Zr(IV)–Fe(III), –Ga(III), and –Sn(IV) Binary Metal Complexes as Synergistic and Reusable Esterification Catalysts

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Abstract: Synergism in catalytic activity with the combined use of Hf(O-*i*-Pr)$_4$ or Zr(O-*i*-Pr)$_4$ and Fe(O-*i*-Pr)$_3$ for direct esterification and a very simple method for their extraction with ionic liquids for their recovery and reuse are described. This Zr(IV)–Fe(III) complex is an environmentally benign catalyst due to its high turnover number, extremely mild Lewis acidity, low toxicity, reusability, and commercial availability at low cost.

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

Table 1. Synergistic effect of the combined use of Zr(OH)$_x$(OAc)$_y$ and additives on the direct esterification of **1** with **2**.[a]

Additive	Yield [%] of **3**[b]	Additive	Yield [%] of **3**[b]
–[c]	44 (50)[d]	Sn(O-*i*-Pr)$_4$	89
Al(O-*i*-Pr)$_3$	77	Fe(O-*i*-Pr)$_3$	89
Ga(O-*i*-Pr)$_3$	82		

[a] A solution of **1** (5 mmol) and **2** (5 mmol) in heptane (2.5 mL) was heated in the presence of Zr(OH)$_x$(OAc)$_y$ (0.1 mmol) and additive (0.1 mmol) at 120 °C (bath temperature) without the removal of water for 12 h.
[b] Determined by ^{1}H-NMR spectral analysis of crude products.
[c] No additive was used.
[d] 4 mol % of Zr(OH)$_x$(OAc)$_y$ was used.

Recently, we found that HfCl$_4$·2 THF and ZrCl$_4$·2 THF are highly effective catalysts for direct esterification using equimolar amounts of carboxylic acids and alcohols.[1] This is one of the ideal methods for preparing esters and polyesters not only because it gives a higher atom efficiency but also because it gives a lower E-factor,[2] defined as the mass ratio of waste to desired product.[3–5] However, these metal(IV) chlorides are moisture-sensitive, and gradually decompose to inactive metal oxychlorides and hazardous hydrogen chloride by hydrolysis.[1c,6] We report here synergism in catalytic activity with the combined use of Hf(O-*i*-Pr)$_4$ or Zr(O-*i*-Pr)$_4$ and Fe(O-*i*-Pr)$_3$ for direct esterification and a very simple method for their extraction with ionic liquids for their recovery and reuse. This Zr(IV)–Fe(III) complex is an environmentally benign catalyst due to its high turnover number, extremely mild Lewis acidity, low toxicity, reusability, and commercial availability at low cost.

We initially investigated the effects of metal alkoxides (2 mol %), which synergistically promote the model esterification reaction of 4-phenylbutyric acid (**1**) with cyclododecanol (**2**) to give the corresponding ester **3** in the presence of Zr(OH)$_x$(OAc)$_y$ ($x+y=4$, 2 mol %).[6] As shown in Table 1, a synergistic effect was observed in combination with Al(III), Ga(III), Sn(IV), and Fe(III) salts. These binary metal ion complexes were much more active than those of previously reported catalysts, HfCl$_4$·2 THF, ZrCl$_4$·2 THF, Zr(OH)$_x$(OAc)$_y$, Zr(O-*i*-Pr)$_4$, ZrOCl$_2$·8 H$_2$O, etc.[5]

Next, we investigated in detail the synergistic effects of the combined use of Zr(O-*i*-Pr)$_4$ and Fe(O-*i*-Pr)$_3$ for the esterification of **1** with **2** because of their low toxicity[7] and commercial availability at low cost. Zr(O-*i*-Pr)$_4$, commercially available at higher purity, was chosen in place of Zr(OH)$_x$(OAc)$_y$. The esterification was conducted in heptane at azeotropic reflux with the removal of water using a Dean–Stark apparatus. The yield of **3** over the course of the reaction is plotted (***A*** in Figure 1). As expected, Fe(III) (x marks) was much less active than Zr(IV) (white circles), but in combination (black circles) they showed synergistic activity. Similar experiments were conducted for Hf(O-*i*-Pr)$_4$–Fe(O-*i*-Pr)$_3$ and Ti(O-*i*-Pr)$_4$–Fe(O-*i*-Pr)$_3$ because Hf(IV) and Ti(IV) are also known to be good catalysts.[1,3,5f] The esterification of **1** with benzyl alcohol (**4**), which is more reactive than **2**, was chosen to reduce the reaction time. As shown in ***B*** in Figure 1, the addition of Fe(III) (black circles) synergistically increased the catalytic ac-

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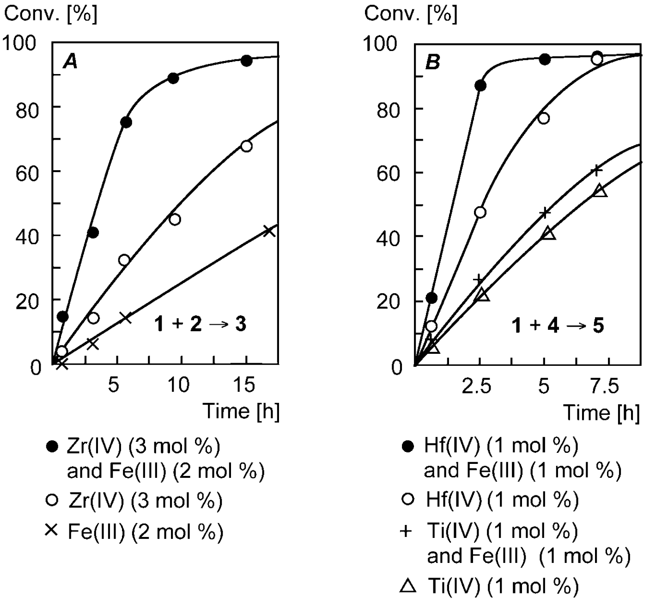


Figure 1. Synergistic effect of the combined use of two different metal species on the esterification rate. A solution of **1** (5 mmol) and **2** (5 mmol) or **4** (5 mmol) in heptane (2.5 mL) was heated at 120 °C (bath temperature) with the removal of water in the presence of Zr(O-*i*-Pr)$_4$, Hf(O-*i*-Pr)$_4$, Ti(O-*i*-Pr)$_4$, or Fe(O-*i*-Pr)$_3$.

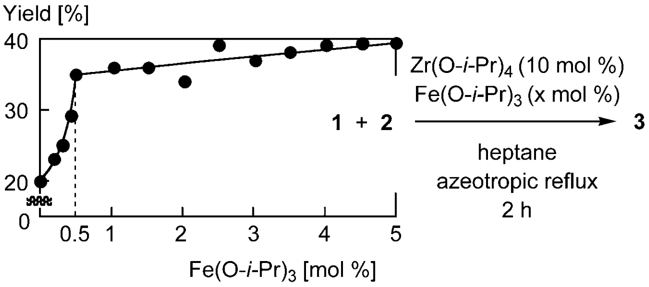


Figure 2. The relationship between the molar ratio of Zr(IV) and Fe(III). A solution of **1** (5 mmol) and **2** (5 mmol) in heptane (2.5 mL) was heated at 120 °C (bath temperature) with the removal of water for 2 h in the presence of Zr(O-*i*-Pr)$_4$ (10 mol %) and Fe(O-*i*-Pr)$_3$ (x mol %).

tivity of Hf(IV) (white circles), with the combined use of Zr(IV) and Fe(III). On the other hand, the addition of Fe(III) (black crosses) slightly inhibited the catalytic activity of Ti(IV) (white triangles). These experimental results indicate that the catalytic activities of Hf(IV) and Zr(IV) for esterification are essentially different from that of Ti(IV).[8]

Next, we explored the recovery and reuse of the Zr(IV) catalyst by biphasic extraction. Ionic liquids are very attractive as solvents for the extraction of inorganic species because of their high polarity.[9] To explore the catalytic activity of Zr(IV)–Fe(III) species in ionic liquids, the esterification of **1** with **4** was conducted in the presence of Zr(O-*i*-Pr)$_4$ and/or Fe(O-*i*-Pr)$_3$ in a biphasic system of heptane and ionic liquid. Their catalytic activities were influenced by the counter anion in the ionic liquid. Surprisingly, Zr(O-*i*-Pr)$_4$ was almost inert in [EMIM][BF$_4$][10] and [BMIM][PF$_6$],[10] but was still active in [EMIM][OTf][10] and [BMIM][NTf$_2$][10] (**6**). The amounts of Zr(IV) and Fe(III) species in the ionic liquid layer after esterification were estimated by ICP (inductively coupled plasma) emission spectroscopic analysis (Table 2). When esterification was carried out using Zr(O-*i*-Pr)$_4$ alone, Zr(IV) species remained in the heptane layer (entry 1). However, when 1 equiv. of Fe(O-*i*-Pr)$_3$ was added per Zr(IV), Zr(IV) species was easily transferred to a layer of **6** together with Fe(III) (entry 2). Three mL of **6** were required to extract Zr(IV) (0.025 mmol) and Fe(III) (0.025 mmol) in quantitative yields (entry 3). However, the use of a large amount of ionic liquid seriously diminished the esterification rate. Fortunately, based on the further screening of ionic liquids, we found that [BPY][NTf$_2$][10] (**7**) was 6 times more effective than **6**: Zr(IV) (0.05 mmol) and Fe(III) (0.05 mmol) were almost completely extracted with 1 mL of **7** (entry 4).

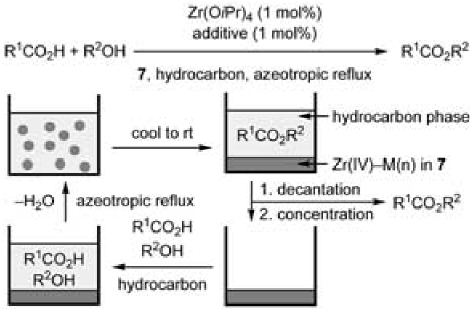
The generality and scope of the direct esterification catalyzed by a Zr(IV)–Fe(III) complex was examined (Table 3). Non-polar hydrocarbon was suitable as a solvent, and the reaction temperature was controlled by the boiling point of the chosen solvent. Most of the aliphatic and aromatic carboxylic acids and primary and secondary alcohols, including sterically hindered and acid-sensitive ones, were suitable as substrates, and their esterification proceeded cleanly to give the desired esters

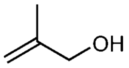
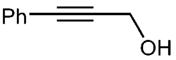
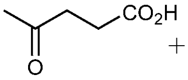
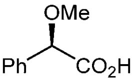
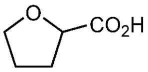
Table 2. Extraction of Zr(IV) and Fe(III) species from the esterification mixture with ionic liquids.[a]

Entry	Catalysts [mol%]		Ionic liquid [mL]	Time [h]	Recovery [% yield]	
	Zr(IV)	Fe(III)			Zr(IV)	Fe(III)
1	1	–	**6**, 1	8	4	–
2	1	1	**6**, 1	8	75	78
3	0.5	0.5	**6**, 3	12	92	>99
4	1	1	**7**, 1	8	>91	>99

[a] A solution of **1** (5 mmol) and **4** (5 mmol) in heptane (2.5 mL) and ionic liquid was heated in the presence of Zr(O-*i*-Pr)$_4$ (1 mol %) and/or Fe(O-*i*-Pr)$_3$ (1 mol %) at azeotropic reflux with removal of water (bath temperature, 115 °C) for 8 h. After the reaction was complete, hexane (2 mL) was added to clearly separate a hydrocarbon layer and an ionic layer.

Table 3. Reusable Zr(IV)–M(n)-catalyzed direct esterification.[a]



Entry	$R^1CO_2H+R^2OH$	Additive M(O-*i*-Pr)$_n$	Solvent, Time [h]	Yield [%] *(Trial Number)*[b]
1[c]	**1**+**4**	Fe(III)	Heptane, 8	99[d] *(15)*
2[c]	**1**+**4**	Sn(IV)	Heptane, 8	96[d] *(3)*
3[c]	**1**+**4**	Ga(III)	Heptane, 8	98[d] *(3)*
4[e]	**1**+**4**	Fe(III)	Octane, 12	99[d] *(2)*
5[c]	**1**+**2**	Fe(III)	Octane, 12	>99[d] *(3)*
6[f]	**1**+ 	Fe(III)	Heptane, 15	>99
7[f]	**1**+ 	Fe(III)	Heptane, 19	>99
8[f]	**1**+PhOH	Fe(III)	*o*-Xylene, 20	53
9[f]	**1**+PhOH	Sn(IV)	*o*-Xylene, 20	89
10[f]	**1**+PhOH	Ga(III)	*o*-Xylene, 20	94
11[f]	**1**+$NCCH_2CH_2OH$	Fe(III)	Heptane, 23	>99
12[f]	 +**2**	Fe(III)	Heptane, 23	91
13[f]	$PhOCH_2CO_2H$+**2**	Fe(III)	Heptane, 18	98
14[f]	 +**4**	Fe(III)	Heptane, 17	99
15[f]	 +**4**	Fe(III)	Octane, 6	>99
16[f]	1-AdCO$_2$H[g]+**4**	Fe(III)	Heptane, 20	>99
17[f]	1-AdCO$_2$H[g]+$cC_6H_{11}OH$	Fe(III)	Heptane, 50	93
18[c]	$PhCO_2H$+**4**	Fe(III)	Toluene, 7	97[d] *(3)*
19[f]	$PhCO_2H+cC_6H_{11}OH$	Fe(III)	Toluene, 45	99

[a] Unless otherwise noted, a solution of carboxylic acid (5 mmol) and alcohol (5 mmol) in hydrocarbon (2.5 mL) and/or **7** (1 mL) was heated in the presence of Zr(O-*i*-Pr)$_4$ (1 mol %)–M(O-*i*-Pr)$_n$ (1 mol %) at azeotropic reflux with the removal of water.

[b] Trial number for reuse of catalysts.

[c] Compound **7** (1 mL) was added in the reaction mixture to recover and reuse catalysts.

[d] An average yield in each recycled run is shown.

[e] Amounts: **1** (100 mmol), **4** (100 mmol), Zr(O-*i*-Pr)$_4$ (0.1 mol %), Fe(O-*i*-Pr)$_3$ (0.1 mol %), octane (10 mL), **7** (2 mL).

[f] Compound **7** was not added.

[g] 1-AdCO$_2$H = 1-adamantylcarboxylic acid.

in high yields. Zr(IV)–Fe(III) catalyst was repeatedly recycled as a solution of **7** without isolation. For example, Zr(IV)–Fe(III) catalyst (1 mol %) could be reused for the esterification reaction of **1** with **4** in a biphasic solvent consisting of heptane and **7** more than 15 times without any loss of activity (entry 1). In a similar manner, Zr(IV)–Sn(IV) and Zr(IV)–Ga(III) complexes were also reusable (entries 2 and 3). While the esterification of phenol was disturbed by the addition of Fe(O-*i*-Pr)$_3$ (entry 8), other additives such as Sn(IV) and Ga(III) could be used in place of Fe(III) (entries 9 and 10). The applicability of the present protocol to a large-scale process (100 mmol scale, 0.1 mol % of Zr(IV)–Fe(III) catalyst) is demonstrated in entry 4.

In summary, Fe(III), Ga(III), or Sn(IV) is required as a co-catalyst of Zr(IV) or Hf(IV) not only to accelerate the reaction rate but also to extract Zr(IV) or Hf(IV) with ionic liquid **7** quantitatively. Although the role of Fe(III), Ga(III), or Sn(IV) is not still clear, stable salt complexes between **7** and the 1 to 1 molar ratio mixture of binary metal ion species may be generated *in situ*. Further studies on the mechanism of the esterification reaction catalyzed by binary metal ion species are in progress in our laboratory.

Experimental Section

N-Butylpyridinium Trifluoromethanesulfonimide (7)[11]

An equimolar of *N*-butylpyridinium bromide (21.6 g, 100 mmol) and lithium trifluoromethanesulfonimide (28.7 g, 100 mmol) in H_2O (175 mL) was heated at 70 °C for 12 h. The resulting mixture was extracted with 100 mL of CH_2Cl_2, and concentrated. The crude oil was washed with a linear EtOAc gradient in hexane and purified by column chromatography on neutral active aluminium oxide using EtOAc, and dried under 0.04 torr to give **7** (*d:* 1.46) in quantitative yield. IR (neat): $\nu = 3095$, 2969, 2880, 1636, 1490, 1351, 1192, 1141, 1057, 789, 770, 740, 685 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 9.08$ (d, $J = 6.3$ Hz, 2H), 8.61 (t, $J = 8.1$ Hz, 1H), 8.16 (dd, $J = 6.9$, 7.2 Hz, 2H), 4.60 (t, $J = 7.5$ Hz, 2H), 1.91 (tt, $J = 7.5$, 7.8 Hz, 2H), 1.28 (tq, $J = 7.2$, 7.8 Hz, 2H), 0.92 (t, $J = 7.5$ Hz, 3H); anal. calcd. for $C_{10}H_{14}N_2F_6O_4S_2$: C 31.73, H 3.39, N 6.73%; found: C 31.74, H 3.44, N 6.80%.

Typical Procedure for Direct Esterification Catalyzed by Zr(IV)–Fe(III) Complex and Catalyst Recycling using 7

A 20-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(O-*i*-Pr)$_4$ (16.3 mg, 0.05 mmol) and Fe(O-*i*-Pr)$_3$ (11.7 mg, 0.05 mmol) as catalysts in **7** (1 mL) and hydrocarbon (2.5 mL). The mixture was brought to reflux with the removal of water. After the reaction was complete, the resulting mixture was cooled to ambient temperature and a colorless hydrocarbon layer was separated from a brown ionic liquid layer by simple extraction with hexane-Et_2O. The desired ester was isolated from a hydrocarbon layer by column chromatography on silica gel. On the other hand, the Zr(IV)–Fe(III) catalyst that remained in **7** was used directly in the next reaction without further purification.

Acknowledgements

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References and Notes

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[6] $Zr(OH)_x(OAc)_y$, which is halide-free and commercially available, is a good catalyst, as well as $ZrCl_4 \cdot 2\,THF$ and $HfCl_4 \cdot 2\,THF$.[5f]

[7] LD_{50} [$ZrCl_4$ oral, rat] =1688 mg kg^{-1}; lethal intake of Fe(II or III) = 7–35 g, see: J. Emsley, *The Elements*; 3rd edn., Clarendon, Oxford, **1998**.

[8] It is known that Hf(IV) and Zr(IV) do not catalyze transesterification, while Ti(IV) catalyzes transesterification.[1]

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[10] [EMIM][BF_4]: ethylmethylimidazolium tetrafluoroborate; [BMIM][PF_6]: butylmethylimidazolium hexafluorophosphate; [EMIM][OTf]: ethylmethylimidazolium trifluoromethanesulfonate; [BMIM][NTf_2]: butylmethylimidazolium trifluoromethanesulfonimide (**6**); [BPY][NTf_2]: butylpyridinium trifluoromethanesulfonimide (**7**).

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