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PII: S0040-4020(19)30081-X

DOI: https://doi.org/10.1016/j.tet.2019.01.042

Reference: TET 30094

To appear in: *Tetrahedron*

Received Date: 11 October 2018

Revised Date: 7 January 2019

Accepted Date: 17 January 2019

Please cite this article as: Dalal A, Singh P, Babu SA, One-pot, solvent-free Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of directing group, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.01.042.

Graphical Abstract

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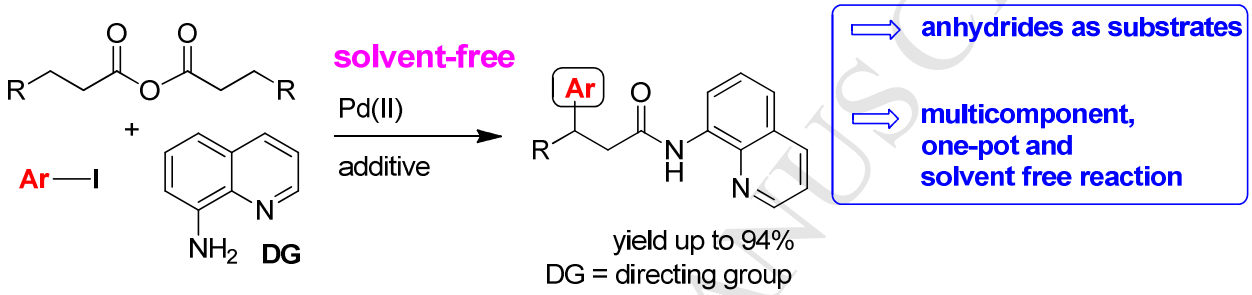
in situ installation of DG and C-H arylation: involving anhydrides as substrates



Tetrahedron
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
carboxamides
C-H activation
multicomponent reaction
palladium
C-H arylation

ABSTRACT

A one-pot, multicomponent-type, solvent-free Pd(II)-catalyzed direct *β*-C-H activation/arylation of carboxamides involving anhydrides as substrates via in situ installation of directing group (DG) is reported. Typically, the DG-assisted *β*-C-H activation/arylation of carboxamides is a two-step process comprising the installation of DG and Pd(II)-catalyzed C-H arylation. We attempted a multicomponent-type reaction comprising an anhydride, a DG (e.g. 8-aminoquinoline), an aryl iodide in the presence of the Pd(II) catalyst and an appropriate additive. Different anhydrides, DGs, aryl iodides, catalysts and additives were screened to reveal the scope of this multicomponent-type C-H arylation reaction process and various *β*-C-H arylated carboxamides were obtained in satisfactory to good yields.

1. Introduction

The sp^2/sp^3 C-H activation and C-C bond forming reactions catalyzed by the transition metal catalysts are considered pivotal organic transformations.[1] The site-selective functionalization of C-H bonds of small organic molecules with the assistance of directing groups (DGs) is one of the important tactics to obtain the corresponding functionalized small organic molecules.[1,2] Especially, the seminal paper[3a,b] by Daugulis et al., which revealed the bidentate DG 8-aminoquinoline (**DG-3a**, Scheme 1) assisted direct arylation of *β*-C(sp^2)–H bonds of benzamides and *β*-C(sp^3)–H bonds of aliphatic carboxamides has led to the development of dependable methods for obtaining various functionalized carboxamides.[3-7] Apart from 8-aminoquinoline (AQ), other DGs similar to AQ were also demonstrated for accomplishing the *β*-C–H functionalization of aromatic and aliphatic carboxylic acids.[2]

While the bidentate DG (e.g., 8-aminoquinoline) assisted C-H functionalization of carboxamides considered important synthetic transformation, however, this process involves two synthetic steps (Scheme 1).[2,3,5-7] In the first step, a carboxylic acid (**1a**) or its derivative such as an acid chloride (**1b**) is linked with a DG (e.g., **DG-3a**) possessing an amine functionality to afford the corresponding carboxamide (**1c**) installed with the **DG-3a**. In the next step, the carboxamide **1c** is subjected to the Pd(II)-catalyzed, DG-assisted C-H activation/arylation in the presence of an additive (e.g., AgOAc, Ag_2CO_3 etc.) to afford the *β*-C-H arylated carboxamide (**5**).[3a,b] The role of additives, such as AgOAc or Ag_2CO_3 in the $Pd(OAc)_2$-catalyzed C-H arylation reactions have been well documented in the literature.[2-7] These additives function as the I^- (iodide anion) scavenger to regenerate the Pd(II)-catalyst in the proposed Pd^{II}-Pd^{IV} catalytic cycle.[2,3a,b]

Development of the ideal and straightforward C-H activation processes, which are multicomponent-based will be well appreciated.[4d] Along this objective, it would be beneficial if the bidentate DG-assisted Pd(II)-catalyzed C-H functionalization of carboxamide (e.g., **1c**) is made as a straightforward process. Towards this, recently our group,[4a] Wan[4b] and Liu[4c] reported the Pd(II)-catalyzed C-H arylation of carboxamides *via* the multicomponent reaction comprising acid chlorides (**1b**), aryl iodides (**4**) and 8-aminoquinoline (**3a**) (Scheme 2). While it was possible to show a straightforward Pd(II)-catalyzed C-H arylation of carboxamides *via* the multicomponent reaction involving acid chlorides,[4] it is to be noted that the storage and handling of some acid chlorides needs certain precautions. Thus, we envisaged to attempt the Pd(II)-catalyzed C-H arylation of carboxamides *via* the multicomponent reaction involving anhydrides as substrates (**2**) instead of acid chlorides (**1b**). In continuation of our work on the C-H activation/arylation reactions,[5] herein we report a multicomponent-type reaction comprising Pd(II)-catalyzed *β*-C-H arylation of carboxamides involving anhydrides as substrates (**2**) via in situ installation of bidentate DG under solvent free condition (Scheme 2).

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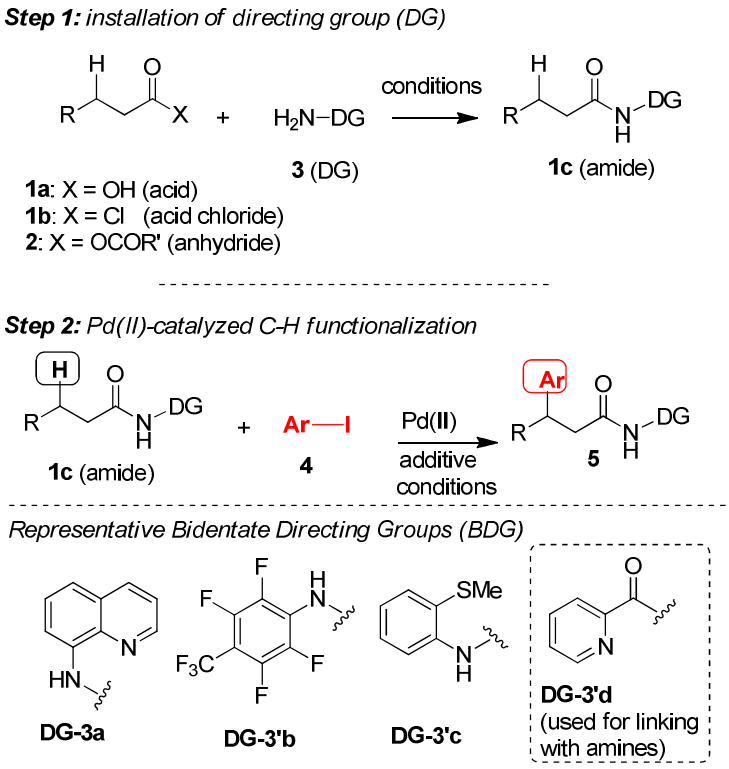
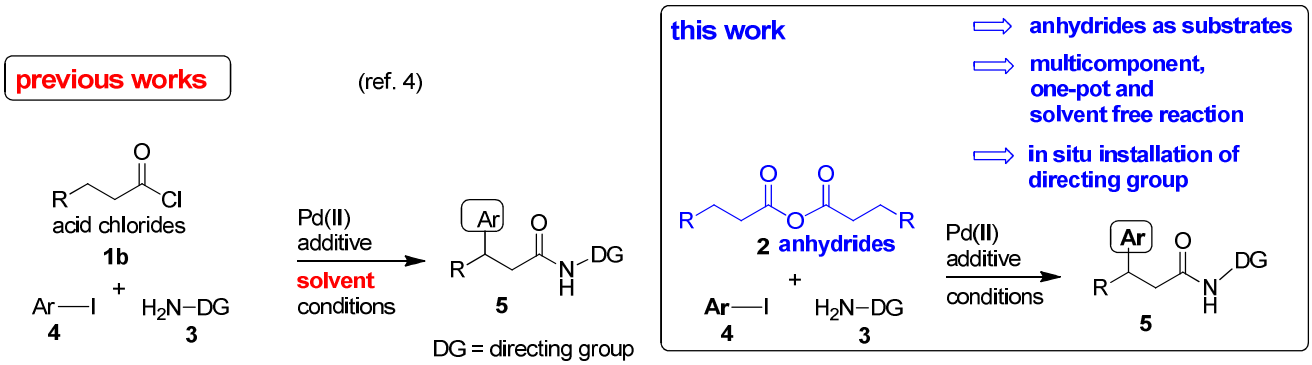


Scheme 1. Steps involved in the typical Pd(II)-catalyzed C-H arylation of carboxamides.



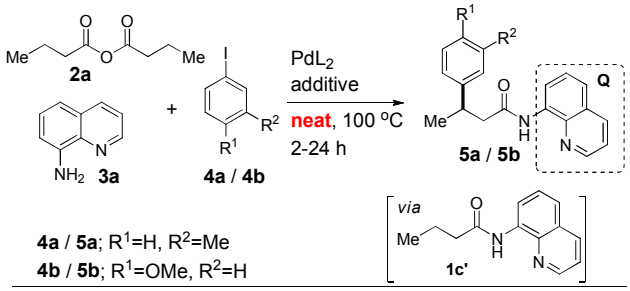
Scheme 2. Multicomponent Pd(II)-catalyzed C-H arylation of carboxamides via in situ installation of directing group.

2. Results and Discussion

To begin the investigation on multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of DG, initially, we performed optimization reactions using butyric anhydride (**2a)** (Table 1). It is to be noted that typically the bidentate DG-assisted C-H arylation of carboxamides were performed using the Pd(II) catalyst and also an additive (e.g., AgOAc or Ag_2CO_3), which will act as the halide ion scavenger to regenerate the Pd(II)-catalyst.[2,3-5,7] At first, we heated a mixture of butyric anhydride (**2a**, 1 equiv), **DG-3a** (1 equiv), *m*-tolyl iodide (**4a**, 6 equiv) and $Pd(OAc)_2$ catalyst (10 mol%) in the absence of any additive at 110 ^oC for 24 h. This reaction did not afford the methylene *β*-C-H arylated product **5a** (entry 1, Table 1). The same reaction was performed in the presence of AgOAc as an additive without any Pd(II) catalyst. However, this reaction also did not afford the *β*-C-H arylated product **5a** (entry 2, Table 1). These reactions indicated that the absence of the $Pd(OAc)_2$ catalyst or additive AgOAc did not promote the C-H arylation reaction.

Subsequently, we heated a mixture of butyric anhydride (**2a**), 8-aminoquinoline, (**3a**), *m*-tolyl iodide (**4a**), $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (additive, 2.2 equiv) at 110 ^oC for 24 h. To our delight, this reaction afforded the expected methylene *β*-C-H arylated product **5a** in 94% yield. This multicomponent-type arylation reaction afforded the product **5a** via in situ formation of carboxamide **1c′** and installation of **DG-3a** under solvent free condition (entry 3, Table 1). Next, we performed the Pd(II)-catalyzed multicomponent-type arylation reaction comprising anhydride **2a** (1 equiv), **3a** (1 equiv) and **4a** (6 equiv) using Ag_2CO_3 instead of AgOAc as an additive. This reaction also gave the product **5a** in 87% yield (entry 4, Table 1). Given that the reactions were performed without any solvent, the above trial reactions were done using 6 equiv of **4a** to have adequate homogeneousness. Notably, use of 4 or 5 equiv of **4a** also gave the product **5a** in appreciable yields (67 and 81%) (entries 5 and 6, Table 1).

Table 1. Optimization of the reaction conditions. One-pot Pd(II)-catalyzed direct *β*-C-H arylation of carboxamide **1c′** derived from butyric anhydride **2a**[a]



4a / **5a**; R^1=H, R^2=Me
4b / **5b**; R^1=OMe, R^2=H

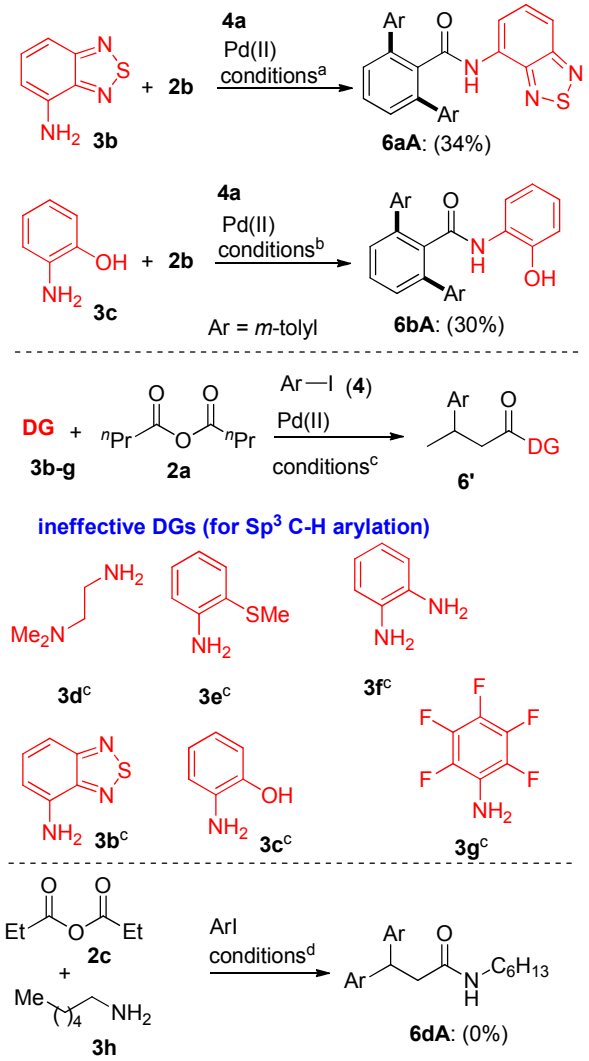
entry	PdL_2 (x mol%)	**4a**: ArI (mmol)	additive (1.1 mmol)	*t* (h)	**5a**: yield (%)
1	$Pd(OAc)_2$ (10)	3	nil	24	0
2	nil	3	AgOAc	24	0
3	**$Pd(OAc)_2$ (10)**	**3**	AgOAc	**24**	**94**
4	$Pd(OAc)_2$ (10)	3	Ag_2CO_3	24	87
5	$Pd(OAc)_2$ (10)	2.5	AgOAc	24	81
6	$Pd(OAc)_2$ (10)	2	AgOAc	24	67
7	$Pd(OAc)_2$ (10)	3	AgOAc	2	81
8	$Pd(OAc)_2$ (10)	0.5	AgOAc	2	0
9	$Pd(OAc)_2$ (10)	1	AgOAc	2	<5
10	$Pd(OAc)_2$ (10)	2	AgOAc	2	60
11	$Pd(OAc)_2$ (10)	2.5	AgOAc	2	67
12	$Pd(OAc)_2$ (5)	3	AgOAc	2	37
13[b]	$Pd(OAc)_2$ (10)	3	AgOAc (0.06 mmol)	24	0
14[b]	$Pd(OAc)_2$ (10)	3	AgOAc (0.15 mmol)	24	0
15[c]	$Pd(OAc)_2$ (10)	**4b**: 0.3	AgOAc (0.66 mmol)	24	**5b**: 32
16[c]	$Pd(OAc)_2$ (10)	**4b**: 0.6	AgOAc (0.66 mmol)	24	**5b**: 40
17[c]	$Pd(OAc)_2$ (10)	**4b**: 0.9	AgOAc (0.66 mmol)	24	**5b**: 46
18[c]	$Pd(OAc)_2$ (10)	**4b**: 1.2	AgOAc (0.66 mmol)	24	**5b**: 62 (70)[b]

[a] Isolated yields are reported. Reactions were carried out using **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol).
[b] **2a** (0.3 mmol), **3a** (0.3 mmol) and ArI (1.8 mmol) in neat condition.
[c] The reaction was performed in toluene (2 mL) using **2a** (0.3 mmol), **3a** (0.3 mmol) at 110 °C.

Then, we desired to reduce the reaction time and accordingly, the Pd(II)-catalyzed multicomponent-type arylation involving anhydride **2a** (1 equiv), **3a** (1 equiv), **4a** (6 equiv) and AgOAc was heated at 110 °C for only 2 h instead of 24 h. This reaction also afforded the product **5a** in good yield (81%, entry 7, Table 1). Having noted that the reaction can be performed in 2 h itself, then we screened the reaction using lesser equiv of ArI **4a** (1-5 equiv). However, the yields of the product **5a** was found to gradually decrease from 67 to 0% when the equiv of **4a** was gradually reduced from 5 to 1 equiv (entries 8-11, Table 1). The multicomponent reaction of anhydride **2a** (1 equiv), **3a** (1 equiv) and **4a** (6 equiv) using 5 mol% of the $Pd(OAc)_2$ catalyst instead of 10 mol% of the $Pd(OAc)_2$ catalyst gave the product **5a** in only 37% yield (entry 12, Table 1). We also screened the reaction using lesser equiv of AgOAc, however, the product **5a** was not obtained when AgOAc was used in catalytic amounts (entries 13 and 14, Table 1). Next, we intended to assess the yield of the arylation reaction in a solvent and accordingly, we performed the arylation of **2a** with varying amounts of ArI **4b** in a solvent (e.g. toluene). The reaction of **2a** and **3a** with varying amounts **4b** (1-4 equiv) in toluene afforded the product **5b** in low to satisfactory yields (32-62%, entries 15-18, Table 1). Thus, the results shown in entries 3 and 7 are the best reaction conditions, which gave the product **5a** in good yield under solvent free condition.

Next, we wished to find out the possibility of using some other DGs[2] that are similar to 8-aminoquinoline for performing the multicomponent-type *β*-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of DG. In this regard, initially we performed the Pd(II)-catalyzed sp^2 arylation benzoic anhydride (**2b**) with **4a** using 4-amino-2,1,3-benzothiadiazole (**3b**) as the DG.[5c] This multicomponent reaction involving **3b** as the DG afforded the bis *β*-C-H arylation product **6aA** in only 34% yield (Scheme 3). Next, we performed the arylation of **2b** with **4a** using 2-aminophenol (**3c**) as the DG.[8c] This multicomponent reaction involving **3c** as the DG also afforded the bis *β*-C-H arylation product

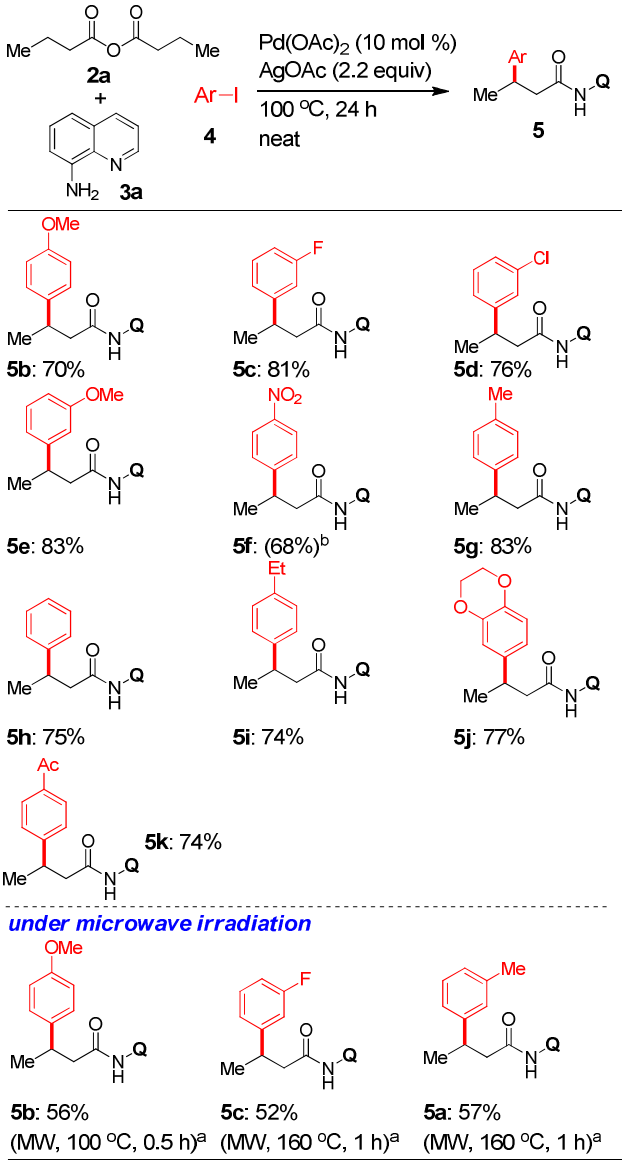
6bA in only 30% yield (Scheme 3). Then, we performed the sp^2 arylation of **2b** involving other DGs, such as N^1,N^1-dimethylethane-1,2-diamine (**3d**)[3b] or 2-(methylthio)aniline (**3e**)[3b] or benzene-1,2-diamine (**3f**)[7c] and these DGs were found ineffective. Furthermore, we also performed the sp^3 arylation of **2a** involving the bidentate DGs **3d-f** and a weakly coordinating monodentate ligand 2,3,4,5,6-pentafluoroaniline (**3g**, Yu's ligand[2n]). The DGs **3d-g** were found ineffective for the sp^3 arylation of **2a** (Scheme 3). It is to be noted that the reaction involving propionic anhydride and simple hexylamine also did not afford the sp^3 arylation product **6dA**. These trials indicated that 8-aminoquinoline (**3a**) is relatively more effective bidentate DG for performing the multicomponent-type *β*-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of the DG (Table 1).



[a] Benzoic anhydride (**2b**, 0.5 mmol), **3b** (0.5 mmol), ArI (**4a**, 3 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.1 mmol), neat, 100 °C, 24 h.
[b] **2b** (0.5 mmol), **3c** (0.5 mmol), ArI (**4a**, 1.5 mmol), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (1.1 mmol), MeCN (2 mL), 90 °C, 12 h.
[c] Butyric anhydride (**2a**, 0.5 mmol), **3b-g** (0.5 mmol), ArI (**4a** or **4b**, 3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (1.1 mmol), neat, 100 °C, 24 h.
[d] Propionic anhydride (**2c**, 0.3 mmol), hexylamine (0.3 mmol), ArI (**4a** or **4b**, 1.5 mmol), $Pd(OAc)_2$ (10 mol%), AgTFA (0.9 mmol), neat, 120 °C, 48 h.

Scheme 3 C-H Arylation trials using other directing groups.

Table 2 Multicomponent one-pot Pd(II)-catalyzed C-H arylation of carboxamide **1c′** derived from anhydride **2a**[a]

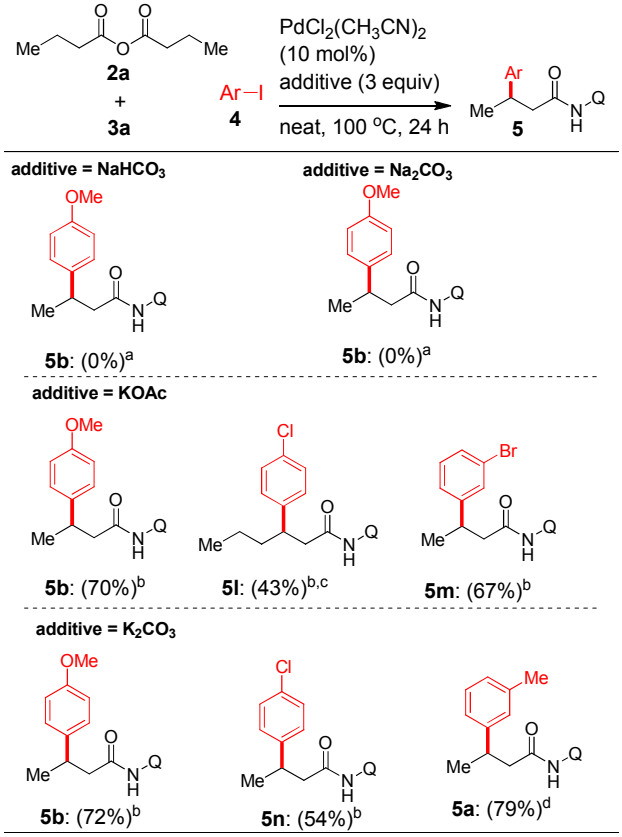


[a] Isolated yields. Reactions were carried out using **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol). Reactions affording **5b**, **5f** and **5k** were done using 0.3 mmol scale.
[b] Toluene (2 mL) was used.

Having found the suitable reaction conditions and DG for the Pd(II)-catalyzed multicomponent-type reaction involving anhydride **2a**, **3a** and **4a**, which afforded the product **5a** in high yield (entry 3, Table 1), next, we wished to extend the scope of this method dealing with one-pot arylation via in situ installation of DG. Accordingly, we carried out the Pd(II)-catalyzed multicomponent-type C-H arylation reaction involving butyric anhydride **2a**, **3a** and a variety of aryl iodides under solvent-free condition (Table 2). The Pd(II)-catalyzed, reaction involving butyric anhydride **2a**, **3a**, and PhI or other aryl iodides containing the electron-withdrawing and donating groups at the *meta* or *para* position afforded the *β*-C-H arylated products **5b-i,k** in good yields (68-83%, Table 2). The Pd(II)-catalyzed, multicomponent-type reaction involving butyric anhydride **2a**, **3a** and a di-substituted aryl iodide, e.g. 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine also afforded the corresponding *β*-C-H arylated aliphatic carboxamide **5j** in 77% yield (Table 2).

In an attempt to improve the efficiency of this protocol, we attempted the multicomponent-type solvent free C-H arylation reaction of anhydride **2a**, **3a** with different aryl iodides under microwave irradiation and the corresponding C-H arylated carboxamides **5a-c** were obtained in 52-57% yields (Table 2). When compared to the reactions performed under conventional heating, the reactions under microwave irradiation afforded the C-H arylated carboxamides **5a-c** in only satisfactory yields. This is perhaps because the reaction of **2a**, **3a** and different aryl iodides were subjected to the microwave irradiation without any solvent and it is to be noted that in general the microwave reactions are efficient when performed using a solvent with high tan δ.

Table 3 The Pd(II)-catalyzed C-H arylation of anhydride **2a** using additives other than silver salts[a]



[a] Isolated yields are reported. **2a** (0.3 mmol), **3a** (0.3 mmol), ArI (1.8 mmol), $Pd(OAc)_2$ (10 mol%), $NaHCO_3/Na_2CO_3$ (0.7 mmol), neat, 100 °C, 36 h.
[b] **2a** (0.3 mmol), **3a** (0.3 mmol) and ArI (2-3 mmol).
[c] Reaction was performed using hexanoic anhydride.
[d] **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol).

Conventionally, the Pd(II)-catalyzed C-H arylation reactions have been performed using a silver salt (e.g., AgOAc and Ag_2CO_3) as an additive, which functions as a scavenger for the iodide anion that is generated in the reaction and also implicitly helps in the regeneration of the Pd(II) catalyst in the catalytic cycle.[2-7] It is to be noted that some of the research papers have revealed the use of relatively inexpensive salts, such as K_2CO_3 and KOAc etc as the additives instead of silver salts.[2-7] Recently, Chen and Quin[6] introduced CsOAc as an additive for the conventional two-step process comprising Pd(II)-catalyzed arylation of carboxamides. Along this line, we also performed the Pd(II)-catalyzed multicomponent reaction of anhydride **2a** (1 equiv), **3a** (1 equiv) and ArI using KOAc or K_2CO_3 as an additive (Table 3). Accordingly, the C-H arylated aliphatic carboxamides **5b,l,m** were obtained in 43-70% yields using KOAc as an additive. Similarly, the C-H arylated aliphatic carboxamides **5a,b,n** were also obtained in 54-79% yields using K_2CO_3 as an additive. The yields obtained for the C-H arylated aliphatic carboxamides **5a,b,l,m,n** using KOAc or K_2CO_3 or AgOAc as an additive were comparable (Tables 1-3).

Then, to extend the substrate scope we intended to carry out the multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of carboxamides using different aliphatic anhydrides as substrates. Accordingly, we treated hexanoic anhydride (**2d**), 8-aminoquinoline, (**3a**) with PhI or different aryl iodides in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive at 110 °C for 24 h under solvent-free condition. These reactions afforded the corresponding *β*-C-H arylated hexanamides **6a-d** in 62-76% yields (Table 4). Next, we performed the Pd(II)-catalyzed reaction of valeric (pentanoic) anhydride (**2e**), **3a** with different mono or di-substituted aryl iodides, which afforded the corresponding *β*-C-H arylated pentanamides **7a-g** in 52-90% yields.

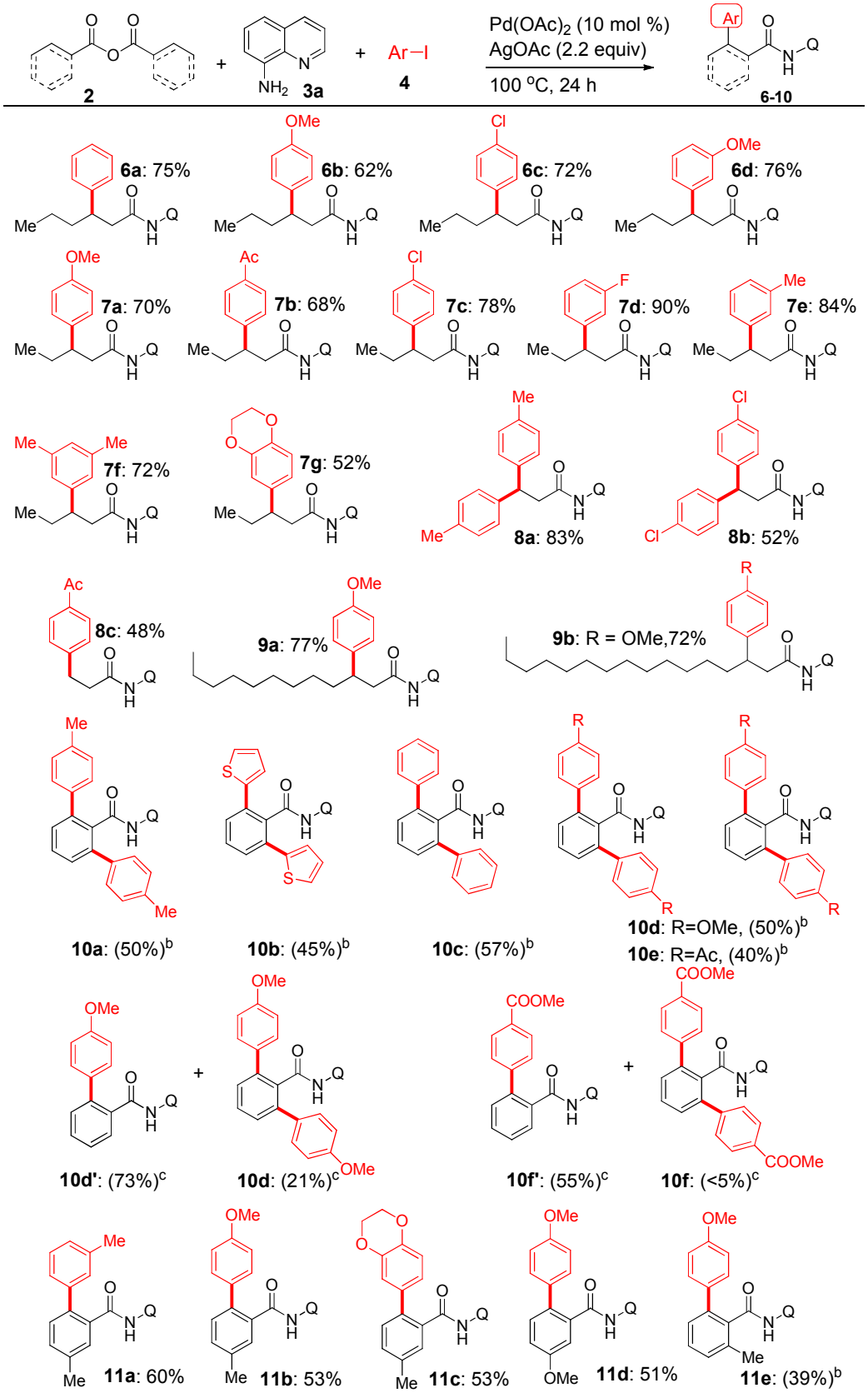
The Pd(II)-catalyzed reaction of propionic anhydride (**2c**), **3a** with aryl iodides containing electron donating or mild withdrawing groups at the *para* position afforded the corresponding bis *β*-C-H arylated propionamides (diarylmethanes) **8a,b** in 52-83% yields (Table 4). The observed bis *β*-C-H arylation of propionamide derived in situ from propionic anhydride (**2f**) and **3a** with aryl iodides containing electron donating or mild withdrawing groups at the *para* position is in accordance with the literature reports.[3b,5c] On other hand, the Pd(II)-catalyzed reaction of propionic anhydride (**2c**), **3a** with an aryl iodide containing electron withdrawing groups at the *para* position afforded the mono *β*-C-H arylated propionamide **8c** in 48% yield. This observation is also in accordance with the literature reports.[3b,5c] In general, the Pd(II)-catalyzed arylation of methylene *β*-C-H bonds of aliphatic carboxamides (generated from carboxylic acid derivatives other than propionic acid) have led to the mono arylation products containing tertiary C-H bonds and further arylation of the tertiary sp^3 C-H bonds are relatively challenging. Often, the arylation of primary (methyl) *β*-C-H bonds of propionamides have afforded the bis *β*-C-H arylation products. This is perhaps the mono arylation of propionamide results into a relatively reactive (benzylic) methylene *β*-C-H bond which further undergo a second arylation to afford the bis *β*-C-H arylation products (e.g. **8a,b**).[3b,5c]

Then, we carried out the multicomponent-type Pd(II)-catalyzed sp^3 *β*-C-H arylation of carboxamides involving fatty acid anhydrides as substrates. Accordingly, the Pd(II)-catalyzed reaction of dodecanoic anhydride (**2f**) or palmitic anhydride (**2g**) and **3a** with different aryl iodides afforded the corresponding *β*-C-H arylated aliphatic carboxamides **9a,b** in 72-77% yields (Table 4).

Subsequently, we intended to carry out the multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of benzamides involving aromatic anhydrides as substrates via in situ installation of DG. In this regard, we treated benzoic anhydride (**2b**), **3a** with *p*-tolyl iodide (6 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive under solvent-free condition. We observed that the reaction was sluggish and not fruitful under solvent-free condition and this perhaps due to the non-homogeneousness of the reaction mixture and poor mixing of benzoic anhydride (or in situ generated benzamide) under solvent-free condition. Then, we treated benzoic anhydride (**2b**), **3a** with *p*-tolyl iodide (6 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive in toluene, which afforded the bis *β*-C-H arylation product **10a** in 50% yield (Table 4).

Then, we carried out the Pd(II)-catalyzed, multicomponent-type C-H arylation reaction involving benzoic anhydride **2b**, **3a** with a variety of aryl iodides to afford the corresponding bis *β*-C-H arylation products **10b-e** in 40-57% yields (Table 4). In accordance with the literature,[3b,5c,4b] the Pd(II)-catalyzed C-H arylation reactions involving benzoic anhydride (**2b**), 8-aminoquinoline (**3a**) with aryl iodides also afforded the corresponding bis *β*-C-H arylation products **10** as the major compounds and the corresponding mono *β*-C-H arylation products **10′** we not obtained in characterizable amounts (Table 4).

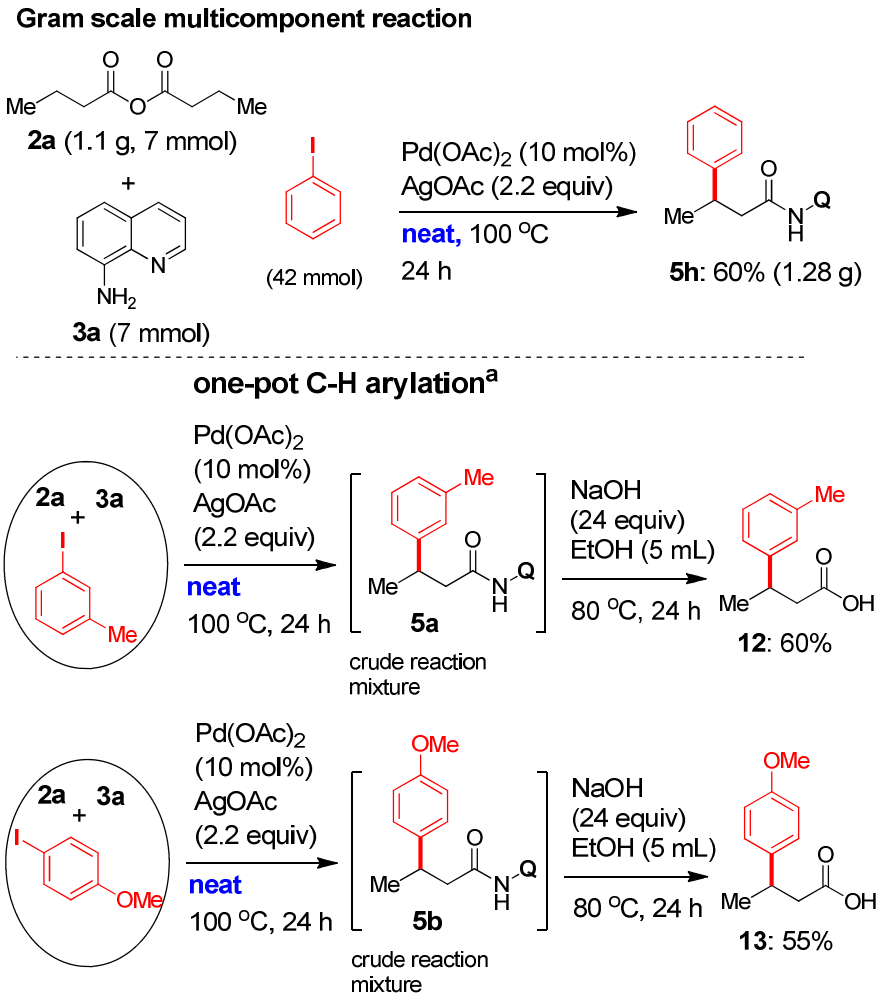
Table 4 Multicomponent Pd(II)-catalyzed C-H arylation of various carboxamides derived from their anhydrides[a]



[a] Isolated yields are reported. Reactions were done using **3a** (0.5 mmol) and ArI (2-3 mmol) and 0.5 mmol of the corresponding anhydride **2** ((hexanoic anhydride (**2d**), valeric anhydride (**2e**), propionic anhydride (**2c**), dodecanoic anhydride (**2f**), palmitic anhydride (**2g**), 3-methylbenzoic anhydride (**2h**), 3-methoxybenzoic anhydride (**2i**) and 2-methybenzoic anhydride (**2j**)). Reactions afforded **6d**, **7b-e**, **9a,b**, **10b**, **10d′** and **10f′** were done using 0.3 mmol of **2**.

[b] Reactions were done using anhydride **2b/2j** (0.5 mmol), **3a** (0.5 mmol), ArI (2-3 mmol), $Pd(OAc)_2$ (10 mol%) and AgOAc (1.1 mmol) in toluene (2 mL), 110 °C, 24-36 h.

[c] Reactions were done using **2b** (0.3 mmol), **3a** (0.3 mmol), ArI (1-1.5 mmol), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (1 mmol), toluene, 160 °C, 36 h.



[a] **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (3 mmol). Isolated yields are reported.

Scheme 4 Gram scale multicomponent reaction and directing group removal.

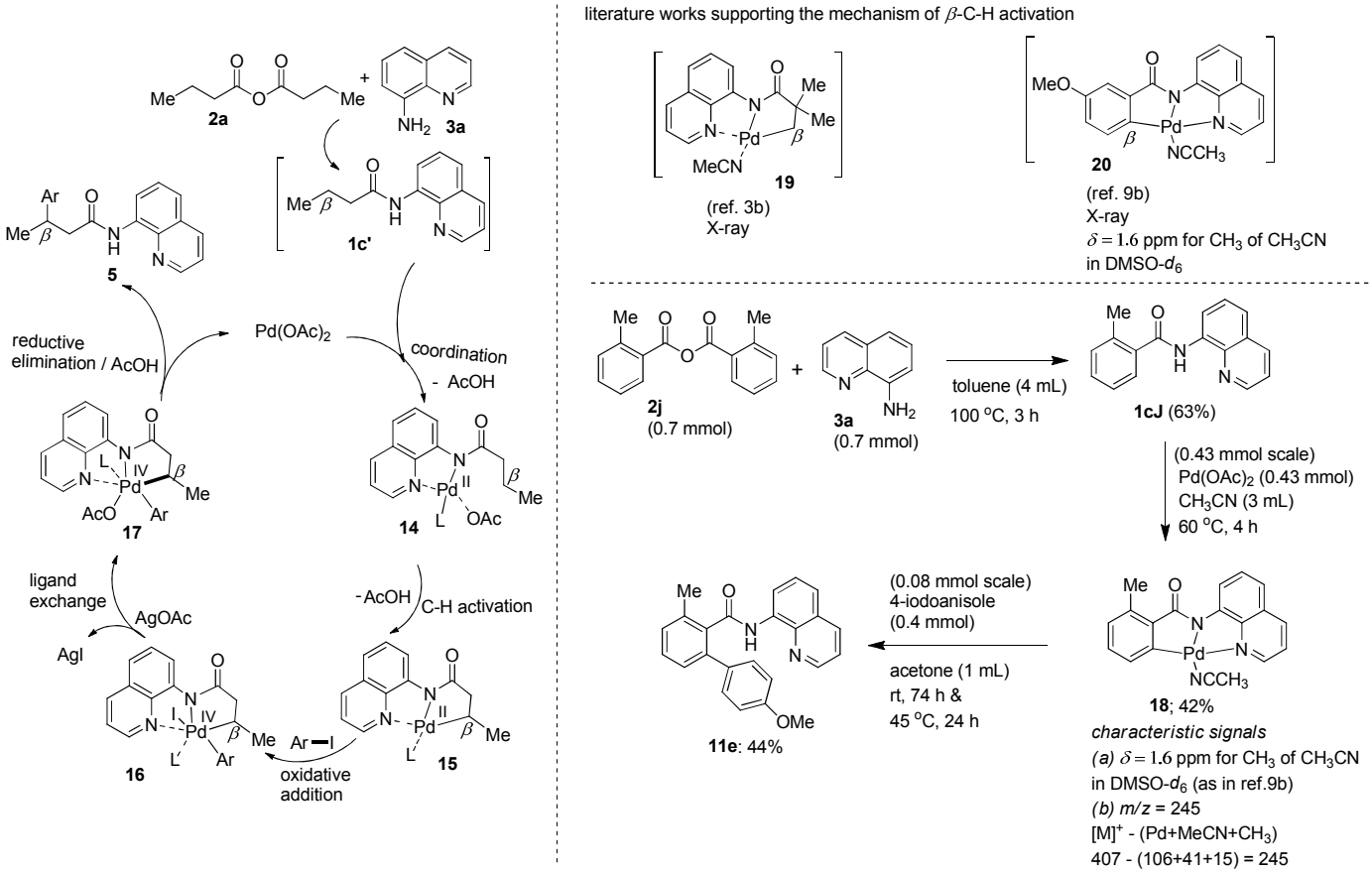
Then, we also desired to obtain the mono *β*-C-H arylation products **10′** using anhydrides as substrates. Accordingly, we have performed the multicomponent-type C-H arylation reaction involving anhydride **2b**, **3a** and ArI using the $Ni(OTf)_2$ catalyst (reported by Chatani)[8d] instead of the $Pd(OAc)_2$ catalyst. These reactions gave the corresponding mono *β*-C-H arylation products **10d′** (73%) and **10f′** (55%) as the major compounds along with the corresponding bis *β*-C-H arylation products **10d** (21%) and **10f** (<5%) as the minor compounds (Table 4). These results indicated that the Ni-catalyzed reactions are relatively slower when compared to the Pd-catalyzed reaction and accordingly, the mono *β*-C-H arylation product can be obtained via the Ni-catalyzed reactions (Table 4).

Next, to extend the sp^2 C-H arylation reaction involving different aromatic anhydrides, we assembled 3-methylbenzoic anhydride (**2h**), 3-methoxybenzoic anhydride (**2i**) and 2-methybenzoic anhydride (**2j**) and then subjected them to the Pd(II)-catalyzed multicomponent C-H arylation reaction under solvent-free condition. The Pd(II)-catalyzed reaction comprising 3-methylbenzoic anhydride **2h**, **3a** and different aryl iodides afforded the corresponding mono *β*-C-H arylation products **11a-c** in 53-60% yields (Table 4). Similarly, the Pd(II)-catalyzed, multicomponent C-H arylation reaction involving **2i** or **2j**, **3a** and *p*-anisyl iodide afforded the corresponding mono *β*-C-H arylation products **11d** and **11e** in 39-51% yields (Table 4). In accordance with literature, the C-H arylation reactions of benzamides involving benzoic anhydrides **2h,i** and **3a** with aryl iodides afforded the corresponding mono *β*-C-H arylation products **11**[3b,5c,4b] and the corresponding bis *β*-C-H arylation products were not obtained in characterizable amounts. This is perhaps the substituent present in the *meta* position of the corresponding benzamides derived from anhydrides **2h,i** presumably imparts the steric hindrance for the second *β*-C-H arylation reaction.

We also attempted the Pd(II)-catalyzed, multicomponent-type C-H arylation reaction in a gram scale and accordingly, we heated a mixture of butyric anhydride (**2a**), **3a**, PhI, $Pd(OAc)_2$ and AgOAc at 110 °C for 24 h under solvent-free condition. This reaction afforded the *β*-C-H arylated aliphatic carboxamide **5h** in 60% yield (1.28 g, Scheme 4). Further, it is to be noted that generally the removal of the DGs was carried using C-H arylated carboxamides, which were obtained after the column chromatographic purification process. It was envisaged to perform the DG removal after the multicomponent C-H arylation reaction by avoiding the column chromatographic purification process.[4] In this regard, after the multicomponent C-H arylation reaction, the crude reaction mixture containing the C-H arylated carboxamide **5a** or **5b** was subjected to the amide hydrolysis reaction condition to afford the corresponding carboxylic acids **12** and **13** in satisfactory yields (55-60%, Scheme 4).

Scheme 5 shows a plausible mechanism for the multicomponent reaction in accordance with the generally accepted proposed mechanism[2,9] for the Pd(II)-catalyzed, AgOAc-promoted, DG-assisted C-H activation of carboxamides. The mechanism involves

the following steps after the in situ formation of carboxamide **1c′** from **2a** and **3a**: (a) An initial coordination of the DG of carboxamide **1c′** to the $Pd(OAc)_2$ catalyst and followed by the C(β)−H activation generates the palladium(II) species **15**. (b) The palladium species **15** undergoes oxidative addition with an ArI to generate the palladium(IV) species **16**. (c) Then, AgOAc acts as an iodide ion scavenger in the ligand exchange step to generate the palladium(IV) species **17**. (d) Next, the reductive elimination of the palladium(IV) species **17** yields the C(β)−H arylated product **5** along with the regeneration of the Pd(II) catalyst.[10]



Scheme 5 Proposed mechanism of multicomponent one-pot Pd(II)-catalyzed β-C-H arylation of carboxamide derived from anhydride.[10]

In summary, we have shown a one-pot, solvent free, multicomponent-type reaction comprising the Pd(II)-catalyzed DG-assisted β-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of DG. It is to be noted that typically, the DG-assisted β-C-H arylation of carboxamides is a two-step process comprising the installation of DG in a carboxylic acid or its derivative (e.g., acid chloride) and then, the Pd(II)-catalyzed C-H arylation. In this paper, we have shown the multicomponent-type Pd(II)-catalyzed β-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of DG. Different anhydrides, DGs, aryl iodides and catalysts and additives were screened to establish the scope of the C-H arylation reaction process and various β-C-H arylated carboxamides were obtained in satisfactory to good yields. This work will be a contribution with regard to the development of simple and multicomponent-based C-H activation reactions.

3. Experimental Section

3.1. General information. ^{1}H and ^{13}C NMR spectra of all compounds were recorded in 400 and ~101 MHz spectrometers (using TMS as an internal standard), respectively. The HRMS data of samples were obtained from QTOF mass analyzer using ESI method. IR spectra of samples were recorded as neat or thin films. Column chromatography purification was carried out on silica gel (100−200 mesh). TLC analyses were performed on silica gel or alumina plates and components were visualized by observation under iodine vapor. Reactions were performed in dry solvents under a nitrogen atm wherever required. Isolated yields of all the C-H arylated products are reported and yields were not optimized.

The compounds **5a**,[4a] **5b**,[6] **5d**,[4a] **5e**,[6] **5f**,[4a] **5g**,[4a] **5h**,[4a] **5k**,[7a] **5l**,[6] **5m**,[6] **5n**,[6] **6a**,[4c] **6b**,[4c] **6c**,[4c] **7a**,[7b] **8a**,[5a] **9a**,[4a] **10a**,[4b] **10c**,[4b] **10d′**,[7c] **10d**,[4b] **10e**,[4b] **11b**,[7d] **11d**,[7e] **12**,[8a] **13**,[8b] **11e**,[7e] and **1cJ**[7f] are reported in the literature.

3.2. General experimental procedure for the multicomponent, solvent-free Pd(II)-catalyzed direct β-C-H arylation of carboxamides involving anhydrides as substrates via in situ installation of the DG**:** A mixture of anhydride (**2**,1 equiv), DG (8-aminoquinoline, **3a**, 1 equiv), ArI (4-6 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (1.1 mmol) was heated at 110 °C for an appropriate time (2-24 h, see the corresponding Tables/Schemes for exact time and other specific conditions). Then, reaction mixture was cooled to rt, filtered on celite® (EtOAc was used as a washing solvent) and the filtrate was treated with aq. $NaHCO_3$ solution and then, extracted using EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford the crude reaction mixture. Then, the crude reaction mixture was subjected to the column chromatographic purification (EtOAc:Hexane =

20:80) to give the corresponding C-H arylated product (see the respective Tables/Schemes for the specific entries).

3.2.1. 3-(3-Fluorophenyl)-*N*-(quinolin-8-yl)butanamide (5c): Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour oil (126 mg, 81%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3351, 2967, 1691, 1589 and 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.80 – 8.77 (m, 2H), 8.16 (d, 1H, J = 8.2 Hz), 7.54 – 7.44 (m, 3H), 7.28 - 7.24 (m, 1H), 7.14 – 7.05 (m, 2H), 6.90 (t, 1H, J = 8.3 Hz), 3.54 – 3.51 (m, 1H), 2.92 - 2.87 (m, 1H), 2.82 – 2.76 (m, 1H), 1.43 (d, 3H J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 163.1 (d, J_{C-F} = 243 Hz), 148.6 (d, J_{C-F} = 6.9 Hz), 148.1, 138.3, 136.3, 134.3, 130 (d, J_{C-F} = 8.1 Hz), 127.9, 127.4, 122.7 (d, J_{C-F} = 2.5 Hz), 121.6, 121.5, 116.5, 113.7 (d, J_{C-F} = 21.1 Hz), 113.3 (d, J_{C-F} = 20.8 Hz), 46.6, 36.6, 21.7; HRMS (ESI): MH^+, found 309.1393. $C_{19}H_{18}FN_2O$ requires 309.1403.

3.2.2. 3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)butanamide (5i): Following the general procedure, **5i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (117 mg, 74%); R_f = 0.5 (EtOAc:Hexane = 20:80); mp 69 – 70 °C; FTIR (DCM): 3354, 2963, 1686, 1526 and 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.83 – 8.79 (m, 2H), 8.15 (d, 1H, J = 8.2 Hz), 7.56 – 7.49 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, J = 7.6 Hz), 7.19 (d, 2H, J = 7.6 Hz), 3.55 – 3.49 (m, 1H), 2.92 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.4 Hz), 2.79 (dd, 1H, J_1 = 14.4 Hz, J_2 = 8.4 Hz), 2.63 (q, 2H, J = 7.6 Hz), 1.44 (d, 3H, J = 6.9 Hz), 1.23 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.1, 143.2, 142.2, 138.3, 136.3, 134.5, 128.1, 127.9, 127.4, 126.8, 121.6, 121.4, 116.4, 47.0, 36.5, 28.4, 21.9, 15.6; HRMS (ESI): MH^+, found319.1794. $C_{21}H_{23}N_2O$ requires 319.1810.

3.2.3. 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)butanamide (5j): Following the general procedure, **5j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour solid (133 mg, 77%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 96 – 98 °C; FTIR (DCM): 3352, 2965, 1682, 1589 and 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.79 – 8.76 (m, 2H), 8.13 – 8.08 (m, 1H), 7.51 – 7.4 (m, 3H), 6.87 – 6.82 (m, 3H), 4.20 – 4.19 (m, 4H), 3.45 – 3.40 (m, 1H), 2.86 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.8 Hz), 2.73 (dd, 1H, J_1 = 14.8, J_2 = 8.0 Hz), 1.39 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.1, 143.5, 142.0, 139.4, 138.3, 136.3, 134.4, 127.9, 127.4, 121.6, 121.4, 119.8, 117.3, 116.4, 115.5, 64.4, 64.3, 47.0, 36.3, 22.0; HRMS (ESI): MH^+, found 349.1535. $C_{21}H_{21}N_2O_3$ requires 349.1552.

3.2.4. 3-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)hexanamide (6d): Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless thick liquid (80 mg, 76%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3353, 2929, 1684, 1595 and 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.78 – 8.76 (m, 2H), 8.13 (d, 1H, J = 8.2 Hz), 7.54 – 7.42 (m, 3H), 7.25 – 7.21 (m, 1H), 6.92 – 6.87 (m, 2H), 6.73 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.4 Hz), 3.79 (s, 3H), 3.34 – 3.30 (m, 1H), 2.86 (d, 2H, J = 7.4 Hz), 1.80 – 1.68 (m, 2H), 1.32 – 1.23 (m, 2H), 0.89 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 159.7, 148.0, 146.1, 138.3, 136.3, 134.4, 129.5, 127.9, 127.4, 121.5, 121.4, 120.0, 116.4, 113.4, 111.6, 55.1, 45.9, 42.5, 38.4, 20.6, 14.1; HRMS (ESI): MH^+, found 349.1925 $C_{22}H_{25}N_2O_2$ requires 349.1916.

3.2.5. 3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)pentanamide (7b): Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (70 mg, 68%); R_f = 0.4 (EtOAc:Hexane = 20:80); FTIR (DCM): 3350, 2963, 1681, 1606 and 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.70 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.0 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.89 (d, 1H, J = 8.2 Hz), 7.51 – 7.40 (m, 3H), 7.39 (d, 1H, J = 8.2 Hz), 3.33 – 3.30 (m, 1H), 2.95 -2.82 (m, 2H), 2.54 (s, 3H), 1.91 – 1.86 (m, 1H), 1.78 – 1.70 (m, 1H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 169.9, 149.9, 148.1, 138.2, 136.3, 135.6, 134.3, 128.7, 127.9, 127.9, 127.3, 121.6, 121.5, 116.4, 45.0, 44.3, 29.0, 26.6, 12.0; HRMS (ESI): MH^+, found 347.1752 $C_{22}H_{23}N_2O_2$ requires 347.1760.

3.2.6. 3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)pentanamide (7c): Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colourless thick liquid (80 mg, 78%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3351, 2928, 1682, 1529 and 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.73 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.54 – 7.44 (m, 3H), 7.27 (d, 2H, J = 7.3 Hz), 7.24 (d, 2H, J = 7.3 Hz), 3.24 – 3.20 (m, 1H), 2.92 – 2.78 (m, 2H), 1.90 – 1.84 (m, 1H), 1.73 – 1.69 (m, 1H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.1, 142.5, 138.2, 136.3, 134.3, 132.0, 129.0, 128.7, 127.9, 127.4, 121.6, 121.5, 116.4, 45.4, 43.8, 29.1, 12.0; HRMS (ESI): MH^+, found 339.1279 $C_{20}H_{20}ClN_2O$ requires 339.1264.

3.2.7. 3-(3-Fluorophenyl)-*N*-(quinolin-8-yl)pentanamide (7d): Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi liquid (87 mg, 90%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3352, 2929, 1684, 1589 and 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.79 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.0 Hz), 8.74 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.55 – 7.44 (m, 3H), 7.28 – 7.23 (m, 1H), 7.09 (d, 1H, J = 7.7 Hz), 7.03 (d, 1H, J = 10.1 Hz), 6.88 (td, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 3.27 – 3.24 (m, 1H), 2.92 – 2.81 (m, 2H), 1.91 – 1.85 (m, 1H), 1.75 – 1.69 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 163.1 (d, J_{C-F} = 243 Hz), 148.1, 146.8 (d, J_{C-F} = 6.8 Hz), 138.2, 136.3, 134.3, 129.9 (d, J_{C-F} = 8.1 Hz), 127.9, 127.4, 123.5 (d, J_{C-F} = 2.7 Hz), 121.6, 121.4, 116.4, 114.3 (d, J_{C-F} = 20.9 Hz), 113.3 (d, J_{C-F} = 21 Hz), 45.3, 44.1 (d, J_{C-F} = 1.3 Hz), 29.1, 12.0; HRMS (ESI): MH^+, found 323.1576. $C_{20}H_{20}FN_2O$ requires 323.1560.

3.2.8. *N*-(Quinolin-8-yl)-3-(*m*-tolyl)pentanamide (7e): Following the general procedure, **7e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi liquid (81 mg, 84%); R_f = 0.6 (EtOAc:Hexane = 20:80); FTIR (DCM): 3366, 2926, 1684, 1527 and 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.78 – 8.77 (m, 2H), 8.14 (d, 1H, J = 8.2 Hz), 7.54 – 7.42 (m, 3H), 7.23 – 7.19 (m, 1H), 7.14 – 7.11 (m, 2H), 7.01 (d, 1H, J = 7.4 Hz), 3.23 – 3.17 (m, 1H), 2.88 (d, 2H, J = 7.4 Hz), 2.34 (s, 3H), 1.92 – 1.85 (m, 1H), 1.77 – 1.69 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.0, 144.0, 138.3, 138.0, 136.3, 134.5, 128.4, 128.4, 127.9, 127.4, 127.2, 124.7, 121.5, 121.4, 116.4, 45.6, 44.3, 29.2, 21.5, 12.1; HRMS (ESI): MH^+, found 319.1823. $C_{21}H_{23}N_2O$ requires 319.1810.

3.2.9. 3-(3,5-Dimethylphenyl)-*N*-(quinolin-8-yl)pentanamide (7f): Following the general procedure, **7f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (119 mg, 70%); R_f = 0.5 (EtOAc:Hexane = 20:80); mp 74 – 75 °C; FTIR (DCM): 3355, 2924, 1689, 1602 and 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.79 – 8.76 (m, 2H), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55 – 7.44 (m, 3H), 6.92 (s, 2H), 6.82 (s, 1H), 3.17 – 3.12 (m, 1H), 2.86 (d, 2H, J = 7.4 Hz), 2.29 (s, 6H), 1.89 – 1.82 (m, 1H), 1.75 – 1.69 (m, 1H), 0.86 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 148.0, 144.0, 138.3, 137.8, 136.3, 134.5, 128.1, 127.9, 127.4, 125.4, 121.5, 121.3, 116.4, 45.6, 44.2, 29.1, 21.4, 12.1; HRMS (ESI): MH^+, found 333.1957 $C_{22}H_{25}N_2O$ requires 333.1967.

3.2.10. 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)pentanamide (7g): Following the general procedure, **7g** was

obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi solid (93 mg, 52%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3352, 2928, 1682, 1589 and 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.79 – 8.75 (m, 2H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.54 – 7.43 (m, 3H), 6.81 – 6.80 (m, 3 H), 4.21 (s, 4H), 3.14 – 3.10 (m, 1H), 2.83 – 2.81 (m, 2H), 1.85 – 1.80 (m, 1H), 1.70 – 1.62 (m, 1H), 0.86 (t, 3H, *J* = 7.32 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.0, 143.4, 142.0, 138.3, 137.4, 136.3, 134.5, 127.9, 127.4, 121.5, 121.3, 120.6, 117.2, 116.4, 116.1, 64.4, 64.3, 45.7, 43.7, 29.2, 12.0; HRMS (ESI): MH^+, found 363.1726. $C_{22}H_{23}N_2O_3$ requires 363.1709.

3.2.11. 3,3-Bis(4-chlorophenyl)-*N*-(quinolin-8-yl)propanamide (8b): Following the general procedure, **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (65 mg, 60%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 163 – 165 °C; FTIR (DCM): 3337, 2920, 1669, 1524 and 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.78 (d, 1H, *J* = 4.1 Hz), 8.71 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.6 Hz), 8.15 (d, 1H, *J* = 7.7 Hz), 7.53 – 7.44 (m, 3H), 7.29 – 7.24 (m, 8H), 4.76 (t, 1H, *J* = 7.7 Hz), 3.27 (d, 2H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 148.1, 141.8, 138.2, 136.4, 134.1, 132.5, 129.1, 128.9, 127.9, 127.3, 121.7, 121.7, 116.6, 45.9, 44.1; HRMS (ESI): MH^+, found 421.0896 $C_{24}H_{19}Cl_2N_2O$ requires 421.0874.

3.2.12. 3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)propanamide (8c): Following the general procedure, **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (44 mg, 47%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 184 – 186 °C; FTIR (DCM): 3341, 3094, 1677, 1577 and 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.79 – 8.78 (m, 2H), 8.17 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 2H, *J* = 8 Hz), 7.55 – 7.53 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.41 (d, 2H, *J* = 8 Hz), 3.22 (t, 2H, *J* = 7.8 Hz), 2.93 (t, 2H, *J* = 7.6 Hz), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 170.2, 148.1, 146.6, 138.2, 136.4, 135.4, 134.3, 128.7, 128.7, 127.9, 127.4, 121.7, 121.6, 116.5, 39.0, 31.3, 26.6; HRMS (ESI): MH^+, found 319.1456 $C_{20}H_{19}N_2O_2$ requires 319.1447.

3.2.13. 3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)hexadecanamide (9b): Following the general procedure, ad **9b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (105 mg, 72%); R_f = 0.6 (EtOAc:Hexane = 20:80); FTIR (DCM): 3353, 2923, 1688, 1525 and 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.78 – 8.74 (m, 2H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.54 – 7.47 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.23 (d, 2H, *J* = 8.3 Hz), 6.84 (d, 2H, *J* = 8.3 Hz), 3.76 (s, 3H), 3.28 – 3.24 (m, 1H), 2.85 – 2.81 (m, 2H), 1.79 – 1.65 (m, 2H), 1.28 – 1.22 (m, 22H), 0.92 – 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 158.0, 148.0, 138.3, 136.4, 136.3, 134.4, 128.4, 127.9, 127.4, 121.5, 121.4, 116.5, 113.9, 55.1, 46.2, 41.9, 36.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 27.4, 24.8, 22.7, 14.2; HRMS (ESI): MH^+, found 489.3503 $C_{32}H_{45}N_2O_2$ requires 489.3481.

3.2.14. *N*-(Quinolin-8-yl)-2,6-di(thiophen-2-yl)benzamide (10b): Following the general procedure, **10c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (55 mg, 45%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 184 – 186 °C; FTIR (DCM): 3341, 3094, 1677, 1577 and 1522 cm^{-1}; HRMS (ESI): ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.78 (d, 1H, *J* = 7.1 Hz), 8.66 (d, 1H, *J* = 3.5 Hz), 8.11 (d, 1H, *J* = 8.2 Hz), 7.60 – 7.49 (m, 5H), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.1 Hz), 7.35 – 7.34 (m, 2H), 7.22 (d, 2H, *J* = 4.9 Hz), 6.93 – 6.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 148.1, 140.9, 138.4, 136.1, 135.7, 134.3, 133.0, 130.0, 129.4, 127.8, 127.6, 127.3, 127.1, 126.2, 121.9, 121.5, 116.8; MH^+, found 413.0764 $C_{24}H_{17}N_2OS_2$ requires 413.0782.

3.2.15. Methyl 2'-(quinolin-8-ylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (10f′): Following the general procedure, **10g′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (63 mg, 55%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 148 – 150 °C; FTIR (DCM): 3337, 1722, 1672, 1596 and 1524 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 9.84 (s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.99 (d, 2H, *J* = 8.3 Hz), 7.94 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 7.63 – 7.48 (m, 7H), 7.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): 167.4, 166.8, 147.9, 144.9, 139.3, 138.4, 136.2, 136.1, 134.4, 130.7, 130.6, 129.7, 129.2, 129.2, 129.0, 128.3, 127.8, 127.3, 121.8, 121.5, 116.4, 52.1; HRMS (ESI): MH^+, found 383.1379 $C_{24}H_{19}N_2O_3$ requires 383.1396.

3.2.16. 3',4-Dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (11a): Following the general procedure, **11a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (105 mg, 60%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 130 – 131°C; FTIR (DCM): 3312, 3051, 1658, 1526 and 1430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.84 (d, 1H, *J* = 7.5 Hz), 8.54 (d, 1H, *J* = 4.0 Hz), 8.09 (d, 1H, *J* = 8.24 Hz), 7.74 (s, 1H), 7.54 – 7.45 (m, 2H), 7.39 – 7.35 (m, 4H), 7.31 – 7.28 (m, 1H), 7.14 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 1H, *J* = 7.5 Hz), 2.50 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 147.7, 139.9, 138.4, 138.0, 137.6, 137.4, 136.0, 135.9, 134.7, 131.3, 130.6, 129.7, 128.2, 128.1, 127.7, 127.3, 126.1, 121.4, 121.4, 116.2, 21.4, 21.1; HRMS (ESI): MH^+, found 353.1664 $C_{24}H_{21}N_2O$ requires 353.1654.

3.2.17. 2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-methyl-*N*-(quinolin-8-yl)benzamide (11c) : Following the general procedure, 11c was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (104 mg, 53%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 174 – 176 °C; FTIR (DCM): 3328, 1660, 1581, 1525 and 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.86 (d, 1H, *J* = 7.5 Hz), 8.62 – 8.61 (m, 1H), 8.09 (d, 1H, *J* = 8.2 Hz), 7.73 (s, 1H), 7.57 – 7.53 (m, 1H), 7.48 – 7.46 (m, 1H), 7.39 – 7.36 (m, 3H), 7.08 (s, 1H), 6.97 (d, 1H, *J* = 8.3 Hz), 6.76 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 4.10 (s, 4H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 147.7, 143.5, 143.2, 138.5, 137.3, 136.9, 136.0, 135.7, 134.7, 133.4, 131.3, 130.5, 129.8, 127.7, 127.4, 122.3, 121.4, 121.3, 117.9, 117.2, 116.3, 64.3, 64.2, 21.1; HRMS (ESI): MH^+, found 397.1534 $C_{25}H_{21}N_2O_3$ requires 397.1552.

3.3. Synthesis of palladium complex 18 from 2-methylbenzoic anhydride (2j) and synthesis of arylated carboxamide 11e from 18: A mixture of 2-methylbenzoic anhydride **(2j**, 0.7 mmol) and 8 -aminoquinoline (0.7 mmol) in anhydrous toluene (4 mL) was heated at 100 °C for 30 h. Then, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography to afford 2-methyl-*N*-(quinolin-8-yl)benzamide (**1cj**) in 63% yield. Next, a mixture of 2-methyl-*N*-(quinolin-8-yl)benzamide (**1cj**, 0.43 mmol) and $Pd(OAc)_2$ (0.43 mmol) in anhydrous MeCN (3 mL) was stirred at 60 °C for 4 h. The reaction mixture was cooled to rt, the resulting yellowish precipitate was collected by filtration, washed with 5 mL of MeCN and then solid was re-dissolved in 10-15 mL CH_2Cl_2, and concentrated under reduced pressure to give the palladium complex **18** in 42% yield (the work up procedure reported in ref.[9b] was followed to isolate **18**). **18**: mp 230-232 °C (decomposed); ^1H NMR (DMSO-d_6, 400 MHz, ppm): δ 9.18 (br. s, 1H), 9.02 (d, 1H, *J* = 7.4 Hz), 8.47 (d, 1H, *J* = 8.0 Hz,), 7.62-59 (m, 1H), 7.48 (t, 1H, , *J* = 7.8 Hz), 7.41 (d, 1H, , *J* = 7.6 Hz), 6.98– 6.91 (m, 2H), 6.85 (d, 1H, *J* = 6.6 Hz), 2.54 (s, 3 H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz, ppm) δ 177.7, 150.0, 147.4, 146.9, 145.3, 143.7, 139.7, 130.9, 130.3, 129.5, 129.1, 128.9, 122.0, 119.5, 119.0, 118.5, 20.2, 1.6; MS (ASAP) *m/z* 245 $[M]^+$ - (Pd+MeCN+CH_3). A mixture of palladium complex **18** (0.08 mmol) and 4–iodoanisole (0.40 mmol) in acetone (1.0 mL) was

stirred at rt 74 h and then was refluxed at 45 °C for 24 h. Then, the reaction mixture was diluted with dichloromethane (2 mL) followed by addition of excess of aqueous HI (1 mL). Resulting solution was stirred for an hour and basified by solid $NaHCO_3$. Then, extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure afforded a crude mixture, which was purified by column chromatography (hexane/EtOAc= 60:40) to afford the arylated product **11e**[7e] in 44% yield.

Acknowledgments

We thank IISER-Mohali for funding and the central analytical facilities (NMR and HRMS) of IISER Mohali. A.D and P. S. thank IISER Mohali for providing the PhD fellowship.

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9. For selected references revealing the mechanism for the Pd(II)-catalyzed, 8-aminoquinoline-assisted *β*-C-H activation of carboxamides, see: (a) Successful isolation of Pd(II) intermediate after the sp^3 *β*-C-H activation of carboxamide, see ref.[3b]; (b) Successful isolation of Pd(II) intermediate after the sp^2 *β*-C-H activation of carboxamide, Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531.
10. It is to be noted that the mechanism represented in the Scheme 5 is well established in the literature and supported

with the studies carried out by various research groups.[2] For example, Daugulis et al have isolated the Pd(II) intermediate **19** after the sp^3 β-C-H activation from the corresponding carboxamide.[3b] Similarly, Chen et al al have isolated the Pd(II) intermediate **20** after the sp^2 β-C-H activation from the corresponding carboxamide.[9b] While the aim of this paper is to improve the existing two step Pd(II)-catalyzed β-C-H arylation of carboxamides as a single step method and multicomponent-type reaction comprising involving anhydride as substrate (**2**) via in situ installation of bidentate DG. Based on the suggestion of the Reviewer(s) we also intended to isolate a Pd(II) intermediate from our reactions and out of various trials we could isolate the Pd(II) intermediate **18** from the reaction of **1cj** with the $Pd(OAc)_2$ catalyst by following the procedure reported by Chen et al for the synthesis of **20**. The Pd(II) intermediate **18** was characterized by the NMR and mass analysis. The NMR pattern of the Pd(II) intermediate **18** was similar to the Pd(II) intermediate **20**. Characteristically, in the ^{13}C NMR, the methyl signal of acetonitrile moiety of the complex **18** appeared at δ 1.6 ppm as observed for the Pd(II) intermediate **20**.[9b] Further, mass analysis (by ASAP method from QTOF mass analyzer) of the Pd(II) intermediate **18** revealed a characteristic and prominent mass value of *m/z* 245 for the possible fragment corresponding to $[M]^+$ - ($Pd+MeCN+CH_3$). Our efforts to obtain a single crystal for X-ray analysis are not fruitful at this stage and will be reported in near future after we succeed in getting suitable single crystal for analysis. However, treatment of the isolated Pd(II) intermediate **18** with 4-idonoanisole gave the sp^2 β-C-H arylated product **11e** in 44% yield (Scheme 5), which is in accordance with the mechanism represented in the literature.

Supplementary data

Supplementary data (copy of ^1H, ^{13}C NMR Charts of compounds) associated with this article can be found, in the online version.