JOC Article

An Improved Method for Lewis Acid Catalyzed Phosphoryl Transfer with Ti(*t*-BuO)$_4$

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Several inorganic esters have been evaluated as phosphoryl transfer catalysts. Of these, Ti(*t*-BuO)$_4$ was found to be the most effective catalyst giving excellent yields of the desired phosphate esters. The loading of the catalyst could be reduced to a little as 5 mol % for a majority of substrates with no loss in the yield of product. This methodology is significantly more versatile than using $TiCl_4$ and is suitable for the phosphorylation of more complex carbohydrates and molecules of biological interest.

Introduction

Phosphate esters play an important role in a wide variety of structurally diverse natural and biologically active compounds, from glycolipids to nucleic acids.[1] Introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes to the polarization and intermolecular bonding characteristics of that molecule. Within the pharmaceutical industry, phosphate esters are often used as pro-drugs to increase the water solubility and hence bio-availability of the agent,[2] such as the antiinflammatory agents dexamethasone and oxyphenbutazone. Given the importance of this functional group to these properties and hence potential biological activities, it is not surprising that many methods have been developed for the introduction of phosphate esters.[3] Perhaps the most widely used and most successful of all phosphorylation techniques has been the use of phosphite esters that are usually introduced via reaction of a phosphoramidite with the requisite alcohol, followed by subsequent oxidation.[4] This methodology has been well-developed and is used extensively in the construction of oligonucleotides, and the phosphoramidite reagents required for the synthesis are usually easy to prepare, but require care in handling and have limited shelf lives. Under certain circumstances oxidation of the P(III) intermediates to P(V) can be a troublesome step especially for substrates containing functional groups such as alkenes that are not tolerant to the oxidizing agents.

Aside from P(III) reagents, the most common phosphorylation reagents used are chlorophosphates.[5] These compounds are generally commercially available and are as stable as their commonly used acyl chloride counterparts to both air and moisture. The problem most commonly encountered with the use of such reagents is the conditions under which they will react. Phosphorylation is usually performed either through formation of the lithium[6] or thallium alkoxide,[7] followed by reaction with the chlorophosphate or simply by use of a proton scavenger such as pyridine[8] or Et_3N.[9] Alternatively, nucleophilic catalysis with DMAP may be employed.[10]

Recently we reported a novel method for the phosphorylation of hydroxyl groups using Lewis acid catalysis.[11] In these studies we found that the most effective catalyst for phosphoryl transfer was $TiCl_4$, giving excellent yields of the desired phosphate esters. In this work we report further studies on the use of inorganic ester based catalysts to effect this reaction and the development of an even more effective catalyst system.

Results and Discussion

During optimization of the reaction conditions in our previous studies with $TiCl_4$ as a catalyst we had observed

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(3) For a review see: Slotin, L. A. *Synthesis* **1977**, 737. Lemmen, P.; Richter, W.; Werner, B.; Karl, R.; Stumpf, R.; Ugi, I. *Synthesis* **1993**, 1.

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(10) Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169−185. Schulz, J.; Beaton, M. W.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 943.

(11) Jones, S.; Selitsianos, D. *Org. Lett.* **2002**, *4*, 3671.

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SCHEME 1

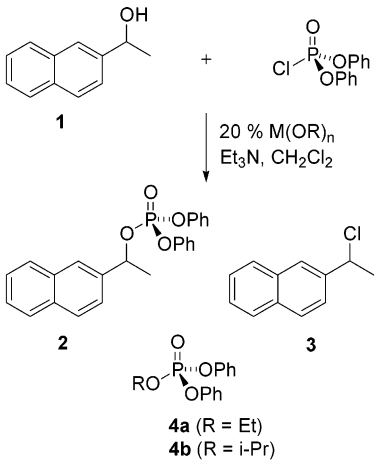

TABLE 1. Comparison of Inorganic Ester Catalysts for the Phosphorylation of 1-(2-Naphthyl)ethanol (1) with $(PhO)_2P(O)Cl$

catalyst $M(OR)_n$	conv (%)[b]	product distribution (%)[a] 2	3	4a	4b
Al(*i*-PrO)$_3$	3	1	2		0
B(OEt)$_3$	36	1	2	33	
Ti(*i*-PrO)$_4$	65	19	1		45

[a] Reactions performed with 10 mol % of catalyst, 1 equiv of Et_3N, and 1 equiv of $(PhO)_2P(O)Cl$ in CH_2Cl_2 at room temperature for 3 h. Conversion and product distribution were determined by comparison of the integrals in the ^1H NMR spectrum. [b] Refers to combined ratio of **2**, **3**, & **4a** or **4b**:**1** calculated from the ^1H NMR spectrum.

that the use of higher catalyst loadings led to a reduced yield of the desired phosphate. This implied reaction of the alcohol substrate with $TiCl_4$ to generate a titanium alkoxide that itself could act as a catalyst. However, under these circumstances, there is an increased chance of S_N2 displacement by chloride in solution thus giving rise to the excess quantities of chloride product observed. If a titanium ester were used instead of $TiCl_4$, this would lower high concentrations of chloride ions at the same time as reducing the opportunity to bind the alcohol substrate, effectively making the inorganic ester a much weaker but more sterically demanding Lewis acid than $TiCl_4$. Several inorganic esters were thus evaluated with 1-(2-naphthyl)ethanol as a test substrate (Scheme 1, Table 1). Titanium once again proved to be the most effective catalyst for this reaction, aluminum and boron esters being significantly less reactive. Formation of chloride **3** was much reduced compared to that observed with catalysts of type MCl_n; however, a problem in the reaction with the aluminum and titanium alkoxides was the formation of substantial quantities of phosphate ester **4a** or **4b** from transphosphorylation with ethanol or isopropyl alcohol originating from the catalyst.

Having established that Ti(*i*-PrO)$_4$ was indeed an active catalyst for this reaction, attempts were made to optimize the reaction conditions and maximize the amount of phosphate product formed while attempting to reduce the quantities of chloride **3** and isopropyl diphenyl phosphate **4b** formed (Table 2). Increased catalyst loadings unsurprisingly generated greater quantities of the undesired phosphate **4b**, while at lower loadings, slower

TABLE 2. Optimization of Reaction Conditions of Ti(*i*-PrO)$_4$ Catalyzed Phosphorylation of 1-(2-Naphthyl)ethanol (1) with $(PhO)_2P(O)Cl$

Ti(*i*-PrO)$_4$	time (h)	conv (%)[b]	product distribution (%)[a] 2	3	4b
1 mol %	3	6	6	0	0
5 mol %	3	21	12	0	9
10 mol %	3	68	41	0	27
20 mol %	3	68	21	10	37
50 mol %	3	56	11	0	45
100 mol %	3	53	6	0	47
20 mol %	3	61	11	12	38
20 mol %[c]	3	67	29	0	38
20 mol %[d]	3	76	19	14	43
20 mol %[e]	3	62	20	0	42
20 mol %	1	58	17	0	42
20 mol %	0.25	59	19	0	41

[a] Reactions performed with 1.0 equiv of $(PhO)_2P(O)Cl$ and 1.0 equiv of Et_3N in CH_2Cl_2 at rt. Product distribution calculated from the integrals in the ^1H NMR spectra. [b] Refers to combined ratio of **2**, **3**, & **4b**:**1** calculated from the ^1H NMR spectrum. [c] 1.5 equiv of Et_3N used. [d] 1.5 equiv of $(PhO)_2P(O)Cl$ used. [e] THF used as solvent.

reactions were observed. Formation of the chloride **3** byproduct could be prevented by adding an excess of Et_3N, which presumably removes any advantageous HCl that catalyzes this side reaction. An excess of chlorophosphate also results in formation of significant quantities of the undesired chloride **3** presumably for the same reasons, since the excess reagent generates more of the isopropyl phosphate **4b**, which in turn generates an excess of HCl compared to the amount of Et_3N present. However, no improvement was noticeable when THF was used as solvent in contrast to previous observations with $TiCl_4$ catalysis, where the yield and reaction rate were considerably enhanced when conducted in this solvent. Thus the optimized reaction conditions for this reaction were established as 20 mol % of catalyst, 1.5 equiv of Et_3N, and 1.0 equiv of chlorophosphate in CH_2Cl_2 for 3 h.

Although the conditions described above essentially gave clean conversion of the alcohol to the desired phosphate, much of the chlorophosphate added serves to phosphorylate isopropyl alcohol either by an intramolecular or intermolecular process. Therefore a catalyst with bulky alkoxide groups should significantly retard the rate of phosphoryl transfer to these groups in comparison to the alcohol substrate. Ti(*t*-BuO)$_4$ was chosen as such a catalyst as the rate of phosphorylation of the *tert*-butyl alcohol generated after transesterification should be significantly slower than that of a primary or secondary alcohol substrate. This catalyst was prepared by established literature procedures[12] and used under the optimized conditions described above. Pleasingly, the ^1H NMR spectrum of the crude reaction mixture indicated that 89% of the starting alcohol had been converted into the phosphate product. As the phosphate product **2** was unstable to column chromatography, the reaction was repeated with anthracene added as an internal standard, which confirmed that the conversion was indeed 90%. Further optimization of reaction conditions with respect to catalyst loading

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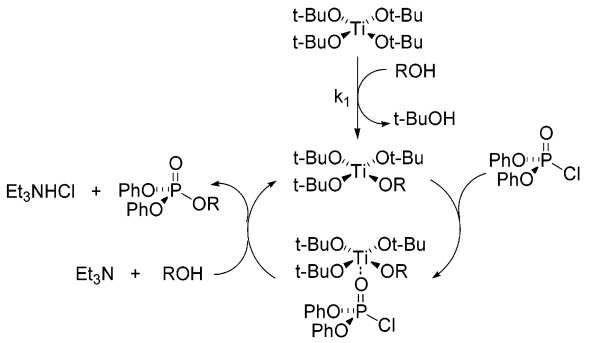
TABLE 3. Optimization of Ti(*t*-BuO)$_4$ Catalyst Loadings for the Phosphorylation of 1(2-Naphthyl)ethanol (1) with (PhO)$_2$P(O)Cl

		product distribution (%)[a]	
Ti(*t*-BuO)$_4$	conv (%)[b]	**2**	**3**
20 mol %	89	89	0
5 mol %	94	93	1
1 mol %	81	74	7

[a] Reactions performed with 1.0 equiv of (PhO)$_2$P(O)Cl and 1.5 equiv of Et$_3$N in CH_2Cl_2 at rt for 1 h. Product distribution calculated from the integrals in the ^{1}H NMR spectra. [b] Refers to combined ratio of **2** & **3**:**1** calculated from the ^{1}H NMR spectrum.

SCHEME 2

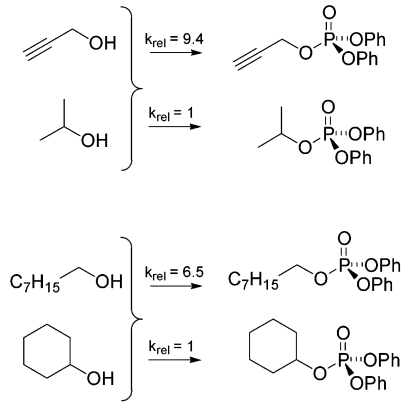


demonstrated that loadings as low as 1% could be employed in this reaction (Table 3), although routinely 5% loading was used to facilitate ease of handling substrates, reagents, and catalyst. The small quantity of chloride **3** obtained in these reactions is variable between reactions and is not problematic when applied to substrates less prone to nucleophilic displacement.

On the basis of observations with Ti(*i*-PrO)$_4$, the mechanism of this reaction is likely to proceed via a relatively fast alcohol exchange to generate a mixed titanium ester that then coordinates with the chlorophosphate, followed by intramolecular transfer of the alcohol and dissociation to regenerate the catalyst and give the phosphate product (Scheme 2). Although it is conceivable that intermolecular transfer of the alcohol is possible, analogies with previous mechanistic studies of Ti(*t*-BuO)$_4$-catalyzed transesterification reactions imply an intramolecular process.[13] In this work the rate of exchange of the alcohol moiety (i.e. k_1) was determined to be very fast, with an estimated rate constant of 10^2 M^{-1} s^{-1} at −90 °C, while modeling studies indicated a negative $\Delta S^{\ddagger}$, consistent with an intramolecular reorganization being important in the transition state. This work also implicated inverse dependence of the reaction rate on catalyst concentration, i.e., higher concentrations of catalyst resulted in lower reaction rates. This was attributed to a monomer/dimer equilibrium that favors dimer at higher concentrations where the dimer is catalytically inactive. These observations are entirely consistent with the results obtained in this study with higher concentrations (loadings) giving less product, thus implicating an active monomeric catalyst. However, one cannot exclude the possibility that higher catalyst concentrations simply facilitate nonreversible transesterification of the titanium ester, essentially removing alcohol substrate from the reaction. In practice, it is feasible that both such mechanisms may operate.

(13) Marsi, M. *Inorg. Chem.* **1988**, *27*, 3062.

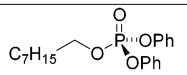
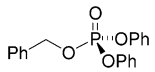
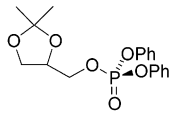
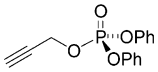
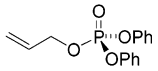
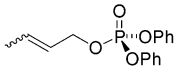
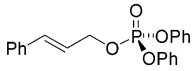
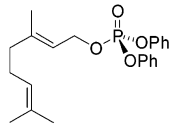
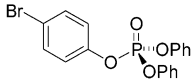
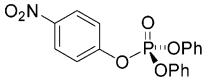
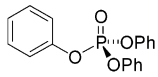
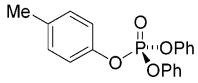
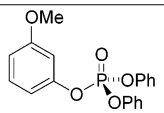
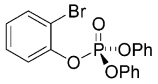
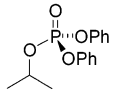
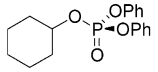
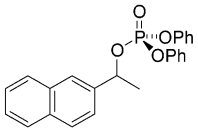
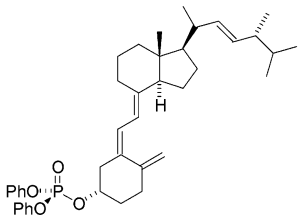
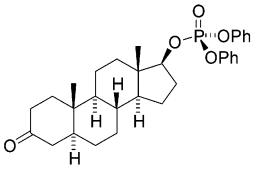
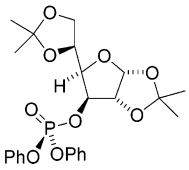
SCHEME 3



Optimized reaction conditions were found to be 5 mol % of catalyst, 1.5 equiv of Et$_3$N, and 1.0 equiv of chlorophosphate in CH_2Cl_2 for 1 h and these were applied to a series of alcohol substrates (Table 4). Furthermore, it was found that an aqueous workup procedure was not necessary for all substrates and in some cases the reaction could be filtered directly through a pad of silica and $MgSO_4$, eluting with an ethyl acetate/petroleum ether mixture, to give the desired phosphate esters without loss of yield when compared to conventional workup procedures and purification. However, this technique was not applicable to all substrates (see below). Primary alcohols in general gave excellent yields (entries 1−8) and appeared to be tolerant of acid-sensitive groups (entry 3) and simple activated alcohols (entries 4−8). Phenols were easily phosphorylated and a wide range of both electron-donating and electron-withdrawing functional groups were tolerated on the aromatic ring (entries 9−14). This is particularly useful for the introduction of phenolic protecting groups with differential phosphate ester hydrolysis rates. No evidence for disproportionation of the aryl diphenyl phosphates was detected in the analytical data accrued for these compounds. Secondary alcohols also were phosphorylated in good yield, although the naphthyl phosphate **2** was unstable to silica gel chromatography and could not be isolated in pure form (entry 17). Interestingly, more complex substrates (entries 18 and 19) required longer reaction times and more catalyst, but were transformed with this catalyst, whereas no reaction was observed with $TiCl_4$. In one case (entry 20) the diphenyl phosphate products were unstable and decomposed after standing for prolonged periods of time. However, this method does provide one of the more convenient methods for the synthesis of these molecules.

The phosphorylation of carbohydrate substrates (entry 20) is particularly intriguing since it raises the issue of whether selective phosphoryl transfer would be possible. This was evaluated by simple competition experiments, whereby 1 mol equiv each of a representative primary and secondary alcohol were allowed to compete with 1 mol equiv of chlorophosphate under otherwise standard reaction conditions (Scheme 3). The results indicated that selective phosphorylation of primary alcohols should be feasible and further application of this selective phosphorylation methodology is currently in progress.

TABLE 4. Yields of the Phosphorylation of Representative Primary Alcohols, Phenols, and Secondary Alcohols with $(PhO)_2P(O)Cl$

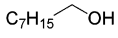
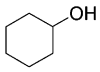
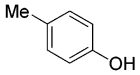
Entry	Phosphate Product		Yield (%)[a]
1		**5**	92[b,d]
2		**6**	97[b]
3		**7**	88[b]
4		**8**	98[b]
5		**9**	66[b,d]
6		**10**	90[b,g]
7		**11**	97[b]
8		**12**	86[b]
9		**13**	98[b]
10		**14**	86[c]
11		**15**	99[b]
12		**16**	87[b]
13		**17**	76[b,d]
14		**18**	74[b,d]
15		**4b**	100[b]
16		**19**	100[b]
17		**2**	97[e]
18		**20**	63[b,f]
19		**21**	56[c,f]
20		**22**	56[b,d]

[a] Reactions performed with 5 mol % of Ti(*t*-BuO)$_4$, 1.5 equiv of Et_3N, 1 equiv of $(PhO)_2P(O)Cl$ in CH_2Cl_2 at rt for 1 h. Isolated yield quoted except where stated. [b] Reaction solution filtered through a pad of silica gel and $MgSO_4$. [c] Standard aqueous workup followed by conventional silica gel chromatography. [d] Yield after additional column chromatography. [e] Product of reaction unstable to silica gel chromatography. Yield established by use of anthracene as an internal standard. [f] Reaction conducted at 10 mol % of catalyst for 20 h. [g] Obtained as a 9:1 mixture of *E* and *Z* isomers from crotyl alcohol (*E*:*Z* = 9:1).

The catalyzed reaction was compared with the background reaction rate conducted without Ti(*t*-BuO)$_4$ and also the classical procedure with the chlorophosphate in pyridine (Table 5), using representative primary, secondary, and phenolic substrates for comparison purposes. Samples were removed at 5 min and 1 h to compare the reactivity and relative reaction rates since the progress of each example in Table 4 was not monitored. Although a significant uncatalyzed reaction was observed in the case of a reactive primary alcohol such as *n*-octanol, the catalyzed reaction was found to be even faster than those conducted in pyridine. Much more noticeable levels of catalysis were observed with the secondary alcohol cyclohexanol, the catalyzed reaction being almost complete within 5 min, whereas no product was obtained from the uncatalyzed reaction and only moderate amounts of product were obtained from the reaction conducted in pyridine after 1 h. Results from reactions involving *p*-cresol were similar to those for primary alcohols, except for those conducted in pyridine which were significantly slower than the catalyzed or uncatalyzed reactions.

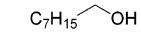
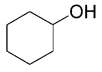
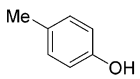
The reaction was found to be applicable to other commercially available chlorophosphates such as diethyl and dimethyl analogues. Representative primary, sec-

TABLE 5. Comparison of the Relative Rates of Phosphorylation of Primary, Secondary, and Phenolic Substrates with and without Ti(*t*-BuO)$_4$ and in the Presence of Pyridine

Substrate	Conditions[a]	Product (%)[b] (t = 5 min)	Product (%)[b] (t = 1 h)
	A	88	100
	B	20	81
	C	81	77
	A	95	100
	B	0	56
	C	50	63
	A	64	91
	B	43	81
	C	16	31

[a] Reaction conditions as follows: A—Reaction performed with 5 mol % of Ti(*t*-BuO)$_4$, 1.5 equiv of Et_3N, 1 equiv of $(PhO)_2P(O)Cl$ in CH_2Cl_2 at rt. Samples removed were filtered directly through a plug of silica gel and $MgSO_4$, washed with EtOAc, then evaporated. B—Reaction performed with 1.5 equiv of Et_3N, 1 equiv of $(PhO)_2P(O)Cl$ in CH_2Cl_2 at rt. Samples removed were filtered directly through a plug of silica gel and $MgSO_4$, washed with EtOAc, then evaporated and dried before analysis. C—Reactions performed with 1.25 equiv of $(PhO)_2P(O)Cl$ in pyridine (0.5 mL/mmol). Samples removed were quenched with H_2O and extracted twice with EtOAc, and the organic extracts were washed twice with 1 M HCl and H_2O and dried over $MgSO_4$. Samples were filtered, evaporated, and dried before analysis. [b] Calculated from the ratio of the integrals in the ^1H NMR spectrum.

TABLE 6. Comparison of the Ti(*t*-BuO)$_4$-Catalyzed Phosphorylation of Primary, Secondary, and Phenolic Substrates with $(EtO)_2P(O)Cl$ and $(MeO)_2P(O)Cl$

Substrate	Product (%)[a] $(MeO)_2P(O)Cl$	Product (%)[a] $(EtO)_2P(O)Cl$
	42[b]	81[b]
	38[b]	90[b]
	33[c]	64[c]

[a] Reactions performed with 5 mol % of Ti(*t*-BuO)$_4$, 1.5 equiv of Et_3N, 1 equiv of $(RO)_2P(O)Cl$ in CH_2Cl_2 at rt for 1 h. Isolated yields are reported. [b] The reaction solution was filtered directly through a plug of silica gel and $MgSO_4$, washed with EtOAc, and evaporated. Conventional silica gel chromatography was used. [c] Aqueous workup was employed followed by conventional silica gel chromatography.

ondary, and phenolic substrates were phosphorylated in good isolated yield (Table 6), although isolated yields of the dimethyl phosphates were considerably lower than those of the corresponding diethyl analogues due to difficulties in purifying these compounds by silica gel chromatography. The small range of chlorophosphates used here allows for a diverse range of existing protecting group strategies to be employed. Thus diphenyl phosphates may be cleaved by hydrogenolysis with PtO_2 as a catalyst in the presence of secondary stereogenic centers[14] and diethyl phosphates in the presence of phenols with TMSBr.[15] Chemoselective deprotection of dimethyl and diethyl phosphates has also been reported.[16]

In conclusion we have further developed the use of a Lewis acid catalyst to effect phosphoryl transfer and have extended the scope to substrates not suited to $TiCl_4$ catalysis, such as carbohydrate and polyprenyl substrates. Although the range of substrates evaluated here is not exhaustive, the reactions appear quite general, the only problematical ones encountered to date being those that are not soluble in THF or CH_2Cl_2 solvents.

Experimental Section

Titanium *tert*-Butoxide.[12] Dry *tert*-butyl acetate (148.0 mmol, 10.00 cm^3) was added to titanium isoproproxide (33.8 mmol, 5.00 cm^3) via syringe and heated with an oil bath at 120 °C under nitrogen. Isopropyl acetate was removed by distillation at 95 °C. After cooling, a further portion of *tert*-butyl acetate (74.0 mmol, 5.00 cm^3) was added via syringe and the solution was heated to 120 °C to remove isopropyl acetate and excess *tert*-butyl acetate. Titanium *tert*-butoxide was distilled at 80 °C/0.4 mmHg. δ_H (10.40 g, 91%); δ_H (300 MHz; $CDCl_3$) 1.31 (s, 36H).

3-Methoxyphenyl Diphenyl Phosphate (17). 3-Methoxyphenol (2.50 mmol, 0.27 mL) was added to a solution of titanium *tert*-butoxide (5 mol %, 0.05 mL) in dry CH_2Cl_2 (12.5 mL) under nitrogen. Et_3N (3.75 mmol, 0.52 mL) and diphenyl chlorophosphate (2.50 mmol, 0.52 mL) were added sequentially via syringe. The reaction mixture was stirred at room temperature for 1 h before being filtered through a layered plug of silica and $MgSO_4$ (ratio 20:1). Washing with EtOAc in petrol (35%, 50 mL) followed by evaporation yielded the crude phosphorylated product (0.85 g). Additional silica gel chromatography (20% EtOAc in petrol 40−60) provided pure phosphorylated product (0.65 g, 76%). IR (film) 1610 (s), 1590 (s), 1490 (s), 1440 (s), 1270 (s), 1220 (s), 1070 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.19 (m, 4H), 7.16−7.07 (m, 7H), 6.75 (m, 1H), 6.66−6.60 (m, 2H), 3.61 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.1, 151.8 (d, J_{C-P} = 7.2 Hz), 150.8 (d, J_{C-P} = 7.5 Hz), 130.6, 130.3, 126.4, 120.5 (d, J_{C-P} = 5.0 Hz), 112.6 (d, J_{C-P} = 4.8 Hz), 112.0, 106.6 (d, J_{C-P} = 5.3 Hz), 55.8; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −17.39; EI-MS *m*/*z* 356 (M^+, 100), 292 (18), 250 (32), 200 (6), 170 (15), 124 (18), 94 (34), 77 (25); exact mass calcd for $C_{19}H_{17}O_5P$ 356.0814, found 356.0815. Anal. Calcd for $C_{19}H_{17}O_5P$: C, 64.05; H, 4.81. Found: C, 64.24; H, 4.65.

2-Bromophenyl Diphenyl Phosphate (18). 2-Bromophenol (2.50 mmol, 0.29 mL) was added to a solution of titanium *tert*-butoxide (5 mol %, 0.05 mL) in dry CH_2Cl_2 (12.5 mL) under nitrogen. Et_3N (3.75 mmol, 0.52 mL) and diphenyl chlorophosphate (2.50 mmol, 0.52 mL) were added sequentially via syringe. The reaction mixture was stirred at room temperature for 1 h then filtered through a layered plug of silica and $MgSO_4$ (ratio 20:1). Washing with EtOAc in petrol (35%, 50 mL) followed by evaporation yielded the crude phosphorylated

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product (0.99 g). Additional silica gel chromatography (7% EtOAc in petrol 40−60) provided pure phosphorylated product (0.75 g, 74%). IR (film) 1589 (s), 1488 (s), 1475 (s), 1311 (s), 1200 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.49 (m, 1H), 7.40−7.25 (m, 11H), 7.09 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.7 (d, $J_{C-P} = 7.7$ Hz), 148.1 (d, $J_{C-P} = 6.1$ Hz), 134.3, 130.3, 129.1, 127.1, 126.2, 121.6 (d, $J_{C-P} = 2.3$ Hz), 120.6 (d, $J_{C-P} = 4.8$ Hz), 114.8 (d, $J_{C-P} = 8.5$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −17.26; EI-MS *m*/*z* 404 (M^+, 8), 326 (21), 325 (100), 77 (22); exact mass calcd for $C_{18}H_{14}BrO_4$ 403.9813, found 403.9799. Anal. Calcd for $C_{18}H_{14}BrO_4$: C, 53.36; H, 3.48. Found: C, 53.36; H, 3.56.

Ergocalciferol Diphenyl Phosphate (20). Ergocalciferol (0.25 mmol, 0.10 g) was added to a solution of titanium *tert*-butoxide (0.1 M, 10 mol %, 0.25 mL) in dry CH_2Cl_2 (1.25 mL) under nitrogen. Et_3N (0.38 mmol, 0.05 mL) and diphenyl chlorophosphate (0.25 mmol, 0.05 mL) were added sequentially via syringe. The reaction mixture was stirred at room temperature for 20 h before being filtered through a layered plug of silica and $MgSO_4$ (ratio 20:1). Washing with EtOAc in petrol (35%, 50 mL) followed by evaporation yielded the pure phosphorylated product (0.10 g, 63%). $[\alpha]_D$ +34.3 (c 1.4, $CHCl_3$); IR (film) 2995 (m), 1580 (m), 1480 (m), 1390 (m), 1005 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.21 (m, 4H), 7.18−7.07 (m, 6H), 6.09 (d, $J = 11.2$ Hz, 1H), 5.91 (d, $J = 11.2$ Hz, 1H), 5.11 (m, 2H), 4.98 (m, 1H), 4.81−4.70 (m, 2H), 2.70−1.14 (m, 21H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H), 0.70 (d, $J = 6.8$ Hz, 3H), 0.49 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.0 (d, $J_{C-P} = 7.2$ Hz), 144.4, 143.1, 136.0, 133.7, 132.3, 130.1, 125.6, 123.6, 120.6 (d, $J_{C-P} = 3.5$ Hz), 117.8, 113.4, 78.4 (d, $J_{C-P} = 6.3$ Hz), 56.9, 46.2, 43.9 (d, $J_{C-P} = 4.6$ Hz), 43.2, 40.8, 33.7, 31.9, 29.5, 28.2, 24.0, 22.5, 21.5, 20.3, 20.0, 18.0, 12.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −12.25; EI-MS *m*/*z* 628 (M^+, 2), 378 (100), 363 (6), 250 (43), 199 (10), 94 (46); exact mass calcd for $C_{40}H_{53}O_4P$ 628.3681, found 628.3665. Anal. Calcd for $C_{40}H_{53}O_4P$: C, 76.40; H, 8.50. Found: C, 76.32; H, 8.31.

17*β*-Hydroxy-5α-androstan-3-one Diphenyl Phosphate (21). 5α-Androstan-17*β*-ol-3-one (0.34 mmol, 0.10 g) was added to a solution of titanium *tert*-butoxide (0.1 M, 10 mol %, 0.34 mL) in dry DCM (2.0 mL) under nitrogen. Et_3N (0.51 mmol, 0.07 mL) and diphenyl chlorophosphate (0.34 mmol, 0.07 mL) were added sequentially via syringe. The reaction mixture was stirred at room temperature for 20 h before being filtered through a layered plug of silica and $MgSO_4$ (ratio 20:1). Washing with EtOAc in petrol (35%, 50 mL) followed by evaporation yielded the pure phosphorylated product as a white solid (0.10 g, 56%). Mp 123−124 °C, $[\alpha]_D$ +19.3 (*c* 1.0, $CHCl_3$); IR (film) 2935 (s), 1712 (s), 1489 (s), 1295 (s), 1286 (s), 1192 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.24 (m, 4H), 7.17−7.08 (m, 6H), 4.38 (dt, $J_{P-H} = 7.8$ Hz and $J = 7.8$ Hz, 1H), 2.36−1.88 (m, 6H), 1.74−0.60 (m, 17H), 0.92 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 150.7, 129.7, 125.1, 120.0 (d, $J_{C-P} = 4.0$ Hz), 88.3 (d, $J_{C-P} = 7.1$ Hz), 53.6, 49.8, 46.6, 44.6, 43.3, 43.2, 38.4, 38.1, 36.3, 35.7, 35.2, 31.1, 28.7, 28.3, 23.3, 20.8, 11.6, 11.4; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −11.22; EI-MS *m*/*z* 522 (M^+, 8), 272 (26), 251 (100), 220 (6), 174 (10), 149 (12); exact mass calcd for $C_{31}H_{39}O_5P$ 522.2535, found 522.2529. Anal. Calcd for $C_{31}H_{39}O_5P$: C, 71.24; H, 7.52. Found: C, 71.10; H, 7.72.

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Supporting Information Available: ^1H, ^{13}C, and ^{31}P NMR data of known phosphate products **2**, **4b**, **5**−**16**, **19**, and **22** and copies of all ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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