SYNTHESIS AND APPLICATION OF NEW ATROPISOMERIC COMPOUNDS

PhD Thesis

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1. Introduction

Development of an organometallic synthetic route for the preparation of a biologically active 4\(H\).6\(H\).pyrrolo-[1,2-a][4,1]benzoxazepine derivative initiated a new research project in our group with the aim of investigating organometallic reactions of 1-arylpyrroles.\(^1\) Detailed investigations on regioselective metalation possibilities of 1-(substituted phenyl)-1\(H\)-pyrroles were accomplished since that time. Fine tuning of the reaction conditions resulted in novel, highly regioselective mono- and dimetalation methods. For instance, simultaneous metalation of the pyrrole C\(\alpha\) and phenyl \textit{ortho} positions (followed by carboxylation) provided dicarboxylic acid derivatives. The 1-(6-carboxy-2-substituted phenyl)-1\(H\)-pyrrole-2-carboxylic acids exist in stable mirror image conformations, called atropisomers (a special case of chirality). The first enantiomerically pure dicarboxylic acid, which is among the model compounds of my thesis work, was prepared by consecutive dimetallation and carboxylation of 1-[2-(trifluoromethyl)phenyl]-1\(H\)-pyrrole followed by optical resolution.\(^2\)

Atropisomeric compounds are widely used in asymmetric synthesis as ligands or organocatalysts, and these research fields has emerged as hot topics in organic chemistry. The well-known BINOL\(^3\) and BINAP\(^4\) are among the most frequently used representatives of these type of compounds.

Numerous articles and reviews has appeared on the application of axially chiral C(aryl)-C(aryl) bond containing biaryls in enantioselective catalytic reactions. However, no examples could be find in the literature on any application of chiral 1-aryl-1\(H\)-pyrrole derivatives as enantioselective catalysts or ligands.

The primary aim of this thesis work was to elaborate efficient methods for the synthesis of enantiomerically pure, new atropisomeric amino alcohol derivatives having 1-phenyl-1\(H\)-pyrrole backbone. Catalytic enantioselective test reactions were also planned to demonstrate the applicability of the new amino alcohols as chiral ligands. Optical resolution via diastereoisomeric salt formation had to develop for separation of the enantiomers of chiral synthetic intermediates. We wished to study the new atropisomeric dicarboxylic acids as resolving agents, too.

Furthermore, we wanted to investigate regioselective bromination possibilities of 1-[2-(trifluoromethyl)phenyl]-1\(H\)-pyrrole and several derivatives, together with further organometallic transformation of the halogenated products.

\(^1\) Schlooser, M.; Faigl, F. \textit{Tetrahedron} 1994, 50, 2071.
2. Literature background

Steric arrangement of compounds has crucial role in the formation of molecular interactions. Receptor-drug interactions are illustrative examples of that fact, because the most part of the biological targets are chiral. In these cases, the different stereoisomers of a compound may cause diverse biological responses. That observation has initiated numerous research programs in order to find efficient synthetic methods for preparation of the useful pure enantiomer of a target compound. Such expectation resulted in the development of the basic methods of asymmetric synthesis. In the last 50 years dozens of chiral organometallic complexes and organocatalysts (chiral organic molecules without coordinated metal atom) have been developed and applied successfully.

The phrase „enantioselective catalysis” denote chemical syntheses in the presence of substoichiometric amount of chiral additives. One can classify these types of chemical transformations from different points of view. Depending on the fashion of asymmetric induction, asymmetric catalysis starting from prochiral compounds, kinetic resolution and dynamic kinetic resolution can be mentioned. Asymmetric catalytic reactions are usually categorized according to the type of the catalyst. It can be an enzyme, organometallic compound or metal free organocatalyst.

Chiral amino alcohol type compounds (e.g. DAIB, 1) may be used in enantioselective addition reactions of aromatic aldehydes and diehtylzinc to produce optically active l-arylpropanols. In these reactions the in situ formed aminozincalkoxide catalyst governs the highly enantioselective addition reaction (Scheme 1).

![Scheme 1. Synthesis of optically active 1-phenyl-1-propanol (10)](attachment:image)

Numerous chiral amino alcohols were applied for enantioselective synthesis of optically active secondary alcohols. There are chiral ligands with biaryl backbone and asymmetric center

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7 A tézisfüzetben szereplő végyületeket a doktori dolgozat végyületszámozását követve jelöltem.
containing N,N-dialkyl-norefriende, proline and β-pinine derivatives.

Functionalization of N-substituted pyrroles can easily be accomplished with different electrophile reagents but the usually applied acidic conditions may cause partial degradation of the pyrrole ring. On the other hand, the electronic and steric effects of the pyrrole substituents strongly influence the position of the next substitution. Application of organolithium reagents may be a convenient solution of these problems providing efficient and regioselective routes to the target compounds.

Shirley published his first results on the lithiation of 1-phenyl-1H-pyrrole (20) in the middle of the last century, but, in the last 20 years, the most achievements in the metalation of substituted 1-phenyl-1H-pyrroles was achieved and published by the research group of our department. Mechanism of the lithiation of 1-phenyl-1H-pyrrole (20) was investigated by Schlosser and Faigl. On the basis of their experimental data they postulated that dilithiation of 20 is a kinetically controlled process. Formation of C2,C2'-dilithio-1-phenyl-1H-pyrrole was described by Cheesman és Greenberg, but efficient (80% yield) preparation of the C2,C2'-dicarboxylic acids were accomplished first by Schlosser and Faigl.

Numerous new dicarboxylic acids were prepared during investigation of the metalation possibilities of 1-(substituted phenyl)-1H-pyrroles (20, R = CF3, OMe, Cl, Me, Et, Ph). One among them is my model compound (35) which was prepared by consecutive superbase (LIC-KOR) metalation carboxylation reaction sequence (Scheme 2).

Organometallic 1-aryl-1H-pyrrole derivatives can also be prepared via halogen/metal interconversion between halogenated 1-aryl-1H-pyrroles and organometallic reagents.

Scheme 2. Synthesis of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid (35)

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Bromination of 1-phenyl-1\textit{H}-pyrrole (20) was investigated several decades ago but that time the researchers achieved only moderate stereoselectivities.\textsuperscript{15}

The first total synthesis of Lamerralines, pentacyclic pyrrolic alkaloids that have been isolated from various marine organisms, was published in 2011. Bromination of \textit{N}-Boc-pyrrole was among the key steps of the synthesis,\textsuperscript{16} and it showed up the practical importance of highly regioselective bromination methods of pyrrole derivatives in the pharmaceutical research and development.

Investigation of the dicarboxylic acid derivatives of 1-(2-substituted phenyl)-1\textit{H}-pyrroles is an interesting part of the research project of our group because these compounds exist as stereochemically stable (until 80–150 °C) mixtures of atropisomers. Development of new resolution methods is a permanent project at our department since several decades.\textsuperscript{17} Due to the special knowledge and experience of the group, several atropisomeric dicarboxylic acids were resolved via diastereoisomeric salt formation using optically active 1-phenyl-ethylamine resolving agent under different conditions.\textsuperscript{18,19} The first optically active member of my model compounds was prepared by the optical resolution of racemic 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1\textit{H}-pyrrole-2-carboxylic acid (35).\textsuperscript{2}

3. Experimental methods

Conventional methods of preparative organic chemistry were used in synthesis. Schlenk technique (continuous dry nitrogen or argon flow, Schlenk flasks) was applied in case of organometallic reactions. The reactions were monitored by thin layer chromatography (TLC). Purification of the crude products were carried out by column- or flash (CombiFlash Rf) chromatographic methods, recrystallizations or fractionated distillations.

Purity of the products and intermediates were controlled by TLC, and/or \textsuperscript{19}F NMR spectroscopy, gas chromatography, determination of specific optical rotatory power and melting points. Enantiomeric excess of the optically active compounds was determined by high performance liquid chromatography or gas chromatography using chiral stationary phase containing columns.

\textsuperscript{17}Optikai izomerek elöállítása; Fogassy, E.; Ács, M.; Tőke, L., Eds.; Akadémiai Kiadó: Budapest, 1987; Vol. 65.
\textsuperscript{18}Faigl, F.; Vas-Feldhoffer, B.; Kudar, V.; Czugler, M.; Pál, K.; Kubinyi, M. \textit{Chirality} 2009, 21, 905.
The new compounds were identified by spectroscopic methods (IR, $^1$H, $^{13}$C and $^{19}$F NMR, MS, HRMS) and, in some cases, by single crystal diffractometric measurements. An InsightII® MOPAC program package was used for semiempirical calculations.

4. New scientific results

Major new results of my research work are as follows:

An improved method was developed using para-toluenesulfonic acid catalyst in toluene instead of acetic acid (catalyst and solvent) in order to prepare the 1-aryl-1$H$-pyrrole type starting materials (20 and 34) with good yields [3]. Then, the atropisomeric dicarboxylic acids 35$^2$ (Scheme 2.) and 46 (Scheme 3.) were prepared via consecutive directed dimetalation carboxylation reactions. The optical isomers of these dicarboxylic acids were separated via diastereoisomeric salt formation and the absolute configuration of the new (+)-(S)-46 diacid was determined by combined application of CD spectroscopy and quantum chemical calculations (Schemes 4. and 5.). [1, 2]

![Scheme 3](image-url)

Scheme 3. Synthesis of 4,4,6,6-tetramethyl-4$H,6$H-pyrrolo[1,2-a][4,1]benzoxazepine-1,10-dicarboxylic acid (46)

![Scheme 4](image-url)

Scheme 4. Optical resolution of 4,4,6,6-tetramethyl-4$H,6$H-pyrrolo[1,2-a][4,1]benzoxazepine-1,10-dicarboxylic acid (46)
Scheme 5. Optical resolution of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid (35) using new resolving agent

A new resolution process was developed for 35 as dicarboxylic acid using (R)-42 as new resolving agent and the optimum parameters of the diastereoisomeric salt crystallization was experimentally determined. It was found that the salt contains the practically pure diacid enantiomer ((S)-35) after short (2–4 hours) crystallization time (Scheme 5.), but the enantiomer content of the salt gradually decreases during longer crystallization. Consequently, the efficiency of the resolution falls down during longer periode of time and the salt contained only a small excess (ee 4.7%) of (S)-35 after 330 hours crystallization (Figure 1.).

Figure 1. Effect of the duration of crystallization on the (S)-35 enantiomer content of (S)-35·(R)-42 diastereoisomeric salt

Series of experiments were carried out to find application possibilities of (S)-35 as resolving agent. Good results were obtained during the reverse resolution of racemic 42. Furthermore, highly efficient thermodynamically controlled second order asymmetric transformation of 42 was developed with (S)-35. This new asymmetric transformation was accomplished in a toluene/acetone/water mixture in which practically the whole amount (92%) of racemic 42 was transformed into (R)-42 enantiomer (ee 95%, Scheme 6.). [2]
Scheme 6. Second order asymmetric transformation of (RS)-42 with (S)-35

Until now, the research group have used only mono- and dimetalation reactions for functionalization of 1-aryl-1H-pyrroles (e.g. 34). In the present thesis a new functionalization method has been developed using sequential bromination and halogen/metal exchange reactions. Optimal conditions of the selective brominations were experimentally determined. It was found, that the most selective reactions can be carried out with N-bromosuccinimide (NBS) in dimethylformamide. Under such conditions, selective bromination of the pyrrole Cα' or Cβ' positions were achieved (Scheme 7.). Further bromination of 34 and its 2-bromo derivative provided Cα' brominated product, exclusively. However, clean Cβ' bromination of the pyrrole moiety was observed when the heteroaromatic ring contained an electron withdrawing substituent in Cα (pyrrole C2) position. The positions of the bromine atoms were confirmed by single crystal X-ray diffraction measurements. The brominated products were transformed into new carboxylic acid derivatives via bromine/lithium exchange reactions (Scheme 7.).

Scheme 7. Selective Cα' and Cβ' bromination of the Cα,ortho-substituted 1-[2-(trifluoromethyl)phenyl]-1H-pyrrole derivatives, and preparation of new carboxylic acids via bromine/lithium exchange reactions

Combination of the new, regioselective bromination methods and organometallic reactions let us to prepare the Cα' (66) and Cβ' (54) brominated regioisomers of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid (35). Further bromine/lithium exchange reactions or other C-C coupling reactions can be used for diverse functionalization of the pyrrole ring. Thus, the electronic and steric behaviours of the amino alcohol type target compounds can
easily be modified in order to provide stereochemically more stable and more active new catalysts and ligands. [3]

New, efficient methods were developed for the synthesis of asymmetrically substituted derivatives via selective monoesterification of the carboxylic groups of (S)-35. Starting from (S)-49, new amino alcohol type products were prepared with primary- and tertiary-alcohol moieties ((S)-75a-f, (S)-77a-c). Special diastereoselective synthetic routes were also developed for preparation of both clean diastereoisomers of the secondary hydroxyl group containing products ((S,K)-83, (S,A)-83, Scheme 8.). [4]

![Scheme 8. Synthesis of the optically active amino alcohols (S)-75a-f, (S)-77a-c, (S,K)-83 and (S,A)-83](image)

The new optically active amino alcohols were tested as catalyst ligands in the addition reaction of diethylzinc and benzaldehyde. The effect of the structural differences of the amino alcohols on the rate and enantioselectivity of the reaction was investigated, then preparation of (S)-1-phenyl-1-propanol ((S)-10) was optimized. The best results were achieved in the presence of 1 mol% of (S)-77a: the desired product ((S)-10) was obtained with 95% yield and 96% ee (Scheme 9.).
Scheme 9. Synthesis of \((S)\)-10 in the presence of 1 mol% of \((S)\)-77a

The highly enantioselective method was extended to the addition reactions of numerous substituted aromatic aldehydes and diethylzinc (ee 66–96%, Table 1.).

Table 1. Preparation of 1-phenyl-1-propanol derivatives in the presence of \((S)\)-77a\(^a\)

<table>
<thead>
<tr>
<th>No.</th>
<th>Aldehyde</th>
<th>Product</th>
<th>ee(^b) (%)</th>
<th>Yield(^c) (%)</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>86</td>
<td>85</td>
<td>93</td>
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<tr>
<td>2</td>
<td></td>
<td>87</td>
<td>95</td>
<td>93</td>
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<td>3</td>
<td></td>
<td>88</td>
<td>94</td>
<td>80</td>
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<tr>
<td>4(^d)</td>
<td></td>
<td>89</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>90</td>
<td>66</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were carried out with 2 equivalent of \(\text{Et}_2\text{Zn}\) (1 M hexane solution) at 0 °C, in the presence of 1 mol% of \((S)\)-77a for 18 hours.

\(^b\) Ee was determined by GC using BETA-DEXMP 120 capillary column.

\(^c\) Preparative yields.

\(^d\) The reaction was carried out with the addition of 20% toluene at 25 °C. Ee was determined by HPLC equipped with chiral column (Lux Cellulose-1).

The above reactions show the efficiency of the new ligand ((S)-77a): 1 mol% of this compound was enough for practically complete conversion (>90%) of the aldehydes and for production of the 1-arylpropanol derivatives in high enantiomeric purities. Consequently, the first, efficient member of a new, atropisomeric, 1-aryl-1\(^H\)-pyrrole type family of chiral catalyst precursors was synthesised and tested in highly enantioselective addition reactions.
5. Thesis

1. We proved that the regioselective Cα,ortho-dimetalation of 4,4,6,6-tetramethyl-4H,6H-pirrolo[1,2-a][4,1]benzoxazepine can be effectively accomplished using LIC-KOR superbse. We prepared the unpublished 4,4,6,6-tetramethyl-4H,6H-pirrolo[1,2-a][4,1]benzoxazepine-1,10-dicarboxylic acid through metalation followed by the reaction with carbon dioxide. We found that the optically stable isomers of the dicarboxylic acid can be separated by diastereoisomeric salt forming resolution, and we determined the absolute configurations of the pure enantiomers as well. [1]

2. We reported a new method for the preparation of the enantiopure optical isomers of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid using a new resolving agent methyl (R)-2-phenylglycinate. This process was found to be four times more efficient than the previously reported method. We established that the optically active 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid can be used as resolving agent, too. We accomplished the effective separation of the enantiomers of the racemic methyl 2-phenylglycinate (reciprocal resolution). [2]

3. We proved that the optically active 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid is stereochemically stable under the suitable conditions for the racemisation of the enantiomers of methyl 2-phenylglycinate. Based on this observation we elaborated a new method for the preparation of enantiopure methyl 2-phenylglycinate by second order asymmetric transformation. [2]

4. Highly selective method was developed for Cα' and Cβ' bromination of the broad scope of Cα−, ortho-disubstituted 1-[2-(trifluoromethyl)phenyl]-1H-pyrrole derivatives. We prepared several new products through halogen-metal exchange reactions from these brominated compounds. [3]

5. Observing the different reactivity of the carboxylic groups of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylic acid, new synthetic routes were elaborated for the asymmetric functionalisation of the pyrrole and the phenyl rings. Novel, highly selective – among these diastereoselective – reactions were performed to prepare the first examples of the primary-, secondary- and tertiary-alcohol function containing atropisomeric amines of the 1-aryl-1H-pyrrole family. [4]
6. We proved that the prepared new enatiopure amino alcohols can be applied as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde. [4] Investigating these amino alcohols in the model reaction of benzaldehyde we showed that \(N,N\)-diethyl-(S)-2-aminomethyl-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-\(1H\)-pyrrole is the first efficient ligand among the syntheised atropisomeric 1-aryl-1\(H\)-pyrrole derivatives. We proved that this compound can be applied efficiently in 1 mol% too. The broad scope of aromatic aldehydes react with diethylzinc nearly quantitatively, resulting in good to high enantiomeric purity (\(ee\) 66–96%) in the presence of this amino alcohol.

6. Application possibilities

Atropisomeric (S)-35 dicarboxylic acid may be used as resolving agent and it can be used in the second order asymmetric transformation of methyl 2-phenylglycinate. [2]

The developed organometallic transformations of the syntheised new bromo derivatives can be used to introduce diverse groups into the molecules (instead of carboxylic functions). Consequently, these synthetic methods may be used in the preparation of practically important, multifunctionalized 1-phenyl-1\(H\)-pyrrole derivatives (active pharmaceutical ingredients, chiral ligands or organocatalysts). [3]

The prepared new, amino alcohol type atropisomeric 1-phenyl-1\(H\)-pyrrole derivatives (e.g. (S)-77a) can be used in the synthesis of optically active 1-arylpropanols. [4] These compounds probably catalyse the addition reactions of other organozinc reagents to aromatic aldehydes and can be used in other known enantioselective reactions, in which amino alcohols can be used as catalysts.

7. Publications

7.1. Papers in periodicals


### 7.2. Book chapter


### 7.3. Proceedings


### 7.4. Lectures


