Towards the enantioselective synthesis of α- and β-amino nitriles via bifunctional ammonium salt catalysis

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to confer the academic degree of
Diplom-Ingenieur
in the Master's Program
Chemistry and Chemical Technology
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Declaration in Lieu of Oath

I hereby declare under oath that the submitted Master’s Thesis has been written solely by me without any third-party assistance, information other than provided sources or aids have not been used and those used have been fully documented. Sources for literal, paraphrased and cited quotes have been accurately credited.

The submitted document here present is identical to the electronically submitted text document.

Linz, December 2019

Paul Zebrowski
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Abstract

The asymmetric synthesis of amino acid analogs remains to be a hot topic in pharmaceutical chemistry, since these compounds are well-established in modern drugs. Over the years, a variety of synthetic approaches emerged, which mainly utilizes chiral auxiliaries, metal complex catalysts and more recently organocatalysts. One of the simplest methodologies is the reaction of cyanide with an imine, which is commonly known as the Strecker reaction. The utilization of other electrophiles as aziridines and aziridinium ions is also possible, but less researched. Bifunctional catalysts based on the cyclohexanediamine backbone, which were devised by our group, may improve the stereoselectivity of these reactions by simultaneously activating the cyanide source and the electrophile.

In summary, this work deals with the enantioselective synthesis of α- and β-amino nitriles, which can be converted to their corresponding amino acids by simple hydrolysis. The main focus was laid on bifunctional phase-transfer catalysis, however, other approaches as the use of chiral auxiliaries were also investigated. The Strecker-type reactions performed well in terms of conversion and yield, but disappointed when it comes to stereoselectivity. The kinetic resolution of a N-Tos aziridine turned out to be more difficult than expected, since nearly no conversion was achieved when PTC with bromide or iodide counter-ions were employed, even under harsh conditions. Halide exchange to fluoride did the trick to some extent, but no selectivity was observed.

The low reactivity of the aziridines was taken as a reason to switch to meso-aziridinium ions, which were generated in-situ from β-chloro amines. These compounds turned out to be more reactive towards the nucleophilic ring-opening reaction, giving full conversion within 72 h in a non-coordinating solvent with retention of the conformation.

Desymmetrization was attempted by use of a chiral auxiliary based on (S)-methylbenzylamine. The auxiliary was incorporated in aziridinium ion precursors synthesized from (Z)-stilbene and cyclohexene, of which only the first one was reactive. The selectivity was easily determined by 1H-NMR spectroscopy of the diastereomeric product mixture, however, no selectivity was found. The utilization of a phase-transfer catalyst, an N-alkylated cinchona species, led to the formation of a side-product, which was identified to be the syn-diastereomer. This phenomenon may be explained due to a nucleophilic substitution of the anti-β-chloro amine with the counter-ion bromide of the catalyst. The resulting syn-β-bromo amine may form an anti-aziridinium ion, which undergoes the reaction with KCN to form the syn-diastereomer. The anti-products were obtained with max. 6 % ee, which of course is negligible. However, this result shows that a stereochemical induction was achieved. Further research in this field, i.e. optimization of catalyst and reaction conditions may improve the diastereomeric ratio and enantioselectivity of this reaction.
1. Introduction

1.1. Amino acids

Amino acids are considered as the “building blocks of life”, since they are found in proteins and peptides in nature. They serve a wide variety of functions in biological systems, such as carriers of bioactive compounds and metabolites. Vauquelin and Robiquet isolated the first amino acid in 1805. The French chemists concentrated a quantity of asparagus juice by evaporation and permitted the residue to stand for a while, whereupon crystal growth was observed. The compound was subsequently named asparagine [1, 2].

1.1.1. Structure and classification

Amino acids contain at least one amino and carboxy functionality. Because this definition is rather ambiguous regarding their structure, amino acids are classified after the carbon atom to which the amino group is attached relative to the carboxy group. The general structures of α-, β- and γ-amino acids are depicted in Figure 1. The substituent “R” (also named sidechain) provides a great variety of amino acids and is also of stereochemical significance. Non-chiral substituents lead to enantiomers, whereas chiral substituents give diastereomers [1].

![Figure 1](image1.png)

**Figure 1:** From left to right: general structures of α-, β- and γ-amino acids. “R” stands for the sidechain of the respective amino acid.

Next to their structure, amino acids are classified after their chemical properties, their incorporation in proteins (proteinogenic and non-proteinogenic), if they can be synthesized by an organism (essential and non-essential) and after their function as substrates in the gluconeogenesis (glucogenic and ketogenic) [1].

1.1.2. Stereochemical aspects

In nature, L-amino acids (from Latin *laevus*, left) are the most common, since they are the building blocks of proteins and peptides. About half a century ago, researcher have assumed that their counterparts—D-amino acids (from Latin *dexter*, right)—have little biological relevancy. Today, it is known that they fulfill specific biological functions, for example D-serine acts as a co-agonist of *N*-methyl-D-aspartate receptors (NMDAR) [3]. Figure 2 shows serine, a proteinogenic and non-essential α-amino acid in its L- (4, 4’) and D-form (5, 5’).
The preference of one of the enantiomers over the other is called homochirality. This phenomenon is seen in nature, as L-amino acids and D-sugars are preferred. It’s responsible, among other things, for the formation of secondary structures as α-helices and β-sheets. Homochirality in proteins plays an important role in the aging process, as isomerized D-aspartic acid residues lead to structural changes, which cause aggregation/malfunctions and ultimately diseases [4].

The origin of biomolecular homochirality is not yet known for certain, but there are theories which are based on chance and deterministic mechanisms [5]. Theories based on chance mechanisms propose that chiral purity is a result of a stochastic process. The initial mixture of enantiomers wasn’t racemic but scalemic (contained an excess of one of its enantiomers) and this asymmetry was later on amplified by autocatalytic reactions. Deterministic theories assume that the initial imbalance in enantiomers was caused by a chiral influence—for example an interstellar object. This theory is supported by the discovery of chiral amino acids in the Murchison meteorite (1969, Australia). The analysis of the organic matter has revealed more than 76 amino acids, known and unknown on Earth. Among them, several compounds showed an excess of L-enantiomer in different degrees (up to 9 %). To minimize the possibility of results based on contamination with terrestrial amino acids, non-terrestrial amino acids were studied which were non-racemizable and not easily impurified [6]. The cause of enantioenriched mixtures in space is currently a matter of speculation, Ultraviolet Circularly Polarized Light (UVCPL) is discussed as initiator of asymmetric photochemistry. Possible sources of UVCPL are neutron stars, magnetic white dwarfs and reflection nebulae [7].

1.1.3. Chemical properties, separation and detection

Amino acids are ampholytes, i.e. they can take up and give off protons and are therefore bases and acids simultaneously. The $pK_a$ of the basic amino functionality is dependent on the sidechain of the amino acid and lies between 9 and 10.5. The carboxy group acts as an acid and its $pK_a$ ranges between 1.7 and 2.4. At physiological pH, the amino group is protonated and the carboxy group deprotonated—this state is often referred to as zwitterion [1]. Figure 3 illustrates this behavior.

![Figure 3: Acid-base behavior of amino acids. The zwitterion 7 has a net charge of 0, the pH at which this species dominates corresponds to its isoelectric point.](image-url)
In addition to the amino and carboxy group, sidechains contribute to the amphoteric character of amino acids. For instance, the sidechain of histidine (1H-imidazole) has an pKₐ of about 6.

Chromatographic separation techniques are used to separate amino acids, among them adsorption and partition as well as ion-exchange chromatography. The adsorption and partition chromatography rely on the relative affinity of compounds towards the stationary and mobile phase. Because amino acids can exist as charged molecules (Figure 3), ion-exchange chromatography and separation by electric methods are possible. Common techniques are electrophoresis, which separates compounds by their electrophoretic mobility and isoelectric focusing (IEF). For the latter method, amino acids respectively peptides/proteins are separated according to their isoelectric point [8].

Amino acids are usually colorless, weak-chromophoric compounds, making them difficult to detect. One way to overcome this is to derivatize the analyte. The classical Ninhydrin method is shown in Scheme 1. Amino acids react with ninhydrin (9) to form a Schiff base, which is blue-violet [1]. Modern methods include mass spectrometry, providing derivatization-free amino acid analysis [9, 10].

![Scheme 1](image)

Scheme 1: Two molecules ninhydrin react with an amino acid to form a colorful Schiff base, which is also known as Ruhemann’s purple.

1.1.4. Industrial uses and production

In addition to their role in nature, amino acids are not less important in industry. In 1908, Japanese chemist Kikunae Ikeda observed the flavor-enhancing effect of monosodium glutamate (MSG). It was the first industrially produced amino acid, commercialized under the trade name Ajinomoto (from Japanese Aji no moto, “at the origin of flavor”) [11]. Since then, the amino acid market demand increased and reached a volume of 8.86 million tons in 2018. With an estimated growth rate of 5–7 % per year, it is expected to reach 11.46 million tons by 2024 [12, 13]. The main applications in industry are flavor enhancers (MSG, serine, aspartic acid, alanine, arginine), animal feed additives (lysine, methionine, threonine, tryptophan), ingredients in cosmetics and medicinal products [13, 14]. In addition, amino acids are common motifs in pharmaceutical drugs, as illustrated in Figure 4 [15].
Figure 4: Small selection of pharmaceutical drugs. Amino acid motifs can be found in Taxol (11) and Bestatin (12) (anti-cancer agents), Reyataz (13) (HIV protease inhibitor), Ritalin (14) (Attention Deficit Hyperactivity Disorder—ADHD—therapeutic) and Onglyza (15) (anti-diabetic medication).

Initially, amino acids were produced by hydrolysis of various protein sources (e.g. blood meal, meat and bone meal, fish meal, soybean meal). The downside of this method is that the process is dependent on the availability of above-mentioned raw materials. However, hydrolysis of protein sources is still performed in industry when it comes to cysteine and cystine (hair and feathers) as well as proline and hydroxyproline (gelatin) [16]. During the 1960s, industry started to shift to the microbiological production of amino acids. Currently, the most widely sold amino acids are L-glutamic acid (in form of MSG), L-lysine and DL-methionine. Glutamic acid and lysine are made by fermentation, whereas methionine is chemically synthesized [14]. Table 1 sums up economically important amino acids with their market size in million metric tons (MMT) and industrial production process.

<table>
<thead>
<tr>
<th>No.</th>
<th>Amino acid</th>
<th>Market size / MMT</th>
<th>Industrial production process</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Amino acid</td>
<td>Market size / MMT (2013)</td>
<td>Industrial production process</td>
</tr>
<tr>
<td>-----</td>
<td>--------------</td>
<td>--------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>13</td>
<td>L-Arginine</td>
<td>0.0015 [19]</td>
<td>Fermentation [19]</td>
</tr>
<tr>
<td>14</td>
<td>L-Alanine</td>
<td>0.0005 [19]</td>
<td>Fermentation, Enzymatic [19]</td>
</tr>
<tr>
<td>15</td>
<td>L-Histidine</td>
<td>0.0005 [19]</td>
<td>Fermentation [19]</td>
</tr>
<tr>
<td>16</td>
<td>L-Proline</td>
<td>0.0005 [19]</td>
<td>Fermentation [19]</td>
</tr>
<tr>
<td>17</td>
<td>L-Serine</td>
<td>0.0004 [19]</td>
<td>Fermentation [19]</td>
</tr>
<tr>
<td>18</td>
<td>L-Tyrosine</td>
<td>0.0002 [19]</td>
<td>Fermentation [19]</td>
</tr>
</tbody>
</table>

Table 1: Global market data of industrially produced amino acids. L-Lysine, DL-methionine, L-threonine and L-tryptophan are used as animal feed additives and make up about 56% of the total market. It is expected that animal feed supplements remain the driving force for market growth in future.

1.1.5. Synthesis

Alongside with biotechnological processes which are used in the production of amino acids in industry, chemical synthesis is performed. Of particular interest are so-called unusual (non-natural) amino acids, which are incorporated in modern drugs [15]. They provide readily functionalized amino and carboxy groups, which are attached to a stereogenic center with one or two diverse sidechains. The major challenge lies in the synthesis of these functionalized compounds in an enantioselective manner. This section focuses on some of the synthetic strategies of the last years.

1.1.5.1. Strecker-type reactions

The Strecker reaction is the oldest known synthesis of α-amino acids. In 1850, Adolph Strecker initially tried to synthesize lactic acid when he treated a solution of acetaldehyde in aqueous ammonia with anhydrous hydrogen cyanide and excess hydrochloric acid. Instead of isolating lactic acid, Strecker obtained an amino acid which he named alanine [20]. The basic reaction scheme is depicted in Scheme 2.

![Scheme 2: Strecker synthesis of α-amino acids. Subsequent hydrolysis of amino nitriles leads to the corresponding amino acids.](image)

The original Strecker reaction only produces a racemic mixture of products. With increasing importance of chirality in drug design, the demand for enantiopure amino acids increased as well, leading to the first asymmetric procedure in 1963 by Harada [21] (Scheme 3). The Japanese chemist treated an aldehyde with optical active α-methylbenzylamine (16) to form a chiral Schiff base. Subsequent addition of HCN afforded the α-amino nitrile, which was then hydrolyzed to the N-protected amino acid. The methylbenzyl group was cleaved off by hydrogenolysis with a palladium catalyst to form the product. Harada’s method is an example of chiral auxiliary mediated asymmetric synthesis, which uses a chiral amine ((S)-methylbenzylamine) as auxiliary.
Scheme 3: Harada’s asymmetric synthesis of (S)-alanine.

This approach turned out to be a general and robust method to prepare α-amino nitriles and amino acids, respectively. Over time, a decent number of chiral auxiliaries have emerged (Figure 5). In addition to α-methylbenzylamine (19) [22], auxiliaries based on sulfinimines [23], hydrazones [24], carbohydrates [25] and phenylglycinol (24) [26] have shown excellent diastereoselectivities.

Figure 5: Chiral auxiliaries used in the asymmetric Strecker reaction.

Unfortunately, the use of auxiliaries comes with major drawbacks. They have to be applied stoichiometrically and need a point of attachment, hence limits the structure of the substrates. Sometimes, auxiliaries need to be removed under harsh conditions (vigorous acid/base treatment, strong reductives such as LiAlH₄), which may lead to product loss [27].

The first metal-catalyzed enantioselective Strecker reaction was reported in 1998 by Jacobsen’s group and involved a chiral aluminum(III)-salen-complex [28]. They observed excellent results when treating aromatic N-allyl aldimines with HCN and catalyst 29 (Scheme 4).

Scheme 4: Jacobsen’s enantioselective Strecker synthesis.

In subsequent years, several others metal complex catalysts followed, including Al, Ti, Yb, V, Ru, Mg and Zr complexed metal catalysts [29]. Some selected examples are shown in Figure 6. The catalyst of choice is strongly dependent on the N-substituent of the imine, respectively on
the electrophile and cyanide source (Table 2). (Hetero-)aromatics usually perform better in terms of conversion and enantioselectivity than aliphatic ones.

Figure 6: Selection of a few chiral metal complex catalysts.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Electrophile</th>
<th>CN⁻ source</th>
<th>Comment</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>N-Diarylphosphinoyl imines</td>
<td>Ethyl cyanoformate</td>
<td>Excellent enantioselectivity at room temperature (r.t.)</td>
<td>[29a]</td>
</tr>
<tr>
<td>32</td>
<td>N-Toluene sulfonyl (tosyl, Tos) imines</td>
<td>Trimethylsilyl cyanide (TMSCN)</td>
<td>Absolute configuration controlled by choice of activator cinchonine or cinchonidine</td>
<td>[29b]</td>
</tr>
<tr>
<td>33</td>
<td>N-Benzyldryl imines</td>
<td>HCN (in-situ)</td>
<td>Hindered 2-substituted aromatic imines don’t decrease the enantioselectivity significantly</td>
<td>[29c]</td>
</tr>
<tr>
<td>34</td>
<td>N-Benzyl (Bn) imines</td>
<td>HCN (in-situ)</td>
<td>Covalent immobilized complexes on organic polystyrene resins (JandaJel and Merrifield). Decrease of enantioselectivity after 3 cycles</td>
<td>[29d]</td>
</tr>
<tr>
<td>35</td>
<td>N-Benzylxocarbonyl (Cbz), N-Benzoyl (Bz) imines</td>
<td>HCN (in-situ)</td>
<td>Addition of PhOLi crucial for stereoselectivity</td>
<td>[29e]</td>
</tr>
<tr>
<td>36</td>
<td>Aromatic and aliphatic nitrones</td>
<td>Acetone cyanohydrin (ACH)</td>
<td>Readily prepared catalyst from commercially available (R,R)- and (S,S)-diethyl tartrates in one step</td>
<td>[29f]</td>
</tr>
<tr>
<td>37</td>
<td>N-(2-Hydroxyphenyl) imines</td>
<td>Bu₃SnCN</td>
<td>Highly-toxic organotin compound used as cyanide source</td>
<td>[29g]</td>
</tr>
</tbody>
</table>

Table 2: Application details of above shown metal complex catalysts. * generated by TMSCN:MeOH (1:1)
Next to chiral auxiliaries and metal complex catalysts, organocatalysts have become quite popular. They tend to be non-toxic, robust, inexpensive and readily available [30]. The first asymmetric Strecker reaction by organocatalysis was performed by Lipton’s group in 1996 [31]. They employed a cyclic dipeptide, composed of (S)-phenylalanine and (S)-α-amino-γ-guanidinobutyric acid. The catalyst turned out to be highly efficient and enantioselective for the cyonation of some N-benzhydryl protected aldimines (Scheme 5). Despite the good results for the unsubstituted, chloro and methoxy-substituted phenyl groups, the enantioselectivity drops significantly when using a nitro-substituted phenyl group or heteroaromatic and aliphatic systems.

![Scheme 5: The first asymmetric Strecker reaction by organocatalysis.](image)

Later, several other organocatalysts emerged, including phase-transfer catalysts (PTC) [32], bifunctional catalysts [33], cinchona alkaloids [34], ureas and thioureas [35], 1,1′-bi-2-naphthol (BINOL) catalysts [36], bisformamides [37] and more.

In 2017, the group of Zhao reported the asymmetric Strecker reaction of N-tert-butyloxycarbonyl (Boc) protected ketimines derived from isatin (2,3-indolindione), catalyzed by thiourea phosphonium salts [33]. Isatin derivatives have attracted strong interest in the last few years, due to their potential biological and pharmaceutical activities [38]. Up until this point, chiral phase transfer catalysts were only applied to catalyze the reaction of aldimines [32]. Several substituted isatins underwent the reaction with TMSCN and NaOAc to give excellent yields (97–99 %) and enantiomeric excesses (72–94 %). Surprisingly, their catalyst turned out to be inefficient in the asymmetric Strecker reaction of N-Boc protected aldimines. Much better results were observed when applying a similar catalyst based on a thiourea and ammonium salt. The group proposed that the narrower space around the ammonia center compared to the phosphonium center may contribute to the stereoselectivity of this reaction. Their most efficient catalysts are illustrated in Figure 7.

![Figure 7: Bifunctional organocatalysts based on thiourea phosphonium and ammonium salts introduced by Zhao and co-workers.](image)
The authors suggested that the actual catalyst is an *in-situ* generated betaine, based on mechanistically studies including $^1$H and $^{31}$P-NMR (Nuclear Magnetic Resonance) experiments. Scheme 6 shows the proposed catalytic pathway and transition-state model. The precatalyst 43 is deprotonated with NaOAc, generating betaine 44, which activates TMSCN to form the actual catalyst 45. In the following step, the isatin derivative undergoes the asymmetric Strecker reaction via the proposed transition state 47.

Scheme 6: Proposed catalytic pathway and transition-state of Zhao's enantioselective cyanation of N-Boc ketimines.

In 2014, He and co-workers reported a highly-enantioselective Strecker reaction of imines containing a thiazole moiety, catalyzed by a cinchona-based squaramide catalyst [39]. Optimization of the reaction conditions allowed yields ranging from 80–99% and enantioselectivities of 86–98%. Imines derived from small-ring heteroaromatic amines (2-methylimidazole, 2-methyl-1,3,4-thiadiazole) resulted the desired product, but without any enantioselectivity. The authors proposed that catalyst 48 activates the heteroaromatic imine by hydrogen-bonding between the two NH groups of the squaramide motif and the two N atoms of the imine. The tertiary amine acts as Lewis base, activating *in-situ* generated HCN from TMSCN. The reaction is assumed to proceed via the suggested transition state 50, yielding the product (Scheme 7). Bifunctional squaramides have proven to catalyze other asymmetric reactions as well, including (sulfa-) Michael additions, aza-Henry and cascade reactions [40].
Scheme 7: Reaction pathway of the enantioselective Strecker reaction by bifunctional squaramide catalysis.

In 2012, the group of Yan devised the enantioselective Strecker reaction by a chiral variant of oligoethylene glycol [41]. The ability of phase-transfer catalysis of such compounds was initially discovered by Lehmkuhl and Rabet in 1977, when they investigated nucleophilic substitution reactions of benzyl bromide with potassium salts in presence of catalytically amounts of poly- and oligoethylene glycols derivatives [42]. The asymmetric approach utilizes 3,3'-diiodine-substituted BINOL-based catalyst 52, which efficiently transforms α-amido sulfones in their corresponding enantoienriched α-amino nitriles (Scheme 8). The α-amido sulfones are precursors of N-Boc protected aldimes and have the advantage that they are usually bench-stable, compared to the latter [43].

Scheme 8: Yan’s asymmetric Strecker reaction catalyzed by a chiral oligoethylene glycol derivative.

The catalytical mechanism is thought to be initialized by simultaneous activation of KCN and amido sulfone (Figure 8). Cyanide eliminates the sulfinate to generate an intermediate imine in
the chiral pocket of the catalyst. Subsequent addition of cyanide affords the optically active α-amino nitrile.

![Chemical structures](image)

**Figure 8:** Suggested catalytic pathway. The enantioselectivity of this catalyst may be ascribed to the ionic and hydrogen-bonding interactions drawn.

Interestingly, carrying out the reaction with N-Boc aldimines as substrates—which are proposed to be generated as intermediates—affords the products with poor yields and lower enantiomeric excesses (24 % yield, 69 % ee). However, when adding one equivalent of phenylsulfinic acid to the reaction mixture of aldime, KCN and catalyst, the enantiomeric excess improves drastically (> 99 % ee). Hence, the sulfinate anion has an important role in the stereocontrol of the catalytic system. It is believed that ionic and hydrogen-bonding interactions between the catalyst, imine, HCN and sulfinate anion are the cause of this.

### 1.1.5.2. Nucleophilic ring-opening of aziridines and aziridinium derivatives

The Strecker reaction is a useful synthetic approach to α-amino nitriles and respectively α-amino acids, as seen in the previous section. They are the most important class of amino acids in nature, but what about the others? With increasing interest of β- and γ-amino acids in pharmaceutical applications, (enantioselective) synthesis strategies seem to be crucial [44, 45]. The nucleophilic ring-opening of aziridines and their positively charged, more reactive analogs, the aziridinium ions, leads to a variety of useful products, including β-amino acids. Reactions of nucleophiles with aziridinium derivatives aren’t as well-researched as with aziridines but of particular interest, because of their potentially higher reactivity [46]. This section will cover some synthetic approaches for the synthesis of β-amino nitriles, originating from aziridines and aziridinium ions.

Aziridines are usually activated to undergo nucleophilic ring-opening reactions. This can be done by derivatizing the nitrogen atom with electron withdrawing groups, specifically the tosyl, o-nitrobenzensulfonyl (nosyl, Nos) and p-nitrobenzoyl (p-NO₂-Bz) group. Due to the relatively low nucleophilicity of the cyanide anion—which may be explained by the negative inductive effect of the more electronegative nitrogen atom [47]—the activation of aziridines is a major step to allow the reaction to occur (Figure 9). Over the years, several catalysts have emerged which mostly belong to the group of Lewis acids (metal complex catalysts, e.g. Yb, La and Y [48]) and bases [49], but also tetrabutylammonium fluoride (TBAF) [50] and lithium perchlorate [51] were successfully employed.
The cleavage of non-activated aziridines (57) with cyanide usually don’t occur. By introducing an EWG (58), the reaction is allowed to proceed. Aziridinium ions (59) have as result of their positive charge a potentially higher reactivity.

To obtain enantioenriched products, two approaches are common. Racemic mixtures can be separated by kinetic resolution, where one enantiomer is stereoselectively converted into the desired optically active product. The other enantiomer either remains untouched or is also converted by means of a parallel kinetic resolution. In the latter case, two enantioenriched products are obtained, increasing the theoretical yield up to 100 %. When the compound is easily racemized, dynamic kinetic resolution may be an option [52]. However, the most common method for aziridines is the enantioselective desymmetrization of meso-compounds. Treating meso-aziridines with a cyanide source and a chiral catalyst leads to enantioenriched β-amino nitriles, which was firstly reported by Shibasaki and co-workers in 2005 (Scheme 9) [48]. In preliminary experiments they identified N-p-nitrobenzoyl aziridines as the best substrates in terms of yield and enantioselectivity. N-Tos, N-Nos and N-Boc aziridines underwent the reaction with insufficient results, N-benzyl and N-phosphinoyl aziridines didn’t undergo the reaction at all. The reaction provided good yields and enantioselectivities for cyclic and acyclic meso-aziridines. The drawback is the relatively high catalyst loading (10–20 mol%).

In 2007, Shibasaki’s group followed up with another paper reporting on improvements of this reaction by optimizing their chiral ligand and reaction conditions, resulting in enantioselectivities of up to 99 % [48].

In 2009, Wu and co-workers reported on the application of discrete dimeric yttrium-salen complexes, that catalyze the enantioselective desymmetrization of N-p-nitrobenzoyl meso-aziridines with trimethylsilyl azide (TMSN₃) and TMSCN (Figure 10). The azidination of most substrates underwent with high yields and enantioselectivities, whereas the cyanation performed with less success. However, the nucleophilic ring-opening of some meso-aziridines led to remarkable results (85–87 % yield, 92–99 % ee).
Figure 10: Dimeric yttrium-salen complex reported by Wu et al. [48*].

In the same year, Minakata’s group introduced a kinetic resolution of aziridines by ring-opening with TMSCN [53]. The reaction utilizes chiral hydroquinidine (anthraquinone-1,4-diyl) diether—(DHQD)$_2$AQN—for asymmetric recognition and subsequent cyanation. 2-substituted-N-nosylaziridines are suitable substrates for this reaction, ring-opening of N-Tos aziridines didn’t proceed the reaction with a noteworthy enantioselectivity (product: 6 % ee, aziridine: 2 % ee). The cyanation of several arylmethylated N-nosylaziridines led to the corresponding β-amino nitriles in moderate to good yields and good to excellent enantioselectivities (Scheme 10).

Scheme 10: Minakata’s kinetic resolution of 2-substituted-N-nosylaziridines.

Aziridinium ions usually don’t need an activation agent to undergo nucleophilic ring-opening reactions. In most cases, they are used as in-situ generated intermediates derived from β-halo amines. In 1999, the group of Anderson observed that β-amino alcohols are converted to β-amino chlorides with net retention of their conformation, when treating them with methanesulfonyl chloride (mesyl chloride, MsCl) and triethylamine (TEA, NEt$_3$) [54]. The stereospecificity of this reaction is explained due to formation of an aziridinium ion intermediate. Subsequent nucleophilic ring-opening of this intermediate leads to a double inversion of the stereocenter. One year later, Gmeiner and co-workers made the same observation when they tried to sulfonate N,N-dibenzylamino alcohols [55]. In addition, they have found that also the reaction of β-chloro amines with NaCN proceeds through an aziridinium intermediate (Scheme 11).

In a first step, the hydroxyl group of β-amino alcohol 67 is mesylated by MsCl, followed by a nucleophilic attack of the adjacent amino group to yield aziridinium intermediate 68. Subsequent chlorination results the β-amino chloride 69. The nucleophilic ring-opening of aziridinium ion 70
with cyanide leads to the desired β-amino nitrile 71, which can be further hydrolyzed to its corresponding β-amino acid 72.

Scheme 11: Stereoselective synthesis of β-amino acids through aziridinium intermediates. The reaction proceeds through overall net retention of conformation.

In 2003, Nelson investigated the ion-pairing capability of aziridinium species with chiral borate anions, which would allow desymmetrization of meso-aziridinium ions by nucleophilic ring-opening [56]. His group chose the amination of a β-chloro amine, which was synthesized in a 3-step procedure from (Z)-stilbene. The experiments were carried out in a refluxing mixture of tetrahydrofuran (THF) and toluene (PhMe). Addition of chiral additives led to rather low yields and enantioselectivities (< 30 %, < 15 %), however, they were comparable with other studies at that time [57]. Better results were reported by Toste and co-workers five years later, when they utilized a phase-transfer catalyst based on an axially chiral phosphate ion [58]. His group published some remarkable results in the nucleophilic ring-opening of meso-aziridinium ions with various alcohols (Scheme 12). In addition, they expanded their methodology to meso-episulfonium ions with good results (4 examples, 90–98 % yield and 87–91 % ee).

Scheme 12: Toste’s nucleophilic ring-opening of aziridinium ions under asymmetric ion pair catalysis.
In 2017, Duarte and Paton published a paper which covers a theoretical study of Toste’s work, including solvation molecular dynamic (MD) simulations. The resulting transition states of the catalyzed ring-opening of meso-aziridinium (5AZR) and meso-episulfonium ions (THR) in toluene are depicted in Figure 11 [59]. The alkyl chain of the nucleophile (neo-pentanol) is oriented away from the catalyst, thus allowing a broad variety of alcohol nucleophiles. This is in agreement with the experimental data obtained by Toste and co-workers.

![Figure 11: Transition states of the \((S,S)\) and \((R,R)\)-enantiomer of meso-aziridinium (5AZR) and meso-episulfonium ion (THR) [58].](image)

Chiral anion mediated asymmetric catalysis may be promising in the ring-opening of aziridinium ions with cyanide. However, to best of my knowledge, no such examples have been reported yet.

In 2015, Chong’s group published a comparative evaluation of nucleophilic ring-opening reactions of β-halo amines and meso-aziridinium ions, respectively [60]. They have verified that aziridinium ions were more sensitive towards nucleophilic ring-opening reactions than their aziridine congeners, based on the substantial difference of reaction times (Scheme 13).
Scheme 13: Reactivity of aziridinium intermediates compared to activated aziridines.

Her group followed up with another publication in 2016, where they demonstrated the one-pot synthesis of N-protected β-amino nitriles from β-amino alcohols [61]. Starting from enantiopure β-amino alcohol 82, bromination with N-bromosuccinimide (NBS) gives β-halo amine 83, which undergoes aziridinium intermediate 84 and is cyanated to yield the desired β-amino nitrile 85 in quantitative yield and excellent stereoselectivity (Scheme 14).

Scheme 14: One-pot synthesis of β-amino nitriles from β-amino alcohols.

1.2. Asymmetric organocatalysis

The journal Nature defines asymmetric catalysis as such: “Asymmetric catalysis is a type of catalysis in which a chiral catalyst directs the formation of a chiral compound such that formation of one particular stereoisomer is favoured.” [62]. Organocatalysts are small organic molecules, predominately composed of carbon, hydrogen, nitrogen, oxygen, phosphorus and sulfur. They catalyze the reaction by lowering the activation barrier and are not consumed by the reaction itself, thus may be used substoichiometrically. The first reports of asymmetric organocatalysis date back more than 100 years ago, e.g. Paul Southard Fiske described the moderately enantioselective cyanation of benzaldehyde (cyanohydrin reaction), catalyzed by alkaloids in his PhD thesis from 1911 [63]. However, the lack of efficiency compared to transition-metal complexes and enzymes led to little attention from the scientific community. It wasn’t until the 1970’s that the groups of Hajos [64] and Wiechert [65] reported on a highly enantioselective aldol reaction catalyzed by simple proline. Since then, organocatalysis emerged and finally became one of the main methodologies in asymmetric synthesis [66]. This section deals with some recent techniques, namely bifunctional and ion pairing catalysis.
1.2.1. Bifunctional catalysis

Bifunctional catalysts activate substrates by two functionalities, e.g. acid, base, hydrogen-bonding, pi-stacking and several other interactions. Nature uses this principle, inter alia, in the Type II zinc enolate aldolase (Scheme 15) [67]. The formation of the enolate from dihydroxyacetone phosphate (86) is eased by Lewis acid catalysis, whereas glyceraldehyde 3-phosphate (87) is activated by hydrogen bonding. Nucleophilic attack of the enolate to the carbonyl group of the aldehyde and subsequent decomplexation yields the aldol product. Lewis and Brønsted acid as well as the surrounding structure of the two active sites are responsible for the high reactivity and stereoselectivity of this reaction.

![Scheme 15: Type II aldolase mediated stereoselective aldol condensation.](image)

This approach, therefore, may increase the selectivity of a catalytic system. However, reaction conditions and catalysts have to be very well optimized, since these systems are usually more complex. For instance, the Lewis acid may react with the Lewis base—known and feared as self-quenching—or a nucleophile [68].

In the following, three out of numerous examples of bifunctional organocatalysts are given. They are especially noteworthy regarding their field of application and selectivity, respectively.

In 2003, Takemoto and co-workers devised an enantioselective Michael reaction of malonates to nitroolefins, catalyzed by bifunctional amino-thiourea catalyst 92 (Scheme 16) [69]. The resulting chiral nitroalkanes are of synthetic interest, since the nitro group provides a versatile reactivity [70]. The catalyst was designed to activate both reactants simultaneously—malonate and nitroolefin. Both oxygen atoms of the nitroolefin are activated by the acidic hydrogens of the thiourea, whereas the malonate is activated by a tertiary amine. Highest enantioselectivities were achieved when using aromatic substituted nitroolefins (> 90 % ee), alkyl nitroolefins performed worse (about 80 % ee).
Scheme 16: Takemoto’s enantioselective Michael reaction of malonates to nitroolefins catalyzed by a bifunctional amino-thiourea catalyst.

Later, Takemoto’s group extended the scope of the nucleophiles to β-ketoesters and 1,3-diketones [71]. The catalyst was applied in aza-Henry reactions with some success using N-phosphinoyl imines as electrophiles (57–91 % yield, 63–76 % ee) [72a]. Interestingly, N-Boc imines underwent the reaction with much better results (75–94 % yield, 89–99 % ee) [72b], indicating that the N-substituent has a determinant effect on yield and enantiomeric excess. Moreover, the change of this group led to products of inverse absolute configuration. Takemoto’s catalyst has been successful employed in various other reactions [73a–d], more recently in the asymmetric aza-Michael addition of α-, β-unsaturated carboxylic acids [73e].

In 2012, Dixon introduced a cinchona-derived bifunctional phase-transfer catalyst. The catalyst turned out to be highly efficient in nitro-Mannich (aza-Henry) reactions, tolerating a variety of α-amido sulfones and nitroalkanes (Scheme 17). Preliminary experiments have shown that the selection of base (KOH) was crucial for the reaction, since K₂CO₃, Cs₂CO₃ and CsOH didn’t give any product. Recently, the group of Duan successfully employed derived catalysts in nitro-Mannich reactions of (trifluoromethyl) ketimines with nitromethane [74a–b] and amido sulfones with β-, γ-unsaturated nitroalkenes [74c]. In addition, this type of catalyst was successfully employed in enantioselective cyclization reactions by Smith and co-workers [75].
Scheme 17: Dixon’s enantioselective nitro-Mannich reaction of nitroalkanes to α-amido sulfones.

In 2016, Chen and co-workers reported on the enantioselective Morita-Baylis-Hillman (MBH) reaction between 7-azaisatins and maleimides, catalyzed by β-isocupreidine (β-ICD, 100) (Scheme 18) [76]. The MBH-reaction is a powerful method for CC-bond formation and widely used in organic synthesis [77]. The general mechanism, composed of three main steps—Michael addition, aldol reaction and elimination—is uncontroversial in the scientific community. However, the elimination step is still discussed [78]. Previous reports of MBH reactions catalyzed by β-ICD suggested that the C6'-OH group of the catalyst facilitates the proton transfer step and stabilizes the transition state [79].

Scheme 18: Enantioselective Morita-Baylis-Hillman reaction catalyzed by β-ICD.
1.2.2. Ion-pairing catalysis

Every chemical reaction proceeds through polarized states and many of them have at least one discrete charged intermediate. The basic idea of (asymmetric) ion-pairing catalysis is to bring charged molecules in the proximity of a chiral catalyst to react in a stereospecific manner. This can either be done with charged or neutral catalysts. Charged catalysts form an ionic pair with the substrates (102, 105), whereas neutral catalysts bind the compounds by various other non-covalent interactions, like hydrogen-bonding (103, 104) (Figure 12).

![Figure 12: Examples of chiral ion-pairs.](image)

Solvation effects are crucial, since solvent molecules may interfere with the chiral binding sites of the catalyst. Therefore, higher selectivities are commonly observed in non-polar solvents. Compared with iminium, Lewis and Brønsted acid catalysis, catalyst-substrate interactions are relatively weak, thus making it more challenging to translate the stereochemical information. Nevertheless, chiral ion-pairing catalysis has been successfully performed in various reactions [80].

Positively charged substrates may form ionic pairs with chiral anionic catalysts. In 2010, Antilla and co-workers reported on the first catalytic enantioselective pinacol rearrangement (Scheme 19) [81]. Protonation of indolyl diol 106 with chiral phosphoric acid derivative 107 and subsequent water elimination gives the ion-pair 108. Rearrangement yields the desired product. Interestingly, decrease of the catalyst loading from 10 to 2.5 % had a beneficial effect on both yield and enantioselectivity, whereas decrease of the reaction temperature to 0 °C caused the enantioselectivity to drop.

![Scheme 19: Proposed mechanism of the catalytic asymmetric pinacol rearrangement.](image)

Cation-binding catalysis utilizes the well-established cation-binding properties of polyethers. These compounds bind the reacting ion-pair, anion and cation, via hydrogen-bonding. This is in
contrast to omnium catalysts, which only transfer the anion into the organic phase. In 2003, Akiyama’s group devised a chiral crown ether for asymmetric Michael additions. The catalyst 112 is derived from a naturally abundant carbohydrate (L-quebrachitol) and has shown remarkable enantioselectivity in the reaction of glycine imine with alkyl vinyl ketones and esters (> 80 % ee) (Scheme 20) [82]. Acrylonitrile performed worse (46 % ee).

![Scheme 20: Akiyama’s enantioselective Michael reaction of glycine Schiff base with various Michael acceptors.](image)

Anion-binding catalysts usually are based on strongly polarized N-H bonds found in ureas, thioureas and thiophosphoramides [83, 84]. More recently, catalysts based on O-H and even less-polarized C-H or C-X bonds have emerged [85]. They have proven to bind several anions, including alkoxides, cyanide and halides through non-covalent interactions [80\textsuperscript{a}]. In 2019, Gouverneur reported on the enantioselective ring-opening reaction of intermediary generated meso-aziridinium ions with fluoride [86] (Scheme 21). Her group employed novel chiral bis-urea catalyst 116, containing the 1,1’-binaphthyl-2,2’-diamine (BINAM) core. Mono-alkylation of the urea turned out to be crucial for the stereoselectivity, since the non-alkylated compounds showed only little selectivity (55:45 enantiomeric ratio, e.r.).
Scheme 21: Gouverneur’s nucleophilic ring-opening auf meso-aziridinium ions with fluoride.

1.2.2.1. Phase-transfer catalysis

When two species are in immiscible phases, the probability of them to collide and therefore react is reasonably low. This problem is addressed by employing phase-transfer catalysts, which provide the necessary spatial proximity by extracting one of the species across the interface into the other phase. The terminus “phase-transfer catalysis” is believed to be coined by Charles M. Starks, however, the foundations were laid by Makosza, Starks and Brandstrom in the 1970s [87]. The substitution of an alkyl halide solved in hydrocarbons with aqueous cyanide solution, catalyzed by a quaternary ammonium salt is a common example (Figure 13).

The mechanism of phase-transfer catalysis is not fully understood, but there are two main theories which differ in the formation of the reactive onium species. Starks proposed that the onium salt is generated in the aqueous phase before it moves into the organic phase (extraction mechanism) [87a]. Makosza suggested that the generation takes place at the interface of both phases (interfacial mechanism) [87b]. Both mechanisms are probably correct, depending on the properties (size, lipophilicity, …) of the catalyst. Starks’s theory is more likely for small to medium sized catalysts, whereas Makosza’s mechanism may fit to medium to large sized compounds [88].

![Figure 13: The phase-transfer catalyzed cyanide displacement reaction. Whereas the mechanism follows the theory of Starks or Makosza, may be dependent on the properties (size, lipophilicity, …) of the catalyst. Q = quaternary ammonium](image-url)
The first efficient chiral phase-transfer catalyst based on an alkaloid as the chiral backbone was introduced by the Merck research group in 1984 [89]. They devised the asymmetric alkylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (119) with methyl chloride (120), catalyzed by N-(4-trifluoromethylbenzyl)cinchoninium bromide (121). The desired product was obtained with excellent yield and selectivity (Scheme 22). Up until today, this type of phase-transfer catalyst is used for various applications because of the readily availability of cinchona alkaloids [90].

Scheme 22: Phase-transfer catalyzed alkylation of 118 by the Merck group.

In 1999, Maruoka’s group introduced C2-symmetric chiral quaternary ammonium salt catalysts for the asymmetric α-alkylation of glycine Schiff base with various alkyl bromides and iodides (Scheme 23) [91a]. The catalyst stabilizes the (E)-conformation of the enolate, which si-face is efficiently shielded by the binaphthyl and β-naphthyl (β-Np) moieties. Subsequent alkylation yields the (R)-enantiomer in excellent selectivities. Further optimization of the catalyst provided the alkylation products in even higher yields and enantiomeric excesses (67−99 % yield, 97–99 % ee) [91b−c]

Scheme 23: Enantioselective α-alkylation of glycine Schiff base with alkyl halides by Maruoka and co-workers.

Maruoka applied this catalyst type to a variety of reactions, including Strecker-type [32a−b] reactions, aldol reactions of glycine Schiff base with aldehyde acceptors [92], conjugate additions of nitroalkanes to alkyldiene malonates and cyclic α-, β-unsaturated ketones [93] as well as additions of β-keto esters to α-, β-unsaturated carbonyl compounds [94]. The catalyst was later on modified by introducing alcohol groups to gain stereocontrol by bifunctionality [95]. In addition, the group introduced chiral bifunctional quaternary phosphonium [96] and tertiary sulfonium salts [97] based on the chiral BINOL backbone (Figure 14). Maruoka has recently published a comprehensive review on this subject [98].
In 2015, the group of Deng devised the asymmetric umpolung reaction of imines. Imine 132 is deprotonated by KOH to form 2-azaallyl anion 135, which acts as nucleophile for Michael additions to enals (Scheme 24) [99a]. This reaction is highly enantioselective and was later on extended to enones and carboxylic acid derivatives [99b-c]. It is noteworthy that imines usually undergo chemical reactions as electrophiles due to their partially positive charge on the carbon atom. Deng and co-workers demonstrated that this polarity can be successfully inverted and that the resulting 2-azaallyl anions undergo conjugate addition reactions.

Scheme 24: Umpolung reaction of N-protected trifluoromethyl ketimines by Deng.
2. Objectives

The main objective of this work was the asymmetric synthesis of \(\alpha\)- and \(\beta\)-amino nitriles via bifunctional phase-transfer catalysis. As shown in section 1.1.5., these compounds are synthesized by Strecker-type reactions and nucleophilic ring-opening reactions of aziridines and aziridinium ions.

The recent success of bifunctional PTC in Strecker-type reactions [33], few reports of kinetic resolution of aziridines by organocatalysts [46, 53] and the fact that there have been no reports on desymmetrization of meso-aziridinium ions with cyanide are encouraging to delve into this field [33]. Since our group has a strong interest in bifunctional ammonia salt catalysis, we were excited to investigate the performance of our catalysts based on the cyclohexanediamine backbone [100].

Three approaches of synthesizing enantioenriched \(\alpha\)- and \(\beta\)-amino nitriles were taken: 1) Strecker-type reactions of \(N\)-protected aldimines, 2) kinetic resolution of \(N\)-tosyl 2-phenylaziridine and 3) desymmetrization of \textit{in-situ} generated meso-aziridinium ions (Figure 15).

\[ \text{Figure 15: Strategies of synthesizing enantioenriched } \alpha\text{- and } \beta\text{-amino nitriles in this work.} \]
3. Results and discussion

3.1. Strecker-type reactions

3.1.1. Preparation of starting compounds

The N-protected aldimines were synthesized following the procedures given in literature [101–103] (Scheme 25). N-Tosyl imine 145 was obtained in 56 % yield by refluxing a solution of benzaldehyde and p-toluenesulfonamide in toluene under acid catalysis. N-Benzyl imine 147 was obtained in 64 % yield by treating benzaldehyde with benzylamine in dichloromethane (DCM) along with 3 Å molecular sieves (M.S). N-Boc imine 153 was obtained in overall 78 % yield following a 2-step procedure. First, a mixture of benzaldehyde, tert-butyl carbamate, sodium p-toluenesulfinate and formic acid was stirred in aqueous methanol. The formed amido sulfone was then subsequently dissolved in a suspension of potassium carbonate in DCM to yield the desired product.

Scheme 25: Synthesis of N-Tos, N-Bn and N-Boc imines for the Strecker-type reactions.
3.1.2. Racemic reactions

Racemic approaches were applied to synthesize small quantities for High Performance Liquid Chromatography (HPLC) standards. Singh et al. reported on a procedure [104] involving catalysis by LiClO₄ with good yields (> 86 %) for several N-tosyl protected imines. Even though the reaction was carried out multiple times, the reported yield of 156 (92 %) couldn’t be reproduced. The main problem with the reactions of N-Tos and N-Bn protected imines was the inability to fully convert even after prolonged reaction times (72 h compared to 6 h in the original publication), whereas the N-Boc imine was sensitive to hydrolyzation. Isolation by column chromatography turned out to be tricky due to the similar retention behavior of imines and products (Scheme 26).

![Scheme 26: Racemic Strecker-type reaction of N-protected aldmines with TMSCN under LiClO₄ catalysis.](image)

Since phase-transfer catalysts are well-known to catalyze Strecker-type reactions (1.1.5.1), the procedure was adapted to use achiral tetra-n-butylammonium bromide (159, TBAB) as PTC and toluene as solvent. In consequence, the conversions and isolated yields increased significantly (Scheme 27). The results of the racemic Strecker-type reactions are summed up in Table 3.

![Scheme 27: Racemic Strecker-type reaction of N-protected aldmines with TMSCN under phase-transfer catalysis.](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>CN⁻ source</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T</th>
<th>t / h</th>
<th>Conversion[^a] / %</th>
<th>Yield[^b] / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>TMS CN</td>
<td>LiClO₄</td>
<td>ACN</td>
<td>r.t.</td>
<td>72</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>147</td>
<td>TMS CN</td>
<td>LiClO₄</td>
<td>ACN</td>
<td>r.t.</td>
<td>72</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>153</td>
<td>TMS CN</td>
<td>LiClO₄</td>
<td>ACN</td>
<td>r.t.</td>
<td>72</td>
<td>99</td>
<td>24</td>
</tr>
<tr>
<td>145</td>
<td>TMS CN</td>
<td>TBAB</td>
<td>PhMe</td>
<td>r.t.</td>
<td>72</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>147</td>
<td>TMS CN</td>
<td>TBAB</td>
<td>PhMe</td>
<td>r.t.</td>
<td>72</td>
<td>96</td>
<td>82</td>
</tr>
<tr>
<td>153</td>
<td>TMS CN</td>
<td>TBAB</td>
<td>PhMe</td>
<td>r.t.</td>
<td>72</td>
<td>99</td>
<td>67</td>
</tr>
</tbody>
</table>

[^a]: Determined by ¹H-NMR spectroscopy
[^b]: Isolated yield after column chromatography

Table 3: Results of the racemic Strecker-type reactions.
3.1.3. Attempted enantioselective reactions

Bifunctional phase-transfer catalysts based on cinchona alkaloids (160, 163) and cyclohexanediamine (161, 162) as well as monofunctional PTC 164 were chosen for catalyst screening (Figure 16).

First tests showed that the \( N\)-Bn imine was less reactive, whereupon it was decided to progress with the \( N\)-Tos and \( N\)-Boc imines. The reason for the lower reactivity of the \( N\)-Bn imine may be explained by the electron-donating effect of the benzyl group, which lowers the electrophilicity of the carbon atom. \( N\)-sulfonyl and \( N\)-carbonyl imines are considered as activated, since these \( N\)-substituents are electron-withdrawing [105].

In general, the base-free reaction of \( N\)-Tos imine with TMSCN underwent with excellent conversions (91–99 %) and good to excellent yields (76–99 %). Interestingly, the addition of \( \text{Cs}_2\text{CO}_3 \) led to a significant reduction of the yield (\( \leq 60 \% \)) when employing catalysts based on the cyclohexanediamine backbone. In these cases, the crude yields were very low (\( \leq 65 \% \)), indicating that the imine decomposed and that its products were extracted during the aqueous work-up process. However, this was not further investigated. The reactions with other cyanide sources such as \( \text{ACH} \) and \( \text{KCN} \) also gave the desired compound, although with varied success. \( \text{ACH} \) was employed as successfully as TMSCN (\( \geq 93 \% \) yield), whereas the reactions with aqueous \( \text{KCN} \) resulted in poor yields (\( \leq 37 \% \)).
The Strecker-type reactions of N-Boc imine with TMSCN gave similar results, but with an interesting exception. In nonpolar toluene, the addition of base—as observed in the reactions of N-Tos imine—decreased the yield of the amino nitrile whereas in the more polar solvents DCM and methyl tert-butyl ether (MTBE), yields were improved. This beneficial effect is probably due to the higher stability of N-Boc imine under basic conditions, thus increasing the time frame in which it may react with TMSCN.

The addition of base was not necessarily needed but seemed to accelerate the conversion rate determined by TLC monitoring. One plausible explanation was given by the group of Zhao [33]. They proposed that deprotonation of an electron-deficient thiourea by a base may form a betaine, which subsequently activates TMSCN by nucleophilic substitution (1.1.5.1, Scheme 6). However, the accelerating effect of Cs$_2$CO$_3$ was also observed in reactions employing monofunctional PTC 164.

Unfortunately, no significant chiral induction was observed. The results of the catalyst screening are depicted in Table 4.

Scheme 28: General reaction scheme of the attempted asymmetric Strecker reaction.

<table>
<thead>
<tr>
<th>No.</th>
<th>Imine</th>
<th>CN source</th>
<th>Cat.</th>
<th>Base</th>
<th>Solvent</th>
<th>$t$ / h</th>
<th>Conv.$^a$ / %</th>
<th>Yield$^b$ / %</th>
<th>e.r.$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>145</td>
<td>TMSCN</td>
<td>160</td>
<td>-</td>
<td>PhMe</td>
<td>24</td>
<td>95</td>
<td>76</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>145</td>
<td>TMSCN</td>
<td>160</td>
<td>Cs$_2$CO$_3$</td>
<td>PhMe</td>
<td>24</td>
<td>99</td>
<td>77</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>147</td>
<td>TMSCN</td>
<td>160</td>
<td>-</td>
<td>PhMe</td>
<td>72</td>
<td>53</td>
<td>21</td>
<td>50:50</td>
</tr>
<tr>
<td>4</td>
<td>147</td>
<td>TMSCN</td>
<td>160</td>
<td>Cs$_2$CO$_3$</td>
<td>PhMe</td>
<td>72</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>PhMe</td>
<td>72</td>
<td>99</td>
<td>90</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>Cs$_2$CO$_3$</td>
<td>PhMe</td>
<td>72</td>
<td>99</td>
<td>61</td>
<td>50:50</td>
</tr>
<tr>
<td>7</td>
<td>145</td>
<td>ACH</td>
<td>161</td>
<td>K$_2$CO$_3$ (aq.)</td>
<td>PhMe</td>
<td>24</td>
<td>99</td>
<td>95</td>
<td>50:50</td>
</tr>
<tr>
<td>8</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>MTBE</td>
<td>72</td>
<td>99</td>
<td>91</td>
<td>50:50</td>
</tr>
<tr>
<td>9</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>Cs$_2$CO$_3$</td>
<td>MTBE</td>
<td>72</td>
<td>99</td>
<td>60</td>
<td>50:50</td>
</tr>
<tr>
<td>10</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>DCM</td>
<td>72</td>
<td>91</td>
<td>85</td>
<td>50:50</td>
</tr>
<tr>
<td>11</td>
<td>145</td>
<td>TMSCN</td>
<td>161</td>
<td>Cs$_2$CO$_3$</td>
<td>DCM</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>153</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>PhMe</td>
<td>72</td>
<td>99</td>
<td>79</td>
<td>50:50</td>
</tr>
<tr>
<td>13</td>
<td>153</td>
<td>TMSCN</td>
<td>161</td>
<td>Cs$_2$CO$_3$</td>
<td>PhMe</td>
<td>72</td>
<td>99</td>
<td>40</td>
<td>50:50</td>
</tr>
<tr>
<td>14</td>
<td>153</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>MTBE</td>
<td>72</td>
<td>99</td>
<td>54</td>
<td>50:50</td>
</tr>
<tr>
<td>15</td>
<td>153</td>
<td>TMSCN</td>
<td>161</td>
<td>Cs$_2$CO$_3$</td>
<td>MTBE</td>
<td>72</td>
<td>99</td>
<td>74</td>
<td>50:50</td>
</tr>
<tr>
<td>16</td>
<td>153</td>
<td>TMSCN</td>
<td>161</td>
<td>-</td>
<td>DCM</td>
<td>72</td>
<td>99</td>
<td>64</td>
<td>50:50</td>
</tr>
</tbody>
</table>
Table 4: Results of the catalyst screening for the Strecker-type reaction. [a] Determined by 1H-NMR spectroscopy [b] Isolated yield after column chromatography [c] Determined by HPLC on a chiral stationary phase

3.2. Kinetic resolution of N-tosyl-2-phenylaziridine

3.2.1. Preparation of the starting compound

N-Tosyl-2-phenylaziridine (139) was synthesized by following a procedure reported by Morgan and co-workers in 2013 [106]. The compound was obtained in 93 % yield by reacting styrene with chloramine-T trihydrate in DCM–H₂O, catalyzed by iodine and tetraethylammonium iodide (Scheme 29).

Scheme 29: Synthesis of starting-compound N-tosyl-2-phenylaziridine (139).

3.2.2. Racemic reaction

Hou’s group has demonstrated that N-tosyl aziridines are efficiently opened with TMSCN when using TBAF (169) as catalyst [50]. When the experiment was replicated in the lab, good conversion and yield were observed in relatively short time (Scheme 30), thus promising that chiral phase-transfer catalysts may be employed in the kinetic resolution of these compounds.
Scheme 30: Hou’s ring-opening of N-tosyl aziridines with TMSCN, catalyzed by TBAF.

3.2.3. Attempted kinetic resolution

Bifunctional ammonia salt catalysts based on the cyclohexanediamine backbone (161, 170) and cinchona alkaloids (171–173) were chosen for catalyst screening (Figure 17).

Figure 17: Catalysts chosen for the attempted kinetic resolution of 139.

In the first experiments, the reaction was carried out under elevated temperatures with and without base (N,N-diisopropylethylamine, DIPEA) for TMSCN activation. Unfortunately, little to none conversion was observed when employing catalyst 161, neither in toluene nor in THF, indicating that the presence of fluoride ions may be crucial for this reaction. Therefore, potassium fluoride was added to the catalytic system, but with no success. The next logical step was to employ chiral PTC with fluoride counter-ions, therefore catalysts 161 and 171 were treated with silver fluoride in aqueous MeOH to form 170 and 172 [107]. Reactions carried out with these compounds indeed showed some catalytic activity in the ring-opening reaction, but with poor conversions and no chiral induction (Table 5, entries 5 and 9).

Because of the low reactivity of the N-Tos aziridine, it was decided to employ aziridinium ions. The results of this approach are discussed in the next section.
Scheme 31: General reaction scheme of the attempted kinetic resolution of 139.

Table 5: Results of the catalyst screening for the nucleophilic ring-opening of 139. [a] Determined by $^1$H-NMR spectroscopy [b] Isolated yield after column chromatography [c] Determined by HPLC on a chiral stationary phase

3.3. Desymmetrization of meso-aziridinium ions

3.3.1. Preparation of starting compounds

Aziridinium-ions are generally more reactive than aziridines (1.1.5.2). Usually, they are non-isolable and therefore prepared in-situ to undergo nucleophilic ring-opening reactions. A common way to do this is by intramolecular ring-closure of β-halo amines. These compounds are most conveniently synthesized in a 3-step sequence: 1) epoxidation of an alkene, 2) ring-opening with an amine and 3) halogenation. Within the scope of this work, four β-chloro amines based on (Z)-stilbene were synthesized (Scheme 32).
Scheme 32: Synthesis overview of β-chloro amines.

Following the procedure of Schneider and Mai [108], meso-epoxide 175 was prepared in 82% yield by epoxidation of the alkene via meta-chloroperoxybenzoic acid (mCPBA) in DCM.

The aminolysis of the epoxide was carried out with or without Lewis acid catalysis, depending on the amine employed. cis-Stilbene oxide was readily converted when treating it with an excess of pyrrolidine or morpholine at 110 °C, whereas it didn’t react with diethylamine or dibenzylamine at these conditions. Introduction of 3 mol% Sc(OTf)₃ as a Lewis acid catalyst eventually led to satisfying conversions (72–88%). The β-amino alcohols 176 were obtained in yields of 52–82% [86, 109].

The β-amino alcohols were chlorinated with MsCl and NEt₃ in DCM. Nelson and co-workers proofed that this reaction proceeds through an aziridinium intermediate, thus retaining the anti-configuration [56]. Attempts to isolate the β-chloro amines 181 by column chromatography (silica gel, aluminum oxide, several mobile phases) inevitably led to hydrolysis, therefore it was decided to use them without any purification. In this case, the yields of 80–94% refer to the crude products. The structures and overall yields of the synthesized β-chloro amines are depicted in Figure 18.
Figure 18: Structures and overall yields of the synthesized β-chloro amines.

It should be noted that the aziridinium ion precursors are surprisingly stable at room temperature. However, it is advisable to store them under inert gas, since they hydrolyze over time.

3.3.2. Racemic reactions

Inspired from the recent fluorination of meso-aziridinium ions by Gouverneur and co-workers (1.2.2., Scheme 21) [86], the racemic reaction was carried out under similar conditions. 1-(2-Chloro-1,2-diphenylethyl)pyrrolidine (181a) was chosen as model substrate and treated with KCN in neutralized CHCl₃ with 5 mol% 1,3-diphenylthiourea (DPTU, 183) as potential hydrogen-bonding catalyst (Scheme 33).

Scheme 33: Racemic ring-opening of 181a with KCN.

It was found that the reaction proceeded readily at room temperature within 72 h to give the crude product in 99 % yield. ¹H, ¹³C and ESI analysis suggested that the product indeed is the desired β-amino nitrile. However, the relative configuration couldn’t be confirmed, since the compound hadn’t been characterized yet. This information is important, as it gives insight into
the reaction pathway—the anti-product is obtained when the reaction proceeds via the proposed aziridinium intermediate 184 (aziridinium ion pathway), whereas the syn-product is generated by a simple nucleophilic substitution (Sn2 pathway). It was therefore decided to isolate and crystallize either the free base or the hydrochloride salt of the product for single-crystal X-ray diffraction (XRD) analysis.

Unfortunately, the purification has proven to be problematic. Isolation by column chromatography and crystallization attempts of the hydrochloride salt inevitably led to amine elimination, indicating an E1-like mechanism (Scheme 34). Only the formation of the (Z)-isomer of 2,3-diphenylacrylonitrile (186) was observed.

Scheme 34: Amine elimination of 185a during purification.

While struggling with the purification of 185a, it was found that the reaction is highly concentration-dependent. Initially, the experiments were carried out in a 5 mL Schlenk flask, which turned out to be incapable of preventing solvent loss over the prolonged reaction times of 48–72 h. The obvious solution to this problem was to employ small, well-sealable GC-vials as reaction tubes. The experiment was repeated and extended to different conditions (Table 6). At low concentrations (0.1 M), no or rather unsatisfying conversions (max. 11 %) were reached. Neither thiourea compound DPTU nor quaternary ammonia salt TBAB were capable to fully convert 181a. On the contrary, the reaction proceeded smoothly at high concentrations (0.5 M) without any catalyst. Under these conditions, the addition of DPTU and/or TBAB generally led to worse results—DPTU seemed to inhibit the conversion, whereas TBAB led to the formation of an unknown side-product, which was believed to be the syn-diastereomer of 185a (this assumption will be addressed again in the next section). The reason for the concentration-dependency probably lies in the low solubility of KCN in CHCl3.

Scheme 35: General scheme of the reactions carried out to investigate the concentration-dependency.

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst (10 mol%)</th>
<th>c / mol·L⁻¹</th>
<th>t / h</th>
<th>Conversion[ª] / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0.1</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DPTU</td>
<td>0.1</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>TBAB</td>
<td>0.1</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DPTU, TBAB</td>
<td>0.1</td>
<td>72</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 6: Results of the investigation of the concentration-dependency. [a] Determined by $^1$H-NMR spectroscopy [b]

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst (10 mol%)</th>
<th>$c$ / mol·L$^{-1}$</th>
<th>$t$ / h</th>
<th>Conversion$^{[a]}$ / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>-</td>
<td>0.5</td>
<td>72</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>DPTU</td>
<td>0.5</td>
<td>72</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>TBAB</td>
<td>0.5</td>
<td>72</td>
<td>99$^{[b]}$</td>
</tr>
<tr>
<td>8</td>
<td>DPTU, TBAB</td>
<td>0.5</td>
<td>72</td>
<td>51</td>
</tr>
</tbody>
</table>

Ratio product:side-product = 1:7

Unless otherwise stated, all following racemic cyanations are carried out with the conditions depicted in Table 6, entry 5.

Since all attempts to purify 185a eventually failed, it was investigated if a structural analog based on cyclohexene can be synthesized. These compounds have the potential benefit that their stereochemistry may be determined more easily by $^1$H-NMR spectroscopy. This is done by calculating the vicinal proton-proton coupling constants ($^3J_{HH}$) of the protons at the stereocenters. In the trans-configuration, the substituents of the 1,2-disubstituted cyclohexane ring are equatorial and the attached protons therefore axial to each other [110]. In this case, $^3J_{HH}$ lies in the range of 9–12 Hz, which is significantly larger than the coupling constant between an equatorial and an axial or two equatorial protons (usually 3–4 Hz) [111]. The protons at the stereocenters have three vicinal proton-proton couplings each—one to the proton at the other stereocenter (proposed to be axial) and two to the protons on the adjacent ring atom (axial and equatorial). Therefore, two ddd splitting patterns with two large and one small coupling constant are expected. Additionally, Nuclear Overhauser effect spectroscopy (NOESY) experiments may provide information about the relative configuration. It is expected that the trans-isomer shows no coupling between the protons at the stereocenters, whereas the cis-isomer would most certainly do.

Compound 187 was successfully synthesized in the same reaction sequence used for 185a (epoxidation, aminolysis, chlorination and cyanation) (Figure 19). It was a pleasant surprise that the purification went without any problems, giving 50 % yield. Unfortunately, the signals of the protons at the stereocenters partly overlap with signals of the pyrrolidine ring, thus preventing an indubitable determination of the relative configuration by $^1$H-NMR spectroscopy. The other (Z)-stilbene based β-amino nitriles 185b–d turned out to be stable and were obtained in decent isolated yields of 46–64 %.
Crystallization attempts of the hydrochloride salts of 185a and 185c failed, as elimination occurred. The β-amino nitrile 187 was successfully converted into its hydrochloride salt, however, no measurable crystals were formed. At last, the compounds 185b and 185d were successfully crystallized. This was done by carefully layering a concentrated solution of β-amino nitrile in DCM with n-hexane. The colorless crystals were analyzed via XRD to confirm the proposed anti-configuration and therefore the aziridinium ion pathway (Figure 20, 21).

Figure 19: Structures and yields of the synthesized β-amino nitriles.

Figure 20: Molecular structure of anti-3-morpholino-2,3-diphenylpropanenitrile (185b). The hydrogen atoms are—with exception of those at the stereocenters—omitted for clarity.
3.3.3. Attempted stereoselective reactions

Having established that the reaction indeed follows the proposed aziridinium ion pathway, it was investigated if enantioenriched products can be obtained. Two different strategies were followed: desymmetrization via a chiral auxiliary and phase-transfer catalysis.

3.3.3.1. Desymmetrization attempts via a chiral auxiliary

(S)-N-Benzyl-1-phenylethan-1-amine (189) was chosen as auxiliary, since it is easily prepared in a chromatography-free 2-step procedure (Scheme 36) [101, 112] and shares a structural similarity with dibenzylamine, which was already successfully employed in the racemic synthesis of β-amino nitrile 185d.

Scheme 36: Synthesis of chiral auxiliary 189.
The synthesis of 192 was carried out analogously to 185a–d and went through pairs of diastereomers, which are known to give different spectra (Figure 22). In the case of 190–192, most signals overlap, with exception of those from the methyl protons of the chiral auxiliary. Therefore, it was possible to determine the selectivities by $^1$H-NMR spectroscopy of the mixtures. Unfortunately, no significant stereoselectivity was observed.

The synthesis of the structural analog 196 based on cyclohexene failed, since β-chloro amine 195 didn’t convert at the proven conditions (Scheme 37). This was surprising, given the usually reactive nature of these compounds. The reason may lie in the combination of the more electron-rich chloroalkane and electron-poor amine, thus aggravating the formation of the aziridinium ion species. However, this is a matter of speculation. The addition of 10 mol% DPTU didn’t catalyze the reaction, neither at lower nor at higher concentrations (0.1 M, 0.5 M CHCl₃).

Figure 22: Attempted stereoselective synthesis of 192.
3.3.3.2. Desymmetrization attempts via phase-transfer catalysis

Inspired from Toste and co-workers [58], chiral phosphoric acid derivative 197 was chosen as catalyst precursor (Scheme 38). The potentially catalytically active phosphate was generated in-situ by addition of Ag$_2$CO$_3$. When toluene was used, no conversion was observed, indicating that the chiral BINOL-phosphate isn’t capable of transferring KCN into the organic phase. In hope to not interfere with the chiral ion pair, the solvent was changed to acetonitrile. After 72 h, 40 % conversion was measured, whereupon the reaction was stopped. Work-up and purification by column chromatography gave 27 % yield. When subjected to chiral HPLC, it was shown that the product was racemic. However, this may be caused by the coordinating solvent.

Scheme 38: Attempted desymmetrization via chiral anion directed catalysis.

Meanwhile, it was investigated if chiral phase-transfer catalysts can be used to obtain enantioenriched products. It was previously observed that the reaction of 181a with addition of 10 mol% TBAB caused the formation of an unknown side-product, which was believed to be the syn-diastereomer (3.3.2., Table 6, entry 7). Since purification led to elimination, 181b−d were
subjected to the reaction, whose products 185b–d were known to be isolable. N-Benzylated quinidine 199 was chosen as PTC (Scheme 39).

Scheme 39: Desymmetrization attempts via phase-transfer catalysis.

The reaction of all β-chloro amines led to the formation of products mixtures. 181b (morpholine derivative) and 181d (dibenzylamine derivative) gave two products each, whereas 181c (diethylamine derivative) mainly yielded the elimination product 186. Ordinary column chromatography failed because of the very similar retention behavior of the compounds. At last, the products of 181d were successfully separated by preparative HPLC. 1H, 13C-NMR and MS-ESI (Electrospray Ionization Mass Spectrometry) analysis confirmed the initial assumption that the side-product is the syn-diastereomer.

Good yields (> 63 %) were achieved for the product mixtures 185b, 200b and 185d, 200d. The yield of 185c, 200c (11 %) suffered from elimination. Unlike the pyrrolidine derivative 185a, elimination predominately occurred during the reaction and not during the purification step. The reaction time decreased from 72 h (non-catalyzed) to 24–48 h and the anti:syn ratios varied from 1.0:0.4 to 1.0:1.6, depending on the substrate. However, the main reason of these experiments was to determine the ee of the anti-products, which were unfortunately disappointing (max. 6 %). The results are depicted in Table 7.

<table>
<thead>
<tr>
<th>Product</th>
<th>t / h</th>
<th>Total yield[a]</th>
<th>Ratio anti:syn[b]</th>
<th>e.r. anti-product[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>185b, 200b</td>
<td>48</td>
<td>63 %</td>
<td>1.0:1.6</td>
<td>49:51</td>
</tr>
<tr>
<td>185c, 200c</td>
<td>24</td>
<td>11 %[d]</td>
<td>1.0:0.4[d]</td>
<td>-</td>
</tr>
<tr>
<td>185d, 200d</td>
<td>48</td>
<td>78 %</td>
<td>1.0:0.6</td>
<td>53:47</td>
</tr>
</tbody>
</table>

Table 7: Results of the desymmetrization attempts via phase-transfer catalysis. [a] Isolated yield after column chromatography [b] Determined by 1H-NMR spectroscopy of the isolated product [c] Determined by HPLC on a chiral stationary phase [d] Calculated yield and ratio determined by 1H-NMR spectroscopy of the crude product

The formation of syn-diastereomers is probably caused by the nucleophilic counter-ion of the phase-transfer catalyst (Scheme 40). In the first step, anti-β-chloro amine 181 undergoes a nucleophilic substitution with bromide, which gives syn-β-bromo amine 201. Change of conformation via rotation, followed by a back-site attack of the amine forms trans-aziridinium ion 203. In the last step, this species is cyanated to yield the syn-diastereomer 200. Attempts to prove this proposal by MS-ESI tracking of the reaction mixtures failed, since only signals for the educts, aziridinium ions and products were found. However, the intermediate β-bromo amines may not be stable at these conditions. Considering the potentially higher reactivity due to the better leaving group, this seems very likely.
Scheme 40: Proposed mechanism for the formation of syn-diastereomers.
4. Conclusions

In this work, the asymmetric synthesis of α- and β-amino nitriles was investigated. The Strecker-type reactions of N-protected aldimines utilizing bifunctional phase-transfer catalysts 161 and 162, which were devised by our group, gave good yields (up to 99 %) but showed no stereoselectivity. This approach used TMSCN, ACH and aqueous KCN as cyanide sources in various solvents. It was found that the addition of a base (Cs₂CO₃) significantly impaired the yield when N-Tos aldimine 145 underwent the reaction in the presence of 161 and 162. N-Boc aldimine 153 showed this behavior only in toluene—in more polar solvents (DCM, MTBE), the yield improved. Additionally, the base seemed to have an accelerating effect on the conversion rate, which was observed when bifunctional as well as monofunctional PTC were utilized.

The kinetic resolution of N-tosyl-2-phenylaziridine via phase-transfer catalysis proved to be tricky, since no chiral PTC catalyzed the ring-opening reaction, even under harsh conditions (up to 80 °C). It was found that PTC 161 and 171 had to be converted to their corresponding fluorides, before subjecting them to the reaction to show activity. However, only low conversions (max. 23 %) and no enantioselectivity were observed.

Since aziridines showed only low reactivity, meso-aziridinium ions were employed. These compounds are generated in-situ from β-halo amines and promised to be more reactive. Indeed, the first few racemic reactions of β-chloro amine 181a turned out to be successful, with full conversion within 72 h in a non-coordinating solvent (CHCl₃). Unfortunately, some setbacks were experienced during the isolation of the synthesized β-amino nitrile, since elimination occurred to give (Z)-cyanoolefin 186—which is easily made by a Knoevenagel condensation of benzaldehyde with benzyl cyanide [114]. The scope was extended to another four substrates, which were in contrary all isolable. XRD measurements of 185b and 185d confirmed the proposed anti-configuration and therefore the aziridinium ion pathway. Desymmetrization was attempted following two strategies: 1) via a chiral auxiliary and 2) via phase-transfer catalysis.

Two diastereomeric mixtures of β-amino chlorides, which incorporate a chiral auxiliary based on (S)-methylbenzylamine, were synthesized. 192, which was made from (Z)-stilbene, reacted readily with KCN but showed no stereoselectivity. The cyclohexene based diastereomeric mixture 195 however, showed no reactivity at all.

Attempts to employ anionic phase-transfer catalyst 197 to form a chiral ion-pair, which undergoes the reaction with KCN failed. Reactions in toluene led to no conversion, indicating that the catalyst isn’t capable of transferring KCN into the organic phase. Some conversion (40 %) was achieved when the experiment was carried out in acetonitrile but without enantioselectivity. Reactions via phase-transfer catalyst 199 led to the formation of the syn-diastereomer as side-product, which of course makes this approach less attractive. However, since it is believed that the nucleophilic counter-ion is responsible for this effect, non-nucleophilic phase-transfer catalysts may be an option. Catalyst 199 induced a low, but present stereoselectivity (6 % ee, anti-product), making it potentially interesting for further research.
5. Experimental part

5.1. General remarks

All chemicals were acquired from commercial sources and used without any further purification, if not otherwise stated. Solvents were used as received or dried with a solvent purification system (MB-SPS-7, M. Braun).

NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer. The obtained spectra were referenced to the solvent peaks (CDCl₃ at δ 7.26 ppm (¹H NMR) & δ 77.36 (¹³C NMR)).

Mass spectrometry was performed using a Shimadzu LCMS-2020 QP system equipped with an electrospray ionization (ESI) source interface. A mixture of 97 % MeOH, 10 mM NH₄COOH and 3 % H₂O (1 % HCOOH) was utilized as mobile phase.

The determination of the enantiomeric ratios was carried out using a Thermo Scientific Dionex Ultimate 3000 HPLC system with a diode array detector. Chiralcel OD-H (250 x 4.6 mm, 5 µm) was used as chiral stationary phase and hexane:i-PrOH as mobile phase.

Preparative HPLC was performed with a Thermo Fisher Dionex Ultimate 3000 Prep system equipped with a UV/VIS detector. Alltima Silica 10 µm (250 x 10 mm) was used as stationary phase and hexane:DCM as mobile phase.

XRD data was collected from a Bruker D8 Quest Eco diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å).

Column chromatography was carried out at ambient conditions using Davisol 60 Å 70–200 µm silica gel. TLC was performed on Merck silica gel 60 F₂₅₄ plates. Heptanes and ethyl acetate were distilled before utilization.

5.2. Preparation of N-protected imines

5.2.1. Preparation of (E)-N-benzylidene-4-methylbenzenesulfonamide 145

\[
\begin{align*}
\text{142} & \quad \text{C}_7\text{H}_6\text{O} \\
& \quad 106.12 \\
\text{143} & \quad \text{C}_7\text{H}_6\text{NO}_2\text{S} \\
& \quad 171.21 \\
\text{144} & \quad \text{C}_7\text{H}_9\text{O}_4\text{S} \\
& \quad 190.21 \\
\text{145} & \quad \text{C}_{14}\text{H}_{13}\text{NO}_2\text{S} \\
& \quad 259.32
\end{align*}
\]

Scheme 41: Preparation of 145.

According to literature [101], benzaldehyde (5.1 mL, 50 mmol), p-toluenesulfonamide (8.56 g, 50 mmol) and p-toluenesulfonic acid monohydrate (96.3 mg, 0.51 mmol) were dissolved in toluene (180 mL). The reaction was carried out in a Dean-Stark trap at 130 °C overnight under argon atmosphere. After completion, the mixture was allowed to cool to room temperature and
subsequently evaporated under reduced pressure to afford the crude product. After twofold re-crystallization (diethyl ether), product 145 was obtained as pale pink solid in 56 % yield (7.22 g, 28 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 9.03 (s, 1H), 7.96–7.86 (m, 4H), 7.62 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 2H), 7.35 (d, $J = 7.9$ Hz, 2H), 2.44 (s, 3H).

5.2.2. Preparation of (E)-N-benzyl-1-phenylmethanimine 147

\[
\begin{array}{c}
\text{O} & \text{NH}_2 \\
142 & 146 \\
C_7H_8O & C_7H_5N \\
106.12 & 107.16 \\
\end{array}
\]

Scheme 42: Preparation of 147.

In accordance with literature [102], benzaldehyde (2 mL, 20 mmol) and benzylamine (2.2 mL, 20 mmol) were dissolved in DCM (20 mL) along with 3 Å molecular sieves. The reaction was stirred at room temperature overnight. After completion, the resulting mixture was dried over Na$_2$SO$_4$ and subsequently filtrated. Evaporation of the solvent and drying in vacuo gave the product 147 as yellow oil in 64 % yield (2.50 g, 12.80 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 8.32 (s, 1H), 7.76–7.67 (m, 2H), 7.37–7.31 (m, 3H), 7.29–7.24 (m, 4H), 7.22–7.14 (m, 1H), 4.75 (s, 2H).

5.2.3. Preparation of tert-butyl (phenyl(tosyl)methyl)carbamate 151

\[
\begin{array}{c}
\text{O} & \text{O} & \text{O} & \text{O} \\
142 & 148 & 149 & 150 \\
C_7H_6O & C_7H_11NO_2 & C_7H_2NaO_2S & CH_2O_2 \\
106.12 & 117.15 & 178.18 & 46.03 \\
\end{array}
\]

Scheme 43: Preparation of 151.

According to literature [103$^a$], benzaldehyde (3.5 mL, 35 mmol), tert-butyl carbamate (2.00 g, 17 mmol) and sodium $p$-toluenesulfinate (7.60 g, 43 mmol) were dissolved in a mixture of MeOH (17 mL) and H$_2$O (34 mL). Formic acid (1.3 mL, 34 mmol) was added at once and the reaction mixture was stirred at room temperature overnight under argon atmosphere. The precipitate formed was vacuum-filtrated, washed with ice-cold diethyl ether and dried in vacuo. The desired product 151 was obtained as white powdery solid in 87 % yield (5.32 g, 14.72 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.78 (d, $J = 8.1$ Hz, 2H), 7.43 (s, 5H), 7.33 (d, $J = 8.0$ Hz, 2H), 5.88 (d, $J = 10.6$ Hz, 1H), 5.70 (d, $J = 10.6$ Hz, 1H), 2.43 (s, 3H), 1.27 (s, 9H).
5.2.4. Preparation of tert-butyl (E)-benzylidene carbamate 153

\[
\begin{align*}
\text{NHBOC} & \quad \text{Tos} & \quad \text{K}_2\text{CO}_3 & \quad \text{DCM, r.t.} & \quad \text{Boc} \\
\text{151} & \quad \text{C}_{19}\text{H}_{23}\text{NO}_5\text{S} & \quad 361.46 & \quad 152 & \quad \text{153} & \quad \text{C}_{12}\text{H}_{15}\text{NO}_2 & \quad 205.26
\end{align*}
\]

Scheme 44: Preparation of 153.

In accordance with literature [103], tert-butyl (phenyl(tosyl)methyl)carbamate (151) (1.0 g, 2.77 mmol) was dissolved in DCM (46 mL) and 1.4 M K$_2$CO$_3$ (46 mL, 64.4 mmol). The biphasic mixture was vigorously stirred at room temperature overnight under argon atmosphere. After completion, the organic phase was separated. The aqueous phase was extracted with DCM (2x 50 mL) and the combined organic phases were dried over Na$_2$SO$_4$. Subsequent filtration and evaporation under reduced pressure gave the product 153 as transparent oil in 90% yield (0.51 g, 2.48 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 8.88 (s, 1H), 7.92 (d, $J = 7.8$ Hz, 2H), 7.57 (t, $J = 7.1$ Hz, 1H), 7.47 (t, $J = 7.1$ Hz, 2H), 1.60 (s, 9H).

5.3. Procedure for Strecker-type reactions

5.3.1. [General] Procedure for Strecker-type reactions in presence of LiClO$_4$

\[
\begin{align*}
\text{R} & \quad \text{PG} & \quad + & \quad \text{TMSCN} & \quad 155 \quad (10 \text{ mol%}) & \quad \text{CH}_3\text{CN} (0.2 \text{ M}), \text{r.t., 72 h} & \quad \text{R} & \quad \text{PG} & \quad \text{HN} \\
\text{137} & \quad \text{C}_{24}\text{H}_{39}\text{NSi} & \quad 99.21 & \quad 154 & \quad 155 \quad 156 & \quad 106.39 & \quad \text{LiClO}_4
\end{align*}
\]

Scheme 45: Procedure for Strecker-type reactions in presence of LiClO$_4$.

Analogously to literature [104], to a flame-dried Schlenk flask equipped with a stirring bar was added N-protected phenylmethanimine 137 (1 mmol), ACN (5 mL) and LiClO$_4$ (0.1 equiv, 10 mol%). The reaction apparatus was flushed with argon followed by addition of TMSCN (300 µL, 2.2 mmol). It was stirred for 72 hours, until when the reaction was quenched with sat. NaHCO$_3$ solution (2 mL). The reaction mixture was transferred with H$_2$O (2 mL) and DCM (8 mL) to a separating funnel, where the organic phase was removed. The aqueous phase was extracted with DCM (2x 10 mL) and the combined organic phases were dried over Na$_2$SO$_4$. Filtration, evaporation of the solvent under reduced pressure and drying in vacuo afforded the crude α-amino nitrile. The crude product was purified by column chromatography (silica gel; heptanes:EtOAc).
5.3.2. [General] Procedure for Strecker-type reactions in presence of TBAB

\[
\begin{align*}
\text{N}^{\text{PG}} & \quad \text{TMSCN} \quad \xrightarrow{159 \ (10 \text{ mol} \%) } \quad \text{HN}^{\text{PG}} \\
\text{R} & \quad \text{Ph}_{2} \text{H}_{2} \text{NSi} \quad \text{99.21} \\
137 & \quad 154 & \quad 138
\end{align*}
\]

Scheme 46: Procedure for Strecker-type reactions in presence of TBAB.

In adoption of a known procedure [104], to a flame-dried Schlenk flask equipped with a stirring bar was added \(N\)-protected phenylmethanimine 137 (0.1 mmol), toluene (1 mL) and TBAB (0.1 equiv, 10 mol%). The reaction apparatus was flushed with argon followed by addition of TMSCN (26.8 \(\mu\)L, 0.2 mmol). It was stirred for 72 hours, until when the reaction was quenched with sat. NaHCO\(_3\) solution (1 mL). The reaction mixture was transferred with H\(_2\)O (4 mL) and DCM (5 mL) to a separating funnel, where the organic phase was removed. The aqueous phase was extracted with DCM (3x 5 mL) and the combined organic phases were dried over Na\(_2\)SO\(_4\). Filtration, evaporation of the solvent under reduced pressure and drying in vacuo afforded the crude \(\alpha\)-amino nitrile. The crude product was purified by column chromatography (silica gel; heptanes:EtOAc).

5.3.3. [General] Procedure for Strecker-type reactions with TMSCN catalyzed by chiral PTC

\[
\begin{align*}
\text{N}^{\text{PG}} & \quad \text{TMSCN} \quad \xrightarrow{\text{Catalyst (4 mol\%)}} \quad \text{HN}^{\text{PG}} \\
\text{R} & \quad \text{Ph}_{2} \text{H}_{2} \text{NSi} \quad \text{99.21} \\
137 & \quad 154 & \quad 204 & \quad 138
\end{align*}
\]

Scheme 47: Procedure for Strecker-type reactions with TMSCN catalyzed by chiral PTC.

In adaption of a literature procedure [33], to a flame-dried Schlenk flask equipped with a stirring bar was added \(N\)-protected phenylmethanimine 137 (0.1 mmol), toluene (1 mL) and a chiral PTC (4 mol%). The flask was additionally charged with Cs\(_2\)CO\(_3\) (65.2 mg, 0.2 mmol) when the experiment was carried out under basic conditions. The apparatus was flushed with argon and TMSCN (26.8 \(\mu\)L, 0.2 mmol) was added. It was stirred for 24–72 hours at r.t. under argon atmosphere. After completion (determined by TLC analysis), the reaction was quenched with sat. NaHCO\(_3\) solution (1 mL). Work-up and isolation of the product was carried out according to the general procedure 5.3.2.
5.3.4. [General] Procedure for Strecker-type reactions with ACH catalyzed by chiral PTC

\[
\begin{align*}
N^\text{PG}R &+ \text{HO-CN} \\
137 &\rightarrow \text{HN}^\text{PG}R \\
C_4H_7NO &\rightarrow \text{138} \\
85.11 &\text{PhMe-50% aq. } K_2CO_3 \\
\text{r.t.} &\end{align*}
\]

Scheme 48: Procedure for Strecker-type reactions with ACH catalyzed by chiral PTC.

In adaption of a known procedure [32], to a flame-dried Schlenk flask equipped with a stirring bar was added \(N\)-protected phenylmethanimine 137 (0.1 mmol), toluene (5 mL), a chiral PTC (4 mol%) and ACH (18.4 \(\mu\)L, 0.2 mmol). The apparatus was flushed with argon, followed by addition of a 50 % (w/w) \(K_2CO_3\) solution (137.6 mg, 0.5 mmol). It was stirred for 24 hours at r.t. under argon atmosphere. After completion (determined by TLC analysis), the reaction was quenched with sat. \(NaHCO_3\) solution (1 mL). Work-up and isolation of the product was carried out according to the general procedure 5.3.2.

5.3.5. [General] Procedure for Strecker-type reactions with KCN catalyzed by chiral PTC

\[
\begin{align*}
N^\text{PG}R &+ \text{KCN} \\
137 &\rightarrow \text{HN}^\text{PG}R \\
C_4H_7NO &\rightarrow \text{138} \\
65.12 &\text{PhMe-H}_2\text{O} \\
\text{r.t.} &\end{align*}
\]

Scheme 49: Procedure for Strecker-type reactions with KCN catalyzed by chiral PTC.

To a flame-dried Schlenk flask equipped with a stirring bar was added \(N\)-protected phenylmethanimine 137 (0.1 mmol), toluene (1 mL) and a chiral PTC (4 mol%). The apparatus was flushed with argon and 0.2 M KCN (1 mL, 0.2 mmol) was added. It was stirred for 24 hours at r.t. under argon atmosphere. After completion (determined by TLC analysis), the reaction was quenched with sat. \(NaHCO_3\) solution (1 mL). Work-up and isolation of the product was carried out according to the general procedure 5.3.2.

5.3.6. Preparation of \(N\)-(cyano(phenyl)methyl)-4-methylbenzenesulfonamide 156

\[
\begin{align*}
156 &\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2\text{S} \\
286.35 &\end{align*}
\]

Figure 23: \(N\)-(cyano(phenyl)methyl)-4-methylbenzenesulfonamide (156).

Applying the general procedure 5.3.2., \((E)-N\)-benzylidene-4-methylbenzenesulfonamide (145) (25.2 mg, 0.1 mmol) was reacted with TBAB (3.29 mg, 10 mol%) and TMSCN (26.8 \(\mu\)L,
0.2 mmol) in toluene (1 mL) to obtain the crude product. Purification by column chromatography (silica gel; heptanes:EtOAc = 3:1) afforded 156 as white solid in 79 % yield (22.6 mg, 0.079 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \(\delta / \text{ppm} = 7.83 \ (d, \ J = 8.4 \text{ Hz}, 2\text{H}), 7.50-7.35 \ (m, 7\text{H}), 5.50 \ (d, \ J = 8.9 \text{ Hz}, 1\text{H}), 4.94 \ (d, \ J = 8.9 \text{ Hz}, 1\text{H}), 2.47 \ (s, 1\text{H}).

HPLC: Chiralcel OD-H; hexane:i-PrOH = 1:1; 0.5 mL·min\(^{-1}\); \(T_{\text{column}} = 10 \text{ °C}; \ t_{\text{ret.}}: 11.0 \text{ min}, 14.2 \text{ min}.

TLC (heptanes:EtOAc = 3:1): \(R_f = 0.34\)

5.3.7. Preparation of 2-(benzylamino)-2-phenylacetonitrile 157

![Figure 24: 2-(Benzylamino)-2-phenylacetonitrile (157).](image)

Applying the general procedure 5.3.2., (E)-\(N\)-benzyl-1-phenylmethanimine (147) (19.1 mg, 0.1 mmol) was reacted with TBAB (3.19 mg, 10 mol%) and TMSCN (26.8 µL, 0.2 mmol) in toluene (1 mL) to obtain the crude product. Purification by column chromatography (silica gel; heptanes:EtOAc = 4:1) afforded 157 as yellow oil in 82 % yield (18.2 mg, 0.082 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \(\delta / \text{ppm} = 7.59-7.52 \ (m, 2\text{H}), 7.47-7.27 \ (m, 8\text{H}), 4.77 \ (s, 1\text{H}), 4.08 \ (d, \ J = 13.0 \text{ Hz}, 1\text{H}), 3.97 \ (d, \ J = 13.0 \text{ Hz}, 1\text{H}), 1.89 \ (s, 1\text{H}).

HPLC: Chiralcel OD-H; hexane:i-PrOH = 20:1; 0.5 mL·min\(^{-1}\); \(T_{\text{column}} = 10 \text{ °C}; \ t_{\text{ret.}}: 34.0 \text{ min}, 37.2 \text{ min}.

TLC (heptanes:EtOAc = 4:1): \(R_f = 0.40\)

5.3.8. Preparation of tert-butyl (cyano(phenyl)methyl)carbamate 158

![Figure 25: Tert-butyl (cyano(phenyl)methyl)carbamate (158).](image)
Applying the general procedure 5.3.2., tert-butyl (E)-benzylidencarbamate (153) (20.5 mg, 0.1 mmol) was reacted with TBAB (3.21 mg, 10 mol%) and TMS-CN (26.8 µL, 0.2 mmol) in toluene (1 mL) to obtain the crude product. Purification by column chromatography (silica gel; heptanes:EtOAc = 4:1) afforded 158 as white solid in 67% yield (15.6 mg, 0.067 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): δ / ppm = 7.52–7.39 (m, 5H), 5.80 (br s, 1H), 5.07 (br s, 1H), 1.49 (s, 9H).

HPLC: Chiralcel OD-H; hexane:i-PrOH = 100:1; 1.0 mL·min\(^{-1}\); \(T_{\text{column}} = 10^\circ\)C; \(t_{\text{ret.}}: 30.1\) min, 33.1 min.

TLC (heptanes:EtOAc = 4:1): \(\eta = 0.37\)

### 5.4. Preparation of \(N\)-tosyl-2-phenylaziridine 139

In analogy to a reported procedure [106], chloramine-T trihydrate (5.1 g, 18.0 mmol) was dissolved in a mixture of DCM (7.5 mL) and \(H_2O\) (22.5 mL). Styrene (1.7 mL, 15.0 mmol), iodine (0.38 g, 1.50 mmol) and tetraethylammonium iodide (0.39 g, 1.52 mmol) were added and it was vigorously stirred at room temperature under argon atmosphere. After 24 hours, the biphasic mixture was transferred with DCM (22.5 mL) to a separating funnel, where the organic phase was removed. The aqueous phase was extracted with DCM (3x 10 mL) and the combined organic phases were washed with 10% (w/w) \(Na_2S_2O_3\) solution (3x 10 mL). The organic phase was dried over \(Na_2SO_4\) and subsequently filtrated. Evaporation under reduced pressure and drying in vacuo gave the crude product. Purification by column chromatography (silica gel; heptanes:EtOAc = 3:1) afforded product 139 as white solid in 93% yield (3.8 g, 13.9 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): δ / ppm = 7.90 (d, \(J = 8.3\) Hz, 2H), 7.39–7.21 (m, 7H), 3.80 (dd, \(J = 4.5, 7.2\) Hz, 1H), 3.01 (d, \(J = 7.2\) Hz, 1H), 2.46 (s, 3H), 2.41 (d, \(J = 4.5\) Hz, 1H).

TLC (heptanes:EtOAc = 3:1): \(\eta = 0.37\)
5.5. Procedure for nucleophilic ring-opening reactions of \( N \)-tosyl aziridines

5.5.1. [General] Procedure for nucleophilic ring-opening reactions of \( N \)-tosyl aziridines with TMSCN in presence of TBAF

Scheme 51: Reaction of \( N \)-tosyl aziridines with TMSCN in presence of TBAF.

According to literature [50], to a flame-dried Schlenk flask equipped with a stirring bar was added \( N \)-tosyl aziridine (0.25 mmol) and dry THF (3 mL) along with 3 Å molecular sieves. After the compound was completely dissolved, TMSCN (34.5 µL, 0.25 mmol) and 1.0 M TBAF in THF (13.0 µL, 5 mol%) were added. It was stirred at 50 °C. After completion (determined by TLC analysis), the reaction was allowed to cool down. The mixture was filtered over silica with DCM (20 mL). Evaporation under reduced pressure and drying in vacuo gave the crude product, which was purified by column chromatography (silica gel; heptanes:EtOAc).

5.5.2. [General] Procedure for nucleophilic ring-opening reactions of \( N \)-tosyl aziridines with TMSCN catalyzed by chiral quaternary ammonium fluorides

Scheme 52: Reaction of \( N \)-tosyl aziridines with TMSCN catalyzed by chiral quaternary ammonium fluorides

In adaption of a known procedure [50], to a flame-dried Schlenk flask equipped with a stirring bar was added \( N \)-tosyl aziridine (0.25 mmol) and dry THF (3 mL) along with 3 Å molecular sieves. After the compound was completely dissolved, TMSCN (34.5 µL, 0.25 mmol) and a chiral quaternary ammonium fluoride (5 mol%) were added. It was stirred at r.t. for 24 h, until when the reaction was allowed to cool down. The mixture was filtered over silica with DCM (20 mL). Evaporation under reduced pressure and drying in vacuo gave the crude product, which was purified by column chromatography (silica gel; heptanes:EtOAc).
5.5.3. Preparation of \(N\)-(2-cyano-1-phenylethyl)-4-methylbenzenesulfonamide 140

![Chemical structure of 140](image)

**Figure 26**: \(N\)-(2-cyano-1-phenylethyl)-4-methylbenzenesulfonamide (140).

Applying the general procedure 5.5.1., \(N\)-tosyl-2-phenylaziridine (69.3 mg, 0.25 mmol) was reacted with TMSCN (34.5 \(\mu\)L, 0.25 mmol) and 1.0 M TBAF in THF (13.0 \(\mu\)L, 5 mol%) in dry THF (3 mL). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 2:1) to afford 140 as white solid in 66% yield (49.9 mg, 0.17 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \(\delta / \text{ppm} = 7.71 \ (d, J = 8.3 \text{ Hz}), \ 7.35-7.27 \ (m, 5H), \ 7.17-7.13 \ (m, 2H), \ 4.99 \ (d, J = 6.5 \text{ Hz}, 1H), \ 4.62-4.55 \ (m, 1H), \ 2.98-2.94 \ (m, 2H), \ 2.44 \ (s, 3H).

HPLC: Chiralcel OD-H; hexane:i-PrOH = 1:1; 0.5 mL·min\(^{-1}\); \(T_{\text{column}} = 10^\circ\text{C}; t_{\text{ret.}}: 15.1 \text{ min, 18.2 min.}

TLC (heptanes:EtOAc = 2:1): \(R_f = 0.22\)

5.6. Preparation of chiral quaternary ammonium fluorides

5.6.1. [General] Preparation of chiral quaternary ammonium fluorides with silver(I) fluoride

\[
\begin{align*}
\text{NR}_4^+ \ 	imes^\ominus + \text{AgF} & \rightarrow \text{NR}_4^+ F^- + \text{AgX} \\
208 & \rightarrow 209 \rightarrow 210 & 211 \\
& \text{MeOH-H}_2\text{O} & \text{r.t.}
\end{align*}
\]

\(X = \text{Br, I}\quad 126.87\)

**Scheme 53**: Preparation of chiral quaternary ammonium fluorides.

In adaption of a reported procedure [107], a Schlenk flask wrapped in aluminum foil was charged with ammonium halide (35 mmol) and 50% (v/v) aqueous MeOH (1 mL). AgF (50 mmol) was added and it was vigorously stirred in the absence of light overnight. After completion, the mixture was filtered over Celite with DCM (3x 10 mL). The filtrate was concentrated under reduced pressure and dried in vacuo, yielding the desired product.
5.6.2. Preparation of chiral bifunctional ammonium fluoride 167

![Chemical Structure]

Figure 27: Chiral bifunctional ammonium fluoride 167.

Applying the general procedure 5.6.1., bifunctional ammonium iodide 161 (10.3 mg, 13.7 mmol) was reacted with AgF (2.5 mg, 19.7 mmol) in 50 % (v/v) aqueous MeOH (1 mL). The product 170 was obtained as white solid in 98 % yield (8.6 mg, 13.4 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 8.05 (s, 1H), 7.94 (s, 1H), 7.91 (s, 1H), 7.39 (s, 1H), 5.35 (d, $J = 12.9$ Hz, 1H), 5.17 (d, $J = 12.9$ Hz, 1H), 4.49–4.36 (m, 1H), 4.33–4.21 (m, 1H), 3.14 (s, 3H), 3.05 (s, 3H), 2.52–2.42 (m, 1H), 2.14–2.05 (m, 1H), 1.98–1.90 (m, 1H), 1.86–1.77 (m, 1H), 1.74–1.65 (m, 1H), 1.57–1.44 (m, 2H), 1.39–1.30 (m, 1H); $^{19}$F NMR (282 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm -63.19 (s, 6F), -63.24 (s, 6F).

5.6.3. Preparation of chiral quaternary ammonium fluoride 169

![Chemical Structure]

Figure 28: Chiral ammonium fluoride 169.

Applying the general procedure 5.6.1., ammonium bromide 171 (15.9 mg, 34.2 mmol) was reacted with AgF (6.4 mg, 50.4 mmol) in 50 % (v/v) aqueous MeOH (1 mL). The product 172 was obtained as brown solid in 48 % yield (6.6 mg, 16.3 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 8.79 (d, $J = 4.0$ Hz, 1H), 8.18 (d, $J = 7.7$ Hz, 1H), 7.83–7.77 (m, 2H), 7.48–7.38 (m, 2H), 7.31–7.27 (m, 2H), 6.90–6.84 (m, 1H), 6.82–6.75 (m, 2H), 6.26 (bs, 1H), 5.95–5.77 (m, 1H), 5.62–5.44 (m, 2H), 5.21–5.08 (m, 2H), 4.62–4.49 (m, 1H), 3.96–3.78 (m, 2H), 3.28–3.16 (m, 1H), 2.76–2.63 (m, 1H), 2.27–2.09 (m, 2H), 1.78–1.69 (m, 1H), 1.27–1.17 (m, 1H), 0.83–0.76 (m, 1H), 0.73–0.59 (m, 1H).
5.7. Preparation of meso-aziridinium ion precursors

5.7.1. Preparation of cis-stilbene oxide 175

Scheme 54: Preparation of cis-stilbene oxide (175)

Following a known procedure [108], mCPBA (< 77 %, 5.52 g, 24.6 mmol) was dissolved in DCM (50 mL) and cooled in an ice bath while stirring. cis-Stilbene (2.0 mL, 11.2 mmol) was added and the mixture was allowed to warm to room temperature overnight under argon atmosphere. After completion, the white precipitate was vacuum filtered and washed with DCM. The filtrate was concentrated under reduced pressure and subsequently transferred with sat. NaHCO$_3$ solution (70 mL) and diethyl ether (30 mL) to a separation funnel, where the organic layer was removed. The aqueous phase was extracted with diethyl ether (3x 30 mL) and the combined organic phases were washed with sat. NaCl solution (90 mL), dried over Na$_2$SO$_4$ and filtered. Evaporation of the solvent and drying in vacuo gave the crude product, which was purified by column chromatography (silica gel; heptanes:diethyl ether = 19:1) to afford product 175 as white solid in 82 % yield (1.80 g, 9.2 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.17 (s, 10H), 4.36 (s, 2H).

TLC (heptanes:diethyl ether = 19:1): $R_f = 0.29$

5.7.2. Preparation of cyclohexene oxide 193

Scheme 55: Preparation of cyclohexene oxide (193).

Analogously to literature [113], cyclohexene (3.4 g, 41.4 mmol) was dissolved in DCM (64 mL) and cooled in an ice-bath while stirring. A solution of mCPBA (< 77 %, 14.8 g, 66.0 mmol) in DCM (208 mL) was added drop-wise over a period of 1 h under argon atmosphere. The ice-bath was removed and the mixture was allowed to warm to room-temperature overnight. Excess mCPBA was quenched by addition of 10 % (w/w) Na$_2$SO$_3$ solution. It was stirred for 1 h, until when the biphasic mixture was transferred to a separation funnel. The organic phase was removed and the aqueous phase was extracted with DCM (3x 100 mL). The combined organic phases were washed with 5 % (w/w) Na$_2$CO$_3$ solution (200 mL), sat. NaHCO$_3$ solution (200 mL),
brine (3x 100 mL) and dried over Na₂SO₄. Filtration and careful evaporation of the solvent under reduced pressure gave product 193 as colorless liquid in 89 % yield (3.6 g, 36.7 mmol).

¹H-NMR (300 MHz, CDCl₃, 298.0 K): δ/ ppm = 3.12 (bs, 2H), 3.02–1.88 (m, 2H), 1.88–1.73 (m, 2H), 1.51–1.33 (m, 2H), 1.33–1.14 (m, 2H).

5.7.3. [General] Preparation of β-amino alcohols

5.7.3.1. Method A

Scheme 56: Preparation of β-amino alcohols: Method A.

In analogy to a reported procedure [86], to a pressure tube equipped with a stirring bar was added cis-stilbene oxide (2.04 mmol) and amine (5.0 equiv, 10.20 mmol). The sealed and argon-flushed tube was stirred at 110 °C until the epoxide was completely consumed (24–48 h, determined by TLC analysis). The reaction mixture was allowed to cool to room temperature and excess amine was evaporated under reduced pressure. The crude product was purified by column chromatography.

5.7.3.2. Method B

Scheme 57: Preparation of β-amino alcohols: Method B.

In adaption of a known procedure [109], to a flame-dried Schlenk flask equipped with a stirring bar was added cis-stilbene oxide (2.04 mmol), dry THF (4 mL), amine (5.0 equiv, 10.20 mmol) and Sc(OTf)₃ (31 mg, 3 mol%). It was refluxed under argon atmosphere until the epoxide was consumed (24–48 h, determined by TLC analysis). After the reaction mixture was allowed to cool to room temperature, it was concentrated under reduced pressure. The crude product was purified by column chromatography.
5.7.4. Preparation of *anti*-1,2-diphenyl-2-(pyrrolidin-1-yl)ethan-1-ol 176a

![Chemical Structure 176a](image)

**Figure 29:** *anti*-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethan-1-ol (176a).

Applying the general procedure 5.7.3.1. (Method A), *cis*-stilbene oxide (400 mg, 2.04 mmol) was reacted with pyrrolidine (0.86 mL, 10.19 mmol) for 24 h. The crude product was purified by column chromatography (silica gel; DCM:MeOH = 100:0–90:10) to afford product 176a as white solid in 82% yield (447 mg, 1.67 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.30–7.07 (m, 10H), 5.01 (d, $J$ = 10.0 Hz, 1H), 3.83 (d, $J$ = 10.0 Hz, 1H), 2.72–2.59 (m, 2H), 2.56–2.44 (m, 2H), 1.77–1.65 (m, 4H).

MS (ESI): $m/z$ calculated for C$_{18}$H$_{22}$NO$: 268.17 [M+H]$^+$, found 268.50

5.7.5. Preparation of *anti*-2-morpholino-1,2-diphenylethan-1-ol 176b

![Chemical Structure 176b](image)

**Figure 30:** *anti*-2-Morpholino-1,2-diphenylethan-1-ol (176b).

Applying the general procedure 5.7.3.1. (Method A), *cis*-stilbene oxide (400 mg, 2.04 mmol) was reacted with morpholine (0.90 mL, 10.22 mmol) for 48 h. The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 60:40) to afford product 176b as white solid in 79% yield (456 mg, 1.61 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.33–7.06 (m, 10H), 5.10 (bs, 1H), 5.08 (d, $J$ = 10.4 Hz, 1H), 3.87–3.72 (m, 4H), 3.59 (d, $J$ = 10.4 Hz, 1H), 2.78–2.64 (m, 2H), 2.50–2.35 (m, 2H).

MS (ESI): $m/z$ calculated for C$_{18}$H$_{22}$NO$_2$: 284.16 [M+H]$^+$, found 284.30

TLC (heptanes:EtOAc = 60:40): $R_f$ = 0.23
5.7.6. Preparation of \textit{anti}-2-(diethylamino)-1,2-diphenylethan-1-ol 176c

![Structure](image1)

\textit{Figure 31:} \textit{anti}-2-(Diethylamino)-1,2-diphenylethan-1-ol (176c).

Applying the general procedure 5.7.3.2. (Method B), \textit{cis}-stilbene oxide (400 mg, 2.04 mmol) was treated with diethyamine (1.06 mL, 10.13 mmol) and Sc(OTf)$_3$ (31 mg, 3 mol%) in dry THF (4 mL) for 48 h. The crude product was purified by column chromatography (silica gel; DCM:MeOH = 98:2–90:10) to afford product 176c as brown oil in 57\% yield (315 mg, 1.17 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$/ ppm = 7.27–7.07 (m, 10H), 5.31 (bs, 1H), 4.99 (d, $J$ = 10.2 Hz, 1H), 3.76 (d, $J$ = 10.2 Hz, 1H), 2.83 (dq, $J$ = 7.3, 12.9 Hz, 2H), 2.20 (dq, $J$ = 6.9, 13.6 Hz, 2H), 1.17 (t, $J$ = 7.1 Hz, 6H).

MS (ESI): $m/z$ calculated for C$_{18}$H$_{24}$NO+: 270.19 [M+H]$^+$, found 270.20

TLC (DCM:MeOH = 98:2): $R_f$ = 0.21

5.7.7. Preparation of \textit{anti}-2-(dibenzylamino)-1,2-diphenylethan-1-ol 176d

![Structure](image2)

\textit{Figure 32:} \textit{anti}-2-(Dibenzylamino)-1,2-diphenylethan-1-ol (176d).

Applying the general procedure 5.7.3.2. (Method B), \textit{cis}-stilbene oxide (400 mg, 2.04 mmol) was treated with dibenzylamine (2.0 mL, 10.19 mmol) and Sc(OTf)$_3$ (31 mg, 3 mol%) in dry THF (4 mL) for 24 h. The crude product was purified by column chromatography (silica gel; heptanes:DCM = 1:3) to afford product 176d as white solid in 52\% yield (418 mg, 1.06 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$/ ppm = 7.45–7.29 (m, 10H), 7.20–7.15 (m, 2H), 7.10–6.98 (m, 5H), 5.25 (bs, 1H), 5.22 (d, $J$ = 10.5 Hz), 4.10 (d, $J$ = 13.2 Hz, 2H), 3.79 (d, $J$ = 10.3 Hz, 1H), 3.12 (d, $J$ = 13.2 Hz, 2H).
MS (ESI): $m/z$ calculated for $C_{28}H_{28}NO^+$: 394.22 [M+H]$^+$, found 394.25

TLC (heptanes:DCM = 1:3): $n = 0.41$

5.7.8. Preparation of trans-2-(pyrrolidin-1-yl)cyclohexan-1-ol 215

![Chemical structure](image)

**Scheme 58:** Preparation of trans-2-(pyrrolidin-1-yl)cyclohexan-1-ol (215).

In adaption of a known procedure [86], to a flame-dried Schlenk tube equipped with a stirring bar was added cyclohexene oxide (0.8 g, 8.2 mmol) and pyrrolidine (3.4 mL, 40.3 mmol). It was stirred at 80 °C for 24 h, whereupon the mixture was allowed to cool down. Evaporation of the excess amine and drying in vacuo gave product 215 as brown oil in 94 % yield (1.3 g, 7.7 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): δ / ppm = 3.40–3.30 (m, 1H), 2.76–2.64 (m, 2H), 2.64–2.52 (m, 2H), 2.51–2.41 (m, 1H), 2.15–2.06 (m, 1H), 1.85–1.64 (m, 7H), 1.34–1.11 (m, 4H).

MS (ESI): $m/z$ calculated for $C_{10}H_{20}NO^+$: 170.15 [M+H]$^+$, found 170.30

5.7.9. [General] Preparation of β-chloro amines

![Chemical structure](image)

**Scheme 59:** Preparation of β-chloro amines (181).

Analogously to literature [56], in a flame-dried Schlenk flask equipped with a stirring bar, a solution of β-amino alcohol (4.30 mmol) in dry DCM (21.5 mL) was prepared. It was cooled in an ice bath while stirring, whereupon NEt$_3$ (0.90 mL, 6.45 mmol) was added at once. MsCl (0.51 mL, 6.45 mmol) was added drop-wise over a period of 10 minutes. The mixture was allowed to warm to room temperature overnight under argon atmosphere. After completion (determined by TLC analysis), the mixture was quenched with sat. NaHCO$_3$ solution (21.5 mL) and transferred to a separation funnel, where the aqueous phase was removed.

**Work-up A:** The organic phase was washed thoroughly with NaHCO$_3$ solution (2x 21.5 mL) and sat. NaCl solution (3x 21.5 mL).
Work-up B: The organic phase was treated with MeOH (20 mL) and concentrated under reduced pressure. The precipitate was dissolved in DCM (25 mL) and washed with NaHCO$_3$ solution (2x 25 mL) and sat. NaCl solution (1x 25 mL).

The organic phase was dried over Na$_2$SO$_4$ and filtered. Evaporation of the solvent under reduced pressure and drying in vacuo gave the crude product

5.7.10. Preparation of anti-1-(2-chloro-1,2-diphenylethyl)pyrrolidine 181a

![181a](image)

Figure 33: anti-1-(2-Chloro-1,2-diphenylethyl)pyrrolidine (181a).

Applying the general procedure 5.7.9., anti-1,2-diphenyl-2-(pyrrolidin-1-yl)ethan-1-ol (1.15 g, 4.30 mmol) was treated with NEt$_3$ (0.90 mL, 6.45 mmol) and MsCl (0.51 mL, 6.45 mmol) in dry DCM (21.5 mL). Work-up B gave the crude product 181a as brown oil in 86 % yield (1.05 g, 3.67 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$/ ppm = 7.21–7.06 (m, 8H), 7.02–6.92 (m, 2H), 5.43 (d, $J$ = 7.5 Hz, 1H), 4.06 (d, $J$ = 7.5 Hz, 1H), 2.75–2.63 (m, 2H), 2.63–2.49 (m, 2H), 1.82–1.64 (m, 4H).

MS (ESI): m/z calculated for C$_{19}$H$_{22}$ClN$: 286.14 [M+H]$^+$, found 286.10

5.7.11. Preparation of anti-4-(2-chloro-1,2-diphenylethyl)morpholine 181b

![181b](image)

Figure 34: anti-4-(2-Chloro-1,2-diphenylethyl)morpholine (181b).

Applying the general procedure 5.7.9., anti-2-morpholino-1,2-diphenylethan-1-ol (309 mg, 1.09 mmol) was treated with NEt$_3$ (0.23 mL, 1.64 mmol) and MsCl (0.13 mL, 1.64 mmol) in dry
DCM (5.5 mL). Work-up A gave the crude product 181b as red solid in 79 % yield (260 mg, 0.86 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.24–7.10 (m, 8H), 7.06–6.92 (m, 2H), 5.42 (bs, 1H), 4.09 (bs, 1H), 3.90–3.71 (m, 4H), 2.71–2.44 (m, 4H).

MS (ESI): $m/z$ calculated for C$_{18}$H$_{21}$ClN$_2$O$^+$: 302.13 [M+H]$^+$, found 302.15

5.7.12. Preparation of anti-2-chloro-N,N-diethyl-1,2-diphenylethan-1-amine 181c

![Diagram of 181c]

Figure 35: anti-2-Chloro-N,N-diethyl-1,2-diphenylethan-1-amine (181c).

Applying the general procedure 5.7.9., anti-2-(diethylamino)-1,2-diphenylethan-1-ol (305 mg, 1.13 mmol) was treated with NEt$_3$ (0.24 mL, 1.70 mmol) and MsCl (0.14 mL, 1.70 mmol) in dry DCM (5.7 mL). Work-up A gave the crude product 181c as brown oil in 80 % yield (261 mg, 0.91 mmol).

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K): $\delta$ / ppm = 7.25–7.07 (m, 10H), 5.63 (bs, 1H), 4.53 (bs, 1H), 3.21–3.05 (m, 2H), 2.67 (bs, 2H), 1.26 (t, $J$ = 6.9 Hz, 6H).

MS (ESI): $m/z$ calculated for C$_{18}$H$_{23}$ClN$^+$: 288.15 [M+H]$^+$, found 288.20

5.7.13. Preparation of anti-N,N-dibenzyl-2-chloro-1,2-diphenylethan-1-amine 181d

![Diagram of 181d]

Figure 36: anti-N,N-Dibenzyl-2-chloro-1,2-diphenylethan-1-amine (181d).

Applying the general procedure 5.7.9., anti-2-(dibenzylamino)-1,2-diphenylethan-1-ol (408 mg, 1.04 mmol) was treated with NEt$_3$ (0.22 mL, 1.56 mmol) and MsCl (0.12 mL, 1.56 mmol) in dry DCM (5.2 mL). Work-up A gave the crude product 181d as ochre solid in 94 % yield (402 mg, 0.98 mmol).
\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \(\delta / \text{ppm} = 7.60 \) (d, \(J = 7.4\) Hz, 4H), 7.40–7.33 (m, 4H), 7.29–7.15 (m, 5H), 7.06 (s, 5H), 6.97–6.91 (m, 2H), 5.56 (d, \(J = 11.3\) Hz, 1H), 4.27 (d, \(J = 11.3\) Hz, 1H), 4.09 (d, \(J = 13.7\) Hz, 2H), 3.11 (d, \(J = 13.7\) Hz, 2H).

MS (ESI): \(m/z\) calculated for C\(_{28}\)H\(_{27}\)ClN\(^+\): 412.18 [M+H]\(^+\), found 412.20

5.7.14. Preparation of trans-1-(2-chlorocyclohexyl)pyrrolidine 218

![Chemical Structure](image)

Figure 37: trans-1-(2-Chlorocyclohexyl)pyrrolidine (218).

Applying the general procedure 5.7.9., trans-2-(pyrrolidin-1-yl)cyclohexan-1-ol (229 mg, 1.35 mmol) was treated with NEt\(_3\) (0.29 mL, 2.12 mmol) and MsCl (0.16 mL, 2.02 mmol) in dry DCM (6.8 mL). Work-up A gave the crude product 218 in 99 % yield (252 mg, 1.34 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \(\delta / \text{ppm} = 4.20–4.06\) (m, 1H), 2.72–2.52 (m, 5H), 2.29–2.19 (m, 1H), 2.01–1.92 (m, 1H), 1.83–1.70 (m, 6H), 1.47–1.17 (m, 4H).

MS (ESI): \(m/z\) calculated for C\(_{10}\)H\(_{19}\)ClN\(^+\): 188.12 [M+H]\(^+\), found 188.30

5.8. Procedure for nucleophilic ring-opening reactions of meso-aziridinium ions

5.8.1. [General] Procedure for nucleophilic ring-opening reactions of meso-aziridinium ions with KCN

\[ \text{Cl} \begin{array}{c} \text{NR}_2 \\ \text{Ph} \end{array} + \text{KCN} \rightarrow \text{CHCl}_3 (0.5 \text{ M}, \text{r.t.}) \rightarrow \text{NC} \begin{array}{c} \text{NR}_2 \\ \text{Ph} \end{array} \]

Scheme 60: Nucleophilic ring-opening reactions of meso-aziridinium ions with KCN.

In adaption of a known procedure [86], to a GC vial equipped with a stirring bar was added a solution of \(\beta\)-chloro amine (0.10 mmol) in neutralized CHCl\(_3\) (0.2 mL, filtered over basic AlOx) and KCN (32.6 mg, 0.50 mmol). It was stirred for 72 h under argon atmosphere, whereupon the reaction was quenched with sat. NaHCO\(_3\) solution (1 mL). The reaction mixture was transferred with H\(_2\)O (4 mL) and DCM (4 mL) to a separating funnel, where the organic phase was removed.
The aqueous phase was extracted with DCM (3x 5 mL) and the combined organic phases were dried over Na₂SO₄. Filtration, evaporation of the solvent under reduced pressure and drying in vacuo afforded the crude β-amino nitrile. The crude product was purified by column chromatography (silica gel; heptanes:EtOAc).

5.8.2. [General] Procedure for nucleophilic ring-opening reactions of meso-aziridinium ions with KCN in presence of a chiral phosphate

![Scheme 61](image)

Scheme 61: Nucleophilic ring-opening reactions of meso-aziridinium ions with KCN in presence of a chiral phosphate.

According to literature [58], to a flame-dried Schlenk flask equipped with a stirring bar was added β-chloro amine (0.1 mmol) and ACN (1 mL) along with 3 Å molecular sieves. It was cooled in an ice-bath, whereupon chiral phosphoric acid 197 (5.4 mg, 15 mol%), Ag₂CO₃ (16.9 mg, 0.06 mmol) and KCN (26.8 mg, 0.4 mmol) were added under argon atmosphere. The ice-bath was removed and the mixture was allowed to warm up to room-temperature. After 72 h, the reaction was quenched with sat. NaHCO₃ solution (1 mL). Subsequent work-up and purification was performed according to 5.8.1. to afford the product.

5.8.3. [General] Procedure for nucleophilic ring-opening reactions of meso-aziridinium ions with KCN catalyzed by a chiral PTC

![Scheme 62](image)

Scheme 62: Procedure for nucleophilic ring-opening reactions of meso-aziridinium ions with KCN catalyzed by a chiral PTC.
Analogously to literature [86], to a flame-dried Schlenk flask equipped with a stirring bar was added β-chloro amine (0.2 mmol), neutralized CHCl₃ (0.4 mL, filtered over basic AlOx), KCN (67.2 mg, 1.0 mmol) and 199 (10.0 mg, 10 mol%). The reaction mixture was stirred at room temperature under argon atmosphere. After completion (determined by TLC analysis), the mixture was quenched with sat. NaHCO₃ solution (1 mL). Subsequent work-up and purification was performed according to 5.8.1. to afford the products. The diastereomers were separated by preparative HPLC (hexane:DCM, normal phase).

5.8.4. Preparation of anti-2,3-diphenyl-3-(pyrrolidin-1-yl)propanenitrile 185a

![Chemical Structure](attachment:structure185a.png)

\[ \text{Figure 38: anti-2,3-Diphenyl-3-(pyrrolidin-1-yl)propanenitrile (185a).} \]

Applying the general procedure 5.8.1, anti-1-(2-chloro-1,2-diphenylethyl)pyrrolidine (28.6 mg, 0.10 mmol) in CHCl₃ (0.2 mL) was reacted with KCN (32.6 mg, 0.50 mmol). The crude product 185a was obtained as yellow oil in 99 % yield (27.6 mg, 0.10 mmol).

\[ ^1\text{H-NMR (300 MHz, CDCl₃, 298.0 K): } \delta / \text{ppm} = 7.24-7.03 \text{ (m, 10H), 4.39 (d, } J = 6.4 \text{ Hz, 1H), } 3.95 \text{ (d, } J = 6.4 \text{ Hz, 1H), 2.71-2.58 \text{ (m, 2H), 2.58-2.44 \text{ (m, 2H), 1.81-1.68 \text{ (m, 4H).} \}

\[ ^13\text{C-NMR (75 MHz, CDCl₃, 298.0 K): } \delta / \text{ppm} = 136.9, 133.6, 129.2 \text{ (2C), 129.1 \text{ (2C), 128.6 \text{ (2C), 128.2 \text{ (4C), 120.6, 72.6, 52.1 \text{ (2C), 43.2, 23.7 \text{ (2C). \}

MS (ESI): m/z calculated for C₁₉H₂₁N₂⁺: 277.17 [M+H]⁺, found 277.10

5.8.5. Preparation of anti-3-morpholino-2,3-diphenylpropanenitrile 185b

![Chemical Structure](attachment:structure185b.png)

\[ \text{Figure 39: anti-3-Morpholino-2,3-diphenylpropanenitrile (185b).} \]
Applying the general procedure 5.8.1, *anti*-4-(2-chloro-1,2-diphenylethyl)morpholine (53.6 mg, 0.18 mmol) in CHCl₃ (0.4 mL) was reacted with KCN (64.3 mg, 0.96 mmol). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 2:1) to afford 185b as white solid in 58 % yield (30.0 mg, 0.10 mmol).

1H-NMR (300 MHz, CDCl₃, 298.0 K): δ / ppm = 7.31−7.15 (m, 8H), 7.08−7.01 (m, 2H), 4.42 (d, J = 9.7 Hz, 1H), 3.95 (d, J = 9.7 Hz, 1H), 3.84−3.70 (m, 4H), 2.63−2.52 (m, 2H), 2.52−2.41 (m, 2H).

13C-NMR (75 MHz, CDCl₃, 298.0 K): δ / ppm = 134.0, 133.5, 129.1 (2C), 129.0 (2C), 128.8 (2C), 128.5 (3C), 128.4, 120.3, 73.7, 67.5 (2C), 50.7 (2 C), 41.2

MS (ESI): m/z calculated for C₁₉H₂₁N₂O⁺: 293.16 [M+H]+, found 293.20

HPLC: Chiralcel OD-H; hexane:i-PrOH = 3:1; 0.5 mL·min⁻¹; T_column = 10 °C; t_ret.: 19.1 min, 30.9 min.

TLC (heptanes:EtOAc = 2:1): ɳ = 0.33

5.8.6. Preparation of *anti*-3-(diethylamino)-2,3-diphenylpropanenitrile 185c

![Chemical structure of 185c](image)

Figure 40: *anti*-3-(Diethylamino)-2,3-diphenylpropanenitrile (185c).

Applying the general procedure 5.8.1, *anti*-2-chloro-N,N-diethyl-1,2-diphenylethan-1-amine (58.4 mg, 0.20 mmol) in CHCl₃ (0.4 mL) was reacted with KCN (64.3 mg, 0.96 mmol). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 5:1) to afford 185c as tan oil in 46 % yield (26.0 mg, 0.09 mmol).

1H-NMR (300 MHz, CDCl₃, 298.0 K): δ / ppm = 7.30−7.14 (m, 8H), 7.12−7.05 (m, 2H), 4.43 (d, J = 10.3 Hz, 1H), 4.22 (d, J = 10.3 Hz, 1H), 2.83 (dq, J = 7.3, 14.5 Hz, 2H), 2.28 (dq, J = 6.9, 13.6 Hz, 2H), 1.16 (t, J = 7.1 Hz, 6H).

13C-NMR (75 MHz, CDCl₃, 298.0 K): δ / ppm = 135.3, 134.8, 129.1 (2C), 128.9 (2C), 128.8 (2C), 128.4 (2C), 128.2, 128.0, 120.8, 68.6, 44.2 (2C), 42.4, 14.2 (2C).

MS (ESI): m/z calculated for C₁₉H₂₃N₂⁺: 279.19 [M+H]⁺, found 279.25

TLC (heptanes:EtOAc = 2:1): ɳ = 0.68
5.8.7. Preparation of anti-3-(dibenzylamino)-2,3-diphenylpropanenitrile 185d

Figure 41: anti-3-(Dibenzylamino)-2,3-diphenylpropanenitrile (185d).

Applying the general procedure 5.8.1, anti-\( N,N\)-dibenzyl-2-chloro-1,2-diphenylethan-1-amine (82.8 mg, 0.20 mmol) in CHCl\(_3\) (0.4 mL) was reacted with KCN (65.0 mg, 0.97 mmol). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 5:1) to afford 185d as white solid in 64 % yield (52.0 mg, 0.13 mmol).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 298.0 K): \( \delta / ppm = 7.61 \) (d, \( J = 7.4 \) Hz, 4H), 7.42–7.35 (m, 4H), 7.32–7.26 (m, 5H), 7.12–7.06 (m, 3H), 7.04–6.95 (m, 4H), 4.55 (d, \( J = 11.7 \) Hz, 1H), 4.21 (d, \( J = 11.7 \) Hz, 1H), 4.06 (d, \( J = 13.6 \) Hz, 2H), 3.09 (d, \( J = 13.6 \) Hz, 2H).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\), 298.0 K): \( \delta / ppm = 139.0 \) (2C), 134.3, 132.4, 129.6 (2C), 129.3 (4C), 129.0 (2C), 128.9 (4C), 128.8 (2C), 128.5 (2C), 128.4, 128.3, 127.6 (2C), 120.8, 66.4, 54.5 (2C), 41.3

HPLC: Chiralcel OD-H; hexane:i-PrOH = 3:1; 0.5 mL·min\(^{-1}\); \( T_{column} = 10 \) °C; \( t_{ret.} : 16.2 \) min, 32.6 min.

Prep HPLC: Alltima Silica 10 \( \mu \)m; hexane:DCM = 70:30; 5 mL·min\(^{-1}\), \( T_{column} = 25 \) °C; \( t_{ret.} : 41.7 \) min.

TLC (heptanes:EtOAc = 5:1): \( R_f = 0.38 \)

5.8.8. Preparation of trans-2-(pyrrolidin-1-yl)cyclohexane-1-carbonitrile 187

Figure 42: trans-2-(pyrrolidin-1-yl)cyclohexane-1-carbonitrile (187).
Applying the general procedure 5.8.1, trans-1-(2-chlorocyclohexyl)pyrrolidine (18.8 mg, 0.10 mmol) in CHCl₃ (0.2 mL) was reacted with KCN (33.4 mg, 0.50 mmol). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc:NEt₃ = 2:1:0.01) to afford 187 as colorless liquid in 50 % yield (9.0 mg, 0.05 mmol).

^1H-NMR (300 MHz, CDCl₃, 298.0 K): δ / ppm = 2.80–2.68 (m, 1H), 2.68–2.52 (m, 4H), 2.18–2.02 (m, 1H), 1.96–1.08 (m, 12H).

^13C-NMR (75 MHz, CDCl₃, 298.0 K): δ / ppm = 122.6, 61.2, 50.0 (2C), 33.3, 27.4, 26.6, 24.0 (2C), 22.7

MS (ESI): m/z calculated for C₁₁H₁₉N₂⁺: 179.15 [M+H]⁺, found 179.35

TLC (heptanes:EtOAc = 2:1): rᵣ = 0.37

5.8.9. Preparation of syn-3-(dibenzylamino)-2,3-diphenylpropanenitrile 200d

Applying the general procedure 5.8.3, anti-N,N-dibenzyl-2-chloro-1,2-diphenylethan-1-amine (82.4 mg, 0.20 mmol) in CHCl₃ (0.4 mL) was reacted with KCN (67.2 mg, 1.03 mmol) and catalyst 199 (10.0 mg, 10 mol%). The crude product was purified by column chromatography (silica gel; heptanes:EtOAc = 5:1) to afford a diastereomeric mixture. Subsequent separation by preparative HPLC (normal phase; hexane:DCM = 70:30) gave syn-200d as white solid in 8 % yield (6.9 mg, 0.02 mmol).

^1H-NMR (300 MHz, CDCl₃, 298.0 K): δ / ppm = 7.52–7.30 (m, 9H), 7.24–7.20 (m, 7H), 7.02–6.95 (m, 4H), 4.49 (d, J = 10.9 Hz, 1H), 4.30 (d, J = 10.9 Hz, 1H), 3.84 (d, J = 13.9 Hz, 2H), 3.08 (d, J = 13.9 Hz, 2H).

^13C-NMR (75 MHz, CDCl₃, 298.0 K): δ / ppm = 138.6 (2C), 134.6, 134.2, 129.5 (2C), 129.4 (2C), 129.1 (4C), 128.8 (2C), 128.7, 128.6 (3C), 127.5 (2C), 120.4, 66.3, 53.9 (2C), 40.4

MS (ESI): m/z calculated for C₂₉H₂₈N₂⁺: 403.22 [M+H]⁺, found 403.30

HPLC: Chiralcel OD-H; hexane:i-PrOH = 3:1; 0.5 mL·min⁻¹; T_column = 10 °C; t_ret.: 11.9 min, 31.7 min.
Prep HPLC: Alltima Silica 10 µm; hexane:DCM = 70:30; 5 mL·min⁻¹, \( T_{\text{column}} = 25 ^\circ \text{C} \); \( \text{t}_{\text{ret.}}: 37.7 \) min.

TLC (heptanes:EtOAc = 5:1): \( r_f = 0.38 \)

5.9. Preparation of chiral auxiliary (S)-\( N \)-benzyl-1-phenylethan-1-amine 189

5.9.1. Preparation of (S)-1-phenyl-\( N \)-(1-phenylethyl)methanimine 188

Scheme 63: Preparation of (S)-1-phenyl-\( N \)-(1-phenylethyl)methanimine (188).

In adaption of a known procedure [101], (S)-1-phenylethan-1-amine (5.0 g, 40 mmol) was dissolved in toluene (200 mL) and benzaldehyde (4.3 g, 40 mmol) was added. The reaction was carried out in a Dean-Stark apparatus at 130 °C overnight under argon atmosphere. After completion, the mixture was allowed to cool to room temperature. Evaporation of the solvent yielded product 188, which was used without further purification.

\(^1\text{H-NMR} (300 \text{ MHz}, \text{CDCl}_3, 298.0 \text{ K}): \delta / \text{ppm} = 8.52 (s, 1H), 7.97-7.90 (m, 2H), 7.62-7.45 (m, 7H), 7.43-7.37 (m, 1H), 4.70 (q, \text{J} = 6.6 \text{ Hz}, 1H), 1.75 (d, \text{J} = 6.7 \text{ Hz}, 3H). \)

5.9.2. Preparation of (S)-\( N \)-benzyl-1-phenylethan-1-amine 189

Scheme 64: Preparation of (S)-\( N \)-benzyl-1-phenylethan-1-amine (189).

According to literature [112], (S)-1-phenyl-\( N \)-(1-phenylethyl)methanimine (approximately 8.5 g, 40 mmol) was dissolved in MeOH (200 mL) and cooled to 0 °C. \text{NaBH}_4 (1.7 g, 45 mmol) was added in portions and it was stirred for 30 minutes, whereupon the mixture was allowed to warm to room temperature. After 5 h, the mixture was concentrated under reduced pressure and the
crude product was dissolved in diethyl ether (100 mL) and sat. NaHCO₃ solution (100 mL). The biphasic mixture was transferred to a separation funnel, where the organic phase was removed. The aqueous phase was extracted with diethyl ether (2x 100 mL). The combined organic phases were extracted with 2.0 M HCl (3x 100 mL). The combined aqueous, acidic extracts were washed with EtOAc (1x 100 mL), basified with NaHCO₃ and extracted with diethyl ether (3x 100 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated under reduced pressure and dried in vacuo to afford 189 as colorless liquid in overall 72 % yield (6.2 g, 29 mmol).

¹H-NMR (300 MHz, CDCl₃, 298.0 K): δ / ppm = 7.40–7.16 (m, 10H), 3.80 (q, J = 6.6 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 13.2 Hz, 1H), 1.60 (bs, 1H), 1.35 (d, J = 6.6 Hz, 3H).
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACH</td>
<td>Acetone cyanohydrin</td>
</tr>
<tr>
<td>ACN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-Bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DPTU</td>
<td>1,3-Diphenylthiourea</td>
</tr>
<tr>
<td>e.r.</td>
<td>Enantiomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>M.S.</td>
<td>Molecular sieve</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>MsCl</td>
<td>Mesyl chloride</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl tert-butyl ether</td>
</tr>
<tr>
<td>NEt$_3$ (TEA)</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting group</td>
</tr>
<tr>
<td>PhMe</td>
<td>Toluene</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetra-$n$-Butylammonium bromide</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-$n$-Butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TMSCN</td>
<td>Trimethylsilyl cyanide</td>
</tr>
<tr>
<td>Tosyl (Tos, Ts)</td>
<td>Toluenesulfonyl</td>
</tr>
<tr>
<td>UV/VIS</td>
<td>Ultraviolet-visible</td>
</tr>
<tr>
<td>XRD</td>
<td>X-ray diffraction</td>
</tr>
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</table>

*Table 8: List of commonly used abbreviations and their meaning.*
References


