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Palladium-catalysed amination of halopyridines on a KF-alumina surface

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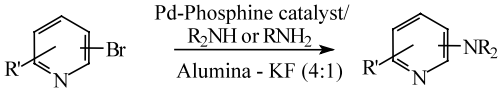
Abstract—Palladium-catalysed C–N hetero cross-coupling reactions between bromopyridines and amines (both primary and secondary) can be efficiently performed on a KF-alumina (basic) surface, thus negating the use of strong bases such as sodium *tert*-butoxide. The reaction conditions are optimised with reference to catalytic systems, solvents and the surface.

Aminopyridines are versatile intermediates for synthetic transformations to biologically active compounds[1] and are known to act as central nervous system stimulants.[2] Their derivatives are often used as ligands in coordination and organometallic chemistry,[3] and have found industrial applications as fluorescent dyes.[4] Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[5] These methods either suffer from a nucleophilic regiocontrol problem, the need for very high temperature or the presence of specific functionality on the heterocyclic ring. None of these methods show a combination of good yields and high selectivity. Buchwald and others[6] have recently developed chelating bis-phosphine-palladium catalysed cross-coupling reactions that allow the preparation of aminopyridines from their corresponding halopyridines.[7] The method involves Pd(0)/bis-phosphine complexes as the effective catalyst for oxidative addition to the carbon–halogen bond, followed by coupling with the amine. The amination is catalyst-specific (Pd–ligand complexes) and very sensitive to the nature of the base.[6a,d] Although this reaction efficiently produces aminopyridines in the presence of chelating bis-phosphine/Pd(0) complexes, the use of strong bases such as sodium *tert*-butoxide is not desirable and remains associated with problems such as in the case of direct amination using NaNHR or $NaNR_2$.[5,8] Furthermore, the use of strong bases greatly limits the functional group tolerance of the process.[9]

The weaker base (Cs_2CO_3) has been employed for haloaromatics[9] and halothiophenes,[10] but not in the case of halopyridines and its use is limited due to high solubility in organic solvents and its hygroscopic nature. Since the use of a base is one of the keys to the success of this coupling reaction, we investigated palladium-catalysed cross coupling of bromopyridines and amines on a KF-alumina (basic) surface. KF-alumina has been successfully employed in many other cases so as to exploit its basicity on the surface[11] and very recently Pd-catalysed C–C couplings (Suzuki, Heck, Stille, Trost-Tsuji) have been reported using KF-alumina under mono-mode microwave irradiation.[12] This report describes our results, which constitute a convenient and efficient heterogeneous method for C–N coupling by Pd-catalysed amination of halopyridines on KF-alumina (basic) surface (Scheme 1).

As can be seen from the results presented in Table 1, the amination on KF-alumina surface works with different bromopyridines. While 2-bromopyridine (entries 1 and 2) reacts with different amines smoothly, 3-bromopyridine (entry 7) undergoes amination in relatively poor yield. Amination of dibromopyridines affords only monoamine derivatives in good to excellent yields. In the case of 2,5-dibromopyridine (entries 8 and 9), amination occurs selectively at the 2-position. Buch-



(*o*-Tolyl)$_3$P, DPPF, BINAP; Pd-sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

Scheme 1.

Keywords: aminopyridines; palladium catalyst; carbon–nitrogen cross coupling; KF-alumina.

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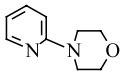
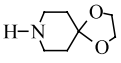
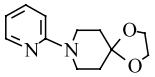
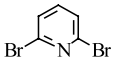
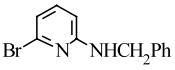
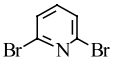
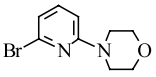
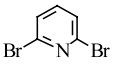
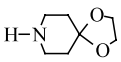
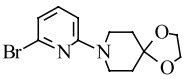
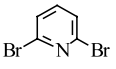
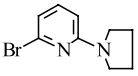
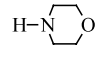
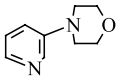
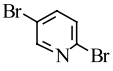
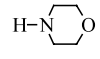
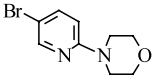
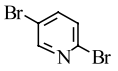
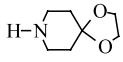
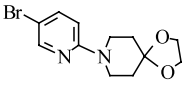
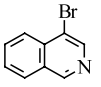
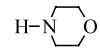
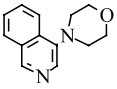
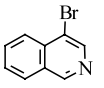
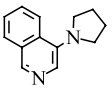
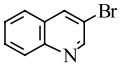
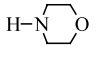
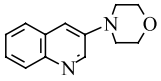
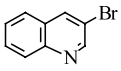
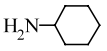
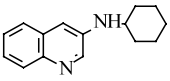
Table 1.

Entry	Bromoarene	Amine	Catalyst	Conditions[b]/ time (h)	Product	Yield(%)[c]
1			[A]	2 / 8		70
2			[A]	2 / 8		58
3		H_2NCH_2Ph	[H]	2 / 8		90
4			[A]	1 , 2 / 5		78
5			[A]	2 / 5		62
6			[A]	2 / 5		91
7			[F]	1 , 2 / 9		48
8			[A]	1 , 2 / 5		92
9			[A]	2 / 5		73
10			[E], [F]	1 , 2 / 6		86
11			[F]	2 / 6		90
12			[F]	2 / 6		78
13			[F]	2 / 8		68

[a] [A] Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$; [B] Pd$_2$(dba)$_3$ - P(*o*-tolyl)$_3$; [C] Pd [PPh$_3$]$_4$; [D] Pd$_2$(dba)$_3$ - dppf; [E] Pd(OAc)$_2$ - dppf ; [F] Pd$_2$(dba)$_3$ - BINAP ; [G] Pd(acac)$_2$ - dppf ; [H] Pd(OAc)$_2$ - BINAP

[b] 1. Alumina - KF in Toluene / 90 - 100 ^{0}C; 2. Alumina - KF without solvent at 90-100 ^{0}C.

[c] Yields are reported on the basis of pure isolated products (2-3 runs) and calculated on the basis of recovered starting material (for entries **6**, **7**, **9**).

wald observed complete bis-amination of 2,6-dibromopyridine using Pd$_2$(dba)$_3$-dppe catalyst in the presence of excess amine.[7a] Our conditions, however, yielded monoamines as the major products even after prolonged reaction times and in the presence of excess amine (entries 3–6). This selectivity offers an advantage for further reaction with the other halogen substituents. In the bicyclic systems, 4-bromoisoquinoline (entries 10 and 11) and 3-bromoquinoline (entries 12 and 13) undergo amination efficiently.

A great deal of experimentation on the cross coupling of bromopyridines with primary and secondary amines was carried out in order to optimise the reaction conditions. Palladium sources, ligand, solvent and the support (KF-Al$_2$O$_3$) were optimised and several details are worthy of comment. Firstly, different palladium sources like PdCl$_2$, Pd(OAc)$_2$, Pd$_2$(dba)$_3$, Pd(acac)$_2$ and Pd[PPh$_3$]$_4$ complexing with either mono-phosphine [(*o*-tolyl)$_3$P] or bis-phosphines (BINAP and DPPF) were employed as the catalytic systems. The Pd[(*o*-

tolyl)$_3$P]$_2$Cl$_2$ and Pd$_2$(dba)$_3$/BINAP complexes were found to be most effective in this amination process (Table 1). The formation of bis-(pyridyl) complexes using monophosphine ligands, as proposed by Buchwald,[7a] might possibly be avoided under these conditions. The reactions were carried out with or without a solvent. Clean reactions and better yields of the aminopyridines were obtained when the reactions were carried out on KF-Al_2O_3 surface with a slight excess of amine and without solvent. Toluene and xylene have been used as solvents with almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination (entry 10). 2-Bromopyridine (entries 1 and 2) also yields 10–15% of 2,2′-bipyridyls by intermolecular coupling and such coupling is further increased in the presence of a solvent. The major limitations of this protocol are that 3-bromopyridine fails to cross-couple with primary amines and partial dehalogenation (<5%) was observed in the case of 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline.

In conclusion, we have shown that Pd(0) catalysed amination of bromopyridines can be performed smoothly on the surface of basic alumina admixed with KF. The simplicity of the experimental conditions, good to excellent yields and favourable safety aspects represent a significant improvement and useful extension relative to Buchwald's procedure using the strong base, sodium *tert*-butoxide. Future work will include studies with more base-sensitive functionalities on the heterocyclic nucleus as well as with chiral amines.

Experimental

General procedure

Preparation of activated Al_2O_3/KF: A mixture of basic alumina (Activity I according to Brockmann) and KF (4:1) (5 g) was taken in THF (5 mL) and after stirring for 30 min at room temperature it was evaporated to dryness. The solid residue was heated at 250°C under vacuum (0.5 mm of Hg) for 4 h, cooled under N_2 and used for reaction.

To a mixture of 2,6-dibromopyridine (473 mg, 2 mmol), benzylamine (856 mg, 8 mmol), Pd(OAc)$_2$ (10 mg, 0.04 mmol) and (±) BINAP (50 mg, 0.08 mmol) was added activated Al_2O_3/KF (2 g). The mixture was intimately stirred at 90–100°C for 8 h under nitrogen. After cooling to room temperature the semi-solid mass was washed repeatedly with ether (4×15 ml), combined and concentrated. The residue was purified by silica gel column chromatography (petroleum-ether:EtOAc = 20:1) to give 2-benzylamino-6-bromopyridine (475 mg, 90%); mp 85°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.46 (d, 2H, J = 5.9 Hz), 5.18 (br.s, 1H), 6.24 (d, 1H, J = 8.2 Hz), 6.73 (d, 1H, J = 7.5 Hz), 7.20 (dd, 1H, J = 8.2; 7.5 Hz), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.3, 104.5, 116.1, 127.3, 127.4, 128.7, 138.3, 139.5, 140.2, 158.7.

Acknowledgements

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