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Graphical Abstract

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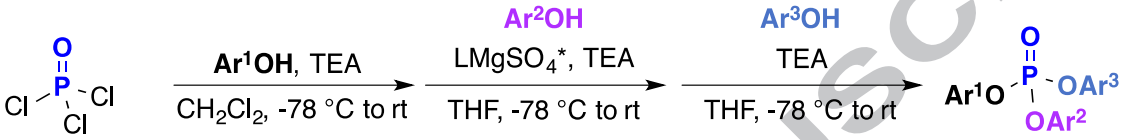

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Exploration of Chiral Lewis Acid Mg^{2+} Catalysts in the Synthesis of Aryl Organophosphate Triesters from Phosphorus Oxychloride through a Three-step, Two-pot Substitution Sequence

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ABSTRACT

A variety of nucleophilic and Lewis acid catalysts were examined for use in promoting the synthesis of organophosphate triesters. eight novel organophosphate triesters are reported here for the first time. $MgSO_4$ was discovered as an inexpensive catalyst capable of improving the synthesis of a variety of aryl organophosphate triesters from the readily available and low cost precursor phosphorus oxychloride in a three-step, two-pot sequence. Yields for this method improve upon the uncatalyzed method by 8-36%. Several chiral catalysts were tested, but none were able to induce enantioselectivity in the reaction.

1. Introduction

Synthetic strategies for the construction of organophosphates and their derivatives (OPs) are reported in the literature, but have seen a lack of attention over the past century.[1–3] However, new synthetic efforts[4–41] have created a resurgence for the "13th" element and have found great utility in the pharmaceutical industry and medicinal chemistry ever since OPs were recognized as a major class of medicinal agents.[42–48] This is largely due to phosphorus being a key element in nature, and use of phosphorylation or dephosphorylation reactions has allowed control over many life processes such as the regulation of proteins, nucleosides (DNA and RNA), and steroids.[49–61] As such, phosphorus chemistry can be used to treat different types of human ailments such as cancer, Hepatitis C, and AIDS.[42–45,47,62–78] Nothing seems to demonstrate the importance of organophosphate derivatives in the pharmaceutical industry more than the wildly successful drug Sofosbuvir (also known as Sovaldi) that has earned $10. 3 billion in 2014 for the treatment of Hepatitis C.[42,43] It represents a transformational shift in strategy for nucleoside-based pharmaceuticals that currently treat HIV, Hepatitus B and C, herpes, and ebola.[62–64,66,68,79] Central to the success of Sofosbuvir is the chiral organophosphate center, which allows for the delivery of a nucleoside 5'-monophosphate in a prodrug fashion that increases absorption and bypasses the slow monophosphorylation step.[40,80–83] Like other chiral drugs, absolute configuration of stereochemistry (in this case at phosphorus) has immense ramifications for drug performance.[84]

Creative efforts have been taken to improve upon the synthetic methodology for the construction of phosphate triesters, although stereospecific methods have been noticeably rare.[37,46,75,85–87] In general, reaction of P(V) compounds equipped with labile groups with nucleophilic attachments remains a popular method for construction of OPs.[1,46,47,67,75,77,84–89] Villard et al. used a typical non-catalytic method to synthesize phenyl phosphorotriester derivatives in good yield (63-76%) through use of a phosphorochloridate with a labile chlorine as a leaving group, but needed 3 equivalents of the P(V) phosphorochloridate

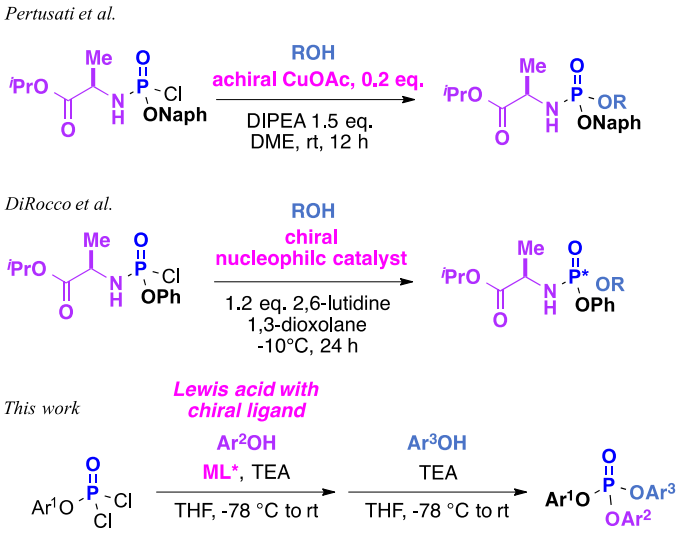


Figure 1. Known catalytic methods with using electrophilic P(V) starting materials.

and 6 equivalents of *N*-methyl imidazole (NMI) per equivalent of the alcohol. Others report control over chirality at phosphorus, but installation of a chiral auxiliary is the most common way to promote a stereoselective process.[75,86,90] Alternatively, chromatographic enrichment can be used as a crutch since catalytic chiral methods have been lacking.[75] However, the removal of the chiral auxiliary can be problematic and creates a need for a catalytic method. DiRocco et al. have recently reported the use of a chiral nucleophilic catalyst with success[87] (**Figure 1**). Unfortunately, not only is the catalyst difficult and expensive to synthesize (requiring separation by preparative chiral SFC), but the work did not demonstrate the synthesis of a P-(*S*) stereocenter in high yield and selectivity. Additionally, their reported yields were not based on isolated chemical yields but relied on internal calibration by ^{1}H NMR (literature[91] shows some drastic decreases in yield between NMR yield vs. isolated yield) or HPLC. Also notable is the requirement to prepare a chlorophosphate starting material in a separate step because it is not commonly commercially available, something that is all too common in the literature. Along the same lines, Pertusati and McGuigan promoted the formation of a phorsphoramidate through catalysis with $Cu(OTf)_2$ using a prefunctionalized phosphochloridate.[83] While the reaction did not proceed at all in the absence of a catalyst, inclusion of $Cu(OTf)_2$ was only able to provide an isolated yield of 35% as a mixture of diastereomers. Surprisingly, McGuigan's work is reflective of the literature as a whole in that only achiral Lewis acids have been tested in this framework.[92–95]

In light of these shortcomings in the literature, we sought to develop a catalyzed enantioselective reaction using either a Lewis acid or nucleophilic catalyst from the inexpensive and easily accessible $POCl_3$ that did not require excessive equivalents of reagents. We envisioned that one, two, or three different nucleophilic appendages can be added during the course of three subsequent nucleophilic substitutions, thereby creating a flexible path for organophosphate (OP) construction (**Figure 2**).

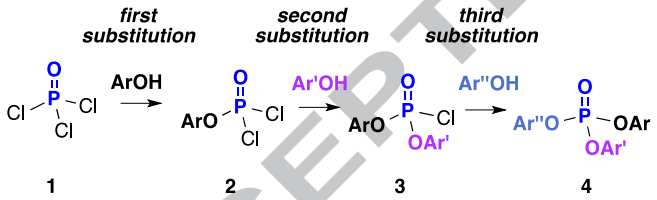


Figure 2. General strategy for the synthesis of organophosphate triesters.

Herein, we report a three-step, two-pot reaction sequence catalyzed by magnesium sulfate that can generate organophosphate triesters using three different phenolic nucleophiles in yields 8-36% higher than the non-catalyzed reaction. These triesters contain a stereocenter at phosphorus, which makes our method distinct from other Lewis acid catalyzed reactions that simply aim to transfer achiral phosphates.[92,96,97] Apart from triphenyl phosphate, we produced eight new organophosphate triesters in this work. In order to continue to fill in the missing gap in the literature, exploration of chiral versions of these metal catalysts is reported. Unfortunately, while we were able to produce the desired phosphorus compounds in higher yields vs. the uncatalyzed reaction, we were unable to do so enantioselectively.

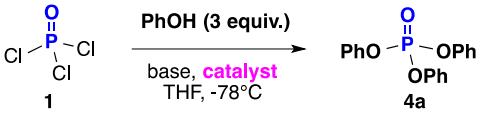
2. Results and Discussion

As stated above, phosphohorus oxychloride (**1**) is an obvious choice of starting material because it is simple, inexpensive, relatively reactive, easy to purify and obtain, and contains a reactive phosphorus with three leaving groups present. Other alternatives are outlined in the literature, but require prior reaction and purification.[1,11,16] The nucleophile of choice was chosen to be phenol since TLC can easily monitor the reaction, products that form from these two reagents have reported chemical shift values in the literature[98–101], it is inexpensive, it should limit any complications from dealkylation side reactions, and is present in many biologically active OPs already in use in medicine.[40]

Initial experiments were aimed at identifying ideal conditions when starting from **1** and forming achiral **4a** through three sequential nucleophilic additions of phenol. We were able to isolate triphenylphosphate **4a** in 55% yield with no catalyst and triethylamine (TEA) as a base. We tested a series of bases in the reaction for comparison (**Table 1**). Interestingly, all inorganic bases that were tested failed to produce the phosphate triester in useful quantities. The results for organic bases were mixed, with triethyl amine (TEA) performing the best and Proton Sponge disappointingly producing the phosphate triester in only trace amounts. Hunig's base, despite a structure similar to TEA, was lower in yield of the triester, **4a,** and showed a larger quantity of Ph_2POCl (**3a**) and more side product by NMR. Based on these results, TEA was used for further experiments. Though a method exists of high yields of **4a** at higher temperatures, we were more interested in lower temperature conditions that might eventually prove more conducive to stereospecific catalysis.[102]

Nucelophilic organocatalysts were also tested alongside TEA as seen in **Table 1**. In each case, the catalyst was added before the first nucleophilc addition to the reaction pot containing **1**. We were especially interested to see whether a catalyst could promote the third nucleophilic step since it did not go to entirely to completion to produce **4a** (entry 1). DABCO, DMAP, HyperBTM, and *N*-methyl imidazole (NMI) were all added prior

Table 1. Screening of bases and catalysts in model reaction.



Entry	base	catalyst(s)	amount	yield*
1	TEA	-	-	55%
2	$CaCO_3$	-	-	trace
3	CaH_2	-	-	trace
4	Proton Sponge	-	-	trace
5	Hünig's base	-	-	17
6	Hünig's base	DABCO®	0.1	12
7	TEA	DMAP	0.1	trace
8	TEA	HyperBTM	0.1	22%
9	TEA	NMI	0.1	27
10	TEA	DABCO	0.1	14
11	TEA	TiO_2	0.1	80%
12	TEA	$MgSO_4$	0.1	70%
13	TEA	$MgSO_4$	1	70%
14	TEA	$MgCl_2$	0.1	70%
15	TEA	Ag_2O	3.0	70%
16	TEA	$Tl(PF_6)$	3.0	0%
17	TEA	$Cu(OTf)_2$	0.1	24%
18	TEA	Pb(TMMD)	0.1	10%
19	TEA	$(PPh_3)_2NiCl_2$	0.1	10%
20	TEA	$Pb(C_5HF_6O_2)_2$	0.1	4.2
21	TEA	$(dpp)NiCl_2$	0.1	7.9%
22	TEA	TiO_2, DABCO	0.1, 0.1	50%
23	TEA	$MgSO_4$, NMI	0.1, 0.4	67%

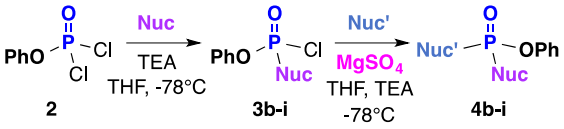
*yields reflect isolated yields obtained after column chromatography

to the nucleophilic additions at room temperature. While NMI proved to be the best of the organocatalyst group when used in catalytic amounts (0.1 equiv.) with a 27% yield of **4a** (entry 9), this was much lower than the 55% yield for the uncatalyzed reaction (entry 1). The crude ^{31}P NMR spectra collected for entries **6-10** showed the phosphochloridate diester **3**, the product **4a**, and a side product peak at -25.4 ppm. We believe this side product may be an anhydride based on literature comparisons[103,104], but unfortunately it could not be isolated nor confirmed by comparison to reported ^{31}P NMR chemical shift data.

Subsequent to nucleophilic catalyst screening, Lewis acid catalysts were examined (entries 11-21, **Table 1**). We had an initial predisposition toward using magnesium salts because of their well known role in life processes,[105–109] as well as their availability, price, and previous literature detailing coordination of Mg^{2+} with chiral ligands.[110,111] However, other metal cations could be potential candidates, as evidenced with Cu^{2+} from McGuigan's work.[83] Out of those tested, $MgSO_4$ and $MgCl_2$ gave good results with an equal yield of 70% for each reaction (entries 12 and 13). TiO_2 gave a slightly higher yield for **4a** at 80% (entry 11), but further experiments revealed that it gave similar yields when compared to magnesium-catalyzed reactions for the synthesis of other organophosphates. The other Lewis acids, including copper, gave lower yields compared to the uncatalyzed reaction. In addition to these catalysts, we used 3 equivalents of Ag_2O and $Tl(PF_6)$ to forcibly remove the chlorides from the phosphate center. Interestingly, the silver gave results akin to magnesium as a catalyst, while thalium did not yield an appreciable amount of product. Addition of both a Lewis acid and nucleophilic catalyst ($MgSO_4$ and NMI, 0.1 equiv and 0.4 equiv. respectively) gave a 67% yield of **4a**. So, when NMI is used in excess of catalytic quantities, it can be combined with a Mg^{2+} Lewis acid in a bifunctional system without much detriment, but also without a benefit to the yield. Because of this, NMI was omitted in subsequent reactions and $MgSO_4$ was used as the sole catalyst unless otherwise specified.

Next, we turned our attention to other OPs (**Figure 3** and **Table 2**). We had the ultimate goal of testing the viability of our method as an enantioselective catalytic process, so we began

Table 2. Comparison of catalyzed vs. uncatalyzed yields of OPs **4b-i**.



Entry	Nuc	Nuc'	catalyst(s)	product	yield*
1	*p*-MeOArOH	*m*-CF_3ArOH	-	4b	14%
2	*p*-MeOArOH	*m*-CF_3ArOH	$MgSO_4$	4b	32%
3	*p*-MeOArOH	sesamol	-	4c	7%
4	*p*-MeOArOH	sesamol	$MgSO_4$	4c	18%
5	*p*-MeOArOH	sesamol	$MgSO_4$, NMI	4c	40%
6	*p*-MeOArOH	*m*-ClArOH	-	4d	17%
7	*p*-MeOArOH	*m*-ClArOH	$MgSO_4$	4d	53%
8	*p*-MeOArOH	*o*-NO_2ArOH	-	4e	24%
9	*p*-MeOArOH	*o*-NO_2ArOH	$MgSO_4$	4e	32%
10	*o*-MeOArOH	*o*-NO_2ArOH	-	4f	27%
11	*o*-MeOArOH	*o*-NO_2ArOH	$MgSO_4$	4f	44%
12	*3,5*-diMeOArOH	*o*-NO_2ArOH	-	4g	28%
13	*3,5*-diMeOArOH	*o*-NO_2ArOH	$MgSO_4$	4g	43%
14	*p*-MeOArOH	*o*-MeOArOH	-	4h	19%
15	*p*-MeOArOH	*o*-MeOArOH	$MgSO_4$	4h	28%
16	4-Br-3-MeOArOH	*o*-NO_2ArOH	-	4i	26%
17	4-Br-3-MeOArOH	*o*-NO_2ArOH	**9****	4i	62%

*yields reflect isolated yields obtained after column chromatography
**catalyst added before the second nucleophilic addition

synthesizing phosphate triesters with three different attachments to phosphorus. As for the choice of which nucleophiles to choose instead of phenol, we ultimately decided that substituted phenol derivatives would be a convenient choice since we already knew how to interpret the chemical shift data in the phosphorus NMR and they are easy to monitor by TLC. While these compounds are not of significant medicinal value, they allowed for investigation of simple P-stereogenic compounds before pursuit of complex pharmaceuticals. Phosphate triesters **4** were also synthesized in the absence of a catalyst for comparison. Unlike the previous model reaction in which three equivalents of phenol were added,

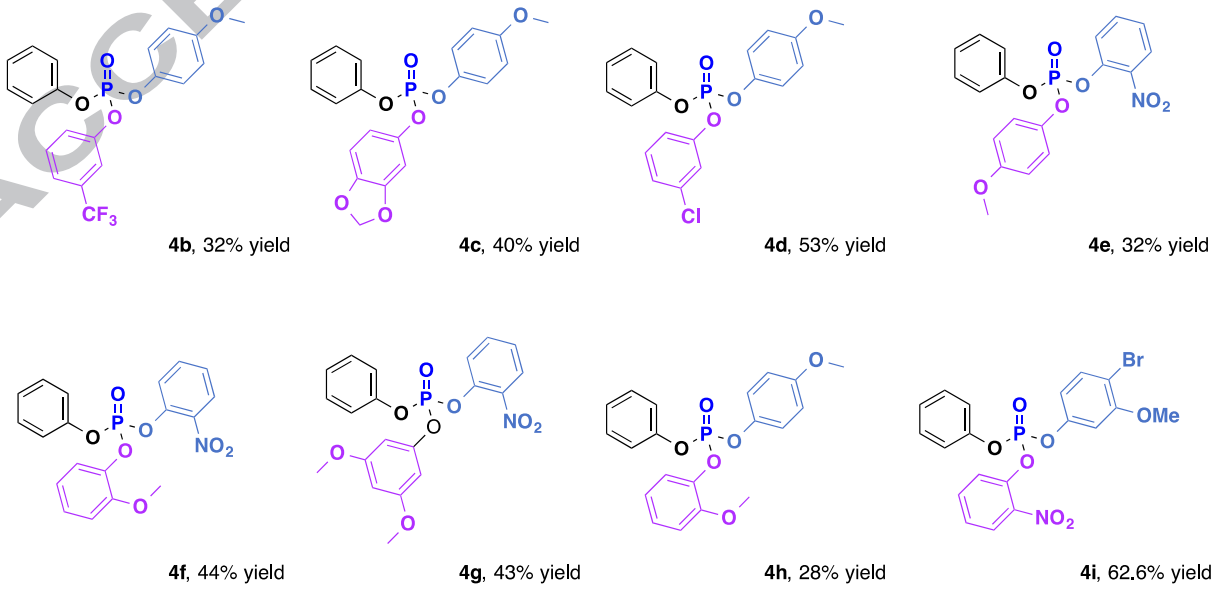


Figure 3. Aryl phosphate triesters synthesized using 3 different phenols.

the additional complication of three *different* nucleophiles needed to be managed. Addition of $MgSO_4$ to a reaction of **1** with different phenols was expected to increase the yield of other phosphate triester derivatives **4b-i**, as had been the case for the model reaction. However, the reactions performed worse with the catalyst at room temperature as revealed by ^{31}P NMR, with multiple substitutions occurring instead of the intended single substitution per nucleophile. Therefore, $MgSO_4$ was removed from the first step and $(PhO)POCl_2$ was prepared and distilled in bulk as a preliminary step to simplify the reaction sequence. Lowering the reaction temperature to -78 °C, adding the nucleophile slowly in the second step over the course of 2 hours, and letting the reaction warm up slowly overnight halted the over addition as evidenced by ^{31}P NMR and produced the intended diester with few side products. $MgSO_4$ can be added either before the second nucleophilic addition or before the last nucleophilic addition to give organophosphates **4b-I** in increased yields. Addition of $MgSO_4$ at the start of the third nucleophilic addition increased the yield of organophosphates by 8-36% as shown in **Table 2**.

Now that a yield increase was seen for the synthesis of both achiral and chiral organophosphate triesters, we turned our attention to evaluation of chiral catalysts. **Figure 4** shows several magnesium catalysts equipped with chiral ligands.

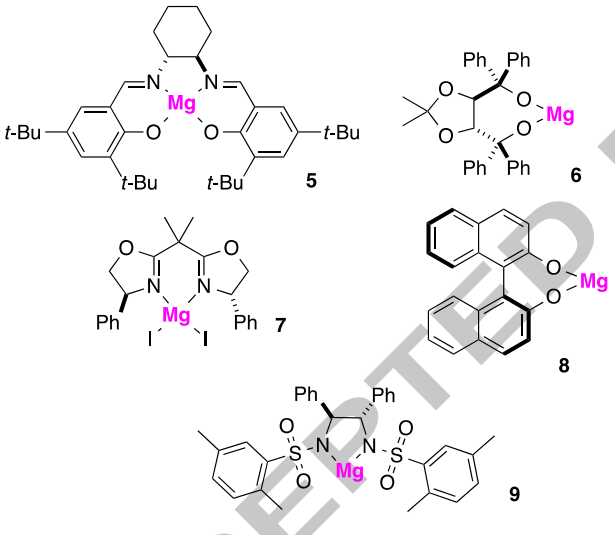


Figure 4. Chiral magnesium catalysts examined for organophosphate synthesis.

These catalysts were added to **2** before the second nucleophilic addition. While the chiral catalysts gave yields comparable to those catalyzed by $MgSO_4$, only racemic mixtures were observed by chiral HPLC (RegisPack 5 Micron, 25cm x 4.6 mm). For example, catalyst **9** gave a 62% yield of **4i** as a racemic mixture vs. 26% yield without magnesium. Thus, while the use of magnesium can enhance the yield of organophosphate triesters, it seems incapable of imparting stereochemical information.

We hypothesized that the phosphoryl chlorides were being activated by coordination of the metal center to the phosphoryl oxygen. This type of activation would be expected to increase the electrophilicity of the organophosphate towards both the second and third nucleophilic additions, which is in agreement with our experimental observations. An NMR experiment was performed on a sample containing $(PhO)POCl_2$ and $MgSO_4$ in $CDCl_3$, but no change in the ^{31}P chemical shift value was observed indicating that the reaction may be occurring by heterogeneous catalysis. However, when $(PhO)POCl_2$ was dissolved in $CDCl_3$, a change from 4.56 ppm to 4.31 ppm was observed in the ^{31}P NMR spectrum upon addition of the soluble magnesium salt MgI_2. This supports the idea that magnesium binds to the organophosphate and increases its electrophilicity. We also chose to examine the effect of magnesium on other reaction components. Addition of MgI_2 to triethyl amine did not show any significant shift in its ^{1}H NMR peaks. On the other hand, addition of MgI_2 to *p*-methoxyphenol induces several changes in the NMR spectrum such as a downfield shift of some aromatic hydrogen atoms by 0.11 ppm and a downfield shift of the OH signal by nearly 2 ppm. Based on the NMR data, we propose that magnesium is serving two functions: first, the magnesium is coordinating to the OP and increasing its electrophilicity; secondly, the Lewis acid is also coordinating to the phenolic nucleophile and bringing it in closer proximity to the electrophile. This is depicted with MgI_2 in **Figure 5**.

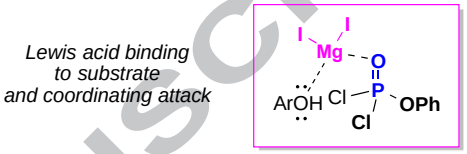


Figure 5. Possible binding modes for magnesium.

In conclusion, we have developed a new catalytic method for the synthesis of organophosphates. This new method uses $MgSO_4$ as an inexpensive catalyst and was able to synthesize 8 new aryl organophosphate triesters from the readily available and low cost precursor phosphorus oxychloride in a three-step, two-pot sequence. Yields for this method improve upon the uncatalyzed method by 8-36%. Based on NMR data, we propose that magnesium increases the electrophilic strength of organophosphates by binding to the phosphoryl oxygen and also brings oxygen-based nucleophiles in close proximity for reaction. Although none of our chiral catalysts provided any enantioselectivity, we propose that $MgSO_4$ could be used in tandem with chiral nucleophilic catalysts to activate organophosphates and improve reaction yields.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version.

Highlights

- Eight new aryl organophosphate triesters were synthesized with a $MgSO_4$ catalyst.
- Yields of phosphates were improved by 8-36% over uncatalyzed reaction.
- Chiral magnesium catalysts did not produce phosphates enantioselectively.