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Final Report

Application of P-based organocatalysts and biocatalysts for the racemic resolution of carbonates – P-RaceCar

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Table of content

* z.B. Conference contributions, publications (with status), funding applications (with status)

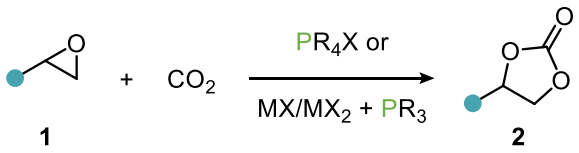
1. Summary

Phosphines proved to be efficient ligands for the CaI_2-catalyzed synthesis of cyclic carbonates from epoxides and CO_2. Ph_3P was also used as co-catalyst for the conversion of internal and bio-based carbonates. Thus, the dual role of phosphines as catalysts was demonstrated: they act as ligands for CaI_2 allowing the activation of the epoxide and they also activate the CO_2 molecule improving its reactivity. Moreover, the hydrolytic kinetic resolution of cyclic carbonates with Pig Liver Esterase was studied with the aim of performing the synthesis of cyclic carbonates catalyzed by a P-based catalyst followed by the enzymatic kinetic resolution to afford the chiral carbonate. Even though the tandem reaction was not successful, further analysis and perspectives on this reaction were presented. As a result, Novozym® 435 in combination with phosphonium salts is a promising alternative for the asymmetric synthesis of cyclic carbonates.

2. Introduction and aim of the project

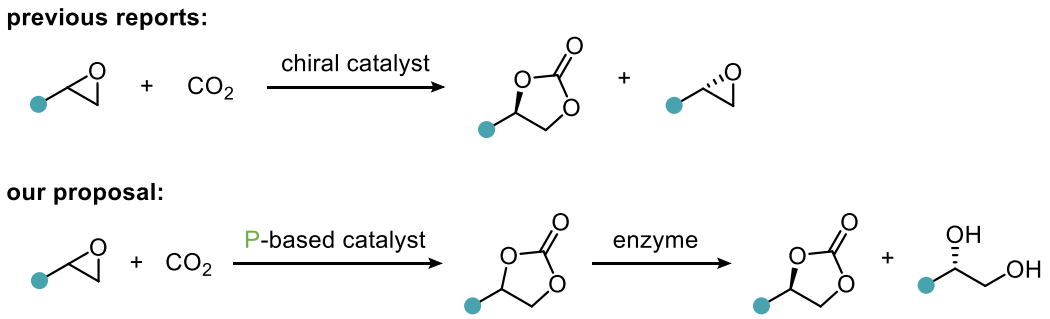
Cyclic carbonates have gained increasing attention in the past decades since they can be synthesized from CO_2, which is no longer considered a waste but rather a nontoxic, abundant and inexpensive C1 source.[1, 2] These carbonates find numerous applications in industry and academia due to their benign properties such as low vapor pressure, low toxicity, high flash point and high dielectric constant. They are considered green solvents and several reports show the advantages of using them in different processes.[3, 4] On the other hand, the cyclic carbonate moiety presents an interesting reactivity that makes these compounds useful building blocks. For example, cyclic carbonates can undergo ring-opening polymerization, decarboxylation, hydrogenation and transesterification.[5-9] In addition to the reactions of the carbonate moiety, the different substituents of the cycle can be further functionalized for the synthesis of different chemicals.[10] Altogether, the versatility of these compounds and their importance in the valorization of CO_2 make their study highly relevant in the context of green chemistry.

Among the different routes for the preparation of cyclic carbonates, the cycloaddition of CO_2 to epoxides is the most studied reaction. However, due to the kinetic inertness and thermodynamic stability of the CO_2 molecule, a catalyst is necessary to overcome the energetic barrier.[11, 12] Since, in general, the use of transition metal catalysts is undesired, organocatalysts and alkaline metal catalysts are preferred among the reported systems. In this regard, phosphorous plays a relevant role in this reaction: several phosphonium salts can catalyze this reaction and the strategic tunning of the structure gives the catalyst different properties; phosphines on the other hand, might act as ligands for metallic centers allowing the reaction to proceed at milder conditions and are effective for the CO_2 activation by forming adducts that facilitate the reaction (**Scheme 1**).[13-15]



Scheme 1. Synthesis of cyclic carbonates from epoxides and CO_2 catalyzed by P-based catalysts.

A vast number of catalytic systems have been reported for the synthesis of cyclic carbonates from epoxides and CO_2 and a high level of understanding of this reaction has been achieved. However, most reports focus on the synthesis of the racemic cyclic carbonates while their asymmetric synthesis remains unexplored. The general strategy is the kinetic resolution of epoxides, this is, the selective cycloaddition of CO_2 to epoxides. Organocatalysts reported so far cannot achieve high selectivity and the transition metal catalysts (Co, Al, Ir, Cr) present good selectivity but a limited substrate tolerance and the disadvantages of air sensitive and toxic complexes.[16-21] Instead, we proposed the hydrolytic kinetic resolution of cyclic carbonates as an alternative. In this approach, the racemic cyclic carbonates are selectively hydrolyzed affording, ideally, the enantiopure diol and unreacted carbonate. Since this proposal consists on the selective hydrolysis of the cyclic carbonate moiety, carboxylesterases emerge as potential catalysts for this reaction. For example, previous studies show that Pig Pancreas Lipase and Pig Liver Esterase (PPL and PLE) can perform this reaction.[22, 23] The use of enzymes is not only an alternative to the use of metal catalysts but also presents additional advantages, including the possibility of immobilizing the catalyst on a support and/or performing modifications to bind covalently a suitable catalyst to be used in a tandem reaction. Therefore, the aim of this work is to prepare enantiopure cyclic carbonates by converting racemic epoxides into racemic cyclic carbonates with the aid of P-based catalysts and further hydrolyze the cyclic carbonates affording the enantioenriched products (**Scheme 2**). As final goal, the tandem chemoenzymatic reaction is desired.

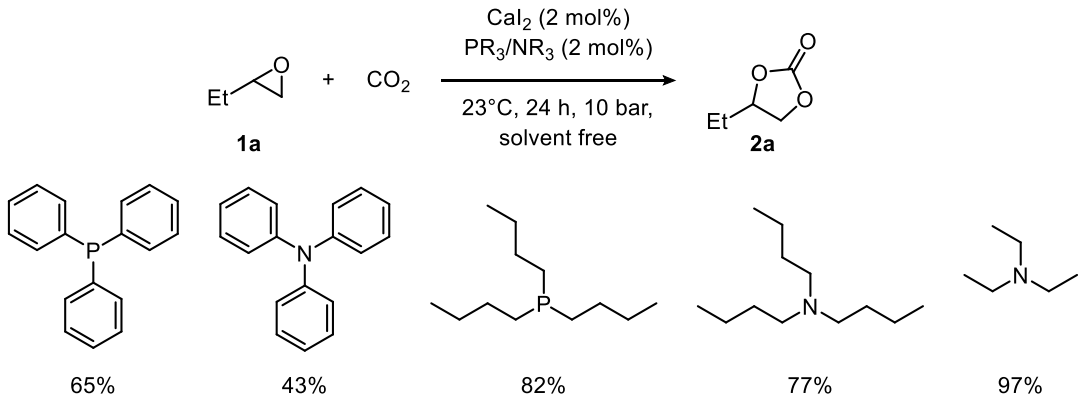


Scheme 2. Different strategies for the asymmetric synthesis of cyclic carbonates.

3. Results and discussion

Alkali metal salts are efficient catalysts for the conversion of epoxides to cyclic carbonates. Their activity relies on the Lewis acidic metallic center that activates the epoxide, enabling the nucleophilic ring opening by the anion that leads to the carbonate formation. These inorganic salts present higher activity in combination with an adequate ligand. In this regard, previous work in our group was carried out using CaI_2 with complexing agents such as crown

ether and polyethers.[14, 24, 25] We became interested in the use of readily available phosphines and amines as potential ligands. Thus, the conversion of butylene oxide (**1a**) to butylene carbonate (**2a**) was chosen as model reaction for the screening of different tertiary phosphines and amines in combination with CaI_2 (**Scheme 3**). In the absence of a ligand the carbonate was obtained in 23%. When triphenylphosphine was added, **2a** was afforded in 65% yield, showing a better activity than its analogous amine, triphenylamine, which gave **2a** in 43% yield. Tributylphosphine showed a good activity, yielding **2a** in 82%, while the use of tributylamine led to **2a** in 77% yield. Surprisingly, triethylamine showed to be an efficient ligand for CaI_2, since the yield increased to 97%. Altogether, two trends can be easily observed: the reaction is favored by a lower steric bulkiness of the ligand and phosphines give slightly better results than the analogous amines.

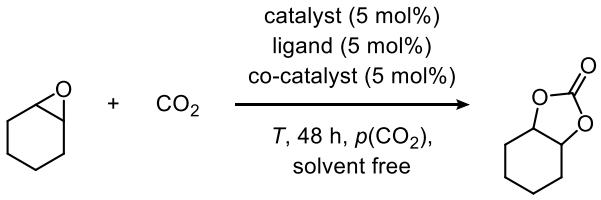


Scheme 3. Selected ligands screened for the conversion of butylene oxide (**1a**) to butylene carbonate (**2a**) with CO_2 catalyzed by CaI_2. Reaction conditions: 1.0 equiv. of **1a** (10.0 mmol), 2 mol% CaI_2 and 2 mol% ligand, 23°C, 24 h, solvent free, $p(CO_2)$ = 10 bar. Yields were determined by ^{1}H NMR using mesitylene as the internal standard.

After exploring the scope of this catalytic system for other terminal substrates (**Appendix**) we decided to further exploit it for the conversion of internal epoxides to their corresponding carbonates. Typically, due to the higher steric restriction, these carbonates are only converted under harsh conditions which makes this reaction challenging. Under the first conditions tested for the conversion of cyclohexene oxide (**3a**) (5 mol% of CaI_2/Et_3N, 45°C, 48 h, 10 bar), the product (**4a**) was obtained only in 27% yield (**Table 1, entry 1**). An increase in the temperature to 70°C resulted in a higher yield of 59%. As an alternative to overcome the kinetic barrier of this reaction, the use of a co-catalyst that activates the CO_2 molecule was evaluated. With this strategy, the simultaneous epoxide activation by the catalytic system in combination with the CO_2 activation can lead to the formation of the desired carbonate. Thus, diazabicyclo-undecene (DBU), 4-Dimethylaminopyridine (DMAP), and triphenylphosphine (Ph_3P) were tested as co-catalyst. Among them, Ph_3P showed to be most effective co-catalyst for the synthesis of internal carbonates, affording **4a** in 84% yield, at 70°C and 10 bar. A further increase in the temperature and pressure to 90°C at 50 bar showed to be detrimental for the reaction due to the formation of by-products. Furthermore, the corresponding control experiments were performed: in the absence of the

ligand, the yield dropped to 27%, and the use of Ph_3P without CaI_2/Et_3N gives only 3% of the product.

Table 1. Co-catalyst screening for conversion of cyclohexene oxide (**3a**) to cyclohexene carbonate (**4a**) with CO_2 catalyzed by CaI_2/Et_3N.



3a **4a**

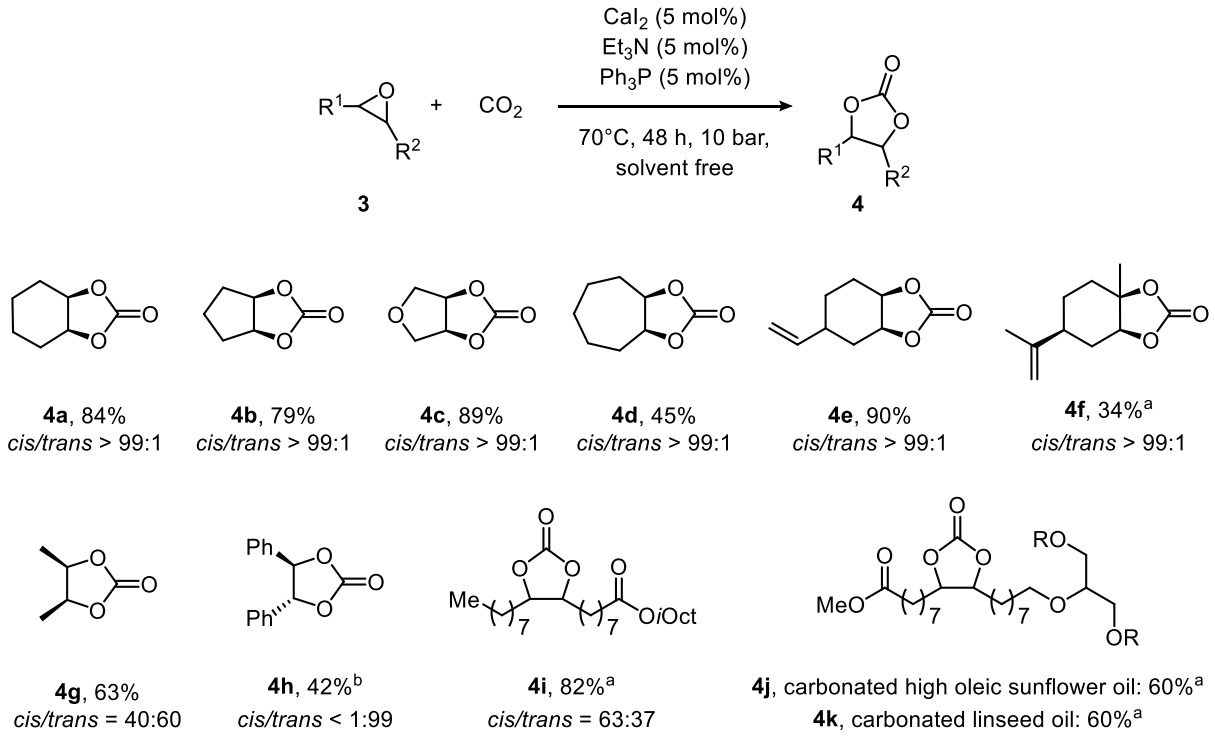
Entry	Catalyst	Ligand	Co-catalyst	T (°C)	$p(CO_2)$ (bar)	Yield 4a[a] (%)
1	CaI_2	Et_3N	–	45	10	**27**
2	CaI_2	Et_3N	–	70	10	**59**
3	CaI_2	Et_3N	DBU	70	10	**54**
4	CaI_2	Et_3N	DMAP	70	10	**72**
5	CaI_2	Et_3N	Ph_3P	70	10	**84**[b]
7	CaI_2	Et_3N	Ph_3P	90	50	**61**
8	CaI_2	–	Ph_3P	70	10	**27**
9	–	–	Ph_3P	70	10	**3**

[a] Reaction conditions: 1.0 equiv. **3a** (10.0 mmol), CaI_2 (0.05 equiv.), Et_3N (0.05 equiv.), and co-catalyst (0.05 equiv.), 48 h, solvent free. Yield determined by ^1H NMR using mesitylene as internal standard. [b] Isolated yield.

Under the optimized conditions several internal epoxides were converted (**Scheme 4**). The bicyclic carbonates **4a**–**4e** were isolated in moderate to excellent yields up to 90% with *cis*/*trans* > 99:1. Linear internal carbonates, **4g** and **4h**, were converted in moderate yields of 63 and 42%, respectively. In this case, while **4h** showed retention of the configuration affording the product with *cis*/*trans* < 99:1, *cis*-**3g** was converted to **4g** with partial loss of the stereochemical information. This can be understood based on the mechanism of the reaction: while in the main pathway there is a double inversion of the configuration that leads to an overall retention of the stereocenter, a second pathway is also possible, in which case, the formation of a carbonium ion leads to the *trans*-**4g** as the thermodynamic product.

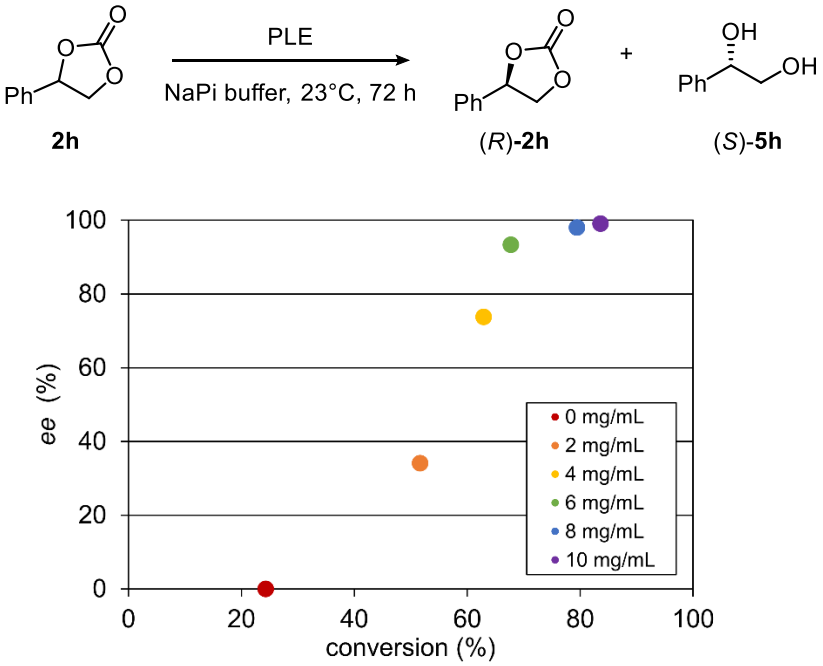
Moreover, we became interested in the synthesis of bio-based cyclic carbonates. These substrates are interesting from the environmental perspective since the replacement of hydrocarbons from crude oil for renewable resources is deemed necessary for a transition to a more sustainable circular economy. Due to the higher demand of these substrates, the catalyst loading had to be increased to 10 mol% and pressures of 30 bar and reaction times of 72 h were needed. While the conversion of *iso*-octyl oleate **4i** was achieved with 82% yield under these conditions, both the epoxidized high oleic sunflower oil and linseed oil afforded the corresponding products **4j** and **4k** in 60% yield. Moreover, the conversion of limonene oxide (**3f**) was achieved in 34% yield, with retention of the configuration (*cis*/*trans* > 99:1). This lower result can be explained by the high steric hindrance present in trisubstituted epoxides that limits their reactivity.

Overall, phosphines showed a double role in the synthesis of cyclic carbonates from epoxides and CO_2: they can act as ligands for CaI_2 enhancing the activity of the salt, while they can also activate the CO_2 molecule for the conversion of challenging internal epoxides.



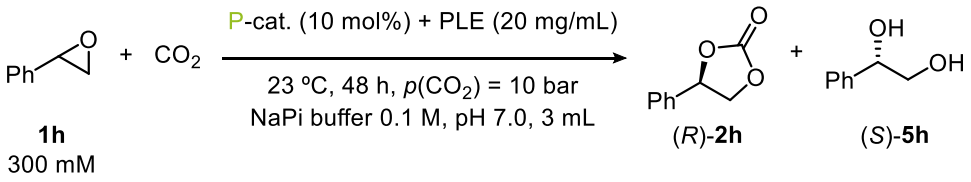
Scheme 4. Reaction conditions: epoxide **3** (25.0 mmol), 5 mol% CaI_2/Et_3N and 5 mol% Ph_3P, 70°C, 48 h, solvent free, $p(CO_2)$ = 10 bar. Isolated yields are given. [a]10 mol% CaI_2/Et_3N and 10 mol% Ph_3P, $p(CO_2)$ = 30 bar, 72 h. [b] CH_3CN was used as solvent.

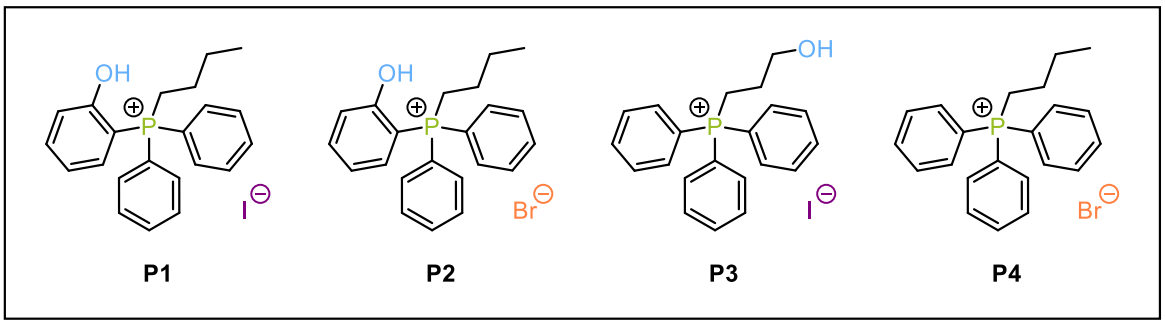
Once the cyclic carbonates were prepared, we became interested in the synthesis of enantiopure cyclic carbonates from epoxides and CO_2. The strategy proposed was to use an enzyme for the hydrolytic kinetic resolution of cyclic carbonates (**Scheme 5**). Preliminary studies were performed using Pig Liver Esterase (PLE) for the kinetic resolution of styrene carbonate. The control reaction without enzyme gave a conversion of 24%, which shows that the non-selective hydrolysis of the carbonate in the aqueous media is a competitive reaction. With a concentration of 2 mg/mL of PLE **2h** was converted in 52% with an *ee* of 32%. Increasing amounts of enzyme led to higher *ee* values. With 8 and 10 mg/mL *ee* values of 98 and 99% were achieved, with conversions of 79 and 83%, respectively.



Scheme 5. Study of enzyme concentration for the kinetic resolution of styrene carbonate (**2h**). Reaction conditions: 10 mM of **2h** in 5 mL of NaPi buffer (0.1 M, pH 7.0), 0–10 mg/mL of PLE, 23°C, 48 h.

Since the enzyme proved to be active for the substrate, obtaining (*R*)-**2h** in high *ee*, the tandem synthesis of cyclic carbonates followed by the enzymatic kinetic resolution was evaluated. Four phosphonium salts were tested as P-based catalysts since these organocatalysts are stable in aqueous media and the presence of water can also be beneficial for the activation of the epoxide.[26] The cycloaddition reaction was performed with 10 mol% of the organocatalysts in 3 mL of buffer with a pressure of 10 bar of CO_2 (**Scheme 6**).





Scheme 6. Cycloaddition of CO_2 to styrene oxide (**1h**) catalyzed by phosphonium salts (P1–P4) followed by enzymatic kinetic resolution of styrene carbonate to afford (*R*)-**2h**. Reaction conditions: 300 mmol/L of **1h** in 3.0 mL of NaPi buffer (0.1 M, pH 7.0), 10 mol% of P-cat., 20 mg/mL of enzyme,

23°C, 48 h. Conversions and *ee* values were determined by GC-FID using hexadecane as the internal standard.

A concentration of 300 mM was chosen for styrene oxide; even though this is a high substrate concentration for the enzyme, the progressive conversion would keep the concentration of styrene carbonate low to further react with the enzyme. As expected, the control reaction without catalyst showed no product (**Table 2**, **Entry 1**) and the enzyme, in the absence of the organocatalysts did not convert the styrene oxide to the carbonate (**Entry 2**). Furthermore, the organocatalyst screening was performed in absence of the enzyme: **P1** showed the best activity affording the racemic carbonate **2h** in 58% yield (**Entry 3**). This is particularly interesting since the analogous catalyst with an alcohol moiety, **P3**, gave only 12% of the product (**Entry 5**), demonstrating that the phenol moiety plays a role in the catalysis of the reaction even in the presence of a large amount of water. Once **P1** was selected as the most suitable catalyst, the chemoenzymatic reaction was performed (**Entry 7**). Even though the activity of the phosphonium salt dropped giving the product in 38%, the synthesis of the racemic carbonate proved to be feasible. Unfortunately, the enzyme showed no activity since only the racemic mixture was obtained (*ee* = 0%).

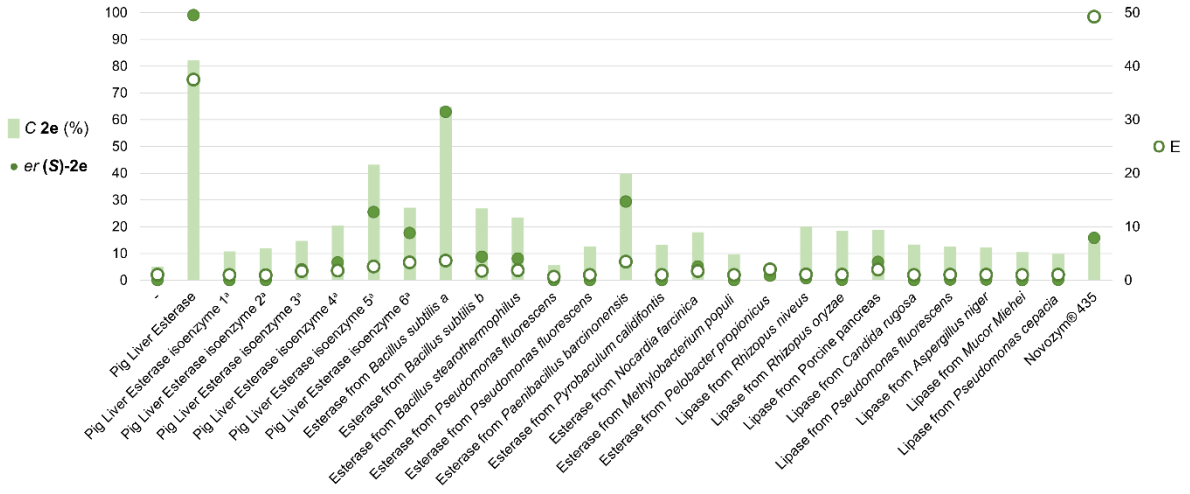
Table 2. Tandem synthesis of cyclic carbonates catalyzed by phosphonium salts followed by enzymatic kinetic resolution.

Entry	P-cat./PLE	yield (*R*)-2h (%)	*ee* (*R*)-2h (%)
1	–/–	0	–
2	–/PLE	0	0
3	P1/–	58	–
4	P2/–	9	–
5	P3/–	12	–
6	P4/–	32	–
7	P1/PLE	38	0

We sought to find alternatives to overcome the inactivity of the enzyme. Thus, we performed an extensive enzyme screening to find a more suitable biocatalyst (**Scheme 7**). In this case, we chose 4-(chloromethyl)-1,3-dioxolan-2-one (**2e**) as substrate for several reasons: 1) it can easily be prepared from epichlorohydrin derived from glycerol, which is a waste from biodiesel production; 2) it is an useful chiral building block since the chlorine moiety can be further functionalized into fine chemicals, such as compounds with pharmacological activity; 3) preliminary experiments with PLE showed promising results in terms of selectivity towards the hydrolysis of the (*R*)-enantiomer; 4) no previous studies report the kinetic resolution of this substrate or its derivatives.

26 esterases and lipases were evaluated for the asymmetric hydrolysis of **2e** (**Scheme 7**). The control reaction gave only 5% conversion of the substrate. Notably, commercial PLE afforded (*S*)-**2e** with a good selectivity factor (E = 38). The rest of the esterases recombinant from *E. coli* (including the recombinant PLE isoenzymes) gave low activity despite the different conversion rates. Lipases also showed low conversion and no selectivity for the asymmetric

hydrolysis with the exception of Novozym® 435, which presented the highest selectivity (E = 49) despite the low conversion (14%). This result is particularly interesting as Novozym® 435 is also active in organic solvents and biphasic systems, meaning that it might be a better choice for the tandem reaction with a phosphonium salt. Moreover, since Novozym® 435 is an immobilized enzyme its recovery and recycling is straightforward and the support of the P-based catalyst on the support is feasible.



Scheme 7. Kinetic resolution of (**2e**) with esterases and lipases. Reaction conditions: 10 mmol/L of **2e** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 4 mg/mL of enzyme, 23°C, 24 h. Conversions (■), *ee* values (●) were determined by GC-FID using hexadecane as the internal standard. E-values (○) were calculated. [a]20 h.

4. Further achievements/ benefit from the project

Poster presentations:

1. "Pig Liver Esterase-Catalyzed Kinetic Resolution of Cyclic Carbonates", C. Terazzi, T. Werner, J. von Langermann, *Biotrans*, 19.–22. July **2021**, Graz, Austria (online).
2. "Cyclic Carbonates Synthesis Catalyzed by CaI_2·Et_3N", C. Terazzi, K. C. Laatz, J. von Langermann, T. Werner, *55. Jahrestreffen Deutscher Katalytiker*, 27.–29. June **2022**; Weimar, Germany.

Oral presentations:

1. "Application of P-based Organocatalysts and Biocatalysts for the Kinetic Resolution of Racemic Carbonates P-RaceCar", C. Terazzi, J. von Langermann, T. Werner, *International P-Campus-Symposium*, 16.–17. Nov. **2020**, Leibniz Institute for Baltic Sea Research Warnemünde (IOW), Warnemünde, Germany (online).
2. "Application of P-based Organocatalysts and Biocatalysts for the Kinetic Resolution of Racemic Carbonates P-RaceCar", C. Terazzi, J. von Langermann, T. Werner, *International P-Campus-Symposium*, 06.–07. Jan. **2022**, Leibniz Institute for Baltic Sea Research Warnemünde (IOW), Warnemünde, Germany (online).

3. "Phosphonium salt catalyzed synthesis of cyclic carbonates and their kinetic resolution", C. Terazzi, J. von Langermann, T. Werner, *International P-Campus-Symposium*, 24.–25. Nov. **2022**, Leibniz Institute for Baltic Sea Research Warnemünde (IOW), Warnemünde, Germany.

Publications:

1. Constanza Terazzi, Karoline Laatz, Jan von Langermann, Thomas Werner, Synthesis of Cyclic Carbonates Catalyzed by CaI_2–Et_3N and Studies on Their Biocatalytic Kinetic Resolution, *ACS Sustain. Chem. Eng.* **2022**, *10*, 13335–13342. DOI: 10.1021/acssuschemeng.2c03210h
2. A manuscript named "Enzymatic Resolution of Glycerol-Derived Cyclic Carbonates and their use as Chiral Building Blocks for Pharmaceuticals" is currently in preparation.

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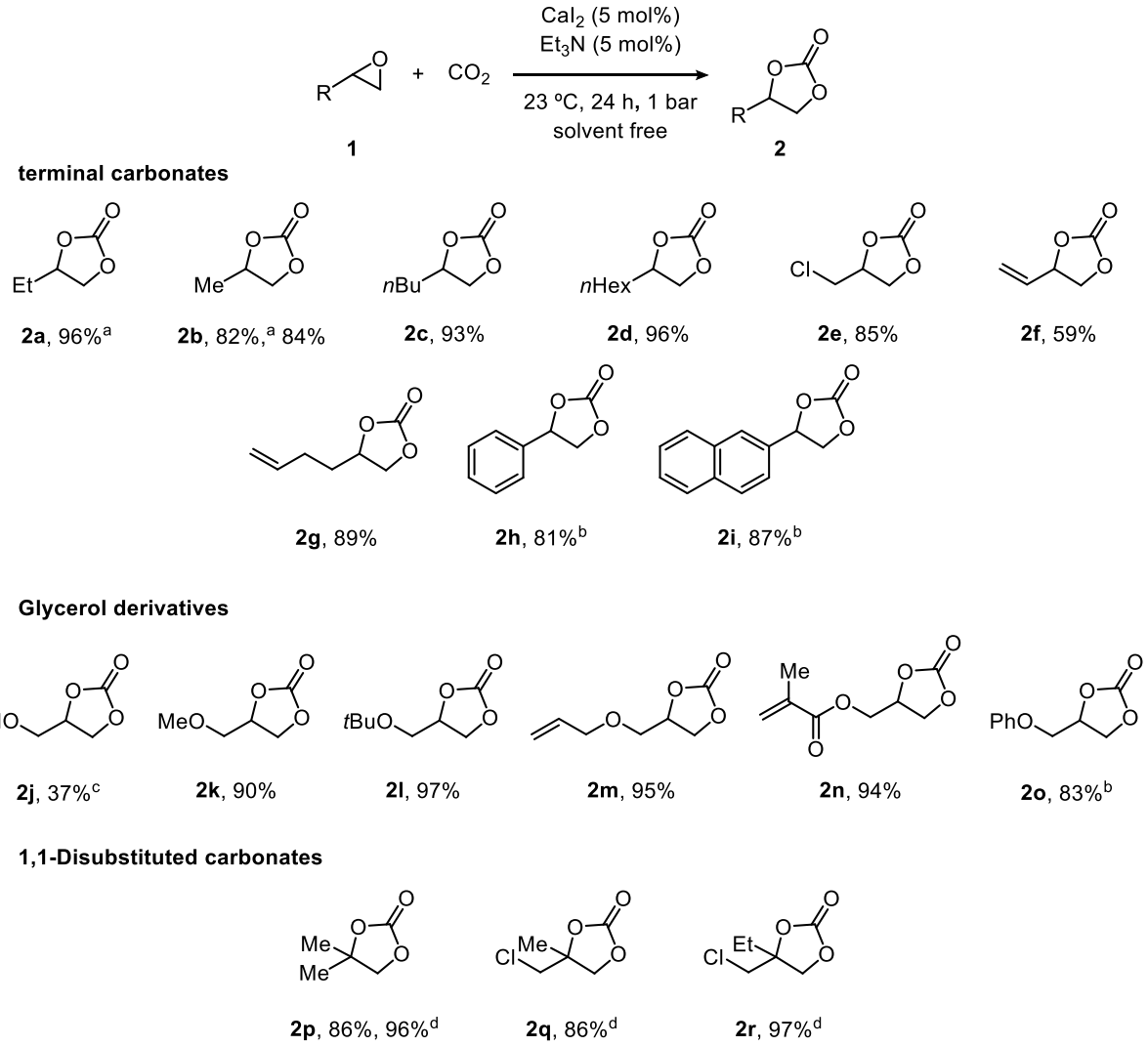
6. Appendix



Scheme 8. Substrate scope: Conversion of terminal epoxides. Reaction conditions: epoxide **1** (25.0 mmol), 5 mol% CaI_2/Et_3N, 23°C, 24 h, solvent free, $p(CO_2)$ = 1 bar. Isolated yields are given. [a]2 mol% CaI_2/Et_3N was used. [b]CH_3CN was used as the solvent. [c]Yield determined by ^1H NMR using mesitylene as the internal standard. [d]$p(CO_2)$ = 10 bar.