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Resolved P-Metalated Nucleoside Phosphoramidites

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Supporting Information

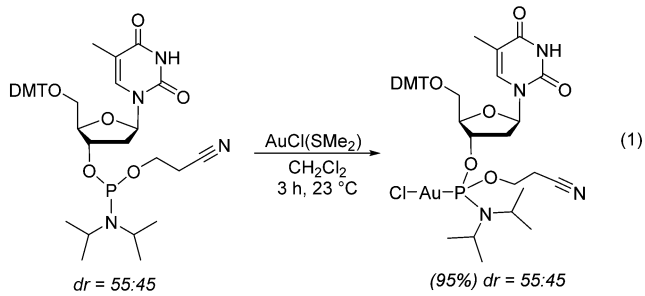
ABSTRACT: The synthesis of resolved P-metalated nucleoside phosphoramidites is described. These rare compounds were initially prepared with gold as the metal center; however, the gold can be removed using basic phosphines or solid-supported triphenylphosphine. Treatment of the free nucleoside phosphoramidite with a platinum source generated a unique platinated dinucleoside species with a diastereomeric ratio of >99:1.

The binding of metal centers to nucleosides and related compounds has been the subject of intense interest in recent years and has resulted in the synthesis of a myriad of new complexes. The resulting metalated compounds have applications in medicine and chemical biology.[1−7] Additionally, functionalized nucleosides and DNA have been used to construct nanostructures with applications in sensing, nanomachinery, and molecular computing.[8−12] For unfunctionalized nucleosides, the metal center is most commonly attached to nitrogen donors on the purine or pyrimidine base.[2−4,6,7] The incorporation of a metal center provides unique geometries and reactivity profiles that are not accessible with purely organic structures.

Nucleoside phosphoramidites are commercially available and could conceivably be excellent donors for metal centers.[13−16] However, to the best of our knowledge, there are no examples of P-metalated complexes containing any of the transition metals. One factor that has contributed to the lack of examples is the presence of an unresolved phosphorus center. This scrambled stereochemistry results from the synthetic methodology used to prepare these compounds.[15] Fundamentally, these nucleoside diastereomers should be separable by chromatography or selective crystallization; however, this separation has been reported to be quite challenging, and attempts to fully separate the two diastereomers have been unsuccessful or low yielding.[17,18] If separated, the resolved phosphoramidites would be attractive ligands for a range of applications including asymmetric catalysis.[19−24] Given the staggering number of functionalized nucleoside phosphoramidites that have been reported, devising a general and efficient strategy for the separation of P-chiral phosphoramidites would facilitate the synthesis of a host of chiral metal complexes with potential applications in medicine, nanotechnology, and catalysis.

Undeterred by the literature reports, we began our studies by attempting to chromatographically separate the nucleoside phosphoramidite diastereomers on a preparative scale prior to the introduction of metal-containing precursors. Despite our best efforts with a range of eluents and gradients, dreadfully low yields of the diastereomers were obtained. As a result of this, another route was sought for the separation/isolation of the diastereomers, and we surmised that the incorporation of a metal center and ligands might increase the order of the system and, therefore, selective crystallization might be a successful approach.

Gold was selected as a representative metal center, and DMT-dT phosphoramidite was chosen as a typical nucleoside phosphoramidite.[25] Treatment of a common gold(I) precursor with the nucleoside phosphoramidite generated the P-aurated species in excellent yield as an air-stable white foam (eq 1).



(1)

Selective crystallization was attempted with a range of solvents; however, only foams or oils were obtained, and crystallization/separation was still not achieved. During the course of the investigation, we noticed that the two metalated diastereomers exhibited significantly different retention times on common silica thin-layer chromatography plates. Building upon this observation, we were delighted to find that the metalated phosphoramidite diastereomers could be completely separated by simple isocratic column chromatography in excellent yield.

Once the model compounds were separated and isolated, the chemistry was extended to the other common nucleoside phosphoramidites (Figure 1). After some optimization, the metalated compounds were generated in excellent yield and the diastereomers were completely separated. All of the new compounds were isolated as white to light tan foams with excellent mass recovery.

With the new gold compounds in hand, we wondered if the resolved nucleoside phosphoramidites could be transferred to other metal centers. The initial step in our approach to the removal of gold entailed the treatment of gold phosphoramidite with a stronger donor that could conceivably abstract the AuCl fragment. Indeed, treating a representative example (**1**) with a strongly basic and fairly bulky phosphine (^{t}BuXPhos)[26] successfully displaced the gold from the phosphoramidite and generated AuCl(^{t}BuXPhos).[27] Treatment of this reaction

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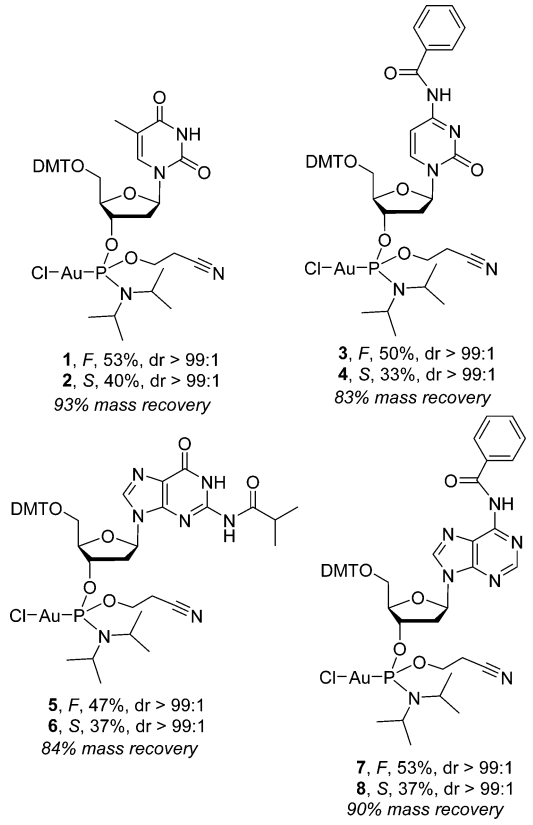
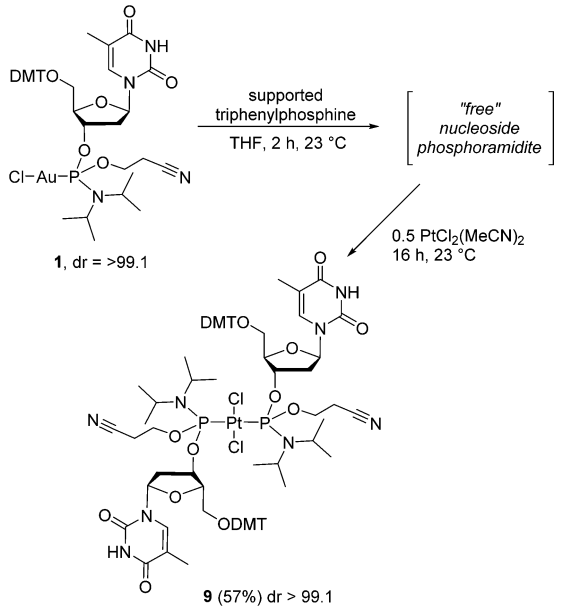


Figure 1. Resolved P-metalated nucleoside phosphoramidites. F and S = fast and slow eluting diastereomers. Initial dr for nucleoside phosphoramidites: DMT-dT phosphoramidite, 55:44; DMT-dC(bz) phosphoramidite, 60:40; DMT-dG(ib) phosphoramidite, 53:47; DMT-dA(bz) phosphoramidite, 56:44.[25]

mixture with 0.5 equiv of $PtCl_2(NCMe)_2$ generated the P-platinated nucleoside phosphoramidite (**9**). While it might seem attractive to separate and isolate the free phosphoramidite following cleavage from the gold, it was convenient for us to simply generate the free phosphoramidites in solution as needed. If isolated material is needed, the resolved phosphoramidite can be isolated in good-to-excellent yield by column chromatography following cleavage of the gold fragment (see the Supporting Information). Following this procedure, the gold can also be recovered (92% as ^{t}BuXPhosAuCl).

During isolation of the new platinum nucleoside, it became necessary to remove (phosphine)gold chloride prior to introduction of the platinum complex in order to circumvent potential ligand-exchange reactions. Although we isolated the free nucleoside phosphoramidite, we were still attracted to a one-pot method for the synthesis of additional P-metalated nucleosides. To that end, we speculated that a solid-supported phosphine might be able to remove the gold from the metalated nucleoside. Separation of the sequestered gold species would then be trivial and achieved by a simple filtration. We were pleased to find that stirring **1** with supported triphenylphosphine in tetrahydrofuran for a few hours sequestered the gold and generated the free nucleoside phosphoramidite (ca. 90% by NMR). Following filtration, the addition of the platinum precursor to the filtrate generated platinum complex **9** in moderate yield with a diastereomeric ratio >99:1 (Scheme 1). The platinum compound was isolated as an air- and moisture-stable white foam following purification by column chromatography. This new complex can also be envisioned as a nucleoside dimer linked by platinum.

Scheme 1. Synthesis of P-Platinated Nucleoside Dimer



In summary, we have outlined a method for the preparation and isolation of resolved P-metalated nucleoside phosphoramidites. In contrast to the challenging separation of the parent nucleoside phosphoramidite diastereomers, the separation of the P-metalated compounds was straightforward and efficient. Once separated, the resolved phosphoramidite could be readily transferred to other metals using supported triphenylphosphine to sequester the gold fragment. This approach provides facile access to an intriguing class of P-chiral ligands and complexes.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) DMT = dimethoxytrityl; DMT-dT phosphoramidite = 5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxythymidine-3′-*O*-[*O*-(2-cyanoethyl)-*N*,*N*′-diisopropylphosphoramidite]; DMT-dC(bz) phosphoramidite = N^4-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxycytidine-3′-*O*-[*O*-(2-cyanoethyl)-*N*,*N*′-diisopropylphosphoramidite]; DMT-dG(ib) phosphoramidite = N^2-isobutyryl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyguanosine-3′-*O*-[*O*-(2-cyanoethyl)-*N*,*N*′-diisopropylphosphoramidite]; DMT-dA(bz) phosphoramidite = N^6-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyadenosine-3′-*O*-[*O*-(2-cyanoethyl)-*N*,*N*′-diisopropylphosphoramidite].
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