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Palladium(II)-Catalyzed Regioselective *Ortho*-C–H Bromination/Iodination of Arylacetamides *via* in situ Generated Imidic Acid as Directing Group: Mechanistic Exploration

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ABSTRACT

In the present study, we report palladium(II)-catalyzed regioselective *ortho*-C-H bromination/iodination of challenging arylacetamide derivatives using *N*-halo-succinimide as halogenating agents. Diverse arylacetamides underwent regioselective *ortho*-bromination and iodination of aromatic C-H bonds in the presence of reactive benzylic C(sp^3)-H bond without installing any bulky auxiliary *via* unfavorable six-membered metallacycle. Weak coordination, usages of ubiquitous primary amide for challenging C-H functionalization, simple catalytic system and wide substrate scope are the key features of this transformation. Further, the halogenated amide derivatives were transformed into a variety of valuable synthons. Detailed mechanistic studies revealed some interesting aspects concerning the reaction pathway. We present first time the strong evidence for the formation of imidic acid (*in situ*) from primary amide under Brønsted acid conditions that eventually aids in the stabilization of palladacycle of amide derivatives and drives for regioselective C-X bonds formation.

INTRODUCTION

Halo-derivatives, in particularly aromatic halides, have attracted much attention from organic chemists owing to their unique electronic features and ubiquitous presence in a large number of biologically relevant natural products and active pharmaceutical ingredients.[1] Moreover,

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aromatic halides (X = Cl, Br, I) serve as versatile synthetic intermediates for the synthesis of functionalized heterocycles, functional materials, and nucleophilic substitution reactions.[2] They are also used as a key precursor for the preparation of organometallic reagents.[3] Due to their intriguing chemical and biological properties, organic chemists have given considerable attention to the development of efficient and selective synthetic strategies for their synthesis. Traditionally, these derivatives were synthesized by following the classical routes a) electrophilic aromatic substitution (S_EAr),[4a-b] b) directed-*ortho*-metallation (DoM),[4c] and c) Sandmeyer reaction[4d]. However, these classical methods have their own limitation such as strong reaction conditions, limited substrate scope, low yields, and poor regioselectivity.

The direct and regioselective installation of halo functional groups (X = Cl, Br, I) on aromatic compounds *via* the activation of unfunctionalized C(sp^2)-H bonds in the presence of transition metal is an alternate and effective route to obtain the desired aromatic halides.[5] Nevertheless, these methods have severe limitations as they strongly depend on the nature of directing groups. In general, directing groups has to be preinstalled on the desired substrate to activate the proximal C-H bond followed by uninstallation of directing groups after the desired operation, which eventually increases the cost and time of overall reactions.[6] Amide groups are key structural motifs in many physiologically active compounds and recent years, it has been extensively employed as a directing group for direct C-H bond functionalization *via* favorable five-membered cyclometallation.[7] Despite the great achievements in transition-metal-catalyzed C-H activation using aromatic amides as versatile directing groups,[8] very limited reports are available in the literature where aliphatic amides were used for distal C(sp^2)-H bond functionalization.[9] Indeed, Yu and co-workers in 2013 reported a very effective method for the regioselective *ortho*-iodination on challenging N-substituted arylacetamides using molecular

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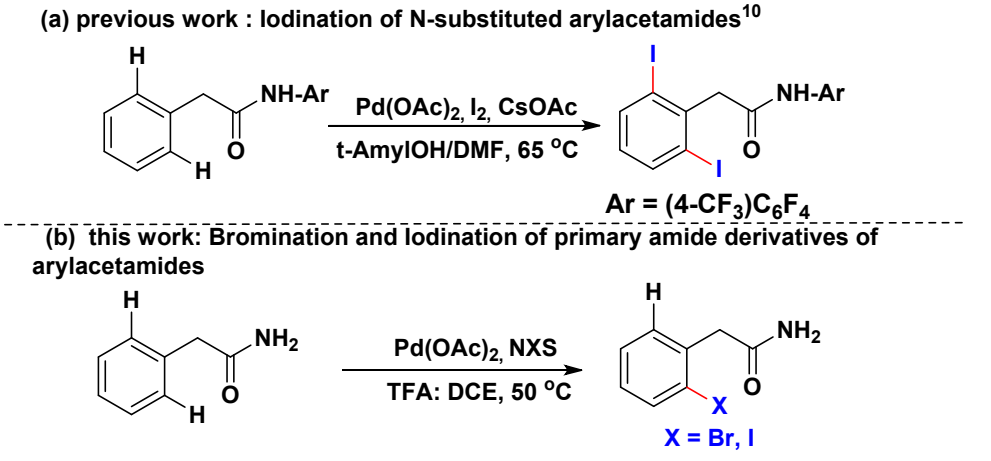
iodine as a sole oxidant (Scheme 1a).[10] However, the success of this strategy completely depends on the nature of amide auxiliaries, where acidic N-H bond coordinates to the metal-salt to minimize the entropic cost for C-H activation. Hence, there is a need to develop an efficient and regioselective approach to introduce the halides on challenging arylacetamides by using diverse primary amide as a directing group without installing the bulky and costly auxiliaries. However, the primary amide group, in particular, aliphatic amide is considered as one of the least reactive functional moiety owing to their high degree of nitrogen lone pair delocalization and eventually responsible for the generation of unfavorable metallacycle during the C-H activation reaction *via* weak coordination. With these limitation in mind and continuation of our own research emphasis on the development of a step-economical approach for C-H functionalization *via* weakly coordinating group,[11] we herein disclose an efficient and simple catalytic system for the regioselective introduction of bromide and iodide on aromatic ring of arylacetamides catalyzed by palladium(II)-salt (Scheme 1b). Detailed experimental and theoretical investigation highlighted some interesting aspects of primary amide directing abilities and a triple role of TFA in this transformation. To the best of our knowledge, aliphatic primary amide directed *ortho*-C-H bromination/iodination has not been reported till date.



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Scheme 1. Acetamide directed catalytic *ortho*- C-H bromination/iodination of arylacetamides.

RESULT AND DISSCUSION

At the outset, we began our experiment by selecting phenylacetamide (**1a)** as designed substrate, where the benzyl group is present adjacent to the amide functionality which makes the substrates more receptive for further functionalization, commercially available NBS (*N*-bromo succinimide) as the brominating reagents, $Pd(OAc)_2$ as a choice of catalyst, DCE (1,2-dichloroethane) as the desired solvent at 60 ^oC (Table 1). The desired *ortho*-brominated phenylacetamide (**2a)** was isolated in 5% yield only, and rest starting material (**1a)** was recovered (entry 1). Previous observations from our laboratory revealed that the presence of strong Brønsted acid is crucial for the primary amide directed palladium(II)-catalyzed activation of C-H bond of arylacetamide derivatives. Therefore, we screened several Brønsted acids in different proportions to get the optimal reaction conditions (entry 2-8), and we found that addition of 10.0 equiv of trifluoroacetic acid (TFA) into the reaction mixture effectively improved the yield of desired products (**2a**/**2aa)** in 60% and 25%, respectively **(**entry 3). The enhanced efficiency of phenylacetamide can be attributed to the formation of imidic acid (OH-C=NH) from amide (H_2N-C=O) under acidic conditions.[12] Indeed, it is well known that benzylic C-H bond undergoes for C-Br bond formation under protic conditions.[13] Interestingly, the benzylic C-H bond remained unaltered under the given conditions, and that was quite commendable achievements. Bromination in several other solvents was also investigated (entry 8-12), and we found that DCE was far superior to other solvents. On the other hand, we also screened the various palladium salts (entry 13-15) and loading of the catalyst in the reaction conditions and observed that 5 mol % of $Pd(OAc)_2$ was best suited to promote the desired transformation with good regioselectivity (entry 19). More importantly, when the reaction was

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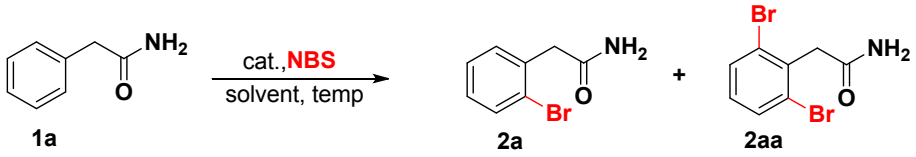
carried out in the absence of Pd(II)-catalyst, the desired *ortho*-brominated **2a** was isolated, albeit in meager yield *via* classical electrophilic aromatic substitution reaction and rest starting materials was recovered (entry 20). This result clearly demonstrates that the *ortho*-bromination product is formed predominantly by the palladium(II)-catalyzed directed C-H activation *via* the six-membered metallacycle transition state. Therefore, the reaction conditions described in entry 19 was selected as an optimal condition for the regioselective *ortho*-bromination/iodination of arylacetamides.

Table 1. Optimization of the reaction conditions for *ortho*-C-H bromination of phenylacetamide[a]



1a 2a 2aa

entry	catalyst	solvent	acid additive (equiv)	temp (°C) and time (h)	yield (%)[b]	
					2a	2aa
1.	$Pd(OAc)_2$	DCE	-	60, 24	5	-
2.	$Pd(OAc)_2$	DCE	TFA (5)	60, 24	40	-
3.	$Pd(OAc)_2$	DCE	TFA (10)	60, 24	60	25
4.	$Pd(OAc)_2$	DCE	TFA (15)	60, 24	55	23
5.	$Pd(OAc)_2$	DCE	TFA (25)	60, 24	52	35
6.	$Pd(OAc)_2$	DCE	AcOH (10)	60, 24	30	-
7.	$Pd(OAc)_2$	DCE	PivOH (10)	60, 24	-	-
8.	$Pd(OAc)_2$	DCE	PTSA (10)	60, 24	36	-
9.	$Pd(OAc)_2$	ACN	TFA (10)	60, 24	18	-
10.	$Pd(OAc)_2$	Toluene	TFA (10)	60, 24	-	-
11.	$Pd(OAc)_2$	TFE	TFA (10)	60, 24	52	18
12.	$Pd(OAc)_2$	Ethyl acetate	TFA (10)	60, 24	23	-

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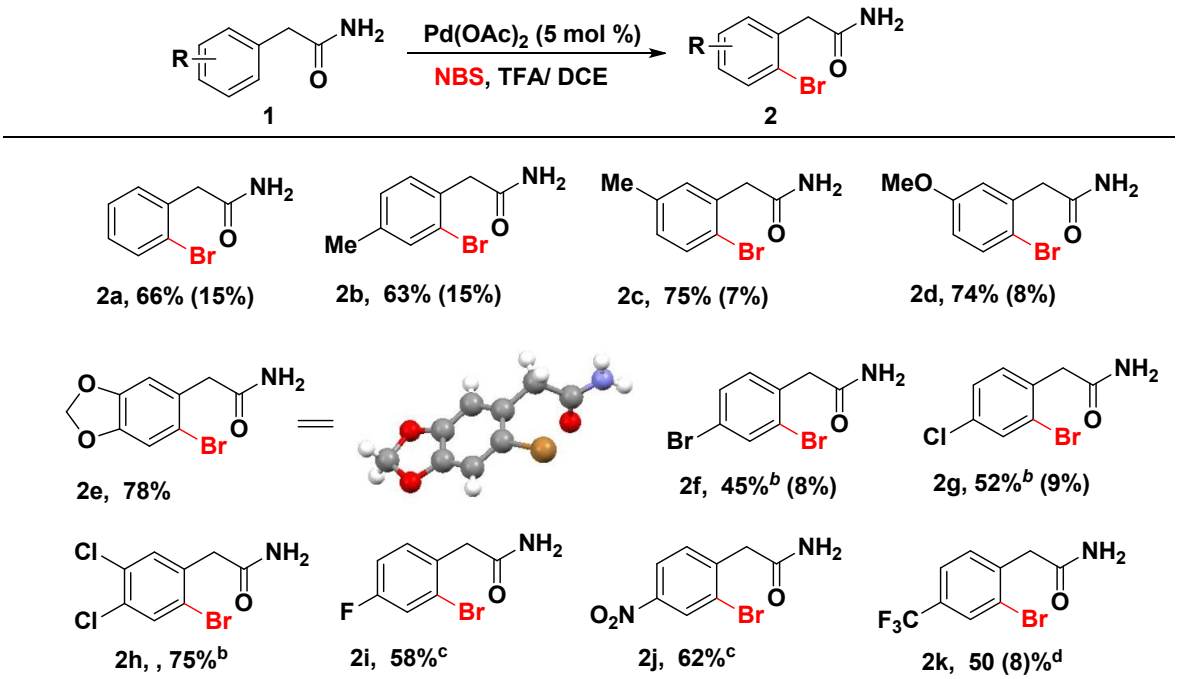
13.	$Pd(TFA)_2$	DCE	TFA (10)	60, 24	55	20
14.	$PdCl_2$	DCE	TFA (10)	60, 24	15	-
15.	$Pd(OAc)_2$	DCE	TFA (10)	50, 24	66	15
16.	$Pd(OAc)_2$	DCE	TFA (10)	80, 24	33	30
17.	$Pd(OAc)_2$	DCE	TFA (10)	r.t., 24	-	-
18.	$Pd(OAc)_2$	DCE	TFA (10)	50, 12	42	5
19.[c]	**$Pd(OAc)_2$**	**DCE**	**TFA (10)**	**50, 24**	**66**	**15**
20.	-	DCE	TFA (10)	60, 24	20	-

[a]Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), NBS (0.3 mmol), solvent (2.0 mL) in sealed tube. [b]Isolated yield after column chromatography. [c]5 mol % of the $Pd(OAc)_2$ was used. PTSA = *p*-Toluenesulfonic acid, TFE = 2,2,2-Trifluoroethanol.

Scheme 2: Substrate scope with respect to *N*-bromo succinimide.[a]



[a]Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (5 mol%), NBS (0.3 mmol), TFA (10 equiv), DCE (2.0 mL) at 50 °C for 24 h in sealed tube. [b]20 equiv of TFA was used. [c] Reaction was

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performed in (4:1) of TFA : DCE at 100 °C. [d]Reaction was performed in (1:3) of TFA : DCE at 80 °C. Yields of dihalogenated products are given in parenthesis.

Under the optimized condition, first we investigated the scope of arylacetamides with NBS and results are summarized in Scheme 2. For instance, electron-rich substituents such as methyl, methoxy, and dioxy attached at *para* and *meta*-positions of arylacetamides were successfully tolerated and afforded the desired *ortho*-bromination products (**2b-e**) in good yields. The structure of regioselective product (**2e**) was confirmed by single X-ray diffraction analysis. Notably, arylacetamides containing moderate electron-withdrawing groups, such as halogen functionality (X= Cl, Br, F) were also successfully employed to provide *ortho*-brominated products (**2f-i**) in moderate to good yields. Indeed, these dihalogented derivatives provide a strong platform for further synthetic manipulation. A substrate bearing a strong electron-withdrawing group like $-NO_2$ and $-CF_3$ at *para*-position also reacted smoothly with NBS to provide mono-brominated products (**2j-k**) in good yields.

Next, we explored the scope for this reaction with NIS (*N*-iodo succinimide), to obtain *ortho*-iodination products. Delightfully, we observed that under the optimized reaction conditions the iodinated product (**3)** was readily obtained using NIS as the source of iodine (Scheme 3). Arylacetamides with electron-rich substituent could easily give the corresponding iodination products (**3b-e**) in good yields with high regioselectivity. Structures of all synthesized products were confirmed through the NMR analysis. Halogen substituent at *para*-position of aryl ring reacted well to afford good yields of monoiodonation products (**3f-g**). When dicholrosubtituted phenylacetamide was reacted under the optimized conditions, iodination occurred at a less hindered site to give the product (**3h**) in 55% yield. However, arylacetamides attached with electron-withdrawing groups (-F, $-NO_2$, $-CF_3$) at a different position of the aromatic ring, gave

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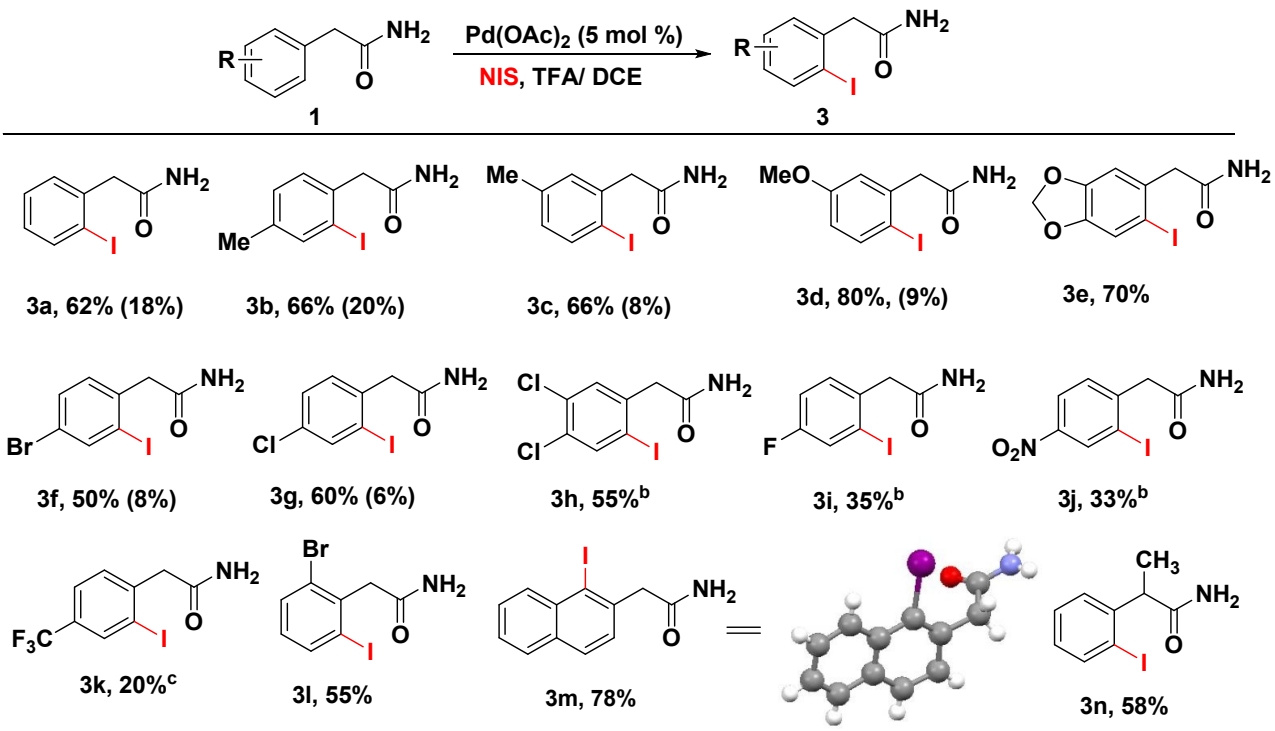
the desired iodination products (**3i-k**) in moderate yields. Gratifyingly, *ortho*-brominated phenylacetamide was also compatible under the reaction condition to give *ortho*-dihalogenated product (**3l**). Also, 2-napthylacetamide underwent the desired transformation smoothly to produce monoiodinated-derivative (**3m**) in good yield and high regioselectivity. Crystal structure of **3m** further confirmed the absolute structure of the *ortho*-iodinated product. Next, we checked the scope of α-methylphenylacetamide as a directing group for *ortho*-iodination under the optimized reaction conditions and furnished the mono-iodinated product (**3n)** in 58% yield.

Scheme 3: Substrate scope with respect to *N*-iodosuccinimide.[a]



[a]Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), NIS (0.3 mmol), TFA (10 equiv), DCE (2.0 mL) at 50 °C for 24 h in sealed tube. [b]20.0 equiv of TFA was used. [c]Reaction was performed in (1:3) of TFA : DCE at 80 °C. Yields of dihalogenated products are given in the parenthesis.

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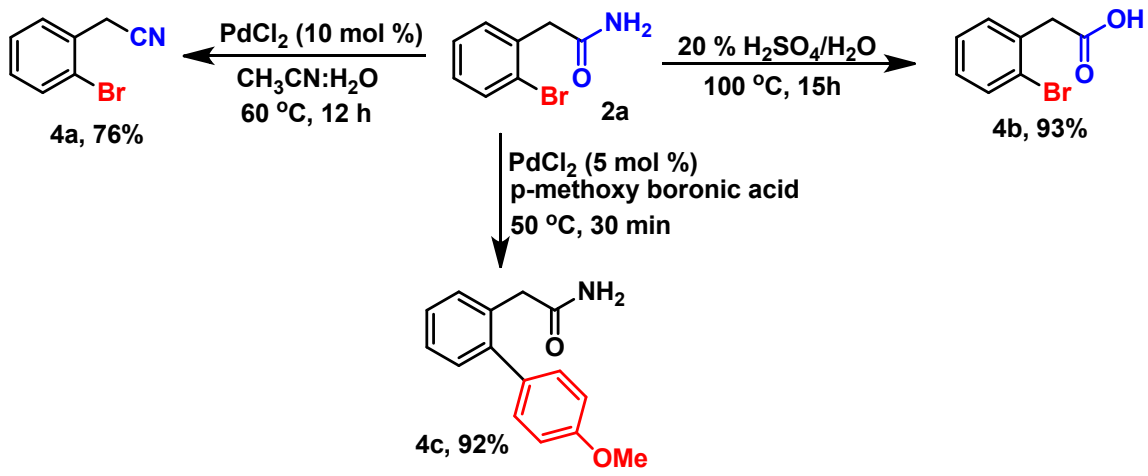
Aware of the facts that aryl halides are the valuable synthons for organic chemists, we became interested in showcasing the synthetic utility of *ortho*-bromo-phenylacetamide (**2a**) for various organic transformation reactions (Scheme 4). The *ortho*-brominated phenylacetamide (**2a)** was efficiently transformed to the halogenated benzyl nitrile (**4a**) and synthetically challenging phenylacetic acid (**4b**) in good yields. Indeed, *ortho*-brominated phenylacetamide was further employed as a key precursor for the cross-coupling reaction to form biarylacetamide (**4c**) *via* Suzuki type cross-coupling reaction with *para*-methoxy-boronic acid.

Scheme 4: Synthetic utility of 2-bromo-phenylacetamide.



Studies were performed to shed some light on mechanistic aspects (Scheme 5).

(1) A competition reaction between electron rich 4-methyl-phenylacetamide (**1b)** and electron deficient 4-nitro-phenylacetamide (**1j)** was carried out under standard conditions and the desired halogenated derivatives (**2b)** and (**2j)** were isolated in 57% and 4% yields, respectively. The result concluded that reaction is strongly favored for the electron-rich amides over the electron-deficient amide derivatives and highlighting that the desired transformation proceeds *via* base-

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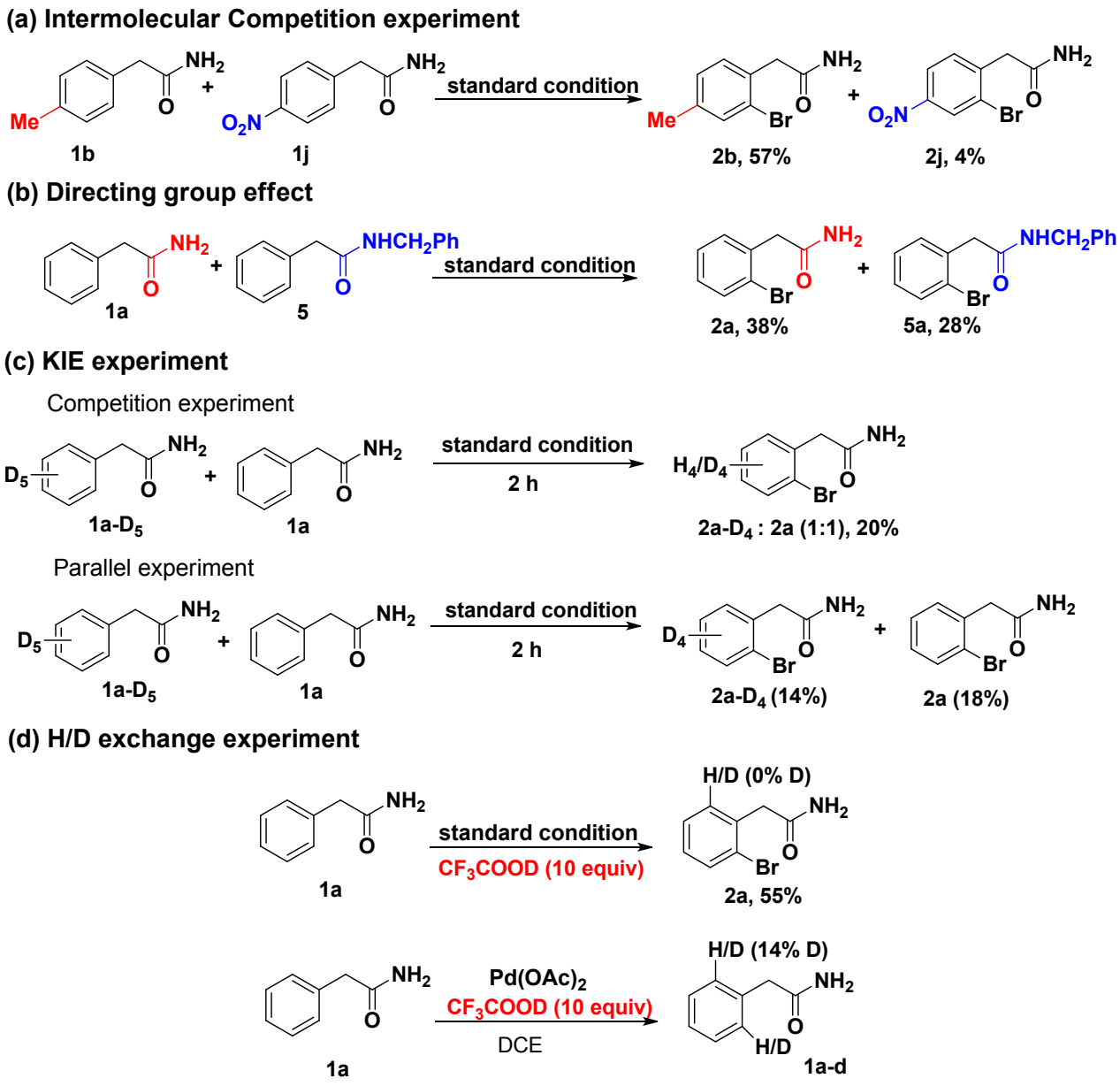
assisted internal electrophilic type substitution (BIES) over the concerted metalation deprotonation (CMD) pathway (Scheme 5a).

Scheme 5: Mechanism study



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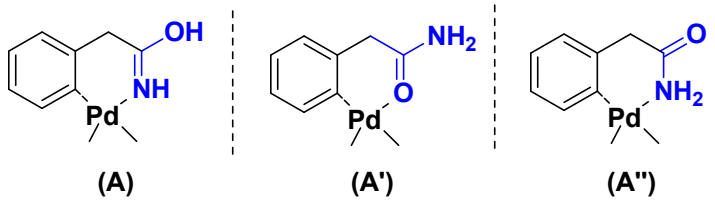
(2) To examine the directing ability of primary amide group under the given conditions, we further set a few competition experiments with differentially substituted amide, in particular to secondary amide. Indeed, results clearly indicate that the challenging primary amide has a higher priority as DG over the secondary amide under optimized reaction conditions (Scheme 5b).

(3) Next, intermolecular reaction (via parallel and competition) between (**1a**) and (**1a-D_5**) were carried out. Moderate values of the KIE were observed, both via competition and parallel reactions, clearly suggests that C-H bond cleavage is not a rate-limiting step in this transformation (Scheme 5c).

(4) Deuterium incorporation experiment with CF_3COOD demonstrates the irreversibility of the C-H activation step in this reaction, both in the presence of the halogenating agent and in the absence of it (Scheme 5d).

Mechanistic investigation: To understand the origin of reactivity of the amide derivatives for distal C-H bond activation under the established conditions, detailed control experiments were further carried out (Figure 2 and 3). The amide has three possible coordinating sites under acidic conditions: (a) carbonyl oxygen (-C=O), (b) imine nitrogen (-C=NH) and (c) electron-rich nitrogen (-NH_2) to form a six-membered palladacycle intermediate (Figure 1).



(A) (A') (A'')

Figure 1: Possible coordination sites of the primary amide with palladium(II) salt.

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Hence, we first decided to investigate how the primary amide group coordinates to the electrophilic palladium(II) center under optimized conditions. It is well known that amide group (H_2N-C=O) undergoes tautomerism to form imidic acid (HO-C=NH) under certain physiological conditions.[12] Considering these facts, we anticipated that primary amide moiety under Brønsted acid conditions might generate an imidic acid and imidic (-NH) coordinates to the palladium(II) salt preferentially over the carbonyl oxygen (-C=O) site of amide moiety. To resolve the ambiguity, we tried to obtain the crystal of the six-membered palladacycle intermediate, but unfortunately, failed. Therefore, we decided to conduct several NMR (^{1}H NMR, ^{13}C NMR, and ^{15}N NMR) and HRMS experiments along with preliminary DFT calculation. First, full quantum chemical calculations were done with density functional theory (DFT) using the Gaussian 09 program package to understand the coordination site of the directing group under standard conditions. The result demonstrates that the formation of complex **A** is more favored (ΔG = 3.6 kcal/mole) over the complex **A′** with palladium (II) salt (for details, see SI). Hence, we believe that under Brønsted acid conditions imidic acid (-NH) coordinates to the palladium(II) salt preferentially over the carbonyl oxygen (-C=O) of phenylacetamide, which is considered to be the starting point of the catalytic cycle.

The ^{1}H NMR of phenylacetamide (**1a)** typically showed amide (-NH_2) peaks around δ 5.46 and 5.91 ppm (Figure 2a). Interestingly, when phenylacetamide was mixed with 10.0 equiv of TFA, a significant shift of amide and benzylic proton peaks were seen in the ^{1}H NMR spectrum (Figure 2b). The new peak appeared at δ 8.31 ppm, which eventually correspond to the -NH of imidic acid and peak at δ 6.59 ppm corresponds to OH of imidic acid. Indeed, we observed that benzylic protons were also deshielded from δ 3.60 to 3.81 ppm.

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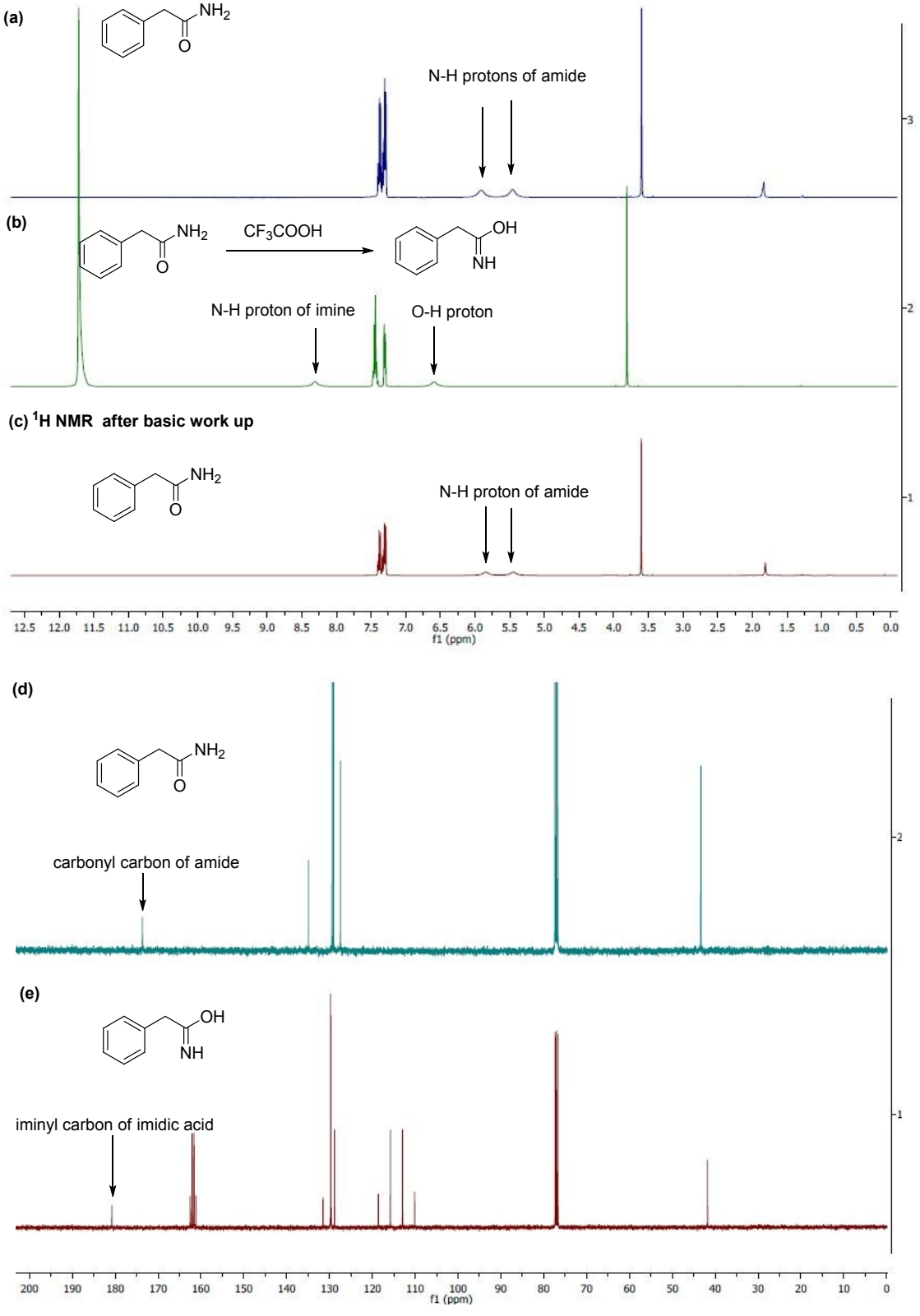

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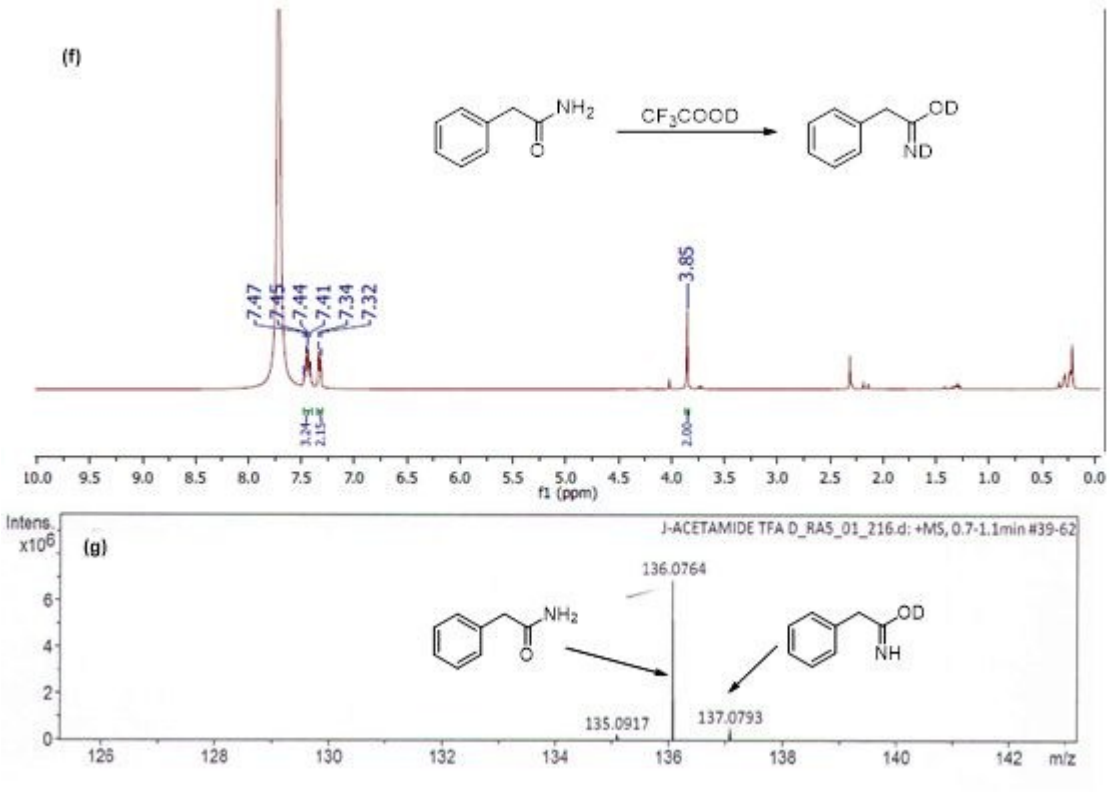

Figure 2. ^{1}H NMR spectra in $CDCl_3$ of (a) pure acetamide **1a,** (b) **1a** plus TFA (10.0 equiv) at rt, (c) after following basic aqueous extraction, (d) ^{13}C spectra of pure 2a (e) ^{13}C spectra of **1a** plus TFA (10.0 equiv) at rt, (f) **1a** in CF_3COOD, and (g) HRMS spectrum of **1a** in the presence of CF_3COOD (10.0 equiv) in acetonitrile.

Further, aqueous workup was carried out of the reaction mixture and ^{1}H NMR of crude material was again recorded. The peaks of phenylacetamide (-NH_2) were again reemerged (Figure 2c). Similarly, amide carbonyl carbon of phenylacetamide **(1a)** was observed at δ 173.6 ppm (Figure 2d), after addition of TFA, this peak shifted to δ 180.7 ppm which support the formation of imidic carbon (Figure 2e). Additionally, both of amide protons were exchanged completely with deuterium, when ^{1}H NMR of (**1a)** was recorded in deuterated trifluoroacetic acid (Figure 2f). The HRMS spectra of phenylacetamide (**1a)** was then recorded in deuterated trifluoroacetic acid, and one small peak at *m/z* = 137.0793 was observed in HRMS spectrometry, which could be

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assigned to the corresponding deuterated imidic acid $[C_8H_9DNO]^+$ (Figure 2g). The ^{15}N NMR spectrum of pure phenylacetamide in DMSO-d_6 features four sharp peaks at δ 199.99, 111.11, 109.63 and 107.46 ppm (Figure 3a). These peaks were assigned to the nitrogen atom of amide form which is present in the different state and peak corresponds to 199.99 may be attributed to the N-O bond.[12e] Interestingly, in the presence of 10.0 euqiv of TFA in the reaction mixture, only one peak retained at 199.99 (N-O bond) in ^{15}N NMR spectrum (Figure 3b). These results illustrate that the Brønsted acid promoted the tautomerization of amide to imidic acid, where imidic acid N atom bonded with the O atom of DMSO-d_6.

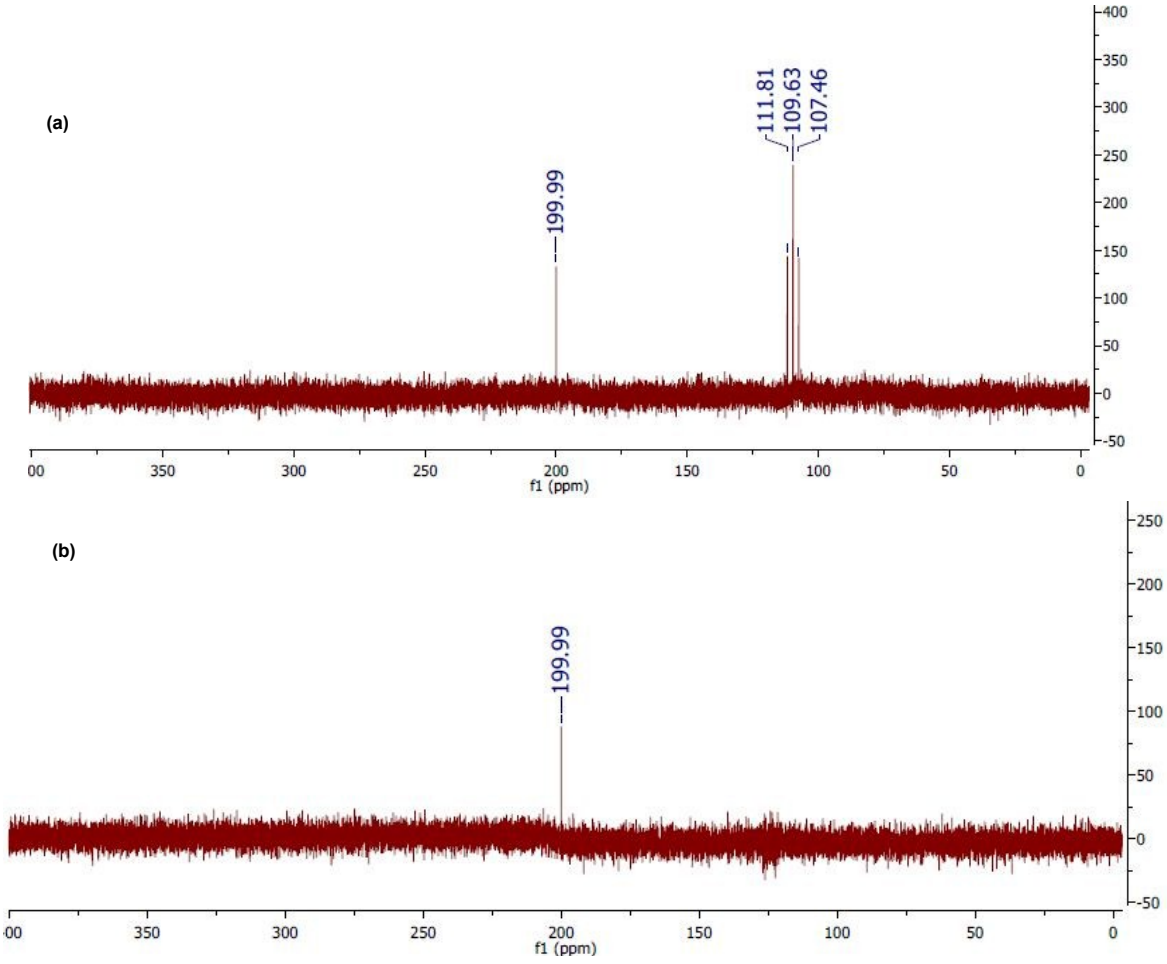

Figure 3. ^{15}N NMR spectra in DMSO-d_6 of (a) pure **1a**, (b) **1a** in the presence of CF_3COOH at rt.

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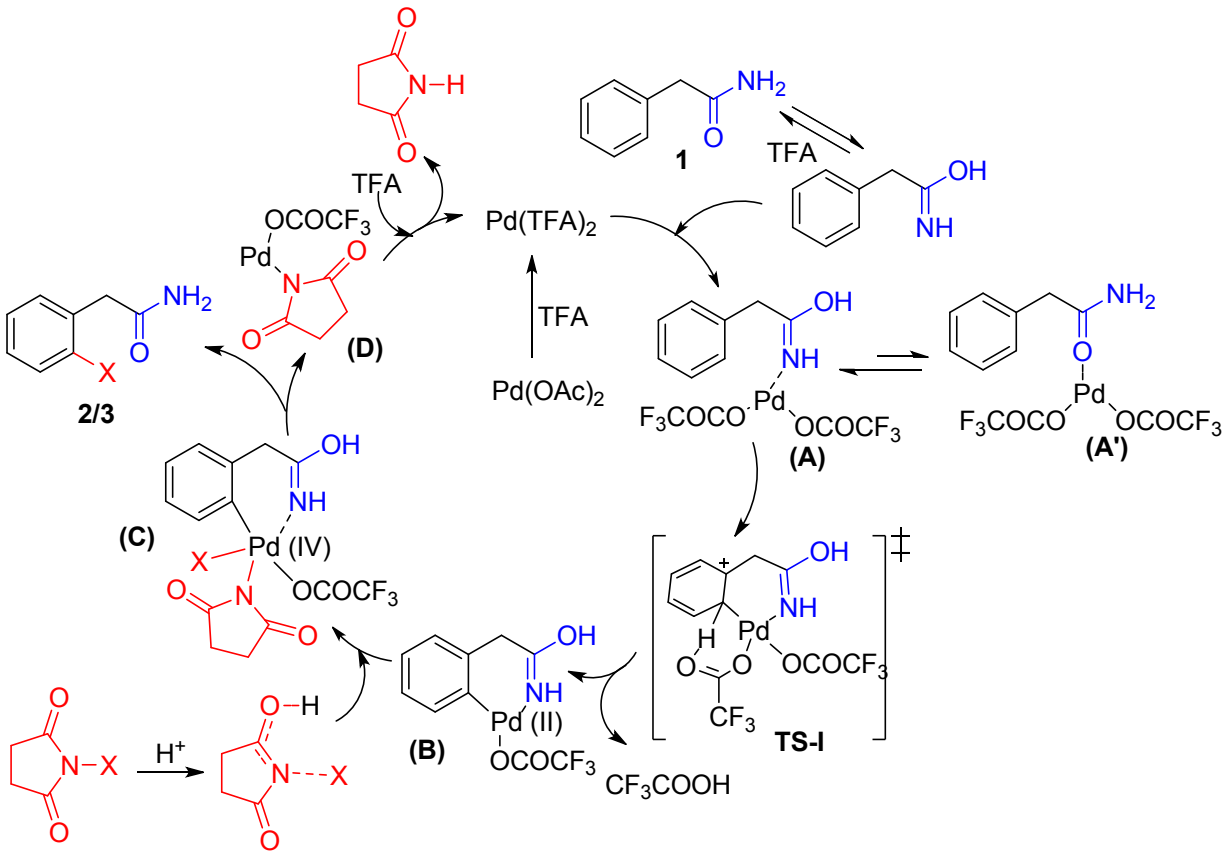

Scheme 6. The proposed reaction mechanism for Pd(II)-catalyzed distal activation of arylacetamides.

Based on these detailed studies and previous reports,[8,14] we propose a plausible reaction mechanism for the *ortho*-bromination/iodination on challenging arylacetamides (Scheme 6). We anticipate that reaction would have started with the generation of imidic acid from primary amide **1a** under Brønsted acid conditions. Subsequently, *in situ* generated imidic acid species coordinates with electrophilic palladium(II) salt to form the complex **A** *via* the imine moiety. A regioselective C-H activation *viz* the base assisted internal electrophilic substitution (BIES)[15] pathway leads to the formation of six-membered palladacycle **B** *via* transition state-I. Followed by oxidative addition of NXS to the palladacycle **B** gave Pd(IV) species **C**. This species then undergoes reductive elimination to afford the desired halogenated derivatives **2/3** and regenerate

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the electrophilic $Pd(TFA)_2$ catalyst from species **D** in the presence of excess TFA. Based on the outcome, we believe that TFA plays a triple role in this transformation. First, it activates N-halosuccinimide *viz* the protonation of one of the two carbonyl groups and enhancing the concentration of halogen cations (Br^+, I^+) and second, it facilitates the tautomerization of amide to imidic acid and third, it increases the electrophilic character of Pd(II)-salt.

CONCLUSION

In summary, we have developed an efficient and practical strategy for regioselective *ortho*-C-H bromination and iodination on the aromatic ring of challenging arylacetamide derivatives under simple catalytic conditions. This protocol represents the first example of direct bromination/iodination of ubiquitous arenes containing the primary amide group by using palladium(II) salt without installing any bulky auxiliary. Detailed mechanistic studies demonstrated that this reaction proceeds *via* generation of imidic acid (*in situ)* from primary amide under Brønsted acidic conditions and possibly facilitate the formation of six-membered metallacycle (-NH coordinated to palladium(II)) and drives C-X bond formation. The key roles of TFA were determined as an activator of N-halosuccinimide through the protonation as well as a facilitator for tautomerization process of amide to imidic acid. Indeed, we believe that these detailed studies may help in better understanding the chemistry of amide and imidic acid in catalytic C-H bond activation/functionalization.

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Experimental Section

1. General Consideration. Unless otherwise noted, all reagents were purchased from a commercial supplier and used without further purification. All arylacetamides derivatives were prepared by following the reported procedure in literature.[16] All the reactions were run in sealed tubes, and the indicated temperature was that of an oil bath. ^{1}H NMR spectra were recorded at 400 MHz, $^{13}C\{^{1}H\}$ NMR spectra were recorded at 100 MHz, ^{19}F NMR were recorded at 376 MHz and ^{15}N NMR were recorded at 40.5 MHz, $CDCl_3$ and DMSO-d_6 were used as solvents. Chemical shifts are reported in δ (ppm) referenced to $CDCl_3$ (δ 7.26), DMSO-d_6 (δ 2.50) for ^{1}H NMR and $CDCl_3$ (δ 77.0), DMSO-d_6 (δ 39.5) for ^{13}C NMR. The following abbreviations are used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet; J, coupling constant (hertz). Infrared spectra were recorded with an FT-IR apparatus. High-resolution mass spectra (HRMS) spectra were obtained on an ESI-TOF (electron spray ionization-time-of-flight) spectrometer, methanol and acetonitrile were used to dissolve the sample. Column chromatography was performed on silica gel (100−200) mesh using ethyl acetate and hexanes as eluents in different ratios.

2. General procedure for palladium catalyzed *ortho*-bromination/iodination of arylacetamides (GP): To a clean oven-dried 15 mL sealed tube equipped with magnetic stir bar was sequentially added arylacetamide (0.25 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %, 2.8 mg), NXS (0.3 mmol, 1.2 equiv.) Then, DCE (2.0 mL) was added followed by trifluoroacetic acid (190 µL, 10.0 equiv) was added to the reaction mixture. The sealed tube was tightly closed and placed in pre-heated oil bath and stirred for 24 h at 50 ^{o}C. The progress of reaction was monitored by TLC and after completion, the reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure and diluted with ethyl acetate followed by neutralization with

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saturated solution of sodium bicarbonate. After extraction with ethyl acetate (15 mL x 3) organic layer was washed with brine solution and dried over sodium sulphate. After evaporation of solvent, the crude mixture was purified by column chromatography silica gel and ethyl acetate/hexanes as eluent or acetone/DCM as eluent.

2-(2-Bromo-phenyl)-acetamide (2a) Following GP isolated as white solid (35 mg, 66% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 168-170 ^oC; IR(ATR) 3385, 3184, 1663, 1394 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 8.0, 1H), 7.46 (brs, 1H), 7.37 – 7.29 (m, 2H), 7.21 – 7.14 (m, 1H), 6.97 (brs, 1H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 136.1, 132.2, 132.0, 128.5, 127.7, 124.5, 42.1. HRMS (ESI-TOF) m/z Calcd for C_8H_9BrNO $[M + H]^+$ 213.9862, found 213.9857.

2-(2,6-Dibromo-phenyl)-acetamide (2aa) Following GP isolated as white solid (11 mg, 15% yield); R_f (6:4 Hexane/EtOAc) = 0.5; Mp 168-170 ^oC; IR(ATR) 3304, 3181, 2925, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.47 (d, J = 8.2 Hz, 2H), 6.94 (t, J = 8.0 Hz, 1H), 6.50 (brs, 1H), 6.24 (brs, 1H), 3.92 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 169.8, 134.7, 131.6, 129.1, 125.7, 43.0. HRMS (ESI-TOF) m/z Calcd for $C_8H_9Br_2NO$ $[M + H]^+$ 291.8967 found 291.8966.

2-(2-Bromo-4-methyl-phenyl)-acetamide (2b) Following GP isolated as white solid (36 mg, 63% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 175-177 ^oC; IR(ATR) 3355, 3174, 2922, 1656, 1410 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.40 (s, 1H), 7.38 (brs, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (brs, 1H), 3.50 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 138.1, 132.9, 132.3, 131.9, 128.1, 124.2, 41.6, 20.0. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}BrNO$ $[M + H]^+$ 228.0019 found 228.0009.

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2-(2,6-Dibromo-4-methyl-phenyl)-acetamide (2bb) Following GP isolated as white solid (12 mg, 15% yield); R_f (6:4 Hexane/EtOAc) = 0.5; Mp 228-230 ^oC; IR(ATR) 3408, 3175, 1665, 1390 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.57 (s, 1H), 7.47 (brs, 1H), 6.99 (brs, 1H), 3.53 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 137.6, 135.7, 134.8, 133.9, 123.3, 122.8, 41.1, 21.5. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}Br_2NO$ $[M + H]^+$ 305.9125 found 305.9116.

2-(2-Bromo-5-methyl-phenyl)-acetamide (2c) Following GP isolated as white solid (43 mg, 75% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 145-147 ^oC; IR(ATR) 3385, 3194, 2922, 1653, 1401cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, J = 8.1 Hz, 2H), 7.16 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.95 (brs, 1H), 3.51 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 136.9, 135.7, 132.6, 131.9, 129.2, 121.2, 42.0, 20.4. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}BrNO$ $[M + H]^+$ 228.0019 found 228.0025.

2-(2-Bromo-5-methoxy-phenyl)-acetamide (2d) Following GP isolated as white solid (45 mg, 74% yield); R_f (1:1 Hexane/EtOAc) = 0.3; Mp 161-163 ^oC; IR(ATR) 3375, 3194, 2928, 1659, 1397 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 8.8 Hz, 1H), 7.40 (brs, 1H), 6.95 (d, J = 2.9 Hz, 2H), 6.78 (d, J = 8.8, 2.9 Hz, 1H), 3.73 (s, 3H), 3.52 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 158.5, 137.0, 132.7, 117.8, 114.9, 114.1, 55.4, 42.2. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}BrNO_2$ $[M + H]^+$ 243.9968 found 243.9969.

2-(6-Bromo-benzo[1,3]dioxol-5-yl)-acetamide (2e) Following GP isolated as white solid (50 mg, 78% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 145-147 ^oC; IR(ATR) 3394, 3207, 2915, 1653 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (brs, 1H), 7.16 (s, 1H), 6.94 (s, 2H), 6.04 (s, 2H), 3.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 146.9, 146.9, 129.1, 114.6, 111.9,

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111.5, 101.8, 41.8. HRMS (ESI-TOF) m/z Calcd for $C_9H_9BrNO_3$ $[M + H]^+$ 257.9760 found 257.9764.

2-(2,4-Dibromo-phenyl)-acetamide (2f) Following GP isolated as white solid (33 mg, 45% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 148-150 ^oC; IR(ATR) 3381, 3185, 2921, 1658, 1397 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.48 (brs, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.01 (brs, 1H), 3.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 135.7, 133.9, 133.6, 130.4, 125.4, 120.1, 41.5. HRMS (ESI-TOF) m/z Calcd for $C_8H_8Br_2NO$ $[M + H]^+$ 291.8967 found 291.8971.

2-(2-Bromo-4-chloro-phenyl)-acetamide (2g) Following GP isolated as white solid (32 mg, 52% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 83-85 ^oC; IR(ATR) 3404, 3197, 2922, 1650 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.49 (brs, 1H), 7.44-7.37 (m, 2H), 7.02 (brs, 1H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 135.3, 133.2, 131.9, 131.3, 127.5, 125.1, 41.4. HRMS (ESI-TOF) m/z Calcd for $C_8H_8BrClNO$ $[M + H]^+$ 247.9472 found 247.9481.

2-(2-bromo-4,5-dichlorophenyl)acetamide (2h) Following GP isolates as white solid (53 mg, 75% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 175-177 ^oC; IR(ATR) 3455, 3300, 3197, 1660, 1460. ^1H NMR (400 MHz, DMSO) δ 7.85 (s, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 7.01 (s, 1H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 171.03, 137.39, 133.51, 130.73, 130.67, 123.73, 41.59. HRMS (ESI-TOF) m/z Calcd for $C_8H_7BrCl_2NO$ $[M + H]^+$ 281.9083 found 281.9082

2-(2-Bromo-4-fluoro-phenyl)-acetamide (2i) Following GP isolated as white solid (34 mg, 58% yield); R_f (1:1 Hexane/EtOAc) = 0.4; Mp 120-122 ^oC; IR(ATR) 3413, 3197, 2924, 1651 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.6 Hz, 1H), 7.44 (brs, 1H), 7.41 – 7.37 (m, 1H), 7.20 (td, J = 8.5, 2.5 Hz, 1H), 6.97 (brs, 1H), 3.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) 170.7, 161.79 and 159.34 (d, J = 245.0 Hz), 133.11 and 133.02 (d, J = 9.0 Hz), 132.5, 124.4,

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119.19 and 118.94 (d, J = 25 Hz), 114.54 and 114.33 (d, J = 21.0 Hz), 41.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ -114.4. HRMS (ESI-TOF) m/z Calcd for C_8H_8BrFNO $[M + H]^+$ 231.9768 found 231.9770.

2-(2-Bromo-4-nitro-phenyl)-acetamide (2j) Following GP isolated as white solid (40 mg, 62% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 198-200 ^{o}C; IR(ATR) 3407, 3201, 2927, 1655, 1339 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.19 (dd, J = 8.4, 2.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.59 (brs, 1H), 7.10 (brs, 1H), 3.73 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 146.8, 144.1, 133.0, 126.8, 124.7, 122.3, 42.0. HRMS (ESI-TOF) m/z Calcd for $C_8H_8BrN_2O_3$ $[M + H]^+$ 258.9713 found 258.9715.

2-(2-bromo-4-(trifluoromethyl)phenyl)acetamide (2k) Following GP isolated as white solid (35 mg, 50% yield); R_f (1:1 Hexane/EtOAc) = 0.4; Mp 162-164 ^{o}C; IR(ATR) 3418, 3292, 1654, 1394 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.07 (s, 1H), 3.68 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 170.1, 141.2, 132.9, 128.9 (q, J = 32.0 Hz), 128.7 (q, J = 3.0 Hz), 124.9, 124.3 (q, J = 4.0 Hz), 123.3 (q, J = 271.0 Hz), 41.9. ^{19}F NMR (376 MHz, DMSO-d_6): -61.02. HRMS (ESI-TOF) m/z Calcd for $C_9H_8BrF_3NO$ $[M + H]^+$ 281.9736 found 281.9735.

2-(2-iodophenyl)acetamide (3a) Following GP isolated as white solid (40 mg, 61% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 175-177 ^{o}C; IR(ATR) 3391, 3188, 2921, 1658, 1390 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.79-7.74 (m, 1H), 7.32 – 7.21 (m, 2H), 6.98 – 6.83 (m, 2H), 6.62 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 171.2, 138.7, 130.3, 128.1, 127.9, 100.8, 46.8. HRMS (ESI-TOF) m/z Calcd for C_8H_9INO $[M + H]^+$ 261.9723 found 261.9724.

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2-(2,6-Diiodo-phenyl)-acetamide (3aa) Following GP isolated as white solid (19 mg, 18% yield); R_f (6:4 Hexane/EtOAc) = 0.6; Mp 238-240 °C; IR(ATR) 3401, 3182, 1649, 1038 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.79 – 7.76 (m, 2H), 7.01 (brs, 1H), 6.66 (brs, 1H), 6.58-6.54 (m, 1H), 4.00 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 169.4, 140.7, 139.1, 129.8, 100.6, 52.7. HRMS (ESI-TOF) m/z Calcd for $C_8H_9I_2NO$ $[M + H]^+$ 387.8690 found 387.8692.

2-(2-iodo-4-methylphenyl)acetamide (3b) Following GP isolated as white solid (44 mg, 66% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 192-194 °C; IR(ATR) 3384, 3198, 2904, 1648 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.39 (brs, 1H), 7.18 (t, J = 8.0 Hz, 2H), 6.97 (brs, 1H), 3.51 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.1, 139.0, 137.9, 136.5, 130.6, 128.8, 101.6, 46.1, 19.8. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}INO$ $[M + H]^+$ 275.9880 found 275.9889.

2-(2,6-Diiodo-4-methyl-phenyl)-acetamide (3bb) Following GP isolated as white solid (20 mg, 20% yield); R_f (6:4 Hexane/EtOAc) = 0.6; Mp 228-230 °C; IR(ATR) 3380, 3166, 1653, 1040 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.72 (s, 1H), 7.44 (brs, 1H), 6.98 (brs, 1H), 3.50 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 141.1, 140.0, 139.1, 101.4, 100.8, 45.2, 26.2. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}I_2NO$ $[M + H]^+$ 401.8846 found 401.8839.

2-(2-iodo-5-methylphenyl)acetamide (3c) Following GP isolated as white solid (45 mg, 66% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 183-185 °C; IR(ATR) 3378, 3191, 1655, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 8.0 Hz, 1H), 7.38 (brs, 1H), 7.12 (s, 1H), 6.96 (brs, 1H), 6.81 (dd, J = 8.0, 1.7 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8,

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139.2, 138.4, 137.5, 131.7, 129.3, 97.6, 46.4, 20.4. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}INO$ $[M + H]^+$ 275.9880 found 275.9889.

2-(2-Iodo-5-methoxy-phenyl)-acetamide (3d) Following GP isolated as white solid (58 mg, 80% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 178-180 ^oC; IR(ATR) 3365, 3178, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.62-7.54 (m, 1H), 6.85 – 6.85 (m, 1H), 6.52 – 6.48 (m, 2H), 6.38 (brs, 1H), 3.69 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 171.3, 159.4, 139.1, 139.2, 116.2, 114.3, 89.0, 54.8, 47.1. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}INO_2$ $[M + H]^+$ 291.9829 found 291.9833.

2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetamide (3e) Following GP isolated as white solid (53 mg, 70% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 148-150 ^oC; IR(ATR) 3400, 3194, 1655, 1474 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (s, 2H), 6.96 (brs, 1H), 6.93 (s, 1H), 6.02 (s, 2H), 3.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.1, 147.8, 146.9, 132.8, 117.7, 111.0, 101.6, 89.6, 46.3. HRMS (ESI-TOF) m/z Calcd for $C_9H_9INO_3$ $[M + H]^+$ 305.9622 found 305.9636.

2-(4-bromo-2-iodophenyl)acetamide (3f) Following GP isolated as white solid (42 mg, 50% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 175-177 ^oC; IR(ATR) 3384, 3194, 1648, 1403 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.55 (dd, J = 8.2, 2.0 Hz, 1H), 7.48 (brs, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.03 (brs, 1H), 3.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 140.0, 139.2, 132.5, 130.9, 120.0, 102.8, 45.8. HRMS (ESI-TOF) m/z Calcd for C_8H_8BrINO $[M + H]^+$ 339.8828 found 339.8841.

2-(4-chloro-2-iodophenyl)acetamide (3g) Following GP isolated as white solid (44 mg, 60% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 168-170 ^oC; IR(ATR) 3384, 3200, 2924, 1648, 1404, 1024 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.48 (brs, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.03 (brs, 1H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

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170.6, 138.8, 137.4, 132.1, 131.6, 128.0, 102.2, 45.7. HRMS (ESI-TOF) m/z Calcd for C_8H_8ClINO $[M + H]^+$ 295.9334 found 295.9343.

2-(2-iodo-4,5-dichlorophenyl)acetamide (3h) Following GP isolated as white solid (44 mg, 55% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 100-102 ^oC; IR(ATR) 3394, 3200, 2923, 1650 cm^{-1}. ^1H NMR (400 MHz, DMSO) δ 8.06 (s, 1H), 7.58 (s, 1H), 7.48 (s, 1H), 7.04 (s, 1H), 3.58 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 170.0, 140.8, 139.1, 132.0, 130.7, 129.8, 100.1, 45.4. HRMS (ESI-TOF) m/z Calcd for $C_8H_7Cl_2INO$ $[M + H]^+$ 329.8944 found 329.8940.

2-(4-Fluoro-2-iodo-phenyl)-acetamide (3i) Following GP isolated as white solid (25 mg, 35% yield); R_f (6:4 Hexane/EtOAc) = 0.3; Mp 158-160 ^oC; IR(ATR) 3381, 3191, 2924, 1651, 1477 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.69 (dd, J = 8.4, 2.7 Hz, 1H), 7.44 (brs, 1H), 7.33 (dd, J = 8.5, 6.2 Hz, 1H), 7.21 (td, J = 8.5, 2.7 Hz, 1H), 7.00 (brs, 1H), 3.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 161.42 and 158.96 (d, J = 246 Hz), 136.08 and 136.04 (d, J = 4.0 Hz), 131.95 and 131.87 (d, J = 8.0 Hz) 125.25, 125.01, 115.06, 114.85, 101.30, 101.22, 45.47. ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.4. HRMS (ESI-TOF) m/z Calcd for C_8H_8FINO $[M + H]^+$ 279.9629 found 279.9648.

2-(2-Iodo-4-nitro-phenyl)-acetamide (3j) Following GP isolated as white solid (26 mg, 33% yield); R_f (6:4 Hexane/EtOAc) = 0.25; Mp 217-219 ^oC; IR(ATR) 3426, 3291, 2921, 1661, 1342 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.19 (d, J = 8.4, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.11 (brs, 1H), 3.74 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 147.6, 146.3, 132.9, 131.7, 122.8, 101.5, 46.3. HRMS (ESI-TOF) m/z Calcd for $C_8H_8IN_2O_3$ $[M + H]^+$ 306.9574 found 306.9589.

2-(2-iodo-4-(trifluoromethyl)phenyl)acetamide (3k) Following GP isolated as white solid (16 mg, 20% yield); R_f (1:1 Hexane/EtOAc) = 0.3; Mp 166-168 ^oC; IR(ATR) 3393, 3204, 1650,

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1323 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.11 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 6.8 Hz, 2H), 7.07 (s, 1H), 3.67 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 170.2, 144.7, 134.9 (q, *J* = 4.0 Hz), 131.6, 128.6 (q, *J* = 32.0 Hz), 124.8 (q, *J* = 3.0 Hz), 123.1 (q, *J* = 271.0 Hz), 101.9, 46.4. ^{19}F NMR (376 MHz, DMSO-d_6): -61.0. HRMS (ESI-TOF) m/z Calcd for $C_9H_8IF_3NO$ $[M + H]^+$ 329.9597 found 329.9575.

2-(2-Bromo-6-iodo-phenyl)-acetamide (3l) Following GP isolated as white solid (45 mg, 55% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 224-226 °C; IR(ATR) 3392, 3194, 1648, 1424 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.47 (brs, 1H), 7.01 (brs, 1H), 6.90 (t, *J* = 7.9 Hz, 1H), 3.89 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 138.6, 138.4, 132.6, 130.3, 124.5, 103.4, 47.7. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}INO$ $[M + H]^+$ 339.8828 found 339.8852.

2-(1-Iodo-naphthalen-2-yl)-acetamide (3m) Following GP isolated as white solid (60 mg, 77% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 205-207 °C; IR(ATR) 3378, 3188, 1648, 1390 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, *J* = 8.6 Hz, 1H), 7.89 (dd, *J* = 8.1, 5.0 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.57-7.50 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.05 (brs, 1H), 3.89 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 139.4, 134.4, 132.5, 132.0, 128.8, 128.3, 128.25, 128.0, 126.3, 106.6, 48.6. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{11}INO$ $[M + H]^+$ 311.9880 found 311.9891.

2-(2-Iodo-phenyl)-propionamide (3n) Following GP isolated as white solid (40 mg, 58% yield); R_f (6:4 Hexane/EtOAc) = 0.4; Mp 55-57 °C; IR(ATR) 3388, 3188, 2984, 1649, 1413cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.38-7.34 (m, 3H), 6.97 (d, *J* = 5.8 Hz, 2H), 3.77 (q, *J* = 7.0 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

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174.4, 144.6, 139.1, 128.6, 128.5, 127.9, 101.5, 49.3, 18.8. HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}INO$ $[M + H]^+$ 275.9880 found 275.9887.

Procedure for synthesis of (2-Bromo-phenyl)-acetonitrile (4a)[13]: By following a reported procedure,[17] **2a** (0.2 mmol, 42 mg) in CH_3CN/H_2O (1:1 = 2.0 mL) was treated with $PdCl_2$ (10 mol %, 3.5 mg) at 60 °C for 12 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate (15 mL × 3). Solvent was removed in vacuum, and crude product was purified by column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0, 1H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1H), 7.29 – 7.22 (m, 1H), 3.86 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 129.9, 129.8, 129.6, 128.1, 123.6, 116.8, 24.8.

Procedure for the synthesis of (2-Bromo-phenyl)-acetic acid (4b)[18a]: By following a reported literature method,[18b] the solution of **2a** (0.25 mmol, 42 mg) in 3 mL of 20% (v/v) sulfuric acid was heated at 100 °C for 15 h. After reaction completion, the mixture was diluted with water and extracted with ethyl acetate (15 mL × 3). The organic layer was washed with brine solution and dried over sodium sulfate and concentrated under reduced pressure to give a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.20 – 7.13 (m, 1H), 3.85 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 133.5, 132.9, 131.5, 129.1, 127.6, 125.1, 41.3.

Procedure for synthesis of 2-(4'-Methoxy-biphenyl-2-yl)-acetamide (4c)[11a]: By following a reported literature method,[19] in 25 mL round bottom flask equipped with magnetic bar was sequently added **2a** (0.25 mmol, 53.5 mg), $PdCl_2$ (5 mol%, 2.5 mg), K_2CO_3 (1.5 equiv, 51.7 mg) followed by 4-methoxy boronic acid (1.5 equiv, 57 mg). Then DMF/H_2O (1:1 = 3.0 mL) was

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added to reaction mixture. The reaction was stirred at 50 °C in open air for 30 minutes. After completion, the mixture was added to brine (15 mL) and extracted four times with ethyl acetate (4 X 15 mL). The solvent was concentrated under vacuum and the product was isolated by chromatography on a silica gel column using acetone in DCM as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 8H), 7.00 – 6.94 (m, 2H), 5.67 (s, 1H), 5.32 (s, 1H), 3.87 (s, 3H), 3.58 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 158.9, 142.2, 133.1, 132.5, 130.7, 130.6, 130.1, 129.4, 129.0, 127.7, 127.5, 113.8, 55.3, 40.9.

N-benzyl-2-(2-bromophenyl)acetamide (5a)[20] : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.29 (m, 6H), 7.17 (td, *J* = 7.7, 1.8 Hz, 1H), 5.88 (s, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 130.8, 127.6, 125.9, 124.5, 122.0, 121.4, 120.8, 120.3, 120.2, 117.8, 70.1, 69.8, 69.5, 36.8, 36.5.

ASSOCIATED CONTENT

Supporting Information

Detailed information on experimental procedures, characterization data, spectra and crystallographic data (PDF).

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The authors declare no competing financial interest.

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