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MECHANOCHEMICAL SYNTHESIS OF FREE- BASE AND METAL CORROLES

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Chemistry and Chemical Technology

SWORN DECLARATION

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Abstract

This master thesis describes the two-step, solventless, mechanochemical synthesis of H₃TpFPC, CuTpFPC, H₃tBuPhC, Cu^tBuPhC and 5-ptBuPhiC. The described method consists of two steps. First, condensation of aldehyde and pyrrole in presence of an acid catalyst was carried out in the ball mill, in which the chemical reaction was promoted by input of mechanical energy. In the second step oxidation was performed in the solution in presence of oxidative agent.

This provides several advantages over synthesis of free-base and metal corroles in solution, such as: reduction of reaction time, elimination of undesirable organic solvents and no need for an additional extraction step. Additionally, it was shown, that the solvent used for oxidation, can be completely eliminated using the ball mill. By performing the direct synthesis of metal corroles, the time and solvent consuming purification was improved. Only one column is needed for the chromatography step, instead of two to three, independent of the corrole type.

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1. Aims and objectives

The aim of this work was the mechanochemical synthesis of free-base and metal corroles in a ball mill. The main challenges were the optimization of the reaction conditions in order to achieve high product yields, up-scaling of the corrole synthesis and simplification of the whole procedure for corrole synthesis.

The objectives of this master thesis are:

- synthesis of Cu-5,10,15-tris(pentafluorophenyl)corrole
- optimization of the 5,10,15-tris(pentafluorophenyl)corrole synthesis
- optimization and up-scaling of the 5,10,15-tris(4-*tert*-butylphenyl)corrole synthesis
- synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole including oxidation in a ball mill
- synthesis of Cu-5,10,15-tris(4-*tert*-butylphenyl)corrole
- synthesis of Mn-5,10,15-tris(4-*tert*-butylphenyl)corrole

2. Theoretical background

2.1. Corroles - tetrapyrrolic systems

Tetrapyrrolic systems are macrocyclic substances consisting of four pyrrole rings, connected together by methine bridges on α positions. Structurally similar porphyrins and corrins are the most important examples of tetrapyrrolic systems. Corrins are characterized by the lack of one carbon atom at the 20th position. Instead of one methine bridge, direct pyrrole-pyrrole bond is present. Corroles share the carbon skeleton with corrins, but possess more unsaturated bonds. Both, corroles and porphyrins are 18π -electron aromatic systems and therefore share similar chemical and photophysical properties. However, the number of the protons at the inner core of corroles and porphyrins is different. The trianionic nature of corroles enables the stabilization of higher oxidation states of transition metal ions, which would not be possible in the case of twoanionic porphyrins. This interesting property allows metalcorroles to be applied as catalysts in various processes. [1–3]

Figure 1: Chemical structure and numeration of porphyrin, corrole and corrin. *Meso*-positions are labelled red and the β -positions - blue. [4]

Numeration is derived from the porphyrin and applies to all compounds despite the lack of one carbon in corrole and corrin structure, so that the numeration of nitrogen atoms remains identical. Carbon atoms of the pyrrole rings (1, 4, 6, 9, 11, 14, 16 and 19) bonded directly to the nitrogen atoms are α -positions and the remaining carbon atoms (2, 3, 7, 8, 12, 13, 17, 18) are β -positions. The carbon atoms 5, 10, 15 and 20 are called *meso*-positions. Structures of all substances together with numeration are shown in Figure 1. [4,5]

Nomenclature of porphyrins is depending on the substitution pattern on *meso*-positions. If the substituents on all positions are the same, they are referred to as A_4 -porphyrins. If two different substituents are present, two different patterns exist – *cis*- A_2B_2 - and *trans*- A_2B_2 -porphyrins. If all substituents are different, the pattern ABCD is used. The same rule applies to corroles, except for the fact, that corroles have one substituent less. Structural representation of these compounds is shown in Figure 2. In this master thesis only A_3 -corroles are of interest. [6,7]

Figure 2: Nomenclature of *meso*-substituted corroles and porphyrins. [6]

As mentioned before, both porphyrins and corroles are 18π -electron aromatic systems. They follow the Hückel's rule of aromaticity, which says, that in presence of $4n+2$ cyclic conjugated π -electrons, a stable aromatic substance is formed. According to the physical data obtained by Sondheimers et al.[8] structural aromaticity of porphyrin or corrole can be represented by multiple-bridged aromatic [18]-annulene system, shown in Figure 3. However, the presence of imino- and ethylidene bridges, donating additional free lone pairs to the system, hinders the complete understanding of the conjugation pathway of porphyrinoids. [9]

Figure 3: π -electron system of [18]-annulene, corrole and porphyrin labelled by red bonds. ^[9]

Tetrapyrrolic systems are the most common pigments occurring in nature. Their derivatives play a vital role in living organisms. The following examples are shown in Figure 4. The most known example can be hemoglobin – a protein complex of iron, responsible for the transport of oxygen and carbon dioxide in the circulatory system. Green pigment present in plants and some bacteria is referred to as chlorophyll. This complex of chlorin (reduced form of porphyrin) and magnesium ion is involved in the photosynthesis process and helps to store light energy in the form of hydrocarbons. Corrole systems are not found in nature. Structurally the closest substance to corrin is present in cobalamin, also known as vitamin B₁₂. ^[10]

Figure 4: Representatives of natural occurring tetrapyrrole systems. ^[10]

2.2. Corrole synthesis – evolution, upscaling and mechanism

2.2.1. First corrole synthesis

Inspired by the naturally occurring corrin macrocycle in Vitamin B₁₂, Johnson and Kay started to conduct research on corrole synthesis. The first two synthesis approaches are dated to 1965 and include the condensation of dipyrromethane- and pyrrole-derivatives in methanol in presence of hydrobromic acid. In the next step, the received intermediate product 1, 19-dideoxobiladien-ac-hydrobromide was oxidized to the corresponding corrole by irradiation with a 200 W tungsten lamp. The reaction scheme is shown below. [4,11]

Scheme 1: Reaction scheme of first corrole synthesis. [11]

Moreover, the same group published the first synthesis of metal corrole. Moderately stable nickel and copper corroles were obtained by adding Ni and Cu cations to a solution of 1, 19-dideoxobiladien-ac-hydrobromide followed by irradiating with tungsten lamp or directly adding them to the corrole-solution. The reaction of a free-base corrole with cobalt acetate in pyridine, led to the formation of a cobalt corrole dipyridyl complex. This template synthesis became the main way of corrole synthesis for the next two decades. Examples of metal corroles are shown in Figure 5. [11]

Figure 5: Metal corroles synthesized by Johnson and Kay. [11]

2.2.2. One pot synthesis of *meso*-substituted corroles

Direct synthesis of *meso*-substituted corroles from aldehyde and pyrrole derivatives was published in 1999 by two independent research groups led by Gross and Paolesse. Gross and his coworkers modified Lindsey's method used for preparation of porphyrin. This synthesis consists of two steps: condensation of pentafluorobenzaldehyde with pyrrole on aluminium oxide as solid support, followed by oxidation in dichloromethane (DCM) after addition of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). 5,10,15-tris(pentafluorophenyl)corrole (H₃TpFPC) was the isolated product with 11 % yield. The same group also tried to synthesize corroles starting from aldehydes with different reactivity. 5,10,15-tri(2,6-difluorophenyl)corrole was obtained in a yield of 6 %, whereby in the reaction between pyrrole and 3,5-dichloro- and 2,6-dichlorobenzaldehydes no product was obtained. Closer investigation of the reaction conditions led to the conclusion that during the condensation step, acid as a catalyst is required. Due to its high reactivity, pentafluorobenzaldehyde undergoes autoxidation to the corresponding carbonic acid relatively fast when exposed to air. Formation of the acid is additionally accelerated by traces of benzyl alcohol. The synthesis of H₃TpFPC was possible, due to pentafluorobenzoic acid present in the educt. The reason, why the corrole synthesis from 3,5-dichloro- and 2,6-dichlorobenzaldehydes failed, was the low strength of the corresponding benzoic acids. The reaction scheme of the H₃TpFPC synthesis is shown below. [4,12,13]

Scheme 2: First solvent-free synthesis of H₃TpFPC.[4]

The second group of researchers led by Paolesse improved the Rothemund synthesis of porphyrins in order to achieve higher yield of corrole. The reaction was carried out under reflux with acetic acid acting as a solvent and catalyst. The ratio between aldehyde to pyrrole was changed to 1:3 to reduce the formation of byproducts, mainly porphyrin. The product 5,10,15-Triphenylcorrole was isolated in a yield of 6 %. Reaction scheme of this reaction is shown below. ^[4,14]

Scheme 3: Modified Rothemund reaction carried out by Paolesse.^[14]

In the year 2002, a group led by Gryko published an article describing improved synthesis of A₃- and A₂B-corroles. The main aim of their work was to maximize the formation of bilane, which is difficult, since the reactivity of the condensation products is increasing with their length and formation of oligomers is favored. The second problem was the different reactivity of various aldehydes, making it hard to achieve the same yields for all types of aldehydes. Optimized reaction conditions for three different sets of aldehydes were developed: very reactive, moderately reactive and sterically hindered, as shown in Table 1. Trifluoroacetic acid (TFA) was used as catalyst during the condensation and the oxidation step was carried out in DCM in presence of DDQ. The highest yield of corrole formation was 17 % for highly reactive aldehydes, 13 % for moderately reactive and 8 % for sterically hindered. Another advantage of this method was almost complete prevention of porphyrin formation. ^[4,15,16]

Table 1: Optimized reaction conditions for A₃-corroles from different aldehydes.^[15]

Entry	Type of aldehyde	TFA/mmol : ald./mmol	Pyrrole/mmol : ald./mmol	Time of acid catalyzed step	DCM/mL per mmol of ald.	DDQ/mmol : ald./mmol
1	Highly reactive	0.012	1.5	10 min	10 mL	1.2
2	Sterically hindered	0.210	5	16 h	10 mL	1
3	Moderately reactive	0.023	3	1 h	10 mL	1

2.2.3. Synthesis of *meso*-substituted corroles in water-methanol system

The biggest improvement in the synthesis of *meso*-substituted corroles was the method published by Gryko and Koszarna in 2006. Based on the work of Kral and coworkers describing synthesis of dipyrromethanes, they increased the yield of formed bilane. The synthesis consists of two steps. In the first step, the reaction is carried out in a mixture of water and methanol in presence of HCl as catalyst. They used the fact that the solubility of pyrrole and aldehyde, dipyrromethane and tripyrromethane in water is high, whereas the solubility of the condensation products with longer chains is lower. The ratio between water and methanol was set exactly to the point at which bilane precipitates in the solution. In an ideal case it could be filtered from the solution, but usually extraction with an organic phase is required. The second step - oxidation, is performed in organic phase (usually chloroform) with a mild oxidative agent - tetrachlor-*p*-benzoquinone (*p*-chloranil). The reaction time is longer than in case of DDQ, but higher yield could be achieved. The ratio of pyrrole to benzaldehyde was reduced to 2:1. Their concentrations in the solvent remain relatively low – about 25 mmol of pyrrole per liter of solvent. Since large amounts of solvent are required for the preparative synthesis of corrole, the group tried to increase the concentration of the starting materials. While two-fold increase of the concentration did not cause any changes, further increase led to reduced corrole yield. The highest yield obtained by this method was at 32 % for 5,10,15-trisphenylcorrole. Using this method corroles with strongly donating groups could be synthesized for the first time. The reaction scheme is shown below. [4,17,18]

Scheme 4: Reaction scheme of the bilane condensation in water-methanol system followed by the oxidation in CHCl₃.^[18]

2.2.4. Upscaling of the corrole synthesis

As mentioned before, the corrole synthesis in water-methanol system requires large amounts of solvent. Additionally, it is not suitable for all type of corroles, for example H₃TpFPC cannot be obtained *via* this method. An article published by Gryko in 2002 describes this procedure only for small-scale corrole preparation. Without significantly decreasing the yield, a batch of maximum 15 mmol of the highly reactive aldehyde was possible, resulting in 630 mg of corrole. Further studies of the H₃TpFPC synthesis carried out by the researchers (Grubbs, Gray and Virgil) indicated that a large-scale synthesis of the corrole is possible. The purpose of their research was to achieve better control of the condensation and oxidation steps. They investigated the influence of different conditions like temperature, catalyst amount, pyrrole to aldehyde ratio and reaction concentration, on the formation of intermediates during the oligomerization. Separation of the substances was performed using preparative HPLC and characterization was done by NMR- and Mass-Spectroscopy. The researchers proved, that the synthesis of H₃TpFPC is possible to carry out on a bigger scale. After a series of tests, the mechanism of condensation as well as the optimal reaction conditions could be presented. Under optimized reaction conditions they were able to synthesize 4.58 g of H₃TpFPC starting from 20 g of pentafluorobenzaldehyde. A total yield of 17 % was achieved by keeping the temperature of the reaction mixture below 15 °C, since the reaction is exothermic and uncontrollable in large-scale conditions. ^[15,16]

2.2.5. Mechanism of the corrole synthesis

The reaction between aldehyde and pyrrole follows the mechanism of electrophilic aromatic substitution. In the first step, the aldehyde group is protonated. The positively charged group is activated towards nucleophilic pyrrole and a new C-C bond is formed. In the next step, the hydroxy group is protonated and eliminated in the form of water. The created carbeniumion reacts with the second molecule of pyrrole to yield dipyrromethane. The formation of products during condensation is dependent on the acid strength and concentration, ratio of pyrrole to aldehyde and reaction time. The reactivity of the condensation products increases with their length, because of their higher electron density. Therefore, formation of longer oligomers is favored, when the reaction is not kept under control. The oxidation mechanism is unknown. According to Blumenfeld et al. the formation of corrole takes place immediately after addition of DDQ and accumulation of partially oxidized species is not present. [4,16,19–21]

Scheme 5: Reaction mechanism of the corrole synthesis.

2.3. Metalation of corroles

Similar to porphyrins, corroles are able to stabilize metal ions at the inner core. However, their properties are slightly different due to the number of protons and cavity size. Corroles are characterized by more anionic nature and therefore are able to stabilize higher oxidation states of metals. The first attempts to obtain metal corroles were carried out with salts of Fe, Mn, Co and Cu due to their chemical accessibility. They were synthesized in a simple reaction of halides or acetates and free-base corrole with or without input of thermal energy. The purification was done by column chromatography. Further developments in this research field led to the creation of a “periodic table of corroles” highlighting all possible elements, which have been successfully coordinated with corroles. It includes group 1, 4 – 15, lanthanoid and actinoid metal ions. However, the most relevant elements for this master thesis were copper and manganese. [1–3]

2.3.1. Copper-corroles

The synthesis of copper *meso*-triarylcorrole complexes is usually carried out in pyridine or tetrahydrofuran (THF) at room temperature with $\text{Cu}(\text{OAc})_2$. The yield of this synthesis is relatively high with amounts of up to 85 %. Determination of the oxidation state of copper in complex was troublesome. Until 1997, copper octaalkylcorroles have been considered as complexes of two corrole ligands and copper (II) in the center. In the same year, the group of Will et al. proposed a new representation of the complex – a fully deprotonated, square-planar coordinated corrole ring with the copper ion in the center. According to their studies a rapid equilibrium between diamagnetic Cu (III) in ground state and paramagnetic (high energy) radical cation of Cu (II) in triplet state exists. The equilibrium between the two proposed structures is shown on the next page. In 2007 the group of Alemayehu et al. demonstrated rare interaction between the d-orbital of copper and the π -orbital of the ligand, resulting in non-planar distortion of the complex. This complex was described as a Cu-corrole radical cation with electronic structure $\text{Cu}^{\text{(II)}}\text{-corrole}^{\cdot-}$. According to computational studies of Lemon et al. in 2016, copper corroles are best expressed as antiferromagnetically coupled, ground state Cu(II) corrole radical cations. It has also been shown, that one-electron oxidations and reductions are dependent on ligand and the oxidation state of copper is changing according to this redox process. [1,11,22–26]

Scheme 6: Structural representation of the copper corrole complex in an equilibrium.^[23]

Due to interesting properties of copper corroles, they are applied as catalysts in hydrogen evolution reactions, water oxidation and in medicine as a drug to prevent human cytomegalovirus infection. The group of Lei et al. examined catalytic properties of different corroles in the hydrogen evolution reaction. The best results were achieved with 5,15-pentafluorophenyl-10-(4-nitrophenyl)corrole due to presence of strong electron-withdrawing groups (-F and -NO₂). The experiment was carried out in acetonitrile and trifluoroacetic acid served as proton source. The electrocatalytic properties of the copper corrole-complex remained unchanged in highly concentrated acid solution. ^[27–31]

2.3.2. Manganese-corroles

Manganese plays a very important role in the nature, it catalyzes production of molecular oxygen from water. Among other d-block elements, manganese is characterized by a high number of oxidation states. The most stable Mn²⁺ species is in its behavior similar to Group 2 elements: hardly forms complexes, owns low redox activity and can be well adsorbed by cells. It can be oxidized to higher states +3, +4 or even +5, which are strongly interacting with oxygen species, only in presence of appropriate ligands. These manganese corroles find main application as catalysts in ring opening polymerization reactions, for example polymerization of epoxides and copolymerization with carbon dioxide even at low temperatures. Moreover, Mn(III) species can be easily oxidized to Mn(V)-oxo corrole complex with an oxidative agent, for example iodosobenzene. This compound can be successfully applied in a wide range of oxygen atom transfer reactions and reduction of oxygen and carbon dioxide. The synthesis of manganese *meso*-triarylcorroles is carried out by the reaction of free-base corrole and Mn(OAc)₂·4H₂O under reflux in dimethylformamide (DMF). The reaction is characterized by high yield – up to 91 %. The model of oxygen evolution from water in Photosystem II, presented by Åkermark et al. includes manganese 5,10,15-tris(4-nitrophenyl)corrole acting as the catalyst. Possible mechanism of the oxygen evolution is shown on the next page. ^[1,2,32–36]

In the first step Mn^{III} corrole complex (**1**) is oxidized to Mn^{V} oxo complex (**2**) by the addition of $t\text{-BuOOH}$. Addition of base – $n\text{-Bu}_4\text{NOH}$ leads to the formation of Mn^{III} hydroperoxy complex (**3**). In the next step, catalyzed by unreacted Mn^{V} oxo species, Mn^{IV} peroxy complex (**4**) is formed under elimination of protons. In the last step molecular oxygen is generated, either by disproportionation, or if the Mn^{IV} peroxy complex is oxidized to Mn^{V} complex, which is converted to the starting species under reductive elimination of oxygen. [36]

Scheme 7: Proposed mechanism of Oxygen Evolution Cycle. [36]

2.4. Mechanochemical synthesis of porphyrins

Similar to corroles, the general procedure for porphyrin synthesis is associated with the use of high amount of organic solvents strongly restricting its production on a large scale. Nowadays, porphyrins are synthesized according to two different methods. The Adler-Longo reaction includes refluxing in acetic or propionic acid and Lindsey synthesis is carried out in two-steps: cyclisation in chlorinated solvents at very low concentration followed by oxidation with DDQ for several hours. In 2014 group of Shy et al. published an article describing solventless synthesis of porphyrins in the ball mill. [37–39]

Scheme 8: Two-step mechanochemical synthesis of porphyrins. [39]

The first synthesis was carried out in simple mortar and pestle, where equimolar amounts of pyrrole (3.73 mmol) and benzaldehyde (3.73 mmol) were ground in presence of toluene sulfonic acid as catalyst (0.151 mmol). After 6 minutes of grinding a dry pink solid was obtained. The solid (porphyrinogen) was exposed to air for 15 days and the porphyrin was obtained in 3 % yield. The next synthesis (the same batch size) of porphyrin was performed using Retsch MM200 mill at frequency of 25 Hz with two stainless steel balls in 10 mL steel grinding jar for 20 minutes. In the next step the obtained mixture was dissolved in 50 mL of chloroform and oxidized with an excess of DDQ (3 equiv.) for 2 hours. After purification, done with column chromatography, tetraphenylporphyrin (TPP) was obtained in 28 % yield. The results of porphyrin syntheses with various *meso*-substituents are shown in Table 2. The group also checked the possibility to perform the oxidation step in the ball mill. The oxidation was carried out with different oxidation agents with or without addition of grinding agents. The milling time of the condensation step in each reaction was set to 20 minutes. The results of the syntheses are shown in Table 3. [39]

Table 2: Results of mechanochemical porphyrin synthesis followed by the oxidation in solution.

Type of aldehyde RCHO; R=	Condensation time (min)	Observations	Yield (%)
Ph	20	Pink powder	29.7
2-ClC ₆ H ₄	20	Pink sticky solid	32.7
3-ClC ₆ H ₄	30	Pink powder	21.9
4-ClC ₆ H ₄	30	Pink sticky solid	20.0
2-FC ₆ H ₄	30	Pink powder	28.1
3-FC ₆ H ₄	20	Pink powder	25.0
4-FC ₆ H ₄	30	Pink powder	9.7
α -naphthyl	30	Brown sticky solid	2.7
β -naphthyl	40	Brown sticky solid	31.3

Table 3: Results of mechanochemical TPP synthesis carried out in ball mill.

Oxidizing Agent	Grinding Agent	Oxidation Time (min)	Yield (%)
None	None	20	0
DDQ	None	20	0
I ₂	None	20	1.6
HNO ₃	None	20	11.5
NaBO ₃ ·4H ₂ O	None	20	8.3
C ₂ H ₅ ONa	None	20	8.2
C ₂ H ₅ ONa	None	480	6.7
C ₂ H ₅ ONa	Silica	20	5.2
C ₂ H ₅ ONa	Sodium chloride	20	0
C ₂ H ₅ ONa	Magnesium sulfate	20	9.3
2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄	None	20	0
2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄	None	480	8.1
2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄	Silica	20	5.3
2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄	Sodium chloride	20	4.7
2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄	Magnesium sulfate	20	0

In the synthesis, where the first step was performed in the ball mill and the second in the solvent, the highest yield was achieved for 5,10,15,20-tetrakis(2-chlorophenyl)porphyrin within 32.7 % yield. The synthesis, in which all steps were carried out in the ball mill, yielded 11.5 % TPP, when nitric acid was used as catalyst. In the reaction with DDQ no product was formed. [39]

2.5. Mechanochemical metalation of porphyrins

Similar to corroles, the common procedure for metalation of porphyrins requires the use of toxic organic solvents, such as DMF, benzene, methanol and chloroform. The reaction is carried out under reflux and can last even up to 5 days. In 2016, Ralphs et al. published an article about solventless metalation of porphyrins in the ball mill. All reactions were carried out between *meso*-Tetraphenylporphyrin and metal acetate monohydrate salts in equimolar ratios in a Retsch MM400 ball mill at 25-30 Hz frequency for 20-90 minutes. The product was purified simply by evaporation of formed acetic acid and water in an oven at 100 °C for 2 h. [40–42]

Scheme 9: Mechanochemical metalation of *meso*-tetraphenylporphyrin. [40]

The group performed metalation of porphyrin with different acetate salts on a small and large scale. The conditions of the reactions are shown in Table 4. Zn-, Ni-, and Cu-porphyrin complexes were successfully obtained by solventless metalation in both large and small scale. The formation of Fe-porphyrin complex was possible by extending the milling time to 3 h. [40]

Table 4: Time and frequency for metalation of porphyrin. [40]

		Small Batch (25.2 mg)		Large Batch (151.2 mg)	
Complex	Acetate Salt	Time (min)	Frequency (Hz)	Time (min)	Frequency (Hz)
ZnTPP	Zn(OAc) ₂ ·2H ₂ O	20	20	20	20
NiTPP	Ni(OAc) ₂ ·4H ₂ O	40	25	90	25
CuTPP	Cu(OAc) ₂ ·H ₂ O	20	25	90	25
FeTPP	Fe(OAc) ₂	180	30	-	-

3. Results and discussion

3.1. Synthesis of copper-5,10,15-tris(pentafluorophenyl)corrole

Scheme 10: Direct synthesis of CuTpFPC in the ball mill.

According to the general procedure for the preparation of metal-corroles, at least two separate syntheses are required. The first synthesis includes condensation of pyrrole and aldehyde to the order to the bilane followed by oxidation, resulting in the free-base corrole. In the case of H₃TpFPC two separate purification steps, by column chromatography, are required to achieve high purity of the free-base corrole. The second synthesis is carried out in solvent, with excess metal salt, leading to the respective metal-corrole. The idea behind the synthesis of copper-5,10,15-tris(pentafluorophenyl)corrole (CuTpFPC) using the ball mill, was the direct synthesis of metal-corrole. The initial assumption was the achievement of higher yield of bilane by addition of metal salt during the condensation step. It was thought, that metal ions could immediately coordinate with condensation products, favoring the formation of bilane. Another advantage would be reduction of time and amount of solvent required for the product purification using column chromatography. Unfortunately, at the time of practical work on this master thesis, no scientific article describing the direct synthesis of metal-corrole in a ball mill, was published. In order to achieve yield comparable with general synthesis of metal-corrole about 15 syntheses with different reaction conditions were carried out in a ball mill. The conditions for the first reactions in the ball mill were set according to the procedure for the synthesis of *meso*-substituted A₃-corroles of highly reactive aldehydes by Gryko.^[15]

The first reaction was carried out according to the following procedure: pentafluorobenzaldehyde (200 μ L, 1.618 mmol) and freshly distilled pyrrole (168 μ L, 2.427 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. The grinding jar was opened and a bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula. The reaction mixture was ground for 2 minutes. The grinding jar was opened again and TFA (1.5 μ L, 0.019 mmol) was added to the mixture. The reaction mixture was ground for 2 more minutes. 200 mL of DCM were poured into the grinding jar and DDQ (0.367 g, 1.618 mmol) was added. After 5 minutes the solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. The solvent was evaporated at reduced pressure and the product was purified with column chromatography (silica, *n*-heptane : DCM = 1:1). Evaporation of the solvent resulted in 54.7 mg (12.7 % of H_3TpFPC) of the purple powder. The reaction progress was monitored with a TLC-Plate, shown in Figure 6.

Figure 6: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

Figure 7: Low-resolution mass-spectrum of the expected CuTpFPC recorded directly from the TLC-plate.

After purification done by column chromatography the following ^1H -NMR- and ^{19}F -NMR-spectra were recorded.

Figure 8: ^1H -NMR spectrum of CuTpFPC.

Figure 9: ^{19}F -NMR spectrum of CuTpFPC.

The mass spectrum (Figure 7) obtained directly from the TLC-Plate of reaction mixture after DDQ addition, shows that free-base corrole ($m/z = 795$) was only partially transformed into copper-corrole ($m/z = 856$). Recorded NMR-spectra are characteristic for the 5,10,15-tris(pentafluorophenyl)corrole. On both ^1H - and ^{19}F -NMR spectra narrow signals can be seen, which would not be possible for copper-corrole due to its paramagnetic properties.

Since the first synthesis led to formation of free-base corrole at a relatively high yield (12.7 %) the **second synthesis** was carried out under the same reaction conditions as described before, except for the amount of copper-salt. Instead of a very small amount, 3 equivalents of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ were added to the reaction mixture in two steps. First, only a bit of salt from the tip of a spatula was added before the condensation step, later the rest of the salt was added for the condensation. After purification with column chromatography 50.3 mg (11.5 % yield) of the product was obtained. However, separation of the two first species visible on the TLC-plate, was not possible, due to their very similar polarity. The spot representing copper-corrole is barely visible. According to mass spectra, recorded directly from the TLC-Plate of the reaction mixture, the expected copper-corrole ($m/z = 856$) was synthesized.

Figure 10: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:2.

Figure 11: Low-resolution mass-spectrum of expected CuTpFPC recorded directly from the TLC-plate.

After purification was done by column chromatography, the following ^1H - and ^{19}F -NMR spectra of the first fraction were recorded. As seen in Figure 12 and 13, the recorded NMR-spectra do not fit for the NMR-spectra of pure copper-corrole. Additional signals are present, meaning that the second fraction contains another substance despite its $m/z = 857$ characteristic for CuTpFPC.

Figure 12: ^1H -NMR spectrum of expected CuTpFPC.

Figure 13: ^{19}F -NMR spectrum of expected CuTpFPC.

Since the first two spots on the TLC-Plate (Figure 10) are characterized by the same m/z ratio and different NMR-spectra, it was assumed, that the undefined species present in the product could have been incompletely oxidized bilane.

Considering the assumption from the previous reaction, the amount of oxidation agent DDQ in the **third synthesis** was increased to 1.2 equivalents and instead of pure TFA a 10 % solution in DCM was used. The reason for the dilution of the catalyst will be explained in the next chapter. Instead of 3 equivalents only 1 equivalent of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added, since it could possibly decrease the strength of the catalyst. Furthermore, the salt was added in one step, directly after mixing of pyrrole and benzaldehyde. The other reaction conditions remained unchanged. According to the TLC-Plate of the reaction mixture, shown in Figure 14, no product was obtained. Since only one spot representing longer oligomers is present on the TLC-plate, it was assumed, that the condensation step was too long and the expected product, namely bilane, reacted further. A second probable reason, why no product was formed, was the presence of high amounts of salt during the condensation, which could have led to the formation of byproducts.

Figure 14: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

The **fourth synthesis** of CuTpFPC was carried out according to the same procedure as the second synthesis. To achieve higher yield of bilane, condensation time was reduced to 1 min. After purification with column chromatography, 19 mg (4.3 % yield) of the product were obtained. As mentioned before, separation of the first two species visible on the TLC-plate (Figure 15), was not possible, due to their very similar polarity.

Figure 15: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:2.

As seen in the fourth synthesis, reduction of condensation time to 1 minute led to a decreased yield. In order to check the influence of the oxidation agent on product formation, the **fifth synthesis** was carried out with a milder oxidation agent *p*-chloranil. The fifth synthesis was carried out according to the following procedure: pentafluorobenzaldehyde (189 μL , 1.530 mmol) and freshly distilled pyrrole (159 μL , 2.295 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. After opening of the grinding jar, a purple colored reaction mixture could be observed. A bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula, and the reaction mixture was ground for a time of 1 minute. The grinding jar was opened again and a 10 % TFA solution in THF (14 μL , 0.018 mmol) was added to the mixture. The reaction mixture was ground for 2 minutes and 30 seconds. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (0.916 g, 4.590 mmol) was added and the reaction mixture was ground of another 2 minutes. 200 mL of DCM were poured into the grinding jar and *p*-chloranil (0.376 g, 1.530 mmol) was added. After 5 minutes, the solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. The solvent was evaporated at reduced pressure and the oxidation step was controlled with TLC-plates. As seen in Figure 16, the spot characteristic for product is visible directly after addition of oxidation agent and disappears after 2 minutes. According to the TLC-plate it was assumed that no product was obtained in this synthesis.

Figure 16: TLC-plates of expected CuTpFPC direct (left) and 2 minutes (right) after addition of oxidative agent performed in DCM : *n*-heptane = 1:1.

As seen on both TLC-Plates the black spot on the bottom also moves from the deposit line, which would not be possible for long-chain oligomers. It means, that the oxidation with *p*-chloranil requires more time and the obtained product mixture was not fully oxidized.

The **sixth synthesis** was carried out according to the following procedure: pentafluorobenzaldehyde (189 μL , 1.530 mmol) and freshly distilled pyrrole (159 μL , 2.295 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. A bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula and the reaction mixture was ground for 1 minute. The grinding jar was opened again and a 10 % TFA solution in THF (14 μL , 0.018 mmol) was added to the mixture. The reaction mixture was ground for 2 minutes and 30 seconds. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (0.916 g, 4.590 mmol) was added and the reaction mixture was ground for another 2 minutes. 200 mL of 0.5 % triethylamine (Et_3N) solution in DCM were poured into the grinding jar and DDQ (0.347 g, 1.53 mmol) was added. The solution was poured into a separatory funnel and extracted one time with 200 mL of saturated solution of NaHCO_3 in order to neutralize the excess of DDQ. The organic phase was separated and evaporated under reduced pressure. After purification with column chromatography, 152.2 mg (34.8 % yield) of the product were obtained. However, separation of the first two species visible on the TLC-plate, was not possible, due to their very similar polarity.

Figure 17: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:2.

The idea behind the use of 0.5 % solution of Et_3N in DCM was to neutralize traces of HCl present in the solvent and TFA in the reaction mixture. Lack of an acid catalyst leads to a stop of condensation therefore preventing further oligomerization.

In order to check the scalability of the reaction, the **seventh synthesis** was carried out on a larger scale according to the following procedure: pentafluorobenzaldehyde (630 μL , 5.100 mmol) and freshly distilled pyrrole (531 μL , 7.650 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. A bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula and the reaction mixture was ground for 1 minute. The grinding jar was opened again and 47 μL of TFA solution (10 % in THF) (0.061 mmol) were added to the mixture. The reaction mixture was ground for 2 minutes and 30 seconds. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (3.055 g, 15.300 mmol) was added and the reaction mixture was ground for another 2 minutes. 200 mL of 0.5 % Et_3N solution in DCM were poured into the grinding jar and DDQ (1.158 g, 5.1 mmol) was added. The solution was immediately poured into a separatory funnel and extracted two times with 200 mL of a saturated solution of NaHCO_3 in order to neutralize excess DDQ. The organic phase was separated and evaporated under reduced pressure. After purification with column chromatography, 22.2 mg (1.5 % yield) of the product was obtained. Very low yield can be explained by short oxidation time. Formation of the byproduct was not observed.

Figure 18: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

The upscaled synthesis of CuTpFPC gave no positive results. The next syntheses were carried out on a lower scale, due to high costs of pentafluorobenzaldehyde.

In order to minimize the influence of Et_3N and $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ on the condensation and oxidation steps, their amount was reduced. In the **eighth synthesis**, the concentration of Et_3N in DCM was reduced to 0.15 % since it can react with DDQ, but can still neutralize HCl traces present in the solvent. Moreover the amount of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was decreased to one equivalent. In order to obtain a more homogenous mixture during the condensation step, the amount of pyrrole equivalents was increased to two. The synthesis was carried out according to the following procedure: pentafluorobenzaldehyde (189 μL , 1.530 mmol) and freshly distilled pyrrole (212 μL , 3.060 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (0.306 g, 1.530 mmol) was added and the reaction mixture was ground for 1 minute. The grinding jar was opened, 10 % TFA solution in THF (14 μL , 0.0184 mmol) was added to the mixture and ground for 2 minutes and 30 second. 200 mL of 0.15 % Et_3N solution in DCM were poured into the grinding jar and *p*-chloranil (0.4514 g, 1.836 mmol) was added. The solvent was refluxed for 75 minutes at 70 °C. Later, the solvent was evaporated under reduced pressure. After purification with column chromatography, 86.5 mg (19.8 % yield) of the product was obtained. Separation of the first two species visible on the TLC-plate, was not possible, due to their very similar polarity. As seen in Figure 19, mostly undefined byproduct was formed.

Figure 19: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

In order to characterize the byproduct, mass-spectra directly from the TLC-plate were recorded.

Figure 20: Low-resolution mass-spectrum of CuTpFPC recorded directly from the TLC-plate.

Figure 21: Low-resolution mass-spectrum of the byproduct recorded directly from the TLC-plate.

As seen in Figure 20 and 21, the byproduct is characterized by the $m/z = 697$. Considering the reactions described in later chapters, this substance is present only in reactions with *p*-chloranil. Moreover, it is formed also in the reactions, in which other aldehydes were used, for example 4-*tert*-butylbenzaldehyde. It is assumed, that the unknown substance is a complex between *p*-chloranil and pyrrole.

Considering the results from the previous reaction, the **ninth synthesis** was carried out under very similar conditions. Only the amount of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ equivalents was decreased to 0.67, for further investigation about its influence on the reaction. As seen in Figure 22, the corresponding TLC-plate of the product mixture, the yield of expected product was very low. The spot representing the product is barely visible. For this reason, purification with column chromatography was not performed.

Figure 22: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

Considering the best yield and purity of the product obtained in the first synthesis, reproducibility of the reactions, in which 10 % solution of TFA was used and optimized condensation time, the **tenth synthesis** was carried out according to the following procedure: pentafluorobenzaldehyde (189 μL , 1.530 mmol) and freshly distilled pyrrole (159 μL , 2.295 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. A bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula and the reaction mixture was ground for 2 minutes. The grinding jar was opened, a 10 % TFA solution in THF (14 μL , 0.0184 mmol) was added to the mixture and ground for 2 minutes and 30 seconds. 150 mL of 0.15 % Et_3N solution in DCM were poured into the grinding jar and *p*-chloranil (0.376 g, 1.530 mmol) were added. The solvent was refluxed for 60 minutes at 70 °C. Later, the solvent was evaporated under reduced pressure. After purification with column chromatography, (DCM : *n*-heptane = 1:1) 57 mg (13 % yield) of pure product were obtained. The TLC-Plate of the reaction mixture is shown in Figure 23.

Figure 23: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

The tenth synthesis led to the best results. High yield and purity of the product were achieved, since the formation of byproducts with similar polarity was not present. In order to check the reproducibility of this batch, the eleventh synthesis was carried out under the same conditions. According to the TLC-plate of the product mixture, shown in Figure 24, no expected product was formed. Obtained TLC-Plate is very similar to the TLC-Plate shown in Figure 22.

Figure 24: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

In order to analyze the byproducts formed in the synthesis, in which DDQ is used as oxidation agent, the **twelfth synthesis** was carried out according to the following procedure: pentafluorobenzaldehyde (189 μL , 1.53 mmol) and freshly distilled pyrrole (159 μL , 2.295 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. A bit of $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was added with the tip of a spatula and the reaction mixture was ground for 1 minute. The grinding jar was opened again and 10 % of TFA solution in THF (14 μL , 0.018 mmol) were added to the mixture. The reaction mixture was ground for 2 minutes and 30 seconds. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (0.916 g, 4.590 mmol) was added and the reaction mixture was ground for another 2 minutes. 200 mL of DCM were poured into the grinding jar and DDQ (0.347 g, 1.530 mmol) was added. The solvent was evaporated under reduced pressure. Product mixture was purified with column chromatography (DCM : *n*-heptane = 2:1), which led to the separation of highly insoluble oligomers. The TLC-plate of product mixture is shown in Figure 25.

Figure 25: TLC-plate of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

The analysis of the obtained mixture was not possible using NMR-Spectroscopy. Polarity of most substances was very similar and their separation was not possible. Solvents of different compositions were tested with no positive result. The TLC-Plates representing separation of substances are shown in Figure 26.

Figure 26: TLC-plates of product mixture (CuTpFPC) after initial purification. First plate was performed in n -Heptane : EA = 5:1, second in n -Heptane : DCM = 5:1 and third in n -Heptane : DCM = 1:4.

The best separation was achieved in a mixture of DCM : n -Heptane = 1:2. The TLC-Plate, shown in Figure 27, also enabled the mass spectroscopy analysis of individual fractions.

Figure 27: TLC-plate of product mixture (CuTpFPC) performed in DCM : n -Heptane = 1:2.

Figure 28: Low-resolution mass-spectrum recorded from spot number **1** on the TLC-plate.

Figure 29: Low-resolution mass-spectrum recorded from spot number **2** on the TLC-plate.

Figure 30: Low-resolution mass-spectrum recorded from spot number 3 on the TLC-plate.

Figure 31: Low-resolution mass-spectrum recorded from spot number 4 on the TLC-plate.

Figure 32: Low-resolution mass-spectrum recorded from spot number 5 on the TLC-plate.

Figure 33: Low-resolution mass-spectrum recorded from spot number 6 on the TLC-plate.

Table 5: Substance structures formed in the synthesis of CuTpFPC.

	Structure	<i>m/z</i> ratio	<i>m/z</i> found
1.		856	856
2.		312	311
3.		1344	1344, 1712
4.		1712	1712
5.	Unknown	-	884, 1699
6.	Unknown	-	884, 1101, 1699, 1740

The first spot visible on the TLC-Plate represents the expected product – CuTpFPC. The second spot is dipyrromethane (DPM). Other substance structures are only suggestions. Their presence has not been proved. Substance number 3 is a ring consisting of five benzaldehyde and six pyrrole species. Substance number 4 is a macrocycle composed of two bilane species. Substances marked with number 5 and 6 could not be assigned according to mass spectra.

Partial separation of pure CuTpFPC was achieved using a special chromatography column (5 cm internal diameter and 120 cm length) and mobile phase characterized by very low polarity (*n*-Heptane : DCM = 5:1). The yield of pure CuTpFPC in the twelfth synthesis amounts to 1.9 % (8.4 mg). The second fraction, consisting of CuTpFPC and DPM, amounts to 2.6 % (11.3 mg). Figure 34 shows the TLC-Plate of the first two fractions obtained during the second column chromatography. The upper, brown spots represent CuTpFPC and the lower, orange spots are DPM.

Figure 34: TLC-plate of fractions obtained during second column chromatography purification.

In order to check the influence of catalyst on the condensation step, two syntheses with acetic acid instead of trifluoroacetic acid were carried out under the reaction conditions as the synthesis before. In the first synthesis a 5 % solution of acetic acid in THF was used and in the second synthesis a lower concentration of 1 %. The amount of equivalents remained unchanged in both reactions. As seen in Figure 35, the product was formed in both cases. However, after purification with column chromatography in the first synthesis only 15.4 mg (3.5 %) of the product were obtained. Due to the large size of the column, no product was obtained in the second synthesis. Very low yield can be explained by the low catalytic reactivity of acetic acid. The strength of the acetic acid was not enough to catalyze the condensation step over a time of 150 seconds. Moreover, on the TLC-Plates of both reaction mixtures, streaking spots on the spotting line can be observed. They are characteristic for unreacted benzaldehyde. The black spots representing longer oligomers are smaller than in case of reactions, where TFA was used.

Figure 35: TLC-plates of expected CuTpFPC performed in DCM : *n*-Heptane = 1:1.

Based on the results of the twelfth synthesis it can be assumed, that the prior undefined byproduct characterized by a orange spot on the TLC-Plate present in almost all syntheses, was dipyrromethane. It means, that the condensation time in all cases was too short and has to be extended. The use of acetic acid instead of TFA led to lower yield, due to its weak reactivity. The synthesis of CuTpFPC was optimized in further segments of this master thesis, after consideration of all reaction conditions and experiences. The precise reaction conditions of this synthesis are described in the experimental section of this master thesis. The synthesis was carried out on a larger scale, which probably had big influence on the formation of byproducts and could be reproduced with the same results.

Table 6: Summary of reaction conditions and results of CuTpFPC syntheses. * - yield for the mixture of CuTpFPC and DPM. Batch 7 – Upscaled Synthesis.

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
Equivalents of Pyrrol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Catalyst Concentration, Equivalents	100% 0.012	100 % 0.012	10% in DCM 0.012	10% in DCM 0.012	10% in THF 0.012	10% in THF 0.012	10% in THF 0.012
Condensation Time	120 s	120 s	120 s	60 s	150 s	150 s	150 s
Cu(OAc) ₂ Addition	one-step	two-step	one-step	two-step	two-step	two-step	two-step
Equivalents Cu(OAc) ₂	spatula tip	3.0	1.0	3.0	3.0	3.0	3.0
Neutralization with Et ₃ N	no	no	no	no	no	yes (0.5 %)	yes (0.5 %)
Oxidation Agent, Equivalents	DDQ 1.0	DDQ 1.0	DDQ 1.2	DDQ 1.0	<i>p</i> -chloranil 1.0	DDQ 1.0	DDQ 1.0
Oxidation Time (including solvent evaporation)	12 min	12 min	12 min	12 min	12 min	~2 min	~1 min
DDQ Extraction	no	no	no	no	-	yes	yes
Yield*	12.7 % (H ₃ TpFPC)	11.5 %	0 %	4.3 %	0 %	34.8 %	1.5 %

Table 7: Summary of reaction conditions and results of CuTpFPC syntheses. * - yield for the mixture of CuTpFPC and DPM.

	Batch 8	Batch 9	Batch 10	Batch 11	Batch 12	Batch 13	Batch 14
Equivalents of Pyrrol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Catalyst Concentration, Equivalents	10% in THF 0.012	10% in THF 0.012	10% in THF 0.012	10% in THF 0.012	10% in THF 0.012	5% AcOH in THF 0.012	1% AcOH in THF 0.012
Condensation Time	150 s	150 s	150 s	150 s	150 s	150 s	150 s
Cu(OAc) ₂ Addition	two-step	two-step	one-step	one-step	two-step	two-step	two-step
Equivalents Cu(OAc) ₂	1.0	0.67	spatula tip	spatula tip	3.0	3.0	3.0
Neutralization with Et ₃ N	yes (0.15 %)	yes (0.15 %)	yes (0.15 %)	yes (0.15 %)	no	no	no
Oxidation Agent, Equivalents	<i>p</i> -chloranil 1.6	<i>p</i> -chloranil 1.6	<i>p</i> -chloranil 1.0	<i>p</i> -chloranil 1.0	DDQ 1.0	DDQ 1.0	DDQ 1.0
Oxidation Time (including solvent evaporation)	75 min at 70 °C	75 min at 70 °C	60 min at 70 °C	60 min at 70 °C	12 min	12 min	12 min
DDQ Extraction	-	-	-	-	no	no	no
Yield*	19.8 %	0 %	13.0 % (pure)	0 %	1.9 % (pure) 2.6 %	3.5 %	0 %

3.2. Synthesis of 5,10,15-tris(pentafluorophenyl)corrole

Scheme 11: Synthesis of H₃TpFPC in the ball mill.

The **first synthesis** of H₃TpFPC was already described in the previous chapter. The aim of this reaction was formation of CuTpFPC. However, the amount of salt added during condensation was not enough for complete metalation of free-base corrole and mostly H₃TpFPC was formed.

In the **second synthesis** no salt was added. The procedure for the synthesis was the following: pentafluorobenzaldehyde (189 μ L, 1.530 mmol) and freshly distilled pyrrole (159 μ L, 2.295 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. The grinding jar was opened and TFA (1.4 μ L of 0.018 mmol) was added to the mixture. The reaction mixture was ground for another 2 minutes. 200 mL of DCM were poured into the grinding jar and DDQ (0.3473 g, 1.530 mmol) was added. After 5 minutes, the solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. The solvent was evaporated at reduced pressure and the product was purified with column chromatography (silica, *n*-heptane : DCM = 1:1). Evaporation of the solvent resulted in 12.3 mg (3.1 % of H₃TpFPC) of the purple powder. The reaction progress was monitored with a TLC-Plate, shown in Figure 36.

Figure 36: TLC-plate of expected H₃TpFPC performed in DCM : *n*-Heptane = 1:1.

During the second synthesis, it was observed, that the catalyst - pure TFA, evaporated immediately after addition into the ball mill. The reason was a very small amount of liquid and a high temperature difference between the milling balls (about 25 °C) and the catalyst (about 4 °C), since it has to be stored in the fridge. To prevent further problems with evaporation of the catalyst, its 10 % solution in DCM was used. Since DCM contains traces of HCl, which could additionally catalyze the condensation step, DCM was exchanged by dry THF.

The next syntheses, carried out simultaneously with the synthesis of CuTpFPC, are summarized in the Table 6. The batch size remained unchanged.

Table 8: Reaction conditions of the H₃TpFPC syntheses.

	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
Equivalents of pyrrole	1.33	1.33	2.0	2.0	1.5
Mixing time of educts	2 min	2 min	2.5 min	2 min	2 min
Catalyst concentration	10%	10%	10%	2.5%	100%
Catalyst equivalents	0.0060	0.0060	0.0045	0.0020	0.0120
Condensation time	180 s	150 s	150 s	135 s	150 s
Oxidation agent	DDQ	<i>p</i> -chloranil	<i>p</i> -chloranil	<i>p</i> -chloranil	DDQ
Oxidation time (including solvent evaporation)	~2 min	60 min at 75°C	60 min at 75°C	60 min at 75°C	12 min
DDQ extraction	yes	-	-	-	no
Addition of Cu(OAc) ₂	-	-	-	-	yes
Pentapyrromethane formation	yes	yes	yes	yes	-
Yield	5.9 %	6.5 %	5.6 %	4.3%	0 %

In the **third synthesis** of H₃TpFPC, the condensation time was extended to 3 minutes. This reaction also included the extraction of DDQ excess with saturated NaHCO₃ solution, described already in the sixth synthesis of CuTpFPC. The **syntheses 4-6** were carried out with *p*-chloranil as oxidation agent. It was observed, that the increase of pyrrole equivalents as well as the reduction of condensation time, led to a decrease in yield.

The **seventh synthesis** of H₃TpFPC was carried out under the same reaction conditions as the **first synthesis**, however, no product was obtained. The probable reason was the use of pure catalyst, which evaporated directly after addition, due to its very small amount.

Based on the results and experiences in the synthesis of CuTpFPC described before and H₃tBuPhC described in a later chapter, the optimization of the H₃TpFPC was finally possible. First of all, the batch size was increased to make the reaction more reproducible. Secondly, the condensation time was increased to achieve higher yields. The synthesis of H₃TpFPC was carried out according to the following procedure: pentafluorobenzaldehyde and of freshly distilled pyrrole were placed in a grinding jar and ground for 2 minutes with 12 balls. The grinding jar was opened and 10 % TFA solution in THF was added to the mixture. The reaction mixture was ground for the time shown in Table 7. The grinding jar was opened and 200 mL of DCM were added. The solution was poured into a round-bottom 500 mL flask. DDQ was added and the reaction mixture was stirred for 15 minutes. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 1:1). Strongly fluorescent fractions were collected, evaporated and purified with a second column chromatography (aluminium oxide 60, basic, activity level II, *n*-heptane : DCM = 1:1).

Figure 37: An example of H₃TpFPC TLC-plate performed in DCM : *n*-Heptane = 1:1.

Figure 38: H₃TpFPC TLC-plate performed in DCM : *n*-Heptane = 1:1 after first column chromatography.

Figure 39: Structural representation of byproduct – pentapyrromethane.

Table 9: Reaction conditions of the optimized H₃TpFPC syntheses.

	Synthesis 1	Synthesis 2	Synthesis 3	Synthesis 4
Batch size (Aldehyde mass)	500 mg	1000 mg	1000 mg	1000 mg
Equivalents of pyrrole	1.5	1.5	3	2
Equivalents of catalyst	0.012	0.012	0.012	0.012
Volume of catalyst (10 % in THF)	23 μ L	47 μ L	47 μ L	47 μ L
Condensation time	8 min	10 min	10 min	10 min
Number of balls	10	12	12	12
Oxidation agent (1 equiv.)	DDQ	DDQ	DDQ	DDQ
Yield	31.8 mg (4.7 %)	237.5 mg (17.5 %)	76.0 mg (5.6 %)	231.0 mg (17.1%)

As seen in Table 7, the highest yield achieved for H₃TpFPC was 17.5 %. The idea behind the increase of pyrrole : aldehyde ratio, was the formation of more homogenous, less sticky mixture during the condensation step. However, this led to a decreased yield of product.

3.3. Synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole

Scheme 12: Synthesis of H₃tBuPhC in the ball mill.

The second corrole synthesis was carried out using moderately reactive aldehyde. The procedure for the **first synthesis** of 5,10,15-tris(4-*tert*-butylphenyl)corrole ($H_3tBuPhC$) was the following: 4-*tert*-butyl-benzaldehyde (1031 μ L, 6.164 mmol) and freshly distilled pyrrole (1283 μ L, 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 25 balls. The grinding jar was opened and 10 % TFA solution in THF (108.5 μ L, 0.142 mmol) was added to the mixture. The reaction mixture was ground for the next 20 minutes. The grinding jar was opened and 200 mL of DCM were added. The solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. *p*-Chloranil (1.516 g, 6.164 mmol) was added and the reaction mixture was refluxed for 90 minutes at 70 °C. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane:DCM = 2:3). Green, fluorescent fractions were collected. Evaporation of the solvent resulted in 160.7 mg (11.3 %) of dark green powder.

Figure 40: TLC-plate of expected H₃BuPhC performed in DCM : *n*-Heptane = 1:1.

Figure 41: Low-resolution mass-spectrum recorded from green spot on the TLC-plate.

In order to check the yield dependency on condensation time, 5 syntheses were carried out under similar reaction conditions. Specification of these reactions are shown in the Table 8.

Table 10: Reaction conditions of the optimized H₃tBuPhC syntheses.

	Synthesis 2	Synthesis 3	Synthesis 4	Synthesis 5	Synthesis 6
Batch size (Aldehyde mass)	1 g	1 g	1 g	1 g	1 g
Equivalents of pyrrole	3	3	3	3	3
Equivalents of catalyst	0.023	0.023	0.023	0.023	0.023
Volume of catalyst (10 % in THF)	108.5 µL	108.5 µL	108.5 µL	108.5 µL	108.5 µL
Condensation time	7 min	12 min	20 min	25 min	30 min
Number of balls	25	25	16	16	16
Oxidation agent (1 equiv.)	<i>p</i> -chloranil	<i>p</i> -chloranil	<i>p</i> -chloranil	<i>p</i> -chloranil	<i>p</i> -chloranil
Yield	121.6 mg (8.5 %)	64.7 mg (4.5 %)	149.6 mg (10.5 %)	138.3 mg (9.7 %)	111.7 mg (7.8 %)

As seen in Table 8, the highest yield was obtained in the reaction with condensation time set to 20 minutes. Change of the condensation time led to lower yield in all cases. During the **third synthesis** the balls were immobilized in the middle of the grinding jar by the sticky reaction mixture, which consequently led to a decrease in yield. To prevent this problem, the number of balls was reduced to 16 in the next syntheses to improve their mobility in the grinding jar.

The next step in the synthesis of H₃tBuPhC was to check its scalability and yield dependency on the batch size. Two reactions were carried out under the reaction conditions shown below in Table 9.

Table 11: Reaction conditions of the optimized H₃tBuPhC syntheses.

	Synthesis 7	Synthesis 8
Batch size (Aldehyde mass)	2 g	5 g
Equivalents of pyrrole	3	3
Equivalents of catalyst	0.023	0.023
Volume of catalyst (10 % in THF)	217 µL	542.5 µL
Condensation time	20 min	12 min
Number of balls	20	25
Oxidation agent (1 equiv.)	<i>p</i> -chloranil	<i>p</i> -chloranil
Yield	348.0 mg (12.2 %)	1037.6 mg (14.5 %)

As seen in Table 9, the yield is increasing with batch size. Since the reaction conditions remain the same, it can be explained by the relatively large volume of the reactor. The reaction mixture is distributed better in the case of larger batches and the product is easier to collect, when the reaction is done. It was also proved, that the synthesis of H₃tBuPhC can be up-scaled. Larger batches have not been carried out, because the purification of the product was limited by the size of chromatography columns available in the laboratory.

3.4. Synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole including oxidation in the ball mill

Scheme 13: Synthesis of H₃tBuPhC in the ball mill.

The next idea of the H₃tBuPhC synthesis, was to completely remove the solvent required in the oxidation step of bilane. Instead of oxidation in the solvent, the oxidative agent was added directly to the grinding jar after the condensation step and ground for the time shown below in Table 10. Other reaction conditions were set, based on the previous syntheses of H₃tBuPhC.

Table 12: Reaction conditions of the optimized H₃tBuPhC syntheses including oxidation in the ball mill.

	Synthesis 1	Synthesis 2
Batch size (Aldehyde mass)	1 g	1 g
Equivalents of pyrrole	3	3
Equivalents of catalyst	0.023	0.023
Volume of catalyst (10 % in THF)	108.5 μ L	108.5 μ L
Condensation time	20 min	20 min
Number of balls	16	16
Oxidation agent (1 equiv.)	<i>p</i> -chloranil	<i>p</i> -chloranil
Oxidation time	10 min	15 min
Addition of solid support	-	1g SiO ₂
Yield	77.6 mg (5.4 %)	66.0 mg (4.6 %)

As seen in Table 10, the oxidation in the ball mill was possible. However, the yield obtained in both reactions was significantly lower than in the reactions, in which the oxidation step was done in solvent. During the oxidation step in the first synthesis, the formation of clumps was observed. It could possibly lead to lower yield, since not all particles have had contact with the oxidation reagent and the oxidation step was not complete. In order to prevent the formation of clumps, 1 g of SiO₂ was added during the oxidation step in the second synthesis. However, the formation of clumps was still present. Lower yield of the second synthesis was probably caused by extended oxidation time.

3.5. Synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole with solid support

Scheme 14: Synthesis of H₃tBuPhC in the ball mill.

In order to simplify the general procedure for H₃tBuPhC synthesis and to optimize the conditions for the reaction in the 250 mL grinding jar, the next two syntheses were carried out in the presence of solid support – NaCl and MgSO₄·7 H₂O. The number of balls was increased to 44 – the maximum number available in the laboratory. The volume of solid support was set to 18.4 cm³ - volume of the balls minus the volume of educts. The procedure for the synthesis was simplified: the grinding jar was filled with balls and solid support. 4-*tert*-butyl-benzaldehyde (2062 μ L of 12.328 mmol), freshly distilled pyrrole (2566 μ L, 36.984 mmol) balls and 10 % TFA solution in THF (217 μ L, 0.284 mmol) were added to the grinding jar. The reaction mixture was ground for a total of 26 minutes. In order to control the reaction progress, every 2 minutes a small sample of reaction mixture was taken and dissolved in 1 mL of water. Condensation products were extracted with 1 mL DCM and oxidized with one droplet of DDQ solution (0.2 g in 25 mL DCM) leading to immediate color change. The prepared solution was put on TLC-plate. Separation of the products was achieved by placing the TLC-plates in DCM : *n*-Heptane = 3:2. The grinding jar was opened and 200 mL of DCM was added. The solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. DDQ (2.798 g, 12.328 mmol) was added and the reaction mixture was stirred for 15 minutes. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 2:3). Green, fluorescent fractions were collected. Evaporation of the solvent resulted in 131 mg (4.6 %) of dark green powder.

Table 13: Reaction conditions of the optimized H₃tBuPhC syntheses with solid support.

	Synthesis 1	Synthesis 2
Batch size (Aldehyde mass)	2 g	2 g
Equivalents of pyrrole	3	3
Equivalents of catalyst	0.023	0.023
Volume of catalyst (10 % in THF)	217 μ L	217 μ L
Condensation time	26 min	20 min
Number of balls	44	44
Solid support	39.7 g NaCl	48.9 g MgSO ₄ ·7 H ₂ O
Oxidation agent (1 equiv.)	DDQ	DDQ
Yield	131 mg (4.6 %)	154 mg (5.4 %)

Figure 42: TLC-plates of expected H₃tBuPhC performed every 2 minutes of the condensation step followed by oxidation with DDQ.

As seen in Figure 42, the formation of product can be observed on the TLC-plate performed at the 20th minute of the condensation. Product is characterized by a green spot in the middle. The described procedure is simplified, compared to the general procedure of H₃tBuPhC synthesis. As opposed to other syntheses, the temperature of the grinding jar was above 70 °C after the reaction was done. Larger amount of balls and solid support increased the friction, which consequently led to a rise in temperature. According to Arrhenius equation, the reaction rate is dependent on the temperature. Higher temperature additionally accelerated the condensation step, favoring the formation of longer oligomers, which finally resulted in lower yield (4.6 %). Slightly higher yield (5.4 %) was achieved in the second synthesis, in which MgSO₄·7 H₂O was used, which can be explained by a shorter condensation time of 20 minutes, instead of 26 minutes.

3.6. Synthesis of copper-5,10,15-tris(4-*tert*-butylphenyl)corrole

Scheme 15: Direct synthesis of CutBuPhC in the ball mill.

The reaction conditions for the second metal-corrole were based on optimized syntheses of CuTpFPC and H₃tBuPhC. The **first synthesis** of copper-5,10,15-tris(4-*tert*-butylphenyl)corrole (CutBuPhC) was carried out according to the following procedure: 4-*tert*-butyl-benzaldehyde (1031 μ L, 6.164 mmol) and freshly distilled pyrrole (1283 μ L, 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 20 balls. CuCl₂ (0.276 g, 2.055 mmol) was added to the reaction mixture and ground for 2 minutes. The grinding jar was opened and 10 % TFA solution in THF (108.5 μ L, 0.142 mmol) was added to the mixture. The reaction mixture was ground for another 20 minutes. The grinding jar was opened and 200 mL of DCM were added. The solution and the balls were moved into a glass beaker. The steel balls were immobilized with a permanent magnet and the liquid was poured into a round-bottom 500 mL flask. *p*-Chloranil (1.516 g, 6.164 mmol) was added and the reaction mixture was refluxed for 90 minutes at 70 °C. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 3:2). Evaporation of the solvent resulted in 147.5 mg (9.5 %) of dark brown powder.

Figure 43: TLC-plate of expected CutBuPhC performed in DCM : *n*-Heptane = 2:3.

Figure 44: Low-resolution mass-spectrum recorded from second spot on the TLC-plate.

Figure 45: Low-resolution mass-spectrum recorded from first spot on the TLC-plate.

The product is represented by the second spot on the TLC-plate. According to the mass spectrum, the first spot is probably pentapyrromethane or metalated porphyrin. The obtained product showed low purity, since the byproduct has similar polarity and complete separation with one column chromatography was not possible.

In the **second synthesis** the order of educt addition was changed, since the salt - CuCl_2 could influence the condensation step. The second synthesis of CutBuPhC was carried out according to the following procedure: 4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 20 balls. The grinding jar was opened and 10 % TFA solution in THF (108.5 μL , 0.142 mmol) was added to the mixture. The reaction mixture was ground for another 18 minutes. CuCl_2 (0.276 g, 2.055 mmol) was added to the reaction mixture and ground for 2 minutes. The grinding jar was opened and 200 mL of DCM were added. The liquid was poured into a round-bottom 500 mL flask. *p*-Chloranil (1.516 g, 6.164 mmol) was added and the reaction mixture was refluxed for 75 minutes at 70 °C. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane:DCM = 3:2). Evaporation of the solvent resulted in 35.7 mg (2.3 %) of dark brown powder.

Figure 46: TLC-plate of expected CutBuPhC performed in DCM : *n*-Heptane = 2:3.

As seen in Figure 46, the spot representing the product is barely visible. It has also been observed, that after the condensation step, all balls stucked together in the middle of the grinding jar. The reaction mixture was not stirred properly, which resulted in a very low yield (2.3 %).

In order to prevent problems with immobility of balls, the batch size in the **third synthesis** was increased. The synthesis of CutBuPhC was carried out according to the following procedure: 4-*tert*-butyl-benzaldehyde (2062 μL , 12.328 mmol) and freshly distilled pyrrole (2566 μL , 36.984 mmol) were placed in a grinding jar and ground for 2 minutes with 20 balls. The grinding jar was opened and 10 % TFA solution in THF (108.5 μL , 0.142 mmol) was added to the mixture. The reaction mixture was ground for another 16 minutes. CuCl_2 (0.553 g, 4.109 mmol) was added to the reaction mixture and ground for 4 minutes. The grinding jar was washed with 200 mL of DCM. The liquid was poured into a round-bottom 500 mL flask. *p*-Chloranil (3.031 g, 12.328 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane:DCM = 3:2). Evaporation of the solvent resulted in 297 mg (9.6 %) of dark brown powder.

Figure 47: TLC-plate of expected CutBuPhC performed in DCM : *n*-Heptane = 2:3.

As seen in Figure 47, byproduct was not formed, which allowed better purification of the product. The yield of 9.6 % was the best result achieved in the syntheses of CutBuPhC.

In order to increase the yield of CutBuPhC formation, the **fourth synthesis** was carried out according to the procedure described in the third synthesis. Condensation time was extended to 17 minutes and metalation time was reduced to 3 minutes. $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ was used instead of CuCl_2 and *p*-chloranil was replaced by DDQ. Oxidation time was set to 15 minutes.

Figure 48: TLC-plate of expected CutBuPhC performed in DCM : *n*-Heptane = 2:3.

As seen in Figure 48, formation of byproduct was observed. The yield of 8.0 % (248.7 mg) was lower than in previous synthesis and due to the formation of byproduct, high purity of the product was not achieved.

The idea behind the **fifth synthesis** of CutBuPhC was the simplification of the general procedure. All of the educts: 4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol), 10 % TFA solution in THF (158.5 μL , 0.207 mmol) and $\text{Cu}(\text{OAc})_2 \cdot (\text{H}_2\text{O})$ (1.23 g, 6.161 mmol) were added to the grinding jar in one step and ground for 20 minutes. The grinding jar was washed with 200 mL of DCM. The liquid was poured into a round-bottom 500 mL flask. DDQ (1.401 g, 6.172 mmol) was added and the reaction mixture was stirred for 15 minutes. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 3:2). Evaporation of the solvent resulted in 60.1 mg (3.9 %) of dark brown powder. Compared to the other syntheses the yield was significantly lower.

Table 14: Summary of reaction conditions and results of CutBuPhC syntheses.

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Batch Size (Aldehyde Mass)	1 g	1 g	2 g	2 g	1 g
Equivalents of pyrrole	3.0	3.0	3.0	3.0	3.0
Equivalents of Catalyst (10% TFA in THF)	0.023	0.023	0.023	0.023	0.034
Oxidation Agent (1.0 eq.)	<i>p</i> -chloranil	<i>p</i> -chloranil	<i>p</i> -chloranil	DDQ	DDQ
Equivalents of copper salt	0.33 CuCl ₂	0.33 CuCl ₂	0.67 CuCl ₂	0.33 Cu(OAc) ₂	1.0 Cu(OAc) ₂
Number of balls	20	20	20	20	12
Procedure: Step + Grinding time	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole + TFA + Salt 20 min
	Salt 2 min	TFA 18 min	TFA 16 min	TFA 17 min	
	TFA 20 min	Salt 2 min	Salt 4 min	Salt 3 min	
Oxidation time	75 min at 75°C	75 min at 75°C	75 min at 75°C	15 min R.T.	15 min R.T.
Yield	147.5 mg (9.5 %)	35.7 mg (2.3 %)	297 mg (9.6 %, pure)	248.7 mg (8.0 %)	60.1 mg (3.9 %)

3.7. Synthesis of manganese-5,10,15-tris(4-*tert*-butylphenyl)corrole

Scheme 16: Direct synthesis of expected MntBuPhC in the ball mill.

The next step of the master thesis was the synthesis of manganese-corrole. The **first** synthesis of manganese-5,10,15-tris(4-*tert*-butylphenyl)corrole (MntBuPhC) was carried out according to the following procedure: 4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 16 balls. The grinding jar was opened and 10 % TFA solution in THF (164 μL , 0.215 mmol) was added to the mixture. The reaction mixture was ground for another 16 minutes. $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (1.007 g, 4.109 mmol) was added to the reaction mixture and ground for 4 minutes. The grinding jar was opened and 200 mL of DCM were added. The liquid was poured into a round-bottom 500 mL flask. DDQ (1.401 g, 6.172 mmol) was added and the reaction mixture was stirred for 15 minutes. In order to control the reaction progress, a TLC-plate of the reaction mixture was performed in DCM : *n*-Heptane = 3:2. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane:DCM = 3:2). Evaporation of the solvent resulted in 12.3 mg (0.9 %) of dark green powder.

Figure 49: TLC-plate of expected MntBuPhC performed in DCM : *n*-Heptane = 2:3.

In order to check the reproducibility, the **second** synthesis was carried out under the same reaction conditions. The only difference was, that the batch size was doubled. According to the low-resolution mass-spectrum recorded from the TLC-plate, mostly free-base corrole was obtained during the synthesis.

Figure 50: TLC-plate of expected MntBuPhC performed in DCM : *n*-Heptane = 1:1.

Figure 51: Low resolution mass-spectrum of the second spot on the TLC-Plate.

To avoid the formation of free-base corrole, the third synthesis was carried out with an excess of Mn-salt, according to the following procedure: 4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 16 balls. The grinding jar was opened and 10 % TFA solution in THF (108.5 μL , 0.142 mmol) was added to the mixture. The reaction mixture was ground for another 16 minutes. $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (5.001 g, 20.406 mmol) was added to the reaction mixture and ground for 4 minutes. The grinding jar was opened and 200 mL of DCM were added. The liquid was poured into a round-bottom 500 mL flask. DDQ (1.401 g, 6.172 mmol) was added and the reaction mixture was stirred for 15 minutes. In order to control the reaction progress, a TLC-plate of the reaction mixture was performed in DCM : *n*-Heptane = 1:1. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 1:1). Evaporation of the solvent resulted in 16.2 mg (1.2 %) of dark green powder.

Figure 52: TLC-plate of expected MntBuPhC performed in DCM : *n*-Heptane = 1:1.

Figure 53: Low resolution mass-spectrum of the second spot (from the top) on the TLC-Plate.

According to the mass-spectrum, the compound with $m/z = 761$ complex was obtained. In order to check the presence of other molecules and the purity of obtained substance the mass-spectrum of the product was recorded using MALDI-TOF technique (matrix-assisted laser desorption/ionization with time-of-flight mass spectrometer).

Figure 54: MALDI-TOF mass spectrum of the product.

According to the mass-spectrum, recorded with MALDI-TOF instrument, mostly the substance with $m/z = 759$ was synthesized, which fits to the 5-ptBuPhiC (5-(pyrrol-2-yl)-5,10,15-tris(4-*tert*-butylphenyl)isocorrole). The reason, why isocorrole was obtained, could be an excess of pyrrole, which reacted with corrole during oxidation step with DDQ. Other substances present in the product are free-base corrole ($m/z = 694$) and free-base porphyrin ($m/z = 838$). Based on high resolution mass- and NMR-spectra, shown in later chapter of this master thesis, the synthesized compound cannot be manganese-corrole.

Figure 55: Probable structure of obtained product.

Table 15: Summary of reaction conditions and results of manganese-corrole syntheses.

	Batch 1	Batch 2	Batch 3
Batch Size (Aldehyde Mass)	1 g	2 g	1 g
Equivalents of pyrrole	3.0	3.0	3.0
Equivalents of Catalyst (10% TFA in THF)	0.035	0.023	0.023
Oxidation Agent (1.0 eq.)	DDQ	DDQ	DQQ
Equivalents of $Mn(OAc) \cdot 4H_2O$	0.67	0.67	3.30
Number of balls	16	16	16
Procedure: Step + Grinding time	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole 2 min	Aldehyde + Pyrrole 2 min
	TFA 16 min	TFA 16 min	TFA 16 min
	Salt 4 min	Salt 4 min	Salt 4 min
Oxidation time	15 min	15 min	15 min
Yield	12.3 mg (0.9 % isocorrole)	0 mg (0 %)	16.2 mg (1.2 % isocorrole)

4. Conclusion

During this master thesis, two free-base and three metal-corroles were successfully synthesized using the ball mill. In order to optimize the synthesis of H₃TpFPC and CuTpFPC several reaction conditions have been tested, for example pyrrole to aldehyde ratio, amount and reactivity of catalyst and reaction time. In the synthesis of H₃TpFPC the highest yield achieved was 17.5 %. The general synthesis of metal-corroles requires the use of two chromatography (or three in case of H₃TpFPC derivatives) columns: one (or two) after corrole synthesis and one after metalation. In the direct synthesis of Cu^tBuPhC, the purification of the product could be reduced to only one column chromatography. The highest yield for this direct synthesis amounted to 9.6 %. In the direct synthesis of CuTpFPC, only one chromatography column instead of three was used. The highest yield for this synthesis was 11.5 %. In the synthesis of H₃^tBuPhC, the use of a water-methanol system required for condensation of pyrrole and aldehyde and extraction with DCM could be completely eliminated. It was also proven that the scalability of the condensation reaction is possible. The yield of H₃^tBuPhC synthesis was depending on the batch size and increased from 10.5 % (batch of 1 g aldehyde) to 14.5 % (batch of 5 g aldehyde). The complete synthesis of H₃^tBuPhC, in which both steps - condensation and oxidation - took place in the ball mill, was possible, but achieved yields were significantly lower (4.6-5.4 %). The use of solid support during the condensation, led to a decrease of yield, probably due to high temperature of the reaction mixture, caused by increased friction between the grinding balls and the solid support. At the end of the master thesis several syntheses of Mn^tBuPhC were performed. The expected manganese-corrole was not synthesized. Two reactions probably led to the formation of isocorrole in yield of 0.9 % and 1.2 %. In the third reaction, mostly free-base corrole was obtained.

5. Experimental section

5.1. Materials and equipment

All chemicals were purchased from Sigma Aldrich, Tokyo Chemical Industries and Fluorochem. Pyrrole required additional purification, which was done by distillation. Deuterated chloroform and trifluoroacetic acid used for NMR-measurements were purchased from Euriso-Top. Thin layer chromatography was performed on Macherey-Nagel silica gel 60 (0.20 mm) with fluorescent indicator UV₂₅₄ on aluminium plates and on Merck aluminium oxide 60 (0.20 mm) with fluorescent indicator UV₂₅₄ on aluminium plates. Column chromatography was carried out on silica-gel 60-70 Å from Grace and aluminium oxide (activated, basic, Brockmann III) from Sigma-Aldrich. Proton (¹H-NMR) spectrum were recorded with Bruker Advance 300 MHz NMR spectrometer and Bruker DRX-500 MHz spectrometer. Carbon (¹³C-NMR) and Fluor (¹⁹F-NMR) spectrum were recorded with Bruker DRX-500 MHz spectrometer equipped with cryoprobe (TXI). The chemical shifts are given in ppm (parts per million) on the delta scale (δ). High resolution mass-spectra were recorded using Agilent 6520 Q-TOF mass spectrometer with an ESI source. UV-Vis absorption spectra were recorded on a Varian CARY 300 Bio spectrophotometer in the range of 200 to 900 nm. Fluorescence spectra were obtained with CARY eclipse fluorescence spectrophotometer. Chemical reactions were carried out using Retsch Planetary Ball Mill PM 100 in a 250 mL grinding jar at 650 rpm. The grinding jar and the balls were made of stainless steel. The diameter of the balls was 1 cm and their number was different, depending on the batch size.

5.2. Synthesis of copper-5,10,15-tris(pentafluorophenyl)corrole

Scheme 17: Synthesis of CuTpFPC.

Pentafluorobenzaldehyde (630 μL , 5.101 mmol) and freshly distilled pyrrole (530 μL , 7.652 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. The grinding jar was opened and 47 μL of the solution containing 4.7 μL TFA (0.061 mmol) and 42.3 μL THF were added to the mixture. The reaction mixture was ground for 8 minutes. The grinding jar was opened, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.339 g, 1.698 mmol) was added and the reaction mixture was ground for another 2 minutes. The grinding jar was washed with 200 mL of DCM. The liquid was poured into a round-bottom 500 mL flask. DDQ (1.158 g, 5.101 mmol) was added and the reaction mixture was stirred for 15 minutes. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 3:2). Evaporation of the solvent resulted in 167.5 mg (11.5 %) of brown, shiny powder.

$^1\text{H-NMR}$ (500.1 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ = 7.98 (2H, bs), 7.38 (2H, bs), 7.21 (2H, bs), 7.02 – 7.01 (2H, d, $J(\text{F},\text{F})$ = 3.6 Hz) ppm.

$^{19}\text{F-NMR}$ (470.6 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ = -136.65 – -135.82 (6F, d, $J(\text{F},\text{F})$ = 76.2 Hz), -151.87 – -151.94 (3F, q, $J(\text{F},\text{F})$ = 31.7 Hz), -160.45 – -160.54 (6F, m, $J(\text{F},\text{F})$ = 42.0 Hz) ppm.

HRMS (ESI, positive): m/z calculated for $\text{C}_{37}\text{H}_8\text{CuF}_{15}\text{N}_4$: 855.9805 [M]; found: 855.9817 [M].

UV/Vis Absorption (DCM): λ_{max} = 406, 560, 685 nm.

5.3. Synthesis of 5,10,15-tris(pentafluorophenyl)corrole

Scheme 18: Synthesis of H₃TpFPC.

Pentafluorobenzaldehyde (630 μ L, 5.101 mmol) and freshly distilled pyrrole (530 μ L, 7.652 mmol) were placed in a grinding jar and ground for 2 minutes with 12 balls. The grinding jar was opened and 47 μ L of the solution containing 4.7 μ L TFA (0.061 mmol) and 42.3 μ L THF were added to the mixture. The reaction mixture was ground for 10 minutes. The grinding jar was washed with 200 mL of DCM. The solution was poured into a round-bottom 500 mL flask. DDQ (1.158 g, 5.101 mmol) was added and the reaction mixture was stirred for 15 minutes. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 1:1). Strongly fluorescent fractions were collected, evaporated and purified with a second column chromatography (aluminium oxide 60, basic, activity level II, *n*-heptane : DCM = 1:1). Evaporation of the solvent resulted in 237.5 mg (17.5 %) of purple powder.

¹H-NMR (500.1 MHz, CDCl₃, 25 °C): δ = 9.13 – 9.12 (2H, d, J (H,H) = 4.2 Hz), 8.82 – 8.81 (2H, d, J (H,H) = 4.65 Hz), 8.64 – 8.63 (2H, d, J (H,H) = 4.65 Hz), 8.60 – 8.59 (2H, d, J (H,H) = 3.45 Hz) ppm.

¹⁹F-NMR (470.6 MHz, CDCl₃, 25 °C): δ = -137.14 – -137.21 (2F_o, dd, J (F,F) = 32.5 Hz), -137.70 – -137.74 (4F_o, dd, J (F,F) = 17.4 Hz), -152.14 (2F_p, bs), -152.68 – -152.77 (1F_p, t, J (F,F) = 41.7 Hz), -161.39 (4F_m, t), -161.80 – -161.91 (2F_p, m, J (F,F) = 53.1 Hz) ppm.

HRMS (ESI, positive): m/z calculated for C₃₇H₁₂F₁₅N₄⁺: 797.0817 [M +H]⁺; found: 797.0821 [M +H]⁺.

UV/Vis Absorption (DCM): λ_{max} = 407, 560, 604 nm.

UV/Vis Emission (DCM): λ_{max} = 646, 711 nm.

5.4. Synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole

Scheme 19: Synthesis of 5,10,15-tris-(4-*tert*-butylphenyl)corrole.

4-*tert*-butyl-benzaldehyde (5155 μL , 30.820 mmol) and freshly distilled pyrrole (6415 μL , 92.461 mmol) were placed in a grinding jar and ground for 2 minutes with 20 balls. The grinding jar was opened, 5 balls and 543 μL of the solution containing 54.3 μL TFA (0.709 mmol) and 488.7 μL THF were added to the mixture. The reaction mixture was ground for another 20 minutes. The grinding jar was washed with 200 mL of DCM. The liquid was poured into a round-bottom 500 mL flask. 7.578 g of *p*-chloranil (30.820 mmol) were added and the reaction mixture was refluxed for 90 minutes at 70 °C. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 2:3). Green, fluorescent fractions were collected. Evaporation of the solvent resulted in 1038 mg (14.5 %) of dark green powder.

$^1\text{H-NMR}$ (500 MHz, TFA : CDCl_3 = 13:1, 25 °C): δ = 8.04 – 8.02 (4H, d, $J(\text{H,H})$ = 8.3 Hz), 7.98 – 7.96 (4H, d, $J(\text{H,H})$ = 8.3 Hz), 7.70 – 7.68 (2H, d, $J(\text{H,H})$ = 8.25 Hz), 7.64 – 7.63 (2H, d, $J(\text{H,H})$ = 4.2 Hz), 7.55 – 7.54 (2H, d, $J(\text{H,H})$ = 4.05 Hz), 7.47 – 7.46 (2H, d, $J(\text{H,H})$ = 4.2 Hz), 7.43 – 7.41 (2H, d, $J(\text{H,H})$ = 8.15 Hz), 6.87 (2H, bs), 1.61 (18H, bs), 1.50 (9H, bs) ppm.

HRMS (ESI, positive): m/z calculated for $\text{C}_{49}\text{H}_{51}\text{N}_4^+$: 695.4108 [$M+\text{H}$] $^+$; found: 695.4105 [$M+\text{H}$] $^+$.

UV/Vis Absorption (DCM): λ_{max} = 439, 615, 669 nm.

UV/Vis Emission (DCM): λ_{max} = 677 nm.

5.5. Synthesis of 5,10,15-tris(4-*tert*-butylphenyl)corrole including oxidation in ball mill

Scheme 20: Synthesis of 5,10,15-tris-(4-*tert*-butylphenyl)corrole, the second step is carried out in ball mill.

4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 16 balls. The grinding jar was opened, 109 μL of the solution containing 10.9 μL TFA (0.142 mmol) and 98.1 μL THF were added to the mixture. The reaction mixture was ground for another 20 minutes. The grinding jar was opened and 1.516 g of *p*-chloranil (6.164 mmol) were added. The reaction mixture was ground for 10 more minutes. The resulting black powder was placed directly on top of the chromatography column and purified (silica, *n*-heptane : DCM = 2:3). Green, fluorescent fractions were collected. Evaporation of the solvent resulted in 77.6 mg (5.4 %) of dark green powder.

$^1\text{H-NMR}$ (500 MHz, TFA : CDCl_3 = 13:1, 25 $^\circ\text{C}$): δ = 8.04 – 8.02 (4H, d, $J(\text{H,H})$ = 8.3 Hz), 7.98 – 7.96 (4H, d, $J(\text{H,H})$ = 8.3 Hz), 7.70 – 7.68 (2H, d, $J(\text{H,H})$ = 8.25 Hz), 7.64 – 7.63 (2H, d, $J(\text{H,H})$ = 4.2 Hz), 7.55 – 7.54 (2H, d, $J(\text{H,H})$ = 4.05 Hz), 7.47 – 7.46 (2H, d, $J(\text{H,H})$ = 4.2 Hz), 7.43 – 7.41 (2H, d, $J(\text{H,H})$ = 8.15 Hz), 6.87 (2H, bs), 1.61 (18H, bs), 1.50 (9H, bs) ppm.

HRMS (ESI, positive): m/z calculated for $\text{C}_{49}\text{H}_{51}\text{N}_4^+$: 695.4108 $[M+\text{H}]^+$; found: 695.4105 $[M+\text{H}]^+$.

UV/Vis Absorption (DCM): $\lambda_{\text{max.}}$ = 439, 615, 669 nm.

UV/Vis Emission (DCM): $\lambda_{\text{max.}}$ = 677 nm.

5.6. Synthesis of copper-5,10,15-tris(4-*tert*-butylphenyl)corrole

Scheme 21: Synthesis of copper-5,10,15-tris-(4-*tert*-butylphenyl)corrole.

4-*tert*-butyl-benzaldehyde (2062 μ L, 12.328 mmol) and freshly distilled pyrrole (2566 μ L, 36.985 mmol) were placed in a grinding jar and ground for 2 minutes with 20 balls. The grinding jar was opened, and 217 μ L of the solution containing 21.7 μ L TFA (0.283 mmol) and 195.3 μ L THF were added to the mixture. The reaction mixture was ground for 16 minutes. The grinding jar was opened, 0.553 g of CuCl₂ (3.964 mmol) were added and the reaction mixture was ground for another 4 minutes. The grinding jar was washed with 200 mL of DCM. The liquid was poured into a round-bottom 500 mL flask. 3.031 g of *p*-chloranil (12.328 mmol) were added and the reaction mixture was stirred at room temperature for 17 hours. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane : DCM = 3:2). Evaporation of the solvent resulted in 297 mg (9.5 %) of brown, shiny powder.

¹H-NMR (500 MHz, CDCl₃, 25 °C): δ = 7.85 (2H, bs), 7.73 – 7.69 (6H, m, $J(\text{H,H})$ = 56.4 Hz), 7.63 – 7.61 (2H, d, $J(\text{H,H})$ = 7.8 Hz), 7.51 – 7.46 (6H, m, $J(\text{H,H})$ = 25.7 Hz), 7.40 – 7.39 (2H, d, $J(\text{H,H})$ = 3.8 Hz), 7.32 – 7.31 (2H, d, $J(\text{H,H})$ = 4.3 Hz), 1.44 (27H, bs) ppm.

HRMS (ESI, positive): m/z calculated for C₄₉H₄₇CuN₄: 755.3130 [M]⁺; found: 755.3138 [M].

UV/Vis Absorption (DCM): λ_{max} = 418, 540, 623 nm

5.7. Synthesis of 5-(pyrrol-2-yl)-5,10,15-tris(4-*tert*-butylphenyl)isocorrole

Scheme 22: Synthesis of 5-ptBuPhiC.

4-*tert*-butyl-benzaldehyde (1031 μL , 6.164 mmol) and freshly distilled pyrrole (1283 μL , 18.492 mmol) were placed in a grinding jar and ground for 2 minutes with 16 balls. The grinding jar was opened and 10 % TFA solution in THF (108.5 μL , 0.142 mmol) was added to the mixture. The reaction mixture was ground for another 16 minutes. $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (5.001 g, 20.406 mmol) was added to the reaction mixture and ground for 4 minutes. The grinding jar was opened and 200 mL of DCM were added. The liquid was poured into a round-bottom 500 mL flask. DDQ (1.401 g, 6.172 mmol) was added and the reaction mixture was stirred for 15 minutes. In order to control the reaction progress, a TLC-plate of the reaction mixture was performed in DCM : *n*-Heptane = 1:1. The solvent was evaporated and the product was purified with column chromatography (silica, *n*-heptane:DCM = 1:1). Evaporation of the solvent resulted in 16.2 mg (1.2 %) of dark green powder.

$^1\text{H-NMR}$ (500 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ = 14.90 – 14.87 (2H, d, $J(\text{H,H})$ = 16.20 Hz), 7.49 – 7.48 (4H, d, $J(\text{H,H})$ = 2.45 Hz), 7.41 (4H, s), 7.26 – 7.25 (2H, d, $J(\text{H,H})$ = 2.85 Hz), 7.19 – 7.17 (2H, d, $J(\text{H,H})$ = 8.45 Hz), 7.07 – 7.06 (1H, d, $J(\text{H,H})$ = 4.5 Hz), 6.95 – 6.94 (1H, d, $J(\text{H,H})$ = 4.5 Hz), 6.65 – 6.64 (2H, d, $J(\text{H,H})$ = 4.6 Hz), 6.60 – 6.58 (1H, t, $J(\text{H,H})$ = 5.75 Hz), 6.48 – 6.47 (1H, dd, $J(\text{H,H})$ = 5.55 Hz), 6.37 – 6.36 (1H, d, $J(\text{H,H})$ = 4.55 Hz), 6.29 – 6.27 (1H, dd, $J(\text{H,H})$ = 6.45 Hz), 6.14 – 6.12 (2H, m), 5.96 – 5.95 (1H, t, $J(\text{H,H})$ = 5.65 Hz), 1.39 – 1.38 (18H, dd, $J(\text{H,H})$ = 3.65 Hz), 1.29 (9H, s) ppm.

UV/Vis Absorption (DCM): λ_{max} = 347, 418, 513, 531, 660, 190 nm.

6. Outlook

The future plan for solventless, mechanochemical syntheses includes the formation of free-base corroles starting from different types of highly reactive, moderately reactive and sterically hindered aldehydes and their metalation with Cr, Fe, Co, Zn, Ni, Al, Ga and Bi. Depending on the reactivity of used aldehydes and catalytic activity of metal compounds the condensation time has to be optimized. To achieve higher yield and make the syntheses more reproducible, also a better ratio of pyrrole to aldehyde has to be developed. In order to completely remove organic solvents required in the oxidation step, some new oxidation agents, for example DDQ, iodine, nitric acid, sodium ethoxide or potassium peroxymonosulfate and longer reaction times have to be tested.

Scheme 23: Plan for the future mechanochemical synthesis of corroles from A: highly reactive, B: sterically hindered and C: moderately reactive aldehydes.

7. Appendix

7.1. Analytics of CuTpFPC

Figure A 1: ^1H -NMR spectrum of purified CuTpFPC.

Figure A 2: ^{19}F -NMR spectrum of purified CuTpFPC.

Figure A 3: UV/Vis spectrum of purified CuTpFPC.

7.2. Analytics of H₃TpFPC

Figure A 4: ¹H-NMR spectrum of purified H₃TpFPC.

Figure A 5: ¹⁹F-NMR spectrum of purified H₃TpFPC.

Figure A 6: UV/Vis absorption spectrum of purified H₃TpFPC.

Figure A 7: UV/Vis emission spectrum of purified H₃TpFPC.

Figure A 8: HRMS-ESI spectrum of purified H₃TpFPC.

7.3. Analytics of H₃tBuPhC

Figure A 9: ¹H-NMR spectrum of purified H₃tBuPhC.

Figure A 10: ¹H-NMR spectrum of purified H₃tBuPhC in aromatic region.

Figure A 11: UV/Vis absorption spectrum of purified H₃tBuPhC.

Figure A 12: UV/Vis emission spectrum of purified H₃tBuPhC.

Figure A 13: HRMS-ESI spectrum of purified H₃tBuPhC.

7.4. Analytics of CutBuPhC

Figure A 14: ¹H-NMR spectrum of purified CutBuPhC.

Figure A 15: ¹H-NMR spectrum of purified CutBuPhC in aromatic region.

Figure A 16: UV/Vis absorption spectrum of purified CutBuPhC.

Figure A 17: HRMS-ESI spectrum of purified CutBuPhC.

7.5. Analytics of 5-ptBuPhiC.

Figure A 18: ^1H -NMR spectrum of purified 5-ptBuPhiC.

Figure A 19: ^1H -NMR spectrum of purified 5-ptBuPhiC in aromatic region.

Figure A 20: UV/Vis absorption spectrum of purified 5-ptBuPhiC.

Figure A 21: HRMS-ESI spectrum of purified 5-ptBuPhiC.

8. References

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