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Synthesis of Pyridoisoindoles through Diazotization Followed by Intramolecular Cyclization from Pyridinylarylacetates in One Pot

Cheol-Eui Kim,[a] Yonghyeon Baek,[a] Sung Hong Kim,[b] and Phil Ho Lee[a,*]

[a] National Creative Research Initiative Center for Catalytic Organic Reactions, Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea
Fax: (+82)-33-259-5667; e-mail: phlee@kangwon.ac.kr
[b] Analysis Research Division Daegu Center, Korea Basic Science Institute, Daegu 702-701, Republic of Korea

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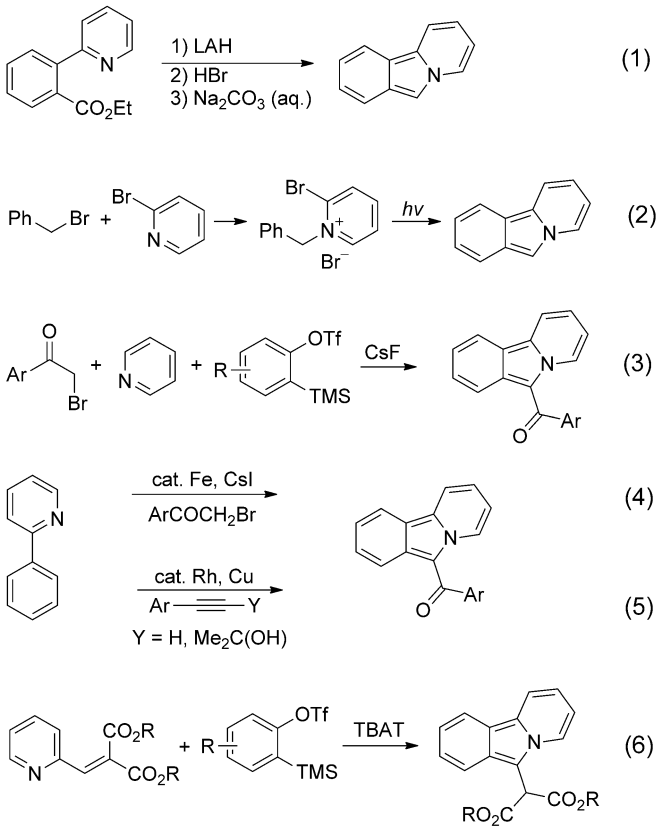
Abstract: A robust synthetic method for a variety of pyridoisoindoles from pyridinylarylacetates has been developed through diazotization using 4-methylbenzenesulfonyl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene followed by intramolecular cyclization *via* elimination of a nitrogen molecule under copper(II) trifluoromethanesulfonate-catalyzed conditions in a one-pot process. The intramolecular cyclization also took place efficiently with diazo substrates to produce pyridoisoindoles in good to excellent yields under metal-free conditions or catalytic conditions [1.0 mol% copper(II) trifluoromethanesulfonate, 25 °C].

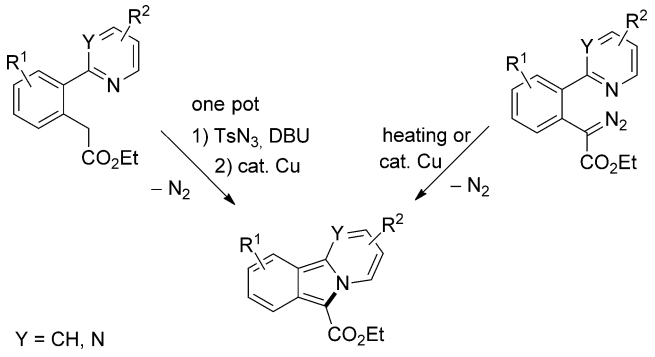
Keywords: carbenes; copper; metal-free conditions; pyridinylarylacetates; pyridoisoindoles

Introduction

Pyridoisoindoles are key priviledged scaffolds in nitrogen-containing heterocyclic compounds, which are widely found in pharmaceuticals,[1] natural products,[2] fluorescent materials,[3] and dyes.[4] Accordingly, the development of synthetic methods for preparing pyridoisoindoles having a variety of functional groups represents a considerable task and a significant challenge.[5] Although some functionalizations of pyridoisoindole derivatives have been reported, only a limited number of synthetic methods has been described. To date, some of the most general synthetic methods reported in the literature contain an approach through reduction, bromination, and cyclization followed by dehydrobromination from ethyl 2-(2-pyridyl)benzoates [Eq. (1), Scheme 1],[6] intramolecular photochemical cyclization of 2-bromo-*N*-benzylpyridinium salts [Eq. (2)],[7] multi-component reactions of pyridines, α-bromo carbonyl compounds, and silylaryl triflates [Eq. (3)],[8] Fe-catalyzed reaction of 2-arylpyridines with 2-bromoacetophenones [Eq. (4)],[9] Rh-catalyzed direct oxidative C–H acylation of 2-arylpyridines with terminal alkynes or γ-substituted *tert*-propargyl alcohols [Eq. (5)],[10] and aryne annulations involving pyridines [Eq. (6)].[11] Thus, a robust synthesis of pyridoisoindole derivatives has been continuously needed. Especially, it is very significant to introduce a wide range of functional groups onto pyrido-



Scheme 1. Previously reported synthetic methods for producing pyridoisoindoles.



Scheme 2. Synthesis of pyridoisoindoles from pyridinylarylacetates in one pot.

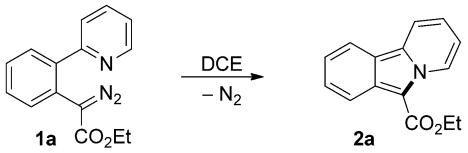
isoindoles and to prepare 6-ethoxycarbonylpyridoisoindoles. Moreover, preparation of pyridoisoindole derivatives having other nitrogen heterocycles besides pyridine provides a synthetic challenge.[5,12]

Since carbene species have an intrinsically electrophilic nature, they can react with a variety of nucleophiles.[13] In this regard, we recently reported a number of synthetic approaches to carbocycles as well as azaheterocycles containing pyrroles, dihydropyrroles, dihydroazepines, bicyclic *N,O*-acetals, pyrazines, and fluorenes[14] and Rh-catalyzed *N*-sulfonylaminoalkenylation of azulenes[15] using imino Rh-carbenoids generated *in situ* from *N*-sulfonyltriazoles.[16] These results stimulated us to explore the feasibility of the synthesis of pyridoisoindoles using carbene intermediates. Consequently, we envisioned that an intramolecular cyclization from treatment of aryl diazoacetates having a pyridine moiety with a transition metal catalyst would take place to produce pyridoisoindoles. Herein, we demonstrate an efficient synthetic method for a wide range of pyridoisoindoles from pyridinylaryl diazocetates under Cu-catalytic or metal-free conditons (Scheme 2). Moreover, these transformations are achieved through diazotization of pyridinylarylacetates using TsN_3 and DBU followed by intramolecular cyclization *via* elimination of a nitrogen molecule under $Cu(OTf)_2$-catalyzed conditions in a one-pot process.

Results and Discussion

First, we attempted an intramolecular cyclization with ethyl 2-diazo-2-[2-(pyridin-2-yl)phenyl]acetate (**1a**)[17] obtained from diazotization of ethyl 2-[2-(pyridin-2-yl)phenyl]acetate with TsN_3 in the presence of DBU (Table 1).[18] This reaction did not proceed in DCE at 25 °C (entry 1). However, when the reaction was carried out at 50 °C for 15 h, the desired pyridoisoindole (**2a**) was produced in 83% yield under a nitrogen atmosphere (entry 2). At 80 °C, the cyclization was accelerated and **2a** was obtained in 88% yield after 30 min (entry 3), indicating that the present reaction is very sensitive to temperature. Eventually, **2a** was produced in 92% yield in DCE at 80 °C after 30 min under metal-free conditions (entry 4). Next, a variety of copper catalysts was examined to access this cyclized product under extremely mild conditions (25 °C). A wide range of copper catalysts such as CuCl, CuI, $Cu(OAc)_2$, $Cu(hfacac)_2$, and $Cu(OTf)_2$ was examined to disclose that $Cu(OTf)_2$ (1.0 mol%) was the catalyst of choice, affording pyridoisoindole (**2a**) in 97% yield at 25 °C for 20 min (entries 5–12). To check the possibility of cyclization by a protic acid, we attempted the cyclization in the presence of 2,6-di-*tert*-butylpyridine (2.0 mol%) as a proton scavenger and found that **2a** was produced in 96% yield (entry 13). This result indicates that the present cyclization reaction proceeds by Cu catalysis.

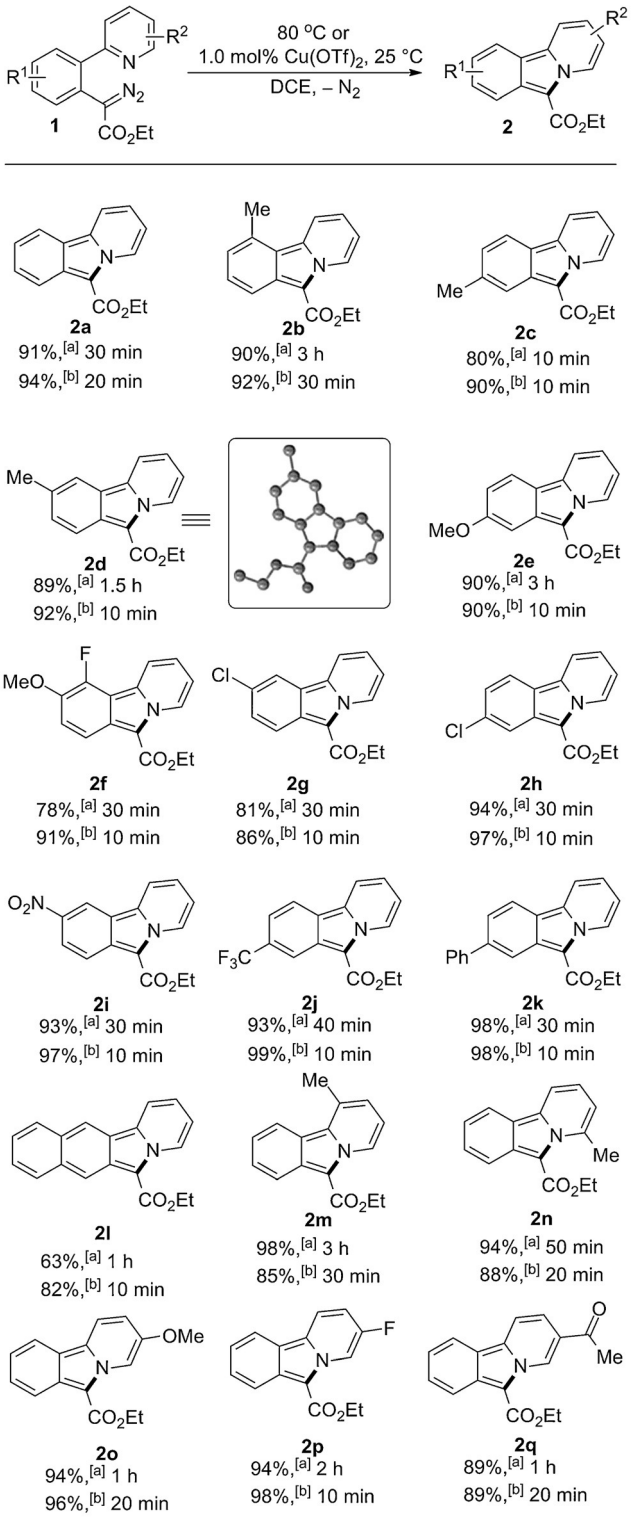
Table 1. Reaction optimization.[a]



Entry	Cat. [mol%]	Temp. [°C]	*t*	Yield [%][b]
1	–	25	15 h	2 (83)[c]
2	–	50	15 h	83
3	–	80	30 min	88
4[d]	**–**	**80**	**30 min**	**92 (91)**[e]
5	CuCl (5)	25	5 min	90
6	CuI (5)	25	5 min	87
7	$Cu(OAc)_2$ (5)	25	2 h	80
8	$Cu(hfacac)_2$ (5)	25	5 min	87
9	$Cu(OTf)_2$ (5)	25	5 min	97
10	$Cu(OTf)_2$ (3)	25	5 min	97
11	$Cu(OTf)_2$ (1)	25	20 min	97
12[d]	**$Cu(OTf)_2$ (1)**	**25**	**20 min**	**97 (94)**[e]
13[f]	$Cu(OTf)_2$ (1)	25	20 min	96

[a] Reactions were carried out with **1a** (0.2 mmol) in DCE (1.0 mL) under a nitrogen atmosphere.
[b] NMR yield using CH_2Br_2 as an internal standard.
[c] NMR yield of **1a**.
[d] Under air.
[e] Isolated yield.
[f] 2,6-Di-*tert*-butylpyridine (2.0 mol%) was added.

Next, the scope of substrates was examined with the two optimal conditions (metal-free and Cu-catalyzed) in hand (Scheme 3). First, metal-free conditions were applied to a large number of pyridinylaryl diazoacetates (**1**). Electronic variation of substituents at the aryl moiety of **1** had little effect on the reaction efficiency. In fact, pyridoisoindole products bearing electron-donating substituents such as methyl (**2b**, **2c**, and **2d**) and methoxy (**2e**) on the aryl ring were produced in good to excellent yields ranging from 80%



[a] Reactions were carried out with **1** (0.2 mmol) in DCE (1.0 mL) at 80 °C.
[b] Reactions were carried out with **1** (0.2 mmol) in the presence of $Cu(OTf)_2$ (1.0 mol%) in DCE (1.0 mL) at 25 °C.

Scheme 3. Substrate scope of pyridinylaryl diazoacetates.

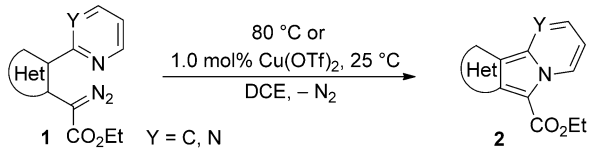
to 90% at 80 °C. The structure of **2d** was confirmed by X-ray crystallography.[19] To our satisfaction, pyridinylaryl diazoacetate (**1f**) having electron-donating methoxy as well as electron-withdrawing fluoro group underwent the intramolecular cyclization, affording the corresponding pyridoisoindole **2f** in 78% yield. Chloro-substituted diazo substrates were also cyclized to give rise to pyridoisoindoles **2g** (81%) and **2h** (94%). Substrates having strong electron-withdrawing groups such as nitro and trifluoromethyl groups are applicable to the present transformation, providing the corresponding pyridoisoindoles (**2i** and **2j**). A diazo compound (**1k**) possessing the biphenyl moiety turned out to be compatible with the reaction conditions, providing **2k** in 98% yield. However, naphthalen-2-yl-substituted substrate (**1l**) was less reactive and the pyridoisoindole **2l** was obtained in 63% yield.

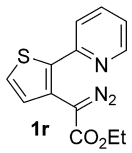
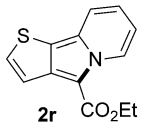
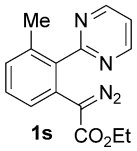
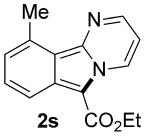
Diazo substrates substituted on the pyridine ring were also employed in the intramolecular cyclization. When a methyl group was substituted at the 3- or 6-position of pyridine (**1m** and **1n**), the pyridoisoindoles (**2m** and **2n**) were produced in excellent yields. The intramolecular cyclization took place efficiently with diazo substrates (**1o** and **1p**) having 5-methoxy- and 5-fluoropyridinyl moieties to furnish **2o** and **2p** in 94% yield. Also, the cyclization of a substrate bearing an acetyl group proceeded smoothly, producing pyridoisoindole **2q** in 89% yield under metal-free conditions.

Second, $Cu(OTf)_2$-catalyzed cyclization conditions which are more reactive than the metal-free ones were applied to a wide range of pyridinylaryl diazoacetates (**1**). Likewise to the metal-free conditions, the presence of various substituents on the aryl group did not influence the efficiency of the reaction. The cyclization reaction was amenable with respect to substrates having substituents such as methyl, methoxy, fluoro, chloro, nitro, and trifluoromethyl to provide the products **2b**–**2j** in good to excellent yields ranging from 86% to 99% in DCE at 25 °C within 30 min. In contrast to the metal-free conditions, the naphthalen-2-yl-substituted substrate (**1l**) was smoothly cyclized to produce the pyridoisoindole **2l** in 82% yield, indicating that catalytic conditions are more reactive than metal-free ones. A variety of substrates having substituents such as methyl, methoxy, fluoro, and acetyl on the pyridine side was also readily used in the intramolecular cyclization process and the desired pyridoisoindoles were produced in good to excellent yields.

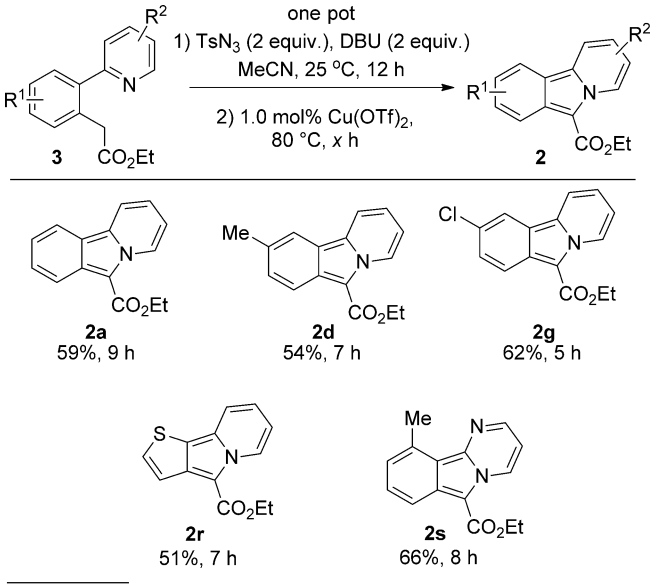
Diazo ester (**1r**) having a pyridinyl-substituted thiophene moiety underwent the intramolecular cyclization, leading to the formation of ethyl thieno[2,3-*a*]indolizine-4-carboxylate (**2r**) in 61% yield (entry 1, Table 2). However, the Cu-catalyzed reaction delivered **2r** in 20% yield because the thiophene moiety having a sulfur atom probably poisoned the catalyst (entry 2). Pyrimidinylaryl diazoacetate (**1s**) also worked well, leading to the formation of pyrimidoisoindole **2s** in 86% yield under metal-free conditions

Table 2. Cyclization of substrates having thiophenyl and pyrimidinyl moieties.



Entry	Reactant	Product	*t*	Yield [%]
1			30 min	61[a]
2	**1r**	**2r**	30 min	20[b]
3			3.5 h	86[a]
4	**1s**	**2s**	10 min	80[b]

[a] Reactions were carried out with **1** (0.2 mmol) in DCE (1.0 mL) at 80 °C.
[b] Reactions were carried out with **1** (0.2 mmol) in the presence of $Cu(OTf)_2$ (1.0 mol%) in DCE (1.0 mL) at 25 °C.



[a] Reactions were carried out with **1** (0.2 mmol), TsN_3 (0.4 mmol), and DBU (0.4 mmol) in CH_3CN at 25 °C for 12 h and then 1.0 mol% $Cu(OTf)_2$ was added.

Scheme 4. Synthesis of pyridoisoindoles from pyridinylarylacetates in one pot.[a]

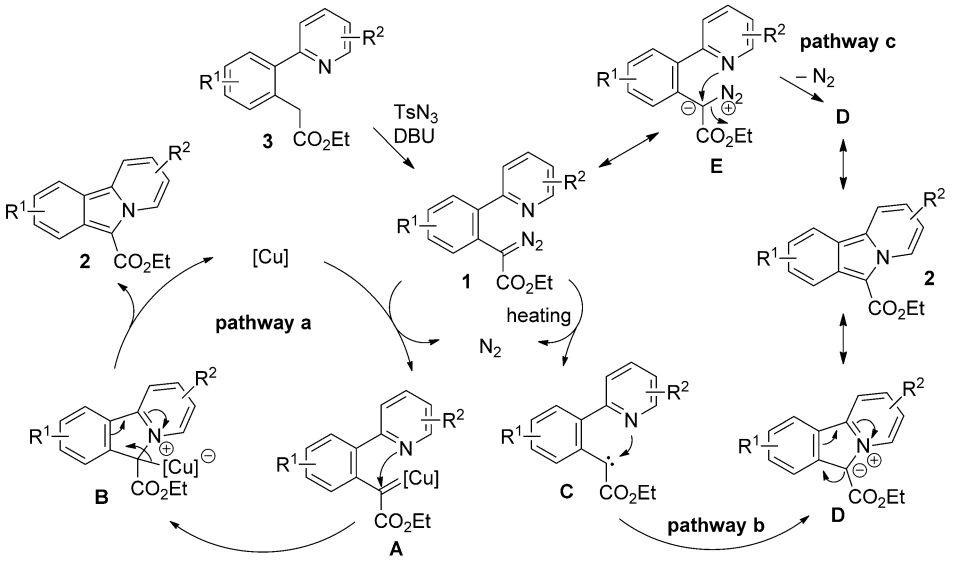
(entry 3). This compound was also obtained in 80% yield in DCE at 25 °C for 10 min in the presence of $Cu(OTf)_2$ (1.0 mol%) (entry 4).

In addition, because the preparation of diazo compounds **1** is a very simple,[17] it was feasible that this cyclization could be performed directly from pyridinylarylacetates in a one-pot fashion (Scheme 4). Pyridinylphenylacetate (**3a**, 0.20 mmol), tosyl azide (2 equiv.), DBU (2 equiv.), and acetonitrile (1.0 mL) were placed in a reaction vessel, and the reaction mixture was stirred at 25 °C. After consumption of **3a** after 12 h, the reaction mixture was treated with 1.0 mol% $Cu(OTf)_2$ and, then, it was successively stirred at 80 °C. After chromatographic separation, the pyridoisoindole **2a** was produced in 59% yield. These results suggest that TsN_3 as well as DBU remaining in the reaction mixture after the first diazotization step have an effect on the formation and reactivity of the carbenoid. Although diazotization followed by the intramolecular cyclization in one pot was influenced to some extent by the electronic nature of the substrate, methyl- and chloro-substituted pyridoisoindoles **2d** and **2g** were obtained in good yields. The substrates having thiophenyl and pyrimidinyl moieties were smoothly converted to the corresponding pyridoisoindoles **2r** and **2s** in one pot.

A plausible reaction pathway for the preparation of pyridoisoindoles **2** from pyridinylarylacetates (**3**) in one pot is shown in Scheme 5. First, **3** was diazotized with TsN_3 and DBU, leading to the formation of diazoacetates **1**.[17] When diazoacetates **1** were treated with the copper catalyst, copper carbenoid **A** was generated through the elimination of a nitrogen molecule.[20] Then, nucleophilic attack of the pyridine moiety to the carbene provides the copper-bound zwitterionic intermediate **B** and the release of an electron pair from the anionic copper of **B** provides pyridoisoindoles **2** (**pathway a**). Heating of diazoacetates **1** to 80 °C produces carbene intermediate **C** through the evolution of nitrogen gas. Nucleophilic attack of the pyridine moiety affords nitrogen ylide **D** and subsequent resonance delivered the pyridoisoindoles **2** (**pathway b**). In addition to the free carbene **pathway b** under 80 °C conditions, **pathway c** cannot be ruled out.

Conclusions

In summary, we have developed a robust synthetic method for a wide range of pyridoisoindoles from pyridinylarylacetates in one pot through diazotization using TsN_3 and DBU followed by intramolecular cyclization *via* elimination of a nitrogen molecule under $Cu(OTf)_2$-catalyzed conditions. Also, the intramolecular cyclization took place efficiently with diazo substrates to furnish pyridoisoindoles in good to excellent yields under metal-free conditions or $Cu(OTf)_2$-catalyzed conditions at room temperature.



Scheme 5. A plausible mechanism.

Experimental Section

General Methods

Reactions were carried out in oven-dried glassware under air or N_2 atmosphere. $Cu(hfacac)_2$, $Cu(OTf)_2$, $Cu(OAc)_2$, CuI, and CuCl were purchased. Commercially available reagents were used without purification. DCE and MeCN were dried with CaH_2. ***Caution:*** 4-Methylbenzenesulfonyl azide and diazo compounds are potential explosives. Many of these compounds are sensitive to heat, light, shock, and metal catalysts. Therefore, precautions should be taken in preparation, storage, and use. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using silica gel precoated glass plates, which were visualized with UV light and then developed using either iodine or a solution of anisaldehyde. Flash column chromatography was carried out using silica gel (230–400 mesh). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on NMR spectrometers. Deuterated chloroform was used as the solvent and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent [$\delta = 7.26$ for ^{1}H (chloroform-*d*), $\delta = 77.16$ for ^{13}C (chloroform-*d*)]. Infrared spectra were recorded on an FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk. Mass spectra were obtained from the KBSI on a high resolution mass spectrometer. Melting points were determined in open capillary tubes.

Synthetic Prodedure for Ethyl 2-Diazo-2-[2-(pyridin-2-yl)aryl]acetate[17]

In a dried 25-mL round-bottom flask, ethyl 2-[2-(pyridin-2-yl)phenyl]acetate (2.5 mmol) and tosyl azide (5.0 mmol, 2 equiv.) were dissolved in MeCN (6.5 mL) under air. After 5 min, DBU (5.0 mmol, 2 equiv.) was added. The reaction mixture was stirred for 12 h at 25 °C. The solvent was then evaporated, and the residue was purified by column chromatography to give the corresponding ethyl 2-diazo-2-[2-(pyridin-2-yl)aryl]acetate.

Ethyl 2-diazo-2-[2-(pyridin-2-yl)phenyl]acetate (1a): yield: 246 mg (92%); $R_f = 0.3$ (ether:dichloromethane:hexane = 1:2:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.71–8.69 (m, 1H), 7.75 (td, $J = 1.82$, 11.57 Hz, 1H), 7.61–7.56 (m, 2H), 7.49–7.45 (m, 1H), 7.44–7.40 (m, 2H), 7.24 (ddd, $J = 1.12$, 4.88, 7.56 Hz, 1H), 4.15 (q, $J = 7.10$ Hz, 2H), 1.19 (t, $J = 7.10$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 166.1, 158.5, 149.9, 139.4, 136.8, 130.8, 130.7, 128.9, 128.5, 123.6, 123.3, 122.0, 61.1, 14.4; IR (film): $\nu = 2981$, 2089, 1696, 1585, 1369, 1173, 1035, 989, 756; HR-MS (FAB): $m/z =$ 268.1089 $[M+H]^+$, calcd. for $C_{15}H_{13}N_3O_2$: 268.1087.

Ethyl 2-diazo-2-[3-methyl-2-(pyridin-2-yl)phenyl]acetate (1b): yield: 211 mg (78%); $R_f = 0.3$ (THF:hexane = 1:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$–8.72 (m, 1H), 7.78 (td, $J = 11.6$ Hz,, $J = 1.8$ Hz, 2H), 7.43 (d, $J =$ 7.7 Hz, 1H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.30–7.26 (m, 3H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.4$, 158.3, 150.4, 140.0, 137.3, 136.8, 130.5, 128.8, 124.5, 124.2, 122.2, 61.1, 20.4, 14.0; IR (film): $\nu = 3062$, 2980, 1732, 1461, 1157, 989, 754 cm^{-1}; HR-MS (FAB): $m/z = 282.1247$ $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_2$: 282.1242.

Ethyl 2-diazo-2-[5-methyl-2-(pyridin-2-yl)phenyl]acetate (1c): yield: 211 mg (75%); $R_f = 0.3$ (THF:hexane = 1:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.69$ (dq, $J =$ 4.9 Hz, $J = 0.9$ Hz, 1H), 7.74 (td, $J = 11.6$ Hz,, $J = 1.8$ Hz, 2H), 7.50–7.45 (m, 2H), 7.41 (s, 1H), 7.25–7.21 (m, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.42 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.2$, 158.6, 149.8, 138.9, 136.8, 136.6, 131.3, 130.6, 129.4, 123.2, 121.7, 61.0, 21.2, 14.4; IR (film): $\nu = 2979$, 1698, 1436, 1191, 788, 768 cm^{-1}; HR-MS (FAB): $m/z = 282.1240$ $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_2$: 282.1242.

Ethyl 2-diazo-2-[4-methyl-2-(pyridin-2-yl)phenyl]acetate (1d): yield: 197 mg (70%); $R_f = 0.3$ (ether:dichloromethane: hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$

8.70 (dq, $J=4.9$ Hz, $J=0.9$ Hz, 1H), 7.74 (td, $J=11.6$ Hz, $J=1.8$ Hz, 2H), 7.48–7.46 (m, 2H), 7.42 (d, $J=0.8$ Hz, 1H), 7.29–7.25 (m, 2H), 4.15 (q, $J=7.1$ Hz, 2H), 2.41 (s, 3H), 1.18 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 158.7, 149.9, 139.6, 138.8, 136.7, 131.4, 131.0, 129.9, 123.4, 122.0, 120.5, 61.1, 21.3, 14.5; IR (film): $\nu=2978$, 1659, 1429, 1295, 810, 769 cm^{-1}; HR-MS (FAB): $m/z=282.1241$ $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_2$: 282.1242.

Ethyl 2-diazo-2-[5-methoxy-2-(pyridin-2-yl)phenyl]acetate (1e): yield: 190 mg (64%); $R_f=0.3$ (ether:dichloromethane: hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.68 (dq, $J=4.8$ Hz, $J=0.9$ Hz, 1H), 7.73 (td, $J=11.6$ Hz,, $J=1.8$ Hz, 2H), 7.52 (d, $J=8.6$ 1H), 7.44 (dt, $J=7.9$ Hz, $J=$ 0.9 Hz, 1H), 7.23–7.20 (m, 1H), 7.16 (d, $J=2.4$ Hz, 1H), 7.00 (dd, $J=8.6$ Hz, $J=2.6$ Hz, 1H), 4.18 (q, $J=7.1$ Hz, 2H), 3.87 (s, 3H), 1.21 (t., $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.0$, 159.9, 158.3, 149.8, 136.6, 131.9, 124.8, 123.2, 121.5, 115.4, 114.5, 61.0, 55.5, 14.4; IR (film): $\nu=2977$, 2832, 1659, 1185, 1213, 1185, 839, 789 cm^{-1}; HR-MS (FAB): $m/z=298.1188$ $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_3$: 298.1191.

Ethyl 2-diazo-2-[3-fluoro-4-methoxy-2-(pyridin-2-yl)phenyl]acetate (1f): yield: 173 mg (55%); $R_f=0.5$ (ethyl acetate:hexane = 1:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.72$ (dq, $J=4.9$ Hz, $J=0.9$ Hz, 1H), 7.78 (td, $J=$ 11.6 Hz,, $J=1.8$ Hz, 1H), 7.44–7.42 (m, 1H), 7.34–7.28 (m, 2H), 7.07 (t, $J=8.6$ Hz, 1H), 4.12 (q, $J=7.1$ Hz, 2H), 3.94 (s, 3H), 1.18 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.3$, 152.8, 151.4, 150.0, 149.0, 148.2 (d, $J=$ 11.5 Hz), 136.6, 129.2 (d, $J=13.2$ Hz), 127.1 (d, $J=4.1$ Hz), 125.7 (d, $J=2.2$ Hz), 122.8, 117.3 (d, $J=2.5$ Hz), 113.5 (d, $J=2.5$ Hz), 61.1, 56.6, 14.5; IR (film): $\nu=2981$, 1728, 1696, 1271, 1218, 912, 750 cm^{-1}; HR-MS (FAB): m/z316.1093 $[M+H]^+$, calcd. for $C_{16}H_{14}FN_3O_3$: 316.1097.

Ethyl 2-[4-chloro-2-(pyridin-2-yl)phenyl]-2-diazoacetate (1g): yield: 187 mg (62%); $R_f=0.3$ (ether:dichloromethane: hexane = 1:2:8); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.72–8.70 (m, 1H), 7.79 (td, $J=1.80$, 7.72 Hz, 1H), 7.58–7.55 (m, 2H), 7.48 (dt, $J=0.93$, 7.82 Hz, 1H), 7.43 (dd, $J=2.32$, 8.48 Hz, 1H), 7.29 (ddd, $J=1.09$, 4.89, 7.59 Hz, 1H), 4.17 (q, $J=7.11$ Hz, 2H), 1.21 (t, $J=7.10$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.5$, 157.2, 150.1, 140.7, 137.0, 134.4, 132.1, 130.7, 129.1, 123.3, 122.6, 122.3, 61.3, 14.5; IR (film): $\nu=2981$, 2088, 1693, 1584, 1462, 1284, 1173, 884, 791; HR-MS (FAB): $m/z=302.0698$ $[M+H]^+$, calcd. for $C_{15}H_{12}ClN_3O_2$: 302.0696,

Ethyl 2-[5-chloro-2-(pyridin-2-yl)phenyl]-2-diazoacetate (1h): yield: 181 mg (60%); $R_f=0.3$ (ether:dichloromethane: hexane = 1:2:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.71–8.69 (m, 1H), 7.76 (td, $J=1.77$, 11.58 Hz, 1H), 7.65 (d, $J=1.92$ Hz, 1H), 7.50 (d, $J=8.32$ Hz, 1H), 7.45 (d, $J=$ 7.88 Hz, 1H), 7.38 (dd, $J=2.08$, 8.32 Hz, 1H), 7.28–7.25 (m, 1H), 4.18 (q, $J=7.10$ Hz, 2H), 1.21 (t, $J=7.12$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.5$, 157.5, 150.0, 137.4, 137.0, 134.8, 132.0, 130.3, 128.4, 125.5, 123.3, 122.3, 61.3, 14.5; IR (film): $\nu=2981$, 2095, 1697, 1590, 1464, 1290, 1173, 1044, 880, 788; HR-MS (FAB): $m/z=302.0699$ $[M+H]^+$, calcd. for $C_{15}H_{12}ClN_3O_2$: 302.0697.

Ethyl 2-diazo-2-[4-nitro-2-(pyridin-2-yl)phenyl]acetate (1i): yield: 203 mg (65%); $R_f=0.3$ (ether:dichloromethane: hexane = 1:2:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.76–8.75 (m, 1H), 8.39–8.38 (m, 1H), 8.29–8.25 (m, 1H), 7.95 (d, $J=8.8$ Hz, 1H), 7.86 (tt, $J=11.6$ Hz, $J=1.6$ Hz, 1H), 7.55–7.52 (m, 1H), 7.38–7.34 (m, 1H), 4.25 (q, $J=$ 7.1 Hz, 2H), 1.27 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.7$, 156.4, 150.3, 146.6, 138.7, 137.5, 131.5, 130.3, 126.1, 123.6, 123.4, 123.1, 61.7, 14.4; IR (film): $\nu=$ 3081, 1700, 1518, 1337, 910, 888, 794 cm^{-1}; HR-MS (FAB): $m/z=313.0940$ $[M+H]^+$, calcd. for $C_{15}H_{12}N_4O_4$: 313.0937.

Ethyl 2-diazo-2-[2-(pyridin-2-yl)-5-(trifluoromethyl)phenyl]acetate (1j): yield: 235 mg (70%); $R_f=0.3$ (ether:dichloromethane:hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.74$–8.72 (m, 1H), 7.94 (s, 1H), 7.82 (td, $J=1.78$, 7.73 Hz, 1H), 7.69–7.64 (m, 2H), 7.50 (dt, $J=$ 0.89, 7.86 Hz, 1H), 7.31 (ddd, $J=1.08$, 4.88, 7.60 Hz, 1H), 4.20 (q, $J=7.11$ Hz, 2H), 1.23 (t, $J=7.12$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.5$, 157.2, 150.2, 142.1, 137.1, 131.3, 131.1 (q, $J=32.79$ Hz), 127.6 (q, $J=3.87$ Hz), 124.9 (q, $J=3.58$ Hz), 125.0, 123.8 ($J=$q, 272.59 Hz), 123.4, 122.7, 61.4, 14.4; IR (film): $\nu=2984$, 2099, 1702, 1504, 1467, 1343, 1312, 900, 794, 744; HR-MS (FAB): $m/z=336.0957$ $[M+H]^+$, calcd. for $C_{16}H_{12}F_3N_3O_2$: 336.0960.

Ethyl 2-diazo-2-[4-(pyridin-2-yl)-[1,1′-biphenyl]-3-yl]acetate (1k): yield: 206 mg (60%); $R_f=0.3$ (ether:dichloromethane:hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.73$ (dq, $J=4.9$ Hz, $J=0.9$ Hz, 1H), 7.84 (s, 1H), 7.78 (td, $J=11.6$ Hz, $J=1.8$ Hz, 1H), 7.66–7.63 (m, 4H), 7.53 (dt, $J=7.9$ Hz, $J=1.0$ Hz, 1H), 7.49–7.45 (m, 2H), 7.40–7.36 (m, 1H), 7.28–7.25 (m, 1H), 4.18 (q, $J=7.1$ Hz, 2H), 1.21 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.2$, 158.3, 150.0, 141.9, 140.1, 138.2, 136.9, 131.3, 129.6, 129.0, 127.9, 127.3, 127.28, 124.1, 123.4, 122.1, 61.2, 14.6; IR (film): $\nu=3057$, 2979, 1696, 1660, 1185, 997, 887, 761 cm^{-1}; HR-MS (FAB): $m/z=344.1399$ $[M+H]^+$, calcd. for $C_{21}H_{17}N_3O_2$: 344.1399.

Ethyl 2-diazo-2-[3-(pyridin-2-yl)naphthalen-2-yl]acetate (1l): yield: 165 mg (52%); $R_f=0.2$ (THF:hexane = 1:10); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.74$–8.72 (m, 1H), 8.09 (s, 1H), 8.06 (s, 1H), 7.89–7.85(m, 2H), 7.79 (td, $J=1.82$, 7.71 Hz, 1H), 7.58 (dt, $J=0.97$, 7.86 Hz, 1H), 7.55–7.48 (m, 2H), 7.29–7.26 (m, 1H), 4.14 (q, $J=7.06$ Hz, 2H), 1.17 (t, $J=7.08$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 166.3, 158.7, 149.8, 137.4, 136.8, 133.2, 132.9, 130.5, 130.3, 128.1, 127.8, 127.1, 127.0, 123.5, 122.1, 121.4, 61.1, 14.5; IR (film): $\nu=2980$, 2087, 1585, 1564, 1476, 1426, 1369, 889, 784; HR-MS (FAB): $m/z=318.1240$ $[M+H]^+$, calcd. for $C_{19}H_{15}N_3O_2$: 318.1242.

Ethyl 2-diazo-2-[2-(3-methylpyridin-2-yl)phenyl]acetate (1m): yield: 208 mg (74%); $R_f=0.3$ (ethyl acetate:hexane = 1:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.52$ (dd, $J=4.8$ Hz, $J=1.1$ Hz, 1H), 7.64–7.59 (m, 2H), 7.47–7.38 (m, 2H), 7.35–7.32 (m, 1H), 7.22–7.19 (m, 1H), 4.20 (q, $J=$ 7.1 Hz, 2H), 2.13 (s, 3H), 1.23 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.0$, 157.7, 147.4, 139.3, 138.2, 131.8, 130.4, 129.9, 128.6, 128.1, 124.1, 122.7, 61.0, 19.0, 14.5; IR (film): $\nu=3057$, 2981, 1696, 1445, 1066, 989, 781 cm^{-1}; HR-MS (FAB): $m/z=282.1246$ $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_2$: 282.1242.

Ethyl 2-diazo-2-[2-(6-methylpyridin-2-yl)phenyl]acetate (1n): yield: 214 mg (76%); $R_f=0.3$ (ether:dichloromethane: hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.65 (t, $J=7.7$ Hz, 1H), 7.60–7.55 (m, 2H), 7.46–7.39 (m, 2H), 7.27 (d, $J=8.1$ Hz, 1H), 7.12 (d, $J=7.7$ Hz, 1H), 4.16 (q, $J=7.1$ Hz, 2H), 2.60 (s, 3H), 1.20 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.4$, 58.6, 157.9, 140.0,

137.0, 131.1, 130.7, 128.8, 128.7, 123.7, 121.6, 120.3, 61.1, 24.7, 14.5; IR (film): ν=3063, 2980, 1698, 1573, 1286, 995, 802, 711 cm^{-1}; HR-MS (FAB): m/z=282.1246 $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_2$: 282.1242.

Ethyl 2-diazo-2-[2-(5-methoxypyridin-2-yl)phenyl]acetate (1o): yield: 190 mg (64%); R_f=0.3 (ethyl acetate:hexane=1:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.40–8.39 (m, 1H), 7.60–7.53 (m, 2H), 7.45–7.38 (m, 3H), 7.30–7.27 (m, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.91 (s, 3H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 154.6, 150.8, 139.2, 137.4, 131.0, 130.6, 128.6, 123.7, 123.6, 121.3, 61.1, 55.8, 14.6; IR (film): ν=3049, 2983, 1639, 1453, 1184, 985, 826, 738 cm^{-1}; HR-MS (FAB): m/z=298.1191 $[M+H]^+$, calcd. for $C_{16}H_{15}N_3O_3$: 298.1191.

Ethyl 2-diazo-2-[2-(5-fluoropyridin-2-yl)phenyl]acetate (1p): yield: 211 mg (74%); R_f=0.3 (THF:hexane=1:10); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.55 (t, J=1.7 Hz, 1H), 7.60–7.53 (m, 2H), 7.50–7.40 (m, 4H), 4.16 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9, 159.7, 157.2, 154.7 (d, J=4.2 Hz), 138.5, 138., 137.8, 130.9, 130.6, 129.0, 28.6, 124.2 (d, J=4.1 Hz), 123.6 (d. J=18.4 Hz), 123.62, 61.1, 14.4; IR (film): ν=2982, 1698, 1476, 1236, 910, 740 cm^{-1}; HR-MS (FAB): m/z=285.0911 $[M]^+$, calcd. for $C_{15}H_{12}FN_3O_2$: 285.0914.

Ethyl 2-[2-(5-acetylpyridin-2-yl)phenyl]-2-diazoacetate (1q): yield: 161 mg (52%); R_f=0.2 (ether:dichloromethane:hexane=1:2:3); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.24 (dd, J=2.2 Hz, J=0.7 Hz, 1H), 8.32 (dd, J=8.2 Hz, J=2.3 Hz, 1H), 7.63–7.60 (m, 3H), 7.53–7.44 (m, 2H), 4.15 (q, J=7.1 Hz, 2H), 2.29 (s, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 162.7, 150.2, 138.6, 136.5, 131.1, 130.9, 130.4, 129.8, 128.8, 124.0, 123.3, 61.0, 26.9, 14.5; IR (film): ν=3061, 2981, 1688, 1590, 1373, 1022, 758, 698 cm^{-1}; HR-MS (FAB): m/z=310.1189 $[M+H]^+$, calcd. for $C_{17}H_{15}N_3O_3$: 310.1191.

Ethyl 2-diazo-2-[2-(pyridin-2-yl)thiophen-3-yl]acetate (1r): yield: 208 mg (76%); R_f=0.4 (THF:hexane=1:10); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.66–8.64 (m, 1H), 7.75 (dt, J=11.7 Hz,, J=1.8 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.45 (d, J=5.3 Hz, 1H), 7.30 (d, J=5.2 Hz, 1H), 7.21–7.18 (m, 1H), 4.30 (q, J=7.1 Hz, 2H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.0, 151.9, 149.8, 136.9, 136.5, 127.0, 122.1, 121.4, 61.5, 14.6; IR (film): ν=3081, 2980, 1696, 1272, 1112, 838, 740 cm^{-1}; HR-MS (FAB): m/z=274.0650 $[M+H]^+$, calcd. for $C_{13}H_{11}N_3O_2S$: 274.0650.

Ethyl 2-diazo-2-[3-methyl-2-(pyrimidin-2-yl)phenyl]acetate (1s): yield: 248 mg (88%); R_f=0.2 (ether:dichloromethane:hexane=1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.88 (d, J=4.9 Hz, 2H), 7.44–7.36 (m, 2H), 7.29–7.25 (m,2H), 4.13 (q, J=7.1 Hz, 2H), 2.21 (s, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.0, 166.1, 157.4, 157.1, 138.4, 137.3, 130.7, 129.1, 128.5, 124.1, 119.1, 61.1, 20.3, 14.5; IR (film): ν=3037, 2980, 1696, 1556, 1408, 1165, 807, 738 cm^{-1}; HR-MS (FAB): m/z=283.1192 $[M+H]^+$, calcd. for $C_{15}H_{14}N_4O_2$: 283.1195.

Synthetic Procedure A for Pyrido[2,1-*a*]isoindoles

In a dried test tube, $Cu(OTf)_2$ (0.002 mmol) was dissolved in DCE (0.5 mL) under air. To the above stirred solution, diazoacetate derivative **1** (0.2 mmol) in 0.5 mL of DCE was added. The reaction mixture was stirred at 25 °C and then evaporated. The residue was purified by column chromatography to give the corresponding ethyl pyrido[2,1-*a*]isoindole-6-carboxylate.

Synthetic Procedure B for Pyrido[2,1-*a*]isoindoles

To a dried test tube, diazoacetate derivative **1** (0.2 mmol) was added in 1.0 mL of DCE under air. The reaction mixture was stirred at 80 °C, and then evaporated. The residue was purified by column chromatography to give the corresponding ethyl pyrido[2,1-*a*]isoindole-6-carboxylate.

Ethyl pyrido[2,1-*a*]isoindole-6-carboxylate[8b] (2a): Method A yield: 45 mg (94%); Method B yield: 44 mg (91%); R_f=0.4 (THF:hexane=1:5); yellow solid; mp 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.99 (d, J=6.67 Hz, 1H), 8.27 (d, J=8.52 Hz, 1H), 8.13–8.08 (m, 2H), 7.57–7.53 (m, 1H), 7.31–7.25 (m, 2H), 7.21 (td, J=1.53, 10.40 Hz, 1H), 4.50 (q, J=7.12 Hz, 2H), 1.52 (t, J=7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.6, 132.8, 131.0, 128.2, 127.6, 121.7, 120.8, 119.9, 119.5, 118.7, 117.5, 117.3, 104.0, 59.6, 14.9; IR (film): ν=2978, 1663, 1436, 1325, 1186, 1112, 1045, 765 cm^{-1}; HR-MS (EI): m/z=239.0948, calcd. for $C_{15}H_{13}NO_2$: 239.0946.

Ethyl 10-methylpyrido[2,1-*a*]isoindole-6-carboxylate (2b): Method A; yield: 47 mg (92%); Method B yield: 46 mg (90%); R_f=0.5 (THF:hexane=1:5); yellow solid; mp 75–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.11 (d, J=6.69 Hz, 1H), 8.31 (d, J=8.68 Hz, 1H), 8.21 (d, J=8.48 Hz, 1H), 7.46 (dd, J=6.94, 8.46 Hz, 1H), 7.35–7.31 (m, 1H), 7.26–7.22 (m, 1H), 7.06 (dt, J=0.90, 6.84 Hz, 1H), 4.51 (q, J=7.12 Hz, 2H), 2.89 (s, 3H), 1.53 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.7, 133.2, 132.0, 131.5, 127.8, 127.5, 122.3, 121.6, 120.0, 117.9, 117.7, 116.7, 104.2, 59.6, 21.8, 14.9; IR (film): ν=2977, 1660, 1428, 1314, 1213, 1121, 1039, 785, 710 cm^{-1}; HR-MS (EI): m/z=253.1100, calcd. for $C_{16}H_{15}NO_2$: 253.1103.

Ethyl 8-methylpyrido[2,1-*a*]isoindole-6-carboxylate (2c): Method A yield: 46 mg (90%); Method B yield: 41 mg (80%); R_f=0.5 (THF:hexane=1:5); yellow solid; mp 69–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.97 (d, J=6.64 Hz, 1H), 8.10 (dt, J=1.13, 8.50 Hz, 1H), 8.06 (s, 1H), 8.01 (d, J=8.36 Hz, 1H), 7.32–7.28 (m, 1H), 7.19 (td, J=1.44, 10.44 Hz, 1H), 7.12 (dd, J=1.28, 8.36 Hz, 1H), 4.52 (q, J=7.10 Hz, 2H), 2.58 (s, 3H), 1.53 (t, J=7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.6, 138.2, 132.9, 131.5, 127.7, 123.1, 121.7, 119.2, 118.9, 117.2, 117.0, 116.8, 103.6, 59.5, 22.7, 15.0; IR (film): ν=2978, 1160, 1437, 1323, 1191, 1173, 1114, 1046, 766 cm^{-1}; HR-MS (EI): m/z=253.1104, calcd. for $C_{16}H_{15}NO_2$:253.1103.

Ethyl 9-methylpyrido[2,1-*a*]isoindole-6-carboxylate (2d): Method A yield: 47 mg (92%); Method B yield: 45 mg (89%); R_f=0.5 (ether:dichloromethane:hexane=1:2:5); yellow solid; mp 100–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.90 (d, J=6.48 Hz, 1H), 8.13 (d, J=8.56 Hz, 1H), 8.0 (d, J=8.40 Hz, 1H), 7.80 (dd, J=0.70, 1.38 Hz, 1H), 7.35 (dd, J=1.36, 8.60 Hz, 1H), 7.23–7.17 (m, 1H), 7.13 (td, J=1.42, 10.32 Hz, 1H), 4.48 (q, J=7.10 Hz, 2H), 2.51 (s, 3H), 1.50 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.5, 132.3, 130.5, 130.2, 129.3, 127.5, 121.1, 119.7, 119.0, 118.3, 117.4, 117.0, 103.8, 59.3, 21.7, 14.9; IR (film): ν=2978,

1659, 1430, 1296, 1115, 1047, 809, 740 cm^{-1}; HR-MS (EI): *m/z* = 253.1099, calcd. for $C_{16}H_{15}NO_2$:253.1103.

Ethyl 8-methoxypyrido[2,1-*a*]isoindole-6-carboxylate (2e): Method A yield: 48 mg (90%); Method B yield: 48 mg (90%); R_f = 0.3 (THF:hexane = 1:5); yellow solid; mp 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1H), 8.01 (dt, *J* = 1.19, 8.58 Hz, 1H), 7.97 (dd, *J* = 0.46, 8.86 Hz, 1H), 7.62 (s, 1H), 7.31–7.26 (m, 1H), 7.14 (td, *J* = 1.42, 10.43 Hz, 1H), 6.92 (dd, *J* = 2.30, 8.86 Hz, 1H), 4.50 (q, *J* = 7.10 Hz, 2H), 3.96 (s, 3H), 1.53 (t, *J* = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 160.3, 133.1, 132.7, 127.8, 122.2, 120.8, 116.7, 116.1, 113.8, 113.7, 103.9, 98.7, 59.4, 55.2, 14.9; IR (film): ν = 2977, 1660, 1481, 1324, 1213, 1112, 1045, 839 cm^{-1}; HR-MS (EI): *m/z* = 269.1053, calcd. for $C_{16}H_{15}NO_3$:269.1052.

Ethyl 10-fluoro-9-methoxypyrido[2,1-*a*]isoindole-6-carboxylate (2f): Method A yield: 52 mg (91%); Method B yield: 45 mg (78%); R_f = 0.4 (THF:hexane = 1:5); yellow solid; mp 110–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (d, *J* = 6.72 Hz, 1H), 8.27 (d, *J* = 8.48 Hz, 1H), 7.94 (d, *J* = 9.04 Hz, 1H), 7.34 (dd, *J* = 8.02, 8.98 Hz, 1H), 7.30–7.26 (m, 1H), 7.22 (td, *J* = 1.60, 10.41 Hz, 1H), 4.49 (q, *J* = 7.12 Hz, 2H), 4.02 (s, 3H), 1.51 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 146.9 (d, 250.14 Hz), 139.6 (d, *J* = 8.52 Hz), 129.9 (d, 3.73 Hz), 128.0 (d, *J* = 4.18 Hz), 127.3, 121.7,120.6 (d, 5.83 Hz), 119.8, 117.6, 115.7 (d, *J* = 4.71 Hz), 109.3 (d, *J* = 14.11 Hz), 104.6, 59.7, 59.0 (d, 1.19 Hz), 14.9; IR (film): ν = 2989, 1650, 1436, 1276, 1218, 1097, 802 cm^{-1}; HR-MS (EI): *m/z* = 287.0958, calcd. for $C_{16}H_{14}FNO_3$: 287.0958.

Ethyl 9-chloropyrido[2,1-*a*]isoindole-6-carboxylate (2g): Method A yield: 47 mg (86%); Method B yield: 44 mg (81%); R_f = 0.3 ether:dichloromethane:hexane = 1:2:8); yellow solid; mp 128–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (d, *J* = 6.76 Hz, 1H), 8.13 (d, *J* = 8.96 Hz, 1H), 8.01 (dt, *J* = 1.21, 8.62 Hz, 1H), 7.98 (dd, *J* = 0.48, 1.84 Hz, 1H), 7.42 (dd, *J* = 1.92, 8.96 Hz, 1H), 7.30–7.26 (m, 1H), 7.21 (td, *J* = 1.48, 10.41 Hz, 1H), 4.48 (q, *J* = 7.12 Hz, 2H), 1.51 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 131.7, 128.9, 128.8, 127.6, 126.2, 121.9, 121.4, 118.9, 118.6, 117.7, 117.6, 104.1, 59.8, 14.9; IR (film): ν = 3421, 2981, 1661, 1428, 1184, 1121, 1043, 839, 766 cm^{-1}; HR-MS (EI): *m/z* = 273.0555, calcd. for $C_{15}H_{12}ClNO_2$: 273.0557.

Ethyl 8-chloropyrido[2,1-*a*]isoindole-6-carboxylate (2h): Method A yield: 53 mg (97%); Method B yield: 51 mg (94%); R_f = 0.3 (THF:hexane = 1:10); yellow solid; mp 63–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (d, *J* = 6.80 Hz, 1H), 8.16 (d, *J* = 1.36 Hz, 1H), 8.02 (dt, *J* = 1.18, 8.52 Hz, 1H), 7.94 (dd, *J* = 0.56, 8.64 Hz, 1H), 7.32–7.28 (m, 1H), 7.21 (td, *J* = 1.46, 10.43 Hz, 1H), 7.16 (dd, *J* = 1.86, 8.62 Hz, 1H), 4.49 (q, *J* = 7.10 Hz, 2H), 1.52 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 134.2, 132.5, 131.3, 127.7, 122.4, 121.6, 120.8, 119.0, 117.5, 117.4, 116.7, 103.7, 59.8, 14.9; IR (film): ν = 2977, 1665, 1436, 1319, 1184, 1114, 998, 762 cm^{-1}; HR-MS (EI): *m/z* = 273.0559, calcd. for $C_{15}H_{12}ClNO_2$:273.0557.

Ethyl 9-nitropyrido[2,1-*a*]isoindole-6-carboxylate (2i): Method A yield: 55 mg (97%); Method B yield: 53 mg (93%); R_f = 0.2 (ether:dichloromethane:hexane = 1:2:8); orange solid; mp 198–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.09 (d, *J* = 7.0 Hz, 1H), 9.13 (dd, *J* = 0.54, 2.02 Hz, 1H), 8.36–8.27 (m, 3H), 7.58–7.54 (m, 1H), 7.43 (td, *J* = 1.38, 10.53 Hz, 1H), 4.54 (q, *J* = 7.13 Hz, 2H), 1.53 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 141.3, 134.5, 132.5, 128.7, 124.6, 122.3, 120.1, 119.1, 118.07, 118.03, 116.8, 105.6, 60.3, 14.8; IR (film): ν = 2985, 1656, 1603, 1495, 1327, 1188, 1087, 1049, 768 cm^{-1}; HR-MS (EI): *m/z* = 284.0794, calcd. for $C_{15}H_{12}N_2O_4$: 284.0797.

Ethyl 8-(trifluoromethyl)pyrido[2,1-*a*]isoindole-6-carboxylate (2j): Method A yield: 61 mg (99%); Method B yield: 57 mg (93%); R_f = 0.1 (THF:hexane = 1:10); yellow solid; mp 129–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94 (d, *J* = 6.84 Hz, 1H), 8.51 (s, 1H), 8.10 (d, *J* = 8.32 Hz, 2H), 7.38 (dd, *J* = 1.38, 8.85 Hz, 1H), 7.35–7.31 (m, 1H), 7.26 (td, *J* = 1.50, 10.41 Hz, 1H), 4.51 (q, *J* = 7.10 Hz, 2H), 1.53 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 132.1, 129.6 (q, *J* = 31.51 Hz), 127.7, 124.9 (q, *J* = 272.40 Hz), 122.3, 120.3, 119.4, 118.2, 118.0, 117.9 (q, *J* = 5.65 Hz), 116.5 (q, *J* = 3.04 Hz), 104.8, 60.0, 14.8; IR (film): ν = 3397, 1676, 1458, 1310, 1187, 1113, 1060, 768 cm^{-1}; HR-MS (EI): *m/z* = 307.0816, calcd. for $C_{16}H_{12}F_3NO_2$: 307.0820.

Ethyl 8-phenylpyrido[2,1-*a*]isoindole-6-carboxylate (2k): Method A yield: 62 mg (98%); Method B yield: 62 mg (98%); R_f = 0.3 (ether:dichloromethane:hexane = 1:2:5); yellow solid; mp 108–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (d, *J* = 6.60 Hz, 1H), 8.47 (s, 1H), 8.09 (dd, *J* = 0.56, 8.48 Hz, 1H), 8.05 (dt, *J* = 1.07, 8.42 Hz, 1H), 7.76–7.73 (m, 2H), 7.51–7.47 (m, 3H), 7.40–7.36 (m, 1H), 7.27–7.22 (m, 1H), 7.16 (td, *J* = 1.46, 10.39 Hz, 1H), 4.50 (q, *J* = 7.10 Hz, 2H), 1.51 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 142.2, 141.0, 132.7, 131.4, 128.9, 127.74, 127.72, 127.3, 121.8, 120.9, 119.9, 118.0, 117.9, 117.5, 117.2, 104.3, 59.6, 14.9; IR (film): ν = 2978, 1661, 1441, 1324, 1186, 1117, 1047, 883, 761 cm^{-1}; HR-MS (EI): *m/z* = 315.1259, calcd. for $C_{21}H_{17}NO_2$: 315.1259.

Ethyl benzo[*f*]pyrido[2,1-*a*]isoindole-6-carboxylate (2l): Method A yield: 47 mg (82%); Method B yield: 36 mg (63%); R_f = 0.3 (THF:hexane = 1:5); orange solid; mp 129–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, 1H), 8.71 (s, 2H), 8.38–8.35 (m, 1H), 8.02 (t, *J* = 9.30 Hz, 2H), 7.48–7.35 (m, 4H), 4.58 (q, *J* = 7.10 Hz, 2H), 1.60 (t, *J* = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 134.1, 133.4, 129.7, 128.7, 128.5, 128.4, 127.8, 125.6, 123.3, 121.8, 120.4, 119.2, 118.3, 117.9, 116.3, 102.5, 59.4, 15.1; IR (film): ν = 2977, 1660, 1504, 1454, 1280, 1185, 1108, 1043, 758 cm^{-1}; HR-MS (EI): *m/z* = 289.1100, calcd. for $C_{19}H_{15}NO_2$: 289.1103.

Ethyl 1-methylpyrido[2,1-*a*]isoindole-6-carboxylate (2m): Method A yield: 43 mg (85%); Method B yield: 50 mg (98%); R_f = 0.4 (THF:hexane = 1:5); yellow solid; mp 82–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.98 (d, *J* = 6.84 Hz, 1H), 8.34 (dt, *J* = 0.91, 8.50 Hz, 1H), 8.24 (dt, *J* = 0.89, 8.42 Hz, 1H), 7.55–7.51 (m, 1H), 7.28–7.24 (m, 1H), 7.13 (t, *J* = 6.98 Hz, 1H), 7.07 (dt, *J* = 0.93, 7.02 Hz, 1H), 4.51 (q, *J* = 7.12 Hz, 2H), 2.87 (s, 3H), 1.53 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 131.8, 131.3, 130.6, 127.4, 125.6, 123.2, 122.2, 120.7, 119.8, 119.4, 116.7, 104.0, 59.6, 20.9, 14.9; IR (film): ν = 2976, 1660, 1446, 1326, 1206, 1076, 775, 709 cm^{-1}; HR-MS (EI): *m/z* = 253.1101, calcd. for $C_{16}H_{15}NO_2$: 253.1103.

Ethyl 4-methylpyrido[2,1-*a*]isoindole-6-carboxylate (2n): Method A yield: 45 mg (88%); Method B yield: 48 mg (94%); R_f = 0.3 (ether:dichloromethane:hexane = 1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* =

8.52 Hz, 1H), 8.09 (d, J=8.20 Hz, 1H), 8.05 (d, J=8.40 Hz, 1H), 7.56–7.52 (m, 1H), 7.30 (t, J=7.74 Hz, 1H), 7.27–7.23 (m, 1H), 7.08 (d, J=7.08 Hz, 1H), 4.48 (q, J=7.10 Hz, 2H), 2.80 (s, 3H), 1.51 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.1, 138.7, 135.3, 133.1, 128.2, 122.5, 120.6, 119.7, 119.6, 119.2, 118.8, 114.9, 105.3, 60.0, 23.5, 15.0; IR (film): ν=2977, 1672, 1443, 1376, 1317, 1185, 1089, 1037, 749 cm^{-1}; HR-MS (EI): m/z=253.1100, calcd. for $C_{16}H_{15}NO_2$: 253.1103.

Ethyl 3-methoxypyrido[2,1-*a*]isoindole-6-carboxylate (2o): Method A yield: 52 mg (96%); Method B yield: 51 mg (94%); R_f=0.4 (THF:hexane=1:5); yellow solid; mp 77–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.63 (s, 1H), 8.19 (d, J=8.44 Hz, 1H), 7.95 (dd, J=0.70, 8.14 Hz, 1H), 7.88 (d, J=9.24 Hz, 1H), 7.49–7.45 (m, 1H), 7.24–7.20 (m, 1H), 6.99–6.96 (m, 1H), 4.48 (q, J=7.10 Hz, 2H), 3.92 (s, 3H), 1.52 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 162.7, 152.8, 130.7, 128.8, 127.1, 120.8, 119.7, 119.0, 118.8, 117.3, 115.4, 110.6, 104.6, 59.5, 56.0, 14.9; IR (film): ν=2987, 1632, 1496, 1429, 1305, 1184, 1051, 874, 742 cm^{-1}; HR-MS (EI): m/z=269.1051, calcd. for $C_{16}H_{15}NO_3$: 269.1052.

Ethyl 3-fluoropyrido[2,1-*a*]isoindole-6-carboxylate (2p): Method A yield: 50 mg (98%); Method B yield: 48 mg (94%); R_f=0.3 (ether:dichloromethane:hexane=1:2:5); yellow solid; mp 105–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.89 (d, J=4.84 Hz, 1H), 8.20 (d, J=8.44 Hz, 1H), 8.01–7.97 (m, 2H), 7.53–7.49 (m, 1H), 7.29–7.25 (m, 1H), 7.14–7.09 (m, 1H), 4.49 (q, J=7.12 Hz, 2H), 1.51 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.4, 156.3 (d, J= 239.68 Hz), 130.9, 129.8, 127.7, 121.4, 119.8, 119.0, 118.9, 117.6 (d, J=9.42 Hz), 115.0 (d, J=44.35 Hz), 112.1 (d, J= 24.47 Hz), 105.4, 59.8, 14.8; IR (film): ν=2988, 1641, 1454, 1336, 1184, 1103, 1041, 826, 755 cm^{-1}; HR-MS (EI): m/z= 257.0850, calcd. for $C_{15}H_{12}FNO_2$: 257.0852.

Ethyl 3-acetylpyrido[2,1-*a*]isoindole-6-carboxylate (2q): Method A yield: 50 mg (89%); Method B yield: 50 mg (89%); R_f=0.4 (ether:dichloromethane:hexane=1:2:3); orange solid; mp 128–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.65 (s, 1H), 8.24 (d, J=8.60 Hz, 1H), 8.11 (dd, J= 0.82, 9.02 Hz, 1H), 8.07 (dt, J=0.95, 8.30 Hz, 1H), 7.81 (dd, J=1.56, 9.0 Hz, 1H), 7.59–7.54 (m, 1H), 7.31–7.27 (m, 1H), 7.31–7.27 (m, 1H), 4.52 (q, J=7.12 Hz, 2H), 2.73 (s, 3H), 1.55 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 195.6, 162.6, 133.0, 132.2, 130.9, 129.1, 127.5, 121.8, 120.2, 119.9, 119.4, 118.5, 117.3, 105.2, 60.0, 26.4, 14.8; IR (film): ν=2980, 1685, 1445, 1281, 1183, 1111, 1040, 764 cm^{-1}; HR-MS (EI): m/z=281.1049, calcd. for $C_{17}H_{15}NO_3$: 281.1052.

Ethyl thieno[2,3-*a*]indolizine-4-carboxylate (2r): Method A yield: 10 mg (20%); Method B yield: 30 mg (61%); R_f= 0.6 (ether:dichloromethane:hexane=1:2:5); white solid; mp 78–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.71 (d, J= 7.08 Hz, 1H), 7.66 (dt, J=1.05, 8.90 Hz, 1H), 7.50 (d, J= 5.12 Hz, 1H), 7.45 (d, J=5.12 Hz, 1H), 7.16–7.12 (m, 1H), 6.95 (td, J=1.17, 10.45 Hz, 1H), 4.44 (q, J=7.10 Hz, 2H), 1.46 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.3, 140.9, 131.4, 129.5, 128.5, 121.4, 118.4, 117.2, 116.3, 113.9, 104.3, 59.7, 14.8; IR (film): ν=2977, 1670, 1416, 1338, 1217, 1093, 761 cm^{-1}; HR-MS (EI): m/z=245.0513, calcd. for $C_{13}H_{11}N_2O_2S$: 245.0510.

Ethyl 10-methylpyrimido[2,1-*a*]isoindole-6-carboxylate (2s): Methoid A yield: 41 mg (80%); Method B yield: 44 mg (86%); R_f=0.3 (ether:dichloromethane:hexane=1:2:5); yellow solid; mp 138–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.15 (d, J=6.72 Hz, 1H), 8.52 (dd, J=1.74, 4.14 Hz, 1H), 8.13 (d, J=8.48 Hz, 1H), 7.50 (dd, J=6.94, 8.46 Hz, 1H), 7.20 (dd, J=4.16, 7.08 Hz, 1H), 7.11 (dt, J=0.89, 6.90 Hz, 1H), 4.51 (q, J=7.12 Hz, 2H), 3.02 (s, 3H), 1.53 (t, J=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.2, 143.2, 140.3, 134.5, 132.8, 132.2, 129.3, 122.7, 117.0, 116.2, 111.9, 101.3, 59.9, 20.5, 14.9; IR (film): ν=2977, 1655, 1432, 1325, 1243, 1207, 1122, 1044, 715 cm^{-1}; HR-MS (EI): m/z= 254.1053, calcd. for $C_{15}H_{14}N_2O_2$: 254.1055.

Synthetic Procedure for Pyridoisoindoles from Ethyl 2-[2-(Pyridin-2-yl)aryl]acetates in One Pot

In a dried long test tube, ethyl 2-(2-(pyridin-2-yl)phenyl)acetate (0.2 mmol) and tosyl azide (0.4 mmol, 2 equiv.) were dissolved in MeCN (1.0 mL) under air. After 5 min, DBU (0.4 mmol, 2 equiv.) was added. The reaction mixture was stirred for 12 h at 25 °C and, then, $Cu(OTf)_2$ (0.002 mmol) was added to the mixture. The mixture was stirred at 80 °C until the diazoacetate derivative was completely consumed on TLC monitoring. Then, the solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography to give ethyl pyridoisoindole-6-carboxylates.

Synthetic Procedure for Ethyl 2-[2-(pyridin-2-yl)aryl]-acetate[18]

A mixture of 2-phenylpyridine (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mg, 2 μmol, 1.0 mol%), and AgF (1 mg, 10 μmol, 5.0 mol%) was stirred in EtOH (2 mL) for 1 h under air. 5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (0.24 mmol, 1.2 equiv.) was added in one pot, and the solution was stirred at 75 °C for 12 h. The mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was then purified by flash column chromatography to give the ethyl 2-[2-(pyridin-2-yl)aryl]acetate.

Ethyl 2-[4-methyl-2-(pyridin-2-yl)phenyl]acetate (3d): R_f=0.3 (ether:dichloromethane:hexane=1:2:5); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.65 (dq, J=4.9 Hz, J= 1.0 Hz, 1H), 7.73 (td, J=11.6 Hz, J=1.8 Hz, 2H), 7.47 (dt, J=7.9 Hz, J=1.0 Hz, 1H), 7.27 (s, 1H), 7.26–7.21 (m, 2H), 7.20–7.18 (m, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.77 (s, 2H), 2.39 (s, 3H), 1.16 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.2, 159.7, 149.1, 140.4, 137.1, 136.5, 131.3, 130.7, 129.5, 129.4, 124.1, 121.8, 60.6, 39.0, 21.2, 14.3; IR (film): ν=2979, 1732, 1563, 1158, 794, 749 cm^{-1}; HR-MS (EI): m/z=255.1261, calcd. for $C_{16}H_{17}NO_2$: 255.1259.

Ethyl 2-[4-chloro-2-(pyridin-2-yl)phenyl]acetate (3g): R_f= 0.2 (ether:dichloromethane:hexane=1:2:5); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.66–8.65 (m, 1H), 7.77 (td, J=1.81, 7.73 Hz, 1H), 7.47–7.45 (m, 2H), 7.35 (dd, J=2.22, 8.22 Hz, 1H), 7.30–7.27 (m, 2H), 4.04 (q, J=7.13 Hz, 2H), 3.78 (s, 2H), 1.16 (t, J=7.14 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5, 158.2, 149.2, 142.0, 136.8, 133.1, 132.8, 131.2, 129.9, 128.6, 124.0, 122.4, 60.8, 38.8, 14.2; IR (film): ν=2980, 2167, 1731, 1586, 1559, 1469, 1293, 1159, 1032, 884, 793 cm^{-1}; HR-MS (EI): m/z=275.0714, calcd. for $C_{15}H_{12}ClNO_2$: 275.0713.

Ethyl 2-[2-(pyridin-2-yl)thiophen-3-yl]acetate (3r): R_f = 0.4 (THF:hexane = 1:10); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (dq, J = 4.8 Hz, J = 0.9 Hz 1H), 7.69 (dt, J = 11.6 Hz,, J = 1.8 Hz, 1H), 7.61 (dt, J = 8.0 Hz, J = 1.0 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.16 (ddd, J = 7.4 Hz, J = 4.8 Hz, J = 1.1 Hz, 1H), 7.06 (d, J = 5.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.00 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 153.0, 149.5, 139.5, 136.7, 132.0, 131.4, 125.5, 122.0, 121.8, 60.9, 35.5, 14.3; IR (film): ν = 3077, 2980, 1731, 1584, 1251, 917, 839, 740 cm^{-1}; HR-MS (EI): m/z = 247.0665, calcd. for $C_{13}H_{13}NO_2S$: 247.0667.

Ethyl 2-[3-methyl-2-(pyrimidin-2-yl)phenyl]acetate (3s): R_f = 0.4 (ethyl acetate:hexane = 1:3); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, J = 4.9 Hz, 2H), 7.32–7.26 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.16 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 167.7, 157.1, 139.0, 136.4, 132.4, 129.6, 128.8, 128.5, 119.1, 60.7, 39.6, 20.3, 14.2; IR (film): ν = 3031, 2979, 1733, 1557, 1411, 1248, 1033, 821, 759 cm^{-1}; HR-MS (EI): m/z = 256.1212, calcd. for $C_{15}H_{16}N_2O_2$: 256.1212.

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[19] CCDC 1058419 (**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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