Journal Name

RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Copper-Catalysed Cross-Couplings of Arylboronate Esters with Aryl and Heteroaryl Iodides and Bromides†

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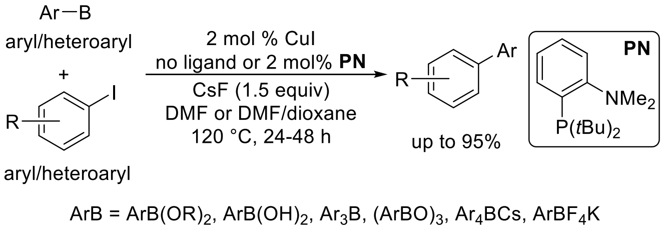
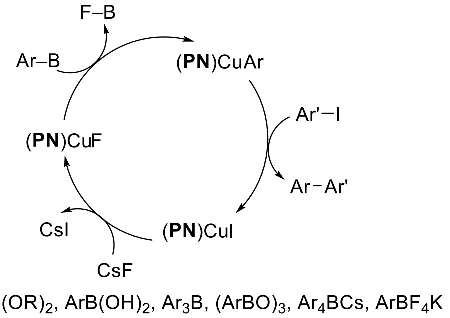
Cu^I-catalysed coupling of arylboronate esters with aryl and heteroaryl iodides and bromides is described. The transformation affords products in good yields using 5 – 10 mol % catalyst loadings. The described reaction requires a P,N-based bidentate ligand in combination with CuI for aryl-aryl coupling, but it proceeds without external ligands for aryl-heteroaryl coupling to afford the products. The reaction protocol can also be applied to achieve biarylation of diiodoarenes in reasonable yields.

Over the last three decades, Pd-catalysed Suzuki-Miyaura coupling has developed into a key synthetic tool that is capable of combining a wide variety of organoboron reagents with organohalides and pseudohalides to construct carbon-carbon (C−C) bonds.[1] As a result, the cross-coupling process has been applied to the synthesis of a wide array of molecular targets, from materials and pharmaceuticals to organic building blocks and natural products.[2] Despite the maturity of the transformation with regard to its substrate scope, catalytic turnover, and varied applications, current desire remains high to achieve the reaction using inexpensive, less toxic, and sustainable transition metal (TM) catalysts. Towards this end, catalysts based on earth-abundant, 1st row late TMs are emerging as viable alternatives to palladium.[3] In particular, Cu has demonstrated a tremendous potential[4] in catalysing such couplings for carbon-carbon (C−C) bond formation.[5]

In 2002, Rothenberg et al. revealed that a copper nanocluster enabled the coupling of phenylboronic acid with iodobenzene.[6] Despite this seminal work from more than a decade ago and subsequent reports,[7] Cu-catalysed coupling was typically limited to the reaction of arylboronic acids with aryl iodides[8] and in most cases required 10-20 mol % catalyst[7b-f] and stoichiometric amounts in others.[7b] In 2011, Liu et al. demonstrated that the reaction could be extended to the coupling of organoboronate esters, $ArB(OR)_2$.[9] However, the reaction was only suitable for coupling with primary alkyl halides and pseudohalides, proceeding via an S_N2 mechanism. Recently, we have shown that a variety of organoboron reagents, such $ArB(OR)_2$, $ArB(OH)_2$, Ar_3B, $(ArBO)_3$, Ar_4BCs and $ArBF_4K$, can undergo cross-coupling with aryl and heteroaryl iodides when CuI was utilized as a catalyst with or without the addition of the ligand *o*-(di-*tert*-butylphosphino)-*N*, *N*-dimethylaniline) (**PN**) (Scheme 1).[10] Brown et al. also demonstrated that a similar reaction of $ArB(OR)_2$ with aryl iodides could be achieved with the application of a bidentate xantphos ligand with CuCl, further attesting to the generality of Cu-based catalytic systems for Suzuki-Miyaura type cross-couplings.[11]



Scheme 1 Cu^I-Catalysed Coupling of Organoboron Reagents with Aryl Iodides



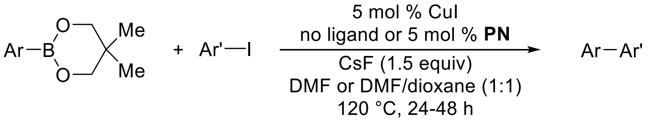
Scheme 2 Proposed Catalytic Cycle

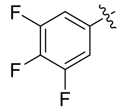
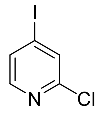
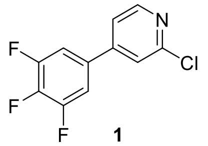
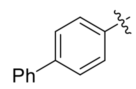
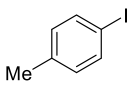
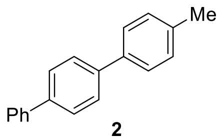
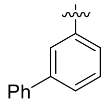
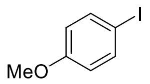
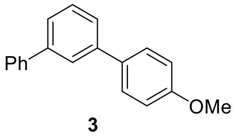
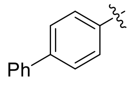
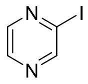
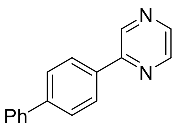
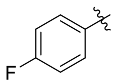
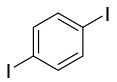
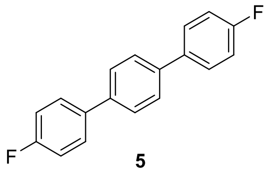
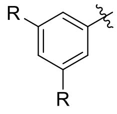
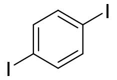
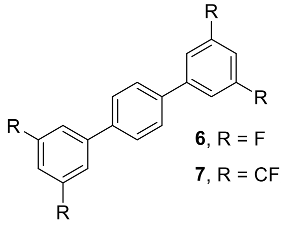
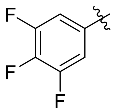
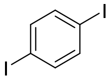
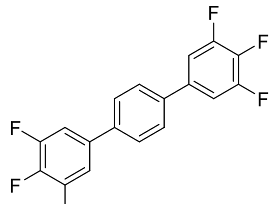
We further conducted detailed mechanistic studies and proposed a catalytic cycle based on the synthesis and characterisation of reaction intermediates, as well as following the progress of the reaction *in situ* by ^1H, ^{11}B, ^{19}F and ^{31}P NMR spectroscopies (Scheme 2).[10] Based on our studies, the cross-coupling proceeds via three elementary steps - exchange of fluoride with the iodide in (PN)CuI, transmetallation of arylboron reagents[12] with (PN)CuF[13], and the reaction of ArI with (PN)CuAr.[14] In this article, we demonstrate that the reaction protocol can be extended to a variety of other mono- and di-iodoarenes and iodoheteroarenes to afford mono- and di-arylated products. In addition, we also show for the first time that these reaction conditions can be easily extended to the couplings of arylboronate esters with electron-deficient and heteroaryl bromides.

The results of our ongoing studies on the substrate scope for aryl-aryl and aryl-heteroaryl couplings in the presence of 5 mol % each of CuI and **PN** are summarized in Table 1. While the reactions of arylboronate esters with non-heteroaryl iodides required the **PN** ligand, the couplings of heteroaryl iodides were conducted with 5 mol % CuI in the absence of **PN** ligands (entries 1, 4).[15] Without **PN**, the heteroaryl substrates and products could function as ligands for Cu. Cross-couplings involving heteroaryl coupling partners are generally challenging for Pd-catalysts because the heteroarenes bind to Pd competitively over the ligands, thus resulting in reaction inhibition and catalyst deactivation. Therefore, Pd-based cross-couplings with heteroaryl coupling partners typically require highly sterically hindered phosphine- and *N*-heterocyclic carbene (NHC)-based ligands.[16] Therefore, our reaction protocol provides an excellent complementary approach to Pd-catalysis for the synthesis of heterobiaryl molecules. In addition, the reaction tolerates halide substituents, such as chloride on the heteroaryl iodides (entry 1) and fluoride on arylboronate esters (entries 1, 2, 5-8), affording cross-coupled products in good to excellent yields. We further demonstrated that the current reaction protocol can also be applied to the synthesis of terphenyl derivatives in reasonable yields either by mono-arylation of iodobiaryls (entries 2-4) or diarylation of di-iodoarenes (entries 5-8) that were not reported previously. Terphenyl derivatives are industrially important molecules that are widely utilized as preservatives, sunscreens, liquid crystals and proteomimics.[17] As shown in entries 6-8, arylboronate esters containing multiple fluorinated and 3,5-bis-trifluoromethylated aryl groups were coupled with 1,4-diiodobenzene to afford the corresponding diarylated products in 47-73% yields.

We also have found that the current combination of CuI with sterically hindered and electron-rich **PN** ligand as a catalyst has enabled us to conduct cross-couplings of activated aryl and heteroaryl bromides to afford the coupled products in reasonable yields (Table 2).[18] Since the Cu-catalysed cross-coupling of aryl bromides, which are less expensive and more readily available than aryl iodides, are rare[5j,7e-f] and generally require stoichiometric quantities of Cu-catalysts,[5k] the current reaction protocol provides an excellent opportunity to synthesize biaryl molecules using catalytic amounts of Cu-salts. The reaction proceeds well with both the electron deficient and electron rich arylboronate esters, affording the products in good yields. The reaction tolerates very sensitive and synthetically useful functional groups, including nitrile (entries 1-7).[19] In addition, the coupling with heteroaryl bromides does not require the addition of any ancillary ligands (entries 8-12), an observation that is analogous to the coupling with heteroaryl iodides. This Cu-catalysed process provides a very cost-effective alternative to Pd-based systems for the synthesis of heterobiaryl molecules.

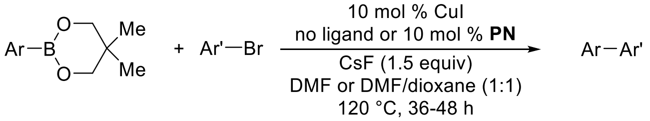
Table 1. Cross-coupling with mono- and diiodoarenes[a]

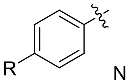
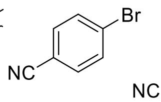
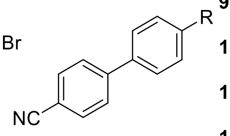
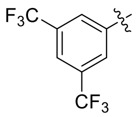
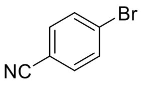
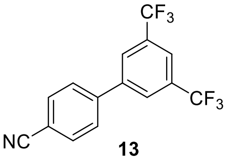
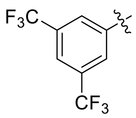
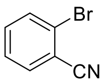
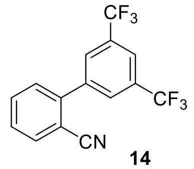
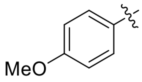
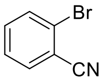
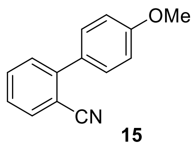
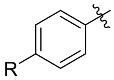
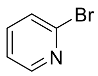
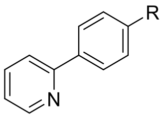
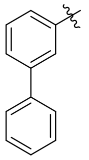
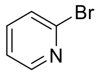
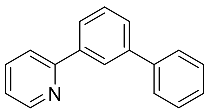


entry	$ArB(OR)_2$	Ar'I	Ar-Ar'	yield (%)[b]
1			 **1**	70
2			 **2**	64
3			 **3**	66
4			 **4**	69
5			 **5**	69[c]
6 7			 **6**, R = F **7**, R = CF_3	71 47
8			 **8**	73[c]

[a]1.0 mmol scale. 5 mL DMF/dioxane (1:1), 48 h for aryl-aryl coupling, and 5 mL DMF, 24 h for aryl-heteroaryl coupling. PN was used for aryl-aryl coupling, and no ligand was used for aryl-heteroaryl coupling CuI (99.999%) and CsF (99.9%) were used. [b]Isolated yields. [c]20 mol % **PN** and CuI used.

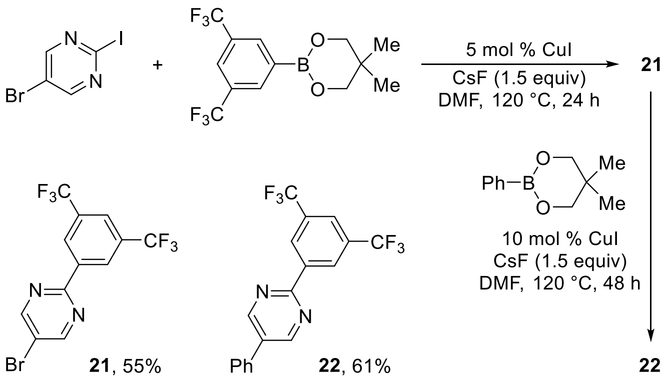
Table 2. Cross-coupling with electron deficient bromoarenes and hetero-bromoarenes



entry	ArB(OR)$_2$	Ar'Br	Ar-Ar'	yield (%)[b]
1			 **9**, R = H	69
2			**10**, R = F	49
3			**11**, R = Me	45
4			**12**, R = Ph	48
5			 **13**	34
6			 **14**	53
7			 **15**	42
8			 **16**, R = H	65[c]
9			**17**, R = F	74
10			**18**, R = Me	47
11			**19**, R = Ph	61
12			 **20**	84

[a]1.0 mmol scale. 5 mL DMF/dioxane (1:1), 48 h for aryl-aryl coupling, and 5 mL DMF, 36 h for aryl-heteroaryl coupling. PN was used for aryl-aryl coupling, and no ligand was used for aryl-heteroaryl coupling CuI (99.999%) and CsF (99.9%) were used. [b]Isolated yields. [c]2-Phenyl-1,3,2-dioxaborolane was used.

Taking advantages of the differential reaction rates of aryl iodides and bromides, we have further demonstrated that the current protocol can be extended to sequential arylations of haloarenes containing both iodo- and bromo-substituents. As outlined in Scheme 3, 5-bromo-2-iodopyrimidine was successively arylated with 3,5-bis(trifluoromethyl)phenyl- and phenylboronic acid neopentyl glycol esters under the standard reaction condition to afford the mono- and diarylated products **21** and **22** in 55% and 61% yields, respectively.



Scheme 3: Sequential arylation of 5-bromo-2-iodopyrimidine

Conclusions

We have demonstrated a broad substrate scope of the Cu^I-catalyzed Suzuki Miyaura-type couplings. The reactions of arylboronate esters proceed well with aryl- and heteroaryl iodides and activated aryl and heteroaryl bromides. In general, the reaction requires a bidentate **PN** ligand for aryl-aryl couplings; however, no ligand is required for aryl-heteroaryl couplings. The current reaction protocol can also be applied to biarylation of diiodoarenes, affording the doubly cross-coupled products in reasonable yields.

Acknowledgements

We thank the University of New Mexico (UNM) for financial support, and upgrades to the NMR (NSF grants CHE08-40523 and CHE09-46690) and Mass Spectrometry Facilities.

Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures and the characterization data of new compounds. See DOI: 10.1039/b000000x/

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