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Lanthanum(III) Isopropoxide Catalyzed Chemoselective Transesterification of Dimethyl Carbonate and Methyl Carbamates

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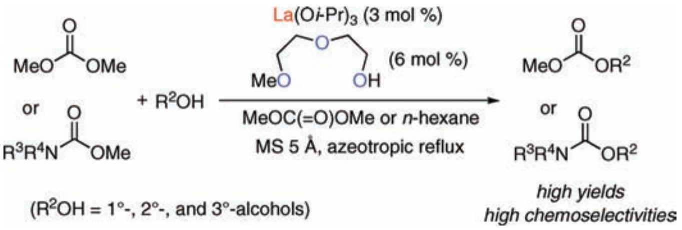
ABSTRACT



A practical transesterification of less reactive dimethyl carbonate and much less reactive methyl carbamates with primary (1°), secondary (2°), and tertiary (3°) alcohols was established with the use of a lanthanum(III) complex, which was prepared in situ from lanthanum(III) isopropoxide (3 mol %) and 2-(2-methoxyethoxy)ethanol (6 mol %). In particular, corresponding carbonates and carbamates obtained were of synthetic utility from the viewpoint of the selective protection and/or deprotection of 1°-, 2°-, and 3°-alcohols.

The direct dehydrative condensation of carboxylic acids with alcohols using small amounts of catalysts is the most ideal method for esterification.[1] However, carboxylic acids often have low solubility in common reaction solvents, and large excess amounts of either carboxylic acids or alcohols are often used for smooth conversion. Moreover, some types of esters such as carbonates ($R^1O{-}CO_2R$) and carbamates (urethanes) ($R^1R^2N{-}CO_2R$) cannot be synthesized by the direct dehydrative condensation method since the starting materials, carbonic acid monoesters ($R^1O{-}CO_2H$) and carbamic acids ($R^1R^2N{-}CO_2H$), are inherently less stable (eq 1). In sharp contrast, the catalytic transesterification of carboxylic esters ($R^1{-}CO_2R$) with alcohols has wide applications in academic and industrial research.[1] Although transesterification of carboxylic esters might be applied to carbonates and carbamates in principle (eq 2); a serious remaining problem is that these compounds are generally much less reactive than carboxylic esters. Moreover, another problem is that traditional transesterification

$$\begin{array}{c} R^1OCO_2H \\ \text{or} \\ R^1R^2NCO_2H \\ \textit{unstable} \end{array} + R^3OH \;\not\longrightarrow\; \begin{array}{c} R^1OCO_2R^3 \\ \text{or} \\ R^1R^2NCO_2R^3 \end{array} + H_2O \qquad (1)$$

$$\begin{array}{c} R^1OCO_2Me \\ \text{or} \\ R^1R^2NCO_2Me \\ \textit{stable but less-reactive} \end{array} + R^3OH \;\longrightarrow\; \begin{array}{c} R^1CO_2R^3 \\ \text{or} \\ R^1R^2NCO_2R^3 \end{array} + MeOH \qquad (2)$$

(R^3OH = 1°-, 2°-, or less-reactive 3°-alcohols)

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[1] For reviews of dehydrative esterifications and transesterifications, 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.

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catalysts could be used for reaction of carboxylic esters with only primary (1°) and secondary (2°) alcohols but scarcely much less reactive tertiary (3°) alcohols due to steric hindrance and acid sensitivity.[2−4] Therefore, a practical transesterification between low reactive substrates, such as carbonates and carbamates with 2°- and 3°-alcohols, has been quite uncommon so far. To overcome these problems, a more efficient transesterification procedure with general applicability involving simple and practical preparations of environmentally benign and active catalysts is still strongly desired in order to promote atom efficiency. We here report that a La(III) catalyst,[5,6] which is prepared in situ from La(O*i*-Pr)$_3$ and monomethyl ether of diethylene glycol (**1**), is highly effective for transesterification of dimethyl carbonate and methyl carbamates with 1°-, 2°-, and 3°-alcohols.

First, we focused on inexpensive dimethyl carbonate (**2**) (bp 90 °C) as a useful transesterification reagent/solvent, since the resultant materials are used as polycarbonates and electrolytic solutions.[7] However, less reactive **2** has been scarcely used in transesterification,[8] although it is much safer and easier to handle under open-air conditions than highly toxic phosgene (bp 8 °C) and harmful methyl chloroformate (bp 70−72 °C). By taking advantage of the high catalytic activity of La(O*i*-Pr)$_3$ with **1** for carboxylic esters in the former report,[9] preliminary examination of transesterification of **2** with 1°- and 2°-alcohols (**3**) showed excellent reactivity in the presence of La(O*i*-Pr)$_3$ (1 mol %) and **1** (2 mol %) under azeotroic reflux conditions (see **4a** and **4b**) (Figure 1). Next, with regard to a small molecule of **2** with minimum steric hindrance, the transesterification of a variety of sterically demanding, less reactive 3°-alcohols (**3**) in **2** was examined. To our delight, the reactions proceeded in the presence of La(O*i*-Pr)$_3$ (3 mol %) and **1** (6 mol %), and the corresponding sterically demanding 3°-alkyl methyl carbonates (**4c**−**l**) were obtained in good to high yields as colorless materials without a complicated purification procedure. In general, transesterification of carboxylic esters with 3°-alcohols is difficult because of steric hindrance between these substratres. In sharp contrast, much less bulky **2** in place of carboxylic esters should be suitable to protect the sterically hindered hydroxy group of 3°-alcohols, although an active catalyst such as La(O*i*-Pr)$_3$ with **1** is critical for less reactive **2**.

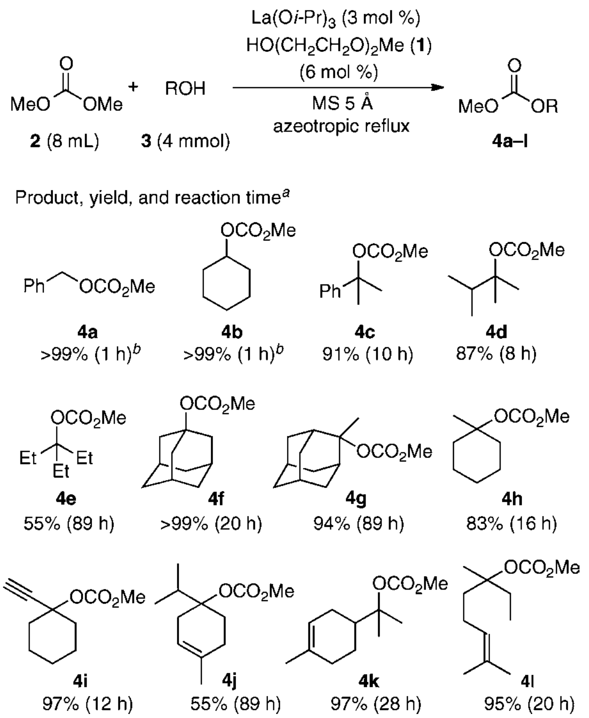
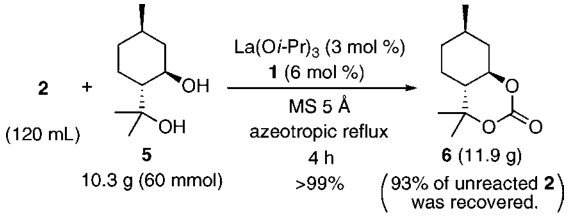


Figure 1. Transesterification of dimethyl carbonate **2**. Conditions: (a) Unless otherwise noted, La(O*i*-Pr)$_3$ (3 mol %) and **1** (6 mol %) were used. (b) La(O*i*-Pr)$_3$ (1 mol %) and **1** (2 mol %) were used.

A gram-scale synthesis was also examined for a 2°/3°-diol (**5**), and the desired colorless product **6** was successfully obtained in >99% yield (11.9 g, 60 mmol) (Scheme 1). It should be noted that 93% of unreacted **2** was recovered by distillation under reduced pressure.

Scheme 1. Catalytic Gram-Scale Synthesis of Cyclic Carbonate **6**



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(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.

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(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 et al. reported La(O*i*-Pr)$_3$-catalyzed transesterification with 1°- and 2°-alcohols: (a) Okano, T.; Hayashizaki, Y.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1863. (b) Okano, T.; Miyamoto, K.; Kiji, J. *Chem. Lett.* **1995**, 246. Brown et al. reported the La(OMe)(OTf)$_2$-catalyzed methanolysis of aryl and alkyl esters based on catalytic Lewis acid−Lewis base dual activation. (c) Neverov, A. A.; Brown, R. S. *Can. J. Chem.* **2000**, *78*, 1247. (d) Neverov, A. A.; McDonald, T.; Gibson, G.; Brown, R. S. *Can. J. Chem.* **2001**, *79*, 1704.

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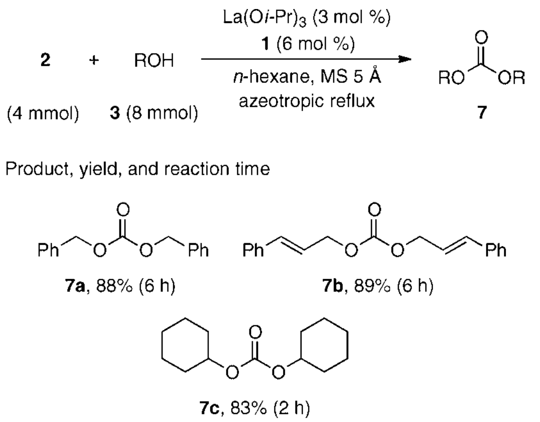
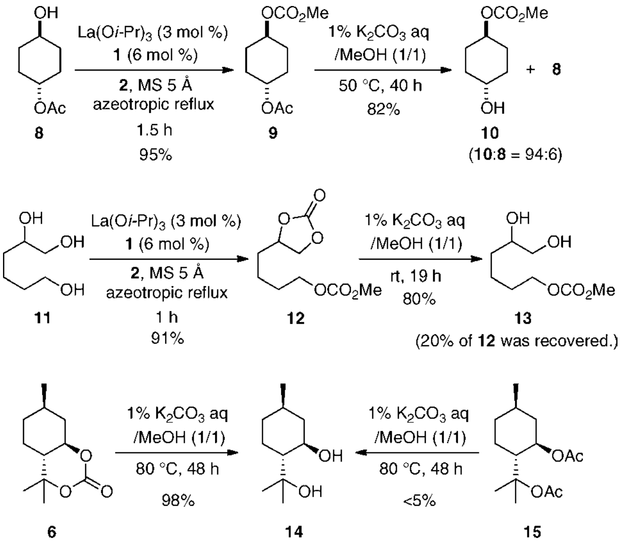


Figure 2. Double transesterification of dimethyl carbonate **2**.

Double transesterification of **2** (1 equiv) with 1°- and 2°-alcohols (2 equiv) was examined (Figure 2). Reactions with 1°-alcohols, such as benzyl alcohol and cinnamyl alcohol, proceeded smoothly in the presence of La(O*i*-Pr)$_3$ (3 mol %) and **1** (6 mol %) in *n*-hexane under azeotropic reflux conditions, and the corresponding products (**7a** and **7b**) were obtained in the respective yields of 88% and 89%. Less reactive cyclohexanol as a 2°-alcohol could be used, and the desired carbonate (**7c**) was obtained in 83% yield.

To demonstrate the utility of carbonates as a protective group of alcohols, we examined hydrolysis under mild basic conditions (Scheme 2).[10] Acyclic carbonates are generally less susceptible to hydrolysis than carboxylic esters because of the resonance effect of the second oxygen. 1,4-Cyclohexanediol-derived **9**, which was readily prepared from monoacetate **8** and **2** in 95% yield by using La(O*i*-Pr)$_3$ (3 mol %) and **1** (6 mol %), could be transformed by treatment of K$_2$CO$_3$/MeOH to monocarbonate **10** in 82% yield with high chemoselectivity. In contrast, probably due to the reduced steric factor of the cyclic carbonate moiety, dicarbonate **12**, which was readily obtained from triol **11** by using La(O*i*-Pr)$_3$ and **1**, provided acyclic monocarbonate **13** in 80% yield without the cyclic monocarbonate. Moreover, cyclic carbonate **6** could provide the corresponding diol (**14**) in 98% yield, while diacetate **15** was almost intact under the same reaction conditions. From these preliminary results, we can expect that the preference of deprotection under mild basic hydrolysis conditions is in the order cyclic carbonate > acetate > acyclic carbonate.

Scheme 2. Chemoselective Deprotection of Carbonates or Esters



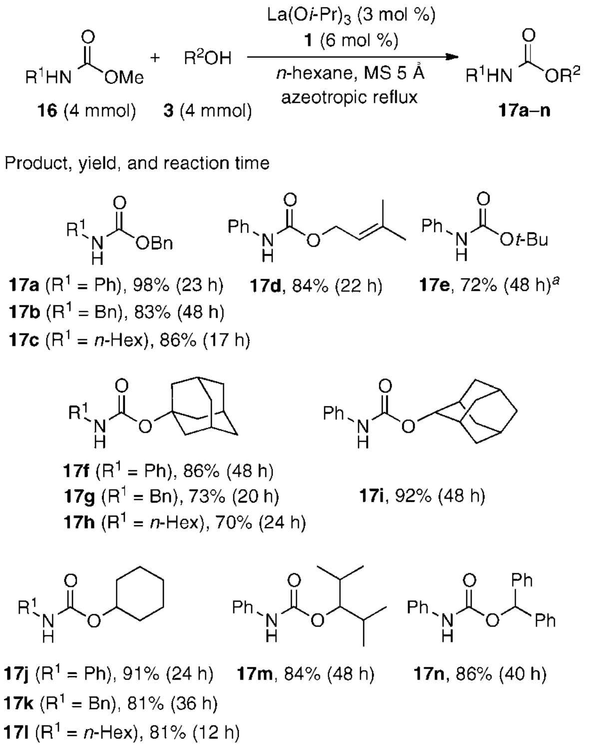


Figure 3. Transesterification of methyl carbamates **16**. Conditions: (a) *t*-BuOH (1 equiv) was added every 10 h, and *t*-BuOH (4 equiv) was used totally.

Since the transesterification of much less reactive carbamates has been reported with stoichiometric activators,[11] we first examined the catalytic transesterification of methyl carbamates (**16**) with equimolar 1°−3° alcohols (**3**) in the presence of La(O*i*-Pr)$_3$ (3 mol %) and **1** (6 mol %) (Figure 3). Fortunately, not only 1°-alcohols but also less reactive 2°-alcohols and much less reactive 3°-alcohols could be used. A variety of the corresponding transformed aliphatic and aromatic carbamates with synthetically useful Cbz (**17a**−**c**), Preoc (**17d**), Boc (**17e**), 1-Adoc (**17f**−**h**), 2-Adoc (**17i**), Hoc

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(10) Very recently, Ohshima and Mashima reported the tetranuclear Zn(II) cluster-catalyzed deprotection of acetates: Iwasaki, T.; Agura, K.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Chem.—Eur. J.* **2010**, *16*, 11567.

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(**17j**−**l**), Doc (**17m**), and CO_2CHPh_2 (**17n**) were obtained in yields of 70−98% as colorless materials. Since a sequential deprotection−protection procedure is usually needed when another carbamate would be introduced, this direct transesterification of methyl carbamates is synthetically useful as an environmentally and industrially ideal method.

In summary, we have developed a practical transesterification of weakly reactive dimethyl carbonate (**2**) and much less reactive methyl carbamates (**16**) with 1°-, 2°-, and 3°-alcohols with the use of a lanthanum(III) complex, which was prepared in situ from lanthanum(III) isopropoxide (3 mol %) and 2-(2-methoxyethoxy)ethanol (**1**) (6 mol %). On one hand, transesterification of **2** should be highly useful for the protection method of less reactive 3°-alcohols by taking advantage of the compact structure of **2** rather than carboxylic esters. On the other hand, transesterification of **16** should be valuable to synthesize a variety of the other carbamates from the original methyl carbamates, without a routine sequential deprotection and protection procedure. Further mechanistic details and application to other catalyses with the present lanthanum(III) complex are underway.

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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.

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