Direct conversion of esters, lactones, and carboxylic acids to oxazolines catalyzed by a tetranuclear zinc cluster†

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The tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ catalyzes the direct conversion of esters, lactones, and carboxylic acids to oxazolines with remarkable chemoselectivity.

Oxazolines are widely present in natural products and their use for pharmaceutical drug discovery has stimulated great interest in recent years.[1] Moreover, enantiomerically pure oxazolines have an important role in the development of new synthetic methods and are commonly present in the ligands used for asymmetric catalysis.[2] A common route to oxazolines is the reaction of an acid chloride with a β-amino alcohol; the corresponding hydroxyamide is then treated with thionyl chloride and cyclized with base *via* inversion of the configuration. Several milder approaches have been developed for the cyclization of the hydroxyamide, including the use of (diethylamido)sulfur trifluoride, the Mitsunobu conditions, and PPh_3–CCl_4.[2] Cyclization of hydroxyamide with PPh_3–CCl_4 allows for the direct conversion of carboxylic acids to oxazolines.[3] In terms of atom-economy, direct conversion of carboxylic acid equivalents to oxazolines in a catalytic manner is highly desirable. Toward this aim, zinc(II) chloride-catalyzed direct conversion of nitriles with β-amino alcohols to oxazolines was developed and widely utilized for the syntheses of a variety of chiral bis(oxazoline) ligands.[2,4] Despite easier accessibility of carboxylic acids and esters than nitriles, they have not been utilized for direct or catalytic synthesis of oxazolines. Recently, Wipf and Wang reported a parallel synthesis of oxazolines by 3-nitrophenylboronic acid catalyzed tandem condensation–cyclodehydration of carboxylic acids with β-amino alcohols.[5] On the other hand, direct use of esters as a substrate for oxazoline synthesis is rarely discussed.[6] It is mainly attributed to the difficulty of *catalytic transamidation of esters*,[7] which is the first step of direct oxazoline synthesis from esters. Herein, we report the first example of a direct catalytic conversion of esters and lactones to oxazolines by a tandem condensation–cyclodehydration reaction, in which the use of a μ-oxo-tetranuclear zinc cluster **1b** (Fig. 1) as a catalyst was pivotal. This catalysis is applicable to the reaction of carboxylic acids and does not require azeotropic dehydration. In addition, we found remarkable chemoselectivity when applied to the synthesis of bis(oxazoline) that contains different oxazoline moieties.

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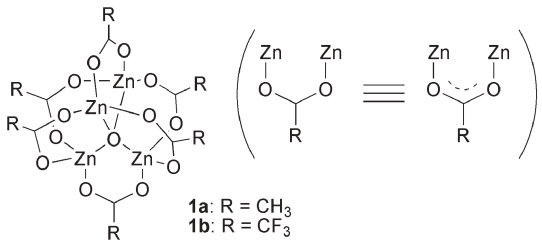
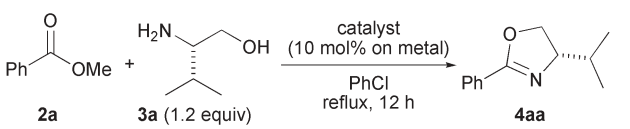


Fig. 1 Structure of μ-oxo-tetranuclear zinc clusters **1**.

Using methyl benzoate (**2a**) with (*S*)-valinol (**3a**) as representative substrates, we screened various zinc(II) and cadmium(II) salts (Table 1).[4] In the presence of 10 mol% of $ZnCl_2$, the reaction was promoted with moderate yield (Entry 2). In contrast to the unsatisfactory results obtained using ZnO, $Zn(OAc)_2$, and $Cd(OAc)_2$, $Zn(OCOCF_3)_2$ improved the yield to 65% (Entry 6). We next examined μ-oxo-tetranuclear zinc clusters **1** (**1a**: R = Me,[8]; **1b**: R = CF_3†), which can be easily prepared from $Zn(OAc)_2$ and $Zn(OCOCF_3)_2$, respectively. Although the catalytic activity of **1a** was moderate (Entry 7), the reactivity of **1b** was superior (Entry 8). The addition of a desiccant such as MS 4A prevented the reaction and azeotropic dehydration had almost no effect.

After determining the most efficient reaction conditions, substrate generality was investigated (Table 2). Only 1.25 mol% of zinc cluster **1b** was needed to catalyze the reactions of various aromatic esters with electron-donating and electron-withdrawing substituents (Entries 1–6). Because zinc cluster **1b** is less acidic than $Zn(OCOCF_3)_2$, methoxyethoxymethyl (MEM) ether and *tert*-butyldimethylsilyl (TBDMS) ether functionality remained intact under these conditions. Various aliphatic esters can also be used

Table 1 Screening of catalysts

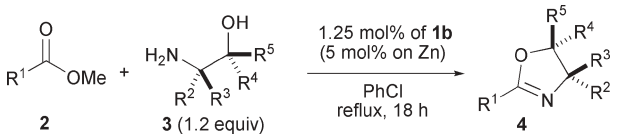


2a **3a** (1.2 equiv) **4aa**

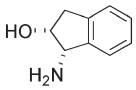
Entry	Catalyst	Yield[a] (%)
1	—	<1
2	$ZnCl_2$	46
3	ZnO	19
4	$Zn(OAc)_2$	40
5	$Cd(OAc)_2$	43
6	$Zn(OCOCF_3)_2$	65
7	$Zn_4(OAc)_6O$ (**1a**)	55
8	$Zn_4(OCOCF_3)_6O$ (**1b**)	83

[a] Yield of **4aa** was determined by GC analysis.

Table 2 Direct conversion of esters to oxazolines



2 4

Entry	Ester (R^1)	β-Amino alcohol[a]	Yield[b] (%)
1[c]	**2b**: 4-MEMO-C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	74 (88)[d]
2[c]	**2c**: 4-TBDMSO-C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	70 (86)[d]
3[c]	**2d**: 4-MEMOCH$_2$-C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	75 (85)[d]
4[c]	**2e**: 4-TBDMSOCH$_2$-C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	87 (99)[d]
5	**2f**: 4-Br-C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	73
6	**2g**: 4-NO_2–C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	71
7	**2h**: $CH_3(CH_2)_3$–	**3a**: R^2 = *i*-Pr, R^3 = H	>99[e]
8	**2i**: $CH_3(CH_2)_{16}$–	**3a**: R^2 = *i*-Pr, R^3 = H	80
9[c]	**2j**: $PhCH_2CH_2$–	**3a**: R^2 = *i*-Pr, R^3 = H	82
10	**2j**: $PhCH_2CH_2$–	**3b**: R^2 = *t*-Bu, R^3 = H	>99
11	**2j**: $PhCH_2CH_2$–	**3c**: R^2 = R^3 = Me	97
12	**2j**: $PhCH_2CH_2$–	**3d**: 	79

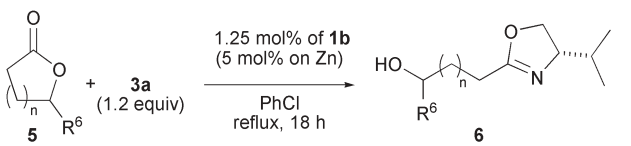
[a] R^4 = R^5 = H except **3d**. [b] Isolated yield. [c] Reaction time was 36 h. [d] Conversion yield based on the recovery of **2**. [e] Determined by GC analysis.

with higher reactivity (Entries 7–9). Moreover, the reaction with other β-amino alcohols, including *tert*-amine derivative **3c** and cyclic *cis*-β-amino alcohol **3d**, proceeded smoothly with retention of configuration (Entries 10–12).

It is noteworthy that zinc cluster **1b** also promoted the reaction of 5- to 7-membered lactones **5** to afford the corresponding hydroxy oxazolines **6** with good to excellent yield (Table 3). Even in the case of less reactive 5-membered lactones **5a** and **5b**, the reaction afforded the desired products **6aa** and **6ba** in reasonable yield (Entries 1, 2). The obtained hydroxy oxazolines **6** should be highly useful for the construction of new functionalized oxazoline libraries. To the best of our knowledge, this is the first example of a *direct catalytic conversion* of esters and lactones to oxazolines.

Furthermore, the optimized conditions using **1b** are applicable to the reaction of carboxylic acids with high efficiency (Table 4). The combination of a variety of carboxylic acids **7** and β-amino alcohols **3** afforded the corresponding oxazolines **4** in high yield, where even sterically hindered *tert*-alcohol derivative **3g** can be utilized (Entry 10). This procedure does not require azeotropic dehydration.

Table 3 Direct conversion of lactones to oxazolines

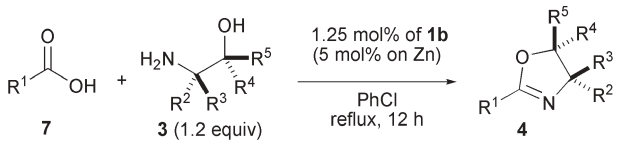


5 6

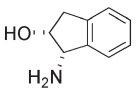
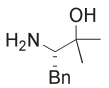
Entry	Lactone	Yield[a] (%)
1	**5a**: *n* = 1, R^6 = H	68
2[b]	**5b**: *n* = 1, R^6 = Et	52
3	**5c**: *n* = 2, R^6 = H	85
4	**5d**: *n* = 3, R^6 = H	>99

[a] Isolated yield. [b] Reaction time was 36 h.

Table 4 Direct conversion of carboxylic acids to oxazolines



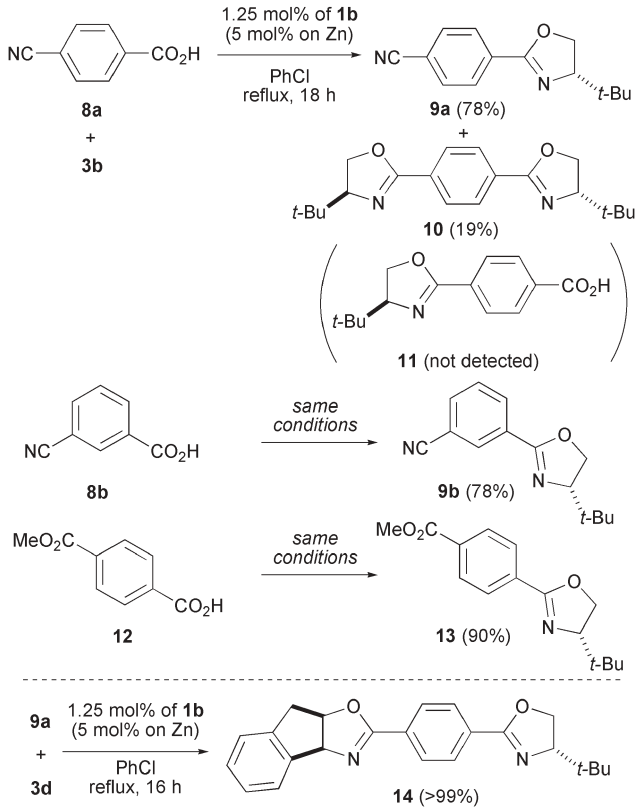
7 4

Entry	Carboxylic acid (R^1)	β-Amino alcohol[a]	Yield[b] (%)
1[c]	**7f**: 4-Br–C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	64
2[c]	**7g**: 4-NO_2–C_6H_4–	**3a**: R^2 = *i*-Pr, R^3 = H	86
3	**7h**: $CH_3(CH_2)_3$–	**3a**: R^2 = *i*-Pr, R^3 = H	95[d]
4	**7j**: $PhCH_2CH_2$–	**3a**: R^2 = *i*-Pr, R^3 = H	86
5	**7j**: $PhCH_2CH_2$–	**3b**: R^2 = *t*-Bu, R^3 = H	>99
6	**7j**: $PhCH_2CH_2$–	**3e**: R^2 = Bn, R^3 = H	97
7	**7j**: $PhCH_2CH_2$–	**3f**: R^2 = H, R^3 = Ph	81
8	**7j**: $PhCH_2CH_2$–	**3c**: R^2 = R^3 = Me	81
9	**7j**: $PhCH_2CH_2$–	**3d**: 	99
10[e]	**7j**: $PhCH_2CH_2$–	**3g**: 	67

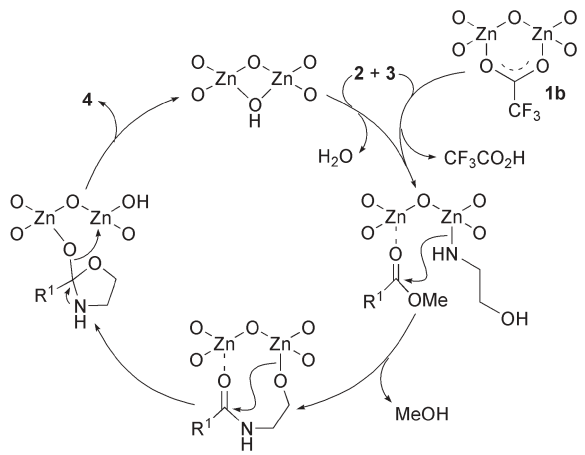
[a] R^4 = R^5 = H except **3d** and **3g**. [b] Isolated yield. [c] Reaction time was 18 h. [d] Determined by GC analysis. [e] Reaction time was 24 h.

During the investigation of substrate scope, we found remarkable chemoselectivity of the present catalysis. As mentioned above, nitriles are the best substrate for the zinc chloride-catalyzed oxazoline synthesis.[2,4] On the other hand, in the presence of 1.25 mol% of zinc cluster **1b**, the reaction of 4-cyanobenzoic acid (**8a**) with β-amino alcohol **3b** provided 78% of mono oxazoline **9a** with 19% of bis(oxazoline) **10** (Scheme 1). Mono oxazoline **11** was not detected in the reaction mixture. In a similar manner, 3-cyanobenzoic acid (**8b**) was converted to mono oxazoline **9b** in 78% yield. Moreover, the reaction of mono-methyl terephthalate (**12**) showed higher chemoselectivity to afford mono oxazoline **13** (90%), in which ester functionality remained intact. These results suggest that carboxylic acids react much faster than nitriles or esters under the present reaction conditions. The obtained mono oxazoline **9a** was successfully converted to bis(oxazoline) **14** that contains different oxazoline moieties. Thus, this new methodology should provide for increased flexibility in designing a synthetic route to heterochiral multi-oxazoline compounds.[9]

Although the precise mechanism and structure of the real active catalyst are not clear, the following studies† suggested that a zinc cluster closely related to μ-oxo-tetranuclear zinc cluster **1b** acts as an active catalyst in the reaction media. Only one set of trifluoroacetate signals was observed in ^{19}F and ^{13}C NMR of **1b**, indicating its highly symmetric structure in solution {^{19}F NMR δ −78.9 (s); ^{13}C NMR δ 163.8 (q, J_{C-F} = 38 Hz, CF_3COO) 117.0 (q, J_{C-F} = 288 Hz, CF_3COO)}. Electrospray ionization mass spectrometry showed that the μ-oxo-tetranuclear structure of **1b** exists even in methanol. Gas chromatography–mass analysis of the reaction mixture revealed that small amounts of trifluoroacetate dissociated from the cluster to afford the corresponding amide and oxazoline, indicating that most of the trifluoroacetate remained in the cluster. The existence of the Zn–O–Zn structure and the higher activity of the cluster than of the monomer suggested a cooperative mechanism of zinc ions (Scheme 2) similar to aminopeptidase[10] and efficient multimetallic catalysts.[7b,11]



Scheme 1 Chemoselective conversion of carboxylic acid to oxazoline and synthesis of heterochiral bis(oxazoline) **14**.



Scheme 2 Postulated catalyst cycle.

Moreover, the control reaction using the hydroxyamide intermediate† revealed that (i) zinc cluster **1b** was essential for the cyclodehydration reaction (1st step) as well as the condensation reaction (2nd step), (ii) the presence of 400 equivalents of water or methanol to **1b** resulted in only a slight decrease in catalyst efficiency, reflecting the stability of the active species against oxygen nucleophiles, and (iii) with excess methanol, **1b** catalyzed esterification of amide, opening up great possibilities for the development of a small artificial peptidase catalyst.[12]

In conclusion, we have developed a new efficient and environmentally benign direct synthetic method of oxazoline from esters, lactones, and carboxylic acids catalyzed by a novel tetranuclear zinc cluster **1b**. The use of zinc cluster **1b** is essential not only for condensation reactions but also cyclodehydration reactions. In the present catalysis, carboxylic acid reacted much faster than nitrile or ester, allowing easy access to heterochiral bis(oxazoline) that contains different oxazoline moieties. Further studies on the precise reaction mechanism, extension to the syntheses of other heterocyclic compounds, and the development of new multimetallic catalysts with multifunctionality, including artificial enzymes, are currently in progress.

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