

Carbonates: eco-friendly solvents for palladium-catalysed direct arylation of heteroaromatics†

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Received 18th June 2010, Accepted 22nd September 2010

DOI: 10.1039/c0gc00229a

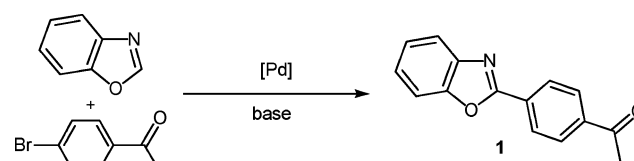
The palladium-catalysed direct 2-, 4- or 5-arylation of a wide range of heteroaromatics with aryl halides proceed in moderate to good yields using the eco-friendly solvents carbonates. The best yields were obtained using benzoxazole or thiazole derivatives. The arylation of furan, thiophene, pyrrole, imidazole or isoxazole derivatives was found to require a more elevated reaction temperature.

The direct arylation of heteroaromatics is an important field for research in organic synthesis due to the biological or physical properties of the aryl-heteroaryl derivatives.¹ Ohta and co-workers reported in 1985–1992 that the direct 2- or 5-arylation of several heteroaromatics with aryl halides proceed in moderate to good yields using Pd(PPh₃)₄ as the catalyst and DMAc as the solvent.² Since these exciting results, the palladium-catalysed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a very powerful method for the synthesis of a wide variety of arylated heterocycles.^{3–10} This reaction provides a cost-effective and environmentally attractive access for the preparation of such compounds. Indeed, the major by-products of the reaction are a base associated to HX, instead of metallic salts produced under classical cross-coupling procedures such as Suzuki, Negishi or Stille reactions. Moreover, the method avoids the preliminary preparation of a requisite organometallic reducing then the number of steps to prepare these compounds. However, these reactions were currently performed in most cases using relatively toxic solvents such as DMF, DMAc, NMP or dioxane. A few palladium-catalysed direct arylations of heteroaromatics have also been performed using toluene, xylene or mesitylene.³ The direct arylation of oxazoles, thiazoles or indazoles using water¹¹ as the solvent has been reported by Greaney. René and Fagnou have developed biphasic conditions using a mixture of water and EtOAc for the direct arylation of thiophenes.¹² Recently, polyethylene glycol (PEG 20000) has been found to be a useful solvent for the direct arylation of triazoles.¹³

Carbonates, such as diethylcarbonate or propylene carbonate, are polar, aprotic, nontoxic, and biodegradable solvents.¹⁴ Based on these properties, such carbonates should offer an environ-

mentally friendly alternative to standard polar solvents. Since a few years ago, carbonates have been employed successfully for some classical metal-catalysed reactions such as enantioselective hydrogenation, alkene metathesis, carbonylation, oxidation, hydroxylation, Sonogashira coupling, Heck vinylation or allylic alkylation.¹⁵ The ruthenium-catalysed direct arylation of 2-arylpyridines has also been reported recently by Fischmeister, Dixneuf and co-workers.¹⁶ However, to our knowledge, so far, carbonates have not been employed as the solvents for palladium-catalysed direct arylations.¹⁷ The use of this family of solvent would provide a cost-effective and environmentally attractive procedure for the preparation of arylated heteroarenes. Herein, we wish to report on the use of diethylcarbonate and propylene carbonate for palladium-catalysed direct 2-, or 5-arylation of a wide range of heteroaromatic derivatives.

In order to determine the suitability of these solvents for palladium-catalysed direct arylations, a first set of direct arylation reactions of several heteroarenes with 4-bromoacetophenone was carried out under previously reported reaction conditions but using diethylcarbonate as the solvent.^{4b,5f,6e} Employing the 2-n-butylthiophene, 2-n-butylfuran or 2-formyl-*N*-methylpyrrole and 4-bromoacetophenone as coupling partners, at 130 °C during 17 h, the corresponding 5-arylation products were obtained in low yields. On the other hand, at this temperature, the direct arylation of benzoxazole proceeded nicely using only 1 mol% of PdCl(C₃H₅)(dppb) as the catalyst to provide **1** in 85% isolated yield (Scheme 1, Table 1, entries 1 and 2). Interestingly, this latter reaction performed in diethylcarbonate was found to be more selective than in DMF,^{9c} DMAc, NMP or dioxane since using this solvent, fewer traces of unidentified side-products were detected (Table 1, entries 3–6).



Scheme 1 Coupling of benzoxazole with 4-bromoacetophenone.

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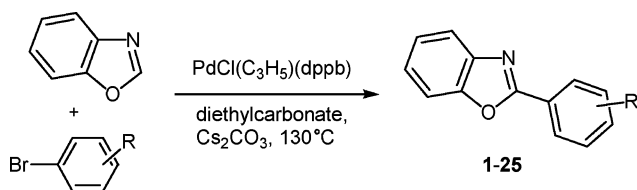
† Electronic supplementary information (ESI) available: NMR data of new compounds. See DOI: 10.1039/c0gc00229a

Table 1 Influence of the reaction conditions for palladium catalysed direct coupling of benzoxazole with 4-bromoacetophenone (Scheme 1)

Entry	Catalyst	Solvent	Conversion (%) ^a
1	Pd(OAc) ₂	diethylcarbonate	11
2	PdCl(C ₃ H ₅)(dppb)	diethylcarbonate	91 (85)
3	PdCl(C ₃ H ₅)(dppb)	DMF	(78) ^b
4	PdCl(C ₃ H ₅)(dppb)	DMAc	31
5	PdCl(C ₃ H ₅)(dppb)	NMP	79 (51)
6	PdCl(C ₃ H ₅)(dppb)	dioxane	88 (73)

^a Conditions: Pd (0.01 eq.), benzoxazole (2 eq.), 4-bromoacetophenone (1 eq.), Cs₂CO₃ (2 eq.), 17 h, 130 °C, conversion of 4-bromoacetophenone, yield in parenthesis is isolated. ^b Pd (0.05 eq.), 100 °C.

Then, we studied the scope and limitations of this procedure, using other aryl bromides (Scheme 2, Tables 2–4). 4-Bromobenzaldehyde, 4-bromopropiophenone or 4-trifluoromethylbromobenzene reacted with benzoxazole gave the expected products **2**, **3** and **5** in 77–92% yields (Table 2, entries 1, 2 and 4). Slower reactions were observed using 4-bromobenzonitrile or methyl 4-bromobenzoate. However, using longer reaction time (72 h), very high conversions of these aryl bromides and high yields of coupling products **4** and **6** were obtained (Table 2, entries 3 and 5). A lower yield of 25% of **7** was obtained using 4-bromonitrobenzene, due to a moderate conversion of this aryl bromide (Table 2, entry 6). This is probably due to a partial poisoning of the palladium catalyst. Using the electron-rich aryl bromides, 4-bromotoluene or 4-bromoanisole, the products **9** and **10** were obtained in 83% and 62% yields, respectively (Table 2, entries 8 and 9). With these two reactants, long reaction times (72 h) had to be employed in order to obtain high conversions. 4-*N,N*-Dimethylaminobromobenzene led to a moderate yield of **11** (Table 2, entry 10). This is certainly due to a slow oxidative addition of this strongly deactivated aryl bromide to palladium. With this catalyst, the oxidative addition of the aryl bromides to palladium appears to be the rate-limiting step of the catalytic cycle. For all these reactions, a very high selectivity in favour of the formation of **2–11** was observed. Moreover, the stability of these products seems to be higher than in DMF, and very limited amount of side-products due to partial degradation was detected.^{9c}

**Scheme 2** Coupling of benzoxazole with aryl bromides.

Then, the reactivity of three *meta*-substituted aryl bromides was examined (Table 3). As expected, similar results than in the presence of *para*-substituted aryl bromides were obtained. 3-Bromobenzaldehyde, 3-bromobenzonitrile or 3,5-bis(trifluoromethyl)bromobenzene gave **12–14** in 85–88% yields (Table 3, entries 1–3).

Ortho-substituents on aryl bromides generally have a more important influence on the yields of palladium-catalysed re-

Table 2 Palladium-catalysed coupling of benzoxazole with *para*-substituted aryl bromides (Scheme 2)

Entry	Aryl bromide	Product	Yield (%) ^a
1			92
2			77
3			87 ^b
4			90 ^c
5			87 ^d
6			25 ^b
7			85 ^c
8			83 ^d
9			62 ^b
10			50 ^d

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), benzoxazole (2 eq.), aryl bromide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 130 °C, 17 h, isolated yields. ^b Reaction time 48 h. ^c Reaction time 24 h. ^d Reaction time 72 h.

actions, due to their steric or coordination properties. *Ortho*-substituted 2-bromobenzaldehyde, 2-bromobenzonitrile, 2-bromobenzotrifluoride or 2-fluorobromobenzene reacted with benzoxazole gave **15–18** in 62–90% yields (Table 2, entries 4–6). Remarkably, the reaction was also successfully realized with the congested and slightly deactivated aryl bromide, 2-bromotoluene to give **19**, albeit in moderate 50% yield (Table 2, entry 8).

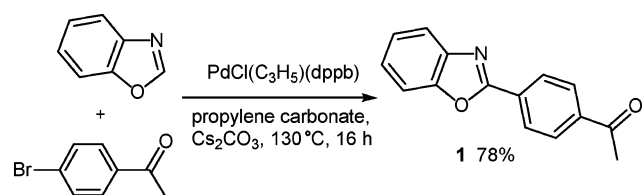
Next, we explored the reactivity of benzoxazole with heteroaryl bromides. The results depicted in Table 4 also revealed clearly the good performance of the novel friendly protocol in direct coupling with benzoxazole. Selective reactions were observed using 2-, 3- or 4-bromopyridines, 3-bromoquinoline, 4-bromoisoquinoline or 5-bromopyrimidine. With these substrates the target products **20–25** were obtained in 64–91% yields. The reaction in the presence of 4-bromoisoquinoline was found to be quite slow. However, a high yield of **24** was obtained after 48 h (Table 4, entry 5).

It should be noted that the direct coupling of benzoxazole with 4-bromoacetophenone using propylene carbonate as the

Table 3 Palladium-catalysed coupling of benzoxazole with *meta*- or *ortho*-substituted aryl bromides (Scheme 2)

Entry	Aryl bromide	Product	Yield (%) ^a
1			85
2			88
3			86
4			62
5			84 ^b
6			90 ^b
7			78 ^b
8			50

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), benzoxazole (2 eq.), aryl bromide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 130 °C, 17 h, isolated yields. ^b Reaction time 48 h.

**Scheme 3** Coupling of benzoxazole with 4-bromoacetophenone using propylene carbonate as the solvent.

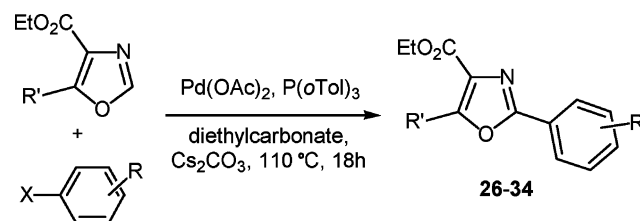
solvent also proceeded nicely, to give **1** in 78% yield (Scheme 3). This solvent is also considered as a “green” alternative to DMF, NMP or DMAc.^{14,15}

As a practical and valuable functionalised oxazole substrate, ethyl oxazole-4-carboxylate was recently successfully evaluated in palladium-catalyzed regioselective 2-(hetero)arylation with a broad variety of iodo, bromo and chloro(hetero)aromatics (Scheme 4).^{9a,9g} Pleasingly, a preliminary assay of direct cou-

Table 4 Palladium-catalysed coupling of benzoxazole with heteroaryl bromides (Scheme 2)

Entry	Heteroaryl bromide	Product	Yield (%) ^a
1			71
2			88
3			64 ^b
4			91
5			80 ^c
6			90 ^c

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), benzoxazole (2 eq.), heteroaryl bromide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 130 °C, 24 h, isolated yields. ^b Cs₂CO₃ 3 eq. ^c Reaction time 48 h.

**Scheme 4** Coupling of ethyl oxazole-4-carboxylate with aryl halides.

pling of ethyl oxazole-4-carboxylate with 4-bromoacetophenone under previously designed conditions Pd(OAc)₂/P(oTol)₃,^{9g} in diethylcarbonate as the solvent, gave the expected 2-arylated oxazole **26** in 56% yield (Table 5, entry 1). It should be noted that the use of PdCl(C₃H₅)(dppb) as the catalyst proved to be less effective, leading to a poor conversion of starting material (<20%) within 48 h. Under the same experimental conditions, the direct arylation of ethyl oxazole-4-carboxylate with several iodo and bromo(hetero)aromatics bearing electron-attractive as well as electron-donating groups were successfully achieved to afford 2-arylated oxazoles **27–30** in good yields (Table 5, entries 2, 4–6). Notably, the novel friendly catalyst system preserve the regiochemical outcome of the direct arylation at the 2-position and proved to be as efficient as the previously designed system.^{9g} Indeed, in the course of this reaction, complete conversion of starting material was observed and the 5-arylated and 2,5-diarylated oxazole-4-carboxylates were isolated in very low yields (<10%). Interestingly, under the same conditions, activated chloro(hetero)aromatics (Table 5, entry 3) appeared to be also useful coupling partners to give selectively the

Table 5 Palladium-catalysed coupling of ethyl oxazole-4-carboxylate derivatives with aryl halides (Scheme 4)

Entry	Aryl bromide	Product	Yield (%) ^a
1			56
2			69 ^b
3			88
4			74 ^b
5			80 ^c
6			80
7			82
8			82 ^d
9			93 ^d
10			72 ^d

^a Conditions: Pd(OAc)₂ (0.05 eq.), P(*o*Tol)₃ (0.1 eq.), ethyl oxazole-4-carboxylate (2 eq.), aryl halide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 110 °C, 18 h, isolated yields. ^b 5-Arylation and 2,5-diarylation products were also isolated (<10%). ^c 2,5-Diarylation product was also isolated (<10%). ^d Oxazole derivative: 1 eq.

2-(hetero)arylated oxazole-4-carboxylates **27** and **31** in good yields.


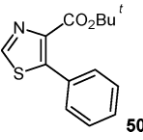

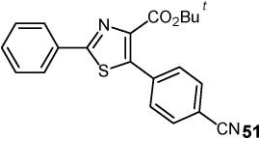

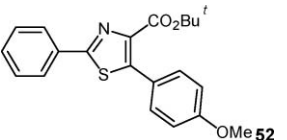
Moreover, the 5-arylated and heteroarylated oxazoles^{9g} showed also a good reactivity in the same experimental conditions providing the 2,5-di(hetero)aryled oxazole-4-carboxylates **32–34** (Table 5, entries 8–10).

Then, we examined the reactivity of thiazole derivatives for the direct arylation in diethylcarbonate (Table 6). Using the quite similar reaction conditions PdCl(C₃H₅)(dppb), 130 °C and KOAc instead of Cs₂CO₃, 2-*n*-propylthiazole was successfully regioselectively arylated on carbon 5. The reaction was found to be

Table 6 Palladium-catalysed coupling of thiazole derivatives with aryl halides

Entry	Aryl bromide	Product	Yield (%) ^a
1			82
2			74 ^b
3			83
4			76
5			78
6			84
7			85
8			86 ^c
9			80
10			87 ^d
11			78 ^b
12			80
13			81
14			73
15			76 ^c

Table 6 (Contd.)

Entry	Aryl bromide	Product	Yield (%) ^a
16			53 ^{e,f}
17			70 ^g
18			83 ^g

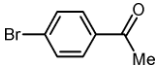
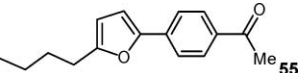
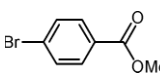
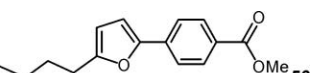
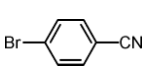
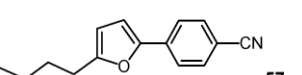
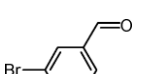
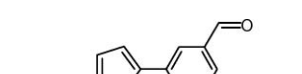
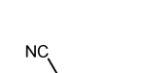
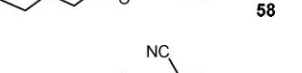
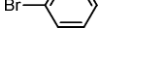
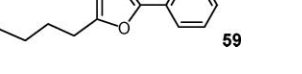
^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), thiazole derivative (2 eq.), aryl halide (1 eq.), KOAc (2 eq.), diethylcarbonate, 130 °C, 24 h, isolated yields. ^b 24 h. ^c 67 h. ^d 140 °C. ^e Pd(OAc)₂ (0.05 eq.), P(*o*Tol)₃ (0.1 eq.), Cs₂CO₃ (2 eq.), 110 °C, 18 h. ^f 2,5-Diphenylthiazole was isolated in 23% yield. ^g Pd(OAc)₂ (0.05 eq.), P(*o*Tol)₃ (0.1 eq.), iodobenzene (2 eq.), thiazole derivative (1 eq.), Cs₂CO₃ (2 eq.), 130 °C, 18 h.

slower than in DMAc,^{8d} however, very high yields of compound **35–42** were obtained (Table 6, entries 1–8). As expected, the use of 2-ethyl-4-methylthiazole also allowed the synthesis of the 5-arylated thiazoles **43–45** in high yields (Table 6, entries 9–11). We also studied this reaction using 4-methylthiazole (Table 6, entries 12–15). With this substrate, we could have observed the formation of the 2- or 5-arylation products. However, in all cases, only the 5-arylation products **46–49** were isolated.

The structurally-related thiazole-4-carboxylate series was recently successfully evaluated in palladium-catalyzed direct (hetero)arylation with halo(hetero)aromatics.^{8c} Starting with *tert*-butylthiazole-4-carboxylate, both P(*o*-tol)₃ and Cy-JohnPhos ligands in DMF were selected for the coupling of iodoaromatics and bromo- and chloroaromatics, respectively, in DMF as solvent, whilst the use of toluene under the same conditions led to a better selectivity for the 5-position, albeit in more modest yields.^{8c} Thus, the preliminary assay of direct coupling of *tert*-butylthiazole-4-carboxylate with iodobenzene under previously designed conditions Pd(OAc)₂/P(*o*Tol)₃ in diethylcarbonate as the solvent was consistent with our previous observations in toluene. Indeed, the 5-phenylthiazole-4-carboxylate **50** was isolated as the major product in 53% yield (Table 6, entry 16). Nevertheless, under the same conditions but by allowing the temperature to 130 °C, the 5-arylated thiazole-4-carboxylate were also successful phenylated providing the 2,5-diarylated thiazole-4-carboxylates **51** and **52** in good yields independently to the electronic effect on the aromatic (Table 6, entries 17 and 18).

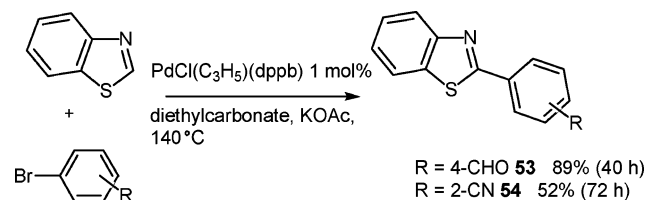
Benzothiazole was found to be less reactive than benzoxazole. However, when we employed a more elevated temperature (140 °C instead of 130 °C), for the coupling with 4-bromobenzaldehyde, a high yield of 89% of the 2-arylated

Table 7 Palladium-catalysed coupling of 2-n-butylfuran with aryl bromides

Entry	Aryl bromide	Product	Yield (%) ^a
1			70 ^b
2			56
3			61 ^c
4			62 ^b
5			84 ^c
6			85

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), furan derivative (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethylcarbonate, 140 °C, 23 h, isolated yields. ^b 72 h. ^c 43 h.

product **48** was obtained (Scheme 5). Using these reaction conditions, the coupling with 2-bromobenzonitrile gave **49** in 52% yield.

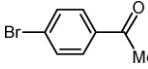
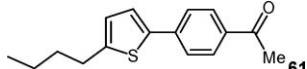
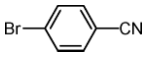
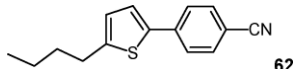
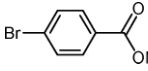
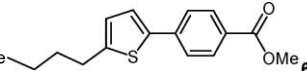
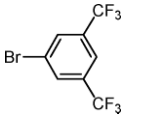
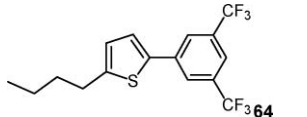
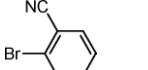
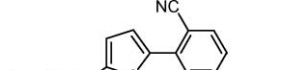
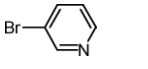
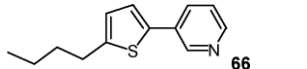


Scheme 5 Coupling of benzothiazole with 4-bromobenzaldehyde.

The direct use of furan derivatives is an important field for research in green chemistry, since some of them can be obtained from agricultural wastes rich in pentosan polymers. Our first attempts to arylate 2-n-butylfuran with 4-bromoacetophenone using 130 °C as the reaction temperature gave very low yields of **55**. On the other hand, we observed that using a more elevated reaction temperature of 140 °C, a moderate yield of **55** could be obtained after 23 h. As the catalyst appears to be quite stable in this solvent, the use of longer reaction times (43 or 72 h) allowed to obtain the 5-arylated furans in good yields (Table 7). For example, after 43 or 72 h, the reaction of 2-n-butylfuran with 2-bromobenzonitrile or 4-bromoacetophenone gave **59** and **55** in 84% and 70% yields, respectively. In all cases, the reaction was very regioselective in favour of the 5-arylation.

The reactivity of 2-n-butylthiophene was found to be similar to 2-n-butylfuran (Table 8). When we employed 140 °C as the

Table 8 Palladium-catalysed coupling of 2-n-butylthiophene with aryl bromides

Entry	Aryl bromide	Product	Yield (%) ^a
1			63
2			78
3			46
4			53
5			81 ^b
6			71

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), thiophene derivative (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethylcarbonate, 140 °C, 72 h, isolated yields. ^b 17 h.

reaction temperature, a variety of aryl bromides was coupled to give **61–66** in moderate to good yields. Again, the arylation was highly regioselective in favour of the 5-arylation. The moderate yields obtained in the presence of methyl 4-bromobenzoate or 3,5-bis(trifluoromethyl)bromobenzene are due to partial conversions of these aryl bromides.

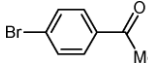
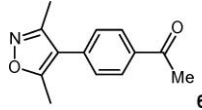
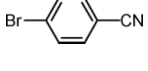
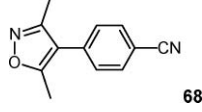
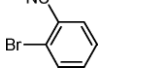
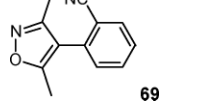
Then, three arylated isoxazoles have been prepared *via* the direct 4-arylation of 3,5-dimethylisoxazole (Table 9).¹⁰ The yields strongly depend on the nature of the aryl bromides. A good yield of 71% of **67** was obtained in the presence of 4-bromobenzoyl bromide; whereas, the use of 2-bromobenzonitrile gave **69** in only 23% yield.

1-Methyl-2-formylpyrrole has a poor reactivity for direct arylation in diethylcarbonate (Table 10). Much slower reactions than in DMAc were observed,^{6e} and low to moderate yields were obtained. For example the coupling of 4-bromobenzonitrile with this reactant gave the 5-arylated pyrrole **71** in only 33% yield.

We have already reported the direct 5-arylation of a range of imidazole derivatives in DMAc.^{7f} Again, the arylations were found to be slower in diethylcarbonate than in DMAc, however, the reactions were very clean using a range of aryl bromides (Table 11). High conversions of 4-bromoacetophenone, 4-bromobenzonitrile or 3-bromopyridine were observed, and **73**, **74** and **76** were obtained in high yields. On the other hand, only a partial conversion of 4-trifluoromethylbromobenzene was observed leading to a moderate yield of **75**.

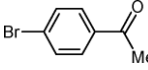
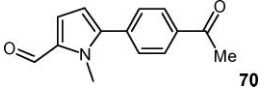
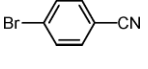
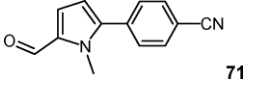
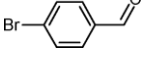
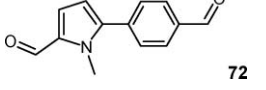
In conclusion, these results demonstrate that carbonates, which are considered to be “green solvents”, can be advantageously employed as an alternative to the solvents usually used

Table 9 Palladium-catalysed coupling of 2,4-dimethylisoxazole with aryl bromides

Entry	Aryl bromide	Product	Yield (%) ^a
1			71
2			47
3			23

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), 2,4-dimethylisoxazole (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethylcarbonate, 140 °C, 72 h, isolated yields.

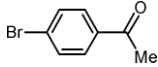
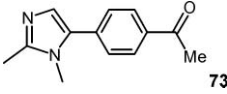
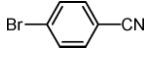
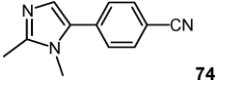
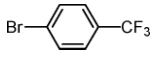
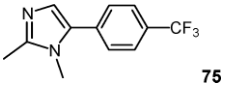
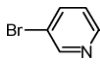
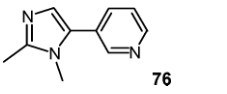
Table 10 Palladium-catalysed coupling of 1-methyl-2-formylpyrrole with aryl bromides

Entry	Aryl bromide	Product	Yield (%) ^a
1			61 ^b
2			33
3			35

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), 1-methyl-2-formylpyrrole (2 eq.), aryl bromide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 140 °C, 72 h, isolated yields. ^b 42 h.

for the direct arylation of several heteroaromatic derivatives. In the presence of diethylcarbonate or propylene carbonate and 1 mol% PdCl(C₃H₅)(dppb) as the catalyst precursor at 130 °C, the direct 2-arylation of benzoxazole, ethyl oxazole-4-carboxylate or the 5-arylation of thiazoles using aryl bromides as coupling partners proceeds in moderate to high yields. The direct arylation of furan, thiophene, pyrrole, imidazole or isoxazole derivatives was found to require a more elevated reaction temperature (140 °C) to give high yields of coupling products. It should be noted that a wide range of functions such as acetyl, propionyl, formyl, ester, nitrile, trifluoromethyl, fluoro or methoxy on the aryl halide is tolerated. The major by-product of these couplings is CsX or KX/AcOH instead of metallic salts with more classical coupling procedures. For these reasons, this novel process should give an economically viable and environmentally attractive access to arylated heteroaromatics.

Table 11 Palladium-catalysed coupling of 1,2-dimethylimidazole with aryl bromides

Entry	Aryl bromide	Product	Yield (%) ^a
1			85 ^b
2			81
3			48
4			65

^a Conditions: PdCl(C₃H₅)(dppb) (0.01 eq.), 1,2-dimethylimidazole (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethylcarbonate, 140 °C, 72 h, isolated yields. ^b 48 h.

Experimental

Diethylcarbonate was purchased from Acros Organics and was not purified before use. Heteroarenes, propylene carbonate, KOAc and Cs₂CO₃ were purchased from Alfa Aesar and were not purified before use. Ethyl oxazole-4-carboxylate was prepared from ethyl isocyanoacetate according to Schöllkopf procedure.¹⁸

Preparation of the PdCl(C₃H₅)(dppb) catalyst:¹⁹

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with [Pd(C₃H₅)Cl]₂ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ³¹P NMR (81 MHz, CDCl₃) δ = 19.3 (s).

Typical experiment for coupling reactions

The reaction of the aryl halide (1 mmol), heteroaromatic (2 mmol) and Cs₂CO₃ (0.651 g, 2 mmol) or KOAc (0.196, 2 mmol) (see Tables) at 130–140 °C (see Tables and Schemes) in diethylcarbonate (5 mL) in the presence of PdCl(C₃H₅)(dppb) (6.1 mg, 0.01 mmol) or Pd(OAc)₂ (0.05 eq.)/P(*o*Tol)₃ (0.1 eq.), (see Tables and Schemes) under argon affords the corresponding product after evaporation and filtration on silica gel (pentane/ether).

2-(4-Acetylphenyl)-benzoxazole (1)^{9c}

4-Bromoacetophenone (0.199 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **1** in 85% (0.202 g) yield.

2-(4-Formylphenyl)-benzoxazole (2)²⁰

4-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **2** in 92% (0.205 g) yield.

2-(4-Propionylphenyl)-benzoxazole (3)^{9c}

4-Bromopropiophenone (0.213 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **3** in 77% (0.193 g) yield.

Methyl 4-benzoxazol-2-yl-benzoate (4)^{9c}

Methyl 4-bromobenzoate (0.215 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **4** in 87% (0.220 g) yield.

2-(4-Trifluoromethylphenyl)-benzoxazole (5)^{9c}

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **5** in 90% (0.237 g) yield.

4-Benzoxazol-2-yl-benzonitrile (6)^{9c}

4-Bromobenzonitrile (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **6** in 87% (0.192 g) yield.

2-(4-Nitrophenyl)-benzoxazole (7)^{9c}

4-Bromonitrobenzene (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **7** in 25% (0.060 g) yield.

2-(4-Fluorophenyl)-benzoxazole (8)^{9c}

4-Bromofluorobenzene (0.175 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **8** in 85% (0.181 g) yield.

2-(4-Methylphenyl)-benzoxazole (9)^{9c}

4-Bromotoluene (0.171 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **9** in 83% (0.174 g) yield.

2-(4-Methoxyphenyl)-benzoxazole (10)^{9c}

4-Bromoanisole (0.187 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **10** in 62% (0.140 g) yield.

2-(4-Dimethylaminophenyl)-benzoxazole (11)^{9c}

(4-Bromophenyl)-dimethylamine (0.200 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **11** in 50% (0.119 g) yield.

2-(3-Formylphenyl)-benzoxazole (12)

3-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **12** in 85% (0.190 g) yield.

3-Benzoxazol-2-yl-benzonitrile (13)^{9c}

3-Bromobenzonitrile (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **13** in 88% (0.194 g) yield.

2-(3,5-Bistrifluoromethylphenyl)-benzoxazole (14)^{9c}

3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **14** in 86% (0.285 g) yield.

2-(2-Formylphenyl)-benzoxazole (15)

2-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **15** in 62% (0.138 g) yield.

2-Benzoxazol-2-yl-benzonitrile (16)^{9c}

2-Bromobenzonitrile (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **16** in 84% (0.185 g) yield.

2-(2-Trifluoromethylphenyl)-benzoxazole (17)

2-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **17** in 90% (0.237 g) yield.

2-(2-Fluorophenyl)-benzoxazole (18)^{9c}

2-Bromofluorobenzene (0.175 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **18** in 78% (0.166 g) yield.

2-(2-Methylphenyl)-benzoxazole (19)^{9c}

2-Bromotoluene (0.171 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **19** in 50% (0.105 g) yield.

2-Pyridin-2-yl-benzoxazole (20)^{9h}

2-Bromopyridine (0.158 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **20** in 71% (0.139 g) yield.

2-Pyridin-3-yl-benzoxazole (21)^{9c}

3-Bromopyridine (0.158 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **21** in 88% (0.173 g) yield.

2-Pyridin-4-yl-benzoxazole (22)^{9c}

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **22** in 64% (0.126 g) yield.

3-Benzoxazol-2-ylquinoline (23)^{9c}

3-Bromoquinoline (0.208 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **23** in 91% (0.224 g) yield.

4-Benzoxazol-2-ylisoquinoline (24)

4-Bromoisoquinoline (0.208 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **24** in 80% (0.197 g) yield.

2-Pyrimidin-5-ylbenzoxazole (25)^{9c}

5-Bromopyrimidine (0.159 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords **25** in 90% (0.177 g) yield.

Ethyl 2-(4-acetylphenyl)-oxazole-4-carboxylate (26)

4-Bromoacetophenone (0.199 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **26** in 56% (0.145 g) yield.

Ethyl 2-(4-cyanophenyl)-oxazole-4-carboxylate (27)^{9g}

4-Iodobenzonitrile (0.229 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **27** in 69% (0.167 g) yield.

Ethyl 2-phenyloxazole-4-carboxylate (28)^{9g}

Iodobenzene (0.204 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **28** in 74% (0.161 g) yield.

Ethyl 2-(4-Methoxyphenyl)-oxazole-4-carboxylate (29)^{9g}

Iodoanisole (0.234 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **29** in 80% (0.198 g) yield.

Ethyl 2-quinolin-3-ylloxazole-4-carboxylate (30)^{9g}

3-Bromoquinoline (0.208 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **30** in 80% (0.214 g) yield.

Ethyl 2-pyridin-2-yl-oxazole-4-carboxylate (31)^{9g}

2-Chloropyridine (0.113 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords **31** in 82% (0.179 g) yield.

5-(4-Cyanophenyl)-2-(4-methoxyphenyl)-oxazole-4-carboxylic acid ethyl ester (32)

4-Bromoanisole (0.065 g, 0.35 mmol) and ethyl 5-(4-cyanophenyl)oxazole-4-carboxylate^{9g} (0.085 g, 0.35 mmol) affords **32** in 82% (0.100 g) yield.

2-(4-Cyano-phenyl)-5-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester (33)

4-Iodobenzonitrile (0.080 g, 0.35 mmol) and ethyl 5-(4-methoxyphenyl)oxazole-4-carboxylate^{9g} (0.086 g, 0.35 mmol) affords **33** in 93% (0.113 g) yield.

2-(4-Methoxyphenyl)-5-pyridin-4-yl-oxazole-4-carboxylic acid ethyl ester (34)

4-Bromoanisole (0.065 g, 0.35 mmol) and ethyl 5-(pyridin-4-yl)oxazole-4-carboxylate^{9g} (0.076 g, 0.35 mmol) affords **34** in 72% (0.082 g) yield.

4-(2-Propylthiazol-5-yl)acetophenone (35)^{8a}

4-Bromoacetophenone (0.199 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **35** in 82% (0.201 g) yield.

5-(4-(Trifluoromethyl)phenyl)-2-propylthiazole (36)^{8a}

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **36** in 74% (0.201 g) yield.

3-(2-Propylthiazol-5-yl)benzaldehyde (37)^{8d}

3-Bromobenzaldehyde (0.184 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **37** in 83% (0.192 g) yield.

2-(2-Propylthiazol-5-yl)benzonitrile (38)^{8a}

2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **38** in 76% (0.173 g) yield.

5-Naphthalen-2-yl-2-propylthiazole (39)²¹

2-Bromonaphthalene (0.207 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **39** in 78% (0.197 g) yield.

3-(2-Propylthiazol-5-yl)pyridine (40)^{8d}

3-Bromopyridine (0.158 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **40** in 84% (0.171 g) yield.

4-(2-Propylthiazol-5-yl)pyridine (41)⁹ⁱ

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **41** in 85% (0.174 g) yield.

2-(2-Propylthiazol-5-yl)quinoline (42)^{8d}

3-Bromoquinoline (0.208 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords **42** in 86% (0.219 g) yield.

4-(2-Ethyl-4-methylthiazol-5-yl)benzaldehyde (43)^{8a}

4-Bromobenzaldehyde (0.184 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords **43** in 80% (0.185 g) yield.

2-(2-Ethyl-4-methylthiazol-5-yl)benzotrile (44)^{8d}

2-Bromobenzotrile (0.182 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords **44** in 87% (0.199 g) yield.

4-(2-Ethyl-4-methylthiazol-5-yl)-pyridine (45)^{8d}

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords **45** in 78% (0.159 g) yield.

4-(4-Methylthiazol-5-yl)-acetophenone (46)^{8d}

4-Bromoacetophenone (0.199 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords **46** in 80% (0.174 g) yield.

4-(4-Methylthiazol-5-yl)-benzotrile (47)^{8d}

4-Bromobenzotrile (0.182 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords **47** in 81% (0.162 g) yield.

3-(4-Methylthiazol-5-yl)-acetophenone (48)

3-Bromoacetophenone (0.199 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords **48** in 73% (0.159 g) yield.

3-(4-Methylthiazol-5-yl)-quinoline (49)

3-Bromoquinoline (0.208 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords **49** in 76% (0.172 g) yield.

***tert*-Butyl 5-phenylthiazole-4-carboxylate (50)**

Iodobenzene (0.055 g, 0.35 mmol) and *tert*-butylthiazole-4-carboxylate^{8c} (0.027 g, 0.35 mmol) affords **50** in 53% (0.037 g) yield.

***tert*-Butyl 5-(4-cyanophenyl)-2-phenyl-thiazole-4-carboxylate (51)**

Iodobenzene (0.110 g, 0.70 mmol) and *tert*-butyl 5-(4-cyanophenyl)thiazole-4-carboxylate²² (0.077 g, 0.35 mmol) affords **51** in 70% (0.068 g) yield.

***tert*-Butyl 5-(4-methoxyphenyl)-2-phenyl-thiazole-4-carboxylate (52)**

Iodobenzene (0.110 g, 0.70 mmol) and *tert*-butyl 5-(4-methoxyphenyl)thiazole-4-carboxylate²² (0.079 g, 0.35 mmol) affords **52** in 83% (0.082 g) yield.

4-Benzothiazol-2-yl-benzaldehyde (53)²³

4-Bromobenzaldehyde (0.184 g, 1 mmol) and benzothiazole (0.270 g, 2 mmol) affords **53** in 89% (0.213 g) yield.

2-Benzothiazol-2-yl-benzotrile (54)²⁴

2-Bromobenzotrile (0.182 g, 1 mmol) and benzothiazole (0.270 g, 2 mmol) affords **54** in 52% (0.123 g) yield.

2-*n*-Butyl-5-(4-acetylphenyl)furan (55)^{5f}

4-Bromoacetophenone (0.199 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **55** in 70% (0.170 g) yield.

Methyl 4-(5-*n*-butyl-furan-2-yl)-benzoate (56)^{5b}

Methyl 4-bromobenzoate (0.215 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **56** in 56% (0.145 g) yield.

2-*n*-Butyl-5-(4-cyanophenyl)furan (57)^{5b}

4-Bromobenzotrile (0.182 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **57** in 61% (0.137 g) yield.

2-*n*-Butyl-5-(3-formylphenyl)furan (58)^{5b}

3-Bromobenzaldehyde (0.184 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **58** in 62% (0.141 g) yield.

2-(5-*n*-Butylfuran-2-yl)benzotrile (59)^{5f}

2-Bromobenzotrile (0.182 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **59** in 84% (0.189 g) yield.

2-*n*-Butyl-5-(3-quinolyl)furan (60)^{5b}

3-Bromoquinoline (0.208 g, 1 mmol) and 2-*n*-butylfuran (0.248 g, 2 mmol) affords **60** in 85% (0.213 g) yield.

4-(5-*n*-Butylthiophen-2-yl)acetophenone (61)^{4c}

4-Bromoacetophenone (0.199 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **61** in 63% (0.163 g) yield.

4-(5-*n*-Butylthiophen-2-yl)benzotrile (62)^{4c}

4-Bromobenzotrile (0.182 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **62** in 78% (0.188 g) yield.

Methyl 4-(5-*n*-butylthiophen-2-yl)-benzoate (63)^{4c}

Methyl 4-bromobenzoate (0.215 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **63** in 46% (0.126 g) yield.

2-3,5-Bis(trifluoromethyl)phenyl-5-*n*-butylthiophene (64)^{4h}

3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **64** in 53% (0.187 g) yield.

2-(5-Butylthiophene-2-yl)benzotrile (65)^{4h}

2-Bromobenzotrile (0.182 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **65** in 81% (0.195 g) yield.

3-(5-*n*-Butylthiophen-2-yl)pyridine (66)^{4c}

3-Bromopyridine (0.158 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **66** in 71% (0.154 g) yield.

4-(3,5-Dimethylisoxazol-4-yl)-acetophenone (67)¹⁰

4-Bromoacetophenone (0.199 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) affords **67** in 71% (0.153 g) yield.

4-(3,5-Dimethylisoxazol-4-yl)-benzotrile (68)²⁵

4-Bromobenzotrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) affords **68** in 47% (0.093 g) yield.

2-(3,5-Dimethylisoxazol-4-yl)-benzotrile (69)¹⁰

2-Bromobenzotrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazole (0.192 g, 2 mmol) affords **69** in 23% (0.046 g) yield.

5-(4-Acetylphenyl)-1-methyl-2-formylpyrrole (70)^{6c}

4-Bromoacetophenone (0.199 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords **70** in 61% (0.139 g) yield.

4-(5-Formyl-1-methylpyrrol-2-yl)-benzotrile (71)^{6c}

4-Bromobenzotrile (0.182 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords **71** in 33% (0.069 g) yield.

5-(4-Formylphenyl)-1-methyl-2-formylpyrrole (72)^{6c}

4-Bromobenzaldehyde (0.184 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords **72** in 35% (0.075 g) yield.

5-(4-Acetylphenyl)-1,2-dimethylimidazole (73)^{7f}

4-Bromoacetophenone (0.199 g, 1 mmol) and 1,2-dimethylimidazole (0.192 g, 2 mmol) affords **73** in 85% (0.182 g) yield.

4-(2,3-Dimethylimidazol-4-yl)-benzotrile (74)^{7f}

4-Bromobenzotrile (0.182 g, 1 mmol) and 1,2-dimethylimidazole (0.192 g, 2 mmol) affords **74** in 81% (0.160 g) yield.

5-(4-Trifluoromethylphenyl)-1,2-dimethylimidazole (75)^{7f}

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and 1,2-dimethylimidazole (0.192 g, 2 mmol) affords **75** in 48% (0.115 g) yield.

5-(3-Pyridyl)-1,2-dimethylimidazole (76)^{7f}

3-Bromopyridine (0.158 g, 1 mmol) and 1,2-dimethylimidazole (0.192 g, 2 mmol) affords **76** in 65% (0.112 g) yield.

Acknowledgements

J. R. is grateful to “Ministère de la Recherche” for a grant. We thank the CNRS and “Rennes Metropole” for providing financial support and C. Fischmeister for helpful discussions.

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