A Simple, General, and Highly Chemoselective Acetylation of Alcohols Using Ethyl Acetate as the Acetyl Donor Catalyzed by a Tetranuclear Zinc Cluster

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Abstract: In the presence of a Zn-cluster catalyst, alcohols are efficiently converted to the corresponding acetate just by refluxing in EtOAc. The mild reaction conditions enabled the reactions of various functionalized alcohols to proceed in good to excellent yield. Moreover, even when a large excess of the acetyl donor is used, the hydroxyl groups are selectively acetylated in the presence of highly nucleophilic aliphatic amino groups, approaching chemoselectivity to that of enzymatic system.

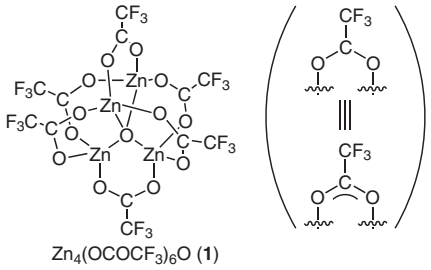
Key words: zinc clusters, catalysis, acetylations, transesterifications, green chemistry

The acetylation of alcohols is one of the most important and fundamental reactions in organic synthesis because the O-acetyl moiety is ubiquitous, not only in synthetic intermediates but also in various biologically active natural products and pharmaceutical compounds.[1] In general, acetylation of hydroxyl groups is conducted with acetyl chloride or acetic anhydride in the presence of greater than stoichiometric amounts of base, resulting in the formation of greater than stoichiometric amounts of unwanted chemical waste.[2,3] Alternatively, acid catalyses with these acetyl donors are also widely used for the acetylation of hydroxyl groups.[2] The unavoidable formation of hydrogen chloride or acetic acid during the reaction, however, leads to the cleavage of sensitive functional groups such as silyl ethers and acetals. Moreover, due to the high electrophilicity of acetyl chloride and acetic anhydride, the acetylation often has poor chemoselectivity.

Catalytic transesterification of esters, especially methyl and ethyl esters, is a highly desirable method for synthesizing diverse esters in terms of atom economy and environmental concerns.[4] In this case, methyl or ethyl alcohol is the only co-product, allowing for neutral reaction conditions. Because of this and additional advantages of transesterification such as ease of handling and high ester stability, transesterification has been applied to acetylation. High conversion, however, is difficult to attain with the direct use of methyl acetate and ethyl acetate for acetylation because of the low electrophilicity of these simple acetates and the existence of a reverse reaction. Thus, most reported acetylations by transesterification use enol esters as the acetyl donor to improve reactivity and prevent the reverse reaction.[5,6] Direct use of methyl acetate and ethyl acetate is limited to only a few examples.[7] Although catalysts such as metallic sulfates,[7a] $Ce(OTf)_4$,[7b] distannoxane,[7c] In/I_2,[7d] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[7e] N-heterocyclic carbene with molecular sieves,[7f] and $H_3PW_{12}O_{40}$[7g] have been reported, the substrate scope needs to be improved. In most cases, only simple alcohols have been used as substrates,[8] and considering its application to complex molecule synthesis, the development of an acetylation with a high level of functional-group compatibility would be particularly valuable.

Recently, we developed a direct conversion of carboxylic acids, esters, and lactones with β-amino alcohols to oxazolines[9a] catalyzed by a μ-oxo-tetranuclear zinc cluster, $Zn_4(OCOCF_3)_6O$ (**1**, Figure 1),[9] based on the cooperative mechanism of zinc ions similar to that of aminopeptidase[10] and efficient multimetallic catalysts.[11] This zinc cluster **1** also efficiently catalyzed the transesterification of various methyl esters under mild conditions and exhibited high tolerance for various functional groups.[9c] Moreover, we successfully developed an O-selective acylation in the presence of primary and secondary aliphatic amino groups using a transesterification catalyzed by **1**.[9b] Herein, we report that the tetranuclear zinc cluster **1** efficiently catalyzed the acetylation of alcohols with various functionalities, such as TES and MEM ethers, acetal, and triene, using ethyl acetate as the acetyl donor. The present catalysis selectively acetylated aliphatic hydroxyl groups in the presence of a phenolic group. Furthermore, even in the presence of a large excess of the acetyl donor, remarkable O-selectivity was achieved in the acetylation of amino alcohols.

We initiated our studies by the catalytic acetylation of a representative substrate, *p*-nitrobenzyl alcohol (**2a**), using various acetates (R^1OAc) as the acetyl donor (Table 1). Although we previously reported that diisopropyl ether is the best solvent for transesterification,[9b,c] here we also



$Zn_4(OCOCF_3)_6O$ (**1**)

Figure 1 Structure of the μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1**)

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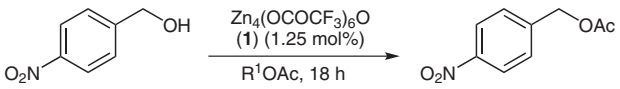
Table 1 Acetylation of *p*-Nitrobenzyl Alcohol (**2a**) Catalyzed by Zinc Cluster **1** Using Various Acetates[a]



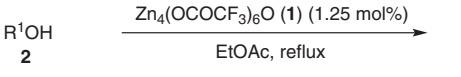
2a **3a**

Entry	R^1OAc, bp (°C)	Temp (°C)	Yield (%)[b]
1	MeOAc, 57–58	reflux	31
2	EtOAc, 77–78	reflux	>99
3[c]	EtOAc, 77–78	reflux	97
4	*i*-PrOAc, 85–91	90	92
5	*n*-PrOAc, 102	90	86
6	PhOAc, 196	90	>99
7	H_2C=CHOAc, 72–73	reflux	>99

[a] Reaction conditions: A solution of **2a** (1.0 mmol), $Zn_4(OCOCF_3)_6O$ (**1**, 1.25 mol%), and R^1OAc (1.7 mL) was refluxed under an argon atmosphere.
[b] GC yield.
[c] Reaction mixture was refluxed under open-air conditions.

used these acetates as a solvent. When alcohol **2a** and 1.25 mol% of **1** were stirred in refluxing ethyl acetate (77 °C, 0.6 M, 17 equiv) for 18 hours, *p*-nitrobenzyl acetate (**3a**) was obtained in greater than 99% yield (entry 2). The reaction under open-air conditions gave a result comparable to that under an argon gas conditions (entry 3). At temperature up to 90 °C (reflux conditions), the reaction using isopropyl acetate (entry 4, 92% yield) and *n*-propyl acetate (entry 5, 86% yield) also proceeded smoothly, in which the existence of excess acetates efficiently prevented the reverse reaction. When methyl acetate was used, low yield was obtained probably due to low reaction temperature (entry 1, 31% yield). Phenyl acetate (entry 6) and vinyl acetate (entry 7) were also good acetyl donors (>99% yield) because the resulting co-products, phenol and acetaldehyde, did not participate in the reverse reaction. Because of the stability, accessibility, and economic advantages of ethyl acetate, we used this as the acetyl donor in the present catalysis.

Table 2 Acetylation of Various Alcohols **2** Catalyzed by Zinc Cluster **1** Using Ethyl Acetate as an Acetyl Donor[a]



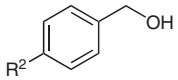
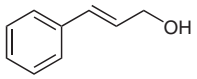
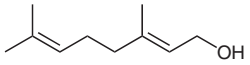
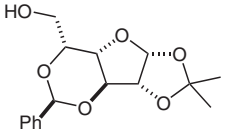
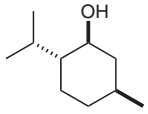
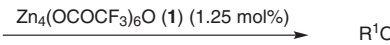
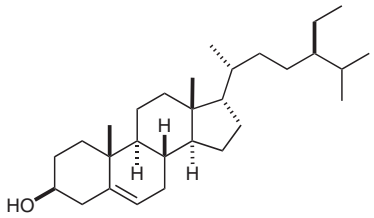
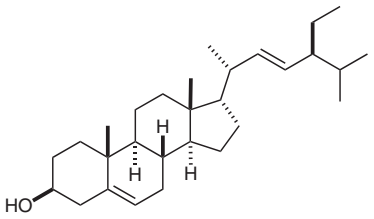
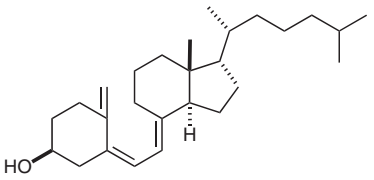
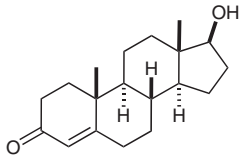
Entry	Substrate: R^1OH **2**			Time (h)	Yield (%)[b]
1		R^2 = H	**2b**	18	98
2		R^2 = Cl	**2c**	38	76
3		R^2 = Br	**2d**	38	81
4		R^2 = OTBS	**2e**	24	97
5		R^2 = CH_2OTES	**2f**	18	89[c]
6		R^2 = CH_2OMEM	**2g**	36	96
7		R^2 = CH_2OBz	**2h**	40	83[c]
8		R^2 = CH_2OPiv	**2i**	36	89[c]
9	$Me(CH_2)_{17}OH$		**2j**	38	>99
10			**2k**	38	94
11			**2l**	24	97
12[d]			**2m**	18	>99
13			**2n**	18	75

Table 2 Acetylation of Various Alcohols **2** Catalyzed by Zinc Cluster **1** Using Ethyl Acetate as an Acetyl Donor[a] (continued)



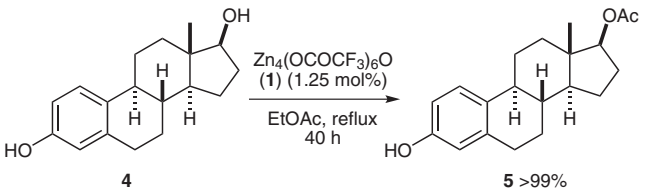
Entry	Substrate: R^1OH **2**		Time (h)	Yield (%)[b]
14[d]		**2o**	40	>99
15[d]		**2p**	40	>99
16[d]		**2q**	40	>99
17[d]		**2r**	40	93

[a] Reaction conditions: A solution of alcohol **2** (3.0 mmol), $Zn_4(OCOCF_3)_6O$ (**1**, 1.25 mol%), and EtOAc (5.0 mL) was refluxed under an argon atmosphere.
[b] Isolated yield.
[c] Unreacted substrate was recovered (entry 5: 5%, entry 7: 9%, and entry 8: 7%).
[d] Reaction was carried out on a 1.0 mmol scale.

We next investigated the scope and limitations of alcohols **2** (Table 2).[12] Benzyl alcohols with various functionalities in the *para* position were successfully converted to the corresponding acetates **3b–i** in good to excellent yield (entries 1–8). Of particular note is that highly acid-sensitive TES ether survived under the reaction conditions (entry 5). Moreover, the benzoyl (entry 7) and pivaloyl (entry 8) groups were not scrambled. Other types of primary aliphatic alcohols were also suitable substrates for this catalysis (entries 9–12). In the case of geraniol (**2l**), neither the isomerization to nerol nor cyclization of the geranyl moiety occurred (entry 11).[13] Acetylation of the D-glucose derivative **2m**, which has both isopropylidene and benzylidene acetal functionalities, proceeded in quantitative yield without cleavage of the acetal protecting groups (entry 12). The present catalysis was also applicable to the acetylation of secondary alcohols. Although the reaction of (+)-menthol (**2n**) had slightly lower reactivity due to the steric hindrance of **2n**, the corresponding acetate **3n** was obtained in reasonable yield (entry 13, 75% yield). Secondary alcohols on various steroid compounds in which triene and enone functionalities remained intact were acetylated in high yield (entries 14–17). Epimerizations of the α-stereocenter of the hydroxyl groups was not observed in any case.

In contrast, the acetylation of tertiary alcohols and phenols[14] did not proceed at all due to steric hindrance and low nucleophilicity, respectively. The steric hindrance and low nucleophilicity can be exploited for selective acetylation of an aliphatic hydroxyl group in the presence of a phenolic group. The reaction of β-estradiol (**4**) resulted in the exclusive formation of monoacetate **5** in greater than 99% yield (Equation 1) and, to the best of our knowledge, this is the first example of a highly chemoselective catalytic acetylation of secondary aliphatic alcohols over that of aromatic alcohols through transesterification.[15]

To expand the synthetic and environmental advantages of this catalysis, we examined additional chemoselective acetylation reactions, namely O-selective acetylation of amino alcohols. O-Selective acylation of amino alcohols is not an easy task because the amino group has much



Equation 1

higher nucleophilicity compared to the hydroxyl group.[16] Thus, although there are a few excellent precedents of O-selective acetylation of amino alcohols using highly reactive acetyl donor,[5f,17] exclusive N-acetylation[17a,b] and partial imine formation[5f] occurred in the presence of aliphatic amino group. Only zinc cluster **1** catalytically promoted a O-acylation of an aliphatic amino alcohol with broad substrate generality, where slightly excess amounts (1.2 equiv) of amino alcohol to methyl ester were used.[9b] For the current acetylation conditions, however, we used ethyl acetate as both the acetyl donor and solvent (17 equiv), which required a higher level of chemoselectivity. To gain insight into the difference in the reactivity between the hydroxyl and amino groups, we followed the time-course of the acetylation using a 1:1 mixture of *n*-hexanol (**2s**) and *n*-hexylamine (**6s**, Figure 2). To our surprise, O-acetylation proceeded quite rapidly as compared with N-acetylation, and the yield of the corresponding *n*-hexyl acetate (**3s**) reached 97% within 1 hour, together with only 2% *n*-hexylacetamide (**7s**). Moreover, even after 2 hours stirring with excess amounts of the acetyl donor, the yield of acetamide **7s** remained very low (6%), demonstrating quite high O-selectivity of the current catalyst system. Acetylations using various combinations of alcohols and amines also gave the corresponding acetates **3** in a highly chemoselective manner.[12]

Finally, we examined O-selective acetylation of amino alcohol using 4-piperidinemethanol (**8**), bearing both primary hydroxyl and secondary amino groups, as a representative substrate (Scheme 1). The acetylation of amino alcohol **8** with ethyl acetate (17 equiv) catalyzed by the zinc cluster **1** proceeded smoothly within 12 hours to exclusively provide the corresponding O-acetylated product **9**.[18] In contrast to our catalysis, acetylation using Ac_2O as the acetyl donor gave N-acetylated product **10** in quantitative yield, consistent with expected chemoselectivity.[12] It is noteworthy that such high chemoselectivities were realized even when a large excess of the acetyl donor was used.[19] This unusual selectivity of **1** may be due to the fact that the simultaneous activation of the ester and hydroxyl groups by the two adjacent zinc ions in the cluster **1** is superior to the simultaneous activation of the ester and amino groups.

In summary, we successfully developed a tetranuclear zinc-cluster-catalyzed acetylation of various primary and secondary alcohols using ethyl acetate as an acetyl donor. The present catalysis has several appealing features, including a high tolerance of acid-sensitive functional

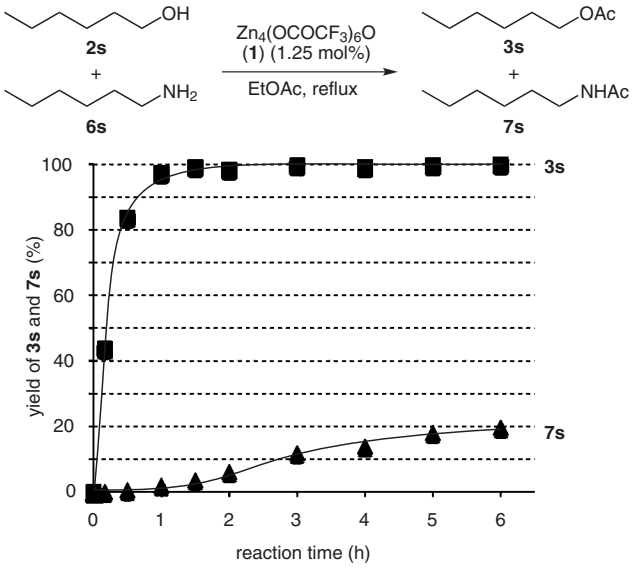
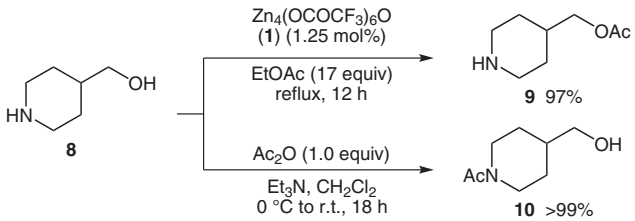


Figure 2 Time-course for the acetylation of alcohol **2s** to acetate **3s** and amine **6s** to acetamide **7s** catalyzed by zinc cluster **1**



Scheme 1 Acetylation of amino alcohol **8**

groups, economical advantages of using ethyl acetate directly as the acetyl donor, low catalyst toxicity, and operationally simple reaction conditions. Moreover, we succeeded in developing a highly O-selective acetylation of a hydroxyl group in the presence of primary and secondary aliphatic amino groups, which is difficult to achieve with other catalysts. Such a high chemoselectivity was achieved even using excess amounts of the acetyl donor. This catalytic system will be useful as an environmentally benign acetylation reaction and provides a useful tool for modern organic synthesis. Further studies of the reaction mechanisms and applications to other environmentally friendly reactions are ongoing.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) See Supporting Information for details.

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(14) In a similar way, acidic alcohols, such as 1,1,1,3,3,3-hexafluoropropan-2-ol (pK_a 9.3), did not participate in the acylation, see ref. 9c.

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(18) Yield of **9** was determined after N-Boc protection to simplify the analysis.

(19) **Typical Experimental Procedure for the Acetylation of Alcohol 2f**

A mixture of $Zn_4(OCOCF_3)_6O$ (**1**, 36 mg, 0.038 mmol), 4-(triethylsiloxymethyl)benzyl alcohol (**2f**, 759 mg, 3.0 mmol), and EtOAc (5.0 mL) was refluxed for 18 h under an argon atmosphere. The resulting mixture was concentrated and purified by silica gel column chromatography (silica gel, hexane–EtOAc = 20:1 to 4:1) to provide the acetate **3f** (790 mg, 89%) as a colorless oil together with unreacted substrate **2f** (38 mg, 5%). IR (neat NaCl): 2955, 2876, 1744, 1517, 1458, 1415, 1379, 1362, 1228, 1092, 1019, 971, 820, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 35 °C): δ = 0.65 (q, *J* = 7.5 Hz, 6 H, $SiCH_2CH_3$), 0.98 (t, *J* = 7.5 Hz, 9 H, $SiCH_2CH_3$), 2.08 (s, 3 H, $COCH_3$), 4.73 (s, 2 H, $ArCH_2OSi$), 5.09 (s, 2 H, $ArCH_2OAc$), 7.32 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C): δ = 4.51, 6.70, 20.92, 64.39, 66.13, 126.32, 128.21, 134.62, 141.54, 170.76. MS (EI): *m/z* (%) = 294 (1) [M^+], 265 (62), 145 (100), 103 (39), 75 (20). HRMS (EI): *m/z* calcd for $C_{16}H_{26}O_3Si$: 294.1651; found: 294.1646.