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Lead-Catalyzed Aqueous Benzoylation of Carbohydrates with an Acyl Phosphate Ester

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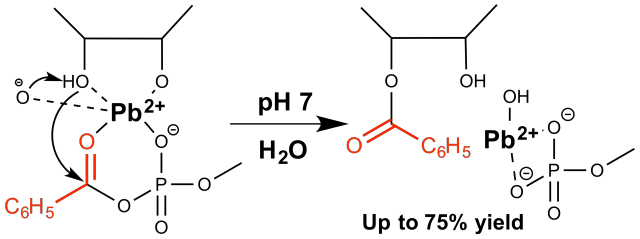


Abstract

Biochemical systems utilize adenylates of amino acids to aminoacylate the 3'-terminal diols of tRNAs. The reactive acyl group of the biological acylation agent is a subset of the general class of acyl phosphate monoesters. Those compounds are relatively stable in aqueous solutions and their alkyl esters are conveniently prepared. It has previously been shown that biomimetic reactions of acyl phosphate monoesters with diols and carbohydrates are promoted by lanthanide salts. However, they also promote hydrolysis of acyl phosphate reagents and the overall yields are modest. An assessment of the catalytic potential of alternative Lewis acids reveals that lead ions may be more effective as catalysts than lanthanides. Treatment of carbohydrates with benzoyl methyl phosphate (BMP) and triethylamine in water with added lead nitrate produces

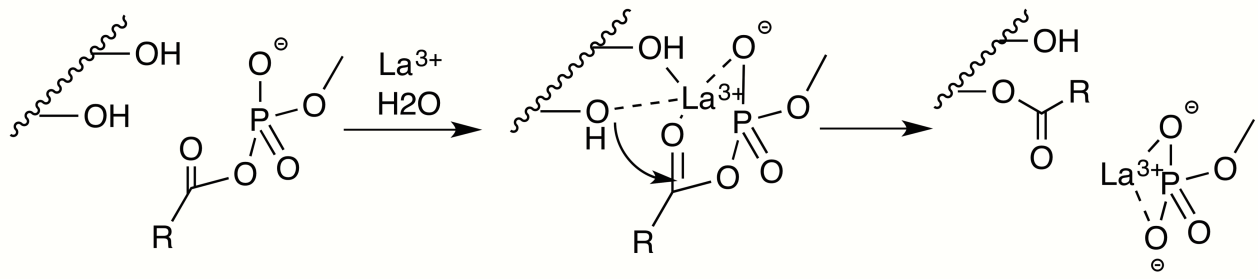
monobenzoyl esters in up to 75% yield. This provides a water-compatible pathway for novel patterns of benzoylation of polyhydroxylic compounds.

Introduction

Enzymes utilize adenylates to aminoacylate the 3'-terminal diols of tRNAs. The key functional group of the biological acylation agent is an acyl phosphate monoester. These compounds are relatively stable in aqueous solutions and the simple esters are conveniently prepared. We have been developing the use of anionic acylation agents in catalyzed reactions with hydroxyls that permit reactions in water with biologically important compounds that contain adjacent hydroxyl groups.[1-3] Well-established methods for catalytic acylation of hydroxyl groups utilize organotin compounds[4,5], organoboron compounds,[6,7] and Lewis acids[8-10] as catalysts or as co-reactants with reagents that are not amenable to use in water. Those processes typically utilize uncharged acyl donors. They are typically subject to rapid hydrolysis, limiting their usage to dry organic solvents, conditions that may not be compatible with the solubility of biological targets.[11]

Previous reports from our laboratory described the use of lanthanide salts to promote monoacylation of diols with biomimetic acyl phosphate monoesters, establishing the potential of a combination of an anionic acylation agent, metal ion, and aqueous reaction medium.[12] The resulting products are typically monoacylated with regioselectivity directed toward hydroxyls located adjacent to a second hydroxyl, consistent with reaction occurring during chelation of the metal ion by the hydroxyls and the reagent. A recent report of a process that utilizes organic cations as catalysts with neutral acylation agents in water and organic cations provides a complementary approach.[13]

The pattern of monoacylation of diols from the reactions with acyl phosphate monoesters and lanthanides in water suggests a transition state that results from the metal ion in bis-bidentate chelation with both the reactant and the reagent. The chelated acyl phosphate esters become activated toward the hydroxyls only within in the chelated assembly (Scheme 1). Recent reports of benzoyl methyl phosphate for the synthesis of a larger scope of compounds have further demonstrated its use as a biomimetic acylating reagent for highly functionalized bioactive substrates. [14,15] However, a significant limitation has been the competing catalysis by lanthanides that promotes the hydrolysis of acyl phosphates as an aspect of their general activation of phosphate esters.



Scheme 1 Lanthanum-catalyzed acylation through bis-bidentate coordinated intermediate

Thus, we sought a method that allows acylation with metal ions by acyl phosphate monoesters that sufficiently exceeds competing hydrolysis using alternative metal ions as catalysts. We now find that lead salts provide an improved alternative to lanthanides for monobenzoylation of carbohydrates with benzoyl methyl phosphate (BMP). We have assessed reactions in combinations with water alone and as a component of mixed solvent systems. We find that the pattern of results provides a basis for developing potentially useful alternatives to existing processes.

Results and Discussion

Our observations indicate that monoacylation of diols and nucleotides by an acyl phosphate monoester is promoted by the presence of lead nitrate in buffered aqueous solutions. The outcomes of reactions of methyl pyranosides with benzoyl methyl phosphate (BMP) are summarized in Table 1. The conditions give a distribution of monoester products. While the hydrolytic competition is slower than with lanthanide-catalyzed reactions, hydrolysis of BMP remains competitive.

Table 1 Monobenzoylation of carbohydrates in aqueous buffer with benzoyl methyl phosphate

			Conversion (%)
Entry	Carbohydrate	$Pb(NO_3)_2$ Equiv.	Benzoyl ester products
1	Me-α-D-Glucopyranoside	2	4-O-Bz (10.3), 6-O-Bz (1.1)
2	Me-β-D-Glucopyranoside	2	4-O-Bz (0.2), 6-O-Bz (1.5)
3	Me-α-D-Galactopyranoside	1	4-O-Bz (7.2), 3-O-Bz (2.7), 6-O-Bz (9.9)
4	Me-β-D-Galactopyranoside	1	4-O-Bz (0.5), 3-O-Bz (2.0),6-O-Bz (10.3)
5	Me-α-D-Mannopyranoside	2	2-O-Bz (6.5), 3-O-Bz (4.7), 4-O-Bz (2.3)
6	Myo-Inositol	2	1-O-Bz (7.5), 2-O-Bz (2.1), 4-O-Bz (2.7), 5-O-Bz (0.5)

Reaction conditions: Carbohydrate (1 equiv.), BMP (1 equiv.), $Pb(NO_3)_2$, 0.2 M EPPS pH 8 aqueous buffer, 25 °C, 24 h. Conversion % based on HPLC area%.

We investigated alternative reaction conditions to minimize hydrolysis and assess acylation of reactants with multiple reaction sites. The outcomes of reactions of methyl-α-D-manno-pyranoside, in dry THF are summarized in Table 2. The products that result from adding monosaccharides to solutions of BMP with lead nitrate at room temperature for 24 hours gave no ester products. Refluxing the same mixture results in formation of monobenzoylated products (2-

O-Bz, 3-O-Bz and 6-O-Bz) of 25% (entry 3). However, rapid hydrolysis of BMP results from water in the hygroscopic BMP. As expected, addition of water (50 mM, 1 equiv.) had no further effect. However, addition of tertiary amines gives monobenzoylated esters of the sugar. Reaction with 1.0 equiv. of N,N-diisopropylethylamine (DIPEA) gives three monobenzoylated products in 41% yield in dry THF (entry 5) and 46% yield with 0.05 M water (entry 6). Additional triethylamine leads to nearly 50 % total yield (entries 7 and 8). Using 2,6-lutidine in place of triethylamine gives lower yields (25% and 17%; entries 9 and 10). This is consistent with the amine acting as a Brønsted base in an acylation step that involves transfer of a proton. Increasing the concentration of the effective amine catalysts (2.5 eq triethylamine and 5 eq. di-isopropyl-ethyl-amine) gives benzoyl esters in 61% yield (entry 11 and 14). Monobenzoylation reactions did not proceed with added inorganic bases (K_2CO_3 and KOtBu). These bases cause precipitation of the lead salts needed for catalysis (entries 15 and 16).

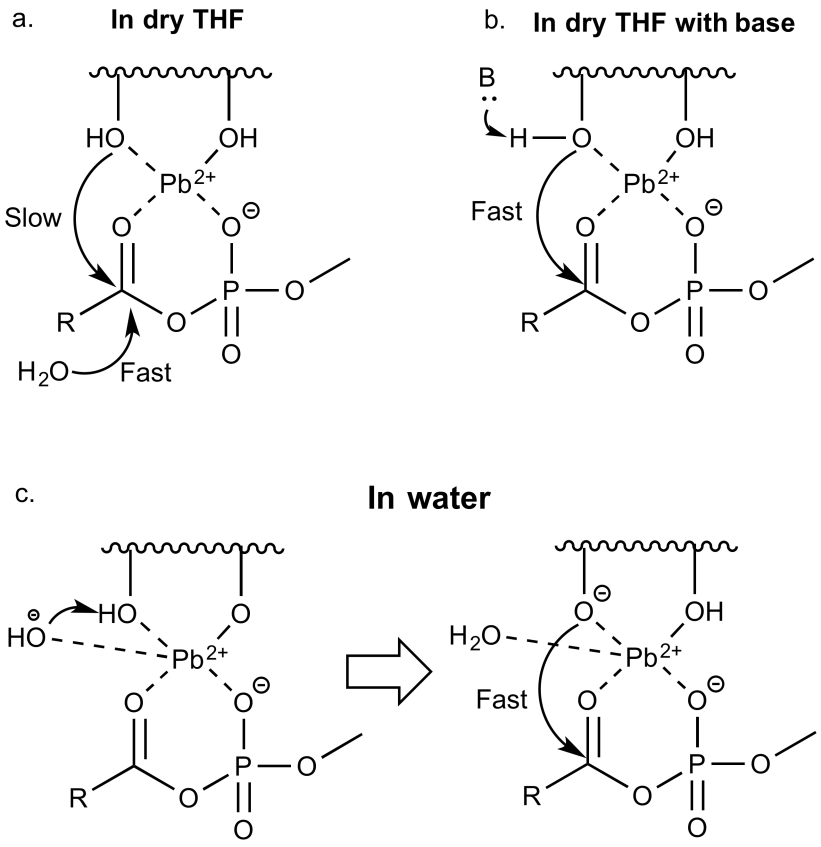
We evaluated diverse metal ions as potential catalysts beyond those that we have previously reported. These include Fe^{2+}, Cu^{2+}, Bi^{2+}, Co^{2+}, Sn^{2+} and Ni^{2+} under the same reaction conditions as described for lead ions. They produce an enhanced rate of hydrolysis of BMP and minimal formation of esters. .The mechanism we propose requires, coordination, chelation and reaction with internal hydroxides, conditions that clearly do not work for all metal ions.

Table 2 Effects of organic base

Entry	Temp. (°C)	$Pb(NO_3)_2$ (equiv.)	H_2O (equiv.)	Amine (equiv.)	Benzoylated Yield (%)
1	reflux	0	0	0	Not detected
2	25	1	0	0	<1
3	reflux	1	0	0	25
4	reflux	1	1	0	14
5	reflux	1	0	DIPEA (1)	41
6	reflux	1	1	DIPEA (1)	46
7	reflux	1	0	TEA (1)	46
8	reflux	1	1	TEA (1)	47
9	reflux	1	0	Lutidine (1)	25
10	reflux	1	1	Lutidine (1)	17
11	reflux	1	1	TEA (2.5)	61
12	reflux	1	1	TEA (5)	58
13	reflux	1	1	DIPEA (2.5)	55
14	reflux	1	1	DIPEA (5)	61
15	reflux	1	0	K_2CO_3	Not detected
16	reflux	1	0	KOtBu	Not detected

Abbreviations: TEA-Triethylamine, DIPEA = di-isopropylethylamine

Our results suggest that the hydrolysis of BMP is accelerated only through its activation by coordinated lead ions without the internal acceleration by bases that we expect to occur with coordinated diols. The chelation of the metal ion by adjacent hydroxyl groups enhances their reactivity relative to that of water (Schemes 2a and 2b)[16]. This results in an improved yield of monobenzoylated products compared to hydrolysis of BMP.



Scheme 2 Modes of activation by Pb^{2+} ions.

We also analyzed the effect of water in the presence of organic bases (Table 3). Increasing the proportion of water from 5% to 100% has only a slight effect on the yield (entries 1 to 5). The use of 2.5 equiv. of TEA and 1.0 equiv. of lead nitrate produces a 40% yield (entry 5).

Table 3. Outcomes for addition of varying amounts of water to benzoylation reaction mixture.

Entry	Temp. (°C)	$Pb(NO_3)_2$ (equiv.)	Water (vol %)	Triethylamine (equiv.)	Ester Yield (%)
1	80	1	5	2.5	52
2	80	1	25	2.5	37
3	80	1	50	2.5	38
4	80	1	75	2.5	39
5	80	1	100	2.5	40

Higher concentrations of water do not affect the extent of formation of esters. This may result from activation by increasing the extent of formation of coordinated lead hydroxides (Scheme 2c). These are among the most potent catalysts of phosphate ester exchange.[17] Similar activation by lead hydroxides should apply to the acylation reaction. In the presence of larger proportions of water, lead hydroxides could function as internal Brønsted bases toward hydroxyl groups of coordinated hydroxyls of the substrates. The combination of a Lewis acid and a Brønsted base will promote ester formation.

For further optimization of the overall process, we assessed the reaction of methyl-α-D-mannopyranoside with varying amounts of BMP (1 – 3 equiv.) while adjusting the quantities of amine (1.1 to 5.0 equiv.) and lead nitrate (0 – 3 equiv.). We also varied temperature from 4 °C to room temperature (Table 4). A combined yield of 76% was obtained when the substrate was treated with 2.5 equiv. of triethylamine, 1.0 equiv. of lead nitrate and 1.0 equiv. of BMP at 4 °C for 24 hours (entry 6). A large excess of triethylamine (5 eq.) accelerates the hydrolysis of BMP. This is likely to be due to the increased basicity of the solution (entry 9). In water-ethanol

mixtures, the lead-catalyzed monobenzoylation reactions produce lower yields (entry 14 to 16). This is likely to be due to the competition of the added ethanol for binding sites on lead ions.

Table 4 Varying combinations of each component and temperature.

Entry	Solvent	Temp. (°C)	$Pb(NO_3)_2$ equiv.	TEA (equiv.)	BMP (equiv.)	Ester Yield (%)
1	H_2O	4	0	2.5	1	12
2	H_2O	25	1	2.5	1	61
3	H_2O	25	1	5	1	6
4	H_2O	4	1	1.1	1	29
5	H_2O	4	1	2	1	63
6	H_2O	4	1	2.5	1	76
7	H_2O	4	1	3	1	71
8	H_2O	4	1	4	1	22
9	H_2O	4	1	5	1	10
10	H_2O	4	2	2	1	29
11	H_2O	4	3	3	1	8
12	H_2O	4	1	2.5	2	49
13	H_2O	4	1	2.5	3	21
14	25% EtOH	4	1	2.5	1	31
15	50% EtOH	4	1	2.5	1	18
16	75% EtOH	4	1	2.5	1	15

The higher yields that we obtain at lower temperatures are consistent with hydrolysis of acyl phosphates being selectively inhibited under those conditions.[18] The highest yield is 75%, which we obtained with 2.5 eq. TEA. This may be due to the low basicity of the reaction mixture. Around 50% of the lead hydroxides ($pK_a = 7.2$)[17] are deprotonated under those reaction conditions, accounting for the effective Brønsted base catalysis. Increased amounts of added

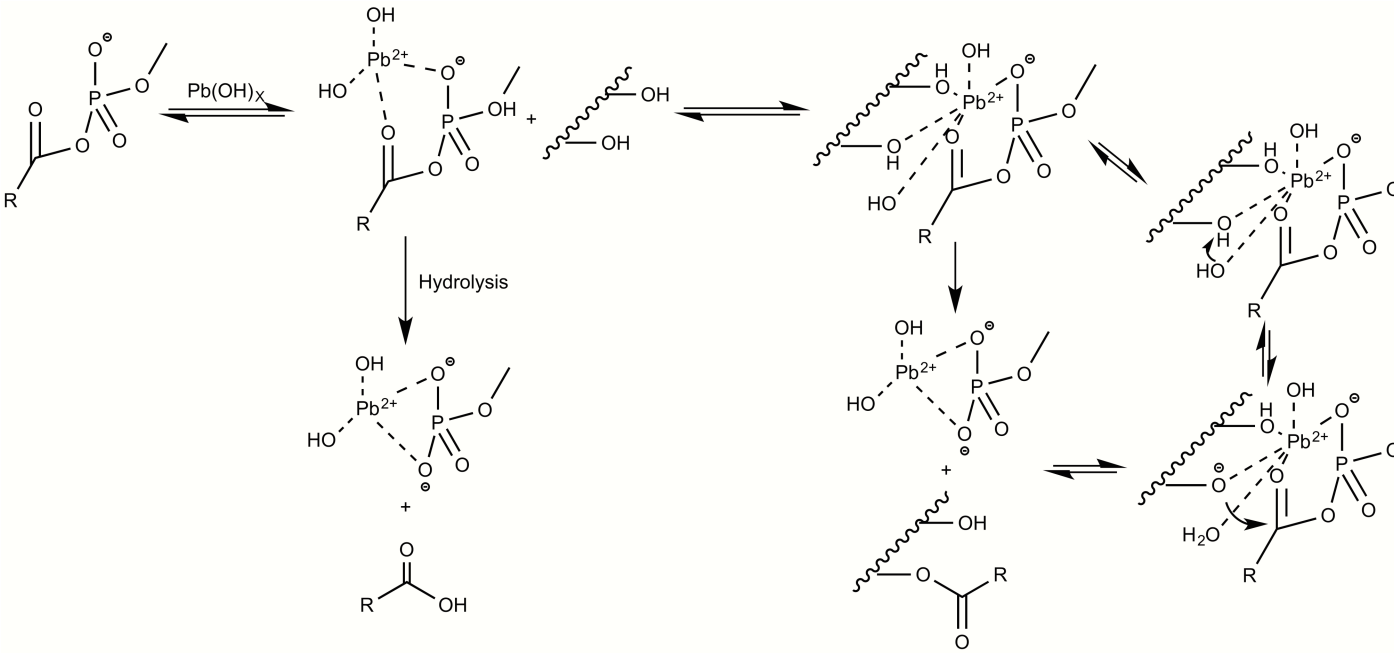
amine promote hydrolysis of BMP. Furthermore, compared with the elevated temperatures required for reactions in dry THF, monoacylation reactions proceed at 4 °C in water, suggesting that the intramolecular Brønsted base catalysis by lead-coordinated hydroxyl groups is more efficient than catalysis by bases in dry solvents.

Table 5. Pb^{2+}-catalyzed monobenzoylation

		Products (%)	
Entry	Carbohydrate	Monobenzoylated Product	Total
1	Me-α-D-Glucopyranoside	4-O-Bz (4), 3-O-Bz (2), 6-O-Bz (33)	39
2	Me-β-D-Glucopyranoside	4-O-Bz (4), 3-O-Bz (3), 6-O-Bz (38)	45
3	Me-α-D-Galactopyranoside	2-O-Bz (7), 3-O-Bz (6), 4-O-Bz (7),6-O-Bz (28)	48
4	Me-β-D-Galactopyranoside	2-O-Bz (3), 3-O-Bz (6), 4-O-Bz (11),6-O-Bz (38)	57
5	Me-α-D-Mannopyranoside	3-O-Bz (10), 2-O-Bz (7), 4-O-Bz (4), 6-O-Bz (55)	76
6	Myo-Inositol	1-O-Bz (15), 2-O-Bz (14), 4-O-Bz (12), 5-O-Bz (6)	46
7	Ethylene glycol	/	24
8	1,2-propanediol	1-O-Bz (13), 2-O-Bz (5)	18
9	1,3-propanediol	/	3
10	Cis-1,2-cyclopentanediol	/	39

Based on these results, we applied the optimized lead ion-catalyzed monobenzoylation reaction to other diols and carbohydrates (Table 5). All methyl pyranosides with multiple hydroxyl groups are converted to monoesters (entries 1 to 5) with the primary hydroxyl group the preferred reaction site. This is likely to be due to that route having the least steric hindrance while permitting chelation. Unlike the existing method[13], secondary hydroxyl groups were also benzoylated under our reaction conditions, with 1,2-cis-diols being slightly more favorable. This

is consistent with our chelation models as the shorter distance between hydroxyl groups facilitates the coordination of lead ions. However, the overall selectivity pattern among secondary hydroxyl groups is not yet apparent. This may be due to the large number of possible chelation modes and bis-bidentate intermediates in pyranosides where all the hydroxyl groups and the methoxy group are capable of metal ion coordination. The reactivity patterns of these intermediates are further complicated by the relative acidities of the hydroxyl groups[19] and the associated steric effects. As a result, we find no general pattern for the regioselectivity in this lead-catalyzed reaction with pyranosides. Monobenzoylation of simpler diols gave lower yields (entry 6-9). This is likely to be due to the free rotation of hydroxyl groups for simple aliphatic, acyclic diols. This makes the bis-bidentate complexes required for catalysis less stable[20]. These selectivity patterns are similar to those in earlier reports with lanthanides.[1]



Scheme 3 Proposed mechanism of Pb^{2+}-catalyzed aqueous monobenzoylation reaction

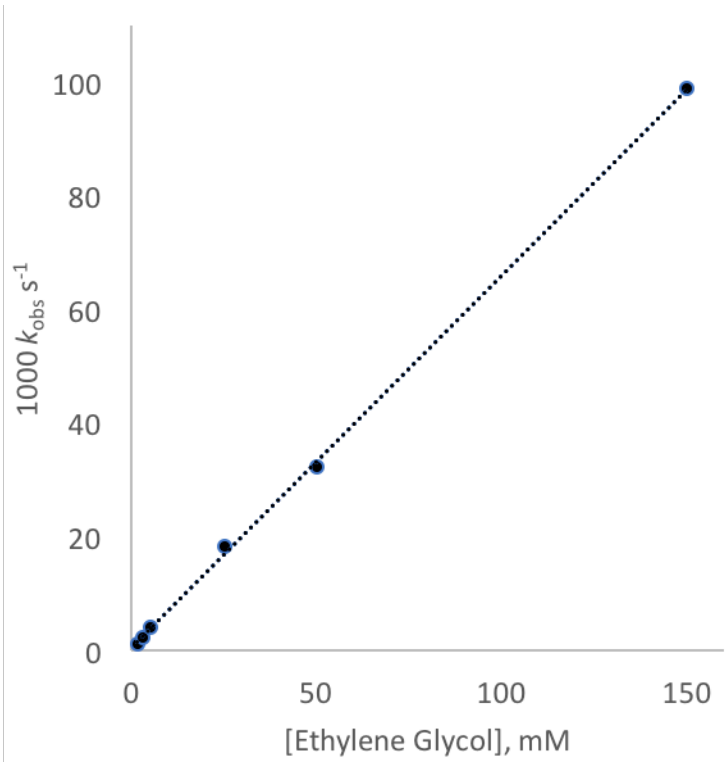


Figure 1 Dependence of k_{obs} for Pb^{2+} -catalyzed monobenzoylation on ethylene glycol with 50 mM lead nitrate and 125 mM triethylamine in water at 4 ℃

A likely route for the reaction of ethylene glycol with BMP to form a monobenzoylated product is shown in Scheme 3. Coordination between lead ions and acyl phosphates is expected to be strong, based on the great affinity of lead for phosphate ions (log K = 3.20).[21] We determined rates of monobenzoylation reactions on ethylene glycol. A plot of initial rates and concentration shows no curvature, even at 0.15 M of ethylene glycol (Figure 1). The lack of saturation prevents determination of the extent to which a complex is formed between lead and ethylene glycol.[22] This also suggests that the bis-bidentate intermediate (EG-Pb-BMP) is higher in energy than the bidentate complex (Pb-BMP), consistent with the rapid competing hydrolysis of acyl phosphates. Organic bases (in dry THF) and lead hydroxides (in water) not only facilitate ionization and

nucleophilicity of the hydroxyl groups of cis-diols, they also stabilize the bis-bidentate coordinated intermediate. The combination of these effects is likely to be the source of the efficiency of the lead-catalyzed reactions.

Other significant catalytic species may be polynuclear lead hydroxide complexes. Dinuclear and trinuclear transition metal complexes catalyze the hydrolysis of phosphate esters, with the Lewis acid activating reaction components.[23,24] Lead ions readily form lead-hydroxo complexes in neutral water.[25] Although the detailed speciation of lead-hydroxo complexes under our reaction conditions is not accessible due to the many variable parameters (pH, concentration of Pb^{2+} and counter ions) [26,27], the presence of polynuclear lead hydroxide should be taken into consideration.[25] Double Lewis acid activation could provide greater rate acceleration than single Lewis acid activation for acylation of diols as coordination between the diol moiety and metal is necessarily stronger in the doubly coordinated system.

Conclusions

We have developed lead-catalyzed monobenzoylation reactions of carbohydrates and polyols that function under mild, aqueous conditions as well as in organic solvents. Regioselective monobenzoylation products can be obtained in water in the presence of BMP and lead nitrate. The efficient catalysis by lead ion, particularly in water, is accomplished through a combination of Lewis acid and Brønsted base catalysis. The development of this efficient pathway contributes not only to direct monobenzoylation of carbohydrates and provides a basis for a better understanding of the activation process of lead ions. Our results suggest that bis-bidentate coordination can be combined with base catalysis to provide an internal promoter for acylation.

Experimental Section

General monobenzoylation procedure of substrates (methyl D-pyranosides and diols) in water.

Methyl D-pyranosides or diols (0.125 mmol, 1 equiv.), $Pb(NO_3)_2$ (0.125 mmol, 1equiv.) and triethylamine (0.313 mmol, 2.5 equiv.) were added to 2.5 ml of ice cooled deionized water. To the solution was added benzoyl methyl phosphate (0.125 mmol, 1 equiv.) and the mixture was allowed to stir at 4 °C for 3 days. Resulting mixture was centrifuged and supernatant was analyzed by reversed-phased HPLC (Jupiter 4μ Proteo 90Å, 10% acetonitrile/water, 1 mL/min, 230nm). Collected products were lyophilized and analyzed by ^{1}H NMR analysis and MS.

Methyl 3-O-benzoyl-α-D-glucopyranoside[28].

Colorless solid (2%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.19 – 7.40 (m, 5H), 5.37 – 5.24 (t, 1H), 4.85 (d, 1H), 4.12 (q, 1H), 3.96 – 3.69 (m, 5H), 3.49 (s, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 4-O-benzoyl-α-D-glucopyranoside[29].

Colorless solid (4%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 – 7.41 (m, 6H), 5.10 (dd, *J* = 10.1, 9.3 Hz, 1H, H-4), 4.89 (d, *J* = 3.9 Hz, 1H, H-1), 4.19 – 4.04 (m, 2H), 3.87 – 3.63 (m, 5H), 3.49 (s, 4H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 6-O-benzoyl-α-D-glucopyranoside[30].

Colorless solid (33%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 7.40 (m, 5H), 4.81 (td, *J* = 6.3, 6.2, 4.2 Hz, 2H), 4.48 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.85 (dddd, *J* = 9.9, 4.1, 2.2, 0.6 Hz, 1H), 3.77 (t, *J* = 9.3, 9.3 Hz, 1H), 3.54 (dd, *J* = 9.5, 3.9 Hz, 1H), 3.46 (s, 4H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 3-O-benzoyl-β-D-glucopyranoside.

Colorless solid (3%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.06 (m, 2H), 7.64 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 5.16 (t, *J* = 9.3 Hz, 1H, H-3), 4.39 (d, *J* = 7.8 Hz, 1H, H-1), 4.02 – 3.81 (m, 3H), 3.70 – 3.62 (m, 1H), 3.61 (s, 3H), 3.54 – 3.49 (m, 1H). MS (ESI) Calcd m/z ($M + Na^+$): 321.09. Found: 321.1.

Methyl 4-O-benzoyl-β-D-glucopyranoside.

Colorless solid (4%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.03 (m, 2H), 7.65 – 7.58 (m, 1H), 7.50 – 7.45 (m, 2H), 5.17 – 5.10 (t, *J* = 9.3 Hz, 1H, H-4), 4.34 (d, *J* = 7.8 Hz, 1H, H-1), 3.92 (t, *J* = 9.2 Hz, 1H), 3.82 (dd, *J* = 12.6, 2.4 Hz, 1H, H-6a), 3.70 (dd, *J* = 12.6, 4.6 Hz, 1H, H-6b), 3.61 (m, 4H, OMe and H-5), 3.54 (dd, *J* = 9.3, 7.7 Hz, 1H ,H-2). MS (ESI) Calcd m/z ($M + Na^+$): 321.09. Found: 321.1.

Methyl 6-O-benzoyl-β-D-glucopyranoside[30].

Colorless solid (38%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.01 (m, 2H), 7.63 – 7.55 (m, 1H), 7.53 – 7.41 (m, 2H), 4.80 (dd, *J* = 12.2, 4.2 Hz, 1H, H-6a), 4.54 (dd, *J* = 12.3, 2.2 Hz, 1H, H-6b), 4.25 (d, *J* = 7.7 Hz, 1H, H-1), 3.66 – 3.52 (m, 5H), 3.49 (dd, *J* = 9.7, 8.9 Hz, 1H), 3.39 (dd, *J* = 9.3, 7.7 Hz, 1H). MS (ESI) Calcd m/z ($M + Na^+$): 321.09. Found: 321.1.

Methyl 3-O-benzoyl-α-D-galactopyranoside[4]

Colorless solid (6%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 – 8.07 (m, 2H), 7.63 – 7.53 (m, 1H), 7.50 – 7.42 (m, 2H), 5.31 (dd, *J* = 10.2, 3.5 Hz, 1H, H-3), 4.93 (d, *J* = 3.9 Hz, 1H, H-1), 4.59 (d, *J* = 2.9 Hz, 1H), 4.18 (dd, *J* = 10.3, 3.9 Hz, 1H, H-2), 4.13 (d, *J* = 1.8 Hz, 2H), 4.11 – 4.07 (m, 1H), 3.51 (s, 3H). MS (ESI) Calcd m/z ($M + Na^+$): 321.09. Found: 321.1.

Methyl 4-O-benzoyl-α-D-galactopyranoside

Colorless solid (7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 – 8.02 (m, 2H), 7.67 – 7.56 (m, 1H), 7.51 – 7.44 (m, 3H), 5.55 (d, *J* = 3.2 Hz, 1H), 4.92 (d, *J* = 3.8 Hz, 1H), 4.12 – 3.94 (m, 3H), 3.69 (dd, *J* = 11.8, 6.6 Hz, 1H), 3.55 (dd, *J* = 11.8, 7.3 Hz, 1H), 3.48 (s, 3H). MS (ESI) Calcd m/z ($M + Na^+$): 321.09. Found: 321.1.

Methyl 2-O-benzoyl-α-D-galactopyranoside[31]**.**

Colorless solid (7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 – 8.02 (m, 2H), 7.67 – 7.55 (m, 1H), 7.50 – 7.42 (m, 2H), 5.21 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2), 5.05 (d, *J* = 3.7 Hz, 1H, H-1), 4.45 (dd, *J* = 3.5, 1.4 Hz, 1H), 4.24 – 4.15 (m, 3H), 4.08 (t, *J* = 1.8 Hz, 1H), 3.42 (d, *J* = 3.8 Hz, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 6-O-benzoyl-α-D-galactopyranoside[32]**.**

Colorless solid (28%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 7.35 (m, 5H), 4.86 (d, *J* = 3.7 Hz, 1H, H-1), 4.66 (dd, *J* = 11.5, 6.1 Hz, 1H, H-6a), 4.49 (dd, *J* = 11.4, 6.8 Hz, 1H, H-6b), 4.13 – 3.97 (m, 2H), 3.83 (qd, *J* = 9.8, 9.7, 9.7, 3.4 Hz, 2H), 3.44 (s, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 3-O-benzoyl-β-D-galactopyranoside[4]**.**

Colorless solid (6%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 – 8.08 (m, 2H), 7.64 – 7.54 (m, 1H), 7.50 – 7.43 (m, 2H), 5.09 (dd, *J* = 10.1, 3.1 Hz, 1H, H-3), 4.60 (dd, *J* = 3.3, 1.2 Hz, 1H), 4.37 (d, *J* = 7.7 Hz, 1H, H-1), 4.25 – 4.11 (m, 2H), 4.03 (dd, *J* = 10.1, 7.8 Hz, 1H, H-2), 3.86 (s, 1H), 3.61 (s, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 4-O-benzoyl- β-D –galactopyranoside.

Colorless solid (11%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 – 8.05 (m, 2H), 7.64 – 7.57 (m, 1H), 7.50 – 7.42 (m, 2H), 5.53 (dd, *J* = 3.5, 1.0 Hz, 1H, H-4), 4.31 (d, *J* = 7.6 Hz, 1H, H-1), 3.93 (dd, *J* = 9.8, 3.5 Hz, 1H, H-3), 3.86 – 3.74 (m, 3H), 3.62 (s, 3H), 3.59 (m, 1H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 2-O-benzoyl-β-D-galactopyranoside.

Colorless solid (3%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.04 (m, 2H), 7.60 – 7.55 (m, 1H), 7.47 – 7.41 (m, 2H), 5.24 (dd, *J* = 9.8, 8.0 Hz, 1H, H-2), 4.53 (d, *J* = 8.0 Hz, 1H, H-1), 4.38 (dd, *J* = 3.7, 1.0 Hz, 1H), 4.27 – 4.09 (m, 2H), 3.86 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.82 (d, *J* = 1.9 Hz,

1H), 3.51 (s, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 6-O-benzoyl-β-D-galactopyranoside[33].

Colorless solid (38%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.02 (m, 2H), 7.63 – 7.55 (m, 1H), 7.52 – 7.42 (m, 2H), 4.70 (dd, *J* = 11.4, 6.8 Hz, 1H, H-6a), 4.53 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6b), 4.25 – 4.16 (m, 1H), 3.99 (dd, *J* = 3.1, 1.2 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.71 – 3.62 (m, 2H), 3.57 (s, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 2-O-benzoyl-α-D-mannopyranoside.

Colorless solid (10%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 – 8.01 (m, 2H), 7.64 – 7.56 (m, 1H), 7.51 – 7.43 (m, 2H), 5.48 – 5.30 (m, 1H), 4.85 (t, *J* = 2.0, 2.0 Hz, 1H), 4.22 – 4.09 (m, 2H), 4.05 – 3.69 (m, 3H), 3.43 (d, *J* = 6.7 Hz, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 3-O-benzoyl-α-D-mannopyranoside.

Colorless solid (7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.03 (m, 2H), 7.65 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 5.45 – 5.29 (m, 1H), 4.80 (t, *J* = 2.1, 2.1 Hz, 1H), 4.40 – 4.17 (m, 2H), 4.02 – 3.88 (m, 2H), 3.81 – 3.75 (m, 1H), 3.45 (d, *J* = 4.2 Hz, 3H). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 4-O-benzoyl-α-D-mannopyranoside[34].

Colorless solid (4%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.03 (m, 2H), 7.65 – 7.58 (m, 1H), 7.50 – 7.44 (m, 2H), 5.28 – 5.21 (t, J = 9.6 Hz, 1H, H-4), 4.86 (d, *J* = 1.7 Hz, 1H, H-1), 4.13 (dd, *J* = 9.3, 3.5 Hz, 1H, H-3), 4.02 (dd, *J* = 3.6, 1.7 Hz, 1H, H-2), 3.87 (ddd, *J* = 10.0, 4.5, 2.4 Hz, 1H, H-5), 3.81 (dd, *J* = 12.5, 2.4 Hz, 1H, H-6a), 3.72 (dd, *J* = 12.5, 4.4 Hz, 1H, H-6b), 3.44 (s, 3H, OMe). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

Methyl 6-O-benzoyl-α-D-mannopyranoside.

Colorless solid (55%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 – 8.05 (m, 2H), 7.63 – 7.55 (m, 1H), 7.50 – 7.42 (m, 2H), 4.86 (dd, *J* = 12.3, 4.1 Hz, 1H, H-6a), 4.78 (d, *J* = 1.6 Hz, 1H, H-1), 4.47 (dd, *J* = 12.3, 2.3 Hz, 1H, H-6b), 3.97 (dd, *J* = 3.4, 1.6 Hz, 1H, H-2), 3.87 (dd, *J* = 9.2, 3.5 Hz, 1H, H-3), 3.82 (dddd, *J* = 9.9, 4.1, 2.3, 0.6 Hz, 1H, H-5), 3.67 (t, *J* = 9.6, 9.6 Hz, 1H, H-4), 3.41 (s, 3H, OMe). MS (ESI) Calcd m/z (M + Na^+): 321.09. Found: 321.1.

1-O-Benzoyl-*myo*-Inositol[35].

Colorless solid (15%).^{1}H NMR (400 MHz, D_2O) δ 8.26 – 8.07 (m, 2H), 7.75 (t, *J* = 7.4, 7.4 Hz, 1H), 7.60 (t, 2H), 5.05 (dd, *J* = 10.3, 2.8 Hz, 1H, H-1), 4.32 (t, *J* = 2.7 Hz, 1H), 4.04 (t, *J* = 9.9 Hz, 1H), 3.81 – 3.67 (m, 2H), 3.47 (t, *J* = 8.9 Hz, 1H). MS (ESI) Calcd m/z (M + Na^+): 307.08. Found: 307.1.

2-O-Benzoyl-*myo*-Inositol[36].

Colorless solid (14%).^{1}H NMR (500 MHz, D_2O) δ 8.12 – 8.05 (m, 2H), 7.87 – 7.64 (m, 1H), 7.62 – 7.54 (m, 2H), 5.72 (t, *J* = 2.5, 2.5 Hz, 1H, H-2), 3.88 – 3.78 (m, 4H), 3.43 (m, 1H). MS (ESI) Calcd m/z (M + Na^+): 307.08. Found: 307.1.

4-O-Benzoyl-*myo*-Inositol[35].

Colorless solid (12%).^{1}H NMR (400 MHz, D_2O) δ 8.23 – 7.96 (m, 2H), 7.66 (t, 1H), 7.51 (t, 2H), 5.30 (t, *J* = 9.7 Hz, 1H, H-4), 4.09 (d, 1H), 3.87 (dd, 1H), 3.73 (t, 1H), 3.63 – 3.54 (m, 2H). MS (ESI) Calcd m/z (M + Na^+): 307.08. Found: 307.1.

5-O-Benzoyl-*myo*-Inositol.

Colorless solid (6%).^{1}H NMR (500 MHz, D_2O) δ 8.21 – 7.46 (m, 5H), 5.06 (t, *J* = 9.6 Hz, 1H, H-5), 4.15 (t, *J* = 2.9 Hz, 1H, H-2), 3.98 (t, J = 9.9 Hz, 2H, H-4, H-6), 3.72 (dd, *J* = 10.1, 2.9 Hz, 2H, H-1, H-3). MS (ESI) Calcd m/z (M + Na^+): 307.08. Found: 307.1.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

- HPLC chromatograms of products and their ^{1}H NMR spectra.

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