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Ligand-Mediated Highly Effective and Selective C−N Coupling for Synthesizing Bioactive *N*-Aryltriazole Acyclonucleosides

Yuting Fan,[†] Yi Xia,[‡] Jingjie Tang,[†] Palma Rocchi,[§] Fanqi Qu,[†] Juan Iovanna,[§] and Ling Peng[‡,*]

State Key Laboratory of Virology, College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, People's Republic of China, and CNRS UPR 3118 CINaM and INSERM U624, 163, avenue de Luminy, 13288 Marseille, France

ling.peng@univmed.fr

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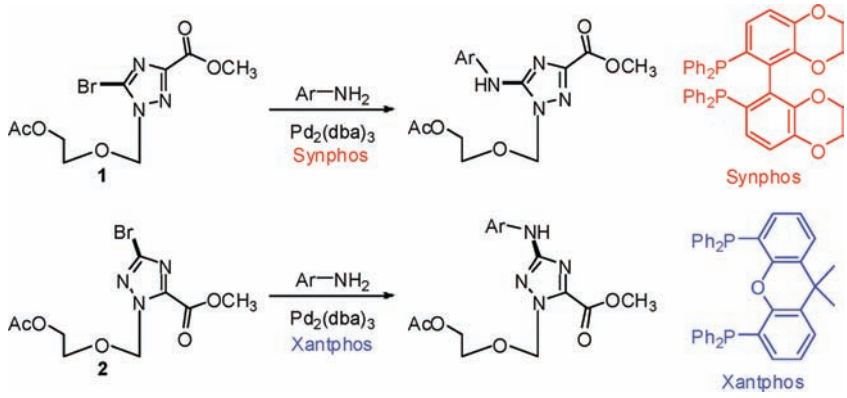
ABSTRACT



***N*-aryltriazole nucleosides are new chemical entities with potential biological activity. The two phosphor ligands, Synphos and Xantphos, had a selective and effective impact on Pd-catalyzed C−N coupling with the 5- and 3-bromotriazole acyclonucleoside isomers, affording the corresponding and otherwise difficult to achieve *N*-aryltriazole nucleosides with good to excellent yields. In addition, two of the synthesized nucleosides showed superior anticancer activity against drug-resistant pancreatic cancer, compared to the reference drug gemcitabine.**

Nucleoside mimics are of considerable importance in the search for antiviral and anticancer drug candidates.[1] Compounds with triazole heterocycles as nucleobases are unusual nucleoside analogues, some of which exhibit biological activity involving unique modes of action. One noteworthy example is ribavirin, the first synthetic triazole nucleoside antiviral drug discovered 40 years ago, which remains the only small molecule approved to treat hepatitis C virus (HCV).[2] Recently, ribavirin has been reported to demonstrate apoptosis-related anticancer effects.[3] Consequently, there is renewed interest in creating new structural entities of triazole nucleosides with the aim of developing potent therapeutic

[†] Wuhan University.
[‡] CNRS UMR 3118, CINaM.
[§] INSERM U624.

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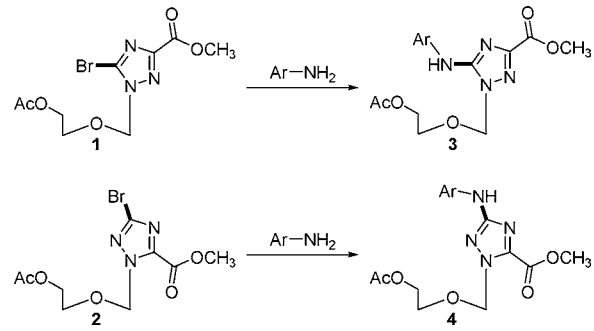
agents with novel mechanisms of action. Over the past few years, we have developed a series of triazole nucleoside analogs bearing aromatic moieties on the triazole nucleobase[4−6] some of which exhibited antiviral and anticancer activity involving novel modes of action.[4−6] Of particular interest are some *N*-aryltriazole nucleosides, which showed potent anticancer activity against drug-resistant pancreatic cancer.[6a] However, their synthesis via Cu-mediated *N*-arylation was far from satisfactory, with narrow substrate scope and low product yields,[6] thus limiting further biological evaluation and structure/activity relationship studies.

Pd-catalyzed C−N coupling[7] is becoming a powerful technique in the synthesis of various *N*-arylated nucleoside analogs.[8] However, no reports exist on Pd-catalyzed C−N cross coupling with triazole nucleoside precursors. In marked contrast to simpler aromatic systems, triazole nucleosides are particularly challenging for Pd-catalyzed cross coupling reactions due to the low reactivity of the triazole ring, the multiple coordinating N- and O-atoms and the labile glycosidic bond. Here, we report the synthesis of novel *N*-aryltriazole acyclonucleosides via highly reactive Pd-catalyzed C−N cross-coupling. The phosphor ligands, Synphos and Xantphos, had a selective and effective impact on the C−N coupling reactions with the bromotriazole nucleoside substrates, giving the corresponding products with good to excellent yields. In addition, some of the synthesized triazole nucleosides showed potent anticancer activity against drug-resistant pancreatic cancer, with potentially novel modes of action.

In this study, we used both 5-bromotriazole acyclonucleoside **1** and its structural isomer, 3-bromotriazole nucleoside **2**[9] as the substrates for Pd-catalyzed C−N coupling (Scheme 1). Under the classical condition of 10 mol % $Pd(OAc)_2$, 12 mol % BINAP and 2 equiv of Cs_2CO_3 in toluene,[10] we only obtained the C−N coupling product with **1** (Table S1, entry 1, Supporting Information), but not with **2**. We therefore first focused our attention on the reaction with **1**. After extensive screening (Table S1, Supporting Information), we defined the optimized condition as $Pd_2(dba)_3$ with the combination of Synphos as the ligand, K_2CO_3 as the base and toluene as the solvent. It is noteworthy that monocoordinating ligands

Scheme 1. Bromotriazole Nucleosides **1** and **2** Were Used As Starting Materials for the C−N Coupling Reactions in This Study



turned out to be inefficient in this reaction (Figure S1, Table S1, entries 4−6, Supporting Information), in concordance with previous report.[11] Although C3-Tunephos yielded considerable amount of the product **3a** (Table S1, entry 2, Supporting Information), it also led to the formation of numerous byproduct. Therefore, Synphos emerged as the most effective ligand in our conditions (Table S1, entry 8, Supporting Information). Furthermore, the nature and the strength of bases affected importantly the reaction. Potassium carbonate was superior to all the other bases tested (Table S1, entry 13, Supporting Information): strong bases such as NaO*t*Bu and LiHMDS resulted in substrate decomposition; whereas weak bases such as Li_2CO_3 were also ineffective and failed to promote the reaction, but did not result in substrate decomposition. The choice of solvent was also critical, and toluene appeared to be the best choice (Table S1, entry 13, Supporting Information), whereas the polar solvent DMF yielded no product, but rather substrate decomposition. Finally, the catalyst precursors also had a considerable impact, with $Pd_2(dba)_3$ proving to be the most efficient (Table S1, entries 19−21, Supporting Information) allowing a high yield even with a catalyst loading of 1 mol % (Table S1, entries 22, Supporting Information).

We next explored the scope of arylamine substrates (Table 1). The reaction worked extremely well with electron-rich arylamines, affording the corresponding products with excellent yields (Table 1, entries 1−7). Arylamines with electron-deficient substituents led to decreased yet very good yields (Table 1, entries 9−10). The use of even sterically hindered arylamines offered the products with good to excellent yields (Table 1, entries 6−7), except for pyrenylamine which gave considerably reduced yields (Table 1, entry 8) probably due to the particularly large pyrenyl moiety which would create steric hindrance during the *N*-arylation process. A support for this hypothesis came from the crystal structure of **3f** (Figure 1). As we can see, the glycosidic moiety in **3f** is in such a position that the approach of an exceedingly larger amine to the reaction center might create steric hindrance and therefore impede the reaction.

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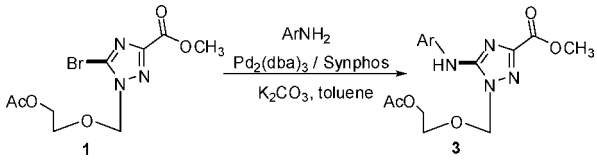
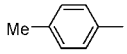
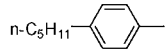
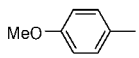
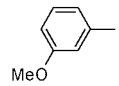
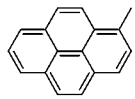
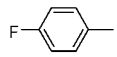
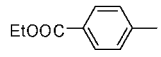
Table 1. Synthesis of *N*-Aryltriazole Acyclonucleosides **3** via Pd Catalyzed C−N Coupling with 5-Bromotriazole Nucleoside **1**[a]



entry	Ar—	product	yield %
1		**3a**	92
2		**3b**	92
3		**3c**	83
4		**3d**	89
5		**3e**	86
6		**3f**	85
7		**3g**	96
8		**3h**	45
9		**3i**	69
10		**3j**	71

[a] Reaction condition is: **1** (0.2 mmol), arylamine (0.4 mmol), $Pd_2(dba)_3$ (0.005 mmol), Synphos (0.012 mmol), K_2CO_3 (0.4 mmol), toluene (2 mL), 100 °C, 16 h.

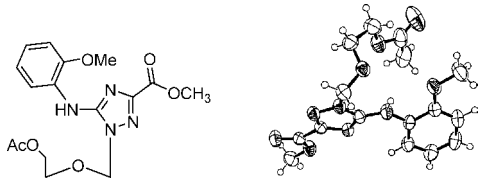


Figure 1. X-ray structure of **3f**.

Encouraged by the extremely positive result with **1**, we further investigated the Pd-catalyzed C−N coupling approach using the 3-bromotriazole nucleoside **2**. Unfortunately, the optimized condition for C−N coupling of **1** was not suitable for **2** (Table S2, entry 1, Supporting Information), obviously owing to the different reactivity of **1** and **2** toward the C−N coupling. We thus further scrutinized the reaction conditions by examining various Pd-catalysts, ligands, bases and solvents (Table S2, Supporting Information). The combination of $Pd_2(dba)_3$ and Xantphos in the presence of K_2CO_3 in toluene emerged as being the most effective for the C−N coupling of **2** (Table S2, entry 17−19, Supporting Information). This condition was itself, however, unsuitable for the C−N coupling of **1** (data not shown). The explanation for the observed difference in reactivity and selectivity of the two catalytic systems for the C−N coupling with **1** and **2** is complex. First, the reactivity of **1** and **2** is considered to be different due to their differing electronic and structural features.[12] Second, Xantphos is a large bite-angle ligand,[13] and its Pd-complexes may be more cumbersome in space. Moreover, on the basis of the structure of the C−N coupling product **4a** (Figure 2), we may speculate that the reaction

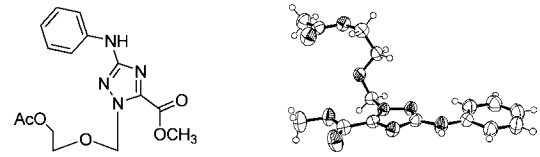


Figure 2. X-ray structure of **4a**.

site of **2** for C−N coupling could be exposed to exterior and easily accessible for Pd-complexes, allowing large-bite angle ligand Xantphos to participate favorably in the catalytic process; whereas the structure of **3f** (Figure 1) might suggest that the reaction site of **1** could be highly congested due to the unfavorable position of the glycosyl moiety, and unable to accommodate favorably the large bite-angle ligand Xantphos, but rather the small bite-angle ligand Synphos.[14] Finally, the triazole ring and the phenyl moiety together with the *N*-linkage are in almost perfect coplanarity in the product **4a** (Figure 2), leading to an enlarged aromatic systems, which might confer a further thermodynamic advantage and contribute favorably to the C−N bond formation with **2**. This might also explain why a good yield could be obtained even with a very low catalyst loading of 0.5 mol % (Table S1, entry 20, Supporting Information).

Under the optimized condition, excellent yields were obtained for the C−N coupling of **2** with arylamines bearing a wide range of functional groups including both electron-donating and electron-withdrawing groups (Table 2). This may be attributed to the highly reactive Pd−Xantphos catalytic system. Even the sterically hindered pyrenylamine gave excellent result (Table 2, entry 8). A hypothesis could be formulated based on the crystal structure of **4a** (Figure 2): with the glycosyl moiety situated far away, the reaction site of **2** might be openly accessible for the C−N bond formation and no steric congestion would be created even with an amine bearing an exceedingly cumbersome aromatic moiety.

We further deprotected **3** and **4** in NH_3/MeOH to give, respectively, the *N*-aryltriazole nucleosides **5** and **6** with good

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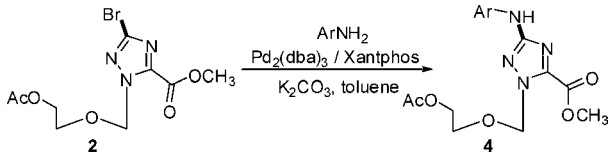
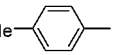
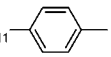
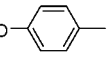
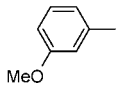
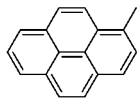
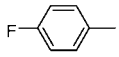
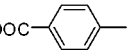
Table 2. Synthesis of *N*-Aryltriazole Nucleosides **4** via Pd Catalyzed C−N Bond Formation Starting with **2**[a]



entry	Ar—	product	yield %
1		**4a**	90
2	Me 	**4b**	90
3	n-C_5H_{11} 	**4c**	90
4	MeO 	**4d**	88
5	 MeO	**4e**	91
6	 OMe	**4f**	93
7	 Me	**4g**	91
8		**4h**	80
9	F 	**4i**	89
10	EtOOC 	**4j**	90

[a] Reaction condition is: **2** (0.2 mmol), arylamine (0.4 mmol), $Pd_2(dba)_3$ (0.002 mmol), Xantphos (0.0048 mmol), K_2CO_3 (0.4 mmol), toluene (2 mL), 100 °C, 16 h.

to excellent yields (Scheme 2, Tables S3 and S4, Supporting Information). Two of them, **6c** and **6h**, were revealed to have superior anticancer activity against drug-resistant pancreatic cancer MiaPaCa-2 cells, compared to gemcitabine (Figure 3A), the current first-line drug used to treat pancreatic cancer.[15] In addion, unlike gemcitabine, neither **6c** nor **6h** inhibited DNA synthesis (Figure 3B), suggestive of potentially novel mechanisms of action underlying their anticancer activity.

In summary, we have reported highly reactive and selective Pd/ligand systems for C−N cross-coupling to synthesize previously unavailable and otherwise difficult to achieve *N*-arylated triazole acyclonucleoside analogs. The two phosphor ligands, Synphos and Xantphos, are fully complementary in terms of selectivity and reactivity for Pd-catalyzed C−N coupling with the two nucleoside isomers **1** and **2**,

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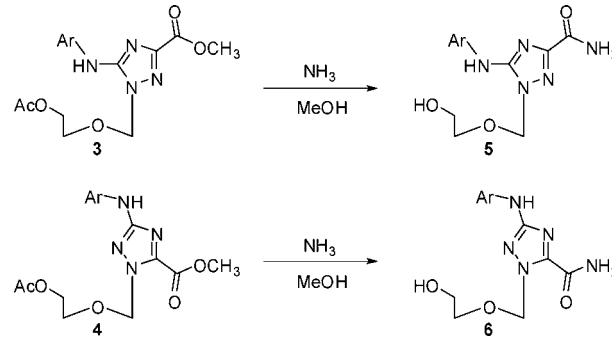
Scheme 2. Deprotection of **3** and **4** Led to the Nucleoside Analogues **5** and **6**, Respectively



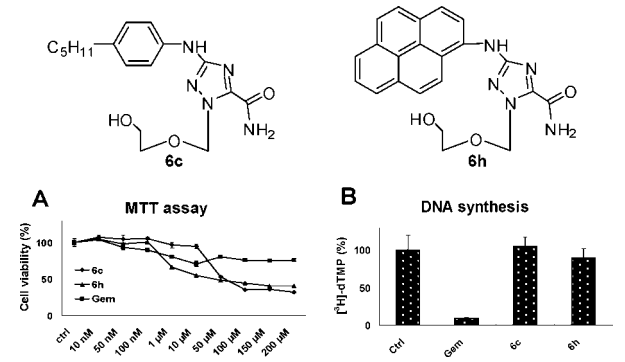


Figure 3. Compounds **6c** and **6h** showed superior anticancer activity to gemcitabine against drug-resistant pancreatic cancer MiaPaCa-2 cells, assessed by MTT assay (A); however, they did not inhibit DNA synthesis as gemcitabine, measured by [^{3}H]-dTMP incorporation (B) (Ctrl, control; Gem, gemcitabine).

respectively. A large array of *N*-aryltriazole nucleosides was synthesized efficiently, and two of them showed remarkable anticancer activity against drug-resistant pancreatic cancer. The synthetic methods presented here not only help us to gain a better knowledge of ligand-impacted Pd-catalyzed coupling reactions in organic synthesis but also provide us with the opportunity to prepare various new structural paradigms of *N*-aryltriazole nucleosides with ease for our drug discovery program based on triazole nucleoside chemistry.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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