Carbamate synthesis via a shelf stable and renewable C1 reactant

Carbamate Synthesis Via a Shelf Stable and Renewable C1 Reactant

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Abstract: *4-Propylcatechol carbonate is a shelf-stable, renewable C1 reactant. It is easily prepared from renewable 4-propylcatechol (derived from wood) and dimethyl carbonate (derived from CO_2) using a reactive distillation system. In this work the carbonate reactant has been used for the two-step synthesis of carbamates under mild reaction conditions. In the first step, 4-propylcatechol carbonate is reacted with an alcohol at 50-80 °C using a Lewis acid catalyst (e.g. $Zn(OAc)_2{\cdot}2H_2O$). With liquid alcohols no solvent and with solid alcohols 2-methyltetrahydrofuran was used as solvent. In the second step, the alkyl 2-hydroxy-propylphenyl carbonates intermediates obtained are reacted with amines at room temperature in 2-methyltetrahydrofuran, forming the target carbamates and by-product 4-propylcatechol, which can be recycled into carbonate reactant.*

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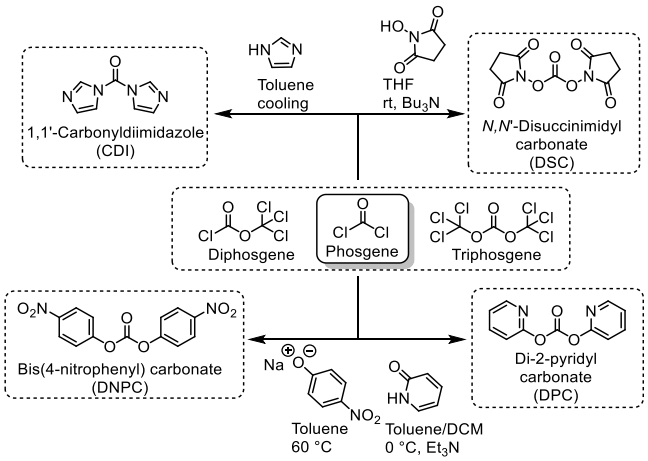
Introduction

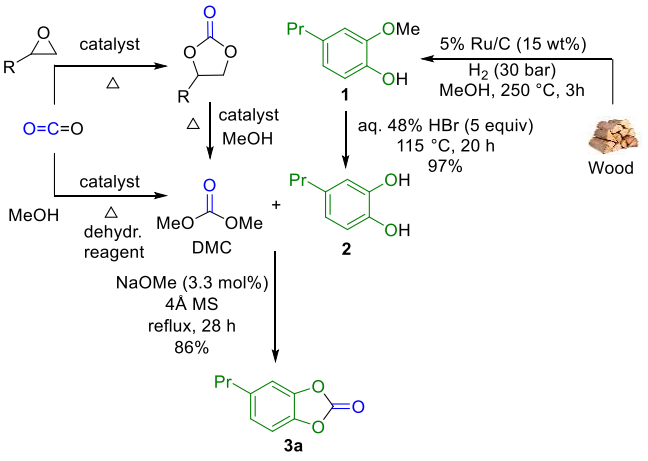
Transition towards a more sustainable chemical industry is an important contemporary challenge.[1] More sustainable processes and products are required as a consequence of the growing awareness of the need to protect the environment and to cope with depletion of non-renewable resources.[2] Hazardous reactants used in organic synthesis need to be replaced by less toxic ones whenever possible, and these alternatives should preferentially be derived from renewable resources. Moreover, the new synthetic methodologies involving these reactants should maximize resource and energy efficiency.[3]

Large-scale industrial synthesis of carbamates relies on one-carbon (C1) reactants, with phosgene being the most important one for polyurethane synthesis (Scheme 1).[2] The major issue related to phosgene is its extreme toxicity.[4-5] It is therefore normally produced and consumed at the same site. Phosgene was used as a chemical warfare agent during World War I, and is currently listed as a Schedule 3 substance of the Chemical Weapon Convention. All production sites manufacturing more than 30 tonnes per year must be declared to the the Organisation for the Prohibition of Chemical Weapons, OPCW.[5] As alternatives for gaseous phosgene, liquid diphosgene and solid triphosgene can be used as they are easier to handle.[2] However, these compounds are also extremely toxic and release phosgene upon reaction with even trace amounts of water and therefore require a similar level of precaution.[4,6] A carbamate group is a key structural motif in many fine chemicals such as approved drugs and prodrugs.[4,7] These require safer phosgene analogues for their synthesis, as based on the production volumes typically no dedicated reactors are used and phosgene cannot be produced on site. Carbonyldiimidazole (CDI), pyrocarbonates, and other activated carbonates (e.g. disuccinimidyl-, di-2-pyridinyl carbonates, bis(4-nitrophenyl)carbonate) have been developed for this purpose (Scheme 1). However, these decompose in the presence of water, requiring dry conditions for handling and storage.[7] As these reactants are prepared from phosgene, they actually do not provide a greener alternative when considering the entire production route.[4] The same is true for benzyl chloroformate (CbzCl) and 9-fluorenylmethyl chloroformate (FmocCl), obtained from reaction of an alcohol with phosgene, which find major application as protecting groups reactants for amines in organic synthesis.[8] Stable and renewable alternative C1 reactants with low toxicity and recyclable by-product formation are therefore required.



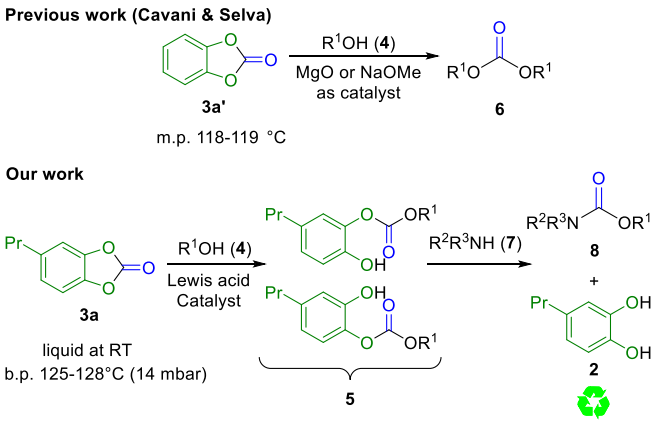
Scheme 1. Phosgene derivatives: Overview of commonly used C1 reactants for carbamate synthesis.[4, 9-11]

In 2016, Beller disclosed a Fe-catalyzed reaction of urea with alcohols for the synthesis of primary carbamates.[12] This is a major step forward towards greener methodologies for the synthesis of carbamates with improvements in both toxicity and flammability of the C1 reactant. Urea is industrially obtained from CO_2 and ammonia. Ammonia is the only by-product formed. However, the low reactivity of urea results in the need for a high reaction temperature in reactions with alcohols (150 °C). Unfortunately, these primary carbamates only substitute the RO-group in a subsequent reaction with amines and can therefore not be used to synthesize secondary or tertiary carbamates. In 2017 the group of Choi described the use of zinc salts as catalysts for the synthesis of secondary carbamates directly from aromatic amines, CO_2, and silicate esters. The latter one acts as a water scavenger and alcohol donor.[13] Organic carbonates are another class of greener alternatives for currently used C1 reactants.[14,15] These reactants are highly desirable from a green chemistry point since they are less toxic, biodegradable and can be obtained via phosgene free routes. Dimethyl carbonate (DMC), one of the most simple organic carbonates, acts as green building block, since it can be made from carbon dioxide and methanol.[16] Moreover methanol can be produced by the hydrogenation of CO_2.[17] The production of one mole DMC therefore requires three moles of CO_2. However, direct DMC synthesis from CO_2 and MeOH has not yet been industrialized.[16,18] The main industrial production processes of DMC are the transition metal-catalyzed oxidative carbonylation of methanol with oxygen (EniChem process) or NO_X (Ube process) and the Asahi Kasei process, involving CO_2 insertion into ethylene/propylene oxide followed by a transesterification of the obtained cyclic carbonate with MeOH (Scheme 2).[16] Unfortunately, transesterification of DMC with alcohols typically requires a high temperature and an (in)organic base or organocatalyst is therefore often used as additive.[14] Interestingly, only methanol is produced as by-product. These transesterifications with aliphatic alcohols are unfavorable (thermoneutral) and usually require both long reaction times and a very large excess of the co-reacting alcohol to shift reaction equilibria to the right.[14] Typically side reactions occur causing a lower selectivity and limiting the yields of the target compounds. One such reaction is competitive methylation of nucleophile, which becomes more important at higher temperatures.[19] The synthesis of carbamates directly from DMC also exists, but is limited to the methoxycarbonylation of amines.[20] An important more reactive industrial carbonate synthesized from DMC is diphenyl carbonate.[21] Its major use is as an intermediate in the phosgene-free production of polycarbonates via reaction with diols, which does not require selective substitution. To obtain mono substitution the more reactive di(4-nitrophenyl) carbonate, synthesized from phosgene (Scheme 1), is typically used.[22]



Scheme 2. Synthesis of 4-propylcatechol carbonate (**3a**) from 4-propylcatechol (**2**) and DMC obtained from wood and CO_2, respectively.

Herein, we report a new safe and thermal and water stable renewable C1 reactant, i.e. 4-propylcatechol carbonate (**3a**) (see SI sections 7 and 9), obtained in high yield (86%) via a reaction of 4-propylcatechol (**2**) with DMC using a reactive distillation system (Scheme 2).[23,24] 4-Propylcatechol (**2**) can be efficiently synthesized from 4-propylguaiacol (**1**) via demethylation with aq. HBr.[25] Catalytic hydrogenolysis of pine sawdust gives a lignin oil consisting for more than 80% of 4-propylguaiacol (**1**) in an amount corresponding to 12 wt% of the original lignin content.[26] There are several routes towards DMC including processes based on CO_2 (*vide supra*). All carbons of 4-propylcatechol carbonate reactant are therefore renewable. Catechol carbonates **3** are also interesting from a reactivity point of view given the simultaneous contribution of the release of steric strain and the leaving group properties (stability) of the catecholate anion, concomitantly produced in the first substitution. In this work 4-propylcatechol carbonate (**3a**) was used in the synthesis of carbamates under mild reaction conditions. The protocol involves two steps, i.e. reaction with alcohol followed by reaction with amine (Scheme 3). This order avoids isocyanate intermediates (or potentially unstable precursors), which are generally toxic.[2] The by-product 4-propylcatechol (**2**) formed in the reaction with amine can be recycled into carbonate reactant **3a**. The propyl chain delivered by nature is advantageous as it makes the catechol carbonate liquid allowing neat reactions with liquid alcohols, reducing solvent use. Catechol carbonates have only been limitedly studied as reactants. In earlier work Cavani and Selva reported the reaction of catechol carbonate (**3a'**) with alcohols under basic catalysis (MgO or NaOMe) providing exclusively symmetrical dialkyl carbonates via a tandem substitution reaction.[27] A selective process towards the intermediate alkyl 2-hydroxyphenyl carbonates (**5**) is unknown and required for a subsequent reaction with amine. These reaction intermediates were sometimes observed but never isolated and therefore presumed to be highly reactive. In this work a catalyst allowing such selective substitution with alcohols into alkyl 2-hydroxyphenyl carbonates (**5**), which proved to be stable, is disclosed. A Lewis acid as catalyst turned out to be crucial as base catalysis only provided symmetrical dialkyl carbonates (**6**) (Scheme 3).



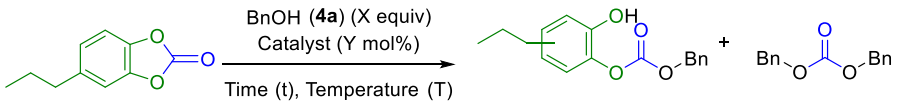
Scheme 3. 4-Propylcatechol carbonate (**3a**) as a C1 reactant for carbamate (this work) and symmetric carbonate (**6**) (previous work) synthesis.

Results and Discussion

Benzyl alcohol (**4a**) was selected as alcohol for the optimization of the selective substitution on 4-propylcatechol carbonate (**3a**). Reactions were run neat with 3 equivalents of benzyl alcohol at 40 °C for 16 h. Without catalyst a modest conversion (61%) of substrate and 57% of the desired benzyl 2-hydroxy-4-propylphenyl carbonate and benzyl 2-hydroxy-5-propylphenyl carbonate (mixture of 2 regioisomers) (**5a**) was obtained (Table 1, entry 1). Besides **5a**, 7% undesired dibenzyl carbonate (**6a**), resulting from a second reaction of **5a** with alcohol **4a**, was also observed. Increasing the reaction temperature to 80 °C increased the conversion, but unfortunately selectivity is lost (Table 1, entry 2). In accordance with the work of Cavani and Selva application of a base as catalyst (5 mol%) provided exclusively **6a**, both with NaOMe and the weaker base NEt_3 (Table 1, entries 3-4).[26] To achieve selective formation of **5a** a suitable catalyst needs to be identified. A variety of Lewis acids based on Li, Mg, Al, Sc, Mn, Fe, Co, Ni, Cu, Zn, Ag, In, La, and Yb were therefore screened as potential catalysts for the model reaction (5 mol%) (See SI, Table S2). More than 80% conversion of **3a** and ≥90% selectivity towards **5a** was obtained with $FeCl_3.6H_2O$ (Table 1, entry 5), $CoCl_2$, $Zn(OAc)_2$, $Zn(OAc)_2{\cdot}2H_2O$ (Table 1, entry 7), $Zn(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$, and $Yb(OTf)_3$. Based on toxicity and price $Zn(OAc)_2{\cdot}2H_2O$ and $FeCl_3.6H_2O$ were retained for further studies. Increasing the temperature from 40 °C to 50 °C slightly increased conversion for $Zn(OAc)_2{\cdot}2H_2O$ resulting in 91% of the desired product, while maintaining a high selectivity (Table 1, entry 8). $FeCl_3.6H_2O$ gave the same result as obtained at 40 °C (Table 1, entry 6). Hydration of $Zn(OAc)_2$ had no effect on the conversion and selectivity (Table 1, entry 9). $Zn(OAc)_2{\cdot}2H_2O$ was finally selected as optimal catalyst considering it is an approved food additive used in chewing gum (E650).[28-31] Reactions were also run at lower catalyst loading. Even 1 mol% $Zn(OAc)_2{\cdot}2H_2O$ gave similar results compared to 5 mol% catalyst (Table 1, entry 10). Next, the effect of solvent on the model reaction was studied (See SI, Table S6). After all, when alcohols are not liquids addition of solvent will be required to get a homogeneous non viscous reaction mixture. Interestingly, the biorenewable solvent, 2-methyltetrahydrofuran (2-MeTHF) gave a similar reaction as under neat conditions with the same catalyst loading (Table 1, entry 11).[32] The formation of undesired **6a** slightly increased with prolongation of the reaction time reducing selectivity (Table 1, entry 12). Lastly, the effect of reducing the number of

equivalent of alcohol on the conversion of **3a** was investigated (Table 1, entries 13-14). When decreasing the amount of **4a** a significant amount of substrate **3a** remained in 16 h.

Table 1. Selected optimization data for the reaction of 4-propylcatechol carbonate (**3a**) with benzyl alcohol (**4a**).[a]



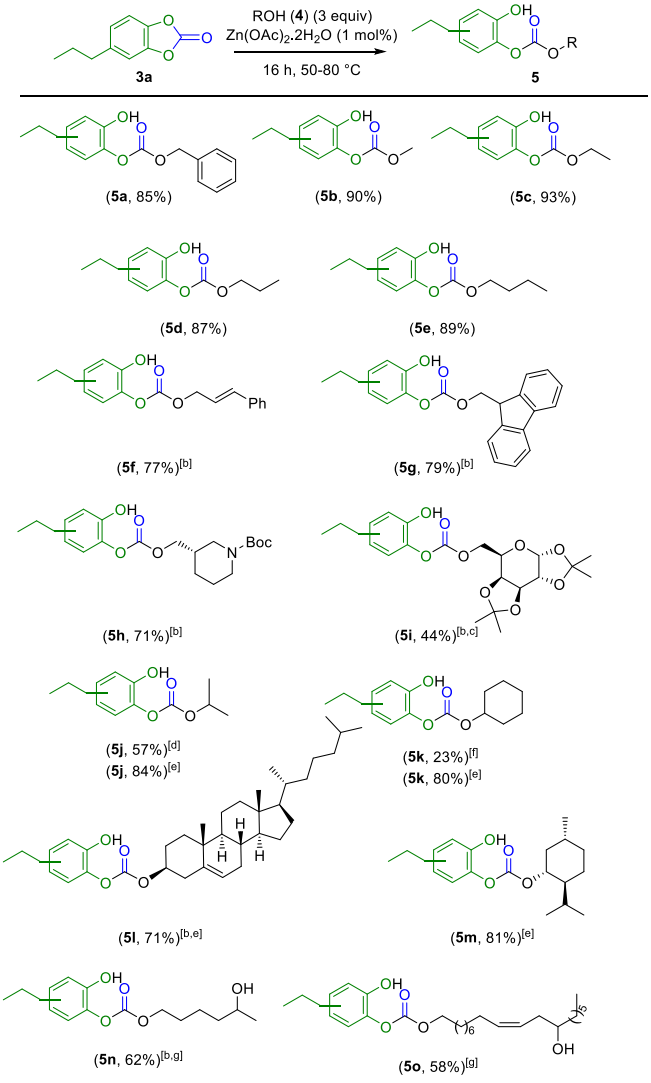
3a **5a** **6a**

Entry	Alcohol loading (X equiv)	Catalyst	Catalyst loading (Y mol%)	Time (h)	Temperature (°C)	Solvent	^{1}H NMR yield (%)[b]				Selectivity
							3a	5a	6a	Mass Balance	5a/(5a+6a)
											%
1	3	-	-	16	40	-	39	57	7	103	89
2	3	-	-	16	80	-	18	53	34	105	61
3	3	NaOMe	5	16	40	-	0	0	95	95	0
4	3	NEt_3	5	16	40	-	0	0	101	101	0
5	3	$FeCl_3$ ·$6H_2O$	5	16	40	-	8[c]	82[c]	2[c]	92	98
6	3	$FeCl_3$ ·$6H_2O$	5	16	50	-	4[c]	82[c]	3[c]	89	96
7	3	$Zn(OAc)_2$ ·$2H_2O$	5	16	40	-	19	79	2	100	98
8	3	$Zn(OAc)_2$ ·$2H_2O$	5	16	50	-	9	91	8	108	92
9	3	$Zn(OAc)_2$	5	16	50	-	6	87	7	100	93
10	**3**	**$Zn(OAc)_2$ ·$2H_2O$**	**1**	**16**	**50**	**-**	**6 (0)[c]**	**88 (85)[c]**	**9 (9)[c]**	**103**	**91**
11	3	$Zn(OAc)_2$ ·$2H_2O$	5	16	50	2-MeTHF (1M)	8	92	9	109	91
12	3	$Zn(OAc)_2$ ·$2H_2O$	5	96	50	-	8	77	17	102	82
13	2	$Zn(OAc)_2$ ·$2H_2O$	5	16	50	-	17	74	10	101	88
14	1.5	$Zn(OAc)_2$ ·$2H_2O$	5	16	50	-	26	67	8	101	89

[a] Reaction conditions: **3a** (1 mmol), **4a** (1.5-3 mmol), catalyst (1-5 mol%). [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard. Sum of **3a**, **5a** and **6a** is the mass balance which can be more than 100% as there is an experimental error on each individual value. [c] Isolated yield. [d] Sum of **3a**, **5a** and **6a**. As there is an experimental error on each individual value, the sum can be more than 100%.

The optimal reactions conditions identified on the model system (3 equiv of alcohol, 1 mol% $Zn(OAc)_2{\cdot}2H_2O$ catalyst under neat conditions) gave 85% benzyl 2-hydroxy-propylphenyl carbonates (**5a**) (mixture of 2 regioisomers). Under these reaction conditions the alcohol scope for the selective opening of 4-propylcatechol carbonate (**3a**) was subsequently tested (Scheme 4). Alcohols that are solids required the addition of a solvent. On the basis of the optimization, 2-MeTHF (1M) was selected for this purpose (Table 1, entry 11). The use of primary aliphatic alcohols (**4a-f**) led to good isolated yields of the corresponding alkyl 2-hydroxy-propylphenyl carbonates (**5a-f**). Also primary alcohols which are secondary at the beta carbon (**4g-i**) performed well (**5g-i**). However, secondary

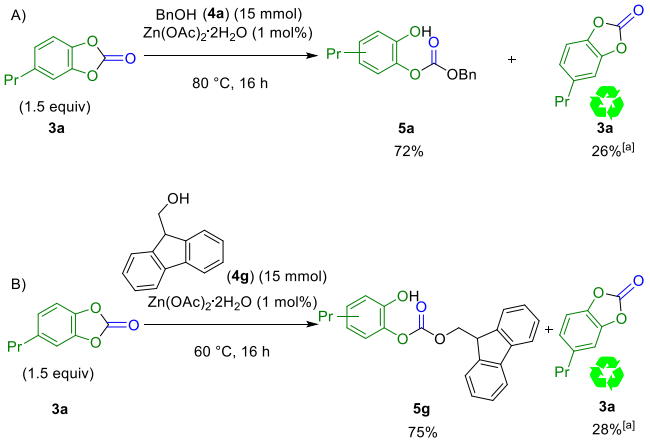
alcohols (**4j-m**), seemed to be more difficult, requiring a higher temperature. This is illustrated for **4j** and **4k** were a large amount of **3a** was remaining when heating at 50 °C for 16 h. Interestingly, at 80 °C high yield and excellent selectivity was achieved with secondary alcohols (**5j-5l**). Besides simple alcohols (**4a-g, 4j-k**), also structurally more complex alcohols were successfully applied, as exemplified by the use of *N*-Boc-piperidine-3-methanol (**4h**), the sugar diaceton-α-D-glucose (**4i**), cholesterol (**4l**), and L-menthol (**4m**) yielding the corresponding alkyl 2-hydroxy-propylphenyl carbonates **5h**, **5i**, **5l** and **5m**. Lastly, chemoselective reaction of a primary alcohol over a secondary alcohol was studied. When using hexane-1,5-diol (**4n**) and (9*Z*)-octadec-9-ene-1,12-diol (**4o**), the desired carbonates (**5n-o**) were obtained in moderate yields with very high chemoselectivity for the primary alcohol. The latter one is a biorenewable alcohol derived from Castor oil.[33]



Scheme 4. Reaction of 4-propylcatechol carbonate (**3a**) with alcohols (**4**).[a]

[a] Conditions: **3a** (5 mmol), **4** (15 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (1 mol%), 50 °C, 16 h. Isolated yield. [b] 2-MeTHF (5 mL). [c] 53% **3a** was recovered. [d] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard, 40% **3a** remaining. [e] 80 °C. [f] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard, 60% **3a** remaining. [g] 4% secondary alcohol product isolated.

The reaction of 4-propylcatechol carbonate (**3a**) with alcohols **4** on a larger scale (15 mmol) was also evaluated. Purification on this scale turned out to be easier when an excess of **3a** was used rather than an excess of alcohol **4** (Scheme 5). In this case a higher reaction temperature (60-80 °C) was beneficial. From a practical point of view an excess of reactant versus alcohol is more interesting in comparison to the reverse. As exemplified for benzyl alcohol (**4a**) and 9-fluorenemethanol (**4e**) with 1.5 equivalents of **3a** the desired alkyl 2-hydroxy-propylphenyl carbonate products, **5a** and **5e**, were obtained in 72% and 75% yield, respectively. Interestingly, the excess of 4-propylcatechol carbonate (**3a**) could be recycled in high yield. Benzyl 2-hydroxy-propylphenyl carbonates (**5a**) and 9*H*-fluoren-9-yl)methyl 2-hydroxy-propylphenyl carbonates (**5e**) are interesting new reactants to introduce a Cbz- or Fmoc protecting group (*vide infra*). After all, the classical CbzCl and FmocCl reactants are prepared from phosgene, need to be stored in the refrigerator and easily decompose in the presence of water.[4] Stability studies have shown that **5a** and **5e** can be stored at room temperature under air (See SI, section 7).



Scheme 5. Synthesis of A) benzyl 2-hydroxy-propylphenyl carbonates (**5a**) and B) (9*H*-fluoren-9-yl)methyl 2-hydroxy-propylphenyl carbonates (**5g**) at 15 mmol scale. [a] The recovered **3a** yield was calculated based on the initial amount of **3a** added (22.5 mmol). Considering full conversion of **4**, the recovered amount of **3a** has a maximum of 33%.

The remarkable difference in selectivity between the use of base (NaOMe) and Lewis acid ($Zn(OAc)_2{\cdot}2H_2O$) as catalyst (Table 1, entries 3 and 10) in the reaction with 4-propylcatechol carbonate (**3a**) prompted us to perform density functional theory (DFT) calculations (see SI, section 8). Catechol carbonate (**3a′**) and methanol (**4b**) were used as model. Both for the Lewis acid and base catalysis the second substitution step on **5b′.Zn(OAc)$_2$.MeOH** (Figure 1) and **5b′-H$^+$** (Figure 2), respectively, is the higher energy step. The activation energy for the former is 53.5 kJ/mol while the latter is substantially lower, i.e. 34.8 kJ/mol, rationalizing the selectivity obtained with Lewis acids. For the reaction with NaOMe catalyst it is important to realize that once the reaction has started this is not the actual catalytic species. Based on pK_A values these are either catecholate (**2a′-H$^+$**) or methoxycarbonyl catecholate (**5b′-H$^+$**) which will act as a base taking up the proton from MeOH. Both bases gave similar computational results (see SI, section 8). The alkali counter ion can sometimes play a significant role in the reaction mechanism, as for example reported by McGuinness.[34] DFT calculations of the base catalyzed cycle with (See SI, Figure S20) and without (Figure 2) the sodium counter ion however revealed no significant differences in the reaction path and their relative energies.

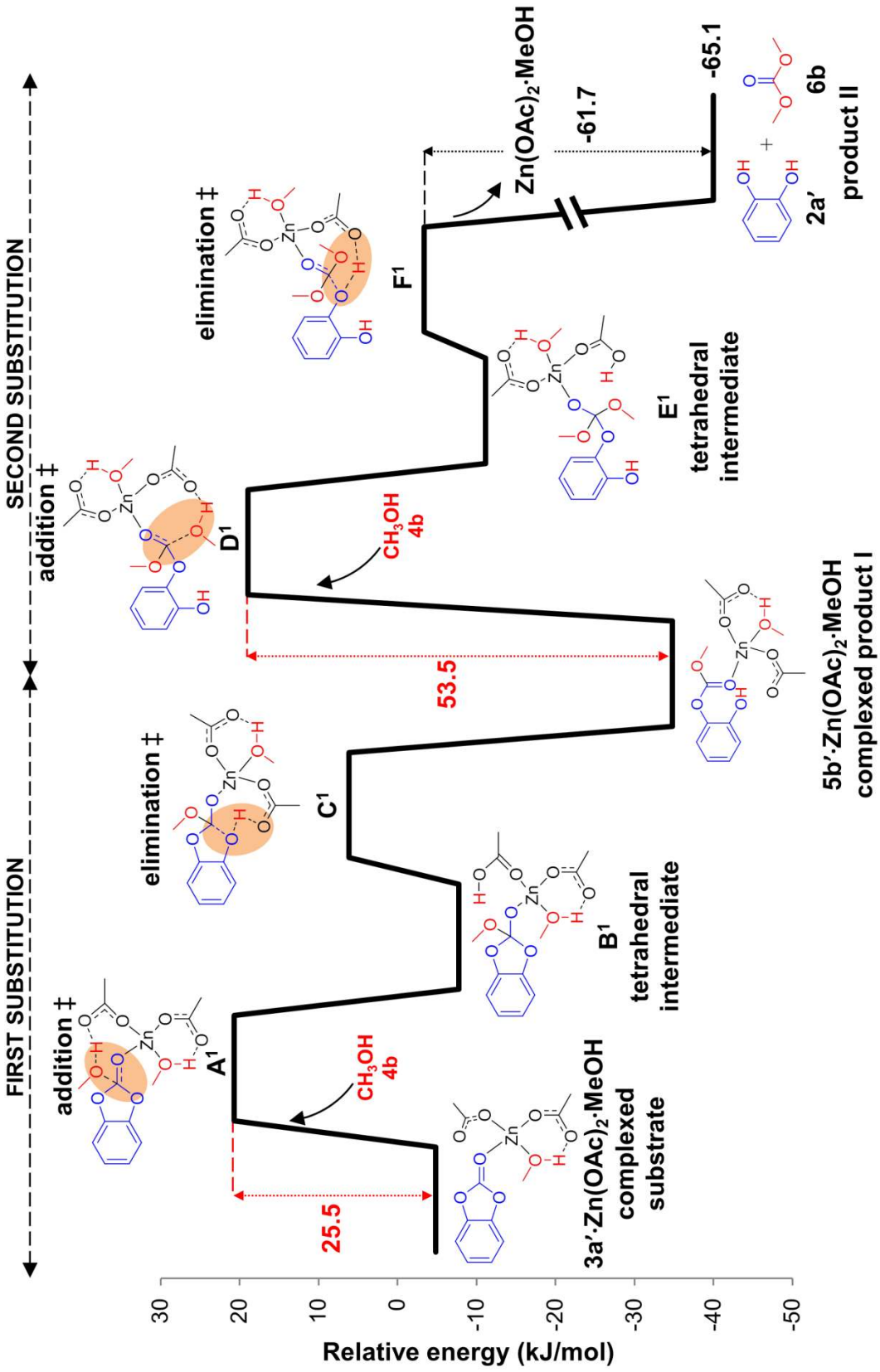


Figure 1. DFT calculation (B3LYP/6-31+G(d)) for the reaction of catechol carbonate (**3a'**) with methanol (**4b**) catalyzed by $Zn(OAc)_2{\cdot}2H_2O$.

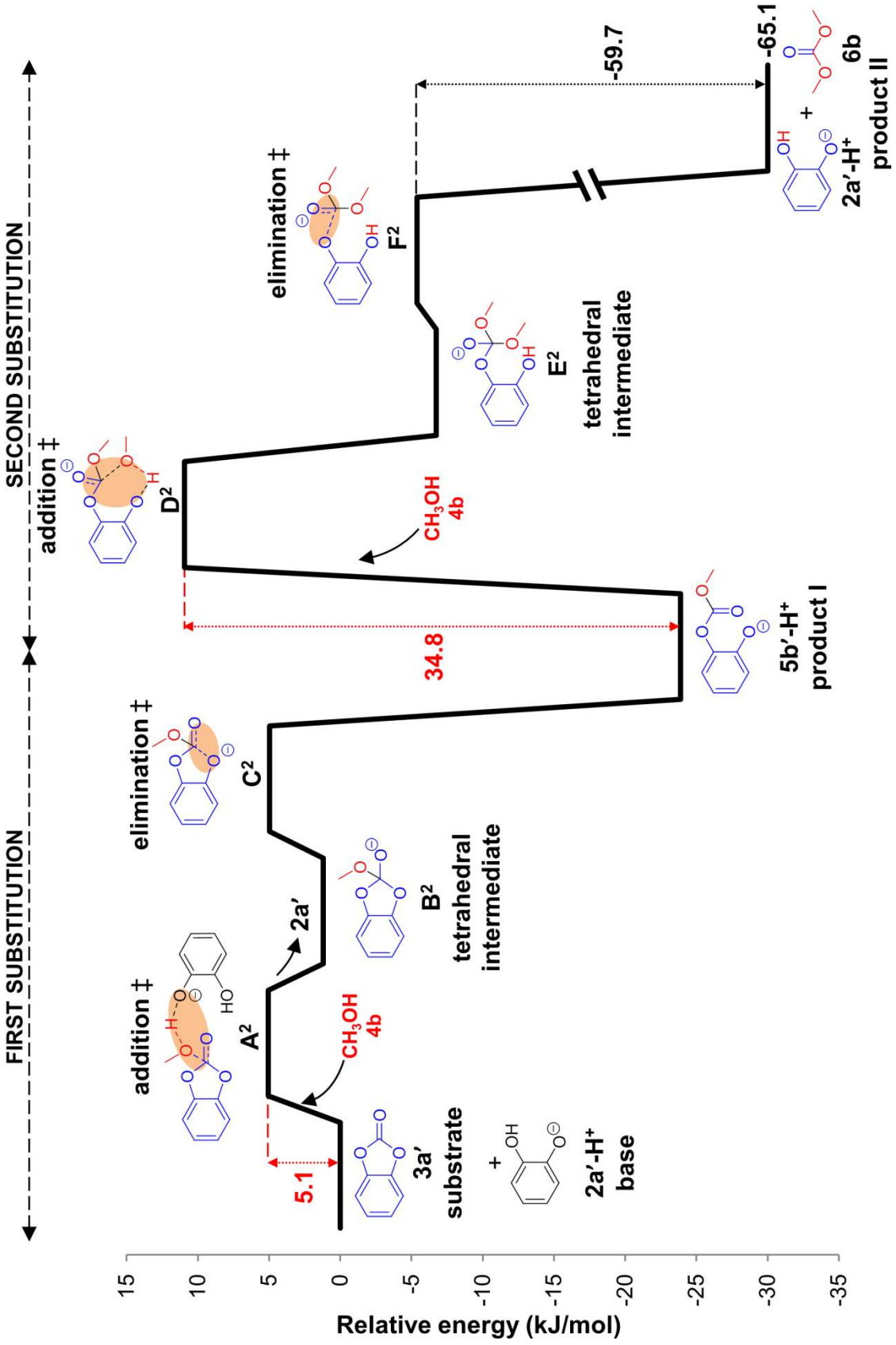
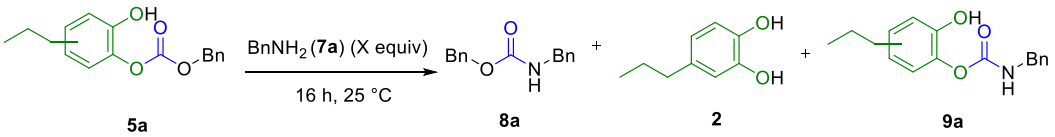


Figure 2. DFT calculation (B3LYP/6-31+G(d)) for the reaction of catechol carbonate (**3a'**) with methanol (**4b**) catalyzed by NaOMe.

Next, the transformation of the alkyl 2-hydroxy-propylphenyl carbonates (**5**) into carbamates (**8**) via reaction with amines was studied. The reaction of benzyl 2-hydroxy-propylphenyl carbonates (**5a**) with benzylamine (**7a**) was used as model. In EtOAc at room temperature 81% of benzyl benzylcarbamate (**8a**) was formed. However, also 2-hydroxy-propylphenyl benzylcarbamates (**9a**) were observed as side compounds. The symmetrical disubstituted urea, i.e. dibenzylurea, was not observed as a side product. **9a** are formed via catechol deprotonation followed by recyclization of **5a** into 4-propylcatechol carbonate (**3a**) and a subsequent reaction with **7a** (*vide infra*). Interestingly, solvent had a big influence on the selectivity (see SI, Table S11). Although all solvents tested gave complete conversion of substrate **5a**, only acetates (e.g. EtOAc, Table 2, entry 1), carbonates (DMC, Table 2, entry 3), and ethers (e.g. 2-MeTHF, Table 2, entry 6) featured >80% selectivity. Based on its biorenewability and non-miscibility with water, 2-MeTHF was selected for further optimization.[32] A decrease in concentration to 0.25 M did not give any improvement regarding selectivity (Table 2, entry 7). Increasing the amount of benzylamine, resulted in >95% selectivity (Table 2, entries 8 and 9). A slight excess of benzylamine (**7a**) (1.5 Equivalents) was found to be optimal as it features a good balance between selectivity for **8a** and excess of amine (Table 1, entry 8). A work-up procedure, containing different extraction steps, was developed to avoid purification via column chromatography (Scheme 6). Diluting the crude with an organic solvent (MTBE) and washing with aqueous NaOH removed the 4-propylcatechol (**2**) by-product. Washing of the organic phase with aqueous HCl allowed to remove the excess of amine, resulting in the desired benzyl benzylcarbamate (**8a**) in 90%. **2** could be isolated in 72% by acidification of the aqueous basic phase and extraction with organic solvent (MTBE) and subsequently recycled into carbonate **3a**. This reaction was also scaled to 10 mmol. At larger scale a higher yield of **8a** (98%) and by-product **2** (91%) was obtained (Scheme 6).

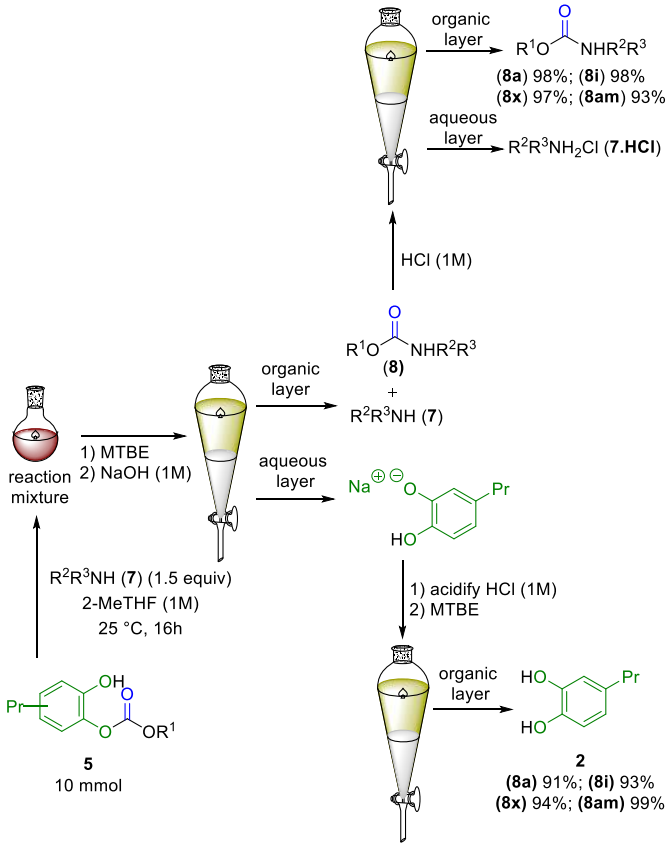
Table 2. Selected optimization data for the reaction of benzyl 2-hydroxy-propylphenyl carbonates (**5a**) with benzylamine (**7a**).[a]



5a **8a** **2** **9a**

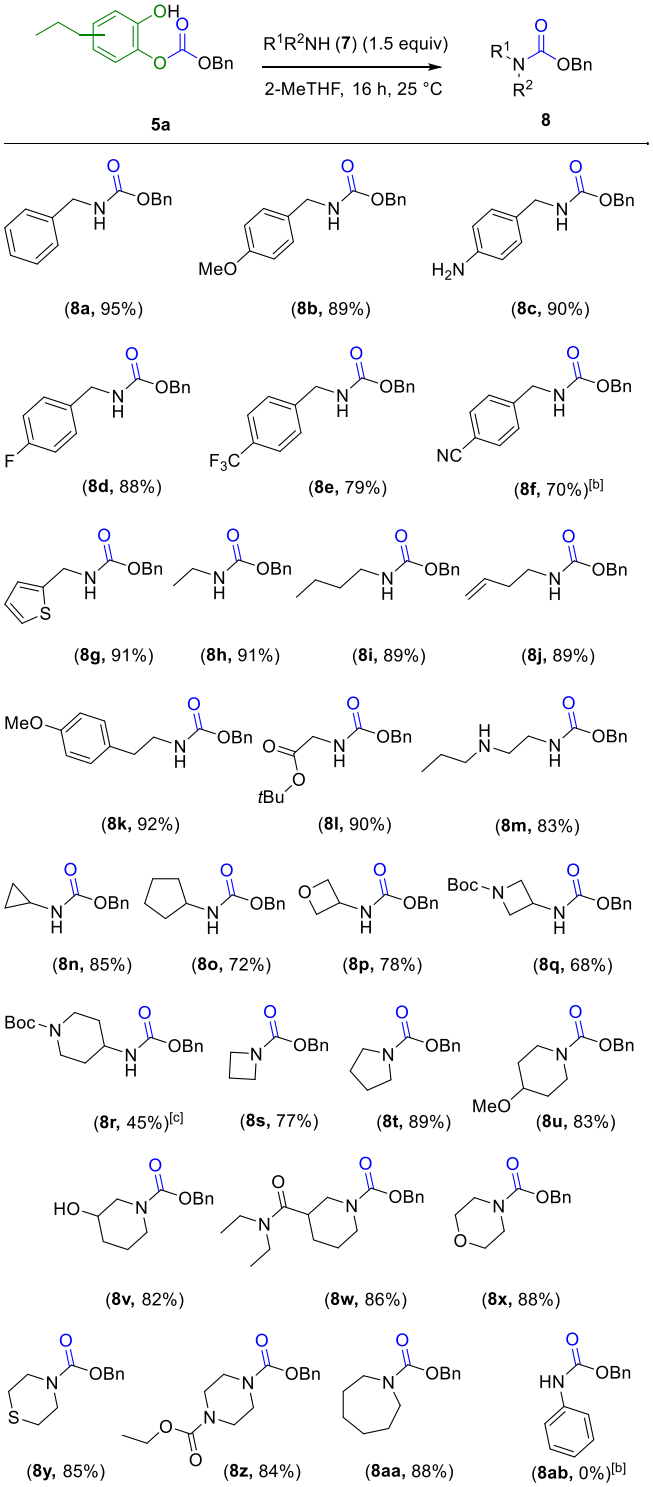
Entry	Amine load (X equiv)	Solvent	Concentration (M)	^{1}H NMR yield (%)[b]					Selectivity
				5a	**8a**	**9a**	**2**	**Mass balance[c]** %	**8a/(8a+9a)** %
1	1	EtOAc	1	0	81	19	82	100	81
2	1	*i*PrOH	1	0	72	23	74	95	76
3	1	DMC	1	0	83	19	79	102	81
4	1	MEK	1	1	54	51	56	106	51
5	1	DCM	1	0	78	25	64	103	76
6	1	2-MeTHF	1	0	92	12	94	96	88
7	1	2-MeTHF	0.25	1	90	14	88	105	87
8	**1.5**	**2-MeTHF**	**1**	**0**	**98 (95%)[d]**	**3 (3)[d]**	**104 (91)[d]**	**101 (98)[d]**	**97**
9	2	2-MeTHF	1	0	98	2	96	100	98

[a] Conditions: **3a** (1 mmol), **6a** (1-2.5 mmol), 16 h , 25 °C. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard. Sum of **5a**, **8a** and **9a** is the mass balance which can be more than 100% as there is an experimental error on each individual value. [c] Sum of **5a**, **8a** and **9a**. As there is an experimental error on each individual value, the sum can be more than 100%. [d] Isolated yield.



Scheme 6. Work-up of the synthesis of carbamates (**8**) at 10 mmol scale.

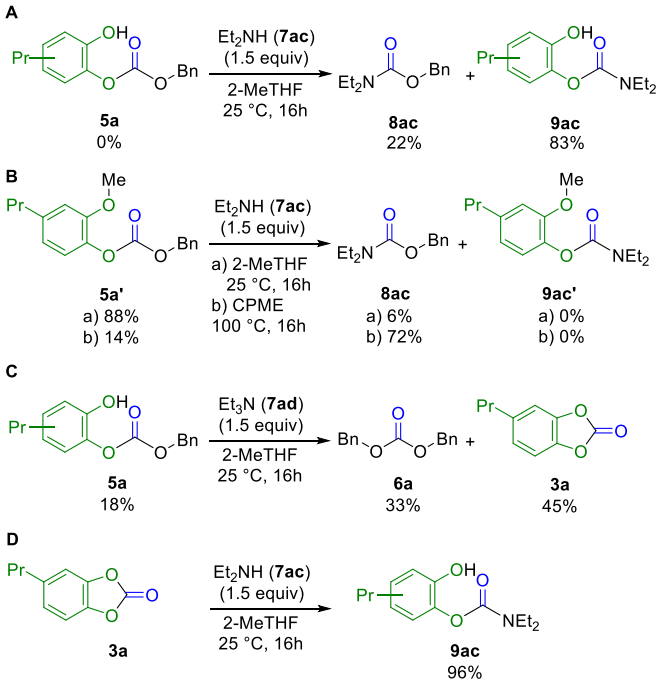
Under the optimal reaction conditions identified a set of different amines **7** was tested on **5a** yielding the corresponding Cbz-protected amines (**8a-aa**) (Scheme 7). Simple unbranched benzylic amines containing electron donating or withdrawing groups (**7a-f**) as well as heteroaromatic derivative (thiophene) (**7g**), and other aliphatic unbranched amines featuring different functionality (e.g. alkene, ether, ester, amine) (**7h-m**) worked well (**8a-m**). Interestingly, 4-aminobenzylamine (**7c**) featured a chemoselective reaction of the primary aliphatic over the primary aromatic amine.[35] Similarly, a primary reacted preferentially over a secondary aliphatic amine as exemplified by *N*^{1}-propylethane-1,2-diamine (**7m**) as the coupling partner (**8m**).[35] Also α-substituted (cyclic) primary amines (**7n-r**) resulted in good isolated yields (**8n-r**). Both carbocyclic (**7n-o**) as well as heterocyclic rings (**7p-r**) could be used (**8n-8r**). Cyclic secondary amines from different ring sizes (4-7) (**7s-aa**) could also be employed, including systems with an additional heteroatom (**7x-z**), producing the corresponding carbamates (**8s-8aa**) in high yield. In the piperidine series some substituents were screened as exemplified by an ether (**8u**), alcohol (**8v**), and carboxamide (**8w**). The alcohol of **7v** proved complete chemoselectivity for amine (**8v**). Unfortunately, less nucleophilic aromatic amine, e.g. aniline (**7ab**), did not afford any conversion and desired product **8ab**.



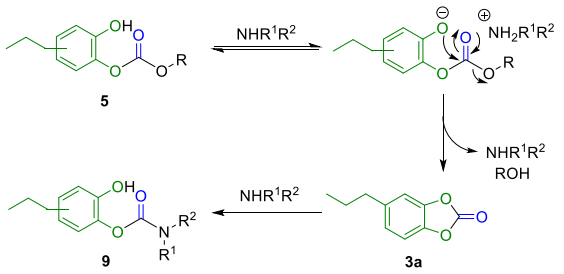
Scheme 7. Reaction of benzyl 2-hydroxy-propylphenyl carbonates (**5a**) with amines (**7**).[a] [a] Conditions: **5a** (1 mmol), **7** (1.5 mmol), rt, 16 h, 2-MeTHF (1 mL). Isolated yield. [b] 40 °C. [c] 45% of **9r** isolated.

Surprisingly, with acyclic secondary amines chemoselectivity was completely lost and 2-hydroxy-propylphenyl dialkylcarbamates (**9**) were the major compounds (Scheme 8). Upon reaction of **5a** with diethylamine (**7ac**) under standard reaction conditions for instance, 83% of undesired carbamate **9ac** was formed and only 22% of the desired carbamate **8ac** (Scheme 8A). Side product **9ac** is presumably formed by deprotonation of the catechol hydroxyl and subsequent recyclization into the cyclic 4-propylcatechol carbonate (**3a**). **3a** can then react with diethylamine giving side products **9ac**. This reaction is expected to be favoured over the desired one when sterically hindered basic amines are used. In line with this, when using cycloalkanamines and heterocyclic analogues a small amount of **9** was observed in the crude ^{1}H NMR spectrum (Scheme 7). Only in the case of the most hindered one, *N*-Boc piperidin-4-amine (**7r**), a substantial amount **9r** was formed which could be isolated (Scheme 7). To support the mechanism of formation of **9** (Scheme 9), three

extra experiments were performed. Methylation of the free OH of **5a** eliminates the possibility to deprotonate and therefore recyclization. Reaction of **5a'** with diethylamine (**7ac**) at room temperature was slow, but at 100 °C indeed only 4-propylcatechol (**2**) substitution occurred resulting in 72% of the desired benzyl diethylcarbamate (**8ac**), while no **9ac'** was observed (Scheme 8B). This supported the free OH plays a role in the formation of side compound **9**. Secondly, **5a** was reacted with triethylamine (**7ad**) which can act as a base but not yield carbamate. Gratifyingly, the crude reaction mixture showed the formation of 4-propylcatechol carbonate (**3a**) and dibenzyl carbonate (**6a**), supporting the basic properties of amines are indeed important (Scheme 8C). Lastly, **3a** was reacted with diethylamine (**7ac**) yielding the carbamate (**9ac**) in 96% yield (Scheme 8D). This implicates **9ac** can be formed from 4-propylcathechol carbonate (**3a**) under the standard reaction conditions, concluding the final step of the reaction mechanism (Scheme 9).

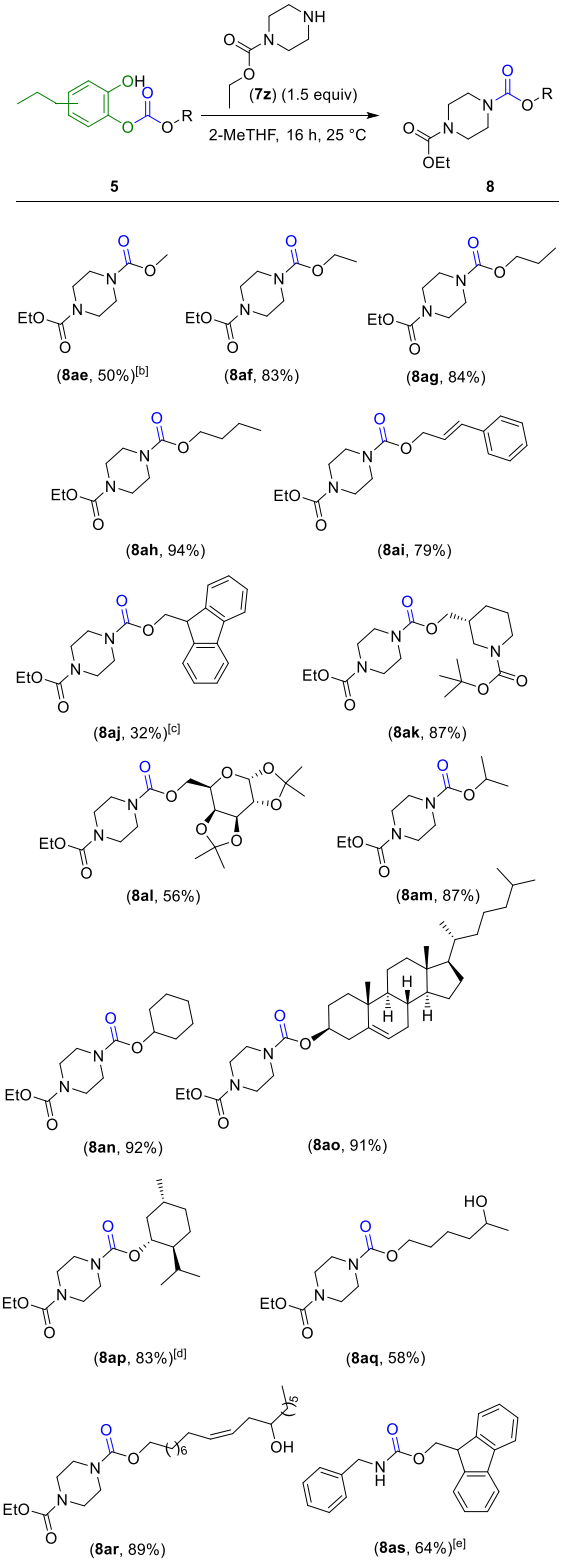


Scheme 8. Reaction of benzyl 2-hydroxy-propylphenyl carbonates (**5a**) with diethylamine (**7ac**) (A) and reactions to support the mechanism of formation of **9** (B – D). CPME = Cyclopentyl methyl ether.



Scheme 9. Mechanism of formation of **9** from **5** and NHR^1R^2.

Next, the other alkyl 2-hydroxy-propylphenyl carbonates **5** (Scheme 4) were also used in a reaction with amines to illustrate applicability. For this purpose ethyl 1-piperazinecarboxylate (**7z**) was chosen as a representative amine, resulting in good isolated yields for most of the substrates used without any further optimization (Scheme 10). However, in some cases a lower yield was obtained due to volatility of the carbamate (**8ae**) or incomplete conversion of substrate (**8ap**) at 25 °C. In the case of (9*H*-fluoren-9-yl)methyl 2-hydroxy-propylphenyl carbonates (**5g**) 21% of 9-methylidene-9*H*-fluorene was found as a side product. Considering Fmoc-deprotection is typically performed with morpholine or piperidine as a base this is not surprising.[36] With benzylamine (**7a**) for instance 64% **8as** was obtained. As mentioned for the model compound (**8a**) extractions were generally suitable to obtain the target compound and to recycle 4-propylcatechol (**2**). **2** was typically recycled in 42-84%. At larger scale recycling gives higher yield as exemplified by **8a** (72% versus 91%), **8i** (67% versus 93%), **8x** (67% versus 94%), and **8am** (60% versus 89%) (Scheme 6). In some cases the carbamate **8** was not pure enough after basic and acid washing and required further chromatography (**8e-f**, **o**, **q**, **r**, **ag**, **aj, al**, **aq, as**) (Scheme 7 and 10).



Scheme 10. Reaction of alkyl 2-hydroxy-propylphenyl carbonates (**5**) with ethyl 1-piperazinecarboxylate (**7z**).[a]

[a] Conditions: **5** (1 mmol), **7z** (1.5 mmol), 25°C, 16 h, 2-MeTHF (1mL). Isolated yield. [b] Lower yield due to the volatility of the compound. [c] 21% 9-methylidene-9*H*-fluorene due to Fmoc deprotection isolated. [d] 40 °C. [e] 1.5 equiv of benzylamine **7a**, 10% 9-methylidene-9*H*-fluorene due to Fmoc deprotection isolated.

To gain more insight on the relative rates of the reactions of **3a** with alcohols **4** and **5** with amines **7** we performed a kinetic study using *in situ* IR monitoring. Both model reactions on which the optimization was performed were followed in function of time; synthesis of carbonate **5a** (Figure 3A) and carbamate **8a** (Figure 3B). For comparison reasons these were executed in 2-MeTHF using the same initial concentration. For the first reaction the concentration of **3a** and **5a** and for the second reaction the concentration of **5a** and **8a** were followed over time. Figure 3 shows the second reaction step is significantly faster compared to the first one. The reaction of **5a**

with benzylamine (**7a**) is already completed in less than 1 hour. However a standard overnight reaction time of 16 hours was applied for the scope study of both reactions.

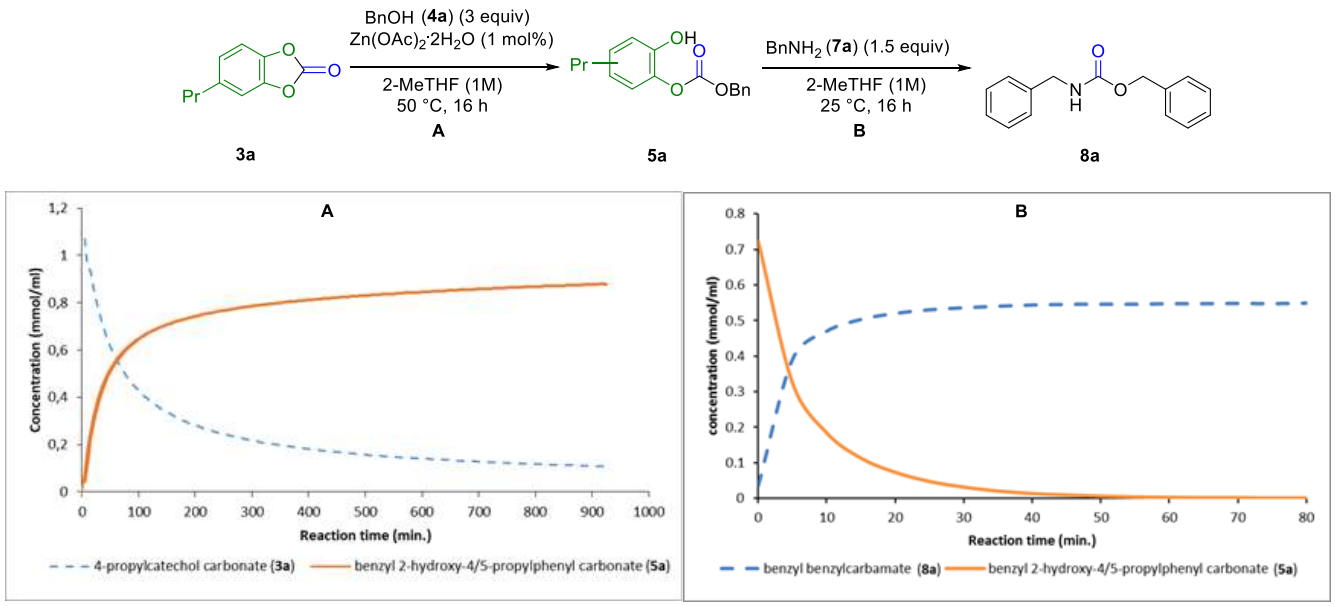


Figure 3. A) Concentration in function of reaction time for (A) the reaction of 4-propylcatechol carbonate (**3a**) with benzyl alcohol (**4a**). After 16h of reaction 10% **3a** remained (Table S6, entry 8) and B) the reaction of benzyl 2-hydroxy-4/5-propylphenyl carbonate (**5a**) with benzylamine (**7a**) (Table 2, entry 8). In both cases the CO stretch frequencies were used.

Conclusions

4-Propylcatechol carbonate has been introduced as a new renewable and stable C1 reactant, derived from wood and carbon dioxide. It features an excellent thermal and water stability. In this work the cyclic carbonate reactant has been used to synthesize carbamates in two steps, i.e. substitution with alcohol followed by amine, under mild reaction conditions. This order avoids isocyanate intermediates (or their unstable precursors), which are generally toxic.[2] In the first reaction step of the process, 4-propylcatechol carbonate is reacted with an alcohol under mild conditions. Secondary alcohols need a higher temperature (80 °C) than primary (50 °C). When the alcohol is liquid no solvent is required and reactions can be run neat which is beneficial from a green chemistry point of view. Alkyl 2-hydroxy-propylphenyl carbonates can be selectively obtained provided a Lewis acid catalyst is used. The cheap and non-toxic $Zn(OAc)_2{\cdot}2H_2O$ was preferred considering its use as a food additive. To the best of our knowledge, these are the first examples of selective ring opening of catechol carbonates with alcohols. Base catalysis exclusively yields symmetrical dialkyl carbonates via double substitution. DFT calculations allowed to rationalize this remarkable difference in reactivity. The alkyl 2-hydroxy-propylphenyl carbonate intermediates generally feature good thermal stability (up to 100 °C) and can subsequently be transformed into carbamates by reaction with amines at room temperature. Basic and sterically hindered amines give competitive intramolecular substitution into 4-propylcatechol carbonate, initiated via phenolic OH deprotonation, which upon subsequent reaction with the amine yield 2-hydroxy-propylphenyl alkylcarbamates side products. Benzyl 2-hydroxy-propylphenyl carbonates and (9*H*-fluoren-9-yl)methyl 2-hydroxy-propylphenyl carbonates are particularly interesting compounds as they can be used as alternative reactants to protect amines with a Cbz- or Fmoc group. These reactants are more stable than the standardly phosgene derived CbzCl and FmocCl used. In the reaction of alkyl 2-hydroxy-propylphenyl carbonates with amines 4-propylcatechol by-product is released. This can be easily separated from the target compound via aqueous basic extraction. Acidification easily allows its recovery and transformation into C1 carbonate reactant.

Experimental Section

Materials

All chemicals used in this report were commercially sourced and used as received unless otherwise stated. For all compounds, full characterization data consisting of ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR, 2D COSY NMR, and HRMS is provided (See ESI).

Synthesis of 4-propylcatechol (2)

A 250 mL roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (**1**) (32.2 g, 200.0 mmol, 1 equiv) and 48% aq. HBr (81.0 g, 1000.0 mmol, 5 equiv). The obtained mixture was stirred for 16 h at 115 °C (oil bath). After cooling down to room temperature, the mixture was diluted with 160 ml MTBE (2-methoxy-2-methylpropane), washed with 50 ml brine, 3x50 ml saturated $NaHCO_3$ solution, and again with 50 ml brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequently, the residue was freeze dried in order to remove the last traces of solvent and to obtain pure 4-propylbenzene-1,2-diol (**2**) as an off-white solid (29.6 g, 97%).

Synthesis of 4-propylcatechol carbonate (3a)

A 500 mL 3-necked roundbottom flask equipped with a stirring bar, an adaptor with side arm bearing 4 Å molecular sieves (8-12 mesh) and a reflux condensor is charged with 4-propylbenzene-1,2-diol (**2**) (25.0 g, 164.0 mmol, 1 equiv,), sodium methoxide (0.293 g, 5.42 mmol, 0.033 equiv) and dimethyl carbonate (518 g, 484 mL, 5749.0 mmol, 35 equiv). The mixture is stirred under argon atmosphere and heated to reflux (oil bath) for 28 h. Afterwards, the crude reaction mixture is cooled to room temperature, and diluted with 200 mL MTBE. The resulting mixture is filtered over a plug of celite. The filtrate is washed with 200 mL aqueous HCl (1M), and the organic phase dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified using automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane to 98% heptane/2% EtOAc over 60 min, 30 mL/min) to give the title compound (**3a**) as a colorless liquid (25.2 g, 86%).

Synthesis of alkyl 2-hydroxy-5-propylphenyl carbonate and alkyl 2-hydroxy-4-propylphenyl carbonate (5)

A 10 mL vial, equipped with a stirring bar, was charged with 4-propylcatechol carbonate (**3a**) (1 equiv), alcohol (3 equiv) and $Zn(OAc)_2{\cdot}2H_2O$ (1 mol%). In case of solid alcohol 2-MeTHF was added (1M). The vial was sealed with an aluminum

crimp cap with septum. The reaction mixture was then stirred at 50 °C for 16 h (primary alcohols) or 80 °C for 16 h (secondary alcohols). Afterwards the mixture was cooled to room temperature, dissolved in a small amount of toluene and transferred directly to a silica cartridge via a syringe for purification. Purification of **5** was carried out using an automated flash chromatography system with a solvent system as specified for the specific compound.

Synthesis of carbamates (8)

A 10 mL vial, equipped with a stirring bar, was charged with the appropriate carbonate **5** (1 equiv), and 2-MeTHF (1M). Afterwards the appropriate amine **7** (1.5 equiv) was added. The vial was sealed with an aluminum crimp. cap with septum. The reaction mixture was then stirred at 25 °C for 16 h. After reaction, the crude was diluted with (30 mL/mmol MTBE, washed with 3x9 mL/mmol aqueous NaOH (1M), 2x9 mL/mmol aqueous HCl (1M), 1x9 mL/mmol saturated $NaHCO_3$ solution, and with 1x9 mL/mmol brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness yielding the desired carbamate **8**. In order to recover 4-propylcatechol (**2**), the NaOH phase was acidified with 35 mL/mmol aqueous HCl (1 M) and extracted with 3x10 mL/mmol MTBE. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give **2**.

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Keywords: C1 reactant • catechol carbonate • renewable • carbamate • Zn catalysis

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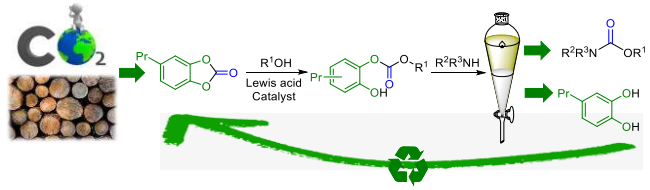
Carbamate Synthesis Via a Shelf Stable and Renewable C1 Reactant



4-Propylcatechol carbonate is a shelf-stable and renewable C1 reactant which has been used for the synthesis of carbamates in two consecutive steps under mild reaction conditions. It is easily prepared from renewable 4-propylcatechol (derived from wood) and dimethyl carbonate (derived from CO_2) using a reactive distillation system. By-product 4-propylcatechol can be recycled.