

**Development of Green Routes and Catalysts for
CO₂ Valorization – Synthesis of Cyclic Carbonates,
N-Methylamines and *N*-Formamides**

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Erklärung

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Abstract

The utilization and valorization of renewable resources, in particular CO₂, has drawn increasing attention in recent years due to the limited fossil-based resources and the necessity of shifting from a linear to a circular carbon economy. In this thesis, reductive and non-reductive catalytic routes for the utilization and valorization of CO₂ and other renewable resources are investigated. The focus is on the development of sustainable catalytic systems based on earth abundant metals, organocatalysts and enzymes, that can operate under mild conditions.

Initially, the non-reductive cycloaddition of CO₂ to epoxides was studied. A catalytic system based on CaI₂ combined with readily available ligands, e.g., Et₃N, was reported for the synthesis of terminal (bio-based) cyclic carbonates under mild conditions (23°C and 1 bar of CO₂ pressure). Moreover, challenging internal (bio-based) epoxides were also converted at 70°C and a CO₂ pressure of 10 bar. Mechanistic investigations revealed the coordination of the amine to the Ca²⁺-center and the activation of the epoxide by the complex. Subsequently, the enzymatic kinetic resolution of the prepared cyclic carbonates was studied to access enantiopure cyclic carbonates. Thus, cyclic carbonates derived from waste glycerol were converted with Pig Liver Esterase and Novozym® 435 to access chiral building blocks. Recycling of the latter and upscaling of the reaction allowed the isolation of the enantiopure (*S*)-epichlorohydrin carbonate, which was used as chiral building block in the synthesis of three terminal aromatic glycidyl ethers (TAGEs): (*S*)-Guaifenesin, (*S*)-Mephenesin and (*S*)-Chlorphenesin in up to 96:4 *er*.

Finally, the reductive functionalization of CO₂ with amines was studied. A phosphonium methylcarbonate salt was found to be an efficient catalyst for the reaction. The use of PMHS, a waste from silicon industry, afforded 15 *N*-methylamines in yields up to 98%, while (MeO)₃SiH gave 15 *N*-formamides in yields up to 94%. In addition, the formation of 5 benzoheterocycles was achieved in one step via the intermediate formamide. Mechanistic studies revealed the formation of silyl intermediates and the different pathways were elucidated. Experiments revealed a novel mechanism, in which the catalytic cycle is initiated by reaction between the methylcarbonate anion and the silane, and later, the catalyst is regenerated by reaction of the intermediate with CO₂.

Kurzfassung

Die Nutzung und Verwertung erneuerbarer Ressourcen, insbesondere von CO₂, hat in den letzten Jahren aufgrund der begrenzten fossilen Ressourcen und der Notwendigkeit einer Umstellung von einer linearen auf eine kreisförmige Kohlenstoffwirtschaft zunehmend an Aufmerksamkeit gewonnen. In dieser Arbeit werden reduktive und nicht-reduktive katalytische Wege zur Nutzung und Wertschöpfung von CO₂ und anderen erneuerbaren Ressourcen untersucht. Der Schwerpunkt liegt auf der Entwicklung nachhaltiger katalytischer Systeme auf Basis von leicht verfügbaren Metallen der Erdkruste, Organokatalysatoren und Enzymen, die unter milden Bedingungen arbeiten können.

Zunächst wurde die nicht-reduktive Cycloaddition von CO₂ zu Epoxiden untersucht. Ein katalytisches System auf Basis von CaI₂ in Kombination mit leicht verfügbaren Liganden wie z.B. Et₃N wurde für die Synthese terminaler (bio-basierter) cyclischer Carbonate unter milden Bedingungen (23°C und 1 bar CO₂-Druck) berichtet. Darüber hinaus wurden auch anspruchsvolle interne (bio-basierte) Epoxide bei 70°C und einem CO₂-Druck von 10 bar umgesetzt. Mechanistische Untersuchungen enthüllten die Koordination der Aminogruppe mit dem Ca²⁺-Zentrum und die Aktivierung des Epoxids durch den Komplex. Anschließend wurde die enzymatische kinetische Racematspaltung der hergestellten cyclischen Carbonate untersucht, um enantiomereinreine cyclische Carbonate zugänglich zu machen. So wurden cyclische Carbonate aus Abfallglycerin mit Pig-Liver-Esterase und Novozym® 435 umgesetzt, um chirale Bausteine zu erhalten. Das Recycling des immobilisierten Enzyms und das Hochskalieren der Reaktion ermöglichten die Isolierung eines enantiomereinreinen (S)-Epichlorhydrin-Carbonats, das als chiraler Baustein bei der Ein-Topf-Synthese von drei terminalen aromatischen Glycidylethern (TAGEs) verwendet wurde: (S)-Guaifenesin, (S)-Mephenesin und (S)-Chlorphenesin in einem Verhältnis von bis zu 96:4 *er*.

Schließlich wurde die reduktive Funktionalisierung von CO₂ mit Aminen untersucht. Es wurde festgestellt, dass ein Phosphoniummethylcarbonatsalz ein effizienter Katalysator für die Reaktion ist. Die Verwendung von PMHS, einem Abfallprodukt der Siliziumindustrie, lieferte 15 *N*-Methylamine in Ausbeuten von bis zu 98%, während (MeO)₃SiH 15 *N*-Formamide in Ausbeuten von bis zu 94% ergab. Darüber hinaus wurde die Bildung von 5-Benzoheterocyclen in einem Schritt über das Zwischenprodukt Formamid erreicht. Mechanistische Studien enthüllten die Bildung von Silyleinheiten, und die verschiedenen Wege wurden aufgeklärt. Experimente enthüllten einen neuen Mechanismus, bei dem der katalytische Zyklus durch die Reaktion zwischen dem Methylcarbonatanion und dem Silan initiiert wird und später der Katalysator durch die Reaktion des Zwischenprodukts mit CO₂ regeneriert wird.

List of abbreviations

APIs	Active pharmaceutical ingredients	<i>i</i> Pr	<i>iso</i> -Propyl
Ac	Acetyl	Me	Methyl
Bn	Benzyl	MPa	Megapascal
C	Conversion	MS	Mass spectrometry
cat.	Catalyst	N435	Novozym® 435
CCS	Carbon capture and storage	NaPi	Sodium phosphate
CCUS	Carbon capture, utilization and storage	<i>n</i> Bu	<i>n</i> -Butyl
cHex	Cyclohexyl	<i>n</i> Hex	<i>n</i> -Hexyl
co-cat.	Cocatalyst	NIPUs	Non-isocyanate polyurethanes
conc.	Concentration	NMP	<i>N</i> -Methyl-2-pyrrolidone
conv.	Conversion	NMR	Nuclear magnetic resonance
DABCO	1,4-Diazabicyclo[2.2.2]octane	Nu	Nucleophile
DAC	Direct air capture	OTs	Tosylate
DBU	1,8-Diaza-bicyclo-[5.4.0]undec-7-en	<i>p</i>	Pressure
DMAP	4-Dimethylaminopyridine	PEG	Poly(ethylene glycol)
DMF	<i>N,N</i> -Dimethylformamide	Ph	Phenyl
DMSO	Dimethyl sulfoxide	PLE	Pig Liver Esterase
E	Electrophile	PMHS	Polymethylhydrosiloxane
E-value	Enantioselectivity value	PPL	Pig Pancreas Lipase
<i>ee</i>	Enantiomeric excess	ppm	Parts per million
<i>er</i>	Enantiomeric ratio	RT	Room temperature
equiv.	Equivalent	<i>t</i>	Time
Et	Ethyl	<i>T</i>	Temperature
FID	Flame ionization detector	TAGEs	Terminal aromatic glycerol ethers
g	Gram	<i>t</i> Bu	<i>tert</i> -Butyl
GC	Gas chromatography	TBAB	Tetra- <i>n</i> -butylammonium bromide
h	Hour	TBAC	Tetra- <i>n</i> -butylammonium chloride
[HMIM]	1-Hexyl-3-methylimidazolium	TBAI	Tetra- <i>n</i> -butylammonium iodide
IPCC	Intergovernmental Panel on Climate Change	THF	Tetrahydrofuran

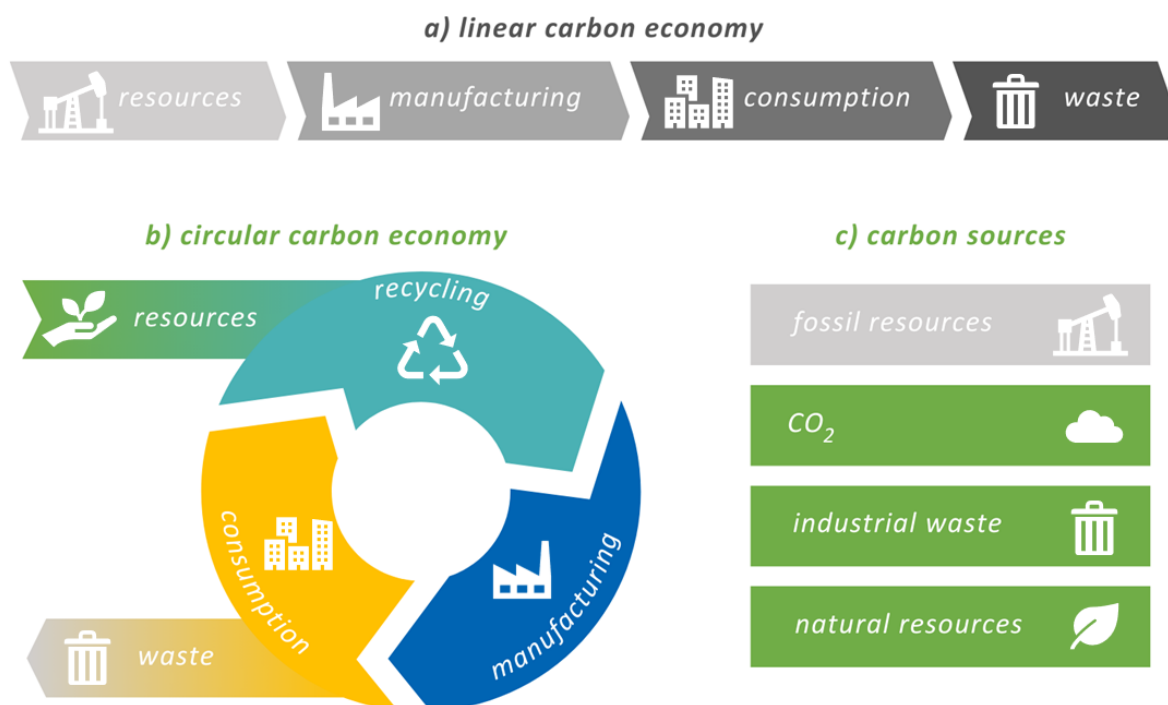
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1 Introduction

1.1 Circular carbon economy and CO₂ utilization

The current manufacturing system is based on the extraction of natural resources from Earth for the manufacturing of goods, whose production and disposal generate large amounts of waste. This linear model (Scheme 1a) faces two core problems: (1) the finiteness of non-renewable resources, and (2) the environmental problems associated with the waste generated. In this regard, one of the most urgent issues is the accelerated consumption of fossil resources to satisfy the increasing demand of energy and products, which results in the release of waste CO₂ to the atmosphere.^[1, 2] In consequence, the atmospheric CO₂ concentration has been rising continuously from 277 ppm in 1750 reaching a historical record of 419 ppm in 2022.^[3] This steady increase over years represents the major contribution to climate change as CO₂ is the most emitted greenhouse gas. In the Paris Climate Agreement, the international community established that the main and most urgent goal is the reduction of CO₂ emissions by limiting the use of fossil fuels and switching to renewable energy sources.^[4] In the latest report released by the IPCC in 2023, a comprehensive assessment on the consequences of climate change is described and the importance of effective climate governance is also addressed.^[5]



Scheme 1. Carbon sources for the production of chemicals and fuels based on linear and circular carbon economy.

Moreover, although the extracted fossil resources are mostly used as fuels, the chemical industry relies on the use hydrocarbons from crude oil as raw materials. To date, the use of petrochemicals accounts for 90% of the current production of organic chemicals, for which the shortage of these feedstocks would endanger the entire supply chain.^[6, 7] The rapid depletion of fossil resources, together with the associated environmental issues, makes carbon recycling imperative. In other words, the challenge is the migration from a linear to a circular model based on the intelligent use of resources, minimization of waste and recycling of the products that cannot longer be used (Scheme 1b and 1c).^[8] In this scenario, the development of processes that follow the 12 principles of Green Chemistry is critical for a sustainable future.^[9]

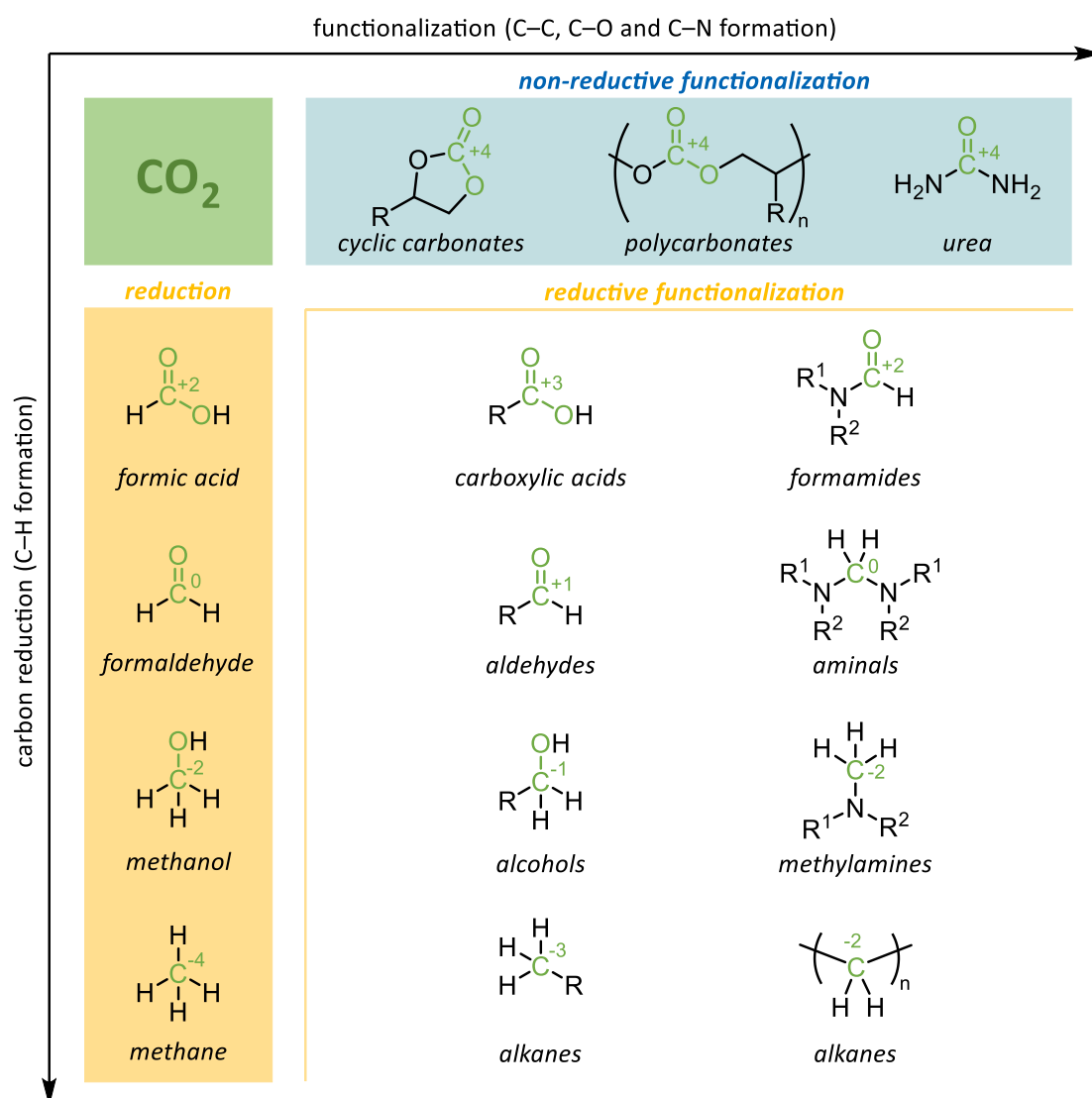
The utilization of CO₂ for the synthesis of valuable products becomes important not only as a global warming issue but also due to the necessity of carbon surrogates.^[10, 11] Ideally, CO₂ would be utilized for the production of fuels and chemicals, avoiding the use of non-renewable resources.^[12, 13] From this perspective, CO₂ is no longer considered as a waste, but it emerges as a renewable, non-toxic and abundant C1-building block for the synthesis of value-added products.^[14-17] This strategy also applies to other industrial wastes, which should be minimized and also reutilized. Their upcycling contributes to a circular carbon economy, makes manufacturing processes more profitable and mitigates the contamination of landfills and waterbodies with industrial residues that are typically harmful for the environment.^[18] On a different note, the use of biomass as renewable feedstock can also offer a viable alternative to the use of fossil sources. Provided that the exploitation of the land is done in a sustainable manner and preservation of the environment is guaranteed, the use of bio-renewables has the potential for the manufacture of a large portfolio of products.^[19]

In order to reduce CO₂ concentration in the atmosphere, the development of carbon capture, utilization and storage (CCUS) technologies is deemed critical. Two strategies can be considered in the context of carbon capture: the carbon capture and storage of CO₂ (CCS) aims for the prevention of emissions by capturing the gas directly from the emission source, whereas the direct air capture (DAC) results in the sequestration of CO₂ directly from the atmosphere. Once captured, the CO₂ can be, for example, stored in geological formations for a long period of time.^[20] As it is essential to close the carbon cycle and make the whole process sustainable from an environmental and economical point of view, the carbon capture and utilization of CO₂ (CCU) became of great importance. For these technologies CO₂ is considered as a valuable raw material that can be used in the production of chemicals and fuels.^[20, 21] Even though current CCU processes still present some disadvantages in terms of energetic consumption and overall carbon footprint, great advances have been made in the past years. Altogether, the integrated capture and conversion of CO₂ contributes to the valorization of this waste towards a more sustainable carbon economy.^[22]

The valorization of CO₂ faces two main challenges which are the thermodynamic stability and kinetic inertness of the CO₂ molecule. As the final product of the oxidation of organic compounds, CO₂ is a very stable molecule which requires a driving force to react. To overcome this, energy-rich reactants and/or a high energetic input are typically required.^[23, 24] Moreover, the kinetic barrier for the activation of CO₂ and the reactants demands an additional activation energy. Therefore, the development of catalysts is needed to allow reactions to proceed under mild conditions and to selectively favor the paths that lead to the desired products.^[25] Although the CO₂ molecule has a zero dipole moment, its reactivity relies on the internal dipole between the C–O bonds. The HOMO of the CO₂ molecule is located on the oxygen atoms and the LUMO on the carbon atom. As a result, the oxygen atoms can react with electrophiles while the carbon is susceptible to a nucleophilic attack.^[26] Scheme 2 shows a selection of products that can be prepared from CO₂, based on the sequential carbon reduction and the different functional groups obtained. First of all, CO₂ transformations can be divided in two categories: non-reductive and reductive reactions. A non-reductive conversion of CO₂ involves the incorporation of the molecule into organic scaffolds without a change in the formal oxidation state of the carbon center (+4). The most common and extensive process is the conversion of CO₂ and NH₃ to form urea, which is largely employed for the production of fertilizers, essential for agricultural activity. However, the synthesis of NH₃ by the Haber–Bosch process is energetically demanding, contributing greatly to the CO₂ footprint of the whole process.^[12] Another useful approach is the synthesis of cyclic carbonates and carbamates by non-reductive cycloaddition of CO₂ to different substrates, such as epoxides, aziridines, propargylic alcohols and amines. These reactions typically present high atom efficiency and relatively low energetic requirements.^[27, 28] Moreover, the copolymerization of epoxides with CO₂ gives the corresponding polycarbonates. Even though the oxidation state of the carbon in the polycarbonate remains unchanged (+4), these products are highly functionalized and relevant at the industrial level due to their unique physical properties.^[15] Although all these non-reductive transformations have been a focus of research in recent years, the synthesis of cyclic carbonates from CO₂ and epoxides is one of the most studied reactions in CO₂ chemistry.^[29]

The CO₂ molecule can be partially or completely reduced giving different products. An increasing number of homogeneous and heterogeneous catalysts have been reported for this class of reactions, including novel photocatalytic and electrocatalytic systems.^[30, 31] Depending on the degree of reduction achieved, the direct CO₂ hydrogenation leads to the reduction of CO₂ to carbon monoxide, formic acid, methanol or methane. Some interesting approaches combine the use of CO₂ and green H₂ for the synthesis of chemicals and sustainable fuels.^[32, 33] Additionally, when the reduction of CO₂ is carried out in the presence of a suitable N-, C- or O-nucleophile, the simultaneous reductive functionalization (of the CO₂ molecule) takes place. Cantat and co-workers described the so-called “diagonal” approach for the transformation of

CO₂ (Scheme 2).^[34] The “horizontal” approach comprises the non-reductive functionalization of CO₂ where new C–O and C–N bonds are formed but there is no reduction of the carbon center. In the “vertical” approach CO₂ is reduced to formic acid, formaldehyde, methanol or methane. Thus, the concept of “diagonal” transformations combines the simultaneous functionalization and reduction of CO₂, giving a wide variety of compounds. With this strategy, CO₂ serves as formyl, methylene or methyl source and numerous products containing new C–N, C–C and C–O bonds can be obtained.^[35] A clear example of this is the industrial synthesis of salicylic acid through the Kolbe–Schmitt reaction. This is one of the oldest processes in CO₂-utilization chemistry and it consists on the carboxylation of phenolate salts with CO₂.^[15] Other valuable processes include the preparation of alcohols (C–O bond), or formamides, amins and methylamines (C–N bond) (Scheme 2).

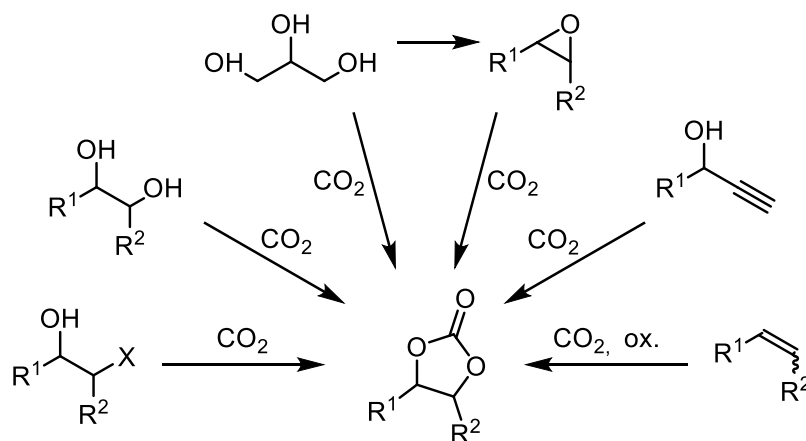


Scheme 2. Selected structures prepared from CO₂ through non-reductive and reductive transformations.

1.2 Methods for the synthesis of cyclic carbonates from CO₂

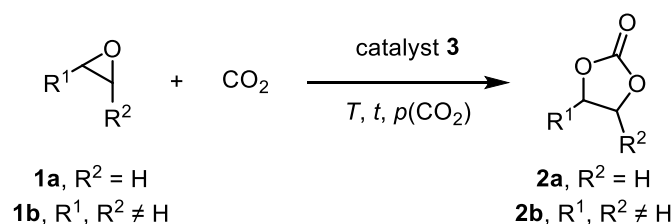
Five-membered cyclic carbonates have gained increasing attention in the last decade in the context of green chemistry. Not only their preparation contributes to the valorization of CO₂, but they also find numerous applications in industry and academia. For example, as they are regarded as green solvents, they offer a sustainable alternative to the use of traditional polar-aprotic solvents with higher environmental impact such as DMF, DMSO, NMP, or acetonitrile.^[36, 37] This is due to their benign properties: they are solvents with high boiling point and flashpoint, low toxicity and their relatively good stability allows the long-term sequestration of CO₂. Cyclic carbonates are also employed as monomers for polycarbonates and polyurethanes,^[38] and as electrolytes in Li-ion batteries, whose demand is increasing together with the manufacture of electric vehicles.^[39] Among other applications, cyclic carbonates serve as intermediates for the synthesis of fine chemicals due to their versatile reactivity.^[40]

As early as 1883, the synthesis of ethylene carbonate was reported from the reaction of toxic phosgene with ethylene glycol.^[41] Besides this traditional preparation with phosgene, other routes involving the conversion of diols to cyclic carbonates with other C1-sources such as dimethyl carbonate, urea, CO and CO₂ have been studied.^[42] However, due to the particular interest on CO₂ valorization, extensive research has been done using this C1-source (Scheme 3). In addition to the use of diols and halohydrins, other substrates have also been explored.^[42, 43] For example, the tandem oxidation of alkenes followed by cycloaddition of CO₂ has been reported several times.^[44] When propargylic alcohols are used as substrates, their reaction with CO₂ gives the corresponding α -alkylidene cyclic carbonates.^[27] Interestingly, glycerol carbonate can be prepared from glycerol, which becomes relevant for its valorization.^[45] Even though this route is in principle limited to glycerol carbonate and requires harsh conditions, glycerol can also be converted to a broad range of glycidyl carbonates via formation of the intermediate epoxide (Scheme 3).



Scheme 3. Synthetic approaches for the preparation of cyclic carbonates with CO₂.

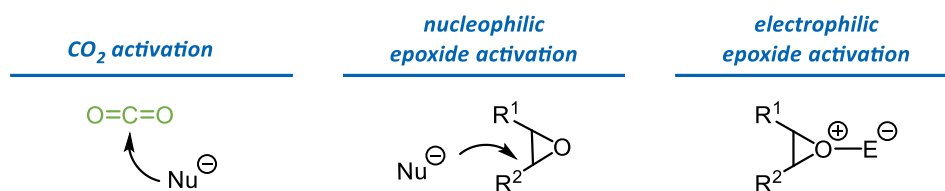
Among the different routes for the synthesis of cyclic carbonates, there is particular interest in the cycloaddition of CO₂ to epoxides, which has been the main focus of attention in this field for more than 20 years (Scheme 4).^[46] One of the main advantages of this reaction is that it is 100% atom efficient and, in many cases, it can be performed without additional solvents, meaning that the waste is considerably reduced in comparison with other routes.^[47] Moreover, it takes advantage of the high energy of the epoxide ring, whose reactivity can overcome the inert nature of the CO₂ molecule.^[10]



Scheme 4. Catalyzed synthesis of cyclic carbonates from epoxides and CO₂.

The cycloaddition of CO₂ to epoxides is driven by the stability of the carbonate and the high energetic epoxide, which makes it an exothermic reaction (i.e. $\Delta H_r = -144$ kJ/mol for ethylene carbonate).^[48] However, the reaction requires a catalyst to overcome the kinetic inertness of the CO₂ molecule, for which the development of catalysts that operate at room temperature and low CO₂ pressure is key to guarantee an efficient energetic process.^[49] Approaches for the rational design of catalysts involve three different strategies and their synergistic combination (Scheme 5):

- CO₂ activation: the nucleophilic activation of the inert CO₂ molecule gives the carboxylate anion, which subsequently reacts with the epoxide giving the cyclic carbonate and regenerating the catalyst. *N*-heterocycles such as DBU, DABCO, DMAP are efficient nucleophiles and can even form stable adducts with CO₂.^[50] Among other catalysts, Ph₃P has also shown good results in previous reports.^[51]
- Nucleophilic epoxide activation: a nucleophile can attack the less hindered carbon on the epoxide ring giving the intermediate alkoxide that reacts with CO₂ to afford the product. In this case, organic onium salts and inorganic halides salts are typically used, and their catalytic activity is balanced by the nucleophilicity and leaving-group ability of the anion and the stabilization of intermediates provided by the counter-cation.^[52]
- Electrophilic epoxide activation: The interaction of the oxygen in the epoxide ring with a Lewis or Brønsted acid weakens the C–O bond in the epoxide facilitating the ring-opening while also stabilizing the intermediate alkoxide. The subsequent reaction with CO₂ gives the cyclic carbonate.^[53]



Scheme 5. Strategies for the synthesis of cyclic carbonates from epoxides and CO₂.

Numerous homogeneous and heterogeneous catalysts have been reported to date, which can be classified according to their nature:

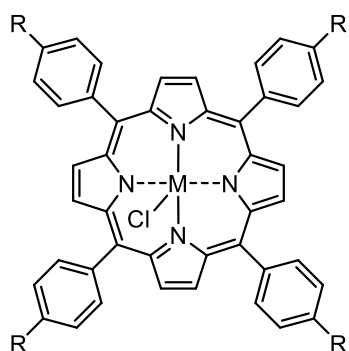
- Organocatalysts: amines, ammonium, phosphonium and imidazolium salts, amidine-based, carbene-based, hydrogen bond donor-based, aminoacids.^[50, 54]
- Metal-based catalysts: based on porphyrins and aminophenolates ligands, Cr(III)(salen), Zn(II)(salen), Al(III)(salen), MOF and ZIFs-based, alkali and alkaline earth metal-based, transition metal-based.^[55]

1.3 Sustainable metal-based catalysts for cyclic carbonates synthesis

The use of metal-based catalytic systems offers several advantages with respect to organocatalysts. Since they normally present higher catalytic activity, they allow the use of milder reaction conditions, lower catalyst loading and the conversion of challenging substrates.^[55] However, many metals are toxic and can also be regarded as “endangered” and “critical elements”, meaning that their supply might face limitations in the upcoming years.^[56] Therefore, it is of major importance that the catalyst design considers not only the catalytic activity but also the sustainability of the whole process. Abundant metals overcome these limitations as they are abundant on the Earth’s crust, readily available, cost-efficient and have already been reported as active for the synthesis of cyclic carbonates. Among all metals, only six are considered as abundant: Na, K, Ca, Ti, Fe and Al and numerous publications regarding their salts and complexes have been reported to date (Table 1).^[57]

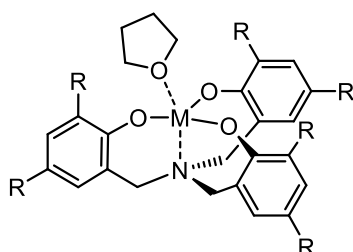
Porphyrin ligands have proven to be efficient for metals such as Fe and Al. In 2015, Wang and co-workers reported a highly active aluminum porphyrin complex (**3a**) that could convert butylene oxide (**1aa**) at 120°C and 30 bar with only 0.001 mol% of catalyst (Table 1, Entry 1).^[58] Later in 2017, the group of Safari reported a complete study on different porphyrin ligands and metals at atmospheric pressure and 70°C.^[59] For example, **3b**, an Fe-based catalyst, converted styrene oxide (**1ab**) to the corresponding carbonate in 99% yield (Entry 2).

Table 1. Selective examples of catalysts **3** based on abundant metals (Al, Fe, Ti) for the synthesis of cyclic carbonates **2a** from epoxides **1a** and CO₂.



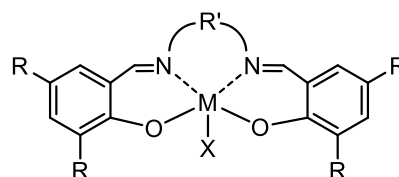
3a, Wang, 2015 (M = Al, R = H)

3b, Safari, 2017 (M = Fe, R = OMe)



3f, Kleij, 2014 (M = Al, R = Cl)

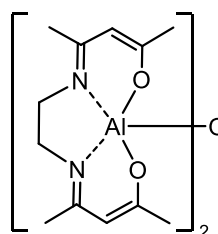
3g, Kleij, 2012 (M = Fe, R = *t*Bu)



3c, Zhang, 2020, (M = Al, R = H, R' = 1,2-naphtalene, X = Cl)

3d, Lamberti, 2018 (M = Fe, R = *t*Bu, R' = -CH₂CH₂-, X = Cl)

3e, North, 2020 (M-X = Ti=O, R = *t*Bu, R' = (1*R*, 2*R*)-cyclohexyl)



3h, North, 2011

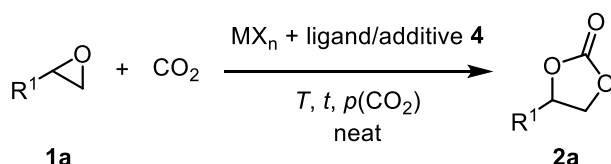
Entry	Catalyst 3 (mol%)	Co-catalyst (mol%)	1a , R ¹	<i>T</i> (°C)	<i>p</i> (CO ₂) (bar)	<i>t</i> (h)	Yield 2a (%)
1	3a (0.001)	PPNCl (0.12) ^a	1aa , R ¹ = Et	120	30	1	> 99
2	3b (1.8)	TBAB (2.3)	1ab , R ¹ = Ph	70	1	5	99
3	3c (0.25)	[HMIM][HCO ₃] (0.25)	1ab , R ¹ = Ph	25	10	24	98
4	3d (0.025)	TBAB (200)	1ac , R ¹ = Me	100	20	16	64
5	3e (0.1)	TBAB (0.5)	1aa , R ¹ = Ph	100	1	24	98
6	3f (0.5)	TBAI (2.5)	1ad , R ¹ = <i>n</i> Bu	30	10	2	91
7	3g (1)	TBAB (100)	1ab , R ¹ = Ph	25	10	18	90
8	3h (2.5)	TBAB (2.5)	1ab , R ¹ = Ph	26	1	24	93

^aPPNCl: Bis(triphenylphosphine)iminium

Salen and salen-like ligands are of easy preparation and form complexes with a wide variety of metals. The tetradentate scaffold can be tuned by changing the bridge between the nitrogen atoms and with different substituents. Zhang reported in 2020 the efficient synthesis of cyclic carbonates catalyzed by complex **3c** at room temperature using an imidazolium salt as co-catalyst, without the need of halide additives (Entry 3).^[60] Similarly, salen, salan and

salalen Fe complexes have also been studied for the addition of CO₂ to epoxides by the group of Lamberti. For example, **3d** afforded propylene carbonate (**2ac**) in 64% yield at 100°C (Entry 4) and also gave good results for the ring opening polymerization reaction.^[61] Titanium-based catalysts have also been reported for the reaction of epoxides with CO₂.^[62] Most studies focus on the ring opening polymerization reaction rather than on the cyclic carbonate formation.^[63] Nevertheless, North and co-workers reported recently the use of Ti salen complexes for the synthesis of several terminal carbonates using CO₂ at atmospheric pressure and 100°C (**3e**, Entry 5).^[64] Kleij reported the use of Al and Fe complexes of amino-tris(phenolate) ligands for the synthesis of cyclic carbonates.^[65, 66] The activity of these catalysts can be tuned by changing the substituents in the phenolic moiety. In particular, catalyst **3f** can convert terminal epoxides under relatively mild conditions (30°C, 10 bar for **1ad**, Entry 6) while **3g** presents good activity at room temperature when 1 equivalent of co-catalyst is used (Entry 7). Bimetallic Fe and Al complexes are also active for this reaction and some of them have showed good activity at mild conditions.^[57] The group of North reported in 2011 a cost efficient synthesis of bimetallic μ -oxoaluminum(acen) complexes that can fully convert terminal epoxides at 1 bar and room temperature (**3h**, 93% yield for **1ab**, Entry 8) and even showed activity at 0°C.^[67]

Metal complexes present good catalytic activity but there are some drawbacks that need to be considered. The ligands required for their synthesis can be expensive and difficult to prepare and the resulting complexes are sometimes sensitive to air and moisture. As an alternative, the use of inorganic salts has attracted attention as they overcome many of these limitations. In this approach, metal halides are used and they follow a simple strategy: the halide acts as nucleophile attacking the epoxide ring, which is activated by the Lewis acidity of the metal cation. Although metal halides such as KI have already been used in industrial scale, these processes suffer from many disadvantages such as high reaction temperatures and pressures (180–200°C, 50–80 bar).^[54, 68] Therefore, the addition of a readily available ligand or additive **4** can improve the performance of the reaction (Scheme 6, Table 2).

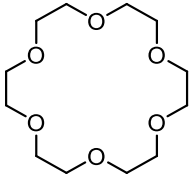
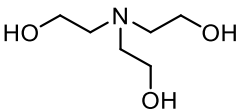
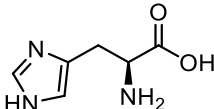
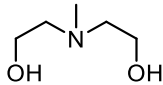


Scheme 6. Synthesis of cyclic carbonates from epoxides and CO₂ catalyzed by a metal salt MX_n and a ligand or additive **4**.

As early as 1984, the group of Kuran reported the use of 18-crown-6 (**4a**) with KI for the conversion of propylene oxide (**1ac**) at 120°C and 40 bar (Entry 1).^[69] It was proposed that the crown ether acts as phase transfer catalyst by increasing the solubility of the salt, which is one

of the limiting factors in this system. Later in 2014 the group of Werner reported the use of KI in combination with amino alcohols.^[70] In this work, the superior activity shown by triethanolamine (**4b**) was explained by a triple action of the additive: (1) complexation of the alkali salt that enhances the solubility of the salt in the organic medium; (2) activation of the epoxide by the hydroxyl moiety acting as hydrogen bond donor; (3) activation of the CO₂ molecule through the formation of an adduct. With this catalytic system it was possible to efficiently convert several substrates at 90°C and 10 bar (Entry 2). Park and co-workers studied the effect of amino acids as eco-friendly additives in the KI-catalyzed reaction and were able to convert **1ac** at 120°C and 10 bar with only 0.2 mol% of **4c**, which is surprisingly low for this type of catalysts (Entry 3).^[71] Even though the use of sodium halides has received significantly less attention than potassium halides, some reports can be found in literature. For example, Ramidi et al. reported the synergistic effect of alkali salts with Lewis bases and found that NaCl/DMAP (0.1 mol%) afforded **2ac** in 78% yield at 130°C and 20 bar (Entry 4). However, under the same conditions, LiCl showed to be more efficient, giving the product in 84% yield.^[72]

Table 2. Selective examples of catalytic systems based on salts of abundant metals and ligands/additives **4** for the synthesis of cyclic carbonates **2a** from epoxides **1a** and CO₂.

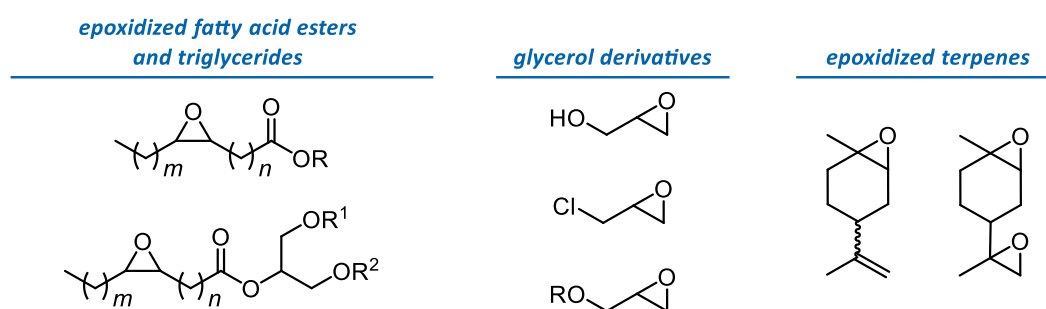
 4a, Kuran, 1984  4b, Werner, 2014  4c, Park, 2014  4d, Zhao, 2018							
Entry	MX _n (mol%)	Ligand/Additive 4 (mol%)	1a , R ¹	T (°C)	p(CO ₂) (bar)	t (h)	Yield 2a (%)
1	KI (0.67)	4a (0.2)	1ac , R ¹ = Me	120	40	4	91
2	KI (2)	4b (2)	1ac , R ¹ = Me	90	10	2	95
3	KI (0.2)	4c (0.2)	1ac , R ¹ = Me	120	10	3	99
4	NaCl (0.1)	DMAP (0.1)	1ac , R ¹ = Me	130	20	3	78
5	CaBr ₂ (5)	DBU (5)	1ac , R ¹ = Me	100	1	12	93
6	CaI ₂ (5)	4a (5)	1ac , R ¹ = Me	23	1	24	85
7	CaI ₂ (5)	PEG (5)	1ab , R ¹ = Ph	25	10	24	90
8	CaI ₂ (10)	4d (10)	1aa , R ¹ = Et	50	1	6	96

Calcium salts are also efficient catalysts for the synthesis of cyclic carbonates; however, their potential has not yet been fully explored. Liu et al. reported in 2016 the use of a calcium-based catalyst with DBU.^[73] In this work, the role of the base DBU is to form a zwitterionic species

with CO₂ and to stabilize the CaBr₂. The superior activity of CaBr₂ in comparison with other salts, allowed the preparation of **2ac** in 93% yield at 100°C and atmospheric pressure (Entry 5). The use of crown ethers with metal salts has also been investigated by the group of Werner. In 2017, they reported an in situ formed Ca²⁺-18-crown-6 complex able to convert a wide variety of epoxides at ambient conditions (room temperature and 1 bar for **1ac**, Entry 6).^[74] Later in 2019, they also published the use of sustainable polyethers as complexing agents for CaI₂ (Entry 7).^[75] Zhao and co-workers also reported the use of *N*-methyldiethanolamine (**4d**) as complexing agent for CaI₂ which allowed the preparation of several terminal cyclic carbonates at mild conditions (Entry 8).^[76]

1.4 Cyclic carbonates from biobased sources

Some considerations need to be made regarding the nature of the epoxide. Since most of the epoxides typically employed are derived from non-renewables fossil sources, the use of epoxides derived from renewable feedstocks is particularly desirable to improve the overall sustainability of the process (Scheme 7).^[54, 77-79]



Scheme 7. Selected examples of bio-based epoxides **1** used to prepare 5-membered cyclic carbonates **2**.

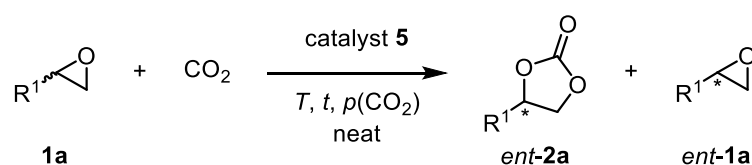
The manufacture of triglycerides and fatty acid derivatives offers a renewable platform for the production of chemicals and fuels. Numerous transformations can be carried out with these substrates, including the epoxidation of the double bond, for which various procedures have been reported.^[80] The subsequent production of cyclic carbonates from epoxidized vegetable oils and fatty acid derivatives is still a topic under development. The interest for these carbonates relies on their use as intermediates for the synthesis of industrial lubricants, fuel additives and monomers for the synthesis of non-isocyanate polyurethanes (NIPUs).^[81, 82] On the other hand, the transesterification of triglycerides from vegetable oils is the basis of the production of biodiesel, which gives glycerol as byproduct in approximately 10% yield.^[83] For this reason, the valorization of low-value glycerol into high value-added products becomes important, especially within the context of a growing demand for renewable energies.^[84, 85] One of the most studied routes for the valorization of bio-glycerol is the direct synthesis of

glycerol carbonate, for which numerous procedures and catalysts have been reported.^[45] Among other reactions, the conversion of bio-glycerol to high reactive epoxides has seen significant development. For example, glycidol can be obtained from glycerol carbonate or directly from glycerol.^[86, 87] More importantly, in the so-called epicerol process, epichlorohydrin is obtained by treating glycerol with hydrochloric acid in the presence of Lewis acid catalysts and subsequent alkaline hydrolysis. The obtained epichlorohydrin is an important building block for many other compounds, mainly used in the production of epoxy resins.^[86] Interestingly, the presence of the chlorine group in epichlorohydrin allows the further functionalization of the epoxide for the synthesis of other glycidyl ethers.^[88, 89]

Within the agro-industrial field, the valorization of crop wastes is highly desirable. For example, orange peels account for 60–65% of the total orange wastes, representing one of the most produced organic wastes worldwide. Due to the high concentration of limonene present in the orange oil extracted from orange peels, the valorization of this compound and the development of processes for its upcycling is highly desirable.^[90]

1.5 Asymmetric synthesis of cyclic carbonates

Even though the synthesis of cyclic carbonates has been developed to sophisticated levels, the asymmetric synthesis is still a challenge. The traditional strategy is the enantioselective conversion of epoxides with CO₂, catalyzed by chiral transition metal complexes **5** as shown in Scheme 8.

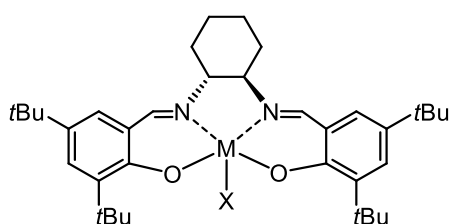


Scheme 8. Kinetic resolution of epoxides **1a** with CO₂ for the asymmetric synthesis of cyclic carbonates catalyzed by **5**.

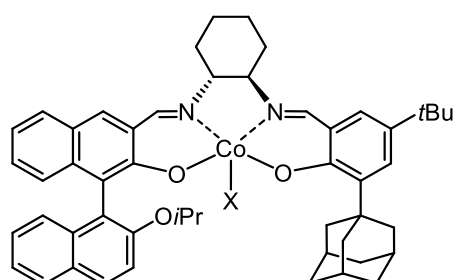
This approach accounts for the majority of the reports not only for the asymmetric synthesis of chiral cyclic carbonates but also for the asymmetric conversion of CO₂.^[91] In this regard, mainly chiral (salen)Co(III)-complexes have been developed. Lu and co-workers reported pioneering work in 2004 for the kinetic resolution of propylene oxide (**1ac**) with CO₂ catalyzed by **5a**, and later in 2012 an improvement on the *E*-value with catalyst **5c** from 9 to 76 under the optimized conditions (Table 3, Entries 1 and 3).^[92, 93] In these works, they found that chiral Co-complexes can selectively activate one enantiomer and the bulkiness and electronic properties of the counterion and co-catalyst can significantly influence the enantioselectivity of the reaction. A similar strategy was proposed by the group of North, as they worked on the

development of inexpensive and sustainable chiral (salen)Al-complexes (**5b**) for the kinetic resolution of several epoxides. This catalyst displayed very different substrate tolerances but achieved an *E*-value of 15 for *N*-(2,3-epoxypropyl)diphenylamine (Entry 2).^[94] Organocatalysts have also been studied for this reaction, but they show inferior selectivity. The group of Ema reported the use of chiral macrocycles (**5d**) for the kinetic resolution of internal and terminal epoxides with CO₂ (*E*-value = 4, Entry 4).^[95] In 2019, Takaishi & Ema reported a novel family of hemisquaramide tweezers (**5e**) that could resolve styrene oxide (**1ab**) with an *E*-value of up to 3 (Entry 5).^[96]

Table 3. Kinetic resolution of epoxides **1a** with CO₂ for the asymmetric synthesis of cyclic carbonates catalyzed by **5**.

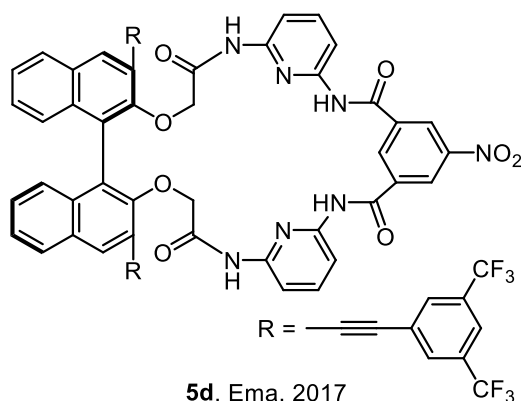


5a, Lu, 2004 (M = Co, X = OTs)

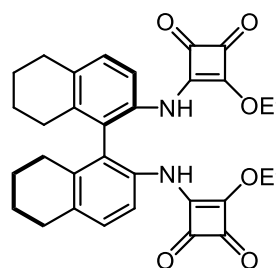


5b, North, 2015 (M = Al, X = OAc)

5c, Lu, 2012 (X = 2,4-dinitrophenoxy)



5d, Ema, 2017



5e, Takaishi & Ema, 2019

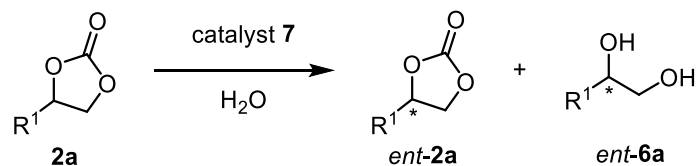
Entry	Catalyst 5 (mol%)	Co-catalyst (mol%)	1a , R ¹	T (°C)	p(CO ₂) (bar)	t (h)	Conv. 1a (%)	ee 2a (%)	<i>E</i> -value ^a
1	5a (0.1)	TBAC (200)	1ac , R ¹ = Me	0	15 ^b	15	40	70	9
2	5b (2.5)	TBAB (2.5)	1ae , R ¹ = CH ₂ NPh ₂	0	1	24	15	86	15
3	5c (0.05)	PPN-DNP (10)	1ac , R ¹ = Me	−25	20 ^b	12	10	97	76
4	5d (3)	TBAI (3)	1af , R ¹ = CH ₂ OPh	50	1	1	54	44	4
5	5e (5.0)	TBAI (5.0)	1ab , R ¹ = Ph	−20	1	72	10	47	3

^a*E*-value = ln[1 − C(1 + ee)]/ln[1 − C(1 − ee)] where C is the conversion and ee the enantiomeric excess of the resulting cyclic carbonate. ^bInitial pressure (0.55–0.60 equiv. of CO₂). ^cPPN-DNP: bis(triphenylphosphine)iminium 2,4-dinitrophenoxide.

The hydrolytic kinetic resolution of the cyclic carbonate moiety is an alternative strategy for the asymmetric preparation of cyclic carbonates. In this approach, the cyclic carbonate is enantioselectively hydrolyzed to the diol, leaving the remaining enantiopure or enantioenriched cyclic carbonate unreacted. Hydrolases appear as promising catalysts for this reaction (**7**).

Biocatalysts are deemed as green catalysts with great potential for the development of sustainable processes. Enzymes (or cells) are non-toxic, they operate with high selectivity under mild conditions, aqueous media is normally used as solvent and they can be prepared from renewable feedstocks.^[97] In particular, hydrolases (E.C. 3) are one of the largest known and most studied protein families. More specifically, carboxylesterases (E.C. 3.1.1.1) and triacylglycerol lipases (E.C. 3.1.1.3) are considered the most important in this class as they catalyze a broad variety of reactions with diverse substrates. These enzymes normally belong to the family of α/β hydrolases and contain a catalytic triad composed of three conserved residues in loops. This active site includes a histidine, an acid (aspartate or glutamate) and a nucleophile (serine, aspartate or cysteine). Due to the conserved catalytic mechanism, the regio- and stereo-selectivity of these enzymes is determined by the location of the substrate and specific regions such as the structure of the active site or the entrance tunnel of the enzyme.^[98] These hydrolases have been intensively studied for the asymmetric transformation of esters, lactones and amides, but carbonates, and in particular, cyclic carbonates lack investigation in literature.

The kinetic resolution of cyclic carbonates catalyzed by esterases has only been reported few times (Table 4). Barton & Page demonstrated in 1992 that Pig Liver Esterase (PLE) is able to selectively hydrolyze (*R*)-styrene carbonate ((*R*)-**2ab**) to the corresponding diol, which makes possible to recover the remaining (*S*)-styrene carbonate ((*S*)-**2ab**) in 78% *ee* (Entry 1).^[99] The group of Kawashima has reported the use of Pig Pancreatic Lipase (PPL) for the kinetic resolution of linear and cyclic carbonates.^[100-102] Interestingly, they showed that Pig Pancreatic Lipase (PPL) affords the enantioenriched cyclic carbonates in *ee* values up to 68% (Entry 2). The group of Matsumoto has further exploited the potential of PPL for the kinetic resolution of several 5- and 6-membered cyclic carbonates which allows the preparation of the enantiopure carbonate (Entry 3).^[103-106] Later in 2006 the group also reported the use of a bacteria, *Pseudomonas diminuta*, for the kinetic resolution of internal cyclic carbonates.^[107] Another bacteria was reported by Xu et al. in 2006. They isolated a *Bacillus* species from soil samples, which was able to selectively hydrolyze **2ab**.^[108] Even though the focus of this work was on the preparation of the enantiopure diol, the carbonate was isolated in 81% *ee* (Entry 4). Overall, carboxylesterases are active towards the hydrolysis of cyclic carbonates. However, this topic lacks deeper investigation, in particular with regard to the use of recombinant enzymes, which offer an animal-free, facile and inexpensive preparation.

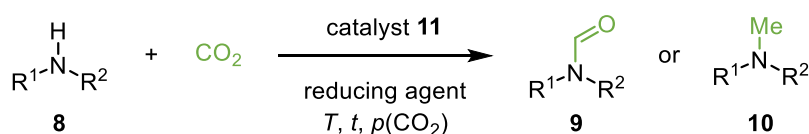
Table 4. Enzymatic kinetic resolution of cyclic carbonates **2a**.

Entry	Catalyst 7 (mg/mL)	2a , R ¹	Substrate conc. (mM)	T (°C)	t (h)	Conv. 2a (%)	ee 2a (%)	E-value ^a
1	PLE (2.2)	2ab , R ¹ = Ph	6	–	10	50	78	19
2	PPL (25)	2ad , R ¹ = <i>n</i> Bu	250	RT	24	51	68	12
3	PPL (12.5)	2af , R ¹ = CH ₂ OPh	10	10	24	72	98	9
4	<i>Bacillus</i> sp. (100) ^c	2ab , R ¹ = Ph	20	30	40	37	81	15

^aE-value = $\ln[1 - C(1 + ee)] / \ln[1 - C(1 - ee)]$ where *C* is the conversion and *ee* the enantiomeric excess of the resulting cyclic carbonate. ^bInitial pressure (0.55–0.60 equiv. of CO₂). ^c*Bacillus* sp. ECU0015.

1.6 Reductive functionalization of CO₂ with amines

The hierarchical reduction of CO₂ is possible by strategically tuning the reaction conditions. This is particularly interesting in the case of the formation of C–N bonds, since the reductive functionalization of CO₂ with amines leads to formamides, amins and methylamines with different degrees of functionalization and carbon reduction (2-, 4-, and 6-electron reduction) (Scheme 9).

**Scheme 9.** Reductive functionalization of CO₂ with secondary amines **8** for the synthesis of formamides **9**, and methylamines **10** catalyzed by **11**.

The formylation of amines has attracted attention since formamides are important compounds in organic synthesis.^[111] The reactivity of the formyl group allows its conversion into a wide variety of compounds which makes formamides useful intermediates for the synthesis of drugs, pesticides and fragrances.^[111–114] Moreover, formamides such as DMF are widely employed in organic synthesis as solvent and reagents.^[115, 116] A traditional path for the synthesis of formamides involves the carbonylation with toxic CO, for which the replacement with CO₂ is highly desirable.^[111] On the other hand, methylation of N–H bonds is also a common structural modification. In this reaction the CO₂ molecule undergoes a 6-electron reduction to give the methyl group. Moreover, the methylation of amines is most widely used in medicinal chemistry for the (late-stage) functionalization of drugs and synthesis of fine

chemicals since the incorporation of a methyl group can modulate their physical and biological activity.^[117] Due to its relevance, the *N*-methylation reaction has been extensively studied and the number of strategies is large. Alkylating reagents for this reaction include: DMF, methanol, acetic acid, DMSO, formic acid, formaldehyde, peroxides, methyl boronic acid, DMC, methyl iodide and, more importantly, CO₂.^[118]

Among the different reductants used for the formylation and methylation of amines with CO₂, the reduction with H₂ is an active field of research. The atom efficiency of the reaction makes it a good choice to avoid undesired co-products. However, high temperatures and pressures are typically required to overcome the strength of the H–H bond.^[119] Metal hydrides and hydroboranes have also been widely investigated due to their strong reduction ability. However, their sensitivity to air and moisture limits their application. Hydrosilanes, on the other hand, present a mild reduction potential, are relatively stable and easy to handle. Numerous catalysts have been reported for the hydrosilylation reduction such as transition metal complexes, solvents, and organocatalysts.^[120, 121] Silanes present different reactivity depending on their structure but the general order of reactivity is: PMHS < (EtO)₃SiH < Ph₃SiH < PhSiH₃. In particular, the use of PMHS is desirable as it is a byproduct of the Müller–Rochow process, used in the manufacture of silicone. This makes PMHS an inexpensive reactant and many reactions and processes have been developed to use it as reductant.^[122] Additionally, PMHS is easy to handle, presents higher stability to air and moisture than other silanes and shows good applicability in industry. Thus, despite its lower reactivity, the use of PMHS is highly desirable in several reduction processes.^[123]

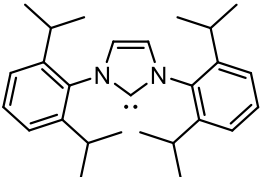
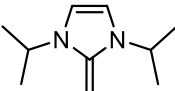
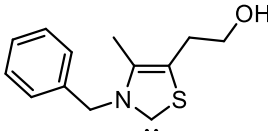
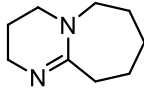
Recent reviews indicate that currently the main challenges for the reductive functionalization of CO₂ with amines are: (1) the development of efficient and environmentally friendly catalysts; (2) the use of green reductants such as PMHS and (3) further investigations of the reaction mechanism.^[124, 125] In this work the formylation and methylation of amines with CO₂ will be addressed, aiming for the development of a novel system that complies with these challenges.

1.7 Organocatalysts for synthesis of formamides and methylamines from CO₂ and amines

The reductive functionalization of CO₂ with amines can be, in principle, carried out using green reductants such as PMHS. Although several catalysts have been reported, most of them consist of toxic metal-based complexes. In contrast, metal-free catalysts overcome this disadvantage but are scarce in literature and, to the best of our knowledge, only cover *N*-based catalysts. Hence, the development of environmentally friendly catalysts is essential for a more sustainable chemistry.

Cantat and co-workers pioneered the use of organocatalyzed reduction of CO₂ with amines and PMHS with a family of *N*-heterocyclic carbenes, from which **11a** showed the best results affording the formylated product in 83% yield (Table 5, Entry 1).^[126] They later used this strategy for the formation of formamidine derivatives in a cascade reaction consisting on the *N*-formylation of amines followed by an intramolecular condensation.^[127] *N*-heterocyclic olefins (NHOs) are known for forming adducts (NHO–CO₂) that activate the CO₂ molecule. In this case, **11b** was reported by Saptal and Bhanage for the *N*-formylation of several amines with CO₂ and PMHS, e.g. benzylamine in 83% yield (Entry 2).^[128] Inspired on the vitamin B1 structure, Das et al. reported in 2016 the thiazolium carbene **11c**, which successfully afforded several *N*-formamides **9** at 50°C. Interestingly, they found that at 100°C the *N*-methylated product **10** could be obtained. Thus, tuning the temperature reaction allowed the selective conversion of *p*-methoxyaniline to the corresponding products (Entries 3 and 4).^[129] More recently, an extensive study by Xia and co-workers reported the use of DBU (**11d**) for the formation of several *N*-formamides and *N*-methalamines. Similarly, at 30°C the reaction allowed the formylation of *N*-methylaniline, while at 100°C the methylated product was obtained (Entries 5 and 6).^[130]

Table 5. Reductive functionalization of CO₂ with amines and PMHS for the synthesis of *N*-formamides **9** and *N*-methalamines **10** catalyzed by organocatalysts **11**.

							
11a , Cantat, 2012		11b , Bhanage, 2016		11c , Das, 2016		11d , Xia, 2018	
Entry	Catalyst 11 (mol%)	Amine 8	<i>p</i> (CO ₂) (bar)	<i>T</i> (°C)	<i>t</i> (h)	Yield 9 (%)	Yield 10 (%)
1	11a (5)	8a , aniline	1	RT	24	83	–
2	11b (5)	8b , benzylamine	20	80	6	83	–
3	11c (7.5)	8c , <i>p</i> -methoxyaniline	1	50	24	83	–
4	11c (7.5)	8c , <i>p</i> -methoxyaniline	1	100	24	–	81
5	11d (10)	8d , <i>N</i> -methylaniline	1	30	72	11	88
6	11d (1)	8d , <i>N</i> -methylaniline	1	100	48	84	14

Besides the previous examples, some catalysts based on *O*-nucleophiles have also shown good results for the reductive functionalization of CO₂. For example, Cs₂CO₃ proved to be a simple yet efficient catalyst for the synthesis of methylamines and formamides using PhSiH₃ as reductant. Interestingly, this procedure was reported at room temperature and a CO₂ pressure

of 1 bar.^[131] In the case of organocatalysts, a glycine betaine was reported by Liang-Nian He and co-workers for the hierarchical reduction of CO₂ with amines and Ph₂SiH₂ to formamides, amins and methylamines. This is a striking result since the synthesis of amins is typically challenging for most catalysts due to the rapid reduction of C(0) species to C(-2).^[132] Furthermore, the group of He studied the activity of different carboxylates as catalysts for this reaction. Their findings show that both cesium carboxylate and tetrabutylammonium carboxylate catalyze the methylation of amines at atmospheric pressure and 50°C.^[133]

2 Objectives of this work

The overall objective of this thesis is the development of catalytic routes for the utilization and valorization of renewable feedstocks. The focus is on the utilization of CO₂ as abundant, non-toxic and inexpensive C1-building block for the synthesis of valuable chemicals in reductive and non-reductive transformations.

In the first part, the aim is to investigate the non-reductive cycloaddition of CO₂ to epoxides using earth abundant metal salts in combination with readily available ligands and co-catalysts. In particular, the goal is to develop an inexpensive and environmentally friendly catalytic system that operates at room temperature and a CO₂ pressure of 1 bar for the conversion of terminal epoxides, including glycidyl ethers that can be obtained from waste glycerol, which increases the number of “green atoms” in the molecule. Internal carbonates are also a scope of this work, with especially interest in the conversion of bio-based epoxides such as fatty acids or limonene derivatives. In this case, the main challenge is to convert these epoxides at lower reaction temperatures and pressures ($T < 100^{\circ}\text{C}$ and $p(\text{CO}_2) < 10 \text{ bar}$).

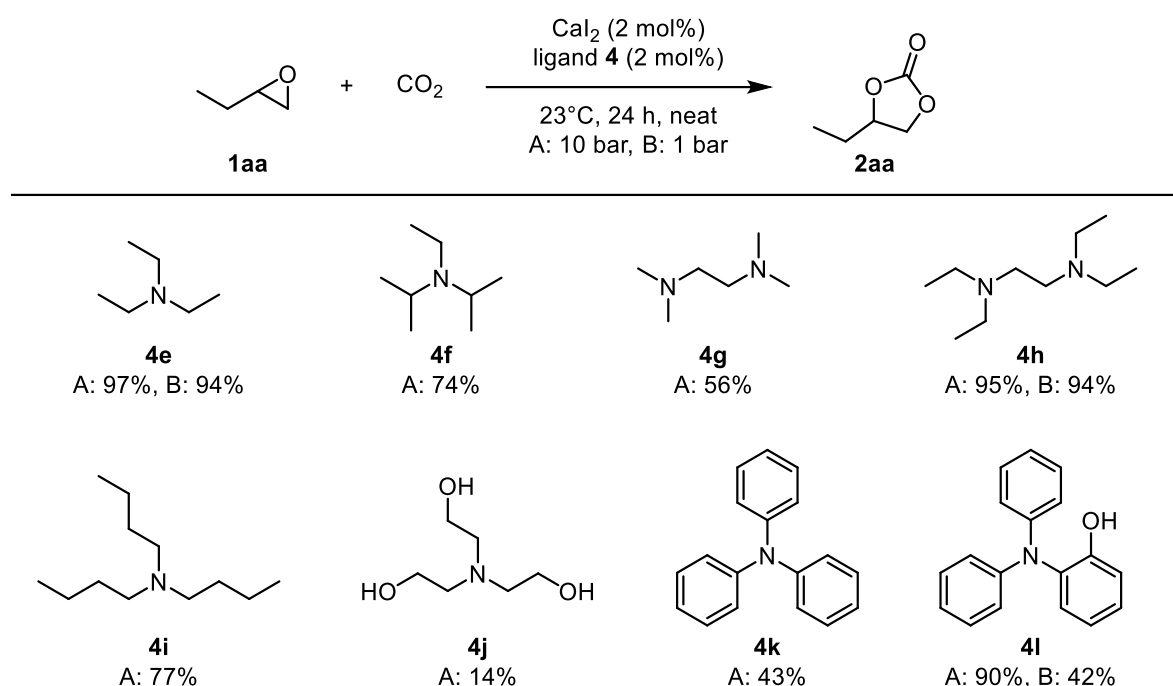
In a second stage of the project, the reaction of interest is the hydrolytic kinetic resolution of the previously prepared cyclic carbonates. The objective in this case is to provide a protocol for the preparation of enantiopure cyclic carbonates derived from waste glycerol using enzymes as biocatalysts. There is special attention in the use of Novozym® 435, widely known for its promiscuity towards numerous reactions and substrates besides its good stability, recyclability, easy scalability and low cost. We envisioned that the enantiopure cyclic carbonates can be further used as chiral building blocks in the synthesis of high value-added molecules, such as pharmaceuticals.

Finally, the focus is shifted to reductive transformations of CO₂. In this case, the functionalization of amines with CO₂ for the synthesis of *N*-formamides and *N*-methyamines is targeted. The interest here is not only on the utilization of CO₂ but also on the use of novel organocatalysts and the utilization of PMHS as environmentally friendly reducing agent.

3 Results and Discussion

3.1 Calcium-catalyzed synthesis of cyclic carbonates from epoxides and CO₂^[134]

Ca₂ was employed as catalyst for the conversion of epoxides with CO₂ to 5-membered cyclic carbonates. Different amines were tested as ligands (**4**) for this reaction (Scheme 10). First experiments were conducted employing butylene oxide (**1aa**) as model substrate at room temperature and a CO₂ pressure of 10 bar with 2 mol% of Ca₂ and 2 mol% of the amine.



Scheme 10. Screening of ligands (**4**) for the conversion of butylene oxide (**1aa**) to butylene carbonate (**2aa**) catalyzed by Ca₂. Reaction conditions: 1.0 equiv. of **1aa** (10.0 mmol), 2 mol% Ca₂ and 2 mol% ligand **4**, 23°C, 24 h, solvent free, *p*(CO₂) = 10 bar (conditions A) or 1 bar (conditions B). Yields were determined by ¹H NMR using mesitylene as the internal standard.

The control reaction in absence of a ligand gave the product in only 23% yield. To our delight, the addition of triethylamine (**4e**) afforded the product in 97% yield. Due to the promising result obtained with **4e**, the CO₂ pressure was decreased to 1 bar, yielding **2aa** in 94%. The use of a higher sterically demanding ligand such as *N,N*-diisopropylethylamine (**4f**) resulted in a moderate yield of 74% at 10 bar. *N,N,N',N'*-tetramethylenediamine (**4g**) gave a yield of 56% which can be explained by the ability of **4g** to act as bidentate ligand, thus forming stable adducts with Ca₂ that hamper its Lewis acidity.^[135] Interestingly, *N,N,N',N'*-tetraethylenediamine (**4h**) in combination with Ca₂ proved to be efficient for this reaction as it gave the product in 95% and 94% yield at 10 and 1 bar, respectively. Due to the

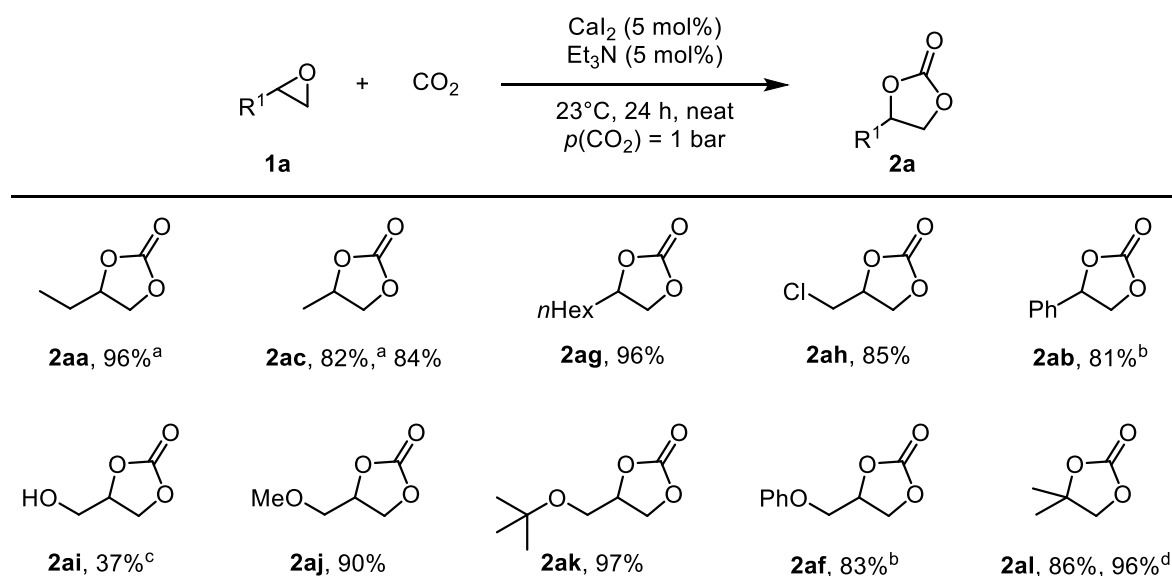
good performance of **4e**, tributylamine (**4i**) was also evaluated, showing that bulkier ligands are detrimental for the reaction, as **2aa** was obtained in a lower yield of 77%. Previous reports show good results for triethanolamine **4j** with KI at 90°C. However, in this system, **4j** gave only 14% of **2aa**, presumably due to the ability of this hydroxylated ligand to form stable species with alkali and alkaline earth ions which are inactive towards the epoxide.^[136] Aromatic ligands were also studied. Triphenylamine (**4k**) showed a moderate activity since **2aa** was obtained in 43% yield. Since several studies show that hydrogen bond donors are beneficial for the reaction, a ligand bearing a phenol moiety was tested. At 10 bar, *o*-(diphenylamino)phenol (**4l**) showed a synergistic effect yielding the product in 90%. However, at 1 bar the yield decreased to 42%. These results show that the Lewis acidity of the Ca²⁺-center can be carefully tuned to achieve optimal epoxide activation. From the ligands tested, **4e** (Et₃N) was chosen as ligand for further experiments for its excellent performance at 1 bar and room temperature, and for being readily available and inexpensive.

The influence of different alkali and alkaline earth metal iodides was investigated using Et₃N as ligand (Figure 1). As expected, in the absence of the catalyst no conversion was observed, indicating that Et₃N alone does not catalyze the reaction. Interestingly, all alkali metal salts were inactive (yields < 5%). Their remarkably lower activity is in line with the poor Lewis acidity of the cation and the halved concentration of the nucleophile due to the atomicity of the iodide anion in these salts. Additionally, the observed lower solubility of the salts in the reaction mixture is a contributing factor to the poor activity. On the other hand, alkaline earth metal iodides gave excellent results (yields > 90%) with the exception of BaI₂, that yielded **2aa** in 25%. CaI₂ was chosen for further investigations for being an inexpensive and abundant metal and for being less sensitive to light and moisture than MgI₂. With regard to the counterion, CaCl₂ and CaBr₂ were also tested. CaCl₂ showed no activity while CaBr₂ gave only 46% of **2aa**, which follows the leaving ability trend.



Figure 1. Screening of alkali and alkaline earth metal iodides with Et₃N for the conversion of butylene oxide (**1aa**) to butylene carbonate (**2aa**). Reaction conditions: 1.0 equiv. of **1aa** (10.0 mmol), 2 mol% salt MI_n and 2 mol% Et₃N, 23°C, 24 h, solvent free, *p*(CO₂) = 1 bar. Yields were determined by ¹H NMR using mesitylene as the internal standard.

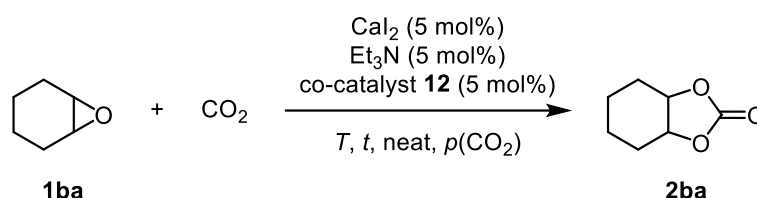
The scope of this catalytic system was evaluated for the conversion of 18 terminal epoxides at room temperature and atmospheric pressure. Scheme 11 shows a selection of 10 cyclic carbonates prepared under optimized conditions. Aliphatic substrates (**2aa**, **2ac**, **2ag**) were converted in excellent yields up to 96%. Even with a catalyst loading of 2 mol% butylene carbonate **2aa** and propylene carbonate **2ac** were obtained in 96% and 82% yield. This is particularly relevant as these carbonates are produced on industrial scale for their use as green solvents.^[36] Epichlorohydrin **1ah**, a useful green building block, was converted to carbonate **2ah** in 85% yield. In this case, the potential substitution of chlorine for iodine did not take place. Substrates with different functional groups, such as styrene oxide (**2ab**), were also tolerated and converted in good yields. Glycerol carbonate **2ai** and other glycerol derivatives (**2aj**, **2ak**, **2af**) were also targeted due to the increasing interest in glycerol valorization. With this approach, two waste products (CO₂ and glycerol) can be utilized for the synthesis of valuable chemicals in a cost-efficient and mild reaction. Glycidol (**1ai**) is susceptible to hydrolysis and polymerization. In our hands, glycerol carbonate **2ai** was obtained in 37% yield giving glycerol as byproduct. Other glycerol derivatives (**2aj**, **2ak**, **2af**) were successfully prepared with this procedure giving the desired products in up to 97% yield. 1,1-Disubstituted epoxides were also evaluated. Remarkably, **2al** was obtained in 86% yield at atmospheric pressure. An increase in the pressure to 10 bar led to the formation of the product in 96% yield.



Scheme 11. Selected examples of synthesis of terminal cyclic carbonates. Reaction conditions: epoxide **1a** (25.0 mmol), 5 mol% Cal₂, 5 mol% Et₃N, 23°C, 24 h, solvent free, $p(\text{CO}_2) = 1$ bar. Isolated yields are given. ^a2 mol% Cal₂, 2 mol% Et₃N. ^bCH₃CN was used as the solvent. ^cYield determined by ¹H NMR using mesitylene as the internal standard. ^d $p(\text{CO}_2) = 10$ bar.

Due to the successful results obtained with terminal substrates, we turned our attention to the conversion of internal epoxides. These substrates are challenging due to their higher steric hindrance, thus their conversion typically requires harsh conditions ($> 100^{\circ}\text{C}$).^[137] With this catalytic system, cyclohexene oxide **1ba** was converted to **2ba** in 27% and 70% yield at 45°C and 70°C , respectively (Table 6, Entries 1 and 2). To tackle this limitation, the use of a co-catalyst **12** for the activation of CO_2 was evaluated. When DBU was added to the reaction, no improvement was found, as **2ba** was obtained in 54% yield (Entry 3). However, upon addition of DMAP and Ph_3P , an increment on the yield to 72% and 84% yield was observed (Entries 4 and 5). Further increment of the pressure to 50 bar and the temperature to 90°C with Ph_3P was not beneficial for the reaction (Entry 6). Control experiments without CaI_2 and Et_3N proved the activity of the co-catalyst (Entries 7 and 8). Thus, Ph_3P was chosen as a cost-efficient co-catalyst for the synthesis of internal cyclic carbonates.

Table 6. Screening of co-catalysts **12** for the conversion of cyclohexene oxide (**1ba**) to cyclohexene carbonate (**2ba**) catalyzed by $\text{CaI}_2/\text{Et}_3\text{N}$.

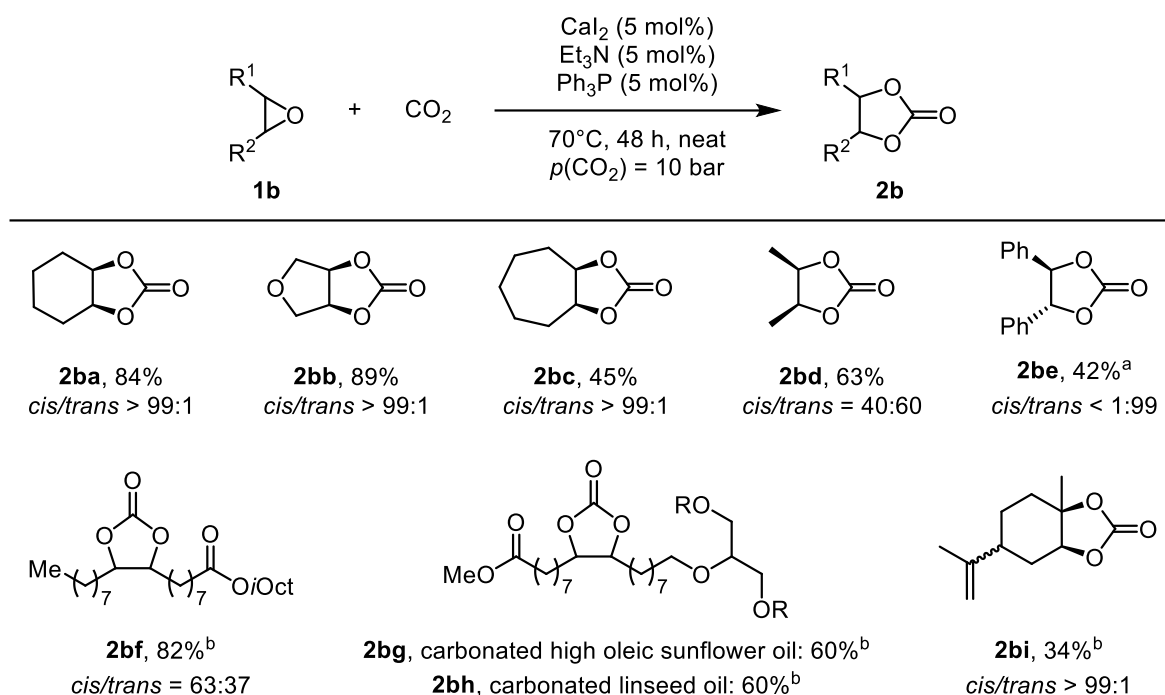


Entry	Catalyst	Co-catalyst 12	$p(\text{CO}_2)$ (bar)	T ($^{\circ}\text{C}$)	Yield 2ba (%) ^a
1	$\text{CaI}_2/\text{Et}_3\text{N}$	—	10	45	27
2	$\text{CaI}_2/\text{Et}_3\text{N}$	—	10	70	59
3	$\text{CaI}_2/\text{Et}_3\text{N}$	DBU	10	70	54
4	$\text{CaI}_2/\text{Et}_3\text{N}$	DMAP	10	70	72
5	$\text{CaI}_2/\text{Et}_3\text{N}$	Ph_3P	10	70	84 ^b
6	$\text{CaI}_2/\text{Et}_3\text{N}$	Ph_3P	50	90	61
7	$\text{CaI}_2/-$	Ph_3P	10	70	27
8	$-/-$	Ph_3P	10	70	3

^aReaction conditions: 1.0 equiv. **1ba** (10.0 mmol), 5 mol% CaI_2 , 5 mol% Et_3N , 5 mol% co-catalyst **12**, 48 h, solvent free. Yield determined by ^1H NMR using mesitylene as internal standard. ^bIsolated yield.

With the simultaneous activation of the epoxide by $\text{CaI}_2/\text{Et}_3\text{N}$ and the additional activation of CO_2 by Ph_3P , several internal epoxides were converted at 70°C and 10 bar. A selection of 9 substrates is shown in Scheme 12. Bicyclic internal carbonates (**2ba–2bc**) were obtained in yields up to 89%. The butene epoxide *cis*-**1bd** was converted to the carbonate **2bd** in 63% yield, with *cis/trans* ratio of 40:60, while *trans*-stilbene oxide **1be** was selectively converted to the *trans*-carbonate **2be** in 42% yield (*cis/trans* < 1:99). Bio-based carbonates (**2bf–2bi**) were

also prepared with this catalytic system. The special interest in these substrates relies not only on the challenge of their synthesis but mostly on the importance of the valorization of oleochemicals as substituents of petrochemicals. Their synthesis required an increase of the catalyst loading to 10 mol% and a CO₂ pressure of 30 bar. Under these conditions, fatty acids derivatives (**2bf–2bh**) were obtained in 60–82% yield, while limonene oxide, a trisubstituted epoxide, was obtained only in 34% yield due to its higher steric demand.



Scheme 12. Selected examples of synthesis of internal cyclic carbonates. Reaction conditions: epoxide **1b** (25.0 mmol), 5 mol% Cal₂, 5 mol% Et₃N, 5 mol% Ph₃P, 70°C, 48 h, solvent free, *p*(CO₂) = 10 bar. Isolated yields are given. ^aCH₃CN was used as the solvent. ^b10 mol% Cal₂, 10 mol% Et₃N, 10 mol% Ph₃P, 72 h, *p*(CO₂) = 30 bar.

Further investigations regarding the impact of the Cal₂/Et₃N ratio on this reaction were conducted. Thus, the model reaction was carried out using 2 mol% of Cal₂ and 0–4 mol% of Et₃N (Figure 2). For a better interpretation of the results, the reaction time was shortened to 12 h, when the reaction is not completed. As expected, in absence of Et₃N a low yield of 20% was obtained. Increasing amounts of Et₃N to 1 and 2 mol% improved the catalytic activity affording **2aa** in 66 and 81%. Interestingly, upon addition of 3 and 4 mol% of Et₃N, the yield decreased to 70 and 23%, respectively. These results suggest the formation of an in situ Cal₂/Et₃N complex, whose optimal activity is reached at a ratio of 1:1 and decreases after an excess of ligand that hinders the Lewis acidity of the Ca²⁺-center.

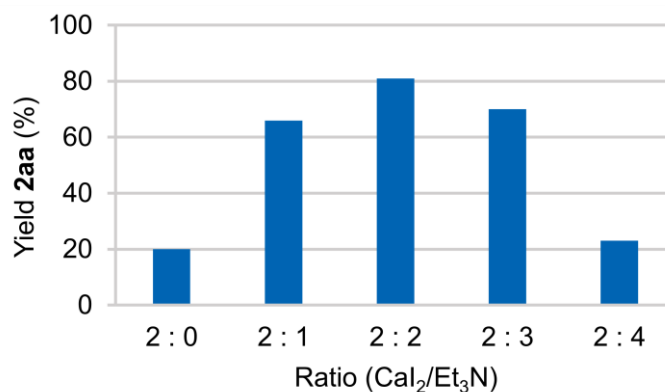


Figure 2. Effect of the CaI₂/Et₃N ratio on the catalytic conversion of butylene oxide (**1aa**) to butylene carbonate (**2aa**). Reaction conditions: 1.0 equiv. of **1aa** (10.0 mmol), 2 mol% CaI₂ and 0–4 mol% Et₃N, 23°C, 12 h, solvent free, *p*(CO₂) = 1 bar. Yields were determined by ¹H NMR using mesitylene as the internal standard.

The formation of the coordination complex was studied by ¹H NMR spectroscopy by preparing CaI₂/Et₃N mixtures in CD₃CN under inert conditions. In Figure 3a a section of the ¹H NMR of pure Et₃N is shown. In the presence of equimolar amounts of CaI₂ (CaI₂/Et₃N = 1:1) the signals shifted significantly from 2.46 to 2.64 ppm for the methylene protons and from 0.96 to 1.05 ppm for the methyl protons (Figure 3b). An excess of Et₃N (CaI₂/Et₃N = 1:2) results in a slightly less pronounced shift of the methylene and methyl protons to 2.62 and 1.04 ppm, respectively (Figure 3c).

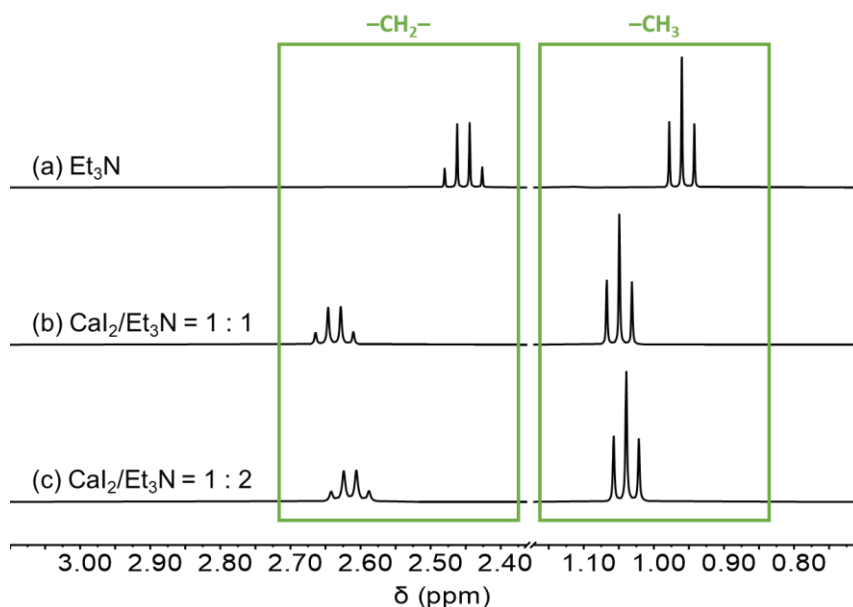
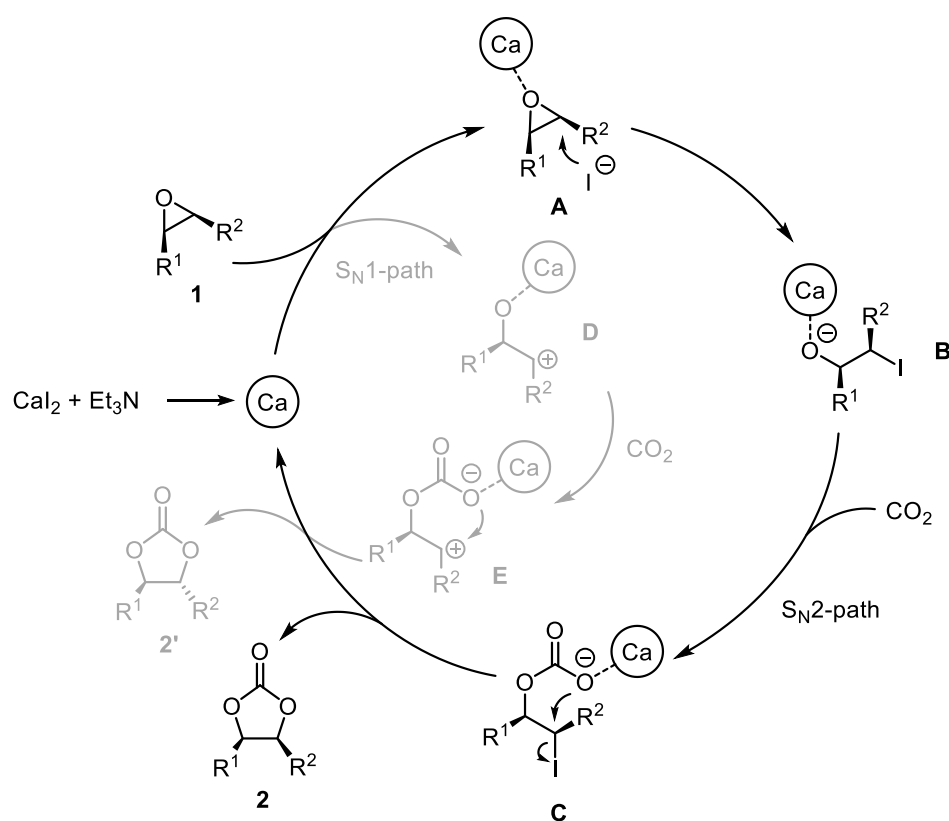


Figure 3. ¹H NMR investigations on the coordination of Et₃N to CaI₂. (a) Section of the ¹H NMR spectrum of Et₃N without CaI₂. (b) CaI₂/Et₃N = 1:1. (c) CaI₂/Et₃N = 1:2. All mixtures were prepared in CD₃CN under inert conditions.

To gain insights into the mechanism of the reaction, ^1H NMR investigations were carried out with butylene oxide (**1aa**) and stoichiometric amounts of CaI_2 and Et_3N in CD_3CN . (Appendix, Figure 8) The ring opening in the presence of this catalytic system was confirmed after complete conversion of the epoxide, and new signals were assigned to the coordinated alkoxide.

Based on the results obtained and ^1H NMR experiments, a mechanism for the synthesis of cyclic carbonates was proposed (Scheme 13). Initially, CaI_2 and Et_3N form a complex in situ. This complex activates the epoxide forming the intermediate **A**, which is susceptible to the nucleophilic attack of the iodide that leads to the ring opening of the epoxide forming **B**. The highly reactive alkoxide attacks the CO_2 molecule forming the linear carbonate **C**. Subsequently, the cyclization takes place by intramolecular substitution of the iodide ($\text{S}_{\text{N}}2$ -path) leading to the desired product with overall retention of the configuration. However, sterically demanding substrates, such as internal epoxides, can form a stabilized carbenium ion **D**, which can undergo an $\text{S}_{\text{N}}1$ -pathway. In this case, the alkoxide **D** forms the linear carbonate **E** with CO_2 that leads to product **2'** after cyclization. In this case, the stereochemical information is lost, which results in the formation of the thermodynamic *trans*-product, as it was observed for **2bd**.

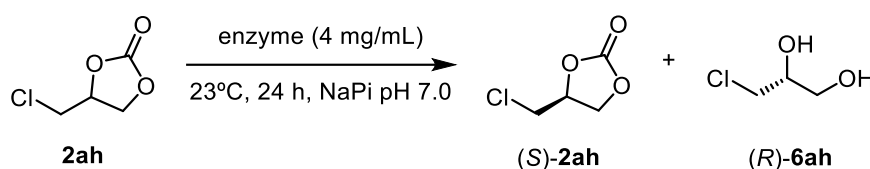


Scheme 13. Proposed mechanism for the synthesis of cyclic carbonates from epoxides and CO_2 catalyzed by $\text{CaI}_2\text{-Et}_3\text{N}$.

3.2 Synthesis of chiral building blocks from glycerol-based cyclic carbonates^[138]

3.2.1 Biocatalytic kinetic resolution of cyclic carbonates

We turned our attention to the synthesis of chiral cyclic carbonates by enzymatic kinetic resolution (Scheme 14). In preliminary studies the kinetic resolution of styrene carbonate by PLE was evaluated.^[134] In further investigations, we turned our attention to glycerol derivatives for the high interest on the upcycling of waste glycerol. The specific goal was to prepare enantiopure building blocks from bio-based derivatives. Thus, epichlorohydrin carbonate (**2ah**) was chosen as model substrate for two main reasons (1) **2ah** can be prepared from epichlorohydrin **1ah**, that is obtained from glycerol through the epicerol process; (2) **2ah** can be easily functionalized into valuable chemicals by substitution of the chloride.



Scheme 14. Enzymatic kinetic resolution of epichlorohydrin carbonate (**2ah**). Reaction conditions: 10 mmol/L of **2ah** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 4 mg/mL of enzyme, 23°C, 24 h.

Overall, 26 enzymes were evaluated for the kinetic resolution of **2ah** (Figure 4). The control reaction without enzyme gave a conversion of 5%, meaning that the non-catalyzed hydrolysis of the substrate occurs slowly under these conditions. Notably, Pig Liver Esterase (PLE) afforded the enantiopure (*S*)-**2ah** (*er* > 99:1) converting the initial substrate in 82%, with an *E*-value of 38. Recombinant Pig Liver Esterases (rPLE) were tested since they offer a good alternative to the use of PLE due to their animal-free manufacture and better reproducibility. However, for the model reaction, all 6 rPLE (rPLE1–rPLE6) gave low *E*-values < 3. Among them, rPLE5 showed to be the most active isoenzyme, converting the substrate in 43%, with a resulting *er* of 63:37, followed by rPLE6 that gave an *er* of 59:41. In particular, rPLE1–rPLE4 converted the substrate in less than 20%, giving racemic mixtures. The focus was shifted to other esterases, hence, 10 recombinant esterases were used. Most of them gave nearly racemic mixtures except from esterase from *Bacillus subtilis* a and esterase from *Paenibacillus barcinonensis*, that gave *er* values of 81:19 and 65:35, respectively. However, all esterases gave poor *E*-values < 4, which represented no improvement with respect to PLE. At last, a series of lipases was evaluated. In this case, all the enzymes gave racemic mixtures with low conversion (< 20%). The exception was found for Novozym® 435 (N435) which gave an *E*-value of 49, despite a conversion of 14%.

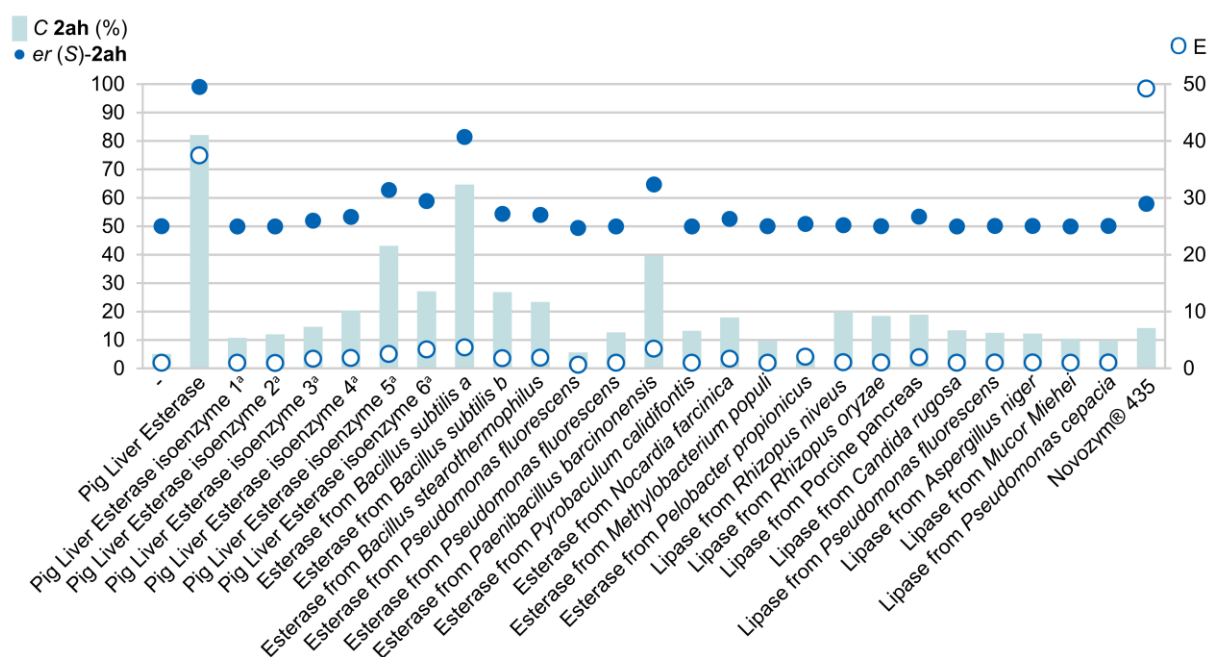


Figure 4. Enzyme screening for the kinetic resolution of **2ah**. Reaction conditions: 10 mmol/L of **2ah** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 4 mg/mL of enzyme, 23°C, 24 h. Conversion (bars, ■), *er* values (blue dots, ●) were determined by chiral GC-FID using hexadecane as the internal standard. E-values (white dots, ○) were calculated from the conversion of **2ah** and *ee* of (*S*)-**2ah**. ^a20 h.

The promising results obtained for PLE and N435 prompted further studies for these enzymes. Optimization experiments showed that the activity of N435 can be significantly improved with an increment in the temperature from 23°C to 40°C despite a slight loss of selectivity. Nevertheless, under optimized conditions (PLE: 4 mg/mL, 23°C; N435: 20 mg/mL, 40°C) both enzymes afforded the enantiopure (*S*)-**2ah** (*er* > 97:3) with a conversion of 73% of the starting material.

N435 is an acrylic resin adsorbed form of Lipase B from *Candida antarctica*. This enzyme has been exploited in recent years and has even been considered as the “perfect” immobilized lipase.^[109] N435 is highly promiscuous and due to its good stability and recyclability N435 is employed in industrial scale. Due to its advantages and the good results obtained for the kinetic resolution of **2ah**, the reaction was upscaled from 5 to 200 mL. At the same time, the recyclability of N435 was evaluated in this system by performing 10 repetitions of the upscaled reaction. Figure 5 shows the isolated yield and *er* of (*S*)-**2ah** obtained for every cycle. Yields varied between 15% and 24% (with 50% being the maximum theoretical yield), while *er* values showed a minor decrease from 96:4 to 92:8 after 10 cycles. The overall process allowed the isolation of 0.5 g of pure (*S*)-**2ah** for its use as chiral building block. Moreover, the diol (*R*)-**6ah** was isolated in yields up to 47%, with *er* values up to 62:38. In this manner, and despite the low yields, an enantiopure building block was prepared and isolated by hydrolytic kinetic resolution of a glycerol-derived substrate with a recyclable enzyme.

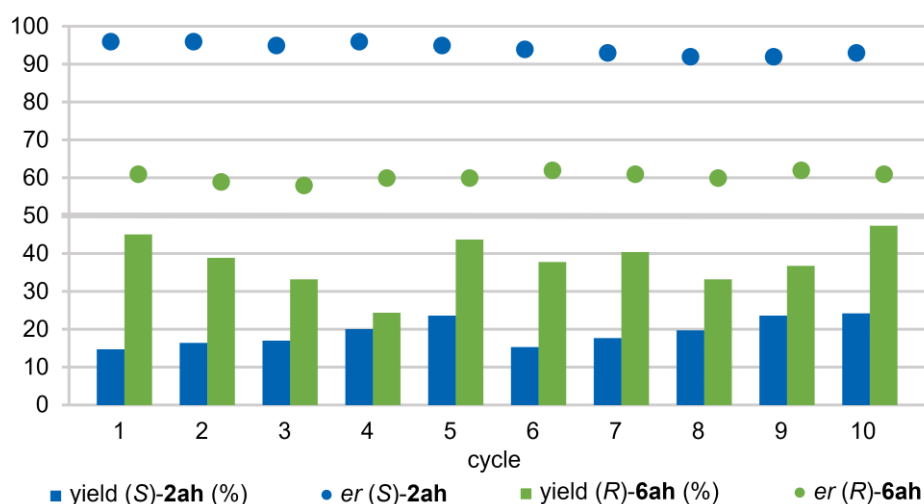


Figure 5. Upscaled of the kinetic resolution of **2ah** and recycling of N435. Reaction conditions: 10 mmol/L of **2ah** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 20 mg/mL of N435, 40°C, 24 h. Isolated yields ((S)-**2ah**, ■), ((R)-**6ah**, ■) are given. *Er* values ((S)-**2ah**, ●), ((R)-**6ah**, ●) were determined by chiral GC-FID.

The procedure was extended to other glycerol-derived cyclic carbonates (selected examples shown in Figure 6). For comparison, both N435 (conditions A) and PLE (conditions B and B') were used. Firstly, glycerol carbonate was converted, giving only racemic mixtures. Due to the good results obtained for the chlorinated carbonate, other halogenated carbonates were tested (**2am–2ao**). The fluorine derivative **2am** was obtained in 64:36 *er* (53% conversion) and 73:27 *er* (conversion 56%) with N435 and PLE, respectively. Bromine (**2an**) and iodine (**2ao**) derivatives gave excellent *er* values ($\geq 99:1$) with both enzymes. Next, we turned our attention to the kinetic resolution of phenoxy-substituted derivatives. The motivation on these compounds arises from their structural similarity with several pharmaceuticals such as TAGEs and their use as APIs for the synthesis of β -blockers. With this procedure, **2af** was not significantly converted by PLE but N435 gave the enantioenriched product in 77:23 *er*, with a conversion of 42%. The guaiacol derivative **2ap** was converted by both enzymes in 69 and 44%, however, with *er* values of 65:35 and 54:46, respectively. **2aq**, the analogous carbonate of Mephesisin, gave the racemic mixture using PLE with low conversion of only 11%. The kinetic resolution of **2aq** with N435 gave 29% conversion with an *er* of 57:43. Finally, PLE and N435 showed good activity for the conversion of **2ar** (87% and 79%), but the product was obtained in poor enantiopurity (61:39 and 51:49 *er*). Further experiments with co-solvents did not show any improvement on the results.

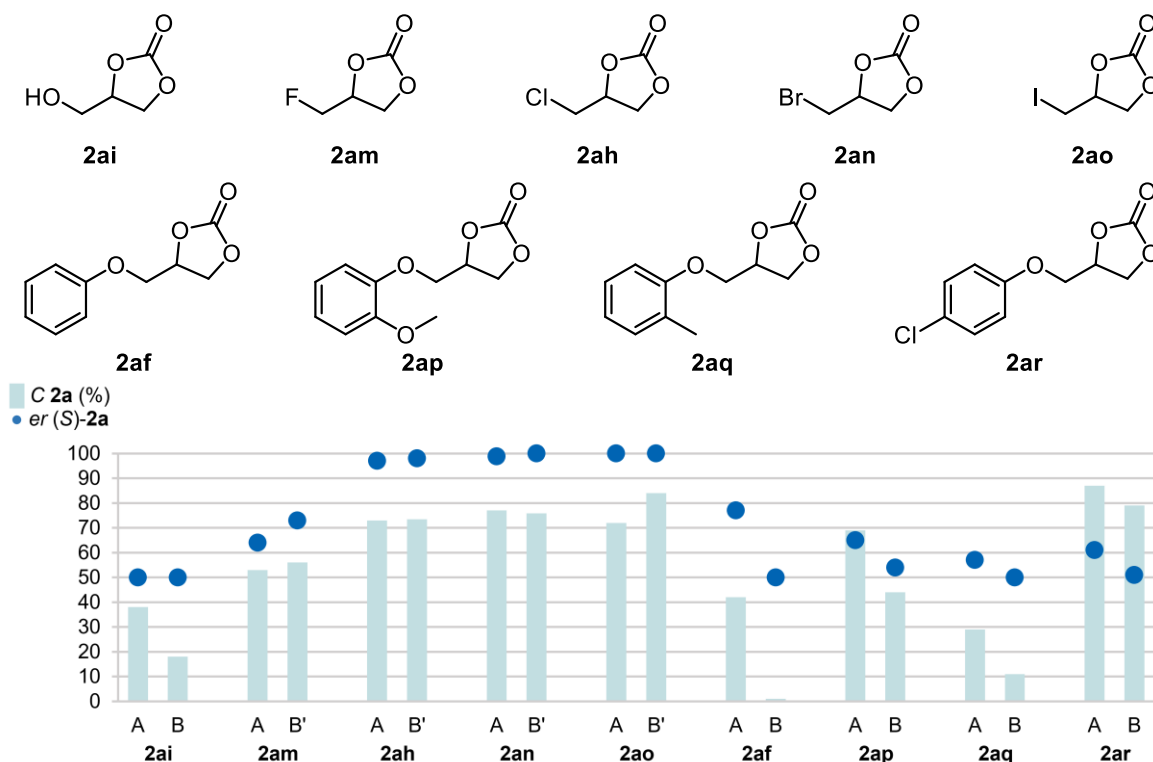
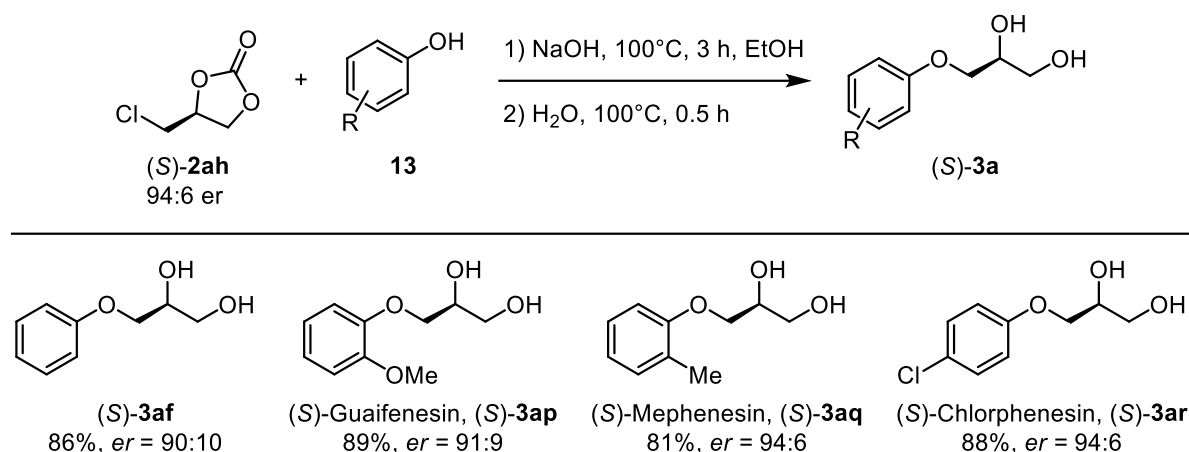


Figure 6. Selected examples of the enzymatic kinetic resolution of glycerol-derived cyclic carbonates with PLE and N435. Reaction conditions: 10 mmol/L of substrate **2a** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). Conditions A: 20 mg/mL of N435, 40°C, 24 h. Conditions B: 4 mg/mL of PLE, 23°C, 24 h. Conditions B': 4 mg/mL of PLE, 23°C, 16 h. Conversions (bars, ■), *er* values (blue dots, ●) were determined by chiral GC-FID using hexadecane as the internal standard. ^a16 h.

3.2.2 Synthesis of pharmaceuticals based on chiral glycerol-derived cyclic carbonates

After demonstrating the scalability and recyclability of the kinetic resolution of cyclic carbonates to access chiral building blocks the goal was to prove the applicability of the procedure for the synthesis of high value-added chemicals. In particular, the synthesis of TAGEs (terminal aromatic glycerol ethers) was targeted due to their structural similarity with the glycerol molecule. The reaction of (*S*)-**2ah** with different phenols **13** was carried out under basic conditions. In this system, a strong base (NaOH) was used for its double role: (1) formation of the phenoxide anion that attacks the carbonate; (2) hydrolysis of the carbonate to the diol.



Scheme 15. Synthesis of (*S*)-TAGEs by substitution of (*S*)-**2ah** with phenols under basic conditions. Reaction conditions: 1.0 mmol of (*S*)-**2ah** added to 3.0 mmol of phenol and 3.0 mmol of NaOH in EtOH at 100°C for 3 h. Isolated yields are informed. *Er* values were determined by chiral GC-FID.

Four different phenols **13** were reacted with (*S*)-**2ah** (*er* = 94:6), giving the resulting (*S*)-**3a** in excellent yields of 81–89% (Scheme 15). More specifically, the reaction of phenol (**13a**) afforded (*S*)-1-phenyl glycerol ((*S*)-**3af**) with *er* = 90:10. In this case, it was possible to isolate two different crystals suitable for X-ray analysis. Figure 7a shows the molecular structure of (*S*)-**3af** in the orthorhombic system and Figure 7b shows the monoclinic structure. (*S*)-Guaifenesin ((*S*)-**3ap**) was obtained from guaiacol **13b** in 91:9 *er*. This is particularly interesting as guaiacol is widely present in biomass and can be extracted from waste lignin, meaning that the overall process can be virtually carried out from renewable feedstocks.^[139] Moreover, the use of *o*-cresol **13c** and *p*-chlorophenol **13d** led to the formation of (*S*)-Mephenesin ((*S*)-**3aq**) and (*S*)-Chlorphenesin ((*S*)-**3ar**), both in *er* = 94:6.

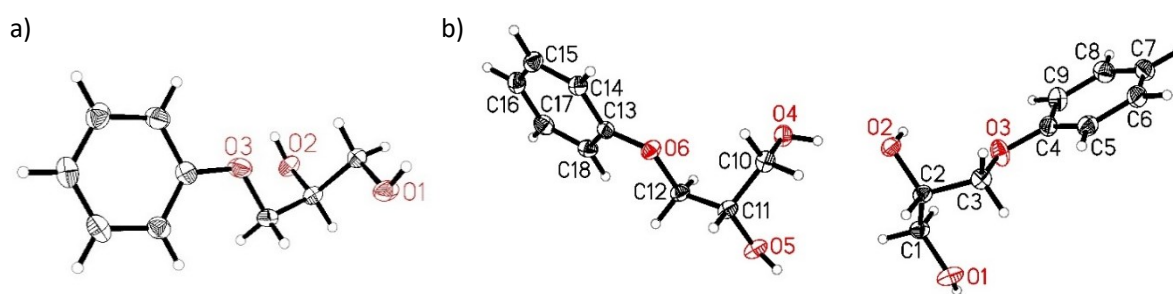
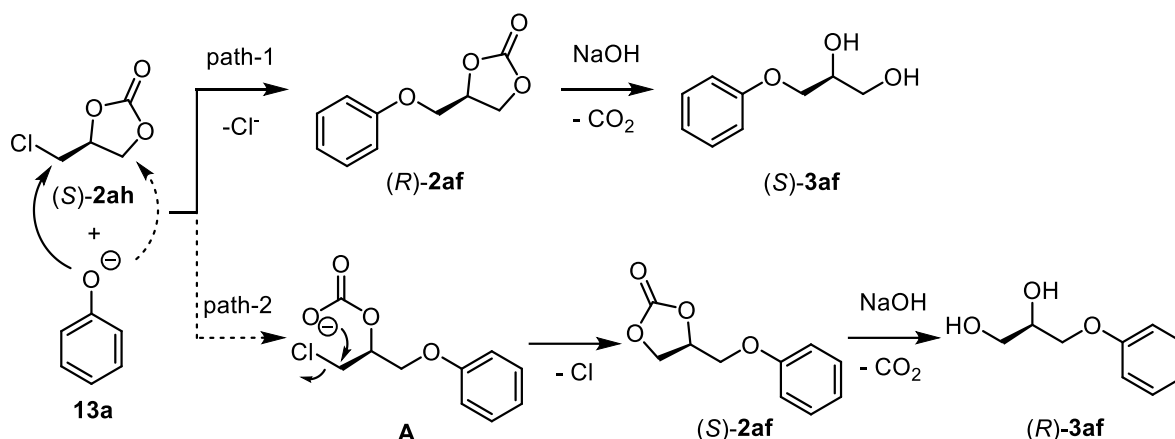


Figure 7. Molecular structure of (*S*)-**3af**. a) Orthorhombic system, CCDC 2263648. b) Monoclinic system, CCDC 2263647. Displacement ellipsoids correspond to 50% probability.

Insights into the different pathways of this reaction and the reactivity of the chiral building block were considered to understand the partial racemization in the formation of (*S*)-**3af** (Scheme 16). The phenoxide anion is formed under basic conditions and subsequently, it attacks ((*S*)-**2ah**) substituting the chloride (path-1). This leads to (*R*)-**2af**, that gives the desired

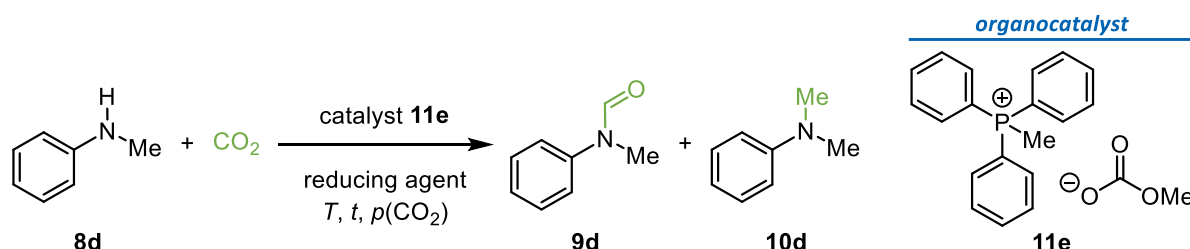
(*S*)-**3af** after basic hydrolysis. However, aromatic nucleophiles can easily attack soft electrophilic centers, especially if they are not sterically hindered. Thus, in the undesired reaction (path-2), the phenoxide attacks the less hindered methylene in the cyclic carbonate giving the intermediate **A**, a linear carbonate that forms the cyclic carbonate (*S*)-**2af** by substitution of the chloride. This carbonate gives the byproduct (*R*)-**3af** after hydrolysis of the carbonate. Therefore, the potential racemization is a consequence of the two different pathways followed by the reaction. Due to the good lability of the chloride, path-1 is favored over path-2. However, the slight lower *er* obtained for (*S*)-**3af** and (*S*)-**3ap** (90:10 and 91:9) can be understood based on this mechanism.



Scheme 16. Proposed pathways for the synthesis of (*S*)-**3af** by substitution of (*S*)-**2ah** with phenol **13a** under basic conditions.

3.3 Organocatalyzed reductive functionalization of CO₂ with amines^[140]

Methyltriphenylphosphonium methylcarbonate (**11e**) was evaluated for the synthesis of *N*-methylamines and *N*-formamides by reductive functionalization of CO₂ with amines (Scheme 17). This catalyst is commercially available and can be easily prepared by reaction of triphenylphosphine with dimethylcarbonate.^[141]



Scheme 17. Reductive functionalization of CO₂ with *N*-methylaniline (**8d**) for the synthesis of the *N*-formylated and *N*-methylated products **9d** and **10d** catalyzed by **11e**.

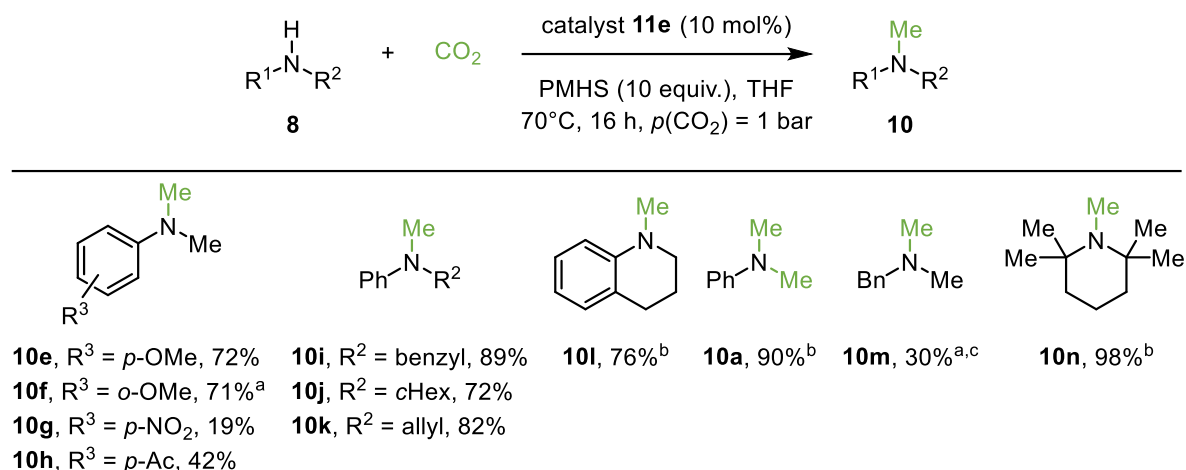
PMHS was chosen as reducing agent due to the interest on the valorization of this inexpensive, non-toxic and stable chemical. First experiments were conducted using *N*-methylaniline (**8d**) as model substrate in THF at 70°C and a $p(\text{CO}_2) = 1$ bar (Table 7). While in the absence of the catalyst no product is observed, a catalyst loading of 10 mol% afforded the methylated product **10d** in 53% yield (Entries 1 and 2). An increase in the amount of PMHS from 4 to 10 equiv. yielded **10d** in 87% (Entry 3). A lower temperature (60°C) resulted in the loss of selectivity due to the formation of **9d** in 17%, while **10d** was obtained in 82% yield (Entry 4). Similarly, a catalyst loading of 5 mol% resulted in the formation of **9d** in 30% and **10d** in 62% (Entry 5).

Table 7. Selected results for the screening of reaction conditions for the conversion of *N*-methylaniline (**8d**) with CO_2 and PMHS catalyzed by **11e**.

Entry	Catalyst loading (mol%)	PMHS (equiv.)	T (°C)	Yield 9d (%) ^a	Yield 10d (%) ^a
1	0	4	70	0	0
2	10	4	70	0	53
3	10	10	70	0	87
4	10	10	60	17	82
5	5	10	70	30	62

^aReaction conditions: *N*-methylaniline **8d** (0.23 mmol, 1 equiv.), PMHS (4–10 equiv.), catalyst **11e** (0–10 mol%), $p(\text{CO}_2) = 1$ bar, 60–70°C for 16 h, 2 mL of THF. Yield was determined by ^1H NMR using mesitylene as the internal standard.

With the optimized conditions in hand for the *N*-methylation of amines (Table 7, Entry 3), several substrates were tested (Scheme 18). *N*-methylanilines (**10e–10h**) gave moderate to good yields. In particular, the *p*- and *o*-OMe substituted anilines **10e** and **10f** gave the corresponding products in 72% and 71% yield, respectively. On the other hand, strong electron withdrawing groups such as *p*-NO₂ and *p*-acetyl yielded the products **10g** and **10h** in 42% and 19%. Other *N*-substituted anilines (**10i–10k**) were successfully converted with this procedure affording the methylated products in good yields 72–89%. Moreover, tetrahydroquinoline (**8l**) was converted to its methylated derivative in 76% yield. Aniline (**8a**) was converted to the *N,N*-dimethylaniline in 90% yield, which shows that even less nucleophilic primary anilines can be converted with this catalyst. Beside anilines, other amines were tested. Although *N*-methylbenzylamine (**8m**) afforded the product **10m** in only 30% yield, the formylated product **9m** was also obtained in 68% yield. Furthermore, it was possible to prepare a ganglion-blocking drug, Pempidine^[142] (**10n**) by methylation of the 2,2,6,6-tetra-methyl-piperidine (**8n**) with an excellent yield of 98%.



Scheme 18. Selected examples for the reduction of amines to *N*-methylanimes with CO₂ and PMHS. Reaction conditions: Amine **8** (0.60 mmol), PMHS (10 equiv.), catalyst **11e** (0.06 mmol, 10 mol%), *p*(CO₂) = 1 bar, 70°C, 16 h, 6 mL of THF. Isolated yields are given. ^a4 h. ^bYield determined by ¹H NMR using mesitylene as the internal standard. ^c**9m** was obtained in 68% yield.

The low selectivity observed for the formylated product **9d** with PMHS motivated to screen other phenyl- and alkylsilanes, in search of a more selective reducing agent (Table 8). The arylsilanes PhSiH₃ and Ph₂SiH₂ showed preference for the methylated product **10d**, both yielding **9d** in only 8% (Entries 2 and 3). Ph₃SiH showed opposite selectivity giving the desired **9d** in 39% yield as only product (Entry 4). Et₃SiH, a milder reducing agent, did not achieve the conversion of either **9d** or **10d** (Entry 5). Finally, (MeO)₃SiH gave an excellent yield of 98% for **9d**, with no **10d** observed (Entry 6).

Table 8. Silane screening for the conversion of *N*-methylaniline (**8d**) with CO₂ to the corresponding formylated product (**9d**).

Entry	Catalyst loading (mol%)	Silane (equiv.)	<i>t</i> (h)	Yield 9d (%) ^a	Yield 10d (%) ^a
1	10	PMHS (4)	16	0	53
2	10	PhSiH ₃ (4)	16	8	31
3	10	Ph ₂ SiH ₂ (4)	16	8	55
4	10	Ph ₃ SiH (4)	16	39	0
5	10	Et ₃ SiH (4)	16	0	0
6	10	(MeO) ₃ SiH (4)	16	98	0

^aReaction conditions: *N*-methylaniline **8d** (0.23 mmol, 1 equiv.), silane (2–4 equiv.), catalyst **11e** (0–10 mol%), *p*(CO₂) = 1 bar, 70°C for 4–16 h, 2 mL of THF. Yield was determined by ¹H NMR using mesitylene as the internal standard.

Further optimization of the reaction conditions was carried out with (MeO)₃SiH (Table 9). A reduction of the reaction time from 16 h to 4 h gave the product in 94% yield (Entry 1). Due to the good results, a catalyst loading of 2 mol% was used, which also resulted in an excellent

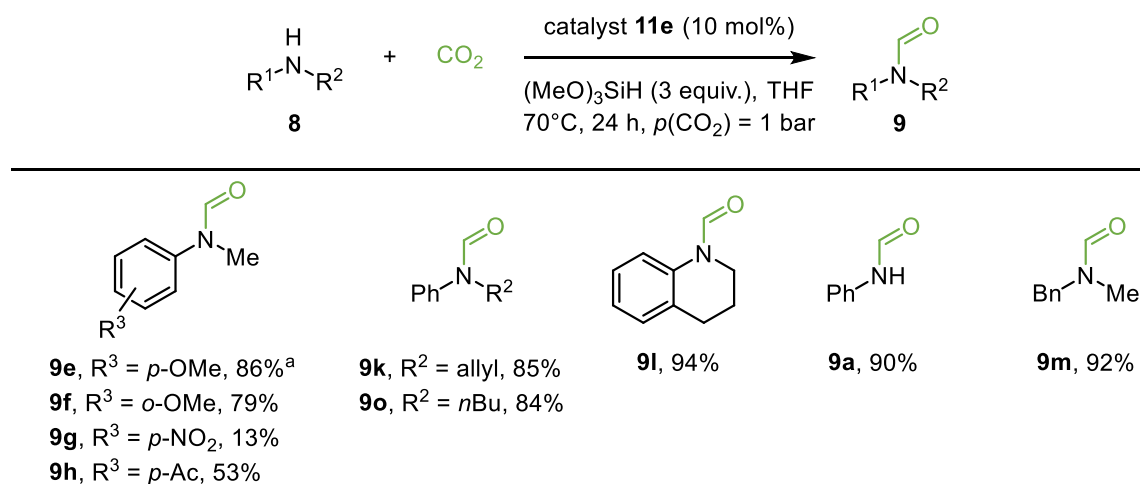
yield of 96% (Entry 2). A decrease in the amount of silane to 3 equiv. was well tolerated as **9d** was obtained in 95% yield (Entry 3). However, a further decrease to 2 equiv. resulted in a drop of the yield to 44% (Entry 4). Finally, the control reaction without catalyst did not afford any product (Entry 5).

Table 9. Optimization of reaction conditions for the conversion of *N*-methylaniline (**8d**) with CO₂ and (MeO)₃SiH to the corresponding formylated product (**9d**).

Entry	Catalyst loading (mol%)	(MeO) ₃ SiH (equiv.)	Yield 9d (%) ^a	Yield 10d (%) ^a
1	10	4	94	0
2	2	4	96	0
3	2	3	95	0
4	2	2	44	0
5	0	3	0	0

^aReaction conditions: *N*-methylaniline **8d** (0.23 mmol, 1 equiv.), (MeO)₃SiH (2–4 equiv.), catalyst **11e** (0–10 mol%), *p*(CO₂) = 1 bar, 70°C for 4 h, 2 mL of THF. Yield was determined by ¹H NMR using mesitylene as the internal standard.

Once the reaction conditions for the synthesis of formamides were optimized, different substrates were evaluated. Scheme 19 shows a selection of amines converted with (MeO)₃SiH under the optimized conditions.

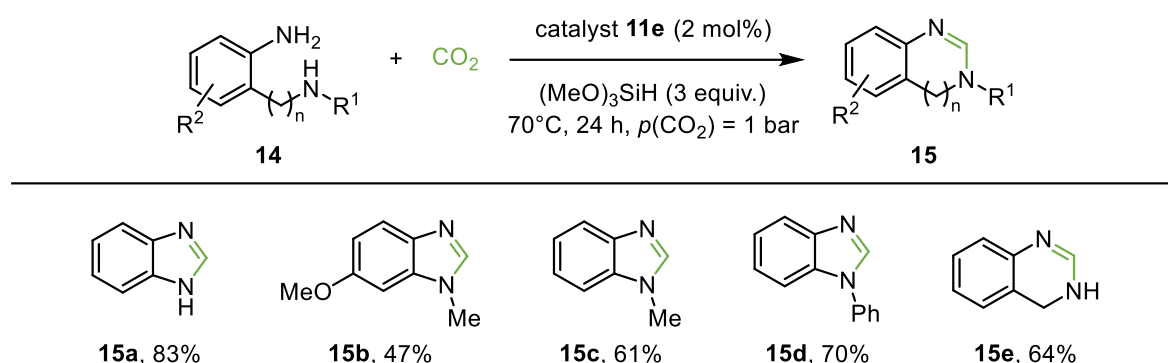


Scheme 19. Selected examples for the reduction of amines to *N*-formylamines with CO₂ and (MeO)₃SiH. Reaction conditions: Amine **8** (0.60 mmol), (MeO)₃SiH (3 equiv.), catalyst **11e** (0.06 mmol, 10 mol%), *p*(CO₂) = 1 bar, 70°C, 24 h, 6 mL of THF. Isolated yields are given. ^a4 h.

The *p*- and *o*-OMe substituted anilines **9e** and **9f** were obtained in 86 and 79% yield. However, anilines with electron withdrawing groups showed to be less reactive. In particular, *p*-NO₂ and *p*-acetyl substituted *N*-methylanilines, **8g** and **8h**, afforded the products **9g** and **9h** in 13% and

53%, respectively. Other *N*-substituted anilines such as **9k** and **9o** were prepared in good yields of 84–85%. Tetrahydroquinoline (**8l**) was converted to the formylated **9l** with an excellent yield of 94%. Primary anilines also proved to be reactive. In particular, aniline **8a** gave the formylated product in 90% yield. Finally, the benzylic amine (**8m**) was converted yielding **9m** in 92%.

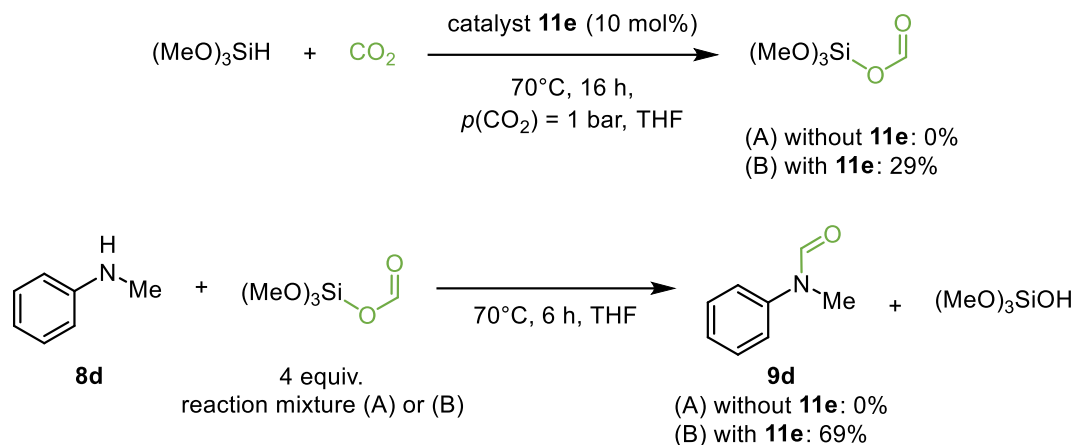
Due to the good results achieved for the formylation of amines, a more challenging reaction was considered. The formation of benzimidazole derivatives by the sequential formylation of amines followed by an intramolecular condensation requires a two-step strategy or harsh conditions,^[143, 144] which motivated us to study the activity of **11e** towards this reaction (Scheme 20). To our delight, under the same conditions optimized for the formation of formamides, 1,2-diaminobenzene **14a**, was successfully converted to benzimidazole **15a** in 83% yield. This promising result motivated us to further study other substrates. *N*-methyl substituted substrates such as **15b** and **15c** were prepared in 47% and 61% yield. These lower yields are explained based on the observed monoformylation of the primary amino group which makes the second condensation step more difficult. Moreover, the *N*-phenyl substituted **14d** was converted in 70% and the six-membered quinazoline **15e** was isolated in 64% yield.



Scheme 20. Selected examples for the reduction of diamines to benzoheterocycles with CO₂ and (MeO)₃SiH. Reaction conditions: Diamine **14** (0.60 mmol), (MeO)₃SiH (3 equiv.), catalyst **11e** (0.06 mmol, 2 mol%), *p*(CO₂) = 1 bar, 70°C, 24 h, 6 mL of THF. Isolated yields are given.

To gain insights into the mechanism of this reaction and its differential selectivity, a series of studies were rationally designed by evaluation of the possible routes and intermediates for both reactions. In line with previous studies reported for the organocatalyzed *N*-formylation reaction,^[120] it was proposed that the formation of the formoxysilane as intermediate was catalyzed by the catalyst **11e**. Once this intermediate is formed, the reaction with the nucleophilic amine gives the *N*-formamide (Scheme 21). The formation of this intermediate was proved by reacting (MeO)₃SiH with CO₂ in presence and absence of **11e**. While the control reaction did not afford the product, the catalyzed reaction gave the formoxysilane in 29%

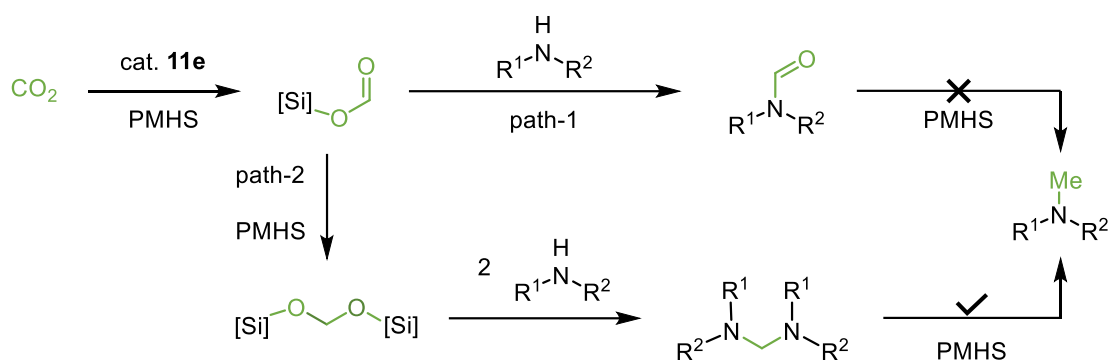
yield. Furthermore, the amine **8d** was added to the resulting reaction mixtures in the absence of CO₂. Under these conditions the desired product of formylation **9d** was obtained in 69% yield.



Scheme 21. Mechanistic studies regarding the formation of formoxysilane and further reaction with the amine. (MeO)₃SiH (1.0 mmol), catalyst **11e** (0–10 mol%), *p*(CO₂) = 1 bar, 70°C, 16 h. 2 mL of THF. *N*-methylaniline **8d** (0.26 mmol) was added under argon atmosphere, 70°C, 6 h. Yield was determined by ¹H NMR using mesitylene as the internal standard.

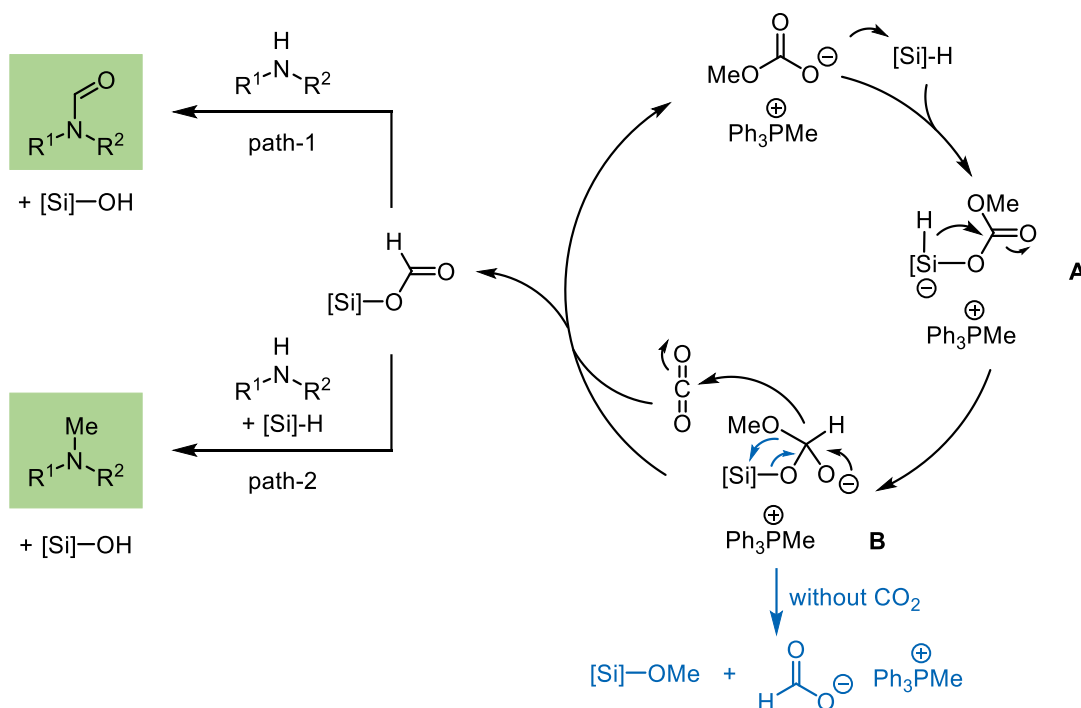
For the elucidation of the *N*-methylation reaction with PMHS two possible reaction pathways were proposed (Scheme 22): the formoxysilane is formed by reduction of CO₂ with PMHS in the presence of the catalyst, reacting with the amine to give the formamide, which can be further reduced with another equivalent of PMHS to afford the methylated amine (path-1). In the second proposal (path-2) the formoxysilane is further reduced to the silyl acetal which reacts with the amine to give the corresponding aminal. Subsequently, the aminal is reduced to the product. Even though multiple catalysts undergo path-1,^[120] this path was proved wrong for catalyst **11e** as the conversion of the formamide did not afford the methylated product in either presence or absence of the catalyst **11e**. Therefore, path-2 was considered. The formation of the aminal was supported by the fact that it was observed in the reaction mixture after short reaction times. It was found that the aminal was initially formed in 9% yield after 2 h, and dropping to < 1% after 8 h. In addition to this, the conversion of the aminal to the methylated product was proved by converting the aminal to the methylated product with PMHS in the presence of the catalyst. In contrast, the control reaction without catalyst only gave traces of the desired product.

After elucidating the different paths for every reaction, the actual role of the catalyst was investigated. Experiments were carried out with (MeO)₃SiH since the polymeric nature of PMHS makes the analysis difficult. The proposed mechanism is presented in Scheme 23.



Scheme 22. Proposed pathways for the *N*-methylation reaction with PMHS.

In the first step the methylcarbonate anion attacks the silane giving intermediate **A**. The formation of this intermediate facilitates the reduction of the carbonyl center by the hydride, thus, forming the tetrahedral intermediate **B**. Experiments showed that the stoichiometric reaction between $(\text{MeO})_3\text{SiH}$ and **11e** in the absence of CO_2 gives the formate ion and tetramethoxysilane as products, which supports the formation of **B** as shown in Scheme 23. Instead, in the presence of CO_2 , the tetrahedral intermediate **B** reacts with CO_2 , thus, regenerating the catalyst and forming the formoxysilane as product. As shown previously, the formoxysilane can undergo path-1 or path-2 giving the *N*-formylated or *N*-methylated product. This was an interesting finding, since the CO_2 does not react directly with the silane but promotes the regeneration of the catalyst, which represents a novel pathway for the reduction of CO_2 .



Scheme 23. Proposed mechanism for the synthesis of *N*-formamides and *N*-methylamines by reductive functionalization of CO_2 with amines catalyzed by **11e**.

4 Summary

In the first part of this work a novel, straightforward and cost-efficient catalytic system consisting of $\text{CaI}_2/\text{Et}_3\text{N}$ was developed for the synthesis of cyclic carbonates from epoxides and CO_2 . Terminal carbonates were synthesized in yields up to 97% at room temperature and a CO_2 pressure of 1 bar. In particular, glycidyl ethers derived from glycerol were successfully converted to their carbonates, which is important not only with regard to the utilization of CO_2 , but also for the valorization of bio-glycerol. Challenging internal carbonates were prepared using Ph_3P as co-catalyst at 70°C and 10 bar, yielding up to 90%. By increasing the catalyst loading from 5 to 10 mol%, bio-based internal carbonates, such as epoxidized oleochemicals and limonene oxide were also converted. Mechanistic studies revealed the coordination of Et_3N to the calcium center and the subsequent epoxide ring-opening.

Subsequently, the enzymatic kinetic resolution of glycerol-based cyclic carbonates was studied. Epichlorohydrin carbonate, was chosen as model substrate as it was considered a promising and sustainable building block. From 26 esterases and lipases tested, PLE and N435 showed the best results with *E* values of 38 and 49, respectively. Under optimized conditions, the kinetic resolution of various glycerol-based cyclic carbonates was performed. The best results were obtained for halogenated carbonates, which afforded the unconverted carbonates in *er* values up to > 99:1. Up-scaling of the reaction and recycling of N435 was demonstrated for the model substrate in 10 cycles, which allowed the successful isolation of 0.5 g of the (*S*)-enantiomer. The potential of enantiopure cyclic carbonates as chiral building blocks was also evaluated. The one-pot substitution of the chloride with phenols and hydrolysis of the carbonate under basic conditions, allowed the preparation of biologically active TAGEs ((*S*)-Guaifenesin, (*S*)-Mephenesin and (*S*)-Chlorphenesin) in excellent yields and *er* values. This chemoenzymatic approach offers a sustainable route for the synthesis of enantiopure pharmaceutical products.

Finally, the reductive functionalization of CO_2 with amines was carried out with a methylcarbonate phosphonium salt. At 70°C and a CO_2 pressure of 1 bar, various methylamines were obtained in yields up to 98%, using PMHS as green reductant. Moreover, formamides were prepared with trimethoxysilane in yields up to 94%. Under these conditions, the catalyst also proved to be efficient for the tandem formylation of amines followed by intramolecular condensation that leads to the corresponding benzoheterocycles. Mechanistic investigations indicated the formation of silyl intermediates and supported that the reaction follows a novel catalytic cycle, in which the CO_2 molecule regenerates the catalyst.

5 References

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6 Appendix

Figure 8a shows a section of the ^1H NMR corresponding to the pure epoxide. After addition of stoichiometric amounts of CaI_2 and Et_3N the epoxide is fully converted ($\text{CaI}_2\text{:1aa} = 1\text{:}1$, Figure 8b and $\text{CaI}_2\text{:Et}_3\text{N:1aa} = 1\text{:}1\text{:}1$, Figure 8c). The ring opening is confirmed by new signals at $\delta = 1.43\text{--}1.61$ ppm assigned to H_a and H_b , which are shifted upfield due to the shielding effect of the iodide. At the same time, the formation of the coordinated alkoxide results in the downfield shift of H_c to $3.37\text{--}3.47$ ppm and H_d to $3.25\text{--}3.35$ ppm.

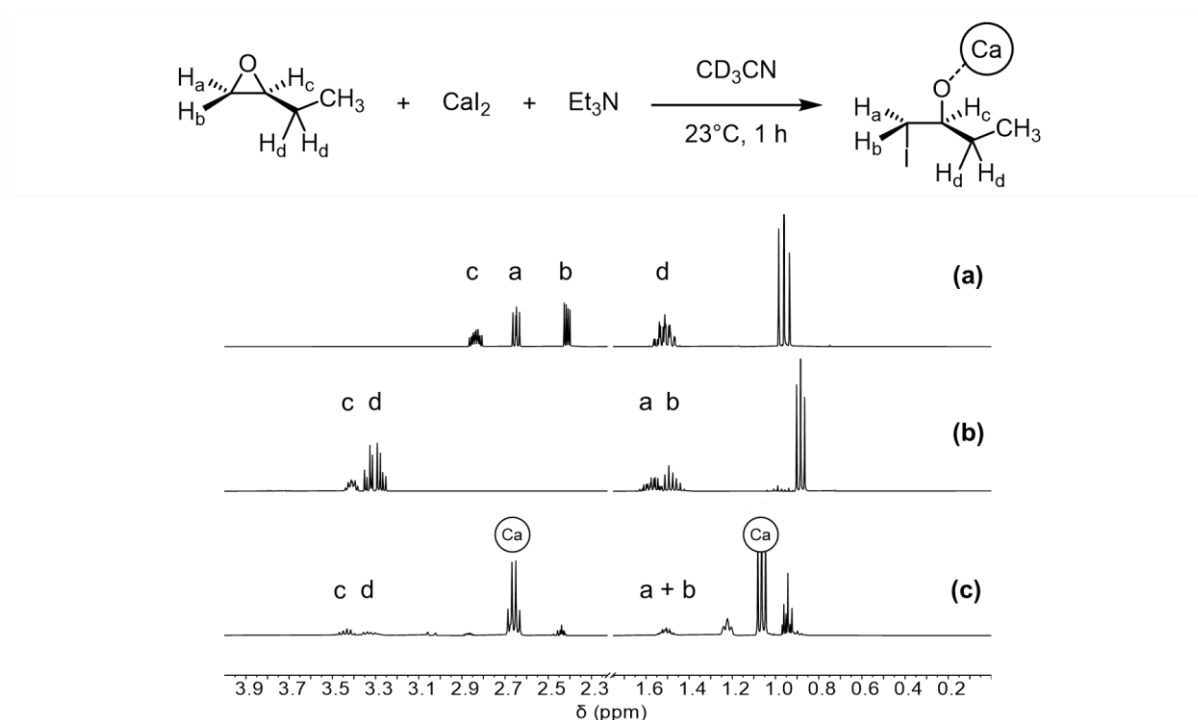


Figure 8. ^1H NMR investigations regarding the ring opening with CaI_2 . All mixtures were prepared in CD_3CN in a Young tube, under inert conditions. Ca represents the complex formed between CaI_2 and Et_3N . (a) Section of the ^1H NMR spectrum of the pure butylene oxide (**1aa**). (b) Section of the ^1H NMR spectrum of butylene oxide after addition of CaI_2 . (c) Section of the ^1H NMR spectrum of butylene oxide after addition of CaI_2 and Et_3N . Reaction conditions: 1.0 equiv. **1aa** (70 μmol), 1.1 equiv. CaI_2 (80 μmol), 1.1 equiv. Et_3N (0–80 μmol), 23°C , 1 h.

My contributions to publications are given.

Original work

Publication 1: C. Terazzi, K. Laatz, J. von Langermann,* T. Werner*, *ACS Sustain. Chem. Eng.* **2022**, *10*, 13335–13342.

“Synthesis of Cyclic Carbonates Catalyzed by $\text{CaI}_2\text{--Et}_3\text{N}$ and Studies on Their Biocatalytic Kinetic Resolution”

In this work, the major part of the experiments were conducted by me. Karoline Laatz carried out the synthesis of internal cyclic carbonates. The manuscript and the supporting information were written by me and corrected by Jan von Langermann and Thomas Werner. My overall contribution to this work is approximately 70%.

Publication 2: C. Terazzi, J. von Langermann,* T. Werner* *ChemCatChem* **2023**, *15*, e202300917.

“Chemoenzymatic Synthesis of Chiral Building Blocks Based on the Kinetic Resolution of Glycerol-Derived Cyclic Carbonates”

In this work, all the experiments were conducted by me. The manuscript and the supporting information were written by me and corrected by Jan von Langermann and Thomas Werner. My overall contribution to this work is approximately 80%.

Publication 3: C. Ren, C. Terazzi, T. Werner* *Green Chem.* **2024**, *26*, 439–447.

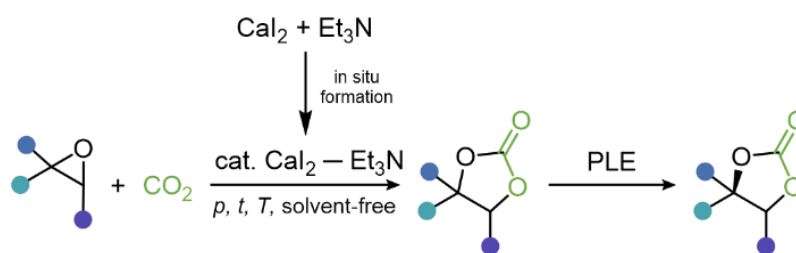
“Tuneable reduction of CO_2 – organocatalyzed selective formylation and methylation of amines”

Changyue Ren performed the initial reaction screening and the substrate scope. I performed part of the optimization of the reaction conditions and mechanistic studies. The manuscript and supporting information were written by Changyue Ren and corrected by me and Thomas Werner. My overall contribution is approximately 30%.

6.1 Synthesis of Cyclic Carbonates Catalyzed by $\text{CaI}_2\text{--Et}_3\text{N}$ and Studies on Their Biocatalytic Kinetic Resolution

C. Terazzi, K. Laatz, J. von Langermann,* T. Werner* *ACS Sustain. Chem. Eng.* **2022**, *10*, 13335–13342.

DOI: 10.1021/acssuschemeng.2c03210h



18 terminal carbonates (23 °C, 1 bar) up to 97% yield
11 internal and bio-based carbonates (70 °C, 10 bar) up to 90% yield
enzymatic kinetic resolution (7 examples) up to 99% *ee*

Abstract: Herein, we report a simple catalytic system consisting of CaI_2 in combination with Et_3N as a ligand for the efficient cycloaddition of CO_2 to a variety of epoxides. Terminal (bio-based) carbonates were obtained under mild conditions (23 °C, 1 bar CO_2 pressure) in excellent yields up to 97%. Under elevated temperature (70 °C) and higher CO_2 pressure (10 bar), even challenging internal epoxides were converted, leading to the desired carbonates in yields up to 90%. ^1H NMR experiments indicated the in situ coordination of the amine to the Lewis acidic calcium center as well as the activation of the epoxide. Furthermore, the enzymatic kinetic resolution of seven cyclic carbonates using readily available pig liver esterase was investigated. Styrene carbonate proved to be the most suitable substrate for the kinetic resolution, leading to (*R*)-styrene carbonate in 99% *ee*.

6.2 Chemoenzymatic Synthesis of Chiral Building Blocks Based on the Kinetic Resolution of Glycerol-Derived Cyclic Carbonates

C. Terazzi, A. Spannenberg, J. von Langermann,* T. Werner* *ChemCatChem* **2023**, *15*, e202300917.

DOI: 10.1002/cctc.202300917

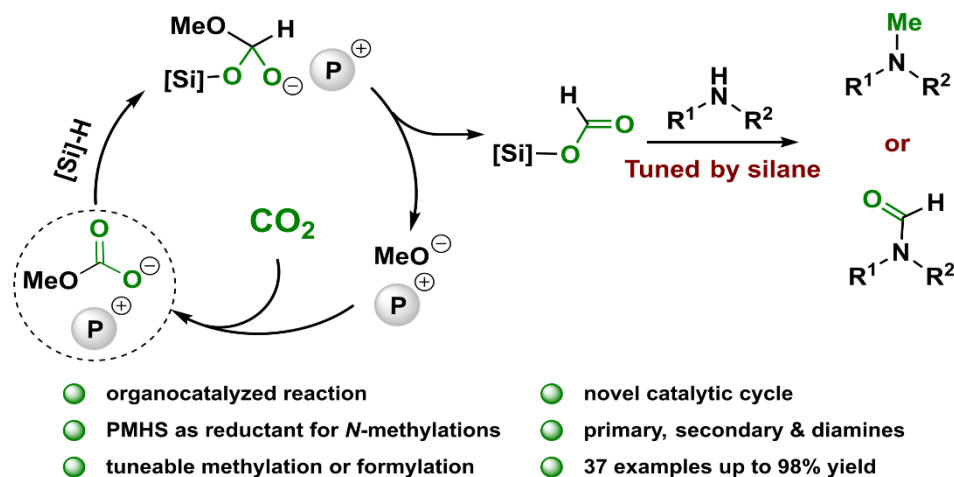


Abstract: The biocatalytic kinetic resolution of cyclic carbonates derived from glycerol is reported. A selection of 26 esterases and lipases was tested for the asymmetric hydrolysis of the model substrate (4-(chloromethyl)-1,3-dioxolan-2-one) in aqueous medium. Among them, Pig Liver Esterase and Novozym® 435 showed the best selectivity with $E = 38$ and 49 , respectively. Both enzymes were employed for the conversion of 12 glycerol derivatives under optimized conditions. The resolution of halogenated carbonates afforded the unconverted enantiomer in up to $> 99:1$ *er*. Furthermore, Novozym® 435 was successfully recycled 10 times without significant loss of activity. Upscaling and isolation of a chiral carbonate was also demonstrated. Subsequent conversion of this chiral building block allowed the direct one-pot synthesis of Guaifenesin, Mephenesin and Chlorphenesin in up to 89% yield and 94:6 *er*.

6.3 Tuneable reduction of CO₂ – organocatalyzed selective formylation and methylation of amines

C. Ren, C. Terazzi, T. Werner* *Green Chem.* **2024**, 26, 439–447.

DOI: 10.1039/D3GC03993E



Abstract: The *N*-formylation and *N*-methylation of amines with carbon dioxide (CO₂) are important types of transformations which give access to a wide range of key intermediates and compounds. Efficient catalytic methods for both reactions are rare because of the challenge of controlling selectivity. Herein, we report the environmentally benign organocatalyzed *N*-formylation and *N*-methylation of primary and secondary amines using CO₂ as the C1 source in the presence of hydrosilanes as the reductant. Readily available methyltriphenylphosphonium methylcarbonate has been proven to be an efficient catalyst for the *N*-methylation of amines and CO₂ in the presence of polymethylhydrosiloxane (PMHS) under mild conditions. In contrast, the selective *N*-formylation is achieved in the presence of trimethoxysilane as the reductant. In both transformations, a wide range of substrates were selectively converted. 15 primary and secondary amines were *N*-methylated and *N*-formylated and the corresponding products were obtained in yields of up to 98% and 94%, respectively. Moreover, benzimidazoles are accessible from diamines and CO₂ in a one-pot reaction in yields of up to 83%. Mechanistic investigations revealed different reaction pathways for *N*-methylation and *N*-formylation depending on the reductant as well as the activation of CO₂ by the catalyst.

Synthesis of Cyclic Carbonates Catalyzed by $\text{CaI}_2\text{--Et}_3\text{N}$ and Studies on Their Biocatalytic Kinetic Resolution

Constanza Terazzi, Karoline Laatz, Jan von Langermann,* and Thomas Werner*

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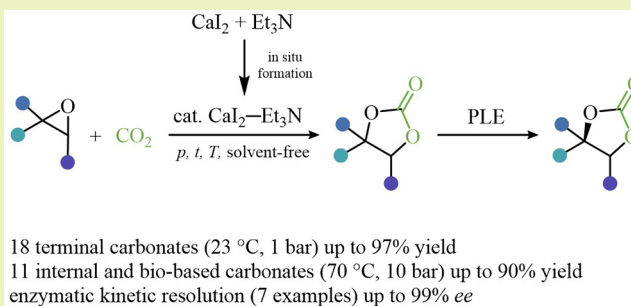
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Supporting Information

ABSTRACT: Herein, we report a simple catalytic system consisting of CaI_2 in combination with Et_3N as a ligand for the efficient cycloaddition of CO_2 to a variety of epoxides. Terminal (bio-based) carbonates were obtained under mild conditions (23 °C, 1 bar CO_2 pressure) in excellent yields up to 97%. Under elevated temperature (70 °C) and higher CO_2 pressure (10 bar), even challenging internal epoxides were converted, leading to the desired carbonates in yields up to 90%. ^1H NMR experiments indicated the in situ coordination of the amine to the Lewis acidic calcium center as well as the activation of the epoxide. Furthermore, the enzymatic kinetic resolution of seven cyclic carbonates using readily available pig liver esterase was investigated. Styrene carbonate proved to be the most suitable substrate for the kinetic resolution, leading to (*R*)-styrene carbonate in 99% *ee*.

KEYWORDS: CO_2 , calcium complexes, cyclic carbonates, pig liver esterase, sustainable catalysis



Styrene carbonate proved to be the most suitable substrate for

INTRODUCTION

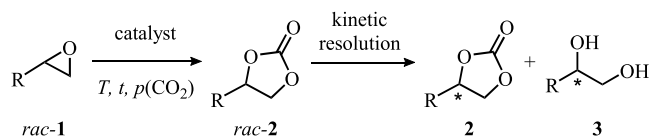
Increasing levels in carbon dioxide (CO_2) emissions have motivated the development of new strategies toward the shift from a linear to a circular economy of this greenhouse gas. In this context, its utilization has gained great attention and it is now considered as a readily available, abundant, cheap, and nonhazardous building block for the synthesis of value-added products.^{1–3} However, due to its high thermodynamic stability, the main challenge relies on the design of methodologies that require a minimum energy input in order to guarantee a sustainable process.⁴ In this regard, the synthesis of cyclic carbonates by the addition of carbon dioxide to epoxides is an interesting and useful reaction (Scheme 1).^{5–9} Cyclic

challenges need to be overcome to improve its ecological and economic feasibility. These challenges include the development of systems operating under ambient conditions,⁹ the conversion of bio-based substrates,¹³ and the sustainability, cost, and selectivity of the catalysts.¹⁴ In this regard, alkali metal salts in combination with additives outstand among reported systems for complying with these requirements.^{15,16}

Previous work in our group was carried out using CaI_2 in the presence of complexing agents such as crown ethers and polyethers.^{17–19} These systems present high activity under mild conditions (1 bar, room temperature) which motivated us to further explore the efficiency of CaI_2 in the presence of readily available ligands.

Furthermore, we became interested in obtaining pure chiral cyclic carbonates since they are potential chiral building blocks^{20–22} and only few studies focus on their enantioselective synthesis. One possible approach is the kinetic resolution of epoxides using chiral metal complexes which selectively convert the epoxide to the corresponding carbonate.²³ Alternatively, we proposed the kinetic resolution of the cyclic carbonates by means of a biocatalytic reaction which selectively hydrolyses the C–O bond to afford the

Scheme 1. Synthesis of Cyclic Carbonates and Access to Chiral Building Blocks via Kinetic Resolution

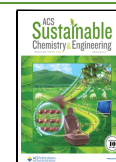


carbonates find numerous applications in industry, such as electrolytes in lithium-ion batteries and green solvents in organic synthesis due to their low toxicity and environmentally benign properties.¹⁰ They are applied as monomers in the production of polycarbonates¹¹ and precursors for the synthesis of several chemicals.¹² Despite the extensive studies on the cycloaddition of carbon dioxide to epoxides, some

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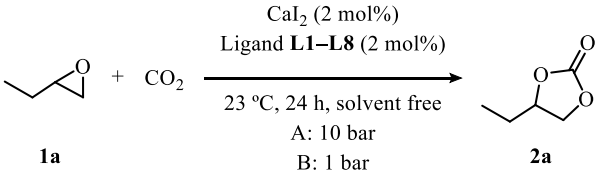
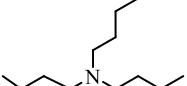
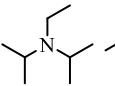
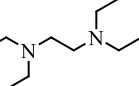
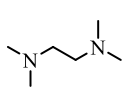
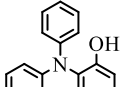
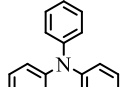
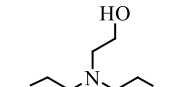


corresponding vicinal diols. These are interesting products that play an important role in the synthesis of natural and biologically active substances.²⁴ Since only few studies on this strategy have been reported,^{25–27} we decided to further investigate this approach using pig liver esterase (PLE) which is widely employed in kinetic resolution and desymmetrizations of esters (Scheme 1).²⁸ In particular, previous studies show its potential toward substrates such as cyclic carbonates.²⁹ Herein, we report the synthesis of cyclic carbonates using a simple catalytic system under mild conditions, as well as the subsequent kinetic resolution of cyclic carbonates to afford the enantiopure carbonate and the corresponding enantioenriched diol.

RESULTS AND DISCUSSION

Catalyst Screening and Optimization. The conversion of butylene oxide (**1a**) to the corresponding carbonate **2a** was chosen as model reaction for the screening of several readily available tertiary amines as potential ligands (Table 1). Initial

Table 1. Ligand Screening for the CaI_2 -Catalyzed Conversion of Butylene Oxide (1a**) with CO_2 to Carbonate **2a**^a**

	
 L1 A: 97%, B: 94%	 L2 A: 77%
 L3 A: 74%	 L4 A: 95%, B: 94%
 L5 A: 56%	 L6 A: 90%, B: 42%
 L7 A: 43%	 L8 A: 14%

^aReaction conditions: 1.0 equiv of **1a** (10.0 mmol), 2 mol % CaI_2 and 2 mol % ligand **L**, 23 °C, 24 h, solvent free, $p(\text{CO}_2)$ = 10 bar (conditions A) or 1 bar (conditions B). Yields were determined by ^1H NMR using mesitylene as the internal standard.

studies were performed at room temperature and a CO_2 pressure of 10 bar (conditions A) and 1 bar (conditions B) using calcium iodide as the catalyst (2 mol %). Notably, in the absence of a ligand, product **2a** was obtained in only 23% yield. In combination with triethylamine (**L1**), the yield significantly increased up to 97% at 10 bar CO_2 pressure. A comparable yield of 94% was achieved at 1 bar. The use of tributylamine (**L2**) led to a lower yield of 77% at 10 bar which can be addressed to increased steric bulkiness compared to **L1**. This is in line with the result achieved with diisopropylethylamine (**L3**) which led to **2a** in 74% yield. The ligand N,N,N',N' -

tetraethylethylenediamine (**L4**) afforded **2a** in 95 and 94% at 10 and 1 bar CO_2 pressure, respectively. In contrast, N,N,N',N' -tetramethylethylenediamine (**L5**) gave a significantly lower yield of 56% which can be explained based on the higher ability of **L5** to act as a bidentate ligand forming stable complexes with CaI_2 , thus preventing the activation of the epoxide.³⁰ Several reports show that hydroxyl groups can activate epoxides through hydrogen bond formation.^{31–34} Thus, hydroxy-functionalized amines were also studied as ligands. Indeed, 2-(diphenylamino)phenol (**L6**) led to higher activity compared to triphenylamine (**L7**) yielding **2a** in 90 and 43%, respectively. However, in the presence of **L6**, the yield decreased to 42% at 1 bar CO_2 pressure. Triethanolamine (**L8**) in combination with potassium iodide is an efficient catalytic system for the synthesis of cyclic carbonates at higher temperatures (90 °C).³² In contrast, **L8** in combination with CaI_2 at room temperature gave **2a** in unsatisfactory 14% yield. This can be explained by the ability of **L8** to form stable complexes with bivalent metal ions, thereby hampering the Lewis acidic activation of the epoxide.^{35–38} 1,4-diazabicyclo[2.2.2]octane (DABCO) and 4-dimethylamino-pyridine (DMAP) are frequently used as co-catalysts in the synthesis of cyclic carbonates.^{39–42} In the presence of DABCO, a yield of 42% was achieved while the use of DMAP gave **2a** in 94% yield.

In order to compare Et_3N with other ligands previously reported, the reaction was performed under conditions B employing a crown ether and a polyether due to their high efficiency for this reaction.^{17–19} To our delight, Et_3N gave the highest yield,⁴³ which indicates that tuning the Lewis acidity of the Ca^{2+} center has considerable impact on the activity of the catalyst.

Furthermore, the activity of alkali metal iodides and other alkaline earth metal salts was studied at room temperature and a CO_2 pressure of 1 bar. The use of alkali metal iodides in combination with Et_3N gave the desired product in low yields <5%, due to an observed lower solubility of the salts in the reaction mixture, in addition to the poorer Lewis acidity of the cation and lower atom economy of iodide in these salts which leads to half of the concentration of the anion. In contrast, when alkaline earth metal iodides (MgI_2 and CaI_2) were employed, excellent yields >90% were achieved with the only exception of BaI_2 which afforded the product in only 25% yield. Since Mg belongs to the endangered elements and CaI_2 is more cost efficient, we focused our further investigations on the utilization of CaI_2 (Table 2).^{44,45} In the absence of Et_3N , the desired product was obtained in a low yield of 23% under solvent-free conditions and 24% when CH_3CN was used as a solvent (Table 2, entry 1). Reducing the catalyst loading from 2 mol % to 1 mol % led to a dramatic decrease in yield from 94 to 10% (entries 2 vs 3).

Tetrabutylammonium iodide (TBAI) is a frequently used co-catalyst in the metal-catalyzed synthesis of cyclic carbonates.^{46–48} The use of 2 and 5 mol % of TBAI led indeed to a significant improvement in yield up to 89% for the $\text{CaI}_2/\text{Et}_3\text{N}$ system (entry 4). A similar increment was observed using 5 mol % of Ph_3P which afforded **2a** in 72% yield (entry 5). Notably, Ph_3P (5 mol %) alone gave no product while with TBAI (2 mol %) it gives 12% yield under the same reaction conditions. When the reaction time was reduced from 24 to 12 h in the presence of 2 mol % CaI_2 and Et_3N , the yield for **2a** decreased from 94 to 81% yield (entry 2 vs 6). An increase of the catalyst loading to 5 mol % $\text{CaI}_2/\text{Et}_3\text{N}$ led to an excellent

Table 2. Optimization of the Reaction Conditions

entry	CaI ₂ (mol %)	Et ₃ N (mol %)	time (h)	yield 2a ^a (%)
1	2	0	24	23 (24) ^b
2	2	2	24	94
3	1	1	24	10
4	1	1	24	66 ^c (89) ^d
5	1	1	24	72 ^e
6	2	2	12	81
7	5	5	12	88
8	5	5	24	99
9	2	2	24	40 ^f
10	5	5	24	97 ^f

^aReaction conditions: 1.0 equiv of **1a** (10.0 mmol), 1–5 mol % CaI₂ and Et₃N (1:1), 23 °C, 24 h, solvent free, *p*(CO₂) = 1 bar. Yields were determined by ¹H NMR with mesitylene as an internal standard. ^b1 mL of CH₃CN was added. ^c2 mol % TBAI was added. ^d5 mol % TBAI was added. ^e5 mol % Ph₃P was added. ^fStyrene oxide (**1h**) was used as the substrate.

yield of 88% after 12 h and 99% after 24 h, respectively (entries 7 and 8). If styrene oxide is used as the substrate, the corresponding cyclic carbonate was obtained in a moderate yield of 40% after 24 h in the presence of 2 mol % catalyst, while in the presence of 5 mol %, an excellent yield of 97% was obtained (entries 9 and 10).

As comparison with state-of-the-art catalysts, the reaction was performed under 1 bar of CO₂ pressure at 23 °C using 2 mol % of TBAC, TBAB, and TBAI finding that these organic salts afford **2a** in ≤12% yield and that addition of Et₃N to TBAI does not provide any improvement.⁴³

We further investigated the impact of the CaI₂/Et₃N ratio in the model reaction (Figure 1). Therefore, the reaction was

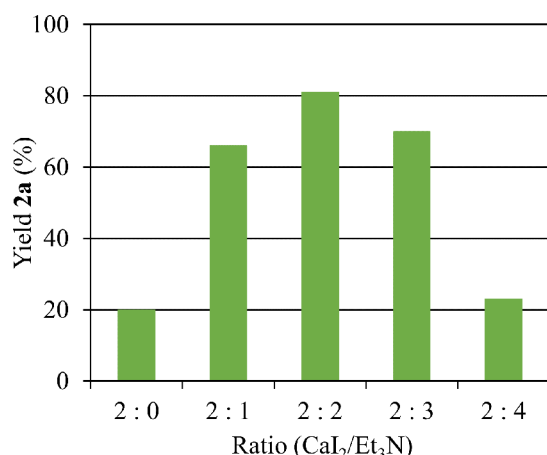


Figure 1. Effect of the CaI₂/Et₃N ratio. Reaction conditions: 1.0 equiv of **1a** (10.0 mmol), 2 mol % CaI₂ and 0–4 mol % Et₃N, 23 °C, 12 h, solvent free, *p*(CO₂) = 1 bar. Yields were determined by ¹H NMR using mesitylene as the internal standard.

carried out using 2 mol % of CaI₂ for 12 h and different amounts of Et₃N (0–4 mol %). In the absence of Et₃N, a low yield of 20% was obtained. In the presence of 1 mol % Et₃N, the yield increased to 66%. The best result is obtained when CaI₂ and Et₃N are employed in a ratio of 1:1 leading to the desired product **2a** in 81% yield. A further increase in the amount of Et₃N to 3 and 4 mol % led to lower yields of 70 and 23%, respectively. The lower activity at higher loadings of Et₃N

might be addressed to a decrease in the Lewis acidity of the Ca²⁺ center upon addition of an excess of Lewis base Et₃N.

The coordination of Et₃N is supported by ¹H NMR experiments (Figure 2). Figure 2a shows a section of the ¹H

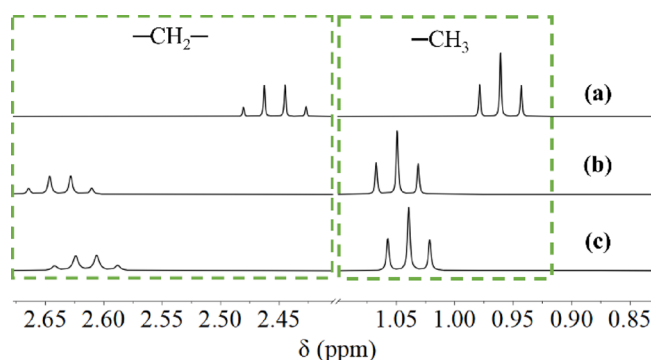


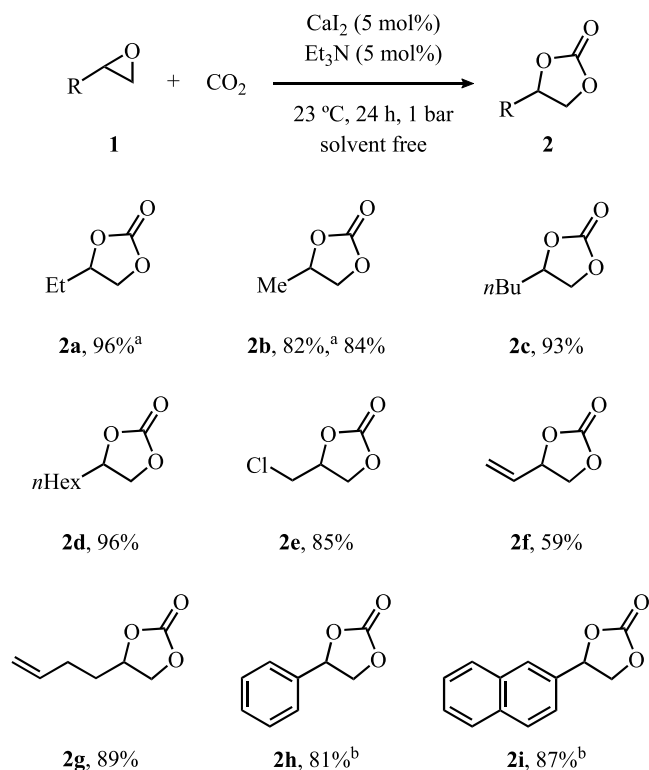
Figure 2. ¹H NMR investigations on the coordination of Et₃N to CaI₂. All mixtures were prepared in CD₃CN under inert conditions. (a) Section of the ¹H NMR spectrum of Et₃N without CaI₂. (b) CaI₂/Et₃N = 1:1. (c) CaI₂/Et₃N = 1:2.

NMR of Et₃N. The significant shift of the methylene protons from 2.46 to 2.64 ppm and for the methyl protons from 0.96 to 1.05 ppm in the presence of equimolar amounts of CaI₂ indicates the coordination of Et₃N to the Lewis acidic Ca²⁺ center (Figure 2a vs 2b). In the presence of an excess of Et₃N (2 equiv), no free Et₃N is observed and a less pronounced shift of the methylene protons from 2.46 to 2.62 ppm is observed (Figure 2a vs 2c).

Evaluation of the Substrate Scope. We turned our attention to the scope and limitations of the catalytic system utilizing the optimized catalytic system (5 mol % CaI₂/Et₃N) under mild conditions (23 °C, 24 h, *p*(CO₂) = 1 bar). Various terminal carbonates were synthesized in good to excellent yields up to 96% (Scheme 2). In particular, carbonates with aliphatic substituents gave the best yields (**2a–2d**). In this regard, it was possible to use a lower catalyst loading of 2 mol % for butylene carbonate (**2a**) and propylene carbonate (**2b**) which were isolated in 96 and 82% yield, respectively. This is of particular interest since these compounds are useful green solvents produced on the industrial scale.^{10,49} Epichlorohydrin (**1e**) was converted to the carbonate (**2e**) in 81% yield after isolation without observing the corresponding iodine carbonate which can be obtained by substitution of the chlorine atom. The conversion of aryl-substituted epoxides **1h** and **1i** led to the corresponding cyclic carbonates **2h** and **2i** in good yields of 81 and 87%, respectively. These reactions were performed in CH₃CN to allow the dissolution of the solid products in the reaction mixture.

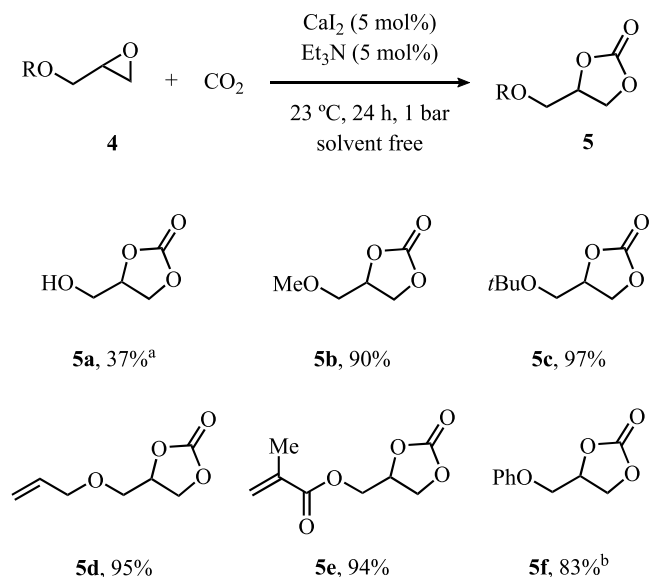
Glycerol derivatives **4** as well as the corresponding carbonates **5** have gained attention as bio-based synthetic building blocks since glycerol is the major byproduct from the manufacturing of biodiesel.^{50,51} Therefore, the conversion of substrates **4** with CO₂ under ambient conditions was further studied (Scheme 3). Glycidol (**4a**) is a challenging substrate which is prone to polymerization and hydrolysis.^{52,53} Under the standard reaction conditions, glycidol carbonate (**5a**) was obtained in 37% yield with glycerol as the side product. In contrast, the reaction of glycidyl methyl- (**4b**), *tert*-butyl- (**4c**), and allyl-glycidylether (**4d**) gave the desired products **5b–5d** in yields up to 97%. Glycerol carbonate methacrylate (**5e**),

Scheme 2. Substrate Scope I: Conversion of Terminal Epoxides^a



^aReaction conditions: epoxide **1** (25.0 mmol), 5 mol % CaI₂/Et₃N, 23 °C, 24 h, solvent free, *p*(CO₂) = 1 bar. Isolated yields are given. ^b2 mol % CaI₂/Et₃N was used. ^c1 mL of CH₃CN was used as the solvent.

Scheme 3. Substrate Scope II: Conversion of Glycerol Derivatives^a



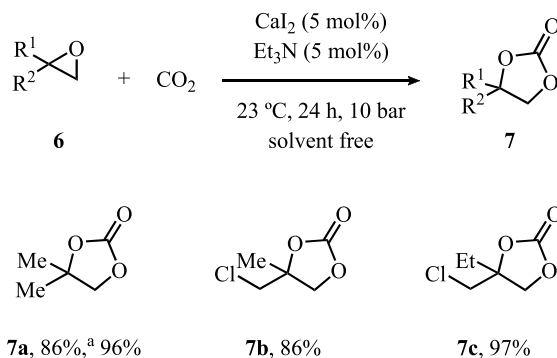
^aReaction conditions: epoxide **4** (25.0 mmol), 5 mol % CaI₂/Et₃N, 23 °C, 24 h, solvent free, *p*(CO₂) = 1 bar. Isolated yields are given. ^bYield determined by ¹H NMR using mesitylene as the internal standard. ^c3 mL of CH₃CN was used as the solvent.

which was obtained in 94% yield from epoxide **4e**, is of particular interest as a monomer since it finds wide applications in polymer synthesis and coatings.⁵¹ Also, the

conversion of phenyl-glycidylether (**4f**) in CH₃CN was successful, yielding **5f** in a good yield of 83%.

The conversion of disubstituted terminal epoxides is in general challenging, and typically, temperatures above 100 °C and pressures above 25 bar are required for their conversion.^{54,55} Therefore, we turned our attention to this class of substrates and initially studied the conversion of **6a** (Scheme 4). Under our standard reaction conditions, **7a** was

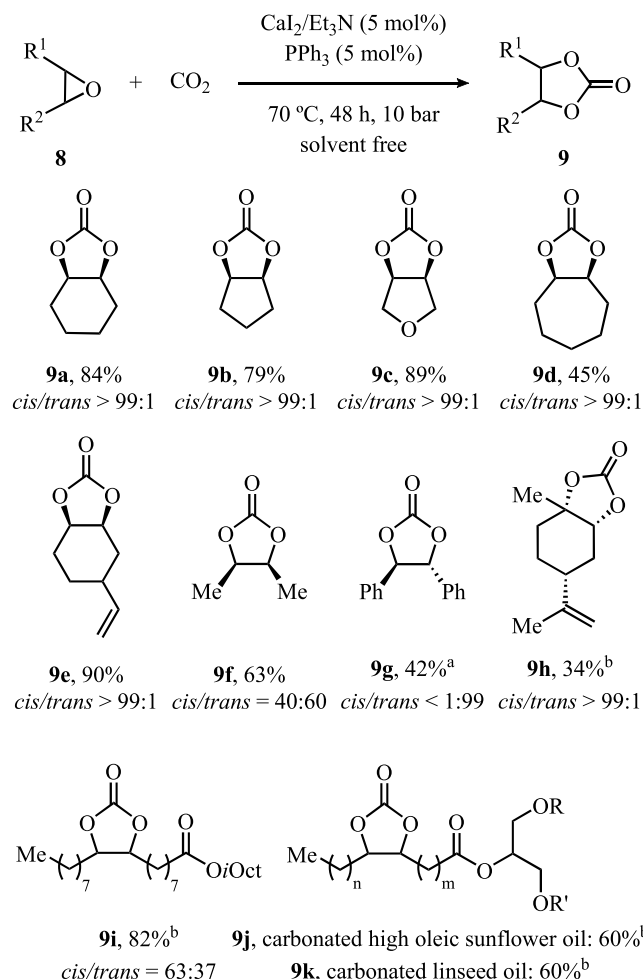
Scheme 4. Substrate Scope III: Conversion of 1,1-Disubstituted Epoxides^a



^aReaction conditions: epoxide **6** (25.0 mmol), 5 mol % CaI₂/Et₃N, 24 h, solvent free, *p*(CO₂) = 10 bar. Isolated yields are given. ^b*p*(CO₂) = 1 bar.

obtained in 86%. The yield improved to 96% when the reaction was performed under 10 bar CO₂ pressure. At this pressure also epoxides **6b** and **6c** were converted at room temperature, yielding the desired cyclic carbonates in up to 97%.

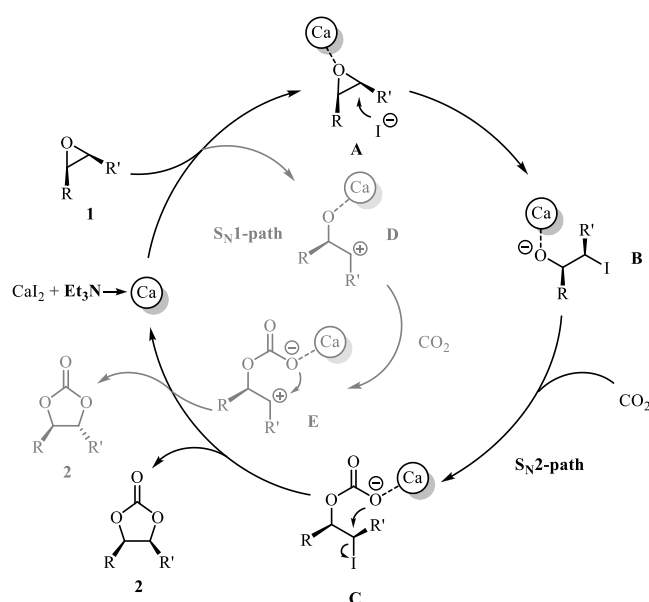
The excellent performance of the catalytic system on terminal epoxides and 1,1-disubstituted epoxides under mild conditions prompted us to investigate the synthesis of internal carbonates **9** (Scheme 5). However, under the standard conditions, only low conversion of cyclohexene oxide (**8a**) was observed. Previous reports showed that the use of co-catalysts can lead to an increase of the catalytic performance.^{18,56,57} Thus, diazabicyclo-undecene, DMAP, and triphenylphosphine (Ph₃P) were studied as co-catalysts, and the reaction conditions for the conversion of **8a** were further optimized.⁴³ Under comparably mild conditions for this substrate class (10 bar, 70 °C), **9a** was obtained in 84% yield using Ph₃P (5 mol %) as the co-catalyst. Under these optimized conditions, different internal epoxides **9b–9e** were converted to the corresponding carbonates in up to 90% yield. The conversion of *cis*-**8f** leads to **9f** as a mixture of *cis/trans* isomers (40:60) in 63% yield. On the other hand, *trans*-stilbene oxide (**8g**) gave the desired cyclic carbonate **9g** in moderate yield of 42% (*cis/trans* ≥ 99:1). There is also increasing interest in the synthesis of oleochemical carbonates.^{13,58} Even though the epoxidation of oleochemicals is well established, the CO₂ cycloaddition to these bio-based internal epoxides remains challenging for many catalysts.^{59,60} Organic halide salts such as TBAB present good activity under supercritical conditions,⁶¹ and their combination with hydrogen bond donors accelerates the conversion of bio-based epoxides giving quantitative conversion within 10 h (120 °C, 50 bar).^{62,63} Moreover, Ca-based catalysts can achieve good yields under milder conditions (45 °C, 5 bar, 24 h).¹⁸ In our hands, the conversion of these demanding bio-based substrates required an increase in the catalyst loading to 10

Scheme 5. Substrate Scope IV: Conversion of Internal and Bio-Based Epoxides^a

^aReaction conditions: epoxide **8** (25.0 mmol), 5 mol % $\text{CaI}_2/\text{Et}_3\text{N}$ and 5 mol % PPh_3 , 70 °C, 48 h, solvent free, $p(\text{CO}_2)$ = 10 bar. Isolated yields are given. ^b CH_3CN was used as the solvent. ^c10 mol % $\text{CaI}_2/\text{Et}_3\text{N}$ and 10 mol % PPh_3 , $p(\text{CO}_2)$ = 30 bar, 72 h.

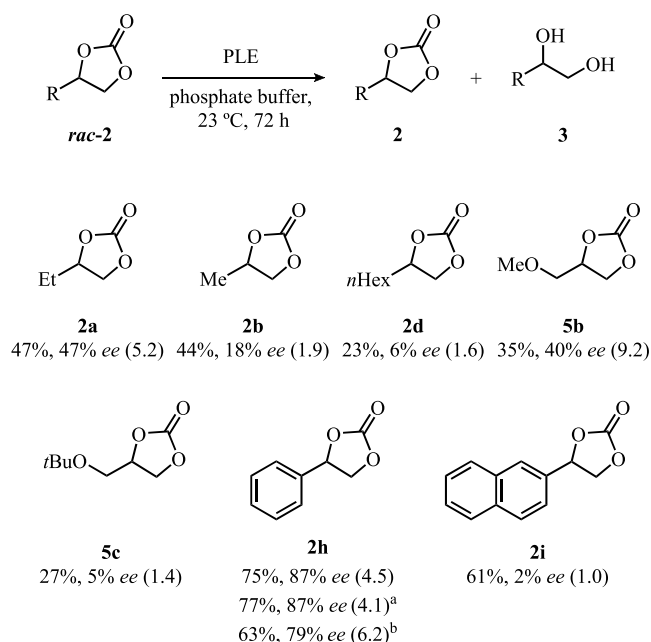
mol % and CO_2 pressures of 30 bar. Under these conditions, the conversion of *iso*-octyl oleate (**8i**) gave **9i** in 82% yield after 72 h. The reaction of epoxidized high oleic sunflower oil (**8j**) and linseed oil (**8k**) gave the corresponding carbonates **9j** and **9k** in moderate yields of 60%. The synthesis of internal trisubstituted carbonates, e.g., from limonene oxide faces many limitations due to the steric hindrance of the substrate and its tendency to side reactions.⁶⁴ However, limonene carbonate (**9h**) could be isolated in a moderate yield of 34% yield.

Mechanistic Studies and Proposal. We propose the initial formation of a Ca-complex from CaI_2 and ligand Et_3N (Scheme 6). This is supported by the observation that CaI_2 alone leads to significant lower yields on **2a** compared to the $\text{CaI}_2/\text{Et}_3\text{N}$ system (23% vs 94%, Table 1, entries 1 and 2). It is further supported by the observed downfield shift of the methylene and methyl protons of Et_3N in the ^1H NMR spectra which indicate the coordination of Et_3N to the Lewis acidic metal center (Figure 2). The formed complex activates the epoxide (Scheme 6, A), thereby facilitating the nucleophilic ring opening of the epoxide by I^- leading to B. Subsequently, the alkoxide attacks CO_2 forming the linear carbonate C which forms the cyclic carbonate **2** through an intramolecular

Scheme 6. Proposed Mechanism for the Formation of Cyclic Carbonates from Epoxides and CO_2 Catalyzed by $\text{CaI}_2\text{--Et}_3\text{N}$ 

nucleophilic substitution of the iodide (S_N2-pathway).³¹ This double inversion of the configuration leads to an overall retention of the stereochemistry in the product and explains the formation of *cis*-**9f** when *cis*-**8f** is employed as the substrate. However, a second pathway (S_N1-path) is also possible if the nucleophilic attack of I^- is hampered, e.g., by steric interaction, and a stabilized carbenium ion can be formed. In this case, the ring opening of the epoxide leads to D and the loss of the stereochemical information. The reaction with CO_2 and subsequent ring closure leads to the formation of the carbonate. This explains that starting from *cis*-2,3-epoxybutane (**8f**), the corresponding product **9f** was obtained in a *cis/trans* ratio of 40:60. In this case, the reaction proceeds partially through the S_N1 path forming predominantly the thermodynamically favored *trans* isomer, *trans*-**9f**.^{17,18,31}

Kinetic Resolution. We turned our attention to the kinetic resolution of cyclic carbonates to evaluate the possibility to access enantiomerically pure building blocks. In this regard, the kinetic resolution of several cyclic carbonates by means of readily available PLE was studied. First experiments were conducted at room temperature for 72 h employing 4 mg/mL of the enzyme with 10 mmol/L of the substrates as suspension or homogeneous mixtures (Scheme 7). While the activity for butylene (**2a**) and propylene carbonate (**2b**) was similar, the *n*-hexyl-substituted carbonate **2d** was converted only with 23%. The best result with regard to the enantiomeric excess was achieved for **2a** with 47% ee at 47% conversion. These results indicate that the steric demand of the substituents affects the enzymatic hydrolysis, an effect well known in enzymatic catalysis.⁶⁵ Glycidyl derivatives were also studied, and a moderate ee of 40% was obtained for **5b** at 35% conversion. Consistent with the aliphatic substrates, the sterically demanding *tert*-butyl-substituted carbonate **5c** showed a significant lower selectivity, giving an ee of only 5% for a conversion of 27%, underlining the effect of the substituents on the selectivity of the PLE. For styrene carbonate (**2h**), a conversion of 75% and an ee of 87% were obtained, being the substrate which gave the highest ee under these conditions.²⁹

Scheme 7. Kinetic Resolution of Cyclic Carbonates with Pig Liver Esterase^a

^aReaction conditions: 10 mmol/L of cyclic carbonate **2** in 5.0 mL of phosphate buffer (0.1 M, pH 7.0), 4 mg/mL of PLE, 23 °C, 72 h. Conversions and *ee* were determined by GC-FID using hexadecane as the internal standard. Selectivity factors are given in parenthesis. ^b48 h, 6 mg/mL of PLE. ^c24 h, 8 mg/mL of PLE.

Under the hypothesis that aryl groups might favor the enantioselectivity, **2i** was used as the substrate giving an *ee* of only 2% despite a conversion of 61%. Even though **2h** and **2i** are insoluble in the reaction mixture, these results demonstrate that this does not affect the hydrolytic activity of the enzyme. Subsequently, the reaction conditions for the kinetic resolution of styrene carbonate (**2h**) were further optimized. It must be considered that the reactions are performed in aqueous media and the nonselective autohydrolysis of the carbonate is a competitive reaction leading to the racemic diol. Thus, in a first attempt to improve the results, the reaction was performed for shorter reaction times to minimize the autohydrolysis while increasing the amount of the PLE slightly to facilitate the enzymatic hydrolysis. When the reaction was conducted for 48 h using 6 mg/mL of PLE, no significant differences were found. In contrast, the use of 8 mg/mL of PLE for 24 h leads to a decrease in conversion and *ee*. Therefore, the reaction time was set to 48 h and the effect of the enzyme concentration was further studied in detail (Figure 3).

The control reaction (0 mg/mL) gave a conversion of 24% (racemic product), which demonstrates that the autohydrolysis competes with the enzymatic reaction. Increasing amounts of PLE (2–10 mg/mL) gave higher *ee* together with higher conversions. Notably, it was possible to achieve an *ee* of up to 99% which is, to the best of our knowledge, the first time that such high *ee* was achieved for an enzymatic kinetic resolution of this class of substrates.

Finally, an upscale of the reaction was performed (Scheme 8). Thus, 82 mg of the carbonate was employed under the optimized conditions (10 mM, pH 7.0, 23 °C, 48 h, 8 mg/mL) giving 70% of the enantioenriched diol **3h** with 26% *ee* and

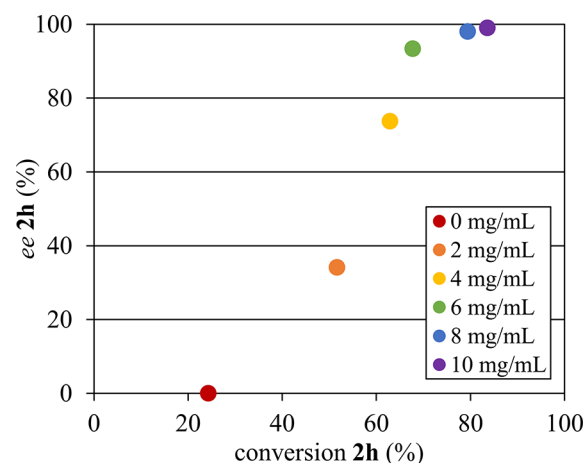
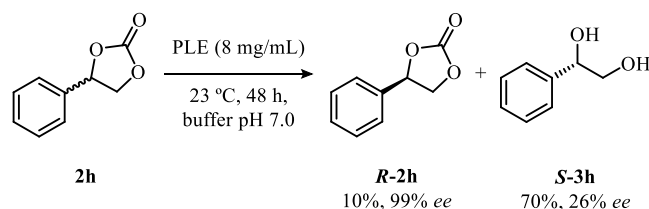


Figure 3. Optimization of the enzyme concentration. Reaction conditions: 10 mM cyclic carbonate (**2h**) in 5 mL of phosphate buffer (0.1 M, pH 7.0), 0–10 mg/mL of PLE, 23 °C, 48 h.

Scheme 8. Kinetic Resolution of Styrene Carbonate with Pig Liver Esterase



10% of the (*R*)-styrene carbonate (**R-2h**) after purification with 99% *ee*.⁴³

CONCLUSIONS

Readily available and cost-efficient CaI_2 in combination with Et_3N proved to be an efficient catalytic system for the cycloaddition of CO_2 to a wide variety of epoxides under mild conditions. ^1H NMR experiments indicate that the amine coordinates to the Lewis acidic metal center. Under the optimized reaction conditions, terminal (bio-based) epoxides were converted to the corresponding carbonates in yields up to 97% under solvent-free conditions even at room temperature and a low CO_2 pressure of 1 bar. Under modified conditions (70 °C, 10 bar), even challenging internal (bio-based) carbonates could be prepared in yields up to 90% using triphenyl-phosphine as a co-catalyst. Furthermore, the possibility of obtaining chiral building blocks from selected cyclic carbonates by means of an enzymatic kinetic resolution with PLE was evaluated. The steric and electronic properties of the substituents strongly influenced the results, leading to moderate *ee*'s in most cases. However, styrene carbonate which proved to be the most suitable substrate for the kinetic resolution was obtained in an excellent *ee* of up to 99%.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.2c03210>.

General information regarding materials and procedures, synthesis and kinetic resolution of cyclic carbonates, NMR spectra, and HPLC chromatograms (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Chemoenzymatic Synthesis of Chiral Building Blocks Based on the Kinetic Resolution of Glycerol-Derived Cyclic Carbonates

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The biocatalytic kinetic resolution of cyclic carbonates derived from glycerol is reported. A selection of 26 esterases and lipases was tested for the asymmetric hydrolysis of the model substrate (epichlorohydrin carbonate) in aqueous medium. Among them, Pig Liver Esterase and Novozym® 435 showed the best selectivity with $E = 38$ and 49, respectively. Both enzymes were employed for the conversion of 12 glycerol derivatives under optimized conditions. The resolution of halogenated carbonates

afforded the unconverted enantiomer in up to $>99:1$ *er*. Furthermore, Novozym® 435 was successfully recycled 10 times without significant loss of activity. Upscaling and isolation of the chiral carbonate was also demonstrated. Subsequent conversion of this chiral building block allowed the direct one-pot synthesis of (S)-Guaifenesin, (S)-Mephesisin and (S)-Chlorphenesin in up to 89% yield and 94:6 *er*.

Introduction

Cyclic carbonates have gained increasing attention in recent years due to their attractive synthesis from CO₂ and their applications in several fields. Both at the industrial and academic level they are widely employed for their properties such as low vapor pressure, low toxicity, high flash point and high dielectric constant.^[1,2] In particular, in synthetic chemistry, organic carbonates present interesting reactivity. The carbonate

moiety can serve for the protection of vicinal diols,^[3,4] and it can also undergo ring-opening polymerization,^[5] decarboxylation,^[6,7] hydrogenation,^[8] transesterification^[9], among other reactions, leading to useful products.^[10–12] Moreover, the functionalization of the substituents adjacent to the carbonate makes these compounds valuable building blocks.^[10]

Among the wide variety of carbonates, glycerol carbonate and its corresponding derivatives are particularly important for the valorization of glycerol as byproduct from biodiesel manufacturing (Scheme 1).^[13–15] Numerous procedures are reported for the direct conversion of glycerol to glycerol carbonate^[16–18] and for the functionalization of the hydroxyl group in the glycerol carbonate molecule, which leads to various valuable glycerol-based carbonates 1.^[19] Conversion of glycerol to cyclic carbonates is also possible via different routes, for example, in the epicerol process glycerol is converted to epichlorohydrin which can be further reacted with CO₂ to the corresponding carbonate.^[20] It is also noteworthy that the

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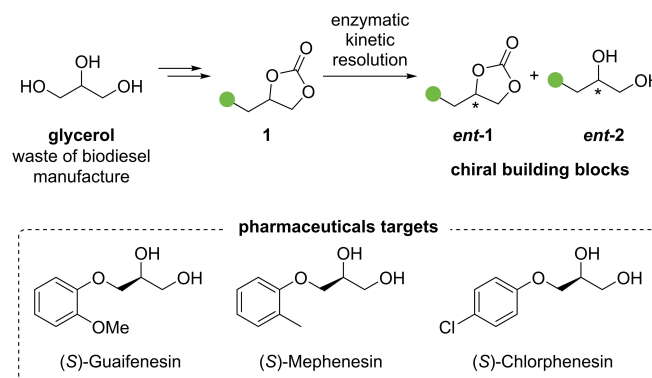
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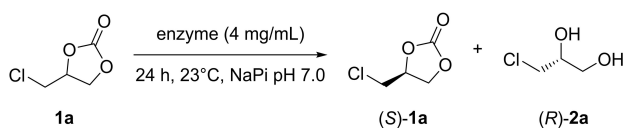
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Scheme 1. Concept for the kinetic resolution of glycerol-derived cyclic carbonates for the preparation of chiral building blocks and potential pharmaceutical targets.

cycloaddition of CO₂ to epoxides is the most common route for the synthesis of 5-membered cyclic carbonates. This reaction presents several advantages in the context of green chemistry since it is 100% atom efficient and uses carbon dioxide as inexpensive, non-toxic, and renewable C1-building block.^[21,22]

Even though the preparation of cyclic carbonates from epoxides has been extensively studied, their asymmetric synthesis remains challenging. Most strategies involve the kinetic resolution of the corresponding epoxides with chiral catalysts based on Co, Al, Ir, Cr and Nb which show good selectivity but moderate substrate tolerance.^[23–28] The use of chiral bifunctional organocatalysts presents more limitations since the products are obtained in low enantiopurity.^[29–31] In this context, the kinetic resolution of the cyclic carbonates **1** emerges as an alternative (Scheme 1). In this approach, the substrates are selectively hydrolyzed, giving the enantioenriched cyclic carbonates and their corresponding diols. Previous studies suggest that carboxylesterases are promising biocatalysts for this reaction.^[32–35] Even though these enzymes are widely known for their activity towards esters, lactones and amides, few reports explore the hydrolysis of the carbonate group. In this regard, we have recently reported the kinetic resolution of styrene carbonate with pig liver esterase (PLE),^[36] which motivated a deeper study towards the potential of carboxylesterases for the synthesis of chiral cyclic carbonates. Special attention was drawn to the activity of Novozym® 435 (N435), an acrylic resin-based adsorbed form of lipase B from *Candida antarctica*, which



Scheme 2. Enzymatic kinetic resolution of 4-(chloromethyl)-1,3-dioxolan-2-one (**1a**). Reaction conditions: 10 mmol/L of **1a** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 4 mg/mL of enzyme, 23 °C, 24 h.

is widely employed due to its promiscuity, stability, recyclability, low production cost and applicability in industrial processes.^[37,38] The resulting chiral carbonates can be employed as chiral building blocks, e.g. for the synthesis of terminal aromatic glycerol ethers (TAGEs) with pharmacological activity, such as (*S*)-Guaifenesin, (*S*)-Mephenesin and (*S*)-Chlorphenesin (Scheme 1).^[39]

Results and Discussion

The kinetic resolution of 4-(chloromethyl)-1,3-dioxolan-2-one (**1a**) was chosen as model reaction for the screening of a series of 26 commercially available hydrolases (Scheme 2). This substrate is an interesting building block since it can be easily prepared from epichlorohydrin derived from glycerol^[20] and the substitution of the chlorine atom can be used for further functionalization. The enzyme screening was conducted under similar conditions to the previously reported kinetic resolution of styrene carbonate (4 mg/mL of enzyme, 23 °C, 24 h, NaPi buffer pH 7.0).^[36] The absolute configuration of the unreacted enantiomer ((S)-**1a**) was determined by chiral GC, comparing the retention time of the unreacted enantiomer with that of an enantiopure standard. For the evaluation of the results, the conversion of **1a**, the enantiomeric purity of the unreacted (S)-**1a** and the resulting *E*-values were determined (Figure 1). Notably, when PLE was employed (S)-**1a** was obtained with an *er* > 99:1 (*E*=38), while the control reaction without enzyme gave only 5% conversion, indicating that the non-catalyzed hydrolysis occurs slowly.

Even though PLE is one of the most used esterases in synthesis due to its wide applicability for the asymmetric hydrolysis of esters, it is prepared by extraction of the pig liver obtaining a batch-depending mixture, which presents several disadvantages.^[40] As an alternative, recombinant Pig Liver

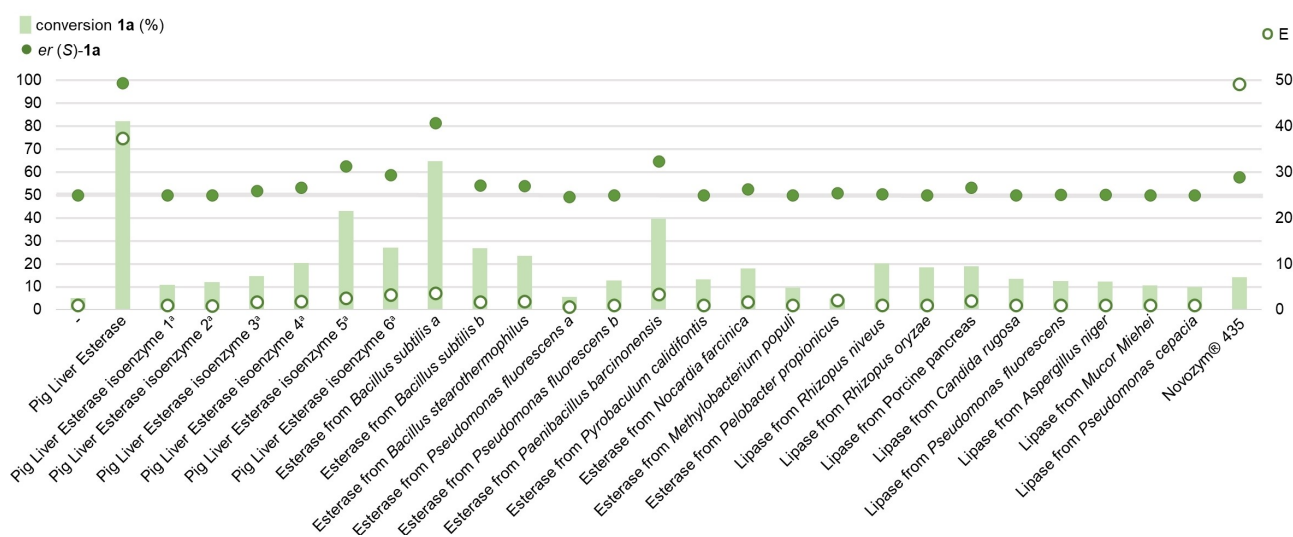


Figure 1. Results of the enzymatic kinetic resolution of **1a** with selected esterases and lipases. Reaction conditions: 10 mmol/L of **1a** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 4 mg/mL of enzyme, 23 °C, 24 h. Conversions (■), *er* values (●) were determined by chiral GC-FID using hexadecane as the internal standard. *E*-values (○) were calculated from the conversion of **1a** and *ee* of (*S*)-**1a**. [a] 20 h.

Esterase isoenzymes (rPLE) offer an animal-free manufacturing, easy scalability and good reproducibility of the results.^[41–43] Thus, six recombinant isoenzymes of PLE were tested in parallel (rPLE1–rPLE6). While rPLE1–rPLE4 gave low conversions (< 20%), PLE5 and PLE6 converted **1a** in 43% and 27%, respectively. However, all rPLE showed low selectivity for the preparation of (S)-**1a** ($E < 3$). Other recombinant esterases were studied, obtaining also poor selectivity for the asymmetric hydrolysis ($E < 4$). Among them, only the esterases from *Bacillus subtilis* A and *Paenibacillus barcinonensis* gave enantiomeric ratios significantly different from 50:50. Finally, lipases were evaluated for the kinetic resolution of **1a**. All of them gave low conversion of the substrate (< 20%) and low selectivity ($E < 2$) except for the immobilized Lipase B from *Candida antarctica*, Novozym® 435, which despite the low conversion under the reaction conditions (14%), showed good selectivity ($E = 49$).

Due to these promising results, all further experiments were carried out with PLE and N435 with the objective of preparing and isolating pure (S)-**1a**. The focus was set on achieving at least an $er > 95:5$, while minimizing the conversion to less than 75% (Table 1). Under the conditions tested for the screening, PLE gave (S)-**1a** with excellent purity ($er > 99:1$), but required high conversion (82%) thus limiting the yield of the desired carbonate (Entry 2). A lower enzyme concentration (2 mg/mL) gave a reduced conversion (57%), as expected, but the er obtained was also considerably decreased (85:15, Entry 1). When the concentration of the substrate was increased from 10 to 40 mM (Entry 3) **1a** was converted in 65% obtaining (S)-**1a** with very good enantiomeric purity ($er = 93:7$). This also highlights the potential applicability of this biocatalyst for the synthesis of chiral building blocks since the enzyme tolerates high concentrations of substrate. Finally, the reaction was carried out for 16 h (Entry 4) obtaining (S)-**1a** in high er of 98:2 with a conversion of 73%. Subsequently, N435 was also evaluated for the synthesis of (S)-**1a**. Increasing the enzyme

concentration from 4 to 10 and 20 mg/mL resulted in an increment of the (S)-**1a** purity from 58% to 71% and 83% (Entries 5–7) with a conversion below 40% in all cases. However, a further increase to 30 mg/mL of N435 did not show significant changes (Entry 8). The effect of the temperature was also studied for N435. However, higher temperature led to higher conversion of both enantiomers at the expense of a loss of selectivity. When the reaction was performed at 40 °C with 10 mg/mL of N435 the substrate was converted in 67%, and an er of 88:12 was obtained (Entry 9). An enzyme concentration of 20 mg/mL at 40 °C resulted in a conversion of 73% and an excellent er of 97:3 of (S)-**1a** (Entry 10). Overall, both PLE and N435 allowed the preparation of pure (S)-**1a** with $er \geq 97:3$ at 73% conversion of the initial substrate (Entries 4 and 7). The optimized conditions for PLE (Entry 4) and N435 (Entry 10) were chosen for further experiments.

The results obtained with PLE and N435 for the model reaction motivated us to explore the activity of these enzymes towards different substrates. Therefore, halogenated derivatives (**1a–1d**) were tested (Figure 2). These carbonates can be easily prepared by transformation of glycerol carbonate by nucleophilic substitution.^[19] Under the conditions previously chosen for PLE and N435, the fluorine derivative (**1b**) gave a poorer result ($er < 73:7$) than its chlorinated analogous **1a** ($er \geq 97:3$), which can be explained considering that fluorinated compounds are known to be enzyme inhibitors.^[44] Notably, the bromine (**1c**) and iodine (**1d**) derivatives gave excellent er values ($\geq 99:1$) with both PLE and N435. Overall, despite the high conversions (72–84%) for **1a**, **1c** and **1d**, the corresponding chiral carbonates were obtained in excellent enantiomeric purity.

Furthermore, glycerol carbonate **1e** and its derivatives **1f–1i** were also evaluated (Figure 3). Kinetic resolution of glycerol carbonate (**1e**) afforded the racemic mixture despite a conversion of 18% with PLE and 38% with N435. Low selectivity was found for the methoxy-substituted carbonate, **1f**, despite the significant conversion (32% for PLE and 45% for N435). For the *tert*-butoxy- and allyloxy-substituted carbonates, **1g** and

Table 1. Optimization of the reaction conditions for the kinetic resolution of **1a** with PLE and N435.

Entry	Enzyme (mg/mL)	Conversion 1a (%) ^[a]	er (S)- 1a ^[a]	E
1	PLE (2)	57	85:15	7
2	PLE (4)	82	> 99:1	37
3	PLE (4)	65 ^[b]	93:7	7
4	PLE (4)	73 ^[c]	98:2	7
5	N435 (4)	14	58:42	49
6	N435 (10)	33	71:29	16
7	N435 (20)	40	83:17	> 200
8	N435 (30)	41	84:16	> 200
9	N435 (10)	67 ^[d]	88:12	5
10	N435 (20)	73 ^[d]	97:3	10

[a] Reaction conditions: 10 mmol/L of **1a** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 23 °C, 24 h. Conversions and er values were determined by chiral GC-FID using hexadecane as the internal standard. E -values (○) were calculated from the conversion of **1a** and ee of (S)-**1a**. [b] 40 mM of **1a**. [c] 16 h. [d] 40 °C.

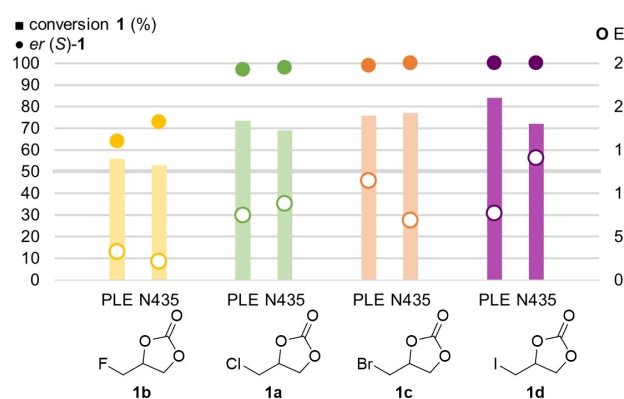


Figure 2. Enzymatic kinetic resolution of **1a–1d** with PLE and N435. Reaction conditions: 10 mmol/L of **1a–1d** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). PLE: 4 mg/mL, 23 °C, 16 h. N435: 20 mg/mL, 40 °C, 24 h. Conversions (■) and er values (●) were determined by chiral GC-FID using hexadecane as the internal standard. E -values (○) were calculated from the conversion of **1** and ee of (S)-**1**.

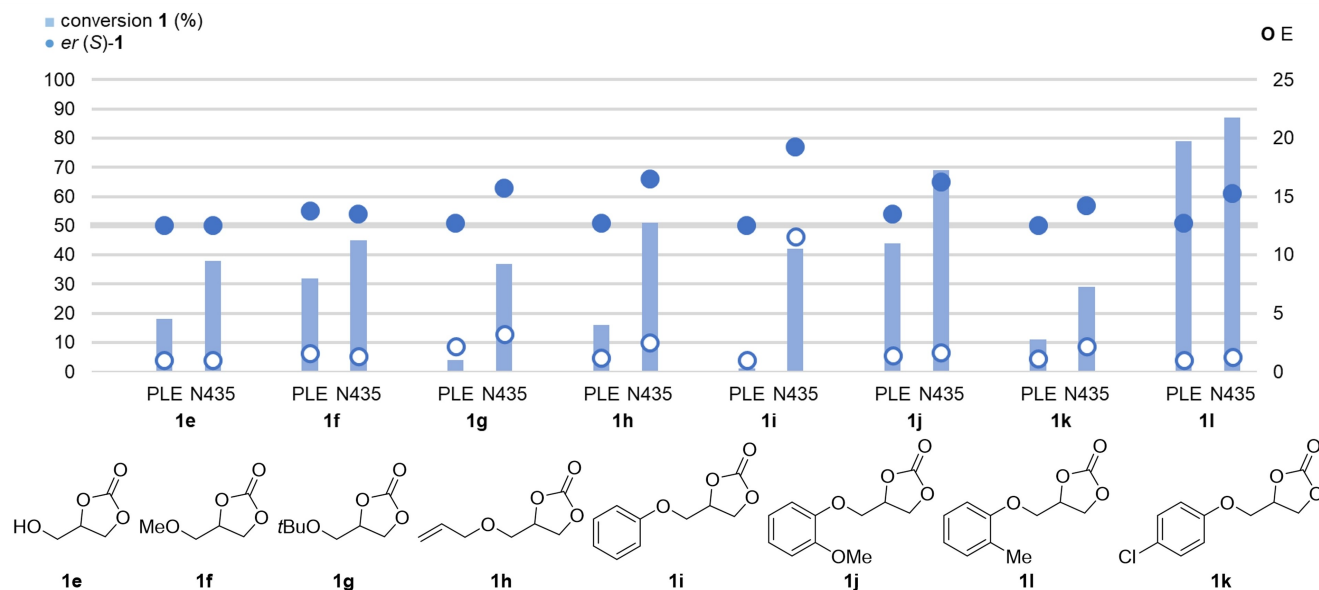


Figure 3. Kinetic resolution of **1e–1l** with PLE and N435. Reaction conditions: 10 mmol/L of **1a–1d** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). PLE: 4 mg/mL of enzyme, 23 °C, 24 h. N435: 20 mg/mL of enzyme, 40 °C, 24 h. Conversions (■) and *er* values (●) were determined by chiral GC-FID using hexadecane as the internal standard. *E*-values (○) were calculated from the conversion of **1** and *ee* of (*S*)-**1**.

1h, the conversion with PLE was low (4 and 16%, respectively). N435 led to higher conversion of **1g** and **1h** giving an *er* of 63:37 and 66:34, respectively. Furthermore, we became interested in phenoxy-substituted derivatives (**1i–1l**) since the hydrolysis of the carbonate moiety in these compounds gives the corresponding diol. Such structural motives can be found in various pharmaceuticals.^[45] For the phenoxy-derivative **1i** the conversion by PLE was <5% but with N435 it gave a moderate *er* (77:23) at a conversion of 42%. The guaiacol derivative **1j** was significantly converted by both enzymes, but with poor selectivity, affording the carbonate in *er*=54:46 with PLE and *er*=65:35 with N435. A similar result was obtained for **1l**, which despite the high conversion (79% and 87%) gave poor *er* values. **1k** was obtained as a racemic mixture after using PLE (11% conversion), while N435 converted **1k** in 29% with 57:43 *er*. Considering the insolubility of **1i–1l** it was hypothesized that a solvent might have a favorable effect on the reaction. As DMSO is a suitable co-solvent for hydrolases,^[32,46] the kinetic resolution of **1i** was carried out using 10% of DMSO. Unfortunately, no significant improvement was obtained with PLE, and a detriment in the selectivity was found for N435 (see Supporting Information).

It is worth to highlight that for the substrates studied (**1a–1l**) both enzymes showed identical enantioselectivity, yielding the same enantiomer. For substrates **1a**, **1i** and **1j** the absolute configuration of the obtained enantiomer was assigned by comparison with the retention times (chiral GC) of the corresponding chiral standard (see Supporting Information). Considering this and the fact that enantiocomplementary enzymes that favor the conversion of opposite enantiomers are very rare,^[47,48] it can be assumed that the same configuration of the chiral center is obtained for all substrates ((*S*)-**1a–1d** and (*R*)-**1e–1l**). Overall, N435 gave a higher conversion rate and

higher selectivity for most substrates. The different results obtained for these substrates underline the high impact of the substituent on enzyme activity and selectivity towards the hydrolysis of cyclic carbonates.

We were also interested in evaluating the synthetic potential of this procedure. The potential recyclability of N435 and the good results obtained for **1a** with this enzyme motivated us to perform the kinetic resolution of **1a** on a larger scale and to study the recyclability of N435 at the same time. Thus, the kinetic resolution of **1a** was scaled up 40 times using 20 mg/mL of N435, at 40 °C (Figure 4). After 24 h, N435 was simply recovered by filtration and (*S*)-**1a** and (*R*)-**2a** were isolated from the aqueous mixture by extraction. The procedure was repeated 10 times isolating (*S*)-**1a** in yields between 15%

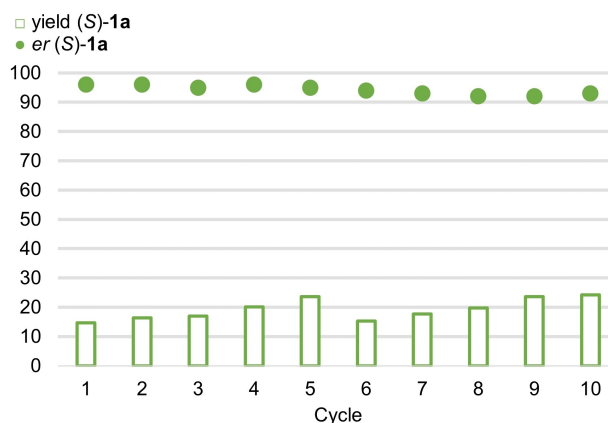
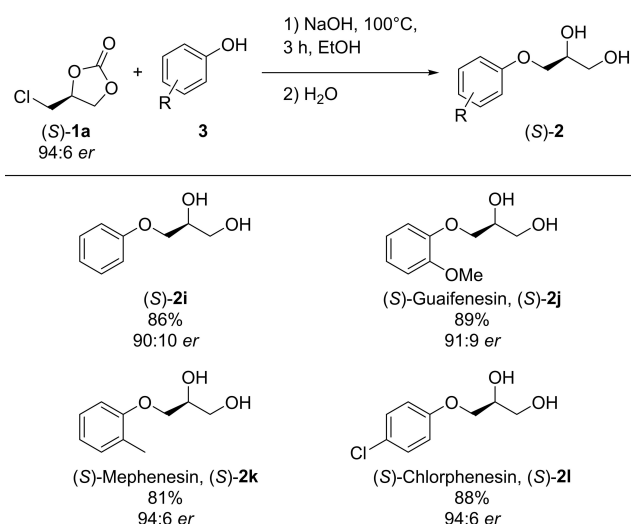


Figure 4. Up-scaling of the kinetic resolution of **1a** and recycling of N435. Reaction conditions: 10 mmol/L of **1a** in 5.0 mL of NaPi buffer (0.1 M, pH 7.0), 20 mg/mL of N435, 40 °C, 24 h. Isolated yields (■) are given. *Er* values (●) were determined by chiral GC-FID.

and 24% (with 50% being the maximum yield). In the first 5 cycles the carbonate was obtained in excellent *er* ($\geq 95:5$) and after 10 cycles the selectivity of the enzyme only dropped slightly giving *er* values $\geq 92:8$. As a result of the successful multiple usages of N435, 529 mg of pure (*S*)-**1a** were isolated. On the other hand, (*R*)-**2a** was isolated in yields up to 47% and *er* values up to 62:38 (see Supporting Information). The diol could in principle also be reconverted to the carbonate and resubmitted to the kinetic resolution. The synthesis of chiral vicinal diols is of great relevance in synthetic chemistry.^[49,50] One of the most common routes for their preparation is the Sharpless asymmetric dihydroxylation of alkenes with OsO₄.^[51] Another well studied reaction is the hydrolytic kinetic resolution of epoxides with Co-complexes.^[52] In this work, cyclic carbonates were envisioned as protected vicinal diols by taking advantage of the carbonate moiety, which uses CO₂ as protecting group giving the diol after hydrolysis with a base.^[3] Additionally, the substitution of a suitable leaving group allows the use of these glycerol-derived cyclic carbonates as building blocks. Thus, the substitution of the chlorine in (*S*)-**1a** by a phenoxide together with the hydrolysis of the carbonate should facilitate the direct synthesis of (*S*)-TAGEs (terminal aromatic glycerol ethers) in one-step (Scheme 3). Moreover, TAGEs serve as precursors for the preparation of other APIs, such as β -blockers, for which is known that their pharmacological activity changes with different enantiomers. For example, (*S*)-propanol and (*S*)-atenolol are more potent than the corresponding (*R*)-enantiomers.^[53,54] To evaluate the feasibility of this approach for the preparation of (*S*)-TAGEs, the obtained product (*S*)-**1a** (*er* = 94:6) was used as starting material with different phenols as nucleophiles under basic conditions. The reaction was carried out with NaOH in ethanol by modification of a protocol reported by Egri et al. for 3-chloropropane-1,2-diol.^[55] The substitution with phenol (**3a**) as a model compound afforded (*S*)-**2i** in 86% yield and 90:10 *er*. Guaifenesin (**2j**) is an



Scheme 3. Synthesis of (*S*)-TAGEs by conversion of (*S*)-**1a** with phenols **3** under basic conditions. Reaction conditions: 1.0 mmol of (*S*)-**1a** added to 3.0 mmol of phenol and 3.0 mmol of NaOH in EtOH at 100°C for 3 h. Isolated yields are informed. *Er* values were determined by chiral GC-FID.

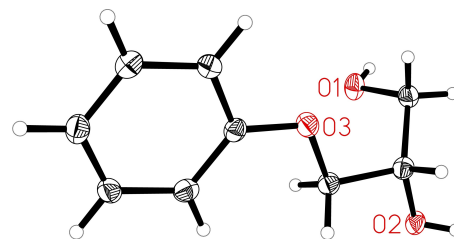


Figure 5. Molecular structure of (*S*)-**2i** in the crystal. Displacement ellipsoids correspond to 50% probability at 110 K.

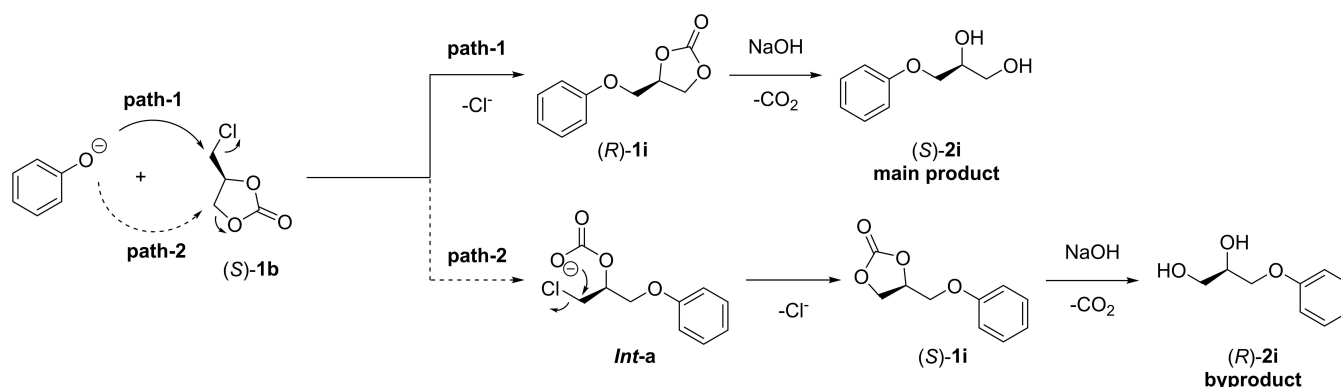
expectorant commonly used for the treatment of mucus and phlegm.^[56,57] With this procedure (*S*)-Guaifenesin ((*S*)-**2j**) was prepared from (*S*)-**1a** and guaiacol (**3b**) in 89% yield with 91:9 *er* (Scheme 3). Mephensin (**2k**) is a muscle relaxant, which was obtained from *o*-cresol (**3c**) and (*S*)-**1a** giving (*S*)-**2k** in 81% yield with total retention of the configuration (94:6 *er*). Chlorphenesin (**2l**) is used as antiseptic and preservative since it presents antifungal and antibacterial properties^[58] and its carbamate acts as muscle relaxant.^[59] Similarly to (*S*)-**2k**, (*S*)-Chlorphenesin ((*S*)-**2l**) was obtained from (*S*)-**1a** and *p*-chlorophenol (**3d**) with 94:6 *er*, in 88% yield.

Furthermore, we were able to isolate crystals of (*S*)-**2i** and (*S*)-**2j** suitable for X-ray crystallographic analysis. The molecular structures confirmed the absolute configuration of the chiral center (Figure 5, and Supporting Information).^[60]

The feasible reaction pathways leading to the formation of (*S*)-**2i** or (*R*)-**2i** are shown in Scheme 4. Attack at the Cl-substituted carbon by aromatic nucleophiles leads to the desired reaction (path-1) and the formation of carbonate (*R*)-**1i**.^[13,61] Subsequently, basic hydrolysis yields the desired vicinal diol (*S*)-**2i**. Due to steric interactions the substitution at the chiral center is not feasible. However, the attack of the phenoxide anion on the less hindered methylene carbon is plausible (Scheme 4, path-2). This leads to linear intermediate *Int-a*, which can undergo an intramolecular nucleophilic substitution, giving (*S*)-**1i**. The subsequent basic hydrolysis yields (*R*)-**2i**. Thus, even though the substitution does not occur at the chiral center, the observed partial racemization is a consequence of the two different pathways. However, the lability of the chloride favors path-1 as path-2 was only observed in the synthesis of (*S*)-**2i** and (*S*)-**2j**, which explains the slightly lower *er* values of 90:10 and 91:9, respectively, compared to the *er* of the starting material (*S*)-**1a** (94:6). In contrast (*S*)-**2k** and (*S*)-**2l** were obtained with complete retention of the configuration.

Conclusions

PLE and N435 proved to be efficient and highly enantioselective for the kinetic resolution of cyclic carbonates derived from glycerol. Among the substrates studied, the best results were found for halogenated carbonates. In particular, cyclic carbonates with chloro-, bromo- and iodomethylene-substituents gave moderate to high conversions affording the remaining (*S*)-



Scheme 4. Proposed pathway for the synthesis of (S)-TAGEs by substitution of (S)-1a with phenol under basic conditions.

enantiomers in excellent enantiomeric ratios of up to $\geq 99:1$. Moreover, the reaction was successfully scaled up, which allowed the isolation of (S)-1a. Notably, N435 could be easily recycled and 9 times reused without significant loss on the activity and selectivity. Finally, the potential of the obtained cyclic carbonates as building blocks was demonstrated by synthesizing pharmaceutically relevant (S)-TAGEs from (S)-1a and simple phenols, under basic conditions.

Experimental Section

General procedure 1 (GP1) for screening of reaction conditions for the kinetic resolution of 1a

0–100 mg of enzyme were added to a solution of the carbonate 1a (0.05 mmol, 10 mM) in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). The mixture was shaken at 300 rpm at 23–40 °C. After 8–24 h, the mixture was filtered and extracted with EtOAc (3×25 mL). The organic layers were combined and dried over Na₂SO₄. All volatiles were removed in vacuum. The resulting crude mixture was transferred to a 5.0 mL volumetric flask with EtOH and analyzed by chiral GC-FID using hexadecane as internal standard.

General procedure 2 (GP2) for the kinetic resolution of 1 with PLE

20 mg of PLE were added to a solution or suspension of the carbonate 1 (0.05 mmol, 10 mM) in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). The mixture was shaken at 300 rpm at 23 °C. After 16 h (1a–1d) or 24 h (1d–1i), the mixture was filtered and extracted with EtOAc (3×25 mL). The organic layers were combined and dried over Na₂SO₄. All volatiles were removed in vacuum. The resulting crude mixture was transferred to 5.0 mL volumetric flask with EtOH and analyzed by chiral GC-FID using hexadecane as internal standard.

General procedure 3 (GP3) for the kinetic resolution of 1 with N435

100 mg of PLE were added to a solution or suspension of the carbonate 1 (0.05 mmol, 10 mM) in 5.0 mL of NaPi buffer (0.1 M, pH 7.0). The mixture was shaken at 300 rpm at 40 °C. After 24 h, the mixture was filtered and extracted with EtOAc (3×25 mL). The organic layers were combined and dried over Na₂SO₄. All volatiles

were removed in vacuum. The resulting crude mixture was transferred to 5.0 mL volumetric flask with EtOH and analyzed by chiral GC-FID using hexadecane as internal standard.

General procedure 4 (GP4) for the up-scaled kinetic resolution of 1a, isolation of (S)-1a and recycling of N435

4.0 g of Novozym 435 were added to a solution (10 mM) of 1a (273 mg, 2.00 mmol) in 200 mL of NaPi buffer (0.1 M, pH 7.0). The mixture was shaken at 120 rpm at 40 °C for 24 h. The mixture was filtered through a Büchner funnel (fritted, porosity 4). The enzyme was washed with 50 mL of water, recovered, and used immediately for the next cycle. The filtrate was extracted with EtOAc (4×300 mL). The organic layers were combined and dried over Na₂SO₄. All volatiles were removed in vacuum and the obtained crude mixture was purified by flash column chromatography (SiO₂, cHex/EtOAc = 2:1 to EtOAc) yielding (S)-1a (40 mg, 0.29 mmol, 15%, 96:4 *er*) and the enantioenriched (R)-2a (100 mg, 0.90 mmol, 45%, 61:39 *er*) both as colorless liquids. The *er* values of the diols were measured as *er* values of their corresponding carbonates by derivatization of 0.10 mmol of diol 2 in dimethylcarbonate (0.5 mL), with K₂CO₃ (0.15 mmol) and molecular sieves (3 Å, 50 mg) at 100 °C for 24 h, according to a reported procedure.^[62] The resulting products were analyzed by chiral GC-FID. The procedure was repeated 10 times (see Supporting Information). ¹H NMR of (S)-1a (400 MHz, CDCl₃, 25 °C): δ = 5.02–4.92 (m, 1H), 4.58 (dd, *J* = 8.9, 8.3 Hz, 1H), 4.40 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.79 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.72 (dd, *J* = 12.2, 3.7 Hz, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 154.3, 74.4, 67.1, 43.8 ppm. ¹H NMR of (R)-2a (400 MHz, CDCl₃, 25 °C): δ = 3.96–3.87 (m, 1H), 3.75 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.69–3.53 (m, 4H), 3.23 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 71.9, 63.8, 45.9 ppm.

General procedure 5 (GP5) for the synthesis of (S)-TAGEs by substitution

In a pressure tube, the phenol 3 (3.0 mmol) was dissolved in EtOH (0.5 mL) and a solution of NaOH (120 mg, 3.0 mmol) in H₂O (0.4 mL) added. The reaction mixture was stirred at 100 °C for 30 minutes. Subsequently, a solution of (S)-1a (136 mg, 1.0 mmol) in EtOH (1.0 mL) was added dropwise and the mixture was stirred at 100 °C for 3 h. Subsequently, H₂O (2 mL) were added, and the reaction mixture was further stirred at 100 °C for 30 min. The mixture was cooled to room temperature, neutralized with 1.0 mL of HCl (1 M) and extracted with EtOAc (3×5 mL). The organic layers were combined and dried over Na₂SO₄. All volatiles were removed in vacuum. The resulting crude products were purified by flash

column chromatography (SiO_2 , $\text{cHex}/\text{EtOAc}=1:1$). The *er* values of the diols were measured as *er* values of their corresponding carbonates by derivatization of 0.10 mmol of diol **2** in dimethylcarbonate (0.5 mL), with K_2CO_3 (0.15 mmol) and molecular sieves (3 Å, 50 mg) at 110 °C for 24 h, according to a reported procedure.^[62] The resulting product was transferred to 5.0 mL volumetric flask with EtOH and analyzed by chiral GC-FID using hexadecane as internal standard.

Synthesis of (S)-3-phenoxypropane-1,2-diol ((S)-2i)

According to **GP5**, (S)-**1a** (134 mg, 0.98 mmol, 94:6 *er*), NaOH (117 mg, 2.93 mmol) and phenol **3a** (293 mg, 3.11 mmol) were converted to yield (S)-**2i** (142 mg, 0.84 mmol, 86%, 90:10 *er*), which was obtained as white needles. ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.36–7.21 (m, 2H), 7.04–6.87 (m, 3H), 4.16–4.08 (m, 1H), 4.08–4.00 (m, 2H), 3.90–3.69 (m, 2H), 2.47 (s, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): δ = 158.5, 129.7, 121.5, 114.7, 70.6, 69.2, 63.8 ppm.

Synthesis of (S)-3-(2-methoxyphenoxy)propane-1,2-diol ((S)-2j)

According to **GP5**, (S)-**1a** (136 mg, 1.00 mmol, 94:6 *er*), NaOH (117 mg, 2.93 mmol) and 2-methoxyphenol **3b** (397 mg, 3.20 mmol) were converted to yield (S)-**2j** (176 mg, 0.89 mmol, 89%, 91:9 *er*), which was obtained as pale yellow needles. ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.02–6.86 (m, 4H), 4.20–4.12 (m, 1H), 4.11–4.02 (m, 2H), 3.86 (s, 3H), 3.84–3.75 (m, 2H), 2.84 (s, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): δ = 149.9, 148.1, 122.5, 121.2, 115.2, 112.0, 72.6, 70.1, 64.0, 55.9 ppm.

Synthesis of (S)-3-(o-tolyloxy)propane-1,2-diol ((S)-2k)

According to **GP5**, (S)-**1a** (135 mg, 0.99 mmol, 94:6 *er*), NaOH (117 mg, 2.93 mmol) and 2-methylphenol **3c** (327 mg, 3.02 mmol) were converted to yield (S)-**2k** (146 mg, 0.80 mmol, 81%, 94:6 *er*), which was obtained as white needles. ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.21–7.09 (m, 2H), 6.96–6.79 (m, 2H), 4.14 (m, 1H), 4.06 (m, 2H), 3.95–3.72 (m, 2H), 2.34 (s, 2H), 2.24 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): δ = 156.6, 131.0, 127.1, 126.8, 121.2, 111.3, 70.6, 69.4, 64.0, 16.4 ppm.

Synthesis of (S)-3-(4-chlorophenoxy)propane-1,2-diol ((S)-2l)

According to **GP5**, (S)-**1a** (137 mg, 1.00 mmol, 94:6 *er*), NaOH (117 mg, 2.93 mmol) and 4-chlorophenol **3d** (396 mg, 3.08 mmol) were converted to yield (S)-**2l** (178 mg, 0.88 mmol, 88%, 94:6 *er*), which was obtained as white needles. ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.34–7.20 (m, 2H), 6.91–6.84 (m, 2H), 4.14 (dddd, J = 6.3, 5.4, 4.4, 3.8 Hz, 1H), 4.07–4.02 (m, 2H), 3.93–3.72 (m, 2H), 2.39 (br, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): δ = 157.2, 129.6, 126.4, 116.0, 70.5, 69.6, 63.7 ppm.

Supporting Information

The authors have cited additional references within the Supporting Information.^[63–67]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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PAPER

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View Journal | View IssueCite this: *Green Chem.*, 2024, **26**, 439Tuneable reduction of CO₂ – organocatalyzed selective formylation and methylation of amines†Changyue Ren,^{a,b} Constanza Terazzi^a and Thomas Werner^{✉a,c}

The *N*-formylation and *N*-methylation of amines with carbon dioxide (CO₂) are important types of transformations which give access to a wide range of key intermediates and compounds. Efficient catalytic methods for both reactions are rare because of the challenge of controlling selectivity. Herein, we report the environmentally benign organocatalyzed *N*-formylation and *N*-methylation of primary and secondary amines using CO₂ as the C1 source in the presence of hydrosilanes as the reductant. Readily available methyltriphenylphosphonium methylcarbonate has been proven to be an efficient catalyst for the *N*-methylation of amines and CO₂ in the presence of polymethylhydrosiloxane (PMHS) under mild conditions. In contrast, the selective *N*-formylation is achieved in the presence of trimethoxysilane as the reductant. In both transformations, a wide range of substrates were selectively converted. 15 primary and secondary amines were *N*-methylated and *N*-formylated and the corresponding products were obtained in yields of up to 98% and 94%, respectively. Moreover, benzimidazoles are accessible from diamines and CO₂ in a one-pot reaction in yields of up to 83%. Mechanistic investigations revealed different reaction pathways for *N*-methylation and *N*-formylation depending on the reductant as well as the activation of CO₂ by the catalyst.

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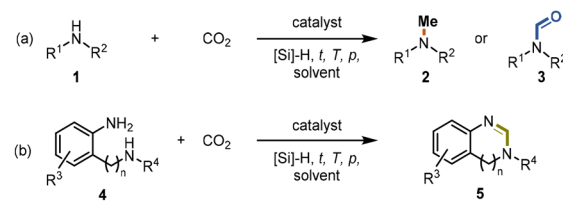
rsc.li/greenchem

Introduction

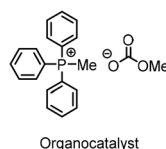
N-Methylamines and *N*-formamides are attractive chemicals that have found extensive applications in the pharmaceutical industry, biological sciences, and agriculture.^{1–8} Formamide derivatives, such as *N*-methylformamide and *N,N*-dimethylformamide (DMF), are among the most used solvents and important intermediates for the synthesis of other valuable materials,⁹ such as isocyanides^{10,11} and benzoheterocycles.^{12,13} *N*-Methylamines are structural subunits that can be found in many significant bioactive compounds and drugs.¹⁴ The common C1 sources for *N*-methylation and *N*-formylation reactions include MeI,¹⁵ CH₂N₂,¹⁶ dimethyl carbonate,¹⁷ methanol,¹⁸ formic acid¹⁹ and CO₂.²⁰ In particular, the use of CO₂ in combination with reducing agents is an attractive alternative to toxic and hazardous reagents (Scheme 1a). CO₂ is a waste product of fuel combustion currently deemed as a promising surrogate of carbon feedstocks. Its utilization has been an active field of research in the past few decades. However, the

kinetic inertness and thermodynamic stability of the CO₂ molecule significantly hinder its efficient valorization under mild conditions.^{21–25}

Although a few catalysts have been reported to be able to perform the *N*-functionalization of amines to form both formamide and methylamine (Scheme 1a),^{26–29} there are several challenges to overcome in terms of these reactions. One of them is employing cost-efficient reductants.³⁰ Phenylsilanes have been widely used in the fixation of CO₂ into amines,^{26,28,29,31,32} but their use presents some disadvantages



This work:



- metal-free
- PMHS as reductant for *N*-methylations
- tuneable methylation or formylation
- novel catalytic cycle
- conversion of primary amines, secondary amines and diamines

Scheme 1 (a) *N*-Methylation and *N*-formylation of amines with CO₂ and silane. (b) The formation of benzoheterocycles from diamines with CO₂ and silane.

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since they are expensive, and the byproducts formed are difficult to remove. Polymethylhydrosiloxane (PMHS) is an abundant, low-cost, non-toxic, and highly moisture-stable chemical waste product generated by the silicone industry.^{33–35} Even though it would be advantageous to use PMHS as the reductant in the reduction of CO₂, very few organic catalysts are reported to be active for both PMHS and CO₂ for the methylation reaction. Dyson *et al.* reported a thiazolium carbene-based catalyst for the *N*-formylation and *N*-methylation of amines using PMHS as a reducing agent, which allows the reaction to proceed under relatively mild conditions.^{36,37}

The Xia group reported diazabicycloundecene (DBU) as an organocatalyst for the selective *N*-methylation and *N*-formylation of secondary amines, converting secondary amines, CO₂ and PMHS into methylamines and formamides at 100 °C and 30 °C, respectively.³⁸ Furthermore, benzoheterocycles can be prepared from *o*-phenylenediamine, CO₂ and silane (Scheme 1b). The formation of the benzimidazole ring is plausible by monoformylation and subsequent imine formation with a suitable catalyst. However, due to the mismatched catalysis, the cyclization reaction normally requires two steps or harsher conditions than the *N*-formylation reaction.^{13,31,32,39,40} In the previous reports, the *N*-formylation and *N*-methylation reactions are assumed to proceed by a general base-catalysed reaction mechanism, in which hydrosilanes are activated by the basic catalyst or the carbamate salt formed.¹³ Most recently, the Song group reported the *N*-methylation and *N*-formylation reaction between CO₂ and secondary amines in the presence of phenylsilane catalyzed by an ammonium carboxylate ionic liquid.⁴¹ In addition, Lin and coworkers reported Cs₂CO₃ to be an efficient inorganic catalyst for these reactions.⁴² These reports and our interest in using phosphonium salts as organocatalysts for the utilization of CO₂ motivated us to explore a phosphorus-based organocatalyst in combination with PMHS as a reductant for the methylation of amines.^{43–46} We focused on methylcarbonate salts which were first reported as a CO₂ surrogate in the preparation of propylene oxide in 2006,⁴⁷ and subsequently have been employed in the transesterification⁴⁸ and Henry reactions,⁴⁹ and as vinylation reagents in the Wittig reaction.⁵⁰

Results and discussion

Methyltriphenylphosphonium methylcarbonate is commercially available and can also be prepared from phosphines and dimethylcarbonate (DMC) according to the literature.⁵⁰ PMHS was selected as the reducing agent and *N*-methylaniline (**1a**) as the model substrate for evaluating the activity of the catalyst towards methylation, utilizing CO₂ as the carbon source at 1 bar and 70 °C (Table 1). In the absence of the catalyst, no conversion was observed (entry 1). A moderate yield of 53% and good selectivity for *N*-methylated product **2a** were obtained in the presence of the catalyst (entry 2). In CH₃CN, *N*-methylaniline (**1a**) gave the *N*-methylated product **2a** and

Table 1 Optimization of the reaction conditions for the conversion of *N*-methylaniline (**1a**) with CO₂ to methylated product **2a**

Entry	Cat. (mol %)	Silane (equiv.)	Solvent	<i>T</i> (°C)	Yield 2a ^a (%)	Yield 3a ^a (%)
1	0	4	THF	70	0	0
2	10	4	THF	70	53	0
3	10	4	MeCN	70	20	6
4	10	4	EtOAc	70	0	0
5	10	4	CH ₂ Cl ₂	70	0	0
6	10	10	THF	70	87	0
7 ^b	10	10	THF	70	29	0
8	10	10	Me-THF	70	83	10
9	5	10	THF	70	62	30
10	10	10	THF	80	72	0
11	10	10	THF	60	82	17
12	10	10	THF	50	55	38

Reaction conditions: *N*-methylaniline (**1a**, 0.233 mmol, 1 equiv.), PMHS (4–10 equiv.), catalyst (0–10 mol%), *p*(CO₂) = 1 bar, 50–80 °C, 16 h, solvent. ^aYield was determined by ¹H NMR using mesitylene as the internal standard. ^bCO₂ balloon.

N-formylated product **3a** with a yield of 20% and 6%, respectively (entry 3). In EtOAc and CH₂Cl₂, **1a** failed to convert to either **2a** or **3a** (entries 4 and 5). Due to its polymeric nature, PMHS is less active than non-polymeric silanes. Thus, an excess of reductant is normally required.^{36–38,51} Full conversion was achieved by increasing the amount of PMHS and **2a** was obtained in a very good yield of 87% (entry 6). Even under 1 atm of CO₂ (balloon), **2a** was accessible in 29% yield (entry 7). Replacing THF with the biomass-derived 2-methyl-tetrahydrofuran (Me-THF) gave **3a** in 83% yield (entry 8). At a lower catalyst loading, an increase in the formation of the *N*-formylated product **3a** was observed (entry 9). Finally, the impact of the reaction temperature was studied (entries 10–12). Neither an increase nor a decrease of the reaction temperature led to an improved yield of **2a**. Notably, at lower temperatures (50 °C), the yield of **2a** decreased to 55% but **3a** was obtained in 38% yield (entry 12).

The scope of the reaction was next investigated by converting a variety of substituted secondary and primary amines **1** under the optimized conditions. While a reaction time of 16 h was required to achieve an appropriate yield for most substrates, full conversion was achieved within 4 h for a few substrates (Table 2). *p*-Methoxy-*N*-methylaniline (**1b**) gave the corresponding dimethylaniline **2b** in 72% yield after 16 h, while 71% yield of *o*-methoxy-*N,N*-dimethylaniline (**2c**) was isolated after only 4 h (entries 1 and 2). Fluoro- and bromo-substituted *N*-methylanilines gave the products **2d** and **2e** in good yields of 86% and 77%, respectively (entries 3 and 4). Substrates with strong electron-withdrawing groups were challenging for the reaction: the methylated products of *p*-nitro- (**2f**) and *p*-acetyl-*N*-methylaniline (**2g**) were isolated in 19% and 42% yields, respectively (entries 5 and 6). Further functiona-

Table 2 Substrate scope for the synthesis of *N*-methylamines from amines with CO₂ and PMHS

$ \begin{array}{c} \text{10 mol\%} \\ [\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me} \\ \text{PMHS (10 equiv.), THF} \\ 16 \text{ h, } 70^\circ\text{C, } p(\text{CO}_2) = 1 \text{ bar} \end{array} \xrightarrow{\text{CO}_2} \begin{array}{c} \text{Me} \\ \\ \text{R}^1\text{N}-\text{R}^2 \\ \text{2} \end{array} $			
Entry	Substrate 1	Product 2	Yield
1		2b , R ³ = <i>p</i> -OCH ₃	72%
2		2c , R ³ = <i>o</i> -OCH ₃	71% ^a
3		2d , R ³ = <i>p</i> -F	86%
4		2e , R ³ = <i>p</i> -Br	77%
5		2f , R ³ = <i>p</i> -NO ₂	19%
6		2g , R ³ = <i>p</i> -Ac	42%
7		2h , R ² = Bn	89%
8		2i , R ² = cyclohexyl	83%
9		2j , R ² = <i>n</i> -butyl	87%
10		2k , R ² = allyl	82%
11		2l ^b	76% ^{a,b}
12			90% ^b
13			42%
14		2o	30% ^{b,c}
15		2p	98% ^b

Reaction conditions: amine **1** (0.600 mmol), PMHS (10 equiv.), catalyst (10 mol%), $p(\text{CO}_2) = 1$ bar, 70 °C, 16 h, THF. Isolated yields are given. ^a 4 h. ^b Yield was determined by ¹H NMR using mesitylene as the internal standard. ^c The *N*-formylated product was obtained in 68% yield.

lized substrates such as *N*-benzyl-, *N*-cyclohexyl-, *N*-butyl-, and *N*-allyl-anilines were converted to the corresponding methylated products **2h–2k** in excellent yields (82–89%) (entries 7–10). Tetrahydroquinoline afforded the methylated product **2l** in a yield of 76% in 4 h (entry 11). In comparison with secondary anilines, primary anilines normally exhibit lower nucleophilicity and form multiple reduction products^{42,52} However, with this catalytic system, aniline (**1m**) and *p*-methoxyaniline (**1n**) afforded dimethylanilines in yields of 90% and 42%, respectively (entries 12 and 13). Besides anilines, benzyl-*N*-methylamine (**1o**) was also tested. However, the formylated product **3o** was obtained in 68% yield as the main product while the methylated product **2o** was obtained in 30% yield (entry 14). Surprisingly, the sterically hindered substrate 2,2,6,6-tetramethylpiperidine was successfully converted to the methylated product pempidine **2p**, which is a ganglion-blocking drug (entry 15).⁵³

Since the formation of the *N*-formylated product **3a** was also observed in significant amounts during the screening

(Table 1, entry 12), we further explored the *N*-formylation of *N*-methylaniline (**1a**) catalyzed by [Ph₃PMe]CO₃Me (Table 3). Initially, we turned our focus to other silanes. PhSiH₃ and Ph₂SiH₂ gave moderate yields of *N,N*-dimethylaniline (**2a**) and poor yields of *N*-methylformanilide (**3a**) (entries 1–5). PhSiH₃ and Ph₂SiH₂ mainly formed methylated product **2a**, and only 8% desired product **3a** was observed (entries 1 and 2). Ph₃SiH converted **1a** to **3a** in a yield of 39% and no **2a** or **3a** was observed with Et₃SiH (entries 3 and 4). (MeO)₃SiH afforded the *N*-formylated product in an excellent yield of 98% with outstanding selectivity (entry 5). Further screening of the reaction conditions was performed in the presence of (MeO)₃SiH (entries 6–10). Reducing the reaction time to 4 h led to a comparable yield and selectivity (entry 6). **1a** was quantitatively converted to the desired product **3a** even with a much lower loading of the catalyst (entry 7). An excellent yield of the formylated product **3a** (95%) was also obtained at 70 °C in 4 hours in the presence of 3 equiv. of (MeO)₃SiH (entry 8). No product was obtained without the catalyst (entry 9). A lower amount of (MeO)₃SiH was not sufficient to convert all the reactant (entry 10).

With the optimal conditions in hand, the scope and limitations of [Ph₃PMe]CO₃Me for the catalytic conversion of amines to their formylated products were studied at 70 °C in the presence of trimethoxysilane as the reductant (Table 4). Under these conditions, *p*-methoxyaniline (**1b**) was converted to **3b** in a high yield of 86% (entry 1). In some cases, extension of the reaction time from 4 to 24 h was necessary. In contrast to the methylation reaction, *o*-methoxy-*N*-methylaniline (**1c**) needed 24 h to be converted to the corresponding formylated product in a good yield of 79% (entry 2). Electron-withdrawing groups were also evaluated: fluoro- and bromo-substituted anilines **1d** and **1e** afforded the corresponding

Table 3 Screening reaction conditions for the conversion of *N*-methylaniline (**1a**) with CO₂ into formylated product **3a**

$ \begin{array}{c} \text{0–10 mol\%} \\ [\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me} \\ [\text{Si-H 2–4 equiv.}] \\ 70^\circ\text{C, } t, p(\text{CO}_2) = 1 \text{ bar} \\ \text{THF} \end{array} \xrightarrow{\text{CO}_2} \begin{array}{c} \text{Me} \\ \\ \text{Ph-N-Me} \\ \text{2a} \end{array} + \begin{array}{c} \text{O} \\ \\ \text{Ph-N-Me} \\ \text{3a} \end{array} $						
Entry	Cat. (mol%)	Si-H (equiv.)	Silane	<i>t</i> (h)	Yield 2a (%)	Yield 3a (%)
1	10	4	PhSiH ₃	16	31	8
2	10	4	Ph ₂ SiH ₂	16	55	8
3	10	4	Ph ₃ SiH	16	0	39
4	10	4	Et ₃ SiH	16	0	0
5	10	4	(MeO) ₃ SiH	16	0	98
6	10	4	(MeO) ₃ SiH	4	0	94
7	2	4	(MeO) ₃ SiH	4	0	96
8	2	3	(MeO) ₃ SiH	4	0	95
9	0	3	(MeO) ₃ SiH	4	0	0
10	2	2	(MeO) ₃ SiH	4	0	44

Reaction conditions: *N*-methylaniline (**1a**, 0.233 mmol), silane (2–4 equiv.), catalyst (0–10 mol%), $p(\text{CO}_2) = 1$ bar, 70 °C for 4–16 h, THF. The yield was determined by ¹H NMR using mesitylene as the internal standard.

Table 4 Substrate scope for the conversion of amines to formamides with CO₂ and trimethoxysilane

$ \begin{array}{c} \text{R}^1\text{--NH--R}^2 + \text{CO}_2 \xrightarrow[\text{THF}]{\substack{2 \text{ mol\%} \\ [\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me} \\ (\text{MeO})_3\text{SiH } 3 \text{ equiv.} \\ 24 \text{ h, } 70^\circ\text{C, } p(\text{CO}_2) = 1 \text{ bar}}} \\ \text{1} \hspace{10em} \text{3} \end{array} $			
Entry	Substrate 1	Product 3	Yield
1		3b , R ³ = <i>p</i> -OCH ₃	86% ^a
2		3c , R ³ = <i>o</i> -OCH ₃	79%
3		3d , R ³ = <i>p</i> -F	86% ^a
4		3e , R ³ = <i>p</i> -Br	76% ^a
5		3f , R ³ = <i>p</i> -NO ₂	13%
6		3g , R ³ = <i>p</i> -Ac	53%
7		3j , R ² = <i>n</i> -butyl	84%
8		3k , R ² = allyl	85%
9		3l	94%
10		3o	92%
11		3q	75%
12		3r	89%
13		3s	69%
14		3t	90%
15		3u	53%

Reaction conditions: amine **1** (0.600 mmol), trimethoxysilane (220 mg, 3 equiv.), catalyst (2 mol%), $p(\text{CO}_2) = 1$ bar, 70 °C, 24 h, THF. Isolated yields are given. ^a 4 h.

N-methylformanilide **3d** and **3e** in good yields in 4 h; while nitro- and acetyl-substituted anilines **1f** and **1g** led to lower yields of 13% and 53%, respectively (entries 3–6). *N*-Substituted anilines were also tolerated, *N*-butyl- and *N*-allyl-substituted anilines **1j** and **1k** were successfully converted to their formylated products **3j** and **3k** in 84% and 85% yield, respectively, after 24 h (entries 7 and 8). Tetrahydroquinoline **1l** gave the formylated product **3l** in 94% yield (entry 9). The conversion of the benzylamines **1o** and **1q** was also successful and 92% and 75% yield, respectively, of the formylated methylbenzeneamine **3o** and dibenzylamine **3q** were isolated (entries 10 and 11). The piperazine derivative **1r** afforded the formylated product **3r** in a yield of 89% (entry 12). A moderate yield of 69% of the formylated product **3s** was obtained from the pyridine-substituted amine **1s** (entry 13). Aniline (**1t**) and pyridine-2-amine (**1u**) were selected as representative substrates of primary amines (entries 14 and 15). An excellent yield of 90% of *N*-formanilide **3t** was obtained from aniline, while 53% of the *N*-formylated-pyridine-2-amine **3u** was isolated.

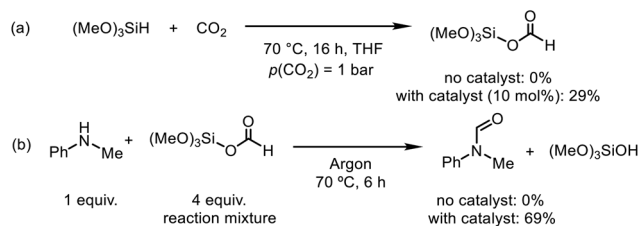
The excellent conversion and selectivity of aniline (**1t**) to *N*-phenylformamide (**3t**) encouraged us to study the possibility of the formation of benzimidazole by monoformylation of the *o*-phenylenediamine (**4a**) followed by subsequent intramolecular condensation with the amino group. Therefore, the reaction was performed under the same reaction conditions as for the formylation of aniline without other additives. To our delight, 83% of benzimidazole **5a** was isolated from 1,2-diaminobenzene and CO₂ in one step (Table 5, entry 1). This prompted us to investigate the synthesis of other imidazole derivatives **5**. *p*-Methoxy-1,2-diaminobenzene (**4b**) afforded the desired product **5b** in a yield of 47% (entry 2). *N*-Disubstituted substrates 1-*N*-methylbenzene-1,2-diamine (**4c**) and *N*-phenyl-*o*-phenylenediamine (**4d**) were evaluated in this protocol: 61% and 70% of the desired products **5c** and **5d** were obtained, respectively (entries 3 and 4). The lower yields were due to the formation of the monoformylation byproduct from the primary amino group that is less nucleophilic and reactive than secondary amino groups. There are only a few examples of the synthesis of quinazoline derivatives utilizing CO₂.^{13,54,55} Under our conditions, the six-membered ring quinazoline derivative **5e** was also isolated in a yield of 64% from *o*-(amino-methyl)aniline **4e** (entry 5).

To gain insights into the reaction mechanism, control experiments were performed to identify the possible intermediates in the *N*-formylation and *N*-methylation reactions (Scheme 2). Initially, trimethoxysilane was reacted with CO₂ in the presence of the catalyst [Ph₃PMe]CO₃Me, affording the silyl formate in 29% yield. Characteristic signals for silylformate were observed in the ¹H and ¹³C NMR spectra at

Table 5 Substrate scope for the conversion of diamines to benzimidazoles with CO₂ and trimethoxysilane

$ \begin{array}{c} \text{R}^2\text{--} \text{C}_6\text{H}_3\text{--} \text{NH}_2 + \text{CO}_2 \xrightarrow[\text{THF}]{\substack{2 \text{ mol\%} \\ [\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me} \\ (\text{MeO})_3\text{SiH } 3 \text{ equiv.} \\ 24 \text{ h, } 70^\circ\text{C, } p(\text{CO}_2) = 1 \text{ bar}}} \\ \text{4} \hspace{10em} \text{5} \end{array} $			
Entry	Substrate	Product	Yield
1		4a → 5a	83%
2		4b → 5b	47%
3		4c → 5c	61%
4		4d → 5d	70%
5		4e → 5e	64%

Reaction conditions: diamine **4** (0.600 mmol), trimethoxysilane (3 equiv.), catalyst (2 mol%), $p(\text{CO}_2) = 1$ bar, 70 °C for 24 h, CH₃CN. Isolated yields are given.

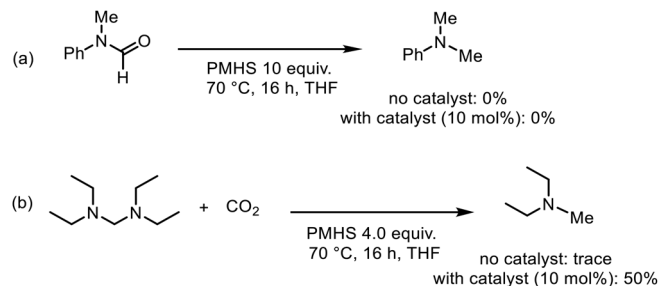


Scheme 2 Control experiments for the *N*-formylation reaction. The yields were determined by ^1H NMR using mesitylene as the internal standard.

$\delta(\text{SiOCHO}) = 7.96$ ppm and $\delta(\text{SiOCHO}) = 158.2$ ppm, respectively (Scheme 2a and Fig. S1†).⁵⁶ Notably, in the absence of the catalyst, this was not observed. Apart from silyl formate, tetramethoxysilane was also observed in the ^1H NMR and ^{29}Si NMR spectra at $\delta(\text{SiOCH}_3) = 3.40$ ppm and $\delta(\text{SiOCH}_3) = -78.6$ ppm, respectively (Fig. S1–S3†). The formation of tetramethoxysilane can be addressed by the over-reduction of silyl formate in the absence of amines.⁵⁷ The resulting reaction mixture was purged with argon to replace the remaining CO_2 . *N*-Methylaniline (**1a**) was added and reacted at 70°C for 6 h, affording *N*-methylformanilide (**2a**) in 69% yield (Scheme 2b). Without the catalyst, the silyl formate was not observed. Moreover, the silyl formate did not react with the amine **1a** in the absence of the catalyst.

Thus we conclude that *N*-formylation proceeds *via* the silyl formate intermediate which has been reported before.⁵⁸ However, for the *N*-methylation of amines by CO_2 in the presence of organocatalysts, two possible pathways are discussed in the literature. Both pathways proceed *via* the initial formation of the silyl formate (Scheme 3). Path I: the *N*-formamide is formed and further reduced to *N*-methylamine by the silane. The majority of catalytic systems were proved to follow this pathway by experimental and computational evidence.^{26,29,41,59,60} Path II: the silane is reduced to silyl acetal, which reacts with the amine to afford the aminor. Subsequently, the aminor is reduced to the methylated product.^{28,38}

The two routes were evaluated by performing a series of test reactions. First, the conversion of *N*-formamide to *N*-methylamine was tested using PMHS as the reductant in the presence and absence of the catalyst under the methylation reaction conditions (Scheme 4a). In both cases, the product

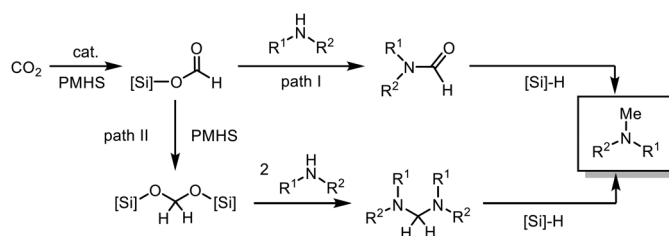


Scheme 4 Control experiments for the *N*-methylation reaction. The yield was determined by ^1H NMR using mesitylene as the internal standard.

could not be obtained. Thus, path I was ruled out. Subsequently, we considered path II. We hypothesized that the intermediate formation of the aminor in the reaction mixture should be detectable by NMR. Indeed, it was possible to detect the formation of the aminor by ^1H NMR spectroscopy. The spectra showed a characteristic signal for the aminor resonance at $\delta(\text{N}-\text{CH}_3) = 2.86$ ppm which agrees with previous reports.⁶¹ Under the optimized reaction conditions, the aminor was initially formed in 9% yield after 2 h (Table S1 and Fig. S5†). This supports the assumed formation of the aminor as an intermediate. Furthermore, the conversion of the aminor to the *N*-methylamine was studied. In this regard, *N,N,N',N'*-tetramethylethanedi-amine (TMEDA), a commercially available aminor, was chosen to react with PMHS in the presence of CO_2 since it is reported that CO_2 contributed to the cleavage of the *N*-C bond.⁵⁸ Under the reaction conditions, the aminor (TMEDA) and PMHS were converted and the corresponding *N*-methylated product was obtained in 50% yield in the presence of the catalyst, which demonstrated that path II is reasonable for this catalytic system (Scheme 4b and Fig. S6†). Only traces of the product were observed in the absence of CO_2 or catalyst.

Interestingly, despite being a milder reducing agent than trimethoxysilane, PMHS was efficient for the 6-electron reduction of CO_2 in the presence of the catalyst.⁶² This might be explained when path II is considered. In this route, due to the polymeric nature of PMHS, the formation of a bis silyl acetal can proceed *via* an intramolecular reduction of the silyl formate (Scheme S1†).

Once the different routes to the formation of products were established, we became interested in understanding the role of



Scheme 3 Possible pathways for the *N*-methylation reaction with PMHS.

the catalyst in this reaction and the different selectivity observed for the reducing agents. Initially, a stoichiometric mixture of PMHS and catalyst $[\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me}$ was heated to 70 °C and analyzed by NMR spectroscopy (Fig. 1c). The characteristic signal at $\delta(\text{Si}-\text{H}) = 4.72$ ppm in PMHS (see 1a) and the signal at $\delta(\text{CO}_3\text{CH}_3) = 3.37$ ppm (see 1b) for the catalyst were not observed in the mixture. Instead, a new signal at $\delta = 8.58$ ppm was observed in the mixture which can be attributed to the formation of the formate anion.⁶³ A signal with the same chemical shift ($\delta(\text{HCO}_2^-) = 8.58$ ppm) was observed in the mixture of trimethoxysilane and the catalyst (Fig. 2c). Also, in this case, the signals at $\delta(\text{Si}-\text{H}) = 4.07$ ppm for the silane and for the catalyst $\delta(\text{CO}_3\text{CH}_3) = 3.37$ ppm were not detectable in the mixture. The signals at 3.37 ppm and -78.60 ppm in the ^{29}Si NMR spectra (Fig. S7†), respectively, indicate the formation of $\text{Si}(\text{OMe})_4$.⁶⁴ The common signal in both mixtures at around 3.30 ppm (marked as *) can be addressed to a methoxy

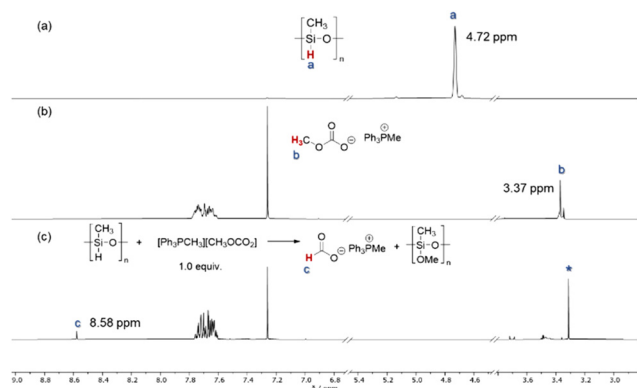


Fig. 1 (a) Section of the ^1H NMR spectra of PMHS. (b) Section of the ^1H NMR spectra of catalyst $[\text{Ph}_3\text{PCH}_3]\text{CO}_3\text{Me}$. (c) Section of the ^1H NMR spectra of a 1:1 mixture of PMHS and $[\text{Ph}_3\text{PCH}_3]\text{CO}_3\text{Me}$ after 16 h at 70 °C. * denotes the methoxy anion.

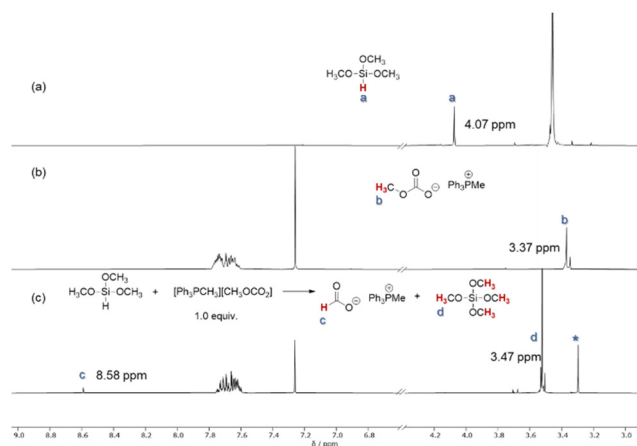
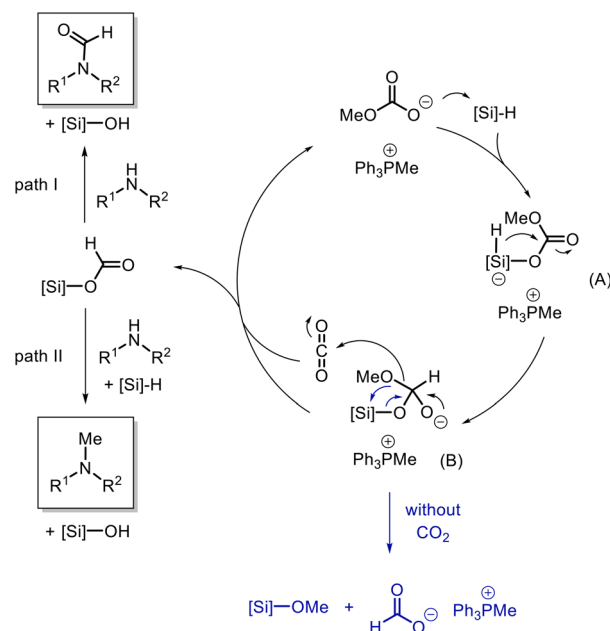


Fig. 2 (a) Section of the ^1H NMR spectra of PMHS. (b) Section of the ^1H NMR spectra of the catalyst $[\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me}$. (c) Section of the ^1H NMR spectra of a 1:1 mixture of PMHS and $[\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me}$ after 16 h at 70 °C. * denotes the methoxy anion.



Scheme 5 Mechanistic proposal for the selective conversion of amines with CO_2 to formamides or methylamines with phosphonium methylcarbonate salts.

anion which is probably formed due to the decomposition of $[\text{Ph}_3\text{PMe}]\text{CO}_3\text{Me}$ to CO_2 and $[\text{Ph}_3\text{PMe}]\text{OMe}$.⁴⁹ These results indicate the conversion of the methylcarbonate anion and silane to formate. This led us to the assumption that the reaction is initiated in this step. Based on these results, we propose the mechanism shown in Scheme 5.

The methylcarbonate anion attacks the silane forming A which facilitates the attack of the hydride to the carbonyl center and the generation of B. The decomposition of B leads to silyl formate and a methoxy anion which reacts with CO_2 to regenerate methylcarbonate (catalyst) and it also leads to the regeneration of the catalyst in the following step, which has no negative impact on the catalytic efficiency. As indicated above, in the absence of CO_2 , this B can undergo a rearrangement resulting in the formate anion, e.g. tetramethoxysilane. In the presence of trimethoxysilane as the reducing agent, the formate further reacts with the amine through path I to the *N*-formylated product which is not further reduced. In contrast, if PMHS is used as the reducing agent, the *N*-formylated product further reacts to form bis silyl acetal which subsequently reacts with the amine and PMHS to give the *N*-methylated product.

Conclusions

Phosphonium methylcarbonate has been proven to be an efficient organocatalyst for the conversion of CO_2 with primary and secondary amines and diamines. Notably, the selectivity of the reaction can be tuned by the choice of the reductant. In the presence of readily available PMHS, selective

N-methylation was achieved under mild conditions. In contrast, the use of trimethoxysilane as the reducing agent leads to the selective *N*-formylation of the amines. Moreover, the one-pot synthesis of imidazoles was possible when diamines were used as the starting material. Mechanistic investigations revealed different reaction pathways for *N*-methylation and *N*-formylation depending on the reductant. *N*-Methylation proceeds most probably *via* silyl formate while *N*-formylation proceeds *via* a bisilyl acetal and amina intermediate. The mechanistic studies also suggest that the catalyst directly activates CO₂. This tuneable process was applied to a broad range of substrates. Under the optimized conditions, 15 primary and secondary amines and anilines were converted to *N*-methylated products in yields of up to 98%. The *N*-formylation of 15 amines led to the desired products in yields of up to 94%. Additionally, this procedure was evaluated for a one-pot *N*-formylation/condensation reaction of diamines leading to the corresponding heterocycles in yields of up to 83%. Thus, the presented mechanistic studies give insights into the *N*-methylation and *N*-formylation of amines with CO₂. In addition, the protocols presented provide straightforward access to valuable intermediates that use CO₂ as a C1 building block.

Experimental

Synthesis of methyltriphenylphosphonium methylcarbonate

In a 10 mL Schlenk tube, triphenylphosphine (0.235 g, 0.896 mmol), dimethylcarbonate (DMC) (0.52 mL, 6.15 mmol), and methanol (0.52 mL) as solvent were introduced in the shortest time possible to limit the exposure of phosphine to air. The Schlenk tube was heated for 24 h at 140 °C. The reaction mixture was allowed to cool to an ambient temperature and volatiles were removed in a vacuum. The off-white solid was stirred under an inert atmosphere with cyclohexane (8.3 mL) at 50 °C for 2 hours. After filtration on a Gooch crucible, the product was obtained in 64% yield as a colorless solid (0.215 mg, 0.580 mmol). ¹H NMR (300 MHz, CDCl₃): δ = 7.82–7.58 (m, 15H), 3.37 (s, 3H) ppm. The methyl protons (P-CH₃) were not detectable due to H/D exchange.⁵⁰ ¹H NMR (300 MHz, CD₃CN): δ = 7.98–7.81 (m, 3H), 7.79–7.62 (m, 12H), 3.29 (s, 3H), 2.89 (d, *J* = 15.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 134.96 (d, *J* = 2.9 Hz), 133.26 (d, *J* = 10.7 Hz), 130.39 (d, *J* = 12.9 Hz), 119.41 (d, *J* = 88.5 Hz), 52.20. ¹³C NMR (75 MHz, CD₃CN): δ = 162.20, 140.32 (d, *J* = 3.1 Hz), 138.68 (d, *J* = 10.8 Hz), 135.47 (d, *J* = 12.9 Hz), 124.98 (d, *J* = 88.9 Hz), 56.17, 13.50 (d, *J* = 57.8 Hz) ppm. ³¹P NMR (122 MHz, CDCl₃): δ = 21.92 ppm. HR-MS (MePh₃P⁺): *m/z* calcd 277.1151, found 277.1153.

Representative procedure for *N*-methylation – the synthesis of *N*-benzyl-*N*-methylaniline (2h)

In a stainless-steel autoclave, PMHS (414 μL) was added to a solution of the catalyst (21.4 mg, 60.0 μmol) and *N*-benzylaniline (**1h**, 110 mg, 0.600 mmol) in THF (5 mL). The

autoclave was purged with CO₂ and the pressure was kept constant at 1 bar. The reaction mixture was stirred at 70 °C for 16 h. Subsequently, CO₂ was released slowly. The solvent was removed in a vacuum and the residue was purified by chromatography (SiO₂, cyclohexane/ethyl acetate = 20/1) to yield *N*-benzyl-*N*-methylaniline (105 mg, 0.533 mmol, 89%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ = 7.37–7.28 (m, 2H), 7.28–7.19 (m, 5H), 6.81–6.69 (m, 3H), 4.55 (s, 2H), 3.03 (s, 3H).

Representative procedure for *N*-formylation – the synthesis of *N*-benzylformamide (3o)

In a stainless-steel autoclave, trimethoxysilane (220 mg, 1.80 mmol) was added to a solution of the catalyst (4.23 mg, 12.0 μmol) and *N*-methyl-1-phenylmethanamine (72.7 mg, 0.600 mmol) in THF (0.6 mL). The autoclave was purged with CO₂ and the pressure was kept constant at 1 bar. The reaction mixture was stirred at 70 °C for 24 h. Subsequently, CO₂ was released slowly. The solvent was removed in a vacuum and the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate = 10/1) to afford *N*-benzylformamide (82.0 mg, 0.552 mmol, 92%) as a colourless oil. ¹H NMR (300 MHz, CDCl₃) δ = 8.21 (s, 0.57H, maj), 8.08 (s, 0.43H, min), 7.38–7.04 (m, 5H), 4.44 (s, 0.89H, min), 4.31 (s, 1.19H, maj), 2.77 (s, 1.33H, min), 2.70 (s, 1.71H, maj).

Representative procedure for the preparation of benzimidazoles – the synthesis of 1*H*-1,3-benzimidazole (4a)

In a stainless-steel autoclave, trimethoxysilane (220 mg, 1.80 mmol) was added to a solution of the catalyst (4.23 mg, 12.0 μmol) and *o*-phenylenediamine (64.9 mg, 0.600 mmol) in THF (6 mL). The autoclave was purged with CO₂ and the pressure was kept constant at 1 bar. The reaction mixture was stirred at 70 °C for 24 h. Subsequently, CO₂ was released slowly. Then the solvent was removed in a vacuum and the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate = 1/1) to yield 1*H*-benzo[*d*]imidazole (58.8 mg, 0.498 mmol, 83%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 8.11 (s, 1H), 7.79–7.59 (m, 2H), 7.35–7.28 (m, 2H), 6.28 (s, 1H).

Author contributions

C. Ren performed the initial reaction screening. C. Ren and C. Terazzi performed the optimization of the reaction conditions and mechanistic studies. C. Ren performed the substrate scope. C. Ren, C. Terazzi and T. Werner wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Curriculum Vitae

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- 03/2011–11/2017 **Faculty of Exact and Natural Sciences, University of Buenos Aires**
Diploma - "Coordinated nitrososulphorous compounds: Study of H₂S/NO reactivity on Ir(III) complexes"
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- 03/2008–12/2010 **Technical School N°2, Merlo, Buenos Aires**
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Professional experience

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List of Publications

- 3) C. Ren, C. Terazzi, T. Werner* Tuneable reduction of CO₂ – organocatalyzed selective formylation and methylation of amines, *Green Chem.* **2024**, 26, 439–447.
- 2) C. Terazzi, A. Spannenberg, J. von Langermann,* T. Werner* Chemoenzymatic Synthesis of Chiral Building Blocks Based on the Kinetic Resolution of Glycerol-Derived Cyclic Carbonates, *ChemCatChem* **2023**, 15, e202300917.
- 1) C. Terazzi, K. Laatz, J. von Langermann,* T. Werner* Synthesis of Cyclic Carbonates Catalyzed by Cal₂–Et₃N and Studies on Their Biocatalytic Kinetic Resolution, *ACS Sustain. Chem. Eng.* **2022**, 10, 13335–13342.

Attended Conferences

- 6) “From Glycerol to Pharmaceuticals: Enzymatic Kinetic Resolution of Cyclic Carbonates” C. Terazzi, A. Spannenberg, J. von Langermann, T. Werner, *Sustainable Future: Dream Reactions with (and without) Hydrogen*, 24. August **2023**, Münster, Germany.
- 5) “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.
- 4) “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) “Cyclic Carbonates Synthesis Catalyzed by Cal₂·Et₃N”, C. Terazzi, K. C. Laatz, J. von Langermann, T. Werner, *55. Jahrestreffen Deutscher Katalytiker*, 27.–29. June **2022**, Weimar, Germany.
- 2) “Pig Liver Esterase-Catalyzed Kinetic Resolution of Cyclic Carbonates”, C. Terazzi, T. Werner, J. von Langermann, *Biotrans*, 19.–22. July **2021**, Graz, Austria (online).
- 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).