Highly Selective Acylation of Alcohols Using Enol Esters Catalyzed by Iminophosphoranes

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The iminophosphorane bases $PhCH_2N{=}P(MeNCH_2CH_2)_3N$ and $PhCH_2N{=}P(NMe_2)_3$ catalyze the acylation of primary alcohols with enol esters in excellent yields and in high selectivity. It was found that acid labile groups such as acetal and epoxide survive under the reaction conditions. Groups such as TBS and disulfide, which undergo cleavage in the presence of Ac_2O and the Lewis acid $Sc(OTf)_3$, are also unaffected. Diene, conjugated acetylene, oxazoline, nitro, and benzodioxane groups are also compatible with our catalyst/reagent system. Because secondary alcohols do not react under our conditions, our methodology is attractive for the selective acylation of primary alcohols. Polymer-supported iminophosphorane catalysts are also shown to be useful in these reactions, thus opening the possibility of wider applications.

Introduction

The acyl group serves as an important protecting group for alcohols because of its stability toward a variety of reagents.[1] Selective protection of an hydroxyl group is often needed in the synthesis of complex natural products and hence a variety of methods have been developed to effect this conversion. Anhydrides are found to be versatile acylating agents in the presence of bases such as pyridine or triethylamine. 4-(Dimethylamino)pyridine, however, was the first efficient basic catalyst used to accelerate the acylation of alcohols by acetic anhydride as the acylating agent.[2] More recently a variety of catalysts have been developed for this purpose, including the Lewis acidic catalysts $Sc(OTf)_3$,[3] $TiCl(OTf)_3$,[4] TMSCl,[5] $Sc(NTf_2)_3$,[6] $CoCl_2$,[7] $Sn(OTf)_2$,[8] $TiCl_4/AgClO_4$,[9] and TMSOTf;[10] the exceedingly strong proazaphosphatrane base **1a**[11] and PBu_3,[12] and the combination Lewis acid/base system $MgBr_2/R_3N$.[13] Other acylating agents (e.g., 3-acetylthiazolidine/NaH[14] and AcCl/hindered amine[15]) have also been used for alcohol acylation. Even though the aforementioned catalysts are effective, the acidic conditions in Lewis acid acylations lead to cleavage of sensitive functional groups such as acetals, TBDMS, dienes, and epoxides. The somewhat basic catalyst PBu_3 suffers from poor air stability and flammability, and very basic catalyst systems lack the ability to select between primary and secondary hydroxyl groups. This selectivity is often needed in the synthesis of complex polyhydroxy natural products.

Due to the aforementioned problems associated with anhydride/catalyst combinations, attention was turned toward other acylating agents. Transesterification with esters as acylating agents[16] is an alternate possibility for mild alcohol acylation, but because of the reversibility of the reaction, high conversions cannot be achieved. However, this problem can be solved by using enol esters as acylating agents, since the resultant enolate is converted to an aldehyde or ketone that is unable to participate in the reverse reaction. Such reactions are catalyzed by simple acids,[17] enzymes,[16,18] and organometallic compounds such as $Cp^*_2Sm{\cdot}thf$[19] and $[ClBu_2SnOSnBu_2Cl]_2$.[20] Although these organometallic catalysts are better than simple acids for this reaction, Schlenk tube techniques are required for $Cp^*_2Sm{\cdot}thf$, and the Lewis acidity of tin halides, which can complex with amino groups (see later), further justify the search for new catalysts for this important reaction.

Polymers are becoming increasingly important in synthesis.[21] Thus, they can be used as supports for solid-

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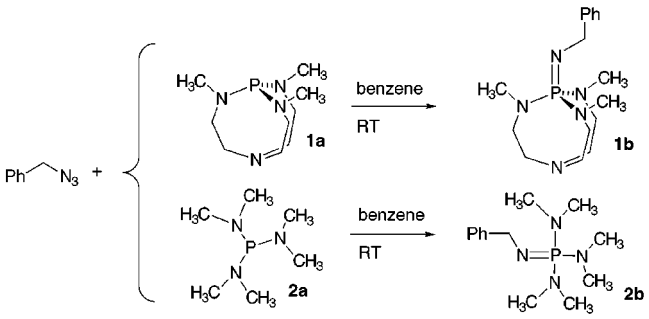
Scheme 1



phase synthesis,[21a−c] for catalysts,[21d] or for quenching reagents in solution-phase synthesis.[21e] Highly basic organic polymers[22] and inorganic solids[23] have also been attractive because of their ability to catalyze a variety of reactions.

Phosphorus-based nonionic bases of the proazaphosphatrane class have recently been shown to be very useful in organic synthesis as stoichiometric bases and as catalysts.[24] Recently we reported the acylation of hindered alcohols using anhydrides or enol esters in the presence of proazaphosphatrane **1a** as a catalyst.[11] Though catalyst **1a** was very efficient for acylating hindered alcohols, it induced desulfurization and desilylation in some substrates. Moreover **1a** does not effect selective acylation of primary alcohols in the presence of secondary alcohols. These problems are attributable to the very reactive trivalent aminophosphine moiety in **1a**, and we therefore decided to use a modification of this catalyst system which was obtained by converting it to a less basic but stable iminophosphorane **1b**. This synthesis was achieved by the procedure in Scheme 1 which we reported earlier.[25] Acyclic derivative **2b** in Scheme 1, derived from hexamethyl phosphorus triamide **2a**, was prepared by the same procedure,[25] and both **1a** and **2a** were evaluated as catalysts for the acylation of primary alcohols using enol esters as acylating agents.

Results and Discussion

Benzyl alcohol **3** was examined as a model substrate by treating it with vinyl acetate **4a** in THF in the presence of 10 mol % of **1b**. After 6 h, benzyl alcohol was quantitatively converted into benzyl acetate **5a**. Similarly, when **2b** was used as the catalyst, the product was obtained in 99% yield in 8.5 h (Scheme 2). Since **2b** appeared to be as effective as **1b** and is cheaper to synthesize, we decided to pursue the use of catalyst **2b** as the catalyst for further acylations. Benzyl alcohol was then treated with vinyl benzoate **4b** and vinyl acrylate **4c** in the presence of **2b** (10 mol %) to afford the corresponding esters **5b** and **5c** in 94% and 87% yields, respectively (Scheme 2).

Scheme 2

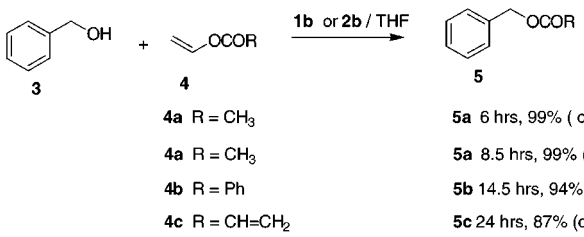
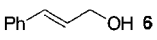
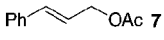
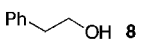
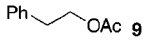
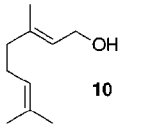
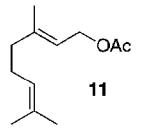
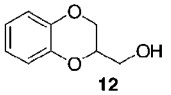
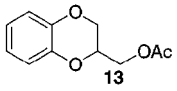
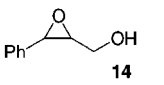
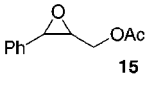
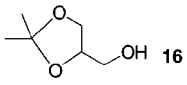
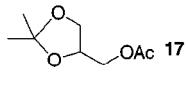
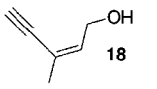
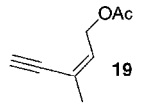
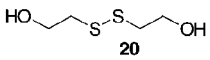
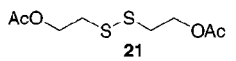
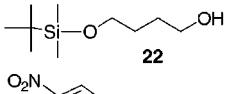
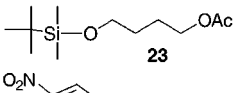
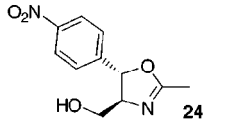
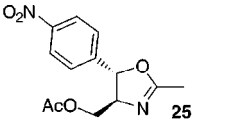


Table 1. Acylation of Alcohols Using Vinyl Acetate Catalyzed by 2b

Substrate	Product	Time (hrs)	Yield (%)
 6	 7	17	99
 8	 9	16.5	98
 10	 11	38	94
 12	 13	15	99
 14	 15	16	99
 16	 17	14	99
 18	 19	15	99
 20	 21	17	98
 22	 23	25.5	82
 24	 25	17	74

To test the selectivity of catalyst **2b** in acylation reactions, alcohols with a variety of functional groups were chosen as substrates, and the results are summarized in Table 1. Cinnamyl alcohol **6** and phenethyl alcohol **8** reacted equally well giving the corresponding acetates **7** and **9** in excellent yields. When geraniol **10** was treated under the same reaction conditions, geranyl acetate **11** was isolated in 94% yield. On the other hand, others have reported that when **10** was subjected to $Sc(OTf)_3/Ac_2O$ conditions, multiple products were obtained,[20] clearly demonstrating that our conditions are

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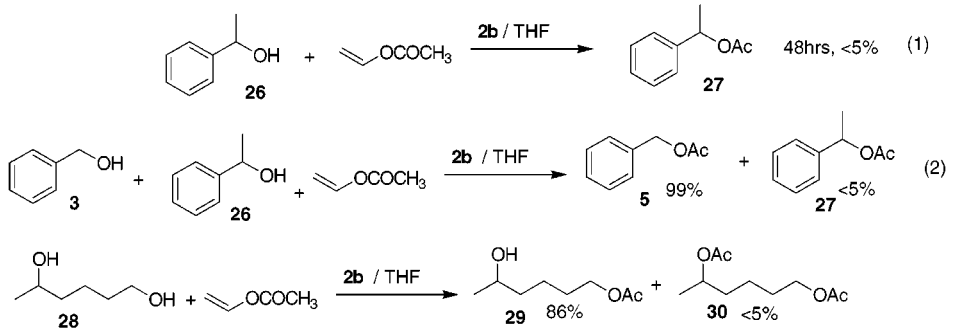
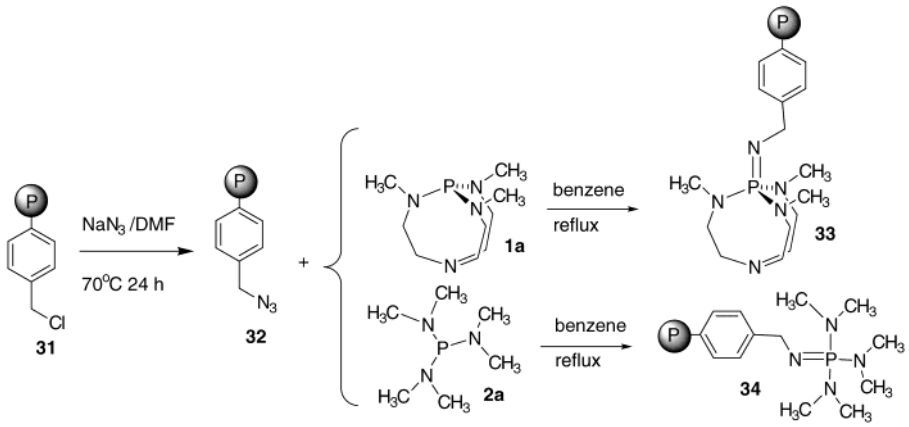
Scheme 3



Scheme 4



milder and more efficient. To further assess the efficacy of **2b** in the presence of sensitive functional groups, alcohols with acid-labile functional groups were employed. Thus, when acid-sensitive alcohol **12** was treated with vinyl acetate in the presence of **2b**, the corresponding acetate **13** was obtained in excellent yield. Acid-labile epoxy alcohol **14** underwent clean acylation with vinyl acetate to give the epoxy acetate **15** in 99% yield. This selectivity cannot be achieved using Cp^*_2Sm·thf since low-oxidation-state samarium reagents are known to reduce epoxides in a few minutes.[26] The **2b**-catalyzed reaction also illustrates the mildness of our catalytic conditions. To explore further the selectivity toward acid-sensitive substrates, alcohol **16** containing an acetonide group was found to give the corresponding acetate **17** in excellent yield. On the other hand, the TMSOTf/Ac_2O system decomposes the acetonide group in a similar substrate.[10] Functional groups such as a conjugated terminal acetylene also survives under our reaction conditions as is seen from the acylation of substrate **18**. To compare the selectivity of our reagent system with weaker bases such as PBu_3, the disulfide-containing diol **20** was treated with vinyl acetate and **2b**. The corresponding diacetate **21** was obtained in almost quantitative yield. When the same substrate was treated with PBu_3 or $Sc(OTf)_3$ in the presence of Ac_2O, the disulfide bond underwent cleavage to give $AcOCH_2CH_2SAc$.[20] In the synthesis of complex natural products, orthogonal stability of protecting groups plays an important role in achieving the target molecule. To determine the stability of other hydroxyl-protecting groups under our reaction conditions, a molecule with a free hydroxyl group and a silyl-protected hydroxyl group was chosen as the substrate. Thus when the mono-TBS-protected 1,4-butanediol **22** was reacted with vinyl acetate in the presence of **2b**, the corresponding acetate **23** was obtained without cleavage of the TBS group. Such selectivity has been reported only for the catalyst $[ClBu_2SnOSnBu_2Cl]_2$.[20] To compare our catalytic system with the important reagents Cp^*_2Sm·thf and $[ClBu_2SnOSnBu_2Cl]_2$, an oxazoline with a hydroxyl group and a nitro group (**24**) was selected as a substrate. When **24** was treated with **2b** and vinyl acetate, the corresponding acetate **25** was obtained in 74% yield. By contrast, our use of $[ClBu_2SnOSnBu_2Cl]_2$ did not provide an appreciable amount of acetate **25**, probably because of the reaction of the Lewis acidic catalyst with the basic oxazoline moiety. Cp^*_2Sm·thf also may not be a suitable catalyst for substrate **24** because it is known that low-oxidation-state samarium reagents reduce the nitro group.[27]

Protection of a primary alcohol in the presence of a secondary alcohol is useful in natural product synthesis. This can be achieved by $Sc(OTf)_3/Ac_2O$,[10] TMSOTf/Ac_2O,[10] $[ClBu_2SnOSnBu_2Cl]_2$/enol ester,[20] and AcCl/hindered amine.[15] When the secondary alcohol **26** was subjected to our the reaction conditions, only a trace of acylated product was obtained (reaction 1). Thus in a mixture of benzyl alcohol **3** and 1-phenylethanol **26** in the presence of **2b** and vinyl acetate, only the benzyl alcohol reacted, providing **5** in 99% yield while the secondary acetate **27** formed in <5% yield (reaction 2). This selectivity was further confirmed by subjecting diol **28**, containing a primary and secondary alcohol in the same molecule, to catalytic acylation with **2b**. In this case the monoacetate **29** was isolated in 86% yield along with a <5% yield of the diacetate **30**. This reaction clearly demonstrates the utility of our catalyst in selecting for primary alcohols.

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Table 2. Acylation of Some Representative Alcohols Using Vinyl Acetate Catalyzed by 33

substrate	product	time (h)	yield (%)
3	**5**	8	99
3	**5**	21	99[a]
6	**7**	5.5	99
10	**11**	25	88
12	**13**	4	97
14	**15**	11	99
16	**17**	21	94
20	**21**	14	97
24	**25**	14	87

[a] Compound **34** was used as a catalyst.

After establishing these applications of our iminophosphoranes as homogeneous catalysts for acylation, we attached **1b** and **2b** to a Merrifield resin to test their properties in heterogeneous form and to take advantage of the ease of their separation from reaction mixtures. The synthesis of the polymer-supported reagents was accomplished by first converting the chloromethylated resin **31** into azidomethylated resin **32** (Scheme 4). The azide resin was then treated with **1a** or **2a** to give the polymer-supported catalysts **33** and **34**. The solid state ^{31}P NMR spectrum of **33** shows a peak at 18 ppm which we assign to the formation of product. For evaluating polymer-supported catalysts, we reacted benzyl alcohol with vinyl acetate in their presence. We found that the bicyclic derivative **33** was faster acting than the acyclic derivative **34**, and the results of acylation reactions catalyzed by **33** are summarized in Table 2. It may be noted, however, that the solution-phase ^{31}P NMR spectrum of **1b** reveals δ^{31}P at 37.8.

As seen from Table 2, **33** is as effective as its homogeneous acyclic counterpart **2b**. In testing the reusability of catalyst **33**, benzyl alcohol was taken as an acylation substrate for vinyl acetate. We found that the catalyst **33** can be used three times without significant loss of product yield. After three cycles, however, the catalyst beads became a fine powder which was more difficult to isolate.

In conclusion we have shown that the highly basic iminophosphoranes **1b** and **2b** (which are made by a simple procedure) catalyze the acylation of sensitive alcohols using enol esters. The selectivities in this reaction are better than those in published procedures; the yields are generally excellent and product purity is better than 95% according to ^{1}H NMR spectroscopy. Sensitive functional groups such as TBDMS, diene, disulfide, and acetonide (which were not stable under Ac_2O/Lewis acid conditions) and groups such as epoxide, nitro, and oxazoline (which are not compatible with $Cp^*_2Sm\cdot thf$ and $[ClBu_2SnOSnBu_2Cl]_2$) were not affected by our procedure. Selective protection of primary hydroxyl groups in the presence of secondary hydroxyl groups makes our procedure attractive for the synthesis of complex natural products. The use of polymer-supported catalysts **33** and **34** in this procedure is potentially attractive in industrial applications. The use of these new basic catalysts, and in particular polymers **33** and **34**, in other transformations such as Michael addition are underway.

Experimental Section

General Procedure for the Esterification of Alcohols with Enol Esters. To a stirred solution of **1b** or **2b** (10 mol %) and 1 mmol of alcohol in THF (0.5 mL) was added enol ester (5 mmol) at room temperature. The mixture was stirred at room temperature for the time given in Table 1, and the solvent and excess enol ester were evaporated in vacuo. The residue was purified by column chromatography on a small pad of silica gel using 0−20% ethyl acetate in hexane as eluent. When polymer-supported catalyst was employed, the polymer was filtered after the completion of the reaction and washed with ether. The solvent was then evaporated in vacuo, and the residue was purified by column chromatography on a small pad of silica gel using 0−20% ethyl acetate in hexane as eluent.

Synthesis of 1b. To a stirred solution of 10 mmol of **1a** (prepared according to our previously reported method[11]) in benzene (10 mL) under argon atmosphere at room temperature was added benzyl azide (10 mmol) and stirred overnight. Benzene was evaporated under reduced pressure and the residue triturated with dry hexanes to give a fine powder which was found to be very pure by ^{1}H and ^{31}P spectroscopy. ^{1}H NMR (C_6D_6): 7.63 (d, J = 8 Hz, 2H), 7.17−7.31 (m, 3H), 5.26 (s, 2H), 2.68 (d, J = 8 Hz, 9H), 2.46 (t, J = 8 Hz, 6H), 2.26 (s, 6H). ^{13}C NMR (CD_3CN): 34.7 (d, J = 3 Hz), 49.2, 51.2, 64.7, 126.3, 128.2, 128.4, 140.4. ^{31}P NMR (C_6D_6): 37.84. LRMS (EI mode): 321 (M^+), 258, 216, 175, 116. HRMS: calcd for $C_{16}H_{28}N_5P$ = 321.20824; measured = 321.20809.

Synthesis of 2b. This can be made using an alternate two-step procedure reported earlier.[28] To a stirred solution of 11 mmol of **2a** (Aldrich) in benzene (10 mL) under argon atmosphere at room temperature was added benzyl azide (10 mmol) and stirred overnight. Benzene was evaporated under reduced pressure, and the residue was distilled under reduced pressure to give **2b**. (bp 160 °C/8 mm). ^{1}H NMR (C_6D_6): δ 7.78 (d, J = 8 Hz, 2H), 7.33 (t, J = 8 Hz, 2H), 7.12−7.18 (m, 1H), 4.62 (d, J = 24 Hz, 2H), 3.38 (d, J = 12 Hz, 6H). ^{13}C NMR (CD_3CN): δ 36.9 (d, J = 3 Hz), 47.9, 125.2, 126.7, 127.6. ^{31}P NMR (C_6D_6): δ 24.16.

Supporting Information Available: ^{1}H and ^{13}C NMR and mass spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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