Fast Addition of s-Block Organometallic Reagents to CO_2-Derived Cyclic Carbonates at Room Temperature, Under Air, and in 2-Methyltetrahydrofuran

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In memory of Prof. Victor Snieckus, a leading authority in organolithium chemistry and directed ortho-metalation reactions.

Fast addition of highly polar organometallic reagents (RMgX/RLi) to cyclic carbonates (derived from CO_2 as a sustainable C1 synthon) has been studied in 2-methyltetrahydrofuran as a green reaction medium or in the absence of external volatile organic solvents, at room temperature, and in the presence of air/moisture. These reaction conditions are generally forbidden with these highly reactive main-group organometallic compounds. The correct stoichiometry and nature of the polar organometallic alkylating or arylating reagent allows straightforward synthesis of: highly substituted tertiary alcohols, β-hydroxy esters, or symmetric ketones, working always under air and at room temperature. Finally, an unprecedented one-pot/two-step hybrid protocol is developed through combination of an Al-catalyzed cycloaddition of CO_2 and propylene oxide with the concomitant fast addition of RLi reagents to the in situ and transiently formed cyclic carbonate, thus allowing indirect conversion of CO_2 into the desired highly substituted tertiary alcohols without need for isolation or purification of any reaction intermediates.

Introduction

Polar organometallic chemistry and, in particular, the chemistry of compounds derived from s-block elements (typically organolithium and organomagnesium reagents), constitutes one of the most commonly used instruments within the synthetic organic chemist's toolbox.[1] In this sense, it is estimated that 95% of drugs manufactured in the pharmaceutical industry use organolithium/Grignard reagents at least in one step of their synthesis.[2] Nevertheless, to try to minimize the undesired decomposition of these highly reactive chemicals and also to be able to control the chemoselectivity of these polar reagents, this s-block organometallic chemistry has been traditionally employed under inert atmosphere, using rigorously dry aprotic organic solvents, and at low temperatures (0 to −78 °C).[1] However, the synthetic work of various research groups worldwide has revealed the possibility to promote organic transformations that involve the use of these polar organometallics in unconventional solvents (like water or traditional ionic liquids).[3] Bearing this idea in mind, and trying to build new bridges between green chemistry[4] and s-block polar organometallic reagents, some of us recently reported the possibility to generate new C–C bonds [through the fast and chemoselective nucleophilic addition of organolithium (RLi) or organomagnesium (RMgX) reagents to different unsaturated organic electrophiles, such as ketones or esters,[5] imines or nitriles,[6] and alkenes[7]]; or C–P bonds [by selective addition of lithium phosphides ($LiPR_2$) to aldehydes or epoxides],[8] working in all cases at room temperature and in the absence of protecting atmospheres, by using biorenewable deep eutectic solvents (*DESs*) based on choline chloride, water, or glycerol as sustainable reaction media.[9,10]

Simultaneously, a huge amount of effort has been dedicated worldwide to try to convert CO_2 (an inexpensive, nontoxic and sustainable C1 feedstock) into value-added chemical products, and therefore this area is becoming nowadays a rapidly growing research field for the scientific community.[11] Although being chemically attractive, the inherent thermodynamic and kinetic stability of carbon dioxide is the major impediment for its direct incorporation into organic frameworks.[12] Meanwhile, the reaction between epoxides and carbon dioxide has been developed into a successful carbon dioxide utilization process,[13] producing cyclic carbonates which

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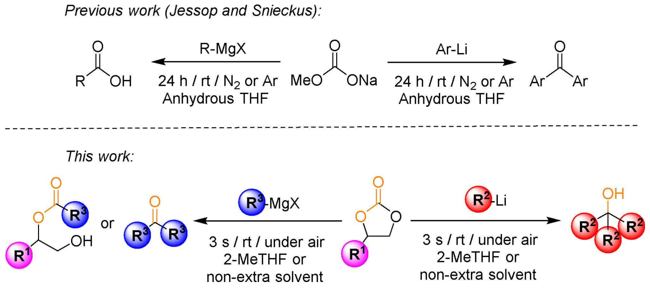


Scheme 1. Fast addition of polar s-block organometallic reagents (RLi/RMgX) to cyclic carbonates at room temperature, under air, and in 2-MeTHF as solvent or in the absence of external *VOC* solvents.

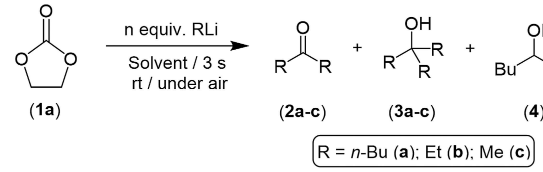
have found application in a myriad of different chemical fields, ranging from lithium-ion batteries or polymer chemistry to lubricants or solvents in industrials processes.[14] Moreover, and as these heterocyclic moieties present a more accessible carbon atom coming from CO_2 than the free molecule, they have been used in the synthesis of a variety of chemical products like methanol,[15] carbamates,[16] different heterocyclic compounds[17] or ionic liquids,[18] among others. Thus, all these encouraging features clearly illustrate that cyclic carbonates are attractive alternatives to the direct use of carbon dioxide as a C1 building block. Therefore, taking into account our aforementioned studies on the fast and chemoselective addition of RMgX/RLi reagents to carbonyl compounds at room temperature and in the presence of air,[5–8] as well as the earlier elegant and illuminating method described by the research groups of Jessop and Snieckus for the conversion of other C1 feedstocks, such as sodium methyl carbonate, into carboxylic acids or ketones through direct addition of RMgX/RLi reagents, with dry organic solvents, under protecting atmosphere, and after 24 h of reaction,[19] we decided to study the use of cyclic carbonates (a CO_2-derived sustainable feedstock) as biorenewable electrophiles capable of suffering the fast addition of RMgX/RLi reagents, at room temperature, under air and using 2-methyltetrahydrofuran (2-MeTHF) as a sustainable solvent or in the absence of external *VOC* solvents (we employed a stock solution of commercially available RLi/RMgX reagents containing various *VOC* solvents; Scheme 1). 2-MeTHF is considered a biorenewable biomass-derived solvent as it can be produced from furfural without the need of petrochemical protocols.[20] Moreover, the intrinsic immiscibility of 2-MeTHF with water allows its direct use in liquid-liquid extractions, preventing the employment of other toxic and nonbiorenewable volatile organic solvents, such as CH_2Cl_2, for extracting the desired organic reaction products.[21] In this sense, a variety of s-block promoted organic transformations have been reported using 2-MeTHF as an alternative and sustainable solvent.[22] Recently, and in line with these studies, some of us (in collaboration with Hevia's group) reported the use of lithium amides in 2-MeTHF for both the fast amidation of esters[23a] and the hydroamination of styrenes,[23b] working at room temperature and in the absence of protecting atmosphere.

Results and Discussion

It is well known that the carbonyl group is a very versatile functional group in organic chemistry. In that way, one of the most important reactions that carbonyl groups can be involved in is the C–C bond formation, through which gives rise to tertiary alcohols.[24,25] In this sense, one of the most powerful strategies for the synthesis of tertiary alcohols is the addition of highly polar organometallic reagents to carbonyl groups.[26] However and as previously mentioned, the employment of meticulously dry organic solvents under inert atmosphere and at low temperature is usually mandatory when those high polar organometallic species are present.[1] Moreover, this route often involves side reactions, due to the strong basicity of the organometallic reagents employed, giving rise to the enolization of the substrates. Thus, and bearing in mind our previous studies on the addition of highly polar organolithium reagents to carbonyl compounds (ketones and imines) under bench-type reaction conditions (room temperature under air) and using sustainable solvents (water or *DESs*),[5,6] we decided to further extend our approach by using in this case biorenewable and sustainable organic electrophiles like cyclic carbonates en route to highly substituted tertiary alcohols, symmetric ketones, or β-hydroxy esters.[27]

Thus, we first explored the straightforward and operationally simple addition of *n*BuLi to ethylene carbonate (**1 a**) in different sustainable solvents, at room temperature and under air. Our first attempts (Table 1, entries 1–3) employing water- or choline chloride (*ChCl*)-based eutectic mixtures (1:2 *ChCl*/urea or 1:2 *ChCl*/glycerol) were totally unsuccessful. Surprisingly, when biorenewable and undistilled 2-MeTHF (i.e., as received from commercially available sources, with air and moisture, see Experimental Section) was used as solvent and after only 3 s, the reaction took place giving rise to the formation of a mixture of three products, **2 a**, **3 a** and **4**, in different proportions depending on the equivalents of *n*BuLi added (Table 1, entries 4–9). Products **2 a** and **3 a** correspond to the double and triple addition process, respectively, whereas **4** is formed, as a side product through the in situ reduction of ketone **2 a**.[28] Remarkably, we experimentally found that the gradual increase of the number of equivalents of *n*BuLi (from 1 to 5 equivalents; Table 1, entries 4–8) correlates with a concomitant improvement of the yield of the desired tertiary alcohol **3 a** (up to 77% yield) containing the crude of the reaction only minor amounts of by-products **2 a** (7%) and **4** (2%). At this point, it is important to note that using larger excess of *n*BuLi (6 equivalents) does not improve the yield of the tertiary alcohol **3 a** (Table 1, entry 9). For completeness of this parametrization studies, we decided to investigate the possibility to run the aforementioned addition reaction in the absence of any additional solvent, this is by using directly the commercially available *n*BuLi solution (hexane) as solvent (Table 1, entries 10–15). As already observed in the reaction that employs 2-MeTHF as solvent, the yield of the desired tertiary alcohol **3 a** increases as the number of equivalents of *n*BuLi increases from 7% (1 equivalent) to 67% (5 equivalents). However, the reactions under these experimental conditions are not able to improve the previous yields and

Table 1. Fast addition of organolithium (RLi) reagents to cyclic carbonate **1a**, at room temperature, in the presence of air and in different sustainable solvents.[a]



Entry	Solvent	RLi	Yield [%][c]		
		(equiv.)[b]	**2a–c**	**3a–c**	**4**
1	H_2O	*n*BuLi (1)	–	–	–
2	*ChCl*/urea[d]	*n*BuLi (1)	–	–	–
3	*ChCl/Gly*[d]	*n*BuLi (1)	–	–	–
4	2-MeTHF	*n*BuLi (1)	1 (**2a**)	13 (**3a**)	11
5	2-MeTHF	*n*BuLi (2)	1 (**2a**)	38 (**3a**)	8
6	2-MeTHF	*n*BuLi (3)	4 (**2a**)	62 (**3a**)	3
7	2-MeTHF	*n*BuLi (4)	4 (**2a**)	62 (**3a**)	3
8	2-MeTHF	*n*BuLi (5)	7 (**2a**)	77 (**3a**)	2
9	2-MeTHF	*n*BuLi (6)	5 (**2a**)	73 (**3a**)	2
10	–	*n*BuLi (1)	1 (**2a**)	7 (**3a**)	14
11	–	*n*BuLi (2)	5 (**2a**)	36 (**3a**)	10
12	–	*n*BuLi (3)	5 (**2a**)	52 (**3a**)	6
13	–	*n*BuLi (4)	6 (**2a**)	62 (**3a**)	4
14	–	*n*BuLi (5)	5 (**2a**)	67 (**3a**)	4
15	–	*n*BuLi (6)	5 (**2a**)	65 (**3a**)	5
16	2-MeTHF	EtLi (5)	0 (**2b**)	90 (**3b**)	–
17	–	EtLi (5)	19 (**2b**)	79 (**3b**)	–
18	2-MeTHF	MeLi (5)	8 (**2c**)	67 (**3c**)	–
19	–	MeLi (5)	12(**2c**)	40 (**3c**)	–

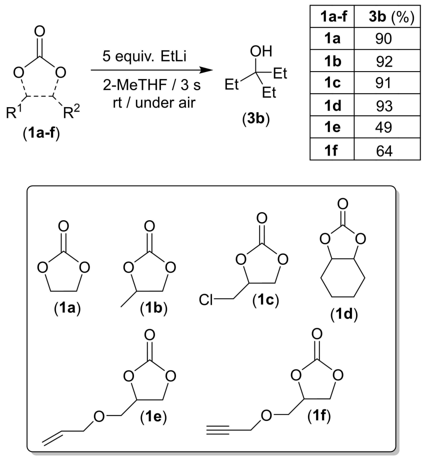
[a] General Conditions: Reactions performed under air, at room temperature, using 1 mmol of cyclic carbonate **1a** and 1–6 mmol of the polar organometallic reagent RLi in 1 mL of the desired solvent. [b] Commercial solution of *n*BuLi (2.5 M in hexanes), EtLi (0.5 M in benzene/cyclohexane) and MeLi (1.6 M in diethyl ether) were employed. [c] Yields determined by GC-FID using trimethoxybenzene as internal standard (1 mmol) after calibration (see the Supporting Information). [d] 1:2 mixture; Gly = glycerol.

selectivities obtained when 2-MeTHF was used as solvent (compare entries 4–9 with entries 10–14 in Table 1). This experimental observation could be directly related with the capability of ethereal solvents (like 2-MeTHF) to solvate the oligomeric structure of *n*BuLi, thus producing kinetically activated smaller aggregates of *n*BuLi which could then preferentially undergo three consecutive addition reactions over competing degradation processes in the presence of air and/or moisture. Thus, and when no additional ethereal solvent are employed, this kinetic activation could not take place as the commercially available *n*BuLi solution contains a non-Lewis donor solvent (hexanes). Interestingly, it is important to note that under our experimental conditions, we never observed the formation of ketone **2a** as the main product of the reaction, in contrast with the previous studies reported by Jessop and Snieckus, in which sodium methyl carbonate was employed as C1 feedstock.[19]

Next, and to expand further the scope of our study, the reactivity of carbonate **1a** with other organolithium reagents (RLi) under the optimized reaction conditions (5 equivalents, ambient temperature, under air) was also investigated by using 2-MeTHF as reaction medium or in the absence of any additional *VOC* solvent. Astonishing, in the case of EtLi and when 2-MeTHF was used as solvent, a near-quantitative yield of **3b** was observed (90%), being the unique product of the reaction, as ketone **2b** was not detected (Table 1, entry 16). As expected, when these conditions were employed, the yield of the desired tertiary alcohol **3b** decreased considerably and ketone **2b** appeared as by-product (Table 1, entry 17). A similar scenario was observed when MeLi was used as alkylating reagent (entries 18–19), obtaining better results when 2-MeTHF was employed as solvent. Finally, when 5 equivalents of the aromatic lithium reagent PhLi were employed, either in 2-MeTHF or in the absence of external solvents, none of the expected products were observed but the corresponding homo-coupling product Ph–Ph.

Trying to have a full picture of the addition of organolithium reagents to cyclic carbonates, we decided to extend our studies to the addition of EtLi to a range of cyclic carbonates (**1b**–**f**) under the best reaction conditions (5 equivalents of EtLi, room temperature, under air with 2-MeTHF as solvent; Scheme 2). As previously observed for **1a**, the almost instantaneous formation of tertiary alcohol **3b** was observed in all cases, finding better yield for purely aliphatic and saturated cyclic carbonates **1a**–**d** (Scheme 2). Replacing these saturated cyclic carbonates by the corresponding counterparts containing allylic or propargylic ethers as substituents (**1e**,**f**; Scheme 2) led to lower yields. In all cases, the formation of **3b** occurs chemoselectively with no side product (ketone **2b**) observed in the crude reaction mixture (only the unreacted cyclic carbonates **1a**–**f** were detected, respectively). These results indicate that the carbonyl carbon in **1a**–**f**, coming from the CO_2, is more accessible than in the high stable free CO_2 molecule and even more than in the acyclic carbonates (like sodium methyl carbonate).[19]

To probe the scope of our methodology in terms of the nature of the polar organometallic reagent employed and bearing in mind the previous work reported by Profs. Jessop and Snieckus in the addition of Grignard compounds to methyl carbonate,[19] we then decided to study the reactivity of cyclic carbonates (derived from CO_2 as sustainable C1 synthon) with RMgX reagents. As we mentioned previously, the employment



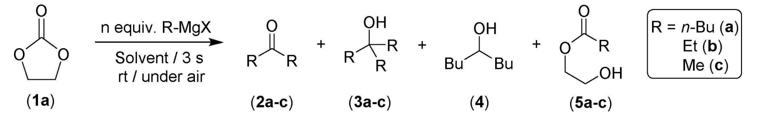
1a-f	3b (%)
1a	90
1b	92
1c	91
1d	93
1e	49
1f	64

Scheme 2. Fast addition of EtLi to cyclic carbonates **1a**–**f** at room temperature, under air, and with 2-MeTHF as solvent.

of these highly polar organometallic reagents in the presence of air and at room temperature is still a challenge due to the possible side reactions (reduction or enolization) or concomitant degradation processes in the presence of air and/or moisture.[1] Thus, we started our experimental studies by exploring the addition of *n*BuMgCl to ethylene carbonate (**1a**) in a variety of sustainable solvents, at room temperature and in the presence of air. As previously observed for RLi reagents, the employment of water or choline-chloride-based eutectic mixtures (1:2 *ChCl*/urea or 1:2 *ChCl*/*Gly*) was totally unsuccessful (Table 2, entries 1–3). However, when undistilled 2-MeTHF (i.e., as received from commercially available sources; Table 2, entry 4) or additional-solvent-free conditions (Table 2, entry 10) were employed, the reaction took place after only 3 s, giving rise a mixture of two products: the previously observed tertiary alcohol **3a** (in only 1% or 3% yield; Table 2, entries 4 and 10) and the new β-hydroxy ester **5a** (2-hydroxyethyl pentanoate) in low (19%, entry 4) to moderate (32%, entry 10) yields, as a result of the mono-addition of *n*BuMgCl to the carbonyl group.[29] In both cases, the gradual increase of the number of equivalents of *n*BuMgCl (from 1 to 5 equivalents; Table 2, entries 4–8 and 10–14) is correlated with a concomitant improvement of the yield of the desired β-hydroxy ester **5a** (up to 58% yield) but at the cost of producing two more side products, the ketone **2a** and the corresponding secondary alcohol **4**. As general pattern in both 2-MeTHF or in the absence of any other external solvents, we observed, in contrast to *n*BuLi, that at low concentration of *n*BuMgCl there is not formation of the secondary alcohol **4** (entries 4–5, 10–11), and when more equivalents of *n*BuMgCl were added, small quantities of **4** were obtained (entries 6–9, 13–15), reaching the maximum yield of 4% and 6% in 2-MeTHF and in the absence of additional solvents, respectively. Ketone **2a** appears from two equivalents and rises with the addition, whereas the tertiary alcohol **3a** was present since the very beginning of the reaction and reaches the highest proportion with 3 equivalents to subsequently decrease. Bearing in mind that the best conditions to obtain β-hydroxy ester **5a** required the use of 3 equivalents of the Grignard reagent, either in 2-MeTHF or in the absence of extra solvents, we decided to extend our studies to other organomagnesium reagents finding that neither EtMgBr or MeMgBr (Table 2, entries 16–19) could improve the previous performance observed for *n*BuMgCl.

Having identified the best condition for the mono-addition of Grignard reagents (RMgX) as follows: 3 equivalents of *n*BuMgCl, at room temperature, under air and in 2-MeTHF as solvent; we next extended our studies to the previously assayed carbonates **1a-f**. For cyclic carbonates **1a** and **1d**, and due to their intrinsic symmetry, only one ring opening product can be formed, whereas with the asymmetric cyclic carbonates (**1b,c,e,f**), two different openings of the cyclic carbonates can take place, thus giving rise to either primary (**7**, **8**, **10**, **11**) or secondary β-alcohol (**7′**, **8′**, **10′**, **11′**; Table 3). In general, these reactions gave moderated to low yields (63–16%) of the mono-addition products as mixtures with the expected ketone **2a** and the tertiary alcohol **3a**. Astonishing, for the cyclic carbonate substituted with a methyl group (**1b**), the major isomer obtained is the primary alcohol **7** (Table 3, entry 1) whereas for

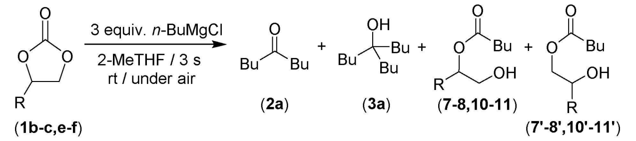
Table 2. Fast addition of Grignard reagents (RMgX) to cyclic carbonate **1a**, at room temperature, in the presence of air and in different sustainable solvents.[a]



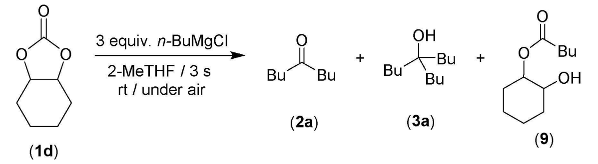
Entry	Solvent	RMgX (equiv.)[b]	Yield [%][c] **2a–c**	**3a–c**	**4**	**5a–c**
1	H_2O	*n*BuMgCl (1)	–	–	–	–
2	*ChCl*/urea	*n*BuMgCl (1)	–	–	–	–
3	*ChCl*/*Gly*	*n*BuMgCl (1)	–	–	–	–
4	2-MeTHF	*n*BuMgCl (1)	0 (**2a**)	1 (**3a**)	0	19 (**5a**)
5	2-MeTHF	*n*BuMgCl (2)	2 (**2a**)	2 (**3a**)	0	47 (**5a**)
6	2-MeTHF	*n*BuMgCl (3)	6 (**2a**)	11 (**3a**)	1	58 (**5a**)
7	2-MeTHF	*n*BuMgCl (4)	24 (**2a**)	17 (**3a**)	2	48 (**5a**)
8	2-MeTHF	*n*BuMgCl (5)	31 (**2a**)	20 (**3a**)	3	46 (**5a**)
9	2-MeTHF	*n*BuMgCl (6)	35 (**2a**)	19 (**3a**)	4	42 (**5a**)
10	–	*n*BuMgCl (1)	0 (**2a**)	3 (**3a**)	0	32 (**5a**)
11	–	*n*BuMgCl (2)	3 (**2a**)	8 (**3a**)	0	47 (**5a**)
12	–	*n*BuMgCl (3)	4 (**2a**)	10 (**3a**)	0	53 (**5a**)
13	–	*n*BuMgCl (4)	15 (**2a**)	16 (**3a**)	1	45 (**5a**)
14	–	*n*BuMgCl (5)	34 (**2a**)	18 (**3a**)	3	38 (**5a**)
15	–	*n*BuMgCl (6)	50 (**2a**)	13 (**3a**)	6	22 (**5a**)
16	2-MeTHF	EtMgBr (5)	11 (**2b**)	33 (**3b**)	–	39 (**5b**)
17	–	EtMgBr (5)	5 (**2b**)	84 (**3b**)	–	0
18	2-MeTHF	MeMgBr (5)	0 (**2c**)	74 (**3c**)	–	0
19	–	MeMgBr (5)	0(**2c**)	57 (**3c**)	–	0

[a] General Conditions: Reactions performed under air, at room temperature, using 1 mmol of cyclic carbonate **1a** and 1–6 mmol of the polar organometallic reagent RMgX in 1 mL of the desired solvent. [b] Commercial solution of *n*BuMgCl (2 M in THF), EtMgBr (1 M in THF) and MeMgBr (3 M in diethyl ether) were employed. [c] Yields determined by GC-FID using trimethoxybenzene as internal standard (1 mmol) after calibration (see the Supporting Information). [d] 1:2 mixture; Gly = glycerol.

Table 3. Fast addition of *n*BuMgCl to cyclic carbonates **1 b**–**f**, at room temperature, under air and using 2-MeTHF as solvent.[a]



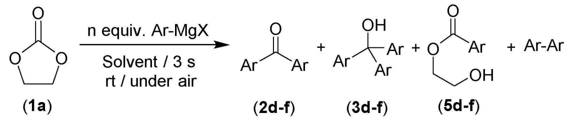
R = CH_3 (**7**); CH_2Cl (**8**); $CH_2OCH_2CH{=}CH_2$ (**10**); $CH_2OCH_2C{\equiv}CH$ (**11**)



Entry	Carbonate	Yields [%][b] 2 a	3 a	7–11	Ratio[c]
1	**1 b**	11	16	63 (**7**)	75:25 (**7/7′**)
2	**1 c**	4	0	31 (**8**)	8:92 (**8/8′**)
3	**1 d**	20	27	32 (**9**)	–
4	**1 e**	5	6	21 (**10**)	18:82 (**10/10′**)
5	**1 f**	1	6	16 (**11**)	1:99 (**11/11′**)

[a] General Conditions: Reactions performed under air, at room temperature, using 1 mmol of cyclic carbonates **1 b**–**f** and 3 mmol of the Grignard reagent *n*BuMgCl (2 M in THF) in 1 mL of 2-MeTHF. [b] Yields refer to isolated products. [c] Ratios determined by NMR spectroscopy.

Table 4. Fast addition of aryl-Grignard reagents to cyclic carbonate **1 a**, at room temperature, in the presence of air and in different sustainable solvents.[a]



Ar= Ph (**d**); *p*-Tolyl (**e**); *p*-Anisole (*p-Anis*, **f**); Mesityl (*Mes*, **g**)

	Solvent	ArMgX (equiv.)[b]	Yields [%][c] 2 d–f	3 d–f	5 d–f	Ar–Ar
1	2-MeTHF	PhMgBr (1)	0 (**2 d**)	2 (**3 d**)	69 (**5 d**)	2
2	2-MeTHF	PhMgBr (2)	52 (**2 d**)	2 (**3 d**)	26 (**5 d**)	2
3	2-MeTHF	PhMgBr (3)	72 (**2 d**)	15 (**3 d**)	25 (**5 d**)	11
4	2-MeTHF	PhMgBr (4)	31 (**2 d**)	30 (**3 d**)	22 (**5 d**)	30
5	2-MeTHF	PhMgBr (5)	28 (**2 d**)	40 (**3 d**)	20 (**5 d**)	39
6	–	PhMgBr (1)	46 (**2 d**)	3 (**3 d**)	23 (**5 d**)	4
7	–	PhMgBr (2)	63 (**2 d**)	3 (**3 d**)	25 (**5 d**)	4
8	–	PhMgBr (3)	79 (**2 d**)	13 (**3 d**)	25 (**5 d**)	13
9	–	PhMgBr (4)	38 (**2 d**)	41 (**3 d**)	24 (**5 d**)	36
10	–	PhMgBr (5)	7 (**2 d**)	44 (**3 d**)	9 (**5 d**)	47
11	2-MeTHF	TolylMgBr (3)	27 (**2 e**)	12 (**3 e**)	67 (**5 e**)	14
12	–	TolylMgBr (3)	21 (**2 e**)	11 (**3 e**)	53 (**5 e**)	15
13	2-MeTHF	AnisMgBr (3)	5 (**2 f**)	2 (**3 f**)	67 (**5 f**)	8
14	–	AnisMgBr (3)	11 (**2 f**)	2 (**3 f**)	28 (**5 f**)	3
15	2-MeTHF	MesMgBr (3)	–	–	–	–
16	–	MesMgBr (3)	–	–	–	–

[a] General Conditions: Reactions performed under air, at room temperature, using 1 mmol of cyclic carbonate **1 a** and 1–5 mmol of the polar organometallic reagent Ar-MgX in 1 mL of the desired solvent. [b] Commercial solution of PhMgBr (1 M in THF), *p*-TolylMgBr (1 M in THF), *p*-AnisMgBr (0.5 M in THF) and MesMgBr (1 M in THF) were employed. [c] Yields refer to isolated products (yields were calculated for each product taking into account that the corresponding product is the only one obtained).

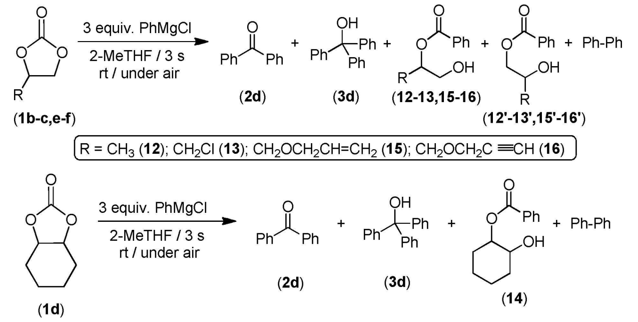
the rest of the asymmetric carbonates (**1 c**,**e**,**f**), the major isomer is the secondary β-alcohol (**8′**, **10′**, **11′**; Table 3, entries 2, 4, 5).

However, when aryl-Grignard reagents were employed, we observed a new product distribution (Table 4). Thus, the addition of PhMgBr to ethylcarbonate (**1 a**) in 2-MeTHF (Table 4, entry 1) gave rise to the formation of a mixture of three products: the corresponding tertiary alcohol (in this case triphenyl alcohol, **3 d**) in only 2% yield, the β-hydroxy ester compound (2-hydroxyethyl benzoate, **5 d**) in good yield (69%), and the previously observed homo-coupling product (Ph–Ph) in very low yield (2%). When the number of equivalents of PhMgBr is raised, the formation of the corresponding ketone (**2 d**) was observed. As expected, the gradual increase of the number of equivalents of PhMgCl (from 1 to 3 equivalents; Table 4, entries 1–3) produces an improvement of the yield of the desired ketone **2 d** (up to 72% yield) but boosting the formation of the corresponding side products (**3 d**, 15%; Ph–Ph, 11%) and with concomitant reducing of the yield of **5 d** (26%). Increasing the amount of PhMgBr up to 5 equivalents (Table 4, entry 5) decreases the formation of both **5 d** (20%) and **2 d** (28%), whereas yields of the tertiary alcohol **3 d** and the homo-coupling product (Ph–Ph) are raised (40% and 20%, respectively).

Nevertheless, when the reaction is carried out in the absence of any external solvent, ketone **2 d** is now formed even with only one equivalent of PhMgBr in moderate yields (Table 4, entry 6) and reach its maximum concentration when three equivalents of PhMgBr are used (Table 4, entry 8). Analogously to when 2-MeTHF is used, increasing the amount of the aryl-Grignard reagent in the absence of external solvents produces an increase of the tertiary alcohol **3 d** and the Ph–Ph product but with simultaneous and parallel increase in the yield of **5 d** (Table 4, entries 6–8). Employing higher amounts of the Grignard reagent is led to a massive decrease in yield for both **2 d** and **5 d** and a huge increase in the production of alcohol **3 d** and the homo-coupling product (Table 4, entries 9 and 10). When the aryl group of the organomagnesium compound is changed by *p*-tolyl (4-methylbenzene), the same behaviour with lower yields was observed (Table 4, entries 11 and 12); but when *p*-anisole (4-methoxybenzene) is used under the aforementioned condition, the β-hydroxy ester **5 f** is obtained now as main product (Table 4, entries 13 and 14). Finally, when the phenyl substituent in PhMgBr is replace by a mesityl group (2,4,6-trimethylbenzene), the reaction is completely shut down and only the corresponding hydrolyzed product (mesitylene) was obtained (Table 4, entries 15 and 16).

Established the best condition for the formation of the ketones **2 d**–**f** as three equivalents of PhMgBr in 2-MeTHF, we extended the scope of our studies to the previously assayed cyclic carbonates **1 b**–**f** (see Table 5). As earlier observed for cyclic carbonate **1 a** (see Table 4), the corresponding benzophenone is in most cases the product obtained in higher yield (**2 d**) with values between moderated to low (64–27%). In contrast, and for the specific case of the symmetric cyclic carbonate **1 d**, we observed the formation of the corresponding β-hydroxy ester compound **14** as the major product of the reaction (50%

Table 5. Fast addition of PhMgCl to cyclic carbonates **1b**–**f**, at room temperature, under air and using 2-MeTHF as solvent.[a]

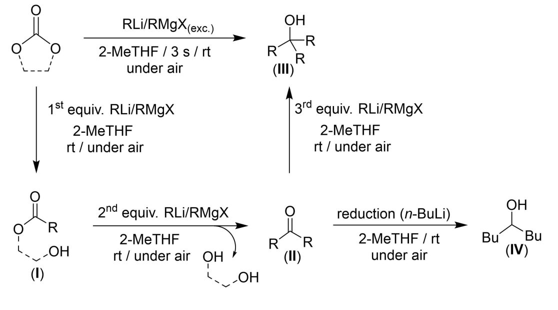


		Yields [%][b] 2d	3d	12–16	Ratio[c]	Ph–Ph [%][b]
1	**1b**	59	10	31 (**12**)	78:22 (**12**/**12'**)	9
2	**1c**	64	15	21 (**13**)	18:82 (**13**/**13'**)	13
3	**1d**	27	15	50 (**14**)	–	7
4	**1e**	56	18	23 (**15**)	5:95 (**15**/**15'**)	12
5	**1f**	58	14	11 (**16**)	14:86 (**16**/**16'**)	16

[a] General Conditions: Reactions performed under air, at room temperature, using 1 mmol of cyclic carbonates **1b**–**f** and 3 mmol of Grignard reagent PhMgBr (2 M in THF) in 1 mL of 2-MeTHF. [b] Yields refer to isolated products (yields were calculated for each product taking into account that the corresponding product is the only one obtained). [c] Ratios determined by NMR spectroscopy.

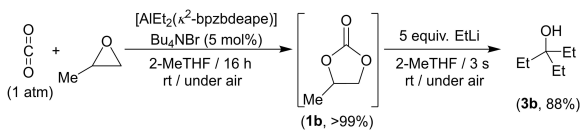
yield). In line with our previous studies with nonsymmetric cyclic carbonates **1b**,**c**,**e**,**f**, two different openings of the cyclic carbonates can take place when these compounds are treated with 3 equiv. of PhMgBr, thus giving rise to either primary (**12**, **13**, **15**, **16**) or secondary β-alcohols (**12'**, **13'**, **15'**, **16'**) (see Table 5). Again, and in accordance with the results obtained with the aliphatic Grignard reagent *n*BuMgCl (see Table 4), we observed that ring-opening products formed in low yields (11–34%; Table 5, entries 1, 2, 4, and 5); and that the major isomer was always the secondary β-alcohol (**13'**, **15'**, and **16'**; Table 5, entries 2, 4, and 5), except for the carbonate with a methyl group (**1b**) from which which the major isomer obtained was the primary alcohol **12** (Table 5, entry 1). For the rest of the asymmetric carbonates (**1c**,**e**,**f**), the major isomer was the secondary β-alcohol (**8'**, **10'**, and **11'**; Table 3, entries 2, 4, and 5).

Taking into account all our experimental studies and every isolated species that we have been able to detect in the crudes reaction media, we can propose a global picture of the reaction between cyclic carbonates and highly polar organometallic reagents (RLi/RMgX), when working at room temperature, under air and in 2-MeTHF as solvent (see Scheme 3). Thus, in a first step of the overall process, one equivalent of the highly polar organometallic reagent (RLi/RMgX) triggers the opening of the cyclic carbonate through its addition to the carbonyl group, giving rise to the corresponding β-hydroxy ester intermediate **I**. Subsequently, a second equivalent of the highly polar organometallic reagents attacks the carbonyl group of the β-hydroxy ester intermediate **I**, producing the concomitant release of the corresponding diol and the formation of the expected ketone **II**. A third equivalent of the polar organometallic reagent is able to undergo an addition process to this ketone **II**, thus producing the corresponding symmetric tertiary alcohol **III**. Only in the case of using *n*BuLi as the alkylation reagent, the formation of the secondary alcohol **IV** was detected, and this experimental observation can be explained as a consequence of the previously reported in situ reduction of ketone **II**.[28]



Scheme 3. Proposed synthetic pathway involving all species detected during the addition of RLi/RMgX reagents to cyclic carbonates, at room temperature, under air, and using 2-MeTHF as solvent.

During the last decade, the design of one-pot tandem protocols has occupied a strategic place in the framework of organic synthesis, as a new greener substitute for standard and tedious stepwise processes. This leads to a drastic reduction of isolation and purification steps of intermediates (thus minimizing both the generation of chemical waste and the required time and energy), thereby simplifying the practical aspects of the synthetic procedures, and to the possibility to work with unstable reaction intermediates (as no isolation of highly reactive and transitory-form species is needed).[30] In most of the cases, these one-pot tandem protocols employ the same synthetic organic utensil (transition metals, enzymes, main-group elements or organocatalysts) throughout all the tandem process, while the corresponding hybrid examples that described the amalgamation of different instruments from the organic synthetic toolbox, is still scarce.[31] In this sense, some of us have previously studied the fruitful combination of transition metal-catalyzed organic transformations in water or *DESs* with the chemoselective addition of organolithium reagents (RLi) to transiently formed ketones,[5b] the enzymatic and enantioselective bioamination (transaminases, ATAs) or bioreduction (ketoreductases, KREDs) of in situ-generated prochiral ketones;[32a–e] or the biocatalytic decarboxylation of *p*-hydroxycinnamic acids.[32f] Taking into account this previous experience in the design of hybrid synthetic protocols, and bearing in mind that the combination of metal-catalyzed organic transformations and main-group chemistry in 2-MeTHF has not been studied (as far as we are aware), we decided to try to finish with this discontinuity by the study of the unprecedented assemble of the aluminum-catalyzed fixation of CO_2 with propylene oxide (for the in situ synthesis of cyclic carbonate **1b** intermediate) with the fast addition of an organolithium reagent (EtLi) to the aforementioned transitory cyclic carbonate **1b** in 2-MeTHF (under air and at room temperature) to obtain the corresponding highly substituted tertiary alcohol **3b** under mild and more



Scheme 4. Design of a hybrid one-pot/two-step method that combines the reaction cycloaddition of CO_2 and propylene oxide with the concomitant and fast addition of EtLi to the transiently formed cyclic carbonate **1 b** at room temperature, under air, and using 2-MeTHF as solvent.

sustainable reaction conditions (Scheme 4). Thus, we firstly studied the aluminum/ammonium-catalyzed cycloaddition of CO_2 (1 atm) with propylene oxide at room temperature in 2-MeTHF employing [$AlEt_2(\kappa^2$-bpzbdeape)]/Bu_4NBr [5 mol%, bpzbdeape = 1,1-bis(4-(diethylamino)phenyl)-2,2-bis(3,5-dimethyl-1H-pyrazol-1-yl)ethan-1-ol)] as catalyst, previously described by some of us as an efficient and selective catalytic system for this transformation.[33] As soon as total conversion of propylene oxide into the desired cyclic carbonate **1 b** was observed (16 h, GC analysis), EtLi was directly added to the reaction mixture, without any intermediate step of isolation or purification of **1 b**, in the absence of protecting atmosphere and at room temperature (conditions usually forbidden for RLi reagents).[1] Astonishing, we observed the almost instantaneous formation (3 s) of the corresponding tertiary alcohol **3 b** as the only product of the reaction, finding an almost quantitative yield for **3 b** (88 %) when five equivalents of the organolithium reagent were employed (see Scheme 4). Thus, this experiment confirms the suitability of our hybrid one-pot/two-step synthetic strategy for the indirect and sustainable conversion of CO_2 into highly substituted tertiary alcohols without the isolation/purification of any reaction intermediate.

Conclusions

In summary, with this work we have demonstrated that the biorenewable solvent 2-MeTHF can be selected as the environmentally friendly reaction medium of choice for the fast addition of highly polar organometallic reagents (RLi/RMgX) to cyclic carbonates (as CO_2-derived sustainable C1 feedstock resources) under standard bench reaction conditions (under air, room temperature), thus allowing the replacement of Schlenk-type experimental techniques in the synthesis of tertiary alcohols (with organolithium reagents), β-hydroxy esters (when alkyl-Grignard reagents are employed), or symmetric ketones (by using aryl-Grignard reagents). Moreover, we have described a greener, and operationally simple one-pot procedure for the effective synthesis of highly substituted tertiary alcohols through the successful combination of aluminum-catalyzed cycloaddition of CO_2 and propylene epoxide with the chemoselective and fast addition of organolithium reagents (EtLi) to the transiently formed cyclic carbonate **1 b** (without tedious and energy- and time-consuming intermediate purification or isolation steps). Thus, these results clearly demonstrate that 2-MeTHF can be used as an optimal reaction media for RLi/RMgX-promoted organic transformations under more sustainable and mild experimental conditions (room temperature and under air). Consequently, our method will offer a new and more environmentally friendly tool for possible application in the manufacture of highly substituted tertiary alcohols, β-hydroxy esters, or symmetrical ketones.

Experimental Section

General considerations

All reagents were obtained from commercial suppliers and used without further purification with the exception of cyclic carbonates **1 a**–**f**[33] and the deep eutectic solvents (*DESs*),[10] which were prepared by following the corresponding reported methods. Grignard and organolithium reagents were purchased from Sigma Aldrich: *n*butyl lithium (2.5 M solution in hexanes); ethyl lithium (0.5 M solution in benzene/cyclohexane); methyl lithium (1.6 M in diethyl ether); phenyl lithium (1.9 M solution in nBu_2O); *n*BuMgCl (2 M solution in THF); EtMgBr (1 M solution in THF); MeMgBr (3 M solution in diethyl ether); PhMgBr (1 M solution in THF); *p*-TolylMgBr (1 M solution in THF); *p*-AnisMgBr (0.5 M solution in THF); MesMgBr (1 M solution in THF). Concentrations of all organolithium reagents were established by titration with ʟ-menthol,[34] and the concentration of Grignard reagents were determined by titrating against iodine.[35] Commercially available 2-MeTHF was directly employed without any previous purification technique (distillation/use of molecular sieves) and was directly opened and stored in the presence of air and moisture.

NMR spectra were recorded on a AV400 MHz spectrometer operating at 400.13 MHz for ^1H, and 100.62 MHz for ^{13}C. All ^{13}C spectra were proton decoupled. ^1H and ^{13}C NMR spectra were referenced against the appropriate solvent signal. GC/FID measurements were made on Agilent Technologies 7890 A chromatograph equipped with a DS-5MS UI (30 m, 0.53 mm) column (for more information on the calibration; see the Supporting Information).

General procedure for the addition of organolithium reagents to cyclic carbonates

Syntheses were performed under air and at room temperature. In a glass tube, the appropriate cyclic carbonate (**1 a**–**f**, 1 mmol) was dissolved in the corresponding alternative solvent (1 mL) under air, followed by the addition of the desired RLi reagent (1 to 5 mmol were employed) at room temperature, and the reaction mixture was stirred for 2–3 s. The reaction was then stopped by addition of a saturated solution of the Rochelle salt (sodium potassium tartrate tetrahydrate) and the mixture was extracted with 2-MeTHF (3 × 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was concentrated in vacuo. Yields of the reaction crudes were determined by GC-FID using trimethoxybenzene as internal standard (1 mmol) after calibration (see the Supporting Information). Separation and purification of every compound was carried out using TLC glass plate silica. All reactions were done in triplicate to ensure good reproducibility of obtained yields.

General procedure for the addition of Grignard reagents to cyclic carbonates

Syntheses were performed under air and at room temperature. In a glass tube, the appropriate cyclic carbonate (**1 a**–**f**, 1 mmol) was dissolved in the corresponding alternative solvent (1 mL) under air, followed by the addition of the desired Grignard reagent (RMgX; 1 to 5 mmol were employed) at room temperature, and the reaction mixture was stirred for 2–3 s. The reaction was then stopped by addition of a saturated solution of the Rochelle salt (sodium potassium tartrate tetrahydrate) and the mixture was extracted with 2-MeTHF (3×5 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was concentrated in vacuo. Yields of the reaction crudes were determined by GC-FID using trimethoxybenzene as internal standard (1 mmol) after calibration (see the Supporting Information). Separation and purification of every compound was carried out using TLC glass plate silica. All reactions were done in triplicate to ensure good reproducibility of obtained yields.

General procedure for the one-pot/two-step reaction between CO_2 and propylene oxide with concomitant fast addition of ethyl lithium

A glass tube was charge with the aluminum catalyst [$AlEt_2(\kappa^2$-bpzbdeape)][33] (bpzbdeape = 1,1-bis[4-(diethylamino)phenyl]-2,2-bis(3,5-dimethyl-1H-pyrazol-1-yl)ethan-1-ol; 0.05 mmol, 29 mg) and tetrabutylammonium bromide (TBAB; 0.05 mmol, 16 mg) using 2-MeTHF (1 mL) as solvent. Next, propylene epoxide (1 mmol, 0.07 mL) was added to the reaction mixture and CO_2 was bubbled with a needle for 16 h (until full consumption of the epoxide was observed by GC-FID). When carbonate **1b** was fully formed (GC-FID), the CO_2 dissolved in the reaction media was removed through a fast vacuum/air cycle and EtLi (5 mmol, 5 mL) was added. We employed the aforementioned work up to purify the obtained reaction crude. Yield of **3b** was determined by GC-FID using trimethoxybenzene as internal standard (1 mmol).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: CO_2 · cyclic carbonates · green chemistry · Grignard reagents · organolithium compounds

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