Trapping Hemiacetals with Phosphono Substituted Palladium π -Allyl Complexes for the Synthesis of Substituted Cyclic Ethers

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ABSTRACT

Oxidation of hydroxy substituted phosphono allylic carbonates gave the aldehyde substituted phosphonates in good yield. Stereospecific palladium (0)-catalyzed cyclization in the presence of methanol or water gave acetal tetrahydrofuran and tetrahydropyran vinyl phosphonate products derived from hemiacetal trapping. The tetrahydrofuran acetals undergo Lewis acid catalyzed addition of nucleophiles to give diastereoisomeric mixtures of substituted tetrahydrofurans.

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Introduction

We recently described the palladium-catalyzed intramolecular addition of hydroxyalkyl phosphono allylic carbonates to give tetrahydrofuran (THF) and tetrahydropyran (THP) vinyl phosphonates.¹ Tetrahydrofurans and tetrahydropyrans are structures frequently found in several important classes of biologically active natural products, such as polyether antibiotics, acetogenins, and C-glycosides. Due to the wide distribution of tetrahydrofurans and tetrahydropyrans in nature, many reactions have been developed for their synthesis.² A popular approach is the addition of carbon nucleophiles to oxacarbenium ions prepared from cyclic acetal containing THF and THP precursors.^{2a-c} The stereochemistry of the addition of nucleophiles to cyclic oxacarbenium ions has been thoroughly analyzed.³

We postulated (Scheme 1) that a mixture of aldehyde **1** and an alcohol would result in an equilibrium concentration of hemiacetal **2**, which could be trapped by an electrophilic palladium π -allyl intermediate **3** to form a cyclic acetal **4**. Alternatively, the aldehydic palladium π -allyl **5** could form first and then cyclize, either directly to give a carbenium ion **6** (which is then trapped by alcohol) or via the hemiacetal **3**. However, if the hemiacetal (or aldehyde) lack sufficient nucleophilicity or concentration, the palladium π -allyl intermediate **3** will likely eliminate producing diene **7**. If successfully formed, the resulting cyclic hemiacetal **4** could then be utilized for the synthesis of cyclic ethers via nucleophilic addition to an oxacarbenium ion.^{2a-c,3}

Scheme 1. Proposed intramolecular trapping of a hemiacetal with a palladium π -allyl complex.

In support of this hypothesis, we reported an adaptation of Leighton's mercuric hemiacetal trapping⁴ using allylic hydroxy phosphonates as the substrate.⁵ A ³¹P NMR spectrum of a solution of the hydroxy phosphonate in a mixture of propanal and

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CDCl_3 clearly showed the presence of equilibrium concentrations of hemiacetal. Further support is found in the report that allenyl aldehydes undergo palladium (II) catalyzed cyclization in alcohol solution under an atmosphere of CO to give THF-substituted unsaturated esters.⁶ In addition, alkylhemiacetals (aldehydes in alcohol solution) with allylic OTHP leaving groups have been shown to react via palladium(II) intermediates to give cyclic acetals.⁷ Thus, it is apparent that a hemiacetal should be both sufficiently nucleophilic and present in high enough concentration, to react with a palladium π -allyl intermediate.

Results and Discussion

The required aldehydes **1a** and **1b** were prepared from the previously reported hydroxy substituted phosphonates **8a** and **8b**.¹ Reaction of phosphonates **8a** and **8b** with pyridinium chlorochromate (PCC) in CH_2Cl_2 gave the aldehydes **1a** and **1b** in 88% and 72%, respectively (Scheme 2). Gratifyingly, treatment of aldehyde **1a** with $\text{Pd}(\text{PPh}_3)_4$ and Hunig's base in a 1:1 mixture of THF and MeOH gave a 3:1 diastereoisomeric mixture of THF-methoxy acetals **4a** in 81% yield. The homolog **1b** reacted under similar conditions to give the THP-methoxy acetals **4b** in 66% yield. The methoxy acetal **4a** was hydrolyzed using Dowex 50 in aqueous THF to give a cyclic hemiacetal **4c** (82%), which reacted with acetic anhydride and DMAP/pyridine in CH_2Cl_2 to give the corresponding acetoxy acetal **9a** in 91% yield. In a more direct route to the acetoxy acetal **9a**, the aldehyde **1a** was reacted with $\text{Pd}(\text{PPh}_3)_4$ in aqueous THF to give the hemiacetal **4c** directly. The solvents were removed and the crude hemiacetal **4c** was acetylated to give the acetoxy acetal **9a** (68% for 2 steps). Again, the homologous aldehyde **1b** was treated under similar conditions to yield the THP-acetoxy acetal in 63% (for 2 steps). Finally, the carboxylic acid **10a** was reacted with $\text{Pd}(\text{PPh}_3)_4$ and Hunig's base in THF to give corresponding lactone **11a**. Surprisingly, the homologous acid **10b** failed to cyclize and only the formation of a mixture of diene products **7b** was observed.

Scheme 2. Palladium-catalyzed cyclization of aldehyde-derived hemiacetals and carboxylic acids.

Reductive removal of the acetal stereocenter allowed an examination of the extent of chirality transfer in the cyclization

reaction. Nonracemic hydroxy phosphonate (**R**)**8a** was oxidized to the aldehyde (**R**)**1a**, which was cyclized using $\text{Pd}(\text{PPh}_3)_4$ and Hunig's base in aqueous THF at 40°C to give the corresponding hemiacetal **4c**, which was acetylated to give the acetoxy acetal **9a**. As expected, HPLC on chiral stationary phase was complicated by the mixture of diastereoisomers which resulted in overlapping peaks. The acetoxy acetal **9a** was reduced (Scheme 3) with Et_3SiH and TMSOTf in CH_3CN to give the previously reported THF-vinyl phosphonate **12**.¹ HPLC analysis showed complete chirality transfer in the transformation of **8** to **12**.

Scheme 3. Reduction of the acetoxy acetal.

We suspected that a chiral center next to the aldehyde would be vulnerable to racemization under the reaction conditions. To examine this potential problem, a nonracemic aldehyde was prepared bearing a α -methyl substituent (Scheme 4). The acyl oxazolidinone **13**, prepared following a literature procedure,⁸ was coupled with nonracemic phosphono allylic carbonate **14** (95% e.e.) using the Grubbs second generation catalyst and copper(I) iodide as co-catalyst to give phosphonate **15**.¹⁹ The oxazolidinone auxiliary was reductively cleaved using lithium borohydride¹⁰ to yield the alcohol **16**, which was oxidized using Dess Martin periodinane¹¹ to the corresponding aldehyde **17**. The aldehyde was cyclized with $\text{Pd}(\text{PPh}_3)_4$ in aqueous THF at 40°C to give the corresponding hemiacetal, which was acetylated to give the acetoxy acetal **18**. Again, HPLC on chiral stationary phase was complicated by overlapping peaks. The acetoxy acetal **9a** was reduced with TMSOTf and Et_3SiH in CH_3CN to give THF-vinyl phosphonate **19** as 3:1 mixture of diastereoisomers. In addition, the acetoxy acetal was hydrolyzed and the hemiacetal oxidized to give the lactone **20** as 2:1 mixture of diastereoisomers. Clearly, significant racemization occurs under the reaction conditions even in the absence of an amine base.

Scheme 4. Palladium-catalyzed cyclization of chiral hemiacetal.

To further examine the substrate scope, ketone **21** was prepared using a cross metathesis reaction of phosphono allylic carbonate **14** with hex-5-en-2-one (Scheme 5). Treatment of ketone **21** with $\text{Pd}(\text{PPh}_3)_4$ and Hunig's base in a 1:1 mixture of THF and MeOH gave a separable mixture of THF-methoxy acetals **22**, methoxy vinyl phosphonate **23** and hydroxy vinyl phosphonate **24**. The hydroxy vinyl phosphonate **24** is formed by hydrolysis of the THF-methoxy acetals **22** on silica gel. Formation of the methoxy vinyl phosphonate is an indication that intermolecular addition of solvent is competitive with the intramolecular addition of the hemiacetal. This could be a consequence of the lower equilibrium concentration of the hemiacetal or the increased steric size of the nucleophile.

Scheme 5. Palladium-catalyzed cyclization of ketone-derived hemiacetals.

Hemiacetals formed by dissolving alcohols in aldehyde solvents should also be substrates for cyclization.^{4,5} Thus, treatment of a propanal solution of the hydroxy substituted phosphono allylic carbonate **8c** with $\text{Pd}(\text{PPh}_3)_4$ gave the cyclic acetal **25** in 68% yield (Scheme 6). However, reaction of the same alcohol **8c** with chloral hydrate in THF followed by treatment with $\text{Pd}(\text{PPh}_3)_4$ and Hunig's base resulted in the formation of formate **26**, presumably by elimination of chloroform from intermediate **27**, which was observed by ^{31}P NMR spectroscopy.

Scheme 6. Palladium-catalyzed cyclization of alcohol-derived hemiacetals.

With cyclic acetals (**4a** and **9a**) in hand, the Lewis acid catalyzed additions of some representative nucleophiles were examined (Scheme 7). Reaction of the THF-methoxy acetal **4a** with allyl trimethylsilane and trimethylsilyl triflate (TMSOTf)¹² gave the allyl substituted THF **28a** as a 2.3:1 mixture of diastereoisomers in 95% yield. The nucleoside analog **28b** was prepared in 61% yield as 2.9:1 mixture of diastereoisomers by reaction with 2,4-bis-(trimethylsilyloxy)pyrimidine¹³ and TMSOTf in CH_3CN . Surprisingly, attempted addition of the silyl ketene acetal [$\text{CH}_2=\text{C}(\text{OTBS})(\text{OEt})$]¹⁴ to the methoxy acetal **4a** or acetoxy acetal **9a** failed and only the THF-vinyl phosphonate **12**,

resulting from reduction of the oxacarbenium ion, was observed. However, reaction of the acetoxy acetal **9a** with the zinc enolate¹⁵ and TiCl_4 in CH_2Cl_2 gave the C-acetate **28c** in 61 % yield as 1.2:1 mixture of diastereoisomers.

Scheme 7. Lewis acid catalyzed addition of nucleophiles.

In summary, we have shown the hemiacetals can be trapped by intramolecular reaction with palladium π -allyls to give cyclic acetals. The resulting cyclic acetals (methoxy **4a** or acetoxy **9a**) undergo Lewis acid catalyzed addition of nucleophiles to give substituted tetrahydrofuran vinyl phosphonates.

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Supplementary Material

Supplementary data (experimental procedures and ^{31}P , ^1H and ^{13}C NMR spectra) associated with this article can be found online. This material is available free of charge via the Internet.

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