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Electrochemical Oxidative Coupling Between Benzylic C(sp^3)−H and N−H of Secondary Amines: Rapid Synthesis of α-Amino α-Aryl Esters

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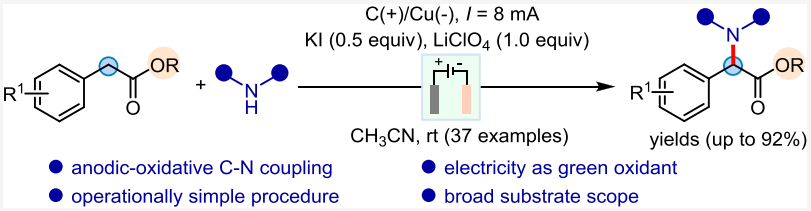

ABSTRACT: An intermolecular electrochemical coupling between the benzylic C(sp^3)−H bond and various secondary amines is reported. The electronic behavior of two electronically rich units viz the α-position of α-aryl acetates and amines was engineered electrochemically, thus facilitating their reactivity for the direct access of α-amino esters. A series of acyclic/cyclic secondary amines and α-aryl acetates were tested to furnish the corresponding α-amino esters with high yields (up to 92%) under mild conditions.

INTRODUCTION

The α-amination of carbonyl compounds remains a transformation of central importance in synthetic and medicinal chemistry as a straightforward route to versatile building units widely present in natural products and pharmaceuticals.[1] A reaction between nucleophilic synthons of carbonyl compounds, such as enolates or enamines, and preformed electrophilic amine reagents is a well-explored technique to access α-amino carbonyls.[2] Besides, the reaction between prefunctionalized carbonyls and nucleophilic amines ($N^{-\delta}$) has also been explored along with other conventional methods.[3] The direct C(sp^3)−H functionalization would offer a straightforward approach to introduce functionality to organic skeletons.[4] The direct dehydrogenative C−N bond formation between the proximal position of carbonyls and the nucleophilic amine is the shortest route to access α-amino carbonyls. However, it requires a polarity reversal of two electronically mismatched units.[5] In this context, MacMillan and co-workers developed a direct α-amination of ketones, esters, and aldehydes with secondary amines under the Cu-catalyzed aerobic condition (Scheme 1a).[5a] Initially, the direct NIS-mediated oxidative coupling between the secondary amine and ketones was explored by Prabhu and co-workers using peroxide as a co-oxidant.[5b] A similar NBS-mediated protocol for oxidative α-amination of in situ-generated ketones was developed by Sekar and co-workers.[5c] Guo and co-workers developed an NH_4I/peroxide-mediated α-amination of ketones.[5d] Liang et al. recently developed an electrochemical oxidative coupling between ketones and secondary amines to access α-amino ketones.[5e] Despite remarkable recent advances made in accessing α-amino carbonyls, more strictly, these methods are mainly limited to the readily enolizable lower-oxidation-state substrates, such as aldehydes/ketones (Scheme 1b), and hardly applicable to esters. The direct decarboxylative coupling between highly activated acids and an amine is an exciting way to access α-amino acid esters[6] and other methods.[7] Thus, developing a direct, simple, and environmentally friendly process accessing α-amino carbonyls such as α-amino acid esters is highly desirable. Notably, α-amino acids and their derivatives have medicinal significance and importance in artificial sweeteners, food additives, and cosmetic additives along with many other applications.[8]

On the other hand, electrochemical organic transformations have recently gained much attention as sustainable protocols under mild conditions.[9] The electrochemical oxidative C−H functionalizations for C−C,[10] C−O,[11] and C−N[12] bond formation have been achieved using metal-catalysis or metal-free conditions. Despite these efforts, the direct electrochemical amination of the C(sp^3)−H bond remains elusive.[13] Herein, we present our efforts toward the synthesis of α-amino acid esters through electrochemical oxidative coupling between benzylic C(sp^3)−H bonds and secondary amines. The protocol offers a mild and direct access to various α-amino acid esters

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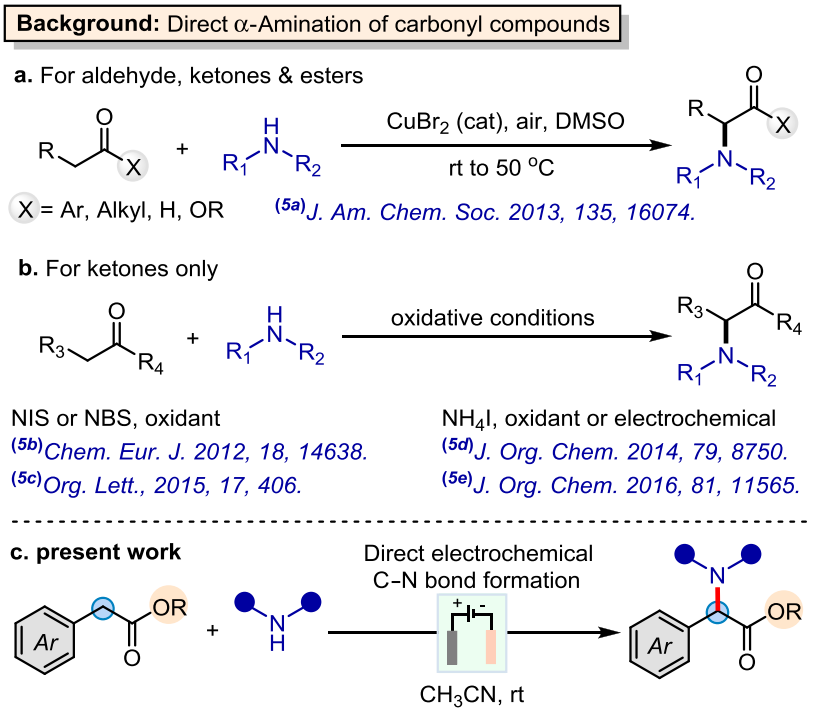
Scheme 1. Background for the Direct α-Amination of Carbonyls and the Present Work on Electrochemical Amination of α-Aryl Acetates

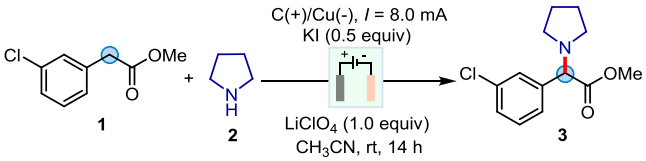


under metal-free conditions while tolerating organic functionalities (Scheme 1c).

RESULTS AND DISCUSSION

At the outset of our investigation, methyl 2-(3-chlorophenyl) acetate **1** and pyrrolidine **2** were employed as model substrates (Table 1). Extensive experiments for finding suitable reaction parameters such as electrodes, electrolyte, catalyst, and solvents (Tables S1–S4; see the Supporting Information, SI) were performed, which led to identifying the optimal reaction conditions. To our delight, the desired α-amino ester **3** was obtained in 89% yield under optimized conditions (entry 1, Table 1). Next, either increasing (entry 2, Table 1) or decreasing the applied current (entry 3, Table 1) from standard conditions to the vessel reduces the reaction yields. A similar result with 65% yield was obtained using C(+)/C(−) electrodes under standardized conditions (entry 4, Table 1). No desired product **3** was detected by switching the electrode position in the absence of KI and electric current (entries 5–7, Table 1). The addition of bases (1.0 equiv) under standard conditions (entries 8–9, Table 1) or varying solvent medium (entry 10, Table 1) did not improve the reaction yields. Thus, we prefer to perform the reaction under optimized conditions.

Table 1. Standardization of Reaction Conditions[ab]



entry	variation from standard conditions	yield (%)
1	none	89
2	I = 10.0 mA, instead of I = 8.0 mA	56
3	I = 6.0 mA, instead of I = 8.0 mA	71
4	C(+)/C(−) used instead of C(+)/Cu(−)	58
5	Cu(+)/C(−) used instead of C(+)/Cu(−)	
6	without KI	
7	without electricity	
8	lutidine (1.0 equiv) used as additive	74
9	K_2CO_3 (1.0 equiv) used as additive	68
10	MeOH as solvent instead of CH_3CN	45

[a]Reaction conditions: **1** (1.0 mmol), **2** (3.0 mmol), KI (0.5 mmol), $LiClO_4$ (1.0 mmol) in MeCN (10 mL), C-anode, Cu-cathode, undivided cell, constant current = 8 mA, at room temperature (rt) under a N_2 atmosphere for 14 h. [b]All isolated yields were based on **1**.

With the optimal conditions in hand, the reaction scope was investigated with various esters and amines (Table 2). Initially, pyrrolidine was tested with multiple meta-chlorophenyl acetic esters (-Me, -Et, -*i*Pr, -*tert*-butyl), which furnished the corresponding α-amino esters **3**–**6** (up to 89%). Moreover, different ortho-chlorophenyl acetic esters (i.e., -Me, -Et, -allyl, -cyclohexyl, -benzyl, and -piperonyl) were initially employed with pyrrolidine to finish the corresponding α-amino esters **7**–**12** (up to 76%). Next, a series of methyl and ethyl α-aryl acetates having substitutions (halogens/electron-withdrawing group) at different aromatic ring positions were tested with pyrrolidine, which furnished the corresponding products **13**–**20** (up to 85%). However, the reaction did not produce the desired outcome in the presence of electron-donating groups (see the SI). The scope of various acyclic/cyclic secondary amines was tested with methyl 2-(3-chlorophenyl) acetate **1** to yield the corresponding products **21**–**28** (up to 92%). A similar trend was observed in the formation of **29**–**32** and **33**–**36**, where piperidine and morpholine, respectively, were coupled with various esters. The protocol was extended with a secondary amine that exists in cetirizine, a drug molecule, and complementary product **37** was obtained with 68% yield under optimized conditions. Presently, the developed method

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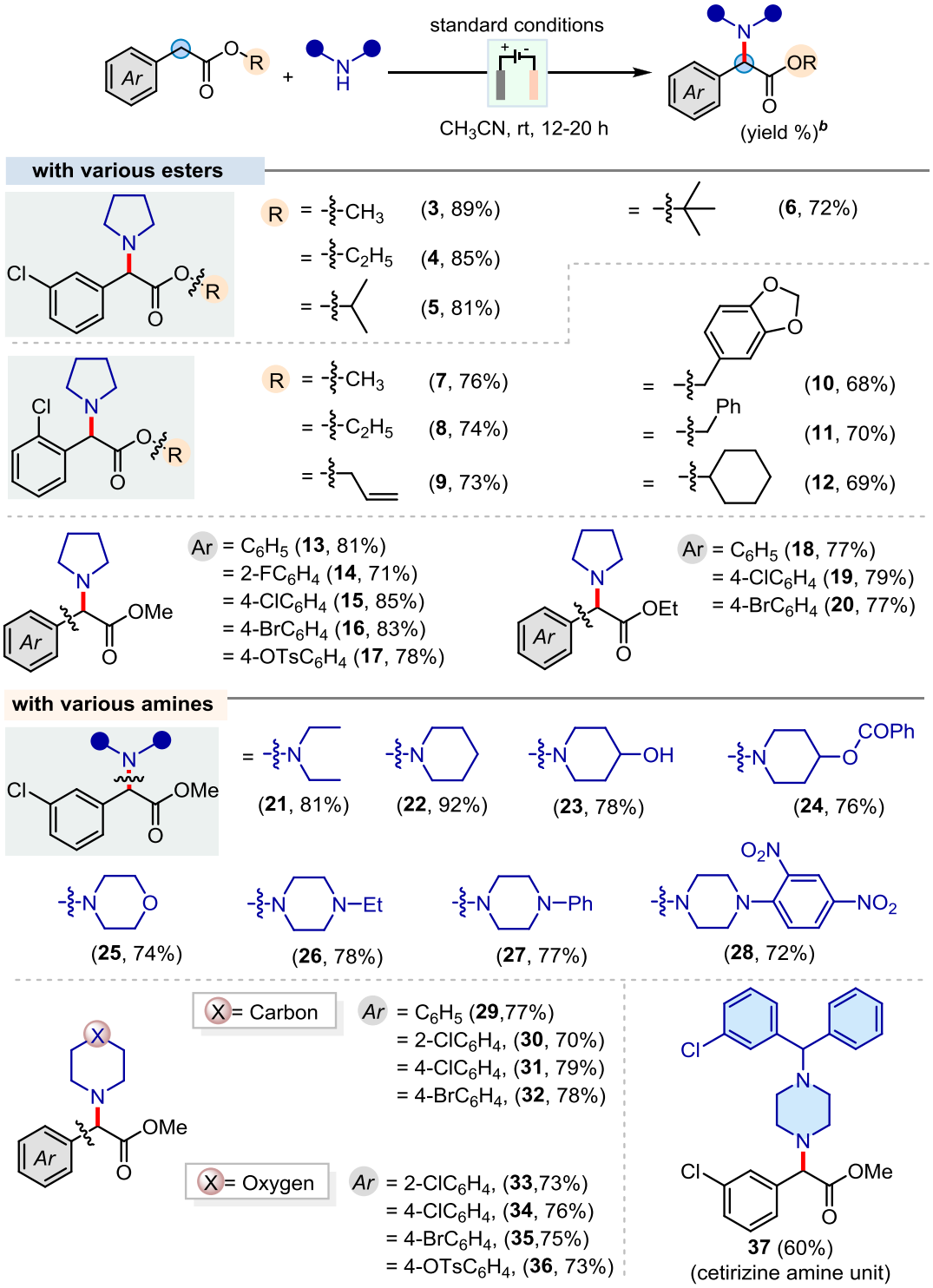
Table 2. Generality Concerning Various Esters and Amines[a]



[a]Reaction conditions: ester (1.0 mmol), amine (3.0 mmol), KI (0.5 mmol), $LiClO_4$ (1.0 mmol) in MeCN (10 mL), C-anode, Cu-cathode, undivided cell, constant current = 8 mA, at rt under a N_2 atmosphere for 12−20 h. [b]All isolated yields were based on ester.

is mainly limited to α-aryl acetates and secondary aliphatic amines. The reaction failed to give α-amino-α-aryl acetates with aniline(s)/primary/secondary aromatic amines or with sterically hindered aromatic esters/acids/amide as well as aliphatic ester under optimized conditions (see the SI for details).

For clarification of the reaction mechanism, electroanalytical measurements were performed. The cyclic voltammogram (CV) of KI with $LiClO_4$, as an electrolyte, showed a redox potential (peak potentials: +0.211 and −0.911 V vs Ag/AgCl as the reference electrode). The CVs of substrates **1**, KI, and $LiClO_4$ showed an oxidation potential of +1.30 V vs Ag/AgCl as the reference electrode. Finally, the CVs of all of the reacting

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species **1**, **2**, KI, and $LiClO_4$ showed an oxidation potential of +1.05 V vs Ag/AgCl as a reference electrode (Figure 1). The formation of the iodo-compound **38** through the combination of ester **1** with in situ-generated I_2 could be the initial outcome before reacting with amine **2**.

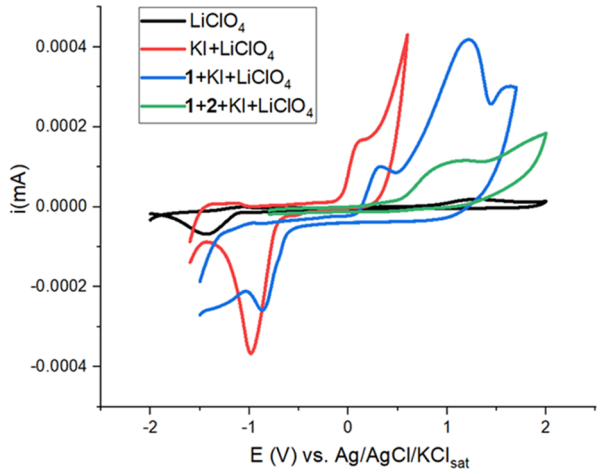


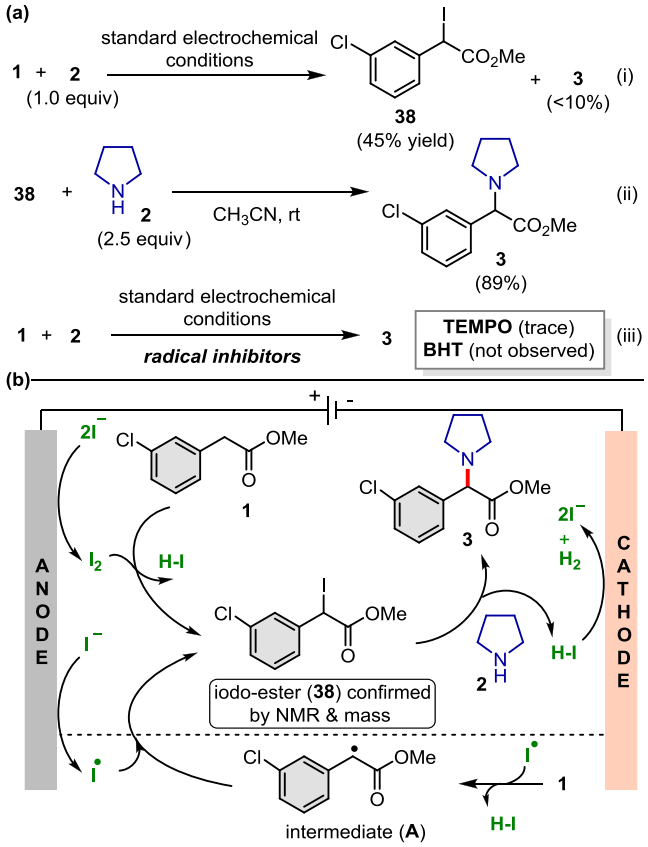
Figure 1. Cyclic voltammograms of $CH_3CN/LiClO_4$ (10 mL, 0.1M) (black); KI (0.01M) in $CH_3CN/LiClO_4$ (10 mL, 0.1M) (red); ester **1** (0.01M) and KI (0.01M) in $CH_3CN/LiClO_4$ (10 mL, 0.1M) (blue); ester **1** (0.01M), pyrrolidine **2** (0.01M), and KI (0.01M) in $CH_3CN/LiClO_4$ (10 mL, 0.1M); reference electrode: Ag/AgCl (3M KCl); scan rate: 0.2 V/s.

A set of control experiments was performed to gain more mechanistic insights into the electrochemical process. Initially, α-iodo-α-aryl methyl acetate **38** (45%) was isolated when a controlled experiment was conducted with amine **2** (1.0 equiv) under optimized conditions (Scheme 2a-i). The resulting iodo-ester **38** was separately reacted with amine **2** (2.5 equiv) to furnish **3** (89% yield), which confirms that the reaction proceeds through α-iodination, followed by displacement with the amine to provide the desired compound (Scheme 2a-ii). On the other hand, formation of product **3** was not observed with BHT or TEMPO, as a radical scavenger, under the standard electrochemical conditions, confirming the radical nature of the reaction at the intermediate steps (Scheme 2a-iii).

We proposed a reaction mechanism based on the cyclic voltammogram (CV) and other controlled experimental observations (Scheme 2b). Ester **38** could be generated through a radical pathway in which intermediate (**A**) developed through the sequential reaction with radical iodine (I*). Once the critical intermediate **38** is formed, it soon undergoes a nucleophilic substitution reaction with an amine, leading to the final α-amination product **3**, accompanying the second molecular HI. Simultaneously, the in situ-generated HI is reduced to evolve H_2 on the cathode surface and regenerate the iodide ion and the step of α-iodination of ester **1**, thus requiring a catalytic amount of KI. Alternatively, ester **1** could react with molecular iodine, in situ-generated through the anodic oxidation, to α-iodo-ester **38**, which will undergo a displacement reaction with an amine.

The practical utility of the developed electrochemical protocol was demonstrated for the gram scale, and **22** (1.30 g, 90% yield) was obtained without much variation in the product yield under optimized conditions (eq 1, Scheme 3).

Scheme 2. (a) Set of Controlled Experiments, (b) Proposed Reaction Mechanism for the Electrochemical Amination of α-Aryl Acetates



Besides, synthetic conversion of ester **22** was performed to the corresponding azido compound **39** (58% yield) with a three-step protocol (eq 2, Scheme 3). Similarly, α-amino ester **30** was efficiently transformed to the corresponding amide **40** (76% yield) (eq 3, Scheme 3).

CONCLUSIONS

In summary, we have developed an efficient electrochemical protocol for intermolecular oxidative coupling between α-aryl acetates ($C(sp^3)$–H bond) and secondary amines (N–H bond). The mild electrocatalytic condition furnishes α-amino esters by stitching together two electronically mismatched units through C–N-bond formation, with a high yield (up to 92%). The reactions can be scaled up without impacting the process efficiency, and the resulting α-amino esters can be functionalized to other similar biorelevant compounds. Further study in this direction is underway.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all commercially available compounds were used as received without further purification. Graphite and other electrodes were purchased from IKA, and all of the electrochemical reactions were performed under N_2 at room temperature using IKA Electrasyn 2.0. Cyclic voltammetric (CV) experiments were performed using the CH Instruments electrochemical analyzer (model CHI1200B). CH_3CN and other solvents were obtained from Merck Life Science Private Limited and were distilled from appropriate drying agents before being used in the reactions. All of the α-aryl acetates were prepared using the reported procedure.[14] Reactions under the standard

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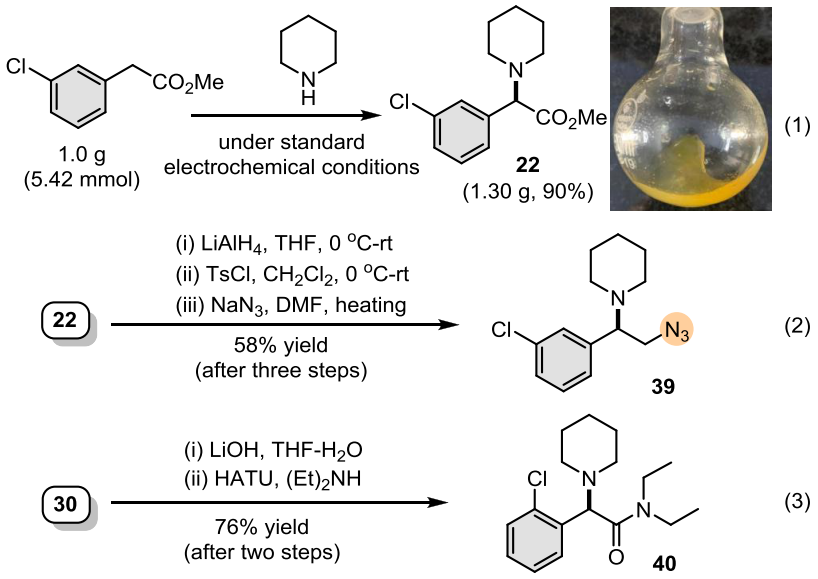
Scheme 3. Gram-Scale Synthesis and Synthetic Applications to Azido- and Amide Compounds



conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 precoated plates (0.25 mm) under UV light at 254 nm. Column chromatographic purification was performed on silica gel (100−200 mesh) using an eluent of petroleum ether and ethyl acetate. Chemical yields refer to pure (>95% purity by ^{1}H NMR), isolated substances. NMR spectroscopy was recorded on a 400 MHz NMR spectrometer (Bruker). ^{1}H and ^{13}C NMR spectra were recorded in CDCl3 and calibrated to the solvent resonance as an internal standard (^{1}H NMR, $CDCl_3$ at 7.26 ppm, ^{13}C NMR, $CDCl_3$ at 77.0 ppm). High-resolution mass spectra were recorded on Agilent 6545 Q-TOF LC/MS. Melting points were determined by the EZ-Melt automated melting point apparatus and are incorrect.

General Procedure for Electrochemical α-Amination of Esters. A 10 mL dried undivided reaction cell equipped with a stirring bar was charged with appropriate α-aryl acetates **1** (1.0 mmol, 1.0 equiv), secondary amine **2** (3.0 mmol, 3.0 equiv), KI (83 mg, 0.5 mmol, 0.5 equiv), and $LiClO_4$ (106 mg, 1.0 mmol, 1.0 equiv) dissolved in CH_3CN (10.0 mL). The reaction mixture was electrolyzed using a graphite plate as the anode and a copper plate as the cathode at a constant current condition (8 mA) under a N_2 atmosphere at room temperature. TLC monitored the reaction progress. The reaction mixture was evaporated under reduced pressure, and the residue mass was quenched by stirring between a saturated aqueous $Na_2S_2O_3$ solution (5.0 mL) and ethyl acetate (10.0 mL). The organic layer was separated and dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification on silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1 to 1:1) as the eluent afforded pure α-amino α-aryl esters **3** (up to 92% yield).

*Methyl 2-(3-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**3**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (226 mg, 89% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 1H), 7.37−7.33 (m, 1H), 7.29−7.23 (m, 2H), 3.90 (s, 1H), 3.68 (s, 3H), 2.54 (td, *J* = 7.0, 2.6 Hz, 2H), 2.44 (qt, *J* = 4.5, 1.8 Hz, 2H), 1.80 (ddd, *J* = 6.4, 4.7, 2.3 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 139.2, 134.4, 129.7, 128.4 (2C), 126.5, 73.2, 52.4 (2C), 52.1, 23.2. HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{13}H_{17}ClNO_2$ 254.0942, found 254.0941.

*Ethyl 2-(3-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**4**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (228 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.1 Hz, 1H), 7.38 (dt, *J* = 6.3, 2.0 Hz, 1H), 7.30−7.26 (m, 2H), 4.27−4.08 (m, 2H), 3.89 (s, 1H), 2.57 (dd, *J* = 6.8, 2.2 Hz, 2H), 2.52−2.41 (m, 2H), 1.86−1.78 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 139.5, 134.4, 129.7, 128.5, 128.4, 126.5,73.4, 61.7, 52.4 (2C), 23.3 (2C), 14.0. HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1098.

*Isopropyl 2-(3-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**5**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (228 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.1 Hz, 1H), 7.40−7.36 (m, 1H), 7.32−7.25 (m, 2H), 5.04 (hept, *J* = 6.6 Hz, 1H), 3.85 (s, 1H), 2.63−2.52 (m, 2H), 2.46 (td, *J* = 8.2, 7.1, 5.1 Hz, 2H), 1.81 (ddd, *J* = 6.3, 4.9, 2.5 Hz, 4H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 139.7, 134.3, 129.6, 128.5, 128.3, 126.5, 73.6, 68.5, 52.4 (2C), 23.4 (2C), 21.7, 21.4. HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{15}H_{21}ClNO_2$ 282.1255, found 282.1263.

*tert-Butyl 2-(3-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**6**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (213 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.41−7.37 (m, 1H), 7.29 (dd, *J* = 4.8, 1.7 Hz, 2H), 3.82 (s, 1H), 2.64−2.56 (m, 2H), 2.54−2.45 (m, 2H), 1.84−1.80 (m, 4H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 139.8, 134.2, 129.5, 128.4, 128.1, 126.5, 81.4, 73.8, 52.2 (2C), 27.8 (3C), 23.3 (2C). HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{16}H_{23}ClNO_2$ 296.1412, found 295.1319.

*Methyl 2-(2-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**7**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (193 mg, 76% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.29−7.24 (m, 1H), 7.21 (td, *J* = 7.6, 1.9 Hz, 1H), 4.67 (s, 1H), 3.68 (s, 3H), 2.63 (qd, *J* = 6.7, 3.0 Hz, 2H), 2.49 (td, *J* = 7.2, 2.5 Hz, 2H), 1.79 (dt, *J* = 6.1, 3.0 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 134.9, 133.9, 130.0, 129.6, 129.1, 127.1, 67.8, 52.1 (2C), 52.0 (2C), 23.3. HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{13}H_{17}ClNO_2$ 254.0942, found 254.0938.

*Ethyl 2-(2-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**8**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (198 mg, 74% yield), ^{1}H NMR (400 MHz, CDCl3) δ 7.72 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.39 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.29 (td, *J* = 7.4, 1.6 Hz, 1H), 7.23 (td, *J* = 7.6, 1.9 Hz, 1H), 4.66 (s, 1H), 4.25−4.10 (m, 2H), 2.66 (td, *J* = 7.1, 2.4 Hz, 2H), 2.52 (td, *J* = 7.2, 2.5 Hz, 2H), 1.81 (dd, *J* = 6.3, 3.2 Hz, 4H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 135.0, 133.9, 130.0, 129.5, 129.0, 127.0, 68.0, 61.0, 52.0 (2C), 23.3 (2C), 14.1. HRMS (ESI-TOF) *m*/*z*: [M + H$^+$] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1095.

*Allyl 2-(2-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**9**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (204 mg, 73% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* =

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7.6, 1.7 Hz, 1H), 7.40 (dd, J = 7.8, 1.4 Hz, 1H), 7.32−7.22 (m, 2H), 5.86 (ddt, J = 16.1, 10.8, 5.5 Hz, 1H), 5.28−5.16 (m, 2H), 4.74 (s, 1H), 4.68−4.56 (m, 2H), 2.70 (dt, J = 10.5, 5.3 Hz, 2H), 2.59−2.50 (m, 2H), 1.90−1.76 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.7, 134.8, 133.9, 131.7, 130.1, 129.5, 129.1, 127.1, 118.1, 67.9, 65.4, 52.1 (2C), 23.3 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{15}H_{19}ClNO_2$ 280.1099, found 280.1106.

*Benzo[d][1,3]dioxol-5-ylmethyl-2-(2-chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**10**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless liquid (254 mg, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.5, 2.0 Hz, 1H), 7.36 (dd, J = 7.5, 1.8 Hz, 1H), 7.28−7.18 (m, 2H), 6.72 (s, 3H), 5.92 (s, 2H), 5.09−4.98 (m, 2H), 4.71 (s, 1H), 2.63 (td, J = 7.1, 2.3 Hz, 2H), 2.53−2.45 (m, 2H), 1.79 (dt, J = 6.0, 3.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 147.5, 147.3, 134.7, 133.8, 130.0, 129.4, 129.3, 129.0, 126.9, 121.8, 108.6, 107.9, 100.9, 67.8, 66.4, 51.9 (2C), 23.3 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{20}H_{21}ClNO_4$ 374.1154, found 374.1158.

*Benzyl 2-(2-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**11**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless liquid (231 mg, 70% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.4, 2.1 Hz, 1H), 7.35 (dd, J = 7.2, 2.1 Hz, 1H), 7.28−7.22 (m, 4H), 7.19 (td, J = 5.4, 2.5 Hz, 3H), 5.12 (q, J = 12.5 Hz, 2H), 4.71 (s, 1H), 2.61 (td, J = 7.1, 2.2 Hz, 2H), 2.52−2.44 (m, 2H), 1.77 (dt, J = 6.1, 3.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.0, 135.7, 134.8, 133.9, 130.1, 129.5, 129.0, 128.4 (2C), 128.0, 127.8 (2C), 127.1, 67.9, 66.5, 52.0 (2C), 23.4 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{19}H_{21}ClNO_2$ 330.1255, found 330.1173.

*Cyclohexyl 2-(2-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**12**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (222 mg, 69% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.70 (m, 1H), 7.35 (dd, J = 7.8, 1.4 Hz, 1H), 7.29−7.17 (m, 2H), 4.80 (tt, J = 8.4, 3.7 Hz, 1H), 4.63 (s, 1H), 2.72−2.62 (m, 2H), 2.56−2.47 (m, 2H), 1.84−1.75 (m, 5H), 1.72−1.60 (m, 2H), 1.47 (m, 3H), 1.30 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 135.2, 133.8, 130.0, 129.4, 128.9, 127.0, 73.0, 68.2, 52.1 (2C), 31.3, 31.0, 25.3, 23.4 (3C), 23.2. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{18}H_{25}ClNO_2$ 322.1568, found 322.1561.

*Methyl 2-Phenyl-2-(pyrrolidin-1-yl)acetate (±**13**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (178 mg, 81% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.8, 1.6 Hz, 2H), 7.27−7.20 (m, 3H), 3.86 (s, 1H), 3.59 (s, 3H), 2.52−2.45 (m, 2H), 2.36 (dd, J = 10.5, 3.2 Hz, 2H), 1.72 (td, J = 9.8, 8.3, 5.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.0, 137.1, 128.4 (2C), 128.3 (2C), 128.2, 73.7, 52.4 (2C), 52.0, 23.2 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1328.

*Methyl 2-(2-Fluorophenyl)-2-(pyrrolidin-1-yl)acetate (±**14**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (168 mg, 71% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (td, J = 7.5, 1.7 Hz, 1H), 7.33−7.26 (m, 1H), 7.19−7.13 (m, 1H), 7.10−7.03 (m, 1H), 4.50 (s, 1H), 3.71 (s, 3H), 2.63 (dt, J = 10.7, 5.3 Hz, 2H), 2.51 (dt, J = 7.9, 5.1 Hz, 2H), 1.85−1.77 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.6, 160.5 (d, J = 247.3 Hz), 130.0 (d, J = 3.4 Hz), 129.6 (d, J = 8.3 Hz), 124.3 (d, J = 3.5 Hz), 123.9 (d, J = 13.4 Hz), 115.5 (d, J = 22.5 Hz), 64.0, 52.1, 51.9 (2C), 23.3 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{13}H_{17}FNO_2$ 238.1238, found 238.1235.

*Methyl 2-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**15**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (216 mg, 85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.90 (s, 1H), 3.68 (s, 3H), 2.58−2.50 (m, 2H), 2.46−2.38 (m, 2H), 1.80 (td, J = 5.7, 3.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 135.8, 134.10 129.6 (2C), 128.7 (2C), 73.0, 52.4 (C), 52.1, 23.2 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{13}H_{17}ClNO_2$ 254.0942, found 254.0937.

*Methyl 2-(4-Bromophenyl)-2-(pyrrolidin-1-yl)acetate (±**16**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (246 mg, 83% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 3.91 (s, 1H), 3.70 (s, 3H), 2.56 (dt, J = 6.0, 3.2 Hz, 2H), 2.48−2.41 (m, 2H), 1.82 (td, J = 5.7, 3.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.8, 136.4, 131.7 (2C), 130.1 (2C), 122.3, 73.2, 52.5 (2C), 52.2, 23.3 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{13}H_{17}BrNO_2$ 298.0437, found 298.0424.

*Methyl 2-(Pyrrolidin-1-yl)-2-(4-(tosyloxy)phenyl)acetate (±**17**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless liquid (304 mg, 78% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 3.92 (s, 1H), 3.70 (s, 3H), 2.57−2.50 (m, 2H), 2.47 (s, 3H), 2.44−2.37 (m, 2H), 1.81 (td, J = 10.2, 8.5, 5.3 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.7, 149.5, 145.4, 136.2, 132.5, 129.8 (2C), 129.7 (2C), 128.5 (2C), 122.5 (2C), 73.0, 52.5 (2C), 52.3, 23.3 (2C), 21.7. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{20}H_{24}NO_5S$ 390.1370, found 390.1377.

*Ethyl 2-Phenyl-2-(pyrrolidin-1-yl)acetate (±**18**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (180 mg, 77% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dt, J = 8.4, 2.2 Hz, 2H), 7.34−7.27 (m, 3H), 4.22−4.06 (m, 2H), 3.89 (s, 1H), 2.55 (td, J = 7.1, 2.4 Hz, 2H), 2.47−2.38 (m, 2H), 1.83−1.73 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.6, 137.4, 128.4 (2C), 128.3 (2C), 128.1, 73.9, 60.8, 52.4 (2C), 23.3 (2C), 14.0. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{14}H_{20}NO_2$ 234.1489, found 234.1486.

*Ethyl 2-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**19**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (212 mg, 79% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.21−4.09 (m, 2H), 3.89 (s, 1H), 2.56 (ddd, J = 8.7, 7.4, 4.2 Hz, 2H), 2.44 (ddd, J = 9.7, 7.7, 4.3 Hz, 2H), 1.81 (td, J = 5.8, 3.1 Hz, 4H), 1.21 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.4, 136.1, 134.0, 129.7 (2C), 128.7 (2C), 73.3, 61.1, 52.4 (2C), 23.3 (2C), 14.1. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1096.

*Ethyl 2-(4-Bromophenyl)-2-(pyrrolidin-1-yl)acetate (±**20**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (240 mg, 77% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 4.20−4.05 (m, 2H), 3.84 (s, 1H), 2.52 (td, J = 7.1, 2.4 Hz, 2H), 2.45−2.37 (m, 2H), 1.82−1.73 (m, 4H), 1.17 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 136.5, 131.6 (2C), 130.0 (2C), 122.1, 73.2, 61.0, 52.4 (2C), 23.3 (2C), 14.0. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{14}H_{19}BrNO_2$ 312.0594, found 312.0571.

*Methyl 2-(3-Chlorophenyl)-2-(diethyl amino)acetate (±**21**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (208 mg, 81% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.45 (m, 1H), 7.35−7.26 (m, 3H), 4.48 (s, 1H), 3.74 (s, 3H), 2.62 (q, J = 7.1 Hz, 4H), 1.02 (t, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 139.3, 134.3, 129.6, 128.7, 128.1, 126.8, 68.7, 51.8, 43.7 (2C), 12.0 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{13}H_{19}ClNO_2$ 256.1099, found 256.1096.

*Methyl 2-(3-Chlorophenyl)-2-(piperidin-1-yl)acetate (±**22**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; light-yellow liquid (246 mg, 92% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.0 Hz, 1H), 7.34−7.30 (m, 1H), 7.30−7.23 (m, 2H), 3.96 (s, 1H), 3.69 (s, 3H), 2.37 (m, 4H), 1.59 (quin, J = 5.5 Hz, 4H), 1.43 (m, J = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.6, 138.3, 134.3, 129.6, 128.7, 128.3, 126.8, 74.2, 52.2 (2C), 51.9, 25.7 (2C), 24.2. HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1104.

*Methyl 2-(3-Chlorophenyl)-2-(4-hydroxypiperidin-1-yl)acetate (±**23**).* Purification with petroleum ether/EtOAc (7:3) as the eluent; colorless liquid (222 mg, 78% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.32−7.23 (m, 3H), 4.01 (s, 1H), 3.69 (s, 3H), 2.70 (ddt, J = 14.9, 9.1, 4.5 Hz, 2H), 2.30−2.20 (m, 1H), 2.19−2.10 (m, 1H), 2.06 (s, 1H), 1.93−1.82 (m, 2H), 1.62 (ddq, J = 18.7, 9.3, 5.8, 4.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 138.1, 134.4, 129.7, 128.6, 128.4, 126.8, 73.3, 67.5, 52.0, 48.7, 48.5, 34.1 (2C). HRMS (ESI-TOF) m/z: [M + H^+] calcd for $C_{14}H_{19}ClNO_3$ 284.1048, found 284.1044.

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*1-(1-(3-Chlorophenyl)-2-methoxy-2-oxoethyl)piperidin-4-ylbenzoate (±**24**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless semisolid (295 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.99 (m, 2H), 7.54 (tt, J = 6.9, 1.3 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.36−7.27 (m, 3H), 5.07 (tt, J = 7.6, 3.8 Hz, 1H), 4.07 (s, 1H), 3.70 (s, 3H), 2.78−2.66 (m, 2H), 2.43 (q, J = 8.4 Hz, 2H), 2.08−1.99 (m, 2H), 1.94−1.83 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 165.7, 138.0, 134.5, 132.8, 130.5, 129.8, 129.5 (2C), 128.7, 128.6, 128.3 (2C), 126.8, 73.3, 70.0, 52.1, 48.4, 48.2, 30.6 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{21}H_{23}ClNO_4$ 388.1310, found 388.1317.

*Methyl 2-(3-Chlorophenyl)-2-morpholinoacetate (±**25**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless semisolid (200 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H), 7.36−7.24 (m, 3H), 3.96 (s, 1H), 3.75−3.71 (m, 4H), 3.70 (s, 3H), 2.45 (dd, J = 6.3, 3.2 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.9, 137.4, 134.5, 129.8, 128.8, 128.7, 126.9, 73.7, 66.7 (2C), 52.1, 51.4 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{13}H_{17}ClNO_3$ 270.0891, found 270.0890.

*Methyl 2-(3-Chlorophenyl)-2-(4-ethylpiperazin-1-yl)acetate (±**26**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless semisolid (230 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 1.8 Hz, 1H), 7.30 (dq, J = 5.5, 1.8 Hz, 1H), 7.27−7.24 (m, 2H), 3.95 (s, 1H), 3.67 (s, 3H), 2.69−2.32 (m, 10H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 137.8, 134.5, 129.8, 128.7, 128.6, 127.0, 73.6, 52.4 (3C), 52.2, 52.1, 50.9, 11.8. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{15}H_{22}ClN_2O_2$ 297.1364, found 297.1352.

*Methyl 2-(3-Chlorophenyl)-2-(4-phenylpiperazin-1-yl)acetate (±**27**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless semisolid (266 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.9 Hz, 1H), 7.37 (dt, J = 6.7, 1.8 Hz, 1H), 7.32 (dt, J = 7.0, 1.6 Hz, 2H), 7.30−7.27 (m, 1H), 7.24 (dd, J = 7.0, 1.8 Hz, 1H), 6.91 (d, J = 1.0 Hz, 1H), 6.90−6.88 (m, 1H), 6.88−6.83 (m, 1H), 4.06 (s, 1H), 3.73 (s, 3H), 3.25−3.20 (m, 4H), 2.66−2.61 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 151.1, 137.7, 134.6, 129.9, 129.1 (2C), 128.8, 128.7, 127.0, 119.8, 116.1 (2C), 73.5, 52.2, 51.0 (2C), 49.0 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{19}H_{22}ClN_2O_2$ 345.1364, found 345.1359.

*Methyl 2-(3-Chlorophenyl)-2-(4-(2,4-dinitrophenyl)piperazin-1-yl)acetate (±**28**).* Purification with petroleum ether/EtOAc (1:1) as the eluent; yellow solid (mp = 185 °C), (314 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.7 Hz, 1H), 8.27 (dd, J = 9.3, 2.7 Hz, 1H), 7.48 (s, 1H), 7.35 (q, J = 5.2, 3.7 Hz, 3H), 7.09 (d, J = 9.3 Hz, 1H), 4.13 (s, 1H), 3.74 (s, 3H), 3.36−3.30 (m, 4H), 2.71−2.65 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 149.1, 138.7, 138.4, 136.8, 134.8, 130.0, 129.0, 128.8, 128.3, 127.0, 123.6, 119.3, 72.6, 52.4, 50.4 (2C), 50.1 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{19}H_{20}ClN_4O_6$ 435.1066, found 435.0993.

*Methyl-2-phenyl-2-(piperidin-1-yl)acetate (±**29**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (180 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dt, J = 8.3, 2.3 Hz, 2H), 7.35−7.28 (m, 3H), 3.97 (s, 1H), 3.67 (s, 3H), 2.38 (m, 4H), 1.59 (quin, J = 5.5 Hz, 4H), 1.42 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ172.3, 136.2, 128.8, 128.4, 128.1, 75.0, 52.4 (2C), 51.8, 25.7 (2C), 24.3. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{14}H_{20}NO_2$ 234.1489, found 234.1489.

*Methyl 2-(2-Chlorophenyl)-2-(piperidin-1-yl)acetate (±**30**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (188 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.7, 1.9 Hz, 1H), 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 7.25 (td, J = 7.5, 1.5 Hz, 1H), 7.19 (td, J = 7.6, 1.9 Hz, 1H), 4.60 (s, 1H), 3.66 (s, 3H), 2.50 (dt, J = 10.6, 5.2 Hz, 2H), 2.39 (dt, J = 10.9, 5.4 Hz, 2H), 1.57 (quin, J = 5.2 Hz, 4H), 1.42 (quin, J = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ171.4, 134.5, 134.1, 129.9, 129.5, 128.9, 126.8, 69.5, 52.1 (2C), 51.8, 25.9 (2C), 24.2. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1100.

*Methyl 2-(4-Chlorophenyl)-2-(piperidin-1-yl)acetate (±**31**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (212 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.37 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 3.94 (s, 1H), 3.67 (s, 3H), 2.35 (m, 4H), 1.57 (quin, J = 5.5 Hz, 4H), 1.43 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ171.9, 134.8, 134.0, 130.1 (2C), 128.6 (2C), 74.1, 52.3 (2C), 51.9, 25.7 (2C), 24.2. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{14}H_{19}ClNO_2$ 268.1099, found 268.1097.

*Methyl 2-(4-Bromophenyl)-2-(piperidin-1-yl)acetate (±**32**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (244 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 3.95 (s, 1H), 3.68 (d, J = 1.1 Hz, 3H), 2.37 (t, J = 5.4 Hz, 4H), 1.59 (quin, J = 5.3 Hz, 4H), 1.47−1.39 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 135.4, 131.5 (2C), 130.4 (2C), 122.1, 74.1, 52.2 (2C), 51.9, 25.7 (2C), 24.2. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{14}H_{19}BrNO_2$ 312.0594, found 312.0571.

*Methyl 2-(2-Chlorophenyl)-2-morpholinoacetate (±**33**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (197 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.5, 2.0 Hz, 1H), 7.39 (dd, J = 7.7, 1.7 Hz, 1H), 7.29 (dd, J = 7.4, 5.6 Hz, 1H), 7.25 (dd, J = 7.5, 5.4 Hz, 1H), 4.68 (s, 1H), 3.72 (t, J = 4.7 Hz, 4H), 3.70 (s, 3H), 2.58 (dd, J = 10.6, 5.6 Hz, 2H), 2.52−2.46 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.0, 134.8, 133.1, 129.9, 129.7, 129.3, 127.0, 68.8, 66.8 (2C), 52.0, 51.2 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{13}H_{17}ClNO_3$ 270.0891, found 270.0896.

*Methyl 2-(4-Chlorophenyl)-2-morpholinoacetate (±**34**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (205 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 3.96 (s, 1H), 3.75−3.70 (m, 4H), 3.69 (s, 3H), 2.47−2.42 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 134.3, 133.9, 130.1 (2C), 128.8 (2C), 73.5, 66.7 (2C), 52.0, 51.4 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{13}H_{17}ClNO_3$ 270.0891, found 270.0893.

*Methyl 2-(4-Bromophenyl)-2-morpholinoacetate (±**35**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (236 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 3.95 (s, 1H), 3.75−3.71 (m, 4H), 3.69 (s, 3H), 2.49−2.41 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 134.4, 131.8 (2C), 130.4 (2C), 122.6, 73.6, 66.7 (2C), 52.1, 51.5 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{13}H_{17}BrNO_3$ 314.0386, found 314.0376.

*Methyl 2-Morpholino-2-(4-(tosyloxy)phenyl)acetate (±**36**).* Purification with petroleum ether/EtOAc (7:3) as the eluent; colorless semisolid (296 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.96 (s, 1H), 3.71−3.68 (m, 4H), 3.67 (s, 3H), 2.44 (s, 3H), 2.43−2.34 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 149.6, 145.5, 134.1, 132.4, 130.1 (2C), 129.7 (2C), 128.4 (2C), 122.5 (2C), 73.4, 66.6 (2C), 52.1, 51.4 (2C), 21.7. HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{20}H_{24}NO_6S$ 406.1319, found 406.1326.

*Methyl 2-(3-Chlorophenyl)-2-(4-((4-chlorophenyl)(phenyl)-methyl)piperazin-1-yl)acetate (±**37**).* Purification with petroleum ether/EtOAc (8:2) as the eluent; colorless semisolid (282 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.38−7.31 (m, 4H), 7.31−7.23 (m, 5H), 7.23−7.14 (m, 3H), 4.23 (s, 1H), 4.00 (s, 1H), 3.68 (s, 3H), 2.46 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 137.7, 134.5, 132.5, 129.7, 129.2 (3C), 128.8, 128.6 (3C), 128.5, 127.8 (3C), 127.2, 126.9, 75.2, 73.4, 52.1, 51.5 (2C), 51.1 (2C). HRMS (ESI-TOF) m/z: [M + H$^+$] calcd for $C_{26}H_{27}Cl_2N_2O_2$ 469.1444, found 469.1453.

Controlled Experiments. Electrolysis with a constant current condition (8 mA) was carried out using a graphite plate as the anode and a copper plate as the cathode for 12 h through an undivided reaction cell equipped with a stirring bar and methyl 2-(3-chlorophenyl)acetate **1** (184 mg, 1.0 mmol, 1.0 equiv), pyrrolidine **2** (71 mg, 1.0 mmol, 1.0 equiv), KI (83 mg, 0.5 mmol, 0.5 equiv), and $LiClO_4$ (106 mg, 1.0 mmol, 1.0 equiv) dissolved in 10.0 mL of CH_3CN. The reaction progress was monitored by TLC. Using a reduced amount of amine **2** (1.0 equiv) under standard conditions, we

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observed the formation of α-iodo-ester **38** (139 mg, 45% yield) and expected product **3** (<10% yield), after purification.

*Methyl 2-Iodo-2-phenylacetate (±**38**).* Purification with petroleum ether/EtOAc (9:1) as the eluent; colorless liquid (139 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 1H), 7.38−7.34 (m, 1H), 7.31−7.26 (m, 2H), 4.32 (s, 1H), 3.46 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 137.9, 134.6, 130.0, 128.5, 128.4, 126.6, 54.4, 52.3. HRMS (ESI-TOF) *m*/*z*: [M + Na^+] calcd for $C_9H_8IClO_2Na$ 332.9150, found 332.9128.

To a stirred solution of **38** (130 mg, 0.4 mmol, 1.0 equiv) and **2** (71 mg, 1.0 mmol, 2.5 equiv) in CH_3CN (4.0 mL) was added Et_3N (61 mg, 0.6 mmol, 1.5 equiv) and left for 3 h at room temperature. Once **38** disappeared from TLC, the reaction mixture was diluted with brine (4.0 mL) and extracted with ethyl acetate (10.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified to afford **3** (90 mg, 89%) as a pale-yellow liquid.

Reaction in the Presence of Radical Inhibitors (TEMPO/BHT). To a 10 mL dried undivided reaction cell equipped with a stirring bar were added methyl 2-(3-chlorophenyl) acetate **1** (100 mg, 0.54 mmol, 1.0 equiv), pyrrolidine **2** (114 mg, 1.6 mmol, 3.0 equiv), KI (45 mg, 0.27 mmol, 0.5 equiv), TEMPO (211 mg, 1.35 mmol, 2.5 equiv) or BHT (297 mg, 1.35 mmol, 2.5 equiv), and $LiClO_4$ (57 mg, 1.0 mmol, 1.0 equiv) dissolved in 10.0 mL of CH_3CN. The combined reaction mixture was electrolyzed under standard conditions. The trace of product **3** was observed (TEMPO) or not observed (BHT) on TLC.

Gram-Scale Synthesis of 22. A 100 mL three-neck round-bottom flask (as an undivided cell) was equipped with a graphite plate as the anode and a copper plate as the cathode, which was connected to a DC regulated power supply. To the cell were added methyl 2-(3-chlorophenyl) acetate **1** (1.0 g, 5.43 mmol, 1.0 equiv), piperidine (1.38 g, 16.25 mmol, 3.0 equiv), KI (0.45 g, 2.71 mmol, 0.5 equiv), and $LiClO_4$ (0.58 g, 5.43 mmol, 1.0 equiv) dissolved in 40.0 mL of CH_3CN. The mixture was electrolyzed under constant current conditions (8 mA) under a N_2 atmosphere at room temperature while stirring. The reaction was monitored by TLC. Electrodes were washed with ethyl acetate (10 mL); when the reaction was finished, the solvent was removed under reduced pressure. The residue was poured into a saturated aqueous $Na_2S_2O_3$ (20.0 mL) and extracted with ethyl acetate (2 × 20.0 mL). The combined organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude cycloadduct was purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1), affording pure **22** (1.30 g, 90%).

*1-(2-Azido-1-(3-chlorophenyl)ethyl)piperidine (±**39**).* To a stirred solution of **22** (200 mg, 0.74 mmol, 1.0 equiv) in dry tetrahydrofuran (THF) (10.0 mL) at 0 °C was added $LiAlH_4$ (93 mg, 2.24 mmol, 3.0 equiv) portionwise over 10 min. The combined mixture was stirred at room temperature for 4 h before cooling to 0 °C and quenched slowly with aqueous NH_4Cl solution (10.0 mL). The reaction mixture was further stirred with EtOAc (30.0 mL). The solid mass was removed by filtration, and the aqueous layer was again extracted with EtOAc (10.0 mL). The combined organic mixture was concentrated under reduced pressure, and crude alcohol was used further without purification.

To a stirred solution of crude alcohol (200 mg, crude weight), Et_3N (146 μL, 1.05 mmol, 1.5 equiv), and DMAP (9.0 mg, 0.07 mmol, 0.1 equiv) in CH_2Cl_2 (5.0 mL), in a 25 mL round-bottom flask, was added a solution of TsCl (147 mg, 0.77 mmol, 1.1 equiv) in CH_2Cl_2 (3.0 mL) at 0 °C under a N_2 atmosphere. The resulting mixture was further stirred at rt for 10 h before being quenched with saturated aqueous $NaHCO_3$ (8.0 mL) and stirred with additional CH_2Cl_2 (10.0 mL). The combined organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, and the crude tosyl product was used further without purification.

To a solution of crude tosylate (315 mg, crude weight) in dimethylformamide (DMF) (4.0 mL) was added NaN_3 (98 mg, 1.5 mmol, 2.0 equiv) and heated at 65 °C for 8 h. The mixture was cooled to room temperature and stirred between H_2O (4.0 mL) and EtOAc (10.0 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography using petroleum ether/EtOAc (8:2) as the eluent afforded **39** as a transparent oil (114 mg, 58% after three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 3H), 7.20 (d, *J* = 10.1 Hz, 1H), 4.64 (dd, *J* = 9.8, 3.9 Hz, 1H), 2.70 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.58 (dd, *J* = 9.9, 5.8 Hz, 2H), 2.52 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.49−2.42 (m, 2H), 1.62 (m, 4H), 1.46 (quin, *J* = 5.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.9, 134.4, 129.8, 128.1, 126.9, 124.9, 65.5, 62.5, 54.8 (2C), 25.8 (2C), 24.2. HRMS (ESI-TOF) *m*/*z*: [M + H^+] calcd for $C_{13}H_{18}ClN_4$ 265.1215, found 265.1219.

*Benzo[d][1,3]dioxol-5-ylmethyl-2-(2-chlorophenyl)-2-(pyrrolidin-1-yl)acetate (±**40**).* To a stirred solution of the ester **33** (100 mg, 0.37 mmol, 1.0 equiv) in THF/H_2O (2:1, 6.0 mL) was added LiOH·H_2O (47 mg, 1.1 mmol, 3.0 equiv) at rt and further stirred for 8−10 h. The reaction mixture was evaporated to dryness, and the resulting solid crude material was taken forward without purification. This crude solid mass was taken in DMF (4.0 mL), *N*,*N*-diisopropylethylamine (DIPEA) was added (70 μL, 0.4 mmol, 1.1 equiv), and subsequently, EDC·HCl (1-ethyl-3(3-dimethylaminopropyl)-carbodiimidehydrochloride) (77 mg, 0.4 mmol, 1.1 equiv), 1-hydroxybenzotriazole (HOBt) (54 mg, 0.4 mmol, 1.1 equiv), and diethyl amine (35 mg, 0.48 mmol, 1.3 equiv) were added at rt and cooled to 0 °C. The reaction mixture was further stirred at rt for 12 h, before quenching with H_2O (5.0 mL) and being stirred with EtOAc (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography using petroleum ether/EtOAc (7:3) afforded **40** (87 mg, 76% after two steps) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.22−7.12 (m, 2H), 4.72 (s, 1H), 3.33 (m, 2H), 3.18 (m, 2H), 2.56−2.45 (m, 2H), 2.41 (m, 2H), 1.56−1.43 (m, 4H), 1.34 (quin, *J* = 5.8 Hz, 2H), 0.99 (q, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.7, 134.4, 133.9, 131.2, 129.1, 128.8, 126.8, 65.6, 51.9 (2C), 41.2, 40.4, 25.9 (2C), 24.3, 14.1, 12.5. HRMS (ESI-TOF) *m*/*z*: [M + H^+] calcd for $C_{17}H_{26}ClN_2O$ 309.1728, found 309.1728.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00944.

Optimization table, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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