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Phosphorylation of Alcohols with *N*-Phosphoryl Oxazolidinones Employing Copper(II) Triflate Catalysis

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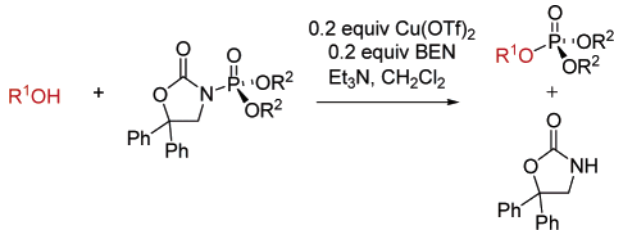
ABSTRACT



Phosphoryl transfer from *N*-phosphoryl 5,5-diphenyl oxazolidinone is efficiently catalyzed by copper(II) triflate. The utility of this method has been demonstrated in the phosphorylation of representative primary, secondary, tertiary, phenolic, and allylic alcohols. These reaction conditions are significantly milder than employing alkoxides and allow the phosphorylation of biologically relevant molecules.

Phosphate esters have been recognized in a variety of biological molecules as diverse as nucleic acids, proteins, carbohydrates, lipids, coenzymes, and steroids.[1] Given the ever blurring distinctions between molecular biology and synthetic chemistry, development of new and efficient methods for the installation of these functional groups is an important goal in organic chemistry. The methods that currently exist for the introduction of a phosphate group into a substrate molecule largely depend on the substrate itself, since functional group tolerance is the key to facilitating efficient phosphorylation.[2] For example, one of the most widely used methods for preparing oligonucleotides is through the use of a phosphoramidite reagent to form the phosphite triester, followed by oxidation to the phosphate triester.[3] Here, care must be taken with the stability of the phosphorus(III) intermediates and sensitivity of other functional groups to the oxidation protocol. Methods also exist employing phosphorus(V) reagents, usually by reaction of the substrate with a chlorophosphate, either through the formation of an alkoxide[4] or by using proton scavengers such as triethylamine.[5] Although widely used, these reaction conditions are not always compatible with the base-sensitive functional groups present in the substrate and are sometimes limited by the stability of the chlorophosphate.

We have previously reported alternative strategies to achieve the phosphoryl transfer employing $TiCl_4$ and titanium esters as catalysts and a chlorophosphate as the phosphate source.[6] We have also shown that *N*-phosphoryl oxazolidinones can be used as an effective phosphate source in the

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presence of lithium and magnesium alkoxides.[7] These reagents are attractive since they are easily prepared, have long shelf lives, and are easy to handle. However, given the need to generate highly basic alkoxides, reactions were limited to substrates with base-tolerant functional groups that could be selectively deprotonated by reactive organo-lithium and magnesium reagents. In this work, we describe progress in the development of milder reaction conditions to facilitate this process by an amalgamation of the use of Lewis acid catalysis and *N*-phosphoryl oxazolidinones.

Initially, we attempted phosphoryl transfer from 5,5-diphenyl oxazolidinone to benzyl alcohol in the presence of $TiCl_4$ according to the procedure that we developed with phosphoryl chlorides.[6a] However, no conversion of starting material was observed. Thus, the catalytic activity of a number of other Lewis acids was evaluated (Scheme 1, Table 1). All reactions were carried out in the presence of 1 equiv of Et_3N and the oxazolidinone with 0.2 equiv of catalyst under a nitrogen atmosphere at room temperature for 48 h.

Scheme 1. Reagents Used for Initial Optimization

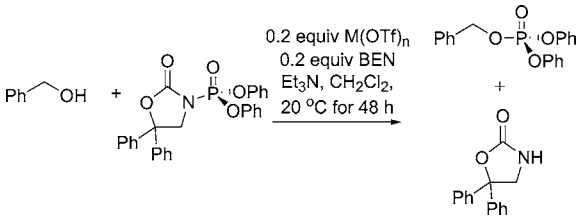

Table 1. Screening of Catalytic Activity for Phosphoryl Transfer as Described in Scheme 1[a]

catalyst $M(OTf)_n$	product (%)[b]
none	0
$Mg(OTf)_2$	50
$Gd(OTf)_3$	34
$Y(OTf)_3$	60
$Sc(OTf)_3$	10
$Eu(OTf)_3$	30
$La(OTf)_3$	20
$Cu(OTf)_2$	70

[a] Reactions performed with 1 equiv of BnOH, 1 equiv of Et_3N, 1 equiv of *N*-phosphoryl 5,5-diphenyl oxazolidinone, 0.2 of equiv $M(OTf)_n$, and 0.2 equiv of BEN in CH_2Cl_2 under a nitrogen atmosphere at 20 °C for 48 h. [b] Calculated from the ratio of the integrals corresponding to representative signals in the ^1H NMR spectrum.

Seven Lewis acids [$Cu(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$, $Eu(OTf)_3$, $Y(OTf)_3$, $Gd(OTf)_2$ and $Mg(OTf)_2$] were screened; however, no product was obtained in any case. The reaction was then repeated in the presence of 0.2 equiv of *N*,*N*′-ethylenebis(benzaldimine) (BEN) under otherwise identical conditions. The results indicated the necessity of ligand-assisted catalysis, the best catalyst being $Cu(OTf)_2$. It is interesting to note that with the exception of titanium esters, the three most active catalysts in this study were identical to those previously observed in the reaction of alcohols with chlorophosphates.[6a]

Having identified a suitable catalyst system, optimization studies were then carried out using benzyl alcohol as the test substrate (Scheme 1, Table 2).

Table 2. Optimization of Reaction Conditions for the $Cu(OTf)_2$-Catalyzed Reaction as Described in Scheme 1[a]

entry	ligand	equiv of $Cu(OTf)_2$ and ligand	base	product (%)[b]
1	none	0.2	Et_3N	0
2	**1**	0.05	Et_3N	25
3	**1**	0.1	Et_3N	50
4	**1**	0.2	Et_3N	70
5	**1**	0.3	Et_3N	80
6	**1**	0.5	Et_3N	90
7	**1**	1.0	Et_3N	95
8	**2**	0.2	Et_3N	10
9	**3**	0.2	Et_3N	15
10	**4**	0.2	Et_3N	20
11	**5**	0.2	Et_3N	40
12	**6**	0.2	Et_3N	55
13	**1**	0.2	none	0
14	**1**	0.2	2,6-lutidine	0
15	**1**	0.2	DBU	10
16	**1**	0.2	DABCO	50

[a] Reactions performed with 1 equiv of BnOH, 1 equiv of base, 1 equiv of *N*-phosphoryl 5,5-diphenyl oxazolidinone, 0.2 of equiv $Cu(OTf)_2$, and ligand in CH_2Cl_2 under a nitrogen atmosphere at 20 °C for 48 h. [b] Calculated from the ratio of the integrals corresponding to representative signals in the ^1H NMR spectrum.

Variation of the catalyst loading indicated a linear increase in the amount of $Cu(OTf)_2$ to the apparent reaction rate (Scheme 1, Table 2, entries 1−7). For further work, 0.2 equiv was chosen as the optimal catalyst loading, which provided sufficient catalytic activity with the lowest acceptable loading. In an attempt to enhance the catalytic activity further, a number of different chelating ligands[8] were also screened, again using the same oxazolidinone and benzyl alcohol

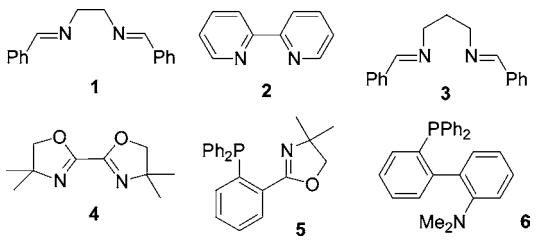

Figure 1. Ligands used in optimization of reaction conditions (Table 2).

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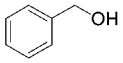
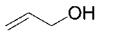
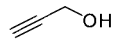
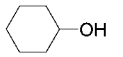
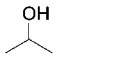
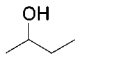
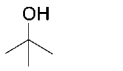
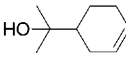
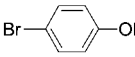
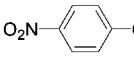
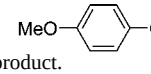
Table 3. Phosphorylation of Representative Alcohols as Described in Scheme 2

entry	time (h)	R^1OH	R^2	product (%)[a]
1	18		Et	86
			Ph	85
2	18		Et	84
			Ph	88
3	18		Et	75
			Ph	84
4	18		Et	80
			Ph	82
5	24		Et	80
			Ph	85
6	24		Et	77
			Ph	75
7	36		Et	55
			Ph	61
8	36		Et	55
			Ph	67
9	48		Et	54
			Ph	49
10	48		Et	51
			Ph	56
11	48		Et	31
			Ph	46

[a] Based on isolated product.

(Scheme 1, Table 2, entries 4 and 8−12). Although all led to rate acceleration compared to reactions conducted without these additives, BEN **1** proved to be the optimal ligand. Use of the correct base in these reactions was also crucial to their success (entries 4 and 13−16). Triethylamine gave the optimum result (entry 4), with other bases being inferior, and no reaction occurring at all without added base (entry 13).

These optimized reaction conditions were then applied to the phosphorylation of a range of representative primary, secondary, tertiary, and phenolic alcohols that had previously been evaluated with the same diethyl and diphenyl *N*-phosphoryl oxazolidinones using *n*-BuLi (Scheme 2, Table 3).[7] Pleasingly these followed the same trend in reactivity that had been reported previously. Primary and secondary alcohols (entries 1−6) led to good yields of the desired phosphate products, and even tertiary alcohols (entries 7 and 8) gave moderate yields. However, phenolic substrates (entries 9−11) once again gave moderate to low yields. In each case, the isolated yields of the diethyl phosphates were

Scheme 2. General Method for Phosphorylation

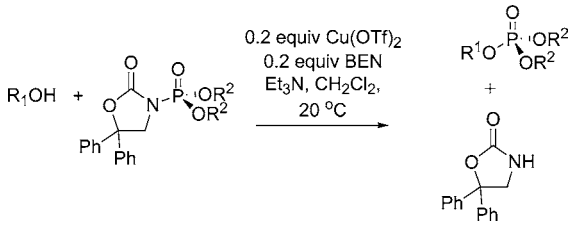
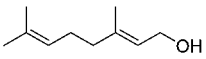
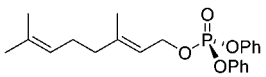
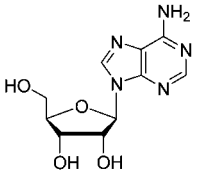
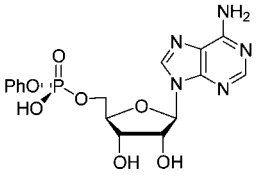
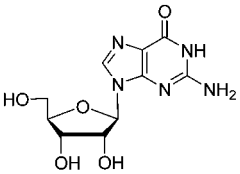
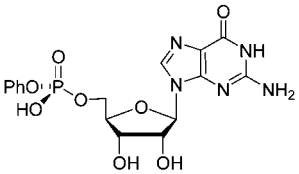
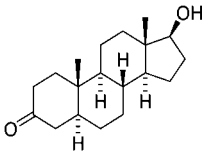
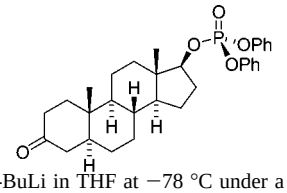


Table 4. Comparison of the Phosphorylation of Biologically Relevant Molecules with Copper Triflate and *n*-BuLi Using *N*-(5,5-Diphenyl oxazolidinyl) Diphenyl Phosphate

entry	substrate	product	yield (%) n-BuLi[a]	yield (%) $Cu(OTf)_2$[b]
1			0	92
2			5	49
3			5	54
4			0	76

[a] Reactions perfomed by pretreatment of the alcohol with 1.0 equiv of *n*-BuLi in THF at −78 °C under a nitrogen atmosphere, followed by addition of 1 equiv of *N*-phosphoryl 5,5-diphenyl oxazolidinone and stirring for 12 h. [b] Reactions performed with 1 equiv of alcohol, 1 equiv of Et_3N, 1 equiv of *N*-phosphoryl 5,5-diphenyl oxazolidinone, 0.2 equiv of $Cu(OTf)_2$, and 0.2 equiv of BEN in CH_2Cl_2 under a nitrogen atmosphere at 20 °C for 48 h.

less than those obtained using the *n*-BuLi protocol, while the yields of diphenyl phosphates were higher.[7] Thus, this method for phosphoryl transfer is more applicable to the synthesis of diphenyl phosphates than diethyl.

Having established reaction conditions that appeared general for a wide range of substrates, a direct comparison of the two procedures was made by considering substrates that appeared to be sensitive to the harsh reaction conditions of the alkoxide reaction. In all cases studied (Table 4), only minor quantities of material were obtained using the *n*-BuLi protocol. However, the $Cu(OTf)_2$ reaction conditions repeatedly gave good yields of the desired phosphate triesters. Geraniol gave the phosphate triester in exceptional yield (entry 1), and more importantly, adenosine and guanosine appeared to be phosphorylated with good chemo and regioselectivity at the 5′ hydroxyl group (entries 2 and 3), leading to phosphate diesters. These were formed by hydrolysis during purification on silica gel, eluting with a methanol/water mixture. The sterol used in this study similarly gave the desired phosphate triester only when treated with the $Cu(OTf)_2$ catalyst (entry 4).

The reaction presumably proceeds through a coordinated species analogous to reactions catalyzed by Cu(II) bound bis-oxazoline complexes.[9] The ligand-bound Cu(II) activates the P═O bond, making it susceptible to nucleophilic attack by the alcohol, and the oxazolidinone then acts as a leaving group.

In summary, we have established a catalytic route for the phosphorylation of a range of alcohols using *N*-phosphoryl oxazolidinones that is comparable to that employing alkoxide substrates. However, the strength of this new method lies in its applicability to phosphorylation of sensitive substrates.

Acknowledgment. We thank the Thai Government for a Royal Thai Scholarship (C.S.) and the University of Sheffield for support.

Supporting Information Available: Experimental details and data and copies of ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) All ligands were either purchased or prepared by literature methods. See Supporting Information for more details.

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