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ARTICLE

Zirconocene-Catalyzed Direct (*trans*)Esterification of Acyl Acids(Esters) and Alcohols in a Strict 1:1 Ratio under Solvent-Free Conditions

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A highly efficient way for direct (*trans*)esterification of acyl acids(esters) and alcohols in a strictly 1:1 ratio using zirconocene complex (**1,** 1 mol%), a strong Lewis acid of good water tolerance, as catalyst under solvent-free condition has been developed. A wide range of acids and alcohols(esters) substrates undergo (trans)esterification to produce carboxylic ester motifs in moderate to good or excellent yields with good functional tolerance, such as that towards C—Br as well as C=C and C≡C bonds. And complex **1** can be recycled in a test of six times without showing significant decline of catalytic efficiency. It was demonstrated that cyclandelate, which is used to treat high blood pressure as well as heart and blood-vessel diseases, can be directly synthesized in gram scale with 81% yield (6.70 g) using complex **1**.

Introduction

Esterification is important for the production of esters that are of high value,[1,2] such as cyclandelate, ciclesonide, chloramphenicol palmitate and benorilate (**Figure 1**), reaching one-quarter of the bulk reactions in the manufacture of drugs and pharmaceuticals.[3] Efforts were made in recent years to develop protocols for esterification of improved efficiency under mild conditins.[4] For instance, Keglevich *et al.* demonstrated the microwave-assisted direct esterification of phosphinic acids.[5] Lei *et al.* reported the aerobic oxidative direct esterification of alcohols catalyzed by palladium.[6] Furthermore, the use of macroporous polymeric acid as heterogeneous catalyst for dehydrative esterification was demonstrated by Uozumi *et al*.[7] For the synthesis of α-acyloxy ethers, Pan *et al.* developed a method based on iron-catalyzed functionalization of unactivated C(sp^3)-H bonds.[8] Later, Xu *et al.* demonstrated a similar method mediated by N-chlorosuccinimide.[9] Yoon et al. reported an efficient esterification method that involved the use of 2-acyl-4,5-dichloropyridazin-3(2H)-ones as a recyclable acyl source.[10] In sustainable biodiesel production via esterification and transesterification, there are significant progresses,[11] and a variety of catalytic systems were established.[12] Nonetheless, there are disadvantages with these methods, e.g. tedious multistep procedures for the preparation of starting materials, expensive reagents, poor substrate generality, low tolerance towards functional groups, large excess of a particular substrate, high catalyst loadings and poor recyclability of catalysts. Thus, despite reaction simplicity, the field is far from maturity.[13]

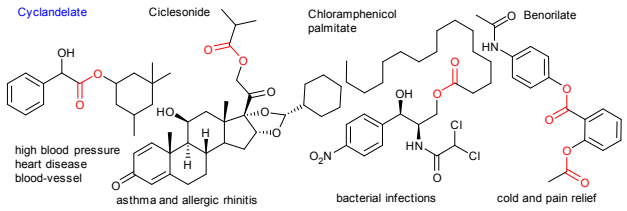

Figure 1. Esters used as pharmaceuticals

To propel green chemistry and sustainable development, we are interested in developing catalytic systems for esterification using readily available substrates in a strictly 1:1 ratio. The pioneer work of Otera *et al.* demonstrated that through the incorporation of $C_6F_{13}C_2H_4$ with long fluorous tail to distannoxanes, the Lewis acid catalysts show high catalytic efficiency in direct esterification in a strictly 1:1 ratio of substrates.[14] Later, Kobayashi *et al.* reported a combined Brønsted acid/surfactant system for high efficient direct esterification of carboxylic acid and alcohol in water using dodecylbenzenesulfonic acid as Brønsted acid,[15] in which the self-separation of products and water is enabled.[16-17] Zirconocene as Lewis acid catalyst shows high catalytic activity in a variety of Lewis-acid-catalyzed reactions,[18] such as Mannich reaction, allylation of aldehydes, the Friedel–Crafts

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Electronic Supplementary Information (ESI) available: [^{1}H NMR and ^{13}C NMR spectra copies of the products as well as other experimental details are shown in ESI]. See DOI: 10.1039/x0xx00000x

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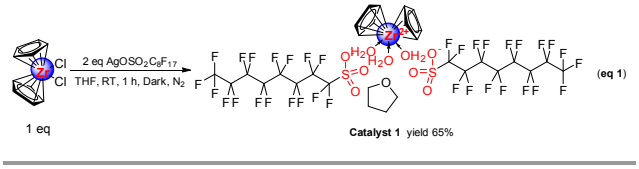
acylation. Herein, we report that through the incorporation of a large electron-withdrawing and hydrophobic counter anion, an air-stable and water-tolerant catalyst of zirconocene complex **1**[18i] can be synthesized for direct esterification and transesterification using readily available acids and alcohols as starting materials in a strictly 1:1 ratio under solvent-free condition.[19] By means of this approach, a wide range of acid and alcohol(ester) substrates undergo (trans)esterification, producing carboxylic ester motifs in moderate to good or excellent yields with good functional tolerance, such as that towards C—Br, C=C and C≡C bonds. And the catalyst can be recycled for at least six times. The chemoselective esterification of mandelic acid is also achieved. With this method, cyclandelate, which is widely used in the treatment of high blood pressure as well as heart and blood-vessel diseases, can be directly synthesized, and the synthesis can be enlarged to gram scale with 81% yield (6.70 g).

Results and discussion



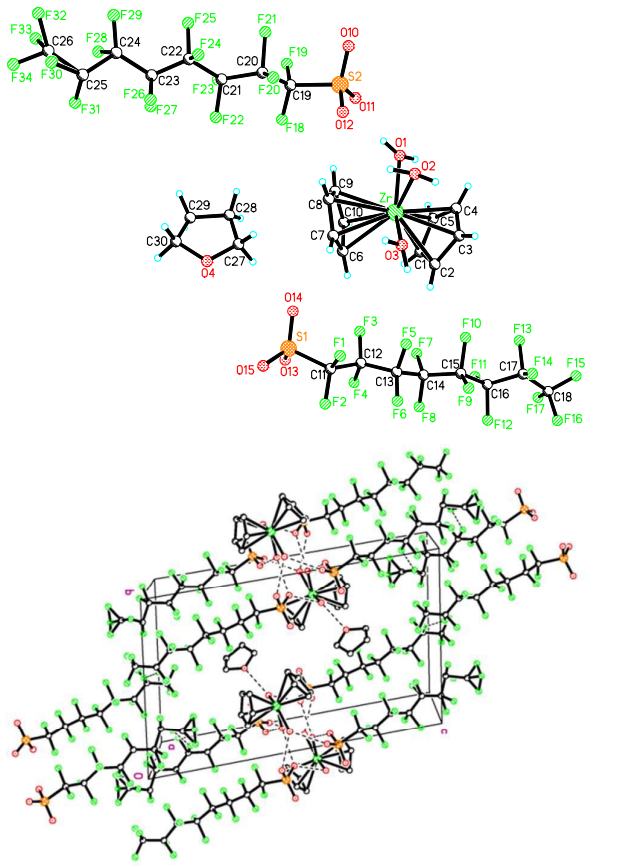


Figure 2. X-Ray structure of complex **1**.[18i]

The synthesis of zirconocene complex $[Cp_2Zr(H_2O)_3\text{-}(OSO_2C_8F_{17})_2]\cdot THF$ (**1**) is straightforward. It is just a matter of treating Cp_2ZrCl_2 with $AgOSO_2C_8F_{17}$ in THF in the dark for one hour, and the yield is 65% (**eq 1**). Complex **1** shows strong Lewis acidity ($0.8<H_o<3.3$) and high air stability (found stable in open air for one year) as well as thermal stability (Figure S1, ESI).

A crystal of complex **1** suitable for X-ray analysis was obtained from THF/hexane solution. The special structure of complex **1** is shown in Figure 2.[18i] Endowed with such a structure, it is deemed efficient catalyst in direct esterification (Figure 3c). First, the C_8F_{17} group enables the Lewis acid center to be water-tolerant and separates the organic layer from the catalyst center (Figure 3a) as described by Otera et al.[14] And the lipophilic cyclopenadienyl (Cp) group acts as an organic directing group while detaching itself from the organic substrates and products. Furthermore, the Zr^{4+} Lewis acid center and coordinated H_2O together act as a hydrophilic area for the reaction to take place. Upon completion of reaction, the lipophilic ester dissociates itself from the Cp group while the side products detach from the coordinated water molecules, pushing the equilibrium to the right in a way described by Kobayashi et al (Figure 3b)[15]. In addition, the produced ester and water molecules leave the catalyst due to the hydrophobic nature of its interior. Therefore, we envision that complex 1 is a micro-catalytic system that combines the advantages of the Otera and Kobayashi systems, and can be used for (trans)esterification of acyl acids(esters) and alcohols in a strictly 1:1 ratio.

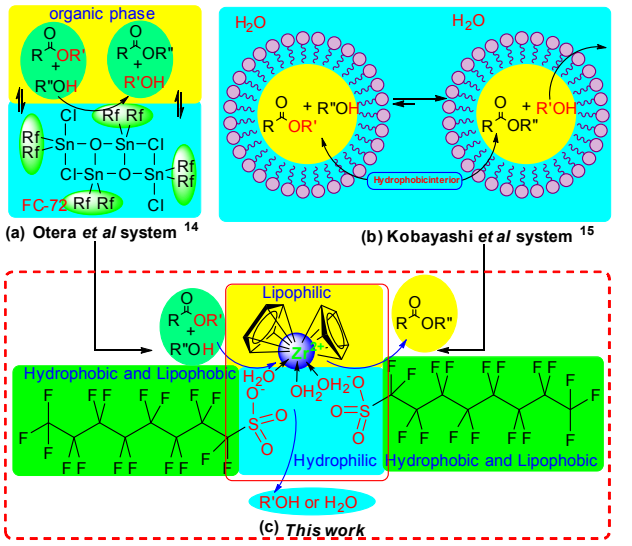


Figure 3. The possible relationship between complex **1** and the (trans)esterification .

Since water is a by-product of direct esterification reaction, we tested the effect of water presence on the catalytic reactions. Using complex **1**, we found that the reaction proceeds in a strictly 1:1 ratio of 2-phenyl ethanol to acetic acid at 80 °C with 99% yield. We added several equivalents of water to the reaction mixture. As shown in **eq 2**, the yield of desired products is still up to 95% at 2 equivalents

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of water. The results illustrate that the hypothesis based on the crystal structure of complex **1** is both reasonable and reliable.

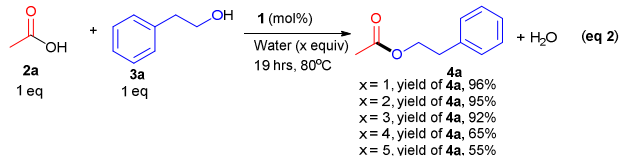
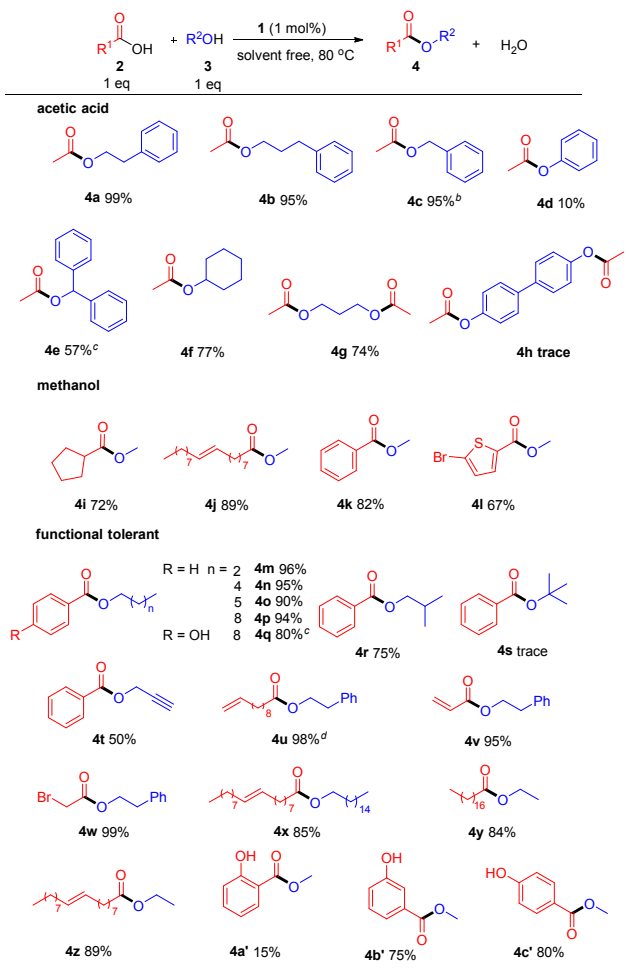


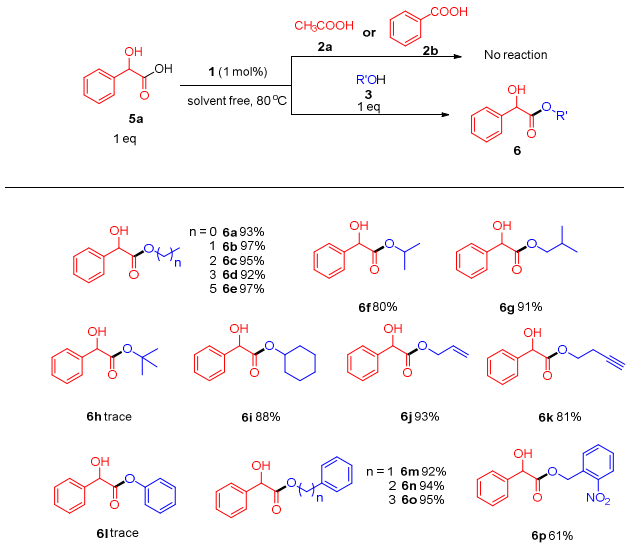
Table 1. Direct esterification of alcohols with acids[a]



[a] Complex **1** (0.01 mmol), acid **2** (1.0 mmol), alcohol **3** (1.0 mmol), 12 h; 80 °C, sealed tube, isolated yield. [b]35 °C. [c]100 °C. [d]0 °C.

We hence screened the substrate scope of the esterification method with complex **1**. As shown in Table 1, complex **1** functions well for the direct esterification of various alcohols with acetic acid in strictly 1:1 ratio. Compared with phenol (**4d**, 10%), 2-phenyl ethanol (**4a**, 99%), benzyl alcohol (**4c**, 95%), and 3-phenyl propanol (**4b**, 95%) show much higher reactivity. When phenol and 2-phenyl ethanol are added simultaneously, it is the latter that undergoes esterification and gives the acylated product. Phenol shows low reactivity in the current system due to the unreacted starting compound (88% of phenol is recovered). It is apparent that primary alcohols react with acetic acid faster than secondary alcohols (**4e–4f**). Furthermore, aliphatic diol **4g** reacts smoothly with acetic acid to give ester, but aromatic diol **4h** shows no interaction with acetic acid, indicating the special chemo-selectivity of the catalyst. Complex **1** also efficiently mediates the esterification of different acids with methanol under the standard conditions, and it was demonstrated that the protocol is applicable for a variety of substrates. For example, the acid bearing C=C double bond, bromo group and heterocyclic scaffold are tolerated (**4j**, **4l**). The catalytic system can also be extended to alcohols with long alkyl chains. The alkyl alcohol is successfully acylated with benzoic acid and p-hydroxylbenzoic acid with yields up to 96% (**4m–4q**). The chain length of alkyl alcohols has little effect on the reactivity (**4m–4p**, 90–96%). *p*-Hydroxylbenzoic acid attached with a hydroxyl group in the phenyl group reacts with long-chain octanol to give **4q** in good yield (80%). A larger steric effect results in lower reactivity: [*n*-butanol (**4m**, 96%) > *n*-hexanol (**4n**, 95%) > *iso*-butanol (**4r**, 75%) > *tert*-butanol (**4s**, 0%)]. In the co-presence of *n*-butanol and *tert*-butanol, the reaction only occurs with the former, suggesting that the system is highly chemoselective. As for propargyl alcohol (**4t**), 50% yield of ester is obtained in a sealed tube. Even the undecylenic acid with long chain shows a product yield of up to 98% (**4u**). The acids bearing C=C double bond and bromo group are both tolerated (**4v**, 95%; **4w**, 99%). For the transformation of free fatty acids (FFAs) in the presence of complex **1**, esterification reactions of high efficient are observed even both the alcohols and acids are with long alkyl chains, giving yields of up to 89% (**4x–4z**). There is also the existence of steric effect on reactivity: *p*-hydroxybenzoic acid (**4c'**, 80%) > m-hydroxybenzoic acid (**4b'**, 75%) > o-hydroxybenzoic acid (**4a'**, 15%).

Table 2. Chemoselective esterification of mandelic acid [a]



[a] Complex **1** (0.01 mmol), Mandelic acid **5a** (1.0 mmol), alcohol **3** (1.0 mmol), 12 h; 80 °C, sealed tube, isolated yield.

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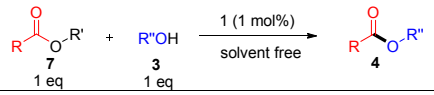
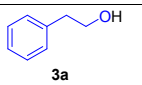
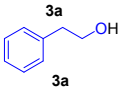
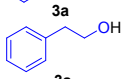
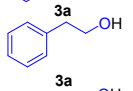
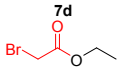
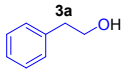
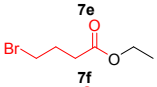
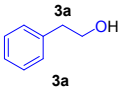
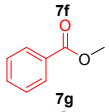
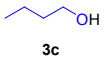
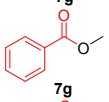
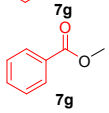
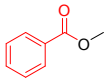
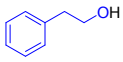
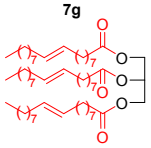
Table 3. Transesterification of ester with alcohol [a]



Entry	5	3	4	Temp (°C)	Time (h)	Yield (%)
1	 7a	 3a	4d'	65	6	90
2	 7b	 3a	4a	65	5	99
3	 7c	 3a	4a	65	5	92
4	 7d	 3a	4v	70	10	90
5	 7e	 3a	4w	60	24	85
6	 7f	 3a	4e'	70	24	90
7	 7g	 3c	4m	85	24	85
8	 7g	 3d	4r	85	30	75
9	 7g	 3e	4s	85	35	0
10	 7g	 3a	4f'	85	22	99
11	 7h	 3f	4z	80	24	85[b]

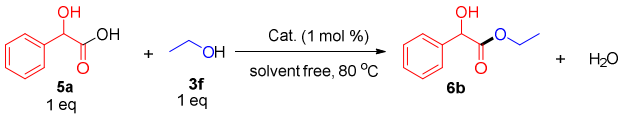
[a] Complex **1**(0.01 mmol), RCOOR' **7** (1.0 mmol), R''OH **3** (1.0 mmol), sealed tube, isolated yield. [b] the yield of **4z** is based on the oleic acid chain

Complex **1** catalyzes the selective esterification of α-hydroxycarboxylic acids without causing significant esterification of acetic acid or benzoic acid at 80°C. We tested the reaction at 160 °C, and there is still no reaction between mandelic acid and acetic acid or benzoic acid. To ascertain the generality and scope of the chemoselective esterification of equimolar α-hydroxycarboxylic acid and alcohol, a number of substrates were examined in the presence of 1.0 mol% of complex **1** under the standard conditions. As shown in Table 2, mandelic acid is successfully acylated with alkyl alcohols with yields up to 97% (**6a–6e**). The acids bearing cyclohexyl group (**6i**, 88%), C=C double bond (**6j**, 93%), C≡C triple bond (**6k**, 81%) and nitro group (**6p**, 61%) are tolerated. It is noted that steric hindrance would result in lower reactivity: *n*-butanol (**6d**, 92%) > *iso*-butnol (**6g**, 91%) > *tert*-butanol (**6h**, 0%). As for the less steric compounds such as benzyl alcohol (**6m,** 92%), 2-phenyl ethanol (**6n**, 94%), and 3-phenyl propanol (**6o**, 95%), there is much higher reactivity.

We also applied the catalytic system for transesterification. As shown in Table 3, the reaction of ester with alcohol in the presence of complex **1** results in good to excellent yields of the desired products. In the cases of vinyl and isopropenyl acetates bearing C=C double bond, the yield of transesterification with 2-phenyl ethanol at 65 °C is up to 99% (entries 2–3). The yield of transesterification of methacrylate with 2-phenyl ethanol at 70 °C is 90% (entry 4) whereas that of brominated alkyl acid esters is up to 90% (entries 5–6). The results indicate that the catalytic system has good tolerance towards C=C and C-Br bonds. It is observed that an alcohol with larger steric hindrance shows lower activity, and reactivity decreases in the order of *n*-butanol > *iso*-butanol > *tert*-butanol (entries 7–9), and aromatic alcohols > alkyl alcohols (entries 9–10). For application in biodiesel synthesis, the catalytic system shows high catalytic efficiency in transesterification of glycerol trioleate with ethanol in a strict equivalent ratio of 1:1 at 80 °C for 24 h, and 85% yield of **4z** is obtained (entry 11).

As shown in Table 4, we also used acid catalysts such as $AlCl_3$(1eq), $Bi(OTf)_3$, $C_8H_{17}SO_3H$, Cp_2ZrCl_2 and [$C_8H_{17}SO_3Ag$ + Cp_2ZrCl_2] for the esterification reaction of mandelic acid and ethanol, and the yields are 0%, 49%, 42%, 56%, 60% respectively, which are inferior to those of using complex **1** (97%). The results illustrate the superiority of complex **1** in direct esterification reactions. And $Cp_2Zr(OSO_2C_4F_9)_2$ is also a catalyst efficient for the reaction (**6b**, 93%) (entry 7), showing catalytic efficiency similar to that of complex **1** (entry 1). The result indicates that it is possible to have the usage of fluorine reduced in our catalyst system. In such a case, the possibility of having fluorine leakage to the environment can be significantly lessened.[20]

Table 4. Comparison with other Lewis acids[a]



Entry	Cat.	Yield (%)
1	Catalyst **1**	97
2	$AlCl_3$	0(60[b])
3	$Bi(OTf)_3$	49
4	$C_8H_{17}SO_3H$	42
5	Cp_2ZrCl_2	56
6	$AgOSO_2C_8F_{17}$ + Cp_2ZrCl_2	60
7	$Cp_2Zr(OSO_2C_4F_9)_2$	93

[a] Catalyst (0.01 mmol), **6a** (1.0 mmol), **3f** (1.0 mmol), 12 h, 80 °C, sealed tube, isolated yield. [b]The yield in parenthesis is obtained with 1 eq of $AlCl_3$ as catalyst.

Complex **1** can be easily recovered, and we evaluated its recyclability in the esterification reaction of mandelic acid and ethanol: the same reaction of Table 4 but with scale enlarged 10 times (10 mmol of **5a**). As depicted in Figure 4, the catalyst

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can be easily recycled six times without showing significant decline of catalytic efficiency. And the ^{1}H NMR analysis suggests that the recycled catalyst still has the skeleton structure of the freshly prepared catalyst (Figure S3, see ESI), clearly indicating that the catalyst is suitable for reuse.

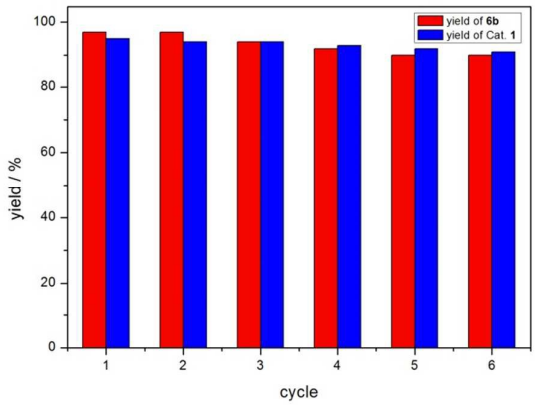
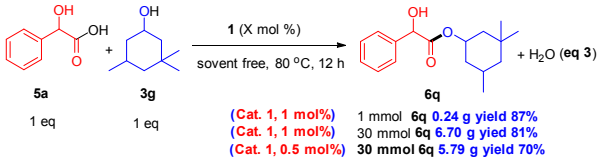


Figure 4. Recyclability of complex **1** in esterification.

To illustrate the applicability of the catalytic system in pharmaceutical synthesis, we use the generation of cyclandelate (**6q**) (Figure 1), which is used to treat high blood pressure as well as heart and blood-vessel diseases, as an example. The compound can be synthesized from mandelic acid **5a** and 3,3,5-trimethylcyclohexanol **3g** over complex **1** (1.0 mol%) in 87% yield (0.24 g). The reaction can be directly enlarged to a scale of 30 mmol, giving **6q** in 81% yield (6.70 g) (**eq 3**). Moreover, the catalyst loading can be reduced to 0.5 mol%, giving **6q** in 70% yield (5.79 g). The reduction of catalyst usage implies the possibility of fluorine-containing compounds leaking into the environment can be significantly lessened. It is a positive aspect of the catalyst system when it comes to industrial application.



Conclusions

In summary, water-tolerant zirconocene complex **1** with strong Lewis acid characteristics was synthesized to catalyze the direct esterification and transesterification of acid and alcohol substrates in a strictly 1:1 ratio. The advantages of the protocol are (i) recyclable catalyst, (ii) solvent-free conditions, (iii) wide substrate scope, and (iv) excellent functional group tolerance.

Experimental Sections

Preparation of zirconocene complex 1[18i]

To a solution of Cp_2ZrCl_2 (292 mg, 0.99 mmol) in THF (20 mL) was added a solution of $AgOSO_2C_8F_{17}$ (1.21 g, 2.0 mmol) in THF (10 mL). The mixture was stirred in the dark at 25 °C for 1 h, and subject to filtration. The filtrate was combined with dry hexane (40 mL). Then, the solution was refrigerated for 24 h to furnish colorless crystals of **1**·THF (794 mg, 65%): M.p.133-136 °C. ^{1}H NMR (400 MHz, Acetone-d_6): δ = 6.76 (s, 10 H, CpH), 3.63 (t, J = 5.6 Hz, 4 H, THF), 1.82 – 1.76 (m, 4 H, THF); ^{19}F NMR (376 MHz; Acetone): δ = -81.65 (t, J = 9.8 Hz, 3 F, CF_3–), -115.02 (s, 2 F, –CF_2–), -121.05 (s, 2 F, –CF_2–), -122.17 to -122.48 (m, 6 F, –$(CF_2)_3$–), -123.28 (s, 2 F, –CF_2–), -126.75 to -126.82 (m, 2 F, –CF_2–). Elemental analysis for $Cp_2Zr(OSO_2C_8F_{17})_2$ after under pumping for a week: calcd. (%) for $C_{26}H_{10}F_{34}O_6S_2Zr$: C, 25.60; H, 0.83; found: C, 25.67; H, 0.82. Elemental analysis for $Cp_2Zr(OSO_2C_8F_{17})_2{\cdot}4H_2O$ after standing in open air for 2 days: calcd (%) for $C_{26}H_{18}F_{34}O_{10}S_2Zr$: C, 24.18; H, 1.40; found: C, 24.34; H, 1.33. $C_{30}H_{24}F_{34}O_{10}S_2Zr$, Prismatic, colorless, Mr = 1345.83, Dx = 1.905 Mg m^{-3}, Triclinic, P$^-$1, a = 9.9295 (13) Å, b = 11.9551 (16) Å, c = 20.269 (3) Å, α = 82.833 (3)°, β = 79.491 (3)°, γ = 87.397 (3)°, V = 2346.7 (5) Å^3, Z = 2, θ = 1.7–25.5°, 0.50 × 0.24 × 0.21 mm, T = 293 (2) K, measured reflections/independent reflections 12436/8583, R_{int} = 0.104, h = −12-11, k = −14-11, l = −24-22, R_1 = 0.095, wR_2 = 0.277, S = 0.95.CCDC No. 631296.

Typical procedure for direct esterification using complex 1

To a round-bottom flask was added 2-phenylethanol (122 mg, 1.0 mmol) and 1 equivalent of acetic acid (60 mg, 1.0 mmol) and complex 1 (12.6 mg, 0.01 mmol, 1.0 mol% relative to 2-phenylethanol). The mixture was stirred at 80°C for 30 min and monitored by TLC. Then the mixture was diluted with petroleum ether (10 mL × 3). By means of filtration, the catalyst was separated and used for the next cycle, and the filtrate was washed twice with 10 mL of saturated brine, and extracted by petroleum ether (10 mL × 2). Subsequently the portions of petroleum ether were combined together, dried by sodium sulfate, and evaporated to obtain the crude ester. Finally, the ester was subject to short flash column chromatography on silica gel (petroleum ether: ethyl acetate = 8:1, Rf = 0.7) to afford the colorless liquid, 162 mg, yield, 99%.

Typical procedure for transesterification using complex 1

To a round-bottom flask was added 2-phenylethanol (122 mg, 1.0 mmol) and 1 equivalent of methyl propionate (88 mg, 1.0 mmol) and complex 1 (12.6 mg, 0.01 mmol, 1.0 mol% relative to 2-phenylethanol). The mixture was stirred at 65°C for 6 h and monitored by TLC. Then the mixture was diluted with petroleum ether (10 mL × 3). By means of filtration, the catalyst was separated and used for the next cycle, and the filtrate was washed twice with 10 mL of saturated brine, and extracted by petroleum ether (10 mL × 2). Subsequently the portions of petroleum ether were combined together, dried by sodium sulfate, and evaporated to obtain the crude ester. Finally, the ester was subject to short flash column

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chromatography on silica gel (petroleum ether: ethyl acetate = 8:1, Rf = 0.7) to afford the colorless liquid, 160 mg, yield, 90%.

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Zirconocene-Catalyzed Direct (*trans*)Esterification of Acyl Acids(Esters) and Alcohols in a Strict 1:1 Ratio under Solvent-Free Conditions

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