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Mild and Chemoselective Phosphorylation of Alcohols Using a Ψ-Reagent

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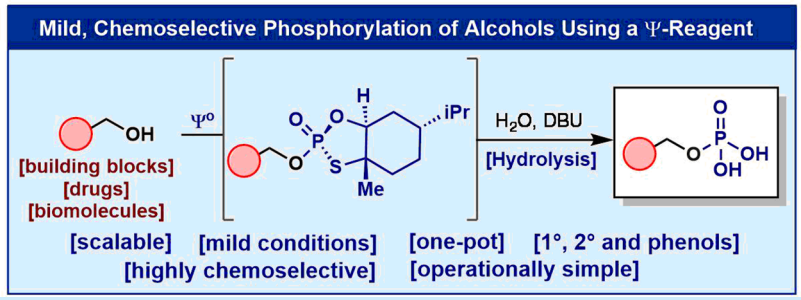

ABSTRACT: An operationally simple, scalable, and chemoselective method for the direct phosphorylation of alcohols using a P(V)-approach based on the Ψ-reagent platform is disclosed. The method features a broad substrate scope of utility in both simple and complex settings and provides access to valuable phosphorylated alcohols that would be otherwise difficult to obtain.

Phosphorylation of alcohol-containing biomolecules is one of Nature's most simple methods for regulating cell circuitry.[1] Introduction of a phosphate group can also be critical in the medicinal,[2] agrochemical,[3] and materials areas.[4] Biological enzymatic phosphorylation overcomes thermodynamic barriers to achieve selective functionalization through molecular recognition and by lowering the activation energy of the P−O bond forming step.[5] Current purely chemical alcohol phosphorylation methods all suffer from various limitations and/or multistep processes (Figure 1).[6−10] For example, the use of P(III)-based phosphoramidites requires a three step process for installation including protecting group removal and oxidation.[7] P(V)-based strategies such as the use of $POCl_3$ and derivatives thereof can be problematic due to over reactivity (often producing mixtures of mono-, di-, and trialkylphosphates) and protecting group manipulations.[8] The direct use of phosphoric acid requires high temperatures and exhibits a limited scope due to the high acidity and harsh conditions.[9] Activation methods used in concert with phosphoric acid or its salts have been employed with limited scope.[10] The recently reported bioinspired method based on an enzymatically produced P(V)-reagent (PEP-K) solves many of these problems despite requiring its use in excess at 100 °C.[11] However, like all known methods it suffers from a lack of chemoselectivity (in this case free amines are not tolerated). The recently disclosed P(V)-based Ψ-platform for the construction of P-linkages has been applied to the simplified synthesis of an ever-growing, diverse range of compounds such as cyclic dinucleotides,[12,13] stereopure antisense oligonucleotides,[12] methylphosphonates,[14] chiral phosphines,[14] DNA,[15] and protein bioconjugates,[16] complex alkaloids,[17] and fully chemically modified oligonucleotides using a commercial automated synthesizer.[18] As part of the ongoing Ψ-platform development, Ψ^{O} (**1**) was identified as a suitable reagent for forging phosphodiester bonds.[18] This Letter builds on those findings to highlight how the chemoselective nature of Ψ-reagents can be leveraged to access phosphates from alcohols in a mild, scalable, and operationally simple (one-pot) fashion across a wide range of alcohol substrates.

Previous work on the Ψ-platform demonstrated that these reagents facilitate formation of phosphate (or thiophosphate) linkages via stepwise nucleophilic addition of two different alcohols.[12] In a similar manner, appendage of an alcohol to the Ψ^{O} reagent to form intermediate Ψ-loaded adduct, followed by addition of water should in principle lead to the formation of monoalkyl phosphate. To explore the feasibility of this idea, alcohol **2** was chosen as a simple substrate to start optimization efforts (Figure 2A). In fully optimized form, the reaction

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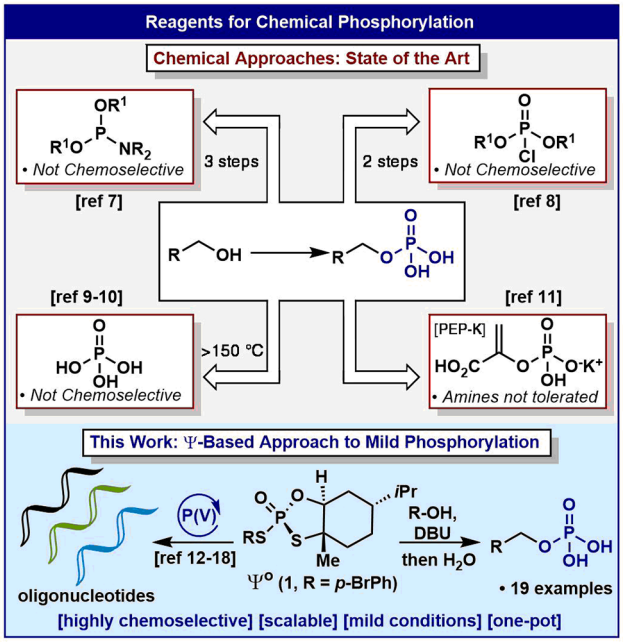
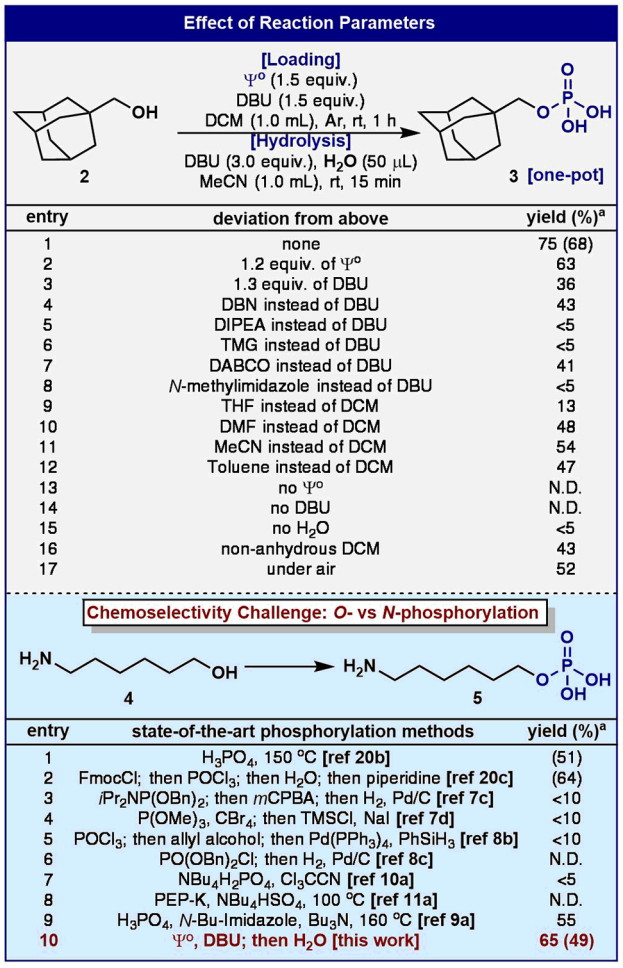


Figure 1. Alcohol phosphorylation: literature precedents, limitations, and a mild solution using the Ψ^{O} reagent (**1**).



entry	deviation from above	yield (%)[a]
1	none	75 (68)
2	1.2 equiv. of Ψ°	63
3	1.3 equiv. of DBU	36
4	DBN instead of DBU	43
5	DIPEA instead of DBU	<5
6	TMG instead of DBU	<5
7	DABCO instead of DBU	41
8	*N*-methylimidazole instead of DBU	<5
9	THF instead of DCM	13
10	DMF instead of DCM	48
11	MeCN instead of DCM	54
12	Toluene instead of DCM	47
13	no Ψ°	N.D.
14	no DBU	N.D.
15	no H_2O	<5
16	non-anhydrous DCM	43
17	under air	52

entry	state-of-the-art phosphorylation methods	yield (%)[a]
1	H_3PO_4, 150 °C [ref 20b]	(51)
2	FmocCl; then $POCl_3$; then H_2O; then piperidine [ref 20c]	(64)
3	$iPr_2NP(OBn)_2$; then *m*CPBA; then H_2, Pd/C [ref 7c]	<10
4	$P(OMe)_3$, CBr_4; then TMSCl, NaI [ref 7d]	<10
5	$POCl_3$; then allyl alcohol; then $Pd(PPh_3)_4$, $PhSiH_3$ [ref 8b]	<10
6	$PO(OBn)_2Cl$; then H_2, Pd/C [ref 8c]	N.D.
7	$NBu_4H_2PO_4$, Cl_3CCN [ref 10a]	<5
8	PEP-K, NBu_4HSO_4, 100 °C [ref 11a]	N.D.
9	H_3PO_4, *N*-Bu-Imidazole, Bu_3N, 160 °C [ref 9a]	55
10	Ψ°, DBU; then H_2O [this work]	65 (49)

Figure 2. (A) Optimization of Ψ-based alcohol phosphorylation and (B) its use in the selective *O*-phosphorylation of aminoalcohol **4**. [a]Yields determined by quantitative ^{31}P NMR (see the Supporting Information). Isolated yields in brackets. DABCO – 1,4-diazabicyclo[2.2.2]octane; DIPEA – *N*,*N*-diisopropylethylamine; DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN – 1,5-diazabicyclo[4.3.0]non-5-ene; TMG – 1,1,3,3-tetramethylguanidine.

requires 1.5 equiv of Ψ^{O} and DBU as lower quantities lead to diminished yield due to formation of double addition products (dialkyl phosphates, Figure 2A, entry 2) or decreased conversion (Figure 2A, entry 3). Consistent with prior findings, the reaction performs best with DBU as a base although DBN and DABCO furnish product in diminished yield (Figure 2A, entries 4–8). The best conversions are achieved in anhydrous DCM although MeCN or DMF can be used with only slightly lower yields (Figure 2A, entries 9–12). Unsurprisingly, control experiments confirm the need for Ψ^{O} and base for initial P–O bond formation, and H_2O for the hydrolysis step (Figure 2A, entries 13–15). The reaction can be performed without using anhydrous solvent and open to air but affords the desired product with diminished yield due to competing hydrolysis of Ψ^{O} reagent during loading step (Figure 2A, entries 16 and 17).

ϖ-Aminoalkyl dihydrogen phosphates and their salts are used as active ingredients in cosmetics, promoting fibroblast proliferation and collagen biosynthesis.[19] They are also employed in biochemistry as linkers for bioconjugates.[20] However, their availability is hampered by inconvenient synthetic routes. For instance, compound **5** was previously synthesized in 51% isolated yield (only melting point and elemental analysis reported) by condensation with crystalline H_3PO_4 at 150 °C under high vacuum (Figure 2B, entry 1).[20b] Milder routes to phosphate **5** require Fmoc-protection of the amine functionality, followed by phosphorylation by $POCl_3$ and deprotection (64% over 3 steps, entry 2).[20c] As it is known that Ψ reagents are exquisitely *O*-selective,[16] the chemoselectivity of the direct phosphorylation in the context of ϖ-aminoalcohol **4** was examined. We started by surveying 7 literature conditions, and out of those reported protocols, six delivered little to no observable **5** with the main byproduct being both *N*- and *O*-phosphorylation as part of a complex mixture (Figure 2B, entries 3–8). Only the harsh conditions of phosphoric acid at 160 °C delivered synthetically useful yields in our hands (entry 9) likely due to the *in situ* protonation of the amine. In stark contrast, our newly developed conditions using **1** followed by hydrolysis cleanly provide **5** at ambient temperature (Figure 2B, entry 10). Importantly, no *N*-phosphorylated product could be observed by ^{31}P NMR.

To gain insight into the possible selectivity between different *O*-nucleophiles, competitive experiments were performed between three protected amino acids (serine, threonine, tyrosine) bearing primary, secondary, and phenolic hydroxyl groups, respectively (see the Supporting Information for details). Analysis of the results by ^{31}P NMR revealed a reactivity profile analogous to that observed during our previous study on bioconjugation.[16] Serine was phosphorylated with exquisite selectivity (>15:1) in the presence of tyrosine, indicating the viability of such an approach for selective peptide functionalization. Moreover, the Ψ^{O} reagent displayed useful levels of selectivity favoring serine over threonine (5:1).

The scope of this method was exemplified by the preparation of 19 different phosphorylated alcohols (Figure 3). It is worth noting that most of the older papers in this field present only analysis based on the melting point and elemental analysis (occasionally ^{31}P NMR). More recent disclosures, with very few notable exceptions,[8b,9b,10a,11] usually do not include

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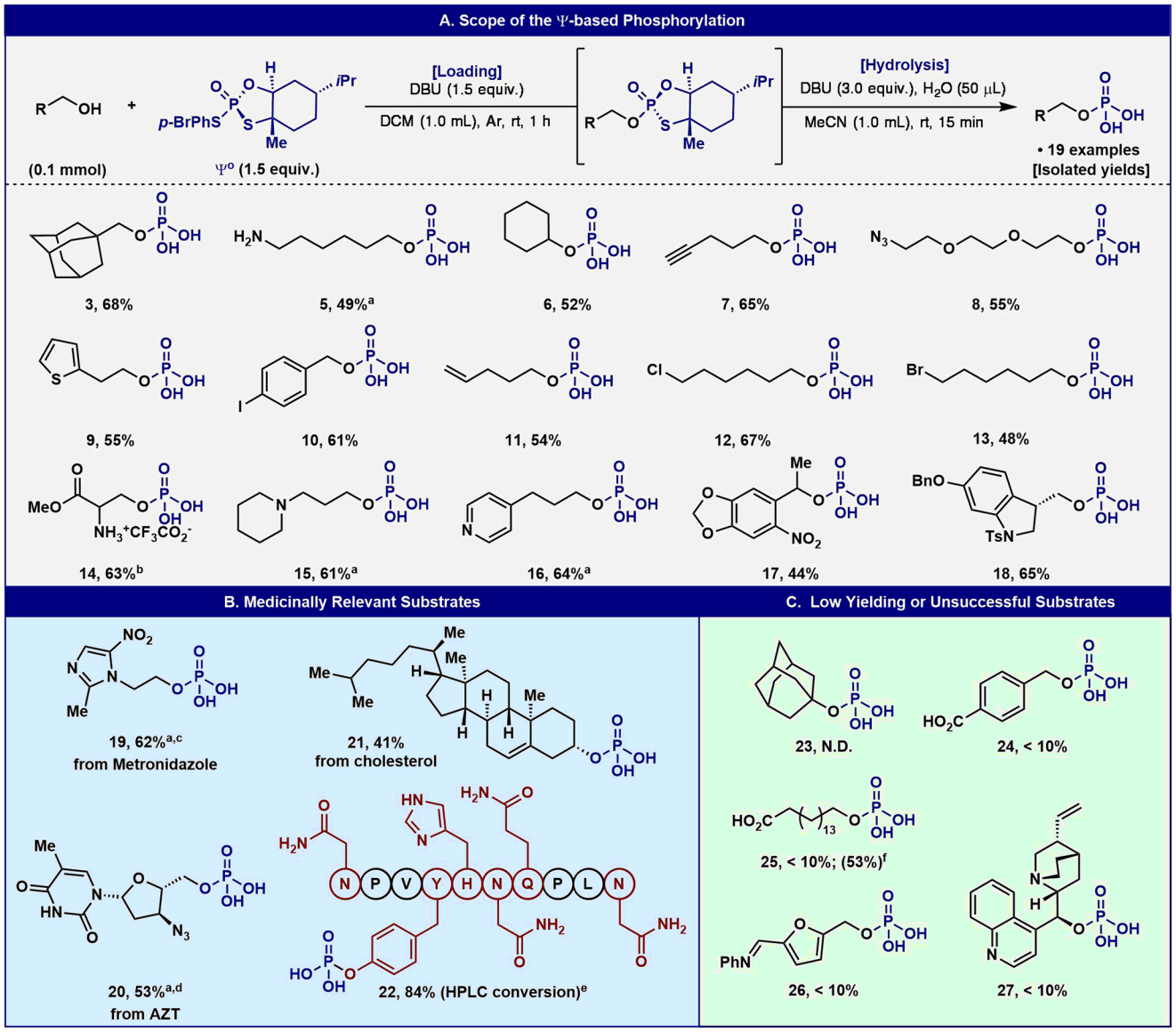

Figure 3. Scope of the Ψ-based alcohol phosphorylation method. [a]Isolated as ammonium salt. [b]From *N*-Boc Serine. [c]Reaction in DMF. [d]Reaction in MeCN. [e]Ψ^{O} (5.0 equiv), DBU (5.0 equiv), reaction in DMF on a 1.0 μmol scale. [f]DBU (2.5 equiv), reaction in DMF, NMR yield.

high resolution images of NMR spectra. It is also common that such methodology papers report only conversions instead of isolated yields, presumably due to the difficulty in handling those polar substances. To be sure, multiple methods have been reported for the purification of phosphates including HPLC,[11a] HILIC,[10a] solid phase ion exchange,[9b,10a] and recrystallization.[10b] We found that in small scale experiments HPLC was superior (see the Supporting Information for column and eluent conditions) whereas HILIC was the method of choice for larger scale preparations or for compounds that are extremely polar. In some cases, it was convenient to isolate phosphates as their ammonium salts. As indicated in Figure 3A, simple amines are tolerated in this reaction (**5**, **14**, **15**) as well as basic heterocycles (**16**, **19**). Alkynes (**7**), azides (**8**), thiophenes (**9**), aryl iodides (**10**), olefins (**11**), alkyl halides (**12**, **13**), nitro arenes (**17**, **19**), and indoline (**18**) were unscathed upon P−O bond formation. Finally, four medicinally relevant substrates were phosphorylated (Figure 3B): metronidazole (**19**), AZT (**20**), cholesterol (**21**), and a peptide containing tyrosine histidine, asparagine, and glutamine amino acids. Prior routes to some of these compounds were either laborious or contained limited experimental data such as the preparation of **7** (three steps,[21] utility in biomolecule functionalization),[22] **14** (three steps),[23] **20** (most methods <35% yield[24a] or multistep procedures[24b] with one paper showing a higher yield with $POCl_3$ and characterization based only on UV spectrum;[24c] enhanced HIV1 activity reported[25]), and **21** (one[10c] and three[26] step routes given with little characterization data). The limitations of this reaction (Figure 3C) stem from a lack of tolerance of preexisting functionality on the alcohol to basic conditions and lower nucleophilicity of sterically hindered substrates (i.e., tertiary alcohol). However, in specific cases the yield of challenging products (i.e., carboxylic acid **25**) could be improved by further modifications of the reaction conditions (see the Supporting Information for details).

The intermediate Ψ-loaded adducts can also be used for the preparation of dialkyl phosphates rather than free phosphates. As shown in Figure 4, alcohol **2** could be loaded with reagent **1** followed by addition of BnOH to deliver dialkyl phosphate **28**

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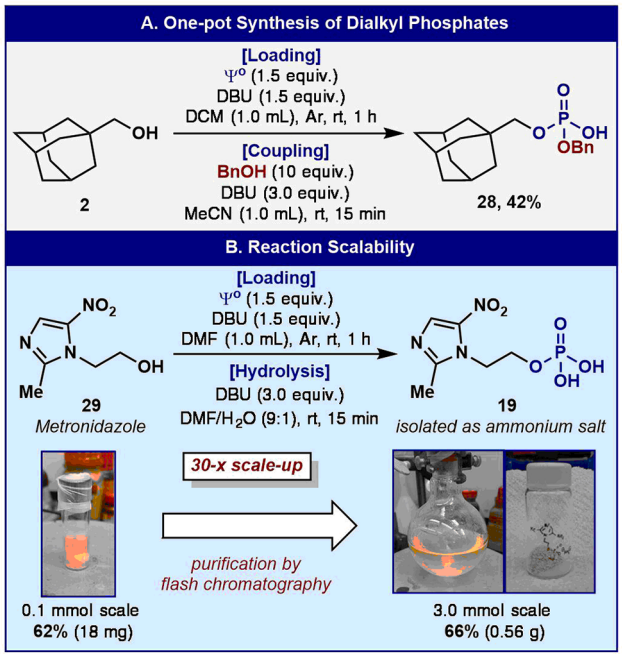

Figure 4. (A) One-pot synthesis of dialkyl phosphate **28** and (B) scale up of Ψ-based phosphorylation of metronidazole.

in 42% isolated yield (without any additional optimization). The scalability of this reaction was also demonstrated using metronidazole wherein the standard protocol (0.1 mmol scale) could be increased 30-fold while maintaining efficiency.

The operationally simple phosphorylation method described herein represents a useful addition to the toolkit for installing this important functional group in a chemoselective fashion and is yet another example of the versatility of the Ψ-platform in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02736.

FAIR data, including the primary NMR FID files, for compounds **3**, **5**−**21**, **28**, and **S9** (ZIP)

Experimental procedures, optimization details, and analytical data (^{1}H, ^{13}C, and ^{31}P NMR, HPLC, and MS) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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