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Chemoselective *O*-*tert*-butoxycarbonylation of hydroxy compounds using $NaLaTiO_4$ as a heterogeneous and reusable catalyst

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ABSTRACT

A facile, efficient and chemoselective protocol for *O*-*tert*-butoxycarbonylation of various hydroxy compounds has been developed using $NaLaTiO_4$ (layered perovskite) as a novel catalyst. The catalyst showed remarkable activity and reusability affording high yields of the desired products under mild reaction conditions.

Organic carbonates constitute an important class of compounds having pharmacological and chemical importance.[1] They are used as alkylating agents in organic reactions, as lubricating oils, pesticides and also in medicinal and pharmaceutical chemistry. Traditionally these compounds are prepared by various methods such as phosgenation, oxidative carbonylation and alkylation of metal carbonates with alkyl halides. However, these methods either involve toxic materials, gaseous reagents or lack simplicity and efficiency.[1a] Di-*tert*-butyl dicarbonate (Boc_2O) is an easily available commercial reagent which is a better choice for preparing unsymmetrical organic carbonates by direct coupling with hydroxy compounds in the presence of a catalyst.[2] Although the application of Boc_2O has been significant for the protection of amino groups,[3] its use for the synthesis of organic carbonates has been limited and is still a fertile area of research.[4] Houlihan et al. have employed a phase transfer protocol for the protection of alcohols and phenols as their *O*-Boc derivatives (unsymmetrical organic carbonates).[4a] There are a few reports on the preparation of organic carbonates in the presence of catalysts such as 4-(dimethylamino)pyridine[4b,c] and zinc acetate.[4d] More recently, oxomolybdenum[5] and oxovanadium[6] species were introduced as amphoteric catalysts for nucleophilic acyl substitutions of anhydrides and dicarbonates. However, most of the methods reported above employ either homogeneous media or homogeneous catalysts, which are not reusable. As per our knowledge, there is only one report on the synthesis of organic carbonates employing diethyl carbonate and an alcohol in the presence of a heterogeneous catalyst under an inert atmosphere at 125 °C.[7] Thus, there was a need to develop an efficient catalytic protocol that could overcome the above disadvantages and facilitate *O*-*tert*-butoxycarbonylation of various hydroxy compounds under milder reaction conditions.

Perovskites are a class of compounds with robust structure and varied physicochemical properties.[8] There are several catalytic applications of perovskites for various vapour phase reactions.[9] However, the catalytic activity of this class of material has not been explored fully in organic synthesis. There are a few reports demonstrating the use of perovskites as catalysts for organic reactions such as catalytic transfer hydrogenation,[10] Ullmann and Sonogashira reactions[11] and Suzuki couplings.[12] Layered perovskites can be structurally described as two-dimensional perovskite slabs that are separated by ion-exchangeable interlayer cations. $NaLaTiO_4$ is one such layered perovskite,[13] which has not been explored as a catalyst to date. $NaLaTiO_4$ has the general formula $A'_2[A_{n-1}B_nO_{3n+1}]$, where A′ = alkali metal, A = alkaline earth or rare earth metal, B = transition metal. The high metal content, insolubility in water and common organic solvents and stability at high temperatures make $NaLaTiO_4$ a promising heterogeneous catalyst for liquid phase organic transformations.[14]

Thus, in continuation of our previous work on the catalytic activity of perovskites,[10] we herein report a simple method for the synthesis of unsymmetrical organic carbonates by *O*-*tert*-butoxycarbonylation of various hydroxy compounds using $NaLaTiO_4$ as a heterogeneous and reusable catalyst under mild reaction conditions (Scheme 1).

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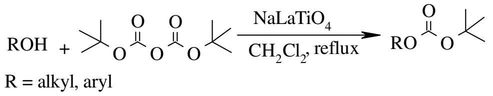


Scheme 1. *O-tert*-Butoxycarbonylation of hydroxy compounds.

Table 1
Influence of catalyst[a]

Entry	Catalyst	Yield[b] (%)
1	None	–
2	$NaLaTiO_4$	92
3	$HLaTiO_4$	90
4	TiO_2	37
5	La_2O_3	20

[a] Reaction conditions: 4-methoxybenzyl alcohol = 1 mmol; Boc_2O = 1.1 mmol; catalyst = 0.1 mmol; solvent = CH_2Cl_2 (1 mL); reflux; time = 7.3 h.

[b] Yield determined by GC and GC–MS analysis.

In order to investigate the influence of catalyst on the reaction system, the reaction of 4-methoxybenzyl alcohol with Boc_2O was chosen as a model (Table 1). Initially, the reaction was performed under catalyst-free conditions and no product formation was observed.

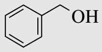
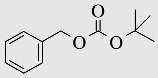
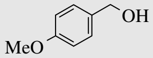
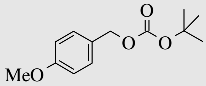
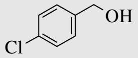
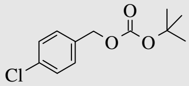
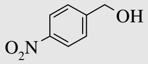
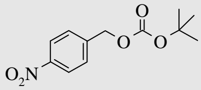
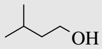
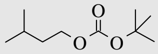
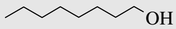
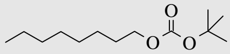
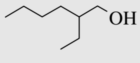
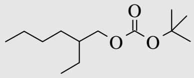
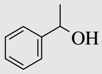
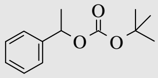
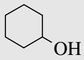
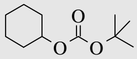
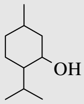
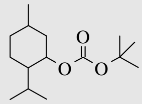
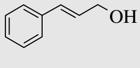
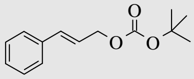
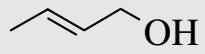
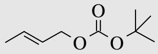
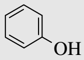
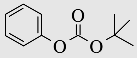
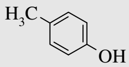
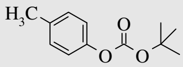
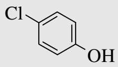
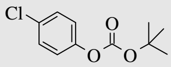
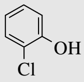
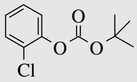
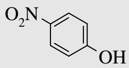
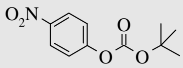
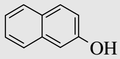
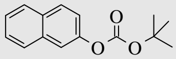
The use of 10 mol % of $NaLaTiO_4$ or $HLaTiO_4$[15] (prepared by exchanging the Na^+ ions of $NaLaTiO_4$ with H^+ ions) catalysts afforded 92% and 90% yields of the desired products, respectively.

The observed similar activity of $NaLaTiO_4$ and $HLaTiO_4$ can be explained on the basis of their structural features as both consist of single layers of TiO_6 octahedra that are separated in alternate layers by monovalent cations, which are ion-exchangeable and La^{3+}, which is non-exchangeable. Thus, the activity may be due to the anionic moiety $[LaTiO_4]^-$ which is the same for both the catalysts. This was further proved when the influence of the component metal oxides on the reaction was studied. It was observed that both the component metal oxides (Table 1, entries 4 and 5) provided lower yields compared to the perovskites indicating that the actual catalytic activity resides in the perovskite structure.

Thus using $NaLaTiO_4$ (10 mol %) as the catalyst, *O-tert*-butoxycarbonylation of various structurally and electronically diverse aliphatic and aromatic hydroxy compounds was carried out in dichloromethane at reflux (Table 2, entries 1–18).[16,17] The reaction of benzyl alcohol with Boc_2O provided a 98% yield of the desired product within 7 h (Table 2, entry 1). Benzyl alcohols possessing electron-donating and electron-withdrawing groups such as OMe, Cl and NO_2 afforded excellent yields of the desired products (Table 2, entries 2–4). Primary and secondary aliphatic alcohols also reacted smoothly under the present conditions giving the corresponding *O*-Boc derivatives in moderate to good yields (Table 2, entries 5–10). Unsaturated alcohols such as cinnamyl alcohol and crotyl alcohol also underwent facile Boc-protection without affecting the ethylenic bond and afforded 92% and 89% yields of the desired products, respectively (Table 2, entries 11 and 12). Thus, both primary and secondary alcohols were viable partners for this transformation.

In order to explore the generality of the protocol, we also studied the protection of aryl alcohols under the same reaction conditions (Table 2, entries 13–18). The reaction of phenol with Boc_2O afforded a 95% yield of phenyl *tert*-butyl carbonate within 8 h (Table 2, entry 13). Phenols having functional groups such as Me, Cl and NO_2 were well tolerated affording their corresponding *O*-Boc derivatives in excellent yields. The presence of substituents at the *ortho* or *para* positions of the phenol did not have much effect on the reaction (Table 2, entries 15 and 16). The *O-tert*-butoxycarbonylation of a bulky phenol, such as 2-naphthol also

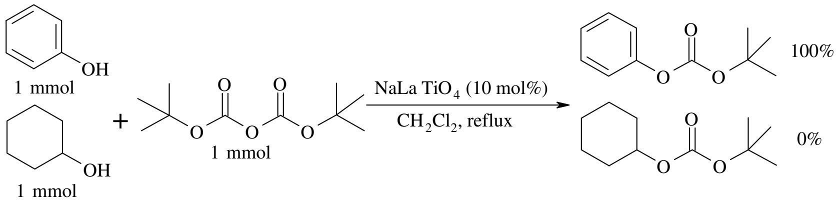
Table 2
$NaLaTiO_4$-catalyzed *O-tert*-butoxycarbonylation of hydroxy compounds[a]

Entry	Hydroxy compound	Time (h)	Product	Yield[b] (%)
1		7		98, 97, 96, 95, 95, 94[c]
2		7.3		92 (88)
3		5.5		97
4		7		83
5		6.85		77
6		7		70
7		7.5		72
8		7		89
9		6.5		50
10		7.25		23
11		6		92
12		6.75		89
13		8		95
14		8		78
15		7.5		88 (83)
16		7.5		84 (80)
17		8		80
18		6.6		91

[a] Reaction conditions: hydroxy compound = 1 mmol; Boc_2O = 1.1 mmol; $NaLaTiO_4$ = 0.1 mmol; solvent = CH_2Cl_2 (1 mL); reflux.

[b] Yield determined by GC and GC–MS analysis. Yields in parentheses are of isolated products.

[c] Yield after sixth cycle.



Scheme 2. $NaLaTiO_4$-mediated chemoselective *O*-*tert*-butoxycarbonylation of hydroxy compounds.

proceeded smoothly under the present reaction conditions providing 2-naphthyl *tert*-butyl carbonate in 91% yield within 6.6 h (Table 2, entry 18). Thus, the methodology was able to tolerate both steric and electronic variations on the aryl alcohols under the adopted reaction conditions.

We further investigated the reusability of the catalyst by separating it from the reaction mass by filtration. After separation, the catalyst was washed with acetone followed by diethyl ether and heated at 150 °C for 2 h before the next cycle. The catalyst was found to be reusable for up to six consecutive cycles with no significant loss in activity (Table 2, entry 1).

The scope of this methodology was further extended by investigating the possible chemoselectivity of the $NaLaTiO_4$-mediated *O*-*tert*-butoxycarbonylation by carrying out competitive reactions of alcohols and phenol (Scheme 2). It was found that phenol reacted exclusively in the presence of *n*-octyl alcohol or cyclohexyl alcohol which was confirmed by GC and GC–MS analysis of the reaction mixture. Thus, the protocol may be useful in the multistep synthesis of bulky organic molecules wherein phenolic hydroxy groups are to be protected selectively in the presence of saturated alcoholic hydroxy functionalities, which either do not contain aryl substituents or have them at remote sites.

In conclusion, we have developed a simple, efficient and chemoselective protocol for the *O*-*tert*-butoxycarbonylation of hydroxy compounds using $NaLaTiO_4$ as a novel heterogeneous catalyst. The methodology offers several advantages such as use of a heterogeneous and reusable catalyst, high chemoselectivity, greater substrate compatibility, high reaction rates, operational simplicity and mild reaction conditions. Further work is in progress to explore this novel catalyst for use in other organic transformations.

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14. *Typical procedure for the preparation of $NaLaTiO_4$*: Stoichiometric amounts of La_2O_3 (preheated at 900 °C for 12 h), TiO_2 and 20% excess of Na_2CO_3 were mixed and heated slowly up to 800 °C in a platinum crucible and the temperature was kept constant for 12 h in air. The resulting powder was ground and heated at 900 °C for 2 days with two intermittent grindings and cooled in a furnace. Twenty percent excess of Na_2CO_3 was added while grinding to compensate for the loss of the volatile sodium component. The resulting product was washed with distilled water and dried at 120 °C.
15. (a) Byeon, S. H.; Yoon, J. J.; Lee, S. O. *J. Solid State Chem.* **1996**, *127*, 119–122; (b) Schaak, R. E.; Mallouk, T. E. *J. Solid State Chem.* **2001**, *161*, 225–232.
16. *General procedure for the O-tert-butoxycarbonylation of hydroxy compounds:* To a dried 10 mL round-bottomed flask containing 1 mmol of alcohol was added 1.1 mmol of Boc_2O followed by 0.1 mmol of $NaLaTiO_4$ and finally 1 mL of CH_2Cl_2. The mixture was stirred under reflux. The reaction was monitored by TLC and GC. After the appropriate time, the reaction mixture was cooled to room temperature and the catalyst was separated by filtration. The products were characterized using GC/GC–MS.
17. *Spectral data of selected products: Table 2, entry 2:* ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.47$ (s, 9H), 3.78 (s, 3H), 5.02 (s, 2H), 6.86 (d, $J = 6.6$ Hz, Ar 2H), 7.30 (d, $J = 6.6$ Hz, Ar 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 27.7$, 55.2, 68.5, 82, 113.8, 127.7, 130.2, 153.5, 159.7. MS (EI, 70 eV): 238 (10) (M^+), 181 (24), 137 (52), 121 (100), 57 (30). *Table 2, entry 15:* ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.46$ (s, 9H), 7.03 (d, $J = 7.1$ Hz, Ar 2H), 7.24 (d, $J = 6.6$ Hz, Ar 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 27.6$, 83.8, 122.6, 129.4, 131.1, 149.6, 151.5. MS (EI, 70 eV): 228 (4) (M^+), 128 (32), 111 (12), 57 (100). *Table 2, entry 16:* ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.56$ (s, 9H), 7.15–7.30 (m, Ar 3H), 7.42 (d, $J = 7.8$ Hz, Ar 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 27.4$, 83.9, 123.3, 126.9, 127.7, 130.2, 147.1, 150.7. MS (EI, 70 eV): 228 (3) (M^+), 128 (35), 111 (16), 57 (100).