Synthesis and application of 1-arylpyrrole derivatives in regio- and stereoselective reactions

PhD Thesis

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1. Introduction

Pyrrole derivatives are widely known as biologically active molecules.\(^1\) Pyrrole ring containing natural compounds also show remarkable biological and pharmacological properties.\(^2\) Due to these advantageous properties numerous articles were published about the synthesis of pyrrole derivatives. Several biologically active pyrroles are described in communications showing different biological effects, such as anticancer, antiviral, anticoagulant, antimicrobial and anti-inflammatory. Pyrroles are also important targets not only in pharmaceutical chemistry but also pesticide industry because of the insecticidal influence of many \(N\)-heterocycles.

Our research group at the Department of Organic Chemistry and Technology has achieved considerable success in the field of the 1-arylpyrrole chemistry in the recent years. Development of effective synthetic methods for the regioselective functionalization of rings via metalation\(^3\) opened a route to axial chiral compounds, whereas the rotation around the C-N single bond is inhibited by bulky groups. Many of these atropisomeric derivatives have been prepared in enantiomerically pure form by diastereomeric salt formation resolution.\(^4\) Based on these compounds, bifunctional catalyst ligands and organocatalysts were synthesized for enantioselective transformations.\(^5\)

One of the aims of my doctoral research work was the synthesis of amino alcohols which are the regioisomers of the earlier synthesized molecules in our group, which were effective for asymmetric catalysis. The target compounds were planned to be tested as catalyst ligands in the enantioselective reaction of an aromatic aldehyde and diethylzinc. Due to the interchange of the connection of the two functions to the backbone, the steric and electronic properties of the amino alcohols were also changed. Moreover, we intended to study the relationship between asymmetric induction of the model reaction and the structure of the ligands. Based on the results and observations, we sought to achieve better selectivity by optimizing the structure of the ligand.

The disadvantage of these new ligands and organocatalysts with 1-arylpyrrole skeleton is that they can be prepared through a multi-step way, and the ligands can be tested in asymmetric model reactions only after a tedious synthetic work. By decreasing

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\(^{1}\) Bhaward, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Adv.* 2015, 5, 15233.


the number of the reaction steps, the syntheses would become cheaper, which could give the possibility to the wide application of the compounds.

Based on these aspects, another aim of my research work was the functionalization of the N-substituted pyrroles via organometallic route, using bromine/lithium exchange reaction. Various functional groups can be formed from brominated heteroaromatic compounds via this organometallic way, including the essential diphenylcarbinol moiety of the amino alcohol ligands. We observed that the product of the reaction of the organolithio pyrrole and benzophenone was not stable, it readily transformed to a conjugated system containing compound, namely to 5-ylidenepyrrrol-2(5H)-one derivatives. We intended to examine this transformation, and extend it to different N-substituted pyrroles and diverse carbonyl electrophile agents. In addition, we planned to investigate the selective functionalization of the endocyclic double bond of 5-ylidenepyrrrol-2(5H)-one derivatives. Besides the synthesis of a wide range of $\alpha,\beta$-unsaturated $\gamma$-lactam structures, our attention was raised to the application of this structural unit, for example its further transformation into potentially biological active compounds.

2. **Review of the literature**

2.1. **Amino alcohol catalyzed enantioselective reaction**

The amino acids are not only used as chiral building blocks in the synthesis, but also as chiral auxiliaries or chiral starting materials as well. The amino alcohols, which can be derived from amino acids by simple reduction, are one of the most common chiral ligands or ligand precursors of asymmetric catalysis. Ogun and Omi published more than 30 years ago that benzaldehyde (27) and diethylzinc undergo catalytic asymmetric reaction in the presence of catalytic amount of chiral amino alcohols (Scheme 1).\(^6\) When leucinol ((S)-29) was used in the model reaction the product ($R$)-1-phenylpropan-1-ol (28) was isolated with moderate enantioselectivity (49% ee). This determinative result influenced several research groups to study the addition reaction with different amino alcohol ligands to develop highly efficient systems.\(^7\)

Noyori and his research group tested a variety of β-amino alcohols for the activation of dialkylzinc.\textsuperscript{8} They observed that the efficiencies of the reactions increased 10 to 100-fold, when sterically hindered tertiary amino group containing amino alcohols were used compared to the primary or secondary analogues. The compound \textit{30} was found the optimal ligand, achieving 99% enantiomeric excess in case of several substituted aromatic aldehydes.

Mainly chirality centre containing amino alcohol ligands were reported in the literature. Besides these molecules, only a few examples of axial chiral ligands can be found, which can effectively catalyze the asymmetric addition (\textit{Scheme 2}). At first, Chan et al applied the atropisomeric \textit{43} ligand, but they achieved only a moderate selectivity (75% \textit{ee}).\textsuperscript{9} The first highly efficient non-C\textsubscript{2} symmetrical amino alcohol was \textit{44},\textsuperscript{10} which resulted similar enantiomeric ratio (99:1) as the classical β-amino alcohols. Another example is the \textit{45} binaphthyl derivative.\textsuperscript{11}

\textbf{2.2. Functionalization of pyrrole derivatives by organometallic route}

Shirley and his research group investigated the first time 1-methyl- and 1-phenylpyrrole metalation and subsequent conversion of organolithium intermediate to carboxylic acids. They also studied dimetalation (\textit{Scheme 3}). It was found that depending on the starting material 2,5-dicarboxylic acid (\textit{58}, 58\% yield) or a cyclic ketone (\textit{60}) were isolated.\textsuperscript{12}

The organometallic research group of Dr. Ferenc Faigl at the Department of Organic Chemistry and Technology, has carried out detailed research on regioselective mono- and dimetalation of different 1-arylpyrroles. Using these organometallic methods, selective functionalization of the pyrrole or the benzene ring can be achieved.

For example, in a previous work of the research group diphenylcarbinol moiety was successfully produced via organometallic way from 1-phenylpyrrole derivative. The α-position of the pyrrole ring and the orto-position of the benzene ring were metalated, and the dilithio intermediate was reacted with benzophenone. The resulting diol could be easily transformed to a benzoxazepine derivative with good yield by an acidic condition (silica gel) influenced water elimination. In the research group, functionalization of the 1-arylpyrroles have only been tested via metalation so far. Another convenient and highly selective organometallic method for the formation of organolithium compounds is the application of halogen/metal exchange reaction. Therefore it is a very good strategy for the preparation of new substituted compounds at various positions, in cases where the conventional metalation cannot be realized.

3. Experimental methods

The inert atmosphere was ensured by using Schlenk technique (continuous dry nitrogen flow) in organometallic and reduction reactions. Purification of the crude products was carried out by column-, flash- or preparative HPLC chromatographic methods, vacuum distillation or recrystallization. For the characterization of new compounds spectroscopic methods (1H, 13C, 19F NMR, HRMS, single-crystal X-ray diffractometric measurement) were used. The quantum chemical calculations were performed by Dr. Péter Ábrányi-Balogh and Dr. Zoltán Mucsi. The calculations were carried out by B3LYP-631g(d,p) (for H, C, N, O and F) and B3LYP-SDD-MDF10 (for

Scheme 3. Dimetalation of 1-methylpyrrole and 1-phenylpyrrole

\[ \text{HOOC} - \text{Py} - \text{COOH} \]

\[ \begin{align*}
1. \text{BuLi} & \quad 2. \text{CO}_2 \\
3. \text{H}_2\text{O}
\end{align*} \]

\[ \begin{align*}
\text{R}=\text{Me} & \quad \text{R}=\text{Ph}
\end{align*} \]

\[ \text{2} \]

\[ \begin{align*}
\text{N} & \quad \text{C}
\end{align*} \]

\[ \text{Me} \quad \text{Ph} \]

\[ \begin{align*}
\text{HOOC} - \text{Py} - \text{COOH} \quad \text{58}
\end{align*} \]

\[ \begin{align*}
\text{N} & \quad \text{R}
\end{align*} \]

\[ \begin{align*}
\text{CO} & \quad \text{2}
\end{align*} \]

\[ \text{59} \]

\[ \text{60} \]

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Zn) methods using the Gaussian 09 programme package. The solvent effect of hexane was taken into account by the calculations of the asymmetric model reactions and active catalyst molecule of the rotation and the bonding energy. Furthermore, by the mechanistic study of the formation of 5-ylidenepyrrol-2(5H)-on derivatives (76) the implicit solvent model was also taken into account (Polarizable Continuum Model, \( \varepsilon = 8.31 \), dichloromethane).

4. New scientific results

4.1. Synthesis and application of enantiomerically pure amino alcohols

During my PhD research work new, 1-phenylpyrrole backbone containing amino alcohols (13 example) were synthesized. In addition, tertiary amino derivatives (Scheme 4.) were tested as ligands in the enantioselective addition reaction of benzaldehyde and diethylzinc, yielding secondary alcohols which can be used as chiral building blocks for the synthesis of practically important chiral compounds.

The functions of the ligand structure were optimized to increase the asymmetric effect, and to find the best enantioselective ligand. We examined the relationship between the structures of the amino alcohols and the obtained enantioselectivities of the model reactions. In order to find optimal conditions for the reaction too, the effect of the temperature, reaction time and ligand/substrate ratio were studied circumstantially.

At first, a variety of amino groups were involved in the optimization of the functional groups of the ligand. The amino group with short and long alkyl chains and the sterically smaller part as the pyrrolidine ring were formed. Among these ligands, the best selectivity (82% \( ee \)) was achieved with \((R_a)-89a\) ligand in the reaction of benzaldehyde and diethylzinc. Thereafter we prepared ligands with primary hydroxyl group containing compounds \((R_a)-85a,b\), and electron withdrawing groups (trifluoromethyl) substituted diphenylcarbinol derivatives \((R_a)-89g-k\).
Amino alcohol | NR'R'' | R |
---|---|---|
(Ra)-85a | NMe₂ | H |
(Ra)-85b | morpholine | H |
(Ra)-89a | NMe₂ | Ph |
(Ra)-89b | NEt₂ | Ph |
(Ra)-89c | NBu₂ | Ph |
(Ra)-89d | pyrrolidine | Ph |
(Ra)-89e | HNβn | Ph |
(Ra)-89f | NHPr | Ph |
(Ra)-89g | NMe₂ | 3-CF₃-C₆H₄ |
(Ra)-89h | pyrrolidine | 3-CF₃-C₆H₄ |
(Ra)-89i | morpholine | 3-CF₃-C₆H₄ |
(Ra)-89j | NMe₂ | 3,5-(CF₃)₂-C₆H₃ |
(Ra)-89k | pyrrolidine | 3,5-(CF₃)₂-C₆H₃ |

**Scheme 4.** Synthesized amino alcohols

When the acidity of the hydroxyl group in (Ra)-89a ligand was increased by the insertion of electron withdrawing trifluoromethyl substituted phenyl groups (compounds (Ra)-89g,h,i,j,k), better asymmetric inductions (up 86% to 94% ee) were achieved. The most effective and widely applicable ligand was (Ra)-89j. A number of substrates (substituted aromatic aldehydes and cinnamaldehyde) were also tested to explore the potential of (Ra)-89j (Scheme 5.), as a result in most cases high enantiomeric excesses (up to 96%) were achieved.

![Scheme 5. Application of ligand (Ra)-89j in the model reaction](image)

27a-q (Ra)-28a-q (Ra)-89j

We were looking for correlations between the enantiomeric excess values of the products and the structures of the ligands. The electronic and steric properties of the amino alcohols were determined with the calculated and measured values of the proton dissociation constants (pKₐ) of the function groups, and with quantum chemical calculations of amino alcohol – zinc complex structure (bonding energy) and the enthalpy of the transition state of the enantioselective reaction.
4.2. Synthesis of brominated amino alcohols

Furthermore, a study on the bromination of the amino alcohols and their intermediates was also carried out, chosen the most efficient ligands from the regioisomeric groups ((R<sub>a</sub>)-93a and (R<sub>a</sub>)-89j, Scheme 6.) for our model compounds. A regioselectivity compared the halogenations (mono-, di-, tribromination) were also observed.

Scheme 6. The most efficient ligands of the two regioisomeric groups (Ar= 3,5-(CF<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>) and their intermediates which were examined in the bromination reaction.

In the case of the amide intermediates of (R<sub>a</sub>)-93a (namely: (R<sub>a</sub>)-96, 99), the monobromination was mainly influenced by the steric effect of the group situated at the ortho-position of the benzene ring (ester group – not regioselective, diphenylcarbinol moiety – β'-regioselective). According to previous experiments, bromination can occur at the β'-position in case of an electron withdrawing function containing pyrrole derivative at the α-position (for example: ester (R<sub>a</sub>)-82a). A bulky substituent located at the α-position of the pyrrole ring (for example substituted diarylcarbinol (R<sub>a</sub>)-88a), cause α'-selective bromination due to its electron donating properties.

In this route (reduction of the brominated amide-alcohol intermediates), further 4 novel chiral brominated amino alcohols were prepared (Scheme 7.). These compounds were also tested as ligands, and in three cases ((R<sub>a</sub>)-107, (S<sub>a</sub>)-109, 110) the asymmetric inductions were significantly larger (up to 97% ee) than those were observed for the halogenfree ligands. These results provide a good basis for the further research work on the binding of these compounds to a solid support. Thus, after utilization in the asymmetric reaction the new solid supported ligand could be recovered easily and economically, moreover it could be reused.
Scheme 7. The brominated amino alcohol ligands (Ar= 3,5-(CF$_3$)$_2$-C$_6$H$_3$)

4.3. Synthesis of 5-ylidenepyrrol-2(5H)-one derivatives

The functionalization of the 1-arylpyrrole was studied by bromine/lithium exchange reaction, too. In our previous work, the developed selective bromination process was extended to 12 N-substituted pyrrole (59a-m, Scheme 8). Transformation into different groups (carboxylic acid, secondary and tertiary alcohol moiety) containing derivatives was implemented via organometallic way. The monolithiation of the 2,5-dibromo-pyrroles provided 2-lithio-5-bromopyrrole intermediates which were reacted with benzophenone. However, the products (113a-m, Scheme 8) proved to be unstable, and spontaneously transformed into 5-ylidenepyrrol-2(5H)-ones (76a-m). The mechanism of the new transformation was proposed based on a detailed experimental research.

Scheme 8. Synthesis and organometallic transformation of α,α’-dibromo-pyrroles
Another interesting feature of the transformation is that the enantiopure brominated atropizomers (e.g. (Sₐ)-109, Scheme 7.) provided optically active 5-ylidenepyrrrol-2(5H)-ones.

Regioselective bromination methods were also developed for functionalization of the α,β-unsaturated γ-lactams (76a,g,l). Depending on the reaction path, the bromine atom was introduced at the 3- or 4-positions of the heterocyclic ring of 76 (products 116a,g,l and 119a,g,l), even 3,4-dibromo derivatives (120a,l) could be prepared in good yields (Scheme 9.).

![Chemical structures and reaction schemes](attachment:image)

**Scheme 9. Synthesis of brominated derivatives of 76**

Our aim was to explore the scope and limitations of the transformation. Therefore the organometallic reaction was carried out with 14 different carbonyl electrophiles (for example: substituted benzaldehydes, alkyl-phenyl-ketones, thienyl-phenyl-ketone and tricyclic ketones). Then the transformations of the obtained alcohol derivatives into the 5-ylidenepyrrrol-2(5H)-ones were studied.

We observed that the transformation is strongly depends on the structure of the oxo-compound. The structure of the forming carbocation is crucial, (it can be formed from the tertiary alcohol after protonation and water elimination). Depending on the adequate stability (delocalization) and the mesomeric structures of the carbocation a
hydroxide ion is able to attack the cation and transform it into the 5-ylidenepyrrrol-2(5H)-one. During these studies, thiophene ring containing compounds (127a,b, Scheme 10.) were also prepared from 111a. These molecules have multiple conjugated systems, which structural elements can be valuable for instance for the development of organic solar cells. The thiophene ring can be simply halogenated at the α'-position and the halogen atom can be used for further functionalization by cross-coupling reactions.

![Chemical structures](image)

**Scheme 10.** Practically useful compounds obtained from α,α'-dibromo-pyrroles

We dealt with further application of the 76 structure. The tricyclic quinolone derivatives (134a,i, Scheme 10.) were prepared from 76 via a few reaction steps. These compounds have similar structures to the antibacterial pefloxacin analogs. The bromine atom of 134i can be converted into various nitrogen containing rings (e.g., N-methyl-piperazine) by using coupling reactions. According to literature data, this part of the molecule is essential to the biological effect.

### 5. Theses

1. We prepared a series of new enantiopure atropisomeric 1-phenylpyrrrole skeleton containing amino alcohols in which diphenylcarbinol moiety was connected to the pyrrole ring and the aminomethyl group situated on the benzene ring. The synthesis were accomplished from (R)-methyl 1-[2-(methoxycarbonyl)-6-(trifluoromethyl)phenyl]-1H-pyrrol-2-carboxylate, taking advantage of the difference in the reactivity between the two ester functions. Absolute configurations of two intermediates and one amino alcohol were confirmed by single crystal X-ray diffraction measurements. [1, 2, 5]

2. First in the literature, the new bifunctional amino alcohols were used in the reaction of benzaldehyde and diethylzinc as catalyst ligands. [1, 2, 5] We elucidated relationship between the structures of the amino alcohols and the enantioselectivities of the model reactions by quantum chemical study, calculated and measured values of pKₐ and pKₐb.
3. We experimentally demonstrated that the best asymmetric induction can be achieved with \((R_a)-2\text{-bis}[(3,5\text{-bis}(\text{trifluoromethyl})\text{phenyl})\text{hydroxymethyl}]1\text{-}[2-(N,N\text{-dimethylcarbamoyl})6-(\text{trifluoromethyl})\text{phenyl}]1H\text{-pyrrole} (94\% ee, 92\% yield). It was proved that in the presence of this ligand the enantioselective reaction occurred smoothly and efficiently with benzaldehyde, 15 differently substituted aromatic aldehydes and cinnamaldehyde. Nearly quantitative yields (87–95\%) and good to excellent enantioselectivities (58%–96\% ee) were achieved in all cases. [1, 2, 5]

4. New, chiral, brominated amino alcohols were synthesized and proved that the additional halogen atom improved the asymmetric induction effect of the ligand in the reaction of benzaldehyde and diethylzinc (97\% ee).

5. We experimentally proved that our regioselective halogenation method (N-bromosuccinimide, N,N-dimethylformamide) which can be applied generally for \(\alpha,\alpha'\)-dibromination of N-substituted pyrroles result the dibrominated pyrroles in high yields and purities. The method was extended to 12 different (N-aryl and alkyl) pyrroles. [3, 4]

6. We invented and developed an efficient method for synthesis of the N-alkyl, aryl and unsubstituted 5-yldene5pyrrol-2(5H)-one derivatives, which are components of several known natural and/or biologically active compounds. Using this new method we prepared and characterized 12 new compounds, and we proposed a reaction mechanism for the formation of 5-yldene5pyrrol-2(5H)-ones. [3, 4]

7. We developed regioselective methods for mono- and dihalogenation of 5-yldene5pyrrol-2(5H)-one derivatives at the endocyclic double bond in the 3- and 4-positions. [3]

6. Application possibilities

According to the literature, the synthesized new optically active amino alcohols can be applied in several enantioselective reactions as bifunctional ligands or as organocatalysts. For one example, we tested amino alcohols in the enantioselective reaction of aromatic aldehydes and diethylzinc. The most effective and widely used ligand proved to be compound \((R_a)-89j\), that was tested with a wide range of substituted aldehydes. In most cases, secondary alcohols \((R)-28a-q\) were prepared in excellent
enantiomeric excess (91-96%) and nearly quantitative yield. These enantiopure alcohols can be used as chiral building blocks to produce enantiopure chiral compounds. [1, 2, 5]

During the investigation of 5-ylidenepyrrrol-2(5H)-one structure formation, we produced 127a.b compounds (Scheme 10). These molecules have multiple conjugated system, which may be valuable structural element during the further research of the group. The thiophene ring can be halogenated simply at the α'-position and bromo atom can be easily substituted by coupling reaction. One possible application of these compounds is in organic dye-sensitized solar cells, as connecting unit of donor and acceptor moiety. In addition, tricyclic quinolone carboxylic acid derivatives were prepared from 5-ylidenepyrrrol-2(5H)-one compounds, which may antibacterial activity, based on literature analogy.

7. Publications

7.1. Scientific publications related to the PhD Thesis


7.2. Additional scientific publications


7.3. Oral presentations


7.4. Poster presentations


