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# Photocatalyzed $Csp^3$–$Csp^3$ cross-dehydrogenative coupling of *N*-Boc-tetrahydroisoquinolines with α,β-unsaturated ketones†

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A novel photocatalyzed cross-dehydrogenative coupling reaction of *N*-Boc-tetrahydroisoquinolines with α,β-unsaturated ketones has been developed. This research provides an easy access to a variety of C1-substituted tetrahydroisoquinolines, which can be further transformed into benzo[*a*]-quinolizine-2-ones, the skeletons of natural products with a wide range of biological activities. The load of the photocatalyst is low and the oxidant is inexpensive and less toxic.



## Introduction

α,β-Unsaturated ketones are key building blocks in modern organic synthesis due to their involvement in various fundamental transformations.[1] So far the reactive sites of α,β-unsaturated ketones are mainly located at the carbonyl group (*e.g.*, 1,2-addition)[2] and the C=C double bond side, such as the α-position (*e.g.*, Baylis–Hillman reaction)[3] and the β-position (*e.g.*, Michael addition)[4] (Fig. 1). In contrast, the direct reaction on the other side of the carbonyl group was much less reported. Herein, we report a new reaction of α,β-unsaturated ketones, a direct functionalization of α′-C ($sp^3$)–H on the other side of the carbonyl group; α,β-unsaturated ketones need not be pre-functionalized.

Due to the abundance of biologically relevant molecules containing the tetrahydroisoquinoline (THIQ) motif (Fig. 2),[5] the cross-dehydrogenative coupling (CDC) reaction of THIQs has attracted intense attention from synthetic chemists.[6] The visible-light-mediated photocatalytic CDC reaction of *N*-aryl-THIQ has obtained extensive attention as a capable and environmentally benign method in the past decade.[7] The aryl group linked to the nitrogen weakens the target C–H bond, but aryl is difficult to remove for the subsequent reaction, which may limit the downstream utility of these products. Compared to the *N*-aryl group, the *N*-carbamyl group decreases the reactivity of THIQ; only a few examples have been reported.[6f–h] Furthermore, ketones as coupling partners were always transformed into more reactive enolates and their derivatives such as silyl enol ethers or enamine, because of the relatively low reactivity of ketones as electrophiles.[7d,f,n] The report on unsaturated ketones was scarce. Thus, realizing this type of reaction under mild conditions is still a challenge. Inspired by the importance of these biological molecules, and based on our long-standing interest in C–H direct functionalization, we would like to develop a visible-light-mediated photocatalytic CDC reaction of *N*-Boc-THIQs with α,β-unsaturated ketones.

## Results and discussion

To begin our study, we examined the CDC reaction of *N*-Boc-tetrahydroisoquinoline **1a** and α,β-unsaturated ketone **2a** in the presence of 5 mol% $Ru(bpy)_3Cl_2{\cdot}6H_2O$ in $CH_3CN$ under 10 W blue LED irradiation with molecular oxygen as the oxidant (Table 1, entry 1). Unfortunately, no desired product was obtained; instead **1a** was oxidized to the corresponding amide (*N*-Boc-3,4-dihydroisoquinolin-1(2*H*)-one). Then, various other oxidants were examined, and in order to avoid the influence of oxygen, the reaction was performed under an Ar atmosphere (entries 2–6). When *tert*-butyl hydroperoxide (TBHP) and 2,3-

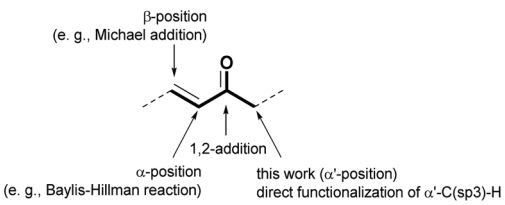


**Fig. 1** The reactions on α,β-unsaturated ketone.

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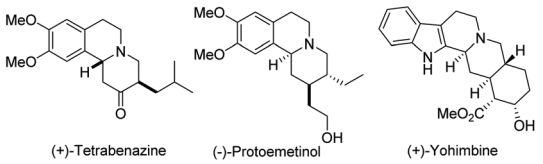
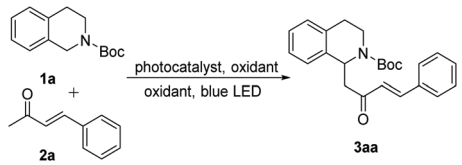



Fig. 2 Natural products containing THIQs.

Table 1 Optimization and control studies[a]

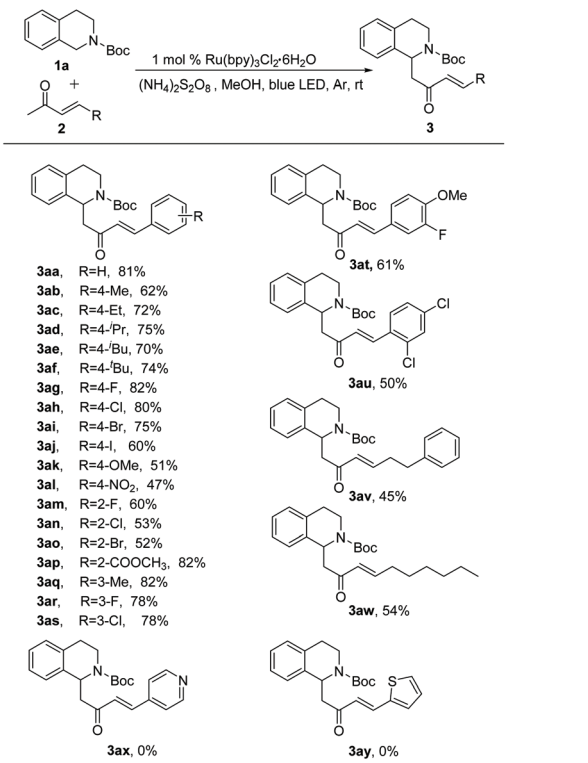



| Entry | Photocat. | Oxidant | Solvent | Yield[b] [%] |
|---|---|---|---|---|
| 1[c] | [Ru] | $O_2$ | $CH_3CN$ | 0 |
| 2 | [Ru] | TBHP | $CH_3CN$ | 0 |
| 3 | [Ru] | DDQ | $CH_3CN$ | 0 |
| 4 | [Ru] | $Na_2S_2O_8$ | $CH_3CN$ | 15 |
| 5 | [Ru] | $K_2S_2O_8$ | $CH_3CN$ | 19 |
| 6 | [Ru] | $(NH_4)_2S_2O_8$ | $CH_3CN$ | 26 |
| 7[d] | [Ru] | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 63 |
| 8 | [Ir] | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 13 |
| 9 | Eosin Y | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 42 |
| 10 | Riboflavin | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 38 |
| 11 | Mes-Acr$^+$$ClO_4^-$ | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 15 |
| 12[e] | [Ru] | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 81 |
| 13[e,f] | [Ru] | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 55 |
| 14[e,g] | [Ru] | None | $CH_3OH$ | 0 |
| 15[h] | None | $(NH_4)_2S_2O_8$ | $CH_3OH$ | Trace |
| 16[e,i] | [Ru] | $(NH_4)_2S_2O_8$ | $CH_3OH$ | 0 |

[a] Unless noted otherwise, reactions were conducted with **1a** (0.2 mmol), **2a** (0.1 mmol), photocatalyst (0.005 mmol, 5 mol%), oxidant (0.2 mmol), solvent (1.0 mL), 10 W blue LEDs at room temperature under an Ar atmosphere for 12 h. [b] Isolated yield. [c] Under an oxygen atmosphere. [d] The yield of other solvents: EtOH (32%), DMF (10%), THF (NR), $Et_2O$ (5%), 1,2-propanediol (12%), $H_2O$ (NR). [e] Photocatalyst (0.001 mmol, 1 mol%). [f] White light. [g] No oxidant. [h] No photocatalyst. [i] In the dark. [Ru] = $Ru(bpy)_3Cl_2{\cdot}6H_2O$. [Ir] = Ir(dtbbpy)$(ppy)_2PF_6$. Eosin Y = 2,4,5,7-tetrabromofluorescein disodium salt.

dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were added, no desired coupling product was obtained (entries 2 and 3). Due to the high potential of the peroxydisulfate ion, peroxydisulfate salts were added. To our delight, the desired product **3aa** was obtained, albeit in a low yield. Among peroxydisulfate salts, $(NH_4)_2S_2O_8$ showed higher efficiency than $Na_2S_2O_8$ and $K_2S_2O_8$ (entries 4–6). Other solvents were then tested, methanol was more suitable than acetonitrile and other solvents with a good yield and reaction rate (entry 7). Then we tested the reactivities of other photocatalysts including the Ir(dtbbpy)$(ppy)_2PF_6$ complex, eosin Y, riboflavin, and Mes-Acr$^+$$ClO_4^-$ (entries 8–11). They showed lower reactivities than $Ru(bpy)_3Cl_2{\cdot}6H_2O$. To our delight, when the photocatalyst loading was reduced to 1 mol%, the amount of the by-product was decreased and **3aa** was obtained with a good yield (entry 12). Changing blue LEDs to white LEDs decreased the rate and yield (entry 13). Little or no conversion was observed without the addition of a photocatalyst or an oxidant, and the reaction hardly proceeded in the dark (entries 14–16). The control experiments showed that the $Ru(bpy)_3Cl_2{\cdot}6H_2O$ photoredox catalyst, the oxidant $(NH_4)_2S_2O_8$ and blue light were essential for the reaction.

With the established optimal reaction conditions in hand, we set out to explore the scope of this transformation (Scheme 1). Firstly, the CDC reaction was applied to various α,β-unsaturated ketones with *tert*-butyl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1a**). The effect of electronic and structural variation on the β-position of aromatic rings was initially examined. The alkyl groups (–Me, –Et, –$^i$Pr, –$^i$Bu, –$^t$Bu) on the *para*-site of aromatic rings of α,β-unsaturated ketones could afford the desired products in moderate to good yields (**3ab–3af**). Halogens (–F, –Cl, –Br, –I) on the *para*-aromatic rings still afforded the corresponding products in good yields (**3ag–3aj**). Both electron-donating group (–OMe) and strong electron-withdrawing group (–$NO_2$) on the *para*-aromatic rings didn't influence the reaction outcome, and they afforded the desired products in moderate yields (**3ak**, **3al**). However, α,β-unsaturated ketones bearing electron-withdrawing groups such as methoxycarbonyl (–COOMe) or cyano (–CN) at the *para*-positions could not afford the desired product, but gave complex by-products. Electron-withdrawing groups such as methoxycarbonyl (–COOMe) or halogen (–F, –Cl, –Br) groups on the *ortho*-aromatic rings were still suitable for the reaction conditions to afford the corresponding products in moderate yields (**3am–3ap**). An



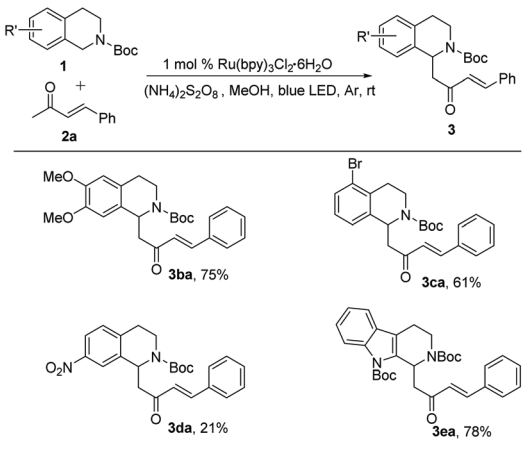

Scheme 1 Substrate scope. Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol%), $(NH_4)_2S_2O_8$ (0.2 mmol), $CH_3OH$ (1.0 mL), 10 W blue LEDs at room temperature under an Ar atmosphere for 12 h. Isolated yield.

alkyl group (–Me) or halogens (–F, –Cl) on the *meta*-aromatic rings could give the products with good yields (**3aq–3as**). Both 1,2-disubstituted and 1,3-disubstituted groups on aromatic rings reacted well with moderate yields (**3at**, **3au**). When the substituent R was an alkyl group (**2av**, **2aw**), the desired products were obtained with 45% and 54% yields, respectively (**3av**, **3aw**). Unfortunately, for aromatic heterocycles, such as 4-(4-pyridinyl)-3-buten-2-one and 4-(2-thienyl)-3-buten-2-one, no reaction occurred (**3ax**, **3ay**).

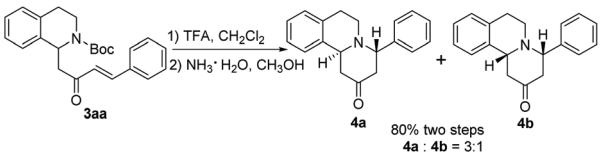
Then the scope of *N*-Boc-THIQs was also examined under the optimal reaction conditions (Scheme 2). The substitution on the benzene ring of *N*-Boc-THIQs with electron-donating groups (6,7-$(MeO)_2$) or an electron-withdrawing group (5-Br) could provide the desired products in good yields (**3ba**, **3ca**). Only a low yield was obtained for the substrate bearing an electron-withdrawing group ($-NO_2$) on the aryl ring of THIQ (**3da**). Pleasingly, dihydro-β-carboline was also suitable for the optimal reaction conditions to give the desired product with 78% yield (**3ea**). When we checked the substrate scope of tetrahydroisoquinolines, other N-protecting groups were examined. However, under the reaction conditions, *N*-phenyl-tetrahydroisoquinoline was decomposed and no desired product was obtained. When the N-protecting groups were tosyl or *o*-nosyl, no reaction occurred.

Next, to test the applicability for the synthesis of benzo[*a*]quinolizine analogs, the protecting group (–Boc) of **3aa** was readily removed by TFA, and then intramolecular Michael addition in $NH_3{\cdot}H_2O$/methanol afforded benzo[*a*]quinolizidine-2-ones (**4a** : **4b** = 3 : 1) (Scheme 3). The relative stereoselectivities were confirmed by comparing with the literature.[5d]

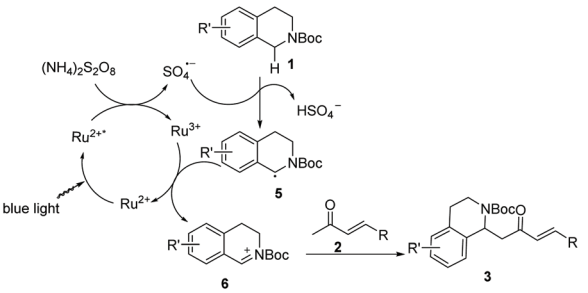
Based on the reaction outcomes and the previous reports,[8] we proposed a catalytic cycle for the CDC reaction (Scheme 4). Under blue LED irradiation, $Ru^{2+}$ was transformed to $Ru^{2+}*$. Then the peroxydisulfate salt $(NH_4)_2S_2O_8$ was reduced by $Ru^{2+}*$ to produce the sulfate radical anion ($SO_4^{\cdot-}$), while $Ru^{2+}*$ was oxidized to $Ru^{3+}$. The hydrogen atom of substrate **1** was abstracted by the sulfate radical anion to produce α-carbamyl radical **5**. Direct oxidation of **5** by $Ru^{3+}$ can lead to the iminium ion **6**, which was susceptible to attack by α,β-unsaturated ketones to afford the desired coupling products.




**Scheme 2** Substrate scope. Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol%), $(NH_4)_2S_2O_8$ (0.2 mmol), $CH_3OH$ (1.0 mL), 10 W blue LEDs at room temperature under an Ar atmosphere for 12 h. Isolated yield.




**Scheme 3** The transformation to benzo[*a*]quinolizidine.




**Scheme 4** Proposed reaction mechanism.

## Conclusions

In conclusion, we have developed a photocatalyzed cross-dehydrogenative coupling reaction of *N*-Boc-tetrahydroisoquinolines with α,β-unsaturated ketones, which provides access to Mannich type products. This research work provides an easy access to a variety of C1-substituted tetrahydroisoquinolines that can be further transformed into benzo[*a*]-quinolizine-2-ones. The application of this reaction to the synthesis of alkaloid natural products is the subject of ongoing research.

## Experimental section

### General information

All dry reactions were carried out under argon. Unless otherwise noted, all commercial reagents and solvents were used as received without further purification. The progress of the reactions was monitored by TLC with silica gel plates (GF254), and the visualization was carried out under UV light. Melting points (m.p.) were measured on electrothermal digital melting point apparatus and were uncorrected. The $^1H$ and $^{13}C$ NMR spectroscopic data were recorded with a Varian Unity Inova-400 spectrometer or a Bruker Ascend 400 spectrometer ($^1H$ and $^{13}C$ NMR at 400 and 100 MHz, respectively). The spectra were referenced internally to the residual proton resonance in $CDCl_3$ ($\delta$ 7.26 ppm), or with tetramethylsilane (TMS, $\delta$

0.00 ppm) as the internal standard. Chemical shifts ($\delta$) were reported as parts per million (ppm) in the $\delta$ scale downfield from TMS. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br. s = broad singlet. Infrared (IR) data were recorded as films on potassium bromide plates on a Bruker Invenio-R FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters ($cm^{-1}$). High resolution mass spectra were acquired on a Bruker Daltonics MicroTof-QII mass spectrometer.

### General procedure

To a 10 mL round-bottom flask were added *N*-Boc-THIQs **1** (0.2 mmol), an unsaturated ketone **2** (0.1 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.001 mmol), and $(NH_4)_2S_2O_8$ (0.2 mmol). The flask was degassed for 1 min and then filled with argon gas. Then MeOH (1.0 mL) was added. Finally, the mixture was stirred at a distance of 5 cm from 10 W blue LED strips for irradiation at room temperature under an Ar atmosphere for 12 h. The reaction was nearly completed, as monitored by TLC analysis. After completion, the reaction mixture was concentrated *in vacuo* and purified using silica gel chromatography to afford the desired product.

***tert*-Butyl(*E*)-1-(2-oxo-4-phenylbut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3aa).**[5d] White solid (30.6 mg, 81%). M.p. = 88–89 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–7.53 (m, 3H), 7.43–7.31 (m, 3H), 7.20–7.14 (m, 4H), 6.90–6.66 (m, 1H), 5.71 (d, $J$ = 32.1 Hz, 1H), 4.21–3.88 (br m, 1H), 3.36–3.27 (br m, 1H), 3.17 (dd, $J$ = 14.5, 7.2 Hz, 1H), 3.08–2.71 (br m, 3H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$ 197.6, 197.4, 154.5, 154.3, 143.1, 143.0, 137.0, 136.9, 134.4, 134.3, 130.6, 130.4, 129.0, 128.8, 128.4, 127.1, 127.0, 126.9, 126.5, 126.4, 126.3, 80.4, 52.0, 51.6, 48.7, 48.5, 39.4, 37.7, 28.4. IR (thin film): 2925, 1687, 1609, 1417, 1365, 1332, 1297, 1165, 1121, 962, 757, 692 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{27}NO_3Na$ $[M + Na]^+$: 400.1883; found: 400.1883.

***tert*-Butyl(*E*)-1-(4-(4-chlorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ab).** Yellow gum (24.26 mg, 62%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67–7.35 (m, 3H), 7.25–7.06 (m, 6H), 6.83–6.72 (m, 1H), 5.72 (d, $J$ = 32.7 Hz, 1H), 4.29–3.83 (br m, 1H), 3.56–3.26 (br m, 1H), 3.17 (dd, $J$ = 14.5, 7.2 Hz, 1H), 3.03–2.78 (br m, 3H), 2.37 (s, 3H), 1.43 (s, 9H). $^{13}$C NMR(100 MHz, $CDCl_3$) $\delta$ 197.5, 197.3, 154.5, 154.2, 143.1, 143.0, 141.1, 140.8, 137.0, 136.9, 134.3, 134.2, 131.8, 131.6, 129.7, 129.6, 129.0, 128.7, 128.3, 127.1, 126.9, 126.8, 126.3, 126.2, 125.5, 125.3, 80.3, 79.9, 51.9, 51.5, 48.5, 48.3, 39.3, 37.5, 28.3, 21.5. IR (thin film): 2926, 1685, 1603, 1416, 1365, 1234, 1162, 1120, 1095, 961, 865, 758 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{25}H_{29}NO_3Na$ $[M + Na]^+$: 400.2040; found: 400.2042.

***t*ert-Butyl(*E*)-1-(4-(4-ethylphenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ac).** Yellow gum (29.2 mg, 72%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–7.46 (br m, 3H), 7.23–7.16 (m, 6H), 6.83–6.72 (m, 1H), 5.72 (d, $J$ = 32.6 Hz, 1H), 4.25–3.89 (br m, 1H), 3.51–3.31 (m, 1H), 3.17 (dd, $J$ = 14.4, 7.2 Hz, 1H), 3.03–2.78 (br m, 3H), 2.67 (q, 7.5 Hz, 2H), 1.43 (s, 9H), 1.25 (t, $J$ = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 197.4, 154.6, 154.3, 147.5, 147.2, 143.2, 143.1, 137.1, 137.0, 134.4, 134.3, 132.1, 131.8, 129.1, 128.7, 128.54, 128.49, 127.2, 127.0, 126.9, 126.4, 125.6, 125.4, 80.3, 79.9, 52.0, 51.6, 48.6, 48.3, 39.4, 37.6, 28.8, 28.4, 15.3. IR (thin film): 2966, 1685, 1602, 1416, 1364, 1233, 1160, 1119, 1094, 961, 823, 753 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{26}H_{32}NO_3$ $[M + H]^+$: 406.2377; found: 406.2378.

***tert*-Butyl(*E*)-1-(4-(4-isopropylphenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ad).** Yellow gum (31.4 mg, 75%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60–7.46 (br m, 3H), 7.25–7.15 (m, 6H), 6.82–6.71 (m, 1H), 5.71 (d, $J$ = 31.3 Hz, 1H), 4.25–3.88 (br m, 1H), 3.50–3.28 (br m, 1H), 3.17 (dd, $J$ = 14.5, 7.1 Hz, 1H), 2.87–2.02 (br m, 4H), 1.42 (s, 9H), 1.25 (d, $J$ = 6.9 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 197.4, 154.6, 154.3, 152.1, 151.8, 143.2, 143.1, 137.1, 134.4, 132.3, 132.0, 129.1, 128.7, 128.5, 127.2, 127.0, 126.9, 126.4, 125.7, 125.5, 80.4, 79.9, 52.0, 51.6, 48.6, 48.4, 39.4, 37.7, 34.1, 28.4, 23.8. IR (thin film): 2961, 1689, 1604, 1417, 1365, 1234, 1164, 1120, 1095, 961, 823, 753 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{27}H_{33}NO_3Na$ $[M + Na]^+$: 442.2353; found: 442.2353.

***tert*-Butyl(*E*)-1-(4-(4-isobutylphenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ae).** White solid (30.3 mg, 70%). M.p. = 90–91 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62–7.45 (br m, 3H), 7.25–7.07 (m, 6H), 6.78 (dd, $J$ = 30.3, 16.1 Hz, 1H), 5.72 (d, $J$ = 30.6 Hz, 1H), 4.26–3.89 (br m, 1H), 3.48–3.30 (br m, 1H), 3.17 (dd, $J$ = 14.3, 7.2 Hz, 1H), 3.02–2.78 (br m, 3H), 2.50 (d, $J$ = 7.1 Hz, 2H), 1.88 (septet, $J$ = 6.8 Hz, 1H), 1.42 (s, 9H), 0.91 (d, $J$ = 6.5 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 197.4, 154.3, 145.0, 143.2, 137.1, 136.9, 134.4, 134.2, 132.2, 131.9, 129.8, 129.7, 129.0, 128.7, 128.3, 127.2, 127.0, 126.9, 126.4, 125.6, 125.4, 80.3, 79.9, 52.0, 51.6, 48.6, 48.3, 45.3, 39.3, 37.6, 30.2, 28.3, 22.3. IR (thin film): 2923, 1685, 1601, 1524, 1416, 1364, 1295, 1161, 1119, 1094, 961, 865, 760 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{28}H_{35}NO_3Na$ $[M + Na]^+$: 456.2509; found: 456.2509.

***tert*-Butyl(*E*)-1-(4-(4-(*tert*-butyl)phenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3af).** White gum (32.1 mg, 74%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–7.40 (br m, 5H), 7.21–7.17 (m, 4H), 6.83–6.72 (m, 1H), 5.71 (d, $J$ = 32.4 Hz, 1H), 4.25–3.88 (br m, 1H), 3.50–3.30 (m, 1H), 3.18 (dd, $J$ = 14.4, 7.0 Hz, 1H), 3.02–2.77 (br m, 3H), 1.43 (s, 9H), 1.32 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 197.4, 154.5, 154.2, 153.9, 143.1, 143.0, 137.1, 136.9, 134.4, 134.2, 131.8, 131.5, 129.0, 128.7, 128.2, 127.2, 127.0, 126.8, 126.4, 126.0, 125.8, 125.7, 125.5, 80.3, 79.8, 51.9, 51.5, 48.5, 48.3, 39.4, 37.6, 34.9, 31.1, 28.3. IR (thin film): 2963, 1686, 1603, 1415, 1364, 1328, 1233, 1163, 1119, 962, 865, 821, 752 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{28}H_{36}NO_3$ $[M + H]^+$: 434.2690; found: 434.2687.

***tert*-Butyl(*E*)-1-(4-(4-fluorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ag).** White solid (32.4 mg, 82%). M.p. = 88–89 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59–7.47 (m, 3H), 7.17–7.05 (m, 6H), 6.73 (dd, $J$ = 41.7, 16.1 Hz, 1H), 5.70 (d, $J$ = 32.8 Hz, 1H), 4.23–3.88 (br m, 1H), 3.49–3.29 (b rm, 1H), 3.18–3.13 (m, 1H), 3.01–2.77 (br m, 3H), 1.41 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 197.1, 163.9 (d, $J$ = 249.0 Hz), 154.6, 154.2, 141.7, 141.6, 137.0, 136.8, 134.4, 134.2, 130.6 (d, $J$ = 5.0 Hz), 130.3 (d, $J$ = 8.0 Hz), 129.1, 128.8, 126.9, 127.1,

126.4, 126.2, 125.9, 116.1 (d, $J$ = 22.0 Hz), 80.4, 79.9, 52.0, 51.5, 48.7, 48.6, 39.3, 37.6, 28.3. IR (thin film): 2926, 1683, 1598, 1508, 1415, 1365, 1230, 1158, 1120, 1095, 961, 827, 760 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3FNa$ $[M + Na]^+$: 418.1789; found: 418.1784.

***tert*-Butyl(*E*)-1-(4-(4-chlorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ah).** Yellow gum (32.9 mg, 80%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.57–7.45 (m, 3H), 7.35 (d, $J$ = 7.9 Hz, 2H), 7.17–7.15 (m, 4H), 6.94–6.55 (m, 1H), 5.70 (d, $J$ = 34.5 Hz, 1H), 4.31–3.79 (br m, 1H), 3.52–3.25 (br m, 1H), 3.16–3.13 (m, 1H), 3.06–2.73 (br m, 3H), 1.41 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 197.1, 154.6, 154.2, 141.5, 141.4, 136.9, 136.8, 136.5, 136.2, 134.4, 134.2, 133.1, 132.9, 129.5, 129.3, 129.1, 128.8, 128.6, 127.1, 126.9, 126.8, 126.5, 126.4, 80.3, 80.0, 51.9, 51.5, 48.8, 48.7, 39.3, 37.6, 28.3; IR (thin film): 2975, 1687, 1609, 1491, 1417, 1365, 1234, 1164, 1120, 1089, 961, 810, 761 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3ClNa$ $[M + Na]^+$: 434.1493; found: 434.1487.

***tert*-Butyl(*E*)-1-(4-(4-bromophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ai).** White solid (34.1 mg, 75%). M.p. = 93–94 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54–7.39 (br m, 5H), 7.16–7.06 (br m, 4H), 6.85–6.71 (m, 1H), 5.70 (d, $J$ = 34.2 Hz, 1H), 4.21–3.88 (br m, 1H), 3.48–3.31 (m, 1H), 3.16–3.12 (m, 1H), 3.02–2.76 (br m, 3H), 1.41 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 197.0, 154.5, 154.1, 141.5, 141.3, 136.8, 136.7, 134.3, 134.2, 133.5, 133.2, 132.2, 132.0, 131.4, 129.7, 129.6, 129.0, 128.7, 127.0, 126.9, 126.5, 126.3, 124.8, 124.5, 80.3, 79.9, 51.9, 51.4, 48.7, 48.6, 39.2, 37.5, 28.4, 28.3. IR (thin film): 2927, 1686, 1609, 1488, 1417, 1365, 1296, 1163, 1120, 1071, 1009, 961, 805, 761 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{27}NO_3Br$ $[M + H]^+$: 456.1169; found: 456.1155.

***tert*-Butyl(*E*)-1-(4-(4-iodophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3aj).** Yellow solid (30.2 mg, 60%). M.p. = 90–91 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.73–7.61 (m, 2H), 7.47 (dd, $J$ = 30.9, 16.1 Hz, 1H), 7.26–7.17 (br m, 6H), 6.80 (dd, $J$ = 43.3, 15.6 Hz, 1H), 5.69 (d, $J$ = 33.6 Hz, 1H), 4.21–3.87 (br m, 1H), 3.45–3.29 (m, 1H), 3.17–3.13 (m, 1H), 3.01–2.78 (br m, 3H), 1.41 (s, 9H). $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 197.2, 197.0, 154.6, 154.2, 141.7, 141.5, 138.2, 138.1, 136.9, 136.8, 134.4, 133.8, 131.4, 129.8, 129.7, 129.3, 129.1, 128.9, 128.7, 127.1, 126.9, 126.7, 126.4, 96.9, 80.3, 79.9, 51.9, 51.5, 48.8, 48.7, 39.3, 37.6, 28.3. IR (thin film): 2925, 1686, 1608, 1484, 1418, 1365, 1235, 1164, 1121, 1005, 803, 761 $cm^{-1}$.HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3INa$ $[M + Na]^+$: 526.0850; found: 526.0850.

***tert*-Butyl(*E*)-1-(4-(4-methoxyphenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ak).** Yellow gum (20.8 mg, 51%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.59–7.48 (br m, 3H), 7.22–7.15 (m, 4H), 6.91 (d, $J$ = 8.2 Hz, 2H), 6.69 (dd, $J$ = 33.2, 16.0 Hz, 1H), 5.71 (d, $J$ = 32.6 Hz, 1H), 4.22–3.78 (br m, 4H), 3.47–3.27 (br m, 1H), 3.15 (dd, $J$ = 14.3, 7.3 Hz, 1H), 3.00–2.77 (br m, 3H), 1.41 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 197.3, 161.7, 161.5, 154.6, 154.3, 142.94, 142.85, 137.1, 137.0, 134.4, 134.3, 130.1, 129.1, 128.7, 127.2, 127.0, 126.98, 126.86, 126.4, 124.3, 124.1, 114.5, 114.3, 80.3, 79.8, 55.4, 52.0, 51.6, 48.6, 48.4, 39.3, 37.5, 28.3. IR (thin film): 2926, 1686, 1598, 1511, 1420, 1365, 1250, 1171, 1119, 1031, 961, 825, 759 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{25}H_{30}NO_4$ $[M + H]^+$: 408.2169; found: 408.2168.

***tert*-Butyl(*E*)-1-(4-(4-nitrophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3al).** Yellow gum (19.8 mg, 47%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 7.6 Hz, 2H), 7.70–7.53 (m, 3H), 7.18–7.09 (m, 4H), 7.02–6.84 (m, 1H), 5.72 (d, $J$ = 37.3 Hz, 1H), 4.21–3.88 (br m, 1H), 3.49–3.32 (m, 1H), 3.24–3.17 (m, 1H), 3.08–2.79 (m, 3H), 1.43 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 154.8, 154.3, 148.6, 141.0, 140.6, 139.8, 139.6, 136.6, 134.4, 131.0, 130.4, 129.8, 129.5, 128.9, 127.1, 127.0, 126.5, 124.1, 123.6, 123.5, 80.5, 80.2, 52.0, 51.5, 49.1, 39.3, 37.7, 28.4. IR (thin film): 2975, 1683, 1595, 1519, 1415, 1342, 1234, 1161, 1119, 961, 860, 742 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}N_2O_5Na$ $[M + Na]^+$: 445.1734; found: 445.1750.

***tert*-Butyl(*E*)-1-(4-(2-fluorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3am).** Yellow gum (23.7 mg, 60%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74–7.55 (br m, 2H), 7.36 (s, 1H), 7.23–7.08 (m, 6H), 6.92–6.82 (m, 1H), 5.71 (d, $J$ = 31.6 Hz, 1H), 4.22–3.92 (br m, 1H), 3.50–3.31 (m, 1H), 3.23–3.13 (m, 1H), 3.06–2.78 (br m, 3H), 1.42 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 197.5, 161.5 (d, $J$ = 252.0 Hz), 154.3, 137.0, 135.5, 135.0, 134.5, 132.1 (d, $J$ = 8.0 Hz), 129.1, 128.9 (d, $J$ = 2.0 Hz), 127.2, 126.9, 126.4, 124.6 (d, $J$ = 8.0 Hz), 122.5 (d, $J$ = 10.0 Hz), 116.3 (d, $J$ = 21.0 Hz), 80.4, 79.9, 52.0, 51.6, 48.5, 48.2, 39.3, 37.6, 28.3; IR (thin film): 2928, 1685, 1609, 1416, 1365, 1230, 1160, 1120, 1094, 961, 861, 755 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3FNa$ $[M + Na]^+$: 418.1789; found: 418.1777.

***tert*-Butyl(*E*)-1-(4-(2-chlorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3an).** Yellow gum (21.8 mg, 53%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.39–7.25 (br m, 3H), 7.17–7.06 (br m, 5H), 7.01 (d, $J$ = 6.9 Hz, 1H), 6.34 (dd, $J$ = 47.6, 8.0 Hz, 1H), 5.60 (d, $J$ = 32.8 Hz, 1H), 4.07–3.87 (br m, 1H), 3.17 (dt, $J$ = 75.2, 6.4 Hz, 1H), 2.87–2.70 (br m, 3H), 2.63 (d, $J$ = 10.0 Hz, 1H), 1.46 (s, 9H). $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 199.9, 199.6, 154.5, 154.2, 137.0, 136.8, 136.3, 134.4, 134.3, 134.1, 133.9, 133.3, 131.2, 131.0, 130.4, 130.3, 130.2, 130.0, 129.4, 129.3, 129.0, 128.7, 127.1, 126.9, 126.8, 126.54, 126.51, 126.3, 80.4, 79.9, 51.7, 51.4, 50.4, 50.3, 38.8, 37.5, 28.4. IR (thin film): 2975, 1687, 1417, 1365, 1296, 1234, 1163, 1121, 1051, 962, 863, 754 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3ClNa$ $[M + Na]^+$: 434.1493; found: 434.1493.

***tert*-Butyl(*E*)-1-(4-(2-bromophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ao).** Yellow gum (23.7 mg, 52%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 6.7 Hz, 1H), 7.33–7.01 (br m, 8H), 6.32 (dd, $J$ = 49.9, 12.2 Hz, 1H), 5.60 (d, $J$ = 31.9 Hz, 1H), 4.08–3.87 (br m, 1H), 3.26–2.05 (m, 1H), 2.87–2.61 (br m, 4H), 1.46 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 199.8, 154.5, 154.2, 139.1, 138.5, 136.8, 136.7, 136.0, 135.8, 134.5, 134.3, 132.6, 132.4, 131.2, 131.1, 130.3, 130.2, 129.0, 128.7, 127.20, 127.15, 126.9, 126.8, 126.3, 123.2, 80.4, 79.9, 51.7, 51.4, 50.4, 50.2, 38.8, 37.5, 28.4, 28.2. IR (thin film): 2974, 1684, 1415, 1364, 1232, 1159, 1119, 1025, 961, 862, 751, 657 $cm^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{27}NO_3Br$ $[M + H]^+$: 456.1169; found: 456.1149.

***tert*-Butyl(*E*)-1-(4-(2-(methoxycarbonyl)phenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ap).** Yellow gum (35.7 mg, 82%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.51–8.44 (m, 1H), 7.99 (s, 1H), 7.63–7.44 (br m, 3H), 7.30–7.15 (br m, 4H), 6.62 (dd, $J$ = 34.1, 16.2 Hz, 1H), 5.76 (d, $J$ = 29.2 Hz, 1H), 4.23–3.93 (br m, 1H), 3.92 (s, 3H), 3.51–3.33 (m, 1H), 3.27–3.07 (m, 2H), 2.97–2.79 (m, 2H), 1.41 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.0, 167.0, 154.2, 142.4, 141.7, 137.0, 136.7, 136.5, 134.5, 134.3, 132.5, 132.4, 131.0, 130.8, 129.9, 129.6, 129.4, 129.0, 128.7, 127.9, 127.7, 127.3, 127.0, 126.8, 126.3, 80.2, 79.8, 52.4, 52.2, 51.6, 47.3, 39.1, 37.4, 28.3. IR (thin film): 2975, 1718, 1687, 1609, 1418, 1365, 1253, 1163, 1122, 1079, 963, 757 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{26}H_{30}NO_5H$ $[M + H]^+$: 436.2118; found: 436.2118.

***tert*-Butyl(*E*)-1-(2-oxo-4-(m-tolyl)but-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3aq).** Yellow gum (32.1 mg, 82%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62–7.31 (br m, 3H), 7.19–7.15 (m, 5H), 6.85–6.72 (m, 1H), 5.73 (d, $J$ = 32.1 Hz, 1H), 4.31–3.81 (br m, 1H), 3.51–3.31 (br m, 1H), 3.20–3.15 (m, 1H), 3.08–2.72 (br m, 3H), 2.37 (s, 3H), 1.44 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 197.3, 154.3, 154.2, 143.2, 143.1, 138.5, 138.4, 137.0, 136.8, 134.3, 134.2, 131.4, 131.2, 129.7, 129.5, 128.9, 128.8, 128.7, 128.3, 127.1, 126.9, 126.8, 126.3, 126.2, 126.0, 125.6, 125.5, 80.2, 79.8, 51.9, 51.5, 48.6, 48.2, 39.3, 37.5, 28.3, 21.4, 21.2. IR (thin film): 2926, 1684, 1605, 1416, 1364, 1232, 1159, 1119, 1095, 961, 755, 691 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{25}H_{29}NO_3Na$ $[M + Na]^+$: 400.2040; found: 400.2043.

***tert*-Butyl(*E*)-1-(4-(3-fluorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ar).** Yellow gum (30.8 mg, 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57–7.46 (m, 1H), 7.34–7.08 (m, 8H), 6.79 (dd, $J$ = 36.6, 15.9 Hz, 1H), 5.70 (d, $J$ = 31.9 Hz, 1H), 4.21–3.89 (br m, 1H), 3.50–3.30 (br m, 1H), 3.16–3.14 (m, 1H), 3.03–2.78 (br m, 3H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 197.1, 163.0 (d, $J$ = 246.0 Hz), 154.6, 154.2, 141.5, 141.4, 136.9 (d, $J$ = 5.0 Hz), 134.4, 134.3, 130.6 (d, $J$ = 7.0 Hz), 129.1, 128.8, 127.5, 127.2 (d, $J$ = 10.0 Hz), 127.0, 126.4, 124.4, 117.5 (d, $J$ = 20.0 Hz), 114.5 (d, $J$ = 22.0 Hz), 80.4, 80.0, 51.9, 51.5, 48.8, 48.7, 39.3, 37.6, 28.3. IR (thin film): 2928, 1686, 1612, 1417, 1365, 1236, 1163, 1121, 1096, 962, 865, 757, 681 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3FNa$ $[M + Na]^+$: 418.1789; found: 418.1781.

***tert*-Butyl(*E*)-1-(4-(3-chlorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3as).** Yellow gum (32.1 mg, 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53–7.33 (br m, 5H), 7.17–7.15 (br m, 4H), 6.79 (dd, $J$ = 35.2, 16.0 Hz, 1H), 5.70 (d, $J$ = 32.4 Hz, 1H), 4.21–3.88 (br m, 1H), 3.47–3.29 (m, 1H), 3.19–3.13 (m, 1H), 3.03–2.77 (br m, 3H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 197.0, 154.6, 154.2, 141.3, 141.1, 136.8, 136.7, 136.5, 136.1, 134.9, 134.8, 134.4, 134.2, 130.4, 130.2, 129.1, 128.7, 127.9, 127.4, 127.2, 126.9, 127.1, 126.5, 126.4, 80.3, 79.9, 51.8, 51.5, 48.8, 48.7, 39.3, 37.6, 28.6, 28.4, 28.3. IR (thin film): 2927, 1683, 1611, 1416, 1364, 1233, 1160, 1119, 1096, 962, 864, 760, 683 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3ClNa$ $[M + Na]^+$: 434.1493; found: 434.1474.

***tert*-Butyl(*E*)-1-(4-(3-fluoro-4-methoxyphenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3at).** yellow gum (25.9 mg, 61%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (dd, $J$ = 31.7, 16.0 Hz, 1H), 7.29–7.16 (br m, 6H), 6.95 (t, $J$ = 8.4 Hz, 1H), 6.66 (dd, $J$ = 35.6, 15.9 Hz, 1H), 5.69 (d, $J$ = 31.9 Hz, 1H), 4.20–3.88 (br m, 1H), 3.91 (s, 3H), 3.45–3.29 (br m, 1H), 3.14 (dd, $J$ = 14.4, 7.3 Hz, 1H), 3.00–2.77 (br m, 3H), 1.41 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 197.1, 154.6, 154.2, 152.3 (d, $J$ = 246.0 Hz), 149.8 (d, $J$ = 11.0 Hz), 141.7, 141.6, 137.0, 136.8, 134.4, 134.3, 129.1, 128.7, 127.9 (d, $J$ = 8.0 Hz), 127.5 (d, $J$ = 6.0 Hz), 126.9, 127.2, 127.0, 126.4, 125.9 (d, $J$ = 2.0 Hz), 125.3, 125.0, 114.8 (d, $J$ = 19.0 Hz), 113.1, 80.3, 79.9, 56.2, 51.9, 51.5, 48.7, 48.6, 39.3, 37.5, 28.3. IR (thin film): 2933, 1682, 1601, 1513, 1417, 1365, 1275, 1160, 1120, 1023, 960, 732 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{25}H_{28}NO_4FNa$ $[M + Na]^+$: 448.1895; found: 448.1895.

***tert*-Butyl(*E*)-1-(4-(2,4-dichlorophenyl)-2-oxobut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3au).** Yellow gum (22.3 mg, 50%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.35 (m, 2H), 7.17–7.08 (br m, 5H), 6.96 (d, $J$ = 12.4 Hz, 1H), 6.40 (dd, $J$ = 55.7, 12.3 Hz, 1H), 5.61 (d, $J$ = 37.5 Hz, 1H), 4.09–3.87 (br m, 1H), 3.35–3.11 (m, 1H), 2.94–2.66 (br m, 4H), 1.45 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.0, 154.6, 154.2, 136.7, 136.1, 135.7, 135.4, 135.1, 134.4, 134.1, 132.5, 132.1, 131.9, 130.3, 130.0, 129.2, 129.0, 128.8, 127.1, 127.0, 126.8, 126.4, 80.5, 80.0, 51.7, 51.3, 50.9, 39.0, 37.7, 28.4. IR (thin film): 2927, 1 685 1415, 1364, 1233, 1159, 1120, 1097, 1050, 961, 862, 751 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{25}NO_3Cl_2Na$ $[M + Na]^+$: 468.1104; found: 468.1104.

***tert*-Butyl(*E*)-1-(2-oxo-6-phenylhex-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3av).** Yellow gum (18.2 mg, 45%). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.30–7.28 (m, 2H), 7.22–7.12 (m, 7H), 6.89–6.79 (m, 1H), 6.22–6.14 (m, 1H), 5.60 (d, $J$ = 32.1 Hz, 1H), 4.16–3.84 (br m, 1H), 3.41–3.21 (m, 1H), 3.05–2.76 (br m, 6H), 2.54 (q, $J$ = 4.8 Hz, 2H), 1.44 (s, 9H). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 197.6, 154.2, 146.8, 146.5, 140.8, 140.6, 137.0, 134.4, 131.4, 130.8, 129.0, 128.5, 128.4, 127.2, 127.0, 126.9, 126.33, 126.27, 80.3, 79.8, 52.0, 51.6, 47.6, 39.3, 37.5, 34.4, 34.2, 28.4. IR (thin film): 2928, 1687, 1416, 1364, 1332, 1295, 1233, 1160, 1119, 961, 747, 699 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{26}H_{31}NO_3Na$ $[M + Na]^+$: 428.2196; found: 428.2195.

***tert*-Butyl(*E*)-1-(2-oxodec-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3aw).** Yellow gum (21.9 mg, 54%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.15–7.12 (m, 4H), 6.90–6.77 (m, 1H), 6.18–6.10 (m, 1H), 5.62 (d, $J$ = 28.7 Hz, 1H), 4.17–3.86 (m, 1H), 3.42–3.23 (m, 1H), 3.08–2.74 (br m, 4H), 2.20 (q, $J$ = 6.9 Hz, 2H), 1.44–1.41 (m, 11H), 1.34–1.24 (m, 6H), 0.88 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 154.2, 148.3, 137.1, 134.3, 130.9, 130.4, 129.0, 128.6, 127.1, 127.0, 126.8, 126.3, 80.2, 79.7, 51.9, 47.5, 39.3, 37.5, 32.5, 31.6, 28.8, 28.3, 28.0, 22.5, 14.0. IR (thin film): 2927, 1688, 1625, 1415, 1364, 1332, 1295, 1231, 1161, 1119, 960, 749 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{36}NO_3$ $[M + H]^+$: 386.2690; found: 386.2691.

***tert*-Butyl(*E*)-6,7-dimethoxy-1-(2-oxo-4-phenylbut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ba).** White solid (32.8 mg, 75%). M.p. = 89–90 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$

7.60–7.53 (m, 3H), 7.38 (s, 3H), 6.86–6.72 (m, 2H), 6.61 (s, 1H), 5.65 (d, $J$ = 39.0 Hz, 1H), 4.24–3.93 (br m, 1H), 3.84 (s, 6H), 3.44–3.26 (m, 1H), 3.21–3.16 (m, 1H), 3.01–2.68 (br m, 3H), 1.43 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 154.4, 154.1, 147.8, 147.5, 143.1, 142.8, 134.4, 134.2, 130.5, 130.3, 128.9, 128.8, 128.2, 126.5, 126.2, 126.0, 111.3, 110.0, 109.69, 80.2, 79.7, 55.9, 55.8, 51.5, 51.0, 48.5, 48.4, 39.1, 37.5, 28.2. IR (thin film): 2931, 1683, 1608, 1515, 1417, 1364, 1254, 1160, 1097, 974, 860, 752, 695 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{26}H_{31}NO_5Na$ $[M + Na]^+$: 460.2094; found: 460.2093.

***tert*-Butyl(*E*)-5-bromo-1-(2-oxo-4-phenylbut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3ca).** Yellow gum (27.8 mg, 61%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55–7.40 (br m, 7H), 7.18–7.06 (m, 2H), 6.86–6.74 (m, 1H), 5.73 (d, $J$ = 36.8 Hz, 1H), 4.31–4.03 (br m, 1H), 3.39–2.89 (br m, 5H), 1.42 (s, 9H). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 197.1, 197.0, 154.1, 143.4, 143.2, 139.6, 134.2, 131.0, 130.8, 130.6, 129.6, 129.0, 128.9, 128.7, 128.4, 127.6, 126.2, 125.5, 80.6, 80.2, 51.7, 51.1, 48.5, 48.2, 38.6, 37.1, 28.3. IR (thin film): 2975, 1686, 1608, 1418, 1365, 1323, 1229, 1162, 1104, 963, 751, 690 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}NO_3BrNa$ $[M + Na]^+$: 478.0988; found: 478.0988.

***tert*-Butyl(*E*)-7-nitro-1-(2-oxo-4-phenylbut-3-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3da).** Yellow gum (8.9 mg, 21%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (s, 1H), 8.01 (d, $J$ = 8.3 Hz, 1H), 7.61–7.55 (m, 3H), 7.40–7.28 (m, 4H), 6.82–6.79 (m, 1H), 5.82 (d, $J$ = 22.7 Hz, 1H), 4.28–3.97 (br m, 1H), 3.49–3.30 (m, 1H), 3.24–3.18 (m, 1H), 3.13–2.89 (br m, 3H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.4, 154.4, 154.0, 146.5, 143.6, 142.2, 138.6, 134.2, 130.8, 130.1, 129.0, 128.4, 125.9, 122.3, 121.8, 80.9, 80.5, 51.5, 51.0, 48.2, 47.7, 38.5, 36.9, 28.3; IR (thin film): 2929, 1685, 1608, 1521, 1413, 1343, 1157, 1132, 1089, 968, 741, 690 cm$^{-1}$; HRMS (ESI) $m/z$ calculated for $C_{24}H_{26}N_2O_5Na$ $[M + Na]^+$: 445.1734; found: 445.1734.

**Di-*tert*-butyl(*E*)-1-(2-methylene-4-phenylbut-3-en-1-ylj)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,9-dicarboxylate (3ea).** Yellow gum (40.3 mg, 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J$ = 7.3 Hz, 1H), 7.82 (d, $J$ = 15.9 Hz, 1H), 7.59 (s, 2H), 7.38–7.23 (br m, 6H), 6.97 (dd, $J$ = 59.4, 16.5 Hz, 1H), 6.43 (dd, $J$ = 67.4, 8.6 Hz, 1H), 4.54–4.27 (br m, 1H), 3.55–3.23 (br m, 2H), 2.96–2.64 (br m, 3H), 1.76 (s, 9H), 1.37 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.1, 197.6, 154.7, 154.2, 150.2, 150.1, 143.2, 142.9, 135.8, 135.6, 134.8, 134.7, 130.4, 130.1, 128.9, 128.7, 128.4, 128.2, 126.5, 125.7, 124.5, 124.4, 122.9, 122.8, 118.1, 116.1, 115.8, 115.4, 84.5, 84.4, 80.3, 79.9, 50.1, 49.1, 45.3, 44.7, 37.0, 35.5, 28.3, 20.7. IR (thin film): 2976, 1723, 1691, 1609, 1455, 1415, 1367, 1311, 1159, 1140, 1117, 991, 747, 695 cm$^{-1}$. HRMS (ESI) $m/z$ calculated for $C_{31}H_{37}N_2O_5$ $[M + H]^+$: 517.2697; found: 517.2719.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

1 For selected reviews, see: (*a*) S. R. Harutyunyan, T. Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (*b*) K. Zheng, X. Liu and X. Feng, *Chem. Rev.*, 2018, **118**, 7586; (*c*) G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2018, **118**, 2080; (*d*) Y.-Q. Zou, F. M. Hörmann and T. Bach, *Chem. Soc. Rev.*, 2018, **47**, 278.

2 For selected examples of 1,2-addition of α,β-unsaturated ketones, see: (*a*) Y. Hanzawa, N. Tabuchi, K. Saito, S. Noguchi and T. Taguchi, *Angew. Chem., Int. Ed.*, 1999, **38**, 2395; (*b*) N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331; (*c*) M. L. Kantam, S. Laha, J. Yadav, B. M. Choudary and B. Sreedhar, *Adv. Synth. Catal.*, 2006, **348**, 867.

3 For selected reviews and examples of the Baylis–Hillman reaction of α,β-unsaturated ketones, see: (*a*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (*b*) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447; (*c*) D. Basavaiah and G. Veeraraghavaiah, *Chem. Soc. Rev.*, 2012, **41**, 68.

4 For selected reviews and examples of Michael addition of α,β-unsaturated ketones, see: (*a*) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; (*b*) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796; (*c*) S. R. Harutyunyan, T. Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824.

5 (*a*) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (*b*) G. A. Cordell, *Phytochemistry*, 2013, **91**, 29; (*c*) M. Iranshahy, R. J. Quinn and M. Iranshahi, *RSC Adv.*, 2014, **4**, 15900; (*d*) H. Zheng, Y. Dong, L. Li, B. Sun, L. Liu, H. Yuan and H. Lou, *J. Med. Chem.*, 2016, **59**, 5063.

6 For selected reviews and examples of the CDC reaction of tetrahydroisoquinolines, see: (*a*) D. Cheng and W. Bao, *Adv. Synth. Catal.*, 2008, **350**, 1263; (*b*) X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2009, **74**, 7464; (*c*) K. Alagiri, P. Devadig and K. R. Prabhu, *Chem. – Eur. J.*, 2012, **18**, 5160; (*d*) A. Tanoue, W.-J. Yoo and S. Kobayashi, *Org. Lett.*, 2014, **16**, 2346; (*e*) Z. Xie, L. Liu, W. Chen, H. Zheng, Q. Xu, H. Yuan and H. Lou, *Angew. Chem., Int. Ed.*, 2014, **53**, 3904; (*f*) W. Chen, H. Zheng, X. Pan, Z. Xie, X. Zan, B. Sun, L. Liu and H. Lou, *Tetrahedron Lett.*, 2014, **55**, 2879; (*g*) C. Yan, Y. Liu and Q. Wang, *RSC Adv.*, 2014, **4**, 60075; (*h*) S. Sun, C. Li, P. E. Floeancig, H. Lou and L. Liu, *Org. Lett.*, 2015, **17**, 1684; (*i*) J.-B. Yu, G. Peng, Z.-J. Jiang, Z.-K. Hong and W.-K. Su, *Eur. J. Org. Chem.*, 2016,

 

5340; (*j*) X. Marset, J. M. Pérez and D. J. Ramón, *Green Chem.*, 2016, **18**, 826; (*k*) N. Fu, L. Li, Q. Yang and S. Luo, *Org. Lett.*, 2017, **19**, 2122.

7 For selected reviews and examples of the visible-light-mediated photocatalytic CDC reaction of tetrahydroisoquinolines, see: (*a*) A. G. Condie, J. C. González-Gómez and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464; (*b*) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 8679; (*c*) D. P. Hari and B. König, *Org. Lett.*, 2011, **13**, 3852; (*d*) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360; (*e*) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (*f*) G. Zhao, C. Yang, L. Guo, H. Sun, C. Chen and W. Xia, *Chem. Commun.*, 2012, **48**, 2337; (*g*) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (*h*) J.-J. Zhong, Q.-Y. Meng, G.-X. Wang, Q. Liu, B. Chen, K. Feng, C.-H. Tung and L.-Z. Wu, *Chem. – Eur. J.*, 2013, **19**, 6443; (*i*) W. Li, X. Zhu, H. Mao, Z. Tang, Y. Cheng and C. Zhu, *Chem. Commun.*, 2014, **50**, 7521; (*j*) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori and C. Vila, *Chem. – Eur. J.*, 2012, **18**, 5170; (*k*) C. S. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen and C. R. J. Stephenson, *Chem. Sci.*, 2014, **5**, 112; (*l*) Q. Yang, L. Zhang, C. Ye, S. Luo, L.-Z. Wu and C.-H. Tung, *Angew. Chem., Int. Ed.*, 2017, **56**, 3694; (*m*) T. Zhang, W. Liang, Y. Huang, X. Li, Y. Liu, B. Yang, C. He, X. Zhou and J. Zhang, *Chem. Commun.*, 2017, **53**, 12536; (*n*) H. Hou, S. Zhu, L. Atodiresei and M. Rueping, *Eur. J. Org. Chem.*, 2018, 1277.

8 (*a*) H. S. White and A. J. Bard, *J. Am. Chem. Soc.*, 1982, **104**, 6891; (*b*) U. Nickel, Y.-H. Chen, S. Schneider, M. I. Silva, H. D. Burrows and S. J. Formosinho, *J. Phys. Chem.*, 1994, **98**, 2883; (*c*) C. Dai, F. Meschini, J. M. R. Narayanam and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 4425.