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The first Cu- and amine-free Sonogashira-type cross-coupling in the C-6-alkynylation of protected 2′-deoxyadenosine

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ABSTRACT

The Sonogashira cross-coupling reaction offers a convenient route to C(sp)–C(sp^2) bond formation. Although the Sonogashira reaction has traditionally been carried out in the presence of Pd catalyst and a co-catalyst of Cu(I) salt, the use of Cu(I) salt is often not efficient because it leads to the formation of unwanted side-products. This has prompted interest in recent years in the development of Cu-free Sonogashira cross-coupling reaction conditions. In addition, the development of Cu-free Sonogashira cross-coupling conditions for the alkynylation of nucleoside derivatives remains largely unexplored. Herein, we demonstrate that Cu- and amine-free Sonogashira-type cross-coupling lead to successful alkynylation of aryl bromides and heteroaryl bromides. For the first time, we have extended this method for the alkynylation of protected 2′-deoxyadenosine at the C-6 position.

1. Introduction

Alkynes are commonly found in many natural products and biologically active compounds.[1] The versatility of alkynes as important synthetic intermediates has prompted interest in designing efficient methods to incorporate alkynes in organic molecules. One commonly used method for incorporation of alkynes in organic molecules, through the formation of C–C bonds, is the Sonogashira cross-coupling method.[2] The Sonogashira coupling reaction has been extensively studied since its discovery in 1975. The Sonogashira cross-coupling reaction involves the coupling of a terminal alkyne with an aryl or vinyl halide or triflate, using a palladium catalyst and a Cu(I) salt as co-catalyst.[3] The creation of the C(sp)–C(sp^2) bond makes the Sonogashira cross-coupling reaction one of the most important reactions in synthetic organic chemistry. It has been reported that the use of CuI does not always have a positive outcome on effective Sonogashira cross-coupling reactions.[4] This is because the use of CuI results in unwanted side-reactions, such as the oxidative homocoupling of alkynes to form the so-called Glaser product.[5] This side-reaction has driven the modification of the original Sonogashira cross-coupling reaction.[6–9] To date, examples of Pd-free,[6] Cu-free,[10] amine-free,[11] ligand-free,[12] and solvent-free[5b] conditions have been reported. The Sonogashira cross-coupling reaction has also been performed in the presence of water as solvent,[12b,13] or using tetrabutyl ammonium salts as additives.[5b,12b,14] Modifications in the original Sonogashira cross-coupling reaction have resulted in the reaction being easily amenable on a laboratory and industrial scale.

Modified nucleosides play important roles in many biological processes. Nucleoside analogs, substituted at the C-6 position, have been shown to display a broad range of biological activities.[15–18] The Sonogashira cross-coupling reaction provides easy access to 6-alkynylpurine nucleosides, which would otherwise be difficult to synthesize using other conventional coupling reactions. Successful Sonogashira cross-coupling reaction has been reported using 6-chloropurine and 6-iodopurine nucleosides with 1-hexyne, and employing $Pd(PPh_3)_4$/CuI/TEA as the catalytic system.[19] However, only one terminal alkyne was used and there is no evidence that the catalytic system could be extended, with equal success, to other terminal alkynes.

Nucleosides can be covalently modified to form fluorescent analogs.[20] Fluorescent nucleoside analogs can serve as valuable probes in cellular and signal transduction pathways.[21] The synthesis of modified nucleosides by Pd-catalysis has been reported.[3c,22] The alkynylation of nucleosides by Sonogashira cross-coupling has also been reported.[3c,20,23] However, most of the successful alkynylation reactions reported so far have involved 8-bromoadenosine and 8-bromoguanosine with terminal acetylenes. Interestingly, development of a catalytic system for the alkynylation at the 6-position of 6-bromo-2′-deoxyadenosine has not been fully explored. To the best of our knowledge, very limited information exists in the literature on the Sonogashira cross-coupling of 6-bromo-2′-deoxyadenosine with terminal alkynes to generate 6-alkynylated-2′-deoxyadenosine derivatives.

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Most biological activities studies with modified nucleosides have been limited to the 6-arylpurine ribonucleosides, with a few studies on the 6-alkynylpurine ribonucleosides. However, biological studies on the 6-alkynylpurine deoxyribonucleosides remain largely unexplored. One reason why the potential biological activities of 6-alkynylpurine deoxyribonucleosides have not been fully explored could be the difficulty in synthesizing 6-alkynylpurine deoxyribonucleosides through cross-coupling reactions between the labile deoxyribonucleosides and terminal alkynes. Although the common Sonogashira cross-coupling method works well in the cross-coupling of terminal alkynes with aryl halides and heteroaryl halides, this method may not necessarily be extended to deoxyribonucleosides with equal success. Although many different variations of the common Sonogashira cross-coupling methods have been reported in the literature, the application of these methods with protected 2′-deoxyribonucleosides requires a careful and systematic approach; the cross-coupling method must be compatible with the protecting group on the sugar moiety and be tolerant to the lability of the nucleosidic bonds. As a result of our ongoing interest in transition metal-mediated syntheses of modified nucleosides,[24] we decided to evaluate the common Sonogashira cross-coupling method and the modified versions in the coupling of protected 2′-deoxyadenosine with terminal alkynes. Herein, we report a convenient Sonogashira cross-coupling protocol for the alkynylation of aryl bromides, heteroaryl bromides, and 6-bromo-2′-deoxyadenosine.

2. Results and discussion

We envisaged the establishment of a general synthetic route to 6-alkynylpurine deoxyribonucleoside derivatives through a Sonogashira-type cross-coupling reaction of protected 6-bromo-2′-deoxyadenosine with a series of terminal alkynes. The Sonogashira cross-coupling reaction was carried out using 3 mol % Pd species and 2 mol % CuI as the catalytic system. For initial optimization, we chose bromobenzene and phenylacetylene as substrates, $Pd_2(dba)_3$, $PdCl_2(CH_3CN)_2$, and $Pd(PPh_3)_4$ as Pd species, **L-1**, **L-2**, **L-3**, and **L-4** as ligands, and Et_3N and DABCO as bases (Fig. 1). The ligands were chosen because of our previous experience with these ligands,[24] and because Buchwald et al. had shown that biaryl dialkyl phosphine ligands are efficient at catalyzing the Sonogashira cross-coupling reaction.[4] Interestingly, in our hands, the Pd species and ligand that were successful in the coupling of aryl chlorides with terminal alkynes, as reported by Buchwald et al. did not work quite as well in the coupling of aryl bromides with terminal alkynes. We chose the more readily available Pd species, which were more promising. In the optimization experiments, four different solvents were tried at 50 °C, 90 °C, or ambient temperature (see Supplementary data for a comprehensive table of results).

In the course of the optimization experiments, some important lessons were learned. The combination of $Pd_2(dba)_3$/CuI, the ligands **L-1**, **L-2**, **L-3**, or **L-4**, any of the solvents, and either Et_3N or DABCO, at 90 °C, 50 °C, or ambient temperature led to no significant product formation over a 24 h period. However, the use of $Pd(PPh_3)_4$/CuI, the ligands **L-1** or **L-2**, Et_3N or DABCO, and the solvent DMF or toluene led to significant improvement in the yield at 90 °C and 50 °C. Although the use of $PdCl_2(CH_3CN)_2$ gave better results when compared to $Pd_2(dba)_3$, the yields were still lower when compared to $Pd(PPh_3)_4$. Our initial experiments established the combination $Pd(PPh_3)_4$/CuI/**L-1**/Et_3N in DMF at 90 °C as the optimal conditions for the common Sonogashira coupling.

Although results from our optimization studies using Et_3N, DMF, $Pd(PPh_3)_4$, and **L-1** at 90 °C were largely satisfactory, we were still concerned with the occasional appearance of the Glaser product, as judged by GC–MS analysis. To combat the problem of Glaser coupling, Cu-free Sonogashira cross-coupling reactions were explored. Three Pd species, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $PdCl_2(CH_3CN)_2$, were used in these Cu-free cross-coupling reactions, with acetonitrile, DMF, and toluene as solvents (Table 1). The $Pd_2(dba)_3$/**L-1** catalytic system provided no coupling under the Cu-free conditions, while the $PdCl_2(CH_3CN)_2$/**L-1** gave a modest 72% yield. However, the $Pd(PPh_3)_4$/**L-1** catalytic system was extremely efficient under these conditions producing a 91% yield of the Sonogashira cross-coupling product. The optimum conditions for the Sonogashira cross-coupling reactions were found to require the use of **L-1** and $Pd(PPh_3)_4$ at 90 °C in acetonitrile (Table 1, entry 2).

In order to study the scope of our optimized reaction conditions, a number of aryl bromides and heteroaryl bromides containing a wide array of functional groups were subjected to Sonogashira cross-coupling with phenylacetylene (Table 2). The yields were good for all substrates; simple aromatic, heteroaromatic, and extended aromatic substrates. Irrespective of the substituents on the aromatic substrates, products were obtained for activated and less activated aryl halides. No significant difference was observed in the reactivity between 2-bromosubstituted and 4-bromosubstituted substrates when the electron-donating group was a methyl group (Table 2, entries 4 and 7). However, there was a significant difference in the reactivity between 2-bromosubstituted and 4-bromosubstituted substrates when the electron-donating group was a methoxy group (Table 2, entries 6 and 8). The reaction with *ortho*-bromoanisole proceeded to afford the desired cross-coupling product in 94% yield (Table 2, entry 6), while the reaction with *para*-bromoanisole gave a modest 69% yield (Table 2, entry 8). In addition, aryl bromides showed selective reactivity in the presence of fluorine and chlorine (Table 2, entries 3 and 5). In the reaction of 4-bromo-2-chlorophenol, selective alkynylation was observed at the 4-bromo position given 53% of the desired product (Table 2, entry 3); there was no evidence of alkynylation at the 2-chloro position.

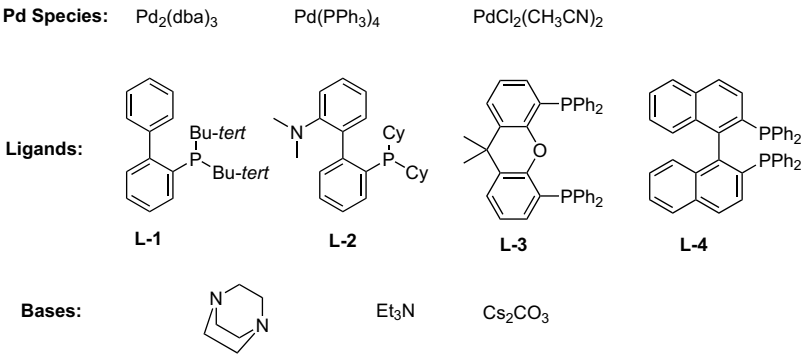
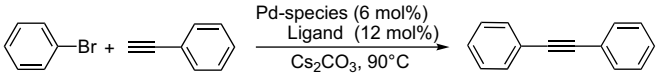


Figure 1. Pd species, ligands, and bases investigated.

Table 1
Optimization study for the Cu- and amine-free Sonogashira cross-coupling of phenylacetylene with bromobenzene



Entry	Ligand	Pd species	Solvent	Time (h)	Yield[a] (%)
1	**L-1**	$Pd_2(dba)_3$	MeCN	24	Mostly starting material
2	**L-1**	$Pd(PPh_3)_4$	MeCN	2	91
3	**L-1**	$Pd(PPh_3)_4$	DMF	2	43
4	**L-1**	$Pd(PPh_3)_4$	Toluene	8	61
5	**L-1**	$PdCl_2(CH_3CN)_2$	MeCN	2	72

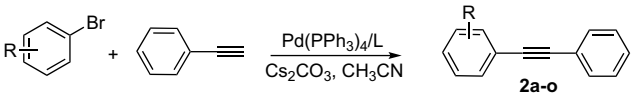
[a] The percentage yield is the calculated yield of recovered product from an average of two runs. The presence or absence of the homocoupling product (Glaser product) was ascertained by GC–MS.

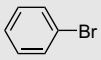
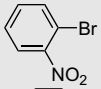
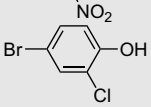
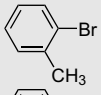
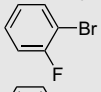
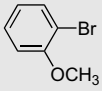
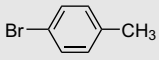
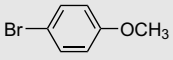
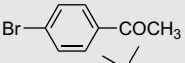
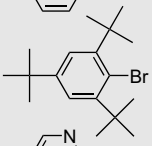
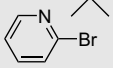
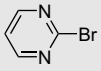
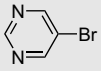
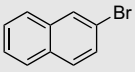
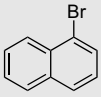
For the 2-bromosubstituted substrates, the electronic effect of the substituents seemed to be important for the reactivity (Table 2, entries 2, 4, and 5). The presence of the electron-withdrawing nitro and fluoro groups resulted in 91 and 93% yield of the desired products, respectively (Table 2, entries 2 and 5). In contrast, the presence of the electron-donating methyl group resulted in a 78% yield of the desired product (Table 2, entry 4). But, it is nebulous to draw a conclusion on the role that the electronic effect has on the reactivity of 2-bromosubstituted substrates since the presence of electron-donating methoxy group at the *ortho* position resulted in excellent yield of 94% (Table 2, entry 6). Results indicate that electronic effect of the *ortho*-substituents is not the only important factor in predicting the outcome of cross-coupling among aromatic substrates. The presence of a heteroatom at the *ortho* position could also result in a chelating effect that might affect the reactivity of the substrate.[25]

In the case of the 4-bromosubstituted substrates, electronic effect of the substrates did not seem to be important in the reactivity (Table 2, entries 7, 8, and 9). In the presence of the electron-donating methyl and methoxy groups, the desired products were obtained in 75% and 69% yields, respectively (Table 2, entries 7 and 8). Similarly, in the presence of the electron-withdrawing acetyl group, the desired product was obtained in 73% yield (Table 2, entry 9).

In order to assess the effect of steric hindrance on the cross-coupling reaction, we decided to use the hindered aryl bromide 2,4,6-tri-*tert*-butylbromobenzene. Results showed that cross-coupling was inhibited by bulky substituents on the benzene ring since no product was obtained using 2,4,6-tri-*tert*-butylbromobenzene as the substrate after 24 h (Table 2, entry 10). In order to explore the versatility of our optimized cross-coupling conditions, we decided to further test the viability using heterocyclic aryl bromides. Using heterocyclic aryl bromides from the pyridine and pyrimidine family, good yields of the desired products were obtained (Table 2, entries 11–13). The reactivity of 2-bromopyridine was better than that of any of the pyrimidine bromides. Using 2-bromopyridine as the substrate, the desired cross-coupling product was obtained in 82% in just 1 h (Table 2, entry 11). For the bromopyrimidine derivatives, 2-bromopyrimidine was more reactive than 5-bromopyrimidine (Table 2, entries 12 and 13). This result is contrary to what had been reported, where 5-bromopyrimidine was said to be more reactive than 2-bromopyrimidine in a Cu-free Sonogashira-type coupling.[26] Satisfied with the results obtained for the heterocyclic aryl halides, we decided to probe the generality of the cross-coupling reaction using extended aromatic systems such as the naphthalene family (Table 2, entries 14 and 15). Although the reactions in this series were generally slower, the cross-coupled products were still obtained in good to excellent yields. Comparing the two

Table 2
Sonogashira cross-coupling of phenylacetylene with aryl bromides



Entry[b]	Ar-X	Product	Time (h)	Yield[a] (%)
1		**2a**	2	91
2		**2b**	6	91
3		**2c**	5	53
4		**2d**	3	78
5		**2e**	4	93
6		**2f**	8	94
7		**2g**	2	75
8		**2h**	8	69
9		**2i**	3	73
10		**2j**	24	0
11		**2k**	1	82
12		**2l**	3	82
13		**2m**	6	65
14		**2n**	8	98
15		**2o**	24	69

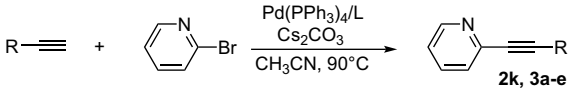
[a] The percentage yield is the calculated yield of recovered product from an average two runs.

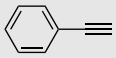
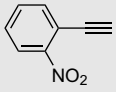
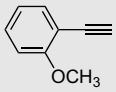
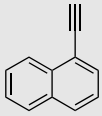
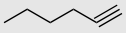
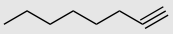
[b] Reactions were carried out in acetonitrile at 90 °C, with 1.0 equiv of aryl bromides, 1.2 equiv of phenylacetylene, 0.06 equiv of $Pd(PPh_3)_4$, 0.12 equiv of 2-(di-*tert*-butylphosphino)-1,1′-biphenyl(**L-1**), and 2.4 equiv of Cs_2CO_3.

naphthalene systems, the least-hindered 2-bromonaphthalene showed a faster reaction and gave an excellent yield of 98% compared to 69% for 1-bromonaphthalene (Table 2, entries 14 and 15).

Next, we studied the coupling of 2-bromopyridine with various acetylenes, using our optimal reaction conditions (Table 3). The structure of the alkyne also had an effect on the efficiency of the coupling reactions. Phenylacetylene reacted with 2-bromopyridine

Table 3
Sonogashira cross-coupling of acetylenes with 2-bromopyridine



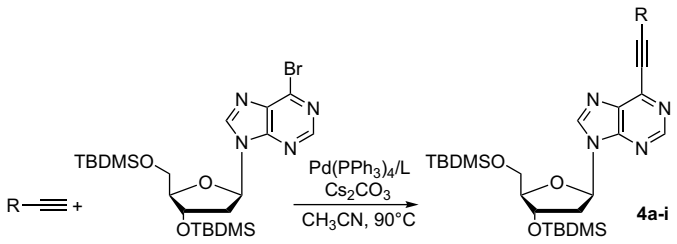
Entry[b]	R	Product	Time (h)	Yield[a] (%)
1		**2k**	1	82
2		**3a**	24	Mostly starting material
3		**3b**	1	86
4		**3c**	1	87
5		**3d**	5	54
6		**3e**	3	78

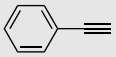
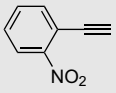
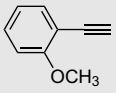
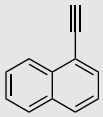
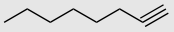
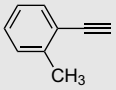
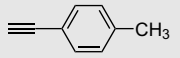
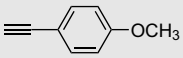
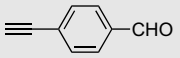
[a] The percentage yield is the calculated yield of recovered product from an average two runs.
[b] Reactions were carried out in acetonitrile at 90 °C, with 1.2 equiv of acetylenes, 1.0 equiv of 2-bromopyridine, 0.06 equiv of $Pd(PPh_3)_4$, 0.12 equiv of 2-(di-*tert*-butylphosphino)-1,1′-biphenyl(**L-1**), and 2.4 equiv of Cs_2CO_3.

to give the cross-coupling product **3k** in 82% yield (Table 3, entry 1). With substituted phenylacetylenes, only the electron-rich derivatives gave the cross-coupled product **3b** in 86% yield (Table 3, entry 3). The electron-poor phenylacetylene, 2-nitrophenylacetylene, gave no cross-coupling product (Table 3, entry 2). The extended aromatic substrate, 1-ethynylnaphthalene, gave the cross-coupling product **3c** in 87% yield (Table 3, entry 4). The simple aliphatic alkynes reacted to give moderate to good yields of the cross-coupling products **3d** and **3e** in 54% and 78% yields, respectively (Table 3, entries 5 and 6).

Alkynylation at the C-6 position of ribonucleosides, using a catalytic system with CuI, was previously reported with only a limited application for the alkyne substrates.[19] We conducted a series of experiments to assess the efficiency of a Cu-free protocol in the Sonogashira cross-coupling of the easily prepared halonucleoside precursor 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine,[27] with various terminal alkynes (Table 4). Generally good to modest yields were obtained for some terminal alkynes (entries 1, 3, 4, and 6). However, the presence of electron-withdrawing nitro group or formyl group on the phenylacetylene resulted in no cross-coupling product even after 24 h (entries 2 and 9). It is currently not clear why the electron-withdrawing substituents are unreactive under this protocol. The presence of electron-donating groups on the phenylacetylene resulted in the desired coupling products, albeit, in comparably lower yields than the unsubstituted phenylacetylene (entries 3, 6, 7, and 8). Among phenylacetylene derivatives with electron-donating substituents, those with *ortho*-substituents gave slightly better yields than their *para*-substituted counterparts (entries 3, 6, 7, and 8). The reaction with 1-octyne, an aliphatic alkyne, gave 52% yield of the desired coupling product (entry 5). For all the coupling reactions, the major NMR signals showed that the desired products were obtained with no significant peaks resulting from a side-product, except some minor uncharacterized impurities in some cases. It should be noted that although the yields obtained for the nucleoside couplings are moderate to good, it is the first time that

Table 4
Sonogashira cross-coupling of acetylenes with 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine



Entry[b]	R	Product	Time (h)	Yield[a] (%)
1		**4a**	6	69
2		**4b**	24	Mostly starting material
3		**4c**	6	60
4		**4d**	5	72
5		**4e**	6	52
6		**4f**	6	63
7		**4g**	8	56
8		**4h**	8	58
9		**4i**	24	Mostly starting material

[a] The percentage yield is the calculated yield of recovered product from an average two runs.
[b] Reactions were carried out in acetonitrile at 90 °C, with 1.2 equiv of acetylenes, 1.0 equiv of bromonucleoside, 0.06 equiv of $Pd(PPh_3)_4$, 0.12 equiv of 2-(di-*tert*-butylphosphino)-1,1′-biphenyl(**L-1**), and 2.4 equiv of Cs_2CO_3.

such modified Sonogashira cross-coupling conditions have been applied to the C-6-alkynylation of 2′-deoxyadenosine. It is also important to note that cross-coupling reactions involving nucleosides are generally difficult due to the many basic nitrogens on the heterocyclic structure of nucleosides.

3. Conclusion

In summary, a Cu-free Sonogashira procedure for the cross-coupling of functionally substituted aryl bromides, and heteroaryl bromides with terminal alkynes has been developed. This procedure was successfully applied in the Sonogashira cross-coupling of 6-bromo-2′-deoxyadenosine with terminal alkynes of various functionality. The reactions are tolerant to different functional groups, generally result in reasonable to good yields, and proceed under relatively mild conditions. Current work in our laboratories is geared toward further optimization of the 6-bromo-2′-deoxyadenosine reaction using different catalytic systems, and extending

the Sonogashira cross-coupling conditions to synthesis involving other halopurine nucleosides. We are currently studying the fluorescent properties of the alkynylated deoxyadenosine derivatives, in view of our interest in evaluating their potential biological applications. As a result of the challenge inherent in coupling reactions involving nucleosides, due to the large number of basic nitrogens, which could potentially serve as ligands, the development of catalytic systems, which can effectively result in cross-coupling of terminal alkynes and modified nucleosides is interesting. This work represents our initial contribution in this endeavor, while work is continuing in our laboratory to optimize the reaction even further with new catalytic systems.

4. Experimental section

4.1. General methods

Reactions were conducted in oven-dried vials under a nitrogen atmosphere. All reactions were carried out in freshly distilled and dried solvents. The ligands, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and all other reagents were obtained from commercial sources and were used without further purification. The protons on the sugar unit are numbered 1′–5′ beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon. ^1H NMR spectra (300 MHz) and ^{13}C spectra (75 MHz) were recorded on a JEOL ECX300 spectrometer in $CDCl_3$ and internally referenced to residual $CHCl_3$ (7.25 ppm, ^1H). Chemical shifts are reported in parts per million (ppm, δ). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), or pentet (p). All first order splitting patterns are assigned based on the appearance of the multiplet. For those splitting patterns that could not be easily visualized or interpreted, a designation of multiplet (m) was used. Coupling constants are reported in hertz (Hz). TLC was carried out on glass-backed Analtech TLC plates precoated with silica gel (250 μm layer thickness) containing a fluorescent indicator. Column chromatographic purifications were performed using 200–300 mesh silica gel from Natland.

4.2. GC/MS conditions

A Finnigan Focus GC/DSQ system with automated liquid sampler and Supelco Equity 5 15 m×0.25 mm×0.25 μm was used with a flow of ultra high purity He. The temperatures for the aryl ethers in dichloromethane were inlet 220 °C, oven 50 °C for 2 min, ramp to 270 °C at 15 °C/min. The flow was set to 50 mL/min, the split ratio was 42:1, and the solvent delay was 1.05 min. The mass scan range was 50–700 *m*/*z*. The syringe wash solvent was dichloromethane.

4.3. General procedure (A) for the common Sonogashira cross-coupling reactions

The Pd species (0.030 mmol), CuI (0.020 mmol), and the desired solvent (1 mL) were added to a screw cap vial and capped with a Teflon coated cap. The mixture was then stirred at room temperature under N_2 for 5 min. The ligand (0.060 mmol), amine (1.2 mmol), and aryl halide (1.0 mmol) were added to the reaction mixture. The alkyne (1.2 mmol) was slowly added and the reaction mixture was placed in an oil bath maintained at a constant temperature and stirred under N_2. The resulting mixture was cooled to room temperature, diluted with EtOAc, and washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc to give the desired product.

4.4. General procedure (B) for the Pd-free Sonogashira cross-coupling reactions

CuI (0.0525 mmol), DABCO (0.121 mmol), Cs_2CO_3 (2 equiv, or 4 equiv), bromobenzene (0.5 mmol) as well as 3 mL DMF were added to a screw cap vial. Phenylacetylene (0.6 mmol) was slowly added, the mixture was placed under N_2, and capped with a Teflon coated cap. The mixture was placed in a 135 °C oil bath and stirred under N_2 until completion. The resulting mixture was cooled to room temperature, vacuum-filtered, and rinsed with hexane. The residue was purified by flash column chromatography on silica gel, eluting with hexane to give the desired product.

4.5. General procedure (C) for the Cu-free Sonogashira cross-coupling reactions

The Pd species (0.030 mmol), ligand (0.060 mmol), Cs_2CO_3 (1.2 mmol), and solvent were added to a screw cap vial. The aryl halide (0.5 mmol) was added and the mixture stirred at room temperature for 25 min under N_2. The desired alkyne (0.60 mmol) was then added. The mixture was placed in a 90 °C oil bath and stirred under N_2 until completion of reaction. The reaction mixture was then cooled to room temperature, diluted with EtOAc, and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel, eluting with the appropriate hexane/EtOAc mixture to give the desired product.

4.6. Literature precedence

Our experimental procedure gave compounds with spectral properties consistent with those in the literature for the following compounds; **2a**, **2b**, **2d**, **2f**, **2g**, **2h**, **2i**, **2k**, **2l**, **2m**, and **2o** (see Supplementary data for details).

*4.6.1. 2-Chloro-4-(phenylethynyl)phenol (**2c**)*

Prepared by general procedure C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.52–7.48 (m, $3H_{Ar}$), 7.37–7.33 (m, $4H_{Ar}$), 6.99 (d, $1H_{Ar}$, J=8.5 Hz), 5.68 (s, $1H_{OH}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.6, 132.2, 132.1, 131.6, 128.5, 128.4, 123.2, 119.9, 116.7, 116.4, 88.9, 87.9; GC/MS rt=13.02 min, M^+=228.1 *m*/*z*; HRMS exact mass calculated for $C_{19}H_9ClO$ (M^++H) 229.0324, found 229.0321.

*4.6.2. 1-Fluoro-2-(phenylethynyl)benzene (**2e**)*

Prepared by general procedure C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.61–7.51 (m, $3H_{Ar}$), 7.40–7.28 (m, $4H_{Ar}$), 7.17–7.10 (m, $2H_{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.3, 131.9, 131.6, 129.6, 128.5, 128.4, 128.3, 125.7, 123.7, 123.1, 93.5, 88.5, 20.9; GC/MS rt=10.60 min, M^+=197.1 *m*/*z*; HRMS exact mass calculated for $C_{14}H_9F$ (M^++H) 197.0688, found 197.0690.

*4.6.3. 2-(Phenylethynyl)naphthalene (**2n**)*

Prepared by general procedure C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (m, $1H_{Ar}$), 7.86–7.82 (m, $3H_{Ar}$), 7.63–7.60 (m, $3H_{Ar}$), 7.54–7.50 (m, $2H_{Ar}$), 7.42–7.36 (m, $3H_{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.8, 131.6, 128.5, 128.5, 128.2, 127.9, 126.8, 126.7, 90.0, 89.9; GC/MS rt=14.58 min, M^+=229.2 *m*/*z*; HRMS exact mass calculated for $C_{18}H_{12}$ (M^++H) 229.0939, found 229.0940.

*4.6.4. 2-((2-Methoxyphenyl)ethynyl)pyridine (**3b**)*

Prepared by general procedure C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.60 (d, $1H_{Ar}$, J=5 Hz), 7.65 (t, $1H_{Ar}$, J=7.7 Hz), 7.56–7.52 (m, $2H_{Ar}$), 7.35–7.29 (m, $1H_{Ar}$), 7.22–718 (m, $1H_{Ar}$), 6.95–6.88 (m, $2H_{Ar}$), 3.89 (s, $1H_{Me}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.5, 150.0, 143.8, 136.1, 134.1, 130.6, 127.3, 122.6, 120.5, 111.6, 110.8, 92.7, 85.9, 55.9; GC/MS

rt=12.95 min, M^+=209.1 *m/z*; HRMS exact mass calculated for $C_{14}H_{11}NO$ (M^++H) 210.0841, found 210.0845.

*4.6.5. 2-(1-Naphthylethynyl)pyridine (**3c**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (s, 1H$_{Ar}$), 8.49 (d, 1H$_{Ar}$, *J*=8.25 Hz), 7.88–7.83 (m, 3H$_{Ar}$), 7.70–7.47 (m, 5H$_{Ar}$), 7.27–7.23 (m, 1H$_{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 143.7, 136.3, 133.4, 133.2, 131.3, 129.6, 128.4, 127.1, 126.7, 126.3, 125.3, 122.9, 119.9, 99.9, 93.6, 87.6; GC/MS rt=14.93 min, M^+=229.1 *m/z*; HRMS exact mass calculated for $C_{17}H_{11}N$ (M^++H) 230.0891, found 230.0894.

*4.6.6. 2-(Hex-1-ynyl)pyridine (**3d**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (m, 1H$_{Ar}$), 7.58 (m, 1H$_{Ar}$), 7.34 (m, 1H$_{Ar}$), 7.15 (m, 1H$_{Ar}$), 2.41 (t, 2H, *J*=7 Hz), 1.64–1.40 (m, 4H), 0.91 (t, 3H, *J*=7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.8, 144.1, 136.1, 126.8, 122.3, 91.2, 80.4, 30.5, 22.1, 19.1, 13.7; GC/MS rt=8.76 min, M^+=159.1 *m/z*; HRMS exact mass calculated for $C_{11}H_{13}N$ (M^++H) 160.1048, found 160.1052.

*4.6.7. 2-(Oct-1-ynyl)pyridine (**3e**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, 1H$_{Ar}$), 7.56 (td, 1H$_{Ar}$), 7.33 (d, 1H$_{Ar}$), 7.13 (m, 1H$_{Ar}$), 2.39 (t, 2H$_{Al}$, *J*=6.8 Hz), 1.59 (p, 2H$_{Al}$, *J*=6.8 Hz), 1.46–1.39 (m, 2H$_{Al}$), 1.29–1.24 (m, 4H$_{Al}$), 0.85 (t, 3H$_{Al}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.8, 144.0, 136.1, 126.8, 122.3, 91.3, 80.4, 31.4, 28.7, 22.6, 19.4, 14.1; GC/MS rt=10.34 min, M^+=186.1 *m/z*; HRMS exact mass calculated for $C_{13}H_{17}N$ (M^++H) 188.1361, found 188.1363.

*4.6.8. 6-(Phenylethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4a**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.93 (s, 1H$_{2,8}$), 8.45 (s, 1H$_{2,8}$), 7.75–7.71 (m, 2H$_{Ar}$), 7.42–7.35 (m, 3H$_{Ar}$), 6.52 (t, 1H$_{1'}$, *J*=6 Hz), 4.63 (m, 1H$_{3'}$), 4.04 (q, 1H$_{4'}$, *J*=3 Hz), 3.90 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.75 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.68 (m, 1H$_{2'}$), 2.47 (m, 1H$_{2'}$), 0.90 (d, 18H, *t*-Bu), 0.08 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.6, 151.2, 143.9, 141.9, 134.9, 132.8, 129.9, 128.5, 121.6, 98.4, 88.2, 84.7, 84.3, 72.1, 62.9, 41.4, 26.0, 25.8, 18.5, 18.1, −4.58, −4.70, −5.27, −5.38. HRMS exact mass calculated for $C_{30}H_{45}N_4O_3Si_2$ (M^++H) 565.2952, found 565.3030.

*4.6.9. 6-((2-Methoxyphenyl)ethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4c**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.91 (s, 1H$_{2,8}$), 8.43 (s, 1H$_{2,8}$), 7.65 (d, 1H$_{Ar}$, *J*=7.4 Hz), 7.35 (t, 1H$_{Ar}$), 6.96–6.88 (m, 2H$_{Ar}$), 6.51 (t, 1H$_{1'}$, *J*=6 Hz), 4.64 (m, 1H$_{3'}$), 4.02 (q, 1H$_{4'}$, *J*=3 Hz), 3.92 (s, 3H$_{OMe}$), 3.86 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.76 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.66 (m, 1H$_{2'}$), 2.45 (m, 1H$_{2'}$), 0.89 (d, 18H, *t*-Bu), 0.06 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.1, 152.5, 151.1, 143.8, 142.2, 134.8, 134.6, 131.6, 120.5, 110.9, 110.8, 95.5, 88.2, 84.6, 72.0, 62.8, 56.0, 41.3, 26.0, 25.8, 18.5, 18.1, −4.62, −4.72, −5.28, −5.38. HRMS exact mass calculated for $C_{31}H_{47}N_4O_4Si_2$ (M^++H) 595.3058, found 595.3123.

*4.6.10. 6-(Naphthalene-1-ylethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4d**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (s, 1H$_{2,8}$), 8.67 (d, 1H$_{Ar}$, *J*=8.5 Hz), 8.52 (s, 1H$_{2,8}$), 8.01–7.87 (m, 3H$_{Ar}$), 7.66 (m, 1H$_{Ar}$), 7.58–7.47 (m, 2H$_{Ar}$), 6.55 (t, 1H$_{1'}$, *J*=6.3 Hz), 4.66 (m, 1H$_{3'}$), 4.06 (q, 1H$_{4'}$, *J*=3 Hz), 3.89 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.80 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.70 (m, 1H$_{2'}$), 2.49 (m, 1H$_{2'}$), 0.92 (d, 18H, *t*-Bu), 0.10 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.6, 151.2, 144.0, 142.0, 139.9, 137.2, 135.2, 133.6, 133.2, 132.3, 130.6, 128.4, 127.5, 129.8, 126.5, 125.2, 119.2, 96.9, 89.2, 88.2, 84.7, 71.9, 62.8, 41.4, 26.1, 25.8, 18.5, 18.1, −4.59, −4.69, −5.26, −5.36. HRMS exact mass calculated for $C_{34}H_{47}N_4O_3Si_2$ (M^++H) 615.3108, found 615.3209.

*4.6.11. 6-(Oct-1-ynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4e**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (s, 1H$_{2,8}$), 8.38 (s, 1H$_{2,8}$), 6.50 (t, 1H$_{1'}$, *J*=6 Hz), 4.61 (m, 1H$_{3'}$), 4.02 (q, 1H$_{4'}$, *J*=3 Hz), 3.86 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.76 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.62 (m, 1H$_{2'}$), 2.58 (t, 2H$_{Al}$, *J*=7 Hz), 2.44 (m, 1H$_{2'}$), 1.70 (m, 2H$_{Al}$), 1.46 (m, 2H$_{Al}$), 1.29 (m, 4H$_{Al}$), 0.90 (d, 18H, *t*-Bu), 0.10 (m, 3H$_{Al}$, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.5, 150.9, 143.6, 142.5, 134.9, 101.7, 88.2, 84.6, 76.2, 72.1, 62.9, 41.4, 31.4, 28.8, 28.2, 26.0, 25.8, 22.6, 20.1, 18.5, 18.1, 14.1, −4.48, −4.59, −5.29, −5.39. HRMS exact mass calculated for $C_{30}H_{53}N_4O_3Si_2$ (M^++H) 573.3578, found 573.3661.

*4.6.12. 6-((2-Methylphenyl)ethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4f**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.96 (s, 1H$_{2,8}$), 8.44 (s, 1H$_{2,8}$), 7.68 (d, 1H$_{Ar}$, *J*=7.6 Hz), 7.34–7.27 (m, 2H$_{Ar}$), 7.21 (m, 1H$_{Ar}$), 6.52 (t, 1H$_{1'}$, *J*=6 Hz), 4.63 (m, 1H$_{3'}$), 4.04 (q, 1H$_{4'}$, *J*=3 Hz), 3.86 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.76 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.69 (m, 1H$_{2'}$), 2.64 (s, 3H$_{Me}$), 2.47 (m, 1H$_{2'}$), 0.90 (d, 18H, *t*-Bu), 0.09 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.6, 151.1, 143.9, 142.1, 141.7, 135.0, 133.1, 129.9, 129.7, 125.7, 121.4, 97.6, 88.2, 88.1, 84.6, 72.0, 62.8, 41.3, 26.0, 25.8, 21.0, 18.5, 18.1, −4.60, −4.70, −5.29, −5.38. HRMS exact mass calculated for $C_{31}H_{47}N_4O_3Si_2$ (M^++H) 579.3108, found 579.3177.

*4.6.13. 6-((4-Methylphenyl)ethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4g**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.92 (s, 1H$_{2,8}$), 8.44 (s, 1H$_{2,8}$), 7.63 (d, 2H$_{Ar}$, *J*=8 Hz), 7.19 (d, 2H$_{Ar}$, *J*=8 Hz), 6.53 (d, 1H$_{1'}$, *J*=6 Hz), 4.63 (m, 1H$_{3'}$), 4.03 (q, 1H$_{4'}$, *J*=3 Hz), 3.88 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.77 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.68 (m, 1H$_{2'}$), 2.47 (m, 1H$_{2'}$), 2.38 (s, 3H$_{Me}$), 0.91 (d, 18H, *t*-Bu), 0.10 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.6, 151.1, 143.8, 142.1, 140.4, 134.8, 132.8, 129.3, 118.5, 98.9, 88.2, 84.7, 83.9, 72.1, 62.9, 41.3, 26.1, 25.8, 21.8, 18.5, 18.1, −4.60, −4.71, −5.26, −5.37. HRMS exact mass calculated for $C_{31}H_{47}N_4O_3Si_2$ (M^++H) 579.3108, found 579.3181.

*4.6.14. 6-((4-Methoxyphenyl)ethynyl)-9-[2′-deoxy-3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranosyl]purine (**4h**)*

Prepared by general procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.90 (s, 1H$_{2,8}$), 8.43 (s, 1H$_{2,8}$), 7.68 (d, 2H$_{Ar}$, *J*=9 Hz), 6.90 (d, 2H$_{Ar}$, *J*=9 Hz), 6.52 (d, 1H$_{1'}$, *J*=6 Hz), 4.63 (m, 1H$_{3'}$), 4.03 (q, 1H$_{4'}$, *J*=3 Hz), 3.87 (dd, 1H$_{5'}$, *J*=4, 11 Hz), 3.83 (s, 3H$_{OMe}$), 3.77 (dd, 1H$_{5'}$, *J*=3, 11 Hz), 2.68 (m, 1H$_{2'}$), 2.46 (m, 1H$_{2'}$), 0.89 (d, 18H, *t*-Bu), 0.09 (d, 12H, –Si((CH$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.0, 152.6, 151.0, 143.7, 142.2, 134.6, 127.1, 114.2, 113.5, 99.1, 88.2, 84.6, 83.7, 72.1, 62.9, 55.4, 41.3, 26.1, 25.9, 18.5, 18.1, −4.60, −4.70, −5.27, −5.37. HRMS exact mass calculated for $C_{31}H_{47}N_4O_4Si_2$ (M^++H) 595.3058, found 595.3124.

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Supplementary data

General experimental procedures and characterization data for all new products (^{1}H and ^{13}C NMR, HRMS, and GC–MS). This material is available via the Internet at www.sciencedirect.com.

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.064.

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