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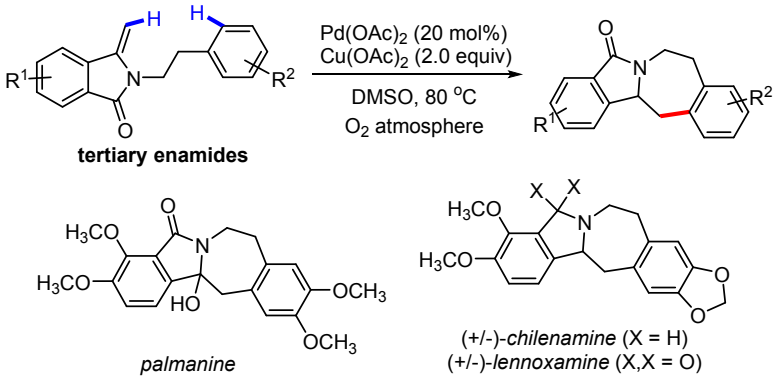
Intramolecular Arylation of Tertiary Enamides through $Pd(OAc)_2$-catalyzed Dehydrogenative Cross-coupling Reaction: Construction of Fused *N*-Heterocyclic Scaffolds and Synthesis of Isoindolobenzazepine Alkaloids

Wenju Zhu,[1,2] Shuo Tong,[2,*] Jieping Zhu,[3] Mei-Xiang Wang[2,*]

[1] State Key Laboratory of Separation Membranes and Membrane Processes, School of Chemistry and Chemical Engineering Tianjin Polytechnic University, Tianjin, 300387, China

[2] MOE Key Laboratory of Bioorganic Phosphorous Chemistry and Chemical Biology, Department of Chemistry, Tsinghua University, Beijing 100084, China

[3] Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland

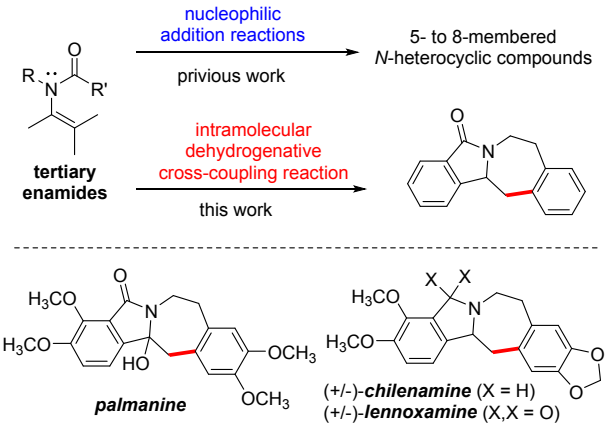


ABSTRACT: $Pd(OAc)_2$-catalyzed intramolecular dehydrogenative cross-coupling reaction between tertiary enamides, which were derived from the condensation of 2-arylethylamines and methyl *o*-acetylbenzoate, and arenes enabled synthesis of 7,8-dihydro-5*H*-benzo[4,5]azepino[2,1-a]isoindol-5-one derivatives under mild conditions. The synthetic method was applied in the total synthesis of aporhoeadane alkaloids *palmanine*, *lennoxamine* and *chilenamine* in only three or four steps.

INTRODUCTION

Enamines are powerful synthetic intermediates and find wide applications in organic synthesis.[1] When one of the *N*-alkyl groups of an enamine is replaced by an electron-withdrawing group such as an acyl, tertiary enamides are generated. In comparison to conventional enamines, tertiary enamides have long been recognized as chemically stable species because of the electron-withdrawing effect of N-acyl group.[2] However, we[3] envisioned that tertiary enamides would be a type of shelf-stable nucleophiles with tunable reactivity based on the cross-conjugational system comprising carbon-carbon double bond, lone-pair electrons on nitrogen atom and carbonyl group (C=C-N-C=O). The enabled regulation of the cross-conjugation system by means of electronic and steric effects of the substituents attached on the enamide segment (C=C-N-C=O), for instance, would enhance the delocalization of the lone-pair electrons of nitrogen into the carbon-carbon-double bone, reviving therefore the nucleophilicity of the tertiary enamides.[3] We have demonstrated in recent years that tertiary enamides behave indeed as nucleophiles to react with epoxides,[4] carbonyls,[5] imines,[6] nitriliums[7] and alkynes.[8] The designed Lewis acid and phosphoric acid catalyzed intramolecular and intermolecular reactions of tertiary enamides with electrophiles provide unique and powerful methods for the synthesis of diverse nitrogenous heterocycles which are not easily obtained by other means[3-9] For example, using tertiary enamides as synthons, various five-,[4b,5a,5b,5e,7c] six-[4b,5c,6,7a,7b,8,9a,9b] and eight-membered[4a,4c] *N*-heterocycles are readily constructed under very mild conditions. Very recently, intramolecular condensation between tertiary enamides and aldehydes led to the facile synthesis of seven-membered 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one derivatives.[5d] To further explore the reactivity of stable tertiary enamides, and also to develop their synthetic applications, we undertook the current study. We report herein an efficient and rapid construction of the 2,3-dihydro-1*H*-benzo[d]azepine, the seven-membered heterocyclic core embedded in 7,8-dihydro-5*H*-benzo[4,5]azepino[2,1-a]isoindol-5-one from intramolecular dehydrogenative cross-coupling of tertiary enamides with arenes. The method has been successfully employed in the total synthesis of aporhoeadane alkaloids *palmanine*, *lennoxamine* and *chilenamine*.

Scheme 1. Exploring tertiary enamides as versatile synthons in organic synthesis

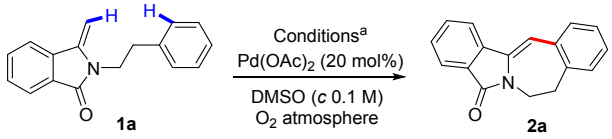


Both 7,8,13,13a-tetrahydro-5*H*-benzo[4,5]azepino[2,1-a]isoindole and 7,8,13,13a-tetrahydro-5*H*-benzo[4,5]azepino[2,1-a]isoindol-5-one scaffolds are found in aporhoeadane alkaloids such as chilenamine, chileninone, lennoxamine, palmanine and pictoamine.[10] Interesting fused heterocyclic structures with sometimes dense functional groups have prompted a myriad of different synthetic approaches. As summarized by Leonard in a review [11] among all synthetic methods reported, late-stage formation of five-membered isoindoline or isoindolinone ring and seven-membered azepine ring, and concurrent construction of the fused five/seven ring system are the most popular strategies by means of various C-C and C-N bond forming protocols. Very recently, intramolecular Suzuki-Miyaura cross-coupling reaction and nucleophilic substitution reaction were applied respectively by Yudin[12] and Yao[13] to assemble the azepine ring, accomplishing the synthesis of 7,8,13,13a-tetrahydro- and 7,8-dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-ones. Inspired by burgeoning dehydrogenative cross-coupling reactions, the more atom-economic and environmentally benign processes,[14] we focused on Palladium-catalyzed direct intramolecular arylation of tertiary enamides.[15] The salient advantage of this design is a one-step access to complexed fused heterocyclic compounds and key intermediates of aporhoeadane alkaloids from tertiary enamides which were prepared conveniently from the condensation of 2-arylethylamines and methyl *o*-acetylbenzoate. It is worth addressing that although intramolecular arylations of enamines through 6-membered palladacycle intermediates are known in the synthesis of indole derivatives,[16] the catalytic C-H bond activation process which proceeds *via* an 8-membered palladacycle (Scheme 1) is very rare and challenging.[17] To our knowledge, no dehydrogenative cross-coupling reactions have ever been used in the synthesis of aporhoeadane alkaloids and their analogs.

RESULTS AND DISCUSSION

We initiated our investigation with evaluating the intramolecular C_{sp}^2-H/C_{arene}-H corss coupling reaction using 3-methylene-2-phenethylisoindolin-1-one **1a** as a model substrate. In the presence of a stoichiometric amount of $Pd(OAc)_2$, the reaction of **1a** under O_2 atmosphere delivered the desired 7,8-dihydro-5*H*-benzo[4,5]azepino[2,1-a]isoindol-5-one **2a** in 68% yield (Table 1, entry 1). However, only a trace amount of **2a** was obtained when $Pd(OAc)_2$ was used as a catalyst (20 mol%) (Table 1, entry 2), implying that O_2 was probably not an effective oxidant to reoxidize Pd(0) to Pd(II). A chemical yield of 12% was obtained after $Cu(OAc)_2$ was added as a terminal oxidant (Table 1, entry 3). Unfortunately, further optimization of reaction conditions by screening reaction media, palladium salts and the oxidants did not lead to the improvement of the efficiency of the catalytic reaction (Supporting information).

Table 1. Optimization of Reaction Conditions



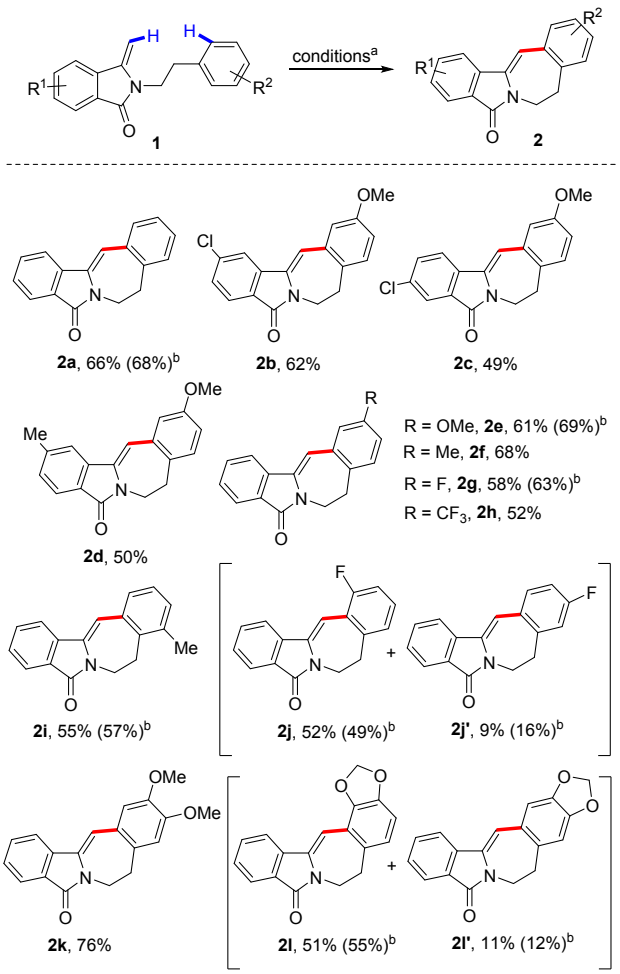
Entry	[Oxi]	Additive (eq)	T (°C)	*t* (h)	**2a** (%)[b]
1[c]	--	--	120	3	68
2	--	--	120	24	tr
3	$Cu(OAc)_2$	--	120	24	12
4	$Cu(OAc)_2$	AcOH (1.5)	120	24	22
5	$Cu(OAc)_2$	TfOH (1.5)	120	24	18
6	$Cu(OAc)_2$	PivOH (1.5)	120	24	41
7	$Cu(OAc)_2$	K_2CO_3 (2.0)	120	24	tr
8	$Cu(OAc)_2$	Py (2.0)	120	24	tr
9	$Cu(OAc)_2$	PivOH (1.5)	150	11	16
10	$Cu(OAc)_2$	PivOH (1.5)	100	13	51
11	$Cu(OAc)_2$	PivOH (1.5)	80	11	61
12	$Cu(OAc)_2$	PivOH (1.5)	60	38	40
13[d]	$Cu(OAc)_2$	PivOH (1.5)	80	36	46
14[e]	$Cu(OAc)_2$	PivOH (1.5)	80	36	48
15[f]	$Cu(OAc)_2$	PivOH (1.5)	80	24	32
16[g]	$Cu(OAc)_2$	PivOH (1.5)	80	11	64
17	$Cu(OAc)_2$	PivOH (3.0)	80	11	66
18	$Cu(OAc)_2$	PivOH (5.0)	80	11	61
19[h]	$Cu(OAc)_2$	PivOH (3.0)	80	12	57

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (2.0 equiv), DMSO (2 mL); [b] Isolated yield; [c] $Pd(OAc)_2$ (1.0 equiv); [d] Air atmosphere; [e] N_2 atmosphere; [f] $Pd(OAc)_2$ (0.1 equiv); [g] $Pd(OAc)_2$ (0.3 equiv) h **1a** (8 mmol) under otherwise identical conditions, **2a** 57% yield, 1.13g.

To our delight, addition of a Brønsted acid greatly improved the transformation (Table 1, entry 4-6). For instance, the presence of pivalic acid (PivOH) (1.5 equiv) resulted in the formation of **2a** in 44% (Table 1, entry 6). Basic reaction condition using either potassium carbonate and pyridine had a detrimental effect on catalysis (Table 1, entry 7-8). Notably, temperature played a crucial role in the conversion of **1a** into **2a**. As indicted by the results compiled in Table 1, the optimal temperature is 80 °C (Table 1, entry 11 vs entry 6, 9, 10, and 12). Oxygen atmosphere was beneficial to facilitate the reaction since reactions slowed down dramatically under air or N_2 atmosphere (entry 13-14). Increase a catalyst loading to 30 mol% did not significantly increase the formation of **2a** whereas a lower catalyst loading (15 mol%) caused the erosion of the chemical yield of the product (Table 1, entry 15-16). Finally, product **2a** was synthesized in 66% yield with the use of 3.0 equiv of PivOH (Table 1, entry 17-18). Overall, the optimum conditions at this stage are comprised of heating a solution of **1a**

with $Pd(OAc)_2$ (0.2 equiv or 1.0 equiv), $Cu(OAc)_2$ (2.0 equiv) and PivOH (3.0 equiv) in DMSO under O_2, from which product **2a** was produced in 66-68% yield. Finally, performing the reaction of **1a** (8 mmol) provided **2a** in 57% yield (1.13g, Table 1, entry 19).

Table 2. Scope of the reaction

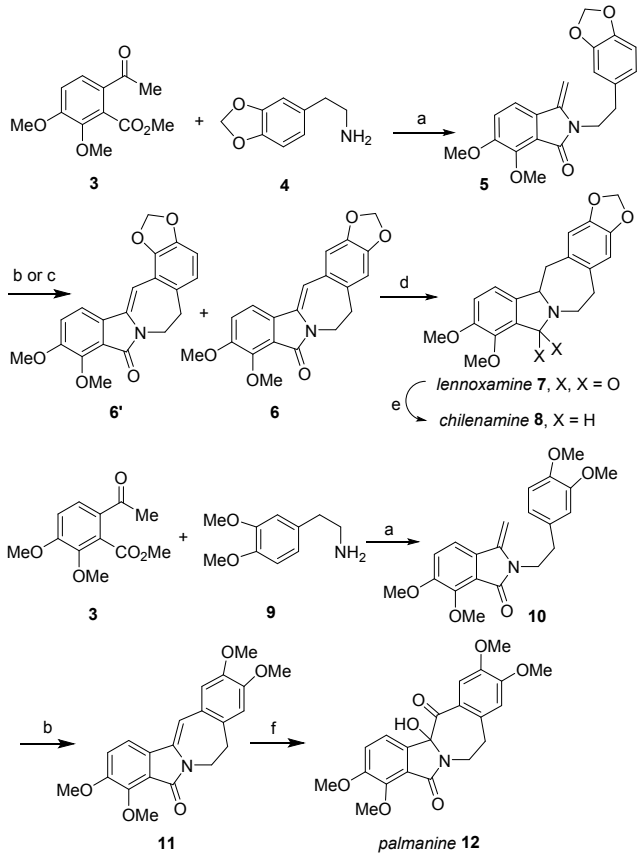


[a] A mixture of **1** (0.2 mmol), $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (2.0 equiv) and PivOH (3.0 eq) was heated at 80 °C in DMSO (2 mL) under oxygen atmosphere. [b] One equivalent $Pd(OAc)_2$ was used under otherwise identical conditions.

With the optimized conditions in hand, the generality of $Pd(OAc)_2$-catalyzed intramolecular dehydrogenative arylation of tertiary enamides was examined. Gratifyingly, all substrates tested underwent cyclization reaction smoothly to afford a variety of 7,8-dihydro-5*H*-benzo[4,5]azepino[2,1-a]isoindol-5-one derivatives in moderate to good yields (Table 2). The nature of and the substitution pattern of a substituent on benzene ring of 2-methyl-3-methyleneisoindolin-1-one unit had a marginal effect on the reaction, as substrates **1a-d** gave the corresponding fused heterocyclic ring products **2a-d** in 49-66% yields. On the other side, the presence of electron-donating group(s) on the arene moiety appeared slightly favorable to the dehydrogenative cross-coupling reaction. Only one regioisomeric product was yielded from the reaction of the substrates which contain a *para*-substituted aryl (**1e-1h**) or an *ortho*-methylphenyl (**1i**). When a fluorine atom was introduced into the *meta* position of arene, the reaction of **1i** produced a mixture of regioisomers **2j** and **2j'** in a total of 61% yield, with a ratio of **2j** over **2j'** being 5.8 : 1. Interestingly, when a pair of regioisomers **2l** (51%) and **2l'** (11%) were also generated similarly from the reaction of benzo[d][1,3]dioxole-bearing substrate **1l**, *N*-2-(3,4-dimethoxyphenethyl)-3-methyleneisoindolin-1-one **1k** underwent cross-coupling reaction to afford product **2k** exclusively. It should be noted that, in some cases, the use of one equivalent of $Pd(OAc)_2$ under otherwise identical conditions increased only slightly the chemical yields of products.

To account for the formation of fused heterocycles, the catalytic arylation proceeds most probably through palladation of tertiary enamides owing to their nucleophilicity to form enamide-palladium species.[18] The following intramolecular C-H activation and carbopalladation gives rise to the formation of an 8-membered palladacycle intermediate which undergoes reductive elimination affording the final product **2** alone with the release of Pd(0). Oxidation of Pd(0) by Cu(II) ion regenerates Pd(II) which enters into the next catalytic cycle (Supporting Information).

Scheme 2. Total synthesis of *lennoxamine* **7**, *chilenamine* **8** and *palmanine* **12**.



Conditions: [a] TsOH (0.05 equiv), toluene, Dean-Stark, reflux, 20 h, **5**, 73%, 20 h, **10**, 67%; [b] $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (2.0 equiv), PivOH (3.0 equiv), DMSO, 80 °C, O_2 atmosphere, 9 h, **6**, 14%, **6'**, 54%, 5.5 h, **11**, 73%; [c] $Pd(OAc)_2$ (1.0 equiv), trichloropropane, 80 °C, 14 h, **6**, 47%, **6'** trace; [d] H_2 (1 atm), Pd/C (10% m/m), EtOAc, rt, 24 h, **7**, 96%; [e] $LiAlH_4$ (5.0 equiv), THF, 80 °C, **8**, 93%; [f] *m*-CPBA (2.5 equiv), THF, rt, 2 h, **12** 43%.

To demonstrate the synthetic utility of the method developed, total synthesis of natural products *lennoxamine*, *chilenamine* and *palmanine* was conducted. As illustrated in Scheme 2, one-step condensation of methyl 2-acetylbenzoate **3** with amines **4** and **9** produced tertiary enamides **5** and **10**, respectively, in 73% and 67% yields. Under the aforementioned optimal catalytic reaction conditions, intramolecular arylation of enamide **10** afforded a good

yield of **11** regioselectively while the reaction of **5** gave a pair of regioisomers **6** and **6'** in 68% yield. Unfortunately, the undesired angularly fused heterocyclic ring compound **6'**, which structure was unambiguously determined by single crystal X-ray diffraction analysis (see Supporting Information for detail), was obtained as a major product.[19] However, slight modification of the conditions (Supporting Information) by using one equivalent of $Pd(OAc)_2$ and 1,2,3-trichloropropane as reaction media, the targeted isomer **6** was synthesized predominantly in an acceptable yield. Catalytic hydrogenation of the carbon-carbon double bond of **6** provided *lennoxamine* **7** in a nearly quantitative yield. Further reduction of lactam **7** with $LiAlH_4$ in THF yielded efficiently *chilenamine* **8** in 93% yield. The synthesis of *palmanine* **12** was accomplished from the treatment of **12** with *m*-CPBA. The structure of *palmanine* **12** was confirmed for the first time by X-ray crystallography (see Supporting Information for detail).[19]

In summary, we have developed a $Pd(OAc)_2$-catalyzed intramolecular arylation of tertiary enamides through an oxidative dehydrogenative cross-coupling process. This reaction enabled one-step construction of isoindolobenzazepine fused heterocyclic ring structure. The developed synthetic method was applied successfully in the step-economic total synthesis of aporhoeadane alkaloids *palmanine, lennoxamine* and *chilenamine*.

EXPERIMENTAL SECTION

General Information. Reagents and solvents were purchased from commercial sources and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted. All reactions were performed under nitrogen or oxygen and stirring unless otherwise noted. When needed oven dried glassware was used (T°>100 °C) or under vacuum with a heat gun (T°>200 °C). Anhydrous solvents were purified and dried following standard procedures. Flash column chromatography was performed using Silicycle SiliaFlash® P60 200-300 mesh. TLC analysis was performed on pre-coated, glass-backed silica gel plates. TLC's were revealed by UV fluorescence (254 nm) then one of the following: $KMnO_4$, phosphomolybdic acid, ninhydrin, pancaldi, p-anisaldehyde, vanillin. Melting points were uncorrected. The ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on a JEOL ECX-400 400 MHz spectrometers. ^1H NMR chemical shifts were reported relative to residual $CDCl_3$ (7.26 ppm). $^{13}C\{^1H\}$ NMR chemical shifts were reported relative to the central line of $CDCl_3$ (77.16 ppm). Abbreviations are used in the description of NMR data as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant (*J*, Hz). The high resolution mass spectra (HRMS) were recorded on a GCT-MS Micromass UK spectrometer or a microTOF-Q spectrometer. Infrared spectra were recorded using a PerkinElmer Spectrum 100 FT-IR spectrometer with KBr pellets in the 4000-400 cm−1 region.

General procedure for the synthesis of substrate 1. A solution of aniline (5.0 mmol), 2-acetylbenzoic acid (5.0 mmol) and $TsOH{\cdot}H_2O$ (43 mg, 0.25 mmol, 0.05 equiv) in toluene (10 mL) was held at reflux for 12 h using a Dean–Stark apparatus. After being cooled to room temperature, the solvent was evaporated in vacuo and the residue was diluted in EtOAc (100 mL). The organic phase was washed with 1.0 M NaOH (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by column chromatography to give the final product **1**.

3-Methylene-2-phenethylisoindolin-1-one (1a): (997 mg, 80% yield) white solid, mp.85-86 °C; R_f = 0.44 (EtOAc/petroleum ether = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.56 (td, *J* = 7.6, 0.9 Hz, 1H), 7.48 (td, *J* = 7.3, 0.9 Hz, 1H), 7.31 - 7.20 (m, 5H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 4.01-3.97 (m, 2H), 2.97 (t, *J* = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 141.5, 138.4, 136.2, 133.8, 131.8, 129.3, 129.2, 128.7, 128.5 126.5, 123.1, 122.9, 119.8, 88.5, 40.9, 34.5; IR (KBr, cm^{-1}): *v* 1699, 1644, 1396. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{17}H_{16}NO$ 250.1226; Found: 250.1228.

2-(4-methoxyphenethyl)-5-chloro-3-methyleneisoindolin-1-one (1b): (1.03g, 73% yield) yellow solid, mp.125-126 °C; R_f = 0.60 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 1.8, 0.4 Hz, 1H), 7.60 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.86 – 6.80 (m, 2H), 5.17 (d, *J* = 2.5 Hz, 1H), 4.85 (d, *J* = 2.6 Hz, 1H), 3.98 – 3.91 (m, 2H), 3.78 (d, *J* = 1.4 Hz, 3H), 2.91 (dd, *J* = 8.6, 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 158.3, 140.7, 138.3, 137.8, 130.4, 129.8, 129.7, 127.7, 124.3, 120.3, 114.0, 89.7, 55.2, 41.35, 33.5; IR (KBr, cm^{-1}): *v* 2932, 1712, 1645, 1513, 1249, 1126. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{17}ClNO_2$ 314.0942; Found: 314.0938.

2-(4-methoxyphenethyl)-6-chloro-3-methyleneisoindolin-1-one (1c): (1.03g, 73% yield) white solid, mp.115-116 °C; R_f = 0.56 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 1.8, 0.4 Hz, 1H), 7.60 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.17 (d, *J* = 2.5 Hz, 1H), 4.85 (d, *J* = 2.6 Hz, 1H), 3.95 (dd, *J* = 5.5, 4.0 Hz, 2H), 3.79 (s, 3H), 2.89 - 2.93 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 158.35, 140.9, 135.7, 134.5, 132.0, 130.9, 130.3, 129.7, 123.3, 121.1, 114.0, 89.4, 55.2, 41.4, 33.6; IR (KBr, cm^{-1}): ν 2930, 1705, 1645, 1513, 1240, 817. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{17}ClNO_2$ 314.0942; Found: 314.0938.

2-(4-methoxyphenethyl)-5-methyl-3-methyleneisoindolin-1-one (1d): (1.0g, 68% yield) white solid, mp.91-92 °C; R_f = 0.50 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.47 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.21 – 7.13 (m, 2H), 6.86 – 6.79 (m, 2H), 5.14 (d, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 2.3 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.78 (s, 3H), 2.95 – 2.83 (m, 2H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 158.3, 142.5, 141.8, 136.7, 130.7, 130.4, 129.75, 126.9, 122.9, 120.2, 114.0, 88.1, 55.2, 41.15, 33.6, 21.95; IR (KBr, cm^{-1}): *v* 2928, 1701, 1635, 1510, 1395, 1246, 1035, 818. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; Found: 294.1484.

2-(4-Methoxyphenethyl)-3-methyleneisoindolin-1-one (1e): (1.04 g, 75% yield) colorless oil, R_f = 0.44 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.57 (td, *J* = 7.6, 1.1 Hz, 1H), 7.49 (td, *J* = 7.3, 0.9 Hz, 1H), 7.18 - 7.15 (m, 2H), 6.84 - 6.82 (m, 2H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 3.97 - 3.93 (m, 2H), 3.77 (d, *J* = 5.0 Hz, 3H), 2.91 (t, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 158.2, 141.6, 136.3, 133.8, 131.8, 130.5, 129.7, 129.4, 129.3, 123.1, 123.0, 119.8, 113.9, 88.6, 55.2, 41.2, 33.6; IR (KBr, cm^{-1}): *v* 1712, 1514. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332 ; Found: 280.1333.

3-Methylene-2-(4-methylphenethyl)isoindolin-1-one (1f): (1.02 g, 73% yield) yellow solid, mp. 86-87 °C; R_f = 0.59 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.17 - 7.11 (m, 4H), 5.20 (d, *J* = 2.3 Hz, 1H), 4.85 (d, *J* = 2.3 Hz, 1H), 3.98 (t, *J* = 7.8 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 141.6, 136.3, 136.0, 135.3, 131.8, 129.4, 129.3, 129.2, 128.6, 123.0, 119.8, 88.5, 41.0, 34.0, 21.0; IR (KBr, cm^{-1}): *v* 1703, 1638, 1393. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{18}NO$ 264.1383; Found: 264.1384.

2-(4-Fluorophenethyl)-3-methyleneisoindolin-1-one (1g): (949 mg, 71% yield) white solid, mp.71-72 °C; R_f = 0.40 (EtOAc/petroleum ether = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.79 (m, 1H), 7.67 - 7.65 (m, 1H), 7.58 - 7.54 (m, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.19 - 7.16 (2H), 6.95 (t, *J* = 8.7 Hz, 2H), 5.17 (d, *J*

= 2.7 Hz, 1H), 4.79 (d, *J* = 2.3 Hz, 1H), 3.96 (t, *J* = 7.8 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 161.6 (d, *J* = 244.4 Hz), 141.5, 136.2, 134.1 (d, *J* = 3.2 Hz), 131.8, 130.2 (d, *J* = 7.9 Hz), 129.4, 129.1, 123.0, 119.8, 115.3 (d, *J* = 21.3 Hz), 88.5, 40.9, 33.6; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -116.3; IR (KBr, cm^{-1}): *v* 1702, 1645, 1509, 1396. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NOF$ 268.1132; Found: 268.1134.

3-methylene-2-(4-(trifluoromethyl)phenethyl)isoindolin-1-one (1h): (872 mg, 55% yield) white solid, mp. 86-87 °C; R_f = 0.35 (EtOAc/petroleum ether = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.56 (td, *J* = 7.5, 1.1 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.48 (td, *J* = 7.4, 0.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.18 (d, *J* = 2.5 Hz, 1H), 4.79 (d, *J* = 2.5 Hz, 1H), 4.00 (t, *J* = 7.6 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 142.7, 141.6, 136.3, 132.1, 129.6, 129.2, 129.0 (q, *J* = 32 Hz), 125.6 (q, *J* = 4 Hz), 124.3 (q, *J* = 271 Hz), 123.1, 120.0, 100.0, 88.6, 40.5, 34.4; IR (KBr, cm^{-1}): *v* 3391, 1701, 1647, 1333, 1119, 1069, 772, 698. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}NOF_3$ 318.1100; Found: 318.1111.

3-Methylene-2-(2-methylphenethyl)isoindolin-1-one (1i): (909 mg, 69% yield) yellow solid, mp.62-63 °C, R_f = 0.59 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 - 7.43 (m, 1H), 7.39 - 7.35 (m, 1H), 7.09 - 7.02 (m, 4H), 5.08 (d, *J* = 2.3 Hz, 1H), 4.73 (d, *J* = 2.3 Hz, 1H), 3.85 - 3.81 (m, 2H), 2.88 - 2.84 (m, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 141.6, 136.6, 136.2, 133.8, 131.7, 130.3, 129.34, 129.32, 129.2, 126.7, 126.1, 122.9, 119.8, 88.3, 39.7, 32.0, 19.2; IR (KBr, cm^{-1}): *v* 1710, 1643, 1396. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO$ 264.1383; Found: 264.1383.

2-(3-Fluorophenethyl)-3-methyleneisoindolin-1-one (1j): (1.08g, 81% yield): yellow solid, mp.75-76 °C; R_f = 0.68 (EtOAc / petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.60 - 7.56 (m, 1H), 7.52 - 7.48 (m, 1H), 7.27 - 7.22 (m, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.97 - 6.89 (m, 2H), 5.18 (d, *J* = 2.7 Hz, 1H), 4.80 (d, *J* = 2.3 Hz, 1H), 4.01 - 3.97 (m, 2H), 2.97 (t, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 162.9 (d, *J* = 246.1 Hz), 141.0 (d, *J* = 7.3 Hz), 140.9, 136.2, 131.9, 130.0 (d, *J* = 8.2 Hz), 129.5, 129.2, 124.45 (d, *J* = 2.6 Hz), 123.1, 119.9, 115.7 (d, *J* = 21.1 Hz), 113.5 (d, *J* = 20.9 Hz), 88.5, 40.7, 34.2; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -113.2; IR (KBr, cm^{-1}): *v* 1702, 1646, 1397. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NOF$ 268.1132; Found: 268.1131.

2-(3,4-Dimethoxyphenethyl)-3-methyleneisoindolin-1-one (1k): (1.24 g, 80% yield) yellow solid, mp.109-110 °C; R_f = 0.27 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.48 - 7.44 (m, 1H), 6.77 (d, *J* = 0.9 Hz, 2H), 6.71 (s, 1H), 5.16 (d, *J* = 2.3 Hz, 1H), 4.80 (d, *J* = 2.3 Hz, 1H), 3.98 - 3.94 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.92 - 2.88 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 148.8, 147.6, 141.5, 136.2, 131.7, 131.0, 129.3, 129.2, 122.9, 120.6, 119.7, 111.9, 111.1, 88.6, 55.7, 55.6, 41.0, 33.9; IR (KBr, cm^{-1}): *v* 1708, 1517, 1397. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NO_3Na$ 332.1257; Found: 332.1256.

2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-3-methyleneisoindolin-1-one (1l): (1.13 g, 77% yield) white solid, mp.105-106 °C; R_f = 0.36 (EtOAc/petroleum ether = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.59 - 7.55 (m, 1H), 7.51 - 7.47 (m, 1H), 6.74 - 6.67 (m, 3H), 5.92 (s, 2H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 3.96 - 3.92 (m, 2H), 2.89 (t, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 147.7, 146.2, 141.7, 136.3, 132.3, 131.8, 129.4, 129.3, 123.1, 121.7, 119.8, 109.2, 108.4, 100.9, 88.5, 41.2, 34.3; IR (KBr, cm^{-1}): *v* 1714, 1395. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}NO_3Na$ 316.0944; Found: 316.0940.

General procedure for the synthesis of 2. Under oxygen protection, $Pd(OAc)_2$ (9.0 mg, 0.02 mmol), $Cu(OAc)_2$ (80 mg, 0.40 mmol), PivOH (68.8 μL, 0.60 mmol) was added to a mixture of tertiary enamides **1** (0.20 mmol) in DMSO (2 mL). The resulting mixture was stirred at 80 °C for a period of time. After being cooled to room temperature, EtOAc (30 mL) and water (30 mL) was added, and filtrated with Celate, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (5 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of solvents in vacuo, the residue was purified by column chromatography (200–300 mesh) eluted with a mixture of ethyl acetate and petroleum (1:20 to 1:5) to give the pure product **2**.

7,8-Dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (2a): (32.8 mg, 66% yield) yellow solid, mp.125-126 °C; R_f = 0.54 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.83 (d, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.58 - 7.54 (m, 1H), 7.48 - 7.44 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.20 - 7.17 (m, 2H), 6.58 (t, *J* = 1.8 Hz, 1H), 4.14 (s, 2H), 3.13 (d, *J* = 4.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 139.6, 137.2, 134.9, 133.7, 131.7, 131.2, 129. 8, 128.8, 128.4, 127.6, 127.0, 123.3, 119.1, 107.0, 41.6, 35.6; IR (KBr, cm^{-1}): *v* 1714. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}NO$ 248.1070; Found: 248.1070.

2-chloro-11-methoxy-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (2b): (38.7 mg, 62% yield) yellow solid, mp.192-193 °C, R_f = 0.52 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.81 – 7.69 (m, 2H), 7.48 – 7.39 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.91 (s, 1H), 6.81 – 6.74 (m, 1H), 6.50 (s, 1H), 4.10 (s, 2H), 3.83 (d, *J* = 2.3 Hz, 3H), 3.09 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 158.6, 138.8, 138.2, 134.4, 134.2, 132.3, 131.0, 129.2, 126.8, 124.65, 119.6, 116.4, 113.6, 108.0, 55.4, 42.1, 34.7; IR (KBr, cm−1): ν 2929, 1685, 1653, 1270, 1049. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}ClNO_2$ 312.0786; Found: 312.0781.

3-chloro-11-methoxy-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (2c): (30.6 mg, 49% yield) yellow solid, mp.154-155 °C, R_f = 0.54 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.81 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.50 (s, 1H), 4.11 (s, 2H), 3.83 (s, 3H), 3.12 – 3.05 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.7, 158.6, 135.5, 135.1, 134.5, 134.4, 132.2, 131.9, 130.9, 129.9, 123.5, 120.5, 116.4, 113.4, 107.8, 55.4, 55.4, 42.15, 34.65; IR (KBr, cm^{-1}): *v* 2931, 1691, 1648, 1273, 829. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}ClNO_2$ 312.0786; Found: 312.0782.

11-methoxy-2-methyl-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (2d): (29.2 mg, 50% yield) yellow solid, mp.158-159 °C, R_f = 0.40 (EtOAc/petroleum ether = 1/3); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.72 – 7.58 (m, 2H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.89 (s, 1H), 6.74 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.48 (d, *J* = 1.4 Hz, 1H), 4.10 (s, 2H), 3.92 – 3.72 (m, 3H), 3.07 (d, *J* = 3.5 Hz, 2H), 2.47 (d, *J* = 1.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 158.5, 139.3, 135.5, 135.0, 134.8, 132.8, 132.15, 130.8, 128.7, 123.6, 119.0, 116.1, 112.9, 106.2, 55.35, 42.0, 34.8, 21.5; IR (KBr, cm^{-1}): ν 2923, 1689, 1653, 1502, 1273, 1122. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found: 292.1327.

11-Methoxy-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (2e): (33.9 mg, 61% yield) yellow solid, mp.146-147 °C; R_f = 0.27 (EtOAc/petroleum ether = 1/4); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.85 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 2.7 Hz, 1H), 6.78 - 6.75 (m, 1H), 6.54 (s,

1H), 4.13 (s, 2H), 3.84 (s, 3H), 3.09 (t, J = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 158.5, 137.3, 135.3, 134.8, 132.2, 131.7, 130.8, 128.9, 128.4, 123.4, 119.2, 116.2, 113.1, 106.9, 55.3, 42.0, 34.7; IR (KBr, cm^{-1}): ν 1719. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_2$ 278.1176; Found: 278.1171.

11-Methyl-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (2f): (35.6 mg, 68% yield): yellow solid, mp.106-107 °C; R_f = 0.39 (EtOAc/petroleum ether = 1/4); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.86 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.57 (s, 1H), 4.15 (s, 2H), 3.12 (t, J = 4.8 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 137.3, 136.8, 136.6, 134.9, 133.6, 131.9, 131.7, 129.8, 128.8, 128.5, 128.4, 123.4, 119.1, 107.2, 41.8, 35.2, 20.9; IR (KBr, cm^{-1}): ν 1705. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}NO$ 262.1226; Found: 262.1223.

11-Fluoro-7,8-dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (2g): (30.9 mg, 58% yield) white solid, mp.137-138 °C, R_f = 0.33 (EtOAc/petroleum ether = 1/4); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.85 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.51 - 7.47 (m, 1H), 7.12 (t, J = 6.9 Hz, 1H), 7.07 - 7.04 (m, 1H), 6.91 - 6.86 (m, 1H), 6.49 (d, J = 1.1 Hz, 1H), 4.12 (s, 2H), 3.11 (t, J = 3.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 161.75 (d, J = 244.4 Hz), 137.1, 135.9, 135.7, 135.7 (d, J = 8.0 Hz), 131.9, 131.26 (d, J = 8.0 Hz), 129.2, 128.4, 123.5, 119.3, 117.1 (d, J = 21.9 Hz), 114.1 (d, J = 21.2 Hz), 105.6, 41.7, 34.9; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -116.7; IR (KBr, cm^{-1}): ν 1699. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}NOF$ 266.0976; Found: 266.0973.

11-(trifluoromethyl)-7,8-dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (2h): (32.8 mg, 52% yield) white solid, mp.202-204 °C, R_f = 0.32 (EtOAc/petroleum ether = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.54 - 7.50 (m, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 4.13 (br s, 2H), 3.20 (br s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 143.1, 137.2, 136.5, 134.8, 132.3, 130.5, 129.8 (q, J = 32 Hz), 129.5, 128.6, 127.8 (q, J = 3 Hz), 124.2 (q, J = 271 Hz), 124.0 (q, J = 3 Hz), 123.8, 119.5, 105.3, 41.5, 35.8; IR (KBr, cm^{-1}): ν 3417, 1688, 1648, 1316, 1169, 1103, 1079. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{13}NOF_3$ 316.0944; Found: 316.0948.

9-Methyl-7,8-dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (2i): (28.8 mg, 55% yield) yellow solid, mp.156-157 °C; R_f = 0.32 (EtOAc/petroleum ether = 1/4); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.88 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.28 (s, 1H), 7.20 - 7.13 (m, 2H), 6.62 (s, 1H), 4.15 (s, 2H), 3.21 (s, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 138.2, 137.3, 135.8, 134.5, 134.3, 131.7, 129.8, 129.6, 128.7, 128.5, 126.6, 123.4, 119.1, 107.5, 41.6, 29.6, 20.7; IR (KBr, cm^{-1}): ν 1706. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}NO$ 262.1226; Found: 262.1224.

12-fluoro-7,8-dihydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (2j): yellow solid, mp.155-156 °C, R_f = 0.54 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.84 (t, J = 8.5 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.18 - 7.13 (m, 1H), 7.03 - 6.95 (m, 2H), 6.87 (s, 1H), 4.16 (s, 2H), 3.16 (J = 4.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 160.8 (d, J = 250.1 Hz), 141.9, 137.3, 136.1, 132.0, 129.1, 128.6 (d, J = 9.3 Hz), 128.4, 125.2 (d, J = 2.8 Hz), 123.4, 122.2, 122.1, 119.5, 113.8 (d, J = 22.8 Hz), 97.4 (d, J = 9.7 Hz), 41.6, 35.7; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$, 60 °C) δ -116.1; IR (KBr, cm^{-1}): ν 1721. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}NOF$ 266.0976; Found: 266.0975.

10,11-dimethoxy-7,8-dihydro-5H-benzo[4,5]azepino[2,1-a] isoindol-5-one (2k): (46.8 mg, 76% yield) yellow solid, mp.195-196 °C, R_f = 0.22 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.85 (d, J = 7.3 Hz, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 6.89 (s, 1H), 6.71 (s, 1H), 6.52 (s, 1H), 4.15 (br, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.10 (t, J = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 148.4, 147.6, 137.3, 133.7, 133.0, 131.6, 128.5, 128.2, 126.2, 123.4, 118.9, 114.1, 113.1, 107.0, 56.0, 56.0, 41.8, 35.3; IR (KBr, cm^{-1}): ν 1700. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_3$ 308.1281; Found: 308.1281.

6,7-Dihydro-9H-[1,3]dioxolo [4'',5'':5',6'] benzo [1',2':4,5] azepino [2,1-a] isoindol-9-one (2l): yellow solid, mp.201-202 °C, R_f = 0.45 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.84 (d, J = 7.3 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 6.67 (s, 1H), 6.23 (s, 2H), 6.02 (s, 2H), 4.12 (br, 2H), 3.07 (t, J = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 146.2, 145.9, 137.1, 135.7, 133.5, 131.8, 128.9, 128.4, 122.1, 119.4, 116.9, 107.2, 101.3, 98.6, 41.8, 35.3; IR (KBr, cm^{-1}): ν 1704. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}NO_3$ 292.0968; Found: 292.0969.

5,6-Dihydro-8H-[1,3] dioxolo [4'',5'':4',5'] benzo [1',2':4,5] azepino[2,1-a]isoindol-8-one (2l'): yellow solid, mp.214-215 °C, R_f = 0.38 (EtOAc/petroleum ether = 1/2); ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.85 (d, J = 7.3 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.59 - 7.55 (m, 1H), 7.46 (d, J = 7.3 Hz, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 6.47 (s, 1H), 5.97 (s, 2H), 4.12 (s, 2H), 3.07 (t, J = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 147.3, 146.7, 137.3, 134.4, 133.8, 131.7, 128.6, 128.3, 127.5, 123.4, 119.0, 110.6, 110.3, 106.9, 101.4, 41.9, 35.6; IR (KBr, cm^{-1}): ν 1718. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}NO_3$ 292.0968; Found: 292.0969.

2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxy-3-methyleneisoindolin-1-one (5): A solution of 2.0 mol of 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-aminium **4**, 2.0 mol of methyl 6-acetyl-2,3-dimethoxybenzoate **3** and $TsOH{\cdot}H_2O$ (17.2mg, 0.1 mmol) in 10 mL of toluene was held at reflux for 20 h using a Dean–Stark apparatus. After being cooled to room temperature, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give the final product (516 mg, yield: 73.1%) white solid, mp. 113-114 °C, R_f =0.59 (EtOAc/petroleum ether 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.73 - 6.67 (m, 3H), 5.91 (s, 2H), 5.02 (d, J = 2.3 Hz, 1H), 4.67 (d, J = 2.3 Hz, 1H), 4.09 (s, 3H), 3.91 (s, 3H), 3.87 (t, J = 8.0 Hz, 2H), 2.85 (t, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 153.6, 147.7, 146.6, 146.1, 141.0, 132.3, 130.0, 121.7, 121.2, 116.2, 115.2, 109.2, 108.3, 100.8, 86.4, 62.5, 56.7, 41.3, 34.1; IR (KBr, cm^{-1}): ν 1694, 1625, 1501. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_5$ 354.1336; Found: 354.1329.

9,10-dimethoxy-5,6-dihydro-8H [1,3] dioxolo [4'',5'':4',5'] benzo [1',2':4,5] azepino[2,1-a]isoindol-8-one (6) and 10,11-dimethoxy-6,7-dihydro-9H [1,3] dioxolo [4'',5'':5',6'] benzo [1',2':4,5] azepino[2,1-a]isoindol-9-one (6'): Under oxygen protection, $Pd(OAc)_2$ (9.0 mg, 0.02 mmol), $Cu(OAc)_2$ (80 mg, 0.40 mmol), PivOH (68.8 µL, 0.60 mmol) was added to a mixture of tertiary enamides **5** (71 mg, 0.20 mmol) in DMSO (2 mL). The resulting mixture was stirred at 80 °C for 9 h. After being cooled to room temperature, EtOAc (30 mL) and water (30 mL) was added, and filtered through a celite, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (5 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of solvents *in vacuo*, the residue was purified by column chromatography (200–300 mesh) eluted with a mixture of ethyl acetate and petroleum (1:20 to 1:5) to give the pure product **6** (14% yield) and its regioisomer **6'** (54% yield).

9,10-dimethoxy-5,6-dihydro-8H [1,3] dioxolo [4'',5'':4',5'] benzo [1',2':4,5] azepino[2,1-a]isoindol-8-one (6): yellow solid, mp. 212-213 °C, R_f = 0.46 (EtOAc/petroleum ether = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.41 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.80 (s, 1H), 6.66 (s, 1H), 6.32 (s, 1H), 5.95 (s, 2H), 4.12 (s, 3H), 4.07 (s, 2H), 3.93 (s, 3H), 3.04 (t, J = 4.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.7, 152.9, 146.9, 146.9, 146.6, 134.0, 133.3, 131.1, 127.8, 120.4, 116.4, 114.4, 110.3, 110.2, 105.0, 101.3, 62.5, 56.8, 41.9, 35.5; IR (KBr, cm^{-1}): ν 1700, 1498. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_5$ 352.1180; Found: 352.1173.

10,11-dimethoxy-6,7-dihydro-9H [1,3] dioxolo [4'',5'':5',6'] benzo [1',2':4,5] azepino[2,1-a]isoindol-9-one (6'): yellow solid, mp.193-194 °C, R_f = 0.50 (EtOAc/petroleum ether = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.44 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.61 (s, 2H), 6.53 (s, 1H), 6.01 (s, 2H), 4.11 (s, 3H), 4.07 (s, 2H), 3.92 (s, 3H), 3.05 (t, J = 4.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.0, 153.3, 146.9, 145.9, 145.8, 135.4, 133.3, 130.8, 122.0, 120.5, 117.3, 116.3, 114.9, 106.8, 101.2, 96.6, 62.5, 56.7, 41.7, 35.3; IR (KBr, cm^{-1}): ν 1692, 1275. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_5$ 352.1180; Found: 352.1173.

Lennoxamine (7): A mixture of **6** (105.4 mg, 0.3 mmol) and Pd/C (30 mg, 10 mol%) was placed in anhydrous EtOAc (9 mL) under an atmosphere (*via* balloon) of H_2 for 24 hours at room temperature. Filtration of the mixture through Celite, the residue was purified by column chromatography (200–300 mesh) eluted with a mixture of EtOAc and petroleum (1:5 to 1:3) to give the pure product *Lennoxamine* **7** (102 mg, 96% yield): white solid, mp.230-231 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.70 (s, 1H), 5.95 (d, J = 2.8 Hz, 2H), 4.75 - 4.71 (m, 1H), 4.28 (d, J = 10.5 Hz, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.11 - 3.07 (m, 1H), 2.93 -2.87 (m, 2H), 2.85 - 2.78 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 152.6, 147.2, 146.3, 146.1, 138.2, 134.8, 130.9, 124.2, 117.1, 116.2, 110.3, 101.0, 62.6, 60.1, 56.7, 42.7, 41.1, 35.9; IR (KBr, cm^{-1}): ν 1684, 1493. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_5$ 354.1336; Found: 354.1329.

Chilenamine (8): Under argon atmosphere, a mixture of **7** (70.6 mg, 0.2 mol) and $LiAlH_4$ (38 mg, 1 mol) was placed in anhydrous THF (2 mL) in a seal tube for 8 hours at 80 °C. The solution was cooled to rt. The reaction mixture was quenched by pouring into ice water (40 mL), extracted with diethyl ether (15 mL) three times. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue were purified by flash column chromatography on silica gel eluted with a mixture of EtOAc and petroleum (1:5 to 1:3) to give the pure product *Chilenamine* **8** (63 mg, 93% yield): yellow solid, mp.174-175 °C, R_f = 0.16 (EtOAc/petroleum ether = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.76 (s, 1H), 6.67 (s, 1H), 5.92 (s, 2H), 4.39 (d, J = 12.8 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.66 (d, J = 12.8 Hz, 1H), 3.39 - 3.30 (m, 2H), 3.16 – 3.04 (m, 3H), 2.79 - 2.73 (m, 1H), 2.64 (t, J = 11.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.3, 145.7, 145.6, 144.1, 137.4, 134.9, 133.9, 131.3, 116.0, 111.1, 110.6, 110.2, 100.8, 67.8, 60.3, 56.8, 56.2, 53.3, 40.8, 37.4, 29.7; IR (KBr, cm^{-1}): ν 1717, 1474. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_4$ 340.1543; Found:340.1536.

2-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3-methyleneisoindolin-1-one (10): A solution of 2.0 mol of 2-(3,4-dimethoxyphenyl)ethan-1-amine **9** , 2.0 mol of methyl 6-acetyl-2,3-dimethoxybenzoate **3** and $TsOH{\cdot}H_2O$ (17.2 mg, 0.1 mmol) in 10 mL of toluene was held at reflux for 20 h using a Dean–Stark apparatus. After being cooled to room temperature, the solvent was evaporated in vacuo and the residue was purified by flash silica gel chromatography to afford the product **10** (496.5 mg, yield: 67.2%). White solid, mp. 117-118 °C; R_f = 0.20 (EtOAc/petroleum ether = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.79 (s, 2H), 6.74 (s, 1H), 5.02 (d, J = 2.3 Hz, 1H), 4.68 (d, J = 2.3 Hz, 1H), 4.08 (s, 3H), 3.91 (t, J = 7.8 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.91 - 2.87 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 153.6, 148.9, 147.6, 146.6, 141.0, 131.1, 130.0, 121.2, 120.7, 116.2, 115.2, 112.0, 111.2, 86.5, 62.5, 56.7, 55.9, 55.8, 41.2, 33.9; IR (KBr, cm^{-1}): ν 1702. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NO_5Na$ 392.1468; Found: 392.1467.

3,4,10,11-tetramethoxy-7,8-dihydro-5H-benzo [4,5] azepino [2,1-a] isoindol-5-one (11): Under oxygen protection, $Pd(OAc)_2$ (9.0 mg, 0.02 mmol), $Cu(OAc)_2$ (80 mg, 0.40 mmol), PivOH (68.8 μL, 0.60 mmol) was added to a mixture of tertiary enamides **10** (74 mg, 0.20 mmol) in DMSO (2 mL). The resulting mixture was stirred at 80 °C for 5.5 h. After being cooled to room temperature, EtOAc (30 mL) and water (30 mL) was added, and filtered through a celite, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (5 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of solvents *in vacuo*, the residue was purified by column chromatography (200–300 mesh) eluted with a mixture of ethyl acetate and petroleum (1:20 to 1:5) to give the pure product **11** (73% yield). Yellow solid, mp.199-200 °C; R_f = 0.12 (EtOAc/petroleum ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.41 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.84 (s, 1H), 6.68 (s, 1H), 6.36 (s, 1H), 4.11 (s, 3H), 4.11 - 4.08 (m, 2H), 3.92 (s, 3H), 3.90 (s, H), 3.89 (s, 3H), 3.06 (t, J = 4.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.7, 152.8, 148.1, 147.5, 146.8, 133.3, 132.6, 131.1, 126.5, 120.4, 116.3, 114.3, 113.7, 113.1, 105.0, 62.5, 56.7, 56.0, 55.9, 41.7, 35.3; IR (KBr, cm^{-1}): ν 1697, 1689. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_5Na$ 390.1312; Found: 390.1311.

Palmanine (12): To a solution of **11** (36.7 mg, 0.1 mmol) in THF (1 mL) was added *m*-CPBA (57 mg, 75%, 2.5 mmol). The reaction mixture was stirred at room temperature for 2 h. Saturated Na_2SO_3 solution (10 mL) was added to quenched the reaction, then Na_2CO_3 (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL), washed with water (20 mL) and brine (20 mL), dried with anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash silica gel chromatography to afford *Palmanine* **12** (17 mg, 43% yield): white solid, mp. 200-201 °C; R_f = 0.21 (EtOAc/petroleum ether = 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 4.28-4.23 (m, 1H), 4.15 (s, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.64-3.58 (m, 1H), 3.39 – 3.31 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.5, 166.2, 154.0, 152.7, 147.7, 146.1, 135.9, 132.8, 127.8, 122.6, 119.1, 116.2, 112.1, 111.9, 90.9, 62.4, 56.4, 56.0, 56.0, 38.0, 31.4; IR (KBr, cm^{-1}): ν 1707. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_7Na$ 422.1210; Found: 422.1208.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reaction optimization

Crystallographic data of **6'**. **12**

Spectroscopic data (^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} spectra) of all new conpounds (PDF)

AUTHOR INFORMATION

Corresponding Author

* Email: tongshuo@mail.tsinghua.edu.cn
* Email: wangmx@mail.tsinghua.edu.cn

Notes

The authors declare no competing financial interest.

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