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Palladium-Catalysed Direct 5-Arylation of Furfurylamine or 2-(Aminoalkyl)-thiophene Derivatives

Julien Roger[a] and Henri Doucet*[a]

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The palladium-catalysed direct 5-arylation of furan or thiophene derivatives bearing CH_2NHR substituents (with R = COMe or CO_2tBu) generally proceeds in good yields by using a catalysts loading of only 0.1–2 mol-%. A wide range of functions such as acetyl, propionyl, formyl, ester, nitrile, trifluoromethyl or fluoro on the aryl bromide is tolerated. Higher yields were generally obtained in the presence of electron-deficient aryl bromides than with electron-rich aryl bromides.

Introduction

Easy access to a variety of furan or thiophene derivatives bearing functional groups such as amino or amide is an important field for research in organic chemistry due to the biological properties of some of these derivatives (Figure 1).

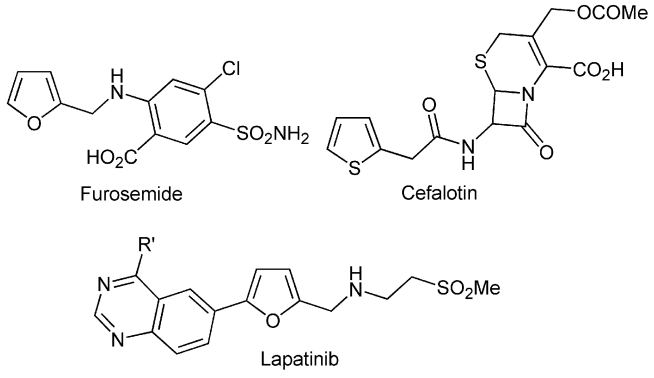
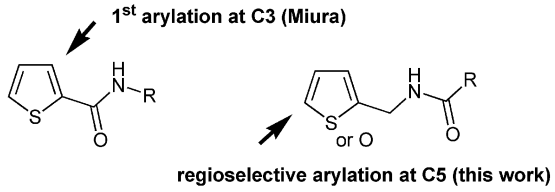


Figure 1. Examples of bioactive furan or thiophene derivatives.

In 1990, Ohta and co-workers reported that the direct 2- or 5-arylation of several heteroaromatics, including furans and thiophenes, with aryl halides proceeded in moderate to good yields by using $Pd(PPh_3)_4$ as the catalyst.[1] Since these results, the palladium-catalysed direct arylation of heteroaryl derivatives with aryl halides has proved to be a very powerful method for the synthesis of a wide variety of arylated heterocycles.[2–6] The direct arylation of quite simple and nonreactive furan, thiophene or thiazole derivatives has been largely described. On the other hand, heteroaromatics bearing aminoalkyl substituents have been rarely employed.[7–12] A few furan or thiophene derivatives substituted at C2 or C3 by an amide or a carbamate have been employed in palladium-catalysed direct intramolecular cyclisations.[7,8] Intermolecular direct arylation with the use of a thiophene with a carboxanilide function at C2 was reported by Miura and co-workers.[9] With this substrate, the carbamoyl group acts as a directing group for the arylation at the 3-position, after which it is cleaved in some cases to give 2,3,5-triarylthiophenes (Scheme 1, left).[9a] With such substrates, the formation of mixtures of 5-arylated and 3,5-diarylated thiophenes has also been observed.[9b] This group also studied the reactivity of *N*-phenyl-3-thiophenecarboxamide.[9c] This reactant was successfully triarylated at C2, C4 and C5.



Scheme 1. Regioselectivity of the arylation of thiophene derivatives.

The palladium-catalysed direct 5-arylation of furfurylamine or 2-(aminoalkyl)thiophene derivatives should provide a cost-effective and an environmentally attractive method for the preparation of arylated furfurylamine or 2-(aminoalkyl)thiophene derivatives. To the best of our knowledge, only one example of intermolecular direct arylation of such substrates has been reported so far, and the coupling product was obtained in 46% yield.[13] The major byproducts of the reaction would be a base associated to HX, instead of metallic salts produced under more classical cross-coupling procedures[14] such as Suzuki, Negishi or Stille reactions. The method avoids the preliminary preparation of the requisite organometallic, reducing the number of steps to prepare these compounds. Moreover, the use of some furan derivatives in organic synthesis, such as furfur-

[a] Institut Sciences Chimiques de Rennes, UMR 6226 CNRS – Université de Rennes 1, "Catalyse et Organometalliques", Campus de Beaulieu, 35042 Rennes, France
Fax: +33-2-23236939
E-mail: henri.doucet@univ-rennes1.fr

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ylamine, which can be obtained from agricultural wastes, is an important field of research in green chemistry. Herein, we wish to report on the use of furfurylamine or 2-(aminoalkyl)thiophene derivatives for palladium-catalysed direct arylation by using a wide variety of electronically and sterically diverse aryl or heteroaryl bromides at moderate to low catalyst loadings.

Results and Discussion

To determine the reactivity of furfurylamine in the palladium-catalysed direct arylation reactions, a set of direct arylation reactions in the presence of 4-bromobenzotrifluoride as the coupling partner, using several reaction conditions, was examined (Scheme 2, Table 1). We observed that in the presence of KOAc as the base and dimethylacetamide (DMAc) as the solvent with the use of $PdCl(C_3H_5)(dppb)$ (2 mol-%) as the catalyst, compounds **2a** or **2b** were not obtained (Table 1, Entry 1). In the course of this reaction, the formation of acetamides **2c** and **2d** in a 67:28 ratio was observed. The formation of 3-arylated furfurylamine derivative **2d** in 28% yield is probably due to the coordination of the amine to palladium.

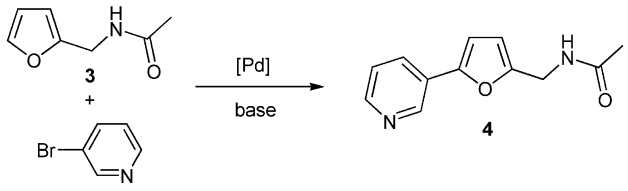
Table 1. Influence of the reaction conditions for the palladium-catalysed direct coupling of furfurylamine with 4-bromobenzotrifluoride (Scheme 2).

Entry	Solvent	Base	Conversion [%][a]	Products	Product ratio
1	DMAc	KOAc	100	**2c**, **2d**	67:28
2	DMF	KOAc	80	**2e**, **2f**	47:12
3	NMP	KOAc	100	**2c**, **2d**	37:18
4	1,4-dioxane	KOAc	0	–	–
5	NMP	K_2CO_3	8	**2g**	–
6	NMP	Na_2CO_3	0	–	–
7	NMP	KOH	48	**2g**, **2i**	21:13
8	DMAc	Cs_2CO_3	45	**2g**, **2h**	19:23
9	DMAc	Na_2CO_3	100	**2c**, **2d**, **2g**, **2h**, **2i**	19:12:34:15:17
10	DMAc	CsOAc	100	**2c**, **2d**	52:42
11	DMAc	NaOAc	57	**2g**, **2h**	31:11
12	DMAc	KOH	100	**2c**, **2g**, **2i**	21:25:32
13	DMAc	–	10	**2h**	–

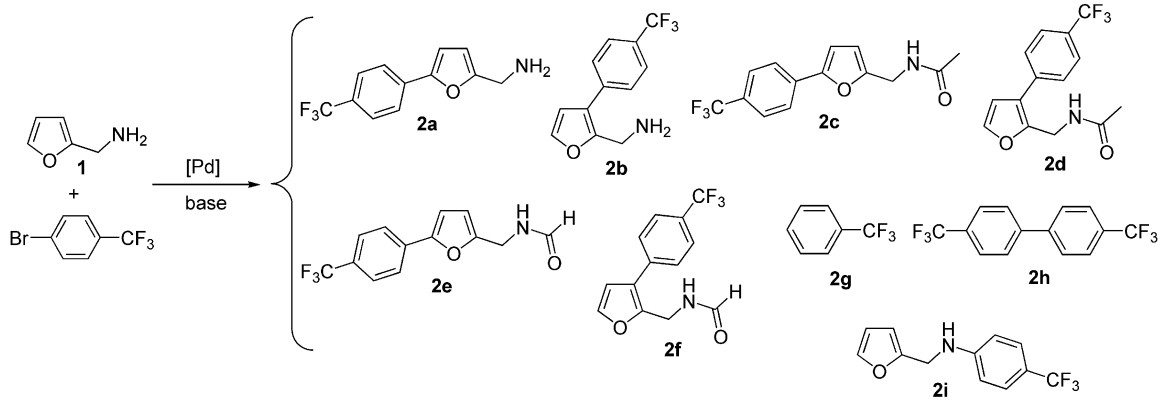
[a] Conditions: $PdCl(C_3H_5)(dppb)$ (2 mol-%), furfurylamine (2 equiv.), 4-bromobenzotrifluoride (1 equiv.), base (2 equiv.), 150 °C, 16 h, conversion of 4-bromobenzotrifluoride.

To avoid the formation of amides in the course of this reaction, the influence of several solvents and bases was examined (Table 1, Entries 2–12). Good conversion of 4-bromobenzotrifluoride was also obtained in DMF; however, the formation of formamides **2e** and **2f** was observed (Table 1, Entry 2). On the other hand, in the presence of *N*-methyl-2-pyrrolidone (NMP), and KOAc as the base, a mixture of acetylated compounds **2c** and **2d** was obtained (Table 1, Entry 3). Dioxane was found to be ineffective in promoting this coupling reaction (Table 1, Entry 4). The nature of the base has also a huge influence on this reaction. K_2CO_3 in NMP or Cs_2CO_3 in DMAc led to side product **2g** or **2h** (Table 1, Entries 5 and 8). The use of KOH was also found to be ineffective (Table 1, Entries 7 and 12). Moreover, with this relatively strong base, amination side product **2i** was also formed.

As the regioselective formation of 5-arylated furfurylamines using free-NH_2 furfurylamine was found to be difficult, we decided to protect this function by using either acetyl or BOC substituents. First, we examined the reactivity of *N*-(furan-2-ylmethyl)acetamide (**3**) for the coupling with 3-bromopyridine (Scheme 3, Table 2). With this substrate, in the presence of $PdCl(C_3H_5)(dppb)$ or $Pd(OAc)_2$ as the catalysts, DMAc as the solvent and KOAc as the base, 5-arylation product **4** was regioselectively obtained (Table 2, Entries 1 and 2). The use of $Pd(OAc)_2$ gave the highest yield. It should be noted that the methylacetamide substituent on the furan ring does not act as a directing group for



Scheme 3. Coupling of *N*-(furan-2-ylmethyl)acetamide with 3-bromopyridine.



Scheme 2. Reaction of furfurylamine with 4-bromobenzotrifluoride.

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Table 2. Influence of the reaction conditions for the palladium-catalysed direct coupling of *N*-(furan-2-ylmethyl)acetamide with 3-bromopyridine (Scheme 3).

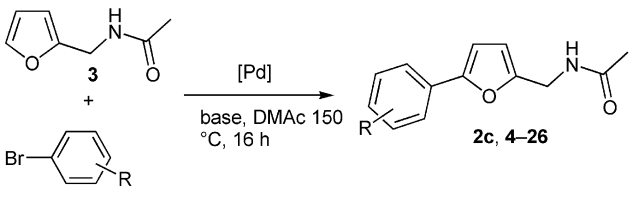
Entry	Solvent	Base	Catalyst	*T* [°C]	Conversion [%][a]	Yield of **4** [%]
1	DMAc	KOAc	$PdCl(C_3H_5)$(dppb)	150	61	59
2	DMAc	KOAc	$Pd(OAc)_2$	150	80	78 (71)
3	DMF	KOAc	$Pd(OAc)_2$	150	81	67
4	NMP	KOAc	$Pd(OAc)_2$	150	79	67
5	1,4-dioxane	KOAc	$Pd(OAc)_2$	150	0	0
6	DMAc	CsOAc	$Pd(OAc)_2$	150	93	82
7	DMAc	NaOAc	$Pd(OAc)_2$	150	29	26
8	DMAc	K_2CO_3	$Pd(OAc)_2$	150	15	14
9	DMAc	Na_2CO_3	$Pd(OAc)_2$	150	24	21
10	DMAc	Cs_2CO_3	$Pd(OAc)_2$	150	0	0
11	DMAc	KOH	$Pd(OAc)_2$	150	55	0
12	DMAc	KOAc	$Pd(OAc)_2$	150	100	90 (80)[b]
13	DMAc	KOAc	$Pd(OAc)_2$	130	63	60
14	DMAc	KOAc	$Pd(OAc)_2$	100	21	20
15	DMAc	KOAc	0.5 $[PdCl(C_3H_5)]_2$	150	31	31
16	DMAc	KOAc	$Pd(OAc)_2$/2 PPh_3	150	85	76
17	DMAc	KOAc	$Pd(OAc)_2$/dppm	150	52	50
18	DMAc	KOAc	$Pd(OAc)_2$/dppe	150	78	76
19	DMAc	KOAc	$Pd(OAc)_2$/dppb	150	71	69

[a] Conditions: [Pd] (0.1 mol-%), *N*-(furan-2-ylmethyl)acetamide (2 equiv.), 3-bromopyridine (1 equiv.), base (2 equiv.), 16 h, conversion of 3-bromopyridine, GC and NMR yields, yields in parenthesis are isolated yields. [b] $Pd(OAc)_2$: 0.5 mol-%.

the direct arylation. Miura and co-workers had observed a very different behaviour in the presence of a 2-thiophenecarboxamide.[11] With this substrate, the carbamoyl group acts as a directing group and favours the arylation at C3 of thiophene (Scheme 1, left).

Next, we examined the influence of several reaction conditions. The use of DMF or NMP gave **4** in slightly lower yields than the reactions performed in DMAc (Table 2, Entries 2 and 3). Again, dioxane was found to be ineffective for this reaction (Table 2, Entry 4). In the presence of carbonates and NaOAc or KOH as the base, poor yields of **4** were obtained as a result of low conversions of 3-bromopyridine (Table 2, Entries 7–11). On the other hand, the use of CsOAc gave **4** in high yield (Table 2, Entry 6). Lower reaction temperatures led to lower yields of **4** (Table 2, Entries 13 and 14). Finally, the addition of phosphane ligands to the reaction mixture did not improve the yield of this reaction (Table 2, Entries 16–19).

Then, the scope and limitations for the coupling of *N*-(furan-2-ylmethyl)acetamide with the use of other aryl bromides was investigated (Scheme 4, Tables 3–5). As CsOAc is a relatively expensive base, we selected KOAc instead in combination with DMAc as the solvent and $Pd(OAc)_2$ (0.5–0.01 mol-%) as the catalyst at 150 °C as the reaction conditions.



Scheme 4. Coupling of *N*-(furan-2-ylmethyl)acetamide with aryl bromides.

First, we studied the reactivity of *para*-substituted aryl bromides (Table 3). In the presence of electron-deficient aryl bromides such as 4-bromoacetophenone, 4-bromobenzaldehyde, methyl 4-bromobenzoate, 4-bromobenzonitrile and 4-trifluoromethylbromobenzene and the catalyst (0.5–0.1 mol-%), products **2c** and **5**–**8** were obtained in good yields (Table 3, Entries 1–10). On the other hand, in the presence of 4-bromonitrobenzene, the formation of several unidentified products was formed, and **9** was not isolated (Table 3, Entries 11–13).

The direct arylation of *N*-(furan-2-ylmethyl)acetamide appears to be more difficult than the arylation of 2-*n*-butylfuran. For example, high yields of coupling products were obtained for the coupling of several electron-deficient aryl bromides with 2-*n*-butylfuran by using only 0.01 mol-% of $Pd(OAc)_2$ as the catalyst.[6f] On the other hand, with *N*-(furan-2-ylmethyl)acetamide, low yields were obtained by using this substrate/catalyst ratio (Table 3, Entries 2 and 4).

As expected, electron-rich aryl bromides were generally found to be less reactive (Table 3, Entries 17–30). In the presence of 4-bromotoluene or 1-bromo-4-*tert*-butylbenzene, good yields of 59 and 80% were obtained in the presence of 0.1 mol-% of $Pd(OAc)_2$ as the catalyst. 4-Bromoanisole was found to have poor reactivity. Several reaction conditions were employed, but the highest yield of **13** was 31% (Table 3, Entries 25–29).

Finally, the strongly deactivated aryl bromide 4-bromo-*N*,*N*-dimethylaniline was employed. However, this substrate was recovered unreacted (Table 3, Entry 30). With 4-bromoanisole or 4-bromo-*N*,*N*-dimethylaniline, the oxidative addition to palladium is probably the rate-limiting step of the reaction. Therefore, with such substrates, palladium associated to electron-rich monodentate phosphane ligands should be employed as the catalyst.[2a]

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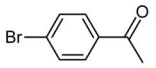
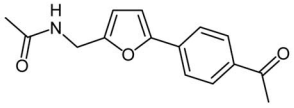
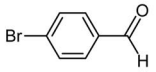
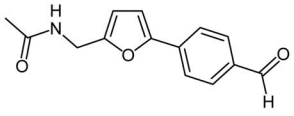
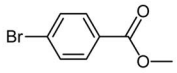
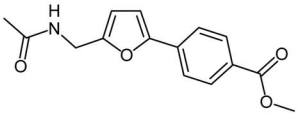
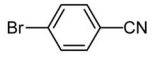
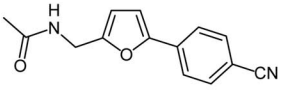
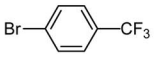
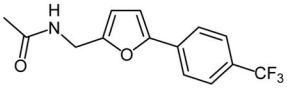
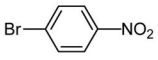
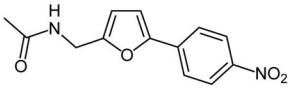
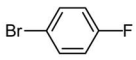
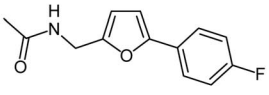
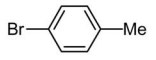
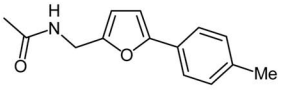
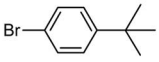
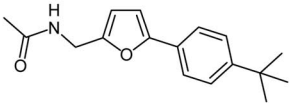
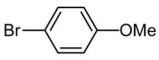
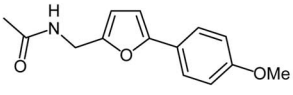
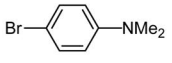
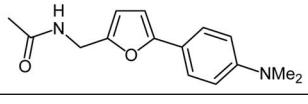
Table 3. Palladium-catalysed coupling of *N*-(furan-2-ylmethyl)acetamide with *para*-substituted aryl bromides (Scheme 4).

Entry	Aryl bromide	Product	Catalyst	Base	Substrate/ catalyst ratio	Yield [%][a]
1		 **5**	$Pd(OAc)_2$	KOAc	1000	86
2			$Pd(OAc)_2$	KOAc	10000	18
3		 **6**	$Pd(OAc)_2$	KOAc	1000	84
4			$Pd(OAc)_2$	KOAc	10000	26
5		 **7**	$Pd(OAc)_2$	KOAc	200	84
6			$Pd(OAc)_2$	KOAc	1000	51
7		 **8**	$Pd(OAc)_2$	KOAc	1000	90
8		 **2c**	$Pd(OAc)_2$	KOAc	200	81
9			$Pd(OAc)_2$	KOAc	1000	71
10			$PdCl(C_3H_5)(dppb)$	KOAc	50	92
11		 **9**	$Pd(OAc)_2$	KOAc	200	0
12			$Pd(OAc)_2$	KOAc	1000	0
13			$PdCl(C_3H_5)(dppb)$	KOAc	100	0
14		 **10**	$Pd(OAc)_2$	KOAc	200	30
15			$Pd(OAc)_2$	KOAc	1000	41
16			$PdCl(C_3H_5)(dppb)$	KOAc	100	78
17		 **11**	$Pd(OAc)_2$	KOAc	200	0
18			$Pd(OAc)_2$	KOAc	1000	59
19			$Pd(OAc)_2$	K_2CO_3	200	60
20			$PdCl(C_3H_5)(dppb)$	KOAc	100	30
21		 **12**	$Pd(OAc)_2$	KOAc	200	0
22			$Pd(OAc)_2$	KOAc	1000	80
23			$Pd(OAc)_2$	K_2CO_3	200	71
24			$PdCl(C_3H_5)(dppb)$	KOAc	100	70
25		 **13**	$Pd(OAc)_2$	KOAc	200	0
26			$Pd(OAc)_2$	KOAc	1000	14
27			$Pd(OAc)_2$	K_2CO_3	200	14
28			$PdCl(C_3H_5)(dppb)$	KOAc	100	30
29			$PdCl(C_3H_5)(dppb)$	K_2CO_3	100	31
30		 **14**	$PdCl(C_3H_5)(dppb)$	KOAc	50	trace

[a] Conditions: *N*-(furan-2-ylmethyl)acetamide (2 equiv.), aryl bromide (1 equiv.), base (2 equiv.), DMAc, 150 °C, 16 h, isolated yields.

It should be noted that with 4-bromotoluene, 4-*tert*-butylbromobenzene or 4-bromoanisole, the use of a higher loading of $Pd(OAc)_2$ (0.5 mol-%) did not give coupling products **11**–**13**. For this ligand-free procedure, under quite high palladium concentrations (>0.5 mol-%), so-called "palladium black" generally forms more rapidly. This "pal-

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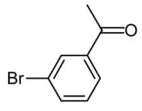
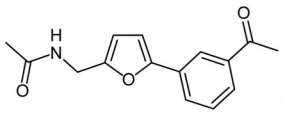
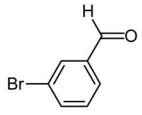
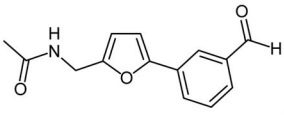
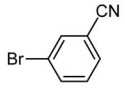
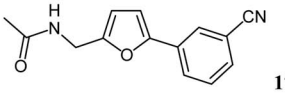
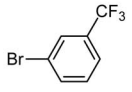
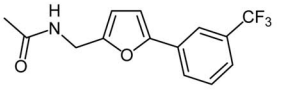
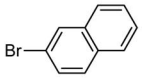
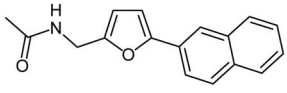
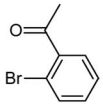
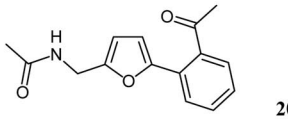
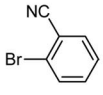
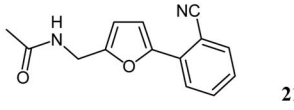
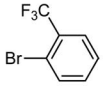
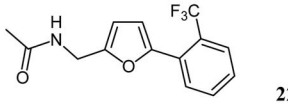
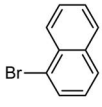
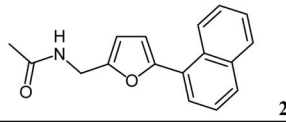
ladium black" is inactive for such catalysed reactions. Consequently, the yields of coupling products are often not increased by a higher catalyst loading.

As expected, the reactivity of *meta*-substituted aryl bromides was found to be very similar to the *para*-substituted ones (Table 4, Entries 1–7). In the presence of 0.1 mol-% of catalyst, products **15**–**19** were obtained in 71–90% yield. *ortho*-Substituents on the aryl bromides generally have a more important influence on the yields of palladium-catalysed reactions as a result of their steric and/or coordination properties.[15] *ortho*-Substituted 2-bromobenzonitrile, 1-bromo-2-(trifluoromethyl)benzene or 1-bromonaphthalene reacted with *N*-(furan-2-ylmethyl)acetamide by using 0.5–0.1 mol-% of $Pd(OAc)_2$ and gave **21**–**23** in 62–90% yield (Table 4, Entries 9–12). On the other hand, in the presence of 2-bromoacetophenone, the formation of **20** was not observed (Table 4, Entry 8).

Next, we explored the reactivity of *N*-(furan-2-ylmethyl)-acetamide (**3**) with four heteroaryl bromides. The results depicted in Table 5 also reveal the good performance of the phosphane-free $Pd(OAc)_2$ procedure in the direct coupling with 3- or 4-bromopyridines, 4-bromoisoquinoline or 5-bromopyrimidine. With these substrates, target products **4** and **24**–**26** were obtained in 80–88% yields.

As the deprotection of BOC-substituted amines is generally easier than the deprotection of amides, we examined the coupling of *tert*-butyl (furan-2-ylmethyl)carbamate (**27**) with three aryl bromides (Scheme 5). Carbamates are less thermally stable than amides; therefore, the reactions were performed at 120 °C instead of 150 °C. Target compounds

Table 4. Palladium-catalysed coupling of *N*-(furan-2-ylmethyl)acetamide with *meta*- or *ortho*-substituted aryl bromides (Scheme 4).

Entry	Aryl bromide	Product	Catalyst	Substrate/catalyst ratio	Yield [%][a]
1		 **15**	$Pd(OAc)_2$	1000	82
2		 **16**	$Pd(OAc)_2$	1000	74
3		 **17**	$Pd(OAc)_2$	1000	90
4			$Pd(OAc)_2$	10000	28
5			$PdCl(C_3H_5)(dppb)$	50	84
6		 **18**	$Pd(OAc)_2$	1000	71
7		 **19**	$Pd(OAc)_2$	1000	87
8		 **20**	$Pd(OAc)_2$	1000	0
9		 **21**	$Pd(OAc)_2$	1000	90
10		 **22**	$Pd(OAc)_2$	200	62
11			$Pd(OAc)_2$	1000	25
12		 **23**	$Pd(OAc)_2$	1000	79

[a] Conditions: *N*-(furan-2-ylmethyl)acetamide (2 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMAc, 150 °C, 16 h, isolated yields.

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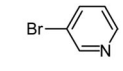
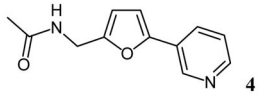
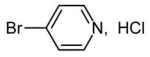
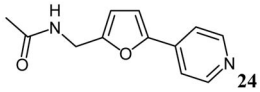
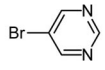
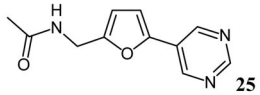
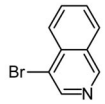
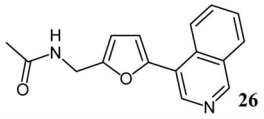
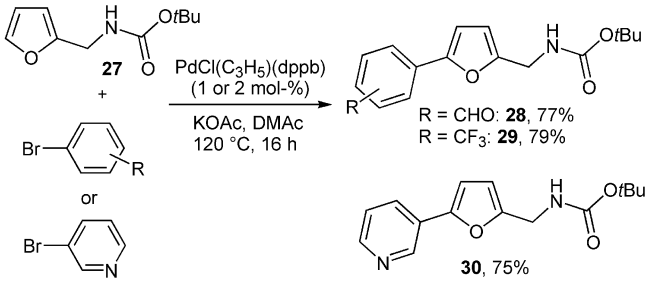
Table 5. Palladium-catalysed coupling of *N*-(furan-2-ylmethyl)acetamide with heteroaryl bromides (Scheme 4).

Entry	Aryl bromide	Product	Substrate/ catalyst ratio	Yield [%][a]
1		 **4**	200	80
2			1000	71
3		 **24**	200	86[b]
4			1000	50[b]
5		 **25**	200	88
6			1000	66
7		 **26**	200	87
8			1000	61

[a] Conditions: $Pd(OAc)_2$, *N*-(furan-2-ylmethyl)acetamide (2 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMAc, 150 °C, 16 h, isolated yields. [b] KOAc (3 equiv.).

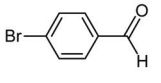
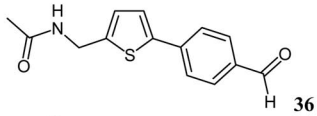
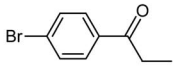
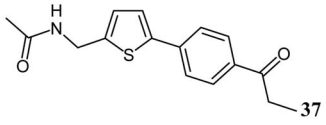
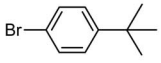
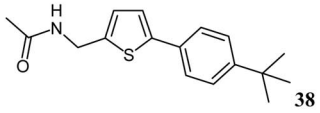
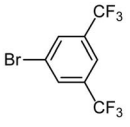
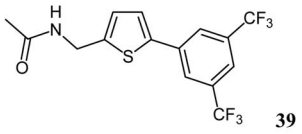
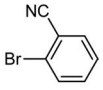
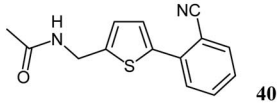
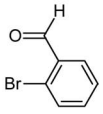
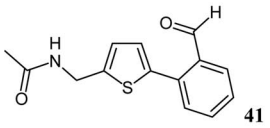
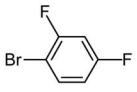
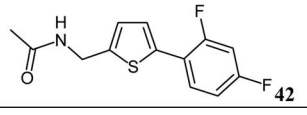
28–**30** were obtained in good yields. Again, the reaction was found to be highly regioselective, as only the 5-arylation products were obtained.



Scheme 5. Coupling of *tert*-butyl (furan-2-ylmethyl)carbamate with aryl bromides.

Then, we protected furfurylamine using a benzyl substituent. In the presence of this reactant, using 3-bromopyridine as the coupling partner and either $Pd(OAc)_2$ or $PdCl(C_3H_5)(dppb)$ as the catalysts. In both cases, a mixture of several unidentified products was formed, and **32** was

Table 6. Palladium-catalysed coupling of *N*-[2-(thiophen-2-yl)methyl]acetamide with aryl bromides (Scheme 8).

Entry	Aryl bromide	Product	Base	Substrate/ catalyst ratio	Yield [%][a]
1		 **36**	KOAc	1000	87
2		 **37**	KOAc	200	84
3			KOAc	1000	44
4		 **38**	KOAc	200	2
5			K_2CO_3	200	85
6		 **39**	KOAc	1000	83
7		 **40**	KOAc	1000	87
8		 **41**	KOAc	1000	71
9		 **42**	KOAc	1000	82

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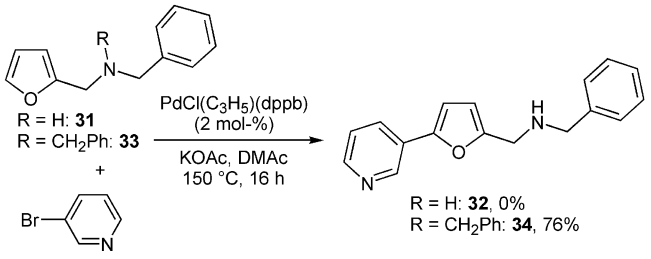
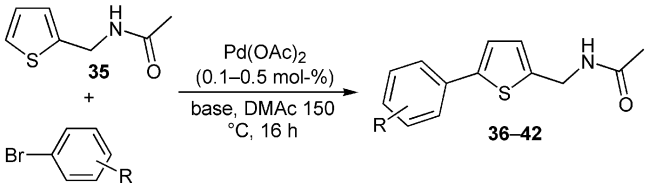
not isolated (Scheme 6). On the other hand, the use of dibenzyl(furan-2-ylmethyl)amine (**33**) led regioselectively to the desired 5-arylated furan compound **34** in 76% yield. However, in terms of atom economy, the use of a BOC protecting group for these reactions is probably more suitable.



Scheme 6. Coupling of benzyl- or dibenzyl(furan-2-ylmethyl)amine with 3-bromopyridine.

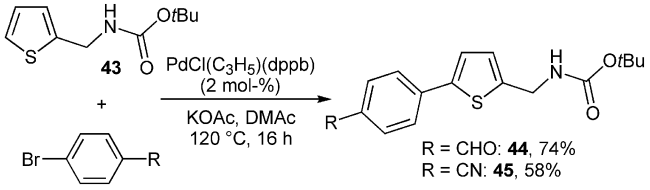
Then, the reactivity of *N*-(thiophen-2-ylmethyl)acetamide (**35**) was examined (Scheme 7, Table 6). We had previously observed that the reactivity of thiophenes and furans for palladium-catalysed direct arylation using Pd(OAc) as the catalyst is quite similar.[5h,6f] As expected, in the presence of **35**, the arylation was completely regioselective at C5. However, the reactivity of **35** was found to be lower



Scheme 7. Coupling of *N*-(thiophen-2-ylmethyl)acetamide with aryl bromides.

than the reactivity of 2-*n*-butylthiophene. In the presence of 2-*n*-butylthiophene, the most reactive aryl bromides were successfully coupled by using only 0.01 mol-% of Pd(OAc)$_2$ as the catalyst.[5h] On the other hand, the reaction of 4-bromobenzaldehyde or 4-bromopropiophenone with **35** required 0.5–0.1 mol-% of catalyst to obtain **36** and **37** in high yields (Table 6, Entries 1 and 2). The use of electron-deficient *meta*- or *ortho*-substituted aryl bromides also gave coupling products **39**–**42** in good yields (Table 6, Entries 6–9). On the other hand, the reactivity of the electron-rich aryl bromide 4-*tert*-butylbromobenzene was found to be different, and a much higher yield was obtained by using K_2CO_3 as the base (Table 6, Entries 4 and 5).

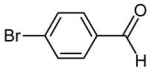
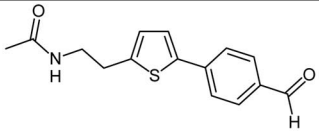
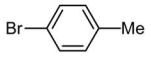
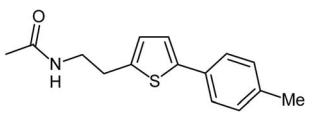
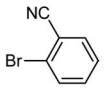
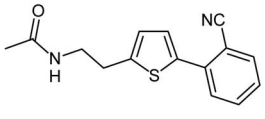
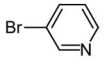
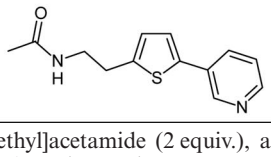
We also studied the reactivity of *tert*-butyl (thiophen-2-ylmethyl)carbamate (**43**; Scheme 8). Both 4-bromobenzaldehyde and 4-bromobenzonitrile gave target 5-arylated thiophenes **44** and **45**. However, as the reactions had to be performed at a lower temperature of 120 °C, 2 mol-% of the catalyst had to be employed to obtain good conversions of these aryl bromides.



Scheme 8. Coupling of *tert*-butyl (thiophen-2-ylmethyl)carbamate with aryl bromides.

Finally, we examined the reactivity of *N*-[2-(thiophen-2-yl)-ethyl]acetamide (**46**; Scheme 9, Table 7). Four aryl bromides were employed, and in all cases, 5-arylated thiophene deriv-

Table 7. Palladium-catalysed coupling of *N*-[2-(thiophen-2-yl)ethyl]acetamide with aryl bromides (Scheme 9).

Entry	Aryl bromide	Product	Base	Substrate/ catalyst ratio	Yield [%][a]
1		 **47**	KOAc	1000	89
2		 **48**	K_2CO_3	200	36
3			K_2CO_3	100	88[b]
4		 **49**	KOAc	1000	91
5		 **50**	KOAc	200	84
6			KOAc	1000	64

[a] Conditions: Pd(OAc)$_2$, *N*-[2-(thiophen-2-yl)ethyl]acetamide (2 equiv.), aryl bromide (1 equiv.), base (2 equiv.), DMAc, 150 °C, 16 h, isolated yields. [b] PdCl(C$_3$H$_5$)(dppb) (0.01 equiv.) as the catalyst.

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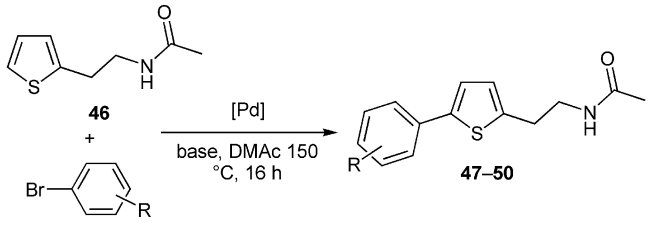
atives **47**–**50** were obtained in very good yields. In the presence of the electron-deficient aryl bromides 4-bromobenzaldehyde and 2-bromobenzonitrile or in the presence of 3-bromopyridine, 0.1 mol-% of $Pd(OAc)_2$ with KOAc were employed as the reaction conditions, whereas in the presence of 4-bromotoluene the use of 1 mol-% of $PdCl(C_3H_5)(dppb)$ with K_2CO_3 as the base should be preferred.



Scheme 9. Coupling of *N*-[2-(thiophen-2-yl)ethyl]acetamide with aryl bromides.

Conclusions

In conclusion, these results demonstrate that protected furfurylamine or 2-(aminoalkyl)thiophene derivatives can be employed in the palladium-catalysed direct 5-arylation. These substrates have been protected with a BOC substituent or as amides. A low loading of a phosphane-free catalyst gave regioselectively the 5-arylated compounds. It should be noted that the 3-arylation products were not detected, as these methylacetamide or methylcarbamate substituents on furan or thiophene do not act as directing groups for the direct arylation reaction. Higher yields were generally obtained in the presence of electron-deficient aryl bromides than with electron-rich aryl bromides. However, a wide range of functions such as acetyl, propionyl, formyl, ester, nitrile, trifluoromethyl or fluoro on the aryl bromide is tolerated. The major byproducts of these couplings are AcOH/KBr instead of metallic salts that are encountered with more classical coupling procedures. For this reason, this reaction should give economically viable and environmentally attractive access to 5-arylated furfurylamine or 2-(aminoalkyl)thiophene derivatives.

Experimental Section

General: Furfurylamine, 2-(aminomethyl)thiophene and DMAc (99%) were purchased from Acros. $Pd(OAc)_2$, [2-(thiophen-2-yl)-ethyl]amine and KOAc (99%) were purchased from Alfa Aesar. These compounds were not purified before use.

Preparation of the $PdCl(C_3H_5)(dppb)$ Catalyst: An oven-dried, 40-mL Schlenk tube equipped with a magnetic stirring bar under an argon atmosphere was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). Anhydrous dichloromethane (10 mL) was added, and the solution was then stirred at room temperature for 20 min. The solvent was removed in vacuo. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 19.3 (s) ppm.

General Procedure for Coupling Reactions: In a typical experiment, the aryl bromide (1 mmol), heteroaryl derivative (2 mmol), base (see Tables, 2 mmol) and [Pd] (see Tables) were dissolved in DMAc (5 mL) under an argon atmosphere. The reaction mixture was stirred at 120 or 150 °C (see Tables) for 16 h. Then, the solvent was evaporated and the product was purified by silica gel column chromatography.

***N*-({5-[4-(Trifluoromethyl)phenyl]furan-2-yl}methyl)acetamide (2c):** The reaction of 1-bromo-4-(trifluoromethyl)benzene (0.225 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **2c** in 81% (0.229 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.0 Hz, 2 H, Ar), 7.58 (d, J = 8.0 Hz, 2 H, Ar), 6.66 (d, J = 4.0 Hz, 1 H, furan), 6.31 (d, J = 4.0 Hz, 1 H, furan), 6.23 (s, 1 H, NH), 4.46 (d, J = 5.2 Hz, 2 H, CH_2), 2.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 152.1, 141.1, 133.6 (q, J = 1.3 Hz), 129.1 (q, J = 32.2 Hz), 125.9 (q, J = 271.6 Hz), 125.6 (q, J = 3.6 Hz), 123.5, 109.9, 107.8, 36.6, 23.1 ppm. $C_{14}H_{12}F_3NO_2$ (283.25): calcd. C 59.37, H 4.27; found C 59.21, H 4.20.

***N*-({3-[4-(Trifluoromethyl)phenyl]furan-2-yl}methyl)acetamide (2d):** ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.0 Hz, 2 H, Ar), 7.54 (d, J = 8.0 Hz, 2 H, Ar), 7.43 (d, J = 1.9 Hz, 1 H, furan), 6.55 (d, J = 1.9 Hz, 1 H, furan), 5.83 (s, 1 H, NH), 4.58 (d, J = 5.3 Hz, 2 H, CH_2), 2.01 (s, 3 H, CH_3) ppm.

***N*-({5-[4-(Trifluoromethyl)phenyl]furan-2-yl}methyl)formamide (2e):** ^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, CHO), 7.71 (d, J = 8.0 Hz, 2 H, Ar), 7.61 (d, J = 8.0 Hz, 2 H, Ar), 6.69 (d, J = 4.0 Hz, 1 H, furan), 6.36 (d, J = 4.0 Hz, 1 H, furan), 6.10 (s, 1 H, NH), 4.55 (d, J = 5.3 Hz, 2 H, CH_2) ppm.

***N*-({3-[4-(Trifluoromethyl)phenyl]furan-2-yl}methyl)formamide (2f):** ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1 H, CHO), 7.67 (d, J = 8.0 Hz, 2 H, Ar), 7.54 (d, J = 8.0 Hz, 2 H, Ar), 7.44 (d, J = 1.5 Hz, 1 H, furan), 6.56 (d, J = 1.5 Hz, 1 H, furan), 5.95 (s, 1 H, NH), 4.64 (d, J = 5.3 Hz, 2 H, CH_2) ppm.

(Trifluoromethyl)benzene (2g): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.25 (m, 5 H, Ar) ppm. Characterised by GC–MS analysis.

4,4′-Bis(trifluoromethyl)biphenyl (2h): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.67 (m, 8 H, Ar) ppm. Characterised by GC–MS analysis.

(Furan-2-ylmethyl)[4-(trifluoromethyl)phenyl]amine (2i): ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.0 Hz, 2 H, Ar), 7.40 (dd, J = 1.8, 0.8 Hz, 1 H, furan), 6.70 (d, J = 8.0 Hz, 2 H, Ar), 6.36 (dd, J = 3.2, 1.8 Hz, 1 H, furan), 6.27 (d, J = 3.2 Hz, 1 H, furan), 4.35 (d, J = 3.2 Hz, 2 H, CH_2) ppm.

***N*-(Furan-2-ylmethyl)acetamide (3):** Acetic anhydride (6.5 mL, 67.5 mmol) was added slowly to a solution of furfurylamine (**1**; 5 mL, 54.0 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give **3** in 70% (5.25 g) yield as a yellow liquid, which was used without any further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1 H, NH), 7.18 (m, 1 H, furan), 6.16 (m, 1 H, furan), 6.06 (m, 1 H, furan), 4.21 (d, J = 5.5 Hz, 2 H, CH_2), 1.82 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 151.1, 141.5, 109.9, 106.7 ppm. $C_7H_9NO_2$ (139.15): calcd. C 60.42, H 6.52; found C 60.60, H 6.47.

General Procedure for Catalysed Reactions: As a typical experiment, the reaction of 3-bromopyridine (0.157 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g,

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2 mmol) at 150 °C during 16 h in DMAc (5 mL) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) under an argon atmosphere afforded the corresponding product *N*-{[5-(pyridin-3-yl)furan-2-yl]-methyl}acetamide (**4**) after evaporation and filtration through silica gel (pentane/ether) in 71% (0.154 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1 H, pyridine), 8.40 (m, 1 H, pyridine), 7.82 (d, J = 4.0 Hz, 1 H, pyridine), 7.24 (m, 1 H, pyridine), 6.70 (s, 1 H, NH), 6.60 (d, J = 4.0 Hz, 1 H, furan), 6.29 (d, J = 4.0 Hz, 1 H, furan), 4.44 (d, J = 5.2 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 152.2, 150.3, 147.9, 144.9, 130.6, 126.6, 123.5, 109.7, 107.3, 36.5, 23.0 ppm. $C_{12}H_{12}N_2O_2$ (216.24): calcd. C 66.65, H 5.59; found C 66.72, H 5.70.

***N*-{[5-(4-Acetylphenyl)furan-2-yl]methyl}acetamide (5):** The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **5** in 86% (0.221 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.3 Hz, 2 H, Ar), 7.64 (d, J = 8.3 Hz, 2 H, Ar), 6.67 (d, J = 4.0 Hz, 1 H, furan), 6.60 (s, 1 H, NH), 6.31 (d, J = 4.0 Hz, 1 H, furan), 4.46 (d, J = 5.2 Hz, 2 H, CH_2), 2.54 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 170.8, 153.1, 152.8, 135.9, 135.2, 129.5, 123.9, 110.5, 109.0, 37.2, 27.1, 23.6 ppm. $C_{15}H_{15}NO_3$ (257.28): calcd. C 70.02, H 5.88; found C 70.04, H 5.98.

***N*-{[5-(4-Formylphenyl)furan-2-yl]methyl}acetamide (6):** The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **6** in 84% (0.204 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.90 (s, 1 H, CHO), 7.80 (d, J = 8.3 Hz, 2 H, Ar), 7.69 (d, J = 8.3 Hz, 2 H, Ar), 6.72 (d, J = 4.0 Hz, 1 H, furan), 6.60 (s, 1 H, NH), 6.33 (d, J = 4.0 Hz, 1 H, furan), 4.45 (d, J = 5.2 Hz, 2 H, CH_2), 2.03 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5, 170.1, 152.8, 151.9, 135.7, 134.6, 130.2, 123.5, 110.0, 109.0, 36.5, 23.0 ppm. $C_{14}H_{13}NO_3$ (243.26): calcd. C 69.12, H 5.39; found C 69.20, H 5.34.

Methyl 4-{5-[(Acetylamino)methyl]-furan-2-yl}benzoate (7): The reaction of methyl 4-bromobenzoate (0.215 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **7** in 84% (0.230 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.3 Hz, 2 H, Ar), 7.65 (d, J = 8.3 Hz, 2 H, Ar), 6.69 (d, J = 4.0 Hz, 1 H, furan), 6.33 (d, J = 4.0 Hz, 1 H, furan), 6.05 (s, 1 H, NH), 4.48 (d, J = 5.2 Hz, 2 H, CH_2), 3.90 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 166.7, 152.5, 152.1, 134.4, 130.0, 128.5, 123.3, 110.0, 108.1, 52.1, 36.7, 23.2 ppm. $C_{15}H_{15}NO_4$ (273.28): calcd. C 65.92, H 5.53; found C 65.80, H 5.61.

***N*-{[5-(4-Cyanophenyl)furan-2-yl]methyl}acetamide (8):** The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **8** in 90% (0.216 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.3 Hz, 2 H, Ar), 7.56 (d, J = 8.3 Hz, 2 H, Ar), 6.71 (d, J = 4.0 Hz, 1 H, furan), 6.60 (s, 1 H, NH), 6.33 (d, J = 4.0 Hz, 1 H, furan), 4.45 (d, J = 5.2 Hz, 2 H, CH_2), 2.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 153.6, 151.9, 134.9, 133.0, 124.2, 119.5, 110.6, 109.8, 109.7, 36.5, 23.6 ppm. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03; found C 70.05, H 5.17.

***N*-{[5-(4-Fluorophenyl)furan-2-yl]methyl}acetamide (10):** The reaction of 4-bromofluorobenzene (0.175 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 0.01 mmol) afforded **10** in 78% (0.182 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (dd, J = 8.6, 5.5 Hz, 2 H, Ar), 7.06 (t, J = 8.6 Hz, 2 H, Ar), 6.48 (d, J = 4.0 Hz, 1 H, furan), 6.28 (d, J = 4.0 Hz, 1 H, furan), 6.06 (s, 1 H, NH), 4.45 (d, J = 5.2 Hz, 2 H, NH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 162.2 (d, J = 247.1 Hz), 152.7, 150.8, 126.9 (d, J = 3.5 Hz), 125.3 (d, J = 7.0 Hz), 115.6 (d, J = 21.6 Hz), 109.7, 105.4, 36.6, 23.1 ppm. $C_{13}H_{12}FNO_2$ (233.24): calcd. C 66.94, H 5.19; found C 66.99, H 5.30.

***N*-{[5-(4-Methylphenyl)furan-2-yl]methyl}acetamide (11):** The reaction of 4-bromotoluene (0.171 g, 1 mmol), *N*-(furan-2-ylmethyl)-acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **11** in 59% (0.135 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.3 Hz, 2 H, Ar), 7.16 (d, J = 8.3 Hz, 2 H, Ar), 6.50 (d, J = 4.0 Hz, 1 H, furan), 6.28 (d, J = 4.0 Hz, 1 H, furan), 6.02 (s, 1 H, NH), 4.45 (d, J = 5.2 Hz, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 153.8, 150.3, 137.2, 129.3, 127.8, 123.6, 109.6, 104.9, 36.7, 23.1, 21.2 ppm. $C_{14}H_{15}NO_2$ (229.27): calcd. C 73.34, H 6.59; found C 73.50, H 6.70.

***N*-{[5-(4-*tert*-Butylphenyl)furan-2-yl]methyl}acetamide (12):** The reaction of 1-bromo-4-*tert*-butylbenzene (0.213 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **12** in 80% (0.217 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.3 Hz, 2 H, Ar), 7.37 (d, J = 8.3 Hz, 2 H, Ar), 6.49 (d, J = 4.0 Hz, 1 H, furan), 6.26 (d, J = 4.0 Hz, 1 H, furan), 6.20 (s, 1 H, NH), 4.44 (d, J = 5.2 Hz, 2 H, CH_2), 1.99 (s, 3 H, CH_3), 1.31 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 153.7, 150.4, 142.0, 127.8, 125.5, 123.4, 109.5, 105.1, 36.7, 34.5, 31.1, 23.1 ppm. $C_{17}H_{21}NO_2$ (271.35): calcd. C 75.25, H 7.80; found C 75.41, H 7.99.

***N*-{[5-(4-Methoxyphenyl)furan-2-yl]methyl}acetamide (13):** The reaction of 4-bromoanisole (0.187 g, 1 mmol), *N*-(furan-2-ylmethyl)-acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 0.01 mmol) afforded **13** in 30% (0.074 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.3 Hz, 2 H, Ar), 6.90 (d, J = 8.3 Hz, 2 H, Ar), 6.41 (d, J = 4.0 Hz, 1 H, furan), 6.26 (d, J = 4.0 Hz, 1 H, furan), 6.20 (s, 1 H, NH), 4.44 (d, J = 5.2 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 159.0, 153.6, 150.1, 125.0, 123.6, 114.0, 109.5, 104.1, 55.2, 36.7, 23.0 ppm. $C_{14}H_{15}NO_3$ (245.27): calcd. C 68.56, H 6.16; found C 68.40, H 6.25.

***N*-{[5-(3-Acetylphenyl)furan-2-yl]methyl}acetamide (15):** The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **15** in 82% (0.211 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H, Ar), 7.75–7.65 (m, 2 H, Ar), 7.37 (t, J = 7.3 Hz, 1 H, Ar), 6.70 (s, 1 H, NH), 6.56 (d, J = 4.0 Hz, 1 H, furan), 6.25 (d, J = 4.0 Hz, 1 H, furan), 4.41 (d, J = 5.2 Hz, 2 H, CH_2), 2.54 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.9, 170.1, 152.2, 151.6, 137.2, 130.9, 128.8, 127.8, 127.0, 122.8, 109.6, 106.7, 36.5, 26.5, 22.9 ppm. $C_{15}H_{15}NO_3$ (257.28): calcd. C 70.02, H 5.88; found C 70.11, H 5.70.

***N*-{[5-(3-Formylphenyl)furan-2-yl]methyl}acetamide (16):** The reaction of 3-bromobenzaldehyde (0.185 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **16** in 74% (0.180 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.95 (s, 1

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H, CHO), 8.82 (s, 1 H, Ar), 7.77 (d, J = 8.3 Hz, 1 H, Ar), 7.68 (d, J = 8.3 Hz, 1 H, Ar), 7.46 (t, J = 7.8 Hz, 1 H, Ar), 6.60 (m, 2 H, NH and furan), 6.29 (d, J = 4.0 Hz, 1 H, furan), 4.44 (d, J = 5.2 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.0, 170.2, 151.9, 151.8, 136.5, 131.4, 129.3, 129.1, 128.5, 124.0, 109.7, 107.1, 36.5, 23.0 ppm. $C_{14}H_{13}NO_3$ (243.26): calcd. C 69.12, H 5.39; found C 69.01, H 5.30.

***N*-{[5-(3-Cyanophenyl)furan-2-yl]methyl}acetamide (17):** The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **17** in 90% (0.216 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.70 (m, 2 H, Ar), 7.45–7.35 (m, 2 H, Ar), 6.87 (s, 1 H, NH), 6.60 (d, J = 4.0 Hz, 1 H, furan), 6.28 (d, J = 4.0 Hz, 1 H, furan), 4.42 (d, J = 5.2 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 152.9, 151.3, 132.1, 130.7, 130.0, 127.9, 127.2, 119.1, 113.1, 110.2, 108.2, 37.0, 23.5 ppm. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03; found C 70.14, H 5.20.

***N*-({5-[3-(trifluoromethyl)phenyl]furan-2-yl}methyl)acetamide (18):** The reaction of 1-bromo-3-(trifluoromethyl)benzene (0.225 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **18** in 71% (0.201 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1 H, Ar), 7.80–7.70 (m, 1 H, Ar), 7.50–7.40 (m, 2 H, Ar), 6.63 (d, J = 4.0 Hz, 1 H, furan), 6.31 (d, J = 4.0 Hz, 1 H, furan), 6.25 (s, 1 H, NH), 4.45 (d, J = 5.2 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 151.9, 151.8, 131.2, 131.1 (q, J = 31.4 Hz), 129.1, 125.7, 124.2 (q, J = 272.4 Hz), 123.6 (q, J = 3.8 Hz), 120.2 (q, J = 3.8 Hz), 109.7, 107.1, 36.6, 23.0 ppm. $C_{14}H_{12}F_3NO_2$ (283.25): calcd. C 59.37, H 4.27; found C 59.45, H 4.40.

***N*-{[5-(Naphthalen-2-yl)furan-2-yl]methyl}acetamide (19):** The reaction of 2-bromonaphthalene (0.207 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **19** in 87% (0.231 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H, Ar), 7.85–7.75 (m, 3 H, Ar), 7.69 (d, J = 8.0 Hz, 1 H, Ar), 7.50–7.40 (m, 2 H, Ar), 6.63 (d, J = 4.0 Hz, 1 H, furan), 6.40 (s, 1 H, NH), 6.31 (d, J = 4.0 Hz, 1 H, furan), 4.48 (d, J = 5.2 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 153.5, 151.1, 133.3, 132.5, 128.3, 128.0, 127.8, 127.6, 126.4, 125.8, 122.0, 121.8, 109.7, 106.3, 36.6, 22.9 ppm. $C_{17}H_{15}NO_2$ (265.31): calcd. C 76.96, H 5.70; found C 76.87, H 5.55.

***N*-{[5-(2-Cyanophenyl)furan-2-yl]methyl}acetamide (21):** The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **21** in 90% (0.216 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.3 Hz, 1 H, Ar), 7.66 (d, J = 8.3 Hz, 1 H, Ar), 7.58 (t, J = 7.7 Hz, 1 H, Ar), 7.30 (t, J = 7.7 Hz, 1 H, Ar), 7.11 (d, J = 4.0 Hz, 1 H, furan), 6.40 (s, 1 H, NH), 6.37 (d, J = 4.0 Hz, 1 H, furan), 4.49 (d, J = 5.2 Hz, 2 H, CH_2), 2.03 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 152.4, 149.2, 134.0, 132.9, 132.8, 127.1, 125.7, 119.0, 111.0, 109.7, 106.6, 36.5, 23.0 ppm. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03; found C 70.18, H 4.87.

***N*-({5-[2-(Trifluoromethyl)phenyl]furan-2-yl}methyl)acetamide (22):** The reaction of 1-bromo-2-(trifluoromethyl)benzene (0.225 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **22** in 62% (0.176 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.3 Hz, 1 H, Ar), 7.66 (d, J = 8.3 Hz, 1 H, Ar), 7.52 (t, J = 7.7 Hz, 1 H, Ar), 7.36 (t, J = 7.7 Hz, 1 H, Ar), 6.11 (d, J = 4.0 Hz, 1 H, furan), 6.45 (m, 1 H, NH), 6.28 (d, J = 4.0 Hz, 1 H, furan), 4.44 (d, J = 5.2 Hz, 2 H, CH_2), 1.96 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 151.9, 149.9, 131.6, 129.6, 129.3, 127.6, 126.5 (q, J = 5.0 Hz), 126.4 (q, J = 30.9 Hz), 124.0 (q, J = 273.3 Hz), 110.7, 109.2, 36.5, 22.8 ppm. $C_{14}H_{12}F_3NO_2$ (283.25): calcd. C 59.37, H 4.27; found C 59.21, H 4.48.

***N*-{[5-(Naphthalen-1-yl)furan-2-yl]methyl}acetamide (23):** The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **23** in 79% (0.209 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.40 (d, J = 8.0 Hz, 1 H, Ar), 7.95–7.80 (m, 2 H, Ar), 7.71 (d, J = 8.0 Hz, 1 H, Ar), 7.60–7.40 (m, 3 H, Ar), 6.70 (m, 1 H, NH), 6.63 (d, J = 4.0 Hz, 1 H, furan), 6.37 (d, J = 4.0 Hz, 1 H, furan), 4.50 (d, J = 5.2 Hz, 2 H, CH_2), 1.97 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 152.6, 151.2, 133.7, 130.0, 128.3, 128.2, 128.1, 126.4, 125.8, 125.7, 125.2, 125.1, 109.9, 109.0, 36.6, 22.8 ppm. $C_{17}H_{15}NO_2$ (265.31): calcd. C 76.96, H 5.70; found C 76.80, H 5.61.

***N*-{[5-(Pyridin-4-yl)furan-2-yl]methyl}acetamide (24):** The reaction of 4-bromopyridine hydrochloride (0.194 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.294 g, 3 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **24** in 86% (0.186 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, J = 6.0 Hz, 2 H, pyridine), 7.46 (d, J = 6.0 Hz, 2 H, pyridine), 6.80 (d, J = 4.0 Hz, 1 H, furan), 6.37 (d, J = 4.0 Hz, 1 H, furan), 6.00 (m, 1 H, NH), 4.49 (d, J = 5.2 Hz, 2 H, CH_2), 2.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 153.1, 150.8, 149.9, 137.2, 117.6, 110.0, 109.7, 36.6, 23.2 ppm. $C_{12}H_{12}N_2O_2$ (216.24): calcd. C 66.65, H 5.59; found C 66.50, H 5.74.

***N*-{[5-(Pyrimidin-5-yl)furan-2-yl]methyl}acetamide (25):** The reaction of 5-bromopyrimidine (0.159 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **25** in 88% (0.191 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.00 (s, 1 H, pyrimidine), 8.88 (s, 2 H, pyrimidine), 6.72 (m, 1 H, NH), 6.71 (d, J = 4.0 Hz, 1 H, furan), 6.35 (d, J = 4.0 Hz, 1 H, furan), 4.47 (d, J = 5.2 Hz, 2 H, CH_2), 2.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 156.6, 153.3, 151.3, 147.0, 124.7, 109.8, 108.8, 36.4, 22.9 ppm. $C_{11}H_{11}N_3O_2$ (217.22): calcd. C 60.82, H 5.10; found C 60.70, H 5.22.

***N*-{[5-(Isoquinolin-4-yl)furan-2-yl]methyl}acetamide (26):** The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol), *N*-(furan-2-ylmethyl)acetamide (0.278 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **26** in 87% (0.232 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.11 (s, 1 H, isoquinoline), 8.64 (s, 1 H, isoquinoline), 8.30 (d, J = 8.0 Hz, 1 H, isoquinoline), 7.94 (d, J = 8.0 Hz, 1 H, isoquinoline), 7.71 (t, J = 7.7 Hz, 1 H, isoquinoline), 7.59 (t, J = 7.7 Hz, 1 H, isoquinoline), 6.67 (d, J = 4.0 Hz, 1 H, furan), 6.60 (m, 1 H, NH), 6.41 (d, J = 4.0 Hz, 1 H, furan), 4.54 (d, J = 5.2 Hz, 2 H, CH_2), 2.02 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 152.3, 152.0, 150.2, 141.6, 132.3, 131.1, 128.3, 128.1, 127.4, 124.4, 122.0, 110.9, 109.5, 36.7, 23.1 ppm. $C_{16}H_{14}N_2O_2$ (266.29): calcd. C 72.16, H 5.30; found C 72.20, H 5.07.

***tert*-Butyl (Furan-2-ylmethyl)carbamate (27):** Furfurylamine (**1**; 2.0 mL, 21.6 mmol) was slowly added to a solution of di-*tert*-butyl dicarbonate (5.3 mg, 23.8 mmol) and triethylamine (3 mL, 21.6 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up in CH_2Cl_2. The solution was washed with saturated

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aqueous $NaHCO_3$, dried and evaporated to give **27** in 67% (2.85 g) yield as a yellow liquid, which was used without any further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, J = 4.0 Hz, 1 H, furan), 6.29 (t, J = 4.0 Hz, 1 H, furan), 6.19 (d, J = 4.0 Hz, 1 H, furan), 4.96 (m, 1 H, NH), 4.28 (d, J = 5.5 Hz, 2 H, CH_2), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 152.6, 142.6, 110.0, 107.5, 80.2, 38.3, 28.0 ppm. $C_{10}H_{15}NO_3$ (197.23): calcd. C 60.90, H 7.67; found C 60.85, H 7.60.

***tert*-Butyl {[5-(4-Formylphenyl)furan-2-yl]methyl}carbamate (28):** The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), *tert*-butyl (furan-2-ylmethyl)carbamate (0.394 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) at 120 °C afforded **28** in 77% (0.232 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.92 (s, 1 H, CHO), 7.82 (d, J = 8.4 Hz, 2 H, Ar), 7.71 (d, J = 8.4 Hz, 2 H, Ar), 6.72 (d, J = 3.3 Hz, 1 H, furan), 6.32 (d, J = 3.3 Hz, 1 H, furan), 5.21 (m, 1 H, NH), 4.35 (d, J = 5.7 Hz, 2 H, CH_2), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 155.5, 153.5, 151.8, 135.8, 134.6, 130.1, 123.4, 109.4, 108.9, 79.7, 37.7, 28.2 ppm. $C_{17}H_{19}NO_4$ (301.34): calcd. C 67.76, H 6.36; found C 67.88, H 6.45.

***tert*-Butyl ({5-[4-(Trifluoromethyl)phenyl]furan-2-yl}methyl)carbamate (29):** The reaction of 1-bromo-4-(trifluoromethyl)benzene (0.225 g, 1 mmol), *tert*-butyl (furan-2-ylmethyl)carbamate (0.394 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 0.01 mmol) at 120 °C afforded **29** in 79% (0.270 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.4 Hz, 2 H, Ar), 7.61 (d, J = 8.4 Hz, 2 H, Ar), 6.69 (d, J = 3.3 Hz, 1 H, furan), 6.33 (d, J = 3.3 Hz, 1 H, furan), 5.03 (m, 1 H, NH), 4.38 (d, J = 5.7 Hz, 2 H, CH_2), 1.40 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 152.9, 151.8, 133.7, 128.8 (q, J = 32.2 Hz), 125.6 (q, J = 3.7 Hz), 123.8 (q, J = 272.0 Hz), 123.5, 109.2, 107.7, 79.8, 37.8, 28.3 ppm. $C_{17}H_{18}F_3NO_3$ (341.32): calcd. C 59.82, H 5.32; found C 59.74, H 5.31.

***tert*-Butyl {[5-(Pyridin-3-yl)furan-2-yl]methyl}carbamate (30):** The reaction of 3-bromopyridine (0.157 g, 1 mmol), *tert*-butyl (furan-2-ylmethyl)carbamate (0.394 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) at 120 °C afforded **30** in 75% (0.206 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1 H, pyridine), 8.48 (m, 1 H, pyridine), 7.90 (d, J = 7.9 Hz, 1 H, pyridine), 7.30 (m, 1 H, pyridine), 6.68 (d, J = 4.0 Hz, 1 H, furan), 6.33 (d, J = 4.0 Hz, 1 H, furan), 5.07 (m, 1 H, NH), 4.37 (d, J = 5.7 Hz, 2 H, CH_2), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 152.9, 149.9, 147.0, 144.2, 131.2, 127.0, 123.7, 109.1, 107.5, 79.8, 37.7, 28.3 ppm. $C_{15}H_{18}N_2O_3$ (274.32): calcd. C 65.68, H 6.61; found C 65.54, H 6.78.

Benzyl(furan-2-ylmethyl)amine (31): Benzyl chloride (2.5 mL, 21.7 mmol) was slowly added to a solution of furfurylamine (**1**; 2 mL, 21.6 mmol) and triethylamine (3 mL, 21.6 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up in CH_2Cl_2. Then, the solution was washed with saturated aqueous $NaHCO_3$, dried, evaporated and purified by flash column chromatography. Elution with pentane/ether (90:10) gave **31** in 69% (2.79 g) yield as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 6 H, Ar and furan), 6.37 (m, 1 H, furan), 6.23 (m, 1 H, furan), 3.81 (m, 4 H, 2 CH_2), 1.82 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5, 141.1, 139.5, 127.8, 127.6, 126.4, 109.6, 106.3, 52.1, 44.7 ppm. $C_{12}H_{13}NO$ (187.24): calcd. C 76.98, H 7.00; found C 76.80, H 7.12.

Dibenzyl(furan-2-ylmethyl)amine (33): Benzyl chloride (5 mL, 43.4 mmol) was slowly added to a solution of furfurylamine (**1**; 2 mL, 21.6 mmol) and triethylamine (6 mL, 43.2 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up in CH_2Cl_2. Then, the solution was washed with saturated aqueous $NaHCO_3$, dried, evaporated and purified by flash column chromatography. Elution with pentane/ether (90:10) gave **33** in 66% (3.95 g) yield as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.44 (m, 11 H, Ar and furan), 6.54 (m, 1 H, furan), 6.42 (m, 1 H, furan), 3.88 (s, 6 H, 3 CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 141.8, 139.3, 128.7, 128.1, 126.8, 109.9, 108.5, 57.4, 49.0 ppm. $C_{19}H_{19}NO$ (277.36): calcd. C 82.28, H 6.90; found C 82.14, H 6.77.

Dibenzyl{[5-(pyridin-3-yl)furan-2-yl]methyl}amine (34): The reaction of 3-bromopyridine (0.157 g, 1 mmol), dibenzyl(furan-2-ylmethyl)amine (0.554 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) afforded **34** in 76% (0.269 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1 H, pyridine), 8.53 (d, J = 4.3 Hz, 1 H, pyridine), 7.94 (d, J = 7.8 Hz, 1 H, pyridine), 7.55–7.28 (m, 11 H, Ar and pyridine), 6.73 (d, J = 3.1 Hz, 1 H, furan), 6.34 (d, J = 3.1 Hz, 1 H, furan), 3.78–3.70 (m, 6 H, 3 CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5, 150.1, 147.8, 145.1, 139.2, 130.3, 128.6, 128.2, 126.9, 123.4, 110.7, 107.0, 57.6, 48.9 ppm. $C_{24}H_{22}N_2O$ (354.44): calcd. C 81.33, H 6.26; found C 81.41, H 6.37.

***N*-(Thiophen-2-ylmethyl)acetamide (35):** Acetic anhydride (1.8 mL, 18.9 mmol) was slowly added to a solution of (thiophen-2-ylmethyl)amine (2 mL, 15.8 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 20 h. Then, the solvent was removed, and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give **35** in 73% (1.79 g) yield as a yellow solid, which was used without any further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (m, 1 H, thiophene), 7.20–6.90 (m, 3 H, thiophene and NH), 4.50 (d, J = 5.7 Hz, 2 H, CH_2), 1.83 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 141.0, 126.6, 125.6, 124.8, 38.0, 22.7 ppm. C_7H_9NOS (155.22): calcd. C 54.17, H 5.84; found C 54.30, H 5.99.

***N*-{[5-(4-Formylphenyl)thiophen-2-yl]methyl}acetamide (36):** The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **36** in 87% (0.225 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.96 (s, 1 H, CHO), 7.83 (d, J = 8.4 Hz, 2 H, Ar), 7.67 (d, J = 8.4 Hz, 2 H, Ar), 7.28 (d, J = 3.7 Hz, 1 H, thiophene), 6.96 (d, J = 3.7 Hz, 1 H, thiophene), 6.32 (m, 1 H, NH), 4.59 (d, J = 5.8 Hz, 2 H, CH_2), 2.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 170.0, 143.0, 142.2, 139.8, 124.9, 130.4, 127.8, 125.6, 124.7, 38.5, 23.1 ppm. $C_{14}H_{13}NO_2S$ (259.32): calcd. C 64.84, H 5.05; found C 64.69, H 5.12.

***N*-{[5-(4-Propionylphenyl)thiophen-2-yl]methyl}acetamide (37):** The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **37** in 84% (0.241 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.4 Hz, 2 H, Ar), 7.60 (d, J = 8.4 Hz, 2 H, Ar), 7.24 (d, J = 3.7 Hz, 1 H, thiophene), 6.94 (d, J = 3.7 Hz, 1 H, thiophene), 6.07 (m, 1 H, NH), 4.59 (d, J = 5.8 Hz, 2 H, CH_2), 2.99 (q, J = 7.5 Hz, 2 H, CH_2), 2.05 (s, 3 H, CH_3), 1.23 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0, 169.8, 142.6, 142.3, 138.3, 135.5, 128.7, 127.2, 125.3, 124.2, 38.6, 31.7, 23.2, 8.2 ppm. $C_{16}H_{17}NO_2S$ (287.38): calcd. C 66.87, H 5.96; found C 66.97, H 5.84.

***N*-{[5-(4-*tert*-Butylphenyl)thiophen-2-yl]methyl}acetamide (38):** The reaction of 1-bromo-4-*tert*-butylbenzene (0.213 g, 1 mmol), *N*-

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(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **38** in 85% (0.244 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.0 Hz, 2 H, Ar), 7.38 (d, J = 8.0 Hz, 2 H, Ar), 7.09 (d, J = 4.0 Hz, 1 H, thiophene), 6.90 (d, J = 4.0 Hz, 1 H, thiophene), 5.88 (m, 1 H, NH), 4.58 (d, J = 5.8 Hz, 2 H, CH_2), 2.02 (s, 3 H, CH_3), 1.33 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 150.7, 144.4, 139.7, 131.4, 127.0, 125.8, 125.4, 122.3, 38.7, 34.6, 31.2, 23.3 ppm. $C_{17}H_{21}NOS$ (287.42): calcd. C 71.04, H 7.36; found C 71.12, H 7.21.

***N*-({5-[3,5-Bis(trifluoromethyl)phenyl]thiophen-2-yl}methyl)acetamide (39):** The reaction of 1-bromo-3,5-bis(trifluoromethyl)-benzene (0.293 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **39** in 83% (0.305 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (s, 2 H, Ar), 7.76 (s, 1 H, Ar), 7.28 (d, J = 4.0 Hz, 1 H, thiophene), 7.00 (d, J = 4.0 Hz, 1 H, thiophene), 6.05 (m, 1 H, NH), 4.65 (d, J = 5.8 Hz, 2 H, CH_2), 2.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 143.3, 140.4, 136.2, 132.7 (q, J = 32.0 Hz), 127.2, 125.3 (m), 124.8, 123.1 (q, J = 272.8 Hz), 120.6 (m), 38.5, 23.1 ppm. $C_{15}H_{11}F_6NOS$ (367.31): calcd. C 49.05, H 3.02; found C 49.11, H 3.17.

***N*-{[5-(2-Cyanophenyl)thiophen-2-yl]methyl}acetamide (40):** The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **40** in 87% (0.223 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.4 Hz, 1 H, Ar), 7.60–7.50 (m, 2 H, Ar), 7.41 (d, J = 3.7 Hz, 1 H, thiophene), 7.32 (t, J = 7.6 Hz, 1 H, Ar), 6.96 (d, J = 3.7 Hz, 1 H, thiophene), 6.50 (m, 1 H, NH), 4.56 (d, J = 5.8 Hz, 2 H, CH_2), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 143.4, 138.7, 137.2, 134.1, 132.9, 129.3, 127.4, 127.2, 126.8, 118.7, 109.5, 38.2, 22.9 ppm. $C_{14}H_{12}N_2OS$ (256.32): calcd. C 65.60, H 4.72; found C 65.70, H 4.83.

***N*-{[5-(2-Formylphenyl)thiophen-2-yl]methyl}acetamide (41):** The reaction of 2-bromobenzaldehyde (0.185 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **41** in 71% (0.184 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.16 (s, 1 H, CHO), 7.97 (d, J = 8.4 Hz, 1 H, Ar), 7.60–7.40 (m, 3 H, Ar), 6.97 (d, J = 3.7 Hz, 1 H, thiophene), 6.88 (d, J = 3.7 Hz, 1 H, thiophene), 6.10 (m, 1 H, NH), 4.62 (d, J = 5.8 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 169.9, 143.4, 138.5, 137.8, 134.0, 133.6, 131.1, 129.3, 128.2, 127.9, 126.5, 38.5, 23.2 ppm. $C_{14}H_{13}NO_2S$ (259.32): calcd. C 64.84, H 5.05; found C 64.71, H 4.87.

***N*-{[5-(2,4-Difluorophenyl)thiophen-2-yl]methyl}acetamide (42):** The reaction of 1-bromo-2,4-difluorobenzene (0.193 g, 1 mmol), *N*-(thiophen-2-ylmethyl)acetamide (0.310 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **42** in 82% (0.219 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.41 (m, 1 H, Ar), 7.15 (d, J = 3.0 Hz, 1 H, thiophene), 6.99–6.80 (m, 4 H, Ar and thiophene), 4.52 (d, J = 5.8 Hz, 2 H, CH_2), 1.98 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 161.8 (dd, J = 249.9, 11.6 Hz), 158.5 (dd, J = 252.4, 11.7 Hz), 141.5, 135.5, 129.2 (dd, J = 9.4, 5.0 Hz), 126.7, 125.6 (d, J = 5.8 Hz), 118.4 (dd, J = 13.0, 4.0 Hz), 111.6 (dd, J = 21.5, 3.7 Hz), 104.3 (t, J = 26.1 Hz), 38.1, 22.7 ppm. $C_{13}H_{11}F_2NOS$ (267.30): calcd. C 58.41, H 4.15; found C 58.60, H 4.27.

***tert*-Butyl (Thiophen-2-ylmethyl)carbamate (43):** (Thiophen-2-ylmethyl)amine (1.1 mL, 8.7 mmol) was slowly added to a solution of di-*tert*-butyl dicarbonate (2.1 mg, 9.6 mmol) and triethylamine (1.2 mL, 8.7 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give **43** in 65% yield (1.20 g), which was used without any further purification as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.20 (m, 1 H, thiophene), 6.95–6.90 (m, 2 H, thiophene), 4.90 (m, 1 H, NH), 4.47 (d, J = 5.5 Hz, 2 H, CH_2), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 141.9, 126.7, 125.3, 124.8, 79.6, 39.5, 28.3 ppm. $C_{10}H_{15}NO_2S$ (213.30): calcd. C 56.31, H 7.09; found C 56.40, H 7.11.

***tert*-Butyl {[5-(4-Formylphenyl)thiophen-2-yl]methyl}carbamate (44):** The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), *tert*-butyl (thiophen-2-ylmethyl)carbamate (0.426 g, 2 mmol), and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) at 120 °C afforded **44** in 74% (0.235 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.96 (s, 1 H, CHO), 7.84 (d, J = 8.4 Hz, 2 H, Ar), 7.68 (d, J = 8.4 Hz, 2 H, Ar), 7.27 (d, J = 3.6 Hz, 1 H, thiophene), 6.95 (d, J = 3.6 Hz, 1 H, thiophene), 5.15 (m, 1 H, NH), 4.47 (d, J = 5.7 Hz, 2 H, CH_2), 1.49 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 155.6, 144.2, 141.9, 140.1, 135.0, 130.4, 126.7, 125.7, 124.8, 79.9, 39.8, 28.4 ppm. $C_{17}H_{19}NO_3S$ (317.40): calcd. C 64.33, H 6.03; found C 64.40, H 6.10.

***tert*-Butyl {[5-(4-Cyanophenyl)thiophen-2-yl]methyl}carbamate (45):** The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), *tert*-butyl (thiophen-2-ylmethyl)carbamate (0.426 g, 2 mmol), and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) at 120 °C afforded **45** in 58% (0.182 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 4 H, Ar), 7.27 (d, J = 3.6 Hz, 1 H, thiophene), 6.96 (d, J = 3.6 Hz, 1 H, thiophene), 5.02 (m, 1 H, NH), 4.49 (d, J = 5.7 Hz, 2 H, CH_2), 1.49 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 144.3, 141.3, 138.6, 132.6, 126.6, 125.7, 124.7, 118.8, 110.4, 80.0, 39.7, 28.3 ppm. $C_{17}H_{18}N_2O_2S$ (314.40): calcd. C 64.94, H 5.77; found C 64.88, H 5.80.

***N*-[2-(Thiophen-2-yl)ethyl]acetamide (46):** Acetic anhydride (0.9 mL, 9.4 mmol) was slowly added to a solution of [2-(thiophen-2-yl)ethyl]amine (1 g, 7.9 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 20 h. Then, the solvent was removed, and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give **46** in 72% (0.96 g) yield as a yellow solid, which was used without any further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.07 (d, J = 5.1 Hz, 1 H, thiophene), 6.87 (dd, J = 5.1, 2.9 Hz, 1 H, thiophene), 6.77 (d, J = 2.9 Hz, 1 H, thiophene), 6.74 (m, 1 H, NH), 3.44 (q, J = 7.0 Hz, 2 H, CH_2), 2.97 (t, J = 7.0 Hz, 2 H, CH_2), 1.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 141.0, 126.6, 124.8, 123.4, 40.7, 29.4, 22.7 ppm. $C_8H_{11}NOS$ (169.25): calcd. C 56.77, H 6.55; found C 56.72, H 6.47.

***N*-{2-[5-(4-Formylphenyl)thiophen-2-yl]ethyl}acetamide (47):** The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), *N*-(thiophen-2-ylethyl)acetamide (0.338 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **47** in 89% (0.243 g) yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.95 (s, 1 H), 7.84 (d, J = 8.4 Hz, 2 H, Ar), 7.67 (d, J = 8.4 Hz, 2 H, Ar), 7.28 (d, J = 3.6 Hz, 1 H, thiophene), 6.85 (d, J = 3.6 Hz, 1 H, thiophene), 5.95 (m, 1 H, NH), 3.56 (q, J = 6.6 Hz, 2 H, CH_2), 3.06 (t, J = 6.6 Hz, 2 H, CH_2), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 170.2, 143.5, 141.0, 140.0, 134.8, 130.4, 126.9, 125.5, 125.0, 40.7, 30.3, 23.2 ppm. $C_{15}H_{15}NO_2S$ (273.35): calcd. C 65.91, H 5.53; found C 65.82, H 5.60.

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***N*-{2-[5-(*p*-Tolyl)thiophen-2-yl]ethyl}acetamide (48):** The reaction of 4-bromotoluene (0.171 g, 1 mmol), *N*-[2-(thiophen-2-yl)ethyl]acetamide (0.338 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (6.1 mg, 0.01 mmol) afforded **48** in 88% (0.228 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.4 Hz, 2 H, Ar), 7.16 (d, J = 8.4 Hz, 2 H, Ar), 7.09 (d, J = 3.6 Hz, 1 H, thiophene), 6.77 (d, J = 3.6 Hz, 1 H, thiophene), 5.78 (m, 1 H, NH), 3.54 (q, J = 6.6 Hz, 2 H, CH_2), 3.00 (t, J = 6.6 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 143.0, 140.4, 137.1, 131.5, 129.4, 126.1, 125.3, 122.2, 40.7, 30.0, 23.1, 31.1 ppm. $C_{15}H_{17}NOS$ (259.37): calcd. C 69.46, H 6.61; found C 69.60, H 6.67.

***N*-{2-[5-(2-Cyanophenyl)thiophen-2-yl]ethyl}acetamide (49):** The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), *N*-[2-(thiophen-2-yl)ethyl]acetamide (0.338 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.23 mg, 0.001 mmol) afforded **49** in 91% (0.246 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.4 Hz, 1 H, Ar), 7.60–7.50 (m, 2 H, Ar), 7.42 (d, J = 3.6 Hz, 1 H, thiophene), 7.40–7.30 (m, 1 H, Ar), 6.83 (d, J = 3.6 Hz, 1 H, thiophene), 6.12 (m, 1 H, NH), 3.52 (q, J = 6.6 Hz, 2 H, CH_2), 3.02 (t, J = 6.6 Hz, 2 H, CH_2), 1.96 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 144.0, 137.7, 137.5, 134.3, 133.1, 129.6, 127.6, 127.4, 126.5, 119.0, 109.3, 40.8, 30.0, 23.1 ppm. $C_{15}H_{14}N_2OS$ (270.35): calcd. C 66.64, H 5.22; found C 66.51, H 5.30.

***N*-{2-[5-(Pyridin-3-yl)thiophen-2-yl]ethyl}acetamide (50):** The reaction of 3-bromopyridine (0.157 g, 1 mmol), *N*-[2-(thiophen-2-yl)-ethyl]acetamide (0.338 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) afforded **50** in 84% (0.207 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (s, 1 H, pyridine), 8.41 (d, J = 3.4 Hz, 1 H, pyridine), 7.75 (d, J = 7.9 Hz, 1 H, pyridine), 7.26 (dd, J = 7.9, 3.4 Hz, 1 H, pyridine), 7.14 (d, J = 3.6 Hz, 1 H, thiophene), 6.80 (d, J = 3.6 Hz, 1 H, thiophene), 6.52 (m, 1 H, NH), 3.52 (q, J = 6.6 Hz, 2 H, CH_2), 3.02 (t, J = 6.6 Hz, 2 H, CH_2), 1.96 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 147.6, 146.0, 142.6, 138.3, 132.6, 130.4, 126.5, 124.1, 123.6, 40.7, 30.0, 23.0 ppm. $C_{13}H_{14}N_2OS$ (246.33): calcd. C 63.39, H 5.73; found C 63.47, H 5.87.

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