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Dehydrogenative Functionalization of C(sp^3)–H Bonds Adjacent to a Heteroatom Mediated by Oxoammonium Salts

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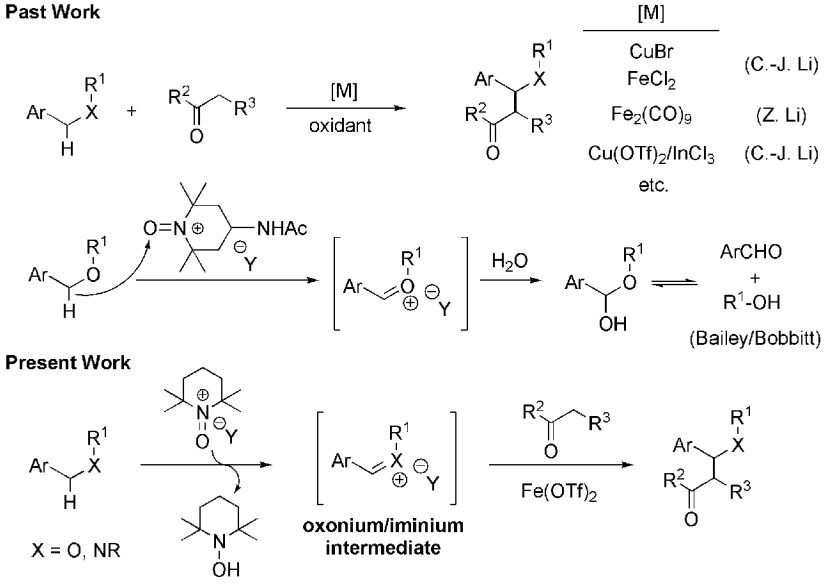
The first oxoammonium salt mediated formation of C–C bonds from benzylic C(sp^3)–H bonds adjacent to an oxygen or nitrogen atom by dehydrogenative coupling with enolizable carbonyls has been developed. The use of these oxidants in combination with catalytic amounts of $Fe(OTf)_2$ as Lewis acid allows the reaction to be carried out under mild conditions, leading to the corresponding coupling products in moderate to good yields.

Introduction

In the last few years, cross dehydrogenative coupling (CDC) reactions have emerged as a powerful and elegant way to form new C–C bonds from two C–H bonds without requiring preactivation.[1] Although remarkable achievements in the area of transition-metal-catalyzed selective C–H bond functionalizations have been made,[2] the direct functionalization of relatively unreactive C(sp^3)–H bonds remains highly challenging. In particular, the oxidative functionalization of C(sp^3)–H bonds adjacent to an oxygen or nitrogen atom[1,3,4] are of high value in organic synthesis, as functionalized ethers and amines are present in many natural and bioactive compounds. In this regard, the seminal work of Li's group[5] recently expanded the scope of these transformations by using copper, copper/indium, or iron as metal catalysts (Scheme 1).[1,3e–3g] Iron is a cheap, nontoxic, and environmentally benign transition metal,[6] thus making iron-catalyzed C–H functionalizations particularly attractive.[7] On the other hand, in metal-catalyzed CDCs, hydrogen acceptors such as organic peroxides, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and dioxygen are employed; however, the use of potentially explosive peroxides as oxidants is still often required under neat conditions.



Scheme 1. Strategies for related dehydrogenative functionalizations.

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We focused our attention on 2,2,6,6-tetramethylpiperidine-1-oxoammonium salts as a new class of hydrogen acceptors for dehydrogenative coupling reactions for various reasons: TEMPO salts (T^+Y^-) are stable, nontoxic, easily accessible from readily available nitroxide TEMPO ($T^{\cdot}$), and known mild oxidation reagents, generally used for the oxidation of alcohols to the corresponding carbonyl compounds.[8] In addition, these salts are used for the rearrangement of tertiary allylic alcohols, oxidative additions to olefins, or coupling with enolates, leading to the formation of C–O bonds.[9] More recently, Bailey and Bobbitt reported the oxidative cleavage of benzylic ethers through direct C–H functionalization by using oxoammonium salts as hydrogen acceptors and water as a nucleophile (Scheme 1).[10]

Although the formation of C–O bonds using TEMPO derivatives is more likely to occur, we envisioned the formation of C–C bonds following this dehydrogenative approach. Thus, a readily formed oxonium or iminium intermediate by dehydrogenation of a C(sp^3)–H bond adjacent to a heteroatom with a TEMPO salt could then react with an enolate-type nucleophile generated in situ by activation of a pronucleophile with a Lewis acid metal catalyst to lead to a new C–C bond (Scheme 1).[11]

Herein we present our recent results on iron-catalyzed dehydrogenative couplings of benzylic C(sp^3)–H bonds adjacent to a heteroatom by using TEMPO oxoammonium salts (T^+Y^-) as alternative, mild, safe, and easy-to-handle oxidizing agents.

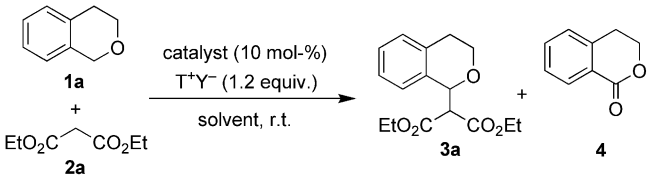
Results and Discussion

The reaction between isochromane (**1a**) and diethylmalonate (**2a**) was chosen as a model reaction for our study (Table 1). Initially, various TEMPO salts[12] were tested by using inexpensive $FeCl_3$ as the catalyst in CH_2Cl_2. We were pleased to observe the formation of desired coupling product **3a** in promising yields of 55–68% with the perchlorate, triflate, and tetrafluoroborate derivatives (Table 1, Entries 1–3), $T^+BF_4^-$ being the most efficient oxidant (68%; Table 1, Entry 3).

Moreover, both the iron catalyst and the oxidant were required to cooperatively activate the pronucleophile and benzyl ether, respectively (Table 1, Entries 4 and 5). This reaction was also very dependent on the solvent used. Thus, other solvents such as DCE, THF, MeCN, and toluene hampered or inhibited the reaction (Table 1, Entries 6–9).[13] Next, we briefly screened different iron catalysts (Table 1, Entries 10–15). Both iron(II) and iron(III) salts were effective, with the exception of $Fe(acac)_3$. The best results were obtained with $Fe(OTf)_2$,[14] which selectively provided **3a** in an excellent yield of 85% (Table 1, Entry 15). Importantly, other transition metals including palladium and copper did not catalyze the reaction as efficiently as iron (Table 1, Entries 16–18), with the exception of commonly used CuBr,[1] which provided **3a** in a comparable 62% isolated yield (Table 1, Entry 19).

Taking $Fe(OTf)_2$ as the catalyst of choice in combination with $T^+BF_4^-$, we next explored the reaction scope (Table 2).

Table 1. Optimization of the dehydrogenative coupling of isochromane (**1a**) with diethylmalonate (**2a**).[a]



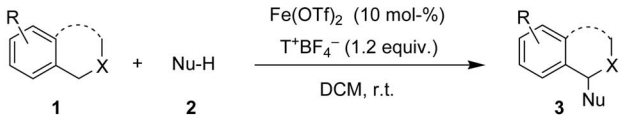
Entry	Catalyst	Y^-	Solvent	t [h]	Yield **3a**/**4** [%][b]
1	$FeCl_3$	ClO_4^-	DCM	24	55/20
2	$FeCl_3$	OTf^-	DCM	24	61/11
3	$FeCl_3$	BF_4^-	DCM	18	68/10
4	$FeCl_3$	–	DCM	24	–
5	–	BF_4^-	DCM	24	–[c,d]
6	$FeCl_3$	BF_4^-	DCE	24	46/nd
7	$FeCl_3$	BF_4^-	THF	24	–[d]
8	$FeCl_3$	BF_4^-	MeCN	24	23/nd
9	$FeCl_3$	BF_4^-	toluene	72	63/–[e]
10	$FeCl_2$	BF_4^-	DCM	18	65/–[e]
11	$FeBr_2$	BF_4^-	DCM	18	31/55
12	$Fe(acac)_3$	BF_4^-	DCM	24	–[d]
13	$Fe(OTf)_3$[f]	BF_4^-	DCM	24	70/–[e]
14	$Fe(OAc)_2$	BF_4^-	DCM	24	50/–[e]
15	***$Fe(OTf)_2$***	***BF_4^-***	***DCM***	***18***	***85***/–[e]
16	$Pd(OAc)_2$	BF_4^-	DCM	24	19/nd
17	$Cu(OTf)_2$	BF_4^-	DCM	24	20/nd
18	CuCl	BF_4^-	DCM	24	–
19	CuBr	BF_4^-	DCM	18	62/–[e]

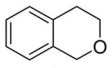
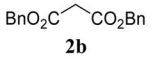
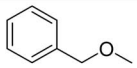
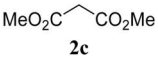
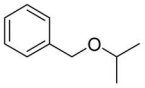
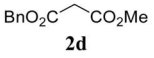
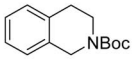
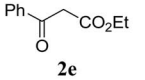
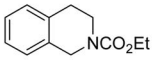
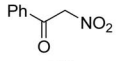
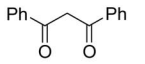
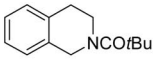
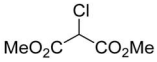
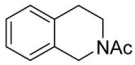
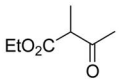
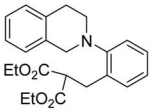
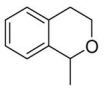
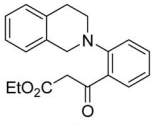
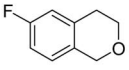
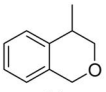
[a] Reaction conditions: **1a** (0.3 mmol), catalyst (10 mol-%), **2a** (1.2 equiv.) and T^+Y^- (1.2 equiv.) in the corresponding dry solvent (0.2 M) at room temperature. [b] Yield after column chromatography. [c] Dimer **7** was formed (see mechanistic discussion below). [d] Trace amounts of **3a** detected by GC–MS. [e] Trace amounts of **4** detected by GC–MS. [f] $Fe(OTf)_3$ was prepared in situ from $FeCl_3$ (98%) and AgOTf.

Various activated carbon pronucleophiles such as malonates and β-keto esters were efficiently utilized in the reaction with isochromane (Table 2, Entries 1–4). Interestingly, β-nitroketone **2f** also worked well (Table 2, Entry 5), thus permitting the introduction of a versatile nitro group that can further be functionalized to the corresponding amine or carboxylic acid. On the other hand, diketone **2g** did not undergo the reaction, probably because of strong coordination to the catalyst (Table 2, Entry 6). The construction of quaternary carbon atoms was also possible by using α-substituted pronucleophiles, providing the desired products in moderate yields (Table 2, Entries 7 and 8). Unfortunately, further substituents at the benzylic position of isochromane hampered the reaction, which could be due to the increase in hindrance of the ether (Table 2, Entry 9). Other benzylic ethers were then tested (Table 2, Entries 10–13). As expected, isochromane and its derivatives **1c** and **1d** were found to be more reactive than noncyclic benzyl ethers **1e** and **1f**. Nevertheless, **1e** and **1f** were able to react with diethyl malonate to give **3m** and **3n** after 16 h in acceptable isolated yields of 46 and 41%, respectively (Table 2, Entries 13 and 14).

The reaction with various nitrogenated substrates such as *N*-carbamoyl- or acyl-protected tetrahydroisoquinolines **1g**–**j** were also investigated (Table 2, Entries 14–18). De-

Table 2. Scope of the Fe-catalyzed dehydrogenative coupling with the use of $T^+BF_4^-$.[a]



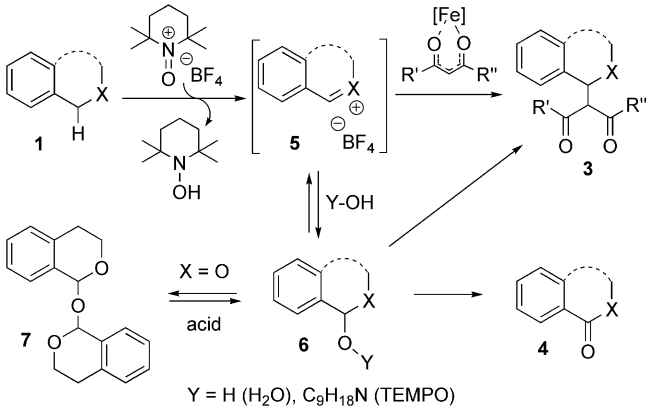
Entry	Substrate	Nu-H	Prod.	Yield [%][b]	Entry	Substrate	Nu-H	Prod.	Yield [%][b]
1	 **1a**	 **2b**	**3b**	72	12	 **1e**	**2a**	**3m**	46 (17)[e]
2	**1a**	 **2c**	**3c**	40 (20)[c]	13	 **1f**	**2a**	**3n**	41 (20)[f]
3	**1a**	 **2d**	**3d**	72 (1:1)[d]	14	 **1g**	**2a**	**3o**	56
4	**1a**	 **2e**	**3e**	63 (1:1.5)[d]	15	 **1h**	**2a**	**3p**	80
5	**1a**	 **2f**	**3f**	80 (1:2)[d]	16	**1h**	**2e**	**3q**	83 (1:1.7)[d]
6	**1a**	 **2g**	**3g**	–	17	 **1i**	**2a**	**3r**	69
7	**1a**	 **2h**	**3h**	51[c]	18	 **1j**	**2a**	**3s**	72
8	**1a**	 **2i**	**3i**	38 (10)[c] (1:3.6)[d]	19	 **1k**	–	**3t**	56
9	 **1b**	**2a**	**3j**	–	20	 **1l**	–	**3u**	68
10	 **1c**	**2a**	**3k**	82	21	 R = Boc **1m**	**2a**	**3v** (R = H)	30 (60)[g]
11	 **1d**	**2a**	**3l**	81 (1:1.1)[d]					

[a] Reaction conditions: **1** (1 equiv.), $Fe(OTf)_2$ (10 mol-%), **2** (1.2 equiv.), $T^+BF_4^-$ (1.2 equiv.) in DCM (0.2 M) at room temperature for 3–32 h. [b] Yield after column chromatography. [c] Only partial conversion of isochromane was observed and isochromanone **4** was also formed (isolated yield indicated in brackets). [d] Diastereomeric ratio determined by NMR spectroscopy is given in brackets. [e] The elimination of MeOH in **3m** led to the corresponding conjugated styrene system in 17% yield after 16 h reaction. Prolonged reaction times provide higher amounts of the elimination product. [f] Benzaldehyde was formed (NMR conversion yield in brackets; see ref.[10a]). [g] *N*-Boc benzylamine was formed (yield in brackets). Trace amounts of the C–O coupling product between malonate and TEMPO salt were also detected by GC–MS (see ref.[9d]).

lightfully, both bulky *tert*-butyl carbamate (Boc) and pivaloyl (Piv) groups at the nitrogen were well tolerated. In general, these nitrogenated substrates showed higher reactivity compared to the oxygenated analogues, leading to desired products **3o**–**s** in good yields after shorter reaction times (3–8 h). The intramolecular reactions of *N*-aryl derivatives **1k** and **1l** to give annulated compounds **3t** and **3u** were also successfully accomplished (Table 2, Entries 19

and 20). Finally, the reaction of a less reactive acyclic benzylic amine was encouraged. Thus, *N*,*N*-diBoc-protected benzylamine **1m** led to mono *N*-Boc-protected derivative **3v** as the major coupling product (30%; Table 2, Entry 21), along with mono-NBoc benzylamine (50–60%), which does not react further under the reaction conditions, and the NH_2-free compound (≤10%). This observation is not surprising because of the acidic reaction media, which can promote the in situ cleavage of the Boc groups.

We also carried out preliminary investigations to shed some light on the reaction mechanism. Two possible mechanisms, radical and ionic, can be envisioned. However, in the above-mentioned related work recently published by Bobbitt et al. (Scheme 1),[10] an ionic mechanism involving the formation of an oxonium intermediate by formal hydride transfer to the oxygen of T^+ was proposed (Scheme 1).[15] Accordingly, the pronucleophile, activated by the iron catalyst would react with oxonium or iminium species **5**, previously generated by dehydrogenation with the TEMPO salt, to form C–C coupling product **3** (Scheme 2).



Scheme 2. Possible ionic mechanistic pathways.

On the other hand, the formation of certain amounts of oxidized product **4** could be explained by the nucleophilic attack of trace amounts of water or the in situ formed TEMPOH[16,17] to the cationic intermediate followed by oxidation. However, when the reaction of isochromane (**1a**) with $T^+BF_4^-$ was performed in the absence of both malonate and the iron catalyst, oxygenated dimer **7** was formed.[18] The generation of **7** under the inert and dry conditions employed is still unclear, but could be the result of the formation of 1-hydroxyisochromane followed by attack to the oxonium intermediate. Unfortunately, neither 1-hydroxyisochromane nor oxonium ion **5** could be isolated. Considering possible first C–O bond formation followed by substitution to generate the new C–C bond, new possible intermediate **7** was then submitted to the reaction with **2a** in the presence of the $Fe(OTf)_2$ catalyst, but no reaction was observed. Taking into account the original acidic conditions and the known cleavage of dimer **7** with acids,[18a] TFA (0.4 equiv.) was added after 18 h to the reaction mixture. Then, **7** was cleanly transformed into desired product **3a** (77%). This latest finding suggested that the iron species acts as a simple Lewis acid, the TEMPO salt being the only responsible reagent in the key oxidation step. Furthermore, we found that the addition of substoichiometric amounts of TFA (e.g. 0.4 equiv.) to the model reaction was beneficial, reducing the reaction time from 18 to 5 h (85 and 80% yield, respectively). More interestingly, it was also possible to perform the reaction in the absence of the metal catalyst. Although less efficiently, TFA could also promote the reaction of **1a** with malonate **2a**, leading to coupling product **3a** in a good 60% yield after 24 h.[19] Unfortunately, these metal-free conditions were not general.[20] Further studies were then carried out for the nitrogenated substrates. Thus, the reaction of **1i** with $T^+BF_4^-$ was followed by ^1H NMR spectroscopy. A broad signal at 9.2–9.0 ppm appeared, which was consistent with the generation of corresponding iminium ion **5**.[21] After **1i** was completely consumed (≤16 h), malonate **2a** and $Fe(OTf)_2$ were added. Expected coupling product **3r** was then formed, although in a low isolated yield of 20%.

Conclusions

In summary, we have developed an efficient method for the selective construction of C–C bonds by functionalization of C(sp^3)–H bonds in the α-position to O and N atoms under mild reaction conditions by using oxoammonium TEMPO salts as easy-to-handle, nontoxic oxidants. This methodology provides a safe and easy way to prepare α-functionalized ethers and amines, such as isochromane and tetrahydroisoquinoline derivatives, which are key structural units in natural and biologically active compounds. Mechanistic studies suggested that the TEMPO salt is the responsible reagent in the oxidation step, which involves the formation of an oxonium or iminium intermediate, and the Fe catalyst acts only as a Lewis acid to activate the pronucleophile.

Experimental Section

General Information: All reactions were carried out in heat-gun-dried glassware under an argon atmosphere. Dichloromethane was distilled from CaH_2. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$, chemical shifts (δ) are given in ppm and spin–spin coupling constants (J) are given in Hz. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Exact masses (HRMS) and elemental analyses were recorded with a Bruker Daltonics MicroTof spectrometer and a Vario ELIII, respectively. $Fe(OTf)_2$ was prepared from iron powder and trifluoromethanesulfonic acid as described in the literature.[14b] Isochromanes **1c** and **1d**[22] and tetrahydroisoquinolines **1g**–**j**[23] and **1m**[24] were prepared following described procedures in the literature. Compound **1k** was prepared by reduction of dimethyl 2-[2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene] malonate[25] and **1l** by coupling of ethyl 3-(2-fluorophenyl)-3-oxopropanoate with tetrahydroisoquinoline.[26] Commercially available chemicals were used without further purification.

2,2,6,6-Tetramethylpiperidine-1-oxoammonium Tetrafluoroborate:[9] In a 25-mL round-bottomed flask, a solution of HBF_4 (48% in H_2O, 1.75 mL, 13.1 mmol) was added to a heterogeneous solution

of 2,2,6,6-tetramethylpiperidine-1-oxyl (1.78 g, 11.4 mmol) in distilled water (6 mL). The reaction mixture was stirred at room temperature for 30 min to give a yellow orange mixture. In an ice bath, a solution of NaOCl (5% in H_2O, 7.8 mL, 5.7 mmol) was added to the above solution over 1 h. The mixture was filtered, and the yellow solid was washed with cooled water (4 °C, 4 × 5 mL) and dichloromethane (3 × 5 mL). After drying under high vacuum at 50 °C overnight, the product was obtained as a bright yellow solid (2.2 g, 79%).

Preparation of Diethyl 2-(Isochroman-1-yl)malonate (3a) as a General Procedure for the $T^+BF_4^-$-Mediated Dehydrogenative Coupling: To a mixture of isochromane (**1a**; 38 μL, 0.30 mmol), diethylmalonate (**2a**; 55 μL, 0.36 mmol), and $Fe(OTf)_2$ (10.6 mg, 0.03 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added $TEMPO^+BF_4^-$ (85 mg, 0.36 mmol). The reaction mixture was stirred until the starting material was consumed (18 h, monitored by GC–MS and TLC). The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography (pentane/ethyl acetate, 20:1–10:1) to give **3a** as a pale-yellow oil (75 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.04 (m, 4 H), 5.47 (d, J = 6.3 Hz, 1 H), 4.27–4.09 (m, 5 H), 3.97 (d, J = 6.3 Hz, 1 H), 3.84–3.75 (m, 1 H), 3.05–2.95 (m, 1 H), 2.71 (dt, J = 16.2, 4.2 Hz, 1 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 166.9, 135.0, 134.5, 129.1, 127.2, 126.3, 124.8, 74.2, 63.5, 61.8, 61.4, 58.3, 28.7, 14.1, 14.0 ppm. HRMS (ESI+): calcd. for $C_{16}H_{20}O_5{\cdot}Na^+$ 315.1203; found 315.1198.

Dibenzyl 2-(Isochroman-1-yl)malonate (3b): Following the general procedure, **3b** was obtained as a pale-yellow oil (72%). Chromatography: pentane/ethyl acetate, 20:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 8 H), 7.24–7.15 (m, 3 H), 7.14–7.07 (m, 2 H), 7.06–7.00 (m, 1 H), 5.56 (d, J = 6.0 Hz, 1 H), 5.23 and 5.18 (AB system, J = 12.3 Hz, 2 H), 5.13 (s, 2 H), 4.21–4.12 (m, 2 H), 3.82–3.72 (m, 1 H), 2.98–2.88 (m, 1 H), 2.68 (dt, J = 16.2, 4.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 166.5, 135.4, 135.2, 134.7, 134.4, 129.1, 128.6, 128.4 (2 C), 128.3, 128.2, 127.1, 126.3, 124.6, 74.2, 67.4, 67.1, 63.5, 58.1, 28.6 ppm. HRMS (ESI+): calcd. for $C_{26}H_{24}O_5{\cdot}Na^+$ 439.1516; found 439.1537.

Dimethyl 2-(Isochroman-1-yl)malonate (3c): Following the general procedure, **3c** was obtained as a pale-yellow oil (40%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.11 (m, 3 H), 7.04–7.01 (m, 1 H), 5.48 (d, J = 6.4 Hz, 1 H), 4.18 (dt, J = 11.3, 4.8 Hz, 1 H), 4.00 (d, J = 6.4 Hz, 1 H), 3.85–3.75 (m, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.05–2.95 (m, 1 H), 2.72 (dt, J = 16.2, 4.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 167.1, 134.7, 134.4, 129.1, 127.2, 126.3, 124.6, 74.1, 63.4, 58.1, 52.7, 52.4, 28.6 ppm. HRMS (ESI+): calcd. for $C_{14}H_{16}O_5{\cdot}Na^+$ 287.0890; found 287.0899.

1-Benzyl 3-Methyl 2-(Isochroman-1-yl)malonate (3d): Following the general procedure, **3d** was obtained as an inseparable mixture of two diastereoisomers in a 1:1 ratio (72%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 8 H), 7.22–6.97 (m, 10 H), 5.51 (d, J = 6.2 Hz, 2 H), 5.24 and 5.17 (AB system, J = 12.3 Hz, 2 H), 5.11 (s, 2 H), 4.20–4.09 (m, 2 H), 4.07 (dd, J = 9.6, 6.2 Hz, 2 H), 3.84–3.72 (m, 2 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.03–2.88 (m, 2 H), 2.77–2.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 167.4, 167.1, 166.6, 135.5, 135.3, 134.7, 134.6, 134.4, 129.2, 129.1, 128.6, 128.5 (2 C), 128.4, 128.2 (2 C), 127.2 (2 C), 126.4, 126.3, 124.7, 124.5, 74.3, 74.1, 67.4, 67.1, 63.7, 63.4, 58.3, 58.0, 52.8, 52.6, 28.7, 28.6 ppm. HRMS (ESI+): calcd. for $C_{20}H_{20}O_5{\cdot}Na^+$ 363.1203; found 363.1212. $C_{20}H_{20}O_5$ (340.37): calcd. C 70.57, H 5.92; found C 70.26, H 6.04.

Ethyl 2-(Isochroman-1-yl)-3-oxo-3-phenylpropanoate (3e): Following the general procedure, **3e** was obtained as a mixture of two diastereoisomers in a 1:1.5 ratio (63%). Chromatography: pentane/ethyl acetate, 20:1–10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.53 (s, enol, 1 H), 8.02–7.96 (m, 2 H, major), 7.94–7.91 (m, 2 H, minor), 7.59–7.52 (m, 1 H, major; 1 H, minor), 7.48–7.40 (m, 2 H, major; 2 H, minor), 7.23–6.99 (m, 4 H, major; 4 H, minor), 5.78–5.74 (m, 1 H, major; 1 H, minor), 4.94 (d, J = 7.7 Hz, 1 H, major), 4.89 (d, J = 7.1 Hz, 1 H, minor), 4.25–4.11 (m, 3 H, major; 2 H, minor), 4.07–4.00 (m, 1 H, minor), 3.90–3.81 (m, 1 H, major), 3.76–3.66 (m, 1 H, minor), 3.00–2.84 (m, 1 H, major; 1 H, minor), 2.78 (dt, J = 16.4, 4.9 Hz, 1 H, major), 2.64 (dt, J = 16.2, 4.2 Hz, 1 H, minor), 1.16 (t, J = 7.1 Hz, 3 H, major), 1.14 (t, J = 7.1 Hz, 3 H, minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4, 193.2, 168.2, 167.1, 137.3, 136.6, 135.9, 135.7, 134.5, 134.1, 133.7, 133.3, 129.1, 128.8, 128.7, 128.6, 127.1 (2 C), 126.3, 125.2, 125.0, 74.7, 74.0, 63.4 (2 C), 61.7, 61.6, 61.4, 60.4, 28.8, 28.7, 14.0 (2 C) ppm. HRMS (ESI+): calcd. for $C_{20}H_{20}O_4{\cdot}Na^+$ 347.1254; found 347.1257.

2-(Isochroman-1-yl)-2-nitro-1-phenylethanone (3f): Following the general procedure, **3f** was obtained as an inseparable mixture of two diastereoisomers in a 1:2 ratio (72 mg, 80%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, J = 8.4, 1.2 Hz, 2 H, major), 7.71 (dd, J = 8.4, 1.2 Hz, 2 H, minor), 7.61 (tt, J = 7.5, 1.2 Hz, 1 H, major), 7.56 (t, J = 7.5 Hz, 1 H, minor), 7.46 (m, 2 H, major), 7.36 (m, 2 H, minor), 7.28–6.98 (m, 4 H, major; 4 H, minor), 6.57 (d, J = 7.2 Hz, 1 H, major), 6.40 (d, J = 5.0 Hz, 1 H, minor), 5.93 (d, J = 5.0 Hz, 1 H, minor), 5.88 (d, J = 7.2 Hz, 1 H, major), 4.23 (dt, J = 11.3, 5.0 Hz, 1 H, major), 4.03 (ddd, J = 11.2, 5.1, 3.1 Hz, 1 H, minor), 3.82 (ddd, J = 11.4, 8.5, 4.1 Hz, 1 H, major), 3.67 (ddd, J = 11.2, 10.1, 3.6 Hz, 1 H, minor), 3.05–2.97 (m, 1 H, major), 2.78 (dt, J = 16.2, 4.4 Hz, 1 H, major), 2.67–2.58 (m, 1 H, minor), 2.54 (dt, J = 16.1, 3.2 Hz, 1 H, minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 187.4, 135.3, 135.0, 134.8 (2 C), 134.7, 134.2, 132.7, 131.2, 129.4 (2 C), 129.1, 128.9 (2 C), 128.8, 128.0 (2 C), 127.2, 126.7, 125.5, 124.7, 93.7, 92.7, 74.8, 74.2, 64.1, 63.4, 28.6, 28.5 ppm. HRMS (ESI+): calcd. for $C_{17}H_{15}NO_4{\cdot}Na^+$ 320.0893; found 320.0883.

Dimethyl 2-Chloro-2-(isochroman-1-yl)malonate (3h): Following the general procedure, **3h** was obtained as a white solid (51%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 2 H), 7.20–7.12 (m, 2 H), 5.94 (s, 1 H), 4.30–4.20 (m, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.80–3.70 (m, 1 H), 3.20–2.90 (m, 1 H), 2.68 (dt, J = 16.1, 3.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 165.3, 136.1, 132.2, 129.0, 127.7, 126.3, 126.0, 78.3, 63.8, 54.3, 54.2, 29.0 ppm. HRMS (ESI+): calcd. for $C_{14}H_{15}ClO_5{\cdot}Na^+$ 321.0500; found 321.0508.

Ethyl 2-(Isochroman-1-yl)-2-methyl-3-oxobutanoate (3i): Following the general procedure, **3i** was obtained as a mixture of two diastereoisomers in a 1:3.7 ratio (38%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–6.95 (m, 4 H, major; 4 H, minor), 5.91 (s, 1 H, major), 5.71 (s, 1 H, minor), 4.34–4.19 (m, 2 H, major; 2 H, minor), 4.16–4.08 (m, 1 H, major; 1 H, minor), 3.68 (td, J = 11.2, 3.1 Hz, 1 H, minor), 3.65 (td, J = 11.3, 2.9 Hz, 1 H, major), 3.17–2.95 (m, 1 H, major; 1 H, minor), 2.62–2.50 (m, 1 H, major; 1 H, minor), 2.37 (s, 3 H, major), 2.23 (s, 3 H, minor), 1.29 (t, J = 7.1 Hz, 3 H, major), 1.27 (s, 3 H, minor), 1.25 (t, J = 7.1·Hz, 3 H, minor), 1.10 (s, 3 H, major) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2, 203.0, 171.2, 135.8, 135.6, 134.6, 134.4, 129.3, 126.9, 126.8, 126.4, 126.2, 125.9, 125.3, 78.4, 77.9, 67.1, 66.6, 64.6, 64.4, 61.9, 61.7, 29.4, 29.3, 27.5, 26.5, 15.2, 14.0, 13.3 ppm. HRMS (ESI+): calcd. for $C_{16}H_{20}O_4{\cdot}Na^+$ 299.1254; found 299.1249. $C_{16}H_{20}O_4$ (276.33): calcd. C 69.54, H 7.30; found C 69.36, H 7.46.

Diethyl 2-(6-Fluoroisochroman-1-yl)malonate (3k): Following the general procedure, **3k** was obtained as a pale-yellow oil (82%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–7.00 (m, 1 H), 6.86–6.78 (m, 2 H), 5.41 (d, J = 6.2 Hz, 1 H), 4.22–4.10 (m, 5 H), 3.91 (d, J = 6.3 Hz, 1 H), 3.79–3.71 (m, 1 H), 3.01–2.91 (m, 1 H), 2.64 (dt, J = 16.4, 4.3 Hz, 1 H), 1.21 (t, J = 7.1 Hz, 1 H), 1.15 (t, J = 7.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 166.7, 163.2, 159.9, 136.9, 136.8, 130.7, 130.6, 126.6, 126.5, 115.6, 115.3, 113.5, 113.2, 73.8, 63.0, 61.8, 61.4, 58.2, 28.8 (2 C), 14.0 (2 C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.5 ppm. HRMS (ESI+): calcd. for $C_{16}H_{19}FO_5{\cdot}Na^+$ 333.1109; found 333.1114. $C_{16}H_{19}FO_5$ (310.32): calcd. C 61.93, H 6.17; found C 61.83, H 6.40.

Diethyl 2-(4-Methylisochroman-1-yl)malonate (3l): Following the general procedure, **3l** was obtained as a mixture of two diastereoisomers in a 1:1.5 ratio (81%). Chromatography: pentane/ethyl acetate, 20:1–10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.11 (m, 3 H, major; 3 H, minor), 7.07–7.04 (m, 1 H, minor; 1 H, major), 5.51 (d, J = 6.7 Hz, 1 H, major), 5.44 (d, J = 5.7 Hz, 1 H, minor), 4.26–4.10 (m, 5 H, major; 4 H, minor), 4.03 (d, J = 5.7 Hz, 1 H, minor), 3.97 (d, J = 6.8 Hz, 1 H, major), 3.87 (d, J = 3.8 Hz, 1 H, major), 3.48 (dd, J = 11.3, 7.2 Hz, 1 H, major), 3.06–2.98 (m, 1 H, major), 2.86–2.79 (m, 1 H, minor), 1.36 (d, J = 7.1 Hz, 3 H, minor), 1.24 (d, J = 7.0 Hz, 3 H, major), 1.24 (t, J = 7.1 Hz, 3 H, minor) 1.23 (t, J = 7.1 Hz, 3 H, major), 1.16 (t, J = 7.1 Hz, 3 H, minor), 1.14 (t, J = 7.1 Hz, 3 H, major) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 166.8, 139.6, 139.5, 134.4, 134.3, 128.4, 127.3, 127.2, 126.1, 126.0, 124.6, 124.3, 74.5, 74.3, 69.3, 69.1, 61.7 (2 C), 61.3 (2 C), 58.3, 57.8, 32.5, 31.7, 20.2, 17.8, 14.0, 13.9 (2 C) ppm. HRMS (ESI+): calcd. for $C_{17}H_{22}O_5{\cdot}Na^+$ 329.1359; found 329.1356. $C_{17}H_{22}O_5$ (306.35): calcd. C 66.65, H 7.24; found C 66.44, H 7.17.

Diethyl 2-[Methoxy(phenyl)methyl]malonate (3m): Following the general procedure, **3m** was obtained as a pale-yellow oil (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 4.78 (d, J = 10.1 Hz, 1 H), 4.35–4.20 (m, 2 H), 3.92 (qd, J = 7.1, 1.2 Hz, 2 H), 3.74 (d, J = 10.1 Hz, 1 H), 3.19 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 0.98 (t, J = 10.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 166.4, 138.0, 128.7, 128.5, 127.9, 81.9, 61.8, 61.5, 60.1, 57.0, 14.2, 13.8 ppm. HRMS (ESI+): calcd. for $C_{15}H_{20}O_5{\cdot}Na^+$ 303.1203; found 303.1203.

Diethyl 2-[Isopropoxy(phenyl)methyl]malonate (3n): Following the general procedure, **3n** was obtained as a pale-yellow oil (41%). Chromatography: pentane/ethyl acetate, 20:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 2 H), 7.33–7.24 (m, 3 H), 4.98 (d, J = 10.2 Hz, 1 H), 4.31–4.18 (m, 2 H), 3.94–3.86 (m, 2 H), 3.70 (d, J = 10.2 Hz, 1 H), 3.48 (hept., J = 6.1 Hz, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.12 (d, J = 6.1 Hz, 3 H), 0.97 (d, J = 6.1 Hz, 3 H), 0.96 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 166.6, 139.7, 128.4, 128.3, 127.9, 77.9, 69.9, 61.6, 61.4, 60.6, 23.4, 21.1, 14.3, 13.8 ppm. HRMS (ESI+): calcd. for $C_{17}H_{24}O_5{\cdot}Na^+$ 331.1516; found 331.1522. $C_{17}H_{24}O_5$ (308.37): calcd. C 66.21, H 7.84; found C 66.22, H 7.96.

Diethyl 2-[2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]malonate (3o): Following the general procedure, **3o** was obtained as a pale-yellow oil (53%). Chromatography: pentane/ethyl acetate, 10:1. This compound exists as a mixture of rotamers in a ratio 1:1.2 in $CDCl_3$ at 23 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 1 H, major; 1 H, minor), 7.20–7.11 (m, 3 H, major; 3 H, minor), 5.99 (d, J = 8.7 Hz, 1 H, minor), 5.91 (d, J = 7.0 Hz, 1 H, major), 4.24–3.98 (m, 5 H, major; 4 H, minor), 3.76–3.70 (m, 2 H, minor; 1 H, major), 3.63–3.56 (m, 1 H, minor), 3.47–3.41 (m, 1 H, major), 2.94–2.82 (m, 2 H, major; 2 H, minor), 1.46 (s, 9 H, major), 1.44 (s, 9 H, minor), 1.30–1.23 (m, 3 H, major; 3 H, minor), 1.14 (t, J = 7.1 Hz, 3 H, minor), 1.07 (t, J = 7.1 Hz, 3 H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.5, 167.3, 167.2, 154.9, 154.4, 135.4, 134.9, 134.7, 129.0, 128.6, 127.9, 127.7, 127.2, 126.3, 126.2, 80.7, 80.1, 61.7, 61.6, 61.5, 59.5, 59.0, 53.9, 53.2, 40.3, 38.5, 28.4, 28.3, 28.1, 28.0, 14.1, 14.0 (2 C), 13.9 ppm. HRMS (ESI+): calcd. for $C_{21}H_{29}NO_6{\cdot}Na^+$ 414.1887; found 414.1903.

Diethyl 2-[2-(Ethoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-malonate (3p): Following the general procedure, **3p** was obtained as a pale-yellow oil (80%). Chromatography: pentane/ethyl acetate, 10:1. This compound exists as a mixture of rotamers in a ratio 1:1.3 in $CDCl_3$ at 23 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, J = 7.3 Hz, 1 H, minor), 7.25 (d, J = 7.8 Hz, 1 H, major), 7.22–7.15 (m, 1 H, major; 1 H, minor), 7.15–7.08 (m, 2 H, major; 2 H, minor), 6.01 (d, J = 8.2 Hz, 1 H, minor), 5.94 (d, J = 8.1 Hz, 1 H, major), 4.25–3.96 (m, 7 H, major; 6 H, minor), 3.87–3.73 (m, 1 H, major; 2 H, minor), 3.69–3.43 (m, 1 H, minor), 3.53–3-46 (m, 1 H, major), 3.01–2.81 (m, 2 H, major; 2 H, minor), 1.33–1.17 (m, 6 H, major, and 6 H, minor), 1.14–1.04 (m, 3 H, major; 3 H, minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 167.0, 155.7, 155.2, 134.6, 134.4, 128.9, 128.5, 127.7, 127.6, 127.2, 126.1, 61.7 (2 C), 61.5, 61.4, 59.0, 58.8, 53.6, 39.7, 38.9, 27.8, 27.5, 14.6, 14.5, 14.0, 13.8 ppm. HRMS (ESI+): calcd. for $C_{19}H_{25}NO_6{\cdot}Na^+$ 386.1574; found 386.1583. $C_{19}H_{25}NO_6$ (363.40): calcd. C 62.80, H 6.93, N 3.85; found C 62.43, H 6.95, N 3.86.

Ethyl 2-[2-(Ethoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-3-oxo-3-phenylpropanoate (3q): Following the general procedure, **3q** was obtained as a mixture of two diastereoisomers in a ratio of 1:1.6, which form rotamers, as a pale-yellow oil (83%). Chromatography: pentane/ethyl acetate, 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.82 (m, 2 H, major; 2 H, minor), 7.63–6.94 (m, 7 H, major; 7 H, minor), 6.44 (d, J = 9.5 Hz, 1 H, minor rotamer of the major diastereoisomer), 6.37 (d, J = 9.5 Hz, 1 H, major rotamer of the major diastereoisomer), 6.24 (d, J = 5.5 Hz, 1 H, minor rotamer of the minor diastereoisomer), 6.17 (d, J = 5.7 Hz, 1 H, major rotamer of the minor diastereoisomer), 4.89–4.73 (m, 1 H, major, and 1 H, minor), 4.26–3.39 (m, 6 H, major; 6 H, minor), 3.10–2.80 (m, 2 H, major, and 2 H, minor), 1.33–1.05 (m, 3 H, minor rotamer of the major diastereoisomer; 3 H, major rotamer of the minor diastereoisomer; 3 H, minor rotamer of the minor diastereoisomer), 0.92 (t, J = 7.1 Hz, 3 H, major rotamer of the major diastereoisomer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 192.1, 191.8, 167.9, 167.5, 167.0, 166.5, 155.6, 155.4, 155.2, 136.5, 136.4, 136.0, 135.9, 134.1, 133.9, 133.6, 133.4, 133.1, 129.1, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 127.2, 126.2, 126.0, 61.8, 61.7, 61.4, 61.0, 53.6, 53.0, 40.0, 39.6, 39.1, 38.8, 28.1, 27.8, 27.7, 27.3, 14.6, 14.5, 14.3, 13.8, 13.6, 13.5 ppm. HRMS (ESI+): calcd. for $C_{23}H_{25}NO_5{\cdot}Na^+$ 418.1625; found 418.1629. $C_{23}H_{25}NO_5$ (395.45): calcd. C 69.86, H 6.37, N 3.54; found C 69.57, H 6.37, N 3.63.

Diethyl 2-(2-Pivaloyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (3r): Following the general procedure, **3r** was obtained as a white solid (69%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, J = 7.6 Hz, 1 H), 7.20–7.09 (m, 3 H), 6.31 (d, J = 6.6 Hz, 1 H), 4.33–4.23 (m, 1 H), 4.19 (qd, J = 7.1, 1.2 Hz, 2 H), 4.02 (q, J = 7.1 Hz, 2 H), 3.81 (d, J = 6.7 Hz, 1 H), 3.80–3.69 (m, 1 H), 2.93 (ddd, J = 17.3, 11.4, 6.2 Hz), 2.82 (ddd, J = 16.6, 4.2, 2.8 Hz, 1 H), 1.29 (s, 9 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.10 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 167.8, 167.4, 134.7, 133.7, 128.9, 127.6, 127.5, 126.3, 61.8, 61.6, 59.4, 52.8, 40.6, 39.2, 28.6, 28.5, 14.1, 13.9 ppm. HRMS (ESI+): calcd. for $C_{21}H_{29}NO_5{\cdot}H^+$ 376.2118; found 376.2118.

$C_{21}H_{19}NO_5$ (365.38): calcd. C 67.18, H 7.79, N 3.73; found C 67.18, H 7.80, N 3.78.

Diethyl 2-(2-Acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (3s): Following the general procedure, **3s** was obtained as a pale-yellow oil (72%). Chromatography: pentane/ethyl acetate, 3:1. This compound exists as a mixture of rotamers in a ratio 1:1.8 in $CDCl_3$ at 23 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.34 (m, 1 H, minor), 7.26–7.09 (m, 4 H, major; 3 H, minor), 6.33 (d, J = 7.8 Hz, 1 H, minor), 5.66 (d, J = 9.5 Hz, 1 H, major), 4.49 (dddd, J = 13.4, 6.7, 4.3, 1.0 Hz, 1 H, major), 4.30–3.97 (m, 4 H, major, and 4 H, minor), 3.90 (d, J = 9.5 Hz, 1 H, major), 3.86 (m, 1 H, minor), 3.71 (d, J = 7.8 Hz, 1 H, minor), 3.67 (m, 1 H, minor), 3.23 (ddd, J = 13.6, 9.5, 5.8 Hz, 1 H, major), 3.07–2.78 (m, 2 H, major; 2 H, minor), 2.26 (s, 3 H, major), 2.11 (s, 3 H, minor), 1.26 (t, J = 7.1 Hz, 3 H, major), 1.26 (t, J = 7.1 Hz, 3 H, minor) 1.17 (t, J = 7.1 Hz, 3 H, major), 1.10 (t, J = 7.1 Hz, 3 H, minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.0, 167.4, 167.3 (2 C), 166.7, 134.7 (2 C), 134.5, 134.1, 129.5, 128.4, 128.3, 128.1, 127.8, 126.7, 126.6, 126.3, 62.3, 62.1, 61.8, 61.5, 58.9, 58.6, 56.2, 51.4, 42.1, 36.8, 28.4, 27.3, 22.0, 21.9, 14.1, 14.0 (2 C), 13.9 ppm. HRMS (ESI+): calcd. for $C_{18}H_{23}NO_5{\cdot}Na^+$ 356.1468; found 356.1467.

Diethyl 11b,13-Dihydro-6*H*-isoquinolino[2,1-*a*]quinoline-12,12(7*H*)-dicarboxylate (3t): Following the general procedure, **3t** was obtained as a pale-yellow oil (56%). Chromatography: pentane/DCM, 1:2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.04 (m, 6 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.72 (td, J = 7.4, 1.0 Hz, 1 H), 5.09 (s, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.13 (q, J = 7.1 Hz, 1 H), 4.05 (q, J = 7.1 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.63 and 3.48 (AB system, J = 16.4 Hz, 2 H), 3.30 (td, J = 11.6, 3.7 Hz, 1 H), 3.25–3.15 (m, 1 H), 2.75 (dt, J = 15.5, 3.0 Hz, 1 H), 1.16 (t, J = 7.1 Hz, 1 H), 1.10 (t, J = 7.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.5, 145.5, 137.0, 135.5, 129.0, 128.7, 127.1, 126.9, 126.2, 125.7, 122.0, 118.3, 112.3, 61.9, 61.6, 61.24, 59.6, 44.2, 33.8, 28.2, 14.0, 13.8 ppm. HRMS (ESI+): calcd. for $C_{23}H_{25}NO_4{\cdot}H^+$ 380.1862; found 380.1856.

Ethyl 13-Hydroxy-7,11b-dihydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carboxylate (3u): Following the general procedure, **3u** was obtained as a green-yellow oil (68%). Chromatography: pentane/ethyl acetate, 6:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.62 (s, 1 H, enol), 7.64 (dd, J = 7.8, 1.6 Hz, 1 H), 7.29–7.33 (m, 1 H), 7.15–7.06 (m, 2 H), 7.04–6.93 (m, 2 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.70 (td, J = 7.8, 0.9 Hz, 1 H), 5.60 (s, 1 H), 4.38 (qq, J = 10.8, 7.1 Hz, 2 H), 4.25–4.15 (m, 2 H), 3.69 (ddd, J = 14.4, 12.3, 5.3 Hz, 1 H), 3.42–3.30 (m, 1 H), 2.75 (dd, J = 16.9, 5.0 Hz, 1 H), 1.34 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 165.2, 147.4, 139.3, 134.0, 133.1, 129.1, 126.9, 125.9 (2 C), 125.7, 117.7, 117.6, 112.1, 93.7, 60.9, 55.6, 45.1, 24.2 ppm. HRMS (ESI+): calcd. for $C_{20}H_{19}NO_3{\cdot}Na^+$ 344.1257; found 344.1264.

Diethyl 2-[(*tert*-Butoxycarbonylamino)(phenyl)methyl]malonate (3v): Following the general procedure, **3u** was obtained as a pale-yellow oil (30%). Chromatography: pentane/ethyl acetate, 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 6.19 (br. s, 1 H), 5.49 (br. s, 1 H), 4.28–4.02 (m, 4 H), 3.88 (br. d, J = 4.5 Hz, 1 H), 1.40 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.12 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 167.3, 155.2, 139.7, 128.6, 127.7, 126.4, 79.8, 62.1, 61.7, 57.0, 28.4, 14.1, 14.0 ppm. HRMS (ESI+): calcd. for $C_{19}H_{27}NO_6{\cdot}Na^+$ 388.1731; found 388.1724. $C_{19}H_{27}NO_6$ (365.42): calcd. C 62.45, H 7.45, N 3.83; found C 62.39, H 7.43, N 3.91.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the NMR spectra.

Acknowledgments

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[16] Highly unstable TEMPOH was partially oxidized to TEMPO during manipulation of the GC–MS samples in air.

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