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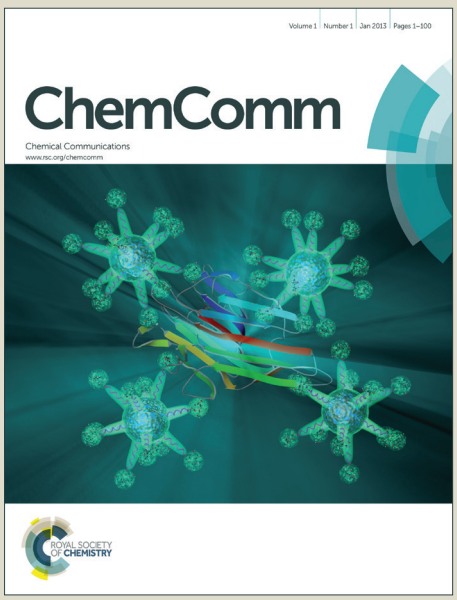

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Palladium (II)-catalysed *ortho*-arylation of *N*-benzylpiperidines

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Pd^{II}- catalysed *ortho*-arylation of benzylic heterocycles with arylboronic acid pinacol esters (Ar-BPin) *via* directed C-H bond activation to generate the desired biaryl products is reported. This methodology is efficient and applicable to a wide range of functionalised Ar-BPin and benzylic heterocycles, allowing the direct synthesis of important biaryl motifs in modest to good yield.

Cross-coupling reactions of aromatic compounds constitute one of the most versatile entries to compounds possessing a biaryl motif.[1] Such transformations are usually performed by traditional cross coupling reactions of organohalides or pseudohalides with organometallic reagents.[2] However, prefunctionalisation of substrates to form specific organohalides for cross coupling can be difficult and this has accordingly led many research groups to develop more direct routes to biaryl scaffolds.[3] Over the last decade, a variety of direct, chelation-assisted, C-H activation on arenes, mainly *via* [Pd][4], [Rh][5] and [Ru][6] catalysis, has been developed using a wide range of directing groups (DGs) such as amides, imines, oximes, ketones and other *N*-heterocycles. Expanding the scope of DGs to include simple amine derivatives that are commonly found in natural products and pharmaceutical compounds is highly desirable. In 2006, Daugulis and co-workers reported an *ortho* arylation of unsubstituted benzylamines directed by the free amine with iodobenzene under Pd catalysis.[7] Meanwhile, Shi *et al.* demonstrated that *N*,*N*-di-alkyl amine is also an effective directing group for *ortho*-olefination[8] and -carbonylation.[9] More recently, Zhang and co-workers[10a] developed a Pd-catalysed *ortho*-arylation of *N*,*N*- dimethylbenzylamines with iodobenzene (Figure 1).[10] Inspired by these findings we envisaged that saturated *N*-containing heterocycles could also serve as efficient DGs for C(sp^2)-H arylation; this would expand the range of DGs in the field (Figure 1) and the new chemistry could be applied directly to the construction of biologically relevant motifs such as those present, for example, in known Bcl-2 antagonists[11], γ-secretase modulators[12] and 5-HT$_7$-antagonists[13] (Figure 2). Herein we report a Pd^{II}- catalysed *ortho*-arylation of a range of benzylic heterocycles with arylboronic acid pinacol esters leading directly to the biaryl product in one step.

Initially we focused on the piperidine moiety as a potentially useful directing group for C(sp^2)-H activation/ arylation. Inspired by Yu's pioneering work[14], a preliminary experiment was conducted on the model substrate 1-(2-methylbenzyl)piperidine **1a** and phenylboronic acid pinacol ester **2a** in the presence of catalytic $Pd(OAc)_2$, and Ag_2CO_3, Na_2CO_3 and 1,4 benzoquinone at 100 °C (Table 1). Encouragingly, *ortho*-arylated product **3a** was observed in 55% NMR yield (entry 1).

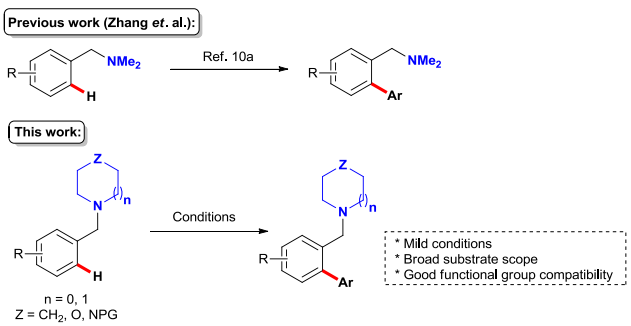


Figure 1: *Ortho*-arylation using benzylic heterocycles as directing groups

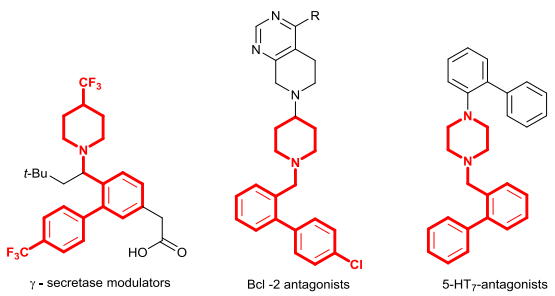
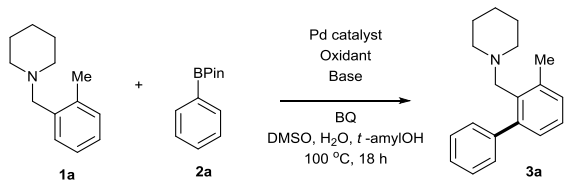


Figure 2: Biologically active compounds containing a benzylpiperidine motif

Further optimisation was then carried out, starting with an investigation of the performance of different bases. Potassium bases, KF and K_2HPO_4, resulted in a reduced yield (entries 2 & 3). Pleasingly, however, $NaHCO_3$ was found to be optimal for this transformation; full conversion of **1a** to the arylated product **3a** was observed after 18 hours (entry 4). Replacement of $Pd(OAc)_2$ with other Pd sources such as $PdCl_2$, $PdCl_2(PPh_3)_2$ and $PdCl_2(CH_3CN)_2$ did not result in the formation of any arylated product (entry 5). Decreasing the catalyst loading to 5 mol% resulted in a decrease in yield and therefore, 10 mol% of catalyst was deemed necessary (entry 6). Other oxidants such as $Cu(OAc)_2$ and CuF_2, were found to give inferior yields (entry 7 & 8) and although AgOAc was found to perform reasonably well (entry 10), Ag_2CO_3 proved optimal (entry 9). 1,4-Benzoquinone was also essential as a promoter; in its absence no reaction was observed in agreement with literature findings relating to its importance in the reductive elimination step.[14b, 15] A decline in yield was also observed without the addition of H_2O and DMSO (see the Supporting Information). *t*-Amyl alcohol was found to be the most suitable solvent for this transformation, followed by 1,4-dioxane and MeCN. Other aryl boronic acid derivatives were investigated, but arylboronic acid pinacol esters, were by far the best in this reaction (see the Supporting Information).

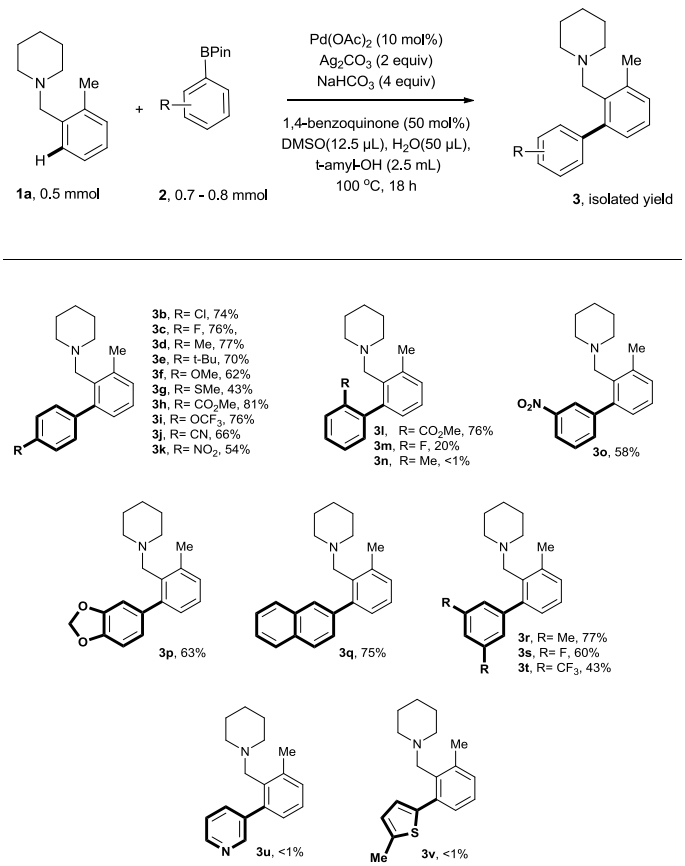
Table 1 Optimisation studies on $C(sp^2)$- H activation / cross coupling reactions of **1a** & **2b**



Entry[a]	Catalyst (mol%)	Oxidant (equiv)	Base (equiv)	Yield[c] (%)
1	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0)	Na_2CO_3 (6.0)	55
2	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0)	KF (6.0)	25
3	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0)	K_2HPO_4 (6.0)	33
4	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1.5)	$NaHCO_3$ (3.0)	82
5[b]	$PdCl_2$ (10)	Ag_2CO_3 (1.5)	$NaHCO_3$ (3.0)	-
6	$Pd(OAc)_2$ (5)	Ag_2CO_3 (1.5)	$NaHCO_3$ (3.0)	43
7	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (1.5)	$NaHCO_3$ (3.0)	11
8	$Pd(OAc)_2$ (10)	CuF_2 (1.5)	$NaHCO_3$ (3.0)	2
9	$Pd(OAc)_2$ (10)	**Ag_2CO_3 (2.0)**	**$NaHCO_3$ (4.0)**	**88 (81)**
10	$Pd(OAc)_2$ (10)	AgOAc (2.0)	$NaHCO_3$ (4.0)	81

[a] Reaction condition: **1a** (0.2 mmol), **2b** (0.28 mmol), Pd catalyst, base, oxidant, BQ (0.5 equiv), DMSO (5 µL), H_2O (20 µL) in *t*-amylOH (1 mL), T = 100 °C, 18 h. [b] Similar results for $PdCl_2(PPh_3)_2$ and $PdCl_2(CH_3CN)_2$. [c] ^1H NMR yield with internal standard (CH_2Br_2), in parenthesis isolated yield.

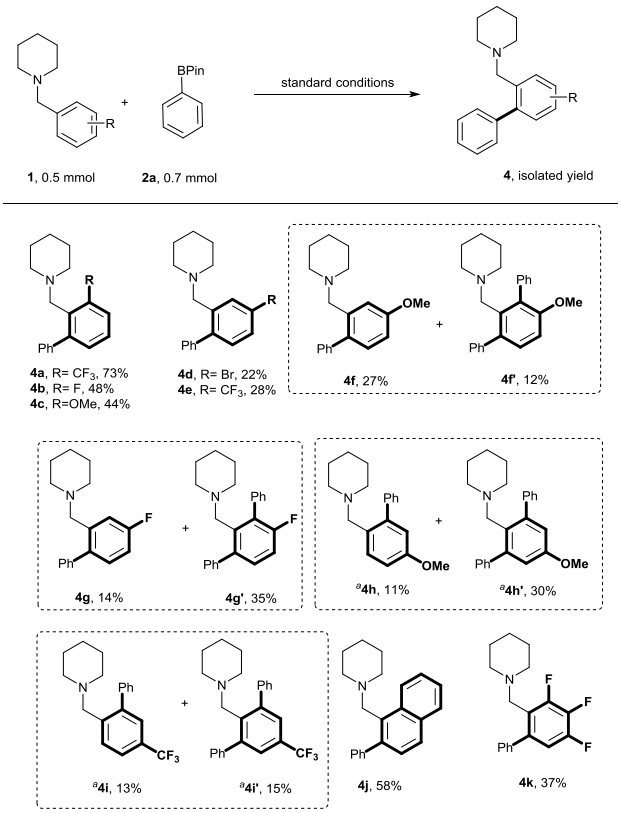
After attaining the optimised conditions, the scope of this methodology was assessed using different functionalized arylboronic acid pinacol esters (Ar-BPins) with 1-(2-methylbenzyl)piperidine (Scheme 1). Generally, a wide range of *para*-substituted Ar-BPin substrates was tolerated and the corresponding biaryl products were obtained in modest[16] to good yields. Ar-BPins substituted with functional groups, such as cyano, nitro and fluorine were suitable substrates under these reaction conditions affording the desired products in respectable yields. Chlorine substituents on Ar-BPin were also well-tolerated, giving rise to biaryl products poised for further transformations. In the case of *ortho*-substituted Ar-BPin substrates, the reaction worked well using the ester **2l** affording the biaryl product **3l** in a yield of 76% but, unfortunately, poor conversions were obtained for other substituents such as fluoro (**3m**) and methyl (**3n**). This methodology was also amenable to *meta*-substituted and 3,5-disubstituted Ar-Bpin derivatives, giving rise to the corresponding products in 43 – 77% yield. In agreement with related studies[14f] heteroarylboronates that contained pyridine- (**3u**), thiophene- (**3v**) were unreactive under these conditions. Similarly, under the optimised conditions attempted *ortho* alkylation using cyclohexylboronic acid pinacol ester failed to yield any desired product.



Scheme 1: $C(sp^2)$-H cross-coupling of 1-(2-methylbenzyl)piperidine with various Ar-BPin.

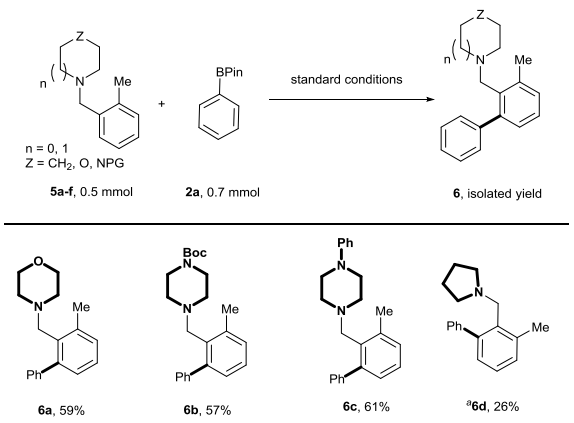
The scope with respect to the substituents on the aromatic ring of the benzylpiperidine in the reaction with phenylboronic acid pinacol ester, was then examined. As presented in Scheme 2, *ortho*-substituted substrates possessing electron withdrawing (F and CF_3) and the electron donating (OMe) substituents performed well, with products being afforded in 44-73% yield. *Meta* substituted substrates with sterically

bulky electron withdrawing substituents (Br and CF_3) underwent monoarylation selectively at the less hindered *ortho* position, presumably due to steric effects, and afforded the products **4d** and **4e** in 22-28% yield. However, for less bulky electron withdrawing groups such as fluorine, products of both mono- and di-arylation, **4g** and **4g'**, were observed in 14% and 30% yield respectively. Notably, for an electron donating substituent at the *meta* position (OMe), other than monoarylation to give **4f** (27 %) as the major product, diarylation was also observed to afford **4f'** in 12 % yield. The reaction conditions were also compatible with *para*-substituted substrates affording a mixture of mono and di arylated products. Electron donating substituents (OMe) at the para position increased reactivity compared to the electron withdrawing groups and the di-arylated compounds **4h'** and **4i'** were obtained as the major products. Naphthyl (**4j**) and tri-fluorophenyl (**4k**) derivatives were also well-tolerated.



Scheme 2: C(sp^2)-H cross-coupling of phenylboronic acid pinacol ester with different functionalised benzylpiperidines. [a] Reaction was carried out with **2a** (1.1 mmol) for 24 h.

After exploring arylations directed by the piperidine moiety, we next investigated other possible saturated nitrogen-containing heterocyclic derivatives that could serve as effective directing groups for this transformation. Accordingly, the benzylic heterocycles **5a-f** were subjected to our previously optimised *ortho*-phenylation conditions. (Scheme 3) Gratifyingly, morpholine (**5a**) and piperazine (**5b** and **5c**) scaffolds worked well, affording the corresponding arylated products in good yield. Reactions with benzylic heterocycles of different ring size was also shown to be successful albeit the yield obtained was low under the standard conditions and no further optimisation was carried out to improve the yield.



Scheme 3: C(sp^2)-H cross-coupling of phenylboronic acid pinacol ester with functionalised benzylic heterocycles . [a] Reaction was carried out with **2a** (1.0 mmol) for 24 h.

In line with previous studies[14], we propose this C-H activation cross-coupling reaction proceeds *via* a Pd(II)/ Pd(0) catalytic cycle (Figure 3). The palladium species activates the *ortho* C-H of **1**, forming a 5-membered palladacycle intermediate **A**. Subsequently, addition of base is necessary for the transmetallation of Ar-Bpin to proceed to generate intermediate **B**. 1,4-benzoquinone then facilitates reductive elimination of the biaryl product **3** forming the Pd(0) species.[14b, 15] Reoxidation of Pd(0) by an oxidant, in this case Ag_2CO_3, is necessary for regeneration of the active Pd(II) species for further turnovers.

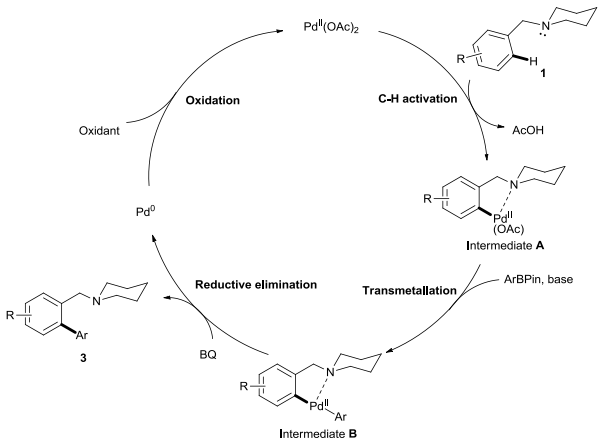


Figure 3: Proposed C(sp^2)-H arylation catalytic cycle

In conclusion, we have demonstrated that a range of saturated nitrogen-containing heterocycles attached via the nitrogen atom to benzylic substrates serve as effective directing groups for palladium catalysed C(sp^2)-H activation / arylation. Under palladium catalysis, the coupling of a range of arylboronic acid pinocol esters to the *ortho* position of N-benzylated pyrrolidines, piperidines, morpholine and piperazine substrates giving direct access, under relatively mild reaction conditions, to important biaryls motifs, was demonstrated. Investigations to develop the related direct *ortho* alkylation reaction are ongoing and our findings will be reported in due course.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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16. In the case of product **3f**, attempts to improve reaction efficiency by the use of additional MPAA ligands (Boc-$_L$-Thr-OH and Boc-$_L$-Leu-OH) were unsuccessful and resulted in lower conversion.

