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Efficient catalyst turnover in the phosphitylation of alcohols with phosphoramidites

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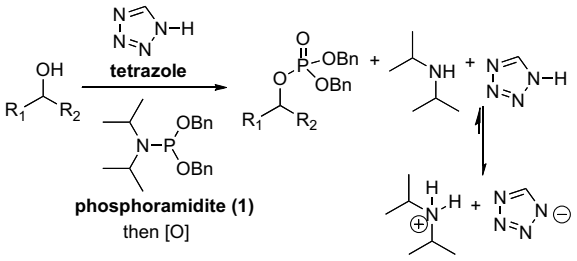
ABSTRACT

We report a method for catalytic phosphitylation utilizing phosphoramidites. Traditionally, this reaction is inefficient unless an excess of catalyst is present due to catalyst deactivation by an amine by-product. Isocyanate additives have been evaluated for scavenging the amine to facilitate catalyst turnover. A variety of alcohols and phosphoramidites were screened with 5 mol % catalyst. In the presence of additive, 83–97% conversion was achieved in contrast to 7–31% conversion without additive.

The derivatization of alcohols to diverse functional groups is a vibrant field in synthetic organic chemistry. One such transformation is the synthesis of phosphates. Phosphates are ubiquitous in nature, and are found in large biopolymers such as DNA, RNA, and proteins as well as in small molecule messengers such as inositol phosphates. Phosphates have also been seen to increase the aqueous solubility of drug candidates.[1] Due to the unique oxidation states of phosphorous (P), synthesis of phosphorylated compounds can be completed with either P(V) reagents (such as chlorophosphates[2] or pyrophosphates[3]) or P(III) reagents (such as phosphoramidites,[4] phosphites,[5] or phosphorochloridites[6]) followed by oxidation.[7]

Catalytic methods for the phosphorylation [P(V)] or phosphitylation [P(III)] of alcohols are beneficial because they can potentially reduce waste and open the possibility to enantioselective syntheses. The P(V) reagent, diphenylchlorophosphate, has been used in the phosphorylation of alcohols with catalytic Lewis acids[2a] and nucleophiles.[2b] To date, other phosphorous-protecting groups have been unsuccessful in catalytic reactions.[8] In order to develop an efficient catalytic reaction that is amenable with a wide array of phosphorous-protecting groups, we explored phosphitylation with phosphoramidites and subsequent oxidation.

Phosphoramidites have witnessed great success in oligonucleotide synthesis.[9] Advantages to using phosphoramidites include robust reagents that are commercially available with a variety of orthogonal phosphorous-protecting groups. A current limitation is the need for excess catalyst, commonly tetrazole.[10] Consequently, attempts to run this reaction with 5 mol % tetrazole lead to poor conversions (vide infra). A possible explanation for low catalyst turnover is the equivalent of diisopropylamine generated during the course of the reaction (Scheme 1). As the concentration of amine increases, the concentration of tetrazole ($pK_a = 5$)[11] decreases. Scavenging the amine by-product should re-adjust the equilibrium in favor of active catalyst.



Scheme 1. Phosphitylation with phosphoramidites.

This idea has been elegantly put into practice by Hayakawa et al.[12] They demonstrated that 5 mol % of the more reactive *p*-nitrophenyltetrazole in the presence of 10 Å molecular sieves (MS) was effective for the phosphoramidite coupling of oligonucleotides. The MS were present to sequester the amine by-product over the larger oligonucleotide building blocks. While this work demonstrated the ability of the catalyst to turnover, the method is only amenable to substrates and catalysts that are larger than diisopropylamine. We envisioned that an alternative method would exploit the unique nucleophilic reactivity of amines. Isocyanates and isothiocyanates have been successfully employed as amine scavengers as solid supported[13] and fluorous tagged[14] reagents. The resulting urea is no longer basic, allowing the active protonated catalyst to circulate.

Our study began by examining the effect of additives in promoting catalyst turnover (Table 1). Reactions were conducted with 5 mol % tetrazole and 1.2 equiv of phosphoramidite **1**. When no

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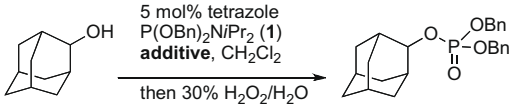
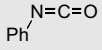
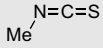
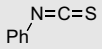
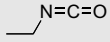
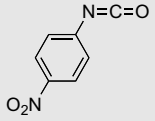
Table 1
Additives for promotion of catalytic phosphitylation[a]



Entry	Additive	Conversion[b] (%)	Time (h)
1	None	18	13
2		96	13
3		27	13
4		42	13
5		3	16
6		>98	16

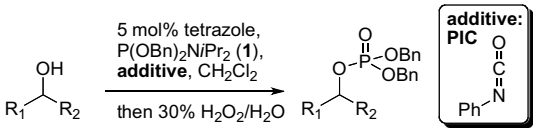
[a] Reactions performed with 1.2 equiv of $P(OBn)_2NiPr_2$ and 1.1 equiv of additive followed by an oxidative workup with 30% H_2O_2/H_2O.
[b] Conversions obtained from integrations of ^1H NMR of unpurified reactions. Data reported are the average of two trials.

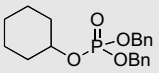
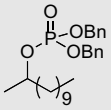
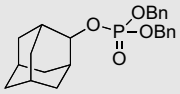
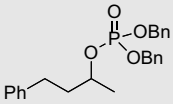
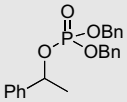
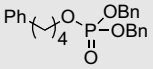
additive was introduced, the phosphitylation of 2-adamantanol proceeded with only 18% conversion (entry 1). To our delight, the addition of 1.1 equiv of phenylisocyanate (PIC) generated 96% conversion (entry 2). The less reactive thioisocyanates (entries 3 and 4) provided only 27% and 42% conversion, respectively. Unfortunately, extremely low conversion (3%) was obtained with ethylisocyanate (entry 5). In this case, the additive must be inhibiting the reaction. Encouragingly, 4-nitrophenylisocyanate also provided high conversions with no detectable starting material by ^1H NMR (entry 6).

Different primary and secondary alcohols were then examined in the presence and absence of PIC (Table 2). Aliphatic alcohols provided between 14% and 26% conversion without isocyanate and 83-96% conversion with PIC (entries 1–4).[15] *sec*-Phenethyl alcohol was also phosphitylated in 83% yield in the presence of PIC; however, purification of this substrate leads to decomposition[16] (Table 2, entry 5). The higher reactivity of primary alcohols toward phosphitylation was witnessed by higher conversion (31%) in the absence of additive (Table 2, entry 6).[17]

To test the effectiveness of the methodology with multiple protecting groups, other phosphoramidites were examined (Table 3). When *ortho*-xylyl phosphoramidite **2** was used in the presence of 1.1 equiv of 4-nitrophenylisocyanate, >97% conversion (79% isolated yield) of **3** was obtained. The structurally defined *ortho*-xylyl group may help to pre-organize the transition state for phosphorous transfer, which may be beneficial in future work involving selectivity.[18] Orthogonal-protecting groups were also examined to facilitate the synthesis of complex phosphorylated products. The isomerization-labile allyl phosphoramidite **4** was used to successfully synthesize diallyl **5**[19] in 80% yield. Lastly, the photo-labile *o*-nitrobenzyl phosphoramidite **6** was synthesized in one step,[20] and was screened in the phosphitylation of 2-dodecanol. Photo-labile-protecting groups have been studied extensively in biological settings for their spatial and temporal release of active phosphorylated targets.[21] While this phosphorylating agent did not provide high conversions (w/o PIC: 10% of **7**, with PIC: 38% of **7**, Table 3), it did demonstrate a preliminary result for future optimization.

Table 2
Phosphitylation of primary and secondary alcohols[a]



Entry	Product	No additive Conversion (%)	With PIC Conversion[b] (isolated yield)
1		17	83% (74%)
2		26	94% (88%)
3		18	96% (85%)
4		14	86% (82%)
5		7	83%
6		31	>99% (84%)

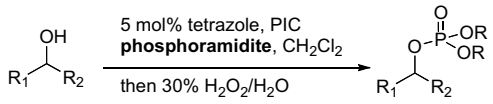
[a] Reactions performed with 1.2 equiv of $P(OBn)_2NiPr_2$ and 1.1 equiv of additive followed by an oxidative workup with 30% H_2O_2/H_2O.
[b] Conversions obtained from integrations of ^1H NMR of unpurified reactions.

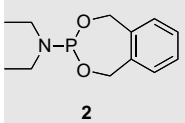
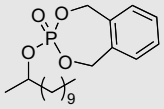
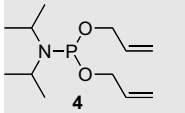
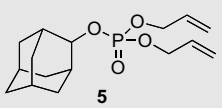
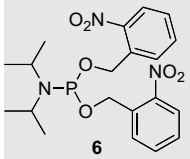
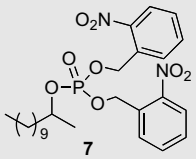
To test the limitations of our method, tertiary alcohols were examined. This substrate class is known to be problematic due to lower reactivity and potential elimination of the products during oxidation.[22] The study began with *n*-butylcyclohexanol, which did not generate any desired product under our standard conditions (Table 4, entry 1). To minimize the congestion of the carbonol center, 2-methyl-3-butyn-2-ol was chosen. The reaction progressed to a single product; however, allene **8** was formed instead of the expected phosphate (Table 4, entry 2). Rearrangements of alkynyl phosphites to allenyl phosphonates have been observed before in phosphitylation with phosphorochloridites, but have not yet been reported with phosphoramidites.[23] Allenyl phosphonates have been successfully employed as versatile starting materials for cross coupling reactions[24] and selective hydrogenations.[25] The synthesis of this substrate class utilizing phosphoramidites will be examined.

To continue our pursuit of the synthesis of phosphates derived from tertiary alcohols, a less sterically demanding phosphoramidite was examined. While *N,N*-diisopropylamidites are the most common phosphitylating agents due to their higher stability, *N,N*-diethylphosphoramidites are also commercially available and offer reduced sterics around the phosphorous atom. When dibenzyl *N,N*-diethylphosphoramidite was used in the phosphitylation of *n*-butylcyclohexanol with 5 mol % tetrazole and 1.1 equiv of PIC, the desired phosphate product **9** was isolated in 68% yield (Table 4, entry 3). This result reinforced the hypothesis that sterics control the lower reactivity of tertiary alcohols, which can be mitigated by managing the sterics of reagents.

In conclusion, we have demonstrated that the introduction of additives to scavenge the amine by-product in the phosphitylation

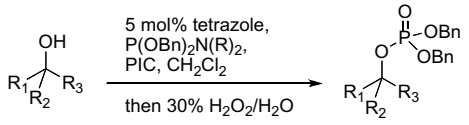
Table 3
Phosphoramidite screen[a]

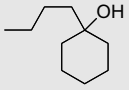
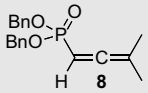
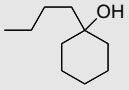
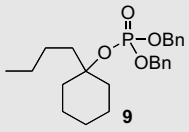


Phosphoramidite	Product	Conv. w/o isocyanate[b] (%)	Yield (conv.)
 2	 3	21	79%[c] (>97%)
 4	 5	NA[d]	80%
 6	 7	10	23% (38%)

[a] Reactions performed with 1.2 equiv of phosphoramidite and 1.1 equiv of additive for 14 h followed by an oxidative workup with 30% H_2O_2/H_2O.
[b] Conversions obtained from integrations of ^1H NMR of unpurified reactions.
[c] 4-Nitrophenylisocyanate was used as the additive for ease of purification.
[d] Conversion could not be obtained due to overlap of NMR resonances.

Table 4
Phosphitylation of tertiary alcohols[a]



Entry	R	Tertiary alcohol	Product	Yield (%)
1	*i*Pr		No reaction	NA
2	*i*Pr		 8	40
3	Ethyl		 9	68

[a] Reactions performed with 1.2 equiv of phosphoramidite and 1.1 equiv of PIC for 14 h followed by an oxidative workup with 30% H_2O_2/H_2O.

of alcohols with phosphoramidites can successfully re-engage the catalyst for further rounds in the catalytic cycle. We postulate that the additive is reacting with the amine by-product, forming a urea that is no longer basic and, therefore, does not deactivate the catalyst. This methodology was validated by examining different alcohols, additives, and phosphoramidites to survey the generality of this process. Encouraging results were found with primary, secondary, and tertiary alcohols, with PIC and 4-nitrophenylisocyanate as additives, and with a variety of phosphoramidites. Efforts will now be focused on determining the mechanistic implications of the additive and on generating chiral catalysts to facilitate a catalytic enantioselective phosphitylation with phosphoramidites.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.065.

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9. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223.
10. For other catalysts see: (a) Hayakawa, Y.; Iwase, T.; Nurminen, E. J.; Tsukamoto, M.; Kataoka, M. *Tetrahedron Lett.* **2005**, *61*, 2203; (b) Hayakawa, Y.; Kawai, R.; Hirata, A.; Sugimoto, J.; Kataoka, M.; Sakakura, A.; Hirose, M.; Noyori, R. *J. Am. Chem. Soc.* **2001**, *123*, 8165.
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14. Linclau, B.; Sing, A. K.; Curran, D. P. *J. Org. Chem.* **1999**, *64*, 2835.
15. *Typical procedure for phosphitylation:* The alcohol (1.20 mmol) was dissolved in 12 mL of CH_2Cl_2. An aliquot of 0.45 M tetrazole solution in acetonitrile was added (134 μL, 0.060 mmol, 5 mol %) followed by dibenzyl *N,N*-diisopropylphosphoramidite (475 μL, 1.41 mmol, 1.2 equiv). For reactions containing the additive, phenylisocyanate (143 μL, 1.32 mmol, 1.1 equiv) was then introduced. After 14 h, the reaction was cooled to 0 °C followed by addition of 3 mL of 30% H_2O_2/H_2O. After 1 h, the solution was quenched slowly with 25 mL of saturated sodium sulfite, while the temperature was maintained at 0 °C. The mixture was then washed with 2 × 25 mL of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and were concentrated under reduced pressure. Crude NMRs were obtained for conversion data. The crude product was then purified by silica gel chromatography with a gradient of 20% ether/petroleum ether to 50% ether/petroleum ether. *Cyclohexyl dibenzyl phosphate.* ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.31 (m, 10H), 5.03 (m, 4H), 4.36 (m, 1H), 1.88 (m, 2H), 1.71 (m, 2H), 1.54–1.43 (m, 3H), 1.33–1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3 (d, J = 6.8 Hz), 128.8, 128.6, 128.1, 77.9 (d, J = 6.0 Hz), 69.2 (d, J = 6.1 Hz), 33.5 (d, J = 4.6 Hz), 25.3, 23.7; ^{31}P NMR ($CDCl_3$, 162 MHz) δ −0.6; IR (film, cm^{-1}) 2937, 2859, 1497, 1455, 1259, 1214; TLC R_f 0.31 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{20}H_{25}O_4P+H]^+$ requires m/z 361.1569. Found 361.1536 (FAB).
16. From NMR analysis, product decomposed slowly on the column to styrene and dibenzylphosphate.

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