The Palladium Catalysed Suzuki Coupling of 2- and 4-Chloropyridines

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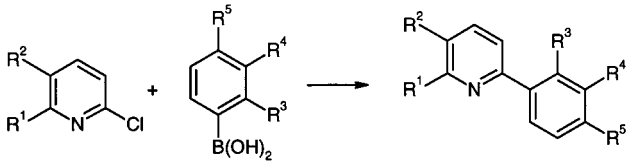
Received 16 October 1998

Abstract: The Suzuki coupling of 2- and 4-chloropyridines with arylboronic acids is successfully performed under $Pd(PPh_3)_4$ catalysis. Moderate to good yields are obtained with 4-chloropyridines while 2-chloropyridines give excellent yields. The corresponding pyridine N-oxides react in the same manner. An easy and cheap access to arylpyridines, a class of compound with medicinal interest, is thus achieved.

Key words: chloropyridines, Suzuki coupling, biaryl, palladium

The current interest in 2- and 4-arylpyridines is based on their pharmacological activities and their potential usefulness as therapeutic agents for the treatment of various diseases.[1-3] They have been studied as cardiotonic agents,[4] gastric secretion inhibitors,[5] potential reactivators of acetylcholinesterase poisoned with organophosphorus compounds[6] and have been used as intermediates for the preparation of 6-arylpyridine semicarbazone insecticides.[7] During the course of chemical development activities, we became interested in 4-aryl-2-carboxypyridines and required a short synthesis that would allow making large quantities of compounds via an ecologically sound and safe process.[8] The Suzuki coupling is a powerful tool for the synthesis of substituted biaryls. High yields are obtained when using aryl bromides, iodides or triflates as coupling partner with boronic acids.[9] Usually, aryl chlorides do not react except when they are activated with electron-withdrawing groups.[10,11] Since chloropyridines are readily available and are "activated" aryl chlorides, we became interested in studying their reactivity in the palladium catalysed Suzuki coupling. The interest in using aryl chlorides in cross-coupling reactions stems from the fact that they are both the least expensive and the most widely available aryl halides. In the case of 2- and 4-halopyridines, the chloro compounds show a better stability in comparison with the bromo or iodo derivatives. Many of the methods used to include aryl chlorides in catalysed carbon-carbon bond-forming reactions are limited by the need for substrates that are activated by electron-withdrawing substituents[11,12] or by complex transition metal fragments.[13] We report here that simple 2- and 4-chloropyridines react smoothly in $Pd(PPh_3)_4$ catalysed Suzuki coupling.

We first investigated the coupling of 2-chloropyridine with phenylboronic acid (Scheme 1). Under standard conditions[14] (toluene, K_2CO_3, 5% $Pd(PPh_3)_4$) 80% conversion was obtained after 18h at reflux (Table 1, entry 1). Anhydrous conditions[15] (DMF, K_3PO_4) proved to be inferior (entry 2). Finally, the Gronowitz conditions[16] (DME, K_2CO_3, 5% $Pd(PPh_3)_4$) gave the best result (entry 3). The reaction was scaled up to 10 g and $Pd(OAc)_2$ was a used as a cheaper source of palladium, yielding 81% of analytically pure 2-phenylpyridine (entry 4).[17] Arylboronic acids bearing electron-withdrawing groups (entry 5) or electron-donating groups (entry 8–10) gave good yields of biaryls. We also compared the reactivity of 2-chloro-5-nitropyridine with that of 1-chloro-4-nitrobenzene.[18] The pyridine substrate was completely consumed after 2 hours at reflux, yielding 78% of biaryl (entry 6), whereas the benzene halide had only reacted to 70% extent after 8 hours. This clearly demonstrated the activating effect of the nitrogen on the aromatic ring.



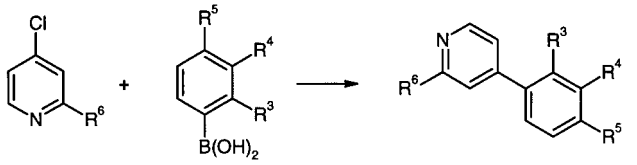
Scheme 1

Table 1. 2-Chloropyridines in Pd catalysed Suzuki coupling

Entry	R^1	R^2	R^3	R^4	R^5	Yield% (GC%)	Conditions
1	H	H	H	H	H	- (80)	A
2	H	H	H	H	H	- (60)	B
3	H	H	H	H	H	71 (90)	C
4	H	H	H	H	H	81	D[a)]
5	H	H	H	H	CF_3	63 (90)	C
6	H	NO_2	H	H	H	78 (95)	C[b)]
7	CH_3	H	H	H	H	75 (90)	C
8	H	H	OMe	H	H	75 (95)	C[a)]
9	H	H	H	OMe	OMe	83 (90)	C
10	CH_3	H	OMe	H	H	46 (60)	C

Unless specified, all compounds were purified by chromatography on silica gel. Yields are for pure isolated products, GC yields are conversion measured on the crude reaction mixture. ^{1}H-NMR, ^{13}C-NMR, GC-MS, IR and combustion analysis are in agreement with all the structures. Conditions: A: Toluene/H_2O/EtOH, K_2CO_3, 5% $Pd(PPh_3)_4$,↑↓18h. B: DMF, K_3PO_4, 5% $Pd(PPh_3)_4$, 100°C. C: Dimethoxyethane (DME)/H_2O, K_2CO_3, 5% $Pd(PPh_3)_4$, ↑↓18h. D: DME/H_2O, K_2CO_3, 2.5% $Pd(OAc)_2$, 10% PPh_3. (a) isolated by distillation. (b) reaction completed after 2 hours.

4-Chloropyridine was also treated with arylboronic acids using $Pd(PPh_3)_4$ as a catalyst (Scheme 2). Although the reaction was slower than in the 2-chloro series, the yields



Scheme 2

were good to moderate with both electron rich (Table 2, entry 1-3) or electron poor arylboronic acids (entry 4).

We next focused our attention to the coupling of 4-chloropicolinic acid derivatives[19] with phenylboronic acid (Table 2, entry 5-10). The methyl ester was hydrolysed under basic aqueous conditions and no biaryl product was obtained (entry 5). Under anhydrous fluoride mediated coupling conditions[20], the expected product was obtained but in only 50% yield (entry 6). The *t*-butyl ester was stable and yielded 81% of biaryl under standard procedure (entry 7). N-methyl 4-chloropicolinamide reacted smoothly with 1% $Pd(OAc)_2$/4 P(*o*-tolyl)$_3$, reaching 97% conversion after 20 hours and gave 63% of biaryl (entry 8). Interestingly, the iodo derivative did not react faster under the same reaction conditions.

Table 2. 4-Chloropyridines in Pd catalysed Suzuki coupling

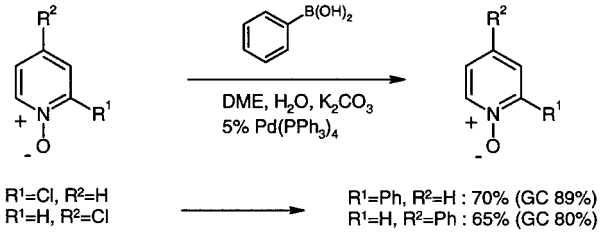
Entry	R^6	R^3	R^4	R^5	Yield% (GC%)	Conditions
1	H	H	H	H	63 (80)	A[a)]
2	H	OMe	H	H	75 (90)	A[a)]
3	H	H	OMe	OMe	65 (78)	A[b)]
4	H	H	H	CF_3	57 (90)	A
5	CO_2Me	H	H	H	0	A[c)]
6	CO_2Me	H	H	H	50 (70)	B
7	CO_2t-Bu	H	H	H	81 (95)	C
8	CONHMe	H	H	H	63 (97)	D[d)]
9	CONHMe	H	H	H	- (16)	E
10	CONHMe	H	H	H	- (63)	F

Unless specified, all compounds were purified by chromatography on silica gel. Yields are for pure isolated products, GC yields are conversion measured on the crude reaction mixture. ^{1}H-NMR, ^{13}C-NMR, GC-MS, IR and combustion analysis are in agreement with all the structures. Conditions: A: DME/H_2O, K_2CO_3, 5% $Pd(PPh_3)_4$, ↑↓18h. B: CsF, DME, $Pd(OAc)_2$, P(*o*-tolyl)$_3$. C: DME/H_2O, K_2CO_3, 5% $Pd(OAc)_2$, 20% P(*o*-tolyl)$_3$, ↑↓5h. D: DME/H_2O, K_2CO_3, 1% $Pd(OAc)_2$, 4% P(*o*-tolyl)$_3$, ↑↓20h. E: DME/H_2O, K_2CO_3, 1% $Pd_2(dba)_3$, ↑↓15h. F: DME/H_2O, K_2CO_3, 1% $Pd(OAc)_2$, 0.5% CuI, 4% P(*o*-tolyl)$_3$, ↑↓20h. (a) ClC_5H_4N.HCl was used. (b) purified via its HCl salt. (c) Hydrolysis of starting material. (d) Purification yield not optimised.

Recently, phosphine-free catalytic systems have been claimed as a major improvement of the Suzuki coupling.[21] When the reaction of N-methyl 4-chloropicolinamide with phenylboronic acid was conducted with 0.5% $Pd_2(dba)_3$ (1% Pd(0)) and no ligand, only 16% conversion was observed after 20 hours at reflux (entry 9). The picolinamide probably binds to the palladium(0) and forms an unproductive complex.[22] Upon addition of P(*o*-tolyl)$_3$ (4%), the reaction was accelerated but did not go above 50% conversion.

Another recent improvement in the palladium catalysed cross-coupling reaction is the observation of an accelerating "copper effect" in the Stille coupling[23a] which was also reported for the Suzuki coupling of some 4-trifluoromethylsulfonyloxycoumarins.[23b] We therefore treated N-methyl 4-chloropicolinamide with phenylboronic acid under catalysis of a copper/palladium mixture (1% $Pd(OAc)_2$, 0.5% CuI, 4% Pd(*o*-tolyl)$_3$). The coupling proceeded twice as fast in the presence of copper during the first hour but it then slowed down. The addition of another 0.5% CuI had no effect and only 63% conversion was obtained after 20 hours at reflux (entry 10).

Lastly, 2- and 4-chloropyridine N-oxide were reacted with phenylboronic acid (DME/H_2O/K_2CO_3/5% $Pd(PPh_3)_4$) to give 2- and 4-phenylpyridine N-oxide, in 70% and 65% yield respectively (Scheme 3). No reaction was observed when $Pd(OAc)_2$/PPh_3 was used.



Scheme 3

During the course of our studies, we also made the following interesting observation. Due to its cost and oxidative lability, tetrakis(triphenylphosphine)palladium (0) is unsuitable for a large-scale process and it was our goal to replace it by in-situ generated Pd(0). Amatore et al. have shown that one equivalent of triphenylphosphine is oxidised to triphenylphosphine oxide during the reduction of palladium acetate to Pd(0).[24a] Indeed, when we used $Pd(OAc)_2$ in combination with PPh_3 as a catalyst system, we always observed the formation of the phosphine oxide[25] (GC-MS, HPLC). However, when the more crowded tri-*o*-tolylphosphine was used as a ligand, we never observed the formation of its oxide. Instead, a stoichiometric amount (based on palladium) of biphenyl was reproducibly obtained by dimerisation of the arylboronic acid.[26] Thus, it appears that, in the case of P(*o*-tolyl)$_3$, it is not the phosphine but the boronic acid that reduces $Pd(OAc)_2$ to Pd(0).[27]

Recently, new palladium catalysts[13d] and nickel catalysts[13b] have allowed the Suzuki coupling of chloroarenes in good yields. Chloropyridines incorporating electron withdrawing substituants were also shown to react smoothly when using $Pd(dppb)Cl_2$.[12e] We could demonstrate that simple 2- and 4-chloropyridines were reactive enough to give good yields of biaryls under $Pd(PPh_3)_4$ catalysis. The reaction was easy to scale up and $Pd(PPh_3)_4$ could then advantageously be replaced by in situ generated Pd(0) from $Pd(OAc)_2$ and PPh_3, which showed even greater reactivity.[24b] 4-Chloropicolinic acid derivatives

were shown to be particularly good substrates for palladium catalysed Suzuki coupling.

Acknowledgement

We thank K. Killius and M. Weibel for their technical assistance and A. Brodbeck for the preparation of large quantities of 4-chloropicolinic acid.

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Typical procedure: 10 g 2-chloropyridine (1 eq.; 88.1 mmol), 12.9 g phenylboronic acid (1.2 eq.; 105.8 mmol) and 2.31 g triphenylphosphine (0.1 eq.; 8.81 mmol) were dissolved in 1,2-dimethoxyethane (100 mL). 120 mL of a 2M K_2CO_3 (2.7 eq.; 240 mmol) aqueous solution were added and the mixture was purged with argon. Palladium acetate (0.494 g; 0.025 eq.) was added and the mixture was refluxed for 18 hours. The two phases were then separated and the aqueous phase was extracted with ethyl acetate (3X 250 mL). The combined organic phases were washed with water (250 mL) and brine (250 mL) and were dried over $MgSO_4$. After evaporation of the solvent, the oily residue was purified by bulb-to-bulb distillation (110°C, 1 mbar) to afford 11.15 g of pure 2-phenylpyridine (81 %).

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