Nitrogen Insertion as a Strategy for the Synthesis of γ-Lactams

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“Don’t wait! Do something when you are young, when you have nothing to lose, and keep that in mind.”

– Steve Jobs

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“Cancers of the Mind: Comparing, Complaining, Criticizing.”

– Jay Shetty

Contents

Abstract

In this thesis, four comprehensive methodologies have been conceived that combine ring-expansion, nitrogen insertion and desymmetrization for the access of achiral and chiral γ-lactams, a pivotal core scaffold in numerous drug molecules.

In the first work, amino diphenylphosphinates have been identified as suitable amine source for the ring-expansion of cyclobutanones towards γ-lactams. Through intensive mechanistic studies, an aza-Baeyer – Villiger rearrangement has been unveiled, showing the tetrahedral Criegee-type structure as important intermediate. The stereochemical course aligned with the parent Baeyer – Villiger reaction, demonstrating a regioselective and siteselective insertion process. Besides that, the synthesized drug molecule Rolipram and its *N*-substituted derivatives display the remarkable principle of late-stage skeletal editing.

The second work builds upon the achievements of my master's thesis. Herein, the desymmetrization of prochiral cyclobutanones was described using a chiral amino alcohol, enabling the straightforward synthetic route to chiral *N*-protected γ-lactams. To conclude this project, an effective deprotection protocol showcased the access of synthetically useful pyrrolidines. In addition to that, the formal synthesis of the drug Pregabalin underscores the importance of this method within the realm of nitrogen insertion processes.

The third work of this research endeavor overcame some of the limitations encountered in the previous works. A synthetic route for the construction of novel chiral amino phosphinates was developed. These chiral amine sources were successfully incorporated into the aza-Baeyer –Villiger methodology, enabling the direct access of γ-lactams in moderate enantioselectivities. Further investigation into the stability of these chiral aminating reagents unveiled slow racemization rates, partially explaining the observed insufficient stereoinduction.

The final work describes a possible alternative for the low stereoinduction by using a catalytic approach. Here, organocatalysts and a chiral *N*,*N'*-dioxide-Sc-complex were employed, which showed a catalytic approach in the presence of $Sc(OTf)_3$. However, neither the a chiral *N*,*N'*-dioxide-Sc-complex nor organocatalysts could induce the enantioselectivity.

Zusammenfassung

In dieser Arbeit wurden vier umfassende Methoden entwickelt, die Ringerweiterungen durch Stickstoffeinfügung mit Desymmetrisierungen zu kombinieren, um den Zugang zu γ-Lactamen zu ermöglichen. γ-Lactame repräsentieren einen entscheidenden Grundkörper in Arzneimittelmolekülen.

In der ersten Studie wurden Amino-diphenylphosphinate als geeignete Aminquelle für die Ringexpansion von Cyclobutanonen zu γ-Lactamen identifiziert. Durch intensive mechanistische Studien wurde eine aza-BAEYER – VILLIGER-Umlagerung aufgedeckt, die die tetraedrische CRIEGEE-typische Struktur als wichtiges Schlüsselintermediat zeigt. Die stereochemische Richtung entspricht der breit eingesetzten BAEYER – VILLIGER-Reaktion und zeigt beispielsweise einen regioselektiven und seitenselektiven Verlauf. Darüber hinaus konnte anhand der Synthese des Arzneistoffes Rolipram und seiner *N*-substi-tuierten Derivate das Prinzip der späten Skelettmodifikation demonstriert werden.

Die zweite Studie baut auf den Errungenschaften meiner Masterarbeit auf. Hierbei wurde die Desymmetrisierung von prochiralen Cyclobutanonen unter Verwendung eines chiralen Aminoalkohols beschrieben, was den synthetischen Zugang zu chiralen *N*-geschützten γ-Lactamen ermöglichte. Zum Abschluss dieses Projekts wurde ein effektives Entschützungsprotokoll präsentiert, das den Zugang zu synthetisch nützlichen Pyrrolidinen zeigte. Darüber hinaus betont die formale Synthese des Arzneimittels Pregabalin den synthetischen Nutzen der entwickelten Methode.

Die dritte Studie der hier präsentierten Forschung umgeht die in den vorherigen Arbeiten aufgetretenen Einschränkungen. Es wurde ein synthetischer Weg für den Aufbau neuartiger chiraler Aminophosphinate entwickelt. Diese chiralen Aminquellen wurden erfolgreich in die aza-BAEYER – VILLIGER-Methodik integriert, was einen direkten Zugang zu chiralen ungeschützten γ-Lactamen mit mäßiger Enantioselektivität ermöglichte. Eine Untersuchung zur Stabilität dieser chiralen Aminierungsreagenzien enthüllte langsame Razemisierungsraten, was die beobachtete unzureichende Stereoinduktion teilweise erklärt.

Die abschließende Arbeit beschreibt eine mögliche Alternative für die geringe Stereoinduktion durch den Einsatz eines katalytischen Ansatzes. Hierbei wurden Organokatalysatoren und ein chiraler *N*,*N*'-Dioxid-Sc-Komplex verwendet. Es konnte gezeigt werden, dass in Gegenwart von $Sc(OTf)_3$ einen katalytischen Ansatz ermöglichte. Jedoch konnten weder der chirale *N*,*N*'-Dioxid-Sc-Komplex noch die Organokatalysatoren die Enantioselektivität induzieren.

Publications

Parts of this dissertation have been previously published:

- **Synthesis of 4-Phenylpyrrolidin-2-one via an Aza-Baeyer–Villiger Rearrangement**
  Ong, M.[#]; Arnold, M.[#]; Wahl, J. M.* *Org. Synth.* **2023**, *100*, 347–360
  [#] These authors contributed equally to this work. * Corresponding .

- **Stereospecific Nitrogen Insertion Using Amino Diphenylphosphinates: An Aza-Baeyer–Villiger Rearrangement**
  Ong, M.; Arnold, M.; Walz, A. W.; Wahl, J. M.* *Org. Lett.* **2022**, *24*, 6171–6175
  * Corresponding author.

- **Desymmetrization of Prochiral Cyclobutanones via Nitrogen Insertion: A Concise Route to Chiral γ-Lactams**
  Sietmann, J.[#]; Ong, M.[#]; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Wahl, J. M.* *Angew. Chem. Int. Ed.* **2021**, *60*, 9719–9723
  [#] These authors contributed equally to this work. * Corresponding author.

Poster Presentation

- ORCHEM 2022 – 22nd Lecture Conference – 09/05 – 09/07/22, Münster, Germany
  Stereospecific Nitrogen Insertion Using Amino Diphenylphosphinates: An Aza-Baeyer – Villiger Rearrangement

Declaration on the Work of Others Contained Herein

The contributions of collaborators, along with the ideas, data and findings from others, that have been instrumental in shaping the research, are presented here.

The synthesis and isolation some of the cyclobutanones have already been conducted during my master's thesis. The starting material **100d** for the synthesis of γ-lactam **88d** was obtained by MARIUS TENBERGE. The diketone **106** was synthesized by Jan SIETMANN. Additionally, the dichlorinated bicyclic cyclobutanone **79** was synthesized by a student during a practical course at the University of Mainz.

Chapter: Nitrogen Insertion *via* aza-BAEYER – VILLIGER Rearrangement

This work was conducted in collaboration with Marlene ARNOLD and Alexander W. WALZ. Initial experiments on the solvent selection were performed by Johannes M. WAHL. Furthermore, A. W. WALZ accomplished the synthesis of the Rolipram precursor **107** during a six week internship as a student. By utilizing the nitrogen insertion strategy, he finished his study by isolating the drug molecule **1**. The large-scale synthesis of **88a** was also a collaborative effort with M. ARNOLD, who was important in both, establishing the reaction process and isolating the desired product.

Chapter: Desymmetrization of Prochiral Cyclobutanones *via* Nitrogen Insertion

The work was initiated by J. M. WAHL, which subsequently evolved into a collaborative project involving Jan SIETMANN and myself. In the subsection ”Recap of this work”, the contributions by SIETMANN, WAHL and myself are outlined, some of which were accomplished during my master's thesis. In the aforementioned project, SIETMANN notably succeeded in demonstrating the desymmetrization strategy, leading to the synthesis of both chiral γ-lactams **120a–c** as well as unprotected γ-lactams **124**, **125** and **126**.

Chapter: Asymmetric Desymmetrization of Prochiral Cyclobutanones Using Chiral Phosphorous Reagents

The X-ray measurement and structure refinement of (*S*)-**143a** was performed by DIETER SCHOLLMEYER.

List of Abbrevations

AcOH	acetic acid
AFC	automated flash chromatography
APCI	atmos-pheric-pressure chemical ionization
API	active pharmaceutical ingredient
AIBN	azobisisobutyronitrile
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
CAN	cerium ammonium nitrate
conc.	concentrated
CPA	chiral phosphoric acid
equiv.	equivalent
d	day
DBTA	*O*,*O*-dibenzoyltartaric acid
DCC	*N*,*N*’-dicyclohexyl carbodiimide
DET	diethyl tartrate
DMA	dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DP	decomposition product
DPH	2,4-dinitrophenylhydroxylamine
DPPH	*O*-(diphenylphosphinyl)hydroxylamine
EDG	electron-donating group
e.g.	for example (Latin: exempli gratia)
ent	enantiomer
ESI	electrospray ionization
EtOAc	ethyl acetate
EWG	electron-withdrawing group
FC	flash column chromatography
FDA	Food and Drug Administration

FT	fourier-transform
g	gram
h	hour
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HR	high resolution
HPLC	high-performance liquid chromatography
Hz.	Hertz
IR	infrared
LG	leaving group
lit	literature
m	multiplet
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl-group
mol%	mole percent
M.P.	melting point
MS	mass spectrometry
MSH	*O*-mesitylene sulfonylhydroxylamine
m/z	ratio of mass-to-charge
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance spectroscopy
OAc	acetoxy group
PDE4	phosphodiesterase-4
PG	protecting group
ppm	parts-per-million
R	unspecified substituent
Re	right (Latin: rectus)
RTK	receptor tyrosine kinase
r.t.	room temperature
R_f	retention factor

Si	left (Latin: sinister)
SM	starting material
SPO	secondary phosphine oxides
SPS	solvent purification system
t, *tert*	tertiary
T	temperature
TCICA	trichloroisocyanuric acid
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t_R	retention time
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
TRK	tropomyosin receptor kinase
uv	ultraviolet
VAPOL	2,2'-Diphenyl-3,3'-(4-biphenanthrol)
vis	visible
wt%	weight percent
WHO	world health organization
X	heteroatom
°C	degree CELSIUS
δ	chemical shift

1 Introduction

Organic chemistry forms the crucial foundation that shapes the dynamic landscape of pharmaceutical compounds and life. Every year dozens of drugs are approved to impact the human health and well-being and these play a fundamental role in the management of a vast array of diseases.[1] One specific example is cancer, which will be discussed in the following. The “C” word refers to cancer and evokes a spectrum of emotions and sentiments, ranging from anxiety to resilience.[2] According to the world health organization (WHO), cancer remains a significant cause of mortality worldwide.[3] In the field of medicine, cancer continues to be one of the pressing challenge. Until now, researchers have made significant strides in understanding its complexity. However, the pursuit of effective cancer therapies remains a paramount quest.[4]

Over the years, the relentless journey is guided by scientific discoveries and clinical insights. The combination of traditional surgery, chemotherapy and targeted therapeutic drugs, each of which is tailored to the treatment of cancer. Since the U.S. Food and Drug Administration (FDA) approval of the first receptor tyrosine kinase (RTK) inhibitor Imatinib, the spotlight has turned to small molecules targeted drugs.[5] Owing to their unique structure, size and selectivity, small molecules can precisely target cellular components within cancer cells.[6] Given cancer’s diverse spectrum of genetic mutations, small molecules can be easily modified in their molecular composition, thus offering a range of therapeutic options.[7,8]

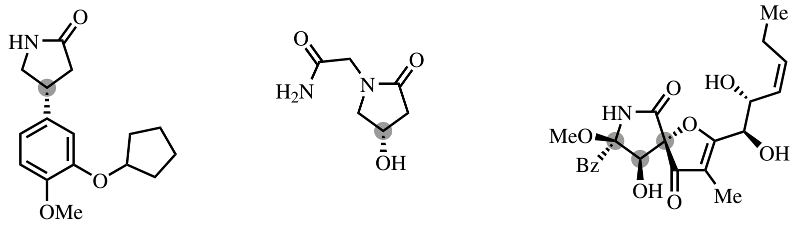
Chirality is a fundamental concept in both chemistry and molecular biology, referring to the geometric property of a molecule having a non-superimposable mirror image. In pharmaceuticals, these chiral molecules are particularly important as it can greatly influence the effectiveness and selectivity of drugs. Especially the chirality is a defining feature within small molecules, promising higher selectivity in targeting cancer cells while minimizing impacts on healthy cells.[9] This contrasts significantly with traditional chemotherapy, which often lacks the ability to distinguish between cancerous and normal cells, leading to widespread side effects.[10] The versatility of small molecules proves crucial not only in cancer treatment, but also in designing various other therapeutic agents. Thus, the dynamic interplay between the design of small molecules and their specific targeting of cellular components highlights these relationships in the development of novel and more effective therapies.[11]

2 Background

The efficient synthesis of small molecules has long captivated the fields of chemistry and biology. Producing a variety of structurally diverse small molecules, it delivers starting points for drug discovery.[12] A notable structural motif can be found in lactams, which are cyclic amides distinguished by unique structural properties. These compounds demonstrate specific biological activities with promising potential in cancer treatment and other applicative fields.[13,14] However, a significant challenge lies in inducing chirality, a crucial step for their application in the pharmaceutical industry.

2.1 Lactams

Lactams represent a class of cyclic amides, which hold considerable significance due to their diverse applications in medicinal chemistry, starting from the groundbreaking discovery of the antibiotic penicilin by FLEMMING, a four-membered lactam structure.[15] The β-lactam antibiotic revolutionized medicine by combating bacterial infections and significantly impacting the public health.[16,17] Their diverse pharmacological properties including anticancer activities make these β-lactam scaffolds a symbolic landmark in modern chemotherapy.[13] BALDWIN and coworkers and other researchers emphasized the significance of the amide bond for antibacterial activity, extending beyond the four-membered ring to encompass five-membered lactam systems.[18] Especially, chiral γ-lactams hold a place of considerable importance in the realm of pharmaceuticals, largely due to their structural complexity and functional versatility. These cyclic γ-lactams have diverse therapeutic applications, spanning from treating depression (Rolipram **1**), cognitive disorders (Oxiracetam **2**) and cancer (Pseurotin A **3**) (Figure 1).[19–21]



Rolipram (**1**)
(antidepressant)

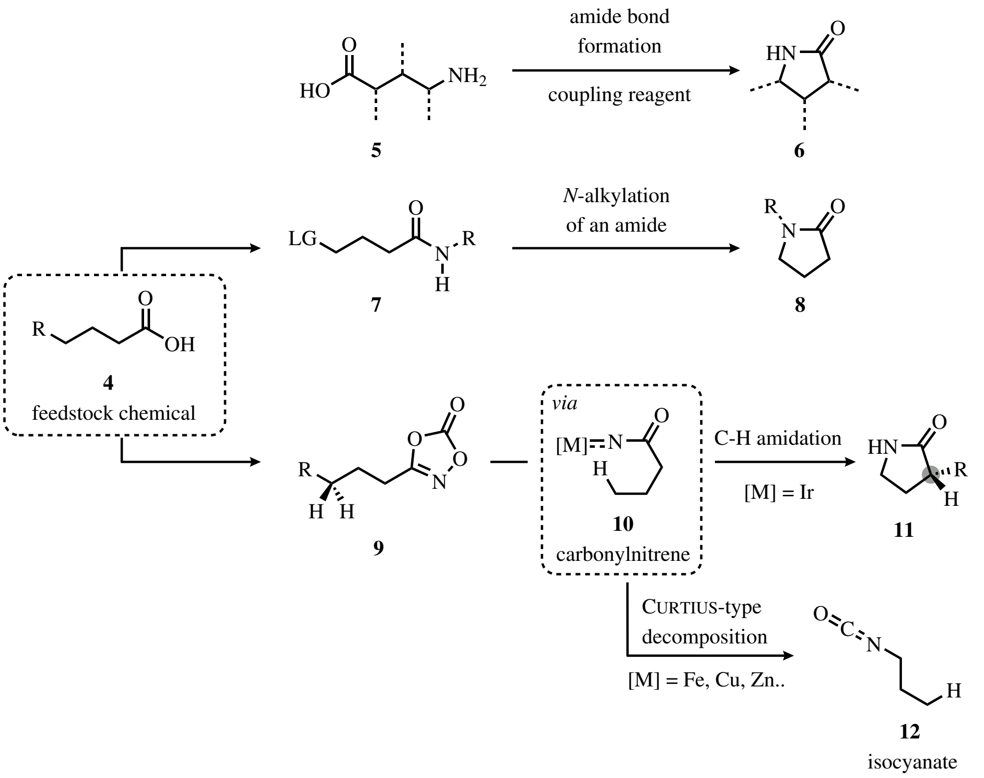
Oxiracetam (**2**)
(antidementia)

Pseurotin A (**3**)
(antitumoral)

Figure 1: Overview of selected drug candidates derived from γ-lactams.

The stereochemistry of chiral γ-lactams can dramatically influence their interaction with biological targets, such as enzymes and receptors. This interaction is key to the efficiency and safety profile of many medications, as the spatial arrangement of atoms in chiral molecules can result in markedly different biological responses.[9] Therefore, the ability to control and manipulate the chirality of γ-lactams is a vital aspect of drug design and synthesis.[22] In addition, the γ-lactam core structure can be easily reduced to pyrrolidines, which hold particular interest, noted as the number five most prevalent nitrogen heterocycle in pharmaceuticals by the U.S. FDA.[23]

The simplest way to prepare amides starts from achiral feedstock chemicals **4**, which are considered both easily accessible and cost-effective. Classically γ-lactams **6** can be obtained intramolecularly *via* amide bond formation.[24] Hereby, amino acid derivatives **5** are condensed in the presence of a coupling reagent, such as *N*,*N*'-dicyclohexyl carbodiimide (DCC) and acetic anhydride. Additionally, the *N*-alkylation and acylation of *N*-protected amides **7** offer alternative pathways to access *N*-substituted γ-lactams **8**.[25,26] Remarkable progress has been made in the synthesis of optical active γ-lactams **11** using dioxazolone precursors **9** through enantioselective metal-catalyzed intramolecular Csp^3 – H amidation reactions (Scheme 1).[27–29]

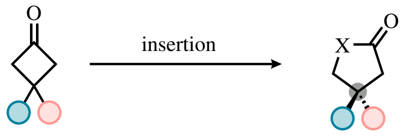


Scheme 1: Selected strategies for the synthesis of γ-lactams. LG = leaving group.

However, one of the major drawbacks using this system is that these methodologies generally necessitated prefunctionalization of substrates and moreover encountered undesirable side reactions. Especially, C–H amidation reactions with the proposed carbonylnitrene intermediates **10** are known for their instability, leading to decomposition and forming isocyanates **12** *via* CURTIUS-type rearrangement. This phenomenon is particularly evident in acyl azides, which are frequently explored as synthetic precursors under transition metal catalysis conditions.[30,31]

2.1.1 Ring-Expansion by SCHMIDT and BECKMANN

In recent research, prochiral cyclobutanones have a profound influence on synthetic strategies. A particularly strategy tailored the field of desymmetrization.[32] The prominent inherent ring strain in cyclobutanones can be alleviated through ring-expansion reactions, a process that is energetically favorable. This elegant strategy enables the ability for insertion processes, which tailored prochiral cyclobutanones for generating five-membered heterocycles **14**, such as γ-lactams and γ-lactones (Scheme 2).[33,34]

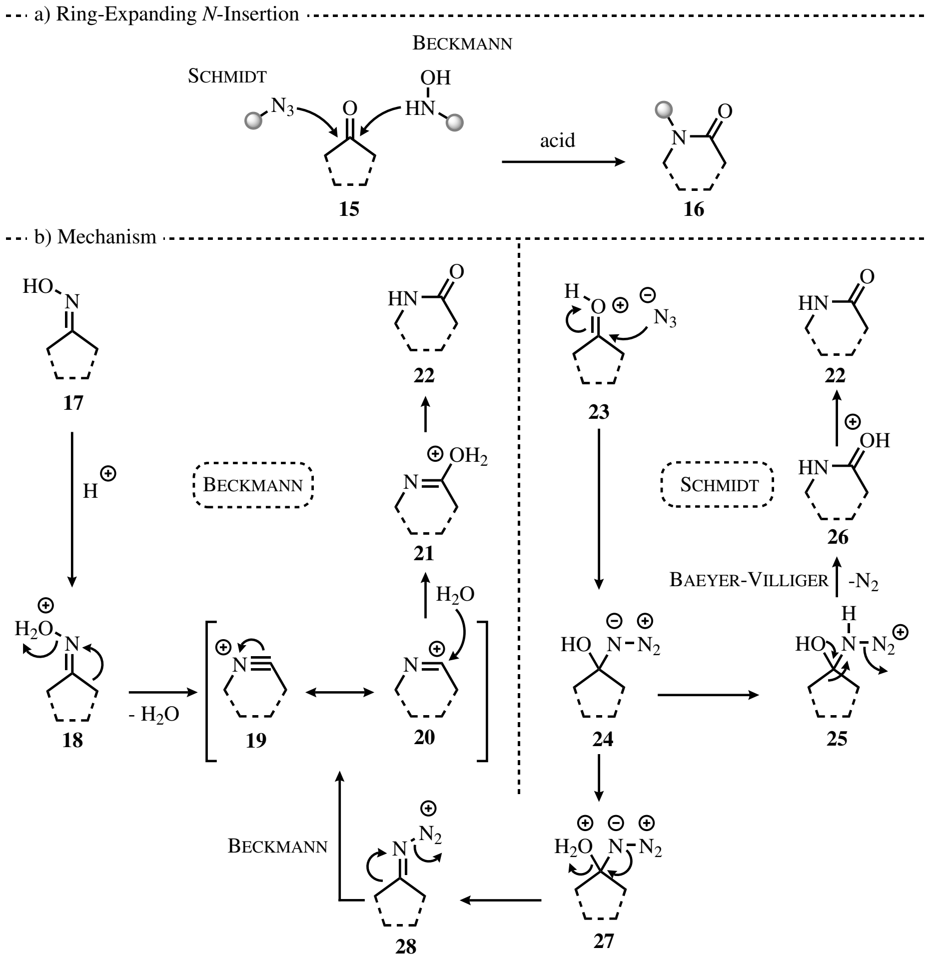


13 **14**

Scheme 2: Synthetic strategy for the desymmetrization of cyclobutanones **13**, X = N or O.

This direct transformation of prochiral cyclobutanones has emerged as a powerful access into a diverse array of enantioenriched compounds, covering several biologically relevant frameworks.

In the realm of ring-expansion of cyclobutanones, a surprising number of literature is present in the BAEYER – VILLIGER oxidation to afford γ-lactones.[35,36] However, the nitrogen insertion based on the strategy of the ring-expansion of cyclobutanones is described either through a SCHMIDT[37] or BECKMANN[38] rearrangement (Scheme 3a).

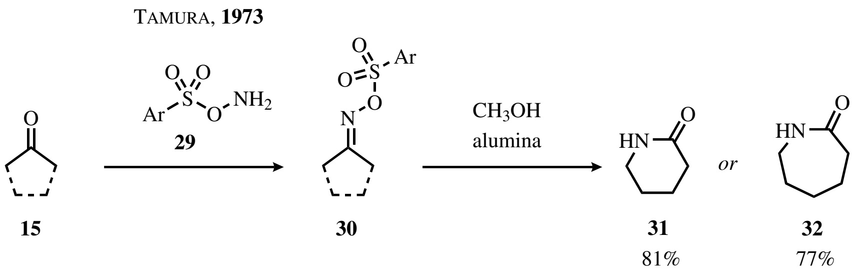


Scheme 3: a) SCHMIDT and BECKMANN reaction in ring-expanding *N*-insertion. b) Mechanism of the SCHMIDT and BECKMANN reaction.

On the one hand, the BECKMANN reaction is an acid-catalyzed rearrangement of an oxime **17** to the cyclic amide **22**. The mechanism is based on 1,2-alkyl migration (**18**), followed by eliminating of water, forming a nitrilium ion **19**, which **20** represents its mesomeric form. The nitrilium ion undergoes hydrolysis to yield **21**, which then forms the respective lactam **22** after deprotonation and tautomerization process.[39] On the other hand, the intramolecular SCHMIDT reaction involves the reaction of hydrazoic acid. After activating the carbonyl ketone **23** and nucleophilic attack of the azide the azidoalkanol **24** can further rearrange through a BAEYER – VILLIGER pathway (**25**). The migration of **25** leads to protonated amide **26**, which then after deprotonation furnishes the desired lactam **22**. In an alternative route, azidohydrin **24** can be protonated under H_2SO_4 to give intermediate **27**. The loss of water delivers the substrate **28**, which undergoes a BECKMANN rearrangement to obtain the nitrilium ion **19** (Scheme 3b).[40]

However, both strategies face major disadvantages. Among the reaction of azides, which are intrinsically hazardous and explosive,[41] the nitrogen insertion strategy demands harsh conditions including strong acids and high reaction temperature, limiting its broader applications. Specifically, the BECKMANN rearrangement in industrial scale suffer from byproducts such as ammonium sulfate.[42]

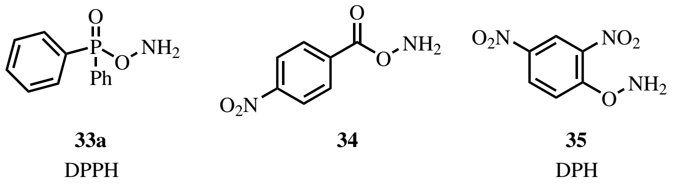
In further development, TAMURA and coworkers synthesized *O*-mesitylene sulfonylhydroxylamine (MSH, **29**) as electrophilic aminating reagent.[43] In the presence of cyclic ketones **15** and MSH (**29**), the corresponding oximes **30** were achieved, which serves as useful precursor for the BECKMANN rearrangement (Scheme 4).



Scheme 4: BECKMANN rearrangement of oximes **30** to lactams **31** and **32**.[43] Ar = mesityl.

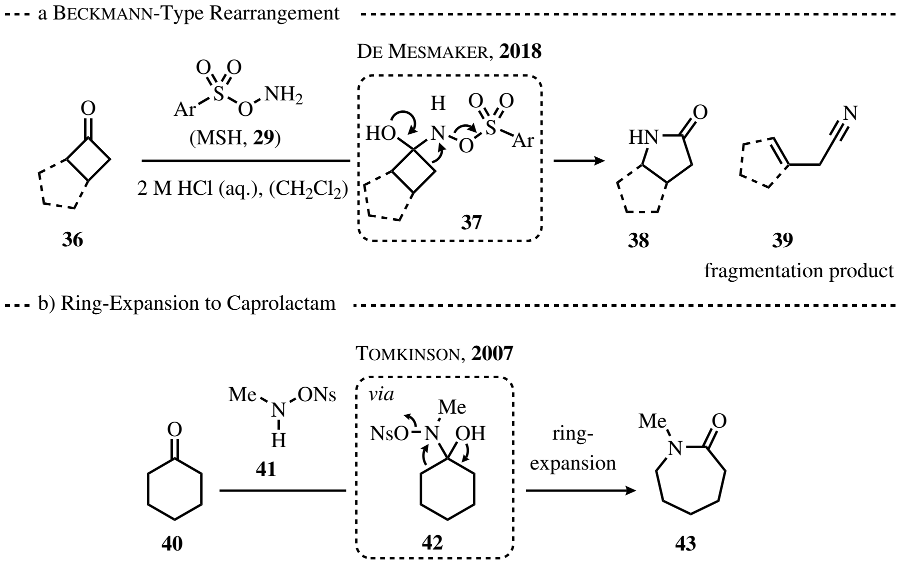
The rearrangement occurred by absorbing the oximes **30** on a column of basic alumina and eluting with methanol. The resulting δ- and ε-lactams were obtained in high yields (**31** and **32**).

In the recent years, electrophilic aminating reagents such as *O*-(diphenylphosphinyl)hydroxylamine (**33a**, DPPH), benzoate **34**, 2,4-dinitrophenylhydroxylamine (**35**, DPH) and MSH **29** have shown remarkable attention in nitrogen transfer reactions on a wide variety of nucleophiles (Scheme 5).[44]



Scheme 5: Overview of *O*-substituted hydroxylamine reagents.

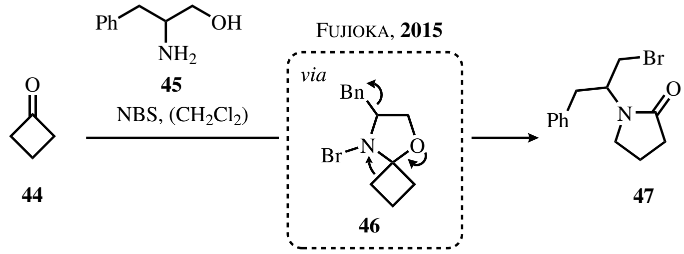
These types of electrophilic aminating reagents are characterized by their α-effect, where the nucleophilicity is significantly enhanced due to the presence of an adjacent electron donating group.[45] In hydroxylamines, this effect arises from the interaction between the lone pair of electrons on the nitrogen atom and the adjacent hydroxyl group. Due to their weak N–O-bond, hydroxylamines are prone to decompose under room temperature.[46] Among them, DPPH (**33a**) is the most stable to provide a powerful amine source for organic transformation reactions.[47] In 2018, De Mesmaker and coworkers further explored MSH (**29**) in strained ring systems. Herein, the group investigated a pathway to access γ-lactams through a Beckmann-type rearrangement under aqueous acidic conditions favorably *via* a tetrahedral intermediate **37** (Scheme 6a).[48]



Scheme 6: a) Beckmann rearrangement using MSH (**29**) *via* a tetrahedral intermediate **37**,[48] Ar = mesityl. b) Beckmann rearrangement using *N*-methyl-*O* hydroxylamine **41**.[49]

By taking the advantage of hydroxylamines, the weak N–O bond in combintation with the ring strain relief provides a thermodynamic driving force for the rearrangement.[50] This strategy allows a facile access to a broad range of γ-lactams **38**. However, one drawback of the achieved strategy is the formation of fragmentation products **39**, which are side products of the Beckmann rearrangement. In addition to prochiral cyclobutanones, Tomkinson and coworkers demonstrated the ring-expansion technique utilizing cyclohexanone (**40**) and the unique properties of hydroxylamines, employing *N*-methyl-*O*-hydroxylamine **41** similar to MSH as nitrogen source (Scheme 6b).[49] This reaction pathway involves an alkanolamine intermediate **42** to obtain the caprolactam framework **43**.

In light of the limitations and harsh conditions in the Schmidt and Beckmann reaction, others established milder procedures to access γ-lactams. *N*-haloamines are a useful nitrogen source for oxidative rearrangements. One example was developed by FUJIOKA and coworkers, who established a one-pot induced oxidative rearrangement of *N*,*O*-ketals to γ-lactams (Scheme 7).[51]

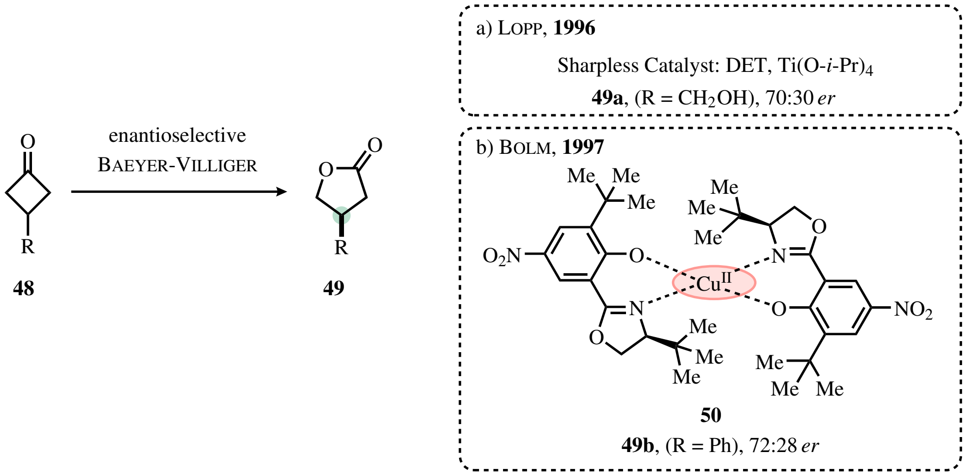


Scheme 7: Synthesis of γ-lactam **47** *via* a *N*,*O*-ketal intermediate **46**.[51]

Starting from unsubstituted cyclobutanone **44** and amino alcohol **45** the reaction undergoes an assisted 1,2-C-to-N migration by *N*-bromosuccinimide (NBS) in the *N*-*O*-ketal intermediate **46**. After oxidative rearrangement and further bromination, the desired γ-lactam **47** can be obtained.

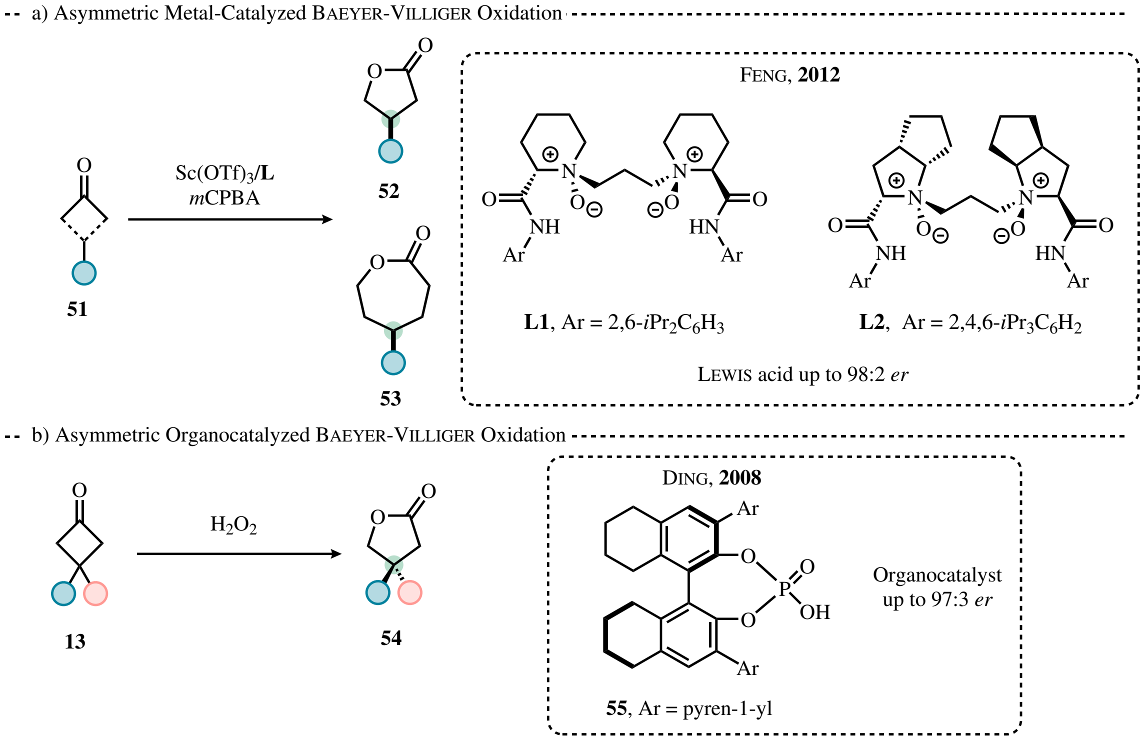
2.1.2 Desymmetrization *via* Ring-Expansion

Apart from the inherent ring strain in cyclobutanones as the driving force to access five-membered ring structures, the ring-expansion technique enables distal stereoinduction *via* a desymmetrization strategy, a concept that has been surprisingly echoed in numerous instances of BAEYER – VILLIGER oxidation.[52,53] Back to the 1990s, pioneering work was made independently by LOPP[36] and BOLM,[35] when both reported synthetic methods to chiral γ-lactones **49** through the desymmetrization of cyclobutanones **48** (Scheme 8).



Scheme 8: Pioneering work by a) LOPP and b) BOLM on the enantioselective BAEYER – VILLIGER oxidation.[35,36]

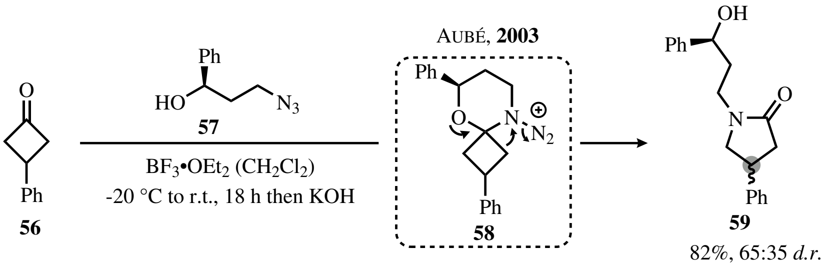
LOPP and coworkers used prochiral cyclobutanones **48** in the presence of the SHARPLESS catalyst, containing (+)-diethyl tartrate (DET) and $Ti(O-i-Pr)_4$, as well as *t*-BuOOH as the oxidant. However, the prochiral cyclobutanone was tested, achieving the chiral γ-lactone **49a** in moderate enantioselectivity and suffered in yield. BOLM and coworkers followed the desymmetrization strategy by employing the chiral copper(II) catalyst **50**. In this case, the enantiomeric induction could not be improved (**49b**). Later, major improvement in the enantioinduction was observed by FENG and coworkers.[54] Herein, the group developed a highly catalytic enantioselective BAEYER – VILLIGER oxidation with chiral scandium(III) complexes derived from their *N,N'* dioxide ligands (Scheme 9a).



Scheme 9: a) Catalytic enantioselective and b) organocatalyzed BAEYER – VILLIGER oxidation of prochiral cyclic ketones.[54,55]

$Sc(OTf)_3$ is characterized by its strong LEWIS acidity, since a high oxophilicity is present due to the electron withdrawing triflate groups. In addition to that, the small radii of the scandium atom is a further contribution to the strong acidity.[56] The combination of the LEWIS acid $Sc(OTf)_3$ and C_2 symmetric *N,N'* dioxide ligands **L1** or **L2** proved to be a highly enantioselective catalyst to deliver γ- **52** and ε-lactones **53** in good yields with up to 98:2 *er*. In addition to that, an outstanding work was further reported by DING and coworkers, who developed an organocatalytic BAEYER – VILLIGER oxidation with the BINOL-derived chiral phosphoric acid (CPA) **55** (Scheme 9b).[55] Under the optimized reaction conditions and aqueous H_2O_2 as the oxidant, prochiral cyclobutanones **13** were oxidized to give chiral γ-lactones **54** in high yield up to 97:3 *er*. Both asymmetric strategies are widely recognized for their effective role in the synthesis of chiral γ-lactones. However, the synthesis of chiral γ-lactams, particularly through enantioselective ring-expansion methods starting from cyclobutanones, remains an unexplored and scarce area of research.

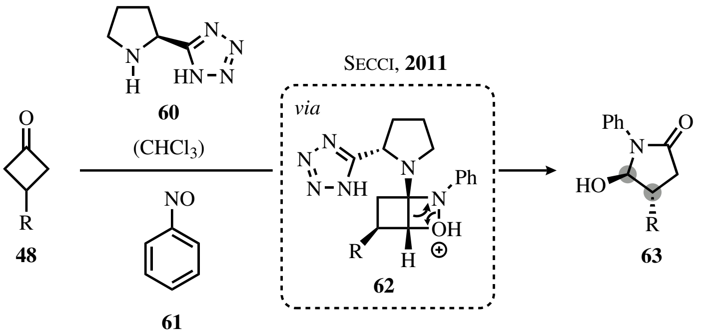
In this field, pioneering work was made by the group of AUBÉ. They introduced an asymmetric SCHMIDT reaction utilizing an *in situ* tethering approach, thus leveraging a strategically positioned linker (Scheme 10a).[57]



Scheme 10: a) SCHMIDT type rearrangement *via* a *N*,*O*-ketal intermediate **58**.[57]

The linker serves to connect two reactive groups seamlessly and can be installed and removed without requiring supplementary steps. The reaction mechanism involves the formation of a spirocycle **58**, followed by a rearrangement and the loss of elementary nitrogen, furnishing the efficient synthesis of γ-lactam **59** with good yield.

Furthermore, the use of small chiral organic molecules as catalysts established a versatile tool in asymmetric organocatalysis. Since 2000, this field has experienced an impressive trend, initiated by MACMILLAN and LIST, who have been awarded the 2021 Nobel prize in chemistry.[58] In the context of desymmetrization, an asymmetric nitrogen insertion was developed by SECCI and coworkers using L-Proline derivative **60** as the organocatalyst and nitrosobenzene (**61**) (Scheme 11).[59]



Scheme 11: Organocatalyzed enantioselective ring-expansion to γ-lactams **63**.[59]

Under the conditions, an enantioselective ring-expansion was developed by desymmetrizing cyclobutanone **56** to obtain γ-lactams **63** with high diastereselectivity. The reaction proceeds *via* an *O*-nitroso aldol-cyclization, which gives after rearrangement of bicyclic intermediate **62** the desired product. However, the proposed method requisites major improvements in yield, enantioselectivity and a broad substrate scope.

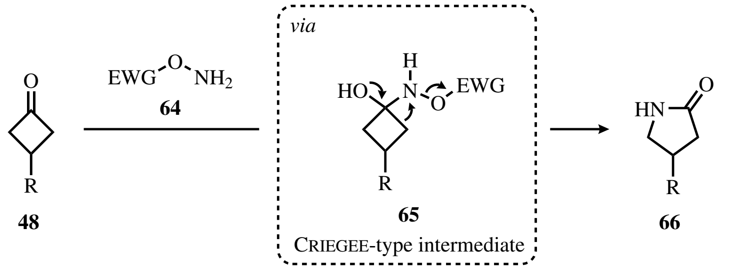
In summary, the inherent ring strain of cyclobutanones and the ability of desymmetrization undermined an elegant strategy in order to provide γ-lactams as privileged pharmacophores in the drug discovery. From the classical amide bond formation *via* SCHMIDT and BECKMANN reactions to organocatalyzed methods, each strategy builds upon ring-size manipulation by nitrogen insertion. The efficient generation of chiral γ-lactams presents a continuing synthetic challenge. The harsh conditions in the SCHMIDT and BECKMANN reactions followed by side reactions within these reactions signal a clear need for continued research into the development of milder methods.

3 Nitrogen Insertion *via* aza-BAEYER – VILLIGER Rearrangement

3.1 Motivation

Given the fundamental role of γ-lactam cores in numerous pharmaceutical compounds, significant efforts have been made to discover alternative strategies and reagents for nitrogen insertion. These efforts are focused on finding approaches that are not only effective, but also mild and user-friendly, enhancing both the safety and efficiency of the synthesis process.

In collaboration with M. ARNOLD and A. W. WALZ, this study concentrates on the synthesis of γ-lactams **66** *via* nitrogen insertion of cyclobutanones **48**. As demonstrated in various studies, cyclobutanones **48** emphasized as reactive precursors due to their inherent ring strain. Therefore, it was important to utilize these cyclic ketones. Moreover, due to the highly reactive and unstable nature of TAMURA's reagent, as well as its explosive character, there was a particular interest in identifying a milder aminating reagent **64** to react with already reactive cyclobutanones **48**.[60] This involved by adjusting the electron-withdrawing group in the hydroxylamine core structure (Scheme 12).

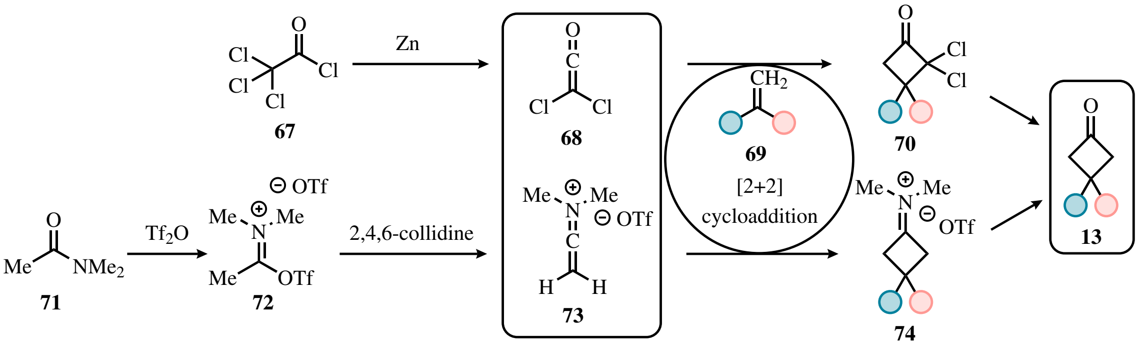


Scheme 12: Proposed aza-BAEYER – VILLIGER reaction to access γ-lactams.

The proposed strategy offers an effective driving force and might go through the tetrahedral intermediate **65** as postulated by CRIEGEE in 1948.[61] The intermediate was further supported by computational studies by DE MESMAKER and coworkers in 2018.[48] In addition, this proposed strategy strives to provide a synthetic route that is in analogue to the BAEYER – VILLIGER reaction.

3.2 Synthesis of Starting Materials

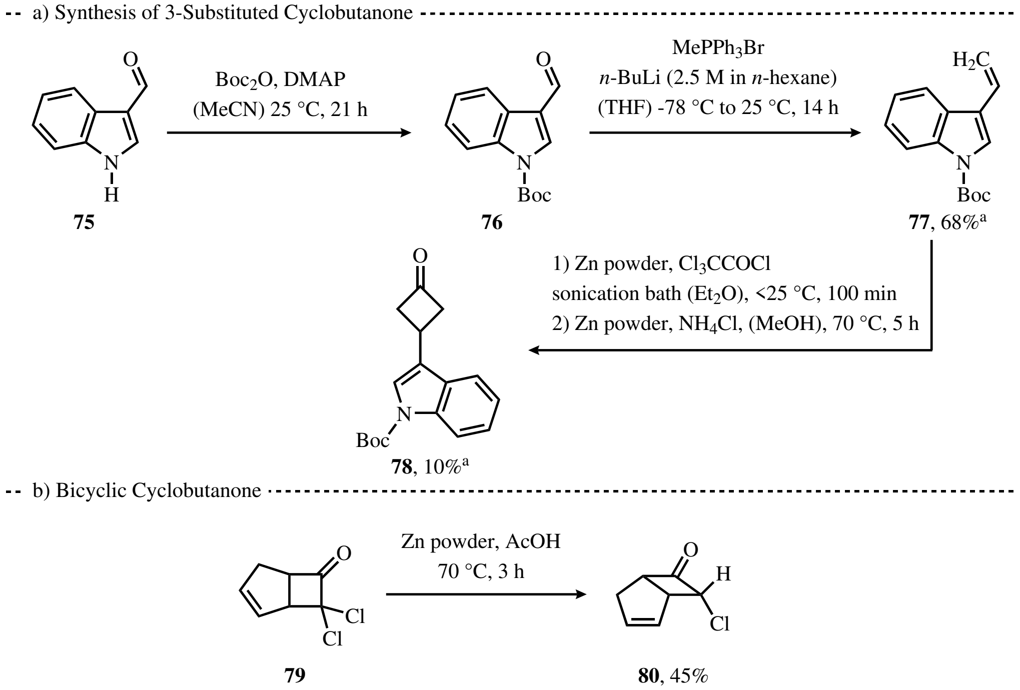
The upcoming section details the synthesis of cyclobutanones, a vital component for this research. A growing body of literature showed two major routes for the access to cyclobutanones (Scheme 13).



Scheme 13: General routes for the synthesis of cyclobutanones **13** *via* dichloroketenes **68** or keteneiminiums **73**.

In the first approach, highly reactive dichloroketenes **68** can be readily synthesized through the dehalogenation of trichloroacetylchloride (**67**) using elementary zinc.[62,63] After [2+2] cycloaddition with alkenes **69**, the resulting dichlorides **70** can be easily eliminated by introducing elementary zinc in acetic acid (AcOH) yielding prochiral cyclobutanones **13**. Beyond dichloroketenes as primary reactive agents, GHOSEZ and coworkers extensively investigated the reaction of tertiary amides with alkenes.[64] Their approach involves harnessing the reactivity of keteneiminium salts **73** intermediate generated *in situ* from dimethylacetamide (DMA, **71**) or other tertiary amides, in the presence of trifluoromethanesulfonic anhydride (Tf_2O) and 2,4,6-collidine. In the presence of alkenes **69**, iminiumsalt **74** can be obtained, which upon hydrolysis yields the corresponding cyclobutanones **13**. Several cyclobutanones that were comprehensively documented in my master's thesis will not be elaborated upon further in this discussion to only focus on the relevant substrates for the current study.[65]

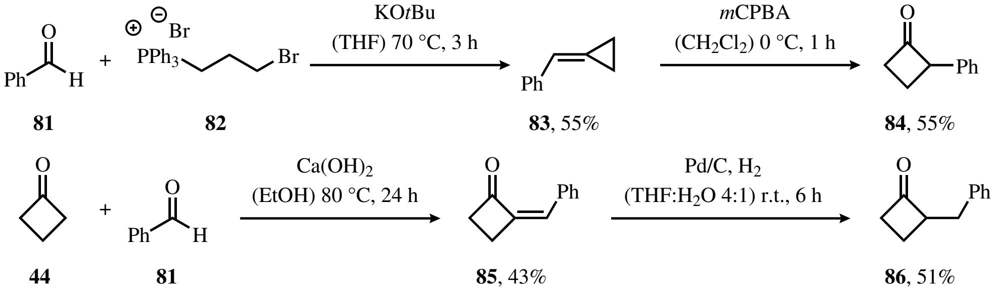
To explore a wide range of functional groups and demonstrate the stability of the nitrogen insertion in the presence of other amine groups, the synthesis of cyclobutanone **78** with a *tert*-butyloxycarbonyl- (Boc)-protected indole scaffold showed significant attention (Scheme 14a).



Scheme 14: a) Synthesis of Boc-protected cyclobutanone **78** *via* [2+2] cycloaddition. b) Dehalogenation of bicyclic cyclobutanone **80**. [a] Overall yield over two steps.

Initially, the indole **75** was protected using di-*tert*-butyl dicarbonate (Boc$_2$O), followed by WITTIG olefination. This process resulted in the formation of the olefin **77** with a moderate yield over two steps. Following the literature procedure outlined by LU and coworkers, the [2+2] cycloaddition was performed using trichloroacetyl chloride, aided by ultrasound irradiation.[66] The crude reaction mixture was then subjected to a mild dehalogenation process, utilizing zinc, ammonium chloride (NH$_4$Cl) and methanol (MeOH) as recommended in the literature.[66] Through these steps, the final product **78** was successfully isolated with an overall yield of 10% over two steps. An exception to Scheme 13 was observed with the bicyclic cyclobutanone **79**. When the established dehalogenation protocol was applied, which involves using zinc powder, AcOH, and heat, the expected dehalogenated product was not observed. Instead, the monochlorinated product **80** was isolated in moderate yield (Scheme 14b).

In addition to the synthesis of 3-substituted cyclobutanones, α-substituted cyclobutanones also garnered special interest in the research (Scheme 15).

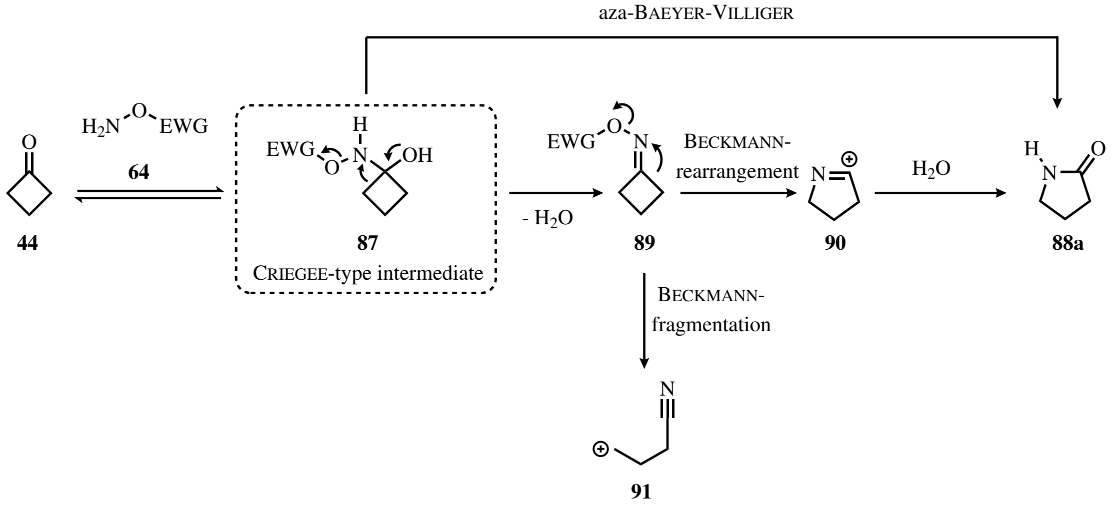


Scheme 15: Synthetic strategies for the synthesis of α-cyclobutanone **84** and **86**.

This was initiated by implementing WITTIG olefination of benzaldehyde **81** with commercially available (3-bromopropyl)-triphenylphosphonium bromide (**82**), leading to the formation of phenylmethylenecyclopropane **83**. Subsequently, oxidation with *m*CPBA induced a MEINWALD rearrangement of the cyclopropane, yielding 2-phenylcyclobutanone (**84**) with moderate success.[67] However, attempts to synthesize 2-benzylcyclobutanone (**86**) *via* a oxidative ring-expansion of methylencyclopropane **83** were not successful. An alternative route was explored through the simple condensation of cyclobutanone (**44**) with benzaldehyde (**81**), resulting in the formation of 2-methylenecyclobutanone (**85**) (Scheme 15). This intermediate was then subjected to hydrogenation using palladium on carbon as the catalyst, successfully producing the desired α-substituted cyclobutanone **86**.[68]

3.3 Mechanistic Outline and Inital Findings

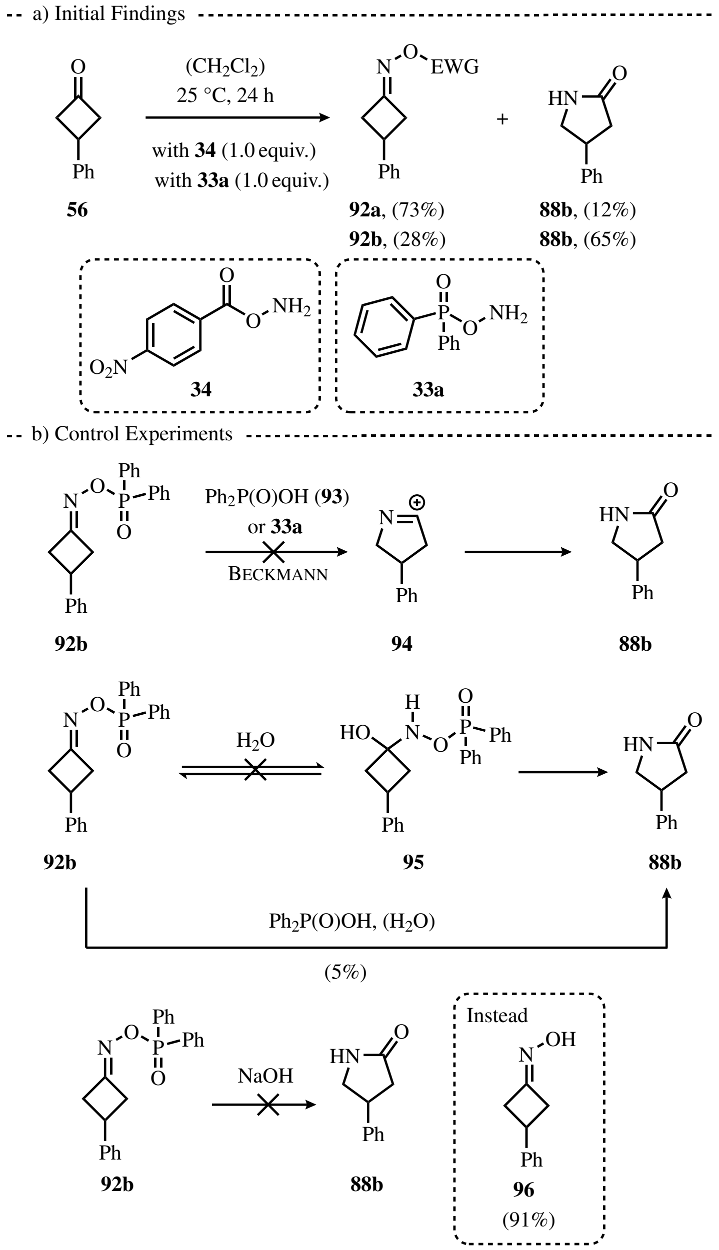
To initiate this study, an appropriate amine source was sought, that exhibited lower reactivity compared to TAMURA's reagent **29**, which was previously utilized in the BECKMANN rearrangement of cyclobutanones.[48] Furthermore, the aminating reagent **29**, was not a viable option due to its limited availability, inherent instability, and potential explosiveness.[60] The ideal amine source **64** should possess an effective leaving group at the nitrogen atom, promoting the rearrangement to yield the γ-lactam structure **88a** (Scheme 16).



Scheme 16: Proposal of the mechanistic outline.

Possible mechanistic pathways include the aza-BAEYER – VILLIGER reaction in the CRIEGEE-type intermediate **87** or the BECKMANN rearrangement from the oxime ester **89**, which can be formed through water expulsion of the CRIEGEE-type intermediate **87**. The BECKMANN rearrangement leads to a nitrilium ion **90**. This is followed by hydrolysis to form the γ-lactam **88a**. As extensively documented, the possibility of BECKMANN fragmentation leading to nitrile formation should be suppressed (**91**).[69]

Based on the attractive properties of hydroxylamines with their weak N–O-bond, the interest was gained in identifying hydroxylamines with good leaving groups. Among them, commercially available amino benzoate **34** and diphenylphosphinate **33a** were devised as potential candidates, which have yet to be explored for nitrogen insertion reactions.[44,47] At the outset, the reactivity of benzoate **34** was evaluated by subjecting the hydroxylamine into a solution of 3-phenylcyclobutanone (**56**) as a less volatile model substrate. The formation of the desired product **88b** was indeed observed along with the undesired oxime ester **92a** as major product. In sharp contrast, diphenylphosphinate **33a** led to moderate production of γ-lactam **88b** (Scheme 17a).



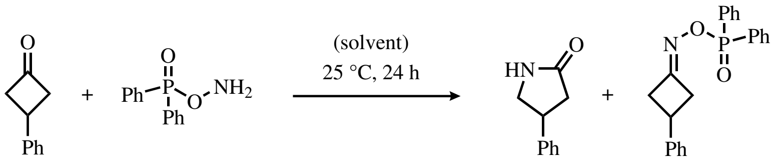
Scheme 17: a) Initial findings and b) Control experiments of the proposed aza-Baeyer – Villiger reaction. Reactions were conducted on a 100 µmol scale of the cyclobutanone **56** and oxime ester **92b**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. NMR yields are in parentheses.

This result can be explained since the diphenylphosphinate **33a** possesses a better leaving group for the rearrangement reaction. After isolation and fully characterization of the undesired oxime ester **92b**, further efforts were made to convert the oxime ester **92b** to γ-lactam **88b** to interrogate the mechanistic pathway. However, the presupposed Beckmann rearrangement was unsuccessful after reapplying the oxime ester **92b** with the same reaction conditions (Scheme 17b). Attempts to induce the lactam formation under harsh conditions using phosphonic acid **93** or DPPH (**33a**) also failed. Additionally, introducing water to potentially revert to the CRIEGEE-type intermediate **95** proved ineffective. Subsequent experiments under aqueous basic conditions were also unsuccessful. Instead, the oxime **96** was achieved in good yield. Further evaluation by using phosphoric acid **93** in water yielded only minimal amounts of the desired product, underscoring the oxime ester's stability. According to the control experiments, the results further support the oxime ester **92b** as a byproduct rather than a key intermediate, thus eliminating the BECKMANN reaction pathway from consideration.

3.4 Optimization

With the proposed mechanism in hand, the reaction between 3-phenylcyclobutanone (**56**) and the aminating reagent **33a** was optimized (Table 1).

Table 1: Optimization studies for the synthesis of γ-lactam using aminating reagent **33a**. The optimization study was evaluated by J. M. WAHL. Reaction was performed on a 100 µmol scale. NMR yields were determined by ^{1}H NMR experiment using mesitylene (500 µmol) as the internal standard.



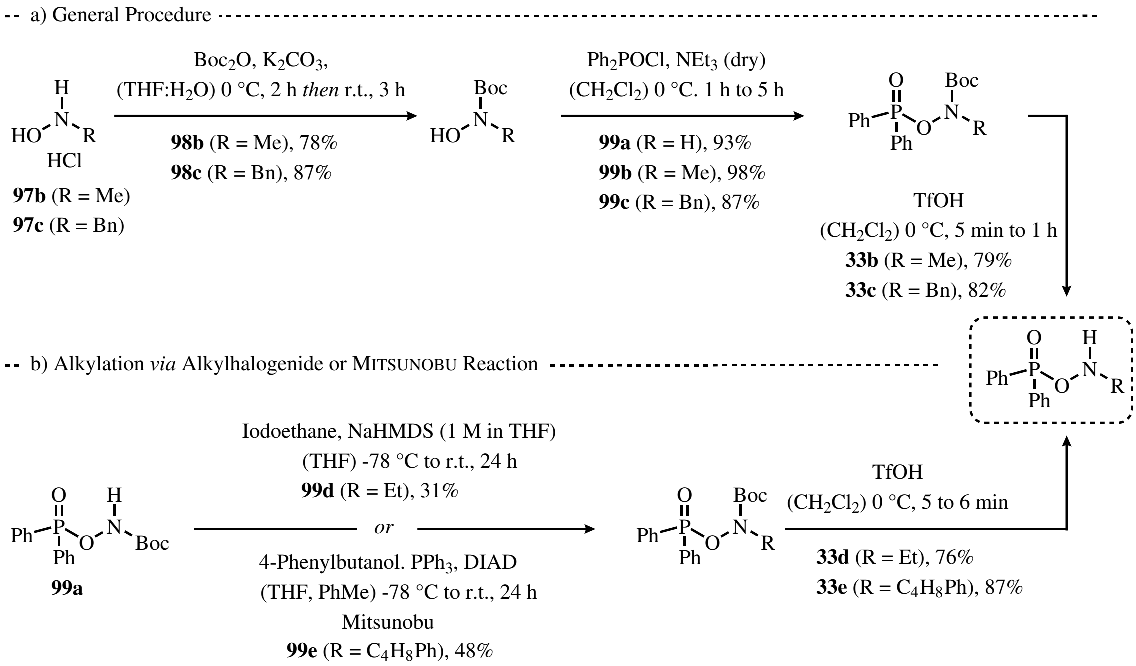
56 **33a** **88b** **92b**

Entry	Solvent	NMR Yield	Lactam:Oxime
1	MeOH	94%	67:33
2	THF	97%	83:17
3	DMF	100%	91:9
4	PhMe	100%	87:13
5	HFIP	89%	79:21
6	MeCN	93%	88:12
7	EtOAc	91%	88:12
8	CH_2Cl_2	93%	80:20
9	H_2O:dioxane 1:1	88%	84:16

The solvent screening, which included a range from polar protic to nonpolar aprotic solvents, consistently resulted in very good to excellent yields. However, it was observed that the ratio of the desired product to the oxime ester byproduct **92b** was only moderate in polar protic solvents such as MeOH and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) (Table 1, entries 1 and 5). In contrast, *N*,*N*-dimethylformamide (DMF) emerged as the superior choice, yielding an optimal product-to-byproduct ratio of 91:9 (Table 1, entry 3). Conclusively, the optimization efforts undertaken in this study have successfully established more efficient and reliable conditions, paving the way for the broader application of this methodology and suppressing the byproduct formation.

3.5 *N*-Alkylated Diphenylphosphinates

To expand the synthesis of a wider array of γ-lactams and to influence the rearrangement rate, special emphasis was placed on the synthesis of *N*-alkylated analogues of DPPH (**33a**) (Scheme 18).

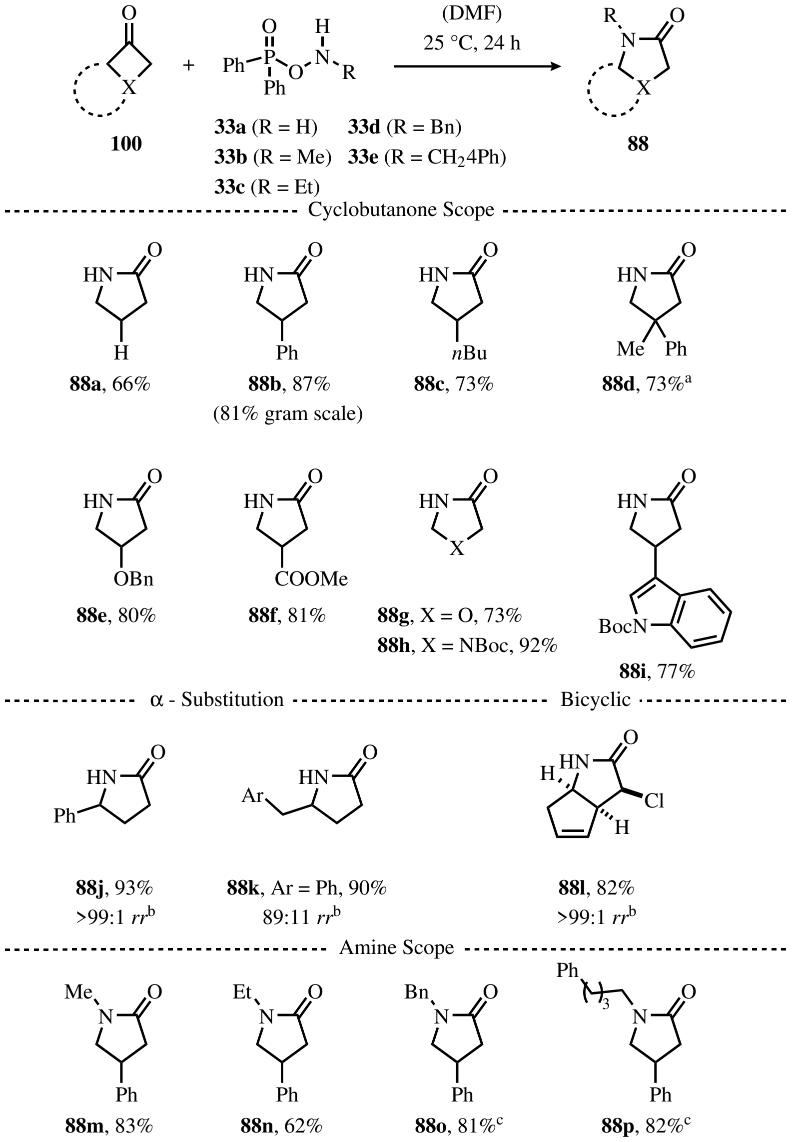


Scheme 18: Overview of the synthetic access of *N*-alkylated diphenylphosphinates **33b–e** using a sequence of phosphinylation, MITSUNOBU alkylation and deprotection.

The synthesis of compounds **33b** and **33c** was followed by a protocol of HUGHES and coworkers which has already established in the literature for the synthesis of DPPH (**33a**).[70] In the initial step, the hydroxylamine salts **97b** and **97c** were Boc-protected with Boc_2O, achieving methylated and benzylated Boc-protected hydroxylamines in good yield (**98b** and **98c**). Subsequently, the phosphonylation was examined, leading to the successful synthesis of **99b** and **99c** with excellent yields. In the last step, the deprotection with trifluoromethanesulfonic acid (TfOH) furnished the desired *N*-alkylated amine source with very good yield (**33b** and **33c**). For the synthesis of other *N*-alkylated diphenylphosphinates, Boc-protected hydroxylamine **99a** underwent an alkylation with iodoethane, employing sodium bis(trimethylsilyl)amide (NaHMDS) as the base. However, this approach resulted in low yield (**99d**). Additionally, the attachment of longer alkyl chains to the amine source was explored, utilizing the privileged conditions of the MITSUNOBU reaction. Employing 4-phenylbutanol under MITSUNOBU conditions, the Boc-protected hydroxylamine (**99e**) was achieved in a moderate yield. The subsequent deprotection process, as mentioned earlier, was carried out smoothly (**33d** and **33e**).

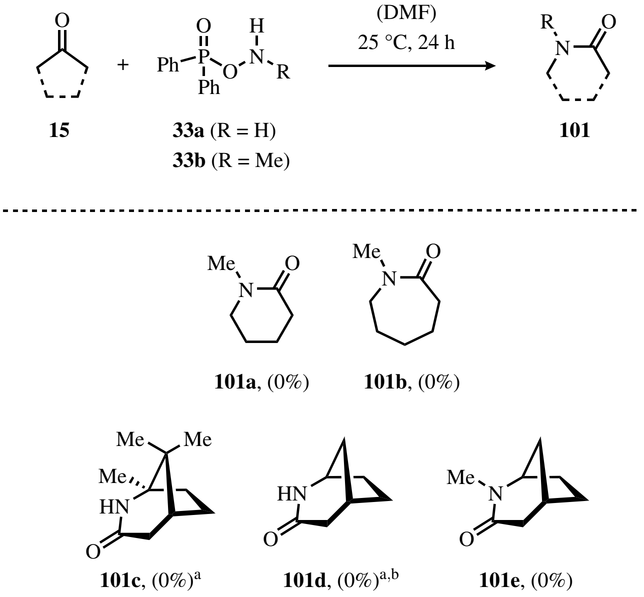
3.6 Scope

In order to expand upon this strategy, the breadth and limitations of this research was explored, providing a detailed overview of the general applicability to various types of cyclic ketones (Scheme 19). The investigation of various cyclobutanone substrates (**100**) revealed a notable tolerance for steric substitutions at the 3-position, ranging from simple, unsubstituted forms to more complex disubstituted variants (**88a–d**). This adaptability extended to gram-scale syntheses of **88b**, demonstrating the method's scalability. Furthermore, the research successfully incorporated a diverse array of functional groups at the 3-position into γ-lactams. The efficient conversion in the presence of benzyl ether and ester groups were observed (**88e** and **88f**). Additionally, oxetanone and Boc-protected azetidinone, along with Boc-protected indoles, proved to be compatible, yielding corresponding γ-lactams with good to excellent yield (**88g–i**). These results underscore the potential of the aza-BAEYER – VILLIGER reaction as a versatile and mild strategy for nitrogen insertion. Going further to α-substituted cyclobutanones, the stereoelectronic effects could be discussed. Remarkably, an exceptional reactivity was observed in phenyl **88j** and benzyl **88k** substituents attached at the α-position, which among them the phenyl-substituent showed the best regioselectivity of >99:1 *rr*. Interestingly, the formation of the oxime ester side products was significantly reduced. Moreover, the research intriguingly demonstrated the effectiveness of the methodology by showing its capability in synthesizing the bicyclic framework **88l** in high regioselectivity. A significant breakthrough in the study was the successful synthesis of *N*-alkylated diphenylphosphinates, which facilitated the production of *N*-substituted γ-lactams in good yield (**88m–p**). This achievement not only demonstrates the robustness of the approach, but also highlights the broad synthetic utility of this methodology in creating structurally diverse lactam compounds.



Scheme 19: Substrate scope of the aza-BAEYER – VILLIGER. Reaction was performed on a 500 µmol scale of cyclobutanones **100**. [a] Starting material was synthesized by TENBERGE. [b] Regioselectivity was determined by NMR from the crude reaction mixture using CH_2Br_2 (500 µmol) as the internal standard. [c] Reaction was performed in CH_2Cl_2.

Apart from five-membered heterocycles, six- and seven-membered rings are interesting motifs in the pharmaceutical industry.[23] The access to those ring systems were tested under the optimized conditions and with DPPH (**33a**) as well as *N*-methylated diphenylphosphinate **33b** (Scheme 20).



15 **33a** (R = H) **33b** (R = Me) **101**

101a, (0%) **101b**, (0%)

101c, (0%)[a] **101d**, (0%)[a,b] **101e**, (0%)

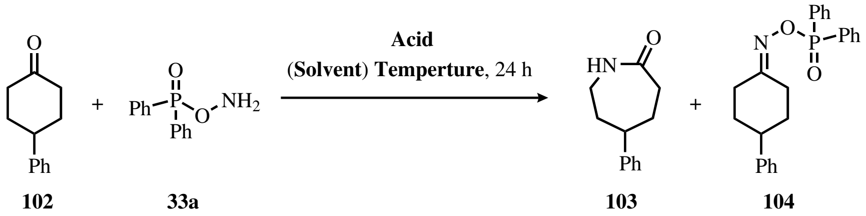
Scheme 20: Substrate scope of the aza-BAEYER – VILLIGER on five- and six-membered rings. Reaction was performed on a 200 µmol scale of cyclic ketones **15**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (200 µmol) as the internal standard. NMR yields are in parentheses. [a] Reaction was performed on a 500 µmol scale. [b] Reaction was performed in EtOAc.

Especially, the *N*-methylated hydroxylamine proved as a powerful aminating reagent, since high capability for nitrogen insertion was observed in the substrate scope (**88m**). However, the ring-expansion on five- and six-membered ketones did not provide the corresponding lactams (**101a** and **101b**). One possible explanation can be found due to the reduced ring strain. Also, the same explanation can be used for the unsuccessful nitrogen insertion on (−)-camphor and norcamphor with neither DPPH (**33a**) nor *N*-Me-DPPH **33b** (**101c–e**). The investigation demonstrated the substantial impact of the inherent ring strain on the reaction outcome. Furthermore, the insufficient reactivitiy of the utilized electrophilic aminating reagent may have contributed to the unsuccessful nitrogen insertion reaction.

3.7 Ring-Expansion on Cyclohexanone

Based on the previous results on the nitrogen insertion on six-membered cyclic ketones, it was interesting to further investigate cyclohexanones and to overcome the limitations of nitrogen insertions at cyclobutanones. Compared to cyclobutanones, the six-membered rings are less strained. To better compare the well-established model substrate, 4-phenylcyclohexanone (**102**) was treated with DPPH (**33a**) under different conditions (Table 2).

Table 2: Investigation on the ring-expansion of **102** to caprolactam **103**. Reaction was performed on a 100 µmol scale of cyclohexanone **102**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. ^{a} Reaction time 20 hours.



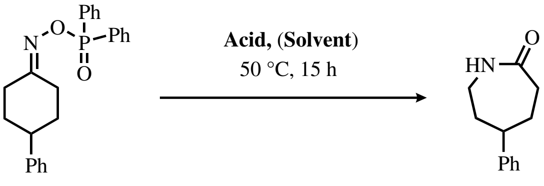
Entry	Acid	Solvent	Temperature/°C	NMR Yield of 103 and 104
1	-	CH_2Cl_2	30	0%, 91%
2	-	HFIP	30	22%, 67%
3	-	HFIP	50^a	54%, 0%
4	-	HFIP	100	65%, 0%
5	TfOH (1.10 equiv.)	CH_2Cl_2	30	62%, 5%
6	TfOH (1.10 equiv.)	THF:H_2O	30	0%, 35%
7	TfOH (1.10 equiv.)	AcOH	30	25%, 35%
8	TfOH (1.10 equiv.)	AcOH	100	62%, 35%
9	-	AcOH	100	85%, 0%

Initially, the model reaction was occurred in CH_2Cl_2. As expected from the ring-expansion to **101b** the caprolactam was not observed due to the less strained cyclohexanone (Table 2, entry 1). Therefore, the reactivity of the reaction has to be increased by adding an acid. Since HFIP contains exclusive properties such as increased acidity and hydrogen bond donation as well as the seamless reaction in subsection 3.4, it was interesting to start the investigation in HFIP.[71] Indeed, the desired caprolactam **103** was detected. However, the undesired oxime ester **104** occurred as the side product (Table 2, entry 2). By increasing the temperature, the side product could be diminished, therefore providing only the desired lactam **103** in moderate yield (Table 2, entries 3 and 4). By adding TfOH and changing the solvent to CH_2Cl_2, the same reactivity was observed (Table 2, entry 5). However, in the presence of water the desired product was not achieved (Table 2, entry 6). Furthermore, AcOH as the solvent was successfully applicable in the rearrangement (Table 2, entry 7). Moreover, high temperature gave rise to moderate yield, but a small amount of the oxime ester **104** was also present (Table 2, entry 8). Without the addition of TfOH, the reaction converted the cyclohexanone

102 to the desired product **103** in good yield, while leaving the amount of the side product untouched (Table 2, entry 9).

Compared to the solvent screening on 3-phenylcyclobutanone (**56**), all tested solvents were tolerated (subsection 3.4). The results for 4-phenylcyclohexanone (**102**) indicated that the solvent choice is crucial for the rearrangment. Since the oxime ester **104** was detected in HFIP as the major product, the reaction was questioned whether the reaction proceeded *via* the aza-BAEYER – VILLIGER reaction or the BECKMANN rearrangement. Herein, the oxime ester **104** was isolated and retreated with HFIP (Table 3).

Table 3: Investigation on the oxime ester **104**. Reaction was performed on a 100 µmol scale of oxime ester **104**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard.



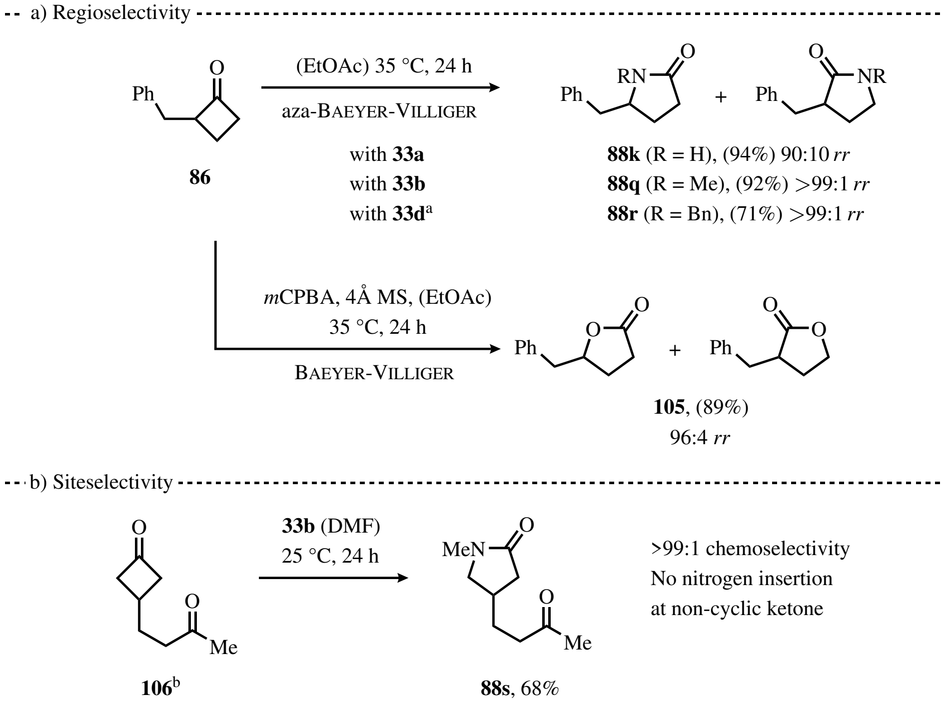
104 **103**

Entry	Solvent	Addition	NMR Yield
1	HFIP	-	39%
2	HFIP	H_2O (1.00 equiv)	42%
4	HFIP	$Ph_2P(O)OH$ (**93**) (1.10 equiv)	88%
3	HFIP	DPPH (**33a**) (1.10 equiv)	72%
5	CH_2Cl_2	-	0%
6	CH_2Cl_2	$Ph_2P(O)OH$ (**93**) (1.10 equiv)	0%

Interestingly, the desired caprolactam was observed in 39% yield, indicating a BECKMANN reaction pathway rather than the aza-BAEYER – VILLIGER reaction (Table 3, entry 1). Even after studying the reaction with additional water added to the reaction mixture, it was unable to find a higher yield. It implies that water is not involved in the process (Table 3, entry 2). The BECKMANN rearrangement could further verified by the addition of diphenylphosphinic acid (**93**) or DPPH (**33a**), resulting in an increased yield (Table 3, entries 3 and 4). However, by switching the solvent to CH_2Cl_2, the lactam was not detected, even in the presence of an acid (Table 3, entries 5 and 6). These results further support the BECKMANN reaction, proving that an acid is essential for the rearrangement.

3.8 Stereochemical Analysis

To analyze the stereochemistry of the rearrangement, α-substituted cyclobutanone **86** was selected, using EtOAc as the solvent (Scheme 21a).

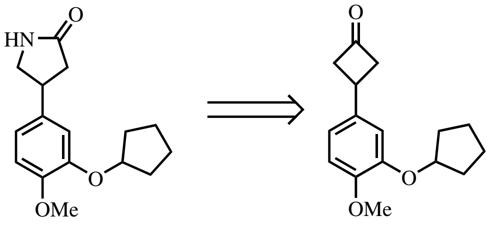


Scheme 21: Examination of a) the regioselectivity and b) siteselectivity. NMR yields and regioselectivity was determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. NMR yields are in parentheses. ^{a} Reaction run in CH_2Cl_2 instead of EtOAc. ^{b} Starting material was isolated by J. SIETMANN.

When utilizing DPPH (**33a**), a regioselectivity was exhibited of 90:10 *rr* (**88k**). Notably, it was surprising to see that the use of *N*-substituted aminating reagents **33b** and **33d** enhanced the regioselectivity to >99:1 *rr* (**88q** and **88r**). One possible reason for the increased regioselectivity is the increased steric hindrance on the nitrogen atom of the hydroxylamine. As can be seen from the reaction with *m*CPBA, the rearrangement follows the same trends as the parent BAEYER – VILLIGER oxidation. The corresponding γ-lactone **105** was synthesized with excellent yield and a regioselectivity of 96:4 *rr*. Additionally, when the diketone **106** was reacted with **33b**, γ-lactam **88s** was successfully produced in good yield, leaving the acyclic ketone component unaffected (Scheme 21b).

3.9 Application for the Synthesis of Rolipram

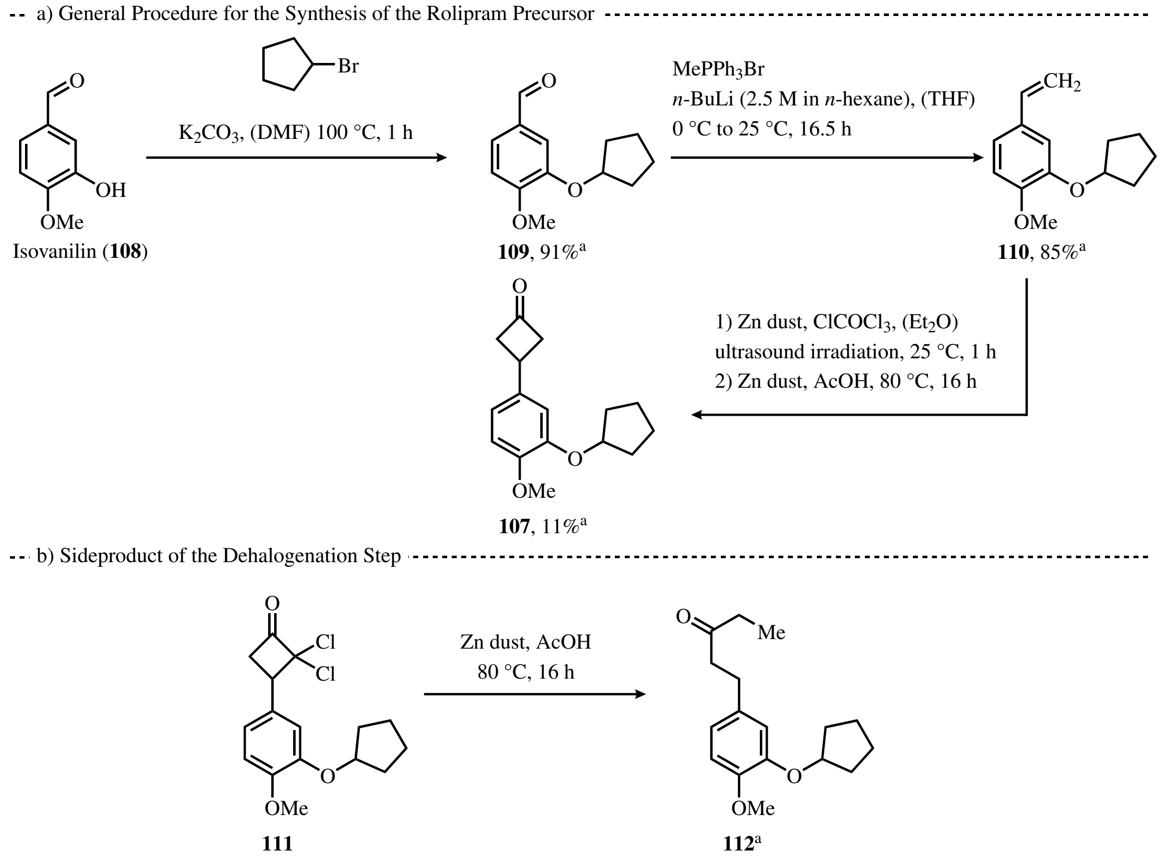
Initially developed as an antidepressant, Rolipram (**1**) has become an important molecule in various drug research and development projects.[19] Rolipram is known as a well-recognized selective inhibitor of the enzyme phosphodiesterase-4 (PDE4).[72] In a collaborative effort with A. W. WALZ to underscore the efficacy of the aza-BAEYER – VILLIGER reaction, the attention was directed towards the synthesis of Rolipram (**1**). To made use of the methodolgy, the drug molecule **1** can be synthesized from the corresponding cyclobutanone **107** (Scheme 22).



1 **107**

Scheme 22: Retrosynthetic plan for the synthesis of Rolipram **1**.

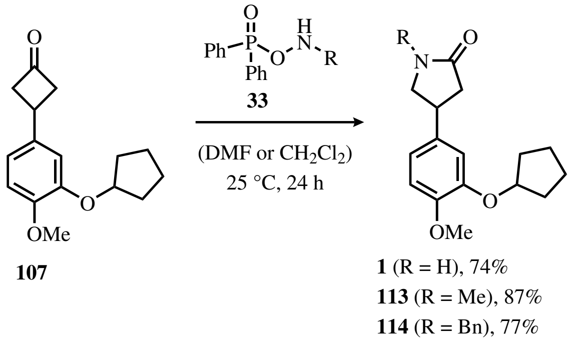
TOMINAGA and coworkers firstly reported its synthesis through a three-step reaction sequence(Scheme 23a).[73]



Scheme 23: a) General procedure for the synthesis of **107** adapted by TOMINAGA and coworkers,[73] b) Sideproduct of the dehalogenation step. [a] Reaction was performed by A. W. WALZ.

Starting with commercially available isovanillin (**108**), the alkylation was first performed with cyclopentyl bromide, followed by WITTIG olefination (**110**). The resulting alkene **110** then underwent a [2+2] cycloaddition protocol, utilizing ultrasound irradiation along with elementary zinc and AcOH for the dehalogenation step. This process, however, yielded the target cyclobutanone **107** in a low yield. Interestingly, the ketone **112** was also produced as a byproduct due to the ring-opening and reduction of dichlorocyclobutanone **111** (Scheme 23b). Based on this observation the low yield can be partly attributed to the challenge in separating the product from the byproduct **112**, as they share similar polarity, making the separation difficult.

With the synthesized cyclobutanone **107**, Rolipram (**1**) was successfully obtained in 74% yield (Scheme 24).

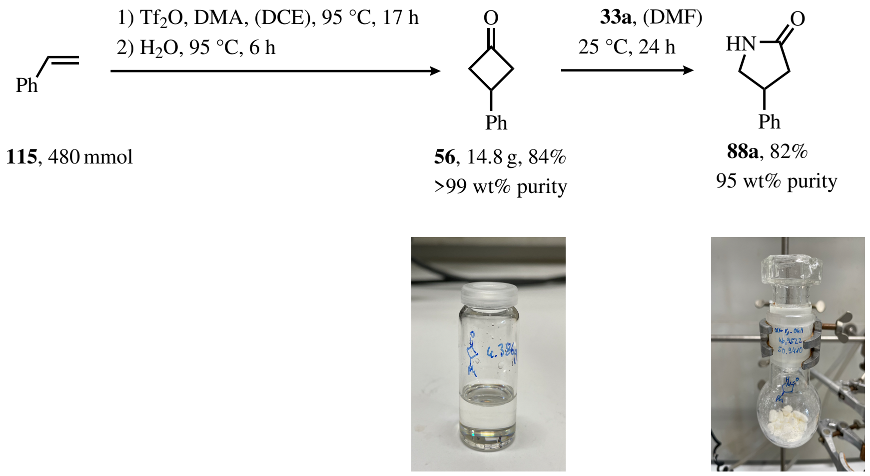


Scheme 24: Synthesis of Rolipram (**1**) and its *N*-alkylated analogs (**113** and **114**).

Highlighting the versatility of late-stage functionalization, the cyclobutanone **107** was further modified with the *N*-substituted hydroxylamines, leading to the synthesis of *N*-Me-Rolipram **113** and *N*-Bn-Rolipram **114**, both of which were also achieved in good yields.

3.10 Scalability of the Method

As demonstrated in this chapter, the ring expansion of cyclobutanones to γ-lactams is a synthetic methodology with immense practicability. In a joint effort with M. ARNOLD, the hypothesis was tested. Firstly, the starting material 3-phenylcyclobutanone (**56**) was synthesized on a 480 mmol scale. Under the reaction conditions, which have been well established, the desired product **56** could be obtained in good yield and excellent purity.[74] This success was achieved through a [2+2] cycloaddition with styrene (**115**) *via* the keteneiminium method. The desired γ-lactam **88a** was synthesized on a 30 mmol scale (Scheme 25).



115, 480 mmol

56, 14.8 g, 84%
>99 wt% purity

88a, 82%
95 wt% purity

Scheme 25: Large-scale synthesis of 3-phenylcyclobutanone (**56**) and the corresponding γ-lactam **88a**. Purity was determined by ^{1}H qNMR experiment using 1,3,5-trimethoxybenzene (100 µmol) as the internal standard. Pictures of the isolated products are shown, left: Amount of the cyclobutanone used for the rearrangement reaction, right: isolated γ-lactam **88a**.

This process involved the use of the synthesized cyclobutanone **56**, commercially available DPPH, and DMF. After 24 hours the reaction was stopped and the solvent was removed. The crude reaction mixture was purified by silica flash column chromatography and led to the isolation of the desired product **88a**, yielding 3.99 grams in 95 wt% purity. In a second attempt, M. ARNOLD repeated the reaction under the same conditions, achieving 3.84 grams and >97 wt% purity. It is worth mentioning, that in both performed reactions the separation from DPPH on this scale by silica flash column chromatography was difficult, since the product and DPPH are similar in R_f values. As a consequence, this might affected the purity of the final compound (Figure 2).

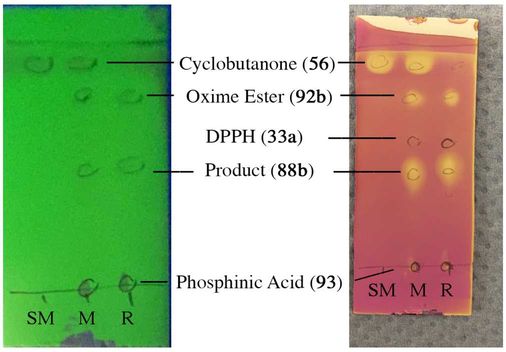
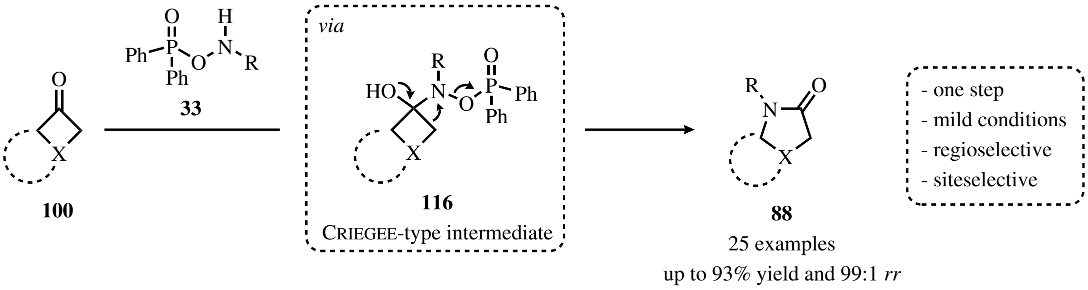


Figure 2: TLC analysis of the starting material (SM), mixture (M) of crude reaction and starting material **56** and crude reaction mixture (R). Solvent mixture EtOAc:MeOH 95:5. Left: Visualized with 275 nm UV lamp. Right: Stained with $KMnO_4$-solution. Pictures were taken by M. ARNOLD.

3.11 Summary and Outlook

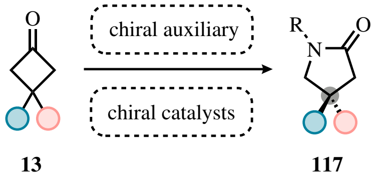
In conclusion, an efficient and straightforward one step aza-BAEYER – VILLIGER approach has been developed utilizing readily available amino diphenylphosphinates. This method facilitates the synthesis of γ-lactams and is compatible with a variety of functional groups. Additionally, this approach is well-suited for the gram-scale production of γ-lactam, highlighting its versatility and applicability (Scheme 26).



Scheme 26: Summary of the main results.

Notably, the use of different *N*-substituted diphenylphosphinates has proven to be an effective means of producing a wide range of *N*-substituted γ-lactams. This versatility is particularly beneficial for implementing late-stage skeletal modifications on the precursor to easily obtain the drug molecule Rolipram. Moreover, a highly regioselective (up to >99:1 *rr*) and siteselective (>99%) insertion process was observed, which corroborate the observations from the BAEYER – VILLIGER reaction. The introduction of this methodology was also successfully applied on larger ring sizes, demonstrating a broad application in synthetic and medicinal chemistry.

Building on the advancements outlined in the mild aza-BAEYER – VILLIGER strategy and considering the importance of chirality in pharmaceuticals, the outlook for this research area should be focused on the exploration of enantioselective methodologies (Scheme 27).[75]



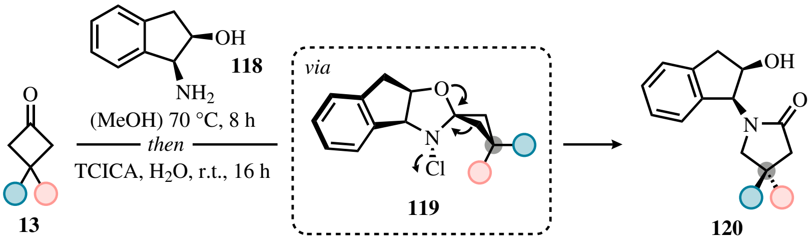
Scheme 27: Future perspective on a enantioselective strategy.

Herein, the tetrahedral intermediate could be used to preserve the prochirality, as shown in this chapter as important key intermediate. Developing strategies that not only maintain the mildness and efficiency of the current process, but also to induce the enantioselectivity could significantly impact the synthesis of chiral drug molecules. The involvement of chiral reagents was considered and will be discussed in section 4 and section 5.

4 Desymmetrization of Prochiral Cyclobutanones *via* Nitrogen Insertion

4.1 Motivation

Building upon the findings of the previous section 3 and the work made by FUJIOKA and coworkers,[51] this chapter should unlock new possibilities in the synthesis of chiral γ-lactams. In a collaborative work with J. SIETMANN, the advantage of the tetrahedral intermediate was capitalized by employing prochiral cyclobutanones **13** and the chiral aminoindanol **118** as chiral amino alcohol. Herein, stoichiometric amount of the chiral *N*,*O*-ketal intermediate **119** should be achieved, which then rearrange to chiral γ-lactams **120** (Scheme 28).



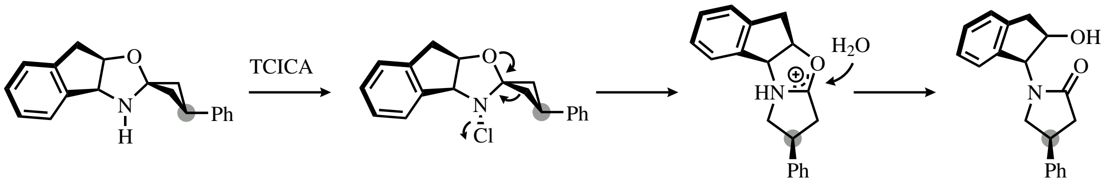
Scheme 28: Overview of the desymmetrization of prochiral cyclobutanones **13** to chiral γ-lactams **120**.

A substantial portion of this work was conducted and published as part of my master's thesis.[65] Therefore, this chapter will mainly focus on the part of research I conducted in the initial phase of my PhD studies. The achievements made by J. SIETMANN were published in his thesis.[76] This work builds upon and expands the foundational research conducted during my master's thesis.

4.2 Recap of this Work

This subchapter summarizes the work, which has been accomplished by J. SIETMANN and myself during my master's thesis.[65,76]

To better understand the desymmetrization strategy, it is crucial to understand the underlying reaction mechanisms that govern the transformation of cyclobutanones (Scheme 29).

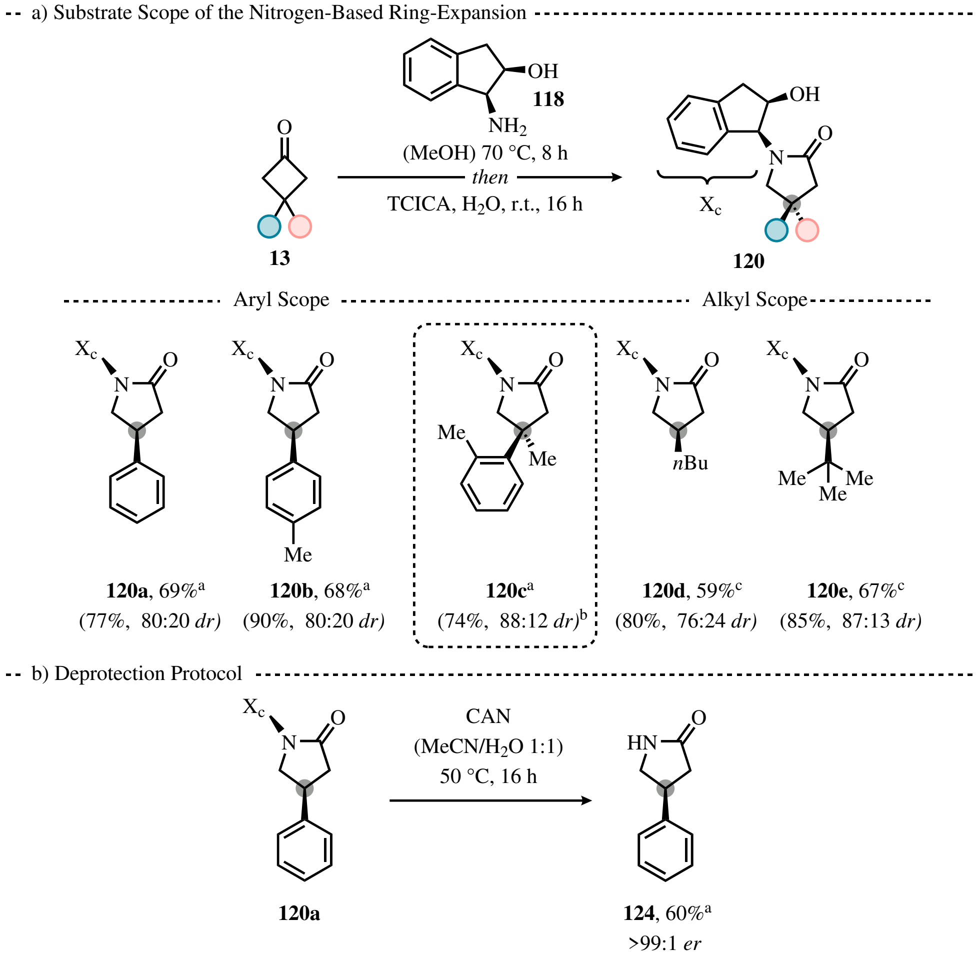


121 75:25 *dr* **122** 49:51 *dr* **123** 80:20 *dr* **120a**

Scheme 29: Mechanism of the nitrogen-based ring-expansion with 3-phenylcyclobutanone (**56**). Major diastereomer is shown.

In the presence of cyclobutanone **56** and chiral amino alcohol **118**, the tetrahedral *N*,*O*-ketal **121** is initially formed, which is then oxidized with trichloroisocyanuric acid (TCICA). Following the oxidation step, the chloramine **122** then undergoes a 1,2-migration to yield oxocarbenium ion **123**. This pivotal step is succeeded by a hydrolysis reaction, ultimately leading to the formation of the γ-lactam as diastereomer **120a**. Interestingly, the selectivity of the intermediates **122** and **123** was monitored by NMR spectroscopy. After the halogenation step, there was a notable decrease in diastereoselectivity, which shifted from 75:25 *dr* to 49:51 *dr*. Despite this, an increase in selectivity induction was observed when the oxidative rearrangement progressed to the oxocarbenium ion **123** stage. This phenomenon effectively demonstrates the concept of downstream stereoinduction in the reaction process. For more details about the downstream stereoinduction can be found in the dissertation by J. SIETMANN.[76]

A selective example of the scope table is shown in Scheme 30a).

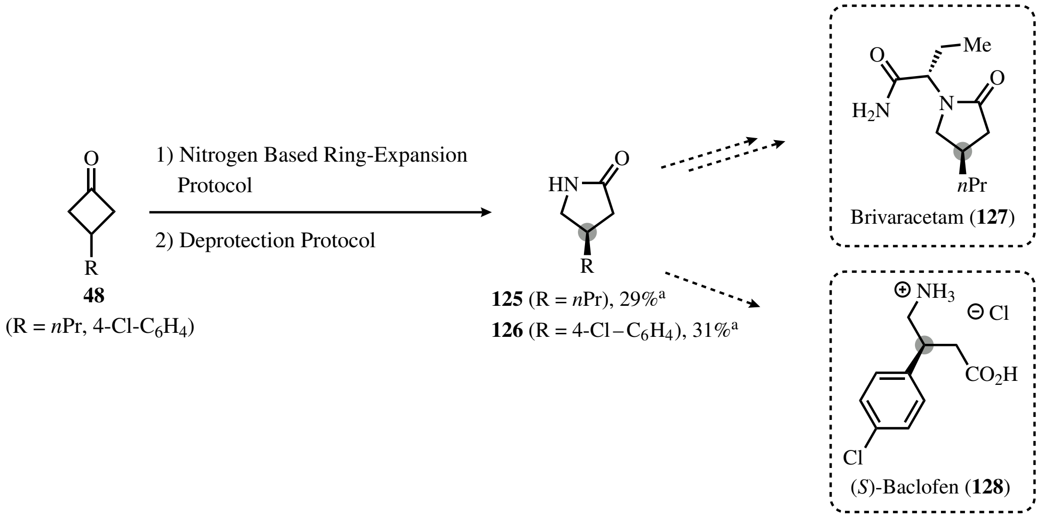


Scheme 30: a) Selected overview of the nitrogen-based ring-expansion of cyclobutanones **13** to chiral γ-lactams **120**. Reaction was performed on 1.00 mmol scale. Yield of major diastereomer is shown. NMR yield and diastereoselectivity were determined by ^{1}H NMR experiment using mesitylene (200 µmol) as the internal standard and are given in parentheses. X_c = chiral amino alcohol. b) Deprotection protocol using CAN. Reaction was performed on a 500 µmol scale of compound **120a**. Value of *er* was determined by HPLC analysis using chiral stationary phases. [a] Reaction was performed by J. SIETMANN. [b] Diastereomers were not separable. [c] Reaction was performed during my master's thesis.

In these cases, aryl substituents attached to the cyclobutanone smoothly underwent nitrogen insertion, furnishing γ-lactams with moderate yield (**120a** and **120b**). Additionally, the process showed tolerance for quaternary all-carbon stereocenters, resulting in the formation of the γ-lactam **120c** with the most favorable diastereomeric ratio at 88:12 *dr* observed in this study. It is also noteworthy, that both primary **120d** and tertiary **120e** alkyl substituents were well accommodated in the reaction. Intriguingly, an enhanced selectivity was noted when the alkyl substituent was more sterically hindered.

The current approach provided protected γ-lactams, which are of limited synthetic utility. Therefore a strong emphasis on developing a dependable deprotection protocol was placed to unlock access to a diverse array of pharmaceutical drugs. In this endeavor, the protected γ-lactam **120a** was treated with cerium ammonium nitrate (CAN), successfully converting it to the free γ-lactam **124** in 60% yield while maintaining an enantiomeric ratio of over >99:1 *er* (Scheme 30b). This transition from the broader scope of this study to the specific case of deprotection demonstrates a powerful protocol to enhance the practical applicability of the research in the pharmaceutical area.

Building upon the discussion of the deprotection protocol, the nitrogen-based ring-expansion and deprotection methods was applied to the substrates **48** (Scheme 31).

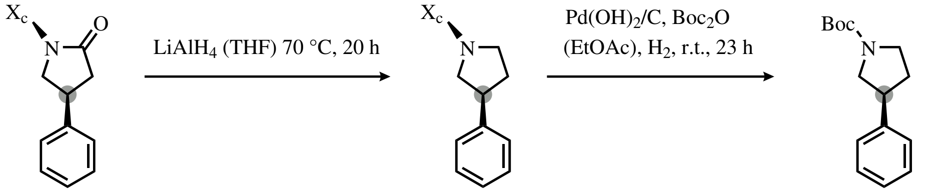


Scheme 31: Application for the formal synthesis of Brivaracetam (**127**) and (*S*)-Baclofen (**128**). Isolated yield over two steps. [a] Reaction was performed by J. SIETMANN.

Notably, the substrate **125** serves as a critical precursor in the two-step synthesis of Brivaracetam (**127**),[77] an antiepileptic drug employed in the treatment of partial onset seizures. Additionally, substrate **126** emerges as another key precursor, facilitating the one-step production of the antispastic medication (*S*)-Baclofen (**128**).[78] Both examples highlight the practical application and importance of the developed protocols in pharmaceutical synthesis.

4.3 Alternative Approach for the Deprotection

The widespread presence of pyrrolidines as the fifth most common heterocycle in the U.S. FDA-approved drugs underlines the importance of a refined deprotection protocol.[23] This context sets the stage for the endeavor to directly synthesize these five-membered rings. In pursuit of this goal, a protocol by FUKUYAMA and coworkers was adapted, which involved initially reducing the protected γ-lactam using $LiAlH_4$ (Scheme 32).[79]



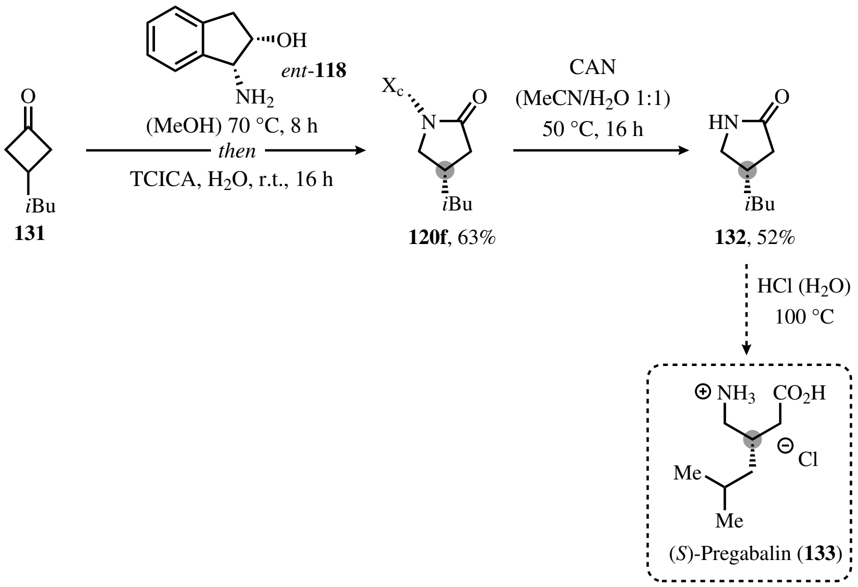
120a **129**, 89%[a] **130**, 75%

Scheme 32: Alternative route for the deprotection protocol to access the pyrrolidine scaffold **130**. X_c = chiral amino alcohol. [a] Reaction was performed by J. SIETMANN.

This was followed by hydrogenolysis in the presence of Boc_2O. This two-step sequence successfully gave the enantiopure Boc-protected pyrrolidine **130** with moderate yield. This synthetic route not only showcases the utility of the deprotection protocol, but also contributes to the broader goal of streamlining the synthesis of pharmacologically significant pyrrolidine heterocycles.

4.4 Synthesis of Pregabalin

Beyond pyrrolidines and drug molecules derived by them, Pregabalin, also known as Lyrica®, is a drug renowned in the field of medicinal chemistry. The drug is well-established as a vital component in the treatment of various neurological conditions such as endogenous depression.[19,72] Utilizing the established ring-expansion process, which here employs the enantiomeric counterpart of aminoindanol (*ent*-**118**) to align with the desired absolute configuration, the protected γ-lactam **120f** was isolated in 63% yield (Scheme 33).

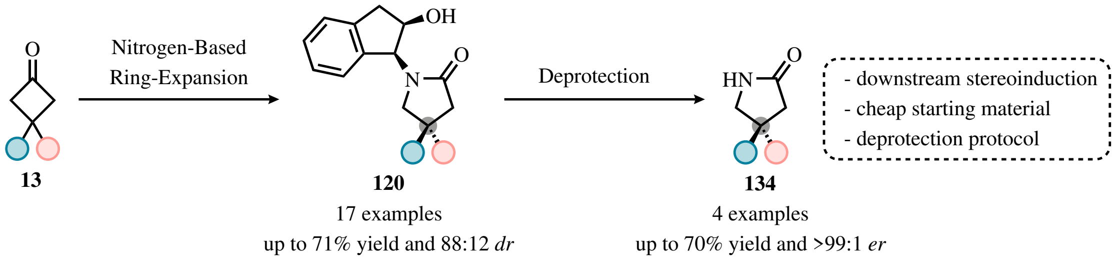


Scheme 33: Formal synthesis of (*S*)-Pregabalin (**133**).

Subsequent deprotection step led to the production of the free γ-lactam **132** as the main precursor of (*S*)-Pregabalin (**133**). For the synthesis of the final drug **133**, it must be theoretically hydrolyzed using aqueous HCl.[80] Overall, this example demonstrates the practical application of this methodology in the synthesis of a clinically relevant compound.

4.5 Summary and Outlook

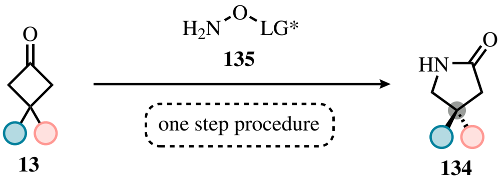
In conclusion, an effective desymmetrization strategy has been developed based on the rearrangement of prochiral tetrahedral *N*,*O*-ketal intermediate. This approach has harnessed the synthesis of a diverse array of chiral γ-lactams from straightforward prochiral cyclobutanones, chiral aminoindanol, and cost-effective cerium ammonium nitrate (CAN) (Scheme 34).



Scheme 34: Summary of the nitrogen-based ring-expansion.

Notably, the selectivity in these syntheses is derived from the chiral amino alcohol **118**. After extensive mechanistic studies a downstream stereoinduction was recognized to significantly enhance the selectivity, especially for quaternary all-carbon centers, which are typically challenging to control.[81] The deprotection protocol further amplifies the practicality of this method. By integrating both the ring-expansion and deprotection protocols, the synthesis of pharmaceutical compounds such as Brivaracetam, (*S*)-Baclofen, and (*S*)-Pregabalin was achieved.

However, it is important to note that the deprotection protocol was tested on only four substrates. The efficacy of this protocol on other indanyl-protected γ-lactams remains unverified. Therefore, a significant scope leaves room for further exploration to establish its general applicability. Despite the overall effectiveness of the demonstrated ring-expansion, a major drawback of this approach is the necessity of a two-step procedure, which underscores the need for further research. Particularly, the absence of protective groups in these lactams is essential for their direct application in further synthetic steps, enhancing the overall efficiency and reducing the complexity of pharmaceutical production.[82] The goal is to streamline the synthesis process even further, ideally simplifying it into a more efficient, single-step procedure (Scheme 35).



Scheme 35: Outlook to enable the chiral γ-lactam synthesis in a one step procedure. LG = leaving group.

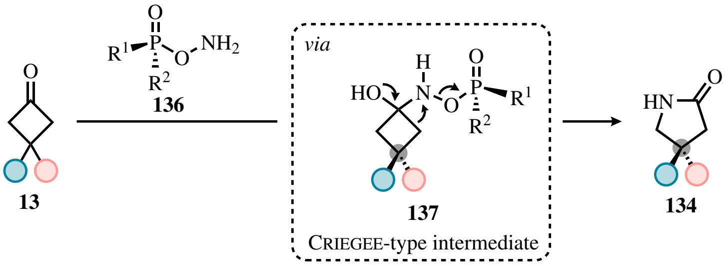
Herein, chiral amine sources **135** with excellent leaving groups (LG) have to be developed (subsubsection 2.1.2). This progression will undoubtedly find significantly broad applications in synthetic and medicinal chemistry.

5 Asymmetric Desymmetrization of Prochiral Cyclobutanones Using Chiral Phosphorous Reagents

5.1 Motivation

The established methods described in section 3 and section 4 faced its own set of challenges: While the initial approach with amino phosphinates resulted in achiral products (section 3), the desymmetrization method using chiral aminoindanol for stereoinduction yielded γ-lactams in their protected form, requiring a reliable deprotection scenario (section 4).

Based on the results of section 3, it was intriguing to develop an asymmetric nitrogen insertion reagent. This can be done by replacing one phenyl group of DPPH (**33a**). Thus, a chiral amine source **136** can be achieved, containing the phosphinate core structure, which has revealed in previous efforts as the suitable amine source for the rearrangement. In this case, the asymmetric aza-BAEYER – VILLIGER reaction is proposed to happen mechanistically *via* a CRIEGEE-type intermediate **137** to synthesize chiral γ-lactams **134** starting from prochiral cyclobutanones **13** (Scheme 36)



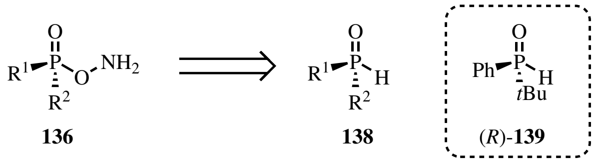
Scheme 36: Proposed asymmetric aza-BAEYER – VILLIGER reaction to access chiral γ-lactams **134**.

The following part focuses on the synthetic efforts to obtain chiral amine sources and to explore the novel reactivity exhibited by these reagents.

5.2 Synthesis of Starting Materials

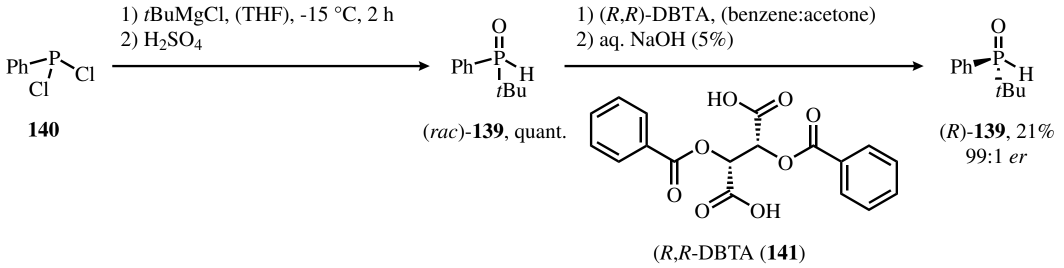
Initiating the validation of the key idea, the first procedural step entailed the identification of a suitable chiral amine source. This source need to encompass a chiral scaffold, a weak N – O bond, and an exceptional leaving group. Following the successful rearrangement achieved with DPPH (**33a**), it became clear that maintaining the phosphinate scaffold was a logical choice. P-chiral phosphine oxides, which are well-recognized in the literature, provide a solid foundation for developing chiral amino secondary phosphine oxides.[83,84]

The idea of a chiral amine source **136** bearing a phosphinate scaffold can be obtained from secondary phosphine oxides **138**, which are well-established and widely available (Scheme 37).[83]



Scheme 37: Retrosynthetic idea for the synthesis of **136**.

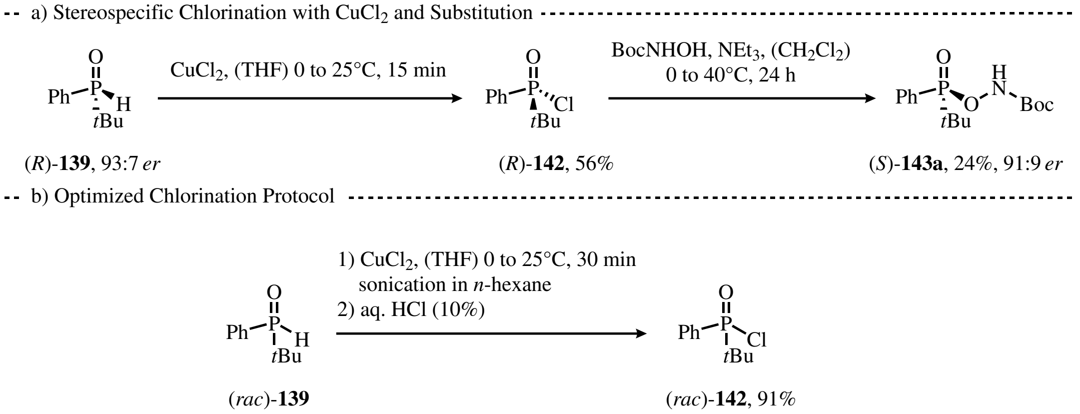
One particular example is the Ph-*t*Bu-phosphine oxide (*R*)-**139**, which stands out as the "*primus inter pares*" (engl. "first among equals").[85] Since the synthesis of the chiral Ph-*t*Bu-phosphine oxide (*R*)-**139** has been widely explored in the literature and can be straightforwardly halogenated to react with nucleophiles, the synthesis of optically active *H*-Ph-*t*Bu-phosphine oxide (*R*)-**139** was initially pursued. Due to the ease of scaling up and the stability of the (*R*,*R*)-*O*,*O*-dibenzoyltartaric acid (DBTA) complex, the synthesis of the chiral phosphine oxide was carried out by adapting the method developed by MINNAARD and coworkers[85] (Scheme 38).



Scheme 38: Synthesis of chiral secondary phosphine oxide (*R*)-**139**. Value of *er* were determined by HPLC analysis using chiral stationary phases.

The racemic *H*-phosphine oxide (*rac*)-**139** was efficiently prepared with an excellent yield *via* the GRIGNARD reaction, involving dichlorophenylphosphine (**140**) and *t*BuMgCl, followed by an acidic hydrolysis. Subsequently, following the procedure outlined by MINNAARD and coworkers, the racemic phosphine oxide (*rac*)-**139** was resolved using (*R*,*R*)-DBTA (**141**).[85] The kinetic resolution process, conducted in a benzene:acetone mixture, resulted in the formation of the [(*R*,*R*)-DBTA] complex. This complex was then liberated from DBTA after aqueous basic work-up, yielding the desired chiral phosphine **139** with excellent enantiomeric purity, specifically as the (*R*)-enantiomer.

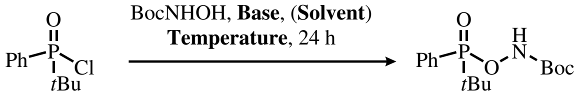
In order to introduce a more effective leaving group on the phosphorus atom, phosphine (*R*)-**139** underwent treatment with $CuCl_2$, which has been reported in the literature.[86] The stereospecific halogenation reaction proceeded in moderate yield ((*R*)-**142**) (Scheme 39a).



Scheme 39: a) Stereospecific chlorination with $CuCl_2$ according to the literature protocol by HAN and coworkers[86] and nucleophilic substitution with Boc-protected hydroxylamine. b) Optimized chlorination protocol.

The subsequent nucleophilic substitution yielded the Boc-protected hydroxylamine (*S*)-**143a** in low yield and additionally the substrate tended to racemize over time. Since the low overall yield was not convenient for a large-scale synthesis, several efforts were made to optimize the protocol. The yield of the chlorination step could be increased to 91% yield by irradiating the reaction mixture with ultrasound and acidic work-up (Scheme 39b). After that, the substitution with Boc-protected hydroxylamine was further tested in DCE at different temperatures (Table 4, entries 1-3).

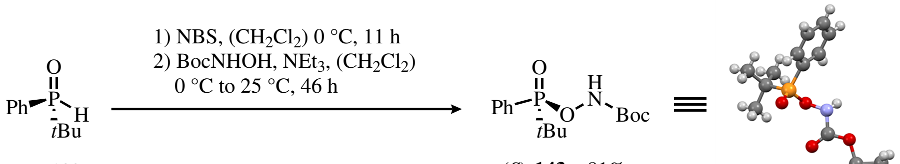
Table 4: Optimization of the nucleophilic substitution with Boc-protected hydroxlamine. Reaction was performed on a 100 µmol scale of organophosphorous chloride (*rac*)-**142**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. Value of *er* was determined by HPLC analysis using chiral stationary phases. [a] Starting from (*R*)-**142**, 84:16 *er*.



(*rac*)-**142** (*rac*)-**143a**

Entry	Solvent	Base	Temperature/°C	NMR Yield, *er*
1	DCE	NEt_3	25	13%
2	DCE	NEt_3	60	24%
3	DCE	NEt_3	90	0%
4	MeCN	NEt_3	25	14%
5	DMF	NEt_3	25	34%
6[a]	THF	NaHMDS	−78	70%, 75:25 *er*

The yield increased at 60 °C but no product was observed at even higher temperature. Furthermore, the yield did not improve in MeCN or in DMF (Table 4, entries 4 and 5). A significant increase in yield was achieved by utilizing sodium bis(trimethylsilyl)amide (NaHMDS) as the base. However, the enantiomeric purity dropped to 75:25 *er* when using chiral (*R*)-**142** with an enantioselectivity of 84:16 *er* (Table 4, entry 6). Since the treatment with $CuCl_2$ turned out to be impracticable, the phosphine (*R*)-**139** underwent in an alternative procedure with NBS.[87] This phosphinic bromide was employed without further isolation in a subsequent reaction with Boc-protected hydroxylamine, which served as the nucleophile (Scheme 40).



(*R*)-**139**
99:1 *er*

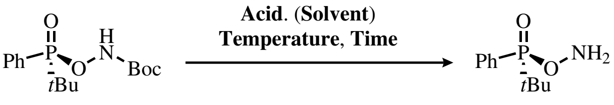
(*S*)-**143a**, 81%
99:1 *er*

Scheme 40: Synthesis of chiral Boc-protected hydroxylamine (*S*)-**143a** using NBS and X-ray structure is shown. Values of *er* were determined by HPLC analysis using chiral stationary phases.

From the nucleophilic substitution, the desired (*S*)-**143a** was isolated with 81% yield and a high enantiomeric ratio. The structure of the Boc-protected aminating reagent (*S*)-**143a** expected to be the (*R*)-enantiomer. Surprisingly, the X-ray crystallographic analysis was unambiguously confirmed the product as the (*S*)-enantiomer. The extensive research indicated that the bromination step led to an inversion of the stereochemical center.[87] Consequently, it is assumed that the stereoinformation was preserved during the nucleophilic substitution step.

In the last step, a reliable deprotection protocol has to be found without affecting the enantiomeric purity. Therefore TFA in CH_2Cl_2 was selected, resulting the chiral free hydroxylamine (*S*)-**145a** in good yield (Table 5, entry 1). Additionally, reducing the reaction time from 1 hour to 15 min at room temperature did not significantly affected the yield (Table 5, entry 2). However, the yield dramatically dropped, when reducing the reaction time to 10 min, indicating an incomplete reaction progress (Table 5, entry 3). Even stirring the reaction mixture in TFA did not improve the yield (Table 5, entry 4). The ^{1}H NMR analysis revealed that a moderate amount of the starting material remained unreacted. Interesting, the desired product was observed in good yield when using TfOH, which is compared to TFA a stronger BRØNSTED acid. However, side products were detected by ^{1}H NMR analysis (Table 5, entries 5 and 6).

Table 5: Optimization on the deprotection of the Boc-protected hydroxylamine (*S*)-**143a**. Reaction was performed on a 100 µmol scale of the Boc-protected hydroxylamine (*S*)-**143a**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard.

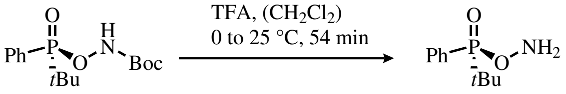


(*S*)-**143a**

(*S*)-**145a**

Entry	Solvent:Acid	Temperature/°C, Time	NMR Yield
1	CH_2Cl_2:TFA 1:1	0 °C, 30 min to 30 °C, 1 h	76%
2	CH_2Cl_2:TFA 1:1	0 °C, 30 min to 25 °C, 15 min	74%
3	CH_2Cl_2:TFA 1:1	0 °C, 10 min	43%
4	TFA (neat)	0 °C, 8 min	47%
5	TfOH (2.3 equiv.) CH_2Cl_2 (0.05 M)	0 °C, 10 min	64%, side product
6	TfOH (1.7 equiv.) CH_2Cl_2 (0.05 M)	0 °C, 8 min	75%

Taken together the results and the possibility of side products, TFA in CH_2Cl_2 was chosen the best condition. The deprotection using TFA provided the desired chiral amine source (*S*)-**145a** in a good yield, while maintaining its enantiomeric purity (Scheme 41).

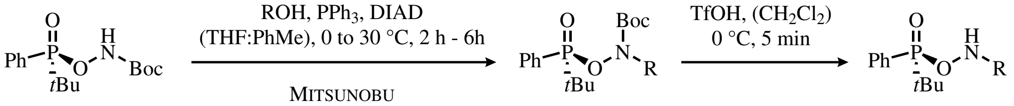


(*S*)-**143a**
99:1 *er*

(*S*)-**145a**, 72%
99:1 *er*

Scheme 41: Synthesis of chiral phosphinate hydroxylamine (*S*)-**145a**. Values of *er* were determined by HPLC analysis using chiral stationary phases.

Based on our findings in the aza-BAEYER – VILLIGER reaction, it was also compelling to explore the synthesis of chiral-at-phosphorus hydroxylamines bearing *N*-substitution (Scheme 42).



(*S*)-**143a**

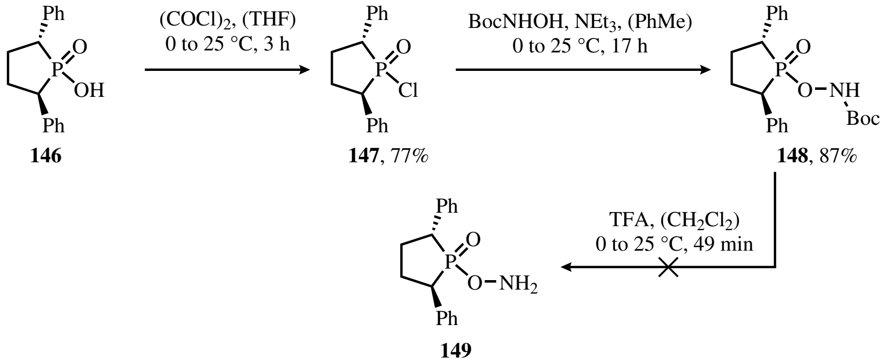
(*S*)-**143b**, R = Me, 73%, 98:2 *er*
(*S*)-**143c**, R = Bn, 94%, 99:1 *er*

(*S*)-**145b**, R = Me, 82%, 98:2 *er*
(*S*)-**145c**, R = Bn, 87%, 99:1 *er*

Scheme 42: Synthesis of chiral *N*-substituted hydroxylamines (*S*)-**145b** and (*S*)-**145c**. Values of *er* were determined by HPLC analysis using chiral stationary phases.

As it has been observed in the regioselective *N*-insertion, an improved regioselectivity was shown (subsection 3.8). Therefore, the increased steric hindrance could potentially favor the stereochemical induction. Under MITSUNOBU conditions, the nitrogen atom was alkylated using methanol or benzylalcohol. This process successfully yielded the desired Boc-protected hydroxylamine, maintaining a good yield and enantioselectivity ((*S*)-**143b** and (*S*)-**143c**). The subsequent deprotection protocol with TfOH proceeded efficiently, resulting in the production of the desired chiral hydroxylamines with very good yield and high enantioselectivity ((*S*)-**145b** and (*S*)-**145c**).

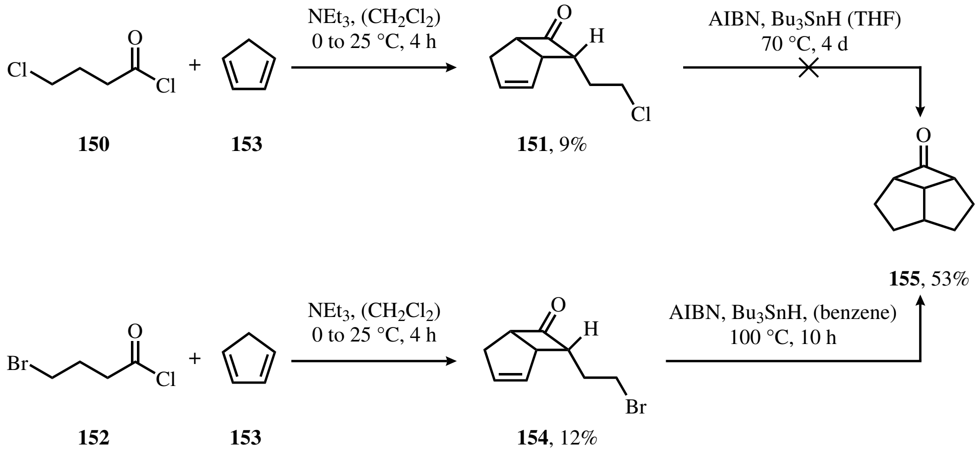
To study the effect of chiral-at phosphorus reagent, C_2 symmetric reagent **149** was thought of (Scheme 43).



Scheme 43: Synthesis of chiral hydroxylamine bearing a chiral 2,5-disubstituted phospholane framework **149**.

The synthesis started with commercially available chiral phosphinic acid **146**, which was treated with oxalylchlorid to obtain phosphinic chloride **147** in good yield. The subsequent functionalization at the phosphorous atom was carried out by nucleophilic substitution using BocNHOH, which led to the formation of **148** with excellent yield. However, the deprotection step, which involved using TFA, encountered difficulties. The challenge arose because the product **149** showed low stability and could not be effectively separated from its impurities. Further, even at low temperature or using TfOH a small amount of the desired product and the impurities were observed by ^{1}H NMR analysis, requiring an *in situ* deprotection protocol.

Among the cyclobutanones from the previous chapters, *meso*-cyclobutanones were synthesized because the stereocenter is closer to the reagent, enhancing the chances of stereoinduction. Due to the literature precdent, the synthesis of the *meso*-ketone **155** was considered (Scheme 44a).[88]

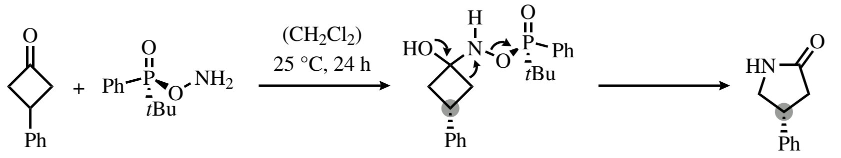


Scheme 44: Synthesis of *meso*-ketone **155**.[89]

According to the literature protocol by WRIGHT and coworkers the synthesis of the *meso*-ketone **155** can be achieved in a two-step sequence.[89] The initial step is the generation of a ketene using 4-chlorobutyryl chloride (**150**), followed by [4+2] cycloaddition with cyclopentadiene (**153**). However, the subsequent radical cyclization process proved ineffective, since the chlorinated alkane **151** showed insufficient reactivity. To enhance the reactivity, the substrate was changed to 4-bromobutyryl chloride (**152**), leading to a better radical formation. In the following, freshly distilled cyclopentadiene (**153**) was treated with **152**, leading to a [4+2] cycloaddition and the formation of the bicyclic ketone **154** in low yield. The radical intramolecular cyclization occurred by using Bu_3SnH and azobisisobutyronitrile (AIBN), thus successfully producing the desired product **155** with moderate yield.

5.3 Initial Findings

In earlier studies of this work, the 3-phenylcyclobutanone (**56**) was identified as a promising prochiral substrate due to its great reactivity in the aza-BAEYER – VILLIGER reaction (section 3). Therefore, the substrate remains of special interest in the ongoing research. Utilizing the chiral aminating reagent (*S*)-**145a**, initial results indicated the successful formation of the γ-lactam structure, achieving good yield and moderate enantiomeric purity. These findings suggest a proof of concept, likely due to an asymmetric aza-BAEYER – VILLIGER rearrangement (Scheme 45).



56 (*S*)-**145a** **158** CRIEGEE-type intermediate **124**, 69% 69:31 *er*

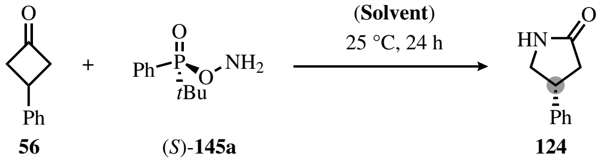
Scheme 45: Initial findings on the asymmetric aza-BAEYER – VILLIGER reaction through the CRIEGEE-type intermediate **158**. Reaction was perfomed on a 100 µmol scale of cyclobutanone **56**. Value of *er* were determined by HPLC analysis using chiral stationary phases.

Similarly to the proposed achiral variant, the rearrangement might proceed through a CRIEGEE-type intermediate **158**. Since the phosphorus atom possesses a stereogenic center and cyclobutanone **56** is prochiral, the desymmetrization strategy employed here enables the distal stereoinduction.

5.4 Reaction Development

Recognizing the initial proof of concept, the selectivity towards asymmetric aza-BAEYER – VILLIGER was evaluated and optimized. For the exploration of the asymmetric aza-BAEYER – VILLIGER reaction, the solvent was considered as a critical component. Therefore, a preliminary solvent screening was conducted with 3-phenylcyclobutanone (**56**) as the model substrate. The solvent screening revealed a broad compatibility, ranging from polar unprotic to nonpolar solvents. All tested solvents delivered comparable yields and enantioselectivity, suggesting an absence of a solvent effect (Table 6, entries 1-5).

Table 6: Solvent screening of the proposed aza-BAEYER – VILLIGER. Reaction was perfomed on a 100 µmol scale of cyclobutanones **56**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. Values of *er* were determined by HPLC analysis using chiral stationary phases. [a] Reaction was performed at 30 °C. [b] Reaction was quenched by using NEt_3 (1.10 equiv.).

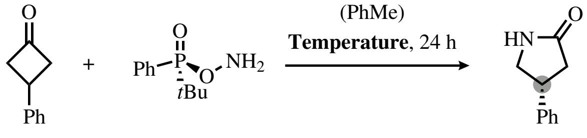


Entry	Solvent	Addition	NMR Yield, *er*
1	CH_2Cl_2	-	74%, 69:31
2	EtOAc	-	82%[a], 68:32
3	THF	-	87%[a], 68:32
4	PhMe	-	73%, 71:29
5	DMF	-	83%, 68:32
6	MeOH	-	46%, 53:47
7	HFIP	-	13%, 58:42
8	anhydrous PhMe	-	83%[b], 71:29
9	anhydrous PhMe	3 Å molecular sieves	83%[b], 69:31

Notably, toluene emerged as the solvent providing the best enantiomeric ratio at 71:29 *er*. However, an interesting observation was made when using polar protic solvents like MeOH and HFIP (Table 6, entries 6 and 7), where a dramatic decrease in enantioselectivity and reactivity was recorded. Moreover, the reduction in selectivity could be also attributed to the formation of hydrogen bonds between the chiral amine source and the solvent, influencing the stereochemical outcome of the reaction. Furthermore, the model reaction and the enantioselectivity were tested in anhydrous toluene. Neither in anhydrous toluene or in the presence of molecular sieves, the yield and the enantiomeric purity was not effected by residual water (Table 6, entries 8 and 9).

Once toluene was identified as the most promising solvent, the next critical step was to adjust the reaction temperature to further improve the enantioselectivity (Table 7).

Table 7: Temperature screening of the proposed aza-BAEYER – VILLIGER reaction. Reaction was perfomed on a 100 µmol scale of cyclobutanone **56**. NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. The reaction was quenched by using NEt_3 (1.10 equiv.). Values of *er* were determined by HPLC analysis using chiral stationary phases.



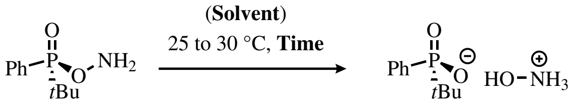
56 (*S*)-**145a** **124**

Entry	**Temperature/°C**	**NMR Yield, *er***
1	25	83%, 69:31
2	0	78%, 75:25
3	−20	80%, 42:58

Lowering the temperature to 0 °C led to an enhancement in enantioselectivity to 75:25 *er* (Table 7, entry 2). An unexpected result was shown when further decreasing the temperature to −20 °C, which was not viable in increasing the level of selectivity (Table 7, entry 3). One potential reason for the substantial deviation in enantioselectivity is due to the low solubility of the aminating reagent at low temperature. Notably, no significant effect of the temperature on the yield of the reaction was observed within the investigated temperature, indicating a high reactivity of the reagents involved.

Since low yield was observed in HFIP, the focus of investigation will now turn to the stability of the chiral amine source (*S*)-**145a** in order to understand the stability profiles of these compounds. One potential reason is that the aminating reagent may have decomposed under this condition. To test the hypothesis, the amine source (*S*)-**145a** was kept in HFIP and the decomposition process was analyzed using ^{1}H and ^{31}P NMR spectroscopy (Table 8).

Table 8: Stability analysis of chiral (*S*)-**145a**. Reaction was performed on a 30.0 µmol scale of the (*S*)-**145a**. The ratio of the starting material (SM) and decomposition product (DP) was determined by ^{1}H NMR without the addition of an internal standard. Value of *er* were determined by HPLC analysis using chiral stationary phases. Irradition using a LUZCHEM photoreactor with either UV-A light (420 nm) or UV-B (300 nm).



(*S*)-**145a**
97:3 *er*

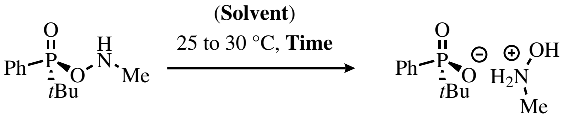
159a
possible decomposing product

Entry	Solvent	Time	λ	SM:DP, *er*
1	HFIP	5 h	-	65:35
2	HFIP	8 d	-	0:100
3	CD_2Cl_2	5 h	-	91:9
4	CD_2Cl_2	23 h	-	71:29, 85:15
5	CD_2Cl_2	5 h	420 nm	83:17
6	CD_2Cl_2	5 h	300 nm	60:40

Remarkably, significant decomposition was observed within 5 hours, and after 8 days, no starting material (SM) was detected (Table 8, entries 1 and 2). When the solvent was switched to non-acidic CD_2Cl_2, the decomposition of the chiral hydroxylamine occurred more slowly (Table 8, entries 3 and 4). Additionally, exposing the NMR tube to light resulted in an accelerated decomposition of the compound, and this effect was intensified when the light was of higher energy (Table 8, entries 5 and 6). This observation underscores the impact of both solvent choice and light exposure on the stability of chiral hydroxylamines. A plausible hypothesis for the decomposition centers on the formation of the hydroxylamine salt **159a**, which could be formed by nucleophilic substitution with water. However, it remains unclear whether a distinct decomposition product was generated, as CD_2Cl_2 should be traceless from water. Furthermore, the decomposition under light radiation can be explained that hydroxylamines generate nitrogen radicals due to their weak N–O bond.[90] Besides the possibility of decomposition, the enantiomeric ratio of the chiral hydroxylamine was is 85:15 *er* after 23 h, indicating a racemization process (Table 8, entry 4). Due to the observations in the stability tests it led to the presumption that their instability of the chiral hydroxylamines could explain the low stereoinduction.

When comparing with *N*-methylated hydroxylamine (*S*)-**145b**, decomposition was scarcely noticeable (Table 9).

Table 9: Stability analysis of chiral (*S*)-**145b**. Reaction was performed on a 30.0 µmol scale of the (*S*)-**145b**. The ratio of the starting material (SM) and decomposition product (DP) was determined by ^{1}H NMR without the addition of an internal standard. Values of *er* were determined by HPLC analysis using chiral stationary phases. Irradition using a LUZCHEM photoreactor with either UV-A light (420 nm) or UV-B (300 nm).



(*S*)-**145b**
98:2 *er*

159b
possible decomposing product

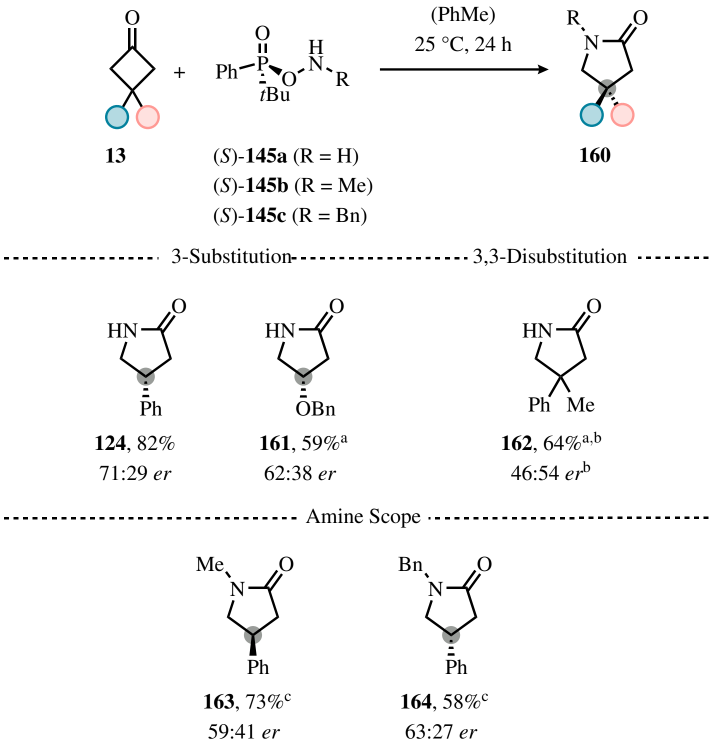
Entry	**Solvent**	**Time**	**λ**	**SM:DP, *er***
1	HFIP	16 h	-	100:0, 98:2
2	CD_2Cl_2	5 h	-	100:0
3	CD_2Cl_2	75 h	-	100:0, 98:2
4	CD_2Cl_2	5 h	420nm	100:0
5	CD_2Cl_2	5 h	300 nm	92:8

No decomposition to the possible **159b** product was detected under either acidic or non-acidic conditions, and the enantioselectivity remained untouched (Table 9, entries 1-3). Additionally, exposure to light did not induce any decomposition reaction (Table 9, entry 4). However, under high-energy radiation, a minor degree of degradation was observed (Table 9, entry 5).

The examined stability tests suggest an overall higher stability on *N*-methylated hydroxylamine (*S*)-**145b** rather than aminating reagent (*S*)-**145a**. This result is consistent with the nitrogen insertion described in subsection 3.6, as it showed high reactivity for *N*-alkylated diphenylphosphinates.

5.5 Substrate Scope

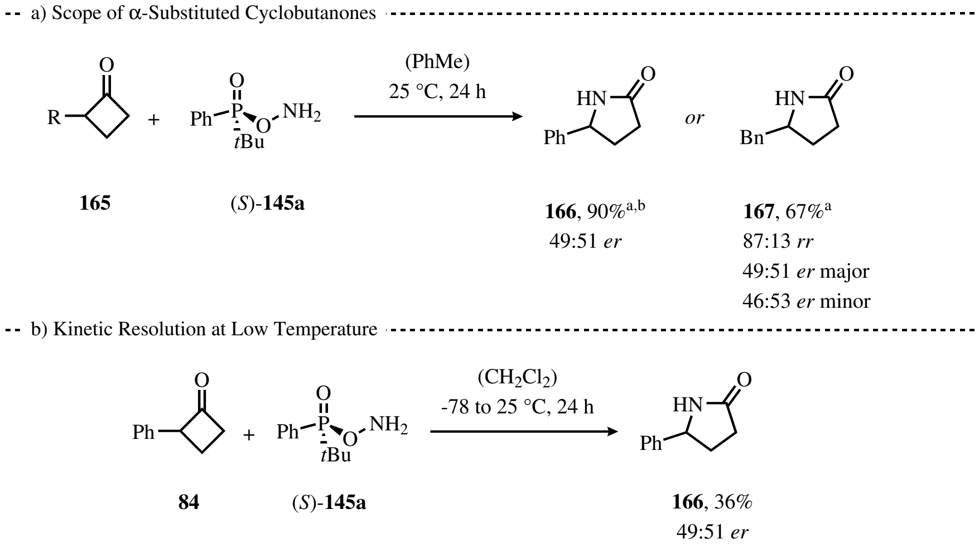
In the following, the general applicability of the asymmetric aza-BAEYER – VILLIGER approach was tested (Scheme 46).



Scheme 46: Substrate scope of the asymmetric aza-BAEYER – VILLIGER reaction. Reaction was performed on a 100 µmol scale of cyclobutanones **13**. Values of *er* were determined by HPLC analysis using chiral stationary phases. [a] Reaction was performed with CH_2Cl_2. [b] Reaction was performed at 30 °C. [c] Reaction was quenched by using NEt_3 (1.10 equiv.).

To investigate the steric hindrance on the stereoinduction, different substituents at the 3-position was tested. Shifting from the phenyl substituent to benzyl ether, the corresponding chiral γ-lactam product **161** was obtained in moderate yield, but relatively low selectivity. The protocol was amenable toward disubstituted cyclobutanone, but the selectivity decreased further, resulting in nearly racemic γ-lactam **162**. The overall low stereoinduction can be explained by the possible racemization process and instability of the chiral aminating reagent (subsection 5.4). Further, it is assumed that *N*-alkylated phosphinates interrogate structural impacts on the selectivity performance due to their increased steric hindrance. However, contrary to the expectations, pertubation on the nitrogen group did not lead to an improvement in enantioselectivity (**163** and **164**). Interestingly, γ-lactam **164** was obtained in moderate yield, which might caused by the more sterically demanding benzyl group on the nitrogen atom compared to (*S*)-**145a** and (*S*)-**145b**. In addition, it should be mentioned, that the level of enantioselectivity of the chiral *N*-Bn hydroxylamine **145c** to furnish γ-lactam **164** was consistent at 99:1 *er* after reisolating the chiral amine source. The observsation can be explained that **145c** did not racemize under the nitrogen insertion process. Further, the result correlates well with the stability of *N*-methylated hydroxylamine (*S*)-**145b**, which was shown in subsection 5.4. In summary, employing less complex cyclobutanones to obtain enantiomeric pure γ-lactams presents a challenge in achieving stereoinduction.

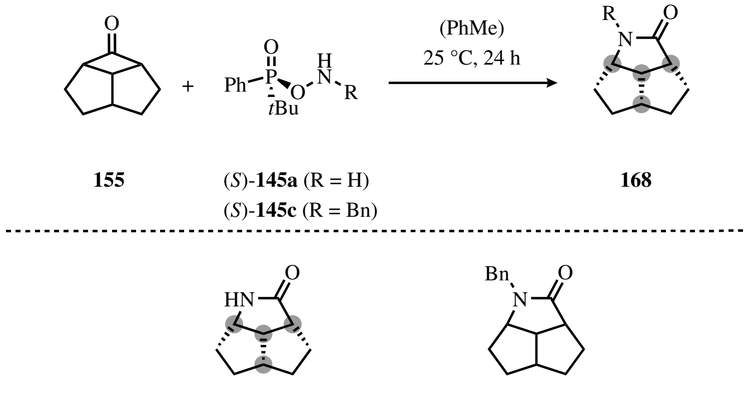
In the case of α-cyclobutanone, the starting material **165** exists in two enantiomeric forms. When a chiral amine source is utilized in the aza-BAEYER – VILLIGER reaction, it can facilitate kinetic resolution (Scheme 47).



Scheme 47: a) Substrate scope on α-substituted cyclobutanones **165**. b) Kinetic resolution on α-substituted cyclobutanone **84**. Reaction was performed on a 100 µmol scale of cyclobutanone **84**. Values of *er* were determined by HPLC analysis using chiral stationary phases. [a] Reaction was performed with CH_2Cl_2. [b] Reaction was performed at 30 °C.

This process involves resolving a racemic mixture through a transformation in which only one enantiomer is converted into the desired product, while the other enantiomer remains untouched. In the case of α-cyclobutanone **84**, the conversion to the γ-lactam was achieved with excellent yield, albeit the resulting pyrrolidinone **166** was racemic. The result showcased an absence of the kinetic resolution. Also, the enantiomeric purity of the γ-lactam with a benzyl group at the α-position was untouched (**167**). In this case, the migration rate of the more substituted carbon atom was predominant, overriding the chiral center at the phosphorous reagent. To further test the kinetic resolution, the amount of the chiral amine source (*S*)-**145a** was reduced to 0.5 equiv. and the reaction was performed at −78 °C and then gradually allowed to warm to room temperature (Scheme 47). By reducing the amount of the hydroxylamine, the effect of the kinetic resolution can be more elucidated. Despite these conditions, the resulting product **166** remained racemic, which further proved that the kinetic resolution did not occur.

To suppress the potential for kinetic resolution, the current protocol was expanded to include the desymmetrization of *meso*-substrates. In particular, the *meso*-ketone **155** was used with the idea that the chiral center of the phosphorus atom is closer to the substrate owing to the strained cyclic ketone. Hence, the compound was tested with the synthesized chiral amine sources (Scheme 48).



155

(*S*)-**145a** (R = H)
(*S*)-**145c** (R = Bn)

168

168a, 84%
77:23 *er*

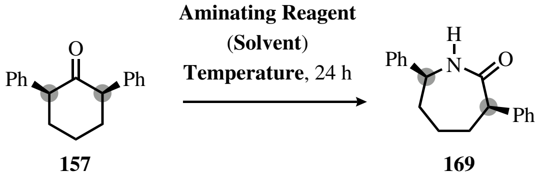
168b, 80%
50:50 *er*

Scheme 48: Substrate scope of *meso*-cyclobutanone **155**. Reaction was performed on a 100 µmol scale of cyclobutanones **155**. Values of *er* were determined by HPLC analysis using chiral stationary phases.

The tricyclic γ-lactam **168a** gave the best enantiomeric purity of 77:23 *er* as well as good yield. One potential reason for the increased selectivity is due to the challenging access of one enantiotopic face compared to the other. By contrast, it was found that chiral *N*-alkylated hydroxylamines significantly influences the enantioselective outcome. The *N*-substituted analog failed to induce any chirality (**168b**), perhaps due to the sterically more demanding substitution at the nitrogen atom. However, an explanation that is plausible remains difficult to find.

Furthermore, *meso*-cyclicketone **157** was also tested to reduce the potential for kinetic resolution. Before the chiral amine source was tested, the conditions were first applied, which were developed during the aza-BAEYER – VILLIGER study using DPPH (Table 10).

Table 10: Attempt of a ring-expansion on *meso*-cyclohexanone **157** to ε-lactam **169**. Reaction was performed on a 100 µmol scale of *meso*-cyclohexanone **157**. Reaction was quenched by using NEt_3 (1.10 equiv.). [a] Reaction was not quenched with NEt_3. NMR yields were determined by ^1H NMR experiment using dibromomethane (100 µmol) as the internal standard.

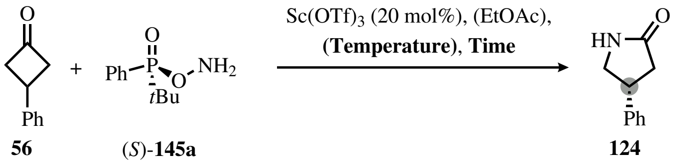


Entry	Aminating Reagent	Solvent	Temperature/°C	NMR Yield
1	DPPH (**33a**)	HFIP	25	0%
2	DPPH (**33a**)	HFIP	50	0%[a]
3	(*S*)-**145a**	PhMe	25	0%

In contrast to the previous results, the desired caprolactam **169** was not observed, neither at room temperature nor at elevated temperatures (Table 10, entries 1 and 2). Furthermore, the chiral hydroxylamine (*S*)-**145a** also proved ineffective in facilitating the rearrangement (Table 10, entry 3). One possible explanation for the unsuccessful rearrangement process could be attributed to the absence of ring strain in cyclohexanones and to the fast decomposition of the chiral aminating reagent (*S*)-**145a**. These results suggests the necessity to reevaluate and adjust the approach for these specific substrates.

Moreover, it was interesting to use Sc(OTf)$_3$ as LEWIS acid to accelerate the reaction and overcome the racemization process (Table 11).

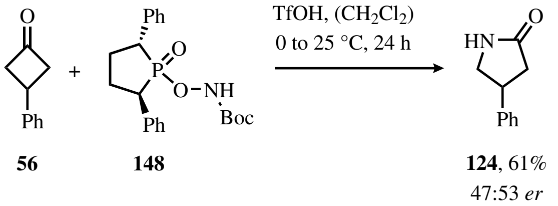
Table 11: Synthesis of γ-lactams using Sc(OTf)$_3$ as LEWIS acid. Reaction was performed on a 100 µmol scale of the cyclobutanone **56**. Reaction was quenched by using NEt$_3$ (1.15 equiv.). NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard. Values of *er* were determined by HPLC analysis using chiral stationary phases.



Entry	Temperature	Time	NMR Yield, *er*
1	−78 °C to 25 °C	21 h	46%, 48:52
2	25 °C	1 h	26%, 54:46

However, there was a substantial decrease in yield, and the amine source failed to induce chirality at low and room temperatures (Table 11, entries 1 and 2). This further substantiate that the chiral amine source may have decomposed under acidic conditions (subsection 5.4). Although the rate of decomposition is slower than the rate of product formation.

Despite the chiral amine source (*S*)-**145a** to validate the effect of the chiral at phosphorus reagent, it was interesting to relocate the chiral center to demonstrate the significance of the stereoinduction originating from the phosphorus atom. Apart from the challenges encountered in the isolation of the unprotected hydroxylamine **149**, the Boc-protected hydroxylamine **148** was utilized in the chiral aza-BAEYER – VILLIGER reaction (Scheme 49).

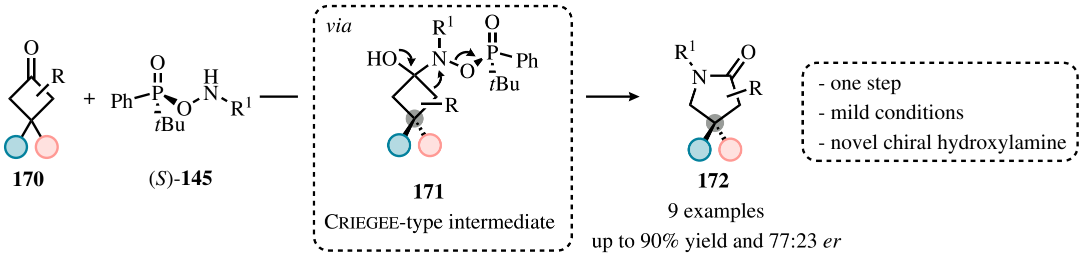


Scheme 49: Asymmetric aza-BAEYER – VILLIGER reaction using Boc-protected hydroxylamine **148**. Reaction was performed on a 100 µmol scale of the cyclobutanone **56**. Value of *er* were determined by HPLC analysis using chiral stationary phases.

In an *in situ* deprotection procedure with triflic acid, the desired γ-lactam **124** was isolated in moderate yield. However, it was observed that the chiral amine source did not induce any enantioselectivity. Compared to the chiral hydroxylamine (*S*)-**145a**, this result indicates that effective distal stereoinduction depends on the presence of a stereocenter at the phosphorus atom.

5.6 Summary and Outlook

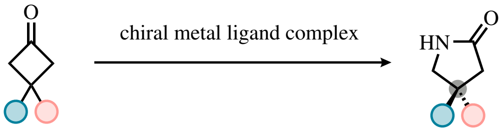
In conclusion, this study presents the first asymmetric aza-Baeyer – Villiger reaction, marking a significant advancement from the previous nitrogen insertion strategies. The journey has deepened the understanding of this reaction and led to the synthesis of novel chiral hydroxylamines based on a phosphine oxide framework. The asymmetric one-step procedure showcased a mild strategy of distal stereoinduction, enabling access to chiral γ-lactams, which are critical in creating more effective and targeted therapeutic agents (Scheme 50).



Scheme 50: Summary of the asymmetric aza-Baeyer – Villiger. R = H, alkyl, aryl. R^1 = H, Me, Bn.

Throughout the study, a variety of substituted cyclobutanones was explored, ranging from mono- to α-substituted types, and demonstrated the feasibility of substituting the nitrogen atom, thus yielding a diverse array of γ-lactams. However, various challenges in achieving enantioselectivity, stability and reactivity have been faced. Overall, low enantioselectivity was observed for even *meso*-compounds due to the potential of the racemization process and instability of the chiral hydroxylamine. The comprehensive investigation into the stability of hydroxylamines has revealed that factors such as acidic conditions, light exposure, and the specific chemical structure of the hydroxylamine significantly influence their stability. These insights emphasize the need for careful consideration of reaction conditions to maintain the enantioselective outcome.

In future studies, refining the reaction conditions, particularly by lowering the reaction temperature, emerges as a crucial step to minimize the racemization process of the amine source, as the current effort has demonstrated that this adjustment has significant potential to improve selectivity. In addition to that, the use of chiral metal ligand complexes or organocatalysts can be used to improve the enantioinduction (Scheme 51).



13 **134**

Scheme 51: Outlook to synthesize chiral γ-lactams by using chiral metal ligand complexes.

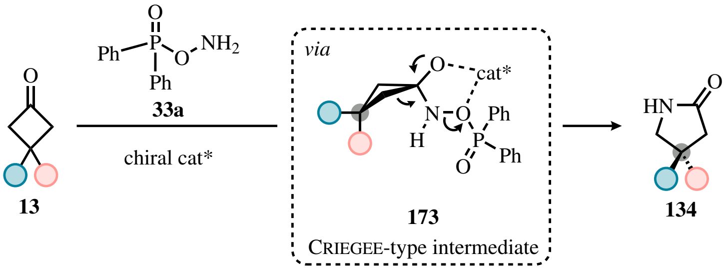
Moreover, further investigation in the phosphorous backbone should be considered, such as changing the Ph-*t*Bu-group to improve the stereoinduction as well as the stability of the reagent. Thus, future research in this area will continue on the improvement of the reaction protocol, seeking to enhance the efficiency and applicability of this novel synthetic approach to access enantiomerically pure γ-lactams.

6 Studies Towards a Catalytic Approach

6.1 Motivation

Due to the low enantioinduction, the potential of racemization and the instability of the synthesized chiral amine source, an alternative protocol for the enantioinduction needs to be considered. Therefore, inspiration was drawn from the metal-catalyzed asymmetric BAEYER – VILLIGER methodology developed by FENG and coworkers using a chiral LEWIS acid and C_2 symmetric *N,N'* dioxide ligands.[54] The use of a chiral LEWIS acid and racemic DPPH could accelerate the reaction rate. If this can be achieved a chiral catalyst can allow enantioselective *N* insertion. The stereoelectronic orientation can be further dictacted with chiral organocatalysts such as chiral BRØNSTED acids, which was reported by DING and coworkers.[55]

In this study, the interest has been stimulated to propose a catalytic approach towards an asymmetric nitrogen-based ring-expansion of prochiral cyclobutanones **13** to chiral γ-lactams **134**. Based on the previous results, the reaction could undergo *via* the tetrahedral intermediate **173** by using DPPH (**33a**), which turned out as effective amine source in section 3 (Scheme 52).

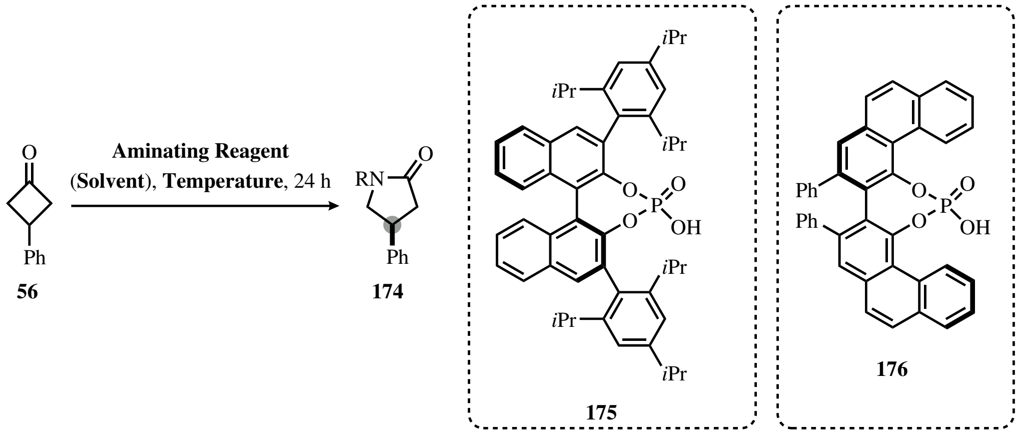


Scheme 52: Proposed catalytic asymmetric aza-BAEYER – VILLIGER reaction to access chiral γ-lactams **134**.

6.2 Initial Findings

In the first approach, the enantioselective BAEYER – VILLIGER methodology developed by DING and coworkers was tested. In the following, several ring-expansion reactions were carried out and stopped by adding NEt_3 to evaluate a catalytic system. In the presence of amino phosphinate **33a** and (*S*)-TRIP CPA **175**, the γ-lactam **88a** was obtained in low yield, but a slight induction in enantioselectivity was observed (Table 12, entry 1).

Table 12: Catalytic approach for the synthesis of γ-lactams **174** using CPA's (10 mol%) as organocatalyst and amino phosphinates **33**. Reaction was performed on a 200 µmol scale of the cyclobutanone **56**. Reaction was quenched by using NEt_3 (1.10 equiv.). Given is the isolated yield after flash column chromatography. Values of *er* were determined by HPLC analysis using chiral stationary phases.

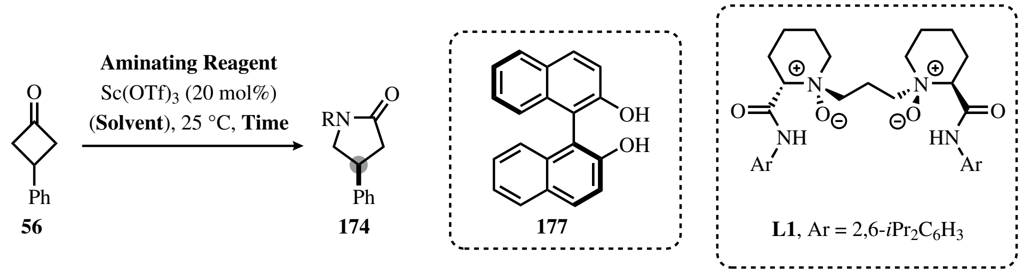


Entry	Aminating Reagent	CPA	Solvent	Temperature/°C	Product, Yield *er*
1	DPPH (**33a**)	**175**	CH_2Cl_2	25	**88a**, 7%, 58:42
2	*N*-Me-**33b**	**175**	CH_2Cl_2	25	**88m**, 86%, 48:52
3	*N*-Me-**33b**	**175**	PhMe	25	**88m**, 90%, 46:54
4	*N*-Me-**33b**	**175**	PhMe	0	**88m**, 88%, 47:53
5	*N*-Me-**33b**	**175**	CH_2Cl_2	−78 to 25	**88m**, 93%, 50:50
6	*N*-Bn-**33c**	**175**	CH_2Cl_2	25	**88o**, 75%, 48:52
7	DPPH (**33a**)	**176**	CH_2Cl_2	25	**88a**, 14%, 48:52

The overall low yield implies a non-catalytic approach and was caused by the formation of the oxime ester, indicating the slow reaction rate of the aza-BAEYER – VILLIGER rearrangement compared to the oxime formation. However, to overcome the formation of the oxime ester *N*-methylated hydroxylamine **33b** was used. The aminating reagent did improve the yield at low temperature and room temperature, since the oxime ester cannot be formed. However, the enantiomeric ratio could not be increased (Table 12, entries 2-5). Further investigations on the oxime esters are carried out by my colleague M. ARNOLD. As indicated by DING and coworkers an improvement in yield and promising enantioselectivity was observed in toluene, but in this model reaction the enantioinduction was not improved (Table 12, entry 3).[55] Also, the formation of **88o** was observed with *N*-Bn hydroxylamine **33c**, but only in low level of enantioselectivity (Table 12, entry 6). This concludes that the background reaction, which characterizes the reaction in the absence of a chiral CPA, plays a significant role under these conditions. By switching to the CPA bearing a (*S*)-VAPOL backbone **176**, the yield and enaniomeric purity could not been improved (Table 12, entry 7). Overall, the results showed that the organocatalyst did not participate in the rearrangement process to induce any enantioselectivity.

Taking the inspiration from the research conducted by FENG and coworkers, the possibility of using a *N*,*N'*-dioxide-Sc-complex was considered.[54] This section will delve into the catalytic efficiency and induction potential of this chiral LEWIS acid. Initially, 3-phenylcyclobutanone (**56**) was selected as the substrate and $Sc(OTf)_3$ as the catalyst, aiming to assess the performance of this catalytic system (Table 13).

Table 13: Catalytic approach for the synthesis of γ-lactams. Reaction was performed on a 200 µmol scale of the cyclobutanone **56**. Reaction was quenched by using NEt_3 (1.10 equiv.). NMR yields were determined by ^{1}H NMR experiment using dibromomethane (200 µmol) as the internal standard. Values of *er* were determined by HPLC analysis using chiral stationary phases. Ntf_2 = triflimide. hfac = hexafluoroacetylacetonate. [a] Reaction was not quenched by using NEt_3 (1.10 equiv.). [b] Reaction was performed in anhydrous CH_2Cl_2. [c] Isolated yield. [d] Instead of $Sc(OTf)_3$. [e] Reaction was performed on a 100 µmol scale of the cyclobutanone **56** and NMR yields were determined by ^{1}H NMR experiment using dibromomethane (100 µmol) as the internal standard.



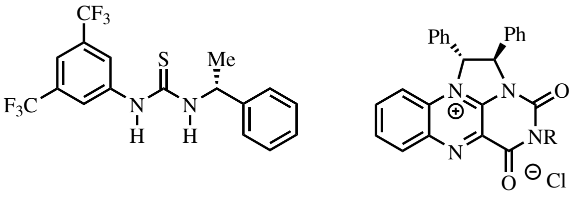
Entry	Aminating Reagent	Solvent	Addition	Time	Product, NMR Yield *er*
1	DPPH (**33a**)	EtOAc	-	24 h	**88a**, 73%[a]
2	DPPH (**33a**)	EtOAc	-	1 h	**88a**, 70%
3	DPPH (**33a**)	EtOAc	without $Sc(OTf)_3$	1 h	**88a**, 11%
4	DPPH (**33a**)	CH_2Cl_2[b]	**L1** (21 mol%)	24 h	**88a**, 58%[a], 50:50
5	DPPH (**33a**)	CH_2Cl_2	**177** (24 mol%)	1 h	**88a**, 43%[a], 50:50
6	DPPH (**33a**)	EtOAc	**177** (24 mol%)	1 h	**88a**, 64%[a], 50:50
7	*N*-Me-**33b**	EtOAc	**L1** (21 mol%)	24 h	**88m**, 85%[a,c], 49:51
8	DPPH (**33a**)	CH_2Cl_2[b]	$Sc(NTf_2)_3$ (20 mol%)[d]	24 h	**88a**, 5%[a,e]
9	DPPH (**33a**)	CH_2Cl_2	$Sc(hfac)_3$ (20 mol%)[d]	24 h	**88a**, 23%[a,e]
10	DPPH (**33a**)	CH_2Cl_2	$Cu(OTf)_2$ (20 mol%)[d]	24 h	**88a**, 0%[a]
11	DPPH (**33a**)	EtOAc	$Mg(OTf)_2$ (20 mol%)[d]	1 h	**88a**, 0%

Furthermore, it was particularly important to employ DPPH (**33a**), which has already been established as a versatile electrophilic aminating reagent. This initial step was crucial for setting a reliable baseline for the subsequent experiments. When the reaction was conducted for 24 hours, high yield was observed (Table 13, entry 1). To confirm that the high reactivity was not a result of background activity, the reaction was terminated after just 1 hour. Interestingly, an excellent yield was still evident, suggesting the presence of an effective catalytic system (Table 13, entry 2). In the absence of the catalyst, only 11% of the desired product was formed, which further substantiated that the high yield was not due to a background reaction (Table 13, entry 3). However, upon introducing a complex catalyst, prepared *in situ* from $Sc(OTf)_3$ and the chiral *N*,*N'*-dioxide ligand **L1**, the system did not efficiently induce chirality in the product (Table 13, entry 4). The outcome showed that either the scandium-complex has not been formed as expected or the ligand was unsuitable for the stereoinduction. When (*S*)-BINOL (**177**) was employed, moderate yields were already achieved after 1 hour, but the enantiocontrol of the reaction was not sensitive to neither CH_2Cl_2 nor EtOAc (Table 13, entries 5 and 6). Even a system with *N*-Me DPPH **33b** and the ligand **L1** did not lead to a stereochemical induction (Table 13, entry 7). Contrary to successful applications observed in alternative strategies using different Sc-complexes such as $Sc(NTf_2)_3$ or $Sc(hfac)_3$, poor yield was obtained in this system (Table 13, entries 8 and 9).[91,92] Various other metal catalysts were surveyed in the nitrogen insertion reaction including $Cu(OTf)_2$ and $Mg(OTf)_2$ to accelerate the catalytic system. However, the use of other metal sources could not afford the γ-lactam **88a** (Table 13, entries 10 and 11).

6.3 Summary and Outlook

In summary, the first metal-catalyzed approach *via* the aza-BAEYER – VILLIGER reaction has been tested using $Sc(OTf)_3$ and DPPH (**33a**). Also, an organocatalyzed approach has been evaluated, exhibiting a weak stereoinduction. Both outcomes shed light on the crucial role of the catalyst in achieving the desired reaction outcome and highlights an area for further exploration in enhancing chiral induction.

Besides the development made by DING and coworkers[55] using CPAs, other potent approaches should include chiral organocatalysts derived from thiourea **178** and chiral flavinium salts **179a–c** in future studies (Figure 3).



178

179a, (R = H)
179b, (R = Me)
179c, (R = Bn)

Figure 3: Chiral thiourea **178** and flavinium salts **179a–c** as potential organocatalysts for the asymmetric aza-Baeyer – Villiger reaction.

These methods have already been tested and shown promise in the Baeyer – Villiger oxidation.[93,94] Thus, a great interest is to propose a catalytic approach towards an asymmetric catalyzed nitrogen-based ring-expansion for the aza-Baeyer – Villiger reaction to improve the enantiomeric purity of γ-lactams.

7 Experimental Part

7.1 General Experimental Methods

Reactions sensitive to air or moisture were carried out in an oven- (125 °C) and flame-dried glassware under nitrogen atmosphere using standard SCHLENK technique. Anhydrous solvents were either dried with standard techniques (EtOH stored over activated 3 Å molecular sieves, THF distilled over sodium metal and benzophenone and stored over activated 4 Å molecular sieves), or collected from a MBRAUN MB SPS-800 (Et_2O: MB-KOL-A and MB-KOL MT2-250, THF: 2×MB-KOL MT2-150 °C, CH_2Cl_2: 2×MB-KOL-A, MeCN: 2×MB-KOL MT2-250, and PhMe:1×MB-KOL-C and 1×MB-KOL-A). A positive argon pressure was used to pass the solvents through the columns. All indicated reaction temperatures refer to the temperature of the water bath or aluminium block. Unless otherwise noted, all workup and purification procedures were carried out with pre-distilled technical grade solvents. Solvents were distilled off at 40 °C under reduced pressure. Isolated compounds which are not volatile were dried under high vacuum ($\sim$ 1.5 mbar). Photochemical reactions were performed in a LUZCHEM LZC-ORG photoreactor with 10×8 watt LUZCHEM LZC-420 mercury lamps or with 10×8 watt LUZCHEM LZC-UVB mercury lamps. Deuterated solvents were used without further purification. All other reagents used for the reactions were purchased from ABCR, ACROS ORGANICS, ALFA AESAR, BLDPHARM, CARBOLUTION, FLUOROCHEM, SIGMA-ALDRICH and TCI.

Melting points (**M.P.**) were measured on a BÜCHI B-540 melting-point instrument and are reported uncorrected.

Infrared (**IR**) spectra were obtained on a PERKIN-ELMER 100 FT-IR spectrometer or on a JASCO FT/IR-4100 and are reported in wavenumbers $\tilde{\nu}$ (cm^{-1}) . Bands are characterized as broad (br), strong (s), medium (m), and weak (w).

Nuclear magnetic resonance (**NMR**) spectra were recorded by the analytical departments of the Organisch-Chemisches Institut at Universität Münster and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Following nuclear resonance spectromers were used:

- BRUKER Avance II 400 (^{1}H 400 MHz, ^{13}C 101 MHz)
- AGILENT DD2 500 (^{1}H 500 MHz, ^{13}C 126 MHz)
- AGILENT DD2 600 (^{1}H 600 MHz, ^{13}C 151 MHz)
- BRUKER Avance III HD 400 (^{1}H 400 MHz, ^{13}C 101 MHz, ^{31}P 162 MHz)

The spectra were recorded at 26 °C (unless otherwise noted). The chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H NMR $CHCl_3$: δ = 7.26 ppm, ^{1}H NMR C_6HD_5: δ = 7.16 ppm, ^{1}H NMR $CHDCl_2$: δ = 5.32 ppm, ^{1}H NMR CHD_2OD: δ = 4.87 ppm, ^{1}H NMR $(CHD_2)(CD_3)SO$: δ = 2.50 ppm; ^{13}C NMR $CDCl_3$: δ = 77.16 ppm, ^{13}C NMR C_6D_6: δ = 128.06 ppm, ^{13}C NMR CD_2Cl_2: δ = 53.84 ppm, ^{13}C NMR CD_3OD: δ = 49.00 ppm, ^{13}C NMR $(CD_3)_2SO$: δ = 39.52 ppm).[95] Chemical shifts of ^{31}P NMR are referenced using a coaxialtube with 85% aqueous phosphoric acid as external standard. The data is reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet or combinations of these), coupling constants (Hz) and integration. Apparent multiplicity, which occurs as a result of accidental equality of coupling constants to magnetically non-equivalent protons, is marked as *app.* The spectra were evaluated with MESTRELAB RESEARCH (Version: 14.1.2 07/19/2020).

High Resolution Mass Spectrometry (**HRMS**) was performed by the analytical departments of the Organisch-Chemisches Institut at Universität Münster and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Spectra were recorded on a BRUKER Daltonics MicroTof, on a THERMO FISHER SCIENTIFIC Orbitrap LTQ XL or an AGILENT G6545AQ-ToF (LC-MS, ionization via electron spray ionization (ESI), atmos-pheric-pressure chemical ionization (APCI). Signals are reported as mass to charge ratio (*m/z*).

Purification was performed either *via* standard flash column chromatography (FC) techniques using 60 M silica gel (0.04 – 0.063 mm, MACHEREY-NAGEL), 40-63 µm silica gel (VWR chemicals) or Geduran® Si 60 (0.04 – 0.063 mm, Millipore) or on an automated flash chromatography (AFC) system BIOTAGE Isolera One utilizing BIOTAGE Sfär Silica D-Duo 60 µm columns (5 g, 25 g, 100 g). Glass silica gel plates 60 F_{254} (MERCK) were used for thin layer chromatography (TLC) using UV light (254/366 nm) and $KMnO_4$ (1.5 g $KMnO_4$, 5 g

$NaHCO_3$ and 5 mL NaOH 10 % in 200 mL H_2O) stain for detection.

Analytical high-performance liquid chromatography (**HPLC**) measurements were performed on the following system: KNAUER HPLC Pump Smartline 1000 with degassing unit, KNAUER Autosampler Smartline 3950, KNAUER UV-detector Smartline 2550, KNAUER RI-detector S2 Smartline 2300. Separation was performed using Lux® i-Cellulose-5 (4.6×250 nm×5 µm, Phenomenex Ltd.), Lux® Cellulose-1 (4.6×250 nm×5 µm, Phenomenex Ltd.), Lux® Amylose-1 (4.6×250 nm×5 µm, Phenomenex Ltd.), Lux® i-Amylose-3 (4.6×250 nm ×5 µm, Phenomenex Ltd.), or Reprosil Chiral-AMS (4.6×250 nm×5 µm, Dr Maisch GmBH.).

Optical rotations were measured on a JASCO P2000 and on a PERKIN-ELMER 241 polarimeter at 589 nm wavelength (sodium D-line) using a standard 10 cm cell (1 mL). Specific rotations, $[\alpha]_D{}^{20}$, are reported in degree $\frac{\mathrm{mL}}{\mathrm{g \cdot dm}}$ at the specific temperature. Concentrations (c) are given in grams per 100 mL of the specific solvent.

The **X-ray diffraction** for the compound (*S*)-**143a** was performed on a STOE IPDS-2T diffractometer.

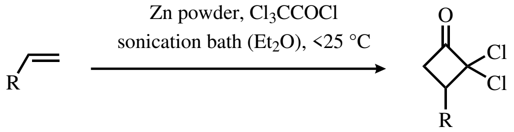
Documentation of the experimental work was done partly using the electronic lab notebook (ELN) Chemotion. Otherwise, the documentation was carried out using conventional lab notebooks in paper form.

7.2 An Aza-BAEYER – VILLIGER Rearrangement for Nitrogen Insertion

7.2.1 Synthesis of Starting Materials

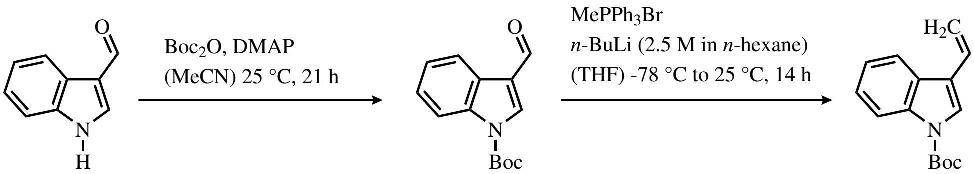
Synthesis of 3-Substituted Cyclobutanones

General Procedure A for the [2+2] Cycloaddition of Dichloroketene



The synthesis of dichlorinated cyclobutanones was conducted according to the methodology outlined in the literature by LU and coworkers.[66] An oven-dried SCHLENK flask was charged with Zn powder (2.00 equiv.) and suspended in anhydrous Et_2O (1.3 M) under inert atmosphere. Following the addition of the olefine (1.00 equiv.), the flask was placed into a sonication bath. The mixture was irradiated with ultrasound while a solution of trichloroacetyl chloride (1.50 equiv.) in Et_2O (2.0 M) was added dropwise over 40 min. The sonication bath was cooled by adding ice to maintain a temperature of below 25 °C. Upon completion of the addition, the mixture was kept under sonication. TLC was employed to monitor the consumption of starting material. The mixture was diluted with Et_2O (20 mL), and the resulting solids were separated by filtration through a CELITE® pad and eluted with Et_2O. The filtrate was washed with H_2O (2 × 50 mL), an saturated aqueous solution of $NaHCO_3$ (4 × 50 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was used without further purification.

tert-Butyl 3-vinyl-1*H*-indole-1-carboxylate (77)

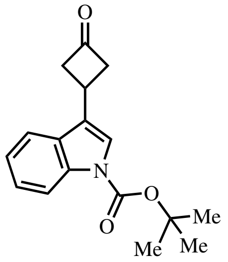


The Boc-protected indole **76** was prepared following a literature protocol by HECHT and coworkers.[96] A round-bottom flask was charged with indole **75** (4.35 g, 30.0 mmol, 1.00 equiv.), di-*tert* butyldicarbonate (contains 95% of the actual substrate, 7.58 g, 33.0 mmol, 1.10 equiv.)

and MeCN (45 mL). *N*,*N*-dimethylpyridin-4-amine (DMAP) (367 mg, 3.00 mmol, 0.10 equiv.) was added at room temperature and the resulting mixture was stirred for 21 h. The solvent was removed under reduced pressure and the residue was dissolved with CH_2Cl_2 and the solution was washed with an aqueous saturated solution of $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic phase was dried over MgSO4, filtered and the solvent was removed under reduced pressure. The resulting crude reaction mixture was directly utilized for the subsequent step without further purification.

The preparation of the olefin **77** was conducted in accordance with the literature protocol outlined by CARREIRA and coworkers[97] In an oven-dried SCHLENK flask, methyltriphenylphosphonium bromide (7.25 g, 20.3 mmol, 1.20 equiv.) was dissolved in anhydrous THF (180 mL). The mixture was allowed to cool down to 0 °C with an ice/water bath. *n*-BuLi (2.5 M in *n*-hexane, 7.44 mL, 18.6 mmol, 1.10 equiv.) was added at 0 °C and the mixture was stirred at this temperature for 2 h. The reaction was cooled down to −78 °C with a dry ice/acetone bath. The aldehyde **76** (4.15 g, 16.9 mmol, 1.00 equiv.) in anhydrous THF (23 mL) was added dropwise and the reaction mixture was stirred at room temperature for 14 h. The reaction was stopped by adding water. The resulting mixture was extracted with Et_2O (3×100 mL) and the combined organic layers were washed with H_2O, brine and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **77** (2.81 g, 11.5 mmol, 68%) was obtained by flash column chromatography (SiO_2, *n*-hexane:EtOAc 95:5, stained with KMnO4) as yellowish oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (d, $J = 8.2$ Hz, 1H), 7.81 (ddd, $J = 7.8, 1.4, 0.8$ Hz, 1H), 7.64 (s, 1H), 7.42 – 7.21 (m, 2H), 6.82 (ddd, $J = 17.8, 11.3, 0.7$ Hz, 1H), 5.82 (dd, $J = 17.9, 0.8$ Hz, 1H), 5.33 (dd, $J = 11.3, 1.3$ Hz, 1H), 1.68 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 149.8, 136.1, 128.9, 128.3, 124.7, 124.1, 123.0, 120.1, 119.4, 115.5, 114.5, 84.0, 28.3.
The obtained spectroscopic data is in agreement to the literature.[98]

tert-Butyl 3-(3-oxocyclobutyl)-1*H*-indole-1-carboxylate (78)



Following the general procedure **A** using alkene **77** (1.22 g, 5.00 mmol, 1.00 equiv.) the synthesis of the dichlorinated cyclobutanone was carried out employing ultrasound irradiation. After 1 h of irradiation, an additional portion of trichloroacetyl chloride (223 µL, 364 mg, 2.00 mmol, 0.4 equiv.) in Et_2O (1.5 mL) was added. Without further purification, the dehalogenation was performed following a modified literature protocol derived from LU and coworkers[66] In a two-neck round-bottom flask, Zn dust (1.64 g, 25.0 mmol, 5.00 equiv.) and NH_4Cl (669 mg, 12.5 mmol, 2.50 equiv.) were suspended in MeOH (2.5 mL). A solution of the halogenated product in MeOH (28 mL) was added slowly to the suspension to prevent reflux. The mixture was stirred at 70 °C for 5 h. The mixture was allowed to cool down to room temperature and the resulting solids were filtered off through a pad of CELITE® and washed with Et_2O. The filtrate was concentrated under reduced pressure, diluted with an aqueous solution of HCl (15 mL, 1.0 M) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired product **78** (150 mg, 524 mmol, 10%) was obtained by flash column chromatography (SiO_2, *n*-hexane:EtOAc 90:10, stained with $KMnO_4$) as a yellowish oil.

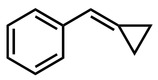
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2979 (br), 2362 (m), 1788 (s),1731 (s), 1454 (m), 1378 (s), 1255 (m), 1156 (s), 1090 (s), 1019 (w), 745 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (d, $J = 8.4$ Hz, 1H), 7.52 – 7.41 (m, 2H), 7.40 – 7.30 (m, 1H), 7.29 – 7.21 (m, 1H), 3.87 – 3.72 (m, 1H), 3.64 – 3.51 (m, 2H), 3.38 – 3.22 (m, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 206.8, 149.7, 136.0, 129.6, 124.8, 123.0, 122.7, 121.7, 119.1, 115.6, 83.9, 53.3, 28.2, 20.3.

HRMS (ESI$^+$): Calculated for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$: 308.1254, Found: 308.1263.

Cyclopropylidenemethylbenzene (83)



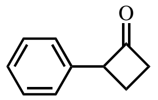
The olefin **83** was prepared following a literature protocol by Liu and coworkers.[99] An oven-dried Schlenk flask under N_2 atmosphere was charged with (3-bromopropyl)-triphenylphosphonium bromide (16.1 g, 34.5 mmol, 1.50 equiv.) and anhydrous THF (0.5 M, 69 mL). A solution of KO*t*Bu (7.74 g, 69.0 mmol, 3.00 equiv.) in THF (1.3 M, 53 mL) was slowly added to the reaction mixture at room temperature. After heating and stirring at 70 °C for 1 h, the reaction mixture was allowed to cool down to room temperature. A solution of benzaldehyde (2.34 mL, 2.44 g, 23.0 mmol, 1.00 equiv.) in THF (2.0 M, 12 mL) was added dropwise to the mixture and the mixture was heated to 70 °C. The reaction mixture was stirred at this temperature for 3 h. The reaction mixture was allowed to cool down to room temperature, followed by filtration of the suspension and elution with Et_2O. The filtrate was concentrated under reduced pressure and the product **83** (1.66 g, 12.7 mmol, 55%) was obtained by distillation in a Kugelrohr short path distillation apparatus (0.7 mbar, 70 °C) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.56 – 7.50 (m, 2H), 7.38 – 7.29 (m, 2H), 7.24 – 7.15 (m, 1H), 6.75 (*app.* p, $J \approx 2.1$ Hz, 1H), 1.47 – 1.38 (m, 2H), 1.21 – 1.13 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 138.4, 128.6, 126.8, 126.7, 124.5, 118.4, 4.4, 0.7.

The obtained spectroscopic data is in agreement to the literature.[100]

2-Phenylcyclobutan-1-one (84)



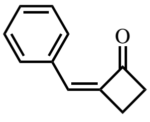
The cyclobutanone **84** was prepared following a literature protocol by Liu and coworkers.[99] An oven-dried round-bottom flask was charged with the olefin **83** (1.56 g, 12.0 mmol, 1.00 equiv.) and CH_2Cl_2 (0.15 M, 80 mL). The mixture was allowed to cool down to 0 °C with an ice/water bath. *m*-Chloroperoxybenzoic acid (*m*CPBA) (2.68 g, 12.0 mmol, 1.00 equiv.) in CH_2Cl_2 (0.38 M, 32 mL) was added dropwise at 0 °C to the reaction mixture and stirred for 1 h. The mixture was allowed to warm to room temperature and diluted with an aqueous saturated solution of $Na_2S_2O_5$. The solution was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phases were washed with an aqueous saturated solution of $NaHCO_3$ (3 × 70 mL), brine, dried over $MgSO_4$ and filtered. The solvent was concentrated under reduced pressure and the obtained product **84** (1.66 g, 12.7 mmol, 55%) was isolated *via* automated flash column chromatography (SiO_2, cyclohexane:EtOAc 90:10, stained with $KMnO_4$) and further purified by distillation in a Kugelrohr short path distillation apparatus (0.7 mbar, 95 °C) resulting in a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.37 – 7.31 (m, 2H), 7.28 – 7.22 (m, 3H), 4.55 (*app.* ddt, $J \approx 10.7, 8.3, 2.7$ Hz, 1H), 3.24 (dddd, $J = 17.7, 10.6, 8.3, 2.5$ Hz, 1H), 3.04 (dddd, $J = 17.6, 9.8, 4.9, 2.6$ Hz, 1H), 2.55 (*app.* dtd, $J \approx 11.2, 10.5, 4.9$ Hz, 1H), 2.25 (*app.* ddt, $J \approx 11.2, 9.8, 8.2$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 208.0, 136.6, 128.8, 127.1, 127.1, 64.7, 45.0, 17.8.

The obtained spectroscopic data is in agreement to the literature.[101]

2-Benzylidenecyclobutan-1-one (85)



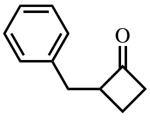
The olefin **85** was prepared following a literature protocol by SONG and coworkers.[102] Under N_2 atmosphere, an oven-dried SCHLENK tube was loaded with $Ca(OH)_2$ (2.10 g, 1.00 mmol, 0.100 equiv.). A solution of anhydrous EtOH (15 mL) solution containing cyclobutanone (2.10 g, 30.0 mmol, 3.00 equiv.) and benzaldehyde (1.0 mL, 1.06 g, 10.0 mmol, 1.00 equiv.) was added. The resulting mixture was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure. The product **85** (687 mg, 4.34 mmol, 43%) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 95:5 to 90:10, stained with $KMnO_4$) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.55 – 7.49 (m, 2H), 7.45 – 7.37 (m, 3H), 7.04 (*app.* t, $J \approx 2.8$ Hz, 1H), 3.21 – 3.10 (m, 2H), 3.06 – 2.94 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 199.8, 146.3, 134.7, 130.3, 130.2, 129.1, 126.7, 45.9, 23.7.

The obtained spectroscopic data is in agreement to the literature.[103]

2-Benzylcyclobutan-1-one (86)



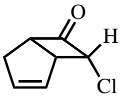
The α-substituted cyclobutanone **86** was prepared following a literature protocol by YU and coworkers.[68] Under N_2 atmosphere, an oven-dried round-bottom flask was charged with Pd/C (220 mg for 5% on activated C, 103 µ, 2.35 mol%.). A solution of the olefin **85** (696 mg, 4.40 mmol, 1.00 equiv.) in anhydrous THF:EtOH (4:1, 35:8.8 mL, 0.1 M) was added. The flask was purged with H_2 and the reaction mixture was stirred for 6 h at room temperature. The separation of the catalyst was achieved by filtration through a pad of CELITE® and elution with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the product **86** (358 mg, 2.23 mmol, 51%) was obtained by automated flash column chromatography (SiO_2, cyclohexane:EtOAc 95:5, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.25 (m, 2H), 7.25 – 7.13 (m, 3H), 3.67 – 3.54 (m, 1H), 3.11 – 2.96 (m, 2H), 2.94 – 2.81 (m, 1H), 2.81 (dd, $J = 14.1, 8.7 Hz$, 1H), 2.23 – 2.09 (m, 1H), 1.75 (*app.* ddt, $J \approx 11.2, 9.7, 7.7$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 211.1, 139.0, 128.9, 128.7, 126.5, 61.4, 44.6, 35.3, 16.8.

The obtained spectroscopic data is in agreement to the literature.[104]

7-*Endo*-chlorobicyclo[3.2.0]hept-2-en-6-one (80)



A round-bottom flask was charged with Zn dust (1.05 g, 16.0 mmol, 4.00 equiv.) and AcOH (13 mL). Under stirring, a solution of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one[105] (**79**) (708 mg, 4.00 mmol, 1.00 equiv.) in AcOH (3.0 mL) was added dropwise. The mixture was heated to 70 °C and stirred at this temperature for 3 h. The mixture was allowed to cool down to room temperature, filtered through a pad of CELITE® and eluted with Et_2O. The solvent was removed under reduced pressure and the residue was redissolved in Et_2O and washed with an aqueous saturated solution of $NaHCO_3$ (3×50 mL) and water (2×50 mL). The organic solvent was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product **80** (258 mg, 1.81 mmol, 45%) was obtained by flash column chromatography (SiO_2, *n*-hexane:Et_2O 80:20, stained with $KMnO_4$) as a yellowish solid.

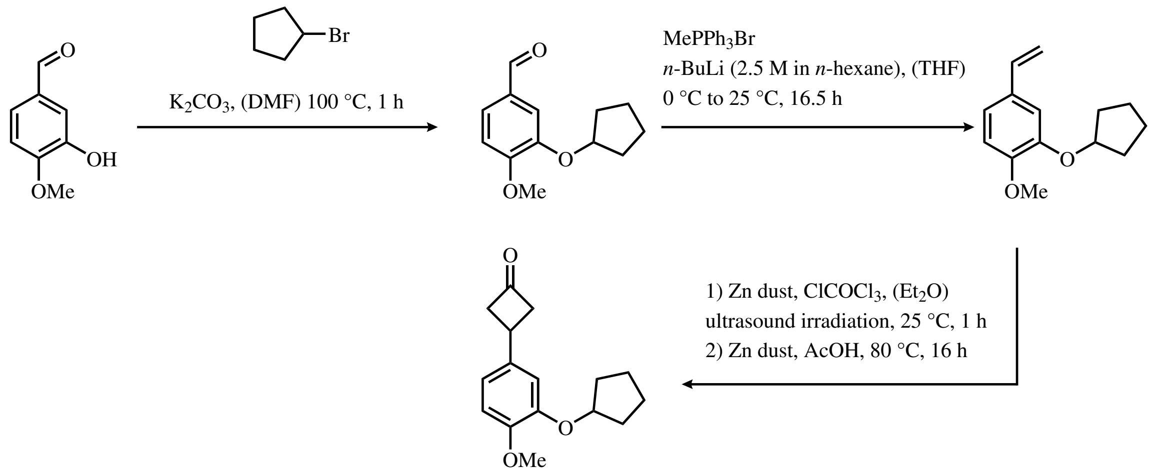
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3573 (br), 2927 (br), 2360 (m), 2328 (w), 1793 (s), 1443 (w), 1350 (m), 1240 (w), 1152 (m), 1023 (m), 736 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.01 – 5.92 (m, 1H), 5.83 – 5.75 (m, 1H), 5.10 (ddd, $J = 8.6, 2.9, 0.9$ Hz, 1H), 3.93 (dddd, $J = 11.2, 6.8, 3.4, 2.0$ Hz, 1H), 3.85 (dddd, $J = 8.4, 7.1, 2.9, 1.1$ Hz, 1H), 2.80 (*app.* dtdd, $J \approx 17.2, 2.8, 2.0, 1.2$ Hz, 1H), 2.53 (*app.* ddq, $J \approx 17.2, 8.7, 2.1$ Hz, 1H).

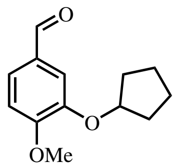
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 205.0, 136.0, 128.5, 65.7, 58.5, 46.2, 35.9.

HRMS (APCI$^+$): Calculated for C_7H_8ClO $[M+H]^+$: 143.0258, Found: 143.0255.
The obtained spectroscopic data is in agreement to the literature.[106]

Synthetic Access to Rolipram Precursor



3-(Cyclopentyloxy)-4-methoxybenzaldehyde (109)



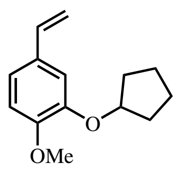
The aldehyde was synthesized in accordance with the literature protocol outlined by WANG and LANGLOIS.[107] A solution of isovanillin **108** (3.80 g, 25.0 mmol, 1.00 equiv.) in DMF (75 mL) was added to a round-bottom flask with K_2CO_3 (10.4 g, 75.0 mmol, 3.00 equiv.) and cyclopentyl bromide (11.1 g, 75.0 mmol, 3.00 equiv.). The mixture was heated to 100 °C and stirred for 1 h. The solvent was removed under reduced pressure. The addition of water (75 mL) allowed for extraction with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **109** (5.03 g, 22.8 mmol, 91%) was obtained by flash column chromatography (SiO_2, *n*-hexane:EtOAc 60:40, stained with KMnO4) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.83 (s, 1H), 7.42 (dd, $J = 8.1, 1.9$ Hz, 1H), 7.39 (d, $J = 1.9$ Hz, 1H), 6.96 (d, $J = 8.1$ Hz, 1H), 4.91 – 4.78 (m, 1H), 3.92 (s, 3H), 2.07 – 1.94 (m, 2H), 1.94 – 1.76 (m, 4H), 1.73 – 1.54 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.2, 155.5, 148.4, 130.1, 126.5, 112.1, 110.9, 80.6, 56.3, 32.9, 24.2.

The obtained spectroscopic data is in agreement to the literature.[107] The reaction was carried out by WALZ.

2-(Cyclopentyloxy)-1-methoxy-4-vinylbenzene (110)



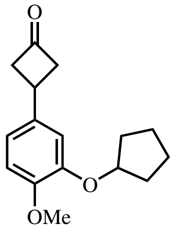
The olefin was synthesized in accordance with the literature protocol outlined by SCHMALZ and coworkers.[108] In an oven-dried SCHLENK flask, triphenyl methyl phosphonium bromide (7.86 g, 22.0 mmol, 1.00 equiv.) was dissolved in anhydrous THF (110 mL) under N_2 atmosphere. The reaction mixture was allowed to cool down to 0 °C with an ice/water bath. *n*-BuLi (2.5 M in *n*-hexane, 8.80 mL, 22.0 mmol, 1.00 equiv.) was added dropwise at 0 °C and stirred at this temperature for further 90 min. Meanwhile, the aldehyde **109** (4.88 g, 22.0 mmol, 1.00 equiv.) was dissolved in anhydrous THF (18 mL) and added to the solution at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 16.5 h. H_2O (20 mL) was added to the mixture. The solvent was removed under reduced pressure and the residue was redissolved with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was redissolved with Et_2O and *n*-hexane was added dropwise until a precipitation was observed. The solid was filtered and the solvent of the filtrate was removed under reduced pressure. The product **110** (4.06 g, 18.6 mmol, 85%) was obtained by flash column chromatography (SiO_2, *n*-hexane:EtOAc 95:5, stained with $KMnO_4$) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.98 (d, $J = 2.0$ Hz, 1H), 6.93 (dd, $J = 8.3, 2.0$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H), 6.64 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.59 (dd, $J = 17.6, 0.9$ Hz, 1H), 5.13 (dd, $J = 10.8, 1.0$ Hz, 1H), 4.84–4.77 (m, 1H), 3.85 (s, 3H), 2.01 − 1.78 (m, 6H), 1.68 − 1.56 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 150.2, 147.8, 136.7, 130.8, 119.5, 112.6, 111.9, 111.8, 80.6, 56.2, 33.0, 24.2.

The obtained spectroscopic data is in agreement to the literature.[109] The reaction was carried out by WALZ.

3-(3-(Cyclopentyloxy)-4-methoxyphenyl)cyclobutan-1-one (107)



Following the general procedure **A** using alkene **110** (1.67 g, 7.70 mmol, 1.00 equiv.), the synthesis of the dichlorinated cyclobutanone was conducted *via* ultrasound irradiation. The dehalogenation was performed following a literature protocol which was previously mentioned by WAHL and coworkers.[110]

In a round-bottom flask, the crude reaction mixture of the [2+2] cycloaddtion was dissolved in AcOH (30 mL). The solution was cooled with a water bath and Zn dust (2.01 g, 40.0 mmol, 30.8 equiv.) was slowly added. The reaction mixture was heated to 80 °C for 16 h. The reaction mixture was allowed to cool down to room temperature and the mixture was filtered through a pad of CELITE® and washed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was redissolved in Et_2O (20 mL), and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (4×50 mL), H_2O (2×100 mL) and brine (2×50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The desired product **107** (226 mg, 868 µmol, 11%) was obtained by flash column chromatography (SiO_2, *n*-hexane:EtOAc 80:20, stained with $KMnO_4$) as a yellowish oil.[1]

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2961 (br), 1783 (s), 1513 (s), 1386 (m), 1259 (m), 1234 (m), 1164 (w), 1137 (w), 1008 (w), 805 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.86 – 6.81 (m, 2H), 6.81 (s, 1H), 4.78 (tt, $J = 5.7, 3.6$ Hz, 1H), 3.84 (s, 3H), 3.69 – 3.54 (m, 1H), 3.53 – 3.40 (m, 2H), 3.27 – 3.14 (m, 2H), 2.02 – 1.88 (m, 4H), 1.88 – 1.75 (m, 2H), 1.70 – 1.53 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 207.3, 149.0, 147.9, 136.2, 118.5, 113.9, 112.2, 80.7, 56.3, 54.9, 33.0, 28.2, 24.2.

HRMS (ESI$^+$): Calculated for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485, Found: 261.1487.

The reaction was carried out by WALZ.

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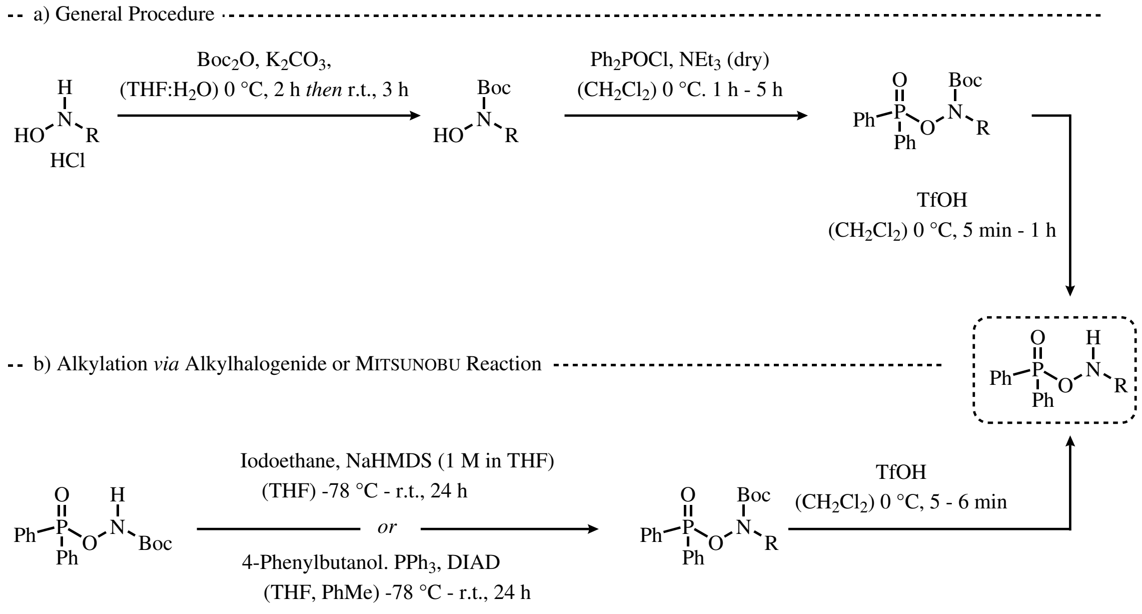
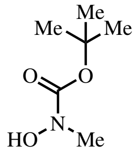
[1] An observation of overreduction, leading from cyclobutanone **107** to the ring-opened 1-(3-(cyclopentyloxy)-4-methoxyphenyl)pentan-3-on **112** was noted. The separation of the product **107** from this accompanying side product **112** proved challenging.

Synthetic Access to *N*-substituted Hydroxylamines



tert-Butyl hydroxy(methyl)carbamate (98b)



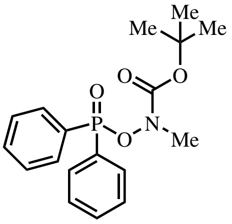
The Boc protected hydroxylamine **98b** was prepared following a literature protocol by TOMKINSON and coworkers.[111] A round-bottom flask was charged with *N*-methyl hydroxylamine hydrochloride (**97b**) (835 mg, 10.0 mmol, 2.00 equiv.) and the substrate was dissolved in a mixture of THF:H_2O (4 mL). The solution was cooled down to 0 °C with an ice/water bath. K_2CO_3 (691 mg, 5.00 mmol, 1.00 equiv.) was added to the solution. A solution of Boc_2O (2.53 mL, 2.40 g, 11.0 mmol, 2.20 equiv.) in THF (3 mL) was added dropwise to the mixture and resulting reaction mixture was stirred at 0 °C for 2 h. The ice/water bath was removed and the mixture was stirred at room temperature for 3 h. The solvent was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with H_2O (3 × 30 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **98b** (1.14 g, 7.76 mmol, 78%) was obtained by distillation in a Kugelrohr short path distillation apparatus (0.40 mbar, 84 °C) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.11 (br s, 1H), 3.15 (s, 3H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.8, 82.0, 37.9, 28.4.

The obtained spectroscopic data is in agreement to the literature.[112]

tert-Butyl ((diphenylphosphoryl)oxy)(methyl)carbamate (99b)



The product **99b** was prepared following a modified literature protocol by HUGHES and coworkers.[70] Under N_2 atmosphere, an oven-dried SCHLENK flask was charged with Boc protected hydroxylamine **98b** (162 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (1.5 mL). The mixture was cooled down to −8 °C using an ice/acetone bath. Once the solid has been dissolved, NEt_3 (173 µL, 126 mg, 1.25 mmol, 1.25 equiv.) was added dropwise over 10 min. In a separate SCHLENK flask, diphenylphosphinic chloride (contains 95% of the actual substrate, 249 mg, 1.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (2.0 mL) under N_2 atmosphere. The solution was then added dropwise to the hydroxylamine solution over 30 min while maintaining the temperature below 0 °C. The reaction was stirred at this temperature for 1 h. The mixture was allowed to warm above 10 °C and an aqueous solution of citric acid (5 wt%, 0.5 mL) was added over 5 min. The phases were separated and the solvent was concentrated under reduced pressure until the product precipitated. Following the addition of *n*-hexane (50 mL) to the slurry and solvent removal under reduced pressure, another portion of *n*-hexane (50 mL) was added and concentrated until approximate 20 mL of the solvent remained. The resulting slurry was stirred at room temperature for 12 h. The solids were collected and washed with a mixture of *n*-hexane:CH_2Cl_2 (4:1). The filtrate was concentrated to obtain the desired product **99b** (340 mg, 980 µmol, 98%) as a colorless solid without further purification.

M.P.: 80 – 81 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2980 (br), 2360 (m), 1719 (s), 1440 (m), 1369 (m), 1334 (m), 1237 (s), 1129 (s), 998 (w), 873 (m), 730 (s), 695 (s).

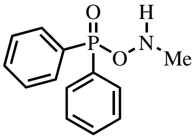
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.02 – 7.86 (m, 4H), 7.59 – 7.51 (m, 2H), 7.51 – 7.41 (m, 4H), 3.39 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.4 (d, $J = 4.0$ Hz), 132.8 (d, $J = 2.8$ Hz), 132.6 (d, $J = 10.2$ Hz), 129.3 (d, $J = 134.8$ Hz), 128.5 (d, $J = 13.2$ Hz), 82.9, 42.1, 28.0.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 38.8.

HRMS (ESI$^+$): Calculated for $C_{18}H_{22}NO_4PNa$ [M+Na]$^+$: 370.1178, Found: 370.1169.

((Methylamino)oxy)diphenylphosphine oxide (33b)



A round-bottom flask was charged with *tert*-butyl ((diphenylphosphoryl)oxy)(methyl)-carbamate **99b** (1.39 g, 4.00 mmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (80 mL). The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (884 µL, 1.50 g, 10.0 mmol, 2.50 equiv.) was added dropwise to the solution. The reaction was allowed to warm to room temperature and the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$ (50 mL) and H_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **33b** (780 mg, 3.16 mmol, 79%) was obtained by recrystallization (CH_2Cl_2:*n*-hexane) as a colorless solid.

M.P.: 132 – 133 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3218 (s), 2362 (s), 2341 (s), 1444 (m), 1128 (s), 1113 (m), 1017 (m), 753 (s), 728 (s), 696 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.91 – 7.79 (m, 4H), 7.57 – 7.50 (m, 2H), 7.49 – 7.37 (m, 4H), 2.89 (s, 3H).

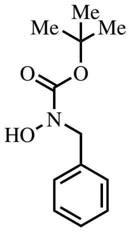
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 132.4 (d, $J = 2.6$ Hz), 132.0 (d, $J = 9.9$ Hz), 130.8 (d, $J = 135.6$ Hz), 128.6 (d, $J = 13.1$ Hz), 41.5 (d, $J = 4.7$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 35.6.

HRMS (ESI$^+$): Calculated for $C_{13}H_{15}NO_2P$ $[M+H]^+$: 248.0835, Found: 248.0835.

The obtained spectroscopic data is in agreement to the literature.[113]

tert-Butyl benzyl(hydroxy)carbamate (98c)



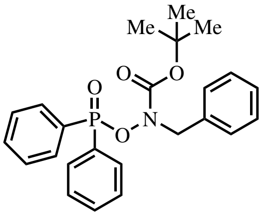
The Boc-protected hydroxylamine **98c** was prepared following a literature protocol by TOMKINSON and coworkers.[111] A round-bottom flask was charged with *N*-benzylhydroxylamine hydrochloride **97c** (3.19 g, 20.0 mmol, 2.00 equiv.) and the substrate was dissolved in a mixture of THF:H_2O (8 mL). The solution was cooled down to 0 °C with an ice/water bath. K_2CO_3 (1.38 g, 10.0 mmol, 1.00 equiv.) was added to the solution. A solution of Boc_2O (contains 95% of the actual substrate, 5.32 mL, 5.05 g, 22.0 mmol, 2.20 equiv.) in THF (6.0 mL) was added dropwise to the mixture and the mixture was stirred at 0 °C for 2 h. The ice/water bath was removed and the mixture was stirred at room temperature for 3 h. The solvent was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with H_2O (3 × 30 mL) and brine. The organic phase was combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **98c** (3.47 g, 15.6 mmol, 78%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 90:10 to 60:40, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 − 7.27 (m, 5H), 6.85 (br s, 1H), 4.65 (s, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.0, 136.7, 128.6, 128.3, 127.7, 82.3, 54.3, 28.4.

The obtained spectroscopic data is in agreement to the literature.[114]

tert-Butyl benzyl((diphenylphosphoryl)oxy)carbamate (99c)



The product **99c** was prepared following a modified literature protocol by HUGHES and coworkers.[70] To an oven-dried SCHLENK flask under N_2 atmosphere, hydroxylamine **98c** (2.46 g, 11.0 mmol, 1.10 equiv.) and CH_2Cl_2 (15 mL) were added. The mixture was cooled down to −8 °C with an ice/acetone bath. When the solid has been completely dissolved, anhydrous NEt_3 (1.73 mL, 1.26 g, 12.5 mmol, 1.25 equiv.) was added dropwise over 10 min. To a separate SCHLENK flask, diphenylphosphinic chloride (1.91 mL, 2.37 g, 10.0 mmol, 1.00 equiv.) and CH_2Cl_2 (20 mL) were added under N_2 atmosphere. The solution was then added dropwise to the hydroxylamine solution over 30 min while the temperature was kept below 0 °C. The reaction was stirred for 5 h. The mixture was allowed to warm above 10 °C and an aqueous solution of citric acid (5 wt%, 5 mL) was added over 5 min. The phases were separated and the solvent was concentrated under reduced pressure until the product starts to precipitate. *n*-Hexane (50 mL) was added to the slurry and the solvent was removed under reduced pressure. The desired product **99c** (3.68 g, 8.70 mmol, 87%) was obtained by flash column chromatography (SiO_2, cyclohexane:EtOAc 60:40, stained with $KMnO_4$) and recrystallization (*n*-hexane) as a colorless solid.

M.P.: 79 – 81 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2976 (br), 2361 (m), 1743 (m), 1717 (m), 1440 (m), 1370 (m), 1232 (m), 1155 (m), 1130 (m), 1057 (w), 878 (m), 697 (s), 604 (s).

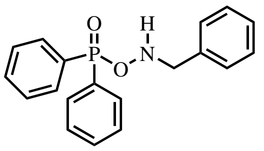
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.97 – 7.88 (m, 4H), 7.58 – 7.51 (m, 2H), 7.48 – 7.41 (m, 4H), 7.41 – 7.34 (m, 2H), 7.34 – 7.23 (m, 3H), 4.93 (s, 2H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 156.3 (d, $J = 3.8$ Hz), 135.8, 132.8 (d, $J = 2.9$ Hz), 132.6 (d, $J = 10.2$ Hz), 129.4 (d, $J = 134.6$ Hz), 129.2, 128.5 (d, $J = 3.3$ Hz), 128.4, 127.9, 83.0, 57.9, 28.0.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 39.4.

HRMS (ESI$^+$): Calculated for $C_{24}H_{26}NO_4PNa$ $[M+Na]^+$: 446.1491, Found: 446.1488.

((Benzylamino)oxy)diphenylphosphine oxide (33c)



A round-bottom flask was charged with *tert*-butyl benzyl((diphenylphosphoryl)oxy)-carbamate **99c** (1.69 g, 4.00 mmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (80 mL). The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (708 µL, 1.20 g, 10.0 mmol, 2.50 equiv.) was added dropwise to the solution. The reaction was allowed to warm to room temperature and the mixture was stirred for 5 min. The mixture was diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$ (50 mL) and H_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **33c** (1.06 g, 3.28 mmol, 82%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 20:80, stained with $KMnO_4$) and recrystallization (CH_2Cl_2:*n*-hexane) as a colorless solid.

M.P.: 99 – 102 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2924 (br), 2363 (s), 2340 (m), 1440 (m), 1217 (m), 1129 (m), 1029 (w), 859 (m), 747 (m), 728 (m), 698 (m), 612 (s), 590 (s).

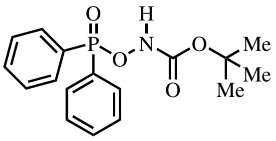
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.82 – 7.73 (m, 4H), 7.55 – 7.48 (m, 2H), 7.47 – 7.37 (m, 4H), 7.32 – 7.26 (m, 3H), 7.26 – 7.19 (m, 2H), 4.19 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 135.8, 132.3 (d, $J = 2.8$ Hz), 132.0 (d, $J = 9.8$ Hz), 130.7 (d, $J = 135.5$ Hz), 129.4, 128.6 (d, $J = 4.7$ Hz), 128.5, 128.1, 58.2 (d, $J = 4.9$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 35.9.

HRMS (ESI$^+$): Calculated for $C_{19}H_{18}NO_2PNa$ $[M+Na]^+$: 346.0967, Found: 346.0967.

tert-Butyl ((diphenylphosphoryl)oxy)carbamate (99a)



The product **99a** was prepared following a modified literature protocol by Hughes and coworkers.[70] An oven-dried and N_2 filled Schlenk flask was charged with *tert*-butyl-*N*-hydroxy carbamate (1.46 g, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (15 mL). The solution was cooled down to −8 °C with an ice/acetone bath. When the solid has been dissolved, NEt_3 (1.74 mL, 1.27 g, 12.5 mmol, 1.25 equiv.) was added dropwise over 10 min. To a separate Schlenk flask, diphenylphosphinic chloride (1.91 mL, 2.37 g, 10.0 mmol, 1.00 equiv.) and CH_2Cl_2 (20 mL) were added under N_2 atmosphere. The solution was then added dropwise to the hydroxylamine solution over 30 min while the temperature was kept below 0 °C. After 1 h of stirring, the mixture was allowed to warm above 10 °C and an aqueous solution of citric acid (5 wt%, 5.0 mL) was added over 5 min. The phases were separated and the solvent was concentrated under reduced pressure until the product precipitated. Following the addition of *n*-hexane (50 mL) to the slurry and solvent removal under reduced pressure the desired product **99a** (3.11 g, 9.34 mmol, 93%) was obtained by recrystallization (CH_2Cl_2, *n*-hexane) as colorless solid.

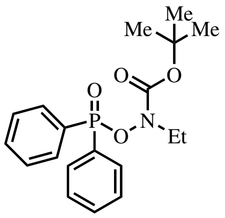
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 9.18 (br s, 1H), 8.01 – 7.90 (m, 4H), 7.57 – 7.50 (m, 2H), 7.48 – 7.40 (m, 4H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 156.2 (d, $J = 5.4$ Hz), 132.8 (d, $J = 2.8$ Hz), 132.5 (d, $J = 10.2$ Hz), 128.9 (d, $J = 135.8$ Hz), 128.5 (d, $J = 13.4$ Hz), 82.8, 28.1.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 40.4.

The obtained spectroscopic data is in agreement to the literature.[70]

tert-Butyl ((diphenylphosphoryl)oxy)(ethyl)carbamate (99d)



To an oven-dried Schlenk flask under N_2 atmosphere, *tert*-butyl ((diphenylphosphoryl)-oxy)carbamate **99a** (333 mg, 1.00 mmol, 1.00 equiv.) was added and dissolved in anhydrous THF (5 mL). The mixture was cooled down to −78 °C using a dry ice/acetone bath. Sodium bis(trimethylsilyl)amide (NaHMDS) (1 M in THF, 1.50 mL, 275 mg, 1.50 mmol, 1.50 equiv.) was added dropwise and the mixture was stirred at −78 °C for 30 min. A solution of iodoethane (137 µL, 265 mg, 1.70 mmol, 1.70 equiv.) in anhydrous THF (1.5 mL) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was slowly allowed to warm to room temperature and the mixture was stirred at this temperature for 24 h. The reaction was quenched by adding an aqueous saturated solution NH_4Cl. The mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The desired product **99d** (113 mg, 313 µmol, 31%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40, stained with $KMnO_4$) as a yellowish oil.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2977 (br), 2363 (m), 1714 (m), 1440 (m), 1369 (m), 1241 (m), 1151 (m), 1129 (m), 1016 (w), 863 (m), 731 (s), 697 (s).

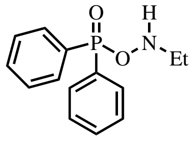
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.00 – 7.89 (m, 4H), 7.59 – 7.50 (m, 2H), 7.50 – 7.39 (m, 4H), 3.80 (q, $J = 6.9$ Hz, 2H), 1.32 (s, 9H), 1.22 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 156.8 (d, $J = 4.0$ Hz), 132.7 (d, $J = 2.9$ Hz), 132.6 (d, $J = 10.2$ Hz), 129.4 (d, $J = 135.1$ Hz) 128.4 (d, $J = 13.3$ Hz), 82.7, 49.8, 28.0, 11.0.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 38.8.

HRMS (ESI$^+$): Calculated for $C_{19}H_{24}NO_4PNa$ $[M+Na]^+$: 384.1335, Found: 384.1335.

((Ethylamino)oxy)diphenylphosphine oxide (33d)



A round-bottom flask was charged with *tert*-butyl ((diphenylphosphoryl)oxy) (ethyl)carbamate **99d** (289 mg, 800 µmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (16 mL). The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (142 µL, 240 mg, 1.60 mmol, 2.00 equiv.) was added dropwise to the solution. The reaction was allowed to warm to room temperature and the mixture was stirred for 6 min. The mixture was diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$ (50 mL) and H_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **33d** (160 mg, 612 µmol, 76%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 20:80, stained with $KMnO_4$) as a colorless solid.

M.P.: 107 – 109 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3236 (br), 2912 (br), 2363 (m), 1439 (m), 1224 (m), 1130 (m), 916 (w), 861 (m), 727 (s), 694 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.92 – 7.78 (m, 4H), 7.57 – 7.49 (m, 2H), 7.49 – 7.41 (m, 4H), 6.04 (br s, 1H), 3.15 (q, $J = 7.1$ Hz, 2H), 1.10 (t, $J = 7.1$ Hz, 3H).

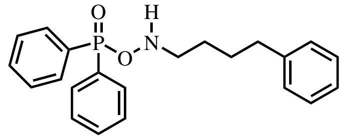
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 132.3 (d, $J = 2.6$ Hz), 132.0 (d, $J = 9.9$ Hz), 130.9 (d, $J = 135.4$ Hz), 128.6 (d, $J = 13.1$ Hz), 48.5 (d, $J = 4.7$ Hz), 12.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 35.3.

HRMS (ESI$^+$): Calculated for $C_{14}H_{16}NO_2PNa$ $[M+Na]^+$: 284.0811, Found: 284.0813.

The obtained spectroscopic data is in agreement to the literature.[113]

Diphenyl(((4-phenylbutyl)amino)oxy)phosphine oxide (33e)



A round-bottom flask was charged with 4-phenylbutanol (191 µL, 188 mg, 1.25 mmol, 1.25 equiv.) and the solution was cooled down to 0 °C with an ice/water bath. THF (1.3 mL) was added followed by *tert*-butyl ((diphenylphosphoryl)oxy)carbamate **99a** (333 mg, 1.00 mmol, 1.00 equiv.), triphenylphosphine (656 mg, 2.50 mmol, 2.50 equiv.) and toluene (3.8 mL). Diisopropyl azodicarboxylate (1.9 M solution in toluene, 1.12 mL, 430 mg, 2.13 mmol, 2.13 equiv.) was slowly added to the solution and the mixture was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and the mixture was stirred at this temperature for 1 h. The solvent was removed under reduced pressure. A mixture of the target product **99e** and isopropyl 2-(isobutyryloxy)hydrazine-1-carboxylate (mixture contains 48% of the target product, 304 mg, 652 mmol, 65%) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 80:20 to 40:60, stained with $KMnO_4$). The mixture (contains of the diphosphine oxide 233 mg, 500 µmol, 1.00 equiv.) and CH_2Cl_2 (10 mL) was added to a round-bottom flask. The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (88.4 µL, 150 mg, 1.00 mmol, 2.00 equiv.) was added dropwise to the solution. The reaction was allowed to warm to room temperature and the mixture was stirred for 5 min. The mixture was diluted with CH_2Cl_2 and washed with H_2O (2 × 50 mL), aqueous saturated solution of $NaHCO_3$ (50 mL) and H_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **33e** (158 mg, 433 mmol, 87%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 40:60, stained with $KMnO_4$) as a colorless solid.

M.P.: 104 – 106 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3224 (br), 2948 (br), 2362 (m), 1440 (m), 1223 (s), 1130 (s), 876 (s), 755 (m), 727 (s), 696 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.89 – 7.77 (m, 4H), 7.57 – 7.49 (m, 2H), 7.49 – 7.40 (m, 4H), 7.31 – 7.22 (m, 2H), 7.21 – 7.14 (m, 1H), 7.14 – 7.09 (m, 2H), 6.13 (br s, 1H), 3.11 (t, $J = 6.5$ Hz, 2H), 2.55 (t, $J = 7.1$ Hz, 2H), 1.65 – 1.48 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 142.2, 132.3 (d, $J = 2.9$ Hz), 132.0 (d, $J = 9.8$ Hz), 130.9 (d, $J = 135.5$ Hz), 128.5 (d, $J = 21.4$ Hz), 128.5, 126.7 (d, $J = 286.8$ Hz), 125.9, 53.7 (d, $J = 4.7$ Hz), 35.6, 28.7, 26.4.

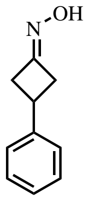
^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 35.4.

HRMS (ESI$^+$): Calculated for $C_{22}H_{24}NO_2PNa$ $[M+Na]^+$: 388.1437, Found: 388.1436.

7.2.2 Mechanistic Analysis

Synthesis, Isolation and Characterization of Oxime Ester Cyclobutanone 92b

3-Phenylcyclobutan-1-one oxime (96)



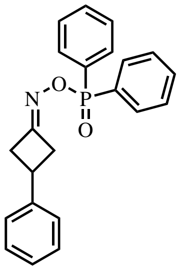
The oxime **96** was prepared following a modified literature protocol by UEMURA and coworkers.[115] A round-bottom flask was charged with hydroxylamine hydrochloride (167 mg, 2.40 mmol, 1.20 equiv.) and NaOAc (246 mg, 3.00 mmol, 1.50 equiv.) in EtOH (1.4 mL) and H_2O (0.6 mL). 3-Phenylcyclobutan-1-one (**56**) (292 mg, 2.00 mmol, 1.00 equiv.) was added dropwise and the reaction mixture was stirred at 100 °C for 15 h. The solvent was removed under reduced pressure and the residue was diluted with H_2O. The mixture was extracted with Et_2O (30 mL). The organic phase was washed with H_2O (30 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The oxime **96** (297 mg, 1.84 mmol, 92%) was obtained by automated flash column chromatography (SiO_2, cyclohexane:EtOAc 80:20, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.29 (br s, 1H), 7.39 – 7.31 (m, 2H), 7.31 – 7.20 (m, 3H), 3.69 – 3.56 (m, 1H), 3.47 (*app.* ddt, $J \approx 17.2, 9.2, 3.1$ Hz, 1H), 3.37 (*app.* ddt, $J \approx 16.4, 9.0, 3.1$ Hz, 1H), 3.06 (dddd, $J = 16.4, 7.3, 3.2, 1.5$ Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 156.7, 144.1, 128.7, 126.7, 126.6, 39.5, 38.3, 32.9.

The obtained spectroscopic data is in agreement to the literature.[116]

Diphenyl(((3-phenylcyclobutylidene)amino)oxy)phosphine oxide (92b)



An oven-dried tube was charged with oxime **96** (210 mg, 1.30 mmol, 1.00 equiv.), NEt_3 (360 µL, 263 mg, 2.60 mmol, 2.00 equiv.) and CH_2Cl_2 (3.0 mL). The mixture was allowed to cool down to 0 °C with an ice/water bath. Diphenylphosphinic chloride (contains 95% of the actual substrate, 453 mg, 1.82 mmol, 1.40 equiv.) in CH_2Cl_2 (0.6 mL) was added and the mixture was stirred at 0 °C for 4 h. H_2O was added and the mixture was diluted with CH_2Cl_2 (20 mL). The phases were separated and the organic layer was washed with H_2O (3×50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The oxime ester **92b** (434 mg, 1.20 mmol, 92%) was obtained by flash column chromatography (SiO_2, PE:EtOAc 20:80, stained with $KMnO_4$) as a colorless solid.

M.P.: 111 – 113 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3061 (br), 2361 (m), 2336 (m), 1439 (m), 1229 (m), 1129 (m), 875 (s), 813 (w), 730 (s), 695 (s).

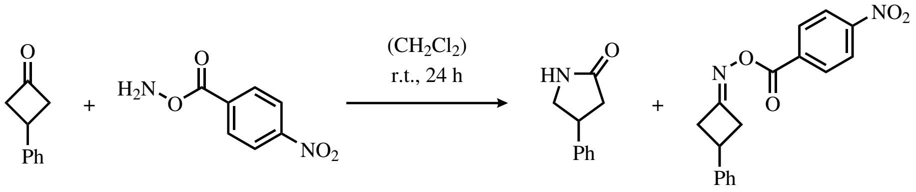
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.95 – 7.80 (m, 4H), 7.58 – 7.51 (m, 2H), 7.51 – 7.41 (m, 4H), 7.39 – 7.30 (m, 2H), 7.29 – 7.20 (m, 3H), 3.71 – 3.53 (m, 2H), 3.50 – 3.35 (m, 1H), 3.26 – 3.02 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 166.4 (d, $J = 12.5$ Hz), 143.2, 132.4 (d, $J = 2.8$ Hz), 132.2 (d, $J = 20.9$ Hz), 130.76 (dd, $J = 135.9, 7.5$ Hz), 130.44 (d, $J = 349.5$ Hz), 128.7 (d, $J = 25.4$ Hz), 127.0, 126.5, 39.6 (d, $J = 21.7$ Hz), 32.6.

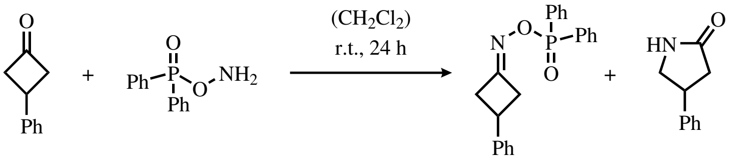
^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 35.2.

HRMS (ESI$^+$): Calculated for $C_{22}H_{20}NO_2PNa$ $[M+Na]^+$: 384.1124, Found: 384.1123.

Initial Findings



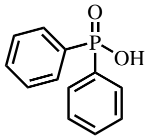
An oven-dried tube was charged with 3-phenylcyclobutan-1-one (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) and *O*-(4-nitrobenzoyl)hydroxylamine (**34**) (18.2 mg, 100 µmol, 1.00 equiv.). The mixture was dissolved in CH_2Cl_2 (1.0 mL) and was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^{1}H NMR analysis revealed the presence of oxime ester **92a** (73%) alongside the observed formation of the desired product (12%).



An oven-dried tube was charged with 3-phenylcyclobutan-1-one (**56**) (29.2 mg, 100 µmol, 1.00 equiv.) and *O*-(diphenylphosphinyl)hydroxylamine (DPPH, **33a**) (23.3 mg, 100 µmol, 1.00 equiv.). The mixture was dissolved in CH_2Cl_2 (1.0 mL) and was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^{1}H NMR analysis revealed the presence of oxime ester **92b** (28%) alongside the observed formation of the desired product **88b** (65%).

Control Experiments for BECKMANN Rearrangement

Diphenylphosphinic acid (93)



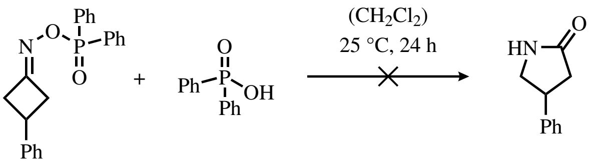
The phosphinic acid **93** was prepared following a literature protocol by MOHAMMADPANAH and coworkers.[117] A round-bottom flask was charged with diphenylphosphinic chloride (237 mg, 1.00 mmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (5 mL). H_2O (18.0 µL, 18.0 mg, 1.00 mmol, 1.00 equiv.) was added and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the solid was washed with cold H_2O. After the product was dried under high vacuum, the product **93** (152 mg, 696 µmol, 70%) was obtained as a colorless solid without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.19 (br s, 1H), 7.81 – 7.63 (m, 4H), 7.51 – 7.40 (m, 2H), 7.40 – 7.28 (m, 4H).

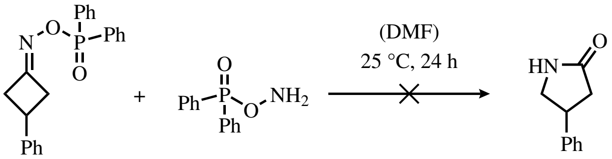
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 132.8 (d, $J = 140.2$ Hz), 132.0 (d, $J = 2.9$ Hz), 131.4 (d, $J = 10.6$ Hz), 128.5 (d, $J = 13.5$ Hz).

^{31}P NMR (162 MHz, CDCl$_3$): δ (ppm) = 33.9.

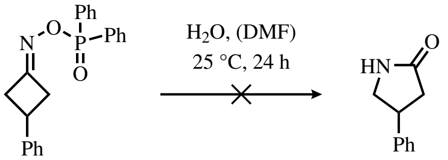
The obtained spectroscopic data is in agreement to the literature.[118]



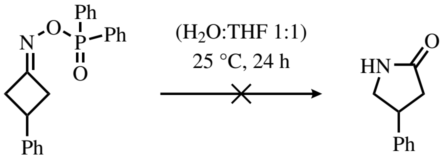
In an oven-dried tube oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.), diphenylphosphinic acid **93** (21.8 mg, 100 µmol, 1.00 equiv.) and CH$_2$Cl$_2$ (1.0 mL) were added. The resulting reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^{1}H NMR analysis revealed the presence of oxime ester **92b** (98%) while indicating an absence of product formation.



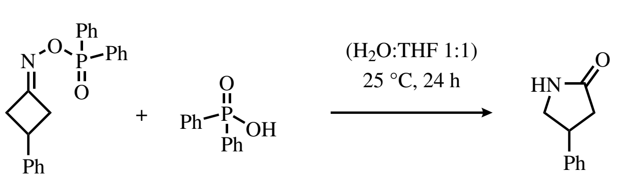
In an oven-dried tube, oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.), DPPH (**33a**) (25.7 mg, 110 µmol, 1.10 equiv.) and DMF (1.0 mL) were added. The resulting reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^{1}H NMR analysis revealed the presence of oxime ester **92b** (87%) while indicating an absence of product formation.



In an oven-dried tube, oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.) was dissolved in DMF (0.5 mL). H_2O (1.8 mg, 100 µmol, 1.00 equiv.) and DMF (0.5 mL) were added to the reaction mixture, which was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^1H NMR experiment using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^1H NMR analysis revealed the presence of oxime ester **92b** (93%) while indicating an absence of product formation.

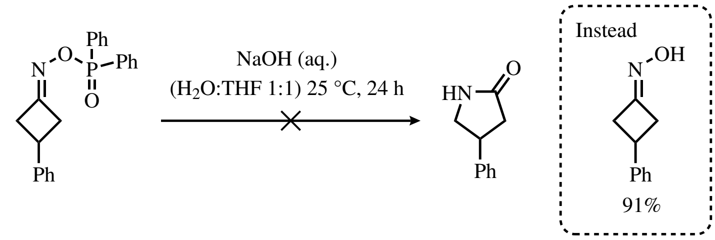


In an oven-dried tube, oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.) was dissolved in H_2O:THF (1:1, 1.0 mL). The mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The NMR yield of the crude reaction mixture was determined using ^1H NMR analysis with dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^1H NMR analysis revealed the presence of oxime ester **92b** (97%) while indicating an absence of product formation.



In an oven-dried tube, oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.) and diphenylphosphinic acid (**93**) (21.8 mg, 100 µmol, 1.00 equiv.) were dissolved in H_2O:THF (1:1, 1.0 mL).

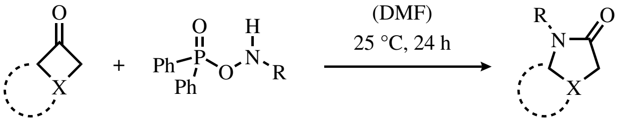
The mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The NMR yield of the crude reaction mixture was determined using ^1H NMR analysis with dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^1H NMR analysis revealed the presence of oxime ester **92b** (88%) alongside the observed formation of the desired product (5%).



In an oven-dried tube, oxime ester **92b** (36.1 mg, 100 µmol, 1.00 equiv.) was dissolved in H_2O:THF (1:1, 1.0 mL). An aqueous solution of NaOH (1 M, 1.0 mL, 40.0 mg, 1.00 mmol, 10.0 equiv.) was added to the reaction mixture and the mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The NMR yield of the crude reaction mixture was determined using ^1H NMR analysis with dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The ^1H NMR analysis revealed the presence of 3-phenylcyclobutan-1-one oxime (**96**) (91%) while indicating an absence of product formation.

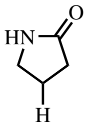
7.2.3 Substrate Scope

General Procedure B for the Ring-Expansion of Cyclobutanones to γ-Lactams



An oven-dried tube was charged with aminating agent **33** (550 µmol, 1.10 equiv.) and suspended in DMF (1.5 mL, 0.33 M). The corresponding cyclobutanone **100** (500 µmol, 1.00 equiv.) was dissolved in DMF (1.0 mL, 0.50 M) and added to the mixture. The resulting reaction mixture was stirred at room temperature for 24 h. The solvent was concentrated under reduced pressure and the NMR yield of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (35.0 µL, 86.9 mg, 500 µmol) as the internal standard. The product was purified by silica gel column chromatography.

Pyrrolidin-2-one (88a)



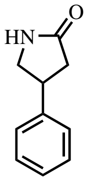
Following the general procedure **B** using cyclobutanone (**44**) (35.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88a** (28.0 mg, 329 µmol, 66%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 90:10, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.65 (br s, 1H), 3.38 (t, J = 7.0 Hz, 2H), 2.28 (t, J = 7.8 Hz, 2H), 2.16 – 2.04 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 179.4, 42.4, 30.2, 20.9.

The obtained spectroscopic data is in agreement to the literature.[119]

4-Phenylpyrrolidin-2-one (88b)



Following the general procedure **B** using 3-phenylcyclobutan-1-one (**56**) (73.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88b** (69.9 mg, 434 µmol, 87%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.39 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 6.70

(br s, 1H), 3.82 – 3.74 (m, 1H), 3.74 – 3.62 (m, 1H), 3.41 (dd, $J = 9.3, 7.2\,\mathrm{Hz}$, 1H), 2.73 (dd, $J = 16.9, 8.8\,\mathrm{Hz}$, 1H), 2.51 (dd, $J = 16.9, 8.8\,\mathrm{Hz}$, 1H).

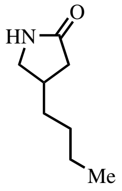
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 177.9, 142.2, 129.0, 127.2, 126.9, 49.7, 40.4, 38.1.

The obtained spectroscopic data is in agreement to the literature.[120]

Gram Scale Synthesis:

3-Phenylcyclobutan-1-one **56** (1.46 g, 10.0 mmol, 1.00 equiv.) and DPPH (**33a**) (2.57 g, 11.0 µmol, 1.10 equiv.) were added and described as above. Separation by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) provided product **88b** (1.30 g, 8.09 mmol, 81%) as a colorless solid.

4-Butylpyrrolidin-2-one (88c)



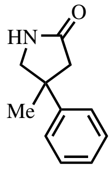
Following the general procedure **B** using 3-butylcyclobutan-1-one (**100c**) (63.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88c** (51.8 mg, 367 µmol, 73%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.50 (br s, 1H), 3.47 (dd, $J = 9.4, 7.4\,\mathrm{Hz}$, 1H), 2.99 (dd, $J = 9.5, 6.6\,\mathrm{Hz}$, 1H), 2.49 – 2.30 (m, 2H), 2.06 – 1.89 (m, 1H), 1.44 (q, $J = 7.0\,\mathrm{Hz}$, 2H), 1.36 – 1.19 (m, 4H), 0.88 (t, $J = 6.9\,\mathrm{Hz}$, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 178.8, 48.3, 37.0, 35.1, 34.4, 29.8, 22.7, 14.1.

The obtained spectroscopic data is in agreement to the literature.[121]

4-Methyl-4-phenylpyrrolidin-2-one (88d)



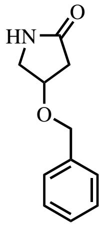
Following the general procedure **B** using 3-methyl-3-phenylcyclobutan-1-one (**100d**) (80.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88d** (63.8 mg, 364 µmol, 73%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.39 – 7.30 (m, 2H), 7.28 – 7.19 (m, 3H), 6.66 (br s, 1H), 3.68 (d, $J = 9.4\,\mathrm{Hz}$, 1H), 3.50 (dd, $J = 9.4, 1.4\,\mathrm{Hz}$, 1H), 2.79 (d, $J = 16.3\,\mathrm{Hz}$, 1H), 2.46 (d, $J = 16.3$ Hz, 1H), 1.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 177.6, 147.1, 128.9, 126.7, 125.4, 54.9, 44.4, 43.5, 29.9.

The obtained spectroscopic data is in agreement to the literature.[122]

4-(Benzyloxy)pyrrolidin-2-one (88e)



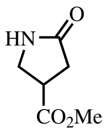
Following the general procedure **B** using 3-(benzyloxy)cyclobutan-1-one (**100e**) (88.1 mg, 500 mmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 μmol, 1.10 equiv.), the product **88e** (76.3 mg, 400 μmol, 80%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.27 (m, 5H), 6.48 (br s, 1H), 4.59 – 4.44 (m, 2H), 4.38 – 4.27 (m, 1H), 3.61 (dd, $J = 10.5, 6.2$ Hz, 1H), 3.43 (dd, $J = 10.6, 2.2$ Hz, 1H), 2.57 (dd, $J = 17.3, 6.9$ Hz, 1H), 2.45 (dd, $J = 17.3, 3.8$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 176.3, 137.6, 128.7, 128.1, 127.9, 73.9, 71.2, 48.8, 37.3.

The obtained spectroscopic data is in agreement to the literature.[123]

Methyl 5-oxopyrrolidine-3-carboxylate (88f)



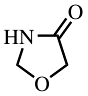
Following the general procedure **B** using 3-oxocyclobutane-1-carboxylate (**100f**) (64.1 mg, 500 μmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 μmol, 1.10 equiv.), the product **88f** (58.1 mg, 406 μmol, 81%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.86 (br s, 1H), 3.73 (s, 3H), 3.65 – 3.56 (m, 2H), 3.40 – 3.26 (m, 1H), 2.65 (dd, $J = 17.2, 7.7$ Hz, 1H), 2.55 (dd, $J = 17.2, 9.8$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 176.6, 173.2, 52.6, 44.5, 38.9, 33.2.

The obtained spectroscopic data is in agreement to the literature.[124]

Oxazolidin-4-one (88g)



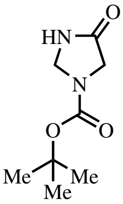
Following the general procedure **B** using oxetan-3-one (**100g**) (36.0 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88g** (37.3 mg, 428 µmol, 86%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 5.07 (*app.* t, $J \approx 1.6$ Hz, 1H), 4.85 (s, 1H), 4.13 (*app.* t, $J \approx 1.6$ Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD): δ (ppm) = 175.8, 79.8, 67.7.

The obtained spectroscopic data is in agreement to the literature.[119]

tert-Butyl 4-oxoimidazolidine-1-carboxylate (88h)



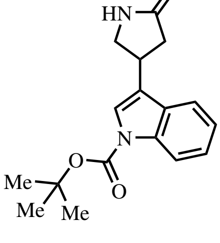
Following the general procedure **B** using *tert*-butyl 3-oxoazetidine-1-carboxylate (**100h**) (85.6 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88h** (85.8 mg, 461 µmol, 92%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 7.63 − 7.33 (m, 1H), 4.77 (*app.* d, $J \approx 11.5$ Hz, 2H), 3.88 (*app.* d, $J \approx 15.7$ Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD)[2]: δ (ppm) = 172.2, 153.2, 152.7, 81.3, 59.1, 58.9, 47.6, 47.1, 28.4.

The obtained spectroscopic data is in agreement to the literature.[125]

tert-Butyl 4-oxoimidazolidine-1-carboxylate (88i)



Following the general procedure **B** using *tert*-butyl 3-(3-oxocyclobutyl)-1*H*-indole-1-carboxylate **100i** (143 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88i** (115 mg, 383 µmol, 77%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 98:2, stained with $KMnO_4$) as a colorless solid.

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[2] The product consists of a mixture of two rotamers.

M.P.: 114 – 116 °C

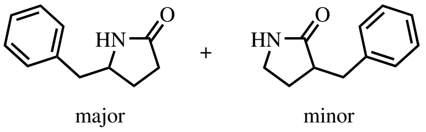
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3209 (br), 2359 (br), 1730 (s), 1698 (s), 1453 (s), 1373 (s), 1309 (m), 1254 (s), 1221 (m), 1155 (s), 1093 (s), 1047 (w), 1021 (w), 909 (w), 729 (s).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.15 (d, $J = 8.3$ Hz, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.45 (s, 1H), 7.35 (ddd, $J = 8.4, 7.2, 1.3$ Hz, 1H), 7.29 – 7.22 (m, 1H), 6.48 (br s, 1H), 3.96 – 3.82 (m, 2H), 3.60 – 3.49 (m, 1H), 2.80 (dd, $J = 16.8, 8.7$ Hz, 1H), 2.60 (dd, $J = 16.8, 8.3$ Hz, 1H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) = 177.7, 149.7, 136.0, 129.3, 124.9, 122.8, 121.9, 121.3, 119.0, 115.7, 84.1, 48.0, 36.6, 31.9, 28.3.

HRMS (ESI$^+$): Calculated for $C_{17}H_{21}N_2O_3$ [M+H]$^+$: 301.1547, Found: 301.1548.

5-Benzylpyrrolidin-2-one, 3-Benzylpyrrolidin-2-one (88k)



Following the general procedure **B** using 2-benzylcyclobutan-1-one (**86**) (80.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), a mixture of regioisomers **88k** (78.6 mg, 449 µmol, 90%, 89:11 *rr*) was obtained by flash column chromatography (SiO$_2$, EtOAc:MeOH 95:5, stained with KMnO$_4$) as a colorless solid.

Major regioisomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.39 – 7.12 (m, 5H), 5.95 (br s, 1H), 3.94 – 3.82 (m, 1H), 2.84 (dd, $J = 13.4, 5.7$ Hz, 1H), 2.72 (dd, $J = 13.4, 8.0$ Hz, 1H), 2.38 – 2.19 (m, 3H), 1.93 – 1.78 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) = 178.1, 137.6, 129.1, 128.8, 126.9, 55.8, 43.0, 30.2, 26.9.

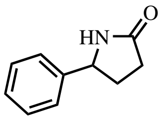
Minor regioisomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.39 – 7.12 (m, 5H), 6.23 (br s, 1H), 3.28 – 3.17 (m, 3H), 2.68 – 2.61 (m, 2H), 2.18 – 2.07 (m, 1H), 1.93 – 1.78 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) = 179.9, 139.6, 129.1, 128.6, 126.4, 42.8, 40.4, 36.7, 27.0.

The obtained spectroscopic data is in agreement to the literature.[126,127]

5-Phenylpyrrolidin-2-one (88j)



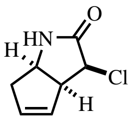
Following the general procedure **B** using 2-phenylcyclobutan-1-one (**84**) (73.1 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88j** (74.9 mg, 464 µmol, 93%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.33 (m, 2H), 7.32 – 7.27 (m, 3H), 6.51 (br s, 1H), 4.75 (*app.* t, $J \approx 7.1$ Hz, 1H), 2.63 – 2.35 (m, 3H), 1.96 (dddd, $J = 12.5, 9.2, 8.2, 6.6$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 178.7, 142.6, 129.0, 128.0, 125.7, 58.2, 31.5, 30.4.

The obtained spectroscopic data is in agreement to the literature.[128]

(3*S*)-3-Chloro-3,3a,6,6a-tetrahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (88l)



Following the general procedure **B** using *tert*-butyl 7-*endo*-chlorobicyclo[3.2.0]hept-2-en-6-one (**80**) (71.3 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **88l** (53.8 mg, 340 µmol, 68%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless solid.

M.P.: 183 – 187 °C

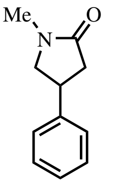
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2355 (br), 1707 (s), 1691 (s), 1429 (w), 1380 (w), 1258 (w), 739 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41 (br s, 1H), 5.87 – 5.70 (m, 2H), 4.64 (d, $J = 8.7$ Hz, 1H), 4.26 (*app.* t, $J \approx 6.2$ Hz, 1H), 3.87 – 3.68 (m, 1H), 2.76 – 2.57 (m, 1H), 2.53 – 2.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 172.2 , 130.8, 128.5, 57.5, 54.8, 50.9, 41.0.

HRMS (APCI$^+$): Calculated for C_7H_9ClNO [M+H]$^+$: 158.0367, Found: 158.0366.

1-Methyl-4-phenylpyrrolidin-2-one (88m)



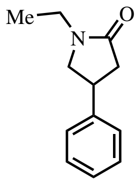
Following the general procedure **B** using 3-phenylcyclobutan-1-one (**56**) (73.1 mg, 500 µmol, 1.00 equiv.) and *N*-methylated hydroxylamine **33b** (136 mg, 550 µmol, 1.10 equiv.), the product **88m** (72.9 mg, 416 µmol, 83%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.37 – 7.30 (m, 2H), 7.28 – 7.19 (m, 3H), 3.74 (dd, $J = 9.6, 8.3$ Hz, 1H), 3.63 – 3.50 (m, 1H), 3.41 (dd, $J = 9.6, 7.0$ Hz, 1H), 2.90 (s, 3H), 2.81 (dd, $J = 16.9, 9.2$ Hz, 1H), 2.54 (dd, $J = 16.9, 8.3$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 174.0, 142.7, 129.0, 127.2, 126.8, 56.8, 38.9, 37.3, 29.7.

The obtained spectroscopic data is in agreement to the literature.[120]

5-Benzyl-1-ethylpyrrolidin-2-one (88n)



Following the general procedure **B** using 3-phenylcyclobutan-1-one (**56**) (73.1 mg, 500 µmol, 1.00 equiv.) and *N*-ethylated hydroxylamine **33c** (144 mg, 550 µmol, 1.10 equiv.), the product **88n** (58.6 mg, 310 µmol, 62%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 20:80, stained with $KMnO_4$) as a colorless oil.

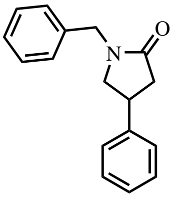
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2974 (br), 2361 (s), 2341 (s), 1686 (s), 1493 (m), 1434 (m), 1257 (m), 910 (w), 763 (m), 702 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 – 7.30 (m, 2H), 7.30 – 7.19 (m, 3H), 3.75 (dd, $J = 9.4, 8.2$ Hz, 1H), 3.63 – 3.49 (m, 1H), 3.49 – 3.28 (m, 3H), 2.82 (dd, $J = 16.8, 9.0$ Hz, 1H), 2.56 (dd, $J = 16.8, 8.3$ Hz, 1H), 1.15 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.5, 142.8, 129.0, 127.2, 126.8, 53.9, 39.3, 37.4, 37.2, 12.7.

HRMS (ESI$^+$): Calculated for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1227, Found: 190.1227.

1-Benzyl-4-phenylpyrrolidin-2-one (88o)



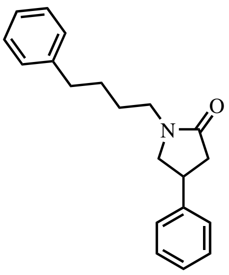
Following the general procedure **B** using 3-phenylcyclobutan-1-one (**56**) (73.1 mg, 500 µmol, 1.00 equiv.) and *N*-benzylated hydroxylamine **33d** (178 mg, 550 µmol, 1.10 equiv.) dissolved in CH_2Cl_2 (2.5 mL), the product **88o** (102 mg, 405 µmol, 81%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40, stained with $KMnO_4$) as a slightly yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.37 – 7.20 (m, 8H), 7.19 – 7.14 (m, 2H), 4.57 (d, $J = 14.6$ Hz, 1H), 4.47 (d, $J = 14.6$ Hz, 1H), 3.63 (dd, $J = 9.4, 8.3$ Hz, 1H), 3.60 – 3.48 (m, 1H), 3.28 (dd, $J = 9.4, 6.9$ Hz, 1H), 2.89 (dd, $J = 16.9, 8.9$ Hz, 1H), 2.63 (dd, $J = 16.8, 8.4$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.8, 142.4, 136.4, 128.9, 128.9, 128.4, 127.8, 127.2, 126.8, 53.9, 46.7, 39.0, 37.3.

The obtained spectroscopic data is in agreement to the literature.[129]

4-Phenyl-1-(4-phenylbutyl)pyrrolidin-2-one (88p)



Following the general procedure **B** using 3-phenylcyclobutan-1-one (**56**) (29.4 mg, 200 µmol, 1.00 equiv.) and *N*-alkylated hydroxylamine **33e** (80.4 mg, 220 µmol, 1.10 equiv.) dissolved in CH_2Cl_2 (1.0 mL), the product **88p** (48.3 mg, 165 µmol, 82%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 40:60, stained with $KMnO_4$) as a colorless oil.

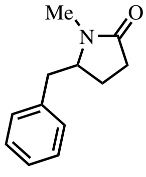
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2925 (br), 2363 (m), 1685 (s), 1493 (m), 1452 (m), 1429 (m), 1256 (w), 909 (w), 747 (m), 700 (s).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.31 (m, 2H), 7.29 – 7.23 (m, 3H), 7.23 – 7.20 (m, 2H), 7.20 – 7.14 (m, 3H), 3.69 (dd, $J = 9.7, 8.3$ Hz, 1H), 3.58 – 3.49 (m, 1H), 3.42 – 3.29 (m, 3H), 2.81 (dd, $J = 16.8, 9.1$ Hz, 1H), 2.64 (t, $J = 7.5$ Hz, 2H), 2.56 (dd, $J = 16.8, 8.3$ Hz, 1H), 1.69 – 1.61 (m, 2H), 1.61 – 1.51 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 173.8, 142.6, 142.2, 129.0, 128.5, 128.5, 127.2, 126.9, 125.9, 54.5, 42.4, 39.2, 37.4, 35.6, 28.7, 26.9.

HRMS (ESI$^+$): Calculated for $C_{20}H_{23}KNO$ [M+K]$^+$: 332.1412, Found: 332.1412.

5-Benzyl-1-methylpyrrolidin-2-one (88q)



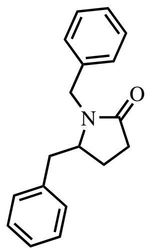
Following the general procedure **B** using 2-benzylcyclobutan-1-one (**86**) (80.1 mg, 500 µmol, 1.00 equiv.) and *N*-methylated hydroxylamine **33b** (136 mg, 550 µmol, 1.10 equiv.), the product **88q** (88.4 mg, 467 µmol, 93%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 7.19 – 7.12 (m, 2H), 3.74 (*app.* hept, $J \approx 4.4\,\text{Hz}$, 1H), 3.03 (dd, $J = 13.5, 4.4\,\text{Hz}$, 1H), 2.88 (s, 3H), 2.63 (dd, $J = 13.5, 8.2\,\text{Hz}$, 1H), 2.26 – 2.08 (m, 2H), 1.98 (*app.* ddt, $J \approx 13.0, 9.9, 7.7\,\text{Hz}$, 1H), 1.74 (dddd, $J = 13.2, 9.1, 5.9, 4.2\,\text{Hz}$, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 175.3, 137.0, 129.4, 128.8, 126.9, 61.2, 39.5, 29.8, 28.3, 23.7.

The obtained spectroscopic data is in agreement to the literature.[130]

1,5-Dibenzylpyrrolidin-2-one (88r)



Following the general procedure **B** using 2-benzylcyclobutan-1-one (**86**) (80.1 mg, 500 µmol, 1.00 equiv.) and *N*-benzylated hydroxylamine **33d** (178 mg, 550 µmol, 1.10 equiv.), the product **88r** (104 mg, 392 µmol, 78%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40, stained with $KMnO_4$) as a colorless oil.

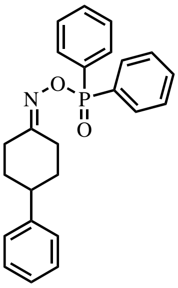
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 – 7.19 (m, 8H), 7.09 – 7.00 (m, 2H), 5.11 (d, $J = 15.0\,\text{Hz}$, 1H), 4.01 (d, $J = 15.0\,\text{Hz}$, 1H), 3.73 – 3.53 (m, 1H), 3.02 (dd, $J = 13.4, 4.3\,\text{Hz}$, 1H), 2.57 (dd, $J = 13.4, 8.6\,\text{Hz}$, 1H), 2.35 – 2.20 (m, 2H), 1.91 (*app.* ddt, $J \approx 13.0, 9.3, 8.0\,\text{Hz}$, 1H), 1.80 – 1.69 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 175.3, 137.1, 136.8, 129.3, 128.8, 128.7, 128.2, 127.7, 126.9, 58.1, 44.5, 39.3, 30.0, 23.8.

The obtained spectroscopic data is in agreement to the literature.[131]

7.2.4 Ring-Expansion on Cyclohexanone

Diphenyl(((4-phenylcyclohexylidene)amino)oxy)phosphine oxide (104)



Following the general procedure **B** using 4-phenylcyclohexan-1-one **102** (436 mg, 2.50 mmol, 1.00 equiv.) and DPPH (**33a**) (641 mg, 2.75 mmol, 1.10 equiv.), the product **104** (862 mg, 2.21 µmol, 89%) was obtained by gradient automated flash column chromatography (SiO_2, CH_2Cl_2:EtOAc 90:10 to 60:40, stained with $KMnO_4$) as a colorless solid.

M.P.: 169 – 171 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2926 (br), 2361 (s), 2337 (s), 1438 (m), 1233 (m), 1130 (m), 885 (s), 729 (s).

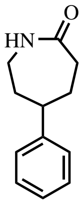
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.87 (dddd, $J = 12.3, 8.5, 6.1, 1.4$ Hz, 4H), 7.61 – 7.51 (m, 2H), 7.51 – 7.39 (m, 4H), 7.35 – 7.28 (m, 2H), 7.25 – 7.10 (m, 3H), 3.65 – 3.47 (m, 1H), 2.79 (tt, $J = 12.3, 3.3$ Hz, 1H), 2.64 (ddt, $J = 14.3, 4.5, 2.5$ Hz, 1H), 2.26 (td, $J = 13.8, 4.8$ Hz, 1H), 2.17 – 2.00 (m, 3H), 1.70 (dddd, $J = 14.5, 13.4, 8.0, 3.0$ Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 168.5 (d, $J = 11.3$ Hz), 145.2, 132.3 (d, $J = 5.5$ Hz), 132.2 (dd, $J = 10.0, 1.7$ Hz), 131.6 (d, $J = 2.0$ Hz), 130.3 (d, $J = 2.2$ Hz), 129.5 (d, $J = 573.1$ Hz), 128.6 (d, $J = 13.4$ Hz), 127.8 (d, $J = 188.6$ Hz), 43.5, 33.4 (d, $J = 89.8$ Hz), 29.1 (d, $J = 555.0$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 34.8.

HRMS (ESI$^+$): Calculated for $C_{24}H_{25}NO_2P$ $[M+H]^+$: 390.1618, Found: 390.1610.

5-Phenylazepan-2-one (103)



An oven-dried tube was charged with DPPH (**33a**) (25.7 mg, 110 µmol, 1.10 equiv.) and the solid was dissolved in CH_2Cl_2 (0.1 mL). TfOH (16.5 mg, 1.10 µmol, 1.10 equiv.) in CH_2Cl_2 (0.4 mL) was added to the mixture and stirred at room temperature for 10 min. 4-Phenylcyclohexan-1-one **102** (17.4 mg, 1.00 µmol, 1.00 equiv.) in CH_2Cl_2 (0.5 mL) was added to the mixture and the reaction mixture was stirred at room temperature for 15 h. The solution was quenched with an aqueous saturated solution of $NaHCO_3$ (10 mL). The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **103** (12.2 mg, 64.5 µmol, 64%) was obtained by gradient automated flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.27 (m, 2H), 7.25 – 7.11 (m, 3H), 6.51 (br s, 1H), 3.48 – 3.23 (m, 2H), 2.76 (tt, $J = 12.1, 3.5$ Hz, 1H), 2.69 – 2.49 (m, 2H), 2.10 – 1.93 (m, 2H), 1.88 – 1.66 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 178.6, 146.5, 128.8, 126.8, 126.7, 49.0, 42.2, 37.5, 36.0, 30.7.

The obtained spectroscopic data is in agreement to the literature.[132]

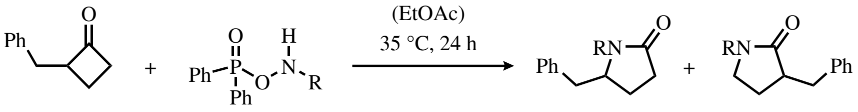
Investigation on the Ring-Expansion to Caprolactam

An oven-dried tube was charged with DPPH (**33a**) (25.7 mg, 110 µmol, 1.10 equiv.) and the solid was dissolved in the corresponding solvent (0.5 mL). 4-phenylcyclohexan-1-one **102** (17.4 mg, 100 µmol, 1.00 equiv.) in the corresponding solvent (0.5 mL) was added to the mixture and the reaction mixture was stirred at the corresponding temperature for 24 h. The solvent wa removed under reduced pressure. In the case with an acid, the solution was quenched with an aqueous saturated solution of $NaHCO_3$ (10 mL). The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The NMR yield of the crude reaction mixture was determined using ^{1}H NMR analysis with dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

Investigation on the oxime ester 104

An oven dried tube was charged with oxime ester (**104**) (38.9 mg, 100 µmol, 1.00 equiv.) and the solid was dissolved in the corresponding solvent (0.5 mL). Additionally, water (1.8 mg, 100 µmol, 1.00 equiv.), diphenyphosphinic acid (**93**) (21.8 mg, 100 µmol, 1.00 equiv.) or DPPH (**33a**) (25.7 mg, 110 µmol, 1.10 equiv.) in the corresponding solvent (0.5 mL) was added to the mixture and the reaction mixture was stirred at 50 °C for 15 h. The solvent wa removed under reduced pressure. The NMR yield of the crude reaction mixture was determined using ^{1}H NMR analysis with dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

7.2.5 Stereochemical Analysis



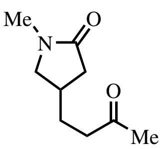
An oven-dried tube was charged with the corresponding *N*-substituted hydroxylamine **33** (550 µmol, 1.10 equiv.) and suspended in EtOAc (1.5 mL, 0.33 M). 2-Benzylcyclobutan-1-one (**86**) (80.1 mg, 500 mmol, 1.00 equiv.) was dissolved in EtOAc (1.0 mL, 0.50 M) and added to the mixture. The mixture was placed into a pre-heated 35 °C metal block and stirred at this temperature for 24 h. The solvent was concentrated under reduced pressure and the NMR yield and regioselectivity of the crude reaction mixture was determined by ^{1}H NMR experiment using dibromomethane (35.0 µL, 86.9 mg, 500 µmol) as the internal standard.

Table 14: Regioselective Analysis of the aza-BAEYER – VILLIGER Reaction with *N*-substituted diphenylphosphinate **88**, [a] Reaction was performed in CH_2Cl_2 (1.0 mL).

Entry	R	Substrate 88, Yield	major:minor *rr*
1	H	**88k**, 94%	90:10
2	Me	**88q**, 92%	>99:1
3	Bn	**88r**, 71%[a]	>99:1

Chemoselectivity

1-Methyl-5-(3-oxobutyl)pyrrolidin-2-one (88s)



Following the general procedure **B** using 3-(3-oxobutyl)cyclobutan-1-one (**106**) (14.0 mg, 100 µmol, 1.00 equiv.) and *N*-methylated hydroxylamine **33b** (27.2 mg, 110 µmol, 1.10 equiv.) in EtOAc (1.0 mL), the product **88s** (11.5 mg, 67.9 µmol, 68%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless oil.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2925, 2360, 2341, 1672, 1507, 1409, 1363, 1173, 914, 674.

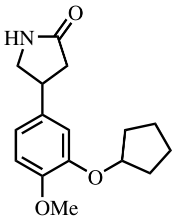
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.45 (dd, $J = 9.7, 8.0$ Hz, 1H), 3.00 (dd, $J = 9.7, 6.6$ Hz, 1H), 2.81 (s, 3H), 2.54 – 2.41 (m, 3H), 2.38 – 2.25 (m, 1H), 2.14 (s, 3H), 2.02 (dd, $J = 16.5, 7.6$ Hz, 1H), 1.81 – 1.61 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 207.9, 174.1, 55.2, 41.3, 37.2, 31.0, 30.1, 29.7, 28.5.

HRMS (ESI$^+$): Calculated for $C_{22}H_{20}NO_2PNa$ [M+Na]$^+$: 384.1124, Found: 384.1129.

7.2.6 Synthesis of Rolipram and Its Derivatives

4-(3-(Cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (1)



Following the general procedure **B** using 3-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclobutan-1-one (**107**) (130 mg, 500 µmol, 1.00 equiv.) and DPPH (**33a**) (128 mg, 550 µmol, 1.10 equiv.), the product **1** (101 mg, 368 µmol, 74%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

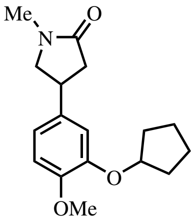
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.85 – 6.80 (m, 1H), 6.79 – 6.74 (m, 2H), 6.28 (br s, 1H), 4.76 (tt, $J = 5.9, 3.4$ Hz, 1H), 3.83 (s, 3H), 3.78 – 3.70 (m, 1H), 3.62 (*app.* p, $J \approx 8.6$ Hz, 1H), 3.38 (dd, $J = 9.4, 7.4$ Hz, 1H), 2.71 (dd, $J = 16.9, 8.9$ Hz, 1H), 2.47 (dd, $J = 16.9, 8.9$ Hz, 1H), 1.99 – 1.87 (m, 4H), 1.86 – 1.75 (m, 2H), 1.68 – 1.55 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 177.8, 149.3, 148.0, 134.7, 118.9, 113.9, 112.3, 80.7, 56.3, 49.9, 40.1, 38.2, 32.9, 24.2.

The obtained spectroscopic data is in agreement to the literature.[109]

The reaction was carried out by WALZ.

4-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-methylpyrrolidin-2-one (113)



Following the general procedure **B** using 3-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclobutan-1-one (**107**) (52.1 mg, 200 µmol, 1.00 equiv.) and *N*-methylated hydroxylamine **33b** (54.4 mg, 220 µmol, 1.10 equiv.) in CH_2Cl_2 (1.0 mL), the product **113** (50.5 mg, 175 µmol, 87%[3]) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 10:90, stained with $KMnO_4$) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 6.81 (d, $J = 8.2$ Hz, 1H), 6.74 (dd, $J = 8.1, 2.2$ Hz, 1H), 6.72 (d, $J = 2.1$ Hz, 1H), 4.75 (tt, $J = 6.4, 3.3$ Hz, 1H), 3.82 (s, 3H), 3.71 (dd,

---

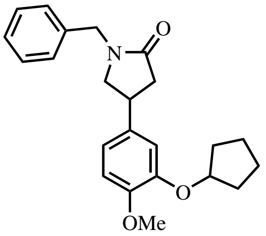
[3] Isolated Product contains 4.3% of ((methylamino)oxy)diphenylphosphine oxide.

$J = 9.7, 8.3$ Hz, 1H), 3.54 – 3.45 (m, 1H), 3.36 (dd, $J = 9.7, 7.1$ Hz, 1H), 2.90 (s, 3H), 2.78 (dd, $J = 16.9, 9.1$ Hz, 1H), 2.51 (dd, $J = 16.9, 8.4$ Hz, 1H), 1.98 – 1.75 (m, 6H), 1.68 – 1.55 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 174.1, 149.2, 148.0, 135.0, 118.8, 113.7, 112.2, 80.6, 57.1, 56.2, 39.1, 37.0, 32.9, 32.9, 29.7, 24.2.

The obtained spectroscopic data is in agreement to the literature.[133]

1-Benzyl-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (114)



Following the general procedure **B** using 3-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclobutan-1-one (**107**) (52.1 mg, 200 µmol, 1.00 equiv.) and *N*-benzylated hydroxylamine **33d** (71.1 mg, 220 µmol, 1.10 equiv.) in CH_2Cl_2 (1.0 mL), the product **114** (56.2 mg, 154 µmol, 77%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40, stained with $KMnO_4$) as a colorless oil.

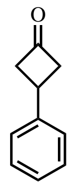
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.31 (m, 2H), 7.30 – 7.25 (m, 3H), 6.77 (d, $J = 8.2$ Hz, 1H), 6.68 (dd, $J = 8.2, 2.2$ Hz, 1H), 6.65 (d, $J = 2.2$ Hz, 1H), 4.69 (tt, $J = 6.3, 3.2$ Hz, 1H), 4.56 (d, $J = 14.6$ Hz, 1H), 4.45 (d, $J = 14.6$ Hz, 1H), 3.81 (s, 3H), 3.61 (dd, $J = 9.8, 8.4$ Hz, 1H), 3.51 – 3.41 (m, 1H), 3.24 (dd, $J = 9.7, 7.1$ Hz, 1H), 2.86 (dd, $J = 16.9, 9.1$ Hz, 1H), 2.59 (dd, $J = 16.9, 8.3$ Hz, 1H), 1.94 – 1.76 (m, 6H), 1.66 – 1.54 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 173.9, 149.1, 148.0, 136.5, 135.0, 128.9, 128.4, 127.8, 118.8, 113.7, 112.1, 80.6, 56.2, 54.2, 46.7, 39.2, 36.8, 32.9, 32.9, 24.2, 24.2.

The obtained spectroscopic data is in agreement to the literature.[134]

7.2.7 Large-Scale Synthesis of γ-Lactam

3-Phenylcyclobutan-1-one (56)



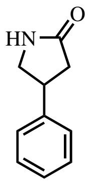
The cyclobutanone **56** was prepared following a literature protocol by GHOSEZ and coworkers.[74] A 1000 mL three-necked round-bottom flask was equipped with a magnetic stir bar, rubber septum, reflux condenser and dropping funnel. The flask was evacuated three times and purged with N_2. The flask was cooled down to −15 °C with an ice/salt mixture and charged with *N*,*N*-dimethylacetamide (DMA) (11.2 mL, 10.5 g, 120 mmol, 1.00 equiv.) in 1,2-dichloroethane (DCE) (320 mL). The dropping funnel was charged with styrene (**115**) (54.9 mL, 50.0 g, 480 mmol, 4.00 equiv.), 2,6-dimethylpyridine (16.7 mL, 15.4 g, 144 mmol, 1.20 equiv.) and DCE (160mL). Tf_2O (40.6 g, 23.7 mL, 144 mmol, 1.20 equiv.) was slowly added into the solution of DMA over 20 min, which formed a precipitate. While adding, the solution was kept at 20 °C with a water bath. The resulting mixture was placed into a metal heating block and heated to 95 °C and stirred for 17 h. Over the time the reaction solution turned from colorless to dark red. The reaction mixture was allowed to cool down to room temperature. The reaction mixture was transferred to a round-bottom flask and eluted with DCE (100 mL). The solvent was removed under reduced pressure and the residue was washed with dry Et_2O (3×64 mL). To the organic phase, DCE (64 mL) and H_2O (64 mL) were added and the mixture was heated to 90 °C and stirred for 6 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×64 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **56** (14.8 g, 101 mmol, 84% yield, 99.9% purity[4]) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 95:5 to 90:10, stained with $KMnO_4$) and distillation in a Kugelrohr short path distillation apparatus (97 °C−125 °C, 0.17 mbar) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.34 (m, 2H), 7.33 – 7.23 (m, 3H), 3.75 – 3.61 (m, 1H), 3.56 – 3.45 (m, 2H), 3.33 – 3.21 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 207.0, 143.7, 128.8, 126.8, 126.6, 54.8, 28.6.

The obtained spectroscopic data is in agreement to the literature.[110]

4-Phenylpyrrolidin-2-one (88a)



A 500 mL three-necked round-bottom flask was equipped with a Teflon-coated magnetic stir bar, a 100 mL dropping funnel, a thermometer and a glass stopper (Figure 4). The flask was charged with DPPH (contains 95% of the actual product, 8.10 g, 33.0 mmol, 1.10 equiv.) and suspended in DMF (100 mL). The addition funnel was filled with a solution of 3-phenylcyclobutanone (**56**) (4.39 g, 30.0 mmol, 1.00 equiv.) in DMF (60 mL). The internal temperature was kept at 25 °C with a metal heating block. The solution

---

[4] 31.3 mg (214 µmol) of product and 12.0 mg (214 µmol) of 1,3,5-trimethoxybenzol in 0.6 mL $CDCl_3$. Integrating the α-CH_2 resonance against the aromatic CH signal showed 99.9% purity.

was added dropwise over 15 min. After completion, the reaction mixture was stirred at 25 °C for 24 h. The reaction progress after 1 h and 18 h are shown in Figure 4b) and c).

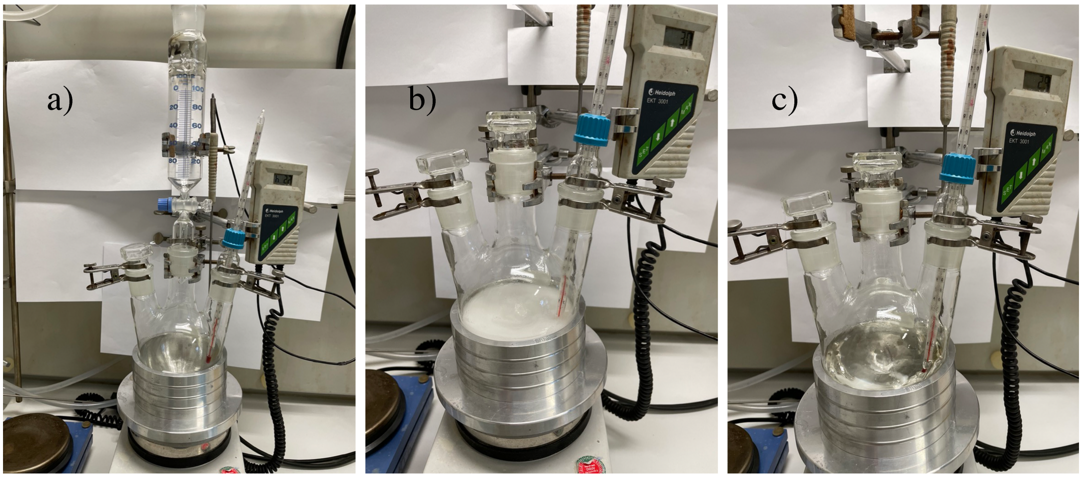


Figure 4: a) Reaction set-up. b) Reaction appearance after 1 h and c) after 18 h.

The reaction mixture was evenly divided between two 250 mL single-necked round-bottom flasks and eluted with CH_2Cl_2 (40 mL). By means of an inverse splash head, the solvent was removed on a rotary evaporator (50 °C, 6 mmHg). The white precipitate was purified twice by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) to obtain the desired product (3.99 g, 24.7 mmol, 82%, 94.5% purity[5]) as a colorless solid. In the first run (column size: 5 × 20 cm, 260 g SiO_2 with 14 g SiO_2 dry load, prerun: 700 mL EtOAc, run: 2.0 L EtOAc:MeOH 95:5), the product was observed in the fraction between 69 – 103. The mixture of product and impurities was separated in the second run (column size: 7.5 × 23 cm, 461 g SiO_2 with 16 g SiO_2 dry load, prerun: 250 mL EtOAc, run: 6.0 L EtOAc:MeOH 95:5), in which the product was collected in the fractions 108 – 282.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3268 (br), 2362 (s), 1693 (s), 1496 (m), 1455 (w), 1293 (w), 1259 (m), 1051 (w), 757 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.31 (m, 2H, $CH_{arom.}$), 7.29 – 7.21 (m, 3H, $CH_{arom.}$), 6.72 (br s, 1H, N*H*), 3.84 – 3.75 (m, 1H, NC*H*H), 3.75 – 3.63 (m, 1H, PhC*H*), 3.43 (dd, $J = 9.3, 7.2$ Hz, 1H, NCH*H*), 2.74 (dd, $J = 16.9, 8.9$ Hz, 1H, COC*H*H), 2.51 (dd, $J = 16.9, 8.8$ Hz, 1H, COCH*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 178.0 (C_q), 142.2 (C_q), 129.0 (*C*H), 127.2 (*C*H), 126.9 (*C*H), 49.7 (NCH_2), 40.4 (*C*H), 38.1 (COCH_2).

The obtained spectroscopic data is in agreement to the literature.[120]

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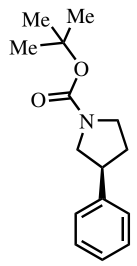
[5] 34.3 mg (213 µmol) of product and 12.0 mg (213 µmol) of 1,3,5-trimethoxybenzol in 0.6 mL $CDCl_3$. Integrating the α-CH_2 resonance against the aromatic CH signal showed 94.5% purity.

7.3 Asymmetric Desymmetrization of Prochiral Cyclobutanones using Chiral Aminoindanol

7.3.1 Deprotection of Hydroxyindenyl γ-Lactam

Protecting-Group Swap

***tert*-Butyl (*S*)-3-phenylpyrrolidine-1-carboxylate (130)**



The product **130** was prepared following a literature protocol by FUKUYAMA and coworkers[79] Pyrrolidin **129** (70.0 mg, 251 µmol, 1.00 equiv.) was dissolved in EtOAc (3.5 mL) and Boc$_2$O (107 mg, 490 µmol, 1.95 equiv.) was added. To the solution, palladium hydroxide (20% on carbon, 34.4 mg, 32.5 µmol, 0.13 equiv.) was added and the atmosphere was changed to hydrogen gas by purging the solution with hydrogen gas. The mixture was stirred at room temperature for 23 h. The reaction mixture was filtered through a pad of CELITE® and washed with CH$_2$Cl$_2$. The filtrate was concentrated under reduced pressure. The yield of the crude reaction mixture was determined by ^{1}H NMR analysis using 1,3,5-trimethylbenzene (7.0 µL, 6.01 mg, 50 µmol) as the internal standard. The residue was separated by flash column chromatography (SiO$_2$, CH$_2$Cl$_2$:EtOAc 95:5, stained with KMnO$_4$) and provided the desired product **130** (46.4 mg, 18.8 mmol, 75%) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.37 – 7.28 (m, 2H), 7.27 – 7.18 (m, 3H), 3.86 – 3.77 (m, 1H), 3.69 – 3.54 (m, 1H), 3.46 – 3.25 (m, 3H), 2.35 – 2.20 (m, 1H), 2.04 – 1.93 (m, 1H), 1.48 (s, 9H).

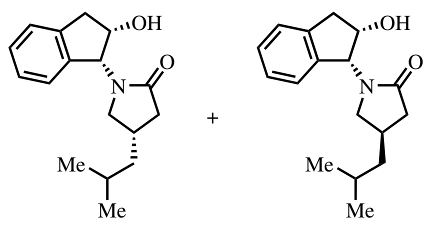
^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) = 154.7, 141.6, 128.7, 127.2, 126.9, 79.4, 52.4, 45.9, 44.0, 33.0, 28.7.

Optical Rotation: $[\alpha]_D^{20} = -11.96$ ($c = 1.00$, CHCl$_3$).

The obtained spectroscopic data is in agreement to the literature.[135]

7.3.2 Synthesis of the Precursor of (*S*)-Pregabalin

1-((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-4-isobutylpyrrolidin-2-one (120f)



major minor

An oven-dried SCHLENK tube was charged with the cyclobutanone **131** (126 mg, 1.00 mmol, 1.00 equiv.) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (*ent*-**118**) (149 mg, 1.00 mmol, 1.00 equiv.). MeOH (5.0 mL) and the mixture was placed into a metal heating block. The reaction mixture was heated to 70 °C and stirred for 8 h. The solution was allowed to cool down to room temperature and trichloroisocyanuric acid (TCICA) (77.5 mg, 333 µmol, 0.33 equiv.) was added under vigorous stirring and stirred for further 5 min. H_2O (180 µmL, 180 mg, 10.0 mmol, 10.0 equiv.) was added and the reaction mixture was stirred for 16 h. The mixture was added to H_2O (100 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was reduced under pressure. The major diastereomer **120f** (169 mg, 618 µmol, 62%) and the minor diastereomer *epi*-**120f** (35.2 mg, 129 µmol, 13%) were obtained by gradient flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) both as colorless oils.

Major diastereomer:

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3363 (br), 2952 (m), 2869 (m), 2114 (w), 1662 (s), 1439 (m), 1293 (m), 1246 (m), 1095 (m), 866 (w), 817 (w), 740 (s).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.32 − 7.22 (m, 3H), 7.20 (d, $J = 7.4$ Hz, 1H), 5.46 (d, $J = 6.7$ Hz, 1H), 4.79 (*app.* q, $J \approx 6.9$ Hz, 1H), 3.24 (dd, $J = 16.2, 7.4$ Hz, 1H), 3.08 (dd, $J = 9.6, 7.9$ Hz, 1H), 2.97 (dd, $J = 9.6, 7.9$ Hz, 1H), 2.91 (dd, $J = 16.2, 6.7$ Hz, 1H), 2.59 (dd, $J = 16.6, 8.4$ Hz, 1H), 2.31 (*app.* sept., $J \approx 8.1$ Hz, 1H), 2.18 (dd, $J = 16.6, 9.1$ Hz, 1H), 1.55 − 1.45 (m, 1H), 1.36 − 1.23 (m, 2H), 0.84 (dd, $J = 6.6, 4.9$ Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 176.3, 141.3, 138.1, 129.0, 127.4, 125.8, 125.5, 73.6, 59.0, 52.0, 43.8, 40.0, 38.5, 31.1, 26.3, 22.9, 22.6.

HRMS (ESI$^+$): Calculated for $C_{17}H_{23}NO_2Na$ $[M+Na]^+$: 296.1621, Found: 296.1619.

Optical Rotation: $[\alpha]_D^{20} = +34.4$ ($c = 1.00$, $CHCl_3$).

Minor diastereomer:

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3330 (br), 2954 (m), 2869 (m), 2243 (w), 1662 (s), 1441 (m), 1293 (m), 1197 (w), 1095 (m), 910 (w), 817 (w), 733 (s).

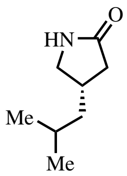
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.22 (m, 3H), 7.19 (d, $J = 7.4$ Hz, 1H), 5.47 (d, $J = 6.7$ Hz, 1H), 4.78 (*app.* q, $J \approx 6.8$ Hz, 1H), 3.34 (dd, $J = 9.6, 7.7$ Hz, 1H), 3.25 (dd, $J = 16.3, 7.3$ Hz, 1H), 2.93 (dd, $J = 16.3, 6.5$ Hz, 1H), 2.70 (dd, $J = 9.6, 6.4$ Hz, 1H), 2.60 (dd, $J = 16.7, 8.5$ Hz, 1H), 2.42 (*app.* sept., $J \approx 7.7$ Hz, 1H), 2.15 (dd, $J = 16.7, 7.4$ Hz, 1H), 1.52 – 1.41 (m, 1H), 1.30 – 1.16 (m, 2H), 0.84 (dd, $J = 10.0, 6.6$ Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 176.3, 141.2, 138.0, 128.9, 127.3, 125.9, 125.5, 73.4, 59.0, 52.2, 43.8, 40.0, 38.3, 30.2, 26.1, 22.8, 22.6.

HRMS (ESI$^+$): Calculated for $C_{17}H_{23}NO_2Na$ $[M+Na]^+$: 296.1621, Found: 296.1617.

Optical Rotation: $[\alpha]_D^{20} = -4.51$ ($c = 0.50$, $CHCl_3$).

(*S*)-4-Isobutylpyrrolidin-2-one (132)



In an oven-dried SCHLENK tube, the indanyl protected γ-lactam **120f** (119 mg, 457 mmol, 1.00 equiv.) was added and dissolved in MeCN (2.3 mL). H_2O (2.3 mL) was added followed by cerium ammonium nitrate (CAN) (504 mg, 919 mmol, 2.00 equiv.). The reaction mixture was heated to 60 °C and stirred for 16 h.The reaction mixture was allowed to cool down to room temperature. H_2O (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (7×30 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The desired product **132** (33.6 mg, 238 µmol, 52%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.16 (br s, 1H), 3.47 (dd, $J = 9.4, 7.8$ Hz, 1H), 2.99 (dd, $J = 9.4, 7.2$ Hz, 1H), 2.63 – 2.46 (m, 1H), 2.41 (dd, $J = 16.6, 8.6$ Hz, 1H), 1.98 (dd, $J = 16.6, 8.5$ Hz, 1H), 1.65 – 1.49 (m, 1H), 1.43 – 1.28 (m, 2H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 178.6, 48.4, 44.0, 37.1, 33.2, 26.3, 22.8, 22.6.

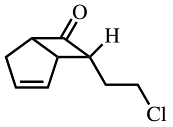
Optical Rotation: $[\alpha]_D^{20} = -2.42$ ($c = 1.00$, $CHCl_3$).

The obtained spectroscopic data is in agreement to the literature.[136]

7.4 Asymmetric Desymmetrization of Prochiral Cyclobutanones using Chiral Phosphorous Reagent

7.4.1 Synthesis of Starting Materials

7-*endo*-(2-chloroethyl)bicyclo[3.2.0]hept-2-en-6-one (151)



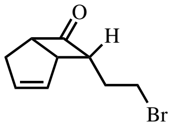
The bicyclic product **151** was prepared following a modified literature protocol by KELLY and coworkers.[89] A round-bottom flask was charged with freshly distilled cyclopentadiene **153** (6.58 g, 99.5 mmol, 3.98 equiv) and 4-chlorobutanoyl chloride (**150**) (3.71 g, 2.32 mL, 20.0 mmol, 1.00 equiv.) in CH_2Cl_2 (12.5 mL). The mixture was cooled down to 0 °C with an ice/water bath and NEt_3 (3.47 mL, 2.53 g, 25.0 mmol, 1.00 equiv.) in CH_2Cl (7.5 mL) was added to the mixture. The mixture was stirred at room temperature for 8 h. The ammonium salt was filtered and washed with Et_2O. The filtrate was washed with H_2O (2×50 mL), an aqueous saturated solution of $NaHCO_3$ (3×50 mL) and H_2O (3×50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **151** (372 mg, 2.18 mmol, 9%) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 95:5 to 90:10, stained with $KMnO_4$) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.93 – 5.87 (m, 1H), 5.75 (dq, $J = 6.1, 2.1$ Hz, 1H), 3.90 – 3.82 (m, 1H), 3.74 – 3.64 (m, 2H), 3.61 (dd, $J = 6.9, 6.3$ Hz, 2H), 2.71 – 2.58 (m, 1H), 2.47 – 2.34 (m, 1H), 2.10 – 1.97 (m, 1H), 1.90 – 1.78 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 214.4, 135.5, 129.4, 62.1, 60.0, 43.3, 42.2, 34.3, 28.3.

The obtained spectroscopic data is in agreement to the literature.[89]

7-*endo*-(2-Bromoethyl)bicyclo[3.2.0]hept-2-en-6-one (154)



The bicyclic product **154** was prepared following a modified literature protocol by XU and coworkers.[137] A three-necked round-bottom flask was charged with freshly distilled cyclopentadiene **153** (2.21 g, 33.4 mmol, 1.67 equiv.) and cyclohexane (100 mL). The reaction flask was purged with N_2 and NEt_3 (2.77 mL, 2.02 g, 20.0 mmol, 1.00 equiv.) was added. The mixture was heated to 100 °C and a solution of 4-bromobutanoyl chloride (**152**)

(3.71 g, 2.32 mL, 20.0 mmol, 1.00 equiv.) in cyclohexane (4.20 mL) was added dropwise (25 mL/h). The mixture was stirred at this temperature for 4 h. The reaction mixture was allowed to cool down to room temperature and filtered. The mixture was eluted with cyclohexane. The filtrate was washed with an aqueous saturated solution of NH_4Cl (3 × 50 mL) and H_2O (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **154** (510 mg, 2.37 mmol, 12%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 95:5, stained with $KMnO_4$) as a yellowish oil.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2920 (br), 1770 (s), 1440 (w), 1346 (w), 920 (w), 703 (w).

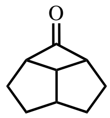
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.93 – 5.87 (m, 1H), 5.75 (dt, $J = 5.7, 2.1$ Hz, 1H), 3.91 – 3.79 (m, 1H), 3.75 – 3.63 (m, 2H), 3.56 – 3.41 (m, 2H), 2.70 – 2.59 (m, 1H), 2.41 (ddq, $J = 17.1, 9.2, 2.0$ Hz, 1H), 2.13 (dq, $J = 14.5, 6.5$ Hz, 1H), 2.00 – 1.86 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 214.3, 135.6, 129.3, 63.1, 60.0, 42.1, 34.3, 31.7, 28.5.

HRMS (APCI$^+$): Calculated for $C_9H_{12}BrO$ $[M+H]^+$: 215.0066, Found: 215.0061.

The obtained spectroscopic data is in agreement to the literature.[137]

Tricyclo[4.2.1.0^{3,9}]nonan-2-one (155)



The tricyclic product **155** was prepared following a modified literature protocol by DOWD and ZHANG.[138] A flame dried three-necked round-bottom flask equipped with a condenser and filled with N_2 was charged with **154** (258 mg, 1.20 mmol, 1.00 equiv.) and benzene (degassed, 45 mL). The mixture was heated to 100 °C and stirred at this temperature. A solution of Bu_3SnH (757 mg, 2.60 mmol, 2.17 equiv.) and azobisisobutyronitrile (AIBN) (10.0 mg, 60.9 µmol, 5mol%) in benzene (degassed, 10mL) was added dropwise over 8 h. After complete addition, the reaction mixture was stirred for another 2 h. The reaction mixture was allowed to cool down to room temperature and the mixture was washed with H_2O (2 × 50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **155** (86.7 mg, 637 µmol, 53%[6]) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 95:5, stained with $KMnO_4$) as a colorless oil.

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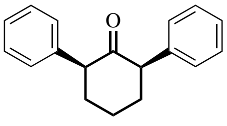
[6] Product contains 4.8w% Bu_3SnH

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.45 (tdd, J = 7.5, 2.9, 1.4 Hz, 2H), 3.16 (q, J = 7.6 Hz, 1H), 2.94 – 2.73 (m, 1H), 2.07 – 1.94 (m, 2H), 1.92 – 1.81 (m, 2H), 1.82 – 1.70 (m, 2H), 1.53 (dtd, J = 11.7, 6.6, 5.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 221.5, 63.1, 45.8, 42.9, 33.2, 29.4.

The obtained spectroscopic data is in agreement to the literature.[88]

(2*R*,6*S*)-2,6-Diphenylcyclohexan-1-one (157)



The *cis* product **157** was prepared following a modified literature protocol by MILLER and coworkers.[139] To a round-bottom flask, *cis*/*trans* isomer 2,6-diphenylcyclohexan-1-one (111 mg, 445 µmol, 1.00 equiv.) and a mixture of MeOH:H_2O (2:1, 3.34 mL) were added and stirred at room temperature. Pyrrolidine (1 drop) was added to the mixture. The reaction mixture was heated to 100 °C and stirred at this temperature for 30 min. Without stirring, the reaction mixture was allowed to cool down to room temperature. The mixture was placed into a 4 °C refrigerator for 20 h. The crystals were isolated and washed with ice cold MeOH:H_2O (2:1, 3 mL). The product **157** (28.0 mg, 112 µmol, 25%) was obtained as yellowish solid. Alternatively, the product **157** (135 mg, 537 µmol, 21%) was obtained by purifying the *cis*/*trans* 2,6-diphenylcyclohexan-1-one (630 mg, 2.52mmol) using flash column chromatography (SiO_2, *n*-pentane:EtOAc 90:10, stained with $KMnO_4$) as colorless solid.

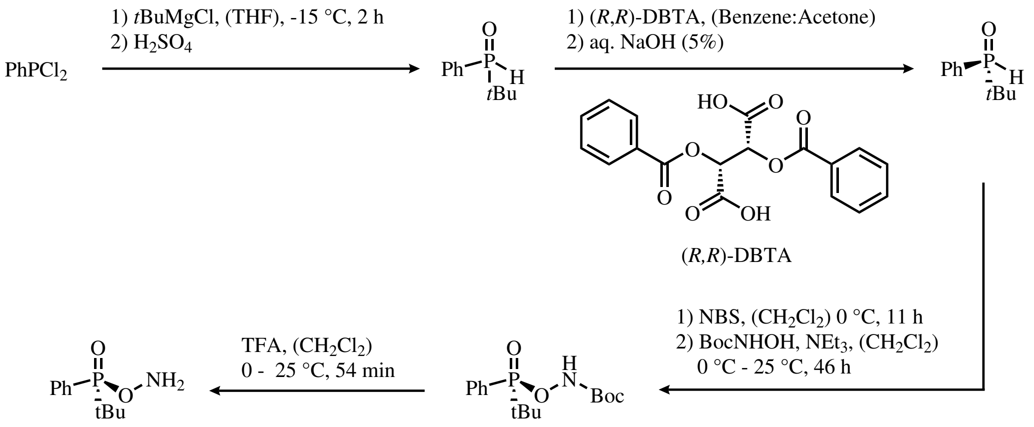
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.28 (m, 4H), 7.26 – 7.21 (m, 2H), 7.20 – 7.13 (m, 4H), 3.82 (dd, J = 12.6, 5.0 Hz, 2H), 2.49 – 2.35 (m, 2H), 2.28 – 1.97 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 208.4, 138.6, 128.9, 128.3, 127.0, 58.1, 36.5, 26.2.

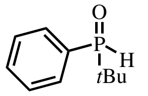
The obtained spectroscopic data is in agreement to the literature.[139]

7.4.2 Synthesis of Chiral Phosphorous Reagents

Synthetic Access to Chiral Phosphorous Reagents



***tert*-Butyl(phenyl)phosphine oxide ((*rac*)-139)**



The racemic phosphine (*rac*)-**139** was prepared following a modified literature protocol by MINNAARD and coworkers.[85] An oven-dried and N_2 filled 500 mL SCHLENK flask equipped with a magnetic stir bar was charged with *t*BuMgCl (1.7 M in THF, 82.4 mL, 16.4 g, 140 mmol, 2.00 equiv.) and anhydrous Et_2O (140 mL). The mixture was cooled down to $-15\,^\circ$C with an ice/salt mixture. $PhPCl_2$ (contains 97% of the actual product, 9.8 mL, 12.9 g, 70.0 mmol, 1.00 equiv.) in Et_2O (8.75 mL) was added over 2 h to the mixture. After 15 min of stirring, precipitation was observed. The mixture was stirred at this temperature for an additional hour. The reaction mixture was allowed to warm to room temperature. The slurry was hydrolized by slowly adding H_2SO_4 (25%, 119 mL, 560 mmol). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (5×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product (*rac*)-**139** (13.6 g, 74.4 mmol, 100%) was obtained as colorless solid and used without further purification.

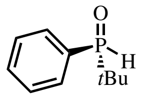
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73 – 7.63 (m, 2H), 7.60 – 7.54 (m, 1H), 7.53 – 7.45 (m, 2H), 7.04 (d, $J = 455.8$ Hz, 1H), 1.14 (d, $J = 16.7$ Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 132.7 (d, $J = 2.9$ Hz), 131.1 (d, $J = 10.1$ Hz), 128.7 (d, $J = 11.8$ Hz), 128.7 (d, $J = 90.3$ Hz), 32.1 (d, $J = 69.3$ Hz), 23.6 (d, $J = 2.2$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 48.5.

The obtained spectroscopic data is in agreement to the literature.[140]

(*R*)-*tert*-Butyl(phenyl)phosphine oxide ((*R*)-139)

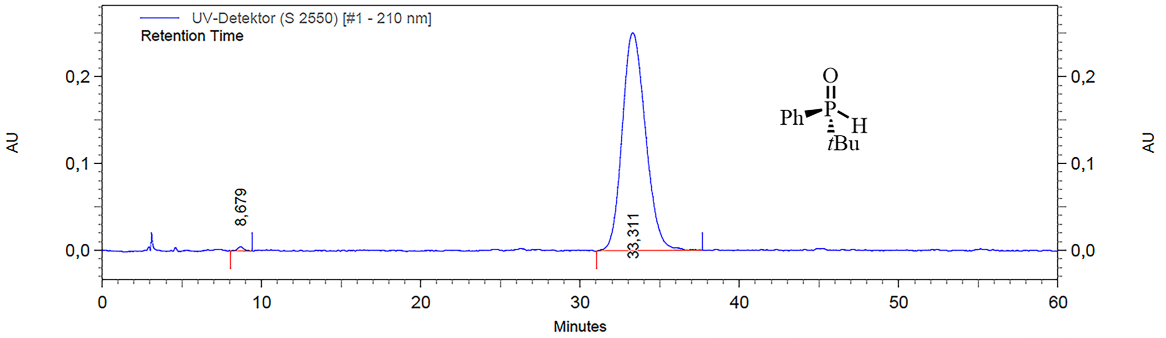


Enantiomericpure phosphine (*R*)-**139** was prepared following a modified literature protocol by Minnaard and coworkers.[85] To a round-bottom flask, a mixture of benzene:acetone (4:1, 196 mL) was added and the solvent mixture was heated to 90 °C. The racemic phosphine (*rac*)-**139** (13.4 g, 73.3 mmol, 1.00 equiv.) and (-)-(*R*,*R*)-dibenzoyltartaric acid (**141**, (*R*,*R*)-DBTA) (26.3 g, 73.3 mmol, 1.00 equiv.) were added to the refluxed reaction mixture. After the mixture was dissolved, the reaction mixture was allowed to cool down to room temperature and kept at this temperature for 17 h. The white crystals were isolated by filtration and washed with benzene:acetone (4:1, 12.6 mL). The crystals were dissolved in $CHCl_3$ (126 mL) and the solution was washed with an aqueous solution of NaOH (5%, 3 × 73 mL) and H_2O (52 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The aboved mentioned reaction steps were performed again. The product (*R*)-**139** (2.77 g, 15.2 mmol, 21%) was obtained as colorless solid and used without further purification.

HPLC: Enantiomerically enriched sample of 99:1 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS, 22 °C, 1.0 mL/min, 60:40 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 33.311 min, t_{minor} = 8.679 min). The absolute configuration was determined by comparison of HPLC with the reported data.

Optical Rotation: $[\alpha]_D^{25} = +0.43$ ($c = 1.29$, $CHCl_3$).

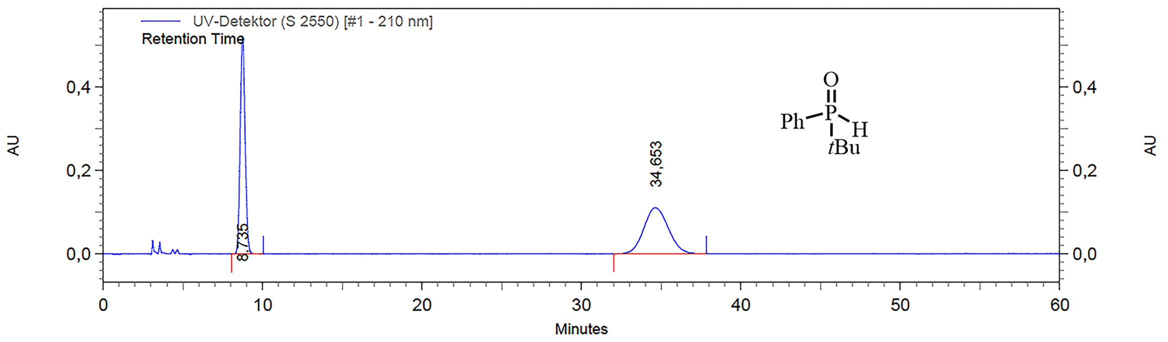
The obtained spectroscopic data is in agreement to the literature.[85]



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
8,679	127611	0,50
33,311	25517200	99,50

Figure 5: HPLC chromatogram for (*R*)-*tert*-butyl(phenyl)phosphine oxide ((*R*)-**139**)

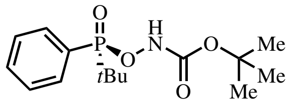


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
8,735	11315945	48,72
34,653	11911052	51,28

Figure 6: HPLC chromatogram for *rac*-*tert*-butyl(phenyl)phosphine oxide (*rac*-**139**)

tert-Butyl-(*S*)-((*tert*-butyl(phenyl)phosphoryl)oxy)carbamate ((*S*)-143a)



The Boc-protected hydroxylamine (*S*)-**143a** was prepared following a modified literature protocol by HAYNES and coworkers[141] and HUGHES and coworkers.[70] An oven-dried and N_2 filled 250 mL SCHLENK flask was charged with *N*-bromosuccinimde (NBS) (845 mg, 4.75 mmol, 0.950 equiv.) and dissolved in anhydrous CH_2Cl_2 (24.0 mL). The solution was cooled down to 0 °C with an ice/water bath. Enantiopure (*R*)-phosphine oxide (*R*)-**139** (455 mg, 2.50 mmol, 1.00 equiv.) in CH_2Cl_2 (24.0 mL) was added dropwise to the solution. The reaction mixture was stirred at 0 °C for 11 h. To a separate SCHLENK flask, *tert*-butyl *N*-hydroxycarbamate (3.99 g, 30.0 mmol, 6.00 equiv.) was added and dissolved in anhydrous CH_2Cl_2 (41.0 mL). The solution was cooled down to 0 °C with an ice/water bath. NEt_3 (5.20 mL, 3.79 g, 37.5 mmol, 7.50 equiv.) was added dropwise over 10 min to the Boc-protected hydroxylamine solution. Phosphinic bromide ?? was added dropwise *via* a syringe to the solution at 0 °C. The mixture was stirred at this temperature for 3 h and then slowly warmed to room temperature. The reaction mixture was continued stirring for 46 h. An aqueous solution of citric acid (5 wt%, 5.5 mL) was added. The phases were separated and the organic phase was washed with H_2O (4 × 50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product (*S*)-**143a** (1.26 g, 4.03 mmol, 81%) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 40:60 to 20:80, stained with $KMnO_4$) as a colorless solid.

M.P.: 62 – 70 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3094 (br), 2362 (s), 1749 (s), 1479 (m), 1161 (s), 1084 (m), 826 (m), 734 (s), 640 (s).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.70 (br s, 1H), 8.03 – 7.85 (m, 2H), 7.60 – 7.49 (m, 1H), 7.49 – 7.35 (m, 2H), 1.43 (s, 9H), 1.18 (d, $J = 15.7$ Hz, 9H).

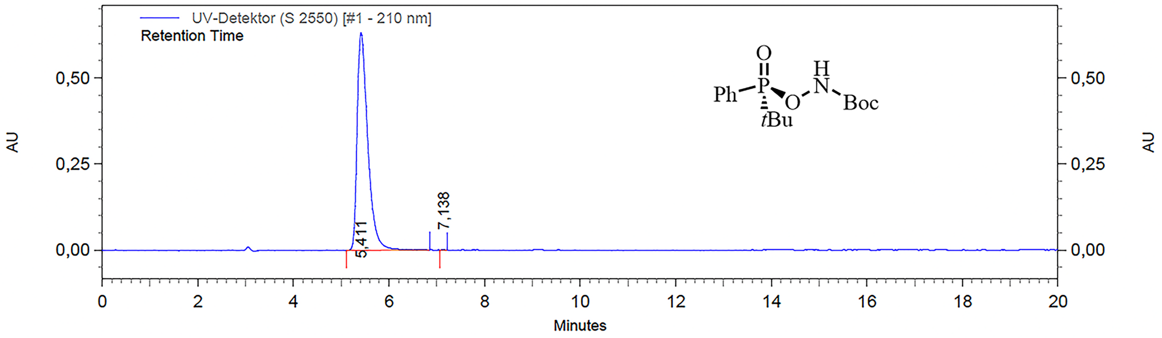
^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) = 156.3 (d, $J = 5.3$ Hz), 133.8 (d, $J = 9.5$ Hz), 132.7 (d, $J = 2.8$ Hz), 128.2 (d, $J = 12.2$ Hz), 126.2 (d, $J = 117.7$ Hz), 82.7, 32.7 (d, $J = 93.5$ Hz), 28.2, 24.5.

^{31}P NMR (162 MHz, CDCl$_3$): δ (ppm) = 60.6.

HRMS (ESI$^+$): Calculated for $C_{15}H_{24}NO_4PNa$ [M+Na]$^+$: 336.1335, Found: 336.1338.

HPLC: Enantiomerically enriched sample of >99:1 er. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS, 22 °C, 1.0 mL/min, 95:5 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 5.411 min, t_{minor} = 7.138 min).

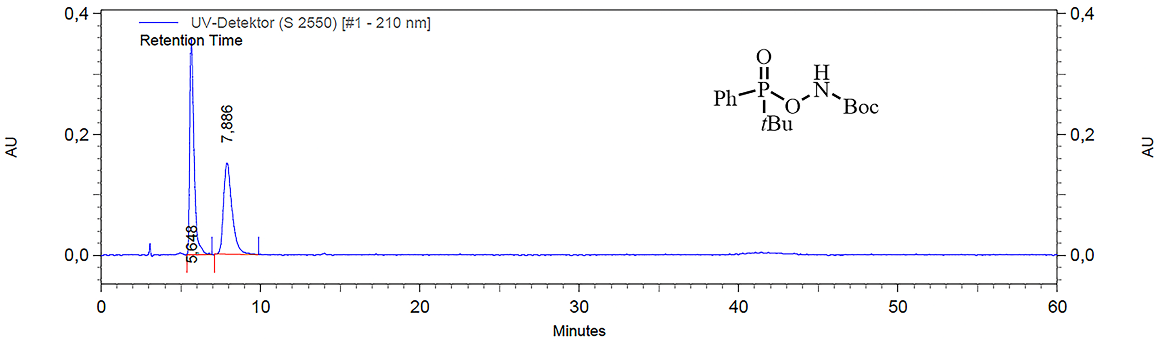
Optical Rotation: $[\alpha]_D^{25} = -0.114$ ($c = 0.50$, CHCl$_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
5,411	9786814	99,95
7,138	4854	0,05

Figure 7: HPLC chromatogram for *tert*-butyl-(*S*)-((*tert*-butyl(phenyl)phosphoryl)oxy)-carbamate ((*S*)-**143a**)

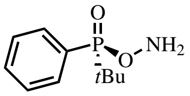


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
5,648	6619809	53,95
7,886	5649352	46,05

Figure 8: HPLC chromatogram for *rac*-*tert*-butyl-((*tert*-butyl(phenyl)phosphoryl)-oxy)carbamate (*rac*-**143a**)

(*S*)-(Aminooxy)(*tert*-butyl)(phenyl)phosphine oxide ((*S*)-145a)



An oven-dried and N_2 filled 50 mL SCHLENK flask equipped with a magnetic stir bar was charged with (*S*)-**143a** (219 mg, 700 µmol, 1.00 equiv.) and CH_2Cl_2 (3.5 mL). The solution was cooled down to 0 °C with an ice/water bath. TFA (3.5mL) was added dropwise over 10 min and the reaction mixture was stirred at this temperature for further 30 min. The reaction mixture was allowed to warm to room temperature and stirred for further 20 min. The mixture was cooled down to 0 °C with an ice/water bath. The mixture was diluted with CH_2Cl_2 (5 mL) and an aqueous saturated solution of $NaHCO_3$ (30 mL) was added dropwise. Then another portion of an aqueous saturated solution of $NaHCO_3$ (20 mL) was added. The phases were separated and the organic phase was washed with H_2O (50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The free chiral hydroxylamine (*S*)-**145a** (108 mg, 507 µmol, 72%) was obtained as colorless solid.

M.P.: 100 – 103 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3496 (br), 2967 (w), 2362 (s), 1478 (m), 1439 (m), 1234 (s), 1119 (s), 888 (s), 817 (s), 757 (s), 639 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.85 – 7.71 (m, 2H), 7.61 – 7.53 (m, 1H), 7.54 – 7.41 (m, 2H), 5.64 (br s, 2H), 1.15 (d, $J = 15.3$ Hz, 9H).

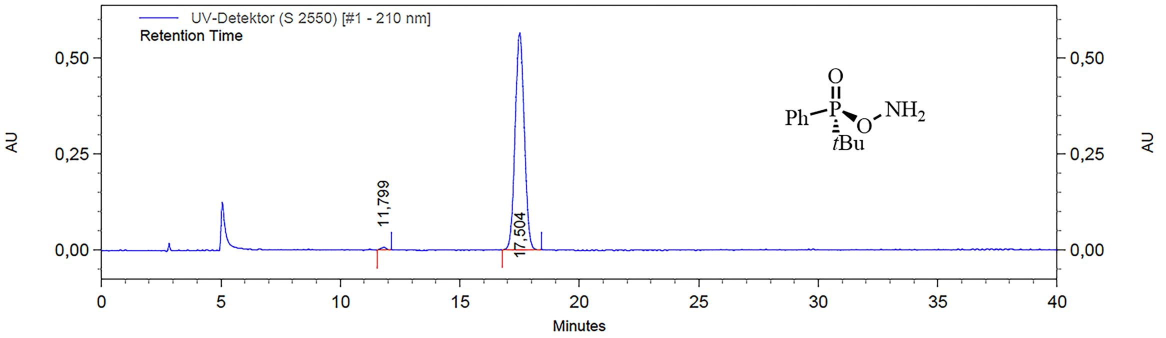
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 133.4 (d, $J = 8.9$ Hz), 132.4 (d, $J = 2.7$ Hz), 128.6 (d, $J = 11.8$ Hz), 127.4 (d, $J = 117.4$ Hz), 32.6 (d, $J = 94.7$ Hz), 24.7.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 58.4.

HRMS (ESI$^+$): Calculated for $C_{10}H_{17}NO_2P$ [M+H]$^+$: 214.0992, Found: 214.0995.

HPLC: Enantiomerically enriched sample of 99:1 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 17.504 min, t_{minor} = 11.799 min).

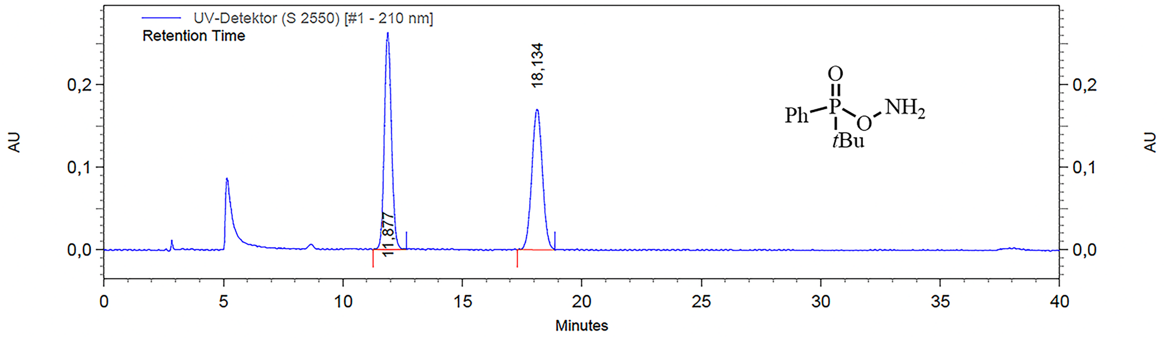
Optical Rotation: $[\alpha]_D^{25} = +0.279$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,799	111306	0,73
17,504	15070951	99,27

Figure 9: HPLC chromatogram for (*S*)-(aminooxy)(*tert*-butyl)(phenyl)phosphine oxide ((*S*)-**145a**)

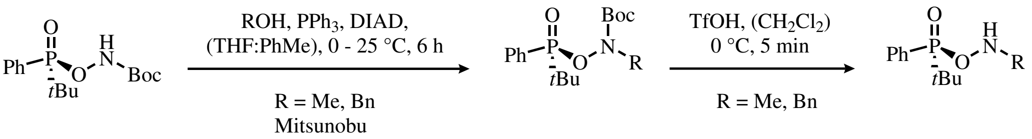


UV-Detektor (S 2550) [#1 - 210 nm] Results

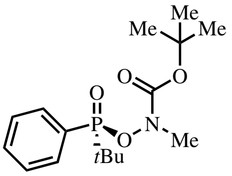
Retention Time	Area	Area %
11,877	5433829	50,82
18,134	5258653	49,18

Figure 10: HPLC chromatogram for *rac*-(aminooxy)(*tert*-butyl)(phenyl)phosphine oxide (*rac*-**145a**)

Synthetic Access to Chiral *N*-Substituted Hydroxylamines



tert-Butyl (*S*)-((*tert*-butyl(phenyl)phosphoryl)oxy)(methyl)carbamate ((*S*)-143b)



A round-bottom flask was charged with MeOH (27.9 µL, 22.0 mg, 688 µmol, 1.25 equiv.) and the solution was cooled down to 0 °C with an ice/water bath. Chiral Boc-protected hydroxylamine **143a** (172 mg, 550 µmol, 1.00 equiv., 98:2 er) and triphenylphosphine (361 mg, 1.38 mmol, 2.50 equiv.) in THF:toluene (1:3, 2.75 mL) were added to the solution. Diisopropyl azodicarboxylate (1.9 M solution in toluene, 615 µL, 236 mg, 1.17 mmol, 2.13 equiv.) was slowly added to the solution and the mixture was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and the mixture was stirred at this temperature for 1 h. The solvent was removed under reduced pressure. The product (*S*)-**143b** (171 mg, 523 µmol, 95%) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40 to 40:60, stained with $KMnO_4$) as a colorless solid.

M.P.: 103 – 107 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2977 (br), 1740 (m), 1720 (m), 1478 (w), 1395 (m), 1239 (m), 1154 (s), 1118 (m), 877 (w), 716 (m), 517 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.03 – 7.93 (m, 2H), 7.60 – 7.50 (m, 1H), 7.49 – 7.39 (m, 2H), 3.31 (s, 3H), 1.44 (s, 9H), 1.20 (d, $J = 15.5$ Hz, 9H).

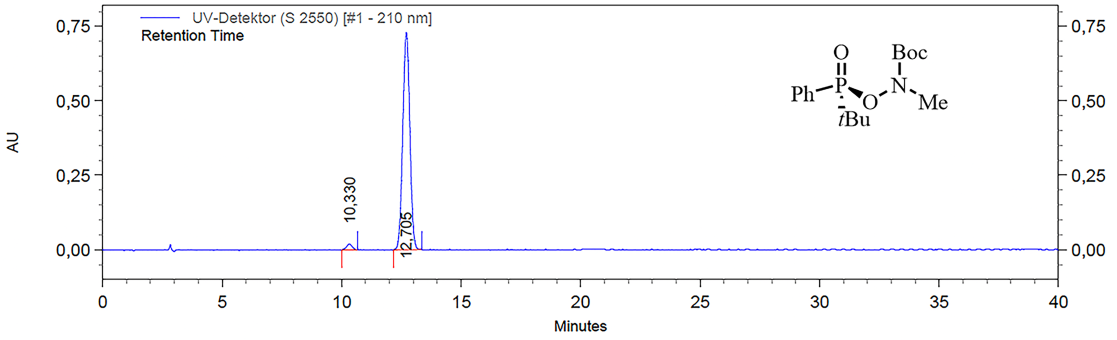
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.9 (d, $J = 4.1$ Hz), 134.0 (d, $J = 9.5$ Hz), 132.6 (d, $J = 2.8$ Hz), 128.0 (d, $J = 12.3$ Hz), 126.9 (d, $J = 116.4$ Hz), 83.0, 42.5, 33.1 (d, $J = 93.3$ Hz), 28.2, 24.6.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 59.1.

HRMS (ESI$^+$): Calculated for $C_{16}H_{26}NO_4PNa$ $[M+Na]^+$: 350.1491, Found: 350.1488.

HPLC: Enantiomerically enriched sample of 98:2 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 1.0 mL/min, 95:5 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 12.705 min, t_{minor} = 10.330 min).

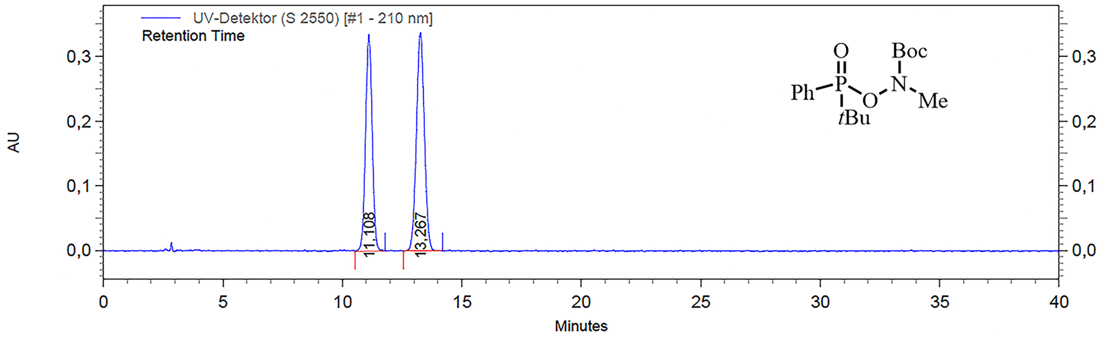
Optical Rotation: $[\alpha]_D^{25} = +0.046$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,330	300133	1,95
12,705	15089006	98,05

Figure 11: HPLC chromatogram for *tert*-butyl (*S*)-((*tert*-butyl(phenyl)phosphoryl)oxy)(methyl)-carbamate ((*S*)-**143b**)

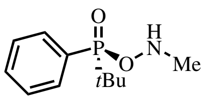


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,108	6516907	45,15
13,267	7916369	54,85

Figure 12: HPLC chromatogram for *tert*-butyl-((*tert*-butyl(phenyl)phosphoryl)oxy)(methyl)carbamate (*rac*-**143b**)

(*S*)-*tert*-Butyl((methylamino)oxy)(phenyl)phosphine oxide ((*S*)-**145b**)



A round-bottom flask was charged with (*S*)-**143b** (173 mg, 530 µmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (10.6 mL). The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (119 mg, 69.8 µL, 795 µmol, 1.50 equiv.) was added dropwise to the solution. The reaction was stirred at this temperature for 5 min. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product (*S*)-**145b** (106 mg, 465 µmol, 88%) was obtained without further purification as colorless solid.

M.P.: 109 – 114 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2967 (br), 1669 (w), 1477 (w), 1229 (m), 1119 (s), 942 (m), 877 (m), 822 (m), 716 (s), 636 (s), 512 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.83 – 7.74 (m, 2H), 7.58 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 6.07 (br s, 1H), 2.90 (s, 3H), 1.14 (d, J = 15.1 Hz, 9H).

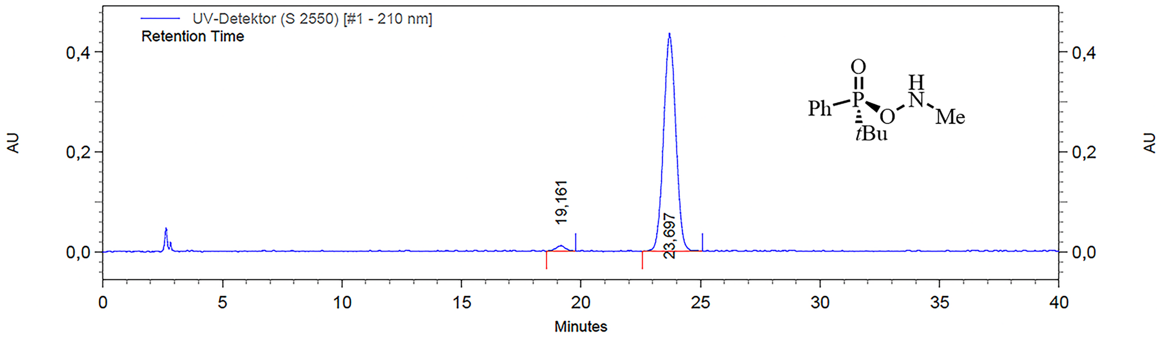
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 133.2 (d, J = 8.9 Hz), 132.1 (d, J = 2.8 Hz), 128.3 (d, J = 12.0 Hz), 128.3 (d, J = 118.8 Hz), 41.4 (d, J = 4.8 Hz), 32.4 (d, J = 94.8 Hz), 24.7.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 55.8.

HRMS (ESI^{+}): Calculated for $C_{11}H_{19}NO_2P$ [M+H]$^{+}$: 228.1148, Found: 228.1145.

HPLC: Enantiomerically enriched sample of 98:2 er. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 1.0 mL/min, 95:5 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 23.697 min, t_{minor} = 19.161 min).

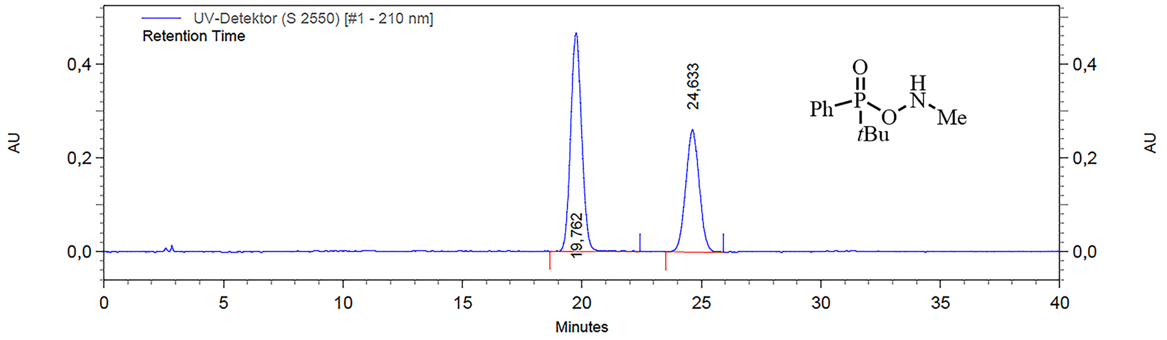
Optical Rotation: $[\alpha]_D^{25} = +0.287$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
19,161	331117	2,08
23,697	15553013	97,92

Figure 13: HPLC chromatogram for (*S*)-*tert*-butyl((methylamino)oxy)(phenyl)phosphine oxide ((*S*)-**145b**)

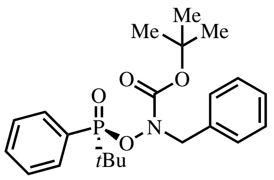


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
19,762	15004516	59,37
24,633	10268782	40,63

Figure 14: HPLC chromatogram for *rac*-*tert*-butyl((methylamino)oxy)(phenyl)phosphine oxide (*rac*-**145b**)

***tert*-Butyl (*S*)-benzyl((*tert*-butyl(phenyl)phosphoryl)oxy)carbamate ((*S*)-143c)**



A round-bottom flask was charged with BnOH (149 µL, 155 mg, 1.44 mmol, 1.25 equiv.) and the solution was cooled down to 0 °C with an ice/water bath. Chiral Boc-protected hydroxylamine **143a** (360 mg, 1.15 mmol, 1.00 equiv., 99:1 *er*) and triphenylphosphine (753 mg, 2.87 mmol, 2.50 equiv.) in THF:toluene (1:3, 5.75 mL) were added to the solution. Diisopropyl azodicarboxylate (1.9M solution in toluene, 1.28 mL, 494 mg, 2.44 mmol, 2.13 equiv.) was slowly added to the solution and the mixture was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and the mixture was stirred at this temperature for 4 h. The solvent was removed under reduced pressure. The product (*S*)-**143c** (435 mg, 1.08 mmol, 94%[7]) was obtained by gradient flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40 to 40:60, stained with $KMnO_4$) as a colorless oil.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2976 (br), 1738 (m), 1368 (m), 1234 (s), 1156 (s), 1117 (m), 880 (w), 699 (m), 521 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.07 – 7.90 (m, 2H), 7.62 – 7.51 (m, 1H), 7.51 – 7.36 (m, 4H), 7.35 – 7.27 (m, 3H), 4.96 – 4.80 (m, 2H), 1.40 (s, 9H), 1.16 (d, J = 15.6 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 156.7 (d, J = 4.1 Hz), 136.0, 134.0 (d, J = 9.5 Hz), 132.6 (d, J = 2.7 Hz), 128.8 (d, J = 81.4 Hz), 128.0 (d, J = 12.2 Hz), 127.9, 126.8 (d,

---

[7] Product contains 8.4wt% DIAD.

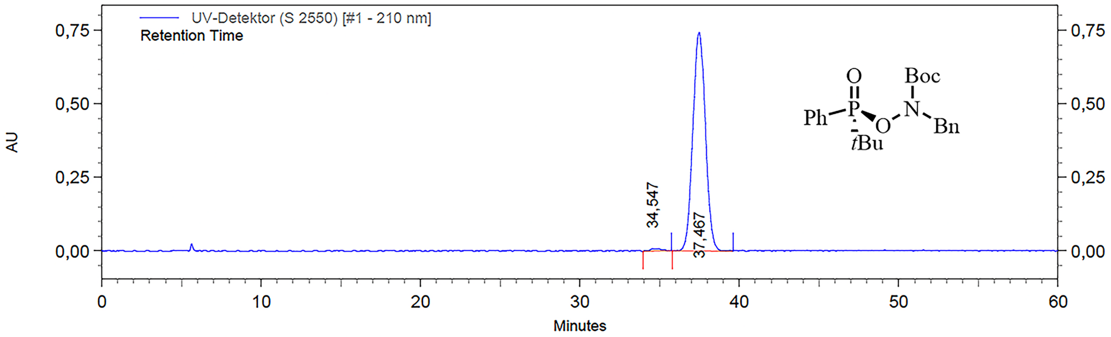
$J = 115.6\,\text{Hz}$), 83.1, 58.1, 33.6, 32.7, 28.1, 24.6, 22.1.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 59.8.

HRMS (ESI$^+$): Calculated for $C_{22}H_{31}NO_4P$ $[M+H]^+$: 404.1985, Found: 404.1989.

HPLC: Enantiomerically enriched sample of 99:1 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 0.5 mL/min, 95:5 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 37.467 min, t_{minor} = 34.547 min).

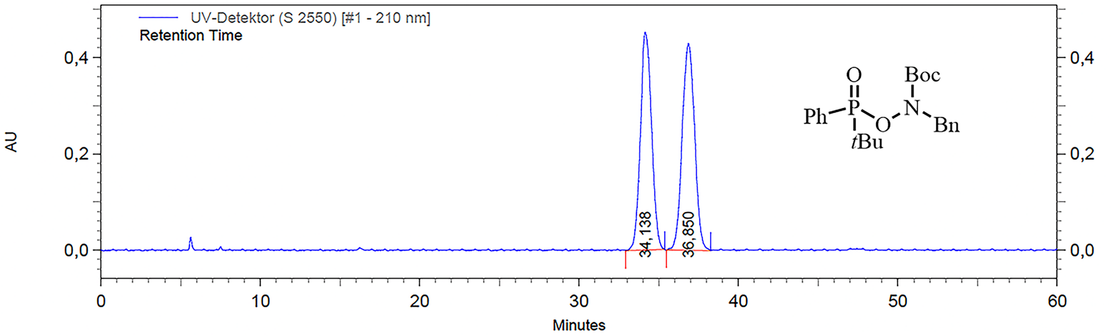
Optical Rotation: $[\alpha]_D^{25} = -0.083$ ($c = 1.0$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
34,547	436087	1,05
37,467	41043334	98,95

Figure 15: HPLC chromatogram for *tert*-butyl (*S*)-benzyl((*tert*-butyl(phenyl)phosphoryl)oxy)carbamate ((*S*)-**143c**)

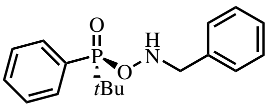


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
34,138	22099387	48,77
36,850	23218708	51,23

Figure 16: *rac*-*tert*-butyl-benzyl((*tert*-butyl(phenyl)phosphoryl)oxy)carbamate (*rac*-**143c**)

(*S*)-((Benzylamino)oxy)(*tert*-butyl)(phenyl)phosphine oxide ((*S*)-145c)



A round-bottom flask was charged with (*S*)-**143c** (91.6% purity, 234 mg, 530 µmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (10.6 mL). The solution was allowed to cool down to 0 °C with an ice/water bath and triflic acid (119 mg, 69.8 µL, 795 µmol, 1.50 equiv.) was added dropwise to the solution. The reaction was stirred at this temperature for 4 min. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product (*S*)-**145c** (140 mg, 462 µmol, 87%)) was obtained by flash column chromatography (SiO_2, n-pentane:EtOAc 10:90, stained with $KMnO_4$) as a colorless solid.

M.P.: 92 – 95 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2966 (br), 1477 (w), 1230 (m), 1119 (s), x (m), 747 (m), 697 (s), 638 (m), 513 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.68 – 7.58 (m, 2H), 7.55 – 7.47 (m, 1H), 7.45 – 7.37 (m, 2H), 7.36 – 7.27 (m, 5H), 4.29 – 4.17 (m, 2H), 1.12 (d, J = 15.2 Hz, 9H).

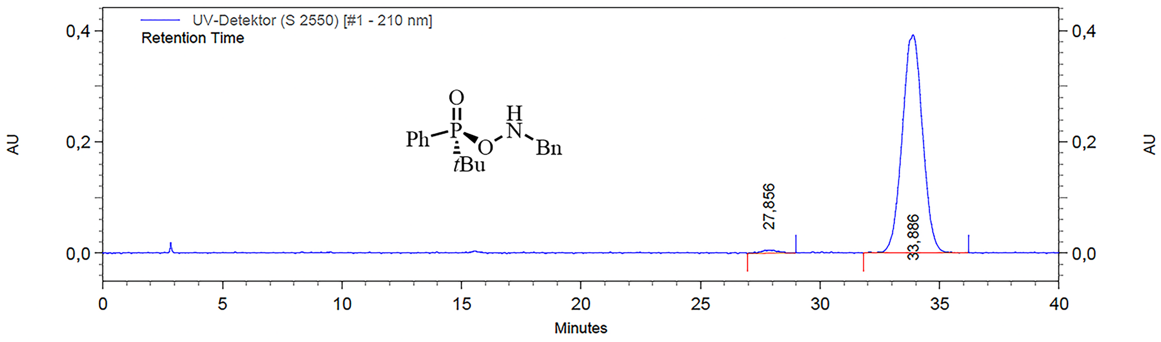
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 136.3, 133.3 (d, J = 8.9 Hz), 132.1 (d, J = 2.7 Hz), 129.1 (d, J = 97.6 Hz), 128.3 (d, J = 12.1 Hz), 128.1, 58.3 (d, J = 4.9 Hz), 32.6 (d, J = 94.7 Hz), 24.8.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 55.9.

HRMS (ESI$^+$): Calculated for $C_{34}H_{452}O_4P_2$ $[2M+H]^+$: 607.2849, Found: 607.2865.

HPLC: Enantiomerically enriched sample of 99:1 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 1.0 mL/min, 95:5 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 33.886 min, t_{minor} = 27.856 min).

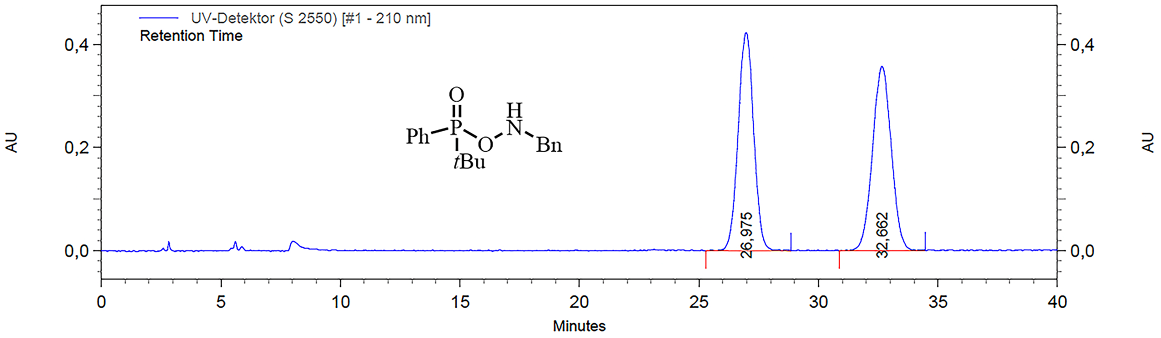
Optical Rotation: $[\alpha]_D^{25} = +0.208$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
27,856	296120	1,25
33,886	23334670	98,75

Figure 17: HPLC chromatogram for (*S*)-((benzylamino)oxy)(*tert*-butyl)(phenyl)phosphine oxide ((*S*)-**145c**)

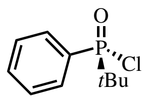


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
26,975	19351319	49,65
32,662	19626113	50,35

Figure 18: *rac*-((benzylamino)oxy)(*tert*-butyl)(phenyl)phosphine oxide (*rac*-**145c**)

(*R*)-*tert*-Butyl(phenyl)phosphinic chloride ((*R*)-142)



The phosphine oxide (*R*)-**142** was prepared following a modified literature protocol by Han and coworkers.[86] A round-bottom flask was charged with $CuCl_2$ (1.41 g, 10.5 mmol, 2.10 equiv) and anhydrous THF (10 mL). The solution was cooled down to 0 °C with an ice/water bath. *tert*-butylphosphonoylbenzene (911 mg, 5.00 mmol, 1.00 equiv, 93:7 *er*) in anhydrous THF (10 mL) was added to the mixture. The mixture was allowed to warm to room temperature and stirred for 10 min. The solvent was removed under reduced pressure and the residue was extracted with with hexane (2 × 50 mL). The organic phase was filtered, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product (*R*)-**142** (609 mg, 2.81 mmol, 56%) was obtained as a colorless solid without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.93 – 7.80 (m, 2H), 7.65 – 7.56 (m, 1H), 7.56 – 7.47 (m, 2H), 1.26 (d, $J = 19.0$ Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 133.1 (d, $J = 3.0$ Hz), 132.8 (d, $J = 9.9$ Hz), 129.9 (d, $J = 103.1$ Hz), 128.5 (d, $J = 12.5$ Hz), 39.1 (d, $J = 77.9$ Hz), 24.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 72.0.

Optical Rotation: $[\alpha]_D^{25} = +0.149$ ($c = 0.50$, benzene).

The obtained spectroscopic data is in agreement to the literature.[86]

Optimized Procedure for the Synthesis of *tert*-butyl(phenyl)phosphinic chloride (142)

A round-bottom flask was charged with pre-dried $CuCl_2$ (dried under high-vacuum at 70 °C) (706 mg, 5.25 mmol, 2.10 equiv) and THF (dried over molecular sieves Å, 10 mL). The solution was cooled down to 0 °C with an ice/water bath. *tert*-butylphosphonoylbenzene (911 mg, 5.00 mmol, 1.00 equiv) in THF (dried over molecular sieves Å, 10 mL) was added to the mixture. The mixture was allowed to warm to room temperature and the mixture was irradiated with ultrasound for 2 h. The solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and an aqueous solution of HCl (10%, 50 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (5×50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **142** (493 mg, 2.28 mmol, 91%) was obtained as a colorless oil without further purification.

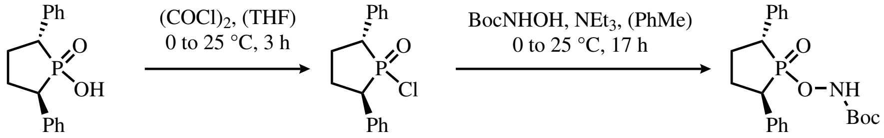
Optimization for the Nucleophilic Substitution with Phosphinic Chloride (*rac*)-142 and Boc-Protected Hydroxylamine

An oven-dried tube was charged with *tert*-butyl-*N*-hydroxy carbamate (14.6 mg, 110 µmol, 1.10 equiv.) and the corresponding solvent (0.5 mL). When the solid has been dissolved, the corresponding base (1.25 equiv.) was added. *tert*-butyl(phenyl)phosphinic chloride (21.7 mg, 100 µmol, 1.00 equiv.) in the corresponding solvent (0.5 mL) was added to the mixture and stirred at the selected temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR analysis using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

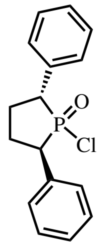
Optimization for the Deprotection of the Boc-Protected Hydroxylamine (*S*)-143a

An oven-dried tube was charged with Boc-protected hydroxylamine (*S*)-**143a** (31.3 mg, 100 µmol, 1.00 equiv.) and CH_2Cl_2 (0.5 mL). The mixture was cooled down to 0 °C with an ice/water bath. The corresponding acid was added and stirred for the selected time. The mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR analysis using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

Synthetic Access to C_2 Symmetric Chiral Phosphorous Reagent 148



(2*R*,5*R*)-1-Chloro-2,5-diphenylphospholane 1-oxide (147)



The phosphinic chloride **147** was prepared following a literature protocol by FIAUD and coworkers.[142] An oven-dried and N_2 filed SCHLENK flask was charged with phosphinic acid **146** (272 g, 1.00 mmol, 1.00 equiv.) and anhydrous THF (4 mL). The mixture was cooled down to 0 °C with an ice/water bath and oxalyl chloride (338 µL, 508 mg, 4.00 mmol, 4.00 equiv.) was added dropwise to the solution. The mixture was stirred for 5 min and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for at this temperature for 3 h. The solvent was removed under reduced pressure and the product **147** (224 mg, 769 µmol, 77%) was obtained as colorless solid without further purification.

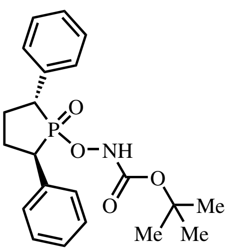
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.47 – 7.29 (m, 10H), 3.90 – 3.60 (m, 2H), 2.82 – 2.60 (m, 1H), 2.60 – 2.40 (m, 1H), 2.40 – 2.18 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 134.8 (d, $J = 5.9$ Hz), 133.9 (d, $J = 7.1$ Hz), 129.1 (d, $J = 2.3$ Hz), 128.9, 128.9 (d, $J = 8.3$ Hz), 128.0 (d, $J = 5.6$ Hz), 127.9 (d, $J = 3.0$ Hz), 127.8 (d, $J = 3.4$ Hz), 51.8 (d, $J = 67.7$ Hz), 50.9 (d, $J = 68.5$ Hz), 30.7 (d, $J = 14.1$ Hz), 25.4 (d, $J = 14.9$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 80.2.

The obtained spectroscopic data is in agreement to the literature.[142]

tert-Butyl (((2*R*,5*R*)-1-oxido-2,5-diphenylphospholan-1-yl)oxy)carbamate (148)



The Boc-protected hydroxylamine **148** was prepared following a modified literature protocol by HUGHES and coworkers.[70] An oven-dried and N_2 filled SCHLENK tube was charged with *tert*-butyl-*N*-hydroxy carbamate (73.2 mg, 550 µmol, 1.10 equiv.) and toluene (1.1 mL). The solution was cooled down to −8 °C with an ice/acetone bath. When the solid has been dissolved, NEt_3 (86.6 µL, 63.2 mg, 625 µmol, 1.25 equiv.) was added dropwise over 10 min. Phosphinic chloride **147** (145 mg, 500 µmol, 1.00 equiv.) and toluene (0.7 mL) were added over 30 min to the reaction mixture while the temperature was kept below 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The solution was washed with H_2O and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **148** (169 mg, 437 µmol, 87%) was obtained by gradient automated flash column chromatography (SiO_2, cyclohexane:EtOAc 70:30 to 10:90, stained with $KMnO_4$) as a colorless solid.

M.P.: 171 – 173 °C

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3119 (br), 2912 (w), 1742 (s), 1497 (w), 1248 (m), 1156 (s), 1083 (s), 759 (m), 696 (s), 548 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.38 (m, 2H), 7.38 – 7.30 (m, 6H), 7.30 – 7.18 (m, 3H), 3.79 – 3.61 (m, 1H), 3.59 – 3.41 (m, 1H), 2.72 – 2.53 (m, 1H), 2.53 – 2.44 (m, 1H), 2.44 – 2.26 (m, 1H), 2.18 (qdd, $J = 12.6, 5.3, 2.4$ Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 156.1 (d, $J = 4.3$ Hz), 135.3 (dd, $J = 241.6, 4.9$ Hz), 128.8 (dd, $J = 4.3, 2.0$ Hz), 128.7 (dd, $J = 59.9, 5.3$ Hz), 127.2 (dd, $J = 15.5, 2.4$ Hz), 83.5, 45.8 (d, $J = 81.9$ Hz), 43.0 (d, $J = 80.0$ Hz), 31.1 (d, $J = 13.2$ Hz), 28.2, 27.0 (d, $J = 12.1$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 72.1.

HRMS (ESI$^+$): Calculated for $C_{21}H_{26}NO_4PNa$ [M+Na]$^+$: 410.1491, Found: 410.1482.

7.4.3 Reaction Development

Solvent Screening

To an oven-dried tube the chiral hydroxylamine (*S*)-**145a** (23.5 mg, 110 µmol, 1.10 equiv.) and the corresponding solvent (0.4 mL) were added. 3-Phenylcyclobutanone (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) in the corresponding solvent (0.6 mL) was added to the reaction mixture and stirred at room temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR analysis using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The product **124** was obtained by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3).

Temperature Screening

To an oven-dried tube the chiral hydroxylamine (*S*)-**145a** (23.5 mg, 110 µmol, 1.10 equiv.) and toluene (0.4 mL) were added. 3-Phenylcyclobutanone (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) in toluene (0.6 mL) was added to the reaction mixture and stirred at the selected temperature for 24 h. The solvent was removed under reduced pressure and NMR yield of the crude reaction mixture was determined by ^{1}H NMR using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard. The product **124** was obtained by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3).

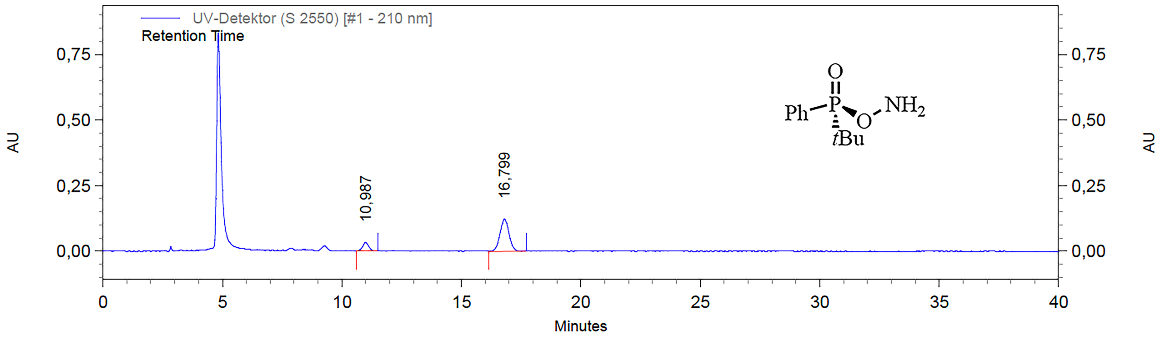
Stability Test

Irradiation of Chiral Hydroxylamine (*S*)-145a and (*S*)-145b with light

A solution of the chiral hydroxylamine (30 mmol, 1.00 equiv.) in CD_2Cl_2 (0.7 mL) was transferred to a NMR tube. The NMR tube was placed into LUZCHEM photoreactor and irradiated with either UV-A light (420 nm) or UV-B (300 nm) for 5 h. The NMR was submitted for NMR analysis and the ratio was determined by integrating the *tert*butyl group of the starting material and from the decomposing product. The enantiomeric purity was established by HPLC analysis using chiral stationary phases.

Racemization of (*S*)-145a in CD_2Cl_2 after 23 h

HPLC: Enantiomerically enriched sample of 85:15 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 16.799 min, t_{minor} = 10.987 min).



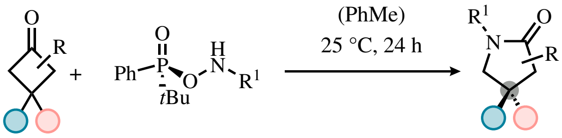
UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,987	590615	15,33
16,799	3261906	84,67

Figure 19: HPLC chromatogram for the racemization process of (*S*)-(aminooxy)(*tert*-butyl)(phenyl)phosphine oxide ((*S*)-**145a**)

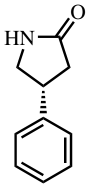
7.4.4 Synthesis of Chiral Lactams

General Procedure C for the Asymmetric Ring Expansion



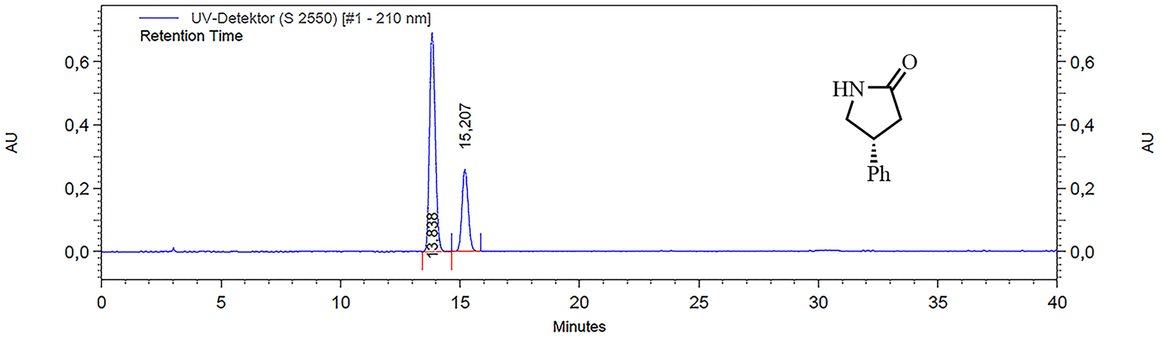
An oven-dried tube was charged with chiral aminating agent **145** (110 µmol, 1.10 equiv.) and dissolved in toluene (0.4 mL, 0.25 M). The corresponding ketone **13** (100 µmol, 1.00 equiv.) was dissolved in PhMe (0.6 mL, 0.17 M) and added to the mixture. The mixture was stirred at room temperature for 24 h. The reaction was stopped by adding NEt_3 (15.2 µL, 11.1 mg, 110 µmol, 1.10 equiv.).The solvent was concentrated under reduced pressure and the NMR yield of the crude reaction mixture was determined by ^1H NMR using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

(−)-4-Phenylpyrrolidin-2-one (124)



Following the general procedure **C** using 3-phenylcyclobutan-1-one (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) and chiral hydroxylamine **145a** (23.5 mg, 110 µmol, 1.10 equiv., 99:1 *er*), the product **124** (13.5 mg, 83.7 µmol, 84%) was obtained by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid.

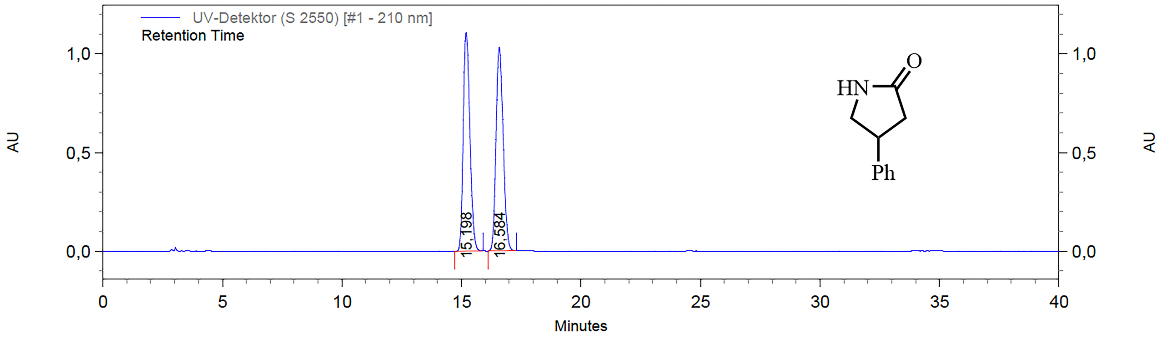
Optical Rotation: $[\alpha]_D^{25} = -0.089$ ($c = 0.50$, $CHCl_3$) for an enantiomerically enriched sample of 71:29 *er*; the major enantiomer is (*R*)-configured, assigned in analogy to the literature ($[\alpha]_D^{25} = -39.4$ ($c = 0.90$, $CHCl_3$), 99.5:0.5 *er* in favor of the (*R*)-enantiomer).[143] The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 13.838 min, t_{minor} = 15.207 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
13,838	11637643	71,22
15,207	4703642	28,78

Figure 20: HPLC chromatogram for (−)-4-phenylpyrrolidin-2-one ((−)-**124**)

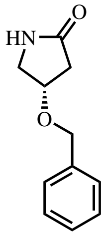


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
15,198	21479768	49,89
16,584	21575519	50,11

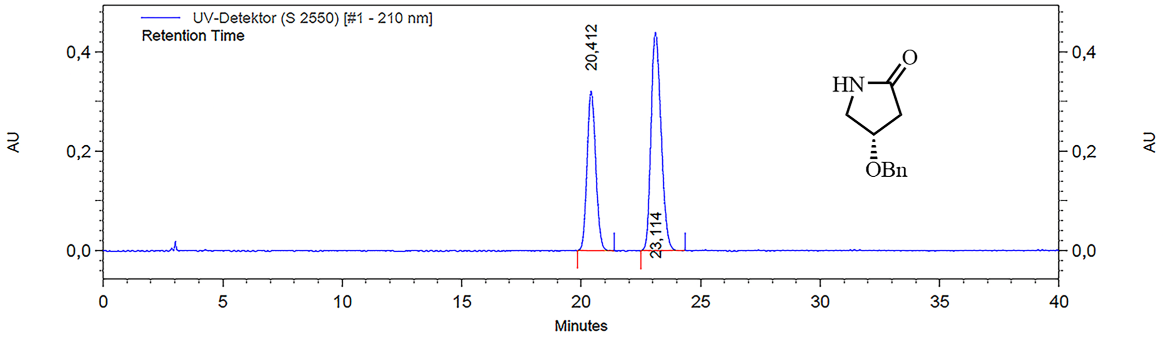
Figure 21: HPLC chromatogram for *rac*-4-phenylpyrrolidin-2-one (*rac*-**124**)

(−)-4-(Benzyloxy)pyrrolidin-2-one (161)



Following the general procedure **C** using 3-(benzyloxy)cyclobutan-1-one (**100e**) (17.6 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145a** (23.5 mg, 110 µmol, 1.10 equiv., 97:3 *er*) and CH_2Cl_2 (1.0 mL), the product **161** (11.3 mg, 59.1 µmol, 59%) was obtained by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid.

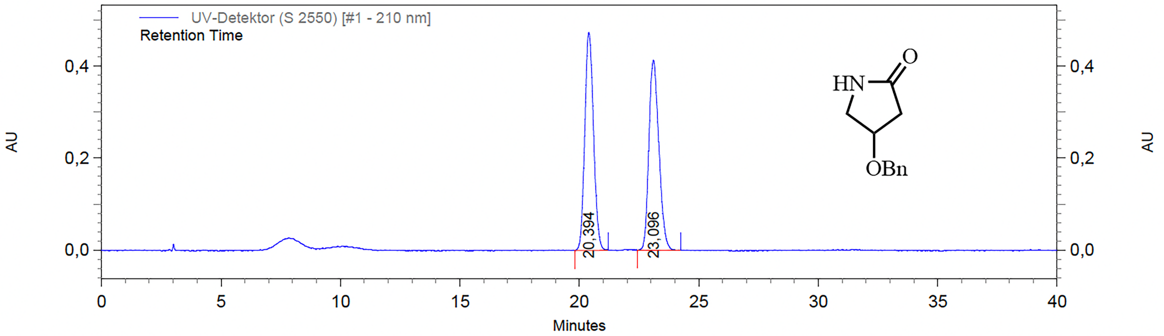
Optical Rotation: $[\alpha]_D^{25} = -0.002$ ($c = 0.50$, $CHCl_3$) for an enantiomerically enriched sample of 62:38 *er*; the major enantiomer is (*S*)-configured, assigned in analogy to the literature ($[\alpha]_D^{25} = +2.4$ ($c = 0.88$, $CHCl_3$), in favor of the (*R*)-enantiomer).[123] The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 23.114 min, t_{minor} = 20.412 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

	Retention Time	Area	Area %
	20,412	8098853	38,51
	23,114	12933781	61,49

Figure 22: HPLC chromatogram for (−)-4-(benzyloxy)pyrrolidin-2-one ((−)-**161**)

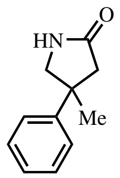


UV-Detektor (S 2550) [#1 - 210 nm] Results

	Retention Time	Area	Area %
	20,394	12035234	49,89
	23,096	12090579	50,11

Figure 23: HPLC chromatogram for *rac*-4-(benzyloxy)pyrrolidin-2-one (*rac*-**161**)

4-Methyl-4-phenylpyrrolidin-2-one (162)



Following the general procedure **C**[8] using 3-methyl-3-phenylcyclobutan-1-one (**100d**) (16.0 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145a** (23.5 mg, 110 µmol, 1.10 equiv., 99:1 *er*) and CH_2Cl_2 (1.0 mL), the product **162** (11.2 mg, 63.9 µmol, 64%) was obtained by flash column chromatography (SiO_2, EtOAc, stained with $KMnO_4$) as a colorless solid.

HPLC: An enantiomeric ratio of 46:54 *er* was established by HPLC analysis using a chiral column (Lux® Cellulose-1, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_1 = 15.196 min, t_2 = 13.444 min).

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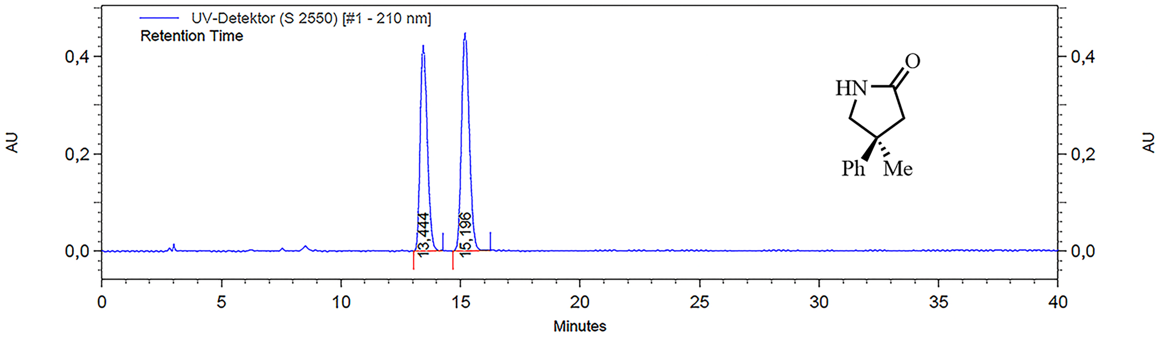
[8] The reaction was performed at 30 °C

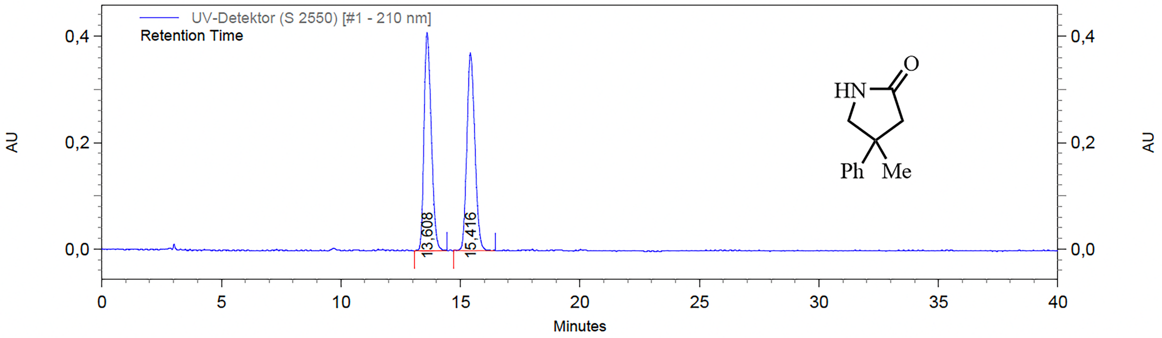
Optical Rotation: $[\alpha]_D{}^{25} = +0.003$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
13,444	8763781	46,28
15,196	10174256	53,72

Figure 24: HPLC chromatogram for 4-methyl-4-phenylpyrrolidin-2-one (**162**)

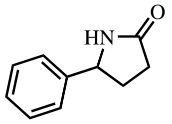


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
13,608	8656617	50,00
15,416	8655251	50,00

Figure 25: HPLC chromatogram for *rac*-4-methyl-4-phenylpyrrolidin-2-one (*rac*-**162**)

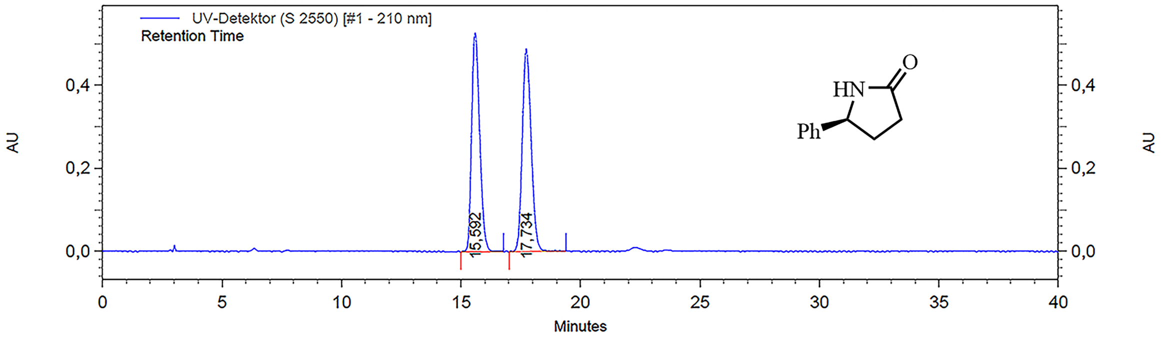
5-Phenylpyrrolidin-2-one (166)



Following the general procedure **C**[9] using 2-phenylcyclobutan-1-one (**84**) (14.6 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145a** (23.5 mg, 110 µmol, 1.10 equiv., 99:1 *er*) and CH_2Cl_2 (1.0 mL), the product **166** (14.5 mg, 90.0 µmol, 90%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

HPLC: An enantiomeric ratio of 49:51 *er* was established by HPLC analysis using a chiral column (Lux® Cellulose-1, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_1 = 17.734 min, t_2 = 15.592 min).

Optical Rotation: $[\alpha]_D^{25} = +0.000$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
15,592	12396602	49,36
17,734	12718996	50,64

Figure 26: HPLC chromatogram for 5-phenylpyrrolidin-2-one (**166**)

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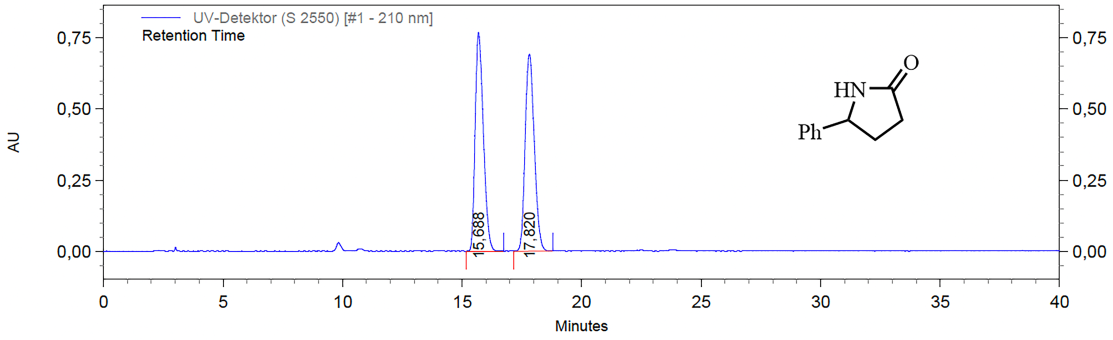
[9] The reaction was performed at 30 °C and stirred for 27 h

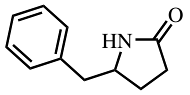


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
15,688	18406990	50,09
17,820	18343338	49,91

Figure 27: HPLC chromatogram for (*rac*)-5-phenylpyrrolidin-2-one (*rac*-**166**)

5-Benzylpyrrolidin-2-one (167)



Following the general procedure **C**[10] using 2-benzylcyclobutan-1-one (**86**) (16.0 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145a** (23.5 mg, 110 µmol, 1.10 equiv., 99:1 *er*) and CH_2Cl_2 (1.0 mL), a mixture of regioisomers **167** (11.8 mg, 67.3 µmol, 67%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

HPLC: An enantiomeric ratio of 49:51 *er* for the major regioisomer and 46:54 *er* for the minor regioisomer was established by HPLC analysis using a chiral column (Lux® Cellulose-1, 22 °C, 1.0 mL/min, 85:15 *n*-hexane:*i*-PrOH, 210 nm, major regioisomer: t_1 = 11.451 min, t_2 = 14.269 min; minor regioisomer: t_1 = 8.744 min, t_2 = 9.032 min).

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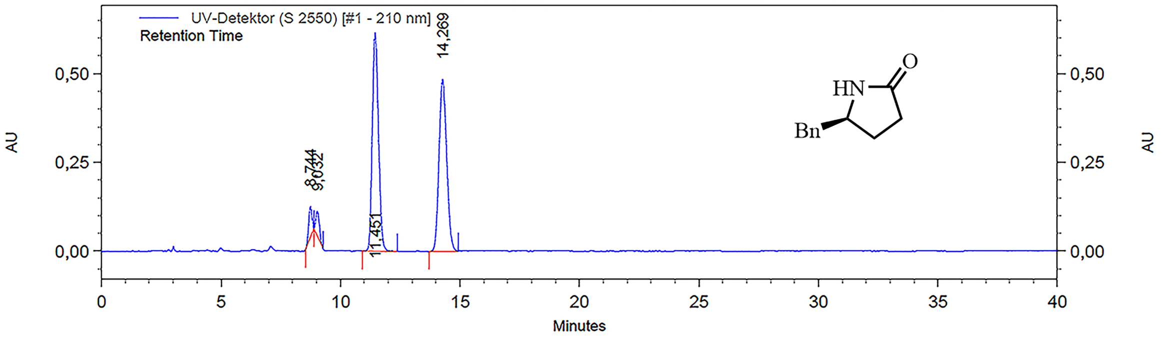
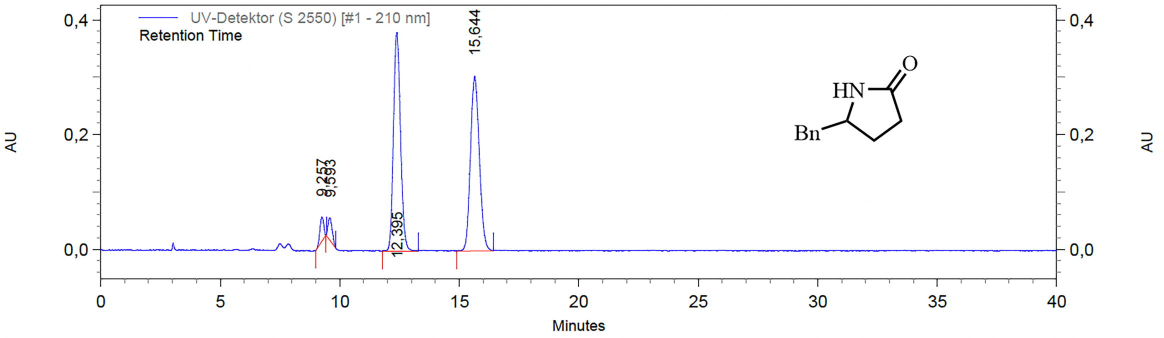
[10] The reaction was performed at 30 °C and stirred for 27 h



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
8,744	858449	3,65
9,032	744549	3,16
11,451	11117254	47,23
14,269	10818590	45,96

Figure 28: HPLC chromatogram for 5-benzylpyrrolidin-2-one (**167**)

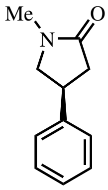


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
9,257	477321	2,87
9,593	481665	2,89
12,395	7819948	46,99
15,644	7863979	47,25

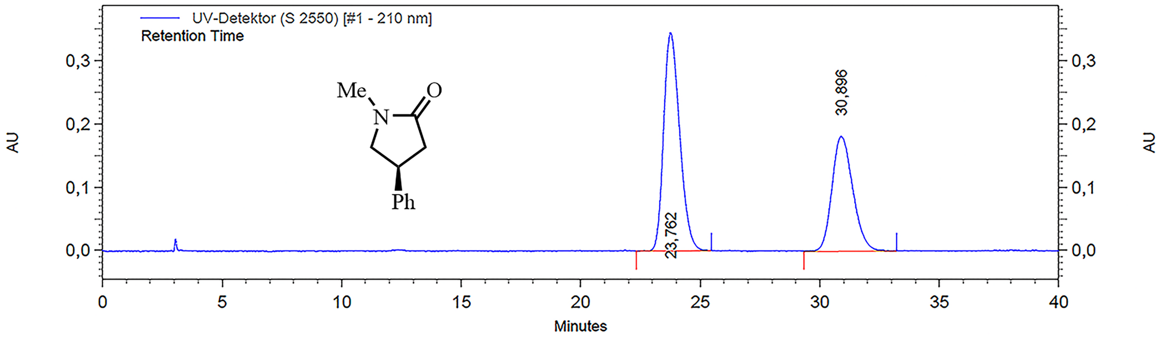
Figure 29: HPLC chromatogram for (*rac*)-5-benzylpyrrolidin-2-one (*rac*-**167**)

(+)-1-Methyl-4-phenylpyrrolidin-2-one (163)



Following the general procedure **C** using 3-phenylcyclobutan-1-one (**56**) (14.6 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145b** (25.0 mg, 110 µmol, 1.10 equiv., 98:2 *er*) and PhMe (1.0 mL), the product **163** (12.8 mg, 73.0 µmol, 73%) was obtained by flash column chromatography (SiO_2, EtOAc:MeOH 95:5, stained with $KMnO_4$) as a colorless solid.

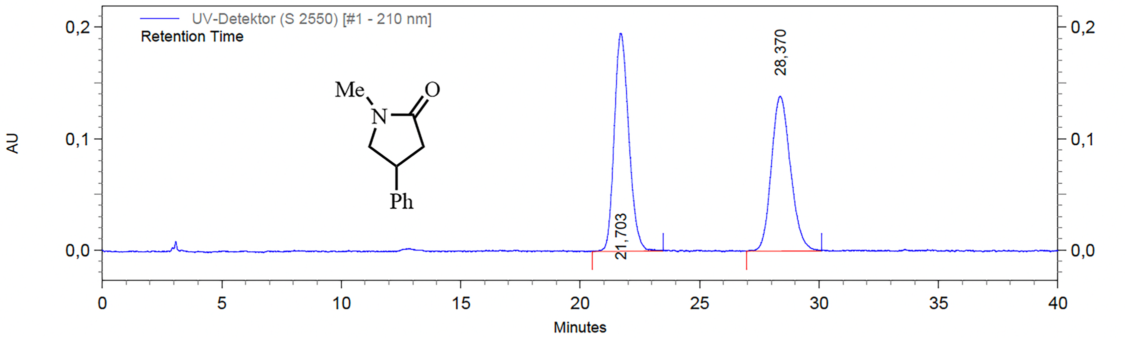
Optical Rotation: $[\alpha]_D{}^{25} = +0.040$ ($c = 0.50$, $CHCl_3$) for an enantiomerically enriched sample of 59:41 *er*; the major enantiomer is (*S*)-configured, assigned in analogy to the literature ($[\alpha]_D{}^{24} = +43.2$ ($c = 0.5$, $CHCl_3$), in favor of the (*S*)-enantiomer).[120] The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS, 22 °C, 1.0 mL/min, 80:20 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 23.762 min, t_{minor} = 30.896 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
23,762	16167217	59,30
30,896	11094668	40,70

Figure 30: HPLC chromatogram for (+)-1-methyl-4-phenylpyrrolidin-2-one ((+)-**163**)

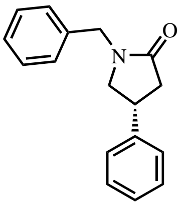


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
21,703	8286641	51,60
28,370	7771851	48,40

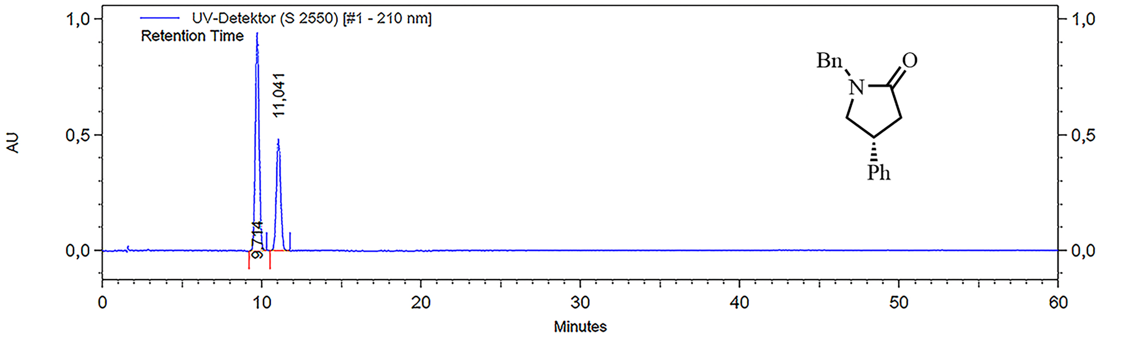
Figure 31: HPLC chromatogram for (*rac*)-1-methyl-4-phenylpyrrolidin-2-one (*rac*-**163**)

(−)-1-Benzyl-4-phenylpyrrolidin-2-one (164)



Following the general procedure **C** using 3-phenylcyclobutan-1-one (**56**) (14.6 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145c** (33.4 mg, 110 µmol, 1.10 equiv., 99:1 *er*), the product **164** (14.7 mg, 58.5 µmol, 58%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 60:40, stained with $KMnO_4$) as a colorless oil.

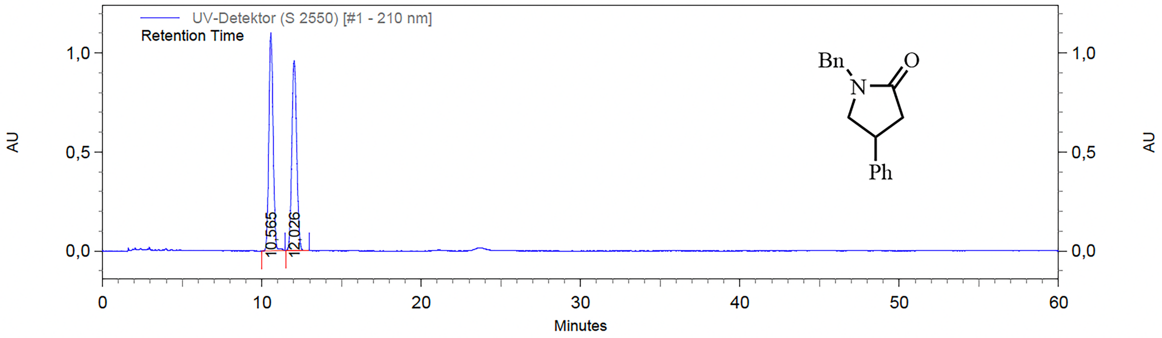
Optical Rotation: $[\alpha]_D^{25} = -0.047$ ($c = 0.50$, $CHCl_3$) for an enantiomerically enriched sample of 63:37 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5, 22 °C, 2.0 mL/min, 80:20 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 9.714 min, t_{minor} = 11.041 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
9,714	15816844	63,27
11,041	9181131	36,73

Figure 32: HPLC chromatogram for (−)-1-benzyl-4-phenylpyrrolidin-2-one ((−)-**164**)

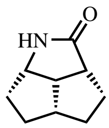


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,565	20532822	50,05
12,026	20488349	49,95

Figure 33: HPLC chromatogram for *rac*-1-benzyl-4-phenylpyrrolidin-2-one (*rac*-**164**)

(−)-Octahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one (168a)



Following the general procedure **C** using tricyclic ketone **155** (12.3 mg, 90.0 µmol, 1.00 equiv.), chiral hydroxylamine **145a** (21.1 mg, 99.0 µmol, 1.10 equiv., 99:1 *er*), the product **168a** (11.4 mg, 75.4 µmol, 84%) was obtained by gradient flash column chromatography (SiO_2, EtOAc:MeOH 100:0 to 95:5, stained with $KMnO_4$) as a colorless solid.

M.P.: 83 – 86 °C

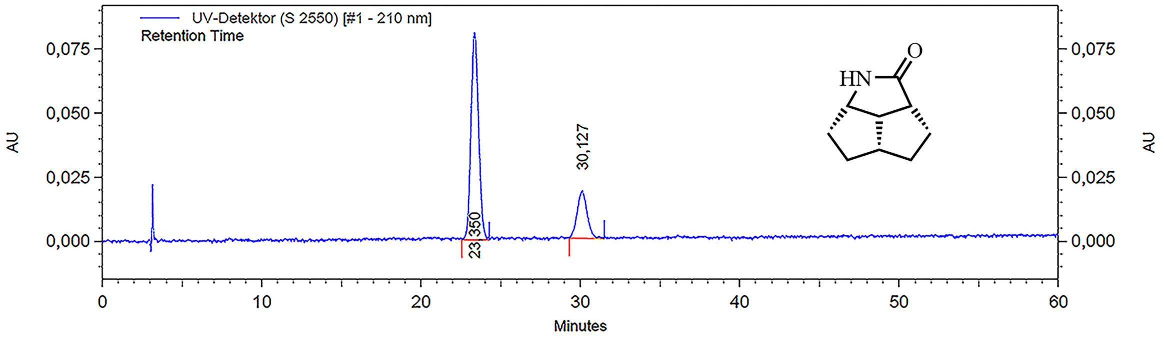
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3222 (br), 2948 (w), 1684 (s), 1449 (w), 1261 (w), 775 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.86 (br s, 1H), 4.08 – 3.98 (m, 1H), 3.09 (*app.* td, $J \approx 9.3, 7.7$ Hz, 1H), 2.82 (*app.* dddd, $J \approx 9.6, 8.7, 5.2, 0.7$ Hz, 1H), 2.53 (*app.* dddd, $J \approx 15.7, 8.5, 6.9, 4.9$ Hz, 1H), 2.14 – 1.94 (m, 2H), 1.87 – 1.66 (m, 4H), 1.56 – 1.34 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 181.0, 57.9, 50.4, 46.4, 46.2, 35.3, 32.0, 31.1, 29.2.

HRMS (ESI$^+$): Calculated for $C_9H_{14}NO$ $[M+H]^+$: 152.1070, Found: 152.1068.

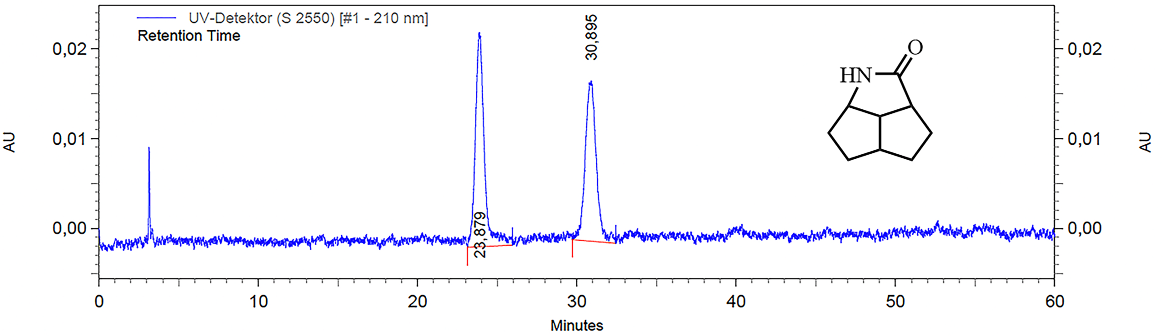
Optical Rotation: $[\alpha]_D^{25} = -0.068$ ($c = 0.50$, $CHCl_3$) for an enantiomerically enriched sample of 77:23 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5, 22 °C, 1.0 mL/min, 80:20 *n*-hexane:*i*-PrOH, 210 nm, t_{major} = 23.350 min, t_{minor} = 30.127 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
23,350	2705333	77,00
30,127	807885	23,00

Figure 34: HPLC chromatogram for (−)-octahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one ((−)-**168a**)

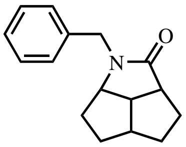


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
23,879	932785	51,84
30,895	866633	48,16

Figure 35: HPLC chromatogram for octahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one (*rac*-**168a**)

2-Benzyloctahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one (168b)



Following the general procedure **C** using tricyclic ketone **155** (13.6 mg, 100 µmol, 1.00 equiv.), chiral hydroxylamine **145c** (33.4 mg, 110 µmol, 1.10 equiv., 99:1 *er*), the product **168b** (19.3 mg, 80.0 µmol, 80%) was obtained by flash column chromatography (SiO_2, *n*-pentane:EtOAc 20:80, stained with $KMnO_4$) as a colorless oil.

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2950 (br), 1678 (s), 1424 (w), 1251 (w), 726 (w).

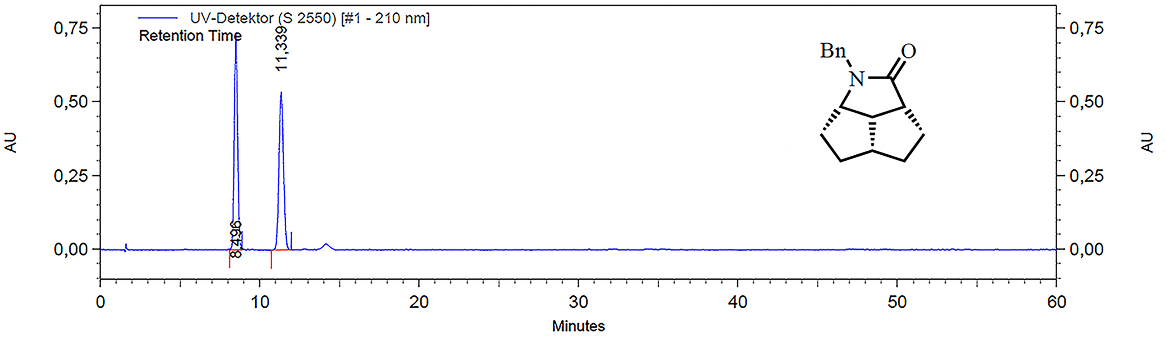
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.27 (m, 2H), 7.27 – 7.21 (m, 3H), 4.92 (d, $J = 14.8$ Hz, 1H), 3.92 (d, $J = 14.8$ Hz, 1H), 3.78 (ddd, $J = 8.0, 6.0, 2.4$ Hz, 1H), 2.99 – 2.85 (m, 2H), 2.59 – 2.45 (m, 1H), 2.16 – 1.97 (m, 2H), 1.84 – 1.75 (m, 2H), 1.75 – 1.56 (m, 2H), 1.44 – 1.33 (m, 1H), 1.33 – 1.22 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 177.4, 136.9, 128.7, 128.4, 127.6, 61.7, 47.3, 47.0, 45.9, 45.1, 31.6, 31.4, 31.4, 29.2.

HRMS (ESI$^+$): Calculated for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1540, Found: 242.1529.

HPLC: An enantiomeric ratio of 50:50 *er* was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5, 22 °C, 2.0 mL/min, 80:20 *n*-hexane:*i*-PrOH, 210 nm, t_1 = 8.496 min, t_2 = 11.339 min).

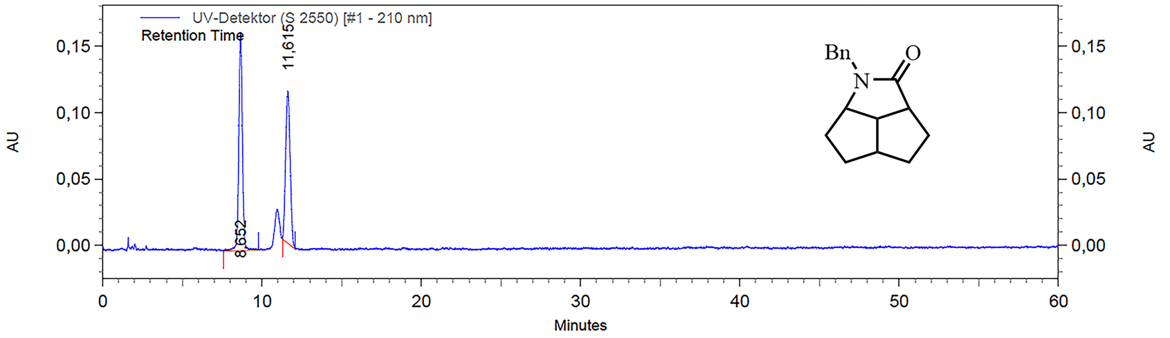
Optical Rotation: $[\alpha]_D{}^{25} = +0.004$ ($c = 0.50$, $CHCl_3$).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
8,496	10776469	50,22
11,339	10679942	49,78

Figure 36: HPLC chromatogram for 2-benzyloctahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one (**168b**)



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
8,652	2601924	53,48
11,615	2262880	46,52

Figure 37: HPLC chromatogram for racemic 2-benzyloctahydropentaleno[1,6-*bc*]pyrrol-1(2*H*)-one (*rac*-**168b**)

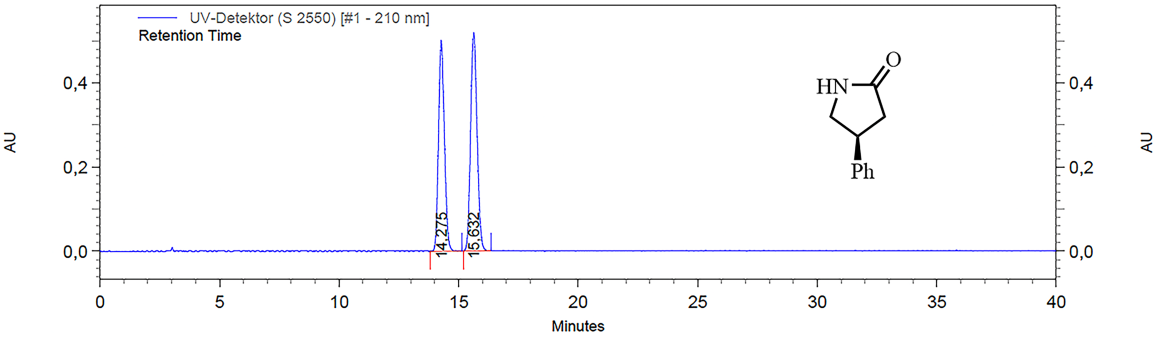
Synthesis of chiral γ-lactams with Sc(OTf)$_3$

An oven-dried tube was charged with Sc(OTf)$_3$ (9.8 mg, 20.0 µmol, 20 mol%) and dissolved in EtOAc (0.10 mL). The mixture was cooled down to −78 °C with a dry ice/acetone bath or kept at room temperature. 3-phenylcyclobutanone (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) in EtOAc (0.60 mL) was added. The chiral aminating reagent **145a** (23.5 mg, 110 µmol, 1.10 equiv., 99:1 *er*) was added followed by EtOAc (0.30 mL). The mixture was slowly allowed to warm to room temperature and the reaction was stirred at the corresponding reaction time. The reaction was stopped by adding NEt$_3$ (15.9 µL, 11.6 mg, 115 µmol, 1.15 equiv.).The solvent was concentrated under reduced pressure and the NMR yield of the crude reaction mixture was determined by ^{1}H NMR using dibromomethane (7.0 µL, 17.4 mg, 100 µmol) as the internal standard.

Synthesis of chiral γ-lactam 124 with C_2 symmetric reagent 148

An oven-dried tube was charged with C_2 symmetric reagent **148** (42.6 mg, 110 µmol, 1.10 equiv.) and dissolved in CH$_2$Cl$_2$ (0.30 mL). The solution was cooled down to 0 °C with an ice/water bath. 3-phenylcyclobutanone (**56**) (14.6 mg, 100 µmol, 1.00 equiv.) in CH$_2$Cl$_2$ (0.70 mL) was added dropwise. TfOH (15.0 mg, 100 µmol, 1.00 equiv.) in CH$_2$Cl$_2$ (0.5 mL) was added dropwise and the solution was stirred at 0 °C for 35 min. The mixture was allowed to warm to room temperature and the mixture was stirred for 24 h. The reaction was stopped by adding NEt$_3$ (15.2 µL, 11.1 mg, 110 µmol, 1.10 equiv.). The solvent was concentrated under reduced pressure and the product **124** (9.8 mg, 60.7 µmol, 61%) was obtained by gradient flash column chromatography (SiO$_2$, EtOAc:MeOH 100:0 to 95:5, stained with KMnO$_4$) as a colorless solid.

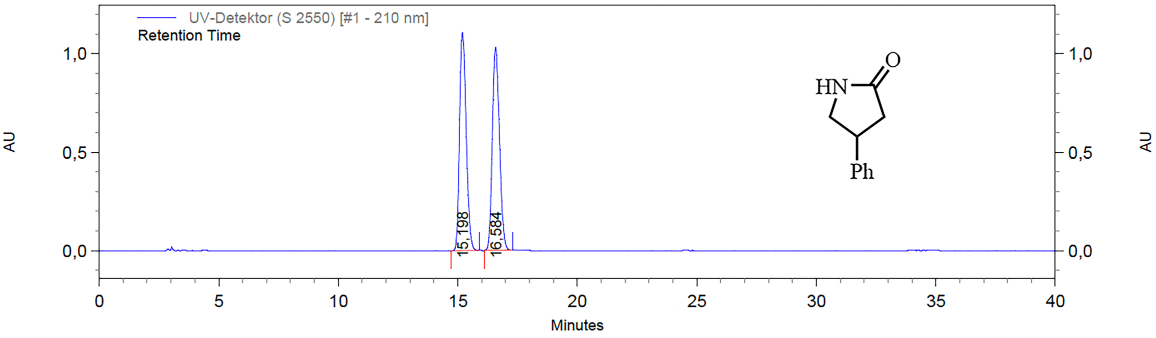
HPLC: An enantiomeric ratio of 47:53 *er* was established by HPLC analysis using a chiral column (Lux® i-Amylose-3, 22 °C, 1.0 mL/min, 90:10 *n*-hexane:*i*-PrOH, 210 nm, t_1 = 15.632 min, t_2 = 14.275 min).



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
14,275	8627114	46,70
15,632	9848189	53,30

Figure 38: HPLC chromatogram for 4-phenylpyrrolidin-2-one (**124**)



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
15,198	21479768	49,89
16,584	21575519	50,11

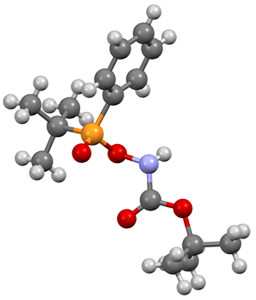
Figure 39: HPLC chromatogram for *rac*-4-phenylpyrrolidin-2-one (*rac*-**124**)

7.4.5 Crystallographic Data

X-Ray Crystal Structure Analysis of (*S*)-143a

The crystal data and structure refinement was measured and performed by SCHOLLMEYER. A colorless block of $C_{15}H_{24}NO_4P$ (0.400×0.410×0.460 mm^3) was used for the X-ray crystallographic analysis, which was measured on a STOE IPDS 2T diffractometer system.

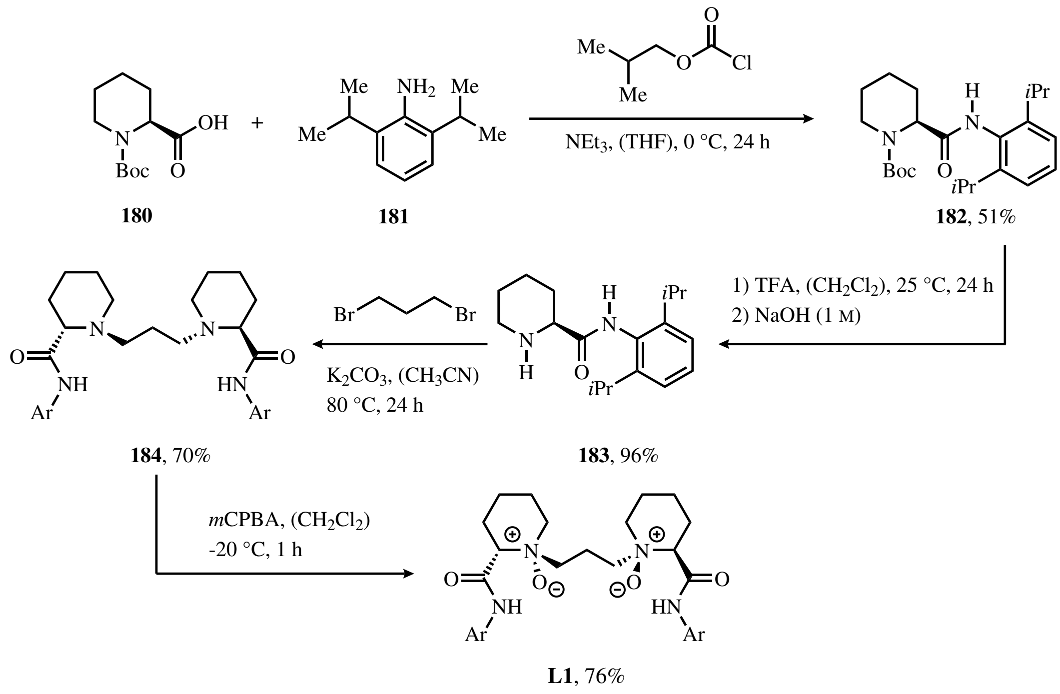
Table 15: Crystal data and structure refinement for (*S*)-**143a**.



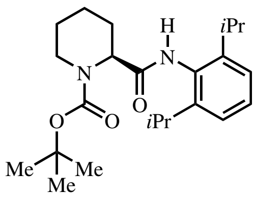
Identification code	iv159
Empirical formula	$C_{15}H_{24}NO_4P$
moiety formula	$C_{15}H_{24}NO_4P$
Formula weight	313.32
Temperature	120(2) K
Wavelength, radiation type	0.71073Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Orthorhombic
Space group name, number	P $2_12_12_1$, (19)
Unit cell dimensions	a = 9.9927(3)Å α= 90 °
	b = 10.9307(2)Å β= 90 °
	c = 15.7239(4)Å γ=90 °
Volume	1717.48(7) Å^3
Number of reflections	33883
and range used for lattice parameters	2.59° <=Θ<= 28.41°
Z	4
Density (calculated)	1.212 $\frac{Mg}{m^3}$
Absorption coefficient	0.174 mm^{-1}
Absorption correction	Integration
Max. and min. transmission	0.9423 and 0.9267
F(000)	672
Crystal size, colour and form	0.400×0.410×0.460 mm^3, colorless block
Theta range for data collection	2.591 to 27.866°
Index ranges	-13<=h<=13, -14<=k<=14, -20<=l<=20
Number of reflections:	
collected	15781
independent	4089 [R_{int} = 0.0159]
observed [I>2sigma(I)]	4015
Completeness to theta = 25.2°	99.9%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4089 / 0 / 274
Goodness-of-fit on F^2	1.094
Final R indices [I>2sigma(I)]	R1 = 0.0264, wR2 = 0.0675
R indices (all data)	R1 = 0.0272, wR2 = 0.0684
Absolute structure parameter	0.02(3)
Largest diff. peak and hole	0.351 and -0.176 eÅ^{-3}
Remark	H-atom isotropic refined

7.5 Studies Towards a Catalytic Approach

7.5.1 Synthesis of Chiral *N,N'*-Dioxide Ligand L1



tert-Butyl (*S*)-2-((2,6-diisopropylphenyl)carbamoyl)piperidine-1-carboxylate (182)



The product **182** was prepared following a literature protocol by FENG and coworkers.[144] The 250 mL round-bottom flask was charged with Boc-protected piperidine **180** (2.29 g, 10.0 mmol, 1.00 equiv.) and dissolved in THF (50 mL). The solution was allowed to cool down to 0 °C with an ice/water bath. NEt_3 (1.52 mL, 1.11 g, 11.0 mmol, 1.10 equiv.) and isobutyl carbonochloridate (1.30 mL, 1.37 g, 10.0 mmol, 1.00 equiv.) were added and the mixture was stirred for 25 min. 2,6-diisopropylaniline (**181**) (1.89 mL, 1.77 g, 10.0 mmol, 1.00 equiv.) was added and the reaction was allowed to warm to room temperature and stirred for 20 h. The mixture was washed with an aqueous solution of $KHSO_4$ (1 M, 50 mL), an aqueous saturated solution of $NaHCO_3$ (50 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **182** (1.98 g, 5.09 mmol, 51%)) was obtained by flash column chromatography (SiO_2, PE:EtOAc 90:10, stained with $KMnO_4$) as a colorless solid.

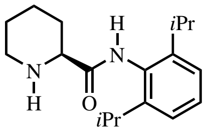
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.49 (s, 1H), 7.29 (t, $J = 7.8$ Hz, 1H), 7.17 (d, $J = 7.7$ Hz, 2H), 4.97 (s, 1H), 4.52 – 3.92 (m, 1H), 3.04 (hept, $J = 7.0$ Hz, 2H), 2.98 – 2.82

(m, 1H), 2.64 – 2.25 (m, 1H), 1.83 – 1.55 (m, 5H), 1.51 (s, 9H), 1.20 (dd, $J = 6.9, 2.0$ Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 170.8, 146.2, 131.1, 128.5, 123.5, 81.0, 56.3, 53.9, 42.7, 41.7, 29.0, 28.5, 25.2, 23.8, 20.9.

The obtained spectroscopic data is in agreement to the literature.[145]

(*S*)-*N*-(2,6-Diisopropylphenyl)piperidine-2-carboxamide (183)



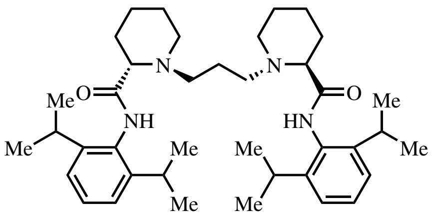
The product **183** was prepared following a literature protocol by FENG and coworkers.[145] To a round-bottom flask, the amide **182** (1.79 g, 4.61 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (8 mL). TFA (4 mL) was added to the reaction mixture and the mixture was stirred at room temperature for 1 d. The solvent was removed under reduced pressure and H_2O (10 mL) was addded. An aqueous solution of NaOH (2 M) was added until the pH value was in the range of 10 - 12. The aqueous phase was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product **183** (1.28 g, 4.42 mmol, 96%) showed sufficient purity and was used for the next step without any purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (s, 1H), 7.31 – 7.23 (m, 1H), 7.21 – 7.12 (m, 2H), 3.43 (dd, $J = 10.2, 3.3$ Hz, 1H), 3.14 (dq, $J = 12.0, 2.4$ Hz, 1H), 3.03 (p, $J = 6.9$ Hz, 2H), 2.80 (ddd, $J = 11.9, 10.6, 3.1$ Hz, 1H), 2.15 – 2.05 (m, 1H), 1.91 – 1.75 (m, 2H), 1.70 – 1.56 (m, 2H), 1.56 – 1.42 (m, 2H), 1.20 (dd, $J = 6.9, 5.1$ Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.5, 146.1, 131.1, 128.3, 123.5, 61.0, 46.1, 30.4, 28.9, 26.1, 24.2, 23.8, 23.7.

The obtained spectroscopic data is in agreement to the literature.[145]

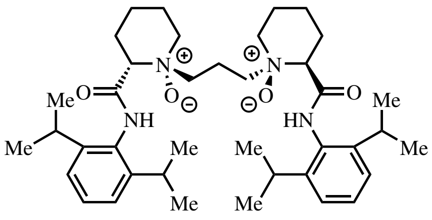
(2*S*,2'*S*)-1,1'-(Propane-1,3-diyl)bis(*N*-(2,6-diisopropylphenyl)piperidine-2-carboxamide) (184)



The product **184** was prepared following a literature protocol by FENG and coworkers.[145] To a round-bottom flask, the compound **183** (1.15 g, 4.00 mmol, 2.00 equiv.) was added and dissolved in MeCN (6.0 mL). K_2CO_3 (1.22 g, 8.80 mmol, 4.40 equiv.) and 1,3-dibromopropane (204 µL, 404 mg, 2.00 mmol, 1.00 equiv.) was added to the mixture. The mixture was heated to 80 °C and stirred for 1 d. K_2CO_3 was removed by filtration and washed by CH_2Cl_2. The filtrate was concentrated and the product **184** (859 mg, 1.39 mmol, 70%) was obtained by automated flash column chromatography (SiO_2, cyclohexane:EtOAc 75:25 to 50:50, stained with $KMnO_4$) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.00 (s, 2H), 7.33 – 7.27 (m, 2H), 7.22 – 7.16 (m, 4H), 3.23 (dt, $J = 11.8, 3.9$ Hz, 2H), 3.06 (hept, $J = 6.9$ Hz, 4H), 2.91 (dd, $J = 10.2, 3.6 Hz$, 2H), 2.87 – 2.73 (m, 2H), 2.33 – 2.20 (m, 2H), 2.15 – 2.00 (m, 4H), 1.91 (p, $J = 8.2$ Hz, 2H), 1.84 – 1.61 (m, 6H), 1.60 – 1.45 (m, 2H), 1.42 – 1.30 (m, 2H), 1.26 – 1.20 (m, 24H).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.8, 146.3, 130.9, 128.4, 123.6, 69.0, 55.9, 52.2, 30.4, 28.9, 27.2, 24.9, 23.9, 23.6, 22.3.
The obtained spectroscopic data is in agreement to the literature.[145]

(1*R*,1'*R*,2*S*,2'*S*)-1,1'-(Propane-1,3-diyl)bis(2-((2,6-diisopropylphenyl)carbamoyl)piperidine 1-oxide) (L1)



The product **L1** was prepared following a literature protocol by FENG and coworkers.[145] An oven-dried round-bottom flask was charged with **184** (740 mg, 1.20 mmol, 1.00 equiv.) and dissolved in CH_2Cl_2 (18 mL). The mixture was cooled down to −20 °C with a NaCl/ice mixture. *m*CPBA (contains 77% of the actual substrate, 672 mg, 3.00 mmol, 2.50 equiv.) was added and stirred at this temperature for 100 min. The solvent was removed under reduced pressure and the crude reaction mixture was purified by gradient flash column chromatography (SiO_2, EtOAc:MeOH 80:20 to 77:33, stained with $KMnO_4$). The desired product was obtained by dissolving in CH_2Cl_2 and filtration through CELITE® to remove the silicon gel. The solvent was removed to achieve the desired *N*,*N'*-dioxide ligand **L1** (591 mg, 911 mmol, 76%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.96 (s, 2H), 7.32 – 7.22 (m, 2H), 7.22 – 7.11 (m, 4H), 3.78 – 3.50 (m, 4H), 3.47 – 3.24 (m, 2H), 3.22 – 2.88 (m, 6H), 2.85 – 2.55 (m, 4H), 2.55 – 2.30 (m, 2H), 2.27 – 2.07 (m, 2H), 1.93 (d, $J = 16.2$ Hz, 2H), 1.82 – 1.55 (m, 2H), 1.55 – 1.34 (m, 2H), 1.28 – 1.15 (m, 24H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm)[11] = 167.9, 145.2, 130.9, 128.1, 123.6, 76.4, 66.2, 65.1, 29.1, 28.7, 26.6, 23.8, 22.5, 20.4, 16.3.

HRMS (ESI$^+$): Calculated for $C_{39}H_{61}N_4O_4$ $[M+H]^+$: 649.4687, Found: 649.4687.

Optical Rotation: $[\alpha]_D^{25} = -0.249$ ($c = 0.50$, $CHCl_3$). The obtained spectroscopic data is in agreement to the literature.[145]

7.5.2 Catalytical Approach

Catalytical approach using CPAs

An oven-dried tube was charged with 3-phenylcyclobutanone (**56**) (29.2 mg, 200 µmol, 1.00 equiv.) and the corresponding aminating reagent **33** (220 µmol, 1.10 equiv.). The mixture was dissolved in the corresponding solvent (0.5 mL) and the reaction mixture was stirred at the temperature for 24 h. NEt_3 (27.7 µL, 20.2 mg, 200 mmol, 1.00 equiv.) was added to the reaction mixture and the solvent was removed under reduced pressure. The NMR yield of the crude reaction mixture was determined by ^{1}H NMR using dibromomethane (14.0 µL, 34.8 mg, 200 µmol) as the internal standard. The enantiomeric purity was established by HPLC analysis using chiral stationary phases.

Metal-catalyzed approach for the access of γ-lactams

To an oven-dried SCHLENK tube, $Sc(OTf)_3$ (19.7 mg, 40 µL, 20 mol%) and chiral *N*,*N*-dioxide ligand **L1** (27.3 mg, 42 µL, 21 mol%) were added and dissolved with EtOAc (1.0 mL). The mixture was stirred at 35 °C for 30 min. The reaction mixture was allowed to cool down to room temperature and 3-phenylcyclobutanone (**56**) (29.2 mg, 200 µmol, 1.00 equiv.) was added. The mixture was stirred at room temperature for the selected time. The solvent was removed under reduced pressure and the NMR yield of the crude reaction mixture was determined by ^{1}H NMR using dibromomethane (14.0 µL, 34.8 mg, 200 µmol) as the internal

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[11] Impurities are shown

standard. The enantiomeric purity was established by HPLC analysis using chiral stationary phases.

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Declaration of Academic Integrity

I hereby confirm that this thesis on “Nitrogen Insertion as a Strategy for the Synthesis of γ-Lactams” is solely my own work and that I have used no sources or aids other than the ones stated. All passages in my thesis for which other sources, including electronic media, have been used, be it direct quotes or content references, have been acknowledged as such and the sources cited.

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Publications

- **Synthesis of 4-Phenylpyrrolidin-2-one via an Aza-Baeyer–Villiger Rearrangement**

  Ong, M.$^{\#}$; Arnold, M.$^{\#}$; Wahl, J. M.* *Org. Synth.* **2023**, *100*, 347–360

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- **Stereospecific Nitrogen Insertion Using Amino Diphenylphosphinates: An Aza-Baeyer–Villiger Rearrangement**

  Ong, M.; Arnold, M.; Walz, A. W.; Wahl, J. M.* *Org. Lett.* **2022**, *24*, 6171–6175

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- **Desymmetrization of Prochiral Cyclobutanones via Nitrogen Insertion: A Concise Route to Chiral γ-Lactams**

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- **Direct β-C(sp^3)–H Acetoxylationof Aliphatic Carboxylic Acids**

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08/19	PROMOS/DAAD - Scholarship
06/15	Abitur - Award/Siemens - Award, Valedictorian in Science and Mathematical Subjects