Asymmetric Synthesis | Hot Paper

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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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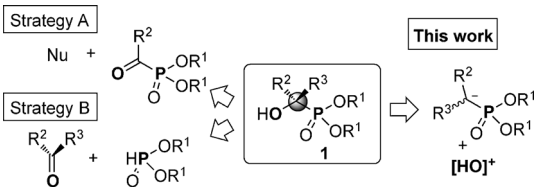
Abstract: *α-Hydroxy phosphonic acids and their derivatives are highly bioactive structural motifs. It is now reported that these compounds can be accessed through the copper-catalyzed direct α-oxidation of β-ketophosphonates using in situ generated nitrosocarbonyl compounds as an electrophilic oxygen 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 phosphonates 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.[9j] 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 organocatalyzed 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, sulfenylation, as well as alkylation

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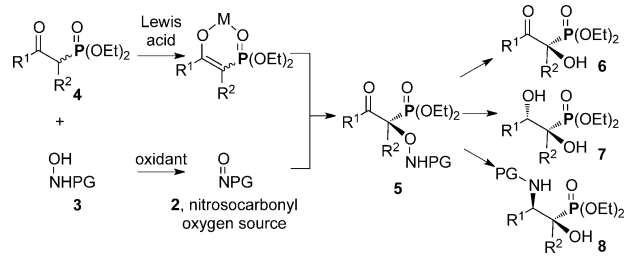
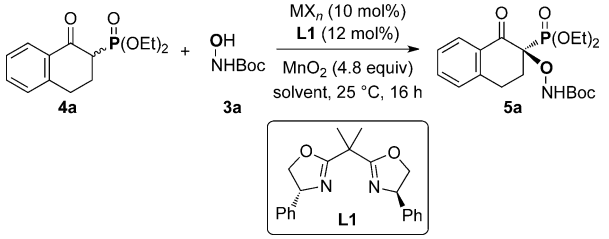


Scheme 2. *O*-Nitroso aldol reaction for the synthesis of various substituted α-hydroxy phosphonates. PG = protecting group.

reactions.[17] However, the asymmetric direct α-oxidation of **4** with an electrophilic source of oxygen for the synthesis of **1** has not been reported.

We commenced our investigation with $Cu(OTf)_2$ as a Lewis acid catalyst in combination with bisoxazoline ligand **L1**[18] in CH_2Cl_2 using β-ketophosphonate **4a** as the model substrate. Commercially available BocNHOH (**3a**; Boc = *tert*-butyloxycarbonyl) was used as the source of the nitrosocarbonyl compound, and MnO_2 was chosen as the oxidant. To our delight, when a solution of **3a** was slowly injected into a mixture of $Cu(OTf)_2$ (10 mol%) and ligand **L1** (12 mol%) in the presence of substrate **4a** and oxidant MnO_2 in CH_2Cl_2 at 25 °C, the *O*-nitroso aldol reaction proceeded smoothly delivering the desired product **5a** in 92% yield and 94% *ee* (Table 1, entry 1). Other metal salts, namely $Zn(OTf)_2$, $Ni(OTf)_2$, and $[Cu(MeCN)_4(OTf)]$, were not efficient at promoting this transformation (entries 2–4). Previously, $Mg(OTf)_2$ had been shown to be a highly effective catalyst for the direct amination of β-ketoesters using nitrosocarbonyl compounds.[13a] In this case, $Mg(OTf)_2$ did not promote the reaction, and more than 85% of unreacted **4a** was recovered (entry 5). Thus, $Cu(OTf)_2$ was chosen as the most suitable Lewis acid catalyst. Further screening with respect to other ligands showed that **L1** was the optimal ligand for this transformation (see the Supporting Information for details). To further improve the enantioselectivity, we then screened various solvents and solvent mixtures using $Cu(OTf)_2$/**L1** as the catalyst system (see the Supporting Information). We were pleased to find that the use of dichloroethane led to increases in both chemical yield and enantioselectivity (entry 6, 94% yield and 96% *ee*). It should be noted that nitrosobenzene, which has previously been utilized for various oxidation reactions,[19] failed to react with **4a** under identical conditions, and >90% of **4a** could be recovered (entry 7). This clearly illustrates the advantage of using nitrosocarbonyl compounds over nitrosobenzene even though the reaction is oxygen-selective. In all cases, the *N*-nitroso aldol product could not be detected.

Table 1: Optimization of the reaction conditions.

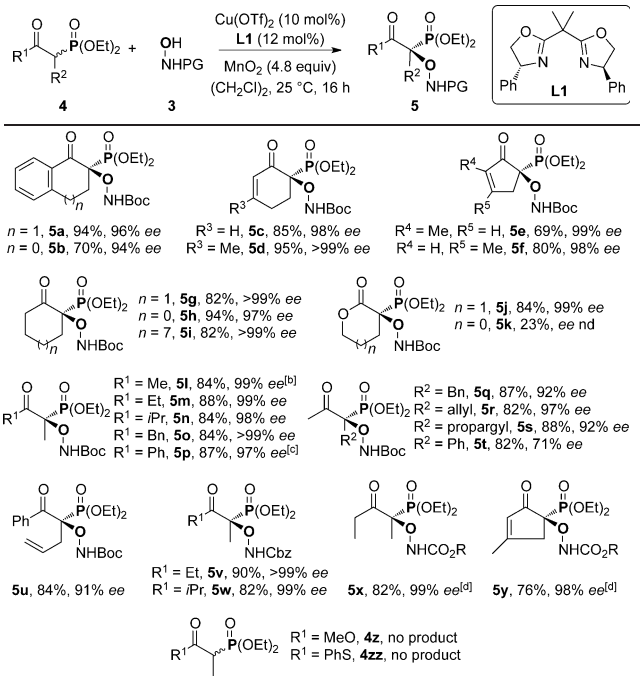


Entry[a]	MX_n	Solvent	Yield[b] [%]	*ee*[c] [%]
1	$Cu(OTf)_2$	CH_2Cl_2	92	94
2	$Zn(OTf)_2$	CH_2Cl_2	73	4
3	$Ni(OTf)_2$	CH_2Cl_2	65	2
4	$[Cu(MeCN)_4(OTf)]$	CH_2Cl_2	87	75
5	$Mg(OTf)_2$	CH_2Cl_2	<10	nd
6	**$Cu(OTf)_2$**	**$(CH_2Cl)_2$**	**94**	**96**
7[d]	$Cu(OTf)_2$	$(CH_2Cl)_2$	<5	nd

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.12 mmol), MX_n (0.01 mmol), ligand **L1** (0.012 mmol), and MnO_2 (0.48 mmol). In all cases, the *N*-nitroso aldol product could not be detected. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] PhNO was used as the oxygen source. nd = not determined.

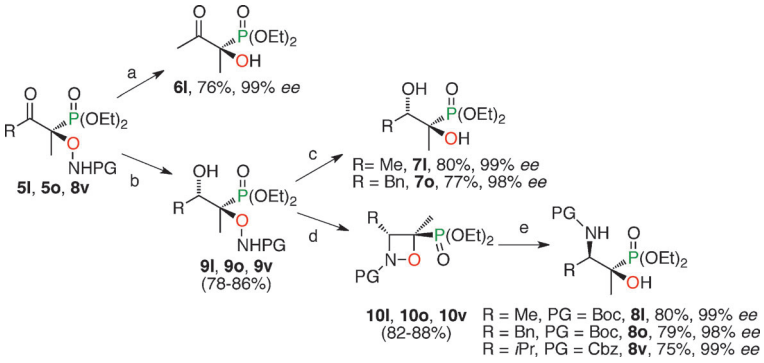
The substrate scope and the generality of this reaction were then evaluated (Table 2). We were delighted to find that the high efficiency demonstrated by the $Cu(OTf)_2$/**L1** catalyst system in the model reaction also applied to the asymmetric α-hydroxylations of a broad range of cyclic as well as acyclic β-ketophosphonates **4**. Cyclic β-ketophosphonates with sensitive cyclohexene and cyclopentene subunits (**4c–f**) are good substrates for this reaction, delivering the desired products (**5c–f**) in high yields (69 to 95%) and excellent enantioselectivities (98 to >99%). The ring size has a minimum effect on the reactivity of saturated cyclic phosphonates (**5g–i**, 82 to 94% yield, 97 to >99% *ee*). A very interesting reactivity pattern was observed for β-ketophosphonates derived from

Table 2: Scope of the asymmetric *O*-nitroso aldol reaction.[a]



[a] Reaction conditions: **4** (0.1 mmol), **3** (0.12 mmol), $Cu(OTf)_2$ (0.01 mmol), **L1** (0.012 mmol), MnO_2 (0.48 mmol). Yields of isolated products are given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] 82%, 99% *ee* (1 mmol scale). [c] 86%, 97% *ee* (1 mmol scale). [d] R = 4-$BrC_6H_4CH_2$. nd = not determined, PG = protecting group.

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.



Scheme 3. *O*-Nitroso aldol reaction for the synthesis of various substituted α-hydroxy phosphonates. Reagents and conditions: a) $[Mo(CO)_6]$, $MeCN/H_2O$ (3:1), AcOH, 70°C; b) $NaBH_4$, EtOH, −20°C; c) $[Mo(CO)_6]$, $MeCN/H_2O$ (6:1), AcOH, 70°C; d) PPh_3, DIAD, THF, 0°C to RT; e) $[Mo(CO)_6]$, $MeCN/H_2O$ (6:1), AcOH, 70°C. DIAD = diisopropyl azodicarboxylate. Bn = benzyl, Cbz = benzyloxycarbonyl.

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.

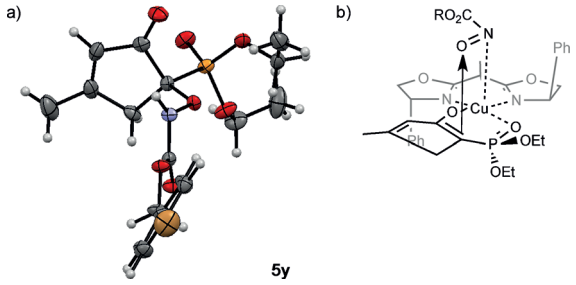


Figure 1. a) X-ray crystal structure of **5y**; ellipsoids set at 50% probability. b) Proposed transition state.

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-aminoxy phosphonate **5l** was easily transformed into the corresponding α-hydroxy phosphonate **6l** by treatment with $[Mo(CO)_6]$ 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-aminoxy 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 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 $Cu(OTf)_2$/**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.

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[20] CCDC 1027682 (**5y**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

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