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Microwave enhanced Suzuki coupling: a diversity-oriented approach to the synthesis of highly functionalised 3-substituted-2-aryl/heteroaryl imidazo[4,5-*b*]pyridines

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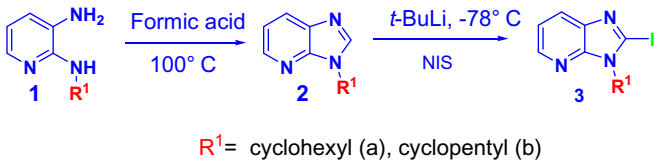
ABSTRACT

A modified approach for the synthesis of 3-substituted 2-aryl/heteroaryl imidazo[4,5-*b*]pyridines utilising palladium catalysed cross-coupling reactions under microwave enhanced conditions has been achieved. utilisation of (A-^{ta}phos)$_2$PdCl$_2$-catalysed cross-coupling reactions enables rapid derivatization of this (imidazo[4,5-*b*]pyridines) pharmaceutically relevant core. This catalytic system is compatible with a broad spectrum of arylboronic acids—electron rich, electron poor, and heteroarylboronic acids.

The synthesis of imidazo[4,5-*b*]pyridine based structures has attracted attention in recent years due to their variety of biological and pharmacological properties. Compounds incorporating this heterocyclic ring can be considered as structural analogues of purines[1] and are of interest as biologically active compounds. The heterocycles derived from these intermediates have recently been evaluated as antagonists of various biological receptors, including angiotensionII,[2] platelet activating factor (PAF)[3] and metabotropic glutamate subtype V.[3] Substituted imidazo[4,5-*b*]pyridines have also been tested for their potential as anticancer,[4] inotropic[5] and as selective antihistamine agents.[6] Imidazo[4,5-*b*]pyridine derivatives were also reported as Aurora kinases,[7] and cyclic PDE inhibitors. These data stimulated our studies on the synthesis of substituted imidazo[4,5-*b*]pyridine derivatives.

The most common methods to access these compounds are from 2,3-diaminopyridines and these diamines are condensed with carboxylic acids (or treated with an aldehyde in presence of an oxidant).[7–10] The synthesis of 3-substituted-2-aryl/heteroaryl imidazo[4,5-*b*]pyridines from N^2-substitutedpyridine-2,3-diamine and carboxylic acids utilising polyphosphoric acid at 150 °C is characterised by poor yields and difficulty in the isolation of pure products from the crude reaction mixtures. Recognising the biochemical utility of these heterocycles and the need for efficient methods to generate various numbers of differently substituted analogues, we sought out alternate synthetic methods.

The utility of palladium catalysed cross-coupling reactions has evolved to become a major foundation by which new carbon–carbon bonds are formed.[11] The inclusion of microwave heating has aided the speed and efficiency of these transformations, particularly in the case of aryl–aryl Suzuki couplings.[12–15] It was our goal to develop a synthetic method for the formation of 3-substituted-2-aryl/heteroaryl imidazo[4,5-*b*]pyridines utilising a microwave-promoted Suzuki coupling between substituted aryl/hetroaryl boronic acids and a common 3-substituted-2-iodo-3*H*-imidazo[4,5-*b*]pyridine derivative. A method for the construction of these derivatives using this approach would allow for the rapid advancement of numerous analogues via a final stage coupling from a common precursor. The commercial availability of wide range of aryl/heteroaryl boronic acids can be explored and by taking advantage of the broad functional group tolerance of the Suzuki–Miyayura coupling, it would be possible to efficiently prepare new analogues.



R^1= cyclohexyl (a), cyclopentyl (b)

Scheme 1. Synthesis of 3-substituted-2-iodo-3*H*-imidazo[4,5-*b*]pyridine intermediate.

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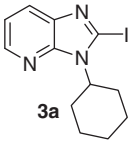
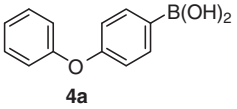
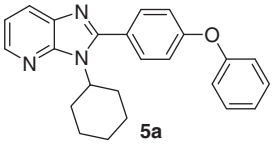
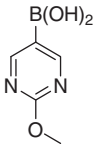
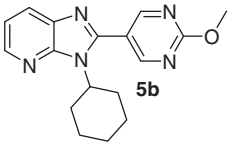
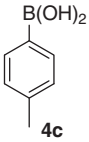
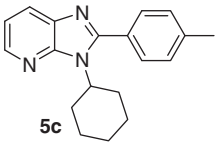
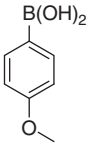
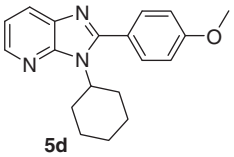
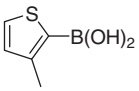
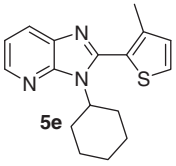
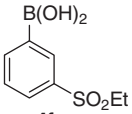
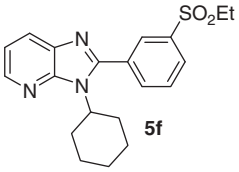
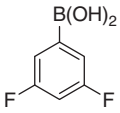
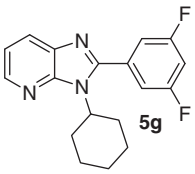
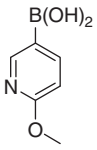
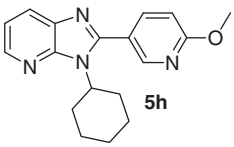
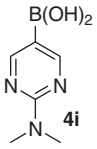
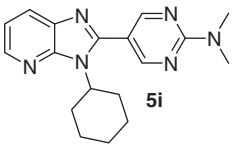
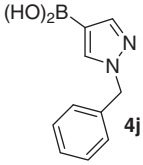
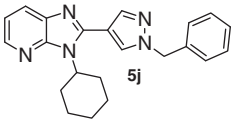
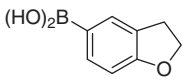
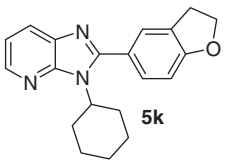
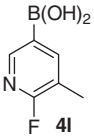
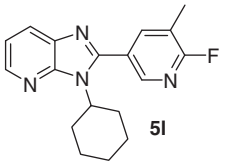
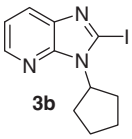
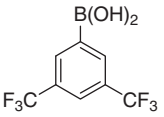
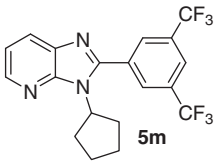
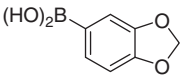
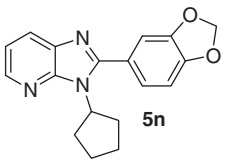
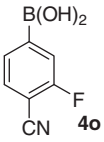
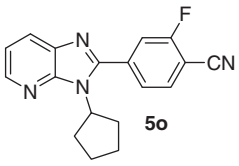
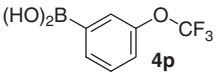
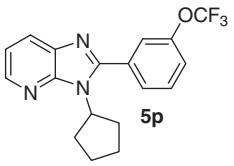
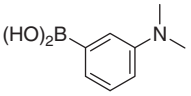
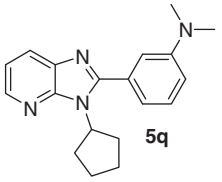
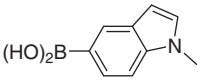
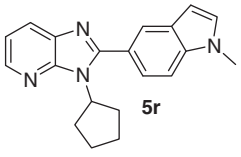
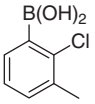
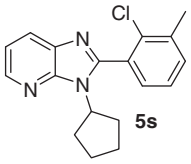
Table 1
Suzuki coupling of 3-substituted-2-iodo-3*H*-imidazo[4,5-*b*]pyridine (**3a**, **3b**) and various boronic acids, **4**[a]

Entry	Iodo intermediate, **3**	$ArB(OH)_2$, **4**	Product, **5**	Yield[b] (%)
1	 **3a**	 **4a**	 **5a**	95
2	**3a**	 **4b**	 **5b**	85
3	**3a**	 **4c**	 **5c**	93
4	**3a**	 **4d**	 **5d**	91
5	**3a**	 **4e**	 **5e**	87
6	**3a**	 **4f**	 **5f**	90
7	**3a**	 **4g**	 **5g**	95
8	**3a**	 **4h**	 **5h**	85
9	**3a**	 **4i**	 **5i**	91
10	**3a**	 **4j**	 **5j**	88
11	**3a**			88

(*continued on next page*)

Table 1 (*continued*)

Entry	Iodo intermediate, **3**	$ArB(OH)_2$, **4**	Product, **5**	Yield[b] (%)
		 **4k**	 **5k**	
12	**3a**	 **4l**	 **5l**	90
13	 **3b**	 **4m**	 **5m**	90
14	**3b**	 **4n**	 **5n**	89
15	**3b**	 **4o**	 **5o**	85
16	**3b**	 **4p**	 **5p**	91
17	**3b**	 **4q**	 **5q**	96
18	**3b**	 **4r**	 **5r**	90
19	**3b**	 **4s**	 **5s**	90

[a] Conditions: catalyst (A-^{t}a phos)$_2PdCl_2$ (5 mol %), 3-substituted-2-iodo-3*H*-imidazo[4,5-*b*]pyridine (**3a**, **b**) (0.1 mmol), boronic acid (0.18 mmol), CsF (0.2 mmol), DME/MeOH (4:1), microwave irradiated at 150 W at 110 °C for 30 min.

[b] Isolated yield.

Our method relies upon the facile synthesis of iodo intermediate **3a, 3b** for the implementation of the final Suzuki reaction (Scheme 1). The diamine derivatives (**1a, 1b**) were taken in formic acid and refluxed overnight to yield compounds (**2a, 2b**). The iodo intermediates were synthesised in excellent yield by treating compounds (**2a**, **2b**) in THF with *t*-butyl lithium at −78 °C for 30 min, followed by the addition of *N*-iodo succinimide in anhydrous THF dropwise at the same temperature and stirring was continued at −78 °C for 1 h. The structure of the iodo compound was confirmed by LC–MS, ^{1}H NMR and 2D-NMR experiments. This key intermedi-

Table 2
Effect of catalyst in Suzuki coupling of **3a** with boronic acid **4i**[a]

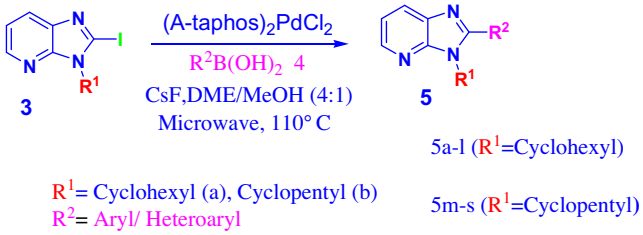
Entry	Catalyst	Base	Solvent	Yield[b] (%)	Yield[b] **2a** (%)
1	$Pd(PPh_3)_4$	Na_2CO_3	DME–H_2O (4:1)	25	62
2	$PdCl_2(dppf)_2$	Na_2CO_3	DME–H_2O (4:1)	30	65
3	$Pd_2(dba)_3$	Na_2CO_3	DME–H_2O (4:1)	25	55
4	$PdCl_2(PPh_3)_2$	Na_2CO_3	DME–H_2O (4:1)	20	68
5	$PdCl_2(PPh_3)_2$	Na_2CO_3	DME–MeOH (4:1)	47	35
6	$PdCl_2(CH_3CN)_2$	CsF	DME–MeOH (4:1)	55	30
7	$PdCl_2(PPh_3)_2$	CsF	DME–MeOH (4:1)	65	20
8	$PdCl_2(PPh_3)_2$	CsF	DMF	45	30
9	(A-^{ta}Phos)$_2PdCl_2$	CsF	DME–MeOH (4:1)	91	Traces

[a] Reaction conditions: **3a** (0.1 mmol), **4i** (0.18 mmol), Catalyst (5 mol %), Base (0.2 mmol), microwave irradiated at 110 W at 110 °C for 30 min.
[b] Isolated yield.

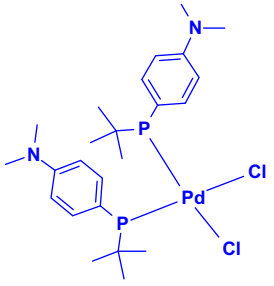
Table 3
Effect of base in Suzuki reaction of **3a** with boronic acid, **4i**

Entry	Base	Yield[a,b] (%)
1	Na_2CO_3	31
2	$NaHCO_3$	35
2	K_2CO_3	25
3	Cs_2CO_3	40
4	NaOH	Traces
5	K_3PO_4	65
6	CsF	91

[a] Reaction conditions: **3a** (0.1 mmol), **4i** (0.18 mmol), (A-^{ta}phos)$_2PdCl_2$ (5 mol %), Base (0.2 mmol), DME/MEOH (4:1), microwave irradiated at 110 W at 110 °C for 30 min.
[b] Isolated yield.



Scheme 2. Synthesis of 3-substituted-2-aryl/heteroaryl imidazo[4,5-*b*]pyridines.



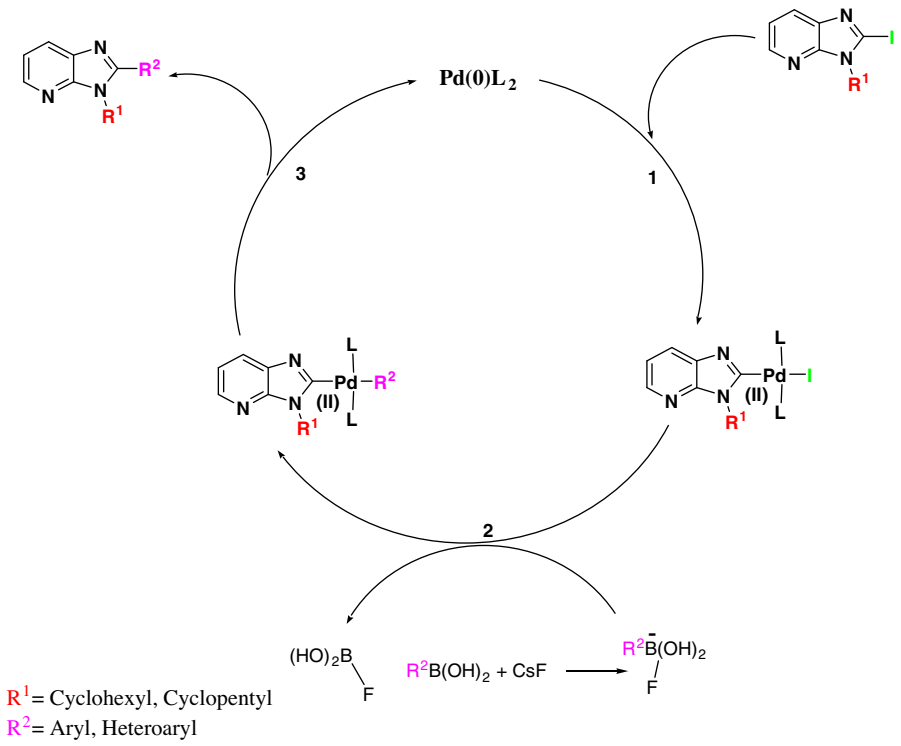
Scheme 3. Structure of the key catalyst used in Suzuki.

ate was then subjected to Suzuki type reaction conditions {(A-^{ta}-phos)$_2PdCl_2$[5 mol %] in DME/MeOH [4:1], purged N_2 for 10 min, followed by 1.8 equiv of boronic acids (**4a–s**) and 2 equiv of CsF}. The mixture was heated via microwave irradiation to 110 °C. Most reactions achieved complete conversions within 30 min. The resulting coupled products were purified by flash column chromatography. Table 1 describes the scope and generality of the procedure utilising variously substituted aryl/heteroaryl boronic acids to yield numerous substituted 2-aryl/heteroaryl imidazo[4,5-*b*]pyridine analogues. Yields were consistently greater than 85% for the coupling procedure. The reaction tolerates both electron rich and electron poor arylboronic acids.

In order to set the reaction parameters, a model system and a range of conditions were explored for the optimisation of Suzuki coupling of the iodo intermediate **3a** and 2-dimethyl aminopyrimidine 5-boronicacid **4i** (Table 1, entry 9). A broad range of catalysts, bases, solvent combinations and temperature ranges were tried on this model system to get the coupled product in good yields (Tables 2 and 3). With most of these palladium catalysts, we observed the deiodinated product **2a** (Scheme 1) as a competing side product along with the required product. Solvent combinations of DME/H_2O, DME/MeOH and DMF were tried on the model system. Table 2 shows that an effective catalytic species was obtained when (A-^{ta}phos)$_2PdCl_2$ (Scheme 2) was used as the catalyst along with CsF as the base in DME/MeOH combination under microwave enhanced conditions. Further investigations were made to explore the effect of base on the Suzuki reaction of **3a** (Scheme 1) with **4i** (Table 1, entry 9) keeping all the other conditions constant (Table 3). It was observed that **4i** was obtained in exceptional yield when CsF was used as the base.

Various catalysts were explored as well as surveys of the inorganic base, solvent combinations and temperature ranges. Better conversions to products were obtained when CsF was used as the base. Higher temperatures with shorter reaction times resulted in decomposition of the iodo intermediate and an inability to recover the coupled biaryl product.

The palladium catalysed dehalogenation of aromatic compounds has been abundantly documented.[16–18] Hydrodehalogenation products have sometimes been observed as byproducts of palladium catalysed cross-coupling reactions. In these cases, water or tertiary amines have been assigned the role of hydride donors. In Table 2, we describe a study of the effect of the catalyst in Suzuki coupling of **3a** with boronic acid **4i**, where we observed the dehalogenated product along with the coupled product. The mechanism of dehalogenation is believed to occur through the attack of metal alkoxides at the Pd(II) oxidative adduct complex formed by the oxidative addition of aryl halide to Pd(0) catalyst.[19,20] Subsequent hydride migration and reductive elimination results in the side product (reduced arene). While the attack of borate complex at the same Pd(II) oxidative adduct complex leads to desired coupled product. The relative rate difference between these two reactions could, in principle, affect the final yield of coupled product. The electronic effect of dimethylamino group (Scheme 3) increases the basicity of phosphine ligand attached to the palladium centre and that facilitates the coupling reaction[21] resulting in improved yield of the coupled product and reduces dehalogenation.



Scheme 4. Mechanism of Suzuki coupling reaction.

Similarly, for the same reason, the base which generates more reactive borate species could facilitate transmetallation.[22] In the present study, CsF was found to lessen the dehalogenated side product (Table 3) suggesting the formation of a highly reactive boronate species, which is in agreement with earlier observations.[21]

The mechanism of Suzuki reaction involves an oxidative addition of iodo intermediate with palladium to form the organo-palladium species. Meanwhile boron atom of the boronic acid forms borate complex with the base which enhances the polarisation of the organic ligand thereby facilitating the transmetallation step. Finally reductive elimination takes place to give the coupled product (Scheme 4).

In conclusion, we have developed a concise, efficient and general method for the synthesis of 3-substituted-2-aryl/heteroaryl imidazo[4,5-*b*]pyridine analogues from a common precursor[23,24]. These intermediates should find utility as synthons for the preparation of medicinally relevant agents. The ready conversion of the iodo intermediate to the boronate ester makes it a more versatile intermediate to synthesise further more novel analogues. Work aimed at investigating the further scope of the iodo intermediate is being pursued.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.051.

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23. *Procedure for the preparation of 3-Cyclohexyl-2-iodo-3H-imidazo[4,5-b]pyridine,* ***3a***

An oven dried flask was charged with imidazo[4,5-*b*]pyridine derivative, **2a** (1 equiv). Freshly distilled THF (5 volumes) was added to the reaction mixture. The reaction mixture was cooled to −78 °C and *t*-butyllitium (1.7 M, 1.3 equiv) in THF was added dropwise to the reaction mixture and stirring was continued for 30 min at −78 °C. A solution of *N*-iodo succinimide (1.3 equiv) in THF (5 volumes) was added dropwise over a period of 20 min at the same temperature. After the addition was complete the reaction mixture was allowed to stir for 1 h at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The ethyl acetate layer was then given water wash, brine wash, and dried over anhydrous sodium sulphate, filtered and concentrated to get the crude mixture as brown oil. The crude was purified by column chromatography using 60–120 mesh silica (10%EtOAc in petroleum ether) to yield the iodo compound (**3a**, Scheme 1). Yellow powder, Yield (89%), mp (110–112 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29–1.47 (m, 4H), 1.70–1.90 (m, 5H), 2.56–2.66 (m, 2H), 4.36–4.42 (m, 1H), 7.21–7.24 (m, 1H), 7.97–7.99 (m, 1H), 8.28–8.29 (m, 1H); IR (KBr) 2924, 2849, 1651, 1600, 1507, 1466, 1343, 1212, 745, 510 cm^{-1}; LCMS 328.16 (M+H); Anal. Calcd for $C_{12}H_{14}IN_3$: C, 44.05; H, 4.31; N, 12.84. Found: C, 44.23; H, 4.40; N, 12.98. Procedure for the synthesis of compound **3b** is provided in Supplementary data.

24. *Procedure for coupling of 3-cyclohexyl-2-(4-phenoxyphenyl)-3H-imidazo[4,5-b]pyridine,* ***5a***

To a solution of 3-Cyclohexyl-2-iodo-3*H*-imidazo[4,5-*b*]pyridine derivative (**3a**, 1 equiv) in dimethoxyethane/MeOH (4:1), was added (A-^{ta}phos)$_2$PdCl$_2$ (5 mol %). The solution was purged with nitrogen and stirred at room temperature for 0.15 h, at which time 4-phenoxyphenyl boronic acid (1.8 equiv), and cesium fluoride (2 equiv) were added. The reaction solution was purged again with nitrogen and then placed in the microwave and heated for 10–30 min at 110 °C. When TLC and LCMS showed full consumption of starting materials, the reaction mixture was diluted with ethyl acetate, separated the ethyl acetate layer, given water wash, brine wash and was dried over anhydrous sodium sulphate and concentrated to get the crude material. The crude product was directly purified by column chromatography (0–20% hexane/EtOAc) to isolate the 3-cyclohexyl-2-(4-phenoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine pyridine (**5a**, Scheme 2). Off white solid, Yield 95%, mp (118.2–119.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27–1.39 (m, 4H), 1.74–1.97 (m, 4H), 2.81–2.85 (m, 2H), 4.38 (m, 1H), 7.11–7.23 (m, 6H), 7.38–7.44 (m, 2H), 7.62 (d, J = 9 Hz, 2H), 8.01 (d, J = 6 Hz, 1H), 8.37 (m, 1H); IR (KBr) 3052, 2934, 2853, 1586, 1488, 1255, 1243, 1230, 857, 775, 744 cm^{-1}; LCMS 370.1 (M+H); Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.05; H, 6.30; N, 11.38. Procedure for the synthesis of compounds **5b**–**5s** is provided in Supplementary data.