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Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 2-pyridyl trifluoroborate with aryl (heteroaryl) halides

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ABSTRACT

Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium pyridine-2-trifluoroborates and various aryl (heteroaryl) halides can generate the corresponding desired coupling products with moderate to good yields. It can be carried out under the conditions with ethanol as solvent, $Pd(OAc)_2$ and SPhos as catalyst system and Na_2CO_3 as a base.

1. Introduction

Substituted heterobiaryls widely exist in natural products, pharmaceutically active molecules, agrochemicals and functional materials, and are mainly prepared by transition-metal-catalyzed cross-coupling reactions,[1,3] such as Kumada–Corriu cross-coupling,[2] Stille cross-coupling,[3] Negishi cross-coupling[4] or Suzuki–Miyaura cross-coupling.[5] Among the various cross-coupling reactions, Suzuki–Miyaura reaction has become an indispensable instrument for preparing these compounds owing to its tolerance of a wide range of functional groups, high stability, relatively low toxicity and ready availability of organoboron compounds.[6]

Considerable efforts have been made to develop metal–ligand catalyst systems that facilitate the Suzuki–Miyaura cross-coupling reaction and increase its scope.[7] In these known reports, the cross-coupling reaction of 2-pyridyl boron-based nucleophiles under palladium catalysis is inherently difficult due to their propensity to decompose via protodeboronation.[8] Regarding Suzuki–Miyaura reaction of 2-pyridyl nucleophiles with aryl halides, only aryl iodides have been demonstrated as suitable coupling partners in the few published reports.[5,9] Recently, some new catalytic system has been developed. Li and co-workers have reported cross-coupling reaction of 2-pyridylboronic esters with aryl bromides by using palladium phosphine chloride and oxide catalysts under Suzuki–Miyaura conditions.[10] Deng and co-workers have reported cross-coupling reaction of 2-pyridylboronic esters with aryl bromides by using palladium acetate and 1,1′-bis(diphenylphosphino) ferrocene with copper (I) halide as additive under Suzuki–Miyaura conditions.[11] And to address this problem, many important surrogates have been developed, including trialkoxy or trihydroxyborate salts, diethanolamine adducts, sterically bulky boronic esters and boroxines.[8,9,12] These methods can perform well for special substrates, but for heteroaryl halides and less expensive substrates, such as aryl chlorides, there is still a lot of challenge. In 2009, Burke and co-workers successfully applied the coupling of 2-pyridyl MIDA boronate with aryl chlorides to get moderate to good yields by using a slow-release strategy to circumvent the instability problems of 2-pyridylboronic acids.[13]

In recent years, organotrifluoroborates have become an important nucleophilic reagent in Suzuki–Miyaura cross-coupling, and it has been widely used due to its stability to air and moisture. Besides, this kind of potassium trifluoroborates can be easily made from a wide variety of organoboron reagents together with inexpensive potassium hydrogen fluoride (KHF_2). For the most part, these salts can be easily purified by recrystallization, precipitation, or Soxhlet extraction.[14–16] Byproducts of the cross-coupling of organotrifluoroborates with organic halides are inorganic salts, which are readily separable from the desired products. However, regarding the direct coupling of potassium pyridine-2-

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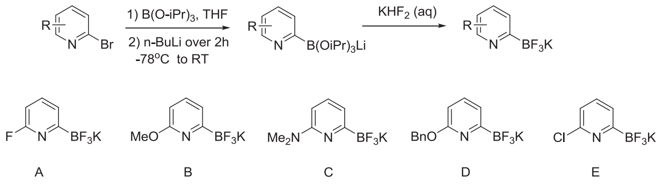
trifluoroborate with aryl halides, there were only two reports previously and the study results were not optimized.[6d,15,16] Therefore, we synthesized a series of potassium pyridine-2-trifluoroborates based on literature methods[16] (Scheme 1). The catalytic system composed of $Pd(OAc)_2$ and SPhos efficiently promotes cross-coupling reactions of various potassium pyridine-2-trifluoroborates with aryl halides and heteroaryl halides, allowing these coupling processes to produce moderate to good yields.

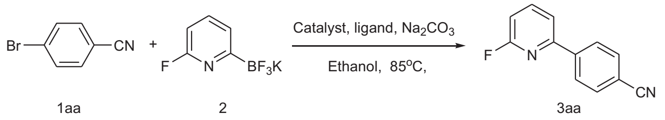


Scheme 1. Synthesis of potassium 2-pyridyltrifluoroborates.

2. Results and discussion

To find optimal cross-coupling conditions for potassium pyridine-2-trifluoroborate with aryl and heteroaryl halides, the coupling between potassium 6-fluoropyridine-2-trifluoroborate and 4-bromobenzonitrile is chosen as a model reaction under the conditions with ethanol as solvent at 85 °C in an oil bath and Na_2CO_3 as a base (as shown in Table 1), with the aim of testing the catalytic activity of different catalysts and ligands (Fig. 1). As seen from Table 1, the combination of $Pd(OAc)_2$ and PPh_3, PCy_3, DavePhos, CyJohnPhos, RuPhos or XPhos generates moderate yields (Table 1, entries 1–6). When SPhos was used as ligand, 83% yield was offered (Table 1, entry 7). When 2 mol % of the catalyst loading was used, the coupling yield was decreased. But the yield was not improved significantly when the catalyst loading was increased to 5 mol %. So 3 mol % loading of catalyst $Pd(OAc)_2$ and 6 mol % SPhos was fixed. Under the same catalytic system, when the equiv of potassium pyridine-2-trifluoroborate was decreased to 1.5 equiv, the yield was comparative lower. Next, the catalyst was changed to a Pd source of $Pd_2(dba)_3 \cdot CHCl_3$, resulting in an 83% yield of **3aa** (Table 1, entry 11). $Pd(OAc)_2$ is chosen as Pd source for this reaction because it is cheaper than $Pd_2(dba)_3 \cdot CHCl_3$.

Table 1
Screen of catalysts and ligands for the cross-coupling of potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile[a]



Entry	Catalyst	Ligand	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	67
2	$Pd(OAc)_2$	PPh_3	72
3	$Pd(OAc)_2$	DavePhos	67
4	$Pd(OAc)_2$	CyJohnPhos	63
5	$Pd(OAc)_2$	XPhos	76
6	$Pd(OAc)_2$	RuPhos	63
7	$Pd(OAc)_2$	SPhos	83
8	$Pd(OAc)_2$	SPhos	61[c]
9	$Pd(OAc)_2$	SPhos	85[d]
10	$Pd(OAc)_2$	SPhos	71[e]
11	$Pd_2(dba)_3 \cdot CHCl_3$	SPhos	83

[a] All reactions are based on 4-bromobenzonitrile (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), catalyst (3 mol %), ligand (6 mol %), Na_2CO_3 (0.50 mmol), ethanol (2.0 ml), 85 °C, 16 h.
[b] Isolated yield based on **1aa**.
[c] Catalyst (2 mol %), ligand (4 mol %).
[d] Catalyst (5 mol %), ligand (10 mol %).
[e] Potassium 6-fluoropyridine-2-trifluoroborate (0.375 mmol).

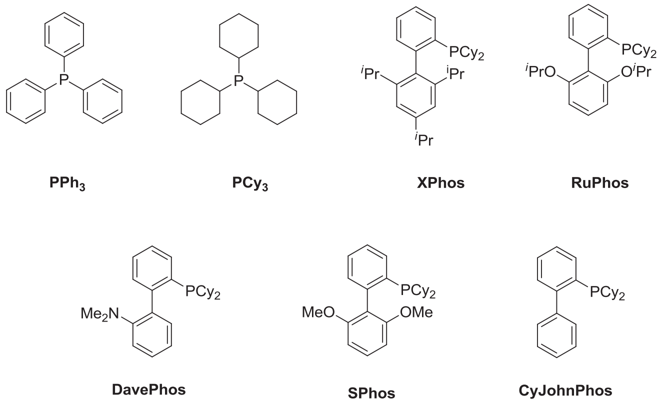
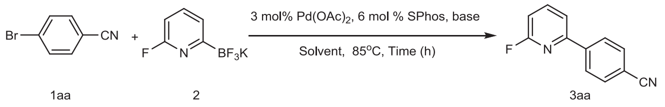


Fig. 1. The structure of phosphine ligands.

To examine the influence of bases and solvents, the potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile was also chosen as the model reaction by fixing 3 mol % loading of $Pd(OAc)_2$ and 6 mol % SPhos. Various bases, such as $NaHCO_3$, Cs_2CO_3, K_3PO_4, K_2CO_3, Na_2CO_3 were examined in the reaction. When Cs_2CO_3 and Na_2CO_3 were used as base, the excellent yield was obtained (Table 2, entries 4 and 5). It was found that the solvent played a critical role on the reaction efficiency (Table 2) by using dioxane and THF as solvent, only lower yield of **3aa** was obtained (Table 2, entries 6 and 7). DMSO, DMF and isopropanol also offer moderate yields in this reaction (Table 2, entries 8 and 9). The desired product was obtained in 83% when ethanol was used as solvent (Table 2, entry 5), and water does not improve this reaction. Moreover, the yield was not improved evidently by prolonging the reaction time from 16 h to 18 h (Table 2, entry 5 vs 12). So, the combination of 3 mol % $Pd(OAc)_2$ and 6 mol % SPhos in ethanol in the presence of Na_2CO_3 at 85 °C in an oil bath is chosed as optimum conditions.

Table 2
Screen of solvents and bases for the cross-coupling of potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile[a]



Entry	Base	Solvent	t/h	Yield[b] (%)
1	$NaHCO_3$	Ethanol	16	78
2	$K_3PO_4 \cdot 7H_2O$	Ethanol	16	80
3	K_2CO_3	Ethanol	16	81
4	Cs_2CO_3	Ethanol	16	83
5	Na_2CO_3	Ethanol	16	83
6	Na_2CO_3	Dioxane	16	14
7	Na_2CO_3	THF	16	30
8	Na_2CO_3	DMF	16	68
9	Na_2CO_3	DMSO	16	77
10	Na_2CO_3	Isopropanol	16	68
11	Na_2CO_3	Ethanol/H_2O (4:1)	16	81
12	Na_2CO_3	Ethanol	18	83

[a] All reactions are based on 4-bromobenzonitrile (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), 3 mol % $Pd(OAc)_2$, 6 mol % SPhos, 0.50 mmol base, 2.0 ml solvent, 85 °C (oil bath), 16 h.
[b] Isolated yield based on **1aa**.

Under the optimized reaction conditions, we extended Suzuki–Miyaura cross-coupling reaction of potassium 6-fluoropyridine-2-trifluoroborate and various aryl halides. It can be seen from Table 3 that the optimized reaction conditions tolerate a variety of functional groups, including acetyl, cyano, nitro, keto, trifluoromethyl and methyl (Table 3, entries 1–11). Moreover, a series of aryl bromides, which contain different substitution groups, such as electron-