Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01933 • Publication Date (Web): 18 Nov 2016

Pd(II)-Catalyzed Bidentate Directing Group-Aided Chemoselective Acetoxylation of Remote ε-C(sp^2)-H Bonds in Heteroaryl-Aryl-Based Biaryl Systems

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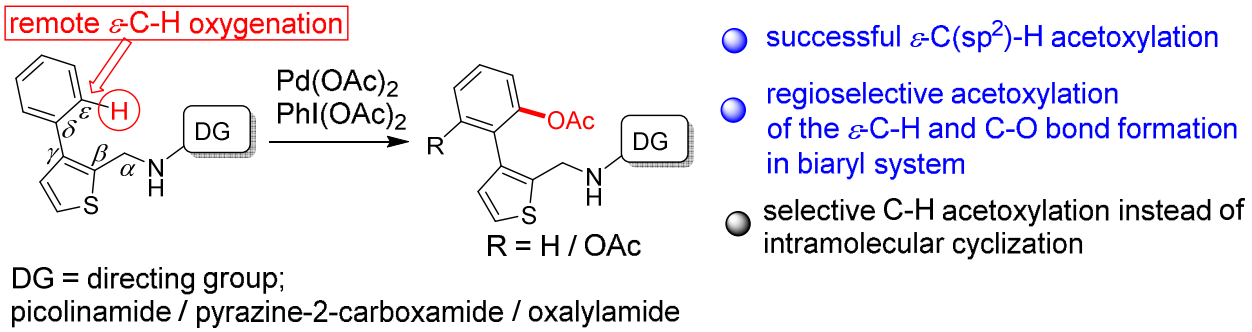
ABSTRACT



In this paper, we report our successful attempt on the Pd(II)-catalyzed, bidentate directing group-aided, chemoselective acetoxylation/substitution of remote ε-C(sp^2)-H bonds using heteroaryl-aryl-based biaryl systems. While the bidentate directing group (BDG)-aided, C-H activation and functionalization/acetoxylation of the β-, γ- and δ-C-H bonds of appropriate carboxamide systems were well documented, there exist only rare reports dealing on the C-H activation and functionalization of remote ε-C-H bonds of appropriate substrates. Especially, the BDG-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond over cyclization has not been explored well. Accordingly, in this work the treatment of various picolinamides / oxalylamides / pyrazine-2-carboxamides **4/7/9/11**, which were derived from the corresponding C-3 arylated furfurylamines or thiophen-2-ylmethanamines with $PhI(OAc)_2$ in the presence of the $Pd(OAc)_2$ catalyst successfully afforded the corresponding ε-C-H acetoxylated products. The

chemoselective acetoxylation of the ε-C-H bond was possible and facilitated by the biaryl substrate **4/7/9/11** and not by the biaryl substrate **2a**.

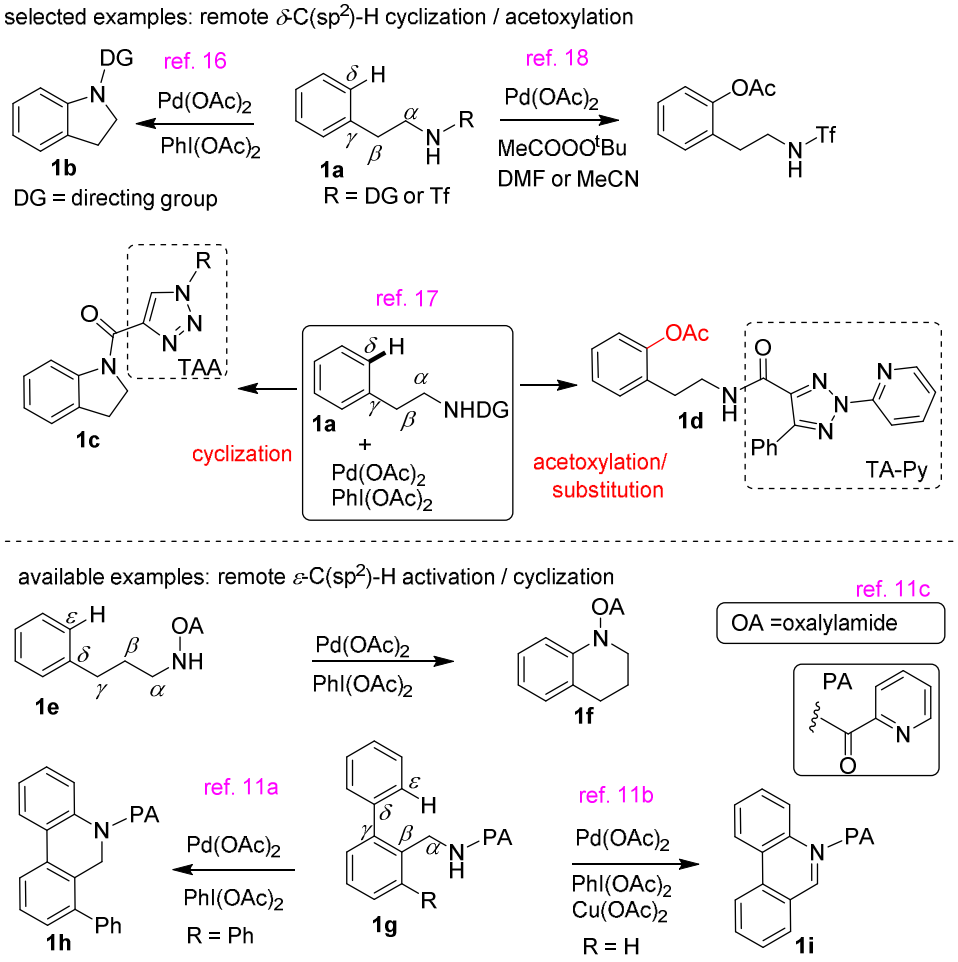
INTRODUCTION

Transition metal-catalyzed sp^2/sp^3 C-H activation/functionalization is one of the remarkable synthetic transformations in organic synthesis.[1-4] While the directing group-free C-H activation/functionalization is well documented, the directing group-aided C-H activation/functionalization has become a powerful synthetic strategy for accomplishing the site-selectivity.[1-4] Especially, the use of the bidentate directing groups (BDGs) has offered a new zeal for achieving the site-selective C-H functionalization (e.g., arylation, alkylation and acetoxylation) of organic molecules.[5-8] The 8-aminoquinoline (8AQ)-type BDGs have preferentially assisted the functionalization of sp^2/sp^3 β-C-H bonds of carboxylic acid substrates.[5-8] The picolinamide (PA)-type BDGs have assisted the functionalization of sp^2/sp^3 γ- and δ-C-H bonds of amine systems.[5-8] The BDG-aided functionalization of sp^2/sp^3 β- and γ-C-H bonds of appropriate carboxamide systems were well documented;[5-8] and there also have been some outstanding efforts on the BDG-aided functionalization of remote sp^2/sp^3 δ- and ε-C-H bonds of appropriate carboxamide systems.[5,8-10] In particular, to the best of our knowledge, there exist only rare reports dealing on the BDG-aided functionalization of remote sp^2/sp^3 ε-C-H bonds.[11]

While the Pd(II)-catalyzed C-H activation strategy has been well explored for the construction of C-C bonds; the Pd(II)-catalyzed, $PhI(OAc)_2$-promoted C-H acetoxylation/oxygenation tactic comprising the conversion of a C-H bond in to a C-O bond has also received substantial attention.[8,12-18] In particular, the acetoxylation of sp^2 C-H bonds of

arenes considered as a direct and efficient method for synthesizing phenolic compounds, which are important substances in industry and academic research.[19]

Scheme 1. Functionalization of Remote δ- and ε-C(sp^2)-H Bonds.



The BDG-aided acetoxylation of sp^2/sp^3 β- and γ-C-H bonds of appropriate carboxamide systems were well documented.[8,12-15] A literature survey[8,16,17] revealed that the attempts on the Pd(II)-catalyzed, BDG-aided functionalization of remote δ- or ε-C(sp^2)-H bonds with $PhI(OAc)_2$ generally gave the cyclized products (e.g., **1b**, **1f**, **1h** and **1i**). The BDG-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond over cyclization has not explored well.[1-5,8] Accordingly, obtaining control on the acetoxylation/substitution over cyclization and chemoselectivity in the

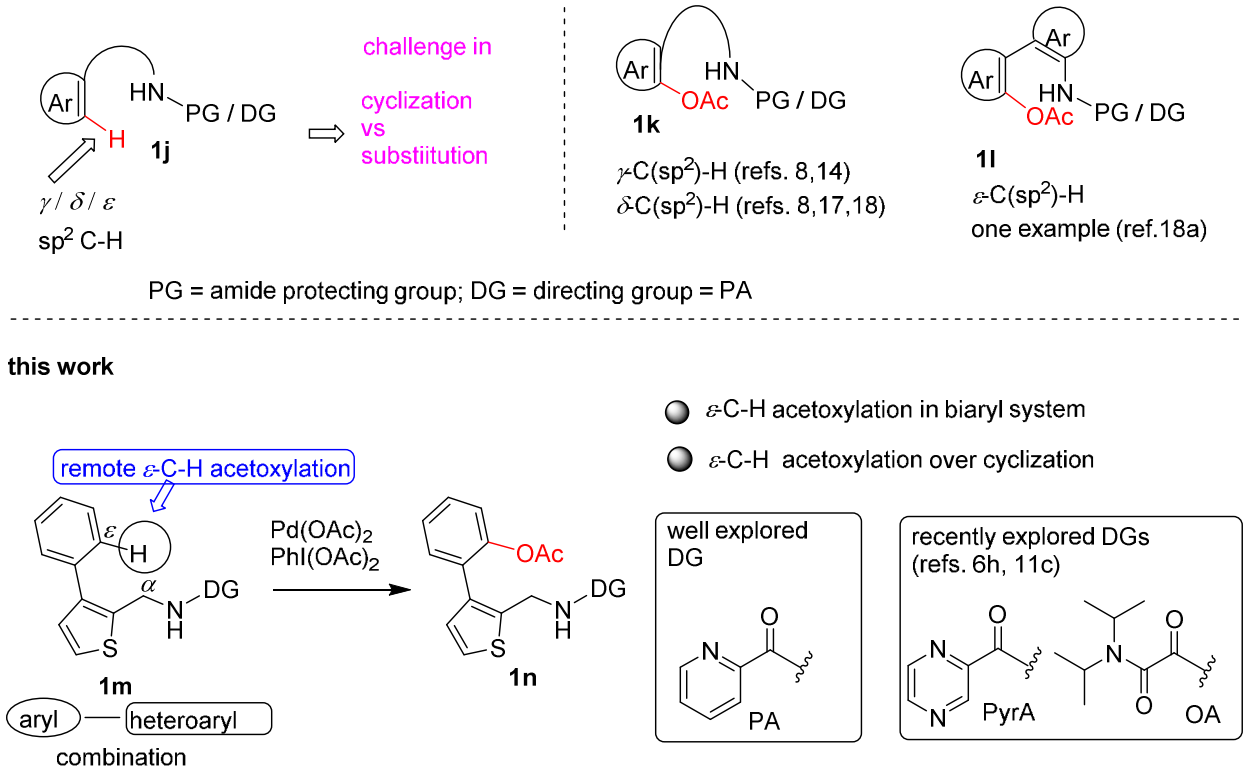
BDG-aided functionalization of remote δ- or ε-C-H bond of a suitable substrate considered to be a challenging task. With regard to the available reports dealing on the Pd(II)-catalyzed, $PhI(OAc)_2$-promoted activation/functionalization of remote ε-C(sp^2)-H bond; Daugulis,[11a] Chen[11b] and Zhao[11c] groups have independently revealed that the reactions of the compounds **1g** and **1e** exclusively gave the corresponding cyclized products (Scheme 1).

In general, the C-H functionalization processes are substrate specific; however, it is possible to achieve the chemoselective acetoxylation/substitution or cyclization using suitably modified substrates[13] or directing groups[17] or changing the reaction conditions.[14a] In this regard, Chen reported[14a] the alkoxylation of remote δ-C(sp^2)-H bond using alcohol as a co-solvent. Shi reported[17] the chemoselective acetoxylation/substitution or cyclization of remote δ-C(sp^2)-H bonds using substrate **1a,** which was installed with different DGs. The chemoselective acetoxylation of remote δ-C(sp^2)-H bond was achieved using TA-Py as the directing group and the cyclization involving the δ-C(sp^2)-H bond was achieved using TAA as the directing group (Scheme 1). It is also worth to mention here that Yu reported[18] the NHTf-group directed Pd(II)-catalyzed δ-C-H (*ortho* C-H) acetoxylation of triflate protected phenethylamine and phenylpropylamine systems with *tert*-butyl peroxyacetate as an oxidant in the presence of either DMF or CH_3CN as the promoter.[18a] Furthermore, Yu has reported an example of NHTf-group directed ε-C-H acetoxylation of triflate protected phenylpropylamine system with *tert*-butyl peroxyacetate as an oxidant in the presence of CH_3CN, which afforded the corresponding ε-C-H acetoxylated product in 33% yield.[18a]

Taking an impetus from the enduring developments on the site-selective acetoxylation of C-H bonds,[8,12-18] we envisaged to study the prevailing subject comprising dominant cyclization[11] over acetoxylation/substitution in the Pd(II)-catalyzed, bidentate ligand picolinamide (PA)-aided

functionalization of ε-C(sp^2)-H bond using an appropriate substrate. Accordingly, herein, we report our successful attempt on the Pd(II)-catalyzed, bidentate directing group-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond using the heteroaryl-aryl-based biaryl system **1m** (Scheme 2).

Scheme 2. Selective Acetoxylation of γ-, δ- and ε-C(sp^2)-H Bonds.

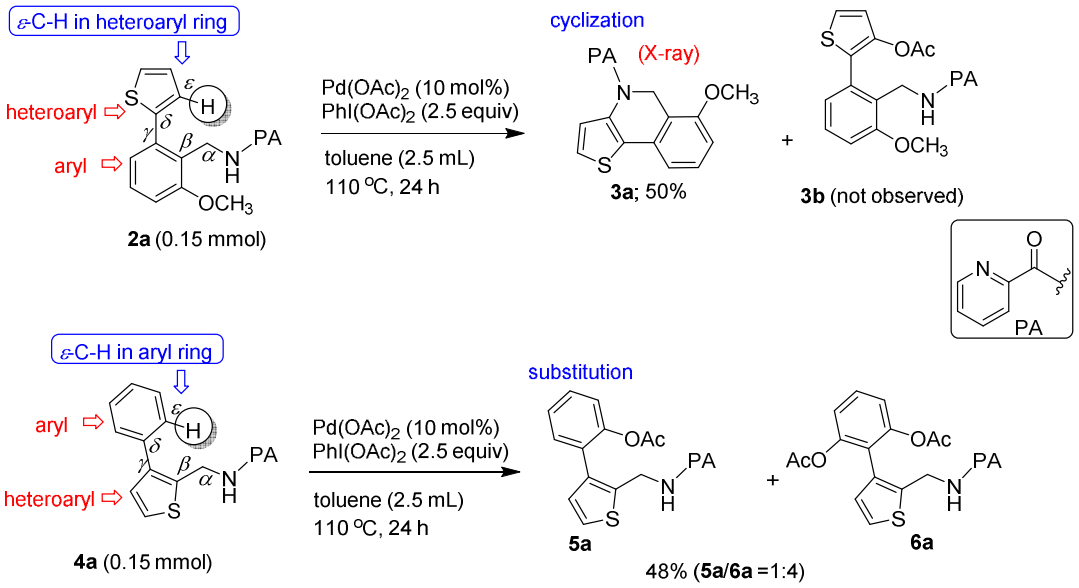


RESULTS AND DISCUSSION

Typically, the suitable systems for attempting the Pd(II)-catalyzed, BDG-aided acetoxylation of remote ε-C(sp^2)-H bond are either the 3-phenylpropan-1-amine-type system **1e** or the biaryl-type system **1g** (Scheme 1). However, the Pd(II)-catalyzed, bidentate directing group-aided reactions of **1g** and **1e** with $PhI(OAc)_2$ were reported to give the corresponding cyclized products (Scheme 1).[11] Hence, we envisaged to attempt the chemoselective acetoxylation of remote ε-C(sp^2)-H bonds using biaryl systems having a combination of

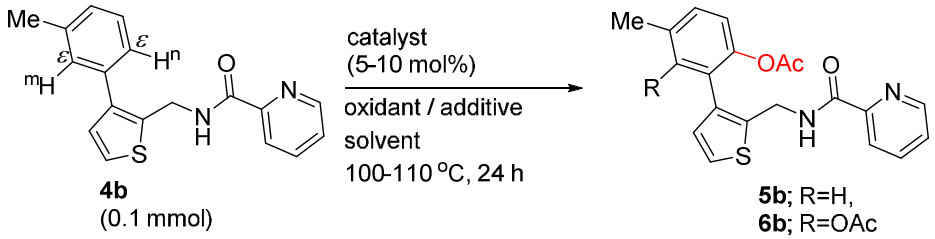
heteroaryl-aryl rings, e.g., thiophene-phenyl system **2a** and furan-phenyl system **4a** (Scheme 3).[20,21]

Scheme 3. Chemoselective Cyclization and Acetoxylation of Remote ε-C(sp^2)-H Bonds.



To begin with our studies on the Pd(II)-catalyzed directing group-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond in the heteroaryl-aryl-based biaryl system, initially we assembled the picolinamide substrates **2a** and **4a** (Scheme 3). Then, we attempted the Pd(II)-catalyzed, functionalization of the ε-C-H bond present in the thiophene ring of substrate **2a** with $PhI(OAc)_2$ as an oxidant. This reaction gave the cyclized product **3a** in 50% yield instead of the ε-C-H acetoxylated product **3b** (Scheme 3). Next, we attempted the Pd(II)-catalyzed functionalization of the ε-C-H bond present in the phenyl ring of substrate **4a** with $PhI(OAc)_2$. Fortunately, our endeavor for accomplishing the ε-C-H acetoxylation went right and this reaction selectively gave the ε-C-H acetoxylated products **5a** (mono OAc) and **6a** (di OAc). These reactions indicated that the substrate **4a** was found to be an appropriate design for accomplishing the ε-C-H acetoxylation, while **2a** was not a suitable design.

Table 1. Picolinamide-Aided ε-C-H Acetoxylation of 4b[22]



4b
(0.1 mmol)

5b; R=H,
6b; R=OAc

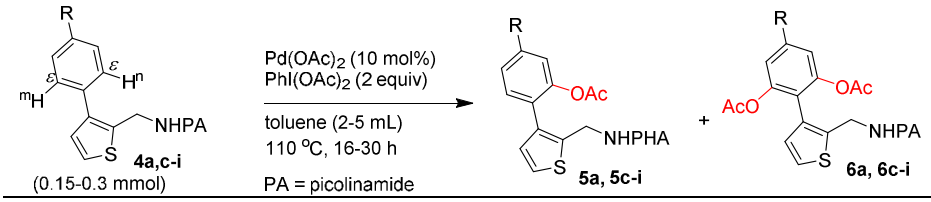
entry	catalyst (mol%)	oxidant / additive (equiv)	solvent (mL)	**5b**: yield (%)
1	nil	$PhI(OAc)_2$ (2.0)	toluene (2)	0
2	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.0)	toluene (2)	70
3	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1.5)	toluene (2)	75
4	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	80
5	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3.0)	toluene (2)	62
6	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)-AcOH (1)/Ac_2O (1)	toluene (2)	64
7	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0) AgOAc (1)	toluene (2)	42
8	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)-oxone (1)	toluene (2)	40
9	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	AcOH (2)	0
10	$Pd(OAc)_2$ (10)	AgOAc (2.0)	toluene (2)	0
11	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2.0)	toluene (2)	0
12	$Pd(TFA)_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	41
13	$Pd(PPh_3)_2Cl_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	45

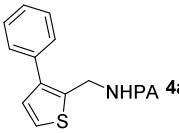
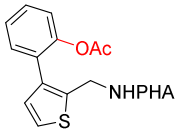
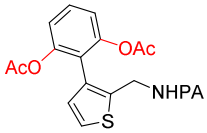
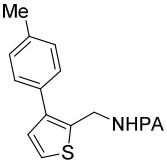
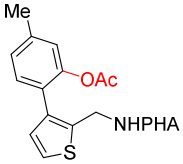
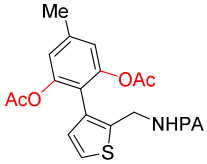
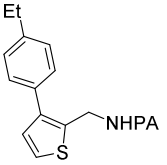
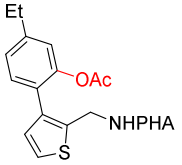
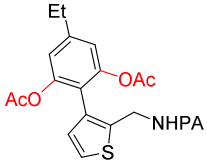
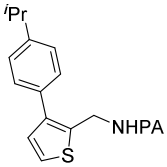
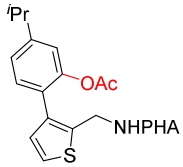
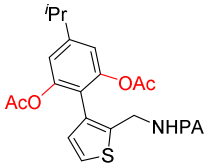
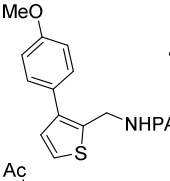
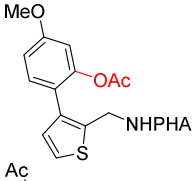
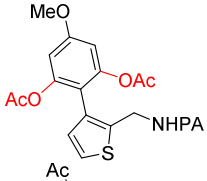
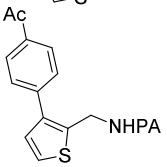
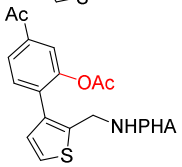
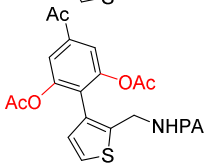
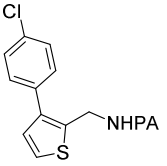
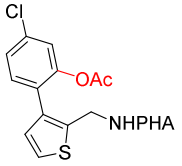
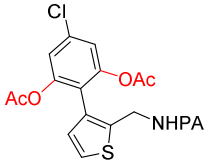
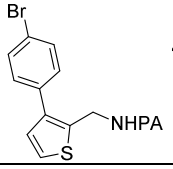
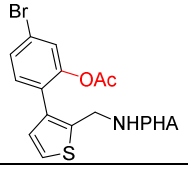
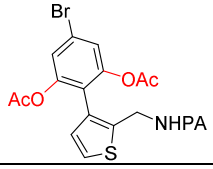
Encouraged by the successful attempt on the ε-C-H acetoxylation reaction using the heteroaryl-aryl-based biaryl system **4a** (Scheme 3); we next performed the optimization of reaction conditions. Table 1 shows the results of the ε-C-H acetoxylation reaction of the picolinamide substrate **4b** in the presence of various oxidants/additives and palladium catalysts. Amongst the optimization reactions performed, the reaction of **4b** with 2 equiv of $PhI(OAc)_2$ and 10 mol% of the $Pd(OAc)_2$ catalyst in toluene at 110 °C for 24 h found to afford the ε-C-H acetoxylated product **5b** in a maximum yield of 80% (entry 4, Table 1).

Noticeably, in the substrate **4b** the ε-C-H^{n} bond was selectively acetoxylated over the ε-C-H^{m} bond to afford the mono acetoxylated product **5b** and the corresponding bis acetoxylated product **6b** was not obtained in characterizable amounts. This is because, in the substrate **4b** the methyl substituent present at the *ortho*-position with respect to the ε-C-H^{m} bond perhaps hinders the acetoxylation of the ε-C-H^{m} bond. It is to be noted that the preliminary acetoxylation reaction of substrate **4a** without any substituent at the *ortho*-position with respect to the ε-C-H$^{m/n}$ bond gave the products **5a** (mono OAc) and **6a** (di OAc, Scheme 3). Thus, in continuation of the optimization of reactions, we desired to reexamine the scope of the preliminary reaction of substrate **4a** using different equiv of $PhI(OAc)_2$ to selectively obtain either the product **5a** (mono OAc) or the product **6a** (di OAc). Accordingly, the reaction of **4a** with 1.1 equiv of $PhI(OAc)_2$ gave only traces of the products **5a** and **6a** (entry 1, Table 2). The reaction of **4a** with 2 equiv of $PhI(OAc)_2$ gave the products **5a** and **6a** in 45 and 16% yields, respectively (entry 2, Table 2). The reaction of **4a** with 3 equiv of $PhI(OAc)_2$ afforded only the product **6a** (di OAc) in 45% yield (entry 3, Table 2). This reaction indicated that it is possible to selectively obtain the bis acetoxylated product **6a** (di OAc) using excess amounts of $PhI(OAc)_2$. Subsequently, the Pd(II)-catalyzed acetoxylation of **4a** was also performed in a gram scale, which gave the products **5a** and **6a** in 42 and 14% yields, respectively (Table 2).

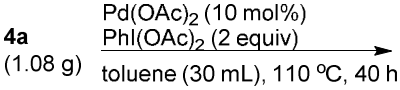
Next, to elaborate the substrate scope, we assembled substrates **4c-i** containing different substituents at the *meta*-position with respect to the ε-C-H$^{m/n}$ bond. Then, we performed the Pd(II)-catalyzed, ε-C-H acetoxylation of substrates **4c-i** with $PhI(OAc)_2$ (Table 2). Except for one case (entry 6, Table 2), irrespective of the substituents in the aryl rings of **4c-i**, the acetoxylation reactions furnished the corresponding products **5c-i** (mono OAc) and **6c-i** (di OAc) in 52-72% yields (combined yields of **5** and **6**).

Table 2. Picolinamide-Aided ε-C-H Acetoxylation of 4a and 4c-i



entry	substrate (**4**)		*t* (h)	**5**: yield (%) (mono OAc)		**6**: yield (%) (di OAc)		**5** + **6**: yield (%)
1[a,b]		**4a**	30		**5a**; 0		**6a**; 0	0
2[a,c]			30		**5a**; 45		**6a**; 16	61
3[a,d]			30		**5a**; 0		**6a**; 45	45
4[e]		**4c**	24		**5c**; 47		**6c**; 25	72
5[e]		**4d**	18		**5d**; 24		**6d**; 44	68
6[f]		**4e**	16		**5e**; 0		**6e**; 55	55
7[g]		**4f**	24		**5f**; 35		**6f**; 27	62
8[e,h]		**4g**	17		**5g**; 26		**6g**; 26	52
9[a]		**4h**	18		**5h**; 36		**6h**; 19	55
10[f]		**4i**	17		**5i**; 37		**6i**; 25	62

gram scale reaction



5a + **6a** = 56%
5a/**6a** = 3:1

[a] 0.3 mmol of **4a/4h** was used. [b] 1.1 Equiv of $PhI(OAc)_2$ was used. [c] 2 Equiv of $PhI(OAc)_2$ was used. [d] 3 Equiv of $PhI(OAc)_2$ was used. [e] 0.2 mmol of **4c/4d/4g** was used. [f] 0.24 mmol of **4e/4i** was used. [g] 0.15 mmol of **4f** was used. [h] Isolated as a mixture of **5g** and **6g**.

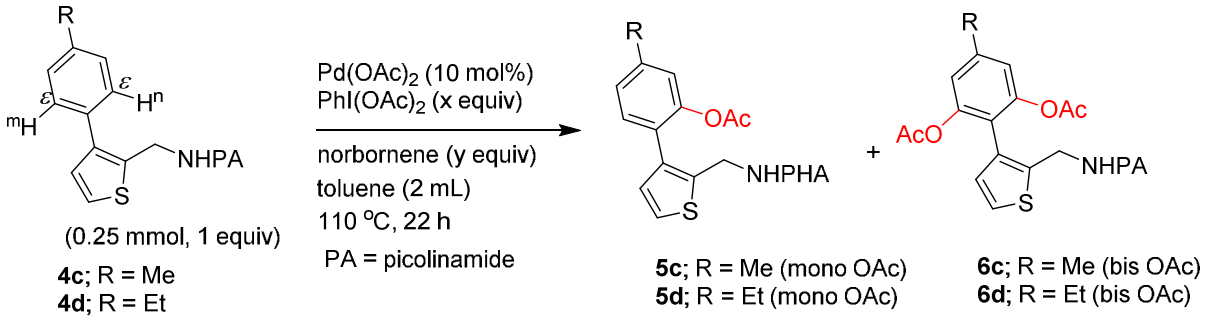
We observed an interesting trend in entries 4-6 (Table 2), which revealed that the selectivity with regard to the mono/bis acetoxylation reaction was found to be dependent on the nature of the alkyl substituents present at the *meta*-position with respect to the ε-C-$H^{m/n}$ bond in the corresponding substrates **4c-e**. Substrate **4c** containing a methyl group in the aryl ring afforded the products **5c** (mono OAc, 47%) and **6c** (di OAc, 25%). Substrate **4d** with an ethyl group in the aryl ring afforded the products **4d** (mono OAc, 24%) and **6d** (di OAc, 44%). However, substrate **4e** with an isopropyl group in the aryl ring selectively afforded **6e** (di OAc, 55%) and the product **5e** (mono OAc) was not obtained in characterizable amounts. These observations indicated that yield of the bis acetoxylation product gradually increased when the alkyl substituent was changed from Me to Et and then to isopropyl. While an exact reason for this trend is not clear at this stage, however, an inductive effect might be operational in the substrates **4c-e**. Apart from this observation, substrates **4f-i** containing other substituents in the aryl ring (e.g., OMe, Ac, Cl and Br) afforded the corresponding mono acetoxylation products (e.g., **5f**, **5h** and **5i**) as the predominant compounds over the corresponding bis acetoxylation products (e.g., **6f**, **6h** and **6i**, Table 2).

Recently, Yu et al. and other research groups have reported an interesting approach for achieving meta selective C−H functionalization using norbornene as the transient mediator.[23] We were interested to use norbornene in the Pd(II)-catalyzed ε-C-H acetoxylation of substrates **4c** and **4d** to improve the mono/bis acetoxylation selectivity. Table 3 shows the results of the Pd(II)-catalyzed ε-C-H acetoxylation of substrates **4c** and **4d** with $PhI(OAc)_2$ in the presence of

norbornene. The reaction of **4c** with 1 equiv of $PhI(OAc)_2$ and without norbornene showed the formation of mono/bis acetoxylated products **5c/6c** in 12% yield with a ratio of 98:2 (entry 1, Table 3). The reaction of **4c** with 2 equiv of $PhI(OAc)_2$ and without norbornene showed the formation of mono/bis acetoxylated products **5c/6c** in 44% yield with a ratio of 75:25 (entry 2, Table 3). The reaction of **4c** with 3 equiv of $PhI(OAc)_2$ and without norbornene showed the formation of mono/bis acetoxylated products **5c/6c** in 61% yield with a ratio of 5:95 (entry 3, Table 3). This reaction indicated that it is possible to selectively obtain the bis acetoxylated product **6c** (di OAc) using excess amounts of $PhI(OAc)_2$. These observed results (entries 1-3, Table 3) with regard to the ratios of mono/bis acetoxylated products were comparable to the results obtained for substrate **4a** (entries 1-3, Table 2). Next, we performed the acetoxylation of **4c** with 1-4 equiv of $PhI(OAc)_2$ and norbornene (1 equiv). While we expected the formation of products **5c/6c** with an improved mono/bis chemoselectivity, however, these reactions showed the formation of products **5c/6c** in low yields (19-28% yields, entries 4-7, Table 3). Further, the observed trend with regard to the ratio of products **5c/6c** obtained using norbornene (entries 4-7, Table 3) was comparable to the reactions carried out without norbornene (entries 1-3, Table 3). Notably, the chemoselectivity was found to shift gradually from mono OAc to bis OAc while increasing the equiv of $PhI(OAc)_2$. Then, we also performed the reaction of substrate **4d** with 2 equiv of $PhI(OAc)_2$ and without norbornene, which showed the formation of mono/bis acetoxylated products **5d/6d** in 56% yield with a ratio of 41:59 (entry 8, Table 3). The reaction of **4d** with 2 equiv of $PhI(OAc)_2$ and norbornene (0.5 equiv) showed the formation of mono/bis acetoxylated **5d/6d** in 41% yield with a ratio of 41:59 (entry 9, Table 3). The same reaction with excess of norbornene (6 equiv) showed the formation of mono/bis acetoxylated **5d/6d** in 36% yield with a ratio of 57:43 (entry 10, Table 3). The use of norbornene as a mediator in the Pd(II)-

catalyzed ε-C-H acetoxylation of substrates **4c** and **4d** were not fruitful and apparently, the corresponding acetoxylated products were obtained in low yields when compared to the reactions carried out without norbornene.

Table 3. Trials to Improve the Chemoselectivity in the Pd(II)-Catalyzed Directed ε-C-H Acetoxylation of 4a and 4d Using Norbornene Additive[a]



entry	R	$PhI(OAc)_2$ (x equiv)	norbornene (y equiv)	combined yield of **5** and **6** (%)	mono/bis ratio **5**:**6**
1	Me	1	0	12	98:2
2	Me	2	0	44	75:25
3	Me	3	0	61	5:95
4	Me	1	1	27	75:25
5	Me	2	1	15	84:16
6	Me	3	1	28	51:49
7	Me	4	1	25	5:95
8	Et	2	0	56	41:59
9	Et	2	0.5	41	41:59
10	Et	2	6	36	57:43

[a] Yields and mono/bis ratio of **5/6** were determined from the crude NMR spectra of the corresponding reaction mixtures.

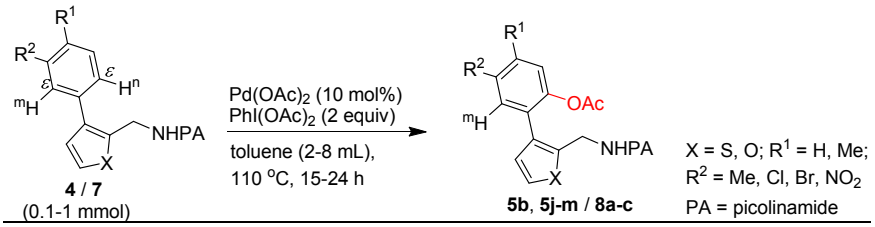
Then, to extend the substrate scope and generality of this work, we assembled substrates **4j-m** and **7a-c** (Table 4), which have different substituents at the *para*-position with respect to the ε-C-H^n bond (or substituents at the *ortho*-position with respect to the ε-C-H^m bond). Initially, we performed the Pd(II)-catalyzed, ε-C-H acetoxylation of substrates **4j-m** with $PhI(OAc)_2$ to afford the products **5j-m** in 32-60% yields, respectively (Table 4). Then, we performed the Pd(II)-catalyzed, ε-C-H acetoxylation of substrates **7a-c** with $PhI(OAc)_2$ to afford the corresponding products **8a-c** in 32-53% yields, respectively (Table 4). It is to be noted that in the substrates **4j-m** and **7a-c** the ε-C-H^n bonds were selectively acetoxylated over the ε-C-H^m bonds. This is because, in the substrates **4j-m**, the corresponding substituents present at the *ortho*-positions with respect to the ε-C-H^m bonds perhaps hinder the acetoxylation of the ε-C-H^m bonds. Hence, the corresponding ε-C-H^n acetoxylated products **5j-m** and **8a-c** were selectively obtained. The low yields of the products **5k-m** may be due to the corresponding electron-withdrawing groups (e.g., Cl, Br, NO_2) present at the *para*-position with respect to the ε-C-H^n bond in the substrates **4k-m**. Subsequently, inspired by the successful attempts of the Pd(II)-catalyzed acetoxylation of ε-C-H bond using substrates **4** and **7**, we also attempted the Pd(II)-catalyzed acetoxylation of ζ-C-H bond using substrate **4n**. However, the reaction of substrate **4n** with $PhI(OAc)_2$ failed to give any acetoxylated product (Table 4).

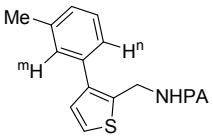
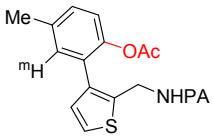
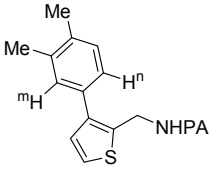
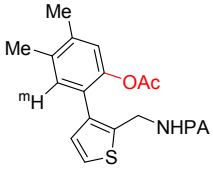
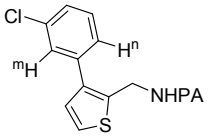
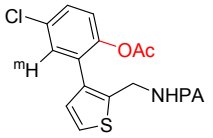
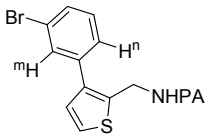
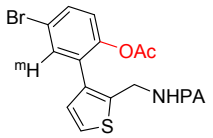
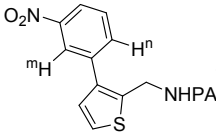
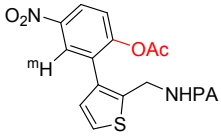
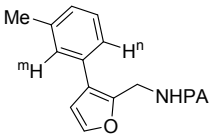
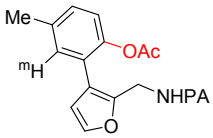
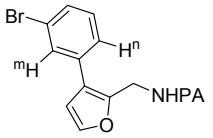
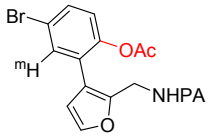
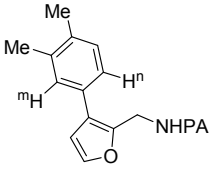
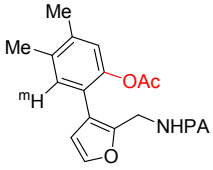
After accomplishing the Pd(II)-catalyzed chemoselective ε-C-H acetoxylation using the bidentate directing group picolinamide (PA), we wished to test the ε-C-H acetoxylation using other bidentate directing groups, such as, pyrazine-2-carboxamide (PyrA)[6h] and oxalylamide (OA).[11c] In this regard, we initially performed the Pd(II)-catalyzed acetoxylation of the pyrazine-2-carboxamide substrates **9a-d** with $PhI(OAc)_2$, which gave the products **10a-d** in 44-57% yields, respectively (Scheme 4). Similar to the PA-directed acetoxylation of substrate **4a** which

gave both the corresponding mono and bis acetoxylation products **5a** and **6a**; the PyrA-directed acetoxylation of substrate **9a** also gave both the corresponding mono and bis acetoxylation products **10a** and **10aA**. Further, the yields obtained for the PA-directed acetoxylation of substrates **4b**,**j**,**l** (46-80%, Table 4) were slightly higher than the yields obtained for the PyrA-directed acetoxylation of substrates **9b-d** (44-57%, Scheme 4). Recently, Yu *et al.* stated[24] that in the directing group-based C-H activation, strongly coordinating N / S/ P heteroatoms often outcompete the directing groups for catalyst binding, thus preventing the C-H activation/functionalization process. In the present case, it seems that the presence of an extra nitrogen atom in the PyrA-BDG did not interfere much with the acetoxylation process. Thus, the efficiency of the pyrazine-2-carboxamide (PyrA) bidentate directing group was comparable to the picolinamide (PA) bidentate directing group.

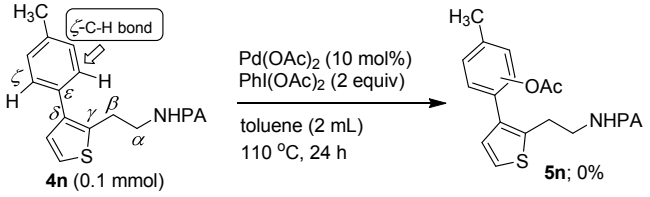
Successively, we attempted the ε-C-H acetoxylation using substrates **11a** and **11b** containing the oxalylamide (OA) directing group (Scheme 4). The Pd(II)-catalyzed acetoxylation of the oxalylamide substrate **11a** with $PhI(OAc)_2$ afforded the expected ε-C-H acetoxylated products **12** (mono OAc) and **13** (bis OAc) in 35 and <15% yields (Scheme 4). Similar to the acetoxylation reaction of substrate **4c**, the acetoxylation of **11a** also afforded the corresponding mono and bis ε-C-H acetoxylated products **12** and **13** were obtained. Finally, the Pd(II)-catalyzed acetoxylation of the oxalylamide substrate **11b** with $PhI(OAc)_2$ afforded the expected product **14** in 48% yield. Similar to the acetoxylation reaction of substrate **4b**, in the substrate **11b** the ε-C-H^n bond was selectively acetoxylated over the ε-C-H^m bond to afford the mono acetoxylated product **14** (Scheme 4).

Table 4. Picolinamide-Aided ε-C-H Acetoxylation of 4/7



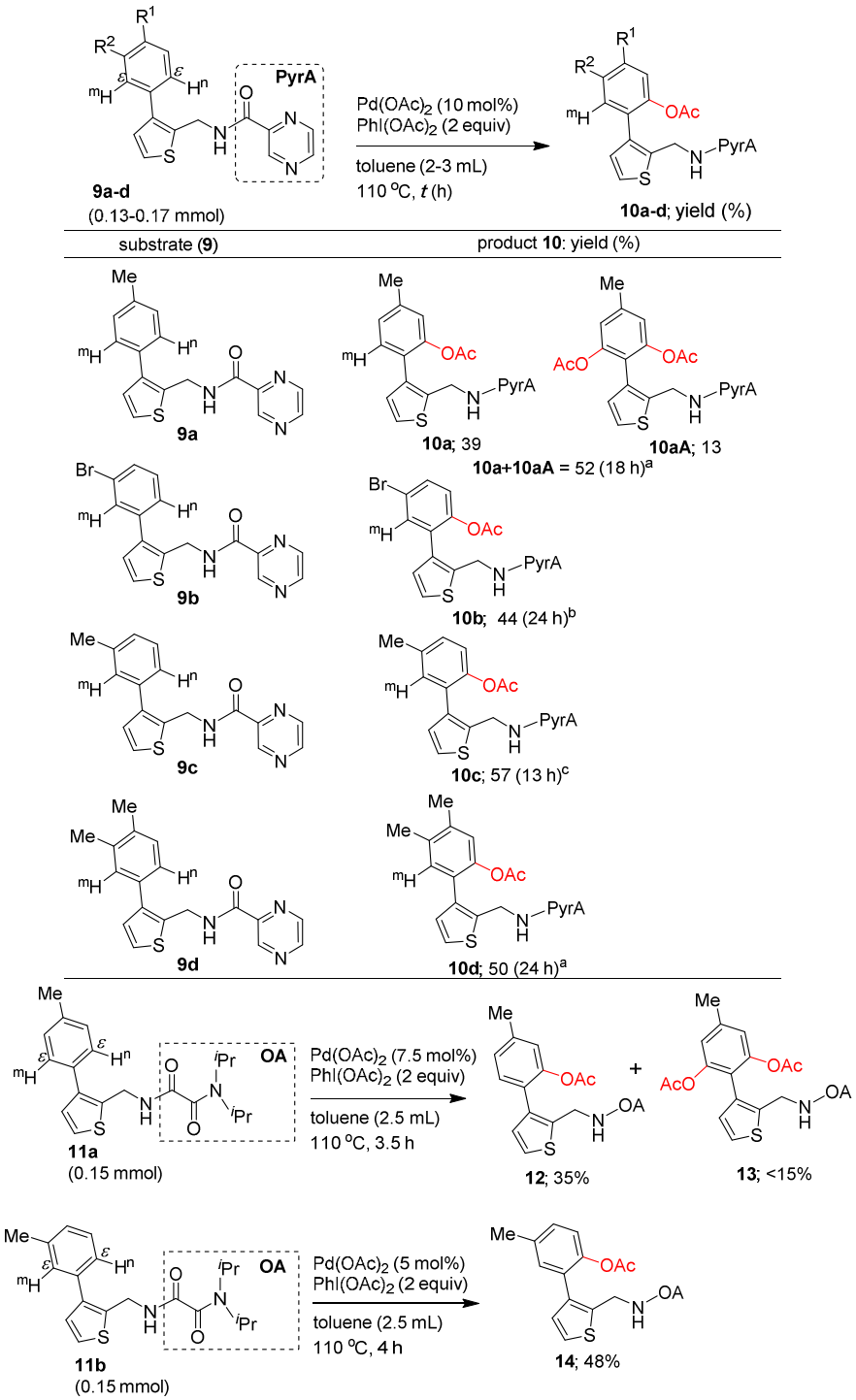
entry	biaryl system (**4**)		*t* (h)	product (**5**)	**5** / **8**: yield (%)
1[a]		**4b**	24		**5b**; 80
2[b]		**4j**	18		**5j**; 60
3[c]		**4k**	16		**5k**; 40
4[c]		**4l**	15		**5l**; 46
5[c]		**4m**	24		**5m**; 32
6[b]		**7a**	18		**8a**; 53
7[d]		**7b**	24		**8b**; 32
8[e]		**7c**	16		**8c**; 35

trial on the remote ζ-C-H acetoxylation



[a] 1 mmol of **4b** was used. [b] 0.18 mmol of **4j/7a** was used. [c] 0.12 mmol of **4k/4l/4m** was used. [d] 0.15 mmol of **7b** was used. [e] 0.2 mmol of **7c** was used.

Scheme 4. Pyrazine-2-Carboxamide and Oxalylamide-Aided ε-C-H Acetoxylation Reactions.



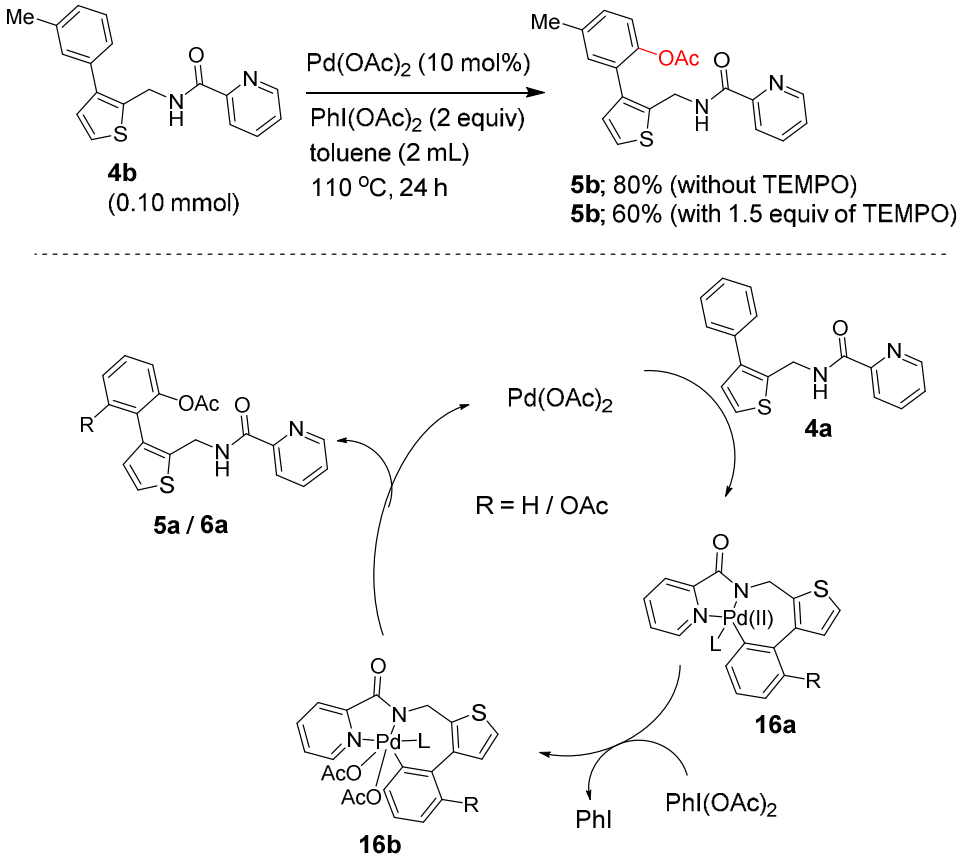
[a] 0.13 mmol of **9a/9d** was used. [b] 0.15 mmol of **9b** was used. [c] 0.17 mmol of **9c** was used.

We faced some difficulty to isolate the corresponding acetoxylated products in pure form from the column chromatography purification process with regard to acetoxylation of the oxalylamide substrates **11a** and **11b**. The acetoxylation reaction need to be performed using 5-7.5 mol% of the $Pd(OAc)_2$ catalyst in <4 h period. The purity of the mono C-H acetoxylated products **12** and **14** is >95%. The NMR spectra of these products revealed the presence of traces of grease and some impurity. The, purity of the bis C-H acetoxylated product **13** is about 85%. Our repetitive efforts to get these compounds in completely pure form were not fruitful. When the acetoxylation of the oxalylamide substrate **11a** was performed using 10 mol% of the catalyst in 5 h, we observed the formation of the expected *ε*-C-H acetoxylated product **13** along with a thiophene C5-acetoxylated product. Similarly, when the acetoxylation of the oxalylamide substrate **11b** was performed using 10 mol% of the catalyst in 5 h, we observed the formation of the expected *ε*-C-H acetoxylated product **14** along with a thiophene C5-acetoxylated product. However, we could not reproduce these results and our trials to get the corresponding thiophene C5-acetoxylated products in pure form led to the decomposition of the products. The ^{1}H NMR of the fractions obtained after column chromatography indicated that the column fractions contained a mixture of compounds and impurities.

It is to be noted that the C(2)-H and C(5)-H bonds of thiophene ring are susceptible for the direct C-H functionalization (e.g. arylation) and the direct functionalization/arylation of the C(2)-H and C(5)-H bonds of the thiophene/furan rings has been well documented in the literature.[25] In the present study comprising the *ε*-C-H acetoxylation of the thiophene-based biaryls **4a-m/9a-d** and furan-based biaryls **7a-c** selectively afforded the corresponding *ε*-C-H acetoxylated products **5a-m/10a-d** and **8a-c**. In these cases, the corresponding bidentate directing

groups, such as, PA and PyrA have effectively directed the ε-C-H acetoxylation of **4a-m/9a-d** and **7a-c** and we did not obtain any of the corresponding thiophene/furan C5-acetoxylated products as the by-products in characterizable amounts.

Scheme 5. Plausible Mechanism for the ε-C-H Acetoxylation of 4a.



While in the literature it is debated that the C-H acetoxylation might occur *via* an oxidative radical mechanism when $PhI(OAc)_2$ is used as an oxidant.[8,12-18] We have found that the reaction of **4b** with $PhI(OAc)_2$ and TEMPO still afforded the product **5b** in 60% yield. This observation indicated that perhaps the ε-C-H acetoxylation of substrates investigated in this work does not proceed *via* the single electron transfer (SET) or free radical pathway. Then, in concurrence with the literature reports,[8,12-18] a plausible mechanism is proposed for the chemoselective ε-C-H acetoxylation of a typical compound **4a** involving the plausible 7-membered palladacycle **16a**,

which is formed after an initial co-ordination followed by the ε-C-H activation. Then, an oxidative addition of **16a** with $PhI(OAc)_2$ followed by the reductive elimination affords the products **5a/6a** (Scheme 5).

The regioselectivity/chemoselectivity of the process comprising the Pd(II)-catalyzed acetoxylation of ε-C-H bonds of aryl rings of **4a-m / 7a-c / 9a-d / 11a,b** and the regiochemistry of the aryl rings of structures of the compounds **5a-m**, **6a-i**, **8a-c**, **10a-d**, and **12-14** were assigned based on the similarity in their ^{1}H NMR spectral pattern and coupling constant values/splitting pattern of the corresponding aryl ring that is subjected to the mono/bis ε-C-H acetoxylation. For example, the proton NMR of the compound **5j** (or **8c** or **10d**) revealed the presence of two singlet peaks for the respective *para* protons of the aryl ring after the ε-C-H acetoxylation of **4j** (or **7c** or **9d**). This observation confirmed that in the substrates **4j** (or **7c** or **9d**), the ε-C-H^n bond was selectively acetoxylated over the ε-C-H^m bond to afford the corresponding mono ε-C-H acetoxylation products (**5a-m**, **8a-c**, **10a-d**, **12** and **14**). Similarly, the double ε-C-H acetoxylation products **6a-i/10aA/13** were assigned based on the similarity in their ^{1}H NMR spectral pattern and coupling constant values/splitting pattern of the corresponding aryl ring that is subjected to ε-C-H acetoxylation. For example, the proton NMR of the compound **6a** revealed the presence of a doublet peak for the respective *para* protons of the aryl ring after the double ε-C-H acetoxylation of **4a**. This observation confirmed that in the substrate **4a**, both the ε-C-H^n and ε-C-H^m bonds were selectively acetoxylated. In an another example, the proton NMR of the compound **6c** revealed the presence of a singlet peak for the respective *para* protons of the aryl ring after the double ε-C-H acetoxylation of **4c**. This confirmed that in the substrate **4c**, both the ε-C-H^n and ε-C-H^m bonds were selectively acetoxylated. Additionally, the proton NMR of all the thiophene-based products **5a-m / 6a-i / 10a-d / 12-14**, revealed the presence of two doublets

with a coupling constant (*J*) value in the range of 5.2 Hz (as usually reported in the literature) for the thiophene C4 and C5 protons respectively. This indicated that the thiophene C4 and C5-protons are intact in the cases of the products **5a-m / 6a-i / 10a-d / 12-14**. Similarly, the proton NMR of the furan-based products **8a-c**, revealed the presence of two doublets with a coupling constant (*J*) value in the range of 1.8 Hz (as usually reported in the literature) for the furan C4 and C5 protons respectively. This indicated that the furan C4 and C5-protons are intact in the cases of the products **8a-c**.

CONCLUSION

In conclusion, we have shown our successful attempts of the Pd(II)-catalyzed, bidentate directing group-aided, chemoselective acetoxylation of remote ε-C(sp^2)-H bond over cyclization using heteroaryl-aryl-based biaryl systems. Notably, the chemoselective acetoxylation of ε-C-H bond was possible in the biaryl substrate **4/7/9/11** and not in the biaryl substrate **2a**. Among the bidentate directing groups used, picolinamide (PA) and pyrazine-2-carboxamide (PyrA) have effectively directed the ε-C-H acetoxylation than the oxalylamide (OA). Given the importance of biaryl systems in medicinal chemistry research,[20a,21] the present work comprising the functionalization of remote ε-C-H bond in biaryl systems will be a contribution towards the enrichment of the library of biaryl systems with the functionalized heteroaryl-aryl-based biaryl systems prepared in this work. Our efforts to remove the bidentate directing group from the biaryl systems after the ε-C-H acetoxylation reactions using the standard reaction conditions were not fruitful at this stage. Nevertheless, we are trying to find a suitable condition for removing of the bidentate directing group from the C-H acetoxylated biaryl systems.

EXPERIMENTAL SECTION

General: IR spectra of compounds were recorded as neat or thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of all compounds were recorded in 400 and 100 MHz spectrometers, respectively, using TMS as an internal standard. The HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography purification was carried out on silica gel (100–200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after work up were dried using anhydrous Na_2SO_4. Reagents were added to the reaction flask using a syringe. Thin layer chromatography (TLC) analysis was performed on alumina plates and components were visualized by observation under iodine vapour. Isolated yields of all the products (Tables 1, 2 and 4 and Schemes 3 and 4) are reported and yields were not optimized. In all the cases, after the Pd(II)-catalyzed acetoxylation reactions, the respective crude reaction mixtures were subjected to column chromatographic purification method. Then, the fractions were collected according to the TLC and in all the cases we focused to isolate the corresponding acetoxylation products reported here to the best of our effort and the column chromatographic purification of the respective crude reaction mixtures did not give and we could not detect any of the corresponding cyclized products in characterizable amount. The starting materials **4a-m / 7a-c / 9a-d / 11a,b** used in this work are known compounds.[6h]

General procedure for assembling the biaryl starting materials 4a-m / 7a-c / 9a-d *via* the Pd(II)-promoted DG-enabled C-H arylation of the C-3 position of the corresponding 2- or 3-(aminoalkyl)-thiophene and furfurylamine derivatives.[6h] A mixture of appropriate 2- or 3-(aminoalkyl)-thiophene and furfurylamine carboxamides (1 equiv, 0.25 mmol), $Pd(OAc)_2$ (10-30 mol%, 5.5-16.7 mg), AgOAc (1-2.2 equiv, 41-82 mg) or Ag_2CO_3 (2.2-4 equiv, 150-273 mg) and

appropriate ArI (3-4 equiv, 0.75-1 mmol) in anhydrous toluene (2.5 mL) was heated at 110 °C for 24–72 h under a nitrogen atm. Then, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography (EtOAc:Hexanes = 40:60) gave the corresponding C3-arylated compounds **4a-m / 7a-c / 9a-d**.

General procedure for obtaining the biaryl scaffolds 11a,b *via* the Pd(II)-promoted DG-enabled C-H arylation of the C-3 position of the corresponding 2-(aminoalkyl)-thiophene derivatives.[6h] A mixture of appropriate 2-(aminoalkyl)-thiophene oxalylamide (1 equiv, 0.25 mmol), $Pd(OAc)_2$ (10 mol%, 5.5 mg), AgOAc (1.2-2.2 equiv, 41-82 mg) and ArI (3-4 equiv, 0.75-1 mmol) in anhydrous toluene (1.5 mL) was heated at 110 °C for 2-8 h under a nitrogen atm. Then, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography (EtOAc:Hexanes = 40:60) gave the corresponding C3-arylated compounds **11a,b**.

General procedure for the Pd(II)-catalyzed acetoxylation of remote *ε*-C(sp^2)-H bond of biaryl systems 4/7/9/11. A dry RB flask (10 mL capacity) containing a mixture of an appropriate biaryl carboxamide **4/7/9/11** (0.15 mmol), $Pd(OAc)_2$ (10 mol%, 3.4 mg) and $PhI(OAc)_2$ (2 equiv, 96.3 mg) in anhydrous toluene (2-2.5 mL) was heated at 110 ^oC for 24 h. After this period, the reaction mixture was cooled to rt, and concentrated in vacuum. The resulting residue was purified by silica gel flash chromatography (EtOAc:Hexanes = 30:70) to give the corresponding *ε*-C-H acetoxylated products (See the corresponding Tables/Schemes for specific entries and conditions).

(6-Methoxythieno[3,2-*c*]isoquinolin-4(5*H*)-yl)(pyridin-2-yl)methanone (3a). The compound **3a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 35:65) as a dark brown colored solid; Yield: 50% (24 mg); R_f = 0.50 (EtOAc/Hexanes = 35:65);

IR (KBr): ν_{max} 2925, 1651, 1475 and 1266 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz, 70 ^oC): δ 8.59 (br. s, 1H), 7.93-7.89 (m, 1H), 7.64 (d, 1H, J = 7.7 Hz), 7.50-7.47 (m, 1H), 7.36-7.20 (m, 3H), 7.08 (d, 1H, J = 7.3 Hz), 6.95 (d, 1H, J = 8.0 Hz), 5.04 (br. s, 1H), 3.85 (s, 3H); HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2S$ $[M+H]^+$ 323.0854 found 323.0861. This compound seems to exist as amide rotomers and we tried to record the NMR for this compound at 70 ^oC. We did not get all the peaks in ^{13}C NMR and a representable ^{13}C NMR spectrum even after 1200 scans and hence, the ^{13}C NMR data is not provided. However, this compound was unambiguously characterized by the X-ray structure analysis.

2-(2-(Picolinamidomethyl)thiophen-3-yl)phenyl acetate (5a). The compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 45% (47 mg) ; R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2927, 1767, 1673, 1518, 1458 and 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 4.6 Hz, 1H), 8.45 (br. s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.45-7.38 (m, 3H), 7.33 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 5.2 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 164.1, 149.7, 148.6, 148.1, 137.7, 137.3, 135.3, 131.3, 129.5, 129.1, 129.0, 126.3, 126.3, 124.1, 122.7, 122.4, 36.8, 20.7; HRMS (ESI): m/z $[M + Na]^+$calcd for $C_{19}H_{16}N_2NaO_3S$: 375.0779; found 375.0769.

2-(2-(Picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6a). The compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 16% (20 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2931, 1768, 1674, 1518, 1458 and 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 4.78 Hz, 1H), 8.55 (br. s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 7.47-7.42 (m, 2H), 7.25 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 5.2 Hz,

1H), 4.62 (d, J = 6.3 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 164.2, 149.9, 149.8, 148.1, 139.5, 137.3, 129.5, 129.4, 128.7, 126.2, 124.3, 124.0, 122.5, 120.4, 36.5, 20.5; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{21}H_{19}N_2O_5S$: 411.1015; found 411.1031.

4-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5b): The compound **5b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 80% (311 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2923, 1761, 1675, 1517 and 1191 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.45 (br. s, 1H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.42 (m, 1H), 7.25 (d, J = 5.2 Hz, 1H), 7.21 (dd, J_1 = 8.1 Hz, J_2 = 1.6 Hz, 1H), 7.17 (d, J = 1.5 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 5.1 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.39 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 164.1, 149.7, 148.1, 146.3, 137.5, 137.3, 136.0, 135.4, 131.8, 129.7, 129.1, 129.1, 126.2, 124.1, 122.4, 122.3, 36.8, 20.9, 20.7; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{20}H_{18}N_2NaO_3S$: 389.0936; found 389.0952.

5-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5c): The compound **5c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 47% (34 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 3055, 2923, 1766, 1675, 1517 and 1202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (m, 1H), 8.44 (br. s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.44 (dd, J_1 = 7.5 Hz, J_2 = 4.7 Hz, 1H), 7.28-7.24 (m, 2H), 7.14 (d, J = 7.7 Hz, 1H), 6.99 (s, 1H), 6.92 (d, J = 5.1 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.41 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.1, 149.7, 148.4, 148.1, 139.5, 137.5, 137.3, 135.4, 131.0, 129.1, 127.1, 126.4, 126.2, 124.0, 123.2, 122.4, 36.8, 21.2, 20.7; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{19}N_2O_3S$: 367.1116; found 367.1130.

5-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6c): The compound **6c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 25% (21 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2931, 1770, 1675, 1464 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (m, 2H), 8.25 (d, J = 7.8 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.44-7.41 (m, 1H), 7.24 (d, J = 5.2 Hz, 1H), 6.92 (d, J = 0.9 Hz, 2H), 6.81 (d, J = 5.2 Hz, 1H), 4.61 (d, J = 6.3 Hz, 2H), 2.42 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.1, 149.8, 149.5, 148.1, 140.0, 139.3, 137.3, 129.6, 128.9, 126.2, 124.2, 122.5, 121.0, 120.8, 36.5, 21.3, 20.5; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{21}N_2O_5S$: 425.1171; found 425.1188.

5-Ethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5d): The compound **5d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 24% (18 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2969, 1769, 1676, 1518 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.44 (br. s, 1H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 2 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.44 (m, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 7.17 (dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1H), 7.0 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 5.1 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.72 (q, J = 7.6 Hz, 2H), 2.10 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.1, 149.7, 148.5, 148.1, 145.7, 137.5, 137.3, 135.4, 131.0, 129.1, 126.6, 126.2, 125.9, 124.0, 122.4, 121.9, 36.8, 28.4, 20.7, 15.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{21}H_{21}N_2O_3S$: 381.1273; found 381.1292.

5-Ethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6d): The compound **6d** was obtained after purification by column chromatography on silica gel

(EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 44% (38 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2978, 1764, 1677, 1449 and 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 2H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.44-7.41 (m, 1H), 7.24 (d, J = 5.2 Hz, 1H), 6.94 (s, 2H), 6.82 (d, J = 5.1 Hz, 1H), 4.62 (d, J = 6.3 Hz, 2H), 2.73 (q, J = 7.6 Hz, 2H), 2.03 (s, 6H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.1, 149.8, 149.6, 148.1, 146.3, 139.3, 137.3, 129.7, 128.9, 126.2, 124.2, 122.4, 120.9, 119.7, 36.5, 28.4, 20.5, 14.7; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{23}H_{23}N_2O_5S$: 439.1328; found 439.1350.

5-Isopropyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6e): The compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 55% (52 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2964, 1770, 1676, 1518 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.53 (m, 2H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.44-7.41 (m, 1H), 7.24 (d, J = 5.2 Hz, 1H), 6.96 (s, 2H), 6.82 (d, J = 5.2 Hz, 1H), 4.62 (d, J = 6.3 Hz, 2H), 3.00-2.93 (m, 1H), 2.03 (s, 6H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.2, 151.0, 149.8, 149.6, 148.1, 139.3, 137.3, 129.8, 128.9, 126.2, 124.2, 122.5, 121.0, 118.4, 36.6, 33.8, 23.6, 20.5; HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{24}H_{24}N_2NaO_5S$: 475.1304; found 475.1290.

5-Methoxy-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5f): The compound **5f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 35% (21 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2937, 1769, 1672, 1518 and 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 4.8 Hz, 1H), 8.43 (br. s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 5.2 Hz, 1H), 6.90-6.87 (m,

1H), 6.72 (d, *J* = 2.4 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.1, 160.1, 149.7, 149.4, 148.1, 137.4, 137.3, 135.2, 131.7, 129.2, 126.2, 124.0, 122.4, 121.6, 112.1, 108.4, 55.6, 36.8, 20.7; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{20}H_{18}N_2NaO_4S$: 405.0885; found 405.0870.

5-Methoxy-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6f): The compound **6f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 27% (18 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2935, 1770, 1674, 1518 and 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (m, 2H), 8.26-8.24 (m, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.41 (m, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 6.81 (d, *J* = 5.2 Hz, 1H), 6.66 (s, 2H), 4.62 (d, *J* = 6.3 Hz, 2H), 3.84 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.2, 160.3, 150.4, 149.8, 148.1, 139.4, 137.3, 129.5, 129.1, 126.2, 124.1, 122.5, 116.0, 106.6, 55.7, 36.5, 20.5; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{21}N_2O_6S$: 441.1120; found 441.1142.

5-Acetyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5g) and 5-acetyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6g): The compounds **5g/6g** were isolated as a mixture and yellow coloured liquid (41 mg, 50%). The column chromatographic purification on silica gel (EtOAc:Hexanes = 35:65), gave the compound **5g/6g** as an inseparable mixture because both compounds have the same R_f values (0.50 (EtOAc/Hexanes = 35:65); repetitive column chromatographic purification of the mixture of compounds **5g/6g** failed to give the corresponding compounds pure compounds. Because of mixture of compounds with similar structure, it was difficult to assign the number of protons; hence, we could not provide the proton and carbon NMR data, however, copies of proton/carbon spectra were included in the NMR spectra section. The NMR spectra of the pure sample

containing the mixture of compounds **5g/6g** showed the signature peaks corresponding to **5g/6g**. Further, the HRMS analysis of the pure sample containing the mixture of compounds **5g/6g** confirmed the presence of **5g** and **6g** in the mixture. **5g**. HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{21}H_{18}N_2NaO_4S$: 417.0885; found 417.0908. **6g**. HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{23}H_{20}N_2NaO_6S$: 475.0940; found 475.0922.

5-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5h): The compound **5h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 36% (41 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2928, 1770, 1674, 1518 and 1188 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.43 (s, 1H), 8.23 (dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.46-7.43 (m, 1H), 7.32-7.31 (m, 2H), 7.27 (d, J = 5.2 Hz, 1H), 7.20 (dd, J_1 = 1.6 Hz, J_2 = 0.7 Hz, 1H), 6.90 (d, J = 5.2 Hz, 1H), 4.69 (d, J = 6.1 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.1, 149.6, 149.0, 148.1, 138.1, 137.4, 134.2, 134.1, 132.0, 128.8, 128.2, 126.6, 126.3, 124.4, 123.3, 122.4, 36.8, 20.6; HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{19}H_{15}ClN_2NaO_3S$: 409.0390; found 409.0388.

5-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6h): The compound **6h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 19% (25 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2931, 1773, 1676, 1518 and 1184 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (m, 2H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.26 (d, J = 5.2 Hz, 1H), 7.13 (s, 2H), 6.80 (d, J = 5.2 Hz, 1H), 4.61 (d, J = 6.3 Hz, 2H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 164.2, 150.1, 149.7, 148.1,

139.8, 137.3, 134.4, 128.6, 128.5, 126.3, 124.6, 122.9, 122.5, 121.1, 36.5, 20.4; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{21}H_{18}ClN_2O_5S$: 445.0625; found 445.0646.

5-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5i): The compound **5i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 37% (38 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2923, 1768, 1672, 1516 and 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.43 (br. s, 1H), 8.23 (dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.47-7.42 (m, 2H), 7.36 (d, J = 1.9 Hz, 1H), 7.28-7.25 (m, 2H), 6.90 (d, J = 5.2 Hz, 1H), 4.69 (d, J = 6.1 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 164.1, 149.6, 149.0, 148.1, 138.1, 137.4, 134.1, 132.3, 129.5, 128.8, 128.7, 126.3, 126.1, 124.4, 122.4, 121.8, 36.8, 20.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{16}BrN_2O_3S$: 431.0065; found 431.0051.

5-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (6i): The compound **6i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 25% (29 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 1772, 1674, 1518, and 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (m, 2H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.46-7.42 (m, 1H), 7.28 (s, 2H) 7.25 (d, J = 5.2 Hz, 1H), 6.79 (d, J = 5.2 Hz, 1H), 4.60 (d, J = 6.1 Hz, 2H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 164.2, 150.2, 149.7, 148.1, 139.8, 137.3, 128.6, 128.5, 126.3, 124.6, 124.0, 123.5, 122.5, 121.6, 36.5, 20.4; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{21}H_{17}BrN_2NaO_5S$: 510.9939; found 510.9930.

4,5-Dimethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5j): The compound **5j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 60% (41 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR

(CH_2Cl_2): ν_{max} 2973, 1766, 1675, 1636 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.45 (br. s, 1H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.41 (m, 1H), 7.23 (d, J = 5.1 Hz, 1H), 7.13 (s, 1H), 6.94 (s, 1H), 6.92 (d, J = 5.2 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 164.0, 149.7, 148.1, 146.3, 137.8, 137.3, 137.2, 135.5, 134.7, 132.2, 129.2, 126.4, 126.2, 124.0, 123.4, 122.4, 36.8, 20.7, 19.7, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{21}H_{20}N_2NaO_3S$: 403.1092; found 403.1110.

4-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5k): The compound **5k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 40% (18 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 1767, 1675, 1639, 1517 and 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (m, 1H), 8.45 (br. s, 1H), 8.23 (dt, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 7.87 (td, J_1 = 7.3 Hz, J_2 = 1.7 Hz, 1H), 7.46-7.43 (m, 1H), 7.39-7.36 (m, 2H), 7.27 (d, J = 5.2 Hz, 1H), 7.12-7.10 (m, 1H), 6.91 (d, J = 5.2 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.1 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.1, 149.6, 148.1, 147.1, 138.3, 137.4, 133.8, 131.6, 131.2, 131.1, 129.0, 128.8, 126.3, 124.5, 124.0, 122.4, 36.7, 20.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{16}ClN_2O_3S$: 387.0570; found 387.0575.

4-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5l): The compound **5l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 46% (23 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 3363, 1762, 1675, 1517 and 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (m, 1H), 8.44 (br. s, 1H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.53-7.50 (m, 2H), 7.46-7.43 (m, 1H), 7.26 (d, J = 5.2 Hz, 1H), 7.06-7.04 (m, 1H), 6.90 (d, J =

5.2 Hz, 1H), 4.70 (d, J = 6.1 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 164.1, 149.6, 148.1, 147.7, 138.3, 137.4, 134.0, 133.7, 132.0, 131.6, 128.8, 126.3, 124.5, 124.4, 122.4, 119.3, 36.7, 20.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{16}BrN_2O_3S$: 431.0065; found 431.0078.

4-Nitro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (5m): The compound **5m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a yellow coloured liquid; Yield: 32% (15 mg); R_f = 0.50 (EtOAc/Hexanes = 40:60); IR (CH_2Cl_2): ν_{max} 2940, 1769, 1674, 1520 and 1189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.43 (br. s, 1H), 8.29-8.26 (m, 2H), 8.21 (dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.87 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.47-7.43 (m, 1H), 7.37-7.34 (m, 1H), 7.33 (d, J = 5.2 Hz, 1H), 6.95 (d, J = 5.2 Hz, 1H), 4.71 (d, J = 6.1 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 164.1, 153.4, 149.4, 148.1, 145.6, 139.0, 137.4, 132.8, 131.2, 128.7, 126.8, 126.4, 124.9, 124.4, 123.9, 122.4, 36.7, 20.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{16}N_3O_5S$: 398.0811; found 398.0826.

4-Methyl-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (8a): The compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 35:65) as a yellow coloured liquid; Yield: 53% (33 mg); R_f = 0.50 (EtOAc/Hexanes = 35:65); IR (CH_2Cl_2): ν_{max} 1762, 1676, 1521, 1435 and 1194 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.35 (br. s, 1H), 8.24-8.22 (m, 1H),7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.42 (m, 2H), 7.20 (d, J = 1.9 Hz, 1H), 7.16 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 1.8 Hz, 1H), 4.68 (d, J = 5.8 Hz, 2H), 2.36 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.1, 149.7, 148.1, 147.5, 146.2, 141.9, 137.3, 136.1, 131.7, 129.5, 126.2, 125.9, 122.4, 119.0, 112.2, 35.3, 20.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{19}N_2O_4$: 351.1345; found 351.1349.

4-Bromo-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (8b): The compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 35:65) as a yellow coloured liquid; Yield: 32% (19 mg); R_f = 0.50 (EtOAc/Hexanes = 35:65); IR (CH_2Cl_2): ν_{max} 2928, 1764, 1674, 1521 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.34 (br. s, 1H), 8.23 (dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.47-7.42 (m, 3H), 7.02 (d, J = 8.6 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 4.68 (d, J = 5.8 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.2, 149.6, 148.1, 148.0, 147.5, 142.1, 137.3, 133.8, 131.7, 128.5, 126.3, 124.4, 122.4, 119.3, 117.7, 112.0, 35.3, 20.8; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{19}H_{15}BrN_2NaO_4$: 437.0113; found 437.0100.

4,5-Dimethyl-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (8c): The compound **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 35:65) as a yellow coloured liquid; Yield: 35% (25 mg); R_f = 0.50 (EtOAc/Hexanes = 35:65); IR (CH_2Cl_2): ν_{max} 2919, 1761, 1674, 1519 and 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.34 (br. s, 1H), 8.23 (dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.43 (m, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.15 (s, 1H), 6.91 (s, 1H), 6.41 (d, J = 1.8 Hz, 1H), 4.68 (d, J = 5.7 Hz, 2H), 2.27 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 164.1, 149.7, 148.1, 147.3, 146.2, 141.8, 137.6, 137.3, 134.8, 132.0, 126.2, 123.5, 123.2, 122.4, 118.9, 112.3, 35.3, 20.9, 19.6, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{21}H_{20}N_2NaO_4$: 387.1321; found 387.1309.

5-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (10a): The compound **10a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 45:55) as a yellow coloured liquid; Yield: 39% (15 mg); R_f = 0.50 (EtOAc/Hexanes = 45:55); IR (CH_2Cl_2): ν_{max} 2969, 1766, 1676, 1521 and 1203 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$): δ 9.43 (d, *J* = 1.4 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.51 (dd, J_1 = 2.4 Hz, J_2 = 1.4 Hz, 1H), 8.19 (br. s, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, J_1 = 7.7 Hz, J_2 = 0.8 Hz, 1H), 6.98 (s, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 4.72 (d, *J* = 6.1 Hz, 2H), 2.41 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 162.7, 148.4, 147.3, 144.6, 144.4, 142.6, 139.6, 136.8, 135.7, 130.9, 129.2, 127.2, 126.3, 124.2, 123.1, 36.7, 21.2, 20.7; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{19}H_{17}N_3NaO_3S$: 390.0888; found 390.0875.

5-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)-1,3-phenylene diacetate (10aA): The compound **10aA** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 45:55) as a yellow coloured liquid; Yield: 13% (7 mg); R_f = 0.45 (EtOAc/Hexanes = 45:55); IR (CH_2Cl_2): ν_{max} 2927, 1761, 1677, 1520 and 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.74 (d, *J* = 2.4 Hz, 1H), 8.52 (s, 1H), 8.32 (br. s, 1H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.91 (s, 2H), 6.82 (d, *J* = 5.2 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 162.8, 149.5, 147.2, 144.6, 144.6, 142.6, 140.3, 138.7, 129.9, 129.0, 124.5, 121.0, 120.8, 36.5, 21.3, 20.5; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{21}H_{19}N_3NaO_5S$: 448.0943; found 448.0929.

4-Bromo-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (10b): The compound **10b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 45:55) as a yellow coloured liquid; Yield: 44% (28 mg); R_f = 0.50 (EtOAc/Hexanes = 45:55); IR (CH_2Cl_2): ν_{max} 2927, 1762, 1676, 152, 1477 and 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (d, *J* = 1.4 Hz, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 8.53-8.52 (m, 1H), 8.19 (br. s, 1H), 7.53-7.50 (m, 2H), 7.28 (d, *J* = 5.2 Hz, 1H), 7.05-7.03 (m, 1H), 6.91 (d, *J* = 5.2 Hz, 1H), 4.73 (d, *J* = 6.1 Hz, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 162.8,

147.7, 147.4, 144.6, 144.2, 142.6, 137.7, 134.0, 134.0, 132.1, 131.6, 128.8, 124.6, 124.3, 119.3, 36.6, 20.6; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{18}H_{14}BrN_3NaO_3S$: 453.9837; found 453.9820.

4-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (10c): The compound **10c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 45:55) as a colourless liquid; Yield: 57% (35 mg); R_f = 0.50 (EtOAc/Hexanes = 45:55); IR (CH_2Cl_2): ν_{max} 2931, 1762, 1677, 1522 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (d, *J* = 1.2 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.51 (dd, J_1 = 2.3 Hz, J_2 = 1.5 Hz, 1H), 8.21 (br. s, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.20 (dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 4.74 (d, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 162.7, 147.3, 146.3, 144.6, 144.4, 142.6, 136.8, 136.1, 135.7, 131.7, 129.8, 129.1, 129.0, 124.2, 122.3, 36.7, 20.9, 20.7; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{18}N_3O_3S$: 368.1069; found 368.1072.

4,5-Dimethyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (10d): The compound **10d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 45:55) as a colourless liquid; Yield: 50% (24 mg); R_f = 0.50 (EtOAc/Hexanes = 45:55); IR (CH_2Cl_2): ν_{max} 2927, 1760, 1676, 1521 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (d, *J* = 1.2 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.51 (dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz, 1H), 8.20 (br. s, 1H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.11 (br. s, 1H), 6.94 (s, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.7, 147.3, 146.3, 144.6, 144.4, 142.6, 138.0, 136.6, 135.8, 134.7, 132.1, 129.2, 126.4, 124.1, 123.4, 36.7, 20.7, 19.7, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{20}H_{19}N_3NaO_3S$: 404.1045; found 404.1031.

2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-5-methylphenyl acetate

(12): The compound **12** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 35% (22 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2925, 1767, 1676, 1633, 1446 and 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.1 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.14 (br. s, 1H), 6.96 (br. s, 1H), 6.90 (d, *J* = 5.1 Hz, 1H), 4.62-4.56 (m, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.53-3.46 (m, 1H), 2.41 (s, 3H), 2.05 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 163.0, 162.9, 148.4, 139.6, 136.3, 135.8, 130.8, 129.1, 127.2, 126.2, 124.2, 123.1, 46.7, 46.4, 36.2, 21.2, 20.8, 20.7, 20.0; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{22}H_{28}N_2NaO_4S$: 439.1667; found 439.1649. Note: The purity of this compound is about 95% and this compound contains traces of grease and some impurity. Our repetitive efforts to get this compound **12** in completely pure form failed.

2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-5-methyl-1,3-phenylene diacetate (13): The compound **13** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: <15% (10 mg); R_f = 0.45 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2973, 1771, 1638, 1368 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.3 Hz, 1H), 7.21 (br. s, 1H), 6.90 (s, 2H), 6.81 (d, *J* = 5.3 Hz, 1H), 4.58-4.51 (m, 1H), 4.44 (d, *J* = 6.1 Hz, 2H), 3.53-3.46 (m, 1H), 2.42 (s, 3H), 2.00 (s, 6H), 1.42 (d, *J* = 6.8 Hz, 6H), 1.21 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.3, 163.1, 149.4, 140.3, 138.1, 130.0, 129.0, 124.5, 121.0, 120.7, 49.7, 46.3, 36.1, 21.3, 20.8, 20.4, 20.0; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{24}H_{31}N_2O_6S$: 475.1903; found 475.1898. Note: The purity of this compound is about 85% and this compound contains some impurity. Our repetitive efforts to get this compound **13** in completely pure form failed.

2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-4-methylphenyl acetate (14): The compound **14** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow coloured liquid; Yield: 48% (32 mg); R_f = 0.50 (EtOAc/Hexanes = 30:70); IR (CH_2Cl_2): ν_{max} 2973, 1766, 1636 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.1 Hz, 1H), 7.22-7.19 (m, 2H), 7.13 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 5.2 Hz, 1H), 4.63-4.56 (m, 1H), 4.53 (d, *J* = 5.9 Hz, 2H), 3.53-3.47 (m, 1H), 2.39 (s, 3H), 2.05 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 163.0, 162.9, 146.3, 136.4, 136.1, 135.9, 131.6, 129.8, 129.1, 128.9, 124.3, 122.3, 49.7, 46.4, 36.3, 20.9, 20.8, 20.6, 20.0; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{22}H_{28}N_2NaO_4S$: 439.1667; found 439.1652. Note: The purity of this compound is about 95% and this compound contains traces of some impurity. Our repetitive efforts to get this compound **14** in completely pure form failed.

ASSOCIATED CONTENT

Supporting Information

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

The X-ray structure and brief X-ray structure data of the data of compound **3a**, copies of $^1H/^{13}C$ NMR charts, HRMS analysis of compounds and copies of crude NMR spectra of experiments related to Table 3 (PDF)

X-ray structure data of compound **3a** (cif)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank IISER-Mohali for providing the financial support for this work and access to the central analytical (NMR, HRMS and X-ray) facilities and X-ray facility of the Department of Chemical Sciences. V. R. and Naveen respectively thank the CSIR and UGC, New Delhi for providing SRF fellowship. B. G. thanks DST, New Delhi for providing the INSPIRE PhD Fellowship. We thank the reviewers for giving valuable suggestions.

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