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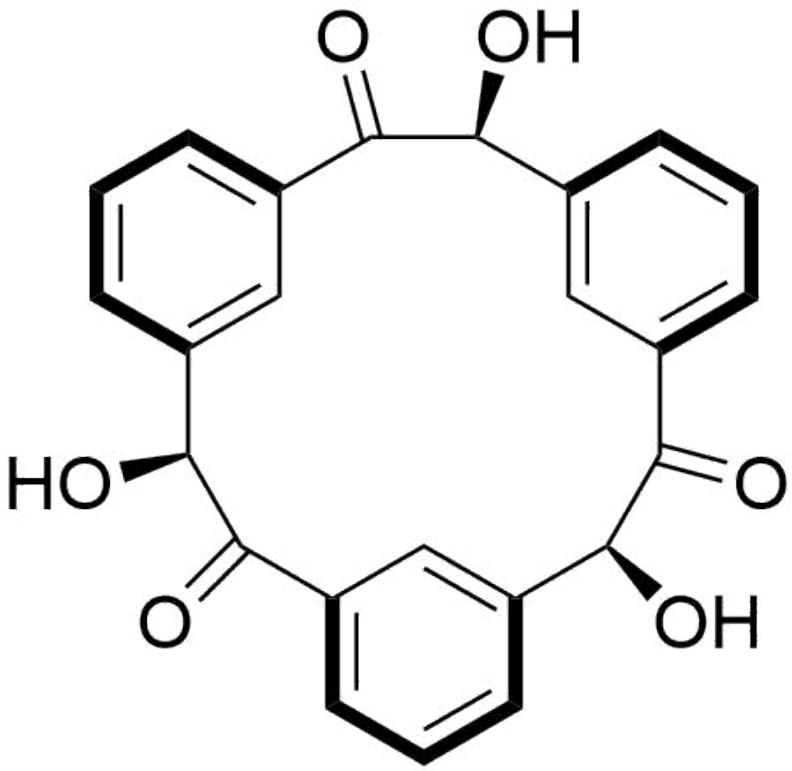

Carbene catalyzed tribezoin condensation

Optimisation of the benzoin condensation with carbene catalysis

Master's thesis in Materials Chemistry

Simon Barrestål

Department of Chemistry and Chemical Engineering
CHALMERS UNIVERSITY OF TECHNOLOGY
Gothenburg, Sweden 2020

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Master's Thesis 2020
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Cover: Lewis structure of cyclotribenzoin.

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Abstract

The benzoin condensation is an useful reaction for the formation of carbon-carbon bonds. Cyclobenzoins are macrocyclic molecules traditionally synthesised with this method. State-of-the-art synthesis of cyclotribenzoins currently employ cyanide as the catalyst. Here, I report the use of safer cyanide free *N*-heterocyclic carbenes (NHCs) as the catalyst. The cyclobenzoin (namely cyclotribenzoin) was synthesised in a good yield (89 %). A range of NHC precatalysts were explored, with triazoles being the most successful.

Keywords: *N*-heterocyclic carbenes, NHCs, cyclotribenzoin, cyclobenzoin, macrocycle

Acknowledgements

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Finally I would like to thank all the lovely people working on the 9th floor of the chemistry building, it has been an absolute pleasure to get to know you all.

Simon Barrestål, Gothenburg, August 2020

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Abbreviations and formulas

^{13}C NMR	carbon-13 nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
Ac_2O	acetic anhydride
ACN	acetonitrile
Bode Catalyst 1	(5aS,10bR)-2-mesityl-5a,10b-dihydro-4H,6H-indeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium chloride
Cat1	1,4-dimethyl-4H-1,2,4-triazolium iodide
Cat101	4,5-dimethyl-3-(phenylmethyl)-thiazolium bromide
Cat101 Cl	4,5-dimethyl-3-(phenylmethyl)-thiazolium chloride
Cat1-Et	4-ethyl-1-methyl-4H-1,2,4-triazolium iodine
Cat5	2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride
Cat5-F6	6,7-dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMSO	dimethyl sulfoxide
ee	percentage enantiomeric excess
EMIM Ac	1-ethyl-3-methylimidazolium acetate
equiv.	molar equivalents
Et_2O	diethyl ether
EtOH	ethanol
H_2O	deionized water
H_2SO_4	sulphuric acid
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
IMes Cl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
IPA	propan-2-ol
LUMO	lowest unoccupied molecular orbital
MeI	iodomethane
MMIM I	1,3-dimethylimidazolium iodide
MS	mass spectrometer
MSM	methylsulfonylmethane
N_2	nitrogen

NaCN sodium cyanide

NHCs *N*-heterocyclic carbenes

rt room temperature

SPNs supramolecular polymeric networks

THF tetrahydrofuran

TIC total ion count

UV-Vis spectrophotometer ultraviolet-visible spectrophotometer

1
Introduction

1.1 Macrocycles

Macrocycles are cyclic compounds containing cyclic structures of at least 12 atoms.[1–3] Macrocyclic compounds can both be found in nature, such as macrolides, or be made synthetically, such as crown ethers and spherands.[1,4,5]

Crown ethers (Figure 1.1) are macrocyclic polyethers first described by Lüttringhaus and Ziegler in 1937.[6,7] The term crown ether comes from their ability to coordinate metal ions, as presented by Pedersen in 1967.[6] Thanks to crown ethers ability to form complexes with inorganic salts they have seen use in phase transfere catalysis since these complexes have a higher solubility in nonpolar solvents compared to the salts. The coordination of the cation also improves the reactivity of the anion by separating it from its cation. Another area where crown ethers have seen use is in the field of supramolecular polymeric networks (SPNs).[8] SPNs contains polymer chains that are cross-linked by non-covalent interactions, such as hydrogen bonding or π-stacking.[8–11] This field has also utilised macrocycle-based host-guest recognition, such as the interaction between crown ethers and specific salts, to cross-link different polymer chains.

The use of macrocycles also includes cyclodextrin, calixarene and cucurbituril.[8] SPNs have gathered attention in recent years due to their potential use as superabsorbers, matrices in analytical chemistry and drug delivery systems.[8,10] Part of the appeal with SPNs is their ability for self healing.

Spherands (Figure 1.1 right) are a group of compounds that were first reported in 1979 by Donald J. Cram et.al.[5,12,13] Spherands as a group consist of macrocyclic molecules with a central cavity lined with electron-pairs. The cavity in these compounds is able to strongly complex bind to different metal ions, such as Li^+ and Na^+.

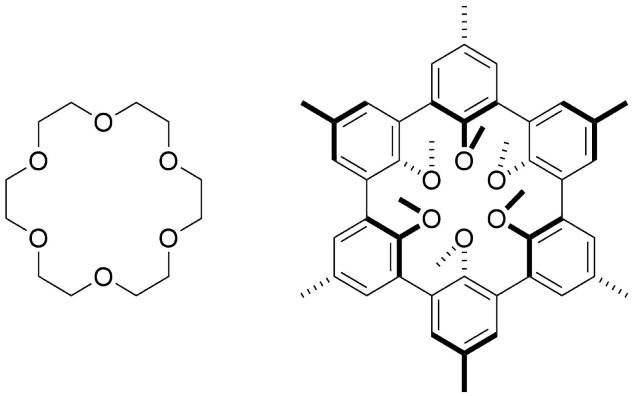


Figure 1.1: Lewis structure of a crown ether (left) and a spherand (right) presented by Donald J. Cram et.al.[12]

The spherand was synthesised by Donald J. Cram et.al.[12] Since their discovery in 1979, this group of macrocycles has seen considerable use in host-guest chemistry.[14]

One potentially limiting factor in researching macrocycles and their application is the often time consuming synthesis of the synthetic compounds, and the limited control of derivation of the nature-based compounds.[15] Because of these obstacles a direct synthesis path resulting in a macrocyclic compound with readily derivatised functional groups could be of great usefulness.

1.2 Benzoin condensation

Benzoin condensation is an addition reaction known since the 1830s which can be used to form a C-C bond between two aldehydes, resulting in a α-hydroxy ketone.[15,16] The benzoin condensation is catalysed by either cyanide ($^{-}$CN) (Figure 1.2) or carbenes (R_2C:) (Figure 1.3). The benzoin condensation utilises a masked acyl anion (or an acyl anion equivalent, Figure 1.2 intermediate iii) to perform a nucleophilic attack on a second aldehyde resulting in the formation of a new C-C bond. A. Hassner and K. Rai explain that these equivalents generally are "of type −RCXY, in which CXY can be reconverted into a carbonyl group".[16] In the particular case of the benzoin condensation X is a hydroxyl group while Y is either a cyano group or carbene depending on the choice of catalyst (intermediate iii in Figure 1.2 and 1.3, respectively).

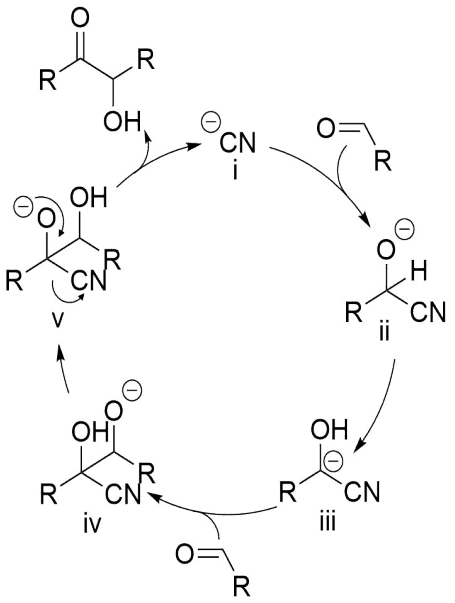


Figure 1.2: Reaction scheme for benzoin condensation using cyanide as catalyst. The cyanide ion (i) performs a nucleophilic attack on the carbonyl carbon of the aldehyde resulting in a tertiary intermediate (ii), which then results in the formation of a masked acyl anion (iii). This anion then performs a nucleophilic attack on a second aldehyde to form intermediate (iv) and after a proton transfer intermediate (v) is formed which then fragments to render the benzoin product and the catalyst is regenerated.

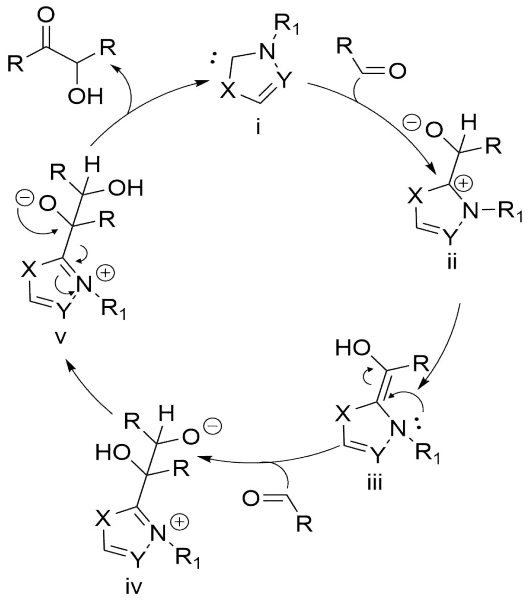


Figure 1.3: Reaction scheme for benzoin condensation using a carbene catalyst. The carbene (i) performs a nucleophilic attack on the carbonyl carbon of the aldehyde resulting in a tertiary intermediate (ii), which then results in the formation of a Breslow intermediate (iii). This intermediate then performs a nucleophilic attack on a second aldehyde to form intermediate (iv). After a proton transfer intermediate (v) is formed. In the final step (v) is fragmented to form the benzoin product and the carbene catalyst is regenerated.

The benzoin condensation is reversible, which can be demonstrated by exposing benzoin to cyanide in the presence of a different aldehyde which will result in a mixture of different benzoins (Figure 1.4).[16]

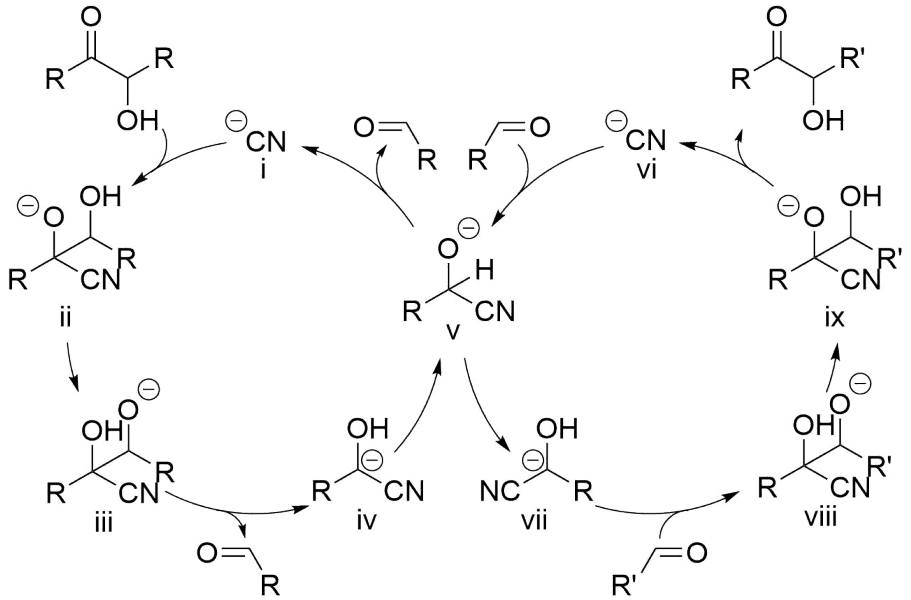


Figure 1.4: Reaction scheme for the cyanide catalysed retro benzoin condensation, as well as the cyanide catalysed benzoin condensation. The cyanide (i) performs a nucleophilic attack on the carbonyl carbon of the benzoin resulting in a tertiary intermediate (ii), which then results in the formation of intermediate (iii) via a proton transfer. This intermediate then an aldehyde in order to form a masked acyl ion (iv). After a proton transfer intermediate (v) is formed. In the final step (v) is fragmented to form an aldehyde and the cyanide is regenerated. For the second catalytic cycle the cyanide (vi) performs a nucleophilic attack on an aldehyde resulting in the formation of a tertiary intermediate (v). The tertiary intermediate then transform in to a masked acyl ion (vii) via a proton transfer. This masked acyl ion can then perform a nucleophilic attack on an aldehyde resulting in the tertiary intermediate (viii). This intermediate then undergoes a proton transfer to generate intermediate (ix) which in turn fragments to generate the new benzoin product containing two different side groups and regenerates the cyanide catalyst.

Furthere more, it has been shown that carbenes can catalyse benzoin condensations in both solvent free conditions (where the aldehyde is in the liquid state) as well as of solid aldehydes.[17,18] In addition, the benzoin produced from the benzoin condensation contains a stereogenic centre, and it has been

demonstrated that this centre can be formed stereoselectively using chiral carbene-catalysts.[19] As for the use of benzoins, α-hydroxy ketones are present in biologically active natural products, in drugs used to treat depression, Alzheimer's, as well as precursors for other chemicals.[19–21]

1.2.1 Cyclobenzoins

It has previously been shown that benzoin condensation of benzene-dicarboxaldehydes such as terephthalaldehyde can be used to form polymeric chains.[22,23] While the synthesis of polymeric chains using the benzoin condensation has been known for decades, the first synthesis of macrocyclic compounds using only the benzoin condensation was first reported in 2015.[15,24,25] The two macrocyclic benzoin products that where first reported is Cyclotribenzoin (**1**, Figure 1.5) and cyclotetrabenzoin (**2**, Figure 1.5) which where reported by Ognjen Š. Miljanić et.al. in 2015.[15,24,25]

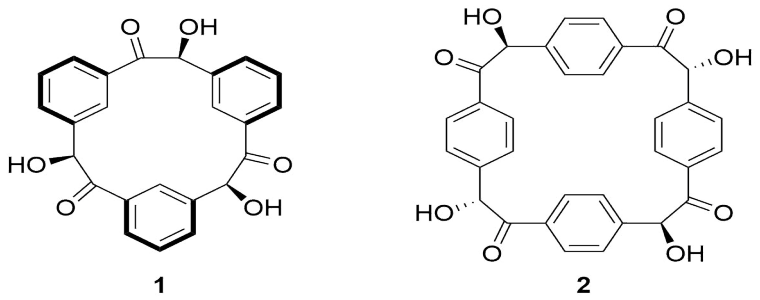


Figure 1.5: Lewis structure of cyclotribenzoin and cyclotetrabenzoin as presented by Ognjen Š. Miljanić et.al.[15,24,25]

In order to synthesise cyclotribenzoin and cyclotetrabenzoin Ognjen Š. Miljanić et.al let isophthalaldehyde (**3**, Figure 2.1) and terephthalaldehyde (**4**, Figure 2.1), respectively, undergo a sodium cyanide (NaCN)-catalysed benzoin condensation.[15,24,25] The yields reported were 41 % for cyclotribenzoin and 21 % for cyclotetrabenzoin, respectively. In addition to synthesising the aforementioned macrocycles, further functionalisation has also been reported such as both acetylation and oxidation of the α-hydroxyl group..[15,26] In addition to derivatization of the hydroxyl group the reduction of the carbonyl group, resulting in a 1,2-diol called hydrobenzoin, have been reported. The reduction of cyclotribenzoin was found to be diastereoselective resulting in all-*cis* cyclotrihydrobenzoin which was able to co-crystallise with water.[15,27]

The crystal structure of cyclotribenzoin has previously been reported (Figure 1.6).[24] The structure of cyclotribenzoin can be viewed as a bowl or a crown with the benzene rings at an angle with the proton ortho to the carbonyl and α-carbon is pointing towards the centre cavity of the structure. The α-proton is also pointing in to the centre cavity. The α-hydroxyl points outward of the cycle while the carbonyls point in the same direction as the adjacent benzene ring.

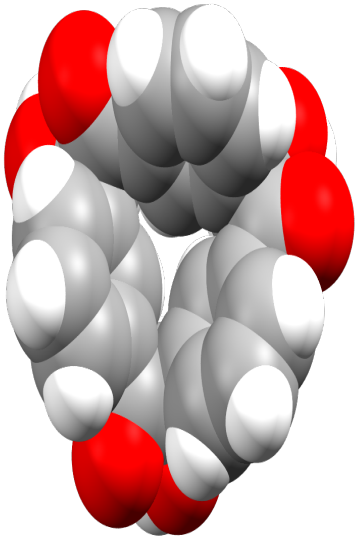


Figure 1.6: Crystal structure of cyclotribenzoin.[24]

1.3 Carbenes

Carbenes are neutral compounds containing one nonbonding π-orbital and one nonbonding σ-orbital.[28–31] The two electrons split between the two orbitals can either have the same spin, or the opposite, resulting in a singlet carben or a triplet carbene, respectively. A simple way to determine whether a carbene is of a singlet or triplet type is to let it react with a *cis*-alkene; a singlet carbene will usually result in a *syn*-product (which is thermodynamically less stable) (Figure 1.7) while a triplet carbene will produce a mixture of *syn*- and *anti*-cyclopropane (Figure 1.8).[28–30]

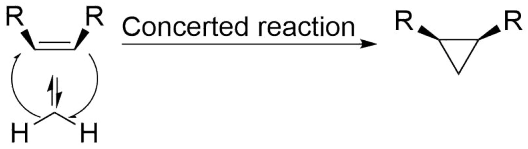


Figure 1.7: Reaction scheme for the reaction of a singlet carbene with a *cis*-alkene.

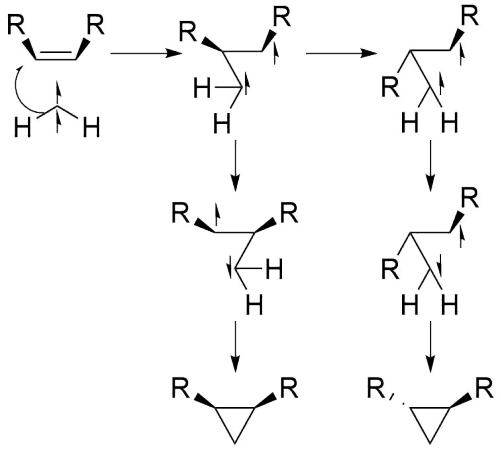


Figure 1.8: Reaction scheme for the reaction of a triplet carbene with a *cis*-alkene.

Carbenes can be used to perform several different reactions such as: π-insertion (as shown in Figure 1.7 and 1.8) and σ-insertion (Figure 1.9).[28,30] Carbenes can also react with unsaturated cyclic compounds

resulting in an expansion of the cyclic compound (Figure 1.10).

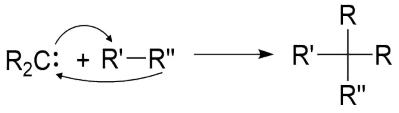


Figure 1.9: Reaction scheme for a σ-insertion.

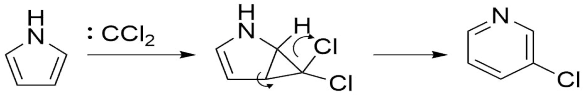


Figure 1.10: Reaction scheme for the insertion of a carbene into pyrrole yielding 3-chloropyridine.

While there are many different methods to produce carbenes this study has only used *N*-heterocyclic carbenes (NHCs) formed via deprotonation of azolium (imidazolium, triazolium and thiazolium) salts (Figure 1.11).[28–30,32] It can also be noted that NHCs do not need to contain two nitrogen atoms adjacent to the carbene, there exist carbenes containing different heteroatoms such as sulphur and oxygen.

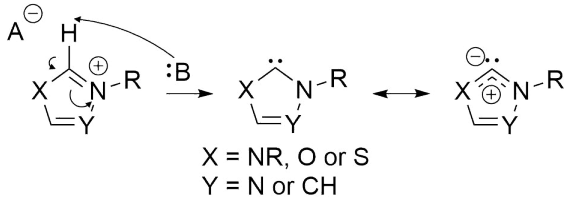


Figure 1.11: Reaction scheme for activation of *N*-heterocyclic carbenes (NHCs) in basic condition, alongside resonance structures for the activated carbene.

NHCs, heterocyclic compounds containing a carbene carbon and at least one nitrogen atom, where first isolated in 1991.[33,34] The stability of the carbene in NHCs is partially due to generally bulky substituents adjacent to the carbene carbon, which disfavours dimerization. The nitrogen atoms also provide electronic stabilisation to the carbene, which contains a singlet ground-state electronic configuration with the highest occupied molecular orbital (HOMO) best described as a sp^2-hybridized lone pair. lowest unoccupied molecular orbital (LUMO) on the other hand is best described as an unoccupied *p*-orbital at the carbene carbon. The adjacent nitrogen atom(s) can stabilise this system by virtue of them being σ-electron withdrawing and π-electron donating, which lowers the energy of the occupied σ-orbital and donates electron density in to the empty *p*-orbital.

1.4 Aim

The aim of this project was to synthesise cyclotribenzoin using NHCs instead of NaCN as catalyst with the goal to demonstrate safer reaction conditions resulting in higher yield. This is also supported by the principles of green chemistry, principle #3 Less Hazardous Chemical Synthesis.[35] In addition to the optimisation of the initial synthesis it was also desired to test these conditions using alternative substrates.

1.5 Focus

The project will be focused on the formation of cyclotribenzoin and its analogous compounds, virtually no chemical reactions using the benzoin as starting material will be undertaken, with the exception of acetylation in order to facilitate the use of high-performance liquid chromatography (HPLC) to compare percentage enantiomeric excess (*ee*) obtained using a chiral catalyst. Neither 5-bromoisophthalaldehyde nor most of the NHCs used where synthesised as part of this project, some where commercially available others had all ready been synthesised by members of this research group.

1.6 Specification of issue under investigation

Questions to be answered:

- Can NHCs catalyse the cyclotribenzoin reaction?
- Can we optimise the reaction so that it is a viable alternative to the cyanide catalysed cyclotribenzoin condensation?
- Can the reaction be expanded to include dialdehydes analogous to isophthalaldehyde?

2

Methodology

Using isophthalaldehyde (**3**, Figure 2.1) and terephthalaldehyde (**4**, Figure 2.1) the synthesis of cyclotribenzoin and cyclotetrabenzoin, respectively, was first reported by Ognjen Š. Miljanić et.al.[15,24,25]

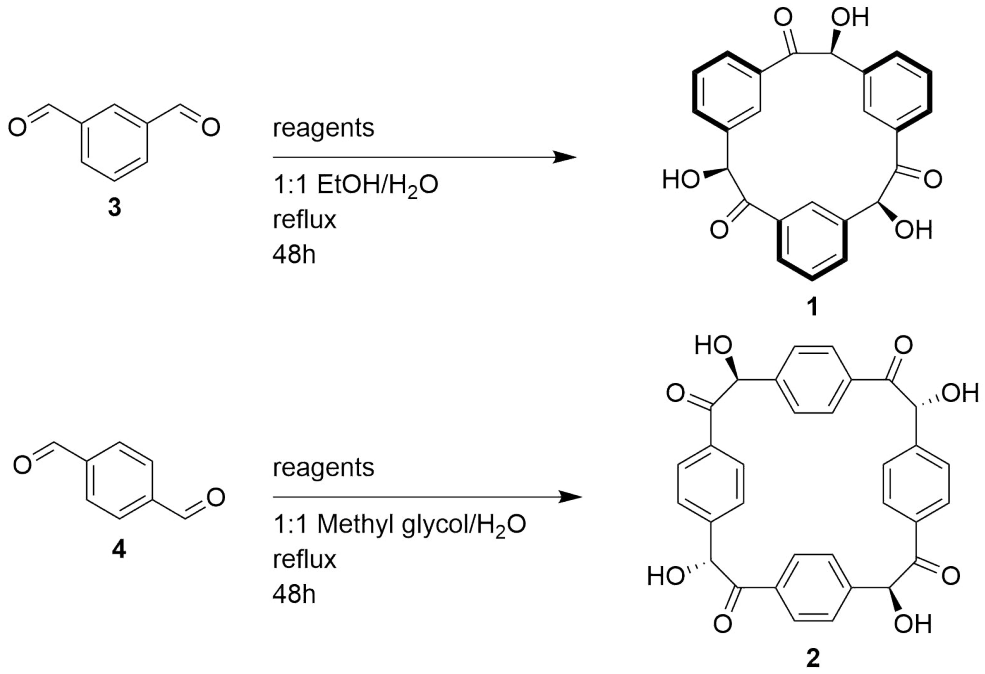


Figure 2.1: Reaction scheme for the synthesis of **1** and **2** using **3** and **4** as starting material, respectively.

In their work they managed to form ring structures containing 3 and 4 benzene-rings for reagent **3** and **4**, respectively. In both cases NaCN (0.1 molar equivalents (equiv.)) was used as a catalyst. In this studdy I will attempt to replace the NaCN catalyst with NHCs, such as 1,4-dimethyl-4H-1,2,4-triazolium iodide (**5a**, Figure 2.2) Synthesis of Cat1 is outlined in Appendix, page IV.

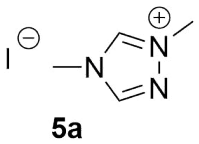
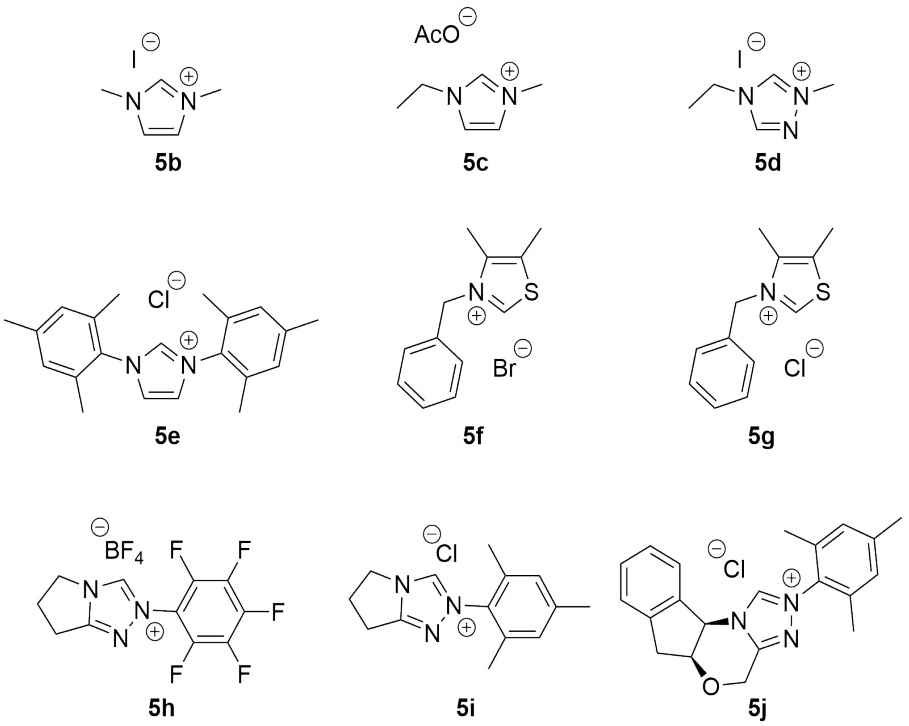


Figure 2.2: Lewis structure of 1,4-Dimethyl-4H-1,2,4-triazolium iodide (**5a**).

The reaction will then be optimised by varying the load of catalyst, amount of base and solvent used and reaction temperature. In addition, apart from **5a** other NHCs (Table 2.1) will be tested. The yield of cyclotribenzoin, which will be measured with proton nuclear magnetic resonance (^{1}H NMR) using methylsulfonylmethane (MSM) as an internal standard.

Table 2.1: List of NHCs included in this study



No.	Name	Abbreviation
5b	1,3-dimethylimidazolium iodide	MMIM I
5c	1-ethyl-3-methylimidazolium acetate	EMIM Ac
5d	4-ethyl-1-methyl-4H-1,2,4-triazolium iodine	Cat1-Et
5e	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride	IMes Cl
5f	4,5-dimethyl-3-(phenylmethyl)-thiazolium bromide	Cat101
5g	4,5-dimethyl-3-(phenylmethyl)-thiazolium chloride	Cat101 Cl
5h	6,7-dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate	Cat5-F6
5i	2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride	Cat5
5j	(5aS,10bR)-2-mesityl-5a,10b-dihydro-4H,6H-indeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium chloride	Bode Catalyst 1

The carbenes that are going to be tested can be divided in to three general groups: imidazole- (Table 2.1 entry 1, 2 and 4) 1,2,4-triazole- (Table 2.1 entry 3, 7-9) and thiazole-based carbenes (Table 2.1 entry 5 and 6). **5b** was chosen as an imidazole analogue to **5a**. **5c** and **5d** were chosen to compare the effect of having a ethyl-group attached to the heterocycle compared to the methyl-group seen in **5b** and **5a**, respectively. The last imidazole **5e** was tested to see if an even more lipophilic carbene could produce improved results. **5f** and **5g** where chosen to see if a thiazole-based carbene could catalyse the synthesis of **1**, and they where both tested to see if the different anion would affect the results. The two triazoles **5h** and **5i** were tested for the same reason as **5e**: to see if lipophilic carbenes gave a better yield. Lastly **5j** was tested because it was desired to try and obtain a homo-chiral sample of **1** in addition to the racemic mixture the other carbenes would produce.

2.1 Alternative substrates

After successful results using isophthalaldehyde it is desired to employ the same methods using an analogous substrate, such as 5-bromoisophthalaldehyde (**6**, Figure 2.3) and 2,6-pyridinedicarboxaldehyde (**7**, Figure 2.3). The synthesis of **7** is shown in Appendix (page VI).

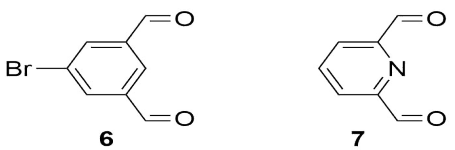


Figure 2.3: Lewis structure for 5-bromoisophthaladehyde (left) and 2,6-pyridinedicarboxaldehyde (right).

The reason for the choice of **6** was that the bromine, placed in a meta position to both carbonyls on the aromatic ring (**8**, Figure 2.4), could potentially allow for a wide range of chemistry such as Suzuki–Miyaura coupling, Stille Coupling and Miyaura Borylation reaction where the first two result in carbon-carbon bonds while the last result in the formation of a boronate .[36,37] The reason for synthesising **7** was that the position of the nitrogen in the final benzoin product, pointing inward to the central cavity, might allow for it to coordinate different species such as metal ions or halides (**9**, Figure 2.4).[38] This coordination might allow **9** to be used, depending on its selectively, to coordinate to other species similar to how other macrocycles, such as crown ethers, have been used to form SPNs.[8]

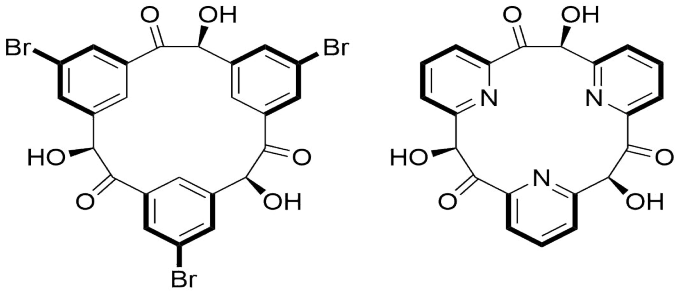


Figure 2.4: Lewis structure for cyclotribenzoin product synthesised from **6** and for cyclotribenzoin product synthesised from **7**.

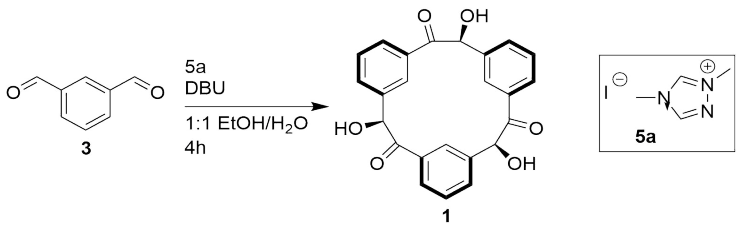
3

Results and Discussion

3.1 Optimisation of Cyclotribenzoin synthesis

Before proceeding to alternative starting materials I went forward to optimise the reaction using isophthalaldehyde. To this end a series of experiments where performed using the same procedures as described in Chapter 5.2 and 5.2.2 (using **5a** as catalyst) but with varying catalyst load, DBU load and reaction temperature used (Table 3.1). The catalyst load was varied between 0.05 and 0.25 equiv., while the DBU load was varied between 0.10 and 0.50 equiv.. The reaction temperature ranged from room temperature (rt) and 150 °C, and three experiments used dichloromethane (DCM) as solvent instead of a 1:1 volume ratio of EtOH and H_2O. The yield was calculated based on ^{1}H NMR using methylsulfonylmethane (MSM) as an internal standard.

Table 3.1: Yield based on ^{1}H NMR obtained when performing optimisation screening*



Entry	5a [equiv.]	DBU [equiv.]	T [°C]	Yield_{NMR} [%]
1	0.05	0.10	80	3
2	0.10	0.10	80	8
3	0.25	0.10	80	39
4	0.25	0.10	50	11
5	0.25	0.10	120	23
6	0.25	0.10	150	1
7	0.25	0.25	80	32
8	0.25	0.50	80	8
9**	0.25	0.10	rt	1
10**	0.25	0.10	50	2
11**	0.25	0.10	80	23

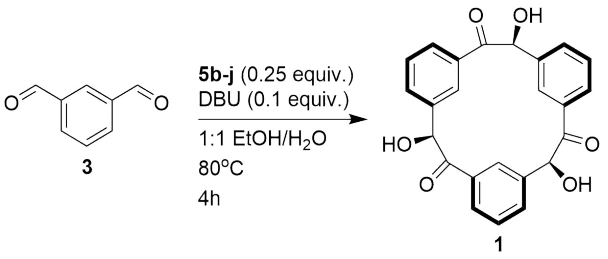
*Conditions: **3** (0.25-1 mmol), **5a** (0.05-0.25 equiv.), DBU (0.10-0.50 equiv.) EtOH (0.98 mL/mmol **3**) and H_2O (0.98 mL/mmol **3**) is added to a microwave vial that is then sealed with a crimp cap. After the vial has been sealed it is evacuated and filled with N_2-gas and then heated to indicated temperature.
DCM (1.96 mL/mmol **3) used as solvent.

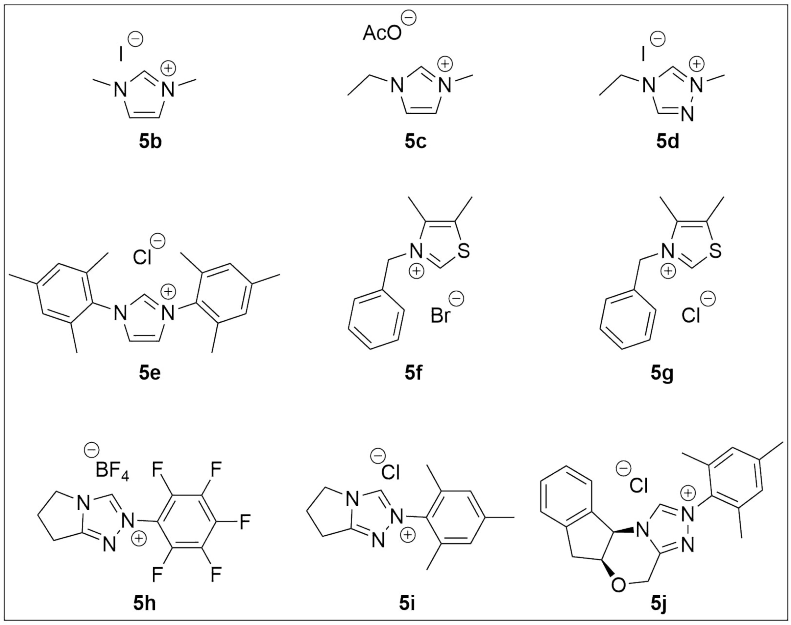
Based on the optimisation study I found that the reaction gave the highest yield at 80 °C. The reason why the lower temperature produced a lower yield might be because **3** does not dissolve untill the mixture is heated to 65-70 °C, while the higher temperature might favour the formation of polymer chains rather than **1**. It was also noted that an increase in the DBU loading had an adverse effect on the yield, the reason for which is not known. This might be due to an increased reaction rate for the retro benzoin condensation. The best result was found when using a catalyst load of 0.25 equiv., DBU load of 0.10 equiv. at 80 °C in a 1:1 mixture of EtOH and H_2O.

With these optimised conditions in hand we compared a number of different NHCs and the resulting yields. Accordingly, 9 experiments where performed using 0.25 equiv. of carbene **5b-5j** as catalysts

(Table 3.2).

Table 3.2: Comparison of different NHCs and their corresponding yield*





Entry	Catalyst	Yield_{NMR} [%]
1	**5b**	0
2	**5c**	0.5
3	**5d**	84
4	**5e**	0
5	**5f**	0
6	**5g**	1
7	**5h**	1
8	**5i**	89
9	**5j**	16

*Conditions: **3** (0.255mmol), **5b-5j** (0.25 equiv.), DBU (0.10equiv.) EtOH (0.98 mL/mmol **3**) and H_2O (0.98 mL/mmol **3**) is added to a microwave vial that is then sealed with a crimp cap. After the vial has been sealed it is evacuated and filled with N_2-gas and then heated to 80 °C.

As it turns out imidazole and thiazole failed to provide results comparable to **5a** (39 % yield). Carbenes **5d** and **5i** resulted in yields superior of what any of the other carbenes provided and was therefore used in subsequent reactions to obtain the isolated yield. The chiral carbene (**5j**) was also reevaluated, but with a longer reaction time, in order to try and obtain a homo-chiral sample of cyclotribenzoin. The reason for the difference in yield between the different carbenes could be due to a difference in nucleophilicity between the carbenes based on triazole when compared to those made of imidazole or thiazole. The variation within the carbenes based on triazole could perhaps be explained by a difference in lipophility, where a higher lipophility is preferable.

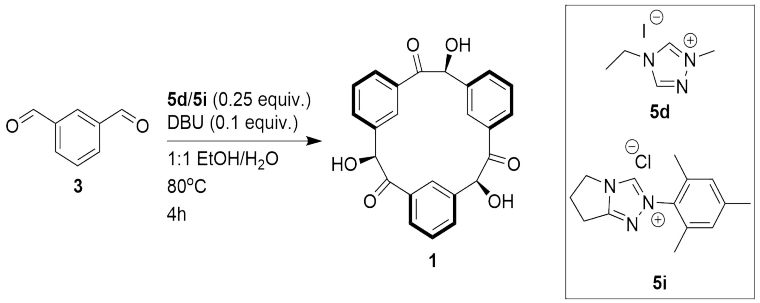
From the optimization study we can conclude that the optimum reaction conditions was determined to be 0.25 equiv. Cat5, 0.10 equiv. DBU, reaction temperature of 80 °C, reaction time of 4 h, 0.98 mL/mmol

EtOH and 0.98 mL/mmol H_2O.

3.2 Synthesis of cyclotribenzoin utilising optimised conditions

Since NHCs **5d** and **5i** gave the highest yield based on conversion measured by NMR on the crude reaction mixture (Table 3.2) it was desired to measure the isolated yield when using these two catalysts. Accordingly, two experiments where performed using the optimised reaction conditions for both carbene **5d** and **5i** (Table 3.3).

Table 3.3: Isolated yield obtained when using **5d** and **5i**, respectively, as catalyst*



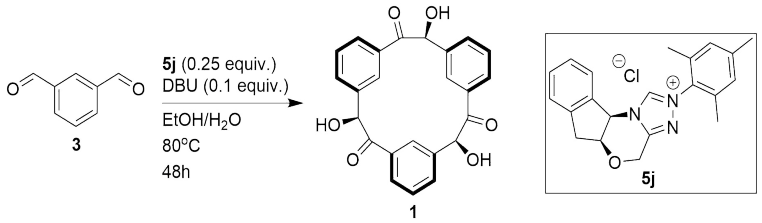
Entry	Catalyst	Yield [%]
1	**5d**	55
2	**5i**	74

*Conditions: **3** (1.27 mmol), **5d**/**5i** (0.25 equiv.), DBU (0.10 equiv.) EtOH (1.25 mL) and H_2O (1.25 mL) is added to a microwave vial that is then sealed with a crimp cap. After the vial has been sealed it is evacuated and filled with N_2-gas and then heated to 80 °C.

In both cases the method outlined in Chapter 5.2 was employed. Carbene **5i** provided the higher isolated yield, which is consistent with the results of the optimisation screening where **5i** gave the highest yield based on NMR.

The experiment using the chiral catalyst **5j** was also repeated, but with a longer reaction time in order to see the yield based on ^{1}H NMR as well as isolated yield obtained after 48 h. The experiment is listed in Table 3.4.

Table 3.4: Yield based on ^{1}H NMR and isolated yield obtained when using **5j** as catalyst*



Entry	Catalyst	Yield_{NMR} [%]	Yield [%]
1	**5j**	70	59

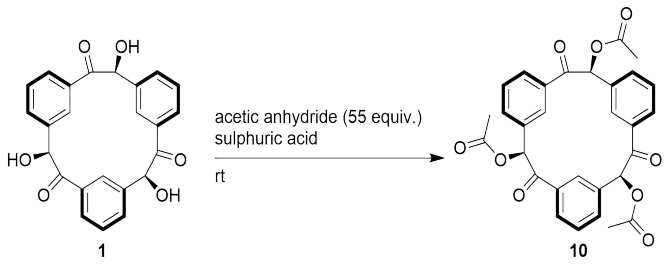
*Conditions: **3** (0.26 mmol), **5j** (0.25 equiv.), DBU (0.10 equiv.) EtOH (0.25 mL) and H_2O (0.25 mL) is added to a microwave vial that is then sealed with a crimp cap. After the vial has been sealed it is evacuated and filled with N_2-gas and then heated to 80 °C.

The workup was performed as outlined in Chapter 5.2.2, after which the remaining THF-solution was reduced *in vacuo* and a workup based on that detailed in Chapter 5.2 performed. ^{1}H NMR spectrum for the purified product can be seen in Figure A.3.

3.3 Acetylation of cyclotribenzoin

In order to determine percentage enantiomeric excess (ee) of the cyclotribenzoin isolated from the reaction catalysed by **5j** chiral HPLC separation needed to be performed. Due to the insolubility of **1** in the mobile phase used in the HPLC (a mixture of propan-2-ol (IPA) and hexane), acetylation of the benzoin was performed and ee was acquired based on the acetylated product (**10**). The acetylation was performed performed as described in Chapter 5.3 using acetic anhydride (Ac_2O). Before acetylation was performed on the cyclotribenzoin obtained using **5j** it was done using the cyclotribenzoin obtained from the reaction with **5i** (Table 3.5)

Table 3.5: Acetylation of **1** using Ac_2O*



Entry	Reaction time [h]	Yield [%]
1	24	86
2	96	24

*Conditions: **1** (0.050-0.075 mmol), Ac_2O (55 equiv.), H_2SO_4 (few drops) is added to a microwave vial that is then sealed with a septum. The reaction mixture is left at rt for the designated period of time.

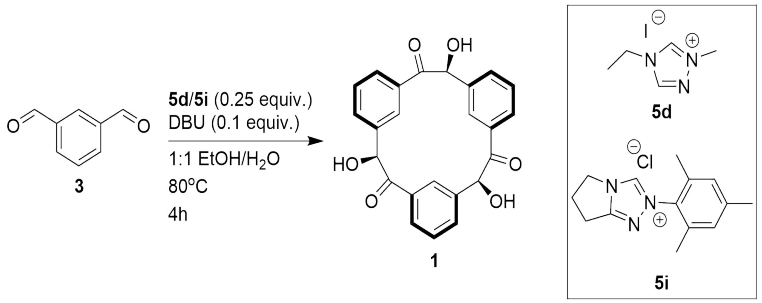
The reason for the difference in yield between the acetylation of **1** synthesised using Cat5 (Entry 1, Table 3.5) and the **1** synthesised using Bode Catalyst 1 (Entry 2, Table 3.5) is not known.

4

Conclusion

By varying the reaction conditions it has been demonstrated that the yield obtained from the synthesis of cyclotribenzoin from isophhtalaldehyde via benzoin condensation can be greatly improved compared to previously reported results. The best results where obtained using 25 mol% of a 1,2,4-triazole-based NHCs, 10 mol% DBU, a reaction temperature of 80 °C and a solvent mixture of 0.98 mL/mmol **3** of EtOH and H_2O. These reaction conditions resulted in a ^1H NMR based yield of 89 % and an isolated yield of 74 % (Table 4.1).

Table 4.1: Optimised reaction conditions*



Entry	Catalyst [equiv.] {name}	DBU [equiv.]	T [°C]	$Yield_{NMR}$ [%]
1	0.25 {**5d**}	0.10	80	84
2	0.25 {**5i**}	0.10	80	89

*Conditions: **3** (0.25 mmol), **5d**/**5i** (0.25 equiv.), DBU (0.10 equiv.) EtOH (0.98 mL/mmol **3**) and H_2O (0.98 mL/mmol **3**) is added to a microwave vial that is then sealed with a crimp cap. After the vial has been sealed it is evacuated and filled with N_2-gas and then heated to indicated temperature.

Based on the results obtained from the different carbenes (Table 3.2) it seems like carbenes based on imidazole are not suitable for use as catalysts when synthesising cyclotribenzoin. While the study only included 4 different achiral carbenes based on 1,2,4-Triazole the trend do suggest that the more lipophilic substituents attached to the triazole the better the yield.

In addition to the improved synthesis it has also been demonstratet that it is possible to perform the synthesis of cyclotribenzoin stereoselectively, obtaining a non-racemic product (based on its ability to rotate plane polarised light).

While an improved synthesis of cyclotribenzoin has been demonstrated there is still several things that remain to be investigated. One thing that remain to be studied is the use of different substrates such as **6** or **7**, although this might necessitate some modifications of the reaction conditions such as the solvent used.

5
Experimental procedure

5.1 Equipment and chemicals used

5.1.1 NMR

^{1}H NMR and carbon-13 nuclear magnetic resonance (^{13}C NMR) was recording using a Varian 400 with the chemical shift reported in parts per milion (ppm) relative to the residual solvent peak. Multiplicities are indicated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). The NMR data was analysed using MestReNova-10.0.1.

5.1.2 Automated flash

Some purifications where performed using an automated flash (Biotage Isolera$^{\text{TM}}$ 2.0.2) with the mobile phase being a mixture either of EtOAc and petroleum spirit or of methanol and DCM at different ratios. The machine is also equipped with a ultraviolet-visible spectrophotometer (UV-Vis spectrophotometer).

5.1.3 HPLC-MS

Some analysis was done using a high-performance liquid chromatography (HPLC) (PerkinElmer Series 200 Autosampler, Micro Pump and micro lc pump) equipped with an UV-Vis spectrophotometer (LINEAR UVIS 200, 254 nm) and a mass spectrometer (MS) (PE SCIEX API 150EX). The mobile phase used was a 1:19 mixture of acetonitrile (ACN) and H_2O with approximately 0.1 % formic acid.

5.1.4 Optical rotation

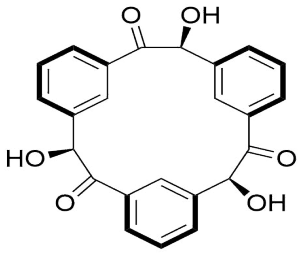
Optical rotation was measured using a Perkin Elmer Polarimeter 341 LC employing a sodium-vapour lamp emitting light with a wavelength of 589 nm.

5.1.5 Chemicals

All chemicals that where used where comercially available, with the exception of some of the NHCs as well as 5-bromoisophthalaldehyde and 2,6-pyridinedicarboxaldehyde which where either synthesised as part of this project or were synthesized previously in our research group.

5.2 General synthesis of cyclotribenzoin

5.2.1 Cyclotribenzoin



1

Figure 5.1: Structure of **1**.

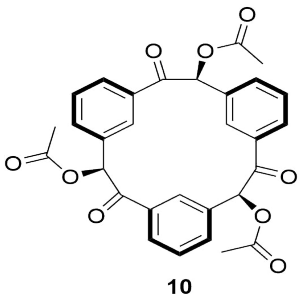
The synthesis of **1** (Figure 5.1) was performed as follows: a magnetic stir bar, **3** 1.27 mmol (171 mg) and **5i** 0.32 mmol (84 mg) was added to a microwave vial. At the same time DBU 0.13 mmol (19 mg) was mixed with EtOH 1.25 mL and H_2O 1.25 mL. The liquid was then added to the vial after which it was capped using a clamp cap. Using a Schlenk line the vessel was evacuated and refilled with nitrogen (N_2) gas, after which the reaction mixture was heated to 80 °C and left to react for 4 h.

After 4 h the reaction mixture was transferred to a number of eppendorf tubes and centrifuged. After centrifugation the supernatant was removed and replaced with H_2O and the tubes was shaken to mix the precipitate with the cleaning liquid. The tubes were then centrifuged again and the supernatant removed. After cleaning with H_2O the same procedure was repeated using EtOH as cleaning liquid and finally it was done using diethyl ether (Et_2O) (each step was performed twice before moving on to the next solvent). After the final trituration the solid was transferred to a vial or small round bottom flask and dried *in vacuo* resulting in a off-white solid (136.3 mg, 74 % yield) NMR-data obtained for compound **1** corresponds with pubished data.[24] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.80 (s, 3 H), 7.67 (d, J = 7.7 Hz, 3H), 7.47 (d, J = 7.8 Hz, 3 H), 7.38 (t, J = 7.7 Hz, 3 H), 6.44 (d, J = 5.5 Hz, 3 H), 6.01 (d, J = 5.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 197.8, 140.2, 134.3, 131.9, 129.7, 129.5, 127.7, 74.2 ppm. (A.1 and A.2)

5.2.2 Optimisation screening

For the optimisation screening the general procedure outlined in the first paragraph of Chapter 5.2 was used (while varying the load of NHCs and DBU alongside reaction temperature) with the exception that MSM was added as a ^{1}H NMR standard. The workup started by reducing the reaction mixture *in vacuo* and then dissolving it in THF in order to get a homogeneous mixture (cyclotribenzoin is insoluble in H_2O and EtOH). Part of this homogeneous mixture was then taken and dried *in vacuo* before it was dissolved in DMSO-d_6 to allow for a ^{1}H NMR to be taken.

5.3 Synthesis of Acetylation of cyclotribenzoin



10

Figure 5.2: Structure of **10**.

Acetylation of compound **1** in order to obtain **10** (Figure 5.2) was based on previously reported procedures.[26] **1** 0.075 mmol (30 mg) and a magnetic stir bar was added to a small round bottom flask. To this vessel acetic anhydride (Ac_2O) 4.065 mmol (415 mg) was added alongside a few drops of sulphuric acid (H_2SO_4). After the addition of acid the vessel was capped using a septum and left to react at room temperature for 24h.

The workup was performed as follows: The reaction was quenched using 0.12 mL 40 %NaOH after which the reaction mixture was transferred to a separation funnel and added H_2O and DCM. The organic phase was collected and reduced *in vacuo* and purified in a automated flash (mobile phase was a 1:4 mixture of EtOAc and petroleum spirit).

NMR-data obtained for compound **10** corresponds with published data.[26] ^{1}H NMR (400 MHz, chloroform-d) δ = 8.53 (s, 3 H), 7.84 (d, J = 8.0 Hz, 3 H), 7.60 (dd, J = 7.8, 1.3 Hz, 3 H), 7.35 (t, J = 7.8 Hz, 3 H), 7.11 (s, 3 H), 2.35 (s, 9 H) ppm. ^{13}C NMR (101 MHz, chloroform-d) δ = 191.9, 171.2, 134.2, 133.6, 133.5, 130.3, 130.2, 129.5, 76.8, 21.0 ppm. (Figure A.4 and A.5, respectively) In addition to ^{1}H NMR and ^{13}C NMR a heteronuclear single quantum coherence (HSQC) was taken (Figure A.6). This analysis indicates which ^{1}H peak correspond to which ^{13}C peak (Table 5.1).

Table 5.1: Correlation between ^{1}H NMRand ^{13}C NMR peaks

^{1}H peak [ppm]	**^{13}C peak** [ppm]
2.35	21.1
7.11	76.2
7.35	130.4
7.60	133.3
7.84	130.0
8.53	129.4

The reason for doing this analysis is that one of the reported ^{13}C peaks (76.8 ppm) overlap with a peak from the solvent used (chloroform-d). Based on the analysis this ^{13}C peak was found to correspond to the ^{1}H with a shift of 7.1 ppm, which is the α-proton. This means that the ^{13}C with a shift of 76.8 ppm is the α-carbon.

In addition to NMR-data, **10** was analysed using HPLC-MS (mass spectrometer) with the mobile phase being a 1:19 ratio of ACN and H_2O. The HPLC is equipped with a UV-Vis spectrophotometer in addition to a MS, with the former being placed before the latter resulting in a time delay between the two detectors. Based on the UV-data (Figure 5.3) the sample is not entirely pure as there is a small signal at 5 min and another at 5.6 min in addition to the main peak at 5.7 min.

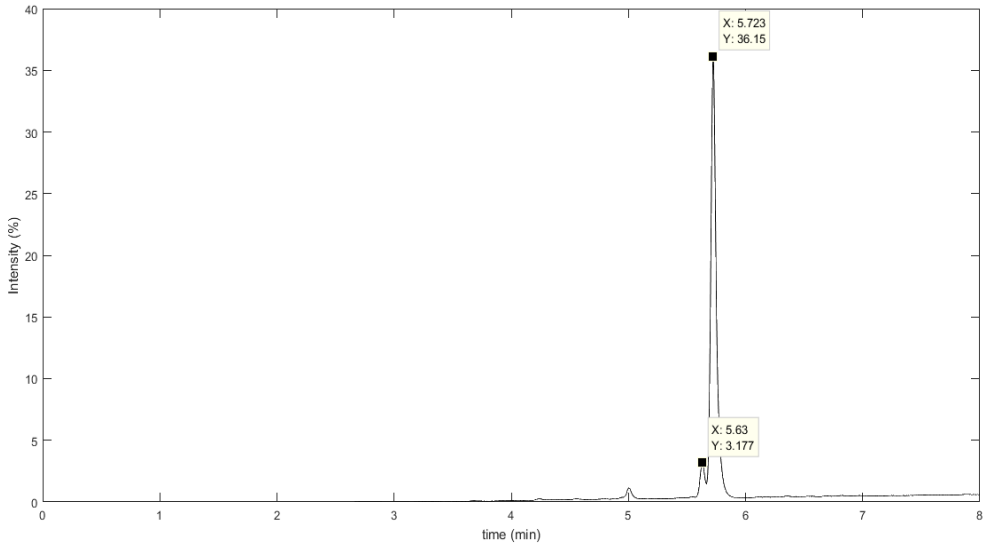


Figure 5.3: Absorbance of light with a wavelength of 254 nm obtained when analysing **10** using 1:19 mixture of ACN and H_2O as mobile phase.

The peak seen in the UV-Vis spectrophotometer at 5.7 min is believed to correspond to that at approximately 6.1 min in the total ion count (TIC) detector (Figure 5.4).

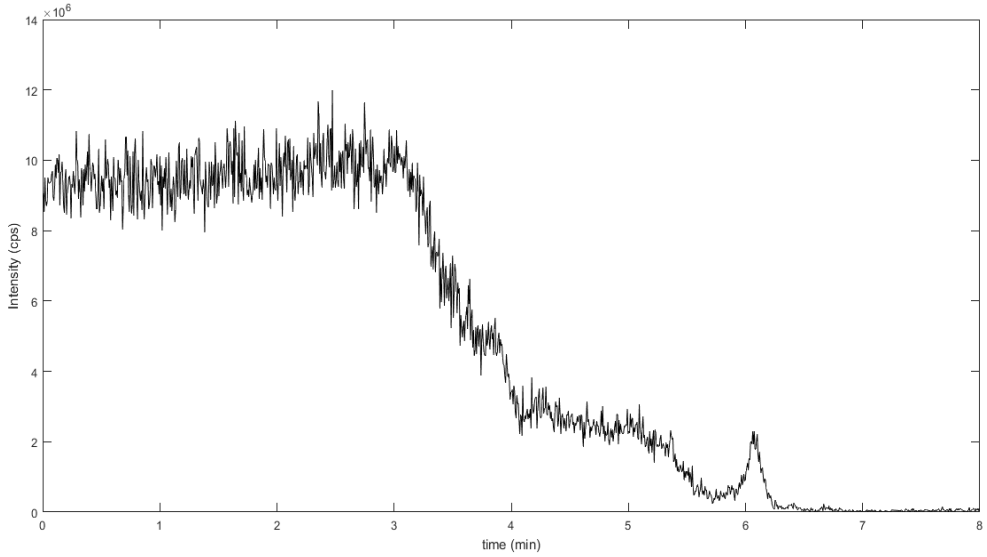


Figure 5.4: TIC obtained when analysing **10** using 1:19 mixture of ACN and H_2O as mobile phase.

The mass/charge distribution at approximately 6.1 min in the TIC detector was collected in order to determine the molar mass of the analyte (Figure 5.5).

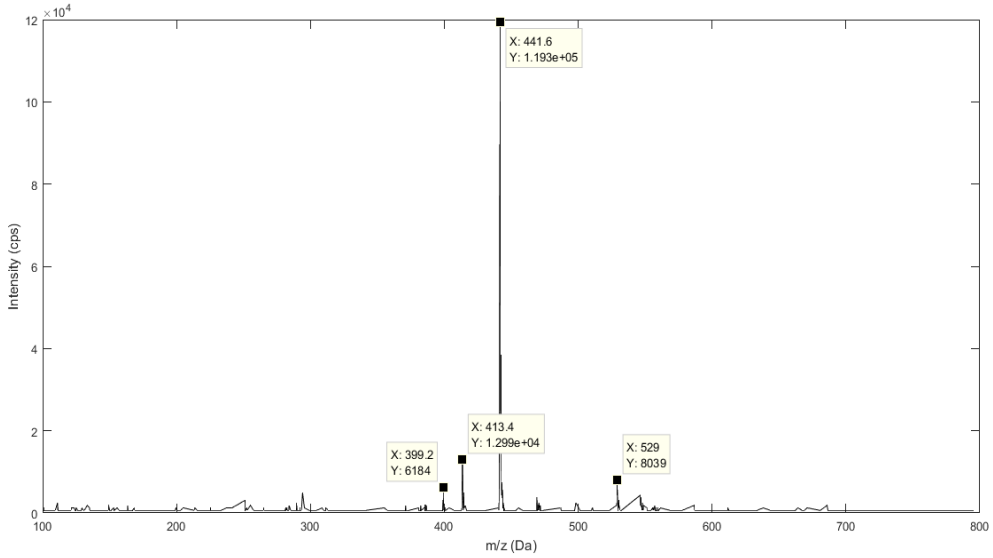


Figure 5.5: MS obtained when analysing **10** using 1:19 mixture of ACN and H_2O as mobile phase.

A protonated molecule of **10** ($C_{30}H_{25}O_9$) would have a molar mass of 529.514 g/mol, the data contains a peak with a m/z of 529 Da which could correspond to a **10** with an additional proton.

5.3.1 Homo-chiral cyclotribenzoin-triacetate

The optical rotation of the **10** obtained from the **1** synthesised using the chiral carbene **5j** was analysed using a polarimeter. This was done by dissolving 1 mg **10** in 1 mL chloroform. The measurement was taken over a period of 20 s after which an average was taken and used to calculate $[\alpha]$ (Table 5.2).

Table 5.2: Obtained results from polarimetry analysis of **10**

l [dm]	**T** [°C]	**c** [g/ml]	λ [nm]	α_λ^T [°]	$[\alpha]_{589}^{20}$
1	20	0.001	589	+0.04	+40 (chloroform)

Based on the obtained measurements the specific optical rotation of **10** was calculated, $[\alpha]_{589}^{20} = +40$ (chloroform). The fact that the sample rotates plane polarised light confirms that the sample is non-racemic.

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Appendix

Obtained ^{1}H NMR and ^{13}C NMR spectra

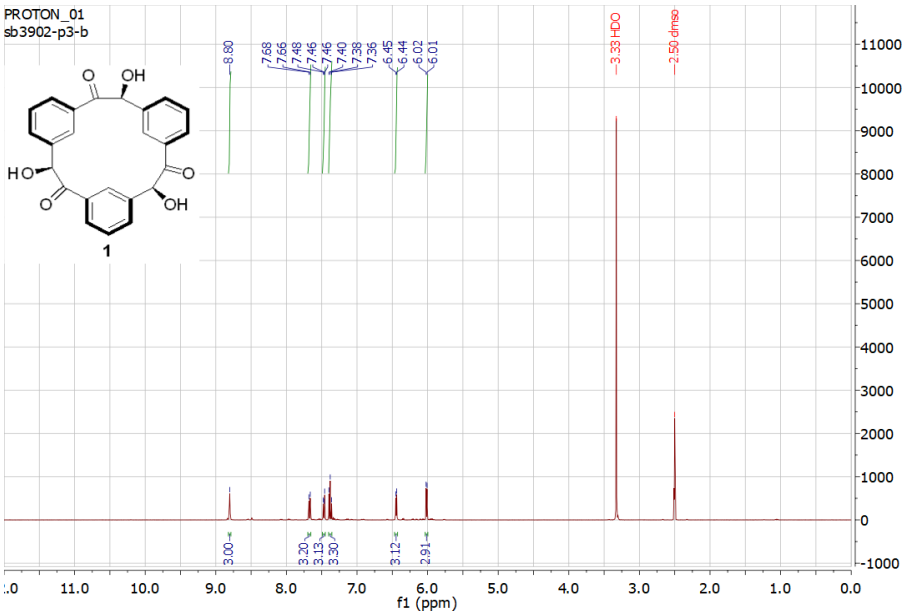

Figure A.1: .

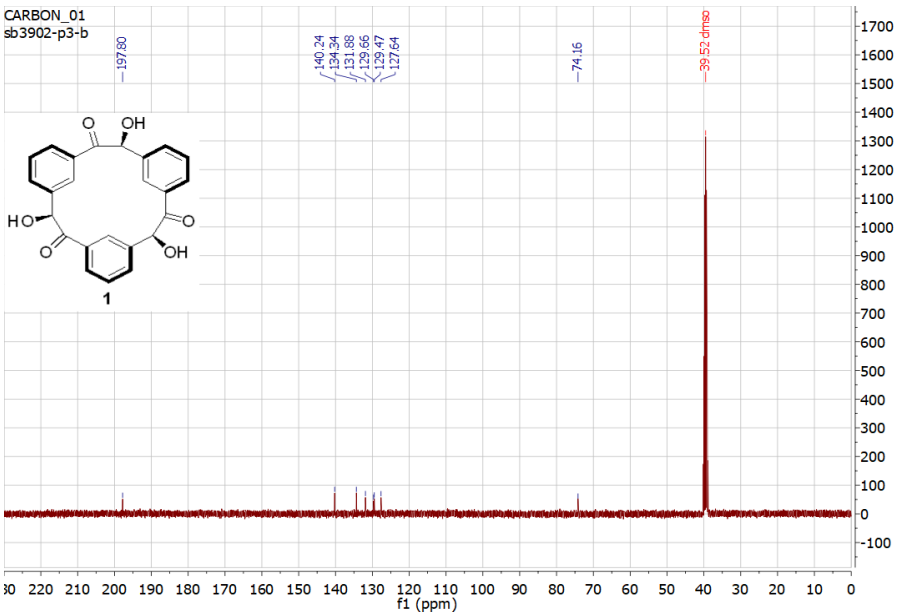

Figure A.2: .

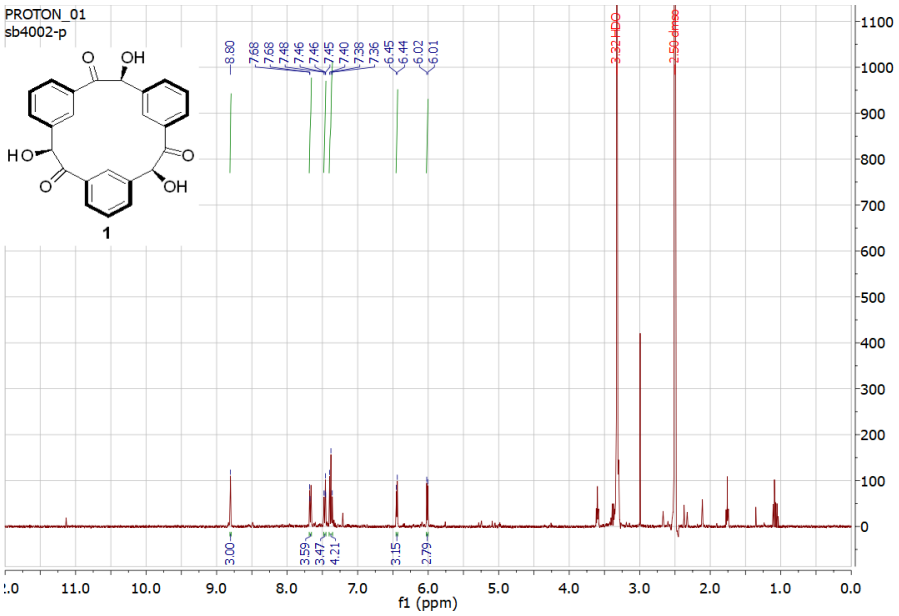

Figure A.3: ^{1}H NMR for synthesis of cyclotribenzoin using 25 mol% Bode Catalyst 1, reaction time of 4 h, reaction temperature of 80°C and MSM as internal standard taken after workup.

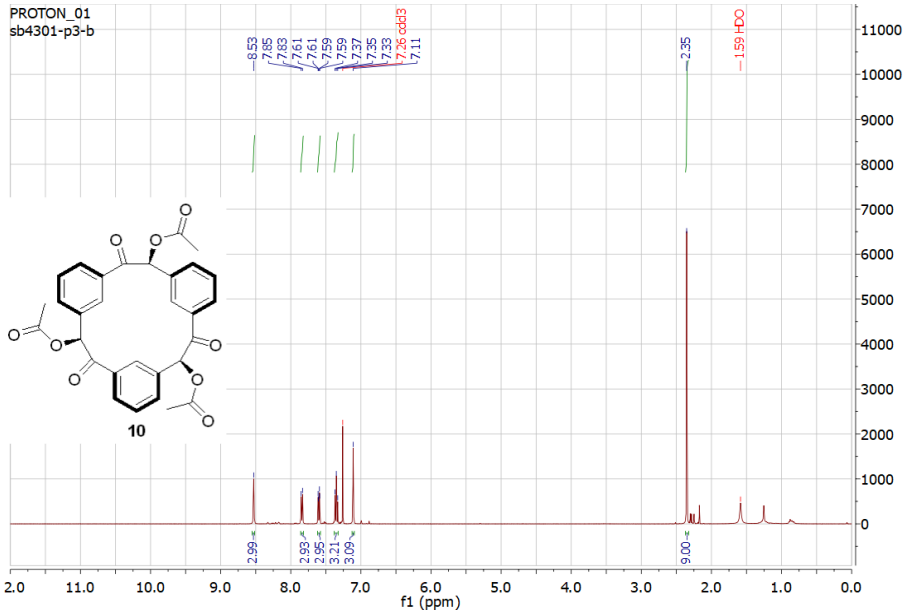

Figure A.4: .

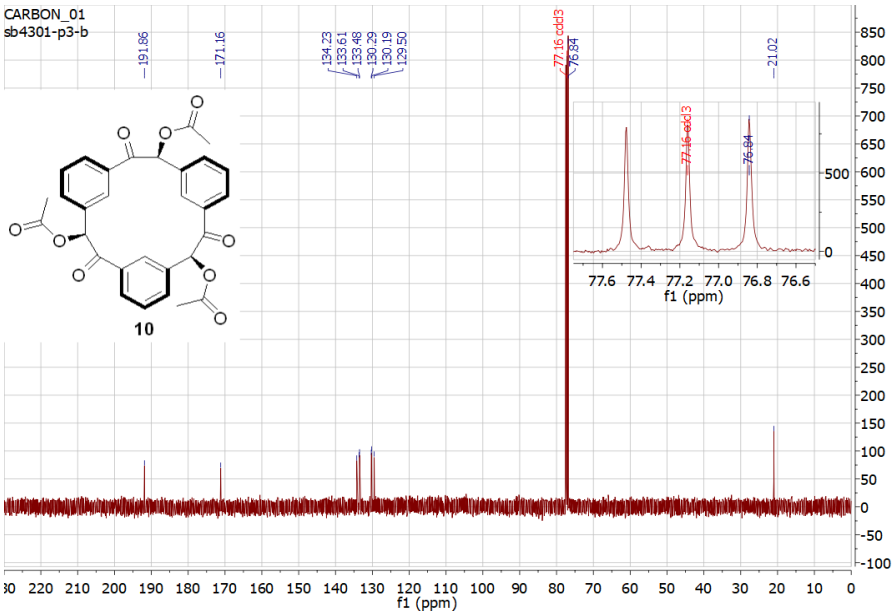

Figure A.5: .

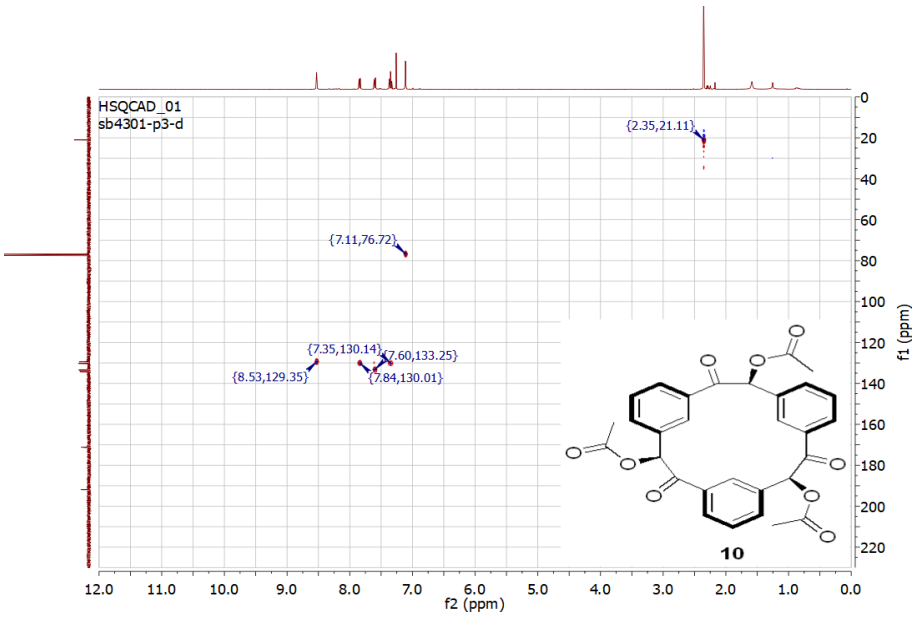

Figure A.6: .

Synthesis of 1,4-dimethyl-4H-1,2,4-triazolium iodide (5a)

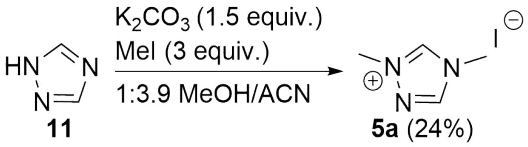

Figure A.7: Reaction scheme for the synthesis of 1,4-dimethyl-4H-1,2,4-triazolium iodide (**5a**) from **11**.

5a was synthesised based on previous work by Xiangcheng Pan et.al.[39] The reaction was performed in a sealed 100 ml round bottom flask, to which 1,2,4-triazole (**11**) 47.93 mmol (3.3 g) and potassium carbonate 72.5 mmol (10 g) was added alongside a magnet stir bar. To this acetonitrile 27 mL, MeOH 6.9 mL and iodomethane (MeI) 147.78 mmol (9.2 mL) was added. As MeI was added the liquid turned yellow. The reaction mixture was heated to 40 °C and left to react under stirring for 48 h. After the reaction time had passed the reaction mixture was filtered and washed with DCM and the filtrate concentrated *in vacuo*. The obtained solid consisted of relatively large yellow flakes that where partially dissolved in DCM and filtered a second time, and once again the filtrate was concentrated *in vacuo*. The obtained orange/brown solid was washed with Et_2O and then put in a 100 ml round bottom flask with Et_2O under stirring for 12 h to dissolve impurities. The solid was then filtered and dried *in vacuo* to obtain 2.6012 g of an off-white/gray **5a** (yield = 24 %). ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.97 (s, 1 H), 9.11 (s, 1 H), 4.07 (s, 3 H), 3.89 (s, 3 H) ppm. These results was found to coincide with results published by Lauren Myles et.al.[40] ^{13}C NMR (101 MHz, DMSO-d6) δ = 145.7, 143.7, 39.0, 34.4 ppm. These results where found to coincide with results published by John L. Belletire et.al.[41]

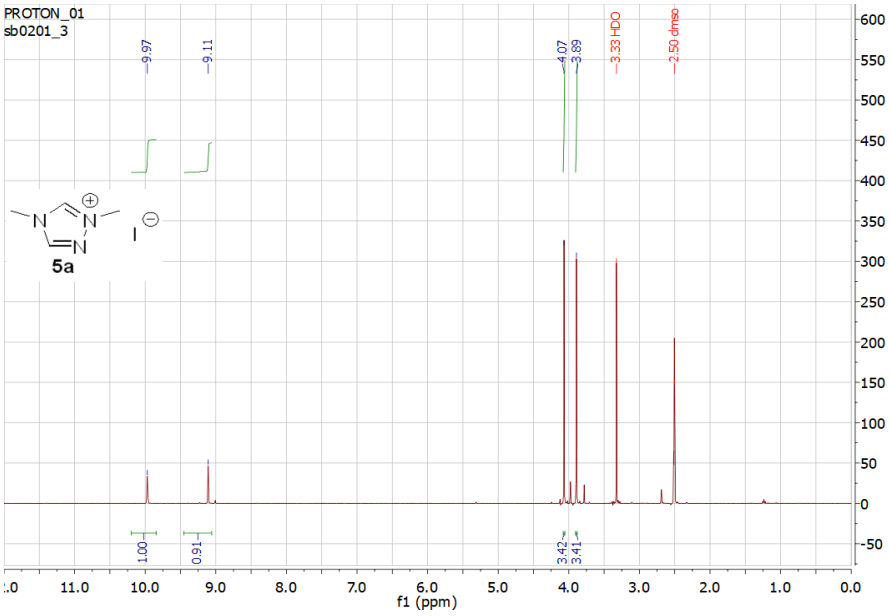

Figure A.8: ^{1}H NMR taken of **5a**. The peaks between 10 ppm and 3.8 ppm correspond well to those reported by Lauren Myles et.al.[40] Reported ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 9.10 (s, 1 H), 4.06 (s, 3 H), 3.88 (s, 3 H) ppm.

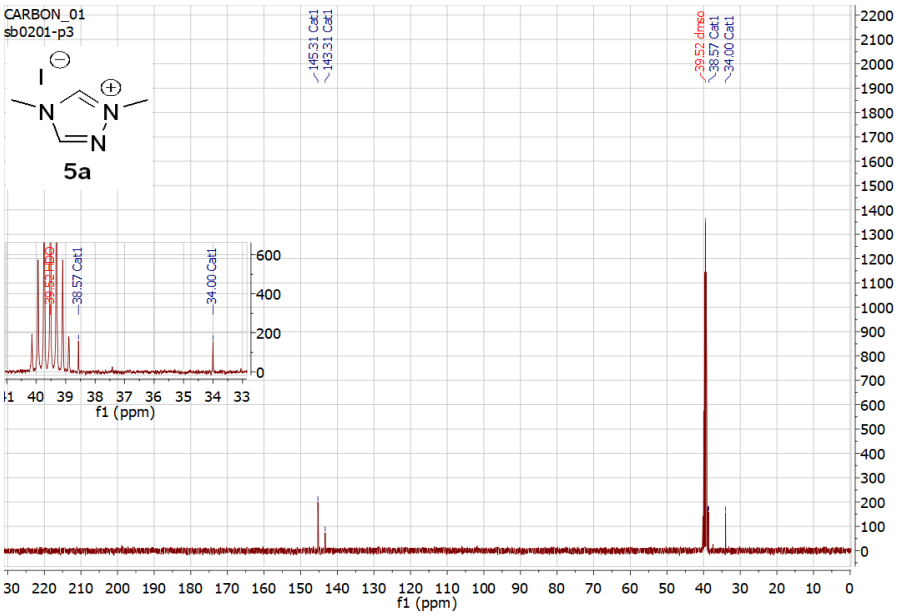

Figure A.9: ^{13}C NMR taken of **5a**. The peaks labelled "cat1" correspond well to those reported by John L. Belletire et.al.[41] Reported ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 145.106, 143.206, 38.787, 34.235 ppm.

Synthesis of 2,6-pyridinedicarboxaldehyde (7)

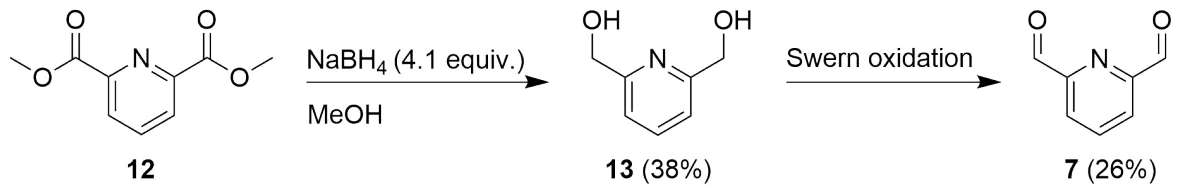

Figure A.10: Schematic for the synthesis of **7**, from **12** via **13**.

2,6-pyridinedimethanol (**13**) was synthesised based on previously reported procedures.[42] Dimethyl pyridine-2,6-dicarboxylate (**12**) 41.6 mmol (8.2 g) and dry MeOH 80 mL was added to a 250 mL round bottomed flask alongside a stir bar. To this mixture $NaBH_4$ 170.5 mmol (6.45 g) was slowly added under stirring at room temperature. As the $NaBH_4$ the mixture started to reflux. After all $NaBH_4$ was added additional MeOH (20 mL) was added and the mixture was left to react over night.

Solvent was then removed *in vacuo*, resulting solvent was then dissolved in chloroform and mixed with a saturated solution of $NaHCO_3$ and added to a separation funnel. The organic phase was collected and dried using $MgSO_4$ and then filtered. Solvent was then removed *in vacuo* yielding 2.18 g of **13** as a white powder (yield = 38 %). ^{1}H NMR (400 MHz, chloroform-d) δ = 7.70 (s, 1 H), 7.20 (d, J = 7.7 Hz, 2 H), 4.78 (s, 4 H), 3.25 (s, 2 H) ppm. These results was found to coincide with results published by T. Shimoda et.al.[43]

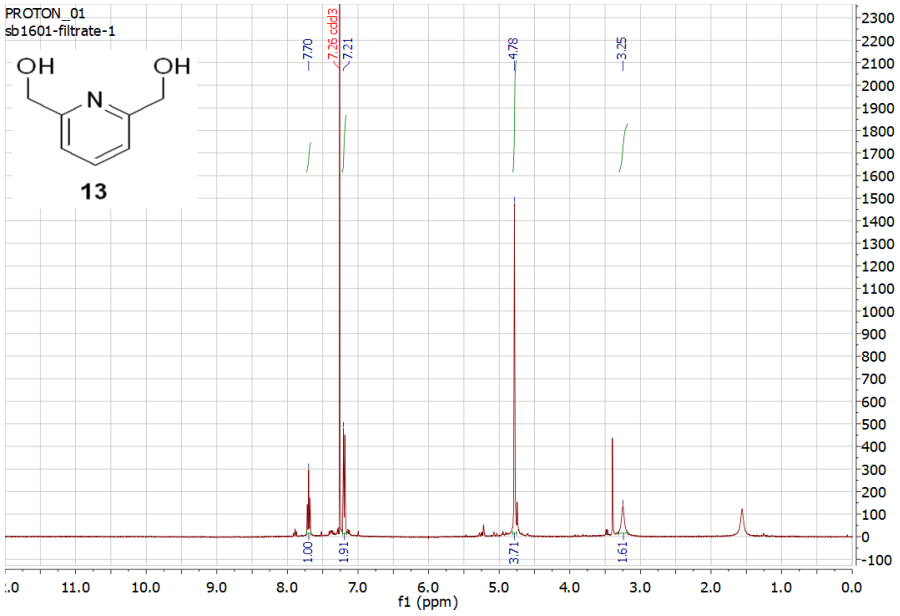

Figure A.11: ^{1}H NMR taken of 2,6-pyridinedimethanol. The peaks between 8 ppm and 3 ppm correspond well to those reported by T. Shimoda et.al.[43] Reported ^{1}H NMR (400 MHz, chloroform-d): δ = 7.70 (t, J = 7.7 Hz, 1 H), 7.20 (d, J = 7.7 Hz, 2 H), 4.79 (s, 4 H), 3.26 (s, 2 H) ppm.

2,6-pyridinedicarboxaldehyde (**7**) was synthesised according based on previously reported procedures[44]: DCM 65 mL and a stir bar was added to a 250 mL 3-necked round bottomed flask. The flask was then evacuated and filled with N_2-gas. The flask was then cooled to -78 °C and DMSO 9 mL and DCM 13 mL was mixed and added dropwise to the vessel using a addition funnel. Mixture was then left to stirr for 5 min, after which a mixture of **13** 15.67 mmol (2.2 g), DMSO 9 mL and DCM 13 mL was added dropwise over a period of ca. 15 min. After another 20 min Et_3N 22 mL was added dropwise. A few minutes after the addition of Et_3N a mixture of oxalyl chloride 45.85 mmol (5.73 mg) and DCM 10 mL was added dropwise, resulting in gas development. The mixture was left to react over weekend and slowly warm to room temperature as the dry ice bath warmed up.

Reaction mixture was quenched by pouring it into 110 mL H_2O. Aqueous phase was washed with 3x100 mL DCM, after which the combined organic phase was washed with 3x100 mL brine and then dried using $NaHSO_4$ and filtered. Solvent was then removed *in vacuo* resulting in a brown liquid, which was purified via vacuum sublimation at 55-65 °C yielding yellow solid of **7** (yield = 26 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.17 (s, 2 H), 8.18 (s, 2 H), 8.08 (s, 1 H) ppm. These results correspond well to those reported by R. Hicks et.al.[44]

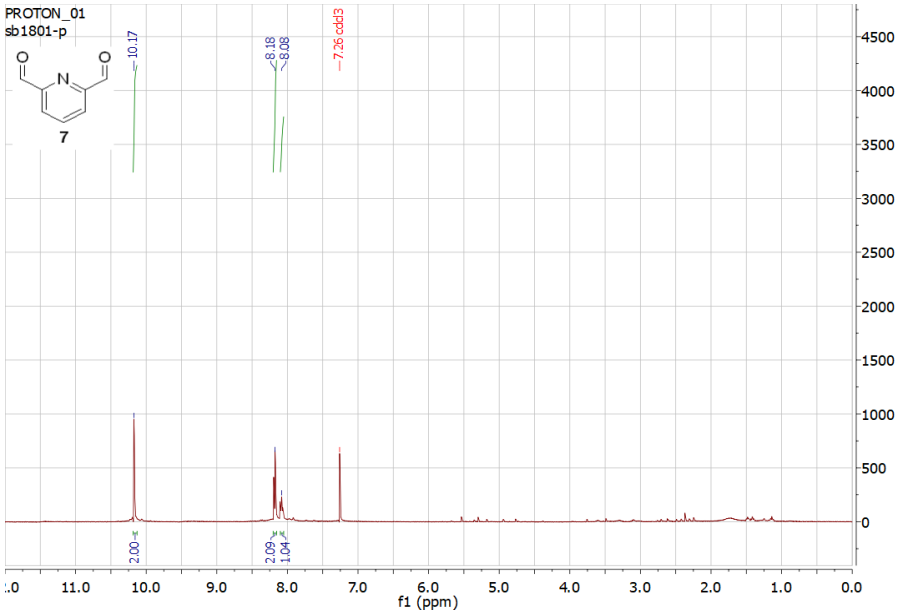

Figure A.12: ^{1}H NMR taken of **7**. The peaks between 10.2 ppm and 8 ppm correspond well to those reported by R. Hicks et.al.[44] Reported ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.14 (s, 2 H), 8.16 (d, J = 7 Hz, 2 H), 8.06 (t, J = 8 Hz, 1 H) ppm.