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A trifluoroacetic acid adduct of a trifluoroacetate-bridged μ_4 -oxo-tetranuclear zinc cluster, $Zn_4(OCOCF_3)_6O \cdot CF_3CO_2H$: synthesis under mild conditions and catalytic transesterification and oxazoline formation†

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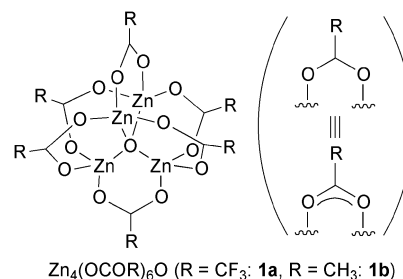
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Synthesis of a trifluoroacetate-bridged tetranuclear zinc cluster and its trifluoroacetic acid (TFA) adduct under mild conditions ($\sim 110^\circ\text{C}$) was achieved. The catalytic activity and functional group tolerance of the TFA adduct in transesterification and oxazoline formation were almost identical to those of the original zinc cluster.

Transesterification is one of the most straightforward organic transformations,¹ and various catalyst systems have been developed.^{2–5} Recently, we reported that a trifluoroacetate-bridged tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1a**) serves as an efficient catalyst with broad substrate generality for the transesterification of various methyl esters with various alcohols,^{6a,b} catalytic acetylation in ethyl acetate,^{6c} and catalytic deacetylation in methanol,^{6d} as well as the direct conversion of esters, lactones, and carboxylic acids to oxazolines.^{6e} Because these catalyses proceed under neutral conditions, various functional groups, such as THP ether, TES ether, acetal, as well as *N*-Boc, *N*-Cbz, and *N*-Fmoc groups, remain intact, and undesirable side reactions, such as elimination, isomerization, and epimerization, are suppressed. Further, a unique hydroxy group-selective acylation in the presence of much more nucleophilic primary and secondary aliphatic amino groups is achieved by **1a**.^{6a,c}

The requirements for any suitable catalyst are easy preparation, easy handling, and ready generation of catalytically active species under desired conditions. Zinc cluster **1a**, the best catalyst for transesterification, was originally synthesized by


 Fig. 1 Structure of μ_4 -oxo tetranuclear zinc clusters **1**.

heating a zinc trifluoroacetate hydrate $Zn(OCOCF_3)_2 \cdot xH_2O$ (**2a**) at 360°C under high vacuum (<0.02 mmHg) to produce solidified zinc cluster **1a** on a glass wall, followed by collection of the resulting white solid under argon atmosphere, avoiding contact with moisture, to give pure **1a** in 84% yield.^{6c,7} This preparation method could be performed in gram-scale. This synthetic methodology was based on the first synthesis of the acetate-bridged tetranuclear zinc cluster $Zn_4(OCOCH_3)_6O$ (**1b**), which was obtained by vacuum distillation of zinc acetate hydrate $Zn(OCOCH_3)_2 \cdot xH_2O$ (**2b**) by Auger and Robin in 1924,⁸ and its μ_4 -oxo structure was later established by X-ray crystallographic analysis by Wyart^{9a} and Koyama and Saito^{9b} (Fig. 1). Other tetranuclear zinc clusters with different carboxylate ligands, such as $Zn_4(OCOR)_6O$ ($R = \text{Et}, n\text{-Pr}, t\text{-Bu}, \text{Ph}, \text{etc.}$), were subsequently prepared using this synthetic route or similar pyrolytic methods.¹⁰ Although such sublimation provides highly pure zinc clusters, the high temperature synthesis and moisture-free handling required for **1a** decrease its accessibility to organic chemists, and thus the development of a more practical synthetic method of **1a** is in high demand. Herein, we report the novel synthesis and catalytic performance of a TFA adduct of **1a**, namely $Zn_4(OCOCF_3)_6O \cdot CF_3CO_2H$ (**3**), which was practically synthesized under toluene refluxed conditions ($\sim 110^\circ\text{C}$) in greater-than kilogram scale. The catalytic activity and functional group tolerance of the TFA adduct **3** were almost identical to those of **1a**. Another great advantage of **3** compared with **1a** is its easy handling due to its much less hygroscopic nature.

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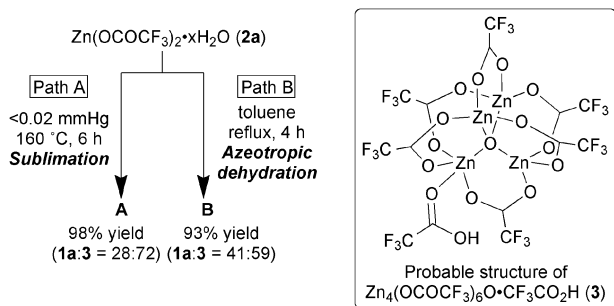


Fig. 2 Synthesis of zinc clusters and probable structure of $\text{Zn}_4(\text{OCOCF}_3)_6\text{O}\cdot\text{CF}_3\text{CO}_2\text{H}$ (**3**).

Intensive studies to evaluate the reaction temperature indicated that even at a much lower temperature ($<160\text{ }^\circ\text{C}$) the assembly of the requisite zinc ions, trifluoroacetates, and μ -oxo ligand proceeded smoothly to form the μ_4 -oxo tetranuclear zinc carboxylate motif. Heating the zinc trifluoroacetate hydrate **2a**¹¹ at $120\text{ }^\circ\text{C}$ under high vacuum conditions for 1.5 h, and then gradually rising the temperature to $160\text{ }^\circ\text{C}$ produced a white solid **A** by sublimation of the reaction product (Fig. 2, path A). Electrospray ionization (ESI) mass analysis of this white solid **A** (negative mode) showed a peak that was assigned to $[\text{Zn}_4(\text{OCOCF}_3)_6\text{O}\cdot\text{CF}_3\text{CO}_2]^-$ (Fig. 3). In addition, ^{19}F -NMR and ^{13}C -NMR spectra of solid **A** were quite similar to those of the zinc cluster **1a**, though the ^1H -NMR spectrum of **A** displayed an additional signal at around 10 ppm, which was assigned to an acidic proton. Based on these results, solid **A** is considered to be a TFA adduct of **1a**, that is, $\text{Zn}_4(\text{OCOCF}_3)_6\text{O}\cdot\text{CF}_3\text{CO}_2\text{H}$ (**3**).¹² To obtain more information about the composition of solid **A**, we investigated the zinc content of **A** by titration. The theoretical zinc content of zinc cluster **1a** and TFA adduct **3** was 27.4% and 24.5%, respectively, and the observed zinc content of **A** was 25.2%, suggesting that solid **A** was a 28 : 72 mixture of **1a** and **3**. Thus, the yield of **A** based on the zinc content was determined to be 98%. Re-sublimation of **A** at $170\text{ }^\circ\text{C}$ with generation of TFA increased the zinc content to 26.6%, suggesting that the ratio of **1a** increased (**1a** : **3** = 75 : 25). These experimental results indicated that high temperature is essentially required, not for

the construction of the μ_4 -oxo tetranuclear zinc carboxylate motif, but for the dissociation of the coordinated TFA in **3**. To confirm this hypothesis, we performed a density functional theory calculation at the B3LYP¹³/(LANL2DZ for Zn and 6-31G(d,p) for others) level and found that the energy of the TFA adduct **3** is $5.18\text{ kcal mol}^{-1}$ lower than that of **1a** + TFA.⁷

The observation that the μ_4 -oxo tetranuclear zinc carboxylate motif is formed at a relatively low temperature ($\sim 160\text{ }^\circ\text{C}$) led us to develop a more practical and scalable method for preparing the zinc cluster. After screening various conditions, we successfully developed a new azeotropic dehydration method as a highly efficient method in industrial preparation of the zinc cluster (Fig. 2, path B). Heating at $60\text{ }^\circ\text{C}$ in toluene dissolved **2a** completely, and then refluxing the resulting solution for 4 h generated white precipitates together with the formation of an azeotropic mixture (pH ≈ 1) of toluene, water, and TFA. The resulting precipitates were filtered, leaving a white solid **B**.¹⁴ The spectroscopic data of **B** were identical to those of **A**, except for a zinc content of 25.6%, suggesting that the white solid **B** was a mixture of **1a** and **3** in a ratio of 41 : 59 and thus the yield of **B**, based on zinc content, was 93%. This reaction protocol was applicable in kilogram scale with the same efficiency. Solids **A** and **B** were much less hygroscopic than **1a**, probably because the additional TFA stabilized the Lewis acidic coordination site of **1a**.

To determine whether the solids **A** and **B** could be alternative catalysts to **1a**, we first examined the catalytic activities of **A** and **B** for the transesterification of methyl 3-phenylpropionate (**4a**) with 1.2 equiv. of *n*-butanol (**5a**) (eqn (1)).^{6b} Under optimized conditions, **A** and **B** efficiently catalyzed the reaction to afford the product **6aa** in excellent yield with the same efficiency as **1a**, suggesting that the coordinated TFA in **A** and **B** readily dissociated to generate the same active species as generated using **1a** under the reaction conditions.

We next examined the effects of additional TFA in **A** and **B** on functional group tolerability using substrates with acid-sensitive functional groups.^{6b} Reactions of methyl 10-(tetrahydro-2*H*-pyran-2-yl)oxy)decanoate (**4b**) with **5a** using 1.25 mol% of either **A** or **B** provided the corresponding product **6ba** in high yield without decomposition of the acid-sensitive THP ether (eqn (2)). Moreover, catalysts **A** and **B** were successfully applied to the acetylation of alcohol **5b**,^{6c} which has a highly acid-sensitive TES ether, to afford the product **7** in 84% and 86% yields, respectively (eqn (3)).

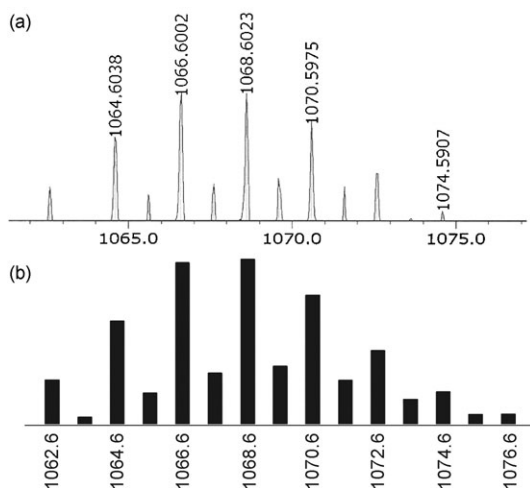


Fig. 3 (a) Negative ion ESI mass spectrum of the obtained compound **A** and (b) calculated isotope pattern for $[\text{Zn}_4(\text{OCOCF}_3)_6\text{O}\cdot\text{CF}_3\text{CO}_2]^-$.

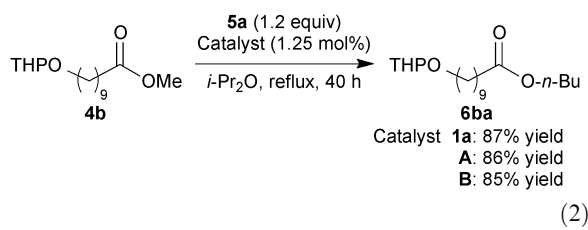
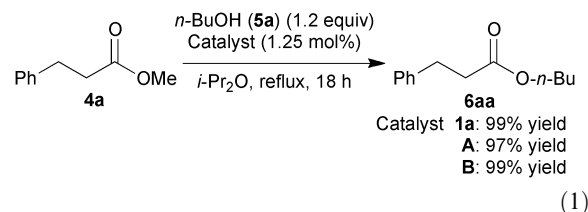
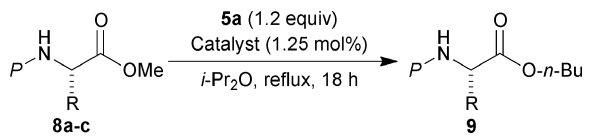
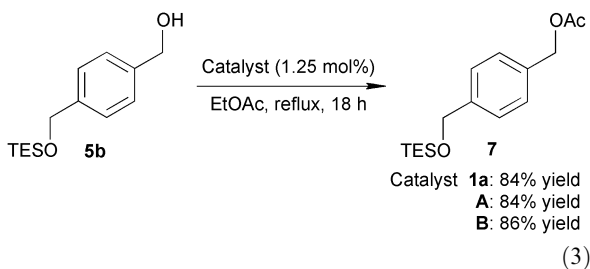


Table 1 Transesterification of *N*-protected amino esters **8^a**


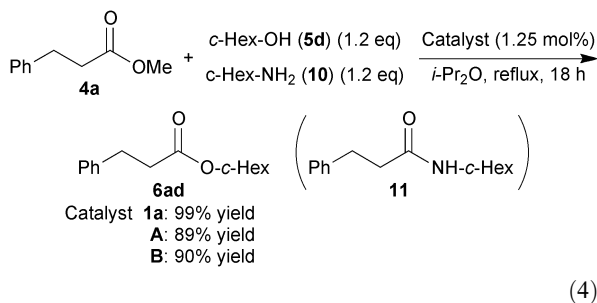
Entry	P	R	8 ^{a-c}	Catalyst	Yield ^b (%)
1	Cbz	H	8a	1a	78
2	Cbz	H	8a	A	80
3	Cbz	H	8a	B	82
4	Fmoc	H	8b	1a	88
5	Fmoc	H	8b	A	89
6	Fmoc	H	8b	B	87
7	Boc	Ph	8c	1a	80 ^c
8	Boc	Ph	8c	A	83 ^c
9	Boc	Ph	8c	B	84 ^c

^a 2 mmol scale, 3.4 mL of *i*-Pr₂O was used. ^b Isolated yield. ^c Without epimerization.



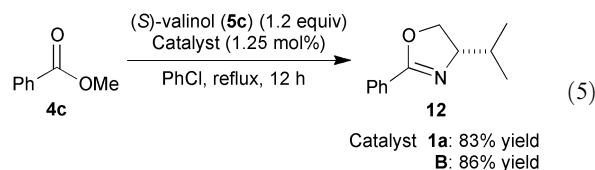
The transesterification of various *N*-protected amino esters **8a–c** with **5a** proceeded smoothly to give the corresponding *n*-butyl esters **9** in high yield without *O*-alkyl transesterification of carbamates (Table 1). Notably, even in the case of the phenylglycine derivative **8c**, no epimerization was observed (entries 7–9).

The most attractive feature of **1a** is its high hydroxy group selectivity over a more nucleophilic amino group in an acylation reaction.^{6a,c} We thus performed chemoselective acylation of cyclohexanol (**5d**) and cyclohexylamine (**10**) using catalyst **A** or **B** (eqn (4)). In both cases, transesterification product **6ad** was obtained in excellent yield along with recovery of **4a** (ca. 8%), and cyclohexylamide **11** was not detected, consistent with the chemoselectivity of zinc cluster **1a**.



Finally, we investigated the catalytic activities of the zinc clusters in the direct conversion of ester to oxazoline (eqn (5)). The reaction of methyl benzoate (**4c**) with (*S*)-valinol (**5c**) using catalyst **B** afforded oxazoline **12** in 86% yield, which

was almost identical to the 83% yield produced using zinc cluster **1a**.



Overall, catalysts **A** and **B** exhibited almost identical catalytic activity and functional group tolerability to **1a**.

In conclusion, we revealed that construction of the μ₄-oxo tetranuclear zinc trifluoroacetate motif proceeded smoothly even at 110 °C, a much milder condition than that used in the preceding synthetic methods (sublimation at 360 °C). Heating zinc trifluoroacetate hydrate **2a** under toluene reflux conditions and simple filtration of the resulting precipitates afforded a white solid **B**, which was a mixture of trifluoroacetate-bridged tetranuclear zinc cluster Zn₄(OCOCF₃)₆O (**1a**) and its TFA adduct Zn₄(OCOCF₃)₆O·CF₃CO₂H (**3**). Because the present method does not require high temperature conditions or a sublimation process, kilogram scale synthesis of the zinc cluster proceeded with the same efficiency. The catalytic activity and functional group tolerance of the TFA adduct **3** in transesterification and oxazoline formation were almost identical to those of **1a**. Another advantage of **3** is its low hygroscopic nature, which allows for handling without the concern to introducing moisture. Industrial application of **3**-catalyzed reactions is under investigation.

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