JOC Note
pubs.acs.org/joc

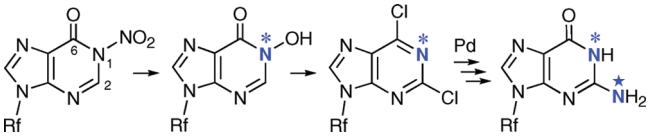
^{15}N Double-Labeled Guanosine from Inosine through Ring-Opening−Ring-Closing and One-Pot Pd-Catalyzed C−O and C−N Cross-Coupling Reactions

Joaquim Caner and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Av. Diagonal 647, 08028 Barcelona, Catalonia, Spain

jvilarrasa@ub.edu

Received April 25, 2010

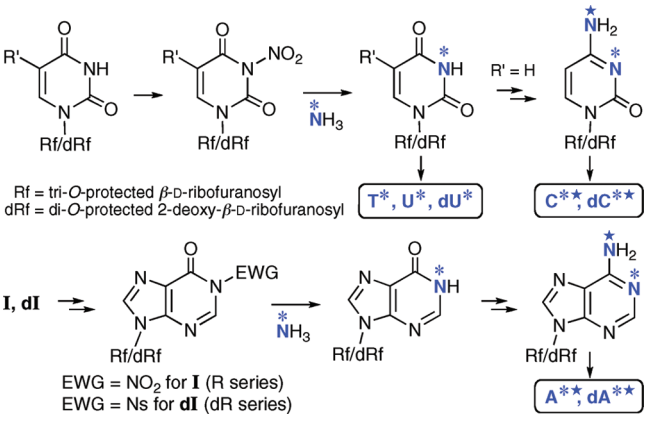


[N,1-$^{15}N_2$]-Guanosine, or [1,NH_2-$^{15}N_2$]-guanosine, and derivatives were prepared from tri-*O*-acetylinosine, via *N*-nitration and reaction with $^{15}NH_2OH$, followed by conversion of the ^{15}N-labeled 1-hydroxyinosine to the corresponding 2,6-dichloropurine riboside. The sequential one-pot C−O and C−N key couplings of this dichloro derivative with $PhCH_2OH$ and $PhCO^{15}NH_2$ or $^{i}PrCO^{15}NH_2$ was achieved in good overall yields, with Pd(0)−Xantphos as the best choice of five different catalytic systems examined.

Nucleosides labeled with ^{15}N at specific positions and, thus, selectively labeled oligonucleotides, DNAs, and RNAs have provided key information (such as distinguishing the $^{15}N-H$ protons and characterizing $^{15}N-H\cdots{}^{15}N$ hydrogen bonds by ^{1}H and ^{15}N NMR) on nucleic acid structures and nucleic acid−protein interactions.[1]

In the 1990s, taking advantage of the unexpectedly easy *N*-nitration of pyrimidine nucleosides, we discovered a new reaction in which the addition of the nucleophile $^{15}NH_3$ was followed by ring-opening−ring-closing (RORC) steps,[2] which showed some parallelism with other S_NRORC or ANRORC processes.[3] The process could be applied to inosines,[4] from which we also obtained ^{15}N double-labeled adenosines. When *N*-nitration failed (dI series), the 2-nitrobenzenesulfonyl group (Ns) was the best alternative.[5,6] The overall process is summarized in Scheme 1, where asterisks on N (N* for internal labels, N★ for amino groups) mean ≥98% of ^{15}N at the indicated position(s). The pros of this general procedure are the following: all internal labels were introduced at room temperature (rt); only 1.1 equiv of ^{15}N-labeled reagents was employed in all labeling steps; and sugar-modified nucleosides and appropriately C-substituted nucleobases may be amenable to it. The con is that we were unable to convert [1-^{15}N]-inosines to the double-labeled [N,1-$^{15}N_2$]-guanosines efficiently, in a short number of steps (not involving the degradation of inosine or ex-novo synthesis[7]). Due to this, G*★ and dG*★ are lacking in Scheme 1.

SCHEME 1. ^{15}N Labeling of Nucleosides by RORC[2,4,5]



Jones et al.,[8] by means of a Dimroth rearrangement from 1-alkoxy adenosines, prepared a series of ^{15}N and ^{15}N,^{13}C-multilabeled guanosines. In connection with our objective of achieving all the $^{15}N_2$-natural nucleosides in the most efficient way, we report here an alternative approach to guanosines labeled both at N1 and on amino N, based on our

(1) For recent, representative applications, see: (a) Bdour, H. M.; Kao, J. L.-F.; Taylor, J.-S. *J. Org. Chem.* **2006**, *71*, 1640. (b) Dingley, A. J.; Nisius, L.; Cordier, F.; Grzesiek, S. *Nat. Protoc.* **2008**, *3*, 242. (c) Wang, W.; Zhao, J.; Han, Q.; Wang, G.; Yang, G.; Shallop, A. J.; Liu, J.; Gaffney, B. L.; Jones, R. A. *Nucleosides, Nucleotides Nucleic Acids* **2009**, *28*, 424. (d) Baral, B.; Kumar, P.; Anderson, B. A.; Ostergaard, M. E.; Sharma, P. K.; Hrdlicka, P. J. *Tetrahedron Lett.* **2009**, *50*, 5850.

(2) (a) Bou, V. Ph.D. Thesis, Universitat de Barcelona, 1992. (b) Ariza, X.; Bou, V.; Vilarrasa, J.; Tereshko, V.; Campos, J. L. *Angew. Chem., Int. Ed.* **1994**, *33*, 2454. (c) Ariza, X.; Farràs, J.; Serra, C.; Vilarrasa, J. *J. Org. Chem.* **1997**, *62*, 1547. (d) Ariza, X.; Vilarrasa, J. *J. Org. Chem.* **2000**, *65*, 2827.

(3) Review: van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 1.

(4) (a) Ariza, X. Ph.D. Thesis, Universitat de Barcelona, 1995. (b) Ariza, X.; Bou, V.; Vilarrasa, J. *J. Am. Chem. Soc.* **1995**, *117*, 3665. (c) Terrazas, M.; Ariza, X.; Farràs, J.; Guisado-Yang, J. M.; Vilarrasa, J. *J. Org. Chem.* **2004**, *69*, 5473.

(5) (a) Terrazas, M.; Ariza, X.; Vilarrasa, J. *Org. Lett.* **2005**, *7*, 2477. (b) Terrazas, M.; Ariza, X.; Vilarrasa, J. *Tetrahedron Lett.* **2005**, *46*, 5127. (c) For a related work, see: Terrazas, M.; Ariza, X.; Farràs, J.; Vilarrasa, J. *Chem. Commun.* **2005**, 3968.

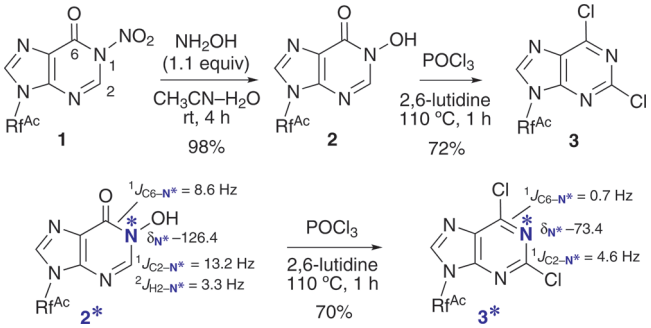
(6) Use of *N*-2,4-dinitrophenyl dI (Scheme 1, EWG = DNP) for the same purpose has been reported: (a) De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G. *J. Org. Chem.* **1995**, *60*, 2251. (b) De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G.; Varra, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2079. (c) Catalanotti, B.; De Napoli, L.; Galeone, A.; Mayol, L.; Oliviero, G.; Piccialli, G.; Varra, M. *Eur. J. Org. Chem.* **1999**, 2235. We also examined the case where EWG = $COO^{t}Bu$ in the inosine series, but nucleophiles tend to attack at the C atom of the carboxyl group (with deprotection) rather than the C2 (or C4) carbon atoms (no RORC process).

(7) For example, from ^{15}N-labeled AICA-riboside: (a) Bleasdale, C.; Ellwood, S. B.; Golding, B. T.; Slaich, P. K.; Taylor, O. J.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2859. (b) Abad, J. L.; Gaffney, B. L.; Jones, R. A. *J. Org. Chem.* **1999**, *64*, 6575.

(8) (a) Pagano, A. R.; Zhao, H.; Shallop, A. J.; Jones, R. A. *J. Org. Chem.* **1998**, *63*, 3213. (b) Shallop, A. J.; Gaffney, B. L.; Jones, R. A. *J. Org. Chem.* **2003**, *68*, 8657 and references cited therein.

Published on Web 06/15/2010 DOI: 10.1021/jo100808w

SCHEME 2. From *N*-Nitroinosines to *N*-Hydroxyinosines and to 2,6-Dichloro Derivative 3



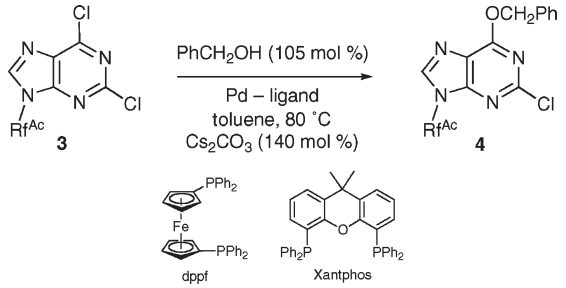
above-mentioned RORC procedure and on Pd-catalyzed C−O and C−N bond forming reactions.

First, triacetylated *N*-nitroinosine **1** was prepared in 80% yield from tri-*O*-acetylinosine by our *N*-nitration protocol[4,5] (with a large excess of CF_3COONO_2 at −40 °C). Treatment of **1** with $HONH_3^+Cl^-$ (1.1 equiv) and NaOAc (2.2 equiv) in 1:1 CH_3CN-H_2O at rt afforded *N*-hydroxy derivative **2** in 98% yield (Scheme 2), via a polar intermediate (an open species according to ^1H NMR) that disappeared to give the desired compound within 4 h. The fact that this RORC step could be carried out with only 1.1 equiv of hydroxylamine was instrumental in using it as an N1-labeling procedure,[9] as otherwise scaling up of the overall process would be economically unpractical. This indirect *N*-hydroxylation procedure is general since it could be applied to other protected inosines (tri-*O*-TBS and 5′-*O*-TBS-2′,3′-*O*-isopropylidene) in ca. 80% overall yields.

A sample of the ^{15}N-labeled compound **2*** was prepared by this protocol, that is, from **1** and only 1.05 equiv of $HO^{15}NH_3^+Cl^-$ (obtained by us from reduction of $Na^{15}NO_2$,[10] but also commercially available with 98% ^{15}N).

We took advantage of a known reaction of purine *N*-oxides[11] for the conversion of *N*-hydroxyinosine **2** to the corresponding 2,6-dichloropurine nucleoside, **3** (Scheme 2). This involves heating with a large excess of $POCl_3$ and 2,6-lutidine or 2-picoline.[12] The same reaction did not work with $POBr_3$ (and only the bromination of position 6 took place with $POBr_3$ and *N*,*N*-diethylaniline in toluene). We applied this procedure to the conversion of a sample of **2*** to **3***.

TABLE 1. Pd-Catalyzed Couplings of 3 with $PhCH_2OH$[a]



entry	Pd source (mol %)	ligand (mol %)	time (h)	**4**, yield[b]
1	none	none	4.0	0
2	$Pd_2dba_3\cdot CHCl_3$, 5	dppf, 15	2.0	66
3	$Pd_2dba_3\cdot CHCl_3$, 2.5	Xantphos, 7.5	1.0	81
4	$Pd_2dba_3\cdot CHCl_3$, 5	Xantphos, 15	0.5	85

[a]At 0.1 M concentrations in toluene at 80 °C. [b]Isolated yield, in %.

We envisaged replacing both chloride ions of **3** consecutively, by means of appropriate Pd-catalyzed couplings. Outstanding studies in the nucleoside field have been published recently, mainly involving C−N couplings (Buchwald−Hartwig reactions) of bromo- and iodopurines.[12] Although C−Cl bonds are much less reactive in Pd-catalyzed couplings, new ligands have been developed to deal with aromatic chlorides.[13]

With this background some approaches were soon ruled out.[14] Moreover, when **3** was heated to 80 °C in toluene, with 1.1 equiv of $PhCONH_2$, small amounts of $Pd_2dba_3\cdot CHCl_3$, diphosphines of different bite angles (dppf,[15] DPEphos,[16a] or Xantphos[16]), and Cs_2CO_3, only the product substituted on C6 was formed, confirming that position 6 is intrinsically more reactive. Thus, the substitution at C6 has to be carried out before that at C2. The S_NAr-like replacement of 6-Cl by different amounts of benzyl alcohol and strong bases gave the desired **4**, although in poor yields; this was mainly due to the workup difficulties, when an excess of benzyl alcohol was used, and to the byproducts from double addition and deacylation reactions.

In this context, we examined the following protocol (see Table 1): **3** was mixed in toluene with $PhCH_2OH$,

(9) Identical treatments of the *N*-Ns derivative relating to **1** (with Ns instead of NO_2 as EWG) afforded complex mixtures (containing *N*-deprotected compounds as well as hydrolyzed and pyrimidine ring-cleaved species) with insignificant amounts of the desired *N*-hydroxy compound, **2**. With DNP instead of NO_2 as EWG, we needed 5−10 equiv of NH_2OH and heating to convert **1** to **2**.

(10) (a) Rajendran, G.; Van Ettern, R. L. *Inorg. Chem.* **1986**, *25*, 876. (b) Tao, T.; Alemany, L. B.; Parry, R. J. *Org. Lett.* **2003**, *5*, 1213.

(11) (a) Kawashima, H.; Kumashiro, I. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 639. (b) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601. (c) We could also have arrived at 2* from [1-^{15}N]-adenosine, through its N-oxide, followed by a deamination−hydroxylation reaction according to the procedure of Robins and Uznanski. However, it was preferable to enter the internal label as late as possible. Also, we were interested in examining the performance of the reaction of N-nitro nucleosides with NH_2OH.

(12) (a) Piguel, S.; Legraverend, M. *J. Org. Chem.* **2007**, *72*, 7026 and references cited therein. (b) Vandromme, L.; Legraverend, M.; Kreimerman, S.; Lozach, O.; Meijer, L.; Grierson, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 130. (c) Li, X.; Vince, R. *Bioorg. Med. Chem.* **2006**, *14*, 5742. For C−N couplings of nucleoside arylsulfonates with aromatic amines, see: (d) Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6372. For alternative routes via S_NAr reactions, see: (e) Liu, J.; Robins, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 5962. (f) Kamaike, K.; Kayama, Y.; Isobe, M.; Kawashima, E. *Nucleosides, Nucleotides Nucleic Acids* **2006**, *25*, 29 and references cited therein.

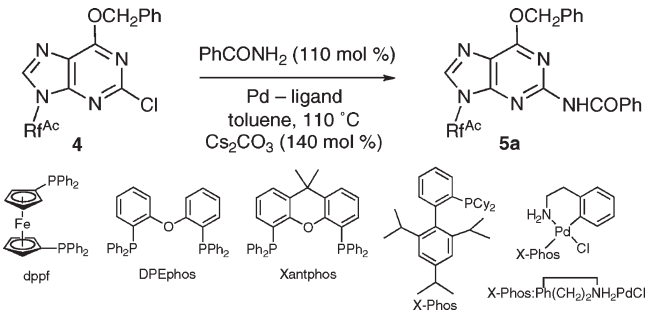
(13) For a review, see: Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(14) (a) Substitution of OH for the more reactive 6-Cl by means of a simple treatment with KOH (1 M in CH_3CN-H_2O) at rt afforded fully deprotected 2-chloroinosine. This compound can be converted to guanosine, but under very harsh conditions, probably because the anion is formed and is very reluctant to undergo a second substitution reaction. (b) For an example of a substitution, with a big excess of NH_3/MeOH in a sealed tube at 145 °C for 72 h, see: Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044.

(15) Recent review: Fihri, A.; Meunier, P.; Hierso, J.-C. *Coord. Chem. Rev.* **2007**, *251*, 2017.

(16) For a very recent review on diphosphines, see: (a) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099. Xantphos preparation: (b) Hillebrand, S.; Bruckmann, J.; Krueger, C.; Haenel, M. W. *Tetrahedron Lett.* **1995**, *36*, 75. (c) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081. $Pd_2dba_3\cdot CHCl_3$ and Xantphos in a 1:3 molar ratio, and 140 mol % of Cs_2CO_3 (in 1,4-dioxane at 100 °C), were recommended for intermolecular amidations of ArBr/ArOTf/ArI: (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (e) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. For the effect of bidentate ligands, see: (f) Fujita, K.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044. Also see ref 12a. Pd(0)/Xantphos was also shown to be useful for the *N*-arylation of amino groups of nucleosides: (g) Ngassa, F. N.; DeKorver, K. A.; Melistas, T. S.; Yeh, E. A.-H.; Lakshman, M. K. *Org. Lett.* **2006**, *8*, 4613.

TABLE 2. Pd-Catalyzed Couplings of 4 with $PhCONH_2$[a]



entry	Pd source (mol %)	ligand (mol %)	time	**5a**, yield[b]
1	none	none	4 h	0
2	$Pd_2dba_3 \cdot CHCl_3$, 5	dppf, 15	4 h	0
3	$Pd_2dba_3 \cdot CHCl_3$, 5	DPEphos, 15	80 min	64 (74)[c]
4	$Pd_2dba_3 \cdot CHCl_3$, 5	Xantphos, 15	60 min	68 (77)[c]
5	$Pd_2dba_3 \cdot CHCl_3$, 2 × 2.5	Xantphos, 2 × 2.5	40 min	72
6	$Pd_2dba_3 \cdot CHCl_3$, 5	X-Phos, 15	80 min	60
7	X-Phos:palladacycle, 10		90 min	54

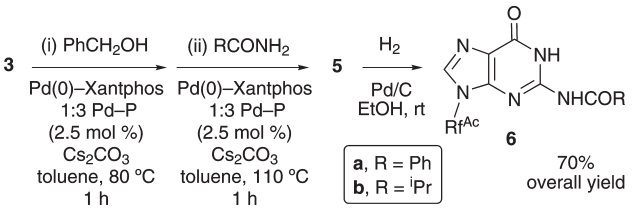
[a]At 0.1 M concentrations in refluxing toluene. [b]Isolated yield, in %. [c]Yields with 10 mol % of $Pd_2dba_3 \cdot CHCl_3$ are in parentheses.

$Pd_2dba_3 \cdot CHCl_3$, dppf or Xantphos, and Cs_2CO_3 and heated to 80 °C. With Cs_2CO_3 but without the catalyst (entry 1) no substitution took place. With all the additives, the 6-*O*-CH_2Ph derivative, **4**, was formed quite rapidly with both diphosphines (entries 2−4). The conditions of choice turned out to be those of entry 3 (2.5 mol % of catalyst, 0.05 equiv of Pd), since the addition of twice the amount of catalyst and ligand (entry 4) improved the yield only slightly. DPEphos gave similar results to Xantphos, while reactions with X-Phos (7.5 mol %, with 2.5 mol % of $Pd_2dba_3 \cdot CHCl_3$) were too slow (data not included in Table 1 to save space).

We then investigated the best phosphine ligand for the replacement of the second Cl (the Cl of **4**) by benzamide ($PhCONH_2$) as an ammonia synthetic equivalent. Table 2 summarizes the main results, in refluxing toluene, since the couplings did not progress at 80 °C. Refluxing 1,4-dioxane and heating for longer times were counter-indicated with our substrate; both increased the percentages of decomposition and deacylation byproducts. Most of the experiments were carried out three times, ensuring that dppf was inappropriate (entry 2),[17] while DPEphos (entry 3) and especially Xantphos (entry 4) afforded the highest yields of **5a**. When the catalyst and ligand were added in two portions (the second one after 20 min of reaction) the disappearance of **4** was faster and the yield improved (entry 5). The monodentate X-Phos (entry 6) and the palladacycle (entry 7) were less efficient. Thus, Xantphos became our preferred ligand for these C−O/N couplings, but the low cost of DPEphos should be taken into account for larger scale reactions.

We were ready to carry out the preparation of **5a** (reaction with $PhCONH_2$) and **5b** (coupling with isobutyramide, $^iPrCONH_2$) via a sequential one-pot reaction (see Scheme 3).[18] We added **4** and 105 mol % of $PhCH_2OH$ to a reaction flask containing the Pd(0)/Xantphos/Cs_2CO_3 mixture in toluene, which was heated to 80 °C. After ca. 1 h (when TLC indicated that **3** had disappeared), 110 mol % of $PhCONH_2$ and a second charge of Pd/Xantphos/Cs_2CO_3 were added, and a gentle reflux was then maintained for 1 h. We noted that this protocol afforded higher conversions and fewer byproduct than in experiments with the full amount of catalyst/ligand/base introduced from the beginning. We also saved Pd and diphosphine. Yields of 70−73% of **5a** were isolated by column chromatography.[19] With $^iPrCONH_2$ instead of $PhCONH_2$, **5b** was similarly obtained.

SCHEME 3. One-Pot Conversion of 3 to 5a and 5b and Cleavage of the O−CH_2Ph Bond To Give 6a and 6b



The removal of the benzyl group of **5a** and **5b** (H_2 balloon, Scheme 3) gave **6a** and **6b**, respectively, in nearly 70% yields (overall for three steps).[20]

With all these "preliminary" studies and results in hand, we carried out the reactions of interest. From **3** or **3***, we achieved the series of mono- and double-labeled **5a** and **5b**, **6a** and **6b**, and guanosines (**7**) shown in Scheme 4, by using $PhCO^{15}NH_2$ (prepared from PhCOCl, $^{15}NH_4Cl$, and KOH in CH_3CN-H_2O in 97% yield) and $^iPrCO^{15}NH_2$, similarly prepared, in the C−N cross-coupling step. In short, ^{15}N-labeled guanosines with the standard amino protecting group for oligonucleotide synthesis (^iPrCO, see the **6b** series) can be prepared efficiently as well.

In summary, we synthesized the desired ^{15}N-labeled guanosines **7*** (G*) and **7**$^{\bigstar}$ (G$^{\bigstar}$) in seven steps from natural inosine (four steps after introducing the first label). Only inorganic sources of ^{15}N ($Na^{15}NO_2$ or $HO^{15}NH_3{}^+Cl^-$, $^{15}NH_4{}^+Cl^-$) were used and only in nearly equivalent amounts. G$^{\bigstar}$ has >98% of ^{15}N at both the relevant positions for examining Watson−Crick interactions. Although the introduction of internal ^{15}N labels in nucleosides (and in heterocyclic compounds in general) is usually much more complicated than in the amino groups, and the substitution of $^{15}NH_2OH$ for NH_2NO_2 took place in a remarkable 98% yield with only 1.05 equiv of labeling source (!), we focused our attention on the optimization of the C−O and mainly the C−N bond formation reactions, as we had to convert an expensive ^{15}N-labeled inosine derivative into single and double ^{15}N-labeled guanosines in few steps and good yields. The sequential, or consecutive, one-pot Pd-catalyzed C−O and C−N couplings from a heteroaryl dichloride, reported here for the first time to the best of our knowledge, allowed us to reduce the amounts of Pd and of our

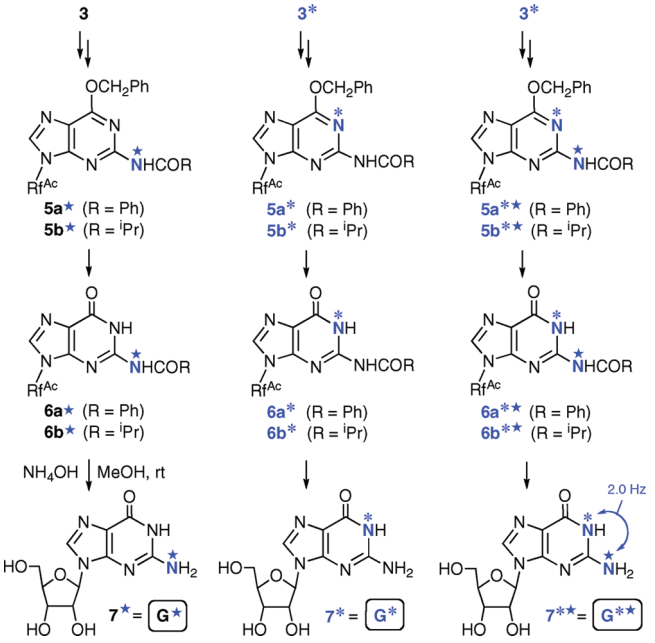
(17) However, in our lab, the analogous 2-Br derivative was replaced efficiently by $PhCONH_2$ with Pd/dppf at 80 °C (Terrazas, M. Ph.D. Dissertation, Universitat de Barcelona, 2006).

(18) For examples of related one-pot intermolecular C−C couplings, see: (a) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493. (b) Zhang, X.; Liu, A.; Chen, W. *Org. Lett.* **2008**, *10*, 3849 and references cited therein. (c) Beaumard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2009**, *11*, 1801. Tandem couplings using two different metallic catalysts are more common. For combinations of S_NAr and Pd-catalyzed reactions, see: (d) Tikad, A.; Routier, S.; Akssira, M.; Guilllaumet, G. *Org. Biomol. Chem.* **2009**, *7*, 5113.

(19) In one-pot C−O and C−N coupling experiments with K_3PO_4 instead of Cs_2CO_3 the coupling reactions did work, but more slowly. With DIPEA no coupling took place.

(20) We isolated **5a** and **5b** and subjected them to simple hydrogenolysis when we might have examined the cleavage of the O−CH_2Ph bond in the same flask (three steps in one pot), but the isolation of **6a** and **6b** from the final mixture was judged to be more cumbersome.

SCHEME 4. Synthesis of ^{15}N-Labeled 5−7



preferred ligand to date (Xantphos) and to increase the overall yields.

Experimental Section

[1-^{15}N]-2′,3′,5′-Tri-*O*-acetyl-1-hydroxyinosine (2*). A solution of $^{15}NH_2OH \cdot HCl$ (116 mg, 1.65 mmol) and NaOAc (271, 3.30 mmol) in water (12 mL) was added to a solution of **1** (660 mg, 1.50 mmol) in acetonitrile (12 mL). The reaction mixture was stirred at rt for 4 h (the pale yellow color faded and a suspension was formed of a more polar intermediate, as indicated by TLC, which slowly disappeared). The solution was partially concentrated (to remove acetonitrile) and CH_2Cl_2 and brine were added. The layers were separated. The organic layer was washed with water and dried over Na_2SO_4. Filtration and evaporation to dryness gave chromatographically pure **2*** (599 mg, 96%) as a yellowish-white foam (spectra in the Supporting Information).

Representative One-Pot Reaction. A reaction flask was charged with $Pd_2dba_3 \cdot CHCl_3$ (6.5 mg, 6.3 μmol), Xantphos (11.2 mg, 18.9 μmol), [1-^{15}N]-2′,3′,5′-tri-*O*-acetyl-2,6-chloropurine (**3***, 112 mg, 0.25 mmol), and Cs_2CO_3 (115 mg, 0.35 mmol). The flask was purged with nitrogen. Anhydrous toluene (1.2 mL) and benzyl alcohol (28 μL, 29.3 mg, 0.27 mmol) were added via syringe. The reaction mixture was magnetically stirred at 80 °C under nitrogen, until the reaction was complete, as shown by TLC (45 to 75 min depending on the batch). Afterward, $Pd_2dba_3 \cdot CHCl_3$ (6.5 mg, 6.3 μmol), Xantphos (11.2 mg, 18.9 μmol), Cs_2CO_3 (115 mg, 0.35 mmol), and [^{15}N]-benzamide (33.5 mg, 0.27 mmol) were added. The reaction mixture was then heated at 110 °C under nitrogen, until the second step was complete (40 to 80 min depending on the batch of Pd). The heating bath was removed. The flask content was diluted with 20 mL of CH_2Cl_2 and filtered through a pad of Celite. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography (7:3 CH_2Cl_2/EtOAc) to afford 110 mg (73%) of **5a*★** as a pale white foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (s, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 4.43−4.55 (m, 3H), 5.66 (s, 2H), 5.98−6.00 (m, 2H), 6.10 (m, 1H), 7.29−7.38 (m, 3H), 7.49−7.60 (m, 5H), 7.93 (s, 1H), 7.98 (m, 2H), 8.66 (dd, $J_{H-N★}$ = 88.9 Hz, J_{H-N*} = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.4, 20.5, 20.7, 63.3, 68.9 (d, J_{C-N*} = 3.8 Hz), 70.7, 73.3, 80.1, 87.0, 119.2 (d, J_{C-N*} = 1.5 Hz, C5), 127.5, 128.2, 128.4, 128.6, 128.7, 132.2, 134.6 (d, $J_{C-N★}$ = 9.2 Hz), 135.8, 140.3, 152.2 (dd, $J_{C-N★}$ = 25.2 Hz, J_{C-N*} = 5.9 Hz, C2), 152.3 (dd, $J_{C-N★}$ = 3.4 Hz, J_{C-N*} = 0.7 Hz, C6), 160.9 (dd, J_{C-N*} = 9.1 Hz, $J_{C-N★}$ = 2.8 Hz, C4), 164.6 (dd, $J_{C-N★}$ = 13.9 Hz, J_{C-N*} = 1.3 Hz, CO), 169.4, 169.6, 170.5; ^{15}N NMR ($CDCl_3$, 40.5 MHz) δ −126.9 (dd, $J_{N*-N★}$ = 6.4 Hz, J_{N*-H} = 2.0 Hz, N*), −208.8 (dd, $J_{N★-H}$ = 88.9 Hz, $J_{N*-N★}$ = 6.4 Hz, N★); HRMS (ESI) calcd for $C_{30}H_{30}N_3{}^{15}N_2O_9^+$ $(M + H)^+$ 606.1979, found 606.1981.

Acknowledgment. J.C. is grateful for a studentship from the Universitat de Barcelona (2003−2006), a stipend from TRIoH (FP7, European Union, contract LHSB-CT-2003-503480, during 2007), and a current fellowship from the Fundació Privada Cellex of Barcelona. The Ministerio de Educación y Ciencia provided additional support (SAF2005-24643-E). Ionela Cialicu carried out experiments with DNP derivatives of inosines and NH_2OH during her DEA studies (2007). The advice given by Dr. Jaume Farràs and Dr. Xavier Ariza (of our Department) to J.C. during his Ph.D. period is also acknowledged. This work is dedicated to Prof. Henk C. van der Plas (Emeritus Prof., University of Wageningen) and Prof. Piet van Leeuwen (ICIQ, Tarragona).

Supporting Information Available: Experimental details and copies of ^{1}H, ^{13}C, and ^{15}N NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.