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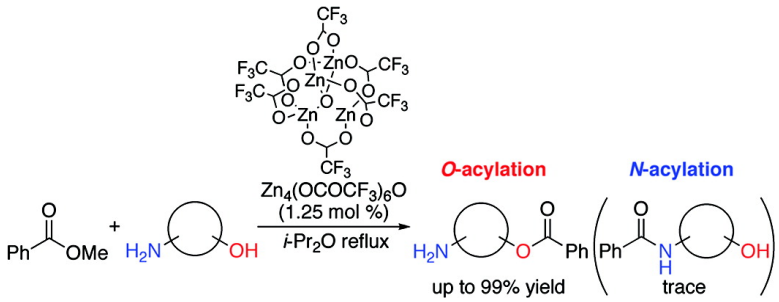

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Enzyme-Like Chemoselective Acylation of Alcohols in the Presence of Amines Catalyzed by a Tetranuclear Zinc Cluster

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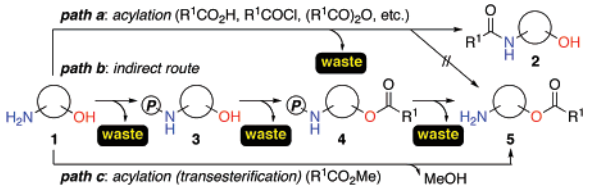
Esters and amides are ubiquitous functional groups in natural and synthetic organic compounds, thus esterification and amidation are among the most fundamental and important reactions in organic synthesis.[1] They are commonly synthesized by acylation of the corresponding alcohol and amine, respectively, with a carboxylic acid, an acid chloride, or an acid anhydride. As the nucleophilicity of the amino group is much greater than that of the hydroxyl group, the amine can be selectively acylated to give the corresponding amide, even in the presence of excess alcohols and/or water.[2] This chemoselectivity has been well utilized for several highly efficient amidation reactions such as the Schotten−Baumann reactions (Scheme 1, *path a*, **1** → **2**).[3] On the other hand, selective *O*-acylation (*path c*, **1** → **5**) is quite difficult to perform in ordinary organic reactions, even though lipase catalyzes highly selective *O*-acylation in the presence of primary alkyl amines.[4] When an aminoester **5** is targeted, the only feasible route is an indirect protection−deprotection process[2] including *in situ* protection with acid[5] (*path b*). The requirement for such a multistep transformation decreases the atom economy of this process. Moreover, some notable exception[6] aside, any acylation, including esterification and amidation, using a carboxylic acid, an acid chloride, or an acid anhydride requires a stoichiometric amount of the condensing reagent or base, resulting in the formation of more than a stoichiometric amount of unwanted chemical waste. To comply with the demand for an environmentally benign process,[7] reversing the normal chemoselectivity of *path a* and minimizing waste are very important. The ideal method leading to the development of a new transformation without using protecting groups[8] is a direct catalytic conversion of aminoalcohol **1** to aminoester **5** in a highly chemoselective manner (*path c*); however, to our knowledge, there are no examples of such a reaction using an artificial catalyst.[9]

Recently, we reported that the newly developed μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**6**) effectively catalyzes the direct conversion of esters, lactones, and carboxylic acids to oxazolines in high yield with broad substrate generality.[10] Because this catalysis proceeds through acylation and cyclodehydration reactions, which utilize a cooperative mechanism of zinc ions similar to that of aminopeptidase[11] and efficient multimetallic catalysts,[12] the zinc cluster **6** is expected to efficiently catalyze the acylation of alcohols in a manner similar to that of lipase.[4] Here we report that the Zn cluster **6** catalyzes selective acylation of hydroxyl groups in the presence of primary and secondary amino groups in a highly chemoselective manner, demonstrating that assembled zinc ions acquire highly enhanced oxophilicity.

We first investigated selective *O*-acylation using a 1:1 mixture of cyclohexanol (**8a**) and cyclohexylamine (**9a**). When PhCOCl or $(PhCO)_2O$ was used as an acylation reagent with triethylamine, the acylation of amine **9a** proceeded exclusively to give the corresponding *N*-cyclohexylbenzamide (**11aa**) in >99% yield and cyclohexyl benzoate (**10aa**) was not detected, consistent with normal chemoselectivity. To tackle the issue of chemoselectivity, we

Scheme 1. Acylation of Aminoalcohol **1**



focused on transesterification[13] using the tetranuclear Zn cluster **6** as a catalyst because this process produces the desired ester without generating stoichiometric amounts of waste. The Zn cluster **6** efficiently catalyzed the transesterification of alcohols without using any additional promoters or a large excess of either alcohols or acyl donors. Surprisingly, under the optimized condition (diisopropyl ether-refluxed conditions),[14] the acylation of amine was quite slow, suggesting that the Zn cluster **6** has high oxophilicity in spite of the general tendency for Zn ions to have an azaphilic nature. Although so-called monomeric Zn complexes $Zn(OCOR)_2$ showed only moderate reactivity,[14] when the Zn cluster **6** was used for this chemoselective acylation reaction, alcohol **8a** was selectively acylated to afford ester **10aa** in 96% yield, along with only 1% of amide **11aa** (Table 1, entry 1). In contrast to our catalysis, the reaction with $Al(O\text{-}i\text{-}Pr)_3$, reported to catalyze the transesterification of aminoesters with low to moderate selectivity,[15] afforded a mixture of ester **10aa** (12%) and amide **11aa** (46%). We next performed the selective *O*-acylation using various combinations of alcohols and amines, and the results are summarized in Table 1 (entries 2−12). Although the reactions using the linear alkyl amine **9b** gave a small amount of amide **11ab**, the chemoselectivity of this catalysis was still high (**10ab**/**11ab** = >11:1) and ester **10ab** was obtained in 92% yield (entries 2 and 3). All of the reactions we evaluated with primary amines proceeded in a highly chemoselective manner (entries 5−9). When the reaction was performed in the presence of secondary amines, we observed some amide due to the higher nucleophilicity of the secondary amines (entries 10−12). The fact that the desired ester **10aa** was obtained in reasonably high yield (82−86%) even in the presence of such good amine nucleophiles, however, clearly indicates the extremely high oxophilicity of this Zn catalysis.[14] We next examined the scope of this method using various methyl esters **7** as the acylation reagent. Under the optimized conditions, aromatic esters with electron-donating and electron-withdrawing substituents (entries 13−20), an α,β-unsaturated ester (entry 21), and aliphatic esters (entries 22−24) were selectively converted to the corresponding cyclohexyl esters **10** in high yields (94−99%) accompanied by only trace amounts of amides **11**. Moreover, the highly acid-sensitive tetrahydropyranyl ether of phenol remained intact (entry 18), demonstrating the high tolerance of sensitive functionalities in this transformation. In the transition state, both esters and alcohols may be simultaneously activated by the two adjacent Zn ions in the cluster, leading to a highly selective *O*-acylation rather than the usual nucleophilicity-dependent

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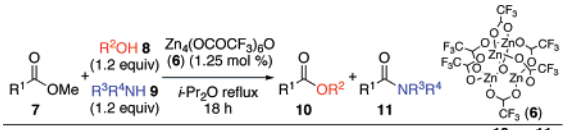
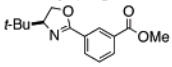
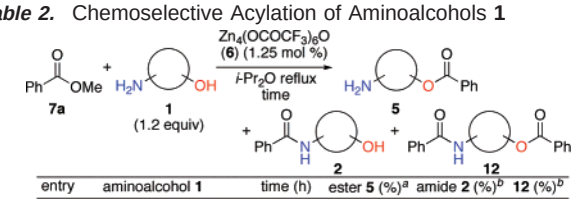
Table 1. Chemoselective Acylation of Alcohols

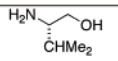
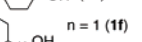


entry	R^1CO_2Me **7**	R^2OH **8**	R^3R^4NH **9**	**10** (%)[a]	**11** (%)[a]
1	$PhCO_2Me$ (**7a**)	*cyclo*-Hex-OH (**8a**)	*cyclo*-Hex-NH_2 (**9a**)	96[b]	1[b]
2	**7a**	$CH_3(CH_2)_5$-OH (**8b**)	$CH_3(CH_2)_5$-NH_2 (**9b**)	92[b]	8[b]
3	**7a**	*cyclo*-Hex-OH (**8a**)	$CH_3(CH_2)_5$-NH_2 (**9b**)	92[b]	5[b]
4	**7a**	$CH_3(CH_2)_5$-OH (**8b**)	*cyclo*-Hex-NH_2 (**9a**)	99[b]	1[b]
5	**7a**	*t*-Bu-CH_2-OH (**8c**)	*t*-Bu-CH_2-NH_2 (**9c**)	94[b]	1[b]
6	**7a**	*n*-Pr_2CH-OH (**8d**)	*n*-Pr_2CH-NH_2 (**9d**)	90[b]	1[b]
7	**7a**	PhCH(Me)OH (**8e**)	PhCH(Me)NH_2 (**9e**)	76[b]	<1[b]
8	**7a**	 n = 1 (**8f**)	 n = 1 (**9f**)	95	n.d.[c]
9	**7a**	n = 2 (**8g**)	n = 2 (**9g**)	78	n.d.[c]
10	**7a**	*cyclo*-Hex-OH (**8a**)	pyrrolidine (**9h**)	82[b]	9[b]
11	**7a**	*cyclo*-Hex-OH (**8a**)	piperidine (**9i**)	83[b]	6[b]
12	**7a**	*cyclo*-Hex-OH (**8a**)	morpholine (**9j**)	86[b]	11[b]
13[d]	4-CH_3-$C_6H_4CO_2Me$ (**7b**)	**8a**	**9a**	>99	n.d.[c]
14[d]	4-Cl-$C_6H_4CO_2Me$ (**7c**)	**8a**	**9a**	>99	<1
15[d]	4-Br-$C_6H_4CO_2Me$ (**7d**)	**8a**	**9a**	94	1
16	4-NO_2-$C_6H_4CO_2Me$ (**7e**)	**8a**	**9a**	>99	<1
17	4-NC-$C_6H_4CO_2Me$ (**7f**)	**8a**	**9a**	91	1
18[d]	4-THPO-$C_6H_4CO_2Me$ (**7g**)	**8a**	**9a**	>99	<1
19	3-Br-$C_6H_4CO_2Me$ (**7h**)	**8a**	**9a**	>99	n.d.[c]
20	 (**7i**)	**8a**	**9a**	>99	<1
21	(*E*)-PhCH=$CHCO_2Me$ (**7j**)	**8a**	**9a**	>99	<1
22	$PhCH_2CH_2CO_2Me$ (**7k**)	**8a**	**9a**	94[b]	<1[b]
23	$CH_3(CH_2)_{16}CO_2Me$ (**7l**)	**8a**	**9a**	98	n.d.[c]
24[d]	TBSO$(CH_2)_9CO_2Me$ (**7m**)	**8a**	**9a**	87	n.d.[c]

[a] Isolated yield. [b]GC yield. [c]Not detected. [d]Reaction time was 24 h.

Table 2. Chemoselective Acylation of Aminoalcohols **1**



entry	aminoalcohol **1**	time (h)	ester **5** (%)[a]	amide **2** (%)[b]	**12** (%)[b]
1	 (**1a**)	24	n.d.[c]	77	23
2	H_2N-$(CH_2)_6$-OH (**1b**)	18	82	n.d.[c]	18
3	H_2N-$(CH_2)_8$-OH (**1c**)	20	90	n.d.[c]	7
4	H_2N-$(CH_2)_{10}$-OH (**1d**)	20	90	n.d.[c]	7
5[d]	 (**1e**)	24	99	n.d.[c]	n.d.[c]
6[d]	 n = 1 (**1f**)	18	88	n.d.[c]	17
7[d]	n = 2 (**1g**)	18	92	n.d.[c]	7

[a] Isolated yield after Boc protection. [b]Isolated yield. [c]Not detected. [d]Solvent was toluene.

reaction.[1−3] Such cooperation between the two Zn ions[11,12] may be closely related to the efficient transesterification catalyzed by alkali-metal alkoxide clusters[16a] and transamidation catalyzed by a trisamidoaluminum(III) dimer.[16b] To the best of our knowledge, this is the first example of a highly chemoselective acylation of alcohols, which is far superior to that of primary and secondary alkyl amines using an artificial catalyst.

To demonstrate the usefulness and effectiveness of this Zn catalysis in organic synthesis, we performed selective *O*-acylation of aminoalcohols **1** (Table 2). When *β*-aminoalcohol **1a** was used as a substrate, hydroxyamide **2aa** was obtained in 77% yield along with diacylation products **12aa** in 23% yield (entry 1). The product **2aa** is produced through *O*-acylation (**1a** → **5aa**) and the following complete *O* → *N* acyl transfer reaction (**5aa** → **2aa**) due to the instability of the resulting aminoester **5aa**.[9,14,17] When aminoalcohols **1b**−**d** tethered by long alkyl chains were treated, we obtained aminoesters **5** in good yields (82−90%) (entries 2−4). Furthermore, the reaction of *trans*-4-aminocyclohexanol (**1e**) provided aminoester **5ae** exclusively (99%), presumably due to *trans*-stereochemistry preventing the intramolecular *O* → *N* acyl transfer reaction. Even when aminoalcohols **1f** and **1g** with highly nucleophilic secondary amino groups (piperidine unit) were used, the reactions proceeded in an *O*-acylation selective manner to give the corresponding aminoesters **5** in high yields (88% and 92%).

In summary, using a Zn cluster-catalyzed transesterification reaction, we succeeded in developing a highly *O*-selective acylation in the presence of primary and secondary alkyl amines, in a manner similar to that of lipase.[4] This catalytic system will be useful as an environmentally ideal acylation and provides an option for developing a new transformation without the use of protecting groups.[8] The results reported here also suggest that the strategy of assembling metal ions as the core structure of an artificial enzyme has a high potential to enhance reactivity as well as to change the azaphilic nature of late transition metals, leading to further enzyme-like chemoselective reactions.

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Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) This result suggests that the Zn cluster-catalyzed oxazoline formation[10] also proceeds through transesterification and the following complete *O* → *N* acyl transfer reaction.

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