JOC Article

Alcohols and Di-*tert*-butyl Dicarbonate: How the Nature of the Lewis Acid Catalyst May Address the Reaction to the Synthesis of *tert*-Butyl Ethers

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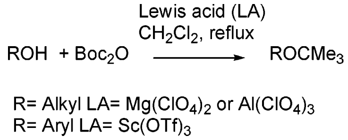


$$\mathrm{ROH} + \mathrm{Boc_2O} \xrightarrow[]{\text{Lewis acid (LA)}\\ \mathrm{CH_2Cl_2},\ \text{reflux}} \mathrm{ROCMe_3}$$

R= Alkyl LA= $Mg(ClO_4)_2$ or $Al(ClO_4)_3$
R= Aryl LA= $Sc(OTf)_3$

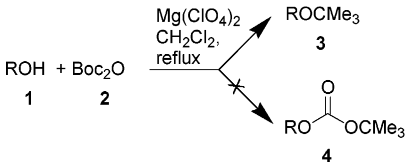
The reaction between alcohols and Boc_2O leads to the formation of *tert*-butyl ethers and/or Boc-alcohols, depending on the nature of the Lewis acid catalyst. Product distribution is mainly tuned by the anionic part of the salt. Perchlorates and triflates, anions with highly delocalized negative charge, give prevalent or exclusive ether formation. On the other hand, Boc alcohols are the main or exclusive products with un-delocalized isopropoxide or low-delocalized acetate ions. The metal ion influences only the reaction rate, roughly following standard parameters for calculating Lewis acidity. A reaction mechanism is supposed, and a series of experimental evidences is reported to support it. These studies allowed us to conclude that, to synthesize *tert*-butyl ethers, in reactions involving aliphatic alcohols, $Mg(ClO_4)_2$ or $Al(ClO_4)_3$ represents the best compromise between costs and efficiency of the reaction, while, in reactions involving phenols, $Sc(OTf)_3$ is the best choice, since aromatic *tert*-butyl ethers are not stable in the presence of perchlorates.

Introduction

In a preliminary communication,[1] we recently reported that, in the presence of magnesium perchlorate, the reaction of alcohols and *tert*-butyl dicarbonate (Boc_2O) leads to the formation of *tert*-butyl ethers in high yields, instead of the expected *tert*-butyl carbonate (Scheme 1). This methodology represents a completely new and efficient entry to *tert*-butyl ethers, in particular to aromatic ones.

The classical route to *tert*-butyl ethers is, in fact, the addition of alcohols to isobutene, catalyzed by strong acids,[2] which involves the formation of carbocationic intermediates, thus preventing its application to aromatic substrates, which under these conditions preferentially give Friedel−Crafts ring alkylation.[3]

SCHEME 1



Besides, *tert*-butyl ethers are very important in the chemistry of protecting groups, since they are stable under strongly basic conditions (e.g., organolithium and magnesium compounds), but they are generally underused owing to the harsh conditions

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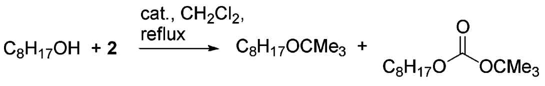
TABLE 1. Reaction between 1-Octanol (1a) (1 equiv) and Boc_2O (2) (2.3 equiv) in Dichloromethane at Reflux in the Presence of Various Lewis Acids (10% mol)



1a **3a** **4a**

entry	catal	conv (%)[a]	*t* (h)	**3a/4a** ratio[a]	**2** recovered (equiv)[a]
			Perchlorates		
1	$Al(ClO_4)_3 \cdot 9H_2O$	89	2.3	100/0	0
2	$Ce(ClO_4)_3 \cdot 6H_2O$	82	4	98/2	0
3	$Zn(ClO_4)_2$	84	4.5	98/2	0
4	$Mn(ClO_4)_2 \cdot 6H_2O$	84	4.5	99/1	0
5	$Mg(ClO_4)_2$ dry	85	4.5	97/3	0
6	$Mg(ClO_4)_2 \cdot 6H_2O$	86	4.5	99/1	0
7	$Ca(ClO_4)_2 \cdot H_2O$	75	7	97/3	0.1
8	$Sr(ClO_4)_2 \cdot 3H_2O$	68	7	99/1	0.9
9	$Ba(ClO_4)_2 \cdot H_2O$	45	7	100/0	1.8
10	$HClO_4$	70	7	100/0	0.1
			Triflates		
11	$In(OTf)_3$	81	4.5	99/1	0
12	$Sc(OTf)_3$	80	4	100/0	0
13	$Al(OTf)_3$	84	4.5	100/0	0
14	$Ce(OTf)_3 \cdot xH_2O$	73	3.5	97/3	0
15	$Zn(OTf)_2$	67	7	94/6	0.13
16	$Mg(OTf)_2$	64	7	94/6	0.7
			Miscellaneous		
17	$ZnBr_2$	27	7	33/67	>2
18	ZnI_2	39	7	28/72	>2
19	$ZnCl_2$	26	7	19/81	>2
20	$CeCl_3$ dry	65	7	18/82	1.3
21	$MgBr_2$	48[b]	7	15/85	1.4
22	$Mg(NO_3)_2 \cdot 6H_2O$	18	7	11/89	>2
23	$MgCl_2$	47	7	9/91	>2
24	$InCl_3$	100	4.5	4/96	0.64
25	$Ti(iPrO)_4$	100	7	0/100	1.2
26	$Zn(OAc)_2$	100	7	0/100	1.2
27	$Zn(OAc)_2 \cdot 2H_2O$	100	7	0/100	0.7

[a] Determined by NMR. [b] Dioctyl carbonate (3%) was also detected.

required for their formation;[2] thus, to place a mild reaction at the chemists' disposition appears to be very important.

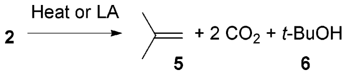
Moreover, an evaluation of the whole set of parameters involved in this new synthesis of *tert*-butyl ethers is needed. In this paper, we report an accurate and detailed study both of the Lewis acid catalysis and of the other factors such as solvent and temperature, which could control the reaction course and the product distribution, to understand the reaction mechanism and to optimize the reaction conditions.

Results

Aliphatic Primary Alcohols. First the influence of the Lewis acid catalyst on the product distribution was tested by modifying the nature of both the metal and the counterion. The reaction between 1-octanol (**1a**) and Boc_2O (**2**) was chosen as the model reaction (Table 1). All the reactions were carried out in dichloromethane under reflux adding a 10% molar amount of catalyst, with a 2.3 molar excess of **2**. An excess of Boc_2O was necessary owing to its instability under heating[4] or in acid conditions (Scheme 2).[1]

All reactions were monitored by TLC and GC-MS analyses and were quenched after the complete disappearance of one of the reagents or, anyway, after 7 h. Product ratio was obtained by NMR integration of the most typical signal of each compound after usual workup.

SCHEME 2



5 **6**

At the end of the reaction, the NMR analysis of the crude always showed only starting materials, ether **3a** and/or carbonate **4a.**

Since Lewis acids can catalyze *tert*-butyl ethers cleavage under certain experimental conditions,[5] stability of pure **3a** was tested and it was found that the employed Lewis acids did not decompose **3a** under these experimental conditions.

As reported in Table 1, only perchlorates and triflates are able to give high yields and selectivity toward ether formation, and among them, $Mg(ClO_4)_2$, $Al(ClO_4)_3$, and $Sc(OTf)_3$ appeared to be the most efficient catalysts, because **3a** was obtained in high yields and reasonably short times. Therefore, we carried out screenings on the influence of other parameters on product distribution and on other substrates considering only these catalysts.

In nonpolar solvents such as chloroform or toluene, the limiting parameter was the solubility of the catalyst. Solubility

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(5) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2006**, *348*, 905−910 and literatures cited therein.

TABLE 2. Influence of Temperature and Solvent on the Reaction between 1-Octanol (1a) (1 equiv) and Boc_2O (2) (2.3 equiv) in the Presence of the Most Efficient Catalysts (10% mol), Except Otherwise Mentioned

entry	catal	solvent	*T* (°C)	*t* (h)[b]	conv (%)[a]	**3a**/**4a** ratio[a]
1	$Al(ClO_4)_3 \cdot 9H_2O$	CH_2Cl_2	40	2.3	89	100/0
2	$Al(ClO_4)_3 \cdot 9H_2O$	CH_2Cl_2	25	10	69	100/0
3	$Al(ClO_4)_3 \cdot 9H_2O$	neat	40	8	87	100/0
4	$Al(ClO_4)_3 \cdot 9H_2O$	neat	25	24	82	100/0
5	$Mg(ClO_4)_2$	CH_2Cl_2	40	4.5	86	99/1
6	$Mg(ClO_4)_2$[c]	neat	40	7	82	99/1
7	$Mg(ClO_4)_2$	neat	25	18	66	100/0
8	$Mg(ClO_4)_2$[d]	neat	40	2	98	99/1
9	$Sc(OTf)_3$	CH_2Cl_2	40	4	80	100/0
10	$Sc(OTf)_3$	CH_2Cl_2	25	4.5	85	98/2
11	$Sc(OTf)_3$	neat	40	1	89	100/0
12	$Sc(OTf)_3$	neat	25	2	92	100/0

[a] Determined by NMR. [b] Times refer to the disappearance of Boc_2O in the reaction mixture. [c] Data from ref 1. [d] 3.5 equiv of **2** is used.

TABLE 3. Influence of the Temperature on the Reaction between 2-Octanol (1b) (1 equiv) and Boc_2O (2) (2.3 equiv) in the Presence of the Most Efficient Catalysts (10% mol), Except Otherwise Mentioned

entry	catal	solvent	*T* (°C)	*t* (h)[b]	conv (%)[a]	**3b**/**4b** ratio[a]
1	$Mg(ClO_4)_2$[c]	neat	50	30	85	100/0
2	$Mg(ClO_4)_2$[d]	CH_2Cl_2	40	4	77	100/0
3	$Mg(ClO_4)_2$[d]	neat	40	6	99	100/0
4	$Al(ClO_4)_3 \cdot 9H_2O$	CH_2Cl_2	40	22	77	100/0
5	$Al(ClO_4)_3 \cdot 9H_2O$	neat	25	67	73	100/0
6	$Sc(OTf)_3$	CH_2Cl_2	25	5.5	79	100/0
7	$Sc(OTf)_3$	neat	25	3.5	86	100/0

[a] Determined by NMR. Times refer to the disappearance of Boc_2O in the reaction mixture. [c] Data from ref 1. [d] 3.5 equiv of **2** is used.

being equal, the reaction proceeded in comparable rate and yields as in dichloromethane, but solvent removal was more difficult because of their higher boiling points. If the solubility was lower, the reaction rate slowed down. In more polar solvents, such as diethyl ether and THF, conversions generally decreased, although the catalyst solubility increased. When the catalyst was soluble in the mixture and its viscosity was not too high, neat conditions gave better or similar results. As a consequence, the best choice appeared to be dichloromethane or neat conditions.

Then we evaluated the influence of decreasing temperature on product distribution especially to depress the thermal acid-catalyzed decomposition of Boc_2O (Table 2). Reactions were carried out at 40 and 25 °C in a thermostatic bath in neat or in dichloromethane solutions. Results reported in Table 2 showed that a temperature decrease did not significantly influence either conversion into ether **3a** or Boc_2O decomposition. In fact, the reaction never went to completion before complete decomposition of the excess of Boc_2O and times reported in Table 2 refer to its disappearance.

To increase yields up to almost quantitative, we had to increase the excess of Boc_2O up to 3.5 equiv (Table 2, entry 8).

Secondary and Tertiary Aliphatic Alcohols. The reaction of 2-octanol (**1b**) was tested as representative of a secondary alcohol under the reported experimental conditions (Table 3). The observed trend was almost superimposable with that of 1-octanol, with the only difference that the reaction time was generally longer and conversion was lower.[1]

Once more, an increase of Boc_2O up to 3.5 equiv allowed an almost quantitative yield to be reached after 6 h under neat conditions (Table 3, entry 3).

Finally, tertiary alcohols failed to give the desired ether and only starting material was recovered after prolonged reaction times.[1] Only 1-adamantol (**1c**) led to a 17% yield of the corresponding adamantyl *tert*-butyl ether (**3c**) after 22 h refluxing in dichloromethane.

Phenols. The reaction of Boc_2O with phenol (**1d**) was then examined. A screening among various Lewis acids allowed concluding that also in this case $Mg(ClO_4)_2$, $Al(ClO_4)_3$, and $Sc(OTf)_3$ are the most efficient catalysts for the *tert*-butoxybenzene (**3d**) synthesis.

Conversely from aliphatic alcohols, the reaction appeared to be more complex. In fact, we found that prolonged reaction times decreased yields in **3d** and ring-alkylated products started to be detected among the reaction products under $Al(ClO_4)_3$ and $Mg(ClO_4)_2$ catalysis. On the other hand, the $Sc(OTf)_3$-catalyzed reaction did not show any variation in yields even after 17 h.

To understand this anomaly, reactions were performed in a NMR tube and monitored at 20 °C. (Figure 1). Since CO_2 and isobutene gases are evolved, the NMR tube was not sealed. The $Al(ClO_4)_3$ amount was increased to a 20% mol amount, to complete the reaction in conveniently short times. However, solvent evaporation could not be avoided in such an extent to allow the consequent concentration variation to be neglected. Under these conditions, a rigorous rate law could not be deduced. Nevertheless, some interesting considerations on the reaction course can be obtained.

The profile of the $Sc(OTf)_3$-catalyzed reaction (Figure 1a) shows, as expected, an increase of product amount within about 3 h and then a plateau at about 89% of conversion. At the same time Boc_2O amount decreases to zero and *tert*-BuOH amount increases until about 2.3 equiv. Also isobutene was detected among the reaction products, but its amount could not be measured, since it rapidly moved away from the mixture.

Some interesting differences can be observed for the $Al(ClO_4)_3$-catalyzed reaction (Figure 1b). First, a rate enhancement is observed only when some *tert*-butanol is formed (about 1.3 equiv, after 100 min). It acts as the solvent for the catalyst,

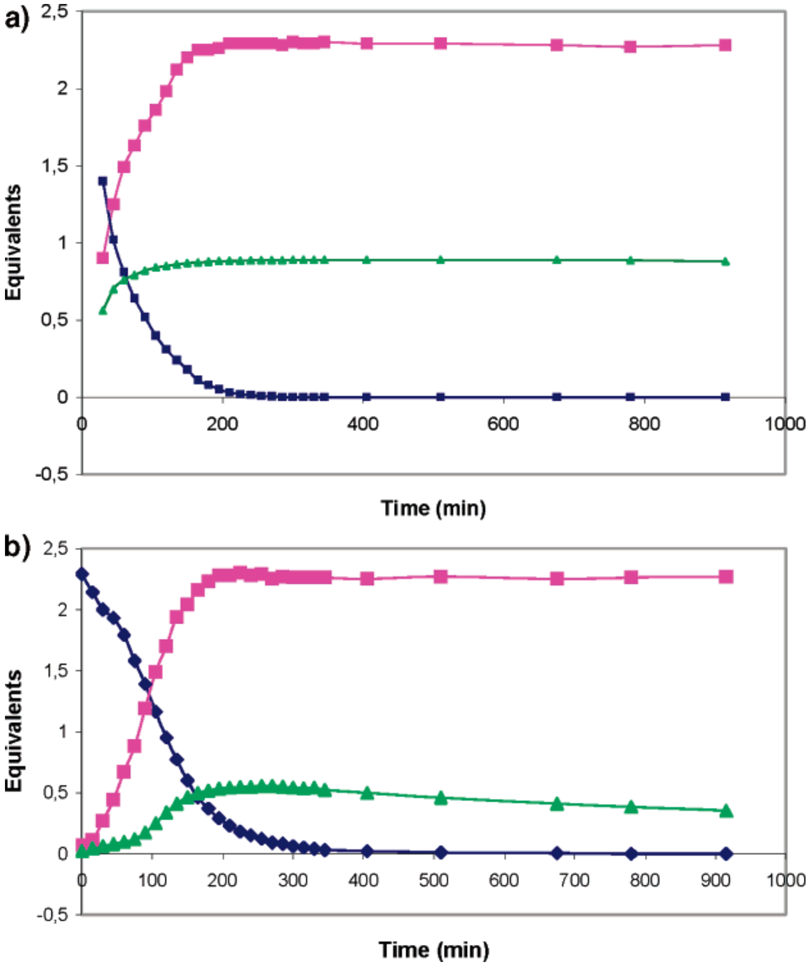


FIGURE 1. Profiles of *tert*-butoxybenzene (**3d**, green), *tert*-butanol (**6**, magenta), and Boc$_2$O (**2**, blue) amounts in the reaction of phenol (**1d**) with **2** in the presence of Sc(OTf)$_3$ (5% mol) (a) or Al(ClO$_4$)$_3$ (20% mol) (b) at 20 °C in CDCl$_3$.

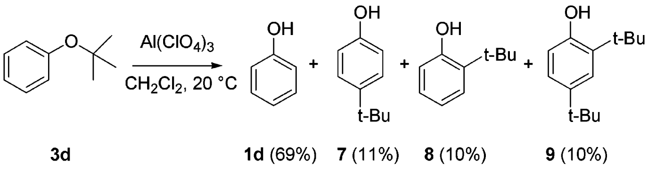
which is not completely dissolved in the reaction mixture at the beginning of the reaction, thus confirming that the reaction rate is favorably influenced by homogeneous catalysis. In fact, when we carried out an experiment using a dichloromethane/*tert*-butanol (6/1) mixture, in which Al(ClO$_4$)$_3$ is completely dissolved, we observed an increase in reaction rate (3 h versus 4.5 h to reach the maximum yield).

tert-Butoxybenzene (**3d**) increases as long as Boc$_2$O is present into the reaction mixture. The top is reached after 4.5 h (55%), when 0.1 equiv of **2** is still present. Then the amount of **3d** starts to slowly decrease and the formation of ring-alkylated phenols is observed. The appearance of ring-alkylated products only after **2** disappearance in the reaction mixture means that, conversely from **3a**, **3d** is cleaved by the Lewis acid.[5]

Then, we allowed **3d** to stand at room temperature for 24 h in the presence of 20% Al(ClO$_4$)$_3$ and actually we recovered phenol (69%) and *tert*-butylphenols (31%) (Scheme 3).

Mg(ClO$_4$)$_2$ itself is able to decompose pure *tert*-butoxybenzene (**3d**) when refluxed in dichloromethane for 5 h, giving unaffected **3d** (16%), **1d** (79%), **7** (1%), and **8** (4%). Nevertheless, the synthesis of **3d** catalyzed by Mg(ClO$_4$)$_2$ was already reported in our preliminary communication and the product was recovered in 90% yields, when the reaction was carried out for 13 h, in refluxing dichloromethane, in the presence of 2.3 equiv of Boc$_2$O/mol of **1d**.[1]

SCHEME 3. Product Distribution after Decomposition of Ether 3d

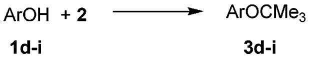


These results evidence that ether decomposition starts only when insignificant amounts of Boc$_2$O are present in the reaction mixture, very likely because it strongly chelates the Lewis acid. Therefore, the acid is not available for O-*tert*-Bu cleavage. Only at the end of the reaction, some metal ions are free to coordinate to the ether oxygen causing the cleavage of the ethereal bond of **3d**.

Finally, we wanted to compare the previous reported conditions [i.e. Mg(ClO$_4$)$_2$ (10% mol), 40 °C][1] with the best conditions set now [i.e. Sc(OTf)$_3$ (5% mol) at room temperature] in reactions of Boc$_2$O with some more phenols (Table 4). Sc(OTf)$_3$ appeared to be generally more effective.

In some cases, Boc$_2$O amount was raised to 3.5 equiv to overcome the lack of reactant due to self-decomposition. However, electron-withdrawing substituents slowed down ether formation rate, so Boc$_2$O self-decomposition occurred at a comparable rate and an increase of its amount did not result in

TABLE 4. Comparison between $Mg(ClO_4)_2$ and $Sc(OTf)_3$ Catalysis in the Reaction between Phenols (1d−i) and Boc_2O (2) [(d) Ar = Ph, (e) Ar = 4-OMePh, (f) Ar = 3-ClPh, (g) Ar = 4-NO_2Ph, (h) Ar = 4-CHOPh, (i) Ar = 1-Naphthyl]



$$\underset{\mathbf{1d\text{-}i}}{ArOH} + \mathbf{2} \longrightarrow \underset{\mathbf{3d\text{-}i}}{ArOCMe_3}$$

entry	substrate	catal	solvent	**2** (equiv)	T (°C)	t (h)[a]	yield (%)
1	**1d**	$Mg(ClO_4)_2$ (10% mol)	CH_2Cl_2	2.3	40	13	90 (**3d**)[b]
2	**1d**	$Mg(ClO_4)_2$ (10% mol)	Neat	2.3	40	21	93 (**3d**)[b]
3	**1d**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	84 (**3d**)
4	**1e**	$Mg(ClO_4)_2$ (10% mol)	Neat	2.3	40	24	84 (**3e**)[b]
5	**1e**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	87 (**3e**)
6	**1e**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	3.5	20	16	94 (**3e**)
7	**1f**	$Mg(ClO_4)_2$ (10% mol)	Neat	2.3	40	32	82 (**3f**)[b]
8	**1f**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	72 (**3f**)
9	**1f**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	3.5	20	23	82 (**3f**)
10	**1g**	$Mg(ClO_4)_2$ (10% mol)	Neat	2.3	40	32	30 (**3g**)
11	**1g**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	35 (**3g**)
12	**1h**	$Mg(ClO_4)_2$ (10% mol)	CH_2Cl_2	2.3	40	13	30 (**3h**)
13	**1h**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	48 (**3h**)
14	**1h**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	3.5	20	18	48 (**3h**)
15	**1i**	$Mg(ClO_4)_2$ (10% mol)	CH_2Cl_2	2.3	40	54	65 (**3i**)[b]
16	**1i**	$Sc(OTf)_3$ (5% mol)	CH_2Cl_2	2.3	20	5	65 (**3i**)

[a] Times refer to the disappearance of Boc_2O in the reaction mixture. [b] Data from ref 1.

a yield improvement. In these cases, the cheapest practice becomes the use of only a low excess of Boc_2O, followed by separation of ether from the unreacted starting alcohol, a very easy process, and finally alcohol can be recycled.

Discussion

Influence of the Lewis Acid on the Product Distribution. From data reported in Table 1, we noticed a good correlation between the reaction rate and the pK_h (hydrolysis constant)[6] of the metal ion in both perchlorate and triflate series, although the reactions were carried out in a nonpolar solvent such as dichloromethane. The lower the pK_h, the faster is the reaction. In the alkaline-earth element series, for example, reactivity follows the order Mg ($pK_h = 11.44$) > Ca ($pK_h = 12.85$) > Ba ($pK_h = 13.47$) (Table 1, entries 6, 7, 9). The trivalent aluminum ($pK_h = 4.97$) should be much more reactive and, in fact, gave the highest conversion (89%) in the least time (Table 1, entry 1).

The efficiency of triflates is lower than that of perchlorates, and the reaction is less selective toward ether **3a** formation, as shown by the comparison between perchlorates and triflates of Al, Ce, Zn, and Mg (Table 1, entries 1/13, 2/14, 3/15, and 5/16, respectively). The higher efficiency of the metal ion of perchlorate vs triflate to act as Lewis acid has been already observed in the acetylation of alcohols[7] and in the Fischer esterification.[8]

In conclusion, the nature of the metal ion only influences the reaction rate but not the product distribution.

On the other hand, the influence of the anion in product distribution was clearly observed. In fact, with increase of the nucleophilicity of the anion, the yield of carbonate **4a** increased despite formation of **3a**. The role of the counterion can be explained in term of HSAB theory.[9] In this theory, hardness and softness of anions are generally correlated to their nucleophilicity or to their capability to delocalize the negative charge. Perchlorate is a very stable anion; in other words it can be classified as “soft”. On the other hand, bivalent and trivalent metal cations are generally considered “hard”. As a consequence, they do not match with perchlorate anion to form a tight ion pair.

Triflates are a little more nucleophilic than perchlorates, since the nucleophilicity of an anion is related both to the electronegativity of the core atom (sulfur instead of chlorine) and to the number of oxygen atoms involved in the delocalized system (three instead of four).[10] As a consequence triflates mostly give ether **3a**, but significant amounts of carbonate **4a** are also recovered. For the same reasons, nitrate ion is harder and, in fact, yields of **4a** are increased (Table 1, entry 22).

Halide anions give a mixture between ether **3a** and carbonate **4a**, since they are still harder. Finally, a highly nucleophilic anion such as acetate leads to the exclusive formation of carbonate **4**. This trend has been observed into a series of both zinc (Table 1, entries 3, 15, 17, 18, 19, 26, 27) and magnesium salts (Table 1, entries 6, 16, 21, 22, 23). Moreover, other metal halides or $Ti(OPr)_4$, a highly nucleophilic anion, confirm our statement.

In conclusion, dissociated salts gave *tert*-butyl ethers, whereas intimate ion pairs led to Boc alcohols.

Reaction Mechanism. The synthesis of ethers is peculiar to Boc_2O, which has a characteristic decomposition (Scheme 4).[4] Other dicarbonates, which follow different decomposition pathways[4a] or do not decompose at all, are unable to give the same reaction. Therefore, a mechanism involving an interaction between some electrophilic species arising from Boc_2O self-decomposition and alcohol (**1**) appeared to be a reasonable hypothesis.

Actually Boc_2O self-decomposition is supposed to occur by initial scission of an internal carbonyl oxygen bond and subsequent loss of carbon dioxide followed by proton abstraction and decarboxylation again (Scheme 4, path a)[9a] or alternatively by formation of the *tert*-butyl cation (path c), which decomposes

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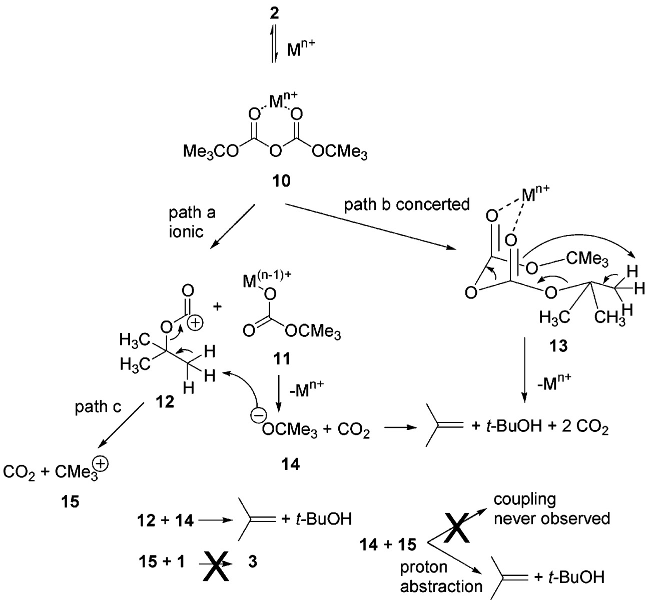
(7) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, 4611−4617.

(8) Bartoli, G.; Boeglin, J.; Bosco, M.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2005**, *347*, 33−38.

(9) (a) Hati, S.; Datta D. *J. Chem. Soc., Dalton Trans.* **1994**, 2177−2180. (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539.

(10) Wulfsberg G. *Principles of descriptive inorganic chemistry*; Wadsworth: Monterey, CA, 1987; Chapter 2.

SCHEME 4. Decomposition of Boc_2O from Literature Data[a]



[a] See ref 4a for paths a,c and ref 4b for path b.

to isobutene (**5**) by loss of a proton. Coupling to di-*tert*-butyl ether has been never observed.

However, a cyclic transition state was also proposed (path b).[4b]

The $Ba(ClO_4)_2$-catalyzed reaction (Table 1, entry 9) provides the first useful suggestions to exclude this hypothesis. After 7 h, the ether **3a** was recovered only in 45% yield, without extensive decomposition of the excess of **2**.

$Ba(ClO_4)_2$ and Boc_2O were allowed to react under the same experimental conditions in a blank run, in the presence of 1,4-di-*tert*-butylbenzene as the internal standard. After 7 h, the NMR signal ratio showed a decrease of Boc_2O signal within 9−10%.

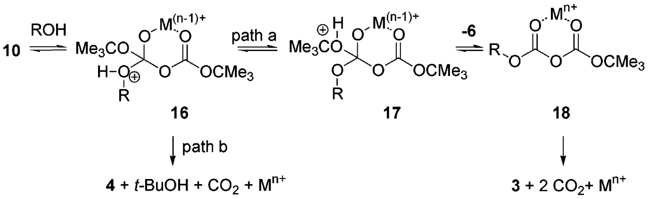
In addition, if free *tert*-butyl cations were involved in the reaction mechanism, we should observe ring-alkylated products in the reaction with aromatic systems. It is well-known, in fact, that phenols undergo electrophilic substitution at the aromatic ring in the presence of alkyl cations.[11] To corroborate this statement, we carried out an independent test, in which **2** was decomposed in the presence of $Mg(ClO_4)_2$ and anisole as the carbocation scavenger. We did not observe the formation of *tert*-butyl anisole, not even in trace amounts.[1]

Results of these trials contrast with any hypothesis of ether formation from reaction between alcohol **1** and an electrophilic *tert*-butyl species arising from Boc_2O self-decomposition and allowed us to confidently affirm that the ether synthesis and the Boc_2O self-decomposition are reactions which run independent and parallel.

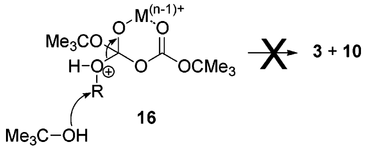
As a rationalization of the whole of the reaction, we propose the independent mechanism, depicted in Scheme 5, which involves the formation of a mixed dicarbonate. This mechanism was already hypothesized in our previous communication,[1] and it is now supported by experimental evidence.

The metal ion activates Boc_2O, forming the chelate complex **10**, already responsible of Boc_2O decomposition (Scheme 4). The solvents medium is an important factor, because solvent with potential electron donor atoms such as diethyl ether and THF can compete for the Lewis acid, so lowering the reaction rate.

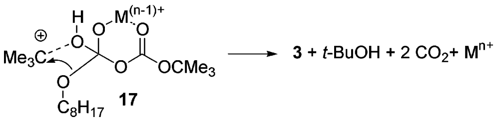
SCHEME 5. Proposed Mechanism



SCHEME 6. A Possible S_N2 Alternative Mechanism



SCHEME 7. A Possible S_N1 Alternative Mechanism



Then, **10** can undergo nucleophilic addition of the alcohol to give **16**, whose efficiency depends on the Lewis acidity of the metal ion. Among parameters used to estimate the Lewis acidity of ions, we found a good correlation with hydrolysis constants: cations with great pK_h values have small $(charge)^2/(ionic radii)$ values and by consequence low Lewis acidity,[6] so the lower pK_h, the more tightened is the chelate complex **10**.

However, dependence of the efficiency of the reaction on pK_h could suggest the generation of a Brønsted acid from the hydrolysis of the crystallization water by the metal ion.[12] However this hypothesis was easily excluded, since perchloric acid, a classical Brønsted acid, is less efficient than the best Lewis acid catalysts (Table 1, entry 10).

Phenols with electron-withdrawing substituents are worse nucleophiles, and consequently their attack onto **10** is delayed. Tertiary alcohols are unable to give this reaction, since a crowded carbonyl function like that of **10** offers steric resistance to the nucleophile approaching. As a consequence, we never observed formation of di-*tert*-butyl ether from reaction of the byproduct *tert*-butanol and Boc_2O.[1] Only 1-adamantol, less hindered than other tertiary alcohols owing to its shape, gave partial attack.

Then ether **3** could be originated together with activated Boc_2O (**10**), by the intervention of adventitious *tert*-butanol from Boc_2O self-decomposition on activated alcohol **16** via a S_N2 pathway (Scheme 6). However, this option can be excluded, because aromatic substrates cannot undergo any nucleophilic substitution, but *tert*-butyl aryl ethers **3d**−**i** are obtained in high yields (Table 4).

The stability of intermediate **16** depends, in our opinion, on the complexation of the metal ion, in other words, on the measure in which the charged oxygen in **16** or the catalyst anion matches with the metal ion.

Highly nucleophilic anions such as isopropoxide and acetate do not dissociate from their metal counter part, and as a

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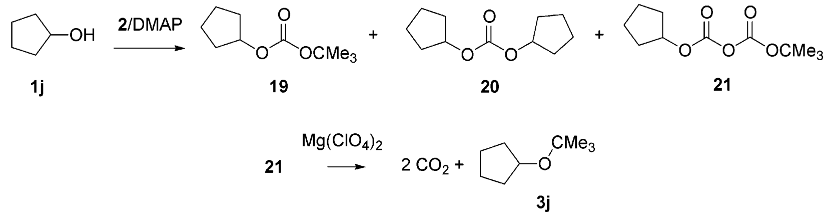
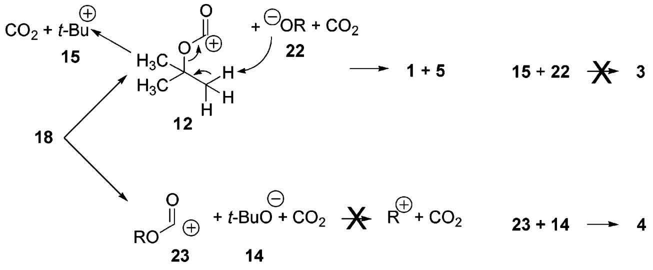
(11) Harris, T.; Campbell, C.; Tang, Y. *J. Phys. Chem. A* **2006**, *110*, 2246−2252.

(12) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.*−Eur. J. **2004**, *10*, 484−493.

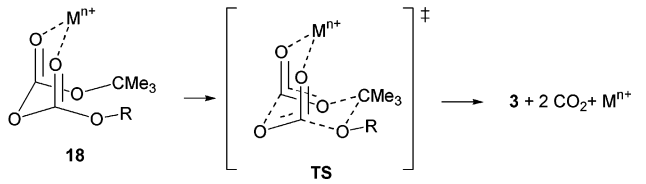
SCHEME 8. Decomposition of a Mixed Pyrocarbonate to *tert*-Butyl Ether



SCHEME 9. Possible Heterolytic Breakdowns



SCHEME 10. Decomposition of 18 through a Six-Ring Mechanism



consequence, **16** is a “naked” anion. So it is more prone to restore the carbon−oxygen double bond, so favoring elimination of the good leaving group carbonate monoester and leading to the exclusive formation of carbonate **4** (path b). Once formed under the experimental conditions, **4** is stable, so it remains unaltered and neither can be responsible for further transformations nor its formation can be involved into an equilibrium reaction, since carbon dioxide evolves from the reaction mixture.

On the other hand “naked” metal ions, such as those of perchlorates and triflates, tightly bind to the oxygen anion of **16** and allow an equilibrium between **16** and **17** to be established (path a).

Ether **3** could arise from intermediate **17**, if it acts as an intimate ion pair between a *tert*-butyl cation and a mixed dicarbonate hydrate, via an intramolecular S_N1-like attack of alcoholic oxygen on incipient *tert*-butyl cation (Scheme 7). Once more the absence of any ring addition product even in traces in the reaction of highly activated 4-methoxyphenol (**1e**) demonstrates that recombination of the two partners must be much faster than any rotation into the solvent cage, which is very unlikely in our opinion.

Then intermediate **17** is able to lose *tert*-butanol leading to the metalated mixed dicarbonate **18**.

We were unable to demonstrate the formation of mixed dicarbonates like **18** along the reaction course, by following the reaction by NMR, since we never observed signals assignable to this compound in a free region of the spectrum.

However, we could independently demonstrate that **18** decomposes to ether. In fact, following literature suggestions,[13] *tert*-butyl cyclopentyl dicarbonate (**21**) was obtained as an inseparable mixture together with *tert*-butyl cyclopentyl carbonate (**19**) and dicyclopentyl carbonate (**20**). Treating this mixture with $Mg(ClO_4)_2$ (Scheme 8), under our experimental conditions, we observed formation of ether **3j** from **21**,[14] while **19** and **20** remained unaffected.

Unfortunately, the lack of efficient syntheses, which allow significant amounts of pure mixed dicarbonate to be obtained, actually prevents us from accurately studying this pivotal decomposition stage. Therefore, every mechanistic hypothesis could appear speculative. Nevertheless, some hypotheses are very unlike on the basis of both the present results and literature data.

Homolytic breakdowns, for example, can be ruled out because it has been demonstrated that coupling of phenoxy and *tert*-butyl radicals leads to ring-alkylated products even if it occurs inside the solvent cage.[15]

A heterolytic breakdown like that supposed in Boc_2O decomposition (Scheme 4, path a) has to occur leading to cation **12** and alcoholate **22** (Scheme 9), but according to Tarbell’s mechanistic hypothesis,[4a] large amounts of isobutene should arise by proton abstraction of alcoholate on **12**. Although isobutene amount cannot be measured, since it evolves rapidly from the mixture, such a mechanism should lead to large amounts of unreacted alcohol, but we had demonstrated that starting materials are completely consumed if a large excess of Boc_2O is used.

Alternatively, we can suppose that **12** decomposes to *tert*-butyl cation (**15**) before interacting with the alcoholate. However, in aromatic systems under homogeneous catalysis, ionic mechanisms lead to mixtures of C- and O-alkylated products.[16] In the $Sc(OTf)_3$-catalyzed reaction we never observed ring-alkylated products, while in the case of $Al(ClO_4)_3$ they are evidently formed by decomposition of **1d**. Therefore, coupling of **15** with **1** or its salt **22** can be excluded.

The opposite breakdown, which can give the cationic species **23** and *tert*-butylate (**14**), can be also ruled out. In fact, Tarbell affirmed that these cations are unable to give alkyl cations, but they couple with alcoholate to give carbonate.[4a] Adamantyl dicarbonate itself decomposes to carbonate,[4a] but we never observed *tert*-butyl adamantyl carbonate among the reaction products, so indicating that such a breakdown cannot happen in our system.

The most conceivable hypothesis remains that the decomposition of **18** occurs through a synchronous mechanism in a “six-

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(13) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368−6380.

(14) Decomposition of **20** is fast, as expected, since asymmetric dicarbonates must be much more reactive than the symmetric ones, as already demonstrated by the $Ba(ClO_4)_2$-catalyzed reaction, where ether formation (from decomposition of asymmetric dicarbonate) largely overwhelms Boc_2O (a symmetric dicarbonate) decomposition.

(15) Galindo, F.; Miranda, M. A.; Tormos, R. *J. Photochem. Photobiol., A* **1998**, *117*, 17−19.

(16) Wilson, K.; Adams, D. J.; Rothenberg, G.; Clark, J. H. *J. Mol. Catal., A* **2000**, *159*, 309−314.

ring" transition state (**TS,** Scheme 10) according to the alternative hypothesis of Boc_2O decomposition (Scheme 4, path b).[4b]

The substantial independence from temperature of the reaction supports the idea of a concerted mechanism. Moreover, recent DFT calculation on the alkylation of phenols demonstrated that *tert*-butyl phenyl ether arises from a neutral six-ring concerted mechanism even under acidic conditions, while C-alkylated products arise from the ionic rearrangement of the early formed ether.[11]

Conclusions

The study of the reaction between alcohols and *tert*-butyl dicarbonate allowed optimizing the choice of the catalyst for addressing the reaction toward *tert*-butyl ethers or Boc-protected alcohols. We found that the metal ion of the catalyst influences only the reaction rate, while product distribution is tuned by counterions. Perchlorates and triflates, anions with highly delocalized negative charge, give prevalent or exclusive ether formation. On the other hand, Boc alcohols are the main or exclusive products with undelocalized isopropoxide or low-delocalized acetate ions.

The results of this study allowed concluding that, to obtain *tert*-butyl ethers, the reaction course must be addressed to the formation of a mixed dicarbonate intermediate, which very likely decomposes through a concerted mechanism.

$Mg(ClO_4)_2$ represents the best compromise between costs and efficiency of the reaction in aliphatic systems. $Al(ClO_4)_3$, which is a little more expensive and efficient, can be used if low temperatures are necessary. We discarded the use of $Sc(OTf)_3$ from an economical point of view, because it did not significantly improve the reaction efficiency and its cost is 100 times higher than that of perchlorates. With a large excess of Boc_2O, the reaction is almost quantitative in the aliphatic series.

Finally, both $Mg(ClO_4)_2$ and $Sc(OTf)_3$ behave as comparably efficient catalysts in the synthesis of aromatic *tert*-butyl ethers. The former Lewis acid is cheaper, but the reaction course must be carefully followed, since prolonged reaction times cause decomposition of the product. On the other hand, the more expensive $Sc(OTf)_3$ offers both warranty that no decomposition of the product occurs and chance of low reaction temperatures, which allows survival of sensitive functions. Overall yields are not very different for both Lewis acids; therefore, the choice can be made at each time.

Experimental Section

General Methods. The ^1H NMR spectra were recorded at 400 MHz or 600 MHz, while ^{13}C NMR spectra were recorded at 100 MHz. Purification of reaction products was carried out by flash chromatography on silica gel (230−400 mesh). Commercial grade reagents and solvents were used without further purification. All starting alcohols, salts, and Boc_2O were purchased and used as received. All reaction products were already fully characterized previously.[1]

General Procedure for the Reactions of Table 1. In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, Lewis acid (0.10 mmol) and **1a** (1.0 mmol) were dissolved in 1.5 mL of solvent. Then **2** (2.3 mmol) was added and a bubbling was immediately observed. The mixture was stirred at reflux until the TLC analysis revealed the presence of Boc_2O or, anyway, for 7 h. The crude reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. The crude mixture was then submitted to ^1H-NMR analysis, and relative amounts of remaining **1a** and **2** or products **3a** and **4a** were determined by integration of signals at $\delta = 3.61$ (CH_2O of **1a**), 1.53 (Me_3C of **2**), 3.31 (CH_2O of **3a**), or 4.05 (CH_2O of **4a**).

Temperature Tests. In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, Lewis acid (0.10 mmol) and **1a** (1.0 mmol) were dissolved in 1.5 mL of CH_2Cl_2 or mixed together. Then **2** (2.3 mmol) was added. The mixture was stirred at 40 or at 25 °C with a thermostatic bath until the TLC analysis revealed the presence of Boc_2O. The crude reaction mixture was worked up as usually and was then submitted to ^1H-NMR analysis. Relative amounts of remaining **1a** and products **3a** and **4a** were determined by integration of signals at $\delta = 3.61$ (CH_2O of **1a**), 3.31 (CH_2O of **3a**), or 4.05 (CH_2O of **4a**).

Reaction of 1b,c and 2. In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, $Mg(ClO_4)_2$ (0.10 mmol) and **1b,c** (1.0 mmol) were dissolved in 1.5 mL of CH_2Cl_2. Then **2** (3.5 mmol) was added. The mixture was stirred at reflux until the TLC analysis revealed the presence of **2**. The crude reaction mixture was worked up as usually and then submitted to ^1H-NMR analysis; relative amounts of **1b** (23%) and **3b** (77%) were estimated. The crude mixture from reaction of **1c** was worked up as usual and filtered on a short silica gel column with recovery of **3c** (17% yield and 99% purity) and **1c** (82% yield and 99% purity). **3c** was submitted to ^1H-NMR analysis, which gave a spectrum superimposable to that of literature data.[17]

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, $Mg(ClO_4)_2$ (0.10 mmol) and **1b** (1.0 mmol) were mixed together. Then **2** (3.5 mmol) was added. The mixture was stirred at 40 °C in a thermostatic bath until the TLC analysis revealed the presence of **2** (6 h). The crude reaction mixture was worked up as usually and filtered on a short silica gel column, and recovered **3b** (99% yield and purity) was submitted to ^1H-NMR analysis, which gave a spectrum superimposable on that for the literature data.[1]

General Procedure for the Synthesis of Aromatic *tert*-Butyl Ethers. All the reactions were carried out in CH_2Cl_2 or without solvent. In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, $Mg(ClO_4)_2$ (0.10 mmol) or $Sc(OTf)_3$ (0.05 mol) and the alcohol **1d−i** (1.0 mmol) were dissolved in 1.5 mL of CH_2Cl_2. Then **2** (2.3 mmol, or 3.5 mmol) was added, and a bubbling was immediately observed. The mixture was stirred at reflux until the TLC analysis revealed the presence of **2**. The crude reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. The *tert*-butyl ethers were separated from the residual alcohol by flash chromatography on silica gel with a mixture of 9:1 petroleum ether/Et_2O. ^1H-NMR analysis gave a spectrum superimposable on that for the literature data.[1]

When the reaction was carried out without solvent, the alcohol and the catalyst were mixed together; then **2** was added, and the mixture was heated at 40 °C until the TLC analysis revealed the presence of **2**.

The reactions with $Sc(OTf)_3$ were carried out as above-described but at 20 °C in a thermostatic bath.

Kinetic Experiment. 1d (0.32 mmol) and $Al(ClO_4)_3$ or $Sc(OTf)_3$ (0.06 mmol) were dissolved in 0.6 mL of $CDCl_3$ and submitted to ^1H-NMR analysis at 600 MHz. After the instrument was set, **2** (0.73 mmol) was added. A spectrum was recorded immediately after and then every 15 min during 6 h. Then spectra were recorded after 7, 9, 11, 13, and 15 h. Amounts of **3d**, **6**, and **2** were measured by integration of signals at $\delta = 1.35$ (CMe_3 of **3d**), 1.23 (CMe_3 of **6**), and 1.53 (CMe_3 of **2**) with respect to the whole aromatic part of the spectrum and related to starting ratio. Among the signals recorded during these experiments, we never observed peaks assignable to mixed pyrocarbonate in a free region of the spectrum.

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[17] Miller, J. B.; Salvador, J. R. *J. Org. Chem.* **2002**, *67*, 435−442.

On the other hand, signals assignable to **5** [$\delta = 1.82$ (Me), 4.75 (CH_2═)] were detected but they were impossible to be quantified.

1d (0.32 mmol) and $Al(ClO_4)_3$ (0.06 mmol) were dissolved in 0.6 mL of $CDCl_3$ and 0.1 mL of *tert*-butanol. The mixture became clear, and **2** (0.73 mmol) was added. A spectrum was recorded immediately after and then every 15 min. In the first time of the reaction (within 2 h), the kinetic profile was very similar to that of $Sc(OTf)_3$.

Ether Decomposition Experiments. In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, ether **3a** (0.5 mmol) was dissolved in 1 mL of dichloromethane and $Mg(ClO_4)_2$ or (0.05 mol) was added. The mixture was stirred at 40 °C in a thermostatic bath for 5 h. The crude reaction mixture was worked up as usually and submitted to ^{1}H-NMR analysis. Signal at $\delta = 3.61$ (CH_2O of **1a**) was less than 3% with respect to that at $\delta = 3.31$ (CH_2O of **3a**).

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, ether **3d** (0.5 mmol) was dissolved in 1 mL of dichloromethane and $Al(ClO_4)_3$ (0.1 mmol) was added. The mixture was stirred at room temperature for 24 h. The crude reaction mixture was worked up as usually and submitted to ^{1}H-NMR analysis. The crude reaction mixture was worked up as usually and submitted to ^{1}H-NMR analysis. The following product ratio was obtained using the whole aromatic region as standard (5H): **1d** [69% based on multiplet at 6.8−6.9 (3H)]; **7** [11% based on singlet at 1.28 (9H)]; **8** [10% based on singlet at 1.41 (9H)]; **9** [10% based on singlets at 1.30 and 1.42 (9H)].

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, ether **3d** (0.5 mmol) was dissolved in 1 mL of dichloromethane and $Mg(ClO_4)_2$ (0.05 mmol) was added. The mixture was stirred at 40 °C in a thermostatic bath for 5 h. The crude reaction mixture was worked up as usually and submitted to ^{1}H-NMR analysis. The following product ratio was obtained using the whole aromatic region as standard (5H): **1d** [79% based on multiplet at 6.8−6.9 (3H)]; **3d** [16% based on singlet at 1.35 (9H)]; **7** [1% based on singlet at 1.28 (9H)]; **8** [4% based on singlet at 1.41 (9H)].

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, ether **3d** (0.5 mmol) was dissolved in 1 mL of dichloromethane and $Sc(OTf)_3$ (0.05 mmol) was added. The mixture was stirred at 40 °C in a thermostatic bath for 5 h. The crude reaction mixture was worked up as usually and submitted to ^{1}H-NMR analysis. A multiplet at 6.8−6.9 typical of **3d** was less than 5% with respect to singlet at 1.35 (CMe_3 of **3d**). No other signals were observed.

Decomposition Test of 2. 2 (0.5 mmol) and 1,4-di-*tert*-butylbenzene (0.5 mmol) were dissolved in 0.6 mL of CD_2Cl_2 and submitted to ^{1}H-NMR. The solution was poured into a two-necked flask equipped with a magnetic stirring bar and a condenser coil containing $Ba(ClO_4)_2$ (0.022 mmol). The mixture was stirred at reflux for 7 h and then resubmitted to ^{1}H-NMR. The intensity of signal at $\delta = 1.53$ decreased of about 9−10%.

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, $Mg(ClO_4)_2$ (0.043 mmol) and anisole (1 mmol) were dissolved in 1 mL of CH_2Cl_2. **2** (1 mmol) was added. The mixture was stirred at reflux until the TLC analysis revealed the presence of Boc_2O and then after usual workup submitted to ^{1}H-NMR. Neither significant modification of the aromatic part of the spectrum nor signals assignable to *o*- and *p*-*tert*-butyl frameworks were observed.

Reaction of 21. Mixed dicarbonate **21** was prepared according to the reported procedure[11] from **1j** and **2** in the presence of DMAP. The crude mixture of mixed dicarbonate (**21**), mixed carbonate (**19**), and symmetric carbonate (**20**) was dissolved in 1.5 mL of CH_2Cl_2, and then $Mg(ClO_4)_2$ (0.1 mmol/mmol of **21**) was added and the mixture was stirred at room temperature. After 18 h (instead of 30 h required by the direct reaction of **1j** and **2**),[1] **21** disappeared and the crude reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. The crude mixture was then submitted to ^{1}H-NMR analysis, which revealed the presence of **3j** together with unreacted mixed carbonate and symmetric carbonate.

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