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The Selective Synthesis of Metallanucleosides and Metallanucleotides: A New Tool for the Functionalization of Nucleic Acids

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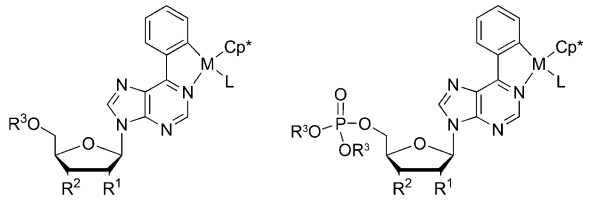
The combination of nucleobases with transition metals[1,2] is an attractive area of research due to the key role of metal complexes in cancer chemotherapy.[3,4] In this context, many efforts in the field have been devoted to nucleobase-Pt coordination complexes with the aim to study the mechanisms of interaction of *cis*-platinum (and its analogues) with DNA.[3] Other modified nucleosides are also known to possess a broad spectrum of biological activities,[5] although to date, the studies have been mostly limited to 6-aryl(heteroaryl) purines and their nucleosides, which have shown to display significant noticeable cytostatic and antibacterial activity and are potent hepatitis C virus (HCV) antivirals.[6–8]

Nucleosides and nucleotides having M–C bonds (in which C is part of the nucleobase skeleton) are essentially different from the known metal-coordination complexes. Their synthesis and properties have not been studied, and the presence of M–C bonds in their structures would also make them interesting building blocks for the construction of new metalla-macrocyclic or supramolecular molecules.[9,10] We now report the successful application of an N-directed cyclometallation reaction to the synthesis of metal-arylpurine nucleosides **1** and nucleotides (or dinucleotides) **2** (M = Ir^{III}, Rh^{III}) and explore their reactivity in the formation of new M–C and M–N bonds. Initially the idea of using an N-directed C–H activation reaction[11] to prepare these purine derivatives was somewhat challenging. First, the presence of several nitrogen atoms in the 6-phenylpurine skeleton could lead to selectivity problems as well as to mixtures of C–H activation/coordination products.[1,2] On the other hand, the incorporation of a sugar unit and a phosphate group in the nucleobase skeleton worsens the scenario, making the choice of the reaction conditions and reagents important to avoid the hydrolysis of the labile glycosidic bond.[12] The results presented in this work provide new pathways to the functionalization of nucleic acids, to the synthesis and study of new unusual nucleosides[13] or to metal-containing unnatural DNA fragments, and could be applied to the preparation of other metal-derived molecules of biological interest.



1 M = Ir, Rh; L = Cl
R^1, R^2 = OH, H, *O*-alkyl; R^3 = H, alkyl **2**

To determine the suitability of our strategy to selectively functionalize the purine ring, we chose the *N*9-tetrahydropyranyl (THP)-protected compound **3** as a purine nucleoside model.[14] The reaction of **3** with [{$IrCl_2Cp^*$}$_2$ ($Cp^* = \eta$-C_5Me_5)] and NaOAc, in CH_2Cl_2 at RT[15] cleanly afforded cyclometallated complex **4** as a diastereomeric (1:0.7) mixture in 75% yield of the isolated product (Scheme 1). The ^{1}H NMR spectrum of **4** clearly indicated that the coordination of the metal to N1 and the C–H activation of the aromatic phenyl ring had occurred. Further confirmation of the structure was gained by X-ray diffraction analysis of a crystal of one of the diasteroisomers of **4** (slow diffusion in $CHCl_3$/hexane) showing the expected pseudo-tetrahedral three-legged piano-stool structure (iridium bite angle 77.51(14)° (N1-Ir1-C12). As far as we are aware, this is the first structure of a metal C,N-bonded purine derivative reported in the literature.[16] The corresponding Rh complex **5** was quantitatively obtained by reaction of **3** and [{$RhCl_2Cp^*$}$_2$] under similar conditions (Scheme 1).

The effect of the free (basic) N9 position was studied with 6-phenylpurine **6** (prepared by removal of the THP group in **3**).[14] Whereas treatment of **6** with [{$RhCl_2Cp^*$}$_2$]/NaOAc in the conditions above led to the C–H insertion product **8** (58%), the reaction with [{$IrCl_2Cp^*$}$_2$]/NaOAc only afforded the N9-[$IrClCp^*$]$_2$ coordinated dimeric product **7** in 71% yield of the isolated product (Scheme 1).[17] Further treatment of **7** with either [{$IrCl_2Cp^*$}$_2$]/NaOAc or [{$RhCl_2Cp^*$}$_2$]/NaOAc did not afford any of the C–H activation products.

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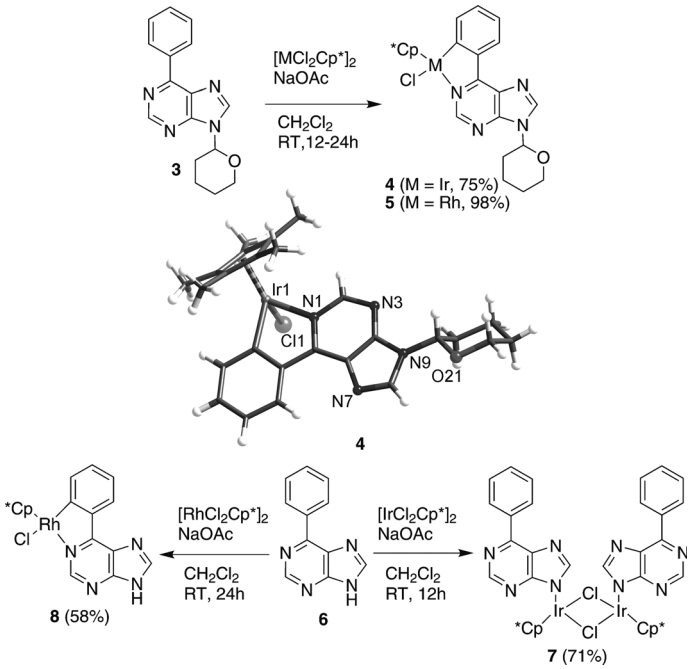
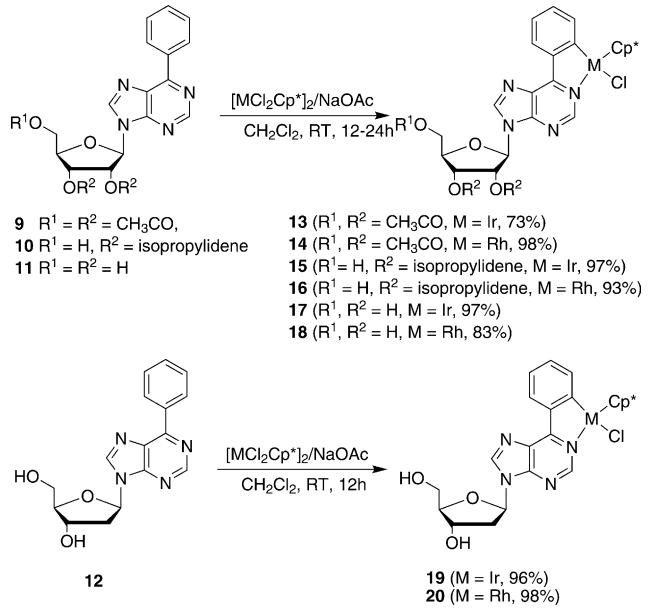


Scheme 1. Synthesis of metal-arylpurines. Yields are for the pure products. Compounds **4** and **5** were obtained as (1:0.7) diastereomeric mixtures.

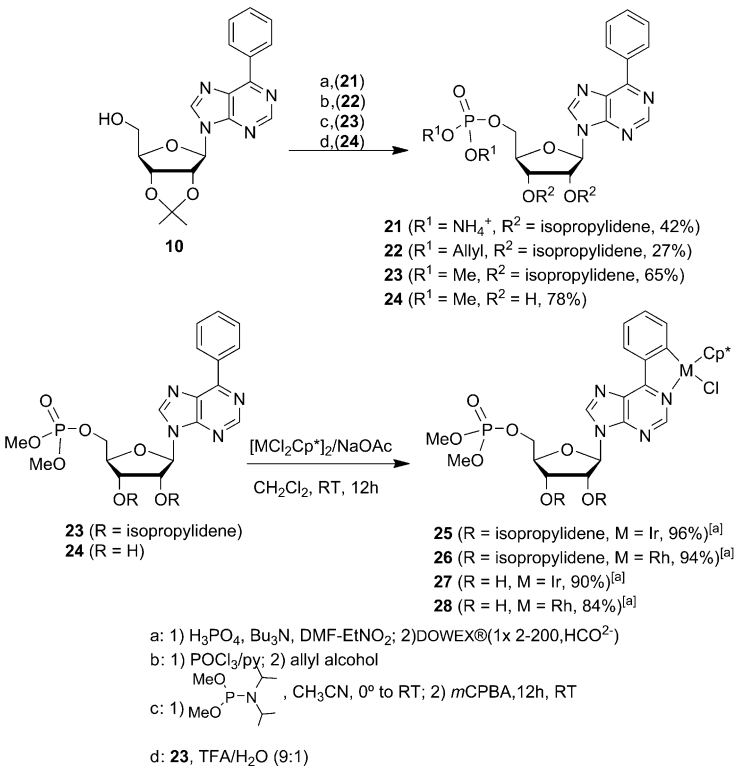
These results show the higher preference of the iridium complex for the N–H activation process in **6** compared with the C–H activation reaction.

Cyclometallation of the more sensitive and densely functionalized 6-penylpurine nucleosides **9**–**12** was next studied (Scheme 2). The compatibility of the reaction conditions with the labile glycosidic bond was first tested with tri-*O*-acetyl derivative **9**, which was prepared in three steps from commercially available inosine.[14] Treatment of **9** with [{MCl_2Cp^*}$_2$]/NaOAc (M = Ir, Rh) afforded the corresponding Ir- and Rh-cyclometallated derivatives **13** and **14** in 73 and 98% yields, respectively. The presence of a free (5′) primary OH group in the sugar moiety did not substantially change the reaction outcome. Thus, isopropylidene derivative **10** (prepared from nucleoside **11** and acetone/*p*TsOH) afforded the corresponding metal-aryl purine derivatives **15** and **16** in 97 and 93% yields, respectively. Finally, the methodology was tested with free ribose and deoxyribose nucleosides **11** (obtained by removal of the acetate groups in **9** with NaOMe/MeOH) and **12** (prepared in a four-step sequence from 2′-deoxyadenosine).[14] In both cases the expected cyclometallated nucleosides **17**–**20** were obtained in nearly quantitative yields (Scheme 2). These results show the complete selectivity of the process and the full compatibility of the reaction conditions with the labile glycosidic bond and also with the free OH groups in the ribose and deoxyribose moieties. Both facts are very important for the use of this methodology in DNA chemistry.

Phosphorylation of isopropylidene derivative **10** afforded phosphate **21** as the ammonium salt (two steps, 42% average yield) (Scheme 3).[14] Unfortunately, the reaction of this compound with [{$IrCl_2Cp^*$}$_2$]/NaOAc failed to yield the expected C–H activation product. Instead, in all the conditions tested (increase of the temperature, use of NEt_3 or $NHiPr_2$ as base), the reaction crudes afforded complex mixtures of



Scheme 2. Synthesis of metal-arylpurine nucleosides. Yields are for the pure products. Compounds obtained as (1:1) diastereomeric mixtures.

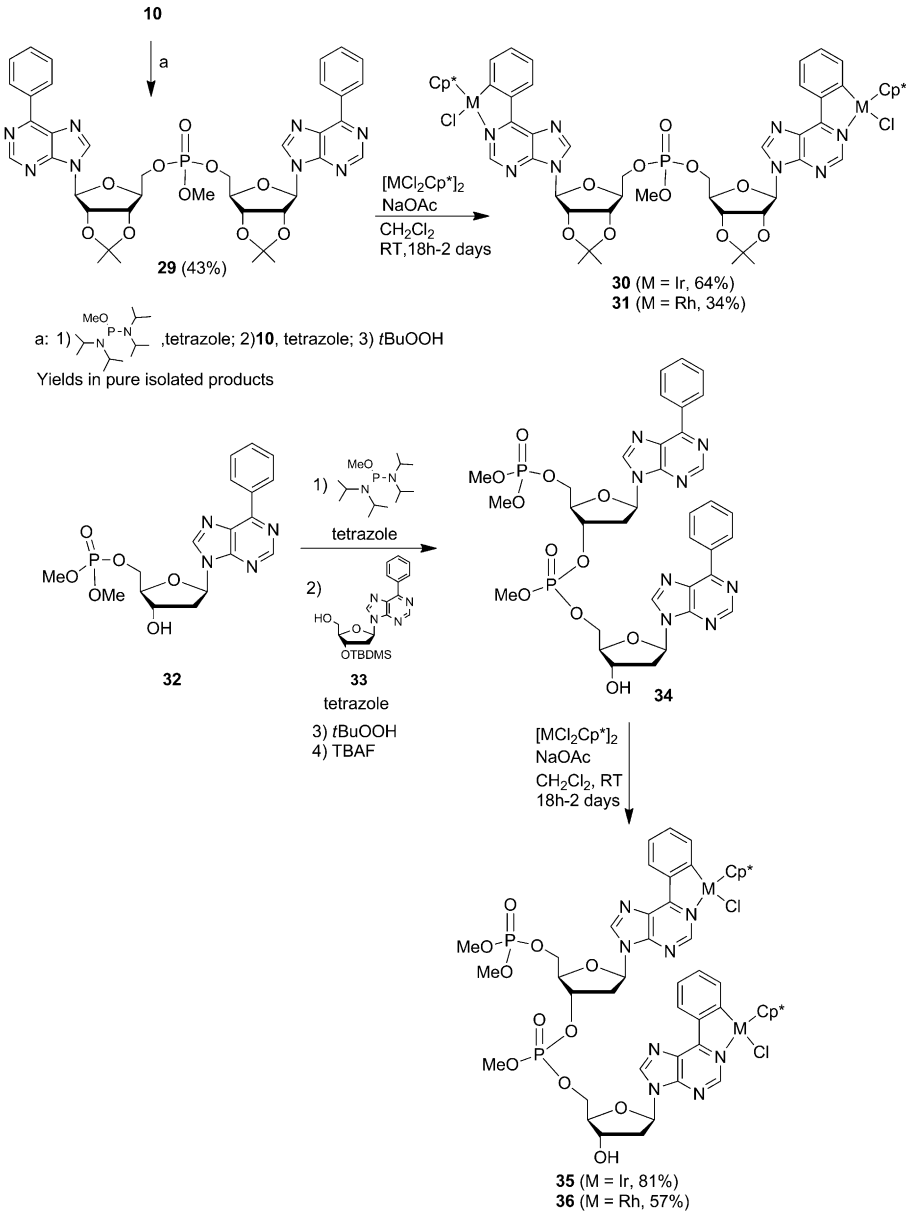


Scheme 3. Synthesis of metal-arylpurine nucleotides. Yields are for the pure isolated products. [a] = Compounds obtained as diastereomeric mixtures.

products compatible with the involvement of the phosphate group in metal coordination and/or ligand displacement processes.[18] To avoid these undesirable competitive reactions, we tested the reaction conditions with allyl phosphate **22**, obtained by reaction of **10** with $POCl_3$ and allyl alcohol (Scheme 3).[14] Reaction of **22** with $[\{IrCl_2Cp^*\}_2]$/NaOAc, however, only yielded complex mixtures of products. Replacement of the allyl with a methyl group in the phosphate proved essential for the reaction success. Phosphorylation of isopropylidene derivative **10** with *N*,*N*-diisopropyl-dimethylphosphoramidite afforded methyl phosphate **23**, which after cyclometallation in the conditions described above, smoothly yielded metal-arylpurine nucleotides **25** and **26** in 96 and 94% yields, respectively (Scheme 3). Removal of the isopropylidene group in **23** followed by reaction with $[\{MCp^*Cl_2\}_2]$/NaOAc yielded the corresponding Ir^{III} and Rh^{III} ribose nucleotides **27** and **28** (in 90 and 84% yields, respectively). These compounds are, to the best of our knowledge, the first examples of cyclometallated nucleotides reported in the literature.

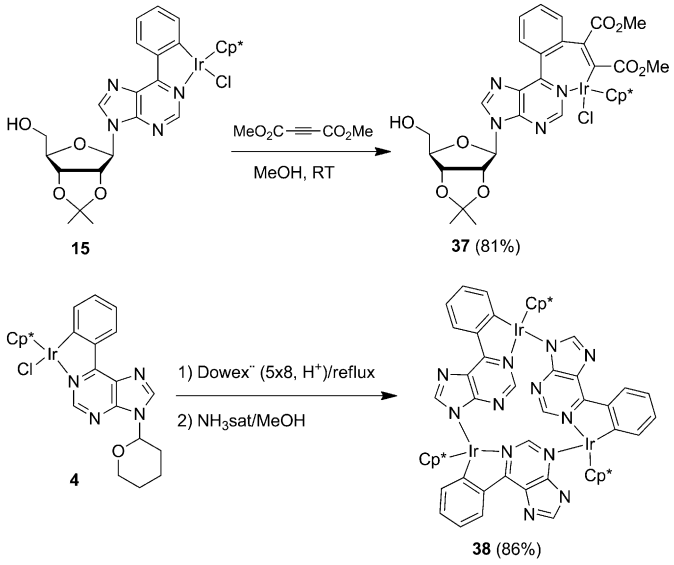
Being aware of the additional stereochemical complexity derived from the presence of the phosphate groups, the synthesis of metal-arylpurine dinucleotides was our final goal. First attempts were made with dimeric ribose derivative **29** (prepared from **10** and bis-*N*,*N*-diisopropyl-methylphosphoramidite using phosphate nucleotide bonding methodology) (Scheme 4).[14] Although the reaction required an excess of NaOAc (three times the stoichiometric amount) and longer reaction times, the Ir^{III} insertion product **30** could be obtained in 64% yield of the isolated product (diastereomeric mixture). In turn, the formation of the corresponding Rh^{III} product was less efficient, and a larger excess of base and two days at room temperature were required to obtain **31** in 34% yield. These optimized reaction conditions were finally used to the preparation of metal-arylpurine dinucleotides **35** and **36**, resembling the structure of a DNA fragment (Scheme 4). The starting dinucleotide **34** was prepared from deoxyribose phosphate **32** and monoprotected nucleoside **33**.[14] Treatment of this compound with $[\{MCl_2Cp^*\}_2]$/NaOAc afforded the metallated Ir- and Rh-DNA segments **35** and **36** in 81 and 57% yields, respectively (diastereomeric mixtures). These results are a promising start for the synthesis of unusual homo- and heterometalla-DNA fragments.

The efficient preparation of cyclometallated Ir^{III} or Rh^{III} complexes derived from purine nucleobases opens new and interesting possibilities for the further functionalization of the nucleosides and nucleotides.[19] In this context, Ir and Rh cyclometallated intermediates structurally related to the metal-arylpurines reported in this work have been proposed to be involved in C–C coupling reactions.[20,21] Also, iridium



Scheme 4. Synthesis of metal-arylpurine dinucleotides.

half-sandwich complexes of the type [Ir(N-C)ClCp*] have shown ability as catalyst precursors for oxidation reactions.[22,23] In a first trial, {IrClCp*}purine **15** was reacted with dimethylacetylenedicarboxylate (DMAD) at room temperature in MeOH.[20] Under these conditions, a cyclometallated complex **37**, derived from the insertion of one molecule of DMAD in the M–C bond, was obtained in 81% yield (Scheme 5). Apart from the interest of the reactivity



Scheme 5. Reactivity examples.

studies, the selective involvement of the N1 position of the purine skeleton in the formation of the metallacycles offers the possibility of exploring the ability of other free nitrogen atoms in the nucleobase for the coordination with metals. In this regard, the basic N9 position could be ideal to make structures that combine C–M and N–M coordination bonds. Thus, removal of the THP-group (Dowex 50×8, H^+) in Ir-metal-arylpurine **4**, followed by treatment with saturated ammonia solution in methanol, smoothly afforded the trinuclear metallacycle **38** (in 86% yield), which was characterized by NMR and MS analysis (Scheme 5). Amazingly, this compound was obtained as a single C_3 diastereoisomer, as shown in the ^{1}H- and ^{13}C NMR spectra.[14] The total selectivity in the formation of **38** can be explained by chiral self-recognition between the metal fragments during the triangle formation, a process that has very few precedents with respect to metallacycles based on metal-coordination bonds.[10e]

In summary, this paper reports for the first time the efficient preparation of purine derived metal-arylpurine nucleosides, metal-arylpurine nucleotides, and metal-arylpurine dinucleotides having M–C bonds (M = Ir^{III}, Rh^{III}). The methodology has been also applied to the preparation of a metalla-DNA segment. The results reported in this work could be applied to the design and synthesis of functionalized nucleic acids, or of DNA/RNA-modified segments, to be used as photochemical or electrochemical markers. Furthermore, the cyclometallated nucleosides and nucleotides prepared are susceptible of selective post-functionalization, either by means of C–C insertion reactions into the M–C bonds or as building blocks for macrocyclic chiral polymetallic structures. Development of the full potential of this chemistry to the study of new metal-derived molecules of biological interest is currently underway in our laboratories.

Experimental Section

The representative experimental procedures followed for the preparation of compounds **4**, **5**, **30**, **36** and **37** are as follows:

Synthesis of 4: NaOAc (12 mg, 0.15 mmol) and **3** (35 mg, 0.12 mmol) were added to a solution of $[IrCl_2Cp^*]_2$ (50 mg, 0.06 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 12 h and filtered through celite. The solvent was removed under reduced pressure. The crude was purified by flash SiO_2 chromatography (hexane/ethyl acetate 3:2 to ethyl acetate) to yield an orange solid **4** (30 mg, 75%) as a mixture of isomers (1:07).

Synthesis of 5: NaOAc (16 mg, 0.20 mmol) and **3** (56 mg, 0.20 mmol) were added to a solution of $[RhCl_2Cp^*]_2$ (50 mg, 0.08 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 24 h and filtered through celite. The solvent was removed under reduced pressure. The crude was purified by flash SiO_2 chromatography (dichloromethane to dichloromethane/ethyl acetate, 10:1) to yield an orange solid **5** (44 mg, 98%) as a mixture of isomers (1:0.7).

Synthesis of 30: NaOAc (12 mg, 0.14 mmol) and **29** (50 mg, 0.06 mmol) were added to a solution of $[IrCl_2Cp^*]_2$ (49 mg, 0.06 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 18 h and filtered through celite. The solvent was removed under reduced pressure. The crude was purified by flash SiO_2 chromatography (hexane/ethyl acetate, 1:1 to ethyl acetate) to yield an orange solid **30** (59 mg, 64%) as a mixture of isomers.

Synthesis of 36: NaOAc (7 mg, 0.09 mmol) and **34** (20 mg, 0.02 mmol) were added to a solution of $[RhCl_2Cp^*]_2$ (15 mg, 0.02 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 12 h and filtered through celite. The solvent was removed under reduced pressure. The crude was purified by flash SiO_2 chromatography (ethyl acetate to ethyl acetate/methanol, 10:1) to yield an orange solid **36** (19 mg, 57%) as a mixture of isomers.

Synthesis of 37: Dimethylacetylenedicarboxylate (12 μL, 0.09 mmol) was added to a solution of **15** (70 mg, 0.09 mmol) in dry methanol (28 mL) and the reaction was stirred for 5 h (during this time the reaction turned from orange to yellow). The solvent was evaporated under reduced pressure and the yellow solid was washed with hexane several times to yield a yellow solid **37** (67 mg, 81%) as a mixture of isomers (1:0.85).

Additional details for the preparation of iridium and rhodium complexes, crystallographic details for the structure of **4**, and full characterization data of all new compounds are provided in the Supporting Information.

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Keywords: cancer · iridium · metalation · metallanucleotides · nucleobases · rhodium

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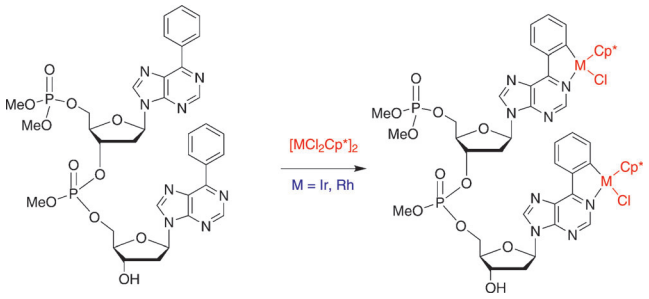

Nucleobases team up: The efficient and selective preparation of purine-derived metallanucleosides, metallanucleotides, and metalladinucleotides having M–C bonds (M = Ir^{III}, Rh^{III}) is reported for the first time (see scheme). The results presented may be applied to the synthesis of functionalized nucleic acids, or DNA/RNA-modified segments.

Metallanucleobases

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The Selective Synthesis of Metallanucleosides and Metallanucleotides: A New Tool for the Functionalization of Nucleic Acids