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An Efficient Mixed-Ligand Pd Catalytic System to Promote C–N Coupling for the Synthesis of *N*-Arylaminotriazole Nucleosides

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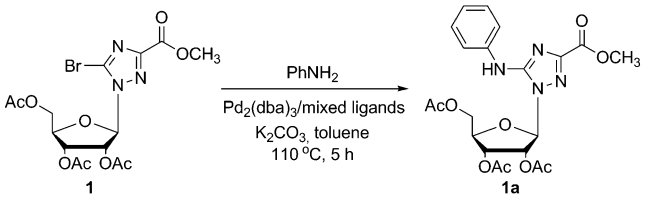
Nucleoside analogues are an important family of candidates in the search for antiviral and anticancer agents.[1] We have been recently engaged in developing various triazole nucleosides bearing aryl moieties on the triazole ring because members of this nucleoside family show extremely promising antiviral and anticancer activity.[2] Of particular interest are the *N*-arylaminotriazole nucleoside analogues, which displayed potent anticancer activity against drug-resistant cancer forms with novel modes of action.[3] However, the synthesis of *N*-arylaminotriazole nucleosides is nontrivial and requires distinct conditions for different substrates with varying reactivity and stability on the reaction sites of the triazole ring and the sugar components.[3–4] Very recently, Buchwald et al. proposed a mixed-ligand Pd catalyst to promote C–N coupling.[5] Such mixed-ligand systems are able to provide enhanced reactivity and selectivity by combining the benefits of single-ligand systems when the ligands are judiciously selected.[6] We therefore wished to develop a general and powerful mixed-ligand catalytic system towards C–N coupling to synthesize various *N*-arylaminotriazole nucleosides with wide substrate scope. It is notable that triazole nucleosides are particularly challenging for metal-catalyzed cross-coupling reactions due to the low reactivity of the heterocyclic triazole ring, the multiple coordinating N- and O-atoms and the labile glycosidic bond. In this work, we report a unique mixed-ligand system of Pd/Synphos/Xantphos to synthesize various *N*-arylaminotriazole nucleosides and *N*-arylaminopurine nucleosides. This catalytic system is extremely powerful, even promoting C–Cl bond activation for C–N coupling.

We started our evaluation of the reaction parameters for mixed-ligand-system-promoted C–N coupling[7] with 5-bromotriazole ribonucleoside (**1**) and aniline as model substrates and by using the two phosphor ligands, Synphos and Xantphos (Table 1 and the Supporting Information, Table S1). According to our previous work, Synphos and Xantphos exercised a selective and effective impact on Pd-catalyzed C–N coupling with the 5- and 3-bromotriazole acyclonucleoside isomers, respectively.[3a] However, using the single-ligand system based on either Xantphos or Synphos, we got rather disappointing results for synthesizing the corresponding triazole ribonucleoside **1a** (Table 1, entries 1 and 2). Xantphos, the most remarkable ligand to promote C–N coupling of 3-bromotriazole acyclonucleoside in our previous study,[3a] gave a poor yield of **1a** (Table 1, entry 1); whereas Synphos, which efficiently enhances the arylamination reaction of 5-bromotriazole acyclonucleoside,[3a] led to an even worse result (Table 1, entry 2). A close analysis of the reactions brought to light the possible reasons for the low yields. When Xantphos was used, many unknown by-

Table 1. Evaluation of Pd/Synphos/Xantphos systems for arylamination of 5-bromotriazole ribonucleoside (**1**).[a]



1 1a

Entry	Catalyst loading [mol %]	Synphos/Xantphos[b]	Yield [%][c]
1	5	0:1	42[d]
2	5	1:0	21[e]
3	5	1:1	80
4	5	2:1	92
5	2.5	2:1	88[f]

[a] The reaction conditions were: **1** (0.1 mmol), aniline (0.2 mmol), [Pd]/[Ligand] = 1:1.2, K_2CO_3 (0.2 mmol), toluene (2 mL). [b] Molar ratio. [c] Isolated product yield. [d] Formation of several by-products. [e] A large amount of **1** was recovered. [f] Reaction time was 14 h.

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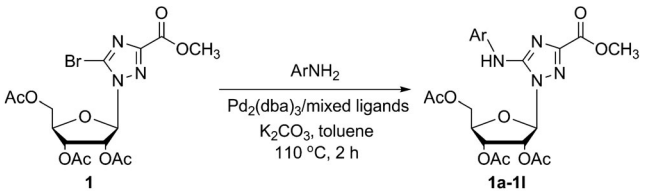
products were also formed, although **1** was completely consumed (as indicated by TLC analysis). This implies that the Pd/Xantphos combination resulted in an active but unselective catalytic system. In the case of Synphos, no by-product was observed; however large amounts of starting material remained. This suggests that while being specific, the Pd/Synphos system was an inefficient catalyst.

On the basis of these findings, we expected that a mixed-ligand Pd catalytic system based on the combination of Xantphos and Synphos might allow the promotion of catalytic reactivity by overcoming the limitations of selectivity and efficiency manifested by the use of the individual ligand systems. We hence developed the mixed-ligand system using Synphos and Xantphos at a 1:1 molar ratio and obtained an excellent yield of 80% for **1a** (Table 1, entry 3). Further adjustment of the ligand ratio led us to obtain the best yield with Synphos and Xantphos at a ratio of 2:1 (Table 1, entry 4 and the Supporting Information, Table S1). Most importantly, the starting material **1** was completely consumed, with a significant reduction in by-product formation. Moreover, reducing the catalyst loading to 2.5 mol% still led to the generation of the product in an 88% yield, although a longer reaction time was required (Table 1, entry 5). We also tried to premix $Pd_2(dba)_3$, Synphos/Xantphos (2:1) and K_2CO_3 with a small volume of toluene for preactivation during 1 h before the reaction. This considerably reduced the reaction time to 2 h (see the Supporting Information, Table S1, entry 4). Consequently, we chose the preactivated catalyst system for subsequent studies on the substrate scope of both the amines and the nucleosides, the representative results of which are summarized in Table 2 and Table 3.

As shown in Table 2, the Pd/Synphos/Xantphos system proved to be widely efficient for the arylamination of **1** with

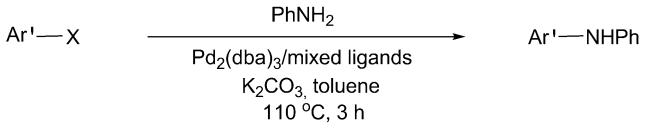
Table 2. Mixed-ligand system of Pd/Synphos/Xantphos to promote the C–N coupling of 5-bromotriazole ribonucleoside (**1**) with various arylamines.[a]

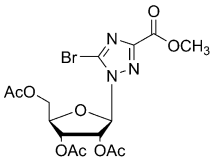
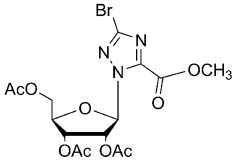
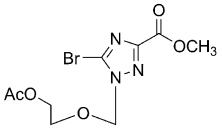
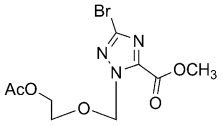
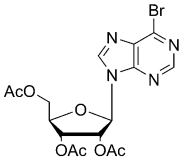
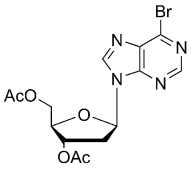
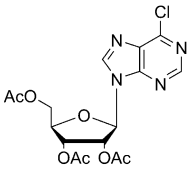


Entry	Ar	Product	Yield [%][b]
1	Ph	**1a**	92
2	4-MePh	**1b**	82
3	4-n-C_7H_{15}Ph	**1c**	73
4	4-OMePh	**1d**	86
5	3-OMePh	**1e**	90
6	2-OMePh	**1f**	89
7	4-FPh	**1g**	86
8	3-FPh	**1h**	90
9	2-FPh	**1i**	88
10	4-CF_3Ph	**1j**	85
11	4-ClPh	**1k**	73
12	1-pyrenyl	**1l**	83

[a] The reaction conditions were: **1** (0.1 mmol), arylamine (0.2 mmol), $Pd_2(dba)_3$ (0.005 mmol), Synphos (0.008 mmol), Xantphos (0.004 mmol), K_2CO_3 (0.2 mmol), toluene (2 mL). $Pd_2(dba)_3$, ligands and K_2CO_3 were premixed in toluene (1 mL) for 1 h before reaction. [b] Isolated product yield.

Table 3. Arylamination of different bromotriazole and halopurine nucleoside substrates using the mixed-ligand catalytic system of Pd/Synphos/Xantphos.[a]



Entry	Ar′–X		Product	Yield [%][b]
1		**1**	**1a**	92[c]
2		**2**	**2a**	91
3		**3**	**3a**	88
4		**4**	**4a**	89
5		**5**	**5a**	86[d]
6		**6**	**6a**	85[d]
7		**7**	**5a**	70[e](90[f])

[a] The reaction conditions were: nucleoside (0.1 mmol), aniline (0.2 mmol), $Pd_2(dba)_3$ (0.005 mmol), Synphos (0.008 mmol), Xantphos (0.004 mmol), K_2CO_3 (0.2 mmol), toluene (2 mL). $Pd_2(dba)_3$, ligands and K_2CO_3 were premixed in toluene (1 mL) for 1 h before reaction. [b] Isolated product yield. [c] Reaction time was 2 h. [d] Reaction time was 4 h. [e] Reaction time was 20 h. [f] 10% $Pd_2(dba)_3$ (0.01 mmol) and reaction time was 14 h.

a multitude of aryl amines bearing various substituents. Notably, arylamines bearing either electron-donating (Table 2, entries 2–6) or electron-withdrawing groups (Table 2, entries 7–11) at various positions (Table 2, entries 4–6 and 7–9) yielded excellent results. The C–N coupling reactions proceeded very smoothly even with the sterically hindered *ortho*-substituent arylamines and pyrenylamine (Table 2, entries 6, 9, and 12). Consequently, a variety of *N*-arylaminotriazole ribonucleoside analogues could be generated effectively through this procedure (Table 2).

Most importantly, this catalytic system is also highly efficient for different nucleoside substrates (Table 3). It is worth mentioning that structural isomers of bromotriazole nucleosides have notoriously different reactivity and require very different conditions for C–N coupling.[3–4] Using the mixed-ligand system of Pd/Synphos/Xantphos, we achieved, for the first time, efficient arylamination of triazole nucleosides with different isomeric structures and different sugar components (Table 3, entries 1–4). Importantly, the 6-bromopurine ribo- and deoxyribonucleosides **5** and **6**[8] could also deliver the corresponding products in excellent yields (Table 3, entries 5 and 6). Even the much less reactive 6-chloropurine ribonucleoside **7**[9] delivered the corresponding product smoothly, with a spectacularly higher yield of 90% being attained with a higher catalyst loading (Table 3, entry 7). Consequently, our mixed-ligand system appears to be a peculiarly powerful catalyst, exhibiting extraordinary reactivity and wide substrate scope in catalyzing the C–N coupling of various triazole and purine nucleosides.

To gain a better understanding of the reason for the catalytic power shown by the Pd/Synphos/Xantphos system, we performed a ^{31}P NMR investigation (Figure 1). In the Pd/Synphos system, we observed that a considerable amount of Synphos existed as free ligand and only a small amount of (Synphos)Pd(dba) species was formed (Figure 1 A, iii). This suggests that the formation of the (Synphos)Pd(dba) complex is slow and inefficient. As (Synphos)Pd(dba) is the precursor of the active catalytic species for C–N coupling,[10] this finding may explain in part why the Pd/Synphos system was not efficient for arylamination of **1** (Table 1, entry 2). As for the Pd/Xantphos system, all of the Xantphos coordinated to Pd and no free ligand was detected (Figure 1 A, iv). These results suggest that Xantphos is more efficient at forming complexes with $Pd_2(dba)_3$ than Synphos. This difference might be ascribed to the more flexible structure and larger bite angle of Xantphos,[11] which makes it more ready to form complexes with Pd compared with the structurally rigid Synphos, which has a small bite angle. Using the mixed-ligand Pd/Synphos/Xantphos system,[12] we surprisingly found no free ligand of Synphos and considerably increased amounts of (Synphos)Pd(dba) were detected (Figure 1 A, v). It is also important to note that Xantphos monodentate-ligated Pd complex,[13] which formed in the single-ligand system of Pd/Xantphos (peak c in Figure 1 A, iv), was diminished completely in the mixed-ligand system (Figure 1 A, v).[14] Collectively, these findings led us to hypothesize that, in the Pd/Synphos/Xantphos system, Xantphos promoted the complex formation between Pd and Synphos through a rapid exchange of ligand at the level of Pd complexes in the mixed-ligand system (Scheme 1A), and the considerably increased formation of the (Synphos)Pd(dba) complex thus resulted in a more efficient catalytic system.

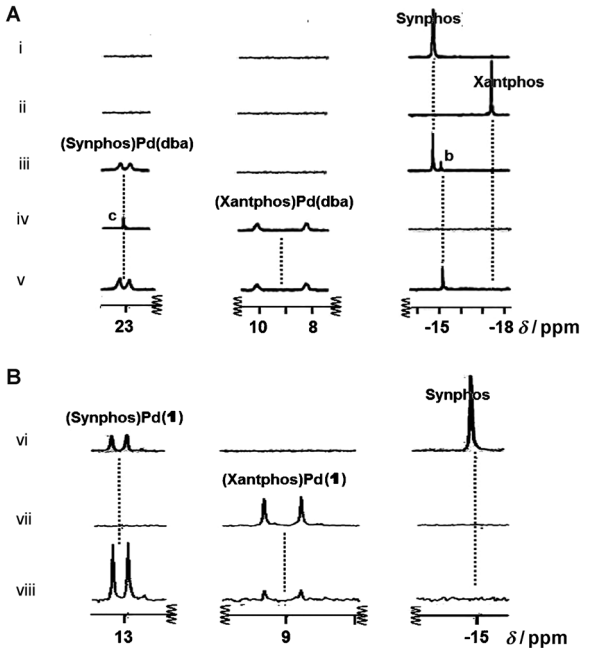
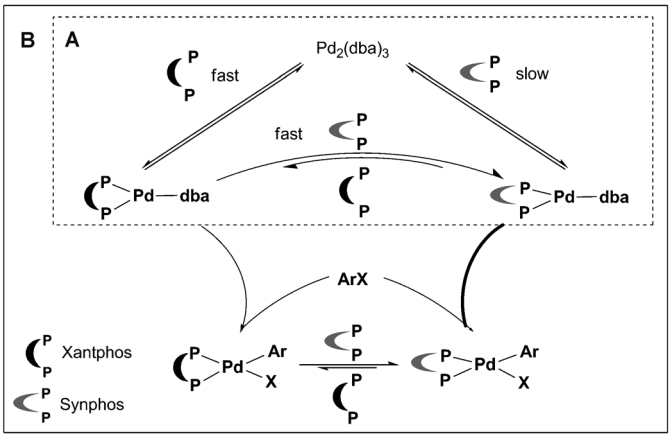


Figure 1. ^{31}P NMR spectra of the Pd/ligand systems in the absence (A) and presence (B) of the substrate **1**. i) free Synphos, ii) free Xantphos, iii) $Pd_2(dba)_3$/Synphos, iv) $Pd_2(dba)_3$/Xantphos, v) $Pd_2(dba)_3$/Synphos/Xantphos, vi) $Pd_2(dba)_3$/Synphos/**1**, vii) $Pd_2(dba)_3$/Xantphos/**1**, and viii) $Pd_2(dba)_3$/Synphos/Xantphos/**1**. The spectra were obtained in [D_8]Toluene. All the reaction mixtures (in the absence of substrate **1**) were first refluxed at 110 °C for 1 h under protection of argon and then cooled at RT. The solutions were subsequently transferred to NMR tubes in a glovebox directly. One more hour was required if substrate **1** was added in the reaction mixture. In mixed-ligand samples, [Synphos]/[Xantphos] = 2:1. The label b denotes the Pd complex in which Synphos works as monodentate ligand; label c denotes the Pd complex in which Xantphos works as monodentate ligand (see ref. [13]).



Scheme 1. Proposed ligand exchange at the level of A) the Pd/ligand complex formation and B) the oxidative insertion.

We further studied the oxidative addition step by adding 5-bromotriazole ribonucleoside (**1**) into the mixed-ligand catalyst system (Figure 1B, viii). Interestingly, in the presence of Xantphos, compound **1** preferentially formed the adduct (Synphos)Pd(**1**) (Figure 1B, viii) compared with the single-ligand system with Synphos (Figure 1B, vi). As a result, the ligand exchange equilibrium could again be shifted towards the formation of the (Synphos)Pd(dba) complex (Scheme 1B), thus further promoting the reaction. Based on these results, we could reasonably conclude that, in the Pd/Synphos single-ligand system, it is not that the catalytic species has lower catalytic activity, but rather that the single-ligand system with Synphos generates only a limited amount of active catalytic species. In the mixed-ligand system, Xantphos promotes the formation of active catalytic species formed between Pd and Synphos, thus leading to powerful catalytic activity (Scheme 1A). In addition, using this mixed-ligand system, the substrate preferentially formed adduct with the (Synphos)Pd(dba) complex, further favoring the equilibrium shift towards the formation of active catalyst (Scheme 1B). Altogether, the ^{31}P NMR studies provided crucial data with which we were able to better understand the origin of the enhanced catalytic effect displayed by this mixed-ligand system to promote C–N coupling. Based on all these results presented above, we hence proposed a general mechanism of this mixed-ligand system assisted C-N coupling involving two independent catalytic cycles between which Pd is shuttled (see the Supporting Information, Scheme S1). This mechanism parallels the one proposed by Buchwald et al, which was formulated on the basis of product analysis by trapping the reactive intermediates.[5]

Finally, we also assessed the newly synthesized *N*-arylaminotriazole ribonucleosides for their anticancer activity against drug-resistant pancreatic cancer MiaPaCa-2 cells. Compound **1c** exhibited particularly interesting anticancer activity (see the Supporting Information, Figure S1), with superior potency compared to gemcitabine, the current clinical drug used to treat pancreatic cancer.[15] This finding further confirmed and warranted the interest in and importance of developing efficient catalytic systems for synthesizing this special family of nucleoside analogues.

In conclusion, we have disclosed a highly efficient mixed-ligand Pd catalytic system for arylamination of triazole nucleoside analogues. It is worth mentioning that the Pd/Synphos/Xantphos catalytic system displayed the unparalleled advantage of catalyzing C–N cross-coupling of different triazole nucleosides and arylamines. In addition, this catalytic system was also powerful at effectively promoting C–N coupling with other halopurine nucleosides including the notoriously less reactive chloropurine ribonucleoside. Furthermore, ^{31}P NMR studies provided us with an insightful understanding of the mechanism underlying the catalytic power displayed by the Pd/Synphos/Xantphos system in promoting arylamination. We anticipate a fueled interest in the mixed-ligand approach, which may be applicable to other cross-coupling reactions for the synthesis of structurally diverse nucleoside analogues, which are currently a class of extremely important compounds in the continued quest for antiviral and anticancer drug candidates.

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Keywords: antitumor agents · arylamination · cross-coupling · nucleosides · palladium

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[12] The total ligand concentration remained the same in the multi-ligand system as in the single-ligand systems.

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[14] We speculate that this monodentate Xantphos-ligated Pd species might be responsible for the by-product formation observed with the single-ligand system of Pd/Xantphos (Table 1, entry 1).

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