Water-Tolerant and Reusable Catalysts for Direct Ester Condensation between Equimolar Amounts of Carboxylic Acids and Alcohols

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Dedicated with friendship to Joe Richmond on the occasion of his 60th birthday.

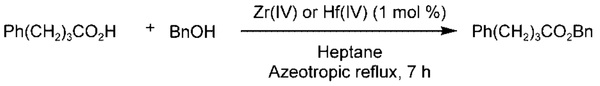
Abstract: $ZrOCl_2 \cdot 8\,H_2O$ and $HfOCl_2 \cdot 8\,H_2O$ are highly effective, water-tolerant, and reusable homogeneous catalysts for direct ester condensation between equimolar amounts of carboxylic acids and alcohols. Notably, zirconium(IV) salts such as $ZrOCl_2 \cdot 8\,H_2O$ and $Zr(OAc)_x(OH)_y$ are potential green catalysts due to their low toxicity, commercial availability at low cost, ease of handling, high catalytic activity, and reusability.

Keywords: dehydration; esterification; esters; green chemistry; recycling catalyst

Replacing current chemical processes with more environmentally benign alternatives is an increasingly attractive subject. In particular, fundamental reactions that are frequently used in large-scale synthesis are in urgent need of improvement using new techniques to develop green and sustainable chemistry. Recently, we found that $HfCl_4 \cdot 2\,THF$[1,3] and $ZrCl_4 \cdot 2\,THF$[2,3] are highly effective catalysts for direct ester condensation using equimolar amounts of carboxylic acids and alcohols. This is one of the most ideal methods for preparing esters and polyesters not only because it gives the highest atom efficiency but also because it gives the lowest E factor.[4–6] However, these metal(IV) chlorides are moisture-sensitive, and are gradually decomposed to inactive metal oxychlorides by hydrolysis.[3,7] We report here that $HfOCl_2 \cdot 8\,H_2O$ and $ZrOCl_2 \cdot 8\,H_2O$ are highly effective and water-tolerant catalysts for direct ester condensation and a very simple procedure for their recovery and reuse.

We initially investigated the catalytic activities of various commercially available hafnium(IV) or zirconium(IV) salts (1 mol %), which promote the model ester condensation reaction between equimolar amounts of 4-phenylbutyric acid and benzyl alcohol in heptane at azeotropic reflux with the removal of water using a Dean–Stark apparatus for 7 h (Scheme 1 and Table 1). $ZrOCl_2 \cdot x\,H_2O$ ($x = 6-8$) was less active and less soluble than $ZrCl_4 \cdot 2\,THF$. This result is consistent with the previous finding that the activities of $ZrCl_4$ and its THF complex decreased with exposure to air.[3] It was ascertained by thermal analysis that $ZrCl_4$ was gradually transformed to $ZrOCl_2 \cdot x\,H_2O$ ($x \leqslant 6$) in air. Surprisingly, however, the activity of $ZrOCl_2 \cdot 8\,H_2O$ was as high as that of $ZrCl_4 \cdot 2\,THF$. $ZrOCl_2 \cdot 8\,H_2O$, like $ZrCl_4 \cdot 2\,THF$, also acted as a homogeneous catalyst. $Zr(OAc)_x(OH)_y$ ($x+y=4$) was also a highly effective catalyst. Although the catalytic activity and solubility of hafnium(IV) salts were almost identical to those of the corresponding zirconium(IV) salts, $ZrOCl_2 \cdot x\,H_2O$ was more soluble than $HfOCl_2 \cdot x\,H_2O$ in the reaction solution. $ZrOCl_2 \cdot 8\,H_2O$ and $Zr(OAc)_x(OH)_y$ are practically useful catalysts because they are very stable in air and less expensive than other active catalysts including hafnium(IV) salts.

Next, to investigate in detail the relationship between the hydration number (x) of $ZrOCl_2 \cdot x\,H_2O$ and its catalytic activity, $ZrOCl_2 \cdot x\,H_2O$ ($x = 0-8$) was prepared by hydrolysis of $ZrCl_4$ and subsequent concentration under vacuum (Scheme 2). The hydration number of the resulting $ZrOCl_2 \cdot x\,H_2O$ was determined by X-ray diffraction (XRD) analysis and thermal analysis.[8] The maximum hydration number of $ZrOCl_2 \cdot x\,H_2O$ and $HfOCl_2 \cdot x\,H_2O$ is known to be eight.[9] The catalytic activity of $ZrOCl_2 \cdot x\,H_2O$ was estimated by its conversion to ester in the model reaction of (Scheme 1). The results



$$Ph(CH_2)_3CO_2H + BnOH \xrightarrow[\text{Heptane, Azeotropic reflux, 7 h}]{\text{Zr(IV) or Hf(IV) (1 mol \%)}} Ph(CH_2)_3CO_2Bn$$

Scheme 1. Hf(IV)- or Zr(IV)-catalyzed esterification of 4-phenylbutyric acid with benzyl alcohol.

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Table 1. Direct esterification of 4-phenylbutyric acid with benzyl alcohol (see Scheme 1).

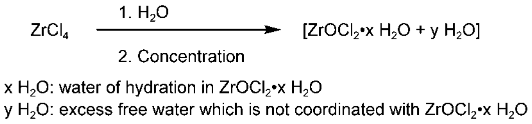
Catalyst[a]	Conversion [%]	Solubility of catalyst
$ZrCl_4 \cdot 2\,THF$[a]	>99	Completely dissolved
$ZrOCl_2 \cdot 8\,H_2O$[b]	>99	Completely dissolved
$ZrOCl_2 \cdot x\,H_2O$ (x = 6–8)[a]	82	Almost dissolved
$Zr(OAc)_x(OH)_y$ (x + y = 4)[a]	>99	Completely dissolved
$HfCl_4 \cdot 2\,THF$[a]	>99	Completely dissolved
$HfOCl_2 \cdot 8\,H_2O$[c]	90	Almost dissolved
$HfOCl_2 \cdot x\,H_2O$ (x = 6–8)[a]	84	Partially dissolved

[a] Purchased from Sigma-Aldrich.
[b] Purchased from Wako Pure Industries, Co. Ltd., Japan.
[c] Purchased from Soekawa Chemical Co. Ltd., Japan.

Table 2. Catalytic activities of $ZrOCl_2 \cdot x\,H_2O$ in the esterification of 4-phenylbutryic acid with benzyl alcohol (see Scheme 1).

Entry	$[ZrOCl_2 \cdot x\,H_2O + y\,H_2O]$[a]		Conversion [%]
	x[b]	y[c]	
1	8	16	>99
2	6 and 8	7~9	96
3	6	0	64
4	0	0	25

[a] $[ZrOCl_2 \cdot x\,H_2O + y\,H_2O]$ was prepared *in situ* (Scheme 2).
[b] Hydration number x was determined by X-ray diffraction analysis and thermal analysis.
[c] Number y was calculated on the basis of the weight of solid $[ZrOCl_2 \cdot x\,H_2O + y\,H_2O]$ and hydration number x.



x H_2O: water of hydration in $ZrOCl_2 \cdot x\,H_2O$
y H_2O: excess free water which is not coordinated with $ZrOCl_2 \cdot x\,H_2O$

Scheme 2. Hydration of $ZrCl_4$.

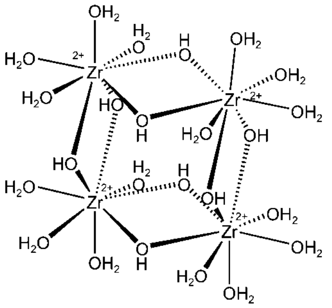
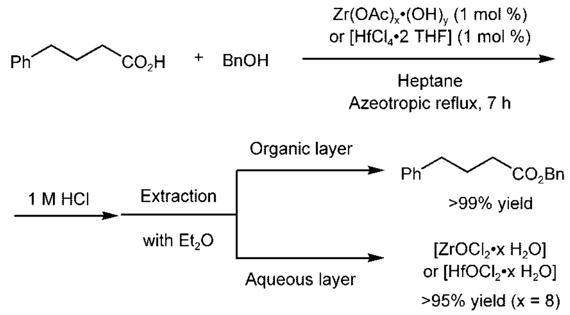


Figure 1. Crystal structure of cationic cluster $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$.

are summarized in Table 2. As expected, the hydration number of $ZrOCl_2 \cdot x\,H_2O$ had to be eight to give it a high enough catalytic activity (Entry 1). The crystal structure of $ZrOCl_2 \cdot 8\,H_2O$ is known to be an ionic cluster $[Zr_4(OH)_8(H_2O)_{16}]Cl_8 \cdot 12\,H_2O$ (Figure 1).[8] The *in situ* prepared catalyst was as active as the isolated catalyst, which is available commercially (Tables 1 and 2). The dehydration of $ZrOCl_2 \cdot 8\,H_2O$ lowered its catalytic activity and solubility in the reaction solution. Anhydrous $ZrOCl_2$ did not dissolve even in water, and this solid was amorphous according to XRD analysis. The cationic cluster structure, which consists of four zirconium atoms, may give us some mechanistic information to better understand the catalysis of esterification. The ester condensation may proceed through a ligand exchange reaction with carboxylic acids and/or alcohols on the cationic cluster. However, the mechanism itself is not clear.

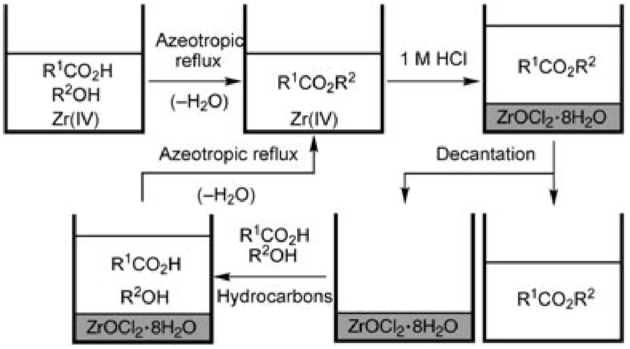
Based on the above results, we sought to recover and reuse the active metal species from the aqueous layers by quenching the reaction mixture with some aqueous solutions in the zirconium(IV)- or hafnium(IV)-catalyzed ester condensation reaction. The reaction of 4-phenylbutyric acid and benzyl alcohol in heptane was carried out under azeotropic reflux conditions with removal of water for 7 h in the presence of 1 mol % of $Zr(OAc)_x(OH)_y$ or $HfCl_4 \cdot 2\,THF$ (Table 3). After cooling to ambient temperature, 1 M hydrochloric acid was poured into the solution and the product was extracted with ether. Zirconium(IV) and hafnium(IV) species were quantitatively recovered as the corresponding metal oxydichloride octahydrates including excess amounts of free water by concentration of the aqueous layers.[10] The recovered light-yellow solids were then used for the next reaction run. The ester product was again obtained in excellent yield. After five consecutive reaction cycles there was no decrease in yield when a reaction time of 7 h was strictly maintained. However, this method is troublesome because concentration of the aqueous layers should be stopped before dehydration of the metal oxychloride octahydrate begins. It was ascertained by thermal analysis that dehydration from $ZrOCl_2 \cdot 8\,H_2O$ to $ZrOCl_2 \cdot 6\,H_2O$ occurred at about 75 °C. This means that dehydration may occur even at room temperature under reduced pressure. In the same manner, the reuse of an aqueous solution of

Table 3. Catalyst recycling in the esterification of 4-phenylbutyric acid with benzyl alcohol.



$Zr(OAc)_x(OH)_y$ Run	Conversion [%]	$HfCl_4 \cdot 2$ THF Run	Conversion [%]
1	98	1	94
2	>99	2	96
3	99	3	94
4	99	4	90
5	97	5	94

$HfOCl_2 \cdot 8\,H_2O$ recovered from the first run using $HfCl_4 \cdot 2$ THF also afforded the ester products with identical yields.

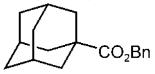


Scheme 3. Simple catalyst recycling system in the esterification.

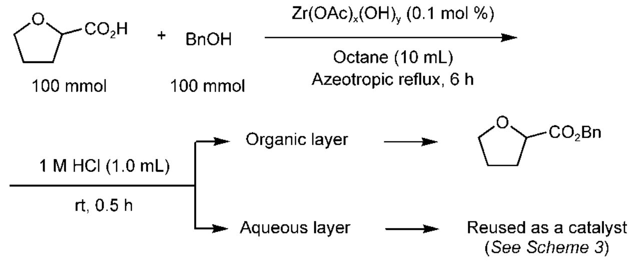
To develop a simple catalyst-recycling system, we attempted to reuse an aqueous solution of $ZrOCl_2 \cdot 8\,H_2O$, which was recovered from the first run, for the next run without any concentration (Scheme 3).[11] We were delighted to find that the reaction of 4-phenylbutyric acid with benzyl alcohol was complete within 8 h as well as in the first run and again provided the ester product in quantitative yield (Table 4). Following at least three consecutive reaction cycles, there was no decrease in yield when a reaction time of 8 h was strictly maintained. The esterification proceeded only in 27% conversion in the presence of 1 M hydrochloric acid without any zirconium(IV) catalysts at azeotropic reflux with removal of water for 8 h. This result is the same as that in the non-catalytic thermal esterification. Encouraged by these promising results, we next examined the present catalyst recycling system in the ester reaction between several alcohols like secondary alcohols and phenol and carboxylic acids like not only 4-phenylbutyric acid but also sterically bulky adamantanecarboxylic acid and benzoic acid (Table 4). In all cases, the reactions proceeded well at azeotropic reflux conditions in hydrocarbons such as octane or toluene in the presence of 1 3 mol% of $Zr(OAc)_x(OH)_y$, and there was no decrease in yield with consecutive reaction cycles using an aqueous solution of $ZrOCl_2 \cdot 8\,H_2O$.

The applicability of the present protocol to a large-scale process was investigated (Scheme 4). Complete ester condensation between tetrahydro-2-furoic acid (100 mmol) and benzyl alcohol (100 mmol) was observed in the presence of $Zr(OAc)_x(OH)_y$ (0.1 mol %), and the corresponding ester was isolated in high yield. The zirconium(IV) catalyst was reused for the same re-

Table 4. Simple catalyst-recycling in zirconium(IV) catalyzed esterification.

Product	Zr(IV) [mol %]	Solvent	Time [h]	Conversion [%] Run: 1→2→3→4→5
$Ph(CH_2)_3CO_2Bn$	1	Heptane	8	95(27[a])→94→93
$Ph(CH_2)_3CO_2c\text{-}C_{12}H_{23}$	3	Octane	13	96→97→93→94→92
$Ph(CH_2)_3CO_2Ph$	3	Octane	35	90→94→99
	1	Octane	4	99→96→95
$Ph(CH_2)_3CO_2(CH_2)_8OTHP$[b]	1	Heptane	5	98→95→95
$Ph(CH_2)_3CO_2(CH_2)_2CN$	1	Heptane	5	>99→>99→>99
$Ph(CH_2)_3CO_2(CH_2)_8OTBDMS$[c]	1	Heptane	5	>99→99→98
(*E*)-PhCH=CHCO$_2$Bn	1	Heptane	5	>99→99→99
$C_7F_{15}CO_2Bn$	1	Heptane	5	>99→>99→98
$PhCO_2Bn$	1	Toluene	24	>99→>99→>99→>99

[a] The reaction was carried out in the presence of 1 M hydrochloric acid without any zirconium(IV) catalysts.
[b] THP: tetrahydropyranyl.
[c] TBDMS: *t*-BuMe$_2$Si.



Conversion to ester: Run 1, 92%; run 2, 93%; run 3, 97%; run 4, 97%

Scheme 4. Application to large-scale synthesis of benzyl tetrahydro-2-furoate.

action (100 mmol scale) more than four times, and no loss of activity was observed for the recovered catalyst. This means that the turnover number (TON) is greater than 4000 and the turnover frequency (TOF) exceeds 170 h^{-1}.

In summary, we have shown that $ZrOCl_2 \cdot 8\,H_2O$ and $HfOCl_2 \cdot 8\,H_2O$ are highly effective, water-tolerant, and reusable homogeneous catalysts for direct ester condensation between equimolar amounts of carboxylic acids and alcohols. Notably, zirconium(IV) salts such as $ZrOCl_2 \cdot 8\,H_2O$ and $Zr(OAc)_x(OH)_y$ are potential green catalysts due to their low toxicity, commercial availability at low cost, ease of handling, high catalytic activity, and reusability.[12] In addition, our new system for recycling of catalysts using water is economically and environmentally superior to recent biphasic systems using fluorous solvents and ionic liquids. We believe that our new method for ester condensation may be useful as an environmentally and industrially ideal condensation method in the near future. Further studies aimed at exploring more active and recyclable catalysts are ongoing.

Experimental Section

General Procedure for the Esterification Catalyzed by $Zr(OAc)_x(OH)_y$ and Catalyst Recycling (Table 4)

A 5-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acid (5 mmol) and alcohol (5 mmol) as substrates and $Zr(OAc)_x(OH)_y$ (1–3 mol %) as a catalyst in hydrocarbons such as octane or toluene (2.5 mL). The mixture was brought to reflux with the removal of water. After the reaction was completed, the resulting mixture was cooled to ambient temperature and 1 M hydrochloric acid (0.5–1.5 mL) was added. After being stirred for 0.5 h, the product was isolated from the organic layer by simple extraction with Et_2O (2 mL) twice. On the other hand, the catalyst remained in the aqueous layer, which was used directly in the next reaction without removing the water. The yields of the 2nd, 3rd, and 4th runs were comparable to that of the 1st run.

Acknowledgements

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[9] The zirconyl group consists of a complex in which four zirconium atoms are at the corners of a slightly distorted square and are linked along each edge of the square by two OH groups: one above and one below the plane of the square. Four water molecules are bound to each zirconium in such a manner that the arrangement of the eight oxygens about each zirconium is a distorted square antiprism. There are no zirconium-halogen bonds in this structure. A. Clearfield, P. A. Vaughan, *Acta Crystallographica* **1956**, *9*, 555.

[10] When neutral water was used in place of 1 M hydrochloric acid to quench the reaction mixture, zirconium(IV) and hafnium(IV) species were not completely extracted from the organic layers. No chloride ions were included in the metal species that were extracted with water, but the recovered metal species were highly active as cata-

lysts. These results mean that no chloride anions are included in the active intermediate in ester condensation and metal oxychloride is reproduced from metal(IV) hydroxides by treatment with 1 M hydrochloric acid.

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