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Base Effect on the Cross-coupling of Bulky Arylboronic Acid with Halopyridines

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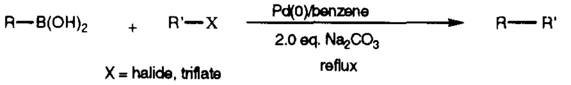
Abstract: Base has been shown to have a remarkable effect on acceleration of the rate of Suzuki coupling of sterically bulky boronic acid with halopyridines in non-aqueous solvent.

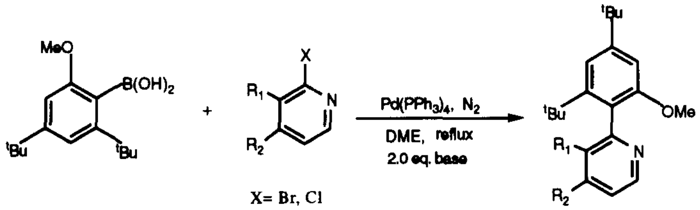
Palladium-mediated cross-coupling reactions of organic electrophiles with organometallics (Li, Mg, Cu, Zn, Zr, Al, Sn, and B) are versatile methods for the formation of carbon-carbon bonds.[1] Notable among these is the Suzuki coupling[2] which is based on reactions between aryl halides and arylboronic acids in the presence of catalytic amount of Pd(0). This route is highly valuable for the synthesis of biaryls and in particular regarding unsymmetrical cases. Suzuki coupling offers the additional advantages of being largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding non toxic byproducts. As a consequence, they have been used extensively in the synthesis of natural products, nucleoside analogs, and pharmaceuticals.[3,4]



$$\text{R—B(OH)}_2 + \text{R'—X} \xrightarrow[\text{2.0 eq. Na}_2\text{CO}_3\text{, reflux}]{\text{Pd(0)/benzene}} \text{R—R'}$$

X = halide, triflate

Our interest in asymmetric catalysts using metal complexes of pyridylphenols has prompted us to utilize Suzuki cross coupling of sterically hindered arylboronic acids and halopyridines. During our initial synthetic effort for compound **6**, we did not observe any coupling products using the typical Suzuki reaction conditions with either NaOH or NaOEt.[5] Arylboronic acids with sterically hindered[6] or electron-withdrawing substitutents[7] have been known to be less successful due to the steric hindrance or competitive hydrolytic deboronation. The modified Suzuki coupling reaction conditions by Gronowitz[7] was believed to suppress deboronation by using glycol dimethyl ether (DME) as the solvent. We have observed a strong base effect upon the cross coupling in DME. The reaction of the extremely sterically bulky arylboronic acid **1** with halopyridines **2**, **3**, and **4** using the standard base (Na_2CO_3) produced either no desired products or only in very low yields with extended reaction time. Increasing the strength of base from NaOH, NaOEt to KO^{t}Bu (2 eq), the yields of products increased with shorter reaction time (Table 1).[†] It is notable that nucleophilic substitution of halopyridines was not a major interfering reaction in most cases. Over 70 % of recovery of starting materials for the synthesis of **6** using Na_2CO_3 was observed while a complex reaction mixture formed with the use of NaOEt. The tolerance of the reactants towards *the strongest base (KO^{t}Bu)* ever used in Suzuki cross-couplings is remarkable. Further applications in synthesis seem fruitful even though the underlying reason of this base effect remains unclear and awaits further experiments.[5,8]



1

2. $R_1=R_2=H$, X=Br
3. R_1=Me, R_2=H, X=Br
4. R_1-R_2=$(CH)_4$, X=Cl

5. $R_1=R_2=H$
6. R_1=Me, R_2=H
7. R_1-R_2=$(CH)_4$

Table 1. Base effect on the cross-coupling of arylboronic acid with halopyridines
Yield (%) / Time (h)

Base	5	6	7
Na_2CO_3	26 / 90	0 / 90	0 / 90
NaOH	40 / 140	22 / 24	44 / 26
NaOEt[a]	74 / 4	0 / 12	45 / 26
KO^{t}Bu[b]	86 / 4	83 / 16	77 / 10

[a] 2.0 M in EtOH; [b] 2.0 M in ^{t}BuOH

In conclusion, we have shown that the Suzuki cross couplings between the extremely sterically bulky arylboronic acid **1** with halopyridines have been successfully carried out using a strong base of KO^{t}Bu to give highly hindered pyridylphenols. Further applications of these ligands in asymmetric catalysis will be reported soon.

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† Satisfactory analytic data was obtained for all new compounds.

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