# Alkyl Carbonates: Efficient Three Component Coupling of Aliphatic Alcohols, CO₂, and Alkyl Halides in the Presence of Cs₂CO₃

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Organic carbonates[1] have been utilized ubiquitously in industry[2] as well as in biological and medicinal fields,[3] and aliphatic carbonates, in particular, have exhibited promise in medical applications.[4] Nonetheless, the lack of facile synthetic methodologies has hampered further studies,[5] prompting us to develop efficient procedures for the preparation of alkyl carbonates via carbon dioxide alkylation.[6] As representatively shown in the Scheme 1, our previously reported method exploited the cesium base promoted *O*-alkylation, allowing primary and secondary alcohols to couple efficiently with various primary alkyl bromides,

Scheme 1

Scheme 2
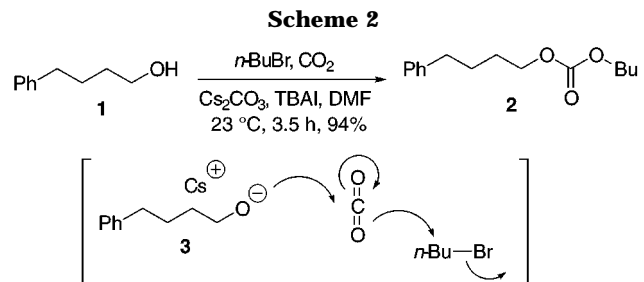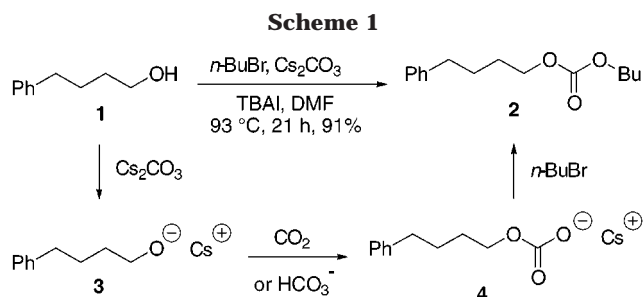
where cesium carbonate was utilized as both a base and a carbon dioxide source.[7] Complementary to this technology, alternative conditions have also been examined to offer a general protocol for unsymmetrical carbonates, where CO₂ gas was employed in the presence of Cs₂CO₃ utilized only as a base.

Unlike other alkali equivalents, cesium alkoxides such as **3** can react with carbon dioxide or bicarbonate to yield alkyl carbonates (*e.g.*, **4**) presumably because alkoxides conjugated with cesium are considered to constitute "naked anions", exhibiting enhanced nucleophilicities.[8] Since carbon dioxide was generated *in situ* from cesium carbonate upon heating (*i.e.*, 93 °C), the concentration of CO₂ was anticipated to be low, thereby retarding the alkylation process. In our continuous efforts to avert these impediments, we envisioned that an additional source of CO₂ gas would facilitate the carbonic acid formation, and the preliminary results are elaborated upon hereafter.

When the reaction mixture was saturated with carbon dioxide by bubbling the gas continuously, carbonylation of alcohol **1** was complete at ambient temperature, rendering exclusively the desired mixed carbonate **2** through the three component coupling of cesium alkoxide **3**, CO₂, and alkyl bromide as mechanistically illustrated in Scheme 2. The addition of tetrabutylammonium iodide (TBAI) accelerated the reactions significantly while *N,N*-dimethylformamide was the solvent of choice. More importantly, cesium carbonate played the most critical role in the three way couplings since the use of different bases including other alkali carbonates and amine bases proved inefficient. It is strongly believed that the cesium alkoxides constitute weakly coordinated species, enhancing the nucleophilicities enough to effect the nucleophilic attack to the relatively inert carbon dioxide at room temperature, which is not the case with other alkali alkoxides.[7,8] These superior procedures were facile, allowing for moderate reaction conditions such as lower temperatures, shorter reaction times, and substrate versatilities better than those in the aforementioned methodology. Some representative examples are discussed below.

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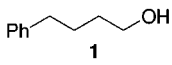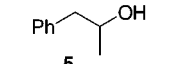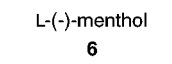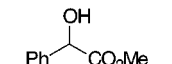
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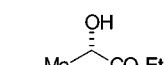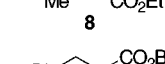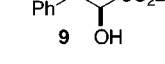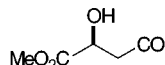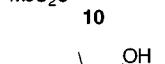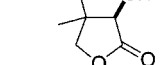
Table 1. Carbonate Formation Using Alcohols, Halides, and CO_2 in the Presence of Cs_2CO_3

$$ROH + R'X \xrightarrow[\text{DMF, 23 °C}]{\text{CO}_2,\ \text{Cs}_2\text{CO}_3,\ \text{TBAI}} RO\overset{O}{\underset{}{\parallel}}OR'$$

Entry	Alcohol (ROH)	Halide (R'X)	Time	Yield
1		$Br\diagup CO_2{}^tBu$	5 h	95%
2		BnCl	2.5 h	94%
3	Ph~~~OH **1**	Allyl Bromide	4 h	91%
4		Br~<	23 h	98%
5		*n*-BuBr	4.5 h	92%
6	Ph~OH / Me **5**	$Br\diagup CO_2{}^tBu$	5 h	96%
7		BnCl	3 h	98%
8	L-(-)-menthol **6**	*n*-BuBr	5 h	96%
9	Ph~OH~CO2Me **7**	MPMCl	3 h	92%

Table 2. Carbonate Formation Using Chiral Templates

Entry	Alcohol (ROH)	Halide (R'X)	Time	Yield	%ee
1		BnCl	3 h	90%	96
2	Me~CO2Et / OH **8**	MPMCl	3 h	94%	
3	Ph~CO2Bn / OH **9**	BnCl	3 h	85%	97
4	MeO2C~CO2Me / OH **10**	BnCl	3 h	65%	95
5		BnCl	3 h	90%	97
6	OH / O lactone **11**	MPMCl	3 h	94%	97

As delineated in Table 1, the newly developed techniques were compatible with various substrates. Primary alcohol **1** was efficiently reacted with active halides (entries 1−3) as well as unreactive secondary bromides (*i.e.*, 2-bromobutane, entry 4) which required prolonged reaction time. The secondary alcohol **5** was also converted exclusively to its corresponding carbonates in high yields (entries 5−7). Menthol, a sterically crowded alcohol, underwent consolidation smoothly to provide the desired carbonate in excellent yield (entry 8). As depicted in entry 9, methyl mandelate **7** was subjected to the same conditions with 4-methoxyphenylmethyl chloride (MPMCl) to afford its MPM carbonate, which could serve as a novel hydroxyl protecting group. Any side reactions including elimination and hydrolysis were not observed within our detection limits, permitting a wide range of applications.

Subsequently, our attention was directed toward *O*-alkylation of chiral alcohols, which are prone to racemization under the known conditions.[9] As demonstrated in Table 2, α-hydroxy esters and lactones underwent facile carbonylation with no or little racemization, providing a new approach to hydroxyl protection. Alkylations of α-hydroxy esters encompassing lactate **8**, phenyllactate **9**, and dimethyl malate **10** were also efficient, resulting in the exclusive formation of their corresponding carbonates with >95% ee values (entries 1−4).[10] Since pantolactone **11** is resistant to most known protection methods,[7] it is noteworthy that the three component couplings with carbon dioxide and benzylic halides took place smoothly, delivering the

desired carbonates in high yields. If any, stereochemical sense was lost to a negligible extent.[10] Using chiral templates, carbonate formation was efficient without any elimination or hydrolysis, where no or little racemization was observed.

In summary, a three way coupling was performed using alcohols, carbon dioxide, and halides, leading to the exclusive synthesis of mixed alkyl carbonates, where the use of cesium bases was crucial due to the inherently enhanced nucleophilicities of the corresponding cesium alkoxides generated *in situ* from various aliphatic alcohols. Primary and secondary alcohols were easily incorporated into CO_2, which then, in turn, reacted with diverse halides including secondary bromides, which are usually resistant to alkylations due to eliminations. In addition, modification of the developed conditions is currently under study to facilitate the carbonate formation from tertiary substrates (*i.e.*, trityl alcohol), which were sluggish or resistant to react, leaving most starting materials intact. Our procedures discussed herein were mild enough to avert side reactions such as hydrolysis and transesterification, common in various *O*-alkylation methods in the presence of ester or its equivalent functionalities. Thus, chiral substrates encompassing α-hydroxy esters, susceptible to racemization, were also durable under the developed conditions. Our synthetic methodology is facile, convenient, and expeditious, and it is believed that this technology will be used generally in the syntheses of various aforementioned carbonates[2−4] as well as in functional group manipulation and protection.[11]

Supporting Information Available: General experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) Under basic conditions, α-hydroxy esters and lactones racemize easily, so alkylations of such moieties are usually carried out under acidic conditions. So far, silver catalyzed alkylations seem to be the most popular alkylation method, which is a costly process. (a) McKenzie, A.; Wren, H. *J. Chem. Soc.* **1919**, *115*, 602. (b) Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.

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