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Direct Arylation of Heteroaromatic Compounds with Congested, Functionalised Aryl Bromides at Low Palladium/Triphosphane Catalyst Loading

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Abstract: A new ferrocenyl triphosphane ligand associated to palladium was found to be an efficient catalyst for the direct coupling of highly congested, functionalised aryl bromides with a variety of heteroarenes. These coupling reactions can generally be performed by using a low-loading (0.1–0.5 mol%) of the catalyst. The present protocol tolerates important and useful functional groups, which allows for further elaboration into more sophisticated heterocyclic molecules. The straightforward arylation of heteroaromatic compounds with congested *ortho*-substituted aryl bromides may permit further convergent syntheses of diverse ligands, biologically active molecules and molecular materials in only a few steps.

Keywords: aryl bromides · C–H activation · ferrocenyl polyphosphane · heterocycles · palladium

Introduction

Palladium-catalysed cross-coupling reactions between nucleophilic organometallic reagents and electrophilic organic halides or pseudo-halides (for example, Stille, Suzuki or Negishi reactions) have emerged as powerful synthetic tools for the construction of carbon–carbon bonds.[1,2] Such catalytic coupling processes are applied to a wide array of endeavours, which range from biological sciences to materials chemistry. Their applications to heteroaromatic substrates provide convergent synthetic routes to substituted heterocyclic structures. One of the major drawbacks of this methodology is the preparation of the organometallic reagents. Recently, to avoid the use of such reagents, research has shifted to the direct arylation of heteroaromatic substrates by C–H bond activation.[3–6] These couplings also avoid stoichiometric formation of metallic byproducts, from which undesired contamination could be potentially appalling for pharmaceutical, agrochemical and related biological applications.

Until now, reports on palladium-catalysed direct arylations of heteroaromatic compounds describe the use of several *para*- or *meta*-substituted aryl halides. The use of *ortho*-substituted aryl halides for such reactions would be very useful for the preparation of bioactive compounds, molecular materials or innovative ligands. Such sterically demanding aryl halides have already been successfully employed by the groups of Buchwald and Ackermann for the preparation of hindered biaryls by Suzuki cross-coupling reactions.[7] Conversely, for palladium-catalysed direct arylation reactions with *ortho*-substituted aryl bromides, the functional group tolerance needs to be extended. Moreover, better yields need to be obtained for several substrates,[8–12] and di-*ortho*-substituted aryl halides remain uncommon coupling partners.[13–15] For furans or thiophenes a few examples of couplings with di-*ortho*-substituted aryl bromides have been described with a tetraphosphine[16] ligand.[13,14a] 2,6-Difluorobromobenzene has also been employed as a coupling partner.[14c,17a] The coupling of a thiophene derivative with 9-bromoanthracene, to give the 2-arylated thiophene in 40% yield, has also been described.[14b] To the best of our knowledge, the direct arylation of pyrroles with di-*ortho*-substituted aryl halides has never been reported.

Despite these relevant advances, efficient catalytic systems for the coupling of a wide range of diversely *ortho*- and, especially, di-*ortho*-substituted aryl halides to different classes of heteroaromatic compounds have not been reported to date. Herein, we disclose the use of a novel, air-stable palladium/ferrocenyl triphosphane system for the direct arylation of heteroaromatic compounds by *ortho*-substituted aryl bromides, efficient at remarkably low catalyst loadings, even for highly congested substrates.

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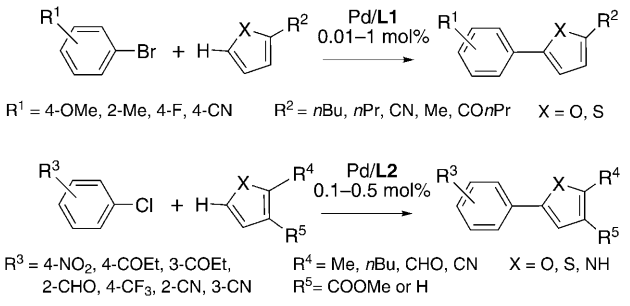
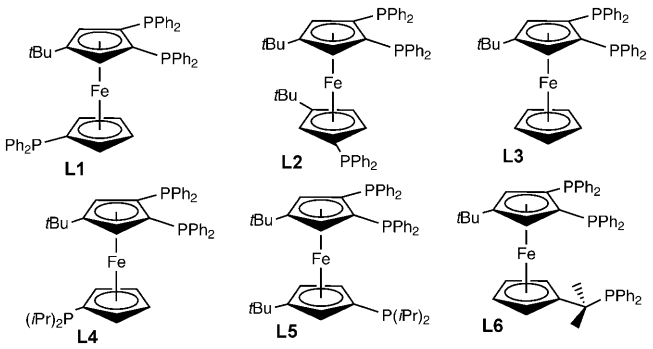
Results and Discussion

Recently, we probed various ferrocenyl polyphosphane ligands[18] for use in direct arylations of heteroaromatic compounds with unactivated and/or functionalised (R^1 = 4-CN is electron-withdrawing group) aryl bromides.[19] We discovered superior efficiency of ferrocenyl triphosphane ligands relative to related mono-, di- and tetraphosphanes. We then focused our efforts to provide an efficient palladium-catalysed methodology for the challenging intermolecular arylation of functionalised aryl chlorides by using systems that incorporated modified ferrocenyl triphosphanes (Scheme 1).[20]



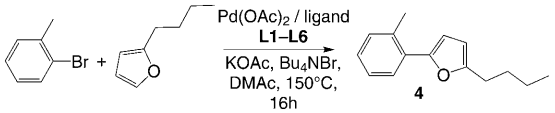
Scheme 1. Palladium-catalysed arylation of unactivated R^1 = 4-CN is electron withdrawing aryl bromides and functionalised aryl chlorides with heteroaromatic compounds at low catalyst loadings (**L1** and **L2** are depicted in Scheme 2).

A further screening of the scope of the palladium catalytic systems with associated ligands **L1** and **L2** (Scheme 2) used in these promising C–H direct activation/functionalisation reactions revealed that these auxiliaries were moderately efficient in the coupling of hindered aryl bromides, such as 2-bromotoluene (Table 1, entries 1 and 2). We had also observed that the coupling of selected heteroaromatic compounds with some *ortho*-substituted electron-deficient aryl bromides proceeds very efficiently when $Pd(OAc)_2$ was used as a catalyst in the absence of any ligand **L** (Table 2, entries 5 and 8, arylation of 2-*n*-butyl furane and 2-*n*-butylthiophene).[17] The ligand-free coupling of 2-*n*-propylthiazole with 2-bromotoluene and 2-bromoanthracene also proceeds



Scheme 2. Polyphosphane ligands for C–H activation/functionalisation of heteroarenes with sterically demanding *ortho*-substituted aryl bromides.

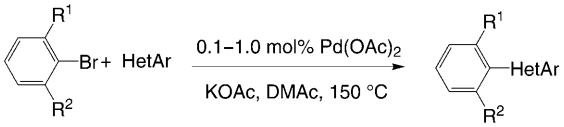
Table 1. Ligand screening for the direct arylation of 2-*n*-butylfuran with 2-bromotoluene catalysed by palladium/ferrocenyl di- or triphosphanes.[a]

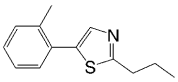
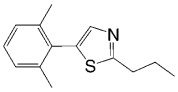
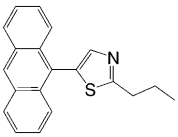
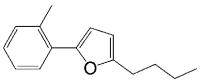
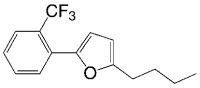
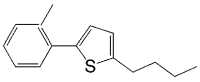
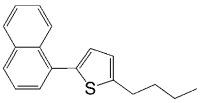
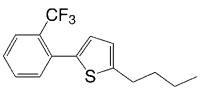
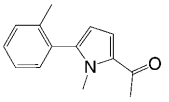


Entry	Catalytic system	Conversion of 2-bromotoluene [%]	Yield [%]
1	$Pd(OAc)_2$/**L1**	56	53
2	$Pd(OAc)_2$/**L2**	59	55
3	$Pd(OAc)_2$/**L3**	71	67
4	$Pd(OAc)_2$/**L4**	49	46
5	$Pd(OAc)_2$/**L5**	84	80
6	$Pd(OAc)_2$/**L6**	82	78
7	$Pd(OAc)_2$/**L5**[b]	75	71

[a] $Pd(OAc)_2$ (0.005 mmol), **L** (0.005 mmol), 2-bromotoluene (1 mmol), 2-*n*-butylfuran (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), *N*,*N*-dimethylacetamide (DMAc), 150 °C, 16 h, under argon. [b] Without Bu_4NBr.

Table 2. Direct arylation of heteroaromatic compounds with *ortho*-substituted aryl bromides with a phosphine-free catalyst.[a]

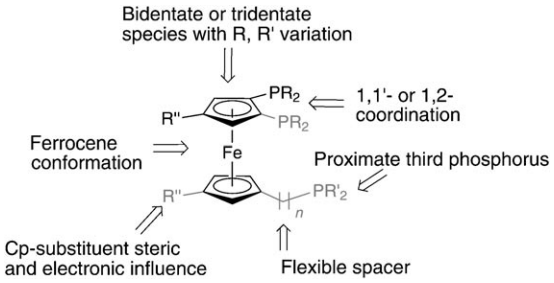


Entry	Product		Cat. [mol%]	Yield [%]
1		**1**	0.1	82
2		**2**	1	0
3		**3**	0.4	75
4		**4**	1	0
5		**5**	0.1	90
6		**6**	1	42
7		**7**	0.1	87
8		**8**	0.1	92
9		**9**	0.5	37

[a] $Pd(OAc)_2$ (cat.), aryl bromide (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), DMAc, 150 °C, under argon; yields are of isolated products.

satisfactorily (Table 2, entries 1 and 3). On the other hand, the reaction of 2-bromotoluene with 2-*n*-butylthiophene or 1-methyl-2-acetylpyrrole in the presence of a phosphine-free $Pd(OAc)_2$ catalyst gave the coupling products **6** and **9** in only 37 and 42% yield, respectively (Table 2, entries 6 and 9). Finally, the couplings of 2-*n*-butylfuran to 2-bromotoluene, and 2-*n*-propylthiazole to 2,6-dimethylbromobenzene were totally inefficient under ligand-free conditions, even at higher catalyst loadings (Table 2, entries 2 and 4).

Thus, we re-examined the modular features of our ligands to design a system able to couple a wider array of heteroaromatic compounds with hindered aryl bromides and to overcome the limitations encountered in the ligand-free palladium-catalysed direct arylation of aryl bromides. The various tuneable features involved in our ligand design are summarised in Scheme 3.



Scheme 3. Tuneable features in the design of ferrocenyl polyphosphane ligands.

Following these trends, several new ligands were synthesised (Scheme 2). Ferrocenyl phosphanes **L1**–**L6** were tested and compared under identical reaction conditions (Table 1) in the arylation of 2-*n*-butylfuran with 2-bromotoluene (an inefficient coupling in the absence of **L**; Table 2, entry 4). As expected, the ferrocenyl phosphanes **L** were generally found to be useful auxiliaries for this palladium-catalysed C–H activation (Table 1). However, the best yield at a low catalyst loading (5×10^{-3} mmol)[18f] was obtained by using **L5** in combination with a Bu_4NBr additive. In the absence of this additive the coupling proceeds but a slightly lower yield was obtained (Table 1, entries 5 versus 7). Ligand **L6** also produced fairly satisfactory results but was more difficult to synthesise and complementary screening studies demonstrated a slightly narrower scope relative to **L5**.

The X-ray diffraction structure of **L5** was determined (Figure 1) to clarify the specific features of this triphosphane relative to the other ligands tested and, in particular, with respect to the previously reported ligands **L1** and **L2**. Ligand **L4** was also of comparative interest because it is the analogue of **L1** bearing a -P(*i*Pr)$_2$ group instead of a PPh_2 group.[15b,19,21] The most striking feature of **L5** compared to the other ligands depicted in Scheme 2 is the net eclipsed position of P2 and P3, possibly due to the lower steric hindrance of the isopropyl groups. Therefore, upon chelation of palladium with P1 and P2, the influence of P3 on the area of

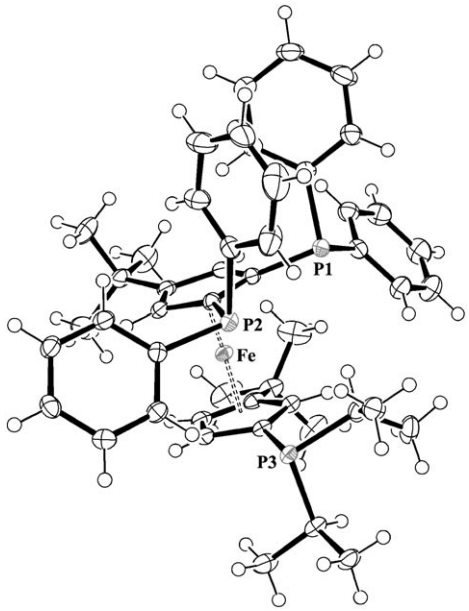
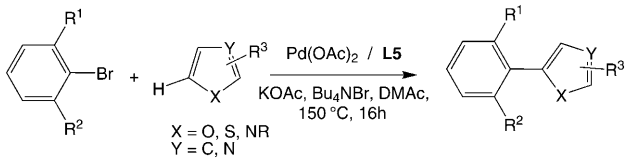


Figure 1. ORTEP representation of the molecular structure of **L5**. Due to the steric influences of the *t*Bu and *i*Pr groups the three phosphorus atoms are pointing in the same direction, contrary to the structures reported previously for related ligands **L2**[15b] and **L4**[21a].

palladium reactivity should be significant enough to promote cross-coupling of congested aryl bromides.

With a suitable palladium-based system indentified for direct heteroarylation of *ortho*-hindered aryl bromides at low catalyst loading, a performance survey of **L5** in the reactions with *ortho*- or di-*ortho*-substituted aryl bromides was conducted (Scheme 4 and Tables 3–10).

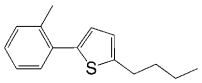
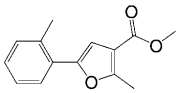
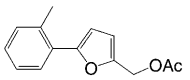
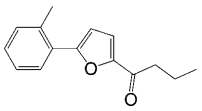
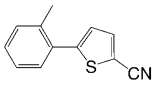
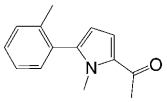


Scheme 4. Palladium-catalysed coupling of *ortho*- and di-*ortho*-substituted aryl bromides with heteroaromatic compounds.

With the $Pd(OAc)_2$/**L5** catalytic system, the coupling of a wide range of heteroarenes with 2-bromotoluene proceeds in the presence of only 0.5 mol% catalyst to give the 5-arylated products **6** and **9**–**13** in good yields (Table 3). The highest yields were obtained in the cases of 2-*n*-butylthiophene and 1-(furan-2-yl)butan-1-one (Table 3, entries 1 and 5).

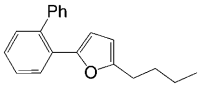
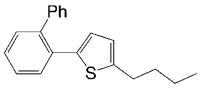
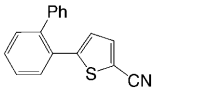
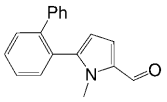
We next examined the reactivity of 2-bromobiphenyl (Table 4). This aryl bromide was found to be less reactive than 2-bromotoluene. In the presence of 2-*n*-butylfuran or 1-methyl-2-acetylpyrrole moderate yields of 39 and 41% of **14** and **17**, respectively, were obtained (Table 4, entries 1 and 5). Much better results were obtained for the coupling of this very hindered aryl bromide with functionalised thiophenes (Table 4, entries 2–4).

Table 3. Direct 5-arylation of heteroaromatic compounds with 2-bromotoluene (Scheme 4).[a]

Entry	Product		Cat. [mol%]	Yield [%]
1		**6**	0.5	90
2		**10**	0.5	71
3[b]			0.5	55
4		**11**	0.5	68
5		**12**	0.5	91
6			0.1	38
7		**13**	0.5	74
8		**9**	0.5	69
9[b]			0.5	63

[a] $Pd(OAc)_2$/**L5** (1:1, cat.), 2-bromotoluene (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products. [b] Without Bu_4NBr.

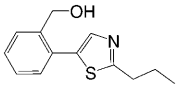
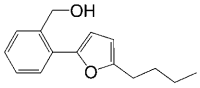
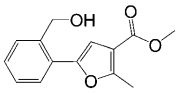
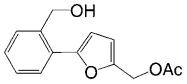
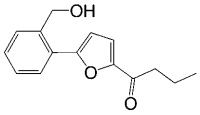
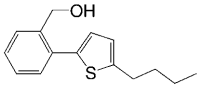
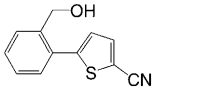
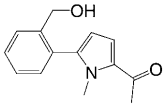
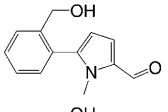
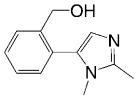
Table 4. Direct arylation of heteroaromatic compounds with 2-bromobiphenyl (Scheme 4).[a]

Entry	Product		Cat. [mol%]	Yield [%]
1		**14**	0.5	39
2		**15**	1	69
3		**16**	0.5	90
4			0.1	85
5		**17**	0.5	41

[a] $Pd(OAc)_2$/**L5** (1:1, cat.), 2-bromobiphenyl (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon, yields are of isolated products.

The direct heteroarylation of C2-substituted aryl bromides that carry reactive functional groups would be useful for the straightforward synthesis of novel ligands.[22] We anticipated that the direct coupling of unprotected (2-bromophenyl)-methanol with heteroaromatic compounds would be very practical because it would avoid a protection/deprotection sequence and, therefore, would provide a more environmentally and economically attractive access to reactive arylated heteroaromatic compounds. We observed that coupling of (2-bromophenyl)-methanol proceeded with a wide range of furan, thiophene and pyrrole derivatives in the presence of as little as 0.1–0.5 mol% catalyst (Table 5, entries 1–11). In all cases, the reaction was regioselective at the C5 position. Conversely, 1,2-dimethylimidazole was recovered without any reaction (Table 5, entry 12). In the course of these reactions, no coupling of the hydroxymethyl function with the aryl bromide was observed.

Table 5. Direct arylation of heteroaromatic compounds with (2-bromophenyl)-methanol (Scheme 4).[a]

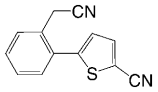
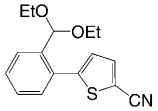
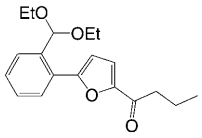
Entry	Product		Cat. [mol%]	Yield [%]
1		**18**	1	78
2		**19**	0.1	86
3			0.05	60
4		**20**	0.1	81
5		**21**	0.5	58
6		**22**	0.5	81
7			0.1	77
8		**23**	0.5	77
9		**24**	0.1	75
10		**25**	0.5	65
11		**26**	0.5	67
12		**27**	0.5	0

[a] $Pd(OAc)_2$/**L5** (1:1, cat.), (2-bromophenyl)-methanol (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products.

The catalytic system tolerates other substituents at the C2 position of bromobenzene derivatives (Table 6). The coupling reactions of (2-bromophenyl)-acetonitrile with thiophene-2-carbonitrile, and 1-bromo-2-diethoxymethylbenzene with thiophene-2-carbonitrile or 1-(furan-2-yl)butan-1-one gave **28**–**30** in moderate yields, due to limited conversions of these aryl bromides.

We had previously observed that direct coupling of 9-bromoanthracene with heteroaromatic compounds is relatively easy. For example, in the presence of 2-*n*-propylthiazole, one of the most reactive heteroaromatic compounds for

Table 6. Direct arylation of heteroaromatic compounds with 2-substituted aryl bromides (Scheme 4).[a]

Entry	Product		Yield [%]
1		**28**	38
2		**29**	56
3		**30**	68

[a] $Pd(OAc)_2$ (0.05 mmol), **L5** (0.05 mmol), aryl bromide (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products.

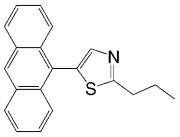
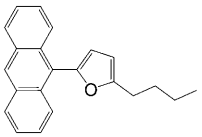
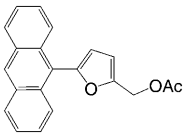
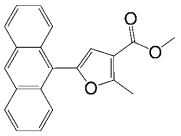
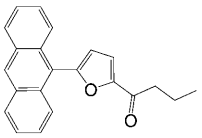
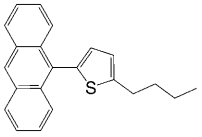
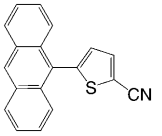
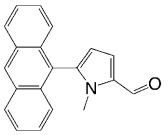
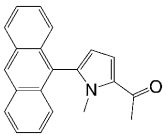
direct arylation, use of a $Pd(OAc)_2$ catalyst (0.4 mol%) without any auxiliary ligand allowed the coupling product **3** to be obtained in 75% yield (Table 2, entry 3).[17b] Conversely, the direct coupling of 9-bromoanthracene to pyrroles has never been reported and its reaction with a thiophene derivative gave the coupling product in only 40% yield.[14b] As anticipated, in the presence of the $Pd(OAc)_2$/**L5** catalyst (0.5–1 mol%) the target products **3** and **31**–**38** were obtained in good to excellent yields (Table 7). By using our new protocol, only a minor influence of the nature of the heteroaromatic compound was observed.

To confirm the wide scope of our system we also examined the coupling of 1-bromo-2-methylnaphthalene with a range of heteroaromatic compounds (Table 8). Until now, this more challenging electron-enriched reactant has not been coupled with heteroaromatic compounds through C–H bond activation. Surprisingly, in most cases, yields similar to those found for the coupling with 9-bromoanthracene were obtained. In the presence of 1-(furan-2-yl)butan-1-one and only 0.05 mol% of catalyst, the desired product **43** was obtained in 90% yield (Table 8, entry 9). High yields of coupling products **39**, **40** and **46** were also obtained in the presence of the catalyst (0.5 mol%) and 2-*n*-propylthiazole, 2-*n*-butylfuran or 2-*n*-butylthiophene, respectively (Table 8, entries 1, 2 and 12). We also examined the reactivity of furfuryl alcohol as a heteroaromatic substrate that bore an unprotected hydroxyalkyl function. The coupling reaction to 1-bromo-2-methylnaphthalene gave the target compound **45** in a satisfactory 68% yield (Table 8, entry 11). In the course of this reaction, no ether formation was detected. In general, the presence of Bu_4NBr slightly improves the yields of the coupling products (Table 8, entries 2 versus 4).

As reported in Table 9, the coupling of 2,6-dimethylbromobenzene with heteroaromatic compounds was more challenging. With some heteroaromatic compounds, such as methyl 2-methyl-3-furancarboxylate, furfuryl acetate or 1-(furan-2-yl)butan-1-one, the coupling products **50**–**52** were obtained in fairly good yields (Table 9, entries 3–5). On the other hand, in the presence of 2-*n*-butylfuran or 2-*n*-butylthiophene the expected products **49** and **53** were only formed in moderate 40 and 35% yields, respectively (Table 9, entries 2 and 6). The coupling with 2-*n*-propylthiazole gave **2** in only 29% yield (Table 9, entry 1).

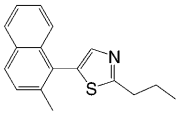
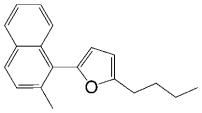
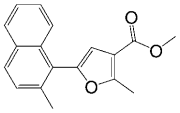
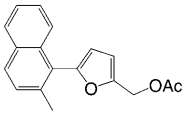
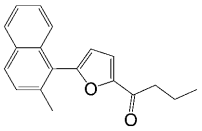
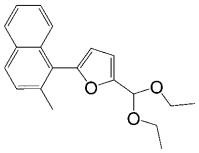
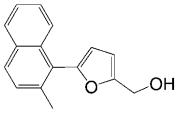
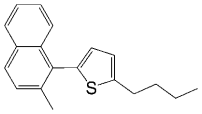
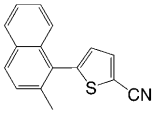
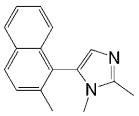
Finally, the reactivity of 2-bromo-3-methylbenzonitrile was examined (Table 10). Due to the presence of a nitrile substituent on the aromatic ring, the oxidative addition to palladium was expected to be easier than the oxidative addi-

Table 7. Direct arylation of heteroaromatic compounds with 9-bromoanthracene (Scheme 4).[a]

Entry	Product		Cat. [mol%]	Yield [%]
1		**3**	0.5	94
2		**31**	0.5	80
3		**32**	1	90
4		**33**	0.5	68
5		**34**	0.5	88
6		**35**	0.5	88
7		**36**	0.5	92
8		**37**	0.5	59
9		**38**	0.5	60

[a] $Pd(OAc)_2$/**L5** (1:1, cat.), 9-bromoanthracene (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products.

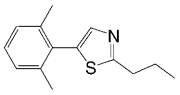
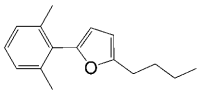
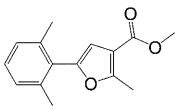
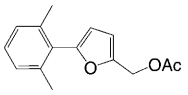
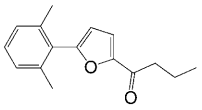
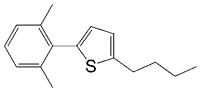
Table 8. Direct arylation of heteroaromatic compounds with 1-bromo-2-methylnaphthalene (Scheme 4).[a]

Entry	Product		Cat. [mol%]	Yield [%]
1		**39**	0.5	88
2		**40**	0.5	92
3			0.1	62
4[b]			0.5	72
5[c]			0.5	77
6		**41**	0.5	72
7		**42**	0.5	61
8			0.1	53
9		**43**	0.05	90
10		**44**	0.5	79
11		**45**	0.5	68
12		**46**	0.5	93
13			0.1	61
14			0.05	57
15		**47**	0.5	68
16			0.05	62
17		**48**	0.5	0

[a] $Pd(OAc)_2$/**L5** (1:1, cat.), 1-bromo-2-methylnaphthalene (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products. [b] Without Bu_4NBr. [c] 2-*n*-Butylfuran (1.2 mmol).

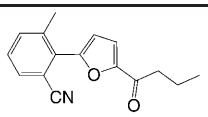
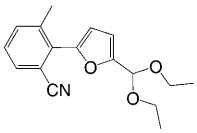
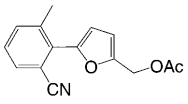
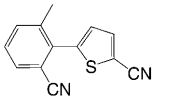
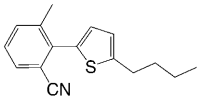
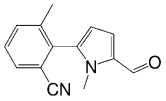
tion of 2,6-dimethylbromobenzene. The reaction proceeded to give products **54**–**58** in very high yields when furan or thiophene derivatives were used as coupling partners (Table 10, entries 1–5). The reaction of this aryl bromide with 1-methyl-2-formylpyrrole was found to be less regioselective and the 5-arylation product **59** was obtained in only 52% yield. Such couplings may allow the synthesis of axially chiral biaryls that could be useful ligands.[22]

Table 9. Direct arylation of heteroaromatic compounds with 2,6-dimethylbromobenzene (Scheme 4).[a]

Entry	Product		Yield [%]
1		**2**	29
2		**49**	40
3		**50**	57
4		**51**	56
5		**52**	71
6		**53**	35

[a] $Pd(OAc)_2$ (0.05 mmol), **L5** (0.05 mmol), 2,6-dimethylbromobenzene (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products.

Table 10. Direct arylation of heteroaromatic compounds with 2-bromo-3-methylbenzonitrile (Scheme 4).[a]

Entry	Product		Yield [%]
1		**54**	92
2		**55**	93
3		**56**	90
4		**57**	91
5		**58**	93
6		**59**	52

[a] $Pd(OAc)_2$ (0.05 mmol), **L5** (0.05 mmol), 2-bromo-3-methylbenzonitrile (1 mmol), heteroaromatic compound (2 mmol), KOAc (2 mmol), Bu_4NBr (1 mmol), DMAc, 150 °C, 16 h, under argon; yields are of isolated products.

Conclusion

We have designed and identified a novel ferrocenyl triphosphane ligand, useful for efficient direct heteroarylation of highly congested and functionalised aryl bromides. These coupling reactions were performed with low catalyst loadings (0.1–0.5 mol%). The $Pd(OAc)_2$/**L5** catalytic system tolerates important and useful functional groups, which can allow for further elaboration into more sophisticated heterocyclic molecules. The wide reactivity scope clearly demonstrates the synthetic utility of this catalytic system. The present study highlights the usefulness of robust tridentate phosphane catalytic auxiliaries in direct C–H activation reactions that involve congested *ortho*-substituted aryl bromides. A number of the products prepared by the reported method have not been described until now, thus, this procedure provides a convenient access to compounds otherwise not easily prepared, especially by the use of more classical cross-coupling methods. Finally, with regards to environmental considerations, the advantages of a procedure that produces only limited amounts of inert waste (in this case, acetic acid and potassium bromide byproducts) has become increasingly important, particularly for industrial processes. More detailed ligand design studies will be reported in due time.

Experimental Section

General: All catalytic reactions were performed in Schlenk tubes under an argon atmosphere. *N,N*-Dimethylacetamide (DMAc) was of analytical grade and was not distilled before use. Potassium acetate (purity = 99%+) was used. Commercial aryl bromides and heteroaromatic derivatives were used without purification. ^1H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (75 MHz) spectra were recorded in $CDCl_3$ solution at 298 K. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (^1H: δ = 7.26 ppm and ^{13}C: δ = 77.0 ppm) (see the Supporting Information). Flash chromatography was performed on silica gel (230–400 mesh). Syntheses of ligands **L1**–**L4** and **L6** have been reported previously.[18,21]

Synthesis of ligand L5: A solution of 1,2-bis(diphenylphosphino)-4-*tert*-butylcyclopentadienyl lithium (5.60 g, 11.3 mmol) in THF (20 mL) was added to a stirred suspension of $FeCl_2$ (1.37 g, 10.8 mmol) in THF (15 mL) at −80 °C. The reaction mixture was allowed to slowly warm to RT and was stirred for 2 h. The reaction mixture was cooled to −80 °C and a solution of di-isopropylphosphino-3-tert-butylcyclopentadienyl lithium (2.65 g, 10.8 mmol) in THF (20 mL) was added. After the addition, the reaction mixture was allowed to slowly warm to RT and was stirred for 1 h. THF was removed in vacuo, the residue was dissolved in toluene (30 mL) and the resulting solution was heated at reflux for 3 h. The brown solution was filtered through silica to yield a mixture of ferrocenyl phosphanes. This mixture was purified by column chromatography (alumina gel, height 30 cm, diameter 5.5 cm), eluted firstly with 3:2 toluene/heptane to separate the symmetric diphosphane, secondly with 1:1 toluene/heptane to elute pure **L5** (2.0 g, 25%). Ligand **L5** was stored and weighed under air without any special precautions.

General procedure for coupling reactions: The aryl bromide (1.00 mmol), heteroaromatic derivative (2.00 mmol), KOAc (2.00 mmol) and Bu_4NBr (1.00 mmol) were introduced to a Schlenk tube equipped with a magnetic stirrer bar. 1:1 $Pd(OAc)_2$/**L5** (0.05–1 mol%) and DMAc (3 mL) were added and the Schlenk tube was purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 150 °C and reactants were allowed to stir for 16 h. The reaction mixture was analysed by gas chromatography to determine the conversion of the aryl bromide. The solvent was removed by heating the reaction vessel under vacuum and the residue was charged directly onto a silica gel column. The products were eluted with an appropriate ratio of diethyl ether and pentane.

Compound ***2***:[15b] The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and 2-*n*-propylthiazole (0.254 g, 2.00 mmol) afforded **2** in 29% (0.067 g) yield.

Compound ***3***:[17b] The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and 2-*n*-propylthiazole (0.254 g, 2.00 mmol) afforded **3** in 94% (0.285 g) yield.

Compound ***4***:[13] The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **4** in 80% (0.171 g) yield.

Compound ***6***:[14a] The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **6** in 90% (0.207 g) yield.

Compound ***9***:[11b] The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and 1-methyl-2-acetylpyrrole (0.247 g, 2.00 mmol) afforded **9** in 69% (0.147 g) yield.

Compound ***10***: The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2.00 mmol) afforded **10** in 71% (0.163 g) yield.

Compound ***11***: The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **11** in 68% (0.156 g) yield.

Compound ***12***: The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **12** in 91% (0.208 g) yield.

Compound ***13***: The reaction of 2-bromotoluene (0.171 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **13** in 74% (0.147 g) yield.

Compound ***14***: The reaction of 2-bromobiphenyl (0.233 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **14** in 39% (0.108 g) yield.

Compound ***15***: The reaction of 2-bromobiphenyl (0.233 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **15** in 69% (0.202 g) yield.

Compound ***16***: The reaction of 2-bromobiphenyl (0.233 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **16** in 90% (0.235 g) yield.

Compound ***17***: The reaction of 2-bromobiphenyl (0.233 g, 1.00 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2.00 mmol) afforded **17** in 41% (0.107 g) yield.

Compound ***18***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 2-*n*-propylthiazole (0.254 g, 2.00 mmol) afforded **18** in 78% (0.182 g) yield.

Compound ***19***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **19** in 86% (0.198 g) yield.

Compound ***20***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2.00 mmol) afforded **20** in 81% (0.199 g) yield.

Compound ***21***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **21** in 58% (0.143 g) yield.

Compound ***22***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **22** in 81% (0.198 g) yield.

Compound ***23***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **23** in 77% (0.190 g) yield.

Compound ***24***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **24** in 75% (0.161 g) yield.

Compound ***25***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 1-methyl-2-acetylpyrrole (0.247 g, 2.00 mmol) afforded **25** in 65% (0.149 g) yield.

Compound ***26***: The reaction of (2-bromophenyl)-methanol (0.187 g, 1.00 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2.00 mmol) afforded **26** in 67% (0.144 g) yield.

Compound ***28***: The reaction of (2-bromophenyl)-acetonitrile (0.196 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol), affords **28** in 38% (0.085 g) yield.

Compound ***29***: The reaction of 1-bromo-2-diethoxymethylbenzene (0.187 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **29** in 56% (0.161 g) yield.

Compound ***30***: The reaction of 1-bromo-2-diethoxymethylbenzene (0.187 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **30** in 68% (0.215 g) yield.

Compound ***31***:[13] The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **31** in 80% (0.240 g) yield.

Compound ***32***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **32** in 90% (0.284 g) yield.

Compound ***33***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2.00 mmol) afforded **33** in 68% (0.215 g) yield.

Compound ***34***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **34** in 88% (0.276 g) yield.

Compound ***35***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **35** in 88% (0.278 g) yield.

Compound ***36***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **36** in 92% (0.262 g) yield.

Compound ***37***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2.00 mmol) afforded **37** in 59% (0.168 g) yield.

Compound ***38***: The reaction of 9-bromoanthracene (0.257 g, 1.00 mmol) and 1-methyl-2-acetylpyrrole (0.246 g, 2.00 mmol) afforded **38** in 60% (0.180 g) yield.

Compound ***39***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and 2-*n*-propylthiazole (0.254 g, 2.00 mmol) afforded **39** in 88% (0.235 g) yield.

Compound ***40***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **40** in 92% (0.243 g) yield.

Compound ***41***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2.00 mmol) afforded **41** in 72% (0.202 g) yield.

Compound ***42***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **42** in 61% (0.171 g) yield.

Compound ***43***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **43** in 90% (0.250 g) yield.

Compound ***44***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and 2-diethoxymethylfuran (0.340 g, 2.00 mmol) afforded **44** in 79% (0.245 g) yield.

Compound ***45***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and furan-2-ylmethanol (0.196 g, 2.00 mmol) afforded **45** in 68% (0.162 g) yield.

Compound ***46***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **46** in 93% (0.261 g) yield.

Compound ***47***: The reaction of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **47** in 68% (0.169 g) yield.

Compound ***49***: The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and 2-*n*-butylfuran (0.248 g, 2.00 mmol) afforded **49** in 40% (0.091 g) yield.

Compound ***50***: The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2.00 mmol) afforded **50** in 57% (0.139 g) yield.

Compound ***51***: The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **51** in 56% (0.137 g) yield.

Compound ***52***: The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **52** in 71% (0.172 g) yield.

Compound ***53***: The reaction of 2-bromo-1,3-dimethylbenzene (0.185 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **53** in 35% (0.085 g) yield.

Compound ***54***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and 1-(furan-2-yl)butan-1-one (0.276 g, 2.00 mmol) afforded **54** in 92% (0.233 g) yield.

Compound ***55***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and 2-diethoxymethylfuran (0.340 g, 2.00 mmol) afforded **55** in 93% (0.265 g) yield.

Compound ***56***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and furfuryl acetate (0.280 g, 2.00 mmol) afforded **56** in 90% (0.230 g) yield.

Compound ***57***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and thiophene 2-carbonitrile (0.218 g, 2.00 mmol) afforded **57** in 91% (0.204 g) yield.

Compound ***58***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and 2-*n*-butylthiophene (0.280 g, 2.00 mmol) afforded **58** in 93% (0.237 g) yield.

Compound ***59***: The reaction of 2-bromo-3-methylbenzonitrile (0.196 g, 1.00 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2.00 mmol) afforded **59** in 52% (0.117 g) yield.

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