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Bis(dimethylamino)phosphorodiamidate: A Reagent for the Regioselective Cyclophosphorylation of *cis*-Diols Enabling One-Step Access to High-Value Target Cyclophosphates

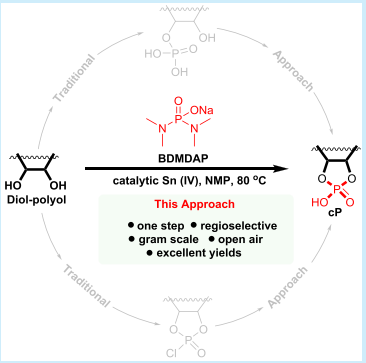
Mahipal Yadav[†,‡] and Ramanarayanan Krishnamurthy*[,†,‡]

[†]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

[‡]NSF-NASA Center for Chemical Evolution, Atlanta, Georgia 30332, United States

Supporting Information

ABSTRACT: Bis(dimethylamino)phosphorodiamidate (BDMDAP) enables an efficient and one-pot cyclophosphorylation of vicinal *cis*-diol moiety of polyol-organics of biological importance without the need for protecting group chemistry and is amenable to large-scale reactions. The utility of this reagent is demonstrated through the synthesis of high-value targets such as cyclic phosphates of *myo*-inositol, nucleosides, metabolites, and drug molecules.



Phosphate esters of organic molecules are ubiquitous in biochemistry and play a central role in many of the essential chemical processes of life.[1] They are nature's preferred modifications of all the four classes of biomolecules, i.e., carbohydrates, proteins, lipids, and nucleosides.[2] They include phosphate esters in RNA and DNA, phospholipids for membrane structure, phosphoproteins for regulation of cellular function, and phosphatidylinositol phosphates for signaling (Figure 1).[2,3] Although these phosphate esters are kinetically stable in aqueous solution at physiological pH, they are easily hydrolyzed by appropriate enzymes,[4,5] proceeding through the assistance of an adjacent hydroxyl group, resulting in cyclophosphate (cP) ester intermediates (Figure 1).[6] Many cyclophosphate intermediates play very important roles in modern biology.[7] For example, *myo*-inositol-1,2-cyclophosphate, produced by the action of enzyme phosphoinositide specific phospholipase C (PI-PLC) on the *sn*-3-phosphodiester bond of phosphatidylinositol, gives rise to inositol based signaling metabolites crucial to signal transductions and metabolic circuits.[8−13]

In another example, 2′,3′-cyclic nucleoside monophosphates, produced by enzymatic and nonenzymatic hydrolysis of RNA,[14−17] are employed in many biological studies[18−20] and synthesis of complex nucleotides.[21−25] Moreover, several glycerolipids containing the 1,2-cyclophosphate moiety form a unique class of compounds called cyclic phosphatidic acid.[26] These compounds affect numerous cellular functions and are involved in various biological activities.[26,27]

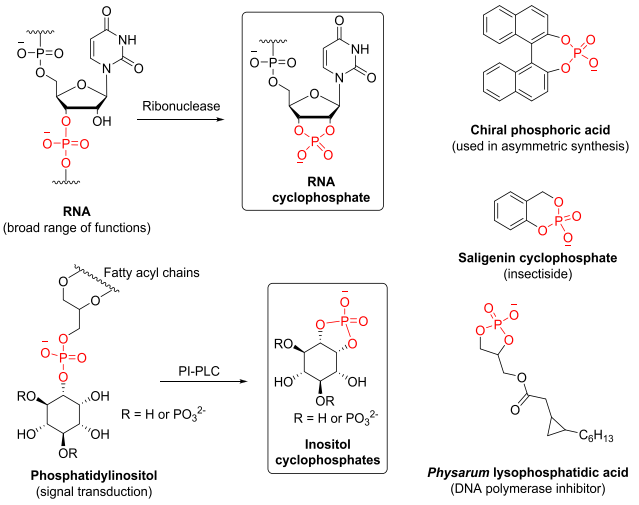


Figure 1. Representative biologically and chemically important molecules that contain a cylcophosphate group.

Apart from these biological roles, the applications of cyclophosphate compounds in organic synthesis as ligands in asymmetric synthesis and as insecticides/pesticides are well recognized (Figure 1).[28−33] These cyclophosphate derivatives are traditionally prepared either by intramolecular dehydra-

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tion/cyclization of a monophosphate derivative[34−36] or by treating the starting diol with $POCl_3$ followed by hydrolysis of the cyclophosphoryl chloride intermediate to cyclophosphate[37,38] (Figure 2). All of these traditional methods are

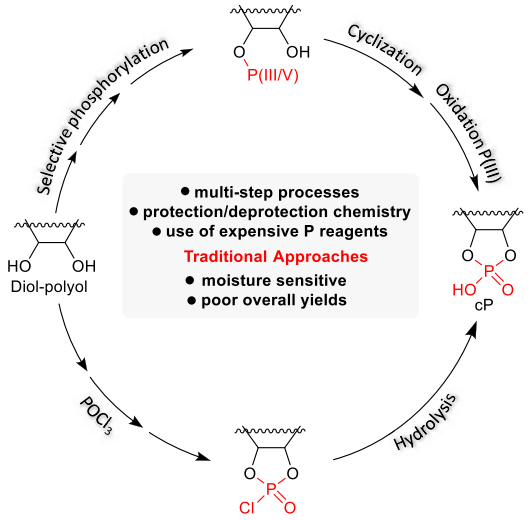


Figure 2. Traditional methods for the preparation of 1,2-cyclophosphates.

multistep processes, require anhydrous reaction conditions, and afford the final cyclic phosphodiesters in moderate to poor yields (Figure 2). Other methods have been developed over the years to address the efficiency and streamline the protocol,[39−42] however, these also require many steps for the synthesis of cyclophosphates and yields are low based on starting diols.

The problem of cyclophosphorylation becomes more acute when it comes to structures such as *myo*-inositol and carbohydrates, which have inherent structural complexity with many free hydroxyl groups. For example, there is no report of a single-step synthesis of inositol-1,2-cyclic phosphate (IcP) to date. However, considering the central role of *myo*-inositol phosphates in metabolism and signaling pathways, they are highly valuable targets for synthetic chemists.[11,43−45] Despite significant advances, most of the synthetic methods described for inositol phosphates still take more than 10 steps starting from inositol involving protection−deprotection chemistry.[11,43,45−47]

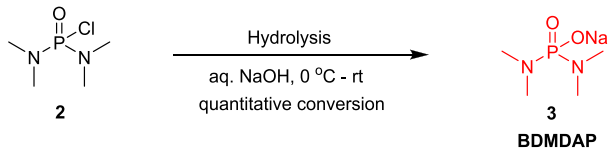
Because of its structural complexity, only a few (but unsuccessful) efforts have been made to explore the chemical-phosphorylation of unprotected inositol in one step.[48,49] Bruzik et al.[10] and Vishwakarma and co-workers[50] have demonstrated the enzymatic synthesis of various of *O*-alkyl inositol phosphates via inositol-1,2-cyclic phosphate (IcP) by using the PI-PLC enzyme. Because the enzymatic synthesis of inositol-1,2-cyclic phosphate involves the isolation of inositol phospholipids and PI-PLC from biological sources, which is not always straightforward, it is still a much sought-after goal to chemically synthesize inositol-1,2-cyclic phosphate from unprotected inositol in a single step. Similarly, all current methods for the preparation of 2′,3′-cyclic nucleoside monophosphates also have either low yield or high price, which greatly limits their further exploration and application. The easy availability of cyclic phosphates of defined structure would further biochemical investigations.

As summarized above, each of the cyclophosphorylation methods have their limits.[51] Recently, we discovered a method for cyclophosphorylation of glycerol and nucleosides in aqueous medium by diamidophosphate (DAP), without the need for protecting groups, under plausible prebiotic conditions.[52] Inspired by this result, we began investigating how best we can take advantage of the moderate reactivity of diamidophosphates, improve yields, and achieve regioselective phosphorylation of other polyols containing *cis*-diol moiety (particularly inositol) in a regioselective fashion, without any protection−deprotection chemistry. After several attempts, we developed the bis(dimethyl) version of DAP (BDMDAP, **3**) as a cyclophosphorylating reagent for the synthesis of cyclophosphates of diols in one step with excellent yields.

Primarily motivated by the importance of inositol phosphates, we started our study to identify optimal conditions for cyclophosphorylation of *myo*-inositol by using diamidophosphate (DAP) as a phosphorylating reagent. All attempts toward regioselective 1,2-cyclophosphorylation of *myo*-inositol **1** by using our previously developed standard phosphorylation conditions with diamidophosphate (DAP)[52] in H_2O were unsuccessful; *myo*-inositol was unchanged, but DAP was hydrolyzed to various inorganic phosphates (Supporting Information (SI), Table 1). *myo*-Inositol and DAP under the low water activity "paste conditions" showed some formation of cyclophosphates (according to ^{31}P NMR), but conversion to the product was poor (SI, Table 1).

Then we explored variants of DAP with better leaving groups for the phosphorylation reaction. Because the phosphorylation is initiated by protonation of the NH_2 group on DAP, we reasoned that making the amino group more basic would make it more reactive. Therefore, we synthesized bis(dimethylamino)-phosphorodiamidate (BDMDAP) by the aq NaOH mediated hydrolysis of commercially available bis(dimethylamino) phosphorochloridate (Scheme 1). BDMDAP has been known in the literature, however, its utility as a phosphorylating reagent has never been explored.[53]

Scheme 1. Synthesis of Bis(dimethylamino)phosphorodiamidate (BDMDAP)[a,b]



[a]Reagents and conditions: **2** (10 mmol), aq NaOH (2 M solution, 21 mmol, 2.1 equiv) for 1 h. [b]Conversion yields were calculated based on ^{1}H, ^{13}C, and ^{31}P NMR.

We determined the pK_a of BDMDAP to be 6.6 (SI, Figure 1), which suggested that it may be suitable for phosphorylation when compared to DAP (pK_a 5.5).[52] The phosphorylation of *myo*-inositol **1** with BDMDAP **3** in aqueous solution or under "paste conditions", under various pH (5.5−7.0) and with imidazole, however, did not afford the cyclic product **4** (SI, Table 2, entries 1−4) and exploration of other solvents (NMP: *N*-methyl-2-pyrrolidone) and Lewis acids resulted in meager conversion to **4** or gave complex mixtures of cyclic phosphates (SI, Table 2, entries 5−10).

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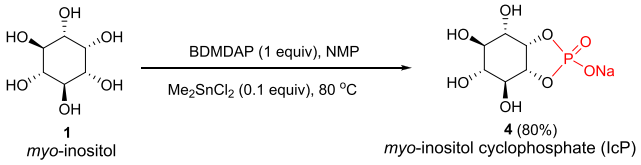
To resolve the regioselectivity issue, we employed the Sn (IV) catalysts because Sn (IV) catalysts are known to form the complex with *cis*-diols in a regioselective manner and increase their reactivity.[54] After systematic exploratory experiments (varying the equivalents of BDMDAP, temperature, solvents, and activators; SI, Table 2), we found that 1 equiv of BDMDAP in NMP as solvent at 80 °C afforded 75% conversion to cyclophosphate product **4** (SI, Table 2, entry 19). The use of tin catalyst Me_2SnCl_2 in place of Bu_2SnO improved the conversion to **4** (80%) (Scheme 2 and SI, Table 2, entry 20); reaction under argon atmosphere did not show any further improvement in yield of the reaction, suggesting that the reaction is insensitive to presence of air-moisture (SI, Table 2, entry 21). No extra precautions (such as dry solvents or oven-dried flasks) were found to be necessary for the reaction to proceed in an efficient manner.

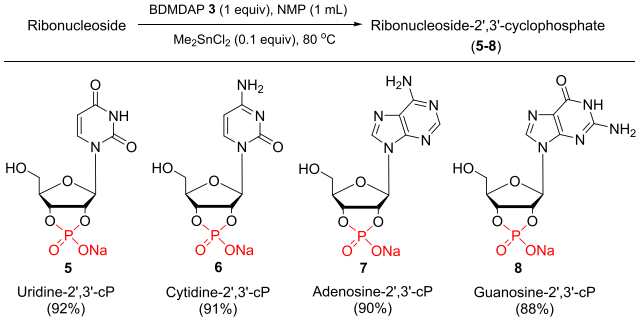
Scheme 2. Regioselective Cyclophosphorylation of *myo*-Inositol with BDMDAP[a,b]



[a]Reagents and conditions: **1** (0.2 mmol), BDMDAP (1 equiv) and Me_2SnCl_2 (0.1 equiv) in NMP solvent (1.0 mL) for 12 h. [b]Isolated yield.

With the optimized conditions for *myo*-inositol cyclophosphorylation in hand, we applied the protocol to RNA nucleosides to investigate the general applicability of our method. Satisfyingly, all four canonical nucleosides afforded the corresponding 2′,3′-cylcophosphates **5**–**8** in excellent (88–92%) isolated yields without the need for any further optimization of the reaction conditions (Scheme 3). We did not observe any phosphorylation at the sterically less hindered 5′-OH position nor on the nucleobases, thus eliminating the need for protecting group manipulations. Notably, because of the clean reaction and high conversion, the purification (Sephadex, ion-exchange column chromatography) of all the cyclophosphate products was straightforward. The reaction mixture was dissolved in an equal amount of H_2O (without removal of the NMP solvent in vacuo) and loaded directly on the ion-exchange column and eluted with buffer to afford pure cyclophosphate products.

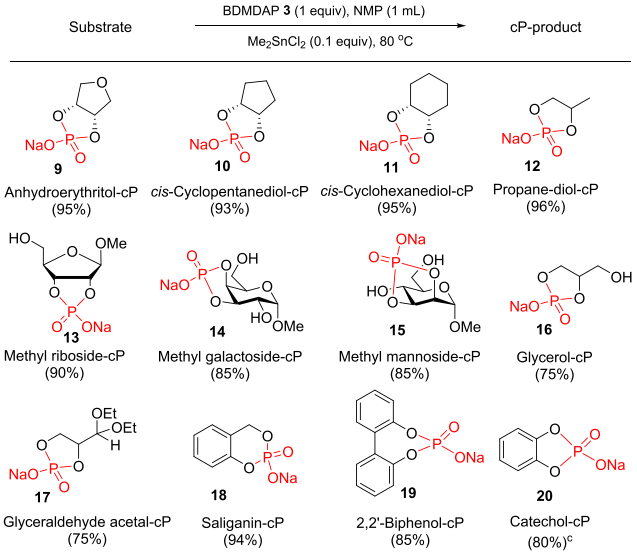
Scheme 3. Cyclophosphorylation of Ribonucleosides with BDMDAP[a,b]



[a]Reagents and conditions: nucleoside (0.5 mmol), BDMDAP (1 equiv), Me_2SnCl_2 (0.1 equiv) in NMP as solvent (1.0 mL) at 80 °C for 8 h. [b]Isolated yields from ion-exchange column chromatography.

To understand the scope of this BDMDAP-phosphorylation protocol, *cis*-diols having different ring sizes, acid-sensitive functional groups, and phenolic groups, with varying reactivities, were investigated as substrates (Scheme 4). All of the compounds underwent the desired transformation smoothly and furnished the corresponding cyclophosphate products. For example, *cis*-diols with or without heteroatoms in the rings were cyclo-phosphorylated with the same ease to give **9**–**11** in very good (>90%) yields (Scheme 4). In the case of carbohydrates, *cis*-diols of furanosides and pyranosides formed their respective cyclophosphates in very good yields (Scheme 4). Cyclophosphates of *cis*-diols in 6-membered rings were also easily formed using BDMDAP under the optimized protocol.

Scheme 4. Cyclophosphorylation of *cis*-Diol Containing Molecules with BDMDAP[a,b,c]



[a]Reagents and conditions: substrate (0.2–0.5 mmol), BDMDAP (1 equiv), Me_2SnCl_2 (0.1 equiv) in NMP as solvent (1.0 mL) at 80 °C for 12 h. [b]Isolated yields after column chromatography. [c]Conversion yield based upon ^{31}P and ^{1}H NMR.

Saligenin cyclic phosphate esters have remarkable insecticidal and fungicidal activities,[55] and their synthesis has been challenging.[51] Our method overcomes this synthetic problem and provides a concise route to saligenin cyclic phosphates. When saligenin was reacted with BDMDAP, it afforded the desired product **18** in an excellent yield of 94% (Scheme 4). 2,2′-Biphenol also afforded the cyclophosphorylated product **19** in 85% yield. For reaction with catechol, the BDMDAP was found to hydrolyze to phosphate faster than the cyclophosphate formation, giving less than 10% conversion. We suppose that because phenolic compounds are more acidic than regular alcohols, the acidic proton of phenols protonates the amino group in BDMDAP and hydrolyzes it to orthophosphate in the reaction mixture. Therefore, we prepared BDMDAP with slightly higher pH ~13 (pH determined in aq soln) and observed that it could be successfully used for the phosphorylation of phenolic compounds. Although the cyclophosphorylation at the higher pH was efficient (80% conversion by NMR of crude reaction

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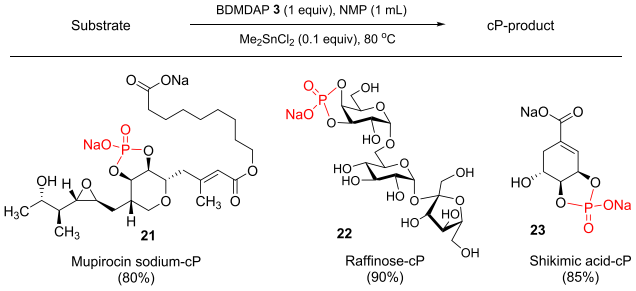
mixture), the cyclophosphate product **20** was sensitive, and we could isolate only the catechol-monophosphate **20a** (see SI). To explore the practical utility and application of BDMDAP under the present phosphorylation protocol, we also performed two representative reactions on larger scale. Reaction of *myo*-inositol (540 mg) and uridine (1 g) smoothly underwent phosphorylation and afforded the desired cyclophosphate products in isolated yields of 80% and 90%, respectively.

As alluded to in the introduction, phosphorylation is one of the most common and physiologically important modifications and phosphorylation of natural products/drugs provide important analogues for structure−activity relationship (SAR), which play a crucial role in a number of biochemical interactions.[56−59] Therefore, we applied our BDMDAP cyclophosphorylation protocols to produce cyclophosphates of three representatives of natural product and drug molecules (Scheme 5). Mupirocin is an antibiotic that targets tRNA

Scheme 5. Cyclophosphorylation of *cis*-Diol Containing Natural Products and Drug Molecules with BDMDAP[a,b]



[a]Reagents and conditions: substrate (0.05−0.5 mmol), BDMDAP **3** (1 equiv), Me_2SnCl_2 (0.1 equiv) in NMP as solvent (1.0 mL) at 80 °C for 12 h. [b]Isolated yields.

synthetase and is a complex molecule and has several functional groups, i.e., carboxylate, ester, epoxide, and an unsaturated double bond.[60] Using the optimized BDMDAP protocol, the corresponding cyclophosphorylated derivative of mupirocin, **21** was formed in a good yield of 80% (Scheme 5), reflecting the wide range of functional group compatible with, and tolerated under, the phosphorylation protocol. The next target raffinose, a naturally occurring trisaccharide (serving many functions in plants)[61] with a myriad of secondary and primary hydroxyl groups, ketal/acetal linkages and a *cis*-diol was investigated with BDMDAP. Phosphorylation of raffinose produced the cyclophosphate product **22** in an excellent yield and highly regioselective fashion (Scheme 5). The last target was shikimic acid, an important metabolite found in plants and microorganisms (but not in animals), connecting carbohydrates and essential aromatic amino acids in a metabolic pathway, which involves phosphorylation of shikimate at 3-hydroxyl group as an important step.[62] BDMDAP treatment of sodium shikimate also delivered the cyclophosphate product **23** in a high yield (Scheme 5). Shikimate cyclophosphate could serve as a starting point, as a potential candidate, for various biological and medicinal studies. It is noteworthy that only the *cis*-diols of **22** and **23** are reactive toward BDMDAP under these conditions.

Upon the basis of the literature precedents,[63] the cyclophosphorylation of the *cis*-diols could proceed via two possible mechanisms (SI, Scheme 1). This involves the formation of the cyclic stannylene acetal or the dichlorostannane complex with the *cis*-diol, which then exchanges in a stepwise fashion with the $P-N(Me)_2$ bonds of BDMDAP to form the cyclicphosphate with the release of methylamine, regenerating the Me_2SnCl to start the next cycle of reaction.

In conclusion, we have developed BDMDAP as an efficient reagent for regioselective and one-step cyclophosphorylation of *cis*-diol containing polyhydroxy compounds. This method affords excellent yields of cyclophophorylated products from a wide variety of high value target substrates including *myo*-inositol and nucleosides. The optimized conditions presented herein are operationally simple (no protecting groups are necessary), scalable, and provide a convenient choice when compared to conventional phosphorylating reagents such as phosphoryl chloride and its derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02694.

Experimental procedures, compound characterization data, mechanistic hypothesis, and ^1H, ^{13}C, and ^{31}P NMR (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rkrishna@scripps.edu.

ORCID

Mahipal Yadav: 0000-0003-4394-9737

Ramanarayanan Krishnamurthy: 0000-0001-5238-610X

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Albert Eschenmoser on his 94th birthday.

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