Ligand-Assisted Rate Acceleration in Lanthanum(III) Isopropoxide Catalyzed Transesterification of Carboxylic Esters
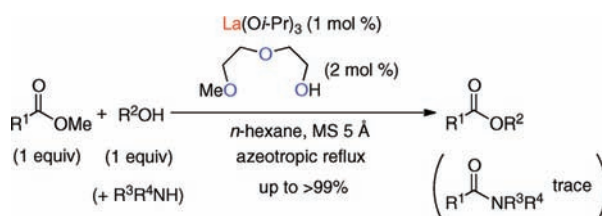
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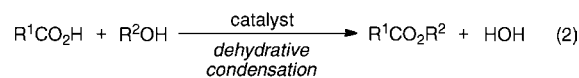
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ABSTRACT

The transesterification of an equimolar mixture of carboxylic esters and primary (1°), secondary (2°), and tertiary (3°) alcohols in hydrocarbon solvents was promoted with high efficiency by a lanthanum(III) complex, which was prepared in situ from lanthanum(III) isopropoxide (1 mol %) and 2-(2-methoxyethoxy)ethanol (2 mol %). The present La(III) catalyst was highly effective for the chemoselective transesterification in the presence of competitive 1°- and 2°-amines. Remarkably, esters were obtained in good to excellent yields as colorless materials without an inconvenient workup procedure.

Catalytic transesterification of carboxylic esters with alcohols and dehydrative condensation of carboxylic acids with alcohols have wide applications in academic as well as industrial research (eqs 1 and 2).[1–3] In particular, transesterification is valuable due to good substrate solubility

$$R^1CO_2Me + R^2OH \xrightarrow[transesterification]{catalyst} R^1CO_2R^2 + MeOH \quad (1)$$

$$R^1CO_2H + R^2OH \xrightarrow[\substack{dehydrative \\ condensation}]{catalyst} R^1CO_2R^2 + HOH \quad (2)$$

(R^2OH = 1° and 2° in many cases, and 3° in a few cases)

in common organic solvents, while carboxylic acids in dehydrative condensation often have low solubility and sometimes large excess amounts of either carboxylic acids or alcohols that are used for smooth conversion. To date, several procedures for transesterification catalyzed by a variety of protic and Lewis acids, organic and inorganic bases, enzymes, and antibodies have been developed.[1] However, an extemely practical catalytic transesterification of rather reactive carboxylic esters with alcohols has not yet

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(1) For reviews of (trans)esterifications, see: (a) Otera, J. *Esterification*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2003. (b) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288. (c) Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 1563. (d) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (e) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. *Top. Catal.* **2004**, *27*, 83. (f) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (g) Ishihara, K. *Tetrahedron* **2009**, *65*, 1085.

(2) For recent contributions to catalytic transesterifications, see these selected examples: (a) Bose, D. S.; Satyender, A.; Rudra Das, A. P.; Mereyala, H. B. *Synthesis* **2006**, 2392. (b) Remme, N.; Koschek, K.; Schneider, C. *Synlett* **2007**, 491. (c) Kondaiah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Huge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. V. *Tetrahedron Lett.* **2008**, *49*, 106. (d) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944. (e) Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* **2008**, *10*, 2187. (f) Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* **2008**, *73*, 5147. (g) Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* **2009**, 1659.

(3) Catalytic transesterifications with 2°- and 3°-alcohols have been limited. (a) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (b) Tanaka, K.; Osaka, T.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 1307. (c) Pericas, À.; Shafir, A.; Vallribera, A. *Tetrahedron* **2008**, *64*, 9258. Catalytic *tert*-butyl ester-interchange reaction: (d) Stanton, M. G.; Gagné, M. R. *J. Org. Chem.* **1997**, *62*, 8240.

been well established, because of the inherently low reactivity of secondary (2°) and tertiary (3°) alcohols rather than primary (1°) alcohols.[3,4] Therefore, a more efficient transesterification procedure with general applicability to 1°-, 2°-, and even 3°-alcohols involving simple preparations and a nontoxic catalyst is still desired. In 1995, Okano and co-workers reported that the transesterification of carboxylic esters (0.1 mmol scale) was efficiently catalyzed by La(Oi-Pr)$_3$ (2 mol %) under heating conditions in excess molar amounts of 1°- and 2°-alcohols (5 mL).[5] According to this pioneering work, the catalytic activity of lanthanoid(III) decreased in the order La(III) > Nd(III) > Gd(III) > Yb(III) and was much higher than those of Al(III) and Ti(IV). After this publication, the La(OMe)(OTf)$_2$-catalyzed methanolysis of aryl and alkyl esters was reported by Brown and co-workers.[6] They proposed that a methoxy-bridged La(III) dimer might efficiently catalyze methanolysis through the corresponding transition-state assembly based on Lewis acid−Lewis base dual activation[7] (Figure 1). Methanol as a
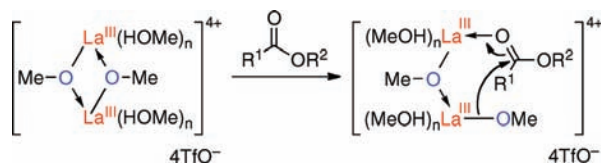

Figure 1. Transition state of the methanolysis of carboxylic esters catalyzed by La(III) dimeric complex proposed by Brown et al.[6]

solvent greatly stabilizes and solubilizes the active La(III) dimer without the need to create specially designed ligands to stabilize the dinuclear core.[6] In general, since the driving force of metal-ion-catalyzed transesterifications should be controlled by a balance between the Lewis acidity of metal ions and the nucleophilicity of the alkoxy moiety on metal ions, we expected that some suitable ligands might more efficiently accelerate La(III)-catalyzed[8] transesterification. In this context, we report here that a simply tuned La(III) salt, which is prepared in situ from lanthanum(III) isopropoxide (1 mol %) and 2-(2-methoxyethoxy)ethanol (2 mol %), is a highly active catalyst and promotes the transesterification of carboxylic esters (1 equiv) with 1°-, 2°-, and 3°-alcohols (1 equiv) under reflux conditions in hydrocarbons such as n-hexane with the removal of methanol.

First, the probe transesterification of an equimolar mixture of methyl benzoate (**1a**) and 5-nonanol (**2a**) was conducted in the presence of La(Oi-Pr)$_3$ (1 mol %) with chelatable

(4) Stoichiometric transesterification with 3°-alcohols: (a) Rossi, R. A.; Rossi, R. H. *J. Org. Chem.* **1974**, *39*, 855. (b) Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1986**, 695. (c) Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559. (d) Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 658.

(5) Okano, T.; Miyamoto, K.; Kiji, J. *Chem. Lett.* **1995**, 246.

(6) (a) Neverov, A. A.; Brown, R. S. *Can. J. Chem.* **2000**, *78*, 1247. (b) Neverov, A. A.; McDonald, T.; Gibson, G.; Brown, R. S. *Can. J. Chem.* **2001**, *79*, 1704.

(7) For acid−base combined catalysis, see: (a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (b) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.

(8) For a recent review of lanthanide catalyses: Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2008; Vol. 2, Chapter 13.

ligands in n-hexane (bp 69 °C) under azeotropic reflux conditions for 3 h with the removal of methanol using MS 5 Å in a Soxhlet thimble (Table 1).
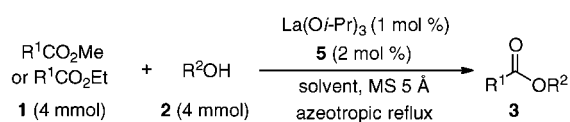
Table 1. Screening of Catalysts[a]

entry	ligand (mol %)	yield (%)
1[b]	–	0
2[c]	–	33
3	O(CH$_2$CH$_2$OH)$_2$ **4** (1)	38
4	**4** (2)	45
5	HO(CH$_2$CH$_2$O)$_2$Me **5** (1)	65
6	**5** (2)	74 [93][d]
7	**5** (3)	70
8	O(CH$_2$CH$_2$OMe)$_2$ **6** (1)	35

[a] See the Supporting Information for detailed procedures. Catalysts were prepared in advance at room temperature for 1 h. [b] Without La(Oi-Pr)$_3$ and a ligand. [c] Without a ligand. [d] The reaction was conducted as soon as La(Oi-Pr)$_3$ and a ligand were mixed.

At the beginning of the preliminary screening, catalysts were prepared in advance at room temperature for 1 h. With regard to the pioneering Okano's report,[5] the transesterification catalyzed by La(Oi-Pr)$_3$ proceeded with only a 33% yield of 5-nonyl benzoate (**3a**) due to the low reactivity of a 2°-alcohol and instability of La(Oi-Pr)$_3$ (entry 2), while the reaction did not occur in the absence of catalyst (entry 1). As a ligand for La(Oi-Pr)$_3$, we found that monomethyl ether of diethylene glycol (**5**) (entry 5) was effective (65% yield), and diethylene glycol (**4**) (entry 4) and its dimethyl ether (**6**) (entry 8) were much less active than **5**. The addition of 2−3 mol % of **5** had a slightly better influence on the catalytic activity (entries 6 and 7). In order to prevent the deterioration of the labile catalyst, when the reaction mixture was heated as soon as La(Oi-Pr)$_3$ (1 mol %) and **5** (2 mol %) were mixed, compound **3a** was ultimately obtained in 93% yield (entry 6, bracket).

To explore the scope of the transesterification reaction, various carboxylic esters **1** with 1°-, 2°-, and 3°-alcohols **2** were examined in the presence of La(Oi-Pr)$_3$ (1 mol %) and **5** (2 mol %) (Figure 2). Particularly, the development of an efficient catalytic methodology for the synthesis of 3°-alcohol-derived carboxylic esters is important since they are valuable photoresistant materials.[9] As a result, not only 1°- and 2°- but also less-reactive 3°-alcohols (see **3n**, **3o**, **3r**, and **3s**) were efficiently transformed with aromatic and aliphatic esters to the desired esters **3** in a colorless state. Broad compatibility was observed

(9) (a) Nozaki, K.; Watanabe, K.; Yano, E.; Kotachi, A.; Takechi, S.; Hanyu, I. *J. Photopolym. Sci. Technol.* **1996**, *9*, 509. (b) Tsuchiya, Y.; Hattori, T.; Yamanaka, R.; Shiraishi, H. *J. Photopolym. Sci. Technol.* **1997**, *10*, 579. (c) Pasini, D.; Low, E.; Fréchet, J. M. J. *Adv. Mater.* **2000**, *12*, 347. (d) Kavitha, A. A.; Singha, N. K. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 7101.

the corresponding product (**3k**) was obtained in good yield. Sterically hindered methyl pivalate transformed to the corresponding 2°-ester (**3l**) smoothly. The transesterification of methyl methacrylate and methyl propiolate as α,β-unsaturated esters proceeded chemoselectively without decomposition (see **3m** and **3o**). Although ethyl esters were generally less reactive than methyl esters, ethyl benzoate was also acceptable for the synthesis of **3a**. Thermal transesterification with ethyl acetate is often difficult because of its low boiling point (77 °C). In contrast, with La(Oi-Pr)$_3$ and **5**, the acetylation of less reactive 2°- and 3°-alcohols with ethyl acetate proceeded in high yields under reflux conditions in n-hexane (bp 69 °C) or ethyl acetate (see **3p−s**). Esters produced by conventional catalysts, particularly metal salt catalysts such as Ti(Oi-Pr)$_4$, are often colored, and this is an industrially serious problem. In contrast, the catalytic transesterification with La(Oi-Pr)$_3$ and **5** gives colorless esters. La(III) catalysts can be easily removed by filtration after a drop of water is added to the reaction mixture, and flash chromatography is effective to obtain the pure products from the condensed colorless residue of the organic filtrate obtained. Moreover, as a great advantage in industrial application, the toxicity of La(III)[10] is much lower than that of other metal ion catalysts such as Hf(IV), Zr(IV), Zn(II), Sn(IV), and Sb(III) which are well-known as esterification catalysts.[1,2,11]

Recently, Ohshima and Mashima et al. demonstrated the enzyme-like selective transesterification of alcohols in the presence of amines catalyzed by a tetranuclear zinc cluster [1.25 mol % of Zn$_4$(OCOCF$_3$)$_6$O = 5 mol % of Zn(II), reaction time 18−24 h].[2d,f,g] Comparatively, we investigated the chemoselectivity of the reactions by using La(Oi-Pr)$_3$ and **5** (Table 2). Fortunately, the highly selective transes-

Figure 2. Transesterification of carboxylic esters. Conditions: (a) Unless otherwise noted, methyl esters were used as starting material. (b) Ethyl esters were used as starting material. (c) Powdered MS 5 Å was used in the reaction mixture, and the temperature was 50 °C. (d) La(Oi-Pr)$_3$ (3 mol %) and **5** (6 mol %) were used.

Table 2. Chemoselective Transesterification

entry	R^1	R^{2}OH	R^{3}R^{4}NH	t (h)	yield (%) 3	7
1	Ph	BnOH	BnNH$_2$	2	**3b**, 76	1
2	Ph	HO(CH$_2$)$_5$NH$_2$		3	**3t**, 91	<1
3	Ph	HO(CH$_2$)$_6$NH$_2$		1	**3u**, 89	2
4	Ph	HO(CH$_2$)$_{10}$NH$_2$		3	**3v**, 90	<1
5	Ph	HO(CH$_2$)$_{12}$NH$_2$		3	**3w**, 87	<1
6^a	Ph	c(C$_6$H$_{11}$)OH	BnNH$_2$	6	**3x**, 86	1
7	Ph	c(C$_6$H$_{11}$)OH	piperidine	1	**3x**, 86	1
8	Bn	c(C$_6$H$_{11}$)OH	piperidine	1	**3y**, 90	<1

^{a} n-Heptane was used as a solvent in place of n-hexane.

when either functionalized alcohols or esters were used. It was noticed that optically active methyl (S)-mandelate and N-Boc-L-Phe-OMe were transformed to the corresponding benzyl esters (**3i** and **3j**) without epimerization at 50 °C in the presence of powdered MS 5 Å in the reaction mixture. Phenol was inherently not so reactive due to its weak nucleophilicity, but

terification but not the possible amidation proceeded even in the presence of primary and secondary amines such as benzylamine and pyperidine (entries 1, 6−8). α,ω-Aminoalcohols were also suitable as substrates (entries 2−5).

(10) Lethal intake of La(Oi-Pr)$_3$: LD$_{50}$ (oral, rat) = >10 000 mg/kg.

Noteworthy, the selective *O*-acylation completed within 6 h in the presence of 1 mol % of La(O*i*-Pr)$_3$ with **5**.

Finally, during the investigation of the tolerance of La(O*i*-Pr)$_3$ with **5**, the generation of a dinuclear La(III) complex, [{La{O(CH$_2$CH$_2$O)$_2$Me}(O*i*-Pr)}$_2$O·EtOAc] (**8**), was found in the mixture of La(O*i*-Pr)$_3$ (1 equiv) and **5** (2 equiv) in ethyl acetate by ESI-MS analysis (m/z = 739 for [M + H]$^+$).[12] Taking advantage of Brown's dinuclear La(III) complex,[6] we can propose that a dinuclear La(III)−O−La(III) salt might efficiently catalyze the transesterification through TS-**9**, which should be regarded as a working model, based on Lewis acid−Lewis base dual activation[7] (Figure 3).
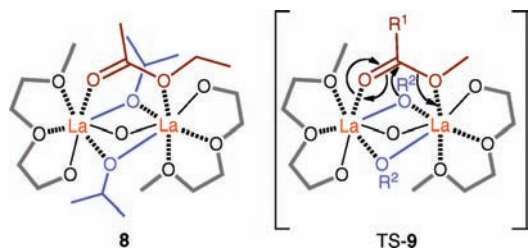

Figure 3. Possible dinuclear La(III) complex **8** and transition-state assembly (TS) **9**.

In summary, we have developed a facile, rapid, atom-economical, and chemoselective transesterification reaction of an equimolar mixture of carboxylic esters and 1°-, 2°-, and 3°-alcohols in hydrocarbon solvents under azeotropic reflux conditions.[13] The highly active La(III) catalyst can be easily prepared in situ from commercially available La(O*i*-Pr)$_3$ and **5**. This La(III) catalyst was also effective for the chemoselective transesterification of carboxylic esters with alcohols in the presence of competitive 1°- and 2°-amines. As a great advantage in industrial application, the toxicity of La(III) is much lower than that other metal ion catalysts such as Hf(IV), Zr(IV), Zn(II), Sn(IV), and Sb(III) which are well-known as conventional esterification catalysts, and moreover, colorless esters were obtained without an inconvenient workup procedure.

Supporting Information Available: Experimental procedures and spectral data, as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Zr(IV) and Hf(IV): (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179. Ti(IV): (c) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138. (d) Krasik, P. *Tetrahedron Lett.* **1998**, *39*, 4223. Sn(IV): (e) Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. Sb(III): Chen, J.-W.; Chen, L.-W. *J. Polym. Sci., Part A* **1999**, *37*, 1797.

(12) See the Supporting Information for details.

(13) General procedure for the transesterification: A mixture of La(O*i*-Pr)$_3$ (12.6 mg, 0.04 mmol) and monomethyl ether of diethylene glycol (**5**) (9.4 mL, 0.08 mmol) in anhydrous *n*-hexane (8 mL) was stirred at room temperature for 1−2 min. As soon as carboxylic ester (**1**) (4.0 mmol) and alcohol (**2**) (4.0 mmol) were added to the solution, the mixture was heated under azeotropic reflux conditions with the removal of methanol. Methanol was removed through a pressure-equalized addition funnel containing a cotton plug and 6.5 g of 5 Å molecular sieves (pellets) and functioning as a Soxhlet extractor. After heating for 1−24 h at reflux temperature, the reaction mixture was allowed to cool to ambient temperature. To quench the catalysts, a drop of water was added, and the mixture was stirred for 5 min. The mixture was dried over MgSO$_4$, the organic phase was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel with *n*-hexane−ethyl acetate as eluents.