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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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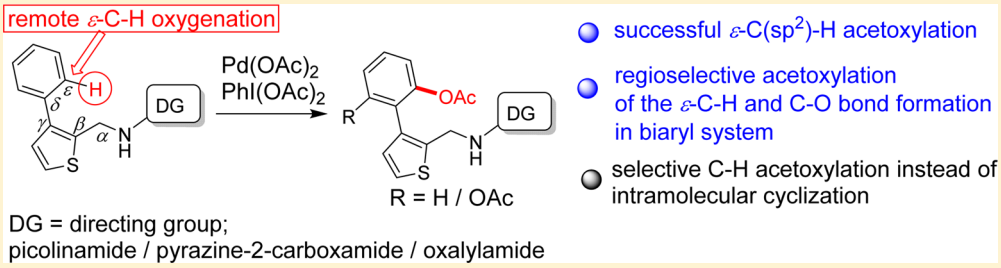
Supporting Information



ABSTRACT: In this Article, 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 the appropriate carboxamide systems were well documented, there exist only rare reports dealing with the C−H activation and functionalization of remote ε-C−H bonds of appropriate substrates. Especially, the BDG-aided chemoselective acetoxylation of the 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 was 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 into a C−O bond has also received substantial attention.[8,12−18] In particular, the acetoxylation of sp^2 C−H bonds of arenes is considered a direct and efficient method for synthesizing phenolic compounds, which are important substances in industry and academic research.[19]

The BDG-aided acetoxylation of sp^2/sp^3 β- and γ-C−H bonds of appropriate carboxamide systems was 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 the 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 a remote δ- or ε-C−H bond of a suitable substrate is

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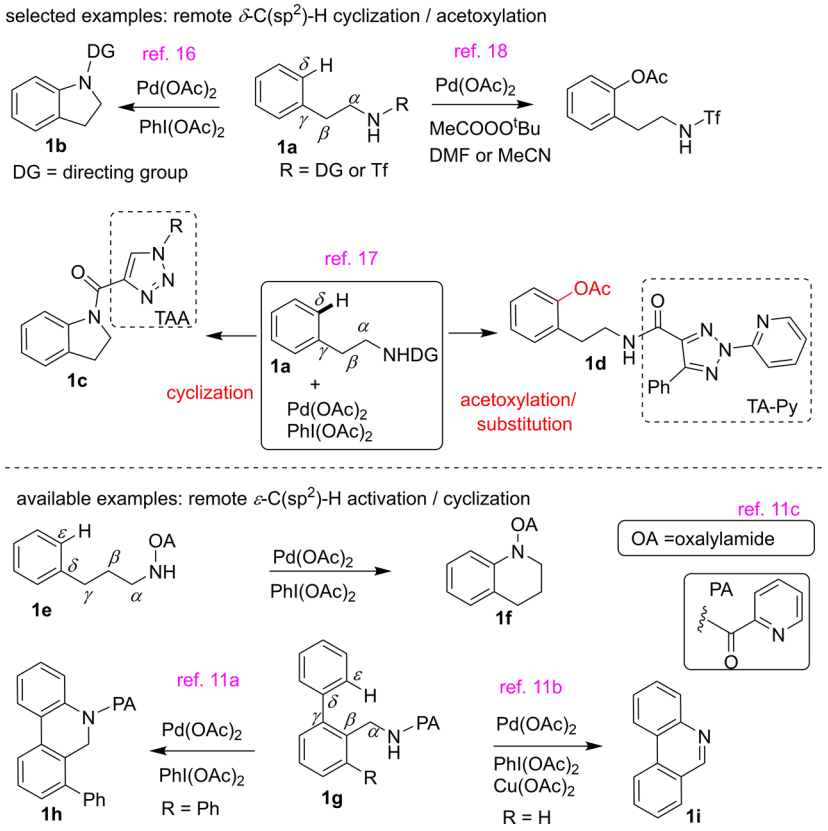
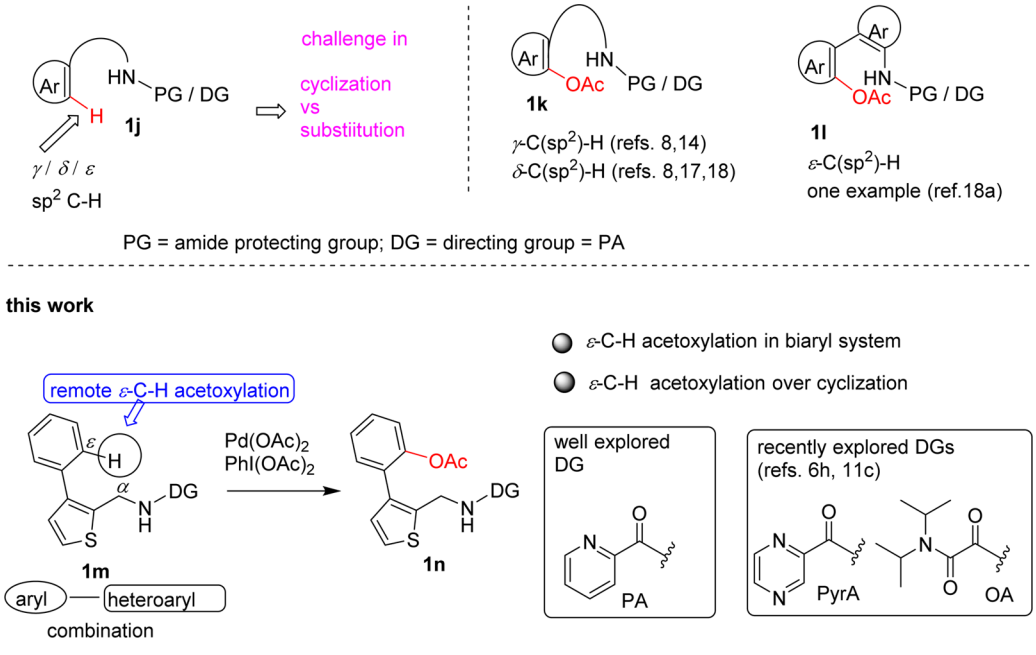
Scheme 1. Functionalization of Remote δ- and ε-C(sp^2)−H Bonds



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



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 a remote ε-C(sp^2)−H bond, the Daugulis,[11a] Chen,[11b] and Zhao[11c] groups have independently revealed that the reactions of 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 the remote δ-C(sp^2)−H bond using alcohol as a cosolvent. 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 the remote δ-C(sp^2)−H bond was achieved

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

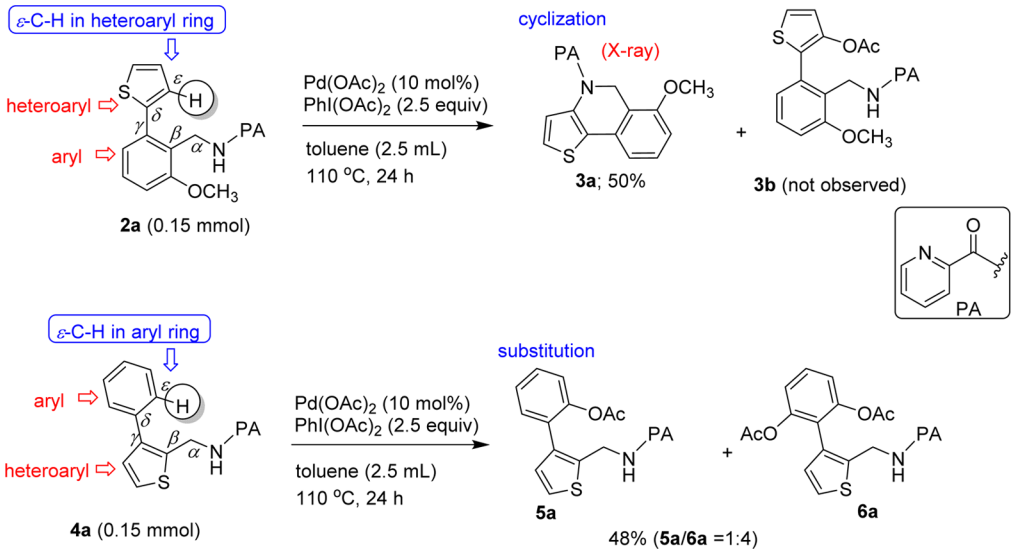
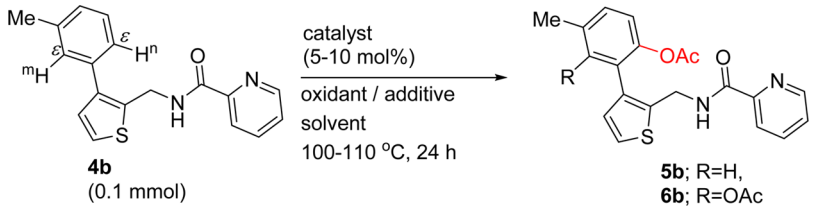


Table 1. Picolinamide-Aided ε-C−H Acetoxylation of 4b[22]



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

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 mentioning 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 the 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 the 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 the remote ε-C(sp^2)−H bond using the heteroaryl−aryl-based biaryl system **1m** (Scheme 2).

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

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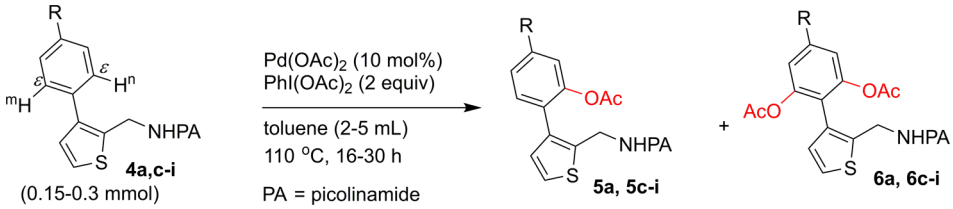
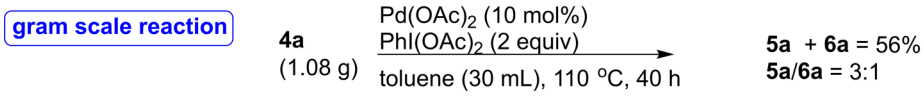
Table 2. Picolinamide-Aided ε-C−H Acetoxylation of 4a and 4c−i



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]	**4a**	30	**5a**; 45	**6a**; 16	61
3[a,d]	**4a**	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



[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**.

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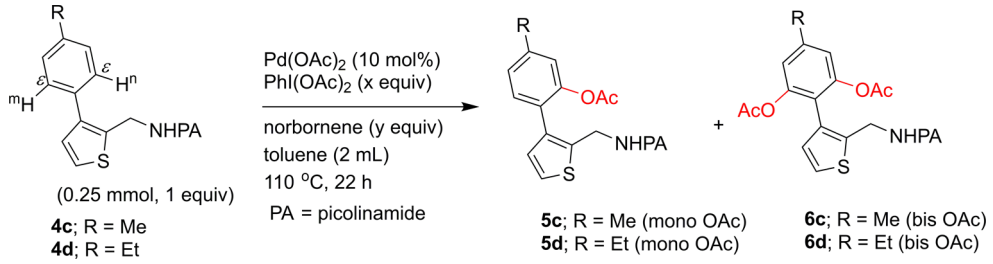
Table 3. Trials To Improve the Chemoselectivity in the Pd(II)-Catalyzed Directed ε-C−H Acetoxylation of 4a and 4d Using Norbornene Additive[a]



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.

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

To begin 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). We then 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.

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. Among 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 was 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 equivalents 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. We then 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**).

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

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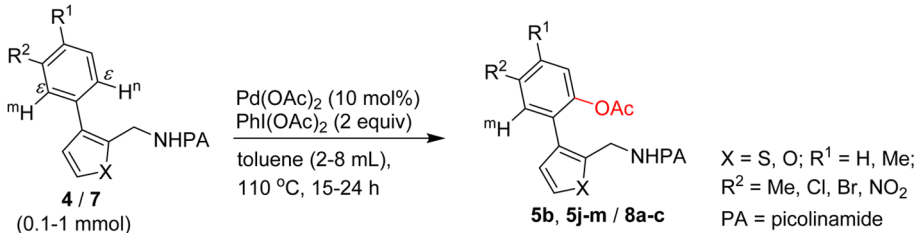
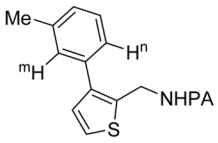
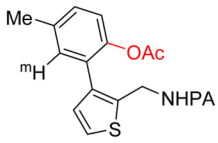
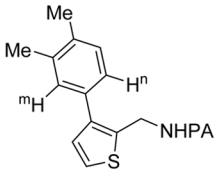
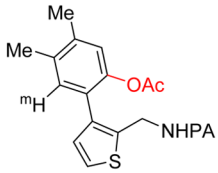
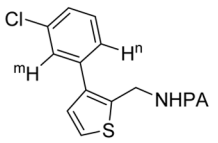
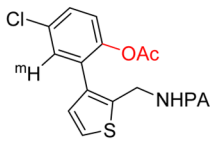
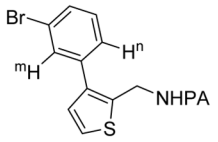
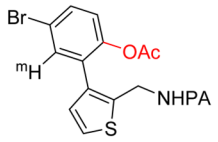
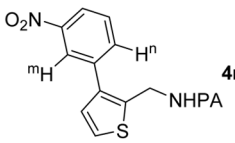
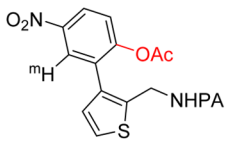
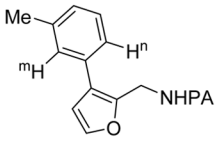
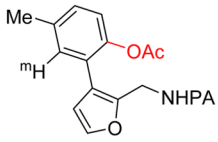
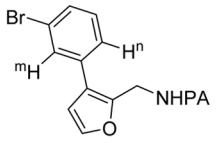
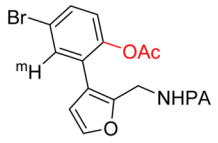
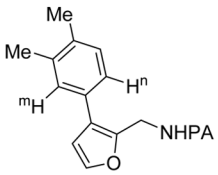
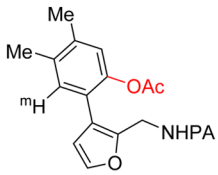
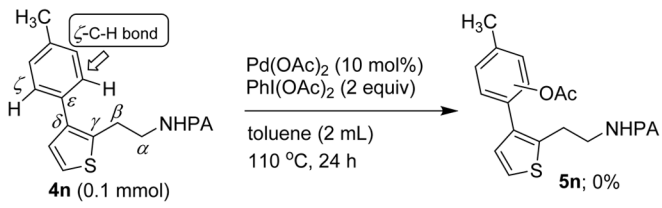
Table 4. Picolinamide-Aided ε-C−H Acetoxylation of 4/7



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.

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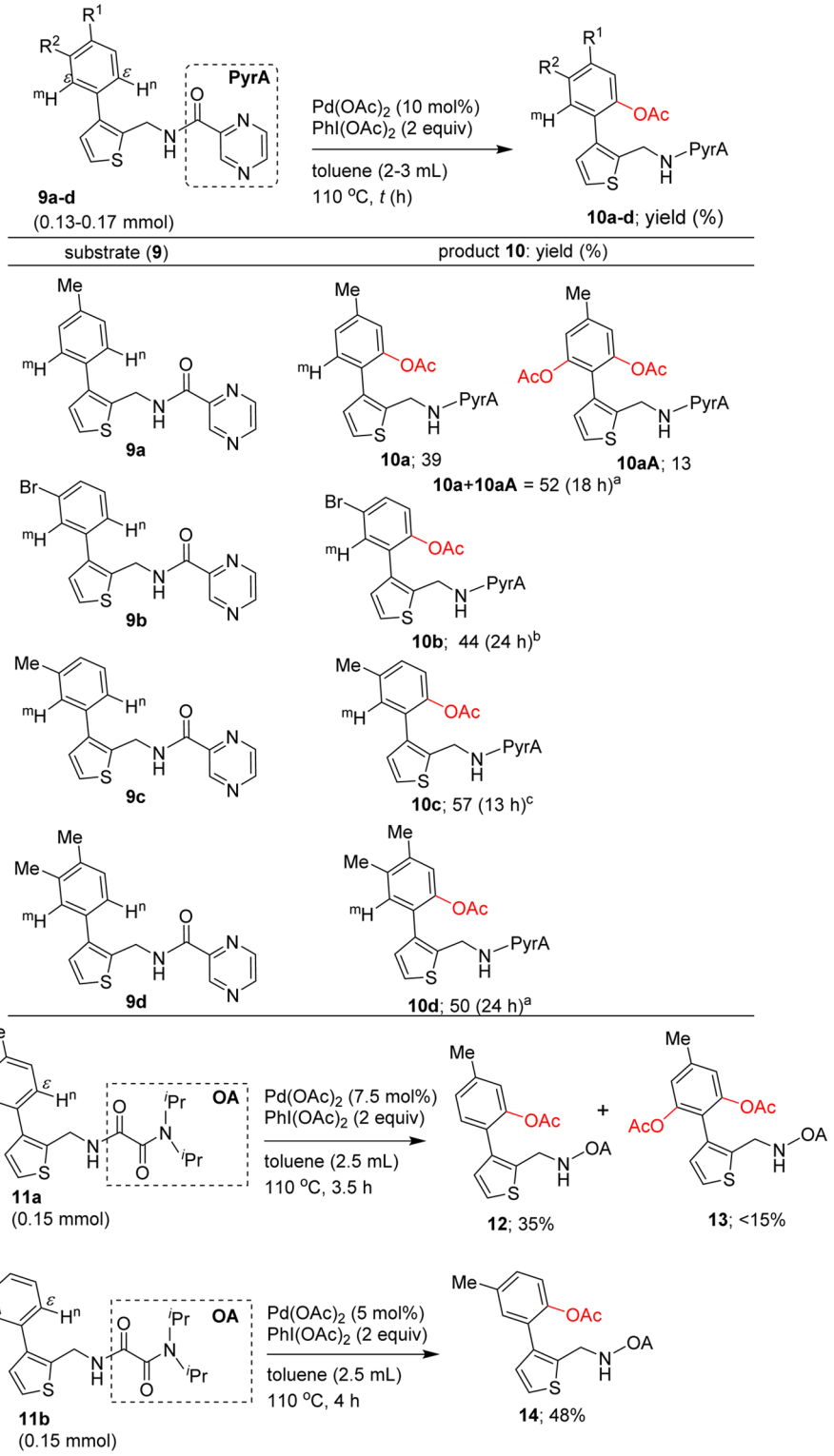
Scheme 4. Pyrazine-2-carboxamide and Oxalylamide-Aided ε-C−H Acetoxylation Reactions[a]



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

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

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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, these reactions showed the formation of products **5c**/**6c** in low yields (15−28% 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 equivalents of $PhI(OAc)_2$. We then 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** was not fruitful, and, apparently, the corresponding acetoxylated products were obtained in low yields when compared to the reactions carried out without norbornene.

Next, 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). We then 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 that of 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**. 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).

We faced some difficulty in isolating 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 needed to be performed using 5−7.5 mol % of the $Pd(OAc)_2$ catalyst in a <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

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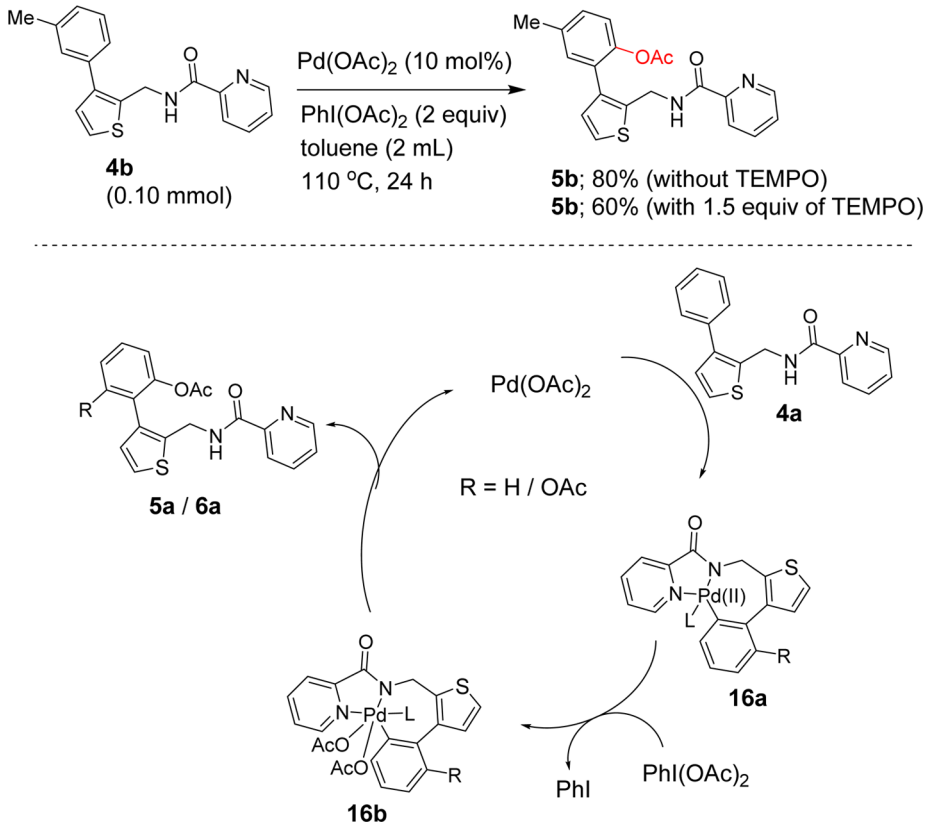
Scheme 5. Plausible Mechanism for the ε-C−H Acetoxylation of 4a



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 spectrum 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 the 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] 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 byproducts in characterizable amounts.

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. 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 seven-membered palladacycle **16a**, which is formed after an initial coordination followed by the ε-C−H activation. Next, 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 on the basis of 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 on the basis of 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

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confirmed that in the substrate **4a**, both the ε-C−H^n and the ε-C−H^m bonds were selectively acetoxylated. In 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 the ε-C−H^m bonds were selectively acetoxylated. Additionally, the proton NMR of all of 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

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 better 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 toward 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 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 workup 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 vapor. Isolated yields of all of the products (Tables 1, 2, and 4 and Schemes 3 and 4) are reported, and yields were not optimized. In all of the cases, after the Pd(II)-catalyzed acetoxylation reactions, the respective crude reaction mixtures were subjected to column chromatographic purification method. The fractions then were collected according to the TLC; in all of 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. The reaction mixture then was concentrated in a 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. The reaction mixture then 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 °C 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(5H)-yl) (Pyridin-2-yl)-methanone (**3a**).* 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}. ^{1}H NMR (CD_3CN, 400 MHz, 70 °C): 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 °C. We did not get all of the peaks in ^{13}C NMR and a representable ^{13}C NMR spectrum even after 1200 scans, and hence the ^{13}C NMR data are not provided. However, this compound was unambiguously characterized by the X-ray structure analysis.

*2-(2-(Picolinamidomethyl)thiophen-3-yl)phenyl Acetate (**5a**).* Compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 4.78 Hz, 1H), 8.55

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(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**).* Compound **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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**).* Compound **5c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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**).* Compound **6c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **5d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **5f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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**).* Compounds **5g**/**6g** were isolated as a mixture and yellow colored liquid (41 mg, 50%). 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 as pure compounds. Because of the 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, yet 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**).* Compound **5h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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,

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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**).* Compound **6h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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**).* Compound **5i** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **6i** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55−8.54 (m, 2H), 8.24 (dt, J_1 = 7.8 Hz, J_2 = 1.0 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**).* Compound **5j** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{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 = 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**).* Compound **5k** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **5l** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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}. ^{1}H 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**).* Compound **5m** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow colored 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**).* Compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 35:65) as a yellow colored 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**).* Compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 35:65) as a yellow colored 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}. ^{1}H 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**).* Compound **8c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 35:65) as a yellow colored 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}. ^{1}H 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**).* Compound **10a** was obtained after purification

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by column chromatography on silica gel (EtOAc:hexanes = 45:55) as a yellow colored 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**).* Compound **10aA** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 45:55) as a yellow colored 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}. ^1H 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**).* Compound **10b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 45:55) as a yellow colored liquid. Yield: 44% (28 mg). R_f = 0.50 (EtOAc/hexanes = 45:55). IR (CH_2Cl_2): ν_{max} 2927, 1762, 1676, 1521, 1477, and 1190 cm^{-1}. ^1H 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**).* Compound **10c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 45:55) as a colorless 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**).* Compound **10d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 45:55) as a colorless 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**).* Compound **12** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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 compound **12** in completely pure form failed.

*2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-5-methyl-1,3-phenylene Diacetate (**13**).* Compound **13** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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 compound **13** in completely pure form failed.

*2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-4-methylphenyl Acetate (**14**).* Compound **14** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored 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 compound **14** in completely pure form failed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01933.

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)

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Notes

The authors declare no competing financial interest.

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