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A Practical and Green Chemical Process: Fluoroalkyldistannoxane-Catalyzed Biphasic Transesterification

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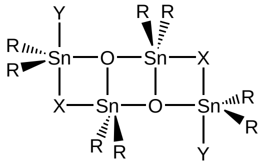
Transesterification is one of the most important reactions in organic synthesis.[1] Besides its utility in the laboratory, this reaction is significant in various industrial processes, such as the production of fatty acids, paints, polyesters, etc. Hence it is important that the reaction be practical and green. In its long history, numerous methods have been advanced, but few are satisfactory in view of process chemistry. The difficulty stems primarily from the equilibration of the reaction. Two strategies are invoked to bias the equilibrium in favor of the product: use of one of the reactants (RCOOR′ or R″OH) in excess or continuous removal of the alcohol formed (R′OH) [Eq. (1)]. The former treatment is not desirable in terms of "atom economy,"[2] but the latter is also not technically easy to realize. Another problem emerges from the use of base or acid catalysts, which are inevitably employed in this reaction. With such catalysts, many functional groups are not tolerated. Furthermore, it is essential to remove the catalyst from the product because contamination of the catalyst residues causes various problems. The ultimate practical transesterification should meet the following requirements: 1) the ester and alcohol reactants are used in a 1:1 ratio, 2) the catalyst is neutral and readily separable from the reaction mixture, 3) no special technology is needed to remove the liberated alcohol, and 4) both conversion and yield are 100%. We report herein a new protocol that almost clears these hurdles.

$$\mathrm{RCOOR'} + \mathrm{R''OH} \longrightarrow \mathrm{RCOOR''} + \mathrm{R'OH} \qquad (1)$$

The present study has its foundation on our previous finding that tetraalkyldistannoxanes work well as mild transesterification catalysts.[3–10] Although these compounds bear a relatively large inorganic metaloxane skeleton, they are soluble in organic solvents. We ascribed the unique solubility to their dimeric formulation in which the central stannoxane core is surrounded by lipophilic alkyl groups, for example, **1**.[11] This structural feature led us to postulate that the incorporation of fluoroalkyl groups on the surface of the stannoxane core would render the distannoxane molecule soluble in fluorocarbon solvents and thus that the fluorous biphasic technology[12–14] could be utilized.

The requisite distannoxane **1a** was readily prepared by treating oxide **2**[15] with aqueous HCl [Eq. (2)]. The ^{119}Sn NMR spectrum of **1a** gave rise to two singlets at $\delta = -178.3$ and -202.5, indicative of the dimeric formulation in solution ($R = C_6F_{13}C_2H_4$ in **1**).[16, 17]



1

$$\underset{\mathbf{2}}{[(C_6F_{13}CH_2CH_2)_2SnO]_n} + n\,HCl \xrightarrow[THF]{} \underset{\mathbf{1a}}{n/2\ [\{Cl(C_6F_{13}CH_2CH_2)_2SnOSn(CH_2CH_2C_6F_{13})_2Cl\}_2]} \qquad (2)$$

This compound is virtually insoluble in most organic solvents except CH_2Cl_2 (slightly soluble), ethyl acetate, and acetone (highly soluble). On the other hand, its solubility in fluorocarbons is good, for example, 41 g L^{-1} in perfluorohexanes (FC-72, 3 M). The partition coefficients (FC-72/organic solvent) for **1a** are high (toluene 99, CH_2Cl_2 99, methanol 49) in marked contrast to the low partition coefficient of oxide **2** (toluene 1.9).[15] Apparently, the increased fluorophilic character of **1a** is induced by the $C_6F_{13}C_2H_4$ groups at the surface, which hamper the exposure of the stannoxane core to the surroundings.

A novel fluorous biphasic transesterification technology has been established with this new catalytic species. As described above, the employment of the reactants in a 1:1 ratio is ideal. To the best of our knowledge, an ultimate stoichiometry that leads to high conversions has not yet been

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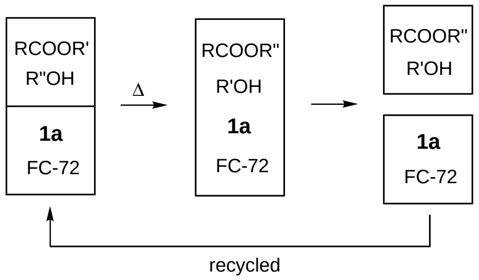
found, except for the transesterification of β-keto esters; but even then the yields were not always satisfactory (50–97%).[18–21] With this in mind, we used the 1:1 stoichiometry in our reaction in a simple procedure (see Scheme 1 and Experimental Section). No apparatus was needed to remove the alcohol formed. GLC analysis of the organic layer indicated the quantitative conversion and yield, without any sign of residual starting materials, except in one case (Table 1). Accordingly, pure esters were obtained simply by evaporating the organic layer, as the ethanol or methanol formed was removed during the evaporation. When the reactants were not completely converted (Table 1, entry 8), the product esters could be readily isolated by column chromatography. Alternatively, the use of excess 2-octanol resulted in 100% conversion (Table 1, entry 9).



Scheme 1. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a**.

Table 1. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a** (ester/alcohol 1:1).[a]

Entry	RCOOR′	R″OH	Yield of RCOOR″ [%] GLC[b]	Isolated
1	$Ph(CH_2)_2COOEt$	$C_8H_{17}OH$	>99	100
2	$Ph(CH_2)_2COOEt$	$PhCH_2OH$	>99	99
3	$Ph(CH_2)_2COOEt$	$PhCH{=}CHCH_2OH$	>99	100
4	$Ph(CH_2)_2COOEt$	geraniol	>99	98
5	$Ph(CH_2)_2COOEt$	$THPO(CH_2)_8OH$	>99	99
6	$Ph(CH_2)_2COOMe$	$TBSO(CH_2)_8OH$	>99	100
7	$Ph(CH_2)_2COOEt$	$PhC{\equiv}CCH_2OH$	>99	100
8	$Ph(CH_2)_2COOEt$	2-octanol	98 (2)	96[c]
9		2-octanol[d]	>99 (10)[e]	100[c]
10	$Ph(CH_2)_2COOEt$	cyclohexanol	>99	99
11	$Ph(CH_2)_2COOMe$	$PhCH{=}CHCH_2OH$	>99	100
12	$PhCH{=}CHCOOEt$	$PhCH{=}CHCH_2OH$	>99	99
13	$PhCOOEt$	$PhCH{=}CHCH_2OH$	>99	100
14	$PhCOOMe$	$PhCH{=}CHCH_2OH$	>99	100

[a] A mixture of ester (2.0 mmol), alcohol (2.0 mmol), and **1a** (0.10 mmol) in FC-72 (4 mL) was heated at 150 °C for 16 h. [b] In the case of >99% yield, no starting materials were detected except for entry 8 in which the ethyl ester and 2-octanol (2% each) were detected. The amount of the remaining starting materials is given in parentheses. [c] Isolated by using column chromatography. [d] 2-Octanol (1.1 equiv). [e] Only 2-octanol but no ethyl ester was detected.

The catalyst can be quantitatively recovered from the fluorous layer. However, it was more practical to reuse the separated FC-72 solution directly in the next reaction by combining with another mixture of reactants. This manipulation could be repeated more than 20 times[22] without depression of catalytic activity, even with different combinations of reactants. As a result, all reactions given in Table 1 were carried out with a single catalyst solution.[23] The fluorous layer was washed simply to remove a small amount of the organic substances that remained on the surface of the FC-72 layer. Hence, washing is no longer necessary if the same reactions are repeated or if the reaction is conducted on a larger scale that allows more efficient phase separation. In such procedures, the pure esters are isolated from the reaction mixture after the ethanol or methanol are pumped off. Hence a process that uses no organic solvents has been established. Of further synthetic significance is the tolerance of labile substrates and functional groups that cannot survive under usual conditions (Table 1, entries 3–7, 11–14).

Another simple and practical operation involved the use of alcohols with a low boiling point as the solvent. Accordingly, a mixture of a solution of **1a** in FC-72 and a solution of an ester in the alcohol was heated at 150 °C for 16 h [Eq. (3)]. GLC analysis indicated a >99% yield of the desired esters, concomitant with the complete disappearance of the reactant esters (Table 2). The pure products were isolated in 100% yield, simply by evaporating the organic layer (in the case of ethyl or methyl esters as starting materials) or by column chromatography to remove benzyl alcohol (benzyl ester as starting material). The use of excess alcohol as solvent allows the reactions to occur in the opposite direction to Equation (1), thus allowing even higher alkoxy moieties of the reactants to be replaced under these conditions. The FC-72 solution of the catalyst was reused, as described before.[24]

Table 2. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a** in alcohol solvent.[a]

Entry	RCOOR′	R″OH	Yield of RCOOR″ [%] GLC	Isolated
1	$Ph(CH_2)_2COOEt$	CH_3OH	>99	100
2	$Ph(CH_2)_2COOEt$	2-butanol	>99	100
3	$Ph(CH_2)_2COOMe$	C_2H_5OH	>99	100
4	$Ph(CH_2)_2COOBn$	CH_3OH	>99	100[b]
5	$Ph(CH_2)_2COOBn$	C_2H_5OH	>99	100[b]
6	$Ph(CH_2)_2COOBn$	$CH_2{=}CHCH_2OH$	>99	100[b]

[a] A mixture of ester (2.0 mmol), alcohol (2.0 mL), and **1a** (0.10 mmol) in FC-72 (4 mL) was heated at 150 °C for 16 h. [b] Isolated by using column chromatography.

$$RCOOR' \xrightarrow[R''OH/FC\text{-}72]{\mathbf{1a}} RCOOR'' + R'OH \qquad (3)$$

In summary, a simple and practical transesterification protocol has been devised on the basis of a novel fluoroalkyldistannoxane catalyst and a fluorous biphasic technique.

Experimental Section

Fluoroalkyldistannoxane **1a**: The Grignard reagent derived from $C_6F_{13}CH_2CH_2I$ (30 mmol) and Mg turnings (34 mmol) was coupled with $(PhCH_2)_2SnBr_2$ (10 mmol) in Et_2O/THF at room temperature for 24 h to afford $(C_6F_{13}CH_2CH_2)_2Sn(CH_2Ph)_2$ in 81% yield. Treatment of $(C_6F_{13}CH_2CH_2)_2Sn(CH_2Ph)_2$ (5.4 mmol) with Br_2 (10.8 mmol, 2 equiv) in

CCl_4 at room temperature for 3 h gave $(C_6F_{13}CH_2CH_2)_2SnBr_2$ (96 %), which was hydrolyzed with aqueous NaOH (4 N)/THF at room temperature for 2 h to furnish polymeric $[(C_6F_{13}CH_2CH_2)_2SnO]_n$ (**2**) (93 %). Treatment of **2** (5 mmol) with aqueous HCl (4 N; 6.5 mmol) in acetone at room temperature for 24 h afforded **1a** in 85 % yield: m.p. 90–91 °C (CH_2Cl_2); ^{119}Sn NMR ([D$_6$]acetone): $\delta = -178.3, -202.5$; elemental analysis: calcd for $C_{64}H_{32}Cl_4F_{104}O_2Sn_4$: C 22.44, H 0.94; found: C 22.58, H 0.54.

Fluorous biphasic transesterification: A mixture of ethyl 3-phenylpropionate(356 mg, 2.0 mmol), 1-octanol (260 mg, 2.0 mmol), and **1a** (171 mg, 0.1 mmol) in FC-72 (4.0 mL) was added to a test tube. The test tube was placed in a stainless-steel pressure bottle and heated at 150 °C for 16 h. The reaction mixture was then cooled to room temperature and toluene (5 mL) was added. The FC-72 layer was washed with toluene (2 × 1 mL) and the combined toluene solution was evaporated to afford pure octyl 3-phenylpropionate (525 mg, 2.0 mmol). The FC-72 solution was used in the next reaction.

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[22] The quantitative recovery of the catalyst without depression of the activity is apparent: the reaction shown in Table 1, entry 2 was repeated and gave >99 % yield (GC) and 98–100 % recovery of the catalyst in every run. For further supporting evidence, see ref. [24].

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[24] The reaction in Table 2, entry 1 was repeated 20 times. The GC yield was constantly >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 repetition.

A Mild and Effective Method for the Transesterification of Carboxylic Acid Esters[**]

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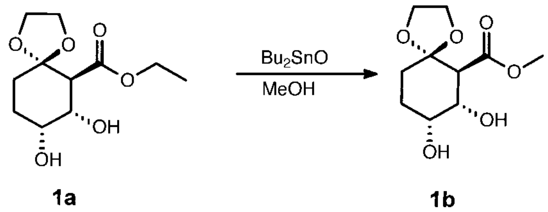
Athanassios Giannis[*]

Transesterification is one of the most important transformations in organic synthesis.[1] The most important methods, besides acid or base catalysis, employ titanium tetraalkoxides,[2] complex tin compounds,[3] indium iodide,[4] or enzymes.[5] During a dibutyltin oxide-mediated selective O-methylation of compound **1a**, we observed the formation of methyl ester **1b** as a side product (Scheme 1). Interestingly, neither elimination nor epimerization at the stereogenic center adjacent to the ester moiety was observed. Previous attempts to obtain methyl ester **1b** by using various acids and bases always led either to complete epimerization or to the decomposition of **1a**. Furthermore, $Ti(OMe)_4$ was not suitable for this purpose owing to its insolubility in methanol.[2]



Scheme 1. Dibutyltin oxide catalyzed transesterification of ethyl ester **1a** into methyl ester **1b**.

The significance of the observed side product encouraged us to optimize this reaction and to investigate the scope and limitations of this method. Several simple as well as highly functionalized aliphatic and aromatic esters were treated with catalytic amounts of dibutyltin oxide (1–10 mol %) in different alcohols as solvents. The isolated derivatives corresponded to the product of transesterification with the alcohol that was used as solvent (Table 1). The reaction conditions are very mild and thus the method is tolerant of several functional groups, for example, acetals, ketals, aliphatic bromides, β-ketoesters, and enol ethers. Most significantly, free hydroxy, phenolic, and even amino groups do not affect the reaction.

The potential scope of this method was clear from the treatment of **4a** with dibutyltin oxide in methanol to afford the desired derivative **4b** in an excellent yield (Table 1, entry 4).[6] We suppose that the *tert*-butyl ester moiety in **4a** is first transformed into the methyl ester, which is then attacked intramolecularly by the free amino group to afford the final product **4b**. To exclude the possibility that the amide was

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