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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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$Pd(OAc)_2$/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. $Na_2CO_3$ and $Li_2CO_3$ 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 uraemic pruritus, Ketotifen an antihistamine drug, and Canagliflozin is an experimental drug for the treatment of type two diabetes (Fig. 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]

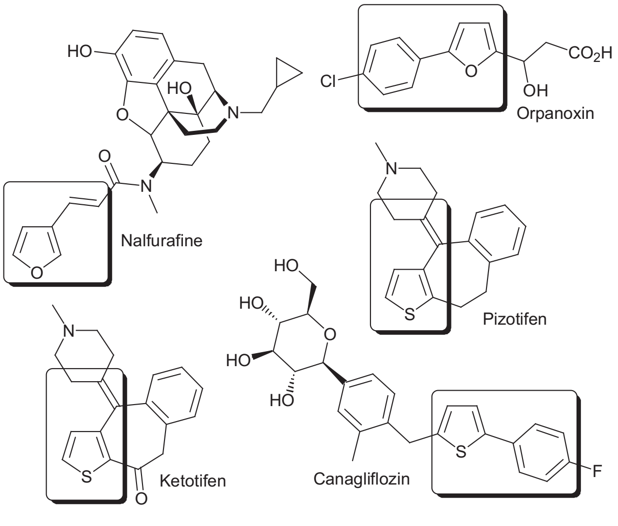

**Fig. 1.** Examples of bioactive furan or thiophene derivatives.

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

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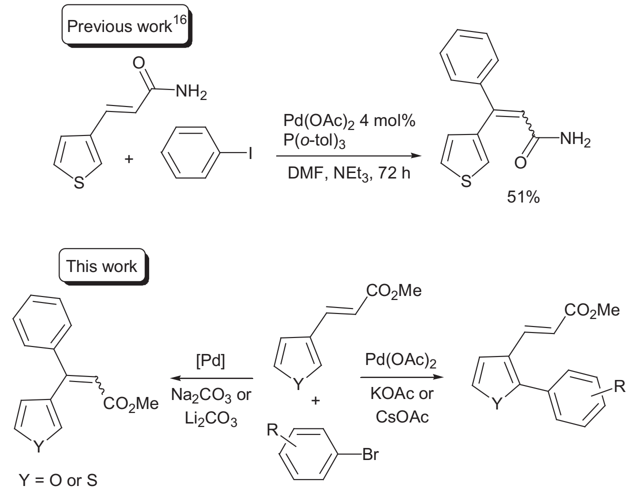
5-arylated thiophenes in a 15:51 ratio. Bilodeau and co-workers have examined the regioselectivity of the arylation of 3-methylthiophene with bromobenzene using Pd[(P(*t*-Bu)$_3$)]$_2$ as the catalyst. They obtained a mixture of the 2- and 5-phenylated thiophenes in a 3.3/1 ratio (30% yield of 2-phenylation 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]



**Scheme 1.**

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.

## 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$_3$H$_5$)(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 metallation deprotonation mechanism.[17a,b] With $^n$Bu$_4$NOAc as the base, **1c** was the major product (Table 1, entry 9). K$_2$CO$_3$, Cs$_2$CO$_3$, KF, and (NH$_4$)$_2$CO$_3$ also led to mixtures of products (Table 1, entries 4, 5, 8, and 10). It should be noted that the use of Na$_2$CO$_3$ or Li$_2$CO$_3$ 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$_2$CO$_3$ or Li$_2$CO$_3$ 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$_2$CO$_3$ 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$_3$H$_5$)]$_2$ 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.

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$_2$CO$_3$ 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$_3$H$_5$)(dppb) 2 mol % was used as the catalyst in the presence of Na$_2$CO$_3$ as the base.

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