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Fluorous Biphasic Esterification Directed towards Ultimate Atom Efficiency**

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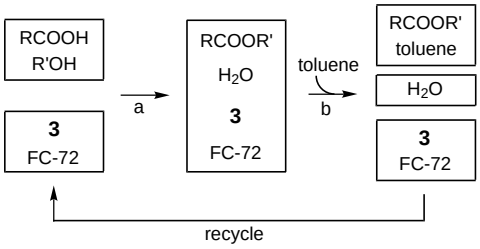
Esterification technology is currently undergoing intensive innovation to meet the rapidly increasing demands for sustainable chemistry.[1] Since the direct reaction between a carboxylic acid and an alcohol is innately an equilibrium process, high atom efficiency[2] is not easy to achieve: either of the reactants must be used in excess and/or the water formed must be removed constantly during the reaction to bias the equilibrium to the product side. In particular, the direct condensation between carboxylic acids and alcohols with a strict 1:1 stoichiometry by use of a simple catalyst system is very difficult to complete, although activation of the carboxylic acid component with a stoichiometric amount of promoter such as DCC[3] or DEAD[4] is another possible but uneconomical choice. In this context, graphite bisulfate was reported to catalyze esterification between equimolar reactants.[5] Later, microwave irradiation coupled with *p*-toluenesulfonic acid catalyst was reported.[6] Recently, a few more related catalysts have appeared. Although the Soxhlet technique must be invoked, $NaHSO_4 \cdot H_2O$[7] and $HfCl_2 \cdot 2\,THF$[8] were found to work well as a catalyst. On the other hand, $Ph_2NH_2^+OTf^-$ served for the present purpose without recourse to any dehydration reagents or apparatus.[9] The yields of all of these reactions were high (mostly $> 85\,\%$) but, unfortunately, not perfectly quantitative, except for two cases in the $HfCl_2 \cdot 2\,THF$ protocol ($> 99\,\%$). This is somewhat problematic, not only in view of atom efficiency but also of practical operation. The 1:1 stoichiometry is truly effective only if 100 % conversion is reached. In this case, the product ester constitutes a sole organic component in the reaction mixture, but otherwise separation of the remaining carboxylic acid and alcohol from the product mixture is unavoidable. As a consequence, an ideal goal of esterification would be 100 % yield by use of equimolar reactants without recourse to any dehydration technique.

Recently, we disclosed that the fluorous biphasic transesterification by use of fluoroalkyldistannoxane catalysts gave rise to virtually 100 % yields with ester and alcohol reactants in a 1:1 ratio.[10] It was suggested in this protocol that liberation of a lighter alcohol from the equilibrium system as a result of its lower solubility in fluorocarbon solvents facilitated the conversion in favor of the esters with a higher alcohol component. Since water is much less fluorophilic than alcohols, we postulated that the condensation between carboxylic acids and alcohols should proceed more efficiently. We report herein the first fluorous biphasic esterification that achieves the above-mentioned goal. Furthermore, facile separation of the catalyst is another notable advantage that results from the fluorous biphasic technology.

As shown in Scheme 1, an equimolar mixture of RCOOH (**1**) and R′OH (**2**) together with $[\{Cl(C_6F_{13}C_2H_4)_2SnOSn(C_2H_4C_6F_{13})_2Cl\}_2]$ (**3**)[11] (5 mol %) in FC-72 (perfluorohexanes) was heated at 150 °C. After being cooled to room temperature, toluene was added to the



Scheme 1. Esterification in a biphasic system. Reagents and conditions: a) acid (2.0 mmol), alcohol (2.0 mmol), **3** (0.1 mmol), FC-72 (5 mL), 150 °C, 16 h; b) extraction with toluene (5 mL and 2 × 2 mL).

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mixture. The organic layer was separated from the fluorous layer and analyzed by GLC. The results are summarized in Table 1. 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, indicative of virtually perfect conversions (Table 1, entries 1–13). It is safe to assume that the GLC results are normally accurate to 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 (Table 1, entries 1, 8–14). It was shown that the detection limit was actually less than 0.1 % and thus the yields could be considered as $> 99.9\,\%$. The yields of isolated products were also consistently quantitative.[12] Furthermore, this protocol is tolerant of various functional groups (Table 1, entries 3–7).

The catalyst was recovered from the FC-72 layer without weight loss, but not in pure form. A portion of the catalyst was converted into unidentifiable species, which were presumably organotin carboxylate derivatives. Nonetheless, the recovered material exhibited similar catalytic activity to that of the original, and thus the FC-72 solution that contained the organotin species could be recycled for repeated use (see below).

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 the quantitative separation of the product (3 mmol). On the other hand, when larger amounts of reactants were used (10 mmol) the product could be pipetted from the surface of the fluorous layer, although a small amount of the ester might have remained. This, however, is not problematic when the same reaction is repeated [Eq. (1)]. In fact, as shown in Table 2, quantitative yields were attained in ten runs with a single catalyst. Notably, only little catalyst loss occurred: the modified catalyst (491 mg) was recovered from 517 mg of the original after the 10th run. Thus, this esterification process does not require the use of conventional organic solvents.

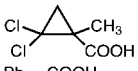
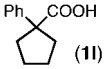
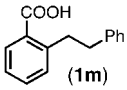
$$PhCH_2CH_2CO_2H + PhCH_2OH \xrightarrow{\mathbf{3}\ (3\ mol\%)} PhCH_2CH_2CO_2CH_2Ph + H_2O \quad (1)$$

Table 2. Esterification using recycled fluorous tin catalyst **3** [Eq. (1)].[a]

Run	Yield [%]	
	Isolated	GC
1	99.8	99.9
2	99.6	99.8
3	99.6	99.9
4	100.0	100.1
5	99.6	99.9
6	99.8	100.0
7	99.8	99.9
8	99.7	99.8
9	99.5	99.7
10[b]	99.6	99.9

[a] Reagents and conditions: acid (10.0 mmol), alcohol (10.0 mmol), **3** (0.3 mmol), FC-72 (50 mL), 150 °C, 20 h. [b] After 10th run, 95 % (491 mg) of the catalyst was recovered.

Table 1. Fluorous biphasic esterification.[a]

Entry	RCOOH	R′OH	Yield (RCOOR′) [%]	
			GLC	Isolated
1	$Ph(CH_2)_2COOH$ (**1a**)	$PhCH_2OH$ (**2a**)	> 99.9	100
2	**1a**	$C_8H_{17}OH$ (**2b**)	> 99	100
3	**1a**	$TBSO(CH_2)_8OH$	> 99	98
4	**1a**	$THPO(CH_2)_8OH$	> 99	98
5	**1a**	geraniol	> 99	100
6	**1a**	$PhCH{=}CHCH_2OH$	> 99	99
7	**1a**	$PhC{\equiv}CCH_2OH$	> 99	99
8	$Ph(CH_2)_3COOH$ (**1b**)	**2a**	> 99.9	100
9	$C_7H_{15}COOH$ (**1c**)	**2a**	> 99.9	99
10	*p*-$NO_2C_6H_4COOH$ (**1d**)	**2a**	> 99.9	100
11	C_6F_5COOH (**1e**)	**2a**	> 99.9	99
12	*p*-$CF_3C_6H_4COOH$ (**1f**)	**2a**	> 99.9	99
13[b]	$CH_2{=}CH(CH_2)_8COOH$ (**1g**)	**2a**	> 99.9	98
14[b]	$(4\text{-}ClC_6H_4O)C(CH_3)_2COOH$ (**1h**)	**2a**	> 99.9	98
15[b]	**1a**	menthol	45	44
16[b]	**1a**	borneol	65	63
17[b]	$Ph_2C(CH_3)COOH$ (**1i**)	**2a**	3.5	
18[b]	1-adamantanecarboxylic acid (**1j**)	**2a**	14	
19[b]	 (**1k**)	**2a**	13	
20[b]	 (**1l**)	**2a**	16	
21[b]	 (**1m**)	**2a**	4	
22[b]	C_6H_5COOH (**1n**)	**2a**	22	
23[b]	*p*-$CH_3C_6H_4COOH$ (**1o**)	**2a**	26	
24[b]	$PhCH{=}CHCOOH$ (**1p**)	**2a**	32	

[a] Reaction conditions: acid (2.0 mmol), alcohol (2.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 10 h. [b] Reaction time: 16 h.

As is apparent from Table 1, the reaction is sensitive to the steric bulk of the reactants (Table 1, entries 15–21). Secondary alcohols as well as carboxylic acids with a bulky group at the α position (except for one case, Table 1, entry 14) did not give satisfactory yields. Neither simple aromatic carboxylic acids nor α,β-unsaturated carboxylic acids gave good yields (Table 1, entries 22–24), whereas electron-deficient aromatic derivatives reacted smoothly (Table 1, entries 10–12). Such differences in reactivity led us to carry out competition reactions between carboxylic acids and either octanol or benzyl alcohol [Eq. (2)]. As summarized in Table 3, equimolar amounts of two carboxylic acids of different reactivity were exposed to one equivalent of the alcohol. Remarkably, complete bias was observed: the ester (R^1COOR^3) derived from the reactive carboxylic acid was produced in $\approx 100\,\%$ yield whereas none of the competing ester (R^2COOR^3) from the less reactive carboxylic acid was detected. The yield of the esters was

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Table 3. Competition between carboxylic acids in fluorous biphasic esterification [Eq. (2)].[a]

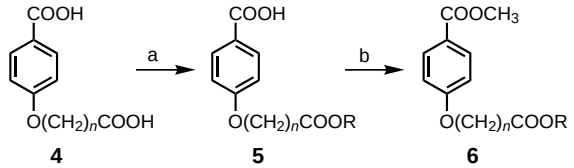
Entry	R^1COOH	R^2COOH[b]	R^3OH	Yield [%]		
				R^1COOR^2		R^1COOR^3
				GLC	Isolated	GLC
1	**1a**	**1i**	**2b**	> 99.9	98	< 0.1
2	**1a**	**1j**	**2b**	> 99.9	98	< 0.1
3	**1a**	**1k**	**2a**	> 99.9	99	< 0.1
4	**1a**	**1k**	**2b**	> 99.9	100	< 0.1
5	**1a**	**1l**	**2b**	> 99.9	100	< 0.1
6	**1a**	**1m**	**2b**	> 99.9	99	< 0.1
7	**1b**	**1i**	**2b**	> 99.9	99	< 0.1
8	**1b**	**1j**	**2b**	> 99.9	98	< 0.1
9	**1b**	**1k**	**2b**	> 99.9	100	< 0.1
10	**1b**	**1l**	**2b**	> 99.9	99	< 0.1
11	**1b**	**1m**	**2b**	> 99.9	98	< 0.1
12	**1c**	**1i**	**2b**	> 99.9	97	< 0.1
13	**1c**	**1m**	**2b**	> 99.9	99	< 0.1
14	**1c**	**1n**	**2b**	> 99.9	97	< 0.1
15	**1f**	**1k**	**2b**	> 99.9	99	< 0.1
16	**1f**	**1j**	**2b**	> 99.9	100	< 0.1
17	**1f**	**1k**	**2a**	> 99.9	98	< 0.1
18	**1f**	**1l**	**2b**	> 99.9	100	< 0.1
19	**1f**	**1m**	**2b**	> 99.9	99	< 0.1

[a] Reaction conditions: R^1COOH (1.0 mmol), R^2COOH (1.0 mmol), alcohol (1.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 16 h. [b] Unreacted R^2COOH was quantitatively converted into the methyl ester (see text).

confirmed to be > 99.9 % on the basis of GLC, which was carefully calibrated as described already. Furthermore, the organic layer was separated from the reaction mixture and treated with trimethylsilyldiazomethane (1.5 equiv) to convert the unreacted carboxylic acids into the methyl esters, the yield of which was found to be more than 99.9 %.[13] Notably, such perfect discrimination is rather surprising because reaction of the less reactive carboxylic acids actually takes place, though to a lesser extent, under noncompetitive conditions, which is suggestive of the involvement of some unique kinetic effects.

$$R^1COOH + R^2COOH + R^3OH \xrightarrow{\mathbf{3}\ (10\ mol\%)} R^1COOR^3 + R^2COOR^3 \qquad (2)$$

The differentiation between aliphatic and aromatic carboxylic acids was highlighted with substrates **4** [Eq. (3); Table 4].



(3)

Exposure of these substrates to an alcohol resulted in the exclusive esterification of the aliphatic alcohol to furnish the single products **5** in quantitative yields. The complete discrimination of the two carboxylic acid functions was further confirmed by transformation of **5** into methyl benzoate derivatives **6.** GLC analysis revealed quantitative formation of the methyl ester without contamination by any other products.[14]

Table 4. Selective esterification of dicarboxylic acid [Eq. (3)].

Entry	*n*	R	Yield (**5**) [%][c]	Yield (**6**) [%][d]
1	1	$PhCH_2CH_2$	100	99.9
2	1	*cyclo*-$C_6H_{11}CH_2CH_2$	100	99.7
3	4	C_8H_{17}	100	99.8

[a] Reaction conditions: **4** (1.0 mmol), ROH (1.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 16 h. [b] Reaction conditions: **5** (1.0 mmol), Me_3SiCHN_2 (1.5 mmol, 2 M solution in hexane, 0.75 mL), toluene (10 mL), MeOH (5 mL), room temperature, 3 h. [c] Yield of isolated product (column chromatography). [d] GLC yield.

In summary, almost complete atom efficiency has been realized in the fluoroalkyldistannoxane-catalyzed fluorous biphasic esterification. This atom efficiency, in conjunction with the facile recovery of the catalyst, holds great promise for developing a green esterification process. The nearly perfect stoichiometry as well as discrimination between carboxylic acids discovered herein may pave the way to elucidate characteristic features of kinetics in the fluorous biphasic system. Further studies are in progress in our laboratories.

Experimental Section

Typical procedure (Table 1, entry 1): A 50-mL test tube was charged with 3-phenylpropanonic acid (**1a**; 300 mg, 2.0 mmol), benzyl alcohol (**2a**; 216 mg, 2.0 mmol), **3** (172 mg, 0.10 mmol, 5 mol %), and FC-72 (5.0 mL). The test tube was placed in a stainless pressure bottle and heated at 150 °C for 10 h. After the pressure bottle had been cooled, toluene (5.0 mL) was added to the reaction mixture. The toluene and FC-72 layers were separated, and the latter was extracted with toluene (2 × 2.0 mL). GC analysis of the combined organic layer showed a quantitative yield of benzyl 3-phenylpropanoate.

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[12] The yields given in this paper were the best among more than two trials and are accurate within ± 1 %.

[13] The control experiments disclosed that the ester formation with trimethylsilydiazomethane proceeds quantitatively (> 99.9 % yield) on the basis of GLC, the detection limit of which was found to be 0.1 % for the methyl esters .

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