COUPLING OF HETEROARYL CHLORIDES WITH ARYLBORONIC ACIDS IN THE PRESENCE OF {1,4-BIS-(DIPHENYLPHOSPHINE)BUTANE]PALLADIUM(II) DICHLORIDE

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The cross-coupling of arylboronic acids with a variety of π -deficient heteroaryl chlorides has been shown to occur in high yield in the presence of [1,4-bis-(diphenylphosphine)butane]palladium(II) dichloride as catalyst.

As part of a programme of work to identify efficient, cost-effective synthetic routes to aryl-substituted heteroaryl compounds of medicinal interest, we considered the synthesis of these compounds by a palladium mediated cross-coupling approach. A variety of organometallic species have been employed successfully for the synthesis of biaryl compounds¹ using this strategy. We selected boron as the organometallic of choice since arylboronic acids are isolable, stable compounds which can be readily prepared,² and furthermore it was hoped that their non-basic nature would offer the possibility of carrying out reactions on substrates bearing labile protons. At the start of our work, a review of the literature revealed that with one exception,³ the reported examples of palladium catalysed cross-coupling with arylboronic acids all used aryl or heteroaryl bromides or iodides.^{2b, 2c, 4} Furthermore, the failure of both chlorobenzene^{4a} and 3 chloropyridine^{4c} to give any reaction with phenylboronic acid (with Pd(PPh₃)₄ as catalyst) had been reported.

We were particularly interested in the introduction of aryl substituents into π -deficient heteroaryl compounds, and for this class of compound the chloro-derivatives are cheaper and considerably more accessible than the corresponding bromides and iodides. We considered that a palladium catalyst bearing a bidentate phosphorus ligand could serve as a superior catalyst to the tetrakis(triphenylphosphine)palladium used in the majority of literature work to date.^{2b, 2c, 4} We now wish to report the successful cross coupling of a variety of π -deficient heteroaryl chlorides with arylboronic acids using [1,4-bis-(diphenylphosphine)butane]palladium(II) dichloride (Pd(dppb)Cl₂)⁵ as catalyst.⁶ The results are shown in the Table.

The simplest coupling to give biphenyl (entry 1) gave a 28% yield. This reaction failed completely with $Pd(PPh_3)_4^{4a}$ as a catalyst. Similarly, 3-phenylpyridine was prepared in 71% yield (entry 2), although this reaction failed completely using Pd (PPh_3)_4^{4c} (our own work has confirmed this latter result). These two results establish the greater effectiveness of the Pd(dppb)Cl₂ in this type of cross coupling.⁶ Using 2-chloro-3-nitro-

Table						
Entry	(1), (3), Ar =	(2) (X=Cl), (3) (X=Ar)	Yield 7 % a			
1	Ph	x	28			
2	թհ	x C	71			
3	Ph	x x	73			
4	Ph	x N CI	83			
5	Ph	x N	65			
6	2-PrOPh	x N N	98			
7	2-PrOPh	N N X N X N	66			
8	Ph	x (N)	78			
9	4-Pyridyl	°₂N x ⊂N	75			
10	Ph	HO	15			
11	Ph	X CN OH	0			
12	Ph		0			

ArB(OH) ₂	+	HetCl	Pd(dppb)Cl ₂	Ar-Het
(1)		(2)		(3)

pyridine as a substrate, (entry 3) a 73% yield of product was obtained and with 2,5-dichloropyridine (entry 4), selective cross-coupling at the 2-position occurs.¹⁰

Chloropyrimidines and chloropyrazines¹² (entries 5-8) also react in high yield with phenylboronic acid, and the presence of electron donating groups on the boronic acid or pyrimidine is tolerated. Bipyridine derivatives may be accessed using the π -deficient 4-pyridylboronic acid (entry 9).

Disappointingly, although a low yield of the required product was obtained with 2-chloro-3-hydroxypyridine (entry 10), cross-coupling using substrates containing labile hydrogens were largely unsuccessful, (entries 11, 12). One additional point of note is that in contrast to the unsuccessful examples referred to above using $Pd(PPh_3)_4$ as catalyst, we have observed a successful reaction between 2-propoxyboronic acid and 4-benzyloxy-2-chloropyrimidine using $Pd(PPh_3)_4$.¹³

In summary, we believe that the successful use of the range of π -deficient heteroaryl chlorides shown in the Table considerably expands the scope and utility of this cross-coupling methodology.

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Table Footnote

a. Refers to isolated yield. Conditions: (2), 1.0 mmol; (1), 1 - 1.3 mmol; 3 - 5 mol % Pd(dppb)Cl₂ at reflux for 2 - 24 hr; for entries 1 - 9 and 12, reactions were carried out in a mixture of toluene (2 - 3 ml), water (1 ml) and ethanol (0.5 ml), containing sodium carbonate (2 mmol); for entries 9 - 11, reactions were carried out in a mixture of DME (2 - 3 ml) and water (1 ml) containing sodium bicarbonate (3 mmol). All reactions were performed on a 1 - 10 mmol scale. Satisfactory analytical data was obtained on all compounds prepared.

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