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# Synthesis of Imidazo[4,5-*b*]pyridines and Imidazo[4,5-*b*]pyrazines by Palladium Catalyzed Amidation of 2-Chloro-3-amino-heterocycles

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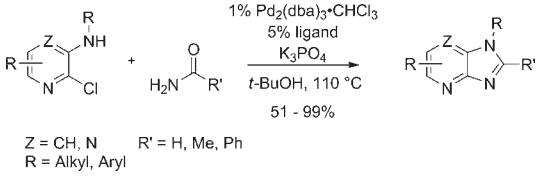
## ABSTRACT




**A facile synthesis of imidazo[4,5-*b*]pyridines and -pyrazines is described using a Pd-catalyzed amide coupling reaction. This reaction provides quick access to products with substitution at N1 and C2. A model system relevant to the natural product pentosidine has been demonstrated, as well as the total synthesis of the mutagen 1-Me-5-PhIP.**

Efficient catalytic methods for the synthesis of imidazo-[4,5-*b*]pyridines, especially those bearing N1 substitution, are in demand. Imidazo[4,5-*b*]pyridine derived structures are of growing interest due to their ability to function as biological mimics of the well-explored and highly developed benzimidazole core structure.[1−3] Imidazo[4,5-*b*]pyridine derived molecules possess diverse pharmacological properties,[4] including anticancer,[5,6] antiviral,[7,8] and other important biological activities.[9−16]

Despite the importance of these structures, imidazo-[4,5-*b*]pyridines are difficult to prepare in a regioselective manner, especially with substitution at the N1-position.

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(Figure 1). Alkylation of the unsubstituted imidazo[4,5-*b*]-pyridine is remarkably unselective. For example, with sodium hydride and benzylbromide a 1:3.6:1.6 (N1:N3:N4) ratio of products has previously been observed.[17] The same problem exists for benzimidazole, as regioisomers are generally observed when the aryl moiety is substituted.[18] Thus, we sought to develop a practical and selective method for the formation of N1 substituted imidazo[4,5-*b*]pyridines. A route that could grant access to analogues with substitution of hydrogen, carbon, halogens, and heteroatoms at C2 was highly desirable. We believe a protocol that incorporates all these criteria would represent a significant advance in this area of heterocyclic chemistry.

Many attempts have been made to address these issues. In 1994 Senanayake et al. reported a multistep sequence utilizing 1,3-diketones, malonamamidine salts, and carboxylic acids to give 2-alkyl substituted imidazo[4,5-*b*]pyridines; however, no substitution at N1 or N3 was reported.[19] Other methods usually require expensive 2,3-diaminopyridines as a starting material and/or proceed in a moderate yield.[18] As such, we choose to explore a metal-catalyzed cross-coupling route. This would allow greater product diversity and the use of the less expensive 2-chloro-3-aminopyridine.

Transition-metal catalyzed cross-coupling reactions have become a reliable, efficient method for C−C and C−heteroatom bond formations.[20−23] Pd-catalyzed C−N couplings have become an increasingly important tool in heterocycle synthesis.[24−26] Recently Buchwald[27] and Ma[28] independently developed complementary syntheses of imidazo[4,5-*b*]pyridines using 2-halo-3-acylaminopyridines and amines to give N3-substituted products, with alkyl substitution at C2. However, these approaches did not allow substitution at N1 or heteroatom substitution at C2. Also, alkyl amines performed poorly in this reaction due to facile $\beta$-hydride elimination of the Pd(II) intermediates.[27] Buchwald and Zheng recently demonstrated that benzimidazole formation tolerated alkylamines when copper was utilized as a catalyst.[29] Ma's approach similarly utilized proline-bound copper which produced N3-substituted imidazo[4,5-*b*]pyridines.[28,30]

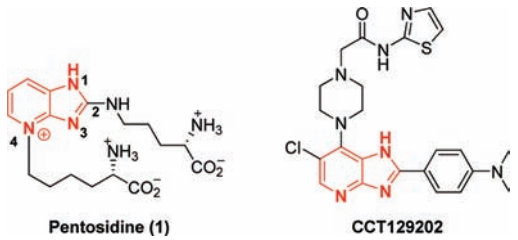


**Figure 1.** Imidazo[4,5-*b*]pyridine containing molecules of interest.

Our interest in imidazo[4,5-*b*]pyridines originates from our work toward the total synthesis of pentosidine (Figure 1). We desired an economical method to produce imidazo[4,5-*b*]pyridines with an electron-donating group at the N1-position[31] and an amine at the 2-position. Herein we report a modular method for the preparation of the imidazo[4,5-*b*]pyridines present in the core of pentosidine and in the Aurora kinase inhibitor lead CCT129202[10,11,32] (Figure 1) through Pd-catalyzed coupling of amides and 2-chloro-3-amino pyridines (Scheme 1).

Our approach is conceptually distinct from those of Buchwald and Ma as we couple a protected 2-chloro-3-aminopyridine with a primary amide, followed by subsequent *in situ* cyclization and dehydration to provide the imidazo[4,5-*b*]pyridine core in a single reaction vessel[26,33] (Scheme 1). Protected 3-amino-2-chloropyridines are easily generated on a multigram scale by reductive amination of the readily available and inexpensive chloro-aminopyridines.[34]

We began our studies with known chloropyridine **2a**. This compound is highly crystalline, and the product possessed the electron-donating group at N1 which we desired for our synthesis of pentosidine.

Initial efforts to couple pyridine **2a** and formamide with standard phosphine ligands (Table 1, entries 1−5; Figure 2) did not show the desired reactivity, presumably due to $\kappa^2$ coordination of the formamide to the Pd center.[35,36]

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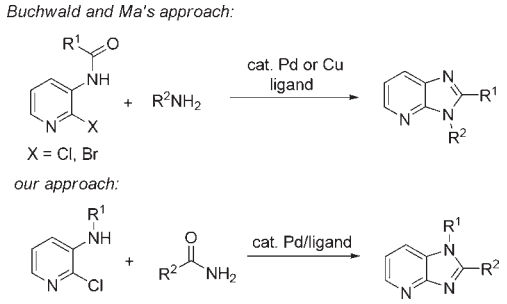
**Scheme 1.** Transition-Metal Catalyzed Cross-Coupling Approaches for the Synthesis of Imidazo[4,5-*b*]pyridines




Next we explored ligands which have recently been shown to be effective in coupling aryl halides with amides. Both $Me_4$-*t*Bu-XPhos[35] (entry 8) and *t*-BuBrettPhos[37] (entry 9) gave the desired product **3a** in excellent yield. The Bippyphos ligand[38] gave only a moderate yield of **3a** (entry 7). Control experiments indicated there was no reaction in the absence of Pd; the absence of ligand also afforded no product. Additionally, no $S_NAr$ products were obtained in the absence of both Pd and ligand. When taken together, these experiments lend evidence to a metal catalyzed cross-coupling mechanism operating under the reaction conditions (entries 10−12). Potassium phosphate base and *tert*-butanol solvent have been previously used for coupling amides and aryl halides;[35] they performed well here, granting the desired products in ≤4 h in all cases under optimized conditions.

With optimized reaction conditions in hand, we explored the reaction scope. As shown in Table 2 the reaction produces the desired imidazo[4,5-*b*]pyridines in good to excellent yields with substituted benzyl derivatives (entries 1−4). Importantly, an aryl chloride (i.e., 2-chlorobenzyl) was tolerated under the reaction conditions (entry 5). Pyridine substitution was well tolerated at N1 despite pyridine's known ability to compete with ligands on Pd (entry 6).[39,40] Alkyl substitution was also well tolerated, and no $\beta$-hydride elimination was encountered in this reaction (entries 7−12). Excellent yields were obtained for both branched and unbranched alkyl groups. Compatibility of chiral substitution at the 1-position was also demonstrated (entries 13 and 14), and the products were isolated without racemization of either isomer **3m** or **3n**.[41]

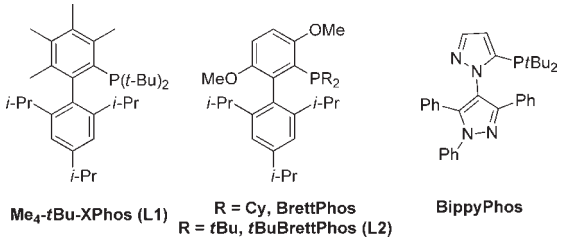
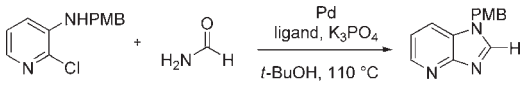



**Figure 2.** Phosphine ligands.

**Table 1.** Reaction Optimization[a]




| entry | Pd source | ligand | yield (%)[b] |
|---|---|---|---|
| 1 | $Pd_2(dba)_3{\cdot}CHCl_3$ | (+/-)BINAP | NR |
| 2 | $Pd_2(dba)_3{\cdot}CHCl_3$ | XantPhos | NR |
| 3 | $Pd_2(dba)_3{\cdot}CHCl_3$ | $P(tBu)_3HBF_4$ | NR |
| 4 | $Pd_2(dba)_3{\cdot}CHCl_3$ | CatacXium A | < 5% Conv |
| 5 | $Pd_2(dba)_3{\cdot}CHCl_3$ | RuPhos | NR |
| 6 | $Pd_2(dba)_3{\cdot}CHCl_3$ | Brettphos | 65% |
| 7 | $Pd_2(dba)_3{\cdot}CHCl_3$ | BippyPhos | 59% |
| 8 | $Pd_2(dba)_3{\cdot}CHCl_3$ | **L1** | 85-90% |
| 9 | $Pd_2(dba)_3{\cdot}CHCl_3$ | **L2** | 86% |
| 10 | $Pd_2(dba)_3{\cdot}CHCl_3$ | - | NR |
| 11 | - | **L1** | NR |
| 12 | - | - | NR |

[a] Reaction conditions: **2a** (0.4 mmol), Pd (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), 2 mL of *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products.

Chiral substrates **2m** and **2n** were prepared through the known Buchwald−Hartwig coupling of 3-iodo-2-chloropyridine with the desired amine.[42] Both phenyl and 4-methoxyphenyl aryl substitutions were well tolerated (entries 15 and 16). Aryl substitution at N1 was installed by Chan−Lam coupling with the corresponding arylboronic acids.[43,44]

Although alkyl and aryl substitution at the 2-position of the imidazo[4,5-*b*]pyridine was not our primary objective, the reaction performs well when the formamide was exchanged for either benzamide or acetamide to give the phenyl (**8**) and methyl (**9**) substituted products respectively (Scheme 2). Other substituted amides such as cyclohexanecarboxamide coupled in 89% yield but failed to undergo the dehydrative cyclization, while cinnamamide gave a 3:1 mixture of uncyclized to cyclized products in 92% yield.[45] Substitution at both the 4- and 6-positions of the pyridine was well tolerated and afforded **10** and **11** in excellent yields.

Pyrazines performed particularly well under the standard reaction conditions; the desired imidazo[4,5-*b*]pyrazines **12** and **13** were isolated in excellent yield with the reaction taking place up to 8-fold faster (Scheme 2). We ascribe this

(36) We briefly explored copper catalyzed conditions, unfortunately without success.

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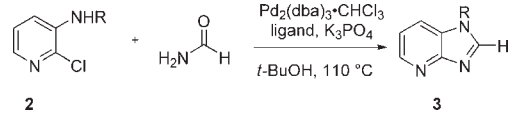
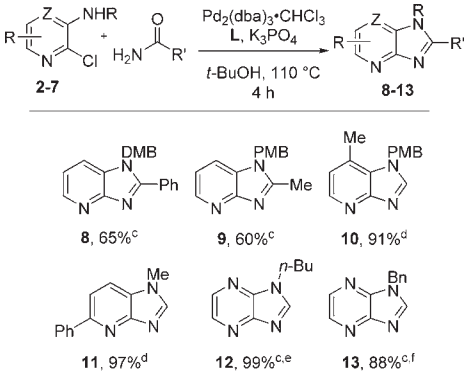
**Table 2.** Reaction Scope[a]




| entry | R | ligand | yield (%)[b] | product |
|---|---|---|---|---|
| 1 | $CH_2$(4-OMeC$_6$H$_4$) **2a** | **L1** | 85 | **3a** |
| 2 | $CH_2$Ph **2b** | **L1** | 85 | **3b** |
| 3 | $CH_2$(2,4-OMeC$_6$H$_4$) **2c** | **L1** | 82 | **3c** |
| 4 | $CH_2$(3-FC$_6$H$_4$) **2d** | **L2** | 90 | **3d** |
| 5 | $CH_2$(2-ClC$_6$H$_4$) **2e** | **L2** | 51 | **3e** |
| 6 | $CH_2$(2-Pyr) **2f** | **L1** | 95 | **3f** |
| 7 | Cy **2g** | **L2** | 90 | **3g** |
| 8 | *i*-Pr **2h** | **L2** | 91 | **3h** |
| 9 | $CH_2C(CH_3)_3$ **2i** | **L2** | 75 | **3i** |
| 10 | Cyp[c] **2j** | **L2** | 85 | **3j** |
| 11 | $CH_2(C_6H_{11})$ **2k** | **L2** | 84 | **3k** |
| 12 | $CH_3$ **2l** | **L1** | 89 | **3l** |
| 13 | (*R*)-CH($CH_3$)Ph **2m** | **L2** | 77 | **3m** |
| 14 | (*S*)-CH($CH_3$)Ph **2n** | **L2** | 79 | **3n** |
| 15 | Ph **2o** | **L2** | 90 | **3o** |
| 16 | 4-OMeC$_6$H$_4$ **2p** | **L2** | 91 | **3p** |

[a] Reaction conditions: **2** (0.4 mmol), Pd (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), 2 mL of *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products. [c] Cyp = Cyclopentyl.

**Scheme 2.** Reaction Scope[a,b]

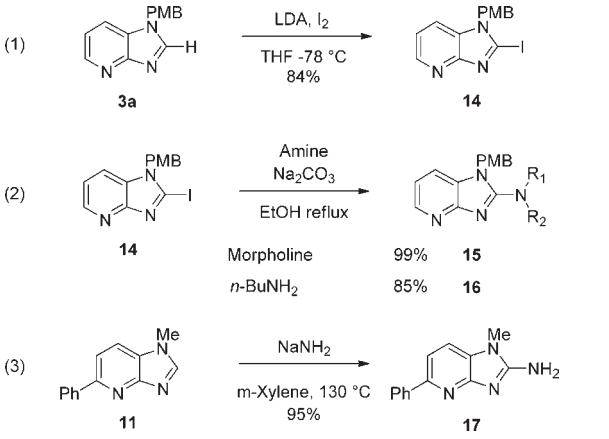



[a] Reaction conditions: Pyr (0.4 mmol), Pd (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), 2 mL of *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products. [c] **L2** was used. [d] **L1** was used. [e] 2 h. [f] 0.5 h.

rate enhancement to faster oxidative addition with the electron-deficient pyrazine moiety.

One advantage of our method is that C2 can be easily functionalized. The 2-position is acidic and can be selectively deprotonated with LDA at low temperature, and subsequently quenched with electrophiles[46] (Scheme 3, eq 1). We choose iodine as an electrophile to demonstrate the potential of this reaction which produced **14** in 84% yield. Further functionalization of **14** by $S_NAr$ with amines as the nucleophiles illustrates the utility of our methodology for the synthesis of pentosidine (eq 2).[47,48] Alternatively, direct functionalization via Chichibabin amination[49,50] was also performed to provide known mutagen 1-Me-5-PhIP **17**[51] from **11** in 95% yield. This represents a short and high yielding synthesis of this naturally occurring N1 substituted imidazo[4,5-*b*]pyridine.

**Scheme 3.** Product Functionalization




In summary, we have developed a regioselective Pd-catalyzed method for the synthesis of imidazo[4,5-*b*]pyridines and -[4,5-*b*]pyrazines. The current protocol is completely selective and grants high yielding access to regioisomers that are difficult to obtain using previous methods. Our method is complementary to the methods developed by Buchwald[27] and Ma,[28] as N1 substituted isomers can now be obtained through metal catalyzed coupling. In addition, we have shown the potential for further functionalization by installation of primary, secondary, and tertiary amines at the 2-position. We are currently exploring the extension of this methodology to other chloro-amino heterocycles for the synthesis of nitrogen-rich bicyclic systems.

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**Supporting Information Available.** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.