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Palladium-Acetate Catalyst for Regioselective Direct Arylation at C2 of 3-Furanyl or 3-Thiophenyl Acrylates with Inhibition of Heck Type Reaction

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Abstract: Pd(OAc)2 / KOAc was found to be an efficient catalytic system for the direct arylation of thiophene and furan derivatives bearing an acrylate at C3. The selectivity of the reaction strongly depends on the nature of the coordinating base. Na2CO3 and Li2CO3 favours the Heck type reaction; whereas the use of KOAc or CsOAc promotes regioselective arylation at C2 of the heteroarene and inhibits the Heck type reaction. The direct arylation products were obtained in moderate to good yields using only 0.1 mol% of catalyst. Electron-withdrawing substituent on aryl bromide such as acetyl, formyl, ester, nitrile or nitro, favours the reaction; whereas electron-donating ones are unfavourable.

1. Introduction

Substituted thiophenes or furans, including arylated or vinylated ones, continue to attract the attention of synthetic organic chemists, due to their inherent biological properties. For example, Pizotifen is used to reduce migraine headaches, Orpanoxin is a nonsteroidal anti-inflammatory drug, Nalfurafine a drug for the treatment of uremic pruritus, Ketotifen an antihistamine drug, and Canagliflozin is an experimental drug for the treatment of type two diabetes.

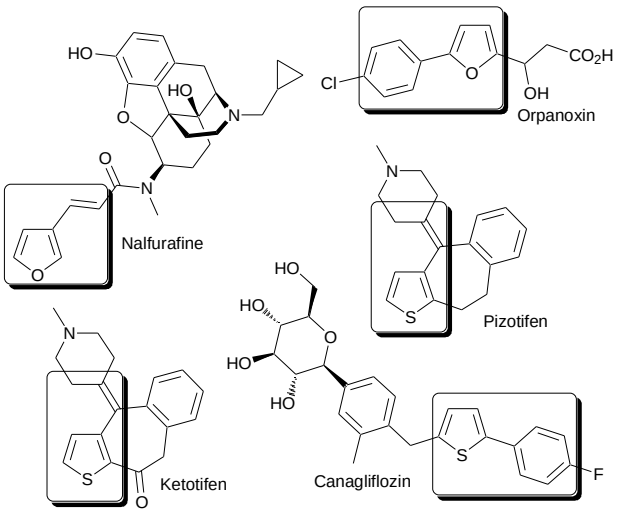


Figure 1.

Conventional methods for the introduction of aryl substituents on such heteroaromatics include metal catalysed cross-coupling reactions such as Suzuki, Stille or Negishi type reactions,[1] which make possible the coupling of aryl halides with organometallic derivatives of thiophenes or furans. However, they require the preliminary preparation of a requisite organometallic species. Ohta and co-workers reported in 1990 that the direct arylation of several heteroaromatics with aryl halides via a C–H bond activation proceed in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst.[2] Since this report, the palladium-catalysed direct arylation of thiophenes or furans derivatives with aryl halides has proven to be a cost-effective and environmentally attractive method for the synthesis of a wide variety of arylated heterocycles.[3-7]

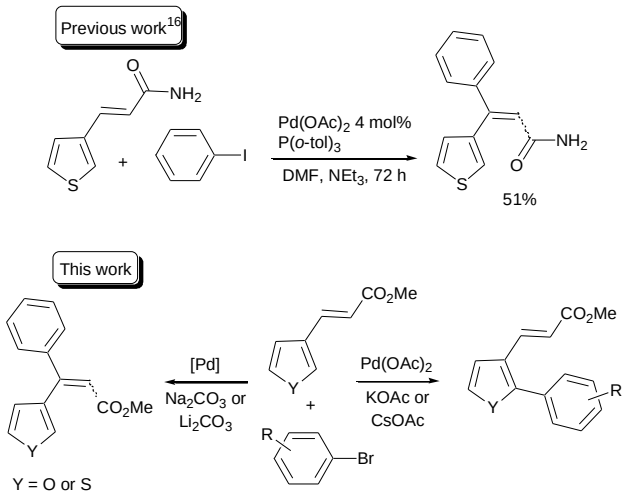
However, so far, the palladium-catalysed *regiocontrolled* direct arylation of 3-substituted thiophenes or furans has attracted less attention.[6,7] In 2003 Sharp and co-workers reported conditions that allowed the regioselective arylation of methyl 3-thiophene carboxylate.[7a] The use of $Pd(PPh_3)_4$ in toluene selectively gave the 2-arylated thiophene; whereas, $Pd_2(dba)_3$ in NMP gave a mixture of 2- and 5-arylated thiophenes in a 15:51 ratio. Bilodeau and co-workers have examined the regioselectivity of the arylation of 3-methylthiophene with bromobenzene using $Pd[(P(t\text{-}Bu)_3]_2$ as the catalyst. They obtained a mix-

ture of the 2- and 5-phenylated thiophenes in a 3.3/1 ratio (30% yield of 2-phenylation and 9% yield of the 5-phenylated thiophene).[7b] Recently, Fagnou and co-workers have reported the direct arylation of 3-*n*-hexylthiophene with 4-bromonitrobenzene.[7c] A mixture of C2 and C5 arylation products was obtained in a 1.3:1 ratio. The direct arylation of 3-methoxythiophene has been explored by Borghese and co-workers.[6b] With this reactant, the 2-arylated thiophenes were regioselectively obtained in 28-60% yields. Thus, for palladium-catalysed direct arylations of 3-substituted thiophenes or furans, mixtures of C2 and C5 arylated products were often obtained, and the influence of the nature of the C3 substituents on the regioselectivity remains largely unexplored.

We have recently reported that $Pd(OAc)_2$ associated to potassium carbonate efficiently catalyses the direct 5-arylation of furans or thiophenes bearing enal, enone or acrylate functions at carbon C2, with inhibition of the Heck type reaction. The nature of the base was found to be crucial to control the selectivity of the arylation.[15] In the presence of potassium carbonate as the base, the direct arylation at C5 is favoured; whereas the use of potassium fluoride selectively gave the Heck type product.

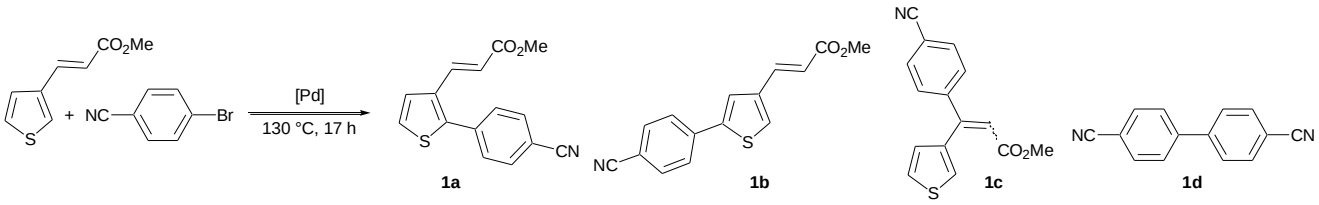
To our knowledge, the intermolecular palladium-catalysed direct arylation of thiophenes or furans bearing acrylate functions at carbon C3 has not been reported (Scheme 1, bottom). This is certainly due to the possible competitive Heck reaction with such substrates.[8-11] Heck reactions with benzalacetone, cinnamates or chalcone, proceed nicely.[12-14] Moreover, an example of Heck type reaction of 3-thiophen-3-ylacrylamide with iodobenzene has been described by Park and co-workers (Scheme 1, top).[16]

Here, we wish to report that $Pd(OAc)_2$ in association with KOAc or CsOAc as the base/ligand provides an efficient catalyst for the regioselective direct arylation at C2 with inhibition of the non-desired Heck type reaction of methyl (*E*)-3-(thiophen-3-yl)acrylate and methyl (*E*)-3-(furan-3-yl)acrylate using a variety of aryl bromides.



Scheme 1.

Table 1. Influence of the reaction conditions for palladium-catalysed coupling of methyl (*E*)-3-(thiophen-3-yl)acrylate with 4-bromobenzonitrile.



Entry	Catalyst (mol%)	Solvent	Base	Conversion of 4-bromobenzonitrile (%)	Ratio **1a**:**1b**:**1c**:**1d** (%)	Yield in **1a** or **1c** (%)
1	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	KOAc	100	87:11:1:1	67[a]
2	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	CsOAc	85	85:12:1:2	65[a]
3	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	NaOAc	88	73:10:13:4	-
4	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	Cs_2CO_3	64	37:10:14:39	-
5	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	K_2CO_3	97	39:9:26:26	-
6	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	Na_2CO_3	97	5:1:80:14	42[b]
7	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	Li_2CO_3	100	2:0:83:15	40[b]
8	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	KF	30	43:7:35:15	-
9	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	nBu$_4$NOAc	31	30:0:60:10	-
10	$PdCl(C_3H_5)(dppb)$ (2)	DMAc	$(NH_4)_2CO_3$	7	0:0:85:15	-
11	$PdCl(C_3H_5)(dppb)$ (2)	NMP	KOAc	100	86:11:1:2	-
12	$PdCl(C_3H_5)(dppb)$ (2)	DMF	KOAc	100	85:10:2:3	-
13	$PdCl(C_3H_5)(dppb)$ (2)	Dioxane	KOAc	100	64:14:16:6	-
14	$PdCl(C_3H_5)(dppb)$ (2)	Cyclopentyl methyl ether	KOAc	100	54:14:28:4	-
15	$PdCl(C_3H_5)(dppb)$ (2)	Xylene	KOAc	100	32:7:58:3	-
16	$PdCl(C_3H_5)(dppb)$ (2)	Xylene	Na_2CO_3	11	0:0:9:91	-
17	$PdCl(C_3H_5)(dppb)$ (2)	Diethyl carbonate	KOAc	100	44:12:37:7	-
15	$Pd(OAc)_2$ (2)	DMAc	KOAc	100	84:10:1:5	-
16	$PdCl_2$ (2)	DMAc	KOAc	100	84:9:1:6	-
17	½ $[PdCl(C_3H_5)]_2$ (2)	DMAc	KOAc	100	86:10:1:3	-
21	$Pd(OAc)_2$ (0.1)	DMAc	KOAc	100	88:11:1:0	71[a]
22	½ $[PdCl(C_3H_5)]_2$ (0.1)	DMAc	KOAc	100	86:13:1:0	69[a]
23	$Pd(OAc)_2$ (0.1)	DMAc	KOAc	100	89:6:1:4	-[c]
24	$Pd(OAc)_2$ (0.1)	DMAc	KOAc	92	88:6:1:5	-[d]

Conditions: methyl (*E*)-3-(thiophen-3-yl)acrylate (2 eq.), 4-bromobenzonitrile (1 eq.), base (2 eq.), 130 °C, 17 h, yield of **1a**. [a] isolated yield of **1a**. [b] isolated yield of *Z* isomer of **1c**. [c] reaction temp. 150 °C. [d] reaction temp. 110 °C.

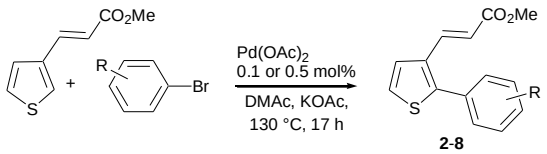
2. Results and discussion

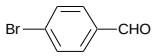
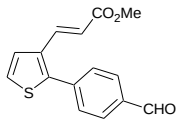
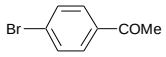
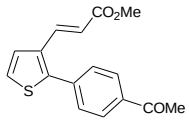
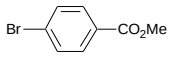
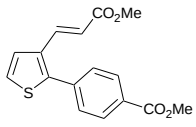
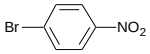
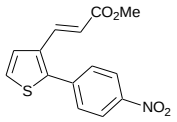
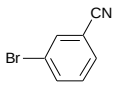
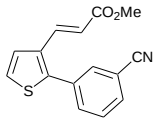
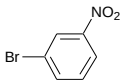
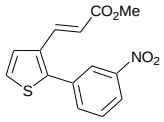
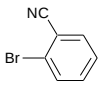
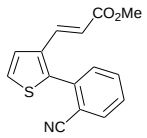
For this study, based on previous results,[15] DMAc was chosen as the solvent. The reactions were performed at 130 °C under argon in the presence 2 mol% of $PdCl(C_3H_5)$(dppb) as the catalyst. Using these conditions, the coupling of methyl (*E*)-3-(thiophen-3-y)lacrylate with 4-bromobenzonitrile using KOAc as the base gave the C2-arylated thiophene **1a** as the major product in 87% selectivity. The C5-arylated thiophene **1b** was also obtained in 11% selectivity; whereas, only trace amount of the Heck type products **1c** were observed (Table 1, entry 1). A very similar regioselectivity was observed in the presence of CsOAc as the base (Table 1, entry 2). On the other hand, NaOAc gave a mixture of C2- and C5-arylated products **1a** + **1b** and Heck type product **1c** in 81:13 ratio (Table 1, entry 3). This difference of selectivity might arise from a stronger interaction of the acetate anion with Na^+ cation than with K^+ or Cs^+ in DMAc. Consequently, the transfer of the acetate to the palladium(II) would be faster with KOAc or CsOAc than with NaOAc and this should favour a C-H concerted metalation deprotonation mechanism.[17a,b] With nBu$_4$NOAc as the base, **1c** was the major product (Table 1, entry 9). K_2CO_3, Cs_2CO_3, KF and $(NH_4)_2CO_3$ also led to mixtures of products (Table 1, entries 4, 5, 8 and 10). It should be noted that the use of Na_2CO_3 or Li_2CO_3 allows the access to the Heck type products **1c** (*Z* + *E* stereoisomers) in 80% or 83% selectivities. Then, *Z* isomer of **1c** was isolated in 42% or 40% yields, respectively (Table 1, entries 6 and 7). This result seems to confirm a slower transfer of the carbonate to palladium(II) with Li^+ or Na^+ cations than with K^+ or Cs^+, which might be due to the poor solubility of Na_2CO_3 or Li_2CO_3 in DMAc.[17c] Such slow carbonate transfer favours Heck type reaction.

Then, we examined the influence of the solvent. Both NMP and DMF led to similar results as DMAc; whereas, poor selectivities were observed in dioxane, cyclopentyl methyl ether, xylene or diethyl carbonate (Table 1, entries 11-15 and 17). The use of xylene associated to Na_2CO_3 gave a mixture of **1c** and **1d** in a 9:91 ratio. Moreover, a very low conversion of 4-bromobenzonitrile was observed (Table 1, entry 16). We also examined the influence of the nature and loading of the catalyst. The use of only 0.1 mol% $Pd(OAc)_2$ or ½ $[PdCl(C_3H_5)]_2$ gave **1a** in 88% and 86% selectivity and in 68% and 66% yields showing that the dppb ligand is not really needed (Table 1, entries 21 and 22). Finally, the influence of the reaction temperature was examined. At more elevated or lower temperatures (110 and 150 °C), very similar selectivities were observed. However, at 110 °C, the conversion of 4-bromobenzonitrile was only 92% (Table 1, entries 23 and 24).

Then, the scope of the coupling of methyl (*E*)-3-(thiophen-3-y)lacrylate using other aryl bromides was investigated (Scheme 3, table 2). These reactions were performed using DMAc, AcOK, 130 °C and 0.5-0.1 mol% $Pd(OAc)_2$ as the catalytic system. From 4-bromobenzaldehyde and 4-bromoacetophenone, the C2-arylated thiophenes **2** and **3** were only obtained in moderate yields due to partial decomposition of the reactants or products (Table 2, entries 1 and 2). On the other hand, good yields of 63% and 69% were obtained from methyl 4-bromobenzoate and 4-bromonitrobenzene (Table 2, entries 3 and 4). The reactivity of *meta*- and *ortho*-substituted aryl bromides was also examined. From 3-bromobenzonitrile and 3-bromonitrobenzene, products **6** and **7** were obtained in 61% and 69% yields, respectively; whereas, from the more congested substrate, 2-bromobenzonitrile product **8** was isolated in only 46% yield (Table 2, entries 5-7). It should be noted that, in all cases, a highly regioselective reaction in favour of the direct arylation at C2 was observed.

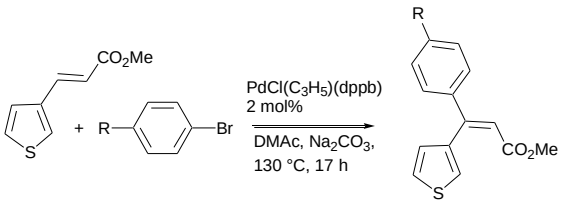
Table 2. Scope of the palladium catalysed direct arylation of methyl (*E*)-3-thiophen-3-yl-acrylate



Entry	Aryl bromide	Product	Yield (%)
1		 **2**	40
2		 **3**	46
3		 **4**	63
4		 **5**	69
5		 **6**	61[a]
6		 **7**	69
7		 **8**	46

Conditions: $Pd(OAc)_2$ 0.1 mol%, methyl (*E*)-3-(thiophen-3-y)lacrylate (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), DMAc, 130 °C, 17 h. [a] $Pd(OAc)_2$ 0.5 mol%.

We also extended the scope of the Heck type reaction with methyl (*E*)-3-(thiophen-3-y)lacrylate using 4-bromoacetophenone and 4-bromobenzaldehyde and Na_2CO_3 as the base (Scheme 2). In both cases the desired Heck type products were selectively obtained as a mixture of *Z* and *E* isomers (Ratio *Z*:*E* = 3:2). Purification on silica gel chromatography gave the Z isomers **9** and **10** in pure forms. For this reaction, $PdCl(C_3H_5)(dppb)$ 2 mol% was used as the catalyst in the presence of Na_2CO_3 as the base.



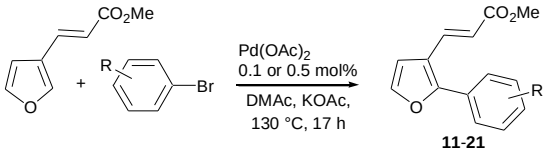
R	Product	Yield (%)
COMe	**9**	52
CHO	**10**	45

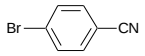
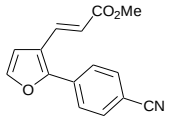
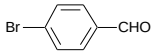
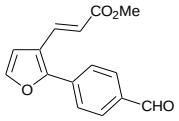
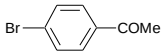
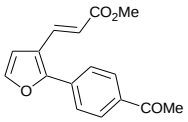
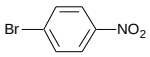
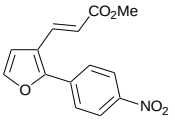
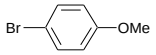
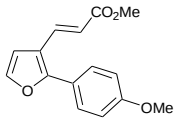
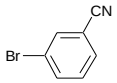
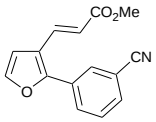
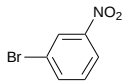
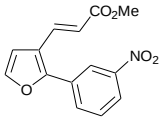
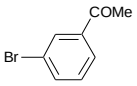
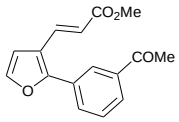
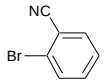
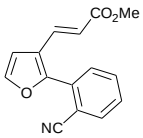
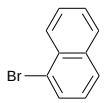
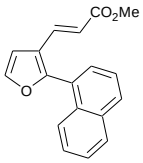
Scheme 2.

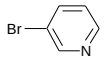
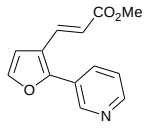
Then, the reactivity of methyl (*E*)-3-(furan-3-yl)acrylate was examined (Table 3). Again, a good yield in C2-arylated furan **11** was obtained in the presence of 4-bromobenzonitrile and 0.1 mol% $Pd(OAc)_2$ / KOAc as the catalytic system (Table 3, entry 1). Similar yields were obtained from 4-bromoacetophenone and 4-bromonitrobenzene (Table 3, entries 3 and 4). On the other hand, from 4-bromobenzaldehyde, **12** was only obtained in 42% yield due to some decomposition of the reactants (Table 3, entry 2). A poor yield in **15** was also obtained in the presence of the electron-rich 4-bromoanisole due to a partial conversion of this aryl bromide (Table 3, entry 5). Both 3-bromobenzonitrile and 3-bromonitrobenzene were successfully coupled to methyl (*E*)-3-furan-3-ylacrylate to give **16** and **17** in good yields (Table 3, entries 7 and 8). A lower reactivity of 1-bromonaphthalene was observed. With this reactant, a higher catalyst loading of 0.5 mol% had to be employed in order to

obtain high conversion of the aryl bromide to produce **20** in 62% yield (Table 3, entry 11). Finally, 3-bromopyridine was employed as the coupling partner. In the presence of 0.1 mol% $Pd(OAc)_2$ as the catalyst, only trace of **19** was detected. On the other hand, the use of 2 mol% $PdCl(C_3H_5)$(dppb) led to **21** in 58% yield (Table 3, entries 12 and 13).

Table 3. Scope of the palladium-catalysed direct arylation of methyl (*E*)-3-(furan-3-yl)acrylate

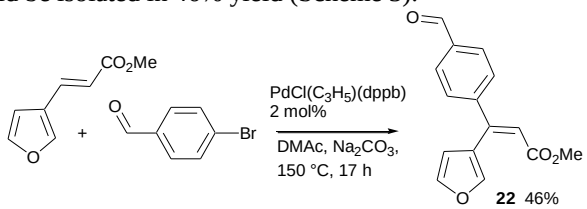


Entry	Aryl bromide	Product	Yield (%)
1		 **11**	70
2		 **12**	42
3		 **13**	73
4		 **14**	76
5			trace
6		 **15**	16[a]
7		 **16**	66
8		 **17**	75
9		 **18**	52
10		 **19**	57
11		 **20**	62[b]

12			trace
13		 **21**	58[a]

Conditions: $Pd(OAc)_2$ 0.1 mol%, methyl (*E*)-3-(furan-3-yl)acrylate (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), DMAc, 130 °C, 17 h. [a] $PdCl(C_3H_5)$(dppb) 2 mol%, 150 °C. [b] $Pd(OAc)_2$ 0.5 mol%, 150 °C.

The use of Na_2CO_3 as the base for the reaction of methyl (*E*)-3-(furan-3-yl)acrylate with 4-bromobenzaldehyde also produced very selectively the Heck type products as a mixture of Z and E stereoisomers (*Z*:*E* ratio = 3:2); whereas, **12** was detected in less than 2%. The Z isomer **22** could be isolated in 46% yield (Scheme 3).



Scheme 3.

In summary, we have demonstrated that the selectivity of palladium-acetate catalysed reaction of 3-thiophen-3-ylacrylate and 3-furan-3-ylacrylate with aryl bromides strongly depends on the nature of the coordinating base. The use of Na_2CO_3 or Li_2CO_3 selectively led to the Heck type products, whereas, KOAc or CsOAc promotes regioselective direct arylation at C2 of the heteroarene. This complete change in selectivity might come from a stronger interaction of the acetate or carbonate anion with Li^+ or Na^+ cation than with K^+ or Cs^+ in DMAc, thus avoiding the acetate to play its coordinating ligand/base role for C-H bond deprotonation. These direct arylations can generally be performed using low catalyst loadings (0.5-0.1 mol%) of a commercially available air-stable and phosphine-free catalyst. Electron-withdrawing substituent on the aryl bromide such as acetyl or nitrile favours the reaction; whereas electron-donating substituents are unfavourable. A range of functions such as acetyl, formyl, ester, nitro or nitrile on the aryl bromide is tolerated. This reaction allows the synthesis in only one step of a variety of 2-arylated furans or thiophenes bearing acrylates at carbon 3 without preparation of organometallic derivatives. Finally, due to environmental considerations, the advantage of such inert wastes procedure (formation of acetic acid and potassium bromide) should become increasingly important for industrial processes.

3. Experimental

General Remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMAc (*N*,*N*-dimethylacetamide) (99%) was purchased from Acros. KOAc (99%), $Pd(OAc)_2$ (45.9-48.4%), $[Pd(C_3H_5)Cl]_2$ (56.5%) and dppb [1,4-bis(diphenylphosphino)butane] (98%) were purchased from Alfa Aesar. Commercial aryl bromides and heteroarenes were used without purification. The reactions were followed by GC and NMR spectroscopic analysis. ^1H and ^{13}C spectra were recorded with Bruker 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography was performed on silica gel (230–400 mesh).

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst:[18] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuo. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure

In a typical experiment, the aryl bromide (1 mmol), heteroaromatic derivative (2 mmol), KOAc (0.196 g, 2 mmol) and $Pd(OAc)_2$ (0.22 mg, 0.001 mmol) or (1.1 mg, 0.005 mmol) or $PdCl(C_3H_5)$(dppb) (13.6 mg, 0.02 mmol) (see tables), were dissolved in DMAc (4 mL) under an argon atmosphere. The reaction mixture was stirred at 130 °C for 17 h. After evaporation of the solvent, the product was purified by silica gel column chromatography.

Methyl (*E*)-3-[2-(4-cyanophenyl)thiophen-3-yl]acrylate (1a)

From 4-bromobenzonitrile (0.182 g, 1 mmol), methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol) and KOAc (0.196 g, 2 mmol) as the base, product **1a** was obtained in 71% (0.191 g) yield.

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 143.3, 137.7,

136.4, 133.9, 132.6, 130.2, 126.7, 126.6, 119.6, 118.5, 112.0, 51.8. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_2S$ (269.32): C 66.89, H 4.12; found: C 66.70, H 4.01.

Methyl (*Z*)-3-(4-cyanophenyl)-3-(thiophen-3-yl)acrylate (1c)
From 4-bromobenzonitrile (0.182 g, 1 mmol), methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol) and Na_2CO_3 as the base (0.212 g, 2 mmol), product **1c** was obtained in 42% (0.113 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.37 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.32 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.02 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.29 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 148.8, 145.7, 137.2, 132.2, 129.0, 128.9, 127.0, 125.2, 119.5, 118.4, 112.9, 51.6. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_2S$ (269.32): C 66.89, H 4.12; found: C 66.99, H 4.25. The formation of **methyl (*E*)-3-[(4-cyanophenyl)-3-thiophen-3-yl]acrylate** was also observed before purification, but was not obtained in pure form: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.62 (s, 3H).

Methyl (*E*)-3-[2-(4-formylphenyl)-thiophen-3-yl]acrylate (2)
From 4-bromobenzaldehyde (0.185 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **2** was obtained in 40% (0.109 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 5.1 Hz, 1H), 7.38 (d, *J* = 5.1 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 167.5, 144.2, 139.1, 136.8, 135.8, 133.7, 130.3, 130.2, 126.5, 126.4, 119.3, 51.7. Elemental analysis: calcd (%) for $C_{15}H_{12}O_3S$ (272.32): C 66.16, H 4.44; found: C 66.04, H 4.59.

Methyl (*E*)-3-[2-(4-acetylphenyl)-thiophen-3-yl]acrylate (3)
From 4-bromoacetophenone (0.199 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **3** was obtained in 46% (0.131 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 2H), 6.27 (d, *J* = 15.9 Hz, 1H), 3.70 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 167.6, 144.6, 137.7, 137.0, 136.6, 133.5, 129.9, 128.8, 126.3, 126.2, 119.0, 51.7, 26.7. Elemental analysis: calcd (%) for $C_{16}H_{14}O_3S$ (286.35): C 67.11, H 4.93; found: C 67.35, H 4.98.

Methyl (*E*)-4-[3-(2-methoxycarbonylvinyl)-thiophen-2-yl]acrylate (4)
From methyl 4-bromobenzoate (0.215 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **4** was obtained in 63% (0.190 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 15.9 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 2H), 6.26 (d, *J* = 15.9 Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 166.6, 144.7, 137.6, 137.0, 133.4, 130.1, 129.9, 129.7, 126.3, 126.1, 119.0, 52.3, 51.7. Elemental analysis: calcd (%) for $C_{16}H_{14}O_4S$ (302.35): C 63.56, H 4.67; found: C 63.68, H 4.50.

Methyl (*E*)-3-[2-(4-nitrophenyl)-thiophen-3-yl]acrylate (5)
From 4-bromonitrobenzene (0.202 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **5** was obtained in 69% (0.199 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.5, 142.8, 139.6, 136.3, 134.2, 130.4, 127.3, 126.6, 124.1, 119.8, 51.8. Elemental analysis: calcd (%) for $C_{14}H_{11}NO_4S$ (289.31): C 58.12, H 3.83; found: C 58.30, H 3.97.

Methyl (*E*)-3-[2-(3-cyanophenyl)-thiophen-3-yl]acrylate (6)
From 3-bromobenzonitrile (0.182 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **6** was obtained in 61% (0.164 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.50 (m, 5H), 7.39 (d, *J* = 5.1 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 142.9, 136.3, 134.5, 134.0, 133.7, 133.0, 131.8, 129.8, 126.4, 126.3, 119.5, 118.2, 113.3, 51.8. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_2S$ (269.32): C 66.89, H 4.12; found: C 66.75, H 4.05.

Methyl (*E*)-3-[2-(3-nitrophenyl)-thiophen-3-yl]acrylate (7)
From 3-bromonitrobenzene (0.202 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **7** was obtained in 69% (0.199 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 15.9 Hz, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.30 (d, *J* = 5.1 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (75

MHz, $CDCl_3$) δ 167.4, 142.7, 136.2, 135.6, 134.8, 133.9, 129.9, 126.5, 126.3, 124.5, 123.2, 119.6, 51.8. Elemental analysis: calcd (%) for $C_{14}H_{11}NO_4S$ (289.31): C 58.12, H 3.83; found: C 58.09, H 3.68.

Methyl (*E*)-3-[2-(2-cyanophenyl)-thiophen-3-yl]acrylate (8)
From 2-bromobenzonitrile (0.182 g, 1 mmol) and methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol), product **8** was obtained in 46% (0.124 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.32 (d, *J* = 5.1 Hz, 1H), 7.31 (d, *J* = 15.9 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 140.4, 136.4, 136.3, 135.4, 133.7, 132.7, 132.2, 129.2, 127.1, 125.6, 119.2, 117.4, 113.9, 51.7. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_2S$ (269.32): C 66.89, H 4.12; found: C 66.99, H 4.21.

Methyl (*Z*)-3-(4-acetylphenyl)-3-(thiophen-3-yl)acrylate (9)
From 4-bromoacetophenone (0.199 g, 1 mmol), methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol) and Na_2CO_3 as the base (0.212 g, 2 mmol), product **9** was obtained in 52% (0.149 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.36 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.32 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.03 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.32 (s, 1H), 3.71 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 166.2, 149.8, 145.8, 137.7, 137.5, 129.1, 128.5, 128.4, 126.8, 124.9, 118.7, 51.5, 26.7. Elemental analysis: calcd (%) for $C_{16}H_{14}O_3S$ (286.35): C 67.11, H 4.93; found: C 67.40, H 4.87. The formation of **methyl (*E*)-3-(4-acetylphenyl)-3-thiophen-3-ylacrylate** was also observed before purification, but was not obtained in pure form: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 3.52 (s, 3H), 2.53 (s, 3H).

Methyl (*Z*)-3-(4-formylphenyl)-3-(thiophen-3-yl)acrylate (10)
From 4-bromobenzaldehyde (0.185 g, 1 mmol), methyl (*E*)-3-(thiophen-3-y)lacrylate (0.336 g, 2 mmol) and Na_2CO_3 as the base (0.212 g, 2 mmol), product **10** was obtained in 45% (0.122 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.28 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.24 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 5.0 Hz, 1H), 6.24 (s, 1H), 3.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 166.0, 149.6, 147.1, 137.6, 136.7, 129.6, 129.0, 128.9, 126.8, 125.0, 119.2, 51.6. Elemental analysis: calcd (%) for $C_{15}H_{12}O_3S$ (272.32): C 66.16, H 4.44; found: C 66.41, H 4.64. The formation of **methyl (*E*)-3-(4-formylphenyl)-3-(thiophen-3-yl)acrylate** was also observed before purification, but was not obtained in pure form: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 6.38 (s, 1H), 3.52 (s, 3H).

Methyl (*E*)-3-[2-(4-cyanophenyl)-furan-3-yl]acrylate (11)
From 4-bromobenzonitrile (0.182 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **11** was obtained in 70% (0.177 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.9 Hz, 1H), 7.66 (s, 4H), 7.45 (s, 1H), 6.65 (s, 1H), 6.24 (d, *J* = 15.9 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.6, 143.8, 134.4, 134.0, 132.7, 127.2, 120.2, 120.1, 118.5, 111.8, 110.2, 51.8. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_3$ (253.25): C 71.14, H 4.38; found: C 71.31, H 4.19.

Methyl (*E*)-3-[2-(4-formylphenyl)-furan-3-yl]acrylate (12)
From 4-bromobenzaldehyde (0.185 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **12** was obtained in 42% (0.108 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 15.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.46 (s, 1H), 6.66 (s, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 167.2, 152.4, 143.7, 135.7, 135.4, 134.8, 130.2, 127.4, 120.1, 119.8, 110.1, 51.8. Elemental analysis: calcd (%) for $C_{15}H_{12}O_4$ (256.25): C 70.31, H 4.72; found: C 70.11, H 4.89.

Methyl (*E*)-3-[2-(4-acetylphenyl)-furan-3-yl]acrylate (13)
From 4-bromoacetophenone (0.199 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **13** was obtained in 73% (0.197 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.1 Hz, 2H), 7.87 (d, *J* = 15.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 3.82 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 167.3, 152.8, 143.5, 136.5, 135.0, 134.1, 128.9, 127.0, 119.6, 119.4, 109.9, 51.8, 26.7. Elemental analysis: calcd (%) for $C_{16}H_{14}O_4$ (270.28): C 71.10, H 5.22; found: C 71.27, H 5.04.

Methyl (*E*)-3-[2-(4-nitrophenyl)-furan-3-yl]acrylate (14)
From 4-bromonitrobenzene (0.202 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **14** was obtained in 76% (0.207 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 15.9 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 151.2, 144.1, 135.8, 134.3, 127.4, 124.3, 120.8, 120.5, 110.3, 51.9. Elemental analysis: calcd (%) for $C_{14}H_{11}NO_5$ (273.24): C 61.54, H 4.06; found: C 61.69, H 4.14.

Methyl (*E*)-3-[2-(4-methoxyphenyl)-furan-3-yl]acrylate (15)
From 4-bromoanisole (0.187 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **15** was obtained in 16% (0.041 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 15.9 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.34 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.58 (s, 1H), 6.14 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 160.1, 154.9, 142.1, 136.1, 128.8, 122.7, 117.4, 116.8, 114.4, 109.2, 55.4, 51.6. Elemental analysis: calcd (%) for $C_{15}H_{14}O_4$ (258.27): C 69.76, H 5.46; found: C 69.89, H 5.60.

Methyl (*E*)-3-[2-(3-cyanophenyl)-furan-3-yl]acrylate (16)
From 3-bromobenzonitrile (0.182 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **16** was obtained in 66% (0.167 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 15.9 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 6.64 (s, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.4, 143.5, 134.3, 131.8, 131.3, 131.1, 130.4, 129.8, 119.9, 119.4, 118.2, 113.4, 109.9, 51.8. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_3$ (253.25): C 71.14, H 4.38; found: C 71.08, H 4.54.

Methyl (*E*)-3-[2-(3-nitrophenyl)-furan-3-yl]acrylate (17)
From 3-bromonitrobenzene (0.202 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **17** was obtained in 75% (0.205 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 15.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (s, 1H), 6.66 (s, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 151.3, 143.6, 134.2, 132.6, 131.6, 130.0, 123.1, 121.8, 120.0, 119.7, 109.9, 51.8. Elemental analysis: calcd (%) for $C_{14}H_{11}NO_5$ (273.24): C 61.54, H 4.06; found: C 61.31, H 4.20.

Methyl (*E*)-3-[2-(3-acetylphenyl)-furan-3-yl]acrylate (18)
From 3-bromoacetophenone (0.199 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **18** was obtained in 52% (0.140 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 15.9 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 6.64 (s, 1H), 6.21 (d, *J* = 15.9 Hz, 1H), 3.73 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 166.3, 152.2, 142.0, 136.7, 134.1, 130.5, 129.5, 128.2, 127.2, 126.1, 117.9, 117.6, 108.6, 50.7, 25.7. Elemental analysis: calcd (%) for $C_{16}H_{14}O_4$ (270.28): C 71.10, H 5.22; found: C 71.01, H 5.30.

Methyl (*E*)-3-[2-(2-cyanophenyl)-furan-3-yl]acrylate (19)
From 2-bromobenzonitrile (0.182 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **19** was obtained in 57% (0.144 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.55-7.42 (m, 4H), 6.68 (s, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 150.7, 144.2, 134.5, 134.3, 132.8, 132.6, 130.5, 129.3, 120.8, 119.5, 117.7, 111.8, 109.3, 51.7. Elemental analysis: calcd (%) for $C_{15}H_{11}NO_3$ (253.25): C 71.14, H 4.38; found: C 71.19, H 4.58.

Methyl (*E*)-3-(2-naphthalen-1-ylfuran-3-yl)acrylate (20)
From 1-bromonaphthalene (0.207 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **20** was obtained in 62% (0.172 g) yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.75 (m, 3H), 7.55-7.40 (m, 6H), 6.72 (s, 1H), 6.16 (d, *J* = 15.9 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 155.2, 143.2, 135.8, 133.8, 131.9, 130.2, 129.3, 128.4, 126.9, 126.8, 126.3, 125.7, 125.2, 120.2, 117.6, 108.7, 51.5. Elemental analysis: calcd (%) for $C_{18}H_{14}O_3$ (278.30): C 77.68, H 5.07; found: C 77.51, H 4.87.

Methyl (*E*)-3-(2-pyridin-3-ylfuran-3-yl)acrylate (21)
From 3-bromopyridine (0.158 g, 1 mmol) and methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), product **21** was obtained in 58% (0.133 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.56 (d, J = 3.9 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 15.9 Hz, 1H), 7.43 (s, 1H), 7.34 (dd, J = 7.7, 3.9 Hz, 1H), 6.65 (s, 1H), 6.23 (d, J = 15.9 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 151.2, 149.5, 148.1, 143.6, 134.5, 134.2, 126.3, 123.6, 119.4, 119.3, 109.7, 51.7. Elemental analysis: calcd (%) for $C_{13}H_{11}NO_3$ (229.23): C 68.11, H 4.84; found: C 68.23, H 4.71.

Methyl (*Z*)-3-[(4-formylphenyl)-3-furan-3-yl]acrylate (22)
From 4-bromobenzaldehyde (0.185 g, 1 mmol), methyl (*E*)-3-(furan-3-yl)acrylate (0.304 g, 2 mmol), and Na_2CO_3 as the base (0.212 g, 2 mmol), product **22** was obtained in 46% (0.118 g) yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.65 (m, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.47 (m, 1H), 7.28 (d, J = 0.6 Hz, 1H), 6.50 (m, 1H), 6.16 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 166.0, 147.5, 146.0, 144.9, 142.6, 136.6, 129.6, 129.1, 122.0, 118.7, 112.0, 51.5. Elemental analysis: calcd (%) for $C_{15}H_{12}O_4$ (256.25): C 70.31, H 4.72; found: C 70.51, H 4.60. **Methyl (*E*)-3-[(4-formylphenyl)-3-furan-3-yl]acrylate** was also isolated in low yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.47 (m, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.02 (m, 1H), 6.65 (dd, J = 2.0, 0.9 Hz, 1H), 6.30 (s, 1H), 3.61 (s, 3H).

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