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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 781–785

Recyclable and selective Lewis acid catalysts for transesterification and direct esterification in a fluorous biphase system: tin(IV) and hafnium(IV) bis(perfluorooctanesulfonyl)amide complexes

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Received 8 October 2003; revised 4 November 2003; accepted 7 November 2003

Abstract—Tin(IV) and hafnium(IV) bis(perfluorooctanesulfonyl)amide complexes were shown to give excellent yield and selectivity for highly practical transesterification and direct esterification, respectively, with an equimolar ratio of the reactants in a fluorous biphase system. It was found that these metal complexes were completely recovered and reused in the immobilized fluorous phase without loss of their catalytic activities.

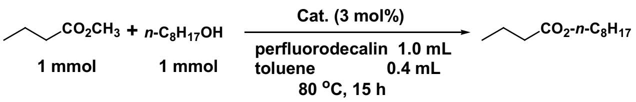
It is well known that transesterification of ester/alcohol and direct esterification of carboxylic acid/alcohol play important roles in the production of organic esters, especially for some important products or intermediates in the chemical and pharmaceutical industries.[1,2] However, either of the reactants in excess and/or the removal of the formed alcohol (or water) from the products are generally required to bias the innate equilibrium process in favor of the product side (Eqs. 1 and 2).[3]

$$RCO_2R^1 + R^2OH \rightarrow RCO_2R^2 + R^1OH \qquad (1)$$

$$RCO_2H + R^3OH \rightarrow RCO_2R^3 + H_2O \qquad (2)$$

In view of the rapidly increasing demands of green and sustainable chemistry, the practical transesterification and direct esterification should be improved at best to meet the following requirements: (1) the ester (or carboxylic acid) and alcohol reactants to be mixed in the ratio of 1:1; (2) no need of special technology to remove the liberated alcohol (or water); (3) easy separation of the catalyst and its recycled use for the next reaction; (4) mild reaction conditions.[4] Fluorous biphase system (FBS), as a phase-separation and catalyst immobilization technique, was shown to be a potential technical candidate.[5] Our recent reports have shown that metal complexes (e.g., Sn, Sc, and Yb) with bis(perfluorooctanesulfonyl)amide and tris(perfluorooctanesulfonyl)methide ponytails are highly active and recyclable catalysts in the fluorous immobilized phase for Baeyer–Villiger oxidation, alcohol acylation, and Friedel–Crafts acylation,[6] which have been approved satisfactorily in a bench-scale continuous-flow system.[7] Here we will report our successful approach to FBS for transesterification and direct esterification in an equimolar ratio of the reactants, under mild operating conditions without recourse to any technique to remove the formed alcohol (or water).

The catalytic activities of various catalysts (3 mol %) were first investigated in FBS with a model reaction of methyl butyrate (1 mmol) and *n*-octanol (1 mmol) under the mild conditions of 80 °C for 15 h, as described in Scheme 1. During the reaction period, the methanol



Scheme 1. Transesterification of methyl butyrate with *n*-octanol in FBS.

Keywords: Lewis acid catalyst; Fluorous biphase system; Perfluorianted ligand; Transesterification; Direct esterification.

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doi:10.1016/j.tetlet.2003.11.035

Table 1. Transesterification of methyl butyrate with *n*-octanol in FBS under the conditions in Scheme 1

Entry	Catalyst	Yield (%)[a]	Selectivity (%)[b]
1	$Sn[N(SO_2C_8F_{17})_2]_4$	89 (88[c])	99
2	$SnCl_4$	9	50
3	$Sn[N(SO_2C_8F_{17})_2]_2$	84	96
4	$Sn(OSO_2CF_3)_2$	83	96
5	$Hf[N(SO_2C_8F_{17})_2]_4$	76	89
6	$Hf(OSO_2CF_3)_4$	65	87
7	$Sc[N(SO_2C_8F_{17})_2]_3$	74	86
8	$Sc(OSO_2CF_3)_3$	59	87
9	$Yb[N(SO_2C_8F_{17})_2]_3$	55	85
10	$Yb(OSO_2CF_3)_3$	12	48
11	Nafion® SAC-13	7	53
12	None	0	0

[a] GC yield (internal standard: *n*-nonane).
[b] Selectivity: mmol product/mmol converted methyl butyrate.
[c] Isolated yield.

Table 2. Recycles of $Sn[N(SO_2C_8F_{17})_2]_4$ catalyst in transesterification of methyl butyrate with *n*-octanol under the conditions in Scheme 1

Cycle[a]	Yield (%)[b]	Selectivity (%)[c]
1	89	99
2	88	97
3	87	97
4	84	97
5	84	96

[a] Cycles of the lower fluorous catalyst phase.
[b] GC yield (internal standard: *n*-nonane).
[c] Selectivity: mmol product/mmol converted methyl butyrate.

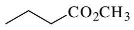
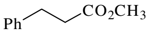
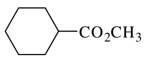
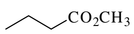
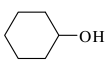
by-product was not removed.† As summarized in Table 1, no product was obtained in the absence of the catalyst (entry 12). On the other hand, all of the metal complexes (Sn^{II}, Hf^{IV}, Sc^{III}, Yb^{III}) with $–N(SO_2C_8F_{17})_2$ ligand[8] (entries 3, 5, 7, and 9) generally gave better yields than those with $–OSO_2CF_3$ ligand (entries 4, 6, 8, and 10), but there was no significant difference in the selectivity except for Yb^{III} complex. These results can be attributed to the presence of the strong electron-withdrawing $–N(SO_2C_8F_{17})_2$ ligand bearing a higher fluorine load on the metal center.[9] It can also be seen that almost the same results were obtained with $Sn(OSO_2CF_3)_2$ and $Sn[N(SO_2C_8F_{17})_2]_2$ in this FBS (entries 3 and 4), but $Sn(OSO_2CF_3)_2$ could not be simply and directly recycled due to its distribution in the upper toluene phase (unlike $Sn[N(SO_2C_8F_{17})_2]_2$ immobilized in the lower perfluorodecalin phase and directly reused for the next reaction), which could lie in the difference of their partition coefficients (perfluorodecalin/toluene), (<0.1)/(>99.9) for $Sn(OSO_2CF_3)_2$ and (>96.0)/(<4.0) for $Sn[N(SO_2C_8F_{17})_2]_2$ determined by atomic emission spectrometry. As for $M[N(SO_2C_8F_{17})_2]_n$ ($n = 3, 4$) complexes, the yield and selectivity were in the order of $Sn^{IV}>Hf^{IV}>Sc^{III}>Yb^{III}$ (entries 1, 5, 7, and 9). It also can be found that the yield of 89% and ester selectivity of 99% were obtained with $Sn[N(SO_2C_8F_{17})_2]_4$ (entry 1),[10] whereas $SnCl_4$ gave quite low results (entry 2). In addition, Nafion® SAC-13 is a well known strong Brønsted acid, but its catalytic activity for transesterification was significantly low in the present reaction system (entry 11).

The recyclable performance of $Sn[N(SO_2C_8F_{17})_2]_4$ was also investigated (Table 2). The operation was quite similar to those we have reported for Baeyer–Villiger oxidation,[6a] that is, the catalyst was completely immobilized in the fluorous phase for the transesterification and the fluorous solution was directly used in the subsequent reaction.[11] As shown in Table 2, even after $Sn[N(SO_2C_8F_{17})_2]_4$ catalyst was recycled five times, the GC yield was still higher than 84%, which confirmed that there was not only no loss of the catalyst amount but also no depression of catalytic activity during its subsequent reuse.

To explore the generality of the above $Sn[N(SO_2C_8F_{17})_2]_4$-catalyzed transesterification, this reaction system was also examined with some other esters and *n*-octanol (Table 3). It was found that, either with aliphatic or with aromatic esters, good yields were obtained under the simple and mild operating conditions, for example, at 80 °C for 15 h without any pressure devices. This can be viewed as more practical than most of the reported catalytic systems[4c,12] on account of the 1:1 reactant ratio and technically easy handling.

Furthermore, the fluorous catalytic phase was directly reused in the next reaction by combining with another mixture of reactants more than five times without loss of catalytic activity[13] for all of the reactions in Table 3 except the transesterification of methyl butyrate/cyclohexanol (entry 6) due to its lower yield of 58%. Further experiments are still under progress.

Table 3. Fluorous biphase transesterifications catalyzed by $Sn[N(SO_2C_8F_{17})_2]_4$

Entry	RCO_2R^1	R^2OH	Yield (%)[a]	Selectivity (%)[b]
1		n-$C_8H_{17}OH$	89	99
2		n-$C_8H_{17}OH$	91	98
3		n-$C_8H_{17}OH$	90	98
4[c]	$PhCO_2CH_3$	n-$C_8H_{17}OH$	91	98
5[c]	$PhCO_2C_2H_5$	n-$C_8H_{17}OH$	90	98
6			58	98

Reaction conditions: see Scheme 1 and footnote †.
[a] GC yield (internal standard: *n*-nonane).
[b] Selectivity: mmol product/mmol converted ester.
[c] 5 mol% $Sn[N(SO_2C_8F_{17})_2]_4$ for 24 h.

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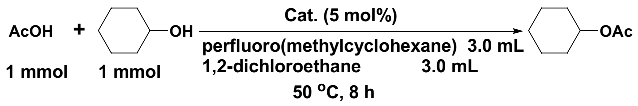
† Typical transesterification procedure (Table 1, entry 1): A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with methyl butyrate (102 mg, 1 mmol), *n*-octanol (130 mg, 1 mmol), $Sn[N(SO_2C_8F_{17})_2]_4$ (121 mg, 0.03 mmol), toluene (0.4 mL), and perfluorodecalin (1.0 mL). The tube was placed in an organic synthesizer equipped with a magnetic stirrer and heated at 80 °C for 15 h. The reaction mixture was cooled to room temperature and then toluene (0.6 mL) was added. After being stirred for 10 min, this mixture was separated into two liquid phases within 10 s. The upper toluene phase afforded pure *n*-octyl butyrate (176 mg, 0.88 mmol) by silica gel chromatography, while the lower fluorous phase was used in subsequent reactions.



Scheme 2. Direct esterification of acetic acid with cyclohexanol in FBS.

Table 4. Direct esterification of acetic acid with cyclohexanol in FBS under the conditions in Scheme 2

Entry	Catalyst	Yield (%)[a]	Selectivity (%)[b]
1	$Hf[N(SO_2C_8F_{17})_2]_4$	82 (81[c])	99
2	$Hf(OSO_2CF_3)_4$	70	88
3	$HfCl_4$	22	61
4	$HfCl_4·2THF$	29	60
5	$Sn[N(SO_2C_8F_{17})_2]_4$	78	98
6	$SnCl_4$	16	45
7	$Zr[N(SO_2C_8F_{17})_2]_4$	73	89
8	$ZrCl_4$	14	77
9	$Yb[N(SO_2C_8F_{17})_2]_3$	28	45
10	Nafion® SAC-13	8	19
11	None	0	0

[a] GC yield (internal standard: *n*-nonane).
[b] Selectivity: mmol product/mmol converted acetic acid.
[c] Isolated yield.

This catalytic FBS system was also evaluated with the direct esterification of acetic acid/cyclohexanol under the mild conditions of 50 °C for 8 h (Scheme 2). Compared with the above-described transesterification of methyl butyrate/*n*-octanol, $Sn[N(SO_2C_8F_{17})_2]_4$ (entry 5) could no longer give the best yield, which was just below $Hf[N(SO_2C_8F_{17})_2]_4$ (entry 1)[14] as summarized in Table 4.[‡] With respect to Hf^{IV}-based catalysts, $Hf[N(SO_2C_8F_{17})_2]_4$ showed significantly higher activity than $Hf(OSO_2CF_3)_4$, $HfCl_4$, and $HfCl_4·2THF$ (entries 1, 2, 3, and 4), even though the latter two are well known efficient catalysts for direct esterification.[3b] In addition, $Zr[N(SO_2C_8F_{17})_2]_4$ can also be thought to be an effective catalyst, but $ZrCl_4$ was much less active (entries 7 and 8). These results indicated that the unique complexation of $–N(SO_2C_8F_{17})_2$ ligand with metals (e.g., Hf, Sn, and Zr) is highly significant for the present esterification system.[8] Accordingly, 5 mol% of $Hf[N(SO_2C_8F_{17})_2]_4$ was considered to be the best catalyst in view of a yield of 82% and excellent selectivity of 99%.

Table 5. Recycles of $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst in direct esterification of acetic acid with cyclohexanol under the conditions in Scheme 2

Cycle[a]	Yield (%)[b]	Selectivity (%)[c]
1	82	99
2	83	97
3	81	97
4	83	97
5	82	98

[a] Cycles of the lower fluorous catalyst phase.
[b] GC yield (internal standard: *n*-nonane).
[c] Selectivity: mmol product/mmol converted acetic acid.

In addition, the recyclabilty of $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst[15] in the direct esterification of acetic acid with cyclohexanol was investigated (Table 5). It was found that there was almost no reduction of the catalytic activity (yield: 81–83%) and no other by-products were detected except for the desired ester formation (selectivity: >97%).

The effectiveness of $Hf[N(SO_2C_8F_{17})_2]_4$ for esterification was examined with some substrates involving bulky carboxylic acids and alcohols (Table 6). It can be seen that cyclohexanecarboxylic acid (entries 2, 3, and 4) gave better yield than benzoic acid (entries 5, 6, and 7), when reacted with either *n*-butanol, benzyl alcohol, or cyclohexanol. Meanwhile, benzyl alcohol (entries 3 and 6) was found to be more easily esterified than cyclohexanol (entries 4 and 7, respectively), which may be ascribed to cyclohexanol being liable to dehydration. In addition, α,β-unsaturated methacrylic acid (entry 8) was shown to be converted to the desired methyl methacrylate (a very important polymer material) in a good yield (86%) and selectivity (98%). Furthermore, the recyclable performance[16] of $Hf[N(SO_2C_8F_{17})_2]_4$ for esterification of cyclohexanecarboxylic acid/*n*-butanol, cyclohexanecarboxylic acid/benzyl alcohol, benzoic acid/*n*-butanol, and methacrylic acid/methanol (entries 2, 3, 5, and 8), was quite similar to the above acetic acid/cyclohexanol esterification (Table 5), that is, reused more than five times without depression of the catalytic activity.

The transesterification and direct esterification catalyzed by $Sn[N(SO_2C_8F_{17})_2]_4$ and $Hf[N(SO_2C_8F_{17})_2]_4$ catalysts in FBS were proved to be highly efficient on the investigated substrates. These experimental results have great potential for large-scale operation in terms of the following: (1) equimolar ratio of ester (or carboxylic acid)/alcohol; (2) no requirement for removal of the formed alcohol (or water); (3) complete immobilization of the $Sn[N(SO_2C_8F_{17})_2]_4$ or $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst in the fluorous phase and their reuse in subsequent reactions; (4) high yield and selectivity under mild conditions.

Acknowledgements

This work was supported by New Energy and Industrial Technology Development Organization (NEDO) and

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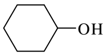
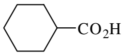
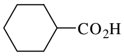
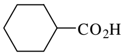
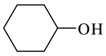
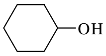
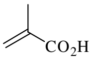
[‡] Typical esterification procedure (Table 4, entry 1): As the above-described transesterification of methyl butyrate/*n*-octanol, acetic acid (60 mg, 1 mmol), cyclohexanol (100 mg, 1 mmol), $Hf[N(SO_2C_8F_{17})_2]_4$ (205 mg, 0.05 mmol), and a mixture of perfluoro(methylcyclohexane) (3 mL) and 1,2-dichloroethane (3 mL) were added to a 20-mL test tube equipped with a Teflon-coated magnetic stirring. The reactant mixture was stirred continuously at 50 °C for 8 h and settled down for 10 s. Then this reacted mixture was turned into an upper 1,2-dichoroethane phase for pure cyclohexyl acetate (115 mg, 0.81 mmol) by silica gel chromatography and a lower fluorous phase for the subsequent reaction.

Table 6. Fluorous biphase esterifications catalyzed by $Hf[N(SO_2C_8F_{17})_2]_4$

Entry	RCO_2H	R^3OH	Conditions	Yield (%)[a]	Selectivity (%)[b]
1	AcOH		50 °C, 8 h	82	98
2		n-C_4H_9OH	70 °C, 15 h	92	97
3		$PhCH_2OH$	50 °C, 24 h	89	98
4			50 °C, 24 h	55	98
5[c]	$PhCO_2H$	n-C_4H_9OH	90 °C, 15 h	85	96
6	$PhCO_2H$	$PhCH_2OH$	50 °C, 24 h	21	98
7	$PhCO_2H$		50 °C, 24 h	12	98
8		CH_3OH[d]	60 °C, 8 h	86	98

Reaction conditions: see Scheme 2 and footnote ‡.

[a] GC yield (internal standard: n-nonane).

[b] Selectivity: mmol product/mmol converted carboxylic acid.

[c] In perfluorodecalin (3.0 mL)/1,2-dichloroethane (3 mL) biphase system.

[d] 5 mol equiv of methanol.

Japan Chemical Innovation Institute (JCII) through the R&D program for Process Utilizing Multi-Phase Catalytic Systems.

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7. Yoshida, A.; Hao, X.; Nishikido, J. *Green Chem.* **2003**, *5*, 554–557.
8. The catalytic activity was investigated in FBS for transesterification of methyl butyrate/n-octanol with 12 mol% $HN(SO_2C_8F_{17})_2$ and esterification of acetic acid/cyclohexanol with 20 mol% $HN(SO_2C_8F_{17})_2$, respectively. The obtained results from these reactions (55% yield and 73% selectivity from the former transesterification; 65% yield and 65% selectivity from the latter esterification) were considerably lower than those with metal complexes (89% yield and 99% selectivity from the former transesterification with $Sn[N(SO_2C_8F_{17})_2]_4$; 82% yield and 99% selectivity from the latter esterification with $Hf[N(SO_2C_8F_{17})_2]_4$). Additionally, $HN(SO_2C_8F_{17})_2$ was found to be difficult for efficient phase separation and recycle due to its weight loss (>53%) in the lower fluorous phase and distribution in the upper organic phase (confirmed by ^{19}F NMR) after the reaction was completed either with the former transesterification or the latter esterification. These results verified that the efficient and recyclable catalysis requires the unique complexation of metal (Sn^{IV} or Hf^{IV}) with $-N(SO_2C_8F_{17})_2$.
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10. Synthesis of $Sn[N(SO_2C_8F_{17})_2]_4$: same as the description in Ref. 6a.
11. The catalyst was recovered from the fluorous phase without apparent weight loss, that is, 119 mg of catalyst was recovered after the original 121 mg was recycled five times. The recovered $Sn[N(SO_2C_8F_{17})_2]_4$ catalyst was characterized by elemental analysis: Calcd C, 19.03; Sn, 2.94; Found: C, 19.41; Sn, 2.92.

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13. Representative results in the subsequent four cycles: methyl cyclohexanecarboxylate/*n*-octanol obtained yields of 92%, 90%, 91%, and 92% (selectivity of 98%, 96%, 100%, and 97%, respectively); ethyl benzoate/*n*-octanol obtained yields of 92%, 90%, 93%, and 92% (selectivity of 98%, 98%, 98%, and 100%, respectively).
14. $Hf[N(SO_2C_8F_{17})_2]_4$: To anhydrous methanol (10 mL) was added $HN(SO_2C_8F_{17})_2$ (6.00 mmol) and $HfCl_4$ (1.50 mmol), which was stirred continuously at 50 °C for 15 h. After being cooled to the room temperature, the reaction mixture was evaporated and dried at 80 °C/0.01 mmHg for 16 h to give hafnium(IV) bis(perfluorooctanesulfonyl)amide complex as a hygroscopic white powder in 97% yield (5.96 g). $Hf[N(SO_2C_8F_{17})_2]_4$ elemental analysis: Calcd C, 18.75; Hf, 4.35; Found: C, 18.65; Hf, 4.33; ^{19}F NMR δ −126.2, −121.1, −114.2, −81.5.
15. The catalyst was recovered from the fluorous phase without apparent weight loss, that is, 203 mg modified catalyst was recovered after the original 205 mg was recycled five times. The recovered $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst was characterized by elemental analysis: Calcd C, 18.75; Hf, 4.35; Found: C, 18.72; Hf, 4.33.
16. Representative results in the subsequent four cycles: cyclohexanecarboxylic acid/*n*-butanol obtained yields of 92%, 93%, 93%, and 92% (selectivity of 98%, 98%, 98%, and 100%, respectively); benzoic acid/*n*-butanol obtained yields of 86%, 85%, 86%, and 87% (selectivity of 100%, 98%, 97%, and 97%, respectively).