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A Tetranuclear-Zinc-Cluster-Catalyzed Practical and Versatile Deprotection of Acetates and Benzoates

Takanori Iwasaki,[a] Kazushi Agura,[a] Yusuke Maegawa,[a] Yukiko Hayashi,[a]
Takashi Ohshima,*[b] and Kazushi Mashima*[a]

Acyl groups, especially acetyl groups, are one of the most common and useful protecting groups in organic synthesis.[1] Consequently, a number of acylation and deacylation methods have been developed[2] and are widely utilized in organic synthesis, such as natural product synthesis and industrial processes.[3] The increased demand for an environmentally benign process with high total efficiency, however, requires the development of more operationally simple, safe, and environmentally friendly alternatives.[4] In this context, transesterifications are especially attractive, because they require only a catalytic amount of reagent and have additional advantages, such as mild reaction conditions, high chemoselectivity, ease of handling, and high ester stability.[5] Indeed, several efficient transesterification catalysts for acetylation have been reported, including a Zn-catalyzed acetylation we developed using ethyl acetate as the acetyl donor.[6] In contrast, deacylation still relies largely on the classical basic hydrolysis because of its efficiency and irreversible nature.[1] The disadvantage of this procedure, however, is the low tolerance to many functional groups and the potential occurrence of undesired side reactions, such as elimination and epimerization.[5,7] Although catalytic cleavage of ester bonds using simple alcohol nucleophiles, such as methanol and ethanol, is a more desirable method, it is not a trivial task; for example, catalytic activity of most of Lewis acid catalysts decreases in the presence of stoichiometric or excess amounts of alcohol. Alkali metal alkoxides,[7] KCN,[8] Sc(OTf)$_3$,[9] organotin dimers,[10] proazaphosphatranes,[11] Yb(OTf)$_3$,[12] tris(2,4,6-trimethoxyphenyl)phosphine,[13] acetyl chloride,[14] ZrCl$_4$,[15] and enzymes[16] have been applied to the deacetylation of aliphatic acetates. Among them, the neutral organotin catalyst [{tBu$_2$SnOH(Cl)}$_2$] developed by Otera et al.[10] is the most efficient catalyst in terms of mild reaction conditions and catalytic activity, though it does require the use of a toxic heavy metal. Even under these neutral conditions, however, undesired reactions such as elimination reactions sometimes occur. Low conversion of sterically congested acetates of secondary and tertiary alcohol is another problem. To date, the best result in deacetylation of tertiary acetate[17] was a yield of only 22% and the harsh conditions resulted in an elimination reaction.[10]

As part of our ongoing studies of environmentally friendly, direct catalytic reactions, we recently developed an μ-oxo-tetranuclear zinc cluster [Zn$_4$(OCOCF$_3$)$_6$O] (**1**),[6,18,19] which efficiently catalyzed the transesterification of various methyl esters under mild conditions.[18b,c] The neutral and mild reaction conditions enabled the transesterification of esters and alcohols with various functional groups, affording highly functionalized esters in good to excellent yield. Moreover, we successfully developed a chemoselective acylation of hydroxyl groups in the presence of primary and secondary aliphatic amino groups.[6,18b] This unusual selectivity of **1** can be ascribed to the simultaneous activation[20,21] of both esters and hydroxyl groups by the two adjacent zinc ions in cluster **1**. This protocol is also applicable to the catalytic acetylation of alcohols with various functionalities through the use of ethyl acetate as the acetyl donor and solvent.[6] Because the zinc cluster **1** retains the high catalyst activity even in the presence of excess amounts of alcohol,[18a] we anticipated that deacetylation, which is the reverse reaction of the above-mentioned acetylation, would also be catalyzed by **1** just by changing the solvent from ethyl acetate to methanol. Here, we report that the zinc cluster **1** efficiently catalyzed deacetylation and debenzoylation when methanol was

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[a] Dr. T. Iwasaki, K. Agura, Y. Maegawa, Y. Hayashi,
Prof. Dr. K. Mashima
Department of Chemistry
Graduate School of Engineering Science
Osaka University, CREST, 1-3 Machikaneyama
Toyonaka, Osaka 560-8631 (Japan)
Fax: (+81) 6-6850-6245
E-mail: mashima@chem.es.osaka-u.ac.jp

[b] Prof. Dr. T. Ohshima
Graduate School of Pharmaceutical Sciences
Kyushu University, CREST, 3-1-1 Maidashi
Higashi-ku, Fukuoka 812-8582 (Japan)
Fax: (+81) 92-642-6650
E-mail: ohshima@phar.kyushu-u.ac.jp

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used as the nucleophile and solvent. Under the present mild reaction conditions, various functional groups, such as tetrahydropyranyl ether, silyl ether, pivaloyl ester, *N*-Boc (*tert*-butoxycarbonyl), and *N*-Cbz (benzyloxycarbonyl), remained intact and there were no undesired side reactions, such as elimination, isomerization, and epimerization, observed. In addition, deacetylation of even low reactive tertiary acetates proceeded in good yield without any elimination reactions.

We initiated our studies of a catalytic deacetylation using *p*-nitrobenzyl acetate (**2a**) as a representative substrate (Figure 1). Because transesterification is an equilibrium reaction,[5] we used the nucleophilic reagents methanol or ethanol as the solvent (0.5 M) to attain high conversion. In the presence of 1.25 mol% of **1**, deacetylation of **2a** was completed within 2 h, both under methanol (▲, b.p. = 65 °C) and ethanol (■, b.p. = 78 °C) reflux conditions. Even at a lower temperature (50 °C), the reactions in methanol (●) and ethanol (◆) proceeded smoothly and the yields of the corresponding alcohol **3a** reached 95% within 6 h, indicating that the steric bulkiness of the nucleophiles has only a limited effect on the reactivity. This process can be conducted very easily and safely; the deacetylation proceeded simply by heating the acetate in commercial methanol in the presence of a catalytic amount of **1** (1.25 mol%). Thus, nearly pure product **3a** was obtained by simple evaporation and filtration through a short-pad silica gel, because methyl or ethyl acetate was the only co-product of this process.

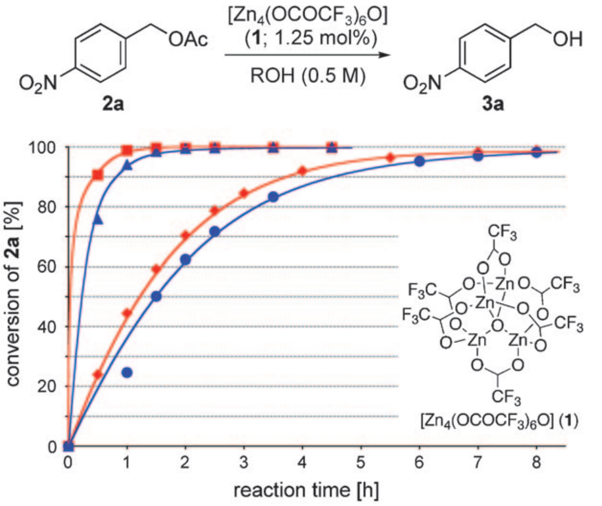
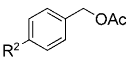
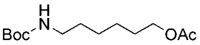
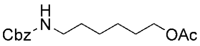
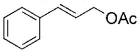
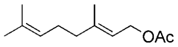
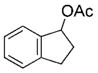
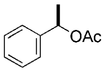
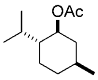
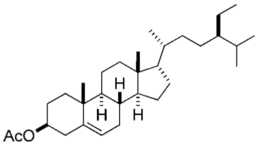


Figure 1. Time-course for the zinc cluster **1** catalyzed deacetylation of acetate **2a** to alcohol **3a** under MeOH reflux (▲), EtOH reflux (■), MeOH at 50 °C (●), and EtOH at 50 °C (◆) conditions.

We then examined the substrate generality of the Zn-cluster-catalyzed deacetylation under methanol reflux conditions (Table 1).[22] Benzyl acetates with various substituents at the *para*-position were successfully converted to the corresponding alcohols **3** in good to excellent yield (Table 1, entries 1–5). Acid-sensitive 2-methoxyethoxymethyl (MEM; entry 1), tetrahydropyranyl (THP; entry 2), and *tert*-butyldimethylsilyl (TBS; entry 3) ethers were all tolerated. In addition, deprotection and scrambling of the pivaloyl group were not observed (entry 4) due to the steric hindrance of the pivaloyl group. [Ti(O-*i*Pr)$_4$], which is often used as a transesterification catalyst, mediates *O*-alkyl transesterification of carbamates, such as *N*-Boc and *N*-Cbz protecting groups, with alcohols.[23] In contrast, under the present conditions, the reactions of acetates bearing *N*-Boc (entry 6) and *N*-Cbz (entry 7) groups afforded the corresponding alcohols **3g** and **3h**, respectively, in quantitative yield without loss of the carbamate-protecting groups. Deacetylation of allylic acetates **2j** (entry 7) and **2k** (entry 8) also proceeded in high yield (**3j**: 92%, **3k**: 96%); neither isomerization nor cyclization of geraniol (**3k**) occurred.[24] While deacetylation of benzylic acetates often causes elimination problems,[5,10] the present

Table 1. Zinc cluster **1** catalyzed deacetylation of acetates **2**.[a]

$$\mathrm{R^1OAc}\ \mathbf{2}\ \xrightarrow[\text{MeOH, reflux}]{[\mathrm{Zn_4(OCOCF_3)_6O}]\ (\mathbf{1};\ 1.25\ \text{mol\%})}\ \mathrm{R^1OH}\ \mathbf{3}$$

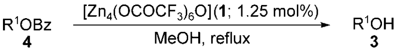
	Substrate: R^{1}OAc **2**		*t* [h]	Yield [%][b]
1		R^2 = CH$_2$OMEM **2b**	12	97
2		R^2 = CH$_2$OTHP **2c**	12	98
3		R^2 = CH$_2$OTBS **2d**	12	96
4		R^2 = CH$_2$OPiv **2e**	12	92
5		R^2 = CH$_2$NHAc **2f**	12	98
6[c]		**2g**	18	>99
7[c]		**2h**	18	>99
8	CH$_3$(CH$_2$)$_{17}$OAc	**2i**	12	96
9		**2j**	12	92
10		**2k**	12	96
11		**2l**	12	85
12		**2m**	18	98
13	(>99% *ee*) 	**2n**	48	(>99% *ee*) 67
14		**2n**	96	81
15[c]		**2o**	18	27[d]
16[c,e]		**2o**	18	83[d]

[a] Reaction conditions: A solution of acetate **2** (3.0 mmol), [Zn$_4$(OCOCF$_3$)$_6$O] (**1**; 1.25 mol%), and MeOH (6.0 mL) was heated to reflux under an argon atmosphere. [b] Isolated yield. [c] Reaction was performed on a 1.0 mmol scale. [d] Yield was determined by ^{1}H NMR analysis. [e] Reaction was performed with EtOH instead of MeOH to be homogeneous.

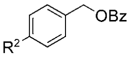
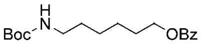
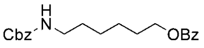
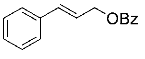
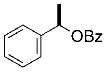
Zn catalysis was also applicable to 1-indanyl acetate (**2l**) (entry 11) and α-methylbenzyl acetate (**2m**) (entry 12), giving **3l** and **3m** in 85 and 98 % yields, respectively. In the latter case, there was no decrease in the enantiomeric excess of **3m** (>99 % *ee*). Although deacetylation of the sterically more congested menthyl acetate (**2n**) occurred in 67 % yield even after 48 h (entry 13), prolonging the reaction time to 96 h improved the yield to 81 % (entry 14). The reaction of β-sitosteroyl acetate (**2o**) was quite slow due to the low solubility of **2o** in methanol (entry 15, 27 % yield). By changing the solvent from methanol to ethanol, the yield of product **3o** improved to 83 % (entry 16).[25]

A benzoyl group is also a commonly used alcohol protecting group.[1] Accordingly, we investigated the applicability of the present Zn catalysis to debenzoylation (Table 2). Although the reactivity of benzoates **4a–d,g,h,j,m** was slightly lower than that of the corresponding acetates **2a–d,g,h,j,m**, longer reaction times led to high yields of the desired products **3a–d,g,h,j,m** (72 to >99 % yields).[26]

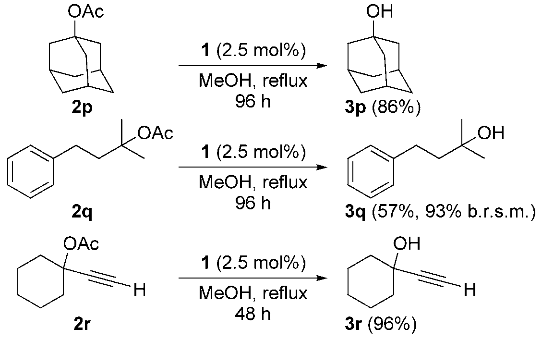
Table 2. Zinc cluster **1** catalyzed debenzoylation of benzoates **4**.[a]



$$\underset{\mathbf{4}}{R^1OBz} \xrightarrow[\text{MeOH, reflux}]{[Zn_4(OCOCF_3)_6O](\mathbf{1};\ 1.25\ \text{mol\%})} \underset{\mathbf{3}}{R^1OH}$$

	Substrate: R^1OBz **4**		*t* [h]	Yield [%][b]
1		$R^2 = NO_2$ **4a**	18	>99[c]
2		$R^2 = CH_2OMEM$ **4b**	25	92
3		$R^2 = CH_2OTHP$ **4c**	18	97
4		$R^2 = CH_2OTBS$ **4d**	18	87
5[d]		**4g**	48	99
6[d]		**4h**	48	93
7		**4j**	16	96
8[d]		**4m**	48	72
	(>99 % *ee*)			(>99 % *ee*)

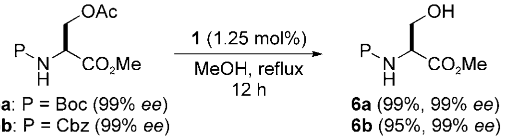
[a] Reaction conditions: A solution of benzoate **4** (3.0 mmol), $Zn_4(OCOCF_3)_6O$ (**1**) (1.25 mol %), and MeOH (6.0 mL) was heated to reflux under an argon atmosphere. [b] Isolated yield. [c] Yield was determined by GC analysis. [d] Reaction was performed on a 1.0 mmol scale.



Scheme 1. Deacetylation of tertiary acetates **2p–r** (b.r.s.m = based on the recovered starting material).

We then turned our attention to the development of a catalytic deacetylation of tertiary acetates, which is more challenging. Although we previously found that **1**-catalyzed acetylation of highly congested 1-adamantanol (**3p**) with ethyl acetate did not give the desired product **2p**,[6] the reverse reaction, namely deacetylation of **2p** to **3p** with methanol, readily proceeded (86 % yield) under the optimized conditions (Scheme 1). Deacetylation of **2q** is another challenging reaction, because elimination of the acetoxy moiety of **2q** readily proceeds.[10] Thus, the reported catalytic deacetylation of this type of tertiary acetate has a very low yield. In contrast, under the present mild conditions, the Zn cluster **1** catalyzed the deacetylation of **2q** without any undesired elimination reaction, leading to the formation of **3q** in 57 % yield (93 % yield based on the recovered starting material). It is worth noting that, although the catalytic activity for sterically congested substrates is not yet highly satisfactory, the present reaction is to our knowledge the most effective catalytic deacetylation of tertiary acetates through transesterification. As in the previous reports,[10c,11] propargylic tertiary acetate **2r** is a rather reactive substrate for catalytic deacetylation, and the product **3r** was obtained in 96 % yield without undesired rearrangement reactions.[27]

Finally, to demonstrate the mildness of the present reaction conditions, we performed the reaction of *O*-acetyl-protected L-serine derivatives **5a** (*N*-Boc) and **5b** (*N*-Cbz) (Scheme 2). In both cases, the deacetylation proceeded efficiently (**6a**: 99 % yield, **6b**: 95 % yield) and neither epimerization of the α-stereocenter[5,7] nor *O*-alkyl transesterification of carbamates[23] was observed.



Scheme 2. Deacetylation of *O*-acetyl-protected L-serine derivatives **5a**,**b**.

Although an exact reaction mechanism is not clear yet, the following studies suggested that a zinc cluster closely related to the μ-oxo tetranuclear zinc cluster **1** acts as an active species in the reaction media. Existence of the tetranuclear zinc cluster and another tetranuclear zinc species, which loses one trifluoroacetate ligand from **1**, are confirmed by electrospray ionization mass spectrometry of the zinc cluster **1** in methanol. This observation indicates that trifluoroacetate in the cluster **1** easily disassociates from the tetranuclear zinc core by nucleophilic attack of methanol, yielding an unsaturated Zn-O-Zn active site. Moreover, our previous investigation on zinc cluster **1** catalyzed transformation showed that Lewis acidity of the zinc cluster **1** did not decrease even in the presence of excess amount of methanol.[18a] Similarly, under the present reaction conditions, both acetates and methanol may be simultaneously activated by the two adjacent zinc ions in the active species in selective manner even in the presence of excess amount of methanol or ethanol.

In conclusion, we achieved a successful catalytic transesterification of various acetates and benzoates with methanol using only a catalytic amount of the tetranuclear zinc cluster **1**. Due to the high tolerance of Lewis acidic catalyst **1** to alcohol and the mild reaction conditions, reactions with various acid- and nucleophile-sensitive functional groups, such as THP ether, silyl ether, pivaloyl ester, *N*-Boc, and *N*-Cbz, proceeded efficiently to provide the corresponding alcohol in high yield without any decomposition of the functional groups, elimination of an acetoxy moiety, or epimerization reactions. In addition, the present catalysis is applicable to less reactive tertiary acetates, the deacylation of which is difficult to achieve by transesterification with other catalysts. Together with the economical advantages of using methanol as the nucleophile and solvent, the low catalyst toxicity, and the operationally simple reaction conditions, this new catalytic system will provide a useful tool not only for modern organic synthesis of highly functionalized complex molecules in a mild and chemoselective deprotection reaction, but also for industrial production as a highly economic and environmentally friendly catalytic process. Further investigation of the reaction mechanisms, modification of the zinc cluster, and applications to other environmentally friendly reactions are ongoing.

Experimental Section

General procedure for the deacetylation of acetate catalyzed by a tetranuclear zinc cluster 1: Cluster **1** (0.038 mmol), acetate **2** (3.0 mmol), and methanol (6.0 mL, 0.5 M) were refluxed for periodic time in an argon atmosphere. The resulting mixture was concentrated and purified by silica gel column chromatography to give deacetylated product **3**.

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Keywords: cluster compounds · deacylation · homogeneous catalysis · transesterification · zinc

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[25] As reported in our previous manuscripts,[18] the Zn cluster showed comparable catalyst activity in various solvents, including hexane, toluene, chlorobenzene, diglyme, dioxane, DMF, and DMSO. Thus, in the case of substrates that are insoluble in alcohols, mix-solvent system would be a good choice of solvents. For example, the deacetylation of **2a** (1.0 mmol) in MeOH/hexane (1:1, 2 mL) gave **3a** in 89 % yield.

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