Carbene-catalyzed Asymmetric Nucleophilic Acylations with Novel Triazolium Salts

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der Rheinisch-Westfälischen Technischen Hochschule Aachen zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigte Dissertation

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The work presented in this thesis was carried out at the Institute of Organic Chemistry of RWTH Aachen University between July 2005 until December 2008 under the supervision of Prof. Dr. Dieter Enders.

Parts of this work have already been published:

1. “Synthesis of Enantiopure Triazolium Salts from Pyroglutamic Acid and Their Evaluation in the Benzoin Condensation”

2. “Asymmetric Intermolecular Stetter Reactions Catalyzed by a Novel Triazolium Derived N-Heterocyclic Carbene”

3. “Asymmetric Intermolecular Stetter Reaction of Aromatic Heterocyclic Aldehydes with Arylidenedmalonates”
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苔

白日不到处，青春恰自来，
苔花如米小，也学牡丹开。

袁枚（清）

蒲

飞堕披轻羽，随风不由已。
漂洋过海来，只为襟抱开。

作者自喻
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1. Introduction

1.1. Carbene Organocatalysis

1.1.1. Organocatalysis

The word, organocatalysis was coined by David MacMillan, however, the term, “Organische Katalysatoren” was already used by Langenbeck in the thirties of last century. It was defined as the catalysis by small organic metal-free compounds. Two pioneering papers were published in 2000: 1) List and co-workers have developed the intermolecular version of the aldol reaction catalyzed by L-proline (Scheme 1).\(^1\)  2) MacMillan has documented a highly enantioselective Diels-Alder reaction catalyzed by a chiral secondary amine-HCl salt (Scheme 2).\(^2\) Subsequently, the last few years have witnessed an explosive and impressive growth in this field with new catalysts and novel methodologies.\(^3\)

![Scheme 1. The aldol reaction catalyzed by L-proline.](image1)

![Scheme 2. The Diels-Alder reaction catalyzed by Macmillan salts.](image2)

To date, a large number of organocatalyzed reactions were reported in the literature. In a review article, List presented a system which is guided by a mechanistic classification for the reactions promoted by organocatalysts. Four categories are considered: Lewis Base, Lewis Acid, Brønsted Acid and Brønsted Base catalysis.\(^4\)
Generally, the majority of organocatalysts are N-, C-, O-, P-, or S-based Lewis bases that operate through diverse mechanisms and convert the substrates either into activated nucleophiles or electrophiles. Among them the only C-based organocatalysts are N-heterocyclic carbenes, which react with aldehydes to form the nucleophilic Breslow intermediate, and then facilitates the addition to an electrophile, overall a nucleophilic acylation (Figure 1).

1.1.2. Introduction to carbenes
A carbene is a highly reactive organic intermediate with a divalent carbon atom which has only six valence electrons. The general formula is $R^1R^2C::$ According to the
influence of the substituents on the groundstate spin multiplicity and hybrid structures, carbenes come in two varieties (Figure 2): a singlet (spin-paired and a sp\(^2\) hybrid structure) and triplet (unpaired electrons). Since the first synthesis of an isolable phosphanylsilylcarbenes 1 (Bertrand et al.\(^7\) in 1988) and imidazol-2-ylidene 2 (Arduengo et al.\(^8\) in 1991), respectively (Figure 3), the chemistry of N-heterocyclic carbenes (NHCs) and, in particular their application as ligands, has been developed rapidly.\(^9\) The inherent stability of NHCs has been attributed to both electronic and steric effects. Moreover, in 1995, Enders et al. together with Teles et al. studied the triazole heterocycle as an alternative structure.\(^10\) The triazol-5-ylidene 3 was obtained from the triazole precursor, and this crystalline carbene proved to be stable at temperatures up to 150 °C in absence of air and moisture. Triphenyl triazol-5-ylidene 3 was the first commercially available (Nr.363940010, Acros) carbene.

It can also be noticed that thiamine (vitamin B1), a naturally occurring thiazolium salt, in combination with transketolase enzymes enables highly enantioselective nucleophilic acylations. For this reason, N-heterocyclic carbenes have raised a wide interest as highly selective catalysts. In the following decades efforts were undertaken to mimic the concept of this efficient biochemical natural process for various transformations.\(^11\) Among them, 1,2,4-triazolylidenes as new efficient catalytic cores as well as thiazolylidenes, imidazolinylidenes, and imidazolyldienes have led to an exceptionally fruitful research area in carbene organocatalysis (Figure 4).
1.2. Nucleophilic acylation reactions

1.2.1 The Umpolung concept

Umpolung also named as polarity inversion, is a procedure which allows the normal reactivity to be reversed. 12 A variant of nucleophilic acylation is shown in Figure 5. After addition of a nucleophile to an aldehyde, the resultant intermediate can react with another electrophile. Subsequent removal of the nucleophile produces the desired carbonyl compound. By utilizing this concept, an indirect method based on some auxiliaries was developed for acyl additions to meet the above requirements. For example: thioacetals, protected cyanohydrins, aldehyde hydrazones and \( \alpha \)-aminonitriles etc. Moreover direct ways have also been used to catalyze this transformation. The catalysts are found among cyanide, metallophosphite and nucleophilic carbenes. Both methods have been incorporated into powerful strategies in synthetic organic chemistry. Some of these methods are described in this thesis.

![Figure 5](image)

**Figure 5.** Variant of the Umpolung of carbonyl groups for nucleophilic acylation.

1.2.2. Indirect acylations by using an auxiliary

1.2.2.1. Thioacetals

In 1965, Corey and Seebach reported that the treatment of 1,3-dithianes with \( n \)-butyllithium generated acyl anion equivalents, which can be trapped with different electrophiles to produce the desired compounds (Figure 6). 13 These nucleophilic acylating reagents have proved to be very useful for many applications in organic synthesis.
In a similar manner, bis(alkylthio)acetals, bis(arylthio)acetals, oxidized thioacetals were developed as acyl anion equivalents. However, only a few asymmetric methodologies relating to thioacetals were reported. In 1978, Colombo and Scolastico et al. synthesized a series of optically active thioacetal monosulfoxides 4 which were further applied in asymmetric synthesis of 11-deoxy-ent-prostaglandin intermediates 7 (Scheme 3).  

In 1992, the Aggarwal group reported the enantioselective synthesis of trans-1,3-dithiane-1,3-dioxide 8 as an acyl anion equivalent. The corresponding anions were formed by deprotonation of 8 with NaHMDS, then added to aldehydes with high diastereoselectivity. This methodology was further developed for the synthesis of (R)-salbutamol 9 as the key step (Scheme 4).
1.2.2.2. Alkyl vinyl ethers, vinyl sulfides and vinyl selenides

Alkyl vinyl ethers 10 could be used as acyl anion equivalents by deprotonation of 10 with t-BuLi, and in some cases in the presence of HMPA or TMEDA, or KO-t-Bu to generate 11, which can react with electrophiles such as alkyl halides, aldehydes and ketones etc. The obtained intermediates can be hydrolyzed to the corresponding ketone 12 by aqueous acids or in the presence of mercury ions (Figure 7).

Figure 7. Alkyl vinyl ethers in nucleophilic acylations.

1.2.2.3. Benzotriazole stabilized acyl anion systems

Benzotriazole-stabilized acyl anion equivalents have been developed by Katritzky et al. in the last 15 years. These synths with the stabilizing influence of a benzotriazolyl group were deprotonated with BuLi and then reacted with electrophiles to form the desired products.

Figure 8. Benzotriazole derivatives as acyl anion equivalents.
1.2.2.4. Aldehyde hydrazones

Aldehyde hydrazones are an additional category of compounds that undergo nucleophilic acylations. Well known ones are monophenylhydrazones, which can attack electrophilic substrates after deprotonation and formation of an ambident anion. In contrast to hydrazone 13, aldehyde N,N-dialkylhydrazones such as 15 bearing a tertiary amino group are also capable of nucleophilic acylations. Baldwin et al. reported hydrazone 14 by the exchange of the phenyl residue for sterically demanding substituents such as tert-butyl, trityl and diphenyl-4-pyridylmethyl group which can block the reactivity of the hydrazone nitrogen atoms for facilitating the reaction at the carbon center. Among these hydrazones, the SAMP and RAMP hydrazones were widely investigated in our research group. They have emerged as a powerful tool for Umpolung of the classical carbonyl reactivity (Figure 9). Notably, the formaldehyde SAMP-hydrazone methodology allows asymmetric formylation easily to develop a variety of densely functionalized compounds, usually in enantiomerically pure form.

![Diagram of aldehyde hydrazones as formylation equivalents.](image)

R = Ph, H; R1, R2 = Alkyl; E = electrophile

Figure 9. Aldehyde hydrazones as formylation equivalents.

1.2.2.5. Protected cyanohydrins

Stork and Maldonado were the first to demonstrate protected cyanohydrins as acyl anion equivalents and their potential utility in the synthesis of ketones in 1971. The aldehydes were treated with cyanide followed by protection with ethyl vinyl ether to form cyanohydrins. The cyanohydrins were deprotonated with lithium diisopropyl
amide, then reacted with another electrophile to afford the alkylated products, which deprotected with 5% aqueous sulfuric acid affording the desired ketones (Figure 10). Later in 1996, Cativiela et al. used camphor-derived chiral auxiliaries to be incorporated into the substrate, which allowed a diastereoselective alkylation of the pendant cyanohydrin. The alkylated product 17 was obtained in 92% yield and 77:23 dr (Scheme 5). Schrader investigated the use of the chiral phosphorus reagents 18 as auxiliaries linked to the OH group of cyanohydrins. The deprotonation with $n$-BuLi, followed by addition of electrophiles afforded the alkylated products 20 with high diastereomeric excesses (de = 82-94%). Treatment with the Lewis acid titanium chloride triisopropoxide followed by selective removal of the auxiliary afforded the tertiary cyanohydrins 21 (Scheme 6).

**Figure 10.** Protected cyanohydrins as acyl anion equivalents.

**Scheme 5.** Asymmetric acyl anion equivalents according to Schrader et al.
1.2.2.6. α-Amino nitriles

Metalated α-amino nitriles were demonstrated to be acyl anion equivalents in 1956 by Hauser et al. The amino nitriles were alkylated with benzyl halides in the presence of potassium amide in liquid ammonia. The resulting alkylation products undergo dehydrocyanation by further treatment with this base to form the enamines 24 in yields of 84-92%. The enamines were hydrolyzed to form the ketones 25 (Figure 11).

Our group reported the first asymmetric nucleophilic acylation reactions employing aminonitriles. For example, 1,2-additions to aldehydes and 1,4-addtions to α,β-unsaturated carbonyl compounds using an enantiomerically pure amine as the the auxiliary were developed. The studies were carried out with (S,S)-2,2-dimethyl-5-N-methylamino-4-phenyl-1,3-dioxane as a chiral amine auxiliary. Initially, the α-amino nitriles 27 were lithiated and treated with (E)-methyl enoates to give the Michael adducts 28 in high diastereomeric purity. Treatment with aqueous copper sulfate in THF resulted in the hydrolysis of the α-amino nitrile moiety to reveal the 1,4-dicarbonyl compounds 29 in 90-96% ee. The methodology has been further
extended to the asymmetric acylation of cyclic enones and $\alpha$, $\beta$-unsaturated lactones, to afford the corresponding acylated products in high enantiomeric excesses.\textsuperscript{25} More recently, this strategy was applied in asymmetric Michael additions to nitroalkenes with nucleophilic glyoxylolation through a metalated $\alpha$-aminonitrile derivative 30 with 91-98\% ee.\textsuperscript{26}

![Scheme 7](image)

**Scheme 7.** Chiral amine auxiliary for asymmetric nucleophilic acylations and glyoxoylations developed by Enders et al.

### 1.2.2.7 Thiazolium carbinols

Recently, Scheidt et al. developed new acyl anion precursors for the direct installation of carbonyl group. Deprotonation of 4,5-dimethylthiazole followed by addition of the resulting anion to an aldehyde, which yielded a carbinol. The carbinol was then silylated and alkylated with iodomethane. The obtained O-silyl thiazolium carbinols are stable salts. With these precursors, they successfully accomplished the nucleophilic acylation of electrophiles such as nitroalkenes and chalcones under mild reaction condition in good yields (Figure 12).\textsuperscript{27}
1.2.2.8. Tributylphosphonium ions

Ohmori et al. reported acyl tributylphosphonium ions as precursors of acyl anions. When these ions were subjected to electrochemical reduction, the cyclic keto phosphonium salts were transformed into bicyclic α-hydroxy ketones in good and fair yields (Figure 13).²⁸

![Figure 13. Tributylphosphonium ions as acyl anion equivalents.](image-url)

1.2.3. Direct acylations by using catalysts

Compared to auxiliary based methods for nucleophilic acylation, direct methods based on catalysis presents several advantages:

1) Avoiding additional steps of installation and cleavage.

2) Catalytic amounts of promoters.

3) Higher efficiency.

4) Easy handling.

In general, a few types of catalysts can be applied in nucleophilic acylation reactions: cyanide, N-heterocyclic carbenes and newly developed metallophosphites as well as some phosphonium compounds. Classifying by acylations, two representative reactions can be mentioned: the benzoin condensation and the Stetter reaction.
1.2.3.1. The benzoin condensation

The benzoin condensation, first discovered by Wöhler and Liebig in 1832, is a cyanide-catalyzed coupling of benzaldehyde. In 1903, Lapworth proposed a mechanism in which an intermediate carbanion is formed by cyanide anion addition to benzaldehyde and then the former carbonyl carbon features an inverted reactivity. A century passed after its discovery until in 1943 Ukai et al. recognized that thiazolium salts could also be used as catalysts in the benzoin condensation. Breslow et al. proposed the mechanism model for the thiazolium salt catalyzed benzoin condensation in 1958 on the basis of the work of Lapworth. In this mechanism, the catalytically active species is a thiazol-2-ylidene, which is formed in situ by deprotonation of the thiazolium salt. A nucleophilic attack of the carbonyl function of an aldehyde molecule then generates the alkylthiazolium salt. Via proton migration, the resonance stabilized hydroxyl-enamine-type intermediate is formed (now named Breslow intermediate). This nucleophilic acylation reagent reacts again with an electrophilic substrate such as the carbonyl group of a second aldehyde molecule. The intermediate affords the benzoin and regenerates the catalyst.
Some years later, Lemal et al. postulated an alternative mechanistic model based on the facile formation of carbene dimers. This proposed mechanism was extended by López Calahorra et al. Although more detailed mechanistic studies supported the Breslow models, carbene dimers also can explain some results well. This model could explain why the highly reactive carbene was not quenched in some protic solvents such as alcohols or even water.

As the product of the benzoin condensation bears a new stereogenic center, controlling the stereochemical outcome caught an attention. Consequently, many chemists have tried to develop NHCs-catalyzed asymmetric benzoin condensations. In 1966 Sheehan et al. were the first to present the results of an asymmetric benzoin condensation in 22% ee by utilizing the chiral thiazolium salt.
as precatalyst. Some years later, they were able to increase the enantiomeric excesses up to 52% with precatalyst 39 but suffered from low yields (6%). Takagi et al. had synthesized chiral methyl-substituted thiazolium salts such as 40 and could catalyze the formation of benzoin in a micellar two-phase reaction system with an enantiomeric excess of 35% and an improved yield of 20%. Zhao et al. combined the Sheehan catalysts with the Takagi reaction conditions and could obtain moderate enantiomeric excesses of 47-57% and yields of 20-30%. In 1993, López Calahorra synthesized bisthiazolium salt catalysts 41 by taking advantage of the C₂-symmetric concept, which imparted benzoin with 26% ee and a yield of 21%. To improve the enantioselectivity, in 1997 Leeper et al. introduced the rigidity of the bicyclic concept for developing novel bicyclic thiazolium salts. They reported chiral bicyclic 42-44 and polycyclic thiazolium salts 45 and applied them in asymmetric benzoin condensations. Unfortunately, the bicyclic ones did not transfer a high degree of stereocontrol. This result was also confirmed by Rawal et al. with a naphthyl substituent on the bicyclic ring 46, which gave 30% ee. Very recently in 2004, Bach and co-workers developed an axially chiral N-arylthiazolium salt 47 as precatalyst. The benzoin product was obtained with 85% yield and with a moderate ee of 40%.  

![Chemical structures](image.png)
In the earlier years, the strategy for modifying the catalysts mostly relied on the thiazolium salts. Since the stable carbene based on the triphenyl triazol heterocycle was disclosed in 1995, our group was the first to apply chiral triazolidenes in benzoin and Stetter reactions. The latter development in carbene catalysis proved that the new skeleton of 1,2,4-triazolium salts shows an efficient activity as a new catalytic core. The promising results with triazolium salts in catalysis inspired our research group to synthesize a variety of chiral triazolium salts for the asymmetric benzoin condensation. Extensive investigation has shown that the enantiomeric excesses and catalytic activities are highly dependent on the substitution pattern of the triazolium system. The most active catalyst provided benzoin with 75% ee and a good yield of 66% (Scheme 9).

In connection with the concept of rigid bicyclic thiazolium salts, Leeper et al. also introduced a bicyclic skeleton to chiral triazolium salts. Chiral, bicyclic triazolium
salts such as 49 and 50 could significantly improve their previous results (22% yield, 63% ee for 49, 45% yield and 80% ee for 50). In addition, they compared the thiazolium and triazolium salts as asymmetric catalysts for the asymmetric benzoin condensation. They believed that the significant difference between triazolium and thiazolium salts is the fact that the N-phenyl group of the former is much more bulky than the sulphur atom of the latter, and that the N-phenyl group is almost perpendicular to the plane of the heterocyclic ring in the Breslow intermediate, thus can have significant steric interactions with the incoming benzaldehyde molecule. Another striking observation is that triazolium salt produced benzoins are of the opposite absolute configuration to those produced by thiazolium salts. It was explained based on molecular mechanics studies, which the carbonyl group of the incoming aldehyde molecule is anti to the carbon-carbon double bond of the Breslow intermediate. For the thiazolium salt catalysis, the phenyl ring of the benzaldehyde molecule has a slight preference for lying under the sulfur atom of the heterocyclic ring, but for the triazolium salts, the phenyl ring of the aldehyde would have an unfavourable steric interaction with the N-phenyl group of the catalyst in the equivalent orientation and therefore the hydrogen atom of the aldehyde occupies this position instead. Inspired by these results, another chiral, bicyclic triazolium salt was developed in our research group in 2002.\(^4\) Triazolium salt 51, derived from (S)-\textit{tert}-leucine, was applied in the asymmetric benzoin condensation. (S)-Benzoin was produced in good yields and excellent enantioselectivity (90% ee, 83% yield).

![Figure 17. Chiral triazolium salts.](image)

The transition state 52, shown in Figure 18, has been proposed to explain the observed
configuration. The *si*-face of the assumed Breslow-type intermediate would be sterically shielded by the *tert*-butyl-group of the bicyclic catalyst. The second aldehyde molecule would then attack the hydroxy enamine from its *re*-face leading to an (*S*)-configured product, which is actually observed in the experiments. In addition, the phenyl substituent of the enol moiety (via π-stacking) as well as the hydroxyl group (via H-bridge activation of the aldehyde) may lead to a pre-organized transition state. However, the (*E/Z*)-geometry of the Breslow intermediate has not yet been determined, but is of relevance for the pre-orientation of the second aldehyde molecule. As shown in transition state 52’, the corresponding (*E*)-isomer would probably favour a *si*-*si*-attack and therefore a (*R*)-configuration in the product. An unfavourable steric interaction between the phenyl substituent of the enol moiety and the phenyl substituent of the attacking aldehyde in 52’ probably disfavours this transition state. The most stable transition state has been determined to be 52’’ after computational calculation by Houk et al.44 In this intermediate no π-stacking occurs, but the substituent of the approaching aldehyde resides in an open pocket of the catalyst with minimum steric repulsion. Thus, the formation of (*S*)-benzoin would be favoured again.

![Figure 18. Possible transition states for the asymmetric benzoin condensation proposed by Enders et al. and Houk et al.](image)

1.2.3.2. Crossed benzoin condensation

An extension of the benzoin reaction is the cross coupling of aldehydes with other
aldehydes or ketones. In crossed acyloin condensations usually a mixture of all possible acyloins were obtained. A selective cross-acyloin condensation of formaldehyde and another aldehyde to yield exclusively 1-hydroxy 2-ones 53 was reported by Inoue et al (Scheme 10).45

\[ R \text{CHO} + H_2\text{C=O} \xrightarrow{10 \text{ mol\% 54, Et$_3$N, EtOH, 60 } ^\circ\text{C}} \text{ROH} \]

\[ \text{R= Me, Et, n/i-Pr, Ph, 2-furyl} \]

Scheme 10. Selective cross-acyloin condensation by Inoue et al.

Johnson et al. reported a crossed silyl benzoin condensation catalyzed by cyanide utilizing acylsilanes 55, which serve as a superior acylanion precursor and avoid the usual problem of self-condensation.46 α-Siloxy ketones 56 could be synthesized via a Brook rearrangement with complete regiocontrol by using the catalyst-system KCN/18-crown-6 (Scheme 11). An enantioselective version was also developed by the same group with the use of chiral metallophosphites as Umpolung catalyst.47 Besides acylsilanes, Demir et al. reported acylphosphates as acyl anion precursors. These acyl phosphates can also readily react with aldehydes under the promotion of cyanide anion via phosphonate-phosphonate rearrangement, and thus can provide the cross-benzoin products in high yields (83-94%).48

\[ R'\text{SiR}_3 + \text{R}^2\text{CHO} \xrightarrow{30 \text{ mol\% KCN, 10 \text{ mol\% 18-crown-6, Et$_2$O, 25 } ^\circ\text{C}}} \text{ROSiR}_3 \]

Scheme 11. Crossed silyl benzoin condensation by Johnson et al.

1.2.3.3. Intramolecular crossed benzoin condensation

In contrast to the intermolecular condensation reaction, intramolecular crossed benzoin reactions have received much less attention for a long time. Cookson and Lane reported a cyclisation of glutaric aldehydes 57 with thiazolium salts as
precatalysts (60) to the corresponding hydroxyl cyclopentanones 58 and 59.\textsuperscript{49}

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{R}^1\text{R}^2\text{R}^3 \quad \text{H} \\
\text{O} & \quad 10 \text{ mol\% 60} \\
& \quad \text{EtN, CH}_3\text{CN,} \\
& \quad 80 \degree \text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{R}^1\text{R}^2\text{R}^3 \quad \text{H} \\
\text{O} & \quad \text{R}^2\text{R}^1\text{R}^3 \quad \text{OH} \\
& \quad + \\
\text{H}_2\text{C} & \quad \text{R}^1\text{R}^2\text{R}^3 \\
\text{O} & \quad \text{HO} \\
& \quad \text{HO} \\
\text{R}^1 &= \text{H, Me, R}^2 = \text{H, Me} \\
\text{Scheme 12. Intramolecular acyloin condensation by Cookson and Lane.}
\]

In 1995, Suzuki et al. have applied the common thiazolium salt for a diastereoselective intramolecular crossed aldehyde-ketone benzoin reaction in the course of an elegant natural product synthesis.\textsuperscript{50}

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{H}_2\text{C} \\
\text{N} & \quad \text{Et} \\
\text{CO}_2\text{Et} & \quad \text{O} \\
& \quad \text{H}_3\text{C} \\
& \quad \text{EtO}_2\text{C} \\
& \quad \text{dr} = 20:1 \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{H}_2\text{C} \\
\text{N} & \quad \text{Et} \\
\text{OCH}_3 & \quad \text{O} \\
& \quad \text{H}_3\text{C} \\
& \quad \text{EtO}_2\text{C} \\
& \quad \text{Br}^\circ \\
& \quad \text{cat. 65b} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{H}_2\text{C} \\
\text{N} & \quad \text{Et} \\
\text{OCH}_3 & \quad \text{O} \\
& \quad \text{H}_3\text{C} \\
& \quad \text{EtO}_2\text{C} \\
& \quad \text{dr} = 20:1 \\
\end{align*}
\]

\textbf{Scheme 13. Intramolecular crossed benzoin reaction by Suzuki et al.}

Parallel to Suzuki et al.,\textsuperscript{50} Enders et al. presented that various five- and six-membered cyclic acyloins can be obtained by employing commercially available thiazolium salts as precatalysts (65a or 65b).\textsuperscript{51} Once the reaction was laid, the search for alternative catalysts for the asymmetric version was started. Enders et al. synthesized the novel triazolium salts 66 and 67 starting from the easily accessible enantiopure polycyclic-lactams. The precatalyst 66 led to excellent results in the intramolecular crossed benzoin condensation of aldehyde ketones 63 to α-hydroxyl ketones 64 as shown in Scheme 14. The quaternary stereocenter of the acyloins 64 was created with very good yields and excellent enantiomeric excesses (93-98% ee).\textsuperscript{52} The precatalyst 67 proved to be even more active, the yields were consistently excellent, albeit accompanied by lower enantiomeric excesses (63-84% ee). Suzuki et al. later published similar excellent results in up to 99% ee by utilizing Rovis’
aminoindanol-derived chiral triazolium salt 68a. Suzuki et al. also modified the Rovis chiral triazolium salts by installing different N-based electron-withdrawing substituents to facilitate the generation of the key carbene species under mild basic conditions for enantioselective benzoin cyclization of enolizable keto-aldehydes. After testing different catalysts, the precatalyst 68d with 2,4-ditrifluoromethyl group(s) on the N-phenyl group was found be capable of suppressing the aldol reaction without sacrificing the enantioselectivity of desired products.

Scheme 14. Asymmetric intramolecular crossed benzoin condensations by Enders et al. and Suzuki et al.

Even recently, You et al. synthesized a series of novel triazolium salts from the readily available D-camphor. The carbene from precatalyst 69 is found to be efficient for the intramolecular crossed aldehyde–ketone benzoin reaction, and α-ketols containing a quaternary stereogenic center are formed in excellent yields with up to 93% ee.

1.2.3.4. Intermolecular Stetter Reactions

In the early 1970s, Stetter and co-workers first succeeded in transferring the concept of the nucleophilic acylation to the substrate class of Michael acceptors, firstly catalyzed by cyanide, then by thiazolium derived carbene. Since that time, the catalytic 1,4-addition of aldehydes to an acceptor bearing an activated double bond 71 is named Stetter reaction. This reaction enables a new catalytic pathway for the
synthesis of 1,4-bifunctional molecules 72, as 1,4-diketones, 1,4-ketoesters and 1,4-ketocarbonitriles, which are valuable building blocks that can easily afford substituted heterocycles. The reaction can be catalyzed by a broad range of thiazolium salts. Stetter and co-workers found the benzyl-substituted thiazolium salt \(65a\) to give the best results for the addition of aliphatic aldehydes, whereas \(65b\) and \(65c\) were chosen for the addition of aromatic aldehydes. Any one of these three compounds was found to be suitable for additions with heterocyclic aldehydes. Salt \(65d\) was utilized with \(\alpha,\beta\)-unsaturated esters.\(^{56}\)

Figure 19. Thiazolium salts 65 for the intermolecular Stetter reaction.

For the synthesis of 1,4-diketones most \(\alpha,\beta\)-unsaturated ketones can serve as acceptors. Aromatic and heterocyclic \(\alpha,\beta\)-unsaturated ketones are particularly well suited. This versatile method has found a broad application in the synthesis of organic key intermediates and diverse natural products. In the catalytic cycle, the carbene adds to the aldehyde to generate the Breslow intermediate 70. A subsequent nucleophilic attack of the acyl anion equivalent to the Michael acceptor 71 occurs, then the desired 1,4-diketones 72 is formed (Scheme 15).

Scheme 15. The Stetter Reaction and its catalytic mechanism.

While many successes have been achieved in the development of asymmetric carbene organocatalysis, the development of an asymmetric intermolecular Stetter reaction has proven to be far more difficult. A first attempt of an asymmetric Stetter reaction was
made in 1989 within our research group, investigating the chiral thiazolium salts 74 as precatalysts. The reaction of n-butanal with chalcone in a two-phase system gave the 1,4-diketone 73 with moderate 39% ee, and a chemical yield of 40% (Scheme 16).58

![Scheme 16. First attempt of an asymmetric Stetter reaction by Enders et al.](image)

Recently, Johnson and co-workers have developed metallophosphite 76 as Umpolung catalyst, which is derived from enantiopure TADDOL combining the strategy of generating carbonyl anion equivalents from acylsilanes. These nucleophilic catalysts have also been shown to promote conjugate additions of acylsilanes to unsaturated amides to form the Stetter products 75 in moderate yields and good enantioselectivities. Moreover, the enantioselectivity could be enhanced to an excellent level (99% ee) by recrystallization (Scheme 17).59

![Scheme 17. TADDOL type compounds as Umpolung catalysts for asymmetric Stetter reaction developed by Johnson et al.](image)

**1.2.3.5. Intramolecular Stetter Reactions**

Ciganek reported an intramolecular version of the Stetter reaction by using thiazolium salts 65a as catalyst.60 Exposed to 65a, 2-formyl phenoxycrotonates and -acrylates 77 have been shown to be highly active substrates for the Stetter reaction (Scheme 18).
Introduction

In 1996, our research group used the triazolium salt 48 in this intramolecular reaction, which has already been applied in benzoin condensations. The enantioselective synthesis of various 4-chromanones 80 via a first asymmetric intramolecular Stetter reaction was performed with enantiomeric excesses of 41-74% and yields of 22-73% (Scheme 19).  

After the pioneering work of our group, not much attention has been paid to this important reaction. In 2002, Rovis et al. achieved a significant progress. Using the aminooindanol-derived triazolium salt 68c or the phenylalanine-based salt 83, a broad range of different chromanones as well as their aza-, thia- and carbacyclic analogues 82 could be obtained from the corresponding starting materials 81 with enantiomeric excesses of 82-97% and yields of 63-95% (Scheme 20).
The Rovis group also expanded this reaction to match other substrates (Scheme 21): unsaturated esters, ketones and nitriles can work well. However, by examining the effect of the Michael acceptor olefin geometry, they found that the reaction is limited to (E)-alkenes as Michael acceptors. Aliphatic substrates lacking a heteroatom in the γ-position of the acceptor were also utilized as substrates in this reaction. As a result of the greater conformational freedom, an increase of the electrophilic character of the Michael acceptor was necessary to enable the formation of the corresponding cycloalcanones. An activation with one ester-substituent for a five-membered ring (86) but not for six-member ring was reported. Nevertheless, two ester-substituents for a six-membered ring (87) was found to be active. Enantioselectivities up to 95% and chemical yields up to 97% could be obtained.

Scheme 21. Different Michael acceptors for the intramolecular Stetter reaction by Rovis et al.

Rovis et al. and Hamada et al. also accepted the challenge of generating quarternary stereocenters. The substitution pattern of the N-phenyl group of the catalyst was found to be a decisive factor. In this case, the N-pentafluorophenyl-substituted catalyst 68c proved to be the most effective for the conversion of the β,β-disubstituted substrates 88 to the corresponding cyclized products 89 with up to 99% enantiomeric excess. This method was successfully extended to corresponding thioethers and aliphatic backbones in good yields and ee’s.
The same group could extend the scope of the intramolecular Stetter reaction for an enantio- and diastereoselective variant utilizing $\alpha,\beta$-disubstituted acceptors $^{90}$.$^{66}$ The key is to secure a diastereoselective proton transfer into the hypothetic enolate intermediate. It showed that HMDS (from the KHMDS base) deteriorates the diastereoselectivity. This problem was overcome by using the free carbene catalyst $^{92}$, i.e. HDMS was removed in high vacuum prior to the reaction (Scheme 23). The free carbene $^{92}$ could afford the chromanones $^{91}$ with enantiomeric excesses up to 95% and diastereomeric ratios up to 35:1. Aliphatic aldehydes were also shown to be viable substrates with >80% yield and good enantio- and diastereoselectivities.

The syn selective formation of the new stereocenters was assumed to arise from a diastereoselective proton transfer of two possible enolate geometric isomers $^{93}$ or $^{94}$. The hypothetical intramolecular proton transfer was supported by the fact that the double bond isomers afford the complementary diastereoselectivity (Figure 20).
In the related investigations around the intramolecular Stetter reaction, Rovis et al. examined the effect of pre-existing stereocenters in the intramolecular asymmetric Stetter reaction (Eq 1. Scheme 24). The racemic substrates rac-96, containing one stereogenic center were utilized in a parallel kinetic resolution for the synthesis of 2,3- and 2,4-disubstituted cyclopentanones 97 and 98. The inseparable cis- and trans-diastereomers were obtained in an equimolar mixture, albeit with high ee’s (84-98%). The cis diastereoisomer of the corresponding 2,5-disubstituted cyclopentanones were generated preferentially but with low ee, indicating the reaction to be substrate controlled. They also utilized the concept of desymmetrization for the enantio- and diastereoselective synthesis of hydrobenzofuranones 100 in 62-94% yields and up to 99% ee from substrates 99, which can be easily synthesized from available phenols in an intramolecular Stetter reaction (Eq 2. Scheme 24).

As is stated above, besides the benzoin reaction, the concept of axial chirality utilized of the menthol-derived triazolium salt 47 (Figure 16) was also applied in the
asymmetric intramolecular Stetter reaction. They were able to isolate the Stetter product with 50% ee in 75% yield with the standard substrate.\textsuperscript{41}

The Miller group applied the concept of small peptide catalysts to the intramolecular asymmetric Stetter reaction and a histidine residue of amino acid derivatives with thiazolylalnine (Taz) derivatives was used.\textsuperscript{69} After screening different peptide catalysts, 101 afforded the corresponding chromanone with up to 80% ee and 40% yield. Using catalyst 102 (Figure 21) with incorporation of Taz into peptide sequences could afford the product in promising 69-73% ee, albeit moderate yield 17-67%.

Tomioka at al. recently showed that chiral $C_2$ symmetric dihydroimidazolium salts, such as 103, are also efficient precatalysts in the asymmetric intramolecular Stetter reaction with aliphatic substrates, such as 79 (the corresponding methyl ester was used).\textsuperscript{70} Due to the product structure, a racemization can be observed under basic conditions. To avoid this, a substoichiometric amount of base was used. A racemization could be suppressed and the cyclohexanone derivative could be obtained with 76% ee and 74% yield (Figure 21).

![Figure 21. Chiral heterazolium salts for the Stetter reaction by Miller et al. and Tomioka et al.](image)

1.2.3.6. Variants of intermolecular Stetter reactions

Murry and Frantz \textit{et al.} from Merck research laboratory developed a thiazolium catalyzed (65a) addition of aldehydes to acylimines 107.\textsuperscript{71} Arylsulfonylamides 105 served as precursors for the acylimines and were generated by elimination.
A successful asymmetric variant of the Imino-Stetter reaction has been presented by Miller et al., who employed chiral peptidic thiazolium salts. They observed a significant influence of bases to racemation. A hindered base (PEMP) was found to be optimal for enantioselectivity (ee up to 87%) (Scheme 26).

In the intermolecular Stetter reaction, self-condensation of the donor aldehyde usually dominates over the conjugate 1,4-addition leading to benzoins as the major product. To circumvent this problem, Scheidt and Mattson et al. addressed thiazolium-catalyzed sila-stetter reaction by acyl silanes as aldehyde surrogates. Typically, the carbene undergoes nucleophilic addition to an acylsilane and promotes a 1,2-silyl shift (Brook rearrangement) from carbon to oxygen. Desilylation in the presence of DBU and alcohol, the acyl anion nucleophile is then generated and added selectively to the acceptor, which avoided the benzoin formation (Scheme 27).
Introduction

Scheme 27. Sila-Stetter reaction by Scheidt et al.

Again the same group adopted a similar strategy with the catalytic addition of acylsilanes to imines \[\text{110}\] for the synthesis of \(\alpha\)-amino ketones \[\text{111}\]. Similar to the catalytic cycle shown above (Scheme 27), the use of a readily available thiazolium salt \[\text{112}\] as carbene precursor in the presence of \(i\)-PrOH enabled the direct formation of N-phosphinylated amino ketones (Scheme 28).

Scheme 28. Synthesis of \(\alpha\)-amino ketones by Scheidt et al.

In a biomimetic fashion, Scheidt and his co-workers carried out the Stetter reaction under neutral aqueous conditions. A thiazolium catalyst adds to the keto group of a pyruvate \[\text{113}\]. The following decarboxylation led to the Breslow intermediate which added to substituted \(\alpha\), \(\beta\)-unsaturated 2-acyl imidazoles \[\text{116}\] for the usual Stetter product \[\text{115}\] (Scheme 29).
Murry, Frantz and Miller et al. found that the product was formed under kinetic control, as the imine must react faster with the Breslow intermediate than another aldehyde molecule. In contrast, You et al. showed that aromatic aldehydes can also be coupled to unactivated imines 117 ($R^2$, $R^3$ = aryl) to $\alpha$-aminoketones 118 under thermodynamic control. Utilizing the thiazolium chloride 65a, a wide range of substrates was capable in this reaction with varying yields (Scheme 30). Studies to understand the reaction mechanism revealed at least a partial thermodynamic control, as the desired product is also formed with benzoin as substrate.

Recently, Wong and Zhang et al. developed NHC-catalyzed direct amidation of aldehydes with nitroso compounds 119 to synthesize $N$-arylhydroxamic acid 120 in high yields. Moreover, this chemistry was extended to the synthesis of chiral products by kinetic resolution of $\alpha$-branched aldehydes in 48% yield and 68% ee (Scheme 31).
Concurrent with our explorations in last three years, the use of carbene as organocatalyst has become a fertile field for the asymmetric catalysis, a striking contribution of a³ to d³ Umpolung reactivity was discovered by Glorius\textsuperscript{78} and Bode\textsuperscript{79} group in 2004. Utilizing N-heterocyclic carbenes bearing N-Mes substituent, α,β-unsaturated aldehydes could be favoured formation of a homoenolate, which can be considered as d³-nucleophiles and thus lead to matchless reaction outcomes. These contributions have widely expanded the application of carbene organocatalysis.

1.3. Summary

A summary of the development in nucleophilic acylations, especially asymmetric versions were described. However, until now there is no general method to address the asymmetric intermolecular Stetter reactions, and the aliphatic benzoin reactions need further improvement. Furthermore, new electrophiles (aldehydes) and Michael acceptors need to be introduced to nucleophilic acylations.
2. Objectives

The aim of the Ph.D thesis was composed of two parts:

i) The first part is to develop novel chiral carbene organocatalytic systems for the asymmetric intermolecular Stetter reaction.

The intermolecular Stetter reaction was selected as a highly desirable target. Based on long-term experiences with carbene catalysis in the Enders group, triazolium salts could be the suitable catalytic core to achieve high enantioselectivity. Considering the aspects of precatalyst design, we changed the different functionality for tuning the electronic and steric nature of the chiral platform. The five key points are stated as below:

1) Different chiral branches which are responsible for high asymmetric induction.
2) The N-substituent group on the triazolium ring for modulating the reactivity of the catalyst.
3) The bicyclic or tetracyclic skeleton for their diverse steric rigid profile and easy availability.
4) The heteroatom in the ring for altering the electronic effects.

5) Changing the counter-ion allows to tune the solubility and solidification characteristics of the triazolium salts for easy preparation.

2) The second part is the application of the carbene catalyzed intramolecular benzoin reaction developed from our group to synthesize the natural product (S)-Eucomol.
3. Results and discussion

3.1 Development of chiral triazolium salts by variation of the steric demand and application in nucleophilic acylations

3.1.1 Design of the catalysts

The extensive knowledge about asymmetric carbene organocatalysis acquired from the benzoin and Stetter reaction during the last more than 30 years has shown that the development of new carbene catalysts is the most instructive. Currently, the triazolium salts have attracted much more attention, because of their inherent nature for high activity and selectivity. These triazolium salts were just treated with bases in situ to generate the corresponding carbenes, which are the catalytic species in the reactions. According to the literature, the simple triazolium salts have been made by three operable approaches:

1) Monocyclic salts were prepared in two ways (Scheme 32, and 33). In 1971, Boyd et al. first synthesized 3-unsubstituted triazolium salts from hydrazine as starting material, a three step sequence followed by formylation, cyclization with HClO₄, then RORC-substitution (ring opening and ring closure). Jochims et al. employed chiral amides as starting material, five steps were successive to produce the triazolium salts as another choice to the substituted triazolium salts. On the basis of the above procedure, Enders and Breuer have prepared a variety of monocyclic stable carbenes, which were successfully applied to carbene organocatalysis.

2) A placement of the stereocenter proximal to the triazolium seemed to be the most promising to achieve good enantioselectivity according to the experiences in asymmetric carbene organocatalysis. For this reason, polycyclic, especially bicyclic triazolium salts were prepared by using lactams as starting materialal. Leeper and Knight first reported this method to synthesize bicyclic triazolium salts. Methylation with Meerwein’s reagent gave the imino ether, then reaction with phenylhydrazine hydrochloride, formylation and cyclization gave the desired salts. The procedure was revised by the Enders group to obtain the pure amidrazone, after treatment with
tetrafluoroboronic acid, then cyclization to give the triazolium tetrafluoroborate. Soon afterwards, the Rovis group simplified this procedure to be more convenient by carrying out the three steps in one pot (Figure 22).\textsuperscript{83}

\textbf{Scheme 32.} The synthetic route for monocyclic triazolium salts by Boyd et al. \textbf{Scheme 33.} The synthetic route for monocyclic triazolium salts by Jochims et al.

\textbf{Figure 22.} Polycyclic triazolium salts preparation in one pot.

As is stated above, generally the accessibility of these triazolium salts was manipulated by the change of chiral scaffolds and different hydrazines. Among them the chiral scaffold incorporation was easily originated from natural amino acid derivatives due to their diverse chiral profile and availability. On the basis of our previous results for the preparation of chiral auxiliaries based on pyrrolidine such as SADP and RADP derived from enantiopure proline as early as 1985,\textsuperscript{84} and also
inspired by recent work in organocatalysis with diphenyl pyrrolidines which transferred a very high enantioselectivity in Michael addition (Figure 23), we started to synthesize the new carbene catalysts bearing this sterically demanding side chains. In comparison with other known triazolium salts, it is expected that these new structures with bulky branches on the bicyclic ring can impart a higher degree of delivering the chirality.

\[ \text{Figure 23. Initial catalyst design.} \]

### 3.1.2. Synthesis of the catalysts

Our focus in the early stage of this research aimed to incorporate the diphenyl pyrrolidene chiral building block into the bicyclic framework. Catalyst preparation from \((S)-\text{glutamic acid}\) was desirable, and from the synthetic view, this preparation allows for a large amount of diversity in the modulation of the bulkiness of substituents on the phenyl group. Considering the silyl protective groups of the tertiary alcohol were very sensitive to nucleophilic reagents, we pursued the synthesis of 127 with the methoxy group as the first choice for the new chiral bicyclic catalysts. As shown in Scheme 34, the synthesis of enantiopure \(\gamma\)-butyro lactams began with \((S)-\text{glutamic acid}\). According to the literature precedent, \((S)-\text{glutamic acid}\) was easily cyclized to the pyroglutamic acid by refluxing in an aqueous basic solution.
Esterification of the acid catalyzed by concentrated sulphuric acid in methanol or treated with thionyl chloride in methanol, gave virtually quantitative yields. Subsequent reaction with sodium hydride and benzyl bromide in THF gave the N-phenylmethyl (benzyl) ester 123. The ester was treated with slow addition of an excess of Grignard reagents (3 eq.) to afford the tertiary alcohol 124. Protecting the alcohol group with sodium hydride and iodomethane provided the desired product 125 as a colorless solid. Then we planned to remove of the N-Bn protecting group with sodium in liquid ammonia. After the sodium sheets were added, the color of the reactant mixture should change into dark blue in the normal cases. However, in this case, the blue color were generated but then disappeared immediately. Disappointingly, we found the obtained solids were not the desired lactam with identification of $^1$H and $^{13}$C NMR spectra. With analysis of the spectra, obviously, the chiral diphenyl branch was destroyed. Unfortunately, it was not possible to characterize the formed byproducts, however, 128 could be a possible structure.

Since the popular Na/liquid NH$_3$ system for the debenzylaion of the lactam was not suitable for this substrate, we turned our attention to other milder conditions. Hydroxyl groups protected with the benzyl group or diphenylmethyl group are readily

Scheme 34. The synthetic route to lactam (I).
cleaved by hydrogenolysis via metal catalysis in a hydrogen atmosphere. In some cases this method can also work in the debenzylation of a benzylacetamide with a slow rate.\textsuperscript{87} Therefore, we decided to apply this method to our case. After screening various reductive systems, unfortunately, only the starting materials were observed. According to some similar conditions to Na/liquid ammonia reported in the literature, debenzylation with Na/ n-butylamine and Li/naphthalene as well as strong acid such as TFA (trifluoroacetic acid) were also tried, but remained unsuccessful (Table 1). Discouraged by these results, we were cognizant of that the N-benzyl group could possess equal reactive activity to the of O-diphenyl group on the same substrate. Then we decided to modify our strategy.

Table 1. The debenzylated conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na, liquid NH\textsubscript{3}, rt for 24 h</td>
<td>byproducts</td>
</tr>
<tr>
<td>2</td>
<td>10% Pd/C, H\textsubscript{2}, MeOH, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>10% Pd/C, HCOOH, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OH)\textsubscript{2}, black, H\textsubscript{2}, MeOH, or EtOH, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>PdCl\textsubscript{2}/CH\textsubscript{3}CO\textsubscript{2}H:EtOAc=1:4, H\textsubscript{2}, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OH)\textsubscript{2}, black, HCOONH\textsubscript{4}, MeOH, refluxing for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>Raney Ni, H\textsubscript{2}, MeOH, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>8</td>
<td>Na, n-butylamine, rt for 24 h</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>Li, naphthalene, rt for 24 h</td>
<td>Some byproducts</td>
</tr>
<tr>
<td>10</td>
<td>CF\textsubscript{3}CO\textsubscript{2}H, refluxing for 24 h</td>
<td>no</td>
</tr>
</tbody>
</table>

Our initial efforts with the benzyl protecting group on the nitrogen atom proved to be unfruitful. We therefore quickly decided to introduce other protective groups, which can be removed easily from the molecule. In a closely related field of protection/deprotection of lactam amines, their carbamate intermediates are extensively employed in organic synthesis. The tert-butoxycarbonyl (Boc) group is
widely recognized as a convenient group for protecting a variety of amino compounds.\textsuperscript{88} Classically, deprotection of the N-Boc group can be performed by the reaction of strong acids such as TFA or HCl, and even much milder reagents such as Yb(OTf)$_3$-SiO$_2$. For this reason, the unprotected ester was directly treated slowly with an excess of Grignard reagents (3 eq.) to afford the tertiary alcohol, then protection of the nitrogen was carried out with DMAP and Boc$_2$O to give the desired N-Boc diphenyl lactam 130. However, for the introduction of the methyl group to the tertiary alcohol it was found that the amine protective groups such as Boc on the molecule 130 were unstable in the NaH/MeI conditions. At the beginning, we ascribed the failure to the strong basicity caused by NaH. Then a procedure using methylating agent such as MeOTf in the presence of 2,6-di-tert-butyl-4-methylpyridine was adopted to avoid the above problem. Unfortunately, even under these conditions, only byproducts (132 or 133) were obtained (Table 2).

Scheme 35. The synthetic route to lactam (II).

Table 2. The methylated conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH, MeI, THF, refluxing</td>
<td>byproduct</td>
</tr>
<tr>
<td>2</td>
<td>DTBDP, MeOTf, DCM, rt, 20 h</td>
<td>byproduct</td>
</tr>
<tr>
<td>3</td>
<td>DMAP, MeOTf, DCM, rt, 20 h</td>
<td>dirty</td>
</tr>
<tr>
<td>4</td>
<td>Et$_3$N, MeOTf, DCM, rt, 2 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>BuLi, MeI, -78 °C</td>
<td>dirty</td>
</tr>
</tbody>
</table>
McAlonan and Stevenson et al. reported that carbonyl based protecting groups such as Boc in pyroglutamates can activate the carbonyl group of the cyclic imides and make it easily be nucleophilic attacked. This account could be a possible reason to explain the above results. In their report, the 4-methoxybenzoyl group as protecting group can be introduced to the molecule and alleviate this problem. The use of 4-methoxybenzyl as an amide N-protecting group and its direct oxidation to 4-methoxybenzoyl using chromium trioxide or ceric ammonium nitrate (CAN) under mild conditions gave rapid access to a range of optically active lactam analogues in modest to good yields. Therefore, we prepared the protected lactam 138 with a 4-methoxybenzyl group. According to the literature precedent, synthesis of enantiopure lactam 138 began with (S)-glutamic acid again. (S)-Glutamic acid was condensed with anisaldehyde in basic solutions to give the Schiff base 134, after treatment with NaBH₄, and cyclization by refluxing in EtOH gave the crude N-4-methoxybenzyl glutamic acid 135 in 65% yield. In a similar manner to the above 125, a Grignard reaction and followed by protection of the alcohol group with MeI afford the desired protected lactam 138 in good yields (Scheme 36). However, the problem remained in the removal the N-4-methoxybenzoyl protecting group. We found that 138 was sensitive to CAN reagents. After screening the different conditions (Table 3), we found that this approach was also impracticable.

**Scheme 36.** The synthetic route to lactam (III)
Table 3. The 4-methoxybenzoyl removal conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>Temperature</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAN, CH₃CN/H₂O=4:1</td>
<td>23°C</td>
<td>byproduct</td>
</tr>
<tr>
<td>2</td>
<td>CAN, CH₃CN/H₂O=2:3</td>
<td>-10°C</td>
<td>Dirty</td>
</tr>
<tr>
<td>3</td>
<td>TEA, anisole</td>
<td>refluxing</td>
<td>byproduct</td>
</tr>
</tbody>
</table>

Discouraged by the unsuccessful deprotection of the methylated lactam, we turned our attention to the silyl protected lactam 140, which is known in the literature. From the enantiopure tertiary alcohol, the corresponding silyl ether was obtained in one step with quantitative yield by protection with R₃SiOTf. The procedure of three steps in one pot was adopted to prepare the corresponding precatalysts: Activation of the amide with Meerwein’s reagent, then addition of the phenylhydrazine, reflux with trimethyl orthoformate to afford the triazolium salts 141a-c. The crude catalysts mixtures were dried in high vacuum for 16 hours, purified by precipitation and recrystallized from ethyl acetate to give colorless crystalline products. Sometimes the residues can be purified by column chromatography to increase the yields.

Scheme 37. The synthetic route to silyl-based precatalysts 141.

According to the synthetic route, we were able to access a number of different triazolium salts to create a library of chiral carbene precatalysts. Indeed, different groups could be inserted during the Grignard reaction and the silylation in order to
investigate the effect of different steric and electronic properties of different branches. Thus three catalysts 141a-c were prepared. Another diphenyl lactam 142 was prepared by reduction of 139 with triethylsilane in DCM without racemization of the product. Following the same cyclization procedure, the catalyst precursor 143 was obtained.

Scheme 38. The synthetic route to the precatalysts 143.

Figure 24. The precatalysts 141a-c and 143.

An X-ray crystal structure of the triazolium salt 141a was obtained. The structure shows that the bicyclic rings are well-twisted as we expected and that the stereocenter is (S)-configured. The angle between the N-C-N of the triazolium ring was determined to be 105.8°, which is consistent with the known triazolium salts. The angle between the N-C-C of the chiral branch was determined to be 105.8°. As shown in Figure 25, the chiral diphenyl branch is sitting above the bicyclic plane, and it is well packed with the bulky O-silyl group.
3.1.3. Application of the catalysts in nuleophilic acylations

The intermolecular Stetter reaction is another variant of the Michael addition. Once the highly desirable intermolecular Stetter reaction was set as a target, initially, following the known procedure, the intermolecular Stetter reaction was performed with the thiazolium salt 65a as precatalyst with DBU as base in THF and afforded the desired product in 65% yield. With the successful experience in mind, the new family of chiral triazolium salts as catalyst precursors were tested. With GC and TLC analysis of the reaction mixture after 24 hours at room temperature, unfortunately, as shown in table 4, no desired products were observed. Varying the aromatic aldehyde to an aliphatic aldehyde was in order to see if the aldehyde can affect the outcome of the reaction. However, only benzoin or starting materials were obtained in each case. The reaction conditions were switched to KHMDS in toluene, which was utilized by the Rovis group for the intramolecular Stetter reaction, but it still resulted in no reaction. KHMDS in THF and even some mixed solvent (Toluene:EtOH) were screened, none afforded the desired products. Next we tried to screen different Michael acceptors such as α, β -unsaturated ketones, esters and the more reactive nitroalkenes. The results were very disheartening, no reaction worked!
Table 4. The catalysts 141a-c and 143 were tested in the intermolecular Stetter reaction

![Stetter Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>EWG</th>
<th>Cat.</th>
<th>conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141a</td>
<td>DBU, THF</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>DBU, THF</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141c</td>
<td>DBU, THF</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>143</td>
<td>DBU, THF</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>KHMDS, THF</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>KHMDS, PhCH₃</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>KHMDS, PhCH₃/EtOH=2:1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>Et₃N, THF</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>(CH₃)₂CHCH₂</td>
<td>Ph</td>
<td>COPh</td>
<td>141a</td>
<td>KHMDS, THF</td>
<td>dirty</td>
</tr>
<tr>
<td>10</td>
<td>(CH₃)₂CHCH₂</td>
<td>Ph</td>
<td>COPh</td>
<td>141a</td>
<td>DBU, THF</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>(CH₃)₂CHCH₂</td>
<td>Ph</td>
<td>COPh</td>
<td>141b</td>
<td>KHMDS, THF</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Ph</td>
<td>H</td>
<td>COOMe</td>
<td>141a</td>
<td>KHMDS, THF</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>H</td>
<td>COMe</td>
<td>141a</td>
<td>KHMDS, THF</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>Ph</td>
<td>COMe</td>
<td>141a</td>
<td>KHMDS, Toluene</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>Ph</td>
<td>NO₂</td>
<td>141a</td>
<td>KHMDS, THF or DBU THF</td>
<td>0</td>
</tr>
</tbody>
</table>

In order to gather more information about the new precatalysts, we decided to investigate the reactivity of the triazolium catalysts in the benzoin condensation and intramolecular Stetter reaction which were previously reported by our group and others. Our initial attempts were to apply chiral triazolium salts to the asymmetric benzoin condensation by using benzylaldehyde as substrate. We were pleased to find that the first conditions utilizing precatalyst 141a with KHMDS in toluene provided a very good result for this transformation. Under the given conditions (entry 1, Table 5), 141a afforded the benzoin product in 66% yield and 95% ee. Under the same
Results and discussion

conditions, precatalyst 141b showed a slightly lower selectivity (91% ee) and provided the product with a much lower yield (entry 2, Table 5). Furthermore, the
dimethylsilyl substituted triazolium salt 141c delivered much lower enantiomeric
excesses (42%) than the diphenyl carbene precursor 141a, but accompanied with good
yields (84%). Precatalyst 143 gave rise to the desired benzoin in good yields, but only
5% enantiomeric excess at room temperature utilizing KHMDS as base and toluene as
solvent. However, by changing the reaction conditions to DBU and THF, the yields
could be increased, while the selectivity for the tested precatalysts drops significantly
(entry 5, Table 5). The enantioselectivity for 141a as precatalyst gave benzoin only in
70% ee, and the product was obtained as racemate when 141c was used as precatalyst.
In the cases of Et3N and i-Pr2NEt as base in THF as solvent, precatalyst 141a did not
afford the product (entry 7, 8. Table 5). An explanation can be that Et3N or i-Pr2NEt
were not basic enough to deprotonate the precatalyst. As described in the summary of
the Introduction Part, the aliphatic benzoin reactions need to be improved. Intrigued
by the prospect of developing an entry to a wide scope of benzoin condensation, the
catalysts were tried with aliphatic aldehydes. Unfortunately, the catalysts were
completely inactive in this reaction (entry 9, Table 5). Moreover, we tested the cross
benzoin condensation. Disappointingly, such a reaction failed (entry.10, Table 5).

![Scheme 39. The benzoin reaction.](image_url)
Table 5. Conditions tested for the benzoin reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹ and R²</th>
<th>Conditions</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R¹=R²=Ph</td>
<td>141a, KHMDS, toluene</td>
<td>66</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>R¹=R²=Ph</td>
<td>141b, KHMDS, toluene</td>
<td>38</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>R¹=R²=Ph</td>
<td>141c, KHMDS, toluene</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>R¹=R²=Ph</td>
<td>143, KHMDS, toluene</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>R¹=R²=Ph</td>
<td>141a, DBU, THF</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>R¹=R²=Ph</td>
<td>141c, DBU, THF</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>R¹=R²=Ph</td>
<td>141a, Et₃N, THF</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>R¹=R²=Ph</td>
<td>141a, i-Pr₂NEt, THF</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>R¹=R²=aliphatic</td>
<td>141a, KHMDS, toluene</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>R¹=Ph, R²=MeOPh</td>
<td>141a, KHMDS, toluene</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated product. <sup>b</sup> ee determined by HPLC.

Since the optimal conditions were determined, we set out to test the scope of the different aromatic aldehydes. Various aromatic or heteroaromatic aldehydes 144 were tested in the benzoin condensation with the optimized protocol to afford the α-hydroxy ketones, which were obtained in modest yield and acceptable enantiomeric excesses determined by HPLC. In general, electron-rich aromatic aldehydes were less active, but showed better asymmetric induction than electron-deficient aldehydes. Aldehydes bearing electron-withdrawing groups could be converted to benzoin products in moderate yields (50-65%). However, the enantioselectivity of the process decreased (50-84% ee). The heteroaromatic aldehydes (144g and h) showed generally higher yields, but the lowest enantioselectivities. The influence of the aldehyde substrates for the benzoin conversion were in accordance with our previous report.⁴³
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Table 6. Scope of the benzoin condensation

<table>
<thead>
<tr>
<th></th>
<th>144, 145</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>Ph</td>
<td>66</td>
<td>95</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>2-Naphthyl</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>4-ClPh</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>3-ClPh</td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>4-MePh</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>4-MeOPh</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>g</td>
<td></td>
<td>2-Furyl</td>
<td>95</td>
<td>21</td>
</tr>
<tr>
<td>h</td>
<td></td>
<td>2-Thiophenyl</td>
<td>77</td>
<td>51</td>
</tr>
</tbody>
</table>

a) All reactions were performed with 10 mol% of the precatalyst and 10 mol% base at room temperature for 16 h.  
b) Yield of isolated product.  
c) ee determined by HPLC.

Notably, the absolute configuration of the benzoin product was determined to be \( R \) by correlation of the measured optical rotation value with the corresponding literature.\(^{43}\) It means the new catalysts can be an alternative choice to obtain the opposite configuration of benzoin product (Figure 26) compared to previous catalysts.

![Figure 26](image-url). Possible transition state for the benzoin condensation.

With the pioneering studies of triazolium-derived catalysts in the context of Stetter reactions, especially the systematic investigations from the Rovis group, we then investigated the intramolecular Stetter reaction. Based on the experiences of the new catalysts in the benzoin condensation, we started to study an examination of the intramolecular Stetter reaction with the standard starting material 146 (Table 7) which
was synthesized from salicylaldehydes. We found that the reaction proceeded in good chemical yield but with no enantioselectivity with the conditions developed for the benzoin condensation. We reasoned that it could be a consequence of racemization due to the basic reaction conditions. In order to test this hypothesis, we changed to weak bases again: Et₃N and Hünig’s base are still not basic enough to generate the carbene catalyst (entry 5, 6, Table 3). Potassium carbonate in THF only improved to 18% enantioselectivity. We in turn considered the feature of catalyst structure with inherit rigidity of diphenyl system, the diphenyl group could be too rigid for the intramolecular reactions. Considering that catalyst 143 can give 27% ee, but 141a can only give racemate, we recognized that the hydrogen-bonding effect caused by the oxygen atom could also be responsible for the induction. Combining with the previously described data about the intermolecular Stetter reaction (Table 4), the new catalysts give some complex results, which cannot be explained quite well by the known mechanism model. Of course, the further understanding of the mechanism model need to be intensively studied.

Table 7. Intramolecular Stetter reaction.²

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)ᵇ</th>
<th>ee (%)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a, KHMDS, THF</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>141b, DBU, Toluene</td>
<td>70</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>143, KHMDS, Toluene</td>
<td>94</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>141a, DBU, Toluene</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>141a, Et₃N, THF</td>
<td>&lt;10</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>141a, Pr₂NEt, THF</td>
<td>&lt;10</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>141a, K₂CO₃, THF</td>
<td>92</td>
<td>18</td>
</tr>
</tbody>
</table>

² Reaction at room temperature for 16hrs. ᵇ Yield of isolated product. ᵇ ee determined by HPLC
3.1.4. Conclusion

In summary, we have prepared a family of new chiral triazolium salts bearing different substituted side chains and silyl protecting groups from the cheap pyroglutamic acid. These chiral triazolium salts turned out to be efficient organocatalysts for nucleophilic aldehyde activation. Catalyst 141a led to good enantioselectivities in the benzoin condensation of aromatic aldehydes. Moreover, they were also very active in the intramolecular Stetter reaction, but unfortunately, gave low enantioselectivities. The new catalysts can support an alternative choice for the benzoin or intramolecular Stetter reactions.
3.2. Development of chiral triazolium salts by changing the N-substituent and their application in the intermolecular Stetter reaction

3.2.1 The intermolecular Stetter reaction

As depicted in the first chapter, 1,4-difunctional compounds such as 1,4-diketones are important and valuable precursors for the synthesis of natural products such as jasmones, cuparenones, prostaglandins, and some five-membered heterocyclic compounds. Recently, Vila et al. reported that using enantiopure starting materials led to 1,4-diketones. Unfortunately, this method is limited to some specific products, another major limitation associated with this method are the many steps of the synthetic route. The intermolecular Stetter reaction is a direct way to 1,4-diketones. Since the formation of the Stetter product included the generation of a new stereocenter, the development of enantioselective versions of this reaction are important. However, only a few reports of enzyme-catalysis and metallphosphite catalysis have appeared. Enzyme-catalysis is costly and gives low yield. Metallphosphite catalysis is limited to acylsilanes and special amides as Michael acceptors. Furthermore, the asymmetric conjugate addition of acyl anion equivalents leading to the less accessible 1,4-dicarbonyl compounds has not been studied thoroughly.

According to our previous experiences and as proven from reported literature, main obstacles for exploring the asymmetric intermolecular Stetter reaction are as follows:

1. Aldehydes can form benzoins. In most cases, aldehydes are more active than the Michael acceptors. Although the self-condensation can be circumvented by the Sila-Stetter reaction, there is no report about an asymmetric Sila-Stetter reaction (Scheme 27).

2. Benzoin can react with activated double bonds to form long-chain diketone products. Some conjugate bases of the precarbene salts could deprotonate the benzoin, then addition of benzoins to Michael acceptors to form the byproduct could occur (Scheme 40).
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Scheme 40. The Michael addition of benzoin to chalcone.

3. Dead end of the carbene adding to the activated double bond. Some carbenes derived from triazolium salts have been shown to be highly reactive, in some cases stable adducts with Michael acceptors have been observed, and which was a possible reason for their failure in carbene catalysis.

Scheme 41. The addition of carbenes to chalcone

4. The reaction always needs high temperature. The upper three points are specific to the reactivity of a carbene in the Stetter reaction, but this point is relevant for both reactivity and enantioselectivity. It is generally well known that a high temperature is harmful to achieve a good enantioselectivity.

3.2.2. Some available catalysts applied in the intermolecular Stetter reaction

Our initial attempts to apply the new catalysts in the intermolecular Stetter reaction were not successful (Chapter 3.1). Therefore, we had to consider the strategy again. We reasoned that the increased reactivity of triazolinylidene carbenes has not much relation with the branches of the chiral moiety on the fused bicyclic ring. To test this hypothesis, again we used DBU as base in THF as solvent as the practical conditions. Our investigation commenced with benzaldehyde and chalcone as model substrates. In seeking the suitable precatalyst, different triazolium salts 151a-g available in our lab were screened. Unfortunately, none of them worked!
3.2.3. Development of N-methyl based triazolium salts

It is worth to point out that in 2005 our colleague Tim Balensiefer in the Enders group made a significant breakthrough concerning the reactivity of carbenes in the intermolecular Stetter reaction.\textsuperscript{96} N-Methyl triazolium salts 153a and b obtained from (S)-glutamic acid were found to be active in the reaction in 73\% yield. Albeit the catalysts were a mixture and they are very difficult to separate from each other, these endeavors opened a door for the development of the suitable triazolium salts. In addition, the triazolium salt 153a not 153b as the precatalyst possessing the catalytic activity was proved. Most importantly, these discoveries did open the door for the development of new more efficient carbene catalysts.

\textbf{Scheme 43.} The N-Methyl triazolium salts developed by Enders et al.

In order to obtain further information about the structure and the reactivity of N-methyl triazolium salts, we began to synthesize the bicyclic triazolium salts with the simple non-chiral pyrrolidinone 154 as starting material. According to the
previously described procedure for the triazolium salts, colorless crystals was formed. We were pleased to find that only one structure was observed as identified by NMR. The field effect explained that the electron donating groups such as methyl increase the basicity of the amine. The secondary amine of the methylhydrazine was more basic than the primary amine at the end of the molecule (Figure 27). Therefore, the precarbene salt was not our desired structure 155 but 156, which was later proved by an X-ray crystal structure analysis. Therefore, It was no surprise that the salt 156 as precatalyst did not show any catalytic activity in the intermolecular Stetter reaction with DBU as base in THF.

\[
\begin{align*}
\text{Me} & \quad \text{NH}_2 \\
\text{NH} & \quad \text{Me}
\end{align*}
\]

More basic

Less basic

Figure 27. The reactivity of methylhydrazine.

Scheme 44. The development of N-Methyl triazolium salts.

We obtained the N-methyl triazolium salt, which is not our desired structure. It seemed to be difficult to install a methyl group in the triazolium ring. However, compared to the precatalyst 153a, by using of a branch on the ring, we could get half of the desired product. This selectivity of installing a methyl group on the different N atom of triazolium salts could be partly due to the steric effect of the side chains, which suggested that it was still possible to get the pure desired precarbene salts, if the suitable branches were employed. Clearly, increasing the steric effect by building up the bulkiness of the branch could be the feasible direction for the catalyst design. As described in the preceding chapter, we in turn reasoned that the desired catalysts
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could be obtained after the installation of a N-methyl group on the triazolium ring by employing the lactams with bulky diphenyl(trialkylsilyloxy)methyl substituent for developing the precursors. As was expected, two new catalysts (157 and 158) were prepared and then subjected to the intermolecular Stetter reaction with DBU as base in THF (Scheme 45). The O-TBS precatalyst 158 gave no conversion to the desired 1,4-diketones, but benzoin products. This result could be attributed to the extreme steric bulk of silyl group around the reactive site of the Breslow intermediate. Interestingly, with the O-TMS precatalyst 157, we found that under the unoptimized conditions, 1,4-diketone can be formed by coupling of benzylaldehyde to chalcone in moderate yields, but only 8% ee. The thorough studies on the reaction conditions with precatalysts containing N-methyl substituent had not been previously reported in the literature. In order to collect more information about N-methyl catalysts for further development, we began to look back at the less hindered catalyst 153. Under the same conditions, precatalyst 153 gave high yields but also low enantioselectivity of 3% ee after 24 hours. The ee value can be increased to 12% by reducing the reaction time.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{O} & \quad \text{Ph} \\
\text{Ph} & \quad \text{O} \\
\text{+} & \quad 10\text{mol\% precatalyst} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\text{BF}_4 & \\
\text{Ph} & \quad \text{OTMS} \\
\text{Yields\%} & = 28\% \\
\text{ee\%} & = 8\% \\
\text{in 72 h} & \\
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{+} & \quad 10\text{mol\% DBU} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\text{BF}_4 & \\
\text{Ph} & \quad \text{OTBS} \\
\text{Yields\%} & = 0 \text{reaction} \\
\text{in 72 h} & \\
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{+} & \quad 10\text{mol\% precatalyst} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\text{BF}_4 & \\
\text{Ph} & \quad \text{OTIPS} \\
\text{Yields\%} & = 70\% \\
\text{ee\%} & = 3\% \text{in 24 h} \\
\text{Yields\%} & = 61\% \text{in 6h} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\text{BF}_4 & \\
\text{OTIPS} & \\
\end{align*}
\]

Scheme 45. N-methyl based catalysts applied in the intermolecular Stetter reaction.

The enantioselectivity of N-Methyl based precatalysts was discouraging again, but we had realized one of our original goals of developing a reactive triazolium salt for the intermolecular Stetter reaction. With this result in hand, the preliminary optimization efforts were carried out by varying the solvents and bases. The yield could be
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improved to 38%, by increasing the temperature to 60°C but the enantioselectivity dropped to 2%. By simply changing the base from DBU to Et$_3$N did not provide the product. Utilization of KHMDS in toluene also did not afford the desired products. Replacement of the order by first deprotonation with base to generate the carbene, also results in no reaction.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBU</td>
<td>THF</td>
<td>r.t.</td>
<td>72 h</td>
<td>28</td>
<td>8.3</td>
</tr>
<tr>
<td>DBU</td>
<td>THF</td>
<td>60 °C</td>
<td>72 h</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>THF</td>
<td>r.t.</td>
<td>72 h</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Toluene</td>
<td>r.t.</td>
<td>12 h</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>KHMDS$^a$</td>
<td>Toluene</td>
<td>r.t.</td>
<td>3 h</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td>10</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

$^a$, Deprotonation the catalysts first with KHMDS, then the substrates were added.

3.2.4. Development of N-Benzyl based triazolium salts

3.2.4.1. Analysis of the triazolium salts

Since we were not able to achieve good results by the use of N-methyl substituted triazolium salts in the intermolecular Stetter reaction, we had to think about the strategy for catalyst design and to consider the experiences from the benzoin condensation again. The thiazolium salts were problematic for achieving good enantioselectivity in catalyzing the benzoin condensation in spite of their high activity. The deficiency in enantioselectivity was demonstrated to be only a sulfur atom but lack of a substituent in three of the four quadrants surrounding the reactive carbene center. This problem was endemic for the thiazolium catalysts. In a comparison of the methyl group to the phenyl group, we analyzed that, 1) the influence of electronic characteristic of carbene carbon by N-substituent group was useful. 2) The steric modification of decreasing the shielding effect was necessary. At this point, the
phenyl group is much bulkier than the methyl group. Therefore, the phenyl group occupied the spaces around the reactive center which could block the attack of another electrophile. These analyses let us try to install other groups on the nitrogen in order to investigate the reactivity.

![Figure 28](image)

**Figure 28.** The comparison of the N-Me to the N-Ph in the Breslow intermediate.

Intrigued by the thiazolium salt used by Stetter et al, we thought that an increase of the activity could be achieved through a N-benzyl substituent. As is seen from the Figure 29, we carried out a MM2 energy minimization for generating a realistic 3D structure of the Breslow intermediate. From the model, we can see that the shielding effect was dramatically decreased compared to the phenyl group (Figure 29).

![Figure 29](image)

**Figure 29.** The MM2 calculation of benzyl-based Breslow intermediate 161.

### 3.2.4.2. Synthesis of the benzylhydrazine

Since benzyl hydrazine is not commercially available, literature methods were adapted to generate these alkaryl hydrazine derivatives. One report is that the benzyl hydrazine was synthesized by direct reductive amination of benzaldehyde with hydrazine (Scheme 46). When we tried to prepare benzylhydrazine according to this method in two steps and in one pot. It was found that the yield was quite low. It is
difficult to separate the products from the side products. In order to get pure products, we employed this approach in two steps: Benzaldehyde was treated first with 85% hydrazine hydrate in isopropyl alcohol at 60 °C to form the Schiff base, followed by recrystallization. The pure Schiff base was obtained as yellow crystalline needles. The Schiff base was then reduced by hydrogen under pressure with palladium on carbon at 50°C. However, we found that there was still a large amount of starting material left. Purification by chromatography was not successful.

\[
\begin{align*}
\text{H}_2\text{N} & \text{NH}_2 \\
\text{PhCHO} & \text{H}_2, \text{Pd/C} \\
\text{MeOH, r.t.} & \rightarrow \text{Ph} \text{NNHNH}_2
\end{align*}
\]

**Scheme 46.** Route (I) for preparing benzylhydrazine.

Therefore, we started to search for an alternative method. Another entry using \textit{tert}-butyl carbazate as starting material was reported (Scheme 47),\textsuperscript{98} but the starting material is expensive, and the product is obtained as hydrochloride salt. At last, we found another old method by reacting the benzyl chloride with 85% hydrazine hydrate to give the desired benzylhydrazine. Although a large amount of disubstituted N,N-dibenzylhydrazines were formed, this reaction with its large scale and the easily available starting materials deserved a good method (Scheme 48). The benzylhydrazine was isolated by distillation as a colorless oil in 30% yield (See warning!).

\[
\begin{align*}
\text{PhCHO} & + \text{t-Bu} \text{NHNHNHNHNHNH}_2 \\
\text{Pt, H}_2 & \rightarrow \text{Ph} \text{NHCO}_2\text{t-Bu} \\
\text{HNH}_2 & \text{NHNHNHNHNHNH}_2 \\
\text{HCl, EtOH} & \rightarrow \text{Ph} \text{HNHNHNHNHNHNH}_2
\end{align*}
\]

**Scheme 47.** Route (II) for preparing benzylhydrazine.

**Please pay attention:** The distillation of the benzylhydrazine mixture was easily explosive!!!
3.2.4.3. Preparation of five membered ring based N-benzyl triazolium salts

As stated in the calculated model (Figure 29), we set out to synthesize the new precatalyst with the N-benzyl group. The non-chiral pyrrolidone was employed as starting material, followed by a three step one pot procedure. The triazolium salt 165 was obtained in 68% yield as a viscous oil.

With the precatalyst 165 in hand, we began to investigate its activity in the intermolecular Stetter reaction under the standard conditions as described above. We obtained the desired product in 63% yield (Scheme 50). This result was very exciting and inspiring.

Soon, we set out upon a journey for exploring the asymmetric version of the intermolecular Stetter reaction. Recently, we had successfully prepared the silyl substituted triazolium salts derived from (S)-pyroglutamic acid. The (S)-pyroglutamic
Results and discussion

acid was reduced to the hydroxymethyl-substituted lactam 166 and subsequent reaction with the silyl chlorides to give tert-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS) protected lactams 167 in quantitative yields. The bulkiness at the stereogenic center might be modified by a simple exchange of the protecting group. The ease of its preparation and the low cost of the starting material makes it very attractive. Taking advantage of this consideration, we employed the silyl protected lactam for the synthesis of the envisaged triazolium salts. The cyclization in the three-step one pot synthesis of the triazolium ring was modified by simple exchange of the hydrazine portion with benzyl hydrazine (Scheme 51).

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Me} & \quad \text{NaBH}_4 \\
\text{EtOH} & \quad \text{OH} \\
\text{quant} & \quad \text{R}_3\text{SiCl} \\
\text{Base} & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{SiR}_3 & \quad \text{Bf}_4^-
\end{align*}
\]

\[
\begin{align*}
\text{3 Steps} & \quad \text{N} \\
\text{Ph} & \quad \text{BF}_4^- \\
\text{40-86\%} & \quad \text{OSiR}_3 \\
\text{168} & \quad \text{167} \\
\text{>90\%} & \quad \text{N} \\
\text{OSiR}_3 & \quad \text{168 a-c}
\end{align*}
\]

Scheme 51. The route to N-benzyl triazolium salts 168 a-c.

The triazolium salt with the TIPS silyl group as a branch did not solidify easily. Triphenylsilyl (TPS) derived catalysts were obtained in low yields. A chiral bicyclic triazolium salt bearing TBDPS branch with the N-benzyl substituent was conveniently prepared in 80% overall yields as a solid. It has been reported that the super silyl group tris(trimethylsilyl)silane (TTMSS) is of comparable size as the tert-butyl group. In order to evaluate the bulky branches for transferring the high degree of ee in the reaction, the TTMSS group as a branch was used too, unfortunately, this supersilyl group is not stable under the triazole cyclization conditions.
As described in the first chapter, we have developed a family of bulky lactams. Therefore, the combination of these lactams with benzyl hydrazine to construct new triazolium salts was also investigated. The diphenylmethyl- and dimethyl-(trialkylsilyloxy)methyl derived precatalysts 169 and 170 were prepared in 55% and 40% yield, respectively. However, the preparation of diphenyl(trialkylsilyloxy)methyl derived precatalysts 169a and 169b was unsuccessful. A possible reason could be that the bulkiness of the branch blocked the attack of benzylhydrazine to the imino ether in the second step of the standard procedure (Scheme 52).

![Scheme 52](image)

**Scheme 52.** The route to N-benzyl triazolium salts 169 a-c and 170.

Rovis *et al.* have reported a family of catalysts derived from pyrrolidiones and successfully applied them in the intramolecular Stetter reaction.\(^8\)\(^3\) Inspired by this results, we pursued the synthesis of some new precatalysts bearing the N-benzyl group. Natural amino acids such as \(S\)-valine and \(S\)-phenylalanine were employed as starting materials. The synthesis of the pyrrolidinone core was realized according to the known literature procedure.\(^8\)\(^3\) First protection with Boc\(_2\)O afforded N-Boc...
protected phenylanine as a pure colorless crystalline solid 171. Then coupling of the N-Boc protected amino acid with Meldrum’s acid in the presence of DMAP and DCC gave the desired product 172 that could be used in the further steps without purification. Reduction of the ketone by slow addition of 3 equivalents of sodium borohydride at 0°C over 1 hour was followed by stirring at 0°C overnight. The desired product 173 was obtained as a thick oil. Cyclization of 173 by refluxing in toluene, followed by removing the N-Boc protecting group with trifluoroacetic acid afforded the final pyrrolidinone 175 as a light yellow solid. With the lactams in hand, another two new triazolium salts were prepared with the three steps one pot procedure. Unfortunately, the final salts could not be precipitated from ethyl acetate and other solvent systems. However, from the crude NMR, we identified that it is the desired compound. At the end, chromatography was adopted to purify the products. 176 was obtained as gelatiniform substances (Scheme 53).

**Scheme 53.** The route to N-benzyl triazolium salts 176.

In 2002, Ulrike Kallfass in our group has developed a four step reaction sequence starting from easily available protected glycol aldehyde hydrazones by alkylation,
1,2-addition, fluorine promoted cyclization and Li/NH$_3$-cleavage of the nitrogen-nitrogen bond to afford a variety of cis-4,5-disubstituted oxazolidin-2-ones in a highly enantioselective manner.$^{99}$ We decided to use this bulky oxazolidinones to prepare a family of new precatalysts. However, it was found difficult to cyclize the oxazolidinones to the triazolium salts 177 and 178. In comparation of closely related precatalyst 176b, the reason of the unsuccessful preparation of 178 could be the oxygen atom in the five member ring. In connection with the tetracyclic triazolium salt 66 developed by Oliver Niemeier in our group, the cis-tricyclic lactam was also chosen as starting material for the synthesis of the precarbene catalyst 179, which was obtained as a solid in 80% yield.

![Structures of the N-benzyl substituted precatalysts.](image)

**Figure 30.** Structures of the N-benzyl substituted precatalysts.
An X-ray crystal structure of salt 168b is shown in Figure 31. The two bicyclic rings are in plane, the phenyl group of the benzyl group is out of the plane as expected to reduce the steric effect. As expected, the bulky silyl group for asymmetric induction is located under the plane.

![Figure 31. X-ray crystal structure of the precatalyst 168b.](image)

### 3.2.4.4. Application in the intermolecular Stetter reaction with the catalysts

With these catalysts in hand, we began to test their activity and selectivity in the intermolecular Stetter reaction with DBU as base in THF as solvent. The results are summarized in Figure 30. Comparing the steric effects of the chiral scaffold in reactivity and selectivity, it is obvious that the bulky scaffolds can increase the selectivity but decrease the reactivity. Therefore, good results were obtained with moderately bulky groups such as 176a and 170 (enantioselectivity 50% and 48% respectively) with moderate conversion in this study. The best conversion was found with the less hindered benzyl-substituted precursors 168a, 168b and 176b. Clearly, these results did not satisfy us. Therefore we set out to further tune the reactivity and selectivity by changing the structure of the precatalysts.

### 3.2.4.5. Further catalyst design and preparation

We postulated that changing the N-based group directly on the triazole might allow to
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improve the reactivity and selectivity of the precatalysts. We decided to implement a diphenylmethyl group in the triazole ring which bear a moderate silyl group on the side chain. As shown in the MM2 calculated model (Figure 32), the steric interaction between one of the phenyl substituents on the N-based portion and the phenyl substituent of the attacking aldehyde can form a π, π-stacking effect, which could lock the configuration of the Breslow intermediate. In theory, this interaction could favour the enantioselection.

![Figure 32. MM2 model of the Breslow intermediate 180.]

Based on the results of the modeling studies, the hydrazine was prepared directly from the chlorodiphenylmethane and hydrazine hydrate. We then chose the silyl protected lactam 152 to obtain the precatalyst 181. Of interest is that the catalyst was also active in the reaction, but it only gave 20% enantioselectivity. Changing the N-based substituents did not cause an improvement in the asymmetric induction.

![Scheme 54. The route to triazolium salts 181.]

Scheme 54. The route to triazolium salts 181.
We looked back to the strategy for the catalysts design again (No. 3, see in Object Part). The fused ring in the bicyclic precatalyst was ignored. It was thus theorized that the six-membered ring would lessen the steric encumbrance of the reactive face of the catalyst. We can anticipate that the substituent of the six membered ring would allow the steric interaction to stabilize the transition state more effectively, which could improve the asymmetric induction (Figure 33). The Leeper group and the Rovis group have reported the aminooindanol-derived morpholinyl precatalysts. Inspired by this, we decided to prepare some six-membered bicyclic chiral catalysts.

![Figure 33. Five membered ring vs Six membered ring of the Breslow intermediate.](image)

As described in Scheme 55, the amino alcohol 182 was obtained by reduction of the natural amino acid S-phenylalanine with LiAlH₄. According to the literature, 182 was treated with sodium hydride, followed by ethyl chloroacetates. Unfortunately, a mixture (183 and 184) was formed. Replacement of ethyl chloroacetate by acetyl chloride, gave only the corresponding morpholinone 184 in good yield. The synthesis of 185 by salification of the S-phenylalanine, followed by a Grinard reaction gave the amino alcohol 186 in a similar manner. Then 187 was obtained in 88% yield. The three steps were then executed to form the triazolium salts 188a and 188b.
Scheme 55. The route to triazolium salts 188.

Another six-member ring of bicyclic precatalyst 195 was prepared from S-Lysine as starting material. Esterification and salification in one pot afforded the product in 92% yield. Protection of the amino group with Boc₂O produced ester 190 in quantitative conversion. Oxidation with RuCl₃ and NaIO₄ gave the product 191 in 74% yield, then cyclization and deprotection with trifluoroacetic acid led to the lactam 192 in 74% yield. The synthesis of 194 was carried out by reduction, followed by protection with the TBDPS silyl group. The three steps were then executed to form the triazolium salt 195.

We next investigated the catalytic activity in the intermolecular Stetter reaction. The precatalysts were subjected to the standard conditions. It was found that the precatalysts containing an oxygen heterocycle (188a and 188b) afforded a large amount of diketone byproducts (Problem 2, Scheme 40). Interestingly, the precatalyst 195 gave the desired product in 30% yield determined by GC but only 28% enantiomeric excess.
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Scheme 56. The route to triazolium salts 195.

From the catalyst design strategy described in the objective part, most of the key points except the counter-ion were considered and modified. However, based on the previous experiences, changing the anion is just to tune the solubility characteristics of the precatalysts and easy to generate the carbene. The N-benzyl substituted triazolium salts have a good solubility in most of the common solvents. Therefore, the counter ion exchange appeared inadequate to realize our goals.

3.2.5. Optimization of the intermolecular Stetter reaction.

Our initial investigation has been carried out with different new catalysts, but we were still unable to perform a highly enantioselective intermolecular Stetter reaction under our current reaction conditions. We next pursued the development of reaction conditions that would improve the selectivity of the Stetter reaction. Triazolium salt 168b can be easily prepared in a large scale. It is air and water stable. For this reason, it was chosen as the precatalyst for the screening of a number of solvents and bases. Firstly, a number of bases were screened for the reaction with catalyst 168b in THF (Table 10). Utilizing weak bases such as Et₃N, diisopropylethylamine and piperidine, we did not observe the desired products. One possible reason is that
these bases are not strong enough to deprotonate the precursor. We were pleased to find out that potassium carbonate led to increased enantioselectivities without decreasing the yields (yield 73%, ee 51%, entry 10). Other practical potassium bases were tested in the reaction with THF as solvent, only a trace amount of products was observed when KHMDS and KOr-Bu were used as the bases. Proton sponge and DABCO could deliver a good enantioselectivity but in very poor yields.

It is worthy to note that KHMDS combined with toluene afforded the desired products in 49% yield. Therefore, we decided to screen the different bases again with toluene as solvent, unfortunately, no better results were observed. Surprisingly, the use of KOr-Bu and K₂CO₃ in toluene gave the opposite configuration. From this point, we can say that the solvent has a significant effect on the conversion.

### Table 10. Screening the different conditions for the Stetter reaction of benzylaldehyde and chalcone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield %</th>
<th>ee %</th>
<th>Reaction time</th>
<th>Deproton sequence¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>THF</td>
<td>72.6</td>
<td>19.5</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>THF</td>
<td>68.1</td>
<td>24.3</td>
<td>6 h</td>
<td>L</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>THF</td>
<td>71</td>
<td>23</td>
<td>6 h</td>
<td>F</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>Et₃N</td>
<td>THF</td>
<td>0</td>
<td>----</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>5ᶜ</td>
<td>Piperidine</td>
<td>THF</td>
<td>----</td>
<td>----</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr₂NEt</td>
<td>THF</td>
<td>0</td>
<td>----</td>
<td>16 h</td>
<td>F</td>
</tr>
<tr>
<td>7</td>
<td>DBN</td>
<td>THF</td>
<td>64.7</td>
<td>9.1</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>8</td>
<td>Proton sponge</td>
<td>THF</td>
<td>&lt;10</td>
<td>44.9</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>9</td>
<td>DABCO</td>
<td>THF</td>
<td>&lt;10</td>
<td>41.9</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>10</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>73</td>
<td>50.1</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>11</td>
<td>KOr-Bu</td>
<td>THF</td>
<td>&lt;10</td>
<td>ND</td>
<td>16 h</td>
<td>F</td>
</tr>
<tr>
<td>12ᵈ</td>
<td>KHMDS</td>
<td>PhCH₃</td>
<td>49</td>
<td>42.8</td>
<td>16 h</td>
<td>F</td>
</tr>
<tr>
<td>13</td>
<td>KOr-Bu</td>
<td>PhCH₃</td>
<td>70</td>
<td>-26</td>
<td>16 h</td>
<td>L</td>
</tr>
<tr>
<td>14</td>
<td>K₂CO₃</td>
<td>PhCH₃</td>
<td>50.5</td>
<td>-5.3</td>
<td>16 h</td>
<td>L</td>
</tr>
</tbody>
</table>
Results and discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield %</th>
<th>ee %</th>
<th>Reaction time</th>
<th>Deproton sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Proton sponge</td>
<td>PhCH\textsubscript{3}</td>
<td>&lt;10</td>
<td>----</td>
<td>48 h</td>
<td>F</td>
</tr>
<tr>
<td>16</td>
<td>DABCO</td>
<td>PhCH\textsubscript{3}</td>
<td>&lt;10</td>
<td>----</td>
<td>48 h</td>
<td>F</td>
</tr>
<tr>
<td>17</td>
<td>DBU</td>
<td>PhCH\textsubscript{3}</td>
<td>67</td>
<td>30.5</td>
<td>16 h</td>
<td>L</td>
</tr>
</tbody>
</table>

\(^a\) the sequence of addition of base, L means at last, F means first deprotonation with base. \(^b\) After that, the reaction was heated for 12hrs to 80\(^\circ\)C, it still shows no desired product but benzoin. \(^c\)2,2,6,6-Tetramethylpiperidine as base, It is strange that the reaction gave a large amount of benzoin, but without stetter products. \(^d\)KHMDS in toluene, gave totally the Michael addition product of benzoin with chalcone.

Next, several solvents were screened in the reaction with precatalyst 149b and K\textsubscript{2}CO\textsubscript{3} as base. The non-protonic polar solvents gave somewhat better yields and selectivities. Interestingly, the protonic solvent such as MeOH also provided products in 60% yield but only with 9% ee. The reaction performed in dichloromethane gave moderate yield, but the product is just a racemate. Only one case is worth to point out that the K\textsubscript{2}CO\textsubscript{3} and DMF showed a moderate yield but good enantioselectivity (entry 21, 55% yield, 52% ee).

Table 10. In continue of upper table.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield %</th>
<th>ee %</th>
<th>Reaction time</th>
<th>Deproton sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>MeOH</td>
<td>60</td>
<td>9.3</td>
<td>16hrs</td>
<td>L</td>
</tr>
<tr>
<td>19</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DCM</td>
<td>42</td>
<td>0</td>
<td>16hrs</td>
<td>L</td>
</tr>
<tr>
<td>20</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>Toluene</td>
<td>51</td>
<td>0</td>
<td>16hrs</td>
<td>L</td>
</tr>
<tr>
<td>21</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>55</td>
<td>51.7</td>
<td>16hrs</td>
<td>L</td>
</tr>
<tr>
<td>22</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DMSO</td>
<td>50</td>
<td>32.5</td>
<td>16hrs</td>
<td>L</td>
</tr>
<tr>
<td>23</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>Et\textsubscript{2}O</td>
<td>39</td>
<td>15.3</td>
<td>16hrs</td>
<td>L</td>
</tr>
</tbody>
</table>

The best conditions were identified with K\textsubscript{2}CO\textsubscript{3} and THF. Unsatisfied with the 50% selectivity, we performed a temperature investigation and found a dramatic effect on the reactivity of the intermolecular Stetter reaction. A modest increase of enantioselectivity (55%) was observed when the reaction was performed at 0\(^\circ\)C but the yield dropped to 52%. When the temperature was lowered to –20 \(^\circ\)C, only benzoin was formed. As low as –40 \(^\circ\)C, only starting materials were observed (Table 11).
Table 11. Temperature investigation in the intermolecular Stetter reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp.</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Benzoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>– 40 °C</td>
<td>0</td>
<td>--</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>– 20 °C</td>
<td>0</td>
<td>--</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>0 °C</td>
<td>52</td>
<td>55</td>
<td>yes</td>
</tr>
</tbody>
</table>

Before we tried to expand the scope, we repeated the reaction for several times in order to test the reproducibility. It was found that the outcome of enantioselectivity swings above or below the 55%. The result was not repeatable quite well. One possible reason was perhaps due to the erosion of product ee. Racemization of the newly formed stereogenic center is always a concern in the development of asymmetric acylation reactions. Furthermore, the conditions we employed were quite basic which can easily racemize the product. This consideration led us to speculate that the optically active Stetter product was subject to the reaction conditions to see if the racemization happened. The enantiomeric excesses decreased from 59% to 29% under the reaction conditions in 12 hours at room temperature, which is consistent with the possibility of enolization at the heart of product racemization. This observation also led to the elucidation of the problem of unreproducibility. Interestingly, under the conditions of only K$_2$CO$_3$ in THF with same time and temperature, only a slight recemization was observed (scheme 57).

![Scheme 57. The racemization investigation of the Stetter product.](image-url)

After different conditions were tested, the problem of recemization was considered. In order to allow only minimal product racemization to occur, once again, with the THF as optimal solvent, we screened the other bases of alkali metal carbonates. An exciting result found that Cs$_2$CO$_3$ could increase the entianoselectivity to 62% with a slight reduction of yields. The results could be reproduce quite well for five times.
Nevertheless, Na₂CO₃ and Li₂CO₃ did not give good results (Table 12).

<table>
<thead>
<tr>
<th></th>
<th>Na₂CO₃</th>
<th>Li₂CO₃</th>
<th>Cs₂CO₃</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>THF  &lt;10</td>
<td>THF  0</td>
<td>THF  65</td>
</tr>
<tr>
<td>2</td>
<td>THF  --</td>
<td>THF  --</td>
<td>THF  66</td>
</tr>
</tbody>
</table>

When we tried to subject the reaction at low temperature such as 0°C, after evaporation of the solvent, we collected the sample to check the ee by HPLC, the enantioselectivity was found as high as 93% ee. When we were trying to expand the scope of substrates (see below), regrettably, we could not get high enantioselectivity with other samples. For this reason, we decided to repeat the reaction again, by following the same procedure, 91% ee was obtained again. After much thought we made a conclusion that a recrystallization by cooling could be done during the process of evaporation of the solvents. To test this hypothesis, we collected all the products and dissolved them in DCM, then the enantiomeric excess was determined with 68%. In this case (and in several others, see blow), however, we found a new catalytic way to the enantiopure 1,4-diketones by recrystallization.

3.2.6. Substrate scope of the intermolecular Stetter reaction.

Next, we examined the scope of the substrates. As shown in Table 13, a variety of arylaldehydes with substituted chalcones as Michael acceptors were investigated. The results showed that, in general, the nucleophilic acylation of the \( \alpha, \beta \)-unsaturated ketone occurred smoothly to afford the products in good yields with acceptable levels of selectivity. Basically, electron-rich aromatic aldehydes showed better asymmetric induction than electron-deficient ones, but they are less active (Entry 5a-5e, Table 13). Notably, heterocyclic aldehydes such as 2-furaldehyde gave the dicarbonyl compounds cleanly in moderate enantioselectivity (56% ee). The nucleophilic acylation is applicable to substituted chalcones containing both electron-donating group and electron-withdrawing groups in the \( \beta \)-position of substrates, which afforded reasonable yields and
enantioselectivities (196 i-j, Table 13).

Table 13. The intermolecular Stetter reaction with different substrates.\(^a\)

\[
\begin{align*}
\text{Entry} & \quad R^1 & \quad R^2 & \quad R^3 & \quad \text{yield } \% ^b & \quad \text{ee } \% ^c \\
196a & \text{Ph} & \text{Ph} & \text{Ph} & 65 (40) & 66 (>99) \\
196b & 4-\text{MeC}_6\text{H}_4 & \text{Ph} & \text{Ph} & 43 (31) & 78 (>99) \\
196c & 3-\text{MeC}_6\text{H}_4 & \text{Ph} & \text{Ph} & 50 (32) & 70 (98) \\
196d & 4-\text{ClC}_6\text{H}_4 & \text{Ph} & \text{Ph} & 55 & 67^d \\
196e & 4-\text{BrC}_6\text{H}_4 & \text{Ph} & \text{Ph} & 68 & 56^d \\
196f & \text{2-naphthyl} & \text{Ph} & \text{Ph} & 65 (41) & 70 (90) \\
196g & \text{2-furyl} & \text{Ph} & \text{Ph} & 98 & 56^e \\
196h & \text{2-furyl} & \text{Me} & \text{Ph} & 80 & 30^e \\
196i & \text{Ph} & 3-\text{ClPh} & \text{Ph} & 36 & 68^e \\
196j & \text{Ph} & 4-\text{MePh} & \text{Ph} & 57 & 56^d \\
196k & \text{Ph} & 4-\text{ClPh} & \text{Ph} & 57 (21) & 72 (94) \\
\end{align*}
\]

\(^a\) All reactions were performed with 10 mol\% of the precatalyst and 10 mol\% base at 0°C for 8 h.

\(^b\) Yields of isolated 1,4-diketones.

\(^c\) The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD), and Value in brackets is the ee after recrystallisation.

\(^d\) The products were obtained as thick oil. \(^e\) Attempts at recrystallization were unsuccessful.

After the significant work for screening the conditions, we could increase the enantioselectivity from 29\% to 66\% ee with precatalyst 168b. From the view of asymmetric catalysis, 90\% ee is an important boundary for judging a catalytic system. Considering that the precatalyst 176a is better than 168b with DBU as base in THF, we tried the Stetter reaction of p-tolualdehyde with chalcone catalyzed by triazolium salt 176a with Cs\(_2\)CO\(_3\) in THF. Unfortunately, only 78\% ee were obtained in a (S)-configuration which is opposite to 196b.
3.2.7. **Mechanism investigation of the intermolecular Stetter reaction.**

With the successful development of an asymmetric intermolecular Stetter reaction, we were interested to understand the mechanism of this carbene-catalyzed process. In cooperation with Alexander Henseler, the reaction process was monitored by gas chromatography at different reaction times. After 0.5 hours, only the starting materials were observed. After 1 hour, some benzoins appeared but still without Stetter product. After 2 hours, 12% yield of products were obtained with 75% ee. Interestingly, the benzylaldehydes were totally consumed. After 3 hours, 26% yield of products were obtained with 69% ee. Similar results such as 30% yield as well as 68% ee were obtained after 5 hours. After 8 hours, we got 55% yields and 67% ee (Figure 34).

![Figure 34. Reaction control via gas chromatography](image)

We proposed a plausible reaction pathway based on the well-accepted mechanism for the benzoin condensation (Figure 35). Deprotonation of triazolium salts generates the carbene catalysts firstly. The nucleophilic addition of NHC to the aldehyde formed the intermediate $\text{200}$. Subsequent proton transfer would afford the acyl anion equivalent $\text{201}$ (after electronic reorganization). Then $\text{201}$ can follow two ways in the reaction: One way termed Michael-Stetter reaction, carbon-carbon formation results from the nucleophilic attack to a Michael acceptor, generating the enolate $\text{203}$. Enolate protonation would afford the desired 1,4-dicarbonyl product, and release the catalyst. Another way is the addition to another molecule aldehyde to give the benzoins. But
under the reaction conditions, the benzoin can form the intermediate 202 with promotion of carbene catalysts. As a result, the benzoin could be reversible to the Breslow intermediate 201 and another molecular aldehyde. The intermediate 201 joins another cycle to give the acylated products. As described above, we could explain the self-condensation in the reaction as well as the good conversation to the 1,4-dicarbonyl products.

![Figure 35. The possible mechanism for intermolecular Stetter reaction.](image)

### 3.2.8. The configuration

The absolute configuration of the 1,4-diketone 196a was determined to be $R$ by comparison of its optical rotation.\(^2\) This stereochemical outcome can be explained by the following transition state models (Figure 36). Assuming that the silyl branch of the catalyst blocks the $Si$-face of the Breslow intermediate, the 1,4-addition would occur at its less hindered $Re$-face. The chalcone then reacts from its $Si$-face to give the observed ($R$)-configured Stetter product.
3.2.9. Other electrophiles for the intermolecular Stetter reaction.

We have developed an effective catalytic system which can be successfully applied in the intermolecular Stetter reaction. The Stetter reaction is the coupling of one electrophile (aldehyde) with a second (Michael acceptor). Stetter et al. have revealed an extensive work that aromatic and aliphatic aldehydes can participate in a conjugate addition to a range of Michael acceptors (Figure 37). In light of this approach, a fundamental question arises: which other electrophiles can be used in the reaction?

Nitroalkenes are a class of widely employed electrophiles, and addition to nitroalkenes affords highly useful compounds because the nitro group can be easily converted into various functionalities such as amines. More importantly, the direct catalytic acylation of nitroalkenes have not been previously reported.

Figure 36. Proposed transition states.

Figure 37. The scope of Stetter reaction.

Our attempts with this catalytic system in nucleophilic acylations of nitroalkenes were
unfruitful. One possible reason is that the nitroalkenes were sensitive to the basic conditions, and polymerization was a result under these conditions. For this reason, the β-methyl-β-nitrostyrene was employed as electrophile because methyl as electron donating group can stabilize the double bond of the nitroalkene. After screening many different conditions, it was still difficult to obtain the pure desired products (Entry c, Table 14).

Since the nitroalkenes were unsuitable electrophiles in the intermolecular Stetter reaction, it seemed that a less active electrophile was necessary. We decided to carry out the investigation of extending the utility of α,β-unsaturated nitrile, α,β-unsaturated sulfonates and α,β-unsaturated esters into the intermolecular Stetter reaction. Unfortunately, various electrophiles were tested with the optimal conditions, which established for the intermolecular Stetter reaction (See: Table 14) that there was only recovery of starting material and benzoins from self-condensation of aldehydes. We then reasoned that improving the electrophilicity of the aldehyde may contribute to this reaction. However, all modifications made to the reaction systems afforded similar results and no product was ever identified from the reaction mixture by TLC and NMR (entry a-j, Table 14). From these results, it was concluded that these Michael acceptors were not electrophilic enough to undergo the addition reaction.

Recently, You et al reported thiazolium-derived N-heterocyclic carbene-catalyzed cross-couplings of aldehydes with inactivated imines. They used imines as the receptor for the acyl anion addition to produce α-amino ketones, and the resulting α-amino ketones are an important class of biologically relevant molecules. Unfortunately, they were unable to develop an asymmetric version of this reaction. Therefore, we decided to apply our new catalytic systems in these reactions. As expected, the reaction gave a moderate yield (40%) under unoptimized conditions. When the benzoaldehyde was switched into the more active 2-furaldehyde, the reaction resulted in virtually quantitative yields. However, in both cases, the products were obtained as a racmate (entry k, l).
Table 14. Different nitroalkenes, α,β-unsaturated nitriles, sulfonates, esters and imines as acceptors.

\[ R^1\text{CHO} + R^2\text{EWG} \xrightarrow{10\text{mol\% } 168b} R^1\text{O}R^2\text{EWG} \]

\[ \text{Cs}_2\text{CO}_3, \text{THF} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Michael acceptor</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhNO2.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>b</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="NO2.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>c</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhNO2.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>d</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhMe.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>e</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhCN.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>f</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhCN.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>g</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhCN.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>h</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhSO2.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>i</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhCO2Me.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>j</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhCO.png" alt="Image" /></td>
<td>n.r.</td>
</tr>
<tr>
<td>k</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhNPh.png" alt="Image" /></td>
<td>47% yield 0% ee</td>
</tr>
<tr>
<td>l</td>
<td><img src="CHO.png" alt="Image" /></td>
<td><img src="PhNPh.png" alt="Image" /></td>
<td>99% yield 0% ee</td>
</tr>
</tbody>
</table>
3.2.8. Alkylidenemalonates as Michael acceptors for the intermolecular Stetter reaction.

After considering the potential problems with this system, we reasoned that there has to be a balance of reactivity between the strong and weak electrophiles. The nucleophiles seemed likely to be effective in certain limits. The electrophilicity could be suitable between the nitroalkenes and α, β-unsaturated esters. Two esters group could generate a suitably active electrophile to enable the acylation event. And more importantly, alkylidenemalonates appear as suitable candidates in this context, and they present with a series of interesting characteristics: 101 (1) They are easily available through Knoevenagel condensation of malonates and different carbonyl compounds. (2) For the most common type of malonates, the presence of two identical carboxyl groups at the same olefinic carbon eliminates the Z/E isomerism, which constitutes a synthetic problem in other classes of substrates. (3) The enhanced electrophilic reactivity provided by the geminal carboxylate functions allows the addition reactions to be carried out with poorer nucleophiles and/or under milder conditions with respect to other Michael acceptors. (4) The presence of two geminal carbonyl groups provides chelating ability to these substrates, which is an essential tool for the control of the stereochemistry in metal-catalyzed additions. These characteristics have stimulated extensive use of these compounds as enoate surrogates for the addition of a variety of nucleophiles, but only a few reports have been written on their nucleophilic acylation reactions, none of them dealing with asymmetric acylation or formylation reactions. 102

In an effort to apply the new methodology to alkylidene malonates, it is surprising to find the 2-furaldehyde coupling to dimethyl benzylidenemalonate catalyzed by 168b resulted in the desired product in high yields with DBU as base and THF as solvent, and the enantiomeric excess is 59%. In light of this results, we initiated the investigations by surveying different triazolium salts, while the triazolium salts (see below) did not produce the desired products, which was determined by GC and TLC. Initially, we tried to survey different triazolium salts and reaction conditions for this reaction. On the basis of preliminary studies, the N-phenyl substituted catalysts 205
only afforded furions. Increasing the steric bulk of the precatalyst by adding dimethyl substituents in the branch such as 169c was found that the Breslow intermediates were inert to the benzylidenemalonate since only furions were observed. We were disappointed to find the phenylalaninol-derived precatalyst 188a bearing a benzyl group also resulted in no desired product.

Since the investigation with 168b had only 59% enantioselectivity with DBU in THF, we began to examine the effect of the bases on the outcome of the reaction. Weak bases such as triethylamine provide only a trace amount of the desired product, strong bases such as Kt-Bu and DBU afforded good results and moderate enantioselectivity (Entry 2, 4, Table 15). Again, Cs2CO3 was selected as the best base to provide the product in 90% yield and 78% ee. After screening the solvents in the reaction with 10mol% catalyst and Cs2CO3 as base (see Table 15), the non-polar solvents did not appear to give good yields. However, even in a protic solvent such as ethanol, the reaction proceeded well in 42% yield and 48% ee.

![Figure 38. Different catalyst structures.](image)

| Table 15. Screening different conditions in the nucleophilic acylation of dimethyl benzylidenemalonate. |

![Reaction Scheme](image)
Results and discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee %&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>THF</td>
<td>0 °C</td>
<td>8</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>THF</td>
<td>0 °C</td>
<td>86</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>0 °C</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>KOt-Bu</td>
<td>THF</td>
<td>0 °C</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>0 °C</td>
<td>90</td>
<td>78 (&gt;99)</td>
</tr>
<tr>
<td>6</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DCM</td>
<td>0 °C</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0 °C</td>
<td>3</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOH</td>
<td>0 °C</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>KHMDS</td>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0 °C</td>
<td>77</td>
<td>70 (98)</td>
</tr>
<tr>
<td>11</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>23 °C</td>
<td>94</td>
<td>60</td>
</tr>
</tbody>
</table>

<sup>a</sup>The yields were determined by GC.  
<sup>b</sup>The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD).  
<sup>c</sup>Value in brackets is the ee after recrystallization.

With the best conditions in hand, we decided to expand the substrate scope of the reaction. The different substituted alkylidenemalonates were prepared from the aldehydes and malonates. A variety of heterocyclic aldehydes and alkylidenemalonates participated in the reaction to afford the desired products in high yields and good enantioselectivity (Table 16). Benzylidenemalonate derived from Knovenagel reaction bearing either an electron-withdrawing group such as Cl, or electron-donating group such as methyl did react with furylaldehyde well in high yields and good enantiomeric excesses. The alkylidenemalonates bearing heterocyclic rings such as 208g and 208h were highly reactive, however, only delivered moderate enantiomeric excesses. A variety of heterocyclic aldehydes were also employed in order to determine the effects of electrophiles in the reaction, furfural and N-containing aldehydes such as pyrrole carbaldehyde were employed, as summarized in Table 16, 2-furfural and pyridine carbaldehyde worked well. In contrast, no reaction was observed in the case of the pyrrole derivative, even N-protected pyrrole carbaldehyde.

Notably, these products are possible to be recrystallized to produce highly
Results and discussion

enantiomerically riched or even enantiomerically pure ones (entry a, c-f, Table 16). Interestingly, two cases after a single recrystallization gave racemic crystals and highly enantioenriched products remained in the mother liquor (entry c and g, Table 16).

Table 16. The reaction scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R¹</th>
<th>R²</th>
<th>Yield, % ⁹</th>
<th>ee, % ⁹⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-Furyl</td>
<td>Ph</td>
<td>Me</td>
<td>90 (53)</td>
<td>78 (99)</td>
</tr>
<tr>
<td>b</td>
<td>2-Pyr</td>
<td>Ph</td>
<td>Me</td>
<td>94</td>
<td>30 ⁶</td>
</tr>
<tr>
<td>c</td>
<td>2-Furyl</td>
<td>4-ClPh</td>
<td>Me</td>
<td>92 (50)</td>
<td>51 (95) ⁹</td>
</tr>
<tr>
<td>d</td>
<td>2-Furyl</td>
<td>3-ClPh</td>
<td>Me</td>
<td>85 (45)</td>
<td>68 (94)</td>
</tr>
<tr>
<td>e</td>
<td>2-Furyl</td>
<td>4-BrPh</td>
<td>Me</td>
<td>88 (42)</td>
<td>70 (99)</td>
</tr>
<tr>
<td>f</td>
<td>2-Furyl</td>
<td>4-MePh</td>
<td>Me</td>
<td>84 (60)</td>
<td>72 (90) ⁹</td>
</tr>
<tr>
<td>g</td>
<td>2-Furyl</td>
<td>2-Furyl</td>
<td>Me</td>
<td>94</td>
<td>15</td>
</tr>
<tr>
<td>h</td>
<td>2-Furyl</td>
<td>2-Pyr</td>
<td>Me</td>
<td>98</td>
<td>40 ⁶</td>
</tr>
<tr>
<td>i</td>
<td>2-Furyl</td>
<td>1-Naphthy</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>j</td>
<td>2-Furyl</td>
<td>4-OMePh</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>k</td>
<td>2-Furyl</td>
<td>2-ClPh</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>l</td>
<td>2-Furyl</td>
<td>i-Butyl</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>m</td>
<td>2-Furyl</td>
<td>Ph</td>
<td>Et</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>n</td>
<td>2-Furyl</td>
<td>Ph</td>
<td>propane</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>o</td>
<td>2-pyrrole</td>
<td>Ph</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>p</td>
<td>N-Me-2Pyrrole</td>
<td>Ph</td>
<td>Me</td>
<td>No reaction</td>
<td>--</td>
</tr>
</tbody>
</table>

⁹ Values in brackets are the yields after recrystallization. ⁹⁹ The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD). ⁹⁶ Value in brackets is the ee after
Racemate was obtained, the enantioenriched products from the mother liquor. The products were obtained as a thick oil.

It is worthy to note that the absolute configurations (R) of the tricarbonyl compounds obtained in this survey are in complete accord with the previously proposed models for precarbene salt 168b catalyzed intermolecular Stetter reactions of benzaldehydes with chalcones (Figure 36).

To illustrate the preparative utility of this new Stetter process, the addition of furaldehyde to benzylidenemalonate (Table 16, entry a) was performed on a 10 mmol scale to afford 2.58 g (82% yield) of 208a in 80% ee. Furthermore the acylation products showed the opportunity to develop a useful chiral compound for the potential precursors of enzymatic inhibitors (Scheme 58).

When a Michael acceptor bearing different electron-withdrawing groups is employed, the enantioselective addition and a selective intramolecular proton transfer could led to a diastereoselective version of this reaction. For this consideration, (E)-Methyl benzylideneacyanoacetate 209 was prepared and subjected to the reaction conditions and found to provide the product 210 in 90% yield with complementary diastereoselectivity (>10:1) but only 40% ee with unoptimized conditions (Scheme 59).
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Scheme 59. Diastereoselective version of intermolecular Stetter reaction.

3.3. Summary

In conclusion, a new family of chiral triazolium based carbene precatalysts were synthesized and successfully employed in the asymmetric intermolecular Stetter reaction. The resulting 1,4-diketones were obtained in moderate to excellent yields and good enantioselectivities. Examination of the reaction course revealed new mechanistic insights about the formation of the Stetter product. Moreover, we extended the reaction scope for the Stetter reaction. The asymmetric version of addition of heterocyclic aldehydes to arylidenemalonates catalyzed by N-heterocyclic carbenes was developed, which afforded polycarbonyl compounds in good yields and good enantiomeric selectivities. For several Stetter products the enantiomeric excess could be enhanced by a single recrystallisation up to 99% ee.
4. Nucleophilic acylations in the synthesis of natural products

4.1 Known examples of nucleophilic acylations applied in total synthesis.

Nucleophilic acylation catalyzed by N-heterocyclic carbenes provided an unrivalled easy access to the α-hydroxyl ketone and 1,4-dicarbonyl compounds as scaffolds which appear usually in natural products. Some examples of the application of nucleophilic acylations in the synthesis of natural products have been reported so far. In 1975, Stetter et al. reported the synthesis of cis-jasmon and dihydrojasmon 213a and b in good overall yields.

\[
\begin{align*}
\text{Scheme 60. Synthesis of cis-jasmon and dihydrojasmon by Stetter et al.}
\end{align*}
\]

In 1979, Trost et al. reported an intramolecular Stetter reaction as one of the key steps in their synthesis of (±)-hirsutic acid C (214), a tricyclic sesquiterpene. In the tricyclic ketone, four of the seven chiral centers of 214 are formed with the correct relative stereochemistry which are able to control the formation of the remaining three stereocenters (Figure 39).

\[
\begin{align*}
\text{Figure 39. Synthesis of hirsutic acid C (214) by Trost et al.}
\end{align*}
\]

Galopin et al. involved an intermolecular Stetter reaction in the synthesis of
(±)-trans-sabinene hydrate \((\text{216})\), a flavour chemical found in essential oils from mint and herbs.\(^\text{106}\) The Stetter reaction of isovaleraldehyde and methylvinylketone \textbf{215} furnishes the dione which upon cyclization yields the corresponding cyclopenenone as key intermediate for the synthesis of \textbf{216} (Figure 40).

![Figure 40. Synthesis of (±)-trans-sabinene hydrate by Galopin et al.](image)

Tius and co-workers have employed a diastereoselective intermolecular Stetter reaction as the key step in their elegant synthesis of roseophilin \((\text{218})\).\(^\text{107}\) The 1,4-dicarbonyl functionality in \textbf{217} served as a precursor for the central pyrrole unit of the natural product (Figure 41).

![Figure 41. Synthesis of roseophilin by Tius et al.](image)

Grée and co-workers developed an interesting application of the intermolecular Stetter reaction for the synthesis of haloperidol \((\text{220})\).\(^\text{108}\) In the key step, room temperature ionic liquids (RTILs) of the imidazolium-type were employed with success as solvents combined with thiazolium catalyst \textbf{65a} in the Stetter reaction (Figure 42).
The Nicolaou group recently employed this method to synthesize some natural products. Firstly, they developed the formal total synthesis of platensimycin \(221\).\(^{109}\) This natural product was isolated from *Streptomyces platensis* as a new structural class of antibiotics. This route involves an intramolecular Stetter reaction as an alternative approach to the polycyclic core of the cage-like structure of the target molecule (Figure 43). Additionally, they reported the total synthesis of kinamycins C, F, J \(222\) through a key step of a NHC catalyzed intramolecular cross benzoin condensation (Figure 44).\(^{110}\)

Suzuki et al. applied the enantioselective benzoin cyclization of an enolizable keto-aldehyde in the total synthesis of (+)-Sappanone B in 95% ee.\(^{111}\)
Results and discussion

**Figure 45.** Synthesis of (+)-Sappanone B by Suzuki et al.

### 4.2. Attempts to synthesize (−)-eucomol

(−)-Eucomol isolated from the bulbs of Eucomis bicolor BAK by Boehler and Tamm in 1967,\[112\] shows some physiologically and biologically activity. Farkas have synthesized rac-eucomol in 1968.\[113\] Much later, Davis and Chen have synthesized (R) as well as (S)-O-dimethyleucomol with lithium enolate in 1990.\[114\]

In 2006, Enders et al. and later Suzuki et al. reported chiral tetracyclic triazolium salts that enable the catalytic, enantioselective aldehyde–ketone benzoin cyclizations of three substrate classes in up to 98% ee.\[52, 53\] It disclosed a concise approach to the asymmetric synthesis of 4-chromanones, a key structural motif in natural products such as (−)-eucomol.

**Figure 46.** (−)-Eucomol.

Our strategic plan involved the intramolecular cross benzoin reaction as a key step. The chromanone \[226\] could be obtained though a coupling reaction in ortho-position of protected 2,4,6-trihydroxybenzaldehyde \[227\] with chloroketone \[228\].
According to the literature, the monohalomethyl ketones 228 could be easily prepared by reaction of the corresponding diazoketone with the appropriate hydrogen halide or hydrohalic acid such as concentrated hydrochloric acid or hydrobromic acid solutions in diethylether at 0°C. The diazoketone could be produced from acyl chloride with diazomethane under cooling conditions.

Another reactant part is prepared directly from selective 2,4-benzylation of 2,4,6-trihydroxybenzaldehyde with benzyl bromide and K$_2$CO$_3$ in DMF. The reaction was carried out at room temperature for 16 hours to afford the desired products in 60% yield. (Scheme 62).

The next step was the coupling reaction of the 2,4-bis(benzyloxy)-6-hydroxybenzaldehyde 227 with the chloroketone 228. However, after screening a variety of conditions, as depicted in Table 17, we found that it was difficult to obtain the desired product.
Table 17. Different conditions for coupling reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Cl</td>
<td>K₂CO₃/KI</td>
<td>Acetonea</td>
<td>Very dirty</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Cl</td>
<td>K₂CO₃/KI</td>
<td>CH₃CN</td>
<td>Very dirty</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Cl</td>
<td>Zn</td>
<td>THF</td>
<td>byproduct</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Cl</td>
<td>K₂CO₃/KI</td>
<td>DMF</td>
<td>Very dirty</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Cl</td>
<td>MeONa</td>
<td>MeOH</td>
<td>-----</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Cl</td>
<td>NaH</td>
<td>THF</td>
<td>-----</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>Cl</td>
<td>K₂CO₃/KI</td>
<td>DMF</td>
<td>dirty</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>Cl</td>
<td>K₂CO₃</td>
<td>Acetone</td>
<td>dirty</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>Cl</td>
<td>K₂CO₃/KI</td>
<td>Acetone</td>
<td>dirty</td>
</tr>
<tr>
<td>10</td>
<td>Bn</td>
<td>Cl</td>
<td>NaH</td>
<td>THF</td>
<td>Aldol product</td>
</tr>
<tr>
<td>11</td>
<td>Bn</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>dirty</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>Br</td>
<td>K₂CO₃/KI</td>
<td>DMF</td>
<td>dirty</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>Br</td>
<td>K₂CO₃/KI</td>
<td>DMSO</td>
<td>dirty</td>
</tr>
<tr>
<td>14</td>
<td>Bn</td>
<td>Br</td>
<td>Cs₂CO₃</td>
<td>DMF</td>
<td>dirty</td>
</tr>
<tr>
<td>15</td>
<td>Bn</td>
<td>Br</td>
<td>Cs₂CO₃</td>
<td>CH₃CN</td>
<td>dirty</td>
</tr>
<tr>
<td>16</td>
<td>Bn</td>
<td>Br</td>
<td>NaH</td>
<td>THF</td>
<td>dirty</td>
</tr>
<tr>
<td>17</td>
<td>Bn</td>
<td>Br</td>
<td>2.5M t-BuLi</td>
<td>THF</td>
<td>dirty</td>
</tr>
<tr>
<td>18</td>
<td>Bn</td>
<td>Br</td>
<td>4N NaOH/ butyl aminium</td>
<td>THF</td>
<td>dirty</td>
</tr>
</tbody>
</table>

In Oliver Niemeier’s work about the cross benzoin reaction,\textsuperscript{115b} he found that 2-hydroxybenzaldehyde can react with 1-bromopropan-2-one to form the coupling product quite well (Reaction 1, Figure 48). Therefore, we decided to investigate the problem of the coupling reaction. Four simultaneous reactions were performed under the same conditions of K₂CO₃ in DMF for 16h. From TLC detection, we found that 1-bromopropan-2-one as coupling partner worked quite well, but 1-bromo-3-(4-methoxyphenyl)propan-2-one gave dirty reaction mixture. This result suggested that the chloroketone \textbf{228} is not stable for the coupling reaction. As reported by Pinder \textit{et al.}, chloroketone \textbf{228} was likely isomerisated to 1-halo-1-phenyl ketones.\textsuperscript{115c} Generally, 1) substitution of the phenyl ring by mesomerically electron-donating
Results and discussion

Group strongly promotes isomerisation. Bromomethyl ketones are more liable to isomerise than chloromethyl ketones. Isomerisation is favoured at room temperature.

\[
\begin{align*}
\text{1} & : \text{H} - \text{O} + \text{O} - \text{Br} \\
\text{2} & : \text{BnO} - \text{O} - \text{Bn} + \text{O} - \text{Br} \\
\text{3} & : \text{BnO} - \text{O} - \text{Bn} + \text{MeO} - \text{C} - \text{Br} \\
\text{4} & : \text{H} - \text{O} + \text{MeO} - \text{C} - \text{Br} 
\end{align*}
\]

**Figure 48.** The TLC results of coupling reaction.

Thus we tried to achieve the desired compound by an alternative route, as showed in Scheme 63. First alkylation of phloroglucinol, cyclization, then 2,4-benzylation gave the compound 235. The next step is the aldol reaction with \( p \)-anisaldehyde. Unfortunately, this reaction was unsuccessful to afford the desired product 236. Considering the limited value for synthesis of \((-\text{eucomol})\) in so many steps, we stopped the further investigation on this route to \((-\text{eucomol})\).
Results and discussion

Scheme 63. Another road to 226.

Table 18. The Aldol reaction of 235 with anisaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄, benzene refluxing</td>
<td>dirty</td>
</tr>
<tr>
<td>2</td>
<td>p-TSA, benzene refluxing</td>
<td>dirty</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OTf)₃, refluxing</td>
<td>dirty</td>
</tr>
<tr>
<td>4</td>
<td>NaOMe, MeOH</td>
<td>dirty</td>
</tr>
<tr>
<td>5</td>
<td>HCl (g), EtOH/THF, r.t</td>
<td>Some deprotected products</td>
</tr>
</tbody>
</table>
5. Conclusions

1) A family of novel chiral bulky silyl based triazolium salts were prepared and successfully applied in the benzoin condensation and intramolecular Stetter reaction.

We have developed a practical and efficient synthesis of a family of new chiral triazolium salts 141a-c and 143 from (S)-glutamic acid. With access to the new precarbene catalysts we started to verify their ability to promote the benzoin condensation and intramolecular Stetter reaction. The optimal conditions were identified and allowed for an expansion of the reaction scope with 8-95% yield and enantiomeric excesses of 21-95% in the benzoin condensation. Furthermore, these carbene precatalysts have been applied to intramolecular Stetter reaction with good efficiency and moderate selectivity (Figure 49).

2) Some N-benzyl substituted triazolium salts were prepared and applied in

Figure 49. The precatalyst applied in the benzoin condensation and the intramolecular Stetter reaction.
asymmetric intermolecular Stetter reactions to give the 1,4-diketones in moderate yield and good ee.

Scheme 64. The intermolecular Stetter reaction.

The asymmetric intermolecular Stetter reaction had been envisaged as a challenging target in the fields of carbene organocatalysis. Based on the strategy of carbene design, we have developed different N-substituted triazolium salts, which successfully catalyzed the intermolecular Stetter reaction. The structure of 1-Methyl triazolidine 164 was elucidated by X-ray structure analysis. Moreover, we have demonstrated that 1-methyl triazolidine lacked catalytic activity in the intermolecular Stetter reaction. In the processes of searching the optimal carbene generating high enantioselectivities, we prepared a variety of chiral, nucleophilic carbenes which has benefited from the expected impact of the fused ring, N-based substituent and nature of the side chain steric demand. Finally, we settled on 168b as precatalyst. After screening different conditions, we were able to obtain the 1,4-diketones in moderate to excellent yields (49-98%) and moderate to good enantioselectivities (56-78% ee), which could be enhanced by one recrystallization to excellent levels (90-99% ee). In addition, examination of the reaction course revealed new mechanistic insights about the formation of the Stetter product.
Conclusions

Figure 50. Different catalysts were developed for the asymmetric intermolecular Stetter reactions.

3) The asymmetric intermolecular Stetter reaction was extended to the nucleophilic acylation of alkylidenemalonates.

We have extended the intermolecular Stetter reaction to a variety of electron rich aldehydes coupled to a variety of Michael acceptors. In this context, we have developed the asymmetric version of the addition of heterocyclic aldehydes to arylidene-malonates catalyzed by N-heterocyclic carbenes, which afforded chiral polycarbonyl compounds in good yields (>85%) and good enantioselectivities (up to 78% ee). More importantly, excellent enantiomeric excesses (up to >99% ee) were obtained after single recrystallization. Furthermore, this method can open a practical
Conclusions

entry to develop gram-scale nucleophilic acylation products for polycarbonyl compounds, which could used for synthesizing potential precursors of enzymatic inhibitors.

\[
\text{ArCHO} + \text{R}^1\text{C} = \text{C} = \text{O} \text{Me} \rightarrow \text{Ar} \text{C} = \text{C} = \text{O} \text{Me}  \\
\text{R}^1 \text{C} = \text{C} = \text{O} \text{Me} \rightarrow \text{Ar} \text{C} = \text{C} = \text{O} \text{Me}  \\
10 \text{ mol}\% \text{ precat.}  \\
\text{Cs}_2\text{CO}_3, \text{THF, rt}  \\
\]

Scheme 63. The intermolecular Stetter reaction of arylidenemalonates

4) The asymmetric synthesis of the natural product (-)-eucomol was attempted by carbene organocatalysis.

The intramolecular benzoin condensation to synthesize natural products have been explored. We were able to find the limitations in the synthesis of (-)-eucomol.

Figure 51. (-)-Eucomol.
5. Outlook

In the context of the intermolecular Stetter reaction, a lot of future work is needed to explore and expand their utility in asymmetric catalysis.

- **New catalyst design, changing the N-based substituent would be an important goal in carbene organocatalysis.**

Although we have opened a way to asymmetric intermolecular Stetter reactions, the enantioselectivity could be further improved. Therefore, the design of new carbene catalysts is still very desirable.

**Figure 52. Structures of triazolium salts**

- **Synthesis of bioactive N-containing 1,4-diketone compounds is very promising.**

The Stetter reaction is the Umpolung of electrophilic aldehydes, which can be achieved by using catalysts such as carbenes. In this reaction, the resulting $d^1$-nucleophiles can react with electron poor, polarized olefins. Searching the suitable Michael acceptors to form the useful compounds deserved an attention. It is well known that N-containing polyfunctional compounds are very important for
Outlook

pharmaceutical and agrochemical research.

![Chemical structures](image)

**Figure 53.** The synthesis of N-containing 1,4-diketone compounds

* Other electrophiles for generating the acyl anion to avoid the self-condensation such as Sila-Stetter reaction.

For the intermolecular Stetter reaction, a major limitation associated with these reactions is the benzoin condensation that can occur. Further the highly reactive nature of an aldehyde reduces the controllable utility of this transformation. Although several alternate acyl anion precursors have been explored, the directly catalytic asymmetric version have not been reported until now (Figure 54).

![Chemical structures](image)

**Figure 54.** New electrophiles for asymmetric intermolecular Stetter reactions.
7. Experimental Section

I will always be grateful to Prof. Dr. Dieter Enders, my supervisor, for giving me a great opportunity to carry out the truly exciting experiences in the world-known group. During the three years of my Ph.D. research, I am especially appreciated his many helpful suggestions and creative ideas. His encouragement, optimism, and enthusiasm certainly helped me to work through my challenging periods. The words for intermolecular Stetter reaction: “sooner or later, it will be worked” did give me the courage to try the next ideas one by one.

I am grateful to Professor Zhongjun Fu, Professor Limin Wang and Professor He Tian for introducing me to the chemistry and continually supporting me.

I gratefully acknowledge Dr. Wolfgang Bettray and Karin Risse for their administrative assistance of my life in Germany.

I would like to thank Sabine Drehsen and Desiree Gilliam for measurement of chromatography, analytic and preparative HPLC, Dr. J. Runsink for NMR-measurements and Prof. G. Raabe for X-ray structure determinations.

I would like to thank my labmates Dirk Iffand, Dr. Tim Balensiefer also the carbene sub-groups members: Chuan Wang, Alexander Henseler, Fabien Tougloat, Dr. Oliver Niemeier for the helpful discussions and invaluable help in the lab. In particular, I would like to thank Alexander Jonas for his help at the beginning of my Ph. D. study. Although I did not mention everyone by name, I am sincerely grateful to everyone in the Enders group. They have all helped me at one time or another, and have been a very friendly and talented group to work with.

Special thanks to Dirk Iffland, Fabien Tougloat, Bastian Wirges, Shengmei Lu, Dominik Göddertz for their patience and generous help to correct this manuscript.

Last but not least, I would like to thank my friends in Aachen, Yutian, Sharon, Lei, Li, Yun for helping to make the life in Aachen more enjoyable. And finally, I thank my parents and Fengfeng for their loving and support.

Thanks!! Danke!! 谢谢！！

Jianwei Han
7.1. General remarks:

All moisture-sensitive reactions were carried out by using standard Schlenk techniques unless stated otherwise. Optical rotation values were measured with a Perkin-Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired with a Finnigan SSQ7000 (CI 100 eV, EI 70 eV) spectrometer. High-resolution mass spectra were recorded with a Finnigan MAT95 spectrometer. IR spectra were taken with a Perkin-Elmer FT/IR 1760 instrument. $^1$H and $^{13}$C NMR spectra were recorded with Gemini 300 or Varian Inova 400 instruments and all measurements were performed with tetramethysilane as internal standard. Melting points were determined with a Tottoli melting point apparatus and are uncorrected.

Solvents

Solvents were dried and purified by conventional methods prior to use. Absolute THF, toluene and Et$_2$O were freshly distilled from sodium-lead alloy under argon. Absolute CH$_2$Cl$_2$ was washed with conc. H$_2$SO$_4$, NaHCO$_3$, dried with MgSO$_4$ and freshly distilled from calcium hydride under argon. MeCN and pentane were distilled from CaH$_2$. Absolute methanol, ethanol and i-propanol was distilled from Mg, Whereas absolute DMF, DMSO were purchased from Acros.

Chemicals

Reagents of commercial quality were used from freshly opened containers or purified by common methods. $n$-BuLi (1.6 M in hexane) was purchased from Merck, Darmstadt. (S)-glutamic acid, pyrog glutamic acid and other natural amino acids were available from the “Chiral Pool” of AKEN. The bases such as KHMDS in toluene were purchased from Acros and used directly, KOtBu was purified by sublimation under the high vacuum, other bases such as Et$_3$N, hünig’s base, DBU were distilled freshly.

Reaction control

Analytical TLC used silica-gel 60 F254 plates with fluorescent indicator from Merck,
Darmstadt. The detection of UV active substances were performed under UV-light ($\lambda = 254$ nm). All substances revealed spots on TLC plates by diving in a molybdatophosphoric acid (5% in ethanol), or mostain solution: 10% $\text{H}_2\text{SO}_4$ (100mL), Ce(IV)$\text{SO}_4$ (30mg), (NH$_4$)$_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ (5g), and following by heating with a heating gun.

**Reaction work-up general remarks**

Except special mention, work-up of reaction followed always the same protocol: after the “quench” (neutralisation) of the reaction with an aqueous reagent (generally pH=7 buffer solution, saturated NaHCO$_3$, NH$_4$Cl solution or $\text{H}_2\text{O}$), the reaction mixture was decanted in a separatory funnel in order to separate the organic layer from the aqueous one. The aqueous phase was extracted several times with an appropriate organic solvent (EtOAc, Et$_2$O or CH$_2$Cl$_2$) and the organic phase was dried over a solid drying agent (generally MgSO$_4$ or Na$_2$SO$_4$). After filtration of the dried organic phase through cotton (in a funnel), the liquid filtrate was concentrated under reduced pressure on a rotary evaporator. Finally, the crude product was directly used in the next step or purified through a column chromatography on silica gel or by distillation. Every work-up is reaction specific, so more informations are added in each reaction protocol.

**Column chromatography**

Due to the specific purification problems, different glass-columns with appropriate diameters and lengths, with or without fritted disc, were used. In order to reach a good separation, a really low air overpression (max. 0.3 bar) was used to push the eluting solvent. For all chromatographies, Preparative column chromatography used Merck silica gel 60, particle size 0.040-0.063 mm (230-240 mesh, flash). After isolation and purification, the substances were concentrated with a rotary evaporator prior to their stability under reduced pressure.
Distillations

Distillations were performed with a short-path or a kugelrohr distillation, with or without use of a vigreux column and reduced pressure prior to the nature and the quantity of substance to distillate. Boiling points were measured with a mercury filled thermometer adapted on the distillation apparatus and are uncorrected.

Gas chromatography

Achiral

Apparatus: Varian CP 3800

Column: CP-SIL 8 (fused silica, 30 m x 0.32 mm ID)

Mobile phase: nitrogen (0.8 bar)

Injector temperature: 280°C

Detector temperature: 300°C

Chiral

Apparatus: Siemens Sichromat 3

Column: Lipodex G (25 m × 0.25 mm ID)

Mobile phase: oxygen (0.8 bar)

Injector temperature: 220°C

Detector temperature: 280°C

The retention time of each not decomposed product will be given. To simplify, the result of the measurement will be presented following this form: type of column, start temperature, temperature gradient and final temperature (respectively in °C).

HPLC

Analytic Apparatus: Helwett-Packard 1050 and 1100 with DAD Column (achiral):

LiChrosorb Si 60 (7 μm) (250 mm x 4.6 mm) Kromasil 100 Sil (5 μm) (250 mm x 4.6 mm)

Column (chiral): Chiralpak AS (10 μm) (250 mm x 4.6 mm)

Chiralpak OD (10 μm) (250 mm x 4.6 mm)

Chiralpak AD (10 μm) (250 mm x 4.6 mm)

Chiralpak IA (5 μm) (250 mm x 4.6 mm)

Whelk 01
7.2. General procedures (GP)

GP 1: The benzoin reaction
The dry flask was charged with the catalyst (0.1 mmol, 10 mol%) in absolute toluene (1 mL), KHMS in toluene (0.5 M, 0.2 mL) was added dropwise at room temperature under argon, then the aromatic aldehyde (1 mmol) was added. The reaction mixture was stirred for 8 h and then the reaction mixture was directly purified by column chromatography (silica gel, Et$_2$O/PE = 1:2) to give the desired acyloins as colorless solids or pale yellow oils.

GP 2: The intramolecular Stetter reaction
A flame dried round bottom flask was charged with triazolium salt (10% mol) and unsaturated methyl ester in absolute solvents. To this solution was added a suitable base (10 mol%) via syringe and the solution was stirred for 15 h at ambient temperature. The reaction was then poured into a column of silica gel and eluted with a suitable solution (Et$_2$O/PE = 4:1) to afford the pure product.

GP 3: The Synthesis of silyl protected lactam 140
Silyl triflate (7.5 mmol) and 2,6-lutidine (1.05 mL, 9.0 mmol) were slowly added to a solution of alcohol 139 (3 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C. After being stirred overnight at room temperature, the reaction mixture was quenched with 5% aqueous HCl. After extraction of the water layer (CH$_2$Cl$_2$, 3×10 mL), the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. After flash chromatography (EtOAc/PE = 1:1) 140 was obtained as a colorless solid or colorless oil.

GP 4: The preparation of N-Ph triazolium salt precursors
A 100 mL round bottom flask was charged with lactam (10 mmol) and CH$_2$Cl$_2$ (30 mL). Trimethylxonium tetrafluoroborate (1.6 g, 11 mmol) was added and the reaction mixture stirred overnight at room temperature. To the solution was added phenylhydrazine (1.1 mL, 11 mmol) and stirred overnight. The solvent was removed in vacuo and the product was used without further purification. To this was added trimethylorthoformate (20 mL). The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The solvent was removed in vacuo and the product was precipitated from ethyl acetate to give an off white/yellow powder. Recrystallization from hot MeOH affords precusor as colorless crystalline solid.

GP 5. The preparation of O-protected pyrrolidinone
To a stirring solution of pyrrolidinone (4.34 mmol) in dry DMF (10 mL), were
sequentially added imidazole (355 mg, 5.21 mmol) and silylchloride (5.21 mmol) at room temperature. After being stirred for 18 h, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl (30 mL) and extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with neutral water (2 × 15 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (EtOAc). A O-protected pyrrolidinone intermediate was obtained as a colourless oil or solid.

**GP 6. The preparation of N-Methyl triazolium salt precursors**

A 100 mL round bottom flask was charged with lactam (10 mmol) and CH₂Cl₂ (30 mL). Trimethyloxonium tetrafluoroborate (1.6 g, 11 mmol) was added and the reaction mixture stirred overnight at room temperature. To the solution was added Methylhydrazine (0.6 mL, 11 mmol) and stirred overnight. The solvent was removed in vacuo and the product was used without further purification. To this was added trimethyl orthoformate (20 mL). The reaction mixture was heated to 80 ºC and stirred at this temperature overnight. The solvent was removed in vacuo and the product was obtained by silica gel flash chromatography (EtOAc) as colorless solid.

**GP 7. The preparation of N-Benzyl triazolium salt precursors**

A 10 mL round bottomed flask was charged with the lactam (1 mmol) and CH₂Cl₂ (10 mL). Trimethyloxonium tetrafluoroborate (0.16 g, 1.1mmol) was added and the reaction mixture stirred for 12 hours at room temperature. Benzylhydrazine (0.11 mL, 1.1 mmol) was added to the solution and stirred for 12 hours. The solvent was removed in vacuo and the product was used without further purification. Trimethyl orthoformate (10 mL) was added and the reaction mixture was refluxing at this temperature for 12 hours. The solvent was removed in vacuo to give the desired products. Purified by chromatography on silica gel (eluent: EtOAc) to yield the product as thick oil or purified by recrystallization from hot EtOAc afforded crystalline solid.

**GP 8. The intermolecular Stetter reaction**

A dry, argon-flushed Schlenk tube was charged with precatalyst 168b (27 mg, 0.05 mmol 10 mol%), dry Cs₂CO₃ (16 mg, 0.05 mmol) and chalcone (0.5 mmol), then absolute THF (1 mL) was added at room temperature, the mixture was cooled down to 0 ºC with an ice bath, then benzaldehyde (0.6 mmol, 1.2 eq) was added dropwise, the reaction mixture was stirred for 8 h. Direct purification by flash chromatography on silica gel (pentane/ether = 9:1) yielded the product as colorless solid. Crystallization from Et₂O gave the enantiaopure 1,4-diketone as colorless crystalline needles.
Experimental part

GP 9. The arylidenemalonates and alkylidenemalonates were prepared by Knoevenagel condensation.

Pipridine (80mg, 1 mmol) was dissolved in 20 mL ethanol, then acetic acid (60 mg, 1 mmol) was mixed at room temperature, after stirring for 20 min, the methylene compound (10 mmol) and carbonyl derivative (10 mmol) were added and stirred for 24 h at room temperature. The reaction was quenched with water, and extracted with diethyl ether for 3 times, then solvents The methanol was then removed under reduced pressure to give the crude products, purified by column chromatography (silica, PE/Et₂O = 4:1) to give the desired products.

GP 10. Asymmetric addition of heterocyclic aldehydes to arylidenemalonates

A dry, argon-flushed Schlenk tube was charged with precatalyst 168b (27 mg, 0.05 mmol 10 mol%), dry Cs₂CO₃ (16 mg, 0.05 mmol) and an alkylidene malonate (0.5 mmol), then absolute THF (1 mL) was added at room temperature, then heterocyclic aldehyde (0.6 mmol) was added, the reaction mixture was stirred for 8h. Direct purification by flash chromatography on silica gel (eluent: pentane/ether = 2:1) yielded the product as colorless solid or clear oil. Crystallization in ether afforded the enantioenriched product as flocy solid.

7.3. Description of the experiments

(S)-Methyl 5-oxopyrrolidine-2-carboxylate (122)

![Structure](image)

A solution of S-pyroglutamic acid (25.37 g, 196 mmol) in MeOH (220 mL) was cooled in a dry ice-MeOH bath. Thionyl chloride (16 mL, 221 mmol) was added over 15 min to the solution at -25 to -20 °C. The mixture was allowed to warm to room temperature and stirred for further 1.5 h. The solvents of the resulting mixture were removed in vacuo, and the residue was purified by a short chromatography column (SiO₂, EtOAc) under pressure to give 122 as a colorless oil.

Yield: m = 22.5 g, 156 mmol, (80%).

TLC: $R_f = 0.30$ ($n$-Pentane/EtOAc=1:1).

Optical rotation: $[\alpha]_D^{23} = -8.0$ (c 1.01, CHCl₃).

^1H NMR (300MHz, CDCl₃):

$\delta = 2.10-2.70$ (m, 4H, C(O)CH₂CH₂), 3.80 (s, 3H, OCH₃), 4.20-4.40 (m, 1H, NCΗ), 7.80 (brs, 1H, NH) ppm.
Experimental part

\[^{13}\text{C}\text{ NMR (75MHz, CDCl})_{3}:\]
\[\delta = 24.5 (\text{C(O)CH}_2\text{CH}_2),\ 29.1 (\text{C(O)CH}_2\text{CH}_2),\ 52.2 (\text{OCH}_3),\ 55.3 (\text{NCH}),\ 127.6 (\text{CO}_2\text{Me}),\ 178.4 (\text{C(O)NH}) \text{ ppm.}\]

All other analytical data correspond to those described in the literature.\(^{86}\)

\((S)\)-Methyl 1-benzyl-5-oxopyrrolidine-2-carboxylate (123)

\[(S)-(+)\-5\text{-Oxoproline methyl ester 122 (2.15 g, 15mmol) was dissolved in 30 mL of dry THF and stirred at ambient temperature for 0.25 h prior to addition of 0.42 g (18 mmol) of 60% NaH in mineral oil in one portion. Evolution of hydrogen ceased after stirring for 0.5 h, 1.97 mL (18 mmol) of distilled benzyl bromide was added, and the solution was stirred for 2h at ambient temperature. Washing with water and extraction with 3\times25 mL of ether was followed by drying over MgSO}_4. Filtration and concentration in vacuo gave a crude brown oil that was purified by short column chromatography (silica, EtOAc) to give 123 as colorless oil.\]

Yield: m = 3.32g (95%).
TLC: \(R_f = 0.6 (n\text{-Pentane/EtOAc}=1:1).\)

Optical rotation: \([\alpha]_D^{23} = -8.1 (c \ 1.01, \text{CHCl}_3).\)

\[^1\text{H NMR (300MHz, CDCl})_{3}:\]
\[\delta = 2.06 (m, 2H, \text{C(O)CH}_2\text{CH}_2),\ 2.24 \text{ and } 2.41 (m, 2H, \text{C(O)CH}_2\text{CH}_2),\ 3.87 (s, 3H, \text{CO}_2\text{C}_3\text{H}_3),\ 3.98 (t, J = 6.1Hz, 1H, \text{NCH}),\ 5.00 (d, J = 15.0Hz, 2H, \text{PhCH}_2\text{N}),\ 7.16-7.26 (m, 5H, Ph-H) \text{ ppm.}\]

\[^{13}\text{C NMR (75MHz, CDCl})_{3}:\]
\[\delta = 28.8 (\text{C(O)CH}_2\text{CH}_2),\ 36.0 (\text{C(O)CH}_2\text{CH}_2),\ 55.6 (\text{CO}_2\text{C}_3\text{H}_3),\ 62.1 (\text{PhCH}_2\text{N}),\ 73.8 (\text{NCH}),\ 125.8,\ 127.1, 128.2 (\text{Ph-C}),\ 159.1 (\text{CO}_2\text{Me}),\ 176.2 (\text{C(O)N}) \text{ ppm.}\]

All other analytical data correspond to those described in the literature.\(^{86}\)

\((S)\)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (124)

Magnesium turnings 0.72g (30 mmol) were placed in an oven-dried roundbottom flask fitted with a reflux condenser. Anhydrous diethyl ether (30 mL) was added via syringe and the mixture was stirred at room under a head of argon. The bromobenzene 4.65 g (30 mmol) was dissolved in 20 mL diethyl ether and added dropwise via dropping funnel over a period of 1 h. After reaction,
Experimental part

resultant solution stirred for 0.5 h. At this time, the Grinard reagents was cooling down to 0°C, a solution of 123 (2.33g, 10 mmol) in 10 mL of ether was added via syringe in dropwise over a period of 1 h. After stirring for 1 h, the mixture was warmed to room temperature, then refluxed for 1 h. The reaction was quenched with 100 mL of saturated ammonium chloride solution. Extraction with EtOAc, drying (MgSO₄), and removal of solvents in vacuo gave the products. Purified by column chromatography (Silica, EtOAc) to give 124 as colorless solid.

Yield: m = 2.7 g, 23 mmol, (72%).
Melting point: 185 °C
TLC: Rₚ = 0.3 (n-Pentane/EtOAc = 1:1)
Optical rotation: [α]D₂₃ = +18.1 (c 1.01, CHCl₃).

¹H NMR (300MHz, CDCl₃):
δ = 1.85-2.10 (m, 1H, C(O)CH₂C₂H₅), 2.21-2.40 (m, 2H, C(O)C₂H₅), 3.05 (dd, J = 15.3, 4.2Hz, 1H, MeOPhCH₂H), 3.40 (s, 1H, OH), 4.58 (t, J = 3.8 Hz, 1H, NCH), 4.94 (dd, J = 7.4, 2.5Hz, 1H, MeOPhCH₂), 6.87 (s, 2H, MeOPh-H), 7.08-7.60 (m, 12H, Ph-H) ppm.

¹³C NMR (75MHz, CDCl₃):
δ = 22.6 (C(O)CH₂C₂H₅), 29.9 (C(O)CH₂), 44.9 (PhCH₃N), 55.1 (PhOCH₃), 63.1 (NCHCH₂), 80.1 (Ph₂OCH₃), 113.7 (MeOC₆H₅), 125.7, 125.8, 127.1, 127.2, 128.2, 128.4, 128.6, 128.8, (Ph-C₆H₅), 144.4, 144.5 (MeOC₆H₅), 158.7 (MeOC₆H₅), 117.9 (C=O) ppm.
All other analytical data correspond to those described in the literature.⁸⁶

(S)-1-Benzyl-5-(methoxydiphenylmethyl)pyrrolidin-2-one (125)

Alcohol 124 (1.78 g, 5 mmol) was dissolved in 30 mL of dry THF, then 0.16 g (6 mmol) of 60% NaH in mineral oil was added in one portion. Evolution of hydrogen ceased after stirring for 0.5 h, 0.6 mL (10 mmol, 2.0 eq) of iodomethane was added, and the solution was refluxing for 2 h. Washing with water and extraction with 3×25 mL of ether was followed by drying over MgSO₄. Filtration and concentration in vacuo gave the product as colorless solid.

Yield: m = 1.3 g, 3.5 mmol (70%).
Melting point: 92 °C.
TLC: Rₚ = 0.6 (n-Pentane/EtOAc=1:1).
Optical rotation: [α]D₂₃ = −14.4 (c 1.01, CHCl₃).
¹H NMR (400MHz, CDCl₃):
δ = 1.68-1.74 (m, 2H, NCHCH₂), 1.92-1.98 (m, 2H, C(O)CH₂), 2.06 (s, 3H, OCH₃), 3.85 (d, J = 15.1Hz, 1H, PhCH(NH)), 4.45 (t, J = 5.5Hz, 1H, NCH), 5.12 (d, J = 15.1Hz, 1H, PhCH(NH)), 7.02 (d, J = 7.1Hz, 2H, Ph-H), 7.14-7.34 (m, 13H, Ph-H) ppm.
Experimental part

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta = 22.0$ (NCH$_2$CH$_2$), 28.9 (C(O)CH$_2$), 45.8 (PhCH$_2$N), 51.6 (OCH$_3$), 61.7 (NCH), 86.9 (Ph$_2$COOMe), 127.2, 127.7, 127.9, 128.0, 128.2, 128.5, 129.3, 129.4, 137.2, 127.3, 128.7 (Ph-C), 177.0 (C(O)) ppm.

IR (KBr):
$\nu = 3982$ (vw), 3856 (w), 3745 (m), 3676 (w), 3433 (m), 3240 (vw), 3053 (w), 2937 (m), 2824 (w), 2677 (vw), 2585 (vw), 2365 (m), 2154 (vw), 1966 (vw), 1833 (vw), 1691 (s), 1553 (w), 1465 (w), 1445 (m), 1412 (m), 1282 (w), 1236 (m), 1072 (m), 931 (w), 847 (vw), 805 (vw), 753 (m), 703 (s), 598 (w), 467 (w) cm$^{-1}$.

MS (EI, 70eV): m/z (100) = 197.1 (80), 174.1 (100), 105.0 (25), 91.1 (100), 77.1 (15), 65.1 (8).

Elemental Analysis: Anal. Calcd for C$_{25}$H$_{25}$NO$_2$: C, 80.03; H, 6.78; N, 3.77; Found 79.89; H, 6.96; N, 3.61.

(S)-5-(Hydroxydiphenylmethyl)pyrrolidin-2-one (129)

Phenylmagnesium bromide (80 mL, 240 mmol, 3.0 M solution in Et$_2$O) was slowly added to a solution of methyl pyroglutamate (11.2 g, 78.5 mmol) in THF (100 mL) at -78°C over 30 min. After that, warmed to 0°C and stirred for 30 min at 0°C, then refluxed for 1h. The reaction mixture was quenched with a 5% aqueous HCl solution. After extraction of the water layer (CH$_2$Cl$_2$, 50mL $\times$ 3), the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The solid residue was recrystallized from Et$_2$O to give colorless crystals.

Yield: m = 14.0 g, 51 mmol (65%).

Melting point: 192°C.

TLC: 0.34 (n-Pentane/EtOAc=1:1).

Optical rotation: $[\alpha]_D^{23} = -88.0$ (c 1.01, CHCl$_3$).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta = 1.87-1.96$ (m, 1H, C(O)CH$_2$CH$_2$H), 2.01-2.2.18 (m, 1H, C(O)CH$_2$CHH), 2.20-2.40 (m, 2H, C(O)CH$_2$), 4.04 (brs, 1H, OH), 4.67-4.72 (dd, 1H, NCH), 4.90 (brs, 1H, NH), 7.08-7.34 (m, 6H, Ph-H), 7.43-7.49 (m, 4H, Ph-H) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta = 21.4$ (C(O)CH$_2$CH$_2$), 30.1 (C(O)CH$_2$CH$_2$), 60.5 (NCH), 78.6 (Ph$_2$COH), 125.5, 125.7,126.9, 127.3, 128.1, 128.7, 143.2, 145.2 (Ph-C), 179.3 (C(O)) ppm.

All other analytical data correspond to those described in the literature.$^{116}$
Experimental part

(S)-Tert-butyl 2-(hydroxydiphenylmethyl)-5-oxopyrrolidine-1-carboxylate (130)

\[
\begin{align*}
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{O} \quad \text{t-Bu}
\end{align*}
\]

To a solution of 2.73 g of lactam 129 (10.3 mmol) in 20 mL of acetonitrile was added 122 mg of DMAP (1.0 mmol) followed by a solution of 2.50 g of di-tert-butyldicarbonate (11.5 mmol) in 10 mL of acetonitrile. The colorless reaction mixture was stirred at rt for 3 h. The resulting orange reaction mixture was concentrated by rotary evaporation in vacuo and the resulting oil was taken up in diethyl ether. The mixture was washed with an aqueous solution of 1N HCl and a saturated aqueous brine solution. The organic phase was dried over sodium sulfate, and concentrated by rotary evaporation in vacuo to afford crude solid. Purification by column chromatography (silica gel, PE/EtOAc = 4:1) afforded 3.40 g (90%) of the title compound as a colorless crystalline solid.

Yield: m = 3.40 g, 9.2 mmol, 90%.
Melting point: 102°C.
Optical rotation: \([\alpha]_D^{23} = -184.0 \; (c \; 1.01, \text{CHCl}_3)\).

\(^1\)H NMR (300MHz, CDCl\(_3\)):
\[\delta = 1.25 (s, 9H, OC(CH\(_3\))) , 1.98 (m, 2H, NCHCH\(_2\)) , 2.30 (m, 1H, C(O)CH\(_2\)) , 2.55 (m, 1H, C(O)CH\(_2\)) , 4.78 (dd, J = 10.2Hz, 1H, NCH) , 5.00 (brs, 1H, O\(_2\)) , 7.11-7.30 (m, 6H, Ph-H), 7.37-7.47 (m, 4H, Ph-H) ppm.

\(^13\)C NMR (75MHz, CDCl\(_3\)):
\[\delta = 22.6 \; (\text{NCHCH}_2) , 25.3 \; (C(O)CH\(_2\)) , 28.0 \; (\text{OC(CH\(_3\)))} , 48.7 \; (\text{NCH}) , \; (80.1 \; (\text{OC(CH\(_3\)))} , 89.5 \; (\text{Ph}_2\text{COH}) , 124.6 , 124.9 , 127.5 , 127.7 , 128.1 , 128.4 , 129.1 , 140.8 , 12.8 \; (\text{Ph-C}) , 155.0 \; (\text{CO}_2\text{CM}_{\text{es}}) , 170.5 \; (\text{C(O)N}) \; \text{ppm.}
\]

IR (KBr):
\[v = 3950 \; (vw), 3853 \; (vw), 3745 \; (w), 3438\; (m), 3062 \; (w), 3029 \; (w), 2939 \; (m), 2591 \; (vw), 2369 \; (w), 2345 \; (w), 1964 \; (vw), 1745 \; (s), 1540 \; (w), 1494 \; (m), 1443 \; (m), 1364 \; (w), 1244 \; (m), 1182 \; (m), 1084 \; (w), 1033 \; (w), 995 \; (m), 920 \; (vw), 880 \; (vw), 836 \; (vw), 754 \; (m), 697 \; (m), 635 \; (vw), 600 \; (vw), 528 \; (vw), 474 \; (w) \; \text{cm}^{-1}.
\]

MS (El, 70eV): m/z (%) = 367.1 (M\(^+\), 5), 295.1 (55), 264.1 (30), 165.1 (45), 129.1 (50), 114.0 (100), 77.1 (20), 56.2 (10).

Elemental Analysis: Anal. Calcd for C\(_{22}\)H\(_{25}\)NO\(_4\): C, 71.91; H, 6.86; N, 3.81; Found 71.84; H, 6.51; N, 4.12.
Experimental part

(S)-1-(4-Methoxybenzyl)-5-oxopyrrolidine-2-carboxylic acid (135)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{MeO} \\
\text{S} \\
\text{-glutamic acid (35.2g, 198 mmol) in dichloromethane (450 mL). After five minutes} \\
4\text{-methoxybenzaldehyde (23.7g, 174 mmol) was added followed by magnesium sulphate (12 g).} \\
The resulting mixture was stirred at room temperature overnight. Whereupon the magnesium sulphate was removed by filtration and the methylene chloride removed under reduced pressure. Methanol (200 mL) was added to the yellow oil. The solution cooled to 0°C and sodium borohydride (6.0 g, 157.4 mmol) added in small portions over five minutes, followed by stirring at 0°C for a further 60 minutes. The methanol was then removed under reduced pressure to give a red oil. Heating the crude reaction mixture in boiling xylene (100 mL) overnight gave after concentration a red oil for next step without further purification.

(S)-Methyl 1-(4-methoxybenzyl)-5-oxopyrrolidine-2-carboxylate (136)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{OMe} \\
\text{MeO} \\
\text{S} \\
\end{array}
\]

The procedure is according to the preparation of 122. The title compound was obtained as oil.

Yield: m = 4.5 g, 17 mmol, 90%.
TLC: \( R_f = 0.41 \) (Pentane/EtOAc= 1:1).
Optical rotation: \([\alpha]_D^{23} = +34.5 \) (c 1.01, CHCl₃).

\(^1\)H NMR (300MHz, CDCl₃):
\[ \delta = 1.90-2.01 \text{ (m, 1H, C(O)CHH)}, 2.07-2.20 \text{ (m, 1H, C(O)CHH)}, 2.24-2.37 \text{ (m, 1H, NCHCHH)}, \\
2.38-2.48 \text{ (m, 1H, NCHCHH)}, 3.57 \text{ (s, 3H, CO₂CH₃)}, 3.67 \text{ (s, 3H, OCH₃)}, 3.90 \text{ (m, 1H, NCH)}, \\
4.80 \text{ (d, } J = 14.5\text{Hz, 2H, PhCH₂N)}, 6.70 \text{ (d, } J = 18.5\text{Hz, 2H, Ph-H)}, 7.05 \text{ (d, } J = 18.5\text{Hz, 2H, Ph-H)} \text{ ppm.}

\(^{13}\)C NMR (75MHz, CDCl₃):
\[ \delta = 22.5 \text{ (C(O)CH₂)}, 29.4 \text{ (NCHCH₂)}, 44.8 \text{ (CO₂CH₃)}, 52.2 \text{ (OCH₃)}, 55.0 \text{ (NCH)}, 58.4 \text{ (PhCH₂N),} \]
Experimental part

113.8, 127.5, 129.7, 159.0 (Ph-C), 172.1 (CO₂Me), 174.9 (C(O)N) ppm.
All other analytical data correspond to those described in the literature.⁸⁹

(S)-5-(Hydroxydiphenylmethyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (137)

The procedure according to the preparation of 124. The title compound was obtained as colorless solid.
Yield: m = 2.5 g, 6.5 mmol, (65%).
Melting point = 75 °C
TLC: R_f = 0.38 (n-Pentane/EtOAc=1:1)
Optical rotation: [α]D²³ = +32.4 (c 1.01, CHCl₃).

¹H NMR (300MHz, CDCl₃):
δ = 1.90-2.10 (m, 2H, C(O)CH₂C₄H₉), 2.21-2.40 (m, 2H, C(O)C₄H₉), 3.05 (d, J = 7.4Hz, 1H, MeOPhCH₂H), 3.82 (s, 3H, PhOC₃H₉), 4.58 (t, J = 5.2Hz, 1H, NCH), 4.90 (d, J = 15.1Hz, 1H, MeOPhCH₂H), 6.87 (m, 4H, MeOPh-H), 7.08-7.60 (m, 10H, Ph-H) ppm.

¹³C NMR (75MHz, CDCl₃):
δ = 22.6 (C(O)CH₂C₄H₉), 29.9 (C(O)CH₂), 45.2 (PhCH₂N), 63.2 (NCH₂C₄H₉), 80.1 (CPh₂OCH₃), 125.6 125.7, 127.1, 127.2, 128.2, 128.3, 128.4, 136.6, 144.4, 144.5 (Ph-C₆H₅), 117.9 (C=O) ppm.

IR (KBr):
ν = 3894 (w), 3854 (w), 3744 (w), 3676 (w), 3620 (vw), 3397 (m), 3057 (w), 2994 (vw), 2935 (m), 2833 (w), 2723 (vw), 2423 (vw), 2361 (m), 2340 (m), 2255 (vv), 2061 (vv), 1835 (vv), 1771 (vw), 1670 (s), 1510 (m), 1449 (m), 1355 (w), 1286 (w), 1243 (m), 1172 (m), 1111 (w), 1030 (m), 897 (w), 822 (m), 757 (m), 702 (m), 632 (w), 579 (w), 515 9w), 463 (w) cm⁻¹.

MS (EI, 70eV): m/z (100) = 388.2 (10, M⁺), 205.1 (30), 183.0 (8), 121.1 (100), 105.0 (10), 97.1 (10), 77.1 (8).

Elemental Analysis: Anal. Calcd for C₂₅H₂₅NO₃: C, 77.49; H, 6.50; N, 3.61; Found 76.99; H, 6.51; N, 3.57.
Experimental part

(S)-1-(4-Methoxybenzyl)-5-(methoxydiphenylmethyl)pyrrolidin-2-one (138)

To a solution of 1.93 g of 137 (5 mmol) in 10 mL of absolute THF was added 48 mg of 60% NaH in oil (1.2 eq, 6.0 mmol) in one portion. After stirring for half an hour until the evolution of hydrogen was stopped. Then 1.42 g (2.0 eq, 10mmol) MeI was added in dropwise. Washing with water and extraction with 3×25 mL of ether was followed by drying over MgSO$_4$. Filtration and concentration in vacuo gave the product as dark yellow oil.

Yield: m = 1.80 g, 4.5 mmol, (90%).

TLC $R_f$ = 1.6 (PE/EtOAc = 2:1).

Optical rotation: $[\alpha]_D^{23} = -41.5$.

$^1$H NMR (300MHz, CDCl$_3$):

$\delta = 1.75-1.80$ (m, 1H, C(O)CH$_2$C$_2$H), 1.81-1.86 (m, 1H, C(O)CH$_2$CH/H), 1.99-2.08 (m, 2H, C(O)CH$_2$), 2.90 (s, 3H, PhCH$_3$), 3.82 (s, 3H, Ph$_2$COCH$_3$), 4.55 (t, $J = 5.4$Hz, 1H, NCH$_2$CH$_2$), 5.13 (s, 1H, MeOPhCH/H), 5.18 (s, 1H, MeOPhCH/H), 6.87 (d, $J = 8.3$Hz, 2H, MeOC$_2$C$_2$(C$_2$H)$_2$), 7.08 (d, $J = 8.3$Hz, 2H, NCH$_2$C$_2$MeOH), 7.30-7.50 (m, 10H, Ph-H) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):

$\delta = 21.9$ (C(O)CH$_2$), 28.9 (C(O)CH$_2$CH$_2$), 45.1 (PhCH$_2$N), 51.5 (CPh$_2$OCH$_3$), 55.3 (4-CH$_3$OPh), 61.6 (NCH$_2$CH$_2$), 86.9 (CPh$_2$OCH$_3$), 113.8 (MeOC$_2$MeOH), 128.0, 128.1, 128.2, 129.2, 129.4, 129.5, (Ph-C$_2$H), 137.3, 138.7, (MeOCC$_2$), 158.8 (MeOC$_2$), 117.1 (C=O) ppm.

IR (KBr):

$\nu = 3988$ (vw), 3940 (vw), 3901 (vw), 3806 (vw), 3800 (vw), 2744 (w), 3448 (m), 3057 (w), 3031 (w), 2937 (m), 2827 (w), 2605 (vw), 2365 (vw), 2344 (vw), 2060 (vw), 1965 (vw), 1894 (wv), 1827 (vw), 1687 (s), 1611 (m), 1444 (m), 1413 (m), 1350 (w), 1285 (w), 1243 (s), 1173 (m), 1073 (m), 1032 (m), 942 (w), 898 (m), 819 (m), 761 (m), 706 (s), 664 (w), 632 (w), 600 (w), 582 (w), 516 (w), 459 (vw) cm$^{-1}$.

MS (EI, 70eV): m/z (%) = 402.2 (5, M+1), 330.0 (3), 275.0 (2), 246.9 (3), 204.1 (55), 194.1 (42), 164.9 (3), 150.0 (2), 121.0 (100), 105.0 (10), 91.1 (5), 77.1 (8).

Elemental Analysis: Anal. Calcd for C$_{26}$H$_{27}$NO$_3$: C, 77.78; H, 6.78; N, 3.49; Found 77.03; H, 6.87; N, 3.48.
(5S)-((Triisopropylsilyloxy)methyl)pyrrolidin-2-one (152)

According to GP 5, the product was obtained as a colorless solid after flash chromatography (EtOAc/PE, 1:1).

Yield: m = 1.16 g, 4.30 mmol, (99%).

$^1$H NMR (400MHz, CDCl$_3$):
$\delta$ = 1.06 (m, 18H, Si(CH$_3$)$_3$), 1.78 (m, 1H, C(O)CH$_2$CHH), 2.18 (m, 1H, C(O)CH$_2$CHH), 2.35 (m, 2H, C(O)CH$_2$), 3.56 (dd, $J$ = 10.0, 7.4Hz, SiOCH$_2$H), 3.71 (dd, $J$=10.0, 4.1Hz, SiOCHH), 3.78 (m, 1H, NCH/CH$_2$), 6.20 (brs, 1H, NH) ppm.

$^{13}$C NMR (100MHz, CDCl$_3$):
$\delta$ = 12.0 (Si(CH$_3$)$_3$), 18.1 (Si(CH$_3$)$_3$), 22.9 (C(O)CH$_2$CHH), 29.9 (C(O)CH$_2$), 56.1 (NCH), 67.3 (SiOCH$_2$), 177.9(C(O)) ppm.
All other analytical data correspond to those described in the literature.$^{96}$

(5S)-[(Trimethylsilyloxy)diphenylmethyl]pyrrolidin-2-one (140a):

According to GP 3, the product 140a was obtained as a colorless solid after flash chromatography (EtOAc/PE, 1:1).

Yield: m = 1.14 g, 3 mmol, 99%.

Melting point: 152 °C.
Optical rotation: $[\alpha]_D^{23} = -75.5$ (c 1.01, CHCl$_3$).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta$ = 0.00 (9H, s, Si(CH$_3$)$_3$), 1.38-1.52 (1H, m, C(O)CH$_2$CHH), 2.02-2.25 (3H, m, C(O)CH$_2$CHH), 4.73-4.77(1H, m, NCH), 5.90 (1H, brs, NH), 7.38-7.47 (10H, m, Ph) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta$ = 1.71 (SiC(CH$_3$)$_3$), 22.11 (COCH$_2$CH$_2$), 28.97 (COCH$_2$), 60.13 (NCH), 82.49 (CPh$_2$), 127.67, 127.85, 127.90, 128.02, 142.71, 142.72, (Ph), 178.46 (C(O)N) ppm.

IR(KBr):
$\nu$ = 3720 (vw), 3450 (vw), 3198 (m), 3087 (m), 3030 (w), 2954 (m), 2896 (w), 2828 (vw), 1957
(vw), 1817 (vw), 1694 (s), 1600 (vw), 1544 (vw), 1447 (m), 1422 (m), 1379 (m), 1281 (m), 1253 (s), 1217 (m), 1190 (w), 1155 (w), 1100 (m), 1069 (w), 1026 (w), 996 (vw), 900 (m), 876 (m), 840 (m), 750 (m), 703 (m), 661 (m), 621 (w), 583 (w), 536 (w), 506 (w), 470 (w) cm\(^{-1}\).

MS (EI, 70eV): m/z (%) = 324.1 (5), 255.1 (100), 157.2 (16), 73.2 (35).

Elemental Analysis: Anal. Calcd for C\(_{20}\)H\(_{25}\)NO\(_2\)Si: C, 70.75; H, 7.42; N, 4.13. Found: C, 70.76; H, 7.47; N, 4.08.

(5S)-[(tert-Butyldimethylsilyloxy)diphenylmethyl] pyrrolidin-2-one (140b):

According to GP 3, the product 140b was obtained as a white solid after flash chromatography (EtOAc/PE, 1:1).

Yield: m = 1.14 g, 3 mmol, 99%.
Optical rotation: \([\alpha]_D^{23} = -65.0 \ (c \ 1.01, \text{CHCl}_3)\).

\(^1\)H NMR (300MHz, CDCl\(_3\)):
\[ \delta = -0.39 \ (3H, s, \text{SiC}_3H_3), -0.34(3H, s, \text{SiC}_3H_3), 0.94 \ (9H, s, \text{SiC(CH}_3)_3), 0.99-1.02 \ (1H, m, COCH}_2CHH), 1.77-1.91(1H, m, C(O) CH}_2CHH), 2.04-2.22 \ (2H, m, C(O)CH}_2), 4.62-4.60(1H, m, NCH), 5.84 \ (1H, brs, NH), 7.31-7.34 \ (10H, m, Ph) \text{ppm.}\]

\(^13\)C NMR (75MHz, CDCl\(_3\)):
\[ \delta = -3.41 \ \text{and} \ -3.33 \ (\text{SiC(CH}_3)_3), 18.63 \ (\text{SiC(CH}_3)_3), 22.21 \ (\text{COCH}_2CH_2), 25.96 \ (\text{SiC(CH}_3)_3), 28.66 \ (\text{COCH}_2), 59.73 \ (\text{NCH}), 82.25 \ (\text{CPH}_2), 127.59, 127.65, 127.05, 128.48, 128.64, 142.13, 142.72, (\text{Ph}), 178.49 \ (\text{CO}) \text{ppm.}\]
All other analytical data correspond to those described in the literature.\(^88\)

(5S)-(2-Hydroxypropan-2-yl)pyrrolidin-2-one (139c):

To a vigorously stirred solution of 11.2 g (78 mmol) of L-pyroglutamic acid methyl ester in 150 mL THF under argon at room temperature, was added a 3.0 M solution of MeMgBr in diethylether (65 mL, 0.19 mol). After refluxed for 3 h, the reaction was quenched with saturated aqueous NaHCO\(_3\) solution and repeatedly extracted with THF. The organic phase was dried over MgSO\(_4\) and concentrated in vacuo, the crude product purified by chromatography with EtOAc/MeOH (40 : 1) afforded 5.4 g (48%) of 139c as a thick oil.
Experimental part

Yield: m = 5.4 g, 37 mmol, (48%).
TLC: Rf = 0.3 (EtOAc:MeOH = 20 : 1).

1H NMR (300MHz, CDCl3):
δ = 0.88 and 0.95 (s, 3H, C(CH3)2), 1.77-1.78 (m, 1H, C(O)CH2CH2H), 1.85-2.05(m, 1H, C(O)CH2CH2H), 2.10-2.30 (m, 2H, C(O)CH2), 2.90 (brs, 1H, OH), 3.85 (m, 1H, NCH), 7.10 ppm.

13C NMR (75MHz, CDCl3):
δ = 21.82 (COCH2CH2), 23.23 and 26.30(C(CH3)2), 30.46 (COCH2),  63.61 (NCH), 71.58 ((CH3)2COH), 179.50 (CO) ppm.
All other analytical data correspond to those described in the literature.

(5S)-(2-(Trimethylsilyloxy)propan-2-yl)pyrrolidin-2-one (140c):

According GP 3, the product 140c was obtained as clear oil after flash chromatography (EtOAc/PE, 1:1).

Yield: m = 0.64 g, 3 mmol, (99%).
Optical rotation: [α]D23 = – 5.3 (c 1.01, CHCl3).

1H NMR (300MHz, CDCl3):
δ = 0.18 (s, 9H, Si(CH3)3), 1.08 and 1.13 (s, 3H, C(CH3)2), 1.75-1.87(m, 1H, C(O)CH2CH2H), 1.89-2.02 (m, 1H, C(O)CH2CH2H), 2.10-2.32 (m, 2H, C(O)CH2), 3.36-3.40 (dd, J = 7.4, 5.2Hz, 1H, NCH), 7.26 (brs, 1H, NH) ppm.

13C NMR (75MHz, CDCl3):
δ = 2.22 (Si(CH3)3), 21.60 (COCH2CH2), 25.10 and 25.72 (C(CH3)2), 30.33 (COCH2), 64.02 (NCH), 75.12 ((CH3)2COH), 179.00 (C(O)) ppm.

IR(KBr):
ν = 3799 (vw), 3746 (vw), 3238 (m), 2972 (m), 2972 (m), 1690 (s), 1460 (m), 1423 (m), 1383 (m), 1254 (m), 1177 (m), 1092 (w), 1043 (m), 953 (vw), 898 (w), 843 (m), 755 (m), 662 (w), 550 (vw), 514 (w), 463 (vw) cm⁻¹.

MS (EI, 70eV): m/z (%) = 214.1 (5, M⁺-1), 200.1 (5), 157.1 (10), 131.1 (20), 85.1 (100), 73.1 (25), 59.1 (40).

(5\textit{R})-Benzhydrylpyrrolidin-2-one (143):

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

Trifluoroborane etherate (8.3 mL, 67.0 mmol) was added to a solution of Et\textsubscript{3}SiH (17.9 mL, 112 mmol) and 13\textsuperscript{9} (6.0 g, 22.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (240 mL) at -20 °C over 5 min. The mixture was stirred at rt for 66 h. During this time, additional Et\textsubscript{3}SiH (28.5 mL, 178 mmol) and BF\textsubscript{3}.OEt\textsubscript{2} (22.0 mL, 178 mmol) were added to complete the reaction. The reaction mixture was washed with saturated aqueous NaHCO\textsubscript{3} solution, brine, and then dried over Na\textsubscript{2}SO\textsubscript{4}. Concentration and chromatography (CHCl\textsubscript{3}/AcOEt=2:1) gave 14\textsuperscript{3} as a colorless solid.

Yield: m = 4.37 g, 52 mmol, (78%).
Optical rotation: \([\alpha]_{D}^{23} = +25.5 (c 1.01, \text{CHCl}_3)\).

\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):
\[\delta = 1.74-1.86 (m, 1H, C(O) CH\textsubscript{2}CH\textsubscript{H}), 2.09-2.21 (m, 1H, C(O)CH\textsubscript{2}CH\textsubscript{H}), 2.30-2.36 (m, 2H, C(O)CH\textsubscript{2}), 3.75/3.78 (d, \textit{J} = 10.4 Hz, 1H, NCH\textsubscript{H}), 4.37-4.45 (m, 1H, NCHCHPh\textsubscript{2}), 5.44 (brs, 1H, NH), 7.22-7.30 (m, 10H, Ph-\textsubscript{H}) \text{ppm.}\]

\textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}):
\[\delta = 26.42 (\text{COCH}_{2}CH\textsubscript{2}), 30.10 (\text{COCH}_{2}), 57.45 (NCH), 58.36 (CHPh\textsubscript{2}), 126.89, 127.10, 127.81, 128.68, 128.98, 140.61, 141.51, 177.24 (Ph-C) \text{ppm.}\]

All other analytical data correspond to those described in the literature.\textsuperscript{118}

\textbf{(S)-2-Phenyl-5-((triisopropylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (205).}

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Ph} \\
\text{BF}_4 \\
\text{OTIPS} \\
\end{array}
\]

According to GP 4, the product 205 was obtained as colorless crystals recrystallized from EtOAc.

Yield: m = 3.2 g, 7 mmol, (70%).

\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):
\[\delta = 0.00 and 1.00 (s, 3H, Si(CH\textsubscript{3})\textsubscript{2}), 0.83 (s, 9H, SiC(CH\textsubscript{3})\textsubscript{3}), 2.76 (m, 1H, NCHCH\textsubscript{H}), 3.06-3.18 (m, 1H, NCHCH\textsubscript{H}), 3.26-3.32 (m, 2H, C(N)CH\textsubscript{2}), 3.91 (dd, \textit{J} = 11.6, 2.5 Hz, 1H, SiOC\textsubscript{HH}), 4.36 (dd, \textit{J} = 11.6, 2.5Hz, 1H, SiOC\textsubscript{HH}), 5.22 (dd, \textit{J} = 8.2, 2.2 Hz, 1H, NCH\textsubscript{H}), 7.61 (m, 3H, Ph-\textsubscript{H}), 7.85 (m, 2H, Ph-\textsubscript{H}), 10.17 (s, 1H, NCH\textsubscript{H}) \text{ppm.}\]
13C NMR (75MHz, CDCl3):
δ = -6.0 and -5.9 (Si(CH3)3), 17.7 (SiC(CH3)3), 22.6 (C(N)CH2CH2), 25.4 (SiC(CH3)3), 29.9 (C(N)CH2), 62.2 (NCH), 64.2 9 (SiOCH3), 120.6, 130.1, 130.6 (Ph-C), 136.4 (NCHN), 163.3 (C(N)) ppm.
All other analytical data correspond to those described in the literature98

(S)-5-(Diphenyl(trimethylsilyloxy)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-lum tetrafluoroborate (141a).

According to GP 4, the product was obtained as colorless solid recrystallized from EtOAc.

Yield: m = 3.0 g, 6.8 mmol, (68%).
Melting point: 215°C.
Optical rotation : [α]D 23 = –130.2 (c 1.01, CHCl3).

1H NMR (300MHz, CDCl3):
δ = 0.00 (s, 9H, Si(CH3)3), 2.08-2.20 (m, 1H, C(N)CH2CHH), 2.82-3.01 (m, 2H, C(N)CHHCHH), 3.31-3.42 (m, 1H, C(N)CHHCH2), 6.20 (d, J = 8.5 Hz, 1H, NCH), 7.34-7.36 (m, 2H, Ph-H), 7.40-7.45 (m, 5H, Ph-H), 7.51-7.54 (m, 3H, Ph-H), 7.64-7.67 (m, 3H, Ph-H), 7.76-7.79 (m, 2H, Ph-H)), 8.95 (s, 1H, NCHN) ppm.

13C NMR (75MHz, CDCl3):
δ = 1.4 (SiC(CH3)3), 21.1 (COCH2CH2), 29.8 (COCH2), 68.1 (NCH), 121.2, 128.0, 128.5, 128.6, 128.75, 129.01, 129.17, 130.18, 135.35 (Ph-C), 136.60 (NCHN), 139.6, 140.0 (Ph-C), 162.5 (CN) ppm.

IR (KBr):
v = 3981 (vw), 3747 (vw), 3694 (vw), 3171 (m), 3065 (w), 3031 (vw), 2958 (w), 2991 (vw), 2815 (vw), 2345 (vw), 1982 (vw), 1899 (vw), 1811 (vw), 1685 (vw), 1594 (m), 1520 (m), 1496 (w), 1444 (m), 1394 (m), 1327 (w), 1254 (s), 1193 (m), 1052 (s), 925 (w), 849 (s), 763 (s), 708 (s), 633 (m), 582 (w), 525 (m), 483 (w) cm⁻1.

MS (ESI): m/z(+) = 440.1 (100, M+), 350.5 (15). m/z (-) = 87.3 (100, BF4).

(S)-5-(((tert-Butyldimethylsilyloxy)diphenylmethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (141b).

According to GP 4, the product was obtained as colorless solid recrystallized from EtOAc.

Yield: m = 4.5 g, 8 mmol, (80%).
Melting point: 186°C.
Optical rotation: $[\alpha]_D^{23} = -137.5$ (c 1.01, CHCl$_3$).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta$ = -0.35 (s, 3H, Si(CH$_3$)$_3$), -0.32 (s, 3H, Si(CH$_3$)$_3$), 0.94 (s, 9H, Si(C(CH$_3$)$_3$)$_3$), 1.60-1.71 (m, 1H, C(O)CH$_2$CH/), 2.72-2.93 (m, 2H, C(O)CH$_2$CH), 3.12-3.27 (m, 1H, C(O)CH$_2$CHH), 6.09-6.12 (d, $J = 7.7$ Hz, 1H, NCH), 7.13-7.15 (m, 2H, Ph-H), 7.31-7.36 (m, 2H, Ph-H), 7.37-7.47 (m, 4H, Ph-H), 7.50-7.55 (m, 5H, Ph-H), 7.65-7.71 (m, 2H, Ph-H), 9.06 (s, 1H, NCHN) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta$ = -3.63 and -3.57 (Si(C(CH$_3$)$_3$)$_3$), 18.62 (Si(C(CH$_3$)$_3$)$_3$), 20.68 (COCH$_2$CH$_2$), 25.99 (Si(C(CH$_3$)$_3$)$_3$), 29.54 (COCH$_2$), 66.30 (NCH), 82.06 (CPh$_2$), 121.39, 127.92, 128.39, 128.85, 129.04, 130.13, 130.94, 135.27 (Ph-C), 136.89 (NCN), 139.60, 140.00 (Ph-C), 163.46 (CN) ppm.

IR (KBr):
$\nu$ = 3928 (vw), 3415 (w), 3105 (m), 3025 (w), 2953 (m), 2930 (m), 2889 (m), 2854 (m), 2763 (vw), 2702 (vw), 1958 (vw), 1906 (vw), 1823 (vw), 1593 (m), 1516 (m), 1493 (m), 1468 (m), 1445 (m), 1385 (m), 1329 (vw), 1265 (m), 1235 (m), 1212 (m), 1064 (s), 937 (m), 873 (m), 836 (m), 810 (w), 779 (m), 706 (m), 642 (vw), 613 (w), 580 (w), 537 (w), 498 (w) cm$^{-1}$.

MS (ESI): m/z(+) = 482.2(100, M$^+$), 350.4 (5), m/z(−) = 87.3(100, BF$_4$).

Elemental Analysis: Anal.Calcd for C$_{27}$H$_{30}$N$_3$OSi$^+$BF$_4^-$: C, 63.27; H, 6.37; N, 7.38. Found: C, 63.75; H, 6.325; N, 7.40.
Experimental part

(S)-2-Phenyl-5-(2-(trimethylsilyloxy)propan-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (141c)

According to GP 4, the product was obtained as colorless solid recrystallized from EtOAc.

Yield: m = 2.5 g, 6.3 mmol, (63%).
Melting point: 110°C.
Optical rotation: \([\alpha]^{23}_D = -46.3 (c 1.01, CHCl_3)\);

\(^1\)H NMR (300MHz, CDCl\(_3\)):
\(\delta = 0.00\) (s, 9H, Si(CH\(_3\))\(_3\)), 1.24 and 1.40 (s, 3H, C(CH\(_3\))\(_3\)), 2.62-2.68 (m, 1H, C(O)CH\(_2\)CHH), 2.83-2.96 (m, 1H, C(O)CH\(_2\)CHH), 3.05-3.12 (m, 2H, C(O)CH\(_2\)H), 4.78-4.81 (dd, J = 8.0, 0.9 Hz, 1H, NCH), 7.48-7.50 (m, 3H, Ph-H), 7.76-7.80 (dd, 2H, Ph-H), 9.89 (s, 1H, NCHN) ppm.

\(^{13}\)C NMR (75MHz, CDCl\(_3\)):
\(\delta = 2.0\) (Si(CH\(_3\))\(_3\)), 22.0 (COCH\(_2\)CH\(_2\)), 26.0 and 26.9 (C(CH\(_3\))\(_3\)), 29.3 (COCH\(_2\)), 70.2 (NCH), 74.7 ((CH\(_3\))\(_2\)COH), 120.8, 130.2, 130.8 (Ph), 137.2 (NCHN), 163.5 (C(N)) ppm.

IR(KBr):
\(\nu = 3822\) (vw), 3749 (vw), 3656 (vw), 3424 (w), 3193 (m), 2977 (m), 2898 (w), 2374 (vw), 2340 (vw), 1592 (s), 1532 (m), 1470 (w), 1438 (m), 1400 (m), 1320 (w), 1288 (w), 1249 (m), 1187 (m), 1144 (m), 1060 (s), 976 (m), 985 (w), 882 (m), 847 (s), 765 (s), 720 (w), 685 (m), 663 (vw), 597 (vw), 520 (w), 498 (w), 470 (vw) cm\(^{-1}\).

MS (ESI): m/z(+) = 316.1(100, M\(^+\)), 226.2 (15). m/z(-)=87.3(100, BF\(_4\)).

Anal.Caled for C\(_{27}\)H\(_{30}\)N\(_3\)O\(_2\)Si\(^+\)BF\(_4\)\(^-\): C, 50.63; H, 6.50; N, 10.42. Found: C, 50.88; H, 6.890; N,10.47.
(S)-5-Benzhydryl-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroboratem (143).

According to GP 4, the product was obtained as colorless solid.

Yield: m = 3.0 g, 6.8 mmol, (68%).
Melting point: 180°C.
Optical rotation: \([\alpha]D^{23} = -130.2\) (c 1.01, CHCl₃).

\(^1\)H NMR (300MHz, CDCl₃):

\(\delta = 2.49-2.60\) (m, 1H, C(O)CH₂CH₃), 2.84-2.97 (m, 1H, C(O)CH₂CH₃), 3.11-3.16 (m, 2H, C(O)CH₂), 4.28/4.31 (d, \(J = 10.9\) Hz, 1H, NCH), 5.83-5.91 (m, 1H, NCHCH₃Ph), 7.24-7.50 (m, 15H, Ph-H), 7.95 (s, 1H, NCHN) ppm.

\(^13\)C NMR (75MHz, CDCl₃):

\(\delta = 21.13\) (COCH₂CH₃), 32.36 (COCH₃), 55.41 (NCH), 64.01 (CH₃Ph), 121.44, 127.73, 127.81, 128.19, 128.32, 129.17, 129.73, 129.95, 130.75, 135.26 (Ph-C), 135.72 (NCHN), 138.77, 139.58 (Ph-C), 162.52 (C(N)) ppm.

IR(KBr):

\(\nu = 3978\) (vw), 3953 (vw), 3906 (vw), 3826 (vw), 3786 (vw), 3755 (vw), 3731 (vw), 3676 (vw), 3650 (vw), 3618 (vw), 3530 (w), 3440 (w), 3308 (w), 3266 (vw), 3166 (m), 3061 (m), 3030 (m), 2960 (w), 2875 (vw), 2844 (vw), 2784 (vw), 2642 (vw), 2600 (vw), 2373 (vw), 2342 (vw), 2101 (vw), 1971 (vw), 1895 (vw), 1814 (w), 1753 (vw), 1657 (vw), 1592 (s), 1522 (m), 1495 (m), 1450 (m), 1387 (m), 1291 (m), 1202 (s), 1069 (s), 977 (m), 921(m), 871 (vw), 832 (m), 764 (s), 703 (s), 630 (m), 607 (m), 588 (m), 520 (m), 493 (m) cm⁻¹.

MS (ESI): m/z(+) = 352.2(100, M⁺), 274.4 (5). m/z(-) = 87.3(100, BF₄⁻).


(R)-(−)-2-Hydroxy-1,2-diphenylethanone (145a).
According to GP 1, the product was obtained as colorless solid.

Yield: m = 70 mg, 0.36 mmol, (66%).
GC: $R_t = 4.43$ min (CP-Sil-8, 160-10-300).
TLC: $R_f = 0.6$ (PE : Et$_2$O = 2:1).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta = 4.55$ (d, $J = 6.1$, 1H, OH), $5.98$ (d, $J = 6.1$, 1H, CHOH), 7.25 – 8.00 (m, 10H, PhH) ppm.

HPLC: $R_t = 13.16$ and 19.21 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 95:5, 1.0 mL/min)
$R_t = 13.16$. ee = 96%.

All other analytical data correspond to those described in the literature$^{43}$

(R)-(+)-2-Hydroxy-1,2-di(naphthalen-2-yl)ethanone (145b)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 110 mg, 0.36 mmol (71%).
GC: $R_t = 4.43$ min (CP-Sil-8, 160-10-300).
TLC: $R_f = 0.4$ (PE : Et$_2$O = 2:1).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta = 4.77$ (s, 1H, O-H), $6.26$ (d, $J = 6.1$, 1H, CHOH), 7.40-8.48 (m, 14H, PhH) ppm.

HPLC $R_t = 18.86$ and 28.58 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 8:2, 1.0 mL/min)
$R_t = 18.86$. ee = 53%.

All other analytical data correspond to those described in the literature$^{43}$

(R)-(+)-1,2-Bis(4-chlorophenyl)-2-hydroxyethanone (145c)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 91 mg, 0.32 mmol (65%)
TLC: $R_f = 0.6$ (PE : Et$_2$O = 2:1).
Experimental part

$^1$H NMR (300MHz, CDCl$_3$):

$\delta = 4.59$ (s, 1H, $O\text{H}$), 5.88 (s, 1H, $CH\text{OH}$), 7.20 – 7.82 (m, 8H, Ph-$H$) ppm.

HPLC $R_t = 15.33$ and 16.70 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 9:1, 1.0 mL/min)

$R_t = 15.33$. ee = 77%.

All other analytical data correspond to those described in the literature. 43

(R)-(+) 1,2-Bis(3-chlorophenyl)-2-hydroxyethanone (145d)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 70 mg, 0.25 mmol (50%)
TLC: $R_f = 0.7$ (PE : Et$_2$O = 2:1).

$^1$H NMR (300MHz, CDCl$_3$):

$\delta = 4.62$ (s, 1H, $O\text{H}$), 5.89 (s, 1H, $CH\text{OH}$), 7.17-7.92 (m, 8H, Ph-$H$) ppm.

HPLC $R_t = 17.17$ and 20.90 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 9:1, 0.7 mL/min)

$R_t = 17.17$. ee = 84%.

All other analytical data correspond to those described in the literature. 43

(R)-2-Hydroxy-1,2-dip-tolylethanone (145e)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 9.6 mg, 0.04 mmol (8%)
TLC: $R_f = 0.6$ (PE : Et$_2$O = 2:1).

$^1$H NMR (300MHz, CDCl$_3$):

$\delta = 2.28$ (s, 3H, $CH(O\text{H})\text{PhCH}_3$), 2.35 (s, 3H, $C(O)\text{PhCH}_3$), 5.98 (d, $J = 6.0$Hz, $CHO\text{H}$), 7.10-7.84 (m, 8H, Ph-$H$) ppm.
Experimental part

HPLC $t_R = 5.73$ and 9.89 (WHELM.M, 250×4 mm, n-Hep/IP= 8:2, 1.0 mL/min)
$R_s = 9.89$. ee = 95%.
All other analytical data correspond to those described in the literature. 43

(R)-(+)2-Hydroxy-1,2-bis-(2-furyl)-ethanone (145g)

![Chemical Structure](image)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 92 mg, 0.48 mmol, (95%)

$^1$H NMR (300MHz, CDCl$_3$):
$\delta = 4.13$ (s, 1H, O$_2$H), 5.81 (s, 1H, C$_2$H$_2$OH), 6.33 – 7.62 (m, 6H, Ph-H) ppm.

HPLC $R_s = 25.73$ and 32.43 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 95:5, 1.0 mL/min)
$R_s = 25.73$. ee = 21%.
All other analytical data correspond to those described in the literature. 43

(S)-2-Hydroxy-1,2-di(thiophen-2-yl)ethanone (145h).

![Chemical Structure](image)

According to GP 1, the product was obtained as colorless solid.

Yield: m = 86 mg, 0.39 mmol, (77%)

TLC: $R_f = 0.3$ (PE : Et$_2$O = 2:1).

$^1$H NMR (400 MHz, CDCl$_3$):
$\delta = 4.14$ (s, 1H, O$_2$H), 5.81 (s, 1H, C$_2$H$_2$OH), 6.60-7.62 (m, 6H, Ph-H) ppm.

HPLC $R_s = 12.99$ and 14.35 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 9:1, 0.5 mL/min)
$R_s = 12.99$. ee = 51%.
All other analytical data correspond to those described in the literature. 43
Experimental part

Methyl 2-(4-oxochroman-3-yl)acetate (147)

According to GP 2, the product was obtained as colorless solid.
GC: R<sub>t</sub> = 4.43 min (CP-Sil-8, 160-10-300).
TLC: R<sub>f</sub> = 0.4 (PE : Et<sub>2</sub>O = 5:1).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):
δ = 2.31-2.39 (dd, J = 17.0, 8.0Hz, 1H, CHHCO<sub>2</sub>Me), 2.82-2.90 (dd, J =17.0, 5.0Hz, 1H, CHHCO<sub>2</sub>Me), 3.15-3.31 (m, 1H, C(O)CH(CH<sub>2</sub>)<sub>2</sub>), 3.65 (s, 3H, OCH<sub>3</sub>), 4.18-4.25 (t, J = 11.5Hz, 1H, OCH/H), 4.49-4.55 (dd, J = 11.0, 5.3Hz, 1H, OCH/H), 6.88-6.96 (m, 2H, Ph-H), 7.37-7.43 (m, 1H, Ph-H), 7.79-7.82 (m, 1H, Ph-H) ppm.

<sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>):
δ = 29.9 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 42.3 (C(O)CH(CH<sub>2</sub>)<sub>2</sub>), 51.9 (OCH<sub>3</sub>), 70.0 (OCH<sub>2</sub>), 117.7, 120.3, 121.4, 128.0, 135.9 (Ph-C), 161.56 (Ph-C), 171.69 (CO<sub>2</sub>Me), 192.43 (COCH<sub>2</sub>) ppm.

HPLC R<sub>t</sub> = 15.25 and 16.67 ((DAICLIA.M, 250×4.6 mm, n-Hep/IP= 95:5, 0.7 mL/min)
R<sub>t</sub> = 15.25. ee value: see the main text.
All other analytical data correspond to those described in the literature. 79

1-Methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-1-ium tetrafluoroborate (156)

According GP 6, lactam 154 (0.85g, 10 mmol) was used. The 156 was purified by crystallization and obtained as colorless crystals.

Yield: m = 1.52 g, 8.5 mmol, (85%).
Melting point = 133 °C.

<sup>1</sup>H NMR (300MHz, <sup>4</sup>DMSO):
δ = 2.78 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.20 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.35 (s, 3H, NCH<sub>3</sub>), 4.26 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 8.94 (s, 1H, NCHN) ppm.

<sup>13</sup>C NMR (75MHz, <sup>4</sup>DMSO):
δ = 21.7 (NCH₂CH₂CH₂), 27.6 (NCH₂CH₂CH₂), 37.5 (NCH₃), 47.1 (NCH₂CH₂CH₂), 140.0 (NCHN), 160.7 (C(N)) ppm.

IR (KBr):
ν = 3674 (vw), 3456 (m), 3364 (m), 3251 (vw), 3162 (w), 3088 (w), 2990 (w), 2371 (vw), 2110 (vw), 1822 (vw), 1618 (m), 1562 (m), 1454 (w), 1423 (vw), 1370 (m), 1300 (m), 1052 (s), 886 (w), 802 (w), 730 (vw), 650 (m), 571 (vw), 524 (w), 497 (w) cm⁻¹.

MS (EI, 70eV): m/z (100) = 200.2 (10, M⁺, BF₄⁻), 198.2 (60), 170.1 (8), 135.2 (15), 127.1 (15), 106.2 (10), 92.2 (20), 91.1 (100), 65.1 (25), 58.2 (25), 58.2 (20), 49.1 (60).


The N-Methyl precatalyst 153.

The Precatalysts 153 were prepared as 1:1 mixture according to the procedure described in Balensiefer’s dissertation. And the NMR spectra were in accordance with the literature.¹³

(S)-5-(Diphenyl(trimethylsilyloxy)methyl)-2-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (157)

According to GP 6, the lactam (1.69 g, 5 mmol) was used, the 157 was purified by column chromatography (silica gel, EtOAc) and obtained as colorless solid.

Yield: m = 0.69 g, 1.5 mmol, (30%).
TLC: Rₜ = 0.2 (EtOAc).
Melting point: 80° C.
Optical rotation: [α]D²⁵ = −44.5 (c 1.01, CHCl₃);
**Experimental part**

\(^1\)H NMR (300MHz, CDCl\(_3\)):
\[\delta = 0.01 \text{ (s, 9H, Si(CH}_3)_3\text{)}, 2.04 \text{ (m, 1H, C(N)CH}_2\text{CH}_2\text{H)}, 2.78-2.94 \text{ (m, 2H, C(N)CH}_2\text{CH}_2\text{)}, 3.23-3.37 \text{ (m, 1H, C(O)CH}_2\text{CH}_2\text{H)}, 4.19 \text{ (s, 3H, NCH}_3\text{)}, 5.97 \text{ (dd, } J = 7.5, 0.2\text{Hz, 1H, NCH)}, 7.35-7.55 \text{ (m, 10H, Ph-H)}, 8.92 \text{ (s, 1H, NCHN) ppm.}

\(^1\)C NMR (75MHz, CDCl\(_3\)):
\[\delta = 0.0 \text{ (Si(CH}_3)_3\text{)}, 19.4 \text{ (C(N)CH}_2\text{CH)}, 28.2 \text{ (C(N)CH}_2\text{CH}_2\text{CH}), 38.2 \text{ (NCH}_3\text{)}, 66.6 \text{ (C(N)CH}_2\text{CH}_2\text{CH), 80.9 \text{ (CPh}_2\text{OSiMe}_3\text{)}, 126.7, 127.0, 127.1, 127.2, 127.5 \text{ (Ph-C)}, 138.2 \text{ (NCHN), 160.8 \text{ (C=NMe) ppm.}}

IR (KBr):
\[\nu = 3944 \text{ (vw), 3406 (w), 3188 (w), 3063 (w), 2957 (m), 2362 (w), 2341 (w), 1967 (vw), 1828 (vw), 1684 (m), 1587 (m), 1548 (vw), 1495 (w), 1448 (m), 1399 (w), 1259 (m), 1071 (s), 846 (s), 759 (m), 704 (m), 582 (vw), 525 (m), 477 (vw) cm}^{-1}.

MS (ESI): m/z (%, +) = 378.2 (100, M\(^+\)); 288.7 (20), m/z (–) = 87.4(100, BF\(_4\)).

\[\text{ms}^2 (378): \text{m/z (}%) = 288.1 (100).

\[\text{ms}^3 (378/288): \text{m/z (}%) = 288.1 (5), 261.2 (10), 247.2 (20), 210.2 (100), 192.3 (30), 172.2 (30), 154.1 (5), 115.2 (10), 91.1 (10).

\[\text{ms}^4 (378/288/210): \text{m/z (}%) = 195.2 (5), 183.2 (5), 169.2 (100), 154.2 (80), 141.9 (5).

HRMS: m/z calcd for [C\(_{22}\)H\(_{28}\)N\(_3\)OSi-2H, M\(^+\)-2]: 376.1840; found: 376.1840.

\((S)-5-((\text{tert-Butyldimethylsilyloxy})\text{diphenylmethyl})-2-\text{methyl-6,7-dihydro-5H-pyrrolo}[2,1-c][1,2,4]\text{triazol-2-ium tetrafluoroborate (158).}

\[\text{According GP 6, the lactam (1.91 g, 5 mmol) was applied, the 158 was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as colorless powder.}

Yield: m = 1.11 g, 2.2 mmol, (43%)
Melting point = 1'85\text{oC}.
TLC: R\(_f\) = 0.2 (EtOAc).
Optical rotation: [\(\alpha\)]\(_{D}^{23}\) = -16.4 (c 1.01, CHCl\(_3\));

\(^1\)H NMR (300MHz, CDCl\(_3\)): 

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125
Experimental part

\[ \delta = \text{-0.43 and -0.41 (3H, s, SiC}_3\text{H}_3), 0.87 (s, 9H, SiC}_3\text{H}_3), 2.53-2.62 (m, 1H, (O)CH}_2\text{CH}_2), 2.75-2.82 (m, 1H, C(O)CH}_2\text{CH}_2), 2.95-3.17 (m, 2H, m, C(O)CH}_2\text{CH}_2), 3.98 (s, 3H, NCH}_3), 5.81 (d, } J = 7.8\text{Hz, 1H, NCH}_3), 6.90-7.51 (m, 10H, Ph-H), 8.98 (1H, s, NCH}_3) \text{ppm.} \]

\[^{13}\text{C NMR (75MHz, CDCl}_3):\]

\[ \delta = \text{-3.6 and -3.7 (SiC}_3\text{H}_3), 18.6 (SiC}_3\text{H}_3), 20.4 (COCH}_2\text{CH}_2), 25.9 (SiC}_3\text{H}_3), 29.5 (COCH}_2), 65.3 (NCH), 81.6 (CPh}_2), 127.6, 128.2, 128.6, 129.0, 129.2, 129.6, 139.5 (Ph-C), 139.8 (NCHN), 162.9 (C(N)) \text{ppm.} \]

IR (KBr):

\[ v = 3777 (vw), 3730 (vw), 3639 (vw), 3552 (vw), 3402 (vw), 3157 (w), 3064 (w), 2956 (m), 2933 (m), 2890 (m), 2858 (m), 2711 (vw), 2366 (vw), 2343 (vw), 1972 (vw), 1693 (m), 1591 (m), 1547 (w), 1494 (m), 1449 (m), 1388 (m), 1362 (w), 1323 (vw), 1259 (m), 1069 (s), 939 (m), 879 (m), 839 (m), 778 (m), 706 (m), 669 (w), 627 (m), 583 (m), 522 (m) \text{ cm}^{-1}. \]

MS (ESI): \text{m/z (%, +) = 420.3 (100, M}^+\text{); 400.7 (5), 288.5 (5). m/z (-) = 87.4(100, BF}_4\text{).} \]

\[^{2}\text{H NMR (400MHz, CDCl}_3):\]

\[ \delta = 1.06 (s, 9H, SiC}_3\text{H}_3), 1.73 (m, 1H, C(O)CH}_2\text{CH}_2), 2.14 (m, 1H, C(O)CH}_2\text{CH}_2), 2.32 (m, 2H, C(O)CH}_2), 3.52 (dd, } J = 10.2, 7.4\text{Hz, SiOC}_3\text{H}_3), 3.63 (dd, } J = 10.2, 4.1\text{Hz, SiOCCH}_3\text{), 3.81 (brs, 1H, NH)), 7.34-7.72 (m, 10H, Ph-H) \text{ppm.} \]

\[^{13}\text{C NMR (100MHz, CDCl}_3):\]

\[ \delta = 19.1 (SiC}_3\text{H}_3), 22.7 (C(O)CH}_2\text{CH}_2), 26.7 (SiC}_3\text{H}_3), 29.7 (C(O)CH}_2), 55.6 (NCHCH}_3), 67.3 (SiOCH}_2), 127.7, 129.7,132.7,135.7 (Ph-C), 177.7 (C(O)) \text{ppm.} \]

All other analytical data correspond to those described in the literature.

\[(S)-5-((\text{tert-Butyldiphenylsilyloxy)methyl})\text{pyrrolidin-2-one (168b)}\]

According to GP 5, the title compound was obtained as colorless solid.

Yield: \text{m = 1.52 g, 4.34 mmol, (99%).}
Experimental part

(S)-5-((1,1,1,3,3,3-Hexamethyl-2-xy)methyl)pyrrolidin-2-one (168c)

According to GP 5, the title compound was obtained as colorless solid.

Yield: m = 1.62 g, 4.34 mmol, (99%).

$^1$H NMR (400MHz, CDCl$_3$):
$\delta$ = 1.64-1.78 (m, 1H, C(O)CH$_2$CH/H), 2.03-2.18 (m, 1H, C(O)CH$_2$CH/H), 2.28 (t, $J$ =7.7Hz, 2H, C(O)CH$_2$), 3.62 (dd, $J$ = 9.8, 6.7Hz, 1H, NC/HCH$_2$(CH$_2$), 3.74 (d, $J$ = 4.1Hz, 1H, SiOCH$\text{CH}$HCH), 3.78 (d, $J$ = 4.1Hz, C(O)CH$_2$CH/H), 5.84 (brs, 1H, NH), 7.33-7.48 (m, 10H, Ph-$\text{H}$), 7.55-7.60 (m, 5H, Ph-$\text{H}$) ppm.

$^{13}$C NMR (100MHz, CDCl$_3$):
$\delta$ = 22.6 (C(O)CH$_2$CH$_2$), 29.5 (C(O)CH$_2$), 55.4 (NCH$\text{CH}$H$_2$), 67.2 (OCH$_2$OPh$_3$), 127.9, 129.7, 130.2, 133.3, 134.9, 135.2 (Ph-$\text{C}$), 177.7 (C(O)NH) ppm.

(S)-5-((Triphenylsilyloxy)methyl)pyrrolidin-2-one (168d)

According to GP 5, the product 168d was obtained as crystalline solid.

Yield: m = 1.25 g, 3.50 mmol (80%).

Melting point = 101 °C.
TLC $R_t$= 0.60 (PE:EtOAc= 1:1).
Optical rotation: $[\alpha]_D^{23} = -23.7$ (c 1.01, MeOH).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta$ = 0.00 (s, 27H, Si(Si(CH$_3$)$_3$)$_3$), 1.52-1.59 (m, 1H, C(O)CH$_2$CH/H), 1.87-2.00 (m, 2H, C(O)CH/HCH/H), 2.15-2.25 (m, 1H, C(O)CH$\text{CH}$H$_2$), 3.24-3.30 (m, 1H, NCH), 3.30-3.42 (m, 2H, SiOCH$_2$) ppm.
Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 0.0$ (Si(Si(CH$_3$)$_3$)$_3$), 23.6 (C(O)CH$_2$CH$_2$), 28.5 ((C(O)CH$_2$CH$_2$), 60.1 (NCH), 63.5 (SiOCH$_2$), 181.9 (C(O)) ppm.

IR(KBr):
$\nu = 3937$ (vw), 3861 (w), 3822 (w), 3744 (w), 3676 (vw), 3341 (s), 2951 (s), 2893 (m), 2683 (vw), 2468 (vw), 2347 (wv), 2233 (vw), 2106 (vw), 1929 (vw), 1869 (vw), 1639 (s), 1507 (vw), 1383 (m), 1305 (w), 1246 (s), 1152 (w), 1109 (m), 1058 (s), 984 (vw), 939 (w), 835 (s), 748 (m), 686 (m), 623 (m), 570 (vw), 474 (w) cm$^{-1}$.

MS (EI, 70eV): m/z (%) = 362.2 (M$^+$, 100), 346.1 (20), 288.2 (30), 165.1 (5), 207.1 (5), 116.1 (10), 73.1 (5).

Elemental Analysis: Anal. Calcd for C$_{14}$H$_{35}$NO$_2$Si$_4$: C, 46.48; H, 9.75; N, 3.87. Found: C, 46.18; H, 10.08; N, 3.87.

**Benzylhydrazine:**

![Benzylhydrazine](image)

A solution of 63.5 g (0.5 mol) benzyl chloride in 200 mL ethanol was added to a refluxing solution of 85% hydrazine hydrate 150 g (5eq, 2.5 mol) in 300 mL ethanol over a period of 1 hour, after a reflux period of 6 hours, the alcohol was removed by distillation. (Warning: explosive) The residue was extracted with ether, the ethereal extracts were dried with potassium hydroxide, filtered and fractionated to obtain the pure benzylhydrazine as colorless oil.

Yield: m = 20 g, (30%).
Boiling point: 120°C, 9 mbar.

$^1$H NMR (400MHz, CDCl$_3$):
$\delta = 3.08$ (brs, 3H, NHNH$_2$), 3.76 (d, $J = 3.5$Hz, 2H, PhCH$_2$N), 7.14-7.28 (m, 5H, Ph-H) ppm.

$^{13}$C NMR (100MHz, CDCl$_3$):
$\delta = 60.0$, 127.4, 128.2, 128.4, 128.6, 128.6, 137.9 ppm.

**2-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate(165).**

![2-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate](image)

According to GP 7, lactam 154 (0.85 g, 10 mmol) was used, the 165 was purified by column
Experimental part

Yield: m = 2.29 g, 8.0 mmol, (80%).
TLC: Rf = 0.38 (PE:EtOAc = 1:1).

\(^1\)H NMR (300MHz, CDCl\(_3\)):  
\(\delta = 2.55-2.65 \text{ (m, 2H, } \text{C(N)CH}_2\text{CH}_2), 2.90 \text{ (t, } J = 7.7 \text{ Hz, } 2\text{H, C(N)CH}_2\text{CH}_3), 4.25 \text{ (t, } J = 7.2\text{Hz, } 2\text{H, NCH}_2), 5.34 \text{ (s, 2H, PhCCH}_2\text{N), 7.02-7.50 \text{ (m, 5H, Ph-H), 9.34 \text{ (s, 1H, NCHN} \text{ ppm.}}

\(^{13}\)C NMR (75MHz, CDCl\(_3\)):  
\(\delta = 21.4 \text{ (C(N)CH}_2\text{CH}_2), 26.4 \text{ (C(N)CH}_2\text{CH}_3), 46.9 \text{ (NCH}_2), 56.0 \text{ (PhCH}_2\text{N), 128.8, 129.1, 132.3 \text{ (Ph-C), 138.8 \text{ (NCHN), 162.7 \text{ (CH}_2\text{C}=N} \text{ ppm.}}

IR (KBr):  
\(\nu = 3967 \text{ (w), 3911 \text{ (w), 3850 \text{ (w), 3712 \text{ (w), 3641 \text{ (m), 3528 \text{ (w), 3462 \text{ (w), 3394 \text{ (m), 3292 \text{ (w), 3143 \text{ (s), 3048 \text{ (w), 2962 \text{ (w), 2917 \text{ (w), 2849 \text{ (w), 2770 \text{ (w), 2724 \text{ (w), 2680 \text{ (w), 2520 \text{ (w), 1687 \text{ (w), 1590 \text{ (s), 1531 \text{ (m), 1498 \text{ (w), 1449(m), 1391 \text{ (m), 1292 \text{ (m), 1075 \text{ (s), 908 \text{ (w), 863 \text{ (m), 747 \text{ (s), 709 \text{ (s), 634 \text{ (s), 595 \text{ (m), 556 \text{ (w), 520 \text{ (m), 480 \text{ (s cm}^{-1}.}}

MS (ESI): m/z (%, +) = 200.5 (100, M\(^+\)); 91.3 (20). m/z (-) = 87.3(100, BF\(_4\)).  
ms\(^2\) (200): m/z (%) = 91.1 (100).

Note: This compound is difficult to purify.

\((S)-2\text{-Benzy l-5-((triisopropylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (168a).}

According GP 7, lactam 167a (2.71 g, 10 mmol) was used, the 168a was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 3.78 g, 8.0 mmol, (80%).
TLC: Rf = 0.38 (PE:EtOAc = 1:1).
Optical rotation: \([\alpha]_{D}^{25} = -17.2 \text{ (c 1.01, CHCl}_3\text{).}

\(^1\)H NMR (300MHz, CDCl\(_3\)):  
\(\delta = 0.81 \text{ (s, 3H, Si(CH}_3\text{Me}_3), 0.83 \text{ (s, 18H, Si(CH}_2\text{CH}_3)\text{), 2.56 \text{ (m, 1H, C(N)CH}_2\text{CH}_2), 2.80-3.11 \text{ (m, 3H, C(N)CH}_2\text{CH}_3), 3.83 \text{ (d, } J = 10.9\text{Hz, 1H, SiOCH}_2\text{H), 4.13 \text{ (d, } J =10.9\text{Hz, 1H, SiOCH}_2\text{H), 4.90 \text{ (m, 1H, NCH}_2\text{CH}_2), 5.30-5.58 \text{ (m, 2H, PhCH}_2\text{N), 7.18-7.45 \text{ (m, 5H, Ph-H), 9.49 \text{ (s, 1H, NCH}_2\text{N) ppm.}}

Experimental part

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta = 11.4$ (Si(CHMe$_3$)$_3$), 17.5 (Si(CH(CH$_3$)$_2$)$_3$), 22.3 (C(N)CH$_2$CH$_2$CH), 29.6 (C(N)CH$_2$CH$_2$CH), 56.5 (SiOCH$_2$), 61.7 (NCHCH$_2$), 64.5 (PhCH$_3$N), 128.9, 129.0, 129.1, 129.3, 131.3 (Ph-C), 138.1 (NCHN), 162.8 (CH$_2$C(N)) ppm.

IR (KBr):
$\nu = 3955$ (vw), 3904 (vw), 3801 (vw), 3736 (vw), 3440 (m), 3229 (vw), 3120 (w), 2920 (m), 2343 (w), 2078 (vw), 1834 (m), 1686 (m), 1582 (m), 1529 (w), 1498 (vw), 1459 (m), 1391 (m), 1306 (w), 1259 (vw), 1065 (s), 947 (vw), 921 (vw), 883 (m), 859 (m), 817 (w), 762 (m), 704 (m), 646 (m), 593 (vw), 563 (vw), 526 (w), 498 (vw), 478 (vw), 458 (w) cm$^{-1}$.

MS (ESI): $m/z$ (%) = 386.2 (100, M). $m/z$ (%) = 386.1 (100), 338.2 (5).

HRMS: $m/z$ calcd for [C$_{22}$H$_{36}$N$_3$OSi - 2 BF$_4$]: 384.2471; found: 384.2471.

(S)-2-Benzyl-5-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (1689b)

According GP 7, lactam 167b (7.06 g, 20 mmol) was used, the 168b was purified by recrystallization from EtOAc and obtained the desired salts as colorless powder.

Yield: $m = 9.5$ g, 17.2mmol, (86%).

Melting point = 159 °C

TLC = 0.4 (EtOAc/MeOH = 10:1)

Optical rotation: $[\alpha]_D^{23} = -3.8$ (c 1.01, CHCl$_3$).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta = 0.72$ (s, 9H, SiC(CH$_3$)$_3$), 2.54 (m, 1H, NCHCHH), 2.92 (m, 1H, NCHCHH), 3.11 (m, 2H, C(N)CH$_2$), 3.78 (dd, $J = 3.6, 11.8$Hz, 1H, PhCHHN), 4.14 (dd, $J = 2.8, 11.8$Hz, 1H, PhCHHN), 5.01 (m, 1H, NCHCH$_2$), 5.43 (dd, $J = 14.2, 36.5$Hz, 2H, SiOCH$_2$), 7.36 (m, 7 H, Ph-H), 7.44 (m, 8H, Ph-H), 9.43 (s, 1H, NCHN) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta = 19.1$ (SiC(CH$_3$)$_3$), 22.22 (NCHCH$_2$), 26.77 (SiC(CH$_3$)$_3$), 29.79 (C(N)CH$_2$), 57.06 (PhCH$_2$N), 61.61 (NCHCH$_2$), 64.67 (SiOCH$_2$), 128.00, 128.12, 129.22, 129.36, 129.62, 130.21, 130.31, 131.52, 131.75, 135.24, 135.32 (Ph-C), 138.50 (NCHN), 162.55 (C(N)CH$_2$) ppm.
Experimental part

IR (KBr):
\(\nu = 3397\text{(vw)}, 3137 \text{(w), 3097 \text{(vw), 3044 \text{(w), 2955 \text{(m), 2933 \text{(m), 2886 \text{(m), 2859 \text{(m), 2371\text{(vw), 2346 \text{(vw), 1971 \text{(vw), 1902 \text{(vw, 1834 \text{(vw, 1684 \text{(w), 1523 \text{(w), 1499 \text{(vw), 1465 \text{(m), 1429 \text{(m), 1389 \text{(m), 1288 \text{(m), 862 \text{(w), 824 \text{(m), 786 \text{(m), 741 \text{(m), 705 \text{(s), 646 \text{(vw), 614 \text{(m), 558 \text{(vw), 507 \text{(m), 459 \text{(w) cm}^{-1}.\text{)}}

MS (ESI): m/z (+) = 468.2 (100, M\text{+}); 382.3 (5). m/z (-) = 87.3(100, BF\text{4}).

Elemental Analysis: Anal. Calcd for C\text{29}H\text{34}N\text{3}OSi\text{+BF\text{4}}: C, 62.70; H, 6.17; N, 7.56. Found: C, 63.01; H, 6.573; N, 7.542.

(S)-2-Benzyl-5-((triphenylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (168c)

According to GP 7, lactam 167c (1.85 g, 5 mmol) was used, the 168c was purified by recrystallization from EtOAc and obtained as colorless powder.

Yield: m = 1.2g, 2.0 mmol, (40 %).
Melting point = 155°C
Optical rotation: \([\alpha]_{D}^{25} = –16.7 \text{(c 1.01, CHCl}_3\text{).}\]

\(^1\text{H NMR (400MHz, CDCl}_3\text{):}\)
\(\delta = 2.45-2.54 \text{(m, 1H, C(N)CH}_2\text{CH}_2\text{H), 2.77-2.87 \text{(m, 1H, C(N)CH}_2\text{C}_3\text{H}_2\text{H), 2.93-3.08 \text{(m, 2H, C(N)CH}_2\text{CH}_2\text{), 3.88 \text{(dd, J = 11.8, 3.6Hz, 1H, Ph}_3\text{SiOCH}_2\text{H), 4.27 \text{(dd, J = 11.8, 3.6Hz, 1H, Ph}_3\text{SiOCH}_2\text{H), 5.0 \text{(m, 1H, NCH}_3\text{CH}_3\text{H), 5.25 \text{(s, 2H, PhCH}_2\text{N), 7.24-7.45 \text{(m, 20H, Ph-H), 9.29 \text{(s, 1H, NCH}_3\text{N ppm.}}}

\(^13\text{C NMR (100MHz, CDCl}_3\text{):}\)
\(\delta = 22.3 \text{ (C(N)CH}_2\text{CH}_2\text{), 29.8 \text{(C(N)CH}_2\text{CH}_2\text{), 57.1 \text{(PhCH}_2\text{N), 61.6 \text{(NCHCH}_3\text{H), 64.5 \text{(Ph}_3\text{SiOCH}_2\text{H), 128.2, 129.1, 129.3, 129.6, 130.6, 132.3, 135.1 \text{(Ph-C, 138.6 \text{(NCHN), 186.8 \text{(CH}_2\text{C(N) ppm.}}}

IR (KBr):
\(\nu = 3948 \text{(w), 3901 \text{(w), 3857 \text{(w), 3443 \text{(w), 3278 \text{(w), 3146 \text{(m), 3061 \text{(m), 3007 \text{(m), 2966 \text{(m), 2880 \text{(w), 2721 \text{(w), 2376 \text{(w), 2344 \text{(w), 2330 \text{(w), 1968 \text{(w), 1898 \text{(w), 1826 \text{(w), 1742 \text{(w), 1586 \text{(s), 1177 \text{(m), 1113 \text{(s), 1056 \text{(s), 955 \text{(m), 866 \text{(m), 816 \text{(w), 707 \text{(s0), 512 \text{(s), 471 \text{(m) cm}^{-1}.\text{)}}\)
Experimental part

MS (ESI): m/z (% , +) = 488.1 (100, M+); 276.7 (5), 259.3 (5). m/z (% , -) = 87.3(100, BF4).

\[ \text{m}^3 \text{(488): } m/z (\%) = 410.1 (100), 332.2 (5), 320.2 (20), 276.8 (25), 259.4 (20), 199.2 (10). \]

\[ \text{m}^3 \text{(488/410): } m/z (\%) = 410.2 (10), 332.0 (100), 254.1 (10), 242.0 (40), 199.1 (20), 120.2 (10). \]

\[ \text{m}^3 \text{(488/410/332): } m/z (\%) = 439.2 (5), 314.2 (50), 254.2 (85), 228.9 (100), 213.1 (95), 153.0 (78). \]

Elemental Analysis: Anal. Calcd for C_{28}H_{40}N_{3}O_{4}Si BF_{4}^{-}: C, 61.20; H, 7.34; N, 7.65. Found: C, 61.15; H, 7.535; N, 7.643.

\((S)-2\text{-Benzy}-5\text{-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (169c)}\)

According to GP 7, lactam (1.28 g, 5 mmol) was used, the 169c was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as thick oil.

Yield: m = 1.25g, 2.75mmol, (55%).
TLC: Rf = 0.4 (PE:EtOAc= 1:1).
Optical rotation: \( [\alpha]_{D}^{23} = -12.6 \) (c 1.01, CHCl3).

\(^1\text{H NMR (300 MHz, CDCl3)}: \)
\[ \delta = 0.00\text{ and }1.10\text{ (s, 3H, SiCH3), 0.67 (s, 9H, SiC(CH3)3), 1.38\text{ and }1.52\text{ (s, 3H, C(CH3)2O), 2.77 (m, 1H, C(O)CH2CH2), 2.97 (m, 1H, C(O)CH3CHH), 3.07-3.16 (m, 2H, C(O)CH2), 4.76 (dd, J = 8.5, 3.6 Hz, 1H, NCH), 5.53 (d, J = 5.8 Hz, 1H, NCH/PH), 5.67(d, J = 5.8Hz, 1H, NCH/PH), 7.23-7.60 (m, 5H, Ph-H). 9.73 (s, 1H, NCHN) ppm.} \]

\(^13\text{C NMR (75MHz, CDCl3)}: \)
\[ \delta = -2.7\text{ and }-2.2\text{ (Si(CH3)2), 17.5 (Si(CH3)3), 21.6 (C(N)CH2CH2), 25.3 (Si(CH3)3), 26.2 (OC(CH3)2), 27.3 (OC(CH3)2), 28.6 (C(N)CH2), 56.4 (PhCH2N), 70.0 (NCHCH2), 73.9 (OC(CH3)2), 108.5, 128.6, 128.8, 129.0, 129.1, 129.2, 132.1 (Ph-C), 138.9 (NCHN), 143.6, 144.1 (Ph-C), 162.8 (C(N)CH2) ppm.} \]

IR (KBr):
\[ \nu = 3950\text{ (w), 3866 (w), 3743 (w), 3649 (w), 3563 (w), 3452 (w), 3392 (w), 3306 (w), 3139 (m), 3036 (m), 2951 (m), 2856 (m), 2812 (w), 2361 (w), 1833 (w), 1648 (w), 1586 (m), 1532 (w), 1459 (m), 1379 (m), 1258 (m), 1218 (w), 1183(w), 1047 (s), 931 (w), 882 (m), 835 (m), 757 (s), 618 ppm.} \]

132
(w), 522 (m).

MS (ESI): m/z (%) = 372.1 (100, M⁺), 240.0 (1), 87.3 (100, BF₄⁻);

HRMS: m/z calcd for [C₂₁H₃₄N₃OSi - 215; found: 370.2309.

(S)-5-Benzhydryl-2-benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (170).

According to GP 7, lactam 143 (0.50g, 2.5 mmol) was used, the 170 was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 0.45 g, 1 mmol, (40 %).
TLC: Rf = 0.4 (PE:EtOAc= 1:1).
Optical rotation: [α]D²³ = +29.5 (c 1.01, CHCl₃).

¹H NMR (300MHz, CDCl₃):
δ = 2.40-2.58 (m, 1H, NCH₂H), 2.80-3.15 (m, 3H, NCHCH₂CH₂), 3.45 (t, J = 7.2Hz, 2H, PhCH₂N), 4.10 (d, J = 7.2Hz, 1H, Ph₂CH), 5.70 (m, 1H, NCH₂), 7.10-7.40 (m, 15H, Ph-H), 7.55 (s, 1H, NCH₂) ppm.

¹³C NMR (75MHz, CDCl₃):
δ = 20.7 (NCH₂CH₂), 32.3 (C(N)CH₂), 55.0 (Ph₂CH), 56.7 (PhCH₂N), 64.2 (NCH₂), 127.7, 127.9, 128.0, 129.0, 129.1, 129.2, 129.4, 129.5 (Ph-C), 131.0(NCH₂), 162.0 (C(N)CH₂) ppm.

IR (KBr):
ν = 3851 (w), 3747 (w), 33431 (s), 3030 (m), 2928 (m), 2729 (vw), 2541 (vw), 2455 (vw), 2366 (w), 2359 (w), 2344 (w), 2321 (vw), 2089 (vw), 1968 (vw), 1895 (m), 1830 (vw), 1674 (m), 1588 (m), 1533 (vw), 1496 (m), 1453 (m), 1386 (w), 1296 (w), 1078 (s), 914 (vw), 871 (vw), 818 (vw), 706 (s), 616 (w), 566 (vw), 522 (m), 464 (w) cm⁻¹.

MS (ESI): m/z (%) = 366.2 (80, M⁺), 339.1 (85), 265.1 (15), 91.1 (10). m/z (%) = 87.3(100, BF₄⁻).

ms² (366.2.1): m/z (%) = 288.1 (85), 198.2 (100), 193.1 (11.7), 186.1 (51), 181.1 (72), 179.4 (29), 167.2 (94), 129.2 (5).
Experimental part

HRMS: m/z calcd for [C_{25}H_{24}N_3 -2H, M^-2]: 369.1814; found: 369.1814.

The lactam 175a and 175b were prepared according to the literature, all the spectra were correct in accordance with the literature.

(R)-2-Benzyl-5-isopropyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (176a).

According to GP 7, lactam 175a (0.64 g, 5 mmol) was applied, the 176a was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 1.5 g, 4 mmol, (68%).
TLC: R_f = 0.25 (PE:EtOAc= 1:1).
Optical rotation: [α]_D^23 = +28.3 (c 1.01, CHCl_3).

^1H NMR (300MHz, CDCl_3):
δ = 0.75 (d, J = 6.6Hz, 3H, CH(CH_3)_2), 0.84 (d, J = 6.6Hz, 1H, CH(CH_3)_2), 2.02-2.14 (m, 1H, CH(CH_3)), 2.25-2.38 (m, 1H, NCHCHH), 2.84-2.94 (m, 2H, C(N)CH_2CH_2), 4.44-4.57 (m, 1H, NCHCH_2), 5.34 (s, 2H, PhCH_2N), 7.12-7.24 (m, 3H, Ph-<H), 7.28-7.58 (m, 2H, Ph-<H), 9.52 (s, 1H, NCHN) ppm.

^13C NMR (75MHz, CDCl_3):
δ = 16.7 (CH(CH_3)_2), 18.0 (CH(CH_3)_2), 21.4 (C(N)CH_2CH_2), 29.1 (C(N)CH_2CH_2), 31.0 (CH(CH_3)_2), 56.3 (PhCH_2N), 65.9 (NCHCH_2), 128.9, 129.1, 19.2, 132.2 (Ph-C), 138.7 (NCHN), 162.1 (C=N) ppm.

IR (KBr):
v = 3738 (vw), 3648 (vw), 3392 (vw), 3305 (vw), 3138 (w), 3036 (w), 2969 (m), 2878 (vw), 2363 (vw), 1695 (w), 1585 (m), 1528 (w), 1498 (vw), 1457 (m), 1398 (m), 1286 (w), 1172 (m), 1062 (s), 870 (vw), 87 (vw), 754 (s), 708 (m), 665 (m), 522 (m) cm^{-1}.

MS (ESI): m/z (%) (+) = 242.1 (100, M^+); 91.2 (20). m/z (%) (-) = 87.3(100, BF_4).

m^2 (242.1): m/z (%) = 157.0 (100), 145.1 (5).

HRMS: m/z calcd for [C_{13}H_{20}N_3 -2H, M^-2]: 240.1501; found: 240.1503.
(R)-2,5-Dibenzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (176b).

According to GP 7, lactam 175b (0.88 g, 5 mmol) was used, the 176b was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 1.5 g, 4 mmol, (80%).
TLC: Rf = 0.30 (PE:EtOAc = 1:1).
Optical rotation: [α]D23 = +31.8 (c 1.01, CHCl3).

$^1$H NMR (300MHz, CDCl3):
$\delta$ = 2.40 (m, 1H, C(O)CH$_2$CH$_2$), 2.78 (m, 2H, C(O)CH$_2$), 2.91 (m, 1H, C(O)CH$_2$CHH), 3.28 (dd, $J$ = 14.0, 4.7Hz, 1H, CHCH$_2$Ph), 3.65 (dd, $J$ = 14.0, 4.7Hz, 1H, CHCH$_2$Ph), 5.02 (m, 1H, NCH), 5.39 (s, 2H, NCH$_2$Ph), 7.05-7.20 (m, 5H, Ph-H), 7.27-7.43 (m, 5H, Ph-H), 9.39 (s, 1H, NCHN) ppm.

$^{13}$C NMR (75MHz, CDCl3):
$\delta$ = 21.1 (C(N)CH$_2$), 32.0 (C(N)CH$_2$CH$_2$), 39.4 (PhCH$_2$CH), 56.4 (PhCH$_2$N), 61.1 (PhCH$_2$CHN)$_2$, 127.4, 128.9, 129.0, 129.1, 129.2, 132.0, 134.4 (Ph-C), 138.5 (NCHN), 161.8 (C(N)N) ppm.

IR (KBr):
$\nu$ = 3955 (w), 3544 (w), 3139 (w), 3033 (m), 1687 (m), 1586 (m), 1529 (w), 1496 (w), 1451 (m), 1388 (w), 1289 (w), 1218 (w), 1171 (s), 1062 (s), 871 (w), 755 (s), 709 (m), 665 (w), 612 (w), 519 (w), 460 (w) cm$^{-1}$.

MS (ESI): m/z (%) = 290.3 (100, M$^+$), 200.6 (5), 91.2 (5), m/z (%) = 87.3 (100, BF$_4$). ms$^2$ (290.1): m/z (%) = 291.1 (5), 212.1 (20), 198.1 (10), 186.1 (10), 181.1 (20), 110.1 (5), 91.1 (100).

HRMS: m/z calcd for [C$_{19}$H$_{20}$N$_3$O - 2H, M$^+$-2] = 288.1501; found: 288.1501.

(6aR, 11aS)-9-[Benzy1-6,6a,7,11a-tetrahydro-5H-benzo[9][1,2,4]triazolo[4,3-a]indol-9-ium] tetrafluoroborate (179)
According to GP 7, the lactam (0.93 g, 5 mmol) was applied, the 179 was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 1.26 g, 3.2 mmol, 65%.
TLC: Rf = 0.30 (PE:EtOAc= 1:1).
Optical rotation: [α]D23 = +73.2 (c 1.01, CHCl3).

1H NMR (300MHz, CDCl3):
δ = 1.01-1.33 (m, 1H, CArCH2CH2), 1.41-1.62 (m, 1H, CArCH2CH2), 1.80-2.08 (m, 1H, C(N)CHHCH), 3.23-3.50 (m, 2H, CArCH2CH2), 5.43 (s, 2H, PhCH2N), 5.82 (d, J = 5.8Hz, 1H, NCHCMe), 7.10-7.58 (m, 9H, Ph-H), 7.71 (d, J = 7.2Hz, 1H, NCHCMeCMeH), 9.60 (s, 1H, NCHN) ppm.

13C NMR (75MHz, CDCl3):
δ = 25.3 (CArCH2CH2), 25.4 (C(N)CH2CH2), 28.1 (CArCH2CH2), 40.6 (C(N)CH2CH2), 56.3 (PhCH2N), 60.8 (NCHCMe), 127.8, 128.1, 128.5, 129.2, 129.9, 132.1, 137.2, (Ph-C), 138.5 (NCHN),160.6 (CH2C=CH) ppm.

IR (KBr):
ν = 3928 (w), 3880 (w), 3829 (w), 3780 (w), 3724 (w), 3658 (w), 3444 (m), 3129 (m), 3093 (m), 3032 (m), 2944 (m), 2853 (m), 2680 (vw), 2345 (vw), 2293 (vw), 2180 (vw), 1970 (vw), 1815 (vw), 1673 (m), 1589 (s), 1526 (m), 1498 (m), 1452 (m), 1382 (m), 1341 (w), 1289 (m), 1065 (s), 875 (m), 811 (w), 522 (m), 482 (vw), 457 (w) cm⁻¹.

MS (ESI): m/z (%, +) = 302.4 (100, M⁺); 297.5 (5), 265.4 (5), 235.3 (2), 203.3 (3),91.1 (15). m/z (%, BF₄⁻) = 87.3(100, BF₄⁻).

ms² (302): m/z (%) = 224.1 (20), 219.0 (60),210.1 (100), 198.1 (20), 172.1 (5), 141.2 (10), 17.1 (5), 91.1 (70).

ms³ (488/410): m/z (%) = 183.1 (10), 141.1 (100), 81.9 (10).

HRMS: m/z calcd for [C₂₀H₂₀N₃·2H⁺, M⁺-2]: 300.1501; found: 300.1496.

(S)-2-Benzhydryl-5-((triisopropylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol 1-2-ium tetrafluoroborate (181)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{BF}_4^- & \quad \text{OTIPS}
\end{align*}
\]

According to GP 7, the TIPS protected lactam 152 (1.35 g, 5 mmol) was used, and
Experimental part

benzhydrolydrazine replaced the benzylhydrazine in the procedure. The 181 was purified by recrystallization from EtOAc and obtained as colorless solid.

Yield: m = 1.39 g, 2.5 mmol, (51%).
Melting point = 174°C.
TLC Rf = 0.60 (PE:EtOAc= 1:1).
Optical rotation: [α]D23 = –80.0 (c 1.01, CHCl3).

1H NMR (300MHz, CDCl3):
δ = 0.87 (s, 3H, Si(CH(CH3)2)3), 0.89 (s, 18H, Si(CH2)3), 2.57–2.67 (m, 1H, NCHCH2), 2.93-3.06 (m, 1H, NCHHH), 3.13 (t, J = 6.9 Hz, 2H, C(N)CH2), 3.84 (dd, J = 11.4, 3.8 Hz, 1H, SiOCHHCH), 4.20 (dd, J = 11.4, 3.8 Hz, 1H, SiOCHHCH), 5.10 (m, 1H, NCHCH2), 6.92 (s, 1H, NH2), 7.28-7.46 (m, 10H, Ph-H), 9.40 (s, 1H, NHN) ppm.

13C NMR (75MHz, CDCl3):
δ = 11.6 (Si(CH(CH3)2)3), 17.7 (Si(CH(CH3)2)3), 22.3 (NCHCH2), 29.7 (C(N)CH2), 62.1 (NCHCH2), 64.6 (SiOCH2CH), 71.1 (Ph2CHN), 128.3, 128.6, 129.3, 129.3, 129.4, 135.4 (Ph-C), 139.2 (NCHN), 163.3 (C=NCH2) ppm.

IR (KBr):
v = 3858 (m), 3745 (m), 3662 (m), 3444 (m), 3131 (m), 3026 (vw), 2946 (s), 2867 (m), 2730 (w), 2608 (vw), 2464 (vw), 2378 (vw), 2345 (vw), 2217 (w), 1916 (vw), 1835 (vw), 1738 (w), 1695 (m), 1648 (m), 1585 (m), 1513 (m), 1459 (m), 1391 (m), 1297 (w), 1250 (w), 1115 (s), 877 (m), 696 (s), 520 (w), 462 (m) cm⁻1.

MS (ESI): m/z (% , +) = 462.1 (100, M+); 167.2 (20). m/z (% , -) = 87.3(100, BF4).


(S)-2-Amino-3-phenylpropan-1-ol (182).

To a cold solution of lithium borohydride (1.32 g, 60.54 mmol) in THF (30 mL) was cooled to 0°C, and l-phenylalanine (5.00 g, 30.27 mmol) was added slowly. The ice/water bath was removed, and the reaction mixture was stirred overnight. The mixture was again cooled to 0 °C, and methanol (45 mL) was added dropwise, followed by 2.5 M aqueous sodium hydroxide (25 mL). This mixture was evaporated in vacuo, and the residue was extracted with DCM. The combined extracts were dried (Na2SO4), filtered, and evaporated in vacuo to leave a white crystalline solid.

Yield: 4.1 g, 27.2 mmol, (90%).
Experimental part

Melting point = 90 °C.

TLC R\(_f\) = 0.10 (PE:EtOAc = 1:1).

Optical rotation: \(\left[\alpha\right]_{D}^{23} = -25.5\) (c 1.01, MeOH).

\(^1\)H NMR (400MHz, CDCl\(_3\)):

\(\delta = 1.90\) (brs, 2H, NH\(_2\)), 2.51 (dd, \(J = 13.5, 8.8\) Hz, 1H, PhCH\(_{2}\)H), 2.79 (dd, \(J = 13.5, 5.2\) Hz, 1H, PhCH\(_{2}\)H), 3.11 (m, 1H, CH\(_{2}\)NH\(_2\)), 3.3 2Hz, 1H, C\(_{2}\)H\(_{2}\)OHOH), 3.63 (dd, \(J = 10.5, 3.8\) Hz, 1H, CH\(_{2}\)OH), 6.95-7.32 (m, 5H, Ph-H) ppm.

\(^{13}\)C NMR (100MHz, CDCl\(_3\)):

\(\delta = 41.0\) (PhCH\(_{2}\)CH), 54.2 (NH\(_2\)C\(_{2}\)H), 66.4 (HO\(_{2}\)C\(_{2}\)H), 126.4, 128.5, 129.2, 138.6 (Ph-C) ppm.

All other analytical data correspond to those described in the literature.\(^{119}\)

(S)-5-(Phenylmethyl)-3-morpholinone (184)

\[\text{Ph} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{O}
\end{array} \]

A 250 mL round bottom flask was charged with 60 mL of a 0.5M aqueous solution of NaOH, to which was added 2.14 g (14.2 mmol, 1.0 equiv.) of (S)-phenylalanine in 15 mL of dichloromethane. The resulting solution was cooled in an ice-water slush bath and a solution of 1.6 mL (20 mmol, 1.4 equiv.) chloroacetyl chloride in 18 mL of dichloromethane was added over a 10 min. period. The ice bath was removed and the resulting mixture was stirred vigorously for 3 h. The layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic phases were dried with sodium sulfate, filtered, and the dichloromethane was removed by rotary evaporation give the crude amide as solid. Under a nitrogen atmosphere, a 100 mL flask was charged with 25 mL of dry tetrahydrofuran, cooled in an ice-water slush bath, and 0.38 g (16 mmol, 1.2 equiv.) of sodium hydride was added. To the resulting suspension a solution of the crude product described above (2.88 g, 12.7 mmol, 1.0 equiv.) dissolved in 25 mL of THF was added with a syringe. The ice bath was removed and the mixture was stirred at r. t. for 72 h. Water (20 mL) was then carefully added to the reaction and the THF was removed by rotary evaporation. The resulting solution was diluted with brine and extracted three times with diethyl ether. The combined organic layers were dried with sodium sulfate and the ether was removed under reduced pressure giving the crude product which was purified by chromatography (PE/EtOAc = 1:1).

Yield: 2.0 g, 11.9 mmol (84%), crystalline solid.

Melting point = 90 °C.

TLC R\(_f\) = 0.20 (PE:EtOAc = 1:1).

Optical rotation: \(\left[\alpha\right]_{D}^{25} = +4.5\) (c 1.01, MeOH).

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(\delta = 2.65\) (dd, \(J = 9.1, 13.5\) Hz, 1H, PhCH\(_{2}\)CH), 2.80 (dd, \(J = 5.8, 13.5\) Hz, 1H, PhCH\(_{2}\)CH), 3.50
Experimental part

(dd, $J = 6.5, 11.2$ Hz, 1H, NCHCHH), 3.70 (m, 1H, NCHCHH), 3.93 (dd, $J = 3.8, 11.7$ Hz, 1H, NCHCHH), 4.10 (d, $J = 3.5$ Hz, 2H, C(O)CH$_2$O), 6.0 (brs, 1H, NH), 7.18 - 7.30 (m, 5H, Ph-H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta$ = 39.2 (PhCH$_2$CH), 52.6 (NH), 67.2 (NCHCH$_2$O), 67.6 (C(O)CH$_2$O), 126.5, 127.0, 128.5, 128.8, 129.0, 129.1, 135.8 (Ph-C), 168.9 (C(O)NH) ppm.

All other analytical data correspond to those described in the literature.

(S)-2,5-Dibenzyl-6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (188a)

According to GP 7, the products 188a was purified by recrystallization from EtOAc and obtained as colorless solid.

Yield: m = 0.34 g, 0.86mmol (84%), Crystals.

Melting point = 132°C.

TLC $R_f$ = 0.20 (EtOAc).

Optical rotation: $[\alpha]_{D}^{23}$ = −46.5 (c 1.01, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ = 1.69 (dd, $J = 13.6, 9.4$ Hz, 1H, PhCHHCH), 3.37 (dd, $J = 13.6, 9.4$ Hz, 1H, PhCHHCH), 3.95 (d, $J = 1.4$ Hz, 2H, CHCH$_2$O), 4.79 (m, 1H, NCHBn), 4.80 (d, $J = 1.6$ Hz, 1H, NCHHPh), 4.96 (d, $J = 16.1$ Hz, 1H, NCHHPh), 5.40 (s, 2H, N$_2$CCH$_2$O), 7.13-7.22 (m, 5H, Ph-H), 7.33-7.40 (m, 5H, Ph-H), 9.37 (s, 1H, NCHNH) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta$ = 38.4 (PhCH$_2$CHN), 56.2 (PhCH$_2$N), 56.8 (NCHCH$_2$O), 61.9 (NCH$_2$C(N)), 65.5 (OCH$_2$CHN), 127.6, 127.7, 129.1, 129.2, 129.3, 129.4, 129.5, 131.6, 134.5 (Ph-C), 141.3 (NCHN), 149.4 (C=N) ppm.

IR (KBr):
$\nu$ = 3853 (vw), 3744 (vw), 3673 (vw), 3437 (m), 3176 (w), 3063 (w), 3030 (w), 2959 (w), 2854 (w), 2361 (w), 2340 (w), 1978 (vw), 1898 (vw), 1831 (vw), 1735 (vw), 1696 (vw), 1537 (m), 1545 (m), 1496 (m), 1453 (m), 1402 (w), 1370 (m), 1305 (w), 1190 (m), 1160 (s), 1062 (s), 941 (w), 903 (w), 868 (w), 830 (w), 761 (m), 709 (m), 638 (w), 596 (w), 521 (w), 501 (w) cm$^{-1}$. 

139
Experimental part

MS (ESI): \( m/z = 306.1 \) (100, M\(^+\)), 240.0 (1), 87.3 (100, BF\(_4^-\));

Anal. Calcd. for C\(_{19}\)H\(_{20}\)N\(_3\)O\(^+\)BF\(_4^-\): C, 58.04; H, 5.13; N, 10.69; Found C, 58.05; H, 5.66; N, 10.42.

**(S)-2-Amino-1,1,3-triphenylpropan-1-ol (186)**

L-Phenylalanine was treated by thionyl chloride in methol to form the corresponding aminoacid ester salt. The aminoacid ester salt (2.15g, 10mmol) was suspended in Et\(_2\)O(50 mL) and extracted with 1 M NaOH solution (1.5 equiv.). The aq. phase was separated and extracted with Et\(_2\)O, the organic phases were dried (MgSO\(_4\)) and evaporated. A solution of the resulting amino-acid ester in Et\(_2\)O (20 mL) was added to a solution of PhMgBr (5 equiv.; freshly prepared from Mg and PhBr) in Et\(_2\)O (1.2m) over a period of 30 min. After addition to the Grignard reagent, the mixture was refluxed for 6 h. Excess PhMgBr and Mg salts were hydrolyzed by careful addition of ice and H\(_2\)O, then NH\(_4\)Cl solutions, then extracted with EtOAc, and the solvents were removed, recrystallized in EtOAc to yield the amino alcohols.

Yield: m = 3.0 g, 7.2 mmol, (72%).
Melting point = 140 °C. Colorless solid.
TLC: \( R_f = 0.2 \) (PE : Et\(_2\)O = 1:1).
Optical rotation: \([\alpha]\)\(_D\)\(^{23} = -87.2 \) (c 1.01, CHCl\(_3\)).

\(^1\)H NMR (400MHz, CDCl\(_3\)):
\[ \delta = 2.47 \text{ (dd, } J = 14.1, 10.9\text{Hz, 1H, PhCHHCH}), 2.68 \text{ (dd, } J = 14.1, 2.5\text{Hz, 1H, PhCHHCH}), 4.21 \text{ (dd, } J = 10.9, 2.7\text{Hz, 1H, PhCH}_2\text{CH}), 7.18-7.38 \text{ (m, 10H, Ph-H), 7.61-7.70 \text{ (m, 5H, Ph-H)} \text{ ppm.}} \]

\(^13\)C NMR (100MHz, CDCl\(_3\)):
\[ \delta = 36.8 \text{ (PhCH}_2\text{CH), 58.2 \text{ (NH}_2\text{CH), 78.5 \text{ (Ph}_2\text{C(OH)CH}_2\text{), 125.4, 125.8, 126.5, 126.6, 126.8, 127.6, 128.3, 128.5, 128.7, 129.1, 139.7, 144.4, 146.9 \text{ (Ph-C)} \text{ ppm.}} \]
All other analytical data correspond to those described in the literature.\(^{121}\)

**(S)-5-Benzyl-6,6-diphenylmorpholin-3-one (187).**

According to the procedure for 184, the title compound 187 was obtained as colorless solid.
Yield: m = 148 mg, 0.42 mmol (85%).
Melting point = 189 °C. Colorless solid.
TLC: Rf = 0.35 (PE : Et2O = 1:1).
Optical rotation: [α] D23 = −434.7 (c 1.01, CHCl3).

1H NMR (400 MHz, CDCl3):
δ = 1.54 (brs, 1H, NH), 2.65 (dd, J = 13.6, 11.1 Hz, 1H, PhCHHCHNH), 3.40 (dd, J = 13.6, 7.2 Hz, 1H, PhCHHCHNH), 4.31 (d, J = 15.5 Hz, 2H, C(O)CH2O), 5.90 (d, J = 3.4 Hz, 1H, NCH), 7.13-7.36 (m, 10H, Ph-H) ppm.

13C NMR (100 MHz, CDCl3):
δ = 39.2 (PhCH2CH), 57.2 (NCH), 63.9 (OCH2C(O)), 80.1 (OCPh2), 125.3, 126.9, 127.2, 127.5, 127.9, 128.5, 128.8, 128.9, 137.6, 140.2, 143.2 (Ph-C), 168.1 (C(O)NH) ppm.

IR (KBr):
v = 3486 (vw), 3174 (m), 3060 (m), 3026 (m), 2955 (m), 2917 (m), 2189 (vw), 1952 (vw), 1878 (vw), 1809 (vw), 1681 (s), 1601 (m), 1490 (m), 1446 (m), 1413 (m), 1319 (m), 1264 (w), 1227 (vw), 1183 (w), 1129 (w), 1080 (m), 1028 (w), 936 (w), 909 (w), 879 (w), 805 (w), 697 (w), 649 (vw), 623 (w), 572 (w), 519 (w), 486 (vw), 458 (w) cm⁻¹.

MS (EI, 70 eV): m/z (%) = 343.1 (2, M⁺), 252.1 (100), 194.1 (15), 167.0 (55), 161.1 (75), 149.0 (30), 133.1 (30), 118.2 (15), 105.0 (25), 91.1 (40), 83.0 (40), 71.3 (20), 57.3 (45).

Elemental Analysis: Anal. Calcd for C23H21NO2: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.24; H, 6.60; N, 4.03.

(S)-2,5-Dibenzyl-6,6-diphenyl-6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (188b).

According to GP 7, the 188b was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as a thick oil.

Yield: m = 0.36g, 6.4 mmol (64%), light yellow oil.
TLC Rf = 0.60 (EtOAc).
Optical rotation: [α] D23 = −310.2 (c 1.01, CHCl3).
Experimental part

$^1$H NMR (400MHz, CDCl$_3$):
$\delta$ = 2.62-2.76 (m, 2H, PhCH$_2$CHN), 4.60 (d, $J$ = 17.0 Hz, 1H, PhCHHN), 5.06 (d, $J$ = 14.3Hz, 1H, PhCHHN), 5.20 (dd, $J$ = 19.5, 17.1Hz, 2H, OCH$_2$C(N)), 6.79 (d, $J$ = 6.8Hz, 2H, Ph-H), 6.96-7.40 (m, 18H, Ph-H), 8.54 (s, 1H, NCHN) ppm.

$^{13}$C NMR (100MHz, CDCl$_3$):
$\delta$ = 37.7 (PhCH$_2$CH), 56.4 (PhCH$_2$N), 57.6 (OCH$_2$), 60.8 (NCH), 81.3 (OCPh$_2$), 127.1, 127.9, 128.0, 128.4, 128.7, 128.9, 129.0, 129.2, 129.3, 131.4, 134.3, 136.8, 140.5 (Ph-C), 141.2 (NCHN), 148.2 (Ph-C-N), 171.1 (C(N)) ppm.

IR (KBr):
$\nu$ = 3633 (m), 3555 (m), 3062 (s), 2967 (s), 2867 (vw), 2596 (vw), 2348 (vw), 2263 (vw), 2122 (vw), 1967 (w), 1892 (w), 1822 (w), 1728 (m), 1671 (m), 1575 (s), 1493 (m), 1448 (s), 1407 (m), 1359 (m), 1278 (m), 1232 (w), 1015 (s), 913 (m), 853 (m), 744 (s), 647 (m), 569 (m), 526 (m), 463 (m) cm$^{-1}$.

MS (EI, 70eV): $m/z$ (%) = 458.3 (20, M$^+$), 366.2 (6), 323.2 (15), 274.2 (15), 252.1 (10), 184.2 (912), 170.1 (15), 105.2 (25), 91.2 (100), 77.2 (15), 49.3 (27).

HRMS: $m/z$ calcd for [C$_{31}$H$_{28}$N$_3$O-2H, M$^+$-2]: 456.2076; found: 456.2062.

(S)-(+) Lysine methyl ester dihydrochloride (189)

To a suspension of (S)-lysine monohydrochloride (50.0 g, 274 mmol) in methanol (400 mL), was added 2,2-dimethoxypropane (350 mL) and concentrated hydrochloric acid (90 mL). The mixture was refluxed for 3 hours, then stirred at room temperature overnight. The solvent removed in vacuo. The remaining oil was dissolved in a minimum of methanol, to which was then added ice-cold ether (450 mL). After standing for 30 minutes, a precipitate formed and was filtered at suction, recrystallised from methanol and then washed with ice-cold ether to give crystals.

Yield: m = 58.5 g, 252 mmol, 92%.
Melting point: 207 °C

(S)-(++) Di-N-(tert- bu tyloxycar bonyl)lysine methyl ester (190).
To a solution of (S)-lysine methyl ester dihydrochloride salt (6.58 g, 28.2 mmol) in methanol (140 mL) was added di-tert-butyl dicarbonate (13.3 g, 2.1 eq) and sodium bicarbonate (14.12 g). The mixture was sonicated for 3 hours, the solution filtered and the solvent removed in vacuo. The residue was redissolved in ether, a plug of celite and the solvent removed in vacuo. The resulting oil was used without further purification.

\((S)\) - (\(+\))-Di-N-(tert-butloxy carbonyl)adipamide methyl ester (191).

\[
\begin{align*}
\text{BocHN} & \quad \text{OMe} \\
\text{Boc} & \quad \text{NHBoc}
\end{align*}
\]

To a vigorously stirred solution of sodium metaperiodate (13.8 g, 5 eq) and RuCl\(_3\) (0.23 g, 0.075 eq) in water (520 mL) was added the \(N\)-Boc methyl ester 190 prepared above (4.65 g, 12.9 mmol) in ethyl acetate (170 mL), and buffered to pH = 4.5 using potassium hydrogen phthalate. The biphasic system was stirred vigorously at room temperature overnight: The ethyl acetate layer was separated and the aqueous portion extracted with ethyl acetate (3 \(\times\) 85 mL). The organic extracts were combined and isopropyl alcohol (9.3 mL) added. The mixture was stirred for 3 hours. The fine RuO\(_2\) suspension was removed by filtering through a plug of celite and solvent removed in vacuo. The orange oil was dissolved up in ethyl acetate (70 mL), washed with 10\% citric acid (2 \(\times\) 30 mL) and dried over sodium sulphate. The solvent was removed in vacuo, and the crude product purified via flash column chromatography (PE/EtOAc = 2:1) to give the title compound as a solid.

Yield: \(m = 3.6 g, 9.5 \text{ mmol}, 74\%\).

TLC \(R_f = 0.40\) (PE : EtOAc = 1:1).

Optical rotation: \([\alpha]_D^{23} = + 9.5 \ (c 1.01, \text{CHCl}_3)\).

\((S)-(\text{-})\)-Methyl 6-oxo-2-piperidinecarboxylate (192).

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{OMe} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

The methyl adipamide (1.95 g, 5.42 mmol) was dissolved in trifluoroacetic acid (50 mL) and then refluxed overnight for 14 hours. The solvent was removed in vacuo, and the crude oil redissolved in chloroform (90 mL), washed with 10\% sodium bisulphate (2 \(\times\) 20 mL), brine (20 mL) and dried over magnesium sulphate. The solvent was removed in vacuo and the yellow oil without further purification.

TLC \(R_f = 0.30\) (PE : EtOAc = 1:1).
Experimental part

(S)-6-(Hydroxymethyl)piperidin-2-one (193)

To a solution of lactam ester 192 (0.81 g, 5.17 mmol) in ethanol (50 mL) was added sodium borohydride (0.25 g, 1.2 eq). The solution was stirred for 3.5 hours at room temperature. The mixture was acidified to pH = 4 using glacial acetic acid and the precipitate removed by filtering through a plug of celite. The solvent was removed in vacuo. The resulting oil was purified by flash column chromatography, eluting with 10% methanol/ethyl acetate, to yield the title compound.

Yield: m = 0.650 g, 5.0 mmol, (98%), colorless oil.
TLC Rf = 0.10 (Methyl : EtOAc = 1:10).
Optical rotation: [α]D23 = + 20.1 (c 1.01, CHCl3).

1H NMR (400MHz, CDCl3):
δ = 1.29 (m, 1H, NCHCH2), 1.58 (m, 1H, NCHCHH), 1.75 (m, 2H, NC(O)CH2CH2), 2.15 (m, 1H, NC(O)CHH), 2.28 (m, 1H, NC(O)CHH), 3.36 (m, 2H, OCH2), 3.54 (m, 1H, NCH), 7.60 (brs, 1H, OH) ppm.

13C NMR (100 MHz, CDCl3):
δ = 19.1 (NCH2CH2), 24.1(NCH2CH2), 30.8 (C(O)CH2), 54.5 (NCH), 65.1 (OCH2), 174.3 (C(O)) ppm.
All other analytical data correspond to those described in the literature.122

(S)-6-((tert-Butyldiphenylsilyloxy)methyl)piperidin-2-one (194)

According to GP 5, the 194 was purified by column chromatography (silica gel, EtOAc/PE = 1:1) and obtained as colorless solid.

Yield: m = 102 mg, 0.33 mmol, (65%).
TLC Rf = 0.50 (PE : EtOAc = 1:1).
Optical rotation: [α]D23 = −7.1 (c 1.01, CHCl3).

1H NMR (400MHz, CDCl3):
δ = 1.05 (s, 9H, SiC(CH3)3), 1.25 (m, 1H, NCHCHHCH2), 1.69 (m, 2H, NCHCHHCHH), 1.84 (m, 1H, NCHCHHCHH), 2.26 (m, 1H, C(O)CHH), 2.41 (m, 1H, OCHHCH2), 3.46 (t, J = 9.8Hz, 1H, OCHHCH2), 3.50-3.58 (m, 1H, NCHCH2), 3.56 (dd, J = 9.3, 3.5Hz, 1H, OCHHCH2), 6.21 (brs, 1H, NH), 7.42 (m, 5H, Ph-H), 7.63 (m, 5H, Ph-H) ppm.
Experimental part

$^{13}$C NMR (100 MHz, CDCl$_3$):
\[ \delta = 19.3 \text{ (SiC(CH$_3$)$_3$)}, 19.8 \text{ (C(O)CH$_2$CH$_3$)}, 24.5 \text{ (NHCHCH$_2$)}, 26.9 \text{ (SiC(CH$_3$)$_3$)}, 31.7 \text{ (C(O)CH$_2$CH$_2$)}, 34.6 \text{ (NHCH$_2$CH$_2$)}, 67.7 \text{ (SiOCH$_2$)}, 127.8, 129.9, 132.7, 132.8, 135.5 \text{ (Ph-C)}, 171.7 \text{ (C(O)) ppm.} \]

All other analytical data correspond to those described in the literature.\(^{123}\)

(S)-2-Benzyl-5-((tert-butyldiphenylsilyloxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium tetrafluoroborate (195)

According to GP 7, the products 195 was purified by recrystallization from Et$_2$O and obtained as colorless solid.

Yield: m = 0.36 g, 6.4 mmol (64%).
Melting point = 141°C
TLC R$_f$ = 0.60 (EtOAc).
Optical rotation: [\(\alpha\)]$_D^{23}$ = -6.7 (c 1.01, CHCl$_3$).

$^1$H NMR (400MHz, CDCl$_3$):
\[ \delta = 0.72 \text{ (s, 9H, SiC(CH$_3$)$_3$)}, 1.76-2.04 \text{ (m, 4H, NCHCCH$_2$H$_2$)}, 2.76 \text{ (m, 1H, C(N)CHH)}, 2.97 \text{ (m, 1H, C(N)CHH)}, 3.72 \text{ (t, J = 6.3 Hz, 1H, NCHHPh)}, 3.95 \text{ (qq, J = 11.5, 4.9 Hz, 1H, NCHHPh)},
4.80 \text{ (m, 1H, 1H, NCHCH$_2$)}, 5.34 \text{ (t, J = 14.2 Hz, 2H, SiOCH$_2$CH)}, 7.26-7.66 \text{ (m, 15H, Ph-H)}, 9.32 \text{ (s, 1H, NCH/N) ppm.} \]

$^{13}$C NMR (100MHz, CDCl$_3$):
\[ \delta = 17.2 \text{ (C(N)CH$_2$CH$_2$), 19.2 \text{ (SiC(CH$_3$)$_3$)}, 21.4 \text{ (C(N)CH$_2$CH$_2$)}, 23.6 \text{ (NCHCH$_2$)}, 26.9 \text{ (SiC(CH$_3$)$_3$)}, 56.6 \text{ (PhCH$_2$N)}, 57.8 \text{ (NCHCH$_2$)}, 64.8 \text{ (SiOCH$_2$CH$_2$)}, 128.0, 128.1, 129.4, 129.6, 129.7, 130.2, 130.3, 131.2, 131.5, 135.3, 135.4 \text{ (Ph-C)}, 140.9 \text{ (NCHN), 153.2 (CH$_2$C(N)) ppm.} \]

IR (KBr):
\[ \nu = 3967 \text{ (vw), 3853 (w), 3745 (w), 3673 (w), 3440 (m), 3159 (w), 3047 (m), 2936 (m), 2888 (m), 2860 (m), 2693 \text{ (vw), 2346 (v), 2188 (vw), 1964 (vw), 1831 (vw), 1740 (vw), 1651 (w), 1580 (m), 1457 (m), 1431 (m), 1388 (w), 1362 (w), 1287 (vw), 1048 (s), 933 (vw), 884 (vw), 793 (m), 735 (m), 703 (s), 651 \text{ (vw), 613 (m), 501 (s) cm}^{-1}. \]

MS (ESI): m/z (%) (+) = 482.2 (100, M$^+$); 200.6 (5), 91.2 (5). m/z (%) (-) = 87.3(100, BF$_4$).
\[ \text{m/z}^2 (482): \text{m/z} (%) = 404.2 (100), 314 (10), 197.3 (10). \]
\[ \text{m/z}^3 (482/404): \text{m/z} (%) = 362.2 (10), 326.1 (100), 284.1 (28), 236.0 (42), 194.1 \]
(40), 192.2 (5).
ms^4(482/404/326): m/z (%) = 302.2 (5), 284.2 (100), 226.0 (10), 168.1 (5).

Elemental Analysis: Anal. Calcd for C_{30}H_{36}N_{3}O Si^{+} BF_4^- : C, 63.27; H, 6.37; N, 7.38. Found: C, 63.70; H, 6.68; N, 7.46.

\((R)-1,2,4\)-Triphenylbutane-1,4-dione (196a)

According to GP 8, the Stetter product 196a was purified by column chromatography (silica gel, Et\textsubscript{2}O/PE = 5:1).

Yield: m = 102 mg, 0.33 mmol, (65%).
TLC R\textsubscript{f} = 0.60 (PE : Et\textsubscript{2}O = 4:1).
GC: R\textsubscript{t} = 12.91 min (CP-Sil-8, 160-10-300).
Optical rotation: [\alpha]_D^{23} = –291.1 (c 1.01, CHCl\textsubscript{3}).

\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):
\(\delta = 3.22 \) (dd, \( J = 18.2, 3.6 \) Hz, 1H, PhC(O)CH\textsubscript{2}HCH), 4.14 (dd, \( J = 18.3, 10.2 \) Hz, 1H, PhC(O)CH\textsubscript{2}HCH), 5.24 (dd, \( J = 9.8, 3.8 \) Hz, 1H, PhCH\textsubscript{2}HCH), 7.12-7.64 (m, 12H, Ph-H), 7.90-8.22 (m, 3H, Ph-H) ppm.

\textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}):
\(\delta = 43.8 \) (PhC(O)CH\textsubscript{2}), 48.6 (PhCH\textsubscript{2}HCH), 127.3, 128.0, 128.1, 128.4, 128.5, 128.6, 128.8, 129.1, 129.9, 132.8, 133.2, 136.3, 138.5 (Ph-C), 197.9 (PhC(O)CH), 198.8 (PhC(O)CH\textsubscript{2}) ppm.

HPLC R\textsubscript{t} = 12.94 and 19.47 (Whelk.M, 250×4 mm, n-Hep/IP= 9:1, 0.7 mL/min)
R\textsubscript{t} = 12.94, ee = 65%. after recrystallization, ee > 99%.
All other analytical data correspond to those described in the literature.\textsuperscript{56}

\((R)-2,4\)-Diphenyl-1-p-tolylbutane-1,4-dione (196b)

HPLC Rt = 12.94 and 19.47 (Whelk.M, 250×4 mm, n-Hep/IP= 9:1, 0.7 mL/min)
R\textsubscript{t} = 12.94, ee = 65%. after recrystallization, ee > 99%.
All other analytical data correspond to those described in the literature.\textsuperscript{56}
According to GP 8, the Stetter products 196b was purified by column chromatography (silica gel, Et\textsubscript{2}O/PE = 5:1).

Yield: m = 69 mg, 0.21 mmol, (43%).
TLC R\textsubscript{f}= 0.65 (PE : Et\textsubscript{2}O = 4:1).
GC: R\textsubscript{t}= 13.33 min (CP-Sil-8, 100-10-300).
Optical rotation: [\alpha]_D^{23} = -251.4 (c 1.01, CHCl\textsubscript{3}).

\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):\n\delta = 2.26 (s, 3H, 4-CH\textsubscript{3}PhC(O)CH), 3.20 (dd, J=17.7, 3.7 Hz, 1H, PhC(O)CHCH), 4.12 (dd, J = 18.1, 9.9 Hz, 1H, PhC(O)CH/CH), 5.23 (dd, J = 9.9, 3.7 Hz, 1H, PhCH/CH\textsubscript{2}), 7.11-7.56 (m, 10H, Ph-H), 7.82-8.04 (m, 4H, Ph-H) ppm.

\textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}):\n\delta = 21.6 (4-CH\textsubscript{3}PhC(O)), 43.8 (PhC(O)CH\textsubscript{2}), 48.6 (PhCH/CH\textsubscript{2}), 125.4, 127.3, 128.2, 128.3, 128.6, 129.1, 129.2, 129.3, 129.6, 129.8,130.6, 131.1, 132.8, 133.2, 133.9, 136.6, 138.9, 143.7, 144.9 (Ph-C), 198.1 (4-MePhC(O)CH), 198.5 (PhC(O)CH\textsubscript{2}) ppm.

HPLC R\textsubscript{t} = 30.68 and 33.04 ((DAICLIA.M, 250×4.6 mm, n-Hep/IP= 9:1, 0.5 mL/min)\nR\textsubscript{t} = 33.04, ee = 79%. after recrystallization, ee > 99%.
All other analytical data correspond to those described in the literature.\textsuperscript{56}

\textbf{\textit{(R)}-2,4-Diphenyl-1-m-tolybutane-1,4-dione (196c)}

![Structure](image)

According to GP 8, the Stetter products 196c was purified by column chromatography (silica gel, Et\textsubscript{2}O/PE = 5:1).

Yield: m = 82mg, 0.25mmol, (50%);
TLC R\textsubscript{f}= 0.65 (PE : Et\textsubscript{2}O = 4:1).
GC: R\textsubscript{t}= 13.78 min (CP-Sil-8, 100-10-300).
Optical rotation: [\alpha]_D^{23} = -334.1 (c 1.01, CHCl\textsubscript{3}).

\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):\n\delta = 2.28 (s, 3H, 3-CH\textsubscript{3}PhC(O)CH), 3.22 (dd, J=17.7, 3.9 Hz, 1H, PhC(O)CH/CH\textsubscript{2}), 4.13 (dd, J = 18.1, 9.9 Hz, 1H, PhC(O)CH/CH), 5.25 (dd, J = 10.1, 3.7 Hz, 1H, PhCH/CH\textsubscript{2}), 7.12-7.54 (m, 10H,
Ph-\(H\)), 7.74-7.78 (m, 2H, Ph-\(H\)), 7.88-7.94 (m, 2H, Ph-\(H\)) ppm.

\(^{13}\)C NMR (75MHz, CDCl\(_3\)):
\[ \delta = 21.4 (3-\text{CH}_3\text{PhC(O)}), 43.9 (\text{PhC(O)}\text{CH}_2), 48.7 (\text{PhCHCH}_2), 126.2, 127.3, 128.2, 128.3, 128.4, 128.6, 129.0, 129.2, 129.4, 133.2, 133.7, 134.1, 136.5, 138.3, 138.7 (\text{Ph-C}), 198.1 (3-\text{MePhC(O)}\text{CH}), 199.1 (\text{PhC(O)}\text{CH}_2) \text{ ppm.} \]

HPLC \(R_t = 11.03\) and 18.39 (Whelk.M, 250×4 mm, n-Hep/IP= 9:1, 1.0 mL/min)
\[ R_t = 11.03, \text{ ee } = 70\%. \text{ after recrystallization, ee } = 98\%. \]
All other analytical data correspond to those described in the literature.\(^{56}\)

\((R)-1-(4\text{-Chlorophenyl})-2,4\text{-diphenylbutane-1,4-dione (196d)}\)

According to GP 8, the Stetter products 196d was purified by column chromatography (silica gel, Et\(_2\)O/PE = 5:1).

Yield: \(m = 95\text{mg}, 0.27 \text{mmol}, (55\%)\);
TLC \(R_f = 0.40\) (PE : Et\(_2\)O = 4:1).
GC: \(R_t = 14.42 \text{ min (CP-Sil-8, 100-10-300)}\).

\(^1\)H NMR (400MHz, CDCl\(_3\)):
\[ \delta = 3.22 \text{ (dd, } J = 18.9, 3.6 \text{ Hz, 1H, PhC(O)C/HHCH), 4.13 (dd, } J = 18.2, 10.2 \text{ Hz, 1H, PhC(O)CH/HHCH), 5.17 (dd, } J = 10.2, 3.6 \text{ Hz, 1H, PhCHCH}_2), 7.12-7.50 \text{ (m, 10H, Ph-}\(H\)), 7.86 - 7.92 \text{ (m, 4H, Ph-}\(H\)) \text{ ppm.} \]

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
\[ \delta = 44.0 (\text{PhC(O)}\text{CH}_2), 48.9 (\text{PhCHCH}_2), 127.5, 128.1, 128.8, 129.3, 130.3, 131.8, 133.3, 134.7, 136.3, 138.2, 139.3 (\text{Ph-C}), 197.6 (4-\text{ClPhC(O)}\text{CH}), 197.9 (\text{PhC(O)}\text{CH}_2) \text{ ppm.} \]

HPLC \(R_t = 15.76\) and 18.92 ((DAICLIA.M, 250×4.6 mm, n-Hep/IP= 9:1, 1.0 mL/min)
\[ R_t = 18.92, \text{ ee } = 56\%. \]
All other analytical data correspond to those described in the literature.\(^{56}\)
Experimental part

(R)-1-(4-Bromophenyl)-2,4-diphenylbutane-1,4-dione (196e).

According to GP 8, the Stetter products 196e was purified by column chromatography (silica gel, Et₂O/PE = 5:1).

Yield: m = 130mg, 0.34mmol, (68%); TLC Rₚ = 0.40 (PE : Et₂O = 4:1).

¹H NMR (400MHz, CDCl₃):
δ = 3.22 (dd, J = 18.1, 3.6 Hz, 1H, PhC(O)CHCH), 4.13 (dd, J = 18.2, 10.5 Hz, 1H, PhC(O)CHCH), 5.17 (dd, J = 10.4, 3.8 Hz, 1H, PhCH₃), 7.12-7.58 (m, 10H, Ph-H), 7.80-7.84 (m, 2H, Ph-H), 7.88-7.93 (m, 2H, Ph-H) ppm.

¹³C NMR (100 MHz, CDCl₃):
δ = 43.9 (PhC(O)CH), 48.8 (PhCCH), 127.5, 128.1, 128.6, 129.3, 130.4, 131.8, 133.3, 135.2, 136.3, 138.2 (Ph-C), 197.8 (4-BrPhC(O)CH), 197.9 (PhC(O)CH) ppm.

HPLC Rₜ = 15.76 and 18.04 (DAICLIA.M, 250×4.6 mm, n-Hep/IP = 7:3, 0.7 mL/min)
Rₜ = 18.04, ee = 70%. after recrystallization, ee = 90%.
All other analytical data correspond to those described in the literature. ⁵⁶

(R)-1-(Naphthalen-2-yl)-2,4-diphenylbutane-1,4-dione (196f)

According to GP 8, the Stetter products 196f was purified by column chromatography (silica gel, Et₂O/PE = 5:1).

Yield: m = 118mg, 0.32mmol, (65%); TLC Rₚ = 0.45 (PE : Et₂O = 4:1).
GC: Rₜ = 12.78 min (CP-Sil-8, 100-10-300).
Optical rotation: [α]D²³ = −106.7 (c 1.01, CHCl₃).
Experimental part

$^1$H NMR (400MHz, CDCl$_3$):
$\delta$ = 3.26 (dd, $J = 18.1$, 3.8 Hz, 1H, PhC(O)CHHCH), 4.19 (dd, $J = 18.1$, 9.8 Hz, 1H, PhC(O)CHHCH), 5.40 (dd, $J = 9.9$, 3.7 Hz, 1H, PhCH$_2$CH$_2$), 7.69-7.50 (m, 10H, Aroma-H), 7.65-8.05 (m, 6H, Aroma-H), 8.51 (s, 1H, Aroma-H) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta$ = 44.0 (PhC(O)CH$_2$), 48.9 (PhCH$_2$CH$_2$), 124.6, 126.5, 127.3, 127.6, 128.1, 128.2, 128.3, 128.4, 128.5, 129.2, 129.7, 130.7, 132.5, 133.3, 133.8, 135.5, 136.5, 138.7 (Aroma-C), 198.0 (Naphthyl-C(=O)), 198.8 (PhC(O)CH$_2$) ppm.

HPLC $R_t = 9.08$ and 10.11 (($DAICLIA.M, 250\times4.6$ mm, n-Hep/IP = 7:3, 0.7 mL/min)
$R_t = 10.11$, ee = 70%.
All other analytical data correspond to those described in the literature.$^{56}$

$(R)$-1-(Furan-2-yl)-2,4-diphenylbutane-1,4-dione (196g)

According to GP 8, the Stetter products 196g was purified by column chromatography (silica gel, Et$_2$O/PE = 5:1).

Yield: m = 148 mg, 0.49 mmol (98%).
TLC: $R_f = 0.20$ (PE : Et$_2$O = 4:1).
GC: $R_t = 12.76$ min (CP-Sil-8, 100-10-300).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta$ = 3.24 (dd, $J = 18.0$, 3.8 Hz, 1H, PhC(O)CHHCH), 4.09 (dd, $J = 18.1$, 10.1 Hz, 1H, PhC(O)CHHCH), 5.04 (dd, $J = 10.1$, 3.7 Hz, 1H, PhCH$_2$CH$_2$), 6.38 (m, 1H, Furyl-OC$_{Furyl}$), 7.10-7.50 (m, 10H, Ph-H), 7.80-7.98 (m, 2H, C$_{Furyl}$) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta$ = 42.8 (PhC(O)CH$_2$CH), 48.7 (PhC(O)CH$_2$CH), 112.3, 118.0, 127.1, 127.5, 128.2, 128.3, 128.4, 128.6, 128.8, 129.0, 133.3, 136.4, 138.3, 146.5 (Aroma-C), 187.7 (Furyl-C(O)CH), 197.8 (PhC(O)CH$_2$) ppm.

HPLC $R_t = 11.41$ and 12.49 (($DAICLIA.M, 250\times4.6$ mm, n-Hep/IP = 6:4, 0.7 mL/min)
$R_t = 12.49$, ee = 56%.
All other analytical data correspond to those described in the literature.$^{56}$
Experimental part

(R)-1-(Furan-2-yl)-2-methyl-4-phenylbutane-1,4-dione (196h)

![Structural formula of 196h]

According to GP 8, the Stetter products 196h was purified by column chromatography (silica gel, Et₂O/PE = 5:1).

Yield: m = 86 mg, 0.40 mmol (80%).
TLC: R_f = 0.30 (PE : Et₂O = 4:1).
GC: R_t = 10.82 min (CP-Sil-8, 100-10-300).

^1H NMR (300MHz, CDCl₃):
δ = 1.30 (d, J = 7.2 Hz, 3H, CH₃CH₂), 3.06 (d, J = 4.9 Hz, 1H, PhC(O)CH₂CH), 3.12 (d, J = 4.9 Hz, 1H, PhC(O)CH₂CH), 3.67 (dd, J = 17.81, 8.7 Hz, MeCH₂), 6.57 (dd, J = 3.7, 1.7 Hz, 1H, Furyl-OC₉F₅C₅F₅H), 7.28 (dd, J = 3.4, 0.7Hz, 1H, Furyl-OC₉F₅CH₅F₅H), 7.40-7.48 (m, 2H, Ph-₅H), 7.51-7.55 (m, 2H, Ph-₅H), 7.62 (dd, J = 1.7, 0.7Hz, 1H, Furyl-OC₉F₅CH₅F₅H ), 7.94-7.98 (m, 2H, Ph-₅H) ppm.

^13C NMR (75MHz, CDCl₃):
δ = 17.8 (CH₃CH₂), 36.9 (MeCH₂CH₂), 41.8 (MeCH₂CH₂), 112.3 (Furyl-OC₉F₅C₅F₅H), 117.6 (Furyl-OC₉F₅CH₅F₅H), 128.1, 128.6 (Ph-C), 136.6 (Furyl-OC₉F₅CH₅F₅H), 136.6, 146.5 (Ph-C), 152.0 (Furyl-OC₉F₅C₅F₅H), 192.1 (Furyl-OC₉F₅C₅F₅H), 198.2 (PhC(O)CH₂) ppm.

HPLC R_t = 8.67 and 13.30 (DAICLIA.M, 250×4.6 mm, n-Hep/IP= 6:4, 0.7 mL/min)
R_t = 8.67, ee = 38 %.
All other analytical data correspond to those described in the literature.⁵⁶

(R)-2-(4-Chlorophenyl)-1,4-diphenylbutane-1,4-dione (196j)

![Structural formula of 196j]

According to GP 8, the Stetter products 196j was purified by column chromatography (silica gel, Et₂O/PE = 5:1).

Yield: m = 99 mg, 0.26 mmol (57%).
TLC: R_f = 0.50 (PE : Et₂O = 4:1).
Optical rotation: [α]D^23 = −220.0 (c 1.01, CHCl₃).
Experimental part

$^1$H NMR (400MHz, CDCl$_3$):
$\delta$ = 3.22 (dd, $J = 18.2$, 4.1 Hz, 1H, PhC(O)CHCH), 4.08 (dd, $J = 17.9$, 9.8 Hz, 1H, PhC(O)CHHCH), 5.23 (dd, $J = 9.8$, 3.8 Hz, 1H, 4-ClPhCH), 7.14-7.52 (m, 10H, Ph-H), 7.87-7.96 (m, 4H, Ph-H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$):
$\delta$ = 43.8 (PhC(O)CH$_2$), 48.0 (4-PhCHCH$_2$), 128.1, 128.4, 128.5, 128.6, 128.8, 129.1, 129.3, 129.6, 129.9, 133.1, 133.3, 133.5, 136.2, 136.3, 137.1 (Ph-C), 197.6 (PhC(O)CH), 198.5 (PhC(O)CH$_2$) ppm.

HPLC $R_t$ = 10.02 and 15.63 (Whelk.M, 250×4 mm, n-Hep/IP= 7:3, 0.7 mL/min)

$R_t$ = 10.02, ee = 56%. after recrystallization, ee = 94%.

All other analytical data correspond to those described in the literature.

$(R)$-1,4-Diphenyl-2-p-tolylbutane-1,4-dione (196k)

![Chemical structure of (R)-1,4-Diphenyl-2-p-tolylbutane-1,4-dione](image)

According to GP 8, the Stetter products 196k was purified by column chromatography (silica gel, Et$_2$O/PE = 5:1).

Yield: $m = 123$mg, 0.37 mmol, (75%).

TLC: $R_f = 0.60$ (PE : Et$_2$O = 4:1).

$^1$H NMR (300MHz, CDCl$_3$):
$\delta$ = 2.21(s, 3H, 4-C$_6$H$_3$PhCH), 3.20 (dd, $J = 17.8$, 3.7 Hz, 1H, PhC(O)CHCH), 4.11 (dd, $J = 18.1$, 10.1 Hz, 1H, PhC(O)CHHCH), 5.21 (dd, $J = 10.1$, 3.7 Hz, 1H, 4-MePhCHCH$_2$), 7.04-7.51 (m, 10H, Ph-H), 7.88-7.97 (m, 4H, Ph-H) ppm.

$^{13}$C NMR (75MHz, CDCl$_3$):
$\delta$ = 21.0 (4-CH$_3$PhCH), 43.9 (PhC(O)CH$_2$CH), 48.3 (PhC(O)CH$_2$CH), 128.1, 128.2, 128.5, 128.6, 128.9, 129.9, 132.8, 133.2, 135.6, 136.5, 137.1(Ph-C), 198.2 (PhC(O)CHCH$_2$), 199.1 (PhC(O)CH$_2$CH) ppm.

All other analytical data correspond to those described in the literature.

HPLC $R_t$ = 9.05 and 13.81 (Whelk.M, 250×4 mm, n-Hep/IP= 7:3, 0.7 mL/min)

$R_t$ = 9.05, ee = 66%.

All other analytical data correspond to those described in the literature.
Experimental part

1,2-Diphenyl-2-(phenylamino)ethanone (204k).

According to GP 8, the Stetter products 204k was purified by column chromatography (silica gel, Et<sub>2</sub>O/PE = 5:1).

Yield: m = 67mg, 0.24 mmol, (47%).
TLC: R<sub>f</sub> = 0.20 (PE : Et<sub>2</sub>O = 1:1).
GC: R<sub>t</sub> = 19.71 min (CP-Sil-8, 100-10-300).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):
δ = 5.33 (brs, 1H, NH), 5.95 (s, 1H, PhC=NH), 6.60 (m, 3H, Ph-H), 7.04-7.30 (m, 5H, Ph-H), 7.35-7.50 (m, 5H, Ph-H), 7.95 (d, J = 7.7Hz, 1H, Ph-H) ppm.

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):
δ = 62.7 (PhCHNH), 113.5, 117.9, 128.2, 128.4, 128.7, 128.9, 129.1, 129.3, 133.4, 133.5, 135.1, 137.8, 146.2 (Ph-C), 197.1 (PhC(O)CH) ppm.

HPLC R<sub>t</sub> = 9.99 and 14.92 (Daicelod.M, 250×4.6mm, n-Hep/IP= 9:1, 1.0 mL/min) ee 3%.
All other analytical data correspond to those described in the literature. 76

1-(Furan-2-yl)-2-phenyl-2-(phenylamino)ethanone (204l)

According to GP 8, the Stetter products 204l was purified by column chromatography (silica gel, Et<sub>2</sub>O/PE = 5:1).

Yield: m = 138mg, 0.5 mmol (99%).
GC: R<sub>t</sub> = 16.12 min (CP-Sil-8, 100-10-300).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):
δ = 5.30 (brs, 1H, NH), 5.77 (s, 1H, PhCHNH), 6.55 (m, 3H, Aroma-H), 7.01 (m, 2H, Aroma-H), 7.15 (m, 1H, Aroma-H), 7.22 (m, 3H, Aroma-H), 7.45 (d, J = 7.1Hz, 2H, Aroma-H), 7.51 (s, 1H,
Aroma-H) ppm.

$^{13}$C NMR (100 MHz, CDCl3):

$\delta = 62.9$ (PhCHNH), 112.7, 113.5, 117.8, 119.1, 120.3, 128.0, 128.1, 128.2, 128.7, 128.8, 129.2, 131.7, 137.6, 145.9, 146.9, 148.2, 150.9 (Aroma-H), 186.6 (Furyl-(O)CH) ppm.

HPLC $R = 7.32$ and $9.01$ (Daicelod.M, 250×4.6mm, n-Hep/IP= 8:2, 1.0 mL/min) ee: 0%

All other analytical data correspond to those described in the literature. 76

**Dimethyl 2-(3-methylbutylidene)malonate (207 I)**

![Dimethyl 2-(3-methylbutylidene)malonate](image)

According to GP 9.

Yield: m = 1.6g, (80%), colorless oil.

$^1$H NMR (300 MHz, CDCl3):

$\delta = 0.91$ (d, $J = 1.3$Hz, 3H), 0.9 (m, 1H), 2.17 (t, $J = 6.8$Hz, 2H), 3.76 (d, $J = 1.5$Hz, 3H), 3.80 (d, $J = 1.5$Hz, 3H), 7.01 (m, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl3):

$\delta = 22.3, 28.1, 38.6, 52.1, 52.2, 128.5, 149.3, 164.3, 165.9$ ppm.

All other analytical data correspond to those described in the literature. 124

**Dimethyl 2-(3-methylbutylidene)malonate (207c)**

![Dimethyl 2-(3-methylbutylidene)malonate](image)

According to GP 9.

Yield: m = 1.7g, (70%), colorless solid.

$^1$H NMR (300 MHz, CDCl3):

$\delta = 3.81$ (s, 6H), 7.27 (m, 4H), 7.62 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl3):

$\delta = 52.7, 52.8, 126.1, 129.2, 130.6, 131.3, 136.8, 141.4, 164.3, 166.8$ ppm.

All other analytical data correspond to those described in the literature. 124
Experimental part

**Dimethyl 2-(naphthalen-1-ylmethylene)malonate (207i)**

![Structure of Dimethyl 2-(naphthalen-1-ylmethylene)malonate]

According to GP 9.

Yield: m = 2.0 g, (75%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ = 3.71 (s, 3H), 3.93 (s, 3H), 7.48 (t, $J = 7.3$Hz, 1H), 7.60 (m, 3H), 7.90 (m, 2H), 8.01 (m, 1H), 8.54 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta$ = 52.5, 52.8, 123.9, 125.3, 128.7, 130.7, 131.4, 133.4, 141.9, 164.3, 166.6 ppm.

All other analytical data correspond to those described in the literature.\(^{124}\)

**Dimethyl 2-(4-methylbenzylidene)malonate (207f)**

![Structure of Dimethyl 2-(4-methylbenzylidene)malonate]

According to GP 9.

Yield: m = 1.8 g, (80%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ = 2.27 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 7.09 (d, $J = 8.1$Hz, 2H), 7.23 (d, $J = 8.4$Hz, 2H), 7.65 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta$ = 21.5, 52.5, 52.6, 124.4, 129.5, 129.6, 141.4, 142.9, 164.6, 167.3 ppm.

All other analytical data correspond to those described in the literature.\(^{124}\)

**Dimethyl 2-(4-methoxybenzylidene)malonate (207j)**

![Structure of Dimethyl 2-(4-methoxybenzylidene)malonate]
According to GP 9.

Yield: m = 2.0 g, (80%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta = 3.73$ (s, 6H), 3.77 (s, 3H), 6.80 (m, 2H), 7.25 (m, 2H), 7.62 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 52.5$, 52.6, 55.3, 114.4, 122.7, 125.2, 13'1.5, 142.6, 161.7, 164.8, 167.6 ppm.
All other analytical data correspond to those described in the literature.\textsuperscript{124}

**Dimethyl 2-(3-chlorobenzylidene)malonate (207d)**

![Dimethyl 2-(3-chlorobenzylidene)malonate (207d)]

According to GP 9.

Yield: m = 1.9 g, (75%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta = 3.86$ (s, 6H), 7.22-7.42 (m, 4H), 7.70 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 52.7$, 52.8, 126.9, 127.3, 129.1, 130.1, 130.5, 134.5, 134.9, 141.2, 164.1, 166.5 ppm.
All other analytical data correspond to those described in the literature.\textsuperscript{124}

**Dimethyl 2-(pyridin-3-ylmethylene)malonate (207q)**

![Dimethyl 2-(pyridin-3-ylmethylene)malonate (207q)]

According to GP 9.

Yield: m = 1.3 g, (60%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta = 3.87$ (s, 3H), 3.92 (s, 3H), 7.20-7.28 (m, 1H), 7.40 (m, 1H), 7.67-7.75 (m, 2H), 8.63 (m, 1H) ppm.
Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 52.5, 52.8, 124.5, 126.3, 128.3, 136.8, 139.9, 149.9, 150.9, 164.4, 167.1$ ppm.
All other analytical data correspond to those described in the literature.$^{124}$

Dimethyl 2-(2-chlorobenzylidene)malonate (207k)

![Chemical structure]

According to GP 9.

Yield: m = 2.1 g, (80%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta = 3.71$ (s, 3H), $3.84$ (s, 3H), 7.20-7.50 (m, 4H), 8.06 (d, $J = 1.9$Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 52.6, 52.7, 126.9, 128.0, 129.0, 129.9, 131.3, 131.8, 134.7, 139.9, 164.0, 166.2$ ppm.
All other analytical data correspond to those described in the literature.$^{124}$

Diethyl 2-benzylidenemalonate (207m)

![Chemical structure]

According to GP 9.

Yield: m = 2.0 g, (81%), colorless solid.

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta = 1.20-1.40$ (m, 6H), $4.20-4.40$ (m, 2H), 7.38 (m, 3H), 7.45 (m, 2H), 7.73 (d, $J = 0.5$Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$):
$\delta = 13.9, 14.1, 61.6, 61.7, 126.4, 128.7, 129.4, 130.5, 132.9, 142.1, 164.1, 166.6$ ppm.
All other analytical data correspond to those described in the literature.$^{124}$
5-Benzyldene-2,2-dimethyl-1,3-dioxane-4,6-dione (207n)

According to GP 9.

Yield: m = 1.9 g, (80%), colorless solid.

$^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ = 1.80 (s, 6H), 7.40-7.60 (m, 3H), 8.05 (s, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$):
$\delta$ = 27.7, 104.6, 114.8, 128.7, 131.6, 133.6, 158.0, 159.6, 163.2 ppm.
All other analytical data correspond to those described in the literature. 124

($E$)-Methyl 2-cyano-3-phenylacrylate (209)

According to GP 9.

Yield: m = 1.7 g, (90%), colorless solid.

$^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ = 3.93 (s, 3H), 7.48-7.56 (m, 3H), 7.77-7.99 (m, 2H), 8.26 (s, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$):
$\delta$ = 53.5, 102.6, 115.5, 129.3, 131.1, 131.4, 133.4, 155.3, 162.9 ppm.
All other analytical data correspond to those described in the literature. 124

($R$)-3-Acetyl-1-(furan-2-yl)-2-phenylpentane-1,4-dione.

According to GP 10.
Yield: m = 130 mg, 0.4 mmol (80%).
Melting point = 113 °C. Colorless solid.
GC: Rf= 13.28 min (CP-Sil-8, 100-10-300).
TLC: Rf = 0.60 (PE : Et₂O = 2:1).

\[ ^1H \text{NMR} (300 \text{ MHz, CDCl}_3): \]
\[ \delta = 1.85 \text{ (s, 3H, C(O)CH}_3), \] 2.20 (s, 3H, C(O)CH₃), 4.78 (d, \( J = 11.4 \text{Hz}, 1\text{H, (MeCO)}_2\text{CH} \)), 5.15 (d, \( J = 11.4 \text{Hz}, 1\text{H, PhCH} \)), 6.38 (dd, \( J = 3.5, 1.7 \text{Hz}, 1\text{H, C}_{\text{Fury}}\text{-H} \)), 7.10, (dd, \( J = 3.4, 0.7 \text{Hz}, 1\text{H, C}_{\text{Fury}}\text{-H} \)), 7.15-7.27 (m, 5H, Ph-H), 7.44 (dd, \( J = 1.7, 0.8 \text{Hz}, 1\text{H, C}_{\text{Fury}}\text{-H} \)) ppm.

\[ ^{13}C \text{NMR} (75 \text{ MHz, CDCl}_3): \]
\[ \delta = 30.2 \text{ (C(O)CH}_3), 31.3 \text{ (C(O)CH}_3), 53.6 \text{ ((MeCO)}_2\text{CH}), 70.5 \text{ (PhCH)}, 112.4, 118.8, 127.6, 128.1, 128.8, 129.2, 134.8, 146.8, 151.5 \text{ (Ar-C), 186.3 (FuryC(O)), 201.3 (C(O)Me), 202.5 (C(O)Me) ppm.} \]

IR (KBr):
\( \nu = 3867 \text{ (w), 3773 (w), 3717 (w), 3659 (w). 3415 (m), 3293 (w), 3125 (m), 3097 (m), 2987 (w), 2917 (w), 2932 (w), 3125 (m), 3097 (m), 2987 (w), 2917 (w), 2860 (w), 2633 (w), 2480 (w), 2290 (w), 1961 (w), 1829 (w), 1783 (w), 1725 (s), 1655 (vs), 1564 (m), 1467 (m), 1395 (s), 1360 (s), 1308 (s), 1254 (s), 1168 (s), 1141 (s), 1094 (m), 1040 (m), 990 (m), 904 (m), 788 (s), 730 (s), 698 (m), 593 (m), 556 (m), 507 (m), 462 (w). \]

MS (EI, 70eV): 285.0 (M+1, 10), (284.0 M+, 4), 266.9 (20), 241 (60), 224 (24), 199 (20), 147 (55), 129 (35), 95 (100), 77(10).

Elemental Analysis: C, 71.82; H, 5.67; Found C, 71.32; H, 5.75;

\((R)-\text{Dimethyl 2-(2-(furan-2-yl)-2-oxo-1-phenylethyl)malonate (208a)}\).

According to GP 10.

Yield: m = 127mg, 0.45 mmol (90%), Colorless solid.
Melting point = 103 °C.
GC: Rf= 14.03 min (CP-Sil-8, 100-12-300).
TLC: Rf = 0.50 (PE : Et₂O = 1:1).
Optical rotation: \([\alpha]_D^{23} = -194.5 \text{ (c 1.01, CHCl}_3\)).
Experimental part

$^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ = 3.46 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 4.45 (d, $J = 11.5$ Hz, 1H, CH(CO$_2$Me)), 5.12 (d, $J = 11.8$ Hz, 1H, PhCH), 6.46 (m, 1H, Furyl-OCHCH/CH), 7.21 (m, 1H, Furyl-OCHCH/CH), 7.23-7.33 (m, 5H, Ph-H), 7.53 (m, 1H, Furyl-OCHCH/CH) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$):
$\delta$ = 52.4 (CH(CO$_2$Me)$_2$), 52.6 (CO$_2$CH$_3$), 53.0 (CO$_2$CH$_3$), 54.7 (3-ClPhCH), 112.4, 118.5, 128.0, 128.8, 128.9, 146.7 (Ph-C), 168.2 (CO$_2$CH$_3$), 168.3(CO$_2$CH$_3$), 185.5 (Furyl-C(O)CH) ppm.

IR (KBr):
$\nu$ = 3854 (m), 3744 (m), 3676 (m), 3647 (m), 3619 (w), 3563 (w), 3432 (m), 3236 (vw), 3130 (w), 2957 (w), 2851 (vw), 2666 (vw), 2361 (s), 2340 (s), 2051 (vw), 1916 (vw), 1742 (s), 1668 (s), 1560 (m), 1464 (m), 1395 (w), 1364 (vw), 1313 (m), 1226 (w), 1194 (m), 1131 (s), 1226 (m), 1194 (m), 1150 (m), 1088 (m), 1015 (m), 939 (m), 906 (w), 784 (m), 714 (vw), 669 (w), 560 (m), 463 (w).

MS (EI, 70eV): m/z (%) = 316.0 (20, M$^+$), 300 (20), 284 (24), 253 (11), 252 (35), 225 (10), 184 (15), 162 (6), 156 (3), 131 (18), 121 (37), 95 (100), 77 (6).

Anal. Calcd. for C$_{17}$H$_{16}$O$_6$: C, 64.55; H, 0.33.

HPLC Rt = 5.75 and 8.02 (Daicelod.M, 2 2, 1.0 mL/min); Rt = 8.02, ee > 99%.

Yield: m = 154mg, 0.47 mmol (92%).

Melting point = 102 °C.

GC: R$_f$ = 15.51 min (CP-Sil-8, 100-10-300).

TLC: R$_f$ = 0.2 (PE : Et$_2$O = 1:1).

Optical rotation: $[\alpha]_D^{23} = -123.1$ (c 1.01, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ = 3.50 (s, 3H, OCH$_3$), 3.71 (s, 3H, OCH$_3$), 4.34 (d, $J = 11.9$ Hz, 1H, CH(CO$_2$Me)$_2$), 5.04 (d, $J = 12.1$ Hz, 1H, PhCH), 7.15-7.28 (m, 3H, Ph-H), 7.37-7.43 (m, 2H, Ph-H), 7.66 (m, 1H, Pyr-H), 8.00 (m, 1H, Pyr-H), 8.70 (m, 1H, Pyr-H) ppm.

$(R)$-Dimethyl 2-(2-oxo-1-phenyl-2-(pyridin-2-yl)ethyl)malonate (208b).

According to GP 10.

Yield: m = 154mg, 0.47 mmol (92%).

Melting point = 102 °C.

GC: R$_f$ = 15.51 min (CP-Sil-8, 100-10-300).

TLC: R$_f$ = 0.2 (PE : Et$_2$O = 1:1).

Optical rotation: $[\alpha]_D^{23} = -123.1$ (c 1.01, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ = 3.50 (s, 3H, OCH$_3$), 3.71 (s, 3H, OCH$_3$), 4.34 (d, $J = 11.9$ Hz, 1H, CH(CO$_2$Me)$_2$), 5.04 (d, $J = 12.1$ Hz, 1H, PhCH), 7.15-7.28 (m, 3H, Ph-H), 7.37-7.43 (m, 2H, Ph-H), 7.66 (m, 1H, Pyr-H), 8.00 (m, 1H, Pyr-H), 8.70 (m, 1H, Pyr-H) ppm.
Experimental part

\[ ^{13}C\text{ NMR (75 MHz, CDCl}_3\text{:)} \]
\[ \delta = 50.3 (\text{CH(NO}_2\text{Me})_2), 52.4 (\text{CO}_2\text{CH}_3), 52.8 (\text{CO}_2\text{CH}_3), 55.2 (\text{PhCHCH}), 122.8 (\text{NC}_\text{pyr}C\text{p}_\text{pyr}\text{H}), 127.1 (\text{NC}_\text{pyr}H\text{pyr}H), 127.7, 128.6, 129.4, 134.3(\text{Ph-C}), 136.7 (\text{NC}_\text{pyr}H\text{pyr}H\text{pyr}H), 149.0 (\text{NC}_\text{pyr}H\text{pyr}H), 152.0 (\text{NC}_\text{pyr}C\text{p}_\text{pyr}H), 168.3(\text{CO}_2\text{Me}), 168.7(\text{CO}_2\text{Me}), 198.2 (\text{C}_\text{pyr} \text{C}(O)) \text{ ppm.} \]

IR (KBr):
\[ v = 3472 (\text{w}), 3435 (\text{w}), 3374 (\text{w}), 3163 (\text{v}), 3049 (\text{m}), 3007 (\text{m}), 2954 (\text{v}), 2844 (\text{vw}), 2651 (\text{v}), 2478 (\text{vw}), 1972 (\text{vw}), 1883 (\text{vw}), 1750 (s), 1728 (s), 1696 (s), 1581 (m), 1493 (m), 1439 (s), 1295 (s), 1258 (s), 1191 (s), 1158 (s), 1093 (m), 1027 (m), 995 (m), 965 (m), 943 (m), 918 (m), 857 (w), 782 (m), 761 (m), 701 (m), 603 (m), 548 (m), 458 (\text{vw}) \text{ cm}^{-1}. \]

MS (EI, 70eV): m/z (%) = 327.1 (85, M+), 295.1 (85), 267.9 (100), 263.0 (70), 235.1 (75), 208.0 (70), 195.1 (75), 180.0 (50), 167.0 (60), 131.0 (85), 120.9 (80), 106.0 (75), 77.8 (80), 59.1 (45), 51.1 (46).

Anal. Calcd. for C_{18}H_{17}NO_{5}: C, 66.05; H, 5.32; N, 4.28. Found: C, 66.06; H, 5.24; N, 4.265.

HPLC R_t = 9.45 and 11.71 (Daicelod.M, :2, 0.7 mL/min)
\[ R_t = 11.71, \text{ ee = } 30\%. \]

\((R)\)-Dimethyl 2-(1-(4-chlorophenyl)-2-(furan-2-yl)-2-oxoethyl)malonate (208c)

According to GP 10.

Yield: m = 161mg, 0.46 mmol (92%).
Melting point = 95°C. Colorless solid.
GC: R_t = 15.45 min (CP-Sil-8, 100-12-300).
TLC: R_f = 0.45 (PE : Et_2O = 1:1).
Optical rotation: [\alpha]_D^{25} = -222.2 (c 1.01, CHCl_3).

\[^1H\text{ NMR (300 MHz, CDCl}_3\text{:)} \]
\[ \delta = 3.42 (s, 3H, \text{OCH}_3), 3.64 (s, 3H, \text{OCH}_3), 4.35 (d, J = 11.6 Hz, 1H, \text{CH(CO}_2\text{Me}_2)), 5.05 (d, J = 11.6Hz, 1H, 4-ClPhCH), 6.52 (dd, J = 3.5, 2.5Hz, 1H, Furyl-OCHCHCHC), 7.15 (m, 1H, Furyl-OCHCHCHC), 7.18-7.21 (m, 4H, Ph-H), 7.64 (dd, J = 0.7, 1.8 Hz, 1H, Furyl-OCHCHCHC) \text{ ppm.} \]

\[^{13}C\text{ NMR (100 MHz, CDCl}_3\text{:)} \]
\[ \delta = 52.2 (\text{CH(CO}_2\text{Me}_2)), 52.6 (\text{CO}_2\text{CH}_3), 52.9 (\text{CO}_2\text{CH}_3), 54.5 (4-ClPhCHCH), 112.5, 118.7, \]

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Experimental part

129.2, 130.2, 132.8, 134.2, 146.9, 151.4 (Ph-C), 167.8 (CO₂CH₃), 168.2(CO₂CH₃), 185.5 (Furyl-C(0)CH) ppm.

IR (KBr):
\[ \nu = 3428 \text{ (w)}, 3319 \text{ (w)}, 3130 \text{ (m)}, 2997 \text{ (w)}, 2959 \text{ (m)}, 2848 \text{ (w)}, 2467 \text{ (w)}, 2344 \text{ (w)}, 1907 \text{ (w)}, 1743 \text{ (s)}, 1668 \text{ (s)}, 1226 \text{ (m)}, 1194 \text{ (s)}, 1149 \text{ (s)}, 1090 \text{ (m)}, 1013 \text{ (m)}, 940 \text{ (m)}, 784 \text{ (s)}, 752 \text{ (m)}, 716 \text{ (m)}, 622 \text{ (m)}, 562 \text{ (m)}, 492 \text{ (w)} \text{ cm}^{-1}. \]

MS (EI, 70eV): \( m/z \) (%) = 350.0 (8, M⁺), 258 (3), 195 (4), 164 (16), 154 (17), 136 (8), 114 (4), 102 (12), 101 (11), 95 (100), 75 (4), 59 (11).


HPLC Rₜ = 7.79 and 9.69 (Daicel 9:1, 1.0 mL/min)
Rₜ = 9.69, ee = 62%, after recrystallization, ee = 97%

\((R)-\text{Dimethyl 2-}(1-(3\text{-chlorophenyl})-2-(furan-2-yl)-2-oxoethyl)\text{malonate (208d).}\)

According to GP 10.

Yield: \( m = 148 \text{ mg}, 0.42 \text{ mmol (85%)}. \)

Melting point = 78°C. Colorless solid.
GC: \( Rₜ = 15.29 \text{ min (CP-Sil-8, 100-12-300)} \)
TLC: \( Rₜ = 0.45 \text{ (PE : EtO = 1:1)} \)
Optical rotation: \( \alpha [\text{D}]^{25} = -240.0 \text{ (c 1.01, CHCl₃)} \)

\(^1\text{H NMR (300 MHz, CDCl₃)}: \)
\( \delta = 3.52 \text{ (s, 3H, OCH₃)}, 3.74 \text{ (s, 3H, OCH₃)}, 4.43 \text{ (d, } J = 11.6 \text{ Hz, 1H, CH(CO₂Me)₂)}, 5.12 \text{ (d, } J = 11.8 \text{Hz, 1H, 3-ClPhCH)}, 6.51 \text{ (dd, } J = 1.7, 3.6 \text{ Hz, 1H, Furyl-OCHCHCHC)}, 7.23-7.24 \text{ (m, 4H, Ph-CH)}, 7.26 \text{ (m, 1H, Furyl-OCHCHCHC)}, 7.58 \text{ (dd, } J = 1.0, 1.8 \text{ Hz, 1H, Furyl-OCHCHCHC) ppm}. \)

\(^{13}\text{C NMR (100 MHz, CDCl₃)}: \)
\( \delta = 52.4 \text{ (CH(CO₂Me)₂)}, 52.6 \text{ (CO₂CH₃)}, 53.1 \text{(CO₂CH₃)}, 54.6 \text{(3-ClPhCHCH)}, 112.6, 118.8, 127.1, 128.5, 128.9, 130.1, 147.1 \text{(Ph-C)}, 167.0 \text{(CO₂CH₃)}, 168.0 \text{(CO₂CH₃)}, 185.0 \text{(Furyl-C(0)CH) ppm}. \)
IR (KBr): 

\[ \nu = 3744 \text{ (w), } 3676 \text{ (w), } 3649 \text{ (w), } 3418 \text{ (m), } 3127 \text{ (m), } 3096 \text{ (m), } 3054 \text{ (w), } 3010 \text{ (w), } 2956 \text{ (m), } 2847 \text{ (w), } 2781 \text{ (w), } 2474 \text{ (w), } 2363 \text{ (m), } 2335 \text{ (w), } 2120 \text{ (w), } 1945 \text{ (w), } 1882 \text{ (w), } 1739 \text{ (s), } 1656 \text{ (s), } 1564 \text{ (m), } 1463 \text{ (s), } 1394 \text{ (s), } 1359 \text{ (w), } 1310 \text{ (s), } 1255 \text{ (s), } 1225 \text{ (s), } 1194 \text{ (s), } 1086 \text{ (m), } 1023 \text{ (m), } 977 \text{ (m), } 615 \text{ (m), } 590 \text{ (m), } 540 \text{ (m), } 511 \text{ (m).} \]

MS (EI, 70eV): \( m/z \) (%) = 350 (10, M⁺), 332 (8), 319 (10), 286 (10), 218 (10), 165 (10), 155 (8), 95 (100).


HPLC \( R_t = 11.62 \) and 13.76 (Whelk H= 95:5, 1.0 mL/min)

\( R_t = 11.62, \) ee = 68%, after recrystallization, ee = 94%

(\( R \))-Dimethyl 2-(1-(4-bromophenyl)-2-(furan-2-yl)-2-oxoethyl)malonate (208e).

According to GP 10.

Yield: \( m = 173\text{mg}, 0.44\text{mmol} \) (88%).

Melting point = 138°C.

GC: \( R_t = 16.35 \text{ min (CP-Sil-8, 100-10-300).} \)

TLC: \( R_f = 0.5 \) (PE : Et₂O = 1:1).

Optical rotation: \([\alpha]_{D}^{23} = -168.6 \) (c 1.01, CHCl₃);

\(^1\)H NMR (300 MHz, CDCl₃):

\( \delta = 3.44 \) (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 4.34 (d, \( J = 12.6\text{Hz}, 1\text{H, } CH(CH₂Me)₂ \)), 5.04 (d, \( J = 11.8\text{Hz}, 1\text{H, } 4\text{-BrPhCH} \)), 6.41 (dd, \( J = 1.7, 3.6\text{Hz}, 1\text{H, Furyl-OCHCHCHCHC} \)), 7.15 (m, 4H, Ph-H), 7.33 (m, 2H, Furyl-H) ppm.

\(^13\)C NMR (75 MHz, CDCl₃):

\( \delta = 52.3 \) (CH(CH₂Me)₂), 52.7 (CO₂CH₃), 52.8(CO₂CH₂), 54.5 (4-BrPhCH), 112.5 (OC₃H₂₃CH₃), 120.2 (OC₃H₂₃CH₂H), 122.3, 130.5, 132.2, 133.2. 146.5 (Ph-C), 149.3 (OC₃H₂₃CH₃), 167.7 (CO₂CH₃), 168.1(CO₂CH₂), 185.3 (FurylC(O)CH) ppm.

IR (KBr):

\( \nu = 3856 \text{ (vw), } 3744 \text{ (vw), } 3673 \text{ (vw), } 3440 \text{ (w), } 3304 \text{ (vw), } 3127 \text{ (m), } 2998 \text{ (w), } 2953 \text{ (m), } 2842 \text{ (vw), } 2361 \text{ (m), } 2339 \text{ (m), } 2254 \text{ (vw), } 2133 \text{ (vw), } 1913 \text{ (w), } 1745 \text{ (s), } 1656 \text{ (s), } 1561 \text{ (m), } 1468 \text{ (w).} \)

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(m), 1435 (m), 1399 (m), 1368 (vw), 1325 (s), 1266 (s), 1231 (m), 1202 (m), 1158 (m), 1076 (w),
1049 (w), 1013 (m), 939 (m), 819 (w), 783 (m), 748 (m), 679 (vw), 593 (w), 556 (m), 492 (w).

MS (EI, 70eV): m/z (%) = 395.8 (1), 364.2 (9.7), 362.0 (9.8), 331.9 (21.0), 329.9 (21.6), 210.8 (7.3),
208.9 (10.8), 200.8 (12.2), 198.9 (15.2), 184.1 (3.1), 155.0 (2.0), 128.0 (3.6), 102.1 (11.0), 95.0
(100)

HRMS: m/z calcd for [C17H15O6 54.4894; found: 54.4892.

HPLC Rt = 8.35 and 9.65 (Daicelod :2, 0.7 mL/min)

Rt = 9.65, ee = 70%, after recrystallization, ee =99%

(R)-Dimethyl 2-(2-(furan-2-yl)-2-oxo-1-p-tolylethyl)malonate (208f)

![Chemical structure]

According to GP 10.

Yield: m = 138mg, 0.42mmol (84%).

Melting point = 82 °C. Colorless solid.

GC: Rt = 14.85 min (CP-Sil-8, 100-12-300).

TLC: Rf = 0.6 (PE : Et2O = 1:1).

Optical rotation: [α]D 23 = – 180.8 (c 1.01, CHCl3).

1H NMR (300 MHz, CDCl3):
δ = 2.19 (s, 3H, 4-CH2Ph), 3.41 (s, 3H, OCH3), 3.49 (s, 3H, OCH3), 4.36 (d, J = 11.8Hz, 1H,
CH(CO2Me)2), 5.01 (d, J = 11.7Hz, 1H, 4-MePhCH), 6.38 (dd, J = 3.7, 1.8Hz, 1H,
Furyl-OCHCHCHC), 7.01 (m, 2H, Ph-H), 7.12 (m, 2H, Ph-H ), 7.13 (m, 1H, Furyl-OCHCHCHC),
7.45 (dd, J = 0.7, 1.8 Hz, 1H, Furyl-OCHCHCHC) ppm.

13C NMR (75 MHz, CDCl3):
δ = 17.9 (4-CH3PhCH), 52.49 (CH(CO2Me)2), 52.60 (CO2CH3), 52.90 (CO2CH3), 54.70
(4-MePhCHCH), 113.1, 118.5, 128.7, 129.6, 131.1, 137.9, 149.4, 151.6 (Ph-C), 168.1 (CO2CH3),
168.5 (CO2CH3), 186.0 (Furyl-C(O)CH) ppm.

IR (KBr):
ν = 3853 (w), 3744 (w), 3674 (vw), 3616 (vw), 3441 (w), 3314 (vw), 3137 (m), 3029 (w), 2958 (m),
2863 (m), 2732 (vw), 2438 (w), 2359 (m), 2341 (m), 2257 (vw), 1921 (vw), 1745 (s), 1667 (s),
1565 (m), 1513 (m), 1465 (m), 1395 (w), 1309 (s), 1228 (m), 1188 (m), 149 (m), 1039 (m), 951
(m), 843 (vw), 776 (m), 725 (vw), 668 (w), 585 (m), 500 (w), 460 (vw).
MS (EI, 70eV): m/z (%) = 330.1 (34.6, M⁺), 298.0 (19.2), 266.0 (49.4), 239.0 (7.5), 235.0 (10.8), 198.0 (4.4), 191.1 (10.5), 176.1 (5.2), 149.0 (2.5), 145.0 (21.2), 135.0 (100), 115.0 (14.2), 95.0 (39.1), 59.0 (6.3).


HPLC Rᵣ = 7.13 and 9.29 (Daicelod.M, 250×4.6mm, n-Hep/IP= 9:1, 1.0 mL/min)
Rᵣ = 9.29, ee = 72%, after recrystallization, ee = 90%

(R)-Dimethyl 2-(2-(furan-2-yl)-2-oxo-1-(pyridin-4-yl)ethyl)malonate (208h)

According to GP 10.

Yield: m = 155 mg, 0.49 mmol (98%).
Melting point = 138°C.
GC: Rᵣ = 14.72 min (CP-Sil-8, 100-10-300).
TLC: Rᵣ = 0.18 (PE : Et₂O = 1:1).
Optical rotation: [α]D²³ = −175.0 (c 1.01, CHCl₃).

¹H NMR (300 MHz, CDCl₃):
δ = 3.54 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 4.69 (d, J = 11.4Hz, 1H, CH(CO₂Me)₂), 5.38 (d, J = 11.4Hz, 1H, PyrCH), 6.50 (dd, J = 17, 3.7Hz, 1H, Furyl-OCHCHCH), 7.15 (m, 1H, Pyr-H), 7.30 (dd, 1H, J = 3.5, 1.0Hz, pyr-H), 7.44 (m, 1H, pyr-H), 7.56 (dd, J = 0.7, 1.7Hz, 1H, Furyl-OCHCHCH), 7.63 (m, 1H, pyr-H), 8.55 (m, 1H, Furyl-OCHCHCH) ppm.

¹³C NMR (75 MHz, CDCl₃):
δ = 52.6 (CH(CO₂Me)₂), 52.9 (CO₂CH₃), 53.4(CO₂CH₃), 55.3(Pyr-CHCH), 112.5, 119.0, 122.7, 124.1, 136.8, 146.8, 149.9, 151.7, 154.7 (Ar-C), 168.27 (CO₂CH₃), 168.57 (CO₂CH₃), 184.5 (Furyl-C(O)CH) ppm.

IR (KBr):
ν = 3854 (w), 3746 (vw), 3621 (vw), 3470 (vw), 3336 (vw), 3135 (w), 3018 (w), 2954 (m), 2849 (w), 2451 (vw), 2359 (m), 2340 (m), 1742 (s), 1677 (s), 1569 (m), 1464 (s), 1438 (w), 1389 (w), 1303 (s), 1198 (m), 1158 (m), 1086 (w), 1027 (m), 942 (vw), 910 (vw), 874 (vw), 825 (vw), 758 (s), 667 (w), 599 (m), 453 (w), 461 (vw) cm⁻¹.

MS (EI, 70eV): m/z (%) = 395.8 (13.3, M⁺), 393.9 (10.3, M⁺), 364.2 (9.7), 362.0 (9.8), 331.9
Experimental part

(21.0), 329.9 (21.6), 210.8 (7.3), 208.9 (10.8), 200.8 (12.2), 198.9 (15.2), 184.1 (3.1), 155.0 (2.0),
128.0 (3.6), 102.1 (11.0), 95.0 (100), 75.3 (2), 59.0 (7), 51.1 (2).

HRMS: m/z calcld for [C_{16}H_{15}NO_4]: 318.0978; found: 318.0978.

HPLC R_t = 9.07 and 11.35 (Daice.d.M, 250×4.6mm, n-Hep/IP= 6:4, 0.7 mL/min)
R_t = 11.35, ee = 40 %.

(3R)-Methyl 2-cyano-4-(furan-2-yl)-4-oxo-3-phenylbutanoate (210)

![Chemical Structure]

According to GP 10.

Yield: m = 138 mg, (98%).
GC: R_t = 13.69 min (CP-Sil-8, 100-10-300).
TLC: R_f = 0.4 (PE : Et_2O = 1:1).

^1H NMR (300 MHz, CDCl_3):
δ = 3.73 (s, 3H, OCH_3), 4.51 (d, J = 10.7Hz, 1H, CH(CN)CO_2Me), 4.93 (d, J = 10.7Hz, 1H, PhCHC(O)), 6.40 (dd, J = 3.7, 1.8Hz, 1H, OC_FurHC_FurH), 7.13 (dd, J = 3.7, 1.8Hz, 1H, OC_FurC_FurH), 7.24-7.31 (m, 5H, Ph-H), 7.46 (dd, J = 1.8, 0.8Hz, 1H, OC_FurH) ppm.

^13C NMR (75 MHz, CDCl_3):
δ = 39.9 (CNCHCO_2Me), 52.7 (PhCHCO), 53.7 (OCH_3), 112.7 (OC_FurHC_FurH), 115.1 (CN), 119.6 (OC_FurHC_FurH), 128.7, 128.8, 128.9, 133.1 (Ph-C), 147.7 (OC_FurH), 165.3 (OC_Fur), 184.1 (FurCO) ppm.

IR (KBr):
ν = 3852 (w), 3746 (w), 3459 (s), 3138 (s), 3022 (s), 2957 (s), 2625 (vw), 2545 (w), 2471 (vvw),
2358 (s), 2339 (m), 2254 (m), 2112 (w), 1965 (w), 1892 (vww), 1738 (s), 1568 (s), 1462 (m), 1385
(m), 1254 (m), 1166 (m), 1087 (w), 1007 (m), 916 (w), 881 (w), 830 (w), 772 (m), 702 (m), 663
(m), 591 (m), 500 (m), 458 (vww) cm^-1.

MS (El, 70eV): m/z (%) = 284.0 (6.6, M+1), 283.0 (18.9, M'), 251.0 (8.5), 224.0 (4.11), 188.0
(3.9), 157.1 (1.8), 129.1 (5.4), 128.1 (5.8), 95.0 (100), 77.1 (3.6), 51.1 (3.2).

HRMS: m/z calcld for [C_{16}H_{13}NO_4]: 283.0845; found: 283.0844.
2,4-Bis(benzyloxy)-6-hydroxybenzaldehyde (227)

![Chemical Structure](image)

To a stirred solution of aldehyde 230 (1.0 g, 7 mmol) in DMF (10 mL) was added K₂CO₃ (1.9 g, 14 mmol) followed by BnBr (1.5 mL, 14 mmol) and the mixture was stirred at rt overnight. The mixture was then diluted with Et₂O (20 mL) and washed with H₂O (20 mL), dried (MgSO₄), filtered and concentrated in vacuo to yield a yellow solid, which was recrystallised from Et₂O to furnish the 4,6-dibenzyl protected aldehyde as a pale yellow solid.

Yield: m =1.4 g, 4.2 mmol, (60%).
GC: Rt = 16.14 min (CP-Sil-8, 140-10-300).
TLC: Rf = 0.6 (PE : Et₂O = 2:1).

¹H NMR (300 MHz, CDCl₃):
δ = 5.07 (s, 2H, HOC₆H₄C₆H₄OCH₂Ph), 5.08 (s, 2H, CHOC₆H₄C₆H₄OCH₂Ph), 6.09 (d, J = 2.2Hz, 1H, HOC₆H₄C₆H₄H), 6.12 (d, J = 1.9Hz, 1H, BnOC₆H₄C₆H₄H), 7.38-7.44 (m, 10H, Ph-H), 10.18 (s, 1H, O-H), 12.52 (s, 1H, CHO) ppm.

¹³C NMR (75 MHz, CDCl₃):
δ = 70.5 (HOC₆H₄C₆H₄OCH₂Ph), 70.6 (CHOC₆H₄C₆H₄OCH₂Ph), 92.4 (HOC₆H₄C₆H₄H), 94.2 (HOC₆H₄C₆H₄H), 127.4, 127.6, 128.1, 128.4, 128.5, 128.8, 135.6, 135.7 (Ph-C), 162.6, 166.3, 167.1 (O-C₆H₄), 191.9 (CHO) ppm.
All other analytical data correspond to those described in the literature.¹²⁵

1-Chloro-3-(4-methoxyphenyl)propan-2-one (228a)

![Chemical Structure](image)

500 mL, three-necked, round-bottomed flask was added a diazomethane (0.11 mol) in dried Et₂O (100 mL) in an ice-cooled bath, a solution of 8.41 g (0.05 mol) of tolylacetyl chloride dissolved in 10 mL of ether was added in dropwise over a 15-min period with stirring. The solution was stirred for 2 hours while warming to 20 °C. Dry hydrogen chloride was then bubbled through the solution for about 30 min. The solution was placed in a separatory funnel and successive small portions of water were added cautiously. The ether layer was washed twice with 50 mL portions of 5 % sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was stripped and the residue vacuum distilled to give the chloro ketone.
Yield: m = 5.9g, 32mmol, (65%).

TLC: \( R_f = 0.26 \) (Et\(_2\)O:Pentane = 1:6).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 
\( \delta = 3.80 \) (s, 3H, OCH\(_3\)), 3.82 (s, 2H, PhCH\(_2\)C(O)), 4.11 (s, 2H, C(O)CH\(_2\)Cl), 6.88 (d, \( J = 9.5\)Hz, 2H, Ph-H), 7.14 (d, \( J = 8.5\)Hz, Ph-H) ppm.

All other analytical data correspond to those described in the literature.\(^{115}\)

1-Bromo-3-(4-methoxyphenyl)propan-2-one (228b)

![Structure of 1-Bromo-3-(4-methoxyphenyl)propan-2-one (228b)]

The procedure was according to preparation of 228a, concentrated HBr (aq.) in place of hydrogen chloride was used.

Yield: m = 4.8g, 20mmol, (40%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 
\( \delta = 3.81 \) (s, 3H, OCH\(_3\)), 3.82 (s, 2H, Ph-H), 7.14 (d, \( J = 8.5\)Hz, Ph-H) ppm.

All other analytical data correspond to those described in the literature.\(^{115c}\)
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