

Synthesis of dibenzyl carbonate: towards a sustainable catalytic approach†

Cite this: *RSC Adv.*, 2014, 4, 1929

Giulia Fiorani and Maurizio Selva*

At 90 °C, in the presence of CsF/ α -Al₂O₃ or [P_{8.8.8.1}][H₃COCO₂] as catalysts, a straightforward protocol was set up for the synthesis of dibenzyl carbonate (DBnC) via the transesterification of dimethyl carbonate (DMC) with an excess of benzyl alcohol. The two catalysts were used in amounts as low as 1% mol (with respect to the limiting reagent DMC). Best results were achieved with CsF/ α -Al₂O₃ that allowed a simpler and reproducible isolation of DBnC in yields up to 70%. Moreover, both the catalyst and the excess BnOH were recovered and could be recycled. The evaluation of mass index (MI) and cost index for the investigated procedure confirmed the economic sustainability and the choice of a rational mass flow throughout the reaction: the method was in the top 7 among 21 protocols selected as the best available options for the synthesis of DBnC.

Received 12th June 2013
Accepted 1st November 2013

DOI: 10.1039/c3ra42904k

www.rsc.org/advances

Introduction

In the past two decades, organic carbonates (OCs) have been extensively studied for a number of applications, from bulk industrial to lab scale chemistry.¹ The flexible reactivity and the non (or low) toxicity of OCs have been key to their successful use as green reagents and solvents. In particular, the lighter terms of the OCs series, dimethyl and diethyl carbonate (ROCO₂R; R = Me, Et; DMC and DEC, respectively) have been exploited to replace hazardous chemicals, such as phosgene and alkyl halides, in carboxyalkylation and alkylation protocols, as well as volatile organic solvents or other polar nonprotic media (*i.e.* DMF and NMP).² As part of our long-standing interest on the synthesis and application of OCs,³ we recently focused on dibenzyl carbonate (PhCH₂OCO₂CH₂Ph, DBnC). DBnC is a promising reagent for niche industrial preparations of pharmaceuticals and fine chemicals, where benzylation protocols are often used in protection strategies.⁴ Remarkable advantages of DBnC over conventional reagents (harmful and lachrymatory benzyl halides) include low toxicity, good solvation capability, and safe handling along with an excellent stability under a wide range of operating conditions. DBnC shows the typical dual reactivity of dialkyl carbonates: in presence of a generic nucleophile (NuH: phenols, thiols, CH₂-active nitriles and esters) DBnC may act selectively either as a carboxybenzylating or as a benzylating agent to produce NuCO₂CH₂Ph or NuCH₂Ph derivatives, respectively (Scheme 1, top and bottom). As

demonstrated independently by us and by other research groups^{3k,4} the discrimination between the two pathways largely relies on the operating temperature and on the choice between basic organic/inorganic compounds (mostly DBU, DABCO and inorganic carbonates) or amphoteric solids (Faujasite zeolites) as catalysts.

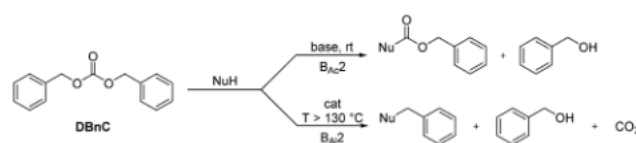
Although the conditions can be tuned to obtain the desired benzyl/carboxybenzylsynthons,⁴ a limitation on the use of DBnC comes from its cost. This aspect becomes obvious when the market price of dibenzyl carbonate is compared to that of other common dialkyl, diaryl, and alkylene carbonates and of other benzylating/carboxybenzylating agents (Table 1).

Not only DBnC is 30–35 times more costly than other carbonates, but is by far, more expensive than both benzyl halides and benzyl chloroformate. Reasons for this unfavourable cost index (CI),⁵ can be found in the synthetic procedures of DBnC rather than in the value/choice of its precursors. Starting from the early Eighties, phosgene-free procedures have been reported for the preparation of dibenzyl carbonate. These methods were essentially based on three reactions:

- alkylation of carbonate salts with benzyl halides mediated by phase-transfer- or organometallic-catalysts;⁶
- catalytic transesterification of light dialkyl carbonates (mostly, the non-toxic DMC) with benzyl alcohol;⁷
- coupling between activated CO₂ with both benzyl-alcohol and halides.^{6d,8}

Department of Molecular Sciences and Nanosystems, Centre for Sustainable Technologies, Università Ca' Foscari Venezia, Calle Larga S. Marta, Dorsoduro 2137, 30123 – Venezia, Italy. E-mail: selva@unive.it

† Electronic supplementary information (ESI) available: Complete characterization of dibenzyl carbonate, EI-MS spectra of all the reaction products. See DOI: 10.1039/c3ra42904k



Scheme 1 Reactivity of DBnC in nucleophilic substitution reactions.

Table 1 Comparison of the prices per gram of various organic carbonates

Dialkyl/Diaryl/Alkylene Carbonates	Benzylating/carboxy-benzylating agents	Price ^a (€ g ⁻¹)
Dimethyl carbonate (DMC)		0.08–0.41
Diethyl carbonate (DEC)		0.15–0.54
Diphenyl carbonate (DPhC)		0.05–0.15
Ethylene carbonate (EC)		0.13–0.17
Propylene carbonate (PC)		0.04–0.55
Dibenzyl carbonate (DBnC)		15.0
	Benzyl chloride	0.03–0.21
	Benzyl bromide	0.29–0.49
	Benzyl chloroformate	0.25–5.3

^a Source: Sigma Aldrich catalogue 2012. Average prices were considered for packaging in the range of 5–1000 g, and purity of OCs $\geq 98\%$.

Although several reaction conditions were examined, two general drawbacks were the use of multi-step reaction sequences, which implied harmful solvents and/or expensive work-up, and the nature of the catalysts involved which, not only triggered the conversion of DBnC to dibenzyl ether (DBnE) and other Cannizzaro-derived by-products,⁹ but also posed toxicity and separation concerns.^{6a}

The optimization of simple and cost-effective methodologies for the synthesis of DBnC remains therefore a desirable target. In this context, we focused on the transesterification of dimethyl carbonate (DMC) with benzyl alcohol (BnOH) (Scheme 2). The investigation aimed at a twofold objective:

(i) the setup of a single-step protocol yielding to DBnC without the isolation of benzyl methyl carbonate (PhCH₂O-CO₂Me, BnMC) as an intermediate;

(ii) the use of safe-to-handle catalysts able to reduce/rule out side reactions of decomposition and disproportionation of DBnC.

A survey on transesterification reactions indicated that several inorganic and organic bases including alkaline carbonates and fluorides, hydrotalcites, amines, phosphines as well as onium salts, could serve as catalysts for the transesterification of light dialkyl carbonates (DMC and DEC, respectively) with benzyl alcohol.^{3f} These processes however, brought to the exclusive formation of unsymmetrical benzyl alkyl carbonates (BnMC, Scheme 2, and benzyl ethyl carbonate, BnEC).^{3f,10,12} In order to implement a new straightforward synthesis of DBnC, two of the most active catalysts were chosen among those available in the literature: a heterogeneous inorganic solid such as CsF supported on α -Al₂O₃,¹⁰ and a homogeneous organocatalyst belonging to a class of newly generated ionic liquids (ILs), methyltrioctylphosphonium

methylcarbonate ([P_{8,8,8,1}][H₃COCO₂]),¹¹ were considered. Both these systems were claimed to be so effective that a loading of the active phase as low as 1% mol (based on the limiting reagent) was sufficient for transesterifications to proceed quantitatively. For comparison, other common basic transesterification catalysts such as hydrotalcites or potassium carbonate must be used in overstoichiometric quantities, requiring difficult product isolation and recycle operations. Moreover, CsF on α -Al₂O₃ was preferred to cheaper KF-supported solids given its enhanced stability (and activity as well), observed for transesterification protocols.¹⁰

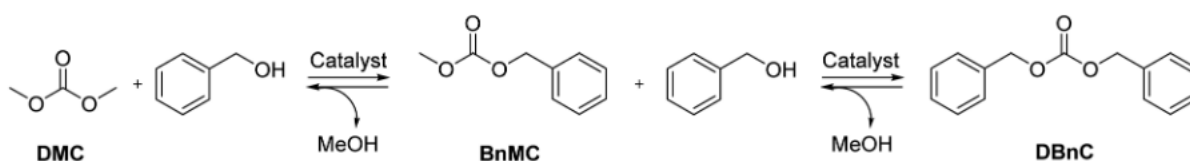
The present work demonstrates that in the presence of either CsF on α -Al₂O₃ or [P_{8,8,8,1}][H₃COCO₂], the transesterification equilibria of Scheme 2 could be optimized for the selective formation of the symmetrical DBnC. In particular, when CsF/ α -Al₂O₃ was the catalyst, the product (DBnC) was obtained through a reproducible one-step method, and isolated in reasonably good yield (up to 70%). However, the success of the procedure was dependent not only on the reaction step. This study provided evidence that even residual traces of the catalyst during the work-up of final reaction mixtures promoted the reaction of DBnC back to the parent reagents BnMC and BnOH, respectively. Finally, the proposed procedure was also evaluated and compared to other reported preparations through the use of atom economy (AE) and mass index (MI) metrics. A cost estimate also corroborated the economic viability of the method which allowed a sharp reduction of synthetic costs of DBnC up to 0.37 € g⁻¹.

Results and discussion

Catalysts were prepared according to previously reported procedures. CsF/ α -Al₂O₃ was obtained by wet impregnation of a CsF water solution on commercial α -Al₂O₃ (Alfa Aesar, surface area 10–16 m² g⁻¹);¹⁰ the final loading of the active phase was 1 mmol CsF g⁻¹ α -Al₂O₃. [P_{8,8,8,1}][H₃COCO₂] was synthesized by our recently developed halide-free methodology based on the methylation of trioctylphosphine with DMC in MeOH as a co-solvent.¹¹ This single step reaction allowed us to get the organocatalyst in a very high purity (>98%), without any further work-up or purification steps.

Reaction conditions

Transesterification experiments were initially carried out at 90 °C (DMC reflux temperature), using a mixture of BnOH, DMC, and the catalyst (either CsF/ α -Al₂O₃ or [P_{8,8,8,1}][H₃COCO₂]). A number of different tests were performed by changing the relative amounts of reagents and catalyst. In all



Scheme 2 The catalytic transesterification of dimethyl carbonate with benzyl alcohol.

cases, reactions were sampled at intervals and followed by GC-MS. This screening showed that the formation of DBnC was favoured in the presence of an excess of BnOH and trace amounts of the catalyst. Best results were achieved using a BnOH–DMC–cat = 10 : 1 : 0.01 molar ratio, respectively.[‡] The volume of the limiting reagent, DMC, was 0.8 mL (9.5 mmol). No advantages were manifest by the removal of MeOH during the reaction. Under such conditions, Fig. 1 shows the product distribution and compares the outcomes of the reaction catalysed by CsF/ α -Al₂O₃ (left) and by [P_{8,8,8,1}][H₃COCO₂] (right). The reversibility of the transesterification reaction resulted in the formation of equilibrium mixtures which, regardless of the catalyst used, were obtained after comparable time intervals, (150–200 min) and with approximately the same composition (left and right, respectively). Two remarkable facts were however observed:

(i) the desired DBnC was the major product. Its amount was more than twice that of the mono-transesterification product BnMC;

(ii) only traces (<3% by GC-MS) of dibenzyl ether (DBnE) were detected.

As could be expected, neither catalysts affected the equilibrium position, though both played a key role in steering and improving the overall selectivity by suppressing by-products, particularly DBnE.

It should be noted that many literature methods for the synthesis of DBnC claimed the formation of sizeable amounts of DBnE (cfr introduction). This may form through the decarboxylation of DBnC (Scheme 3). In the presence of amphoteric catalysts (zeolites), such a reaction was recently highlighted also by us.^{3f} Whatever the catalyst, the presence of DBnE not only decreased the yield of the carbonate product, but was also detrimental for the purification/isolation work-up.

Reproducibility, work-up, recycle, and scale up

To substantiate the initial results, four additional experiments were carried out:

(i) the first two were conducted under the conditions of Fig. 1. These tests were useful not only to reproduce the reaction course, but also to devise and implement a protocol for the isolation of the product.

(ii) all the other conditions remaining unaltered, the third and the fourth tests were performed by increasing the catalyst loading from 1 to 5% mol with respect to DMC.

All reactions were allowed to proceed for 5 hours and they were followed by GC-MS and ¹H NMR. In this way, an exhaustive monitoring of all reagents and products was possible, including DMC and MeOH which were hardly detectable by GC-MS. At the end of each reaction, the product DBnC was isolated and the corresponding yields were determined. The results are reported in Table 2. Experiments were highly reproducible: for both the organic and the inorganic catalyst, the increase of the loading from 1 to 5% mol, did not appreciably alter the product

[‡] In the case of CsF/ α -Al₂O₃, the DMC/cat molar ratio was referred to the active phase CsF. The use of an excess of DMC brought about the formation of benzyl methyl carbonate as a major product. This was of no use, since a further addition of BnOH was necessary to produce DBnC.

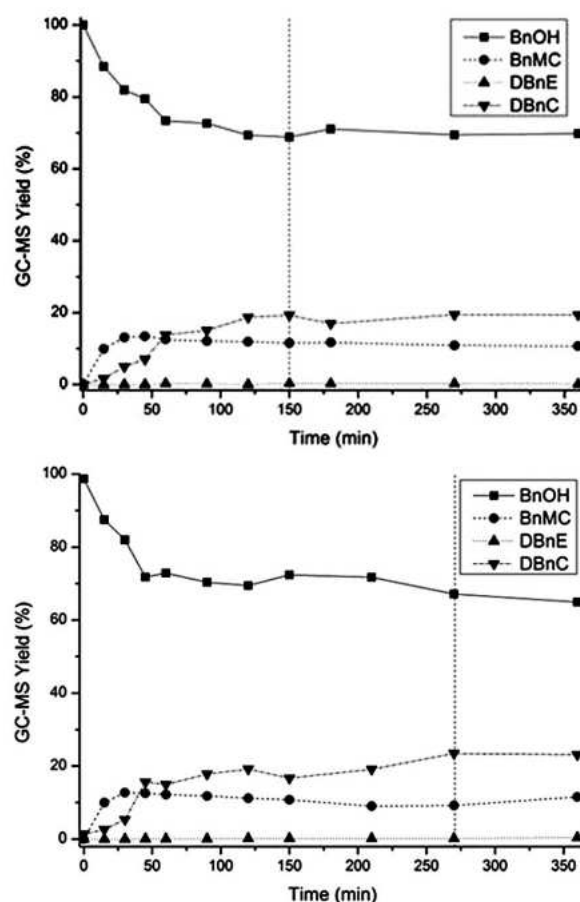
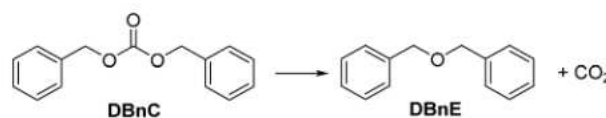


Fig. 1 Transesterification of DMC with BnOH, with CsF/ α -Al₂O₃ (top) and [P_{8,8,8,1}][H₃COCO₂] (bottom) as catalysts (reaction conditions: BnOH–DMC = 10 : 1 (mol mol⁻¹), $T = 90^\circ\text{C}$, $t = 6\text{ h}$, cat: 1% mol based on DMC).



Scheme 3 The decarboxylation of DBnC to DBnE.

distribution, but it allowed to reach the equilibrium position faster, in about 1/3 the time required under the previous conditions of Fig. 1 (50–60 min vs. 150–200 min; compare entries 1, 2 and 3, 4, Table 2). In all cases, the equilibrium composition of the reacting mixtures showed DBnC, BnMC, and DBnE in 62–70%, 27–37%, and 1–3% relative amounts, respectively. The minor formation of DBnE (<3%) confirmed that the chosen catalysts highly improved the selectivity (97–98%) towards the transesterification reaction. Moreover, we were able to prove the total conversion of the limiting reagent (DMC) as well as the absence of any other by-products, except for MeOH: both aspects were verified by ¹H NMR. Different treatments were then tested to isolate DBnC. Direct distillation, though possible, was not convenient: event at reduced pressure, dibenzyl carbonate partially decomposed because of its high boiling point (185–190 °C/2.7 mbar). We therefore opted for a

Table 2 Synthesis of DBnC by the transesterification reaction of DMC with BnOH

Entry	Catalyst	BnOH-DMC-Cat (molar ratio)	T^a (min)	Conv. ^b (%)	Equilibrium mixture ^c (%)			
					DBnC	BnMC	DBnE	DBnC Yield ^d , (%)
1	[P _{8,8,8,1}][O(CO)OCH ₃]	10 : 1 : 0.01	200	>99	69	29	2	47
2		10 : 1 : 0.05	60		70	27	3	42
3	CsF/ α -Al ₂ O ₃	10 : 1 : 0.01	150	>99	62	37	1	61
4		10 : 1 : 0.05	50		65	32	3	61

^a Reaction time at which the equilibrium position was reached (no more changes of the product distribution were observed). ^b DMC conversion determined by ¹H NMR. ^c Composition of the equilibrium mixture determined by GC-MS. ^d Yield of DBnC isolated by vacuum distillation (entries 1 and 2) or by crystallization (entries 3 and 4). In all cases, the purity of DBnC was >95%.

mild vacuum distillation (80 °C @ 0.8 mbar) of the unconverted benzyl alcohol and benzyl methyl carbonate (BnMC). An oily residue of DBnC was so obtained. This was shaken with a small aliquot of *n*-pentane (DBnC-*n*-pentane = 1 : 0.5 v/v) and the mixture was allowed to settle at -18 °C. Although *n*-pentane was not a solvent for DBnC, the treatment favoured a rapid crystallization of the carbonate as a white solid.

Notably, when the heterogeneous catalyst was used, the isolated yield (61%) of DBnC was comparable to the GC yield (62–65%, entries 3 and 4, Table 2) and it was remarkably higher than that achieved with the homogeneous catalyst (42–47%: entries 1 and 2, Table 2). An analysis of the work-up of organocatalyzed reactions gave an explanation of this result: we observed that during the distillation step, about 10% of DBnC reverted to the parent compounds BnMC and benzyl alcohol, respectively (Scheme 2). This meant that not only minor amounts of MeOH or water could be present, but also that [P_{8,8,8,1}][H₃COCO₂] was not completely removed. Traces of the phosphonium salt were confirmed by GC-MS analyses that showed small quantities of benzyl octyl carbonate (C₈H₁₇OCO₂CH₂Ph, <1%) in the distillate. This compound was likely due to a partial decomposition of the organocatalyst. Although this reaction (decomposition of onium salts) was documented in the literature,¹³ the reasons why the breakdown of [P_{8,8,8,1}][H₃COCO₂] occurred during the distillation, while the catalyst was perfectly stable throughout the transesterification reaction (with an excess of PhCH₂OH), are still obscure.

To further investigate the behaviour of this catalyst, two sets of experiments (A and B) were carried out. In the first set (A) the leaching of the active phase (CsF) was studied: two portions (47 and 470 mg, respectively) of CsF/ α -Al₂O₃ were each suspended in the same volume of benzyl alcohol (5 mL) and heated at 90 °C for 150 min. This treatment aimed at mimicking reaction conditions of Table 2. Then at r.t., after the filtration of the catalyst, the resulting liquids were distilled to dryness, recovered in Milli-Q water (10 mL), and analyzed by ion-chromatography (IC).[§] In the second set (B), recycle tests were considered:

[§] The leaching of the active phase from the catalyst was evaluated by ion-chromatography (IC) to measure the possible release of F specie. Unfortunately, the transesterification mixtures resulting from the reaction of BnOH with DMC (Table 2) could not be analysed by the IC technique: DBnC was a high boiling product, the presence of which – even at a trace level – interfered with IC-analyses carried out in aqueous solutions.

to the scope, a transesterification reaction was carried out under the conditions of entry 3 of Table 2. After 5 hours, CsF/ α -Al₂O₃ was filtered, washed with diethyl ether, dried, and activated under vacuum (1 mbar) at 70 °C, overnight. The recovered catalyst was used for a 2nd run.

Results of both sets of experiments are summarised in Table 3. IC analyses showed that, regardless of the amount of the catalyst used, the F content was below the detection limit of 0.009 mg L⁻¹ (entries 1 and 2, Table 3). This evidence ruled out not only the leaching of CsF from the support, but also the partitioning of any solid CsF/ α -Al₂O₃ in the organic solution during both the reaction and the final work-up.

The recycle test (2nd run) offered a product distribution and a isolated yield of DBnC (56%) comparable to the 1st run and to those of previously described in Table 2. However, a prolonged time (up to 12 h) was required to reach equilibrium (entries 3 and 4, Table 3). This matched the behaviour already reported in other applications of CsF/ α -Al₂O₃ as a transesterification catalyst:^{12a,c} for example, the reaction of 1-phenylethanol with diethyl carbonate (DEC) for the synthesis of ethyl(1-phenylethyl)-carbonate [CH₃CH₂(Ph)OCO₂CH₂CH₃] showed that CsF/ α -Al₂O₃ as a catalyst could be recycled for four subsequent runs without loss of selectivity, though a drop of the catalytic activity occurred after the first recycle. The reasons for such a result are not obvious. As no loss of solid occurred in the organic solution, the progressive inhibition of the catalyst was perhaps due to traces of water in each new feed of reactants, or to some alterations on the availability of the active phase (CsF) over the catalytic surface, that might be caused by the activation–reaction cycles. At present however, no experiments support these hypotheses.

The scale up of the reaction was also investigated. Under the conditions of entry 3, Table 2 ($T = 90$ °C, BnOH-DMC-Cat = 10 : 1 : 0.01 molar ratio, respectively), an experiment was carried out with a fivefold increase of the amount of each reactant (BnOH and DMC in 52.0 and 4.2 mL, respectively). After 150 min, the above described work-up (distillation and crystallization) allowed to isolate DBnC in a 67% yield. Notably, being all the other conditions the same, an additional reaction performed with a lower amount of BnOH (molar ratio BnOH-DMC = 5), gave the final product in a 70% yield. The results not only confirmed that the preparation of DBnC was possible on a larger scale, but also that a moderate improvement of isolated yields (from ~60 to 70%) could be achieved. Moreover, in the economy of the overall process, BnOH was definitely not a

Table 3 Investigation of the leaching and the recycle of CsF/ α -Al₂O₃

Entry	Cat	Leaching tests ^a (mg)	Recycle tests ^b	<i>T</i> ^c (°C)	<i>T</i> ^d (min)	F content ^e	Equilibrium mixture ^f (%)			DBnC Yield ^g , (%)
							DBnC	BnMC	DBnE	
1	CsF/ α -	47		90	150	Bdl				
2	Al ₂ O ₃	470				Bdl				
3			1 st run		150		63	35	2	61
4			2 nd run		720		59	39	2	56

^a Weight of the catalyst used for leaching tests. ^b The molar ratio BnOH–DMC–Cat was that of entry 3, Table 2 (10 : 1 : 0.01, respectively). ^c Reaction temperature at which both leaching and reactivity tests were carried out. ^d Entries 1 and 2: total time of the leaching tests. Entries 3 and 4: time at which the equilibrium position was reached during the reactivity tests (no more changes of the product distribution were observed). ^e Determined by ion-chromatography analyses: bdl (below detection limit of 0.009 mg L⁻¹). ^f Composition of the equilibrium mixture determined by GC-MS. ^g Yield of DBnC isolated by crystallization.

residue/waste: the excess of BnOH was quantitatively distilled off and it could be reused for the investigated reaction without any further purification. Accordingly, a further experiment carried out under the above described conditions (*T* = 90 °C, BnOH–DMC–Cat = 10 : 1 : 0.01 molar ratio, respectively) with the use of recycled BnOH (10 mL), allowed to isolate DBnC in a 62% yield. To conclude this section, two additional reactions were performed by using diethyl carbonate (DEC) in place of DMC. A mixture of BnOH (5 mL), DEC, and CsF/ α -Al₂O₃ (1 : 5 : 0.01 molar ratio, respectively) was set to react for 150 min at two different temperatures: (i) at 90 °C (conditions of Table 2), the conversion of DEC was 88%. Two products, benzyl ethyl carbonate (PhCH₂OCO₂Et: major, 58%) and DBnC (30%) were observed; (ii) at 128 °C (reflux of DEC), the results were comparable to those described for DMC. The conversion was quantitative and the yield of DBnC was 62% (by GC-MS). Although the procedure could be effectively extended to DEC, a reaction temperature of about 40 °C higher than that used for DMC (128 vs. 90 °C), was necessary. This confirmed a behaviour already reported by us:³⁴ regardless of the examined reaction, the replacement of DMC with its higher homologues (diethyl-, dipropyl-, dibutyl-, *etc.* carbonate) implied a drop of the reaction rate, requiring energy intensive processes.

Comparison between different syntheses of DBnC

Three major green/synthetic advantages could be recognized from the analysis of the investigated procedure:

- the use of trace amounts of the catalyst;
- the setup of solventless one-pot conditions;
- the recycle of both the catalyst and the excess of BnOH for further transesterification reactions. To further measure the sustainability of the overall process, we decided to undertake a comparison between our method and other protocols reported for the synthesis of DBnC. For simplicity, only the reaction catalysed by CsF/ α -Al₂O₃ was chosen as our representative case. The assessment was carried out using both the chemical yield and modern metrics including atom economy (AE%) and mass index (MI).^{36,5} Table 4 reports the scrutiny of 21 different procedures (including ours) based on the most commonly used transesterifications (*T*) with benzyl alcohol, alkylations of carbonate salts (AC), couplings with activated CO₂ (Cact) (see

introduction), and one additional reaction using CO (CO cond). The Table also highlights the presence/absence of solvents which is of help to understand the trend of MI values. Entries of Table 4 were sorted in increasing order of the MI metric. Though simple, this index provided valuable information on the overall reaction mass flow calculated from the experimental procedures described in each of the methods considered. Notwithstanding the fact that our procedure (line 2) was one with moderate-to-medium isolated yields (60–70%) of DBnC, we were delighted to discover that it could be ranked in the top 7 of the 23 methods listed in Table 4. More specifically, our procedure alternated between the 2nd and 7th positions depending on the different reaction conditions which were optimized (see above, Tables 2 and 3 and scale up tests): the change of the BnOH : DMC molar ratio from 5 to 10 brought about MI values of 3.8 and 8.0, respectively (entry 2, Table 4).

It should also be noted that the first position of Table 4 corresponded to an excellent MI value of 1.5 (entry 1, Table 4). The result however, was achieved with a highly dangerous and pollutant organotin (Bu₂SnO) catalyst. Other top methods (entries 3–5: MI = 4.4–7.7) referred either to a two-step procedure involving the purification of benzyl methyl carbonate (BnMC) as an intermediate (entry 3, Table 4), or to the use of expensive and not fully characterized catalysts (entries 4 and 5, Table 4). Therefore, the low MI was somewhat offset by unfavourable reaction/work up conditions.

Transesterification reactions (*T*) were apparently more efficient than other reactions listed in Table 4 (AC, Cact, and CO cond). From entry 5 on, the progressive increase of the MI was due to the use of solvents and in some cases, to a rather low atom economy (39–50%: entries 10, 13–15, and 20, Table 4) which implied sizeable amounts of residual wastes. Remarkable examples were the reactions with activated organic carbonate analogues such as 1-benzylcarbonylimidazolide and 1-benzyloxycarbonyl-3-nitro-1,2,4-triazole (BCIm and BCNT, respectively; entries 20 and 21, Table 4): although these were formal transesterification processes, they showed the highest MI (62–64) among the examined procedures.

In general, the presence of solvents not only burdened the reaction mass flow, but also added separation and purification steps to the synthetic procedures. Not to consider that most of the reported solvents (DMSO, NMP, DMAC, and volatile

Table 4 Comparison of different methods for the synthesis of DBnC

Entry	Reaction type ^a	Benzyl source	Carbonate source	Cat	T (°C)	Solvent	Chemical yield (%)	AE (%)	MI	Ref.
1	T	BnOH	DMC	Bu ₂ SnO	120	—	64	79	1.5	7a
2	T	BnOH	DMC	CsF/ α -Al ₂ O ₃	90	—	61–70	79	3.8–8.0	Our procedure
3	T	BnOH	DMC	KW2000	90, 110	—	83	79	4.4	3k, 14
4	T	BnOH	PC	Fe–Zn	170	—	78	76	6.4	7b
5	T	BnOH	DMC	La(O- <i>i</i> Pr) ₃	90	Hexane	88	79	7.7	15
6	AC	BnCl	KHCO ₃	TBPBr, KBr	150	NMP	80	69	8.6	6c
7	AC	BnCl	KHCO ₃	THABr, KBr	150	NMP	79	69	8.8	6c
8	CO cond	BnOH, BnONa	CO	Metallic Se	20	THF	76	91	9.4	16
9	AC	BnCl	K ₂ CO ₃	18-crown-6, KI	110	DMAC	63	61	10	6c
10	AC	BnBr	K ₂ CO ₃	Bu ₃ SnCl	40	DMF	50	50	10.9	6a
11	AC	BnCl	KHCO ₃	TBABr	150	NMP	61	69	11.2	6c
12	Cact	BnOH, BnCl	CO ₂	CyTMG	5	NMP	97	61	12.5	6a
13	AC	BnCl	Cs ₂ CO ₃	—	110	DMAC	70	42	13.2	6c
14	AC	BnCl	Cs ₂ CO ₃	18-crown-6, KI	110	DMAC	63	42	14.8	6c
15	AC	BnBr	K ₂ CO ₃	18-crown-6, KBr	80	—	98	50	14.8	6b
16	Cact	BnOH	CO ₂	Cs ₂ CO ₃	100	NMP, CH ₂ Cl ₂	90	93	21	17
17	AC	BnCl	K ₂ CO ₃	18-crown-6	80	—	51	62	22	6b
18	Cact	BnOH	CO ₂	P(Ph) ₃ , DEAD	90–100	DMSO	90	93	53.4	8b
19	Cact	BnOH, BnBr	CO ₂	K ₂ CO ₃ , TBAI	r.t.	DMF	82	75	54.1	18
20	T	BnOH	BCIm	—	0	THF	74	39	62	19
21	T	BnOH	BCNT	—	r.t.	CH ₂ Cl ₂	98	68	64	20

^a T: transesterification; AC: alkylation of carbonate salts; Cact: coupling with activated CO₂; CO cond: CO-based reaction.

chlorinated compounds) are hazardous chemicals for human health and the environment. As a final point of this analysis, the fairly good atom economy (79%) of the transesterification of BnOH with DMC suggested that methods based on this reaction (including ours) offered the best option to implement a sustainable synthesis of DBnC.

An overall cost estimation for the proposed DBnC synthetic methodology was also evaluated. Current standard prices of reagents and solvents were gathered from the Aldrich catalogue (<http://www.sigmaaldrich.com>), except for α -Al₂O₃ which was supplied by Alfa-Aesar (<http://www.alfa.com>). Table 5

summarizes the results. As was mentioned above, although benzyl alcohol was used in a 5 molar excess over the limiting reagent (DMC), it (BnOH) could be quantitatively recovered by distillation, and reused. Therefore, two options were examined for the cost analysis: (i) in the first one, the recycle of BnOH was considered. Accordingly, only two equivalents of alcohol were computed per each mole of the final product (entry 1a); (ii) in the second case, all the starting alcohol was consumed (5 equiv.) with no reuse (entry 1b). Whatever the circumstances (i) or (ii), results indicated the economic viability of the method: the cost index of DBnC was remarkably decreased in the range of 0.28–

Table 5 Cost estimate for the synthesis of DBnC via the method investigated in this work

Entry	Compound	Role in the synthesis	Price ^a (€ g ⁻¹)	Purity Spec. ^b	Amount used ^c (g)	Cost in the synthesis (€ g ⁻¹)
1a	BnOH	Reactant	0.043	>99%	1.3 ^d	0.05
1b	BnOH	Reactant	0.043	>99%	3.2 ^d	0.14
2	DMC	Reactant	0.048	99%	0.5	0.02
3	CsF	Catalyst	2.75	99%	9.0 × 10 ⁻³	0.02
4	α -Al ₂ O ₃	Catalytic support	2.90	>99%	6.76 × 10 ⁻²	0.17
5	<i>n</i> -Pentane	Separation Solvent ^e	0.06	98%	0.3	0.02

DBnC cost^f (€ g⁻¹)

No recycle of BnOH

0.37

Recycle of BnOH

0.28

^a Aldrich source (<http://www.sigmaaldrich.com>), except for α -Al₂O₃ which was supplied by Alfa-Aesar (<http://www.alfa.com>). Prices were those of the packaging used in this work. ^b Purity specification of chemicals used in the synthesis. ^c Although BnOH was used in a 5 molar excess with respect to the limiting reagent DMC, it (BnOH) could be recycled. The two reported amounts were referred to the reaction carried out with and without the recycle of BnOH (entries 1a and 1b, respectively). ^d Amounts were normalized to the synthesis of 1 g of DBnC. ^e *n*-Pentane was used to induce the crystallization of DBnC although it was not a solvent for the organic carbonate. ^f Total cost per gram of DBnC as the sum of costs of each compound used.

0.37 € g^{-1} . This value was in line with that reported for other organic carbonates (Table 1), and it further corroborated the sustainability of the procedure.

Conclusions

Compared to commonly used dialkyl carbonates, dibenzyl carbonate suffers from a moderate availability and a high cost due to the lack of efficient methods for its synthesis.

We have found that a straightforward procedure for the preparation of DBnC can be devised by the transesterification of DMC with a 5–10 molar excess of benzyl alcohol in the presence of either CsF/ α -Al₂O₃ or [P_{8,8,8,1}][H₃COCO₂] as catalysts. Both catalysts show comparable activity and, most importantly, they allow to boost the reaction selectivity by preventing side processes. However, not only the reaction setup is important, but also the purification method must be optimized to favour the isolation of DBnC. The success of this operation (isolation work-up) depends on the sensitivity of dibenzyl carbonate to water or residual MeOH and it is determined by the nature/choice of the catalyst. CsF/ α -Al₂O₃ is the preferable system since it is readily and quantitatively separated from the reaction mixture: this improves the final yields of DBnC up to 70%, making the overall procedure highly reproducible. By contrast, the presence of residual phosphonium salt ([P_{8,8,8,1}][H₃COCO₂], at trace levels) during the work-up, promotes a significant conversion of dibenzyl carbonate back to parent BnMC and BnOH.

The combination of solventless conditions, very low amounts of catalysts (1% mol), and a moderate excess of BnOH, allows a rational mass flow throughout the reaction. This is confirmed by the analysis of the mass index (MI) which shows that the investigated procedure is among the top 7 of 21 methods chosen as the best available options for the synthesis of DBnC. The ranking is even better (2nd position) when the reaction is scaled up by using a molar ratio BnOH–DMC = 5. Moreover, our procedure allows the recycle of both the CsF/ α -Al₂O₃ catalyst and the excess of benzyl alcohol that are recovered during the work-up of the final mixture.

Although this scrutiny is far from being exhaustive, it highlights major aspects for a sustainable preparation of DBnC and, at the same time, it marks a starting point to further improve key reaction parameters including reagent ratios and catalyst loadings.

Experimental section

All reagents and solvents were ACS grade. Before use, benzyl alcohol (BnOH, Sigma Aldrich, >99%) was distilled under vacuum (39 °C @ 0.8 mbar) to remove benzaldehyde impurities.²¹ Other compounds were used as received. α -alumina (>99%, surface area: 10–16 m² g⁻¹) was purchased from Alfa Aesar. Doubly distilled MilliQ water was employed throughout the study.

GC-MS (EI, 70 eV) analyses were performed with a HP5890 gas chromatograph equipped with a HP-5 MS capillary column (30 m × 0.25 mm; coating thickness 0.25 μ m) and a HP 5970 quadrupole mass detector (EI, 70 eV). NMR spectra were recorded

using a Varian Unity 400 MHz spectrometer, CDCl₃ was used as a solvent, the residual signal of the deuterated solvent was used as internal reference. FT-IR spectra were recorded with a Perkin Elmer Spectrum One Instrument on KBr pellets. Melting points were collected by a Scott Scientific melting point apparatus. Ion-chromatography analyses were carried out at 30 °C, using an IonPac AS23 Anion-Exchange column (4 × 40 mm) and an aqueous solution of Na₂CO₃ and NaHCO₃ (4.5 mM and 0.8 mM, respectively) as an eluant (1 mL min⁻¹).

Structures of dibenzyl carbonate and by-products were assigned by both comparison to authentic samples and GC-MS and ¹H NMR analyses.

Catalysts preparation

Both the homogeneous and the heterogeneous catalysts used in this work were prepared and characterized according to previously reported procedures.^{10,11}

[P_{8,8,8,1}][H₃COCO₂]. A mixture of trioctylphosphine (25 mL, 56 mmol), dimethyl carbonate (30 mL, 356 mmol), and MeOH as a co-solvent (30 mL) was set to react in an autoclave at 140 °C for 20 h, after three freeze–pump–thaw cycles. Then, at r.t., the autoclave was vented and MeOH was removed under vacuum. Methyltrioctylphosphoniummethylcarbonate, [P_{8,8,8,1}][H₃COCO₂], was recovered as a pale yellow liquid (27.5 g, >99%). The product was >99% pure by ¹H NMR and was used without further purification. Characterization data were in agreement to those reported in the literature.¹¹

CsF/ α -Al₂O₃. A 1 M aqueous solution of CsF (1.5 g, 10 mmol) was added to solid α -Al₂O₃ (10 g). The slurry was kept under vigorous stirring for 2 hours at r.t. Then, after water removal by evaporation at reduced pressure, a white fluffy powder of CsF/ α -Al₂O₃ was obtained. The loading of the active phase (CsF) was 1 mmol g⁻¹ α -Al₂O₃. Prior to use, the catalyst was activated by heating at 70 °C under vacuum for 12 h.

Transesterification of DMC with BnOH. In a typical procedure, a mixture of BnOH (97.0 mmol, 10 mL), DMC (9.7 mmol, 0.8 mL), and CsF/ α -Al₂O₃ as a catalyst (96 mg; 0.01 molar equiv. with respect to DMC; the amount was calculated based on the CsF loading) was charged in a 25 mL two-neck flask equipped with a reflux condenser and an adapter with screw-cap septum for the withdrawal of samples. The mixture was then heated at the reflux temperature of DMC ($T = 90 \text{ °C}$), and the reaction was followed by both GC-MS and ¹H NMR analyses of samples collected at time intervals. Once the reaction mixture reached the equilibrium composition, it was cooled to r.t., and the solid catalyst was filtered through a Gooch funnel (pore size 4). The liquid solution was distilled under vacuum to remove the more volatile components (BnOH and benzyl methyl carbonate, BnMC), and *n*-pentane (1 mL) was added to the viscous residue. Upon cooling at -18 °C for 2 hours, DBnC was isolated as a white solid (1.4 g, 61%) with a very high purity (>99% by GC-MS).

The same procedure was used to scale up the reaction. Two tests were performed using BnOH–DMC molar ratios of 10 and 5, respectively: accordingly, volumes of BnOH were 52.0 and 26.0 mL, while the amount of DMC was always 4.2 mL. Isolated yields of DBnC were 67 and 70%, respectively (8.1 and 8.4 g).

When $[P_{8,8,8,1}][H_3COCO_2]$ was used, the transesterification step was carried out as above described: a mixture of BnOH (97.0 mmol, 10 mL), DMC (9.7 mmol, 0.8 mL), and the organocatalyst (48 mg; 0.01 molar equiv. with respect to DMC) was set to react at 90 °C, for 4.5 hours. Once the reaction was complete, the phosphonium salt was removed by adsorption on a silica gel pad (3 g) through which the reaction mixture was eluted. Then, BnOH and BnMC were distilled under vacuum. A partial conversion of DBnC back to parent BnMC and BnOH was promoted by traces of the phosphonium salt that were still present during the distillation. DBnC was finally purified after washing with *n*-pentane (1 mL) and isolated in a 47% yield.

For both $CsF/\alpha-Al_2O_3$ and $[P_{8,8,8,1}][H_3COCO_2]$, the above described procedures were also used by increasing the cat-DMC molar from 0.01 to 0.05.

Mass index. MI was calculated for the reaction step of all methods listed in Table 4. The following expression was used:⁵

$$MI = \frac{\sum \text{reagents} + \text{catalyst} + \text{solvents (Kg)}}{\text{Product (Kg)}}$$

Atom economy. AE was calculated according to the following equation:²²

$$AE = \frac{\text{MW (g mol}^{-1}\text{) product}}{\sum \text{MW (g mol}^{-1}\text{) reagents}}$$

Characterization data. All compounds were characterised by GC-MS and ¹H NMR. Spectroscopic properties were in agreement to those reported in the literature.

Dibenzyl carbonate (BnC).^{4a,23} ¹H NMR (400 MHz, CDCl₃, 298 K, δ): 7.41–7.30 (m, 10H), 5.18 (s, 4H). ¹³C NMR (101 MHz, CDCl₃, 298 K, δ): 155.23, 135.31, 128.73, 128.68, 128.47, 69.88.

EI-MS (70 eV): 180 [M⁺ – 62] (10); 151 (12); 107 (41); 92 (24); 91 (100); 79 (40); 77 (24); 65 (22); 51 (13). IR (KBr): 1744 (br); 1456 (sh); 1385 (sh); 1259 (br); 1224 (br); 934 (sh); 907 (sh); 788 (sh); 747 (sh); 695 (sh); 591 (sh); 482 (sh). Mp = 32–33 °C.

Benzyl methyl carbonate (BnMC).²⁴ EI-MS (70 eV): 166 [M⁺] (23); 121 (13); 107 (42); 92 (11); 91 (100); 90 (47); 89 (21); 79 (33); 77 (32); 65 (25); 63 (10); 51 (20); 50 (10).

Dibenzyl ether (DBnE). EI-MS (70 eV): 107 [M⁺ – 91] (14); 92 (100); 91 (89); 79 (16); 77 (21); 65 (24); 51 (14); 44 (10). Database NIST: Ref. #118448, match quality 94%.

Benzyl octyl carbonate. EI-MS (70 eV): 112 [M⁺ – 76] (8); 84 (54); 83 (46); 77 (100); 70 (45); 69 (40); 67 (12); 59 (15); 57 (26); 56 (40); 55 (49). Database NIST: Ref #314620, match quality 89%.

Acknowledgements

Prof. Paolo Pavan (Dipartimento di Scienze Ambientali, Informatica e Statistica, Università Ca' Foscari Venezia) is kindly acknowledged for his support in ion-cromatography analyses.

References

- (a) A.-A. G. Shaikh and S. Sivaram, *Chem. Rev.*, 1996, **96**, 951–976; (b) J. P. Parrish, R. N. Salvatore and K. W. Jung,

Tetrahedron, 2000, **56**, 8207–8237; (c) B. Schäffner, F. Schäffner, S. P. Verevkin and A. Börner, *Chem. Rev.*, 2010, **110**, 4554–4581.

- P. Tundo and M. Selva, *Acc. Chem. Res.*, 2002, **35**, 706–716.
- (a) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, 2003, **68**, 7374–7378; (b) M. Selva, P. Tundo and T. Foccardi, *J. Org. Chem.*, 2005, **70**, 2476–2485; (c) M. Selva, P. Tundo, A. Perosa and F. Dall'Acqua, *J. Org. Chem.*, 2005, **70**, 2771–2777; (d) F. Bonino, A. Damin, S. Bordiga, M. Selva, P. Tundo and A. Zecchina, *Angew. Chem., Int. Ed.*, 2005, **44**, 4774–4777; (e) M. Selva, A. Perosa, P. Tundo and D. Brunelli, *J. Org. Chem.*, 2006, **71**, 5770–5773; (f) M. Selva, P. Tundo, D. Brunelli and A. Perosa, *Green Chem.*, 2007, **9**, 463–468; (g) M. Selva and A. Perosa, *Green Chem.*, 2008, **10**, 457–464; (h) M. Selva, A. Perosa and M. Fabris, *Green Chem.*, 2008, **10**, 1068–1077; (i) M. Selva and M. Fabris, *Green Chem.*, 2009, **11**, 1161–1172; (j) M. Selva, M. Fabris and A. Perosa, *Green Chem.*, 2011, **13**, 863–872; (k) M. Selva, V. Benedet and M. Fabris, *Green Chem.*, 2012, **14**, 188–200; (l) M. Selva, M. Noe, A. Perosa and M. Gottardo, *Org. Biomol. Chem.*, 2012, **10**, 6569–6578.
- (a) M. Selva, C. A. Marques and P. Tundo, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1889–1893; (b) W.-C. Shieh, M. Lozanov, M. Loo, O. Repič and T. J. Blacklock, *Tetrahedron Lett.*, 2003, **44**, 4563–4565; (c) W.-C. Shieh, M. Lozanov and O. Repič, *Tetrahedron Lett.*, 2003, **44**, 6943–6945; (d) A. Loris, A. Perosa, M. Selva and P. Tundo, *J. Org. Chem.*, 2004, **69**, 3953–3956.
- Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes*, ed. A. Lapkin and D. Constable, John Wiley & Sons, Chichester, 2008.
- (a) T. Fujinami, S. Sato and S. Sakai, *Chem. Lett.*, 1981, **10**, 749–752; (b) G. Rokicki, J. Pawlicki and W. Kuran, *Polym. J.*, 1982, **14**, 839–845; (c) J. A. Cella and S. W. Bacon, *J. Org. Chem.*, 1984, **49**, 1122–1125; (d) W. McGhee and D. Riley, *J. Org. Chem.*, 1995, **60**, 6205–6207.
- (a) A. A. G. Shaikh and S. Sivaram, *Ind. Eng. Chem. Res.*, 1992, **31**, 1167–1170; (b) R. Srivastava, D. Srinivas and P. Ratnasamy, *J. Catal.*, 2006, **241**, 34–44.
- (a) K. Abe, I. Akikazu, *Eu Pat.*, EP 2330096, 2009; (b) D. Chaturvedi, N. Mishra and V. Mishra, *Tetrahedron Lett.*, 2007, **48**, 5043–5045.
- J. L. R. Williams, D. D. Reynolds, K. R. Dunham and J. F. Tinker, *J. Org. Chem.*, 1959, **24**, 64–68.
- J.-M. Clacens, D. Genuit, B. Veldurthy, G. Bergeret, L. Delmotte, A. Garcia-Ruiz and F. Figueras, *Appl. Catal., B*, 2004, **53**, 95–100.
- M. Fabris, V. Lucchini, M. Noè, A. Perosa and M. Selva, *Chem.–Eur. J.*, 2009, **15**, 12273–12282.
- (a) B. Veldurthy, J.-M. Clacens and F. Figueras, *J. Catal.*, 2005, **229**, 237–242; (b) B. Veldurthy, J.-M. Clacens and F. Figueras, *Eur. J. Org. Chem.*, 2005, 1972–1976; (c) J. Ni, D. Rooney and F. C. Meunier, *Appl. Catal., B*, 2010, **97**, 269–275.
- C. J. Bradaric, A. Downard, C. Kennedy, A. J. Robertson and Y. Zhou, *Green Chem.*, 2003, **5**, 143–152.
- P. Tundo, F. Aricò, A. E. Rosamilia and S. Memoli, *Green Chem.*, 2008, **10**, 1182.

- 15 M. Hatano, S. Kamiya, K. Moriyama and K. Ishihara, *Org. Lett.*, 2011, **13**, 430–433.
- 16 K. Kondo, N. Sonoda and H. Sakurai, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 108–111.
- 17 Y. Yamazaki, K. Kakuma, Y. Du and S. Saito, *Tetrahedron*, 2010, **66**, 9675–9680.
- 18 M. Shi and Y.-M. Shen, *Molecules*, 2002, **7**, 386–393.
- 19 G. Bertolini, G. Pavich and B. Vergani, *J. Org. Chem.*, 1998, **63**, 6031–6034.
- 20 M. Shimizu and M. Sodeoka, *Org. Lett.*, 2007, **9**, 5231–5234.
- 21 W. L. E. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth Heinemann, Amsterdam, 2003.
- 22 B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.
- 23 E. Alonso, D. Guijarro, P. Martínez, D. J. Ramón and M. Yus, *Tetrahedron*, 1999, **55**, 11027–11038.