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Synthesis of (pyridin-2-yl)hydrazine conjugates as bifunctional chelates using the Suzuki–Miyaura reaction

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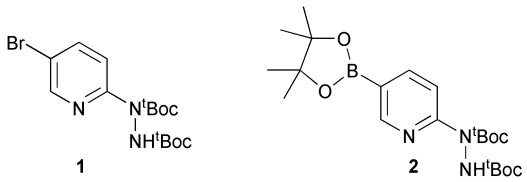
Palladium catalyzed C–C couplings were used to connect (pyridin-2-yl)hydrazine to organic substrates, including a phenylalanine derivative, providing a new method for introducing this important ligand.

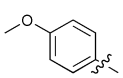
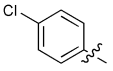
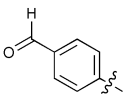
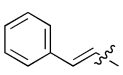
There is currently a great deal of interest in the development of receptor-targeted Tc-99m radiopharmaceuticals for medical diagnostic imaging applications.[1] The bifunctional chelate approach involves conjugation of a receptor ligand with a linking molecule that possesses a chelating moiety for metal coordination. The synthesis of hydrazinonicotinamide (HYNIC) conjugates has been widely applied to the Tc-99m labeling of proteins.[2] Hydrazinopyridine ligands are known to form stable complexes with Tc(III,IV) and the activated succinimidyl ester of 6-hydraziniumnicotinate is an effective bifunctional chelate for coupling to amine groups. (Pyridin-2-yl)hydrazine also coordinates $[^{99m}Tc(H_2O)_3(CO)_3]^+$ rapidly and quantitatively, even at stoichiometric μm concentrations.[3] Our goals to develop targeted radiopharmaceuticals from organic receptor ligands were not amenable to the HYNIC approach due to the absence of free amine groups for conjugation. We therefore sought an alternative method for the synthesis of (pyridin-2-yl)hydrazine conjugates based on organometallic C–C coupling reactions. We recently reported the direct synthesis of (5-bromo-pyridin-2-yl)hydrazine **1** by the Pd-catalyzed amination of 2,5-dibromopyridine with di-*tert*-butylhydrazodiformate.[4] Herein, we describe the palladium-catalyzed Suzuki–Miyaura reaction of **1** with aryl- and vinyl-boronic acids; while a series of halides, including a phenylalanine derivative, were coupled with boronate **2**.



Suzuki–Miyaura reactions using a variety of Pd/phosphine ligand combinations have been effective for C–C coupling reactions between a wide range of aryl- and vinyl-boronic acids and halides, including heterocyclic substrates.[5] The exclusion of oxygen is necessary, but the couplings are conveniently performed using aqueous systems, an obvious advantage for derivatization of biomolecules. Initially, we were aware that the presence of the (pyridin-2-yl)hydrazine moiety in substrate **1** adds additional complications due to its strong ligating properties and sensitivity towards oxidation. There are few reported examples of Pd-catalyzed couplings with hydrazine substrates.[6] We investigated a variety of conditions for the reaction of 4-methoxyphenylboronic acid with **1** and compared these results with 3-bromopyridine. The catalyst system $Pd(0)(PPh_3)_4$in aqueous $NaHCO_3$ 1,2-dimethoxyethane (DME) was very efficient for the coupling of 3-bromopyridine (93%), but resulted in degradation of the starting compound **1** and only trace amounts of the desired product **3b** were evident (< 5%).[7] A similar trend was observed for the "ligand free" reaction conditions using $Pd(OAc)_2$ in aqueous K_2CO_3 with tetrabutylammonium bromide (89%), while the desired product of **1** was isolated in low yield (17%).[8] The oxime-carbapalladacycle catalyst also proved to be compatible with the simple pyridyl-substrate (96%). The yield of this reaction conducted in the presence of 10 mol% hydrazine **1** was dramatically reduced (14%). These conditions were ineffective for the coupling of **1**.[9] The possibility for disruption of the catalytic cycle initiated by complexation of palladium with **1** suggested that chelating phosphine ligands would better facilitate the desired coupling. Moderate yields of **3b** were obtained using the catalyst precursor $Pd(OAc)_2$ in DMF with the chelating ligands 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (XANTPHOS) (42%, 63%) respectively. However, both pre-catalysts $Pd(OAc)_2$ and $PdCl_2$ with ligand 1,1′-bis(diphenylphosphino-)ferrocene (dppf) provided efficient systems for coupling **1** to produce **3b** (> 80%).[10] The procedure was optimized using commercially available catalyst, $PdCl_2dppf{\cdot}CH_2Cl_2$, to give the product **3b** in excellent yield (97%).

The $PdCl_2$/dppf catalyst system was used to couple **1** with a broad range of boronic acid substrates [eqn. (1)] as shown in Table 1. The reaction was successful using electroneutral, electron-rich, and electron deficient aryl-, heteroaryl-, and vinyl-boronic acids.

Table 1 Couplings of boronic acids with **1**

Entry	R	Compound	Yield (%)
1		**3a**	96
2		**3b**	97
3		**3c**	85
4		**3d**	89
5		**3e**	94
6		**3f**	91
7		**3g**	92
8		**3h**	81

[a] **1** (0.25 mmol), $R(BOH)_2$ (0.31 mmol), $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.01 mmol), 0.4 ml DMF, and 2 M Na_2CO_3 (0.6 ml). [b] All isolated yields.

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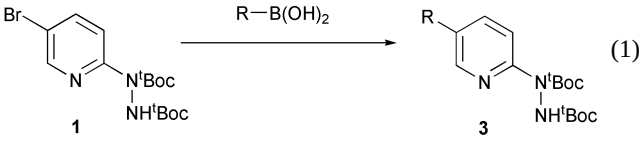
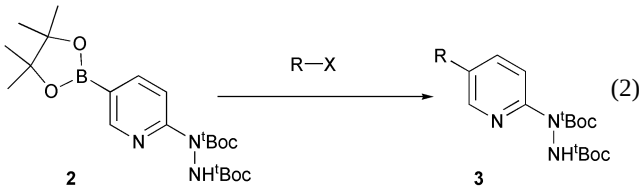


(1)

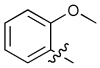
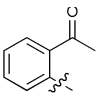
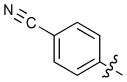
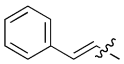
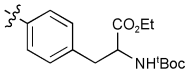
The coupling reaction was extended to aryl-, heteroaryl-, and vinyl-halide substrates [eqn. (2)] as shown in Table 2 using boronate **2**.



(2)

Two sequential additions of catalyst were necessary for complete conversion of **1** to **2** with bis-pinacolatodiboron and KOAc in DMF.[11] Attempts to prepare **2** by direct borylation with dialkoxyborane resulted in degradation of **1**.[12] The C–C couplings were conveniently accomplished by a one-pot procedure in which **2** was generated *in situ*, followed by addition of the halide substrate and Na_2CO_3 (aq).[11] The isolated boronate **2** was not stable to silica gel chromatography, but was purified by crystallization from cyclohexane. The yields for the one-pot procedure with a variety of bromo- and iodo-aryl substrates were comparable to those obtained using isolated **2**. The electron deficient 2′-chloroacetophenone was coupled effectively, but chlorobenzene was not (entries 2, 5). A 9 : 1 (*E*/*Z*) stereoisomeric mixture of β-bromostyrene produced the *E*-product in good yield with no observed *Z*-isomer (entry 8).

Table 2 Couplings of boronic ester **2**

Entry	X	R	Compound	Yield[a] (%)
1	Br		**3a**	89[b], 96
2	Cl		**3a**	15
3	I		**3a**	90[b]
4	I		**3i**	88[b]
5	Cl		**3j**	84[b]
6	Br		**3k**	82[b]
7	Br		**3g**	85[b]
8	Br[c]		**3h**	74[b,d]
9	I		**3l**	78

[a] Isolated yield. [b] **2** formed *in situ*: **1** (0.25 mmol), bis(pinacolato)diboron (0.275 mmol), KOAc (0.75 mmol), $PdCl_2dppf{\cdot}CH_2Cl_2$ (2 × 3 mol%, t = 0.4 h). After 8 h aryl halide and 2 M Na_2CO_3 (0.6 ml) was added. Total reaction time = 16 h. [c] E/Z = 7 : 1. [d] Only *E* stereoisomer detected.

Peptides constitute the majority of receptor ligands; as such, they are of great significance for Tc-99m labeling. Phenylalanine derivatives can be incorporated using standard methods for peptide synthesis and would provide a convenient site for attaching a complex. As an initial test of this approach, we investigated the one-pot coupling of 4-iodophenylalanine derivative **4**.[13] The resulting protected 4-(pyridin-2yl)phenylalanine derivative **5**, was isolated in 78% yield [eqn. (2)].

In conclusion, we have demonstrated an efficent procedure for introducing the pyridin-2-yl hydrazine group by catalytic C–C coupling. The bidentate ligand dppf was far superior to other ligands in the coupling reactions of **1** and **2**. The reactions were conducted in aqueous DMF, and were compatible with diverse functional groups. Current efforts are focused on the application of this chemistry to the synthesis of receptor-targeted radiopharmaceuticals.

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