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Graphical Abstract

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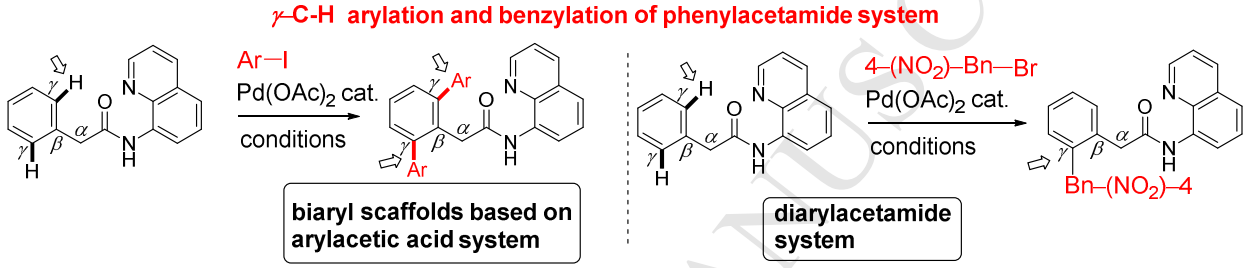

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Synthesis of *Ortho*-Arylated/Benzylated Arylacetamide Derivatives: $Pd(OAc)_2$-Catalyzed Bidentate Ligand-Aided Arylation and Benzylation of the γ-C-H Bond of Arylacetamides

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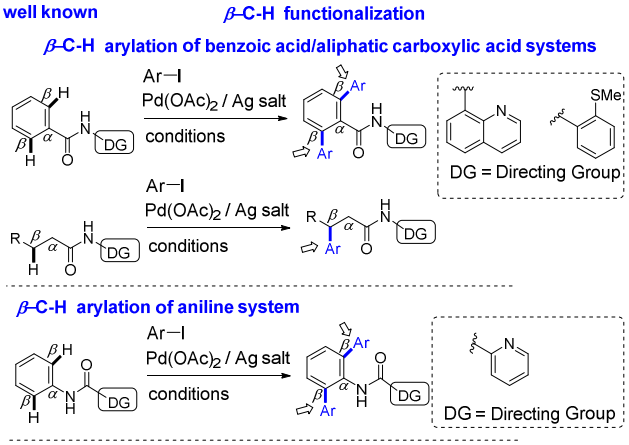
ABSTRACT

In this paper, we report the $Pd(OAc)_2$/AgOAc, bidentate ligand-directed C-H functionalization of the sp^2 γ-C-H bond of arylacetamides. While, the bidentate ligand-directed site selective functionalization of the β-C-H bond of aromatic carboxylic acid derivatives is well known, we herein, report our attempts on the Pd(II)-catalyzed, bidentate ligand-directed arylation, benzylation, alkylation, acetoxylation and hydroxylation of the sp^2 γ-C-H bond of the arylacetamide systems. The arylation and benzylation of arylacetamides were successful; however, the alkylation and acetoxylation/hydroxylation of arylacetamides were not successful. Various ligands were screened to substantiate the need for the bidentate ligand in the arylation/benzylation of arylacetamides, and 8-aminoquinoline was found to be the best bidentate ligand. Several substituted aryl-/heteroaryl iodides, 4-nitrobenzyl bromide and arylacetamide substrates were used to examine their reactivity pattern and accomplish the substrate scope/generality. In general, the bidentate ligand 8-aminoquinoline-directed arylation of arylacetamides gave the corresponding *ortho*-diarylated arylacetamides and benzylation of arylacetamides gave the corresponding *ortho*-mono benzylated arylacetamides as the predominant compounds. Overall, this method has led to the synthesis of new *ortho*-substituted arylacetamides in good to high yields.

1. Introduction

In recent years, the transition metal-catalyzed C-H activation/functionalization reaction has become a popular tool for forming the C-C bond.[1-3] There exist several exceptional reports dealing on the synthesis of biaryls *via* the direct functionalization of the sp^2 C-H bond of arenes and heteroarenes without any directing groups.[1-4] Nevertheless, the transition metal-catalyzed, directing group-enabled, site selective C-H activation/functionalization reactions have been found to be highly efficient and practically simple methods for synthesizing functionalized organic molecules.[1-5] Functional groups, such as ketone, amide, carbamate, carboxylic acid, aldehyde, ether, etc were identified as weakly coordinating directing groups for accomplishing the site selective C-H activation/functionalization.[1-5] Along this line, since the seminal work by Daugulis *et al.*,[6] bidentate ligands (e.g., 8-aminoquinoline and picolinamide) were found to be very efficient to accomplish the site selective sp^2 and sp^3 C-H activation/functionalization of various aliphatic-, alicyclic- and aromatic carboxamide derivatives[1-5] (Scheme 1).



Scheme 1. Functionalization of sp^2 and sp^3 β-C-H bond.

With regard to the site selectivity, in general, the C-H bond of the β-position of aliphatic-, alicyclic- and aromatic carboxamide

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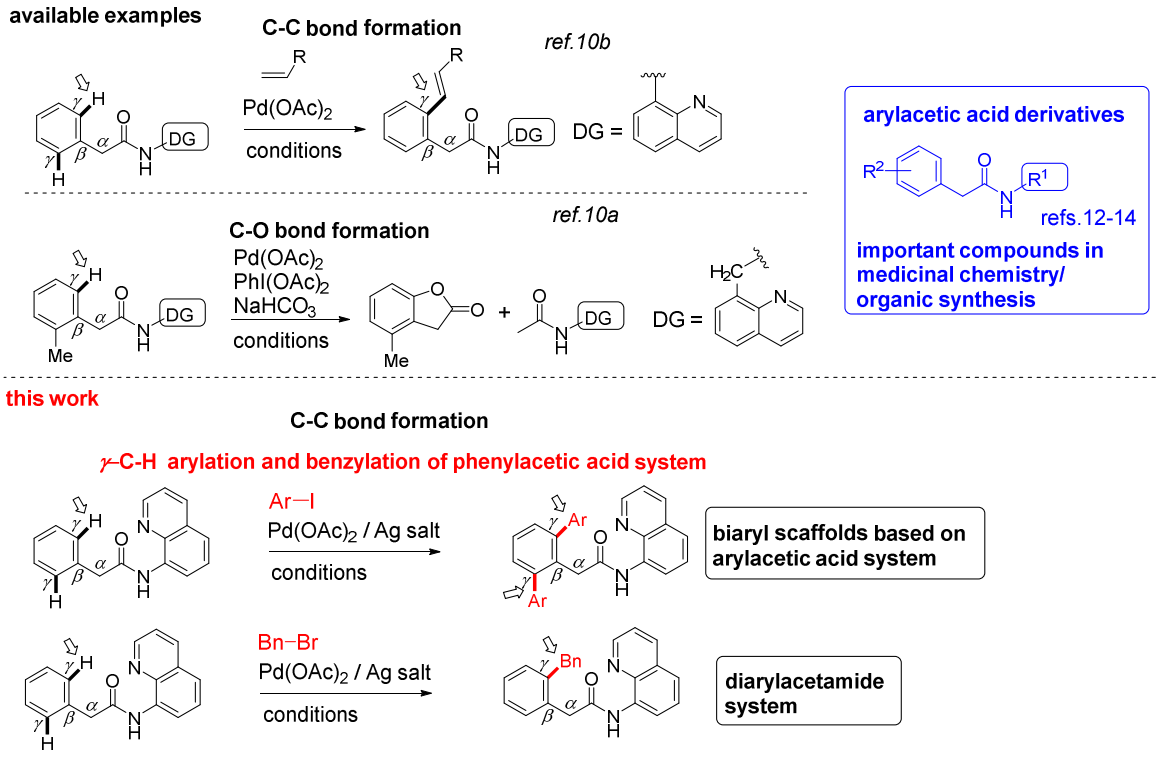
derivatives containing the bidentate ligands have been efficiently functionalized[3d,5a,b,f,6] (Scheme 1). Accordingly, the bidentate ligand-directed arylation, alkylation, acetoxylation of C-H bond of the *β*-position of carboxamide derivatives have been well explored.[1-8] On the other hand, the functionalization of remote C-H bond, (e.g., *γ*-C-H bond) of carboxylic acid derivatives is relatively less explored.[9-11] Although, the ligand-directed functionalization (e.g., olefination, acetoxylation, carbonylation, amidation, etc) of remote sp^3 C-H bond (other than the *β*-C-H bond) of aliphatic carboxylic acids has met with some notable success;[9] the bidentate ligand-directed site selective functionalization of remote sp^2 C-H bond other than *β*-C-H bond of aromatic carboxylic acid derivatives, (e.g., arylacetamides) has not been explored well.[10]

Prior to this work and to the best of our knowledge, there exist only two reports dealing on the bidentate ligand-directed functionalization of the sp^2 *γ*-C-H bond of the arylacetamide systems.[10] Chatani *et al.* reported the lactonization of the arylacetamide system *via* the acetoxylation of the sp^2 *γ*-C-H bond of the phenylacetamide system.[10a] Maiti *et al.* reported the Pd(II)-catalyzed olefination of the sp^2 *γ*-C-H bond of the phenylacetamide system (Scheme 2).[10b]

arylacetic acid derivatives including arylacetamides are versatile synthetic intermediates in synthetic organic chemistry and medicinal chemistry.[13,14] Hence, given the importance of the arylacetic acid derivatives and in continuation of our interest on the bidentate ligand-enabled C-C bond construction *via* the C-H activation reactions,[8] we envisaged the Pd(II)-catalyzed, 8-aminoquinoline-directed functionalization (arylation/alkylation) of the sp^2 *γ*-C-H bond of the phenylacetamide systems and to assemble new *ortho*-arylated/alkylated arylacetamide derivatives[15] (Scheme 2).

2. Results and Discussion

At the outset, we planned to attempt the Pd(II)-catalyzed arylation of the *γ*-C-H bond of the phenylacetamide system. To find out the optimized reaction conditions, we performed several reactions comprising the Pd(II)-catalyzed, 8-aminoquinoline-directed *γ*-C-H arylation of the substrate **1a** (Table 1). The reaction of **1a**, **2a** and AgOAc in the absence of any catalyst did not give any C-H arylated product (entry 1, Table 1) and we also tested the reaction of **1a**, **2a** and 10 mol% of the $Pd(OAc)_2$ catalyst in the absence of any additive, and this reaction also did not give any C-H arylated product, Then, the reaction of **1a** (1

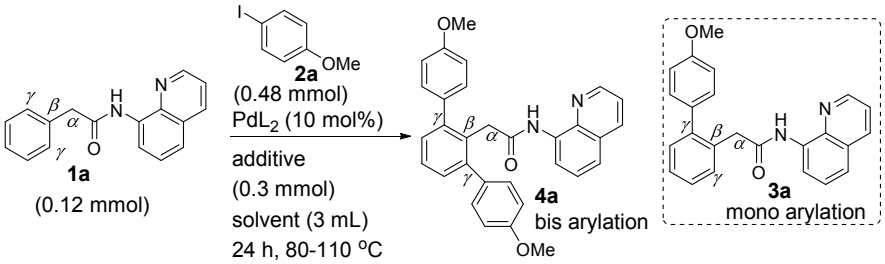


Scheme 2. Functionalization of the sp^2 *γ*-C-H bond of the phenylacetamide systems.

It is worth to mention that the arylacetic acid derivatives are imperative structural units commonly found in analgesics and antiinflammatory drugs (e.g., ibuprofen, naproxen).[12] Further,

equiv) with **2a** (4 equiv) in the presence of the well-explored $Pd(OAc)_2$/AgOAc-catalytic system[5a,f,6] gave the expected bis *γ*-C-H arylated product **4a** in high yield (85%, entry 2, Table 1).

Table 1. Optimization reactions. γ-C-H Arylation of the phenylacetamide system **1a**.



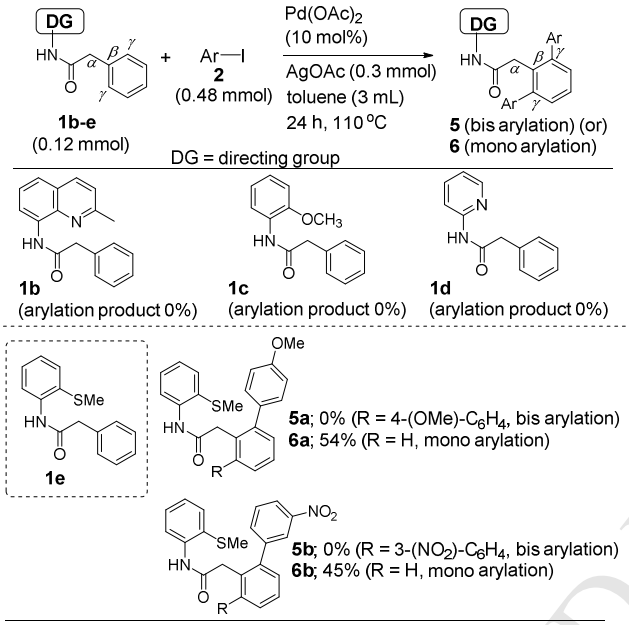
entry	PdL_2	additive	solvent (3 mL)	*t* (°C)	**4a**; yield (%)	**3a**; yield (%)
1	–	AgOAc	toluene	110	0	-
2	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**85**	**-**
3	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	30	-
4	$Pd(OAc)_2$	K_2CO_3	toluene	110	67	-
5	$Pd(OAc)_2$	KOAc	toluene	110	0	-
6	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0	-
7	$PdCl_2$	AgOAc	toluene	110	25	-
8	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	46	-
9	$Pd(TFA)_2$	AgOAc	toluene	110	0	-
10	$Pd(PPh_3)_4$	AgOAc	toluene	110	0	-
11	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	0	-
12	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	0	-
13	$Pd(OAc)_2$	AgOAc	1,4-dioxane	100	53	-
14	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	53	-
15[a]	$Pd(OAc)_2$	AgOAc	toluene	110	14	25
16[b]	$Pd(OAc)_2$	AgOAc	toluene	110	34	25
17[c]	$Pd(OAc)_2$	AgOAc	toluene	110	53	-
18[d]	$Pd(OAc)_2$	AgOAc	toluene	110	-	-
19[e]	$Pd(OAc)_2$	AgOAc	toluene	110	37	36

[a] 1 Equiv (0.12 mmol) of **2a**.
[b] 2 Equiv (0.24 mmol) of **2a**.
[c] 3 Equiv (0.36 mmol) of **2a**.
[d] 0.1 Equiv (0.012 mmol) of AgOAc.
[e] 1 Equiv (0.12 mmol) of AgOAc.

We then carried out further optimization reactions to improve the efficiency of the process and yield of the product **4a** (Table 1). Accordingly, the arylation of **1a** with **2a** in the presence of additives, such as, Ag_2CO_3 or K_2CO_3 gave the product **4a** in 30 and 67% yields (entries 3 and 4, Table 1). The arylation of **1a** with **2a** in the presence of additives, such as, KOAc or $PhI(OAc)_2$ did not give the product **4a** (entries 5 and 6, Table 1). The arylation of **1a** with **2a** in the presence of the palladium catalysts $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ gave the product **4a** in 25 and 46% yields, respectively (entries 7 and 8, Table 1). The arylation of **1a** with **2a** in the presence of the palladium catalysts $Pd(TFA)_2$ and $Pd(PPh_3)_4$ did not give the product **4a** (entries 9 and 10, Table 1). The arylation of **1a** with **2a** in solvents, such as, 1,2-DCE or *tert*-butanol failed to give the product **4a** (entries 11 and 12, Table 1). However, the arylation of **1a** with **2a** in 1,4-dioxane or *tert*-amylOH gave the product **4a** in 53% yield (entries 13 and 14, Table 1). In these reactions, the formation of the mono arylated product **3a** is also expected. However, we did not get any characterizable amounts of the product **3a** from the column chromatographic purification of the respective crude reaction mixtures of the reactions shown in Table 1 (entries 1-14). Our previous experience[8] and a survey of the literature[5,6] indicated that generally, 3-4 equivalents of aryl iodide are used for obtaining the mono arylated products in high yields under the palladium-catalyzed C-H arylation method. In the present case, it seems that the bis arylation of **1a** is a facile reaction and the arylation of **1a** with 4 equivalents **2a** directly gave the bis arylated product **4a** in a maximum of 85% yield (entry 2, Table 1).

Then, we performed the arylation of **1a** with fewer equivalents of **2a** to check whether we can obtain the mono arylation product. The arylation of **1a** with one equivalent of **2a** gave the mono arylated product **3a** in 25% yield and bis arylated product **4a** in 14% yield (entry 15, Table 1). A similar trend was observed when the arylation of **1a** was carried out with two equivalents of **2a** and in this case, the compounds **4a** and **3a** were obtained in 34 and 25% yields, respectively (entry 16, Table 1). These two reactions indicated that the bis arylation of **1a** is a facile though fewer equivalents of **2a** were used. The arylation of **1a** with three equivalents of **2a** gave the bis arylated product **4a** in 53% yield

(entry 17, Table 1). This reaction and the reaction of entry 2 (Table 1) revealed that the second arylation of the product **3a** is a facile reaction and 3-4 equivalents of **2a** are needed for obtaining the bis γ-C-H arylated product **4a** in high yield from the phenylacetamide system **1a**. Furthermore, we also performed the arylation of **1a** with **2a** (4 equiv) in the presence of catalytic amounts of AgOAc and this reaction gave an inseparable reaction mixture containing the starting material as the predominant compound (entry 18, Table 1). The arylation of **1a** with **2a** (4 equiv) in the presence of one equivalent of AgOAc instead of 2.5 equivalents of AgOAc (entry 2) gave the mono arylated product **3a** in 36% yield and the bis arylated product **4a** in 37% yield (entry 19, Table 1).



Scheme 3. Bidentate ligands explored for the γ-C-H arylation of the phenylacetamide system.

Having found the optimized reaction conditions for the bis arylation of the γ-C-H bond of the phenylacetamide system **1a** containing 8-aminoquinoline as the directing group; then, we wished to establish the efficiency of 8-aminoquinoline directing group and find out the other suitable directing groups for the γ-C-H arylation reactions. Accordingly, we performed the C-H arylations of the substrates **1b-e** (derived from the corresponding bidentate ligands). The arylation of the substrates **1b-d** failed to afford the corresponding γ-C-H arylated products (Scheme 3). However, the γ-C-H arylation of the substrate **1e** (derived from the bidentate ligand 2-(methylthio)aniline) with **2a** successfully afforded the mono arylated product **6a** in 54% yield (Scheme 3). Similarly, the mono arylated product **6b** was obtained in 45% yield from the γ-C-H arylation of the substrate **1e** with the corresponding aryl iodide compound (Scheme 3).

Next, to expand the substrate scope and generality, we performed the bis γ-C-H arylation of **1a** with aryl iodides containing an electron donating group at the *para* position, which afforded the products **4a-d** in 63-85% yields, respectively (Table 2). The bis γ-C-H arylation of **1a** with iodobenzene gave the product **4e** in 81% yield (Table 2). Then, the bis γ-C-H arylation of **1a** with di-substituted aryl iodides furnished the products **4f-i** in 45-73% yields, respectively (Table 2). Further, we performed the direct bis arylation of **1a** with aryl iodides containing an electron withdrawing group at the *para*/*meta* position, which afforded the products **4j-o** in 50-70% yields, respectively (Table 2). In one of the case, the mono arylated product **3o** (43%) was also obtained along with the bis arylated product **4o** (56%, predominant product). Next, we performed the direct bis arylation of the γ-C-H bond of the phenylacetamide system **1a** with heteroaryl iodides, which also gave the corresponding bis arylated products **4p** (44%) and **4q** (70%). In an another reaction comprising the γ-C-H arylation of the substrate **1a** with 5-iodoindole afforded only the mono arylated product **3r** (44%) as the predominant isomer and the corresponding bis arylated product was not obtained in any characterizable amounts from the column chromatographic purification of the crude reaction mixture of this reaction. Presumably, since the indole unit is relatively bigger and installation of a second indole moiety in **3r** seems to be difficult as it may result a steric crowding in the bis arylated compound and hence, only the mono arylated product **3r** was obtained as the predominant isomer (Table 2).

Table 2. The Pd(II)-catalyzed synthesis of the *ortho*-arylated arylacetamide derivatives **4a-q**/**3o,r**.

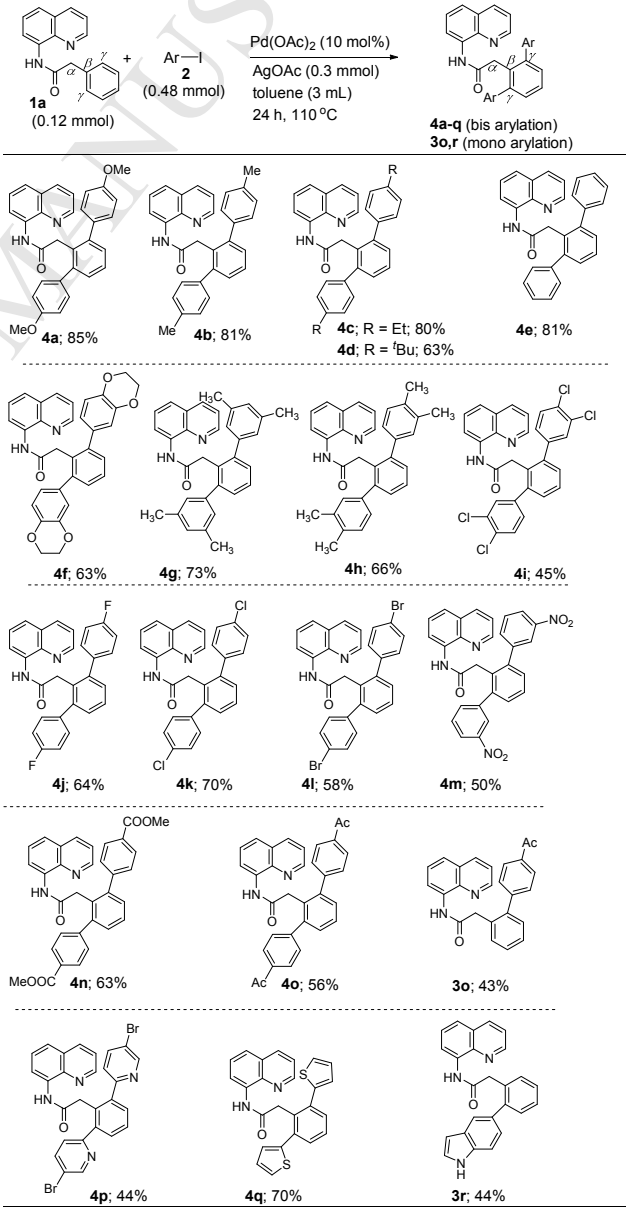
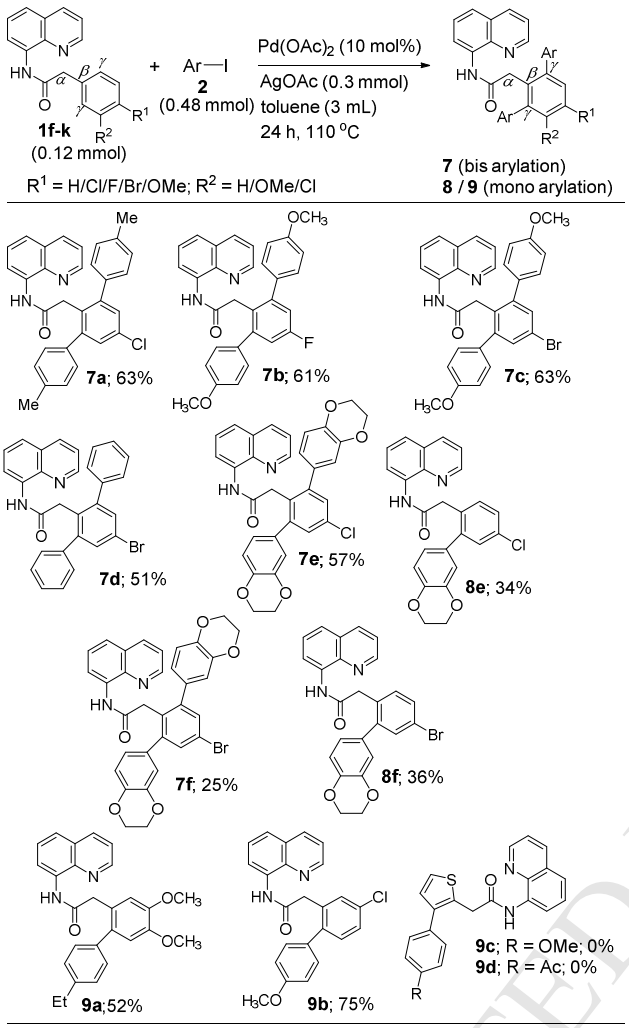


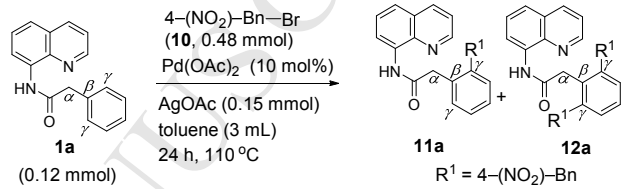
Table 3. The Pd(II)-catalyzed synthesis of the *ortho*-arylated arylacetamide derivatives **7**/**8**/**9**.



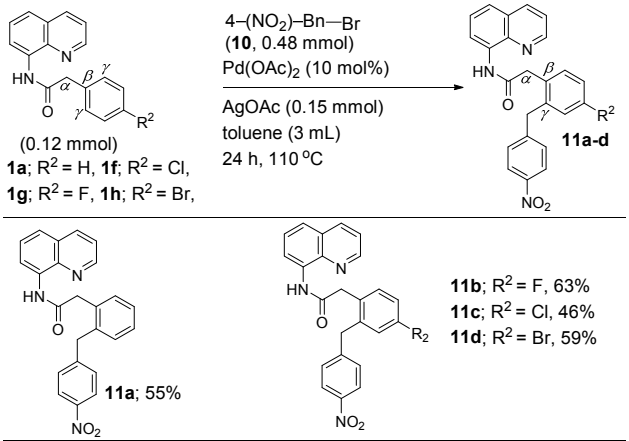
Successively, to further extend the substrate scope of this method, we performed the *γ*-C-H arylation of various phenylacetamides containing different substituents in the aryl ring. Accordingly, we synthesized the bis arylated products **7a-f** in 25-63% yields from their respective starting materials (Table 3). In some exceptional cases, the mono arylated products, such as, **8e** (34%) and **8f** (36%) were also obtained along with their corresponding bis arylated products **7e** and **7f**. Along this line, we also obtained the mono arylated products **9a** (52%) and **9b** (75%) exclusively from their respective starting materials (Table 3). In our further trials to extend the substrate scope, we did not get the arylated products **9c** and **9d** from the corresponding thiophenylacetamide starting material **1k**, which is structurally similar to the phenylacetamide **1a**. The reason for the failure of the arylation of thiophenylacetamide **1k** was not clear at this stage.

Finally, we attempted the benzylation of the *γ*-C-H bond of the phenylacetamide systems (Table 4). Fortunately, in an initial trial, the benzylation of the *γ*-C-H bond of the phenylacetamide system **1a** successfully afforded the mono benzylated phenylacetamide system **11a** in 55% yield (Table 4). The column chromatographic purification of the crude reaction mixture gave only the product **11a** and the bis benzylated compound **12a** was not obtained in any characterizable amounts. In order to improve the yield of **11a** we have carried out the benzylation of **1a** by using different reaction conditions (entries 2-9, Table 4). However, we did not find any other suitable reaction conditions for obtaining the product **11a** in better yield than the initial reaction (entry 1, Table 4). Similarly, the *γ*-C-H benzylation of the phenylacetamide substrates **1f-h** gave the mono benzylated phenylacetamide systems **11b-d** in 46-63% yields, respectively (Table 4). The reason for the formation of only mono benzylated products **11a-d** is not clear at this stage. Generally, the benzyl bromide reagent is highly reactive and hence, it is assumed that the benzyl bromide reagent might be decomposed or converted into 4-nitrobenzyl acetate under the experimental condition[16a,b] and hence, the second benzylation of the substrates **11a-d** did not occur to afford the corresponding bis benzylated products (e.g. **12a**).

Table 4. The Pd(II)-catalyzed synthesis of the *ortho*-benzylated arylacetamide derivatives **11a-d**.



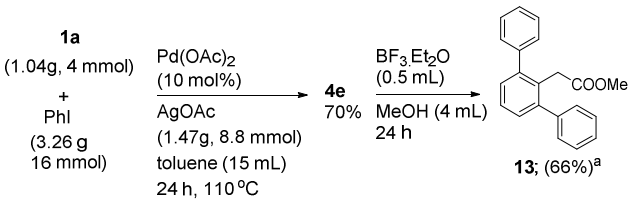
entry	PdL_2	additive	solvent (3 mL)	*t* (°C)	yield (%)
1[a]	$Pd(OAc)_2$	AgOAc	toluene	110	55
2	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	20
3	$Pd(OAc)_2$	KOAc	toluene	110	43
4	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0
5	$PdCl_2$	AgOAc	toluene	110	0
6	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	28
7	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	0
8	$Pd(OAc)_2$	AgOAc	1,2-DCE	110	0
9	$Pd(OAc)_2$	AgOAc	^{t}BuOH	110	0



[a] The reaction was performed using **1a** (0.12 mmol), **10** (0.48 mmol) and AgOAc (0.15 mmol).

We also performed the double arylation of the *γ*-C-H bond of the phenylacetamide system **1a** with iodobenzene in a gram scale and this reaction furnished the product **4e** in 70% yield (Scheme 5). Then, we wished to remove the bidentate ligand (8-aminoquinoline) from the representative *γ*-C-H arylated arylacetamide system. Accordingly, we treated the bis arylated arylacetamide system **4e** with BF_3-OEt_2 in MeOH, which

successfully furnished the methyl ester of *ortho*-diarylated phenylacetic acid **13** after the removal of the bidentate ligand 8-aminoquinoline in 66% yield (Scheme 4).



[a] The conversion of **4e** to **13** was performed using 1.4 mmol of **4e**.

Scheme 4. Gram scale reaction of the γ-C-H arylation of **1a** and the removal of the bidentate ligand 8-aminoquinoline.

Overall, while the arylation and benzylation of arylacetamides were successful, our various attempts on the 8-aminoquinoline-directed alkylation, acetoxylation and hydroxylation of phenylacetamides were not successful (See the Supplementary data). Apparently, the bidentate ligand 8-aminoquinoline seems to be not assisting the C-O bond formation in the arylacetamide system. Notably, Chatani's group[10a] was successful in constructing the C-O in the phenylacetamide system by using a less common bidentate ligand, quinolin-8-ylmethanamine (Scheme 2). Different ligands were screened for performing the arylation/benzylation of phenylacetamides and 8-aminoquinoline was found to be best ligand. Various aryl iodides containing electron- donating and withdrawing groups, heteroaryl iodides, benzyl bromides and phenylacetamide starting materials were used to examine their reactivity pattern. In general, the γ-C-H arylation of arylacetamides with aryl iodides containing electron donating groups gave *ortho*-diarylated arylacetamides as the predominant compounds in high yields (Table 2). The γ-C-H arylation of arylacetamides with aryl iodides containing electron withdrawing groups gave *ortho*-diarylated arylacetamides as the predominant compounds in moderate yields (Table 2). Depending on the substituents in the aryl iodides and only in specific cases the mono *ortho*-arylated arylacetamides were obtained. The γ-C-H arylation of arylacetamides containing a substituent at the *meta* position with aryl iodides gave only mono *ortho*-arylated arylacetamides as the predominant compounds in moderate to good yields (Table 3). Presumably, the installation of a second aryl moiety may result a steric crowding in the bis arylated compound and hence the arylation of arylacetamides containing a substituent at the *meta* position gave only the mono *ortho*-arylated arylacetamides. While, the γ-C-H benzylation of arylacetamides gave only the mono *ortho*-benzylated arylacetamides as the predominant compounds (Table 4), our other trials to get the bis γ-C-H benzylated compounds were not fruitful at this stage.

In summary, we have revealed our investigations on the Pd(II)-catalyzed, bidentate ligand-directed arylation and benzylation of the sp^2 γ-C-H bond of arylacetamide derivatives.[17] Given the importance of the arylacetic acid derivatives in organic synthesis and medicinal chemistry, this method has provided an access to assemble new *ortho*-substituted arylacetamides.

3. Experimental Section

3.1. General

IR spectra were recorded as KBr pellets or thin films. $^1H/^{13}C$ NMR spectra of were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out using anhydrous solvents under a nitrogen atm and anhydrous solvents. Organic layers after the work up procedure were dried using anhydrous sodium sulphate. TLC analysis was carried out on silica gel and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported and yields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures.[9h, 10b, 18] Characterization data of the arylated compounds, **4a**, **4b**, **4e**, **4g**, **4k**, **4l**, **4o**, **3o** and **7a** are reported in the literature.[15]

3.2. Procedure for synthesis of phenylacetamides 1a-e and 1k.

A dry flask the corresponding containing amine (1 mmol) and Et_3N (121 mg, 1.2 mmol) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by drop-wise addition of the corresponding acid chloride. The resulting mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dried over anhydrous Na_2SO_4 and then, the solvent was evaporated in *vacuo* to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography (silica gel, 100–200 mesh, (EtOAc/hexanes = 20:80) furnished the corresponding products **1a-e** and **1k**.

3.2.1. 2-Phenyl-*N*-(quinolin-8-yl)acetamide (1a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1a** as a dark brown color solid (449 mg, 68%); R_f (20% EtOAc/hexane) 0.5; mp: 91-93 °C; IR (KBr): ν_{max} 3345, 3055, 1681, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.94 (1 H, br. s), 8.79 (1 H, dd, J_1 = 7.3, J_2 = 1.7 Hz), 8.71 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.4 Hz), 7.55-7.51 (1 H, m), 7.49 (1 H, dd, J_1 = 8.6, J_2 = 1.7 Hz), 7.46-7.40 (5 H, m), 7.38-7.33 (1 H, m), 3.92 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.5, 148.2, 138.4, 136.3, 134.7, 134.4, 129.6, 129.0, 127.9, 127.4, 121.6, 121.6, 116.4, 45.4; HRMS (ESI): MH^+, found 263.1177. $C_{17}H_{15}N_2O$ requires 263.1184.

3.2.2. *N*-(2-Methylquinolin-8-yl)-2-phenylacetamide (1b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1b** as a yellow color solid (480 mg, 86%); R_f (20% EtOAc/hexane) 0.5; mp: 86-88 °C; IR (KBr): ν_{max} 3307, 3055, 1679, 1532, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.97 (1 H, br. s), 8.73 (1 H, dd, J_1 = 6.9, J_2 = 2.0 Hz), 7.96 (1 H, d, J = 8.4 Hz), 7.48-7.44 (4 H, m), 7.44-7.40 (3 H, m), 7.23 (1 H, d, J = 8.4 Hz) 3.93 (2 H, s), 2.55 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.5, 157.1, 137.8, 136.2, 134.7, 133.7, 129.9, 129.2, 127.5, 126.3, 125.9, 122.3, 121.4, 116.0, 45.5, 25.0; HRMS (ESI): MH^+, found 277.1333. $C_{18}H_{17}N_2O$ requires 277.1341.

3.2.3. *N*-(2-Methoxyphenyl)-2-phenylacetamide (1c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1c** as an orange color solid (210 mg, 72%); R_f (20% EtOAc/hexane) 0.4; mp: 85-87 °C; IR (KBr): ν_{max} 3385, 3056, 1683, 1530, 1263, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42 (1 H, d, J = 6.8 Hz), 7.93 (1 H, br. s),

7.46-7.36 (5 H, m), 7.06 (1 H, td, J_1 = 7.7, J_2 = 1.4 Hz), 6.98 (1 H, td, J_1 = 7.7, J_2 = 1.4 Hz), 6.83 (1 H, d, J = 8.3 Hz), 3.81 (2 H, s), 3.73 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.4, 148.0, 134.6, 129.6, 129.5, 129.1, 128.6, 127.5, 127.2, 124.0, 121.1, 119.7, 110.1, 55.7, 45.1; HRMS (ESI): MH^+, found 242.1174. $C_{15}H_{16}NO_2$ requires 242.1181.

3.2.4. 2-Phenyl-*N*-(pyridin-2-yl)acetamide (1d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1d** as a pale yellow color solid (150 mg, 89%); R_f (20% EtOAc/hexane) 0.3; mp: 115-117 ^{o}C; IR (KBr): ν_{max} 3233, 3053, 1650, 1578, 1291, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.25-8.22 (2 H, m), 8.12 (1 H, br. s), 7.70 (1 H, td, J_1 = 8.5, J_2 = 1.7 Hz), 7.42-7.34 (5 H, m), 7.04 (1 H, t, J = 7.6 Hz), 3.77 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.6, 151.6, 147.7, 138.4, 133.9, 129.5, 129.3, 127.7, 120.0, 114.0, 45.0; HRMS (ESI): MH^+, found 213.1022. $C_{13}H_{13}N_2O$ requires 213.1028.

3.2.5. *N*-(2-(methylthio)phenyl)-2-phenylacetamide (1e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1e** as a colorless solid (449 mg, 87%); R_f (20% EtOAc/hexane) 0.5; mp: 94-96 ^{o}C; IR (KBr): ν_{max} 3311, 3055, 1683, 1517, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (2 H, d, J = 8.0 Hz), 7.46-7.35 (6 H, m), 7.30 (1 H, t, J = 7.1 Hz), 7.03 (1 H, t, J = 6.7 Hz), 3.82 (2 H, s), 2.04 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.3, 138.5, 134.4, 133.6, 129.7, 129.3, 129.2, 127.8, 125.0, 124.3, 120.0, 45.4, 18.7;. HRMS (ESI): MH^+, found 258.0946. $C_{15}H_{16}NOS$ requires 258.0953.

3.2.6. *N*-(Quinolin-8-yl)-2-(thiophen-2-yl)acetamide (1k): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1k** as a brown solid (449 mg, 68%); R_f (20% EtOAc/hexane) 0.4; mp: 70-72 ^{o}C; IR (KBr): ν_{max} 3339, 3054, 2308, 1527, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.0 (1 H, br. s), 8.79 (1 H, dd, J_1 = 7.1, J_2 = 1.8 Hz), 8.73 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.55-7.49 (2 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.32 (1 H, dd, J_1 = 5.1, J_2 = 1.2 Hz), 7.14 (1 H, d, J = 3.4 Hz), 7.08 (1 H, dd, J_1 = 5.2, J_2 = 3.5 Hz), 4.12 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.3, 148.3, 138.5, 136.3, 135.3, 134.2, 127.9, 127.5, 127.3, 125.6, 121.6, 116.4, 39.1;. HRMS (ESI): MH^+, found 269.0742. $C_{15}H_{13}N_2OS$ requires 269.0749.

3.3. Procedure for synthesis of phenylacetamides 1f-j.

A dry flask containing carboxylic acid (1 mmol) and $SOCl_2$ (0.6 mL) was heated at 80 ^{o}C for 4 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (2 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (1 mmol), Et_3N (111 mg, 1.1 mmol) and DCM (4 mL) under a nitrogen atmosphere. The resulting mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dried over anhydrous Na_2SO_4 and then, the solvent was evaporated in *vacuo* to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography (neutral alumina (EtOAc/hexanes = 25:75) furnished the corresponding products **1f-j**.

3.3.1. 2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)acetamide (1f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1f** as a yellow color solid (153 mg, 79%); R_f (20% EtOAc/hexane) 0.6; mp: 95-97 ^{o}C; IR (KBr): ν_{max} 3343, 3054, 1682, 1527, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (1 H, br. s), 8.77-8.74 (2 H, m), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.56-7.50 (2 H, m), 7.44 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.39 (4 H, s), 3.88 (2 H, s) ;^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.9, 148.3, 138.4, 136.3, 134.2, 133.3, 133.2, 130.9, 129.1, 127.9, 127.3, 121.8, 121.6, 116.4, 44.5; HRMS (ESI): MH^+, found 297.0788. $C_{17}H_{14}ClN_2O$ requires 297.0795.

3.3.2. 2-(4-Fluorophenyl)-*N*-(quinolin-8-yl)acetamide (1g): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1g** as a yellow color solid (197 mg, 23%); R_f (20% EtOAc/hexane) 0.5; mp: 88-90 ^{o}C; IR (KBr): ν_{max} 3345, 3054, 1682, 1529, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (1 H, br. s), 8.78 (1 H, d, J = 7.2 Hz), 8.72 (1 H, d, J = 4.2 Hz), 8.11 (1 H, d, J = 8.2 Hz), 7.53-7.47 (2 H, m), 7.42-7.39 (3 H, m), 7.10 (2 H, t, J = 8.6 Hz), 3.87 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.3, 162.2 (d, J_{C-F} = 243.6 Hz), 148.2, 138.4, 136.3, 134.3, 131.2, (d, J_{C-F} = 8.0 Hz), 130.5 (d, J_{C-F} = 3.1 Hz), 127.9, 127.3, 121.7, 121.6, 116.4, 115.8 (d, J_{C-F} = 21.2 Hz), 44.3; HRMS (ESI): MH^+, found 281.1082. $C_{17}H_{14}FN_2O$ requires 281.1090.

3.3.3. 2-(4-Bromophenyl)-*N*-(quinolin-8-yl)acetamide (1h): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1h** as a brown color solid (624 mg, 52%); R_f (20% EtOAc/hexane) 0.6; mp: 104-106 ^{o}C; IR (KBr): ν_{max} 3342, 3054, 1682, 1527, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (1 H, br. s), 8.76 (1 H, dd, J_1 = 7.0, J_2 = 2.0 Hz), 8.74 (1 H, dd, J_1 = 4.3, J_2 = 1.7 Hz), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.55-7.48 (4 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.32 (2 H, d, J = 8.4 Hz), 3.85 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.8, 148.3, 138.3, 136.3, 134.2, 133.7, 132.0, 131.3, 127.9, 127.3, 121.8, 121.7, 121.4, 116.4, 44.5; HRMS (ESI): MH^+, found 341.0278. $C_{17}H_{14}BrN_2O$ requires 341.0290.

3.3.4. 2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)acetamide (1i): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1i** as a colorless solid (218 mg, 45%); R_f (20% EtOAc/hexane) 0.4; mp: 108-110 ^{o}C; IR (KBr): ν_{max} 3339, 3055, 1679, 1527, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.97 (1 H, br. s), 8.77 (1 H, dd, J_1 = 7.3, J_2 = 1.6 Hz), 8.70 (1 H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.12 (1 H, d, J = 8.3 Hz), 7.54-7.47 (2 H, m), 7.40 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 6.99-6.97 (2 H, m), 6.91 (1 H, d, J = 8.6 Hz), 3.93 (3 H, s), 3.91 (3 H, s), 3.84 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.8, 149.3, 148.4, 148.2, 138.5, 136.3, 134.4, 127.9, 127.3, 127.1, 121.8, 121.6, 121.6, 116.3, 112.5, 111.5, 56.0, 55.9, 45.0; HRMS (ESI): MH^+, found 323.1384. $C_{19}H_{19}N_2O_3$ requires 323.1396.

3.3.5. 2-(3-Chlorophenyl)-*N*-(quinolin-8-yl)acetamide (1j): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **1j** as an orange color solid (550 mg, 61%); R_f (20% EtOAc/hexane) 0.6; mp: 84-86 ^{o}C; IR (KBr): ν_{max} 3341, 3055, 1682, 1527, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.96 (1 H, br. s), 8.76 (1 H, dd, J_1 = 7.0, J_2 = 1.9 Hz), 8.74 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.12 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.54-7.46 (3 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.34-7.31 (3 H, m), 3.87 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.6, 148.3, 138.4, 136.6,

136.3, 134.7, 134.2, 130.2, 129.7, 127.9, 127.8, 127.5, 127.3, 121.8, 121.7, 116.4, 44.7; HRMS (ESI): MH^+, found 297.0786. $C_{17}H_{14}ClN_2O$ requires 297.0795.

3.4. General procedure for the Pd(II)-catalyzed arylation of phenylacetamides and preparation of the compounds 4a-q/7a-f (bis arylation products), 3o,r/6a,b/8e,f/9a,b (mono arylation products). An appropriate phenylacetamide (0.12 mmol, 1 equiv), an appropriate iodo compound (0.48 mmol, 4 equiv), $Pd(OAc)_2$ (2.7 mg, 10 mol%), and AgOAc (50 mg, 0.3 mmol, 2.5 equiv) in anhydrous toluene (3 mL) was heated at 110 ^oC for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in *vacuo* to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding arylated products **4a-q/7a-f** (bis arylation products), **3o,r/6a,b/8e,f/9a,b** (mono arylation products) (see corresponding Tables/Schemes for specific examples and reaction conditions).

3.4.1. 2-(4,4''-Diethyl-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (4c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4c** as a yellow color semi-solid (45 mg, 80%); R_f (20% EtOAc/hexane) 0.7; IR (KBr): ν_{max} 3349, 3054, 2305, 1682, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (1 H, br. s), 8.68 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.65 (1 H, dd, J_1 = 7.1, J_2 = 1.8 Hz), 8.14 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.49 (2 H, m), 7.47-7.45 (1 H, m), 7.44-7.40 (2 H, m), 7.38-7.34 (1 H, m), 7.35 (4 H, d, J = 8.1 Hz), 7.14 (4 H, d, J = 8.1 Hz), 3.83 (2 H, s), 2.54 (4 H, q, J = 7.6 Hz), 1.13 (6 H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.2, 147.9, 143.8, 143.0, 138.9, 138.3, 136.2, 134.5, 130.7, 129.6, 129.2, 127.8, 127.7, 127.4, 127.0, 121.4, 121.2, 116.0, 40.5, 28.4, 15.3; HRMS (ESI): MH^+, found 471.2424. $C_{33}H_{31}N_2O$ requires 471.2436.

3.4.2. 2-(4,4''-Di-*tert*-butyl-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (4d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4d** as a pale yellow solid (40 mg, 63%); R_f (20% EtOAc/hexane) 0.7; mp: 161-163 ^oC; IR (KBr): ν_{max} 3353, 3054, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ_H 9.45 (1 H, br. s), 8.67-8.64 (2 H, m), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.46 (3 H, m), 7.44-7.40 (1 H, m), 7.39-7.37 (6 H, m), 7.32 (4 H, d, J = 8.5 Hz), 3.85 (2 H, s), 1.21 (18 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.3, 149.8, 148.0, 143.8, 138.7, 136.2, 134.5, 130.8, 129.6, 128.9, 127.8, 127.4, 127.0, 125.1, 121.5, 121.2, 116.0, 40.6, 34.4, 31.2; HRMS (ESI): MH^+, found 527.3045. $C_{37}H_{39}N_2O$ requires 527.3062.

3.4.3. 2-(2,6-Bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (4f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4f** as a yellow color solid (40 mg, 63%); R_f (20% EtOAc/hexane) 0.3; mp: 98-100 ^oC; IR (KBr): ν_{max} 3343, 3054, 2986, 1680, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (1 H, br. s), 8.69 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.65 (1 H, dd, J_1 = 7.3, J_2 = 1.6 Hz), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.46 (2 H, m), 7.44-7.39 (2 H, m), 7.32 (2 H, d, J = 7.1 Hz), 6.94 (2 H, d, J = 2.0 Hz), 6.90 (2 H, dd, J_1 = 8.6, J_2 = 2.1 Hz), 6.79 (2 H, d, J = 8.2 Hz), 4.12 (8 H, s), 3.87 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.0, 148.0, 143.2, 143.1, 142.8, 138.3, 136.1, 135.0, 134.5, 131.0, 129.6, 127.8, 127.4, 126.9, 122.4, 121.4, 121.2, 118.3, 117.0, 116.1, 64.2, 64.2, 40.4; HRMS (ESI): MH^+, found 531.1904. $C_{33}H_{27}N_2O_5$ requires 531.1920.

3.4.4. *N*-(Quinolin-8-yl)-2-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide (4h): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4h** as a colorless solid (37 mg, 66%); R_f (20% EtOAc/hexane) 0.7; mp: 99-101 ^oC; IR (KBr): ν_{max} 3349, 3054, 1681, 1525, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.38 (1 H, br. s), 8.71 (1 H, dd, J_1 = 4.1, J_2 = 1.3 Hz), 8.66 (1 H, dd, J_1 = 7.1, J_2 = 1.5 Hz), 8.15 (1 H, d, J = 8.0 Hz), 7.53-7.47 (2 H, m,), 7.45-7.41 (2 H, m), 7.34 (2 H, d, J = 7.9 Hz), 7.20-7.18 (4 H, m), 7.07 (2 H, d, J = 8.1 Hz), 3.82 (2 H, s), 2.10 (12 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.3, 147.8, 143.8, 139.2, 138.2, 136.3, 136.1, 135.4, 134.7, 130.8, 130.6, 129.5, 129.4, 127.8, 127.4, 126.8, 126.6, 121.4, 121.1, 116.0, 40.6, 19.6, 19.3; HRMS (ESI): MH^+, found 471.2422. $C_{33}H_{31}N_2O$ requires 471.2436.

3.4.5. *N*-(Quinolin-8-yl)-2-(3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)acetamide (4i): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4i** as a yellow color solid (30 mg, 45%); R_f (20% EtOAc/hexane) 0.6; mp: 210-212 ^oC; IR (KBr): ν_{max} 3345, 3055, 2305, 1422, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.36 (1 H, br. s), 8.74 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.61 (1 H, t, J = 4.6 Hz), 8.17 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.54-7.51 (4 H, m), 7.48-7.42 (2 H, m), 7.36-7.29 (6 H, m), 3.73 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.2, 148.3, 141.5, 141.2, 138.1, 136.3, 134.0, 132.4, 131.8, 131.2, 130.7, 130.3, 130.0, 128.7, 127.9, 127.3, 127.3, 121.7, 121.6, 116.2, 40.2; HRMS (ESI): MH^+, found 551.0263. $C_{29}H_{19}Cl_4N_2O$ requires 551.0251.

3.4.6. 2-(4,4''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (4j): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4j** as a yellow color solid (35 mg, 64%); R_f (20% EtOAc/hexane) 0.5; mp: 116-118 ^oC; IR (KBr): ν_{max} 3345, 3055, 1681, 1525, 1262, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (1 H, br. s), 8.69 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.63 (1 H, dd, J_1 = 5.8, J_2 = 3.2 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.52-7.50 (2 H, m), 7.46-7.39 (6 H, m), 7.34 (2 H, d, J = 7.4 Hz), 7.02-6.98 (4 H, m), 3.76 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.7, 162.2 (d, J_{C-F} = 244.6 Hz), 148.1, 142.9, 138.2, 137.4 (d, J_{C-F} = 3.1 Hz), 136.3, 134.2, 130.8 (d, J_{C-F} = 8.7 Hz), 129.9, 127.9, 127.3, 127.1, 121.6, 121.5, 116.1, 115.3 (d, J_{C-F} = 21.2 Hz), 40.3; HRMS (ESI): MH^+, found 451.1607. $C_{29}H_{21}F_2N_2O$ requires 451.1622.

3.4.7. 2-(3,3''-Dinitro-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (4m): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4m** as a brown color solid (30 mg, 50%); R_f (20% EtOAc/hexane) 0.3; mp: 97-99 ^oC; IR (KBr): ν_{max} 3340, 3054, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.32 (1 H, br. s), 8.67 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.56 (1 H, dd, J_1 = 5.6, J_2 = 3.3 Hz), 8.35 (2 H, t, J = 1.9 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 8.10 (1 H, dd, J_1 = 2.2, J_2 = 0.9 Hz), 8.08 (1 H, dd, J_1 = 2.1, J_2 = 0.8 Hz), 7.83 (2 H, d, J = 7.6 Hz), 7.56-7.54 (1 H, m), 7.51-7.49 (3 H, m), 7.47-7.44 (2 H, m), 7.42 (2 H, d, J = 7.6 Hz), 3.74 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.7, 148.2, 148.1, 142.7, 141.6, 138.0, 136.4, 135.5, 133.7, 130.6, 130.4, 129.4, 127.8, 127.7, 127.3, 124.2, 122.5, 121.9, 121.7, 116.3, 40.1; HRMS (ESI): MH^+, found 505.1495. $C_{29}H_{21}N_4O_5$ requires 505.1512.

3.4.8. Dimethyl 2'-(2-oxo-2-(quinolin-8-ylamino)ethyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (4n): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4n** as a yellow color solid (40

mg, 63%); R_f (20% EtOAc/hexane) 0.3; mp: 144-146 ^oC; IR (KBr): ν_{max} 3343, 3055, 1721, 1422, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.33 (1 H, br. s), 8.65 (1 H, dd, J_1 = 4.1, J_2 = 1.6 Hz), 8.59 (1 H, dd, J_1 = 5.8, J_2 = 3.0 Hz), 8.14 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.98 (4 H, d, J = 8.2 Hz), 7.53 (4 H, d, J = 8.2 Hz), 7.51-7.49 (3 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.37 (2 H, d, J = 7.7 Hz), 3.85 (6 H, s), 3.75 (2 H, br. s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.3, 166.8, 148.0, 146.1, 143.0, 138.1, 136.2, 134.2, 130.2, 129.7, 129.6, 129.4, 129.4, 129.1, 127.8, 127.4, 127.3, 121.5, 121.4, 116.1, 52.1, 40.1; HRMS (ESI): MH^+, found 531.1902. $C_{33}H_{27}N_2O_5$ requires 531.1920.

3.4.9. 2-(2,6-Bis(5-bromopyridin-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (4p): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4p** as a pale yellow color solid (30 mg, 44%); R_f (20% EtOAc/hexane) 0.4; mp: 209-211 ^oC; IR (KBr): ν_{max} 3375, 3055, 2987, 1422, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (1 H, br. s), 8.82-8.79 (3 H, m), 8.59 (1 H, dd, J_1 = 5.8, J_2 = 3.3 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.88 (1 H, d, J = 2.4 Hz), 7.86 (1 H, d, J = 2.4 Hz), 7.52-7.48 (7 H, m), 7.45 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 4.15 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.7, 158.0, 150.2, 148.1, 141.1, 139.4, 136.2, 135.0, 131.5, 130.7, 128.0, 127.4, 127.3, 125.9, 121.5, 121.4, 119.6, 116.7, 39.3; HRMS (ESI): MNa^+, found 594.9766. $C_{27}H_{18}Br_2N_4NaO$ requires 594.9745.

3.4.10. 2-(2,6-Di(thiophen-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (4q): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **4q** as a yellow color solid (36 mg, 70%); R_f (20% EtOAc/hexane) 0.2; mp: 144-146 ^oC; IR (KBr): ν_{max} 3338, 3055, 1681, 1525, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.73 (1 H, br. s), 8.76 (1 H, dd, J_1 = 7.3, J_2 = 1.6 Hz), 8.67 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.57-7.53 (3 H, m), 7.51 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.47-7.41 (2 H, m), 7.29 (2 H, dd, J_1 = 5.1, J_2 = 1.1 Hz), 7.15 (2 H, dd, J_1 = 3.5, J_2 = 1.1 Hz), 7.00-6.98 (2 H, m), 4.04 (2 H, br. s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.0, 148.1, 141.9, 138.4, 136.5, 136.2, 134.5, 132.6, 131.7, 127.9, 127.4, 127.3, 127.1, 126.0, 121.6, 121.5, 116.3, 41.0; HRMS (ESI): MH^+, found 427.0924. $C_{25}H_{19}N_2OS_2$ requires 427.0939.

3.4.11. 2-(2-(*1H*-Indol-5-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (3r): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **3r** as a brown color solid (20 mg, 44%); R_f (20% EtOAc/hexane) 0.4; mp: 159-161 ^oC; IR (KBr): ν_{max} 3329, 3055, 1422, 1265, 896, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.75 (1 H, br. s), 8.74 (1 H, dd, J_1 = 7.8, J_2 = 0.8 Hz), 8.65 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.23 (1 H, br. s), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.67 (1 H, br. s), 7.58-7.56 (1 H, m), 7.53-7.49 (2 H, m), 7.46-7.38 (4 H, m), 7.25-7.22 (2 H, m), 6.51 (1 H, t, J = 2.1 Hz), 3.92 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.2, 148.0, 143.9, 138.4, 136.1, 135.0, 134.5, 132.8, 132.7, 131.1, 130.5, 127.9, 127.8, 127.5, 127.3, 127.2, 124.8, 123.6, 121.5, 121.4, 121.3, 116.3, 110.8, 102.8, 42.8; HRMS (ESI): MH^+, found 378.1594. $C_{25}H_{20}N_3O$ requires 378.1606.

3.4.12. 2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-*N*-(2-(methylthio)phenyl)acetamide (6a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford (**6a**) as a pale yellow color solid (25 mg, 54%); R_f (20% EtOAc/hexane) 0.5; mp: 108-110 ^oC; IR (KBr): ν_{max} 3309, 3055, 2305, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.62 (1 H, br. s), 8.47 (1 H, dd, J_1 = 8.2, J_2 = 1.0 Hz), 7.46 (1 H, dd, J_1 = 7.7, J_2 = 1.4 Hz), 7.43-7.28 (7 H, m), 7.06 (1 H, td, J_1 = 7.6, J_2 = 1.2 Hz), 6.93 (2 H, d, J = 8.8 Hz), 5.15 (1 H, s), 3.82 (3 H, s), 2.04 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.7, 158.9, 139.4, 138.6, 133.7, 131.1, 130.2, 129.3, 129.0, 129.0, 127.5, 125.1, 124.4, 120.1, 114.4, 59.9, 55.4, 18.9; HRMS (ESI): MNa^+, found 386.1190. $C_{29}H_{27}NNaO_3S$ requires 386.1191.

3.4.13. *N*-(2-(Methylthio)phenyl)-2-(3'-nitro-[1,1'-biphenyl]-2-yl)acetamide (6b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **6b** as a pale yellow color solid (20 mg, 45%); R_f (20% EtOAc/hexane) 0.3; mp: 87-89 ^oC; IR (KBr): ν_{max} 3312, 3055, 1686, 1526, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.61 (1 H, br. s), 8.40 (1 H, dd, J_1 = 8.2, J_2 = 1.0 Hz), 8.27 (1 H, br. s), 8.19 (1 H, dd, J_1 = 7.5, J_2 = 1.3 Hz), 7.76 (1 H, d, J = 7.8 Hz), 7.57 (1 H, t, J = 8.0 Hz), 7.48-7.38 (4 H, m), 7.35-7.31 (1 H, m), 7.09 (1 H, td, J_1 = 1.2, J_2 = 7.6 Hz), 5.25 (1 H, s), 2.09 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.9, 148.5, 141.1, 139.1, 137.7, 135.3, 133.5, 129.7, 129.5, 129.2, 129.0, 128.3, 125.4, 124.9, 124.2, 122.5, 120.3, 59.8, 18.9; HRMS (ESI): MH^+, found 379.1102. $C_{21}H_{19}N_2O_3S$ requires 379.1116.

3.4.14. 2-(5'-Fluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (7b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **7b** as a pale yellow color solid (30 mg, 61%); R_f (20% EtOAc/hexane) 0.4; mp: 145-147 ^oC; IR (KBr): ν_{max} 3345, 3055, 2305, 1514, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.43 (1 H, br. s), 8.71 (1 H, dd, J_1 = 4.1, J_2 = 1.9 Hz), 8.65 (1 H, dd, J_1 = 6.4, J_2 = 2.0 Hz), 8.15 (1 H, d, J = 8.2 Hz), 7.52-7.50 (2 H, m), 7.46-7.43 (1 H, m), 7.34 (4 H, d, J = 8.6 Hz), 7.07 (2 H, d, J = 9.1 Hz), 6.83 (4 H, d, J = 8.6 Hz), 3.75 (2 H, s), 3.68 (6 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.0, 161.0 (d, J_{C-F} = 245.5 Hz), 159.0, 148.1, 145.4 (d, J_{C-F} = 8.0 Hz), 138.2, 136.2, 134.4, 133.1, 133.1, 130.1, 127.8, 127.4, 127.2 (d, J_{C-F} = 3.0 Hz), 121.5, 121.3, 116.3 (d, J_{C-F} = 20.6 Hz), 116.0, 113.7, 55.1, 39.8; HRMS (ESI): MH^+, found 493.1931. $C_{31}H_{26}FN_2O_3$ requires 493.1927.

3.4.15. 2-(5'-Bromo-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (7c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **7c** as an orange color solid (35 mg, 63%); R_f (20% EtOAc/hexane) 0.4; mp: 149-151 ^oC; IR (KBr): ν_{max} 3343, 3053, 2926, 1682, 1264, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.40 (1 H, br. s), 8.71 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.64 (1 H, dd, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.49 (4 H, m,), 7.44 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.33 (4 H, d, J = 8.7 Hz), 6.83 (4 H, d, J = 8.7 Hz), 3.74 (2 H, s), 3.66 (6 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.6, 159.0, 148.1, 145.3, 138.2, 136.2, 134.4, 132.6, 132.3, 130.5, 130.2, 127.8, 127.4, 121.6, 121.4, 120.6, 116.0, 113.8, 51.1, 40.0; HRMS (ESI): MH^+, found 553.1105. $C_{31}H_{26}BrN_2O_3$ requires 553.1127.

3.4.16. 2-(5'-Bromo-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (7d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **7d** as a pale red color solid (25 mg, 51%); R_f (20% EtOAc/hexane) 0.6; mp: 150-152 ^oC; IR (KBr): ν_{max} 3343, 3049, 1688, 1525, 1422, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (1 H, br. s), 8.70 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.60 (1 H, dd, J_1 = 6.3, J_2 = 2.6 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.54 (2 H, s), 7.51-7.49 (2 H, m), 7.45-7.40 (5 H, m), 7.34-7.30 (4 H, m), 7.26 (2 H, t, J = 7.2 Hz), 3.73 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.3, 148.1, 145.7, 140.2, 138.2, 136.2, 134.3, 132.3, 129.8, 129.0, 128.4, 127.8, 127.7, 127.4, 121.6, 121.4, 120.7, 116.1,

39.9; HRMS (ESI): MH^+, found 493.0899. $C_{29}H_{22}BrN_2O$ requires 493.0916.

3.4.17. 2-(4-Chloro-2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (7e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **7e** as a colorless solid (32 mg, 57%); R_f (20% EtOAc/hexane) 0.4; mp: 168-170 °C; IR (KBr): ν_{max} 3343, 3054, 1679, 1422, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (1 H, br. s), 8.73 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.63 (1 H, dd, J_1 = 7.0, J_2 = 1.6 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.47 (2 H, m), 7.44 (1 H, dd J_1 = 8.3, J_2 = 4.3 Hz), 7.32 (2 H, s), 6.91-6.86 (4 H, m), 6.79 (2 H, d, J = 8.2 Hz), 4.13-4.10 (8 H, m), 3.79 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.6, 148.1, 144.8, 143.2, 143.1, 138.2, 136.2, 134.4. 133.7, 132.3, 129.8, 129.4, 127.8, 127.5, 122.2, 121.5, 121.3, 118.1, 117.2, 116.2, 64.2, 64.2, 39.8; HRMS (ESI): MH^+, found 565.1553. $C_{33}H_{26}ClN_2O_5$ requires 565.1530.

3.4.18. 2-(4-Chloro-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (8e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **8e** as a pale yellow color solid (15 mg, 34%); R_f (20% EtOAc/hexane) 0.5; mp: 141-143 °C; IR (KBr): ν_{max} 3339, 3054, 2305, 1422, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.71 (1 H, dd, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.43 (4 H, m), 7.38-7.34 (2 H, m), 6.91-6.86 (3 H, m), 4.25-4.21 (4 H, m), 3.85 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.3, 148.2, 148.2, 143.8, 143.4, 143.3, 138.3, 136.2, 134.3, 133.1, 132.9, 132.0, 131.1, 130.4, 130.4, 127.8, 127.8, 127.4, 122.3, 121.6, 118.1, 118.0, 117.4, 116.3, 64.4, 64.3, 42.0; (ESI): MH^+, found 431.1156. $C_{25}H_{20}ClN_2O_3$ requires 431.1162.

3.4.19. 2-(4-Bromo-2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (7f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **7f** as a brown color solid (15 mg, 25%); R_f (20% EtOAc/hexane) 0.3; mp: 197-199 °C; IR (KBr): ν_{max} 3343, 3057, 1682, 1423, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (1 H, br. s), 8.73 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.63 (1 H, dd, J_1 = 7.0, J_2 = 1.9 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.47 (4 H, m), 7.44 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 6.90-6.85 (4 H, m), 6.78 (2 H, d, J = 8.2 Hz), 4.13-4.10 (8 H, m), 3.79 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.5, 148.1, 145.0, 143.2, 143.1, 138.2, 136.2, 134.4, 133.5, 132.3, 130.3, 127.8, 127.5, 122.2, 121.5, 121.2, 120.6, 118.1, 117.2, 116.2, 64.2, 64.2, 39.9; HRMS (ESI): MH^+, found 609.1002. $C_{33}H_{26}BrN_2O_5$ requires 609.1025.

3.4.20. 2-(4-Bromo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (8f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **8f** as a brown color thick liquid (17 mg, 36%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): ν_{max} 3339, 3057, 2926, 1682, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.71 (1 H, dd, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.50 (4 H, m), 7.45 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.40 (1 H, d, J = 8.0 Hz), 6.91-6.87 (2 H, m), 6.84 (1 H, dd, J_1 = 8.3, J_2 = 1.9 Hz), 4.25-4.21 (4 H, m), 3.84 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.2, 148.2, 144.1, 143.4, 143.3, 138.3, 136.3, 134.3, 133.3, 133.0, 132.2, 131.7, 130.7, 127.8, 127.3, 122.3, 121.6, 121.1, 118.1, 117.3, 116.3, 64.2, 64.3, 42.1; HRMS (ESI): MH^+, found 475.0640. $C_{25}H_{20}BrN_2O_3$ requires 475.0657.

3.4.21. 2-(4'-Ethyl-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (9a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **9a** as a yellow color solid (20 mg, 52%); R_f (20% EtOAc/hexane) 0.4; mp: 101-103 °C; IR (KBr): ν_{max} 3335, 3055, 2987, 1681, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (1 H, br. s), 8.75 (1 H, dd, J_1 = 7.1, J_2 = 1.8 Hz), 8.72 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.55-7.49 (2 H, m), 7.44 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.34 (2 H, d, J = 8.1 Hz), 7.23 (2 H, d, J = 8.1 Hz), 7.05 (1 H, s), 6.89 (1 H, s), 3.97 (3 H, s), 3.92 (3 H, s), 3.81 (2 H, s), 2.67 (2 H, q, J = 7.6 Hz), 1.26 (3 H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.2, 148.5, 148.1, 148.0, 143.1, 138.5, 138.3, 136.2, 135.3, 134.5, 129.4, 127.9, 127.4, 124.3, 121.6, 121.5, 116.3, 113.5, 113.2, 56.1, 56.0, 42.4, 28.5, 15.5; HRMS (ESI): MH^+, found 427.2009. $C_{27}H_{27}N_2O_3$ requires 427.2022.

3.4.22. 2-(4-Chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (9b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **9b** as an orange color solid (30 mg, 75%); R_f (20% EtOAc/hexane) 0.4; mp: 118-120 °C; IR (KBr): ν_{max} 3338, 3055, 2305, 1682, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (1 H, br. s), 8.75-8.71 (2 H, m), 8.16 (1 H, dd, J_1 = 8.2, J_2 = 1.2 Hz), 7.55-7.52 (3 H, m), 7.45 (1 H, dd, J_1 = 8.2, J_2 = 4.3 Hz), 7.36 (1 H, dd, J_1 = 8.2, J_2 = 2.0 Hz), 7.31-7.26 (3 H, m), 6.91 (2 H, d, J = 8.6 Hz), 3.83 (2 H, s), 3.78 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 169.0, 159.0, 148.2, 140.9, 138.4, 136.3, 134.4, 134.3, 133.3, 132.2, 131.8, 130.6, 130.3, 127.9, 127.5, 127.4, 121.7, 121.6, 116.4, 113.9, 55.2, 42.5; HRMS (ESI): MH^+, found 403.1198. $C_{24}H_{20}ClN_2O_2$ requires 403.1213.

3.5. General procedure for the Pd(II)-catalyzed benzylation of phenylacetamides and preparation of the compounds 11a-d. An appropriate phenylacetamide (0.12 mmol), $Pd(OAc)_2$ (2.7 mg, 10 mol%), 4-nitrobenzyl bromide (103 mg, 0.48 mmol, 4 equiv) AgOAc (25 mg, 0.15 mmol, 1.2 equiv) in anhydrous toluene (3 mL) was heated at 110 °C for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in *vacuo* to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding benzylated compounds **11a-d** (see Tables/Schemes for specific examples).

3.5.1. 2-(2-(4-Nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (11a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **11a** as a brown color viscous liquid (26 mg, 55%); R_f (20% EtOAc/hexane) 0.3; IR (KBr): ν_{max} 3341, 3055, 2987, 1522, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.67 (1 H, br. s), 8.64 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.58 (1 H, t, J = 4.7 Hz), 8.14 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.83 (2 H, d, J = 8.8 Hz), 7.49-7.46 (3 H, m), 7.44-7.40 (4 H, m), 7.24 (2 H, d, J = 8.8 Hz), 4.23 (2 H, s), 3.85 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.7, 148.1, 147.7, 138.2, 138.0, 136.3, 133.9, 133.5, 131.8, 131.3, 129.4, 128.3, 128.0, 127.8, 127.2, 123.6, 123.5, 121.8, 121.6, 116.2, 43.1, 39.2; HRMS (ESI): MH^+, found 398.1491. $C_{24}H_{20}N_3O_3$ requires 398.1505.

3.5.2. 2-(4-Fluoro-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (11b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **11b** as a yellow color solid (26 mg, 63%); R_f (20% EtOAc/hexane) 0.2; mp: 94-96 °C; IR (KBr): ν_{max} 3353, 3055, 1738, 1519, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1 H, br. s), 8.68

(1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.59 (1 H, dd, J_1 = 5.7, J_2 = 3.3 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.88 (2 H, d, J = 8.8 Hz), 7.49-7.42 (4 H, m), 7.25 (2 H, d, J = 8.8 Hz), 7.11 (1 H, td, J_1 = 8.3, J_2 = 2.3 Hz), 6.96 (1 H, dd, J_1 = 9.4, J_2 = 2.7 Hz), 4.20 (2 H, s), 3.83 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.4 (d, J_{C-F} = 1.0 Hz), 162.4 (d, J_{C-F} = 245.6 Hz), 148.2, 146.7, 146.3, 140.4 (d, J_{C-F} = 7.3 Hz), 138.2, 136.4, 133.8, 133.3 (d, J_{C-F} = 8.1 Hz), 129.5, 129.3 (d, J_{C-F} = 3.5 Hz), 127.8, 127.2, 123.6, 121.9, 121.6, 118.0 (d, J_{C-F} = 21.5 Hz), 116.2, 114.7 (d, J_{C-F} = 21.0 Hz), 42.3, 39.2, 39.1; HRMS (ESI): MH^+, found 416.1395. $C_{24}H_{19}FN_3O_3$ requires 416.1410.

3.5.3. 2-(4-Chloro-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (11c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **11c** as a colorless solid (20 mg, 46%); R_f (20% EtOAc/hexane) 0.3; mp: 134-136 ^{o}C; IR (KBr): ν_{max} 3339, 3055, 1682, 1523, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1 H, br. s), 8.69 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.57 (1 H, dd, J_1 = 6.1, J_2 = 2.9 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.89 (2 H, d, J = 8.8 Hz), 7.49-7.44 (3 H, m), 7.41-7.40 (2 H, m), 7.26-7.24 (3 H, m), 4.20 (2 H, s), 3.81 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.1, 148.2, 146.7, 146.4, 139.9, 138.2, 136.4, 133.9, 133.8, 133.0, 132.1, 131.0, 129.4, 128.0, 127.8, 127.2, 123.7, 122.0, 121.7, 116.2, 42.4, 39.0; HRMS (ESI): MH^+, found 432.1099. $C_{24}H_{19}ClN_3O_3$ requires 432.1115.

3.5.4. 2-(4-Bromo-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (11d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **11d** as a yellow color solid (25 mg, 59%); R_f (20% EtOAc/hexane) 0.2; mp: 139-141 ^{o}C; IR (KBr): ν_{max} 3339, 3054, 1681, 1523, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1 H, br. s), 8.70 (1 H, dd, J_1 = 4.1, J_2 = 1.4 Hz), 8.57 (1 H, dd, J_1 = 6.2, J_2 = 2.7 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.4 Hz), 7.89 (2 H, d, J = 8.6 Hz), 7.55 (1 H, dd, J_1 = 8.0, J_2 = 1.8 Hz), 7.49-7.44 (3 H, m), 7.40 (1 H, d, J = 1.6 Hz), 7.35 (1 H, d, J = 8.1 Hz), 7.25 (2 H, d, J = 8.1 Hz), 4.20 (2 H, s), 3.80 (2 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.0, 148.2, 146.7, 140.2, 138.1, 136.4, 133.9, 133.7, 133.3, 132.6, 131.0, 129.4, 127.8, 127.3, 123.7, 122.0, 122.0, 121.7, 116.2, 42.4, 39.0; HRMS (ESI): MH^+, found 476.0595. $C_{24}H_{19}BrN_3O_3$ requires 476.0610.

3.6. Procedure for the preparation of the compound 13: To dry flask was added the compound **4e** (1.4 mmol) dissolved in MeOH (4 mL) and then, $BF_3.Et_2O$ (0.5 mL) was added slowly and the reaction mixture was heated at 90 °C for 24 h. After this period, the reaction mixture was neutralized with NEt_3 and the solvent was evaporated in *vacuo* to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the compound **13**.

3.6.1. Methyl 2-([1,1':3',1''-terphenyl]-2'-yl)acetate (13): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **13** as a viscous liquid (28 mg, 66%); R_f (20% EtOAc/hexane) 0.8; IR (KBr): ν_{max} 3412, 3053, 2926, 1740, 1523, 1264 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45-7.34 (11 H, m), 7.30 (2 H, d, J = 7.4 Hz), 3.53 (2 H, s), 3.45 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 172.6, 143.4, 141.6, 130.0, 129.3, 129.2, 128.2, 127.2, 126.8, 51.7, 36.9; HRMS (ESI): MH^+, found 303.1374. $C_{21}H_{19}O_2$ requires 303.1385.

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15. While we finalized this manuscript for submission, we came to know that Wan *et al.* also done a parallel investigation and reported a similar theme as a communication involving the Pd(II)-catalyzed arylation of γ-C-H bond of phenylacetamides, see: Liu, Y.; Huang, B.; Cao, X.; Wan, J.-P. *ChemCatChem* **2016**, **8**, 1470. While nine of the examples (**4a**, **4b**, **4e**, **4g**, **4k**, **4l**, **4o**, **3o** and **7a**) are common between this work and Wan's work, in the present work, we were involved to realize the Pd(II)-catalyzed functionalization of γ-C-H bond of the arylacetamide systems including, arylation, benzylation, alkylation and acetoxylation/hydroxylation of the sp^2 γ-C-H bond of arylacetamides. The arylation and benzylation of the γ-C-H bond of the arylacetamide systems were successful; however, the alkylation and acetoxylation/hydroxylation of the γ-C-H bond of the arylacetamide systems were not successful in our hand. Various ligands were screened to substantiate the need for the bidentate ligand in the Pd(II)-catalyzed arylation/benzylation of phenylacetamides. Several substituted aryl-/heteroaryl iodides, benzyl bromide and phenylacetamide substrates were used to examine their reactivity pattern and accomplish the substrate scope/generality. We have also shown a gram scale γ-C-H arylation of the arylacetamide system and the removal of the bidentate ligand after the γ-C-H arylation of the arylacetamide system.

16. (a) In some of the reactions, we have isolated the 4-nitrobenzyl acetate after the C-H benzylation reaction. (b) To find out a reason for the formation of only mono benzylation product and to obtain the bis benzylated compound we have tried the benzylation of **1a** by adding a total of 0.48 mmol 4-nitrobenzyl bromide in small amounts (0.12 mmol) after every 6 h. This reaction gave only the compound **11a** in 17% yield. Then, we have tried the benzylation of **1a** by using excess of 4-nitrobenzyl bromide (0.96 mmol). This reaction also gave only the mono benzylated compound **11a** in decreased yield 20% yield and there might be of an over-reaction, which could be a reason for the decreased yield this reaction.

17. (a) The observed *ortho* selective functionalization of the γ-C-H bond of the phenylacetamide system linked with the bidentate ligand (e.g., 8-aminoquinoline) can be exemplified *via* the plausible chelation-assisted reaction pathway in concurrence with the generally accepted proposed Pd(II/IV) catalytic cycle mechanism involving the $Pd(OAc)_2$/AgOAc catalytic system. (see the Supplementary data); (b) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70; (c) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (d) See refs[2-7]; (e) Furthermore, we also attempted the

alkylation/hydroxylation/acetoxylation of the *γ*-C-H bond of the phenylacetamide system **1a** by using the standard reaction conditions reported in the literature. Unfortunately, these reactions failed to afford the corresponding *γ*-C-H alkylated/hydroxylated/acetoxylated products (see the Supplementary data).

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- **Supplementary data**

Supplementary data (copy of ^{1}H, ^{13}C NMR Charts of compounds and unsuccessful trials on the *γ*-C-H acetoxylation/hydroxylation/alkylation and proposed mechanism for the *γ*-C-H arylation) associated with this article can be found in the online version.