FACULTY OF BIOSCIENCE ENGINEERING

Synthesis of azaheterocycles through CO_2 fixation by 3-amino-β-lactams

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Ghent, 1 juni 2024

The promoter, The author,

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Robbe Thiebaut, June 2024

Table of contents

Samenvatting

In deze Masterthesis was het doel om CO_2 te fixeren via monocyclische 3-amino-β-lactamen en te kijken of deze konden gebruikt worden om farmaceutische bouwstenen zoals oxazolidinonen en/of imidazolidinonen te produceren. Deze heterocyclische vijfringen hebben potentieel antimicrobiële activiteit. Dit is belangrijk omdat er in de wereld algemeen een groeiende antimicrobiële resistentie wordt vastgesteld.

Onderzoek naar CO_2-fixatie is en blijft interessant omdat het een niet toxische, in de natuur aanwezige en groene molecule is. Het kan namelijk dienen als potentiële vervanger voor fosgeen en fosgeenderivaten die wel toxisch zijn. De molecule waaruit gestart werd, waren 3-amino-β-lactamen. Eerder werd er al onderzoek gedaan of deze 3-amino-β-lactamen CO_2 kunnen fixeren. In voorafgaand onderzoek werd in een studie aan de vakgroep Groene Chemie en Technologie (Faculteit Bio-ingenieurswetenschappen, Universiteit Gent) voor het eerst CO_2 gefixeerd door 3-amino-β-lactamen en relatief efficiënte procedures gevonden voor het vormen van deze moleculen. Hierop werd verder gebouwd in deze thesis.

Uit vorig onderzoek bleek dat rechtstreekse vorming van oxazolidinonen en/of imidazolidinonen uit 3-amino-β-lactamen via CO_2 moeilijkheden had. In de plaats hiervan werd er eerst CO_2 gefixeerd met vorming van de overeenkomstige methylcarbamaten. Hierna werd er een ringopening gedaan van de β-lactamring. Deze reactie bevestigde dat de methylcarbamaten bruikbare beginproducten zijn. Vervolgens werd in deze Masterthesis onderzocht of deze ringgeopende methylcarbamaten in staat zijn om te ringsluiten met vorming van een imidazolidinon.

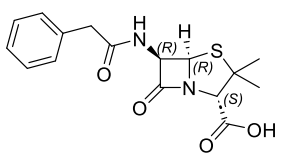
Scope and goal

1. Scope

1.1. β-lactams: still viable or an outdated medicine?

β-Lactams are one of many families of antibiotics, such as tetracyclines and aminoglycosides. The first discovery of β-lactam antibiotics was in 1928 by Alexander Fleming, albeit 'accidental'. The molecule in question was called penicillin G **1**, named after the fungus *Penicillium chrysogenum*.[1,2] From this point on, penicillin was mostly the only viable way to treat bacterial infectious diseases.

In the middle of the 20th century, the development of new antibacterial compounds progressed at a fast pace. All known families were discovered and developed from 1940 up until late 1960, which is called 'the golden age of antibiotics'.[1,2] After 1970, no new families were immediately discovered and development plateaued because the amount of antibiotics was thought to be sufficient. Because of this lack of development and constantly using the same antibiotics, bacteria had the time to develop resistance, which poses a great threat to the medical world. Nowadays, 35000 people die annually because of antimicrobial resistance (AMR) in the EU alone.[3] When resistance became a problem, the scientific world was pushed to find new ways to counteract AMR. Firstly, this was done by modifying the antibiotics that already existed at that time.[1] As an example, penicillin G **1** was modified into ampicillin **2**. On the other hand, other families were synthesized, such as oxazolidinones. The most well-known oxazolidinone antibiotic is linezolid **3**, which is used for treating Gram-positive infections and multidrug-resistant tuberculosis.[4,5] The class of the oxazolidinones, which inhibit protein synthesis in bacteria, is one of the more recent discoveries that are fully synthetic and not present in nature.[5] Other applications of oxazolidinones are anti-inflammatory treatment, anti-cancer therapy and treatment of neurologic disorders, but these are still studied and need to undergo clinical trials.[6] Because of their great potential value in medicines, the oxazolidinones are of high importance to investigate further.[7] Another class that resembles the oxazolidinones is the one of the imidazolidinones. In the present day, no more than a handful of imidazolidinone medicines, such as imidapril **4**, are available.



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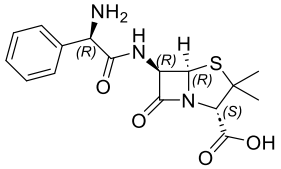

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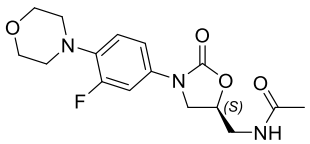

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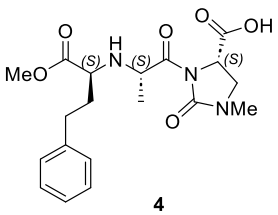

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1.2. CO_2 fixation by chemical means

CO_2 is the 4th most abundant gas on earth, taking up 0.04% of the atmosphere.[8] CO_2 is naturally used in photosynthesis where plants convert it to glucose as a source of energy. On the other hand, animals release CO_2 because of respiration occuring in the cells. Another outlet of CO_2 is the industry, which emits nine Gt of CO_2 annually. This emission accounts for a quarter of the global CO_2 output.[9] CO_2 is the main protagonist in the problem that continues to rise: global warming. CO_2 is a greenhouse gas that absorbs infrared light and re-emits it in all directions.

In other words, it absorbs heat and releases it again into our atmosphere. CO_2 is vital to keep a constant surface temperature, but because of the extra CO_2 gas released the earth is constantly warming up. Therefore it is necessary to minimise the concentration of CO_2 in our atmosphere. To do this, CO_2 capture and use as a building block in chemical synthesis could be interesting for organic chemistry.

When looking from a chemical standpoint, CO_2 is a non-flammable, colourless and odourless gas. CO_2 suffers from a low thermodynamic energy level, which hinders its reactivity in chemical synthesis.[10] This means that additional energy is needed to perform reactions with CO_2. Because of this, higher temperatures and catalysts are not uncommon when using CO_2 in a reaction. An example of this is the methanation reaction, where CO and CO_2 are converted into methane.[11,12]

An example of carbon fixation finds itself in the biotechnical industry. The company Arcelor-Mittal has made a significant improvement in its CO_2 emissions. It has set up a plant called Steelanol, which uses waste gas, containing CO/CO_2 and H_2, from the blast furnaces in Arcelor-Mittal's steel plant to produce ethanol. Steelanol has a capacity of 80 million litres of ethanol annually, which accounts for half the demand in Belgium.[13] The fertilizing industry is another industry in need of CO_2. Annually this industry uses 130 Mt of CO_2, which is the biggest CO_2 user in the world.[14] CO_2 is reacted with ammonia to produce urea, which is the key component in fertilizer.

The increasing amount of CO_2 in the atmosphere is a driving force to use it in chemical fixation, but CO_2 can also replace toxic and non-sustainable reagents that are currently used as C1 building blocks in chemical synthesis. An example of this is phosgene, which is typically used in reactions for the formation of carbonates.[15] Industrial production of isocyanates is also done using phosgene. Ren succeeded in the production of isocyanates using CO_2, which can be processed further into polyurethanes.[16] Polyurethanes (PUR) are mostly used in the insulation industry as PUR foams. The PUR foam industry is large, which is estimated to be 50 billion USD.[17]

CO_2 is sometimes called green according to the twelve green chemistry principles, which are shown in Figure 1. These principles are used to rate the sustainability level of a chemical reaction or process. The usage of CO_2 can be linked to several principles such as waste prevention (1), safer chemicals (3) and usage of renewable feedstocks (7). It does not produce waste in reactions because it is fully incorporated in the structure of the molecule, whereas other reagents such as phosgene produce byproducts. Compared to processes using phosgene, CO_2 is not as hazardous as phosgene and thus safer. Next to that, CO_2 is a renewable feedstock because of its natural abundance. These principles have to be taken into account to ensure sustainable production processes.[18]

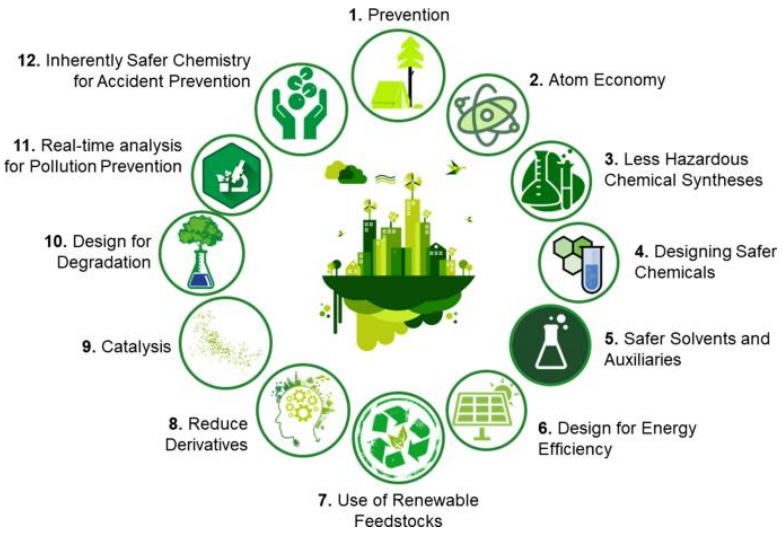
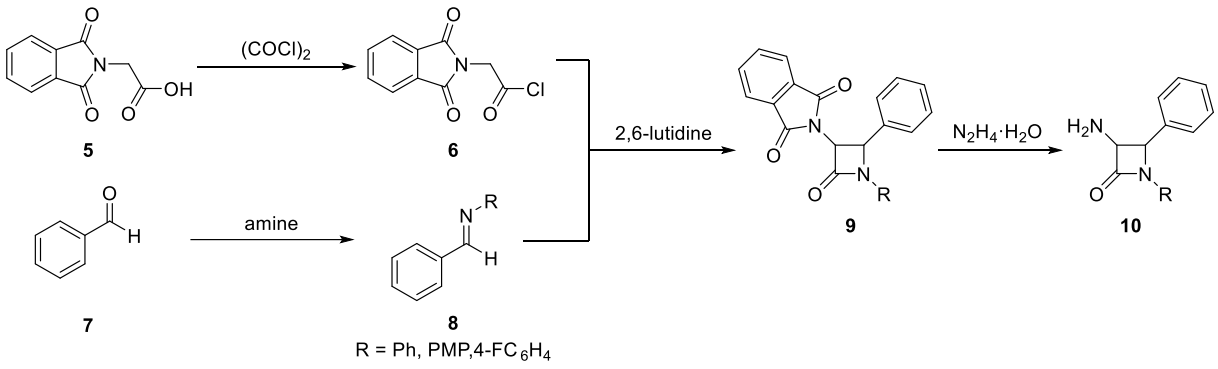


Figure 1: The 12 principles of green chemistry[19]

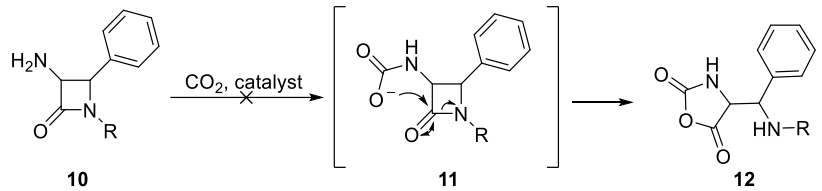
2. Goal

In the previous chapter, oxazolidinones and imidazolidinones have shown some potential to society as medicines. This means there is all the more reason to investigate new pathways towards these five-membered heterocyclic rings. In this thesis, the possibility to synthesize these rings starting from 3-amino-β-lactams **10** is examined. This was already investigated in the past; but incorporation of CO_2 is now a second goal.[20,21] Again, CO_2 is a inexpensive, non toxic and abundant C1 building block, which makes it more green than other molecules such as phosgene. This thesis is a continuation of previous research done in the Department of Green Chemistry and Technology (Faculty of Bioscience Engineering, Ghent University), by a former thesis student Laura Surdiacourt.[22]

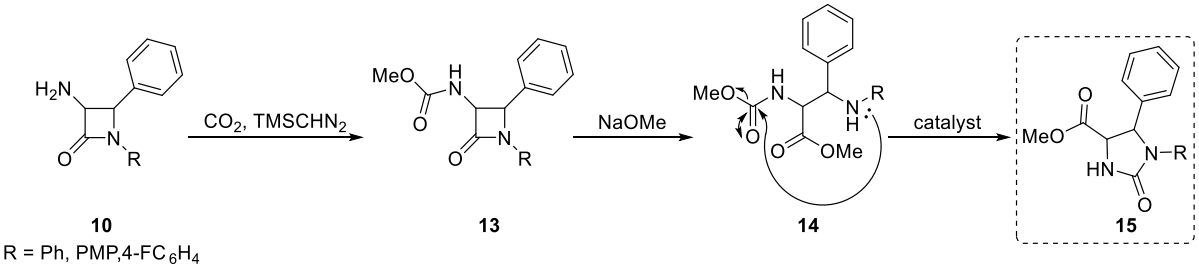
First of all, the 3-amino-β-lactams **10** have to be synthesized. β-Lactams are generally produced by a Staudinger cycloaddition. Here, an *N*-aryl-substituted imine **8** reacts with an acid chloride **6** in combination with a base such as 2,6-lutidine. Prior to this, **6** and **8** have to be prepared. **8** is synthesized by a condensation reaction, where benzaldehyde **7** is reacted with an amine. *N*-Phthaloylglycine **5** is reacted with oxalyl chloride, which forms *N*-phthaloylglycyl chloride **6**. To form the desired 3-amino-β-lactams, 3-phthalimido-4-phenylazetidin-2-ones, **9** need deprotection by hydrazine monohydrate.[22]



Now, the search for a pathway from 3-amino-β-lactams **10** to oxazolidinones and imidazolidinones starts. First, CO_2 has to be incorporated to achieve the second goal of this thesis. In previous research, structure **10** was reacted with CO_2 under atmospheric pressure in order to effect sequential *in situ* ring opening and closure. This would form an oxazolidine-2,5-dione **12**. The substituent group (R) which formed an imine, is thought to be important. An aryl group is an electron-withdrawing substituent, which makes the β-lactam ring more electrophilic. Because of that, the β-lactam ring is more susceptible to ring opening than what would be the case with other substituents like alkyl groups. Sadly, this did not succeed.[22]



To prove the CO_2 capture by 3-amino-β-lactams **10**, trimethylsilyldiazomethane ($TMSCHN_2$) was added to the reaction. This served a purpose as it methylates the carboxylate after the addition of CO_2, to produce methyl (2-oxo-4-phenylazetidin-3-yl)carbamate **13**. This means that the β-lactam ring opening is the limiting step.[22]



Subsequently, a ring opening will be attempted with sodium methoxide (NaOMe) to give methyl 3-arylamino-2-methoxycarbonylamino-3-phenylpropanoate **14**.[23] Desirably, the R-substituted nitrogen would attack the carbamate functionality of **14**. This would give an imidazolidin-2-one **15**. This will be investigated in a catalyst-free reaction and, if the need arises, catalysts will be tested.

In previous work, product **13** has been synthesized and thus CO_2 was already incorporated. The goal is to synthesize compounds **14** and **15** and also to prove that **13** is a stable and useful product. Also, improvements of the reaction procedures, yields and purification of previous reactions have to be investigated where possible.

Literature study

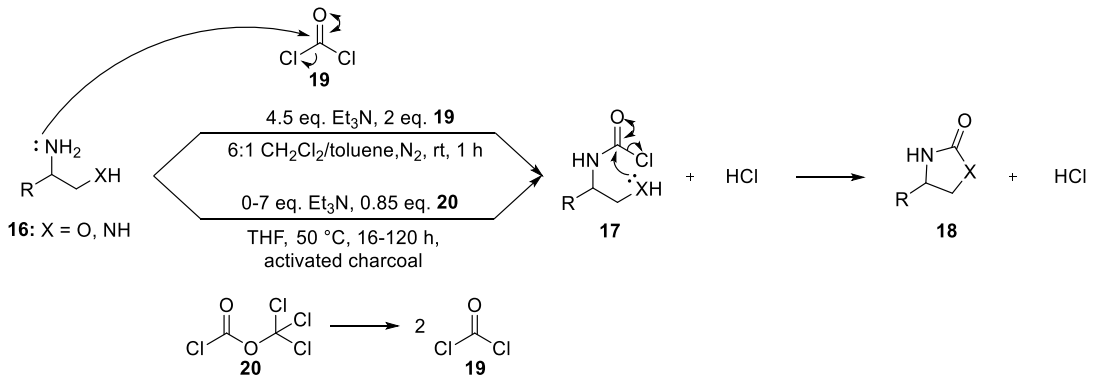
The aim of this thesis is to fixate CO_2 and synthesize heterocyclic five-membered rings: oxazolidinones and imidazolidinones. These rings can then be used to produce valuable pharmaceutical building blocks. The importance of oxazolidinones and imidazolidinones, as explained in the chapter 'Scope', has made the scientific world to search for numerous ways to produce OAI. This does not mean that every option was as sustainable as the other. Nonetheless, they were part of innovation that led the scientific world to where it is now.

The key structures of oxazolidinones and imidazolidinones are not always the same. There is a difference in where the carbonyl is situated on the ring. In general, oxazolidin-2-ones and imidazolidin-2-ones, such as **3** and **4**, respectively, are compounds with the most applications in medicine and thus this chapter will only contain synthesis routes to those five-membered rings. Many of the synthetic pathways share different starting materials to make the same compound, which will be summarized here. Most research is focused on oxazolidinones. Because of this, imidazolidinone production will only be mentioned where possible.

1. Oxazolidinone and imidazolidinone production

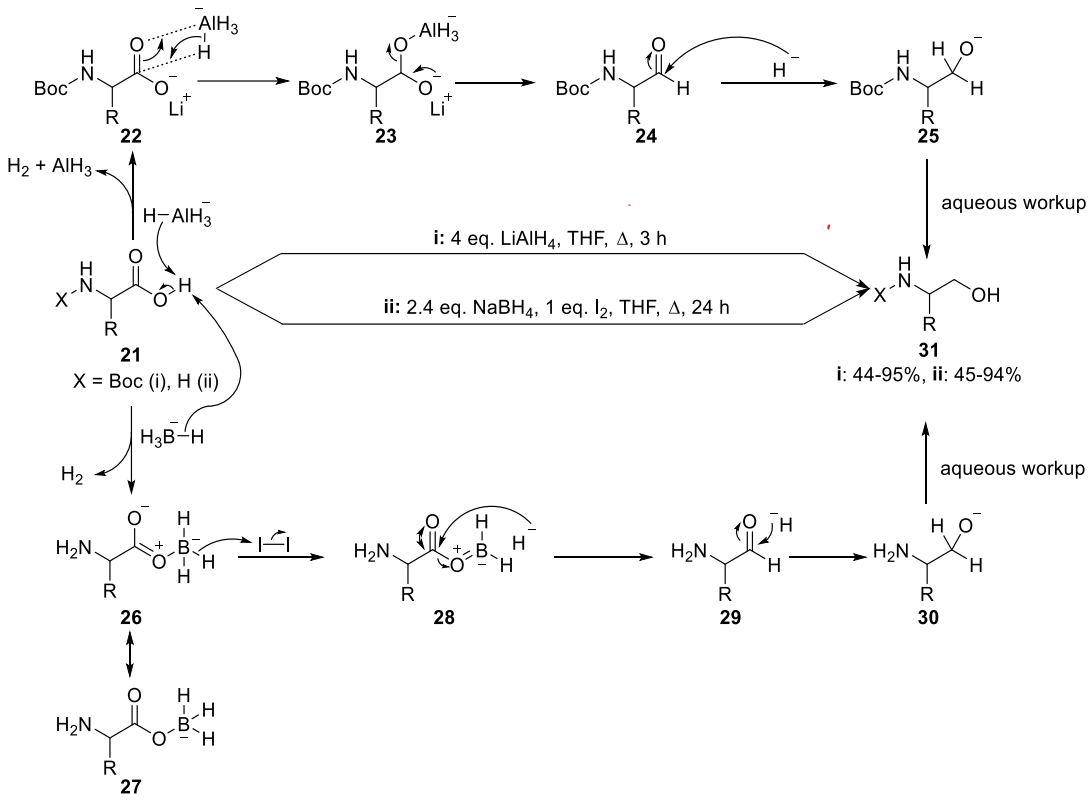
1.1. β-Amino alcohols

The most common reagents for the production of oxazolidinones are β-amino alcohols, epoxides and carbamates. One of the oldest reactions uses amino alcohols and phosgene.[24] When looking at this reaction there is one problem, which is phosgene. Phosgene has been used as a chemical weapon in World War I. It causes problems at the blood-air barrier in the lungs, leading to liquid accumulation.[25] This is one of the many possible symptoms. Because of the safety hazard associated with phosgene, this reaction can be seen as non-sustainable. In the general reaction scheme below, the amino group with its lone electron pair **16** acts as nucleophile and attacks phosgene **19**, forming the carbamoyl chloride functionality in **17**. Now, the hydroxy group performs an intramolecular addition and elimination reaction to form the oxazolidinone **18** (X = O) with a yield of 96%.[26] In the same way as amino alcohols, diamines can also undergo this reaction, but with formation of imidazolidinones **18** (X = NH).[27] A paper explained the reaction between an amino alcohol or a diamine with diphosgene **20** and activated charcoal as a catalyst. The yields for both oxazolidinones and imidazolidinones were above 80%.[28]

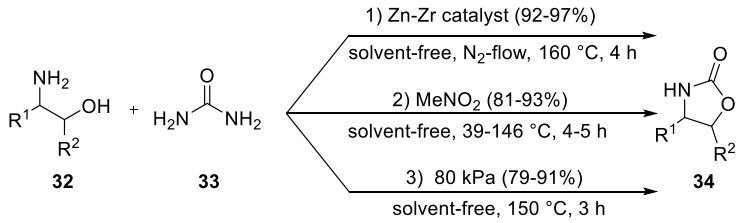


Amino acids **21** are also interesting in this case. The reason for this lies in the reducibility of the carboxylic acid functional group **21** by $NaBH_4$ and I_2 or $LiAlH_4$ to amino alcohols **31**. This

means amino acids are also eligible for the production of oxazolidinones.[29–32] These oxazolidinones possess a predetermined stereochemistry equal to the stereochemistry of the amino acid.

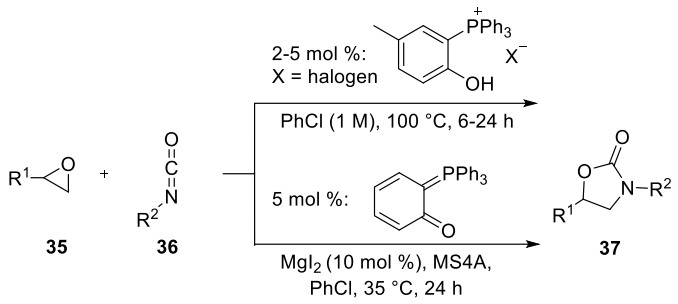


Other reactions with a β-amino alcohol as a starting reagent use urea **33** instead of phosgene to produce oxazolidinones **34**. Urea is produced from ammonia and CO_2, which means CO_2 fixation has already taken place. In most cases, catalysts such as $ZnZrO_x$ or high temperatures are used to facilitate the reaction.[33–35]

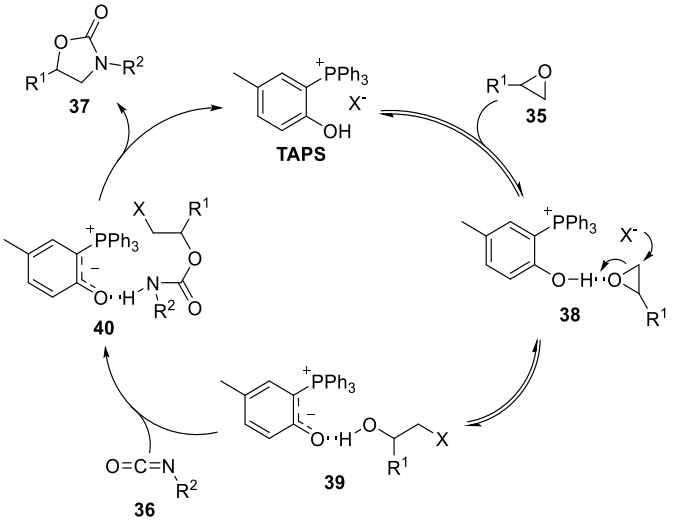


1.2. Epoxides

Instead of using an amino alcohol, epoxides can be used for the synthesis of oxazolidinones. Epoxides are three-membered rings with one oxygen atom, which are reactive reagents due to the high ring strain. The electrophilic carbon atom in the carbon-oxygen bond can undergo a nucleophilic attack, which opens the ring. An example of this is the reaction between epoxides **35** and isocyanates **36**, which is explained below.[36,37] On the other hand, epoxides can also react with amines to form amino alcohols and follow the reaction scheme as described in 1.1.[34,38]



In the first reaction, a tetra-arylphosphonium salt (TAPS) works as a Brønsted acid to catalyse the reaction, which can be seen in the scheme below. Here, the epoxide forms a hydrogen bridge with the hydroxy group on the salt. The anion of the salt causes the epoxide ring **35** to open and to form an alcohol **39**, which is followed by a hydrogen transfer from the cation to the ring-opened epoxide. The alcohol will react with the isocyanate **36** to form a carbamate **40**, which will *in situ* rearrange to an oxazolidinone **37** where the Brønsted acid is released and can thus participate in another cycle.[36]



The previous two examples are a couple of many possibilities found in the literature to produce oxazolidinones from epoxides. In the table below, some of these possibilities are mentioned.

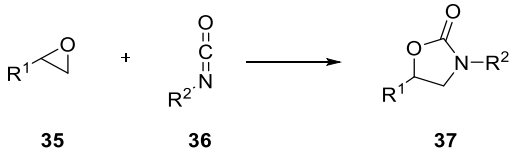


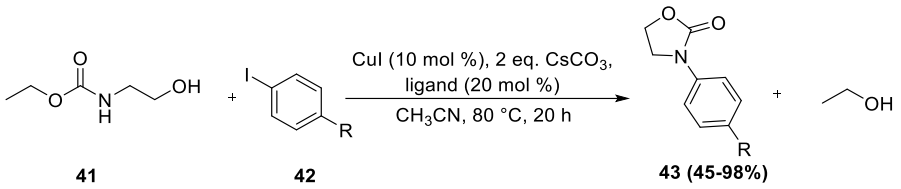
Table 1: Using epoxides to synthesize oxazolidinones

Entry	R^1	R^2	Catalyst	Solvent	T (°C)	Yield (%)	Ref.
1	CH_3	Ph	(salcen)Cr^{III} (3 mol%) $PPhO_3$ (6 mol%)	Toluene	60	93	[39]
2[c]	CH_2Cl	Ph				100	
3[c]	CH_2Ph	Ph				98	
4[c]	CH_3	4-MeO-Ph				97	
5[c]	CH_3	1-Napthyl				96	
6	CH_3	/[a]	ZnMgAlOx	/	140	80[b]	[40]

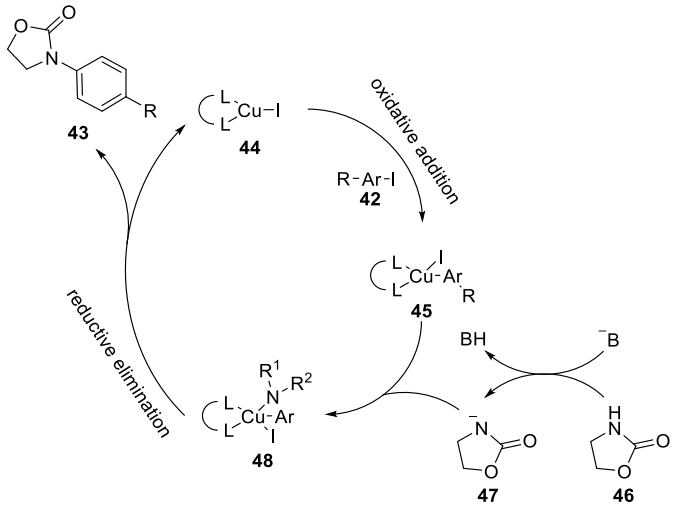
[a] *Urea **22** instead of isocyanate **25** was used.*
[b] *The paper only reported conversion and selectivity. This is multiplied to become the yield.*
[c] *Entries **1**-**5** used the same conditions, catalyst and reference.*

1.3. Amino- and hydroxyalkyl carbamates

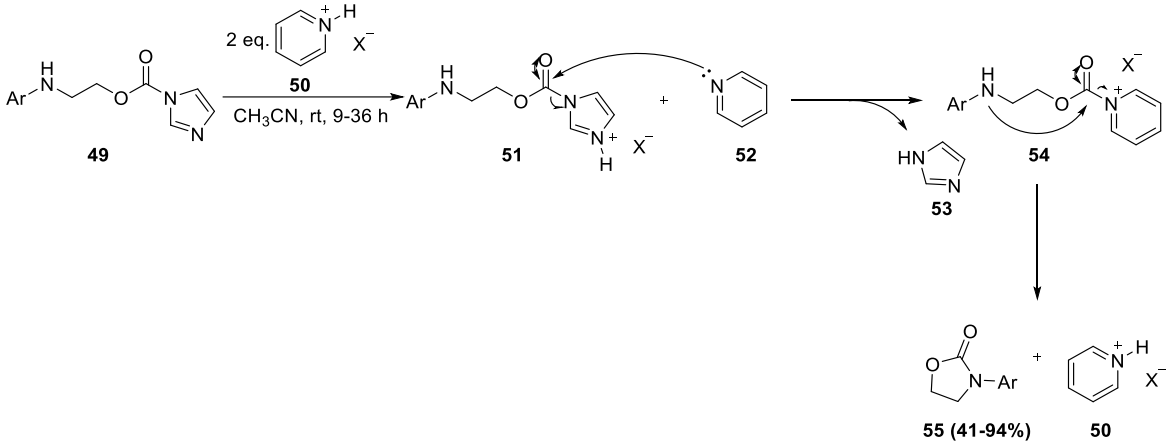
When searching for other methods, carbamates are one of the most frequently used reagents for the production of oxazolidinones. A carbamate cannot produce an oxazolidinone on its own; it needs a second functional group. In most cases an amine, hydroxy, alkyne or alkene functional group is required. In the first example, a hydroxyethyl carbamate **41** undergoes an intramolecular cyclization before a copper-catalysed cross coupling reaction, called the Ullman-Goldberg coupling, occurs.[41,42] This is explained further in the following paragraph.



The cyclization is straightforward, where the hydroxy group in **41** attacks the carbamate with release of ethanol and the formation of an oxazolidinone ring **46**. The coupling itself is a useful way to change the substituent on the nitrogen of the oxazolidinone ring **46**. The mechanism of the coupling reaction is common in organic chemistry. It starts with an oxidative addition of **42** to produce **45**, followed by the attack of a nucleophile, which is the deprotonated oxazolidinone **47**. The last step is a reductive elimination with release of **43** and **44**.[42]

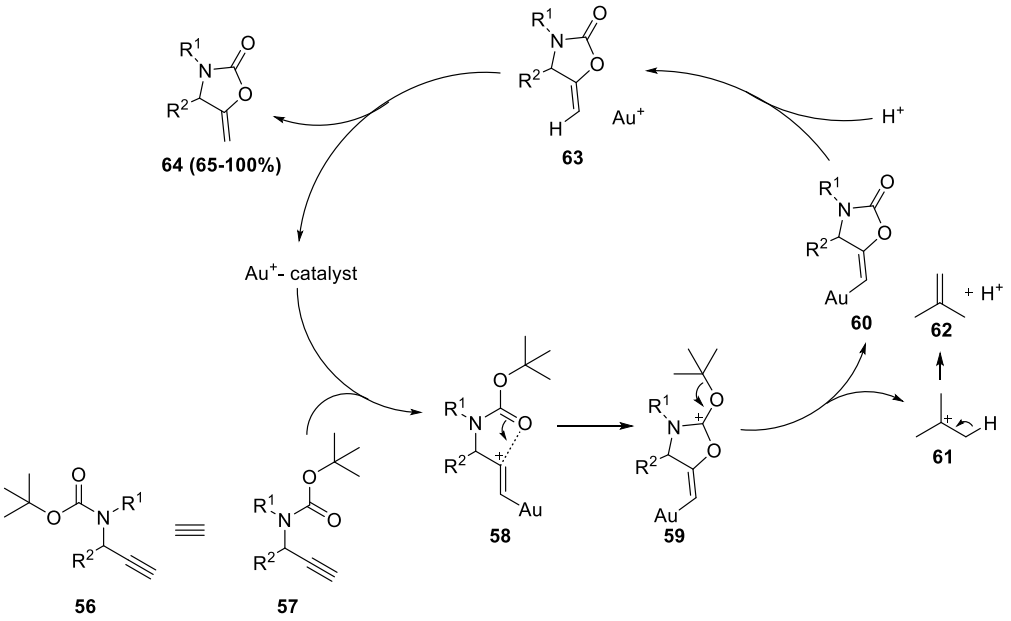


An aminoethyl carbamate **49** can also produce an oxazolidinone by using a Brønsted acid. The Bronsted acid **50** can activate the reagent **49** by release of the imidazole ring **53** and attaching the pyridine ring **52**. This makes it possible to perform a cyclization.[43]

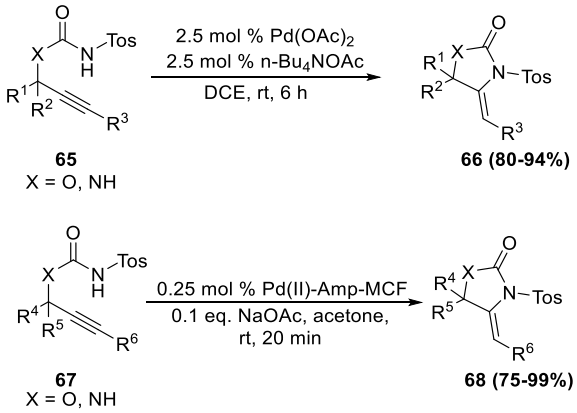


1.4. Propargylic carbamates

Propargylic carbamates are characterized by the alkyne functional group. Alkyne groups easily react with organometallic compounds containing copper, gold, and silver to produce an alkene-metal group.[44] The alkyne must be activated to facilitate the intramolecular cyclization with the carbamate functional group. There are a couple of ways to perform the reaction. One paper used a gold(I) catalyst to react with the alkyne and proposed a mechanism which goes as follows.[45] After reaction between the gold catalyst and the alkyne, a cationic species **58** is produced. The carbamate chain will turn into the position where the oxygen atom of the carbonyl function is the closest to the cationic alkene group. As a consequence, the oxygen atom of the carbonyl attacks the positively charged alkene. This provides a way to produce a five-membered ring to stabilize the positive charge. This produces a new cation **59**, which is stabilized by the release of the *tert*-butyl group. This will rearrange and produce a carbocation **61** as a byproduct. A tertiary carbocation is the most stable out of the carbocations, which makes this rearrangement possible. This carbocation will produce an isobutylene **62** molecule with exclusion of a proton, which reacts with the alkene **60** to free the gold catalyst and the product **64**.[45]

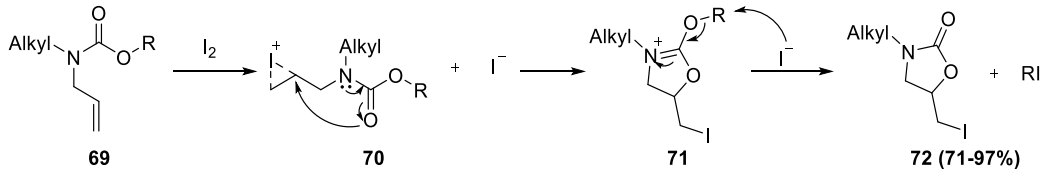


With this method, yields of minimum 65% were possible, but were mostly above 80%.[45] Another paper researched similar compounds **68** but used a different catalyst named Pd(II)-AmP-MCF. All yields were reported to be above 75%.[46] The catalyst was also used to make a heterocyclic five-membered ring such as an imidazolidinone with a reported yield of 75%. A third paper used a $Pd(II)(OAc)_2$ catalyst, in which it was possible to synthesize oxazolidinones **66** with a yield higher than 80%.[47] This catalyst also made it possible to make imidazolidinones which had the same yield as the oxazolidinones.[47]



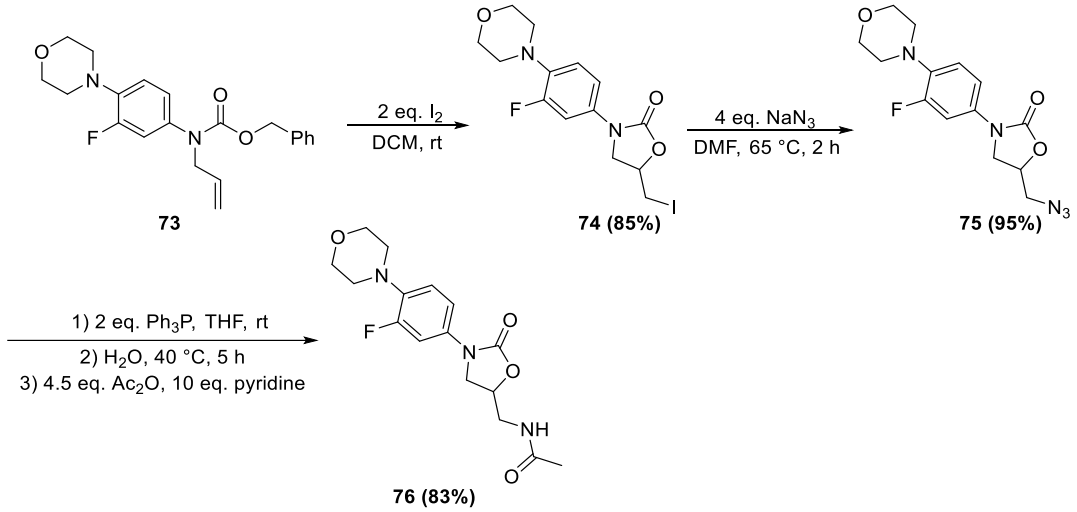
1.5. Allenic carbamates

Allenic carbamates **69** are not all that different from propargylic carbamates **56**. Nonetheless, the process to produce an oxazolidinone can differ significantly. One has reported a non-catalytic method.[48] This was done by using iodine, which splits heterolytic and the iodide cation coordinates to the alkene functional group **70**. Again, the carbamate turns the carbonyl closest to the alkene side chain, where it attacks to stabilise the positive charge. The positive charge left on the nitrogen of **71** is neutralised by the R-substituted oxygen atom. This makes the oxygen atom positively charged, but can react with the anionic iodide which binds with the R-group. This creates a 5-iodomethyl-substituted oxazolidinone **72**.[48]



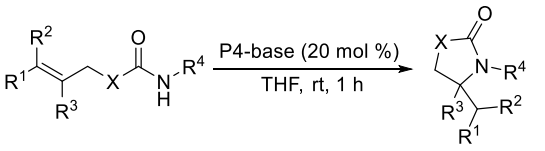
69 70 71 72 (71-97%)

The researchers did not stop there and went one step further. A method for the production of linezolid **3** was investigated with one of the products **73** that was synthesized according to the mechanism explained before.[48] The pathway started with a substitution of iodide by sodium azide. Lastly, a three-step one-pot reaction occurred, where structure **75** underwent a Staudinger reduction reaction with subsequent hydrolysis and acetylation to produce **76** as a racemic mixture.[48]



73 74 (85%) 75 (95%) 76 (83%)

A second paper did research on allenic carbamates with secondary amines **77** instead of tertiary amines **69**. They used a phosphazene catalyst, called a P4-base. This phosphine-based catalyst deprotonates the nitrogen, making it a nucleophile. This makes it possible to attack the alkene functional group, which is followed by ring closure.[49]



77: X = O or NH

78 (60-96%)
X = O or NH

1.6. Propargylic amines

The conversion of propargylic amines into oxazolidinones is characterised by the usage of catalysts. Possibilities are almost endless when looking at a review paper by Yang *et al*.[50] All possibilities that the researchers reviewed used CO_2 to produce the oxazolidinones. These are discussed in chapter 2.2.[22]

2. CO_2 as a reagent with formation of an oxazolidinone

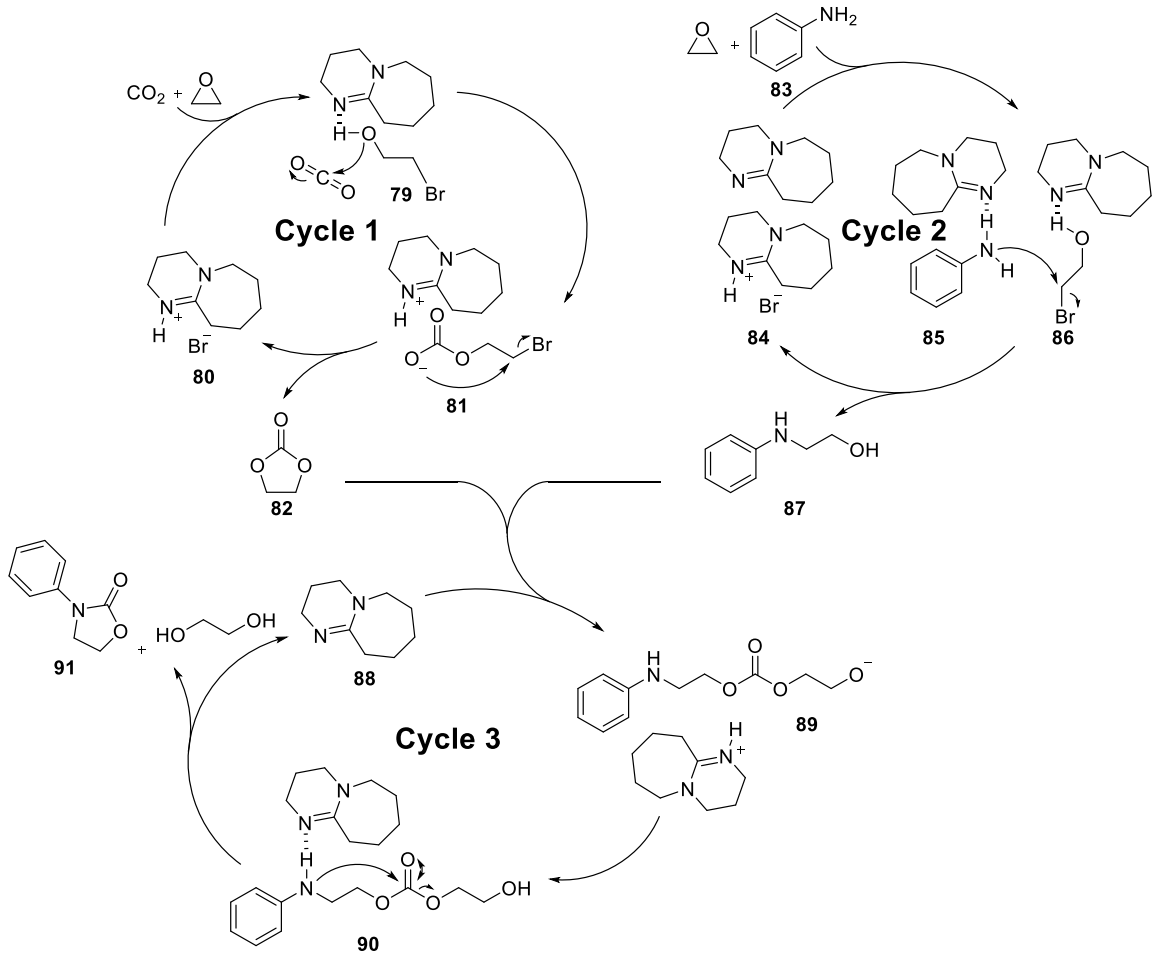
CO_2 is, as already explained, the protagonist in global warming. CO_2 emissions should be kept at a minimum, therefore it is beneficial to use CO_2 as a C1 building in a chemical reaction. As said before, higher temperatures and catalysts are needed to let CO_2 react. Also, CO_2 is not always very soluble in organic solvents, which makes it difficult to perform the reaction in a

reasonable time frame, or recycling of CO_2 is needed in order to not lose a considerable amount of it. Sometimes reactors are used to raise the pressure of CO_2, which results in a higher concentration of CO_2 in solution in acceptance of Henry's law. Another disadvantage is the inverse relation between temperature and solubility of CO_2. The higher the temperature, the lower the solubility. Therefore, on the one hand, high temperatures make the reaction go faster but on the other, this makes CO_2 less soluble.

In this part, reactions between organic compounds and CO_2 which directly form oxazolidinones and imidazolidinones will be discussed. CO_2 itself is a big part of the these five-membered rings (especially oxazolidinones), which makes that the other starting organic reagents can be relatively simple and smaller molecules. An example of this is the production of an oxazolidinone from propargylic carbamates versus propargylamines.

2.1. Three-membered rings

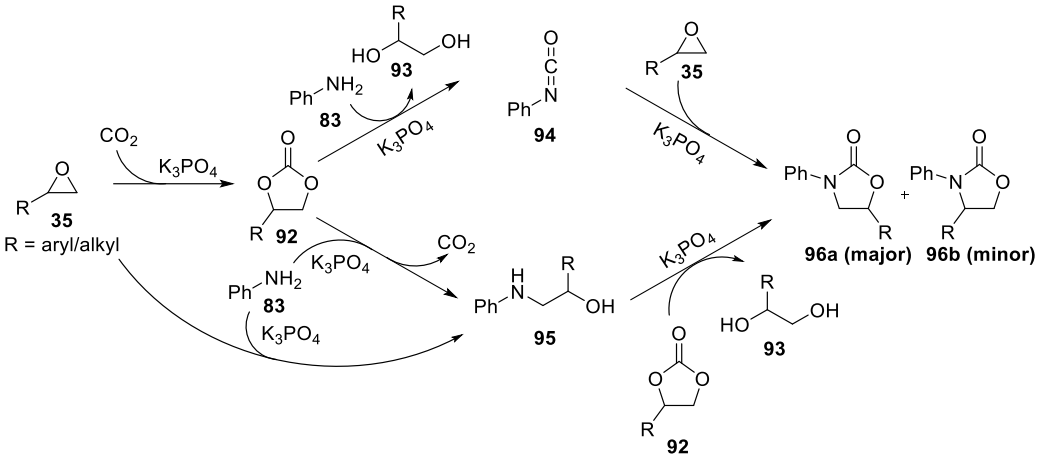
Three-membered rings such as aziridines and epoxides easily react due to the high ring strain. This helps to react with CO_2. Most reactions that use epoxides and CO_2 do this in combination with an amine such as aniline **83**. In this first reaction a base and an ionic liquid, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **88** and a DBU-based bromide ionic liquid (HDBUBr) **80**, respectively, are used, which catalyse three individual cycles.[51] This mechanism is proposed by the authors and is not certain.



A relatively complex catalytic system arises. In cycle 1, CO_2 (2.5 MPa) is incorporated into the ring-opened epoxide **79**, which was ring opened by bromide, with the formation of ethylene

carbonate **82**. In this process, HDBUBr is temporarily converted into DBU and its role is to increase the electron density of oxygen by making a hydrogen bond with **79**. Parallel to cycle 1, a second cycle begins. The epoxide is again ring opened with a subsequent attack of the arylamine **83**. Here, DBU again withdraws electron density by pulling on the hydrogen of **86**. The product is a *N*-arylamino alcohol **87**. In a 3rd cycle, the products of the first and second cycle combine using an addition followed by elimination to produce an anionic hydroxy carbonate **89**, which is neutralised by a hydrogen transfer. This is converted into oxazolidinone **91** by *in situ* cyclisation. In the end, **91** is synthesized with glycol as a byproduct. This reaction was also performed with a methyl-substituted epoxide, but not with other alkyl-substituted epoxides. Yields of all reactions could be found in the 70 to 100% range.[51]

In another paper, researchers performed the same reaction but with another base. They used K_3PO_4 as a simple inorganic base, which is inexpensive. Another difference is the pressure of CO_2 in the reaction. This was 0.1 MPa compared to 2.5 MPa in the previous example.[52]



The provided scheme has three different possible pathways. The first and most used path follows the upper pathway, where an isocyanate intermediate **94** is formed. This starts with the reaction of CO_2 with the epoxide **35** with the formation of substituted ethylene carbonate **92**, which is helped by the catalyst. Afterwards, aniline **83** will perform a nucleophilic addition with subsequent removal of CO_2 and a diol **93**. Another attack takes place on the isocyanate intermediate **94** by a second ring-opened epoxide, with the formation of the oxazolidinone **96a-b**. The selectivity depends on where PO_4^{3-} will attack the epoxide. Logically, the methylene is preferred because of the steric hindrance of the substituent, which resulted in ratios higher than 3:1. A second pathway was also tested, which mixed **92** and **83** to determine if there was a preference between **94** and **95**. No favourite could be determined.[52] A last pathway, producing **95** from **35** using **83** without the formation of **92**, was also tested by these researchers and reached only 11% of **95**. After reaction, minimal yields of 70% (**96a**+**96b**) were determined for aryl-epoxides and less than 45% for alkyl-epoxides.[52]

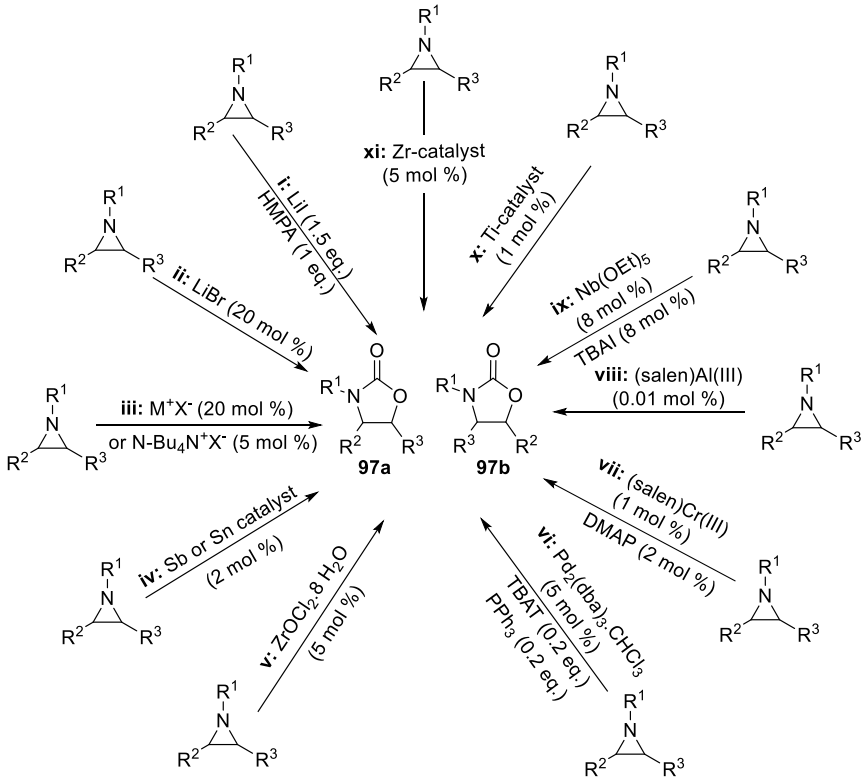
Aziridines are the counterpart of epoxides. They possess similar chemical properties because of the high ring strain. One difference with epoxides is that there are no additional reactions needed to introduce the nitrogen atom required for the formation of an oxazolidinone. There are already a lot of possibilities explored in the literature, which will be summarized below.[53–62]

Table 2: The formation of an oxazolidinone starting from an aziridine

Method	Solvent	CO_2 (bar)	Yield (%)	Selectivity for 97 (%)	Ref.
Homogenous catalysis					
i	THF	N/A	83-99	95-97 **a**	53
ii	NMP	1	42-79	100 **a**	54
iii	THF (mostly)	1	10-95	100 **a**	54
iv	HMPA or DMSO	60	0-86[a]	/	55
v	/	60	71-97	87-99 **a**	56
vi	Toluene	1	40-92	100 **b**	57
vii	CH_2Cl_2	28	82-93	87-97 **b**	58
viii	$CHCl_3$	25	N/A	100 **b**	59
ix	OEt_2	30	40-94	88-100 **b**	60
Heterogenous catalysis					
x	/	30	90-98	95-99 **b**	61
xi	/	20	92-97	93-98 **b**	62

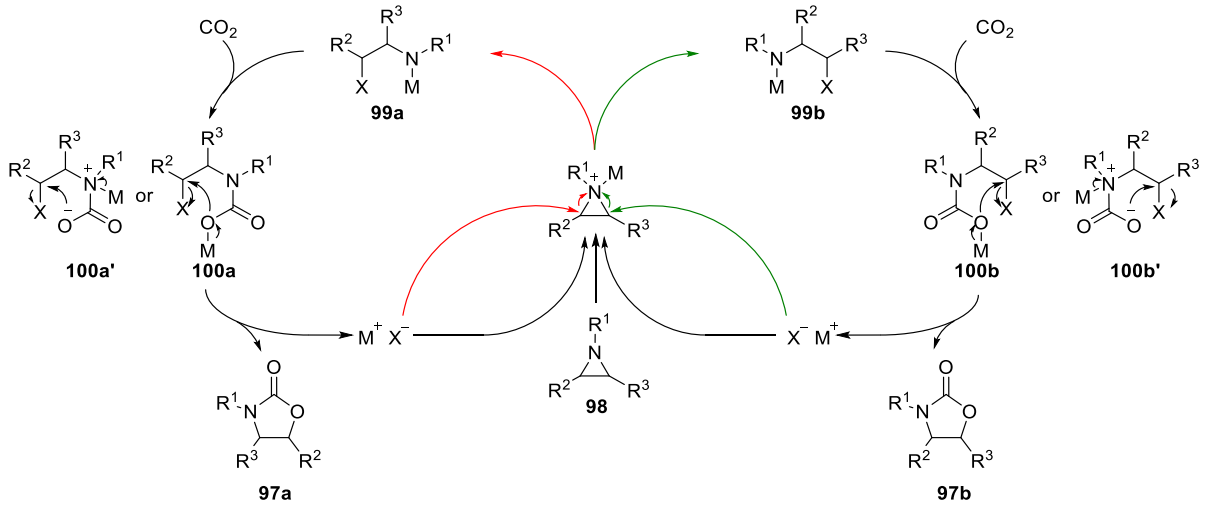
Abbreviations (for scheme below): HMPA = hexamethylphosphoramide, NMP = *N*-methylpyrrolidone, TBAT = tetrabutylammonium difluorotriphenylsilicate, DMAP = 4-dimethylaminopyridine, TBAI = tetrabutylammonium iodide

[a]Researchers also reported side product formation where two aziridines formed a dimer (1,4-diphenylpiperazine)



There is a large disparity between the different methods. Homogenous catalysis has overall lower yields, but has the choice between the procedures to either form **97a** or **97b**. Likewise, it has also the choice in the applied CO_2 pressure. In some cases, co-catalysts such as DMAP

and TBAT are used to elevate the conversion and yield of the reaction. The following scheme gives a general idea of what happens in some of these reactions such as **vii** and **viii**.[63]



The way the reaction proceeds is dependent on the steric hindrances of R^2 and R^3 on the one hand and electrophilicity on the other. Generally, an anion or a Lewis base such as DMAP will cause ring opening, which produces in this case **99a-b**.[58,59] Sadly, no explanation was given for CO_2 incorporation in the scheme above.[59] In **100a-b**, the M-O bond breaks, which gives oxygen a chance to remove the leaving group and form the end product **97a-b**. Another mechanism was found, where CO_2 incorporation was explained in a different way.[58] Here, the nitrogen of **99a-b** attacks the CO_2 and the formed carbonyl anion subsequently attacks the carbon atom linked to the leaving group (X) in **100a'-b'**. At the same time, the N-M bond breaks to stabilise the positive charge on the nitrogen. Normally, stereochemistry is supposed to remain the same when transitioning from the aziridine to the oxazolidinone because of double inversion happening in the cycle.[63]

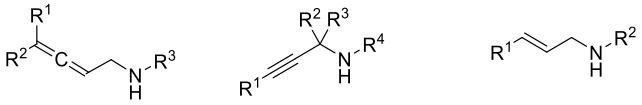
2.2. Propargylic and allenic amines or alcohols

As already stated, CO_2 reaction with propargylic amines is already covered extensively in the literature. Most of the time, catalysts are used in these reactions. All sorts of metal catalysts are used, which was reviewed in depth by Yang *et al*.[50] A table is made, which summarizes what was reviewed with regard to the three different starting products shown in the figure below.

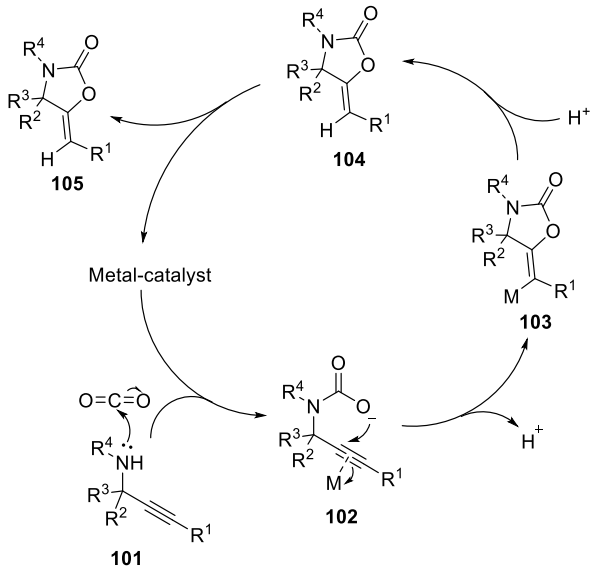
Table 3: Formation of oxazolidinones starting from allenic or propargylic amines

Entry	Catalyst	Solvent	T (°C)	CO_2 (bar)	Yield (%)	Ref.
1	Ag(OBz)(IPr)[a] (2 mol%)	Propan-2-ol	30	1-7	85	64
2	Ag(OAc)(IPr) (2 mol%)	Propan-2-ol	30	1-7	32-87	64
3	AuCl(IPr)[a] (2 mol%)	MeOH/THF	40	1	16-91	65
4	Au-cat.[b] (1 mol%)	MeOH	40	1	50-84	66
5	$2G_n(X)$[c] (1-2 mol%)	H_2O	rt	1	49-87	67
6	$Pd(OAc)_2$[a] (5 mol%)	Toluene	20	39	0-85	68
7	CuI (10 mol%); DBU (1 mol%)	DMSO	50	1	47-97	69
8	Al_2O_3 (5 mol%)	N/A	90	80	85	70
9	[DBUH][MIm] (2 eq.)	[DBUH][MIm]	60	1	85-90	71
10	C(+) Pt(-) electrolysis; DBU	MeCN	rt	1	55-91	72

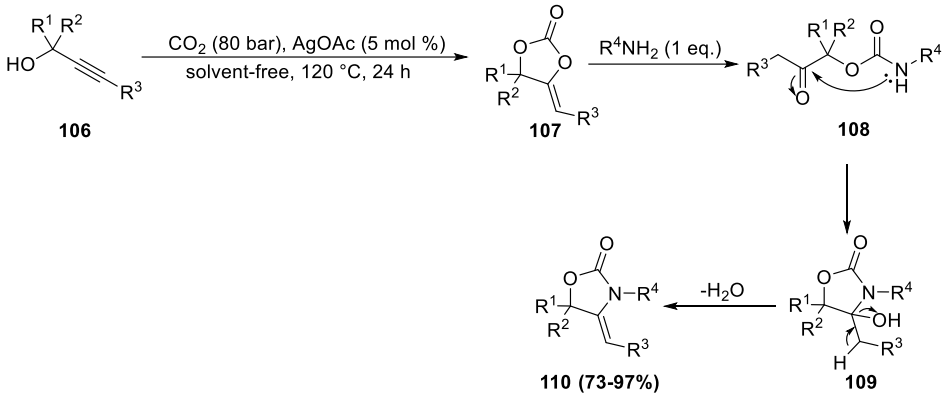
[a]This is one of the catalysts tested, next to AgCl(IPr), $Ag(OAc)(PPh_3)$ …
[b]Bimetallic gold-NHC catalyst.
[c]n = 1,2 and X = TEG, PEG, DEG (example: TEG = triethylene glycol) which is a gold-NHC catalyst.



In this table some examples are presented. Almost all of them are catalysed by different metals, that follow a similar pathway, which is similar as the pathway in 1.4. In the same way, entry **1** and **2** also follow this. Entries **9** and **10** use no metals, but an ionic liquid and electrolytic cell, respectively.



Next to the use of a propargylic amine, the reaction of a propargylic alcohol **106** with CO_2 is also possible. This follows the same reaction mechanism as the previous scheme. Here, it forms a five-membered carbonate ring **107**. Logically, the introduction of an amine is necessary to synthesize an oxazolidinone **110**, which is shown below in an one-pot reaction.[73]



The same researchers found another way to produce an oxazolidinone. They used CuCl, only 1 bar of CO_2 pressure and the reaction was solvent-free. Yields were dependent on the R groups used. Better yields were observed when R^1 and R^2 were methyl substituents and R^3 was an alkyl group. No product formation was obtained when the substituent of R^1 and R^2 were protons. This was also seen when R^3 equalled a phenyl group. Otherwise the yields ranged from 63 to 87%.[74] Other researchers used an Ag_2WO_4 catalyst along with PPh_3 to produce the oxazolidinone **110** with a yield of 83-95%.[75] Xu *et al*. developed a method where no catalyst was required, but a high CO_2 pressure of 140 bar. Here, the amine plays two roles, on the one hand as a base catalyst and on the other as a substrate.[76]

2.3. Amino alcohols or diamines

Reactions of amino alcohols and diamines with CO_2 have been studied extensively in the past. This caused the production of all sorts of synthesis pathways. There exist homogenous, heterogeneous and no-catalyst systems.[77–84] One of the best-performing reactions uses CeO_2 as a heterogenous catalyst. CeO_2 is a catalyst with a cubic structure in which oxygen sits on the inside and cerium on the outside.

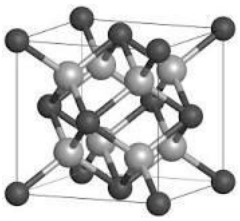
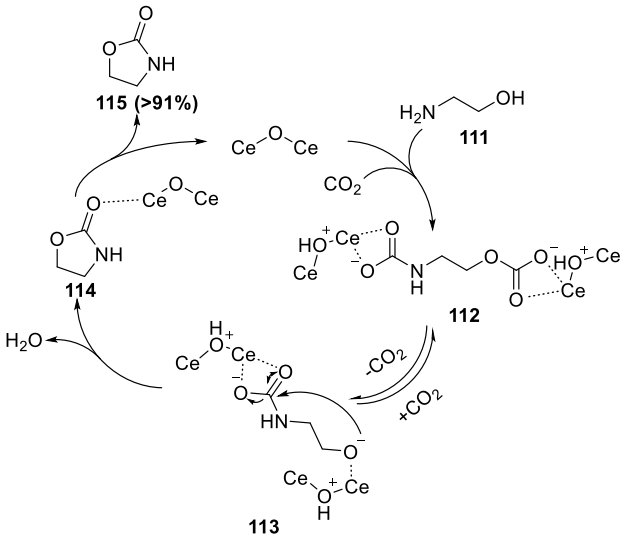


Figure 2: Structure of the CeO_2 catalyst

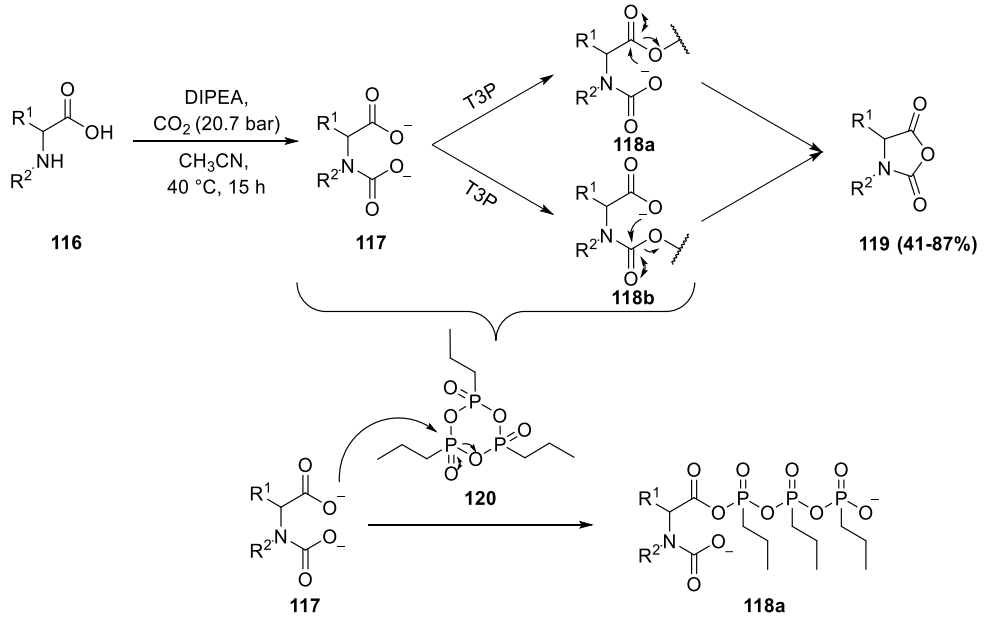
Here, CeO_2 stabilises the anion carbonyl formed after attack by an amino alcohol **111**. This can be done two times and CO_2 can also dissociate from **112**. This leaves a deprotonated hydroxy group behind on **113**, which can be activated by a catalyst molecule to attack the carbamate. This in turn yields an oxazolidinone **115**.[85] The amount of CO_2 that attaches to the amino

alcohol is dependent on the pressure. This reaction has different yields when using different solvents. Propan-2-ol was the most effective solvent, with a yield higher than 91%.[85]



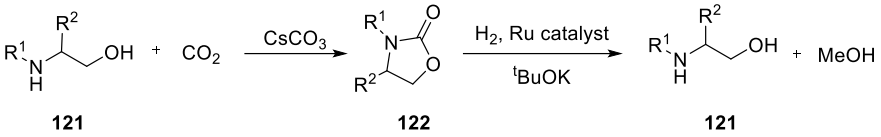
Diamines obey the same mechanism when using CeO_2. Yields are higher than 88% except for one, 1,2-dimethylethylenediamine, where the yield was 78% in propan-2-ol.[85] Six-membered heterocyclic rings can also be made by changing the alkane chain of the diamine in length.

Another interesting paper used a *N*-substituted amino acid **116** to react with CO_2. Diisopropylethylamine (DIPEA) can deprotonate the carboxylic acid and the secondary amine can react with CO_2 under pressure, which leads to **117**. In the presence of propane phosphonic acid anhydride **120** (T3P), one of the anionic oxygen atoms of **117** can react with **120**. This in turn becomes a good leaving group in both instances, and therefore the normally weak anion can perform a nucleophilic attack and form an oxazolidinone **119**.[86]



In 2015 a paper was published that indicates the possibility of methanol production with low pressure CO_2.[87] This was done by the production of an oxazolidinone intermediate **122** and conversion back into the β-amino alcohol **121** with methanol as a second product.[87] The

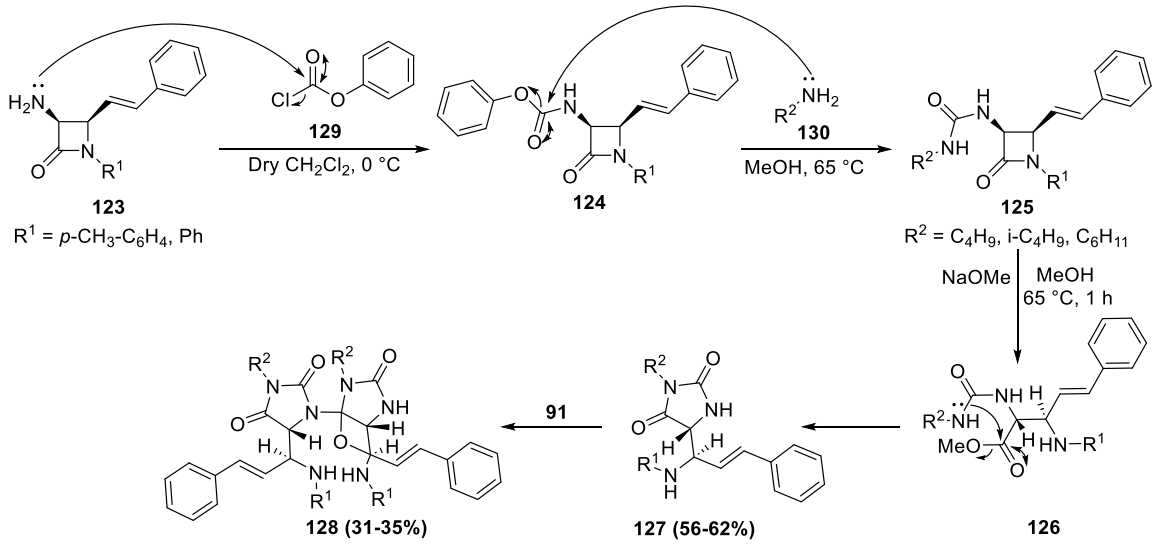
advantage of this method is its yield, which is in the best-case scenario 92%. Most of the time CO_2 conversion into methanol has yields lower than 18% and requires high pressure.[88] This resulted in high costs with relatively low methanol yield. This relatively new method could prove useful.



121 **122** **121**

3. Rearrangement of 3-amino-β-lactams to imidazolidinones

3-Amino-β-lactams are very useful and interesting molecules. These compounds possess a high ring strain, but lower than aziridines and epoxides. The amino functional group readily reacts. In the case of this study, the production of oxazolidinones and imidazolidinones is the main goal. Usage of the amino group can be a first step in the production of these compounds. One of the main pathways to accomplish this, is a nucleophilic attack by the amino group onto another molecule, which preferably bears a good leaving group. In a first example, the 3-amino-β-lactam **123** is first reacted with phenyl chloroformate **129** to form a carbamate **124**. This is reacted with an amine **130** to form a urea functional group **125**. Sodium methoxide is then used to cause a N-C2 ring opening. The R-substituted nitrogen from the urea functionality will attack the produced methyl ester **126** to form an imidazolidinone **127**. In this instance, also the dimer **128** is synthesised as an undesirable side product.[20]



123
R^1 = *p*-CH_3-C_6H_4, Ph

124

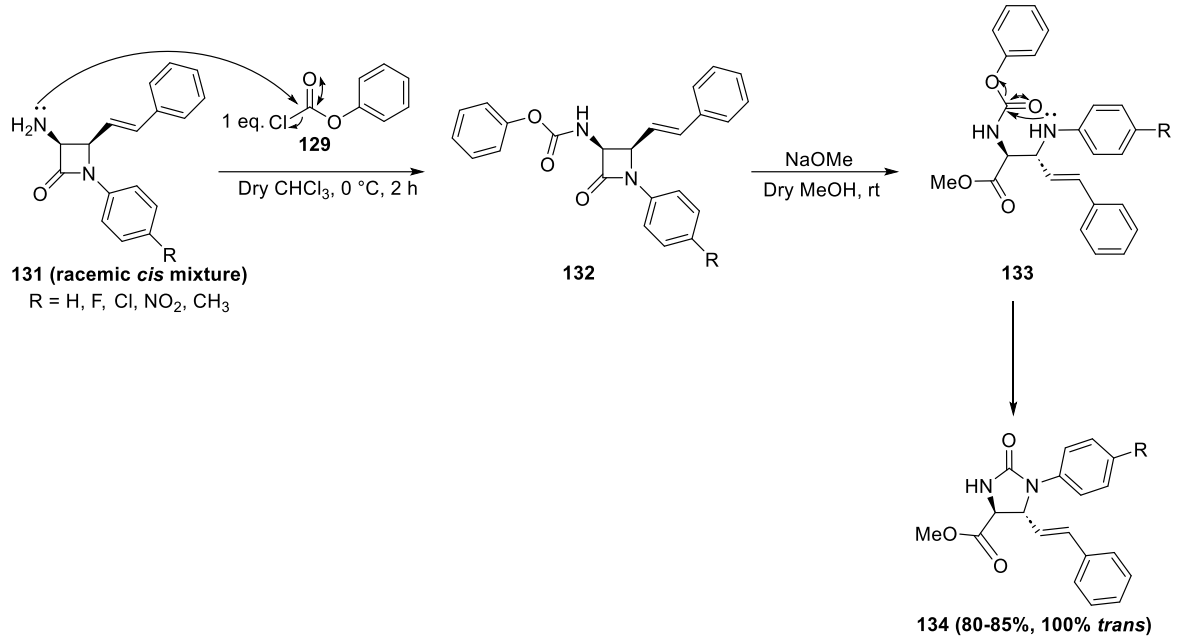
125
R^2 = C_4H_9, i-C_4H_9, C_6H_{11}

126

127 (56-62%)

128 (31-35%)

Another possibility given by Mehra *et al*. is to ring open the β-lactam **132** with sodium methoxide after reaction with phenyl chloroformate **129**. This causes the nitrogen, originally from the β-lactam, to attack the phenyl carbamate *in situ* to form an imidazolidinone **134**.[21] Here, there is a slight difference with the previous method. There is no usage of an amine **130**, which results in a different end product **134**.



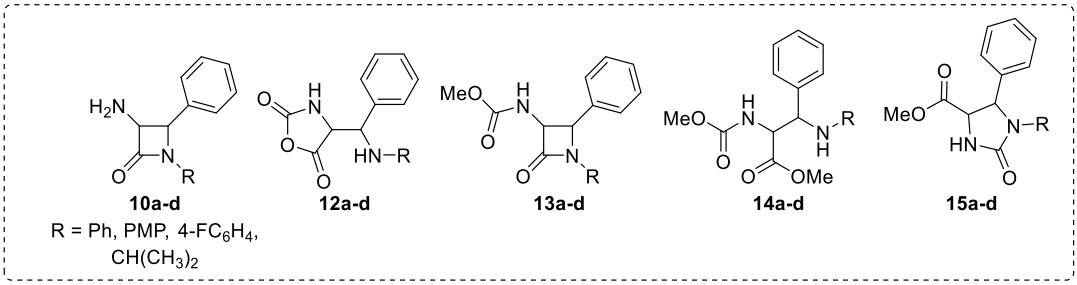
4. Conclusion

Oxazolidinones and imidazolidinones production has been researched extensively in the past when looking at this literature study. Compounds can range from molecules such as epoxides and aziridines to carbamates in combination with an alkyne or alkene functionality. In most reactions, a catalyst is required to synthesize the five-membered rings. Additionally, a second compound such as phosgene, phenyl chloroformate, an amine, isocyanate and even the more green C1 building block CO_2 is needed. CO_2 is more green than compounds such as phosgene and phenyl chloroformate (phosgene based), which is why pathways using CO_2 are researched intensively. Production of an imidazolidinone from an 3-amino-β-lactam is already done in the past but not with CO_2. But this gives an indication that imidazolidinone production with CO_2 could be done. As already mentioned, this is the main objective of this thesis and will be discussed in the following chapters.

Results and discussion

The literature review has shown that the production of oxazolidinones and imidazolidinones, with or without CO_2, can be done by numerous strategies. In the case of CO_2, yields were not underwhelming. As previously said, CO_2 can be difficult to work with because of its limited reactivity and solubility. In the literature review, relatively simple catalysts, bases and acids were used, with the exception of a couple of less used catalysts (see entry 5 in Table 3). This proves that CO_2 can be an excellent C1 building block that can serve as a substitute for other more hazardous C1 building blocks such as phosgene and other phosgene-based compounds. As a consequence, this substantiates the goal of this thesis, where CO_2 can be used to produce oxazolidinones and imidazolidinones from 3-amino-β-lactams **10**.

This Master's thesis will evaluate the conversion of *N*-aryl-substituted methyl (2-oxo-4-phenylazetidin-3-yl)carbamates **13** into oxazolidinones **12** or imidazolidinones **15**. If this succeeds, this will prove that **13** is a stable and usable CO_2-containing molecule. First, 3-amino-β-lactams **10** are produced via a Staudinger cycloaddition with subsequent removal of the phthaloyl group with the help of hydrazine monohydrate ($N_2H_4 \cdot H_2O$). Secondly, methylation by $TMSCHN_2$ will take place after the addition of CO_2. Thirdly, a ring opening with NaOMe will be done with formation of **14**. The last step is to find a way to ring close **14** to its five-membered heterocyclic rings **15**.



5. Production of 3-amino-β-lactams

This first part contains the synthesis of 3-phthalimido-4-phenylazetidin-2-ones **9**. This is done by a Staudinger synthesis, which is a [2+2] cycloaddition of an imine and a ketene (generated *in situ*). This synthesis route is based on previous research done at the Department of Green Chemistry and Technology (Faculty of Bioscience Engineering, Ghent University).[22]

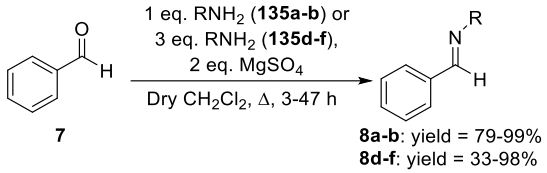
5.1. Production of 3-phthalimido-4-phenylazetidin-2-ones

5.1.1. Synthesis of *N*-aryl and *N*-alkyl imines 8

The desired imines can be easily produced by a condensation reaction between benzaldehyde **7** and an amine (aniline **135a**, *p*-anisidine (PMP = *p*-methoxyphenyl) **135b**, 4-fluoroaniline **135c**). In a condensation reaction water is produced as a byproduct, which can have a negative impact on the reaction. Synthesis of an imine is reversible, where water can hydrolyse the imine again. This requires the removal of water. This can be done by adding magnesium sulphate ($MgSO_4$). To produce the imines, benzaldehyde **7** was treated with one equivalent of amine **135a-c**. Anhydrous dichloromethane (CH_2Cl_2) was used as a solvent and the reaction mixture was left to react at reflux temperature. Furthermore, two equivalents of $MgSO_4$ were added and the reaction was done under nitrogen atmosphere to further reduce the presence

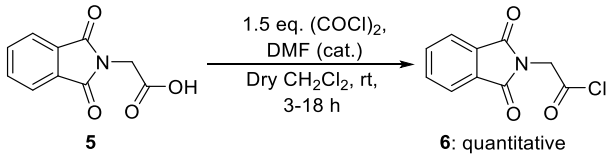
of water. The anhydrous solvent is needed to reduce the initial water concentration in the reaction mixture. Purification consisted of filtration and subsequent *in vacuo* removal of the solvent. Most reactions were completed after a couple of hours and had yields of 79% or above. The 4-fluorophenyl substituent was not tested here and also not in the upcoming Staudinger cycloaddition. The reason for this had to do with enough product **9c** that was left behind in previous research, and therefore it was not necessary to produce it again.

The substituent groups of previous imines are always aryls. The choice was made to do the whole synthesis for alkyls too. The reason for this is described in chapter 7.1. The alkyl-based amines that were used are isopropyl- **135d**, butyl- **135e** and *tert*-butylamine **135f**. Isopropylamine was chosen as the one to start with. If the synthesis of imidazolidinone **15d** succeeded, the other ones would be tested. The procedure was exactly the same as with the *N*-aryl imines **8a-c**, but three equivalents of amine were used because of the volatility of the alkyl amines. One difference was seen in the purification when compared to the aryl imines. The reaction mixture sometimes became viscous to the point where filtration was almost impossible and it had to be done by using a coffee filter and pushed through manually. The reason for this is unknown and yields were to be 53-98% **8d**, 37% **8e** and 33% **8f**.

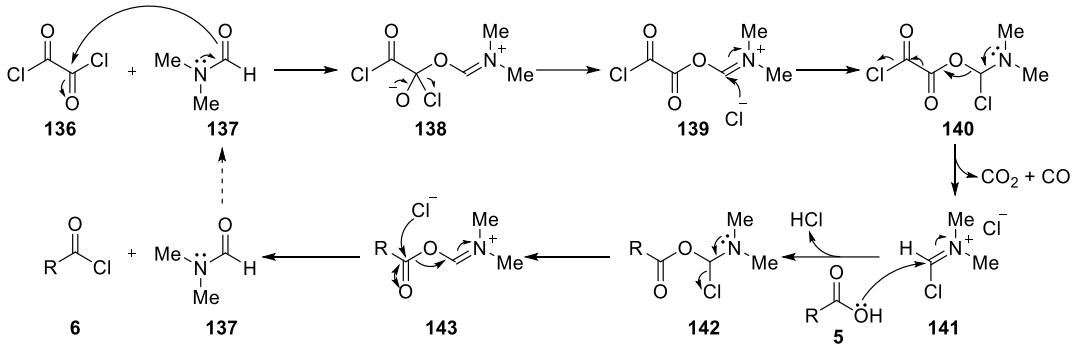


5.1.2. Preparation of *N*-phthaloylglycyl chloride 6

Producing the acid chloride **6** from carboxylic acid **5** is a relatively simple reaction that proceeds easily to the end product by using a catalytic amount of *N*,*N*-dimethylformamide (DMF) and 1.5 equivalents of oxalyl chloride. This reaction is also done in a dry environment by using anhydrous CH_2Cl_2 and nitrogen atmosphere. Purification only consisted of *in vacuo* removal of the solvent. This reaction always had a quantitative yield. The end product should be stored in the freezer because of conversion back into the starting product and should be used as soon as possible.

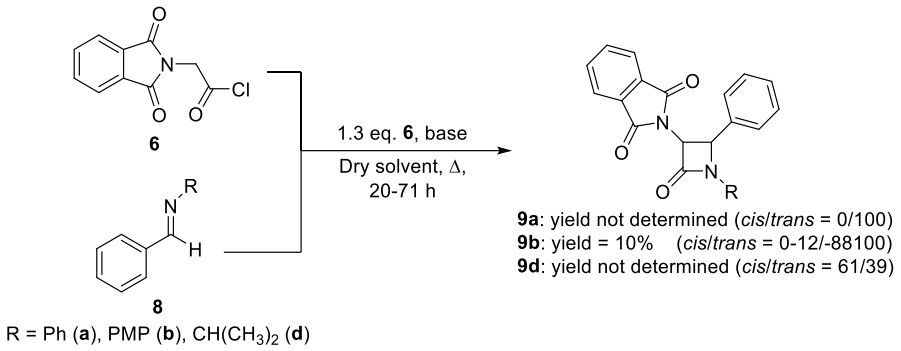


The reaction mechanism itself is not self-explanatory. First, reaction between oxalyl chloride **136** and DMF **137** happens. This forms the Vilsmeier reagent **141**. This molecule is used in the Vilsmeier-Haack reaction, which adds an aldehyde or a ketone functionality onto aryls.[89] In this case, the carboxylic acid **5** can perform a nucleophilic addition on the Vilsmeier reagent **141**. In the end, the chloride that was removed in molecule **142** does a nucleophilic addition and elimination with the formation of the desired acid chloride **6**.

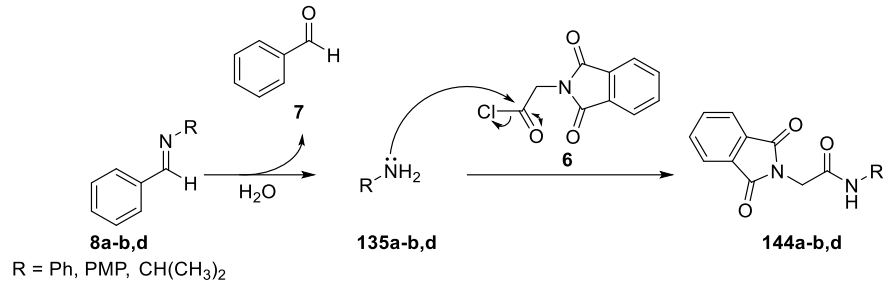


5.1.3. Method 1: Staudinger synthesis with *N*-phthaloylglycyl chloride

When both imine and acid chloride are prepared, the Staudinger cycloaddition can be started. Generally, the procedure started with adding imine **8**, 1.3 equivalents of acid chloride **6** and four equivalents of base to a setup that was flame dried, flushed with nitrogen and dry solvent added (Table 4). In entries 2-4, $MgSO_4$ was added in an arbitrary amount to further reduce the reversible reaction where the imine decomposed to the amine and benzaldehyde.



Purification consisted of filtration if $MgSO_4$ was used. Subsequently, solvent was removed *in vacuo* and the crude product dissolved in ethyl acetate. An extraction was done with water and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution, water and brine. $MgSO_4$ was added and the mixture was filtrated. Again, the solvent was removed *in vacuo*. Only in entries **4** and **7** it was worth doing reversed-phase automated column chromatography (C18, gradient water/acetonitrile: 70/30-0/100). The product after purification was always >95% pure according to LC-MS. As can be seen in the table below, when using reflux temperatures *trans* enantiomers were favoured. This is also what is expected because higher temperatures result in more isomerization from *cis* to *trans*.[90] Besides, the reactions were underwhelming but entries 4, 6 and 7 were reasonable. Side product **144a-b,d** formation was significant and sometimes took over the whole reaction. This means that there was always water present, otherwise the imines **8** could not decompose into their respective amines **135** and benzaldehyde **7**, where the amine would attack the acid chloride **6**. Entry 10 was a test reaction to investigate if there was any difference between alkyls and aryls. There is indeed a difference, where the isopropyl substituent produces more *cis* enantiomer. This can be linked to its electron-donating capability nature in comparison to the electron-withdrawing capability of aryls.[90]



Also, a different order in which the starting reagents were added was tested. In most entries, the acid chloride, imine and base were added at the same time, but not in entry **9**. Here the acid chloride was dissolved in dry CH_2Cl_2 beforehand and added in multiple times to a stirred imine and base solution in dry CH_2Cl_2 that was cooled to 0 °C. The cold temperature was used to look if there was any difference in *cis* to *trans* ratio. Theoretically, this would form more *cis* due tot the cold temperature.[90] This procedure did not help to synthesize more end product **9** and minimize side product formation. In hindsight, maybe it was better to let the acid chloride react with the base to form the ketene and combine it with the imine fraction.

A remarkable difference between bases was not seen. When comparing entries 4 and 6, similar end product **9b** is noticed with a slight difference in side product formation **144b**. On the other hand, a change of anhydrous solvent had an impact. In entries 6 and 8, a higher amount of side product **144b** was noticed after stopping the reaction, in comparison with entry 7. Toluene has a higher boiling point, which means a higher reflux temperature. This seems to produce more side product.

Table 4: Synthesis of 3-phthalimido-4-phenylazetidin-2-ones using method 1

Entry	8	Dry solvent	Base	Time (h)	8/144/9 (%)[a]	Yield (%)	*Cis*/*trans* of 9
1	**a**	Toluene	2,6-lutidine	24	26/74/0	-	-
2	**a**	Toluene	2,6-lutidine	53	7/79/14	-	0/100
3	**a**	Toluene	2,6-lutidine	43	43/51/6	-	0/100
4	**b**	Toluene	2,6-lutidine	25	7/37/56	10	0/100
5	**b**	Toluene	2,6-lutidine	60	21/40/39	-	12/88
6	**b**	Toluene	Et_3N	71	17/27/55[b]	-	0/100
7	**b**	CH_2Cl_2	Et_3N	71	29/10/61[b]	-[c]	12/88
8	**b**	Toluene	Et_3N	20	45/28/27[b]	-	0/100
9	**b**	CH_2Cl_2	Et_3N	17	86/3/11	-	-[d]
10	**d**	CH_2Cl_2	Et_3N	71	33/18/49	-	39/61

[a]The displayed ratios were measured via LC-MS after reaction and before purification
[b]Entries 6-8 were combined and purified. This result is shown in entry 7
[c]Yield was not measured because the mass was too low
[d]The LC-MS spectra showed four peaks instead of two. No exact *cis*/*trans* ratio could be determined. This was tought to be a side product which could not be determined

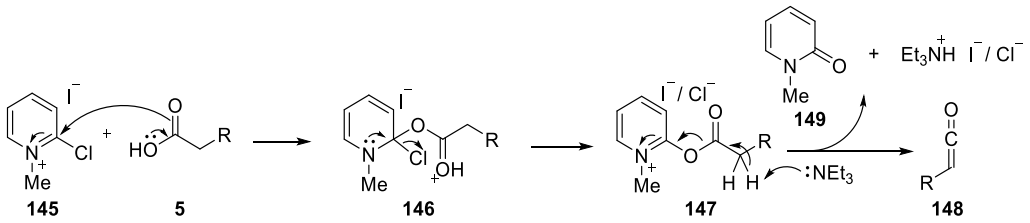
The results of previous research could not be repeated, where in the table below a comparison is presented. In this thesis, method 1 underperformed, which meant another method was needed. Another procedure was searched and found. One was tested and is discussed in paragraph 5.1.4.

*Table 5: Yields of **9a-b**: previous work versus current*

Amine	Previous work	Current
135a	33-50%	-
135b	28%	10%

5.1.4. Method 2: Staudinger synthesis using the Mukaiyama reagent

The Mukaiyama reagent (2-chloro-*N*-methylpyridinium iodide) **145** is a pyridinium salt. This salt aids the *in situ* formation of the ketene **148**, starting from a carboxylic acid **5**. This removes the need for the production of an acid chloride **6** in a separate reaction, which is an improvement of the previous method. Additionally, this reagent is inexpensive. The mechanism is relatively simple, in which the pyridinium ring is susceptible to nucleophilic addition reactions. This is what the carboxylic acid **5** does, which neutralises the positive charge on the nitrogen. The electron pair on nitrogen removes the chloride, which produces hydrochloric acid or hydrogen iodide. With the help of triethylamine, an elimination reaction is initiated. This produces hydrogen iodide and **149** as byproducts. The end product is a ketene **148**.[91]



Generally, the synthesis started with a nitrogen-flushed and flame dried setup. After this, dry CH_2Cl_2 was added. Subsequently, 1.5 equivalents of *N*-phthaloyl glycine **5**, three equivalents of Mukaiyama reagent and six equivalents of Et_3N were added and left to react at 0 °C for two hours. Thereafter, the imine was dissolved in dry CH_2Cl_2. This was added to the solution over the course of two hours, where the temperature remained at 0 °C. After a total of four hours (two times two hours), the reaction was brought to reflux and left to react.

At a first look, this method works better. Conversion of the imine is always 100% and amide **145** formation is less (2-27% in crude product). Purification was performed for entries 4-6. For entry 4, a normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 75/25-0/100) was done. This failed to give pure fractions of the end product **9d**. So a reversed-phase automated column chromatography (C18, gradient water/acetonitrile: 90/10-0/100) was tried. Part of the product eluted in a pure fraction, but not everything. On the impure fraction, another reversed-phase automated column chromatography (C18, gradient water/acetonitrile: 70/30-0/100) was done and this purified all end product. Both fractions were combined and had a yield of 43%. This is lower than expected, but this could be caused by the first (less efficient) chromatography on the same reaction. With this knowledge, in entries 5 and 6 a reversed-phase automated column

chromatography (C18, gradient water/acetonitrile: 70/30-0/100) was used directly. This worked much better than the normal-phase previously done in entry 4. This was also shown in the achieved yields. Purification of entries 1-3 was not performed. At the time, the focus shifted towards *N*-alkyl imines, which meant there was no need to work further on *N*-aryl imines. The reason for this, will be explained in chapter 7.1.

Table 6: Synthesis of 3-phthalimido-4-phenylazetidin-2-ones using method 2

Entry	8	Time (h)	Purity crude product (%)	*Cis*/*trans*[a]	Yield (%)	Purity (%)	*Cis*/*trans*[b]
1	**a**	20	32	87/13	-	-	-
2	**b**	24	76	72/28	-	-	-
3	**b**	20	39	67/33	-	-	-
4	**d**	23	59	96/4	43	100	100/0
5	**d**	26	75	88/12	68	100	82/18
6	**d**	24	83	62/38	quant.	87	76/24

Everything is measured using LC-MS
[a]Ratio of *cis* and *trans* after reaction
[b]Ratio of *cis* and *trans* after purification

When comparing method 1 and method 2, the second one is clearly better for entries 4-6. For entries 1-3, this statement can be disputed. As a little conclusion to chapter 5.1, method 1 had lower yields and produced the *trans* product, because of the higher reaction temperature. Method 2 had better yields and produced the *cis* product, caused by the initial reaction temperature of 0 °C. Reflux temperature after four hours did seem to make less difference in the ratio of *cis* to *trans*, but can also be caused by the isopropyl substituent which gives more *cis* because of its electron-donating nature.[90]

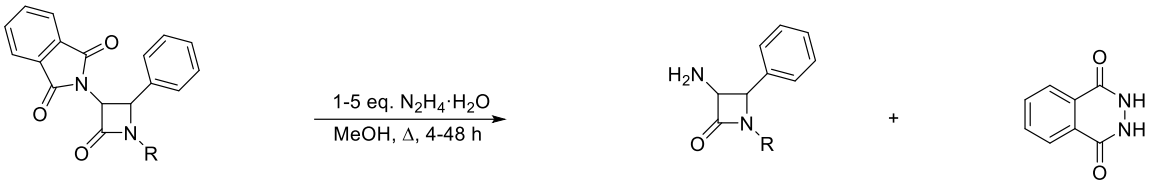
*Table 7: Comparison of cis/trans ratio between N-aryl-β-lactams **9a-b** and an N-alkyl-β-lactam **9d***

	Method 1	Method 2
Aryl	0-12/88-100	67-87/13-33
Alkyl	39/61	62-96/4-38

5.2. Deprotection of 3-phthalimido-4-phenylazetidin-2-ones

A phthaloyl group is a protection group that protects an amino functional group. This phthaloyl group in 3-phthalimido-4-phenylazetidin-2-ones **9b-d** can be removed by $N_2H_4 \cdot H_2O$. Notice that **9a** is not mentioned because this product was never purified in the previous step. Production of **9a** was always underwhelming. **9b** and **9c** were already available.

This is a relatively simple reaction where hydrazine does a double nucleophilic addition and elimination reaction on the phthaloyl group. This gives the desired 3-amino-β-lactams **10** and a byproduct **151**. The reaction procedure was started by adding methanol to a flask with the protected β-lactam **9**. $N_2H_4 \cdot H_2O$ was added and the mixture was heated under reflux.



9b: R = OMe (*cis*/*trans* = 0-12/88-100)
9c: R = 4-FC_6H_4 (*cis*/*trans* = 0/100)
9d: R = $CH(CH_3)_2$ (*cis*/*trans* = 76-100/0-24)

10b: yield = not determined (*cis*/*trans* = 0/100)
10c: yield = 55%-quant. (crude) (*cis*/*trans* = 0-16/84-100)
10d: yield = 69-88% (*cis*/*trans* = 85-100/0-15)

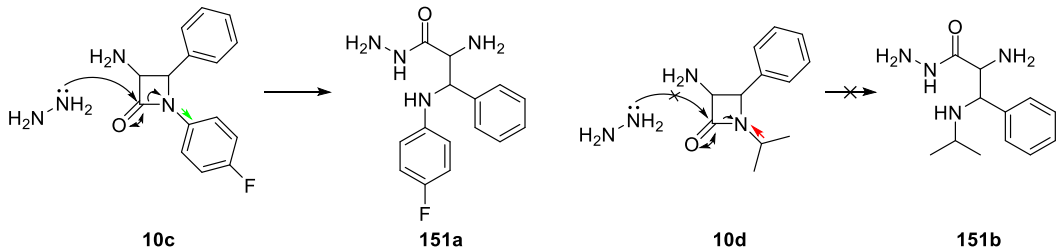
150

Looking at the table below, *cis* to *trans* ratios stayed relatively the same and reasonable side product formation was noticed in entries 4 and 10. What changed in comparison to previous research, is the amount of $N_2H_4{\cdot}H_2O$ added. Previously, one or two equivalents were added most of the time and the reaction had a full conversion of the starting reagent **9**. Here, the amount of hydrazine monohydrate quickly rose to five equivalents to achieve full conversion. An exact reason for this could not be found, because reaction conditions were the same. The use of different bottles of hydrazine monohydrate could lead to a different reactivity.

Previous research always performed a normal-phase automated column chromatography because of side product formation, which is less of a problem here. In entries 1, 6 and 7, no purification was done because these were test reactions. The amount of product after reaction was too low to do any further reactions.

In entries 2-5, a different purification method (method 1) was used in comparison to previous research. After the reaction, the byproduct crystallised out of the solution, but even after cooling the reaction mixture not everything crystallised out looking at the LC-MS after filtration. This meant that additional steps were required. After filtration, the solvent was removed *in vacuo*. To also try to remove hydrazine monohydrate at the same time, a solvent such as diethyl ether, chloroform or CH_2Cl_2 was added. Hydrazine monohydrate is insoluble in these solvents.[92] Now, a filtration can be done to remove $N_2H_4{\cdot}H_2O$ but the byproduct still could not be separated fully. A problem occurred while performing this purification method. Nothing seemed to dissolve in one of the three solvents after removal of the solvent. At the time, the choice was made to work further with the impure products in Table 8.

In entries 3 and 4, some side product **151a** was noticed, which was not seen as much in entries 8-10. This outcome is coupled with the fact that the substituent is an isopropyl group, which is more electron-donating (red arrow) than aryls. This means that ring opening does not happen and the ring is less reactive than in the case of aryls, which are electron-withdrawing (green arrow).



10c **151a** **10d** **151b**

With purification, another approach (method 2) was taken. Here, the solution was set in the freezer to let the byproduct crystallize out. A filtration was carried out and the solvent was removed *in vacuo* like in entries 2-5. Now, CH_2Cl_2 and water were added to dissolve the excess

hydrazine monohydrate and product. The remaining byproduct did not dissolve in either solvent, but rested on top of the CH_2Cl_2 layer. This meant that the CH_2Cl_2 layer could be separated from the water layer and byproduct. $MgSO_4$ was added to the CH_2Cl_2 fraction and filtrated. The solvent was removed *in vacuo*. Using enough water in the extraction step could improve the purification. This method also removed the side product **151**.

Table 8: Deprotection of 3-phthalimido-4-phenylazetidin-2-ones

Entry	9	Time (h)	$N_2H_4 \cdot H_2O$[b] (eq.)	*Cis/trans* of 9	9/10/151 (%)	Yield (%)	Purity (%)	*Cis/trans* of 10
1	**b**	24	3/2 (5)	0/100	0/100/0	-[b]	-	0/100
2	**c**	78	1/1/1 (3)	0/100	25/75/0	quant.	30[c]	6/94
3	**c**	48	3/1/1 (5)	0/100	4/91/5	55	43[c]	10/90
4	**c**	23	3/2 (5)	0/100	0/82/18	88	82[c]	16/84
5	**c**	47	3/2 (5)	0/100	0/100/0	88	85[c]	0/100
6	**d**	5	5	100/0	0/97/3	quant.[b]	-	59/41
7	**d**	71	5	100/0	1/98/1	quant.[b]	-	100/0
8	**d**	46	5	82/18	0/97/3	88	91	91/9
9	**d**	46	5	83/17	0/98/1	86	85	85/15
10	**d**	20	5	76/24	0/95/5	69	100	100/0

Everything is measured with LC-MS

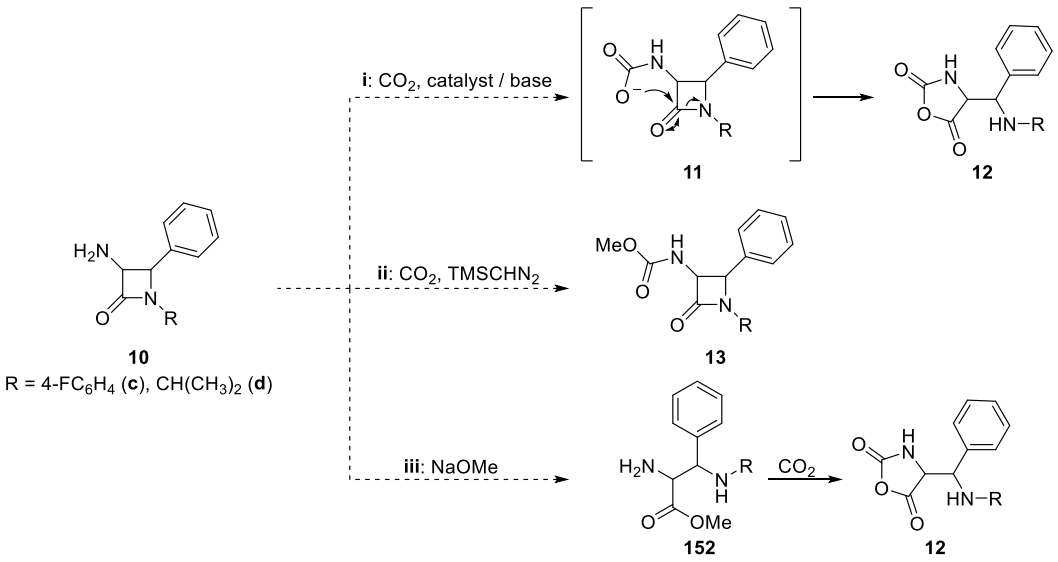
[a]Amount of hydrazine added in different time stamps given in the form x/y/z. The number in brackets equals the total amount

[b]No purification done because these were test reactions

[c]Purification method 1 was tried but ultimately had some to no effect. The yield for these entries is seen as crude and is not depicted in the scheme above. Also on LC-MS and ^{1}H NMR ($CDCl_3$), the byproduct **150** is not very visible. As a result, purity is an overstatement

6. Reactions with 3-amino-β-lactams

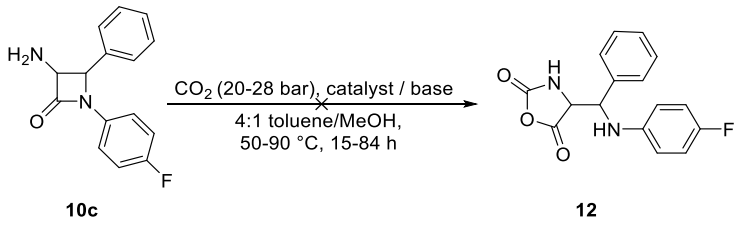
Now, the possibilities are numerous. To look back at the goal of this thesis, CO_2 has to be incorporated and used to produce an oxazolidin-2-one or imidazolidin-2-one. There are three routes this thesis has covered. Product **13** will be used in further synthesis in chapter 7.



6.1. Pathway i: addition of CO_2 with oxazolidinone production

This pathway starts with an addition of 3-amino-β-lactams **10** onto CO_2. The carbamate anions **11** that are formed would attack the β-lactam ring, which would form an oxazolidin-2-one **12**. This reaction was investigated on **10c** in previous research but with no success. Bases such as $NaHCO_3$, Et_3N, DBU, Cs_2CO_3 and K_2CO_3 were used.[22] Also, catalysts such as $BF_3{\cdot}2H_2O$ and $BF_3{\cdot}OEt_2$ were tested. The reactions that used bases did this with a CO_2 pressure of 20-50 bar to no avail. The catalysts were used under atmospheric CO_2 pressure and room temperatures, which means higher pressures and temperatures (Table 9) can still be tested in this thesis. Another, not previously researched, base was also tested at higher pressures in a reaction.

The procedure started with adding a combination of methanol and toluene in a 1/4 ratio in a reactor, like previous research. A catalyst was added and the reaction was started.



No product was formed, which again proves the fact that the anion **11** is too weak of a nucleophile to open the β-lactam ring. The reason why only **10c** was tested, and not **10d**, finds itself again in the electron-withdrawing capability of this substituent as already explained in chapter 0. A more electron-withdrawing substituent should make the carbonyl carbon of **10** more electrophilic and thus more susceptible to nucleophilic attack. As a *para*-fluorophenyl group is the most electron-withdrawing group used in this thesis, it should be the most efficient in facilitating oxazolidin-2-one **12** formation. Electron-donating groups such as an isopropyl group should not work, because they make the carbonyl carbon less electrophilic and make it more difficult to attack it.

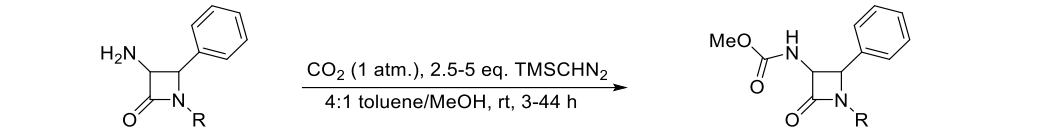
*Table 9: Testing of other catalyst and base to produce oxazolidin-2-one **12** from β-lactam **10c***

Entry	Time (h)	T (°C)	CO_2 pressure	Catalyst	Equivalents
1	15	90	20 bar	$BF_3{\cdot}OEt_2$ & Et_3N	1 & 2
2	84	50	28 bar	Bu_4NF	5

As in previous research, oxazolidinone **12** production failed. This proves that even higher temperature and pressure do not facilitate the opening of the β-lactam ring **10**.

6.2. Pathway ii: incorporation of CO_2 with subsequent methylation

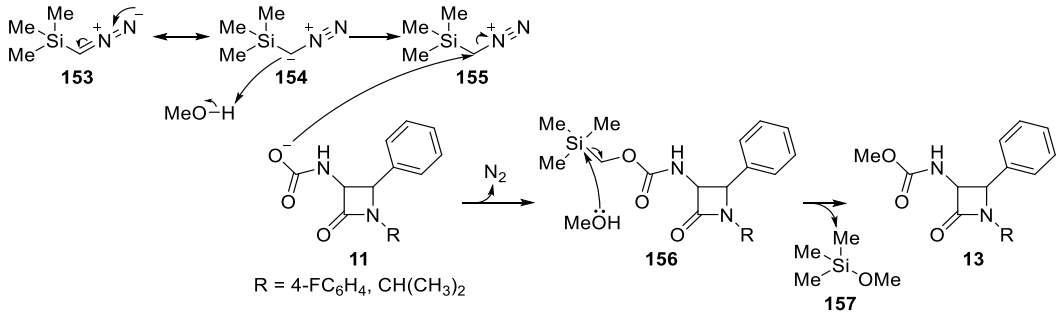
In previous research, production of oxazolidin-2-ones was not achieved. To prove the capture of CO_2 by the 3-amino-β-lactams **10**, a methylation was done.



10c: R = 4-FC_6H_4 (*cis*/*trans* = 16/84)
10d: R = $CH(CH_3)_2$ (*cis*/*trans* = 85-100/0-15)

13c: yield not determined (*cis*/*trans* = 0-4/96-100)
13d: yield = 63-69% (*cis*/*trans* = 67-97/3-33)

The reaction mechanism starts with $TMSCHN_2$ **153**, which is a less toxic version than diazomethane that also does methylation reactions. First, a mesomerization of **153** occurs. The negative charge on **154** can deprotonate a methanol molecule. Now, nitrogen gas is released because of attack by **11**, which forms **156**. Here, the anionic carboxylic acid **11** can bond with the positively charged methylene group of tetramethylsilane. Parallel to this, methanol attacks tetramethylsilane with the release of the methylene group. This methylene group binds with the proton left behind by the methanol molecule. This produces the desired methyl carbamate **13** and byproduct (methoxytrimethylsilane) **157**.



The reaction started with again adding toluene and methanol in a 4:1 ratio. Reagent **10** is added and the reaction mixture is stirred for 20-30 minutes under CO_2 bubbling to let the addition of CO_2 happen. Something to keep in mind is the reversibility of this addition, where CO_2 can be released again at any point. After this time period, $TMSCHN_2$ is added and the mixture is left to react at room temperature with continuous bubbling of CO_2. Entry 8 (Table 10) was the only reaction done in the reactor at 20 bar.

This reaction was not done for **10b** because product was never purified; interest shifted towards the isopropyl substituent **10d** and the reaction was already done for another aryl derivative **10c**. Generally, *cis* and *trans* ratios stayed relatively the same. Yields of the reactions that produced **13d** (entries 5-7) were sufficient. For **13c** (entries 1-3), yields could not be

determined due to the high amount impurities. These could not be removed, because the mass was too low to do automated chromatography. Only removal of the solvent *in vacuo* was done. These three entries were combined. Looking at the distributions in column six of entries 1-3, the conclusion can be made that these are relatively the same as the distribution of entries 4-8. This means that the reaction should perform similarly.

Entry 8 was performed in a reactor with a CO_2 pressure of 20 bar. Here, the ratio of side product formation to the desired end product was researched. Conversion of starting product **10d** was lower than in entry 7, which used product with the same *cis*/*trans* ratio as entry 7. An explanation for this is not found. A disadvantage of the reactor finds itself in the fact that $TMSCHN_2$ has to be added at the same time as the starting reagent. Nothing can be added when the reaction is ongoing because of the high pressure in the reactor. This means that $TMSCHN_2$ can directly start reacting with the 3-amino-β-lactams **10** without incorporating CO_2. However this is not seen in the ratio of side product to end product, which was always between 26 and 30% in all entries. Maybe $TMSCHN_2$'s reactivity is not fast enough and the reactor has enough time to supply the CO_2. This could not be tested.

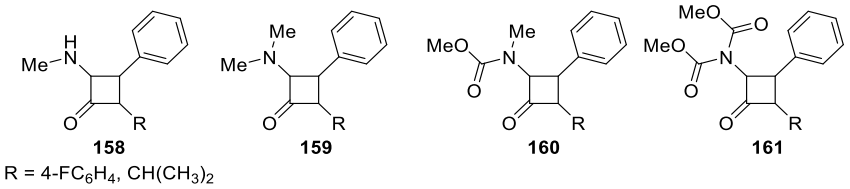
In entries 5-8 (entry 4 was a test reaction), purification consisted of removal of the solvent *in vacuo* and normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 75/25-0/100). This worked with little overlap with other components. This resulted in relative good purities except for entry 5. Again, the solvent was removed *in vacuo*.

*Table 10: Production of methyl carbamates **13***

Entry	10	Time (h)	*Cis*/*trans* of 10[b]	$TMSCHN_2$ (eq.)	10/13/159-162 (%)[f]	Cis/ *trans*[b]	Yield (%)	Purity (%)	*Cis*/*trans* of 13[c]
1	**c**	18	16/84	2.5	0/73/27	4/96	quant.[e]	36	-
2	**c**	6	16/84	2.5	22/56/22	4/96	51[e]	40	-
3	**c**	3	16/84	5	-[g]	0/100	quant.[e]	83	-
4	**d**	6	100/0	5	33/47/20	100/0	-	-	-
5	**d**	44	91/9	3/2 (5)	31/52/17	100/0	69	72	67/33
6[d]	**d**	48	85/15	3/2 (5)	21/57/22	82/18	F1: 34 F2: 29	F1: 97 F2: 70	70/30 71/29
7	**d**	23	100/0	5	9/63/28	96/4	66	96	97/3
8	**d**	23	100/0	5	26/54/19	96/4	-	-	-

Everything is measured with LC-MS
[a]Ratio of *cis* and *trans* of the starting reagent
[b]Ratio of *cis* and *trans* at the end of the reaction of **13**
[c]Ratio of *cis* and *trans* after purification
[d]Purification yielded two fractions with their respective purity
[e]These are crude yields. Purification was not done due the mass being too low to perform automated chromatography
[f]Side products' separate percentages were added together
[g]No LC-MS was taken at the time. Impossible to measure all side products formation via ^{1}H-NMR

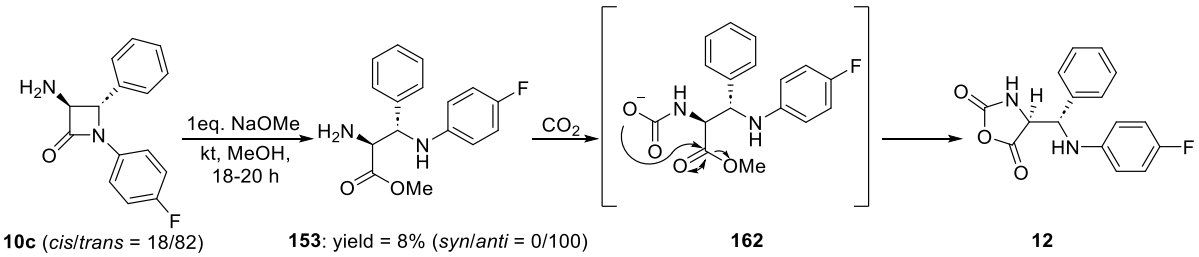
This reaction produced four side products according to LC-MS, which was also seen on ^{1}H-NMR. This was not mentioned in previous research, but may be a reason that the yields were poor (6-30%). Below, a visual presentation of these side products is given. The formation of these side products is simple to explain. Products **158** and **159** are formed because no CO_2 reacted with the 3-amino-β-lactams **10**. Subsequently, a methylation happens once or twice, in which the former is more likely to occur. The other two side products **160** and **161** are formed when the desired end product reacts further. One option is that a methylation happens without additional CO_2 incorporation. The second option is where a second CO_2 molecule is incorporated, which means two equivalents of CO_2 are used.



Side product formation was reasonable, reaching 28% as a maximum. Generally, **158** is the most favourable of the side products. This is logical because other side products first require another methylation. **158** accounted for around 50% of the side products. The other 50% was distributed evenly between the other three side products. Lowering side product formation was not researched because the achieved yields were satisfactory. The product **13** of this reaction is further used in chapter 7.

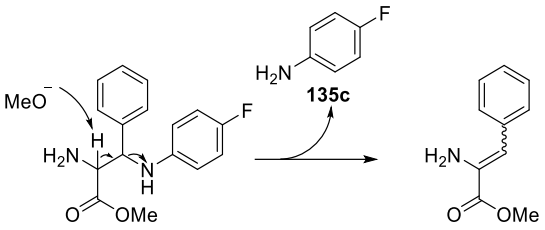
6.3. Pathway iii: ring opening of 3-amino-β-lactam 10c before reaction with CO_2

In this third pathway, ring opening of **10c** was researched. This reason for this finds itself in the inability of **10** to directly ring open after CO_2 addition in pathway i. Now, after ring opening in a first reaction and CO_2 addition in a second, another option for ring closing arises. Here, the newly formed **162** may undergo an *in situ* ring closing.



The ring opening was done by adding one equivalent of NaOMe to a mixture of methanol and the starting product. This mixture was cooled beforehand, because the heat that is released by the reaction of NaOMe can elevate the reaction temperature. This was left to stir and stopped when no further conversion was noticed on LC-MS.

Entry 1 was a test reaction that showed ring opening was possible using NaOMe. Another observation was made when looking at LC-MS spectra. Side product formation was noticed. NaOMe is a strong nucleophile, which means an elimination reaction could be the case. When looking at the molecule, a possible structure **163** was identified that matched with the m/z of 177.



Purification started with the quenching of NaOMe by NH_4Cl dissolved in water. Methanol was removed *in vacuo* and water remained. Ethyl acetate was added to create two layers. The two were separated and the water layer was washed three times with ethyl acetate. The organic layer was washed with water and brine. $MgSO_4$ was added to remove the remaining water. A filtration was done with subsequent solvent removal. This was not enough to purify the reaction mixture. In entry 2, a normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 70/30-0/100) was done. Separation was poor, which resulted in a low yield.

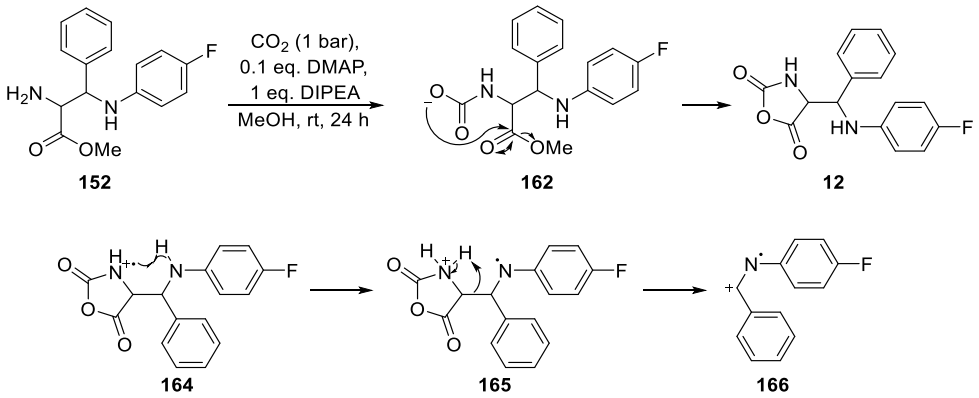
*Table 11: Ring opening of 3-amino-β-lactam **10c***

Entry	Time (h)	*Cis/trans* of 10[a]	10/153/164 (%)	*Syn/anti*[b]	Yield (%)	Purity (%)	*Syn/anti* of 153[c]
1	18	18/82	2/46/52	0/100	59[d]	46	-
2	20	18/82	17/72/11	0/100	8	100	0/100

Everything is measured with LC-MS
[a]Ratio of *cis* and *trans* of the starting reagent
[b]Ratio of *syn* and *anti* at the end of the reaction of **X**
[c]Ratio of *syn* and *anti* after purification
[d]Crude yield

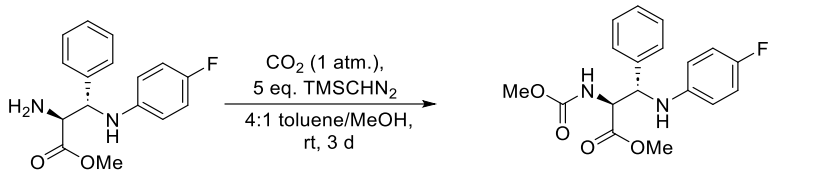
6.3.1. Ring closure of the ring-opened 3-amino-β-lactam using CO_2

The β-lactam ring was exchanged for an open structure containing a methyl ester functionality. Again, CO_2 can react with the amino group to form an anion **162**, which could react with the methyl ester and would result in the synthesis of an oxazolidin-2-one **12**. This reaction was started by adding methanol and the unpurified product from entry 1 in Table 11. DMAP and DIPEA were added in 0.1 and one equivalent, respectively.[23] CO_2 bubbling was started immediately and the reaction was followed up by LC-MS. After one day, 1% of m/z equal to 300 (t_R = 3 min.) was seen. This corresponds to the oxazolidin-2-one **12**. This was also confirmed by looking at the MS-fragmentation pattern, where an m/z of 199 **166** could be found.



6.3.2. Methylation of the ring-opened 3-amino-β-lactam 10 using CO_2

After ring opening, **152** underwent a methylation after the addition of CO_2 just like in pathway ii. The reaction was also set up in the same manner, using five equivalents of $TMSCHN_2$ and atmospheric pressure for CO_2 bubbling.



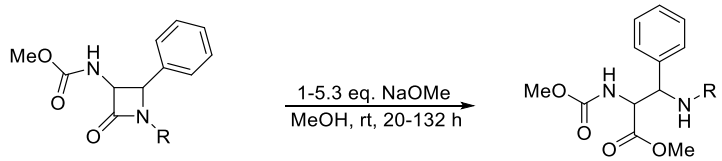
152 (*cis*/*trans* = 0/100) **14**: yield not determinded (*syn*/*anti* = 0/100)

After 3 days, the reaction did not react any further. As this was a reaction that was done on a 20 mg scale, no full purification was done. In the end, the reaction mixture contained 70% end product **14** (t_R = 3 min.), 17% starting product and 13% side product **167** formation just like in chapter 6.2. This reaction had a purity of 70% according to LC-MS. This meant that **152** also incorporates CO_2 and this is not the limiting step in chapter 6.3.1.

7. Reactions with methyl (2-oxo-4-phenylazetidin-3-yl)carbamates 13

7.1. Ring opening using NaOMe

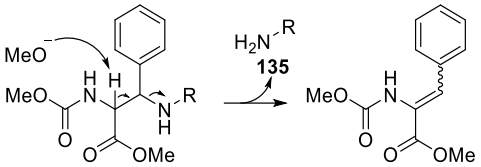
The first goal of this thesis is achieved. CO_2 incorporation was successful, in combination with sufficient yields of 63-69% with purities of 70-96% (LC-MS) for the isopropylamine derivative **13d**. *In situ* ring opening of the β-lactam is very difficult. As a consequence, ring opening was done with NaOMe, replicating what was done in chapter 6.3.



13c: R = 4-FC_6H_4 (*cis*/*trans* = 0/100) **14c:** yield not determined (*syn*/*anti* = 0/100)
13d: R = $CH(CH_3)_2$ (*cis*/*trans* = 70-97/3-30) **14d:** crude yield = 6-98% (*syn*/*anti* = 58-86/14-42)

Again, elimination is the main side reaction that has to be minimized. Temperature is the crucial reaction parameter here. Higher temperatures, generally, cause more elimination and lower temperatures less.[93] This statement was confirmed by the results in Table 12. Reflux temperature caused an increase in elimination to the point almost no end product was left in entry 6, which was confirmed by ^{1}H-NMR ($CDCl_3$). At room temperature, a lower amount of side product was formed, but this also depended on the amount of NaOMe added. NaOMe

was added when no further reaction was noticed in entries 3-5. In entries 7 and 8, the choice to not add anymore NaOMe was made to prevent side product formation but this also lowers the overall conversion. On the other hand, the starting product **13** can be almost fully recuperated.



14 **167**

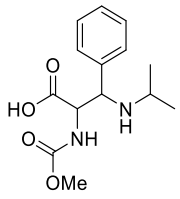
In entry 7, the reaction was started at 0 °C and stayed there for five hours. This is different from the other entries, where 0 °C was only used when adding NaOMe. After five hours, no elimination product was detected and conversion was only 6%. The choice was made to let the reaction react further at room temperature to increase the formation of **14**.

Entries 1 and 2 were not purified due to the low amount of product. Entry 6 was not purified either because there was almost no desired end product. For the other entries, purification was copied from chapter 6.3, but chromatography was also done. In entries 4 and 5, a normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 75/25-0/100) was done. This did not work very well. Everything was combined back and a reversed-phase automated column chromatography (C18, gradient water/acetonitrile: 70/30-0/100) was performed. Reversed-phase chromatography was also performed for entries 7 and 8. This worked better than normal-phase chromatography. Full purification could not be accomplished, but there was another problem. As an example, 45% of end product **14** was formed in entry 5. This reaction was done on a scale of 0.750 g, which would result in around 300-400 mg of product. Looking at the diagram after automated chromatography, separation was excellent but after *in vacuo* removal of the solvent, almost no product was left (10 mg in most cases). Adding to this, another mass (m/z = 280) showed up on the LC-MS which was not in the reaction mixture. The m/z equal to 280 **168** or **169** is believed to be a hydrolysed form of the end product, but this could not be confirmed by ^{1}H NMR. Which methyl ester was hydrolysed could not be determined. In entry 7, during the automated chromatography the program was lengthened to look whether more product would come of the column, but this was not the case. Presumably, the product does not elute from the column. This meant there was a limited amount of end product to work further with.

*Table 12: Ring opening of methyl (2-oxo-4-phenylazetidin-3-yl)carbamates **13***

Entry	13	Time (h)	T	*Cis/trans* of 13[a]	NaOMe[c] (eq.)	13/14/167 (%)	*syn/anti* of 14[b]	Yield (%)
1	**c**	20	rt	0/100	1	0/100/0	0/100	-
2	**c**	20	rt	0/100	1	2/97/1	0/100	71[d]
3	**d**	132	rt	82/18	1.3/1/2 (4.3)		63/37	-
4	**d**	68	rt	82/18	1.3/1/2/1 (5.3)	40/30/30	76/24	6[d,e]
5	**d**	69	rt	70/30	1.5/1 (2.5)	39/45/16	60/40	98[d]
6	**d**	69	Δ	71/29	1.5	0/5/95	58/42	-
7	**d**	31	0 °C → rt	97/3	1.5	59/39/2	86/14	95[d]
8	**d**	72	rt	97/3	1.5	37/52/11	78/22	68[d]

Everything is measured with LC-MS
[a]Ratio of *cis* and *trans* of the starting reagent
[b]Ratio of *syn* and *anti* at the end of the reaction of **14**
[c]Amount of NaOMe added in different time stamps given in the form x/y/z. If there are multiple time stamps, the total amount is given in brackets
[d]Crude yield. The reason why no purity is given
[e]Flask was broken, most product lost



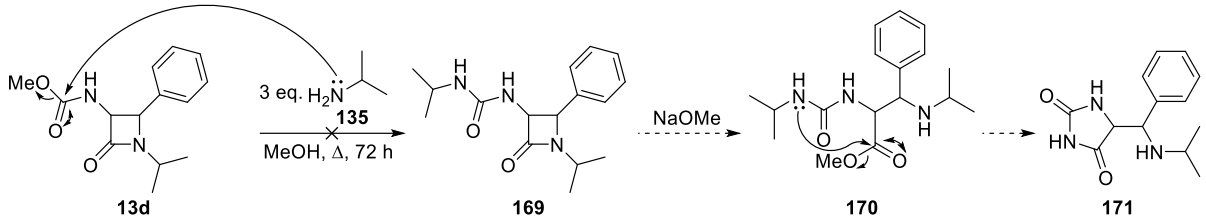
168

Looking at the amount of side product formed between both substituent groups, a greater amount of side product is expected with the 4-FC_6H_4 substituent group. Again this is linked to its electron-withdrawing capability. This would mean that this side chain is a better leaving group than the isopropyl substituent, which means that more elimination should happen. This was not the case. Overall, more elimination product **167** was seen, when using the isopropyl substituent (2-30%) versus the 4-FC_6H_4 substituent (0-1%) in similar reaction conditions.

To produce the five-membered heterocyclic ring **15** in chapter 8, the R-substituted nitrogen atom must attack the methyl carbamate of **14** that was produced in this chapter. An electron-donating substituent should help this, which is the main reason alkyl amines such as isopropylamine were also used in this thesis. In chapter 6.1, aryls should have the advantage with their electron-withdrawing capability. This facilitates ring opening in structure **11**. Here, alkyls have the advantage because they are electron donating, which they need to ring close and form a imidazolidine-2-one **15**.

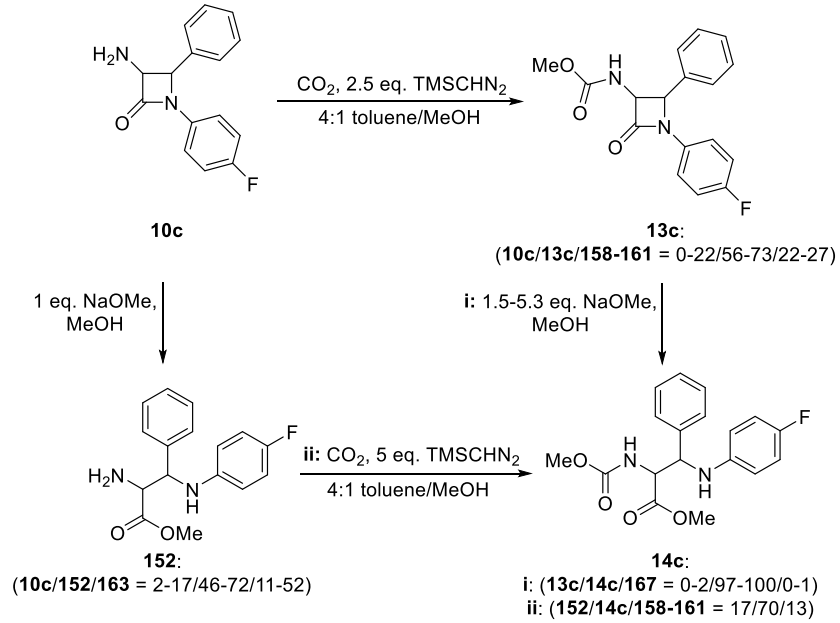
7.2. Reaction with isopropylamine

In chapter 3 of the literature study, the conversion of 3-amino-β-lactams into imidazolidinones was discussed. The reaction from **124** to **127** was done via reaction with an amine.[20] This can be applied here. After nucleophilic attack of the amine onto **13d** to produce **169**, the isopropyl-substituted nitrogen could attack the β-lactam ring and *in situ* ring close. **13** was added together with 3 equivalents of isopropylamine to methanol. The reaction stirred under reflux temperatures. After 2 days, the first step to produce **169** did not occur, which means that isopropylamine is not strong enough of a nucleophile to remove a methoxide group from a methyl carbamate functionality.



7.3. Which route is the best to synthesize methyl 3-[(4-fluorophenyl)amino]-2-(methoxycarbonyl)amino-3-phenylpropanoate 14c?

When looking back at chapter 6 and 7, a comparison can be made between different routes. The ring opening and CO_2 incorporation can be changed in the order in which they happen. A general scheme is given below, where every ratio is measured with LC-MS.

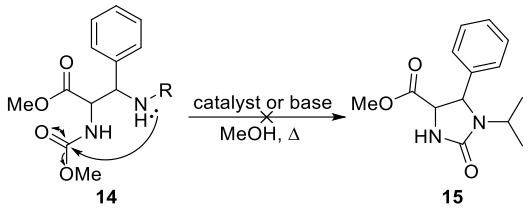


In the scheme above, the ratios between start, end and side products are given for each reaction after stopping the reaction without purification. This makes it possible to compare the different reactions. When looking at the methylation reactions, both reactions have a similar conversion from **10c** and **152** towards the end products **13c** (56-73%) and **14c** (70%), respectively. The ring-opening reactions have a slight difference. Here, it seems that more side product (11-52%) **163** is formed in the ring opening of the 3-amino-β-lactam (**10c** → **152**). Ring opening of the methyl carbamate **13c** only produced 13% side product **167** as a maximum.

Based on the ratios, an indication is found where the path that follows through **13c**, performs better. It should be noted that this does not include purification. This was only performed on **152**.

8. Formation of imidazolidin-2-one 15

With little to no product **14d**, everything (10 mg) was added into a vial, dissolved into methanol and heated under reflux. Now, a catalyst was added and left to react overnight or 5-8 hours during the day. In the end, no indication of ring closure and imidazolidin-2-one formation was found. The tested catalysts and bases were $CsCO_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, $Sc(SO_3CF_3)_3$ and DIPEA.[94–96] These were always added in a catalytic amount. **14c** was also tested (10 mg, purity = 53%). This reaction had the same procedure as **14d** and used a catalytic amount of DMAP and DIPEA.



14 **15**

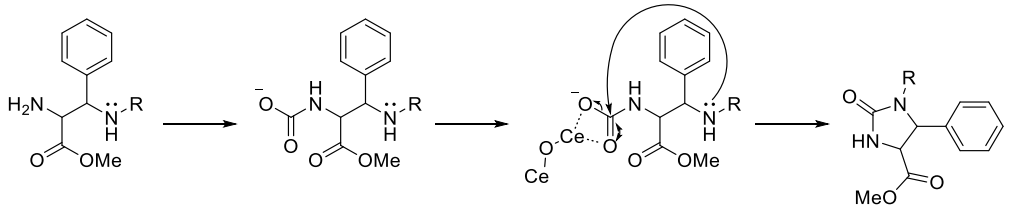
R = 4-FC_6H_4 (**c**), $CH(CH_3)_2$ (**d**)

For **14d**, bases such as $CsCO_3$ and DIPEA were chosen to investigate if they could deprotonate the isopropyl-substituted nitrogen to facilitate ring closure. On the other hand, the proton on the other nitrogen is thought to be more acidic and thus can be deprotonated more easily. This shields the carbonyl carbon of the methyl carbamate and makes the attack of the isopropyl-substituted nitrogen more difficult. This yielded no imidazolidinone. Catalysts such as $ZnCl_2$, $BF_3{\cdot}OEt_2$ and scandium triflate complex with carbonyls, which induce higher electrophilicity in the carbonyl carbon. This makes it more susceptible to nucleophilic attack.[94–96] Sadly, this also did not yield the desired imidazolidinone. For **14c**, also, no imidazolidinone **15c** was detected.

9. Future prospects

9.1. Imidazolidinone production using ring-opened 3-amino-β-lactam 153 and CO_2

In chapter 6.3.1, an indication was found where an imidazolidinone was formed. This could be explored further. Looking at the literature review in this thesis, cerium oxide (CeO_2) is a valid candidate because it produces a complex with the already reacted CO_2.[85] This makes ring closure possible.

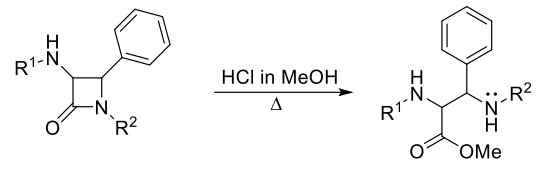


153 **172** **173** **15**

R = 4-FC_6H_4, $CH(CH_3)_2$

9.2. Ring opening in acidic environment

Ring opening was always done in basic environments, which led to side product formation due to elimination. To minimize this, an acid can be used such as HCl. With the help of methanol, ring opening can be facilitated.[97]

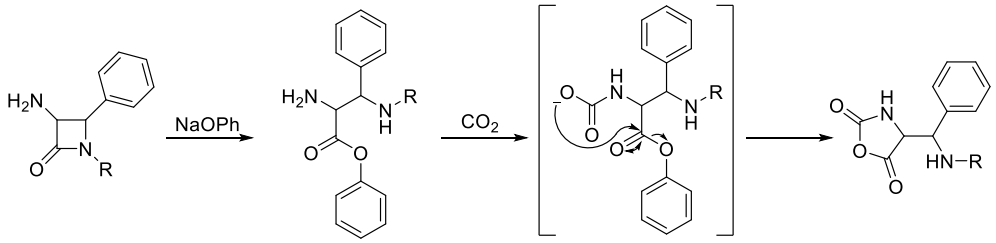


10 or **13**
R^1 = H, CO_2Me
R^2 = 4-FC_6H_4, $CH(CH_3)_2$

152 or **14**

9.3. Ring opening with another base

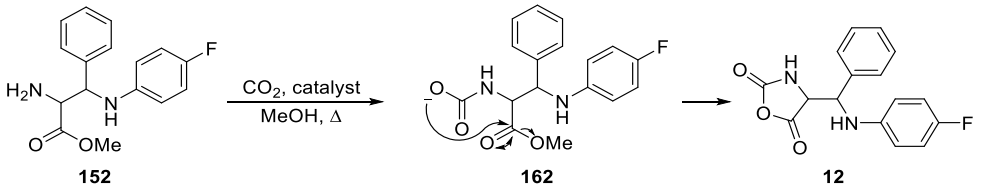
NaOMe is a strong base, which causes ring opening of the β-lactam ring of **10** and **13**. As previously seen, this can cause elimination reactions to occur. To lower elimination reactions, another, less reactive, base could be used instead of NaOMe. A candidate could be sodium phenoxide. This base is less reactive than NaOMe but has a better leaving group than it. This would mean that after ring opening, ring closing to a five-membered heterocyclic ring **15** would be easier in theory.[96,98]



10 **174** **175** **12**

9.4. Ring closing after CO_2 addition

Reaction of **152** with CO_2 produces **163**. This can *in situ* ring close with formation of **12**. There has been an indication that this happens. This reaction was only done with an atmospheric pressure of CO_2 and at room temperature. So, higher temperatures and pressures can be tested in the future. Also, other catalysts and substituents, such as isopropylamine, can be tried.

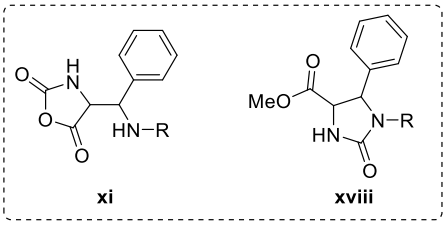


152 **162** **12**

Summary and conclusion

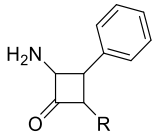
10. Summary

The goal of this thesis was to evaluate if oxazolidinones **xi** or imidazolidinones **xviii** could be synthesized by 3-amino-β-lactams that incorporate CO_2. This C1 building block is naturally abundant, non-toxic and a green alternative to phosgene, a hazardous reagent. Due to characteristics such as low reactivity and solubility of CO_2, it can be difficult to work with. While fixating CO_2 can be challenging, searching for ways to eventually synthesize oxazolidinones and for imidazolidinones can be more demanding. These would serve as pharmaceutical building blocks for antibiotic research and could play a role in searching for ways that work against the growing bacterial resistance.



xi **xviii**

This Master's thesis consisted of one large synthesis pathway with different branches at certain points. It all started with the production of 3-amino-β-lactams **i**, whose synthesis was based on preliminary research conducted at Ghent University's Department of Green Chemistry & Technology.

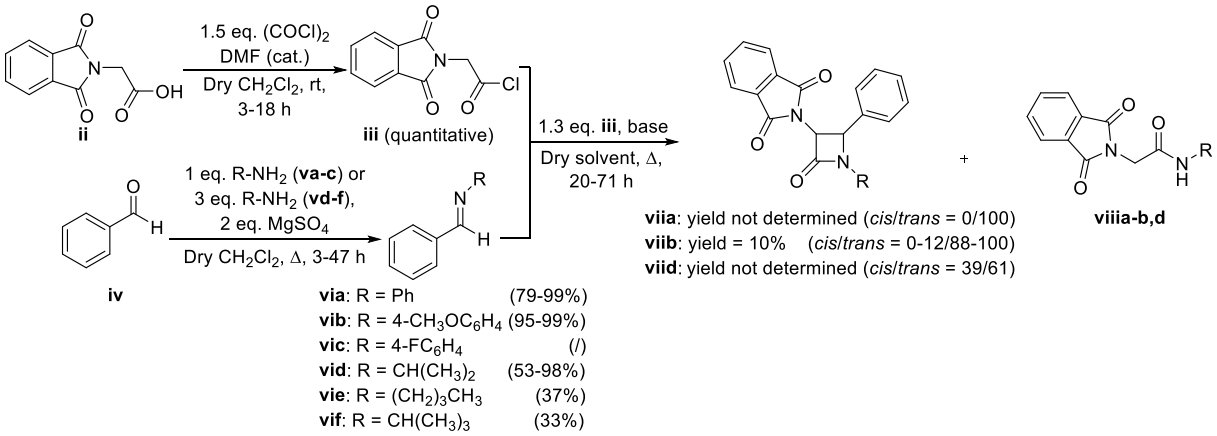


ia-d

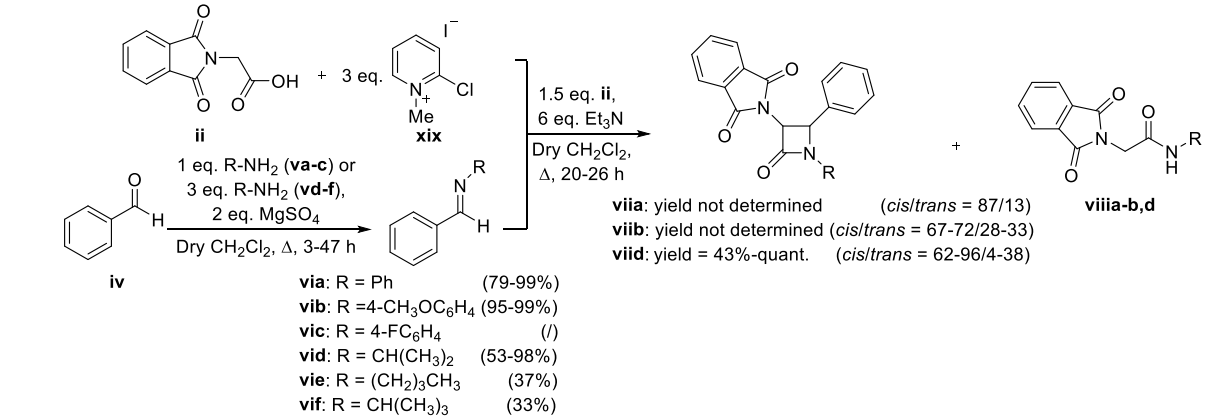
R = Ph, PMP, 4-FC_6H_4, $CH(CH_3)_2$

This was done using a Staudinger [2+2] cycloaddition, which used an imine **vi** and an *in situ* formed ketene. The imines were produced by reacting benzaldehyde **iv** with the respective amine **v**. In method 1, the acid chloride was synthesized from *N*-phthaloyl glycine **ii** using oxalyl chloride and DMF. Method 1 favoured *trans* diastereomer production, which is caused by the high temperature. Due to the low performance of method 1, another method was searched. In method 2, the Mukaiyama reagent **xix** was reacted with *N*-phthaloyl glycine **ii**, which directly synthesized the ketene *in situ*. This removes the need for the production of an acid chloride **iii** in a separate reaction and achieves better yields (43%-quant.) than method 1 in previous research (20-50%). This method favoured *cis* diastereomer formation caused by using a lower temperature. The Staudinger cycloaddition had always side product **viii** formation due to the presence of water. The ratio after reaction was on average 1.15/1 **viii**/**vii** for method 1 and 4.11/1 **viii**/**vii** for method 2. This could be separated from the end product.

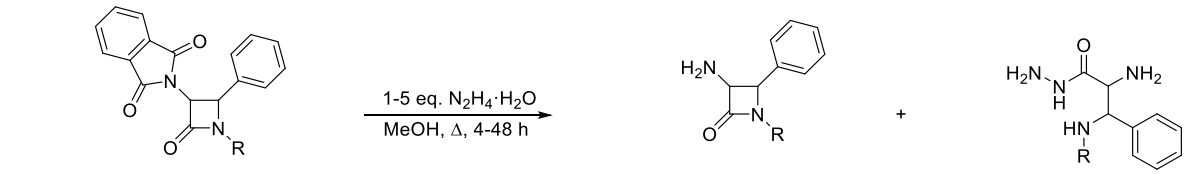
Method 1



Method 2

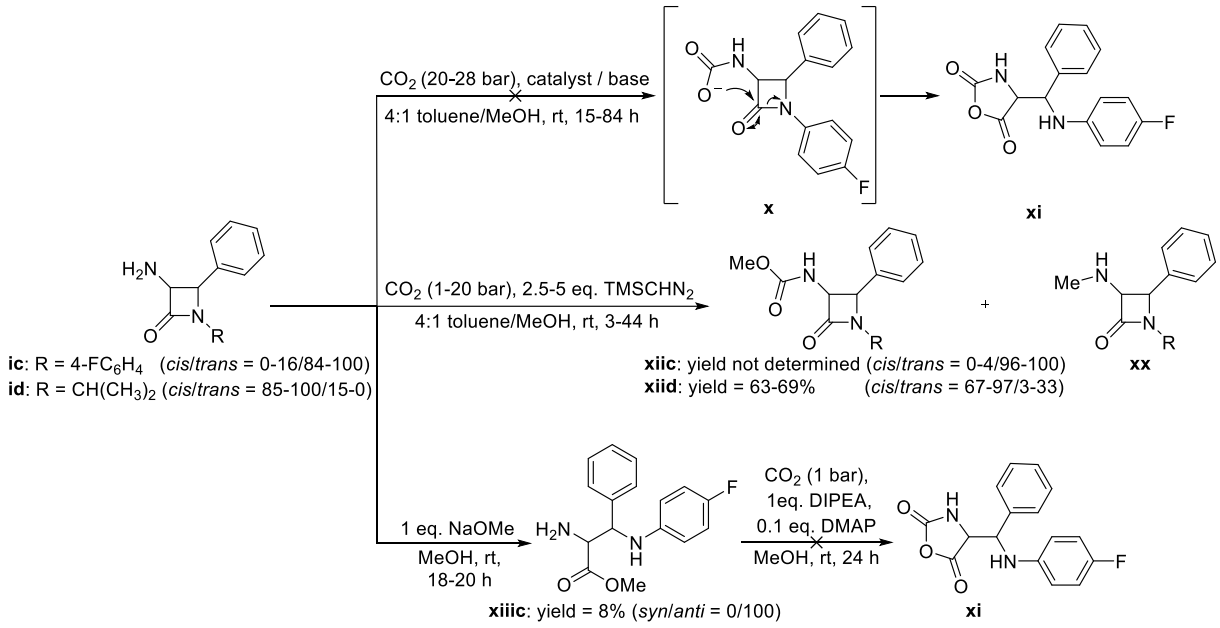


To produce the 3-amino-β-lactams **i**, the phthaloyl protecting group had to be removed using hydrazine monohydrate. Like in previous research, side product **ix** (ratio on average 26/1 **i**/**ix**) was formed during the deprotection of both *N*-alkyl- and *N*-aryl-β-lactams due to the N-C2 ring opening of the β-lactam ring. Fortunately, this side product could be removed.

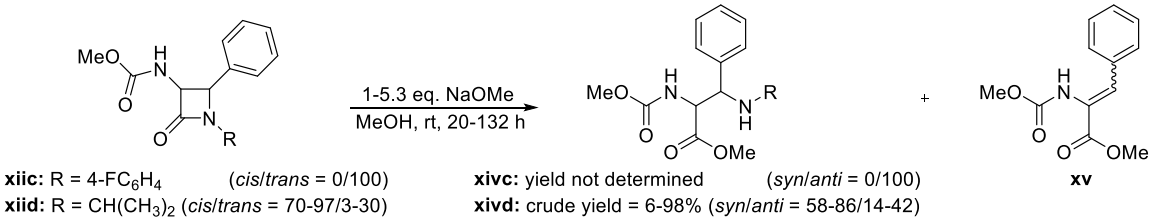


The 3-amino-β-lactams **i** are versatile and multiple different reactions can be performed. In a first pathway, CO_2 incorporation was done with possible subsequent oxazolidinone **xi** production. Sadly, this did not succeed, which probably means the anion **x** is too weak of a nucleophile to open the ring. In a second pathway, the reaction starts, again, with CO_2 fixation and a methylation takes place with the help of trimethylsilyldiazomethane to permanently fixate CO_2. This succeeded with the formation of methyl (2-oxo-4-phenylazetidin-3-yl)carbamate **xii**. This also produced four side products where **xx** was mainly formed. On average, the ratio between the end product **xii** and all side products was 2.61 to one, respectively. Lastly, the 3-amino-β-lactam can be ring opened by sodium methoxide to **xiii**. This

can capture CO_2 and *in situ* ring close to **xi** like in the first pathway. A small indication of oxazolidinone formation was seen.

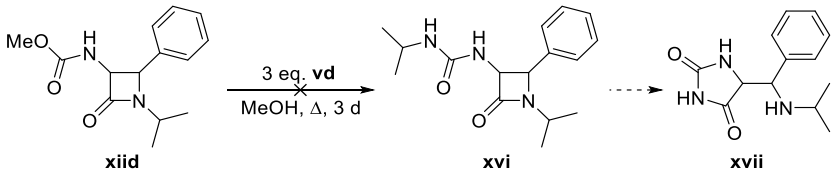


Working further with **xii**, NaOMe was used to open the β-lactam ring. This worked to a certain extent where side product **xv** caused by elimination was seen. Here, a trade-off had to be made. Lower temperatures led to lower amounts of side product but longer reaction times. Higher temperatures had the opposite effect. Fortunately, the side product could be separated. On the other hand, extracting the full amount of product was challenging and hindered the next synthesis step where an imidazolidinone **xix** would be formed. Ratio of the end product **xiv** and side product **xv** was on average 6.05 to one, respectively.

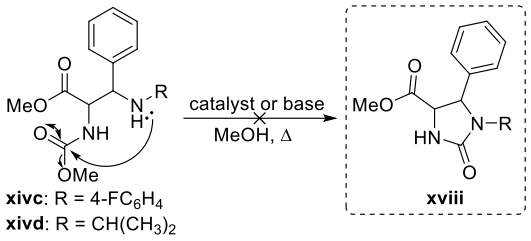


Production of **xiv** could also be done by first ring opening of **i** with the formation of **xiii** and then performing a methylation reaction to incorporate CO_2. This is the inverse order of the reaction above. The upper pathway (**i** → **xii** → **xiv**), seemed to have a better performance. This pathway had, overall, less side product formation.

xii was also reacted with isopropylamine **vd** with the possible formation of a urea compound **xvi** and an imidazolidinone **xvii** after ring closure. This was investigated because a similar reaction was successful in literature. This was not the case here.

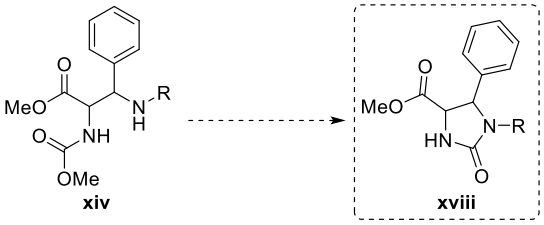


As the last step in the thesis, imidazolidinone **xviii** production was investigated with **xiv**. Different catalysts and bases such as $BF_3{\cdot}OEt_2$ and DIPEA, respectively, were used but nothing helped to synthesize the end product.



11. Conclusion

A new ring-opened *O*-methyl carbamate **xivc-d** was synthesized. This is not only one step closer to an imidazolidinone **xviii** but also confirms that **xiic-d** is a usable compound. No oxazolidinone **xi** or imidazolidinone **xvii** and **xviii**, apart from a small indication, could be produced in the time frame of this thesis, which was the main goal. On the other hand, the performance of reactions was improved. Examples of this, are the Staudinger [2+2] cycloaddition using method 2 (Mukaiyama reagent) instead of method 1 (acid chloride) and deprotection of **vii**. Also, side products, such as **viii** and **xv**, were found that were not seen in previous research. This will not only give future researchers more insight into these reactions but can have an impact on whether to follow the same strategy as this Master's thesis. Nonetheless, even with previous research and this thesis, oxazolidinone **xi** and imidazolidinone **xvii** and **xviii** production with CO_2 fixation is difficult to achieve but makes it all the more interesting and worth doing.



Experimental part

12. Laboratory instruments and general analytic methods

12.1. Liquid Chromatography Mass Spectrometry (LC-MS)

Liquid Chromatography Mass Spectrometry was used to monitor reaction progression and analyse reaction mixtures and purity. This used an Agilent 1200 Series LC/MSD SL and a Supelco Ascentis Express C18 column (internal diameter = 4.6 mm, length = 3 cm, 2.7 µm fused core particles with a pore of 90 Å). Additionally, the apparatus has a UV-DAD detector and an Agilent 1100 Series MSD SL mass spectrometer with electrospray ionisation (ESI, 4000 V, 70 eV), and a single quadrupole detector. The mobile phase consisted of a solvent mixture of acetonitrile and water. The ratio depends on the method that was used.

12.2. Nuclear Magnetic Resonance Spectroscopy (NMR)

A Bruker Avance Nanobay III NMR spectrometer with a 5 mm 1HH/BB z-gradient high resolution probe was used to execute ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz), and ^{19}F NMR (376 MHz) analyses of reaction mixtures and pure compounds. The components that needed to be analysed, were dissolved in a deuterated solvent ($CDCl_3$), with tetramethylsilane (TMS) as an internal standard. The chemical shift was reported as a δ-value in ppm. Coupling constants (*J*) were expressed in Hertz (Hz). All spectra were processed using TOPSPIN 4.2.0.

12.3. Mass Spectrometry (MS)

Mass spectrometry was done by an Agilent 1100 Series MSD SL mass spectrometer with electrospray ionisation (ESI, 4000 V, 70 eV) and a single quadrupole detector. This was used for characterizing isolated compounds.

12.4. Infrared spectroscopy (IR)

Infrared spectra were measured using a Fourier Transformed Infrared spectrometer (FTIR), Shimadzu IRAffinity-1S, and an Attenuated Total Reflectance crystal. The acquired infrared spectra were processed using LabSolutions IR software.

12.5. Melting point (Mp)

Melting points of pure solid compounds were measured using a Büchi Melting Point M-560 apparatus. This could determine the melting range in a temperature range of 30-400 °C via visual confirmation.

12.6. Automated column chromatography

Automated column chromatography could be used for the separation and purification of crude reaction mixtures. A Büchi Reveleris® X2 Flash Chromatography system was employed for reversed-phase column (C18) purification, while a Büchi Pure Flash C-815 Chromatography system was used for normal-phase (SiO_2) purification. Different reusable columns were available for the purification process (C18, particle diameter of 20-40 µm; SiO_2, particle diameter of 40-63 µm). Three UV detectors and an ELSD (Evaporative Light Scattering Detector) detector were available in the Büchi Reveleris® X2 system. In the Büchi Pure Flash C-815 Chromatography system four UV detectors and an ELSD were available. The UV wavelengths were determined with LC-MS analysis.

12.7. Anhydrous solvents

Anhydrous solvents were used while performing water-sensitive reactions. Five different anhydrous solvents such as acetonitrile, diethyl ether, tetrahydrofuran, dichloromethane, and toluene are supplied by the MBraun SPS-800 solvent purification system. These solvents were stored in a safety closet in Pure-Pac storage tanks of 17 L, where an inert gas (N_2) pressurized them. These were then passed through two filtering/drying columns. The filtering material (molecular sieves with an internal volume of 4.8 L) in these stainless steel columns (1.4301/ US 304), has different characteristics based on the solvent. A vacuum had to be established in the flasks before the solvent could be extracted under an inert atmosphere (N_2), using a membrane pump (type MPC 301 Zp).

13. Safety aspects

13.1. General safety aspects

Before entering the lab and starting this thesis, three documents, 'Safety and hygiene in chemical laboratories', 'Safety instructions: how to work with chemicals', and 'Welzijns- en Milieugids UGent', had to be read and signed. While this thesis was ongoing, the lab work was performed with the 'Internal guidelines' in mind. These guidelines were developed by the SynBioC Research Group (Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University). Additionally, a safety presentation with a test and a full lab tour was given, which gave insight into where safety was extra important. This also gave a first introduction to how the lab equipment worked to minimize accidents.

13.2. Specific safety aspects

The usage of hazardous chemicals was avoided as much as possible, but is sometimes necessary. In that case, the Safety Data Sheets (SDS) were consulted before starting the reaction. The most hazardous components are presented below.

13.2.1. Solvents

Methanol (CH_3OH): Causes damage to organs; Highly flammable liquid and vapor; Harmful if swallowed, in contact with skin or if inhaled.

Dichloromethane (CH_2Cl_2): Possible cancer hazard; Causes skin and severe eye irritation.

Acetonitrile (CH_3CN): Highly flammable liquid and vapor; Harmful if swallowed, in contact with skin or if inhaled and serious eye irritation.

Toluene: Causes skin irritation; Highly flammable liquid and vapor; May be fatal if swallowed and enters airways; Suspected of damaging the unborn child; May cause damage to organs through prolonged or repeated exposure.

Diethyl ether: Extremely flammable liquid and vapor; Harmful if swallowed; May cause drowsiness or dizziness.

Deuterated chloroform ($CDCl_3$): Harmful if swallowed; Toxic if inhaled; Causes skin irritation and serious eye irritation; Suspected of causing cancer; Suspected of damaging the unborn child

13.2.2. Reagents

Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$): Flammable liquid and vapor; Harmful if inhaled; Causes severe skin burns and eye damage; Causes damage to organs through prolonged or repeated exposure.

Caesium carbonate (Cs_2CO_3): Causes skin irritation; Causes serious eye damage; May cause respiratory irritation; Suspected of damaging fertility (if swallowed); May cause damage to organs (kidney) through prolonged or repeated exposure (if swallowed).

Hydrazine monohydrate ($N_2H_4 \cdot H_2O$): Toxic if swallowed or in contact with skin; Causes severe skin burns and eye damage; May cause an allergic skin reaction; Fatal if inhaled; May cause cancer; Very toxic to aquatic life with long lasting effects.

2,6-Lutidine: Flammable liquid and vapor; Harmful if swallowed; Causes skin irritation and serious eye irritation.

Oxalyl chloride: Causes severe skin burns and serious eye damage; Toxic if inhaled; May cause respiratory irritation.

***p*-Anisidine (PMP)**: May cause cancer; May cause damage to organs through prolonged or repeated exposure; Fatal if swallowed, in contact with skin or if inhaled.

Triethylamine (Et_3N): Highly flammable liquid and vapor; Harmful if swallowed; Causes severe skin burns and eye damage; May cause respiratory irritation; Toxic in contact with skin or if inhaled.

Trimethylsilyldiazomethane ($TMSCHN_2$): Highly flammable liquid and vapor; Harmful if swallowed; Fatal if inhaled; May cause cancer; Causes damage to organs (lungs) if inhaled.

Sodium methoxide (NaOMe): Flammable solid; Self-heating; May catch fire; May be corrosive to metals; Harmful if swallowed; Causes severe skin burns and eye damage.

Zinc chloride ($ZnCl_2$): Harmful if swallowed; Causes severe skin burns and eye damage; May cause respiratory irritation; Very toxic to aquatic life with long lasting effects.

Scandium triflate: Causes skin irritation; Causes serious eye irritation; May cause respiratory irritation.

***N*,*N*-Diisopropylethylamine (DIPEA):** Highly flammable liquid and vapor; May be corrosive to metals; Harmful if swallowed; Causes serious eye damage; Toxic if inhaled; May cause respiratory irritation.

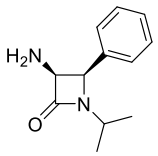
Tetrabutylammonium fluoride solution (Bu_4NF): Highly flammable liquid and vapor; Harmful if swallowed; Causes skin irritation; Causes serious eye irritation; May cause respiratory irritation; May cause drowsiness or dizziness; Suspected of causing cancer; Harmful to aquatic life with long lasting effects.

14. Synthetic procedures and spectral data

14.1. Synthesis of 3-amino-1-isopropyl-4-phenylazetidin-2-one 10d

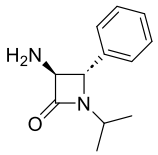
This is the procedure for the *trans* diastereomer of **10d**. 5.32 mmol of 1-isopropyl-4-phenyl-3-phthalimido-β-lactam **9d** (1.78 g, 1.00 eq.) was dissolved in methanol (100 ml) and treated with 1.29 ml (26.6 mmol, 5.00 eq.) hydrazine monohydrate.[22] The reaction mixture was left to stir for 46.0 hours under reflux. After the reaction, the reaction mixture was put in the freezer for 2.00 hours. A filtration was carried out and the solvent was removed *in vacuo*. The crude solid mixture was dissolved into CH_2Cl_2 (100 ml) and water (50.0 ml). The CH_2Cl_2 layer was separated and $MgSO_4$ was added. A filtration was done and the solvent was removed *in vacuo*. The collected material had a yield of 88% (0.962 g, 4.71 mmol) and a *cis* to *trans* ratio of 91/9.

cis-3-Amino-1-isopropyl-4-phenylazetidin-2-one **10d**



Off-white solid, Mp = 92 °C, crude yield = ~100%, purity = 94% (LC-MS), *cis*/*trans*: 100/0. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.11 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 1.32 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 3.82 (1H, septet, *J* = 6.7 Hz, C$\underline{H}(CH_3)_2$); 4.35 (1H, d, *J* = 5.1 Hz, H_2NC$\underline{H}$); 4.83 (1H, d, *J* = 5.1 Hz, C$\underline{H}$Ph); 7.26-7.29 (2H, m, 2 x $(CH_{arom})_{ortho}$); 7.33-7.37 (1H, m, $(CH_{arom})_{para}$); 7,40-7,44 (2H, m, 2 x $(CH_{arom})_{meta}$) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 20.4 (CH$\underline{C}H_3$); 21.4 (CH$\underline{C}H_3$); 45.0 ($\underline{C}H(CH_3)_2$); 61.4 ($\underline{C}$HPh); 63.3 (H_2NCH); 127.4 (2 x $(CH_{arom})_{ortho}$); 128.4 ($(CH_{arom})_{para}$); 128.9 (2 x $(CH_{arom})_{meta}$); 136.3 ($C_{quat,arom}$); 170.5 (C=O) ppm. **IR** (cm^{-1}): ν_{NH2} = 3385 (broad), $\nu_{C=O}$ = 1736; ν_{max} = 1454, 1385, 704. **MS**: m/z (%) = 409 ($[2M+H]^+$, 72); 205 ($[M+H]^+$, 100).

trans-3-Amino-1-isopropyl-4-phenylazetidin-2-one **10d**

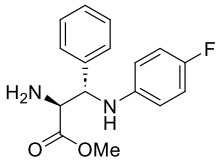


Off-white solid, Mp = 92 °C, yield = 88%, purity = 91% (LC-MS), *cis*/*trans*: 91/9. **^{1}H-NMR** (400 MHz, CDCl3): δ = 1.05 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$); 1.28 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$); 3.73 (1H, septet, *J* = 6.6 Hz, C$\underline{H}(CH_3)_2$); 3.90 (1H, d, *J* = 1.9 Hz, H_2NC$\underline{H}$); 4.20 (1H, d, *J* = 1.9 Hz, C$\underline{H}$Ph); 7.27-7.29 (2H, m, 2 x $(CH_{arom})_{ortho}$); 7.33-7.37 (1H, m, $(CH_{arom})_{para}$); 7.40-7.44 (2H, m, 2 x $(CH_{arom})_{meta}$) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 20.3 (CH$\underline{C}H_3$); 21.4 (CH$\underline{C}H_3$); 44.9 ($\underline{C}H(CH_3)_2$); 65.6 ($\underline{C}$HPh); 68.9 (H_2NCH); 126.6 (2 x $(CH_{arom})_{ortho}$); 128.5 ($(CH_{arom})_{para}$); 128.8 (2 x $(CH_{arom})_{meta}$); 138.5 ($C_{quat,arom}$); 170.4 (C=O) ppm. **IR** (cm^{-1}): ν_{NH2} = 3377, $\nu_{C=O}$ = 1721; ν_{max} = 1456, 1387, 704. **MS**: m/z (%) = 409 ($[2M+H]^+$, 100); 205 ($[M+H]^+$, 22).

14.2. Synthesis of methyl (2*S**,3*S**)-2-amino-3-[(4-fluorophenyl)amino]-3-phenylpropanoate 153

To an ice-cooled (0 °C) solution of 1.08 mmol (0.276 g, 1.00 eq.) **10c** dissolved in methanol (40 ml), 0.200 ml of 30% sodium methoxide (0.0580 g, 1.00 eq.) in methanol solution was added.[23] This was left to stir at room temperature for 18.0 hours. Afterwards, the reaction mixture was quenched with 10.0 ml of a saturated aqueous NH_4Cl solution. The solvent was removed *in vacuo* to the point only water remained. Ethyl acetate (50.0 ml) was added and the two layers were separated. The water layer was washed three times with ethyl acetate (10.0 ml, 5.00 ml and 5.00 ml). The organic layers were combined and washed with brine (10.0 ml) and water (10.0 ml). $MgSO_4$ was added to the organic layer, which removed the remaining water. This was filtrated and the solvent was removed *in vacuo*. This afforded crude **153** (100% *anti*). A normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 70/30-0/100) was performed. Purification obtained an 8% yield (0.0233 g, 0.0808 mmol).

Methyl (2*S**,3*S**)-2-amino-3-[(4-fluorophenyl)amino]-3-phenylpropanoate **153**



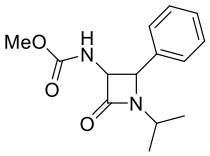
Brown viscous liquid, yield = 8%, purity = 82% (^{1}H-NMR). **^{1}H-NMR** (400 MHz, CDCl3): δ = 3.69 (3H, s, OCH_3); 3.90 (1H, d, *J* = 4.3 Hz, C<u>H</u>NH_2); 4.81 (1H, d, *J* = 4.3 Hz C<u>H</u>Ph); 6.48-6.51 (2H, m, 2 x $F(CH_{arom})_{meta}$); 6.76-6.80 (2H, m, 2 x $F(CH_{arom})_{ortho}$); 7.21-7.33 (5H, m, 5 x CH_{arom}) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 52.1 (OCH_3); 59.0 ($CHNH_2$); 59.4 (<u>C</u>HPh); 114.6 (d, *J* = 7.4 Hz, 2 x $F(CH_{arom})_{meta}$); 115.6 (d, *J* = 22.0 Hz, 2 x $F(CH_{arom})_{ortho}$); 127.2 (2 x $CH(\underline{C}H_{arom})_{ortho}$); 127.9 ($CH(\underline{C}H_{arom})_{para}$); 128.6 (2 x $CH(\underline{C}H_{arom})_{meta}$); 137.9 ($CH\underline{C}_{quat,arom}$); 142.8 (d, *J* = 1.5 Hz, $NH\underline{C}_{quat,arom}$); 155.8 (d, *J* = 235.3 Hz, $F\underline{C}_{quat,arom}$); 174.0 (C=O) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = (-127,86) - (-127,79) (1F, m, $FC_{quat,arom}$) ppm. **IR** (cm^{-1}): ν_{NH} = 3377, $\nu_{C=O}$ = 1736; ν_{max} = 1508, 1211, 820. **MS**: m/z (%) = 289 ($[M+H]^+$, 100).

14.3. Synthesis of methyl (1-isopropyl-2-oxo-4-phenylazetidin-3-yl)carbamate 13d

4.23 mmol of **10d** (0.864 g, 1 eq.) was dissolved in a 4/1 ratio of toluene and methanol (150 ml) solution. CO_2 was bubbled through for 20.0 minutes and 6.04 ml of a 1.80-2.40 M trimethylsilyldiazomethane in hexane (12.7 mmol, 3.00 eq.) solution was added. The reaction was left to stir for 44.0 hours at room temperature. After 22 hours, another 4.02 ml of 1.80-2.40 M trimethylsilyldiazomethane in hexane (8.46 mmol, 2.00 eq.) solution was added. The solvent was removed *in vacuo* and the result was a crude mixture with a *cis*/*trans* ratio of 82/18. Purification consisted of a normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 80/20-0/100), which resulted in a yield of 69% (0.769 g, 2.93 mmol) with a *cis*/*trans* ratio of 67/33.

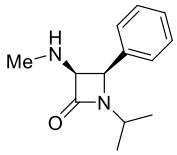
In another reaction, characterisation of side product **159** was performed. This is a side product caused by a methylation reaction without CO_2 incorporation on **10d**. 7.49 mmol of 3-amino-1-isopropyl-4-phenylazetidin-2-one (1.53 g, 1.00 eq.) **10d** was dissolved in a 4/1 ratio of toluene and methanol (150 ml) solution. CO_2 was bubbled through for 20 minutes and 17.8 ml of a 1.80-2.40 M trimethylsilyldiazomethane in hexane (37.5 mmol, 5.00 eq.) solution was added. The reaction was let to stir for 23.0 hours at room temperature. The solvent was removed *in vacuo* and the result was a crude mixture with a *cis*/*trans* ratio of 96/4. Purification consisted of a normal-phase automated column chromatography (SiO_2, gradient petroleum ether/ethyl acetate: 80/20-0/100), which resulted in a yield of 66% (1.46 g, 5.56 mmol) of **13d** with a *cis*/*trans* ratio of 97/3. Besides the end product **13d**, a pure fraction of **159** (20.0 mg) could be collected.

Methyl (1-isopropyl-2-oxo-4-phenylazetidin-3-yl)carbamate **13d**



Yellow viscous liquid, yield = 69%, purity = 96% (^{1}H-NMR), *cis*/*trans*: 67/33. ***cis* isomer ^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.11 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$); 1.33 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$); 3.44 (3H, s, H_3CO); 3.83 (1H, septet, *J* = 6.6 Hz, C$\underline{H}(CH_3)_2$); 4.93 (1H, d, *J* = 5.0 Hz, C$\underline{H}$Ph); 5.20 (1H, dxd, *J* = 9.1, 5.0 Hz, C$\underline{H}$NH); 5.68 (1H, d, *J* = 9.1 Hz, NH), 7.29-7.40 (5H, m, 5x CH_{arom}) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 20.3 (CH$\underline{C}H_3$); 21.2 (CH$\underline{C}H_3$); 45.4 ($\underline{C}H(CH_3)_2$); 52.3 (H_3CO); 60.8 ($\underline{C}$HPh); 61.0 (HNCH); 127.5 (2 x $(CH_{arom})_{ortho}$); 128.55 ($(CH_{arom})_{para}$); 128.8 (2 x $(CH_{arom})_{meta}$); 135.3 ($C_{quat,arom}$); 156.2 (NHC=O); 166.8 (($\underline{C}$=OCH) ppm. ***trans* isomer ^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.06 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 1.31 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 3.67 (3H, s, H_3CO); 3.75 (1H, septet, *J* = 6.7 Hz, C$\underline{H}(CH_3)_2$); 4.33 (1H, br. d, *J* = 7.5 Hz, HNC$\underline{H}$); 4.63 (1H, br. s, C$\underline{H}$Ph); 6.26 (1H, d, *J* = 7.5 Hz, NH); 7.29-7.40 (5H, m, 5x CH_{arom}) ppm. **^{13}C-NMR** (100,6 MHz, $CDCl_3$): δ = 20.1 (CH$\underline{C}H_3$); 21.1 (CH$\underline{C}H_3$); 45.2 ($\underline{C}H(CH_3)_2$); 52.4 (H_3CO); 61.9 ($\underline{C}$HPh); 66.1 (HNCH); 126.6 (2 x $(CH_{arom})_{ortho}$); 128.5 ($(CH_{arom})_{para}$); 128.64 (2 x $(CH_{arom})_{meta}$); 138.0 ($C_{quat,arom}$); 156.3 ((C=O)NH); 167.3 (($\underline{C}$=OCH) ppm. **IR** (cm^{-1}): ν_{NH} = 3305 (broad), $\nu_{C=O}$ = 1746, $\nu_{C=O}$ = 1721; ν_{max} = 1256, 702. **MS**: m/z (%) = 547 ($[2M+Na]^+$, 15); 263 ($[M+H]^+$, 100).

cis-1-Isopropyl-3-methylamino-4-phenylazetidin-2-one **159**

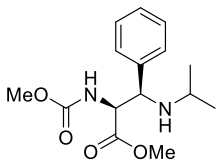


Brown viscous liquid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.08 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 1.30 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); 2.08 (3H, s, NCH_3); 3.80 (1H, septet, *J* = 6.7 Hz, C$\underline{H}(CH_3)_2$); 4.14 (1H, d, *J* = 4.8 Hz, HNC$\underline{H}$); 4.85 (1H, d, *J* = 4.8 Hz , C$\underline{H}$Ph); 7.33-7.43 (5H, m, 5 x CH_{arom}) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 20.4 (CH$\underline{C}H_3$); 21.3 (CH$\underline{C}H_3$); 32.4 (NCH_3); 44.9 ($\underline{C}H(CH_3)_2$); 60.7 ($\underline{C}$HPh); 70.8 (HNCH); 127.4 (2 x (CH_{arom}); 128.3 (CH_{arom}); 128.6 (2 x (CH_{arom}); 136.3 ($C_{quat,arom}$); 169.3 (C=O) ppm. **IR** (cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 1456, 1387, 1333, 704. **MS**: m/z (%) = 437 ($[2M+H]^+$, 70); 219 ($[M+H]^+$, 100).

14.4. Synthesis of methyl (2*S**,3*R**)-3-isopropylamino-2-methoxycarbonylamino-3-phenylpropanoate 14d

To an ice-cooled (0 °C) solution of 3.39 mmol (0.888 g, 1.00 eq.) **13d** dissolved in methanol (150 ml), 0.940 ml of 30% sodium methoxide (0.274 g, 1.50 eq.) in methanol solution was added. This was left to stir at room temperature for 72.0 hours. Afterwards, the reaction mixture was quenched with 20.0 ml of a saturated aqueous NH_4Cl solution. The solvent was removed *in vacuo* to the point only water remained. Ethyl acetate (120 ml) was added and the two layers were separated. The water layer was washed two times with ethyl acetate (20.0 ml and 20.0 ml). The organic layers were combined and washed with brine (40.0 ml) and water (40.0 ml). $MgSO_4$ was added to the organic layer, which removed the remaining water. This was filtrated and the solvent was removed *in vacuo*. This afforded crude **14d** (100% *syn*). A reversed-phase automated column chromatography (C18, gradient water/acetonitrile: 80/20-0/100) was performed. At the time, there was not enough product to measure the mass precisely.

Methyl (2*S**,3*R**)-3-isopropylamino-2-methoxycarbonylamino-3-phenylpropanoate **14d**



White viscous liquid, purity = 90%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 0.97 (3H, d, *J* = 6.2 Hz, CHC<u>H</u>$_3$); 1.01 (3H, d, *J* = 6.2 Hz, CHC<u>H</u>$_3$); 2.63 (1H, septet, *J* = 6.2 Hz, C<u>H</u>$(CH_3)_2$); 3.63 (3H, s, C<u>H</u>$_3$O(C=O)NH); 3.68 (3H, s, C<u>H</u>$_3$O(C=O)CH); 4.21 (1H, d, *J* = 4.5 Hz, C<u>H</u>Ph); 4.38 (1H, br. d, *J* = 4.5 Hz, HNC<u>H</u>(C=O)); 5.68 (1H, br. s, NH(C=O)); 7.26-7.40 (5H, m, 5 x CH_{arom}) ppm. **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 22.1 (CH<u>C</u>H$_3$); 23.9 (CH<u>C</u>H$_3$); 45.6 (<u>C</u>H$(CH_3)_2$); 52.31 (<u>C</u>H$_3$O(C=O)CH); 52.35 (<u>C</u>H$_3$O(C=O)NH); 59.6 (<u>C</u>H(C=O)OCH$_3$); 60.6 (<u>C</u>HPh); 127.2 (2 x CH_{arom}); 127.8 (CH_{arom}); 128.5 (2 x CH_{arom}); 139.8 ($C_{quat,arom}$); 156.7 (NH(C=O)); 171.8 ((<u>C</u>=O)CH) ppm. **IR** (cm^{-1}): ν_{NH} = 3345, $\nu_{C=O}$ = 1721; ν_{max} = 1211, 1061, 703. **MS**: m/z (%) = 295 ($[M+H]^+$, 100).

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