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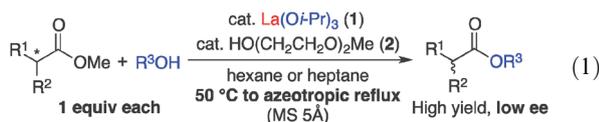
***In situ* generated “lanthanum(III) nitrate alkoxide” as a highly active and nearly neutral transesterification catalyst†**Manabu Hatano,^a Sho Kamiya^a and Kazuaki Ishihara^{*ab}

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***In situ* generated lanthanum(III) nitrate alkoxide is a highly active and nearly neutral transesterification catalyst, which can promote non-epimerized transesterification of α -substituted chiral carboxylic esters under reflux conditions.**

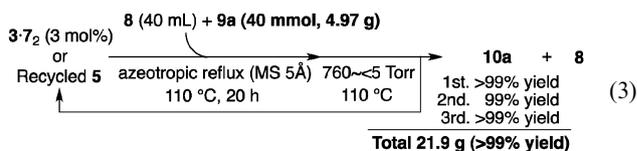
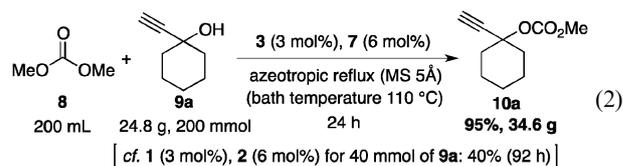
The transesterification of carboxylic esters with alcohols is one of the most valuable methods for ester synthesis.¹ In particular, harmless and colorless La(III) complexes, unlike conventional Al(III),² Ti(IV),³ Sb(III),⁴ Sn(IV),⁵ Zr(IV),^{3a,6} Hf(IV),^{3a,6} B(III),⁷ Zn(II),⁸ etc., have been proved to be one of the most effective catalysts by Okano, Brown, and Li *et al.*⁹ We also recently reported that lanthanum(III) isopropoxide (**1**)–(2-methoxyethoxy)ethanol (**2**) as an acid–base combined catalyst¹⁰ promoted the transesterification of carboxylic esters, less-reactive dimethyl carbonate (**8**), and much less-reactive methyl carbamates with an equivalent amount of 1°, 2°, and less-reactive 3°-alcohols.¹¹ In this catalysis, however, **1** is highly Brønsted basic and cannot be used for non-epimerized transesterification of chiral α -substituted esters under the practical azeotropic reflux conditions (> 50 °C) (eqn (1)). Also, **1** is expensive for industrial application, not available in bulk quantities, and unstable under moist conditions to decompose into inactive lanthanum(III) oxide. Therefore, alternative low-priced and much more stable La(III) precursors are desired.¹²



To overcome these subjects, we envisioned that inexpensive lanthanum(III) nitrate, which is much more stable than **1** due to the coordinative NO₃[−] moieties and less hygroscopic than La(OTf)₃, can be one of the most promising compounds.¹³ Moreover, we here selected to use highly Brønsted basic [PMe(octyl)₃](OCO₂Me) (**4**) as a key additive in the presence of alcohol (ROH). Compound **4** would react with ROH

besides irreversible decomposition to MeOH and CO₂ under mild azeotropic reflux conditions, and give an uncertain mixture of La(OR)_{*m*}(NO₃)_{3−*m*} (*m* = 1–3) (**5**) *in situ* without removal of [PMe(octyl)₃](NO₃) (**6**) (Fig. 1). Pentacoordinated **6** with soft character would unlikely ligate to the Lewis acidic lanthanum center, and thus high catalytic activity will be maintained. Moreover, the preparation technique according to the amount of starting **4** might control the ratio of these active catalysts in the equilibrium. In particular, we assumed that more neutral and thus less basic La(OR)₂(NO₃) (**5a**) and LaOR(NO₃)₂ (**5b**) rather than strongly basic La(OR)₃ (**5c**) should be of great advantage for undeveloped non-epimerized transesterification of chiral α -substituted esters.

At the outset of our study, by taking advantage of the low price and high polarity of dimethyl carbonate (**8**) (bp 90 °C) for La(III) catalysts, we examined the probe transesterification of **8** with 1-ethynyl-1-cyclohexanol (**9a**) (2 mmol scale) as a less-reactive 3°-alcohol (Table 1). In the presence of 3 mol% of La(NO₃)₃·H₂O (**3**) from La(NO₃)₃·6H₂O,¹⁴ the reaction was conducted under azeotropic reflux conditions with the removal of methanol using MS 5 Å in a Soxhlet thimble. However, **3** was hardly soluble in **8**, and the product (**10a**) was obtained in only 38% yield after 12 h (entry 1). In sharp contrast, addition of [PMe(octyl)₃](OCO₂Me) (**4**) (6 mol%) to **3** (3 mol%) was expectedly effective to promote the reaction (98% yield within 10 h) under homogeneous reaction conditions (entry 2).



Remarkably, the use of much less expensive La(NO₃)₃·*x*H₂O (*x* = 3–5) showed almost the same catalytic activity after desiccation to **3** under <3 Torr at 170 °C for 12 h¹⁴ (entry 2, parentheses). The yield slightly decreased (86%) when 3 mol% of **4** was used, while 9 mol% of **4** exhibited a comparable result

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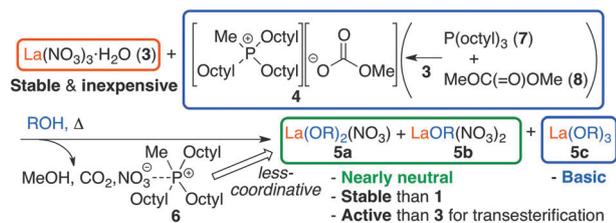
Fig. 1 “Lanthanum(III) nitrate alkoxide” *in situ*.

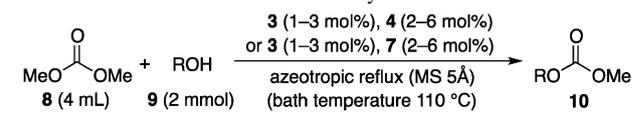
Table 1 Optimization of La(III) catalysts

Entry	La(III)	Additive	Time [h]	Yield [%]
1	3	—	12	38
2	3	[PMe(octyl) ₃](OCO ₂ Me) (4) (6 mol%)	10	98 (> 99) ^a
3	3	4 (3 mol%)	10	86
4	3	4 (9 mol%)	10	98
5	—	4 (6 mol%)	10	<1
6	—	[PMe(octyl) ₃](NO ₃) (6) (6 mol%)	10	0
7	—	HNO ₃ (6 mol%)	10	<1
8	3	KO <i>t</i> -Bu (9 mol%)	10	24
9	3	P(octyl) ₃ (7) (6 mol%)	10	> 99

^a Catalyst 3 was prepared from $\text{La}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$ ($x = 3-5$).

(98%) to that obtained using 6 mol% of 4 (entries 2–4). As other active candidates *in situ*, compound 4, [PMe(octyl)₃](NO₃) (6),¹⁵ and HNO₃ were much less effective (<1% yields for 10 h) (entries 5–7), and these results strongly suggest that 3 and 4 are critical precursors for the active La(III) catalysts *in situ*. Additionally, it is noted that highly basic “La(OR)₃”, which was prepared *in situ* from 3 (3 mol%) and KO*t*-Bu (9 mol%), showed low catalytic activity (24% yield), since much less active La(III) ate species such as K[La(OR)_m(NO₃)_{4-m}] might be involved under basic conditions (entry 8). It is noted that, according to Perosa’s report,¹⁵ compound 4 can be synthesized from P(octyl)₃ (7) and 8 in methanol at 0 °C in the presence of 3. As expected, the perfect yield was established when 6 mol% of technical-grade 7 was used in the presence of 3 mol% of 3 (entry 9). We observed, in the resulting crude mixture, a sole ³¹P NMR (CDCl₃) signal at 32.35 ppm and *m/z* = 385.39 in ESI-MS analysis, which can be attributed to the [PMe(octyl)₃]⁺ moiety (Fig. 1). Moreover, when the reaction was conducted on the 200 mmol scale (24.8 g) of 9a, catalyst 3·7₂ showed high catalytic activity, and 10a was obtained in 95% yield (34.6 g) (eqn (2)). On the other hand, moisture-sensitive 1·2₂^{11a} was much less effective (40% yield), even on the 40 mmol scale with prolonged reaction time (92 h) (eqn (2)). Moreover, the catalyst 5 *in situ* from 3·7₂ was active after removal of products and volatiles *in vacuo*, and could be recycled three times on the 40 mmol scale (4.97 g of 9a each time, 99–> 99% yields) (eqn (3)).

With the optimal homogeneous reaction conditions in hand, we next examined other alcohols (Table 2).¹⁶ Due to the minimal steric hindrance of 8, not only 2°-alcohols but also 3°-alcohols were used, and the desired products (10b–d) were

Table 2 Transesterification with dialkyl carbonate^a

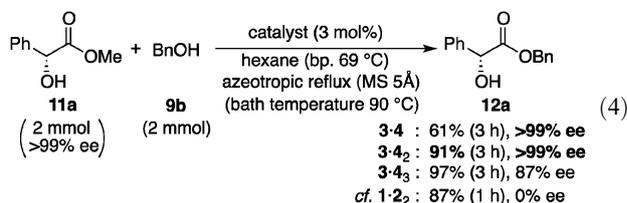
Product (10), isolated yield, and reaction time

Substrate	Yield [%]	Time [h]
10b	> 99%	1 h ^b
10c	99%	12 h
10d	97%	5 h
10e	98%	1 h ^{b,c}
3·4 ₂	> 99%	1 h ^b
3·7 ₂	> 99%	1 h ^b
1·2 ₂	12%	1 h ^b
3·4 ₂	96%	17 h
3·7 ₂	97%	28 h
1·2 ₂	> 99%	20 h
3·4 ₂	98%	1 h ^{b,c}
3·7 ₂	98%	1 h ^{b,c}
1·2 ₂	98%	12 h ^{b,c}

^a Unless otherwise noted, 3 mol% of 3·4₂, 3·7₂, or 1·2₂ was used. ^b 1 mol% of 3·4₂, 3·7₂, or 1·2₂ was used. ^c Diethyl carbonate was used in place of 8. Bath temperature was 145 °C.

obtained in 96–> 99% yields. Compared with the previous catalyst 1·2₂, 3·4₂ or 3·7₂ provided much higher catalytic activity. Moreover, less-reactive diethyl carbonate in place of 8 could be used, and the corresponding cyclohexyl ethyl carbonate (10e) was obtained in 98–99% yield after 1 h in the presence of 1 mol% of 3·4₂ or 3·7₂. Totally, the transesterification of much harmless dialkyl carbonates with various alcohols is highly useful in industry, since phosgene as a traditional reactant is deadly toxic.

In transesterification, epimerization of the substrate and/or the product is a serious problem. In particular, synthesis of chiral α -substituted ester under harsh basic conditions at azeotropic reflux temperature is one of the challenging issues in really practical transesterification. As expected, our previous basic catalyst 1·2₂ caused racemization under reflux conditions (bath temperature, 90 °C), and the corresponding product (12a) was obtained in 87% yield as a complete racemate from (*R*)-mandelate (11a) (>99% ee) and benzyl alcohol (9b) (eqn (4)). In sharp contrast, the use of much more neutral 3·4 and 3·4₂ provided 12a in 61% and 91% yield, respectively, without a loss of optical purity (>99% ee), although we observed the decrease in optical purity (87% ee) when 3·4₃ was used. These results strongly suggest that the actual catalysts *in situ* should be LaOR(NO₃)₂ (5a) and/or La(OR)₂NO₃ (5b) rather than La(OR)₃ (5c), which would be in equilibrium in the reaction mixture as shown in Fig. 2.



Furthermore, the non-epimerized transesterification of other unstable chiral substrates (11) was demonstrated (Table 3).¹⁶ Some substrates were applicable under the optimized reaction conditions at 90 °C in the presence of 3·4₂ without serious loss of optical purity (96–> 99% ee in 12d, 12e, and 12h). However, other substrates showed the decrease in optical purity (87–94% ee in 12b, 12c, 12f, and 12g) even if the reaction temperature was

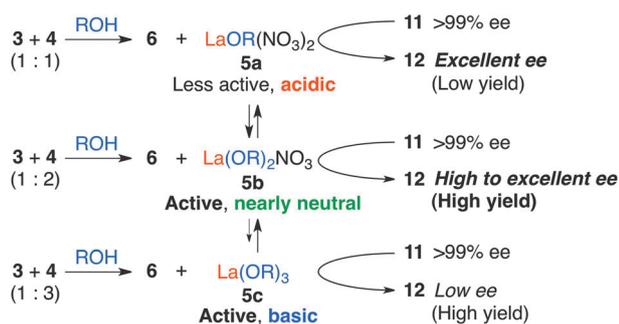


Fig. 2 Catalysts *in situ*, ee, and the yield of the products.

Table 3 Non-epimerized transesterification

$\text{R}^1\text{-C}(\text{R}^2)\text{-CO}_2\text{Me} + \text{R}^3\text{OH} \xrightarrow[\text{rt-azeotropic reflux (MS 5\AA)}]{\text{3 (3 mol\%), 4 (3-6 mol\%)}} \text{R}^1\text{-C}(\text{R}^2)\text{-CO}_2\text{R}^3$		
11 (2 mmol, >99% ee)	9 (2 mmol)	12
Product (12), isolated yield, optical purity, and reaction time		
 3:4 ₂ : 92% (90 °C, 3 h) 93% ee 3:4: 88% (70 °C, 9 h) 99% ee ^a	 3:4 ₂ : 91% (90 °C, 1 h) 94% ee 3:4: 84% (70 °C, 20 h) >99% ee ^a	 3:4 ₂ : 90% (90 °C, 24 h) >99% ee 3:4: 84% (70 °C, 20 h) >99% ee ^a
 3:4 ₂ : 90% (90 °C, 48 h) 96% ee 3:4: 84% (70 °C, 20 h) >99% ee ^a	 3:4 ₂ : 78% (70 °C, 9 h) 94% ee 3:4: 97% (70 °C, 24 h) 96% ee ^b	 3:4 ₂ : 95% (70 °C, 48 h) 87% ee 3:4: 99% (rt, 16 h) 97% ee ^c
 3:4 ₂ : 95% (90 °C, 2 h) >99% ee 3:4: 97% (70 °C, 24 h) 96% ee ^b		

^a 2 equiv. of **9** was used. ^b 1 mol% of **3**·**4** was used. ^c Powdered MS 5 Å was used *in situ*.

70 °C. According to the hypothesis of the equilibrium among the catalysts (**5a–c**) as shown in Fig. 2, the reactions proceeded smoothly without a loss of optical purity or with almost intact optical purity (96–>99% ee) when **3**·**4** was used in place of **3**·**4**₂. Totally, not only α -oxy-substituted esters (**12b** and **12h**), but also α -amino esters (**12c–e**), α -chloro ester (**12f**), and naproxen derivative (**12g**) could be used in **3**·**4**₂- or **3**·**4**-catalyzed transesterification.

In summary, we have developed highly useful and homogeneous acid–base combined catalysts for transesterification, nearly neutral lanthanum(III) nitrate alkoxide, which can be readily prepared *in situ* from inexpensive La(NO₃)₃·H₂O and [PMe(octyl)₃](OCO₂Me). The most privilege of these active La(III) catalysts is highly practical non-epimerized transesterification of chiral α -substituted esters under azeotropic reflux conditions (96–>99% ee). Since really practical catalysts for transesterification

are still strongly desired in both laboratory and industry, we believe that this new methodology without a complicated procedure can help problems for further improvements in transesterification.

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Notes and references

- (a) For reviews: J. Otera, *Esterification*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2003; (b) J. Otera, *Acc. Chem. Res.*, 2004, **37**, 288; (c) M. Nahmany and A. Melman, *Org. Biomol. Chem.*, 2004, **2**, 1563; (d) G. A. Grasa, R. Singh and S. P. Nolan, *Synthesis*, 2004, 971; (e) H. E. Hoydonckx, D. E. De Vos, S. A. Chavan and P. A. Jacobs, *Top. Catal.*, 2004, **27**, 83; (f) D. Enders, O. Nie-meier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (g) K. Ishihara, *Tetrahedron*, 2009, **65**, 1085.
- R. H. Baker, *J. Am. Chem. Soc.*, 1938, **60**, 2673.
- (a) R. C. Mehrotra, *J. Am. Chem. Soc.*, 1954, **76**, 2266; (b) D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann and M. Züger, *Synthesis*, 1982, 138; (c) P. Krasik, *Tetrahedron Lett.*, 1998, **39**, 4223.
- J.-W. Chen and L.-W. Chen, *J. Polym. Sci., Part A*, 1999, **37**, 1797.
- (a) J. Otera, T. Yano, A. Kawabata and H. Nozaki, *Tetrahedron Lett.*, 1986, **27**, 2383; (b) J. Otera, N. Danoh and H. Nozaki, *J. Org. Chem.*, 1991, **56**, 5307; (c) L. A. Hobbs and P. J. Smith, *Appl. Organomet. Chem.*, 1992, **6**, 95; (d) J. Xiang, S. Toyoshima, A. Orita and J. Otera, *Angew. Chem., Int. Ed.*, 2001, **40**, 3670.
- K. Ishihara, S. Ohara and H. Yamamoto, *Science*, 2000, **290**, 1140.
- (a) K. Ishihara, S. Kondo and H. Yamamoto, *Synlett*, 2001, 1371; (b) S. Oishi and S. Saito, *Angew. Chem., Int. Ed.*, 2012, **51**, 5395.
- (a) T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama and K. Mashima, *J. Am. Chem. Soc.*, 2008, **130**, 2944; (b) T. Iwasaki, Y. Maegawa, Y. Hayashi, T. Ohshima and K. Mashima, *J. Org. Chem.*, 2008, **73**, 5147; (c) T. Iwasaki, Y. Maegawa, Y. Hayashi, T. Ohshima and K. Mashima, *Synlett*, 2009, 1659; (d) Y. Hayashi, T. Ohshima, Y. Fuji, Y. Matsushima and K. Mashima, *Catal. Sci. Technol.*, 2011, **1**, 230.
- (a) T. Okano, K. Miyamoto and J. Kiji, *Chem. Lett.*, 1995, 246; (b) A. A. Neverov and R. S. Brown, *Can. J. Chem.*, 2000, **78**, 1247; (c) A. A. Neverov, T. McDonald, G. Gibson and R. S. Brown, *Can. J. Chem.*, 2001, **79**, 1704; (d) F. Mei, E. Chen and G. Li, *React. Kinet. Catal. Lett.*, 2009, **96**, 27.
- (a) For acid–base combined catalysis, see: M. Kanai, N. Kato, E. Ichikawa and M. Shibasaki, *Synlett*, 2005, 1491; (b) K. Ishihara, A. Sakakura and M. Hatano, *Synlett*, 2007, 686.
- (a) M. Hatano, Y. Furuya, T. Shimmura, K. Moriyama, S. Kamiya, T. Maki and K. Ishihara, *Org. Lett.*, 2011, **13**, 426; (b) M. Hatano, S. Kamiya, K. Moriyama and K. Ishihara, *Org. Lett.*, 2011, **13**, 430.
- Price list and toxicity of catalysts are summarized in the ESI†.
- Shibasaki *et al.* reported that, in their asymmetric amination, La(NO₃)₃·6H₂O could be a useful La(III) source in place of **1**. Their approach with La(NO₃)₃·6H₂O was not the generation of La(OR)_m(NO₃)_{3–m} *in situ*, but La(III)–chiral salicylic amide–H-D-Val-Or-Bu as an active ternary complex T. Mashiko, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 14990.
- Commercially available La(NO₃)₃·nH₂O are hygroscopic, and were used after desiccation to a monohydrate at 170 °C W. W. Wendlandt, *Anal. Chim. Acta*, 1956, **15**, 435.
- M. Fabris, V. Lucchini, M. Noè, A. Perosa and M. Selva, *Chem.–Eur. J.*, 2009, **15**, 12273.
- For other examples of **8**, a variety of carboxylic esters, and ethyl acetate with 1–3°-alcohols are shown in the ESI†.