REVIEW

Valorization of Carbon Dioxide into Oxazolidinones from Aziridines

Katie J. Lamb[a], Ian D. V. Ingram[a], Michael North[a]*, Mani Sengoden[a]

[a]Green Chemistry Centre of Excellence, Chemistry Department, University of York, York, UK;

• **Abstract:** The reduction of carbon dioxide has gained much attention due to increasing environmental concerns about global warming associated with carbon emission from industrial effluents and public transport etc. In this regard, over the past few years considerable attention has been made on the development for the chemical conversion of carbon dioxide and its incorporation into synthetic organic molecules under mild and "green" conditions. In recent years, significant effort has been dedicated to study the fixation of carbon dioxide with aziridines to afford oxazolidinones, which is an environmental friendly and atom economical process. In this review, we would like to discuss the efficiency of different developed catalytic systems, by comparing and analyzing each reaction matrix such as pressure, temperature, substrate scope, and product selectivity

Keywords: Carbon dioxide, oxazolidinones, aziridines, metal catalysis, organocatalysis.

1. INTRODUCTION

Oxazolidinones comprise a very significant class of molecules, with uses both as synthetic auxiliaries and as pharmaceuticals. Oxazolidinone antibiotics, most notably Linezolid, are important monoamine oxidase inhibitors for the treatment of resistant infections including MRSA and drug-resistant tuberculosis.[1-3] The anticoagulant Rivaroxaban, used for treating deep vein thrombosis,[4] has a very similar structural motif to 1, also based around an oxazolidinone (Figure 1). Chiral oxazolidinone "Evans" auxiliaries have been important for asymmetric synthesis, especially aldol reactions, for several decades.[5]
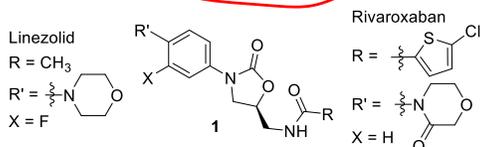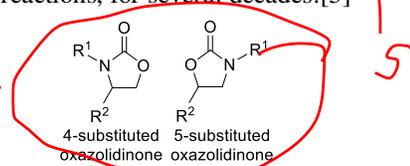

Figure 1: General structures of oxazolidinones (top) and examples of important oxazolidinone pharmaceuticals (bottom).

Several approaches exist to prepare oxazolidinones (Scheme 1), with the most obvious being the reaction of an amino alcohol with phosgene. Whilst this approach has advantages in terms of preserving the regio- and stereochemical arrangement of the starting amino alcohol, the drawbacks both in terms of the toxicity of phosgene and the relatively poor atom economy of the reaction, which loses two equivalents of chloride, are obvious. Similar chemistry with dialkyl carbonates or urea has also been reported and clearly these represent a more sustainable approach from these amino alcohol substrates.[6,7]
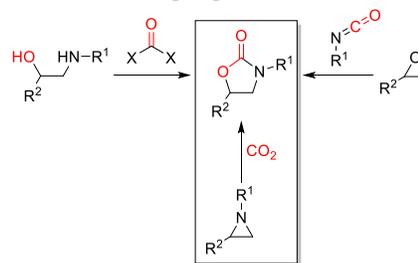
Scheme 1: Main routes to oxazolidinones.

Perhaps the most significant non-aziridine route to oxazolidinones is the reaction of isocyanates with epoxides. This has several advantages in that epoxides are easily prepared from alkenes, often with the use of mild reagents, and the reaction with the isocyanate is fully atom economical. In many ways this chemistry is analogous to the similar reaction between epoxides and carbon dioxide,[8] and many of the same Lewis acid catalysts can be used to activate the epoxide substrate.[9-11] The disadvantage of this approach lies with the use of isocyanates, which are very

* Address correspondence to Professor Michael North at Green Chemistry Centre of Excellence, Chemistry Department, University of York, P.O. Box: YO10 5DD, York, United Kingdom; Tel: +44-1904-324545; E-mails: michael.north@york.ac.uk

toxic with methyl isocyanate being the chemical involved in the 1984 Bhopal disaster, the most serious chemical accident in history.[12] Isocyanates can also react violently with water, increasing the chances of being unintentionally dispersed, as happened at Bhopal.

The preparation of oxazolidinones from aziridines and carbon dioxide, therefore, is clearly attractive: Carbon dioxide is a non-toxic and inexpensive reagent, commonly available as a waste product from a number of industrial processes, and the reaction with the aziridine occurs with 100% atom economy. However, some caution is necessary as aziridines themselves are toxic and expected to be carcinogenic due to their ability to alkylate biological molecules, including DNA, though toxicity data is not available for many examples.[13] Due to the substantial variety of chemistries used to produce these aziridine substrates, discussion of the sustainability of these is outside the scope of this review. The synthesis and chemistry of aziridines was reviewed in detail by Sweeney in 2002.[14]

There is considerable variation in the mechanism of the reaction between an aziridine and carbon dioxide, and a wide variety of catalysts have been used, and some reports exist of catalyst-free reactions. However, in general, a Lewis (or Brønsted) acid catalyst is used in conjunction with a nucleophile, usually a halide, analogously to catalyst systems used for the reaction between epoxides and carbon dioxide.[8] Unlike this reaction, however, there are two possible regioisomers (known as 4-substituted and 5-substituted) of oxazolidinone product depending on which side of the parent aziridine the new oxygen-carbon bond is formed. A plausible general mechanism for this reaction is given in Scheme 2. The selectivity with which either regioisomer is produced is determined by a combination of the electrophilicity of the two sites in the catalyst-aziridine complex, and steric influence upon nucleophilic attack of the same species. In general, this mechanism leads to retention of stereochemistry at the carbon atom bonded to oxygen due to double inversion; however, in some specialised cases, multiple inversions due to excess nucleophile or S_N1 character may lead to racemisation.

This chemistry has not been reviewed since 2012 to our knowledge,[15] and the prior review did not have a strong emphasis on green chemistry, therefore this review will attempt to be comprehensive. Reaction conditions and catalysts will be discussed critically with respect to their sustainability and in accordance with the principles of green chemistry as well as in more traditional catalysis comparative terms such as pressure, temperature, substrate scope, and selectivity. This will include discussions of elemental sustainability where elements are used that are not earth-abundant, are only available in restricted geographical areas, are difficult to recycle, or are in high demand for other essential applications.[16,17] The sustainability of solvents, where they are used, and the overall atom economy of the processes, considering solvent, any sacrificial reagents, and the feasibility of catalyst recovery and re-use will also be discussed.

Scheme 2: Generalised mechanism for the catalysed reaction of aziridines with carbon dioxide.

This chemistry has not been reviewed since 2012 to our knowledge,[15] and the prior review did not have a strong emphasis on green chemistry, therefore this review will attempt to be comprehensive. Reaction conditions and catalysts will be discussed critically with respect to their sustainability and in accordance with the principles of green chemistry as well as in more traditional catalysis comparative terms such as pressure, temperature, substrate scope, and selectivity. This will include discussions of elemental sustainability where elements are used that are not earth-abundant, are only available in restricted geographical areas, are difficult to recycle, or are in high demand for other essential applications.[16,17] The sustainability of solvents, where they are used, and the overall atom economy of the processes, considering solvent, any sacrificial reagents, and the feasibility of catalyst recovery and re-use will also be discussed.

2. DISCUSSION

2.1. Reaction Using Metal Catalysis

Metal catalysis has been researched as an attractive method of aziridine synthesis, as this method requires mild conditions compared to traditional and other synthetic methods.[18-20] The concept of using metal catalysts to promote CO_2 utilization is not new, for example cyclic carbonate synthesis from epoxides and CO_2 is an large area of research.[8,21,22] Oxazolidinone synthesis via metal catalyzed CO_2 utilization, using homogenous or heterogeneous catalysts, has also been researched since the late 20th Century.

Despite epoxides and aziridines only differing by one atom, aziridines have not received as much attention as a reagent for CDU compared to epoxides. This is could be, as phrased by Sweeney in 2002, because they are seen as "*epoxides' ugly cousins.*"[14] Research into synthesizing oxazolidinones via reacting epoxides with isocyanates is therefore a favored route.[9,23] The lower electronegativity of nitrogen does inherently mean that ring-opening of aziridines is not as straightforward as epoxides, but nonetheless is not difficult.

One important factor to always consider when using metal catalysts is the reaction mechanism. The mechanism of oxazolidinone synthesis determines the regioselectivity of the reaction, as depending on which carbon atom of the aziridine is ring-opened will dictate whether the 3,4-oxazolidinone (**4-sub**, **A**) or 3,5-oxazolidinone (**5-sub**, **B**), or a mixture of both, is formed. Factors such as electronic and steric effects of the aziridine functionality, Lewis acidity, and steric hindrance/size of the nucleophile and/or metal catalyst all influence which isomer is favored. The favorability of different metal catalysts systems will therefore be discussed.

2.1.1 Homogenous catalysts

In the late 20th and early 21st century, numerous metal complexes and salts such as LiI[24,25] (**2**, Scheme 3), alkali metal halides[26] (**3**, Scheme 3) and organotin complexes[27] (**4**, Scheme 3) were the first metal catalysts tested in the transformation of CO_2 into oxazolidinones. These catalysts required high catalytic loadings (at least 25 mol% in the case of LiI), high pressures of CO_2 (50-55 bar in the case of organoantimony salts) and reported poor isomer selectivity. The toxicity of organoantimony and organotin components is also undesirable from a green chemistry perspective.
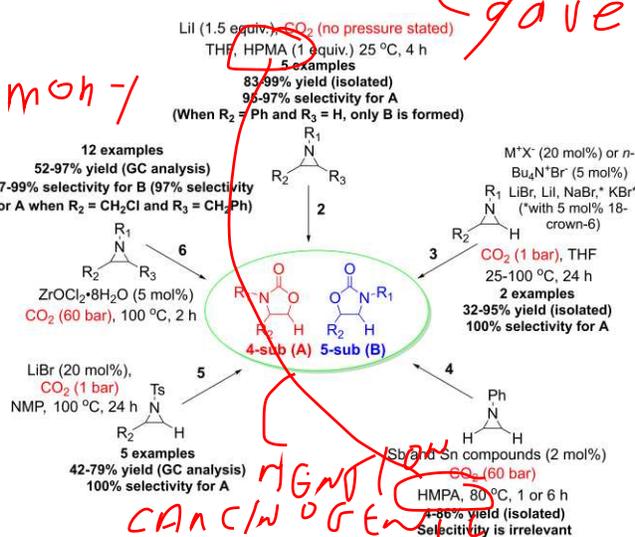
Scheme 3: Early examples of metal catalysts used to synthesis oxazolidinones from aziridines and CO_2

One interesting, and unique, example of metal catalysis was the electrocatalysis of aziridines reported by Tascedda and Duñach in 2000. By using a single component cell, with a Mg anode and steel, carbon or Ni cathode with a current density of 0.3 A dm^{-2}, different Ni(II) complexes at 10 mol% could synthesize oxazolidinones under ambient conditions over 7 h. Conversions however are low compared to other systems, regioselectivity was poor and DMF (now considered a "non" green solvent)[28] was employed as a supporting catalyst.[29]

In 2004, Sudo *et al.* studied the reactivity of N-tosylaziridine with LiBr as a catalyst.[30] Intriguingly, Sudo reported that electron donating groups on N-tosylaziridine lead to an increase in conversion, which was opposite to the trend observed when ring-opening epoxides. Sudo proposed that ring-opening occurred at the unsubstituted/less sterically hindered position of the aziridine. Unfortunately, no isolated yields or conversions close to 100% were reported. The high catalyst loading of LiBr (20 mol%) is also undesirable in terms of reaction mass efficiency (**5**, Scheme 4).

In 2009, Wei Li *et al.* reported that Zirconyl chloride alone could form oxazolidinones from aziridines (up to 12 examples) with different functionalities.[31] Interestingly, the catalyst could be used up to five times and showed an *increase* in activity when used multiple times (**6**, Scheme 4). Extremely high, and energy intensive, pressures of CO_2 (60 bar) were required for the reaction to occur and once again no isolated yields were reported.
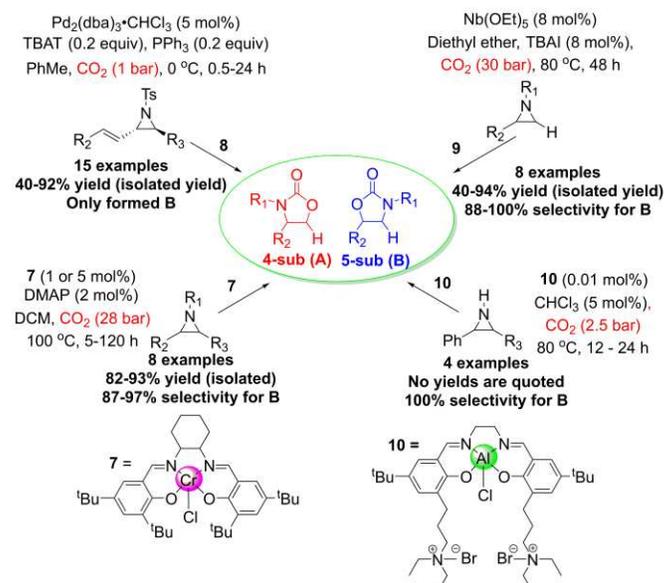
Scheme 4: Homogeneous metals catalysts used in the synthesis of oxazolidinones from aziridines and CO_2.

Metal complexes that can form cyclic carbonates from epoxides and CO_2 can also be used to transform aziridines into oxazolidinones. In 2004, Nguyen used Cr(salen) complex **7** to ring-open aziridines,[32] and reported the most active metal catalyst for this reaction at that time (**7**, Scheme 4). The reaction could even proceed without a Lewis base (co-catalyst). Interestingly, this catalyst also reported favorability for the 5-isomer rather than the 4-isomer, and was affected by which Lewis base was used and the catalyst:co-catalyst ratio. This is also one of the few studies to report the conversion of a disubstituted aziridine.

In 2011, Aggarwal *et al.* investigated transformation of vinylaziridines into vinyloxazolidinones using a Palladium catalyst (**8**, Scheme 4).[33] This work reports one of the few examples in which a conversion of an aziridine with CO_2 into an oxazolidinone occurs under mild conditions (due to the vinyl group being present).

In 2017, Lewis acidic transition metal catalysts YCl$_3$, ScCl$_3$, ZnCl$_4$, Zn(OEt)$_4$, Ti(OEt)$_4$, NbCl$_5$ and Nb(OEt)$_5$ were all screened in the conversion of N-tosyl aziridines. These

aziridines are less reactive than traditional aziridines, due to the presence of an electron withdrawing group on the nitrogen. The catalyst Nb(OEt)$_5$ in conjunction with TBAI was the most active catalyst (**9**, Scheme 4).[34] DFT studies supported preferential ring-opening at the phenyl substituted carbon, in a similar manner to when a Lewis acid and nucleophile/co-catalyst ring-open styrene oxide at the substituted carbon to form styrene carbonate.

In 2014, a bifunctional aluminum catalyst was reported by Xiao-Bing Lu, which could ring-open aziridines as well as epoxides (**10**, Scheme 4).[35] In terms of regioselectivity, ring-opening occurs at the methine carbon to form the 5-substituted oxazolidinone, with a retention of configuration due to double inversion at the methine carbon. Impressively, low catalytic loading of the catalyst was required (only 0.01 mol%) but no isolated yields and conversions were reported for this catalyst.

The use of metal complexes to form oxazolidinones has shown promising results. However, only one catalytic system employed the sustainable metal (aluminum). The use of more abundant metals, and environmentally friendly, green and atom efficient catalytic systems, will be more desirable in the future.

2.1.2 Heterogeneous catalysts

Due to the promising results obtained using homogenous catalysis, recent research has been devoted towards investigating heterogeneous catalysts. These catalysts can be re-used and thus recycled, unlike the majority of homogeneous catalysts, and can therefore potentially provide a "greener" catalyst.

In 2014, a titanium mesoporous metal phosphonate catalyst was reported by Shi Zhang Qiao *et al.* to synthesize numerous oxazolidinones with superb regioselectivity. This catalytic system worked without any co-catalysts, additives or solvent (**11**, Scheme 5).
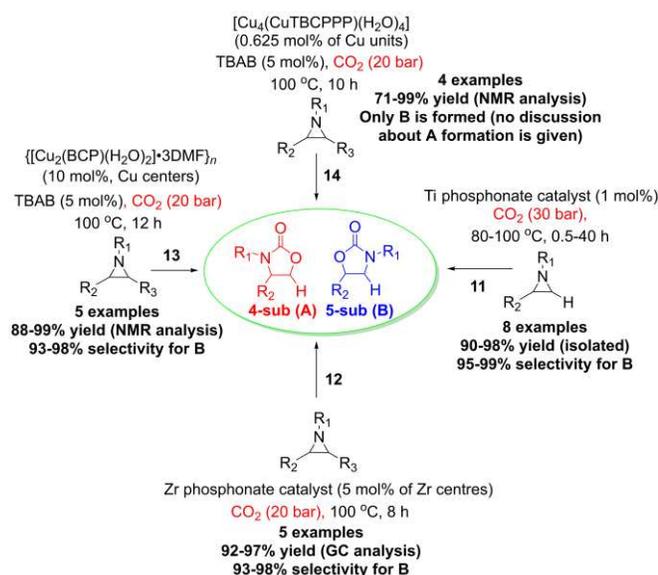
Scheme 5: Heterogeneous metals catalysts used in the synthesis of oxazolidinones from aziridines and CO_2

The catalyst can be isolated after each reaction and was used 10 times with no decline in catalytic activity. Qiao proposed the catalytic activity of the titanium catalyst was due to the combination of P–OH and –NH$_2$ groups in the catalyst, which could ring-open the aziridine and activate CO_2 respectively. The activity of the catalyst was comparable to previously reported catalytic systems.[36]

In a similar study, Yuan *et al.* in 2015 developed mesoporous Zirconium phosphonates as heterogeneous catalysts (**12**, Scheme 5), which could also synthesize oxazolidinones under solvent-free conditions without a co-catalyst. Superb regioselectivity was reported and the catalyst could be recycled five times without a dramatic drop in activity. The absence of isolated yields however is disappointing and further work is required to understand the reaction mechanism of this catalyst.[37]

Metal Organic Frameworks (MOFs) has been investigated as an attractive heterogeneous catalyst to synthesize oxazolidinones using CO_2. In 2016, Liang-Nian He *et al.* reported the first MOF catalyst for aziridine conversion into oxazolidinones, and reported that a [Cu$_{30}$] nanocage based MOF ([Cu$_2$(BCP)(H$_2$O)$_2$]•3DMF)$_n$ **13**, (Scheme 5) could be used up to ten times without losing catalytic activity and showed high regioselectivity.[38] Optimum conditions however were 100 °C and 20 bar of CO_2 for maximum conversions. This catalyst was more active than standard copper salts, but was arguably as active as the standard Copper MOF HKUST. It is therefore debatable if this catalyst is more beneficial to use compared to much simpler standard MOFs. Unfortunately, DMF is required to make the catalyst, which is listed as a "*substance of high concern*" under the Registration, Evaluation, Authorization & restriction of CHemicals (REACH) protocol, due to its high reproduction toxicity.[39] No isolated yields were also reported for this work.

In 2018, the first reported synthesis of oxazolidinones from aziridines using a Copper(II) Metal–MetalloPorphyrin Framework (MMPF, a subclass of MOFs) was performed by Shengqian Ma *et al.* (**14**, Scheme 5). Impressively, this catalyst only required 0.625 mol% catalytic loading of **14** (Cu active sites) and 5 mol% of TBAB to achieve 47% conversion under ambient conditions. This catalyst was more active than the standard Copper MOF HKUST-1, and Mai hypothesized this was due to the ease in accessibility of the metal active site in **14** by the aziridine substrate. This catalyst however required three days to achieve this conversion, and 100 °C and 20 bar of CO_2 to report increased conversions.[40] No isolated yields again are reported. Synthesis of **14** also requires N,N-dimethylacetamide (DMA), which is another "*substance of high concern*" according to REACH.[41] These results nonetheless are promising, and future work is underway to improve **14**'s catalytic performance under milder conditions.

2.1.3 Mechanism considerations

In 2008, Li performed detailed DFT analysis[42] of the reaction mechanism between aziridines and CO_2 conversion into oxazolidinones, via Pinhas's LiI catalytic route.[24,25] Li concluded that changing alkyl substituents on the three

membered ring strongly affects regioselectivity, whereas changing groups on the nitrogen atom seemed to have little to no effect at all.[42] Li proposed that when simple alkyl groups are present on the three membered ring (with functional groups on the nitrogen) ring-opening only occurs at the less sterically hindered carbon-nitrogen bond. Thus, leading to the preferential formation of the 4-substitued regioisomer (**4-sub**). Alternatively, when phenyl is present, ring-opening will only occur at the more substituted carbon-nitrogen bond (i.e. the methine carbon atom), only forming 5-substitued regioisomer (**5-sub**), due to the electronic of the phenyl group stabilizing the reaction intermediate. Changing functional group combinations on the carbon ring and nitrogen, will change regioselectivity and lead to a mixture of products. The more sterically hindering the functional group on the ring, the more likely that the 5-substitued isomer will be formed. Li also concluded that a complex consisting of one molecule of aziridine and CO_2, with Li^+ and I^-, is formed prior to ring-opening (Scheme 6).
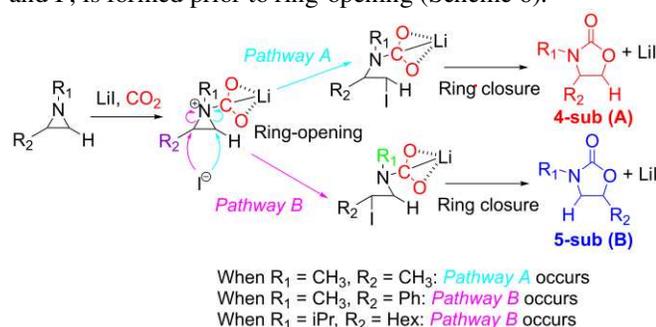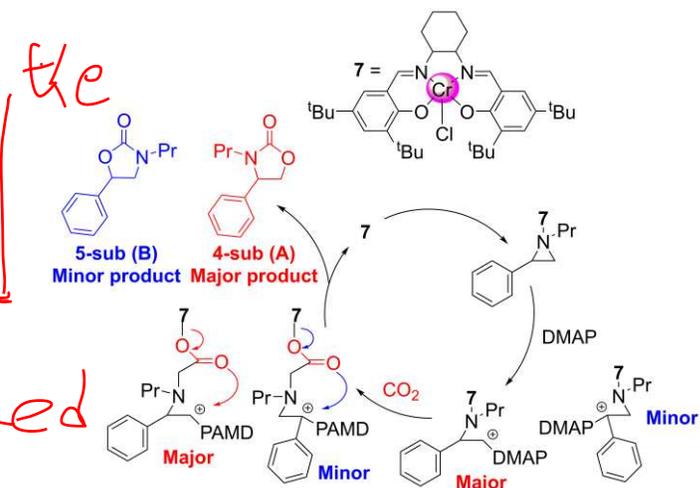

Scheme 6: Reaction mechanism proposed for Pinhas's LiI route by Li via DFT calculations.[42]

In 2014, ten years after their original work into using **7** to form oxazolidinones from aziridines,[32] Nguyen *et al.* analyzed the reaction mechanism via DFT calculations.[43] By studying the ability of **7** to form oxazolidinones in the absence and presence of DMAP, Nguyen deduced that regioselectivity was nucleophile dependent. In the presence of DMAP, ring-opening of the metal-coordinated aziridine intermediate will occur at the less substituted carbon due to the steric bulkiness of DMAP (Scheme 7).

In the absence of DMAP, ring-opening occurs at the substituted position, in a similar manner to Li's findings for the reaction mechanism of Pinhas's catalytic system (Scheme 8). Nguyen reported this this distinctive selectivity was due to "*preferential intramolecular ring-opening at the more substituted carbon of the aziridine ring in a (salen)CrIII(aziridiumcarbamate) intermediate*."

In terms of reaction mechanisms, different catalysts, mixtures of catalysts/co-catalysts and reaction conditions, have reported different regioselectivity. It is therefore important to note that the reaction mechanism for aziridine-CO_2 conversion is still unclear and has currently been analyzed on a case-by-case basis.[42] Ultimately, more detailed mechanistic studies like these need to be done, with an emphasis towards how the mechanism changes using a wide scope of aziridine substrates.

Scheme 7: Reaction mechanism proposed for catalyst 7 route by Nguyen via DFT calculations in the presence DMAP.[43]
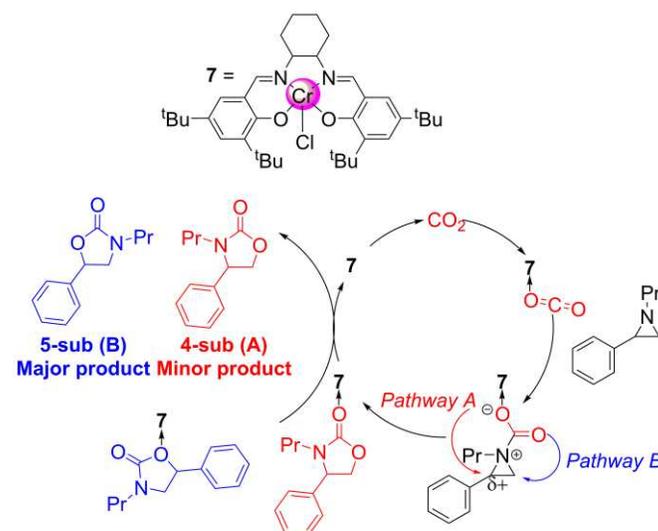
Scheme 8: Reaction mechanism proposed for catalyst **7** route by Nguyen via DFT calculations in the absence of DMAP.[43]

Reaction using Organocatalysis

In recent years, organocatalysis has emerged as a powerful catalyst in the synthetic community as they have high stability, are environmentally benign, inexpensive, easy preparation and simple to use.[44-45] Considerable attention has been given to the chemical transformation of carbon dioxide and aziridines to form oxazolidinones using organocatalysts, with the aim to develop new effective catalytic systems that can tackle a broad substrate scope, with high selectivities under mild reaction conditions.

2.2.1 Organocatalysis with small molecules

In 2008, He and co-workers developed a recyclable quaternary ammonium bromide organocatlayst bound to polyethylene glycol (($NBu_3Br)_2$/PEG6000), for the cycloaddition of aziridines with CO_2.[46] The reaction was carried out using 0.25 mol% of PEG6000($NBu_3Br)_2$ at 80 bar CO_2 and 100 °C (Scheme 9). It is worth mentioning that the reaction rate was greatly influenced by CO_2 pressure,

across the range of 10 to 80 bar. However, a low reaction rate was observed with further increases in CO_2 pressure. This may have been due to the lower vicinity of the catalyst with aziridine.
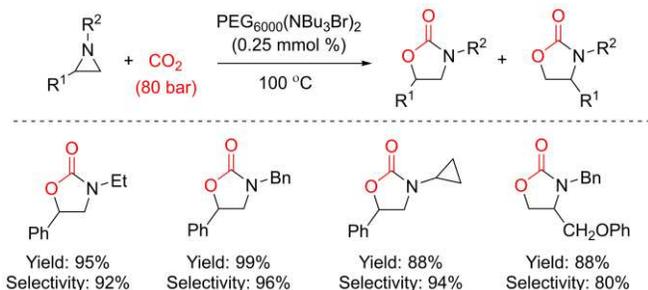
Scheme 9: PEG6000(NBu_3Br)_2 catalysed chemical fixation of CO_2 with aziridines.

Furthermore, the same group utilized Lewis basic ionic liquids as a catalyst for the synthesis of oxazolidinones from 2-aryl aziridines and CO_2.[47] A series of ionic liquids based on $C_{n+1}DABCO^+$ cations and Cl^-, Br^-, OH^-, BF_4^-, PF_6^- or Tf_2N^- anions were investigated for the fixation of CO_2 fixation with 1-ethyl-2-phenylaziridine, at 90 °C and 60 bar CO_2 for 3 h under solvent free conditions (Scheme 10). It was found that [C_4DABCO]Br was the most active catalyst. The desired oxazolidinones were obtained with yields up to 95% and 99% selectivity. The authors also demonstrated the reusability of the catalyst, as it could be used in four cycles without a significant loss in activity.


Scheme 10: [C_4DABCO]Br catalysed synthesis of substituted oxazolidinones.

An improvement of the above work was reported using protic onium salts to synthesise 5-aryl-2-oxazolidinones under a CO_2 atmosphere at room temperature.[48] By testing various pyridinium salts, it was found that the activity of the catalyst was greatly influenced by nucleophilicity and leaving ability of the anion. Anions such as HSO_4^-, $H_2PO_4^-$ and NO_3^- were found to be ineffective and halides showed an increase in activity going from chloride to iodide anion. Notably, the reaction was promoted by hydrogen bonding between the aziridine and protic onium salts, which in turn could activate the aziridine ring (Scheme 11). The catalyst could be reused five times, yielding corresponding oxazolidinones in 94-98% yields with excellent selectivity.

Qi *et al.* reported that polystyrene supported threonine (PS-Thr) has good activity for the synthesis of oxazolidinones from the fixation of CO_2 with 2-aryl aziridines.[49] When the reaction was carried out using 2-phenylaziridine and 1-methyl-2-phenylaziridine as the substrate, low yields were reported due to self-oligomerization of the aziridines. On the other hand, alkyl

aziridines, such as ethyl, butyl and cyclohexyl derivatives, gave the desired oxazolidinones in good to high yields.
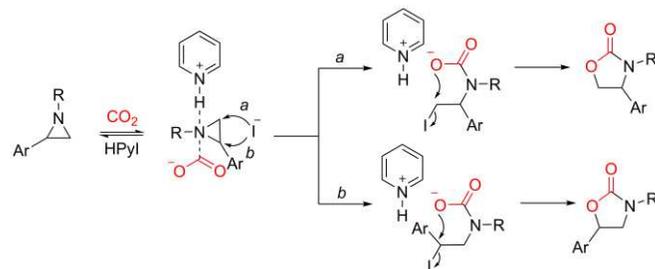
Scheme 11: Pyridinium iodide (HPyI) catalyzed synthesis of substituted oxazolidinones.

Qi *et al.* reported that polystyrene supported threonine (PS-Thr) has good activity for the synthesis of oxazolidinones from the fixation of CO_2 with 2-aryl aziridines.[49] When the reaction was carried out using 2-phenylaziridine and 1-methyl-2-phenylaziridine as the substrate, low yields were reported due to self-oligomerization of the aziridines. On the other hand, alkyl aziridines, such as ethyl, butyl and cyclohexyl derivatives, gave the desired oxazolidinones in good to high yields.

In a subsequent study from the same group, it was found that simple, naturally occurring α-amino acids could catalyse the cycloaddition of CO_2 to 2-aryl aziridines.[50] A variety of α-amino acids were screened and *L*-histidine was found to be the most active α-amino acid, yielding 99% of desired 5-aryl oxazolidinone with 93% regioselectivity, at 80 bar CO_2 pressure and 110 °C. Mechanistically, the authors suggest that the aziridine is first activated by forming a hydrogen bond with the amino acid. Nucleophilic attack of the aziridine then occurs by the carboxylate ion of another amino acid. Since the bond dissociation energy is lower for nucleophilic attack at the benzylic position, ring-opening at this position (intermediate *a*, Scheme 12) is more favored than the terminal position (intermediate *b*, Scheme 12).[51] According to Baldwin's rules, nucleophilic attack of the aziridine by the carboxylate ion of the same amino acid engaging in hydrogen bonding is unfavorable.[52] Consequently, Dou *et al.* reported that *L*-proline could be used as a catalyst for the coupling of CO_2 and aziridines.[18] The optimum reaction conditions were when 5 mol% of *L*-proline was employed at 60 bar of CO_2 and 110 °C.
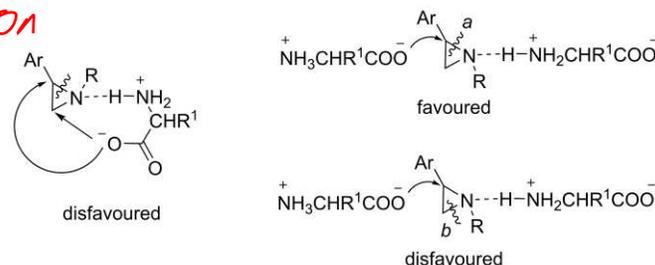

Scheme 12: Proposed mechanism for the α-amino acid catalyzed reaction.

Wu and Liu reported that 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) could catalyse the fixation of CO_2 and aziridines to form 2-substituted

oxazolidinones, using LiI as an additive under atmospheric pressure.[53] Different catalysts, such as, 1,8-diazabi-cyclo[5.4.0]undec-7-ene (DBU), DMAP, triethylamine and DBN, as well as different additives, like KI, LIBr and LiI were all screened. By testing all of these systems in toluene, it was found that the combination of 10 mol% DBN and 20 mol% LiI gave the best yields for the desired 2-oxazolidinone derivatives. Various N-alkyl aziridines reacted under these conditions to give the corresponding 2-oxazolidinones in 82-95% yield (Scheme 13). The only exception is the 2-methyl substituted aziridine, which only gave 65% yield of the corresponding oxazoldinone and reported poor regioselectivity. The high use if Li is not ideal in terms of sustainability, as it is one of the more rare elements in the periodic table.
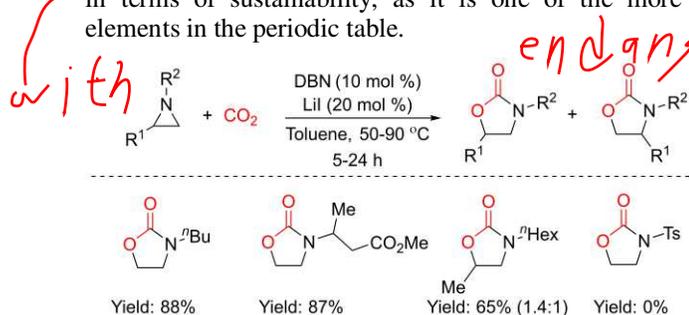
Scheme 13: DBN catalysed synthesis of 2-substituted oxazolidinones.

Zhang *et al.* reported that potassium phthalimide could capture, and easily desorb, almost equimolar amounts of CO_2. Subsequently, it was found by reacting CO_2 captured K[Phth] with 1-ethyl-2-phenylaziridine, the synthesis of 3-ethyl-5-phenyloxazolidin-2-one was afforded in 90% yield at 40 °C (Scheme 14).[54]
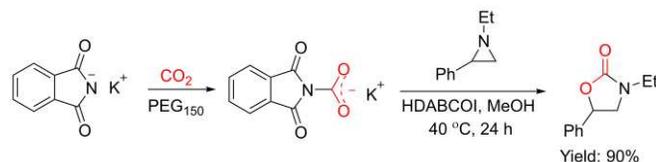

Scheme 14: Transformation of CO_2 captured K[Phth] into oxazolidinone. HDABCOI = 1,4-diazabicyclo[2.2.2]octan-1-ium iodide.

In 2013, Ikariya and co-workers developed the first N-heterocyclic carbenes (NHCs) based systems for this transformation.[55] The reaction was carried out employing NHC-CO_2 adducts as an active catalytic system for the chemical fixation of CO_2 with aziridines for the synthesis of 2-substituted oxazolidinones. 1,3-Bis(*tert*-butyl)-imidazolium-2-carboxylate (NHC-CO_2) could be generated by treating CO_2 (1 bar) with imidazolium tetrafluoroborate and an equimolar amount of KO^{t}Bu in THF. When the catalytic activity of this catalyst was investigated over increasing temperatures of 60-100 °C, under 50 bar CO_2 pressure for 15 h in 2-propanol, the maximum yield (92%) was obtained at 90 °C. This could be due to a dynamic catch and release process occurring with the presence of the NHC catalyst in the reaction. However, the reaction could not occur under atmospheric pressures of CO_2. The reusability of

the catalyst was investigated using N-benzylaziridine, and found it could be reused six times, affording the corresponding oxazolidinone in 90-92% yields.

Recently, Saptal and Bhanage investigated the activity of N-heterocyclic olefins (NHOs) for the fixation of CO_2 and aziridines to form oxazolidinones.[56] Different substituted aziridines were reacted with CO_2 in the presence of 0.4 mol% NHO, under 20 bar pressure of CO_2 at room temperature to give corresponding the oxazolidinones in good to high yields (Scheme 15). Although increasing the steric hindrance of the aziridines led to lower yields, this could be overcome by increasing the reaction temperature (60 °C) or CO_2 pressure (40 bar).
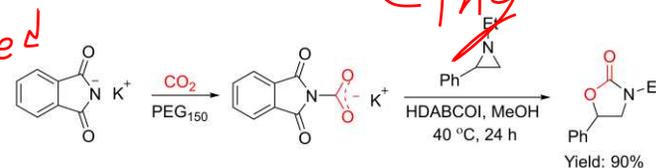
Scheme 15: NHO catalysed synthesis of substituted oxazolidinones.

2.2.2 Polymer and supported catalysts

Polymeric or polymer supported catalysts offer a number of advantages over homogeneous catalysts; they are usually heterogeneous and easily recycled, the polymer might improve the practical activity of an otherwise insoluble active functionality, and multiple, cooperative, catalytic moieties might be tethered in close proximity, leading to improved reaction kinetics relative to an otherwise intermolecular solution-phase mechanism.

The first recyclable polymer-tethered catalyst for this chemistry was developed by Du *et al.* in 2008 and employed a simple tributylammonium bromide tethered to polyethylene glycol.[46] This catalyst **18** acts solely as a source of bromide, with no hydrogen bonding or Lewis acid component present to activate the aziridine. Interestingly, the activity of the catalyst is significantly higher than a simple binary mixture of PEG with tetrabutylammonium bromide. The authors speculate that tethering to PEG allows the ammonium halide to be fully soluble and well mixed into the carbon dioxide expanded PEG reaction mixture (Figure 2).
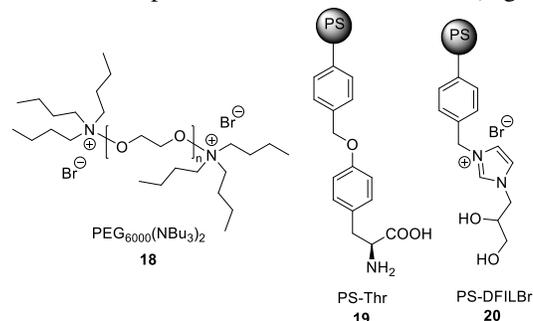

Figure 2: Polyethylene glycol and polystyrene supported catalysts developed by Du,[46] Qi,[49] and Watile.[57]

The reaction is carried out at 100 °C under 80 bar of carbon dioxide using 0.25 mol% of catalyst. Reaction times

range from 15 minutes (R_1 = Me, H) to 24 hours (R_1 = ^{i}Pr) for full conversion depending on the substrate, with the most sterically demanding at nitrogen being the slowest and the example where R_1 = ^{t}Bu only reaching 50% conversion after 72 hours.

In 2010, Qi *et al.* used polystyrene supported amino acids **19** as catalysts for the reaction of both epoxides and aziridines with carbon dioxide.[49] Threonine supported on polystyrene was the most successful catalyst, with the supported amino acid being more active than threonine alone, perhaps due to reduced solubility requirements. For a variety of N-alkyl substituted (R_1 = alkyl) aryl (R_2 = phenyl/substituted phenyl) aziridines, the reaction was performed using 0.6 mol% of the supported catalyst at 80 bar carbon dioxide pressure and 100 °C for 24 hours without solvent. In most cases these reactions were selective for the 5-substituted oxazolidinone (>95% selectivity) with the exception of the unalkylated (R_1 = H) example, which gave 15% of the 4-substutited regioisomer. Conversions were generally quantitative over this timescale, with the exception of very sterically demanding (R_1 = ^{t}Bu) aziridines. The authors propose that the protonated ammonium centre of the amino acid zwitterion acts as a Lewis acid, with a neighbouring carboxylate acting as a nucleophile as the carboxylate on the same amino acid functionality is forbidden from acting as a nucleophile in this context by Baldwin's rules. Re-use of the catalyst was demonstrated over 5 cycles with only a minor loss of activity.

Watile *et al.* used a similar polystyrene based support to immobilise their diol-functionalised imidazolium ionic liquid type catalyst **20** in 2011.[57] This system is particularly remarkable for being effective at room temperature, using 1.5 mol% catalyst at 50 bar pressure of carbon dioxide. TOF values up to 22 h^{-1} are quoted for a variety of phenyl aziridines (R_2 = Ph) with various N-alkyl substituents. In all cases, selectivity towards the 5-substituted regioisomer is >90%. Mechanistically, the diol moiety is supposed to activate the aziridine by a cooperative hydrogen bonding mechanism, with the halide counterion acting as nucleophile.

The same group also approached the same chemistry from a very different direction in 2012, using unmodified chitosan as single-component catalyst **21** (Figure 3).[58] Chitosan is a widely available amino-polysaccharide usually derived from crustacean shell waste, though it is also alternatively available from fungi, including in the waste products of industrial fungal fermentation and agricultural mushroom waste.[59] Given the lack of a nucleophilic co-catalyst and with only amine and hydroxyl functionalities present to act as hydrogen-bonding donor and nucleophile respectively, the performance of the catalyst is surprisingly good. A very high catalyst loading of 20 wt% is used, without solvent, at 70 °C for 7 hours under 50 bar of carbon dioxide. Again, a variety of phenyl aziridines were demonstrated with various alkyl groups on the nitrogen atom, with most examples giving yields in excess of 90% except the most sterically demanding examples (R_1 = ^{t}Bu, Cyclohexyl) or R_1 = H, which showed lower selectivity (11% 4-substituted) and lower yield (61%). Recyclability of

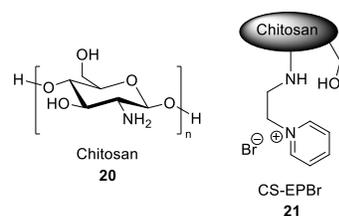the catalyst was demonstrated over 5 cycles with only a minor loss of activity.

Figure 3: Chitosan and chitosan based pyridinium catalysts developed by Watile[58] and Kathalikkattil.[60]

Kathalikkattil *et al.* took a slightly different approach in the same year, using chitosan functionalised with a pyridinium halide catalyst **22**, with the best performing being bromide (Figure 3).[60] The only substrate demonstrated was methyl aziridine (R_1 = H, R_2 = CH_3) which achieved 98% conversion in a semi-batch process where carbon dioxide was continuously supplied to maintain a pressure of 8 bar using 0.71 mol% of catalyst at 100 °C for 4 hours in tetrahydrofuran. Interestingly, this method gave 94% selectivity to the less-common 4-substituted isomer. The catalysis is believed to involve hydrogen bonding to the chitosan backbone, with the bromide acting as a nucleophile. After 5 cycles of re-use, this catalyst still gave conversions in excess of 80%.

CONCLUSION AND SUMMARY

Forming oxazolidinones via metal catalysis and organocatalysis is still in its infancy, compared to other well-established CDU routes. Metal catalysts have shown promising results, with some cases reporting great yields and superb regioselectivity, with extremely low catalytic loading in some cases. On the other hand, there needs to be a real emphasis towards creating sustainable catalysts with more abundant metals. Organocatalysis can provide an alternate method to afford oxazolidinones from aziridines and carbon dioxide, with the majority of examples using abundant and green reagents and showing superb reusability. Finding reaction systems that require less strenuous reaction conditions would be ideal. More catalytic systems also need to be tested against di-substituted aziridines overall. Nonetheless, the current literature is promising, and as Sweeney said in his 2002 review "*the future is bright for aziridine research.*"[14]

CONFLICT OF INTEREST

All authors declare no conflict of interest

ACKNOWLEDGEMENTS

REFERENCES

1. Pradeep, S. J.; Maulikkumar, D. V.; Tejas, M. D.; Asit, K. C., Oxazolidinones as Anti-tubercular Agents: Discovery, Development and Future Perspectives. *Curr. Med. Chem.* **2015**, *22* (38), 4379-4397.

2. Giovanni, Z.; Pilar, M.; Giuliano Delle, M.; Domenico, M.; Laura, N.; Bruno, B., The Contribution of Oxazolidinone Frame to The Biological Activity of Pharmaceutical Drugs and Natural Products. *Mini-Rev. Med. Chem.* **2007**, *7* (4), 389-409.

3. Douglas, K. H., Oxazolidinone Antibacterial Agents: A Critical Review. *Curr. Trends Med. Chem.* **2003**, *3* (9), 1021-1042.

4. Investigators, E.; Bauersachs, R.; Berkowitz, S. D.; Brenner, B.; Buller, H. R.; Decousus, H.; Gallus, A. S.; Lensing, A. W.; Misselwitz, F.; Prins, M. H.; Raskob, G. E.; Segers, A.; Verhamme, P.; Wells, P.; Agnelli, G.; Bounameaux, H.; Cohen, A.; Davidson, B. L.; Piovella, F.; Schellong, S., Oral rivaroxaban for symptomatic venous thromboembolism. *N. Engl. J. Med.* **2010**, *363* (26), 2499-510.

5. Evans, D. A.; Bartroli, J.; Shih, T. L., Enantioselective aldol condensations. 2. Erythro-selective chiral aldol condensations via boron enolates. *J. Am. Chem. Soc.* **1981**, *103* (8), 2127-2129.

6. Yadav, G. D.; Pawar, S. V., Novelty of immobilized enzymatic synthesis of 3-ethyl-1,3-oxazolidin-2-one using 2-aminoalcohol and dimethyl carbonate: Mechanism and kinetic modeling of consecutive reactions. *J. Mol. Catal. B: Enzym.* **2014**, *109*, 62-69.

7. Dinsmore, C. J.; Mercer, S. P., Carboxylation and Mitsunobu Reaction of Amines to Give Carbamates: Retention vs Inversion of Configuration Is Substituent-Dependent. *Org. Lett.* **2004**, *6* (17), 2885-2888.

8. Comerford, J. W.; Ingram, I. D. V.; North, M.; Wu, X., Sustainable metal-based catalysts for the synthesis of cyclic carbonates containing five-membered rings. *Green Chem.* **2015**, *17* (4), 1966-1987.

9. Castro-Osma, J. A.; Earlam, A.; Lara-Sánchez, A.; Otero, A.; North, M., Synthesis of Oxazolidinones from Epoxides and Isocyanates Catalysed by Aluminium Heteroscorpionate Complexes. *ChemCatChem* **2016**, *8* (12), 2100-2108.

10. Speranza, G. P.; Peppel, W. J., Preparation of Substituted 2-Oxazolidones from 1,2-Epoxides and Isocyanates. *J. Org. Chem.* **1958**, *23* (12), 1922-1924.

11. Beattie, C.; North, M., Mechanistic Investigation of the Reaction of Epoxides with Heterocumulenes Catalysed by a Bimetallic Aluminium Salen Complex. *Chem.-Eur. J.* **2014**, *20* (26), 8182-8188.

12. Varma, D. R.; Guest, I., The Bhopal accident and methyl isocyanate toxicity. *J. Toxicol. Environ. Health* **1993**, *40* (4), 513-529.

13. Ulrich Steuerle, R. F. Aziridines In: *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley: 2006.

14. Sweeney, J. B., Aziridines: epoxides' ugly cousins? *Chem. Soc. Rev.* **2002**, *31* (5), 247-258.

15. Qing-Wen, S.; Ya-Nan, Z.; Liang-Nian, H.; Jian, G.; Zhen-Zhen, Y., Synthesis of Oxazolidinones/Polyurethanes from Aziridines and CO_2. *Curr. Catal.* **2012**, *1* (2), 107-124.

16. Hunt, A. J.; Farmer, T. J.; Clark, J. H., *Element Sustainability and the Importance of Scarce Element Recovery*. **2013**; pp 1-28.

17. Hunt, A.; Kraus, G. A.; Clark, J. H., *Element Recovery and Sustainability*. Royal Society of Chemistry: **2013**.

18. Dou, X. Y.; He, L. N.; Yang, Z. Z., Proline-catalyzed synthesis of 5-aryl-2-oxazolidinones from carbon dioxide and aziridines under solvent-free conditions. *Synth. Commun.* **2012**, *42* (1), 62-74.

19. Kawanami, H.; Ikushima, Y., Regioselectivity and selective enhancement of carbon dioxide fixation of 2-substituted aziridines to 2-oxazolidinones under supercritical conditions. *Tetrahedron Lett.* **2002**, *43* (21), 3841-3844.

20. Shen, Y. M.; Duan, W. L.; Shi, M., Chemical fixation of carbon dioxide co-catalyzed by a combination of Schiff bases or phenols and organic bases. *Eur. J. Org. Chem.* **2004**, (14), 3080-3089.

21. North, M.; Pasquale, R.; Young, C., Synthesis of cyclic carbonates from epoxides and CO_2. *Green Chem.* **2010**, *12* (9), 1514-1539.

22. Martin, C.; Fiorani, G.; Kleij, A. W., Recent Advances in the Catalytic Preparation of Cyclic Organic Carbonates. *ACS Catal.* **2015**, *5* (2), 1353-1370.

23. Baronsky, T.; Beattie, C.; Harrington, R. W.; Irfan, R.; North, M.; Osende, J. G.; Young, C., Bimetallic Aluminium(salen) Catalyzed Synthesis of Oxazolidinones from Epoxides and Isocyanates. *ACS Catal.* **2013**, *3* (4), 790-797.

24. Hancock, M. T.; Pinhas, A. R., Synthesis of oxazolidinones and 1,2-diamines from *N*-alkyl aziridines. *Synthesis (Stuttg)* **2004**, (14), 2347-2355.

25. Hancock, M. T.; Pinhas, A. R., A convenient and inexpensive conversion of an aziridine to an oxazolidinone. *Tetrahedron Lett.* **2003**, *44* (29), 5457-5460.

26. Sudo, A.; Morioka, Y.; Koizumi, E.; Sanda, F.; Endo, T., Highly efficient chemical fixations of carbon dioxide and carbon disulfide by cycloaddition to aziridine under atmospheric pressure. *Tetrahedron Lett.* **2003**, *44* (43), 7889-7891.

27. Matsuda, H.; Ninagawa, A.; Hasegawa, H., Reaction of carbon-dioxide with 1-phenylaziridine catalyzed by organo-antimony and organotin compounds. *Bull. Chem. Soc. Jpn.* **1985**, *58* (9), 2717-2718.

28. Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F., Updating and further expanding GSK's solvent sustainability guide. *Green Chem.* **2016**, *18* (13), 3879-3890.

29. Tascedda, P.; Dunach, E., Electrosynthesis of cyclic carbamates from aziridines and carbon dioxide. *Chem. Commun.* **2000**, (6), 449-450.

30. Sudo, A.; Morioka, Y.; Sanda, F.; Endo, T., *N*-tosylaziridine, a new substrate for chemical fixation of carbon dioxide via ring expansion reaction under atmospheric pressure. *Tetrahedron Lett.* **2004**, *45* (7), 1363-1365.

31. Wu, Y.; He, L. N.; Du, Y.; Wang, J. Q.; Miao, C. X.; Li, W., Zirconyl chloride: an efficient recyclable catalyst for synthesis of 5-aryl-2-oxazolidinones from aziridines and CO_2 under solvent-free conditions. *Tetrahedron* **2009**, *65* (31), 6204-6210.

32. Miller, A. W.; Nguyen, S. T., (Salen)chromium(III)/DMAP: An efficient catalyst system for the selective synthesis of 5-substituted oxazolidinones from carbon dioxide and aziridines. *Org. Lett.* **2004**, *6* (14), 2301-2304.

33. Fontana, F.; Chen, C. C.; Aggarwal, V. K., Palladium-Catalyzed Insertion of CO_2 into Vinylaziridines: New Route to 5-Vinyloxazolidinones. *Org. Lett.* **2011**, *13* (13), 3454-3457.

34. Arayachukiat, S.; Yingcharoen, P.; Vummaleti, S. V. C.; Cavallo, L.; Poater, A.; D'Elia, V., Cycloaddition of CO_2 to challenging *N*-tosyl aziridines using a halogen-free niobium complex: Catalytic activity and mechanistic insights. *Mol. Catal.* **2017**, *443*, 280-285.

35. Ren, W. M.; Liu, Y.; Lu, X. B., Bifunctional Aluminum Catalyst for CO_2 Fixation: "Regioselective Ring Opening of Three-Membered Heterocyclic Compounds. *J. Org. Chem.* **2014**, *79* (20), 9771-9777.

36. Ma, T. Y.; Qiao, S. Z., Acid-Base Bifunctional Periodic Mesoporous Metal Phosphonates for Synergistically and Heterogeneously Catalyzing CO_2 Conversion. *ACS Catal.* **2014**, *4* (11), 3847-3855.

37. Lin, X. Z.; Yang, Z. Z.; He, L. N.; Yuan, Z. Y., Mesoporous zirconium phosphonates as efficient catalysts for chemical CO_2 fixation. *Green Chem.* **2015**, *17* (2), 795-798.

38. Xu, H.; Liu, X. F.; Cao, C. S.; Zhao, B.; Cheng, P.; He, L. N., A Porous Metal-Organic Framework Assembled by [Cu_{30}] Nanocages: Serving as Recyclable Catalysts for CO_2 Fixation with Aziridines. *Adv. Sci.* **2016**, *3* (11).

39. European Chemicals Agency. *N,N*-dimethylformamide. https://echa.europa.eu/substance-information/-/substanceinfo/100.000.617 (accessed December 12th **2018**).

40. Wang, X.; Gao, W. Y.; Niu, Z.; Wojtas, L.; Perman, J. A.; Chen, Y. S.; Li, Z.; Aguila, B.; Ma, S. Q., A metal-metalloporphyrin framework based on an octatopic porphyrin ligand for chemical fixation of CO_2 with aziridines. *Chem. Commun.* **2018**, *54* (10), 1170-1173.

41. European Chemicals Agency. *N,N*-dimethylacetamide. https://echa.europa.eu/substance-information/-/substanceinfo/100.004.389 (accessed December 12th **2018**).

42. Mu, W. H.; Chasse, G. A.; Fang, D. C., High level a initio exploration on the conversion of carbon dioxide into oxazolidinones: The mechanism and regioselectivity. *J. Phys. Chem. A* **2008**, *112* (29), 6708-6714.

43. Adhikari, D.; Miller, A. W.; Baik, M. H.; Nguyen, S. T., Intramolecular ring-opening from a CO_2-derived nucleophile as the origin of selectivity for 5-substituted oxazolidinone from the (salen)Cr-catalyzed aziridine + CO_2 coupling. *Chem. Sci.* **2015**, *6* (2), 1293-1300.

44. Reetz, M.; List, B.; Jaroch, S.; Weinmann, H., *Organocatalysis*. Springer-Verlag Berlin Heidelberg: Germany, **2007**.

45. Moyano, A.; Rios, R., Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions. *Chem. Rev.* **2011**, *111* (8), 4703-4832.

46. Du, Y.; Wu, Y.; Liu, A. H.; He, L. N., Quaternary ammonium bromide functionalized polyethylene glycol: A highly efficient and recyclable catalyst for selective synthesis of 5-aryl-2-oxazolidinones from carbon dioxide and aziridines under solvent-free conditions. *J. Org. Chem.* **2008**, *73* (12), 4709-4712.

47. Yang, Z. Z.; He, L. N.; Peng, S. Y.; Liu, A. H., Lewis basic ionic liquids-catalyzed synthesis of 5-aryl-2-oxazolidinones from aziridines and CO_2 under solvent-free conditions. *Green Chem.* **2010**, *12* (10), 1850-1854.

48. Yang, Z. Z.; Li, Y. N.; Wei, Y. Y.; He, L. N., Protic onium salts-catalyzed synthesis of 5-aryl-2-oxazolidinones from aziridines and CO_2 under mild conditions. *Green Chem.* **2011**, *13* (9), 2351-2353.

49. Qi, C. R.; Ye, J. W.; Zeng, W.; Jiang, H. F., Polystyrene-Supported Amino Acids as Efficient Catalyst for Chemical Fixation of Carbon Dioxide. *Adv. Synth. Catal.* **2010**, *352* (11-12), 1925-1933.

50. Jiang, H. F.; Ye, J. W.; Qi, C. R.; Huang, L. B., Naturally occurring alpha-amino acid: a simple and inexpensive catalyst for the selective synthesis of 5-aryl-2-oxazolidinones from CO_2 and aziridines under solvent-free conditions. *Tetrahedron Lett.* **2010**, *51* (6), 928-932.

51. Luo, Y.-R., *Handbook of Bond Dissociation Energies in Organic Compounds*. Science Press: Beijing, China, **2005**.

52. Baldwin, J. E., Rules for ring-closure. *J. Chem. Soc., Chem. Commun.* **1976**, (18), 734-736.

53. Wu, Y. C.; Liu, G. S., Organocatalyzed cycloaddition of carbon dioxide to aziridines. *Tetrahedron Lett.* **2011**, *52* (48), 6450-6452.

54. Zhang, S.; Li, Y. N.; Zhang, Y. W.; He, L. N.; Yu, B.; Song, Q. W.; Lang, X. D., Equimolar Carbon

Absorption by Potassium Phthalimide and In Situ Catalytic Conversion Under Mild Conditions. *ChemSusChem* **2014**, *7* (5), 1484-1489.

55. Ueno, A.; Kayaki, Y.; Ikariya, T., Cycloaddition of tertiary aziridines and carbon dioxide using a recyclable organocatalyst, 1,3-di-*tert*-butylimidazolium-2-carboxylate: straightforward access to 3-substituted 2-oxazolidones. *Green Chem.* **2013**, *15* (2), 425-430.

56. Saptal, V. B.; Bhanage, B. M., *N*-Heterocyclic Olefins as Robust Organocatalyst for the Chemical Conversion of Carbon Dioxide to Value-Added Chemicals. *ChemSusChem* **2016**, *9* (15), 1980-1985.

57. Watile, R. A.; Bagal, D. B.; Deshmukh, K. M.; Dhake, K. P.; Bhanage, B. M., Polymer supported diol functionalized ionic liquids: An efficient, heterogeneous and recyclable catalyst for 5-aryl-2-oxazolidinones synthesis from CO_2 and aziridines under mild and solvent free condition. *J. Mol. Catal. A - Chem.* **2011**, *351*, 196-203.

58. Watile, R. A., Bhanage, Bhalchandra M., Chitosan biohydrogel beads: A recyclable, biodegradable, heterogeneous catalyst for the regioselective synthesis of 5-aryl-2-oxazolidinones from carbon dioxide and aziridines at mild conditions. *Indian J. Chem.* **2012**, *51A*, 1354-1360.

59. Ghormade, V.; Pathan, E. K.; Deshpande, M. V., Can fungi compete with marine sources for chitosan production? *Int. J. Biol. Macromol.* **2017**, *104*, 1415-1421.

60. Kathalikkattil, A. C.; Tharun, J.; Roshan, R.; Soek, H.-G.; Park, D.-W., Efficient route for oxazolidinone synthesis using heterogeneous biopolymer catalysts from unactivated alkyl aziridine and CO_2 under mild conditions. *Appl. Catal. A-Gen.* **2012**, *447-448*, 107-114.

.