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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.

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.[42–45,47,62–76,40,77] 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, Hepatitis B and C, herpes, and ebola.[62–64,66,68] 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.[40,78–80,46] Like other chiral drugs, absolute configuration of stereochemistry (in this case, at phosphorus) has immense ramifications for drug performance.[81]

Creative efforts have been taken to improve upon the synthetic methodology for the construction of phosphate triesters, although stereospecific methods have been noticeably rare.[37,46,75,82–84] In general, reaction of P(V) compounds equipped with labile groups with nucleophilic attachments remains a popular method for construction of OPs.[1,46,47,67,75,40,81–84,14,85] 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 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.[75,83] 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[84] (Fig. 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

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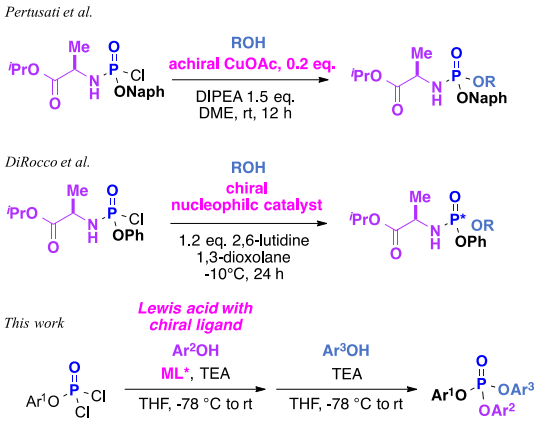


Fig. 1. Known catalytic methods with using electrophilic P(V) starting materials.

relied on internal calibration by ^{1}H NMR (literature[86] 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 phosphoramidate through catalysis with $Cu(OTf)_2$ using a prefunctionalized phosphochloridate.[46] 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.[87–90]

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 (Fig. 2). 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.[87,91,88] 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.

Results and discussion

As stated above, phosphorus 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,[92–95] 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]

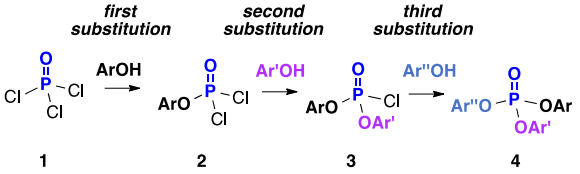
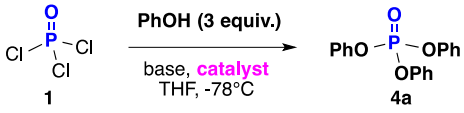


Fig. 2. General strategy for the synthesis of organophosphate triesters.

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.[96]

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 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.)

Table 1
Screening of bases and catalysts in model reaction.



Entry	Base	Catalyst	Amount	Yield*
1	TEA	–	–	55%
2	$CaCO_3$	–	–	trace
3	Proton Sponge	–	–	trace
4	Hünig's base	–	–	trace
5	Hünig's base	–	–	17%
6	TEA	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	$Pb(CF_5HF_6O_2)_2$	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.