Synlett J. Zhou et al. Letter

CF_3COOH/O_2-Mediated Metal-Free Domino Construction of the Isatin Skeleton

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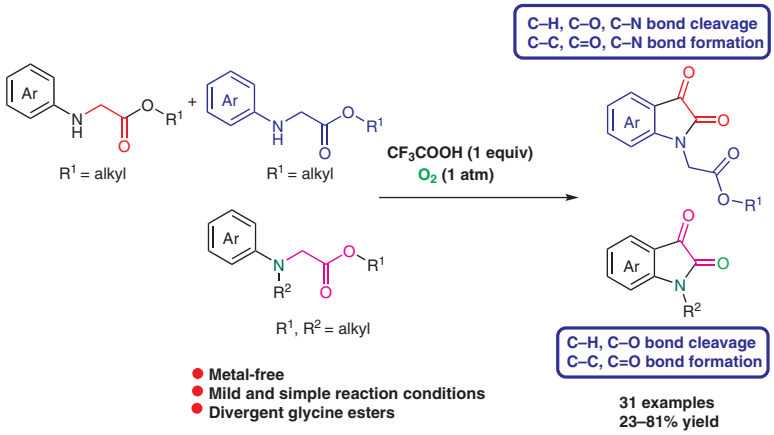

Received: 18.06.2019
Accepted after revision: 28.07.2019
Published online: 14.08.2019
DOI: 10.1055/s-0039-1690018; Art ID: st-2019-u0315-l

Abstract Directed by the strategy of C–H activation, an efficient construction of the isatin skeleton was developed through aerobic oxidation of glycine esters. The reactions were performed under CF_3COOH/O_2 conditions in the absence of metal catalysts. The reaction mechanisms were investigated with control experiments.

Key words metal-free, isatin skeleton, C–H activation, CF_3COOH, oxygen

Isatin and its derivatives exist widely in natural products and many of them are bioactive compounds or pharmaceutics.[1] Although, a number of methods have been established for the construction of such structures, the reported syntheses of isatins often require substrate prefunctionalization, multiple steps, and starting materials that are not readily available.[2] Therefore, the development of novel and practical methods for the synthesis of isatins by double carbonylation of aromatic C–H bonds *ortho* to an amino group has drawn much attention. In recent years, Cu-based,[3] Sb-based,[4] Pd-based,[5] and Oxone/$NaNO_2$-based[6] coupling reactions have been developed (Scheme 1). Nevertheless, the development of more practical methods for the synthesis of isatin and its derivatives remains highly desirable.

The direct α-C–H bond functionalization of glycine derivatives has become a straightforward strategy for the synthesis of α-substituted amino acid derivatives[7] and other useful structures.[8] Nevertheless, the oxidative coupling of glycine derivatives without metal catalysts and chemical oxidants is rare.

Here, we reported an efficient construction of the isatin skeleton through aerobic oxidation of glycine esters under mild reaction conditions that requires only CF_3COOH and O_2.

Our efforts toward this C–H activation strategy for the synthesis of isatins initially focused on intramolecular cyclization of *N*-alkyl-*N*-arylglycinates. When a mixture of **1a** (1.0 mmol), CuCl (10 mol%), and O_2 (1 atm) was stirred in acetonitrile at 70 °C for 12 hours, a trace amount of **2a** was indeed formed (Table 1, entry 1). This encouraging result prompted us to optimize the reaction conditions further. A series of Brønsted acids, such as CCl_3COOH, CF_3COOH, H_2SO_4, and TfOH were screened, and the results indicated that CF_3COOH (1 equiv) could promote the aerobic oxidation to a significant extent (entries 2–5). To our surprise, a similar yield of **2a** was obtained without copper catalyst, albeit with an extended reaction time of 48 hours (entry 7). Screening of the loading amounts of CF_3COOH indicated that 1 equiv was optimal (entries 7–10). In the absence of CuCl, other Brønsted acids were also less active (entries 11–13).

Acid could promote the formation of intermediates **A**, **E**, and **H** by the generation of H_2O_2, which is crucial to the reaction (Scheme 3 and Scheme 4). On the other hand, in the absence of O_2, almost none of the desired product was detected (Table 1, entry 14). Various solvents, such as, DCE, THF, MeOPh, and EtOH were further examined, and MeCN was still the best solvent (entries 15–18). The optimal reaction conditions were thus established as **1a** (1.0 mmol), CF_3COOH (1.0 mmol), and O_2 (1 atm) stirring in acetonitrile at 70 °C for 48 hours.

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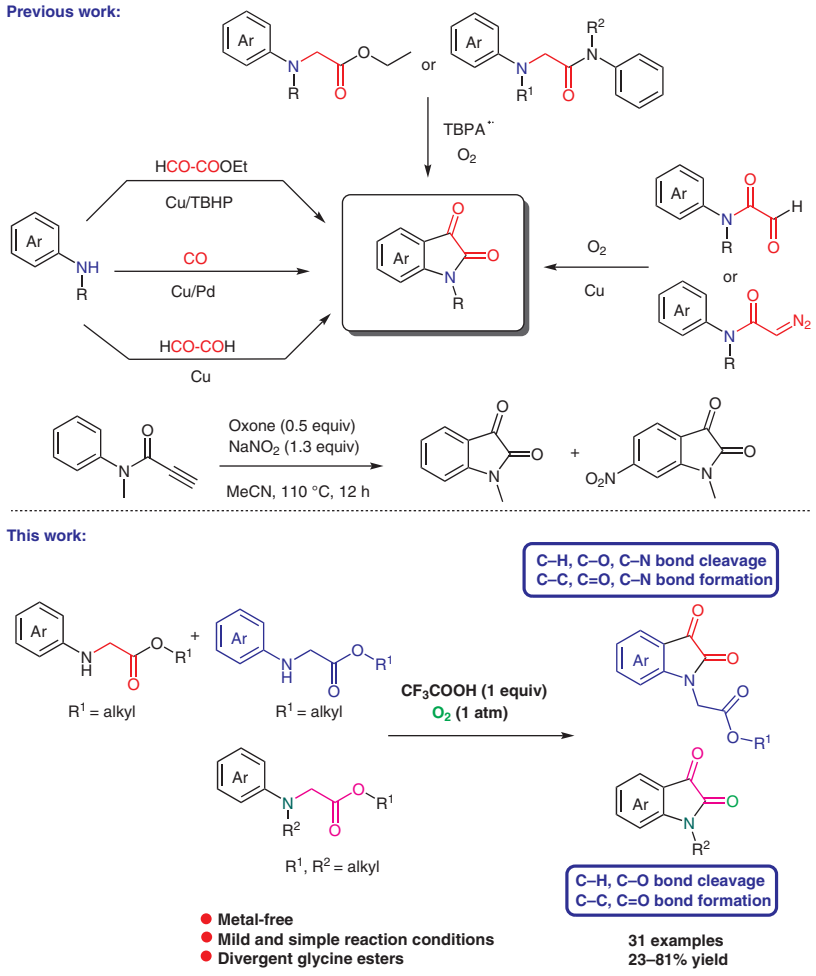
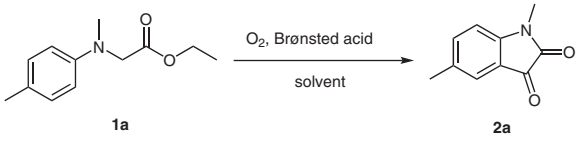


Scheme 1 Synthesis of isatins via carbonylation of C–H bonds

Table 1 Optimization of Reaction Conditions[a]



1a 2a

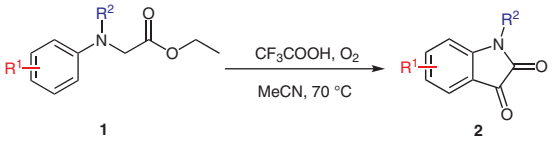
Entry	Cat. (10 mol%)	Acid (equiv)	Solvent	Time (h)	Yield (%)[b]
1	CuCl	–	MeCN	12	trace
2	CuCl	CCl_3COOH (1)	MeCN	12	57
3	CuCl	CF_3COOH (1)	MeCN	12	67
4	CuCl	H_2SO_4 (1)	MeCN	12	trace
5	CuCl	CF_3SO_3H (1)	MeCN	12	trace
6	–	CF_3COOH (1)	MeCN	12	31
7	–	CF_3COOH (1)	MeCN	48	65
8	–	CF_3COOH (0.5)	MeCN	48	40
9	–	CF_3COOH (2)	MeCN	48	63
10	–	–	MeCN	48	n.d.
11	–	CCl_3COOH (1)	MeCN	48	50
12	–	H_2SO_4 (1)	MeCN	48	trace
13	–	CF_3SO_3H (1)	MeCN	48	trace
14[c]	–	CF_3COOH (1)	MeCN	48	trace
15	–	CF_3COOH (1)	MeOPh	48	61
16	–	CF_3COOH (1)	DCE	48	53
17	–	CF_3COOH (1)	EtOH	48	12
18	–	CF_3COOH (1)	THF	48	50

[a] Reaction conditions: **1a** (1.0 mmol), catalyst, acid, O_2 (1 atm) in the solvent at 70 °C.
[b] Isolated yield.
[c] The reaction was performed under N_2 atmosphere.

With the best conditions established, the scope of the reaction with substituted *N*-alkyl-*N*-arylglycinates was investigated (Table 2).[9] Electron-donating groups on the *para*-

position of the phenyl ring of **1** enhanced the efficiency of the reaction, giving the desired products **2a–i** in moderate to good yields (52–81%). However, when electron-withdrawing groups were introduced, the desired products **2k** and **2l** were obtained in low yields. A *meta*-substituted glycine ester also delivered the corresponding product **2j**. Notably, when substrates with *ortho*-methyl substituted or unsubstituted aromatic moiety were used, the reaction became complex (**2m** and **2n**). We then investigated the substrate scope with respect to the *N*-groups, such as methyl, ethyl, *n*-propyl, and *n*-butyl, which also gave the corresponding isatins **2a–d** in moderate yields.

Table 2 Reaction of *N*-Alkyl-*N*-arylglycinates[a]

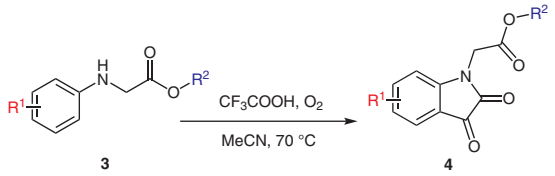


Entry	R^1	R^2	Product	Yield (%)[b]
1	4-methyl	methyl	**2a**	65
2	4-methyl	ethyl	**2b**	66
3	4-methyl	*n*-propyl	**2c**	62
4	4-methyl	*n*-butyl	**2d**	52
5	4-isopropyl	methyl	**2e**	81
6	4-isopropyl	ethyl	**2f**	70
7	4-*tert*-butyl	methyl	**2g**	74
8	4-*tert*-butyl	ethyl	**2h**	64
9	4-methoxy	methyl	**2i**	63
10	3,5-dimethyl	ethyl	**2j**	72
11	4-fluoro	methyl	**2k**	25[c]
12	4-chloro	methyl	**2l**	23[c]
13	2-methyl	methyl	**2m**	mixture
14	H	methyl	**2n**	mixture

[a] Reaction conditions: **1** (1 mmol), CF_3COOH (1 equiv), MeCN (5 mL), 70 °C under O_2 (1 atm).
[b] Isolated yield.
[c] NMR yield.

The scope of the reaction with substituted *N*-H-*N*-arylglycine esters **3** were investigated (Table 3).[10] None of intramolecular cyclization products were detected, which indicated that the reaction proceeded through different mechanism. To our delight, several functional groups, such as methyl, isopropyl, *tert*-butyl, methoxy, fluoro, chloro, and bromo groups, on the aromatic moiety were well-tolerated, gave the corresponding products **4a–p** and **4s** in moderate to good yields. When *meta*-methyl substituted substrates were reacted, the target products **4q** and **4r** were obtained in 70% and 66% yields, respectively. However, *ortho*-methyl substituted and unsubstituted aniline glycine derivatives gave a complex reaction mixture (**4t** and **4u**). If strong EWGs (NO_2, and CF_3) were introduced, no desired products were detected due to poor conversion of the starting materials (**4v** and **4w**).

Table 3 Reaction of *N*-Alkyl-*N*-arylglycinates[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	4-methyl	methyl	**4a**	65
2	4-isopropyl	methyl	**4b**	75
3	4-*tert*-butyl	methyl	**4c**	78
4	4-methoxy	methyl	**4d**	56
5	4-fluoro	methyl	**4e**	62
6	4-chloro	methyl	**4f**	53
7	4-methyl	ethyl	**4g**	64
8	4-isopropyl	ethyl	**4h**	79
9	4-*tert*-butyl	ethyl	**4i**	51
10	4-fluoro	ethyl	**4j**	72
11	4-chloro	ethyl	**4k**	55
12	4-bromo	ethyl	**4l**	52
13	4-methyl	isopropyl	**4m**	46
14	4-*tert*-butyl	isopropyl	**4n**	72
15	4-methoxy	isopropyl	**4o**	50
16	4-fluoro	isopropyl	**4p**	46
17	3,5-dimethyl	methyl	**4q**	70
18	3,5-dimethyl	isopropyl	**4r**	66
19	4-methyl	benzyl	**4s**	70
20	2-methyl	ethyl	**4t**	mixture
21	H	ethyl	**4u**	mixture
22	4-nitro	ethyl	**4v**	none
23	4-trifluoromethyl	ethyl	**4w**	none

[a] Reaction conditions: **3** (1 mmol), CF_3COOH (1 equiv), MeCN (5 mL), 70 °C under O_2 (1 atm).
[b] Isolated yield (based on 0.5 equiv of **3**).

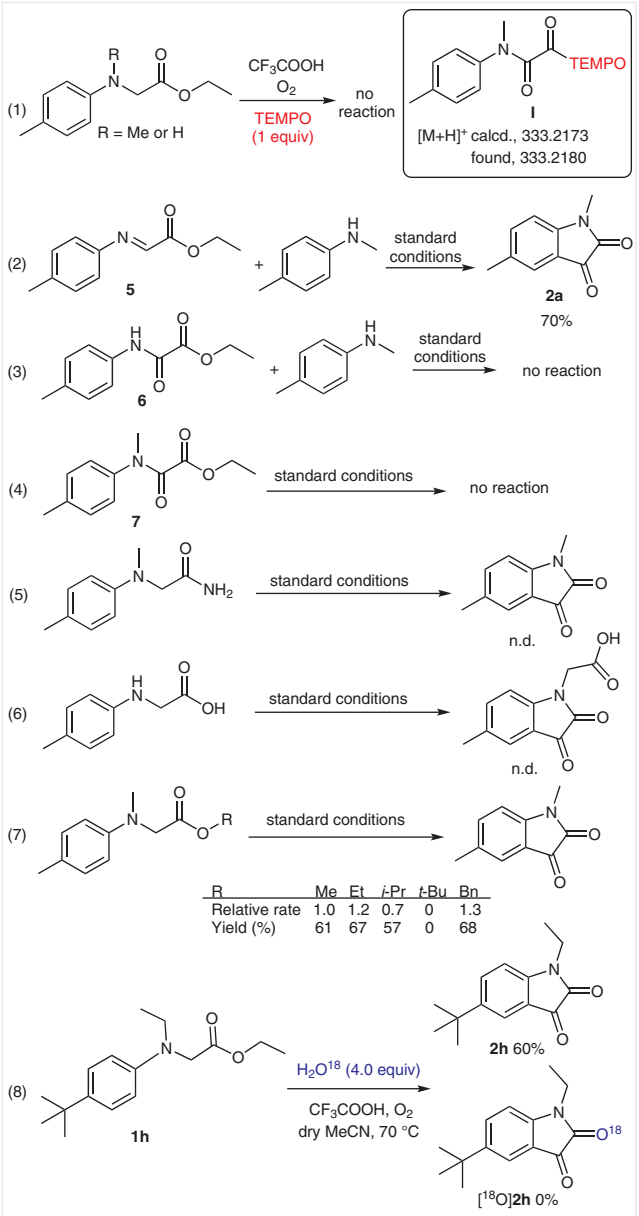
To explore the mechanism, a series of control reactions were conducted, as shown in Scheme 2. It was found that the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1 equiv) inhibits the reaction, suggesting a single-electron-transfer pathway might be involved. We are delighted to detect compound **I** by high-resolution mass spectrometry (HRMS), implying that the C–O bond in the ester was activated (Scheme 2, eq. 1).[11] Under the standard intermolecular cyclization, intermediates **D**, **E**, **F**, and **H** were detected by a similar method (Scheme 4).[11] Compound **5** was found

to react with *N*-methyl-*p*-toluidine under the standard conditions, and **2a** was obtained in 70% yield (Scheme 2, eq. 2). Then the standard conditions were applied to **6** and **7** (Scheme 2, eq. 3 and 4), and no reaction occurred, which ruled out the possibility of a direct intramolecular Friedel–Crafts type reaction of glycine ester. 2-(Methyl(*p*-tolyl)amino)-acetamide and *p*-tolylglycine showed no reactivity (Scheme 2, eq. 5 and 6). Furthermore, substrates with different ester groups were investigated: the methyl ester, ethyl ester, isopropyl ester, *tert*-butyl ester, and benzyl ester gave **2a** in 61, 67, 57, 0, and 68% yield, respectively (Scheme 2, eq. 7). The results show that the α-proton adjacent to the ester group is crucial for the formation of isatin. Finally, the source of the oxygen atom in the amide was studied by adding H_2O^{18} to the reaction mixture, whereupon product **2h** was formed in 60% yield without the ^{18}O-incorporation product [^{18}O] **2h** (Scheme 2, eq. 8). The possibility that the oxygen atom comes from H_2O was thus excluded.

Based on the above results, a possible mechanism of intramolecular cyclization was proposed (Scheme 3). In the presence of dioxygen, the relatively active C–H bond of the glycine ester is oxidized by O_2 to give a radical intermediate **A**. Second, **A** is trapped by dioxygen to produce a peroxide radical **B**. After a possible intramolecular 1,6-H shift, the C–H bond adjacent to the oxycarbonyl group is activated, followed by β-cleavage and elimination of water, to give acyl radical **C**. This species is further oxidized to a carbonyl cation, which is followed by an intramolecular Friedel–Crafts cyclization. After a proton loss and rearomatizaion, the isatin product is afforded.

A plausible mechanism for intermolecular cyclization is depicted in Scheme 4. The glycine ester **3g** was first oxidized by O_2 to give the hydroperoxide intermediate **D**. The iminium ion intermediate **E** could then be formed through an acid-catalyzed S_N1-type procedure from **D**. Subsequently, coupling of **E** with another **3g** results in the intermediate **F**; intramolecular nucleophilic attack of the NH group to the ester in **F** affords the intermediate **G**, which is further oxidized to give the intermediate **H**. Finally, hydrolytic cleavage of **H** produces the isatin product.

In conclusion, a metal-free domino construction of the isatin skeleton was developed through aerobic oxidation of glycine esters. The reaction thus provides a new way to achieve C–H activation. Based on the published reports and on our experiments, two plausible mechanisms were proposed. A detailed investigation of the mechanism and further application of this protocol is under way in our laboratory.



Scheme 2 Control experiments

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690018

Funding Information

We are grateful to the National Natural Science Foundation of China (No. 21776254) for financial help.

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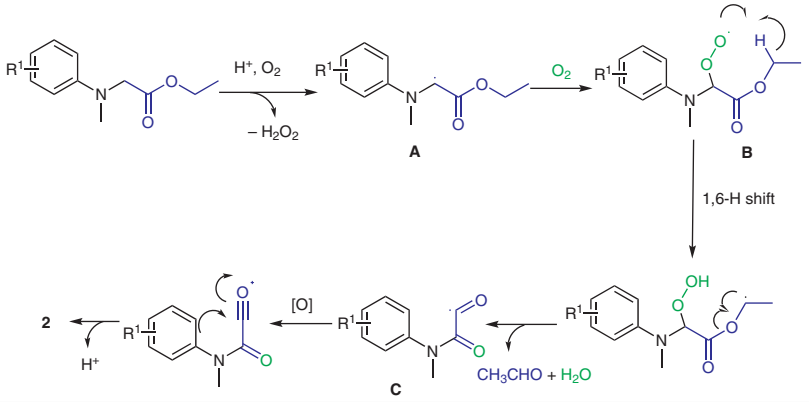
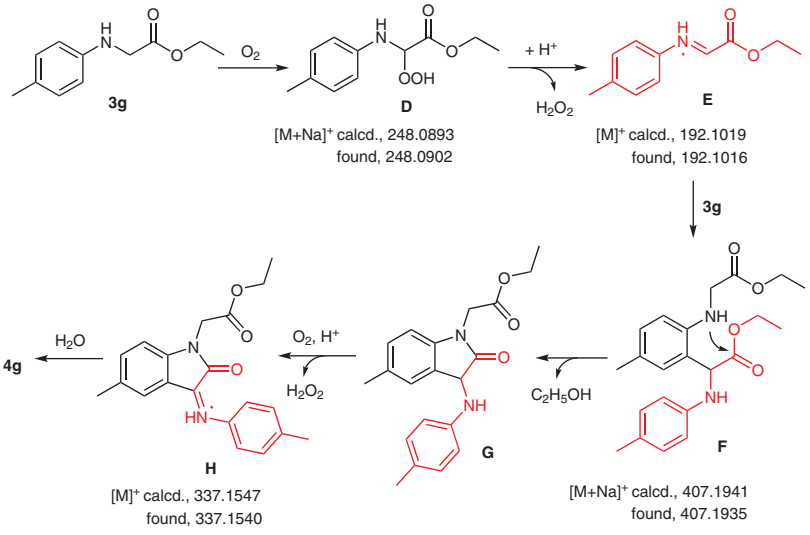


Scheme 3 A possible mechanism for intramolecular cyclization



Scheme 4 A possible mechanism for intermolecular cyclization

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(9) **Intramolecular Cyclization; General Procedure A:** A 25 mL round-bottom flask containing *N*-alkyl-*N*-arylglycinate (1 mmol), CF_3COOH (0.5 mmol), and MeCN (5 mL) was stirred at

70 °C under O_2 (1 atm) for 12 h. CF_3COOH (0.5 mmol) was added and, after stirring for 36 h, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel.

5-Methoxy-1-methylindoline-2,3-dione (2i)

Prepared by following General Procedure A using ethyl *N*-(4-methoxyphenyl)-*N*-methylglycinate (223 mg, 1.0 mmol). Purification by column chromatography (*n*-hexane/EtOAc, 5:2) gave **2i** (120 mg, 63%) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.13 (m, 2 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 3.81 (s, 3 H), 3.22 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 183.7, 158.3, 156.6, 145.3, 124.6, 117.8, 110.9, 109.6, 56.0, 26.2. HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_9NNaO_3$: 214.0475; found: 214.0476.

(10) **Intermolecular Cyclization; General Procedure B:** A 25 mL round-bottom flask with *N*-H-*N*-arylglycinate (1 mmol), CF_3COOH (0.5 mmol) and MeCN (5 mL) was stirred at 70 °C under O_2 (1 atm) for 6 h. CF_3COOH (0.5 mmol) was added and, after stirring for 6 h, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel.

Methyl 2-(5-Isopropyl-2,3-dioxoindolin-1-yl)acetate (4b)

Prepared by following General Procedure B using methyl (4-isopropylphenyl) glycinate (207 mg, 1.0 mmol). Purification by column chromatography (*n*-hexane/EtOAc, 8:1) gave **4b** (98 mg, 75%) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 4.49 (s, 2 H), 3.79 (s, 3 H), 2.90 (hept, *J* = 6.8 Hz, 1 H), 1.24 (d, *J* = 6.9 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.8, 167.4, 158.3, 148.3, 145.3, 136.8, 123.4, 117.7, 110.0, 52.8, 41.1, 33.5, 23.8 (2C). MS (ESI$^+$): *m*/*z* = 262.05 [M + H]$^+$. HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NNaO_4$: 284.0893; found: 284.0889.

(11) Detailed analysis conditions for intermediates **I**: A 25 mL round-bottom flask containing **1a** (1 mmol), CF_3COOH (0.5 mmol), TEMPO (1 equiv), and MeCN (5 mL) was stirred at 70 °C under O_2 (1 atm) for 12 h. The reaction mixture was concentrated under reduced pressure and the crude material was analyzed by HRMS-APCI using ESI$^+$ ionization.Detailed analysis conditions for intermediates **D**, **E**, **F**, and **H**: To a 25 mL round-bottom flask containing **3g** (1 mmol), CF_3COOH (0.5 mmol), and MeCN (5 mL) was stirred at 70 °C under O_2 (1 atm) for 2 h, then the reaction mixture was concentrated under reduced pressure and the crude material was analyzed by HRMS-APCI using ESI$^+$ ionization.