in principle, olefinated isocoumarins are synthesizable from a cyclization−oxidative olefination cascade starting from *o*-alkynylbenzoic acids and olefins. Thus, we initiated our studies using 2-(phenylethynyl)benzoic acid as a substrate. Given that DMF and DMSO are commonly used as solvents in this type of reaction, this acid was allowed to react with *n*-butyl acrylate in DMSO using $PdCl_2$ (10 mol %) as a catalyst (Table 1, entry 1). To our disappointment, the simple cycloisomerization product **4a** was isolated as the major one in 45% yield, together with some unidentifiable decomposition products. The failure of any olefination reaction likely indicates that the Pd−C bond in the carboxypalladation intermediate is irreversibly cleaved by an acid in the reaction media. To enable efficient olefination, we resorted to *tert*-butyl *ortho*-alkynylbenzoate as a substrate, which can be regarded as a protected form of the corresponding benzoic acids. Indeed, smooth cyclization−olefination occurred, and the desired product was isolated in 71% yield with no simple cyclization product being isolated (Table 1, entry 2). It should be noted that this ester substrate is superior to the acid analogue not only in terms of reaction selectivity and efficiency, but also by saving one less step for the preparation of the ester substrate. With this preliminary result in hand, we have explored the more readily available *iso*-propyl ester as a substrate. Reactions conducted under the same conditions using this *iso*-propyl ester also afforded **3aa** as the major product, but the yield is somewhat lower (65%). Thus, the *tert*-butyl ester was retained for further screening. By simply lowering the reaction temperature to 85 °C, the isolated yield of the product **3aa** was improved to 87%. These optimal conditions are eco-friendly since molecular oxygen is the sole oxidant for this facile construction of C−O and C−C bonds in high regioselectivity.

With the optimized conditions in hand, we next examined the scope and generality of the olefin substrate in the coupling with alkyne **1a**. Various acrylate esters readily coupled with **1a** under the standard conditions to afford the olefination products in yields ranging from 48 to 92% (Scheme 3, **3aa**−**ad**), with the lowest yield being obtained for *tert*-butyl acrylate. In the case of benzyl acrylate, the simple cyclization product **4a** was isolated in 23% yield in addition to the major desired product **3ab** (71%). In addition, various styrenes are also applicable, and full conversion of substrate **1a** was reached when it was allowed to react with simple styrene at 85 °C, where product **3ae** was isolated in 64% yield. This indicates the limited selectivity of this reaction. Gratifyingly, by lowering the reaction temperature to 75 °C, the selectivity is improved and product was isolated in 74% yield. Under these conditions, 4-chlorostyrene readily coupled with **1a** to afford **3af** in 79% yield. In contrast, acrylonitrile failed to give any olefination product, and only the cyclization product **4a** was isolated in 87% yield. Substituents such as Me, Cl, and OMe are well tolerated when they are introduced to both phenyl rings of the arylalkyne−ester substrate, and these substituted substrates smoothly coupled with acrylates and styrenes. The reaction seems insensitive to the Me and Cl substituents introduced into the benzoate ring, and comparably high yields were isolated. While in most cases high selectivity was achieved, the coupling of a *p*-MeO(C_6H_4)-functionalized alkyne (**1e**) with benzyl acrylate afforded the cyclization product as the minor product (35%) along with the expected major olefination product (56%). Here, the electronic perturbation with the introduction of a donating *para*-OMe

Table 1. Screening of Conditions for Cyclization−Olefination[a]



entry	R	temp (°C)	**3aa** (%)[b]	**4** (%)[b]
1	H	100		45
2	*t*Bu (**1a**)	100	71	
3	*i*Pr	100	65	13
4	*t*Bu (**1a**)	85	87	

[a]Conditions: **1** (0.5 mmol), **2a** (1.0 mmol), O_2 balloon, $PdCl_2$ (0.05 mmol), DMSO (3 mL), 16 h. [b]Isolated yield.

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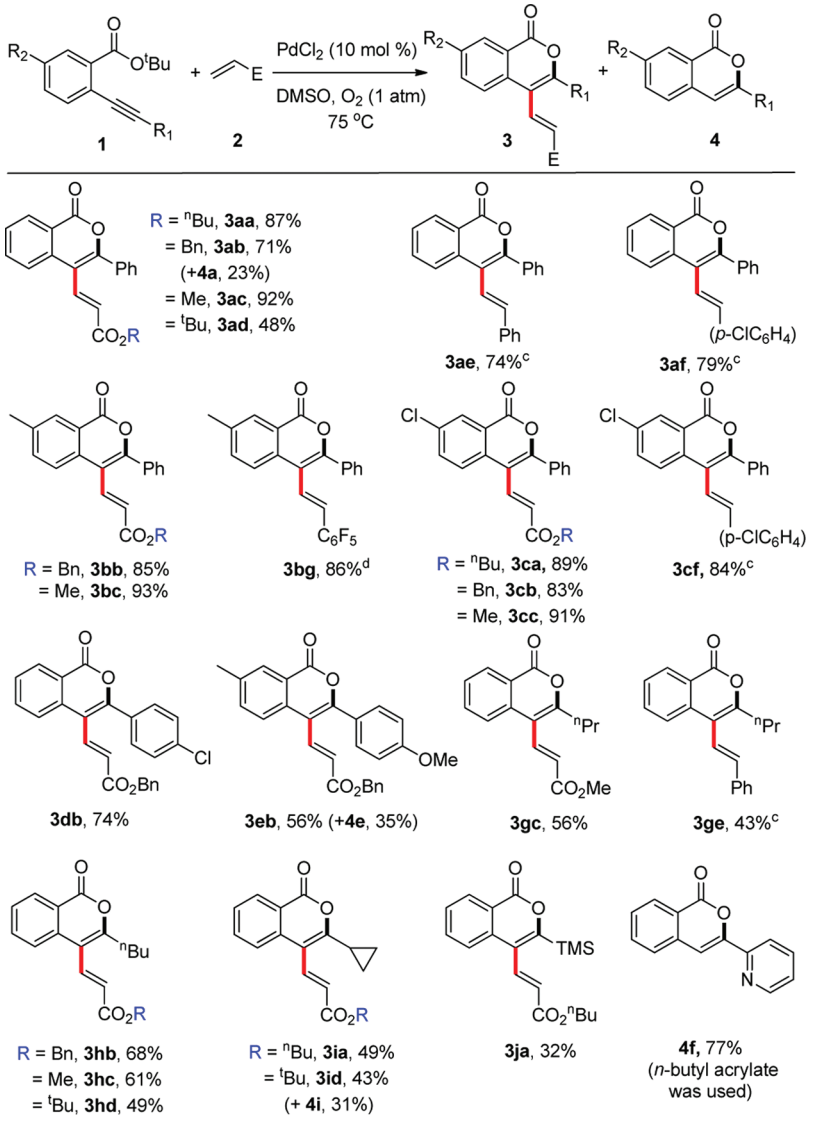
Scheme 3. Cyclization–Oxidative Olefination of *tert*-Butyl *ortho*-Alkynylbenzoates[a,b]



[a]Conditions: 2-alkynylbenzoate (0.25 mmol), alkene (0.5 mmol), $PdCl_2$ (0.025 mmol), O_2 (balloon), DMSO (2 mL), 85 °C, 16 h. [b]Isolated yield. [c]75 °C. [d]70 °C.

group in the alkynyl unit likely renders the resulting Pd–C bond more susceptible to protonolysis, leading to lower selectivity.

The alkyne terminus in the substrate plays an important role in the reactivity and selectivity of this reaction. By attaching a 2-pyridyl group to the C≡C bond, only the cyclization product (**4f**) was isolated (77%). Here, the oxypalladation intermediate is further stabilized by nitrogen chelation, and the subsequent reaction with an olefin is rendered less favorable possibly because the pyridyl nitrogen occupies a coordination site and the coordination saturation disfavors consequent alkene ligation. In contrast, substrates bearing an alkyl-functionalized alkynyl group readily coupled with acrylates and styrenes in moderate to good yields. Furthermore, a silyl-functionalized alkyne substrate is also applicable and product **3ja** was isolated in 32% yield. The relatively low yield is likely ascribed to steric effects of this alkyne group. Product **3ja** should be further functionalizable by desilylation, leading to a less-substituted isocoumarin.

A plausible mechanism is given in Scheme 4. Upon coordination to a palladium(II) catalyst, the alkyne is activated toward the nucleophilic addition of the ester carbonyl group in 6-*endo*-selectivity to generate a key oxypalladation intermediate with a stabilized carbocation. This benzylic carbocation is further stabilized by two adjacent oxygen atoms and thus should have a relatively long lifetime. This alkenyl Pd(II) species then undergoes insertion of an incoming olefin to afford a palladium(II) alkyl. At this stage, E_1 elimination is proposed for this intermediate to give an isobutene coproduct. The neutral Pd(II) alkyl then undergoes β-hydride elimination to furnish the olefination product. The Pd(0) species is then oxidized by molecular oxygen to regenerate the Pd(II) catalyst. Alternatively, the oxypalladation intermediate can undergo E_1 elimination and protonolysis to yield the undesired simple cyclization product. Clearly, the success of this reaction relies on the buffering of protons in the form of a stabilized carbocation.

In summary, we have demonstrated a cascade heterocyclization–oxidative olefination reaction in the coupling of *ortho*-

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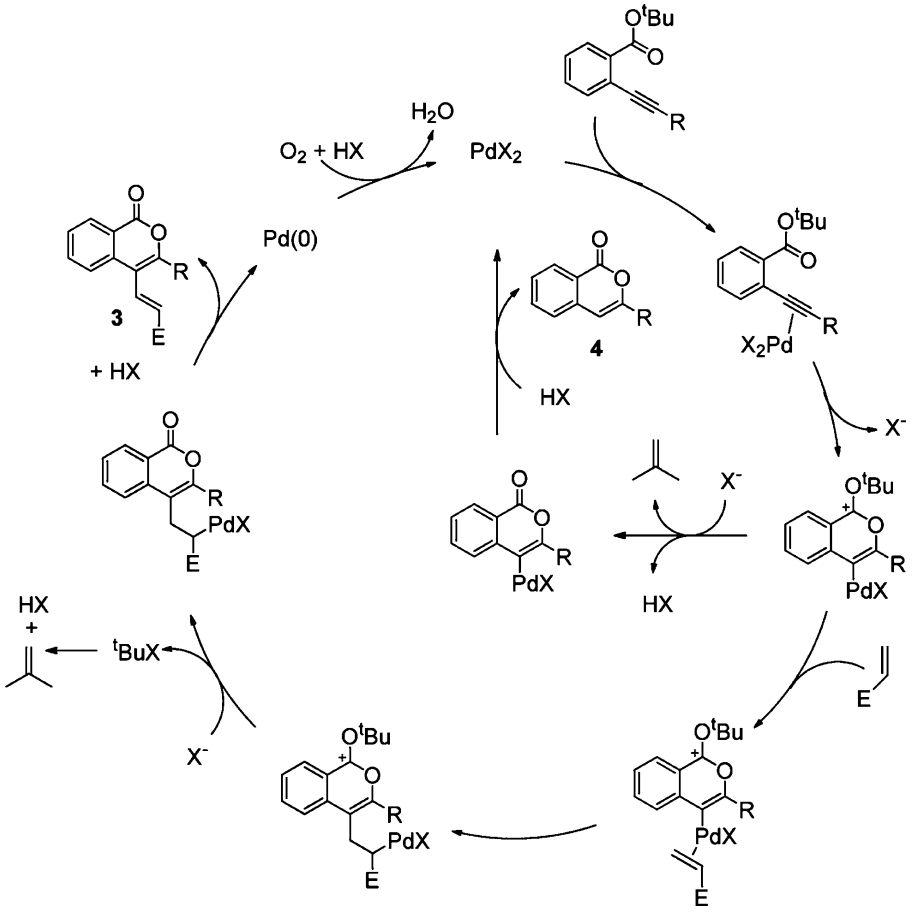
Scheme 4. Proposed Mechanism for the Formation of Isocoumarins



alkynylbenzoates with acrylates and styrenes. *tert*-Butyl benzoates proved to give the highest selectivity, and the *tert*-Bu group serves as a protected proton in this reaction such that the carbocation species generated is sufficiently stabilized. This transformation provided vinylated isocoumarins in high efficiency and step-economy using molecular oxygen as the sole oxidant. In most cases, high selectivity was achieved, and structural diversity has been attained. This protocol may find applications in the synthesis of useful complex structures.

EXPERIMANTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. All coupling constants (*J*-values) were reported in Hertz (Hz). Column chromatography was performed on silica gel (200−300 mesh) with freshly distilled ethyl acetate and petroleum ether. The alkyne substrates were prepared by following a literature report.[13]

Representative Procedure for the Preparation of Compound 3. Ester-alkyne **1a** (69.5 mg, 0.25 mmol), $PdCl_2$ (4.4 mg, 0.025 mmol), DMSO (2.0 mL), and *n*-butyl acrylate (64 mg, 0.50 mmol) were sequentially charged into an oven-dried Schlenk tube. An O_2 balloon was then attached to the reaction mixture, which was then heated at 85 °C for 16 h. The reaction mixture was then washed with saturated aqueous NaCl solution, followed by extraction with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. All volatiles were removed under reduced pressure to give a crude product, which was purified by silica gel chromatography using petroleum ether and ethyl acetate. Yield of **3aa**: 76 mg (0.22 mmol, 87%). Other cyclization−olefination products (and cyclization products **4**) were prepared by following this procedure.

3-(1-Oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Butyl Ester (3aa). White solid: mp 141−143 °C; yield 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.0, 1.0 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.79 (td, J = 8.0, 1.0 Hz, 1H), 7.68 (d, J = 16.5 Hz, 1H), 7.63−7.60 (m, 2H), 7.59−7.56 (m, 1H), 7.46−7.43 (m, 3H), 6.26 (d, J = 16.5 Hz, 1H), 4.20 (t, J = 6.8 Hz, 2H), 1.67−1.63 (m, 2H), 1.43−1.36 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 161.3, 153.6, 138.1, 136.0, 135.0, 132.3, 130.2, 130.1, 129.6, 128.5, 128.4, 125.8, 124.1, 120.5, 110.9, 64.7, 30.6, 19.1, 13.7; HRMS (ESI) Calcd for $[C_{22}H_{20}O_4 + H]^+$ 349.1440, found 349.1442.

3-(1-Oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Benzyl Ester (3ab). White solid: mp 138−140 °C; yield 71%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.0, 1.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.78 (td, J = 7.5, 1.5 Hz, 1H), 7.75 (d, J = 16.5 Hz, 1H), 7.63−7.61 (m, 2H), 7.59−7.56 (m, 1H),7.47−7.44 (m, 3H), 7.39−7.34 (m, 5H), 6.34 (d, J = 17.0 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 161.3, 153.9, 138.8, 135.9, 135.8, 135.1, 132.4, 130.5, 130.3, 129.8, 128.7 (two overlapping signals), 128.5, 128.4, 128.3, 125.3, 124.1, 120.6, 110.9, 66.6; HRMS (ESI) Calcd for $[C_{25}H_{18}O_4 + H]^+$ 383.1283, found 383.1285.

3-(1-Oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Methyl Ester (3ac). White solid: mp 144−145 °C; yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, J = 8.0, 0.8 Hz, 1H), 7.84−7.82 (m, 1H), 7.79 (td, J = 6.8, 1.2 Hz, 1H), 7.70 (d, J = 16.0 Hz, 1H), 7.62−7.56 (m, 3H), 7.47−7.44 (m, 3H), 6.27 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 161.3, 153.6, 138.4, 135.9, 135.0, 132.3, 130.2, 130.2, 129.6, 128.6, 128.4, 125.4, 124.0, 120.5, 110.8, 51.9; HRMS (ESI) Calcd for $[C_{19}H_{14}O_4 + H]^+$ 307.0970, found 307.0971.

3-(1-Oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Tert-Butyl Ester (3ad). White solid: mp 113−115 °C; yield 48%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.80 (td, J = 7.5, 1.5 Hz, 1H), 7.64−7.62 (m, 2H), 7.59−7.55

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(m, 2H), 7.46 (t, J = 3.0 Hz, 3H), 6.19 (d, J = 16.0 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 161.4, 153.4, 137.0, 136.2, 135.0, 132.4, 130.2, 130.1, 129.7, 128.6, 128.4, 127.6, 124.3, 120.6, 111.1, 81.1, 28.2; HRMS (ESI) Calcd for $[C_{22}H_{20}O_4 + H]^+$ 349.1397, found 349.1400.

3-Phenyl-4-styryl-isochromen-1-one (3ae). White solid: mp 112−114 °C; yield 74%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.0, 1.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.77−7.73 (m, 3H), 7.58−7.55 (m, 1H), 7.45−7.36 (m, 7H), 7.33−7.30 (m, 1H), 6.97 (d, J = 18.0 Hz, 1H), 6.80 (d, J = 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 151.2, 137.6, 136.9, 136.8, 134.7, 133.3, 129.9, 129.6, 129.5, 128.8, 128.2, 128.1, 128.0,126.4, 124.7, 121.1, 120.8, 113.1; HRMS (ESI) Calcd for $[C_{23}H_{16}O_2 + H]^+$ 325.1197, found 325.1201.

4-[2-(4-Chloro-phenyl)-vinyl]-3-phenyl-isochromen-1-one (3af). White solid: mp 120−122 °C; yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.72−7.70 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.41−7.32 (m, 7H), 6.94 (d, J = 16.4 Hz, 1H), 6.75 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 151. 4, 137.3, 135.4, 135.1, 134.7, 133.9, 133.1, 130.0, 129.6, 129.5, 129.00, 128.2, 128.1, 127.5, 124.4, 121.7, 120.7, 112.8; HRMS (ESI) Calcd for $[C_{23}H_{15}ClO_2 + H]^+$ 359.0839, found 359.0842.

3-(7-Methyl-1-oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Benzyl Ester (3bb). Yellowish solid: mp 133−135 °C; yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.76−7.70 (m, 2H), 7.62−7.58 (m, 3H), 7.46−7.43 (m, 3H), 7.38−7.34 (m, 5H), 6.31 (d, J = 16.5 Hz, 1H), 5.25 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 161.4, 153.2, 139.1, 139.0, 136.2, 135.8, 133.3, 132.4, 130.1, 130.0, 129.7, 128.6, 128.4, 128.3, 128.2, 125.0, 124.1, 120.4, 110.8, 66.5, 21.2; HRMS (ESI) Calcd for $[C_{26}H_{20}O_4 + H]^+$ 397.1406, found 397.1401.

3-(7-Methyl-1-oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Methyl Ester (3bc). White solid: mp 150−151 °C; yield 93%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 16.0 Hz, 1H), 7.62−7.58 (m, 3H), 7.46−7.43 (m, 3H), 6.25 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 161.4, 152.9, 139.0, 138.5, 136.2, 133.4, 132.4, 130.1, 129.9, 129.6, 128.4, 125.2, 124.0, 120.4, 110.8, 51.8, 21.2; HRMS (ESI) Calcd for $[C_{20}H_{16}O_4 + H]^+$ 321.1127, found 321.1129.

7-Methyl-4-(2-pentafluorophenyl-vinyl)-3-phenyl-isochromen-1-one (3bg). White solid: mp 148−150 °C; yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.72−7.67 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 4.4 Hz, 3H), 7.32 (d, J = 17.2 Hz, 1H), 6.63 (d, J = 16.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.8, 151.6, 144.7 (dm, J = 252 Hz), 140.3 (dm, J = 250 Hz), 138.9, 137.8 (dm, J = 250 Hz), 136.2, 134.3, 132.8, 130.7 (m), 130.0, 129.8, 129.6, 128.3, 124.0, 121.0, 120.5, 112.8, 111.7 (m), 21.3; HRMS (ESI) Calcd for $[C_{24}H_{13}F_5O_2 + H]^+$ 429.0897, found 429.0903.

3-(7-Chloro-1-oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Butyl Ester (3ca). White solid: mp 120−122 °C; yield 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 2.5 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.73 (dd, J = 9.0 Hz, 1.0 Hz, 1H), 7.63−7.59 (m, 3H), 7.46−7.44 (m, 3H), 6.24 (d, J = 16.5 Hz, 1H), 4.20 (t, J = 6.8 Hz, 2H), 1.69−1.63 (m, 2H), 1.42−1.37 (m, 2H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 159.9, 153.6, 137.5, 135.1, 134.4, 134.3, 131.8, 130.3, 129.8, 129.5, 129.4, 128.3, 126.0, 125.6, 121.6, 110.2, 64.6, 30.5, 19.0, 13.5; HRMS (ESI) Calcd for $[C_{22}H_{19}ClO_4 + H]^+$ 383.1050, found 383.1053.

3-(7-Chloro-1-oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Benzyl Ester (3cb). White solid: mp 128−129 °C; yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.73−7.67 (m, 2H), 7.62−7.60 (m, 2H), 7.48−7.43 (m, 3H), 7.38−7.36 (m, 5H), 6.31 (d, J = 16.5 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 160.0, 154.0, 138.3, 135.6, 135.2, 134.6, 134.3, 131.9, 130.5, 129.6, 129.6, 128.6, 128.5, 128.4, 128.2, 125.8, 125.6, 121.8, 110.3, 66.6; HRMS (ESI) Calcd for $[C_{25}H_{17}ClO_4 + H]^+$ 417.0799, found 417.0787.

3-(7-Chloro-1-oxo-3-phenyl-1*H*-isochromen-4-yl)-acrylic Acid Methyl Ester (3cc). White solid: mp 118−120 °C; yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.4, 1.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.63−7.59 (m, 2H), 7.47 (m, 3H), 6.25 (d, J = 16.4 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.1, 153.8, 137.9, 135.2, 134.6, 134.4, 131.9, 130.5, 129.6, 129.6, 128.5, 125.7, 125.7, 121.8, 110.3, 51.9; HRMS (ESI) Calcd for $[C_{19}H_{13}ClO_4 + H]^+$ 341.0581, found 341.0576.

7-Chloro-4-[2-(4-chloro-phenyl)-vinyl]-3-phenyl-isochromen-1-one (3cf). White solid: mp 156−158 °C; yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.71−7.69 (m, 3H), 7.40 (m, 3H), 7. 34 (s, 4H), 6.90 (d, J = 16.8 Hz, 1H), 6.73 (d, J = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 135.7, 135.0, 134.9, 134.2, 134.1, 132.7, 129.7, 129.5, 129.4, 129.0, 128.9, 128.3, 127.5, 126.2, 125.3, 121.9, 121.3, 112.2; HRMS (ESI) Calcd for $[C_{23}H_{14}Cl_2O_2 + H]^+$ 393.0449, found 394.0443.

3-[3-(4-Chloro-phenyl)-1-oxo-1*H*-isochromen-4-yl]-acrylic Acid Benzyl Ester (3db). White solid: mp 118−120 °C; yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 7.84−7.77 (m, 2H), 7.71 (d, J = 16.4 Hz, 1H), 7.61−7.55 (m, 3H), 7.44−7.39 (m, 7H), 6.31 (d, J = 16.4 Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 136.6, 135.7, 135.2, 131.0, 130.8, 130.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.34, 125.87, 124.2, 120.6, 111.3, 66.7; HRMS (ESI) Calcd for $[C_{25}H_{17}ClO_4 + H]^+$ 417.0796, found 417.0787.

3-[3-(4-Methoxy-phenyl)-7-methyl-1-oxo-1*H*-isochromen-4-yl]-acrylic Acid Benzyl Ester (3eb). White solid: mp 129−131 °C; yield 56%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 16.5 Hz, 1H), 7.58−7.55 (m, 3H), 7.41−7.35 (m, 5H), 6.97−6.94 (m, 2H), 6.36 (d, J = 16.5 Hz, 1H), 5.26 (s, 2H), 3.86 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 161.6, 161.1, 153.4, 139.5, 138.7, 136.2, 135.9, 133.6, 131.4, 130.0, 128.7, 128.4, 128.3, 124.8, 124.4, 123.9, 120.3, 113.9, 101.0, 66.5, 55.4, 21.2; HRMS (ESI) Calcd for $[C_{27}H_{22}O_5 + H]^+$ 427.1545, found 427.1548.

3-(1-Oxo-3-propyl-1*H*-isochromen-4-yl)-acrylic Acid Methyl Ester (3gc). White solid: mp 103−105 °C; yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.0, 1.0 Hz, 1H), 7.73(d, J = 8.0 Hz, 1H), 7.75−7.69 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 6.23 (d, J = 16.0 Hz, 1H), 3.85 (s, 3H), 2.64 (t, J = 7.6 Hz, 2H), 1.79−1.72 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 166.4, 161.7, 156.8, 137.7, 136.2, 134.9, 129.9, 128.0, 125.4, 123.4, 120.7, 110.6, 51.9, 33. 4, 21.2, 13.7; HRMS (ESI) Calcd for $[C_{16}H_{16}O_4 + H]^+$ 273.1127, found 273.1126.

3-Propyl-4-styryl-isochromen-1-one (3ge). White solid: mp 108−110 °C; yield 43%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, J = 8.0, 1.0 Hz, 1H), 7.72−7.69 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.55−7.53 (m, 2H), 7.50−7.47 (m, 1H), 7.43 (t, J = 8.5 Hz, 2H), 736−7.32 (m, 1H), 6.97 (d, J = 16.5 Hz, 1H), 6.76 (d, J = 16.5 Hz, 1H), 2.71 (t, J = 7.5 Hz, 2H), 1.83−1.76 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 155.1, 137.9, 136.7, 136.6, 134.6, 129.6, 128.8, 128.3, 127.5, 126.5, 123.9, 120.5, 120.2, 112.7, 33.4, 21.2, 13.8; HRMS (ESI) Calcd for $[C_{20}H_{18}O_2 + H]^+$ 291.1385, found 291.1386.

3-(3-*n*-Butyl-1-oxo-1*H*-isochromen-4-yl)-acrylic Acid Benzyl Ester (3hb). Colorless oil; yield 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.0, 1.0 Hz, 1H), 7.78−7.71 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.52−7.49 (m, 1H), 7.45−7.36 (m, 5H), 6.29 (d, J = 16.5 Hz, 1H), 5.29 (s, 2H), 2.67 (t, J = 7.7 Hz, 2H), 1.75−1.68 (m, 2H), 1.42−1.38 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 161.7, 157.3, 138.1, 136.2, 135.7, 134.9, 129.9, 128.7, 128.4, 128.3, 128.0, 125.3, 123. 5, 120.1, 110.4, 66.7, 31.4, 29.9, 22.3, 13.7; HRMS (ESI) Calcd for $[C_{23}H_{22}O_4 + H]^+$ 363.1605, found 363.1612.

3-(3-Butyl-1-oxo-1*H*-isochromen-4-yl)-acrylic Acid Methyl Ester (3hc). Colorless oil; yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.6 Hz, 1H), 7.73−7.68 (m, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 6.22 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 2.65 (t, J = 7.6 Hz, 2H), 1.74−1.66 (m, 2H), 1.41−1.34 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 161.7, 157.1, 137.7, 136.2, 134.9, 129.9, 128.0, 125.3, 123.4, 120.0, 110.4, 51.9, 31.4, 29.8, 22.3, 13.7; HRMS (ESI) Calcd for $[C_{17}H_{18}O_4+H]^+$ 287.1283, found 287.1280.

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3-(3-Butyl-1-oxo-1*H*-isochromen-4-yl)-acrylic Acid *tert*-Butyl Ester (3hd). White solid: mp 90−92 °C; yield 49%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (J = 8.0, 1.0 Hz, 1H), 7.74−7.71 (m, 1H), 7.59 (t, J = 8.3 Hz, 2H), 7.50(t, J = 7.3 Hz, 1H), 6.14 (d, J = 16.0 Hz, 1H), 2.66 (t, J = 7.8 Hz, 2H), 1.73−1.68 (m, 2H), 1.55 (s, 9H), 1.42−1.38 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 161.9, 156.9, 136.5, 136.3, 134.9, 129.9, 128.0, 127.7, 123.6, 120.2, 110.6, 81.2, 31.4, 29.9, 28.2, 22.3, 13.8; HRMS (ESI) Calcd for $[C_{20}H_{24}O_4 + H]^+$ 329.1701, found 329.1710.

3-(3-Cyclopropyl-1-oxo-1*H*-isochromen-4-yl)-acrylic Acid Butyl Ester (3ia). Colorless oil; yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.0, 1.0 Hz, 1H), 7.84 (d, J = 16.0 Hz, 1H), 7.74−7.69 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48−7.44 (m, 1H), 6.36 (d, J = 16.0 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 2.17−2.13 (m, 1H), 1.73−1.67 (m, 2H), 1.47−1.41 (m, 2H), 1.27−1.23 (m, 2H), 1.01−0.95 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.3, 161.2, 156.5, 137.4, 136.6, 135.0, 129.9, 127.5, 125.9, 122.7, 119.6, 109.7, 64.8, 30.7, 19.2, 13.7, 12.3, 8.3; HRMS (ESI) Calcd for $[C_{19}H_{20}O_4 + H]^+$ 313.1440, found 313.1444.

3-(3-Cyclopropyl-1-oxo-1*H*-isochromen-4-yl)-acrylic Acid *tert*-Butyl Ester (3id). Colorless oil; yield 43%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.0, 1.0 Hz, 1H), 7.74−7.70 (m, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 6.27 (d, J = 16.0 Hz, 1H), 2.17−2.15 (m, 1H), 1.56 (s, 9H), 1.26−1.23 (m, 2H), 1.01−0.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 161.4, 156.3, 136.8, 136.4, 135.0, 129.9, 127.8, 127.5, 122.9, 119.7, 109.8, 81.2, 28.3, 12.3, 8.3; HRMS (ESI) Calcd for $[C_{19}H_{20}O_4 + H]^+$ 313.1401, found 313.1409.

3-(1-Oxo-3-trimethylsilanyl-1*H*-isochromen-4-yl)-acrylic Acid *n*-Butyl Ester (3ja). Yellow solid: mp 79−80 °C; yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.93 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 6.05 (d, J = 16.0 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 4.23 (t, J = 7.2 Hz, 2H), 1.47−1.42 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 161.4, 152.4, 142.9, 137.8, 134.6, 130.6, 125.9, 125.6, 125.1, 123.5, 121.7, 64.7, 30.8, 19.3, 13.8, 0.1; HRMS (ESI) Calcd for $[C_{19}H_{24}O_4Si + H]^+$ 345.1497, found 345.1504.

3-Phenyl-isochromen-1-one (4a). White solid: mp 79−81 °C; yield 23%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 7.89−7.87 (m, 2H), 7.73−7.69 (m, 1H), 7.50−7.41 (m, 5H), 6.95 (s, 1H). The NMR data agree with those reported in a literature.[14]

3-(4-Methoxy-phenyl)-7-methyl-isochromen-1-one (4e). White solid: mp 134−135 °C; yield 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.80 (s, H), 3.86 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 152.9, 137.9, 136.1, 135.4, 129.3, 126.6, 125.6, 124.7, 120.0 114.2, 100.2, 55.4, 29.7, 21.3; HRMS (ESI) Calcd for $[C_{17}H_{14}O_3 + H]^+$ 267.1002, found 267.1008.

3-Pyridin-2-yl-isochromen-1-one (4f). Yellow solid: mp 103−105 °C; yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 4.4 Hz, 1H), δ 8.34 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.67 (s, 1H), 7.59−7.52 (m, 2H), 7.32 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.7, 149.6, 137.2, 137.1, 134.9, 129.7, 128.8, 128.7, 126.8, 124.2, 121.3, 119.9, 103.8; HRMS (ESI) Calcd for $[C_{14}H_9NO_2 + H]^+$ 224.0705, found 224.0699.

3-Cyclopropyl-isochromen-1-one (4i). White solid: mp 70−72 °C; yield 31%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 6.30 (s, 1H), 1.84−1.77 (m, 1H), 1.09−1.06 (m, 2H), 0.95−0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 158.5, 138.0, 134.8, 129.6, 127.1, 124.6, 120.0, 101.4, 13.8, 7.0; HRMS (ESI) Calcd for $[C_{12}H_{10}O_2 + H]^+$ 187.0698, found 187.0703.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the NMR spectra of the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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