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Palladium(II)/Lewis Acid Catalyzed Oxidative Olefination/Annulation of *N*-methoxybenzamides: Identifying the Active Intermediates through NMR Characterizations

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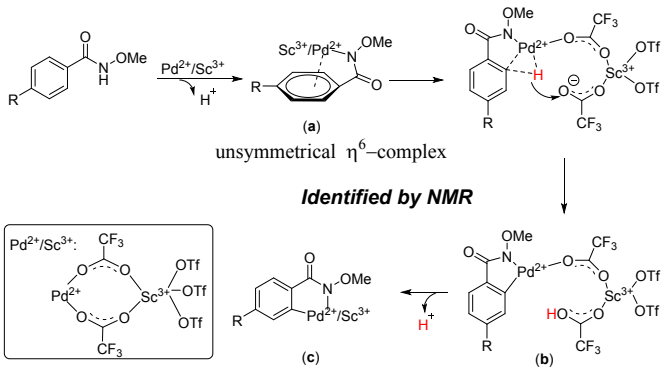


ABSTRACT: Although Pd(II)-catalyzed C-H activation in arenes has been widely successful in organic synthesis with many palladacycle compounds isolated as the intermediates in ligand

directed C-H activation, direct identification of the reaction intermediates such as π-complex prior to the C-H activation is still not successful due to their instability. In the present study, we introduce a Pd(II)/LA (LA: Lewis acid) catalyzed oxidative olefination/annulation reaction between *N*-methoxybenzamides and acrylates with oxygen as the oxidant source, in which two intermediates, including an unsymmetrical η^6-complex and a palladacycle species without the proton releasing to the environment were identified through NMR characterizations. The *in-situ* formation of the heterobimetallic Pd(II)/LA species such as Pd(II)/Sc(III) may have enhanced the electrophilic properties of the Pd^{2+} cation, thus improving the stability of the π-complex, herein, an unsymmetrical η^6-complex, and improving its catalytic efficiency. The observed insensitive electronic effect preferred the concerted metalation-deprotonation (CMD) mechanism for this C-H activation, and the detected palladacycle intermediate without the proton releasing to the environment offered an experimental clue to support the proposed CMD mechanism.

INTRODUCTION

Transition metal ions catalyzed activation and functionalization of the C-H bond in (hetero)arenes is one of the most active topics in organic synthesis;[1] among various redox metal catalysts, palladium is the most popularly investigated one because of its high activity in catalysis. Up to now, several mechanisms have been proposed for Pd(II)-catalyzed C-H activation of (hetero)arenes, including electrophilic aromatic substitution (S_EAr),[2,3] concerted metalation-deprotonation (CMD),[4] Heck-like, oxidative C-H insertion and anionic cross-coupling.[5,6] In these mechanisms, S_EAr and CMD mechanisms received the most support, in which S_EAr was convinced by the NMR identifications of the Wheland-type σ-complex and σ-π continuum intermediates in C-H activation of electron-rich indoles,[7] while CMD, characteristic

of proton abstraction *via* a base-assisted agostic interaction, was proposed on the basis of theoretical calculations for the C-H activation in arenes.[8,9] Due to the low stability, the agostic C-H complex with its plausible precursors such as π-complex was not directly identified yet.[10]

Over the recent decade, ligand-directed C-H activation has attracted much attention in organic synthesis.[11-13] The ligand-anchoring apparently increased the opportunity of the C-H activation by the metal ions, and improved the stability of the C-H bond activated intermediates, that led to the isolation of a series of cyclometalation compounds.[14-16] Even so, the experimental identification of the Pd(II)-ligated arene intermediates, that is, the π-complex and/or the agostic hydrogen complex, is still not successful in those ligand-directed C-H functionalization reactions. Interestingly, there also have many arene-coordinated transition metal complexes that were isolated with the X-ray crystal characterizations such as $[Ru(p\text{-cymene})Cl_2]_2$ and various metallocenes;[17,18] however, these coordinated arenes generally did not proceed further C-H activation and functionalization through the mechanisms described above. Even more, $[Ru(p\text{-cymene})Cl_2]_2$ could function as a catalyst to activate the C-H bond from exogenous arenes through the CMD mechanism.[19] We suspect that the direct observation of the Pd(II)-ligated arene intermediate, that is, π-complex, may be accessible in Pd(II)-catalyzed C-H activation through certain strategies to enhance the electrophilic properties of the Pd^{2+} cation, thus strengthening its interaction with arene, but not harming its catalytic activity.

In investigating the reactivity of the active metal moieties with related Lewis acid (LA) promoted catalytic oxidation by redox metal ions,[20,21] we unexpectedly found that, in addition to its redox properties, the Lewis acid properties of the Cu^{2+} cation may also play a significant role in Pd(II)-catalyzed Wacker-type oxidations.[22] As an evidence, the redox inactive Sc^{3+} can accelerate Pd(II)-catalyzed olefin oxidation more efficiently than Cu^{2+} does, which inspired us to

define the Pd(II)/LA catalyst strategy for organic synthesis. Currently, the Pd(II)/LA catalysis has been successful in a list of synthetic reactions,[23-27] and it has also been expanded to Ni(II)/LA catalyzed oxidative S-P bond formation.[28] In literature, directing group assisted olefination/annulation has been convinced as an efficient protocol to synthesize isoindolinone compounds.[29] Herein, we present a Pd(II)/LA catalyzed oxidative olefination/annulation of *N*-methoxybenzamides to synthesize isoindolinones, in which two reaction intermediates including π-complex and cyclopalladation species without the proton releasing to the environment were identified through NMR characterizations. Notably, this is the first experimental identification of the π-complex in the Pd(II)-catalyzed C-H activation in arenes.

RESULTS AND DISCUSSION

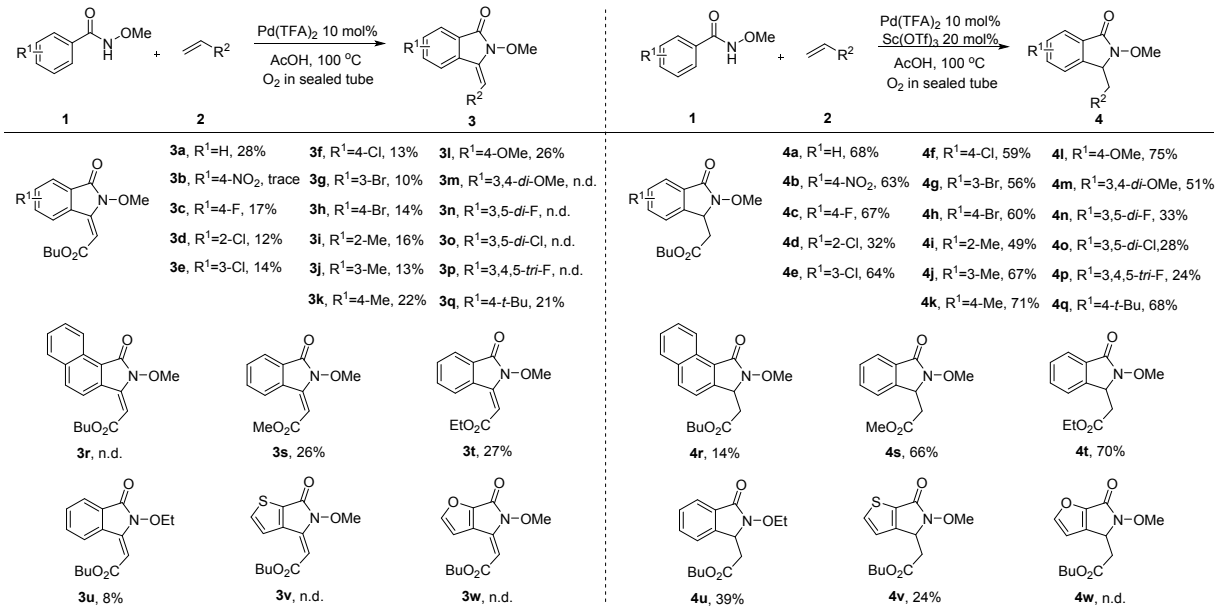
The investigation was initiated by using *N*-methoxylbenzamide **1a** and butyl acrylate **2a** as the model substrates for the olefination/annulation reaction to optimize the reaction conditions. In the presence of $Pd(TFA)_2$ catalyst with oxygen as the oxidant source, the reaction of *N*-methoxylbenzamide (**1a**) and butyl acrylate (**2a**) in HOAc at 100 °C gave the isoindolinone derivative butyl (*E*)-2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate (**3a**) as the product in a low yield (28%) (Table S1, entry 2). Gratifyingly, when $Sc(OTf)_3$ was added to $Pd(TFA)_2$ as the catalyst, butyl 2-(2-methoxy-3-oxoisoindolin-1-yl)acetate (**4a**) was identified as an unexpectedly product without **3a** formation, and a 68% isolated yield of **4a** was achieved (Table S1, entry 4). In the control experiment, when $Sc(OTf)_3$ alone was employed as the catalyst, neither **3a** nor **4a** was detected as the product (Table S1, entry 16). Subsequently, a series of condition optimizations including Pd(II) sources, Lewis acids, solvents, temperature and the time-course of the reaction were investigated (see Table S1-S3 and Figure S1); it was found that $Pd(TFA)_2/Sc(OTf)_3$ provided the best catalytic efficiency in the sealed tube with oxygen as the

oxidant source in HOAc solvent at 100 °C. Therefore, the following investigations on the substrate scope were based on $Pd(TFA)_2/Sc(OTf)_3$ catalyst.

As shown in Scheme 1, $Pd(TFA)_2/Sc(OTf)_3$ can catalyze olefination/annulation of a list of substituted *N*-methoxybenzamides with butyl acrylate **2a** to give the compound **4** in the moderate to good yields (**4b**-**4q**), and the reaction was insensitive to the electronic effects on the aromatic ring of *N*-methoxybenzamides. With an electron-withdrawing group (NO_2, F, Cl or Br) at the *meta* or *para* position of the aromatic ring, it provided the product **4** in good yields (56-67%, **4b, 4c, 4e**-**4h**); the electron-donating groups (Me, OMe or *t*-Bu) at the *meta* or *para* position also gave 66%-75% yields of **4** (**4j**-**4l** and **4q**), just slightly higher than those from electron-withdrawing groups. Notably, no matter electron-withdrawing group or electron-donating group bearing on the *ortho* position of the aromatic rings, it led to a low yield of **4** possibly due to the steric effect. The substrate scope of this reaction can be extended to 3,4-dimethoxy substituted *N*-methoxybenzamide, which gave **4m** in 51% yield, and 3,5-difluoro and 3,5-dichloro substituted *N*-methoxybenzamides gave **4n** and **4o** in 33% and 28% yields, respectively, while 3,4,5-trifluoro-*N*-methoxybenzamide gave **4p** in 24% yield. In addition, using 1-naphthamide as the substrate gave **4r** in 14% yield. **2a** can also be replaced by methyl acrylate or ethyl acrylate, which reacted with **1a** to give the corresponding **4s** and **4t** in 66% and 70% yields, respectively. Notably, the reaction between *N*-ethoxybenzamide and **2a** provided only 39% yield of **4u**, much less than 68% yield of **4a**, indicating that the electronic effect of the directing group also played a significant role in this Pd(II)/Sc(III) catalyzed olefination/annulation reaction. Other heterocyclic amides were also tested for this reaction; disappointingly, only thiophene reacting with **2a** provided the corresponding **4v** in 24% yield. In addition, when the olefination/annulation reaction of *N*-methoxylbenzamide **1a** and butyl acrylate **2a** was performed on a gram scale, 60%

yield of product **4a** was obtained under the optimized conditions. Anyway, adding Lewis acid to $Pd(TFA)_2$ can substantially improve its catalytic efficiency and change the product distribution in this olefination/annulation reaction. In the case of without LA added, using $Pd(TFA)_2$ alone as the catalyst always provided **3** as the product in a low yield, thus highlighting the crucial role of LA in this Pd(II)/LA catalyzed olefination/annulation reaction.

Scheme 1 Substrate scope for the Pd(II)/Sc(III)-catalyzed olefinatin/annulation reaction.

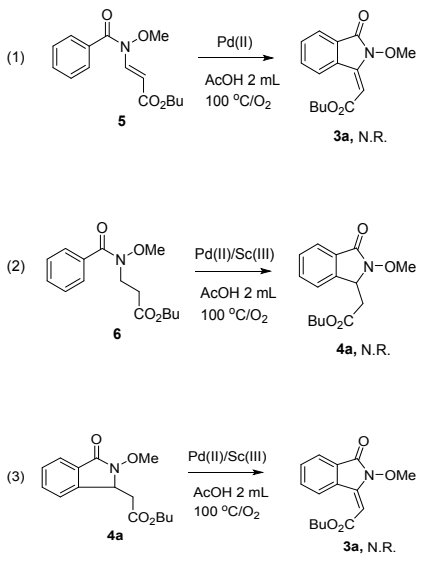


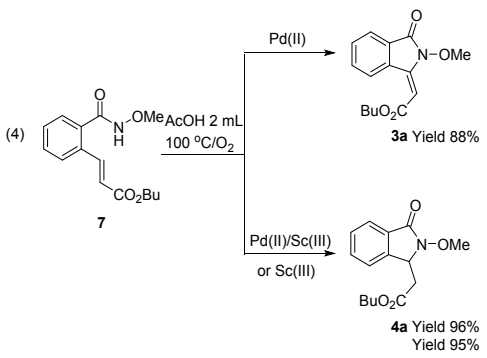
Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(TFA)_2$ (10 mol%), and $Sc(OTf)_3$ (20 mol%) with O_2 in sealed tube in HOAc (2.0 mL), stirring at 100 °C for 12 h. Isolated yield.

Mechanistically, this olefination/annulation reaction should proceed through a C-C/C-N bond formation process no matter **3a** or **4a** was generated as the final product. In order to clarify the sequence of the reaction steps, several possible intermediates were synthesized to test the following control experiments (Scheme 2). Firstly, when butyl (*E*)-3-(*N*-methoxybenzamido)acrylate (**5**) was treated with $Pd(TFA)_2$ alone in HOAc at 100 °C, the formation of **3a** was not observed in thin-layer-chromatography (TLC) analysis (Scheme 2, eq.1). Secondly, **4a** was also not obtained from butyl 3-(*N*-methoxybenzamido)propanoate (**6**) in

the presence of $Pd(TFA)_2/Sc(OTf)_3$ catalyst (Scheme 2, eq.2). These two experiments clearly disclosed that the C-N bond formation is not a prior step in the generation of **3a** or **4a**. Thirdly, **4a** was tested as a substrate to address whether **3a** was obtained through dehydrogenation of **4a**; however, the reaction did not proceed to generate **3a** (Scheme 2, eq.3). Finally, butyl (*E*)-3-(2-(methoxycarbamoyl)phenyl)acrylate (**7**), the olefination compound was tested as the substrate. When $Pd(TFA)_2$ alone was employed as the catalyst, **3a** was obtained in 88% yield from **7**, whereas using $Pd(TFA)_2/Sc(OTf)_3$ or $Sc(OTf)_3$ as catalyst, it provided **4a** in 96% and 95% yields, respectively, possibly through intramolecular aza-Michael addition (Scheme 2, eq.4). Taken together, these control experiments clearly supported that the C-C bond formation through oxidative olefination occurred prior to the C-N bond formation in the whole reaction; then, Pd(II)/Sc(III) or Sc(III) itself catalyzed annulation of the intermediate **7** to achieve the final product, **3a** or **4a**, respectively.

Scheme 2 Control experiments for Pd(II)/Sc(III)-catalyzed olefination/annulation reaction.





In reported Lewis acid-involved transition metal catalyzed organic synthesis,[30-32] if a substrate contains one carbonyl group, it was generally believed that LA was coordinated to the carbonyl, which improved the catalytic efficiency in the consecutive reaction. In the present study, a series of experiments was designed to address the similar role of LA in this Pd(II)/LA catalysis. In the case of using *N*,4-dimethoxybenzamide (**1l**) as substrate, if $Sc(OTf)_3$ was ligated to the carbonyl group of **1l**, two series of protons may be observed for **1l** in its ^1H NMR spectrum when the ratio of $Sc(OTf)_3$/**1l** was less than one. However, as shown in Figure S2, no matter the ratio of $Sc(OTf)_3$/**1l** was 1, 0.5 or 0.25, only one series of protons was observed with slightly downshifted aromatic protons. Interestingly, the magnitude of the downshift was related to the proportion of the $Sc(OTf)_3$ loading, which may be attributed to the change of the solvent properties due to the $Sc(OTf)_3$ addition, but not conclusively. To further address the possibility of the carbonyl group coordination on the Sc^{3+} cation, two more sets of control experiments were designed by using *N*-benzyl-*O*-methylhydroxylamine (**8**) and *N*-(4-methoxybenzyl)-*O*-methylhydroxylamine) (**9**) as the substrate which do not contain the carbonyl group. As shown in Figure S3, both of them also displayed a similar downshift of protons in their ^1H NMR spectra upon adding $Sc(OTf)_3$. Taken together, these ^1H NMR experiments supported that the downshift of protons in ^1H NMR spectrum was not caused by the carbonyl group coordination of **1l** on the

Sc^{3+} cation, thus excluding it as a clue to indicate the interaction between Sc^{3+} and the carbonyl group of **1l**.

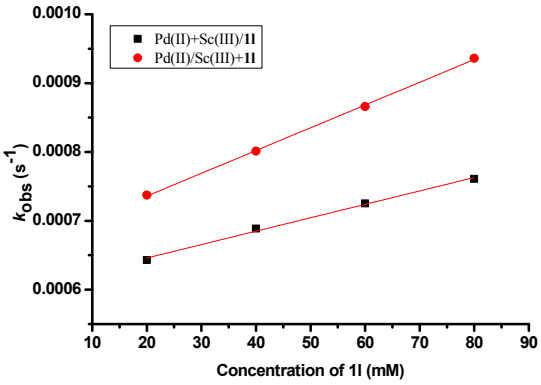


Figure 1 Correlation of substrate concentration with the k_{obs} constant for the disappearance of the characteristic peak of the catalyst when reacted with *N*,4-dimethoxybenzamide (**1l**).

To further address the role of the Sc^{3+} in this Pd(II)/Sc(III) catalysis, two parallel kinetic experiments were conducted through UV-vis monitoring of the Pd(II) species decay at its characteristic absorbance band, including 1) the reaction of **1l** with the pre-mixed $Pd(TFA)_2/Sc(OTf)_3$ in HOAc, and 2) the reaction of $Pd(TFA)_2$ with the pre-mixed **1l**/$Sc(OTf)_3$ in HOAc. As shown in Figure 1, the reaction rate between **1l** and pre-mixed $Pd(TFA)_2/Sc(OTf)_3$ was faster than that of the reaction between $Pd(TFA)_2$ and **1l**/$Sc(OTf)_3$, giving k_2 values of 3.31×10^{-9} M^{-1} s^{-1} and 1.95×10^{-9} M^{-1} s^{-1}, respectively. Clearly, it is the interaction between Pd^{2+} and Sc^{3+}, rather than the interaction between **1l** and Sc^{3+}, which accelerated the C-H activation of **1l** by the Pd^{2+} cation. Additionally, in UV-vis characterization of the Pd(II)/Sc(III) catalyst, adding $Sc(OTf)_3$ to $Pd(TFA)_2$ in HOAc solution revealed an obvious increase of its characteristic band around 396 nm, which also indicated the formation of a new Pd(II) species (see Figure S7).[26] Taken together, these experiments strongly supported that Sc^{3+} interacting with the Pd^{2+} cation,

rather than coordinating to the carbonyl group of the substrate, accelerated this Pd(II)/Sc(III) catalyzed olefination/annulation reaction.

In our previous studies, the promotional effect of LA in Pd(II)/LA catalysis was attributed to the formation of the heterobimetallic Pd(II)/LA species, which enhanced the electrophilic properties of the Pd^{2+} cation, thus accelerating Pd(II)-catalyzed organic synthesis.[22-27] In addition, one heterobimetallic Ni(II)/Y(III) species was detected through the MS detections in Ni(II)/Y(III) catalyzed oxidative S-P formation reaction, which was assigned as a diacetate bridged Ni(II)/Y(III) species.[28] Although the X-ray crystal structures of the Pd(II)/LA catalysts were not obtained yet in those studies, various heterobimetallic Pd(II) species with acetate bridge were widely reported with X-ray crystal characterizations in literatures.[33-36] Notably, in investigating the influence of the Pd(II) sources on this olefination/annulation reaction, it was found that $Pd(TFA)_2/Sc(OTf)_3$ catalyst demonstrated a much better catalytic efficiency than $Pd(OAc)_2/Sc(OTf)_3$ (68% vs 43% yield, entries 3 and 4, Table S1), even though HOAc was employed as the solvent, indicating that the trifluoroacetate anion from $Pd(TFA)_2$ was not exchanged with the free OAc^- anion in the solvent. In addition, using $Pd(OTf)_2$ or $Pd(OTf)_2/Sc(OTf)_3$ as catalyst also demonstrated a much poorer efficiency (21% and 37% yield, respectively, entries 14 and 15, Table S1) than that of $Pd(TFA)_2/Sc(OTf)_3$ (68% yield, entry 4, Table S1), indicating the OTf^- anion exchange did not occur for $Pd(TFA)_2/Sc(OTf)_3$ to provide $Pd(OTf)_3$ as catalyst, and the OTf^- bridged Pd(II)/Sc(III) species was also eliminated for this catalysis. Taken these experimental data together with previous studies in this Pd(II)/LA catalysis,[22-28] a similar heterobimetallic Pd(II)/Sc(III) species having the trifluoroacetate bridge may be *in-situ* generated in the solution and served as the active species for catalysis. In the Pd(II)/Sc(III) structure, while the Sc^{3+} cation should have six ligands to form an octahedral

structure, a few of its ligands such as OTf^- anion or water may dissociate from Sc^{3+}, thus a clean octahedral structure of the Sc^{3+} cation was omitted in the coming discussion.

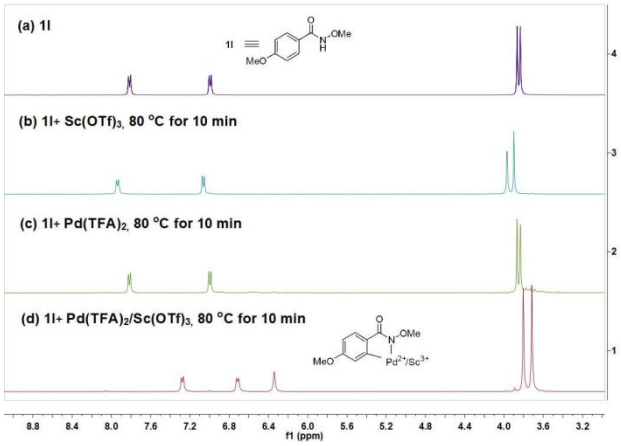


Figure 2 ^{1}H NMR spectra of the interaction between catalyst and *N*,4-dimethoxybenzamide (**1l**) in HOAc-d_4 at 80 °C. The trifluoroacetate bridged Pd^{2+}/Sc^{3+} structure is abbreviated as Pd^{2+}/Sc^{3+} in the graph.

To elucidate the mechanistic details of this reaction, several ^{1}H NMR studies on the semi-reaction between *N*,4-dimethoxybenzamide (**1l**) and different catalysts in HOAc-d_4 were conducted, which were displayed in Figure 2. The ^{1}H NMR spectrum of *N*,4-dimethoxybenzamide (**1l**) in HOAc-d_4 showed an AA'XX' system peaks in the aromatic region (δ_H = 7.81 and 6.99 ppm, Figure 2a), corresponding to the *ortho*- and *meta*-protons of the aromatic ring in **1l**. Next, two experiments were conducted by treating **1l** with one equiv. $Pd(TFA)_2$ or $Sc(OTf)_3$ at 80 °C for 10 min, respectively, prior to their ^{1}H NMR detections. No C-H bond activated intermediates/products were observed in either reaction (Figures 2b and 2c), except that the chemical shifts of **1l** slightly downshifted in the presence of $Sc(OTf)_3$. Remarkably, when **1l** was treated with pre-mixed $Pd(TFA)_2/Sc(OTf)_3$ catalyst under 80 °C for 10 min, its ^{1}H NMR signals changed completely, that is, the original proton peaks of **1l** disappeared,

meanwhile, three new proton peaks emerged with an integral ratio of 1:1:1, and exhibited as two doublet peaks (δ_H = 7.27, 6.71 ppm, J_{H-H} =8.4 Hz) with one singlet peak (δ_H = 6.34 ppm, Figure 2d). These new protons can be assigned to a new generated palladacycle compound as well as those palladacycles in literatures.[37,38] Clearly, the formation of the heterobimetallic Pd(II)/Sc(III) species greatly improved the C-H activation capability of the Pd^{2+} cation, leading to the formation of the palladacycle compound.

To further trap the reaction intermediates prior to the palladacycle formation, a list of ^{1}H NMR kinetic experiments was conducted under different conditions. Firstly, ^{1}H NMR kinetics of the reaction between **1l** and $Pd(TFA)_2$ in HOAc-d_4 at 80 °C for 180 min was conducted. In the ^{1}H NMR monitored time-course of this reaction, many new peaks appeared while some of them overlapped each other, and the final palladacycle compound was not as clean as that from Pd(II)/Sc(III) catalyst (Figure S8). As a result, the confused spectrum made the reaction intermediates unidentifiable. Similar phenomena may have frequently occurred in other Pd(II)-catalyzed C-H bond activation of arenes, which blocks the chemists to identify the reaction intermediates up to now.

Next, similar ^{1}H NMR kinetics was examined for the semi-reaction of $Pd(TFA)_2$/$Sc(OTf)_3$ with **1** having different substituents. Gratifyingly, a clean, potentially resolvable ^{1}H NMR kinetics was observed in most cases (see Figures S9-S13), and two simplified ^{1}H NMR kinetics of using **1l** and 4-bromo-*N*-methoxybenzamide (**1h**), respectively, as substrate were exampled for the discussion about the reaction intermediate identifications (Figures 3 and 4). The ^{1}H NMR spectra of substrate **1l** and **1h** are shown in Figure 3a and Figure 4a, respectively; in Figure 3c and Figure 4c**,** the chemical shifts of the final product can be assigned to the palladacycle compounds **1l-c** and **1h-c**, respectively. In Figure 3b, the chemical shifts of aromatic protons in

substrate **1l** showed a slightly downshift when compared with those in Figure 3a (δ_H = 7.94 and 7.06 ppm *vs* δ_H = 7.81 and 6.99 ppm), in which the peak at δ_H = 7.06 ppm is overlapped with a new small peak at δ_H = 7.07 ppm. Fortunately, in the case of **1h** substrate (Figure 4b), this overlap was avoided, and two cleanly separated peaks including δ_H = 7.73 and 7.68 ppm, corresponding to a new generated small AA'XX' system peak and the AA'BB' system peak of *meta*-proton on the aromatic ring of **1h**, were observed. This new AA'XX' system peak at δ_H = 7.73 ppm exhibited a 1:1 integral ratio to that of the AA'XX' system peak at δ_H = 8.30 ppm, while the AA'BB' system peaks at δ_H = 7.8 and 7.68 ppm also exhibited an integral ratio of 1:1, which can be assigned to the aromatic protons of **1h**. In Figure 3b, since the integral area of the peak at δ_H = 7.06 ppm combined with the overlapped small peak at δ_H = 7.07 ppm is equal to the total integral areas of the peaks at δ_H = 7.94 and 8.41 ppm, it can be feasibly deduced that this overlapped small peak at δ_H = 7.07 ppm exhibited an integral ratio of 1:1 to that at δ_H = 8.41 ppm. Thus, these two new peaks could be assigned to the aromatic protons of a new generated reaction intermediate, abbreviated as **1l-a** in Figure 3b and **1h-a** in Figure 4b (see *vide infra* for detailed structural assignments).

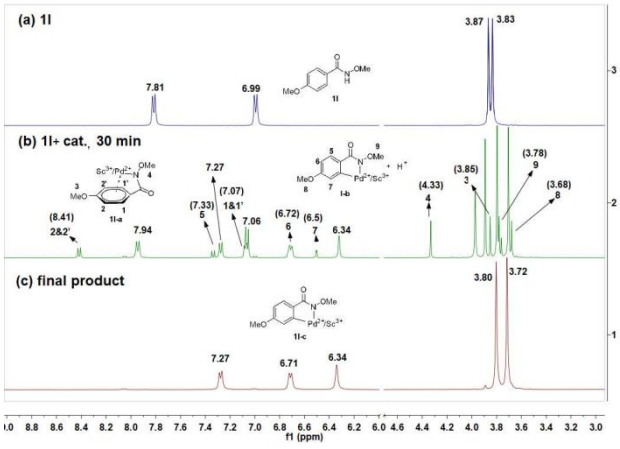


Figure 3 ^{1}H NMR spectra of the interaction between *N*,4-dimethoxybenzamide (**1l**, 0.02 mmol) with pre-mixed $Pd(TFA)_2/Sc(OTf)_3$ catalyst (0.02 mmol/0.02 mmol) in HOAc-d_4 (0.5 mL) at room temperature. The trifluoroacetate bridged Pd^{2+}/Sc^{3+} structure is abbreviated as Pd^{2+}/Sc^{3+} in the graph.

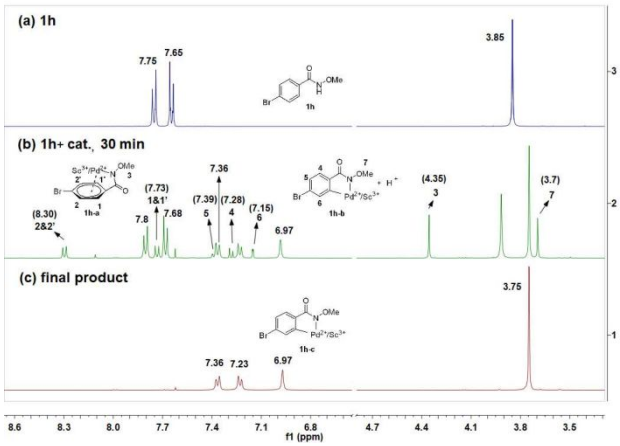


Figure 4 ^{1}H NMR spectra of the interaction between 4-bromo-N-methoxybenzamide (**1h**, 0.02 mmol) with pre-mixed $Pd(TFA)_2/Sc(OTf)_3$ catalyst (0.02 mmol/0.02 mmol) in HOAc-d_4 (0.5 mL) at room temperature. The trifluoroacetate bridged Pd^{2+}/Sc^{3+} structure is abbreviated as Pd^{2+}/Sc^{3+} in the graph.

In the aromatic area of ^{1}H NMR spectra in Figure 3b and 4b, in addition to the substrate (**1l** and **1h**), palladacycle product (**1l-c** and **1h-c**) with the assigned intermediate **1l-a** and **1h-a**, there still exists another set of aromatic protons. In Figure 3b, analyzing the integral areas of the aromatic protons of palladacycle compound **1l-c** (δ_H = 7.27, 6.72 and 6.34 ppm) disclosed that there should have a small peak completely overlapped with the aromatic *meta*-proton of **1l-c** (δ_H = 6.71 ppm), giving the apparent chemical shift at δ_H = 6.72 ppm. On the other side, the aromatic protons at δ_H = 7.33 and 6.5 ppm demonstrated an integral ratio of 1:1 in Figure 3b. Notably, in place of **1l** with **1h** as the substrate, the completely overlapped small peak at δ_H = 6.72 ppm in

Figure 3b was clearly separated from the aromatic *meta*-proton of **1h-c** at δ_H = 7.23 ppm (doublet, J_{H-H}=8.0 Hz), giving the chemical shift of 7.28 ppm (doublet), while the aromatic proton at δ_H = 7.36 ppm in Figure 4b was partly overlapped with the aromatic *meta*-proton of **1h-c**, giving the chemical shift of 7.39 ppm. Notably, in Figure 4b, the integral areas of the aromatic protons at δ_H = 7.28 and 7.15 ppm disclosed a ratio of 1:1. Taken together the 1:1 integral ratio of the protons at δ_H = 7.33 and 6.5 ppm in Figure 3b, it can be deduced that these three aromatic protons, that is, the chemical shifts at 7.39, 7.28 and 7.15 ppm in Figure 4b, exhibited an integral ratio of 1:1:1, which can be assigned to another reaction intermediate, abbreviated as **1l-b** in Figure 3b and **1h-b** in Figure 4b, respectively (see *vide infra* for detailed structural assignments). Now, two reaction intermediates, **a** and **b**, prior to the final palladacycle **c** formation, have been successfully identified in this semi-reaction based on the ^{1}H NMR information from the aromatic area in Figures 3 and 4.

The chemical shifts of methoxyl groups in Figures 3b and 4b also indicated that two reaction intermediates occurred prior to the palladacycle formation, and both of them disappeared finally in Figures 3c and 4c. The confusing fact is that, their integral areas are almost identical, and the similarly identical integral areas were also observed in the aromatic protons of the intermediate **a** and **b** in both Figures 3b and 4b. Particularly, similar 1:1 integral ratio of **a** and **b** intermediates was further observed in other *para*-substituted *N*-methoxybenzamides (Figures S11 and S12), which blocks the assignment of the methoxyl groups to the intermediate **a** and **b** in these semi-reactions. Fortunately, this phenomenon of 1:1 integral ratio was broken in using 2,4-dichloro-N-methoxybenzamide as the substrate (Figure S13), in which the ^{1}H NMR signals for the aromatic and methoxyl protons of the intermediate **a** was still observed, whereas those for **b** disappeared, thus excluding the tied 1:1 relationship of the intermediate **a** and **b** in

this semi-reaction. Accordingly, the methoxyl group at low-field can be reasonably assigned to the intermediate **a**, and the other at up-field is assigned to **b** in Figure 3b and 4b, respectively. The 1:1 ratio of the intermediate **a** and **b** observed in different *para*-substituted *N*-methoxybenzamide substrates can be attributed to that the C-H activation with this Pd(II)/Sc(III) catalyst was insensitive to the substituent effect as shown in the studies on the substrate scope (see Scheme 1). As a result, the change on the *para*-substituent did not affect the stability of the intermediate **a** and **b** significantly, thus their 1:1 ratio was not broken in these semi-reactions. However, the sharp change of the electronic effect on aromatic ring by using 2,4-dichloro-*N*-methoxybenzamide as the substrate made a stability difference between **a** and **b**, resulting in the disappearance of **b** in ^{1}H NMR detection, whereas **a** was still observed, thus breaking the 1:1 ratio of **a** and **b**.

Taken together, these NMR data clearly evidenced the occurrence of two reaction intermediates, **a** and **b**, prior to the palladacycle formation in this Pd(II)/Sc(III) catalyzed olefination/annulation reaction. For the intermediate **1h-a** in Figure 4b, only two chemical shifts at 8.30 and 7.73 ppm displayed as AA'XX' system peaks, were disclosed for its aromatic protons, indicating that its two protons on the *ortho*-positions of aromatic ring have the identical chemical environment, and so do the two *meta*-protons. Therefore, it can be concluded that the interaction of the Pd(II)/Sc(III) species with **1h** to generate the intermediate **1h-a** did not make a difference in the chemical environment of its two *ortho*-protons, and so did for two *meta*-protons. However, the chemical environment of aromatic protons in **1h-a** did change when compared with those in **1h**, giving two chemical shifts at 8.30 and 7.73 ppm. On the other side, the chemical shift of the methoxyl group in **1h-a** downshifted to 4.35 ppm, indicating the nitrogen atom of the amide group was ligated to the Pd^{2+} cation in the Pd(II)/Sc(III) species.

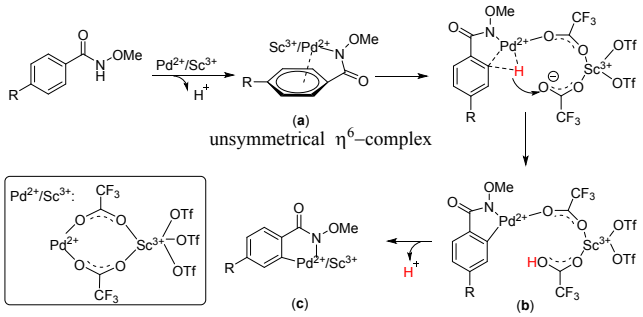
Accordingly, an unsymmetrical η^6-coordination of the Pd^{2+} cation on the aromatic ring could be assigned to the chemical structure of the intermediate **a** as shown in Figures 4b and 5b. Due to the unsymmetrical η^6-coordination of the Pd^{2+} cation, it made two distal *meta*-protons on the aromatic ring more electro-deficient, causing its significantly downshifted to 8.30 ppm, while two *ortho*-protons slightly upshifted to 7.73 ppm due to the shielding effect of the Pd(II)/Sc(III) species. Because of the identical chemical environment of two *ortho*-protons was not broken by the unsymmetrical η^6-coordination of the Pd^{2+} cation, they disclosed only one AA'XX' system peak in its ^{1}H NMR spectrum, and so do the two *meta*-protons.

For the intermediate **b**, comparing Figures 4b and 5b, it disclosed two doublet peaks at δ_H = 7.33 and 6.72 ppm, while another peak occurred at δ_H = 6.5 ppm which is plausibly singlet (Figure 3b). Significantly, the integral areas of three peaks indicated a ratio of 1:1:1 as stated above, and there was no other aromatic proton observed, clearly indicating that the intermediate **b** had lost one aromatic proton, that is, the C-H bond in arene had been cleaved after Pd(II)/Sc(III)-catalyzed C-H activation. Additionally, the ^{1}H-^{13}C HSQC spectrum disclosed that the carbon linked to this singlet proton (δ_H = 6.5 ppm) is still in sp^2 hybridization, not sp^3 hybridization (Figure S14), thus confirming that the intermediate **b** is not a Wheland intermediate. Furthermore, the pattern of three aromatic protons in the intermediate **b** is very similar to that of the palladacycle compound **c**, except that their chemical shifts are slightly downshifted, implying that the chemical environments of aromatic protons in **b** would be very similar to those in the palladacycle product **c**. According to these clues, the chemical structure of the intermediate **b** can be assigned as a palladacycle compound structurally similar to **c** but with the cleaved proton, that is, H^+, not released to the environment. One more unit of the positive

charge on the intermediate **b** led to its aromatic protons slightly downshifted when compared with the final palladacycle compound **c**.

In literature, the CMD mechanism was popularly proposed for Pd(II)-catalyzed C-H activation in arenes based on DFT calculations.[8-10] In the present study, no Wheland complex was observed, and the substituent effect was also not sensitive in the studies on substrate scope and ^{1}H NMR kinetics. Particularly, in competitive olefination/annulation reaction using *N*,4-dimethoxybenzamide (**1l**) and 4-fluoro-N-methoxybenzamide (**1c**) as the substrate mixtures under the standard conditions, it provided an 1.08:1 ratio of **4l**/**4c** as the product, and similar 1.04:1 ratio of **4k**/**4c** was obtained by using *N*-methoxy-4-methylbenzamide (**1k**) and 4-fluoro-N-methoxybenzamide (**1c**) as the substrate mixtures. Clearly, this Pd(II)/Sc(III) catalyzed olefination/annulation reaction is insensitive to the substituent effect, leading to the conclusion that the Wheland intermediate, that is, σ-complex, was not involved in this process, and the CMD mechanism was preferred.

Scheme 3 The proposed C-H activation process and hetero-bimetallic Pd(II)/Sc(III) species.



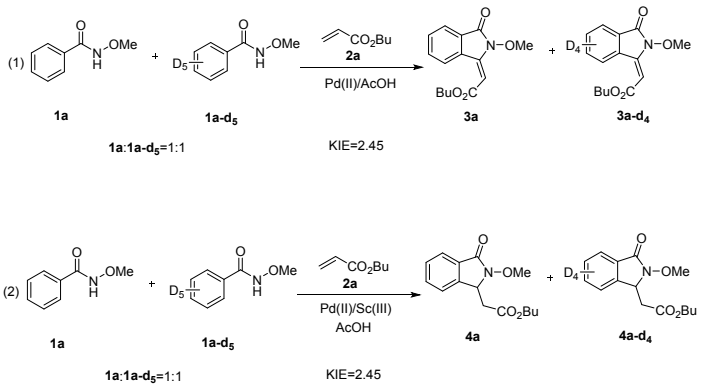
As discussed early, in investigating the influence of the Pd(II) sources on the catalytic efficiency, it was observed that using $Pd(TFA)_2$ as the Pd(II) source demonstrated a much better catalytic efficiency than $Pd(OAc)_2$ did (68% vs 43% yield, entries 3 and 4, Table S1), even

though HOAc was employed as the solvent. Clearly, trifluoroacetate served as the bridge in the heterobimetallic Pd(II)/Sc(III) species, and it was not exchanged with the acetate anion from solvent. Accordingly, the CMD mechanism through intramolecular proton abstraction *via* a base-assisted agostic interaction was proposed for this Pd(II)/Sc(III) catalyzed C-H activation as shown in Scheme 3. First of all, the *N*-methoxy amide group functioned as the directing group to facilitate the formation of the unsymmetrical η^6-complex, that is, the observed intermediate **a**. Next, *via* an intramolecular agostic hydrogen abstraction by CMD mechanism, the intermediate **b** was generated with the proton transferred to the ligated trifluoroacetate, thus the valence of Pd^{2+} did not go to +4 charge by oxidative addition, and it still remained at the level of the +2 charge as well as those in other Pd(II)-catalyzed C-H activation by CMD mechanism.[8,39] Releasing of the proton from **b** to the environment generated the final palladacycle **c** in this semi-reaction. Compared with the intermediate **c**, the slightly downshifted aromatic protons of the intermediate **b** in ^{1}H NMR spectrum can be attributed to its one more unit of positively charged state with H^+. In addition, in view of that $Pd(OAc)_2/Sc(OTf)_3$ demonstrated a poorer catalytic efficiency than $Pd(TFA)_2/Sc(OTf)_3$, the electrophilic properties of the Pd^{2+} cation in the heterobimetallic Pd(II)/Sc(III) species played a more significant role than the base-assisted intramolecular agostic hydrogen abstraction in catalysis.

Although Pd(II)-catalyzed C-H activation of arenes have been extensively investigated in the presence/absence of the directing group,[13,40] the direct observation of the π-complex was not reported yet, possibly due to its instability, even though such a π-complex was proposed as an intermediate prior to the C-H activation in the CMD mechanism.[10] Here, in the case of using $Pd(TFA)_2$ alone as the catalyst, the time-course of this semi-reaction monitored by ^{1}H NMR also disclosed a confused and unresolvable ^{1}H NMR spectrum which blocked the assignments of

protons to any plausible intermediate. Fortunately, using $Pd(TFA)_2/Sc(OTf)_3$ as the catalyst makes the ^1H NMR kinetics of this semi-reaction becoming clean, and an unsymmetrical η^6-complex could be successfully identified for the first time. The success of this assignment can be attributed to the formation of the heterobimetallic Pd(II)/Sc(III) species which served as the active species for C-H activation in this reaction. Binding a strong Lewis acid such as Sc^{3+} to the Pd(II) species through trifluoroacetate bridge may have enhanced its electrophilic properties, thus improving the stability of the η^6-complex **a**, and making it ^1H NMR distinguishable.

Scheme 4 KIE experiments for Pd(II)/Sc(III)-catalyzed olefination/annulation reaction.



To address whether the C-H activation is the rate determining step (rds) in this Pd(II)/Sc(III) catalyzed olefination/annulation reaction, kinetic isotopic effect (KIE) experiments were performed through competitive olefination/annualation reaction under the standard conditions (For more details, see Supporting Information). As shown in Scheme 4, using $Pd(TFA)_2$ alone as the catalyst, the reactions of *N*-methoxylbenzamide **1a/1a-*d*$_5$** with **2a** provided **3a** and **3a-*d*$_4$** as the product with a ratio of 2.45, indicating a KIE value of 2.45. Interestingly, in the case of using $Pd(TFA)_2/Sc(OTf)_3$ as the catalyst which provided **4a** and **4a-*d*$_4$** as the products, the KIE value was also 2.45, identical to that of using $Pd(TFA)_2$, except that the products were different. This

information not only supports that the C-H activation is the rds, and the coming olefination/annulations are fast steps, but also may have implied that formation of the heterobimetallic Pd(II)/Sc(III) species did not change the properties of the transition state in C-H activation when compared with the C-H activation by the Pd(II) species alone, for example, shifting from an early transition state to a late transition state, or vice versa.

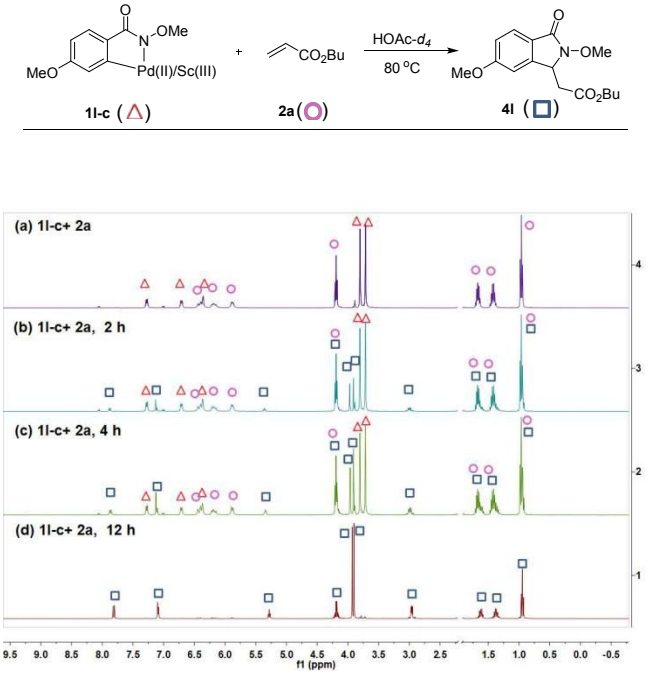
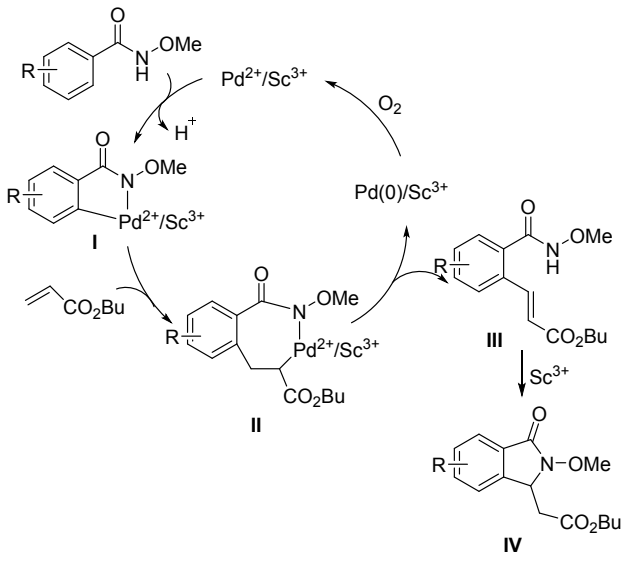


Figure 5 ^{1}H NMR kinetics of the semi-reaction between butyl acrylate (**2a**) and palladacycle intermediate **1l-c** with equivalent $Sc(OTf)_3$ in HOAc-d_4 at room temperature.

To further detect the reaction intermediate for this Pd(II)/Sc(III) catalyzed olefination/annulation reaction, the ^{1}H NMR kinetic experiments between the palladacycle **1l-c** and **2a** were conducted. The reaction proceeded smoothly to give the final product **4l** (Figure 5), the ^{1}H NMR kinetics clearly displayed the disappearance of two substrate with the formation of **4l**; however, there was no reaction intermediate observed, even though several intermediates such as the olefination intermediate **7** could be expected before **4l** formation (see Scheme 2, eq.

4). This ^{1}H NMR kinetics is consistent well with the results from above KIE experiments, that is, the activation of C-H bond in arene is the rds of the whole reaction, and the follow-up olefination/annulation steps are fast.

Scheme 5 A simplified mechanism for Pd(II)/Sc(III)-catalyzed olefination/annulation reaction.



Taken together, a simplified catalytic cycle was proposed in Scheme 5 as well as those in literatures.[37,41-43] First, the *N*-methoxyl amide group directed C-H activation by the Pd(II)/Sc(III) species led to the formation of the palladacycle compound **I,** and its detailed formation process was described in Scheme 3. Next, olefin insertion of the compound **I** provided another palladacycle compound **II**, which next generated the olefination product **III** through β-hydride elimination with the Pd(0)/Sc(III) species formation. Finally, the intermediate **III** was catalyzed by Sc^{3+} to provide the annulation product **IV** through aza-Michael addition, meanwhile the Pd(0)/Sc(III) species was re-oxidized to the active Pd(II)/Sc(III) species by O_2 to achieve the catalytic cycle.

CONCLUSION

In summary, a Pd(II)/LA-catalyzed olefination/annulation reaction was explored with oxygen as the oxidant source, in which two reaction intermediates including an unsymmetrical η^6-complex and a palladacycle species without the proton releasing to the environment were identified through NMR characterizations. Adding LA such as $Sc(OTf)_3$ to the $Pd(TFA)_2$ catalyst significantly improved its catalytic efficiency and changed the product distribution. The improved catalytic activity was attributed to the formation of the trifluoroacetate bridged heterometallic Pd(II)/Sc(III) species, which enhanced the electrophilic properties of the Pd^{2+} cation, thus stabilizing the π-complex, herein, η^6-complex, and making its identifiable through NMR characterizations. The observed insensitive electronic effect in catalysis supported that a CMD mechanism mediated this Pd(II)/Sc(III)-catalyzed olefination/annulation reaction, and the identified palladacycle intermediate without the proton releasing to the environment also provided a clue to support this mechanism. The intermediates identified in the present study may benefit a better understanding of the fundamental knowledge about the Pd(II)-catalyzed C-H activation in arenes.

EXPERIMENTAL SECTION

1. Materials and Analytical Methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Compounds **1a-1t** was synthesized following the literature.[29b] Compounds **8** and **9** were synthesized following the literature.[44] Compounds **5**, **6** and **7** were synthesized following the literature with modifications.[29b] UV-vis spectra were collected on Agilent Technologies Cary-8454 UV-vis spectrometer. The reactions were monitored by TLC with Haiyang GF-254 silica gel plates (Qingdao Haiyang chemical industry Co. Ltd, Qingdao,

China) using UV light or $KMnO_4$ as visualizing agents as needed. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. ^1H NMR spectra and ^{13}C NMR spectra for the synthesized compounds were recorded in $CDCl_3$ or DMSO-d_6 while ^1H NMR and ^1H-^{13}C HSQC spectra for kinetic analysis were recorded in HOAc-d_4 on a Brüker AV-400 spectrometer. Chemical shifts (δ) were expressed in ppm (parts per million) with TMS as the internal standard, and coupling constants (*J*) were reported in hertz (Hz). High-resolution mass spectra were obtained on mass spectrometer by using ESI FT-ICR Mass.

2. General Procedure for Oxidative Olefination/Annulation of *N*-methoxybenzamides with $Pd(TFA)_2$/$Sc(OTf)_3$ Catalyst in HOAc

In a typical procedure, $Pd(TFA)_2$ (6.6 mg, 0.02 mmol) and $Sc(OTf)_3$ (19.7 mg, 0.04 mmol) were dissolved in HOAc (2 mL) in a glass tube. After pre-stirring the prepared solution for 20 min under 70 °C, **1** (0.2 mmol) and **2** (0.4 mmol) were added in. The glass tube was next sealed under O_2 atmosphere, and then stirred at 100 °C using IKA heating mantle for desired reaction time. After the reaction, the solvent was removed under reduced pressure. The residual was purified by column chromatography on a silica gel (Petroleum Ether/Ethyl Acetate: 1/1–3/1) to give the corresponding products.

3. General Procedure for Oxidative Olefination/Annulation of *N*-methoxybenzamides with butyl acrylate using Pd(II)/Sc(III) catalyst on a gram scale

In a typical procedure, $Pd(TFA)_2$ (166.2 mg, 0.5 mmol) and $Sc(OTf)_3$ (246.1 mg, 0.5 mmol) were dissolved in HOAc (50 mL) in a round-bottom flask. After pre-stirring the prepared solution for 20 min under 70 °C, **1a** (755.8 mg, 5 mmol) and **2a** (720 μL, 5 mmol) were added in. The reaction flask was next sealed under O_2 atmosphere, and then stirred at 100 °C using oil

bath for 12 h. After the reaction, the solvent was removed under reduced pressure. The residual was purified by column chromatography on a silica gel (Petroleum Ether/Ethyl Acetate: 3/1) to give the corresponding products **4a** (0.832 g, 60% yield).

4. General Procedure for the Synthesis of butyl (*E*)-3-(N-methoxybenzamido)acrylate (5):

A mixture of *N*-methoxybenzamides **1a** (75.6 mg, 0.5 mmol), butyl acrylate **2a** (144 μL, 1 mmol), $PdCl_2(CH_3CN)_2$ (25.6 mg, 0.1 mmol) and CuCl (54.6 mg, 0.11 mmol) in Et_2O was stirred for 8 h at 50 °C using oil bath in a high pressure reactor under O_2 atmosphere. After that, the solvent was removed by rotary evaporation. Finally, the residual was purified by column chromatography on a silica gel (Petroleum Ether/Ethyl Acetate: 5/1 as the eluent) to give the desired products **5** (31.9 mg, 23%).

5. General Procedure for the Synthesis of butyl 3-(N-methoxybenzamido)propanoate (6):

A mixture of *N*-methoxybenzamides **1a** (75.6 mg, 0.5 mmol), butyl acrylate **2a** (144 μL, 1 mmol) and *t*-BuOK (14.0 mg, 0.125 mmol) in MeOH was stirred overnight at room temperature. After that, the solvent was removed by rotary evaporation. The residual was purified by column chromatography on a silica gel (Petroleum Ether/Ethyl Acetate: 3/1 as the eluent) to give the desired products **6** (81 mg, 58%).

6. General Procedure for the Synthesis of Butyl (*E*)-3-(2-(methoxycarbamoyl)phenyl)acrylate (7):

Methyl anthranilate (1.51 g, 10 mmol) was dissolved in 10% NaOH aqueous solution and stirred at 60 °C in a water bath overnight. The mixture was then acidified to pH=4 ~ 5 with 12 M

HCl solution, and a white solid was precipitated, then filtered and dried in a vacuum oven to give 2-aminobenzoic acid as a white solid (1.32 g, 96% yield).

A solution of $NaNO_2$ (552 mg, 8.0 mmol) in water (3 mL) was added dropwise to an ice-cold 2-aminobenzoic acid (1.1 g, 8.0 mmol) in 42% HBF_4 (3.3 mL). The mixture was stirring continued for 1 h at 0 °C after which methanol (0.5 mL), butyl acrylate (1.6 mL, 11.2 mmol) and $Pd(OAc)_2$ (35 mg, 0.15 mmol) were added to the mixture, which was then heated to 60 °C in a water bath for 1 h. Then the mixture was extracted with diethyl ether, and the extract was washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4 and concentrated by rotary evaporator. Then the residue was purified by column chromatography on silica gel gave (*E*)-2-(3-butoxy-3-oxoprop-1-en-1-yl)benzoic acid as a white solid (1.79 g, 90% yield).

Subsequently, (*E*)-2-(3-butoxy-3-oxoprop-1-en-1-yl)benzoic acid (1.24 g, 5 mmol), $SOCl_2$ (0.73 mL, 10 mmol) and pyridine (0.5 mL) in a CH_2Cl_2 (20 mL) solution was stirred at 40 °C in a water bath for 4 h, then the butyl (*E*)-3-(2-(chlorocarbonyl)phenyl)acrylate containing mixture was used for next step without further isolation after remove the solvent.

O-Methylhydroxylamine hydrochloride (0.42 g, 5 mmol) and K_2CO_3 (1.38 g, 10 mmol) were dissolved in a mixture of H_2O (15 mL) and EtOAc (30 mL) in a round bottom flask which was cooled to 0 °C in an ice bath. Subsequently, butyl (*E*)-3-(2-(chlorocarbonyl)phenyl)acrylate was added into above solution via syringe. Then the mixture was stirring at room temperature for 0.5 h. After that, the organic layer was washed with brine, dried with Na_2SO_4 and evaporated. Finally, the residue was recrystallization from petroleum ether/ethyl acetate to give the desired product **7** Butyl (*E*)-3-(2-(methoxycarbamoyl)phenyl)acrylate (0.83 g, 60% yield).

butyl (E)-2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate[29a,29b] ***(3a):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.58, 15.4 mg, 28% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 9.01

(d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 6.00 (s, 1H), 4.24 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 1.72 (dd, *J* = 9.2, 5.3 Hz, 2H), 1.46 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 161.8, 143.8, 133.7, 131.6, 130.3, 128.3, 127.5, 123.4, 97.9, 64.7, 64.5, 30.9, 19.3, 13.9.

butyl (E)-2-(6-fluoro-2-methoxy-3-oxoisoindolin-1-ylidene)acetate ***(3c):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.5, 10 mg, 17% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.28 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.00 (s, 1H), 4.22 (t, *J* = 6.6 Hz, 2H), 4.02 (s, 3H), 1.74-1.65 (m, 2H), 1.44 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.4, 165.8, 164.8, 160.8, 142.9 (d, $J_{C\text{-}F}$ = 2.9 Hz), 132.4 (d, $J_{C\text{-}F}$ = 11.7 Hz), 125.4 (d, $J_{C\text{-}F}$ = 9.8 Hz), 123.4 (d, $J_{C\text{-}F}$ = 2.6 Hz), 119.0, 118.7, 116.3, 116.0, 98.7, 64.8, 64.5, 30.7, 19.2, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{16}FNO_4$ $[M+H]^+$: 294.1136, found: 294.1131.

butyl (E)-2-(4-chloro-2-methoxy-3-oxoisoindolin-1-ylidene)acetate ***(3d):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.68, 7.4 mg, 12% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 1.74-1.68 (m, 2H), 1.46 (dd, *J* = 15.0, 7.5 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 159.5, 142.1, 134.2, 133.2, 132.4, 131.5, 126.8, 123.4, 98.2, 64.7, 64.4, 30.7, 19.2, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{16}ClNO_4$ $[M+H]^+$: 310.0841, found: 310.0836.

butyl (E)-2-(5-chloro-2-methoxy-3-oxoisoindolin-1-ylidene)acetate ***(3e):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.7, 8.7 mg, 14% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 1.5 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.01 (s, 1H), 4.24 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 1.76-1.67 (m, 2H), 1.52-1.40 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 160.4, 142.9, 138.0, 133.5, 129.7, 129.1, 128.3, 123.5, 98.5, 64.7, 64.5, 30.7, 19.2, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{16}ClNO_4$ $[M+H]^+$: 310.0841, found: 310.0836.

butyl (E)-2-(6-chloro-2-methoxy-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3f):*** Yellowish solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.6, 8 mg, 13% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.97 (s, 3H), 1.69-1.61 (m, 2H), 1.39 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.7, 160.7, 142.6, 140.0, 131.7, 131.5, 128.5, 125.6, 124.4, 98.8, 64.8, 64.4, 30.8, 19.2, 13.7.

butyl (E)-2-(5-bromo-2-methoxy-3-oxoisoindolin-1-ylidene)acetate ***(3g):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.75, 7 mg, 10% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (t, *J* = 14.7 Hz, 1H), 7.98 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.03 (s, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 4.04 (s, 3H), 1.72 (dd, *J* = 9.7, 5.2 Hz, 2H), 1.46 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 160.3, 143.0, 136.4, 129.8, 129.1, 128.7, 126.5, 126.1, 98.6, 64.8, 64.5, 30.7, 19.2, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{16}BrNO_4$ $[M+H]^+$: 354.0335, found: 354.0330.

butyl (E)-2-(6-bromo-2-methoxy-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3h):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.7, 9.9 mg, 14% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 1.2 Hz, 1H), 7.78-7.69 (m, 2H), 6.02 (s, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 1.75-1.70 (m, 2H), 1.46 (dd, *J* = 15.1, 7.5 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.7, 160.9, 142.4, 134.7, 131.6, 131.3, 128.4, 126.1, 124.5, 98.9, 64.9, 64.5, 30.7, 19.2, 13.7.

butyl (E)-2-(2-methoxy-4-methyl-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3i):*** Yellowish solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.7, 9.2 mg, 16% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 5.87 (s, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.95 (s, 3H), 2.63 (s, 3H), 1.68-1.58 (m, 2H), 1.46-1.31 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 162.5, 143.7, 137.8, 133.9, 133.0, 130.7, 125.8, 124.2, 96.7, 64.5, 64.2, 30.8, 19.2, 17.5, 13.8.

butyl (E)-2-(2-methoxy-5-methyl-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3j):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.71, 7.5 mg, 13% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 5.95 (s, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 4.04 (s, 3H), 2.48 (s, 3H), 1.77-1.66 (m, 2H), 1.53-1.39 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 161.9, 143.9, 142.4, 134.2, 128.1, 127.6, 127.5, 123.7, 97.0, 64.5, 64.3, 30.8, 21.7, 19.2, 13.7.

butyl (E)-2-(2-methoxy-6-methyl-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3k):*** Yellowish solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.5, 12.7 mg, 22% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 4.01 (s, 3H), 2.49 (s, 3H), 1.75 – 1.64 (m, 2H), 1.44 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 161.9, 144.6, 144.0, 132.2, 130.4, 128.7, 124.8, 123.2, 97.4, 64.6, 64.3, 30.8, 22.4, 19.2, 13.8.

butyl (E)-2-(2,6-dimethoxy-3-oxoisoindolin-1-ylidene)acetate[29b] ***(3l):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.48, 15.9 mg, 26% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.0 Hz, 1H), 5.94 (s, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 4.01 (s, 3H), 3.92 (s, 3H), 1.75-1.64 (m, 2H), 1.50-1.38 (m, 2H), 0.96 (t, *J* = 7.4

Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2, 164.4, 161.9, 144.2, 132.5, 124.9, 119.6, 118.1, 113.1, 97.6, 64.7, 64.4, 56.0, 30.9, 19.3, 13.9.

butyl (E)-2-(6-(tert-butyl)-2-methoxy-3-oxoisoindolin-1-ylidene)acetate ***(3q):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.67, 13.9 mg, 21% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 5.96 (s, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 4.01 (s, 3H), 1.75 – 1.66 (m, 2H), 1.45 (dd, *J* = 15.1, 7.5 Hz, 2H), 1.39 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 161.9, 157.9, 144.2, 130.4, 128.6, 125.6, 124.7, 123.0, 97.4, 64.6, 64.3, 35.9, 31.4, 30.8, 19.3, 13.8; HRMS (ESI) m/z: calculated for $C_{19}H_{25}NO_4$ $[M+H]^+$: 332.1856, found: 332.1850.

methyl (E)-2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate[29a] ***(3s):*** White solid (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.56, 12.1 mg, 26% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 6.00 (s, 1H), 4.04 (s, 3H), 3.84 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 161.6, 143.9, 133.6, 131.5, 130.1, 128.1, 127.4, 123.3, 97.2, 64.3, 51.8.

ethyl (E)-2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate[45] ***(3t):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.5, 13.4 mg, 27% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 6.00 (s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 4.04 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 161.6, 143.7, 133.5, 131.5, 130.2, 128.2, 127.4, 123.3, 97.8, 64.3, 60.7, 14.3.

butyl (E)-2-(2-ethoxy-3-oxoisoindolin-1-ylidene)acetate ***(3u):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.63, 4.6 mg, 8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 5.98 (s, 1H), 4.33-4.20 (m, 4H), 1.77-1.68 (m, 2H), 1.47 (dt, *J* = 14.2, 7.3 Hz, 5H), 0.98 (t, *J* = 7.3 Hz,

3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 162.1, 144.6, 133.5, 131.4, 130.3, 128.1, 127.5, 123.3, 97.8, 72.9, 64.6, 30.8, 19.2, 13.7, 13.6; HRMS (ESI) m/z: calculated for $C_{16}H_{19}NO_4$ $[M+H]^+$: 290.1387, found: 290.1382.

butyl 2-(2-methoxy-3-oxoisoindolin-1-yl)acetate[29a] ***(4a):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.35, 37.7 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.58 (dd, *J* = 10.8, 4.1 Hz, 1H), 7.53-7.41 (m, 2H), 5.21 (t, *J* = 6.2 Hz, 1H), 4.26-4.07 (m, 2H), 3.96 (s, 3H), 2.94 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.74 (dd, *J* = 16.1, 6.4 Hz, 1H), 1.71-1.56 (m, 2H), 1.46-1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.7, 164.7, 141.7, 132.7, 129.8, 129.0, 124.1, 122.7, 65.2, 63.9, 56.3, 37.3, 30.6, 19.1, 13.8.

butyl 2-(2-methoxy-6-nitro-3-oxoisoindolin-1-yl)acetate ***(4b):*** Yellowish oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.23, 40.6 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.8 Hz, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 5.29 (t, *J* = 6.3 Hz, 1H), 4.25-4.15 (m, 2H), 4.00 (s, 3H), 3.08 (dd, *J* = 16.5, 5.7 Hz, 1H), 2.77 (dd, *J* = 16.5, 7.0 Hz, 1H), 1.62 (dd, *J* = 14.7, 7.0 Hz, 2H), 1.36 (dt, *J* = 14.6, 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.9, 161.9, 150.5, 142.5, 135.4, 125.1, 124.5, 118.7, 65.5, 64.1, 56.2, 36.4, 30.5, 19.1, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{18}N_2O_6$ $[M+H]^+$: 323.1238, found: 323.1242.

butyl 2-(6-fluoro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4c):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.6, 39.6 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.9, 5.3 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 2H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.17 (dd, *J* = 11.4, 6.4 Hz, 2H), 3.95 (s, 3H), 3.00 (dd, *J* = 16.4, 5.9 Hz, 1H), 2.69 (dd, *J* = 16.4, 7.0 Hz, 1H), 1.69-1.56 (m, 2H), 1.44-1.30 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 166.7, 164.2, 163.8, 144.1 (d, J_{C-F} = 9.8 Hz), 126.2 (d, J_{C-F} = 9.7 Hz), 125.7 (d, J_{C-F} = 2.4 Hz),

116.6 (d, J_{C-F} = 23.1 Hz), 110.5 (d, J_{C-F} = 24.4 Hz), 65.2, 64.0, 56.1 (d, J_{C-F} = 2.3 Hz), 36.9, 30.5, 19.0, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{18}FNO_4$ $[M+H]^+$: 296.1293, found: 296.1288.

butyl 2-(4-chloro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4d):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.67, 19.9 mg, 32% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 5.13 (t, *J* = 6.2 Hz, 1H), 4.20-4.09 (m, 2H), 3.95 (s, 3H), 2.94 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.71 (dd, *J* = 16.2, 6.4 Hz, 1H), 1.64-1.56 (m, 2H), 1.35 (dq, *J* = 14.6, 7.4 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 162.9, 144.1, 133.1, 132.0, 130.6, 126.1, 121.2, 65.2, 64.0, 55.6, 37.2, 30.6, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{18}ClNO_4$ $[M+H]^+$: 312.0997, found: 312.0992.

butyl 2-(5-chloro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4e):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.6, 40 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.51 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 5.15 (t, *J* = 6.3 Hz, 1H), 4.13 (dt, *J* = 10.2, 5.1 Hz, 2H), 3.93 (s, 3H), 2.94 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.67 (dd, *J* = 16.2, 6.7 Hz, 1H), 1.64 – 1.52 (m, 2H), 1.35 (dt, *J* = 14.8, 7.4 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 163.2, 139.8, 135.4, 132.6, 131.6, 124.3, 124.2, 65.3, 64.1, 56.1, 37.0, 30.6, 19.2, 13.8; HRMS (ESI) m/z: calculated for $C_{15}H_{18}ClNO_4$ $[M+H]^+$: 312.0997, found: 312.0992.

butyl 2-(6-chloro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4f):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.58, 36.8 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 5.9 Hz, 2H), 5.18 (t, *J* = 6.4 Hz, 1H), 4.18 (td, *J* = 6.6, 2.6 Hz, 2H), 3.95 (s, 3H), 2.99 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.70 (dd, *J* = 16.4, 6.9 Hz, 1H), 1.68-1.56 (m, 2H), 1.38 (dt, *J* = 15.0, 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ

170.3, 163.6, 143.1, 138.8, 129.5, 128.1, 125.3, 123.3, 65.2, 64.0, 55.9, 36.8, 30.5, 19.0, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{18}ClNO_4$ $[M+H]^+$: 312.0997, found: 312.0999.

butyl 2-(5-bromo-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4g):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.62, 39.8 mg, 56% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 5.13 (t, *J* = 6.3 Hz, 1H), 4.18-4.09 (m, 2H), 3.93 (s, 3H), 2.95 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.67 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.64-1.52 (m, 2H), 1.34 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 163.1, 140.3, 135.4, 131.8, 127.2, 124.6, 123.1, 65.3, 64.1, 56.2, 36.9, 30.6, 19.2, 13.8; HRMS (ESI) m/z: calculated for $C_{15}H_{18}BrNO_4$ $[M+H]^+$: 356.0492, found: 356.0486.

butyl 2-(6-bromo-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4h):*** Yellowish oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.38, 42.7 mg, 60% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 5.2 Hz, 2H), 5.17 (t, *J* = 6.3 Hz, 1H), 4.18 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.98 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.70 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.68-1.57 (m, 2H), 1.44-1.31 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 163.7, 143.3, 132.4, 128.6, 127.1, 126.3, 125.4, 65.2, 64.0, 55.9, 36.8, 30.5, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{18}BrNO_4$ $[M+H]^+$: 356.0492, found: 356.0487.

butyl 2-(2-methoxy-4-methyl-3-oxoisoindolin-1-yl)acetate ***(4i):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.5, 28.6 mg, 49% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 2H), 5.13 (t, *J* = 6.4 Hz, 1H), 4.22-4.09 (m, 2H), 3.94 (s, 3H), 2.88 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.77-2.64 (m, 4H), 1.60 (dd, *J* = 14.8, 7.0 Hz, 2H), 1.36 (dq, *J* = 14.7, 7.5 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 166.1, 142.4, 138.4, 132.0, 130.9, 126.8, 120.0, 65.1, 63.9, 56.0, 37.7, 30.7, 19.2, 17.4, 13.8; HRMS (ESI) m/z: calculated for $C_{16}H_{21}NO_4$ $[M+H]^+$: 292.1543, found: 292.1545.

butyl 2-(2-methoxy-5-methyl-3-oxoisoindolin-1-yl)acetate ***(4j):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.42, 39 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.28 (m, 1H), 5.16 (t, *J* = 6.4 Hz, 1H), 4.15 (dt, *J* = 10.6, 5.4 Hz, 2H), 3.94 (s, 3H), 2.91 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.70 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.43 (s, 3H), 1.66-1.56 (m, 2H), 1.42-1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 164.8, 139.1, 138.8, 133.3, 129.7, 124.2, 122.4, 65.0, 63.8, 56.1, 37.4, 30.6, 21.4, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{16}H_{21}NO_4$ $[M+H]^+$: 292.1543, found: 292.1546.

butyl 2-(2-methoxy-6-methyl-3-oxoisoindolin-1-yl)acetate ***(4k):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.52, 41.4 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.29-7.23 (m, 1H), 7.20 (s, 1H), 5.12 (t, *J* = 6.4 Hz, 1H), 4.14 (td, *J* = 6.5, 4.1 Hz, 2H), 3.91 (s, 3H), 2.89 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.68 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.42 (s, 3H), 1.67-1.53 (m, 2H), 1.33 (dt, *J* = 14.6, 7.3 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 165.1, 143.4, 142.1, 130.0, 127.0, 124.0, 123.2, 65.1, 64.0, 56.3, 37.4, 30.7, 22.2, 19.2, 13.8; HRMS (ESI) m/z: calculated for $C_{16}H_{21}NO_4$ $[M+H]^+$: 292.1543, found: 292.1545.

butyl 2-(2,6-dimethoxy-3-oxoisoindolin-1-yl)acetate ***(4l):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.4, 46.1 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 5.11 (t, *J* = 6.5 Hz, 1H), 4.18-4.09 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 2.90 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.68 (dd, *J* = 16.2, 6.5 Hz, 1H), 1.62-1.56 (m, 2H), 1.38-1.30 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 165.4, 163.5, 144.1, 125.7, 121.9, 115.3, 108.0, 65.1, 64.0, 56.4, 55.8, 37.5,

30.7, 19.2, 13.8; HRMS (ESI) m/z: calculated for $C_{16}H_{21}NO_5$ $[M+H]^+$: 308.1492, found: 308.1495.

butyl 2-(2,5,6-trimethoxy-3-oxoisoindolin-1-yl)acetate ***(4m):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 2/1, R_f = 0.3, 34.4 mg, 51% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.91 (s, 1H), 5.08 (t, *J* = 6.4 Hz, 1H), 4.21-4.09 (m, 2H), 3.92 (d, *J* = 10.2 Hz, 9H), 2.94 (dd, *J* = 16.2, 6.1 Hz, 1H), 2.66 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.68-1.53 (m, 2H), 1.35 (dt, *J* = 14.4, 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 165.9, 153.3, 150.2, 135.6, 121.7, 105.7, 105.1, 65.0, 64.0, 56.3, 56.2, 37.5, 30.6, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{17}H_{23}NO_6$ $[M+H]^+$: 338.1598, found: 338.1593.

butyl 2-(5,7-difluoro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4n):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.46, 20.6 mg, 33% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.04 (td, *J* = 9.0, 2.2 Hz, 1H), 5.31 (dd, *J* = 7.0, 3.9 Hz, 1H), 4.18-4.05 (m, 2H), 3.95 (s, 3H), 3.07 (dd, *J* = 15.9, 4.0 Hz, 1H), 2.76 (dd, *J* = 15.9, 7.4 Hz, 1H), 1.57 (dt, *J* = 8.5, 6.7 Hz, 2H), 1.35 (dt, *J* = 15.1, 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.7, 164.8 (d, J_{C-F} = 9.7 Hz), 162.6-162.1 (m), 158.7 (d, J_{C-F} = 11.7 Hz), 156.2 (d, J_{C-F} = 11.7 Hz), 133.7 (dd, J_{C-F} = 9.9, 5.7 Hz), 122.8 (dd, J_{C-F} = 16.8, 3.2 Hz), 108.1-107.3 (m), 65.1, 64.0, 54.2 (d, J_{C-F} = 1.7 Hz), 35.7, 30.5, 19.0, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{17}F_2NO_4$ $[M+Na]^+$: 336.1018, found: 336.1019.

butyl 2-(5,7-dichloro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4o):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.5, 19.4 mg, 28% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 5.32-5.26 (m, 1H), 4.18-4.02 (m, 2H), 3.93 (s, 3H), 3.31 (dd, J = 16.3, 2.9 Hz, 1H), 2.70 (dd, J = 16.3, 7.8 Hz, 1H), 1.62-1.53 (m, 2H), 1.34 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.8, 162.3, 136.5, 136.1, 133.6,

132.5, 129.9, 122.9, 65.1, 64.0, 55.8, 34.4, 30.5, 19.0, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{17}Cl_2NO_4$ $[M+Na]^+$: 368.0427, found: 368.0427.

butyl 2-(5,6,7-trifluoro-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4p):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.42, 15.9 mg, 24% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, J = 7.7, 6.1, 1.6 Hz, 1H), 5.31 (t, *J* = 5.5 Hz, 1H), 4.12 (qt, *J* = 10.8, 6.7 Hz, 2H), 3.95 (s, 3H), 3.07 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.80 (dd, *J* = 16.0, 7.2 Hz, 1H), 1.60-1.55 (m, 2H), 1.41-1.32 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.3, 162.2, 153.6 (d, $J_{C\text{-}F}$ = 12.7 Hz), 151.1 (d, $J_{C\text{-}F}$ = 11.3 Hz), 147.7 (d, $J_{C\text{-}F}$ = 12 Hz), 145.2 (d, $J_{C\text{-}F}$ = 9.8 Hz), 144.1 (dd, $J_{C\text{-}F}$ = 9.4, 4.8 Hz), 141.5 ($J_{C\text{-}F}$, J = 16.3 Hz), 126.3-125.6 (m), 124.2 (dd, $J_{C\text{-}F}$ = 13.3, 3.1 Hz), 108.7 (dd, $J_{C\text{-}F}$ = 19.8, 3.9 Hz), 65.2, 64.2, 54.2, 35.5, 30.5, 19.0, 13.6; HRMS (ESI) m/z: calculated for $C_{15}H_{16}F_3NO_4$ $[M+Na]^+$: 354.0924, found: 354.0924.

butyl 2-(6-(tert-butyl)-2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4q):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.4, 45.3 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 5.19 (t, *J* = 6.4 Hz, 1H), 4.18 (t, *J* = 6.3 Hz, 2H), 3.94 (s, 3H), 2.93 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.73 (dd, *J* = 16.0, 6.3 Hz, 1H), 1.68-1.56 (m, 2H), 1.42-1.29 (m, 11H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 164.9, 156.5, 141.7, 126.9, 126.3, 123.6, 119.3, 65.0, 63.8, 56.4, 37.5, 35.5, 31.3, 30.6, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{19}H_{27}NO_4$ $[M+H]^+$: 334.2013, found: 334.2007.

butyl 2-(2-methoxy-1-oxo-2,3-dihydro-1H-benzo[e]isoindol-3-yl)acetate ***(4r):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.46, 9.2 mg, 14% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 5.26 (t, *J* = 6.3 Hz, 1H), 4.23-4.12 (m, 2H), 4.01 (s, 3H), 2.96 (dd, *J* = 16.1, 6.6 Hz, 1H), 2.83 (dd, *J* = 16.1, 6.0 Hz, 1H), 1.59 (dd, *J*

= 14.6, 6.9 Hz, 2H), 1.34 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.7, 166.7, 142.1, 133.4, 133.3, 129.3, 128.3, 128.2, 127.0, 124.0, 123.9, 119.4, 65.1, 64.1, 56.5, 37.2, 30.6, 19.1, 13.6; HRMS (ESI) m/z: calculated for $C_{19}H_{21}NO_4$ $[M+H]^+$: 328.1543, found: 328.1539.

methyl 2-(2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4s):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 2/1, R_f = 0.3, 31 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 5.19 (t, *J* = 6.4 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 2.93 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.70 (dd, *J* = 16.2, 6.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.0, 164.5, 141.5, 132.4, 129.6, 128.9, 124.0, 122.6, 63.8, 56.1, 52.1, 37.0; HRMS (ESI) m/z: calculated for $C_{12}H_{13}NO_4$ $[M+H]^+$: 236.0917, found: 236.0914.

ethyl 2-(2-methoxy-3-oxoisoindolin-1-yl)acetate ***(4t):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 2/1, R_f = 0.38, 34.9 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.38 (m, 2H), 5.18 (t, *J* = 6.3 Hz, 1H), 4.27 – 4.08 (m, 2H), 3.93 (s, 3H), 2.90 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.71 (dd, *J* = 16.1, 6.4 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 164.7, 141.7, 132.5, 129.8, 129.0, 124.1, 122.8, 64.0, 61.3, 56.3, 37.4, 14.2; HRMS (ESI) m/z: calculated for $C_{13}H_{15}NO_4$ $[M+H]^+$: 250.1074, found: 250.1070.

butyl 2-(2-ethoxy-3-oxoisoindolin-1-yl)acetate ***(4u):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.37, 22.7 mg, 39% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 5.20 (t, *J* = 6.4 Hz, 1H), 4.23-4.11 (m, 4H), 2.94 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.70 (dd, *J* = 16.2, 6.3 Hz, 1H), 1.69-1.55 (m, 2H), 1.38 (dt, *J* = 14.1, 7.2 Hz, 5H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101

MHz, $CDCl_3$) δ 170.7, 164.7, 141.7, 132.2, 129.8, 128.8, 124.0, 122.6, 71.9, 65.0, 56.7, 37.4, 30.5, 19.1, 13.7, 13.6; HRMS (ESI) m/z: calculated for $C_{16}H_{21}NO_4$ $[M+H]^+$: 292.1543, found: 292.1538.

butyl 2-(5-methoxy-6-oxo-5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-yl)acetate ***(4v):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.38, 13.6 mg, 24% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 4.8 Hz, 1H), 5.12-5.04 (m, 1H), 4.23-4.10 (m, 2H), 3.95 (s, 3H), 3.04 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.64 (dd, *J* = 16.3, 7.9 Hz, 1H), 1.67-1.58 (m, 2H), 1.38 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 162.9, 151.6, 135.5, 132.0, 121.7, 65.1, 64.5, 57.1, 36.8, 30.6, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{13}H_{17}NO_4S$ $[M+H]^+$: 284.0951, found: 284.0947.

butyl (E)-3-(N-methoxybenzamido)acrylate ***(5):*** White solid (Petroleum Ether/Ethyl Acetate = 5/1, R_f = 0.52, 31.9 mg, 23% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 11.9 Hz, 1H), 7.75 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 5.67 (d, *J* = 13.7 Hz, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.66 (s, 3H), 1.67-1.61 (m, 2H), 1.40 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.2, 166.6, 136.6, 132.2, 131.8, 129.0, 128.5, 99.7, 64.3, 62.4, 30.8, 19.2, 13.8; HRMS (ESI) m/z: calculated for $C_{15}H_{19}NO_4$ $[M+Na]^+$: 300.1206, found: 300.1203.

butyl 3-(N-methoxybenzamido)propanoate ***(6):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 3/1, R_f = 0.5, 81 mg, 58% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.43 (dt, *J* = 23.8, 7.1 Hz, 3H), 4.08 (dt, *J* = 22.2, 6.8 Hz, 4H), 3.54 (s, 3H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.67-1.56 (m, 2H), 1.38 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 170.2, 134.1, 130.7, 128.1, 64.7, 61.6, 42.3, 32.3, 30.6, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{21}NO_4$ $[M+Na]^+$: 302.1363, found: 302.1359.

Butyl (E)-3-(2-(methoxycarbamoyl)phenyl)acrylate[29a] ***(7):*** White solid (Recrystallization from Petroleum Ether/Ethyl Acetate, 0.83 g, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.94 (d, *J* = 15.9 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51-7.43 (m, 2H), 7.43-7.35 (m, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 4.17 (t, *J* = 6.7 Hz, 2H), 3.91 (s, 3H), 1.72-1.61 (m, 2H), 1.41 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5 (d, *J* = 16.7 Hz), 141.2, 133.4, 130.9, 129.7, 128.1, 127.1, 121.1, 64.6 (d, *J* = 4.1 Hz), 30.7, 19.1, 13.7; HRMS (ESI) m/z: calculated for $C_{15}H_{19}NO_4$ $[M+Na]^+$: 300.1206, found: 300.1207.

N-benzyl-O-methylhydroxylamine[44] ***(8):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 8/1, R_f = 0.32, 34.3 mg, 50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 5.75 (s, 1H), 4.08 (s, 2H), 3.54 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.7, 128.9, 128.5, 127.5, 61.8, 56.2.

N-(4-methoxybenzyl)-O-methylhydroxylamine[44b] ***(9):*** Colorless oil (Petroleum Ether/Ethyl Acetate = 10/1, R_f = 0.35, 44.3 mg, 53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.64 (s, 1H), 3.99 (s, 2H), 3.80 (s, 3H), 3.50 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.0, 130.1, 129.6, 113.9, 61.8, 55.6, 55.3.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."

Detailed optimization studies of reaction conditions, synthesis and characterization of the products, and ^{1}H NMR, ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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