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Substitution- and Elimination-Free Phosphorylation of Functionalized Alcohols Catalyzed by Oxidomolybdenum Tetrachloride

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Abstract: Among 14 oxidometallic species examined for catalytic phosphorylation of the tested alcohols, oxidomolybdenum tetrachloride ($MoOCl_4$) was found to be the most efficient with a negligible background reaction mediated by triethylamine (Et_3N). The new catalytic protocol can be applied to the chemoselective phosphorylations of primary, secondary and tertiary alcohols as well as the substitution-free phosphorylations of allylic, propargylic, and benzylic alcohols. Functionalized alcohols bearing acetonide, tetrahydropyranyl ether, *tert*-butyldimethylsilyl ether, or ester group are also amenable to the new catalytic protocol. The most difficult scenarios involve substitution-free phosphorylations of 1-phenylethanol and 1-(2-naphthyl)ethanol which can be effected in 95 and 90% yields, respectively. ESI-MS, IR, ^1H, and ^{31}P NMR spectroscopic analyses of the reaction progress suggest the intermediacy of an alkoxyoxidomolybdenum trichloride-triethylamine adduct such as $[(RO)Mo(O)Cl_3\text{-}Et_3N]$ to be responsible for the catalytic turnover.

Keywords: catalysis; chemoselectivity; diphenyl phosphates; oxidometallic species; sensitive benzyl phosphates

Introduction

Phosphoryl group transfer to a given protic nucleophile constitutes an important process towards the synthesis of biologically active molecules. Many important bioactive components in nature contain phosphate esters. Major proteins of bone, teeth, eggs, and milk are also enriched with phosphates. Glycosides/glycoproteins possessing phosphate ester residues are mostly found as a component of the cell wall and are implicated in many biological processes such as regulating immune response and tumor metastasis.[1] Phosphorylated natural products like D-*myo*-inositol 1-phosphate[2] have been shown to play an imperative role in regulating transmembrane signalling.[3]

A tremendous amount of work has been reported for the preparation of phosphate esters.[4] Introduction of phosphate ester groups was sometimes accomplished by oxidation of moisture-sensitive P(III) intermediates to the corresponding O=P(V) analogues. Besides, milder methods include reactions of chlorophosphates with lithium or thallium alkoxides[5,6] or with straight alcohols in the presence of a proton scavenger like pyridine[7] or triethylamine.[8] Alternatively, the use of *N*,*N*-dimethylaminopyridine (DMAP) as a nucleophilic catalyst was also reported.[9] Transition metal catalysts such as Cu(II), La(III), Fe(III), Cr(III), Ti(IV), Zr(IV), Y(III), and Sn(IV) have been widely employed for the hydrolysis of phosphonates, fluorophosphates, and phosphate esters.[10] However, relatively fewer efforts have been devoted to studies of the catalytic phosphorylation of alcohols. One seminal methodology was reported with the use of bis(2-oxo-3-oxazolinyl)phosphinate as the phosphoryl source in a catalytic fashion by Zr(IV).[11] Very recently, Jones and co-workers realized such a transformation by using $TiCl_4$,[12] $Ti(O\text{-}t\text{-}Bu)_4$,[13] and $Cu(OTf)_2$ with chlorophosphates or *N*-phosphoryloxazolidinone in the presence of a stoichiometric amount of Et_3N.[14] In addition, $Mg(OTf)_2$ in combination with a bifunctional imidazole and metal hexafluorophosphate salts were also examined for alcohol phosphorylation in the presence of Et_3N.[15] Notably, these catalytic systems involve the use of strong Lewis acids. As part of our ongoing programs utilizing oxidometallic species in the catalysis of C–C and C–

X bond formation,[16] we sought to evaluate the feasibility of catalyzing the phosphorylation event by using neutral, amphoteric, and water-tolerant oxidometallic species. Herein we disclose our preliminary finding towards this end.

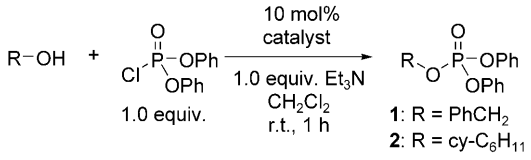
Results and Discussion

We began our investigation with an extensive survey of various oxidometallic species as catalysts from groups IVB-VIB with benzyl alcohol and cyclohexanol as representative primary (1°) and secondary (2°) substrates, respectively. The test phosphorylations were carried out by using $ClP(O)(OPh)_2$ in the presence of Et_3N (1 equiv.) in CH_2Cl_2 and were stopped within the same period of reaction time (i.e., 1 hour). The extent of background phosphorylation without any catalyst was also quantified to be 62% and 25%, respectively, as shown in entry 1 (Table 1). It was found that oxidometallic species from group IVB [e.g., $TiO(acac)_2$, $TiOCl_2$, $ZrOCl_2$, and $HfOCl_2$] tend to slow down or completely suppress the conversion of the starting alcohols to the corresponding phosphate products **1** and **2** (entries 2–5). Among members in group VB (entries 6–9), only VCl_3 shows significant improvement in chemical conversions over those from the background reactions mediated by Et_3N. In marked contrast, group VIB oxidometallic species except WO_2Cl_2 and $MoO_2(acac)_2$ exhibit significant conversion increments (entries 10–14). Notably, MoO_2Cl_2[17] and $MoOCl_4$ were found to be the most promising catalysts particularly for the phosphorylation of 2° alcohols (76 and 81% yields). Conversely, the use of $MoCl_5$ led to only 54% yield for **2**, indicating the unique role of the oxidomolybdenum unit(s) in the catalytic process.

To further differentiate the catalytic function from the background intervention, we performed both the optimal catalytic reactions and the background reaction at 0 °C on the test alcohols (entries 16–18). It was found that the phosphorylation of cyclohexanol is essentially silent in the background at 0 °C. Conversely, $MoOCl_4$ (42% yield) shows significantly better performance than MoO_2Cl_2 (14% yield) at 0 °C for the same process. Therefore, the operating role of $MoOCl_4$ as the best catalyst is confirmed. By systematically varying the catalyst loadings, we also found that 10 mol% is optimal in terms of reaction conversion in 1 hour.[18] Notably, $MoOCl_4$ can even be recovered as the $MoOCl_3(OCH_2Ph)$-NEt_3 and $MoOCl_4$-NEt_3 adducts (91–95% recovery yield) from the aqueous layer and re-used with 84–93% of the original catalytic efficiency for four consecutive runs.[19] Among seven organic and two inorganic bases examined, Et_3N (entry 1) remains the most appropriate base for the catalytic phosphorylation of cyclohexanol (Table 2). Further optimization of the reaction conditions and solvent led to the recipe of 1.2 equivalents of diphenyl chlorophosphate, 1.2 equivalents of Et_3N, and 10 mol% of $MoOCl_4$ in CH_2Cl_2 at ambient temperature.

The optimal catalytic system was then applied to the phosphorylation of various 1°–3° alcohols and phenolic alcohols (Table 3 and Table 4).[20] In general, primary alcohols can be transformed to the corresponding phosphates in excellent isolated yields (88–

Table 1. Catalyst screening for the tested phosphorylation of benzyl and cyclohexyl alcohols.



Entry	Catalyst	% Conv. of 1° ROH[a]	% Conv. of 2° ROH[a]
1	none	62	25
2	$TiO(acac)_2$	71	31
3	$TiOCl_2$	24	trace
4	$ZrOCl_2$	29	trace
5	$HfOCl_2$	24	trace
6	$VO(OTf)_2$	62	22
7	VCl_3	90	63
8	$VOCl_3$	52	44
9	$VO(O\text{-}i\text{-}Pr)_3$	29	17
10	$WOCl_4$	90	62
11	WO_2Cl_2	37	trace
12	MoO_2Cl_2	83	76
13	$MoOCl_4$	90	81
14	$MoO_2(acac)_2$	57	47
15	$MoCl_5$	49	54
16	none (at 0 °C)	14	trace
17	MoO_2Cl_2 (at 0 °C)	14	14
18	$MoOCl_4$ (at 0 °C)	52	42

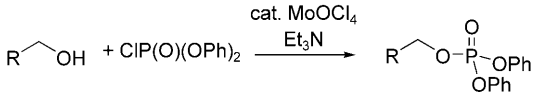
[a] Conversions calculated from integration values in the ^1H NMR spectrum.

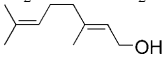
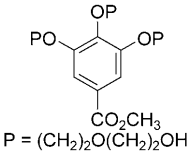
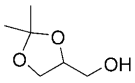
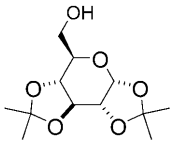
Table 2. Effect of bases on the catalytic phosphorylation of cyclohexanol by $MoOCl_4$.

Entry	Base	% Conversion[a]
1	Et_3N	81
2	$(i\text{-}Pr)_2NEt$	58
3	quinuclidine	51
4	DABCO	23
5	DBU	19
6	pyridine	13
7	2,6-lutidine	12
8	NaOAc or K_2CO_3	0
9	none	0

[a] Determined by ^1H NMR.

Table 3. Catalytic phosphorylation of various 1° alcohols by $MoOCl_4$.[a]



Entry	Starting alcohol	Time [h]	Yield [%][b]
1	$PhCH_2OH$	1	98 (**1**)
2	$PhCH_2CH_2OH$	1	99 (**3**)
3	$Cl\text{-}(CH_2)_2OCH_2CH_2OH$	1	97 (**4**)
4	$H_2C{=}CH(CH_2)_2CH_2OH$	1	99 (**5**)
5	$H_2C{=}CHCH_2OH$	1	99 (**6**)
6		1	88 (**7**)
7	$HC{\equiv}CHCH_2CH_2OH$	1	95 (**8**)
8	$HC{\equiv}CHCH_2OH$	1	99 (**9**)
9		1	89 (**10**)
10		1	94 (**11**)
11		1	92 (**12**)
12	$TBSO(CH_2)_2OCH_2CH_2OH$	1	98 (**13**)
13	$THPO(CH_2)_2OCH_2CH_2OH$	1	92 (**14**)

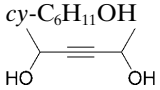
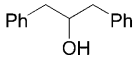
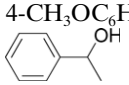
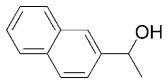
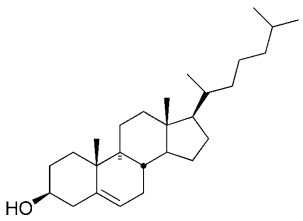
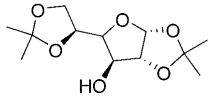
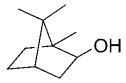
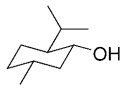
[a] Reactions performed with 1.2 equiv. of $ClP(O)(OPh)_2$, 1.2 equiv. of Et_3N, and 10 mol% of $MoOCl_4$ in CH_2Cl_2 at room temperature.
[b] Isolated, pure product yields after column chromatography.

99%) in 1 h (entries 1–13, Table 3). Activated alcohols like benzylic (entry 1), allylic (entries 5 and 6), propargylic (entry 8), and an S_N2 sensitive one (entry 3) are tolerated. No signs of etherification between the starting alcohol and the corresponding phosphate product were observed in all cases. The current catalytic protocol tolerates ethylene glycol and ester functionalities (entry 9) as illustrated in the phosphorylation of methyl gallate bearing diethylene glycol terminals. Notably, the phosphorylated product **10** may act as an important building block towards hydrophilic nanohybrids.[21] Furthermore, the functional group compatibility of the new catalytic system was illustrated by its applications to alcohols bearing Lewis acid-sensitive components such as acetonide (entries 10 and 11), glycosidic acetal (entry 11), *tert*-butyldimethylsilyl (TBS) (entry 12), and tetrahydropyranyl (THP) ethers (entry 13).

Furthermore, simple secondary alcohols can be readily phosphorylated in 90–95% yields (entries 1–3, Table 4) in 1–1.5 h. It takes slightly longer (3 h) for a 2° alcohol bearing two flanking benzyl groups (entry 4) to be completely phosphorylated, presumably due to increased steric effects. Notably, no elimination by-product of the phosphate **17** was observed under the reaction conditions (entry 4, Table 4). Phenolic substrates were easily phosphorylated (92–98% yields) in 1 hour with negligible electronic effects of the *para*-substituents (entries 5–7, Table 4).

Notably, the most challenging phosphorylations of 1-phenylethanol and 1-napthalen-2-ylethanol (entries 8 and 9) were accomplished in 3 h with quantitative conversions as judged by ^1H NMR and in 95% and 90% isolated yields, respectively. No etherification or chlorination product resulting from the nucleophilic attack of **21a**, **b** by chloride or the starting alcohol was observed. To the best of our knowledge, this represents one of the most successful catalytic systems[15] that can achieve the syntheses of **21a** and **21b** in high yields. Substrates derived from natural sources like cholesterol, diacetonide-D-glucose, isoborneol, and menthol can also be smoothly phosphorylated in 90–92% yields (entries 10–13, Table 4) albeit with longer reaction times (8–24 h). The ability of tolerating Lewis acid-sensitive groups was again demonstrated in the case of diacetonide-D-glucose

Table 4. Catalytic phosphorylation of various 2–3° and phenolic alcohols by $MoOCl_4$.[a]

Entry	Starting alcohol	Time [h]	Yield [%][b]
1	$CH_3CH(OH)CH_2CH_3$	1	95 (**15**)
2	*cy*-$C_6H_{11}OH$	1.5	90 (**2**)
3		1	90 (**16**)
4		3	90 (**17**)
5	C_6H_5OH	1	98 (**18**)
6	4-$NO_2C_6H_4OH$	1	92 (**19**)
7	4-$CH_3OC_6H_4OH$	1	92 (**20**)
8		3	95 (**21a**)[c]
9		3	90 (**21b**)[c]
10		14	92 (**22**)
11		24	90 (**23**)
12		10	90 (**24**)
13		8	92 (**25**)
14	$(CH_3)_3COH$	30	96 (**26**)
15	H-C≡C–$C(CH_3)_2OH$	30	92 (**27**)
16	CH_3CH_2-$C(CH_3)_2OH$	30	90 (**28**)

[a] Reactions performed with 1.2 equiv. of $ClP(O)(OPh)_2$, 1.2 equiv. of Et_3N, and 10 mol% of $MoOCl_4$ in CH_2Cl_2 at room temperataure.

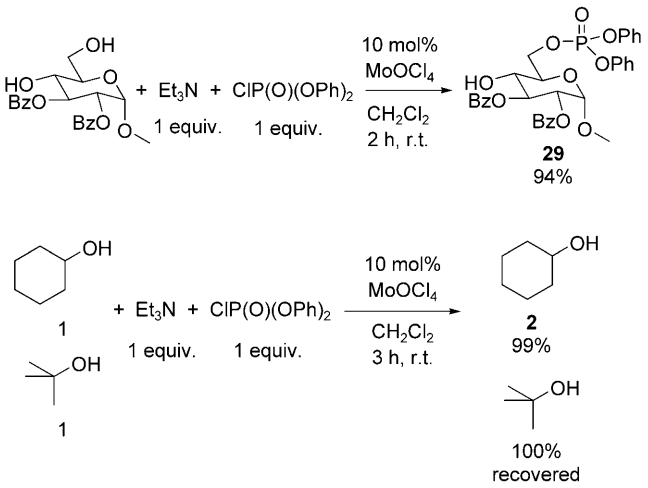
[b] Isolated, pure product yields after column chromatography.

[c] Product unstable to silica gel and 2 equiv. of Et_3N were used.

(entry 11). The phosphorylated product **23** was isolated in 90% yield without glycosidic acetonide opening or acetonide migration.

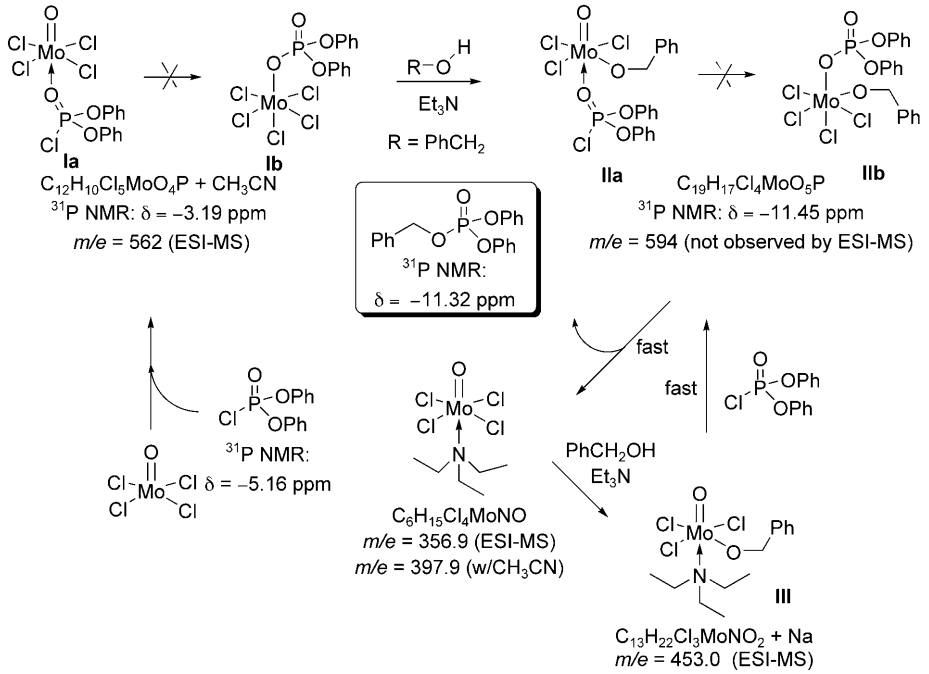
To extend the substrate scope of the new catalytic protocol, three representative tertiary alcohols were further examined (entries 14–16, Table 4). It was found that all these reactions proceeded cleanly in 90–96% isolated yields in 30 h, which were by far not equaled by other catalytic systems.

As a final demonstration regarding the utility of the new catalytic protocol, we have performed a chemoselective phosphorylation of a monosaccharide – methyl (O^2,O^3-dibenzoyl-α-D-glucopyranoside). The reaction was complete in 2 h leading to product **29** with exclusive phosphorylation at the primary, C6-hydroxy group in 94% yield along with recovery of the remaining starting material in 5% yield, Scheme 1. To the best of our knowledge, this is the first successful example for this type of substrate. Furthermore, an intermolecular competition experiment for the chemoselective phosphorylation of a 1:1 mixture of cyclohexanol and *tert*-butanol under the standard catalytic protocol led to only cyclohexyl diphenyl phosphate **2** in 99% yield.



Scheme 1. *Top:* Chemoselective phosphorylation. *Bottom:* Intermolecular competitive phosphorylation between a 2° and a 3° alcohol.

Since $MoOCl_4$ and MoO_2Cl_2 are catalytically more active than $MoCl_5$, we speculate that $ClP(O)(OPh)_2$ is activated by its coordination to the Mo=O unit, leading to an adduct **Ia** (Scheme 2). ESI-MS analysis (CH_3CN as the eluent) of a 1/1 mixture of $MoOCl_4$/$ClP(O)(OPh)_2$ in CD_2Cl_2 reveals of the existence of **Ia** which supports this presumption. The IR spectrum of the same solution mixture shows a shift of the P=O signal from 1310 to 1280 cm^{-1} and the Mo=O signal remains intact without any discernible signal related Mo–O stretching around 800–900 cm^{-1}.[19,22] Further supportive insights were provided by ^1H NMR studies. After addition of $MoOCl_4$ into $ClP(O)(OPh)_2$, (1:1 ratio) in CD_2Cl_2, the signal at $\delta = 7.44$ ppm was shifted upfield to $\delta = 7.42$ ppm, and the one at $\delta = 7.31$ ppm was downfield shifted to $\delta = 7.32$ ppm (Figure 1). The chemical shift change profile is similar to that upon mixing $MoOCl_4$ and $P(O)(OPh)_3$ (1:1 ratio). Therefore, the alternative, nucleophilic acyl substitution of $ClP(O)(OPh)_2$ by $MoOCl_4$ to form adduct **Ib** is ruled out (Scheme 2). In addition, ^{31}P NMR analysis for the same mixture in CD_2Cl_2 led to complete formation of only one downfield signal at $\delta = -3.19$ ppm as compared to that of the original



Scheme 2. Proposed mechanism for the catalytic phosphorylation by $MoOCl_4$.

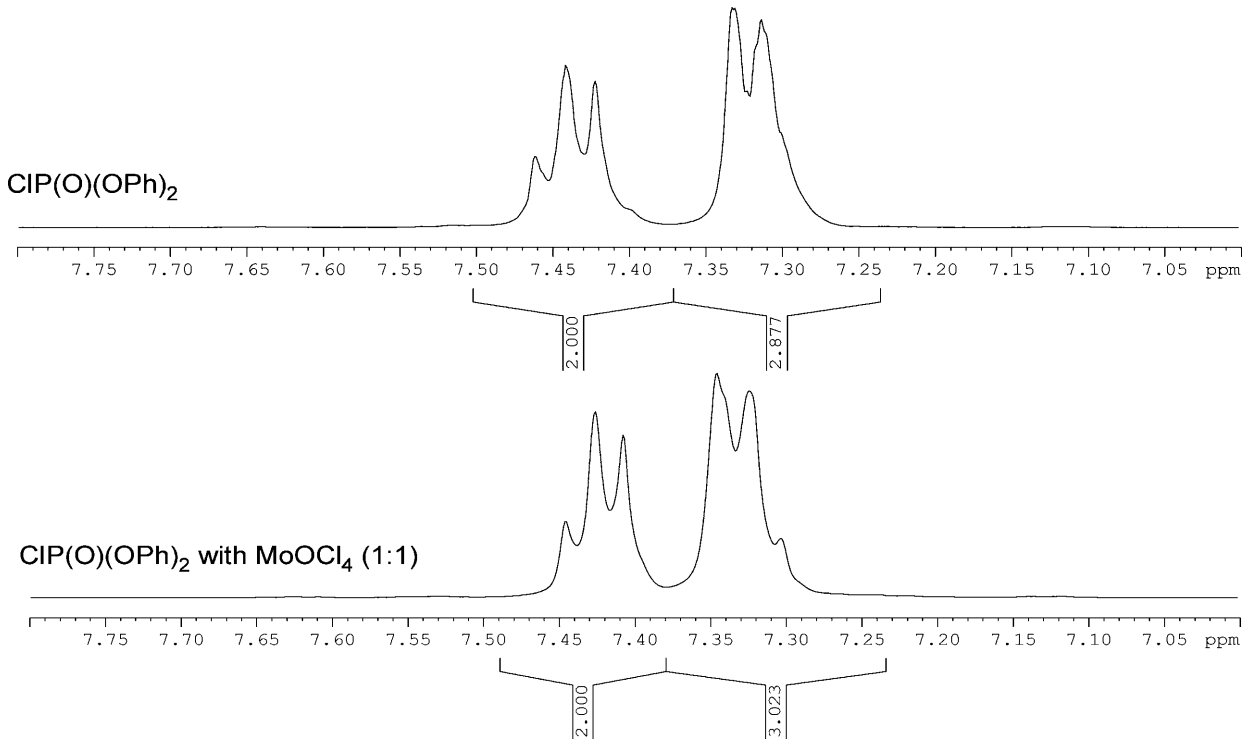


Figure 1. ^1H NMR spectroscopic analyses for $ClP(O)(OPh_2)_2$ in CD_2Cl_2 before (*top*) and after (*bottom*) addition of 1 equivalent of $MoOCl_4$.

$ClP(O)(OPh)_2$ at $\delta = -5.13$ ppm, which is consistent with the findings from ESI-MS, IR, and ^1H NMR analyses.[19]

ESI-MS analysis (CH_3CN as the eluent) of an aliquot from a catalytic reaction mixture with benzyl alcohol in CD_2Cl_2 suggests the formation of an adduct between $Cl_3Mo(O)(OCH_2Ph)$ and NEt_3 (i.e., adduct

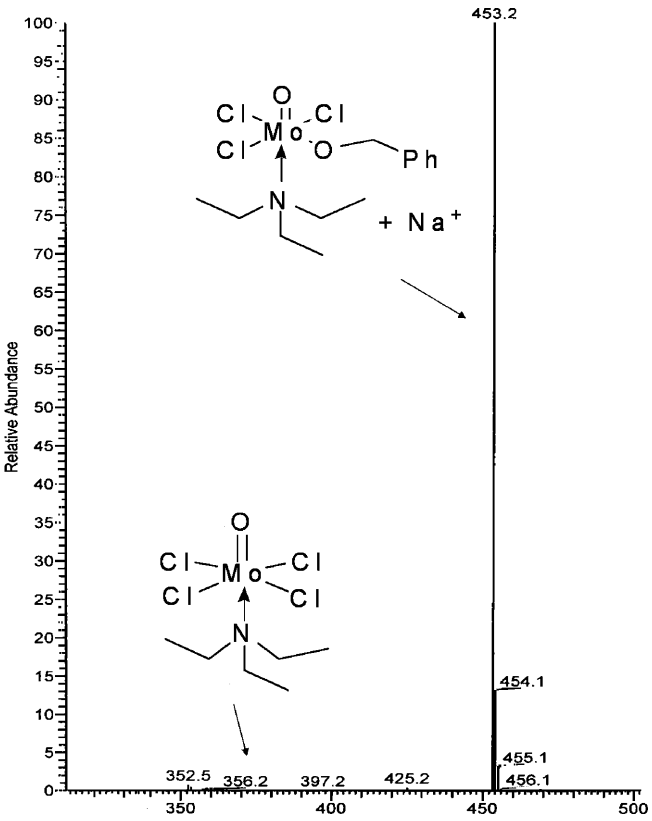


Figure 2. ESI-mass spectrum of the adduct **III**.

III) even after completion of the reaction (Figure 2). A series of ^{31}P NMR analyses for the same mixture in CD_2Cl_2 with time showed only the signal for $ClP(O)(OPh)_2$ at $\delta = -5.13$ ppm with decreasing intensity and an increasing, broad product signal at $\delta = -11.39$ ppm.

Conversely, the original catalyst ($MoOCl_4$-L, L = CH_3CN and/or Et_3N) was detected in negligible amounts during the the course of the reaction. Since the catalytic reaction cannot proceed in the absence of Et_3N and the original catalyst is present in a minimal amount or is short-lived during the reaction, the initial adduct **Ia** may undergo subsequent reaction with an alcohol (e.g., $PhCH_2OH$) in the presence of Et_3N. The resultant Mo-bound alkoxide **IIa** (^{31}P NMR: $\delta = -11.45$ ppm) would further undergo phosphorylation either in an inter- or intramolecular fashion with concomitant release of $MoOCl_4$-L. A residing and turnover species **III** is formed once $MoOCl_4$-L further reacts with a given alcohol in the presence of Et_3N.

Conclusions

We have developed a new and highly potent phosphorylation catalyst, $MoOCl_4$, that is compatible with substrates possessing a wide range of functionalities including Lewis acid-sensitive glycosidic acetal, acetonide, silyl, and THP ether units. Furthermore, this new catalytic protocol represents a mild and practical synthetic approach to effect the phosphorylation of substrates that are sensitive to intervening substitution or elimination and to access phosphates derived from sterically hindered alcohols in high yields. Glycosides bearing Lewis-acid labile groups can also be smoothly phosphorylated. Chemoselective phosphorylation can be achieved in an intramolecular or intermolecular diol system. ESI-MS, IR, ^{1}H NMR, and ^{31}P NMR spectroscopic analyses of the reaction mixture with $PhCH_2OH$ before, during, and after the phosphorylation indicate the Lewis acid nature of $MoOCl_4$ and the intermediacy of $(PhCH_2O)MoOCl_3$-Et_3N (i.e., adduct **III**). Further studies are underway to expand the scope of the catalytic process to asymmetric variants and alcohol substrates of biological interest.

Experimental Section

General Procedure for Catalyst Screening

Catalyst (10 mol%) was stirred in CH_2Cl_2 (5 mL) at room temperature under nitrogen. A solution of a given alcohol in CH_2Cl_2 (5 mL) was added followed by Et_3N (1.0 equiv.) and $ClP(O)(OPh)_2$ (1.0 equiv.). The resulting mixture was stirred at room temperature for 1 hour and then quenched with distilled water (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The reaction conversion was determined by integration ratios of the protons of C-1 with attached OH in the alcohol and C-1 in the phosphate, respectively, in the ^{1}H NMR spectra.

Representative Procedure for the Phosphorylation of Alcohols

In a 25-mL, two-necked, round-bottomed flask was placed the alcohol (0.1 mmol) in CH_2Cl_2. To the reaction flask was added $MoOCl_4$ (10 mol%), Et_3N (0.12 mmol, 1.2 equiv.), and $ClP(O)(OPh)_2$ (0.12 mmol, 1.2 equiv.) at ambient temperature. The reaction mixture was stirred for the designated time as evidenced by TLC analysis and then quenched with distilled water (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography on silica gel to provide the pure diphenyl phosphate product.

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