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Evaluation of most promising options for the C1 to C2-coupling:

alternative formate coupling

Tesi di laurea sperimentale

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Keywords

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Abstract

This thesis work contains an overview of potential alternative options to couple formate produced from CO_2 with other coupling partners than formate itself. Ultimately, the intent is to produce high value chemicals from CO_2 at a high selectivity and conversion, whilst keeping the required utility of electrons in the electrochemical CO_2 conversion at a minimum.

To select and find new coupling partners, a framework was developed upon which a broad variety of candidates were assessed and ranked. A multi-stage process was used to select first potential classes of molecules. For each class, a variety of commercially available compounds was analysed in depth for its potential suitability in the reaction with the active carbonite intermediate. This analysis has shown that a wide variety of factors come into play and especially the reactivity of the hydride catalyst poses a mayor challenge. The three major potential classes of compounds suitable for the coupling are carbon oxides (CO_2 & CO), and aldehydes.

As a second step the remaining options were ranked to identify which compound to test first. In this ranking the reactants sustainability, ease of commercial operation and commercial attractiveness of the corresponding product were considered. The highest-ranking compounds that proposed the highest potential are CO_2, benzaldehyde and para-formaldehyde.

In proof-of-principle experiments CO_2 could successfully be incorporated in the form of carbonate, oxalate and potentially formate. The overall incorporation efficiency based on the hydride consumption was shown to be 50%. It is suggested to continue this work with mechanistic studies to understand the reaction in detail as, based on further gained knowledge, the reaction can then be optimized towards optimal CO_2 incorporation in the form of oxalate.

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Aim of the study

Nowadays there is a widespread awareness that for the last century the levels of CO_2 in the atmosphere have experienced a continuous increment due to anthropogenic emissions. CO_2 is one of the main greenhouse gases (GHGs) associated with global warming and climate change. Although energy production from fossil resources contributes to the most extent in releasing CO_2 in the atmosphere, energy-intensive industries such as the chemical, cement, and steel sectors represent still 20% of the global GHGs emissions. [1] Significant reductions from these sectors are essential to achieve the targets posed for abruptly reducing GHGs in the next years. For this reason, decoupling production from the utilization of fossil resources is an additional necessary step towards achieving a more sustainable society.

In this regard, the approach of CO_2 capture and utilization (CCU) has gained more and more attention, representing a very compelling option. With the aim of introducing CO_2 into the chemical value chain, CO_2 may be transformed into a wide range of products, for various applications. This could be achieved through different technologies and processes, transforming CO_2 from waste streams, or even air, into a wide array of added-value products, ranging from fuels to chemicals. [1]

This research is part of the OCEAN project, an EU-funded consortium which pose the objective of producing valuable goods such as polymers using CO_2 as a carbon feedstock.

The CCU process begins with the electrochemical conversion of CO_2 into formate salts. This step is relatively energy-demanding, so using formate as starting substrate to produce added-value products is crucial to compensate the costs of CO_2 conversion. It is well acknowledged that formate can couple thermochemically to obtain oxalate, which is a product with a solid market. This study aims to investigate the possibility of coupling formate salts with different partners, other than formate, in order to obtain valuable products of interest. The whole concept revolves around the production of carbonite, a very reactive intermediate obtained from formate using strong bases, like metal hydrides, as catalyst. Potentially, finding suitable partners for this 'alternative' formate coupling (AFC) could lead to new pathways of CCU. A framework was developed to select the best candidates for this reaction, considering chemical criteria, physical properties, practical and commercial aspects.

The most appealing partner for the AFC turned out to be CO_2 in its supercritical state, on which most of the proof of principle experiments were performed.

Despite the drawback of stochiometric consumption of metal hydrides to generate the active species, using scCO$_2$ brings many advantages such as the absence of a solvent to mediate the reaction, other than the great sustainability of CO$_2$ as a reactant.

An equimolar mixture of formate and hydride was used to perform the reaction, exploring different conditions in terms of time and temperature focusing on maximizing CO$_2$ incorporation and optimizing oxalate yields.

Qualitative and quantitative infrared spectroscopy (IR) and liquid chromatography (LC) were used to analyze the post-reaction mixture, showing carbonate, oxalate and formate as available species. Up to 50% additional carbon atoms were captured in the process and the oxalate yields amounts to nearly 50%, using the optimized reaction conditions of T=200°C and t=15 min.

1. Introduction

The continuing growth of anthropogenic greenhouse gas (GHG) emissions in the past decades is the leading direct cause of global climate change. These emissions are mainly carbon dioxide (CO_2) from fossil fuel combustion.[2] Despite a growing number of climate change mitigation policies, every year of the 21st century has seen a yearly increase in anthropogenic CO_2 emissions.[3] Also in the chemical industry most energy and feedstock is obtained from oil and other fossil resources. The overall fossil carbon use is used as carbon feedstock (58%) or to generate process energy (42%). [4] Although the chemical industry has already reduced the use of fossil resources, deeper reductions in GHGs emissions require more significant changes such as the use of biomass feedstock[5], carbon capture and storage (CCS)[6], and carbon capture and utilization (CCU). [7] In particular, carbon capture and utilization has started to attract attention worldwide. It can turn waste CO_2 emissions into valuable products such as chemicals and fuels and contribute to climate change mitigation. In figure 1 are shown different ways of for CO_2 capture and utilization.
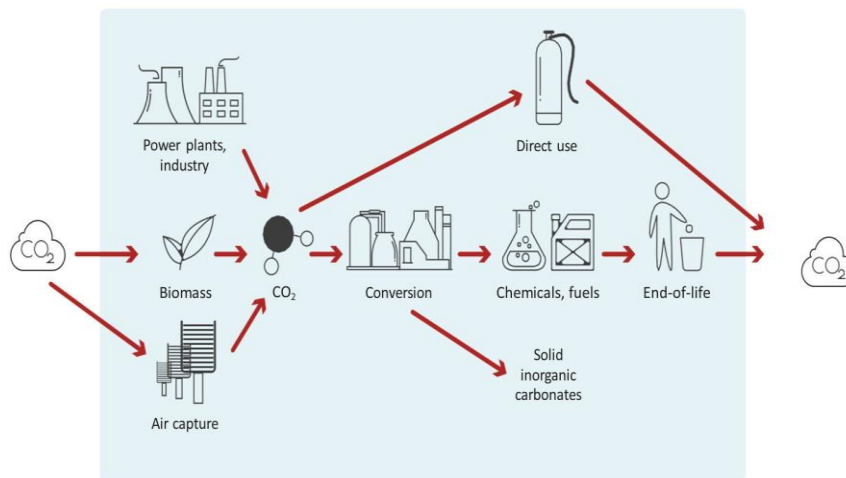
Figure 1: CO_2 conversion into products via CCU processes.

Besides, CCS faces many technical and economic barriers significantly because it is an unprofitable activity. On the other hand, CCU is usually a profitable activity as its products can be sold. [8]

The polymer industry is a manufacturing sector highly dependent on carbon feedstock from fossil fuels. It produces polymer materials with a wide range of applications that in the modern world have become essential goods.[9] For this reason, an appealing perspective is to involve

a CCU process to produce polymers, using CO_2 as a renewable, non-toxic carbon feedstock. CO_2-based chemicals such as oxalic acid will become new platform chemicals for a wide range of downstream products such as mono-ethylene glycol (MEG) as well as glycolic and glyoxylic acid.[10]

OCEAN is an EU-funded consortium which aims to produce polymers from CO_2 at an industrial demonstration scale (acronym stands for **O**xalic acid from **C**O2 using **E**lectrochemistry **A**t demonstratio**N** scale). The consortium consists of a diverse set of partners from industry and academic community.

The first step of this CCU process consist of electrochemical conversion of CO_2 into formate salts. As second step, catalytically induced coupling of these formate salts to produce oxalate. The resulting oxalic acid and derivative forms such as glycolic acid can be used as monomers for new polymers. The process can be summarized in Scheme 1 below.
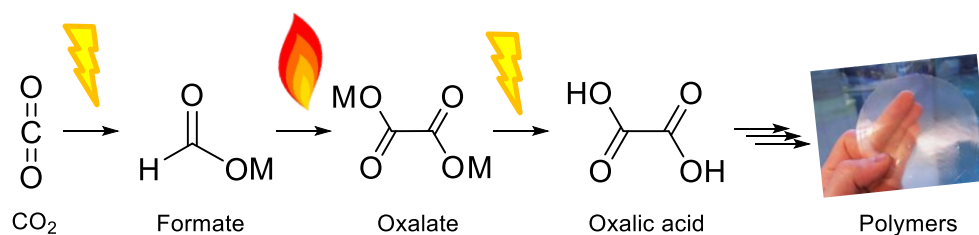
Scheme 1: CO_2 conversion into valuable products via formate coupling.

Recently, the formate coupling reaction gained more interest with the upcoming of CCU pathways, to obtain formate salts from CO_2 conversion. Formate salts are salts of formic acid, where different metals are possible as counter ions. At high temperatures all formate salts undergo decomposition to carbonates, metal oxides or metals.[11] However, alkali formates can also be converted to corresponding oxalates by a coupling reaction, although a catalyst is required to use lower temperature and reach high selectivity.[12] Alkali hydrides like KH, NaH and LiH can be used for this purpose with remarkable yields. They are characterized by a difference in basic strength conferred by the metal cation. The chemistry involved in the formate coupling reaction and optimization of the commercial process has been of industrial and scientific interest since the late 19th century. Numerous patents were published since 1900 covering chiefly a reactor design and the reaction conditions on a large scale.[13][14]

A mechanistic study of the formate coupling reaction catalyzed by metal hydrides was published by Lakkaraju *et al.* in 2016. They suggested a reaction mechanism and possible intermediates using density functional theory (DFT) (see figure 2) calculations and Raman spectroscopy as proof.[12] The mechanism involves dehydrogenation of the formate moiety by hydride anion to form carbonite and molecular hydrogen (see scheme 2). Schuler *et al.* were able to confirm the participation of the carbonite species in this reaction using isotope labelling studies (see scheme 3) and mass spectroscopy for detection.[15]
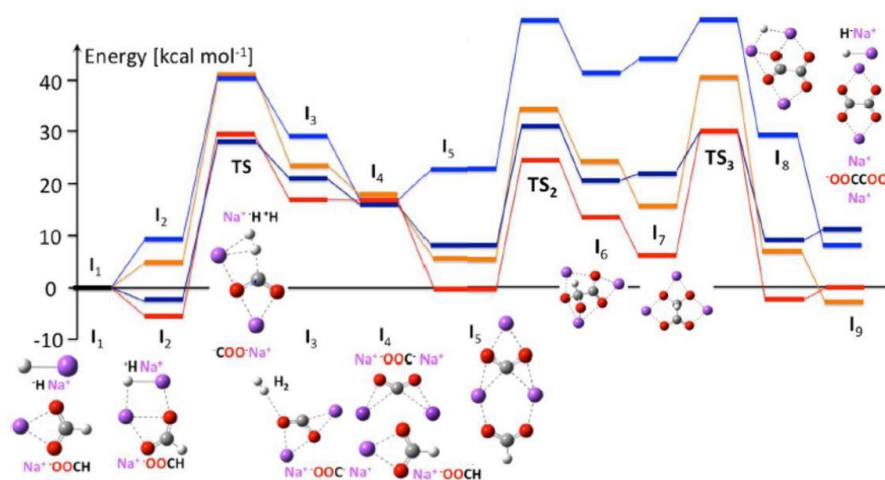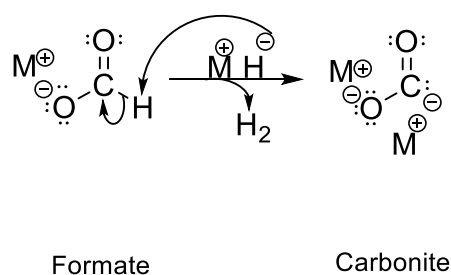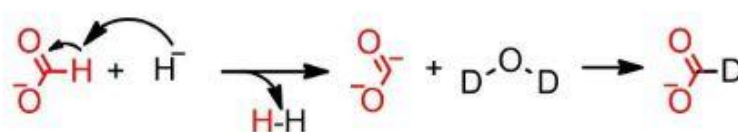

Figure 2: DFT free-energy calculations of the catalytic conversion of formate into oxalate as salts of sodium (red 663 K, orange 298 K) and potassium (navy 713 K, blue 298 K).[12]

Scheme 2: general mechanism of carbonite formation catalyzed by metal hydrides.

Scheme 3: Reaction pathway for isotope labelling of carbonite intermediate with D₂O.

The carbonite intermediate originates from the proton abstraction of formate, which is achieved by heating formate with strong bases. Commercially, the formate coupling reaction is performed at high temperatures of 380–420°C using hydroxides as catalysts. [16][17] With these hydroxide bases, the reaction takes more than 30 minutes to proceed, and selectivity towards oxalate is not optimal leading to significant production of side products that require intensive a downstream separation step.

Schuler *et al.* did an intensive study on different catalysts for formate coupling to produce oxalate. Different catalysts were tested in terms of performances[15], mainly superbases such as lithium, sodium, and potassium hydride as well as sodium amide (NaH, KH, LiH, and NaNH$_2$). If superbases are used, the abstraction occurs at the melting point of formate which corresponds to 168 °C for potassium formate. In table 1 below are shown the results obtained by the research of Schuler *et al.*

| Catalyst	Loading (wt%)	Reaction onset T (°C)	Ideal reaction T[a] (°C)	Oxalate yield[b] (%)	Reaction time[c] (min)
NaH[d]	2.5	350	380-420	99	10
NaH	2.5	153	180-200	95	0.5-2
KH	2.5	153	180-200	97	1-2
LiH	2.5	153	180-200	95	1-2
NaNH2	2.5	154	180-200	95	<1
KOH	2.5	327	410-430	63	10-30
-	-	360	420-440	21	150-200

Table 1: Performance indicators of catalysts for coupling of potassium formate. [a] Temperature at which highest yields were achieved. [b] Highest yield achieved with 2.5 wt% catalyst loading. [c] Time at which 90% conversion was achieved. [d] Reference from Lakkaraju et al. using sodium formate and NaH as catalyst.[12] The reaction was observed at 350°C. No observation of reaction starts at melting point of formate.

Out of the tested bases, sodium hydride turned out to be the best option in terms of performances. For this reason, this study was focused on its utilization as active catalyst.

As an initiation step, the superbase abstracts a proton from the formate C-H covalent bond. The two electrons are delocalized on the carbon atom leading to the carbonite species, a CO$_2$ molecule with two delocalized negative charges. This carbonite intermediate is very reactive due to its negative charge high density. For this reason, it can react as a Lewis base with a nucleophilic attack to an electrophile acting as a Lewis acid. In this reaction, the carbonite shares the two surplus electrons to form a new covalent bond between its carbon atom and the targeted species.

This research is focused on the formate coupling step. The general idea is to make use of the reactive carbonite intermediate in the formate coupling reaction. This nucleophile should be

able to react with molecules other than formate as well. Our scope is to investigate different categories of chemicals suitable for this reaction. This alternative coupling could produce valuable products, that might partially compensate the costs for formate production, which is very energy demanding. Potassium was selected as the counter ion for formate because it gives by far the best reduction efficiency. [18] In scheme 4 a reaction with an electron-deficient species is shown as an example. The aim is to investigate the carbonite intermediate reactivity with different electrophiles to obtain new coupling products.


| Formate | Carbonite | e⁻ deficient species | Coupling product |
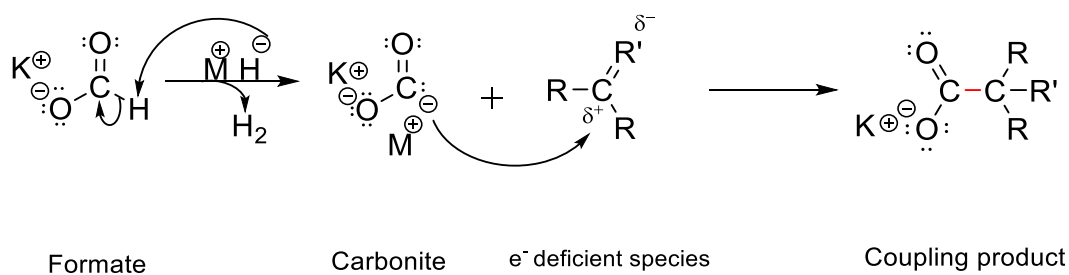
Scheme 4: general mechanism of carbonite formation and reaction with an electrophile.

The identification of suitable reaction partners was based on diverse criteria including aspects of chemistry, engineering, business, and sustainability. In a first step, chemical criteria are used to assess the feasibility of the intended reaction, such as the presence of a partial positive charge. As a second step, include physical properties were included, such as phase transition temperatures. These have an influence on engineering aspects both in the reactor design, separation, and scalability. In a third step, the potential products are evaluated for their attractiveness with regards to economic, ecologic, and social sustainability regarding their applications and environmental impact of the process. The most promising candidates are then tested in proof-of-principle experiments. To confirm the formate incorporation, both online and offline analytic strategies were used. Liquid chromatography (LC), infrared spectroscopy (IR), and nuclear magnetic resonance (NMR) were used as offline methods, to assess the presence of the desired coupling products of the reaction. With in-situ Raman spectroscopy the course of the reaction was followed to gain kinetic information and detect intermediate species. Each reaction partner might need a specific set of analysis. They are discussed in detail in each reaction partner section.

The main criterium that suits our selection are the presence of an electrophilic group in the reaction partner, thermal stability, and reactivity with hydride. Additionally, the potential to

keep up the carbonite formation was considered, by hydride release from the reaction partner to facilitate the upkeep of the catalytic cycle. As the first criterion, a reaction partner is supposed to have an electrophilic group for the nucleophilic attack of formate, so that incorporation of it can be possible. In scheme 5 below the potential coupling partners are illustrated including: molecules that contain an electrophilic carbonyl group, such as aldehydes, ketones, and esters, as well as alkenes, molecules that contain leaving groups, CO_2, and CO.
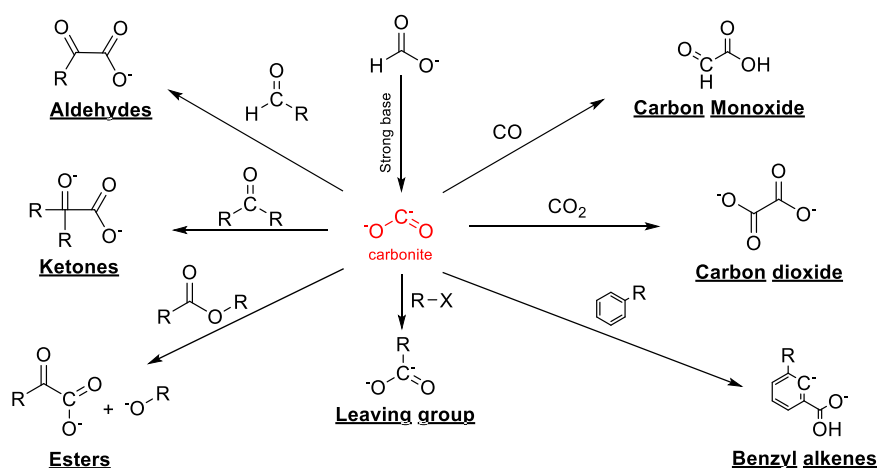
*Scheme 5: Different routes for alternative formate coupling*

The thermal stability of the reaction partner is another variable that must be considered, so that it does not decompose at the reaction conditions. To produce the reactive carbonite species, it is necessary to use a temperature of 170°C. Therefor only candidates with higher decompositions temperature were ranked candidates which decompose at temperatures below 200°C were not considerd. This way it can be certain that the reaction partner does not decompose in the temperature operating window.

Side reactions leading to by-products need to be avoided, as these may interfere with the process. Avoiding side reactions allows better process control aiming to choose operating conditions favoring the synthesis of the main product and maximize selectivity. Most of these side-reactions can be classified into two categories: parallel and consecutive reactions. Consecutive reactions are those occurring sequentially through intermediates or primary products. Parallel reactions are others proceeding along multiple independent pathways starting from a same species.[19] These reaction patterns are represented in scheme 6 below. Reagent A is transformed into C via the reversible formation of intermediate B, and A also undergoes an independent and concurrent reaction to yield product D.
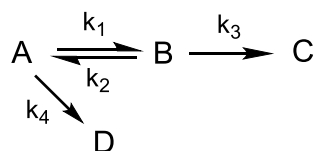
Scheme 6: parallel-consecutive first-order reaction with a reversible first step.

As main parallel unwanted reactions the reaction of the partner with the hydride ion was first considered and assessed, then the reaction within carbonite and formate to produce oxalate (see scheme 7), and decomposition of formate and oxalate to form carbonates (Eq.1 and Eq.2). Changing reaction conditions and the use of a suitable catalyst can change the reaction course and can help to avoid these reactions.

Formate   Carbonite   Formate   Oxalate
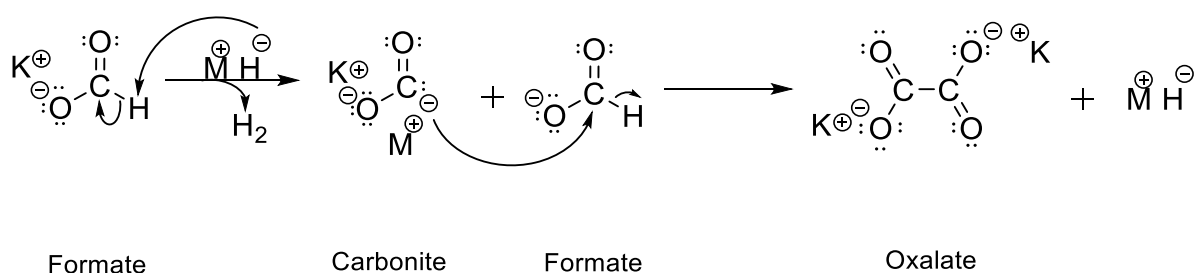
Scheme 7: mechanism of formate coupling via carbonite intermediate

$$2HCOOK \rightarrow K_2CO_3 + H_2 + CO \qquad\qquad\qquad\text{(Eq.1)}$$

$$K_2C_2O_4 \rightarrow K_2CO_3 + CO \qquad\qquad\qquad\text{(Eq.2)}$$

As consecutive reactions we may consider the possibilities of the primary products to engage in reactions with reagents and products such as condensation reactions. The hydride ion could interact with the reaction partner acting like a base or a reducing agent. The former case it is particularly likely for carbonyl compounds that can undergo enolization if treated with strong bases and for molecules with protons with higher acidity then formate. An example of this reaction is shown with a generic aldehyde in scheme 8 below.
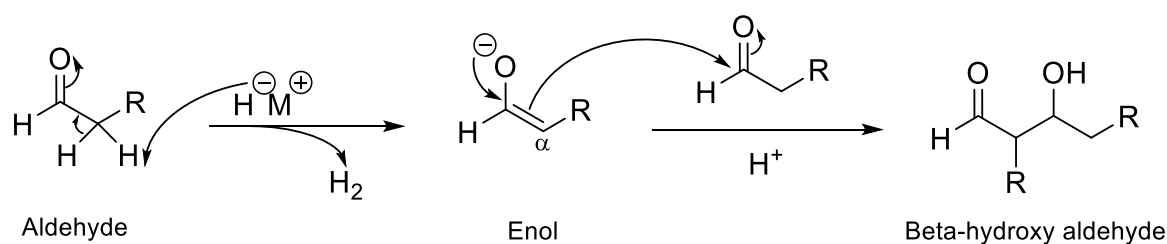
Scheme 8: Aldol reaction which lead to unwanted products.

The hydride ion deprotonates the aldehyde at the α-carbon leading to the enol species. Moreover, the enolate can further react at the α-carbon with the carbonyl of another aldehyde molecule to obtain β-hydroxy aldehyde. These reactions would reduce the amount of hydride available for carbonite formation and lead to a mixture of products which is difficult to analyze and separate. In the evaluation process the reactivity of the reactants with hydride was ranked in the categories low, medium, high. Low reactivity includes molecules with protons with lower acidity then formate and not prone to form enols for α-hydrogen abstraction. Medium reactivity includes molecules with protons with similar acidity then formate and/or prone to form enol for α-hydrogen abstraction. High reactivity includes molecules with protons with higher acidity then formate (e.g. –OH; -COOH, $-NH_4$) and/or highly prone to form enol for α-hydrogen abstraction. The hydride ion could attack the carbonyl carbon by nucleophilic addition, acting as a reducing agent. This might happen according to the basic strength of the metal hydride and the reactivity of the carbonyl compound. [20]; this is a possible outcome that needs to be verified empirically and has to be considered as a side reaction.

Physical properties of the reaction partner have impact on the overall process, so they cloud be tuned to ease of products separation and overall process. A reactants phase at room temperature and the boiling point of the reaction partner can be determinant. They can ease the overall process and make it more efficient for the success of the reaction. Particularly, in considering all the means feasible for this investigation on lab scale. Using a liquid partner would ease the process of introduction, moreover it could serve as a solvent/dispersant for formate and hydride. For these reasons, using a liquid partner is a preferable option. Another option for CO_2, CO and other gas reaction partners, is to use either a large excess of it, to pressurize the reactor with the reactants or to bubble it thought the reagents once melted.

A detailed section was dedicated for each of the categories of coupling partners. In particular, the selection process for the best candidates to perform experiments and possible side reactions

are discussed. Besides, practical aspects to perform the tests were included, such as separation strategies of the products and their analysis.

1.1 Aldehydes

The first group of possible reaction partners is aldehydes. They are a highly reactive class of compounds and engage in many reactions, like catalyzed reduction reactions to obtain primary alcohols, oxidation reaction to get the corresponding carboxylic acids, and nucleophilic addition to obtain diverse products.[21][22][23] For this reason, they are attractive building blocks for differentiated products, such as resins, plasticizers, solvents or pharmaceutical.[24][25][26] For reactions with highly reactive carbonites, nucleophilic addition reactions at the aldehyde's carbonyl group are an appealing option.

As a result of the reaction, according to the chosen aldehyde, alpha-keto acids are obtained, which share a ketone group vicinal to a carboxylic group in their molecular structure (see figure 3).
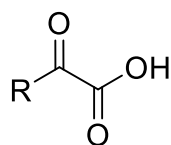

Alpha-keto acid

Figure 3: general structure for alpha-keto acids.

The applications for this kind of product can be diverse, for instance, they can serve as monomers for the manufacture of polymers as well as intermediates for chemical synthesis in the development of pharmaceuticals. [27][28]

The expected reaction mechanism with an aldehyde is presented in scheme 9 below. The first step of the reaction involves formate and hydride, where the latter acts as a catalyst characterized by powerful basic strength. The highly nucleophilic carbonite dianion attacks the electrophilic carbon of the aldehyde. The resulting tetrahedral intermediate then collapses and leads to the desired product and hydride anion is released. This way the catalyst is regenerated.

The elimination step confers a negative charge to leaving group. The tetrahedral intermediate might eliminate another group rather than hydride when collapsing. This might be the case when the leaving group shows peculiar stability with a negative charge. In other words, It might occur that the C-C bond rather than the C-H bond is broken during the elimination step, leading

to different reaction products that are not in our primary interest and may be difficult to assess. This is a possible issue that needs to be considered when assessing the products of the reaction.
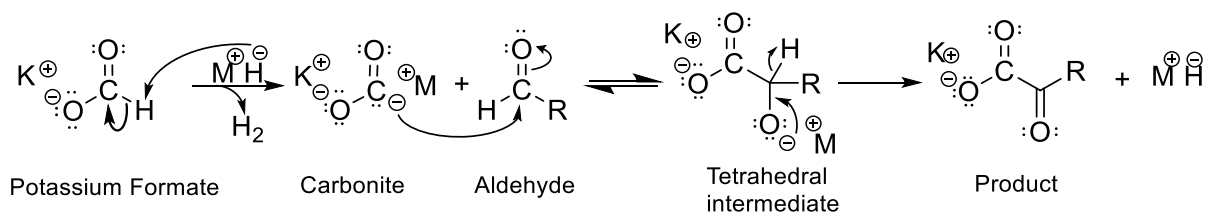
Scheme 9: General reaction mechanism for the coupling of formates with aldehydes via carbonite as the reactive intermediate.

In table 2 commonly available aldehydes that are used in large quantities in the chemical industry are presented. Only aldehydes with a decomposition temperature above 200°C are considered. Their suitability in the reaction was evaluated, starting from the simplest to more complex structures.

Table 2: List of aldehydes candidates for coupling with formate, physical properties and reactivity towards nucleophilic attack by hydride.

Reactant	Reactivity with Hydride	Phase at formate activation	Melting point °C	Boiling point °C
Para-Formaldehyde	low	gas	120-170	-
Acetaldehyde	high	gas	-	21
Propionaldehyde	high	gas	-80	49
Butyraldehyde	high	gas	-	76
Acrolein	low	gas	-	53
Crotonaldehyde	low	gas	-	104
Formylcyclohexane	medium	gas/liq	-	161
Benzaldehyde	low	liq	-26	178
Glucose	high	liq	150	-
Furfural	low	Gas/liq	-37	162
Methylbenzaldehyde	low	liq	-	200

Cinnamaldehyde	low	liq	-	248
Glutaraldehyde	high	liq	-14	187
Phtalaldehyde	low	liq	56	266

The first selection criterium is the aldehyde's potential reactivity with hydride. By virtue of their reactivity, aldehyde can readily undergo enolization. The only aldehydes where enolization is no occurring are (para)-formaldehyde, acrolein, benzaldehyde, crotonaldehyde, furfural, methylbenzaldehyde, cinnamaldehyde, and phataldehyde. The last two selection criteria are related to the physical property of the reaction partner, in particular its state at room temperature and its boiling point, which can play a role in easing the overall process and make it more efficient for the success of the reaction as stated. Out of preview listed aldehydes only Formaldehyde, Benzaldehyde, Methylbenzaldehyde, Cinnamaldehyde and Phataldehyde are liquid at the reaction temperature. As best suitable candidates for the reaction benzaldehyde and cinnamaldehyde were selected. Para-formaldehyde was also included, as it creates a possible pathway to produce directly glyoxylic acid.

1.1.1 Benzaldehyde

Benzaldehyde is the simplest aromatic aldehyde and is widely used by the chemical industry to produce fine chemicals and specialties, for example to formulate cosmetics, fragrances and flavoring agents. [29] It represents a valuable option for the formate coupling as it is liquid at room temperature, has a relatively high its boiling point does not have α-hydrogens which can react with hydride.

For the desired reaction, a possible mechanism is shown on scheme 10 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the benzaldehyde. The expected outgoing products of the coupling are phenylglyoxylate and hydride anion, which allows the upkeep of the catalyst to further react with other formate.

| Formate | Carbonite | Benzaldehyde | | Phenylglyoxylate |
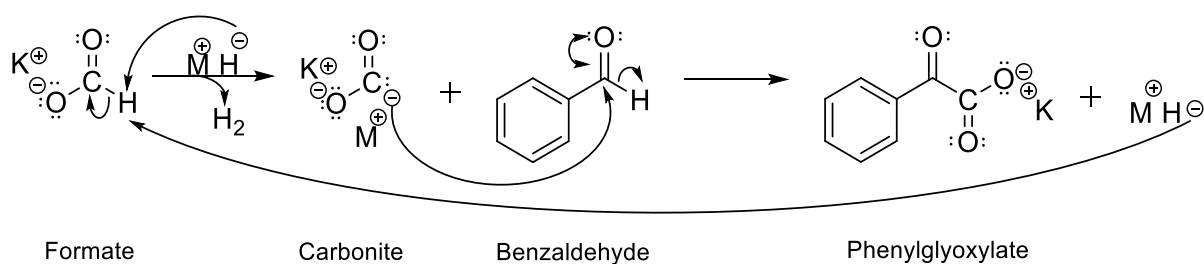
Scheme 10: Reaction mechanism for the coupling of formate with benzaldehyde via carbonite as the reactive intermediate

Phenylglyoxylic acid is the desired product of the coupling reaction of formate with benzaldehyde. It can be obtained by acidification of phenylglyoxylate. At atmospheric pressure, phenylglyoxylic acid has a melting point of 66°C and a boiling point of 147-151°C (see on table 3 below). At standard condition of temperature and pressure phenylglyoxylic acid is solid, while benzaldehyde (mp -26°C) is liquid. This would ease the separation process of reagents and products, achievable with a filtration step. Another separation strategy might be distillation, but since phenylglyoxyliyc acid and benzaldehyde have their boiling points in a close range (147-151°C against 178°C), it may not be the best choice.

Table 3: Physical properties of phenylglyoxylic acid, desired coupling product of formate with benzaldehyde.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)
Phenylglyoxylic acid		611-73-4	66	147-151

Phenylglyoxylic acid can be used as an intermediate for the synthesis of pharmaceuticals as well as monomer to produce poly(α-esters).[30][31] A current process to produce Phenylglyoxylic acid uses mild conditions via electrochemically activated insertion of carbon dioxide into benzoyl halides. However, only benzoyl bromide affords good yields (88%).[32]

Potential side reactions include reaction with hydride with the reaction partner, subsequent reaction of the obtaining product and Cannizzaro reaction. A first side reaction involves potassium hydride acting as a reducing agent for benzaldehyde, where the hydride directly attacks the electrophilic carbon of the aldehyde and leads to phenylmethanolate (see scheme 11). This reaction was reported by Govindan and Pinnick (1981), however cryptands were used to enhance the basic strength of the hydride, a condition that is not present in the formate

coupling. [33] In any case, the direct reduction by hydride is a possible side reaction that needs to be taken in account for all the reaction partner with a carbonyl group. A possibility to lessen the tendency through this reaction could implicate a less basic hydride, for instance sodium hydride.
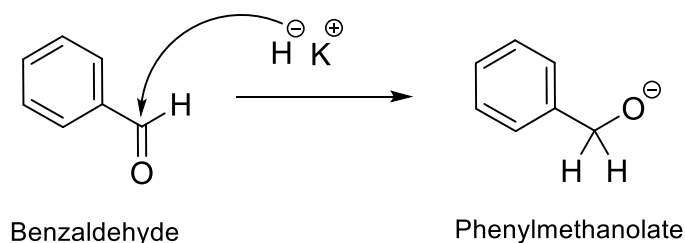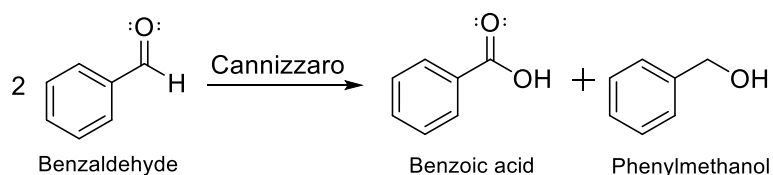

Scheme 11: Side reaction mechanism of benzaldehyde reacting with potassium hydride

In 1981 Govindan and Pinnick reported another possible reaction of benzaldehyde with potassium hydride. [33] Potassium hydride could attack the electrophilic carbon of the benzaldehyde, leading to phenylmethanolate (see scheme 12). This is due to the powerful basic strength of potassium hydride, further enhanced by the presence of potassium ion specific 18-crown-6. Then this anion would attack another benzaldehyde molecule and form a tetrahedral intermediate. After elimination, the expected products would be benzyl benzoate and hydride anion.
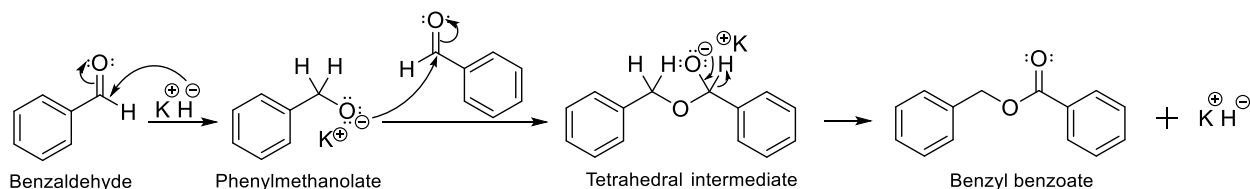
Scheme 12: Side reaction mechanism of benzaldehyde reacting with potassium hydride

Aldehydes without α-hydrogens treated in strong basic conditions are prone to undergo Cannizzaro reaction[34], shown in the scheme 13 below. The presented side reaction involves two molecules of benzaldehyde in which one is oxidized to benzoic acid and the other reduced to phenylmethanol. This reaction requires a hydroxide ion molecule to happen. It is crucial to use a dry environment and dry reagents as even small traces of moist would interfere with the reaction, both deactivating the catalyst and causing this side reaction to occur.

Lastly, inert atmosphere is needed to prevent oxidation of benzaldehyde to benzoic acid, which occur also at room temperature.[35]

To conclude, benzaldehyde is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. It is not prone to enolization, so it should poorly react with the metal hydride. Finally, there is a significant difference in melting point of benzaldehyde and phenylglyoxylic acid. It is possible to exploit this difference to separate them and isolate the product.

1.1.2 Cinnamaldehyde

Cinnamaldehyde is an active aromatic compound, widely studied for its peculiar antimicrobial and antioxidant properties. It is naturally occurring predominantly as the trans (E) isomer, and it is responsible for cinnamon's flavour and odour. In the chemical industry, it is considered a fine chemical, used as a flavour additive as well as in the development of pharmaceuticals for its medicinal properties.[36] Cinnamaldehyde represents a valuable candidate for the formate coupling as it is liquid at room temperature, has a relatively high boiling point. It is unlikely to react with hydride although it has an α-hydrogen, since the hydrogen is tightly bonded to a sp2 carbon.
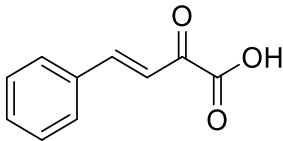
For the desired reaction, a possible mechanism is shown on scheme 14 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the cinnamaldehyde. The expected outgoing products of the coupling are benzylidene pyruvate and hydride anion, which allows the upkeep of the catalyst to further react with other formate.

Formate   Carbonite   Cinnamaldehyde   Benzylidene pyruvate
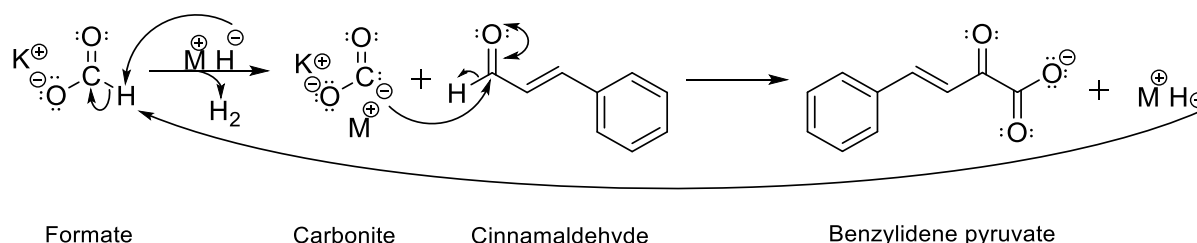
Scheme 14: Reaction mechanism for the coupling of formate with cinnamaldehyde via carbonite as the reactive intermediate

Benzylidene pyruvic acid is the desired product of the coupling reaction of formate with cinnamaldehyde. It can be obtained by acidification of benzylidene pyruvate. At atmospheric pressure, the final product has a melting point of 61-62°C and a boiling point of 320°C (see on table 4 below). At standard condition of temperature and pressure benzylidene pyruvic acid is solid, while cinnamaldehyde is viscous liquid. This would ease the separation process of reagents and products, achievable with a filtration step.

Table 4: Physical properties of benzylidene pyruvic acid, desired coupling product of formate with cinnemaldehyde.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Benzylidene pyruvic acid		17451-19-3	61-62	319.7	161.3

The product of interest belongs to a class of compounds Arylidene pyruvic acids (APAs), in their simplest form are molecules containing an aryl moiety, double bond, carbonyl group and an acid functionality, respectively (See figure 4). They have distinct structural features for synthetic organic chemists and can behave as Michael acceptors, enones, dienophiles, ketones, carboxylic acids, α-ketoacids, etc. This feature facilitates the synthesis of complex molecules by starting from APAs and have gradually attracted much attention, due to their importance as precursors. [37] A reaction reported in literature to obtain benzylidene pyruvic acid involves condensation of 2-oxosuccinic acid with benzaldehyde, followed by decarboxylation.[38]

Arylidene pyruvic acid (APA)

Figure 4: general structure for arylidene pyruvic acids.
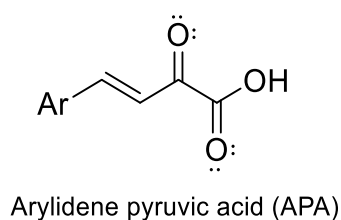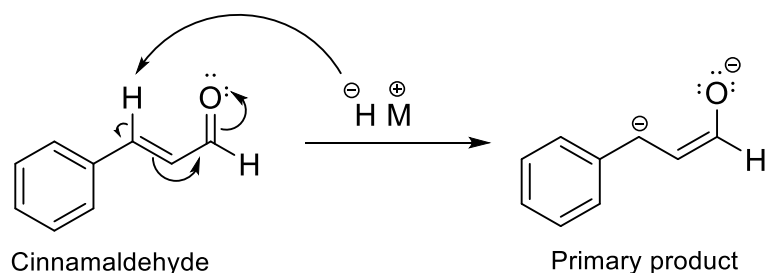
Potential side reactions include reaction with hydride with cinnamaldehyde, subsequent reaction of the obtaining product and retro Aldol condensation of the product. The first possible side reaction involves cinnamaldehyde and hydride, where the latter acts as a base causing deprotonation of the β-carbon, as shown in scheme 15. This primary product could further react

acting as a nucleophile. However, this primary product is not as stable as 1-3 dicarbonyls which are stabilized through resonance, so it might not be formed; this is a possible outcome to keep in mind in assessing the reaction products.

Scheme 15: Side reaction mechanism of cinnamaldehyde reacting with hydride.

Another potential side reaction involves the product benzylidene pyruvic acid, which could undergo a retro Aldol condensation if treated in alkaline conditions, leading to benzaldehyde and pyruvic acid, as shown in scheme 16. [37]
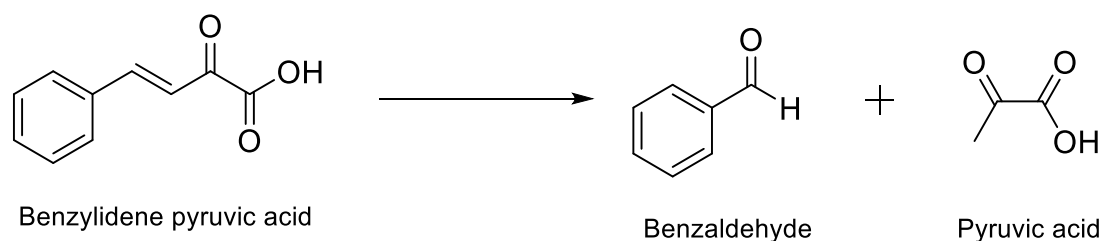
Scheme 16: Side reaction of benzylidene pyruvic acid treated in alkaline conditions.

To conclude, cinnamaldehyde is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. It is not prone to enolization, so it should poorly react with the metal hydride. Finally, there is a significant difference in melting point of cinnamaldehyde and benzylidene piruvic acid. It is possible to exploit this difference to separate them and isolate the product.
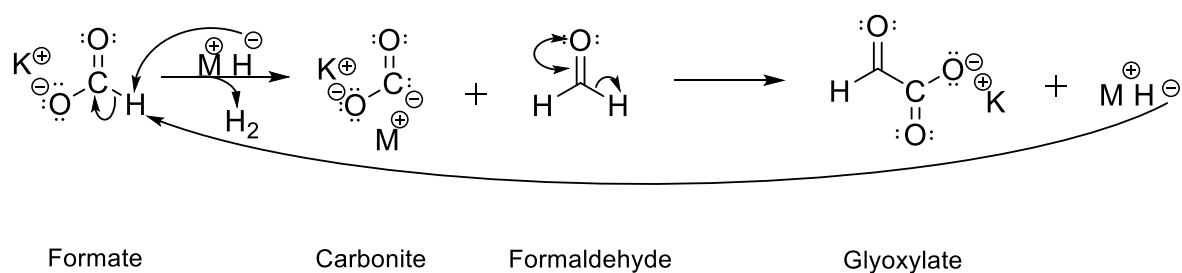
1.1.3 Formaldehyde

Formaldehyde is a natural occurring chemical, as a metabolic product in plants and animals or photochemically produced from organic material in the atmosphere. Generally, it occurs in low but measurable concentrations and due to its powerful reactivity is regarded as a highly harmful chemical.[33] However, formaldehyde is an important industrial chemical, used in the

manufacture of diverse industrial products and consumer goods. More than 50 branches of industry now use formaldehyde. It is used mainly in the form of aqueous solutions and formaldehyde-containing resins. Nowadays it is industrially produced by heating methanol vapor in presence of a catalyst. [34]

According to the selection criteria, formaldehyde does not fit the characteristic for a good reaction partner. It is susceptible to temperature, since decomposes into methanol and carbon monoxide at temperatures above 150°C, though uncatalysed decomposition is slow at temperatures below 300°C. [35] Apart from being toxic and difficult to handle, formaldehyde is highly reactive and could lead to a mixture of undesired products.

However, the coupling of formaldehyde with formate could lead directly to glyoxylic acid, a product of great interest. For this reason, it was decided to consider formaldehyde as a reaction partner. Besides from using it in gas phase, it was also considered the possibility of using its derivative polymer para-formaldehyde, which is in solid phase at atmospheric conditions.
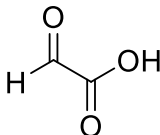
For the desired reaction, a possible mechanism is shown on scheme 17 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the formaldehyde. The expected outgoing products of the coupling are glyoxylate and hydride anion, which allows the upkeep of the catalyst to further react with other formate.

Formate   Carbonite   Formaldehyde   Glyoxylate

Scheme 17: Reaction mechanism for the coupling of formate with formaldehyde via carbonite as the reactive intermediate

Glyoxylic acid is the desired product of the coupling reaction of formate with formaldehyde. It can be obtained by acidification of glyoxylate. At atmospheric pressure, the final product has a melting point range of 48-52°C and a boiling point of 100°C (see on table 5 below). At standard condition of temperature and pressure glyoxylic acid is solid, while formaldehyde is gas. This would ease the separation process of reagents and products, achievable with a filtration step. Another option is to use distillation as separation process.

Table 5: Physical properties of glyoxylic acid, desired coupling product of formate with formaldehyde.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Glyoxylic acid		563-96-2	48-52	100	>110

Glyoxilic acid is an important component in fine organic synthesis and is widely used owing to its bifunctional nature. It is used in pharmaceutical, food, and perfume industry. Two of the major production processes that use this aldo-acid are the synthesis of vanilline and allatoin. Examples of how glyoxilic acid can be obtain are oxidation of glycolic acid, glyoxal, ethanol and various other compounds. A major throwback in the current methods often consists of high costs associated with the whole process. [39]

Due to the significant reactivity of formaldehyde, particularly if concentrated, several side reactions can occur. In scheme 18 are presented some possible side reaction: initial step of Formose reaction, photo-oxidation, thermal decomposition, and reaction with metal hydride. In basic condition, formaldehyde can undergo an autocatalytic reaction called Formose reaction, which involves the formation of sugars, polyols and hydroxy acid in a series of carbon-to-carbon condensations.[40] Under atmospheric conditions, formaldehyde is readily photo-oxidized by sunlight to carbon dioxide. However, a metal catalyst seems to enhance the process.[41] Formaldehyde can also undergo thermal decomposition to hydrogen and carbon monoxide, and methanol, with the former being the predominant mechanism. However, the process seems to be relevant only at temperature above 500°C. [42]

Finally, formaldehyde could potentially react with the metal hydride, causing hydrogen abstraction. In this case, this species could further react and lead to oligomerization products. An example of these products is polyoxymethylene.
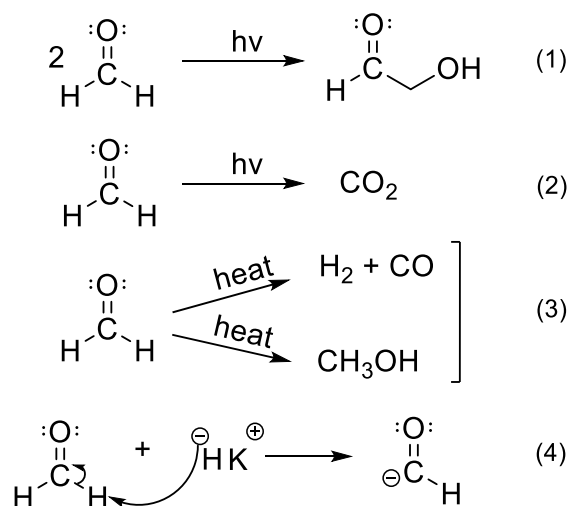
Scheme 18: side reaction of formaldehyde; (1) initial step of Formose reaction (2) photo-oxidation (3) thermal decomposition (4) abstraction of H from formaldehyde

Regarding the desired product glyoxylic acid, it could react with the metal hydride. The resulting hydrogen abstraction (see scheme 19) would lead to an active species that could cause further polymerization reactions.
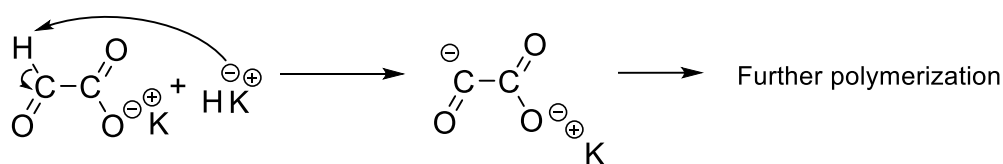
Scheme 19: side reaction of glyoxylic which undergo further deprotonation by hydride

To conclude, even if formaldehyde pose some difficulties for the reaction, it represents an appealing candidate for the coupling with carbonite, due to the attractiveness of the main product. The source of formaldehyde can be used either in gas or solid phase by using its polymer para-formaldehyde. In the latter case, formaldehyde is released under heating by depolymerization. At room temperature and atmospheric pressure, formaldehyde is in gas phase while glyoxylic acid is solid. For this reason, the separation process should be eased.

1.2 Esters

A second group of possible reaction partners is esters. They are naturally abundant, and they can be readily synthesized from acids. [43][44] They are also present in essential biological molecules and have diverse commercial and synthetic applications. For instance, esters can serve as monomers for the production of excellent fibers, as well as for the production of PET (polyethylene terephthalate), the most important polyester. Moreover, polyesters materials can

be employed in medical applications, being biologically inert.[45] For reactions with highly reactive carbonites, nucleophilic addition reactions at the ester's carbonyl group are an appealing option.

As a result of the reaction, according to the chosen ester, alpha-keto acids are obtained, which share a ketone group vicinal to a carboxylic group in their molecular structure (see figure 5).
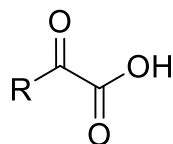

Alpha-keto acid

Figure 5: general structure for alpha-keto acids.

The applications for this kind of product can be diverse, for instance, they can serve as monomers for the manufacture of polymers as well as intermediates for chemical synthesis in the development of pharmaceuticals. [27][28]

The expected reaction mechanism with an ester is presented in scheme 20 below. The first step of the reaction involves formate and hydride, where the latter acts as a catalyst characterized by powerful basic strength. The highly nucleophilic carbonite dianion attacks the electrophilic carbon of the ester. The resulting tetrahedral intermediate then collapses and leads to the desired product and alkoxide anion is released. This way the catalyst is not regenerated during the reaction

The elimination step confers a negative charge to leaving group. The group that is more likely to be eliminated is the alkoxide ion, which is considered a good leaving group due to its stability with a negative charge.

Potassium Formate   Carbonite   Ester   Tetrahedral intermediate   Product
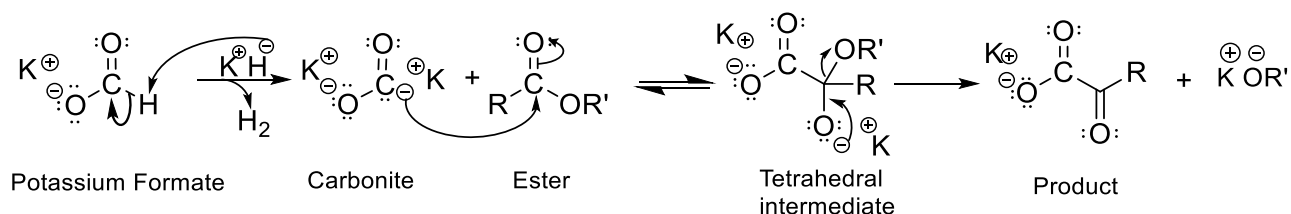
Scheme 20: General reaction mechanism for the coupling of formate with esters via carbonite as the reactive intermediate.

In table 6 commonly available esters that are used in large quantities in the chemical industry are presented. Only esters with a decomposition temperature above 200°C are considered. Their suitability in the reaction was evaluated, starting from the simplest to more complex structures.

Table 6: List of esters candidates for coupling with formate, physical properties, and reactivity towards nucleophilic attack by hydride.

Reactant	Reactivity with Hydride	Phase at formate activation	Melting point °C	Boiling point °C
Dimethyl terephthalate	low	gas/liquid	142	288
methyl butyrate	high	gas	-85	102
ethyl butyrate	high	gas	-101	121
pentyl acetate	high	gas/liquid	-71	148
isopentyl acetate	high	gas/liquid	-79	142
benzyl acetate	high	liquid	-51	215
pentyl butyrate	high	liquid	-73	185
octyl acetate	high	liquid	-39	210
Methyl benzoate	low	liquid	-12,5	199
Methyl cinnamate	low	liquid	35	261

The first selection criterium is the ester's potential reactivity with hydride. Ester can undergo enolization and subsequent Claisen condensation, leading to β-keto esters. The only esters where enolization is less likely to occur are methyl terephthalate, methyl benzoate, and methyl cinnamate. The last two selection criteria are related to the physical property of the reaction partner, in particular its state at room temperature and its boiling point, which can play a role in easing the overall process and make it more efficient for the success of the reaction. Out of preview listed esters, methyl terephthalate and methyl cinnamate are solid at room temperature and liquid at the reaction temperature. Methyl benzoate is liquid at both room temperature and reaction temperature. These three esters were selected as best suitable candidates for the reaction.

1.2.1 Methyl terephthalate

Dimethyl terephthalate is widely used in the chemical industry and is readily obtained by oxidation of p-xylene.[46] to produce saturated polyesters with aliphatic diols as the comonomer. These includes polyethylene terephthalate (PET), and polybutylene terephthalate (PBT). [47]
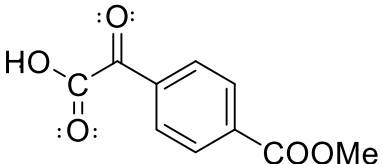
It represents a valuable option for the formate coupling as it is liquid at the reaction temperature, has a relatively high its boiling point, and does not have α-hydrogens which can react with hydride. For the desired reaction, a possible mechanism is shown on scheme 21 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the dimethyl terephthalate. The expected outgoing products of the coupling are oxalyl benzoic acid methyl ester and methoxide anion. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.

| Formate | Carbonite | Dimethyl terephthalate | Product |
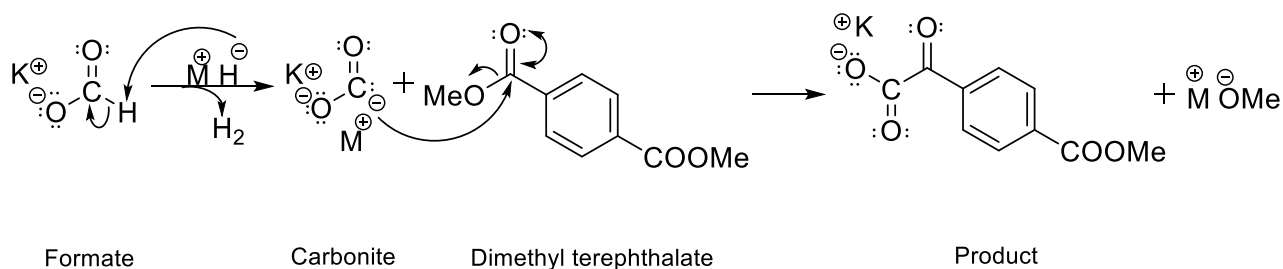
Scheme 21: Reaction mechanism for the coupling of formate with dimethyl terephthalate via carbonite as the reactive intermediate

Oxalyl benzoic acid methyl ester is the desired product of the coupling reaction of formate with DMT. It can be obtained by acidification of the product. There are not available data for the melting point nor boiling point of oxalyl benzoic acid methyl ester. The presence of an alcoholic group in the final product could be exploited, which confers a difference in polarity with the dimethyl terephthalate (see table 7 below).

Table 7: Physical properties of Oxalyl benzoic acid methyl ester, desired coupling product of formate with DMT.

Name	Structure	InchI	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Oxalyl benzoic acid methyl ester		InChI=1S/C10H8O5/c1-15-10(14)7-4-2-6(3-5-7)8(11)9(12)13/h2-5H,1H3,(H,12,13)	/	/	/

This product can serve as a building block for fine chemicals. There are various patents reporting this product as a possible intermediate for the manufacturing of cancer therapeutics, such as SHP2 inhibitors. [48][49][50]

A potential side reaction that can occur is shown in scheme 22 below. It involves the metal hydride acting as a reducing agent with dimethyl terephthalate, either at one of the carbonyls or both functionalities. This reaction would lead to alkoxide species.

Dimethyl terephthalate   Primary product
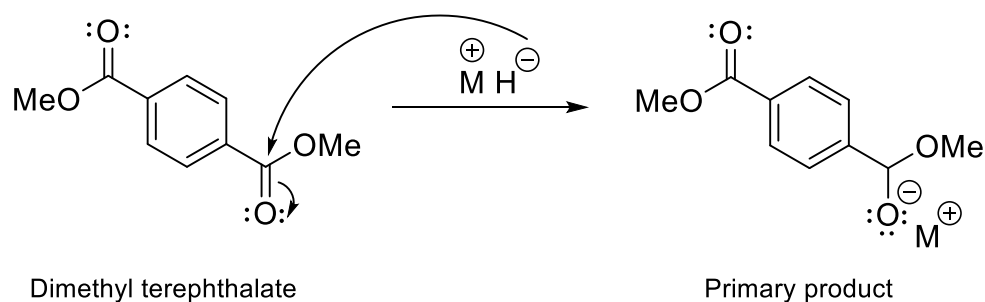
*Scheme 22: Side reaction mechanism of DMT reacting with the metal hydride*

To conclude, dimethyl terephthalate is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. It is not prone to enolization, so it should poorly react with the metal hydride. Finally, the difference in polarity within the product and DMT could be exploited to separate them from the reaction mixture.

1.2.2 Methyl benzoate

Methyl benzoate can be produced by the condensation of benzoic acid and methanol, treated in strong acidic conditions.[51]

It represents a valuable option for the formate coupling as it is liquid at the reaction temperature, has a relatively high its boiling point, and does not have α-hydrogens which can react with

hydride. For the desired reaction, a possible mechanism is shown on scheme 23 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the dimethyl terephthalate. The expected outgoing products of the coupling are benzoylformate and methoxide anion. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.

Formate   Carbonite   Methyl benzoate   Benzoylformate
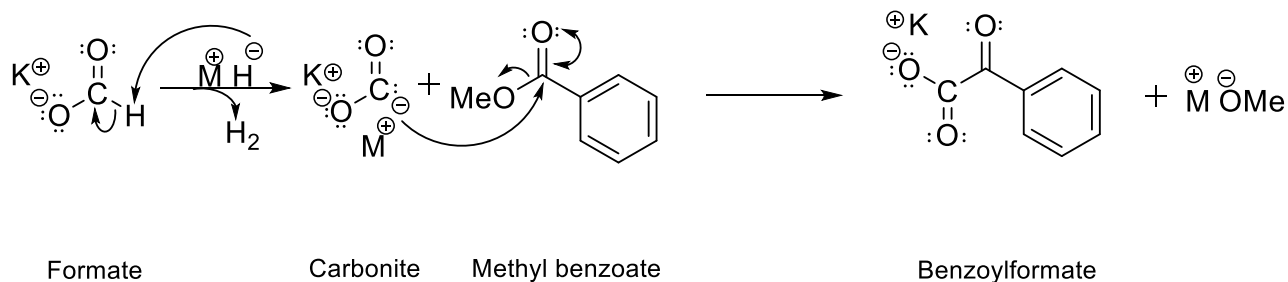
Scheme 23: Reaction mechanism for the coupling of formate with methyl benzoate via carbonite as the reactive intermediate

Benzoyl formic acid is the desired product of the coupling reaction of formate with methyl benzoate. It can be obtained by acidification of the product. At atmospheric pressure, the final product has a melting point of 66°C and a boiling point of 163°C (see on table 8 below). At standard condition of temperature and pressure benzoyl formate is solid, while methyl benzoate is liquid. This would ease the separation process of reagents and products, achievable with a filtration step. Another option is to use distillation as separation process.

Table 8: Physical properties of benzoyl formic acid, desired coupling product of formate with methyl benzoate.

Name	Structure	CAS number	Melting point °C	Boiling point °C (150 mmHg)	Flash point (°C)
Benzoyl formic acid		611-73-4	66	163	/

Benzoyl formic acid belongs to the class of organic compounds known as benzoyl derivatives. These are organic compounds containing an acyl moiety of benzoic acid. It is classified as a human metabolite.[52] This product could be involved in the manufacturing of specialties and

pharmaceuticals. It is an important intermediate for the drugs of thromboxane synthetase inhibitors as well as antihypertensive agents. [53]

A potential side reaction that can occur is shown in scheme 24 below. It involves the metal hydride acting as a reducing agent with methyl benzoate. This reaction would lead to alkoxide species.


Methyl benzoate   Methoxy(phenyl)methanolate
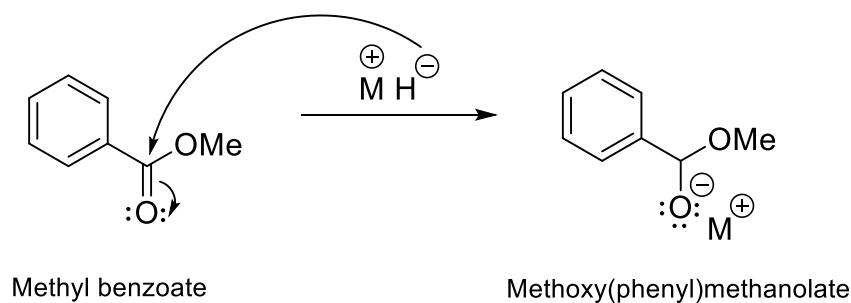
Scheme 24: Side reaction mechanism of methyl benzoate reacting with the metal hydride.

To conclude, methyl benzoate is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. It is not prone to enolization, so it should poorly react with the metal hydride. Finally, there is a significant difference in both the melting point and boiling point of benzoyl formic acid and methyl benzoate. These differences could be exploited to isolate the product.

1.2.2 Methyl cinnamate

Methyl cinnamate is widely used in the chemical industry as a fine chemical to specialties such as perfumes and flavors. It is found in nature in a variety of fruits and plants.[54]

It represents a valuable option for the formate coupling as it is liquid at the reaction temperature, has a relatively high its boiling point, and do not α-βhydrogens that are unlikely to react with hydride. For the desired reaction, a possible mechanism is shown on scheme 25 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the methyl cinnamate. The expected outgoing products of the coupling are benzylidene pyruvate and methoxide anion. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.

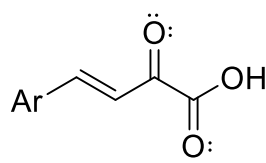| Formate | Carbonite | Methyl cinnamate | Benzylidene pyruvate |
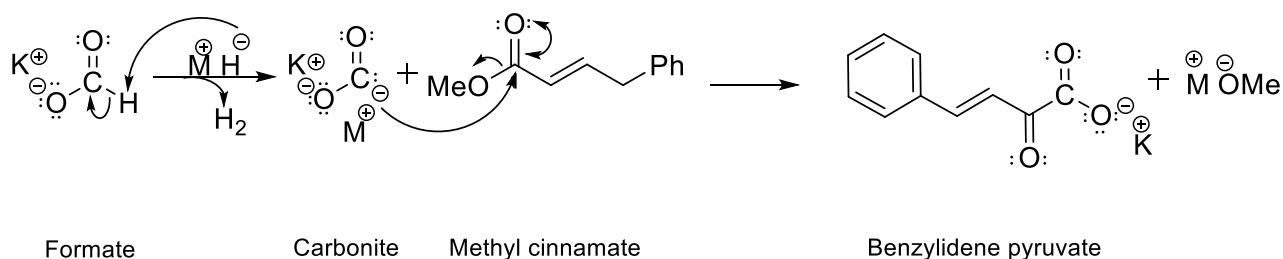
Scheme 25: Side reaction mechanism of methyl cinnamate reacting with the metal hydride.

Benzylidene pyruvic acid is the desired product of the coupling reaction of formate with methyl cinnamate. It can be obtained by acidification of the product. At atmospheric pressure, the product has a boiling point of 320°C (see on table 9 below), and a melting point of 61-62°C. The separation process could be achieved by exploiting the difference in boiling point as well as the difference in melting point between benzylidene pyruvic acid and methyl cinnamate.

Table 9: Physical properties of benzylidene pyruvic acid, desired coupling product of formate with methyl cinnamate.

| Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Benzylidene pyruvic acid		17451-19-3	61-62	320	161

The product of interest belongs to a class of compounds Arylidene pyruvic acids (APAs), in their simplest form are molecules containing an aryl moiety, double bond, carbonyl group and an acid functionality, respectively (See figure 6). They have distinct structural features for synthetic organic chemists and can behave as Michael acceptors, enones, dienophiles, ketones, carboxylic acids, α-ketoacids, etc. This feature facilitates the synthesis of complex molecules by starting from APAs and have gradually attracted much attention, due to their importance as precursors. [37] A reaction reported in literature to obtain benzylidene pyruvic acid involves condensation of 2-oxosuccinic acid with benzaldehyde, followed by decarboxylation.[38]


Arylidene pyruvic acid (APA)

A potential side reaction that can occur is shown in scheme 26 below. It involves the abstraction of a proton of methyl cinnamate by the metal hydride, leading to an enolate primary product that could engage in further reactions. However, the abstraction of the hydrogen is unlikely to happen. This because the carbon that carries the proton at issue is sp2 hybridized, so their bond is stronger and less prone to break.

Methyl cinnamate   Primary product
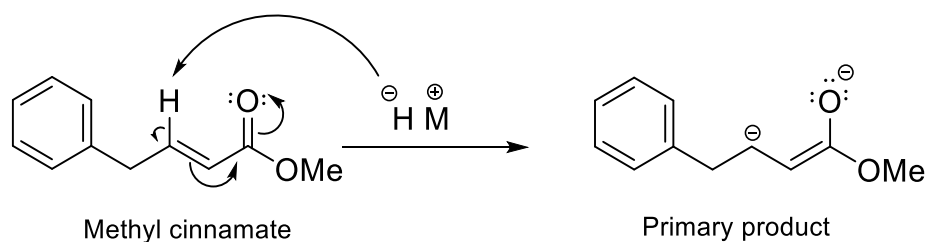
Scheme 26: Side reaction mechanism of methyl cinnamate reacting with the metal hydride to form the corresponding enolate

Another potential side reaction that can occur is shown in scheme 27 below. It involves the metal hydride acting as a reducing agent with methyl cinnamate. This reaction would lead to alkoxide species.

Methyl cinnamate   Product
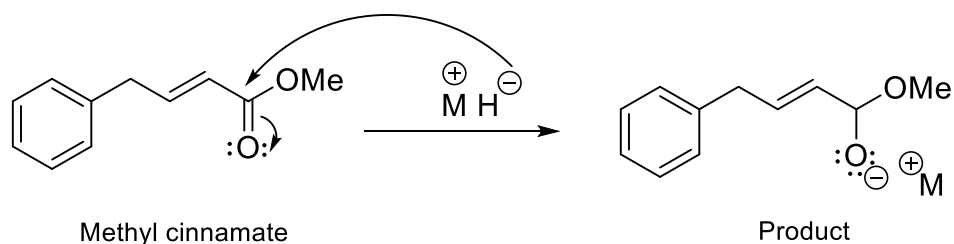
Scheme 27: Side reaction mechanism of methyl cinnamate reacting with the metal hydride as a reducing agent

To conclude, methyl cinnamate is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. It is not prone to enolization, so it should poorly react with the metal hydride. Finally, there is a significant difference in both the melting point and boiling point of benzylidene pyruvic acid and methyl cinnamate. These differences could be exploited differences to isolate the product.

1.3 Ketones

A third group of possible reaction partners is ketones. They are of relevant importance in the chemical industry as well as in biology. They are produced in bulk quantities as commodities

as well as fine chemicals, such as solvents, polymer precursors and pharmaceuticals. [55][56] Ketones engage in many reactions towards nucleophile substitution at the carbonyl functionality.[57] For reactions with highly reactive carbonites, nucleophilic addition reactions at the ketone's carbonyl group are an appealing option.

As a result of the reaction, according to the chosen ketone, alpha-keto acids are obtained, which share a ketone group vicinal to a carboxylic group in their molecular structure (see figure 7).
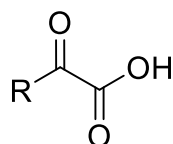

Alpha-keto acid

Figure 7: general structure for alpha-keto acids.

The applications for this kind of product can be diverse, for instance, they can serve as monomers for the manufacture of polymers as well as intermediates for chemical synthesis in the development of pharmaceuticals. [27][28]

The expected reaction mechanism with a ketone is presented in scheme 28 below. The first step of the reaction involves formate and hydride, where the latter acts as a catalyst characterized by powerful basic strength. The highly nucleophilic carbonite dianion attacks the electrophilic carbon of the ketone. The resulting tetrahedral intermediate then collapses and leads to the desired product and carbanion is released. This way the catalyst is not regenerated during the reaction.

The elimination step confers a negative charge to leaving group. The group that is more likely to be eliminated depends on the molecular structure of the ketone. However, to eliminate a carbanion is an unlikely outcome of the reaction, due to the relatively instability of the R^- group.

Potassium Formate   Carbonite   Ketone   Tetrahedral intermediate   Product
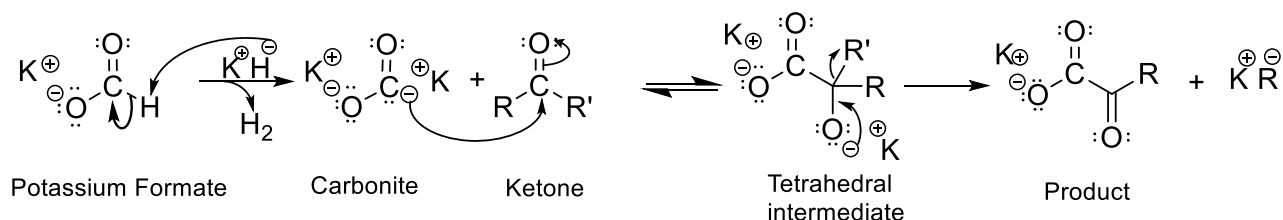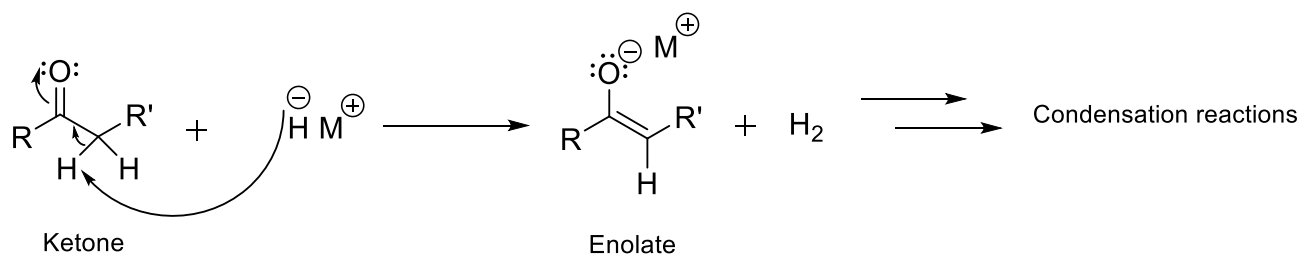
Scheme 28: General reaction mechanism for the coupling of formate with ketones via carbonite as the reactive intermediate.

In table 10 commonly available ketones that are used in large quantities in the chemical industry are presented. Only ketones with a decomposition temperature above 200°C are considered. Their suitability in the reaction was evaluated, starting from the simplest to more complex structures.

Table 10: List of ketones candidates for coupling with formate, physical properties, and reactivity towards nucleophilic attack by hydride.

| Reactant	Reactivity with Hydride	Phase at formate activation	Melting point °C	Boiling point °C
Acetone	high	gas	-95	56
Ethyl methyl ketone	high	gas	-86	80
Diethyl ketone	high	gas	-40	102
Cyclohexanone	high	gas/liquid	-31	155
Methyl phenyl ketone	high	liquid	20	202
Acetic acid anhydride	high	liquid	-73	140

The first selection criterium is the ketone's potential reactivity with hydride. By virtue of the general molecular structure of ketones, every candidate that was considered possess α-hydrogens. The metal hydride would cause enolization of the ketone, leading to further condensation reactions (see scheme 29).

Scheme 29: General reaction mechanism for the enolate formation, with metal hydride acting as a base.

This outcome is not desired for the intended reaction of coupling with formate. Even in the fortuitous event where the metal hydride reacts only with formate, the expected reaction mechanism is unlikely to occur. The tetrahedral intermediate originated by the attack of carbonite onto the carbonyl group would questionably eliminate a R^- group.

The intermediate could rather eliminate the carbonite, which is stabilized to a greater extent due to resonance (see scheme 30).
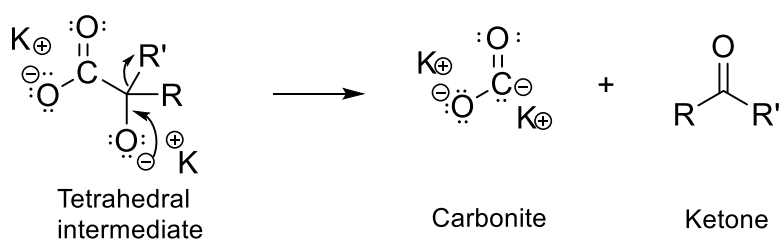
Scheme 30: Collapse of tetrahedral intermediate returning to the initial condition.

To conclude, the conditions used for the alternative formate coupling are not suitable for ketones as reaction partners. There is room for investigation for alternative structures of ketones that might solve these inconveniencies. For instance, consider α-β unsaturated ketones with good leaving groups in their molecular structure. But in this research, this category of reaction partneres will not be assessed further.
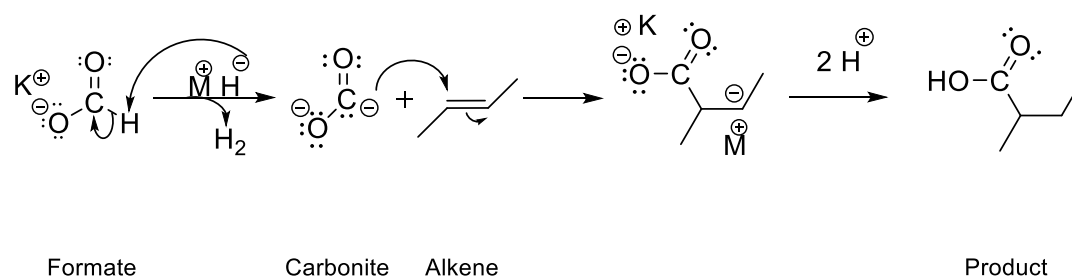
1.4 Alkenes

A fourth group of possible reaction partners is alkenes. Alkenes (or olefins) are linear hydrocarbons having one carbon-to-carbon double bond (C=C) and the general molecular formula C_nH_{2n}, assuming no ring structure present.[58] Alkenes find diverse applications in the chemical industry. They are used as feedstock in the syntheses of alcohols, plastics, detergents, and fuels. The most important alkenes for industrial applications are ethene, propene and 1,3-butadiene.

Alkenes are rich in electrons due to presence of a π-bond, available to engage in reactions. They are generally prone to react as nucleophiles, opening the double-bond and following the mechanism of electrophilic addition. Some examples are hydrohalogenation, halogenation, catalytic hydrogenation and epoxidation. [59][60][61][62]

Aromatics are cyclic structures with delocalized unsaturated C-C bonds. In contrast to olefins, the electrons in these structures are delocalized which leads to increased stability compared to alkenes. Aromatics such as benzene, toluene or xylene find large scale industrial application in the production of polymers and commodity chemicals.

Generally, ordinary alkenes are not susceptible to nucleophilic attacks. However, there can be some exceptions. For instance, it has been shown that styrene reacts with toluene towards nucleophilic addition if catalyzed by solid sodium. [63] Considering the powerful strength of the carbonite as a nucleophile, nucleophilic addition reactions at one of the unsaturated carbon of alkenes are an appealing option.

The expected reaction mechanism with an alkene is presented in scheme 31 below. The first step of the reaction involves formate and hydride, where the latter acts as a catalyst characterized by powerful basic strength. The highly nucleophilic carbonite dianion attacks one of the unsaturated carbons of the alkene, leading to a negatively charged product. This way the catalyst is not regenerated during the reaction.

Formate   Carbonite   Alkene   Product

Scheme 31: General reaction mechanism for the coupling of formate with alkenes via carbonite as the reactive intermediate.

In table 11 some potential reaction partners are presented. Only alkenes with a decomposition temperature above 200°C are considered.

Table 11: List of alkenes candidates for coupling with formate, physical properties and reactivity towards nucleophilic attack by hydride.

Reactant	Reactivity with Hydride	Phase at formate activation	Melting point °C	Boiling point °C
5-decene	medium	gas	-73/-112	170
2-heptene	medium	gas	/	99
toluene	medium	gas	-95	110
Xylene	medium	gas/liquid	-10	140

The first selection criterium is the alkene's potential reactivity with hydride. The last two selection criteria are related to the physical property of the reaction partner, in particular its

state at room temperature and its boiling point, which can play a role in easing the overall process and make it more efficient for the success of the reaction. Two linear alkenes and an aromatic compound were taken in consideration, in order to compare possible differences in terms of reactivity and reaction outcomes. As best suitable candidates for the reaction 5-decene, 3-hexene and toluene were selected. Even if these molecules do not contain electron-deficient species and are in gas phase at the temperature of formate activation, it is worth to investigate their reactivity with carbonite.

A side reaction that might involve every reaction partner is the hydrogenation to the corresponding alkenes (see scheme 32). Molecular hydrogen is produced in the reaction media due to formation of the carbonite intermediate. However, hydrogenation is generally conducted in presence of a catalyst that assists the process, so it could poorly take place. It is a possible outcome to consider when assessing the reaction products.
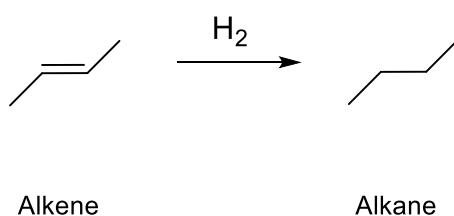

Alkene   Alkane

Scheme 32: General side reaction of alkene reacting with hydrogen to form the corresponding alkane

Another common side reaction that might take place for the reaction partners is shown in scheme 33 below. In this mechanism, the hydride abstracts a proton from the alkene, leading to a carbanion. This outcome is not desired for the intended reaction with formate.
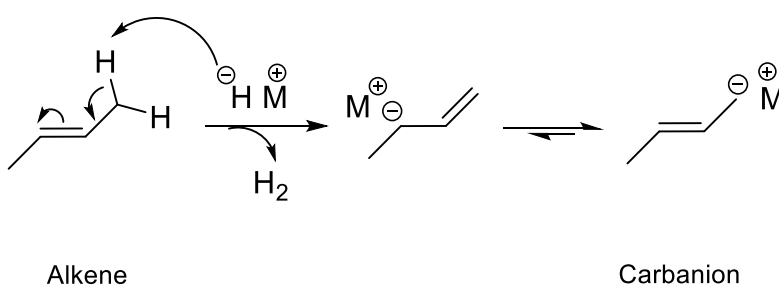
Alkene   Carbanion

Scheme 33: general side reaction of alkene reacting with hydrogen to form a carbanion

The carbanion produced by this side-reaction could potentially engage in subsequent reactions with unreacted alkene. This would lead to oligomeric branched species that are not desired for the outcome of the reaction (see scheme 34 below).

32
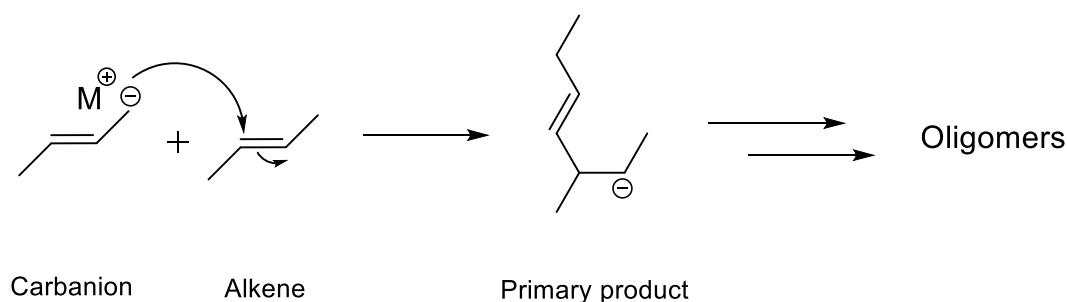
Scheme 34: side reaction of alkene reacting with carbanion.

1.4.1 5-decene and 2-heptene

Two different linear alkenes were chosen, that can be considered apolar. They differ in the position of the π-bond; 5-decene is symmetric, whilst in 3-nonene the π-bond is located near to a terminal carbon, and for this reason should be more accessible. For both the reagents, the expected product is a carboxylic acid branched to an aliphatic linear molecule. In literature there are reported various carbonylation reactions for alkenes, but they generally involve terminal unsaturated reagents and complexes catalysts. [64]
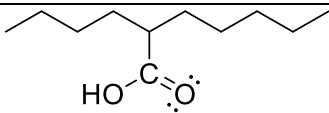
For the desired reaction with 5-decene, a possible mechanism is shown on scheme 35 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks one of the two unsaturated carbon of the alkene, resulting in the product shown below. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.
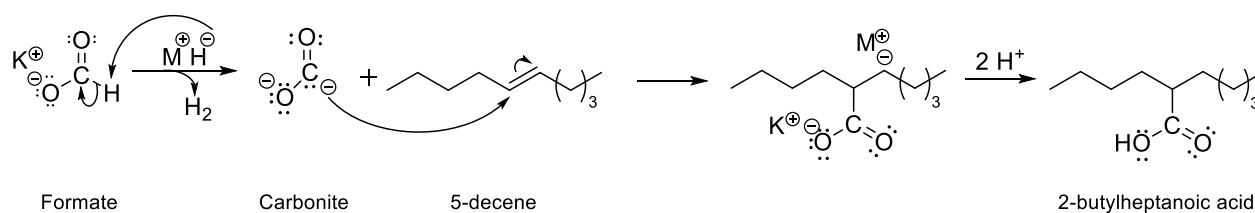
Scheme 35: Reaction mechanism for the coupling of formate with 5-decene via carbonite as the reactive intermediate
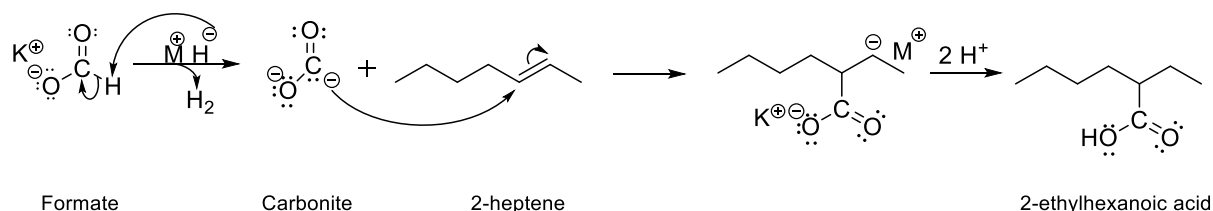
2-butylheptanoic acid can be obtain by acidification of the product (see table 12). There are no data available relatively to the melting point nor the boiling point. A separation strategy for the reaction mixture could rely on the difference in polarity within the reagent and the product. For instance, chromatographic techniques could serve for this purpose.

Table 12: Physical properties of 2-butylheptanoic acid, desired coupling product of formate with 5-decene.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
2-butylheptanoic acid		22058-70-4	/	/	/

As practical application of the product, for instance, butylheptanoic acid is used in the manufacturing of superconductors.
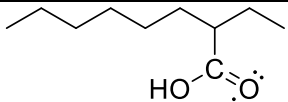
For the desired reaction with 3-nonene, a possible mechanism is shown on scheme 36 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks one of the two unsaturated carbon of the alkene, resulting in the product shown below. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.

Formate   Carbonite   2-heptene   2-ethylhexanoic acid

Scheme 36: Reaction mechanism for the coupling of formate with 3-nonene via carbonite as the reactive intermediate

2-ethyloctanoic acid can be obtain by acidification of the product. There are no data available relatively to the melting point nor the boiling point. A separation strategy for the reaction mixture could rely on the difference in polarity within the reagent and the product. For instance, chromatographic techniques could serve for this purpose.
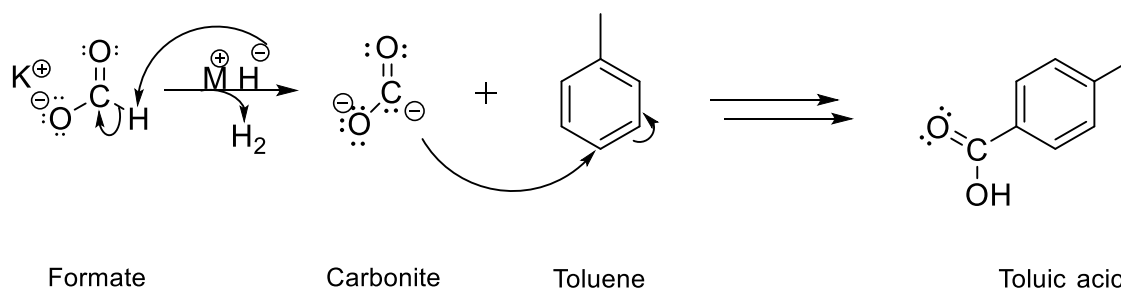
Table 13: Physical properties of 2-ethyloctanoic acid, desired coupling product of formate with 3-nonene.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
2-ethylhexanoic acid		149-57-5	/	/	/

2-Ethylhexanoic acid (EHXA, 2-EHA) is an industrially important aliphatic carboxylic acid. It is widely used as a stabilizer and a wood preservative. It is used for other application such as wetting agent, lubricant and co-solvent.

1.4.2 Toluene
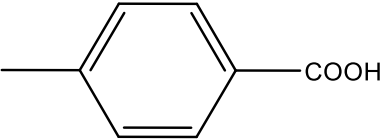
For the desired reaction, a possible mechanism is shown on scheme 37 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks on the ring structure, most likely on the ortho or para position. The product is known as toluic acid.

Formate   Carbonite   Toluene   Toluic acic

Scheme 37: Reaction mechanism for the coupling of formate with toluene via carbonite as the reactive intermediate

Toluic acid can be obtained by acidification. At room temperature it is present as a solid and can therefore easily be separated from toluene by filtration.

Table 14: Physical properties of toluic acid, desired coupling product of formate with toluene.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Toluic acid	(structure: methylbenzene ring with —COOH)	99-94-5	180	274	150

The resulting toluic acid is an intermediate in the production of terephthalic acid from xylene and could open a new pathway to terephthalic acid starting from toluene.

To conclude, toluene is an appealing candidate for the coupling with carbonite and for proof of principle experiment. It is not susceptible to the temperature operating condition, so it should not lead to significant decomposition products. However, since the aromaticity of the ring represents a very stable system, the feasibility of the reaction needs to be assessed empirically.

1.5 Leaving groups

Another category of possible reaction partner involves molecules that bear a leaving group in their molecular structure, such as halo compounds. This might be in favor for the formate incorporation via SN^2 nucleophilic substitution. The mechanism and outcome of the reaction can vary according to the chosen reaction partner. A general mechanism is shown in scheme 38 below. Halides are well known and suitable leaving groups for these reactions. Although chloro-compounds are more commonly available they might not perform as well as their bromo relatives.

Formate   Carbonite   Reaction partner   Product
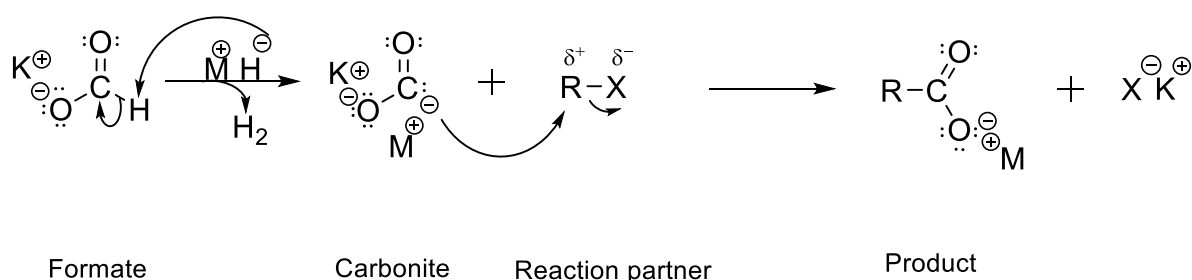
Scheme 38: Reaction mechanism for the coupling of formate with a molecule bearing a leaving group via carbonite as the reactive intermediate

In table 15 some potential reaction partners are presented. Only molecules with a decomposition temperature above 200°C are considered.
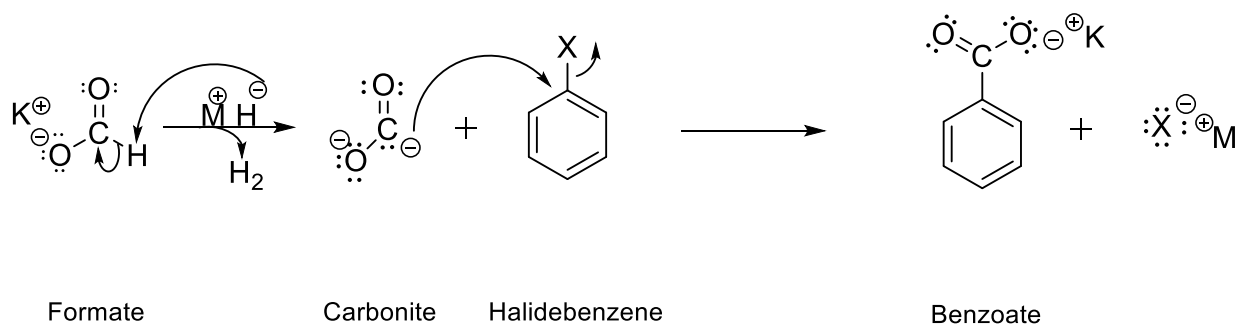
Table 15: List of candidates containing a leaving group for coupling with formate, physical properties, and reactivity towards nucleophilic attack by hydride.

Reactant	Reactivity with Hydride	Phase at formate activation	Melting point °C	Boiling point °C
Cis 1,2-dichlorobutene	medium	gas	-81,47	155
Chlorobenzene	low	gas	-45	132
Chloronaphtalene	low	liquid	/	256
1-chlorohexane	medium	gas	-94	135
Cis 1,2-dibromobutene	medium	gas	/	150
Bromobenzene	low	gas	-30.8	156
Bromonaphtalene	low	liquid	1-2	280

The first selection criterium is the molecule's potential reactivity with hydride. The last two selection criteria are related to the physical property of the reaction partner, in particular its state at room temperature and its boiling point, which can play a role in easing the overall process and make it more efficient for the success of the reaction.

1.5.1 Halide substituted benzene and naphtalene
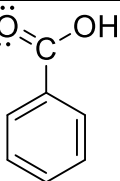
Benzene substituted with chloro or bromo leaving groups are leading to the formation of benzoic acid. The carbonite formed by proton abstraction attacks the carbon adjacent to the halide due to its lower electron density (scheme 39). The attack then leads to the elimination of the leaving group which forms a salt with the counter-ion introduced with the hydride catalyst. After acidification, benzoic acid is obtained.

Formate   Carbonite   Halidebenzene   Benzoate

Benzoic acid is solid at ambient conditions which makes its separation from the starting compound formate more challenging. Due to its lower melting point compared to formate with a difference of more than 60 °C, a filtration straight after the reaction could be a viable option.

Table 16: Physical properties of benzoic acid, desired product of formate and halide substituted benzene

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Benzoic acid		65-85-0	122.4	249.2	121

Sodium benzoate is used directly as a pharmaceutical.[65] Benzoic acid is used as antimicrobial preservative in food and beverages, especially in carbonated beverages. [66][67]
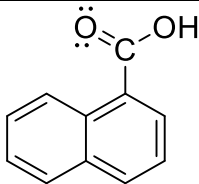
The reaction between the carbonite and the halide naphthalene as shown in scheme 41 follows the same principle as the benzene analogue (scheme 40).

Formate   Carbonite   Bromonaphtalene   1-naphtoic acid
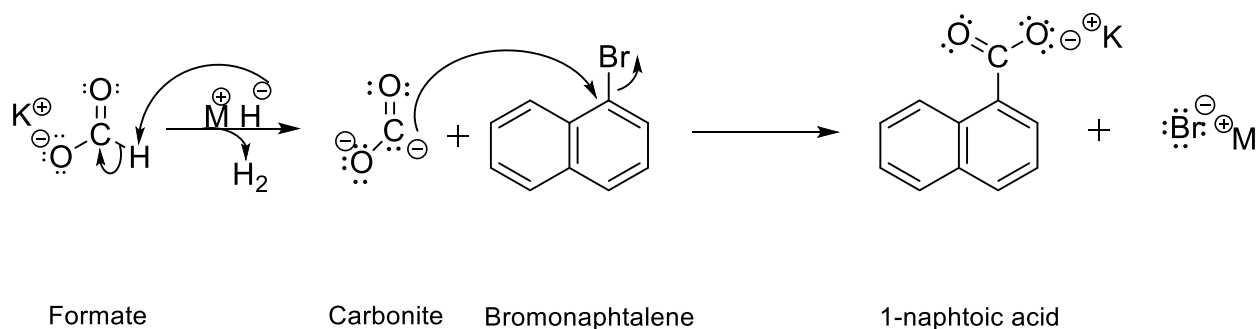
Scheme 40: Reaction mechanism for the coupling of formate with halide naphtalene via carbonite as the reactive intermediate

Naphtoate can be further converted to benzoic acid by acidification. Naphtoic acid is solid at ambient conditions which makes its separation from the potential unreacted starting compound formic acid a filtration step.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
1-naphtoic acid		86-55-5	157-160	300	/

Naphtoic acid finds frequently use as a substrate for C-H activation reactions and is used as a buildingblock for specialty chemicals. [68][69]

1.5.2 Terminal halide substituted hexane
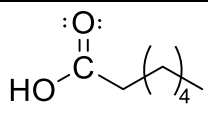
For the desired reaction, a possible mechanism is shown on scheme 41 below. The first step consists in the formation of the carbonite dianion intermediate. The highly nucleophilic carbonite carbon attacks the electrophilic carbon of the 1-chlorohexane. The expected outgoing products of the coupling are heptanoate and chloride ion. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase might be implied to reach optimum results.

Formate   Carbonite   1-chlorohexane   Heptanoate
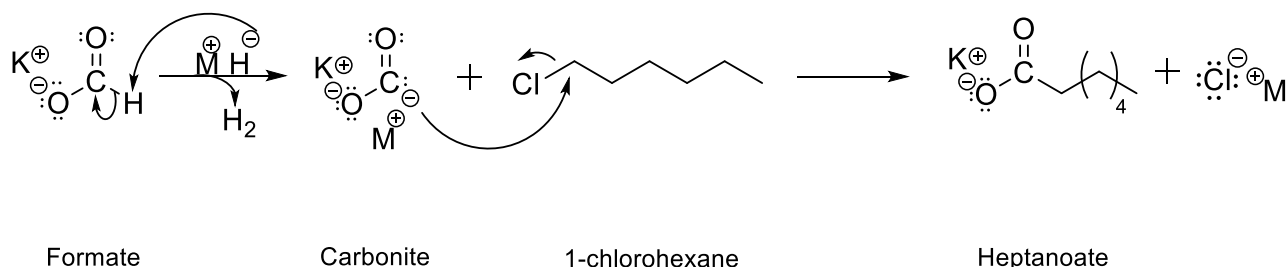
Scheme 41: Reaction mechanism for the coupling of formate with 1-chlorohexane via carbonite as the reactive intermediate

Heptanoic acid can be obtain by acidification of heptanoate. At atmospheric pressure, the final product has a melting point of -7.5°C and a boiling point of 223°C (see on table 18 below). A separation strategy for the reaction mixture could rely on the difference in polarity within the reagent and the product. For instance, chromatographic techniques could serve for this purpose. Also, there is a significant difference in boiling points within the product and the reagents. The separation process could exploit this difference to isolate the product.

Table 18: Physical properties of heptanoic acid, desired coupling product of formate with 1-chlorohexane.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Heptanoic acid	:O: ‖ HO–C⤳⤳⤳₄	111-14-8	-7.5	223	/

Heptanoic acid is a C7, straight-chain fatty acid that contributes to the odor of some rancid oils. Used in the preparation of esters for the fragrance industry, artificial flavor preparations, and as an additive in cigarettes. It has a role as a plant metabolite.[70]

1.6 Carbon dioxide CO_2

CO_2 is an attractive building block for producing organic chemicals and materials, as an economical, abundant, and nontoxic carbon source. [71] Valorization and utilization of CO_2 has received considerable and ever increasing attention by the scientific community, using CO_2 based on its unique chemical properties to be incorporated with high 'atom efficiency' in reactions such as carboxylation or carbonate synthesis. [72][73][74] The utilization of CO_2 as a feedstock for producing chemicals provides a grand challenge in exploring new options for catalytic and industrial development. Use and activation of CO_2 is problematic since it is the most oxidized form of carbon, which is thermodynamically stable and kinetically inert in certain desired conditions. The most desirable form of CO_2 fixation is to form C-C or C-H bonds with CO_2. To accomplish this, it is necessary to use of strong nucleophilic carbon nucleophiles. For example, organolithiums or Grignard reagents, as well as phenolates, to furnish valuable carboxylic acids and their derivatives. As an example, the current industrial synthesis of salicylic acid derivatives employs CO_2 as a reaction partner and solvent, making use of supercritical carbon dioxide (scCO2). [75] An advantage of using supercritical fluids is that their density and solvating power can be regulated by adjusting pressure and temperature; they have been implied in extraction and separation process as well as reaction media. [76] CO_2 reaches its critical state at relatively mild conditions, at temperatures greater than 31.1°C and pressures greater than 7.38 MPa (critical point). Its phase diagram is shown on figure 8. Below these temperature and pressure, CO_2 will be either a gas or a liquid. Moreover, the reactivity of

CO_2 itself is often improved drastically under supercritical conditions. [77] For these reasons, it is worthy to investigate the possibility to use $scCO_2$.
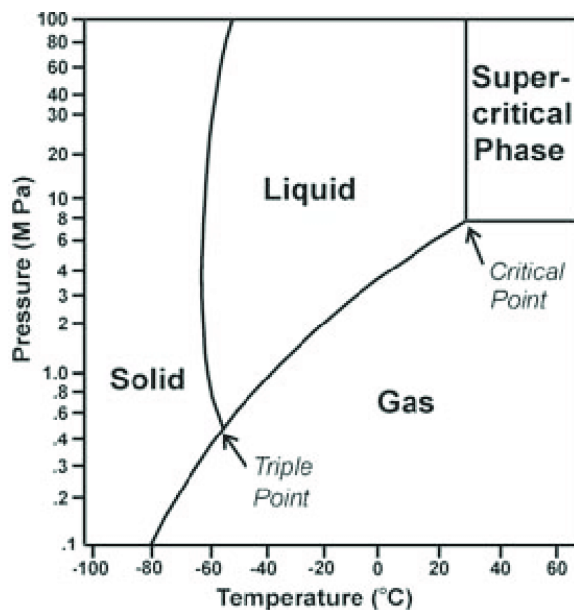

Figure 8: Carbon dioxide phase diagram. The critical point for CO2, when it reaches supercritical state, is 31.1°C and 7.38 MPa.[78]

An appealing option is to introduce CO_2 as a reaction partner to react with formate, by virtue of the great nucleophilicity of the dianion carbonite. The mechanism is shown in scheme 42 below. The first step consists in the formation of the carbonite dianion intermediate. Then, the carbonite carbon attacks the electrophilic carbon of CO_2. The expected outgoing product of the coupling is oxalate. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible. Stochiometric amounts of superbase are required for this reaction.

Formate   Carbonite CO_2 Oxalate
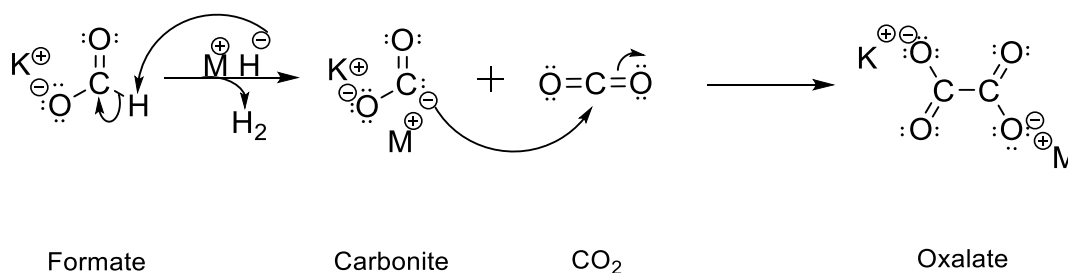
Scheme 42: Reaction mechanism for the coupling of formate with CO2 via carbonite as the reactive intermediate

Oxalic acid is the desired product of the coupling reaction of formate with CO_2. It can be obtained by acidification of oxalate. At atmospheric pressure, the final product has a melting

point of 190°C and a boiling point above 340°C (see on table 5 below). At standard condition of temperature and pressure oxalic acid is solid.

Table 19: Physical properties of oxalic acid, desired coupling product of formate with CO_2.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Oxalic acid		144-62-7	189.5	365.1 ± 25.0	188.8 ± 19.7

Oxalic acid is the simplest of the dicarboxylic acid. It has a role as a metabolite in plants and animals and is naturally occurring in many foods. It is extensively used in various industries such as textiles, leather, and pharmaceuticals. The latter is currently the predominant area, but oxalic acid is recently gaining more interest as a platform molecule to produce high-value chemicals. For example, glyoxylic acid can be obtained as the first reduction product of oxalic acid.[79][80] Oxalic acid can be obtained from different sources, including CO_2, propylene, and biomass. The oldest process to industrially produce oxalic acid used nitric acid to oxidize biomass. [81]

A potential side reaction that can occur is shown in scheme 43 below. It involves the metal hydride acting as a reducing agent with CO_2. This reaction would lead to formate.
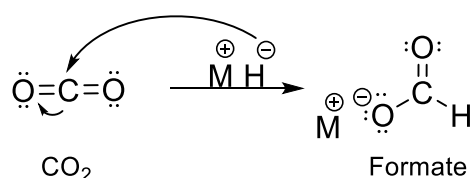
Scheme 43: side reaction mechanism of CO_2 with the metal hydride.

1.7 Carbon monoxide CO

As a last category of reaction partners, carbon monoxide (CO) has been taken into consideration. It is used as a significant carbonyl group-introducing reagent in organic synthesis. A number of synthetic reactions using CO have been developed. [82][83] It is a colorless, odorless, and toxic gas at room temperature. For these reasons, it poses many difficulties in terms of performing proof of principle experiments, but it is worth to discuss the

possible outcome if involved in the alternative formate coupling. According to the phase diagram of CO (see Figure 9), carbon monoxide reaches its supercritical state at -140.23°C and 34.99 bar. There is no information reported in literature that involves CO in its supercritical state (scCO) as a reagent, but it is a condition that might be worth to investigate.
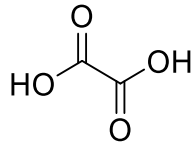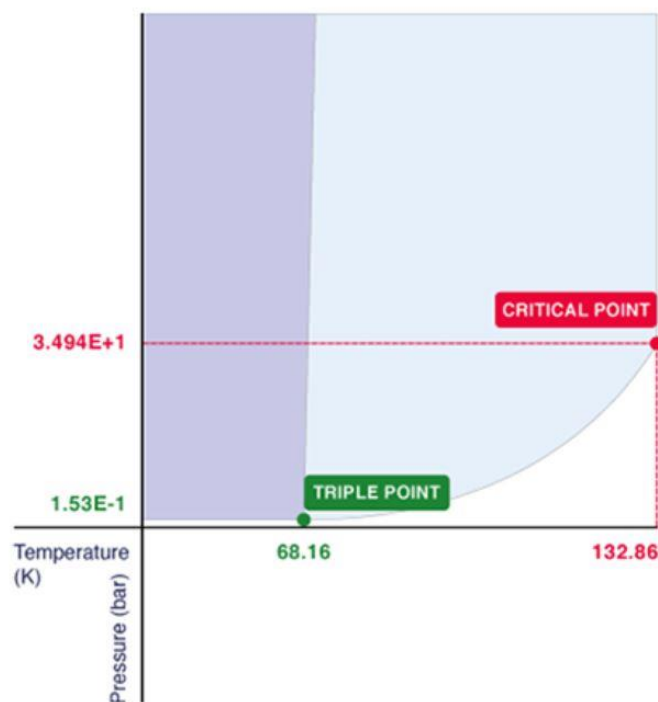

Figure 9: Carbon monoxide phase diagram. The critical point for CO, when it reaches supercritical state, is -140.23°C and 34.99 bar

However, even if scCO might be a better option in order to obtain a better mixed reaction media, for the intended purpose liquid CO could be a good option. To reach the liquid state is sufficient to reach a pressure above 35 bar, even at room temperature.

Introducing CO as a reaction partner to react with formate is an appealing option, by virtue of the great nucleophilicity of the dianion carbonite. The mechanism is shown in scheme 44 below. The first step consists in the formation of the carbonite dianion intermediate. Then, the carbonite carbon attacks the electrophilic carbon of CO. The expected outgoing product of the coupling is shown in the scheme below. In these steps, no hydride release is involved, thus the upkeep of the catalyst is not possible.
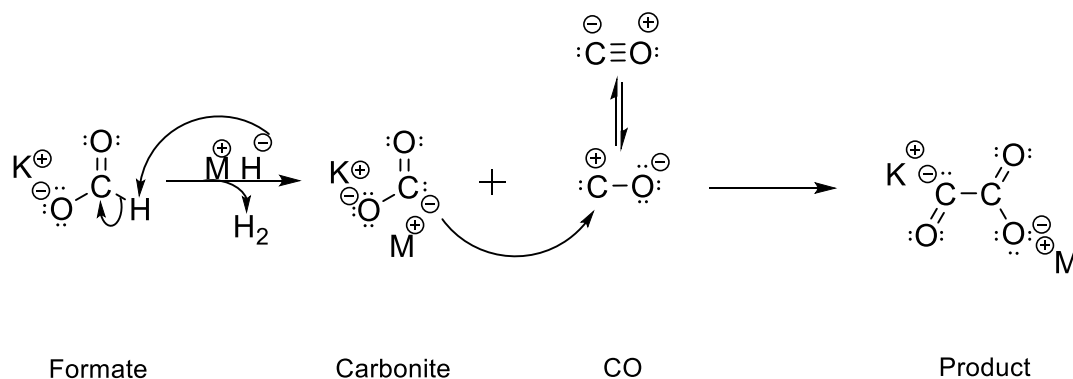
Scheme 44: Reaction mechanism for the coupling of formate with CO via carbonite as the reactive intermediate

Glyoxylic acid is the desired product of the coupling reaction of formate with CO. It can be obtained by acidification of the product. At atmospheric pressure, glyoxylic acid has a melting point of 49-52°C and a boiling point of 111°C (see on table 20 below). At standard condition of temperature and pressure glyoxylic acid is solid. The separation process might exploit the difference in polarity within formate and glyoxylic acid.

Table 20: Physical properties of glyoxylic acid, desired coupling product of formate with CO.

Name	Structure	CAS number	Melting point °C	Boiling point °C (760 mmHg)	Flash point (°C)
Glyoxylic acid		563-96-2	49-52	111	/

Glyoxylic acid is a colorless solid that occurs in nature as a metabolite in both animals and plants and has many industrial applications. For instance, it serves as a cleaning agent for a variety of industrial applications, as a specialty chemical for cosmetics, or as a feedstock for biodegradable polymers. [84]

1.8 Overall ranking of most promising candidates

Overall, 13 potential reactions partners were evaluated in depth. The aim of this chapter is to rank those candidates based on 3 criteria which culminate all the previously assessed aspects. These three criteria include:

1) Sustainability of the reactant;

2) Ease of commercial operation;

3) Commercial attractiveness of product.

Category 1, sustainability of the required reactant(s), considers its origin and means of production, its potential in mitigating climate change and its large-scale availability. In category 2, ease of commercial operation, the potential of side reactions is considered, ease of introduction of the reactants in a process, potential flow-type operation and downstream separation. Category 3 aims to assess the commercial attractiveness of the product. This includes current uses and market volumes as well as potential future applications. This ranking method is arbitrary.

Table 21: ranking of coupling partners for AFC.

Coupling partner	Product	Sustainability of Reactant	Commercial operation	Attractiveness of product	Overall
Carbon Dioxide	Oxalic acid	10	7	8	8.3
Carbon Monoxide	Glyoxylic acid	7	7	9	7.6
Cinnamaldehyde	Benzylidene pyruvic acid	4	7	7	6
Formaldehyde	Glyoxylic acid	6	3	9	6
Toluene	Toluic acid	3	6	7	5.3
Benzaldehyde	Phenylglyoxylic acid	3	7	6	5.3
Methyl terephthalate	Oxalyl benzoic acid methyl ester	4	5	5	4.6
Methyl cinnamate	Benzylidene pyruvic acid	3	5	5	4.3
Methyl benzoate	Benzoyl formic acid	2	5	5	4
5-decene	2-butylheptanoic acid	4	5	3	4
2-heptene	2-ethylhexanoic acid	4	5	3	4
1-chlorohexane	Heptanoic acid	3	5	3	3.7
Bromonaphtalene	1-naphtoic acid	3	5	3	3.7

In the end carbon dioxide leads the overall ranking. Despite the drawbacks of stochiometric consumption of metal hydrides, the absence of potential side-reactions other than formation of formate, the ease of separation and simple reactor design play a crucial role here. The sustainability of CO_2 as a reactant is without doubt, yet the metal hydride should ideally be produced in sustainable fashion. Oxalic acid has a large commercial market already and the potential to take the role as one of the major platform chemicals for polymer production in the future. Second comes CO, which outperforms carbon dioxide in terms of product attractiveness, however its origin is – although possible from renewables – not as sustainable as carbon dioxide.

2. Experimental

The coupling of formate with CO_2 was the highest-ranking option and therefore it was selected for the proof-of-principle experiments. From previous experiments, targeted at optimization of traditional formate coupling, it is known that carbon dioxide inhibits the coupling of formate. For those experiments, a stream of carbon dioxide was applied to an equimolar mixture of K-formate and NaH at ambient pressure. The mixture was heated to 200 °C and analyzed based on weight gain and quantitative product using an IR-spectroscopy. Yet, these experiments did not show any incorporation of CO_2 in solid form. CO_2 in gaseous form is not suitable for the reaction because the gas-liquid mixing is limited. Therefore, it was decided to approach the proof-of-principle experiments providing CO_2 in the liquid form, more precisely in its supercritical state ($scCO_2$).

2.1 Reaction set-up for alternative coupling with $scCO_2$

For the reaction to occur, it is necessary to provide conditions at which the carbonite formation is facilitated. It was shown that this only occurs when the formate is present as a molten salt, hence a temperature above 170°C is required. To supply CO_2 in liquid form, a pressurized system which can withstand pressures at above 60 bar is required. Due to the high reactivity of hydrides in air, specifically with the contained moisture, the samples were prepared using a water-free environment. In our case this environment was provided by a glove-box in nitrogen atmosphere with water and oxygen levels below 1 ppm. Stainless steel, 70 mL volume reactors from Parr were chosen, which can withstand pressures as high as 200 bar and temperatures up to 250 °C. In order to prevent potential reactions with the metal of reactor walls, a borosilicate glass insert was used. The reactors and insert are shown in figure 10.

Figure 10: Reactor assembly for proof-of-principle reactions of alternative formate coupling with CO_2. On the left the reactor assembly consisting of the reactor lid with gas port, metal reaction vessel and glass insert are shown. On the right the heating unit is shown in which the reactor is heated, and the pressure is controlled.

A pressurizer was used to load the reactors with liquid CO_2. By means of a CO_2 bottle, the reactor was first pressurized with 54 bar. After that, 100 ml of CO_2 at 54 bar were additionally forced into the reactor leading to a final pressure of 65-75 bar. This reactor was then heated by means of a heating mantle and pressure is closely monitored.

Figure 11: Pressurizer used for filling of reactors with CO_2 prior Proof-Of-Principle experiments. CO_2 was compressed into liquid form in the reactor.

2.1.2 Product analysis

To identify and quantify the incorporation of CO_2 an array of strategies were used. These measurements included:

1) *Weight-gain measurements to detect increase in mass during reaction*

   The weight of the solids in the reactor before and after the reactions were measured using a fine balance.

2) *Volumetric quantification of hydride consumption*

   The remaining amount of hydride after reaction was estimated indirectly by measuring the evolving gas volume produced in the vigorous reaction of the hydride with added water. A fraction of the obtained solid was transferred to a sealed vial and water was added in known small amounts. The increase in gas volume was measured with a burette attached to the sealed vial.

3) *Qualitative and quantitative IR analysis of the products*

   The solution obtained in 2) was analysed in a liquid IR cell. Species present in the solution were both identified and quantified based on the Lambert-Beer-Law

4) *Quantitative LC analysis of the products to confirm IR measurements*

   To confirm the accuracy of the method the liquid products were also separated and quantified using a liquid chromatograph equipped with a TCD sensor.

2.1.3 Reaction conditions

For proof-of-principle reactions, the experience with the traditional formate coupling reaction was used and adopted the conditions that were necessary:

1) Reaction temperature: 200°C
2) Heating rate: 10°C / min
3) Reaction time: 3-60 minutes
4) Reaction mixture: Equimolar mix of K-Formate and NaH
5) Reaction mass: 50 mg – 500 mg
6) CO_2 pressure: 78 – 180 bar

Overall 4 types of reactions were performed including:

A) Desired reaction: K-Formate + NaH + CO_2
B) Blank 1 (B): CO_2 + Hydride
C) Blank 2 (C):   K-Formate + Hydride
D) Blank 3 (D):   K-Formate + CO_2

2.1.4 Reaction procedure

The reaction mixture was prepared by mechanical mixture of the formate and hydride in dry nitrogen atmosphere. A precise amount of the mixture was then added to the glass reactor inserts in the glovebox. Once the reactor was filled and sealed it was removed from the glovebox and then prepared for the reaction as previously described. If criticality, indicated by the rapidly rising of pressure readings, was reached earlier, the compression was stopped. The reactor was then heated in a Parr parallel autoclave system. The reaction time was counted from the moment the reactor reached 170°C. The pressure drops or increase was monitored with the pressure gauge of the system.

After reaction, the reactors were rapidly cooled in an ice-bath and remaining CO_2 was released and purged out with nitrogen. Back in the glovebox the reactors were opened and the obtained solid was first weighed and then homogenized using a mortar. A precise amount of the mixture was then transferred to a glass vial for further volumetric and spectroscopic analysis.

2.2 Reaction set-up and procedure for alternative coupling with p-formaldehyde

For the reaction to occur it is necessary to provide conditions at which the carbonite formation is facilitated. It was shown that this is only the case if formate is present as a molten salt and hence a temperature above 170°C is required. Due to the high reactivity of hydrides in air, specifically with the contained moisture, the samples were prepared using a water-free environment. In our case this environment was provided by a glove-box in nitrogen atmosphere with water and oxygen levels below 1ppm. For para-formaldehyde a reaction setup analogue to the one used for $scCO_2$ was used, thus a 70 mL stainless steel reactor from Parr and a borosilicate glass insert were implied. Para-formaldehyde was added in solid form to the mixture of formate and hydride directly in the glove-box in nitrogen atmosphere, in equimolar quantities to the added formate.

2.2.1 Reaction conditions

For proof-of-principle reactions, the experience with the traditional formate coupling reaction was used and adopted the conditions that were necessary:

1) Reaction temperature: 200°C
2) Heating rate: 10°C / min
3) Reaction time: 15 minutes
4) Reaction mixture: Equimolar mix of K-Formate, NaH, and p-formaldehyde
5) Reaction mass: 50 mg – 100 mg
6) N_2 pressure: 1 bar

2.3 Reaction set-up and procedure for alternative coupling with benzaldehyde

For the reaction to occur it is necessary to provide conditions at which the carbonite formation is facilitated. It was shown that this is only the case if formate is present as a molten salt and hence a temperature above 170°C is required. Due to the high reactivity of hydrides in air, the samples were prepared using a water-free environment. In our case this environment was provided by a glove-box in nitrogen atmosphere with water and oxygen levels below 1 ppm. A batch of equimolar mixture of K-formate and NaH was prepared. In the glove-box, several 5 mL glass screw cap septum vials were filled with the mixture.

Liquid benzaldehyde was dried using 4A molecular sieve in N_2 atmosphere, thus water would not interfere with hydride, keeping it available for the desired reaction. Benzaldehyde was then added to the screw cap septum vials containing the formate-hydride mixture using a syringe. The vials were inserted in an aluminium heating block. To each vial, a syringe with a balloon filled with N_2 was attached to the septum, in order to keep an inert atmosphere while dealing with pressure changes. (figure 12)
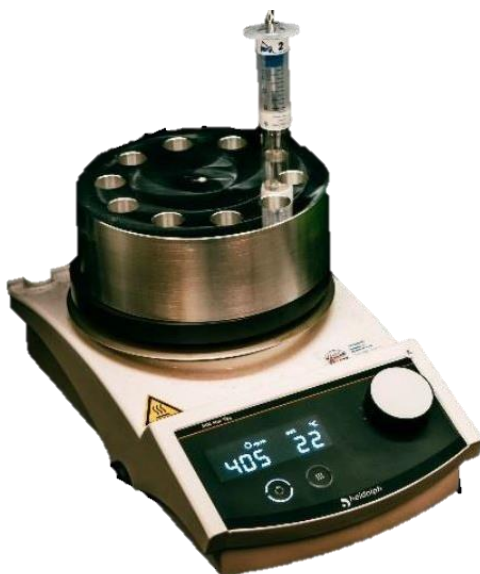
Figure 12: setup with self-made reactor and aluminum heating block for isothermal experiments.

2.3.1 Reaction conditions

For proof-of-principle reactions, the experience with the traditional formate coupling reaction was used and adopted the conditions that were necessary:

1) Reaction temperature: 200°C
2) Heating rate: 20°C / min
3) Reaction time: 3-30 minutes
4) Reaction mixture: Equimolar mix of K-Formate and NaH, and excess of benzaldehyde (2-5 mL)
5) Reaction mass: 50 mg – 100 mg

3. Results and discussion

3.1 Alternative coupling with scCO$_2$

Working reaction conditions:

Initially, several reactions were performed to check for working reaction conditions. The best reproducibility of results was obtained at 200°C final temperature, 15 minutes reaction time (time at above 170°C) and pressures in the range 130-200 bar. The reaction conditions were not further as this was out of scope for proof-of-principal reactions. All results presented below were obtained under the mentioned conditions.

3.1.1 Weight balance:

The success of CO_2 incorporation could be confirmed from the increase of weight of solids obtained in the reactions. Figure 13 shows that the weight increased for both the desired reaction mixture and the blank B, where CO_2 and hydride were made react. However, the overall weight increase was bigger for the reaction mixture.
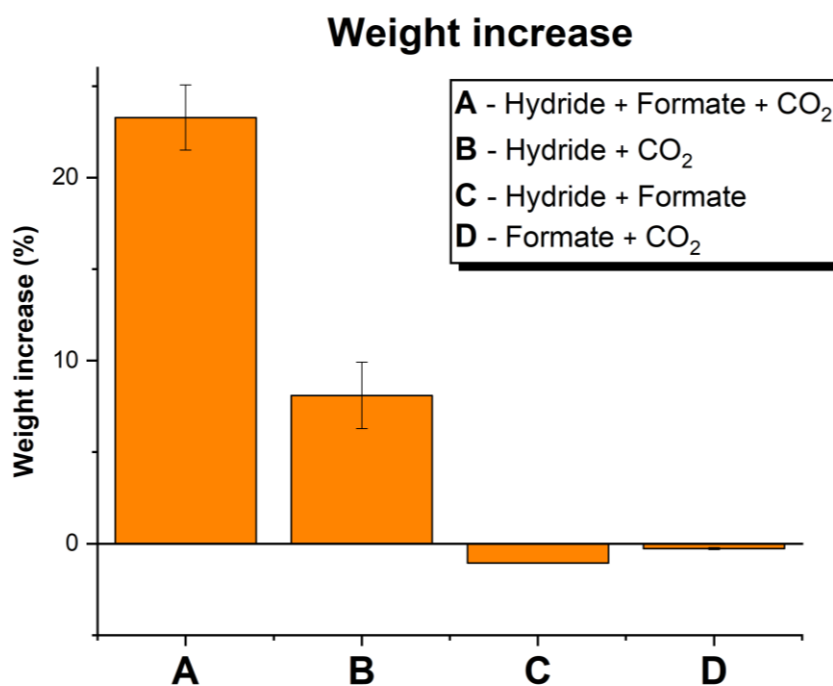

Figure 13: Increase in weight of solids after alternative coupling reaction as a percentile in relation to the initially added amount of solid in the reactor.

3.1.2 Consumption of hydride:

In the alternative coupling reaction 95% of the hydride was consumed during the reaction. This number was much lower for the hydride catalyzed formate coupling and the CO_2 fixation with hydride (blank B).
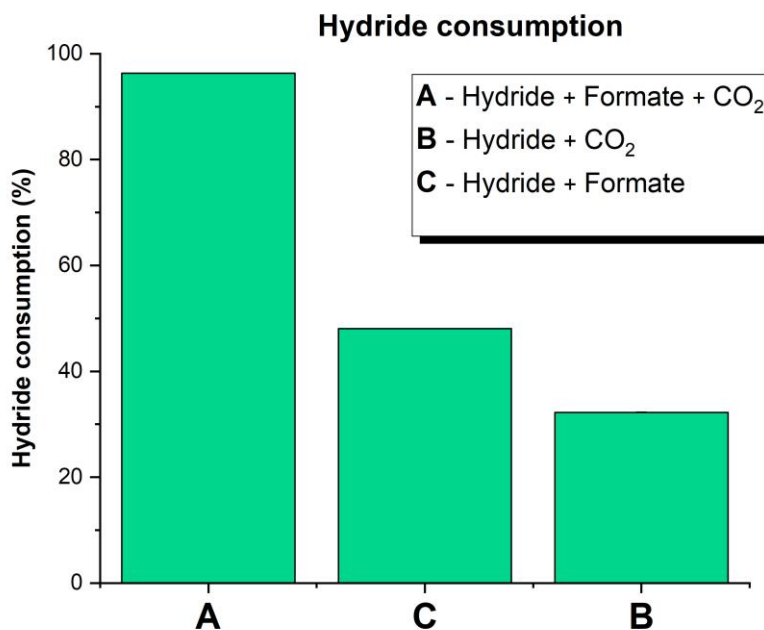
Figure 14: Consumed Hydride during alternative coupling reaction as a fraction of initially added hydride.

3.1.3 IR characterization and carbon balance:

The dissolved solids were analyzed using IR and LC. The qualitative analysis shows the presence of the following species in solution: formate, carbonate and oxalate.

To characterize the products after reaction there was a need to implement a technique for the quantification of components in the reaction mixture. It was found in literature that the amount of formate, oxalate, and carbonate can be quantified by titration.[85] However, a main disadvantage of this method is a need to titrate each sample twice. First, the amount of carbonate can be measured by titrating with either phenolphthalein or methyl orange in presence of calcium salts. In a second titration the amount of oxalate can be estimated as formate does not react with potassium permanganate $KMnO_4$, used in the titration.[86]

Instead of using the titration method, an IR estimation method was developed. This method is based on the Beer-Lambert law and the fact that analytes concentration linearly depends from the absorbance intensity.[87] To quantify different chemical species they must differ in their IR absorption pattern.[88] In figure 15 the IR spectra recorded in the region between 1200 and 1500 cm^{-1} for the three main possible components are shown. The absorption patterns differed for all components. This allows to treat the IR spectrum of the quenched reaction as derived from the superposition of these three components. A combined spectrum thus can be

deconvoluted into its individual components and the molar concentrations of each species evaluated.
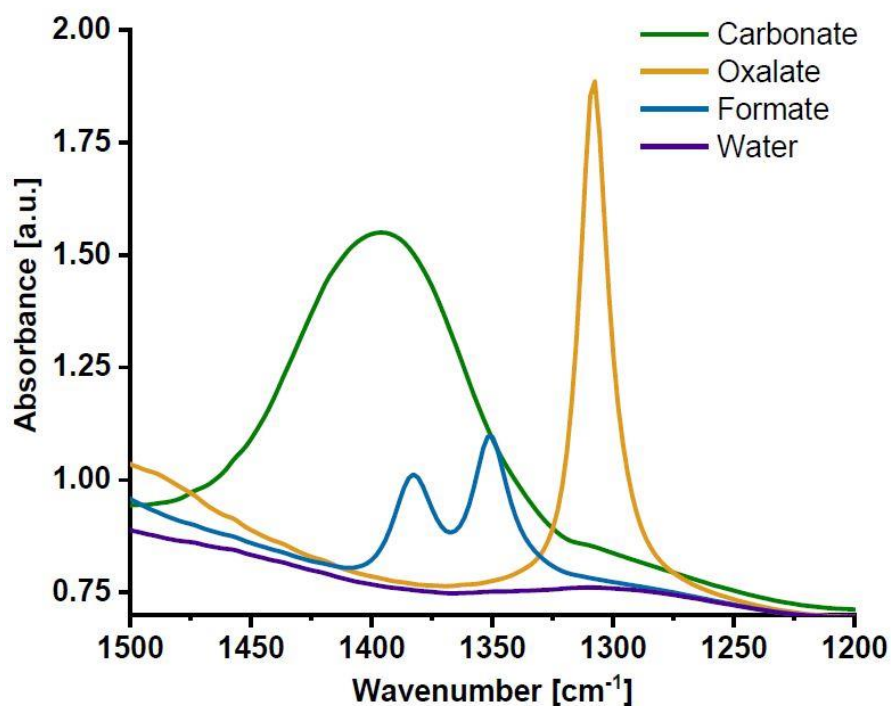

Figure 15: IR spectra of the main components of the reaction. All three mixture components have different absorbance bands. This allows to use Beer-Lambert law to deconvolute the mixture spectra after the reaction.

Those components in the mixtures were then quantified with bot IR and LC. The results, as shown in figure 16, are reproducible with a small error. Furthermore, the results clearly show the difference between the four reaction types. The mixture consisted of carbonate, oxalate and formate. The C percentage on the y axis represents the amount of carbon output in relation to the initially added carbon in the form of potassium formate.
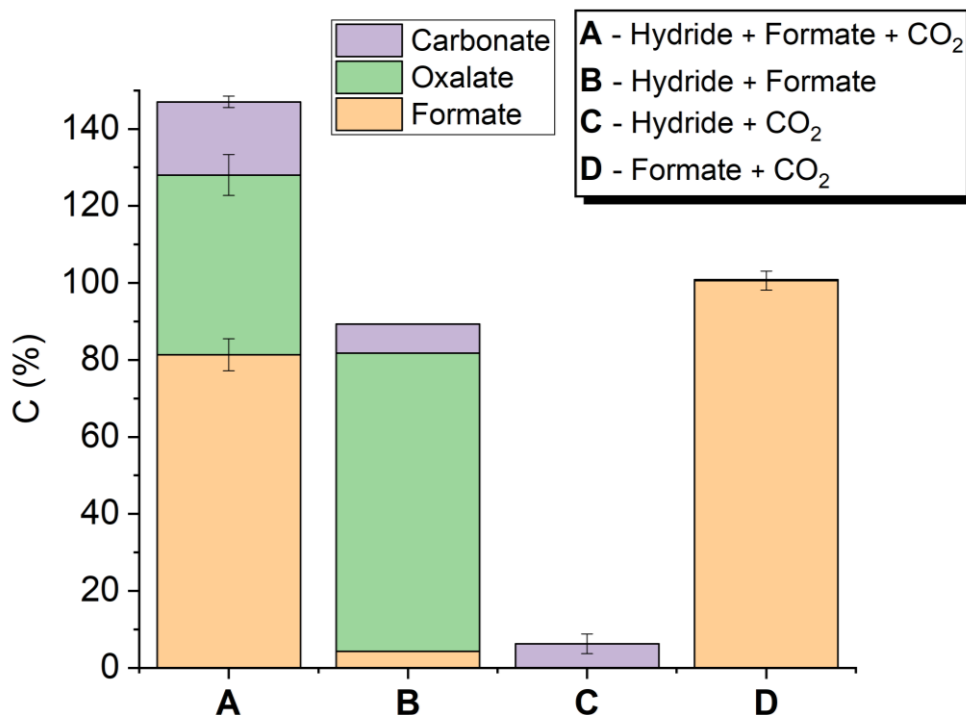
Figure 16: Carbon balance for solid product formed in alternative coupling reaction as a fraction of initially added solid carbon in the form of potassium formate.

For the blank reactions, if no hydride is added (Blank C), some of the added CO_2 is bound in the form of carbonate. In none of the samples the presence of formate or oxalate was observed. If only formate and CO_2 are heated without the presence of hydride (Blank D), the formate remains unchanged. If formate and hydride are heated in a nitrogen atmosphere (Blank B), the formate is converted mainly to oxalate and some carbonate. In this case a loss in carbon is observed, most likely as a consequence of formate or oxalate decomposition to carbonate.

The biggest increase in overall carbon could be detected for the desired reaction mixture with formate, hydride and CO_2 (reaction A). In this case, up to 50% additional carbon atoms were captured in the process. The mixture compromises of carbonate, oxalate and formate. Interestingly, more than 80% of the original formate were preserved. The content of carbonate amounts to up to the 40% of the newly present carbon which leads to the conclusion that either some of the oxalate or the formate originated from bound CO_2.

3.1.4 Mechanistic insight and outlook:

From the reactions performed it was possible to exclude some pathways. But both oxalate and carbonate could be derived either from the formate alone or from CO_2 (see figure 17 and figure 18)
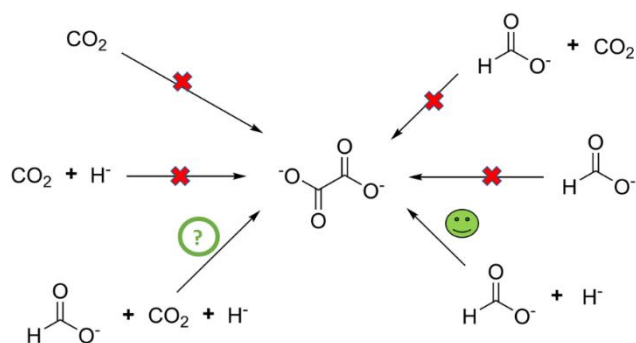

Figure 17: potential pathways for the production of oxalate in the alternative coupling experiment with CO_2. The pathways marked with the red cross were shown not to be present. Production from formate and hydride has been proven before. A production from formate and CO_2 needs proof.
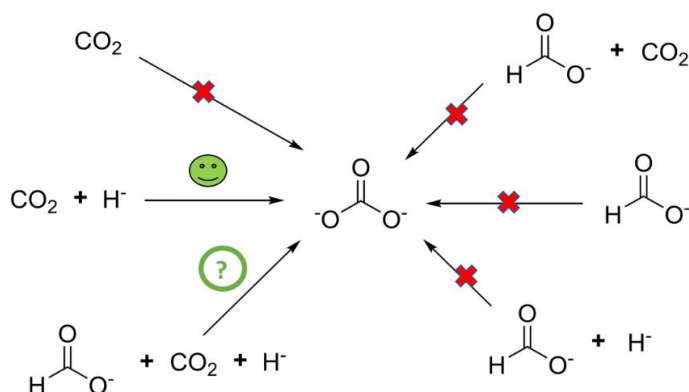

Figure 18: potential pathways for the production of Carbonate in the alternative coupling experiment with CO_2. The pathways marked with the red cross were shown not to be present. Production from CO_2 and hydride have been Proven. A production from formate and CO_2 needs proof.

To focus on this mechanistic insight and better understand the reaction, labeling studies were considered. ^{13}C formate was used to distinguish carbons atoms stemming from formate and carbon dioxide, using gas chromatography-mass spectrometry (GC-MS) to detect them. By carring out some GC-MS analysis on the post reaction mixture with non-labeled reagents, only formate was detected.

Since GC-MS is a performant technique to detect light, volatile compounds, in order to detect these species it was considered to convert them to the corresponding esters, so making them

more volatile.[89] The focus was on the conversion of oxalate into an ester, so to make it detectable, using inorganic salts as the starting material.

The esterification reaction was performed with potassium oxalate, using an excess of ethanol as both reagent and solvent, and stochiometric amounts of concentrated sulfuric acid (scheme 45). The reaction was conducted in an open stirred system in order to let the water evaporate, at T=78°C and for t= 2 hours.
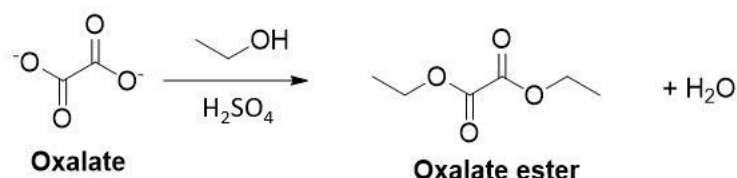
Scheme 45: esterification reaction of oxalate using ethanol as both solvent and reactant and H₂SO₄ to mediate the process.

Using nuclear magnetic resonance (NMR) 500 MHz, the conversion into the ester was confirmed (figure 19).

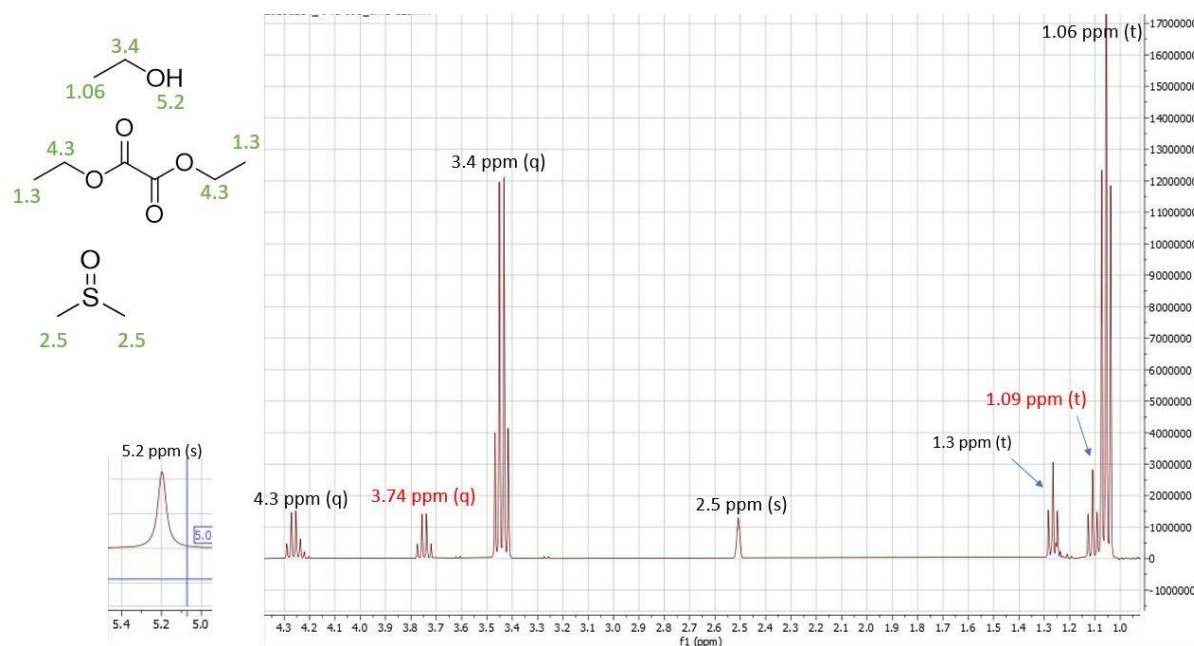*Figure 19: NMR (500Mhz) spectra of the post-reaction mixture after esterification. The different signals are attributed to each species. The red marked signals can be attributed to the mono ester of oxalate.*

Labelling studies could help to understand the reaction better. A mechanistic insight is crucial to optimize the reaction conditions and unleash the full potential of this reaction system.

In figure 20 the strategy for these labelling studies is illustrated:
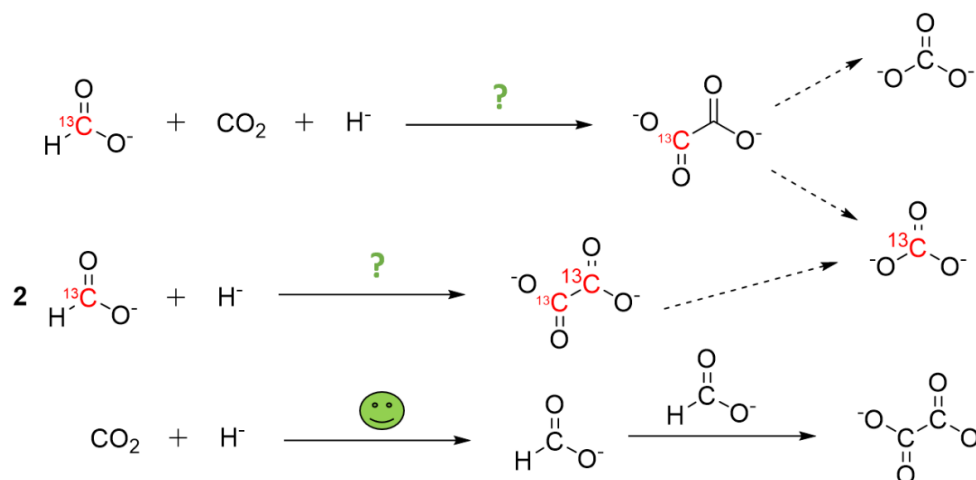
3.1.5 ^{13}C formate synthesis and AFC with scCO$_2$

The isotope ^{13}C of formic acid was available as labeled species. It was necessary to covert the acid form into an inorganic salt to replicate conditions comparable to previous experiments and perform the alternative formate coupling with CO_2.

An equimolar mixture of ^{13}C formic acid and KOH were let to react for 2h at room temperature, adding the acid dropwise into the basic solution, with water as solvent. The mechanism is shown in scheme 46. After the acid-base reaction, the solvent was evaporated under vacuum and the mixture was dried in a vacuum oven to remove all the traces of water. It is crucial to remove all the moist as it interferes with the conditions needed for the AFC reaction. Before removal of the solvent, the pH was checked to be neutral.
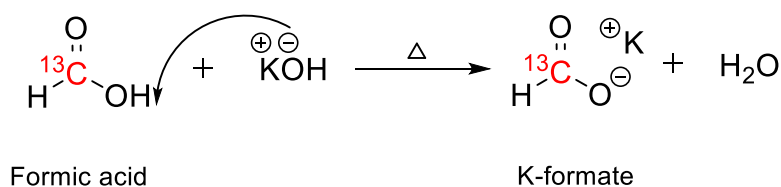
Formic acid   K-formate

An aliquot of the dried mixture was analyzed with differential scanning calorimetry (DSC) to verify the melting point of the obtained salt (figure 21). The analysis was conducted in air and with a heating rate of 5°C/min.
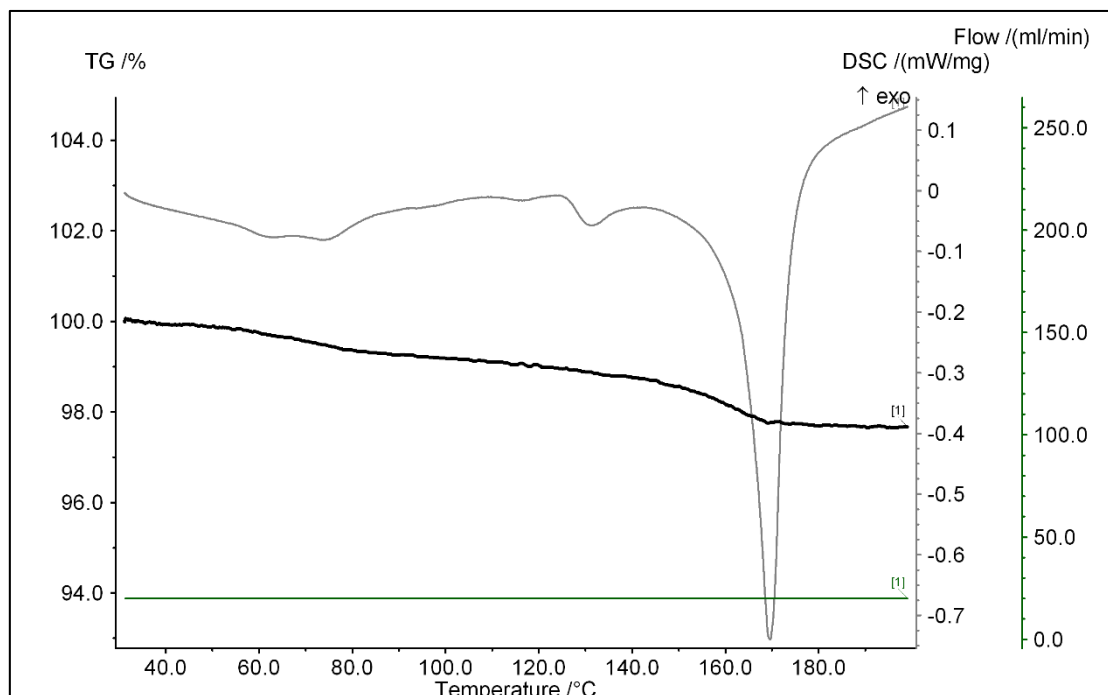
Figure 21: DSC-TGA analysis of post-reaction mixture

In literature, the melting point of potassium formate is in the range of T= 165-168°C. [90] The thermogram of the sample shows an endothermic peak at around 170°C, which indicates the melting of the solid sample. This confirms the formation of ^{13}C potassium formate.

The alternative formate reaction with scCO2 using ^{13}C-labeled formate was performed under the reaction conditions that had shown the best results, namely T=200°C and t=15min.

The outcome in terms of weight increase and hydride consumption was similar to previous experiments performed with regular formate. An aliquot of the post reaction mixture was submitted for GC-MS analysis, in order to detect stemming of formate.

From the IR analysis of the post reaction mixture obtained with ^{13}C labeled formate it is possible to make some preliminary observations (figure 22).

Figure 22: IR spectra of post-reaction mixture of alternative coupling with ^{13}C labeled formate (blue star), standard of ^{12}C oxalate (yellow circle), standard of ^{13}C formate (red pentagon), standard of ^{13}C labeled formate (green triangle).

The blue spectrum represents the alternative coupling experiment performed with the labeled formate, while the other spectra correspond to the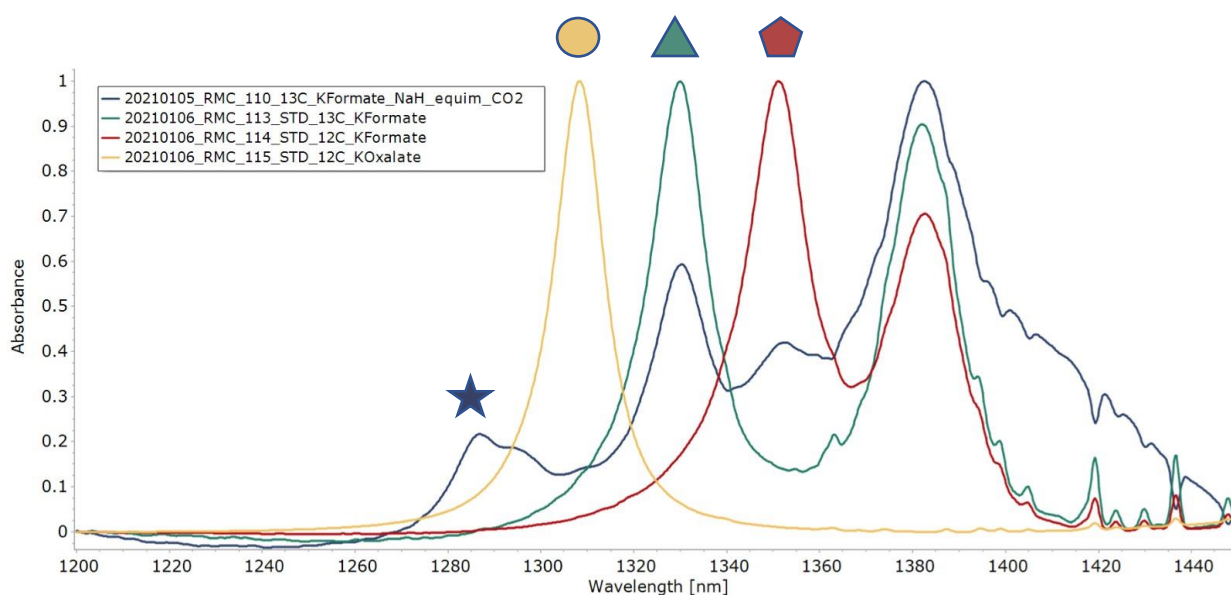 standards. Three standards were prepared in order to compare the different bands: ^{12}C formate, ^{12}C oxalate and ^{13}C formate. In the post-reaction mixture, there is clearly ^{13}C formate (1330cm^{-1}), and there seems to be ^{12}C formate as well (1350cm^{-1}). It looks like there is no oxalate from ^{12}C only, and there is another peak (1285cm^{-1}) which could correspond to the ^{13}C or the $^{13}C/^{12}C$ mixed oxalate, where the presence of the isotope causes the shifting of the peaks. The hypothesis of a mixed $^{13}C/^{12}C$ oxalate is suggested by the shape of the peak around 1285cm^{-1}, which displays a shoulder that could indicate the overlap of two different signals. IR spectroscopy observes the vibrations of molecules, displaying the normal and local modes of the molecule in the spectra.

Normal modes describe the possible movements/vibrations of each of the atoms in a system. The normal modes of an isotopically substituted molecule are different from the normal modes of an unsubstituted molecule, leading to different corresponding vibrational frequencies for the substituted atoms. The reduced mass μ and vibrational energy levels v^e are bounded by the equation:

$$\nu^e = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}} \qquad \text{(Eq.3)}$$

with:

$$\mu = \frac{m_1 m_2}{m_1 + m_2} \qquad \text{(Eq. 4)}$$

When an atom is replaced by an isotope of larger mass, μ increases, leading to a smaller ν^e and a downshift (or blue shift) in the spectrum of the molecule.[91][92][93]

Due to this shifting of the peaks, the method developed for IR quantification of formate, carbonate and oxalate can not be used.

Subsequently, a portion of the post-reaction mixture was taken to perform the esterification. The reaction conditions were the same used previously: T=78°C and t=2h, ethanol as solvent and reagent, and concentrated H_2SO_4 as catalyst. After the reaction, an aliquot of the mixture was analyzed by means of GC-MS, in order to detect stemming of oxalate.

As future work, the GC-MS data of these analysis need to be processed, to establish if further conclusions regarding this labelling approach can be made.

3.1.6 Effect of reaction conditions:

In parallel to the mechanistic investigation, different values of reaction time and temperature were explored in order to maximize CO_2 fixation and oxalate yields. In figure 23 is reported the carbon balance of this screening. The carbon input is referred to the initially added solid carbon in the form of potassium formate, while the carbon output is detected by the reaction mixture using quantitative IR spectroscopy.
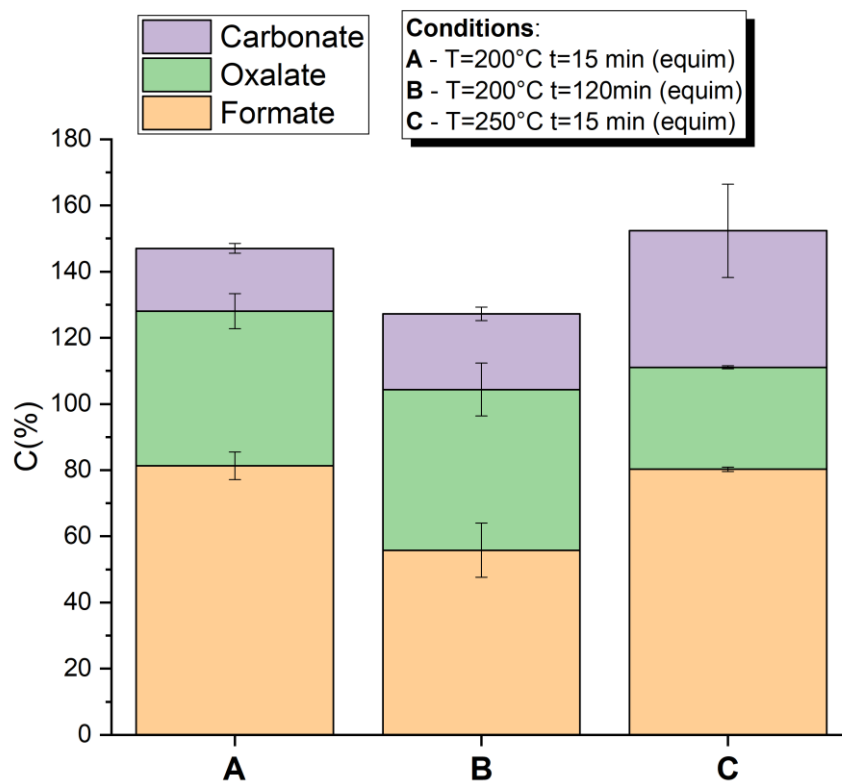
Figure 23: carbon balance comparison for different conditions of time and temperature: case A (T=200°C, t=15 min), case B (T=200°C, t=120min), case C (T=250°C, t=15min)

The conditions investigated were as shown for case A (T=200°C, t=15 minutes), case B (T=200°C, t=120 minutes), and case C (T=250°C, t=15 minutes).

For all these experiments, the outcome of weight increase and hydride consumption was comparable to previous experiments: weight gain around 25% and almost full consumption of the hydride.

For experiments at longer time (t=120min), conversion of the initial formate was around 50%, with good selectivity to the oxalate, but just slightly better if compared to experiments performed at t=15 min at T=200°C. These conditions showed a poorer CO_2 incorporation, a suggesting that formate may undergo some degree of decomposition if exposed for a longer time at a temperature above its melting point.

For experiments at higher temperature (T=250°C), conversion of the initial formate was around 20%. Even though CO_2 fixation was higher if compared with experiments conducted for a longer time, there seems to be a higher selectivity to carbonate and a lower one to oxalate.

In figure 24 are reported the oxalate yields for the different cases.
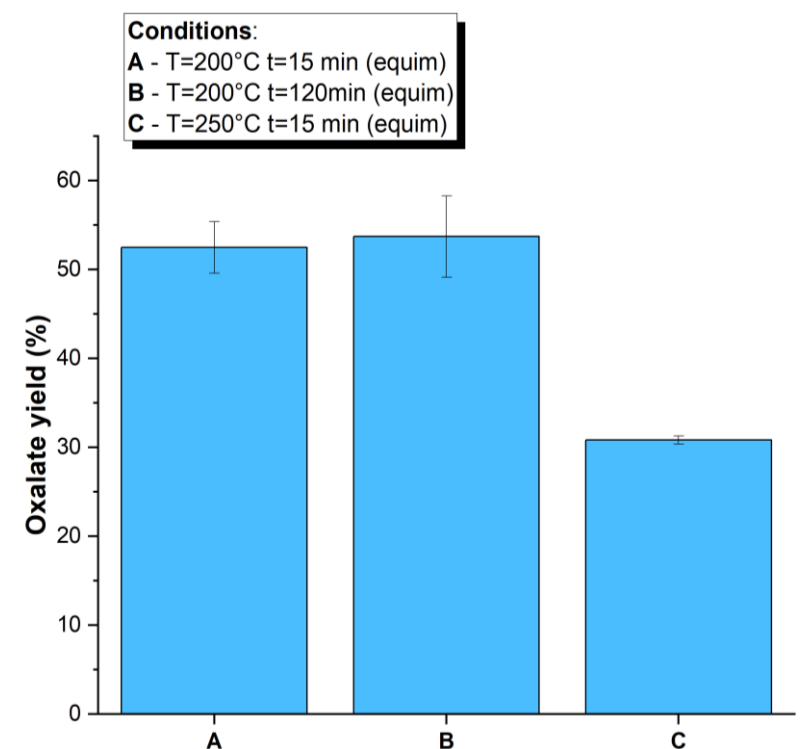
Figure 24: oxalate yields comparison for different conditions of time and temperature: case A (T=200°C, t=15 min), case B (T=200°C, t=120min), case C (T=250°C, t=15min)

The experiments conducted at a higher temperature (case C) showed the lower oxalate yields. On the other hand, oxalate yields of case A and B were comparable.

From the results obtained it is possible to conclude that, out of tested conditions, the optimal ones were for T=200°C and t=15 min.

There is still room for further investigate these conditions. Moreover, there is the need to investigate on what leads to almost full consumption of the hydride during reaction, without leading to almost full conversion of the present formate. It could be the case where there is carbonite trapped in the solid products, without any reagent left to react. To investigate this possibility, it was attempted to fill the reactor with CO_2 and perform the reaction twice in a row, but there were some problems with pressurizing the CO_2 in the reactors. As a matter of fact, the obtained results of this investigation showed that there were not enough CO_2 available to react, as it seems that regular formate coupling took place.

3.2 Alternative coupling with aldehydes – p-formaldehyde and benzaldehyde

Para-formaldehyde and benzaldehyde were considered for proof of principles, as they exhibit suitable proprieties for the reaction conditions and for the attractiveness of the desired product. On one hand, out of the possible aldehydes partners, benzaldehyde would be less prone to undergo undesired reactions and its physical properties allow to carry on the process in an ideal system. On the other hand, although p-formaldehyde poses many difficulties in terms of side reactions, the prospective of obtaining glyoxylic acid as desired product is very appealing. Thus, the AFC was performed for both reagents, using an equimolar mixture of potassium formate and sodium hydride and different reaction setups.

The appearance of the post-reaction mixtures is different for both partners: with p-formaldehyde the mixture is in solid form, while for benzaldehyde the mixture is in a foam-like structure.

The post-reaction mixtures of these partners were both analysed using GC (temperature ramp from 60°C to 280°C), using a chromatogram of the desired product as comparison. According to the results obtained, apparently these reactions did not work.

The post-reaction mixture with p-formaldehyde as reaction partner was analysed using a liquid cell in IR spectroscopy, while for benzaldehyde as reaction partner IR spectroscopy in ATR mode was used. However, due to the various products present in the mixture, these analyses are hard to interpretate, so they do not supply any further information.

The post-reaction mixture with p-formaldehyde as reaction partner was analysed using liquid chromatography LC, to look for traces of glyoxylic acid. Instead, very little traces of glycolic acid were found. This could suggest a side reaction took place, an aldol condensation within two molecules of formaldehyde.

There is still room to further investigate these setups, especially regarding the separation and analysis of the reaction mixture, as a complex mixture of products is obtained, which is difficult to assess.

4. Conclusions

A broad variety of potential alternative coupling partners for formate utilizing the active carbonite intermediate were assessed and ranked. A multi-stage process was used in which first potential classes of molecules were selected. For each class, a variety of commercially available compounds was analysed in depth for its potential suitability in the reaction. This analysis has shown that a wide variety of factors come into play and especially the reactivity of the hydride catalyst poses a mayor challenge. The three major potential classes of compounds suitable for the coupling are carbon oxides (CO_2 & CO) and aldehydes.

To find the overall best coupling partner with the highest potential for commercial success an arbitrary ranking was applied as the second step to identify which compound to test first. In this ranking the reactants sustainability, ease of commercial operation and commercial attractiveness of the product were considered. The three highest ranking compounds were CO_2, CO, benzaldehyde and para-formaldehyde. As CO_2 showed the highest potential, proof-of-principle experiments with the formate – hydride- CO_2 system were performed.

In proof-of-principle experiments CO_2 was successfully incorporated in the form of carbonate, oxalate and potentially formate. The overall incorporation efficiency based on the hydride consumption was shown to be 50%. It is suggested to continue this work with mechanistic studies to understand the reaction in detail. Based on further gained knowledge, the reaction can then be optimized towards optimal CO_2 incorporation in the form of oxalate.

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