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Ligand-Free-Palladium-Catalyzed Direct 4-Arylation of Isoxazoles Using Aryl Bromides

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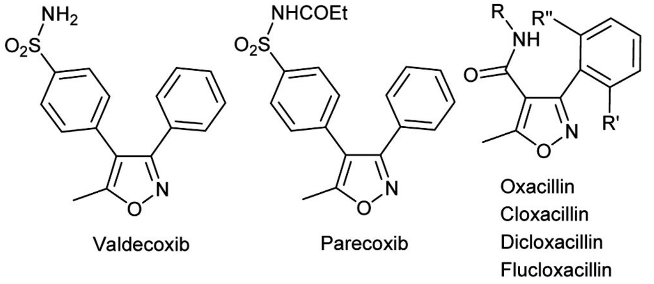
4-Arylisoxazoles can be easily prepared by a palladium-catalysed C–H bond activation/arylation of 3,5-disubstituted isoxazoles using aryl or heteroaryl bromides. Good yields were generally obtained by using 0.1–0.5 mol-% of the air-stable $PdCl_2$ complex as the catalyst. A range of functional groups such as acetyl, formyl, ester, fluoro, nitro, trifluoromethyl or nitrile on the aryl bromide is tolerated. This reaction is environmentally attractive, as the major waste is KBr/AcOH instead of the metallic salts arising from classical cross-coupling procedures.

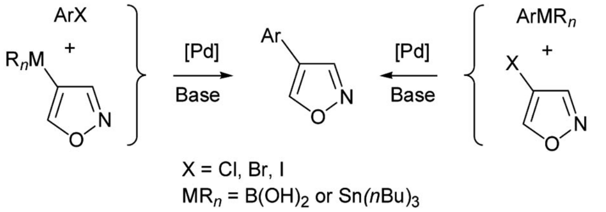
Introduction

3- or 4-arylisoxazoles such as Valdecoxib, Parecoxib or Oxacillin and its derivatives are useful compounds due to their specific biological properties (Scheme 1).



Scheme 1.

Palladium-catalysed Suzuki or Stille cross-coupling reactions between aryl halides and organometallic derivatives of isoxazole and also between 3- or 4-haloisoxazoles and arylmetal derivatives are some of the most important methods for the synthesis of such compounds.[1–3] However, these reactions require the preliminary preparation of an organometallic derivative and provide an organometallic salt (MX) as a by-product (Scheme 2).



Scheme 2.

The arylation of several heteroaromatics by C–H bond activation using aryl halides has been reported in recent years. For such couplings, no preparation of an organometallic derivative is required.[4–6] Moreover, this reaction provides only HX associated with a base as a by-product and, therefore, is very interesting both in terms of atom economy and relatively inert wastes. However, even though this procedure has been widely applied for the synthesis of arylthiophenes, arylfurans, aryloxazoles or arylthiazoles, relatively few results have been reported with isoxazole derivatives. In the presence of 3,5-disubstituted isoxazoles, this procedure should provide an economic and environmentally attractive procedure for the preparation of a variety of 4-arylisoxazoles. However, to date, only a few examples of 4-arylation of such heteroaromatics have been reported.[7–9] In 1982, the intramolecular cyclisation of a 3-substituted isoxazole was described by the group of Nakamura.[7] By employing 10 mol-% of $Pd(OAc)_2/PPh_3$ as a catalyst, the desired compound was formed in 45% yield. 5-Subtituted isoxazoles have also been cyclised to give tricyclic compounds in 9–60% yield.[8] The bimolecular 4-arylation of isoxazoles was also found to be possible, though it required higher temperatures and longer reaction times. With iodobenzene or 4-iodotoluene in the presence of 3,5-disubstituted isoxazoles, the 4-arylated isoxazoles were obtained in 30–48% yields.[7] These reactions were performed by using 10 or

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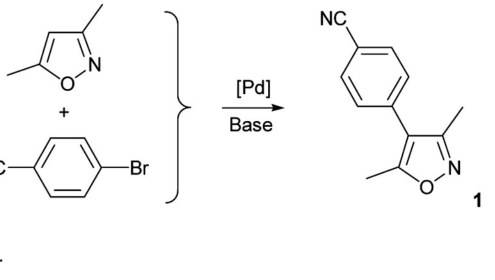
5 mol-% of Pd/C or $Pd(OAc)_2$ as a catalyst, respectively. Recently, the scope of this reaction was extended to an aryl chloride, 1-chloronaphthalene.[9] For this reaction, in order to facilitate the oxidative addition of 1-chloronaphthalene to palladium, 5 mol-% of $Pd(OAc)_2$ was associated with 10 mol-% of the bulky and electron-rich ligand, bis(1-adamantyl)butylphosphane, to form the catalyst. The expected (3,5-dimethyl-4-naphthalen-1-yl)isoxazole was obtained in 76% yield.

Since only a few syntheses of 4-arylisoxazoles by palladium-catalysed C–H bond activation of isoxazole derivatives followed by arylation have been described, the scope of the reaction needs to be largely extended to a wider variety of aryl halides. Moreover, higher yields for the coupling of such compounds have to be obtained in using lower catalyst loadings, in order to obtain economically viable procedures. Herein, we wish to report on the reaction of a set of electronically and sterically diverse aryl bromides using 3,5-disubstituted isoxazoles at low catalyst loadings with ligand-free palladium catalysts.

Results and Discussion

We have recently reported that ligand-free $Pd(OAc)_2$ or $[PdCl(C_3H_5)]_2$ are very powerful catalyst for the direct arylation of furans, thiophenes, thiazoles or pyrroles.[5g–5i,10] With these heteroaromatics, several reactions can be performed with as little as 0.5–0.001 mol-% of catalyst. At an elevated temperature, when ligand-free $Pd(OAc)_2$ is employed as a catalyst precursor, soluble palladium(0) colloids or nanoparticles are formed. These nanoparticles seem to produce monomeric or dimeric anionic palladium complexes that are very active catalysts. For this ligand-free procedure, low catalyst loadings have to be employed (less than 0.5 mol-%). Under relatively high palladium concentrations (>1 mol-%), so-called palladium black forms more rapidly. This palladium black is generally inactive for such catalyzed reactions. Consequently, the conversions of aryl bromides and the yields of coupling products are not increased by a higher catalyst loading.

First, we examined the reactivity of 3,5-dimethylisoxazole in the palladium-catalysed coupling reaction with 4-bromobenzonitrile by using 0.5 mol-% of $Pd(OAc)_2$ or ½$[PdCl(C_3H_5)]_2$ as catalyst precursors, DMAc as the solvent and AcOK as the base at 130 °C in the absence of ligand (Scheme 3, Table 1).



Scheme 3.

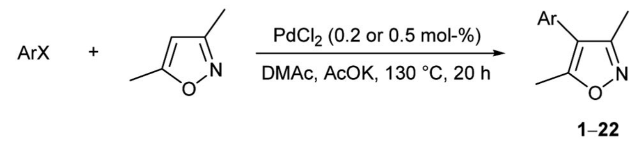
Table 1. Palladium-catalysed cross-coupling with 3,5-dimethylisoxazole and 4-bromobenzonitrile (Scheme 3).[a]

Entry	[Pd]	Substrate/ catalyst	Solvent	Base	Conversions (%)
1	$Pd(OAc)_2$	200	DMAc	AcOK	100
2	½$[PdCl(C_3H_5)]_2$	200	DMAc	AcOK	98
3	$Pd(OAc)_2$	1000	DMAc	AcOK	96
4	$Pd(OAc)_2$	1000	DMAc	K_2CO_3	10
5	$Pd(OAc)_2$	1000	DMAc	Cs_2CO_3	25
6	$Pd(OAc)_2$	1000	DMAc	AcONa	70
7	$Pd(OAc)_2$	1000	xylene	AcOK	15
8	$Pd(OAc)_2$	1000	DMF	AcOK	52
9	$Pd(OAc)_2$	1000	NMP	AcOK	92
10	½$[PdCl(C_3H_5)]_2$	1000	DMAc	AcOK	95
11	½$Pd_2(dba)_3$	1000	DMAc	AcOK	96
12	$PdCl_2$	1000	DMAc	AcOK	100 (90)
13	$PdCl_2/2P(Ad)_2$*n*Bu	1000	DMAc	AcOK	28
14	$Pd(OAc)_2$	2000	DMAc	AcOK	53
15	½$[PdCl(C_3H_5)]_2$	2000	DMAc	AcOK	72
16	½$Pd_2(dba)_3$	2000	DMAc	AcOK	71
17	$PdCl_2$	2000	DMAc	AcOK	60
18	$PdCl_2$	100	DMAc	AcOK	15[b]

[a] Conditions: 4-bromobenzonitrile (1 equiv.), 3,5-dimethylisoxazole (1.5 equiv.), base (2 equiv.), 20 h, 130 °C; GC and NMR conversion of 4-bromobenzonitrile; yield in parentheses is isolated. [b] Reaction temperature: 100 °C.

Under these conditions, the target product **1** formed in almost quantitative yield (Table 1, Entries 1 and 2). We then studied this reaction using various bases and solvents in the presence of only 0.1 mol-% $Pd(OAc)_2$ or ½$[PdCl(C_3H_5)]_2$ (Table 1, Entries 3–10). The conversion was still almost quantitative by using AcOK as the base, whereas K_2CO_3 or Cs_2CO_3 gave much lower yields (Table 1, Entries 3–5 and 10). We obtained a conversion of 70% in the presence of NaOAc (Table 1, Entry 6). When we employed xylene or DMF as the solvent instead of DMAc, we observed conversions of 15% and 52% (Table 1, Entries 7 and 8). On the other hand, we found NMP gave a high conversion of 4-bromobenzonitrile, and we obtained **1** in very good yield (Table 1, Entry 9). We also examined the influence of the palladium source. $Pd(OAc)_2$, $Pd_2(dba)_3$ or $[PdCl(C_3H_5)]_2$ gave **1** in high yields, and very clean reactions were observed (Table 1, Entries 3, 10 and 11). However, we obtained the most selective reaction using $PdCl_2$ (Table 1, Entry 12). With this catalyst, we detected no trace of side products and isolated **1** in 90% yield. We note that the addition of 0.2 mol-% of $P(Ad)_2$*n*Bu to the reaction mixture led to a lower yield of **1** (Table 1, Entry 13). With this electron-deficient aryl bromide, the oxidative addition to palladium is not the rate-limiting step of the catalytic cycle; therefore, the presence of an electron-rich phosphane ligand is useless. We then studied the reaction using a substrate/catalyst ratio of 2000 with $Pd(OAc)_2$, ½$Pd_2(dba)_3$, ½$[PdCl(C_3H_5)]_2$ and $PdCl_2$ as catalyst precursors (Table 1, Entries 14–17). We observed relatively similar conversions with these four catalysts (53–72%), but again, we observed the most selective reaction using $PdCl_2$ as the catalyst. Finally, we found a lower reaction temperature of 100 °C instead of 130 °C gave **1** in only 15% conversion (Table 1, Entry 18). At this temperature, we recovered most of the aryl bromide unreacted.

We then investigated the scope and limitations of this reaction using other aryl bromides and also aryl chlorides (Scheme 4, Tables 2, 3 and 4). First, we studied the reactivity of *para*-substituted aryl bromides (Scheme 4 and Table 2). We performed these reactions using DMAc, AcOK, 130 °C and 0.2 mol-% of $PdCl_2$ as reaction conditions. In the presence of electron-deficient aryl bromides such as 4-bromoacetophenone, 4-bromobenzophenone, 4-bromobenzaldehyde, 4-bromonitrobenzene and 1-bromo-4-(trifluoromethyl)benzene, we obtained the products **2**–**7** in 84–93 % yield (Table 2, Entries 2, 4, 6, 7, 11 and 12).



Scheme 4.

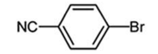
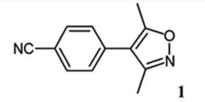
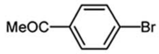
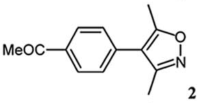
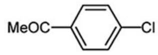
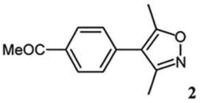
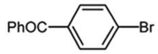
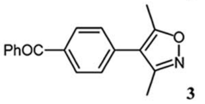
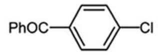
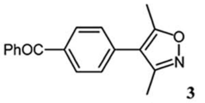
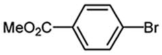
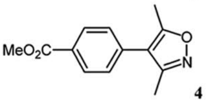
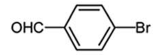
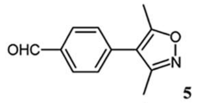
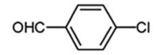
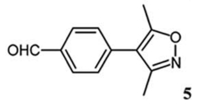
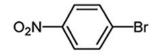
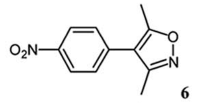
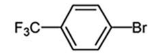
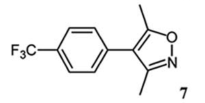
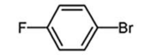
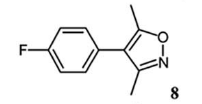
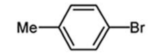
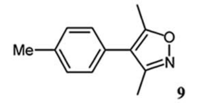
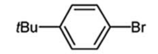
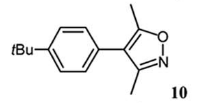
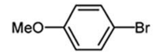
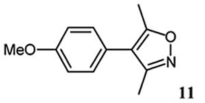
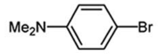
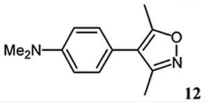
A slightly activated aryl bromide, 1-bromo-4-fluorobenzene gave the expected product **8** in a high yield of 90 % (Table 2, Entry 13). Deactivated aryl bromides, 4-bromotoluene, 1-bromo-4-*tert*-butylbenzene and 4-bromoanisole gave **9**–**11** in 87, 55 and 58 % yields, respectively, by using 0.5 mol-% of catalyst (Table 2, Entries 14–16). With these substrates, we obtained lower yields using 0.2 mol-% of catalyst. Using the strongly deactivated aryl bromide, 4-bromo-*N*,*N*-dimethylaniline, in the presence of 0.5 mol-% of catalyst, we obtained **12** in only 44 % yield (Table 2, Entry 17). As expected, we found the aryl chlorides, 4-chloroacetophenone, 4-chlorobenzophenone and 4-chlorobenzaldehyde gave products **2**, **3** and **5**, respectively, in very low yields using this catalyst (Table 2, Entries 3, 5 and 8). For this reaction, the oxidative addition of aryl chlorides to palladium appears to be the rate-limiting step of the catalytic cycle. Therefore, for such challenging substrates, the use of palladium associated with electron-rich and congested phosphane ligands should be preferred.[9] With 1 mol-% of $PdCl_2$ and 2 mol-% of $P(Ad)_2nBu$ as the catalyst, the reaction of 4-chlorobenzaldehyde with 3,5-dimethylisoxazole gave **5** in 58 % yield (Table 2, Entry 10).

We next examined the reactivity of *meta*-substituted aryl bromides with 3,5-dimethylisoxazole (Table 3). As expected, the electron-deficient aryl bromides, 3-bromoacetophenone, 3-bromonitrobenzene and 1-bromo-3,5-bis(trifluoromethyl)benzene could be brought to reaction by using 0.2 mol-% of catalyst as with the *para*-substituted aryl bromides (Table 3, Entries 1–3).

ortho-Substituents on the aryl bromides generally have a more important effect on the reactions rates and yields of most palladium-catalysed reactions due to their steric and/or coordination properties. However, we also obtained good yields of coupling product **17** or **18** in the presence of 2-bromobenzonitrile or 1-bromonaphthalene and 3,5-dimethylisoxazole (Table 3, Entries 5 and 6).

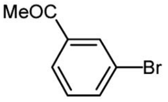
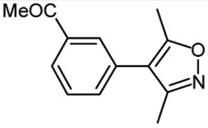
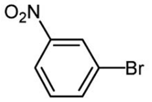
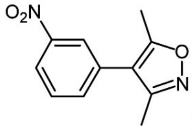
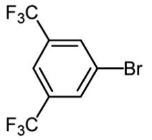
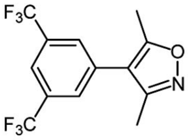
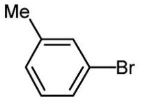
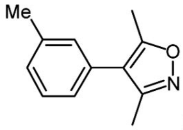
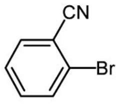
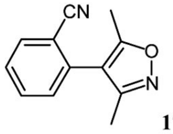
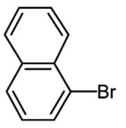
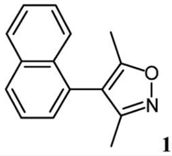
We then examined the reactivity of a few heteroaryl bromides (Table 4). The unique characteristics of palladium chemistry involving heterocycles stem from the inherently

Table 2. Palladium-catalysed direct coupling of *para*-substituted aryl halides with 3,5-dimethylisoxazole (Scheme 4).[a]

Entry	Aryl bromide	Product	Yield (%)
1		 **1**	90[b]
2		 **2**	84
3		 **2**	6[c]
4		 **3**	88
5		 **3**	4[c]
6		 **4**	93
7		 **5**	90
8		 **5**	6[c]
9			21[d]
10			58[e]
11		 **6**	85
12		 **7**	92
13		 **8**	90
14		 **9**	87[c]
15		 **10**	55[c]
16		 **11**	58[c]
17		 **12**	44[c]

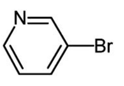
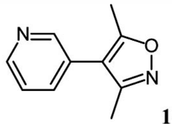
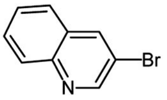
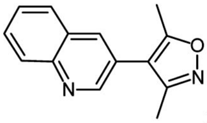
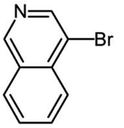
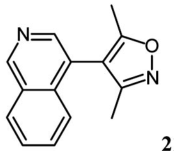
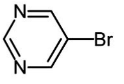
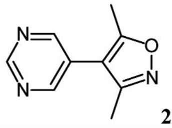
[a] Conditions: $PdCl_2$ (0.002 equiv.), aryl halide (1 equiv.), 3,5-dimethylisoxazole (1.5 equiv.), AcOK (2 equiv.), DMAc, 20 h, 130 °C; isolated yields. [b] 0.001 equiv. of $PdCl_2$ was employed. [c] 0.005 equiv. of $PdCl_2$ was employed. [d] $PdCl_2$ (0.001 equiv.) and $P(Ad)_2nBu$ (0.002 equiv.) were employed. [e] $PdCl_2$ (0.01 equiv.) and $P(Ad)_2nBu$ (0.02 equiv.) were employed.

Table 3. Palladium-catalysed direct coupling of *meta*- and *ortho*-substituted aryl bromides with 3,5-dimethylisoxazole (Scheme 4).[a]

Entry	Aryl bromide	Product	Yield (%)
1		 **13**	89
2		 **14**	88
3		 **15**	92
4		 **16**	89[b]
5		 **17**	83
6		 **18**	91

[a] Conditions: $PdCl_2$ (0.002 equiv.), aryl bromide (1 equiv.), 3,5-dimethylisoxazole (1.5 equiv.), AcOK (2 equiv.), DMAc, 20 h, 130 °C; isolated yields. [b] 0.005 equiv. of $PdCl_2$ was employed.

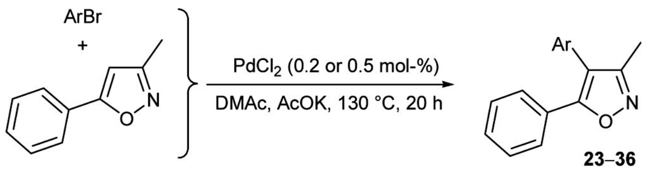
Table 4. Palladium-catalysed direct coupling of heteroaryl bromides with 3,5-dimethylisoxazole (Scheme 4).[a]

Entry	Aryl bromide	Product	Yield (%)
1		 **19**	95
2		 **20**	92
3		 **21**	89
4		 **22**	84

[a] Conditions: $PdCl_2$ (0.002 equiv.), aryl bromide (1 equiv.), 3,5-dimethylisoxazole (1.5 equiv.), AcOK (2 equiv.), DMAc, 20 h, 130 °C; isolated yields.

different structural and electronic properties of heterocycles in comparison to the corresponding carbocyclic aryl compounds. Pyridines and pyrimidines are π-electron-deficient heterocycles. Therefore, their reactivity is quite similar to electron-deficient aryl bromides. As expected, using 3-bromopyridine, 3-bromoquinoline, 4-bromoisoquinoline or 5-bromopyrimidine, we obtained the coupling products **19**–**22** in very high yield with only 0.2 mol-% of catalyst.

The reaction was not limited to the use of 3,5-dimethylisoxazole. We also found 3-methyl-5-phenylisoxazole to be a suitable reactant for this reaction (Scheme 5 and Table 5). We coupled a variety of aryl bromides with this substrate to give the desired products **23**–**35**. First, we studied the reactivity of *para*-substituted aryl bromides. Again, we obtained higher yields using electron-deficient aryl bromides. In the presence of 4-bromobenzaldehyde, 4-bromoacetophenone, 4-bromobenzonitrile and 4-bromonitrobenzene we obtained the products **23**–**26** in 85–90% yields using only 0.2 mol-% of catalyst (Table 5, Entries 1–4).



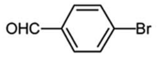
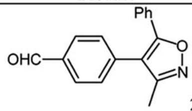
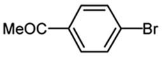
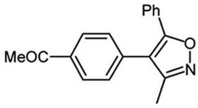
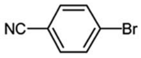
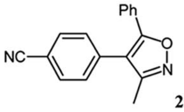
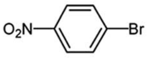
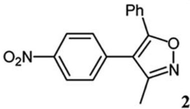
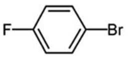
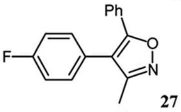
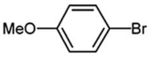
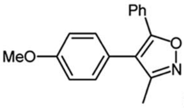
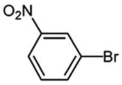
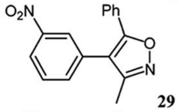
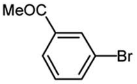
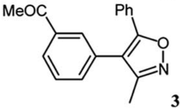
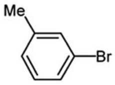
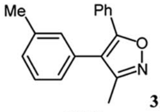
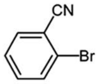
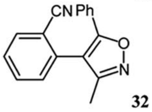
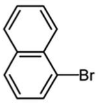
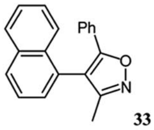
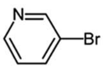
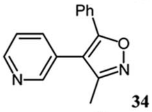
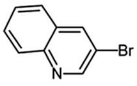
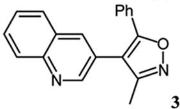
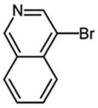
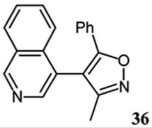
Scheme 5.

On the other hand, using 4-bromoanisole, we had to employ 0.5 mol-% of catalyst in order to obtain a good yield of 77% of **28** (Table 5, Entry 6). Electron-deficient *meta*- and *ortho*-substituted aryl bromides also gave the coupling products **29**, **30**, **32** and **33** in very high yield with 0.2 mol-% of catalyst (Table 5, Entries 7, 8, 10 and 11). We also tested the coupling with the three heteroaryl bromides. 3-Bromopyridine, 3-bromopyridine and 4-bromoisoquinoline gave the expected 4-arylated isoxazoles **34**–**36** in very good yields (Table 5, Entries 12–14).

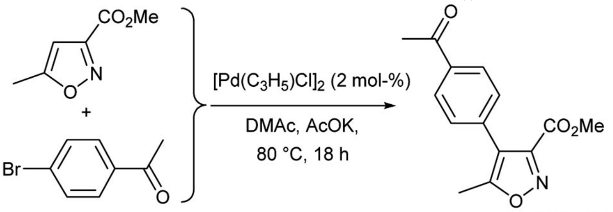
Finally, we examined the reactivity of functionalised isoxazoles. The presence of an ester function in position 3 led to an important change in the reactivity. Using 0.5 or 2 mol-% of $PdCl_2$, AcOK, and DMAc, 80 or 130 °C as the reaction temperature and 4-bromoacetophenone as the reaction partner, we detected no arylation product **37**. On the other hand, in the presence of 2 mol-% of $[Pd(C_3H_5)Cl]_2$ as a catalyst precursor at 80 °C, we obtained product **37** in 27% yield (Scheme 6). During the course of this reaction, we also observed the formation of a very important amount of 4,4′-diacetylbiphenyl. We found methyl 5-methylisoxazole-4-carboxylate to be even less reactive. With this reactant, we did not detect the formation of **38** using various reaction conditions (Scheme 7).

In order to confirm this important change in reactivity in the presence of a functional group on isoxazoles, we also studied the 4-arylation of 3-formyl-5-methylisoxazole with 4-bromobenzonitrile (Scheme 8). With this reactant, 26% of product **39** formed when we used $[PdCl(C_3H_5)]_2$ as the catalyst at 60 °C. During the course of this reaction, we

Table 5. Palladium-catalysed direct coupling with 3-methyl-5-phenylisoxazole (Scheme 5).[a]

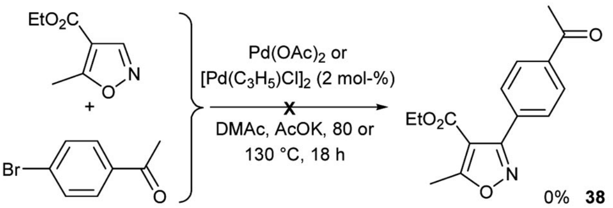
Entry	Aryl bromide	Product	Yield (%)
1		 **23**	86
2		 **24**	85
3		 **25**	88
4		 **26**	90
5		 **27**	88
6		 **28**	77[b]
7		 **29**	90
8		 **30**	80
9		 **31**	84[b]
10		 **32**	86
11		 **33**	90
12		 **34**	90
13		 **35**	91
14		 **36**	91

[a] Conditions: $PdCl_2$ (0.002 equiv.), aryl bromide (1 equiv.), 3-methyl-5-phenylisoxazole (1.5 equiv.), AcOK (2 equiv.), DMAc, 20 h, 130 °C; isolated yields. [b] 0.005 equiv. of $PdCl_2$ was employed.



27% **37**

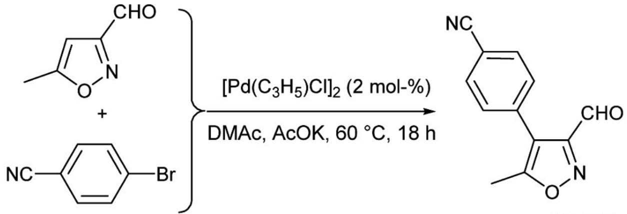
Scheme 6.



0% **38**

Scheme 7.

observed the formation of a very important amount of biphenyl-4,4′-dicarbonitrile. This oxazole derivative appeared to be quite unstable under the reaction conditions at more elevated temperatures (80–130 °C). At these temperatures, we did not recover the starting isoxazole material at the end of the reaction, and several unidentified compounds formed.



39 26%

Scheme 8.

Conclusions

A wide variety of 4-arylisoxazole derivatives can be prepared easily and in good yields by the direct 4-arylation of 3,5-disubstituted isoxazole derivatives. This reaction can be performed by using as little as 0.1–0.5 mol-% of a ligand-free palladium catalyst. Therefore, this low catalyst loading procedure is economically attractive. Moreover, there is no need to eliminate phosphane derivatives at the end of the reaction. At such low catalyst concentrations, palladium-stabilizing agents like ammonium salts are useless, thus reducing the amount of wastes. Both 3,5-dimethyl- and 3-methyl-5-phenylisoxazole can be employed as coupling partners. On the other hand, we found isoxazoles substituted by electron-withdrawing substituents to be less reactive. We generally obtained better results using electron-deficient aryl bromides. However, it should be noted that a wide range of groups such as acetyl, formyl, ester, nitro, trifluoromethyl, fluoro, amino and nitrile on the aryl bromide were tolerated. This procedure is very simple, uses commercially available substrates and catalyst, and the air stability of the catalyst also makes this procedure very convenient. We note that an important number of the products prepared by this method have never been described so far, indicating that this procedure provides a convenient access to compounds which cannot be prepared very easily by more classical cross-coupling methods. Finally, due to environmental considerations, the advantage of such an atom-economical and inert-waste procedure (formation of acetic acid and potassium bromide) should become increasingly important for industrial processes.

Experimental Section

General Remarks: All reactions were run under argon in Schlenk tubes by using vacuum lines. DMAc (analytical grade) was not distilled before use. Potassium acetate (99 %) was used. Commercially available aryl halides and isoxazole derivatives were used without purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.25 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). Flash chromatography was performed on silica gel (230–400 mesh).

General Procedure for Coupling Reactions: In a typical experiment, the heteroaryl bromide (1 mmol), isoxazole derivative (1.5 mmol), AcOK (0.196 g, 2 mmol) and $PdCl_2$ (0.0004 g, 0.002 mmol) were dissolved in DMAc (5 mL) under argon. The reaction mixture was stirred at 130 °C for 20 h. The product was then extracted three times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

4-(3,5-Dimethylisoxazol-4-yl)benzonitrile (1):[11] The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **1** in 90 % (0.178 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.2 Hz, 2 H, Ar), 7.36 (d, J = 8.2 Hz, 2 H, Ar), 2.41 (s, 3 H, Me), 2.26 (s, 3 H, Me) ppm.

4-(3,5-Dimethylisoxazol-4-yl)acetophenone (2): The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **2** in 84 % (0.181 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.2 Hz, 2 H, Ar), 7.34 (d, J = 8.2 Hz, 2 H, Ar), 2.60 (s, 3 H, COMe), 2.40 (s, 3 H, Me), 2.25 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 165.7, 158.2, 135.9, 135.3, 128.9, 128.7, 115.7, 26.5, 11.6, 10.7 ppm. $C_{13}H_{13}NO_2$ (215.25): calcd. C 72.54, H 6.09; found C 72.41, H 6.07.

4-(3,5-Dimethylisoxazol-4-yl)benzophenone (3): The reaction of 4-bromobenzophenone (0.261 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **3** in 88 % (0.244 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.2 Hz, 2 H, Ar), 7.80 (d, J = 8.2 Hz, 2 H, Ar), 7.58 (t, J = 7.9 Hz, 1 H, Ar), 7.47 (t, J = 7.9 Hz, 2 H, Ar), 7.36 (d, J = 8.2 Hz, 2 H, Ar), 2.43 (s, 3 H, Me), 2.29 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.9, 165.7, 158.2, 137.3, 136.4, 134.7, 132.4, 130.4, 129.9, 128.7, 128.2, 115.8, 11.6, 10.8 ppm. $C_{18}H_{15}NO_2$ (277.32): calcd. C 77.96, H 5.45; found C 77.99, H 5.58.

Methyl 4-(3,5-dimethylisoxazol-4-yl)benzoate (4): The reaction of methyl 4-bromobenzoate (0.215 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **4** in 93 % (0.215 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.2 Hz, 2 H, Ar), 7.34 (d, J = 8.2 Hz, 2 H, Ar), 3.94 (s, 3 H, CO_2Me), 2.43 (s, 3 H, Me), 2.29 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 166.1, 158.7, 135.7, 130.4, 129.5, 129.2, 116.3, 52.6, 12.0, 11.2 ppm. $C_{13}H_{13}NO_3$ (231.25): calcd. C 67.52, H 5.67; found C 67.60, H 5.57.

4-(3,5-Dimethylisoxazol-4-yl)benzaldehyde (5):[12] The reaction of 4-bromobenzaldehyde (0.187 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **5** in 90 % (0.181 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.01 (s, 1 H, CHO), 7.92 (d, J = 8.2 Hz, 2 H, Ar), 7.41 (d, J = 8.2 Hz, 2 H, Ar), 2.41 (s, 3 H, Me), 2.27 (s, 3 H, Me) ppm.

3,5-Dimethyl-4-(4-nitrophenyl)isoxazole (6):[13] The reaction of 1-bromo-4-nitrobenzene (0.202 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **6** in 85 % (0.185 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.2 Hz, 2 H, Ar), 7.43 (d, J = 8.2 Hz, 2 H, Ar), 2.44 (s, 3 H, Me), 2.29 (s, 3 H, Me) ppm.

3,5-Dimethyl-4-[4-(trifluoromethyl)phenyl]isoxazole (7): The reaction of 1-bromo-4-(trifluoromethyl)benzene (0.225 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **7** in 92 % (0.222 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.2 Hz, 2 H, Ar), 7.37 (d, J = 8.2 Hz, 2 H, Ar), 2.41 (s, 3 H, Me), 2.27 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 158.3, 134.3, 129.6 (q, J = 32.7 Hz), 129.3, 125.8, 124.1 (q, J = 271.9 Hz), 115.6, 11.5, 10.7 ppm. $C_{12}H_{10}F_3NO$ (241.21): calcd. C 59.75, H 4.18; found C 59.70, H 4.13.

4-(4-Fluorophenyl)-3,5-dimethylisoxazole (8): The reaction of 1-bromo-4-fluorobenzene (0.175 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **8** in 90 % (0.172 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (dd, J = 8.7 and 5.5 Hz, 2 H, Ar), 7.37 (t, J = 8.7 Hz, 2 H, Ar), 2.39 (s, 3 H, Me), 2.26 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 247.2, 158.5, 130.7 (d, J = 8.1 Hz), 126.3 (d, J = 3.4 Hz), 115.8 (d, J = 21.7 Hz), 115.7, 11.4, 10.6 ppm. $C_{11}H_{10}FNO$ (191.20): calcd. C 69.10, H 5.27; found C 69.19, H 5.34.

3,5-Dimethyl-4-*p*-tolylisoxazole (9):[14] The reaction of 4-bromotoluene (0.171 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **9** in 87 % (0.163 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.2 Hz, 2 H, Ar), 7.23 (d, J = 8.2 Hz, 2 H, Ar), 2.48 (s, 6 H, Me), 2.35 (s, 3 H, Me) ppm.

4-(4-*tert*-Butylphenyl)-3,5-dimethylisoxazole (10):[13] The reaction of 1-bromo-4-*tert*-butylbenzene (0.213 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **10** in 55% (0.126 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.2 Hz, 2 H, Ar), 7.27 (d, J = 8.2 Hz, 2 H, Ar), 2.49 (s, 3 H, Me), 2.36 (s, 3 H, Me), 1.44 (s, 9 H, *t*Bu) ppm.

4-(4-Methoxyphenyl)-3,5-dimethylisoxazole (11):[13] The reaction of 4-bromoanisole (0.187 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **11** in 58% (0.118 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.2 Hz, 2 H, Ar), 7.96 (d, J = 8.2 Hz, 2 H, Ar), 3.84 (s, 3 H, OMe), 2.37 (s, 3 H, Me), 2.24 (s, 3 H, Me) ppm.

4-(3,5-Dimethylisoxazol-4-yl)-*N*,*N*-dimethylaniline (12):[15] The reaction of 1-bromo-4-(dimethylamino)benzene (0.200 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **12** in 44% (0.095 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, J = 8.2 Hz, 2 H, Ar), 6.77 (d, J = 8.2 Hz, 2 H, Ar), 2.98 (s, 6 H, NMe_2), 2.37 (s, 3 H, Me), 2.25 (s, 3 H, Me) ppm.

3-(3,5-Dimethylisoxazol-4-yl)acetophenone (13): The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **13** in 89% (0.192 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.2 Hz, 1 H, Ar), 7.81 (s, 1 H, Ar), 7.52 (t, J = 7.7 Hz, 1 H, Ar), 7.43 (d, J = 8.2 Hz, 1 H, Ar), 2.60 (s, 3 H, COMe), 2.37 (s, 3 H, Me), 2.23 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 165.5, 158.3, 137.5, 133.4, 131.0, 129.0, 128.5, 127.4, 115.8, 26.6, 11.4, 10.6 ppm. $C_{13}H_{13}NO_2$ (215.25): calcd. C 72.54, H 6.09; found C 72.68, H 6.17.

3,5-Dimethyl-4-(3-nitrophenyl)isoxazole (14):[14] The reaction of 1-bromo-3-nitrobenzene (0.202 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **14** in 88% (0.192 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.2 Hz, 1 H, Ar), 8.11 (s, 1 H, Ar), 7.64 (t, J = 7.7 Hz, 1 H, Ar), 7.59 (d, J = 8.2 Hz, 1 H, Ar), 2.43 (s, 3 H, Me), 2.28 (s, 3 H, Me) ppm.

4-[3,5-Bis(trifluoromethyl)phenyl]-3,5-dimethylisoxazole (15): The reaction of 1-bromo-3,5-bis(trifluoromethyl)benzene (0.293 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **15** in 92% (0.285 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (s, 1 H, Ar), 7.73 (s, 2 H, Ar), 2.47 (s, 3 H, Me), 2.31 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 158.0, 132.9, 132.5 (q, J = 33.8 Hz), 129.0, 122.5 (q, J = 273.1 Hz), 121.4, 114.5, 11.6, 10.6 ppm. $C_{13}H_9F_6NO$ (309.21): calcd. C 50.50, H 2.93; found C 50.61, H 3.07.

3,5-Dimethyl-4-*m*-tolylisoxazole (16): The reaction of 3-bromotoluene (0.171 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **16** in 89% (0.167 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (t, J = 7.8 Hz, 1 H, Ar), 7.16 (d, J = 8.2 Hz, 1 H, Ar), 7.05 (s, 1 H, Ar), 7.04 (d, J = 8.2 Hz, 1 H, Ar), 2.39 (s, 6 H, Me), 2.26 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 158.7, 138.4, 130.3, 129.7, 128.6, 128.2, 126.1, 116.6, 21.4, 11.5, 10.8 ppm. $C_{12}H_{13}NO$ (187.24): calcd. C 76.98, H 7.00; found C 76.89, H 6.88.

2-(3,5-Dimethylisoxazol-4-yl)benzonitrile (17): The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **17** in 83% (0.165 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.3 Hz, 1 H, Ar), 7.64 (t, J = 7.7 Hz, 1 H, Ar), 7.49 (t, J = 7.7 Hz, 1 H, Ar), 7.32 (d, J = 8.3 Hz, 1 H, Ar), 2.35 (s, 3 H, Me), 2.20 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 158.4, 134.0, 133.4, 132.9, 131.1, 128.5, 117.6, 113.9, 113.5, 11.8, 10.4 ppm. $C_{12}H_{10}N_2O$ (198.22): calcd. C 72.71, H 5.08; found C 72.79, H 5.09.

3,5-Dimethyl-4-(naphthalen-1-yl)isoxazole (18):[9] The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **18** in 91% (0.203 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.70 (m, 2 H, Ar), 7.60–7.45 (m, 4 H, Ar), 7.32 (dd, J = 6.9 and 1.1 Hz, 1 H, Ar), 2.26 (s, 3 H, Me), 2.09 (s, 3 H, Me) ppm.

3-(3,5-Dimethylisoxazol-4-yl)pyridine (19): The reaction of 3-bromopyridine (0.158 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **19** in 95% (0.166 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (dd, J = 4.7 and 1.3 Hz, 1 H, Ar), 8.50 (d, J = 1.7 Hz, 1 H, Ar), 7.57 (dt, J = 7.7 and 1.7 Hz, 1 H, Ar), 7.35 (dd, J = 7.7 and 4.7 Hz, 1 H, Ar), 2.39 (s, 3 H, Me), 2.24 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 158.4, 149.8, 148.7, 136.2, 126.5, 123.5, 113.4, 11.5, 10.6 ppm. $C_{10}H_{10}N_2O$ (174.20): calcd. C 68.95, H 5.79; found C 68.78, H 5.89.

3-(3,5-Dimethylisoxazol-4-yl)quinoline (20): The reaction of 3-bromoquinoline (0.208 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **20** in 92% (0.206 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.78 (d, J = 2.3 Hz, 1 H, Ar), 8.08 (d, J = 8.5 Hz, 1 H, Ar), 7.98 (d, J = 2.3 Hz, 1 H, Ar), 7.80 (d, J = 8.5 Hz, 1 H, Ar), 7.70 (t, J = 7.7 Hz, 1 H, Ar), 7.54 (t, J = 7.7 Hz, 1 H, Ar), 2.42 (s, 3 H, Me), 2.27 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 158.5, 150.5, 147.1, 135.4, 129.7, 129.2, 127.6, 127.5, 127.1, 123.6, 113.5, 11.5, 10.6 ppm. $C_{14}H_{12}N_2O$ (224.26): calcd. C 74.98, H 5.39; found C 75.01, H 5.28.

4-(3,5-Dimethylisoxazol-4-yl)isoquinoline (21): The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **21** in 89% (0.200 g) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.28 (s, 1 H, Ar), 8.36 (s, 1 H, Ar), 8.06 (d, J = 8.5 Hz, 1 H, Ar), 7.71 (t, J = 7.8 Hz, 1 H, Ar), 7.64 (t, J = 7.7 Hz, 1 H, Ar), 7.55 (d, J = 8.5 Hz, 1 H, Ar), 2.27 (s, 3 H, Me), 2.09 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 159.8, 153.0, 144.3, 134.8, 131.0, 128.4, 128.2, 127.6, 124.0, 121.3, 111.6, 11.4, 10.5 ppm. $C_{14}H_{12}N_2O$ (224.26): calcd. C 74.98, H 5.39; found C 75.04, H 5.47.

5-(3,5-Dimethylisoxazol-4-yl)pyrimidine (22): The reaction of 5-bromopyrimidine (0.159 g, 1 mmol), 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **22** in 84% (0.147 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1 H, Ar), 8.66 (s, 2 H, Ar), 2.43 (s, 3 H, Me), 2.27 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 158.1, 157.6, 156.4, 125.1, 110.2, 11.5, 10.6 ppm. $C_9H_9N_3O$ (175.19): calcd. C 61.70, H 5.18; found C 61.79, H 5.27.

4-(3-Methyl-5-phenylisoxazol-4-yl)benzaldehyde (23): The reaction of 4-bromobenzaldehyde (0.187 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **23** in 90% (0.226 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05 (s, 1 H, CHO), 7.94 (d, J = 8.2 Hz, 2 H, Ar), 7.52–7.20 (m, 7 H, Ar), 2.27 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5, 165.1, 159.4, 137.1, 135.7, 130.4, 130.2, 130.1, 128.7, 127.3, 127.0, 115.0, 10.6 ppm. $C_{17}H_{13}NO_2$ (263.29): calcd. C 77.55, H 4.98; found C 77.60, H 4.87.

4-(3-Methyl-5-phenylisoxazol-4-yl)acetophenone (24): The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **24** in 85% (0.236 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.3 Hz, 2 H, Ar), 7.55–7.20 (m, 7 H, Ar), 2.64 (s, 3 H, COMe), 2.26 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 164.9, 159.6, 136.5, 135.7, 130.0, 129.9, 129.0, 128.7, 127.4, 127.0, 115.2, 26.6, 10.6 ppm. $C_{18}H_{15}NO_2$ (277.32): calcd. C 77.96, H 5.45; found C 77.99, H 5.37.

4-(3-Methyl-5-phenylisoxazol-4-yl)benzonitrile (25): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **25** in 88% (0.229 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.4 Hz, 2 H, Ar), 7.50–7.20 (m, 7 H, Ar), 2.26 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 159.2, 135.6, 132.7, 130.4, 130.2, 128.8, 127.0, 126.9, 118.3, 114.5, 111.8, 10.6 ppm. $C_{17}H_{12}N_2O$ (260.29): calcd. C 78.44, H 4.65; found C 78.50, H 4.79.

3-Methyl-4-(4-nitrophenyl)-5-phenylisoxazole (26): The reaction of 1-bromo-4-nitrobenzene (0.202 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **26** in 90% (0.252 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.2 Hz, 2 H, Ar), 7.52–7.20 (m, 7 H, Ar), 2.28 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 159.2, 147.5, 137.7, 130.6, 130.3, 128.9, 127.1, 124.2, 114.2, 10.6 ppm. $C_{16}H_{12}N_2O_3$ (280.28): calcd. C 68.56, H 4.32; found C 68.64, H 4.14.

4-(4-Fluorophenyl)-3-methyl-5-phenylisoxazole (27): The reaction of 1-bromo-4-fluorobenzene (0.175 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **27** in 88% (0.223 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.45 (m, 2 H, Ar), 7.40–7.20 (m, 5 H, Ar), 7.13 (t, J = 8.2 Hz, 2 H, Ar), 2.23 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 162.1 (d, J = 247.2 Hz), 160.0, 131.6 (d, J = 8.1 Hz), 129.8, 128.7, 127.4, 126.9, 126.5 (d, J = 3.4 Hz), 116.2 (d, J = 21.7 Hz), 115.2, 10.5 ppm. $C_{16}H_{12}FNO$ (253.27): calcd. C 75.88, H 4.78; found C 75.62, H 4.80.

4-(4-Methoxyphenyl)-3-methyl-5-phenylisoxazole (28): The reaction of 4-bromoanisole (0.187 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **28** in 77% (0.204 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.50 (m, 2 H, Ar), 7.30–7.25 (m, 3 H, Ar), 7.20 (d, J = 8.2 Hz, 2 H, Ar), 6.97 (d, J = 8.2 Hz, 2 H, Ar), 3.86 (s, 3 H, OMe), 2.23 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 160.2, 159.4, 130.9, 129.5, 128.5, 128.0, 126.7, 122.6, 115.8, 114.5, 55.2, 10.5 ppm. $C_{17}H_{15}NO_2$ (265.31): calcd. C 76.96, H 5.70; found C 76.97, H 5.57.

3-Methyl-4-(3-nitrophenyl)-5-phenylisoxazole (29): The reaction of 1-bromo-3-nitrobenzene (0.202 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **29** in 90% (0.252 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (m, 1 H, Ar), 8.16 (m, 1 H, Ar), 7.62 (d, J = 8.4 Hz, 2 H, Ar), 7.50–7.25 (m, 5 H, Ar), 2.27 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 159.4, 148.6, 135.9, 132.4, 130.2, 130.1, 128.8, 127.0, 126.8, 124.5, 123.0, 113.9, 10.5 ppm. $C_{16}H_{12}N_2O_3$ (280.28): calcd. C 68.56, H 4.32; found C 68.59, H 4.21.

3-(3-Methyl-5-phenylisoxazol-4-yl)acetophenone (30): The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **30** in 80% (0.222 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dt, J = 7.2 and 1.7 Hz, 1 H, Ar), 7.90–7.81 (m, 1 H, Ar), 7.60–7.45 (m, 4 H, Ar), 7.35–7.28 (m, 3 H, Ar), 2.57 (s, 3 H, COMe), 2.24 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 164.8, 159.8, 138.0, 134.5, 131.4, 130.0, 129.7, 129.5, 128.8, 128.0, 127.6, 126.9, 115.3, 26.7, 10.6 ppm. $C_{18}H_{15}NO_2$ (277.32): calcd. C 77.96, H 5.45; found C 77.79, H 5.54.

3-Methyl-5-phenyl-4-*m*-tolylisoxazole (31): The reaction of 3-bromotoluene (0.171 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0009 g, 0.005 mmol) afforded the corresponding product **31** in 84% (0.209 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.50 (m, 2 H, Ar), 7.40–7.00 (m, 7 H, Ar), 2.38 (s, 3 H, Me), 2.24 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 160.1, 138.7, 130.5, 130.4, 129.5, 128.9, 128.8, 128.5, 128.0, 126.9, 126.8, 116.2, 21.3, 10.5 ppm. $C_{17}H_{15}NO$ (249.31): calcd. C 81.90, H 6.06; found C 82.04, H 6.14.

2-(3-Methyl-5-phenylisoxazol-4-yl)benzonitrile (32): The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **32** in 86% (0.224 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (dd, J = 8.2 and 1.1 Hz, 1 H, Ar), 7.68 (td, J = 7.7 and 1.5 Hz, 1 H, Ar), 7.54 (td, J = 7.7 and 1.5 Hz, 1 H, Ar), 7.45–7.25 (m, 6 H, Ar), 2.24 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 159.6, 134.6, 133.6, 133.3, 131.6, 130.1, 128.9, 128.8, 127.2, 126.6, 117.1, 114.0, 112.7, 10.3 ppm. $C_{17}H_{12}N_2O$ (260.29): calcd. C 78.44, H 4.65; found C 78.57, H 4.71.

3-Methyl-4-(naphthalen-1-yl)-5-phenylisoxazole (33): The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **33** in 90% (0.256 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.2 Hz, 2 H, Ar), 7.75–7.30 (m, 7 H, Ar), 7.25–7.10 (m, 3 H, Ar), 2.09 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 161.1, 133.9, 132.1, 129.5, 128.8, 128.7, 128.6, 128.5, 128.0, 127.7, 126.7, 126.3, 126.2, 125.7, 125.0, 114.0, 10.3 ppm. $C_{20}H_{15}NO$ (285.34): calcd. C 84.19, H 5.30; found C 84.40, H 5.15.

3-(3-Methyl-5-phenylisoxazol-4-yl)pyridine (34): The reaction of 3-bromopyridine (0.158 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **34** in 90% (0.213 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (dd, J = 4.8 and 1.6 Hz, 1 H, Ar), 8.52 (d, J = 2.3 Hz, 1 H, Ar), 7.57 (dt, J = 8.0 and 2.0 Hz, 1 H, Ar), 7.50–7.20 (m, 6 H, Ar), 2.21 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 159.6, 150.3, 149.1, 137.0, 129.9, 128.7, 127.2, 126.7, 123.6, 112.5, 10.4 ppm. $C_{15}H_{12}N_2O$ (236.27): calcd. C 76.25, H 5.12; found C 76.41, H 5.18.

3-(3-Methyl-5-phenylisoxazol-4-yl)quinoline (35): The reaction of 3-bromoquinoline (0.208 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **35** in 91% (0.260 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (d, J = 2.3 Hz, 1 H, Ar), 8.15 (d, J = 8.5 Hz, 1 H, Ar), 8.08 (d, J = 2.3 Hz, 1 H, Ar), 7.81 (d, J = 8.5 Hz, 1 H, Ar), 7.75 (t, J = 7.5 Hz, 1 H, Ar), 7.57 (t, J = 7.5 Hz, 1 H, Ar), 7.50 (d, J = 7.5 Hz, 2 H, Ar), 7.33–7.20 (m, 3 H, Ar), 2.28 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 159.9, 151.1, 147.3, 136.3, 130.0, 129.9, 129.3, 128.7, 127.7, 127.6, 127.2, 127.1, 126.7, 123.9, 112.6, 10.5 ppm. $C_{19}H_{14}N_2O$ (286.33): calcd. C 79.70, H 4.93; found C 79.84, H 4.98.

4-(3-Methyl-5-phenylisoxazol-4-yl)isoquinoline (36): The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol), 3-methyl-5-phenylisoxazole (0.239 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 130 °C in dry DMAc (5 mL) in the presence of $PdCl_2$ (0.0004 g, 0.002 mmol) afforded the corresponding product **36** in 91% (0.260 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.35 (s, 1 H, Ar), 8.47 (s, 1 H, Ar), 8.30–8.05 (m, 1 H, Ar), 7.75–7.50 (m, 3 H, Ar), 7.38 (d, J = 7.5 Hz, 2 H, Ar), 7.30–7.10 (m, 3 H, Ar), 2.09 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 161.0, 153.2, 144.4, 134.7, 131.3, 129.8, 128.6, 128.4, 128.2, 127.8, 127.3, 126.3, 124.0, 121.9, 110.4, 10.3 ppm. $C_{19}H_{14}N_2O$ (286.33): calcd. C 79.70, H 4.93; found C 79.84, H 4.71.

Methyl 4-(4-Acetylphenyl)-5-methylisoxazole-3-carboxylate (37): The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), methyl 5-methylisoxazole-3-carboxylate (0.212 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 80 °C in dry DMAc (5 mL) in the presence of $[PdCl(C_3H_5)]_2$ (0.007 g, 0.02 mmol) afforded the corresponding product **37** in 27% (0.070 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.3 Hz, 2 H, Ar), 7.41 (d, J = 8.3 Hz, 2 H, Ar), 3.88 (s, 3 H, CO_2Me), 2.62 (s, 3 H, COMe), 2.46 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 168.7, 160.2, 153.4, 136.7, 133.6, 130.1, 128.3, 116.8, 52.7, 26.6, 11.5 ppm. $C_{14}H_{13}NO_4$ (259.26): calcd. C 64.86, H 5.05; found C 64.69, H 5.20.

4-(3-Formyl-5-methylisoxazol-4-yl)benzonitrile (39): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 3-formyl-5-methylisoxazole (0.167 g, 1.5 mmol) and AcOK (0.196 g, 2 mmol) at 60 °C in dry DMAc (5 mL) in the presence of $[PdCl(C_3H_5)]_2$ (0.007 g, 0.02 mmol) afforded the corresponding product **39** in 26% (0.055 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.18 (s, 1 H, CHO), 7.72 (d, J = 8.3 Hz, 2 H, Ar), 7.45 (d, J = 8.3 Hz, 2 H, Ar), 2.51 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.9, 169.4, 158.2, 132.2, 130.4, 118.4, 114.5, 112.2, 11.4 ppm. $C_{12}H_8N_2O_2$ (212.20): calcd. C 67.92, H 3.80; found C 67.87, H 3.69.

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