Diastereoselective Lithiation-Substitution of N-Silyl-Protected-(S)-Tetrahydro-$1H$-pyrrolo[1,2-c]imidazole-$3(2H)$-ones and Applications of Their Derivatives

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of the requirements for the degree of

Master of Science

Faculty of Mathematics and Science, Brock University
St. Catharines, Ontario

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Abstract

This thesis describes a method involving the preparation of an \( L \)-proline-derived imidazolone protected with an \( N \)-triethylsilyl group that undergoes diastereoselective lithiation followed by electrophile quench to give C5-substituted products with \( \text{syn} \) stereochemistry. The \( N \)-silylated derivatives may be more easily \( N \)-deprotected as compared to previous \( N \)-t-Bu analogues to give secondary ureas. These may serve as precursors to \( N \)-phenyl chiral bicyclic guanidines or as NHC precursors for synthesis of corresponding complexes.
Acknowledgments

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I would like to thank the Metallinos group members for sharing their knowledge in this field and support throughout my two years here at Brock including: Joshni John, Kassandra Emberson and Cody Wilson Konderka, in particular Joshni John for helping me both in the lab and with questions I had.

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<td>KOt-Bu</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LiAlH4</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>MVK</td>
<td>methyl vinyl ketone</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
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</tr>
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<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser enhancement</td>
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<tr>
<td>NOESY</td>
<td>nuclear Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>OAc</td>
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<tr>
<td>Ph</td>
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</tr>
<tr>
<td>pin</td>
<td>pinacolate</td>
</tr>
<tr>
<td>POC_13</td>
<td>phosphoryl chloride</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
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<tr>
<td>--------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TC</td>
<td>thiophene-2-carboxylate</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilane</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>Trityl (triphenylmethyl)</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt;</td>
<td>retention time</td>
</tr>
</tbody>
</table>
1. Introduction

Saturated cyclic amines are a common structural motif in natural products and biologically active compounds, and an important template for versatile catalysts for a wide range of organic transformations. Piperidine and pyrrolidine heterocyclic amines occur widely in nature as constituents of quinolizidine, pyrrolizidine and indolizidine alkaloids, which exhibit interesting and diverse biochemical, pharmaceutical and agricultural properties as a result of their diverse biological activities.\(^1\) Prominent examples of these systems are natural compounds such as nicotine and coniine, anisomycin, oxiracetam, plakoridine, as well as the opiates codeine and morphine (Figure 1).

![Figure 1](image-url)

**Figure 1.** Some biologically active nitrogen-containing heterocycles.\(^1\)

Achiral and chiral pyrrolidine heterocyclic amines are important structural motifs in potential catalysts for asymmetric synthetic chemistry and in natural products. Asymmetric lithiation is the most powerful synthetic method for synthesis of chiral pyrrolidine derivatives.\(^2\)
1.1. Direct $\alpha$-Functionalization of Saturated Cyclic Amines

The direct functionalization of nitrogen-containing heterocycles has recently become an important route in organic synthesis.\(^2\) This is achieved with saturated cyclic amines by the addition of a protecting group to the nitrogen, $\alpha$-lithiation, electrophilic substitution, and finally, deprotection of nitrogen.\(^3\) In fact, this straightforward way for direct $\alpha$-functionalization of the saturated cyclic amines\(^3\) has great utility in the alkaloid synthesis of potential pharmaceuticals and natural product synthesis.\(^4\) Thus, this method may lead to further development of related compounds as potential medicinal agents.

The direct functionalization of nitrogen-containing heterocycles can be derived by $\alpha$-lithiation by alkyllithium and appropriate diamine complexes, production of active carbanion, followed by electrophilic substitution.\(^3\) Several protecting groups, including carbamates, formadines, oxazolines, amides and phosphoramides, were effective in $\alpha$-functionalization of the nitrogen containing-heterocycles, which were reported by Beak and Hoppe (Scheme 1).\(^5a,b\)

\[ \begin{align*}
&\text{N} \\
&\text{PG} \\
&\text{7} \\
&\text{1. RLi, L} \\
&\text{solvent, low temp} \\
&\text{E}^+ \\
&\text{2. E}^+ \\
&\text{N} \\
&\text{PG} \\
&\text{E} \\
&\text{8}
\end{align*} \]

R = s-Bu, n-Bu, i-Pr
PG = Boc, Et, n-Bu, i-Bu, CH\(_2\)CH\(_2\)OMe
trimethylallyl, 3-methylbut-2-enyl

**Scheme 1.** Asymmetric deprotonation of N-protected pyrrolidines with chiral diamine and alkyllithium\(^4,5\)
O’Brien and co-workers have reported the asymmetric deprotonation of pyrrolidine by the use of 
(−)-sparteine as a chiral diamine, which allows for removal of one of the pro-S protons. They also used 
other diamine ligands such as TMEDA, PMDETA as well as the (+)-sparteine surrogate, which have 
caused significant development in the α-lithiation strategy and provided a synthetic route to access both 
enantiomeric forms of α-substituted pyrrolidine derivatives (Figure 2).6

![Structures](image)

Figure 2. Structures (−)-sparteine 9 and (+)-sparteine surrogate 10, PMDETA and TMEDA.6

They have highlighted the importance and effectiveness of both (+)-surrogate and (−)-sparteine in 
the asymmetric deprotonation with the opposite sense of enantioselectivity (Scheme 2). (+)-Surrogate 10 
was generated from cytisine 16 in excellent yield (Scheme 3).7

![Scheme](image)

Scheme 2. Influence of both (+)-sparteine surrogate and (−)-sparteine in asymmetric deprotonation.7
Scheme 3. Synthesis of (+)-sparteine surrogate 10.\textsuperscript{7}

Pre-complexation of nitrogen with borane or boron trifluoride for the activation of tertiary amines to regioselective lithiation-substitution reactions play important role as a valuable method in organic synthesis.\textsuperscript{8} The most of studies in this area have focused on lithiation of $sp^3$-hybridized carbon atoms alpha to nitrogen in cyclic amines such as Troeger's base 18, isoindolines 19, \textsuperscript{10a,b} pyrrolidines 20,\textsuperscript{11} and indolizidines 21.\textsuperscript{12} For these substrates 19 and 20, lithiation of prochiral $\alpha$-methylene groups with alkyllithiums in the presence of the chiral diamine (+)-sparteine after electrophile quench gave enantiomERICALLY enriched products. For example, (+)-sparteine-mediated lithiation-substitution of isoindolines gave products ranging from 78:22–94:6 er via intermediate 19. Under the same conditions, enantiomERICALLY enriched carbanion 20 was generated in 85:15–86:14 er, determined as the benzophenone adducts (28–78% yield) (Figure 3).

Figure 3. Previous examples of BF$_3$- or BH$_3$-activated lithiation of tertiary amines.
Metallinos and co-workers reported the first example of BF$_3$-activated asymmetric lithiation of an sp$^2$-hybridized carbon atom of a prochiral aromatic amine, and the first application of bulky chiral 1,2-diaminocyclohexane ligands such as 22-24 in the BF$_3$-activated tertiary aminoferrocenes, rather than (−)-sparteine. The process provided access to a broad range of enantiomerically enriched 2-substituted-1-aminoferrocenes in high enantioselectivity (87:13 to 91:9 er) after simple recrystallization (Scheme 4).

![Scheme 4](image)

**Scheme 4.** Asymmetric lithiation of boron trifluoride-activated amino-ferrocenes.

Recently, this method has become more versatile by the development of (+)-sparteine surrogate and it is also now possible to install vinyl and aryl substituents with retention of stereochemical integrity of the chiral carbanion. The first synthesis of chiral benzylamines 29 from oxazolidones via diastereoselective lithiation was reported by Gawley and co-workers with good yields and excellent diastereoselectivities (Scheme 5).

![Scheme 5](image)

**Scheme 5.** Diastereoselective synthesis of chiral benzylamines from oxazolidones.
Following diastereoselective lithiation procedure, Beak examined competition experiments between a series of \( N \)-Boc amines and bicyclic carbamates. The results indicated that rigid carbamates were deprotonated faster than \( N \)-Boc amines. Beak determined that these reactions undergo diastereoselective lithiation in the presence of a chiral centre in the substrate to give products 31 with syn stereochemistry (Scheme 6).

![Scheme 6. Diastereoselective lithiation of bicyclic carbamate 31.](image)

It was indicated that removal of one of the pro-\( S \) protons is favoured and the resulting anion is configurationally stable. These results proposed that appropriate restriction of the geometry of the substrate can increase the ability of the lithiation reaction and a small dihedral angle between the carbonyl group and the proton that is being removed is favoured.

The distance between the carbamate carbonyl group and the proton removed was calculated at the PM3 level. These computational calculations showed that the pro-\( R \) proton had a much longer distance to the carbonyl oxygen (3.70 Å) than the pro-\( S \) proton (2.78 Å). Removal of the pro-\( S \) proton which is nearest proton to the carbonyl oxygen is kinetically, as well as thermodynamically favored (Figure 4).
Figure 4. Geometry between the lithium and the carbonyl group in cis and trans carbanions.\textsuperscript{11}

Following a similar procedure, Metallinos and co-workers reported in 2007\textsuperscript{17} asymmetric lithiation alpha to nitrogen of urea-fused piperidines by using \textit{i-PrLi} (\textendash)-sparteine. According to the procedure described for bicyclic carbamates, an octahydrophenanthroline-derived urea \textbf{34} was lithiated by \textit{i-PrLi} followed by electrophile quench to generate \textbf{35} in low yield and moderate enantioselectivities (\textbf{Scheme 7}). The transition state analysis for the lithiation of urea \textbf{34} by the \textit{i-PrLi} and (\textendash)-sparteine complex was performed at the MP2/G-31G(d)//B3LYP/6-316(d) level of theory, and showed that the removal of the axial pro-R hydrogen is less favoured than equatorial pro-S hydrogen.\textsuperscript{12}

\textbf{Scheme 7.} Lithiation of octahydrophenanthroline-derived urea \textbf{34}.\textsuperscript{12}
Notably, they reported a new method to access enantiomerically enriched products of both pyrrolo[1,2-c]imidazolin-3-ones and pyrrolo[1,2-c]imidazol-3-ones, which are relatively challenging and problematic to make by conventional ways. They showed that 5-substituted pyrroloimidazolium and pyrroloimidazolium precatalysts can be prepared in two steps by stereoselective lithiation followed by electrophilic quench of their lithio derivatives (Scheme 8).\textsuperscript{18}

Scheme 8. Synthesis of saturated and unsaturated ureas by stereoselective lithiation.\textsuperscript{13}

The next section will briefly introduce pyrrolidine-containing molecules which are used as catalysts in organic reactions.

1.2. Guanidines

Guanidines (Figure 5) are present in many natural products, which are often found to have significant biological activities\textsuperscript{19} as well their potential as substrate specific oxoanion hosts.\textsuperscript{20} Guanidines are obtained by the oxidation of guanine, synthesized for the first time by oxidative degradation of an aromatic natural product in 1861.\textsuperscript{21}
A large number of guanidines consist of marine guanidines, which are found as anionic receptors that can react with phosphates and carboxylates due to hydrogen bonding.\textsuperscript{15}

Guanidines are classified as organic superbases and catalyze a variety of base-assisted organic transformations due to the resonance stability of their conjugate acids. The guanidine compound, 1,1,3,3-tetramethylguanidine (or \(N,N,N,N\)-tetramethylguanidine; TMG) \textbf{40} has been used in a wide range of organic transformations as its substituted ones \textbf{41} used by Barton (Figure 6).\textsuperscript{22}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Structures of TMG \textbf{40} and Barton’s bases \textbf{41}.\textsuperscript{17}}
\end{figure}

1.2.1. Synthesis of Polysubstituted Acyclic and Monocyclic Guanidines and Their Applications

TMG was synthesized for the first time by Schneck by treatment of 1,1,3,3-tetramethyl-2-methylthioamidinium salt and ammonia in 1912 (Scheme 9).\textsuperscript{23}
As an application of monocyclic guanidines, guanidine 44 was used by Ishikawa and co-workers to catalyze the Michael reaction of glycinate under solvent-free conditions, in which they obtained a high yield of 85% and good enantiomeric excess (ee). However, 48 only gave 49 in 79% yield and 55% ee, and required 3-5 days to reach completion (Scheme 10).  

The hydroxyl group in the catalyst 44 was crucial for asymmetric induction in this process. Further attempts to optimize asymmetric induction were done by Ishikawa by using another monocyclic guanidine 50 in the asymmetric epoxidation of chalcone with different hydroperoxides. The result indicated epoxides 52 in 49% and 64% ees (Scheme 11).
1.2.2. Synthesis of Bicyclic Guanidines and Their Applications

Corey and Grogen synthesized pseudo $C_2$-symmetric bicyclic guanidines for the first time from $(R)$-phenylglycine and used it as a symmetrical bicyclic guanidine catalyst in a Strecker reaction in 1999 (Scheme 12). A trityl-protected diamine was obtained by reacting methyl $(R)$-phenylglycinate with ammonia-saturated methanol to afford the desired amide. Subsequent to reduction of 53 by lithium aluminum hydride in ether, and coupling of 54 to CBz protected phenylglycine yielded amide 55. Conversion to triamine 56 was completed by carbamate hydrogenolysis, and reduction with sodium bis (2-methoxyethoxy) aluminum dihydride. Thiourea was generated by treatment of 56 with thiophosgene and aqueous sodium carbonate. After methylation with iodomethane, the desired guanidine 57 was obtained in a 55% yield after heating in DMF at 100 °C.

Scheme 11. Epoxidation of chalcone catalyzed by monocyclic guanidine 50.\textsuperscript{20}
Scheme 12. Synthesis of pseudo $C_2$-symmetric bicyclic guanidine 57.\textsuperscript{21}

Ishikawa and co-workers used pseudo $C_2$-symmetric bicyclic guanidine 58 in the TMS cyanation of aliphatic aldehydes and ketones, obtaining the products 60\textsubscript{a,b} with moderate enantiomeric excess (Scheme 13).\textsuperscript{27}

Scheme 13. Cyanation of aliphatic aldehydes and ketones catalyzed by pseudo $C_2$-symmetric guanidine 58.\textsuperscript{22}
In a following attempt, they applied the 1,3-dimethyl-4,5-bis(2-methylphenyl) imidazolidine and the related 1,3-dibenzyl-4,5-diphenylimidazolidine in the asymmetric Michael reaction of \( t \)-butyl diphenyliminoacetate and ethyl acrylate. The results showed good selectivity (79-98% ee). Also they found that selectivity and activity can be improved by installing the methyl group on the ortho position of the phenyl pendant in 1,3-dimethyl-4,5-bis(2-methylphenyl) imidazolidine and the related 1,3-dibenzyl-4,5-diphenylimidazolidine (Scheme 14).^28

Scheme 14. Asymmetric Michael reaction of \( t \)-butyl diphenyliminoacetate and ethyl acrylate catalyzed by guanidines 61, 62, 63.1

Kinetic resolution of sec-alcohols by silylation catalyzed by a variety of modified guanidines did not provide good selectivity, among them only 67a, 67b and 68 gave moderate enantioselectivity (31-50% ee).^29 Ishikawa and co-workers improved selectivity when they used a bulkier triisopropylsilyl
chloride as a silylating agent (70% ee) as compared to tert-butyldimethylsilyl chloride (TBDMS) in reaction of indanol 69 (Scheme 15).

Scheme 15. Reaction of indanol 68 with tert-butyldimethylsilyl chloride catalyzed by 67a, 67b and 68.\(^{24}\)

Quaternary carbon stereocentres are found in a wide range of organic compounds, including important medicinal agents and bioactive natural products. A variety of modified guanidines were examined in construction of quaternary carbon centres in the chromane skeleton by intramolecular oxo-Michael addition.\(^{30}\) Good asymmetric induction was observed when Z unsaturated esters were used as the substrates in reactions catalyzed by \((4S,5S)-2-[(R)-1-hydroxymethyl-2-phenylethylimino]-1,3-dimethylimidazolidine 73 (Scheme 16).
Scheme 16. Construction of quaternary carbon centre by intramolecular oxa-Michael addition catalyzed by guanidines 72-76.25

1.2.3. DMC Chemistry

Chloroamidinium salts such as 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and \(N,N',N'-\)tetramethylchloroformamidinium chloride are strong dehydration agents, and can chlorinate alcohols and reduce sulfoxides.31 DMC is stable toward moisture and oxygen. Chloroamidinium salts have two advantages: 1) the easy removal of the excess starting material and regenerated salt by work-up, and 2) straightforward preparation (Scheme 17). DMC 79 is generated by reaction of 80 with phosphoryl chloride, oxalyl chloride or trichloromethyl chloroformate.
Scheme 17. Conversion of DMI to DMC and vice versa.

Guanidines can be synthesized by reaction of DMC with the appropriate amines. Thus DMC chemistry has developed into a methodology for obtaining both mono and bicyclic guanidines. Scheme 18a shows the synthesis of trisubstituted monocyclic guanidines via the reaction of DMC-type chloroamidine compounds with amines. Scheme 18b shows cyclization of guanidines by DMC chemistry.\textsuperscript{32ab}

Scheme 18a. Synthesis guanidines via reaction of DMC-type chloroamidine compounds.\textsuperscript{27a}
1.2.4. Guanidines as Synthetic Tools

Chiral guanidines have been used as potential catalysts in numerous asymmetric transformations. Ishikawa, in 2005, designed several polymer-based chiral guanidines and used them in the asymmetric Michael reaction of \( t \)-butyl diphenyliminoacetate with MVK (Scheme 19).\textsuperscript{33}

The turnover was observed to range from low to good enantioselectivity. In the case of polymer-supported guanidine 90, no selectivity was observed. This might be caused by the steric hindrance around the active site due to the polystyrene group directly attached to the guanidine. A Michael reaction in the presence of catalyst guanidines 92 and 93 afforded moderate selectivity. (Scheme 19).
Scheme 19. The turnover of the polymer-based chiral guanidines in asymmetric Michael reaction of \( t\)-butyl diphenyliminoacetate with MVK 95.\(^{28}\)

The development of active chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones has attracted much attention due to the applications of homochiral secondary alcohols in organic and medicinal chemistry. Basavaiah and co-workers applied guanidine 97 in the borane-mediated reduction of phenacyl bromide (Scheme 20).\(^{34}\) They reported that higher enantioselectivity values were achieved when the reaction was done in reflux conditions as compared to room temperature.
1.3. NHC Carbenes

Carbenes are classified as Lewis bases, which act as excellent $\sigma$-donors and poor $\pi$-acceptors. Although they are often less economical and environmentally friendly than other metal-free catalysts, $N$-heterocyclic carbenes (NHCs) belong to the family of nucleophilic carbenes, which are known as organocatalysts and are considered as excellent ligands for metal-based catalysis.\(^{35}\) Most heterocyclic carbenes are stable and can be isolated. Deprotonation of imidazolium or imidazolinium salts with a strong base such as sodium hydride, potassium hexamethydisilazane, (KHMD) or potassium tert-butoxide (KOT-Bu) (Scheme 21a). This approach was used by Arduengo in the original isolation of a free carbene.\(^{36}\) Alternatively, the desired carbene species can be thermodynamically generated from the related 2-trichloromethyl, 2-pentafluorophenyl, 2-carboxylated, or 2-dithiocarboxylated “protected” NHC adducts (Scheme 21b).\(^{37a,b}\)
1.3.1. Application of N-Heterocyclic Carbenes in Asymmetric Organic Reaction

*N*-Heterocyclic carbenes (NHCs) can act as effective nucleophilic catalysts in organic reactions. Rovis reported synthesis of quaternary stereocenters by using triazolium catalysts. The 1,4-dicarbonyl compounds were generated in high yield and enantioselectivity under mild conditions. Moreover, the effect of a series of the aminoundanol-derived catalysts in construction of the quaternary stereocentre of compound determined that in all cases tertiary ether was generated in excellent enantioselectivity (Scheme 22). Attempt to the synthesis of the 1,4-dicarbonyl compounds using the less activated olefin (R = Me) in methyl ester failed, but compound with CO$_2$Me group gave bis-methyl ester in 78% yield and 65% ee (Scheme 23).
Scheme 22. Synthesis of quaternary stereocenters by using triazolium catalysts.\textsuperscript{33}

\[ \text{Scheme 23. Cyclization of bis-methyl ester catalyzed by 108 and 109.}\textsuperscript{33} \]

Aoyama designed a new class of \(N\)-heterocyclic carbene ligands for asymmetric catalysis in the Pd-catalyzed intramolecular \(\alpha\)-arylation of anilides for generation of 3,3-disubstituted oxindoles with moderate enantioselectivity (Scheme 24).\textsuperscript{39}
Scheme 24. Intramolecular α-arylation of anilides catalyzed by N-heterocyclic carbene derived from 12.34

Hartwig and co-workers highlighted the application of a large number of chiral ligands in Pd-catalyzed intramolecular α-arylation of anilides to give 3,3-disubstituted oxindoles.40 In this case, chiral bidentate phosphine ligands did not give good selectivity. Several groups tried to improve selectivity of this reaction including Glorius,41 but only moderate selectivity was obtained. Bulky t-Bu groups at the stereogenic centres to nitrogen gave moderate enantioselectivity. Ortho-substituents on the phenyl ring played key roles in the enantioselective formation of the product and obtained good enantioselectivity (Scheme 25).42

Scheme 25. Several Pd-catalyzed asymmetric intramolecular α-arylation of anilides by using chiral NHC ligands.35,36,37
An *E*-selective catalytic method for preparation of Si-containing alkenes through protosilylation of terminal alkynes was reported by Hoveyda. They also demonstrated Cu-catalyzed copper–boron additions to vinylsilanes derivatives catalyzed by *N*-heterocyclic carbene copper complexes to generate vicinal or geminal borosilanes (Scheme 26).

Scheme 26. Formation of vicinal or geminal borosilanes catalyzed by an *N*-heterocyclic carbene.

1.3.2. *N*-Heterocyclic Carbene Metal Complexes

1.3.2.1. Historical perspective

Complex of 124 was the first example of transition metal carbene which was reported by Fischer and Maasböl. Since their landmark report in 1964, transition metal carbene complexes in inorganic chemistry have become of great interest.
In 1968 the first syntheses of NHC metal complexes 125 and 126 were reported by Wanzlick and Öfele (Figure 7).\textsuperscript{31,45} Then Schrock in 1974, developed a new type of carbene with a different reactivity, called the Schrock carbenes,\textsuperscript{46} which are identified by more nucleophilic carbene carbon centres; these species mainly feature higher valent metals.

![Figure 7. The first examples of a transition metal carbene complex.\textsuperscript{31,39,40}](image)

\textit{N}-Heterocyclic carbenes are $\sigma$-donor ligands, NHC ligands have been considered to be mainly inert. This inert property is the reason for their resistance to oxidation and thermal stability. In 1993, Öfele and co-workers showed that the metal-carbon bond in NHC complexes, trialkylphosphanes and alkylphosphinates have the same bonding properties.\textsuperscript{47}

### 1.3.2.2. Complexation to Metals

Different synthetic routes have been discovered for the synthesis of NHC metal complexes such as using external base,\textsuperscript{48} transmetalation,\textsuperscript{49} oxidative addition\textsuperscript{50} and co-condensation.\textsuperscript{51}

Öfele utilized an anionic carbonyl hydride complex in the synthesis of the first M-NHC complex.\textsuperscript{40} The basic metalate ion [HCr(CO)$_3$]\textsuperscript{−} deprotonated an imidazolium salt to afford the M-NHC complex. Du Pont reported the first 14-electron carbene complexes with two-fold coordinated Ni(0) and Pt(0) were synthesized in 1994 via reaction of a metal precursor with carbene in appropriate solution.\textsuperscript{52} Cloke reported the first homoleptic zerovalent carbene complexes by co-condensation of NHCs with metal vapor in reasonable yields.\textsuperscript{46}
The NHC complexes can also be synthesized by the reaction of imidazolinium or imidazolium salts with an external proper bases.43

In the second generation of ruthenium-NHC complexes, Grubbs and co-workers highlighted deprotonation of the imidazolinium salts by using potassium hexafluoro-tert-butoxide as the external base, followed by direct complexation of the in situ-generated NHCs at room temperature (Scheme 27).53

\[
\text{Scheme 27. Synthesis of NHC-complexes by deprotonation of imidazolinium salt with external base.}^{48}
\]

Silver N-heterocyclic carbene complexes have played an important role in the development of metal-carbene systems. Deprotonation of imidazolium or imidazolinium salt by use of a silver base has been the most widely used method in the synthesis of N-heterocyclic carbene complexes of silver. Silver NHCs could be synthesized from different silver sources. In 1997, Bertrand used silver acetate in the synthesis of a silver-NHC from triazolium salts.54 In 2000, Danopoulos reported application of silver carbonate in the formation of silver NHCs.55 In 2007, synthesis of silver NHCs by using Ag₂O was reported by Wang and co-workers.56

Silver N-heterocyclic carbenes have attracted much attention in the development of other NHC complex systems by way of transmetalation reactions. Transmetalation reactions using silver NHCs have been reported for a large number of transition metals: Ir(I), Ir(III), Cu(I), Cu(II), Pd(II), Ru(II), Ru(III), Ru(IV), Pt(II), Au(I), Rh(I), Rh(III), and Ni(II). Recent reviews dealing with transmetalation reactions
using silver NHCs have been published by Lin.\textsuperscript{57} For example, Gimeno reported synthesis of silver(I)–NHC complexes for transmetalation to gold-NHC complexes (Scheme 28).\textsuperscript{58}

\begin{center}
\begin{tikzpicture}
  \node (129) at (0,0) {129};
  \node (131) at (6,0) {131};
  \node (130) at (3,0) {130};

  \draw[->] (129) -- node[midway,above] {$[\text{AuCl(SMe}_2\text{)}]$} (130);
  \draw[->] (130) -- node[midway,above] {1. Ag$_2$O, CH$_2$Cl$_2$} node[midway,below] {2. [AuCl(SMe$_2$)]} (131);

  \node at (0,0.5) {R = 2, 6-i-Pr$_2$C$_6$H$_3$};
  \node at (6,0.5) {R = 2, 4, 6-Me$_3$C$_6$H$_2$};

  \def\c{0.12}
  \draw (129) -- (129 |- 129 + \c,0); \node[inner ysep=0] at (129 |- 129 + \c,0) {$N$};
  \draw (129) -- (129 + \c,0); \node[inner xsep=0] at (129 + \c,0) {$N$};
  \draw (129) -- (129 + \c,0) -- (129 + \c,0 |- 129 + \c,0); \node[inner ysep=0] at (129 + \c,0 |- 129 + \c,0) {$R$};
  \draw (129 + \c,0) -- (129 + \c,0 + \c,0); \node[inner xsep=0] at (129 + \c,0 + \c,0) {$N$};
  \draw (129 + \c,0 + \c,0) -- (129 + \c,0 + \c,0 + \c,0); \node[inner ysep=0] at (129 + \c,0 + \c,0 + \c,0) {$R$};
  \draw (129 + \c,0 + \c,0 + \c,0) -- (129 + \c,0 + \c,0 + \c,0 - \c,0); \node[inner xsep=0] at (129 + \c,0 + \c,0 + \c,0 - \c,0) {$N$};
  \draw (129 + \c,0 + \c,0 + \c,0 - \c,0) -- (129 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0); \node[inner ysep=0] at (129 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0) {$R$};

  \def\c{0.12}
  \draw (130) -- (130 |- 130 + \c,0); \node[inner ysep=0] at (130 |- 130 + \c,0) {$N$};
  \draw (130) -- (130 + \c,0); \node[inner xsep=0] at (130 + \c,0) {$N$};
  \draw (130) -- (130 + \c,0) -- (130 + \c,0 |- 130 + \c,0); \node[inner ysep=0] at (130 + \c,0 |- 130 + \c,0) {$R$};
  \draw (130 + \c,0) -- (130 + \c,0 + \c,0); \node[inner xsep=0] at (130 + \c,0 + \c,0) {$N$};
  \draw (130 + \c,0 + \c,0) -- (130 + \c,0 + \c,0 + \c,0); \node[inner ysep=0] at (130 + \c,0 + \c,0 + \c,0) {$R$};
  \draw (130 + \c,0 + \c,0 + \c,0) -- (130 + \c,0 + \c,0 + \c,0 - \c,0); \node[inner xsep=0] at (130 + \c,0 + \c,0 + \c,0 - \c,0) {$N$};
  \draw (130 + \c,0 + \c,0 + \c,0 - \c,0) -- (130 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0); \node[inner ysep=0] at (130 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0) {$R$};

  \def\c{0.12}
  \draw (131) -- (131 |- 131 + \c,0); \node[inner ysep=0] at (131 |- 131 + \c,0) {$N$};
  \draw (131) -- (131 + \c,0); \node[inner xsep=0] at (131 + \c,0) {$N$};
  \draw (131) -- (131 + \c,0) -- (131 + \c,0 |- 131 + \c,0); \node[inner ysep=0] at (131 + \c,0 |- 131 + \c,0) {$R$};
  \draw (131 + \c,0) -- (131 + \c,0 + \c,0); \node[inner xsep=0] at (131 + \c,0 + \c,0) {$N$};
  \draw (131 + \c,0 + \c,0) -- (131 + \c,0 + \c,0 + \c,0); \node[inner ysep=0] at (131 + \c,0 + \c,0 + \c,0) {$R$};
  \draw (131 + \c,0 + \c,0 + \c,0) -- (131 + \c,0 + \c,0 + \c,0 - \c,0); \node[inner xsep=0] at (131 + \c,0 + \c,0 + \c,0 - \c,0) {$N$};
  \draw (131 + \c,0 + \c,0 + \c,0 - \c,0) -- (131 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0); \node[inner ysep=0] at (131 + \c,0 + \c,0 + \c,0 - \c,0 - \c,0) {$R$};

  \node at (129) [left] {129};
  \node at (130) [right] {130};
  \node at (131) [right] {131};
\end{tikzpicture}
\end{center}

**Scheme 28.** Example of using silver (I) transmetalation in formation of NHC complexes.\textsuperscript{53}

Following oxidative insertion, metal–diaminocarbene complexes were synthesized by Fürstner and colleagues by oxidative insertion of [Pd(PPh$_3$)$_4$] or [Ni(COD)$_2$] with PPh$_3$ into the C-Cl bond of 2-chloro-1,3-disubstituted imidazolinium salts (Scheme 29).\textsuperscript{59}

\begin{center}
\begin{tikzpicture}
  \node (132) at (0,0) {132};
  \node (133) at (3,0) {133};

  \draw[->] (132) -- node[midway,above] {Thiophosgene, Et$_3$N, CH$_2$Cl$_2$} (133);

  \node at (132) [left] {132};
  \node at (133) [right] {133};
\end{tikzpicture}
\end{center}

**Scheme 29.** Synthesis of NHC-complexes by oxidative addition.\textsuperscript{54}
A lithium-halogen exchange route has been used to prepare different kind of complexes via one pot transmetalation. This method has been developed by Hong and co-workers in the synthesis of acyclic diaminocarbenes via lithium-halogen exchange (Scheme 30).\textsuperscript{60}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme30.png}
\end{center}

**Scheme 30.** Synthesis of NHC-complexes by a lithium-halogen exchange.\textsuperscript{55}

1.3.2.3. Application of NHC-complexes

In 1996 Enders applied chiral carbenes in the the first asymmetric intramolecular Stetter reaction.\textsuperscript{61} Since then, different kinds of chiral NHC ligands have been used in various asymmetric reactions. The following section will describe some examples of the application of chiral NHC ligands in asymmetric organic reactions. Several attempts have been performed for achieving good selectivity by using chiral NHC-complexes in asymmetric organic reactions. Several kinds of metals were used for the synthesis of NHC-complexes and applied in asymmetric organic reactions.

Several chiral rhodium-NHC complexes have been prepared and found useful in asymmetric organic reactions. Helmchen designed rhodium-NHC complexes with the combination of two different
backbones, including a rigid 2-(diphenylphosphino)naphthyl group connected to the dihydroimidazole moiety via a stereogenic axis to one nitrogen and a phenyl group with an i-Pr-substituent to the other nitrogen.62 These are disposed anti- to the phenyl groups of the dihydroimidazole moiety on another side in the asymmetric hydrogenation of substrates dimethyl itaconate and N-acetyldehydroamino acid derivatives (Scheme 31).

![Scheme 31](image)

**Scheme 31.** Asymmetric hydrogenation catalyzed by (S,S)-139.57

A year later, Helmchen used this catalyst in asymmetric conjugate additions of arylboronic acids to enones and α,β-unsaturated esters.63 The results showed of arylboronic acids to enones and α,β-unsaturated esters excellent catalytic activity in conjugate additions of phenylboronic acids due to steric and electronic properties of the catalyst (Scheme 32).

![Scheme 32](image)

**Scheme 32.** Conjugate addition of phenylboronic acid to α,β-unsaturated ester catalyzed by (S,S)-139.58
In 2005, Grubbs and co-workers won the Nobel Prize for development of olefin metathesis in organic reactions. Grubbs reported the first enantioselective olefin metathesis by using NHC catalysts in the desymmetrization of achiral trienes with high enantiomeric excess (Scheme 33).⁵⁰

![Scheme 33](image)

Scheme 33. Desymmetrization of achiral trienes catalyzed by Grubbs’ catalyst.⁵⁰

Several N-heterocyclic carbene ligands have been applied in the copper catalyzed 1,4-addition of a dialkylzinc reagent to an unactivated β-substituted cyclicenones.⁶⁴ Recently, selective allylic substitutions by using copper derivatives and Grignard or dialkylzinc reagents catalyzed by N-heterocyclic carbenes as ligands have been reported.⁶⁵ Roland and Alexakis reported an enantioselective copper catalyzed 1,4-conjugate addition reactions by using chiral diaminocarbenes as ligands in silver complexes.⁶⁶ Analysis of the catalytic data demonstrated the effect of low temperature conditions using diethyl ether and CuTC was superior in terms of enantiomeric excess for this reaction, and also higher selectivity was observed when they employed the m-OMe substituted analogue 151. The corresponding adduct was obtained in a 100% yield with an enantiomeric excess of 88% (Scheme 34).
Scheme 34. Addition of Et₂Zn to cyclohexenone catalyzed by 150, 151.⁶¹

An attempt to synthesize NHC-palladium complexes with a chiral N-heterocycle and naphthyl side chains by Dorta gave three different isomers, which were separated successfully and applied in the asymmetric intramolecular α-arylation of amides, leading to the formation of oxindoles containing quaternary carbon centres in high yield and high enantiomeric purity.⁶⁷ The results showed that orientation of the aromatic side chains had an effect on selectivity in this reaction. Oxindoles with quaternary carbon centres were formed with high yield and selectivity (86% ee) when [(Ra,Ra)-154] was applied (Scheme 35).

Scheme 35. Intramolecular α-arylation of amides catalyzed by NHC-palladium complexes 154.⁶²
The first example for the application of chiral rhodium(I)-NHC complexes as enantioselective hydrosilylation catalysts was reported by Herrmann and co-workers.\textsuperscript{68} In 2009, they considered the catalytic activity and selectivity of the rhodium(I) complex for the hydrosilylation of prochiral ketones. The result showed only significant enantioselectivity (73\% ee) being obtained with 4-(trifluoromethyl)acetophenone at ambient temperature (Scheme 36).\textsuperscript{69}

\begin{center}
\textbf{Scheme 36.} Hydrosilylation of prochiral ketones by catalyst 157.\textsuperscript{64}
\end{center}
1.4. Aims and Objectives

There have been a number of previous attempts via lithiation–substitution of t-Bu protected ureas to afford series of C5-substituted products with syn stereochemistry, but there were two challenges in synthesis of N-substituted products. The first challenge was generation of inconstant yields upon scale up. The second was the harsh reaction conditions required for deprotection of the C5-substitution product 159, such as reflux for 48 hours with trifluoroacetic acid, which posed stability issues in some derivatives. These issues encouraged us to explore a viable synthetic method to synthesize an L-proline hydantoin-derived N-silyl protected version of 159, which undergoes analogous diastereoselective lithiation and substitution to obtain substituted products that may be readily N-desilylated with dilute acid at room temperature to generate secondary ureas (Scheme 37).

The ureas 163 undergo N-arylation leading to chiral pyrroloimidazolinones, which undergo POCl₃ or (COCl)₂ activation to generate the target biological active compounds. Treatment of compound 163 with POCl₃ will afford chiral annulated chloroimidazolinium salts 164, which can be applied as an intermediate for the synthesis of chiral guanidines 165 by using the appropriate amines (Scheme 38).
Scheme 38. Proposed method to synthesize guanidine 165.

The chiral urea 166 will also be converted to the compound 167 via reduction by DIBAL-H in THF at –78 °C. The chiral aminal 167 will undergo salt formation by oxidation to give 168, which may serve as a precursor to NHC 169 by using external base. The resulting NHC ligands will be used for formation of transition metal complexes 170 (Scheme 39).

Scheme 39. Proposed method to synthesize complex 170.
2. Results and Discussion

2.1. Preparation of 2-Triethylsilyl-hexahydro-pyrrolo[1,2-c]imidazol-3-one

The L-proline hydantoin is synthesized from readily available starting materials and its application as a precursor to a chiral auxiliary for diastereoselective lithiation of ferrocenes made it an attractive starting material for the synthesis of C5-substituted imidazolinones. L-proline hydantoin was prepared easily from L-proline 171 in the presence of potassium cyanate in water, followed by treatment with 6 M aqueous HCl in 61% yield (Scheme 40).

![Scheme 40. Synthesis of L-proline hydantoin from L-proline.](image)

The proline hydantoin was reduced with lithium aluminium hydride in THF at room temperature to give compound 161 in moderate yield (56%). Compound 161 was prepared in large-scale without racemization of the pyrrolidine chiral centre (Scheme 41).

![Scheme 41. Synthesis of compound 161.](image)
Based on previous research in ortho lithiation by Hoppe,\textsuperscript{74} imidazolinone \textbf{161} was initially \textit{N}-protected by deprotonation of nitrogen with \textit{i}-PrLi/TMEDA, followed by addition of TMSCl. Although product \textbf{174} was air-stable and could be purified by flash column chromatography, subsequent attempts to induce diastereoselective lithiation at the C5 position by sequential treatment with \textit{i}-PrLi and TMEDA at \(-78\, ^\circ\text{C}\) in diethyl ether, followed by TMSCl quench, resulted in the formation of the \textit{N} [bis(trimethylsilyl)methyl]dimethylsilyl product \textbf{175} (Scheme 42).

![Scheme 42. Formation of \textit{N}-[bis(trimethylsilyl)methyl]dimethylsilyl compound \textbf{175}.](image)

The observed regiochemistry was presumably due to the greater acidity of the \textit{\alpha}-silylmethyl groups over the C5 position. This result was in contrast with the behavior of \textit{N}-trimethylsilyl protected aryl-\textit{O}-carbamate \textbf{177} reported by Hoppe,\textsuperscript{69} which gave phenol \textbf{179} by ortho lithiation after electrophile quench, deprotection and hydrolysis of the secondary carbamate \textbf{177} (Scheme 43).
To prevent α-silyl carbanion formation, triethylsilyl chloride was used with the expectation that the α-silyl methylene groups would be less prone to deprotonation (Scheme 44).

**Scheme 43.** N-trimethylsilyl protected aryl-O-carbamate 177.\textsuperscript{69}

**Scheme 44.** N-protection of compound 161.

### 2.2. Diastereoselective Lithiation-Substitution of Compound 159

Computational studies were done on 159 to determine the distances between the urea oxygen atom and the pro-S and pro-R alpha methylene hydrogens. The results showed that the pro-S proton alpha
to nitrogen was closer to the carbonyl oxygen (2.505 Å) compared to the pro-\( R \) proton (3.692 Å);\(^{13}\) lithiation will take place at the pro-S proton over the pro-\( R \) proton because of the shorter distance between the alkyllithium base to that hydrogen upon coordination to oxygen (red = oxygen, blue = nitrogen, white = hydrogen, grey = carbon) (Figure 8). The structure of compound 159 was optimized at the B3LYP/6-31G(d) level as implemented in Gaussian 03.\(^{13}\)

![Figure 8](image_url)  
**Figure 8.** Minimum energy structure of 159.\(^{13}\)

The first attempt of diastereoselective lithiation of compound 162 was done by using \( i \)-PrLi and TMEDA and Et\(_2\)O in \(-78 \, ^\circ\)C followed by electrophilic quench. sec-BuLi was also examined for this reaction based on previous research, which was done by our group for diastereoselective lithiation of tert-butyl \( N \)-protected urea (2-\( tert \)-butyl-hexahydro-pyrrolo[1,2-c]imidazol-3-one) 159 (Scheme 45).\(^{13}\)
E = Ph₂COH, Me, allyl, SnMe₃, SiMe₃, CO₂H

**Scheme 45.** Diastereoselective lithiation of compound 159.¹³

Several electrophiles were used for diastereoselective lithiation of compound 162 (Scheme 46), such as dimethyl sulfate, trimethylsilyl chloride, benzophenone and tributyltin chloride (Table 1). These reactions gave moderate to good yields and single diastereomers, which were determined by ¹H and ¹³C NMR analysis. All obtained products are exclusively in the syn configuration, which is proven by NOE spectroscopy.

**Scheme 46.** Diastereoselective lithiation of compound 162.

**Table 1.** Results of diastereoselective lithiation of compound 162.

<table>
<thead>
<tr>
<th>compound</th>
<th>E⁺</th>
<th>E</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>Me₂SO₄</td>
<td>Me</td>
<td>65</td>
</tr>
<tr>
<td>182</td>
<td>Ph₂CO</td>
<td>C(OH)Ph₂</td>
<td>61</td>
</tr>
<tr>
<td>183</td>
<td>allyl bromide*</td>
<td>allyl</td>
<td>47</td>
</tr>
<tr>
<td>184</td>
<td>SiMe₃Cl</td>
<td>SiMe₃</td>
<td>86</td>
</tr>
<tr>
<td>185</td>
<td>SnBu₃Cl</td>
<td>SnMe₃</td>
<td>60</td>
</tr>
</tbody>
</table>

*via CuCN-2LiCl transmetalation.

Allylation of 162 by transmetalation of the alpha lithio intermediate with a mixture of copper cyanide and lithium chloride in the presence of TMEDA gave 31% yield. Surprisingly, a slightly better yield was obtained when the reaction was performed without TMEDA (47%) (Scheme 47).
Scheme 47. Transmetalation of alpha lithio intermediate for allylation.

Several attempts were made with different kinds of electrophiles such as benzaldehyde, dimethyl disulfide and 3-bromocyclohexene, but no product was produced (Scheme 48).

Scheme 48. Several attempts to diastereoselective lithiation

Several reaction conditions were examined to optimize the reaction conditions. For example, different kinds of lithium species and solvents were tested. The results showed that i-PrLi and Et₂O were superior in terms of yield in the diastereoselective lithiation reaction. Stereochemistry of all these products was confirmed by NMR spectroscopy. For example, analysis of 181 by HSQC showed the proton connected to the corresponding carbon atom to identify the proton-carbon connectivities, then NOSEY or NOE showed that the methine protons of interest of chiral centres were on the same side of the molecule, a correlation cross peak between these same methine protons of chiral centres (indicated by arrows) was obtained (Figure 9).
For example, in the 1D-NOE of 181, irradiation of a proton from the pyrrolidine methine groups at 1.91 led to enhancements of the key methane proton (indicated by arrows) at 3.98 and irradiation of a proton at 3.98 lead to enhancement of the key methane protons at 3.69 and 1.91 ppm respectively (Figure 10). Similar enhancements were observed in the 1D-NOE spectra of 182, 183, 184, 185.
Figure 10. 1D-NOE of 181.
2.3. N-Desilylation of secondary ureas

Deprotection of the N-t-Bu group on the C5-substituted compound 159 requires harsh reaction conditions, such as using trifluoroacetic acid in reflux for 48 hours, which may lead to stability issues for certain derivatives (Scheme 37). Products 181-185 underwent smooth N-desilylation upon treatment with 2M aqueous HCl for 30 min at room temperature to give secondary ureas 186-190 in good yields (71-91%). It is notable that potentially sensitive substituents, such as the diphenylhydroxymethyl group of 182 or the stannane of 185, remained intact under these conditions (Table 2).

![Diagram of the reaction](image)

**Table 2.** Results of N-desilylation.

<table>
<thead>
<tr>
<th>compound</th>
<th>product</th>
<th>E</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>186</td>
<td>Me</td>
<td>84</td>
</tr>
<tr>
<td>182</td>
<td>187</td>
<td>Ph₂COH</td>
<td>80</td>
</tr>
<tr>
<td>183</td>
<td>188</td>
<td>allyl</td>
<td>82</td>
</tr>
<tr>
<td>184</td>
<td>189</td>
<td>SiMe₃</td>
<td>91</td>
</tr>
<tr>
<td>185</td>
<td>190</td>
<td>SnBu₃</td>
<td>71</td>
</tr>
</tbody>
</table>
2.4. N-Alkylation

The ability to remove the N-TES group in the preceding products allows for the introduction of new N-substituents. For example, compound 189 underwent N-alkylation by using sodium hydride and methyl iodide in DMF at 0 °C to room temperature (Scheme 49).

![Reaction diagram for N-alkylation of compound 189.](image)

**Scheme 49.** N-alkylation of compound 189.

2.5. N-Arylation

Leung reported synthesis of symmetrical and unsymmetrical N-aryl-substituted cyclic ureas by employing copper(I) iodide and ligand in toluene in the presence of base (Scheme 50). Leung mentioned that ligands play an important role in the reactivity of copper catalysts in this reaction. They examined different ligands such as trans-\(N,N\)'-dimethylcyclohexane-1,2-diamine (DMCHDA) and trans-cyclohexane-1,2-diamine (CHDA) with different bases and solvents (Table 3).

![Reaction diagram for N-arylation.](image)

**Scheme 50.** Synthesis of N-aryl-substituted cyclic urea 193.
Table 3. Results of the \( N \)-arylation of cyclic urea 193.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Diamine ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{K}_3\text{PO}_4 )</td>
<td>CHDA</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>( \text{K}_2\text{CO}_3 )</td>
<td>CHDA</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>CHDA</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>( \text{K}_3\text{PO}_4 )</td>
<td>DMCHDA</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>( \text{K}_2\text{CO}_3 )</td>
<td>DMCHDA</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>DMCHDA</td>
<td>44</td>
</tr>
</tbody>
</table>

A Goldberg–Buchwald–Nandakumar C–N coupling, using different diamine ligands, such as cyclohexane-1,2-diamine (CHDA) and tetramethylethylenediamine (TMEDA), with copper(I) iodide, potassium carbonate, iodobenzene in toluene at 110 °C for 48 h, provided the desired coupling product (Scheme 51). \( N \)-Arylation of compounds 186 and 189 by employing CHDA gave low yields (5-20%). \( N \)-phenylation of either 186 or 189, with a mixture of copper iodide and TMEDA, gave better yields (40-74%) (Table 4).

Scheme 51. \( N \)-Arylation of compound 186 and 189.

Table 4. Results of \( N \)-arylation of compounds 186 and 189.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Diamine ligand</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186</td>
<td>CHDA</td>
<td>166</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>189</td>
<td>CHDA</td>
<td>194</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>186</td>
<td>TMEDA</td>
<td>166</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>189</td>
<td>TMEDA</td>
<td>194</td>
<td>40</td>
</tr>
</tbody>
</table>
Lithiation of compound 166, using i-PrLi in the presence of TMEDA in THF at $-78 \, ^\circ C$ followed by electrophilic quenching, gave the desired ortho-substituted product (Scheme 52). Compounds 195 and 196 were obtained in 67% and 47% yields. Asymmetric lithiation with other lithium species, such as n-BuLi and t-BuLi, failed.

![Scheme 52. Synthesis of ortho substituted ureas 195 and 196.](image)

$N$-Arylation of the bulky urea 187 under the same conditions as Scheme 52 gave compound 197 in a 49% yield (Scheme 53).

![Scheme 53. $N$-Arylation of compound 187.](image)

The hydroxyl group of 197 was subjected to protection to prevent side reactions of the hydroxyl group in the next step, which consists of guanidine formation with POCl₃. Protection of the hydroxyl group in compound 197 via alkylation with an excess amount of methyl iodide at room temperature failed. Protection of the hydroxyl group also failed using dimethyl sulfate under reflux conditions (Scheme 54).
Compound 199 was synthesized with hexafluorobenzene and sodium hydride in DMF, due to significant rate enhancement in the catalytic performance of metal–NHC catalysts bearing fluorinated aryl groups on the NHC ligand. We observed the formation of compound 199 in 35% yield and by-product 200 in 23% yield (Scheme 55).

2.6. Guanidine Formation by POCl₃ Activation and Their Applications in Catalysis

Compound 191 was converted to the 3-chloroimidazolinium salt by using excess amounts of neat phosphoryl chloride at 110 °C. In this process, the intermediate 3-chloroimidazolinium salt 201 could not be isolated, and was therefore exposed without further purification to benzyl amine and triethylamine in acetonitrile to give the desired guanidine 202 (Scheme 56).
Scheme 56. Synthesis of guanidine 202 by POCl₃ activation.

The guanidine formation of compounds 202 and 203 by using ureas 166 and 191 gave moderate yields of 35% and 61%, respectively (Scheme 57). The ¹H NMR analysis showed a large number of broad peaks, which converted to the clear corresponding peaks after heating at 120 °C. This process indicated the presence of two isomers for compounds 202 and 203, which were slowly interconverting via isomerization about a C=N bond via an inversion of the nitrogen substituent.

Scheme 57. Synthesis of guanidines 202 and 203.

Guanidine 204 bearing a hydroxyl group was obtained in 31% yield to use of hydrogen bonding interactions to accelerate and control organic reactions, and also this hydrogen bonding can be used to stabilize anionic intermediates and transition states (Scheme 58).
Scheme 58. Synthesis of compound 204.

Compound 205 was synthesized by using aqueous ammonia and triethylamine in 30% yield (Scheme 59). Then ureas 166 and 194 were converted into the corresponding guanidine products by the same synthetic method as used in the synthesis of 205. This reaction gave 206 and 207 in 41% and 34% yields (Table 5).

Scheme 59. Synthesis of guanidine 205.

Table 5. Results of synthesis of compounds 206 and 207.

<table>
<thead>
<tr>
<th>Entry</th>
<th>compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>206</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>207</td>
<td>34</td>
</tr>
</tbody>
</table>
The formation of compound 208 in neat POCl₃ at 110 °C failed and only the starting material was recovered (Scheme 60).

![Scheme 60. Attempted salt formation of compound 199.](image)

2.7. Application of Guanidines

Previous studies by Ishikawa and co-workers showed that the Michael addition of cyclopentenone with dibenzyl malonates catalyzed by guanidine 209, resulted in moderate to good asymmetric inductions (Schemes 61, 11).  

![Scheme 61. Reaction of cyclopentenone with dibenzyl malonates catalyzed by guanidine 209.](image)

To improve the enantioselectivity of the reaction depicted in (Scheme 61) by addition of a chiral centre at alpha position and also presence a hydroxyl group functionality at catalysts, guanidines 202,
203 and 204 were employed in the Michael addition of dimethyl malonate with cyclopentenone in solvent free conditions. The results gave only racemic products (Scheme 62). Optical rotation measurements were used to determine the enantioselectivity of the products.

![Michael addition of cyclopentenone with dimethyl malonate catalyzed by guanidines 202, 203 and 204.](image)

**Scheme 62.** Michael addition of cyclopentenone with dimethyl malonate catalyzed by guanidines 202, 203 and 204.

Guanidines 202, 203 and 205 were applied to the epoxidation of chalcone by using sodium hypochlorite in toluene. The product was not formed and only the starting material was recovered (Scheme 63).

![Attempts at epoxidation of chalcone catalyzed by guanidines 202, 203, 205.](image)

**Scheme 63.** Attempts at epoxidation of chalcone catalyzed by guanidines 202, 203, 205.

Previous studies by Basavaiah and co-workers\(^2^9\) showed that borane-mediated reduction of phenacyl bromide 98 catalyzed by guanidine 97 (Scheme 5) to generate corresponding alcohol.
In order to understand the stability of the guanidine moiety in the presence of BH$_3$•SMe$_2$, Basavaiah and co-workers treated guanidine derivatives and BH$_3$•SMe$_2$ in toluene at room temperature for 15 min in a ratio of 1:20. The $^{13}$C NMR spectrum showed that the guanidine moiety remained intact as demonstrated by; peaks in the region between δ 70-110 and the presence of a peak at 162.0 ppm, belonging to carbon nitrogen double bond were unchanged. However, when the reaction was performed in toluene under reflux conditions, they observed the presence of a peak at δ 85.0 ppm and absence of a peak at 162.0 ppm, which verifies that a reaction occurred (Scheme 64).

![Scheme 64. Structure of the actual catalyst 97 in BH$_3$•SMe$_2$ at room temperature or under reflux conditions.](image)

To improve the enantioselectivity, the bulkier N-phenyl and N-methyl guanidines 205, 206 and 207 were used in the reduction of phenacyl bromide (Scheme 65). The results indicated that only compound 207 gave any selectivity, with 8% ee (S-configuration), and all other products were obtained as racemates.
Reduction of acetophenone 222 under identical conditions obtained (S)-223b in marginally better 24% ee for 212 and 10% ee for 211. Both sets of experiments had to be performed in refluxing toluene as there was no observable reduction at room temperature (Scheme 66). It is clear from the reduction of 98 that the additional stereocentre at C5 is detrimental to the enantioselectivity of this process, possibly by virtue of a “mismatch” with the nature of chirality that is induced by the original stereogenic centre of L-proline. Additional support for this hypothesis would require synthesis of the anti-stereoisomers of 206 and 207, which unfortunately are not accessible by the current synthetic method.

Scheme 65. Reduction of phenacyl bromide catalyzed by guanidines 205, 206 and 207.

Scheme 66. Reduction of acetophenone catalyzed by guanidines 206 and 207.
Research attempts were directed towards converting \(N\)-aryl urea 166 into \(N\)-heterocyclic carbenes for transition metal catalysis. The synthesis of these complexes is the topic of the next section.

2.8. Synthesis of Metal \(N\)-Heterocyclic Carbone Complexes

There are not many examples of \(N\)-heterocyclic carbene complexes with annulated NHC ligands, most likely because they are unattainable from the common synthetic routes for these compounds. The most common way to synthesize these compounds is the \(N\)-alkylation and amination with aryl halides (Scheme 67).\(^{78,79}\)

![Scheme 67. \(N\)-Alkylation and amination of the appropriate aryl halides.\(^{73,74}\)](image)

Synthesis of metal \(N\)-heterocyclic carbene complexes was started with reduction of 191 with DIBAL-H in THF at \(-78 \, ^{\circ}C\) (Scheme 68). The result showed cleavage of the carbon-nitrogen bond instead of reduction of carbonyl group.

![Scheme 68. Attempt to make aminal.](image)
Interestingly, reduction of compound 166 under identical conditions gave the desired product 167 in 52% yield (Scheme 69).

Scheme 69. Synthesis of aminal 167.

Oxidation of aminal, followed by addition of a base to the salt is the another way to make $N$-heterocyclic carbenes (Scheme 70).\textsuperscript{80}

Scheme 70. Synthesis of $N$-heterocyclic carbene by oxidation of aminal.

Iodine, triphenylcarbenium tetrafluoroborate and $N$-bromosuccinimidine have been reported as oxidizing agents.\textsuperscript{75,81,82}

Blechert reported the synthesis of the imidazolium salt 230 by using tritylium tetrafluoroborate in the synthesis of ruthenium alkylidene complexes (Scheme 71).\textsuperscript{75}
Collins and Fournier synthesized compound 233 by adding iodine and sodium bicarbonate in dichloromethane, followed by NH$_4$BF$_4$ addition (Scheme 72).

Buchmeiser indicated another method to oxidize aminals, using N-bromosuccinimide in DME to synthesize tetrahydropyrimidin-1-ium bromide 235 (Scheme 73).

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**Scheme 71.** Synthesis of imidazolinium salt 230 by using tritylium tetrafluoroborate by Blechert.\(^75\)

**Scheme 72.** Synthesis of compound 233 by using iodine and sodium bicarbonate in dichloromethane.\(^76\)

**Scheme 73.** Synthesis of tetrahydropyrimidin-1-ium bromide by using NBS.\(^77\)
Oxidation of aminal 167 by employing iodine and sodium bicarbonate was not successful and starting material was recovered (Scheme 74).

![Scheme 74](image)

**Scheme 74.** Attempt of salt formation by using iodine.

We attempted to hydrolyze aminals in order to determine the best method for the salt formation (Scheme 75). The synthesis of N-heterocyclic carbenes via hydrolyzing the aminal, followed by addition of triethyl orthoformate and ammonium tetrafluoroborate, failed in the first step. The aminal 167 was then screened with different acids in ethylene glycol under reflux, such as sulfuric acid and p-toluenesulfonic acid. However, the desired product was never made (Scheme 76).

![Scheme 75](image)

**Scheme 75.** Hydrolysis of aminal by using acid.

![Scheme 76](image)

**Scheme 76.** Attempts to hydrolyze aminal by using different acids.
Imidazolinium salts 168 and 238 were generated by reaction of N-bromosuccinimide with aminal 166 in 1,2-dimethoxyethane (DME) followed by anion exchange with sodium tetraphenylborate in methanol in overall 73% yield (Scheme 77). Although this reaction gave good crude yield, it was not possible to purify the bromine salt.

![Scheme 77. Synthesis of compound 168 and 238 by employing NBS.](image)

The synthesis of pure 168 with triphenylcarbenium tetrafluoroborate in dichloromethane was performed in 63% yield (Scheme 78).

![Scheme 78. Salt formation by using triphenylcarbenium tetrafluoroborate.](image)

2.9. Synthesis of NHC complexes

As mentioned earlier in the Introduction in section 1.3, N-heterocyclic carbenes are generated by using a base. The appropriate choice of bases depends on the relative strength of the acid.

Several bases were applied in the synthesis of N-heterocyclic carbenes, such as t-BuOK, KHMDS, NaH, KOC(CH₃)₂CH₂CH₃ and organolithium species (such as n-BuLi, s-BuLi, t-BuLi or LDA) (Scheme 79).
bases = KOC(CH$_3$)$_2$CH$_2$CH$_3$, 
NaH, KHMDS, t-BuOK
organolithium species

Scheme 79. Synthesis of $N$-heterocyclic carbenes.

Compound 168 was treated with $t$-BuOK, the most common base in $N$-heterocyclic carbene formation, followed by addition of [Rh(COD)Cl]$_2$. The result showed that no $N$-heterocyclic carbene was formed ($t$-BuOK, pKa of the conjugate acid is around 17) (Scheme 80). When the imidazolinium salt 168 was treated with potassium bis(trimethylsilyl)amide (pKa of the conjugate acid is around 26), only the starting material was recovered. Probably, KHMDS is not strong enough to deprotonate the salt 168. Attempts at deprotonation of 168 with organolithium species (pKa of conjugate acid is ≤ 36), resulted in decomposition of the starting material.

Scheme 80. Attempts to prepare complex by using different bases.
Another attempt to formation of $N$-heterocyclic carbene via using lithium bases failed, when lithium species were used after formation of chloroimidazolinium salt intermediate by using phosphoryl chloride (Scheme 81).

![Scheme 81. Attempts to make carbene complex via chloroimidazolinium.](image)

Generation of $N$-heterocyclic carbenes with sodium hydride (pKa of conjugate acid is around 37) was successful. Thiourea 241 was obtained via successful generation of an $N$-heterocyclic carbene intermediate, followed by addition of $S_8$ in THF (Scheme 82).

![Scheme 82. Synthesis of thiourea via generation of an $N$-heterocyclic carbene.](image)
Complex 240 was formed by addition of sodium hydride to a mixture of salt 168 and [Rh(COD)Cl]₂ in THF. The result show that the desired chiral Rh–NHC complex as a mixture of coordination isomers in 58 % yield (Scheme 83).

![Scheme 83](image)

**Scheme 83.** Synthesis of complex 240 by using sodium hydride.

However, synthesis of a ruthenium N-heterocyclic carbene complex failed under this reaction condition maybe due to steric hindrance between substituents of NHC ligands and the alkylidene group or chloride of the ruthenium catalyst. The steric hindrance between adjacent groups can also lead to decrease of stability of the pentacoordinate NHC-Ru complexes (Scheme 84).

![Scheme 84](image)

**Scheme 84.** Attempt to make ruthenium N-heterocyclic carbene complex.

Rh-NHC carbonyl complex 242 was synthesized in 78% yield as mixture of isomers in a roughly 10:1 ratio, by bubbling CO through a solution of 240 in methylene chloride for 3 h and stirring for 16 h under CO atmosphere (Scheme 85).

To establish the feasibility of its use as a catalyst in hydroformylation reactions, complex 242 was tested in the hydroformylation of allyl benzene with CO at 20 bar pressure, at 60 °C in the presence of triphenylphosphine as a ligand. Reduction with NaBH₄ gave the corresponding linear and branched alcohols in overall 54% yield in a ratio of 1:2, unfortunately no enantioselectivity was observed (Scheme 86).

Scheme 86. Hydroformylation of allyl benzene catalyzed by complex 242.
3. Conclusions and Future Work

In summary, the N-protection of the imidazolinone 161 was done successfully by using TESCl without α-silyl carbanion formation. Different alpha to nitrogen substituted groups such as methyl, (diphenylhydroxy)methyl, allyl, silyl and stannyl derivatives were introduced diastereoselectively in syn fashion in yields ranging between 47% and 60%.

In contrast to the previously reported N-t-Bu derivatives, products 181-185 underwent smooth N-desilylation upon treatment with 2M aqueous HCl for 30 min at room temperature to give secondary ureas 186-190 in good yields (71-91%). The removal of the N-TES group from the product allowed the generation of new N-substituents. Transformation of ureas into guanidines and complexes was done by generation of imidazolinium salts via two different pathways and reagents. A number of Chloroimidazolinium salts were formed by using excess amounts of neat phosphoryl chloride and employed for guanidine formation. On the other hand, an imidazolinium salt was generated by reduction of urea by DIBAL-H, followed by oxidation by triphenylcarbenium tetrafluoroborate and finally, formation of N-heterocyclic carbene by employing sodium hydride to generate N-heterocyclic carbene complex.

Guanidines 206 and 207 were applied in borane-mediated asymmetric reduction of phenacyl bromide. A previous study by Basavaiah showed that S-configured alcohol product 99 in 83% ee. Attempts to improve enantioselectivity of this reaction by using bulkier guanidines 207 gave 8% ee with S-configuration or as a racemate using 203. Reduction of acetophenone under this conditions gave (S)-220 in marginally better 24% ee for 207 and 10% for catalyst 206. It is obvious from the reduction of phenacyl bromide that the additional stereocentre at C5 is detrimental to the enantioselectivity of this process. Higher selectivity probably could be achieved using anti-stereoisomers, which unfortunately are not accessible by this methodology.

The imidazolinium salt underwent complex formation by using sodium hydride at −78 °C to room temperature. This reaction gave a mixture of coordination isomers, after that Rh-NHC carbonyl complex
242 was synthesized smoothly by bubbling CO through a solution of 240 in methylene chloride, but NMR techniques showed presence of mixture of isomers. No enantioselectivity was observed when complex 242 was applied to hydroformylation of allylbenzene.

Future work will consider two different areas—modification of the ligand structure, and use of these ligands in different catalytic reactions, such as conjugate additions, hydrogenation or hydroformylation.

Further modifications on the ligand may include variation of the phenyl substituents, such as phosphorus derivatives with various electronic and steric properties. These properties can have direct effects on asymmetric induction in many catalytic organic reactions.

Although complex 242 did not give enantioselectivity in hydroformylation, this problem may be addressed by demanding synthesis of bidentate ligands, including phosphine as reported by Helmchen.62

Product 246 can be prepared by lithiation of 166 followed by diphenylphosphine chloride quench to generate 196, and then compound 196 can be protected by an appropriate protecting group such as borane to give compound 243. Compound 243 may be reduced by DIBAL-H to generate 244, which may convert to imidazolinium salt 245 after treatment with oxidizing agent. Subsequent deprotection of phosphorus, followed by N-heterocyclic carbene complex formation in presence of appropriate complex would provide 246 (Scheme 87).
Scheme 87. Proposed synthetic route for a chiral bidentate complex 246.
4. Experimental

**General.** All reagents were purchased from commercial sources and used as received unless otherwise indicated. Tetrahydrofuran (THF) was freshly dried and distilled over sodium/benzophenone ketyl under an atmosphere of nitrogen. Diethyl ether was distilled over LiAlH$_4$ and stored under an argon atmosphere. All alkyllithium bases were titrated against N-benzylbenzamide to a blue endpoint. All reactions were performed under argon in flame- or oven-dried glassware using syringe-septum cap techniques unless otherwise indicated. Column chromatography was performed on silica gel 60 (70-230 mesh). NMR spectra were obtained on a Bruker Avance 300 or 600 MHz instrument and are referenced to TMS or to the residual proton signal of the deuterated solvent for $^1$H spectra, and to the carbon multiplet of the deuterated solvent for $^{13}$C spectra according to known values. Enantiomeric ratios were determined on an Agilent 1100 series HPLC system at $\lambda = 254$ nm using a Chiralcel OD-H column, and were compared against racemic material. FT-IR spectra were obtained on an ATI Mattson Research Series spectrometer as KBr pellets for solids or on KBr discs for liquids. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. Mass spectra were obtained on an MSI/Kratos Concept 1S Mass Spectrometer. Melting points were determined on a Kofler hot-stage apparatus on recrystallized material unless otherwise indicated, and are uncorrected.
(−)-(S)-Tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (161).

A solution of L-proline hydantoin 173 (3.00 g, 0.02 mol) in THF (130 mL) was transferred by cannula into a stirred suspension of lithium aluminum hydride (2.45 g, 0.06 mol) in THF (130 mL) at 0 °C, and the mixture was thereafter allowed to stir at room temperature for 16 h. After cooling to 0 °C in an ice-water bath, workup was performed by sequential addition of water (2.5 mL), 15% aqueous NaOH solution (2.5 mL), and after 15 min, additional water (2.5 mL). The crude mixture containing aluminum salts was passed through a pad of Celite, rinsing with CH₂Cl₂. The organic phase was separated, dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure. Column chromatography (silica gel, 95:5 CH₂Cl₂:MeOH, Rₓ = 0.33) gave 161 as a colorless solid that was recrystallized from CH₂Cl₂ (1.52 g, 56%); mp 178-180 °C (CH₂Cl₂); [α]D²⁰ = -102.0 (c 0.50, CHCl₃); IR (KBr) νmax 3264, 2955, 2886, 1693, 1481, 1433, 1404, 1313, 1260, 1091 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.47 (b, 1H), 3.78-3.71 (m, 1H), 3.65-3.53 (m, 2H) 3.32 (dd, 1H, J = 8.9, 2.4 Hz) 3.06-2.98 (m, 1H), 2.00-1.87 (m, 2H), 1.84-1.72 (m, 1H), 1.49-1.36 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 166.3, 59.4, 45.0, 42.9, 30.3, 25.1; EIMS [m/z(%)] 126 (M⁺, 7), 98 (67), 70 (35), 55 (100), 41 (34); HRMS (EI) calcd for C₆H₁₀N₂O: 126.0793; found: 126.0794.

(−)-(S)-2-(Trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (177).

A solution of 161 (500 mg, 3.96 mmol) and TMEDA (0.71 mL, 4.75 mmol) in THF (20 mL) at 0 °C was treated with i-PrLi (6.10 mL, 0.8 M, 4.75 mmol), which was added dropwise over 15 min. After stirring for an additional 15 min, TMSCl (0.76 mL, 5.90 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water (20 mL), and extracted with CH₂Cl₂ (4 × 20 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rₓ = 0.28) to give 174 as a colorless oil (310 mg, 46%); [α]D²⁰ = -53.7 (c 1.00, CHCl₃); IR (KBr, neat) νmax 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162 cm⁻¹; ¹H NMR (300
MHz, CDCl$_3$) $\delta$ 3.54-3.22 (m, 3H), 3.20 (dd, 1H, $J = 7.8$, 1.5 Hz), 3.03-2.95 (m, 1H), 1.94-1.75 (m, 3H), 1.33-1.26 (m, 1H), 0.24 (s, 9H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 167.5, 59.1, 45.8, 45.3, 30.6, 25.0, -1.2; EIMS [m/z(%)] 198 (M$^+$, 8), 183 (100), 100 (29), 55 (62), HRMS (EI) calcd for C$_9$H$_{18}$N$_2$OSi: 198.1188; found 198.1190.

$(-)$-((Bis(trimethylsilyl)methyl)dimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (175).

A solution of 174 (40 mg, 0.32 mmol) and TMEDA (0.10 mL, 0.67 mmol) in THF (4 mL) at $-78 \, ^\circ$C was treated with $i$-PrLi (0.60 mL, 1.1 M, 0.67 mmol). After 2 h, the reaction mixture was quenched with TMSCl (0.09 mL, 0.67 mmol) and, after 15 min, was stirred at room temperature for 16 h. After cooling in an ice-water bath, the reaction mixture was worked up by addition of water (7 mL) and extracted with CH$_2$Cl$_2$ (4 $\times$ 7 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, R$_f$ = 0.66) to give 175 as a colorless glass (29 mg, 26%); $[\alpha]_D^{20}$ $-26.9$ (c 0.27, CHCl$_3$); IR (KBr) $\nu_{\text{max}}$ 2955, 1675, 1481, 1397, 1319, 1256, 1010 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.69-3.53 (m, 3H), 3.21 (dd, 1H, $J = 7.8$, 1.6 Hz), 3.03-2.94 (m, 1H), 1.96-1.83 (m, 2H), 1.82-1.71 (m, 1H), 1.36-1.23 (m, 2H), 0.25 (d, 6H, $J = 3.7$ Hz), 0.1 (s, 18H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 167.5, 58.8, 46.1, 45.4, 30.8, 25.0, 2.9, 2.3, 1.7; EIMS [m/z(%)] 342 (M$^+$, 88), 217 (62), 129 (73), 73 (100); HRMS (EI) calcd for C$_{15}$H$_{34}$N$_2$OSi$_3$: 342.1979; found: 342.1978.
\[\text{(-)-(S)-2-(Triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (162).}\]

A solution of 161 (800 mg, 6.34 mmol) and TMEDA (1.13 mL, 7.60 mmol) in THF (35 mL) at 0 °C was treated with \(i\)-PrLi (5.85 mL, 1.3 M, 7.60 mmol), added dropwise over 15 min. After stirring for an additional 15 min, chlorotriethylsilane (1.60 mL, 9.51 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water, and extracted with \(\text{CH}_2\text{Cl}_2\) (4 × 30 mL). The combined organic phase was dried over anhyd. \(\text{Na}_2\text{SO}_4\), filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, \(R_f = 0.54\)) to give 162 as a colorless oil (1.17 g, 77%); [\(\alpha\)]\(_{D}^{20}\) –46.2 (c 0.10, CHCl\(_3\)); IR (KBr, neat) \(\nu_{\text{max}}\) 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162, 1007 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.74-3.59 (m, 3H), 3.25 (d, 1H, \(J = 7.8\) Hz), 3.05-2.97 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.73 (m, 1H), 1.40-1.26 (m, 1H), 0.96 (t, 9H, \(J = 7.1\) Hz), 0.77 (q, 6H, \(J = 7.1\) Hz); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 167.9, 59.2, 46.4, 45.5, 30.6, 25.0, 6.9, 3.4; EIMS [\(m/z\)\%(\%)] 240 (M\(^+\), 7), 211 (100), 100 (11); HRMS (EI) calcd for C\(_{12}\)H\(_{24}\)N\(_2\)Si: 240.1658; found: 240.1661.

\[\text{(-)(5S,7aS)-5-Methyl-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (181).}\]

A solution of 162 (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et\(_2\)O (30 mL) at –78 °C was treated with \(i\)-PrLi (1.92 mL, 1.30 M, 2.50 mmol). After 2 h, Me\(_2\)SO\(_4\) (0.40 mL, 3.12 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL), and extracted with CH\(_2\)Cl\(_2\) (4 × 10 mL). The combined organic phase was dried over anhyd. \(\text{Na}_2\text{SO}_4\), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, \(R_f = 0.32\)) gave 181 as a colorless oil (315 mg, 60%); [\(\alpha\)]\(_{D}^{20}\) –24.4 (c 1.01, CHCl\(_3\)); IR (KBr, neat) \(\nu_{\text{max}}\) 2954, 2875, 1678, 1460, 1400, 1266, 1132, 1006 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.01-3.96 (m, 1H), 3.69-3.57 (m, 1H), 3.49 (t, 1H, \(J = 8.9\) Hz), 3.12 (dd, 1H, \(J = 7.1, 2.5\) Hz), 2.16-2.13 (m, 1H), 1.92-1.81 (m, 1H), 1.75-1.70 (m, 1H), 1.62-1.49 (m, 1H), 1.39 (d, 3H, \(J = 6.4\) Hz), 1.26 (d, 3H, \(J = 7.1\) Hz), 0.78 (q, 6H, \(J = 7.1\) Hz).
0.98 (t, 9H, J = 7.5 Hz), 0.82-0.75 (m, 6H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 163.9, 56.4, 46.3, 45.9, 38.5, 30.7, 24.9, 12.7, −2.5; EIMS \([m/\text{z}(\%)]\) 254 (M\(^+\), 7), 25 (100), 211 (11), 100 (7); HRMS (EI) calcd for C\(_{13}\)H\(_{26}\)N\(_2\)OSi: 254.1814; found: 254.1821.

\((+)-(5R,7aS)-5-(\text{Hydroxydiphenylmethyl})-2-(\text{triethylsilyl})\text{tetrahydro-1H-pyrrolo}[1,2-c]\text{imidazol-3(2H)}\)-one (182).

A solution of 162 (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et\(_2\)O (30 mL) at −78 °C was treated with \(i\)-PrLi (1.56 mL, 1.6 M, 2.50 mmol). After 2 h, a solution of benzophenone (568 mg, 3.12 mmol) in THF (5 mL) was added slowly by cannula, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with CH\(_2\)Cl\(_2\) (4 \(\times\) 10 mL). The combined organic phase was dried over anhyd. Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, \(R_f\) = 0.62) gave 182 as a colourless oil (495 mg, 56%); \([\alpha]_{D}^{20}\) +153.0 (c 1.10, CHCl\(_3\)); IR (KBr, neat) \(\nu_{\text{max}}\) 3206, 2954, 1647, 1414, 1262, 1145, 1006, 636, 600 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, 2H, \(J = \) 7.5 Hz), 7.45 (d, 2H, \(J = \) 7.5 Hz), 7.34-7.16 (m, 6H), 4.32-4.26 (m, 1H), 3.90-3.85 (m, 1H), 3.63 (t, 1H, \(J = \) 7.5 Hz), 3.20 (dd, 1H, \(J = \) 7.6, 3.1 Hz), 2.17-2.04 (m, 1H), 1.97-1.83 (m, 1H), 1.58-1.45 (m, 1H), 1.42-1.30 (m, 2H), 0.94 (t, 9H, \(J = \) 7.5 Hz), 0.80-0.72 (m, 6H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 166.0, 147.7, 146.3, 128.2, 127.8, 127.7, 126.4, 126.3, 126.0, 76.8, 66.9, 60.7, 47.8, 29.2, 25.9, 6.8, 3.3; EIMS \([m/\text{z}(\%)]\) 422 (M\(^+\), 21), 239 (25), 182 (53), 105 (92), 77 (100), 51 (64); HRMS (EI) calcd for C\(_{25}\)H\(_{34}\)N\(_2\)O\(_2\)Si: 422.2390; found: 422.2384.
(+)-(5R,7aS)-5-allyl-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (183).

A solution of 162 (1.00 mg, 4.16 mmol) and TMEDA (0.74 mL, 5.00 mmol) in THF (30 mL) at -78 °C was treated with i-PrLi (3.84 mL, 1.3 M, 5.00 mmol). After 2 h, a solution of CuCN (185 mg, 2.08 mmol) and LiCl (176 mg, 4.16 mmol) in THF (5 mL) was added slowly by cannula, and stirring was continued at -78 °C. After 1 h, allyl bromide (0.43 mL, 4.50 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (30 mL) and extracted with CH₂Cl₂ (4 × 30 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.33) gave 183 as a colorless oil (518 mg, 47%); [α]D²⁰ +10.2 (c 0.75, CHCl₃); IR (KBr, neat) νmax 2955, 1687, 1460, 1251, 1124, 1005 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.73 (m, 1H), 5.15-5.04 (m, 2H), 4.04-3.93 (m, 1H) 3.60-3.50 (m, 2H) 3.18 (dd, 1H, J = 7.4, 2.1 Hz), 3.04-2.96 (m, 1H), 2.44-2.33 (m, 1H), 2.14-2.00 (m, 1H), 1.94-1.85 (m, 2H), 1.56-1.45 (m, 1H), 0.98 (t, 9H, J = 7.5 Hz), 0.82-0.77 (m, 6H); ¹³C NMR (75.5 MHz, CDCl₃); δ 163.0, 135.5, 117.1, 60.6, 56.0, 48.9, 35.2, 32.5, 29.9, 6.9, 3.5; EIMS [m/z (%)] 280 (M⁺, 4), 251 (30), 239 (100), 115 (36), 87 (53), 59 (35); HRMS (EI) calcd for C₁₅H₂₈N₂Si: 280.1971; found: 280.1974.

(−)-(5S,7aS)-2-(Triethylsilyl)-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (184).

A solution of 162 (800 mg, 3.33 mmol) and TMEDA (0.60 mL, 4.00 mmol) in Et₂O (32 mL) at -78 °C was treated with i-PrLi (2.50 mL, 1.60 M, 4.00 mmol). After 2 h, TMSCl (0.64 mL, 5.00 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath and worked up by addition of water (30 mL). After separation of the layers, the aqueous phase was extracted with CH₂Cl₂ (4 × 30 mL), and the combined organic extract was dried over anhyd Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by flash column
chromatography (silica gel, 9:1 hexane:EtOAc, Rf = 0.54) to give 184 as a colorless oil (893 mg, 86%); [α]D20 –45.1 (c 0.59, CHCl3); IR (KBr, neat) νmax 2953, 1689, 1461, 1399, 1251, 1134, 1005 cm−1; 1H NMR (600 MHz, CDCl3) δ 3.74-3.70 (m, 1H), 3.61 (t, 1H, J = 9.0 Hz), 3.18 (dd, 1H, J = 9.6 Hz), 2.46 (t, 1H, J = 8.7 Hz), 2.02-1.97 (m, 1H), 1.92-1.86 (m, 1H), 1.71-1.66 (m, 1H), 1.49-1.45 (m, 1H), 0.96 (t, 9H, J = 7.8 Hz), 0.84-0.76 (m, 6H), 0.19 (s, 9H); 13C NMR (150.9 MHz, CDCl3) δ 166.1, 60.5, 49.7, 31.6, 27.9, 6.8, 3.4, –1.0; EIMS [m/z (%)] 312 (M+, 12), 297 (100), 283 (70), 239 (58), 87 (36), 73 (32), 59 (40); HRMS (EI) calcd for C15H32N2OSi2: 312.2053; found: 312.2045.

(−)-(5S,7aS)-2-(Tributylstannyl)-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (185).

A solution of 162 (207 mg, 0.86 mmol) and TMEDA (0.15 mL, 1.03 mmol) in Et2O (10 mL) at −78 °C was treated with i-PrLi (0.65 mL, 1.6 M, 1.03 mmol). After 2 h, Bu3SnCl (0.35 mL, 1.29 mmol) was added, and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an iced-water bath, worked up with water (10 mL) and extracted with Et2O (4 × 10 mL). The combined organic extract was dried over anhyd. Na2SO4, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.92) gave 185 as a colorless oil (358 mg, 60%); [α]D20 –17.8 (c 0.59, CHCl3); IR (KBr, neat) νmax 2954, 1674, 1462, 1401, 1257, 1204, 1123, 1005 cm−1; 1H NMR (300 MHz, CDCl3) δ 3.69-3.63 (m, 1H), 3.59 (t, 1H, J = 9.0 Hz), 3.18 (dd, 1H, J = 7.4, 1.6 Hz), 2.69 (t, 1H, J = 8.3 Hz), 2.07-1.92 (m, 2H), 1.83-1.73 (m, 1H), 1.58-1.46 (m, 6H), 1.39-1.26 (m, 7H), 0.99-0.74 (m, 24H), 0.81-0.74 (m, 6H); 13C NMR (75.5 MHz, CDCl3) δ 167.5, 59.7, 46.6, 44.9, 31.6, 29.7, 29.3, 27.6, 13.8, 11.4, 6.8, 3.4; EIMS [m/z(%)] 473 (M-C4H9, 71), 239 (32), 209 (69), 41 (100); HRMS (EI) calcd for C20H41N2OSiSn: 473.2010; found: 473.2006.
(-)-(5S,7aS)-5-Methyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (186).

A solution of 181 (333 mg, 1.32 mmol) in MeOH (1.3 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rₛ = 0.10) gave 186 as a colorless solid (155 mg, 84%) that was recrystallized from EtOAc/hexane; mp 65-67 °C (EtOAc/hexane); [α]ᵢ²⁰ –20.9 (c 1.00, CHCl₃); IR (KBr, neat) νₘₐₓ 3298, 2968, 1697, 1487, 1440, 1271, 1155, 1125, 1093 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.77 (b, 1H), 4.13-4.03 (m, 1H), 3.74-3.68 (m, 1H), 3.58 (t, 1H, J = 8.5 Hz), 3.24 (t, 1H, J = 8.2 Hz), 2.26-2.13 (m, 1H), 2.01-1.92 (m, 1H), 1.79-1.69 (m, 1H), 1.67-1.56 (m, 1H), 1.43 (d, 3H, J = 6.8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 162.0, 60.9, 51.8, 46.0, 35.8, 29.5, 18.3; EIMS [m/z(%)] 140 (M⁺, 26), 125 (100), 69 (71). HRMS (EI) calcd for C₇H₁₂N₂O: 140.0950; found: 140.0947.

(+)-(5R,7aS)-5-(Hydroxydiphenylmethyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (187).

A solution of 182 (100 mg, 0.24 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (4 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 7 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rₛ = 0.19) gave 187 as a colorless oil (58 mg, 80%); [α]ᵢ²⁰ +146.0 (c 0.65 , CHCl₃); IR (KBr, neat) νₘₐₓ 3206, 2955, 1668, 1487, 1448, 1416, 1266, 1150, 1005 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 2H, J = 7.5 Hz), 7.47 (d, 2H, J = 7.5 Hz), 7.34-7.17 (m, 6H), 5.34 (b, 1H), 4.30-4.24 (m, 1H), 3.95-3.92 (m, 1H), 3.56 (t, 1H, J = 8.4 Hz), 3.20 (dd, 1H, J = 8.4, 1.8 Hz), 2.17-2.03 (m, 2H), 2.00-1.88 (m, 1H), 1.66-1.60 (m, 1H), 1.36-1.29 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 163.6, 147.5, 145.9, 127.9, 127.8, 126.6, 126.5, 126.4, 125.8, 77.2, 66.6, 60.6, 44.0, 28.9, 25.7;
EIMS [m/z(%)] 308 (M⁺, 17), 182 (44), 125 (68) 105 (100), 77 (40); HRMS (EI) calcd for C₁₉H₂₀N₂O₂: 308.1525; found: 308.1529.

(--)(5R,7aS)-5-Allyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (188).

A solution of 183 (238 mg, 0.89 mmol) in MeOH (1.2 mL) was treated with 2 M aq. HCl (6 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.11) gave 188 as a colorless oil (111 mg, 82%); [α]D²⁰ = −5.3 (c 1.01, CHCl₃); IR (KBr) νmax 3229, 2968, 1682, 1490, 1451, 1404, 1281, 1145, 1004 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.84-5.72 (m, 1H), 5.18-5.04 (m, 2H), 4.13-4.02 (m, 2H), 3.63-3.54 (m, 2H), 3.23 (t, 1H, J = 8.0 Hz), 3.08-3.00 (m, 1H), 2.36-2.26 (m, 1H), 2.16-2.03 (m, 1H), 1.97-1.90 (m, 1H), 1.65-1.52 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 161.4, 135.3, 117.4, 60.8, 55.4, 46.1, 35.4, 32.4, 29.3; EIMS [m/z(%)] 166 (M⁺, 3), 125 (100); HRMS (EI) calcd for C₉H₁₄N₂O: 166.1106; found: 166.1105.

(--)(5S,7aS)-5-(Trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (189).

A solution of 184 (413 mg, 1.32 mmol) in MeOH (1.8 mL) was treated with 2 M aq. HCl (10 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.13) gave 189 as a colorless solid (238 mg, 91%) that was recrystallized from EtOAc/hexane; mp 100-103 °C (EtOAc/hexane); [α]D²⁰ = −67.1 (c 0.52,
CHCl₃); IR (KBr) νamax 3259, 2948, 1682, 1446, 1411, 1272, 1243, 1126 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.40 (b, 1H), 3.92-3.81 (m, 1H), 3.65 (t, 1H, J = 8.5 Hz), 3.26 (dd, 1H, J = 8.7, 3.4 Hz), 2.47 (dd, 1H, J = 7.8, 2.4 Hz), 2.12-1.88 (m, 2H), 1.79-1.52 (m, 2H), 0.18 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 164.1, 60.6, 49.2, 44.0, 31.2, 27.9, –1.1; EIMS [m/z (%)] 199 (M⁺, 37) 183 (100), 73 (36); HRMS (FAB) calcd for C₉H₁₈N₂O Si: 199.1267; found: 199.1266.

(--)(5S,7aS)-5-(Tributylstannyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (190).

A solution of 185 (240 mg, 0.58 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.17) gave 190 as a colorless oil (141 mg, 71%); [α]D20 −16.5 (c 0.40, CHCl₃); IR (KBr, neat) νmax 3229, 2954, 1692, 1453, 1265, 1072 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.47 (b, 1H), 3.82-3.75 (m, 1H), 3.63 (t, 1H, J = 8.0 Hz), 3.24 (dd, 1H, J = 8.7, 2.4 Hz), 2.67 (t, 1H, J = 8.5 Hz), 2.07-1.98 (m, 2H), 1.84-1.74 (m, 1H), 1.55-1.47 (m, 6H), 1.36-1.29 (m, 7H), 0.93-0.88 (m, 15H); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.8, 59.7, 44.4, 43.3, 31.5, 29.7, 29.3, 27.3, 13.8, 11.2; EIMS [m/z (%)] 359 (M–C₄H₆, 68), 125 (73), 68 (56), 41 (100); HRMS (EI) calcd for C₁₄H₂₅N₂O Sn: 359.1145; found: 359.1149.

(5S,7aS)-2-Methyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (191).

A solution of 189 (270 mg, 1.36 mmol) in DMF (5 mL) at 0 °C was transferred by cannula into a stirred suspension of sodium hydride (131 mg, 5.46 mmol) in DMF (5 mL) at 0 °C. After 45 min iodomethane (0.24 mL, 3.82 mmol) was added into mixture at 0 °C, the mixture was thereafter allowed to stir to at room temperature for 16 h. After cooling
to 0 °C in an ice-water bath, workup was performed by sequential addition of NH₄Cl (20 mL) and water (80 mL), and the mixture was extracted with CH₂Cl₂ (4 × 10 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.51) gave 191 as a colourless oil (171 mg, 60%); [α]D²⁰ +10.0 (c 0.75, CHCl₃); IR (KBr) νmax 2955, 1687, 1460, 1393, 1251, 1124, 1005, 961, 740 cm⁻¹;¹H NMR (300 MHz, CDCl₃): δ 3.69-3.60 (m, 1H), 3.47 (t, 1H), 3.18 (dd, 1H, J = 6.7, 2.5 Hz), 2.76 (s, 3H) 2.43 (dd, 1H, J = 7.7, 2.9 Hz), 2.09-1.97 (m, 1H), 1.92-1.81 (m, 1H), 1.71-1.58 (m, 1H), 1.57-1.43 (m, 1H), 0.17 (s, 9H);¹³C NMR (75.5 MHz, CDCl₃); δ 162.7, 57.4, 50.8, 50.1, 31.4, 31.01, 27.6; EIMS [m/z(%)] 213 (M⁺, 6.3), 197 (100), 139 (28.2), 73 (25.7). HRMS (EI) calcd for C₁₀H₂₀N₂Si: 212.1345; found: 212.1349.

(--)-(5S,7aS)-5-Methyl-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (166).

A 2-necked flask under argon was charged with 186 (643 mg, 4.59 mmol), CuI (700 mg, 3.67 mmol), TMEDA (0.09 mL, 0.90 mmol), iodobenzene (1.13 mL, 10.12 mmol), K₂CO₃ (1671 mg, 12.20 mmol), and toluene (6 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH₂Cl₂ (50 mL), filtered through Celite and washed with additional CH₂Cl₂ (4 × 30 mL). The organic filtrate was washed with H₂O (4 × 50 mL), dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, Rf = 0.18) gave 166 as a colorless solid (738 mg, 74%) that was recrystallized from EtOAc/hexane; mp 110-112 °C (EtOAc/hexane); [α]D²⁰ –22.5 (c 0.90, CHCl₃); IR (KBr) νmax 2890, 1943, 1862, 1681, 1598, 1384, 1280, 1153, 1085, 1054 cm⁻¹;¹H NMR (300 MHz, CDCl₃) δ 7.51-7.48 (m, 2H), 7.36-7.28 (m, 2H), 7.04-6.99 (m, 1H), 4.09-4.01 (m, 1H), 3.91 (t, 1H, J = 8.4 Hz), 3.87-3.82 (m, 1H), 3.69 (t, 1H, J = 8.4 Hz), 2.25-2.19 (m, 1H), 2.14-2.07 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.64 (m, 1H), 1.44 (d, 3H, J = 6.3 Hz);¹³C NMR (75.5 MHz, CDCl₃) δ 156.7, 140.7, 128.7, 122.04, 117.3, 56.6, 52.2, 50.7 35.6, 29.9, 18.4; EIMS [m/z(%)] 217 (M⁺, 14), 201 (74), 69 (100), 55 (49); HRMS (EI) calcd for C₁₃H₁₆N₂O: 216.1263; found: 216.1262.
(−)-(S,S,7aS)-2-Phenyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (194).

A 2-necked flask under argon was charged with 189 (100 mg, 0.51 mmol), CuI (77 mg, 0.40 mmol), TMEDA (0.01 mL, 0.10 mmol), iodobenzene (0.12 mL, 1.10 mmol), K$_2$CO$_3$ (138 mg, 1.00 mmol), and toluene (1mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH$_2$Cl$_2$ (15 mL), filtered through Celite and washed with additional CH$_2$Cl$_2$ (4 × 15 mL). The organic filtrate was washed with H$_2$O (4 × 15 mL), dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, R$_f$ = 0.41) gave 194 as a colorless solid (56 mg, 40%) that was recrystallized from EtOAc/hexane; mp 138–140 °C (EtOAc/hexane); [α]$_D^{20}$ −70.1 (c 1.50, CHCl$_3$); IR (KBr) $\nu_{max}$ 3396, 2917, 1704, 1600, 1502, 1481, 1402, 1317, 1243, 1153, 1128, 1076, 1027 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.57 (dd, 2H, $J$ = 7.8, 1.3 Hz), 7.54-7.39 (m, 2H), 7.03 (t, 1H, $J$ = 7.3 Hz), 4.03-4.00 (t, 1H, $J$ = 8.9 Hz), 3.88-3.79 (m, 1H), 3.66 (dd, 1H, $J$ = 9.0, 3.3 Hz), 2.56 (dd, 1H, $J$ = 10.2, 7.8 Hz), 2.19-2.10 (m, 1H), 1.92-1.84 (m, 1H), 1.80-1.71 (m, 1H), 1.64-1.60 (m, 1H), 0.23 (s, 9H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 159.2, 140.6, 128.8, 122.4, 117.7, 56.5, 49.8, 48.9, 31.8, 27.9, −0.99; EIMS [m/z(%)] 274 (M*, 11), 259 (81), 183 (76), 73 (100); HRMS (EI) calcd for C$_{15}$H$_{22}$N$_2$OSi: 274.1501; found: 274.1491.

(5S,7aS)-2-(2-Iodophenyl)-5-methyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (195).

A solution of 166 (100 mg, 0.46 mmol) and TMEDA (0.08 mL, 0.55 mmol) in THF (4 mL) at −78 °C was treated with $i$-PrLi (0.44 mL, 1.2 M, 0.55 mmol). After 2 h, a solution of 1,2-diiodoethane (197 mg, 0.70 mmol) in THF (2 mL) was added slowly by cannula, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with CH$_2$Cl$_2$ (4 × 10 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R$_f$ = 0.23) gave 195 as a colorless solid (106 mg, 67%) that was recrystallized from EtOAc/hexane; mp 144-
147 °C (EtOAc/hexane); [α]_D 20° –29.5 (c 2.50, CHCl₃); IR (KBr) ν max 3072, 2987, 2955, 2887, 2839, 1685, 1565, 1468, 1440, 1397, 1280, 1103, 1019, 949, 862, 759, 717, 678, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (dd, 1H, J = 7.2, 1.4 Hz), 7.40–7.34 (m, 1H), 7.30 (dd, 1H, J = 6.5, 1.4 Hz), 7.00 (dd, 1H, J = 6.1, 1.8 Hz), 4.13–4.05 (m, 1H), 3.85–3.77 (m, 2H), 3.70–3.66 (m, 1H), 2.26–2.14 (m, 1H), 2.08–2.00 (m, 1H), 1.85–1.71 (m, 2H), 1.50 (d, 3H, J = 6.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.1, 141.9, 139.7, 129.3, 129.1, 128.9, 99.2, 57.9, 52.9, 52.4, 35.4, 29.7, 18.4; HRMS (EI) calcd for C₁₃H₁₅N₂O: 342.0221; found: 342.0218.

(5S,7aS)-2-(2-(Diphenylphosphino)phenyl)-5-methyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (196).

A solution of 166 (100 mg, 0.46 mmol) and TMEDA (0.08 mL, 0.55 mmol) in THF (4 mL) at –78 °C was treated with i-PrLi (0.44 mL, 1.2 M, 0.55 mmol). After 2 h, PPh₂Cl (0.12 mL, 0.70 mmol) was added, and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath and quenched with a saturated solution of NH₄Cl (4 mL), worked up with water (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane : EtOAc, Rf = 0.21) gave 196 as a colorless oil (85 mg, 47%); [α]_D 20° +15.9 (c 1.00, CHCl₃); IR (KBr, neat) ν max 3054, 2966, 1691, 1584, 1471, 1435, 1347, 1217, 741, 694, 663, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83–7.64 (m, 2H), 7.34–7.32 (m, 10H), 7.20–7.15 (m, 1H), 6.89–6.85 (m, 1H), 3.88–3.80 (m, 1H), 3.70–3.61 (m, 1H), 3.60 (t, 1H, J = 8.3 Hz), 2.10–1.99 (m, 1H), 1.93–1.85 (m, 1H), 1.56–1.51 (m, 2H), 1.28 (d, 3H, J = 6.8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.9, 143.7 (d, J = 20.8 Hz), 137.1 (d, J = 13.6 Hz), 136.5 (d, J = 10.5 Hz), 134.2, 134.1, 134.0, 133.9, 133.7, 130.1, 128.8, 128.5, 128.4, 128.0, 127.4, 57.8, 53.3, 52.8, 35.1, 29.5, 18.0; HRMS (EI) calcd for C₂₅H₂₅N₂OP: 400.1699; found: 400.1701.
(5R,7aS)-5-(Hydroxydiphenylmethyl)-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (197).

A 2-necked flask under argon was charged with 187 (500 mg, 1.62 mmol), CuI (247 mg, 1.30 mmol), TMEDA (0.1 mL, 0.65 mmol), iodobenzene (0.4 mL, 3.56 mmol), K₂CO₃ (560 mg, 4.05 mmol), and toluene (3 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH₂Cl₂ (15 mL), filtered through Celite and washed with additional CH₂Cl₂ (4 × 15 mL). The organic filtrate was washed with H₂O (4 × 15 mL), dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, Rᶠ = 0.41) gave 197 as a colorless solid (303 mg, 49%) that was recrystallized from EtOAc/hexane; mp 195-198 °C (EtOAc/hexane); [α]D²⁰ = -153.8 (c 1.15, CHCl₃); IR (KBr) νmax 3216, 3059, 3024, 2954, 2918, 1655, 1598, 1500, 1451, 1384, 1268, 1170, 965, 725, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, 2H, J = 7.8 Hz), 7.51-7.47 (m, 4H), 7.37-7.17 (m, 8H), 7.07 (t, 1H, J = 7.4 Hz), 4.44-4.40 (dd, 1H, J = 7.1, 1.7 Hz), 4.03-3.37 (m, 3H), 3.67 (dd, 1H, J = 7.0, 2.0 Hz), 2.30-2.16 (m, 1H), 2.12-2.00 (m, 1H), 1.72-1.59 (m, 1H), 1.47-1.36 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 159.9, 148.0, 146.4, 140.2, 129.3, 128.5, 128.4, 127.2, 127.0, 126.9, 126.4, 123.8, 119.1, 77.2, 68.0, 57.0, 49.4, 30.0, 26.2; HRMS (EI) calcd for C₂₅H₂₄N₂O₂: 384.1847; found: 384.1838.

(5S,7aS)-5-Methyl-2-(perfluorophenyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (199).

A solution of 186 (200 mg, 1.43 mmol) in DMF (5 mL) at 0 °C was transferred by cannula into a stirred suspension of sodium hydride (68 mg, 2.87 mmol) in DMF (5 mL) at 0 °C, after 45 min hexafluorobenzene (0.17 mL, 1.44 mmol) was added into mixture at 0 °C, the mixture was thereafter allowed to stir to at room temperature for 16 h. After cooling to 0 °C in an ice-water bath, workup was performed by sequential addition of NH₄Cl (20 mL) and water (80 mL), and extracted with CH₂Cl₂ (4 × 10 mL). The combined
organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane : EtOAC, R$_f$ = 0.59) gave 199 as a colourless oil (212 mg, 48%); [α]$_D^{20}$ – 56.1 (c 3.5, CHCl$_3$); IR (KBr) $\nu_{\text{max}}$ 2944, 2877, 1706, 1651, 1505, 1397, 1308, 1168, 982, 748 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 4.24-4.14 (m, 1H), 3.85-3.76 (m, 2H), 3.65 (t, 1H, $J$ = 8.3 Hz), 2.82-2.20 (m, 1H), 2.12-2.03 (m, 1H), 1.88-1.79 (m, 1H), 1.75-1.65 (m, 1H), 1.43 (d, 3H, $J$ = 7.12 Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$); δ 156.4, 144.1 (d, $^1J_{13C-19F}$ = 251.3 Hz), 140.1 (d, $^1J_{13C-19F}$ = 253.8 Hz), 137.9 (d, $^1J_{13C-19F}$ = 251.3 Hz), 114.9-114.5 (m), 58.6, 52.2, 35.5, 29.6, 29.6, 18.1; $^{19}$F NMR (282.4 MHz, CDCl$_3$); –144.9, –156.8, –162.5; HRMS (EI) calcd for C$_{13}$H$_{11}$F$_5$N$_2$O: 306.0789; found: 306.0792.

(Z)-N-((5S,7aS)-2-Methyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-ylidene)-1-phenylmethanamine (202).

A solution of 191 (119 mL, 0.56 mmol) in POCl$_3$ (0.5 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl$_3$ was removed by under reduced pressure. The crude intermediate was dissolved in MeCN (0.5 mL) and transferred to a solution of benzylamine (0.07 mL, 0.67 mmol) and triethylamine (0.16 mL, 1.12 mmol) in MeCN (0.5 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). After evaporation of the combined organic extract, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH$_2$Cl$_2$ (4 × 15 mL). The combined organic extract was dried over anhyd. Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to yield 202 as a colorless oil (57 mg, 35%); [α]$_D^{20}$ +54.6 (c 0.6, CHCl$_3$); IR (KBr, neat) $\nu_{\text{max}}$ 2955, 1675, 1481, 1397, 1319, 1256, 1010, 889 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.28 (dd, 4H, $J$ = 7.8, 6.6 Hz), 7.15 (t, 1H, $J$ = 6.18 Hz), 4.58 (d, 1H, $J$ = 15.5 Hz), 4.39 (d, 1H, $J$ = 15.5 Hz), 3.76 (s, 1H), 3.33 (t, 1H, $J$ = 8.7 Hz), 3.17 (dd, 1H, $J$ =...
= 5.5, 3.6 Hz), 2.76 (s, 4H), 2.09-1.93 (m, 2H), 1.83 (s, 1H), 1.54-1.41 (m, 1H), 0.06 (s, 9H); $^{13}$C NMR (75.5 MHz, DMSO-d$_6$); δ 157.4, 143.9, 128.1, 127.5, 126.0, 59.7, 56.2, 52.1, 51.2, 40.8, 30.8, 29.5, 0.38; EIMS [m/z(%)] 302 (M$^+$, 2), 228 (40), 91(100). HRMS (EI) calcd for C$_{17}$H$_{27}$N$_3$Si: 301.1974; found: 301.1982.

(5S,7aS)-2-Methyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-imine (205).

A solution of 191 (10 mg, 0.47 mmol) in POCl$_3$ (0.5 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl$_3$ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (0.5 mL) and transferred to a solution of aqueous ammonia (0.18 mL, 4.57 mmol) and triethylamine (2.55 mL, 18.00 mmol) in MeCN (0.5 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH$_2$Cl$_2$ (4 × 15 mL). The combined organic extract was dried over anhyd. Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to yield 205 as colorless oil (29 mg, 30%) [α]$_D^{20}$ −18.6 (c 0.35, CHCl$_3$); IR (KBr, neat) $\nu_{max}$ 3428, 2946, 1641, 1490, 1407, 1301, 1024, 973, 904, 840, 755, 593 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d$_6$); δ 3.62-3.55 (m, 1H), 3.39 (dd, 1H, $J = 7.26, 1.5$ Hz), 3.12 (dd, 1H, $J = 3.3, 2.7$ Hz), 2.90 (s, 1H), 2.65 (s, 3H), 2.46-2.4 (m, 1H), 1.86-1.81 (m, 2H), 1.60-1.42 (m, 2H), 0.15 (s, 9H); $^{13}$C NMR (75.5 MHz, acetone-d$_6$); δ 163.1, 59.4, 53.8, 52.0, 32.8, 30.9, 28.5, −0.3; EIMS [m/z(%)] 212 (M$^+$, 4.8), 196 (100), 138 (62), 73 (35). HRMS (EI) calcd for C$_{10}$H$_{21}$N$_3$Si: 211.1505; found: 211.1493.
(5\text{S},7\text{aS})-5-Methyl-2-phenyltetrahydro-1\text{H}-pyrrolo[1,2-c]imidazol-3(2\text{H})-imine (206).

A solution of 166 (218 mg, 1.02 mmol) in POCl$_3$ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl$_3$ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.53 mL, 10.00 mmol) and triethylamine (6.75 mL, 40.0 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH$_2$Cl$_2$ (4 × 15 mL). The combined organic extract dried over anhyd. Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to yield 206 as colorless oil (82 mg, 41%) $[\alpha]_{D}^{20} -49.0$ (c 0.35, CHCl$_3$); IR (KBr, neat) $\nu_{\text{max}}$ 3457, 2919, 2057, 1629, 1500, 1153, 1018 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40-7.35 (m, 4H) 7.10-7.05 (m, 1H), 4.17-4.05 (m, 1H), 4.05-3.95 (m, 1H), 3.84 (t, 2H, $J = 8.8$ Hz), 3.65 (t, 1H, $J = 8.5$ Hz), 2.31-2.18 (m, 1H), 2.13-2.04 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.60 (m, 1H), 1.44 (d, 3H, $J = 6.4$ Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 156.4, 141.0, 129.2, 123.1, 120.1, 58.6, 55.2, 52.1, 36.2, 28.7, 18.0; EIMS [m/z(%)] 215 (M$^+$, 6), 160 (100), 106 (30); HRMS (EI) calcd for C$_{13}$H$_{17}$N$_3$: 215.1422; found: 215.1421.

(5\text{S},7\text{aS})-2-Phenyl-5-(trimethylsilyl)tetrahydro-1\text{H}-pyrrolo[1,2-c]imidazol-3(2\text{H})-imine (207).

A solution of 194 (230 mg, 0.87 mmol) in POCl$_3$ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl$_3$ was removed by under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.63 mL, 8.50 mmol) and triethylamine (5.77 mL, 33.30 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 ×
10 mL). After evaporation of the combined organic extract, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield 207 as a colorless oil (78 mg, 34%); [α]D²⁰ – 19.3 (c 0.6, CHCl₃); IR (KBr, neat) νmax 3384, 2929, 1646, 1596, 1502, 1405, 1319, 1240, 1116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.39 (m, 2H), 7.31-7.25 (m, 2H), 7.19-7.09 (m, 1H), 3.99-3.86 (m, 2H), 3.64-3.60 (m, 1H), 2.90-2.85 (m, 1H), 2.14-2.02 (m, 2H), 1.93-1.82 (m, 1H), 1.70-1.59 (m, 2H), 0.23 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.6, 141.2, 129.3, 123.5, 121.0, 58.8, 53.3, 51.2, 31.0, 29.2, 0.1; EIMS [m/z(%)] 273 (M⁺, 9), 258 (100), 200 (72), 182 (47), 73 (44); HRMS (EI) calcd for C₁₅H₂₃N₃Si: 273.1661; found: 273.1669.

\((E)-N-((5S,7aS)-5-Methyl-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-ylidene)-1-phenylmethanamine\) (203).

A solution of 166 (110 mg, 0.51 mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of benzylamine (0.07 mL, 0.61 mmol) and triethylamine (0.14 mL, 1.02 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield 203 as colorless oil (95 mg, 61%) [α]D²⁰ – 49.0 (c 0.35, CHCl₃); IR (KBr, neat) νmax 2996, 1683, 1517, 1469, 1332, 1195, 1006, 782, 640, 497 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.81-7.78 (d, 2H, J = 7.9 Hz), 7.56-7.53 (d, 2H, J = 7.4 Hz), 7.42-7.25 (m,
5H), 7.39-6.96 (t, 1H, J = 7.4 Hz), 4.71 (d, 1H, J = 15.8 Hz), 4.53 (d, 1H, J = 15.8 Hz), 4.20-4.04 (m, 2H), 3.92 (t, 1H, J = 8.3 Hz), 3.64 (t, 1H, J = 8.9 Hz), 2.42-2.30 (m, 1H), 2.22-2.13 (m, 1H), 1.95 (dd, 1H, J = 5.7, 6.5 Hz), 1.87-1.79 (m, 1H), 1.18 (d, 3H, J = 6.4 Hz) ; 13C NMR (75.5 MHz, CDCl3); δ 152.7, 143.1, 142.3, 128.4, 128.1, 127.4, 125.9, 121.1, 118.6, 58.4, 55.8, 55.0, 52.9, 35.5, 28.6, 19.3. ; EIMS [m/z(%)] 305 (M+, 38), 250 (53), 215 (37), 160 (100), 105 (66), 91 (84), 77 (70). HRMS (EI) calcd for C20H23N3: 305.1895; found: 305.1895.

2-((E)-((5S,7aS)-5-Methyl-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-ylidene)amino)ethanol (204).

A solution of 166 (190 mg, 0.88 mmol) in POCl3 (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl3 was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of ethanolamine (0.07 mL, 0.61 mmol) and triethylamine (0.14 mL, 1.02 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH2Cl2 (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH2Cl2 (4 × 15 mL). The combined organic extract dried over anhyd. Na2SO4, filtered, and concentrated under reduced pressure to yield 204 as colorless oil (71 mg, 31 %) [α]D20 +10.1 (c 0.35, CHCl3); IR (KBr, neat) νmax 3394, 2939, 1639, 1596, 1502, 1400, 1259, 1189, 1145, 1016, 892, 752, 514 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 7.61 (d, 2H, J = 7.8 Hz), 7.31 (dd, 2H, J = 8.9 Hz), 6.96 (t, 1H, J = 7.3 Hz), 4.14-4.06 (m, 1H), 3.96-3.87 (m, 2H), 3.81-3.75 (dd, 2H, J = 7.0, 4.6 Hz), 3.61 (t, 1H, J = 9.0 Hz), 3.52-3.34 (m, 2H), 2.84 (b, 1H), 2.37-2.24 (m, 1H), 2.19-2.11 (m, 1H), 1.92 (dd, 1H, J = 6.6, 5.2 Hz), 1.86-1.74 (m, 1H), 1.09 (d, 3H, J = 6.4 Hz) ; 13C NMR (75.5 MHz, CDCl3); δ 153.6, 142.0, 128.5, 121.6, 118.9, 63.4,
(+)-(S)-2-Bromo-1-phenylethanol (99).

A solution of guanidine 205 (27 mg, 0.10 mmol) in toluene (3 mL) at room temperature was treated with added BH$_3$•SMe$_2$ (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction was mixture heated at 110 °C for 20 min. A solution of phenacyl bromide (100 mg, 0.50 mmol) in toluene (2 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave (R)-99 as a colorless oil (84 mg, 83%); [α]$_D^{20}$ +3.6 (c 1.00, CHCl$_3$) [lit.$^{83}$ [α]$_D^{25}$ = 39.0 (c 8.00, CHCl$_3$) for (R) enantiomer]; CSP HPLC analysis (Chiralcel OD-H, 90:10 hexanes:i-PrOH, 1.0 mL/min) determined an er of 54:46 (8% ee) [t$_R$(major) = 7.77 min, t$_R$(minor) = 9.03 min]; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.49–7.34 (m, 5H), 5.01–4.85 (m, 1H), 3.69–3.48 (m, 2H), 2.64 (b, 1H).

(−)-(S)-1-Phenylethanol (220b).

A solution of guanidine 207 (27 mg, 0.10 mmol) in toluene (1 mL) at room temperature was treated with added BH$_3$•SMe$_2$ (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction mixture was heated at 110 °C for 20 min. A solution of acetophenone (0.06 mL, 0.50 mmol) in toluene (1 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave (S)-220b as a colorless oil (47 mg, 77%); [α]$_D^{20}$ = −10.1 (c 2.00, CHCl$_3$) [lit.$^{84}$ [α]$_D^{25}$ = −57.0 (c 5.13, CHCl$_3$) for (S) enatiomer]; CSP HPLC analysis (Chiralcel OD-H, 95:5 hexanes:i-
PrOH, 0.4 mL/min) determined an er of 62:38 (24% ee) \( t_R(\text{minor}) = 19.49 \text{ min}, \ t_R(\text{major}) = 23.72 \text{ min} \);

\(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.38–7.28 (m, 5H), 4.95–4.90 (m, 1H), 1.80–1.79 (b, 1H), 1.44 (d, 3H, \( J = 6.5 \text{ Hz} \)).

**(5S,7aS)-5-Methyl-2-phenylhexahydro-1H-pyrrolo[1,2-c]imidazole (167).**

A solution of \( 166 \) (600 mg, 2.77 mmol) in THF (150 mL) at –78 °C was treated with DIBAL-H (24 mL, 1.00 M, 22.22 mmol) and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of saturated solution of potassium sodium tartrate (10 mL) and water (135 mL), and extracted with CH\(_2\)Cl\(_2\) (4 × 100 mL). The combined organic phase was dried over anhyd. Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 97:3 EtOAc: Et\(_3\)N, \( R_f = 0.27 \)) gave \( 167 \) as a colorless oil (289 mg, 52%); \([\alpha]_D^{20} +14.2\) (c 1, CHCl\(_3\)); IR (KBr, neat) \( \nu_{\text{max}} \) 3053, 3039, 2953, 2904, 2870, 2836, 1594, 1504, 1365, 1341, 1154, 1120, 992, 742, 688, 511 cm\(^{-1}\); \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.26 (t, 2H, \( J = 8.1 \text{ Hz} \)), 6.74 (t, 1H, \( J = 7.5 \text{ Hz} \)), 6.57–6.54 (d, 2H, \( J = 8.0 \text{ Hz} \)), 4.37–4.30 (d, 1H, \( J = 6.8 \text{ Hz} \)), 4.13 (d, 1H, \( J = 6.8 \text{ Hz} \)), 3.91–3.85 (m, 1H), 3.52–3.40 (m, 2H), 3.11–3.07 (m, 1H), 2.20–2.07 (m, 1H), 2.04–1.93 (m, 1H), 1.87–1.70 (m, 1H), 1.68–1.62 (m, 1H), 1.3 (d, 3H, \( J = 6.8 \text{ Hz} \)); \(^{13}C\) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 146.7, 129.2, 116.6, 112.4, 64.4, 63.8, 58.0, 53.7, 32.2, 30.0, 16.9; EIMS [m/z(\%)] 217 (M\(^+\), 14), 201 (74), 69 (100), 55 (48). HRMS (EI) calcd for C\(_{13}\)H\(_{18}\)N\(_2\): 216.1262; found: 216.1262.

**(5S,7aS)-5-Methyl-2-phenyl-1,2,5,6,7,7a-hexahydropyrrolo[1,2-c]imidazol-4-ium tetraphenylborate (168).**

A solution of \( 167 \) (202 mg, 1.00 mmol) and tritylium tetrafluoroborate (330 mg, 1.00 mmol) in CH\(_2\)Cl\(_2\) (12 mL) was stirred at room temperature for 16 h in a sealed tube under argon. The mixture was cooled to room temperature and CH\(_2\)Cl\(_2\) was removed under reduced pressure. The crude mixture was dissolved in MeOH (3 mL), and a solution of NaBPh\(_4\) (342 mg, 1.00 mmol) in MeOH (3 mL) was added dropwise. The resulting precipitate
was filtered, washed with cold MeOH and dried under high vacuum to give 168 as a beige powder (33 mg, 63%); mp 189-192 °C; [α]_D^20 +149.0 (c 0.5, CHCl₃); IR (KBr) ν_max 3051, 1608, 1587, 1502, 1477, 1425, 1315, 1280, 1251, 1135, 1066, 1031, 1007, 946, 847, 823, 734, 705, 604, 512 cm⁻¹; ^1H NMR (300 MHz, acetone-d₆): 9.15 (s, 1H), 7.68 (d, 1H, J = 8.3 Hz), 7.36 (d, 11H, J = 5.8 Hz), 6.94 (t, 9H, J = 7.0 Hz), 6.80 (t, 4H, J = 7.2 Hz), 4.79-4.70 (m, 1H), 4.50-4.35 (m, 2H), 4.15 (d, 1H, J = 6.5 Hz), 2.50-2.25 (m, 2H), 2.01-1.81 (m, 2H), 1.60 (d, 3H, J = 6.2 Hz); ^13C NMR (75.5 MHz, acetone-d₆): 164.3 (q, J ^13C-^11B = 49.2 Hz), 152.2, 136.1, 132.7, 129.8, 125.2, 125.1, 121.4, 119.9, 64.6, 64.5, 54.9, 54.2, 33.4, 18.2; FABMS [m/z(%)] 201 (M–BPh₄, 100), 149 (9), 41 (84); HRMS (ESI) calcd for C₁₀H₁₇N₂: 201.1398; found: 201.1392.

**Chloro(q^4-1,5-cyclooctadiene)(5-methyl-2-phenylhexahydro-1H-pyrrolo[1,2-c]imidazolidine-2-ylidene)rhodium (240).**

A solution of 168 (50 mg, 0.10 mmol) and [Rh(COD)Cl]₂ (25 mg, 0.05 mmol) in THF (2 mL) was stirred at -78 °C in a sealed tube under argon. After 30 min sodium hydride (5 mg, 60% dispersion in mineral oil, 0.12 mmol) was added. The mixture was stirred at room temperature for 16 h, during which time the color changed from orange to brown. After removing the solvent on a rotary evaporator, the crude product was purified by column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.21) gave 240 as a 56:44 mixture of coordination isomers as an orange-yellow oil in a 3:1 ratio. (25 mg, 58%); [α]_D^20 –21.0 (c 1.5, CHCl₃); IR (KBr, neat) ν_max 3341, 3047, 2920, 2870, 2828, 2116, 1943, 1598, 1559, 1494, 1469, 1364, 1230, 1183, 1084, 1021, 995, 958, 863, 814, 756, 694, 644, 516 cm⁻¹; Main isomer: ^1H NMR (300 MHz, CDCl₃) δ 8.07 (d, 1H, J = 7.7 Hz), 7.47-7.39 (m, 2H), 7.25-7.17 (m, 2H), 5.15-5.08 (m, 1H), 5.03-4.96 (m, 1H), 4.36-4.20 (m, 1H), 4.16-3.96 (m, 1H), 3.79-3.72 (m, 2H), 3.24-3.18 (m, 1H), 2.51-2.14 (m, 3H), 2.23 (d, 3H, J = 6.5 Hz), 2.07-1.54 (m, 10H), ^13C NMR (75.5 MHz, CDCl₃) δ 204.6, 143.5, 128.3, 124.8, 120.8, 97.7, 97.4, 72.0, 69.7, 66.9, 65.4, 55.1, 51.7, 36.3, 32.1, 29.1, 28.6, 27.5, 22.4; EIMS [m/z(%)] 446 (M⁺, 2.2), 411 (12.2), 302 (18.4 ), 201 (33.7), 55 (100); HRMS (EI) calcd for C₂₁H₂₈N₂RhCl: 446.1021; found: 446.1029.
Dicarbonylchloro(5-methyl-2-phenylhexahydro-1H-pyrrolo[1,2-c]imidazolidine-2-ylidene)rhodium (242).

To a solution of 240 (60 mg, 0.13 mmol) in DCM (7 mL) carbon monoxide was bubbled into the reaction mixture. The mixture was stirred at room temperature for 16 h under CO atmosphere, during which time the color changed from orange to red. After removing the solvent on a rotary evaporator, the crude product was purified by column chromatography (silica gel, 7:3 hexane:EtOAc, R_{f} = 0.26) gave 242 as an orange-yellow oil mixture of rotamers in a roughly 10:1 ratio. (40 mg, 78%); [α]_{D}^{20} –33.1 (c 1.8, CHCl_{3}); IR (KBr, neat) ν_{max} 3150, 2922, 2873, 2068, 1987, 1596, 1479, 1641, 1394, 1309, 1237, 1187, 754, 691, 579, 510 cm^{-1}; Main isomer: ^1H NMR (300 MHz, CDCl$_3$) δ 7.69 (d, 1H, J = 7.49 Hz), 7.37 (t, 2H, J = 8.2 Hz), 7.28-7.22 (m, 2H), 4.54-4.40 (m, 1H), 4.29-4.22 (m, 1H), 4.06 (dd, 1H, J = 9.8, 3.2 Hz), 3.96-3.81 (m, 1H), 2.53-2.39 (m, 1H), 2.20-2.14 (m, 1H), 2.05-1.99 (m, 1H), 1.83 (d, 3H, J = 7.0 Hz), 1.80-1.74 (m, 1H); ^13C NMR (75.5 MHz, CDCl$_3$) δ 197.1 (d, J = 40.1 Hz), 186.2 (d, J = 55.0 Hz), 182.8 (d, J = 75.1 Hz), 142.2, 128.6, 125.7, 121.4, 66.8, 55.7, 51.8, 36.2, 28.0, 23.9; HRMS (EI) [M-Cl-2CO] calcd for C$_{15}$H$_{16}$ClN$_2$O$_2$Rh: 303.0356; found: 303.0369.

2-Methyl-3-phenylpropan-1-ol (245).

A solution of 242 (4 mg, 0.01 mmol, 0.2 mol%), allyl benzene 243 (0.07 mL, 0.5 mmol) and (triphenyl phosphite (0.02 mL, 0.01 mmol, 2 mol%) in toluene (2 ml) was placed into the bomb under 20 bar of CO/H$_2$ pressure at 60 °C and stirred for 48 h. The crude reaction was dissolved in EtOH (4 ml) and NaBH$_4$ (111 mg, 3.00 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and worked up by careful addition of 5% aqueous HCl (4 mL). The crude mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL), and the combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 4:1 hexane:EtOAC, R$_f$ = 0.41) gave combined yield of both branched and linear alcohols as a
colourless oil (212 mg, 54%); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 3.59-3.47 (m, 2H), 2.79 (dd, 1H, \(J = 13.4, 6.3\) Hz), 2.44 (dd, 1H, \(J = 13.4, 8.1\) Hz.), 2.03-1.94 (m, 1H), 1.45 (br, 1H), 0.94 (d, 3H, \(J = 6.8\) Hz).

**4-phenylbutan-1-ol (244).** \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.33-7.20 (m, 5H), 3.68 (t, 2H, \(J = 6.5\) Hz), 2.67 (t, 2H, \(J = 7.6\) Hz), 1.76- 1.61 (m, 4H), 1.45 (br s, 1H).
5. References


6. Appendix: Spectra

1D proton

173

300 MHz, CHCl₃

1D carbon with proton decoupling

173

75 MHz, CHCl₃
1D proton

181

150 MHz, CDCl₃

1D carbon with proton decoupling

181

150 MHz, CDCl₃
1D proton

300 MHz, CDCl$_3$

1D carbon with proton decoupling

75 MHz, CDCl$_3$
ld proton.

![NMR Spectroscopy Image](image_url)

300 MHz, CDCl₃

ld carbon with proton decoupling

![NMR Spectroscopy Image](image_url)

150 MHz, CDCl₃
1D proton

300 MHz, CDCl₃

1D carbon with proton decoupling

150MHz, CDCl₃
1D proton

189

300 MHz, CDCl₃

1D carbon with proton decoupling

189

75 MHz, CDCl₃
1D proton

![1D proton spectrum of compound 190](image)

300 MHz, CDCl$_3$

1D carbon with proton decoupling

![1D carbon spectrum with proton decoupling](image)

300 MHz, CDCl$_3$
1D proton

300 MHz, CDCl₃

174

1D carbon with proton decoupling

TMS

174

150 MHz, CDCl₃

107
1D proton

175

300 MHz, CDCl₃

ld carbon with proton decoupling

175

150 MHz, CDCl₃
1D proton

194

300 MHz, CDCl$_3$

ID carbon with proton decoupling

191.18 140.55 128.79 127.40 55.96 49.84 48.05 31.82 27.88

194

75 MHz, CDCl$_3$

111
1D proton

196

300 MHz, CDCl₃

1D carbon with proton decoupling

196

75 MHz, CDCl₃
**1H proton**

![1H proton spectrum](image)

**202**

300 MHz, DMSO

**13C carbon with proton decoupling**

![13C carbon spectrum](image)

**202**

150 MHz, DMSO
1D proton

300 MHz, CDCl₃

1D carbon with proton decoupling

75 MHz, CDCl₃
1D proton

300 MHz, CDCl₃

1D carbon with proton decoupling

75 MHz, CDCl₃
1D proton

300 MHz, CDCl₃

1D carbon with proton decoupling

75 MHz, CDCl₃
150 MHz, CDCl₃

75 MHz, CDCl₃
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