

Toward Ideal (Trans)Esterification by Use of Fluorous Distannoxane Catalysts

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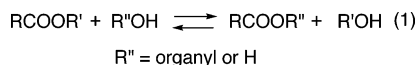
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ABSTRACT

1,3-Disubstituted tetrakis(fluoroalkyl)distannoxanes, $(XR_2SnOSnR_2Y)_2$ ($R = C_6F_{13}C_2H_4$ and $C_4F_9C_2H_4$), are highly fluorophilic and exhibit large partition coefficients in favor of fluorocarbon solvents over common organic solvents due to a double-layered structure where the stannoxane core is covered by fluoroalkyl groups. Under catalysis of these Lewis acids, fluorous technology allows novel transesterification and esterification in which a 100% yield of the desired esters is achievable with reactants in a strict 1:1 ratio. The catalysts are recovered from the fluorous phase quantitatively. More practically, the catalyst in fluorocarbon solution can be recycled for use in the next reaction repeatedly.

Introduction

Both esterification and transesterification (eq 1) are classical reactions that still find great demand in modern



synthetic chemistry.¹ Of particular significance is the practical industrial utilization of (trans)esterification. Because of its long history, as well as the simplicity of the reaction, one assumes that the field is mature. This is not true, however. Since the reaction is an equilibrium, either of the reactants must be charged in excess or the product water or alcohol remaining in the reaction mixture must be constantly removed during the reaction or both to force the reaction forward to the product side. These conditions never meet the requirements of “green chemistry”, the significance of which is rapidly increasing. The use of excess reactant is not atom-economical,² while the removal of the coproduct by azeotropic distillation demands energy consumption. Needless to say, addition of dehydration reagents increases the complexity of the reaction system. It should be further pointed out that the employment of equimolar reactants is meaningful only if 100% conversion is reached. Otherwise, a four-component

mixture consisting of two reactants and two products remains in the reaction mixture, which needs to be separated afterward. Attention also should be paid to the nature of the catalyst. The catalyst should be used in a minimal amount and readily recovered to enable the recycled use. The development of mild catalysts is another important requirement for expanding the scope of the reaction because acidic catalysts are usually employed, restricting the substrates to acid-stable ones. As a whole, it is reasonable to summarize that the ultimate goal of the esterification is to achieve a 100% yield with the reactants in a strict 1:1 ratio by use of mild, recyclable catalysts without recourse to any technology to remove the coproduct water or alcohol.³

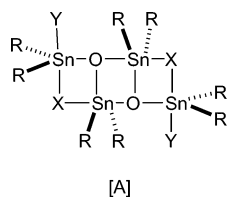
In the above context, exploitation of catalysts effective for esterification with 1:1 reactant stoichiometry has been an attractive challenge for synthetic chemists. Graphite bisulfate⁴ and $NaHSO_4 \cdot H_2O$,⁵ with the aid of a Soxhlet apparatus, were reported to serve for the condensation of an equimolar mixture of carboxylic acid and alcohol. More recently, it was found that $HfCl_4 \cdot 2THF$ /Soxhlet apparatus⁶ catalyzed a wide variety of the desired condensations, while $Ph_2NH_2^+OTf^-$ worked for the present purpose without recourse to the dehydration techniques.⁷ Condensation in water with catalysis by dodecylbenzenesulfonic acid as Brønsted acid/surfactant combination was also reported to be effective.⁸ Yields in the above reactions are generally high (> 85%), but not always perfectly quantitative, although some examples giving rise to quantitative yields (>99%) were reported in the $HfCl_4 \cdot 2THF$ protocol. On the other hand, no transesterification protocols were known to give a 100% yield starting from equimolar reactants. Although a triglyceride was successfully transesterified with 3 equiv of alcohol by the dodecylbenzenesulfonic acid catalyst, the yield was not perfect but 94% at best.⁸ Exceptionally, β -ketoester substrates readily undergo transesterification with equimolar alcohol⁹ on account of a rather different reaction mechanism: the reaction is initiated by formation of ketene intermediates from β -ketoesters, to which irreversible addition of alcohol takes place. As such, (trans)esterification protocols that are truly atom-economical in a strict sense remained unexplored.

The past decade has witnessed the usefulness of fluorous biphasic technology.¹⁰ The basic idea of this technology stemmed from facile separation of organic products and fluorous catalysts, staying in the organic and fluorous phases, respectively, owing to incompatibility of the two reaction media. We assumed that such unique solubility characteristics might be reflected in the equilibrium as well. This simple expectation led us to tackle fluorous biphasic (trans)esterification. Since we had already accumulated much information on distannoxane-catalyzed (trans)esterification, we decided to synthesize fluorous distannoxane catalysts and apply them to the present goal.

Junzo Otera was born in Hyogo, Japan, in 1943. He received his undergraduate, as well as graduate, education in Osaka University. Immediately after earning the Ph.D. degree in 1971, he became a research chemist in Central Research Laboratories of Kuraray Co. In 1979, he moved to Okayama University of Science as Associate Professor and has been Full Professor since 1986. In the meantime, he served as a visiting professor in many universities in Japan, U.S.A., France, Spain, and Australia. His research interests are focused on Lewis acid catalysts, heteroatom chemistry, and green process chemistry.

Prologue

1,3-Disubstituted tetraalkyldistannoxanes are soluble in most organic solvents even though they have a large inorganic metaloxane core. This solubility is ascribed to a dimeric formulation [A] in which the metaloxane core



is surrounded by eight alkyl groups, making the surface of the molecule lipophilic.¹¹ In addition to the unique solubility, the dimeric structure gives rise to high catalytic activity for transesterification¹² thanks to a template effect induced by the two kinds of tin atoms, which are located close to each other but in different coordination environments. Mildness is another notable feature of the distannoxane catalysts. Since the distannoxane-catalyzed reactions proceed under almost neutral conditions, various functional groups can survive, and these merits found a wide range of synthetic applications.¹³

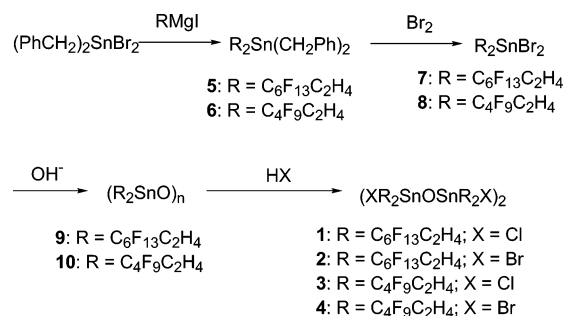
The hydrophobic nature of distannoxane also plays an interesting role in the condensation between carboxylic acids and alcohols, especially in macrolactonization of ω -hydroxy carboxylic acids.¹⁴ To bias the equilibration, this type of reaction is usually conducted with the aid of dehydration techniques such as azeotropic distillation of water. In striking contrast, macrolactonization proceeded simply by heating the ω -hydroxy carboxylic acid in the presence of distannoxane catalyst without recourse to the dehydration technique. If the same reaction was conducted with $(\text{Bu}_2\text{SnO})_n$, lower yields resulted even with the use of a Dean–Stark apparatus.¹⁵ Apparently, the hydrophobic surface of the distannoxane catalyst prevents the water formed from approaching the active site, resulting in suppression of the reverse hydrolysis reaction.

It was reasonable for us to postulate that replacement of surface alkyl groups on the distannoxanes with fluoroalkyl groups should render the molecules fluorophilic and that mild catalysts would be accessible that are workable under fluorous biphasic conditions.

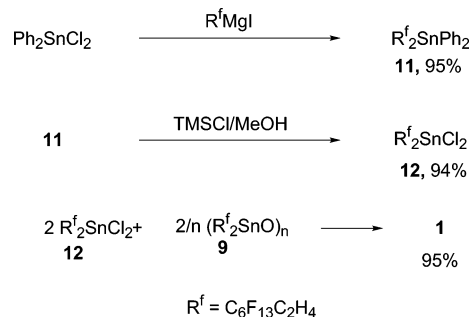
Synthesis of Fluorous Distannoxanes

Two fluoroalkyl groups, $\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4$ and $\text{C}_4\text{F}_9\text{C}_2\text{H}_4$, were employed in which the $\text{C}_n\text{F}_{2n+1}$ moiety endowed the molecules with fluorophilicity while the C_2H_4 spacer insulates the electronic influence of the fluoroalkyl moieties. The synthetic route for fluoroalkyldistannoxanes **1–4** is shown in Scheme 1.¹⁶ Treatment of dibenzyltin dibromide, which is readily obtained from benzyl bromide and tin powder, with $\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4\text{MgI}$ or $\text{C}_4\text{F}_9\text{C}_2\text{H}_4\text{MgI}$ furnished tetraalkyltins **5** and **6** in 80% and 99% yields, respectively. Bromination of these compounds cleaved the benzyl groups selectively to afford dibromides **7** and **8** (~95% yield), and subsequent alkaline hydrolysis led to oxides **9**

Scheme 1. Synthesis of Fluorous Distannoxanes



Scheme 2. Convenient Synthesis of **1**



and **10** in ca. 93% yields. These compounds were amorphous solids like other organotin oxides and difficult to obtain in analytically pure form. Treatment of the crude oxides with a slight excess of aqueous HCl or HBr in acetone furnished 1,3-dihalodistannoxanes **1–4** in 80–85% yields.

A more convenient method for **1** was developed starting from commercially available Ph_2SnCl_2 (Scheme 2).¹⁷ The first step is to attach the fluoroalkyl groups to the phenyltin moiety to afford **11** by the Grignard method, a protocol employed by Curran et al.¹⁸ and Gielen et al.¹⁹ previously. Then, **11** was converted to the corresponding dichloride **12**. The phenyl groups could be cleaved by bubbling HCl gas into a CCl_4 solution of **11**, but handling of HCl gas is not operationally convenient. Alternatively, an in situ HCl generation method²⁰ served to effect more practical chlorination in satisfactory yields. Heating the dichloride thus obtained with an equimolar amount of oxide **9** in refluxing acetone or toluene afforded a quantitative yield of **1**. This procedure is much more convenient because the ratio of the reactants can be adjusted accurately by weight and the reaction is totally reproducible.

When an FC-72 (perfluorohexanes, 3M Company, St. Paul, MN) solution of **1** was combined with an aqueous solution of NaSCN and the mixture was stirred at room temperature for 20 h, only the terminal chlorine atoms were replaced to give **13** (eq 2).¹⁶

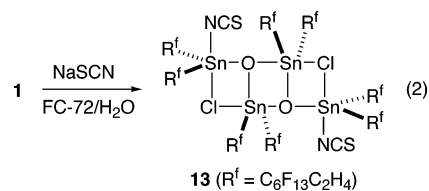


Table 1. Solubility of Fluorous Tin Compounds in FC-72

compound ^a	solubility (g/L)
1	153
R ^f ₃ SnCl	59
R ^f ₂ SnCl ₂ (12)	32
R ^f ₃ SnC ₆ F ₅	freely miscible
R ^f ₂ Sn(C ₆ F ₅) ₂	~500
R ^f ₄ Sn	freely miscible

^a R^f = C₆F₁₃C₂H₄.**Table 2. Partition of Fluorous Tin Compounds Between FC-72 and Organic Solvents**

compound ^a	F-content (%)	organic solvent	partition (FC-72/organic solvent)
1	57.68	toluene	~100:0
		benzene	~100:0
		hexane	~100:0
		CH ₂ Cl ₂	99:1
		MeOH	98:2
		acetone	97:3
		THF	96:4
R ^f ₃ SnCl	61.98	toluene	92:8
		THF	73:27
12	55.89	toluene	82:18
		THF	68:32
R ^f ₃ SnC ₆ F ₅	62.99	toluene	99:1
		THF	97:3
R ^f ₂ Sn(C ₆ F ₅) ₂	59.63	toluene	92:8
		THF	88:12
R ^f ₄ Sn	65.55	toluene	99:1
		THF	97:3

^a R^f = C₆F₁₃C₂H₄.

All fluoroalkyldistannoxanes thus prepared were isolated as crystalline materials, but they were not obtained in a suitable form for X-ray analysis. However, ¹¹⁹Sn NMR spectra gave rise to two distinct singlets diagnostic of the characteristic dimeric distannoxane formulation.²¹

Solubility of Fluorous Distannoxanes

As expected, these compounds are sparingly soluble in common organic solvents except acetone and ethyl acetate.¹⁶ The solubility of **1** (g/L) at room temperature is as follows: toluene, benzene, <<1; hexane, <1; CH₂Cl₂, ca. 1; methanol, 2; acetonitrile, 9; acetone, 40; ethyl acetate, 48. On the other hand, this compound is well soluble in fluorocarbon solvents such as FC-72, FC-40 (perfluorododecanes), and octafluorocyclopentene.

Table 1 summarizes the solubility of **1**, together with relevant fluoroalkyltin compounds.¹⁷ Compounds **1** and (C₆H₁₃C₂H₄)_nSnCl_{4-n} (*n* = 2 and 3)²² exhibit fair to good solubility, while replacement of chlorine(s) of these chlorides with the perfluorophenyl group(s) results in a great increase in the solubility. In particular, (C₆H₁₃C₂H₄)₃-SnC₆F₅²² and (C₆H₁₃C₂H₄)₄Sn²² seem to be miscible with FC-72 in any ratio, while an upper limit, though very high, of solubility exists for (C₆H₁₃C₂H₄)₂Sn(C₆F₅)₂²² (~500 g/L). Thus, it is apparent that the C₆H₁₃C₂H₄ group is more effective than the perfluorophenyl group for increasing fluorophilicity.

Partition of these compounds between FC-72 and conventional organic solvents was determined (Table 2).¹⁷ All exhibited high preference for FC-72. In accordance

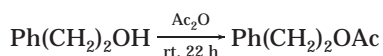
**FIGURE 1.** Double-layered structure of fluorous distannoxane.

with their solubility in FC-72, the partition coefficients of (C₆H₁₃C₂H₄)_nSn(C₆F₅)_{4-n} are larger than those of (C₆H₁₃-C₂H₄)_nSnCl_{4-n}. Quite reasonably, the value decreases with decreasing numbers of fluoroalkyl groups in both series of (C₆H₁₃C₂H₄)_nSn(C₆F₅)_{4-n} and (C₆H₁₃C₂H₄)_nSnCl_{4-n} although virtually no difference was observed between (C₆H₁₃C₂H₄)₄Sn and (C₆H₁₃C₂H₄)₃SnC₆F₅. The perfect bias of **1** into the FC-72 phase against hydrocarbons such as toluene, benzene, and hexane is remarkable. Furthermore, the unique solubility is highlighted by comparison with (C₆F₁₃C₂H₄)₂SnO (**9**). According to Curran et al., partition coefficients of this compound are as follows: toluene, 1.9; CH₂Cl₂, 1.7; CH₃CN, 0.28.¹⁸ On account of these relatively low partition coefficients, repeated washings were necessary for recovery of the oxide from the reaction mixture in fluorous biphasic sulfonylation of diols. By contrast, as described below, virtually 100% recovery of **1** was achievable by a single separation with the 1:1 FC-72/toluene binary system in our transesterification. It follows that the double-layered structure composed of the surface fluoroalkyl groups and the stannoxane core renders **1** completely fluorophilic (see Figure 1) while the wrapping of the inorganic moiety by the fluoroalkyl groups may be insufficient in **9**, which has simple oligomeric structures. It should be noted that dibromide **2** exhibited similar solubility to that of **1**.

Nonafluorohexyl derivatives **3** and **4** are also essentially fluorophilic, but the degree is somewhat lower than that of **1** and **2**: for example, partition coefficients (FC-72/toluene) are 32 for **3** and 24 for **4**, respectively.¹⁶ This is consistent with the well-accepted notion that the solubility in fluorocarbon solvents increases as the fluorine content of the molecule increases.²³ It should be pointed out, however, that the partition coefficients of distannoxane **1** are the same as or higher than those of (C₆H₁₃-C₂H₄)_nSn(C₆F₅)_{4-n} and (C₆H₁₃C₂H₄)₄Sn although the fluorine content of **1** is smaller than those of the latter compounds (Table 2). These outcomes imply that the partition is not governed solely by the fluorine content, but that the effective coverage of the molecular surface with fluorine is another important aspect that should be taken into account for increasing the fluorophilicity.

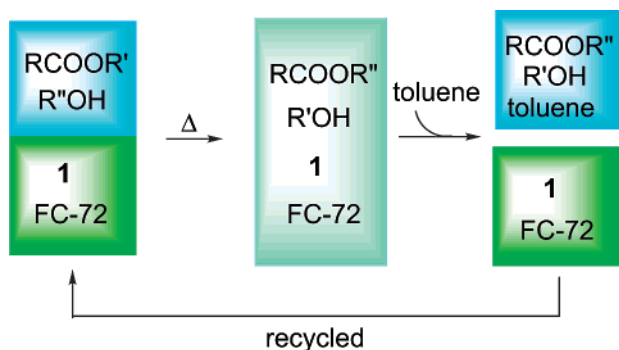
Comparison of Fluorous Organotin Catalysts

The activity of fluorous organotin compounds as Lewis acid catalysts was assessed for acetylation of 2-phenylethanol (Table 3).¹⁷ The reaction was conducted in homogeneous 1,1,1-trifluorotoluene (benzotrifluoride, BTF) solution to render the conditions as identical as possible. Remarkably, a quantitative yield was obtained with **1** even

Table 3. Acetylation of 2-Phenylethanol Catalyzed by Fluorous Tin Catalysts^a

entry	catalyst ^b	yield of ester (%)
1	1	>99
2	R ^f ₃ SnC ₆ F ₅	54
3	R ^f ₂ Sn(C ₆ F ₅) ₂	60
4	R ^f ₄ Sn	40
5	none	15

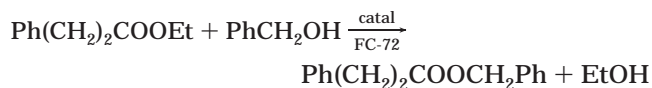
^a One equivalent of Ac₂O was used. ^b R^f = C₆F₁₃C₂H₄.

Scheme 3. Transesterification in Single Fluorous Solvent System

with the use of an equimolar amount of Ac₂O at room temperature (entry 1). On the other hand, the yields were much lower with (C₆H₁₃C₂H₄)_nSn(C₆F₅)_{4-n} and (C₆H₁₃C₂H₄)_{4-n}Sn under the same conditions (entries 2–4), although comparison with a control experiment (entry 5) unambiguously showed that the activity is retained to some degree even in these less active compounds. Obviously, the distannoxane catalyst is more active than the mono-nuclear tin compounds, (C₆H₁₃C₂H₄)_nSn(C₆F₅)_{4-n} and (C₆H₁₃C₂H₄)₄Sn.

Transesterification

Single Fluorous Solvent System. Upon confirmation of the highly fluorophilic character of fluorous distannoxanes, these compounds were utilized as catalysts for fluorous biphasic transesterification.²⁴ We first addressed ourselves to the simplest system where FC-72 was the sole solvent. The general procedure is illustrated in Scheme 3: the reactants in a 1:1 ratio were heated at 150 °C in FC-72 for 16 h, and the reaction mixture was washed with toluene. The catalytic activity was examined for the reaction between ethyl 3-phenylpropionate and benzyl alcohol. As given in Table 4, gas–liquid chromatography (GLC) analysis of the toluene layer exhibited a single peak assignable to the benzyl ester, the yield of which was found to be >99% with 5 mol % loading of the dichloro- and dibromodistannoxane catalysts (entries 1, 4, 6). The ethyl ester and benzyl alcohol were completely consumed. No virtual difference was observed between tridecafluorooctyl (**1** and **2**) and nonafluorohexyl (**3**) catalysts, and the chain length of fluoroalkyl groups proved to exert no influence on the catalytic activity. However, the distinction was apparent between these two types of fluoroalkyl-distannoxanes with respect to recovery from the reaction

Table 4. Evaluation of Fluoroalkyltin Catalysts for Transesterification in Single Fluorous Solvent System^a

entry	catalyst (mol %)	GLC yield (%)	catalyst recovery (%)
1	1 (5.0)	>99	100
2	1 (2.0)	>99	100
3	1 (1.0)	96	100
4	2 (5.0)	>99	100
5	13 (1.0)	>99	100
6	3 (5.0)	>99	98
7	none ^b	65	

^a Reaction conditions: ester, 1.0 mmol; alcohol, 1.0 mmol; FC-72, 5 mL; 150 °C; 16 h; washing with toluene (1 mL × 2). ^b Control experiment.

mixture. From the FC-72 layer, **1** and **2** returned in 100% recovery, a rather surprising outcome in such a small scale reaction (1 mmol) where only 20–90 mg of the catalyst are employed. On the other hand, a fraction of **3** leaked into the organic layer, resulting in 98% recovery of the catalyst from the fluorous layer. This decrease in the recovery ratio, although trivial for an individual run, becomes serious upon recycled use of the catalyst because the deviation from the 100% recovery is multiplied (vide infra). Consequently, tridecafluorooctyl-distannoxanes were the catalysts of choice. Even with 2 mol % of **1**, a quantitative yield was obtained (entry 2), yet 1 mol % loading failed to furnish quantitative yield (entry 3). Notably, however, chlorisothiocyanate **13** is active enough to afford a quantitative yield with 1 mol % loading (entry 5). The somewhat enhanced activity of isothiocyanato derivatives was also found with tetrabutyl-distannoxane catalysts for urethane formation.²⁵ Of course, the effectiveness of the catalysts is apparent from comparison with a control experiment, which gave a lower yield (entry 7).

With these results in hand, we performed transesterification with various reactants with catalysis of **1**, **2**, and **13** (Table 5). Although the 2 mol % catalyst loading is enough for the completion of the reaction as described above, it is actually not necessary to decrease the amount of the catalyst to such a level because of its facile recovery and recycling (vide infra). Thus, the 5 mol % catalyst was loaded; this is easier for exact weighing of the catalyst than the 2 mol % loading. On the other hand, 1 mol % of **13** was loaded to highlight its higher catalytic activity. The reaction proceeded perfectly even using the reactants in the 1:1 ratio. No starting materials were detected after 16 h by GLC analysis. Aliphatic, α,β-unsaturated, and aromatic derivatives can be used as ester components. A variety of alcohols are also employable such as primary, secondary, allylic, and propargylic alcohols. Geraniol suffered neither isomerization nor the cyclization that easily occurs under acidic conditions (entry 5). Other acid-sensitive functions such as propargylic, tetrahydropyranyl (THP), and *tert*-butyldimethylsilyl (TBS) groups survived

Table 5. Transesterification in Single Fluorous Solvent System^a

$$\text{RCOOR}' + \text{R}''\text{OH} \xrightarrow[\text{FC-72}]{\text{catal}} \text{RCOOR}'' + \text{R}'\text{OH}$$

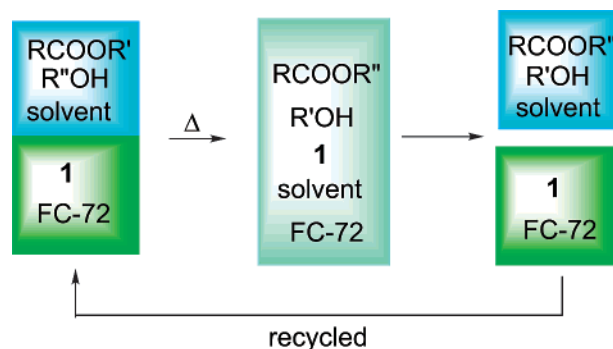
entry	RCOOR'	R''OH	catal	yield (%)	
				GLC	isolated
1	Ph(CH ₂) ₂ COOEt	C ₈ H ₁₇ OH	1	>99	100
2	Ph(CH ₂) ₂ COOMe	PhCH=CHCH ₂ OH	1	>99	100
3	Ph(CH ₂) ₂ COOEt	PhCH=CHCH ₂ OH	2	>99	100
4		PhCH=CHCH ₂ OH	13	>99	
5		geraniol	1	>99	98
6		PhC≡CCH ₂ OH	1	>99	100
7		THPO(CH ₂) ₈ OH	1	>99	99
8		TBSO(CH ₂) ₈ OH	1	>99	100
9		2-octanol	1	>99	100
10		cyclohexanol	1	>99	99
11		menthol	1	>99 ^b	
12		borneol	1	>99 ^b	
13		cholesterol	13	>99	
14	PhCH=CHCOOEt	PhCH=CHCH ₂ OH	1	>99	99
15	PhCOOEt	PhCH=CHCH ₂ OH	1	>99	100
16	PhCOOMe	PhCH=CHCH ₂ OH	1	>99	100

^a Reaction conditions: RCOOR', 1.0 mmol; R''OH, 1.0 mmol; **1** or **2**, 0.05 mmol, or **13**, 0.01 mmol; FC-72, 5 mL; 150 °C; 16 h; washing with toluene (1 mL × 2). ^b At 160 °C.

(entries 6–8). Apparently, the neutral reaction conditions are responsible for the tolerance of these functional groups.

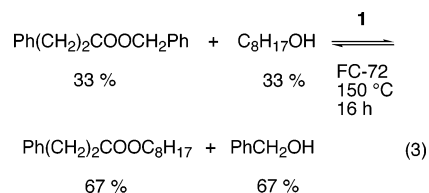
Evaporation of the FC-72 layer led to complete recovery of the catalyst. A ¹¹⁹Sn NMR spectrum of the recovered catalyst exhibited the same signals as the original ones, implying a catalytic mechanism different from that proposed for tetraalkyldistannoxanes. In the latter case, the initial step is substitution of the bridging X group to give an alkoxydistannoxane intermediate, (YR₂SnOSnR₂OR)₂, which works as an alkoxy donor.¹¹ In contrast, the recovery of the fluoroalkyldistannoxane catalyst in the original form suggests that no substitution took place at the bridging position by an alkoxy group. As described above, the bridging chlorine in **1** was never substituted by isothiocyanate ion (eq 2), in contrast to the conventional distannoxanes, which undergo facile replacement by the isothiocyanato group at both bridging and terminal positions. The present findings imply that the fluoroalkyldistannoxanes experience stronger association than the conventional alkyldistannoxanes. We suggest that both alcohol and ester coordinate on the terminal tin atom, on which the interchange of the alkoxy groups takes place.²⁶

Instead of isolating the catalyst from the FC-72 solution, the separated catalyst solution could be more conveniently used directly for the next reaction. The washing of the FC-72 solution twice with toluene is sufficient to remove the product remaining on the surface of the FC-72 layer. The separated FC-72 solution could be forwarded to other reactions. Thus, many of the reactions shown in Table 5 were conducted with the same catalyst solution. On the other hand, the washing is not necessary if the same reaction is repeated. For instance, the reaction of entry 1 was repeated 10 times with a single catalyst solution. The yield of the first run was found to be 95% without washing. However, >99% yield was constantly obtained on the basis

Scheme 4. Transesterification in Binary Solvent System

of GLC analysis during the second and tenth runs, indicating that nearly the same amount of the product remained on the FC-72 surface in each run. After tenth run, 97% of the catalyst was recovered.

In the above experiments, 100% yield with equimolar amounts of the reactants has been realized when substrate esters with a lighter alcohol component (methoxy or ethoxy) were treated with a heavier alcohol. It turned out that the situation changed if an ester with a heavy alkoxy group was subjected to the same reaction. A benzyl ester was treated with 1-octanol in the presence of 5 mol % of **1**. After 16 h, equilibrium was reached where 67% of octyl ester formed while 33% of the benzyl ester remained (eq 3). Treatment of the octyl ester with benzyl alcohol in a

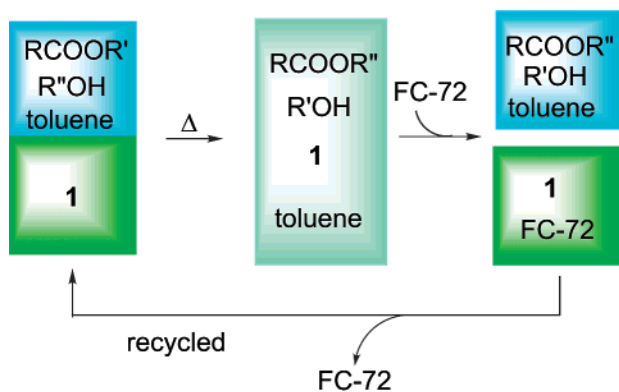


1:1 ratio under the same conditions induced a reaction in the opposite direction, resulting in the same distribution of the esters and alcohols. It follows therefore that the complete bias in the reactions shown in Tables 4 and 5 can be ascribed to facile liberation of light alcohols.

Binary Solvent System. If the use of solvent is preferable, an FC-72/organic solvent binary system is employable (Scheme 4). The reaction was conducted in a 1:1 mixture of FC-72 and toluene. However, a mixture of equimolar reactants failed to give complete conversion in this protocol. The use of a slight excess of alcohol (1.2–1.3 equiv) was required for satisfactory yields (>99%). The catalyst was recovered without loss (>99%) from the FC-72 layer. A control experiment without the catalyst afforded only a 23% yield.

Complete conversion was accessible when substrate alcohol was used as cosolvent. When the reaction was performed in a mixture of FC-72 (4 mL) and alcohol (2 mL), the desired esters (2 mmol) were obtained in 100% yields. It should be noted that this protocol enables the conversion of substrate esters bearing a heavier alcohol component to the lower analogues. Apparently, use of the alcohol component in large excess allows the equilibrium to shift in favor of the product side. This is a useful

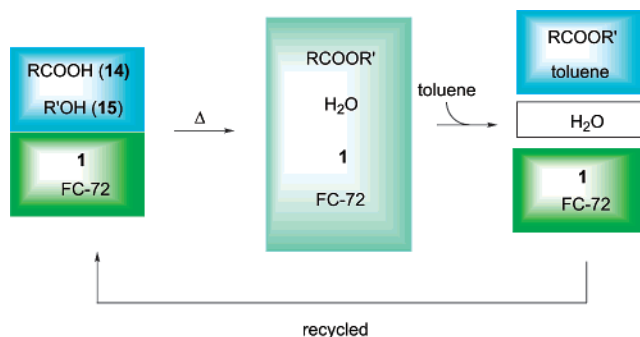
Scheme 5. Transesterification in Single Organic Solvent System



procedure to arrive at a variety of esters irrespective of the kind of substrate esters. Moreover, the operation is quite simple because evaporation of the organic layer to remove the low-boiling point alcohol leaves pure esters. Notably, the reaction between $\text{Ph}(\text{CH}_2)_2\text{COOEt}$ and $\text{CH}_3\text{-OH}$ was repeated 20 times. The GLC yield was constantly over 99% each time, and 91% of the catalyst was recovered after the 20th run indicative of virtually no loss and no deactivation of the catalyst during the repeated operations.

Single Organic Solvent System. The fluororous biphasic technology is also invoked to recover catalysts in normal transesterification. The reaction was conducted by fluoroalkyldistannoxane catalysts (5 mol %) in refluxing toluene (Scheme 5). However, the use of equimolar amounts of $\text{Ph}(\text{CH}_2)_2\text{COOMe}$ and PhCH_2OH failed to achieve perfect conversion (91% yield), and the alcohol component was employed in excess (1.2 equiv) to give quantitative yields. Such a smooth reaction was rather unexpected since the catalysts are insoluble in toluene at room temperature, yet the reaction mixture looked to be homogeneous at reflux temperature. This finds strong support from the following fact: catalysts that had been powdery before use turned crystalline in toluene after the reaction mixture had been cooled.²⁷ The catalysts were as active as in the previous protocols, and thus, there is no difference in activity between FC-72 and toluene solvents. Quantitative yields of the desired esters were obtained in various combinations of reactant esters and alcohols. The same chemoselectivity as found formerly holds in the present case as well, and of more synthetic significance is the successful use of ethyl acetoacetate. This substrate was not employable in the reaction using FC-72 because the reaction at 150 °C induced thermal decomposition of the ester. By contrast, no decomposition occurred in refluxing toluene. After 16 h, the reaction mixture was washed with FC-72. Evaporation of the FC-72 solution returned the catalyst, recovery yields of which are 100% for **1** and 99% for **3**. This difference was increased upon recycled use of the catalysts. Apparently, the catalyst with higher fluorine content is more efficiently recovered.

Scheme 6. Esterification in Fluorous System



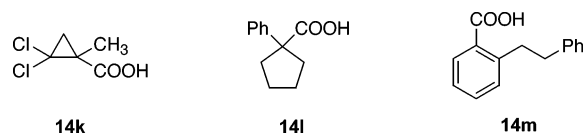
Esterification

It was suggested in the fluororous biphasic transesterification that liberation of a lighter alcohol from the equilibrium system facilitated the formation of the esters with a higher alcohol component. Since water is much less fluorophilic than alcohols, it was natural for us to postulate that the condensation between carboxylic acids and alcohols should proceed more efficiently.

As shown in Scheme 6, esterification of an equimolar mixture of RCOOH (**14**) and R'OH (**15**) was conducted in the presence of **1** (5 mol %) in FC-72.²⁸ Perfect conversion was realized as shown in Table 6. With less sterically demanding reactants, no sign of the reactant alcohol was detected in the reaction mixture and only a single peak attributable to the ester was observed (entries 1–13). It is safe to assume that the GLC results are normally accurate within $\pm 1\%$, and thus the yields are $>99\%$. Notwithstanding, a higher level of precision was pursued by calibrating our GLC machine with some representative esters (entries 1, 8–14). It then turned out that the detection limit was less than 0.1%, and thus the yields could be $>99.9\%$. Consistently, the isolated yields were also quantitative. Further practical usefulness of this protocol is apparent from tolerance of various functional groups (entries 3–7). Without the catalyst, the reaction was slower (entries 25 and 26) and never reached the high conversion even after prolonged reaction time (44 h). Apparently, the catalyst plays a crucial role to attain the perfect conversion.

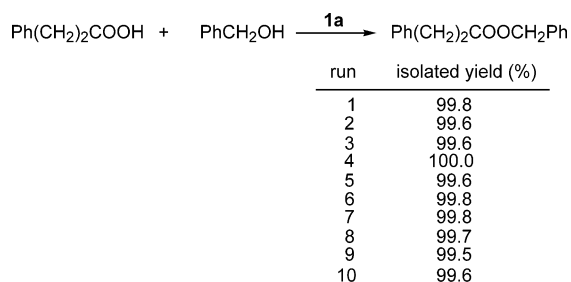
From the FC-72 layer, the catalyst was recovered without weight loss but not in pure form. Some portion of the catalyst was changed to unidentifiable species, which were presumably organotin carboxylate derivatives. Nonetheless, the recovered material exhibited similar catalytic activity to the original one, and thus, the FC-72 solution containing the organotin species could be recycled for the repeated use (*vide infra*).

In the above procedure, toluene was added to the reaction mixture to recover the ester from the FC-72 solution simply because the small scale reaction did not mechanically allow us to separate the product (3 mmol) quantitatively. On the other hand, the use of larger amounts of reactants (10 mmol) enabled us to pipet off the product from the surface of the fluororous layer although a small amount of the ester might have remained. This, however, is not problematic when the same reaction is repeated (Scheme 7). In fact, quantitative yields were

Table 6. Fluorous Biphasic Esterification^a

entry	RCOOH	R'OH	yield of RCOOR' [%]	
			GLC	isolated
1	Ph(CH ₂) ₂ COOH (14a)	PhCH ₂ OH	>99.9	100
2 ^b	14a	C ₈ H ₁₇ OH	>99	100
3 ^b	14a	TBSO(CH ₂) ₈ OH	>99	98
4 ^b	14a	THPO(CH ₂) ₈ OH	>99	98
5 ^b	14a	geraniol	>99	100
6 ^b	14a	PhCH=CHCH ₂ OH	>99	99
7 ^b	14a	PhC-CCH ₂ OH	>99	99
8	Ph(CH ₂) ₃ COOH (14b)	PhCH ₂ OH	>99.9	100
9	C ₇ H ₁₅ COOH (14c)	PhCH ₂ OH	>99.9	99
10	<i>p</i> -NO ₂ C ₆ H ₄ COOH (14d)	PhCH ₂ OH	>99.9	100
11	C ₆ F ₅ COOH (14e)	PhCH ₂ OH	>99.9	99
12	<i>p</i> -CF ₃ C ₆ H ₄ COOH (14f)	PhCH ₂ OH	>99.9	99
13 ^b	CH ₂ =CH(CH ₂) ₈ COOH (14g)	PhCH ₂ OH	>99.9	98
14 ^b	2-(4-ClC ₆ H ₄ O)OC(CH ₃) ₂ COOH (14h)	PhCH ₂ OH	>99.9	98
15 ^b	14a	menthol	45	44
16 ^b	14a	borneol	65	63
17 ^b	Ph ₂ C(CH ₃)COOH (14i)	PhCH ₂ OH	3.5	
18 ^b	1-adamantanecarboxylic acid (14j)	PhCH ₂ OH	14	
19 ^b	14k	PhCH ₂ OH	13	
20 ^b	14l	PhCH ₂ OH	16	
21 ^b	14m	PhCH ₂ OH	4	
22 ^b	C ₆ H ₅ COOH (14n)	PhCH ₂ OH	22	
23 ^b	<i>p</i> -CH ₃ C ₆ H ₄ COOH (14o)	PhCH ₂ OH	26	
24 ^b	PhCH=CHCOOH (14p)	PhCH ₂ OH	32	
25 ^{b,c}	14a	PhCH ₂ OH	67	
26 ^{c,d}	14a	PhCH ₂ OH	93	

^a Reaction conditions: acid, 2.0 mmol; alcohol, 2.0 mmol; **1**, 0.10 mmol; FC-72, 5.0 mL; 150 °C; 10 h. ^b Reaction time = 16 h. ^c Without catalyst. ^d Reaction time = 44 h.

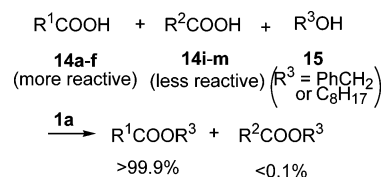
Scheme 7. Recycled Use of **1** in Esterification^a

^a Reaction conditions: acid, 10 mmol; alcohol, 10 mmol; **1**, 0.3 mmol; FC-72, 50 mL; 150 °C; 20 h.

attained in the 10 repetitions with a single catalyst. Notably, only a little catalyst loss occurred: the modified catalyst (491 mg) was recovered from 517 mg of the original one after the 10th run. As such, an esterification process that requires no use of conventional organic solvents has been realized.

As is apparent from Table 6, the reaction is sensitive to the steric bulk of the reactants (entries 15–21). Secondary alcohols, as well as carboxylic acids with a bulky group at the α -position (except one case, entry 14), failed to afford satisfactory yields. Neither simple aromatic carboxylic acids nor α,β -unsaturated carboxylic acid provided good yields (entries 22–24) whereas electron-deficient aromatic derivatives reacted smoothly (entries 10–12). Such differences in the reactivity led us to carry out a competition reaction between different carboxylic acids

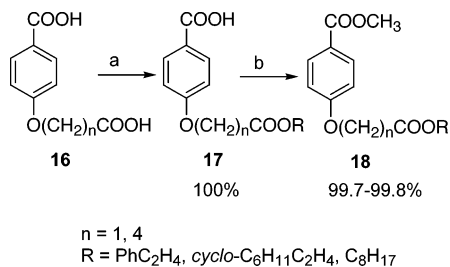
Scheme 8. Competition between Carboxylic Acids in Esterification



toward benzyl alcohol or octanol (Scheme 8). Equimolar amounts of two carboxylic acids of different reactivity were exposed to 1 equiv of an alcohol. Remarkably, a complete bias was observed: the ester (R^1COOR^3) derived from the more reactive carboxylic acid was produced in $\sim 100\%$ yield whereas no rival ester (R^2COOR^3) from the less reactive carboxylic acid was detected. Note that the yield of the esters was confirmed to be $>99.9\%$ on the basis of GLC, which was carefully calibrated as described above.

The differentiation between aliphatic and aromatic carboxylic acids was highlighted with substrates **16** (Scheme 9). Exposure of these substrates to an alcohol resulted in the exclusive esterification of the aliphatic alcohol function to furnish the single product **17** in quantitative isolated yields. The complete discrimination of the two carboxylic acid functions was further confirmed by transformation of **17** to methyl benzoate derivatives **18**. GLC analysis revealed quantitative formation of the methyl ester without contamination by any other products.

Scheme 9. Selective Esterification of Aliphatic Carboxylic Acids over Aromatic Ones



^a Reaction conditions: **16**, 1.0 mmol; ROH, 1.0 mmol; **1**, 0.10 mmol; FC-72, 5.0 mL; 150 °C; 16 h. ^bReaction conditions: **17**, 1.0 mmol; Me₃SiCHN₂, 1.5 mmol; toluene, 10 mL; rt; 3 h.

Epilogue

Fluorous distannoxanes exhibit unusually high preference for fluorous solvents over common organic solvents thanks to coverage of the molecular surface with fluoroalkyl groups. As a consequence, it is now apparent that molecular design serves to enhance the fluorophilicity of molecules. Once the surface of molecule was fully covered, then no more fluorous moieties are necessary. This is of great significance from the economical point of view because the fluorous content could be minimized. Needless to say, this idea is applicable to the design of other fluorous catalysts.

While the fluorous biphasic technology had been highlighted mainly in terms of facile separation of products and fluorous catalysts, it has now been revealed that the equilibrium is also controllable under fluorous biphasic conditions. Thus, the (trans)esterification has been completely driven in the desired direction by use of a 1:1 ratio of starting materials without recourse to any dehydration technique. Such technology, I believe, can be applied to other reactions and paves the way for an ultimate goal of organic synthesis, "100% yield with 100% selectivity".

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