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Solvent-Free Palladium-Catalyzed Direct Arylation of Heteroaromatics with Aryl Bromides

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Solvent is one of the major sources of waste in the course of catalyzed direct arylations. Some palladium-catalyzed direct arylations of heteroaromatics can be advantageously performed without any solvent. In the presence of palladium catalysts (1 mol%) and potassium acetate as the base, the direct 5-arylation of some thiazoles, thiophenes, furans, or pyrroles with aryl bromides as coupling partners proceeds highly regioselectively and in moderate to high yields. However, the use of these solvent-free conditions is limited to electron-deficient aryl bromides.

Introduction

The direct arylation of heteroaromatics is an important field for research in organic synthesis due to the biological or physical properties of aryl/heteroaryl derivatives. Ohta et al. have reported that the direct 2- or 5-arylation of several heteroaromatics with aryl halides proceed in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst and *N*,*N*-dimethylacetamide (DMAc) as the solvent.[1] Since these innovative results, the palladium-catalyzed direct arylation of heteroaryl derivatives with aryl halides has proved to be a powerful method for the cost-effective and environment-friendly synthesis of a wide variety of arylated heterocycles.[2] Indeed, the major byproducts of the reaction are a base associated to HX (X = Cl, Br, I), instead of metallic salts produced under classical procedures (Suzuki, Negishi, or Stille cross-coupling).[3] Moreover, the method avoids the preliminary preparation of a requisite organometallic compound thus reducing the number of steps to prepare these compounds. However, the majority of these reactions are currently performed in relatively toxic solvents, such as DMF, DMAc, *N*-methylpyrrolidone (NMP), dioxane, or xylene.[4–10]

Recently, a few solvents, which can be considered as "greener"[11] according to principles by Anastas et al., have been employed for direct arylations.[12] For example, the direct arylation of oxazoles, thiazoles, indazoles, or indoles using water as the solvent was reported by the research groups of Greaney and Djakovitch.[13] René et al. developed biphasic conditions using water and EtOAc for the direct arylation of thiophenes.[14a] Polyethylene glycol (PEG 20 000) has been found to be a useful solvent for the direct arylation of triazoles.[14b] Carbonates, ethers, or alcohols have also been used successfully for the direct arylation of heteroaromatics (thiazole, thiophene, or oxazole derivatives).[15] Finally, the ruthenium-catalyzed direct arylation of 2-arylpyridines in carbonates or water has been recently reported by Dixneuf et al.[16]

Waste prevention is a major requirement in organic syntheses. One of the most promising approaches to reduce waste is solvent-free reactions.[17] Solvent-free organic reactions make syntheses easier due to the reduction in reactor size and simpler workup. Such conditions also save energy, and reduce solvent waste, hazards, and toxicity. Therefore, the use of solvent-free conditions for palladium-catalyzed direct arylations would provide an environmentally attractive procedure for the preparation of arylated heteroarenes.[12a]

To our knowledge, only one example of direct arylation using solvent-free conditions has been reported. Bedford et al. described the reaction of aryl *N*,*N*-diethyl carbamates with diaryliodonium salts, [ArI(mes)][OTf] (OTf = CF_3SO_3, mes = 2,4,6-$Me_3C_6H_2$), using 5 mol% $Pd(OAc)_2$ as the catalyst to selectively give monoarylated free phenol products in the absence of solvent.[18] Notably, phenols were isolated in yields that were higher than those achieved previously in acetic acid. On the other hand, to our knowledge, solvent-free conditions have not been employed for the direct arylation of heteroaromatics. Herein, we report the use of such conditions for palladium-catalyzed direct arylations of a range of heteroaromatic derivatives with aryl bromides.

Results and discussion

To determine the suitability of these conditions for palladium-catalyzed direct arylations, a first set of reactions using benzoxazole and 4-bromobenzonitrile as the coupling partners was carried out under previously reported conditions, but without solvent (Scheme 1). In the presence of polar solvents such as DMF, NMP, dioxane, or diethylcarbonate, high yields of coupling product (**1**) were obtained.[9b,14b] However, in the absence of a solvent, **1** was not obtained, and several unidentified products were formed. The direct arylation of oxazoles at C2

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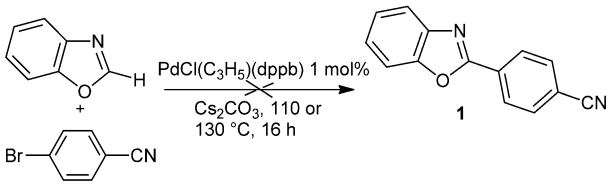


Scheme 1. Attempts at coupling benzoxazole with 4-bromobenzonitrile.

seemed to proceed through a simple deprotonation of the oxazole by the base.[19] Such deprotonated oxazoles were probably less stable in the absence of solvents than in DMF or in carbonates.

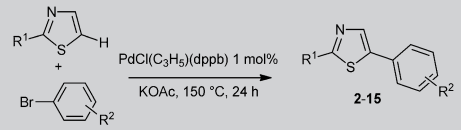
Then, we examined the reactivity of 2-*i*-butylthiazole with a set of aryl bromides without solvent. Because 5-arylation of thiazoles proceeded through a different mechanism than 2-arylation (concerted metallation–deprotonation mechanism)[2i,j,8b] we could expect a different reactivity of these two heteroarenes.[15d] Moreover, such couplings have already been performed by Greaney et al. using water as the solvent.[13a]

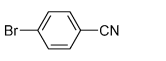
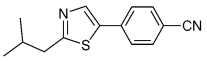
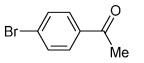
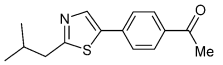
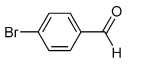
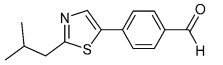
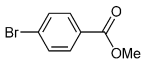
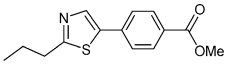
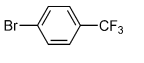
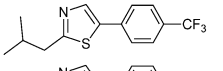
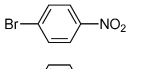
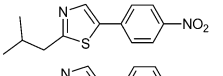
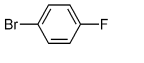
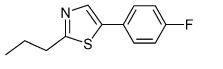
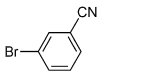
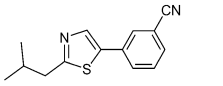
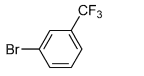
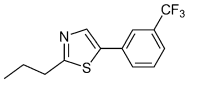
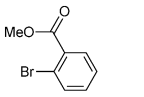
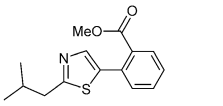
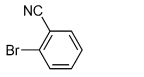
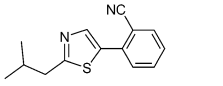
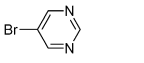
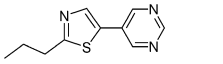
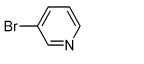
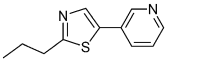
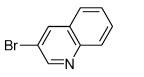
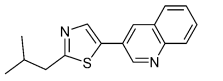
Employing 2-*i*-butylthiazole and 4-bromobenzonitrile as the coupling partners at 150 °C during 24 h with KOAc as the base and 1 mol% [$PdCl(C_3H_5)(dppb)$] (dppb = 1,4-bis(diphenylphosphino)butane) as the catalyst without solvent, the desired 5-arylation product (**2**) was obtained in 90% yield (Table 1, entry 1). No formation of 4-arylated or 4,5-diarylated thiazoles was detected. A slightly lower yield in **2** was obtained when the reaction was performed at 120 °C; whereas at 80 °C the conversion of 4-bromobenzonitrile was poor (Table 1, entries 3 and 4).

The reaction of other *para*-substituted electron-deficient aryl bromides such as 4-bromoacetophenone, 4-bromobenzaldehyde, methyl 4-bromobenzoate, 4-trifluoromethylbromobenzene, or 4-bromonitrobenzene with 2-alkylthiazoles also gave the desired products (**3**—**7**) in 73–92% yields (Table 1, entries 5, 6, and 8–10). 4-Fluorobromobenzene gave the expected coupling product (**8**) in 79% yield (Table 1, entry 11). As expected, the reactivity of *meta*-substituted aryl bromides was found to be similar to *para*-substituted aryl bromides (Table 1 entries 13 and 14). Next, the reactivity of two *ortho*-substituted aryl bromides was examined. Due to their steric or coordination properties, *ortho*-substituents on aryl halides generally have a more important influence on the yields of palladium-catalyzed reactions.[20] However, both methyl 2-bromobenzoate and 2-bromobenzonitrile were successfully coupled with 2-*i*-butylthiazole to give **11** and **12** in good yields (Table 1, entries 15 and 16). We also explored the reactivity of 2-alkylthiazoles with some heteroaryl bromides (Table 1, entries 17–20). Good performance of this novel friendly protocol in direct couplings with 5-bromopyrimidine, 3-bromopyridine, or 3-bromoquinoline was observed. With these substrates, target products **13**–**15** were obtained in 85–87% yield.

We have recently reported that the phosphine-free $Pd(OAc)_2$ catalyst promotes the direct arylation of some heteroaromatics.[4f,8c] This procedure was also examined for the coupling of four aryl bromides in absence of solvent. Surprisingly, high yields of **2** and **14** were obtained in the presence of 4-bromobenzonitrile or 3-bromopyridine (Table 1, entries 2 and 17). On the other hand, in the presence of 4-bromobenzaldehyde, **4** was only obtained in 70% due to the formation of biphenyl-4,4′-dicarbaldehyde as side-product in 12% yield. With 4-bromofluorobenzene another side-product was detected by GC-

Table 1. Palladium-catalyzed coupling of thiazole derivatives with aryl bromides.



Entry	Aryl bromide	Product		Yield[a] [%]
1			**2**	90
2				89[b]
3				78[c]
4				35[d]
5			**3**	73
6			**4**	78
7				70[b,e]
8			**5**	86
9			**6**	88
10			**7**	92
11			**8**	79
12				62[b,f]
13			**9**	77
14			**10**	79
15			**11**	69
16			**12**	62
17			**13**	87
18			**14**	85
19				81[b]
20			**15**	86

[a] Conditions: $[PdCl(C_3H_5)(dppb)]$ (0.01 equiv), thiazole derivative (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h. [b] $Pd(OAc)_2$ (0.01 equiv). [c] Reaction temperature: 120 °C. [d] Reaction temperature: 80 °C. [e] The formation of biphenyl-4,4′-dicarbaldehyde (12%) was also detected. [f] The formation of a diarylated thiazole was also detected.

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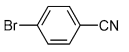
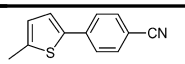
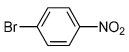
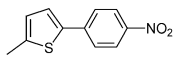
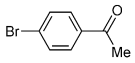
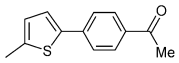
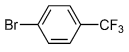
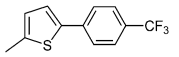
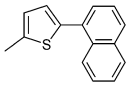
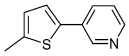
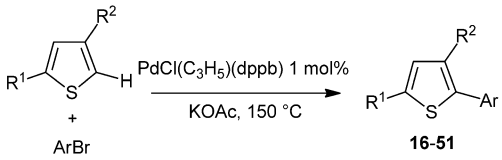
MS analysis due to diarylation of thiazole (Table 1, entries 5 and 10). In the absence of solvent, the aggregation of palladium species to form microparticles seemed faster. Such aggregates are known to promote side-reactions, such as the homocoupling of aryl bromides. Therefore, even if it is possible for the phosphine-free procedure to be employed with some aryl bromides, the use of [$PdCl(C_3H_5)(dppb)$] as the catalyst appears to be more reliable for such solvent-free reactions.

Then, we studied the reactivity of several other heteroaromatics in absence of solvent. High yields were generally obtained for the coupling of thiophene derivatives with aryl bromides (Table 2–6). 5-Arylation of 2-methylthiophene was found to proceed nicely with electron-deficient aryl bromides (Table 2, entries 1–4); whereas the coupling of 1-bromonaphthalene gave **20** in only 20% yield due to a partial conversion of this aryl bromide (Scheme 2 and Table 2, entry 5).

Table 2. Palladium-catalyzed coupling of 2-methylthiophene with aryl bromides (Scheme 2).

Entry	Aryl bromide	Product		Yield[a] [%]
1			**16**	84
2			**17**	80
3			**18**	77
4			**19**	74
5			**20**	20
6			**21**	71

[a] Conditions: [$PdCl(C_3H_5)(dppb)$] (0.01 equiv), 2-methylthiophene (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

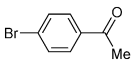
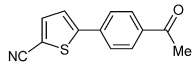
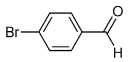
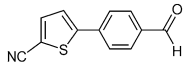
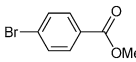
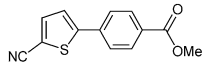
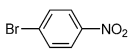
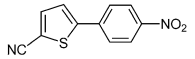
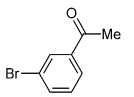
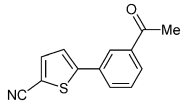
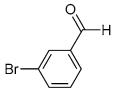
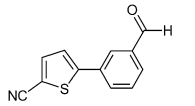
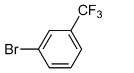
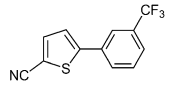
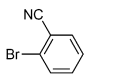
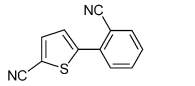


Scheme 2. Coupling of thiophene derivatives with aryl bromides.

Thiophene 2-carbonitrile has also been coupled successfully to several electron-deficient aryl bromides (Table 3). Similar yields to those previously obtained in cyclopentyl methyl ether[15d] were obtained.

Then, both protected and nonprotected 2-acetylthiopenes were employed (Table 4). In most cases, similar yields of coupling products were obtained using these two reagents. For example, in the presence of 4-bromobenzonitrile, **30** and **35** were obtained in 74 and 72% yield (Table 4, entries 1 and 6).

Table 3. Palladium-catalyzed coupling of thiophene 2-carbonitrile with aryl bromides (Scheme 2).

Entry	Aryl bromide	Product		Yield[a] [%]
1			**22**	74
2			**23**	73
3			**24**	71
4			**25**	73
5			**26**	61
6			**27**	64
7			**28**	73
8			**29**	75

[a] Conditions: [$PdCl(C_3H_5)(dppb)$] (0.01 equiv), thiophene 2-carbonitrile (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

The acetyl function appeared to be quite stable under these conditions.

A highly functionalized reagent (2-acetyl-4-chlorothiophene) reacted with aryl bromides (e.g., 4-bromoacetophenone, 4-trifluoromethylbromobenzene, 2-bromobenzonitrile, or bromopyridines) and gave **42**–**46** in 75–79% yield (Table 5). Notably, in the course of these reactions no cleavage of the C–Cl bond of the chlorothiophene derivative was detected, thus allowing further transformations.

Then, a thiophene substituted by an ester function at the C2 position was employed (Table 6). The target compounds (**47**—**51**) were obtained in 71–80% yield. Decarboxylation of some thiophene derivatives has been previously observed in DMAc at elevated temperatures.[4i] However, in the course of these reactions only traces of decarboxylated thiophenes were detected.

Several aryl bromides were also coupled with furan derivatives (Table 7). These reactions had been previously observed to proceed nicely in DMAc or diethylcarbonate.[5d,15b] Again, for these reactions, [$PdCl(C_3H_5)(dppb)$] was employed as the catalyst. A poor reactivity of 2-*n*-butylfuran was observed (Table 7, entries 1 and 2). Due to its poor coordination properties, this furan derivative is probably not as good a stabilizing agent for palladium species as thiophenes or thiazoles; whereas furan-2-ylmethyl acetate and methyl 2-methylfuran-3-carboxylate were found to be more reactive under these solvent-free conditions, and produced **54**–**57** in 61–74% yield. These two substrates gave rise to similar results in diethylcarbonate.[15b]

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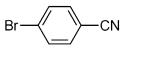
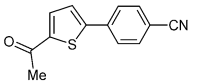
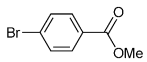
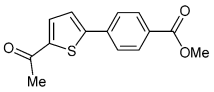
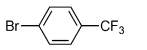
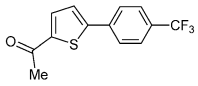
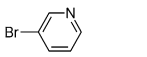
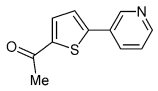
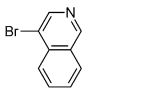
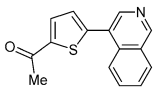
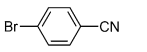
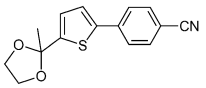
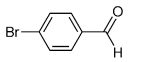
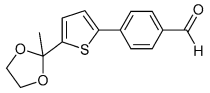
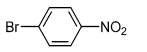
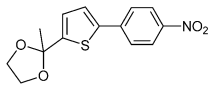
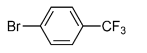
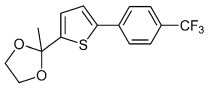
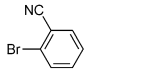
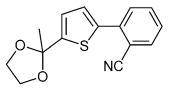
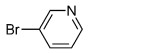
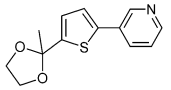
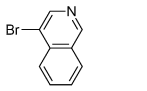
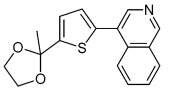
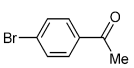
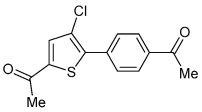
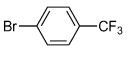
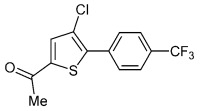
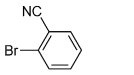
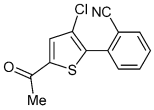
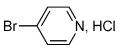
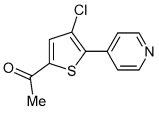
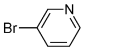
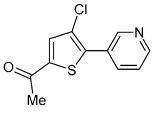
Table 4. Palladium-catalyzed coupling of 2-acetylthiophenes with aryl bromides (Scheme 2).

Entry	Aryl bromide	Product		Yield[a] [%]
1			**30**	74
2			**31**	71
3			**32**	70
4			**33**	78
5			**34**	32
6			**35**	72
7			**36**	70
8			**37**	74
9			**38**	71
10			**39**	75
11			**40**	82
12			**41**	77

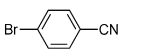
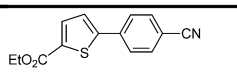
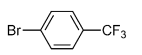
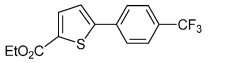
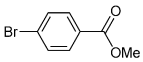
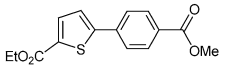
[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), 2-acetylthiophene (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

Table 5. Palladium-catalyzed coupling of 2-acetyl-4-chlorothiophene with aryl bromides (Scheme 2).

Entry	Aryl bromide	Product		Yield[a] [%]
1			**42**	79
2			**43**	78
3			**44**	75
4			**45**	76
5			**46**	78

[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), 2-acetyl-4-chlorothiophene (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h, yield in isolated product.

Table 6. Palladium-catalyzed coupling of ethyl thiophene-2-carboxylate with aryl bromides (Scheme 2).

Entry	Aryl bromide	Product		Yield[a] [%]
1			**47**	78
2			**48**	71
3			**49**	80
4			**50**	77
5			**51**	75

[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), ethyl thiophene-2-carboxylate (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

We previously observed that 1-methyl-2-formylpyrrole had a poor reactivity in direct arylations in diethylcarbonate.[15b] In absence of solvent, the coupling of this heteroaromatic with 4-bromobenzonitrile led to **58** in only 41% yield (Table 8, entry 1). Better results were obtained for the coupling of 1-methylpyrrole with 4-bromobenzonitrile, 4-bromonitrobenzene, or methyl 4-bromobenzoate (Table 8, entries 2–4).

Finally, three aryl bromides were coupled with 2,5-dimethylisoxazole (Table 9). Yields of 75–86% in **62**–**64** were obtained using 1 mol% catalyst at 150 °C. Notably, lower yields in **62** (47 and 40%) were obtained for the coupling of 4-bromobenzonitrile with this isoxazole derivative in diethylcarbonate or cyclopentyl methyl ether; whereas the use of di-*n*-butyl ether produced **62** in 89% yield.[15b,d]

Conclusions

These results demonstrated that, in several cases, the direct arylation of heteroaromatics could be performed without solvent. In the presence of palladium catalyst (1 mol%) at 150 °C, the direct 5-arylation of some thiazoles, thiophenes, furans, pyrroles, or isoxazoles using aryl bromides as coupling partners proceeded highly regioselectively and in moderate to high yields. Under these solvent-free conditions, palladium catalysts associated to a phosphine ligand should be preferred, even if a phosphine-free catalyst could be employed in some cases.

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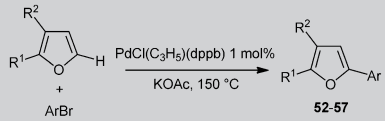
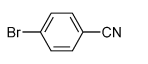
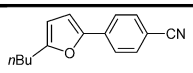
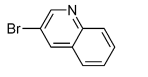
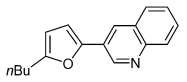
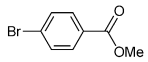
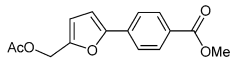
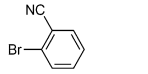
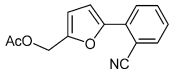
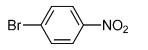
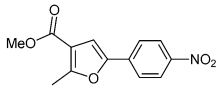
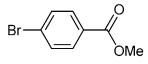
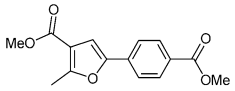
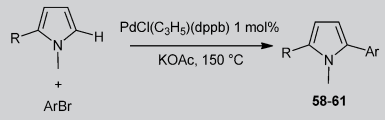
Table 7. Palladium-catalyzed coupling of furan derivatives with aryl bromides.

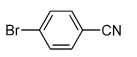
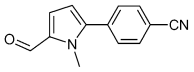
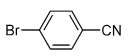
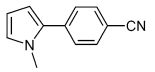
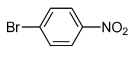
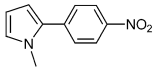
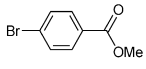
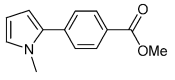


Entry	Aryl bromide	Product		Yield[a] [%]
1			**52**	15
2			**53**	17
3			**54**	61
4			**55**	71
5			**56**	65
6			**57**	74

[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), furan derivative (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

Table 8. Palladium-catalyzed coupling of pyrrole derivatives with aryl bromides.

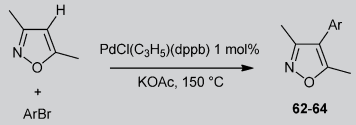


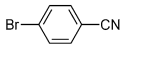
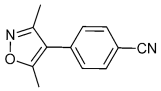
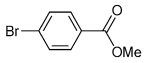
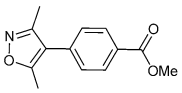
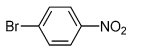
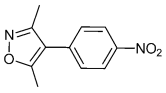
Entry	Aryl bromide	Product		Yield[a] [%]
1			**58**	41[b]
2			**59**	74
3			**60**	68
4			**61**	77

[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), pyrrole derivative (4 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h. [b] 1-methyl-2-formylpyrrole (2 equiv).

Notably, only electron-deficient aryl bromides were reactive under these conditions. However, a wide range of functions such as acetyl, propionyl, formyl, ester, nitro, nitrile, trifluoromethyl, or fluoro on the aryl bromide was tolerated. The major byproduct of these couplings was KBr and AcOH instead of metallic salts in more classical coupling procedures. Solvent-free reactions avoid the hazards and toxicity associated with the use of solvents, reduce waste costs, and simplify separation procedures at the end of the reaction. For these reasons, this novel process should give an economically viable and environmentally attractive access to several arylated heteroaromatics. Moreover, these results indicated that most of these couplings should also proceed using highly concentrated reaction mixtures, thus allowing industrially viable processes.

Table 9. Palladium-catalyzed coupling of 3,5-dimethylisoxazole with aryl bromides.



Entry	Aryl bromide	Product		Yield[a] [%]
1			**62**	75
2			**63**	81
3			**64**	86

[a] Conditions: [PdCl(C_3H_5)(dppb)] (0.01 equiv), 3,5-dimethylisoxazole (2 equiv), aryl bromide (1 equiv), KOAc (2 equiv), 150 °C, 24 h.

Experimental Section

$Pd(OAc)_2$, $[Pd(C_3H_5)Cl]_2$, dppb, heteroarenes, KOAc (99%), and Cs_2CO_3 (99%) were purchased from Alfa Aesar and were not purified before use.

Preparation of the [PdCl(C_3H_5)(dppb)] catalyst[21]

An oven-dried Schlenk tube (40 mL) 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). Then, anhydrous dichloromethane (10 mL) was added and the solution was stirred at room temperature for 20 min. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 19.3$ ppm (s).

Typical experiment for coupling reactions

The reaction of aryl bromide (1 mmol), heteroaromatic (2 mmol), and KOAc (0.196, 2 mmol) at 150 °C in the presence of $Pd(OAc)_2$ or [PdCl(C_3H_5)(dppb)] under argon afforded the corresponding product after filtration on silica gel (pentane/ether).

4-(2-Isobutylthiazol-5-yl)benzonitrile (2)

4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **2** (0.218 g, 90%). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.97$ (s, 1H), 7.70 (d, $J = 8.5$ Hz, 2H), 7.65 (d, $J = 8.5$ Hz, 2H), 2.95 (d, $J = 7.5$ Hz, 2H), 2.18 (m, 1H), 1.08 ppm (d, $J = 7.5$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.7$, 139.5, 136.5, 136.2, 132.8, 126.8, 118.5, 111.2, 42.6, 29.8, 22.2 ppm; elemental analysis calcd (%) for $C_{14}H_{14}N_2S$ (242.34): C 69.39, H 5.82; found: C 69.31, H 5.68.

4-(2-Isobutylthiazol-5-yl)acetophenone (3)[14a]

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **3** (0.189 g, 73%).

4-(2-Isobutylthiazol-5-yl)benzaldehyde (4)

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The reaction of 4-bromobenzaldehyde (0.184 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **4** (0.191 g, 78%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.00 (s, 1H), 7.97 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 2.95 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.08 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.2, 171.4, 139.4, 137.5, 137.0, 135.5, 130.4, 126.7, 42.6, 29.8, 22.3 ppm; elemental analysis calcd (%) for $C_{14}H_{15}NOS$ (245.34): C 68.54, H 6.16; found: C 68.41, H 6.28.

Methyl 4-(2-propylthiazol-5-yl)benzoate (5)[8c]

The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and 2-*i*-butylthiazole (0.264 g, 2 mmol) affords **5** (0.225 g, 86%).

5-[4-(Trifluoromethyl)phenyl]-2-isobutylthiazole (6)[8f]

The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **6** (0.251 g, 88%).

5-(4-Nitrophenyl)-2-isobutylthiazole (7)

The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **7** (0.241 g, 92%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.5 Hz, 2H), 7.99 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 2.95 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.08 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 146.9, 140.0, 138.1, 136.0, 126.8, 124.4, 42.6, 29.8, 22.2 ppm; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_2S$ (262.33): C 59.52, H 5.38; found: C 59.38, H 5.20.

5-(4-Fluorophenyl)-2-propylthiazole (8)[8c]

The reaction of 4-fluorobromobenzene (0.175 g, 1 mmol), and 2-propylthiazole (0.264 g, 2 mmol) afforded **8** (0.175 g, 79%).

3-(2-Isobutylthiazol-5-yl)benzonitrile (9)

The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **9** (0.186 g, 77%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.87–7.75 (m, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 8.5 Hz, 1H), 2.95 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.08 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 138.9, 136.0, 133.1, 131.1, 130.6, 129.9, 129.8, 118.2, 113.4, 42.6, 29.8, 22.2 ppm; elemental analysis calcd (%) for $C_{14}H_{14}N_2S$ (242.34): C 69.39, H 5.82; found: C 69.24, H 6.02.

2-Propyl-5-(3-trifluoromethylphenyl)thiazole (10)[8c]

The reaction of 3-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-propylthiazole (0.264 g, 2 mmol) afforded **10** (0.214 g, 79%).

Methyl 4-(2-isobutylthiazol-5-yl)benzoate (11)

The reaction of methyl 2-bromobenzoate (0.205 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **11** (0.190 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.5 Hz, 1H), 7.54 (s, 1H), 7.52–7.36 (m, 3H), 3.21 (s, 3H), 2.91 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.04 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 168.3, 140.2, 135.8, 131.7, 131.6, 131.3, 131.0, 129.9, 128.3, 52.1, 42.3, 29.8, 22.3 ppm; elemental analysis calcd (%) for $C_{15}H_{17}NO_2S$ (275.37): C 65.43, H 6.22; found: C 65.24, H 6.10.

2-(2-Isobutylthiazol-5-yl)benzonitrile (12)

The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **12** (0.150 g, 62%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.70–7.52 (m, 2H), 7.43 (t, J = 8.5 Hz, 1H), 2.91 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.04 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 141.6, 134.9 134.3, 133.6, 133.1, 130.0, 128.1, 118.3, 110.6, 42.5, 29.8, 22.3 ppm; elemental analysis calcd (%) for $C_{14}H_{14}N_2S$ (242.34): C 69.39, H 5.82; found: C 69.58, H 6.00.

5-(2-Propylthiazol-5-yl)pyrimidine (13)[8c]

The reaction of 5-bromopyrimidine (0.159 g, 1 mmol) and 2-propylthiazole (0.264 g, 2 mmol) afforded **13** (0.178 g, 87%).

3-(2-Propylthiazol-5-yl)pyridine (14)[8c]

The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 2-propylthiazole (0.264 g, 2 mmol) afforded **14** (0.173 g, 85%).

3-(2-Isobutylthiazol-5-yl)quinoline (15)

The reaction of 3-bromoquinoline (0.208 g, 1 mmol) and 2-*i*-butylthiazole (0.282 g, 2 mmol) afforded **15** (0.230 g, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.08 (s, 1H), 8.12 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.97 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 2.91 (d, J = 7.5 Hz, 2H), 2.18 (m, 1H), 1.04 ppm (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 148.5, 147.4, 138.8, 135.0, 132.3, 129.6, 129.3, 127.7, 127.4, 125.0, 42.6, 29.8, 22.3 ppm; elemental analysis calcd (%) for $C_{16}H_{16}N_2S$ (268.38): C 71.60, H 6.01; found: C 71.84, H 5.92.

4-(5-Methylthiophen-2-yl)-benzonitrile (16)[4f]

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **16** (0.167 g, 84%).

2-Methyl-5-(4-nitrophenyl)thiophene (17)[22]

The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **17** (0.175 g, 80%).

4-(5-Methylthiophen-2-yl)-acetophenone (18)[22]

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **18** (0.166 g, 77%).

2-Methyl-5-(4-trifluoromethylphenyl)thiophene (19)[22]

The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **19** (0.179 g, 74%).

2-Methyl-5-naphthalen-1-ylthiophene (20)[23]

The reaction of 1-bromonaphthalene (0.207 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **20** (0.045 g, 20%).

3-(5-Methylthiophen-2-yl)pyridine (21)[24]

The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afforded **21** (0.124 g, 71%).

5-(4-Acetylphenyl)thiophene-2-carbonitrile (22)[4f]

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **22** (0.168 g, 74%).

5-(4-Formylphenyl)thiophene-2-carbonitrile (23)[4f]

The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **23** (0.156 g, 73%).

Methyl 4-(5-cyanothiophen-2-yl)benzoate (24)[4f]

The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **24** (0.173 g, 71%).

5-(4-Nitrophenyl)thiophene-2-carbonitrile (25)[17]

The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **25** (0.168 g, 73%).

5-(3-Acetylphenyl)thiophene-2-carbonitrile (26)[15d]

The reaction of 3-bromoacetophenone (0.199 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **26** (0.139 g, 61%).

5-(3-Formylphenyl)thiophene-2-carbonitrile (27)[15d]

The reaction of 3-bromobenzaldehyde (0.185 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **27** (0.136 g, 64%).

5-[3-(trifluoromethyl)phenyl]thiophene-2-carbonitrile (28)[15d]

The reaction of 3-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **28** (0.185 g, 73%).

5-(2-Cyanophenyl)thiophene-2-carbonitrile (29)[4f]

The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) afforded **29** (0.157 g, 75%).

4-(5-Acetylthiophen-2-yl)benzonitrile (30)[4f]

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) afforded **30** (0.168 g, 74%).

Methyl 4-(5-acetylthiophen-2-yl)benzoate (31)[4f]

The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) afforded **31** (0.185 g, 71%).

1-[5-(4-Trifluoromethylphenyl)-thiophen-2-yl]-ethanone (32)[4f]

The reaction of 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) afforded **32** (0.189 g, 70%).

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1-(5-Pyridin-3-ylthiophen-2-yl)-ethanone (33)[25]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) afforded **33** (0.158 g, 78%).

1-(5-Isoquinolin-4-ylthiophen-2-yl)-ethanone (34)
The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) afforded **34** (0.081 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.20$ (s, 1H), 8.51 (s, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 3.8$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.58 (t, $J = 7.5$ Hz, 1H), 7.26 (d, $J = 3.8$ Hz, 1H), 2.55 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 190.6$, 153.4, 146.5, 145.2, 143.4, 133.7, 132.7, 131.5, 129.0, 182.3, 128.2, 127.8, 125.4, 124.1, 26.8 ppm; elemental analysis calcd (%) for $C_{15}H_{11}NOS$ (253.32): C 71.12, H 4.38; found: C 71.20, H 4.51.

4-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzonitrile (35)[15d]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **35** (0.195 g, 72%).

4-[5-(2-Methyl-1,3-dioxolan-2-yl)-thiophen-2-yl]-benzaldehyde (36)[4f]
The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **36** (0.192 g, 70%).

2-Methyl-2-[5-(4-nitrophenyl)-thiophen-2-yl]-[1,3]dioxolane (37)
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **37** (0.215 g, 74%).

2-Methyl-2-[5-(4-trifluoromethylphenyl)-thiophen-2-yl]-[1,3]dioxolane (38)[4f]
The reaction of 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **38** (0.223 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (d, $J = 8.5$ Hz, 2H), 7.71 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 3.8$ Hz, 1H), 7.09 (d, $J = 3.8$ Hz, 1H), 4.15–4.00 (m, 4H), 1.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.1$, 146.6, 140.9, 140.6, 125.8, 125.6, 125.4, 124.4, 107.0, 65.1, 30.9, 27.4 ppm; elemental analysis calcd (%) for $C_{14}H_{13}NO_4S$ (291.32): C 57.72, H 4.50; found: C 57.60, H 4.37.

2-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzonitrile (39)[4f]
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **39** (0.203 g, 75%).

3-[5-(2-Methyl-1,3-dioxolan-2-yl)-thiophen-2-yl]-pyridine (40)[4f]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **40** (0.203 g, 82%).

4-[5-(2-Methyl-1,3-dioxolan-2-yl)-thiophen-2-yl]-isoquinoline (41)[4f]
The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) afforded **41** (0.229 g, 77%).

1-[4-(5-Acetyl-3-chlorothiophen-2-yl)-phenyl]-ethanone (42)[15d]
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) afforded **42** (0.220 g, 79%).

1-[4-Chloro-5-(4-trifluoromethylphenyl)-thiophen-2-yl]-ethanone (43)[15d]
The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol) and 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) afforded **43** (0.237 g, 78%).

2-(5-Acetyl-3-chlorothiophen-2-yl)-benzonitrile (44)[4h]
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) afforded **44** (0.196 g, 75%).

1-(4-Chloro-5-pyridin-4-yl-thiophen-2-yl)-ethanone (45)[15d]
The reaction of 4-bromopyridine hydrochloride (0.195 g, 1 mmol) and 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) afforded **45** (0.180 g, 76%).

1-(4-Chloro-5-pyridin-3-ylthiophen-2-yl)-ethanone (46)[4h]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) afforded **46** (0.185 g, 78%).

Ethyl 5-(4-cyanophenyl)thiophene-2-carboxylate (47)[5c]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.312 g, 2 mmol) afforded **47** (0.201 g, 78%).

Ethyl 5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (48)[4f]
The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol) and methyl thiophene-2-carboxylate (0.312 g, 2 mmol) afforded **48** (0.213 g, 71%).

Ethyl 5-(4-methoxycarbonylphenyl)thiophene-2-carboxylate (49)
The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.312 g, 2 mmol) afforded **49** (0.232 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 4.0$ Hz, 1H), 7.69 (d, $J = 8.5$ Hz, 2H), 7.38 (d, $J = 4.0$ Hz, 1H), 4.37 (q, $J = 7.5$ Hz, 2H), 3.94 (s, 3H), 1.40 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.4$, 162.0, 149.3, 137.5, 134.1, 133.8, 130.3, 129.9, 125.8, 124.7, 61.3, 52.2, 14.3 ppm; elemental analysis: calcd (%) for $C_{15}H_{14}O_4S$ (290.34): C 62.05, H 4.86; found: C 62.14, H 4.99.

Ethyl 5-(2-cyanophenyl)thiophene-2-carboxylate (50)
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.312 g, 2 mmol) afforded **50** (0.201 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 4.0$ Hz, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.67–7.63 (m, 2H), 7.59 (d, $J = 4.0$ Hz, 1H), 7.50–7.45 (m, 1H), 4.37 (q, $J = 7.5$ Hz, 2H), 1.40 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.8$, 145.6, 136.6, 135.2, 134.4, 133.9, 133.2, 129.9, 128.7, 128.0, 118.3, 110.5, 61.4, 14.3 ppm; elemental analysis: calcd (%) for $C_{14}H_{11}NO_2S$ (257.31): C 65.35, H 4.31; found: C 65.20, H 4.47.

Ethyl 5-pyridin-3-ylthiophene-2-carboxylate (51)[4f]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.312 g, 2 mmol) afforded **51** (0.175 g, 75%).

2-*n*-Butyl-5-(4-cyanophenyl)furan (52)[5d]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) afforded **52** (0.034 g, 15%).

3-(5-*n*-Butylfuran-2-yl)quinoline (53)[15b]
The reaction of 3-bromoquinoline (0.208 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) afforded **53** (0.043 g, 17%).

Methyl 4-(5-acetoxymethylfuran-2-yl)benzoate (54)
The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and acetic acid furan-2-ylmethyl ester (0.280 g, 2 mmol) afforded **54** (0.167 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 8.5$ Hz, 2H), 7.71 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 3.5$ Hz, 1H), 6.50 (d, $J = 3.5$ Hz, 1H), 5.10 (s, 2H), 3.90 (s, 3H), 2.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 166.3, 153.1, 149.7, 134.0, 129.7, 128.5, 123.2, 112.6, 107.6, 57.7, 51.7, 20.5 ppm; elemental analysis calcd (%) for $C_{15}H_{14}O_5$ (274.27): C 65.69, H 5.15; found: C 65.87, H 5.04.

Acetic acid 5-(2-cyanophenyl)furan-2-ylmethyl ester (55)[15b]
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and acetic acid furan-2-ylmethyl ester (0.280 g, 2 mmol) afforded **55** (0.171 g, 71%).

Methyl 2-methyl-5-(4-nitrophenyl)furan-3-carboxylate (56)[5d]
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2 mmol) afforded **56** (0.170 g, 65%).

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Methyl 5-(4-methoxycarbonylphenyl)-2-methylfuran-3-carboxylate (57)[5d]
The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2 mmol) afforded **57** (0.203 g, 74%).
4-(5-Formyl-1-methylpyrrol-2-yl)benzonitrile (58)[6e]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) afforded **58** (0.086 g, 41%).
4-(1-Methylpyrrol-2-yl)benzonitrile (59)[6e]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol) afforded **59** (0.135 g, 74%).
1-Methyl-2-(4-nitrophenyl)pyrrole (60)[26]
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol) afforded **60** (0.137 g, 68%).
Methyl 4-(1-Methylpyrrol-2-yl)benzoate (61)[27]
The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol) afforded **61** (0.166 g, 77%).
4-(3,5-Dimethylisoxazol-4-yl)benzonitrile (62)[10]
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) afforded **62** (0.148 g, 75%).
Methyl 4-(3,5-dimethylisoxazol-4-yl)benzoate (63)[10]
The reaction of methyl 4-bromobenzoate (0.205 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) afforded **63** (0.187 g, 81%).
3,5-Dimethyl-4-(4-nitrophenyl)isoxazole (64)[10]
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) afforded **64** (0.188 g, 86%).

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Keywords: catalysis · cross-coupling · heterocycles · palladium · synthetic methods

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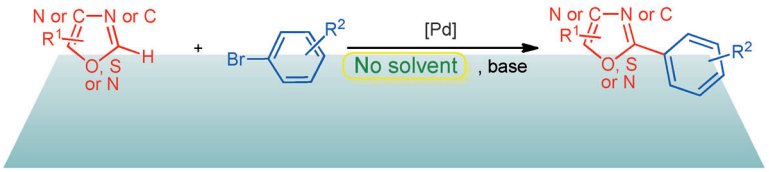
Solvent-Free Palladium-Catalyzed Direct Arylation of Heteroaromatics with Aryl Bromides



Dry, with some palladium overcast: Several palladium-catalyzed direct arylations of heteroaromatics, performed without solvent, proceeded nicely (see scheme). The yield in coupling products strongly depended on the nature of heteroaromatics and aryl bromide substituents.

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