NIH Public Access
Author Manuscript
Chem Asian J. Author manuscript; available in PMC 2013 August 01.

Published in final edited form as:
Chem Asian J. 2012 August ; 7(8): 1853–1861. doi:10.1002/asia.201200093.

C–C Cross-Coupling Reactions of O^6-Alkyl-2-Haloinosine Derivatives and a One-Pot Cross-Coupling/O^6-Deprotection Procedure

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Abstract

Reaction conditions for the C–C cross-coupling of O^6-alkyl-2-bromo- and 2-chloroinosine derivatives with aryl-, hetaryl-, and alkylboronic acids were studied. Optimization experiments with silyl-protected 2-bromo-O^6-methylinosine led to the identification of $[PdCl_2(dcpf)]/K_3PO_4$ in 1,4-dioxane as the best condition for these reactions (dcpf = 1,1'-bis(dicyclohexylphosphino)ferrocene). Attempted O^6-demethylation, as well as the replacement of the C-6 methoxy group by amines, was unsuccessful, which led to the consideration of Pd-cleavable groups such that C–C cross-coupling and O^6-deprotection could be accomplished in a single step. Thus, inosine 2-chloro-O^6-allylinosine was chosen as the substrate and, after re-evaluation of the cross-coupling conditions with 2-chloro-O^6-methylinosine as a model substrate, one-step C–C cross-coupling/deprotection reactions were performed with the O^6-allyl analogue. These reactions are the first such examples of a one-pot procedure for the modification and deprotection of purine nucleosides under C–C cross-coupling conditions.

Keywords

cross- coupling; inosine; nucleosides; one-pot reactions; palladium

Introduction

Recognition of the importance of Pd-catalyzed C–C bond-forming processes came in 2010 with the award of the Nobel Prize to Heck, Negishi, and Suzuki. These reactions, named after their discoverers, continue to evoke much interest from a variety of viewpoints. The Pd-catalyzed reaction of organoboron derivatives with organic electrophilies-known as the Suzuki reaction- is a mild and highly versatile method for the construction of a wide range of C–C bonds.[1–7]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200xxxxxx

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In the context of biomolecular modification, several research groups,[8–12] including our own,[13,14] have been interested in the C–C bond-forming reactions of nucleosides.[15] In comparison to the chemistry of simpler molecules, polynitrogenated heterocyclic bases, the presence of multiple oxygen atoms in the saccharide, and a labile glycosidic bond can all pose considerable challenges in the metal-mediated reactions of nucleosides. Although a substantial number of arylation reactions of purines and purine nucleosides at the C-6 position are known, there is comparatively little information on reactions at the C-2 position.

Herein, we report C–C bond-forming reactions at the C-2 position of purine nucleosides by using both C-2- bromo and chloro purine derivatives, as well as a one-step method for the introduction of a C-2 aryl group and subsequent O^6-deprotection of the purine nucleus. We also compare the reactivities of C-2-bromo and chloro purine nucleosides and evaluate the effect of microwaves on some of these reactions.

Results and Discussion

This work was based on our earlier study[13] that involved O^6-benzyl-2-bromo-3',5'-di-*O*-(*t*-butyldimethylsilyl)-2'-deoxyinosine.[16] In that work, we explored the reactivities of four arylboronic acids with the C-2-brominated nucleoside by using a $Pd(OAc)_2$/2-cyclohexylphosphinobiphenyl/K_3PO_4 catalyst system. [13] Although this system provided good results, catalyst optimization was performed with a C-6-bromopurine nucleoside, and no separate evaluation of the catalytic systems was conducted with the C-2- bromo derivative.

Thus, herein, we wanted to understand the influence of the catalytic systems on the efficiency of the Suzuki reactions at the C-2 position of purine nucleosides in greater detail and to evaluate a much wider substrate scope than had been reported previously. We chose 2-bromo-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-O^6-methylinosine (**1**, a riboside) for our initial studies for the following reasons: ribonucleosides are more economical than their deoxy analogues and O^6-protection as a methyl ether, by using our reported procedure,[17] is more convenient than the Mitsunobu reaction that would otherwise be required.[16,18,19] Thus, 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-O^6-methylguanosine was brominated by using *t*-BuONO/TMSBr (TMS = trimethylsilyl) in CH_2Br_2[19,20] to afford the requisite precursor (**1**; for details, see the Supporting Information). $Pd(OAc)_2$ and $[Pd_2(dba)_3]$ were chosen as metal sources in combinations with five ligands (**L1**–**L5**; Scheme 1). In addition, three ferrocenyl Pd^{II} precatalysts were selected for our initial analysis (Scheme 1).

Initial, various Pd/ligand combinations and ferrocenyl systems were tested in the reactions of compound **1** with $PhB(OH)_2$ (Table 1). From these data, $Pd(OAc)_2$/**L3** (XPhos) was superior to the other biaryl-ligand-based catalysts, which gave product yields in the range of 40–50%. $[Pd(PPh_3)_4]$ was the next best catalyst, but the use of Na_2CO_3 could prove to be incompatible with some boronic acids. Among the ferrocene-based pre-catalysts that were tested, $[PdCl_2(dcpf)]$ was the best, and was superior to $Pd(OAc)_2$/**L3**.

However, the catalyst loading that was required was a concern and, therefore, these reactions were tested further. By varying the amount of $[PdCl_2(dcpf)]$, it became clear that decreasing the amount from 20 mol% to 15, 10, and 5 mol% produced progressively lower yields (70, 50, and 30%, respectively, as analyzed by LC/MS). Because all of these reactions were conducted in closed vials, one reaction with $PhB(OH)_2$ was conducted in a round-bottomed flask under a reflux condenser. This reaction was complete within 18 hours at 100°C, and gave compound **2a** in 85% yield. Next, coupling of a potentially problematic hetarylboronic acid was evaluated. For this evaluation, 3,5-dimethyl-1*H*-pyrazol-4-yl-boronic acid was chosen, because, in addition to the nitrogen atoms, the reactive carbon

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atom was flanked by two methyl groups. With this boronic acid, no reaction was observed (by LC/MS) with ligands **L1**-**L3** under their respective conditions (Table 1). With ligand **L4**, the product was isolated in 50% yield, whereas low yields (< 40%) were obtained with [$Pd(PPh_3)_4$] and ligand **L5**. Again, [$PdCl_2$(dcpf)] was a superior system, thereby affording the cross-coupled product in 65% yield. No reaction was observed with [$PdCl_2$(dppf)] (as analyzed by LC/MS).

The influence of the solvent and base were then evaluated. 1,4-Dioxane was significantly superior to toluene, 1,2-dimethoxyethane, and tetrahydropyran, in that order, and no reaction was observed in tetrahydropyran (THF) and *t*BuOH (as analyzed by LC/MS). Among the bases tested, K_3PO_4 was far superior to K_2CO_3, KOAc, and *t*BuOK, whereas CsF was ineffective. With these assessments completed, the substrate scope was evaluated by using a wide range of boronic acids (Table 2).

All of the reactions proceeded quite efficiently (Table 2) and the presence of a single ring-nitrogen atom in the arylboronic acids did not create any problems (Table 2, entries 9 and 12). The presence of multiple nitrogen atoms lowered the product yield somewhat (Table 2, entries 2 and 13); nevertheless, respectable yields were obtained in these cases. The reactions of arylboronic acids that contain electron-withdrawing groups can be problematic; they can be reluctant towards transmetalation[21] and prone to proto deboronation[22] and/or dimerization reactions.[23] However, 4-cyanophenyl-, 4-carboxamidophenyl-, and 3,5-bis(trifluoromethyl)phenylboronic acids all reacted in good yields (Table 2, entries 4, 7, and 8). Alkylboronic acids, including those that contained β-hydrogen atoms, also underwent the reaction without any problems (Table 2, entries 15–17). We also briefly investigated the influence of microwave irradiation on the reactions that gave somewhat lower yields. For comparison, $PhB(OH)_2$ was also included in this analysis. Microwave irradiation provided a significant rate enhancement (reaction time of 30 min at 100°C) but the increase in yield was only modest (5–10%; Table 2 entries 1, 2, 13, and 15)).

At this stage, O^6-demethylation was attempted to obtain the base-deprotected nucleosides. The use of TMSI or TMSCl/NaI in MeCN[24,25] led to the deglycosylation of compound **2a** and cleavage of the silyl groups, but the methyl ether remained intact. LiCl/*p*-TsOH (5 equiv each) in *N,N*-dimethylformamide (DMF), a system that was selective for the cleavage of azaheterocyclic methyl ethers,[26] caused silyl group cleavage at room temperature and decomposition at elevated temperature. The use of EtSNa in DMF (room temperature to elevated temperature) caused the deglycosylation of compound **2a** and cleavage of the silyl protecting group. No reaction was observed with either neat *n*-decyl mercaptan or as a solution in DMF, under various conditions. Pyridinium hydrogen chloride (3 equiv) in MeCN (room temperature to elevated temperature) gave only decomposition.[27] Next, we considered the displacement of the C-6 methoxy group with a nucleophile. However, heating compound of **2a** with morpholine and pyrrolidine in DMF at reflux or in a microwave reactor at 100°C for 30 min only returned unconverted compound **2a**.

Because deprotection at the O^6-position was difficult, we decided to reconsider the protecting group for the amide. We had previously reported the synthesis of O^6-allyl-3',5'-di-*O*-(*t*-butyldimethysilyl)-2-chloro-2'-deoxyinosine[28] and, in that work, we demonstrated that, in the presence of a Pd catalyst and an amine, the removal of the allyl group and the displacement of the C-2 chloride atom from the purine could be accomplished in a single step. Thus, C–C bond formation and deallylation under Pd-catalyzed conditions appeared applicable here. Of course, the first consideration would be the relative reactivity of a C-2 chloride compared to a bromide under C–C cross-coupling conditions. For this evaluation, 2',3',5'-tri-*O*-(*t*-butyldimethysilyl)-2-chloro-O^6-methylinosine (**3**) was synthesized by diazotization/chlorination with *t*BuONO and TMSCl in CH_2Cl_2 (for details, see the

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Supporting Information).[20] Then, Chloro-nucleoside **3** was evaluated in C–C cross-coupling reactions under the same conditions as for compound **1** (Table 3).

On the basis of the results given in Table 3, it appeared that chloro-nucleoside **3** underwent C–C cross-coupling just about as effectively as its bromo analogue (**1**). Thus, O^6-allyl-2',3',5'-tri-*O*-(*t*-butyldimethysilyl)-2-chloroinosine (**4**) was synthesized according to our previously reported procedure (for details, see the Supporting Information).[28] An Initial assessment of the C–C cross-coupling of compound **4** with $PhB(OH)_2$, as well as with 4-pyridylboronic acid, indicated the successful formation of the corresponding C-2-arylated, O^6-deprotected products. Further optimization led to the identification of conditions in which the C–C bond-formation and O^6-deallylation reaction could be conducted as a one-pot procedure. In these cases, to obtain high product purities, the final products were purified by preparative HPLC (Table 4).

Comparison of the Reactivities of Bromo-Nucleoside 1 and Chloro-Nucleoside 3

In terms of product yield, the reactivities of C-2-halopurine nucleosides **1** and **3** appeared to be comparable under the C–C cross-coupling conditions (Table 3). Hence, we decided to assess their relative reactivities in a competitive experiment. For this investigation, an equimolar amount of compound **1** and **3** (1.5 molar equiv of each) was reacted with one molar equivalent of $PhB(OH)_2$ under the optimized conditions. Complete consumption of $PhB(OH)_2$ was observed and the residual starting materials (**1** and **3)**, as well as product **2a,** were collected together by column chromatography. Analysis of this mixture of **1**, **3**, and **2a** by LC/MS and ^{1}H NMR spectroscopic analysis indicated that it contained 19% of bromopurine nucleoside **1** and 47% of its chloropurine analogue **3**. ^{1}H NMR analysis of the mixture was performed by integrating the H-8 resonances of compound **1** (δ = 8.30 ppm), **3** (δ = 8.29 ppm), and **2a** (δ = 8.34 ppm), and the ratio that was obtained was consistent with the LC/MS analysis. In addition, LC/MS analysis indicated the formation of the dehalogenated trisilyl O^6-methylinosine in about 2.5% yield. This experiment revealed two two important factors: 1) C-2-bromopurine precursor **1** was more rapidly consumed than Chloro-analogue **3**, and **2**) that reductive dehalogenation did not appear to be significant. Figure 1 shows the LC/MS trace of the reaction mixture from this competition experiment. The MS analysis and ^{1}H NMR data are given in the Supporting Information.

Conclusion

Herein, we have investigated the C–C bond-forming chemistry of O^6-alkoxy C-2 halopurine ribonucleosides. The combination of $[PdCl_2(dcpf)]/K_3PO_4$ in 1,4-dioxane successfully promoted the reactions of 2-bromo-O^6-methyl-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)inosine (**1**) with a variety of arylboronic acids, as well as alkylboronic acids, including those with β-hydrogen atoms.

However, O^6-demethylation, as well as the replacement of the C-6 methoxy group, was problematic. Therefore, a one-pot approach towards C–C cross-coupling and purine deprotection was envisioned that proceeded through an O^6-allyl nucleoside derivative. Based on our previous studies,[28] this approach required a C-2 chloride moiety rather than a bromide. Thus, 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-chloro-O^6-methylinosine (**3**) was synthesized and its reactivity was assessed in the C–C cross-coupling reactions. Our results showed that the C-2-bromo- and chloropurine nucleosides had comparably reactive. Thus, the one-pot C–C cross-coupling and simultaneous O^6-allyl deprotection were investigated, by using O^6-allyl-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-chloroinosine (**4**); the results indicate that such a two-step approach was viable.

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Finally, we investigated the relative reactivities of 2-bromo- 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-O^6-methylinosine (**1**) and 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-chloro-O^6-methylinosine (**3**) with $PhB(OH)_2$. In this analysis it was found that compound **1** was consumed more rapidly than compound **3**. However, in terms of product recovery, both halopurine nucleosides were comparably effective as reaction precursors.

Experimental Section

General Considerations

Thin-layer chromatography was performed on 250 μm silica plates and column chromatography was performed on 100–200 mesh silica gel. All boronic acids, $Pd(OAc)_2$, [$Pd_2(dba)_3$], ligands **L1**–**L5**, [$PdCl_2$(dppf)], [$PdCl_2$(dcpf)], and [$PdCl_2$(d*t*bpf)], and all other reagents were obtained from commercial suppliers and were used without further purification. 1,4-Dioxane was distilled over $NaBH_4$ and then stored over Na. 1,4-dioxane was freshly distilled.prior to each reaction. For syntheses of compounds **1**, **3**, and **4** as well as their precursors, see the Supporting Information. ^{1}H NMR spectra were either recorded at 400 MHz or at 300 MHz and were referenced to the solvent. ^{13}C NMR spectra were either recorded at 100 MHz or at 75 MHz and were referenced to the carbon resonance of the deuterated solvent. The NMR Spectra were either recorded in deacidified $CDCl_3$ (deacidification was performed by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina) or in DMSO-d_6 (for details on specific compound, see below) HRMS analysis was performed at the Mass Spectrometry Laboratory at GVK Biosciences Pvt Ltd. LC/MS analysis was performed with electrospray ionization (ESI) and operated in the positive-ion mode. LC analysis was performed by using a diode array detector.

General Procedure for the Cross-Coupling of Bromo-Nucleoside 1 with Boronic Acids

Bromo-nucleoside **1** (50 mg, 0.07 mmol), boronic acid (150 mol%), and K_3PO_4 (200 mol%) in anhydrous 1,4-dioxane (2 mL) were added to a dry, screw-capped vial that was equipped with a stirring bar. The vial was flushed with argon gas for a few minutes and [$PdCl_2$(dcpf)] (20 mol%) was added. The vial was sealed with a Teflon-lined cap and the mixture was heated at 100°C with stirring for 8 h. The mixture was cooled and the solvent was evaporated under reduced pressure and dried under high vacuum. Flash column chromatography on silica gel afforded the various products (for specific details, see the individual compound headings).

General Procedure for the Cross-Coupling of Bromo-Nucleoside 1 with Boronic Acids under Microwave Conditions

Bromo-nucleoside **1** (50 mg, 0.07 mmol), boronic acid (150 mol%), and K_3PO_4 (200 mol%) in anhydrous 1,4-dioxane (2 mL) were added to a microwave vial (10 mL) that was equipped with a stirring bar. The vial was flushed with argon gas for a few minutes and [$PdCl_2$(dcpf)] (20 mol%) was added. The vial was sealed with a aluminum cap, and the mixture was subjected to microwave irradiation at 100°C with stirring for 30 min. The mixture was cooled and the solvent was evaporated under reduced pressure and dried under high vacuum. Purification of the crude material by flash chromatography on silica gel gave the various products (for specific details, see the individual compound headings).

General Procedure for the Cross-Coupling of Chloro-Nucleoside 3 with Boronic Acids

Chloro-nucleoside **3** (50 mg, 0.07 mmol), boronic acid (150 mol%), and K_3PO_4 (200 mol%) in anhydrous 1,4-dioxane (2 mL) were added to a dry, screw-capped vial that was equipped with a stirring bar. The vial was flushed with argon gas for a few minutes and [$PdCl_2$(dcpf)] (20 mol%) was added. The vial was sealed with a Teflon-lined cap and the mixture was

heated at 100°C with stirring for 8 h. The mixture was cooled and the solvent was evaporated under reduced pressure and dried under high vacuum. Column chromatography on silica gel (see above) gave the various products.

General Procedure for the *One-Pot* C–C Cross-Coupling and O^6-deprotection of Chloro-Nucleoside 4

Chloro-nucleoside **4** (50 mg, 0.07 mmol), boronic acid (200 mol%), and K_3PO_4 (200 mol%) in anhydrous 1,4-dioxane (2 mL) were added to a dry, screw-capped vial that was equipped with a stirring bar. The vial was flushed with argon for a few minutes and [$PdCl_2$(dcpf)] (20 mol%) was added. The vial was sealed with a Teflon-lined cap and the mixture was heated at 100°C with stirring for 8 h. The mixture was cooled and the solvent was evaporated under reduced pressure and dried under high vacuum. The crude product was loaded onto a silica gel column that was packed with CH_2Cl_2. Flash chromatography (see above) gave the various products.

Preparative HPLC Conditions for Purification of 5a–5i

Preparative HPLC was performed on a Sunfire C-18 column (5 μ, 250 × 25 mm) by using isocratic elution with MeCN/MeOH (1:1), at a flow rate of 25 $mLmin^{-1}$ and at a column temperature of 25°C. Absorbance was recorded at 210 nm.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-phenyl-inosine (2a)

Chromatography was performed using 7% EtOAc in *n*-hexane to yield a colorless, gummy solid. R_f (10% EtOAc in *n*-hexane) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (m, 2H), 8.34 (s, 1H), 7.47 (m, 3H), 6.16 (d, *J* = 4.4 Hz, 1H), 4.71 (t, *J* = 4.2 Hz, 1H), 4.39 (t, *J* = 4.2 Hz, 1H), 4.29 (s, 3H), 4.17 (q, *J* = 3.8 Hz, 1H), 4.09 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.85 (dd, *J* = 11.6, 2.4 Hz, 1H), 0.96 and 0.82 (2s, 27H), 0.15, −0.02, and −0.01 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 158.5, 152.5, 141.5, 137.8, 130.1, 128.3, 128.2, 120.8, 88.6, 84.8, 75.7, 71.5, 62.3, 53.8, 29.6, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, −0.4.3, −4.7, −4.8, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{61}N_4O_{54}Si_3$ $[M + H]^+$ 701.3950; found 701.3964.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)inosine (2b)

Chromatography was performed using 20% EtOAc in *n*-hexane to yield a brown, gummy solid. R_f (40% EtOAc in *n*-hexane) = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1H), 6.28 (d, *J* = 6.4 Hz, 1H), 4.47 (t, *J* = 4.2 Hz, 1H), 4.25 (t, *J* = 4.0 Hz, 1H), 4.20 (s, 3H), 4.10 (q, *J* = 3.6 Hz, 1H), 3.89 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.81 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.70 (s, 6H), 0.96 and 0.77 (2s, 27H), 0.14, −0.08, and −0.36 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 157.3, 152.8, 146.0, 139.6, 132.1, 132.0, 128.5, 128.4, 118.2, 115.7, 86.3, 86.0, 75.0, 72.9, 63.1, 54.0, 29.6, 26.0, 25.7, 25.5, 25.4, 24.8, 18.4, 17.9, 17.7, 14.4, −4.5, −4.6, −5.2, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{63}N_6O_5Si_3$ $[M + H]^+$ 719.4168; found 719.4171.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-(4-methoxyphenyl)inosine (2c)

Chromatography was performed using 8% EtOAc in *n*-hexane to yield a light-yellow, gummy solid. R_f (20% EtOAc in *n*-hexane) = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 9.0 Hz, 2H), 8.29 (s, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.13 (d, *J* = 4.4 Hz, 1H), 4.68 (t, *J* = 4.2 Hz, 1H), 4.38 (t, *J* = 4.2 Hz, 1H), 4.25 (s, 3H), 4.14 (q, *J* = 2.8 Hz, 1H), 4.07 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.88 (s, 3H), 3.84 (dd, *J* = 11.8, 2.8 Hz, 1H), 0.95 and 0.81 (2s, 27H), 0.12, −0.01, and −0.14 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 160.4, 158.5, 152.6, 141.1, 130.6, 129.8, 120.2, 116.2, 116.1, 114.6, 113.5, 88.5, 84.7, 75.7, 71.5, 62.3, 55.7, 55.3, 53.7, 29.6, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.7, −4.8, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{63}N_6O_5Si_3$ $[M + H]^+$ 731.4168, found 731.4226.

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2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(4-cyanophenyl)-O^6-methylinosine (2d)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a white, gummy solid. R_f (20% EtOAc in *n*-hexane) = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 8.4 Hz, 2H), 8.45 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 6.20 (d, *J* = 4.4 Hz, 1H), 4.58 (t, *J* = 4.2 Hz, 1H), 4.38 (t, *J* = 4.2 Hz, 1H), 4.29 (s, 3H), 4.17 (q, *J* = 2.8 Hz, 1H), 4.06 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.85 (dd, *J* = 11.2, 2.0 Hz, 1H), 0.97 and 0.81 (2s, 27H), 0.15, −0.02, and −0.17 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 156.4, 152.4, 142.0, 141.9, 132.0, 128.6, 121.2, 118.8, 113.2, 88.3, 84.9, 76.4, 71.5, 62.2, 54.0, 33.7, 31.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 26.0, 25.8, 25.6, 22.6, 18.5, 18.0, 17.8, −4.3, −4.7, −4.9, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{60}N_5O_5Si_3$ $[M + H]^+$ 726.3902, found 726.3903.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(4-(cyanomethoxy)phenyl)-O^6-methylinosine (2e)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a light-yellow, gummy solid. R_f (20% EtOAc in *n*-hexane) = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 9.0 Hz, 2H), 8.35 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.17 (d, *J* = 4.8 Hz, 1H), 4.85 (s, 2H), 4.64 (t, *J* = 4.0 Hz, 1H), 4.38 (t, *J* = 4.2 Hz, 1H), 4.26 (s, 3H), 4.16 (q, *J* = 2.8 Hz, 1H), 4.07 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.85 (dd, *J* = 11.6, 2.8 Hz, 1H), 0.95 and 0.82 (2s, 27H), 0.14, −0.02, and −0.14 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 158.1, 157.8, 152.6, 141.3, 133.0, 130.1, 120.5, 114.9, 114.5, 88.4, 84.8, 76.0, 71.5, 62.3, 53.8, 53.4, 33.7, 31.8, 29.6, 29.4, 29.3, 29.1, 28.9, 26.0, 25.8, 25.6, 22.6, 18.5, 18.0, 17.8, 14.0, −4.3, −4.7, −4.8, −5.3; HRMS (ESI): *m/z* calcd for $C_{37}H_{62}N_5O_6Si_3$ $[M + H]^+$ 756.4008, found 756.4041.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-(thien-3-yl)inosine (2f)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f (10% EtOAc in *n*-hexane) = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 3.2 Hz, 1H), 8.25 (dd, *J* = 3.2, 0.8 Hz, 1H), 7.92 (d, *J* = 3.6 Hz, 1H), 7.35 (m, 1H), 6.13 (d, *J* = 4.0 Hz, 1H), 4.63 (t, *J* = 4.4 Hz, 1H), 4.37 (t, *J* = 4.2 Hz, 1H), 4.24 (s, 3H), 4.15 (q, *J* = 2.0 Hz, 1H), 4.09 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.85 (dd, *J* = 11.2, 2.4 Hz, 1H), 0.95 and 0.83 (2s, 27H), 0.15, −0.01, and −0.11 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 155.7, 152.3, 141.9, 141.2, 127.6, 127.0, 125.4, 120.4, 88.4, 84.7, 75.9, 71.4, 62.2, 53.7, 29.6, 29.3, 26.1, 25.8, 25.6, 22.6, 18.5, 18.0, 17.8, −4.3, −4.7, −5.3; HRMS (ESI): *m/z* calcd for $C_{33}H_{59}N_4O_5Si_3S$ $[M + H]^+$ 707.3514, found 707.3518.

2',3',5'-Tri-*O*-(*t*-butyldimethylsily)-2-(4-carbamoylphenyl)-O^6-methylinosine (2g)

Chromatography was performed using 25% EtOAc in *n*-hexane to yield a brown, gummy solid. R_f (40% EtOAc in *n*-hexane) = 0.34; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 8.8 Hz, 2H), 8.43 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 4.0 Hz, 1H), 5.75 (br s, 2H), 4.59 (t, *J* = 4.2 Hz, 1H), 4.38 (t, *J* = 4.4 Hz, 1H), 4.30 (s, 3H), 4.18 (q, *J* = 3.6 Hz, 1H), 4.08 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.86 (dd, *J* = 11.6, 2.4 Hz, 1H), 0.95 and 0.81 (2s, 27H), 0.13, 0.08, and −0.11 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 160.5, 157.3, 152.4, 141.7, 141.2, 134.4, 128.4, 127.3, 121.0, 88.4, 84.7, 76.3, 71.3, 62.1, 60.3, 54.0, 29.6, 26.1, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.7, −5.3; HRMS (ESI): *m/z* calcd for $C_{36}H_{62}N_5O_6Si_3$ $[M + H]^+$ 744.4008, found 744.4011.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(3,5-bis-(trifluoromethyl)phenyl)-O^6-methylinosine (2h)

Chromatography was performed using 7% EtOAc in *n*-hexane to yield a light-yellow, gummy solid. R_f (10% EtOAc in *n*-hexane) = 0.39; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (s, 2H), 8.57 (s, 1H), 7.95 (s, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 4.38 (m, 2H), 4.32 (s, 3H), 4.19 (q, *J* = 2.0 Hz, 1H), 4.08 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.87 (dd, *J* = 11.6, 2.0 Hz, 1H), 0.95 and 0.84 (2s, 27H), 0.17, 0.01, and −0.03 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8,

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155.5, 152.3, 141.7, 139.8, 131.9, 128.2, 127.5, 124.7, 123.3 (d, J = 271 Hz), 122.0, 121.2, 88.2, 84.4, 70.9, 61.8, 54.2, 30.0, 29.6, 26.1, 25.7, 25.5, 18.6, 18.0, 17.8, −4.3, −4.7, −4.8, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{37}H_{59}N_4O_5F_6Si_3$ $[M + H]^+$ 837.3698, found 837.3690.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-*O*^{6}-methyl-2-(4-pyridyl)inosine (2i)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a colorless solid. R_f (30% EtOAc in *n*-hexane) = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, J = 4.8 Hz, 2H), 8.45 (s, 1H), 8.35 (d, J = 5.6 Hz, 2H), 6.20 (d, J = 4.4 Hz, 1H), 4.61 (t, J = 4.2 Hz, 1H), 4.38 (t, J = 4.2 Hz, 1H), 4.30 (s, 3H), 4.17 (q, J = 2.8 Hz, 1H), 4.08 (dd, J = 11.4, 3.6 Hz, 1H), 3.86 (dd, J = 11.4, 2.4 Hz, 1H), 0.95 and 0.81 (2s, 27H), 0.16, 0.12, 0.01, and −0.16 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 156.2, 152.4, 150.1, 145.1, 142.2, 122.1, 121.6, 88.4, 85.0, 76.2, 71.5, 62.3, 54.1, 29.6, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.6, −4.7, −4.8, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{60}N_5O_5Si_3$ $[M + H]^+$ 702.3902, found 702.3928.

2',3,'5'-Tri-*O*-(*t*-butyldimethylsilyl)-*O*^{6}-methyl-2-(1-naphthyl)inosine (2j)

Chromatography was performed using 6% EtOAc in *n*-hexane to yield a colorless, gummy solid. R_f (10% EtOAc in *n*-hexane) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (t, J = 9.6 Hz, 1H), 8.36 (s, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.96–7.90 (m, 2H), 7.58–7.48 (m, 3H), 6.16 (d, J = 4.8 Hz, 1H), 4.74 (t, J = 4.4 Hz, 1H), 4.34 (t, J = 3.8 Hz, 1H), 4.25 (s, 3H), 4.13 (q, J = 3.6 Hz, 1H), 4.00 (dd, J = 11.2, 4.4 Hz, 1H), 3.78 (dd, J = 11.2, 2.4 Hz, 1H), 0.91 and 0.78 (2s, 27H), 0.17, −0.05, and −0.20 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 160.4, 152.4, 141.7,136.2, 134.1, 131.2, 129.9, 129.1, 128.3, 126.3, 125.6, 125.0, 120.4, 88.5, 85.2, 76.6, 75.7, 71.8, 62.4, 54.1, 29.6, 26.0, 25.8, 25.6, 18.4, 18.0, 17.8, − 4.4, −4.6, −4.7, −4.9, −5.4, −5.5; HRMS (ESI): *m/z* calcd for $C_{39}H_{63}N_4O_5Si_3$ $[M + H]^+$ 751.4106, found 751.4059.

2-(2-Benzofuranyl)-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-*O*^{6}-methylinosine (2k)

Chromatography was performed using 15% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f (20% EtOAc in *n*-hexane) = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 7.68 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 4.2 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.18 (d, J = 3.6 Hz, 1H), 4.64 (t, J = 3.8 Hz, 1H), 4.38 (t, J = 4.6 Hz, 1H), 4.31 (s, 3H), 4.19 (q, J = 2.8 Hz, 1H), 4.13 (dd, J = 11.2, 3.6 Hz, 1H), 3.87 (dd, J = 11.2, 2.0 Hz, 1H), 0.95 and 0.87 (2s, 27H), 0.15, 0.01, and −0. 03 (3s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 155.7, 154.0, 152.0, 151.6, 141.6, 128.4, 125.6, 123.1, 121.7, 121.1, 111.8, 108.7, 89.0, 84.5, 76.1, 71.0, 61.9, 54.1, 29.6, 26.1, 25.8, 25.7, 25.5, 18.5, 18.0, 17.9, −4.3, −4.7, −4.8, −5.3; HRMS (ESI): *m/z* calcd for $C_{37}H_{61}N_4O_6Si_3$ $[M + H]^+$ 741.3899, found 741.3901.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-*O*^{6}-methyl-2-(3-quinolinyl)inosine (2l)

Chromatography was performed using 15% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f (20% EtOAc in *n*-hexane) = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (d, J = 1.5 Hz, 1H), 9.20 (d, J = 1.8 Hz, 1H), 8.49 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 6.9 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 6.29 (d, J = 4.2 Hz, 1H), 4.53 (t, J = 4.0 Hz, 1H), 3.97 (t, J = 4.6 Hz, 1H), 4.34 (s, 3H), 4.19 (q, J = 2.4 Hz, 1H), 4.09 (dd, J = 11.6, 2.7 Hz, 1H), 3.87 (dd, J = 11.7, 2.1 Hz, 1H), 0.95 and 0.84 (2s, 27H), 0.11, 0.06, and 0.04 (3s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 156.6, 152.5, 150.5, 148.6, 141.4, 135.6, 130.4, 130.2, 129.2, 128.6, 127.6, 126.8, 120.9, 88.2, 84.7, 71.2, 62.1, 54.1, 29.6, 26.1, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.6, −4.7, −4.8, −5.3, −5.4.; HRMS (ESI): *m/z* calcd for $C_{38}H_{62}N_5O_5Si_3$ $[M + H]^+$ 752.4059, found 752.4070.

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2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-[2-(dimethylamino)pyrimidin-5-yl]inosine (2m)

Chromatography was performed using 15% EtOAc in *n*-hexane to yield a white solid. R_f (20% EtOAc in *n*-hexane) = 0.46; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.32 (s, 2H), 8.28 (s, 1H), 6.12 (d, *J* = 5.1 Hz, 1H), 4.63 (t, *J* = 4.5 Hz, 1H), 4.34 (t, *J* = 4.0 Hz, 1H), 4.21 (s, 3H), 4.14 (q, *J* = 2.1 Hz, 1H), 4.06 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.84 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.28 (s, 6H), 0.95 and 0.78 (2s, 27H), 0.14, 0.01, and −0.20 (3s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 160.5, 157.9, 156.3, 152.5, 140.9, 120.2, 119.2, 88.1, 85.3, 76.0, 71.9, 62.5, 53.7, 37.2, 2.6.0, 25.8, 25.6, 18.5, 18.0, 17.8, −4.4, −4.7, −4.9, −5.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{64}N_7O_5Si_3$ $[M + H]^+$ 746.4277, found 746.4286.

2-(3-Biphenyl)-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-O^6-methylinosine (2n)

Chromatography was performed using 12% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f(20% EtOAc in *n*-hexane) = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (s, 1H), 8.50 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.42 (s, 1H), 7.71–7.67 (m, 3H), 7.57–7.45 (m, 3H), 7.40–7.35 (m, 1H), 6.24 (d, *J* = 4.2 Hz, 1H), 4.61 (t, *J* = 4.2 Hz, 1H), 4.40 (t, *J* = 4.3 Hz, 1H), 4.31 (s, 3H), 4.19 (q, *J* = 2.7 Hz, 1H), 4.09 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.86 (dd, *J* = 11.4, 2.4 Hz, 1H), 0.95 and 0.83 (2s, 27H), 0.14, 0.01, and −0.08 (3s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 158.5, 152.6, 141.3, 141.1, 138.3, 128.8, 128.7, 127.3, 127.2, 127.1, 120.7, 88.3, 84.6, 71.3, 62.1, 53.9, 26.1, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.6, −4.7, −5.3, −5.4. HRMS (ESI): *m/z* calcd for $C_{41}H_{65}N_4O_5Si_3$ $[M + H]^+$ 777.4263, found 777.4266.

2-(*i*-Butyl)-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-O^6-methylinosine (2o)

Chromatography was performed using 8% EtOAc in *n*-hexane to yield a light-yellow, thick oil. R_f(10% EtOAc in *n*-hexane) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 5.99 (d, *J* = 4.4 Hz, 1H), 4.71 (t, *J* = 4.4 Hz, 1H), 4.34 (t, *J* = 4.2 Hz, 1H), 4.14 (s, 3H), 4.13 (q, *J* = 2.8 Hz, 1H), 4.09 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.81 (dd, *J* = 11.0, 2.8 Hz, 1H), 2.76 (d, *J* = 7.6 Hz, 2H), 2.35 (m, 1H), 0.95, 0.87, and 0.82 (m, 33H: 27H from *t*-Bu + 6H *i*-butyl Me_2), 0.10, 0.13, and 0.08 (3s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.3, 152.0, 140.8, 120.0, 88.9, 84.8, 75.2, 71.4, 62.2, 53.7, 48.2, 28.4, 26.0, 25.8, 25.7, 22.5, 18.5, 18.0, 17.8, −4.3, −4.7, −4.9, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{33}H_{65}N_4O_5Si_3$ $[M + H]^+$ 681.4263, found 681.4261.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-O^6-methyl-2-methylinosine (2p)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f(10% EtOAc in *n*-hexane) = 0.24; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 6.01 (d, *J* = 4.8 Hz, 1H), 4.65 (t, *J* = 4.4 Hz, 1H), 4.34 (t, *J* = 4.2 Hz 1H), 4.15–4.11 (m (Me + q), 4H), 4.08 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.81 (dd, *J* = 11.2, 3.2 Hz, 1H), 0.95 and 0.82 (2s, 27H), 0.13, 0.10, −0.02, and −0.16. (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 160.4, 152.1, 140.6, 119.9, 88.7, 84.9, 75.6, 71.5, 62.2, 53.8, 29.6, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, −4.3, −4.7, −5.0, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{59}N_4O_5Si_3$ $[M + H]^+$ 639.3793, found 639.3766.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-cyclopropyl-O^6-methylinosine (2q)

Chromatography was performed using 10% EtOAc in *n*-hexane to yield a light-brown, gummy solid. R_f(10% EtOAc in *n*-hexane) = 0.24; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 5.99 (d, *J* = 4.4 Hz, 1H), 4.63 (t, *J* = 4.4 Hz, 1H), 4.34 (t, *J* = 4.6 Hz, 1H), 4.13–4.10 (m (Me + q), 4H), 4.05 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.82 (dd, *J* = 11.4, 2.8 Hz, 1H), 2.21–2.18 (m, 1H), 1.16 (ddd, *J* = 5.2, 4.4, 3.8 Hz, 2H), 1.02 (ddd, *J* = 4.4, 4.0, 3.2 Hz, 2H), 0.95 and 0.83 (2s, 27H), 0.14, 0.10, −0.01, and −0.13. (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =

166.3, 160.4, 152.2, 140.3, 120.0, 88.6, 84.6, 75.4, 71.4, 62.2, 53.5, 29.6, 26.0, 25.8, 25.7, 18.5, 18.1, 18.0, 17.8, 10.4, 10.2, −4.3, −4.7, −5.0, −5.3, −5.4; HRMS (ESI): *m/z* calcd for $C_{32}H_{62}N_4O_5Si_3$ $[M + H]^+$ 665.3950, found 665.3915.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-phenylinosine (5a)

Chromatography was performed using 3% MeOH in CH_2Cl_2 to yield a colorless solid. R_f (40% MeOH in CH_2Cl_2) = 0.57; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.61 (br s, 1H D_2O exchangeable), 8.33 (s, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.55 (m, 3H), 5.96 (d, *J* = 6.4 Hz, 1H), 4.94 (t, *J* = 4.4 Hz, 1H), 4.30 (s, 1H), 4.00 (s, 1H), 3.95 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.76 (dd, *J* = 10.8, 3.6 Hz, 1H), 0.92, 0.86, and 0.73 (3s, 27H), 0.13, 0.03, −0.02, and −0.28 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 153.4, 148.3, 139.8, 132.2, 131.3, 128.6, 127.6, 123.4, 87.4, 85.2, 74.1, 72.0, 62.4, 40.1,39.9, 39.7, 39.5, 39.2, 39.0, 38.8, 25.7, 25.6, 25.3, 17.9, 17.7, 17.4, −4.6, −4.8, −5.5, −5.6; HRMS (ESI): *m/z* calcd for $C_{34}H_{58}N_4O_5Si_3Na$ $[M + Na]^+$ 709.3613, found 709.3665.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(4-cyanophenyl)inosine (5b)

Chromatography was performed using 5% MeOH in CH_2Cl_2 to yield a light-pink solid. R_f (10% MeOH in $CHCl_3$) = 0.52; ^{1}H NMR (400 MHz CDCl3): δ = 12.35 (br s, 1H D_2O exchangeable), 8.48 (d, *J* = 8.4 Hz, 2H), 8.32 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 6.15 (d, *J* = 4.8 Hz, 1H), 4.48 (t, *J* = 4.4 Hz, 1H), 4.32 (t, *J* = 4.0 Hz, 1H), 4.15 (d, *J* = 2.4 Hz, 1H), 4.01 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.84 (dd, *J* = 11.2, 1.6 Hz, 1H), 0.97 and 0.79 (2s, 27H), 0.16, 0.10, −0.02, and −0.19 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 151.6, 149.2, 139.7, 135.9, 132.8, 128.4, 123.8, 115.0, 87.9, 85.4, 76.6, 71.8, 62.4, 29.6, 26.1, 25.8, 25.6, 18.5, 18.1, 17.8, −4.3, −4.6, −4.7, −4.9, −5.3; HRMS (ESI): *m/z* calcd for $C_{35}H_{58}N_4O_5Si_3$ $[M + H]^+$ 712.3746, found 712.3747.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(thien-3-yl)inosine (5c)

Chromatography was performed using 3% MeOH in CH_2Cl_2 to yield a dark-brown solid. R_f (10% MeOH in $CHCl_3$) = 0.54; ^{1}H NMR (400 MHz $CDCl_3$): δ = 12.22 (br s, 1H D_2O exchangeable), 8.58 (d, *J* = 2 Hz, 1H), 8.20 (s, 1H), 7.89 (d, *J* = 4.8 Hz, 1H), 7.45 (dd, *J* = 5.2, 2.8 Hz, 1H), 6.10 (d, *J* = 5.2 Hz, 1H), 4.56 (t, *J* = 5.2 Hz, 1H), 4.34 (t, *J* = 5.2 Hz, 1H), 4.14 (d, *J* = 3.2 Hz, 1H), 4.01 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.84 (dd, J = 11.2, 2.4 Hz, 1H), 0.96 and 0.81 (2s, 27H), 0.14, 0.11, and −0.15 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 149.7, 149.6, 139.1, 134.6, 129.0, 127.1, 126.6, 123.1, 87.9, 85.3, 76.3, 71.9, 62.6, 26.1, 25.8, 25.6, 18.5, 18.0, 17.8, −4.4, −4.4, −4.7, −4.9, −5.3; HRMS (ESI): *m/z* calcd for $C_{32}H_{57}N_4O_5Si_3S$ $[M + H]^+$ 693.3358, found 693.3360.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(3,5-bis-(trifluoromethyl)phenyl)inosine (5d)

Chromatography was performed using 4% MeOH in CH_2Cl_2 to yield a light-brown, gummy solid. R_f (10% MeOH in $CHCl_3$) = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.98 (br s, 1H D_2O exchangeable), 8.81 (s, 2H), 8.37 (s, 1H), 8.05 (s, 1H), 6.21 (d, *J* = 2.8 Hz, 1H), 4.36-4.34 (t, *J* = 4.4 Hz, 2H), 4.16 (s, 1H), 4.02 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.84 (dd, *J* = 11.4, 2.4 Hz, 1H), 0.95 and 0.86 (2s, 27H), 0.15, 0.11, 0.07, and −0.11 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 149.1, 139.6, 139.2,134.2, 132.7, 128.1, 124.8, 124.3, 123.9, 121.6, 114.0, 87.8, 84.9, 71.3, 62.1, 33.8, 31.9, 29.6, 29.4, 29.3, 29.1, 28.9, 26.1, 25.7, 25.5, 22.6, 18.5, 18.0, 17.7, 14.1, −4.7, −4.9, −5.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{57}N_4O_5Si_3F_6$ $[M + H]^+$ 823.3541, found 823.3541.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(4-pyridyl)inosine (5e)

Chromatography was performed using 6% MeOH in CH_2Cl_2 to yield a light-brown solid. R_f (10% MeOH in $CHCl_3$) = 0.46; ^{1}H NMR (400 MHz DMSO-d_6): δ = 12.91 (br s, 1H D_2O

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exchangeable), 8.79 (d, J = 4.8 Hz, 2H), 8.40 (s, 1H), 8.00 (d, J = 4.8 Hz, 2H), 5.98 (d, J = 6.0 Hz, 1H), 4.88 (t, J = 4.0 Hz, 1H), 4.37 (d, J = 4.8 Hz, 1H), 4.00 (br s, 1H), 3.95 (dd, J = 10.8, 5.6 Hz, 1H), 3.76 (dd, J = 10.8, 3.6 Hz, 1H), 0.92, 0.86, and 0.73 (3s, 27H), 0.13, 0.03, −0.02, and −0.28 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 151.4, 150.1, 147.9, 140.3, 139.4, 124.2, 121.5, 87.5, 85.3, 74.4, 72.0, 62.4, 61.3, 57.9, 56.2, 48.9.45.6, 40.1, 39.9, 39.7, 39.5, 39.2, 39.0, 38.8, 28.9, 25.7, 25.6, 25.3, 17.9, 17.7, 17.4, 8.5, −4.6, −4.8, −4.9, −5.5, −5.6; HRMS (ESI): *m/z* calcd for $C_{33}H_{58}N_5O_5Si_3$ $[M + H]^+$ 688.3746, found 688.3749.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-(1-naphthyl)inosine (5f)

Chromatography was performed using 4% MeOH in CH_2Cl_2 to yield a light-brown, gummy oil. R_f (10% MeOH in $CHCl_3$) = 0.56; ^{1}H NMR (300 MHz $CDCl_3$): δ = 10.58 (br s, 1H D_2O exchangeable), 8.23 (d, J = 6.9 Hz, 1H), 8.17 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (m, 1H), 7.79 (d, J = 7.5 Hz, 1H)), 7.63–7.53 (m, 3H), 6.04 (d, J = 5.4 Hz, 1H), 4.60 (t, J = 4.2 Hz, 1H), 4.30 (t, J = 3.3 Hz, 1H), 4.08 (d, J = 3.6 Hz, 1H), 3.90 (dd, J = 11.2, 2.1 Hz, 1H), 3.77 (dd, J = 11.2, 1.4 Hz, 1H), 0.94 and 0.73 (2s, 27H), 0.16, 0.10, −0.02, and −0.19 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 154.0, 148.8, 139.3, 133.9, 131.5, 130.6, 130.2, 128.7, 127.7, 127.5, 126.6, 125.0, 124.7, 123.8, 88.3, 85.6, 76.1, 71.9, 62.5, 31.9, 29.6, 29.3, 26.0, 25.8, 25.6, 22.6, 18.4, 18.0, 17.8, 14.1 −4.4, −4.6, −4.7, −5.0, −5.5; HRMS (ESI): *m/z* calcd for $C_{38}H_{61}N_4O_5Si_3$ $[M + H]^+$ 737.3950, found 737.3980.

2-(4-(Acetyl)phenyl)-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)inosine (5g)

Chromatography was performed using 7% MeOH in CH_2Cl_2 to yield a light-pink solid. R_f (10% MeOH in $CHCl_3$) = 0.51; ^{1}H NMR (400 MHz $CDCl_3$): δ = 12.77 (br s, 1H D_2O exchangeable), 8.41 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H), 8.17 (d, J = 8.0 Hz, 2H), 6.18 (d, J = 2.8 Hz, 1H), 4.51 (t, J = 4.6 Hz, 1H), 4.33 (s, 1H), 4.14 (d, J = 6.0 Hz, 1H), 4.01 (dd, J = 11.3, 2.8 Hz, 1H), 3.84 (dd, J = 11.3, 1.6 Hz, 1H), 2.68 (s, 3H), 0.95 and 0.81 (2s, 27H), 0.16, 0.11, −0.00, and −0.19 (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) = δ 197.4, 159.0, 152.3, 149.2, 139.5, 139.0, 135.9, 128.9, 127.9, 123.8, 88.1, 85.2, 76.6, 71.7, 67.9, 62.9, 31.8, 29.6, 29.3, 26.8, 26.1, 25.8, 25.6, 25.5, 22.6, 18.5, 18.0, 17.8, 14.0, 0.9, −0. 0, −4.3, −4.6, −4.7, −4.9, −5.3; HRMS (ESI): *m/z* calcd for $C_{36}H_{61}N_4O_6Si_3$ $[M + H]^+$ 729.3899, found 729.3836.

2-*i*-Butyl-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)inosine (5h)

Chromatography was performed with 2% MeOH in $CHCl_3$ to yield a yellow solid. R_f (5% MeOH in $CHCl_3$) = 0.40; ^{1}H NMR (400 MHz DMSO-d_6): δ = 12.70 (br s, 1H D_2O exchangeable), 8.13 (s, 1H), 5.95 (d, J = 4.8 Hz, 1H), 4.56 (t, J = 4.6 Hz, 1H), 4.31 (t, J = 4.2 Hz, 1H), 4.11 (q, J = 3.6 Hz, 1H), 4.02 (dd, J = 11.6, 4.4 Hz, 1H), 3.80 (dd, J = 11.2, 2.8 Hz, 1H), 2.70 (d, J = 7.2 Hz, 2H), 2.30 (m, 1H), 0.99, 0.92, and 0.85 (m, 33H: 27H from *t*-Bu + 6H *i*-butyl Me_2), 0.14, −0.0, and −0.13 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 158.3, 149.4, 146.9, 139.2, 138.8, 138.7, 122.8, 114.0, 88.5, 88.0, 85.5, 84.9, 71.8, 71.5, 62.4, 62.2, 43.8, 29.3, 28.9, 26.1, 25.8, 25.6, 22.6, 22.2, 22.2, 18.5, 18.0, 17.8, 14.1, −4.3, −4.7, −4.9, −5.0, −5.3; HRMS (ESI): *m/z* calcd for $C_{32}H_{63}N_4O_3Si_3$ $[M + H]^+$ 667.4106, found 667.4113.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-2-methylinosine (5i)

Chromatography was performed using 4% MeOH in CH_2Cl_2 to yield a light-brown, gummy solid. R_f (10% MeOH in $CHCl_3$) = 0.52; ^{1}H NMR (400 MHz DMSO-d_6): δ = 12.26 (br s, 1H D_2O exchangeable), 8.21 (s, 1H), 5.84 (d, J = 5.2 Hz, 1H), 4.80 (t, J = 4.0 Hz, 1H), 4.29 (s, 1H), 3.95–3.93 (m (q + dd), 2H), 3.74 (dd, J = 10.8, 3.6 Hz, 1H), 2.35 (s, 3H), 0.91 and 0.74 (2s, 27H), 0.12, 0.08, and −0.29 (3s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9,

155.2, 148.5, 138.5, 122.5, 87.2, 85.1, 74.4, 72.1, 62.3, 40.1, 39.9, 39.7, 39.5, 39.3. 39.1, 38.8, 28.9, 25.7, 25.6, 25.4, 20.9, 17.9, 17.7, 17.5, −4.6, −4.8, −5.5; HRMS (ESI): *m/z* calcd for $C_{29}H_{57}N_4O_5Si_3$ $[M + H]^+$ 625.3637, found 625.3618.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support and encouragement from GVK Biosciences is gratefully acknowledged. Dr. Subhabrata Sen is thanked for his immense assistance. Infrastructural support at CCNY was provided by the National Institutes of Health through grants from the National Center for Research Resources (2G12RR03060-26A1) and the National Institute on Minority Health and Health Disparities (8G12MD007603-27).

References

1. Grate JW, Frye GC. Baltes H, Göpel W, Hesse J. Sensors Update. 1996; Vol. 2WeinheimWiley-VCH:10–20. Suzuki A. Diederich F, Stang PJ. Metal-Catalyzed Cross-Coupling Reactions. 1998New YorkWiley-VCH:49–97. Miyaura N. Top. Curr. Chem. 2002; 219:11–59. Tsuji J. Palladium Reagents and Catalysts: New Perspectives for the 21st Century. 2004John Wiley and Sons:288–313. Suzuki A. Hall DG. Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine. 2005WeinheimWiley-VCH:123–170. f) For a review of the Suzuki-Miyaura reactions of heteroaryl boronic acids, see: Tyrrell E, Brookes P. Synthesis. 2004:469–483.
2. a) Suzuki A. J. Organomet. Chem. 1999; 576:147–168.Miyaura N, Suzuki A. Chem. Rev. 1995; 95:2457–2483.b) Suzuki A. Pure & Appl. Chem. 1991; 63:419–422.
3. Bellina F, Carpita A, Rossi R. Synthesis. 2004:2419–2440.
4. Hassan J, Sévignon M, Gozzi C, Schulz E, Lemaire M. Chem. Rev. 2002; 102:1359–1470. [PubMed: 11996540]
5. Miyaura N. Top. Curr. Chem. 2002; 219:11–59.
6. Kotha S, Lahiri K, Kashinath D. Tetrahedron. 2002; 58:9633–9695.
7. Little AF, Fu GC. Angew. Chem. Int. Ed. 2002; 41:4176–4211.
8. a) Čapek P, Pohl R, Hocek M. Org. Biomol. Chem. 2006; 4:2278–2284. [PubMed: 16729137] b) Čapek P, Pohl R, Hocek M. J. Org. Chem. 2005; 70:8001–8008. [PubMed: 16277321] c) Hocek M, Nauš P, Pohl R, Votruba I, Furman PA, Tharnish PM, Otto MJ. J. Med. Chem. 2005; 48:5869–5873. [PubMed: 16134952] d) Hocek M, Holý A, Votruba I, Dvořáková H. Collect. Czech. Chem. Commun. 2001; 66:483–499.e) Hocek M, Holý A, Dvořáková H. J. Med. Chem. 2000; 65:1683–1697.f) Havelková M, Hocek M, Česnek M, Dvořák D. Synlett. 1999:1145–1147.
9. a) Western EC, Shaughnessy KH. J. Org. Chem. 2005; 70:3678–3688.b) Western EC, Daft JR, Johnson EM II, Gannett PM, Shaughnessy KH. J. Org. Chem. 2003; 68:6767–6774. [PubMed: 12919046]
10. Collier A, Wagner GK. Synth. Commun. 2006; 36:3713–3721.
11. Kohyama N, Katashima T, Yamamoto Y. Synthesis. 2004:2799–2804.
12. Amann N, Wagenknecht H-A. Synlett. 2002:687–691.
13. Lakshman MK, Hilmer JH, Martin JQ, Keeler JC, Dinh YQV, Ngassa FN, Russon LM. J. Am. Chem. Soc. 2001; 123:7779–7787. [PubMed: 11493051]
14. a) Kang SB, De Clercq E, Lakshman MK. J. Org. Chem. 2007; 72:5724–5730. [PubMed: 17595142] b) Lakshman MK, Gunda P, Pradhan P. J. Org. Chem. 2005; 70:10329–10335. [PubMed: 16323841] c) Gunda P, Russon LM, Lakshman MK. Angew. Chem. Int. Ed. 2004; 43:6372–6377.d) Lakshman MK, Thomson PF, Nuqui MA, Hilmer JH, Sevova N, Boggess B. Org. Lett. 2002; 4:1479–1482. [PubMed: 11975608]
15. For reviews on the topic, please see: Agrofoglio LA, Gillaiziau I, Saito Y. Chem. Rev. 2003; 103:1875–1916. [PubMed: 12744695] Hocek M. Eur. J. Org. Chem. 2003:245–254. Lakshman MK. J. Organomet. Chem. 2002; 653:234–251.

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16. Harwood EA, Sigurdsson ST, Edfeldt NBF, Reid BR, Hopkins PB. J. Am. Chem. Soc. 1999; 121:5081–5082.
17. Lakshman MK, Ngassa FN, Keeler JC, Dinh YQV, Hilmer JH, Russon LM. Org. Lett. 2000; 2:927–930. [PubMed: 10768188]
18. a) Zajc B, Lakshman MK, Sayer JM, Jerina DM. Tetrahedron Lett. 1992; 33:3409–3412.b) Himmelsbach F, Schulz BS, Trichtinger T, Charubala R, Pfeiderer W. Tetrahedron. 1984; 40:59–72.
19. Qian M, Glaser R. J. Am. Chem. Soc. 2005; 127:880–887. [PubMed: 15656626] In this work, the *O*6-benzyl analogue of **1** has been synthesized via the use of $SbBr_3$/*t*-BuONO/CH_2Br_2 as described in ref [16].
20. Francom P, Robins MJ. J. Org. Chem. 2003; 68:666–669. [PubMed: 12530909]
21. Barder TE, Walker SD, Martinelli JR, Buchwald SL. J. Am. Chem. Soc. 2005; 127:4685–4696. [PubMed: 15796535]
22. Kuivila HG, Reuwer JF, Mangravite JA. J. Am. Chem. Soc. 1964; 86:2666–2670.
23. a) Yamamoto Y, Suzuki R, Hattori K, Nishiyama H. Synlett. 2006; 7:1027–1030.b) Wong SH, Zhang XI. Tetrahedron Lett. 2001; 42:4087–4089.
24. a) Nair V, Turner GA, Buenger GS, Chamberlain SD. J. Org. Chem. 1998; 53:3051–3057.b) Nair V, Turner GA, Chamberlain SD. J. Am. Chem. Soc. 1997; 109:7223–7224.
25. Kamal A, Laxman E, Rao NV. Tetrahedron Lett. 1999; 40:371–372.
26. Soni A, Dutt A, Sattigeri V, Cliffe I. Synthetic Commun. 2011; 41:1852–1856.
27. Kulkarni P, Kadam AJ, Mane RB, Desai UV, Wadgaonkar PP. J. Chem. Res., Synop. 1999; 6:394–395.
28. Pottabathini N, Bae S, Pradhan P, Hahn H-G, Mah H, Lakshman MK. J. Org. Chem. 2005; 70:7188–7195. [PubMed: 16122237]

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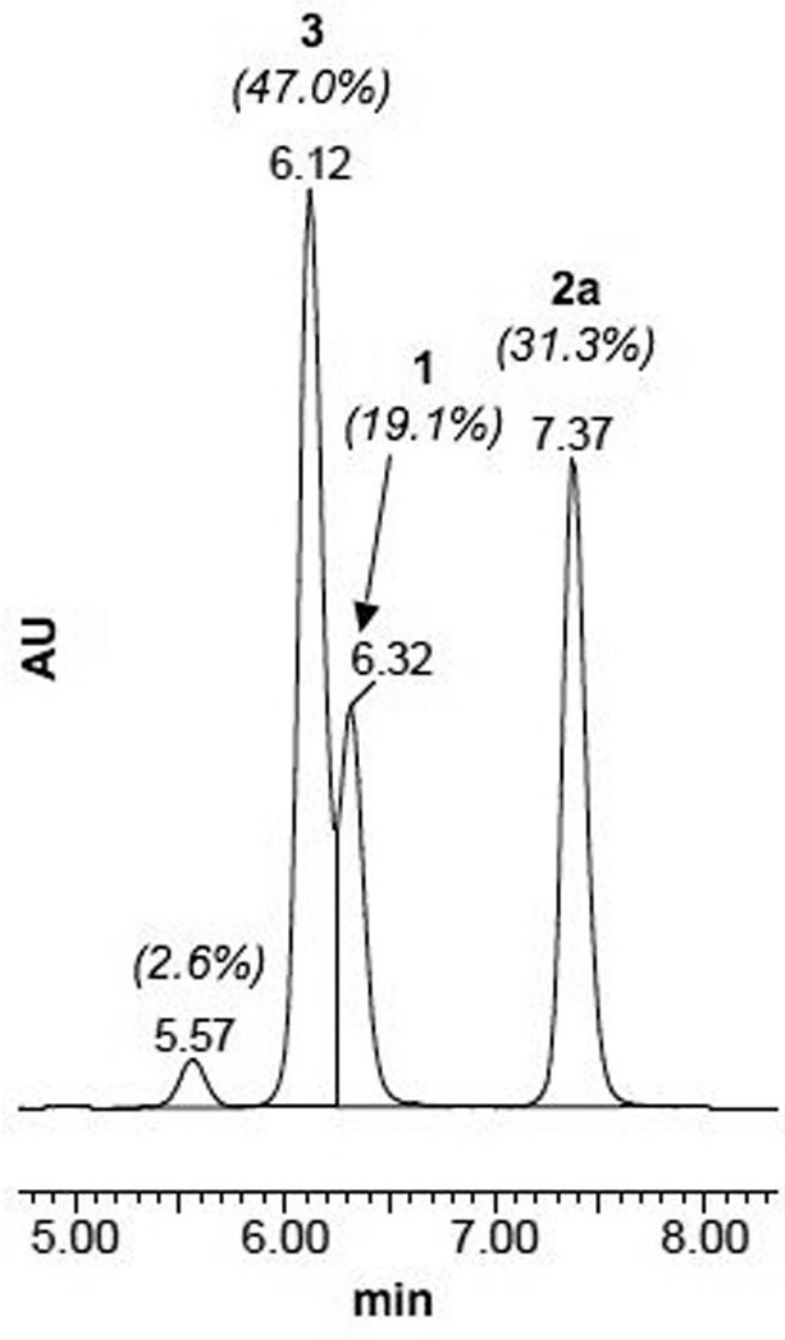
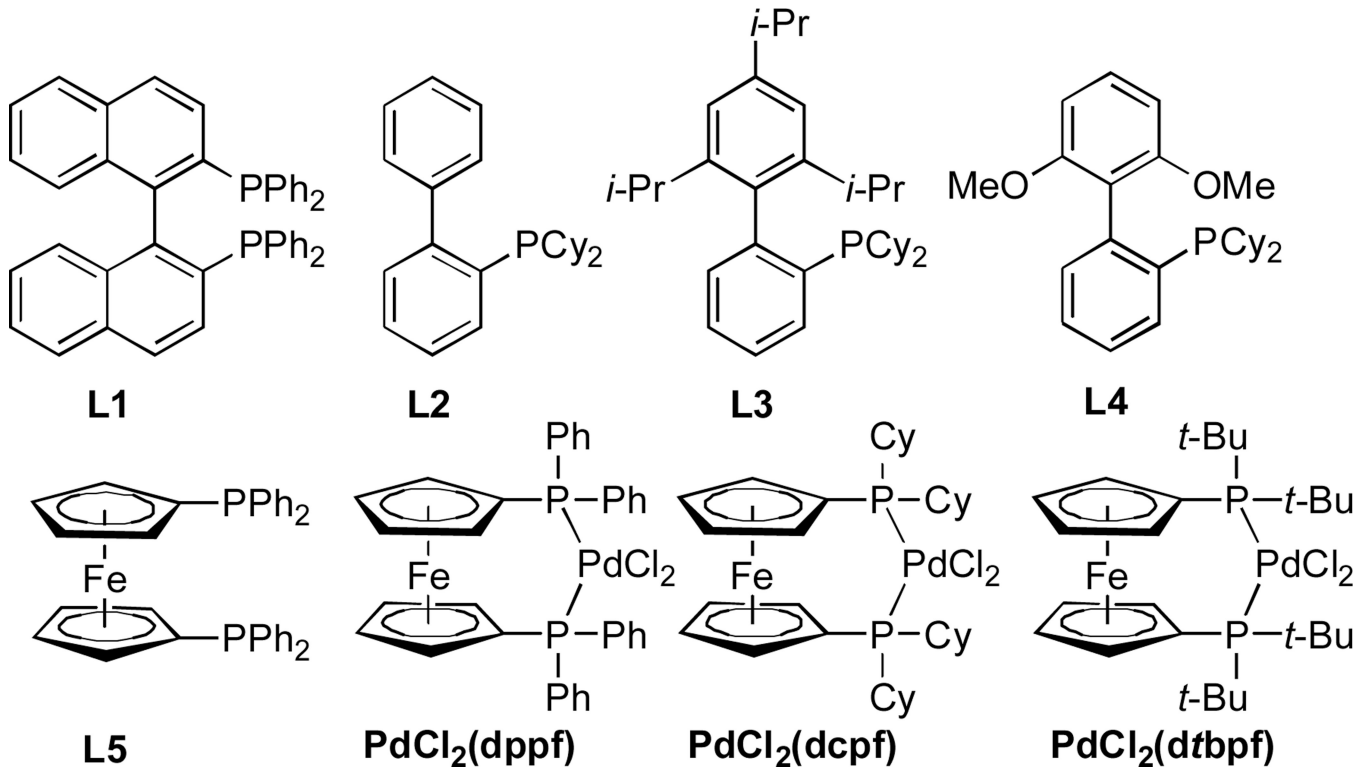


Figure 1.
LC analysis of the reaction mixture from a competitive reaction of compound **1** and **3** with $PhB(OH)_2$; percentages integrals are shown in parentheses.



Scheme 1.
Ligands and Pd^{II} pre-catalysts that were chosen for the initial analysis.

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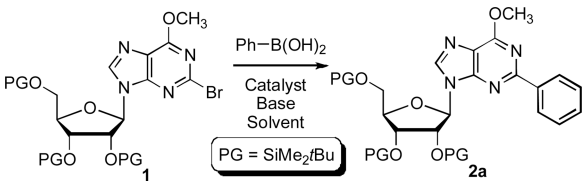
Table 1

Initial optimization experiments.[a,b]



Entry	Catalytic system, conditions, T = 100°C, t = 8 h	Yield[c]
1	25 mol% $Pd(PPh_3)_4/Na_2CO_3$ (2 M aq solution), 3:1 1,4-dioxane-H_2O	62%
2	10 mol% $Pd(OAc)_2$/15 mol% **L1**/K_3PO_4, 1,4-dioxane	49%
3	10 mol% $Pd(OAc)_2$/15 mol% **L2**/K_3PO_4, 1,4-dioxane	50%
4	10 mol% $Pd(OAc)_2$/15 mol% **L3**/K_3PO_4, 1,4-dioxane	75%
5	5 mol% $Pd_2(dba)_3$/10 mol% **L4**/K_3PO_4, 1,4-dioxane	50%
6	10 mol% $Pd(OAc)_2$/15 mol% **L5**/K_3PO_4, 1,4-dioxane	49%
7	20 mol% $PdCl_2$(dppf)/K_3PO_4, 1,4-dioxane	37%
8	20 mol% $PdCl_2$(dcpf)/K_3PO_4, 1,4-dioxane	85%
9	20 mol% $PdCl_2$(d*t*bpf)/K_3PO_4, 1,4-dioxane	65%

[a] Reactions were conducted at a nucleoside concentration of 0.071 M, with 150 mol% $PhB(OH)_2$, and 200 mol% of base, T = 100°C, t = 8 h.

[b] Reactions were conducted in closed vials that were sparged with argon.

[c] Yield of isolated and purified product; dba = dibenzylideneacetone; dppf = 1,1'-bis(diphenylphosphino)ferrocene; dcpf = 1,1'-bis(dicyclohexylphosphiono)ferrocene; dtpf = 1,1'-bis(di-*tert*-butylphosphino)ferrocene.

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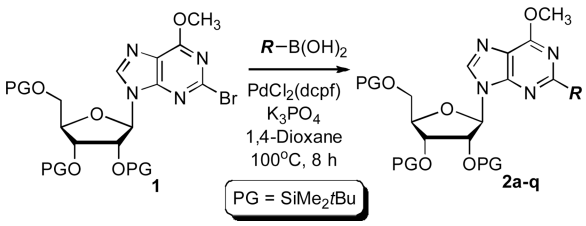
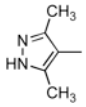
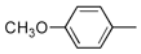
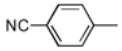
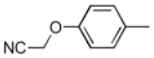
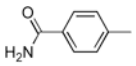
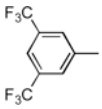
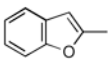
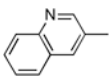
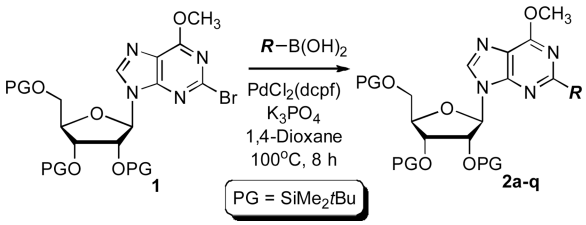
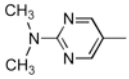
Table 2

Evaluation of the scope of the C–C bond-forming reaction, as well as the influence of microwave irradiation. *[a,b]*



Entry	*R* =	Compound: yield*[c]*
1		**2a:** 85%, 90%*[d]*
2		**2b:** 65%, 70%*[d]*
3		**2c:** 85%
4		**2d:** 65%
5		**2e:** 75%
6		**2f:** 85%
7		**2g:** 70%
8		**2h:** 80%
9		**2i:** 75%
10		**2j:** 70%
11		**2k:** 80%
12		**2l:** 85%



Entry	*R* =	Compound: yield[c]
13		**2m:** 55%, 65%[d]
14		**2n:** 75%
15		**2o:** 52%, 62%[d]
16		**2p:** 85%
17		**2q:** 85%

[a]Reactions were conducted at a nucleoside concentration of 0.071 M, with 20 mol% [$PdCl_2$(dcpf)], 150 mol% of the boronic acid, and 200 mol% of K_3PO_4.

[b]Reactions were conducted in closed vials that were sparged with argon.

[c]Yield of isolated and purified products.

[d]Yield obtained under microwave irradiation conditions (100°C, 30 min).

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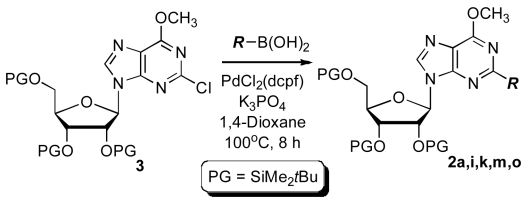
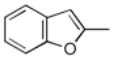
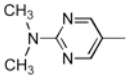
Table 3

Some C–C cross-coupling reactions of Chloro-nucleoside **3**.[a,b]



Entry	*R* =	Compound: yield[c]
1		**2a:** 82% (85%)
2		**2i:** 75% (75%)
3		**2k:** 75% (80)
4		**2m:** 52% (55%)
5		**2o:** 50% (52%)

[a]Reactions were conducted at a nucleoside concentration of 0.071 M, with 20 mol% [$PdCl_2$(dcpf)], 150 mol% of the boronic acid, and 200 mol% of K_3PO_4.

[b]Reactions were conducted in closed vials that were sparged with argon.

[c]Yield of isolated and purified products; Yield obtained with bromo-nucleoside **1** is shown in parenthesis.

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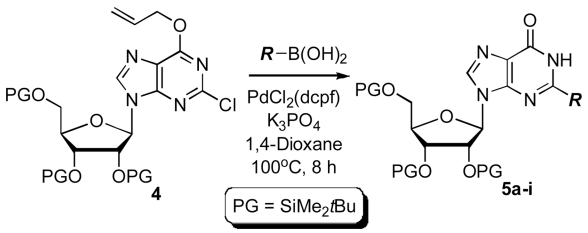
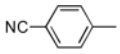
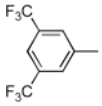
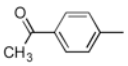
Table 4

One-pot C–C cross coupling and O^6-deprotection of Chloro-nucleoside **4**.[a,b]



Entry	*R* =	Yield of product in the crude reaction mixture (estimated by LC/MS)	Yield after purification by column chromatography and preparative HPLC[c]
1		82%	**5a:** 52%
2		67%	**5b:** 63%
3		77%	**5c:** 60%
4		50%	**5d:** 40%
5		71%	**5e:** 60%
6		70%	**5f:** 37%
7		53%	**5g:** 35%
8		62%	**5h:** 37%
9		59%	**5i:** 38%

[a]Reactions were conducted at a nucleoside concentration of 0.071 M, with 20 mol% [$PdCl_2$(dcpf)], 200 mol% of the boronic acid, and 200 mol% of K_3PO_4.

[b]Reactions were conducted in closed vials that were sparged with argon.

[c]Yield estimated by LC/MS.

[d]Products were purified by column chromatography on silica gel and then by preparative HPLC (HPLC conditions are provided in the Experimental Section).