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Zinc-Catalyzed Phosphonylation of Alcohols with Alkyl Phosphites

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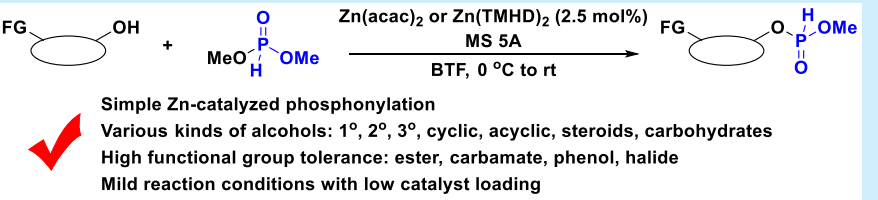

ABSTRACT: In the presence of a catalytic amount of either $Zn(acac)_2$ or bis(2,2,6,6-tetramethyl-3,5-heptanedionato)zinc(II) ($Zn(TMHD)_2$), primary, secondary, and tertiary alcohol substituents on a wide range of substrates, including acyclic and cyclic structures, carbohydrates, steroids, and amino acids, reacted with dimethyl phosphite to afford the corresponding H-phosphonate diesters in high to excellent yields.

Phosphorylation of alcohols is a fundamental organic reaction in both life science and synthetic organic chemistry. In biological systems, it is known that phosphorylation of serine hydroxyl groups in proteins drastically changes the properties of the protein and triggers various kinds of biological events in the cell.[1−3] In the field of organic chemistry, phosphorylation of alcohols is the most straightforward way to access organophosphate molecules. Such phosphates are found in natural products and pharmaceutical agents as well as in functional materials.[4−9] For example, the glucocorticoid class of steroids is phosphorylated when used for medical treatment to improve water solubility.[10] One of the most important applications is the synthesis of oligonucleotides, which are oligomers of nucleotides linked by phosphates; these systems have gained much attention in recent years because they offer a new generation of therapeutic modality.[11−15]

Phosphorylation of alcohols can be achieved by substitution on the phosphorus atom, and synthetic chemists have devoted much effort to designing efficient phosphorylating reagents and activating reagents such as phosphoryl chlorides and pyrophosphates to effect such transformations.[16−25] On the other hand, P(III) is sometimes more reactive than P(V), and phosphorus compounds are used as starting materials to react with alcohols providing phosphites/phosphonates, which are readily oxidized to phosphates efficiently. For example, the use of phosphoramidites and H-phosphonates[26−28] has enabled highly reliable methods to be developed that are currently used for the manufacture of oligonucleotides, mainly in solid-phase synthesis.[29−33] In spite of intense efforts, however, a drawback to the use of such compounds is that they require an excess of activating reagent and produce large amounts of waste. Although Ishihara and co-workers reported catalytic phosphorylation of alcohols with phosphoric acid, reaction temperatures above 150 °C were needed for the reaction, and substrates were limited to alcohols with simple alkyl chains.[34,35] Catalytic phosphorylation/phosphitylation/phosphonylation reactions with readily available and nonactivated reagents under mild reaction conditions to provide sustainable synthetic access to various kinds of phosphates/phosphites/phosphonates with minimal waste are clearly desired.[36]

Herein, we report highly active Zn complex-catalyzed phosphonylation reactions of a wide range of alcohols using alkyl phosphites as phosphonylating reagents to provide H-phosphonate diesters under mild reaction conditions.

We used dimethyl phosphite **2** as a phosphonylation reagent not only because it is an inexpensive and readily available reagent but also because the corresponding H-phosphonates would be easily converted into phosphates and thiophosphates under suitable oxidation conditions. Various Lewis acids were examined using cyclohexanol (**1a**) as a model alcohol in the presence of MS 4A (Table 1).

We started by examining the use of early transition-metal catalysts that are known to be hard Lewis acids, such as $Sc(OTf)_3$, $La(OTf)_3$, and $Hf(OTf)_4$ (entries 1−3). However, the best yield for the first screening was only 19% with $La(OTf)_3$. Accordingly, we turned our attention to late-transition-metal Lewis acids (entries 4 and 5). Interestingly, the use of $Co(acac)_2$ led to a moderate yield of the desired product **3a**. Further extensive evaluation of various Lewis acids finally revealed that $Zn(acac)_2$ had good catalyst activity,

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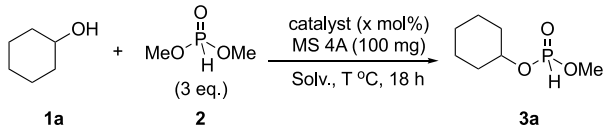
Table 1. Optimization of Reaction Conditions



1a 2 3a

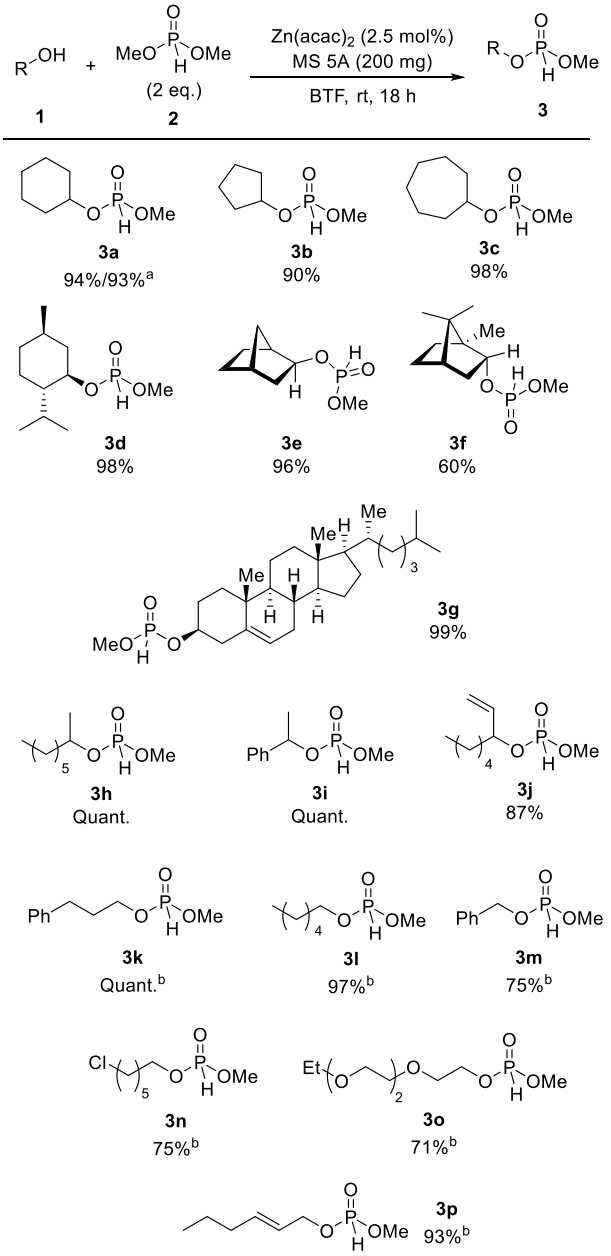
entry	catalyst	*x* (mol %)	solvent	*T* (°C)	yield (%)
1	$Sc(OTf)_3$	10	toluene	60	<5
2	$La(OTf)_3$	10	toluene	60	19
3	$Hf(OTf)_4$	10	toluene	60	<5
4	$Co(acac)_2$	10	toluene	60	58
5	$Cu(TMHD)_2$	10	toluene	60	<5
6	$Zn(acac)_2$	10	toluene	60	77
7	$Zn(OTf)_2$	10	toluene	60	56
8	$ZnEt_2$	10	toluene	60	46
9	$Zn(Salicylate)_2$	10	toluene	60	64
10	$Zn_4(TFA)_6O$	2.5	toluene	60	77
11	$Zn(acac)_2$	10	toluene	40	87
12	$Zn_4(TFA)_6O$	2.5	toluene	40	65
13	$Zn(acac)_2$	2.5	toluene	40	41
14	$Zn(acac)_2$	2.5	THF	40	40
15	$Zn(acac)_2$	2.5	MeCN	40	18
16	$Zn(acac)_2$	2.5	BTF	40	68
17[a]	$Zn(acac)_2$	2.5	BTF	40	88
18[b]	$Zn(acac)_2$	2.5	BTF	40	<5
19[a,c]	$Zn(acac)_2$	2.5	BTF	rt	94

[a]MS 5A (200 mg) was added instead of MS 4A (100 mg). [b]In the absence of MS 4A. [c]Compound **2** (2 equiv) was used.

affording the target compound in 77% yield (entry 6). We tested other Zn catalysts, and it was revealed that square-planar Zn complexes such as $Zn(acac)_2$ and $Zn(salicylate)_2$ gave higher yields than other Zn salts, although most of the Zn salts showed higher catalytic activity than other metal salts (entries 7−9). Interestingly, the Zn oxo-cluster $Zn_4(TFA)_6O$, which is known to be a good catalyst for transesterification,[37,38] showed catalytic activity that was comparable to that of $Zn(acac)_2$ (entry 10). Further comparison of these active Zn salts was performed with decreased reaction temperature. It was found that the reaction proceeded smoothly even at 40 °C, and Zn $(acac)_2$ showed higher catalytic activity than the Zn cluster catalyst (entries 11 and 12). With a decreased amount of catalyst, the effect of solvent was examined (entries 13−16). While the use of acetonitrile as solvent resulted in a significant decrease in yield, probably due to undesired coordination of the solvent to the catalyst, the use of THF gave almost the same result as with toluene. The use of benzotrifluoride (BTF) gave the best yield of **3a**, and further improvement of the yield could be achieved by the addition of 200 mg of MS 5A instead of 100 mg of MS 4A (entries 16 and 17). The yield was low in the absence of molecular sieves (entry 18). Finally, decreasing the reaction temperature to room temperature and reducing the amount of dimethyl phosphite to 2 equiv suppressed the overreaction of **3a** and improved the yield to 94% (entry 18).

With optimized conditions in hand, we next examined the scope of the reaction with structurally simple alcohols (Scheme 1). We initially focused on cyclic alcohols with different ring sizes, and found that cyclopentanol and cycloheptanol afforded the desired H-phosphonate diesters **3b** and **3c**, respectively, in high yields. Substituents on the cyclohexyl ring did not affect the reactivity, and phosphonylated menthol **3d** was obtained in excellent yield. Bicyclic structures were also applicable in this

Scheme 1. Substrate Scope of the Reaction with Simple Alcohols*



*The reactions were performed on 0.3 mmol scale unless otherwise noted. [a]Reaction was performed in 1.2 mmol scale. [b]Reaction was performed at 0 °C.

reaction, and H-phosphonate diesters **3e** and **3f** were obtained in high yields. Furthermore, structurally complex steroid **1g** reacted smoothly under the standard reaction conditions to afford **3g** in excellent yield. Linear secondary alcohols also showed similar reactivity to cyclic alcohols. In addition to simple alkyl-substituted alcohol **1h**, phenyl- and vinyl-substituted alcohols **1i** and **1j** also afforded the corresponding H-phosphonate diesters in excellent yields.

For primary and secondary alcohols, the former showed higher reactivity than the latter, and overreaction of the products resulted in decreased final yields. This problem could be solved by simply decreasing the reaction temperature to 0 °C. Under these reaction conditions, simple alkyl alcohols 3-

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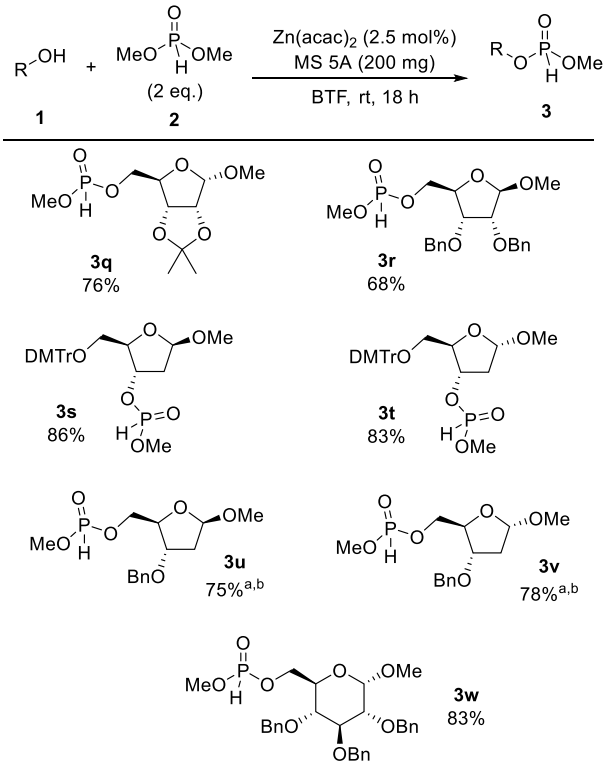
phenylpropanol (**1k**) and *n*-hexanol (**1l**) gave the desired products in excellent yields. However, benzyl alcohol (**1m**) suffered from the required compromise between reactivity and selectivity, and the desired product **3m** was obtained in 75% yield. In contrast, alcohol **1n**, bearing a primary alkyl chloride, gave the corresponding product **3n** in good yield while retaining the potentially electrophilic chloride group. Polyether **1o** and alkene **1p** were also tolerated under the reaction conditions, and **3o** and **3p**, respectively, were obtained in high yields.

We then explored the potential of our methodology by using carbohydrates as substrates (Scheme 2). First, 1-*O*-methyl-2,3-

Scheme 2. Substrate Scope of the Reaction with Carbohydrate Derivatives

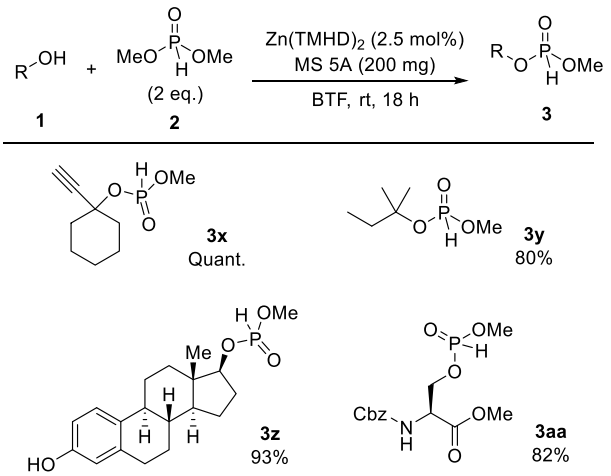


[a]Reaction was performed at 0 °C. [b]Dimethyl phosphite (3 equiv) was used.

acetonide-protected ribose was employed under the standard reaction conditions. To our delight, the desired product **3q** was obtained in high yield. The protecting group at the 2,3-positions could be changed to Bn groups without significant loss of reactivity, and **3r** was obtained in good yield. Encouraged by the successful results of the ribose substrates, we next investigated 2-deoxyribose substrates. 5-DMTr-protected 2-deoxyriboses **1s** and **1t** worked well, and the target H-phosphonate diesters **3s** and **3t**, respectively, were obtained in good yields. The stereocenter at the 1-position (*α*- and *β*-) did not affect the reactivity or selectivity. Similarly, 3-BnO-protected 2-deoxyriboses **1u** and **1v** afforded 5-phosphonylated compounds **3u** and **3v** in good yields. In addition to pentose derivatives, protected glucose **1w** also gave the corresponding H-phosphonate diester **3w** in high yield.

Apart from primary and secondary alcohols, to our knowledge, there has been no successful example of the use of tertiary alcohols in reported catalytic systems. In our study, an initial investigation with a tertiary alcohol also suffered from low reactivity, which led us to explore the use of more active Zn catalysts for more demanding substrates. After extensive studies, we finally identified sterically hindered bis(2,2,6,6-tetramethyl-3,5-heptanedionato)zinc(II) ($Zn(TMHD)_2$) as the most active catalyst. With the new active catalyst in hand, we investigated the scope of the reaction with challenging alcohols (Scheme 3). To our delight, a sterically

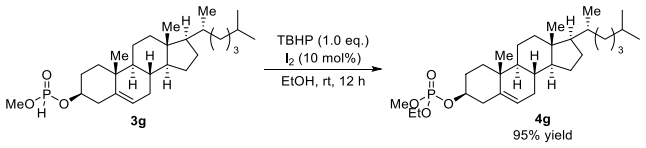
Scheme 3. Substrate Scope of the Reaction with Demanding Alcohols



hindered tertiary alcohol gave **3x** in quantitative yield. Acyclic tertiary alcohol **1y** also gave the desired product **3y** in good yield. Unexpectedly, this catalyst possessed extraordinary functional group tolerance. Using steroid **1z**, which features a free phenol group, the secondary alcohol reacted selectively to smoothly afford **3z** in excellent yield. Substrates with carbamate and ester groups were also tolerated, with CbZ-protected serine ester **1aa** giving the desired H-phosphonate diester **3aa** in high yield. Notably, in this case, the carbamate moiety was tolerated in this reaction system.

As described previously, the product **3g** could be easily oxidized to biologically important trialkyl phosphate **4g** in high yield by a slightly modified, reported procedure (Scheme 4).[38] This result suggests that combining the currently described method with the oxidation protocol would allow access to a wide variety of trialkyl phosphates with high efficiency.[39]

Scheme 4. Oxidation of H-Phosphonate



In conclusion, we have developed a highly active and selective Zn-catalyzed phosphonylation of alcohols with dimethyl phosphite. The reaction proceeded smoothly even at 0 °C to give the target H-phosphonate diesters in high to excellent yields. Various alcohols including primary, secondary, and even tertiary alcohols of acyclic and cyclic structures, carbohydrates, steroids, and amino acids reacted smoothly with excellent functional group tolerance, and interestingly, a sterically hindered Zn complex demonstrated the best activity

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for sterically hindered alcohols. Extensive investigations focusing on the synthesis of other useful phosphorus compounds as well as on the reaction mechanism of this phosphonylation are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00932.

Synthesis and characterization of products; general procedure for the phosphonylation reaction; copies of NMR charts (PDF)

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Notes

The authors declare no competing financial interest.

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