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The stereochemical outcome of the palladium catalyzed addition of nucleophiles to the carbonate derivative, the [3,3] rearrangement of the imidate and carbamate derivatives, and the epoxidation and cyclopropanation of hydroxy allylic phosphonates is presented.

Keywords: phosphonates; stereoselective; asymmetric; cyclopropanation; epoxidation

INTRODUCTION

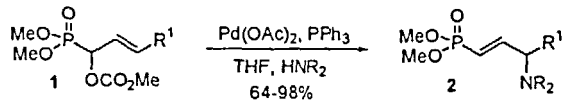
The last five years have witnessed a rapid advance in methods for the enantioselective synthesis of hydroxyphosphonates.[1] Recent advances include the use of homochiral phosphite equivalents, enzymatic resolution, asymmetric reduction, asymmetric hydroxylation, and in particular chiral metal catalysts, which have given access to hydroxyphosphonates of high enantiomeric purity. It has been recognized that α-hydroxyphosphonates are attractive not only for their biological activity, but because they are potentially useful intermediates in the synthesis of many other α and γ substituted phosphonates.[2] However, research in this area has failed to keep pace with the developments in asymmetric phosphonylation and there has been very little exploration of stereoselective transformations of hydroxy phosphonates.

We have begun to explore applications of asymmetric phosphonylation to the synthesis of structurally more complex, and biologically interesting molecules.[3] This endeavor required an initial investigation of suitable stereoselective (or stereospecific) transformations of allylic hydroxy phosphonates.

RESULTS

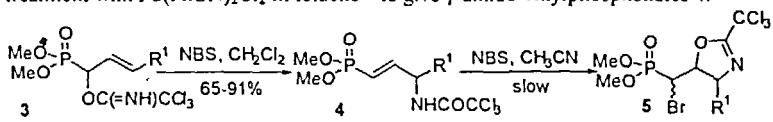
It is now well established that acyclic stereocontrol is an efficient strategy for the generation of new stereocenters, and allylic alcohols are perhaps the best recognized substrates in this regard. Allylic alcohols posses the ability to efficiently control stereochemical induction in a number of alkene addition reactions.[4] In addition, derivatives of allylic alcohols undergo rearrangement with chirality transfer and 1,3 transposition of functionality.[5] Allylic hydroxy phosphonates display some of the chemistry associated with allylic alcohols, however, the steric and electronic influence of the phosphorus moiety may perturb the stereochemical and regiochemical outcome of the reactions.

Our initial investigations concentrated on reactions that would lead to 1,3 transposition of functionality. The carbonate derivatives of allylic hydroxy phosphonates **1** underwent palladium-catalyzed amination to give amines **2** in high yield. The amine nucleophile adds exclusively to the 3 position, with migration of the double bond into "conjugation" with phosphoryl group. The allylic carbonates **1** undergo palladium-catalyzed addition more rapidly than the corresponding acetates.[6] The range of amine nucleophiles and phosphonates compatible with the reaction conditions is also increased.



R^1 = Ph, Me R = Bn, Et, $(CH_2CH_2)_2O$

We have previously described[2b] (as was reported independently by Ohler et. al)[2a] that allylic hydroxy phosphonates would react with trichloroacetonitrile and DBU to give the corresponding trichloroacetimidates **3**, which rearranged upon heating[2a] or treatment with $Pd(PhCN)_2Cl_2$ in toluene[2b] to give γ-amido vinylphosphonates **4**.

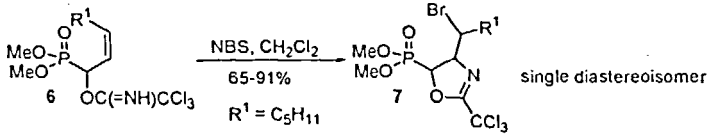


R^1 = Ph, Me, C_5H_{11}, 2-furanyl, cyc-C_6H_{11}

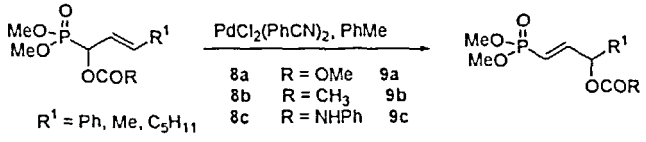
In addition, we recently observed that the trichloroacetimidates **3** reacted with NBS or NIS in CH_2Cl_2 or $CHCl_3$ solution at room temperature.[3] However, rather than the expected halocyclized products, the major product (>85%) was the γ-amido vinyl phosphonate **4**. Further investigation showed that the final outcome of the reaction of the imidates **3** with NBS was dependent upon the solvent used and the reaction time. For example, prolonged exposure to NBS in acetonitrile resulted in the initially formed amide **5** undergoing some further halocyclization via addition of the carbonyl oxygen into the vinyl phosphonate. However, under standard conditions (NBS 1eq.,

$CHCl_3$, 24 hrs.) the rearrangement was high yielding and was observed with both alkyl and aryl allylic phosphonates.

The unusual reactivity of imidates **3** can be rationalized on the basis of the stereoelectronic effect of the electron withdrawing phosphonate group. The observed results are consistent with a mechanism which is comparable to that of the metal ion catalyzed [3.3] rearrangements.[5] In the halocyclization of imidates, the *E* alkenes generally give oxazines (6-endo cyclization), due to destabilization of the incipient β cation by the electron withdrawing imidate group.[7] The additional inductive electron demand of the phosphonate enforces this effect, but also increases susceptibility to neighboring group attack by the halide, leading to rearrangement. Interestingly, the imidate derivative Z allylic phosphonate **6** underwent a 5-exo cyclization to give the oxazoline **7**.[3]



Allylic carbonates, acetates, and carbamates are known to rearrange stereoselectively in the presence of palladium (II) salts.[5] The allylic hydroxy phosphonate derivatives **8a-c** were investigated. The cinnamyl system (R^1 = Ph) failed to rearrange, but all of the crotanyl derivatives (R^1 = Me) showed some tendency system to rearrange. Rearrangement was most facile with the carbamate **8c** and 100% conversion was achieved.

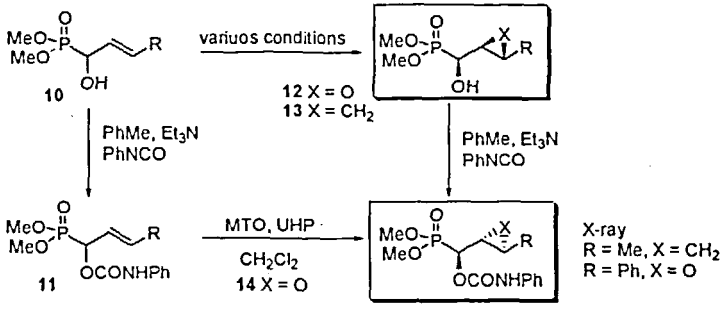


The allylic rearrangements discussed above are expected to be stereospecific and should result in the transfer of the stereochemical information at C-1 to C-3 (C_α to C_γ). A sample of hydroxy phosphonate was prepared in 97% e.e. (S isomer). Carbonate formation and palladium (0) catalyzed addition of dibenzylamine (Table 1, entry 1) gave γ-amino vinyl phosphonate (R=Bn) with at least 95% e.e. by HPLC. Similarly, the NBS catalyzed aza-Claisen rearrangement and the N-phenyl carbamate rearrangement were shown to proceed with complete chirality transfer.

Table 1. Chirality Transfer.

R^1	R^2	Config.	% e.e.	X	Config.	% e.e
Ph	CO_2Me	S	97	$N(CH_2Ph)_2$	--	97
Ph	$C(=NH)CCl_3$	R	60	$NHCOCCl_3$	S	60
Me	CONHPh	R	60	OCONHPh	S	60
n-C_5H_9	CONHPh	R	57	OCONHPh	--	57

The phosphoryl oxygen is an excellent Lewis base and hydrogen bond acceptor, and could potentially have deleterious effects on reactions that rely on coordination to the hydroxyl oxygen for stereocontrol. We pleased to observe that expoxidation of allylic hydroxy phosphonates using either $Ti(O^iPr)_4$ and *t*-BuOOH or methyl trioxorhenium (MTO) and urea hydrogen peroxide (UHP)[8] gave the syn epoxides with good diastereoselectivities (3.5:1 – 9:1). Whereas, epoxidation of the carbamate derivative gave the anti isomer (3.5:1).[8] The stereochemistry was assigned by X-ray crystallography.[9]



Cyclopropanation of the allylic hydroxy phosphonates using modified Simmons-Smith conditions[10] proved to be highly diastereoselective (>95%syn). Again, the relative stereochemistry was determined by X-ray crystallography.

Acknowledgments

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References

[1] For a recent review see; D.F. Wiemer, *Tetrahedron* **53,** 16609 (1997).

[2] a) E. Öhler and S. Kotzinger, *Synthesis* 497 (1993); b) M. A. De la Cruz Ph.D. Thesis University of Missouri-St. Louis, 1996, and references cited therein.

[3] H. Shabany and C.D. Spilling, *Tetrahedron Lett.* **39,** 1465 (1998).

[4] A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.* **93,** 1307 (1993); R. W. Hoffman, *Chem. Rev.* **89,** 1841 (1989).

[5] L. E. Overman, *Ang. Chem. Int. ed. Engl* **23,** 579 (1984); L. E. Overman, *Acc. Chem. Res.* **13,** 218 (1980).

[6] J. Zhu and X. Lu, *J. Chem. Soc., Chem. Commun.*, 1318 (1987); E. Ohler and S. Kanzler, *Liebigs Ann.* 1437 (1997).

[7] A. Bongini, G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *J. Org. Chem.* **51,** 4905 (1986).

[8] T.R. Boehlow and C.D. Spilling Tetrahderon Lett. **37,** 2717, (1996).

[9] T.R. Boehlow, A.M. De la Cruz, N. P. Rath and C.D. Spilling, *Acta Cryst.* **C53,** 1947, (1997).

[10] A.B Charrette and H. Lebel, *J. Org. Chem.* **60,** 2966 (1995).