



Copper-Catalyzed Asymmetric Synthesis of Tertiary α -Hydroxy Phosphonic Acid Derivatives with In Situ Generated Nitrosocarbonyl Compounds as the Oxygen Source**

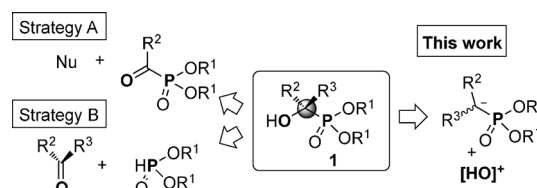
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Abstract: α -Hydroxy phosphonic acids and their derivatives are highly bioactive structural motifs. It is now reported that these compounds can be accessed through the copper-catalyzed direct α -oxidation of β -ketophosphonates using in situ generated nitrosocarbonyl compounds as an electrophilic oxygen source. These reactions proceeded in high yields (up to 95 %) and enantioselectivities (up to >99 % ee) for both cyclic as well as acyclic substrates. This method was also applied for the synthesis of α,β -dihydroxy phosphonates and β -amino- α -hydroxy phosphonates.

Since the first discovery of a phosphonic acid in rumen protozoa, a plethora of phosphorus-containing substances were detected in a variety of microorganisms as well as in higher forms of life.^[1] α -Hydroxy phosphonic acids and their derivatives are a particularly interesting subset among them.^[2] They are regarded as bioisosteric and isopolar replacements of natural α -hydroxycarboxylic acids despite of the fundamental structural difference that the geometry of the acid moiety is tetrahedral instead of trigonal planar.^[3] The physiological properties of these classes of compounds include activity against the human immunodeficiency virus (HIV),^[4] excellent inhibitory bioactivities towards a wide range of enzymes,^[5] such as renin,^[5a,b] HIV protease,^[5c] and various classes of protein tyrosine kinases and phosphatases.^[5d] α -Hydroxy phosphonocarboxylates, analogues to 1,1-bisphosphonates, are also used for the treatment of osteoporosis and similar bone diseases.^[6] Apart from their biological activities, α -hydroxy phosphonates are versatile synthetic precursors as they can be transformed into a variety of α -functionalized compounds.^[7]

Given their various biomedical as well as synthetic applications, the development of methods for the preparations of α -hydroxy phosphonates has received deserved attention. The current state of art, however, dictates that the asymmetric synthesis of α -hydroxy phosphonates mainly concentrates on the synthesis of secondary α -hydroxy phos-

phonates by means of enzymatic^[8] and chemical methods.^[9] On the contrary, the synthesis of more challenging tertiary α -hydroxy phosphonates (of general structure **1**, Scheme 1)



Scheme 1. Strategies for the synthesis of tertiary α -hydroxy phosphonates.

has received less attention.^[9] Since the pioneering work of Zhao and Samanta on the proline-catalyzed acetone aldol addition to acyl phosphonates, optically active α -hydroxy phosphonates **1** have usually been synthesized by means of nucleophilic addition reactions to acyl phosphonates (Strategy A, Scheme 1).^[10] Asymmetric hydrophosphonylation reactions of ketones have also been utilized for the synthesis of **1** (Strategy B, Scheme 1).^[11] Herein, we present a conceptually new method for the synthesis of tertiary α -hydroxy phosphonates **1** by the direct α -oxidation of β -activated phosphonates using nitrosocarbonyl compounds that are generated in situ as an electrophilic oxygen source (Scheme 1).

Nitrosocarbonyl compounds **2** are highly reactive transient species and usually generated in situ by oxidation of hydroxamic acids **3**.^[12] Despite their high synthetic potential, they have long been utilized mainly in hetero-Diels–Alder and ene reactions. Recently, independent reports by our group^[13] and the groups of Read de Alaniz,^[14] Maruoka,^[15] and Luo^[16] have shown that ambident nitrosocarbonyl compounds **2** can be utilized as a source of both electrophilic “oxygen” and “nitrogen” in Lewis acid- as well as organo-catalyzed asymmetric oxidations. We envisioned that the in situ generated nitrosocarbonyl compounds **2** can also be utilized in asymmetric *O*-nitroso aldol reactions of β -ketophosphonates **4**^[17] for the synthesis of enantioenriched α -aminoxy- β -ketophosphonates **5**, which will be the feedstock for the preparation of highly substituted non-racemic tertiary α -hydroxy phosphonates **6** and their derivatives **7** and **8** (Scheme 2).

It should be noted that the β -ketophosphonates **4** have previously been utilized as highly reactive nucleophiles for a variety of direct α -functionalization reactions, including amination, halogenation, sulfonylation, as well as alkylation

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[**] This work is supported by a Grant-in-Aid for Scientific Research (23225002), the Advance Catalytic Transformation program for Carbon utilization, The Uehara Memorial Foundation, Nippon Pharmaceutical Chemicals Co., Ltd, and Advance Electric Co., Inc.



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201408893>.

lactones. Whereas a β -ketophosphonate derived from δ -valerolactone (**4j**) yielded the desired product (**5j**) in 84% yield and 99% *ee*, only 23% of the desired product (**5k**) could be isolated for the β -ketophosphonate derived from γ -butyrolactone (**4k**). The R^1 substituent could also be varied, and the incorporation of various aliphatic and aromatic groups at this position had minimal effect on the outcome of the reaction, providing α -hydroxy phosphonates (**5l–p**) in high yield and with excellent enantiocontrol (84 to 88%, 97 to >99% *ee*). On the other hand, the reaction is slightly sensitive to the nature of the R^2 substituent (**4q–u**). The reaction is also compatible with other protected hydroxamic acids yielding products **5v–y** in high yield and with high enantiocontrol (76 to 90%, 98 to >99% *ee*). However, phosphonates with an ester or thioester subunit (**4z**, **4zz**) failed to deliver any product under identical conditions. The reactions could also be performed on a 1 mmol scale without significant losses in yield and enantioselectivity, which demonstrates the synthetic utility and reliability of the current method.

The absolute configuration of compound **5y** was assigned to be *R* by analyzing its X-ray crystal structure (Figure 1 a).^[20] The configurations of all other products **5** were assigned in analogy.

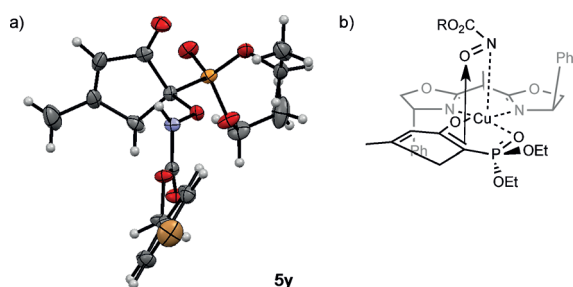
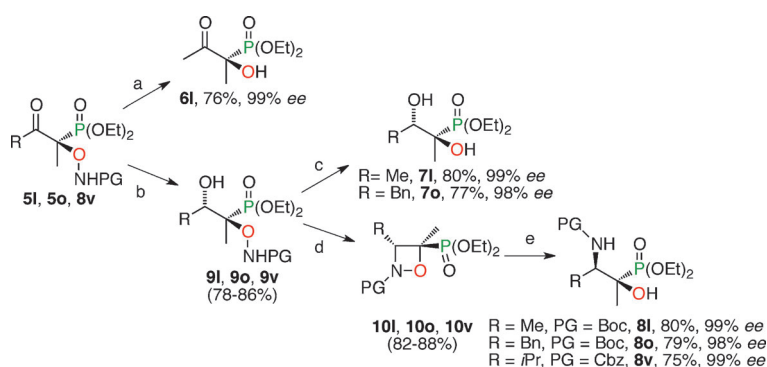


Figure 1. a) X-ray crystal structure of **5y**; ellipsoids set at 50% probability. b) Proposed transition state.

Based on the X-ray analysis and previous studies with β -ketophosphonates, we propose that in the transition state, the β -ketophosphonate coordinates to the Cu^{II} species in a bidentate fashion, and the nitrosocarbonyl compound then approaches from the *si* face (Figure 1 b). Coordination of the nitrogen atom of the nitroso compound to the Cu^{II} center could also explain the high chemoselectivity of this transformation.

Finally, the synthetic utility of our method was demonstrated. The α -aminoxyl phosphonate **5l** was easily transformed into the corresponding α -hydroxy phosphonate **6l** by treatment with $[\text{Mo}(\text{CO})_6]$ in good yield without affecting the enantiopurity (Scheme 3).^[21] The β -keto group of **5** could be reduced with NaBH_4 to access β -hydroxy- α -aminoxyl phosphonates (**9**, 78–86%, major diastereomer). Compound **9** is a valuable synthetic intermediate that can either be transformed into α,β -dihydroxy phosphonate **7**, or alternatively, the appended nitrogen functional group can be utilized. For



Scheme 3. *O*-Nitroso aldol reaction for the synthesis of various substituted α -hydroxy phosphonates. Reagents and conditions: a) $[\text{Mo}(\text{CO})_6]$, $\text{MeCN}/\text{H}_2\text{O}$ (3:1), AcOH , 70°C ; b) NaBH_4 , EtOH , -20°C ; c) $[\text{Mo}(\text{CO})_6]$, $\text{MeCN}/\text{H}_2\text{O}$ (6:1), AcOH , 70°C ; d) PPh_3 , DIAD , THF , 0°C to RT ; e) $[\text{Mo}(\text{CO})_6]$, $\text{MeCN}/\text{H}_2\text{O}$ (6:1), AcOH , 70°C . DIAD = diisopropyl azodicarboxylate. Bn = benzyl, Cbz = benzyloxycarbonyl.

example, under Mitsunobu conditions, **9** was converted into novel 1,2-oxazetidine **10** (82–88% yield), which is otherwise a challenging structural motif.^[22] Finally, the N–O bond of **10** can be cleaved to access β -amino- α -hydroxy phosphonate **8** (Scheme 3).^[23] These transformations provide an attractive and synthetically useful approach to access compounds **7–10**, which bear a quaternary stereogenic center adjacent to a tertiary one. α,β -Dihydroxy phosphonate **7** and β -amino- α -hydroxy phosphonate **8** are valuable structural motifs that are isosteres of natural β -hydroxy and β -amino acids, respectively.

In summary, we have developed an *O*-nitroso aldol reaction of β -ketophosphonates that is catalyzed by the $\text{Cu}(\text{OTf})_2/\text{L1}$ system and makes use of in situ generated nitrosocarbonyl compounds as an electrophilic oxygen source. This transformation represents a new strategy for the synthesis of α -hydroxy phosphonates. The reactions proceeded in high yields and enantioselectivities with both cyclic and acyclic substrates and can be scaled up. Compounds with α,β -dihydroxy phosphonate and β -amino- α -hydroxy phosphonate structural motifs could also be accessed in high yields and enantioselectivities. We hope that the mildness of the reaction conditions should allow the use of this method even for the late-stage functionalization of complex molecules. Investigations to further explore the use of the nitrosocarbonyl chemistry in catalytic asymmetric reactions are underway.

Received: September 8, 2014

Published online: October 27, 2014

Keywords: asymmetric synthesis · bisoxazoline · copper · oxidation · phosphonic acids

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