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Palladium-Catalyzed Multi-step Tandem Carbonylation/N-dealkylation/Carbonylation Reaction: Access to Isatoic Anhydrides

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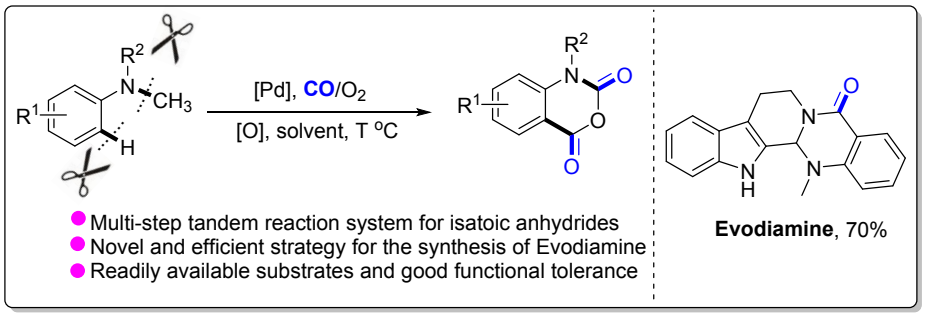


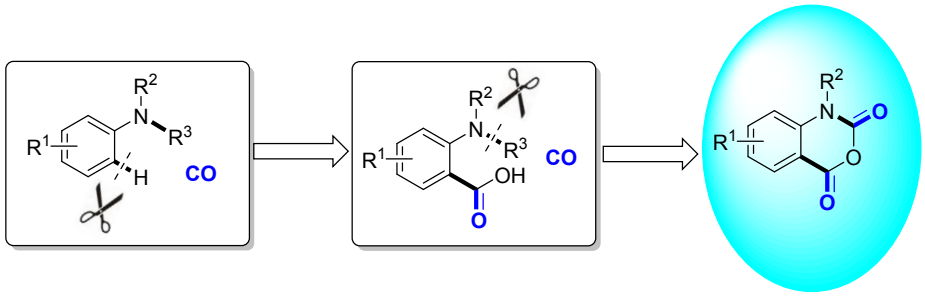
Abstract: A novel and efficient synthesis of isatoic anhydride derivatives was developed via palladium-catalyzed multi-step tandem carbonylation/*N*-dealkylation/carbonylation reaction with alkyl as leaving group and tertiary anilines as nitrogen nucleophiles. This approach features good functional group compatibility and readily available starting materials. Furthermore, it provided a convenient approach for the synthesis of biologically and medicinally useful Evodiamine.

Carbonylation, the incorporation of CO into an organic molecule, is now widely recognized as an attractive strategy in organic synthesis, which meets the requirements of "atom economy" and "green chemistry".[1] In recent decades, much

progress has been made in C-H carbonylation.[2] In this area, palladium-catalyzed oxidation carbonylation reactions using CO as simplest C-1 unit have proven to be one of the most important methods for the synthesis of many carbonyl-containing compounds. On the other hand, C-N bond activation has attracted more attention and become a hot research topic in organic synthesis, in which most efforts were focused on the amination transformation.[3] Tertiary anilines are valuable commodity chemicals and useful core structures for agrochemicals, pharmaceutical ingredients, and functional materials.[4] As a typical example, tertiary anilines have also been utilized in C-N bond cleavage transformations.[5] However, most C-N bond activation of tertiary anilines has focused on the cross-coupling of the Csp^2-N bond with organometallic reagents.[6] Therefore, the development of a simple, efficient, and atom-economical methods to access diverse functionalized tertiary anilines remains highly desirable.

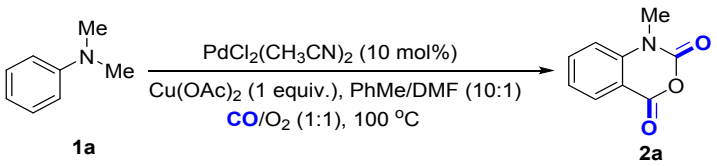
Isatoic anhydride is an important scaffold found in many natural products and valuable pharmaceuticals with various biological activities.[7] Consequently, considerable efforts have been made to develop efficient methods for the synthesis of isatoic anhydride derivatives. However, present methods for the synthesis of isatoic anhydrides involve cyclization of anthranilic acid by highly toxic chloroformate or triphosgene.[8] Based on our continuous interest in trasition-metal-catalyzed oxidative carbonylation and C-N bond activition,[9] we designed a reasonable approach to synthesize isatoic anhydrides utilizing palladium-catalyzed multi-step tandem carbonylation/*N*-dealkylation/carbonylation reaction with alkyl as leaving group and tertiary anilines as nitrogen nucleophiles (Scheme 1).

Scheme 1. Strategies towards Syntheses of Isatoic Anhydrides.



We began our investigation by utilizing *N*, *N*-dimethylaniline(**1a**) as a model substrate in the presence of 1 atm CO/O_2, using $PdCl_2$ as catalyst and $Cu(OAc)_2$ as oxidant in a mixed solvent of toluene and DMF (10:1) at 100 °C, which afforded **2a** in only 27% (Table 1, entry 1). Gratifyingly, the experiment results showed that the yield increased obviously when $PdCl_2(CH_3CN)_2$ was used as a catalyst (Table 1, entry 4). Furthermore, O_2 was vital to the reaction, the corresponding yield was decreased to 17% without the use of O_2 (Table 1, entry 7). By switching different oxidants, we found that other common oxidants such as CuO, BQ, $K_2S_2O_8$, Ag_2CO_3 and $CuCl_2$ turned out to be unfavorable in the system (Table 1, entries 8-12). No product was detected without the addition of $Cu(OAc)_2$ (Table 1, entry 13). It is worth noting that other solvents including toluene, DMF, DMSO, CH_3CN and dioxane are less effective in the system (Table 1, entries 14-18). Furthermore, the ratio variation of the mixed solvent also led to lower yields (Table 1, entries 19 and 20). Decreasing and increasing the reaction temperature slowed the reaction, affording 45% and 55% yields of **2a** (Table 1, entries 21 and 22).

Table 1. Optimization of the Reaction Conditions [a]



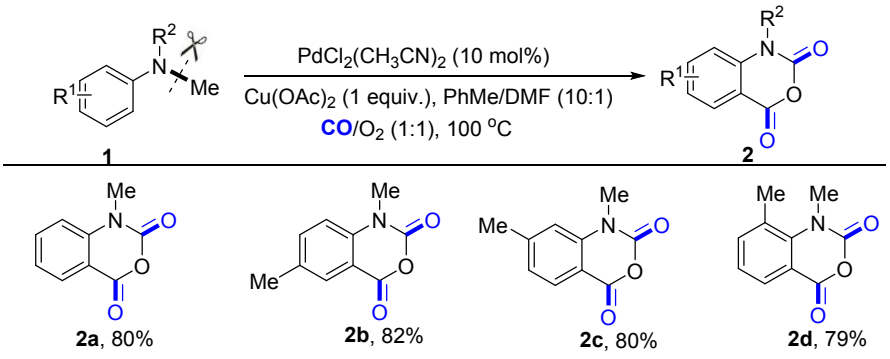
entry	[Pd]	oxidant	solvent	yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	27
2	$Pd(OAc)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	0
3	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	49
4	**$PdCl_2(CH_3CN)_2$**	**$Cu(OAc)_2$**	**PhMe/DMF (10:1)**	**80**
5	$PdBr_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	Trace
6	PdI_2	$Cu(OAc)_2$	PhMe/DMF (10:1)	Trace
7[c]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	17
8	$PdCl_2(CH_3CN)_2$	CuO	PhMe/DMF (10:1)	0
9	$PdCl_2(CH_3CN)_2$	BQ	PhMe/DMF (10:1)	0
10	$PdCl_2(CH_3CN)_2$	$K_2S_2O_8$	PhMe/DMF (10:1)	0
11	$PdCl_2(CH_3CN)_2$	Ag_2CO_3	PhMe/DMF (10:1)	0
12	$PdCl_2(CH_3CN)_2$	$CuCl_2$	PhMe/DMF (10:1)	Trace
13	$PdCl_2(CH_3CN)_2$	----	PhMe/DMF (10:1)	0
14	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe	0
15	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	DMF	10
16	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	DMSO	0
17	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	CH_3CN	0
18	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	dioxane	0
19	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (5:1)	37
20	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (1:1)	21
21[d]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	45
22[e]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	55
23[f]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	PhMe/DMF (10:1)	12

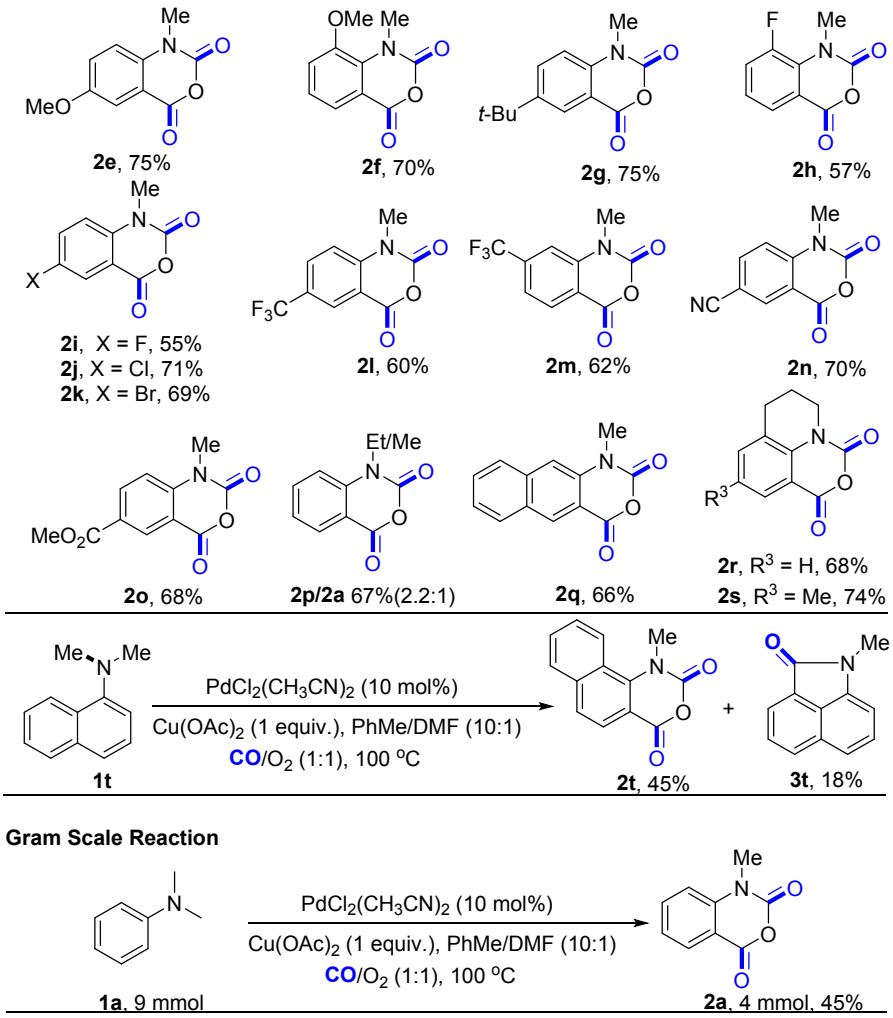
[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), [Pd] (10 mol %), oxidant (1 equiv), CO/O_2 (1:1) 1 atm, 100 °C, 24 h. [b]Isolated yield. [c]Reactions were carried out without O_2. [d]The reaction temperature is 90 °C. [e]The reaction temperature is 110 °C. [f]The loading of $Cu(OAc)_2$ is 10 mol %.

With the optimized conditions in hand, the carbonylation of a variety of *N*, *N*-dialkylanilines were tested (Table 2). *N*, *N*-dimethylanilines substituted with electron-donating (methyl, methoxy and *tert*-butyl) groups in different positions all

gave the corresponding substituted isatoic anhydrides in good yields (**2b**-**2g**). *N*, *N*-dimethylanilines bearing halogens and electron-withdrawing substituents reacted satisfactorily to give the corresponding products in moderate yields (**2h**-**2o**). Interestingly, when *N*-ethyl-*N*-methylaniline was used as substrate, two types of products **2p** and **2a** were obtained in 46% and 21% yields respectively, indicating that the less sterically hindered alkyl group is much more facile for cleavage.[10] The isatoic anhydride **2q** from the carbonylation of *N*, *N*-dimethylnaphthalen-2-amine **1q** was observed as the only product in 66% yield. Moreover, the carbonylation of 1-methyl-1,2,3,4-tetrahydroquinoline **1r** and 1,6-dimethyl-1,2,3,4-tetrahydroquinoline **1s** proceeded smoothly to give the tricyclic isatoic anhydrides **2r** and **2s** in 68% and 74% yields respectively. To our surprise, *N*, *N*-dimethylnaphthalen-1-amine afforded the corresponding isatoic anhydride **2t** in 45% yield, in which 1-methylbenzo[*cd*]indol-2(1*H*)-one **3t** was detected as a byproduct.[11]

Table 2. Palladium-Catalyzed Multi-step Tandem Carbonylation/N-dealkylation/Carbonylation Reaction of *N*, *N*-dimethyl Anilines[a]

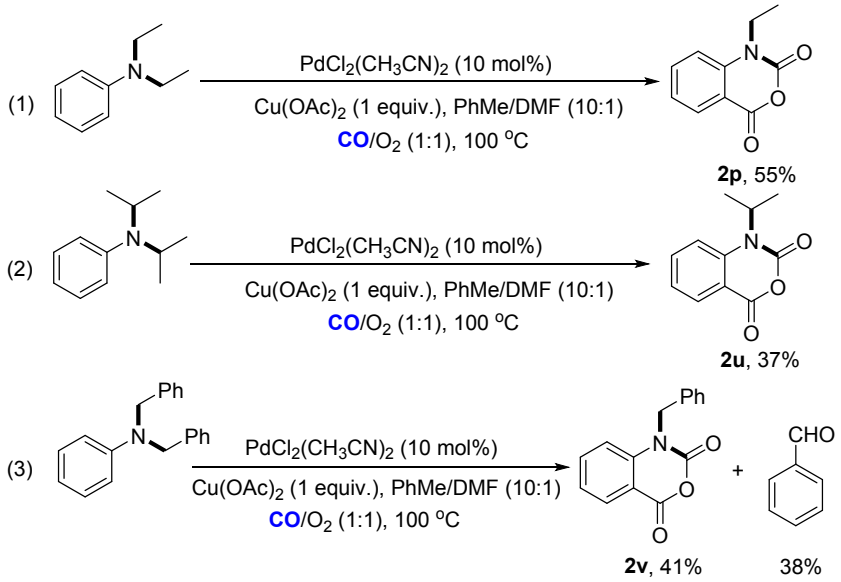




[a]Reaction conditions: **1** (0.2 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), $Cu(OAc)_2$ (0.2 mmol), PhMe/DMF (10: 1) (2.5 mL), CO/O_2 (1:1) 1 atm, 100 °C, 24 h. Yields referred to isolated yields.

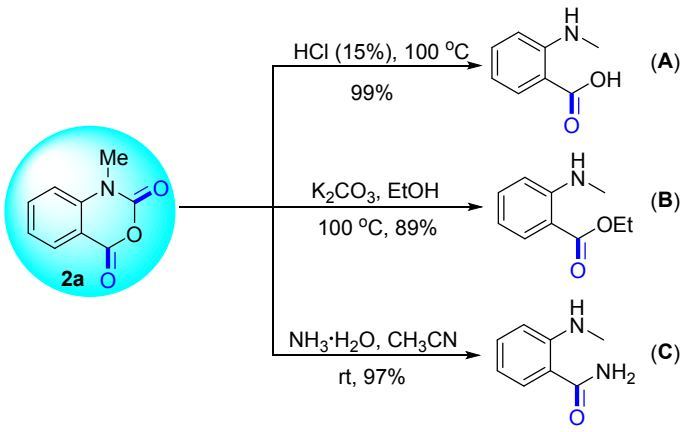
Furthermore, this protocol could also be applied to *N*, *N*-dialkylanilines with different *N*-alkyl substituents (Scheme 2). When *N*, *N*-diethylaniline and *N*, *N*-diisopropylaniline were employed as a substrates, the reaction also took place smoothly to furnish the desired isatoic anhydrides **2p** and **2u** in 55% and 37% yields (Scheme 2, Eq. 1 and Eq. 2). The reaction of *N*, *N*-dibenzylaniline afforded the desired product **2v** in 41% yield as well as 38% yield of benzaldehyde, which indicated that the benzyl group was converted into benzaldehyde by C-N bond cleavage in our reaction system (Scheme 2, Eq. 3).[12]

Scheme 2. Palladium-Catalyzed Multi-step Tandem Carbonylation/N-dealkylation/Carbonylation Reaction of *N*, *N*-dialkyl Anilines[a]



[a]Reaction conditions: *N*, *N*-dialkylanilines (0.2 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), $Cu(OAc)_2$ (0.2 mmol), toluene/DMF (10: 1) (2.5 mL), CO/O_2 (1:1) 1 atm, 100 °C, 24 h. Yields referred to isolated yields.

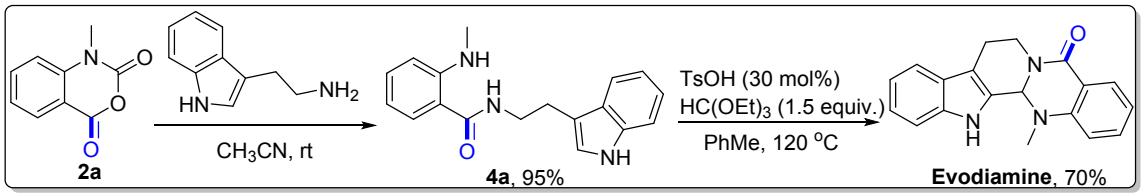
Scheme 3. Subsequent Decarboxylative Transformations



To demonstrate the utility of this protocol, isatoic anhydride **2a** was easily transformed into *N*-methylanthranilic acid **A**, ethyl 2-(methylamino)benzoate **B** and 2-(methylamino)benzamide **C** (Scheme 3). Through our protocol, we could

achieve these products in high yields starting from isatoic anhydride **2a** via a series of decarboxylative transformations.

In order to highlight the synthetic application of the carbonylation product isatoic anhydrides, we successfully converted our product **2a** to the clinically useful Evodiamine with 70% overall yield (Scheme 4).[13] Compared with previously reported procedures for the synthesis of Evodiamine, our synthetic protocol is much more facile and convenient.[14]

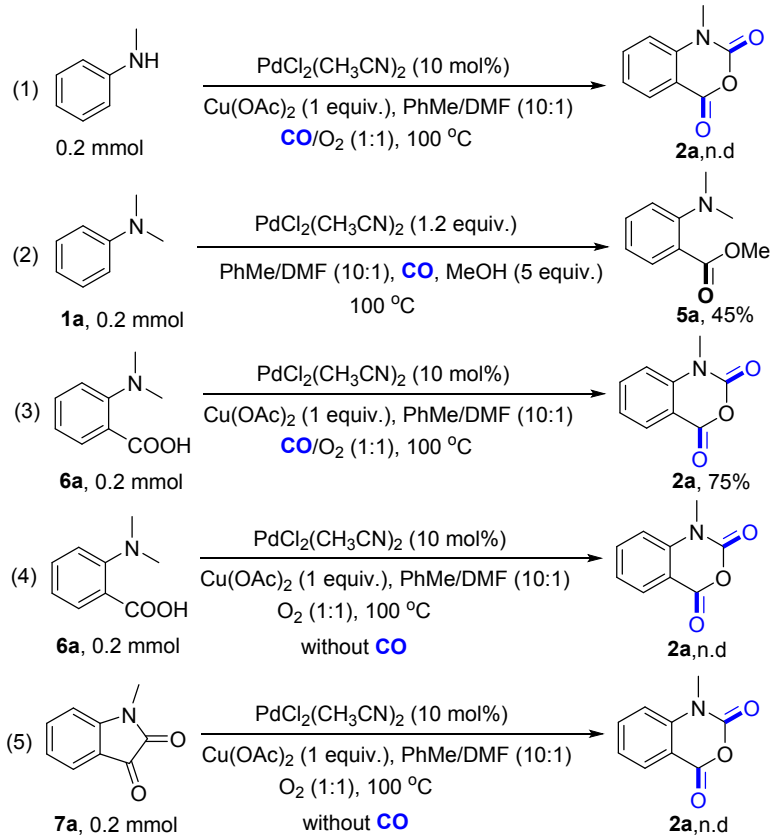


Scheme 4. Synthesis of Evodiamine

To gain some preliminary understanding of the reaction mechanism, control experiments were carried out. Firstly, no desired product was detected by utilizing *N*-methylaniline as the substrate under the standard conditions, which indicated that this transformation is different from Guan's research for the synthesis of isotoic anhydrides starting from *N*-methylaniline (Scheme 5, Eq. 1).[15] Furthermore, when **1a** was used to react with MeOH (5 eq.) using 1.2 eq. of $PdCl_2(CH_3CN)$, corresponding oxidative C-H alkyloxycarbonylation product **5a** was detected, indicating that the *N*, *N*-dimethylamino group could be directly used as the directing group (Scheme 5, Eq. 2). Under the standard conditions, 2-(dimethylamino)benzoic acid **6a** underwent carbonylation reaction smoothly to afford **2a** in 75% yield, indicating that **6a** was the intermediate in the catalytic system (Scheme 5, Eq. 3). Additionally, no product was detected starting from **6a**

without the use of CO, which implied that the carbonyl source is not from the methyl group of DMF (Scheme 5, Eq. 4). To our delight, no reaction occured starting from 1-methylindoline-2,3-dione **7a**, a possible precursor of **2a**, indicating that **7a** was not the intermediate in this catalytic system (Scheme 5, Eq. 5).

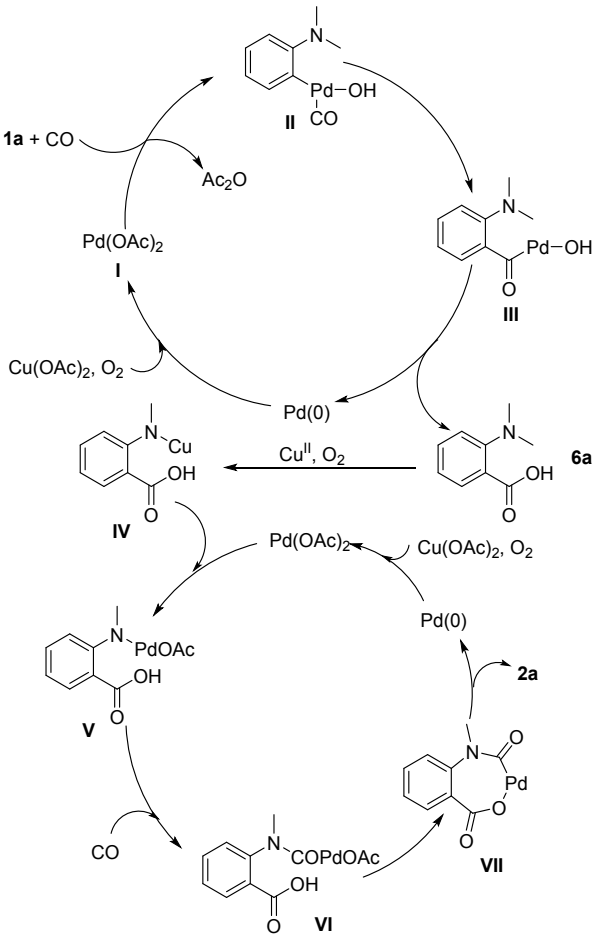
Scheme 5. Preliminary Mechanistic Studies



Huang et al. proposed that C-N bond activation was promoted by copper and oxygen. The above experimental results induced us to propose a mechanism for this novel palladium-catalyzed multi-step tandem carbonylation/*N*-dealkylation/carbonylation reaction (Scheme 6).[15-16] Taking *N*, *N*-dimethylaniline **1a** as an example, the electrophilic palladation of **1a** afforded the intermediate **II**, followed by CO insertion and reductive elimination produced intermediate **6a**. Then, **6a** underwent C-N bond cleavage in the presence of copper

salts and O_2, giving the intermediate **IV**, which further underwent transmetalation with palladium catalyst and sencondary CO insertion to form the intermediate **VI**. The subsequent nucleophilic reaction and reductive elimination afforded the annulation product **2a** and released Pd(0) species, which was oxidized by copper salts and oxygen to regenerate Pd(II).

Scheme 6. Proposed mechanism



In conclusion, we have developed a novel palladium-catalyzed multi-step tandem carbonylation/*N*-dealkylation/carbonylation reaction of tertiary aniline to form isotoic anhydrides. Moderate to good yields were obtained and a variety of functional groups were tolerated. This transformation provides an effective and straightforward method

towards the synthesis of biologically and medicinally useful Evodiamine from commercial and simple substrate *N*, *N*-dimethylaniline. Preliminary mechanism studies revealed that the *N*, *N*-dimethylamino group could be directly used as the directing group. A detailed mechanistic investigation and further application in C-N bond cleavage transformations are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All purchased reagents and solvents were used without further purification unless otherwise noted. Melting points were measured with a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX-400 or Bruker DRX-600 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively. TLC was performed by using commercially prepared 100-400 mesh silica gel plates and visualization was effected at 254 nm.

General Procedure for the Synthesis of *N*-methyl isatoic anhydrides.[15] The mixture of **1** (0.2 mmol, 1.0 equiv), $Cu(OAc)_2$ (0.2 mmol， 1.0 equiv) and $PdCl_2(CH_3CN)_2$ (0.02 mmol, 0.1 equiv) was stirred in PhMe/DMF(10:1) (2.5 mL/mmol) in an oil bath at 100 °C, in a 20 mL tube with a balloon CO/O_2 (1:1). When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3×10 mL) or CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding isatoic anhydrides **2** with

CH_2Cl_2 /ethyl acetate as the eluent (the synthesis of other compound 2 was previously reported).[15]

Experimental Procedure for Evodiamine. (a) The mixture of 1-Methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (**2a**) (1.0 mmol) and 2-(1*H*-indol-3-*yl*)ethan-1-amine (1.0 mmol) were stirred in CH_3CN in an oil bath at room temperature for 8 h. The desired products **4a** were obtained in 95% yield; (b) The mixture of **4a** (1.0 mmol), TsOH (0.3 mmlol) and triethoxy methane (1.5 mmol) were stirred and refluxed in toluene in an oil bath at 120 °C. The desired products Evodiamine were obtained in 74% yield after purified by column chromatography on silica gel with mixture of petroleum ether and ethyl acetate.

Experimental Procedure for Gram Scale Reaction

The mixture of **1a** (1089.0 mg, 9.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (1620.0 mg, 9.0 mmol， 1.0 equiv) and $PdCl_2(CH_3CN)_2$ (232.2 mg, 0.9 mmol, 0.1 equiv) was stirred in PhMe/DMF(10:1) (25 mL/mmol) in an oil bath at 100 °C, in a 100 mL round-bottom flask with a balloon CO/O_2 (1:1). When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (50 mL) and extracted with EtOAc (3×50 mL) or CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding isatoic anhydrides **2a** (716.6 mg, 45%) with CH_2Cl_2 /ethyl acetate as the eluent.

1-Methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2a)

Yield 28.3 mg (80%, white solid); mp 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.9 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.0, 152.7, 135.7, 132.6, 114.6, 110.9, 108.6, 29.6. HRMS Calcd (ESI-TOF) m/z for $C_9H_7NNaO_3$ $[M+Na]^+$, 200.0318; Found 200.0326.

1,6-Dimethyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2b)

Yield 31.3 mg (82%, white solid); mp 166-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 3.56 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 148.0, 139.9, 138.4, 134.2, 130.3, 113.9, 111.4, 31.8, 20.4. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_9NNaO_3$ $[M+Na]^+$, 214.0475; Found 214.0482.

1,7-Dimethyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2c)

Yield 30.6 mg (80%, brown solid); mp 162-164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 1H), 6.51 (s, 1H), 6.48 (d, J = 8.1 Hz, 1H), 2.95 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 174.1, 174.1, 152.7, 146.7, 132.6, 116.1, 111.1, 106.3, 29.6, 22.3. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_9NNaO_3$ $[M+Na]^+$, 214.0475; Found 214.0480.

1,8-Dimethyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2d)

Yield 30.2 mg (79%, brown solid); mp 187-188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (dd, J = 7.7, 1.7 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 3.56 (s, 3H), 2.57 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.0, 149.6, 143.0, 141.4, 127.8, 126.7, 124.6, 114.5, 38.5, 22.2. HRMS Calcd (ESI-TOF) m/z for

$C_{10}H_9NNaO_3$ $[M+Na]^+$, 214.0475; Found 214.0480.

6-Methoxy-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2e)

Yield 31.1 mg (75%, brown solid); mp 238-239 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (m, 3H), 3.84 (s, 3H), 3.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.4, 155.7, 148.1, 136.8, 125.5, 117.1, 112.7, 111.3, 56.3, 32.2. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_{10}NO_4$ $[M+H]^+$, 208.0604; Found 208.0606.

8-Methoxy-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2f)

Yield 28.9 mg (70%, white solid); mp 162-164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (dd, J = 7.8, 1.4 Hz, 1H), 7.53 (dd, J = 8.2, 1.5 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.6, 149.1, 148.6, 132.9, 125.3, 121.5, 121.4, 114.7, 57.5, 37.4. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_{10}NO_4$ $[M+H]^+$, 208.0604; Found 208.0606.

6-(tert-Butyl)-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2g)

Yield 34.9 mg (75%, white solid); mp 165-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 3.58 (s, 3H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 148.1, 147.6, 139.8, 135.0, 127.0, 113.7, 111.2, 34.6, 31.8, 31.1. HRMS Calcd (ESI-TOF) m/z for $C_{13}H_{16}NO_3$ $[M+H]^+$, 234.1125; Found 234.1127.

8-Fluoro-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2h)

Yield 22. mg (57%, white solid); mp 205-206 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.49 (dd, J = 9.8, 3.2 Hz, 1H), 7.29 (ddd, J = 9.2, 8.0, 3.2 Hz, 1H), 6.68 (dd, J = 9.2, 4.5 Hz, 1H), 2.82 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 169.6, 152.5 (d, J =

228.0 Hz), 149.2, 130.1, 122.3 (d, J = 22.5 Hz), 112.6 (d, J = 6.0 Hz), 116.9 (d, J = 22.5 Hz), 110.6, 30.0. HRMS Calcd (ESI-TOF) m/z for $C_9H_6FNO_3Na$ $[M+Na]^+$, 218.0224; Found 218.0226.

6-Fluoro-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2i)

Yield 21.5 mg (55%, yellow solid); mp 137-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (t, J = 8.2 Hz, 2H), 7.50 (dd, J = 8.7, 4.0 Hz, 1H), 3.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.6 (d, J = 3.0 Hz), 158.1 (d, J = 158.0 Hz), 147.9, 139.4 (d, J = 1.0 Hz), 125.0 (d, J = 23.0 Hz), 117.8 (d, J = 8.0 Hz), 115.0 (d, J = 25.0 Hz), 113.3 (d, J = 9.0 Hz), 32.4. HRMS Calcd (ESI-TOF) m/z for $C_9H_6FNO_3Na$ $[M+Na]^+$, 218.0224; Found 218.0225.

6-Chloro-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2j)

Yield 29.9 mg (71%, white solid); mp 118-119 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 9.0, 2.6 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 3.46 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.5, 147.9, 141.6, 137.1, 128.4, 128.1, 117.6, 113.7, 32.4. HRMS Calcd (ESI-TOF) m/z for $C_9H_6ClNNaO_3$ $[M+Na]^+$, 233.9928, Found: 233.9936.

6-Bromo-1-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2k)

Yield 35.1 mg (69%, white solid); mp 202-203 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 8.9, 2.4 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 3.45 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.4, 147.9, 141.9, 139.9, 131.3, 117.8, 115.6, 114.1, 32.4. HRMS Calcd (ESI-TOF) m/z for $C_9H_6BrNNaO_3$ $[M+Na]^+$, 277.9423; Found 277.9424.

1-Methyl-6-(trifluoromethyl)-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2l)

Yield 29.4 mg (60%, brown solid); mp 188-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43-8.05 (m, 2H), 7.65 (d, J = 8.8 Hz, 1H), 3.52 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.6, 147.9, 145.5, 133.7 (q, J = 3.0 Hz), 126.6 (q, J = 4.0 Hz), 124.3 (q, J = 33.0 Hz), 124.0 (d, J = 270.0 Hz), 116.7, 112.8, 32.5. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_7F_3NO_3$ $[M+H]^+$, 246.0373; Found 246.0373.

1-Methyl-7-(trifluoromethyl)-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2m)

Yield 30.4 mg (62%, white solid); mp 136-137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 3.53 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.7, 147.9, 143.3, 136.5 (q, J = 32.0 Hz), 131.1, 123.7 (q, J = 272.0 Hz), 120.1 (q, J = 3.0 Hz), 115.6, 112.5 (q, J = 4.0 Hz), 32.5. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_7F_3NO_3$ $[M+H]^+$, 246.0373; Found 246.0373.

1-Methyl-2,4-dioxo-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazine-6-carbonitrile (2n)

Yield 28.3 mg (70%, white solid); mp 235-236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 3.50 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.1, 147.8, 145.7, 140.2, 134.2, 118.0, 116.7, 113.2, 106.4, 32.6. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_7N_2O_3$ $[M+H]^+$, 203.0451; Found 203.0453.

Methyl 1-methyl-2,4-dioxo-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazine-6-carboxylate (2o)

Yield 31.9 mg (68%, yellow solid); mp 163-164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ δ 8.40 (d, J = 1.8 Hz, 1H), 8.28 (dd, J = 8.7, 2.2 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H),

3.89 (s, 3H), 3.50 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 165.1, 158.8, 147.9, 145.9, 137.4, 130.7, 124.9, 116.0, 115.9, 112.3, 52.9, 32.5. HRMS Calcd (ESI-TOF) m/z for $C_{11}H_{10}NO_5$ $[M+H]^+$, 236.0553; Found 236.0557.

1-Ethyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2p)

Yield 17.6 mg (46%, white solid); mp 123-125 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (dd, J = 7.9, 1.6 Hz, 1H), 7.77 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 159.5, 147.8, 141.6, 137.7, 130.1, 124.0, 115.1, 112.3, 40.00, 12.4. HRMS Calcd (ESI-TOF) m/z for $C_{10}H_9NO_3Na$ $[M+Na]^+$, 214.0475; Found 214.0478.

1-**Methyl-2*H*-naphtho[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione (2q)**

Yield 29.9 mg (66%, brown solid); mp 222-224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 3.54 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 159.5, 148.0, 137.6, 137.4, 132.4, 130.8, 129.9, 128.9, 127.9, 126.4, 112.3, 111.3, 32.4. HRMS Calcd (ESI-TOF) m/z for $C_{13}H_{10}NO_3$ $[M+H]^+$, 228.0655; Found 228.0658.

6,7-Dihydro-1*H*,3*H*,5*H*-[1,3]oxazino[5,4,3-*ij*]quinoline-1,3-dione (2r)

Yield 27.6 mg (68%, white solid); mp 184-186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 7.8 Hz, 1H), 7.62 (dd, J = 7.4, 1.4 Hz, 1H), 7.22 (td, J = 7.7, 1.5 Hz, 1H), 3.88 (td, J = 5.6, 1.4 Hz, 2H), 2.86 (t, J = 6.2 Hz, 2H), 2.18-1.82 (hept, J = 4.3 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 159.6, 147.6, 139.0, 137.0, 127.7, 125.9,

123.6, 111.5, 44.2, 26.3, 20.1. HRMS Calcd (ESI-TOF) m/z for $C_{11}H_{10}NO_3$ $[M+H]^+$, 204.0655; Found 204.0658.

9-Methyl-6,7-dihydro-1*H*,3*H*,5*H*-[1,3]oxazino[5,4,3-*ij*]quinoline-1,3-dione (2s)

Yield 32.1 mg (74%, white solid); mp 220-221 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (s, 1H), 7.45 (s, 1H), 4.07-3.60 (m, 2H), 2.81 (t, J = 6.2 Hz, 2H), 2.31 (s, 3H), 1.97 (p, J = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.6, 147.6, 137.9, 136.9, 133.0, 127.2, 125.9, 111.2, 44.1, 26.2, 20.4, 20.2. HRMS Calcd (ESI-TOF) m/z for $C_{12}H_{12}NO_3$ $[M+H]^+$, 218.0812; Found 218.0820.

1-Methyl-2*H*-naphtho[1,2-*d*][1,3]oxazine-2,4(1*H*)-dione (2t)

Yield 20.4 mg (45%, brown solid); mp 69-70 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.85 (q, J = 8.5 Hz, 2H), 7.77 (t, J = 7.0 Hz, 1H), 7.67 (t, J = 7.1 Hz, 1H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.9, 150.2, 143.9, 138.6, 130.2, 129.4, 127.0, 126.6, 125.5, 123.0, 122.9, 110.4, 41.5. HRMS Calcd (ESI-TOF) m/z for $C_{13}H_{10}NO_3$ $[M+H]^+$, 228.0655; Found 228.0659.

1-Methylbenzo[*cd*]indol-2(1*H*)-one (3t)

Yield 13.1 mg (18%, white solid); mp 77-79 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 8.1, 6.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 8.4, 7.0 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 3.42 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.30, 140.17, 130.78, 129.07, 128.72, 128.57, 126.87, 125.20, 124.28, 120.39, 104.75, 26.40. HRMS Calcd (ESI-TOF) m/z for $C_{12}H_{10}NO$ $[M+H]^+$, 184.0757; Found 184.0759.

1-Isopropyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2u)

Yield 15.2 mg (37%, white solid); mp 115-116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.29 – 7.21 (m, 1H), 4.77 (d, *J* = 8.3 Hz, 1H), 1.59 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 159.06, 146.34, 141.87, 137.09, 131.10, 123.84, 114.32, 112.39, 50.09, 19.34. HRMS Calcd (ESI-TOF) m/z for $C_{11}H_{11}NO_3Na$ $[M+Na]^+$, 228.0631; Found 228.0637.

1-Benzyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (2v)

Yield 20.7 mg (41%, white solid); mp 136-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.83-7.61 (m, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.39-7.21 (m, 5H), 5.30 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.3, 148.8, 141.8, 137.5, 135.8, 130.0, 129.1, 127.9, 127.1, 124.2, 115.6, 112.5, 48.1. HRMS Calcd (ESI-TOF) m/z for $C_{15}H_{12}NO_3$ $[M+H]^+$, 254.0812; Found 254.0819.

2-(Methylamino)benzoic acid (A)

Yield 29.9 mg (99%, brown solid); mp 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.39-7.33 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.60-6.56 (m, 1H), 2.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.2, 151.2, 133.6, 128.2, 114.4, 113.0, 111.4, 29.7.

Ethyl 2-(methylamino)benzoate (B)

Yield 31.8 mg (89%, white solid); mp 38-39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.54- 6.45 (m, 2H), 4.20 (q, *J* = 7.0 Hz,

2H), 1.26 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168. 7, 151.9, 134.5, 131.5, 114.4, 110.8, 110.4, 60.2, 14.4.

2-(Methylamino)benzamide (C)

Yield 29.1 mg (97%, white solid); mp 161-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 6.71, 6.69-6.62 (m, 2H), 2.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.9, 152.5, 135.7, 132.6, 114.7, 111.1, 108.8, 29.7.

N-(2-(1*H*-indol-3-*yl*)ethyl)-2-(methylamino)benzamide (4a)

Yield 55.7 mg (95%, yellow solid); mp 207-209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.12-7.08 (m, 2H), 6.95 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.48 (t, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 3.70 (q, *J* = 6.4 Hz, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 2.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 150.5, 136.5, 132.8, 127.3, 127.2, 122.2, 122.2, 119.5, 118.8, 115.5, 114.6, 113.0, 111.4, 111.2,40.0, 30.0, 254. HRMS Calcd (ESI-TOF) m/z for $C_{18}H_{20}N_3O$ $[M+H]^+$, 294.1601; Found 294.1600.

Evodiamine

Yield 42.2 mg (70%, yellow solid); mp 277-278 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.48-7.47 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.13-6.95 (m, 4H), 6.12 (s, 1H), 4.66- 4.62 (m, 1H), 3.23-3.17 (m, 1H), 2.94-2.78 (m, 5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 164.7, 149.3, 137.0, 133.9, 131.1, 128.5, 126.5, 122.3, 120.8, 119.8, 119.4, 118.7, 118.0, 112.1, 112.0, 70.2, 41.3, 36.9, 20.0. HRMS Calcd (ESI-TOF) m/z for $C_{19}H_{18}N_3O$ $[M+H]^+$, 304.1444; Found 304.1444.

Supporting Information

^{1}H and ^{13}C NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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