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An Improved Synthesis of Imidazo[4,5-*b*]pyridines and Imidazo[4,5-*b*]pyrazines by Palladium Catalyzed Amidation using Xantphos in a 1,4-Dioxane:*tert*-Amyl Alcohol Solvent System

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Abstract: Herein an improved protocol for the synthesis of imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyrazines using a palladium-catalyzed amidation that utilizes Xantphos as an ancillary phosphine ligand is reported. The use of a binary solvent system comprised of 1,4-dioxane and *tert*-amyl alcohol was crucial in eliminating unwanted by-products.

Keywords: nitrogen heterocycles; P ligands; palladium

Imidazopyridines are an important class of structures commonly utilized in pharmaceuticals due to their many beneficial qualities including solubility and hydrogen bonding capabilities (Figure 1).[1–11] We recently reported a method of preparing these moieties using a palladium-catalyzed coupling between an amide and substituted 3-amino-2-chloropyridines.[12] This method of preparing imidazo[4,5-*b*]pyridines (IP_b) and their derivatives represents a useful protocol for obtaining these sought-after compounds. Due to our ongoing interest in this class of heterocycles,[12–13] further improvements were desired for IP_b synthesis.

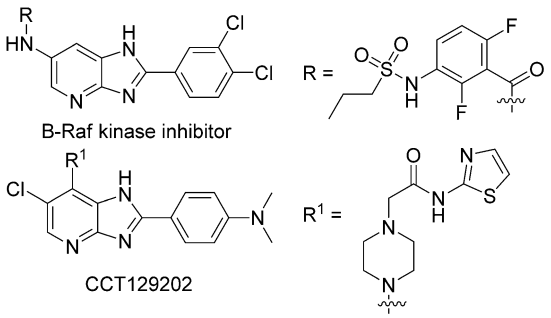


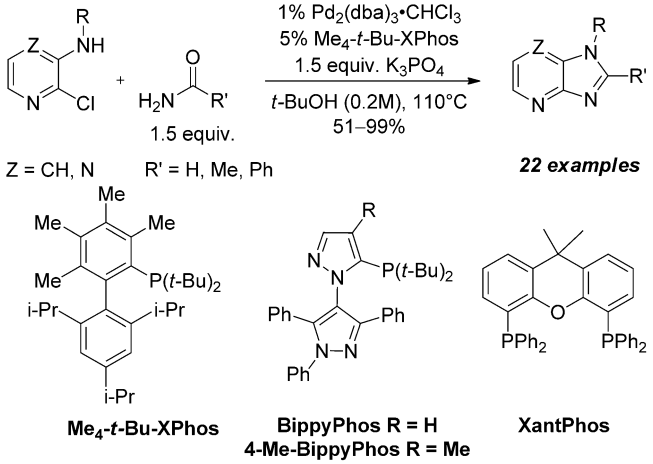
Figure 1. Selected imidazo[4,5-*b*]pyridines.

The goal of the current study was to obtain IP_b in high yield using readily available starting materials, including the pre-catalyst and ligand.[14,15] Our previous methodology utilized commercial 3-amino-2-chloropyridines and amides, and $Pd_2(dba)_3{\cdot}CHCl_3$ as our precatalyst of choice.[12,16] However, the method relied on biarylphosphine ligands, a potential limiting factor in wide-spread use of this methodology.[16] While recent progress has been achieved in addressing the cost of these ligands,[17,18] they remain, in our mind, prohibitively expensive.

Thus, we pursued the use of alternate phosphine-based ligands which were financially more viable. Additionally, expanded scope with regard to substrates and amide coupling partners was desired. In particular, the use of electron-deficient benzyl moieties was ineffective using our previous protocol. Substrates that had unhindered chlorides (i.e., 4-chlorobenzyl) were also not compatible with our previous method. Finally, we sought to incorporate additional functionality on the amide partner. Here, we discuss further investigations which address these previous limitations.

In our initial report, various ligands were screened and only biaryl ligands (*i.e.*, Me_4-***t***-Bu-XPhos) displayed acceptable reactivity (Scheme 1).[12]

The non-proprietary BippyPhos ligand gave a moderate yield, while related 4-MeBippyPhos gave comparable yields to the biaryl ligands. Unfortunately, the high cost and difficult preparation of 4-methylpyrazole, needed for the synthesis of the 4-MeBippyPhos, led us to explore other options.

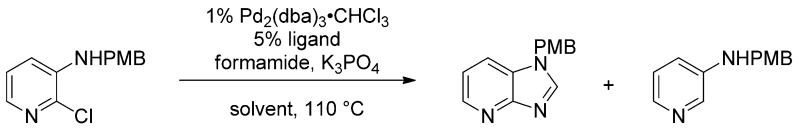


Scheme 1. Previous work.

In our previous study we observed no reaction when Xantphos was used in *tert*-butyl alcohol. A survey of the literature revealed that Pd-catalyzed C–N amide bond formation had been accomplished using Xantphos in aprotic solvents.[19–24] Further scrutiny of the literature revealed an interesting trend; alcoholic solvents were used with ancillary ligands bearing a biarylphosphine motif. Conversely, bidentate phosphine ligands required the use of aprotic solvents for positive outcomes with little to no conversion observed in alcoholic solvents.[12,25–29] Re-examination of our reaction revealed that XantPhos and DPEPhos in aprotic solvents produced the desired cyclization product **2a** along with reduced pyridine **3** (entries 1–5, Table 1). The identity of **3** was confirmed through independent synthesis from 3-aminopyridine. It is believed that formamide acts as the reductant in the formation of pyridine **3** (*vide infra*). Furthermore, when formamide is exchanged for other amides **3** was not observed.

Having not observed the formation of **3** in previous studies (Scheme 1), alternative solvents were screened in order to eradicate this unwanted by-product. No reaction was observed using DMF or NMP (entries 6 and 7); while the reaction in diglyme showed moderate conversion with no observable **3** by ^{1}H NMR (entries 8 and 9). These results combined with our previous success using *tert*-butyl alcohol suggested a protic solvent would minimize formation of pyridine **3**. Unfortunately, as aforementioned, protic solvents were deleterious to the reaction when bidentate ligands were utilized (entry 1). To overcome these difficulties we examined mixed solvent systems using aprotic solvents and *tert*-amyl alcohol (*t*-AmOH).[30–32] The

Table 1. Reaction optimization.[a]



Entry	Ligand	Solvent	Yield [%] **2a** (**3**)[b]	Conversion [%][b]	Reaction time
1	XantPhos	*t*-BuOH	NR	–	18 h
2	XantPhos	toluene	22 (42)	79	18 h
3	XantPhos	1,4-dioxane	83 (15)	100	18 h
4	DPEPhos	1,4-dioxane	37 (46)	87	18 h
5	XantPhos	DME	22 (31)	53	18 h
6	XantPhos	DMF	NR	–	18 h
7	XantPhos	NMP	NR	–	18 h
8	DPEPhos	diglyme	36 (0)	56	18 h
9	XantPhos	diglyme	33 (0)	51	18 h
10	XantPhos	toluene:*t*-AmOH (10:1)	11 (79)	100	6 h
11	XantPhos	toluene:*t*-AmOH (1:1)	13 (29)	42	6 h
12	XantPhos	dioxane:*t*-AmOH (1:1)	84 (0)	85	18 h
13	**XantPhos**	**dioxane:*t*-AmOH (10:1)**	**93 %[c]**	**100**	**6 h**
14	DPEPhos	dioxane:*t*-AmOH (10:1)	27 (35)	71	18 h
15	dppb	dioxane:*t*-AmOH (10:1)	trace (45)	48	18 h
16	dppf	dioxane:*t*-AmOH (10:1)	23 (19)	50	18 h
17	*rac*-BINAP	dioxane:*t*-AmOH (10:1)	4 (36)	40	18 h

[a] *Reaction conditions:* **2a** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol%), ligand (0.02 mmol, 5 mol%), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C.
[b] Based on crude ^{1}H NMR using mesitylene as an internal standard.
[c] Isolated yield. NR = no reaction.

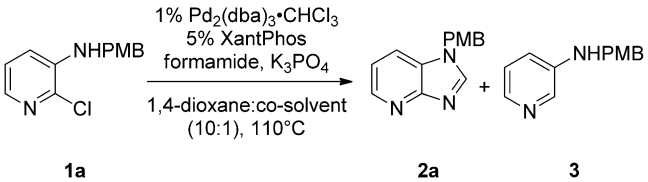
choice of additive was determined based on previous literature precedents demonstrating the effectiveness of binary solvent systems.[31,33,34] The Fu group has also demonstrated the advantage of mixed protic and aprotic solvent systems.[35–37]

First, mixtures of toluene and *t*-AmOH were examined. While excellent conversion was obtained in a 10:1 mixture, pyridine **3** was the primary product (entries 10 and 11). Switching to 1,4-dioxane, which demonstrated promise as the sole solvent, gave positive results (entries 12–14). In a 1:1 1,4-dioxane:*t*-AmOH mixture using XantPhos, little change was observed from solely 1,4-dioxane. XantPhos in a 10:1 dioxane:*t*-AmOH solvent system gave a 93% yield in only six hours with no observable **3** in the crude ^{1}H NMR (entry 13). Other bidentate ligands, with bite angles similar to XantPhos (111°), such as DPEPhos (102°), dppb (99°), dppf (96°), and BINAP (85°), proved inferior (entries 15–17).[38]

With the ligand and solvent ratio selected, we explored alternatives to *tert*-amyl alcohol as the co-solvent to determine their effect on the reaction (Table 2). Water resulted in rapid consumption of **1a**, however, pyridine **3** was the sole product observed (Table 2, entry 2). We attribute this to the hydrolysis of formamide to furnish ammonium formate.[39,40] Changing the co-solvent to methanol provided minimal amounts of desired IP$_b$ **2a** and poor conversion (entry 3). Switching to the more hindered isobutyl alcohol and isopropyl alcohol offered a higher degree of conversion (entries 4 and 5). Isobutyl alcohol gave 30% yield of **2a** with 20% **3**, while isopropyl alcohol provided 69% of **2a** at 78% conversion after 24 h. Interestingly, no reduction was observed in isopropyl alcohol, suggesting that it does not participate as a reducing agent in this reaction.[34,41–45] Based on these results, we posited that the reaction mandates the use of a sterically hindered protic co-solvent to give high conversion of **1a** and provide **2a** in high yield, while avoiding the reduction to **3**. The exact nature of the co-solvent and the role it plays in inhibiting the formation of **3** is currently being investigated.

With optimal conditions in hand, we turned our attention toward the scope of the reaction. As shown in Table 3, the new reaction conditions provided the desired IP$_b$ **2** in good to excellent yields with substituted benzylic derivatives (entries 1–15). Electron-donating substituents (entries 1–4), as well as halogenated substrates (entries 5–8) performed well, giving 79–94% yields. Notably, using our previous conditions, the *ortho*-chlorobenzyl subtrate **1g** provided **2g** in 51% yield; this new protocol provided a much improved 79% yield of **2g** (entry 7). In contrast to **1g**, the *para*-

Table 2. Co-solvent screen.[a]



1a 2a 3

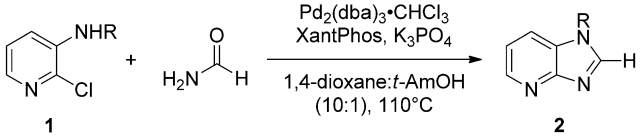
Entry	Co-solvent	Yield [%] **2a** (**3**)[b]	Conversion of **2a** [%][b]
1	*t*-AmOH	93 (0)	100
2	H_2O	0 (74)	100[c]
3	MeOH	13 (18)	31
4	*i*-BuOH	30 (20)	84
5	*i*-PrOH	69 (0)	78

[a] *Reaction conditions:* **1a** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol%), ligand (0.02 mmol, 5 mol%), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C, 24 h.

[b] Based on crude ^{1}H NMR using mesitylene as an internal standard.

[c] Full conversion was observed at 1 h.

Table 3. Substrate scope.[a]



1 2

Entry	R	Yield [%][b]	Product
1	**1a** $CH_2(4\text{-}MeOC_6H_4)$	93	**2a**
2	**1b** $CH_2(2,4\text{-}MeOC_6H_3)$	81	**2b**
3	**1c** $CH_2(2,5\text{-}MeOC_6H_3)$	85	**2c**
4	**1d** $CH_2(4\text{-}Me_2NC_6H_4)$	94	**2d**
5	**1e** $CH_2(3\text{-}FC_6H_4)$	94	**2e**
6	**1f** $CH_2(4\text{-}FC_6H_4)$	96	**2f**
7	**1g** $CH_2(2\text{-}ClC_6H_4)$	79	**2g**
8	**1h** $CH_2(4\text{-}ClC_6H_4)$	94	**2h**
9[c]	**1i** $CH_2(4\text{-}PhC_6H_4)$	70	**2i**
10	**1j** CH_2Ph	85	**2j**
11	**1k** *(R)*-$CH(CH_3)Ph$	96	**2k**
12[c,d]	**1l** $CH_2(3,5\text{-}MeOC_6H_3)$	71	**2l**
13	**1m** $CH_2(4\text{-}CF_3C_6H_4)$	95	**2m**
14[e]	**1n** $CH_2(3\text{-}NO_2C_6H_4)$	57	**2n**
15[c,d]	**1o** $CH_2(4\text{-}CNC_6H_4)$	70	**2o**
16	**1p** Ph	94	**2p**
17	**1q** $CH_2(C_6H_{11})$	77	**2q**
18[c]	**1r** Cy	63	**2r**
19	**1s** Cyp	85	**2s**
20	**1t** *i*-Pr	91	**2t**

[a] *Reaction conditions:* **1** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol%), XantPhos (0.02 mmol, 5 mol%), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C, 6.5 h.[b] Isolated yields.

[c] 90% conversion based on crude ^{1}H NMR using mesitylene as an internal standard.

[d] 2 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol% XantPhos.

[e] 65% conversion based on crude ^{1}H NMR using mesitylene as an internal standard.

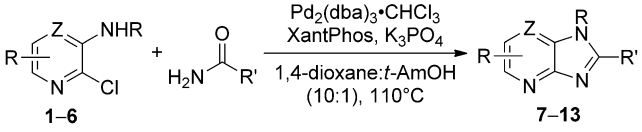
chlorobenzyl substrate **1h** was not amenable to our previous conditions and resulted in multiple coupling events followed by decomposition of **1h**. Under the current conditions **2h** was formed in 94% yield (entry 8). Benzyl and 4-biphenylbenzyl substrates were also well tolerated under the reaction conditions (entries 9 and 10). As anticipated, chiral subtrate **1k** showed no racemization and provided **2k** in excellent 96% yield (entry 11). Another important improvement was the greater propensity for electron-deficient benzyl groups to participate in the reaction. Compound **1l** bearing inductively withdrawing methoxy groups provided **2l** in 71% yield (97% conversion with a trace of dechlorination observed by ^{1}H NMR of the crude reaction mixture) (entry 12).

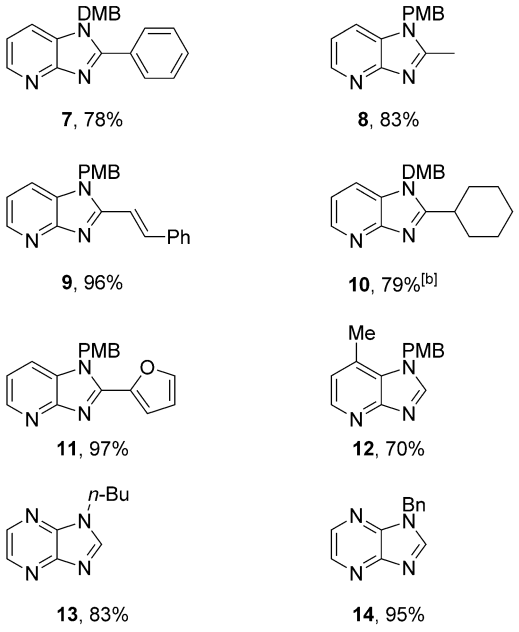
Pyridine **1m** bearing a trifluoromethyl group afforded 95% yield of **2m** (entry 13). In addition, *meta*-nitrobenzyl **1n** and *para*-cyano **1o** gave **2n** and **2o** in 57% (65% conversion by ^{1}H NMR) and 70% (90% conversion by ^{1}H NMR) yields, respectively (entries 14 and 15). Nitro groups previously proved detrimental to the reaction and substantial decomposition of the starting material and extremely poor yields were observed for **2n**. Under the current conditions, decomposition of the starting material was not observed by ^{1}H NMR in the crude reaction mixture. Aryl subsituents continue to perform well, with **1p** giving a 94% yield of **2p** (entry 16). *N*-Alkyl substrates were again well tolerated. Substrate **1q** and **1r** with the sterically encumbered cyclohexylmethyl and cyclohexyl gave **2q** and **2r** in 77% and 63% yields, respectively (entries 17 and 18). Pyridines **1s** and **1t** bearing cyclopentyl (Cyp) and isopropyl moieties afforded **2s** in 85% and **2t** in 91% yield (entries 19 and 20).

One of the goals of this endeavor was to broaden the scope of amide coupling partners. Previously, only benzamide and acetamide were utilized to afford IP$_b$ **7** in 65% and **8** 60% yield, respectively (Table 4). Significantly improved 78% yield of **7** and 83% yield of **8** were obtained in this study. Previously, no reaction or incomplete conversion was observed with cyclohexanecarboxamide and *trans*-cinnamamide. Here, yields of 96% for **9** and 79% for **10** were achieved. Additionally, 2-furanamide also performed well giving **11** in 97% yield. Substitution at the four position of the pyridine was well tolerated providing substituted IP$_b$ **12** in 70% yield albeit with extended reaction time (24 h). In agreement with our previous report, pyrazines performed exceedingly well giving **13** in 83% and **14** in 95% yield; with reduced reaction times (1 h).

In summary, we have developed an improved protocol for the synthesis of imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyrazines. A palladium-catalyzed amidation procedure using readily available XantPhos as a ligand in a binary solvent system proved crucial to the success of this approach. These conditions allowed the efficient coupling of chlorinated benzyl derivatives, and substrates with electron-poor benzyl functionality including nitro and cyano groups. Additionally, we were able to expand the scope of the amide coupling partner granting access to a wider selection of C-2 substituted imidazo[4,5-*b*]pyridines. We are currently working to expand this methodology to regioselectively couple multi-chlorinated aminopyridines, as well as exploring the mechanism of the formamide-mediated reduction of chloropyridines.

Table 4. Amide scope.[a]





[a] *Reaction conditions:* **1–6** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol%), Xantphos (0.02 mmol, 5 mol%), amide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C. All yields are isolated.

[b] Amide used as limiting reagent.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Amide Coupling and Dehydration of 3-Amino-2-chloropyridines: Synthesis of Imidazo[4,5-*b*]pyridine 2a

To an oven-dried 25-mL Schlenk tube equipped with a magnetic stir bar were added $Pd_2(dba)_3{\cdot}CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (11.6 mg, 0.02 mmol), K_3PO_4

(128 mg, 0.6 mmol) and the chloropyridine **1a** (100 mg, 0.4 mmol). The reaction vessel was evacuated and refilled with argon gas. 1,4-Dioxane and *t*-AmOH (10:1, 2 mL) were then added *via* syringe followed by formamide (24 μL, 0.6 mmol) and the reaction mixture was degassed by three vacuum/argon$_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger condenser and immersed in a pre-heated (110 °C) oil-bath and the content stirred for 6 h. Upon consumption of the pyridine (as judged by TLC analysis) the reaction mixture was allowed to cool to room temperature, diluted with methanol (10 mL), and passed through a Celite® plug, rinsing with additional methanol. The crude mixture was concentrated under vacuum and applied to a silica gel column, eluting with 3% MeOH in CH_2Cl_2 to afford product **2a** as an off-white solid; yield: 89 mg (93%).

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