# Pd-Catalyzed Regiodivergent *N*$^6$ *Versus* C$^{\text{vinyl}}$ Arylation of 8-Vinyl Adenine Nucleosides, Sequential Diarylation, Fluorescence Properties, and Computational Evaluations**

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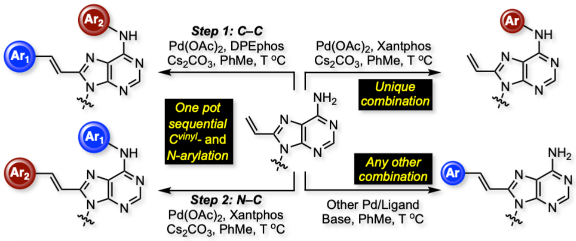


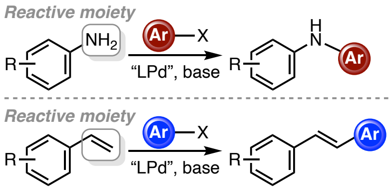
- ■ *Reactions of both 2'-deoxyribo and ribonucleoside precursors.*
- ■ *Selective N-arylation with aryl bromides and iodides.*
- ■ *Sequential C$^{\text{vinyl}}$- and N-arylation to yield diarylated compounds.*
- ■ *Fluorescence and associated TDDFT computational studies.*

Palladium-catalyzed aryl amination and Heck arylation reactions are complementary transformations, generally requiring a suitable catalyst combination and a base. With substrates containing both an amino group and a vinyl moiety, control of C–N versus C–C reactivity can lead to regiodivergent functionalizations. With this focus, reactions of silyl-protected 8-vinyl 2'-deoxyadenosine and adenosine with aryl bromides and iodides have been studied. Pd(OAc)$_2$, Pd$_2$(dba)$_3$, and preformed dichloro[1,1'-bis(di-*t*-butylphosphino)ferrocene]palladium (II) (Pd-118) were evaluated as metal sources. Ligands tested were Xantphos, DPEphos, BIPHEP, and

DPPF, with $Cs_2CO_3$ and $K_3PO_4$ as bases. In toluene as solvent, the $Pd(OAc)_2$/Xantphos/$Cs_2CO_3$ combination was uniquely capable of predominant $N^6$ arylation. Aryl bromides and iodides gave comparable product yields. Replacement of $Cs_2CO_3$ with $K_3PO_4$ redirected arylation from the nitrogen atom to the vinyl carbon atom, and all other catalyst, ligand, and base combinations gave $C^{vinyl}$ arylation as well. Simply switching from $Pd(OAc)_2$ to $Pd_2(dba)_3$ resulted in loss of the $N^6$-selectivity and $C^{vinyl}$ arylation was favored. Based upon these results, using two structurally similar catalytic systems sequential $C^{vinyl}$ and $N^6$ arylations of the nucleosides were accomplished. Some of the products were converted to other novel nucleoside analogues. Because some compounds were fluorescent, their photophysical properties were assessed experimentally and computationally.

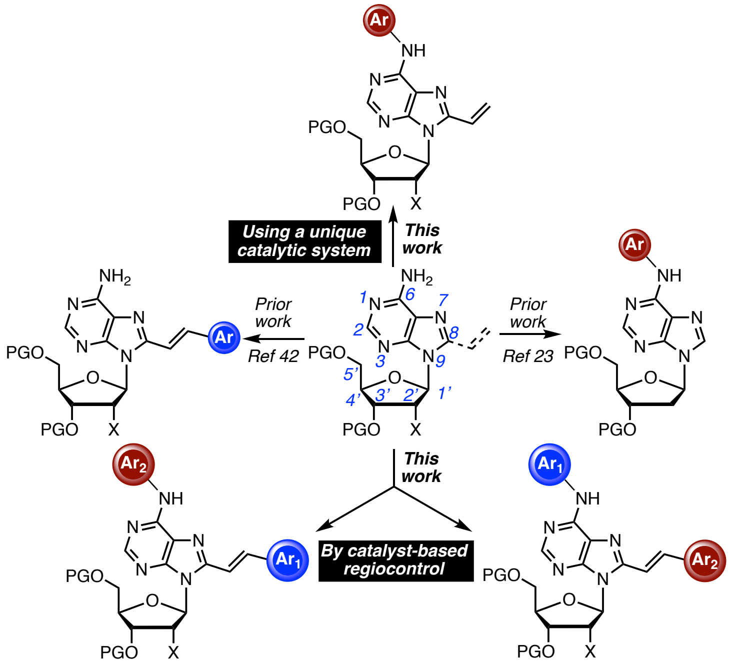
## 1. Introduction

From the discovery of the amination of PhBr by *n*-$Bu_3SnNEt_2$ with a Pd-catalyst,[1] to an improvement of this reaction,[2] and subsequent developments in tin-free C–N bond-formation, this reaction has become invaluable in the synthesis repertoire.[3–13] A typical contemporary C–N bond-forming reaction involves an amine, an aryl electrophile (halide or sulfonate), a suitable base, and a metal catalyst with a supporting ligand. A complementary and equally important transformation is the Heck, C–C bond-forming reaction.[14–19] Like amination, this transformation of an olefin also involves an aryl (or vinyl) halide or sulfonate, a ligand-metal catalyst, and a suitable base. Scheme 1 shows these complementary transformations.



**Scheme 1.** Complementarity of *N*- and Heck arylation.

In the context of modifying the important family of nucleoside biomolecules by palladium catalysis, we[20–29] and others[30–40] have explored a variety of C–N bond-forming reactions.[41] We have studied the difficult $N^6$ arylation of silyl-protected 2’-deoxyadenosine[23] and Heck-like reactivity of C-8 vinyl adenosine and 2’-deoxyadenosine (Scheme 2).[42] Extending the conjugation of adenine nucleosides with an 8-vinyl substituent gave products with good fluorescence emission, red-shifted wavelength, and quantum yield.[43–46] Therefore, 8-vinyl adenine nucleoside analogues are excellent fluorescent probes. In addition, an 8-vinyl-2’-deoxyadenosine analogue was shown to possess solvatochromic properties.[47] In the quest for novel nucleoside modification methods and for diversification of the nucleoside scaffold, we were interested in probing *control of C–N versus C–C bond formation and then utilizing that control for sequential diarylation (hyperfunctionalization)* of 8-vinyl adenosine and 2’-deoxyadenosine (Scheme 2). The labile glycosidic bond and the multiple potential metal-sequestering Lewis basic atoms in



**Scheme 2.** C–N and C–C bond-forming reactions of adenine nucleosides, and sequential C–C and C–N bond formation by catalyst control.

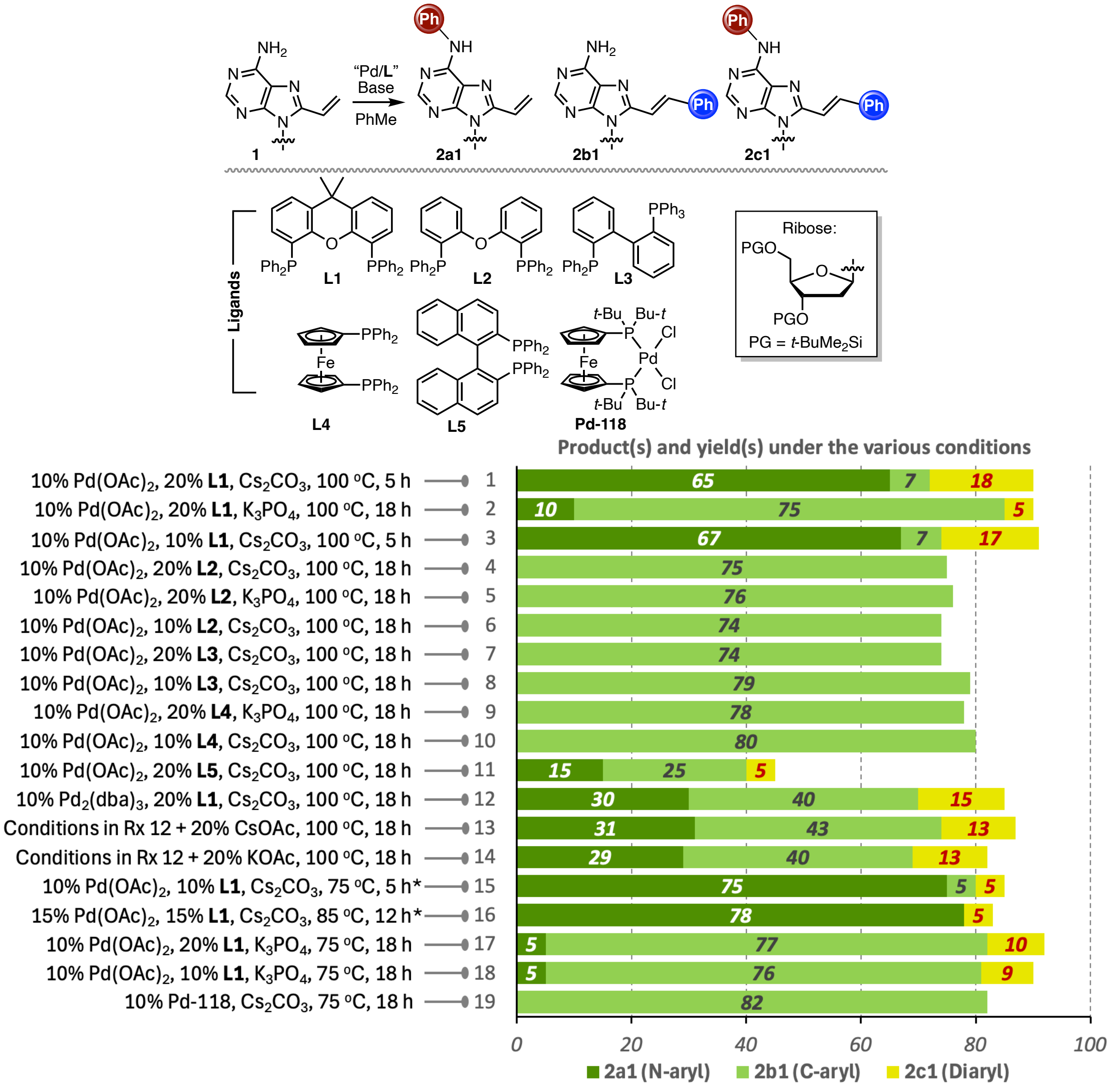
nucleobases can pose significant problems to the reactions of nucleosides.[48] Notably, metal binding to $N^1$ and $N^7$ atoms of adenine is documented.[49,50]

## 2. Results and Discussion

The present work commenced with an analysis of reactions of disilyl 8-vinyl-2′-deoxyadenosine (**1**, 0.1 mmol) and PhI (1.5 mmol, unless noted otherwise), in PhMe (1 mL). The metal sources analyzed were $Pd(OAc)_2$, $Pd_2(dba)_3$, and [1,1′-bis(di-*t*-butylphosphino)ferrocene]dichloropalladium(II) complex (Pd-118, shown in Scheme 3). The ligands evaluated are shown in Scheme 3, and the bases tested were $Cs_2CO_3$ and $K_3PO_4$ (1.5 equiv. of each). The results from these initial reactions, numbered 1–19, are graphically shown in Scheme 3 (% indicates mol%). With the $Pd(OAc)_2$/Xanthphos (**L1**)/$Cs_2CO_3$ combination (reaction #1), the major product **2a1** resulted from $N^6$ arylation, with minor $C^{vinyl}$ arylation, as well as $N^6$,$C^{vinyl}$ diarylation. The total yield of products was a high 90%. Just replacement of $Cs_2CO_3$ with $K_3PO_4$ led to a selectivity reversal, with the $C^{vinyl}$ arylated product **2b1** becoming major, but the total yield of products remained 90% (reaction #2). Reducing the amount of **L1** had little effect on the yield or selectivity (reaction #3). Intriguingly, use of DPEPhos (**L2**) led to exclusive $C^{vinyl}$ selectivity, yielding product **2b1** in every case (reaction #4–#6); this was independent of the base used and the Pd/ligand ratio. *Thus, dismantling the Xantphos scaffold removes the chemoselectivity for $N^6$ arylation!*

BIPHEP (**L3**) and DPPF (**L4**) also showed $C^{vinyl}$-selective arylation (reaction #7–#10), comparable to **L2**. BINAP (**L5**) gave overall poorer results and low $N^6$/$C^{vinyl}$ selectivity as well (reaction #11). Unexpectedly, use of $Pd_2(dba)_3$ instead of $Pd(OAc)_2$, in combination with **L1** and

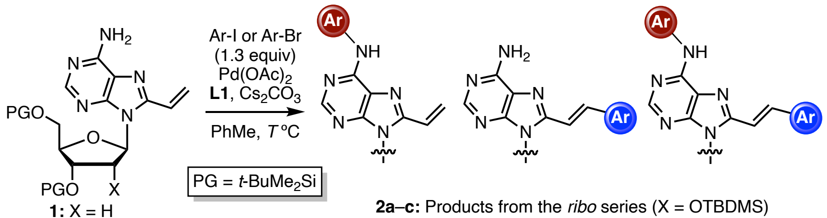
$Cs_2CO_3$, gave a 1.3 : 1 ratio of C$^{vinyl}$- and $N^6$-arylation (reaction #12), but the overall yield of products in this case was a high 85%. Notably, in our prior work on *N*-arylation of 2'-deoxyadenosine,[23] where a competitively reactive vinyl moiety was absent, $Pd_2(dba)_3$/**L1**/$Cs_2CO_3$ gave a reaction at the exocyclic nitrogen atom. To assess whether acetate had any influence on the product distribution, two reactions were conducted under conditions of reaction #12 but with 20 mol% of added CsOAc or KOAc (reaction #13 and #14). The outcomes were not markedly different from that of reaction #12.



**Scheme 3**. Evaluation of conditions for the arylation of disilyl 8-vinyl 2′-deoxyadenosine **1** (*reaction # 15 and #16 were conducted with 1.3 equiv. of PhI and PhBr, respectively).

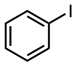
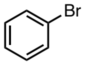
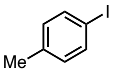
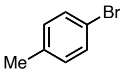
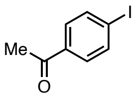
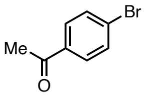
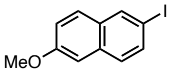
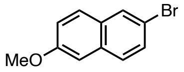
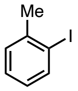
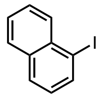
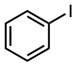
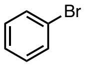
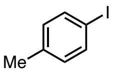
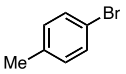
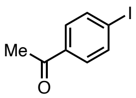
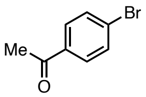
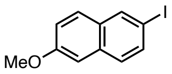
In an effort to improve the selectivity of *N*$^6$-arylation, a lower reaction temperature of 75 °C (instead of 100 °C) and a lowered amount of PhI (1.3 equiv. instead of 1.5 equiv.) were tested (#15). A high overall 85% yield of products was obtained and, in comparison to reaction #3, these conditions gave higher *N*-selectivity at the cost of the C–C reaction (15 : 1 *versus* 9.6 : 1). A reaction with PhBr (1.3 equiv.) was also tested (#16) but this required a slightly higher amount of Pd(OAc)$_2$ and **L1** (15 mol% each), as well as a temperature of 85 °C. This reaction was slower, but the overall yield of products was 83%. Notably, in comparison to the reaction with PhI (#15), this reaction did not produce the C$^{vinyl}$-arylation product **2b1**, but the amount of *N*$^6$,C$^{vinyl}$ diarylated **2c1** was comparable. Reactions using Pd(OAc)$_2$/**L1**/K$_3$PO$_4$ at the lower temperature were also evaluated (#17 and #18). Under these conditions, in comparison to reaction #2, *N*$^6$ arylation was slightly suppressed and *N*$^6$,C$^{vinyl}$ diarylation increased, while the extent of C$^{vinyl}$ arylation remained similar. Finally, with Pd-118/Cs$_2$CO$_3$ exclusive reaction at the vinyl moiety occurred (#19). This result is similar to that obtained with Pd(OAc)$_2$/**L4**/Cs$_2$CO$_3$ (#10), albeit at a lower temperature. A tabular form of these results is provided in the Supporting Information (Table S1). Thus, the current results show that a fine balance between the Pd source, ligand, and base influences the *N*$^6$ *versus* C$^{vinyl}$ arylation selectivity, and this can be exploited for regiodivergent arylation. First, based on these observations, a variety of *N*$^6$-aryl 8-vinyl 2′-deoxyadenosine and adenosine analogues were synthesized from the corresponding precursors **1** and **3**, using a series of aryl iodides and bromides. These results are summarized in Table 1.

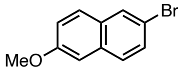
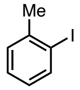
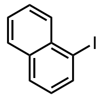
**Table 1.** Yields of the *N*$^6$-aryl 8-vinyl 2′-deoxyadenosine and adenosine analogues, and the accompanying minor products.[a,b]



**1:** X = H
**3:** X = OPG

**2a–c:** Products from the *ribo* series (X = OTBDMS)
**4a–c:** Products from the *2'-deoxyribo* series (X = H)

| Entry | Ar-X | Conditions[c] | $N^6$-aryl [%] | $\mathrm{C}^{\mathrm{vinyl}}$-aryl [%] | Diaryl [%] |
|---|---|---|---|---|---|
| *2'-Deoxyribo series* | | | | | |
| 1 |  | A | **2a1:** 75 | **2b1:** 5 | **2c1:** 5 |
| 2 |  | B | **2a1:** 78 | **2b1:** –[d] | **2c1:** 5 |
| 3 |  | A | **2a2:** 71 | **2b2:** 7 | **2c2:** 4 |
| 4 |  | B | **2a2:** 70 | **2b2:** trace | **2c2:** 3 |
| 5 |  | A | **2a3:** 77 | **2b3:** 6 | **2c3:** 7 |
| 6 |  | B | **2a3:** 80 | **2b3:** trace | **2c3:** 4 |
| 7[e] |  | A | **2a4:** 64 | **2b4:** –[d] | **2c4:** –[d] |
| 8[e] |  | B | **2a4:** 65 | **2b4:** –[d] | **2c4:** –[d] |
| 9 |  | A | **2a5:** 72 | **2b5:** 6 | **2c5:** 5 |
| 10[e] |  | A | **2a6:** 71 | **2b6:** trace | **2c6:** –[d] |
| *Ribo series* | | | | | |
| 11 |  | C | **4a1:** 71 | **4b1:** 3 | **4c1:** 7 |
| 12 |  | D | **4a1:** 74 | **4b1:** trace | **4c1:** 6 |
| 13 |  | C | **4a2:** 70 | **4b2:** 7 | **4c2:** 5 |
| 14 |  | D | **4a2:** 69 | **4b2:** 2 | **4c2:** 2 |
| 15 |  | C | **4a3:** 78 | **4b3:** 5 | **4c3:** –[d] |
| 16 |  | D | **4a3:** 79 | **4b3:** trace | **4c3:** –[d] |
| 17[e] |  | C | **4a4:** 64 | **4b4:** –[d] | **4c4:** –[d] |

|  |  |  |  |  |  |
|---|---|---|---|---|---|
| 18[e] |  | D | **4a4:** 62 | **4b4:** –[d] | **4c4:** –[d] |
| 19 |  | C | **4a5:** 71 | **4b5:** 7 | **4c5:** 4 |
| 20[e] |  | C | **4a6:** 68 | **4b6:** 4 | **4c6:** 3 |

[a] Reactions were conducted using 0.1 mmol of nucleoside **1** in 1 mL of PhMe or 0.08 mmol of nucleoside **3** in 0.8 mL of PhMe, and 1.5 equiv of $Cs_2CO_3$, over a reaction time of 12 hours (5 hours for entries 1 and 2, also see footnote [e]).

[b] Yields are of isolated and purified products.

[c] Conditions *A:* 10 mol% of $Pd(OAc)_2$, 10 mol% of **L1**, 85 °C (75 °C for entry 1). *Conditions B:* 15 mol% of $Pd(OAc)_2$, 15 mol% of **L1**, 85 °C. *Conditions C:* 15 mol% of $Pd(OAc)_2$, 15 mol% of **L1**, 100 °C. *Conditions D:* 20 mol% of $Pd(OAc)_2$, 20 mol% of **L1**, 100 °C.

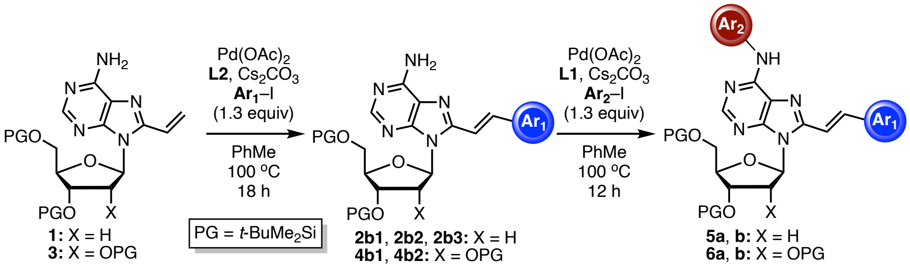
[d] Not detected.

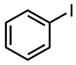
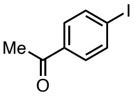
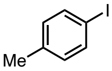
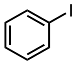
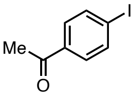
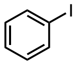
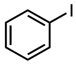
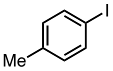
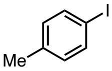
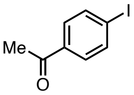
[e] Reaction time was 24 hours.

Minor modifications to the reaction conditions were necessary at this stage. Although the reaction of PhI with substrate **1** was complete in 5 hours at 75 °C, that of *p*-iodotoluene remained incomplete. A slight increase in temperature to 85 °C and a longer reaction time of 12 hours, led to a complete reaction. Thus, these conditions were applied to the remaining reactions with substrate **1** and, as in previous studies, 10 mol% of Pd was necessary for efficient conversion. However, with the ribonucleoside precursor **3**, reactions with 10 mol% catalyst and a lower temperature produced incomplete reactions. Thus, the catalyst load and reaction temperature had to be elevated to attain complete conversions (entries 11–18). Other than for these differences, the 2'-deoxyribo and ribo precursors, **1** and **3**, gave generally similar outcomes. With 2-halo 6-methoxynaphthalenes, a longer 24 hour reaction time was needed with both nucleoside substrates. In many cases, reactions with the aryl bromides gave none to trace amounts of $C^{vinyl}$ arylation products (e.g., entries 2, 4, 6, 12, and 16). An *ortho*-methyl group of *o*-iodotoluene and the *peri* proton of 1-iodonaphthalene *did not* deter reaction, but reaction of the latter with substrates **1** and **3** required 24 hours for an optimal outcome.

These data then led to a question on using the results from the regiodivergent arylation for sequential arylation at the two reactive centers, as a *two-step, one-pot transformation*. In initial studies, it was determined that the sequence of $C^{vinyl}$ arylation and then $N^6$ arylation was superior to the opposite order, due to ease of purification of the final products. Although a variety of conditions could be utilized for C–C bond formation, we selected **L2** to further bolster our hypothesis that dismantling the Xantphos (**L1**) structure redirects catalytic activity from $N^6$ arylation to $C^{vinyl}$ arylation. In the course of these investigations, we conducted a reaction of substrate **1** with PhI, where $Pd(OAc)_2$ was added only at the start of the reaction. With **L2** and $Cs_2CO_3$ present in this step, $C^{vinyl}$ arylation occurred smoothly. Upon completion of this step, *p*-iodoacetophenone, **L1**, and additional $Cs_2CO_3$ were added, and the reaction was continued. However, this did not result in $N^6$ arylation, but the intermediate Heck-like product **2b1** was isolated in a 65% yield. Although Pd black was not observed, it appears that metal deactivation occurs at the end of step 1. On the other hand, when $Pd(OAc)_2$ was also added in the second step, $N^6$ arylation occurred. Thus, on the basis of these collective observations several $C^{vinyl}$, $N^6$ diarylations were successfully performed (Table 2).

**Table 2.** Sequential $C^{vinyl}$ and $N^6$ arylation of 8-vinyl nucleoside substrates **1** and **3**.[a,b]



| Entry | Substrate | **Ar$_1$**–I | Step 1 conditions | **Ar$_2$**–I | Step 2 conditions | Final yield % |
|---|---|---|---|---|---|---|
| 1 | **1** |  | A[c] |  | B[d] | **5a:** 38 |
| 2 | **1** |  | A[c] |  | B[d] | **5b:** 42 |
| 3 | **1** |  | A[c] |  | B[d]<br>C[f] | ND (56%)[e]<br>ND[g] |
| 4 | **3** |  | A[c] |  | C[f] | **6a:** 35 |
| 5 | **3** |  | A[c] |  | C[f] | **6b:** 37 |

[a] Reactions were conducted using 0.1 mmol of nucleoside **1** in 1 mL of PhMe or 0.08 mmol of nucleoside **3** in 0.8 mL of PhMe, and 1.5 equiv of $Cs_2CO_3$ for each step.
[b] Yields are of isolated and purified products.
[c] *Conditions A:* 10 mol% of $Pd(OAc)_2$, 10 mol% of **L2**, 100 °C.
[d] *Conditions B:* 10 mol% of $Pd(OAc)_2$, 10 mol% of **L1**, 100 °C.
[e] The diaryl product was not detected but intermediate product **2b3** was isolated in a 56% yield.
[f] *Conditions C:* 20 mol% of $Pd(OAc)_2$, 20 mol% of **L1**, 100 °C.
[g] The diaryl product was not detected, but intermediate product **2b3** was identified from the $^1$H NMR spectrum of the crude product mixture.

As shown in entries 1 and 2, sequential C$^{vinyl}$ and $N^6$ arylation of 8-vinyl 2'-deoxyadenosine derivative **1** can be accomplished in a two-step, one-pot conversion, giving products **5a** and **5b** (entries 1 and 2). Entry 3 is the reverse order of events of entry 1. Here, although C$^{vinyl}$ arylation proceed effectively (**1** was fully consumed), the subsequent $N^6$ arylation did not proceed. This is likely due to the highly extended electronic conjugation in the intermediate C$^{vinyl}$ aryl product **2b3** (Figure 1). In one case (entry 3) this intermediate was isolated (56% yield) and characterized, and in the second instance, it was identified by $^1$H NMR analysis of the crude reaction mixture. We have previously synthesized and characterized the C$^{vinyl}$ arylation product from the reaction of substrate **1** with *p*-iodoacetophenone.[42] The 8-vinyl adenosine derivative **3** also underwent comparable reactions, leading to products **6a** and **6b** in marginally lower isolated yields as compared to those from substrate **1**. The two-step yields indicate that, on average, each step proceeded in *ca.* 60% yield. Product **6b** was prone to isomerization on silica gel and neutralized silica gel was used for its purification, leading to predominantly the trans isomer. We have previously observed such isomerization of 8-styryl adenine nucleoside derivatives.[42]

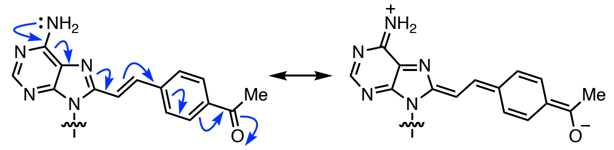
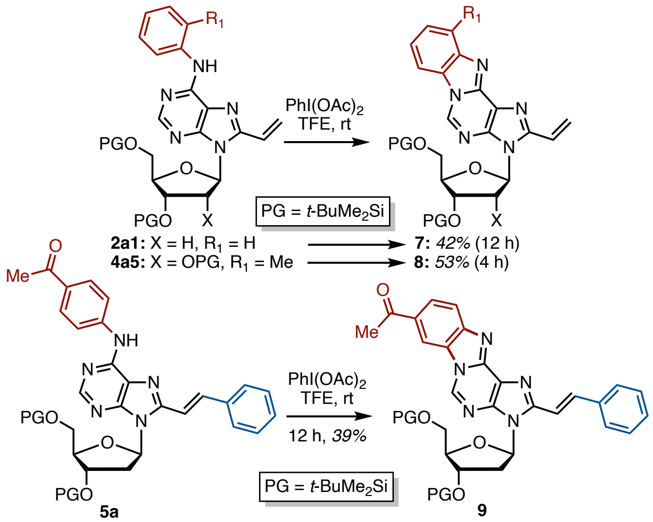


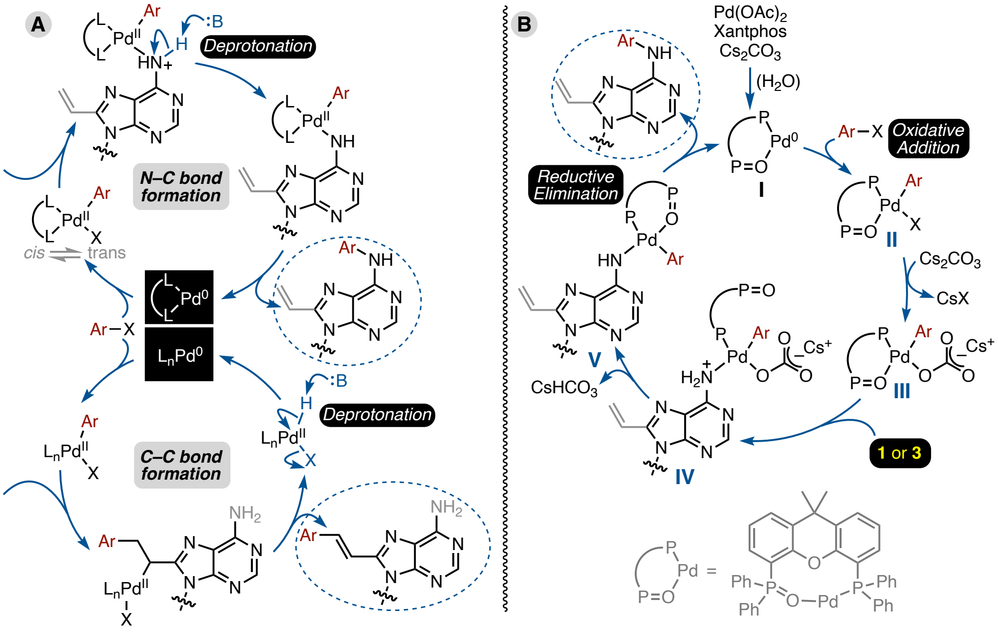
**Figure 1.** Resonance interaction leading to the diminished reactivity of the exocyclic amino group.

Finally, we have combined the unique arylation capability offered by the Pd(OAc)$_2$/**L1**/Cs$_2$CO$_3$ combination and our metal-free PhI(OAc)$_2$-mediated cyclizations[51,52] to access novel nucleoside derivatives. Two *N*$^6$-aryl 8-vinyl nucleosides **2a1** and **4a5**, and one *N*$^6$-aryl 8-(β-styryl) nucleoside **5a** were converted to the corresponding benzimidazopurine nucleoside derivatives **7**, **8**, and **9** using PhI(OAc)$_2$-mediated cyclizations as shown in Scheme 4. We have noted that compounds **7** and **8** were somewhat sensitive to purification whereas compound **9** was substantially more sensitive, but such motifs are nevertheless attainable.



**Scheme 4.** Synthesis of novel 8-vinyl and 8-(β-styryl) benzimidazopurine nucleoside analogues.

Unraveling the mechanistic underpinnings of the observed catalyst-dependent regio differentiation is not trivial. However, some factors may be worth consideration in the two catalytic cycles, which share some similarities (Scheme 5A). Notably, the role of base is quite different in the two processes. Whereas in the amination reaction base is involved in deprotonation of the amido-Pd complex, in the Heck reaction base serves to regenerate the Pd$^0$ catalyst (shown in Scheme 5A).



**Scheme 5.** (A) The complementary regiodivergent catalytic cycles. (B) Postulated rationale for the Pd(OAc)$_2$/Xantphos/Cs$_2$CO$_3$ combination for the $N^6$ arylation.

Among the various ligands **L1** is unique, with a wide bite angle and multiple coordination modes.[53–55] Mechanistic studies of Pd/**L1**-catalyzed C–H bond activation[56] may be instructive in understanding the Pd(OAc)$_2$/**L1**/Cs$_2$CO$_3$ catalyzed $N^6$ arylation reported here. It has been shown that **L1•**PdCl$_2$ undergoes monooxidation at one phosphorus atom concomitant with reduction of Pd$^{II}$ to Pd$^0$,[56] possibly due to adventitious moisture that can produce hydroxide ion in the presence of a base. This monoxidation results in a bidentate species containing P$^V$O–Pd$^0$–

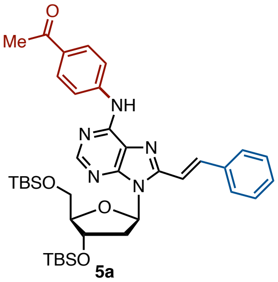
$P^{III}$ (**I** in Scheme 5B), involving hemilabile phosphine oxide coordination. Such a $Pd^0$ species may be catalytically competent here. In contrast to the predominant *trans* coordination in the oxidative-addition complexes of **L1**/Pd complexes, the bisphosphine monoxide complexes (of aryl iodides) show a *cis* coordination, with a *trans* disposed $P^VO$ and the aryl moiety.[57] In the present scenario, reaction of intermediate **II** with $Cs_2CO_3$ could result in species **III** with $\kappa^1$-coordinated $CO_3^-$. Such a species has previously been observed in the formation of a $Pd^0$ catalyst from a $Pd^{II}$ allyl precursor, with $K_2CO_3$ as base.[58] In the present case, this would place the base needed in a subsequent deprotonation step on the Pd center. Next, reaction of the amino group of the nucleoside (**1** or **3**) at the Pd center by displacement of the hemilabile $P^VO$ unit could result in species **IV**. Such an entity is well positioned to undergo an intramolecular deprotonation. Ligation of the $P^VO$ moiety to the metal center and loss of $CsHCO_3$ can lead to intermediate **V**, from which reductive elimination will result in the product and regeneration of the catalytic species **I**. Notably, $Cs_2CO_3$ and $Rb_2CO_3$ are unique due to their low Pauling electronegativities and large ionic radii. Thus, weak association of the cation with carbonate may have a role in this mechanistic manifold.

To rationalize the difference observed in the products obtained from $Pd(OAc)_2$ and $Pd_2(dba)_3$, (at the suggestion of a reviewer) two reactions were conducted with added acetate (Scheme 3, reaction #13 and #14). The outcomes from these were no different from reaction #12, indicating no role of acetate in the amination process. However, a redox process between $Pd^{II}$ salts and bisphosphines, in the presence of hydroxide, is responsible for ligand monoxidation, and formation of catalytically active Pd complexes.[57] The absence of such a process with a $Pd^0$ precatalyst is likely responsible for the difference we have observed. However, if *in situ* formed

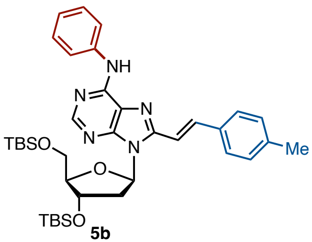
**L1** monoxide is key to the amination reactions reported herein, then it contrasts with the role of BINAP monoxide that does not promote amination reaction between *m*-$CF_3$-PhBr and 1-aminohexane.[57]

Modified nucleosides are potentially important biological probes and fluorescent ones are, therefore, of special interest in studying conformational dynamics and interactions of nucleic acids with their targets.[59–64] In such a context, in the course of their syntheses, we had observed diaryl compounds **5a**, **5b**, **6a**, and **6b** to be quite fluorescent in TLC analyses. Thus, the photophysical properties of these compounds as well as those of cyclized products **7**, **8**, and **9**, which were not as fluorescent, were interesting to evaluate by computations and experiments.

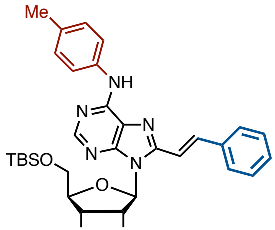
**Table 3.** Computed HOMO-LUMO gap energies, experimental UV absorption and fluorescence data, Stokes shift, and quantum yields.



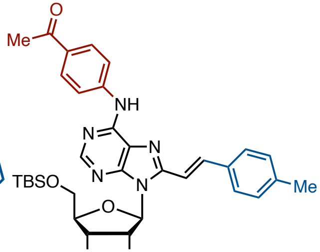
**5a**



**5b**



**6a**



**6b**

| Compd | HOMO-LUMO gap | UV $\lambda_{max}$ | Em $\lambda_{max}$ | Stokes shift | $\Phi$ [a] |
|---|---|---|---|---|---|
| **1** | 2.957 eV | 295 nm | 377 nm | 82 nm | 0.66 |
| **5a** | 3.487 eV | 356 nm | 450 nm | 94 nm | 0.46 |
| **5b** | 3.928 eV | 352 nm | 461 nm | 109 nm | 0.23 |
| **6a** | 3.596 eV | 357 nm | 478 nm | 121 nm | 0.27 |
| **6b** | 3.450 eV | 357 nm | 443 nm | 86 nm | 0.14 |

[a] For determination of quantum yields, compound **1** and the reference were excited at 320 nm, whereas compounds **5a**, **5b**, **6a**, and **6b** as well as the reference were excited at 352 nm.

DFT based computations were performed to calculate the frontier orbitals, the HOMO and the LUMO. A smaller HOMO-LUMO gap of 2.0–4.0 eV in a molecule corresponds to absorption/emission in the ultraviolet-visible region (620–310 nm) of the electromagnetic spectrum. On this basis, a HOMO-LUMO gap calculation was initially performed by DFT methods using the B3LYP functional with 6-311++G(d,p) basis set that includes polarization functions (d and p) on all atoms and diffuse functionals (++) to better describe electron distributions (Table 3). Next the fluorescence spectra were obtained in MeCN, at a concentration of 0.085–1.0 µM for quantum yield ($\Phi$) measurements. MeCN served as a suitable solvent as the refractive index ratio of MeCN and $H_2O$ is ≈ 1.0. Fluorescence quantum yields were determined compared to quinine sulfate.[65] As such, the saccharide is not expected to contribute to the fluorescence properties. However, to ensure that the silyl protection on the nucleosides did not influence the quantum yields, the quantum yields of silyl-protected 8-vinyl-2'-deoxyadenosine (**1**) and unprotected 8-vinyl-2'-deoxyadenosine were compared,[43,44] and these were found to be the same ($\Phi = 0.66$ in each case). The photophysical data for the nucleosides are also shown in Table 3. The absorbance and fluorescence spectra are shown in Figure 2.

Analog **5a** showed the highest quantum yield ($\Phi = 0.46$), whereas those of analogs **5b** and **6a** were lower ($\Phi = 0.23$ and 0.27, respectively). The lowest quantum yield was obtained for analogue **6b** ($\Phi = 0.14$). The structural difference between compounds **5a** and **5b** is that in the former the $C^{vinyl}$ bears a phenyl ring and the $N^6$ atom an electron-deficient *p*-acetylphenyl group. In the latter, whereas the vinyl group has a modestly electron-rich *p*-tolyl moiety, the adenine amino group only bears a phenyl ring. In a previous study,[46] presence of a *p*-methyl substituent on 8-styryladenosine was shown to lower $\Phi$ by 6.5-fold. In contrast to this, a phenyl moiety at the $N^6$ position in compound **5b** increased Φ by 57-fold. Compound **6a** that presents an interchange of the phenyl and *p*-tolyl groups, showed a Φ value marginally higher than that of the deoxyribose analogue **5b**. Whereas we cannot provide an explanation for the low Φ value of compound **6b**, we speculate that this may be due to the relocated *p*-methyl group. Nevertheless, this compound also showed a 35-fold increase in Φ as compared to 8-vinyladenosine bearing a *p*-tolyl group.[46] The differences in the quantum yields do not seem to correlate to the computationally determined HOMO-LUMO energy gaps. Because the rigidity of the scaffold in all the compounds is similar, their non-radiative deactivation pathways are expected to be similar. Therefore, the observed difference between their quantum yields could be related to their radiative decay rates, which relates to $S_0$-$S_1$ oscillator strength.[66]

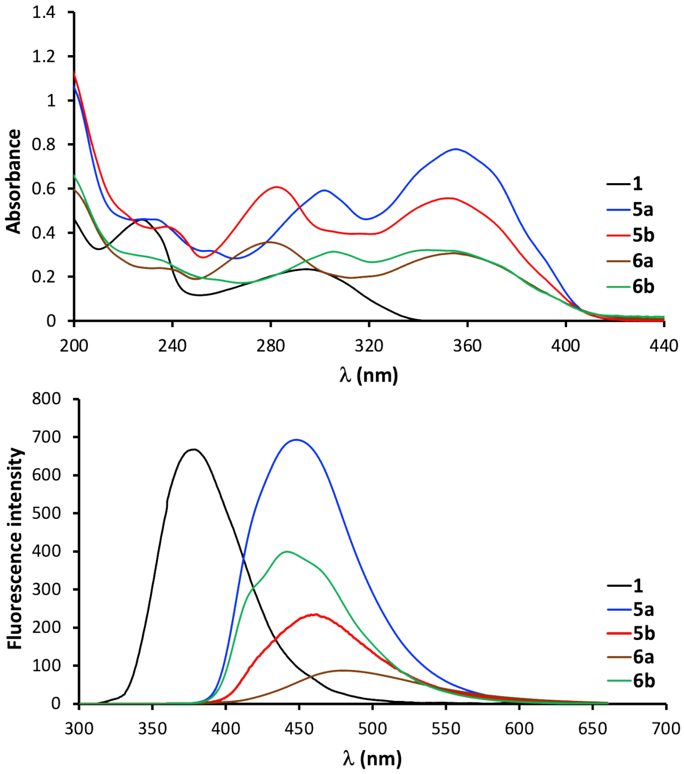


**Figure 2.** Absorption spectra (top) and fluorescence spectra (bottom) of compounds **5a**, **5b**, **6a**, and **6b** in MeCN. Sample concentrations were 0.85–1 µM for the fluorescence measurements.

The ability of time-dependent density functional theory (TDDFT) to provide excited state geometries and reproduce absorption and emission energies of modified nucleosides were evaluated.[67–73] High-level density functional and TDDFT methods with several density functionals were employed to investigate the ground state geometry, structural features, absorption, and emission properties of the modified nucleosides and 8-vinyl-2'-deoxyadenosine. The performance of five functionals (B3LYP, M06-2X, ωB97X-D, CAM-B3LYP and PBE1PBE) in combination with 6-311+G(3df,2p) were analyzed. The CAM-B3LYP and others functionals incorporate the long-range correction in addition to the hybrid qualities of B3LYP.[68,71] Solvent effects were incorporated by means of a polarizable continuum model.[72] Fluorescence emission spectra were obtained by TDDFT calculations on optimized excited singlet-state geometries.[73] For the fluorescence data, the polarization components of the basis sets have been changed to (d,p) level for convergence. These data are shown in Table 4. The fluorescence maxima obtained by TDDFT methods agreed well (as close as 6 nm to the experimental data) when M062X and CAM-B3LYP functionals were used. B3LYP appears to over-estimate but still within 30 nm of the experimental values, whereas ωB97X gave lower fluorescence maxima than experimental.

**Table 4.** A comparison of the experimental *versus* TDDFT-computed absorption and emission properties of the five compounds, using five functionals (wavelengths are in nm).

| Compd | Experimental | | B3LYP | | M062X | | ωB97X-D | | CAM-B3LYP | | PBE1PBE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | UV $\lambda_{max}$ | Em $\lambda_{max}$ | UV $\lambda_{max}$ | Em $\lambda_{max}$ | UV $\lambda_{max}$ | Em $\lambda_{max}$ | UV $\lambda_{max}$ | Em $\lambda_{max}$ | UV $\lambda_{max}$ | Em $\lambda_{max}$ | UV $\lambda_{max}$ | Em $\lambda_{max}$ |
| **1** | 295 | 377 | 310 | 399 | 275 | 371 | 264 | 363 | 276 | 374 | 300 | 387 |
| **5a** | 356 | 450 | 408 | 482 | 344 | 444 | 317 | 424 | 345 | 445 | 393 | 482 |
| **5b** | 352 | 461 | 356 | 487 | 337 | 448 | 312 | 429 | 339 | 449 | 386 | 487 |
| **6a** | 357 | 478 | 390 | 486 | 321 | 438 | 292 | 420 | 316 | 438 | 390 | 486 |
| **6b** | 347 | 443 | 407 | 485 | 337 | 451 | 333 | 431 | 343 | 457 | 392 | 485 |

Cyclized compounds **7** and **8** showed unusual absorption spectra (please see the Supporting Information) and were therefore, not studied further. On the other hand, cyclized compound **9** showed different absorption patterns at low and high concentrations (Figure 3). We currently do not have explanations for the behavior of these compounds in relation to the observations.

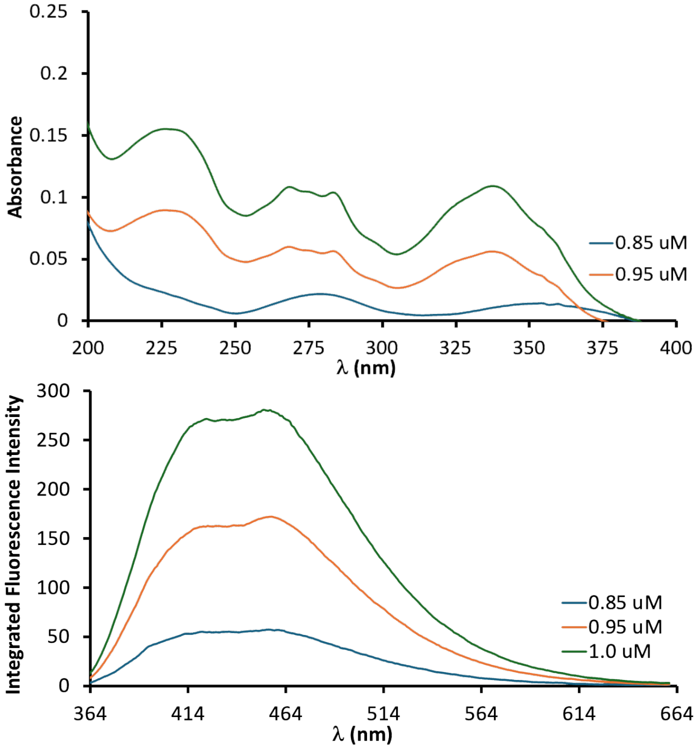


**Figure 3.** Absorption (top) and emission (bottom) spectra of compound **9** at high and low concentrations (excitation wavelength 352 nm).

## 3. Conclusions

We have demonstrated, for the first time, that the catalytic combination of Xantphos (**L1**), $Pd(OAc)_2$, and $Cs_2CO_3$ is uniquely capable of highly chemoselective $N^6$ arylation of the dually reactive 8-vinyl adenine nucleosides. Aryl bromides and iodides can be used in these reactions and yields of the *N*-arylation products were generally comparable with either. Aryl iodides seemed to yield slightly more of the minor $C^{vinyl}$ arylated products. In many cases minor $C^{vinyl}$, $N^6$ diarylation was also observed. All other metal/ligand/base combinations led to predominant

Heck-like reactivity at the $C^{vinyl}$. Interestingly, use of $Pd_2(dba)_3$ in place of $Pd(OAc)_2$ resulted in a slow and generally unselective reaction. Using the knowledge gained, a variety of $N^6$-aryl 8-vinyl adenine nucleoside derivatives were synthesized. Subsequently, a two-step, one-pot, sequential diarylation at the $C^{vinyl}$ and the $N^6$ positions of the 8-vinyl adenine nucleoside derivatives was explored. Because the diarylated products were fluorescent, their photophysical properties were examined and the HOMO-LUMO energy gaps were computationally evaluated. There does not appear to be a correlation between the computed values and the photophysical data. We surmise that the differences in quantum yields may be related to their radiative decay rates. In order to gain an understanding of the predictive value of TDDFT, five functionals were utilized to compute the absorption and emission properties of interesting candidates for comparisons with the experimental results.

***Author Contributions***

H.K.A and G.G. contributed equally to this work. M.K.L. conceptualized the work, obtained funding, provided input as necessary, wrote the manuscript, audited the Supporting Information, combined all aspects of the collaborative endeavor. H.K.A. worked on the entire experimental aspects, generated a draft containing the synthetic procedures and experimental data, performed compound characterization, generated copies of the NMR spectra, provided the FID files, reviewed the manuscript and Supporting Information. G.G. and A.G. performed the absorbance and fluorescence experiments, compiled these data, generated the original Excel files with these data and first versions of the corresponding figures, reviewed the manuscript and Supporting Information. P.P. performed the computational analysis and compiled these data, reviewed the manuscript and Supporting Information.

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### *Conflicts of Interest*

The authors declare no conflicts of interest.

### *Data Availability Statement*

Experimental procedures, characterization data, fluorescence data collection, computational data, copies of NMR spectra and associated free induction decay (FID) files can be found in the Supporting Information. Additional references are cited within the Supporting Information.[74,75]

**Key words:** C–N bond formation • C–C bond formation • Buchwald-Hartwig amination • Heck reaction • nucleosides

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