# Multiple Kinetic Resolution of Tetrathia[7]helicenes.

## Towards the Study of Two Photon Circular Dichroism.

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Doctoral Thesis

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# Preface.

The research in this thesis is, to the best of my knowledge, original except where due reference has been made.

J. Doulcet

March 2014

# Abstract.

This doctoral thesis had as its aim the asymmetric synthesis of tetrathia[7]helicene derivatives using a newly developed multiple kinetic resolution (multi-KR) approach. The derivatives obtained (formyl- and diformylhelicene) should also be useful intermediates for the synthesis of chiral push-pull systems.

The first part of the project was devoted to the synthesis of 7,8-dipropyltetrathia[7]helicene reported by Licandro and Maiorana. A key intermediate in this synthesis is the benzo[1,2-b:4,3-b']thiophene building block, previously obtained via a photochemical reaction, and for which we developed an alternative chemical synthesis[1].

The second part of the project focused on the kinetic resolution, designed to obtain formyl- and diformylhelicene. Two strategies were identified to obtain the desired aldehydes: direct asymmetric formylation using novel chiral formamide reagents and/or asymmetric lithiation using (–)-sparteine followed by a DMF quench. The chiral auxiliaries were first examined in single kinetic resolution experiments in order to identify the most suitable conditions and auxiliaries. Asymmetric lithiation proceeded in up to 84% e.e. and the asymmetric formylation using a chiral formamide gave at best 42% e.e. The most successful examples were chosen to design several multi-KR approaches using a suitable combination of matched and/or mismatched steps. These strategies have allowed us to synthesise very highly enantioenriched helicene derivatives that can be recrystallized to enantiopurity.

Finally, the synthesis of (electron donor)-(chiral-π)-(electron acceptor) [D-(chiral-π)-A] and (electron acceptor)-(chiral-π)-(electron acceptor) [A-(chiral-π)-A] chiral push-pull systems was examined. Racemic A-(chiral-π)-A structures were readily obtained, and although one racemic D-(chiral-π)-A target was synthesised; the synthesis of this latter class of compound has proved to be more challenging because of issues with the stability of the synthetic intermediates. Both D-(chiral-π)-A and A-(chiral-π)-A structures are to be examined in photophysics experiments by Pr. T. Verbiest at the University of Leuven.

[1] G. R. Stephenson, S. Cauteruccio, J. Doulcet, *Synlett* **2014**, *25*, 701.

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# Abbreviations.

| | |
|---|---|
| A | electron acceptor |
| Ac | Acetyl |
| APCI | atmospheric pressure chemical ionisation |
| aq. | aqueous |
| Ar | argon |
| Ar | aryl |
| atm | atmosphere |
| ATOP | amino-thienyl-dioxocyano-pyridine |
| ATR | attenuated total reflectance |
| br. | broad |
| Bu | butyl |
| BINAP | 2,2’-bis(diphenylphosphino)-1,1’binapthyl |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| calcd. | calculated |
| CD | circular dichroism |
| cod | 1,5-cyclooctadiene |
| Cp | η5-cyclopentadienyl |
| CuTC | copper thiophene carboxylate |
| Cy | cyclohexyl |
| δ | chemical shift |
| D | electron donor |
| d | doublet |
| d.e. | diastereomeric excess |
| dba | dibenzylideneacetone |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| dd | doublet of doublet |
| ddd | doublet of doublet of doublet |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4 benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DEANOL | dimethylethanolamine |

| | |
|---|---|
| DIAD | diisopropyl azodicarboxylate |
| DMAD | dimethyl acetylene dicarboxylate |
| DMAP | *N*,*N*-4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DMSO-d6 | deuteriated dimethylsulfoxide |
| dt | doublet of triplets |
| DuPhos | 1,2-bis[2,5-dialkylphospholano]benzene |
| e.r. | enantiomeric ratio |
| $E^+$ | electrophile |
| e.e. | enantiomeric excess |
| eq | equivalents |
| ESI | electrospray ionisation |
| Et | ethyl |
| FT-IR | fourier transformed infra red spectroscopy |
| GC | gas chromatography |
| HMDS | 1,1,1,3,3,3-hexamethyldisilazane |
| HPLC | high pressure liquid chromatography |
| hr(s) | hour(s) |
| HRMS | high resolution mass spectrometry |
| hυ | UV irradiation |
| IPA | 2-propanol |
| *i*-Pr | iso-propyl |
| IR | infra red |
| *J* | coupling constant |
| KR | kinetic resolution |
| LDA | lithium diisopropylamide |
| litt. | literature |
| m | multiplet |
| M | molar |
| *m* | meta |
| min | minute(s) |
| Me | methyl |
| MePhos | 2-dicyclohexylphosphino-2′-methylbiphenyl |

| | |
|---|---|
| mol | mole(s) |
| MOP | 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl |
| Mp. | melting point |
| Ms | methanesulfonyl |
| MTBE | tert-butyl methyl ether |
| multi | multiple |
| μW | microwave |
| N | normal |
| Naphth | naphthyl |
| NBS | *N*-bromosuccinimide |
| Nf | nonafluorobutanesulfonyl |
| NLO | nonlinear optics |
| NMP | *N*-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| Nuc | nucleophile |
| ORD | optical rotatory dispersion |
| *p* | para |
| Ph | phenyl |
| ppm | parts per million |
| nPr | propyl |
| *n*- | normal |
| PCC | pyridinium chlorochromate |
| PTSA | *p*-toluenesulfonic acid |
| piv | pivaloyl |
| pyr. | pyridine |
| q | quartet |
| *rac* | racemic |
| RBF | round-bottomed flask |
| RCM | ring closing metathesis |
| Red-Al | sodium bis(2-methoxyethoxy) aluminium hydride |
| RT | room temperature |
| rxn | reaction |
| s | singlet |
| *s*- | secondary |
| sat. | saturated |

| | |
|---|---|
| SegPhos | 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole |
| SGH | second harmonic generation |
| $S_EAr$ | electrophilic aromatic substitution |
| SM | starting material |
| $S_NAr$ | nucleophilic aromatic substitution |
| *t*- | tertiary |
| t | triplet |
| TAPA | α-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | tert-butyldimethylsilyl |
| TEA | triethylamine |
| Temp. | temperature |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N*',*N*'-tetramethylethylenediamine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | trimethylsilyl |
| Tol | tolyl |
| TPA | two photon absorption |
| TPCD | two photon circular dichroism |
| Ts | *p*-toluenesulfonyl |
| Tf | trifluoromethane |
| UV | ultra violet |
| v | volume |
| VCD | vibrational circular dichroism |
| VROA | vibrational Raman optical activity |
| XantPhos | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene |

# Introductory chapter

## I) Aims of the project

Although there is a doubt on the exact date of the discovery, which varies depending on sources and gets older as more journals get available online, helicenes were first reported in the early years of the twentieth century.[1] The first fifty years of helicene chemistry saw helicenes and heterohelicenes of different sizes being reported; however since helicenes are chiral, the first great advance in the field came with Newman's report, in 1955, of the isolation of [6]helicene (**1**) in enantiopure form (Figure 1).[2] This triggered chemists' interests and the following years saw increasing numbers of reports concerning helicene chemistry.

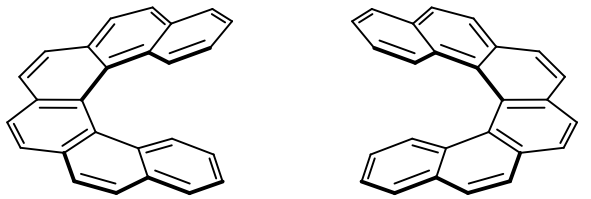


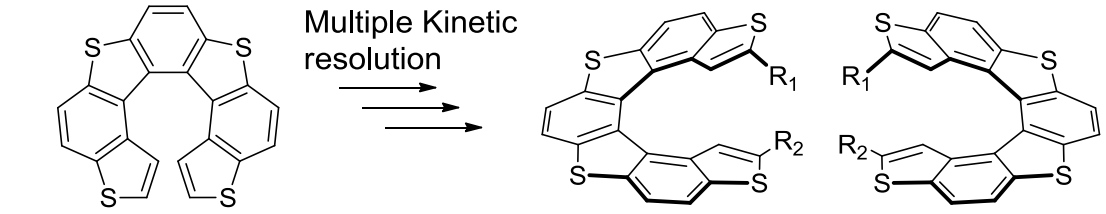

**Figure 1: (–)-[6]helicene and (+)-[6]helicene reported by Newman**

However, helicene synthesis was still a long and tedious process, and the real change in helicene chemistry came with the report of the successful extension of the photodehydrocyclisation of stilbene derivatives to larger structures, thereby affording helicenes.[3] In the following years, several groups (Martin, Wynberg, Kagan, Laarhoven) extensively studied and developed the photochemical methodology, producing [n]helicenes and hetero[n]helicenes in many different sizes ($5 < n < 15$) and in good yields. Also, these research groups participated in developing resolution techniques sufficiently efficient to allow the study of the chiro-optical properties of helicenes. The great interest in helicenes was at that time driven by wider interests in the understanding of the origin of chirality, for which studying the optical properties of the unique twisted pi-systems of helicenes could be expected to give novel results.[4]

However, although the early access route gave sufficient quantities to establish their interesting properties, helicenes needed to be more easily obtained in large quantities and in enantiomerically pure form, in order to exploit their nonlinear optical properties and to assess their potential in organocatalysis. Towards this goal, several synthetic methods and routes (camphanate resolution,[5] Diels-Alder,[6] [2+2+2]cycloisomerisation[7]) that do not

involve the scale-limiting photocyclisation have since then been developed, allowing the study of the properties of helicenes with many different structural modifications and bearing a wide range of functionalities. Unfortunately, despite all these efforts deployed towards the synthesis of enantioenriched helicenes, remarkably little success has been gained since the first report of enantiopure [6]helicene in 1955. Indeed, while early techniques that mostly consisted in preferential crystallisation of one enantiomer did not provide sufficiently good results to be generalised to large scale preparation of enantiomerically pure substrates, most of efficient techniques developed since rely on the synthesis of a racemic helicene, its transformation into a diastereomeric mixture and subsequent separation of diastereoisomers using silica gel chromatography. Nonetheless, the past fifteen years saw major improvements, since good progress has been made in diastereoselective and enantioselective synthesis of helicenes, frequently obtaining products with high selectivities. A consequence of the larger number of available techniques for the preparation of enantiopure helicenes was a major increase in the quantity of reports concerning NLO studies[8] and asymmetric catalysis using a helicene scaffold,[9] in the past ten years. As a domino effect, this has generated an even larger demand for enantiopure helicenes; therefore the need for more efficient techniques affording enantiopure helicenes is more than ever a priority.

In this context, our project finds its originality in an enantioselective approach based on the kinetic resolution of racemic tetrathia[7]helicene (Scheme 1). Indeed, rather than trying to achieve a completely novel asymmetric helicene synthesis, it was decided to use an already known helicene, whose properties would make it a good target for nonlinear optical studies as well for catalysis. Tetrathia[7]helicene meets perfectly all those requirement as it has been described[10] as a very good candidate to observe Two Photon Circular Dichroism (TPCD: a nonlinear optical phenomenon arising from the conjunction of two photon absorption and circular dichroism) and similarly offers opportunities as a new scaffold in catalysis.[11] Also, it belongs to the class of thiahelicenes which possess the attributes of being very easily functionalised at each end of the helix, at the C2 and C13 positions adjacent to the sulfur atom.




**Scheme 1: Multiple kinetic resolution of tetrathia[7]helicene**

The aim of our project, would be to synthesise tetrathia[7]helicene derivatives (**3**), via a new approach based on the concept of multiple kinetic resolution being developed at UEA in the Stephenson group, affording enantiomerically pure products. This will much improve access to useful intermediates for both NLO studies and catalysis (further modification of functionalities could easily be achieved if required) by installing adequate functional groups at each end of the helix. For the NLO applications, our intention is to transform the functionalised tetrathia[7]helicenes into powerful push-pull systems [(electron donor)-(chiral pi system)-(electron acceptor) or (electron acceptor)-(chiral pi system)-(electron acceptor)], based on the model of the ATOP dyes,[12] in order to study the predicted good ability of thiahelicene towards second order nonlinear optical phenomena. Moreover, considering the potential use as catalysts, the use of racemic starting material can be justified, making both enantiomers readily accessible from one synthesis.

## II) Discovery and properties of helicenes

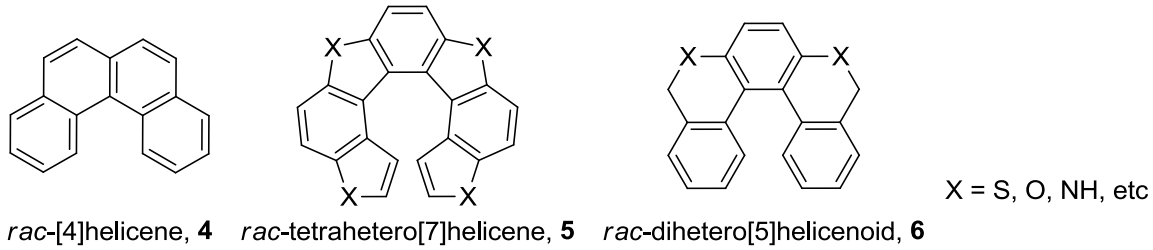
### 1) Name and nomenclature

Helicenes are molecules made of ortho-fused aromatic rings, forming an inherently regular helical shape, which arises from the steric hindrance between aromatic rings. The name helicene was introduced by Newman in 1956[2] and although IUPAC rules A-21, A-22, B-3 and B-4 define nomenclature concerning fused aromatics, there is no precise denomination for the naming of helicenes; therefore, in following paragraphs we will define the system used in this thesis. Geometrical properties define whether a molecule is a helicene or not, and also determine which class a helicene belongs to: carbohelicene, heterohelicene and helicenoid structure. The properties rising from the chiral fully delocalised pi-system, generally referred to as chiro-optical properties, have always brought a large interest from transversal disciplines such as molecular electronics and photonics.

2) Geometrical/structural properties of helicenes

a) Size and nature of the rings

According to IUPAC rules, the minimal number of rings necessary to obtain a helicene is five.[13] However, many compounds constituted of four ortho-fused rings have shown a stable helical shape; therefore in this thesis, the term helicene will be used to describe molecules possessing as few as four ortho-fused aromatic rings. Since the early reports in 1903,[1] helicenes of many different compositions and sizes have been synthesised, up to 15 rings,[14] and including a range of heteroatoms, sulfur, nitrogen, oxygen being the most common ones. Unofficial nomenclature defines that the ring-count should be noted in the following way: [number of rings]helicene, so in the case of a n-ring system, the generated name would be [n]helicene. The nature of the rings also matters; strictly benzene-based helicenes are generally called carbohelicenes or more simply [n]helicenes, whereas helicenes including heteroaromatic rings are called heterohelicenes (Figure 2). Therefore, including the ringcount, we get the following name hetero[n]helicene.

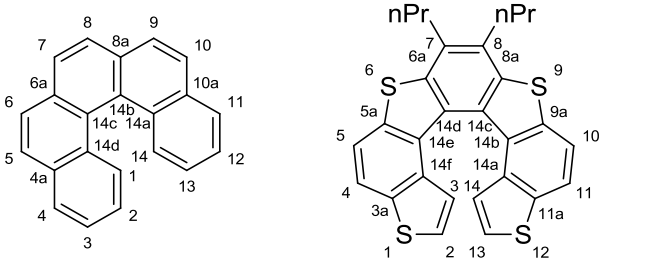



*rac*-[4]helicene, **4** *rac*-tetrahetero[7]helicene, **5** *rac*-dihetero[5]helicenoid, **6**

**Figure 2: Helicene nomenclature**

The number of heterocycles can also be accounted for by a "prefix" derived from the number (di for 2, tri for 3, tetra for 4, etc) of heteroatom-containing rings; thus, four thiophene rings interspersed between three benzene rings gives the name: tetrathia[7]helicene (**2**). Our work concentrates on helicenes containing thiophene (thiahelicenes) but furan (oxahelicene), pyridine or pyrrole (azahelicene) and more exotic examples have also been reported. In this thesis I will also discuss the synthesis of a closely related type of compound: helicenoid structures. Just like helicenes, they present a helical structure, but do not possess a fully conjugated system of pi electrons. They do not have a particular nomenclature, and this thesis refers to them simply as helicenoids following the same naming description as helicenes, ie hetero[n]helicenoid (Figure 2, **6** for example). Concerning the numbering of substituents, the rules for [n]helicene will follow Newman's suggestion of numbering in order, starting at the first proton inside the helix

(Figure 3), whereas rules IUPAC B-3 will be followed for hetero[n]helicenes because the heteroatom takes priority.

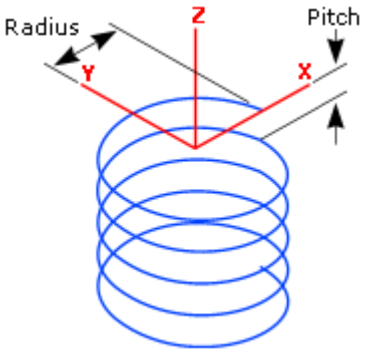



*rac*-[5]helicene, **7** *rac*-dipropyltetrathia[7]helicene, **8**

**Figure 3: Numbering of the substituents**

b) Properties of the helix

The structural characteristics of helicenes can be described in relation to the geometry of helixes, and particularly pitch is of significant importance. Helixes are defined this way: a helix is a type of smooth space curve, (*i.e.* a curve in three-dimensional space) which has the property that the tangent line at any point makes a constant angle with a fixed line called the axis. The axis of the helix, running through the centre, can be used as a ruler to measure the pitch. The pitch of the helix is defined by the width of a complete helix turn, measured on the axis or parallel to the axis (Figure 4).

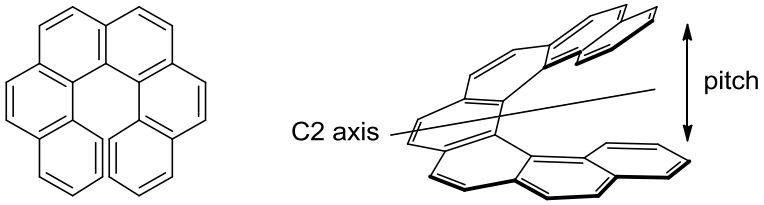



(http://www.ezcam.com/web/products/help/ezmill/curve_handling_mill/create_helical_curve.htm)

**Figure 4: Helical curve: defining helix properties**

The pitch of the helix is one of the key features of a helicene as it will influence its electronic, and spatial properties. Indeed, since electron transfers/movements could also occur through space instead of going through the helix, the spacing between each overlapping ring defined by the pitch will therefore establish differences in electronic

properties. The size of the pitch is influenced by the nature and the number of rings present in the helicene (every aromatic ring has got different bond length and bond angles); hence different helicenes, or helicenes with different substituents, should produce a change in the pitch value. The invaluable ability of tuning the pitch of the helix could be used in many different ways, for example, with helical catalysts by allowing screening of various bite angles. Also, symmetrically substituted helicenes possess a C2 symmetric core (Figure 5); this rotational symmetry feature indicates that the molecule unchanged by a rotation of 180 degrees around the C2 axis, which also means that both ends of the helicene are equivalent.



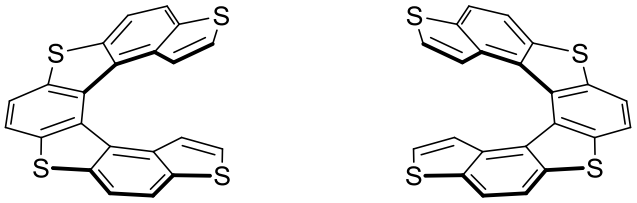

[6]helicene, **1** (-)-[6]helicene, (-)-**1**

**Figure 5: [6]-helicene, geometrical properties**

3) Chiro-optical properties

a) Chiral properties

The inherent chirality of helicenes arises from the helical structure which can either be left- or right-handed; it is a type of axial chirality. A helicene can have either *M* or *P* configuration (defined by the right hand rule), left-handed helixes will be assigned with *M* configuration and right-handed helixes with *P* configuration (Figure 6).




(*M*)-tetrathia[7]helicene, (*M*)-**2** (*P*)-tetrathia[7]helicene, (*P*)-**2**

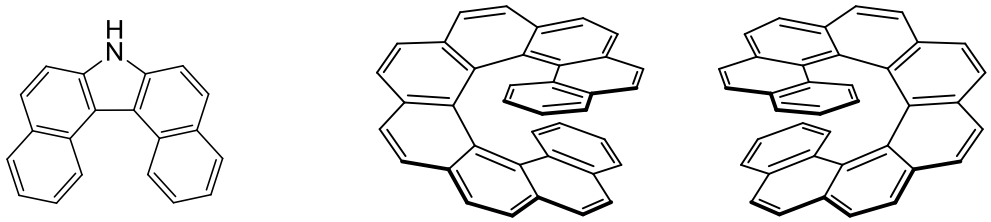
**Figure 6: Enantiomers of tetrathia[7]helicene**

As for any chirality, there is no direct link between sign of specific rotation and absolute configuration of the enantiomer. However, it has been shown that within a class of helicenes sharing the same core structure, all enantiomers of one configuration correspond to a sign of rotation and the other enantiomer to the opposite sign. Since the early years of

helicene chemistry, the question of absolute configuration has always been an issue. Early reports in the 1960s based their results on calculation using computing models, before progress in X-ray crystallography enabled correct assignment of helicene absolute configuration.[15] However, this is still a problem for non-crystalline compounds, and for those, absolute configurations are determined using circular dichroism (CD) and correlation with CD curves calculated by computing models.

b) Graphic representation of helicenes

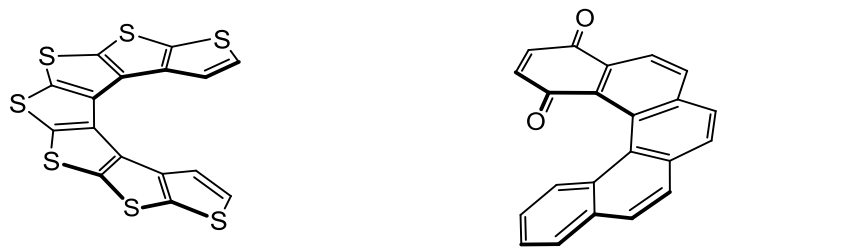
In an attempt to be as clear as possible, this section will display the graphic representation of helicenes, whether they are representing a racemic mixture or enantioenriched form. Racemic helicenes will be drawn flat when there is no overlap of the rings, and to improve the clarity, both mirror images will be drawn for larger structures when rings do overlap (Figure 7).




*rac*-aza[5]helicene, **9** *rac*-[9]helicene, **10**

**Figure 7: Representation of racemic helicenes**

Enantioenriched or enantiomerically pure forms will only be drawn using the structure of the major enantiomer (Figure 8); subheadings might be added to indicate enantiomeric excesses of represented structures.




(*M*)-heptathia[7]helicene, **11**, xx% e.e. (*P*)-[5]helicene-1,4-dione, **12**, xx% e.e.

**Figure 8: Representation of non-racemic helicenes**

c) Optical properties

The surprising combination of exhibiting full delocalisation of pi electrons in a chiral non-planar structure has fascinated chemists from the early years of helicene research because of the exceptional chiro-optical properties that arise from it.[16] Indeed, helicenes exhibit very high specific rotations (Figure 9) because the chromophore itself is inherently dissymmetric or asymmetric. These observations made in the 1960s, showing high specific rotation values, increased helicene popularity as small asymmetric inductions would be easily quantifiable with accuracy which was seen as something that should help to understand better and to quantify chirality.

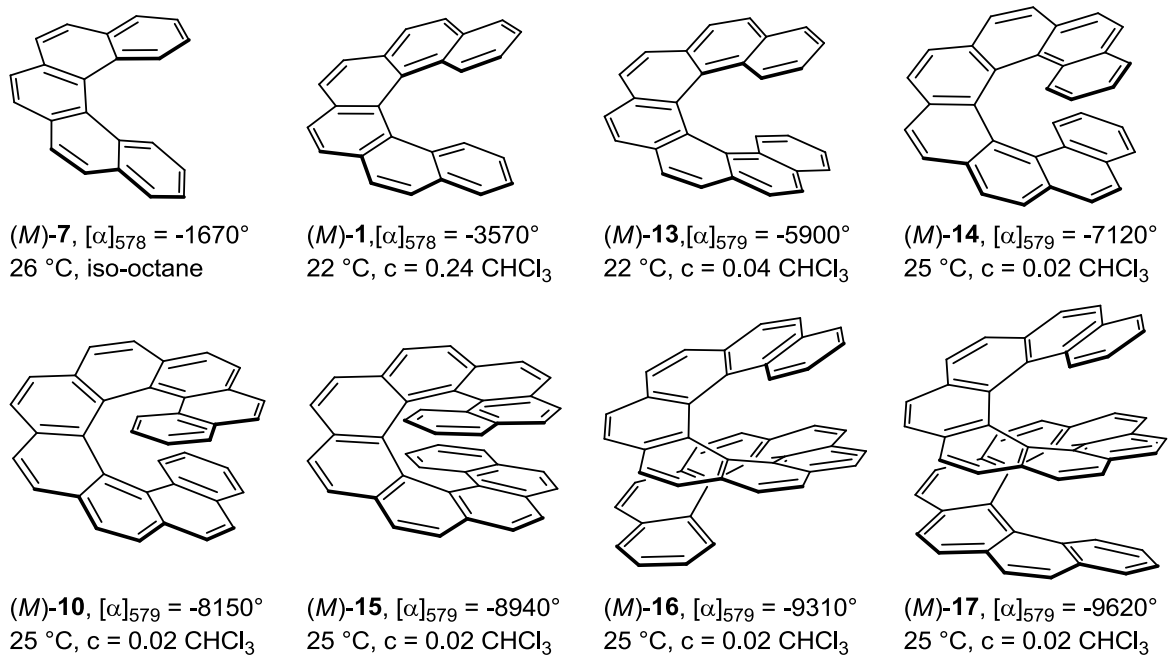



**Figure 9: Specific rotation of notable helicenes**

d) Nonlinear Optical experiments

The study of the structure-chiro-optics relationship has always been important to provide a deeper understanding of chirality. Indeed, the understanding of small chiral systems has been made possible by the development of techniques like CD and ORD.[17] However, these methods based on one photon absorption have several limitations, notably the inability of working at shorter wavelength (UV region).[18] Despite the development of more modern techniques like vibrational circular dichroism (VCD) and vibrational Raman optical activity (VROA) spectroscopy, more powerful techniques need to be developed to access further details of chiral systems.[19] For this purpose, new techniques based on two-photon

absorption (TPA) and second harmonic generation (SGH) (the emission from an irradiated sample of a photon at frequency 2ω resulting from two incoming photons at frequency ω) are potentially important with biological samples to access the UV region at reduced wavelength with longer wavelength irradiation. Combining it with the excellent 'molecular fingerprinting' abilities of circular dichroism that is already widely used to provide structural information, would make a powerful tool for biomolecular recognition.[20] This unique combination can be described as Two Photon Circular Dichroism (TPCD), the combination of two photon absorption (TPA) and circular dichroism (CD), which was originally predicted in 1975.[21] However, these higher order nonlinear optical effects suffer from low responses, making them hardly observable; TPCD although first predicted in 1975 was only observed in 1995,[22] in inorganic crystals. The calcualtions to estimate the TPCD properties of helicenes have established[10] that, because of their exceptional chiro-optical properties, TPCD emission should be above the known detection limits for direct observation of the TPCD phenomenon. Because of these predictions, helicenes are now accepted as an ideal class of organic molecules to develop into novel microscopy stains for TPCD imaging.[23]

The synthetic chemistry described in this thesis has been aimed at producing (electron donor)-(chiral-π-system)-(electron acceptor) push-pull systems capable of displaying TPCD effects as well as other NLO effects such as SGH-CD. This doctoral project has been a synthetic chemistry research programme to develop new methods of enantioselective synthesis (multi-KR) and to apply them to prepare novel molecules for important photophysics measurements, and the discussion of TPCD and NLO properties in this introductory chapter aims only to put the objectives of the synthetic work into a wider context. No attempt has been made to present here an in-depth/mathematical discussion of these complex optical phenomena and the results and discussion chapters of the thesis will display synthetic chemistry results and eventually mention the use of final target molecules for NLO studies, but will not present in detail the photophysics data.

### 4) Helicene synthesis

As indicated at the start of this introductory chapter, the date of first reported helicene is difficult to find and frequently, in recent articles concerning helicenes, authors' views on the actual date of helicene discovery seem to differ. Indeed, the term "helicene" was only

introduced the 1950s. Older syntheses do not mention the name helicene at all, and structure data based searches of articles published before the 1930s are difficult. It was noted that the date of the first report seems to be "ageing". Therefore, the terms of "first" report and "discovery" will be used with caution in this thesis, and I have not attempted a comprehensive search of the early literature.

a) Early syntheses

i) Racemic helicene

To the best of our knowledge, the first reported syntheses of helicenes were as early as the 1900s, with Meisenheimer and Witte in 1903[1] reporting aza[5]helicene (**9**) and diaza[5]helicene (**18**) (by the reductive cyclization of 2-nitronaphthalene) followed by Lieb *et al.* reporting[24] [4]helicene-6-carboxylic acid (**19**) in 1912 (Figure 10).

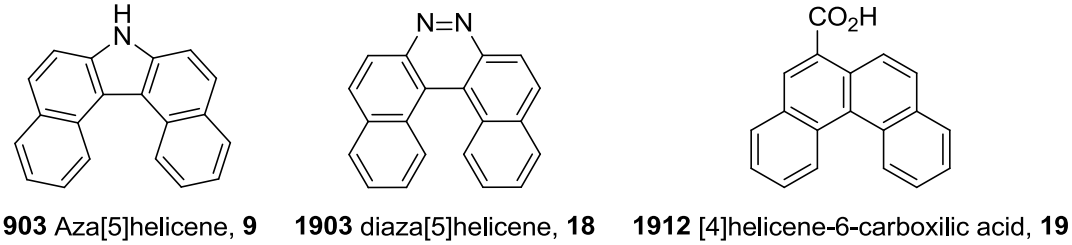
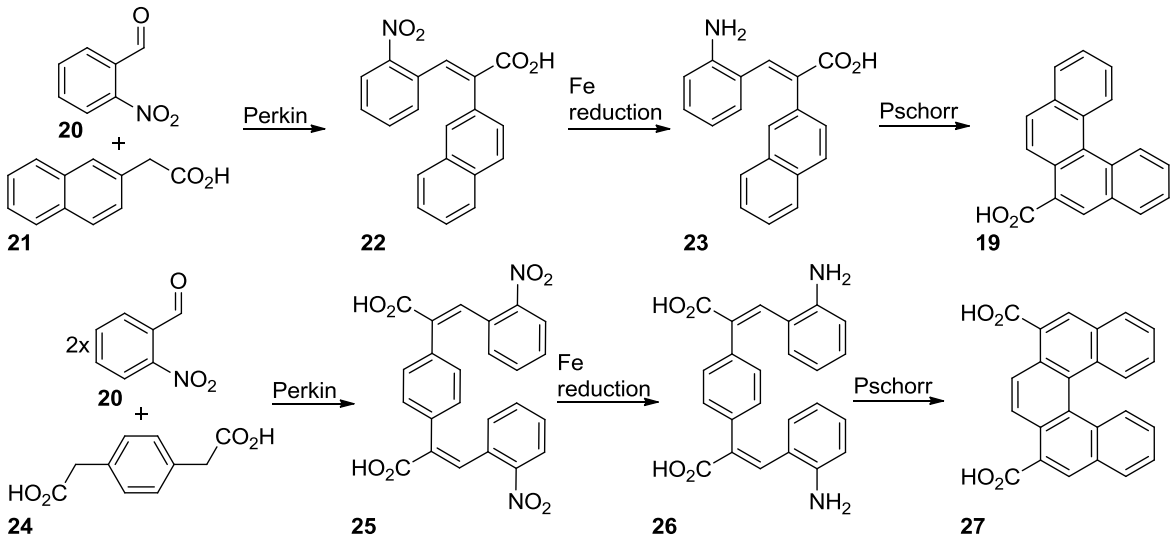


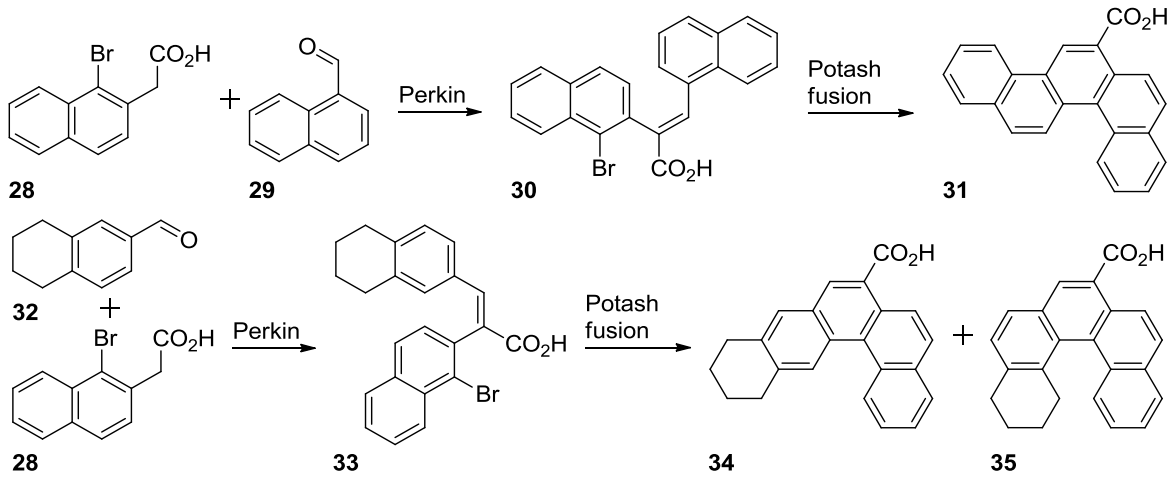

**Figure 10: First historical helicenes**

Several other reports of helicenes appeared during the following decade,[25] all having in common a methodology using the Pschorr reaction[26] as the ring closing step. The full synthesis involves a Perkin reaction to form alkenes with both aromatic moieties in the *cis* configuration. Then, the nitro group in ortho position, is reduced and converted into a diazonium salt, and upon heating, ring closing occurs; the resulting helicene is formed bearing a carboxylic acid on the newly constructed ring (Scheme 2). The parent helicene can be obtained upon heating, by a decarboxylation reaction.



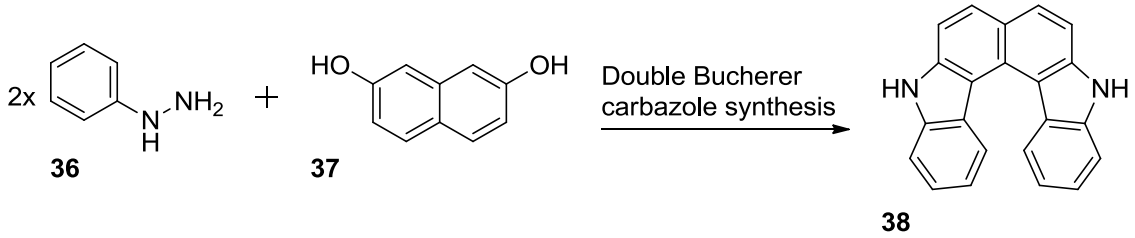

**Scheme 2: Synthesis of [4]helicene 19 and [5]helicene 27**

The main issue with this technique was the lack of selectivity in the ring closing step, allowing competing formation of linear isomers. This problem was first encountered by Lieb,[24] who thought he obtained pure [4]helicene, but instead obtained a mixture with the linear isomer. Another method was developed by Hewett *et al.* in 1938,[27] where the ring closing step was performed using a potash fusion on 1,2-diarylethene (with aryl in *cis* conformation) substrates, bearing an ortho-bromo substituent (**30** and **33**, Scheme 3).




**Scheme 3: Hewett's potash fusion mediated annelation**

Using a completely different approach, Fuchs prepared in 1927, diaza[6]helicene[28] (**38**) by a double Bucherer carbazole synthesis from 2,7-dihydroxynaphthalene (**37**) and phenyl hydrazine (**36**) (Scheme 4).

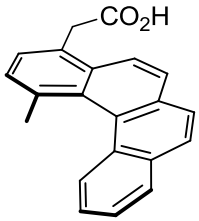



**Scheme 4: Fuchs' diaza[6]helicene (38) synthesis**

ii) First report of non-racemic helicene

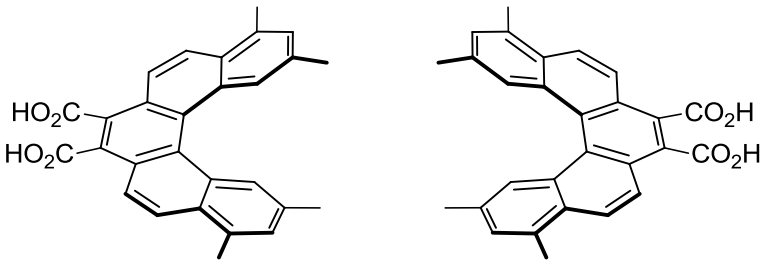
The story of non-racemic helicenes started with Newman who reported, in 1948, the first partial resolution of a helicene, [4]helicene derivative **39** (Figure 11).[29] He managed to obtain the optically active helicene after a kinetic resolution of its acid chloride derivative using *l*-menthol. However, due to the poor optical stability of [4]helicenes, no optical activity could be measured after one day. Then, Bell reported in 1949 the partial resolution of [5]helicene derivative **40**[30] (Figure 11) by treatment with morphine and preferential crystallisation of one diastereomeric morphine salt. Bell also mentioned that the partially resolved [5]helicene did not show any optical activity after a few hours in an acetone solution.

**1948: 2-(1-methyl[4]helicen-4-yl)acetic acid**




(*P*)-(+)-**39**; $[\alpha]^{25}$ = +2.1°

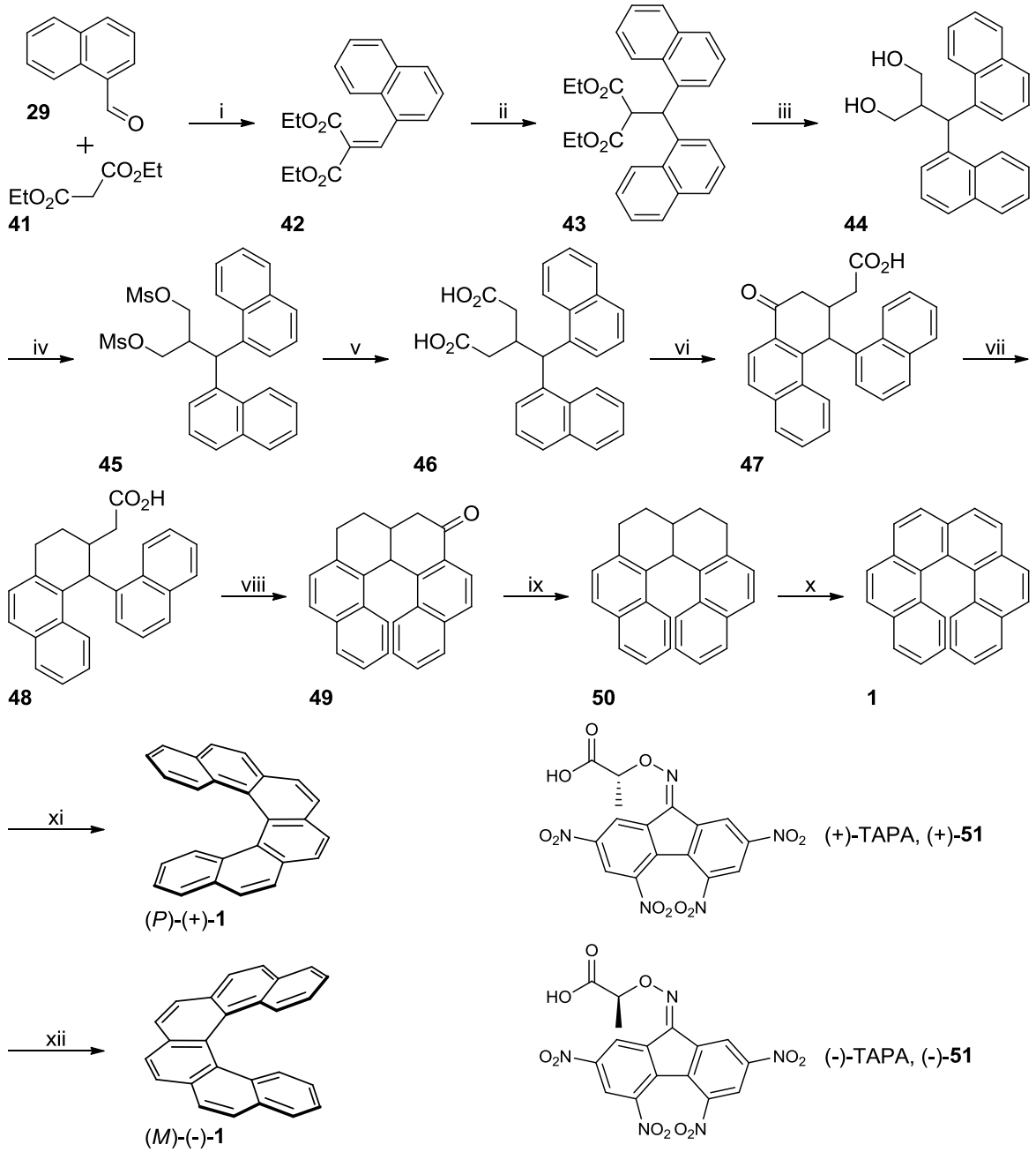
**1949: 2,4,11,13-tetramethyl[5]helicene-7,8-dicarboxylic acid**




(*M*)-(-)-**40**; $[\alpha]^{20}$ = -47.2° (*P*)-(+)-**40**; $[\alpha]^{20}$ = +18°

**Figure 11: First reported non-racemic helicenes, 39 and 40**

Following these reports, Newman established a landmark when he reported in 1955 the complete resolution [6]helicene (**1**) (Scheme 5).[2,31]




i) PhH reflux, 70%; ii) naphthyl magnesium bromide, THF, 56%; iii) $LiAlH_4$, PhH, 93%; iv) MsCl, pyr.; v) KCN, DMF, then NaOH, ethylene glycol, 55%; vi) HF, 67%; vii) $NH_2NH_2.H_2O$, KOH, diethylene glycol reflux, 87%; viii) $PCl_5$, o-PhCl, $SnCl_4$, 56%; ix) $NH_2NH_2.H_2O$, KOH, diethylene glycol reflux, 89%; x) $Rh/Al_2O_3$, PhH, 63%; xi) (+)-TAPA, PhH; followed by recrystallizations xii) (-)-TAPA, PhH; followed by recrystallizations

**Scheme 5: Synthesis and resolution of [6]helicene**

The synthesis, although novel, was still cumbersome, involving as many as ten steps for an overall yield of only 3.7%. Using α-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA, **51**)[32] in the recrystallization step, they obtained partially resolved [6]helicene, and, after several recrystallizations (nine in total), they eventually obtained enantiomerically pure (+)- and (−)-[6]helicene. Interestingly, Newman reported in the same year the successful resolution of configurationally stable 2-(1,12-dimethyl[4]helicen-5-yl)acetic acid (**52**) using *l*-cinchonidine (**78**) (Figure 12).[33]


(M)-(-)-**52**; $[\alpha]^{25}$ = -362° (P)-(+)-**52**; $[\alpha]^{25}$ = +348°

**Figure 12: Enantiomerically pure 2-(1,12-dimethyl[4]helicen-5-yl)acetic acid (52)**

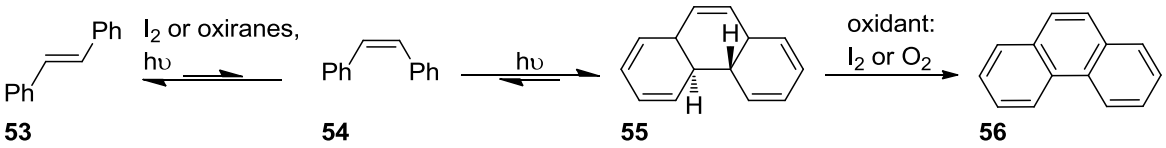
Newman's demonstration of the possibility to resolve helicenes had great impact and triggered the interest of many scientists in these elegant helically shaped molecules. From the early 1960s, onwards, intensification of the research in helicene chemistry occurred rapidly, giving rise to a large number of publications. However, from a synthetic point of view the strategy used to obtain helicenes was still too complicated, long and low yielding, and the final re-aromatisation using high temperature restricted the possible functionalities present on the helicene.

b) Development of photochemical syntheses

i) Photodehydrocyclisation

The way to easier syntheses of helicenes was paved by the report of successful photocyclisation of stilbene derivatives in 1964 by Wood and Malory (Scheme 6).[34] This reaction allows the formation of polycyclic aromatics under UV irradiation, from *cis* or *trans* 1,2-diarylethene, in the presence of a catalyst for the *E*/*Z* isomerisation and an oxidant for the rearomatisation. The addition of catalysts/reagents like iodine, propylene oxide or ethylene oxide to provide the *trans*/*cis* isomerisation is necessary to obtain an efficient photocyclisation reaction. Indeed, the *trans* double bond is first isomerised to the *cis* structure which then cyclises readily, driving the reaction forward. The usual oxidant

providing rearomatisation would be air, even though iodine in stoichiometric amounts has been shown to provide significant results in some examples (also the addition of propylene oxide can help to destroy some of the HI formed).[35] It has to be noted that the reaction would be made much faster if alkenes with aryl groups in the *cis* configuration were used, however most of chemical reactions (Wittig, McMurry, etc) lead to the formation of alkenes with aryl groups in a *trans*-configuration. Exceptions to this are the Perkin reaction and the McMurry reaction of ketones which afford tetrasubstituted alkenes with both aryl groups *cis* to each other.



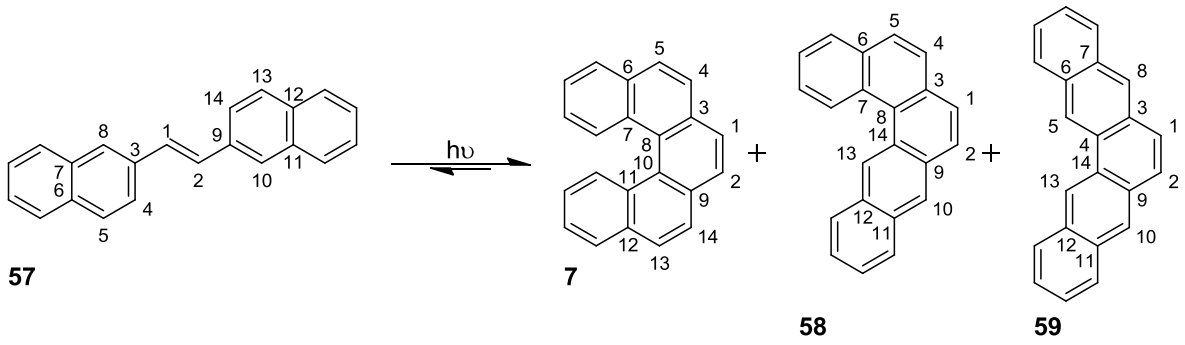

**Scheme 6: Photodehydrocyclisation of stilbene**

The reaction was originally carried out in benzene; however since the discovery of its carcinogenicity benzene has been replaced in most cases by toluene, which is not without its own disadvantages (reduced solubility of reactants and more difficult removal by evaporation). Indeed, helicene precursors are large conjugated flat structures which tend to be highly insoluble in most of solvents because of pi-stacking phenomenon, so the use of toluene does not generally allow for a successful cyclisation of those species. The use of tetrasubstituted alkenes bearing bulky groups (alkyl, carbonyl, $CF_3$, $NO_2$) generally reduces or prevents completely pi-stacking of the precursors, improving solubility. Also, benzene is considered as a photoinitiator, which might facilitate the isomerisation process.

ii) Carbohelicenes

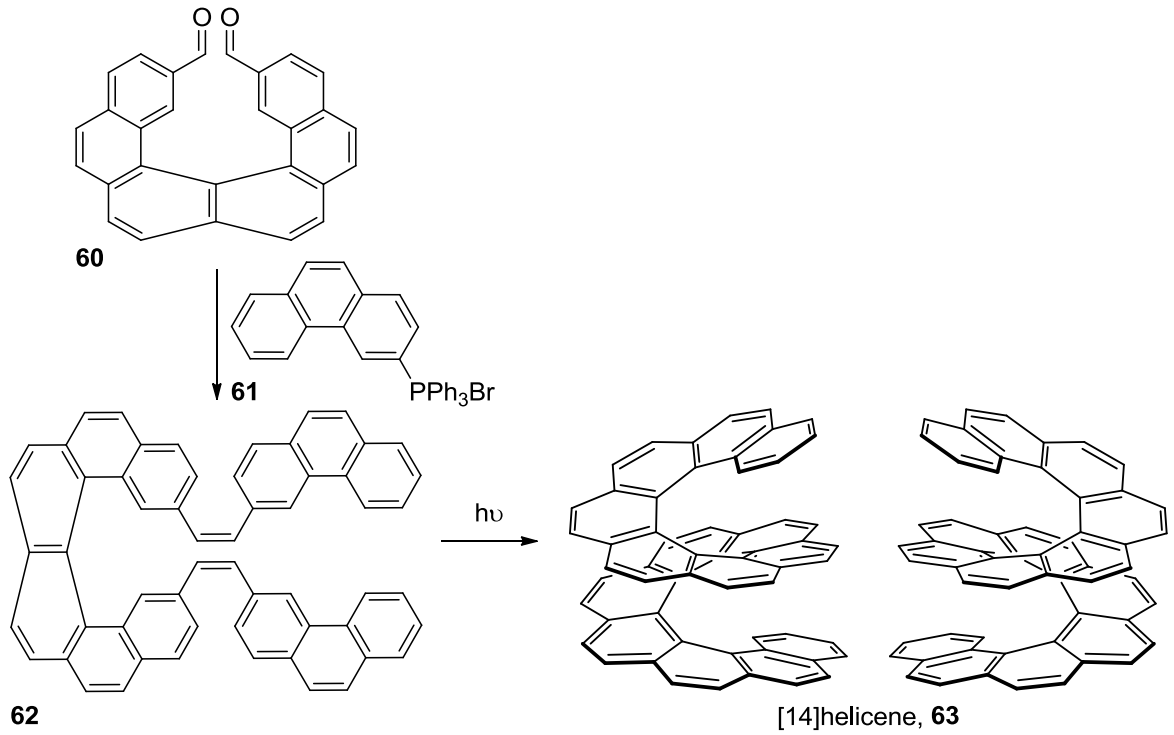
Wood and Malory's report in 1964 unravelled the accessibility problems of helicenes and the relative convenience of the photochemical method triggered a considerable amount of research on helicene synthesis. The main concern for the photocyclisation of 1,2-diarylethenes bearing larger aryl groups than phenyl (ie, naphthyl see **57**, phenanthrenyl) was that the two ortho-positions (4 and 8 or 10 and 14, Scheme 7) of the aromatic moeities are no longer chemically equivalent and can give rise to more than one possible regioisomer upon cyclisation (**7**, **58**, **59**, Scheme 7). However, Scholz showed that when transferred to larger structures, the regioselecvity of photodehydrocyclisation was not

unfavourable to the formation of specific helical structures, reporting the synthesis of [7]helicene in 1967.[36]




**Scheme 7: Possible regioisomers from photocyclisation of 1,2-diarylethylenes**

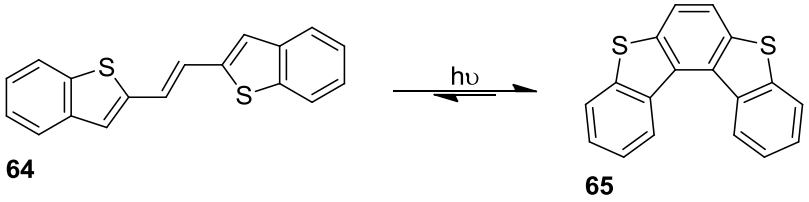
Subsequently, several research groups (Martin, Wynberg, Laarhoven, Kagan) tackled the photosynthesis of helicenes of various shapes and sizes, up to [14]helicene[37] (**63**, Scheme 8). However, the larger structures proved to be very challenging as the number of possible isomers arising from a one-step multi-cyclisation is far greater than for smaller structures.




**Scheme 8: Notable helicene obtained via photosynthesis**

iii) Heterohelicenes

Besides the early reports of aza[5]helicene in 1903 and aza[6]helicene in 1927, heterohelicenes had been under-studied before the era of photo-induced cyclisation. This was changed by photo-induced cyclisation methods, especially when it was confirmed that heterocyclic analogues of stilbene (for example **64**, Scheme 9) cyclise in the same fashion affording corresponding heterophenanthrene analogues. Wynberg proved that using a benzene-thiophene scaffold was very successful as it does not allow the formation of isomers in the cyclisation step, only one ortho position being available (Scheme 9).[38]




**Scheme 9: Photocyclisation of thiophene analogues of stilbene**

His group reported several syntheses of thia[n]helicenes, of many sizes from 4 to 11 rings[39] (Figure 13), and using building blocks[38] **67**, **68**, **69** and **70** (Figure 14), pretty much any thia[n]helicene can be synthesised, within the acceptable limits of size. Moreover, considering that among heterocycles, thiophene is the closest to benzene concerning aromaticity,[40] thiophene-derived helicenes exhibited similar properties to carbohelicenes.

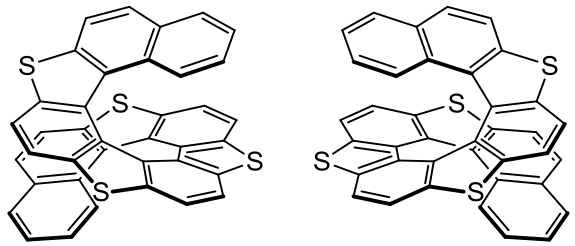



**Figure 13: Tetrathia[11]helicene (66)**

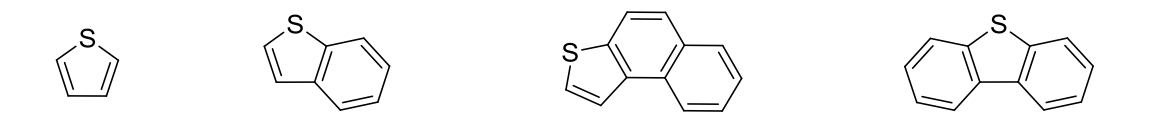
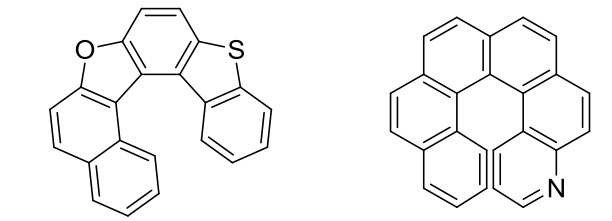



**Figure 14: Building blocks for thia[n]helicenes**

Then, in 1981, Yamada *et al.* reported[14] the synthesis of several thia[n]helicenes, in particular octathia[15]helicene. More recently, Licandro and Maiorana have improved the synthesis of thia[7]helicenes, using a McMurry coupling reaction to generate the 1,2-diarylethene species directly from the aldehyde.[41]

Besides thiahelicenes, not many other heterohelicenes have been synthesised using photochemical conditions. Martin in 1969[42] and Wynberg in 1971[39] respectively synthesised aza[6]helicene (**71**) and mixed oxa-thia[6]helicene (**72**) (Figure 15), using the same methodology as for the photocyclisation of thiahelicenes. More importantly, this period (late '60s / early '70s) saw a rapid growth of the interest for obtaining enantioenriched helicenes.




8-oxa-5-thia[6]helicene, **71** 4-aza[6]helicene, **72**

**Figure 15: Hetero[n]helicene obtained via photosynthesis**

III) Heterochiral and homochiral helicenes

1) Racemisation and inversion barrier

The chirality displayed by helicenes arises directly from the conformation of their helix, therefore if the left- or right-handedness can be inverted/reversed this would in theory result in a racemisation process. Although it is hard to imagine a long helical shape, like a spring for example, switch from left- to right-handedness, as helicenes rarely display more than one or two turns of the helix, we should think of them more as a 'key ring', and when enough energy is brought to the system racemisation can sometimes operate; the shorter the helix is, the faster it happens. This phenomenon was first observed by Newman, in 1948,[29] when the optical activity of partially resolved 2-(1-methyl[4]helicen-4-yl)acetic acid (**39**) disappeared after one day at room temperature. This is a reason why [4]helicenes have for a long time not been considered as true helicenes, as the equilibrium between configurations did not allow any lasting resolution, and no optical activity could be measured. Since then, it has been shown that helicenes can be stabilised by hindering the "bay area" (see Figure 16) when adding bulky groups on end rings. Also, some

phenanthrene structures bearing extremely large substituents have exhibited optical activity, so they could, in principle, be regarded as [3]helicenes.[43]

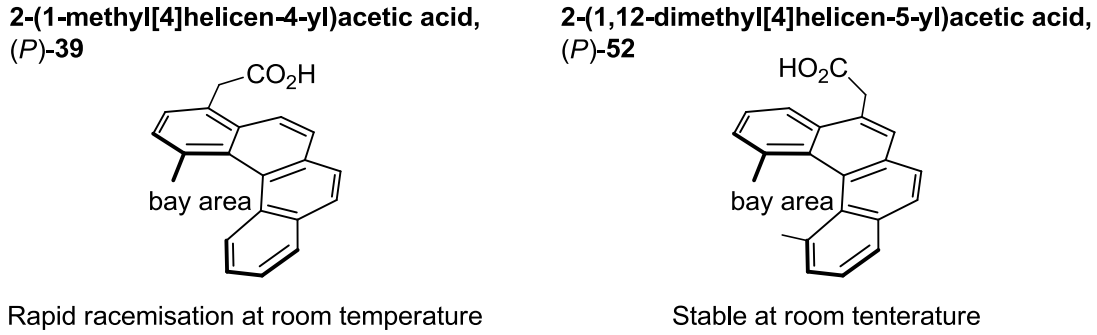



**Figure 16: Stabilisation by crowding the helicene bay area.**

Helicene racemisation has always been an issue for synthetic chemists from the time they first tried to obtain non-racemic material. Wynberg was the first to report in 1969 the racemisation rates of dithia[6]helicene and trithia[6]helicene.[39] Since then, many reports on racemisation rates and energy of inversion barriers have flourished, especially more recently with more complete computational studies.[44] The general idea being that stability of [n]helicene increases with n growing, that heterohelicene are in general less stable that carbohelicenes, that [n]helicenoids are also generally more likely to invert, and finally, addition of substituents in the inner side of the helix, crowding the bay area increases the stability.

2) Resolution techniques

a) Selective crystallisation

The resolution of enantiomers via selective crystallisation usually relies on the preferential formation of a diastereomeric complex / ion pairs upon addition of an external chiral auxiliary, followed by the crystallisation (and filtration) of the complex. For that purpose many alkaloids have been, and still are, commonly used, such as quinine, quinidine, strychnine, brucine, cinchonine, cinchonidine (Figure 17).

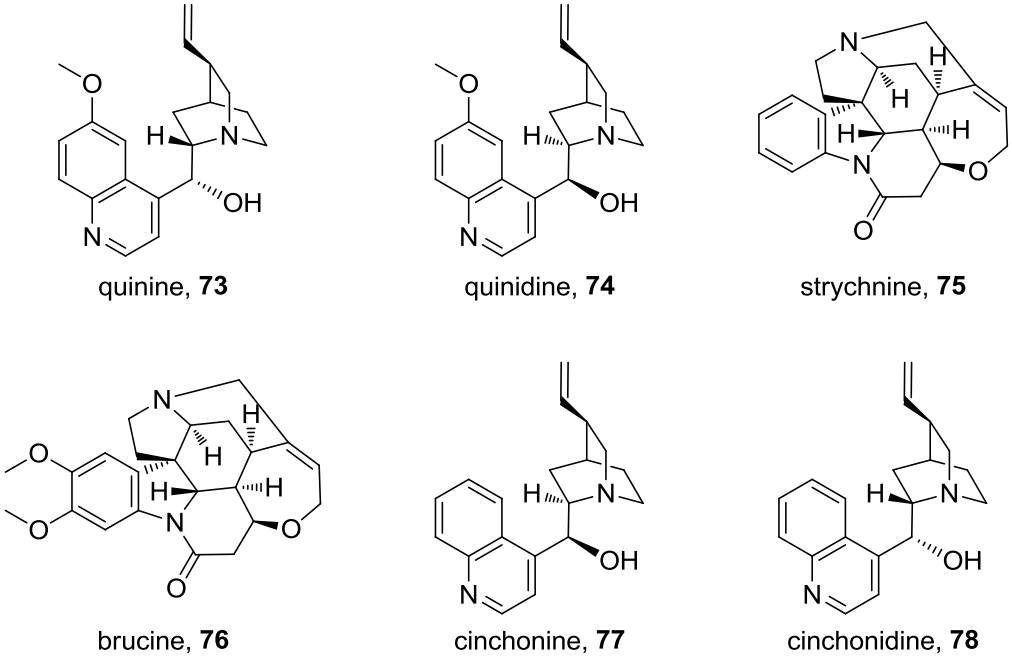



**Figure 17: Some alkaloids used for resolutions of racemic species**

In 1949, Bell even reports the partial resolution of [5]helicene dicarboxylic acid when treated with morphine (see paragraph II)4)a)ii) First report of non-racemic helicene).[31] Newman's 1955-1956 breakthroughs obtaining optically active [6]helicene (**1**, see above) by crystallisation with (+)- and (–)-TAPA[32] relied for their success on the fact that TAPA (**51**), as a chiral pi acceptor, forms charge-transfer complexes preferentially with one helicene enantiomer. This was, in fact, the first report of a resolution using the preferential formation of diastereomeric charge transfer complexes. The same year, Newman, used more conventional *l*-cinchonidine to partially resolve 2-(1,12-dimethyl[4]helicen-5-yl)acetic acid (**52**).[33] In 1972, he also reported the selective recrystallisation of one diastereomeric salt of phosphonium[6]helicene **79** and silver (–)-hydrogendibenzoyltartrate (**80**) (Figure 18).[45]

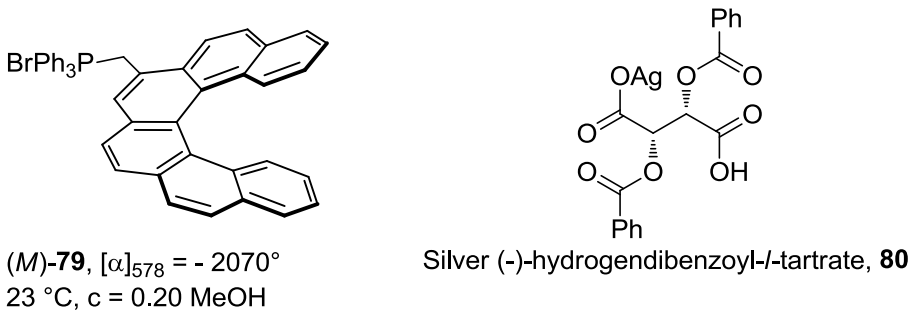
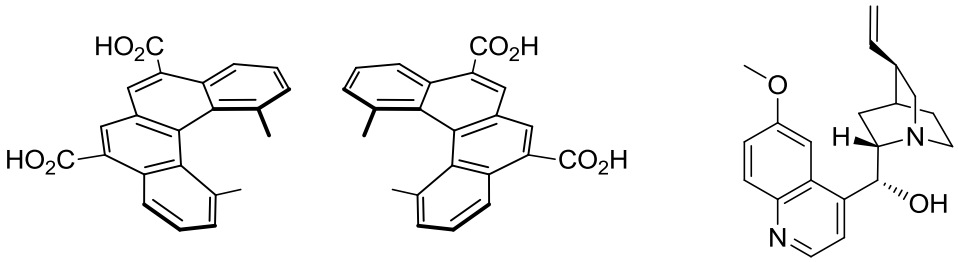



**Figure 18: Resolution of a [6]helicene**

In 1996, Yamagushi reported the resolution of 1,12-dimethyl[4]helicene-5,8-dicarboxylic acid (**81**) by selective crystallisation with quinine (**73**) (Figure 19),[46] whereas Starý used (+)-*O,O*'-dibenzoyl-D-tartaric acid (**84**) to resolve 1-aza[6]helicene (**82**) and 2-aza[6]helicene (**83**) in 2008 (Figure 20).[47] One might add that the successful isolation of enantiopure material relies in those cases on recrystallization of partially enantioenriched material to further enantiopurity.




(*M*)-**81,** $[\alpha]^{25}$ = -332° (*P*)-**81,** $[\alpha]^{25}$ = +313° quinine, **73**

**Figure 19: Resolution of 1,2-dimethyl[4]helicene-7,8-dicarboxylic acid with quinine**

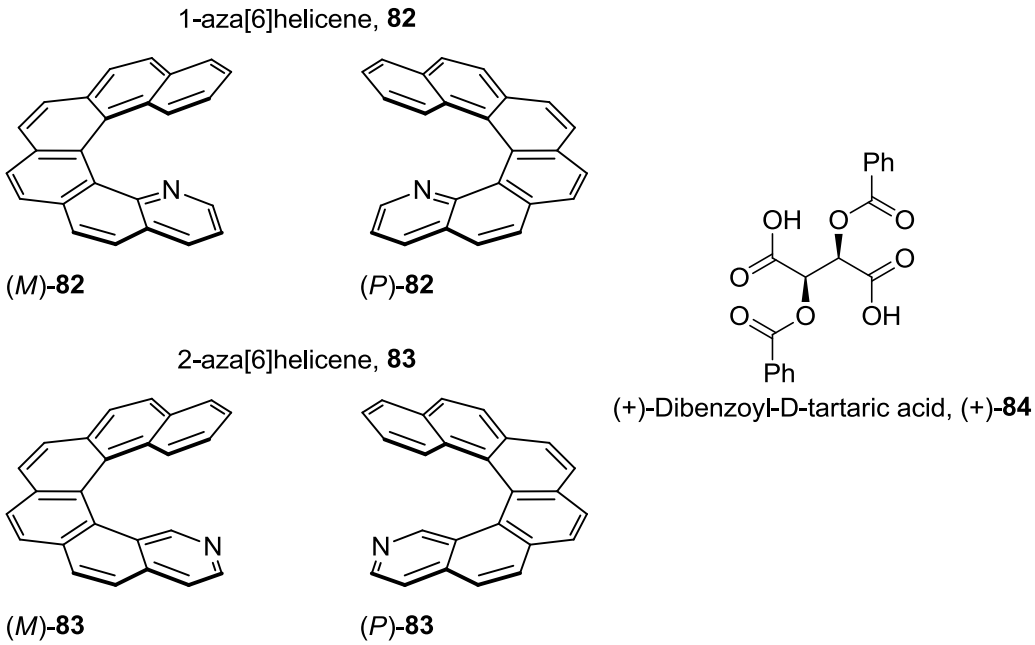



**Figure 20: Resolution of aza[6]helicene with (+)-*O,O*'-dibenzoyl-D-tartaric**

Also, reports of resolutions of ionic helicenes or helicenoids have been made (diaza[4]helicenium, diaza[5]helquat)[48] but will not be described in detail in this thesis.

In the 1960s Martin and coworkers reported several results affording enantioenriched and enantiopure helicenes.[49] Their technique consisted of hand picking single crystals, followed by systematic analysis of every single crystal by measurement of their specific rotations. Their results were really precarious, affording material in a range of optical purities from its racemic to enantiopure form, despite all efforts to control better the crystallisations. Their major discovery was that most helicenes do not crystallise as enantioenriched crystals, putting an end to this particularly time-consuming technique.

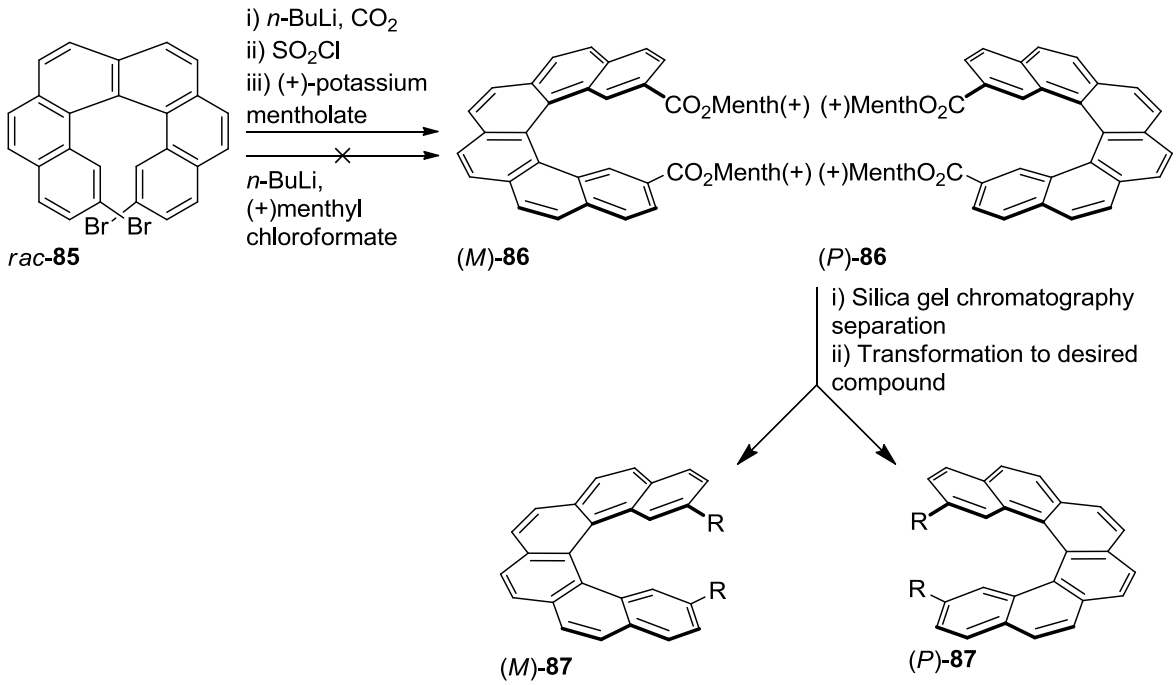
b) Separation of diastereoisomers

i) Method

Another way to obtain an enantiomerically pure helicene is to transform it into a diastereomeric mixture. As diastereoisomers exhibit different physical properties, it is possible to separate them using simple column chromatography (and in principle distillation, crystallisation, etc). The only limititation to this technique is the removal of the chiral auxiliary used for the transformation into diastereoisomers. However, helicene derivatives presenting carboxylic acid, hydroxyl or amine functional groups can easily be derivatised to form diastereomeric mixtures.

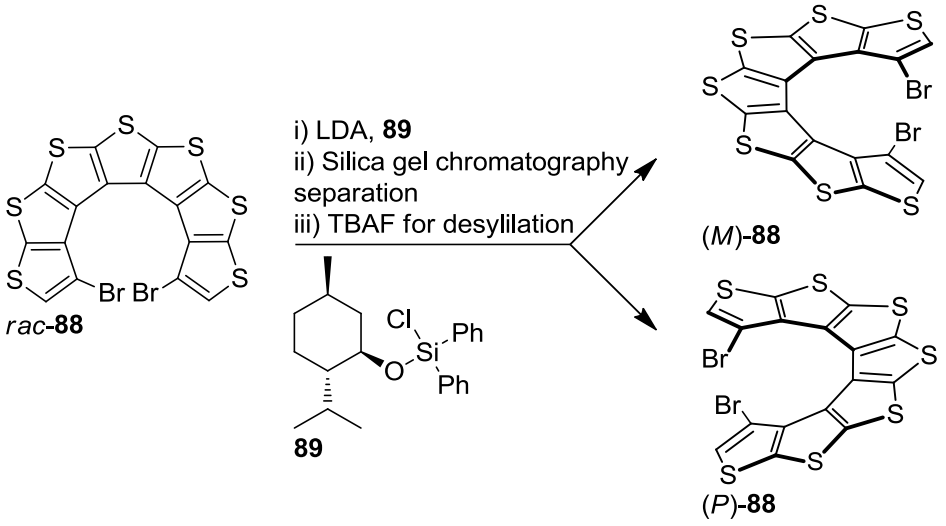
ii) Menthol auxiliaries

As early as 1948, Newman *et al.* attempted the resolution of menthyl ester derivatives of [4]helicene carboxylic acid **39**, with little success (specific rotation of product +2.1°, and racemisation at room temperature).[29] Then, Martin mentions in his review in 1974[50] that Jespers and Libert had successfully resolved the menthyl ester of [6]helicene carboxylic acid. Although Wynberg, in his review in 1971,[38] mentions good progress resolving 2-formyltrithia[7]helicene following Woodward's technique for the resolution of camphor which uses *l*-menthydrazine,[51] there is no other report of this in the literature until the end of the 1970s.[52] In 1998, Fox reported the separation of the di-menthylester of [6]helicene-2,15-dicarboxylic acid **86**;[53] he noted that menthyl ester groups could only be introduced from dibromide **85** in a stepwise sequence forming the diacid first, followed by esterification, as the quench of di-lithiated helicene with menthylchloroformate was not efficient/working (Scheme 10).




**Scheme 10: Resolution of [6]helicene derivatives**

More recently, Rajca used *l*-menthol as a scaffold for a chiral chorosiloxane reagent that he used for the resolution of diastereoisomers of 3,11-dibromoheptathia[7]helicenes[54] (**88**, Scheme 11). He successfully resolved both diastereoisomers bearing two menthyl auxiliaries, which were reconverted into the parent structure using TBAF. From the literature comments, it seems that two menthyl auxiliaries are necessary to obtain efficient separation of diastereoisomers on silica gel chromatography.




**Scheme 11: Resolution of heptathia[7]helicene using (–)-menthyl siloxane**

iii) Camphor derived auxiliaries

Following their early work on the resolution of carboxylic acids, in 1996, Hirama used a camphor derivative to resolve helicenes[46]. They successfully employed camphorsultam **90** to resolve 1,12-dimethyl[4]helicene-5,8-dicarboxylic acid (**81**) attaching the chiral auxiliary by a simple amide synthesis followed by silica gel chromatography affording enantiopure (*M*)- and (*P*)-**91** (Figure 21).

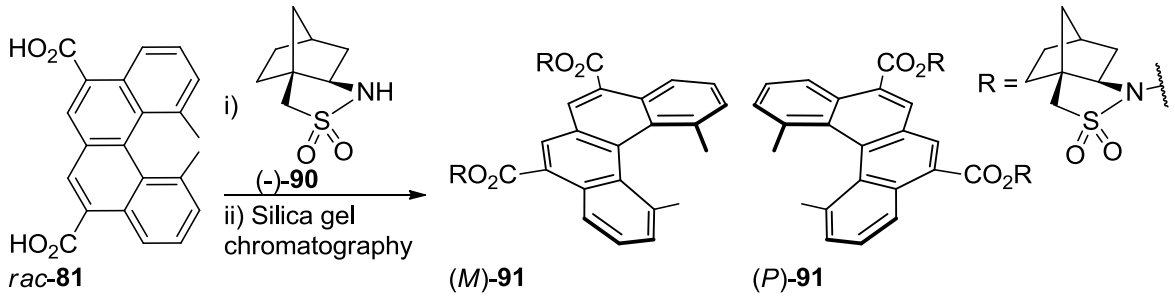
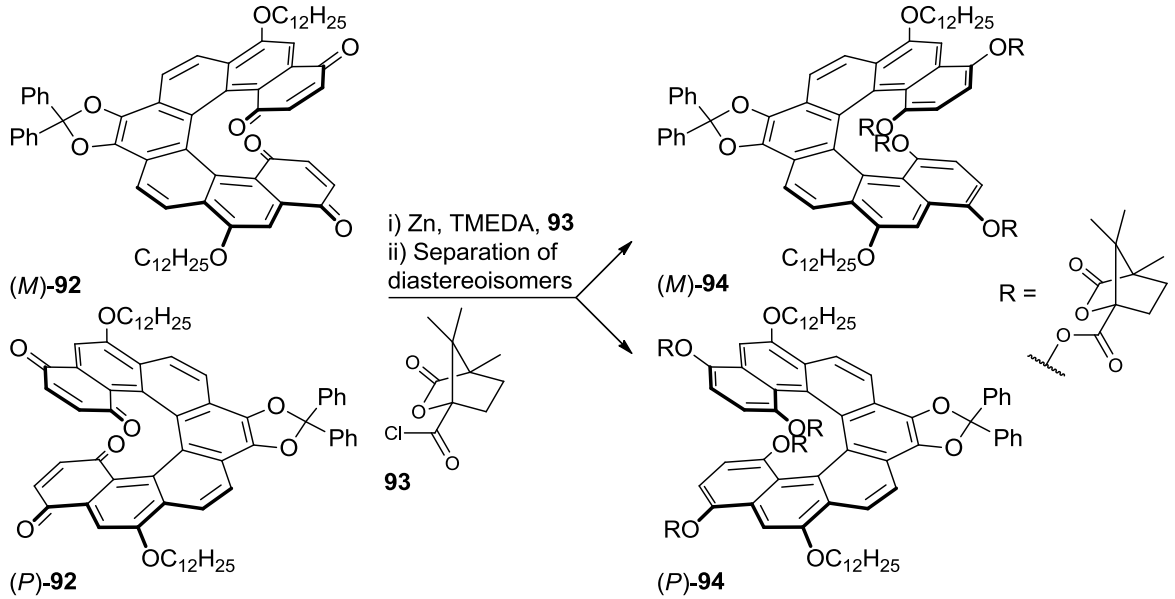


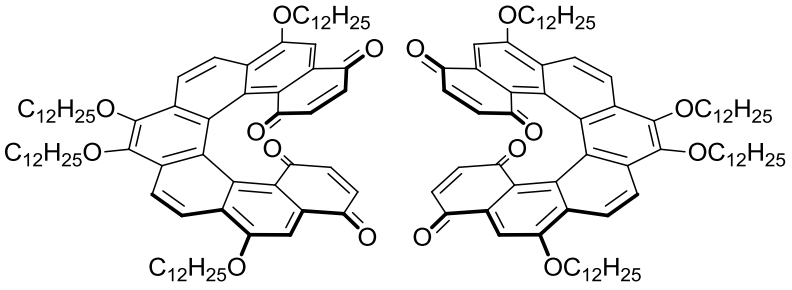

**Figure 21: Resolution of 1,12-dimethyl[4]helicene-5,8-dicarboxylic acid (81) by chromatographic separation of its (–)-camphorsultam amide 91**

The generalisation of the camphor-based approach came with Thomas Katz's work on the separation of some of his helicene bisquinones -using a camphanate auxiliary, published in 1998 (for example **92**, Scheme 12). Indeed, in this work, he sets out the use of camphanoyl chloride (**93**) in single or multiple esterification reactions as a mean to introduce the auxiliary[55].

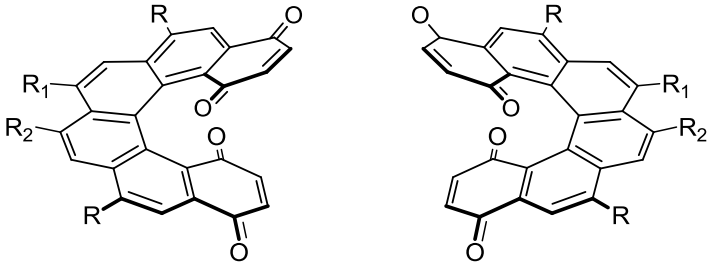



**Scheme 12: Resolution of [7]helicenebisquinones using (*S*)-(–)-camphanoyl chloride**

His method has been extensively detailed in his publications, establishing that the method can be generalised (Figure 22). He even published in 2000[5] an extensive study that explained why camphanates are such good resolving agents for helicenols. The camphanate method has since then been used by several different groups[56] (Carreño, Venkataraman, Aloui did not succeed) proving the wide adoption of the method (Figure 23, Figure 24).

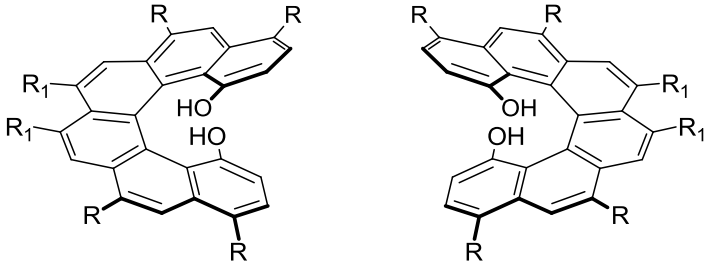


6,9,10,13-tetradodecyloxy[7]helicene-1,4,15,18-tetraone, **95**



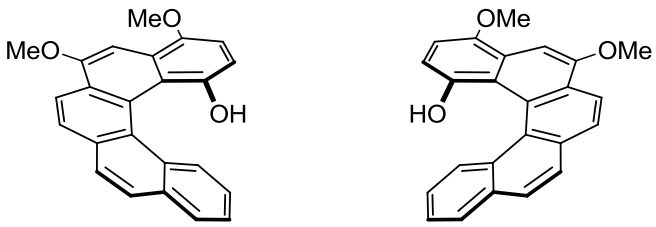
**96**, R = $R_1$ = $R_2$ = $OC_{12}H_{25}$
**97,** R = OTBDMS, $R_1$ = $R_2$ = OPiv
**98,** R = $R_1$ = $R_2$ = OTIPS
**99,** R = $R_2$ = OTIPS, $R_1$ = H

[6]helicene-1,4,13,16-tetraones



**100**, R = $R_1$ = $OC_{12}H_{25}$
**101**, R = OMe, $R_1$ = H

1,16-dihydroxy[6]helicenes



4,7-dimethoxy-1-hydroxy[5]helicene, **102**

**Figure 22: Katz's helicenes resolved using (*S*)-(–)-camphanoyl chloride**

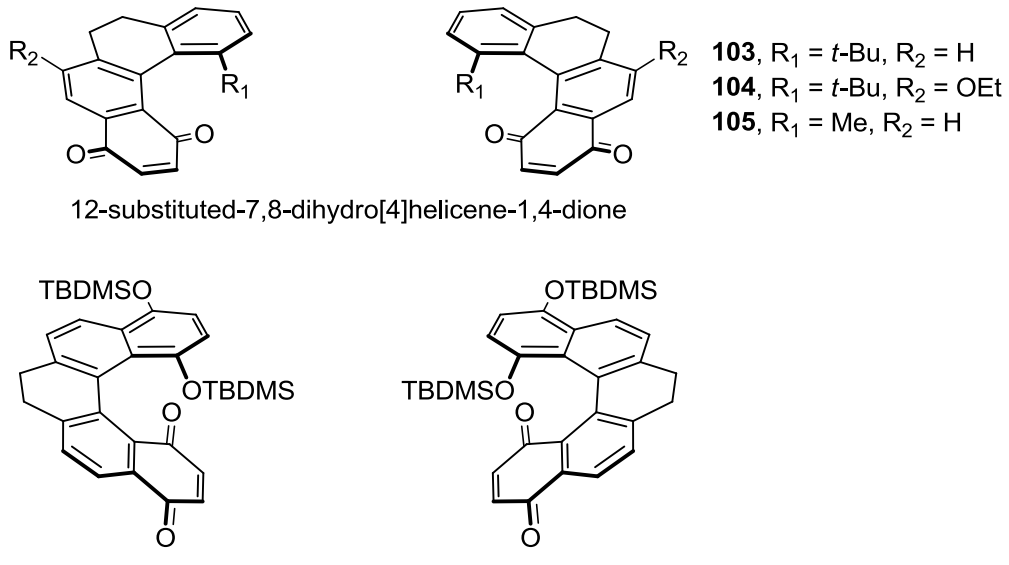



**Figure 23: Carreño's helicenes resolved with (*S*)-camphanoyl chloride**

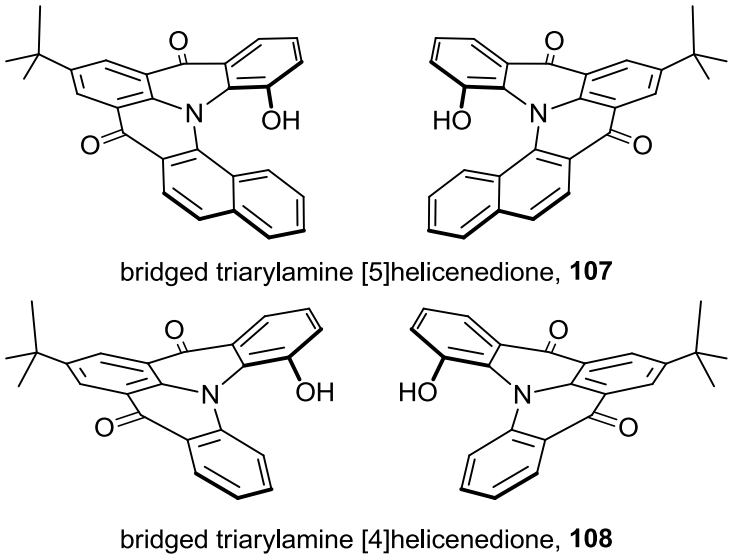
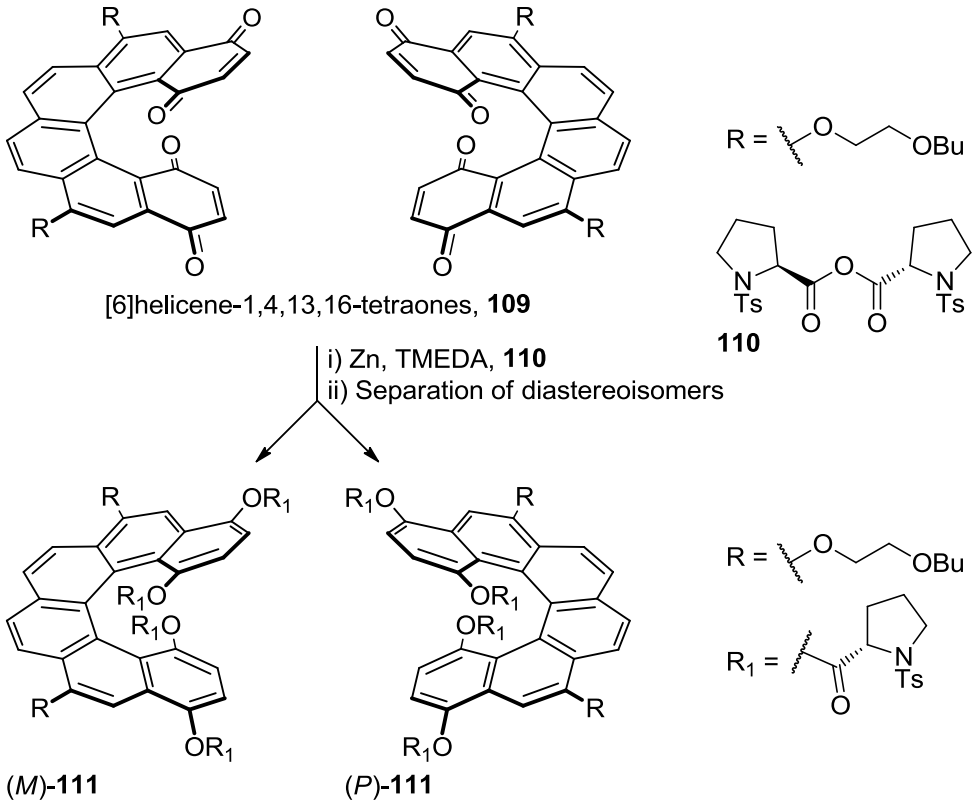



**Figure 24: Camphanate mediated resolution of bridged triarylamine helicenols**

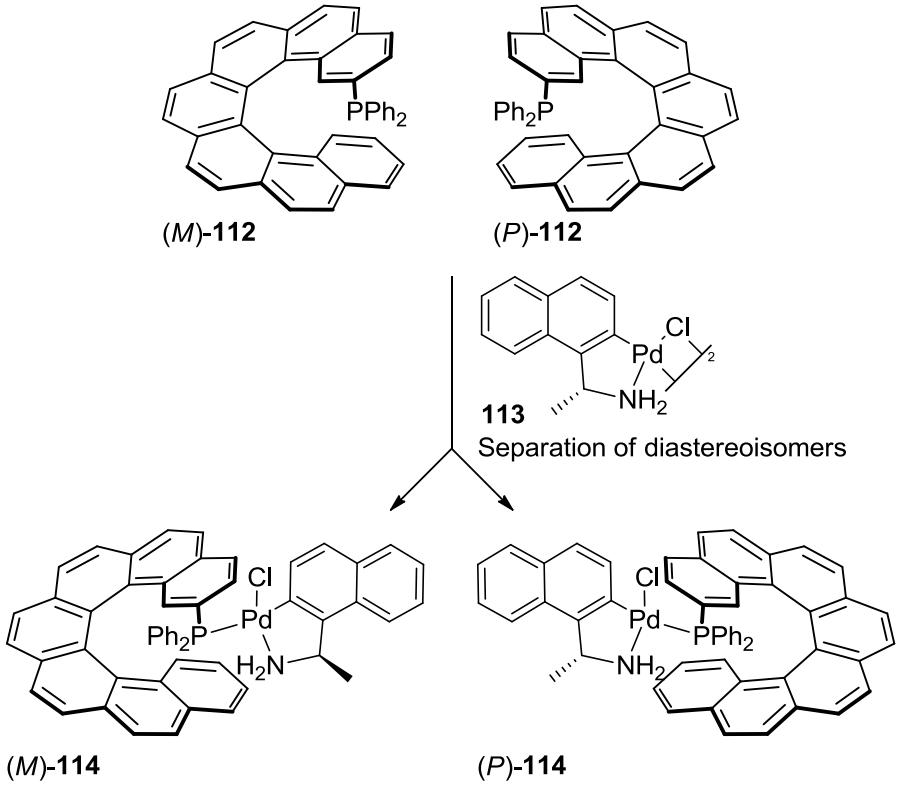
iv) Other auxiliaries

Katz also attempted the resolution of helicenes using *l*-proline derivatives,[57] prior to developing the camphanate methodology. Indeed, using *N*-tosyl-L-proline anhydride (**110**), [6]helicenebisquinone **109** was resolved after converting the quinones into hydroquinone esters thereby forming the two diastereoisomers of tetraester **111** (Scheme 13). However, this method was not further used, for unidentified reasons.



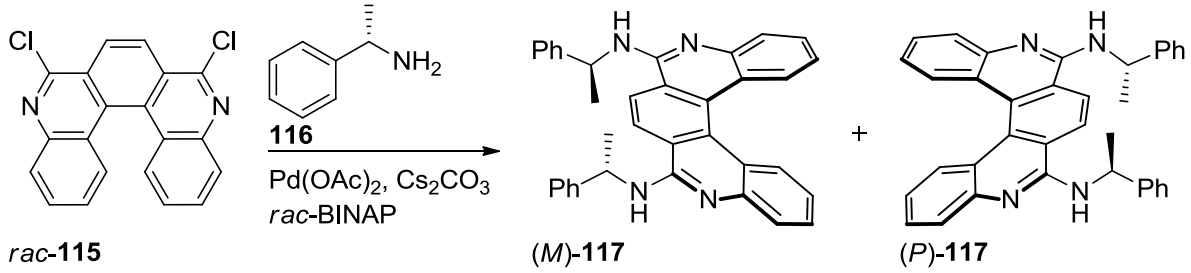

**Scheme 13: Resolution of helicenebisquinone 109 using *N*-tosyl-*l*-proline anhydride (110)**

El Abed *et al*., reported in 2007 the successful resolution of 2-(diphenylphosphino)-[7]helicene (**112**).[58] The reaction with ortho-palladated (*R*)-1-(naphthyl)ethylamine complex **113** (a well-established technique for the resolution of chiral phosphines) afforded two diastereoisomers which were separated by silica gel chromatography. Reaction of the palladium complex **114** with bis(diphenylphosphino)ethane, afforded enantiopure helical phosphines (*M*)- and (*P*)-**112**.




**Scheme 14: Resolution of 2-diphenylphosphino[7]helicene (112)**

Recently, Dehaen reported the resolution of dichloro-diaza[5]helicene[59] using a double Buchwald-Hartwig coupling with (*S*)-(–)-1-phenylethylamine affording both diastereoisomers in a 1:1 ratio, and separating them on silica gel chromatography (Scheme 15).




**Scheme 15: Resolution of 5,8-dichloro-4,9-diaza[5]helicene (115)**

c) Separation of enantiomers on chiral HPLC

The end of the 1970s saw the development of analytical techniques, in particular high pressure liquid chromatography (HPLC). The use of chiral HPLC stationary phases is now

a well-established technique to analyse chiral compounds and amongst them helicenes. Although preparative scale chiral HPLC is still used in some cases to obtain enantiopure material, the columns are very expensive and enough progress in resolution techniques and asymmetric synthesis has been made to make chiral HPLC an obsolete method for isolation of enantiomers in a large scale. Therefore, this thesis will not discuss chiral HPLC methods, unless mentioning sample analysis.

## 3) Asymmetric syntheses of helicenes

### a) Introduction

In this section 3, we will discuss the asymmetric syntheses of helicenes and some helicenoid molecules. All results concerning the asymmetric synthesis of helicenes will be described whereas syntheses of helicenoids will be restricted to molecules with structures closely related to helicenes. The material is organised based on the origin of the asymmetric induction. Two categories can be described for asymmetric synthesis: enantioselective and diastereoselective synthesis. Also, methods where the helical chirality directly arises from the enantiodefined chirality of the non-helical substrates (e.g. atropoisomeric substrates) with retention of configuration will be treated separately.

### b) Diastereoselective syntheses

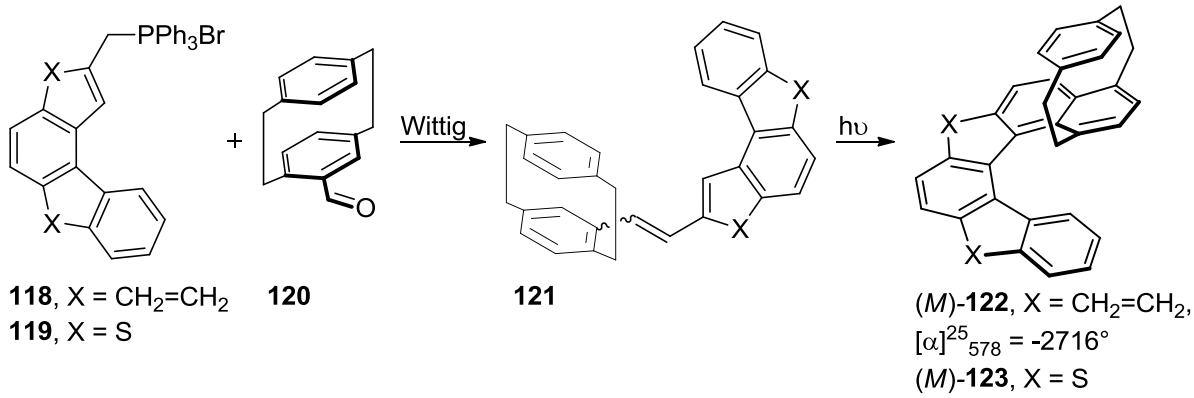
As for traditional resolution, a number of chiral auxiliaries have been used to induce chirality in the formation of helicenes, however in this case auxiliaries are introduced before the helicene formation.

#### i) Photocyclisation of precursors bearing chiral groups

##### 1. Paracyclophane

The way was paved by Martin and coworkers, who attempted photocyclisations of diarylethenes bearing chiral substituents. In 1972, Martin and Wynberg published the synthesis of [6]helicene **122**, structure that included (in place of one of the rings) a paracyclophane unit of known absolute configuration.[60] This enantiopure paracyclophane auxiliary/unit was introduced at the first step of the synthesis, building the helicene precursor from [2,2]paracyclophane-4-carbadehyde (**120**). The final step, the

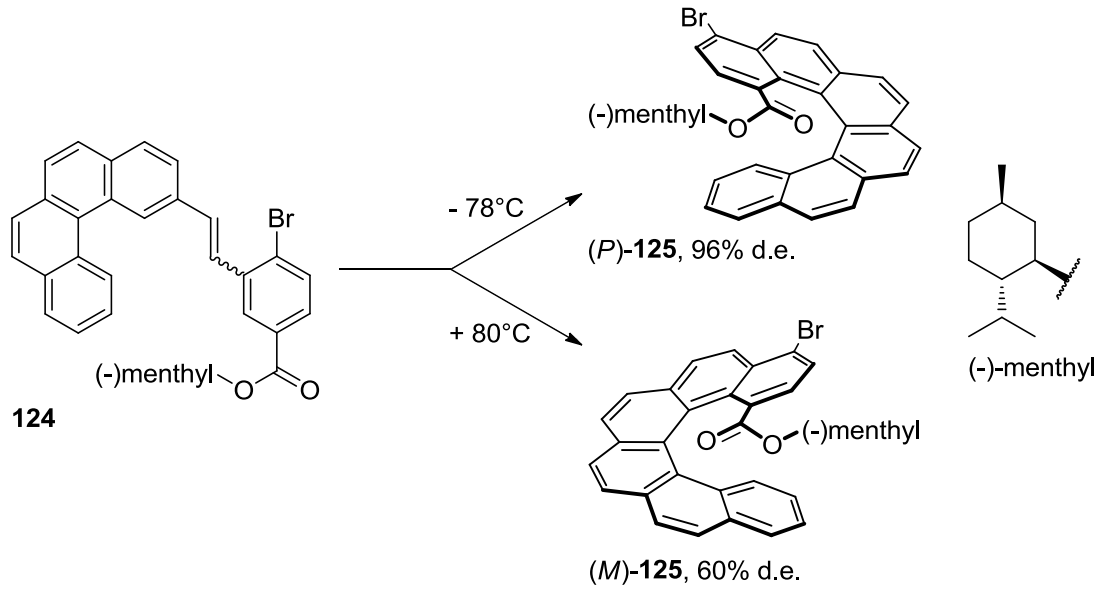
photocyclisation of (*R*)-diarylethene **121** afforded (–)-[2,2]paracyclophano-[6]helicene (**122**) in about 5% yield as a single diastereoisomer (Scheme 16). Wynberg, in collaboration with Martin, achieved a similar synthesis of (*M*)-(–)-[2,2]paracyclophano-dithia[6]helicene (**123**, Scheme 16) (no specific rotation nor CD curve was recorded because **123** was not stable). This low yielding synthesis did not provide a true solution to the synthetic challenge, but was of great importance because it allowed the determination of the absolute configuration of [6]helicene. Considering the absolute configuration of paracylophane **120**, the helix formed had to be left handed, therefore by comparison of specific rotation and ORD curves with the ones of [6]helicene, it was confirmed that (–)-[6]helicene had the *M* configuration.




**Scheme 16: Diastereoselective synthesis of [2,2]paracyclophanohelicenes 122 and 123**

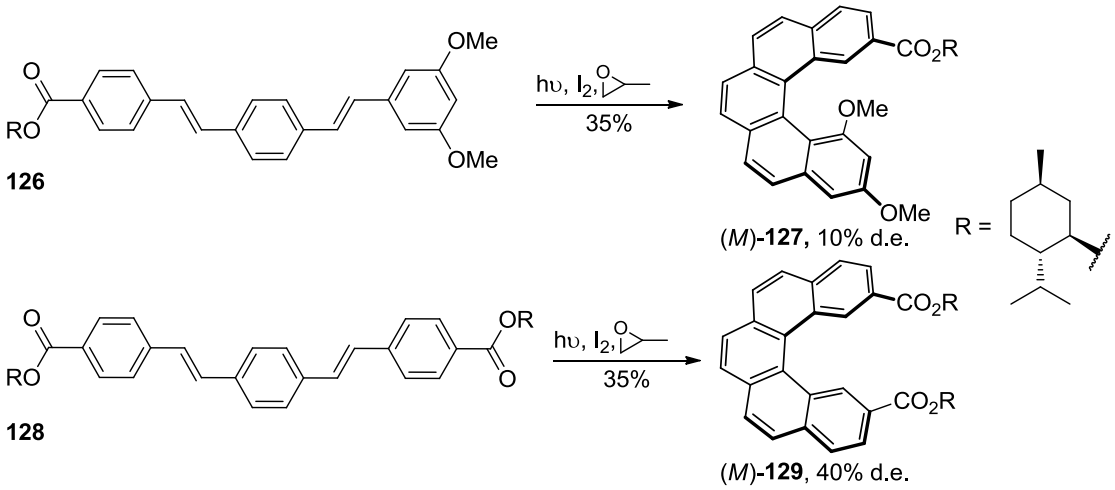
### 2. Menthol

Following their results for the synthesis of the paracyclophano[6]helicene, in the 1970s Martin's group used a similar strategy in synthesis of a [6]helicene. The menthyl ester group was introduced to the helicene precursor before the photochemical step, which showed at first poor selectivities (about 5% d.e.).[61] However, optimisation involving the introduction of the menthyl group at different positions on the end benzene ring helped to improve selectivities particularly when causing steric interactions in the hindered "bay area" of the helicene. When using menthyloxycarbonyl substituted precursors in this way (**124**), great diastereoselectivities were obtained, reaching 96% d.e. for the synthesis of the (+)-[6]helicene derivative **125** when the cyclisation was performed at –78 °C, and 60% d.e. for the synthesis of the (–)-[6]helicene derivative **125** when the cyclisation was performed at 80 °C (Scheme 17).[62,52b]




**Scheme 17: Diastereoselective photosynthesis of [6]helicene 125 using (–)-menthol auxiliary**

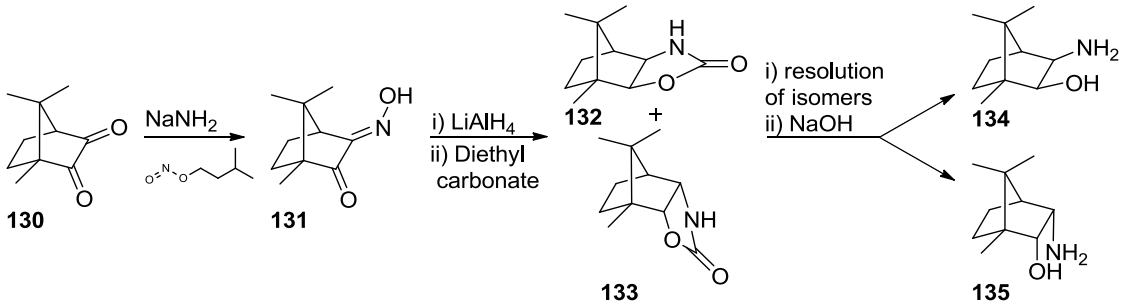
More recently, Carbery and coworkers attempted the photochemical synthesis of several bis-stilbenes with various degree of success. Surprisingly, no asymmetric induction was observed with [6]helicene precursors, whereas the photocyclisation of [5]helicene precursors **126** and **128** gave interesting diastereoselectivities; [5]helicene ester (*M*)-**127** was obtained with 10% d.e. and the photocyclisation of precursors bearing two menthyl ester groups **128** afforded [5]helicene diester (*M*)-**129** with 40% d.e. (Scheme 18).[63] Also, to link this with the previous paragraph concerning the separation of diastereoisomers, the authors noted that no separation on various chromatographic stationary phases was obtained.



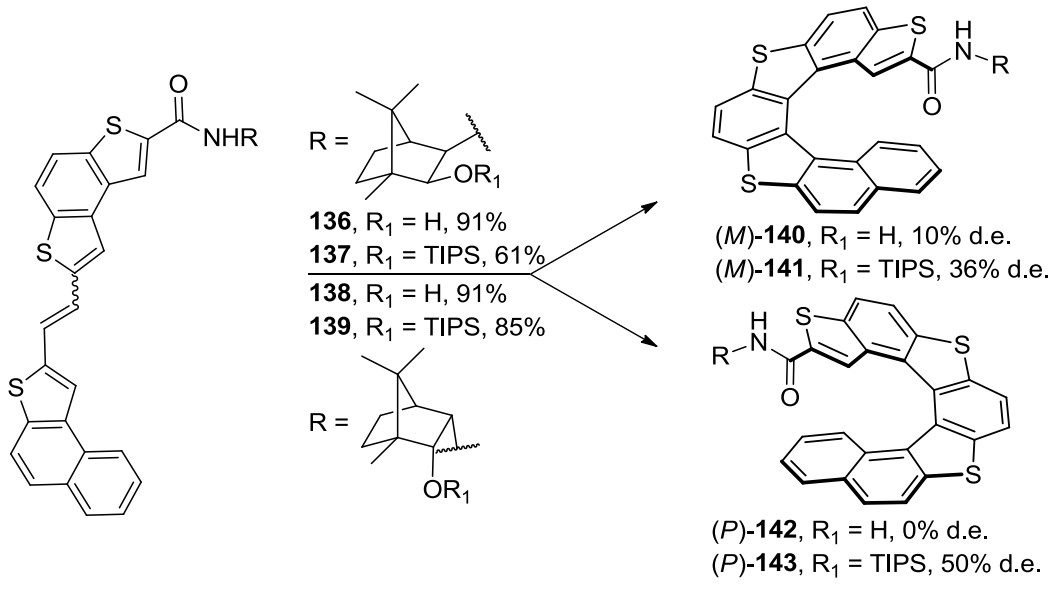

**Scheme 18: Diastereoselective photosynthesis of [5]helicenes using menthol auxiliary**

### 3. Bornane

In the 1990's, Tanaka achieved the diastereoselective syntheses of various thiahelicenes with good success using bornane auxiliaries, as well as managing the separation of diastereoisomers.[64] Indeed, using both *endo* and *exo* 3-amino-2-hydroxybornane **134** and **135** (Scheme 19), they obtained divergent configurations of trithia[7]helicene-2-carboxamide (**140**, **141**, **142** and **143**, Scheme 20) with selectivities reaching at best 50% d.e. The key factor that produced substantial selectivities was the incorporation of the bulky TIPS group on the bornane hydroxyl (**137** and **139**, Scheme 20). They also mentioned that despite the need of the TIPS group for diastereoselectivity, the free hydroxyl had to be used to achieve the chromatographic separation of diastereoisomers. Later, in 1995 and 1996,[65] Tanaka used the same strategy for the synthesis of tetrathia[7]helicene **144** and azatrithia[7]helicene **145** (Figure 25) that were obtained respectively with 24% and 26% d.e.




**Scheme 19: Synthesis of bornane auxiliaries**




**Scheme 20: Diastereoselective syntheses of trithia[7]helicene, 140, 141, 142 and 143**

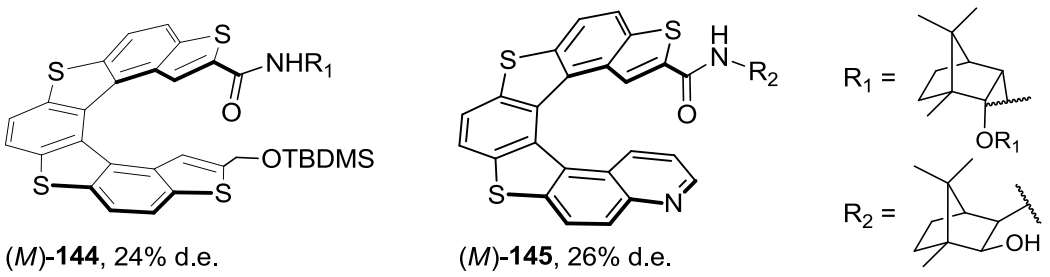
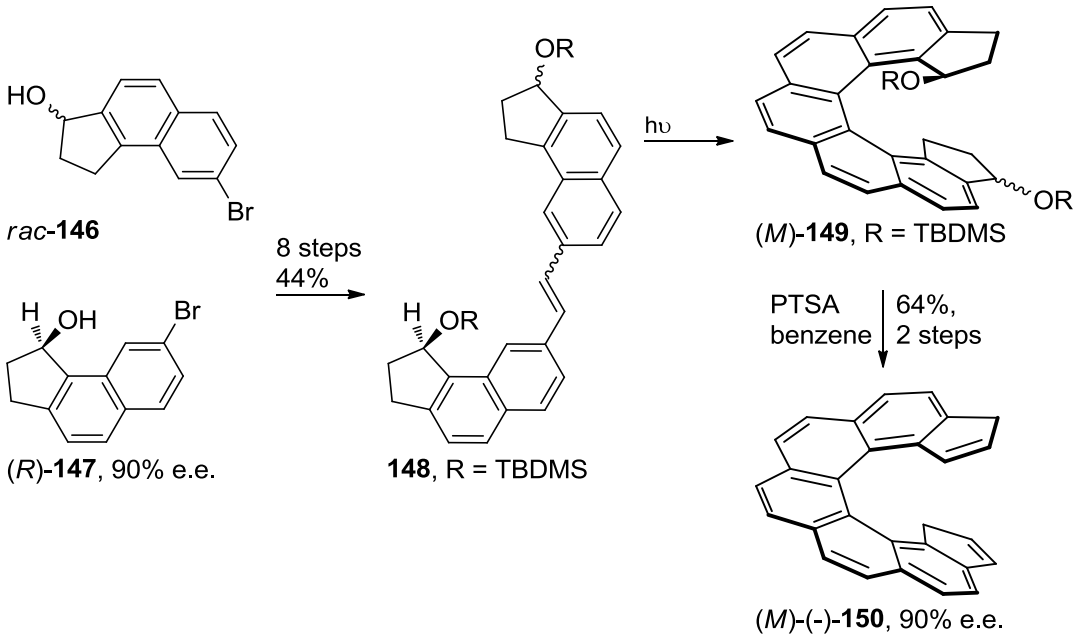



**Figure 25: Helicenes obtained via a diastereoselective synthesis using bornane auxiliary**

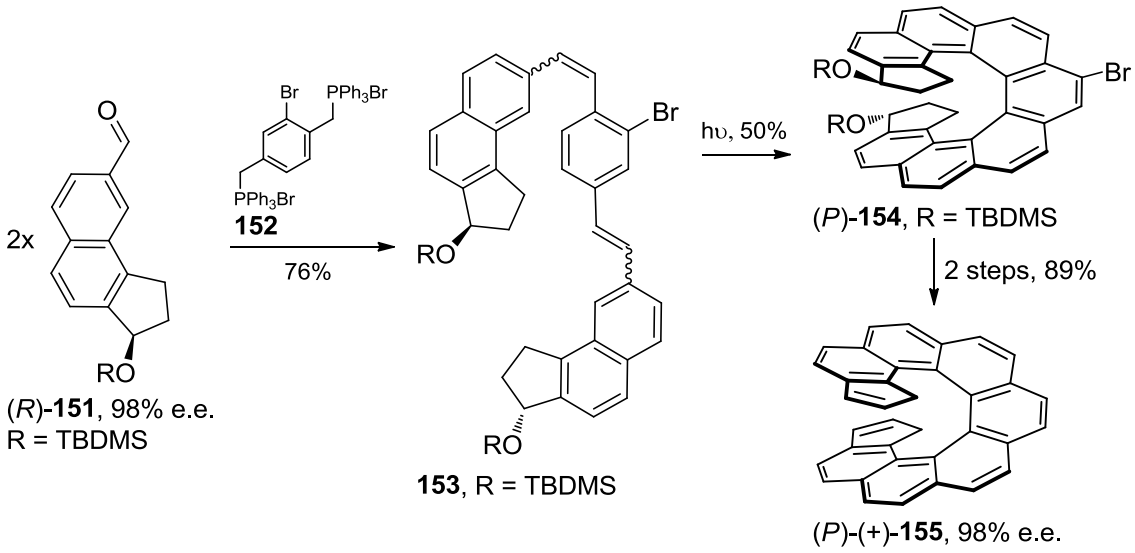
4. Chiral substituent

In 1986, following their report[66] on helical ferrocene synthesis (in 1982), Katz's group developed a highly diastereoselective synthesis of [7]helicenoid **149** bearing two cyclopentane rings at each end of a [5]helicene core.[67] Their strategy was to build a photochemical precursor (**148**) bearing an appropriate chiral auxiliary built on a cyclopentane terminal ring (Scheme 21). A TBDMS group on the hydroxyl of each of the cyclopentane rings was introduced, and upon cyclisation, the formation of the helix with the silyl ether pointing outwards was favoured. There was no attempt at the separation of diastereoisomers of **149**, and removal of the silyl ether groups yielded helicene (*M*)-**150** in over 90% e.e. (the e.e. of the starting material (*R*)-**147** is directly taken through to the product).



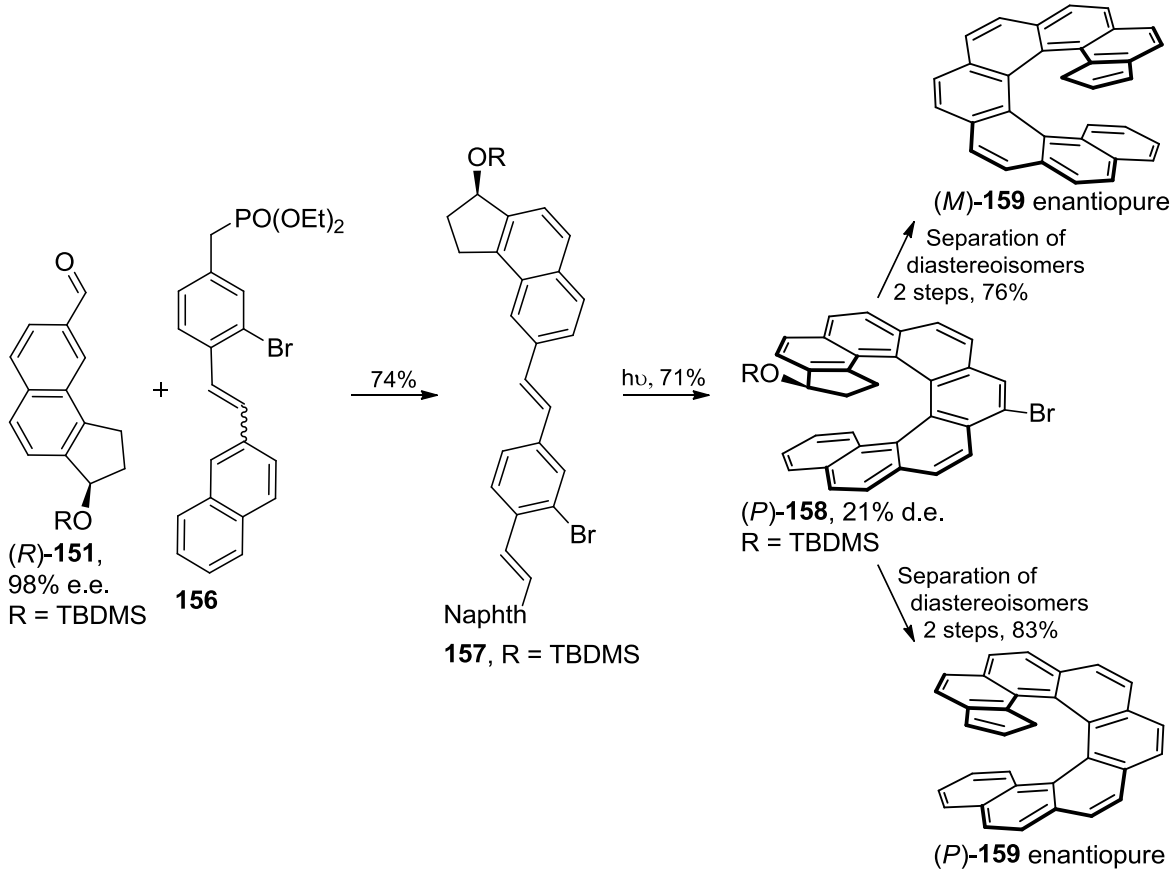

**Scheme 21: Diastereoselective synthesis of [7]helicenoid (*M*)-150**

Later, in 1993, they published the diastereoselective synthesis of [9]helicenoid **154** using the same strategy,[68] the only difference being the use of two tert-butyldimethylsilylether groups at positions with defined absolute configuration (**153**), instead of one. In this case, after removal of silyl ether groups, they obtained 17,18-dihydrodicyclopenta[a,k][7]helicene (**155)** as a single enantiomer (Scheme 22). They also note that if using a regioismer of starting material **151** where the silyl ethers would be in the bay area of the helicene, the photocyclisation does not proceed well. Also, they explain that, as it had already been shown in the literature,[69] the role of the bromine atom is to orientate the cyclisation towards the formation of a helical structure.




**Scheme 22: Diastereoselective synthesis of [9]helicenoid (*P*)-154**

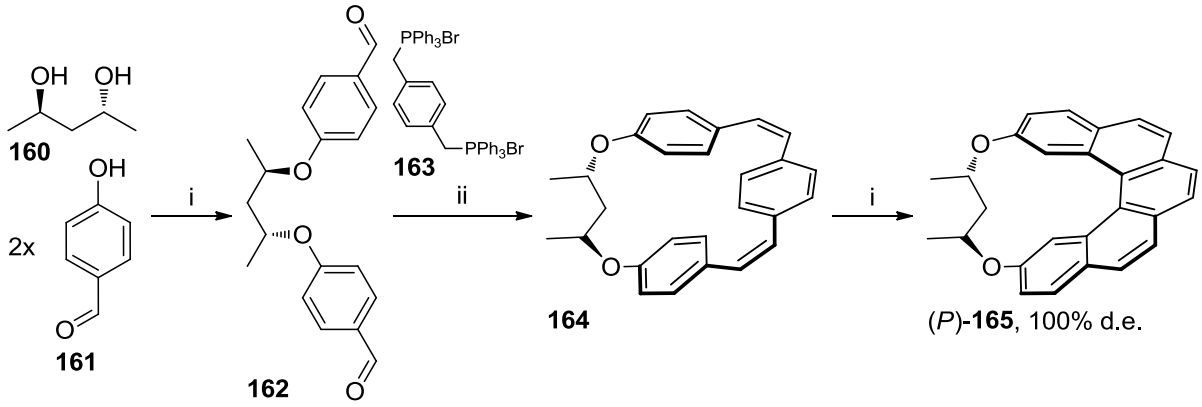
We can also note that for the purposes of a study of chiral helical cobaltocene[70] they synthesised [8]helicenoids **158** and **159** using the methodology previously described in this paragraph with only one chiral directing cyclopentane silyl ether auxiliary (Scheme 23). They obtained (*P*)-**158** with 21% d.e. and after separation of the diastereosomers by silica gel chromatography and subsequent transformations they obtained enantiopure (*M*)- and (*P*)-1*H*-cyclopenta[c][7]helicene (**159**).




**Scheme 23: Diastereoselective synthesis of [8]helicenoid 158**

### 5. Locked cyclic conformation

Another interestingly short strategy was used by El Abed and coworkers for their synthesis of [5]helicene.[71] By locking the conformation of precursor **164** before the photochemical step, using a chiral cyclic diether functionality, they achieved the highly diastereoselective synthesis of cyclic [5]helicene diether (*P*)-**165** which was formed as a single diastereoisomer. The chiral auxiliary was introduced from the first step by reacting enantiopure (*R*,*R*)-2,4-pentanediol (**160**) with 4-hydroxybenzaldehyde (**161**) in a double Mitsunobu reaction (Scheme 24); this was followed by an inter-intra molecular double Wittig reaction affording the bis-stilbene precursor for the cyclisation. As [5]helicenes are known to be somewhat configurationally unstable, there were considerations about the optical stability of the product; it was found, however, that the cyclic helical compound did not epimerise even at temperatures reaching 80 °C. Also no attempt was made to transform the cyclic product into a simpler non-cyclic helicene; especially as it would undoubtedly be subject to racemisation.

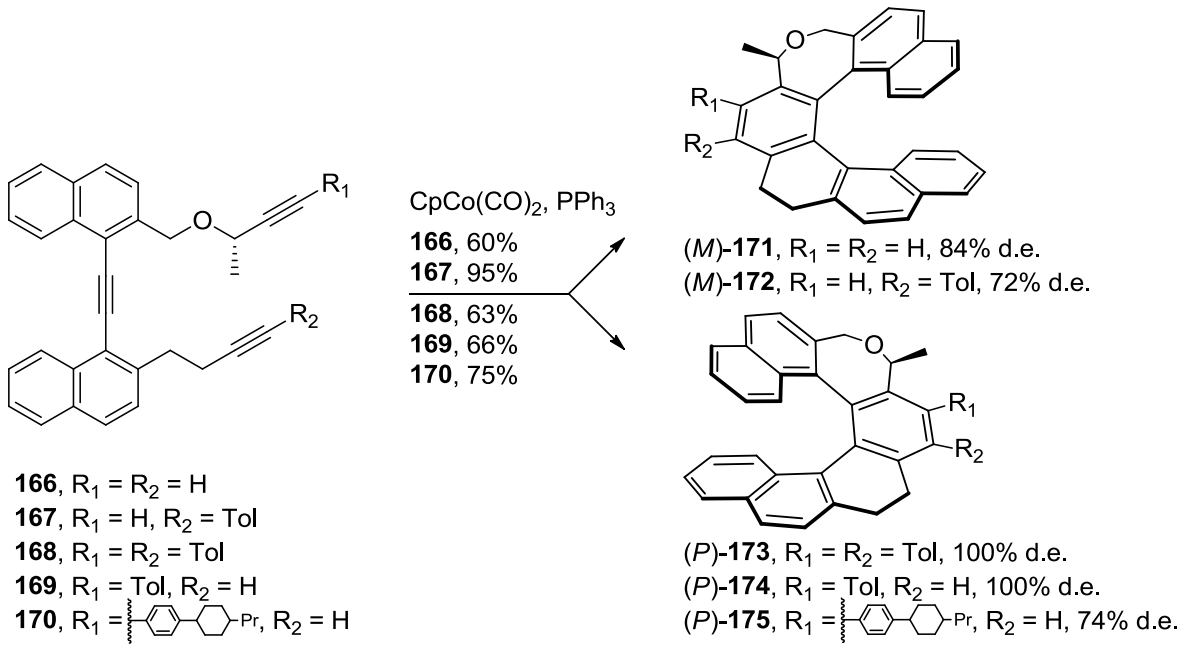



i) DEAD, $PPh_3$, THF, 54%; ii) EtOLi, EtOH, 35%; iii) hυ, $I_2$, propylene oxide, PhMe, 63%

**Scheme 24: Diastereoselective synthesis of cyclic [5]helicene diether 165**

ii) Diastereoselective [2+2+2]cycloisomeristion of alkynes

Stary's group, who developed from 1998 the efficient powerful methodology for the synthesis of helicenes using a cobalt catalysed [2+2+2]cycloisomeristion of alkynes,[72] also attempted a diastereoselective version for their synthesis of [5], [6] and [7]helicenoid molecules. Inspired by the central to axial chirality transfer observed in the literature,[73] and using chiral triyne precursors, they hoped to achieve efficient diastereoselective syntheses. Previous studies had also shown good to excellent diastereoselectivities for the [2+2+2]cycloisomerisation of ene-diynes[74] (up to 74% d.e.), using chiral substituents on one of the terminal alkynes. Based on these facts, Stary *et al.* decided to introduce a chiral centre adjacent to the alkyne (between the alkyne and the ether moiety, see Scheme 25).[75] Using unsubstituted alkynes (R, $R_2$ = H, **166**), and after optimisation of the reaction conditions (bringing yields over 60%), they obtained oxo[7]helicenoid (*M*)-**171** in 84% d.e. (Scheme 25). However, it was found that the key factor for further increase of diastereoselectivities was the introduction of steric bulk at the terminal alkyne position, of the alkyne adjacent to the chiral centre. By introducing a tolyl group on the terminal alkyne position (**168**, and **169**), they managed to perform a completely diastereoselective synthesis but, unexpectedly, discovered that it favoured the formation of the other diastereoisomer (see Scheme 25, **173** and **174** were obtained in 100% d.e. in the *P* configuration).




**Scheme 25: Diastereoselective [2+2+2] cycloisomerisation**

Following the same strategy, they synthesised oxo[5]helicenoids (*P*)-**176** and (*P*)-**177** with high diastereoselectivities, around 80% d.e., oxo[6]helicenoids (*P*)-**178** and (*P*)-**179** at respectively 80% and 74% d.e. and oxo[7]helicenoids (*P*)-**180**, (*P*)-**181** and (*M*)-**182** at respectively 46%, 66% and 68% d.e., all in good to excellent cycloisomerisation yields (50% to 95% yield) (Figure 26).[76]

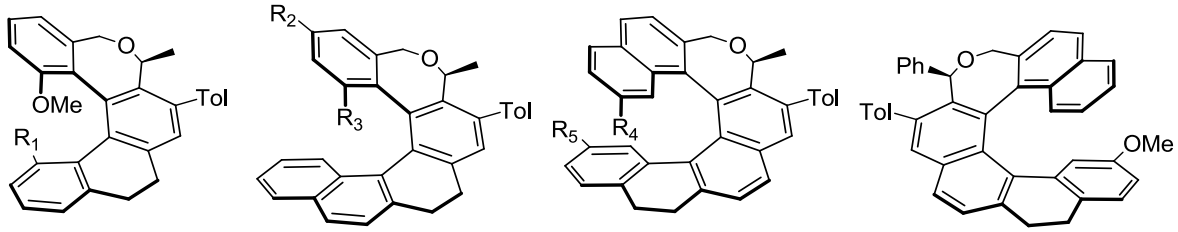
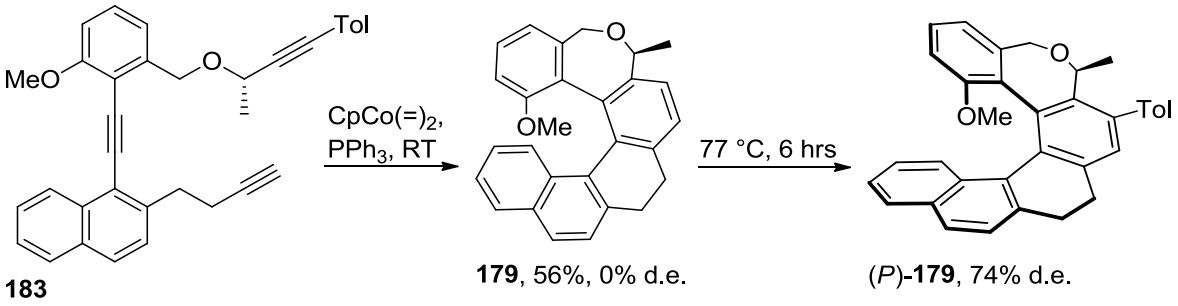



**Figure 26: Helicenoids synthesised via diastereoselective [2+2+2] cycloisomerisation**

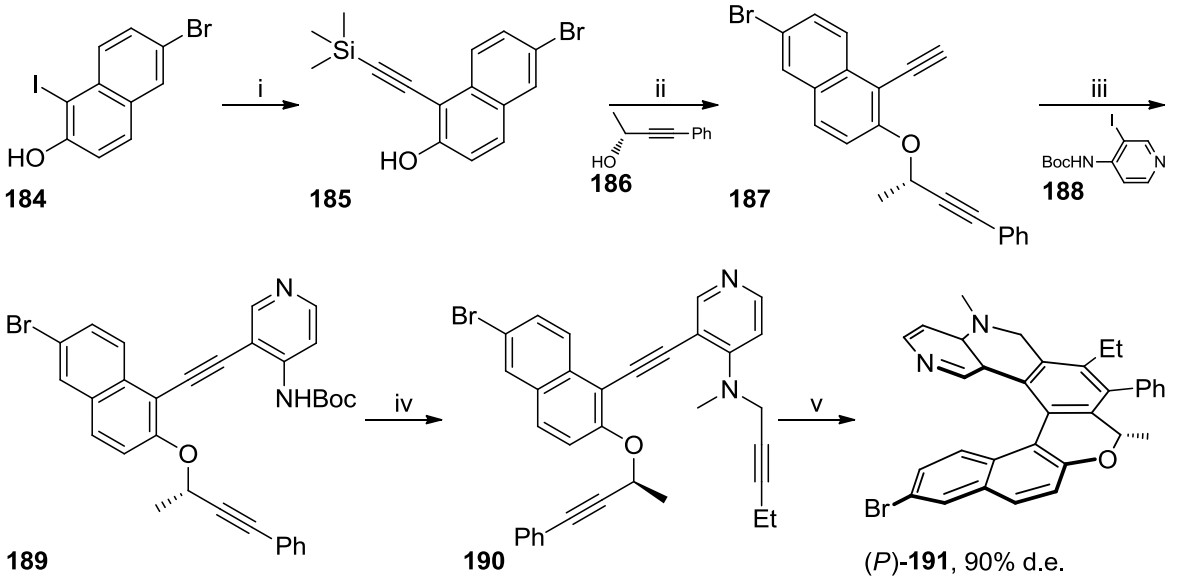
The authors wondered if the cyclisation reaction proceeded via a thermodynamic or a kinetic control.[76] They found that when performing the cyclisation of **183** at RT, [6]helicenoid **179** was obtained in 0% d.e. and more surprisingly heating the mixture at 77

°C epimerisation occured, and after 6 hours the diastereoselectivity of (*P*)-**179** reached 74% d.e. (Scheme 26). This level of selectivity is equivalent to what they obtained in the standard reaction (Figure 26), proving that the cyclisation is thermodynamically controlled. Experiments were made to calculate epimerisation barriers and it was found that they are lower than the racemisation barriers of the corresponding fully aromatic helicenes. Also, they successfully recrystallized the diastereomeric mixtures to obtain optically pure products.




**Scheme 26: Epimerisation experiment, thermodynamic control**

More recently, Carbery's group followed the same strategy for the synthesis of their helicenoid chiral DMAP analogue **191** (Scheme 27).[77]




i) TMS-acetylene, 5% $PdCl_2(PPh_3)_2$, CuI, diisopropylamine,86%; ii) 1) DIAD, $PPh_3$, THF, 2) $K_2CO_3$, MeOH, 63%; iii) $Pd(PPh_3)_4$, CuI, diisopropylamine, PhMe, 99%; iv) 1) 1-bromopent-2-yne, NaH, 2) TMSOTf, 3) MeI, NaH, 73%; v) $RhCl(PPh_3)_3$, PhMe, 88%.

**Scheme 27: Diastereoselective synthesis of helical DMAP**

Indeed, using triyne precursor **190**, bearing a phenyl group on the terminal alkyne next to the chiral centre, they obtained, after a highly diastereoselective rhodium catalysed [2+2+2]cycloisomerisation, their aza-oxo[6]helicenoid DMAP (*P*)-**191** in 88% yield and 90% d.e. (Scheme 27). Moreover, the authors add that their synthesis is scalable up to gram scale, and that the diastereoisomers were easily separated by column chromatography on silica gel, affording major product as a single diastereoisomer.

c) Enantioselective syntheses

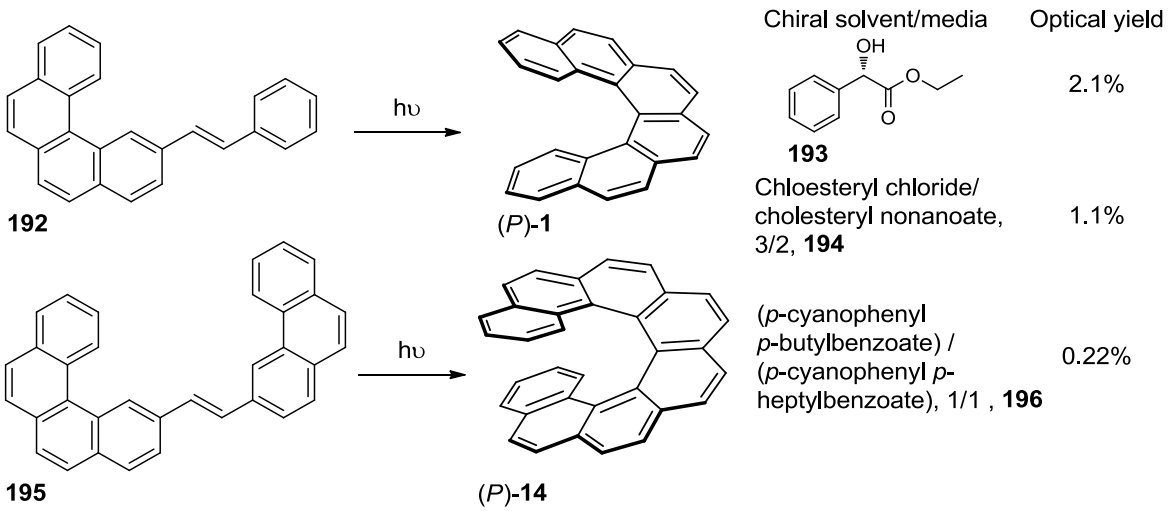
i) Circularly polarised light

At about the same time as the early diastereoselective syntheses of helicenes, the enantioselective synthesis of helicenes was first reported in the 1970's by Kagan's group. Indeed, in parallel to the efforts made with diastereoselective photocyclisation, they reported the first enantioselective synthesis of helicenes using circularly polarised light. Their early attempts, published in 1971, yielded [6]helicene in less than 1% e.e.[78] Following this report, efforts were made to improve these results, and shortly after, Kagan obtained similar results for the synthesis of [8] and [9]helicene.[79] Later, in 1972 and 1973, Buchardt *et al*., published similar results for [6]helicene synthesis again with low optical yields of about 2%.[80] In 1975, Kagan reported the asymmetric synthesis of [10]helicene in less than 1% e.e. but failed to see any asymmetric induction for higher helicenes.[81] This method never showed any success despite the amount of work put into trying to develop it.[82] Indeed, it was only because helicenes have such high specific rotations that these studies were possible at all, allowing valid conclusions to be drawn despite the low optical yields.

ii) Use of chiral solvent/chiral media

Again in the 1970s, other reports of asymmetric photochemical syntheses were made, this time using a chiral media/solvent. In 1978, Laarhoven reported the synthesis of [6]helicene performing photocyclisations in several chiral solvents, with little success, obtaining the products in a maximum of 2.1 % optical yield using (*S*)-(+)-ethyl mandelate (**193**).[83] Similarly, Nakazaki *et al*., reported low asymmetric inductions for photocyclisation reactions done in cholesteric liquid crystals **194**, or mechanically right-handed twisted

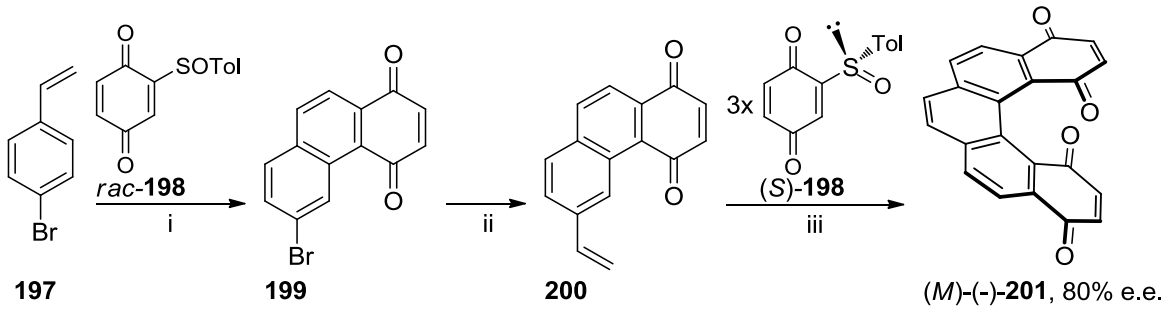
nematic mesophases **196**, achieving the syntheses of [6]helicene (**1**) and [8]helicene (**14**) with respectively a 1.1% and 0.22 % optical yield (Scheme 28).[84]




**Scheme 28: Enantioselective photochemical syntheses in chiral media**

iii) Asymmetric Diels-Alder reaction

Following their work on enantioselective Diels-Alder cycloadditions using enantiopure sulfinylquinones,[85] and inspired by Katz's reports on Diels-Alder mediated helicenebisquinone synthesis, Carreño *et al.* published in 1999 a striking three step asymmetric synthesis (overall yield 4.6%) of [5]helicenebisquinone (*M*)-**201** obtained with excellent selectivity reaching 80% e.e.[86] Starting with 3-bromostyrene (**197**), they used a sequential double Diels-Alder reaction to build the helicene skeleton, the key step residing in the second cycloaddition using enantiopure sulfinylquinone (*S*)-**198** which installs the helicene chirality in an enantioselective fashion, as the chiral sulfoxide is concomitantly eliminated in the cycloaddition step (Scheme 29).

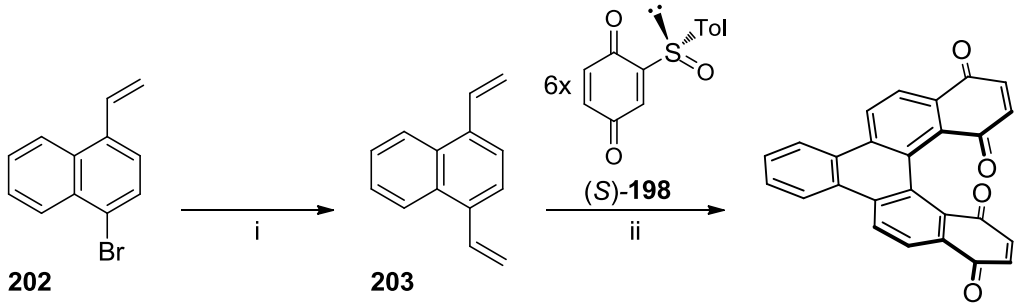



i) 12 Kbar, DCM, 2 days, 53%; ii) $CH_2$=$CHSnBu_3$, $Pd(PPh_3)_4$, PhMe, 110 °C, 5 hrs, 40%; iii) 4 Kbar, DCM, 7 days, 22%.

**Scheme 29: Synthesis of [5]helicene-1,4,11,14-tetraone (*M*)-201 via enantioselective Diels Alder cycloaddition**

Interestingly, the use of quinone **198** (that belongs to the family of benzoquinones which are known to favour dehydrogenation reactions) in excess does not only allow to build the helicene skeleton with high selectivities, it also rearomatises the final molecules, *in situ*.

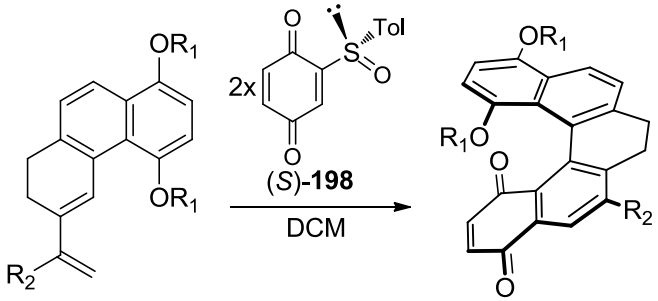
In the same study, as an attempt to improve the methodology, they tried to use two different divinyl dienes, *p*-divinylbenzene and 1,4-divinylnaphthalene (**203**), in a one-step double Diels-Alder cycloaddition. Despite the absence of reactivity shown by *p*-divinylbenzene, **203** reacted to give the double cycloaddition product, [5]helicenebisquinone (*M*)-**204** with increased enantioselectivity to 88% e.e., albeit at a low 12% yield. Despite these good selectivities, the cycloaddition reaction suffered from a few issues, as it still required high pressures and long reaction times (7 days for (*M*)-**201** and 4 days for (*M*)-**204**) and only afforded the desired products in low yields. With milder conditions, it is possible that the product e.e.s might be even higher.




i) $CH_2$=$CHSnBu_3$, $Pd(PPh_3)_4$, PhMe, 110 °C, 2 h, 65%;
ii) 4 Kbar, DCM, 4 days, 12%.

**Scheme 30: Enantioselective one-step double Diels-Alder cycloaddition**

In an effort to overcome this problem, Carreño's group attempted the same chemistry using more reactive vinyl-dihydrophenanthrene dienes **205**, **206** and **207**, allowing the reaction to occur at room temperature or below, and at atmospheric pressure, in good conversions and good selectivities.[56a] Indeed, using diene **207**, with the usual chiral sulfoxide (*S*)-**198** at –40 °C (for 17 days), they obtained their best result for the synthesis of [5]helicenoid (*P*)-**106** with 75% yield and over 98% e.e. (Scheme 31).




**205,** $R_1$ = Me, $R_2$ = H
**206,** $R_1$ = Me, $R_2$ = OEt
**207**, $R_1$ = TBDMS, $R_2$ = H

(*P*)-**208**, $R_1$ = Me, $R_2$ = H; -40 °C, 12 days, 72%, 84% e.e.
(*P*)-**209**, $R_1$ = Me, $R_2$ = OEt; -60 °C, 6 days, 62%, 84% e.e.
(*P*)-**106**, $R_1$ = TBDMS, $R_2$ = H; -40 °C, 6 days, 75%, 98% e.e.

**Scheme 31: Enantioselective synthesis of [5]helicenoids, use of more reactive dienes**

Interestingly, they saw an increased reactivity combined to an increased selectivity, using the more reactive dienes and introducing steric bulk with a TBDMS group. Also it can be noted that they obtained the opposite absolute configuration for the helicene; their rationale was that of the possible *endo* approaches, the diene's approach from the lower face of quinone (*S*)-**198** in the *s-trans* configuration is less sterically demanding than the approach from the upper face with quinone (*S*)-**198** in favourite *s-cis* configuration (sulfinylquinones adopt preferentially a *s-cis* configuration[87]) (Figure 27).

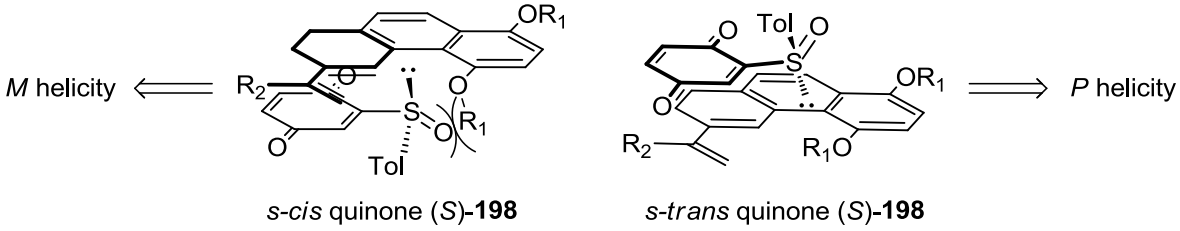
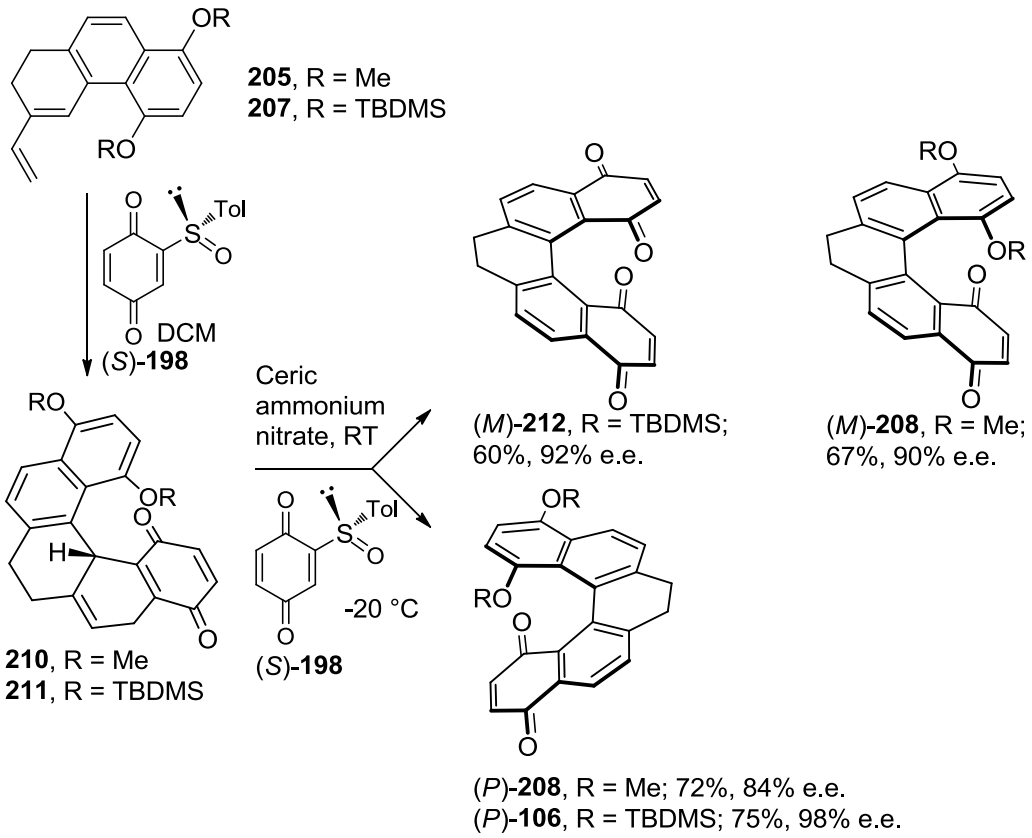



**Figure 27: Rationale for *P* helicity: possible *endo* approaches**

Using a similar strategy, they achieved asymmetric syntheses of (*P*)-12-(*t*-butyl)-7,8-dihydro[4]helicene-1,4-dione (**103**, Figure 23) in good 72% e.e. with the same rationale for the selectivity.[56b]

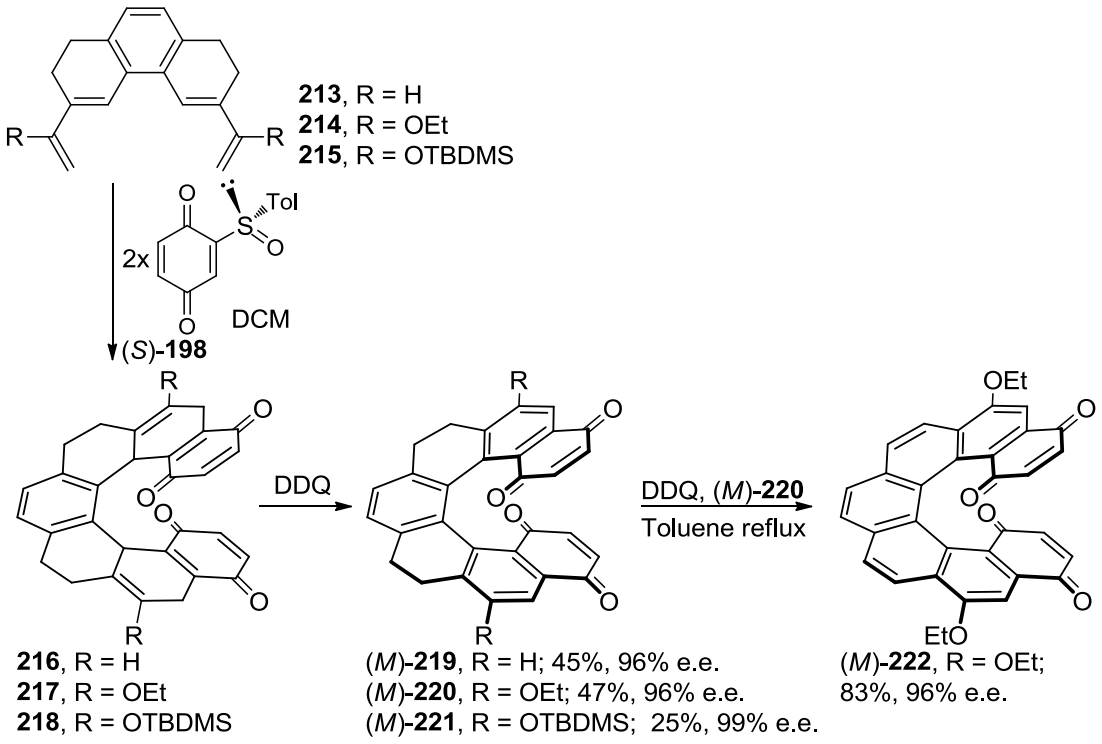
In the following study,[88] they showed that from a single [5]helicenoid precursor (*i.e.* **210** or **211**) they could obtain divergent asymmetric induction by changing the oxidant to form [5]helicenoids. Indeed, as noted above, the rearomatisation of the ring formed in the cycloaddition is performed *in situ* with excess sulfinylquinone (*S*)-**198**, however when the sulfinyl quinone is not used in excess, the use of a different oxidant can produce the

opposite enantiomer. For example, oxidation of **210** with the usual (+)-sulfinylquinone, gave [5]helicenoid (*P*)-**208** in 84% e.e. whereas using ceric ammonium nitrate gave (*M*)-**208** in 90% e.e. Similar outcomes were observed for the oxidation of **211**, when using sulfinylquinone (*S*)-**198**, [5]helicenoid (*P*)-**106** was obtained over 98% e.e. whereas with ceric ammonium nitrate [5]helicenoid (*M*)-**212** was preferentially obtained in 92% e.e. (Scheme 32). These results are extremely important allowing the use of only one enantiomer of the sulfinylquinone to access both enantiomers of the helicene structures.



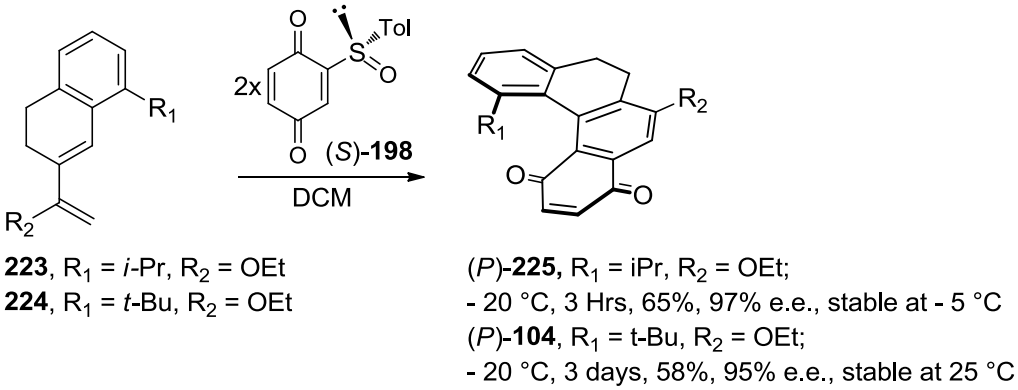

**Scheme 32: Divergent enantioselective syntheses of dihydro[5]helicenes**

Later Carreño's group also tackled the asymmetric synthesis of [7]helicenebisquinones using a similar double Diels-Alder strategy[89] and obtained (*M*)-**219** at 96% e.e., (*M*)-**220** at 96% e.e., (*M*)-**221** at 99% e.e. and (*M*)-**222** at 96% e.e., the difference in selectivity again arising from the larger steric bulk of the TBDMS groups (Scheme 33). These examples are among the best available for the almost completely enantioselective synthesis of helicenes, but is specialised for helicenes with their end-rings present in the quinone oxidation state.




**Scheme 33: [7]helicenes synthesis: enantioselective double Diels-Alder cycloaddition.**

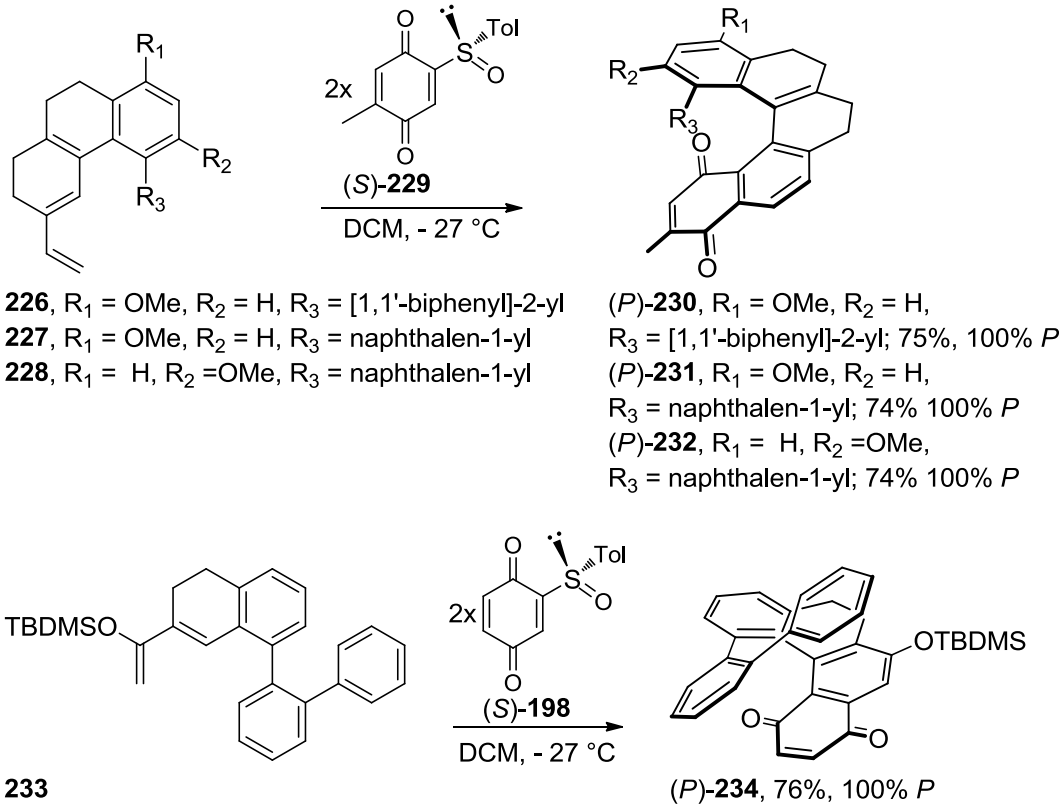
The same research group has synthesised a large number of configurationally stable 12-substituted dihydro[4]helicenequinones (for example, (*P*)-**225**, (*P*)-**104**, Scheme 34) with high enantioselectivities.[56c] The stabilities of the [4]helicenequinone structure were increased but still depend largely on the substituent at the C12 position, only helicenes presenting large substituents showed decent optical stability (Scheme 34).




**Scheme 34: Enantioselective synthesis of stable 12-substituted[4]helicenes**

Her group also reported the highly enantioselective synthesis of [5]heliceneoids (*P*)-**230**, (*P*)-**231**, (*P*)-**232** and [4]helicenoid (*P*)-**234** bearing axially chiral biaryl moieties in the

inner part of the helix.[6] These reactions could/should be classed as diastereoselective, however, for ease of reporting, and because the reaction gives exclusively the *P* helicity independently of the configuration of the atropoisomer, they are presented here, in the enantioselective synthesis section. These reactions afforded helicenes where the racemic biaryl moeity of the vinyl starting materials **226**, **227**, **228** and **233** was present in enantiomerically enriched form in the resulting helicenes, showing that a dynamic kinetic resolution of the biaryl moiety had occurred.

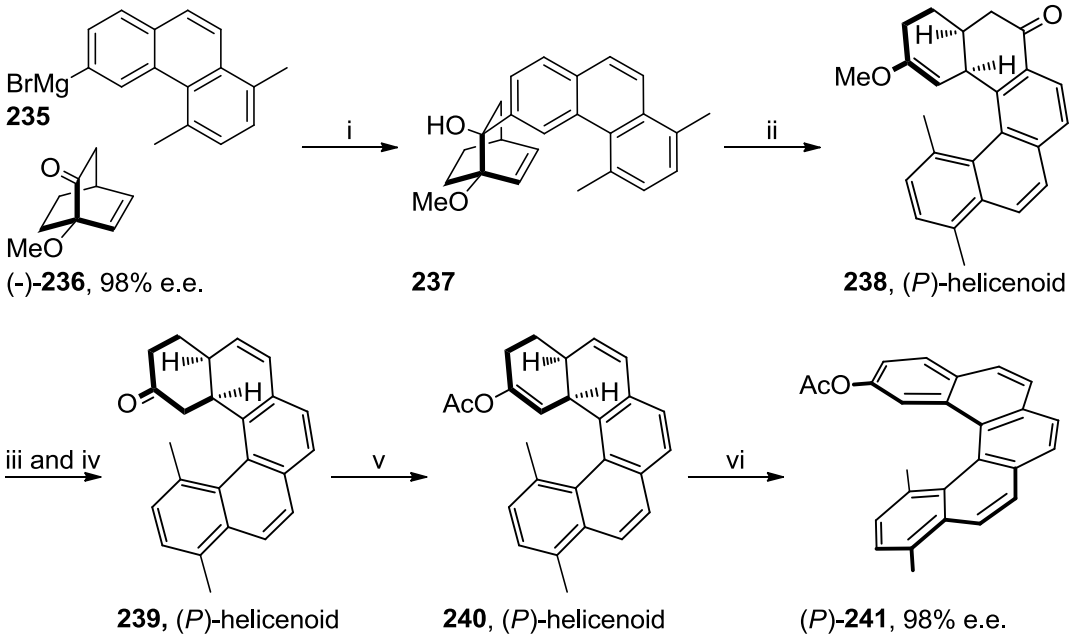



**Scheme 35: Diastereoselective synthesis of [4] and [5]helicene-1,4-diones bearing atropoisomeric bi-aryls**

iv) Asymmetric oxy-Cope rearrangement

Following their early work on oxy-Cope rearrangements,[90] Ogawa *et al.* used in 2003 an original strategy for their synthesis, forming the 5 ring-core of the helicene via an asymmetric stereoselective oxy-Cope rearrangement.[91] In this case, the chiral auxiliary, enantiopure / stereochemically defined bicyclo[2.2.2]octanone (–)-**236** (resolved using an enzymatic method) attached to a phenanthrene moiety (see **237**), was transformed into two fused six-menbered rings, introducing the helical structure (**238**, (*P*)-helicenoid). Subsequent rearomatisation yielded optically stable [5]helicene (*P*)-**241** in 98% e.e.

(Scheme 36). It can be noted that enantiomeric excesses from chiral octanone (–)-**236** are completely transferred to the final [5]helicene. They also synthesised helicene (*M*)-**241** with 83% e.e., starting from the opposite enantiomer of the ketone, (+)-**236** in 83% e.e. The authors also note that, unlike some unsubstituted [5]helicenes, their 2-acetoxy-11,14-dimethyl[5]helicene (**241**), does not undergo any epimerisation, even when heated for 24 hours at 120 °C.




i) THF, 60%; ii) KHMDS, 18-crown-6, THF, 47%; iii) $NaBH_4$, EtOH; iv) PTSA, PhH,
v) LiHMDS, $Ac_2O$, THF; vi) DDQ, PhH, 24% over 4 steps

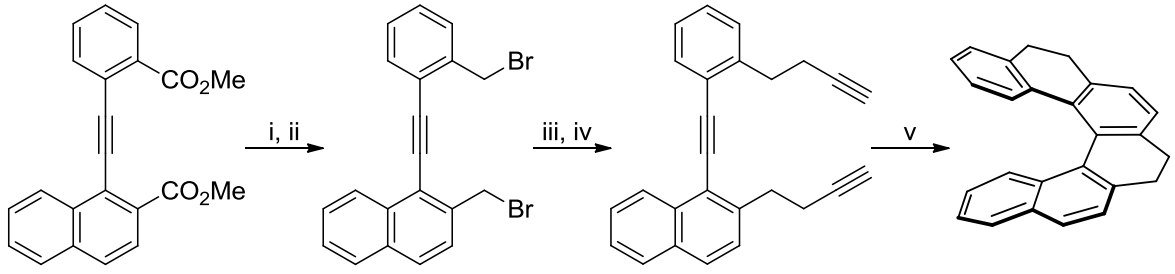
**Scheme 36: Enantioselective synthesis of 2-acetoxy-11,14-dimethyl[5]helicenes**

Although the authors claim that they achieved an enantioselective synthesis, careful examination of the strategy is needed to rule out the possibility that it may be more properly classified as diastereoselective. Scheme 36 shows that step (ii) produces two stereogenic centres (see (*P*)-helicenoid **238**) as well as controlling the twist of the helix. Relative to the configuration of the inducing chirality (the bicyclo[2.2.2]octanone, (–)-**236**), the reaction is both diastereoselective and enantioselective. The aromatisation (step vi), however, leaves only a pair of enantiomers, which are formed in the same e.e. as the that of the inducing chirality. Thus, the overall asymmetric control of the helix is indeed enantioselective.

v) Asymmetric [2+2+2] cycloisomerisation

1. Intramolecular

Shortly after reporting the cobalt catalysed [2+2+2]cycloisomerisation of triynes, Starý developed an enantioselective nickel catalysed version of the reaction.[92] In this report they showed an increase of reactivity using $Ni(cod)_2$ as the catalyst, and with the addition of the chiral phosphine (*S*)-MOP they obtained tetrahydro[6]helicene (*P*)-**245** in 53% yield and 48% e.e. In the same report, they show the possibility of oxidation to the parent helicene using DDQ, but no mention is made of this reaction in the enantioenriched series.

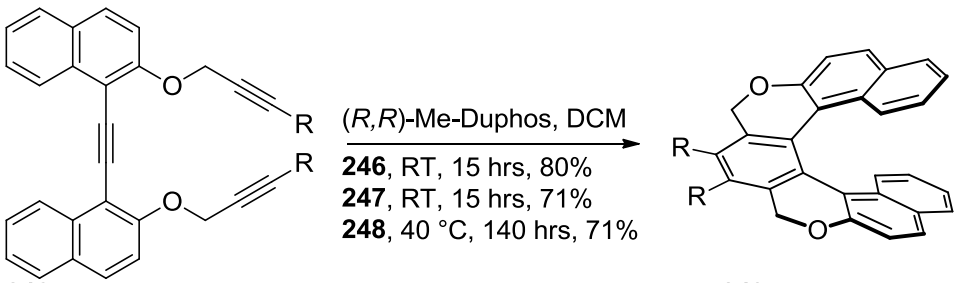



**242** **243** **244** (*P*)-**245**, 48 % e.e.

i) Red-Al ® (1.4 eq), PhMe, 0 °C, 2 hrs, 99 %; ii) $PBr_3$ (2.3 eq), THF, 0 °C, 2 hrs, 69 %;
iii) $LiCH_2C{\equiv}CTIPS$ (2.2 eq), THF, -78 °C, 1 hr, 74 %; iv) TBAF (5 eq), THF, RT, 1 hr, 97 %;
v) $Ni(cod)_2$ (20 mol %),(*S*)-(-)-MOP (40 mol %), THF, -20 °C, 2 hrs, 53 %.

**Scheme 37: Nickel catalysed enantioselective [2+2+2]cycloiosmerisation**

Following Starý's early report on nickel catalysed enantioselective [2+2+2]cycloisomerisation of triynes and their own work on the rhodium catalysed [2+2+2]cycloaddition reactions,[93] Tanaka and coworkers developed a rhodium catalysed enantioselective version of the cycloisomerisation (Scheme 38).[7]




**246**, R = $CO_2Me$
**247**, R = $CO_2$*n*-Bu
**248**, R = *n*-Bu

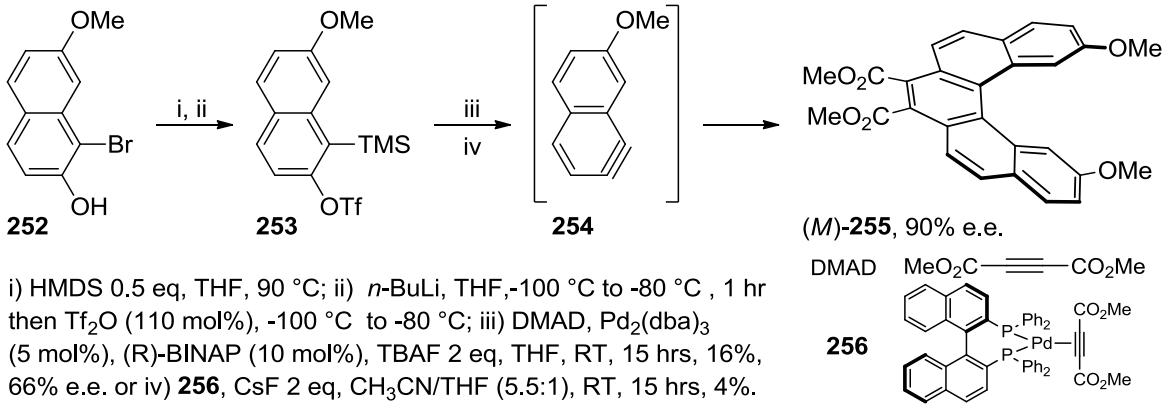
(*M*)-**249**, R = $CO_2Me$, 71% e.e.
(*M*)-**250**, R = $CO_2$*n*-Bu, 77% e.e.
(*M*)-**251**, R = *n*-Bu, 85% e.e.

**Scheme 38: Enantioselective [2+2+2]cyloisosmerisation: synthesis of dioxa[7]helicenoids**

Starting with symmetrical trialkynes bearing different terminal groups (**246**, **247** and **248**) and including an two ether bridges / functionalities, they reported the asymmetric synthesis of three analogues of dioxa[7]helicenoids (*M*)-**249**, (*M*)-**250** and (*M*)-**251** obtained in high yields and high enantioselectivities, catalysed by cationic $[Rh(cod)_2]BF_4$ and using (*R*,*R*)-Me-Duphos as the chiral ligand. The best result was obtained for a dibutylsubstituted alkyne **248**, obtaining [7]helicenoid (*M*)-**251** in 71% yield and 85% e.e.

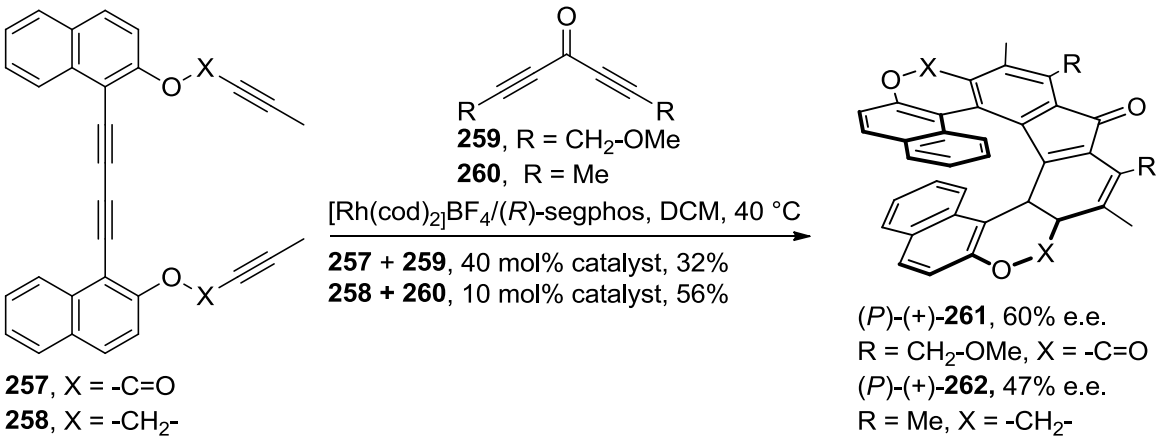
### 2. Intermolecular

There are also some examples of asymmetric intermolecular [2+2+2] cycloisomerisation, the first one reported by Guitián in 2006.[94] Indeed, they show an interesting palladium catalysed cyclotrimerisation between *in situ* formed aryne **254** and commercially available DMAD, allowing for the synthesis of [5]helicene **255**. They report the screening of several palladium catalysts in order to obtain efficient regioselectivity and to optimise the enantioselectivities. They rapidly found that BINAP was the best ligand, and when used with stoichiometric amounts of palladium (using **256**) they obtained [5]helicene (*M*)-**255** in 4% yield and 90% e.e. (Scheme 39). However, in catalytic conditions they did not manage to reach the same selectivities despite having optimised every aspect of the reaction (fluoride source, solvent). Nonetheless they obtained reproducible results with a slow addition of TBAF in THF, 5 mol% of palladium catalyst and 10 mol% (*R*)-BINAP ligand, affording [5]helicene (*M*)-**255** in 16% yield and 66% e.e. Also, they added that their racemisation studies gave (*M*)-**255** a half-life of 9.7 days at 20 °C.




**Scheme 39: Intermolecular enantioselective [2+2+2]cycloisomerisation**

Tanaka, who obtained high enantioselectivities in his intramolecular [2+2+2]cyloisomerisation,[7] used the same catalyst $[Rh(cod)_2]BF_4$, for a double intermolecular [2+2+2]cycloisomerisation of a tetrayne and a diyne leading to the formation of [9]helicenoid structures.[95] They obtained moderate enantioselectivities, using (*R*)-segphos, reaching 60% e.e. for the reaction of **257** and **259**, and 47% e.e. for the reaction of **258** and **260** (Scheme 40) despite attempts of further optimisation. Nonetheless, these examples showed that a single reaction allows for the creation of five fused rings as well as installing asymmetrically the winding of the helix, which is quite an achievement in asymmetric helicene synthesis.



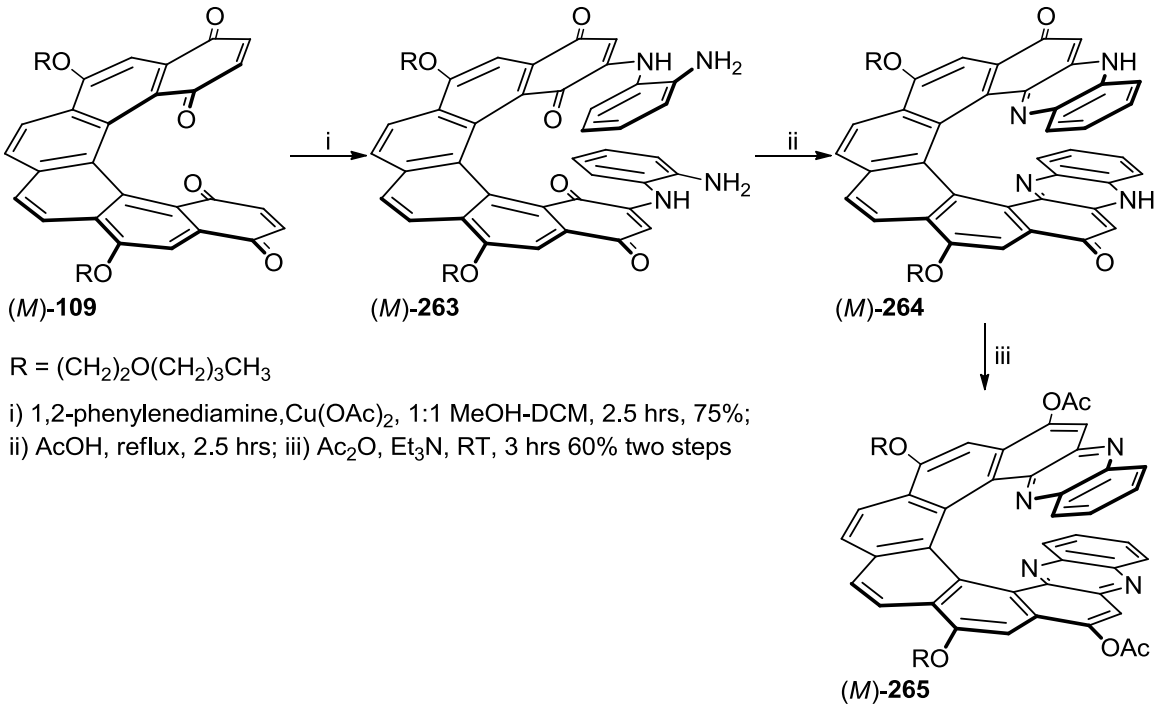

**Scheme 40: Intermolecular enantioselective double [2+2+2]cycloisomerisation**

d) Use of axially chiral precursors: retention of chirality

i) From small helicenes

In the 1970's, the development of the photolysis method to provide helicenes, combined with their resolution using menthyl derivatives, gave assess to enantioenriched helicenes. These small helicenes with 5, 6 or 7 rings are a perfect scaffold to extend the chirality to build larger helicenes in an enantiodefined form as the configuration of the small helix should be retained when creating a larger one. Using partially resolved trithia[7]helicene,[96] Martin obtained the larger tetrathia[11]helicene with the same configuration. (*M*)-[8]-, (*M*)-[9]-, (*M*)-[10]-, (*M*)-[11]-, and (*M*)-[13]helicenes were all synthesised using the same strategy.[97,52a]

Katz used a similar strategy to build phenazine[8]helicene (*M*)-**265** with complete retention of configuration reacting enantiopure [6]helicenetetraone (*M*)-**109** with 1,2-phenylenediamine, followed by subsequent condensation and aromatisation (Scheme 41).[98]

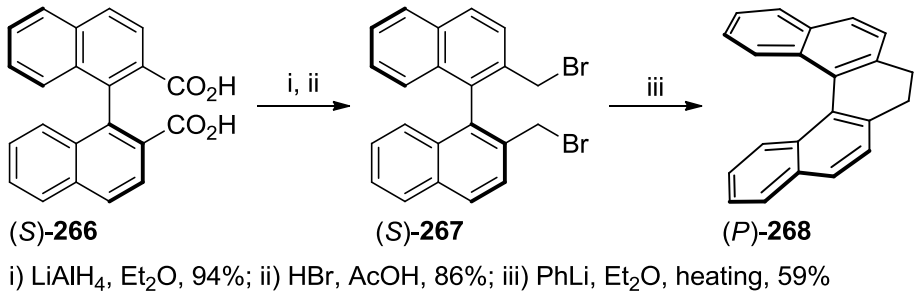



**Scheme 41: Synthesis of phenazine[8]helicene (*M*)-265 from [6]helicenetetraone (*M*)-109**

ii) From biaryl atropoisomers

In this paragraph we will not detail how the optically pure / enriched bi-aryl starting materials were obtained.

As early as 1955, enantiopure (*S*)-[1,1'-binaphthalene]-2,2'-dicarboxylic acid [(*S*)-**266**] was converted in a three step synthesis into optically active (specific rotation +1496°) 7,8-dihydro[5]helicene [(*P*)-**268**].[99] No rearomatisation was attempted (Scheme 42).

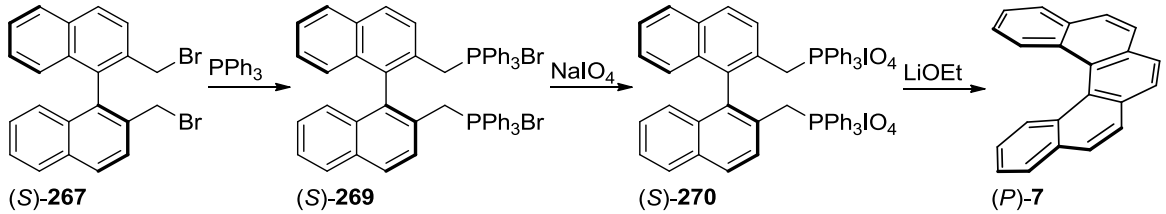



**Scheme 42: [5]helicenoid synthesis from enantiopure binaphthyl precursors**

In 1999, just like Hall and Turner in 1955, Gingras converted enantioenrinched (*R*)-2,2'-bis(bromomethyl)-1,1'-binaphthalene [(*R*)-**267**] into (*M*)-7,8-dihydro[5]helicene [(*M*)-**268**]

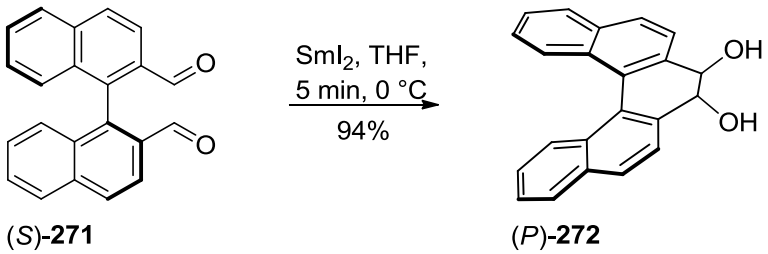
by treating it with phenyllithium, achieving a 95% retention of configuration.[100] It is possible that the 5% loss of optical purity is due to epimerisation of [5]helicenoid (*M*)-**268** which is far less optically stable that dibromo precursor (*R*)-**267**. Although he showed the transformation of the same racemic dibromo precursor **267** to [5]helicene (**7**) (treating it with LiHMDS), no attempt was made with the enantioenriched versions.

In 1972, Both converted (*S*)-2,2'-bis(bromomethyl)-1,1'-binaphthalene into (*P*)-[5]helicene in a three step reaction with complete retention of configuration (Scheme 43).[101]




**Scheme 43: [5]helicene synthesis from enantiopure binaphthyl precursors**

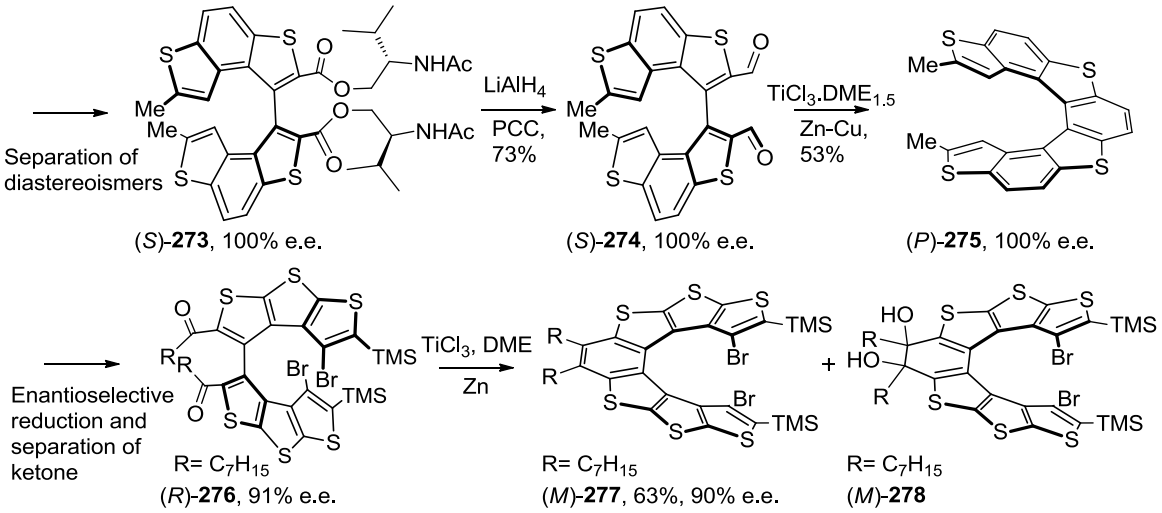
Ohmori *et al.* showed that several enantiopure atropoisomeric biaryls can be transformed into the corresponding fused ring structures with complete retention of configuration, by performing a samarium iodide mediated pinacol coupling of dialdehydes.[102] In particular, he synthesised enantiopure [5]helicenoid (*P*)-**272** (complete retention of configuration) in 94% yield, with *trans* configuration of the hydroxyls (Scheme 44).




**Scheme 44: 7,8-dihydro-7,8-dihydroxy[5] helicene synthesis via samarium iodide pinacol coupling of enantiopure atropoisomeric aldehydes**

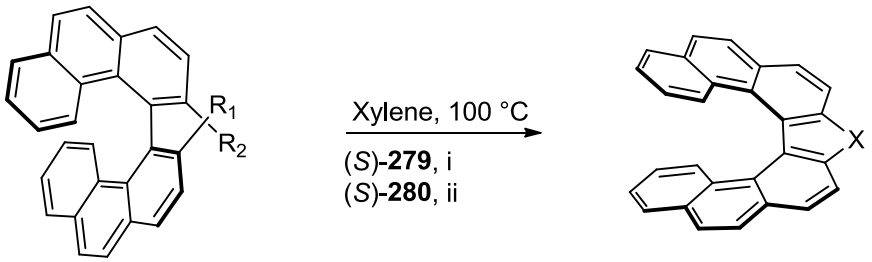
In 1997, Tanaka reported an asymmetric synthesis of 2,13-dimethyltetrathia[7]helicene [(*P*)-**275**] using McMurry coupling of aldehydes.[103] The final annelation step of enantiopure atropoisomer (*S*)-**274** was achieved in 53% yield and with complete retention of configuration (Scheme 45). Similar results were obtained by Rajca for the ring closing step of the synthesis of heptathia[7]helicene (*M*)-**277**.[104] The final McMurry reaction of the diketone afforded the helicene in 63% yield with 99% retention of configuration in the best

case (Scheme 45). However it seems that this result was not always repeatable, possibly due to a competing pinacol reaction. When the McMurry reaction was high yielding, good retention of configuration was possible, but when a high quantity of pinacol product (*M*)-**278** was encountered there was poor retention of configuration.




**Scheme 45: Synthesis of [7]helicenes via McMurry coupling with retention of configuration of atropoisomers**

In 2005, Nozaki reported the synthesis of aza[7]helicene (*P*)-**281** and oxa[7]helicene (*P*)-**282** via a palladium catalysed double *N*-arylation or intramolecular *O*-arylation.[105] He applied this method to previously resolved biphenanthryl precursors (*S*)-**279** and (*S*)-**280** obtaining enantiopure *N*-phenylaza[7]helicene (*P*)-**281** in excellent 94% yield and 99% e.e. with complete retention of configuration, and the oxa[7]helicene (*P*)-**282** in 49% yield and 94% e.e. with little loss of selectivity (Scheme 46).

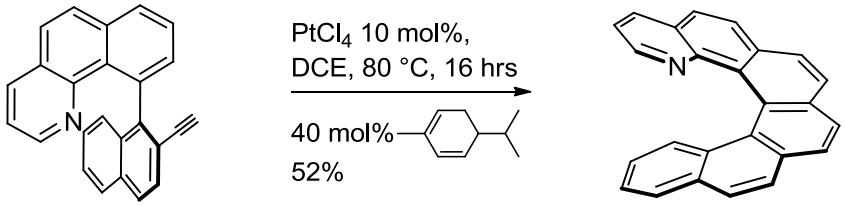



(*S*)-**279**, $R_1 = R_2$ = ONf, 99% e.e.
(*S*)-**280**, $R_1$ = OH, $R_2$ = ONf, 99% e.e.
(*P*)-**281**, X = N-Ph, 99% e.e.
(*P*)-**282**, X= O, 94% e.e.
i) $H_2NPh$ 1.2 eq, $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%), xantphos (20 mol%), $K_3PO_4$ 2.8 eq, 94%;
ii) $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%), Mephos (40 mol%), $K_3PO_4$ 2 eq, 49%.

**Scheme 46: Aza and oxa[7]helicene synthesis via *N*- and *O*-arylation reactions of enantiopure atropoisomers**

They attributed the loss of enantiopurity to the reaction conditions and not to the mechanism, as under these conditions enantioenriched (92% e.e.) oxa[7]helicene (*P*)-**282** underwent epimerisation when heated for a long time (42% e.e. after 88 hours).

Recently, Fuchter showed excellent retention of configuration for the synthesis of aza[6]helicene (*M*)- and (*P*)-**82**, from respectively axially chiral (*R*)- and (*S*)-**283**.[106] Indeed, the platinum catalysed ($PtCl_4$) cycloisomerisation yielded the respective *M* and *P* enantiomers in good 65% yields, with only a 2% erosion of enantiopurity. It is noted the axially chiral starting material does not racemise in reaction conditions.




(*S*)-**283**, 94% e.e. (*P*)-**82**, 92% e.e.

**Scheme 47: Aza[6]helicene synthesis: cycloisomerisation of ethynyl biaryls**

iii) Comments

It can be added that these methods are far less attractive as they rely on resolution of atropoisomers to introduce chirality. Also, Rajca's example presented in the next section is at the border-line between retention of configuration / dynamic kinetic resolution / enantioselective synthesis depending on whether we consider that the biaryls he used are atropoisomers or not and whether they interconvert in reactions conditions or not. If they are not atropoisomers, it would purely be an enantioselective asymmetric synthesis; if they are atropoisomers that do not interconvert, it would be a kinetic resolution with retention of configuration (as is the case for the olefin metathesis described in the next section); if they interconvert, it would be a dynamic kinetic resolution.

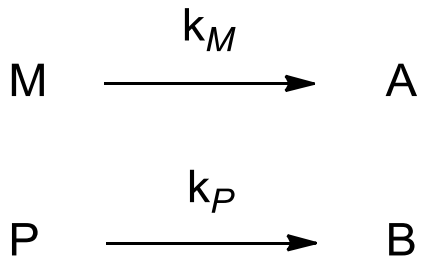
e) Kinetic resolution of helicenes

i) Kinetic resolution, definition, characteristics

1. Definition

A kinetic resolution can be defined as a reaction/transformation where enantiomers of a racemic substrate / compound react with a third component (either a chiral molecule or an

achiral molecule and a chiral catalyst) at different rates ($k_{fast}$ and $k_{slow}$) to form a chiral or achiral product. For a racemic mixture of *M* and *P* helicenes with $k_M$ and $k_P$ denoting the kinetic constants of the reaction of each enantiomer, a kinetic resolution could also be defined as a reaction where the conversion $\boldsymbol{c}$ is stopped between 0 and 100% ( $0 < \boldsymbol{c} < 100\%$) and where $k_M \neq k_P$ (Scheme 48).[107]




**Scheme 48: Kinetic resolution of M and P**

Considering the reaction shown in Scheme 48, we have the following equation:

**1** $$\boldsymbol{c} = \frac{[\text{Products}]}{[\text{M}]_0 + [\text{P}]_0} = \frac{([\text{M}]_0 + [\text{P}]_0) - ([\text{M}] + [\text{P}])}{[\text{M}]_0 + [\text{P}]_0} = 1 - \frac{[\text{M}] + [\text{P}]}{2[\text{M}]_0}$$

and if $k_M > k_P$, enantiomeric excess e.e. and selectivity factor *S* of the kinetic resolution / reaction can be defined as:

**2** $$\text{e.e.} = \frac{[\text{P}] - [\text{M}]}{[\text{P}] + [\text{M}]}$$

**3** $$S = \frac{k_M}{k_P}$$

Combining **1** and **2**, we can express [*M*] and [*P*] as a function of $\boldsymbol{c}$ and e.e:

**2** gives $$[\text{M}] = \frac{(1 - \text{e.e.})}{(1 + \text{e.e.})}\,[\text{P}] \quad \textit{and} \quad [\text{P}] = \frac{(1 + \text{e.e.})}{(1 - \text{e.e.})}\,[\text{M}]$$

put into **1**:

**4** $$[\text{M}] = [\text{M}]_0\,(1 - \boldsymbol{c})(1 - \text{e.e.})$$

**5** $$[\text{P}] = [\text{P}]_0\,(1 - \boldsymbol{c})(1 + \text{e.e.})$$

Considering that the reaction is of first order or pseudo-first order, the rate laws for M and P are the following:

$$\frac{\mathrm{d[M]}}{\mathrm{d}t} = -\mathrm{k}_M[\mathrm{M}] \quad \text{and} \quad \frac{\mathrm{d[P]}}{\mathrm{d}t} = -\mathrm{k}_P[\mathrm{P}]$$

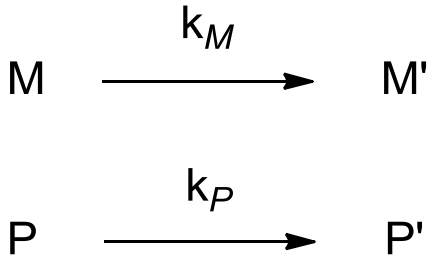
Integration of these two rate laws gives:

$$\ln[\mathrm{M}]/[\mathrm{M}]_0 = -k_M t \text{ and } \ln[\mathrm{P}]/[\mathrm{P}]_0 = -k_P t$$

Combining the two integrated rate laws and equation **3**, **4** and **5**, we can express *S* as a function of ***c*** and e.e.:

**6** $$S = \frac{\mathrm{k}_M}{\mathrm{k}_P} = \frac{\ln[\mathrm{M}]/[\mathrm{M}]_0}{\ln[\mathrm{P}]/[\mathrm{P}]_0} = \frac{\ln[(1-c)(1-\mathrm{e.e.})]}{\ln[(1-c)(1+\mathrm{e.e.})]}$$

In some cases, kinetic resolutions (Scheme 49) also afford chiral products M' and P'.




**Scheme 49: Kinetic resolution of M and P affording chiral products M’ and P’**

For this the following equations apply:

**7** $$\boldsymbol{c} = \frac{[\mathrm{Products}]}{[\mathrm{M}]_0 + [\mathrm{P}]_0} = \frac{[\mathrm{M}'] + [\mathrm{P}']}{[\mathrm{M}]_0 + [\mathrm{P}]_0}$$

and considering that $k_M > k_P$ (like in Scheme 48), enantiomeric excess e.e.′ can be defined:

**8** $$\mathrm{e.e.}' = \frac{[\mathrm{M}'] - [\mathrm{P}']}{[\mathrm{M}'] + [\mathrm{P}']}$$

Combining **7** and **8**, we can express [M’] and [P’] as a function of c and e.e.′:

**8** gives $$[\mathrm{M}'] = \frac{(1+\mathrm{e.e.}')}{(1-\mathrm{e.e.}')}\,[\mathrm{P}'] \quad \textit{and} \quad [\mathrm{P}'] = \frac{(1-\mathrm{e.e.}')}{(1+\mathrm{e.e.}')}\,[\mathrm{M}']$$

put into **7**:

**9** $$[\mathrm{M}'] = [\mathrm{M}]_0\,\boldsymbol{c}(1+\mathrm{e.e.}')$$

**10** $$[\mathrm{P}'] = [\mathrm{P}]_0\,\boldsymbol{c}(1-\mathrm{e.e.}')$$

Considering that $[M]_0 = [M'] + [M]$ and that $[P]_0 = [P'] + [P]$, combining equation **3** with the integrated laws **9** and **10** gives:

**11** $$S = \frac{k_M}{k_P} = \frac{\ln[M]/[M]_0}{\ln[P]/[P]_0} = \frac{\ln(1 - \frac{[M]}{[M]_0})}{\ln(1 - \frac{[P]}{[P]_0})} = \frac{\ln[1 - \boldsymbol{c}(1 + e.e.')]}{\ln[1 - \boldsymbol{c}(1 - e.e.')]}$$

Also, as using equation **6** and **11**, the following relationship between $\boldsymbol{c}$, e.e. and e.e.′ can be found:

**12** $$\boldsymbol{c} = \frac{e.e.}{e.e. + e.e.'}$$

However, the rate of the reaction towards *M* and *P* has to be of the first order or pseudo first order in order to use those equations correctly. Interestingly, Jacobsen reports that rates of reaction in kinetic resolutions are rarely determined; therefore it is safer / more correct to quote conversions, e.e. of starting materials and e.e. of products.[108]

2. Historical kinetic resolutions

Historically, Pasteur was the first to come across a kinetic resolution when he studied the fermentation of ammonium tartrate by a *Penicillium glaucum* mould. The remaining tartrate recovered from the reaction showed optical activity.[109] Later in 1898, the first purely chemical kinetic resolution was reported by Marckwald, after esterifying mandelic acid with (–)-menthol and recovering optically active starting material.[110] Many other examples followed, and the ones concerning helicenes are described in the following sections.

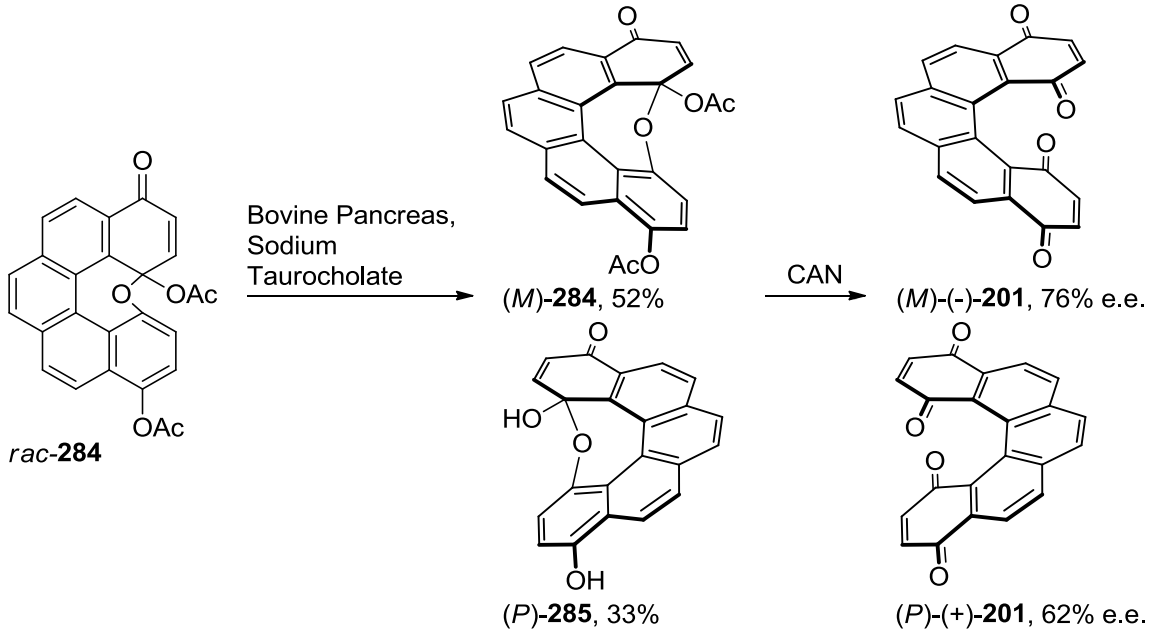
ii) Results

1. Enzymatic kinetic resolution

a. Bovine pancreas acetone powder

As for many areas of helicene chemistry, Tomas Katz was also a pioneer in enzymatic kinetic resolution of helicenes.[111] After transforming racemic [5]helicenetetraone **201** into the acetylated cyclic hemiacetal **284**, the enantioselective hydrolysis reaction using Bovine pancreas acetone powder and sodium taurocholate, gave hemiacetal (*P*)-**285**, in 33% yield. After subsequent transformation of recovered **284** and of **285** into parent helicene **201** (and

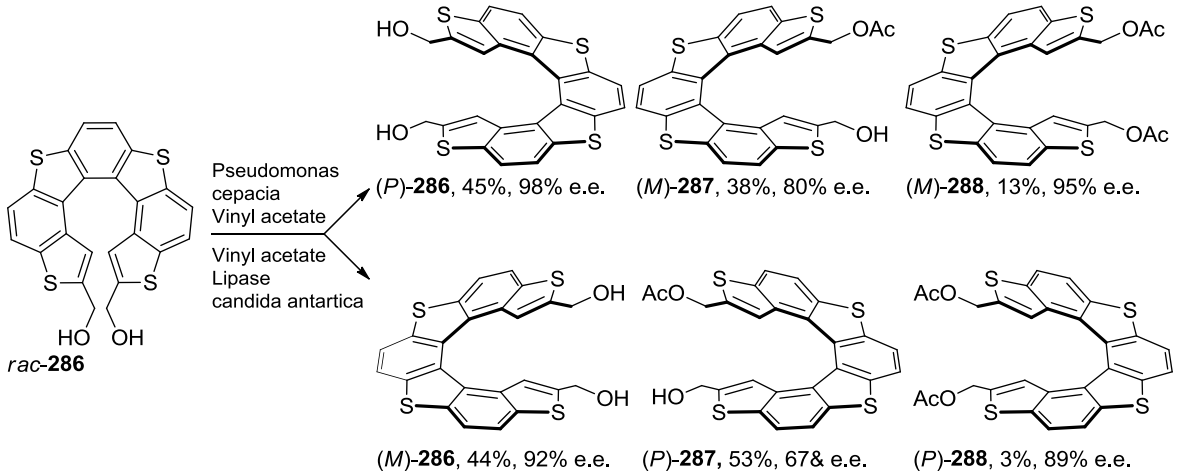
assuming no racemisation occurred), the enantiomer derived from **285** showed 62% e.e. and the other enantiomer showed 76% e.e. (Scheme 50).




**Scheme 50: Sodium taurocholate KR of [5]helicenoid 284**

b. Lipase catalysed transesterification

In 1995, Tanaka reported two different kinetic resolutions of 2,13-bis(hydroxymethyl)tetrathia[7]helicene (**286**) using lipase catalysed transesterifications with vinyl acetate, affording both enantiomers.[112] Indeed, using *Pseudomonas cepacia*, (*P*)-**286** was recovered in 45% yield and 98% e.e. after the transesterification. Mono ester **287** and diester **288** were obtained in 38% and 13% yield, and after reduction with lithium aluminium hydride, (*M*)-**286** was obtained respectively with 80% and 95% e.e. Whereas, when using *Candida antarctica*, (*M*)-**286** was recovered after the transesterification reaction in 42% yield with 92% e.e. Mono ester and diester were obtained respectively in 53% and 3% yield and after hydrolysis chiral analysis showed respectively 67% and 89% e.e.[113] (Scheme 51). We have to note that in both cases, highly enantioenriched diester **288** was obtained, respectively 95% e.e. and 89% e.e. which constitute the first reports of what can now be identified as a one-pot double kinetic resolution of helicenes.

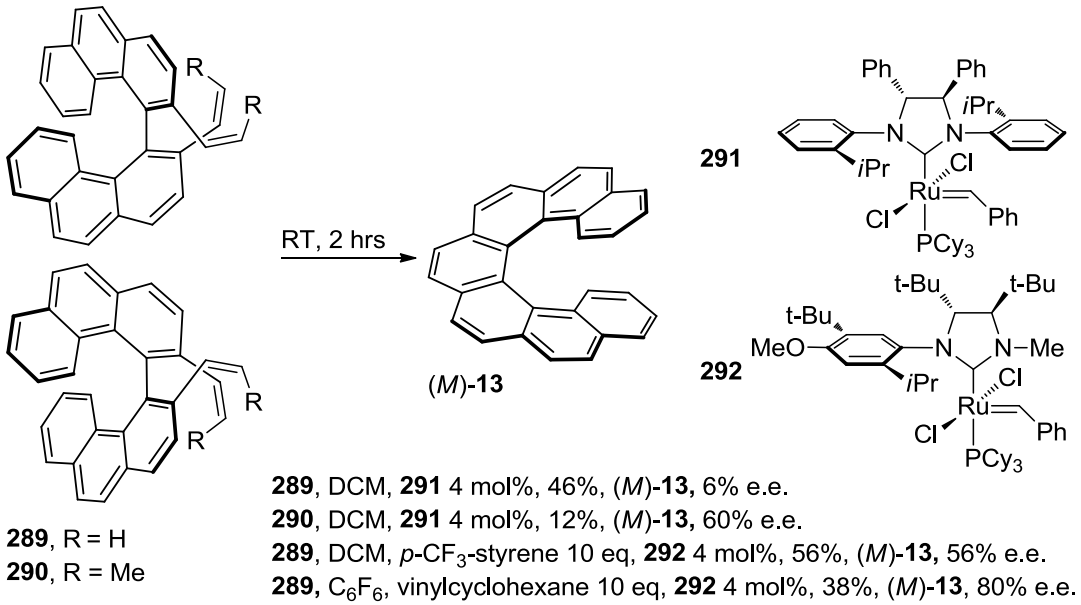



**Scheme 51: Kinetic resolution of tetrathia[7]helicene by lipase catalysed transesterification**

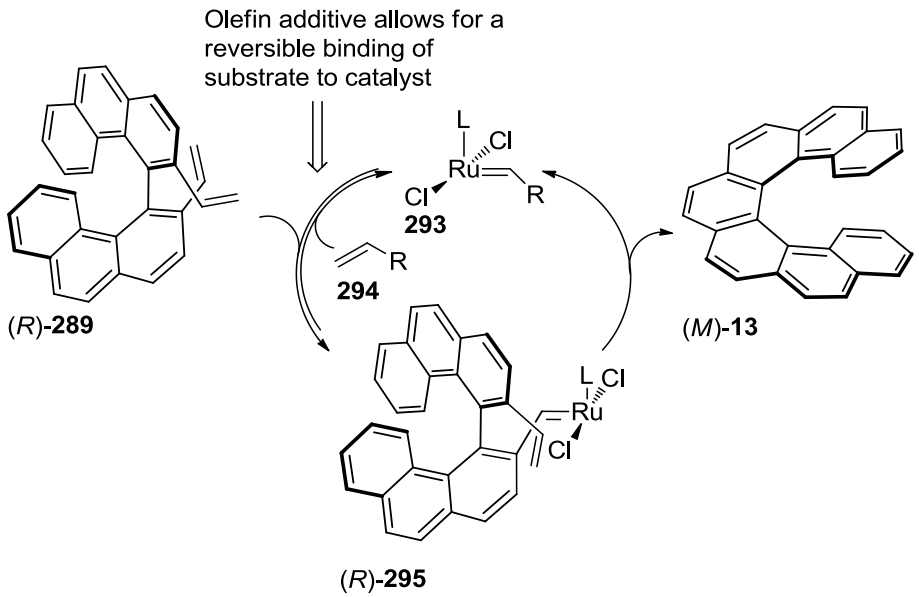
## 2. Asymmetric RCM

After reporting in 2006 that olefin metathesis of divinyl biaryl atropoisimers successfully forms helicenes (using second the generation Grubbs and second generation Hoveyda-Grubbs catalysts),[114] Grandbois and Collins showed that the reaction could be performed in an asymmetric fashion.[115] Switching their initial RCM catalyst for a more bulky one (**291**) and getting slower reactions, they obtained encouraging results, giving [7]helicene in 12% yield and 60% e.e. using methyl substituted divinyl starting material **290** (Scheme 52). The next step of their work involved the screening of various divinyl compounds (like **289** and **290** but bearing different R groups) in order to evaluate the substrates' influence in the reaction; this proved unsuccessful as the original dimethyl precursor **290** remained the most suitable one. Addition of halides also failed to improve the selectivities, and it was concluded that the formation of the first metallacyclobutane intermediate **295** might be enantiodetermining. They decided that the addition of achiral olefins (**294**, see Scheme 53) could help controlling and stabilising the propagating carbene, which could help to improve selectivities by making reversible the binding of the substrate (**289** for example, Scheme 53) onto the catalyst (**293**, Scheme 53). Using 1-hexene immediately demonstrated the viability of the approach, and after screening several olefins, and switching to a more efficient catalyst **292** (developed in the same lab), the product of the kinetic resolution, [7]helicene [(*M*)-**13**], was obtained in 56% yield and 56% e.e. using *p*-trifluoromethylstyrene as the additive (Scheme 52). Careful screening of the solvent,

having in mind that solvent could interact both with the heterocyclic carbene ligand and with the divinyl substrate, showed that poor solubilisation of precursor **289** improved selectivities, and performing the reaction in hexafluorobenzene with vinylcyclohexane additive, they obtained [7]helicene [(*M*)-**13**] in 38% yield and 80% e.e. (Scheme 52).




**Scheme 52: RCM mediated asymmetric synthesis of [7]helicene: kinetic resolution of biaryl atropoisomers**

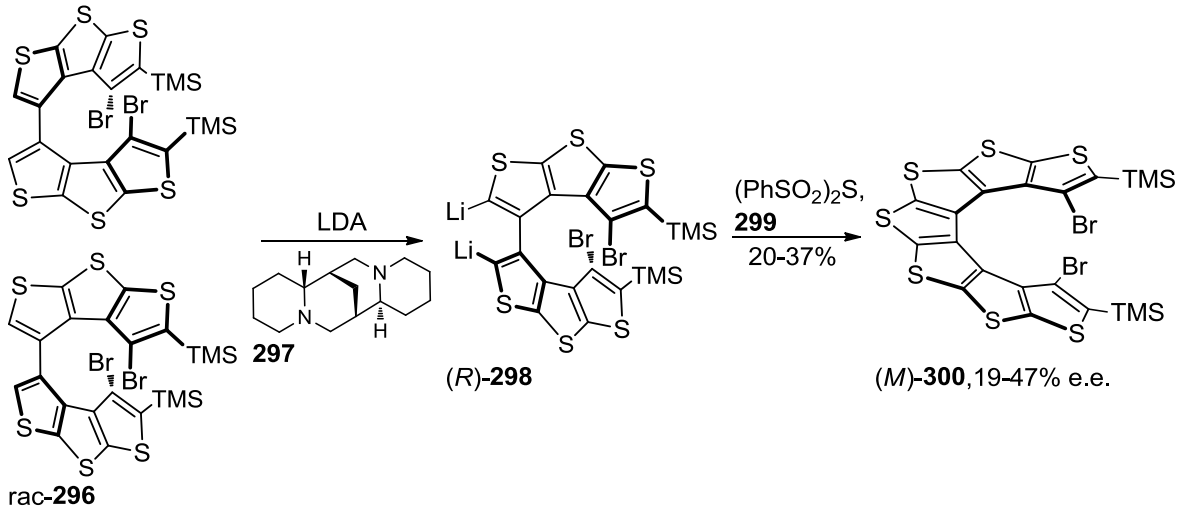



**Scheme 53: Mechanistic insight for the increased selectivity when using olefin additives**

### 3. (−)-Sparteine mediated asymmetric lithiation

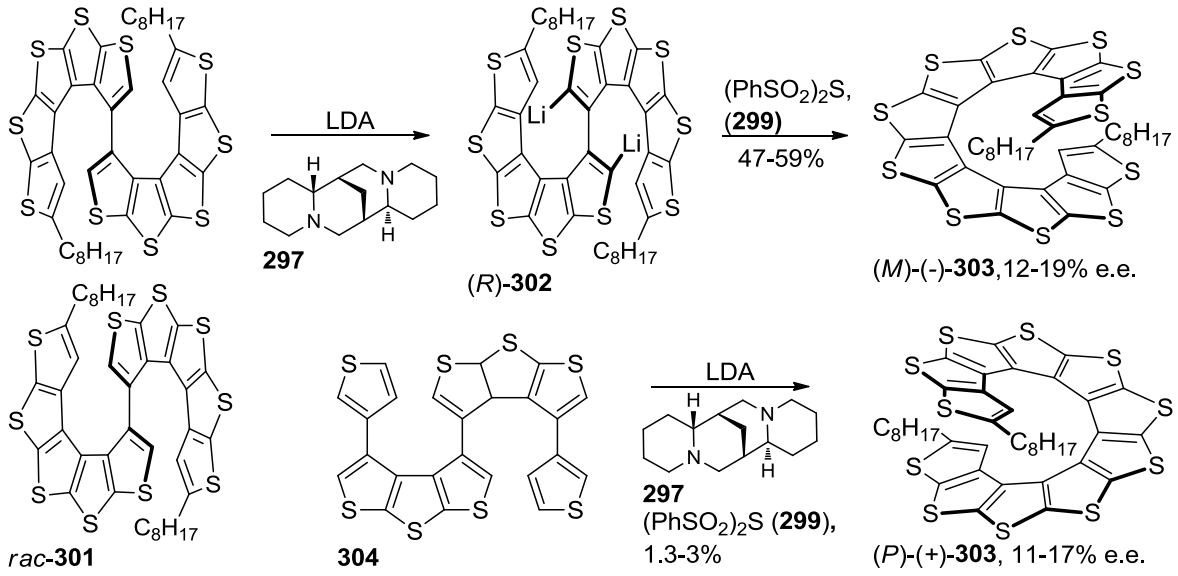
#### a. Results

Using the well-established literature procedure for sulfur annelation reactions,[116] Rajca synthesised all-thiophene thia[7]helicenes in good yields.[117] He adapted the procedure to allow an asymmetric reaction, using the famous chiral diamine (−)-sparteine (**297**) to perform an asymmetric double lithiation reaction of racemic biaryl **296**.[54] Although, the reaction is not clearly presented as a kinetic resolution, it is noted that biaryl atropoisomers **296** are stable in the conditions of the reaction (*i.e.* at least 1 hour at RT), therefore the enantioselective formation of one enantiomer arises from a double kinetic resolution in asymmetric lithiation conditions that (−)-sparteine provides. Subsequent quench of the dilithiated species **298** with bis(phenylsulfonyl)sulfide (**299**) gave heptathia[7]helicene (*M*)-(−)-**300** in 20 to 37% yield and 19 to 47% e.e. (Scheme 54).



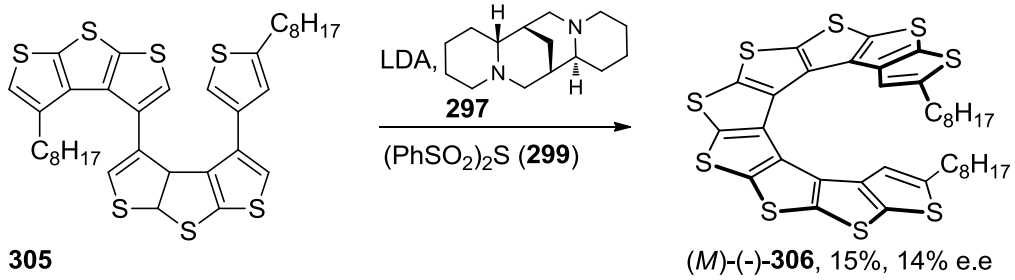

**Scheme 54: Synthesis of heptathia[7]helicene via the (−)-sparteine mediated kinetic resolution of bi-aryls atropoisomers**

In 2005, Rajca published the synthesis of all-thiophene thia[11]helicene **303** using the same strategy.[118] He presented two routes. The first was a double kinetic resolution of racemic biaryl **301** by selective lithiation of one of the atropoisomers using (−)-sparteine and obtaining (after quenching with **299**) thia[11]helicene (*M*)-**303** in up to 59% yield and 19% e.e. The second is a challenging tri-annelation, for which the multiple kinetic resolution gave thia[11]helicene (*P*)-**303** only 3% yield and up to 17% e.e. (Scheme 55).




**Scheme 55: Synthesis of undecathia[11]helicene via the (–)-sparteine mediated kinetic resolution of bi-aryls atropoisomers**

Recently, he reported the synthesis of all-thiophene thia[9]helicene (*M*)-**306**, using the same sparteine mediated asymmetric lithiation and subsequent di-annelation.[119] Thia[9]helicene (*M*)-**306** was obtained in 15% yield and 14% e.e (Scheme 56).




**Scheme 56: Synthesis of nonathia[9]helicene via the (–)-sparteine mediated kinetic resolution of bi-aryls atropoisomers**

b. Multiple kinetic resolution

In the case of di-annelation and tri-annelation, the precursors present more than one bi-aryl motif and therefore the enantio-enriched products are obtained via multiple kinetic resolutions processes. However considering the lower selectivities for di- and tri-annelation reactions, it is unlikely that multiple stereodifferentiation effects added to each other to form products with greater selectivity.

## IV) Conclusion

The examples discussed in this introductory chapter demonstrate the wide variety of methods that have been employed in asymmetric helicene synthesis. Among them there are examples of highly efficient procedures in individual cases, particularly helicenes terminating in quinone rings, but truly generally applicable methodologies still await to be developed. Some reactions (performed for other reasons) have been interpreted in this discussion as early examples of double or multiple kinetic resolutions, although this was not pointed out by the original authors at the time. The work performed in this doctoral project has the objective of establishing the principles of double and multi-KR as a strategy for synthesis design, and to exemplify them in the context of tetrathia[7]helicene synthesis. This approach still has the potential to be developed into one of the best, and most widely-applicable approaches for the preparation of enantiopure helicenes since the principle is not restricted to the thiahelicene case. Indeed, the double and multi-KR approach can be suitable in any situation where a sequence of two or more kinetic resolution steps are included in a single reaction sequence starting from racemic substrate, or from the enantioenriched product of an asymmetric induction that lacked high levels of stereocontrol.

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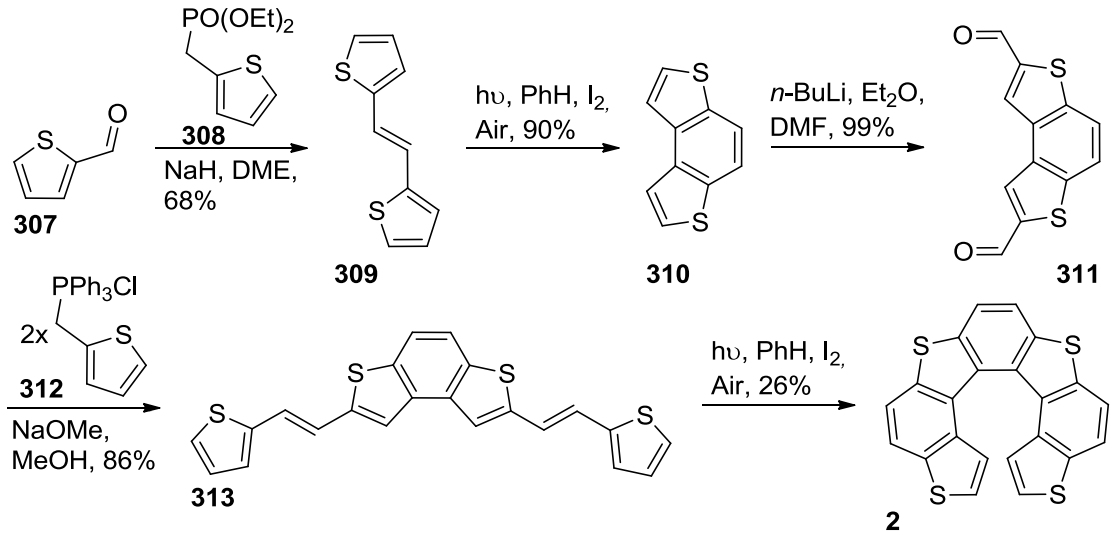
# Chapter 1:
# Synthesis of tetrathia[7]helicenes

I) Generalities on thia[7]helicenes

1) First synthesis

Tetrathia[7]helicenes were first synthesised in 1971 by Wynberg, using a technique in fast development at that time, photodehydrocyclisation (Scheme 1).[1] This method was particularly popular at the time because of its tolerance to a wide range of substrates, allowing the synthesis of many helicenes of different lengths and compositions (see intro) in a limiting amount of time.




**Scheme 1: Original synthesis of tetrathia[7]helicene**

2) Method scope and limitations

This method suffers from two main problems, the high dilution required for the photolysis and the low solubility of unsubstituted alkenes due to pi-stacking phenomena (pi stacking phenomena are caused by electrostatic interactions between aromatic systems that bring aromatic molecules together to form larger molecular assemblies preventing the solubilisation). Indeed, concentrations of alkene precursors for the cyclisation are always very low, ranging from 0.1 millimoles per litre to a few millimoles per litre, not allowing easy access to large scale synthesis. Also, the solubility of unsubstituted alkenes is pretty poor in benzene (generally the completion of the reaction is judged by the disappearance of insoluble starting material), and even worse in the modern substitute, toluene.

While we do not claim to solve these issues by performing the synthesis of our tetrathia[7]helicenes entirely without using the photodehydrocyclisation method, the results discussed in this first chapter will detail adjustments made to simplify the photochemical synthesis (based on Maiorana and Licandro's work[2]) as well as our

development of an alternative non-photochemical synthesis of the key thiahelicene intermediate benzo[1,2-b:4,3-b']thiophene.

II) Chemical synthesis of benzo[1,2-b:4,3-b']thiophene (**BDT**)

1) **BDT** properties

The combination of thiophenes and benzene rings in high-performance chromophores has proved to be a powerful strategy for functional materials in nonlinear optics (NLO)[3] because of the lower aromatic resonance energy of thiophene compared to benzene.[4] Linear structures of the type R($C_4H_2S$)-($C_6H_4$)-($C_4H_2S$)R', and fused-ring structures of which the simplest are benzothiophenes, benzodithiophenes (**310**, **313**, **314**) and benzothienobenzothiophenes **316** (Figure 1), are widely studied and have found significant commercial applications in organic field effect transistors[5] (OFETs), organic light-emitting diodes[6] (OLEDs) and solar cells.[7] In practice, 1,2-b:4,5-b' and 2,1-b:3,4-b' isomers are by far the most widely used, and are of growing importance,[8] however, a recent paper describing benzodithiophene applications in dye-sensitized solar cells (DSCs) points out that the symmetrical benzo[1,2-b:4,3-b']dithiophene (**BDT**, **310**) has been very little used in that field.[9] For our own interests in tetrathia[7]helicenes [which are useful as D-(chiral-pi)-A components in nonlinear optics,[10] as novel chelating diphosphine ligands,[9b] in organocatalysis[11] and to bind DNA[12]], [1,2-b:4,3-b'] regioisomer **310** is a well-established key intermediate for which we have developed a new chemical synthesis.[13]

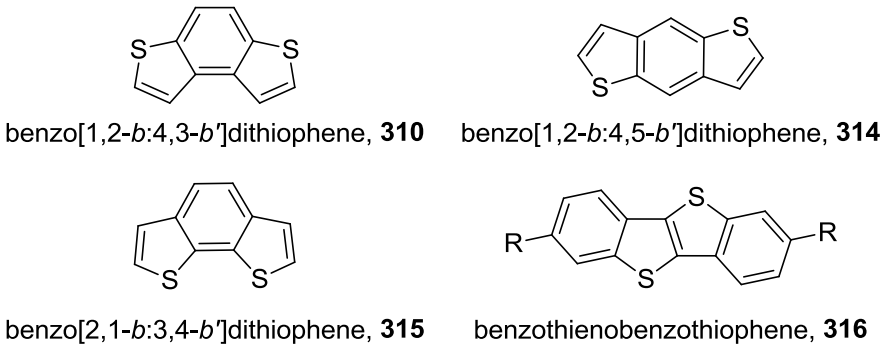
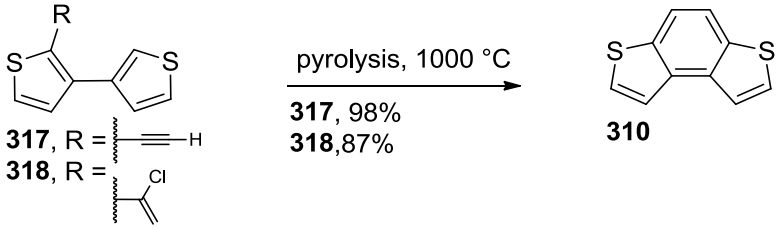



**Figure 1: Structures of thiophene-based cores of high-performance chromophores**

2) Previous syntheses

Previously to our report,[13] the synthesis of benzo[1,2-b:4,3-b']thiophene (**BDT**, **310**) has almost exclusively relied on the photodehydrocyclisation of 1,2-di(thiophen-2-yl)ethene (**309**)[14] (Scheme 1), which suffers from all the drawbacks presented in the previous

paragraph and in the discussion in the introduction. Indeed, the few other routes that provide **BDT** or its derivatives, whether by chemical syntheses[15] or by pyrolysis[16] (Scheme 2), are only partially successful for substituted **BDT**s and cannot be efficiently applied to the non-substituted isomer even with the otherwise versatile pyrolysis reaction.

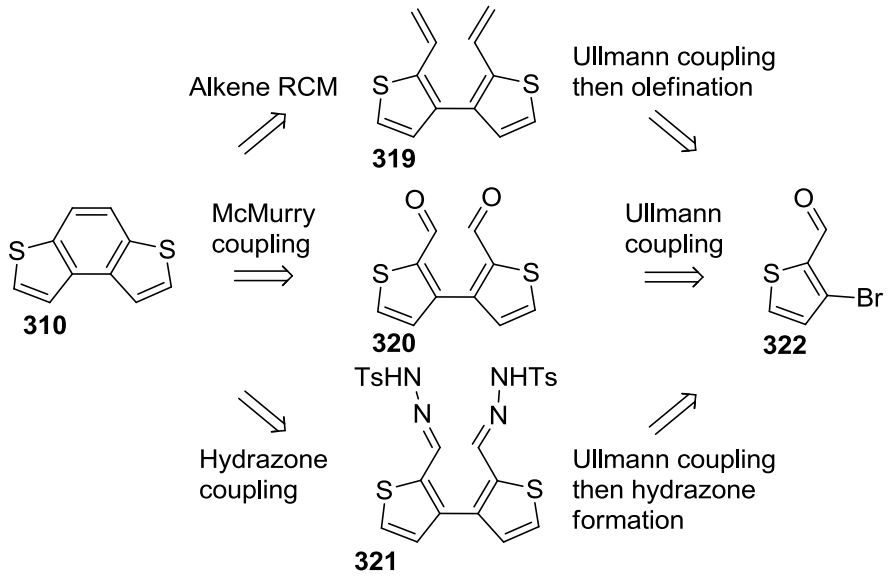



**Scheme 2: Synthesis of BDT via pyrolysis reaction**

3) Our approach

a) Strategy

The development of the three strategies shown in Scheme 3 requires 3-bromo-2-formylthiophene (**322**). Several possibilities are available for the synthesis of bithiophenes relying on the homo-coupling of 3-substituted-thiophenes, but few are applicable when attempting the coupling of 3-substituted-2-formylthiophenes. Alternatively, palladium catalysed homo-coupling of *o*-halobenzaldehyde derivatives[17] as well as several variations of the traditional Ullmann coupling,[18] can all be transposed to thiophene-based substrates because examples of their application with other systems are available in the literature.



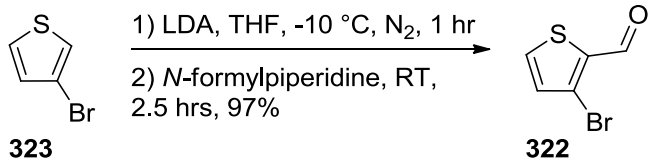

**Scheme 3: Retrosynthetic analysis for BDT synthesis**

Concerning these strategies (Scheme 3), the most appealing to us was the direct, intramolecular McMurry coupling that would give **BDT** (**310**) directly from bis aldehyde **320**. Indeed, this method has given some encouraging results for the cyclisation of a similar bis-ketone derivative[15c] (70% yield for the cyclisation), despite tricky reaction conditions which require the slow addition of reactants over several hours, and rigorously anhydrous solvents (the most successful reagents, $TiCl_3$ or $TiCl_3.DME_{1.5}$, are particularly air and moisture sensitive). The other two methods require an additional step, olefination for the RCM route and hydrazone formation for the hydrazone coupling, but are expected to be efficient strategies because the final metathesis step is known to work well in the corresponding cyclisation of 2,2'-divinylbiphenyl to form phenanthrene,[19] and the coupling of bis-hydrazone[20] has also been successful for the synthesis of phenanthrene, the carbon version of **BDT**.

b) Synthesis of 2,2'-diformyl-3,3'-bithiophene

i) Synthesis of coupling precursor

Although 3-bromo-2-formylthiophene (**322**) is commercially available, it is cheaper and easy enough to prepare from 3-bromothiophene (**323**) by simple a lithiation reaction using LDA and quenching with any formylating compound (DMF, *N*-formylpiperidine, *N*-formyl-*N*-methylaniline). 3-Bromo-2-formylthiophene (**322**) was prepared by this method on a large scale (87 g) in 97% yield using *N*-formylpiperidine (Scheme 4), improving the 86% yield[21] previously reported.




**323** **322**

**Scheme 4: Synthesis of 3-bromo-2-formylthiophene**

ii) Palladium coupling

Next, we examined the homo-coupling reaction initially using the palladium mediated homo-coupling procedure.[17] Knowing that the standard dimerisation method uses (2-formyl-3-thienyl)boronic acid but gives the product in only 36% yield[22] (and 18% yield from from 3-bromo-2-formylthiophene (**322**), requiring three steps[23]) we preferred to avoid

the use of boronic acids by means of the alternative and more accessible 3-bromo derivative **322**, because of the wider possibilities for the coupling reaction. Using $Pd(PPh_3)_4$ and copper powder in DMSO, despite several attempts, we obtained the desired dialdehyde **320** in a maximum 35% yield (Table 1, entry 1), which is comparable to the 36% yield previously reported for the coupling of boronic acid derivative.[22a] Although confirming the principle of our approach, this was a disappointing result, and taking in consideration the cost of palladium coupling chemistry, we switched to a study of the Ullmann coupling reaction.

| Entry | Substrate | Catalyst (eq) | Solvent | T (°C) | Time (hrs) | Yield [%] |
|---|---|---|---|---|---|---|
| 1 | **322** | Cu (10)/ $Pd(PPh_3)_4$ (0.1) | DMSO | 100 | 15 | 35[a] |
| 2 | **324** | CuTC (2.2) | NMP | RT | 60 | 25[b] |
| 3 | **326** | CuTC (3.0) | NMP | RT | 60 | 29[b] |
| 4 | **326** | CuI-$P(OEt)_3$ (1.5) | THF | –78 to RT | 60 | 15[b] |
| 5 | **327** | CuTC (3.0) | NMP | RT | 60 | 14[b] |

[a] isolated yield; [b] based on NMR of crude bis aldehyde 8a or 8b

**Table 1: Preliminary results of the coupling reactions**

iii) Ullmann coupling

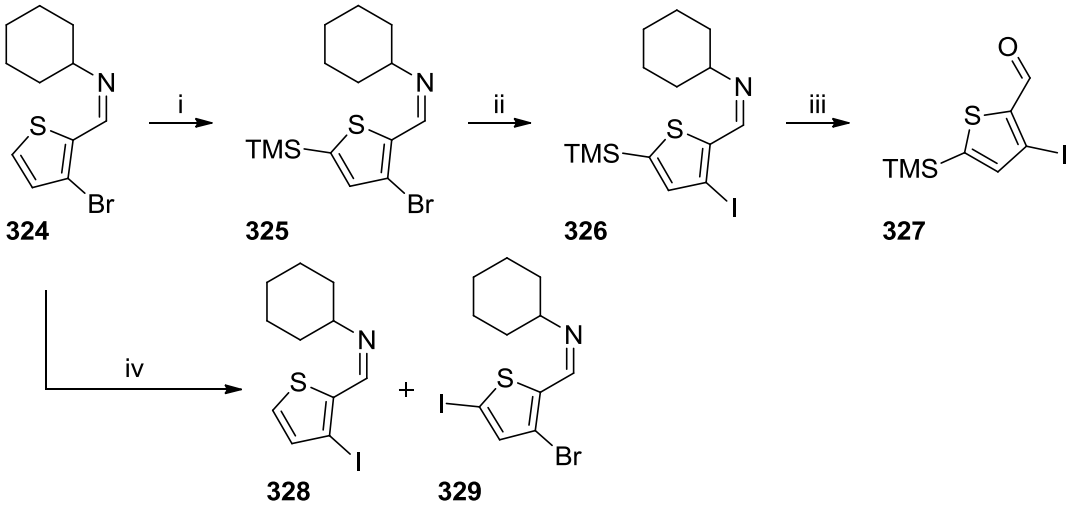
1. Preliminary results

Rajca had previously reported the homo-coupling of 3,4-dibromothiophene affording a bithiophene moiety in a decent 40% yield[24] despite using the classic high temperature conditions. Hence, we thought that a modern version of the Ullmann coupling allowing the reaction to proceed at room temperature should enable us to use our preferred 3-bromo-2-formylthiophene **322** and provide improved yields.

For our first attempt, it was decided to use Liebeskind's catalyst CuTC (**330**),[18a,b,c] especially as the coupling could be directly performed with 3-bromo-2-formylthiophene (**322**). The reaction at room temperature, with three equivalents of catalyst gave none of the desired product so we immediately looked into making a more reactive iodothiophene derivative. Instinct and literature would probably lead us to use the dioxolane acetal,[25] but interestingly we came across a publication from Ziegler[18d,e] about Ullmann coupling, where to access the iodo-compound they protected the aldehyde by transformation to its

cyclohexylimine. The imine **324** was easily made in quantitative yield by refluxing aldehyde **322** in toluene with cyclohexylamine using a Dean-Stark trap.

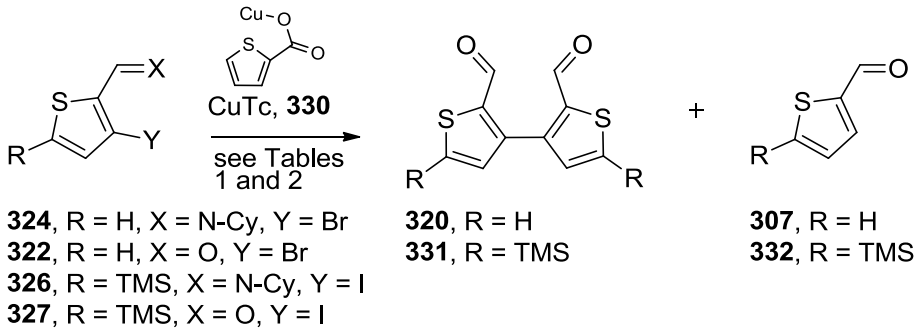
The direct iodination of the imine **324** was unsuccessful, giving us an inseparable mixture the desired compound **328** and 3-bromo-2-formyl-5-iodothiophene (**329**), which suggested competing lithiation at C-5. To avoid this, we protected the 5-position with a trimethylsilyl group (**325**) by selective C-5 lithiation which is possible in the presence of the 3-bromo substituent by using LDA.[24] This was then followed by bromine-lithium exchange using *n*-BuLi and quenching with $I_2$ which successfully gave us the iodothiophene derivative **326** (Scheme 5).



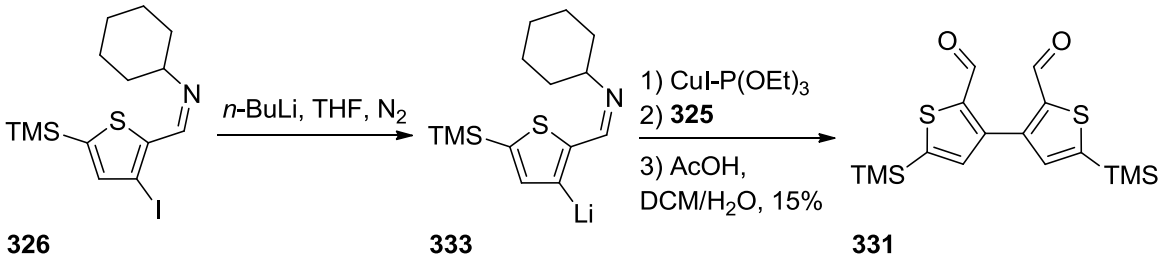

i) LDA, TMSCl, THF, $N_2$, 99%; ii) *n*-BuLi, $I_2$, THF, $N_2$, 90%; iii) AcOH, DCM, $H_2O$, 88%; iv) *n*-BuLi, $I_2$, THF, $N_2$

**Scheme 5: Preparation of the iodothiophenes 326 and 327**

In contrast to our attempts using aldehyde **322** we were agreeably surprised to find that the Ullmann coupling (Scheme 6) of the iodoimine **326** with Liebeskind catalyst in NMP at room temperature afforded the desired product, however it was obtained in only 29% yield (Table 1, Entry 3). The C-5 silyl-protected aldehyde **327**, was also examined in the Ullmann step and gave 14% yield (Table 1, Entry 5). An attempt at the Ullmann coupling of the bromo-cyclohexylimine **324** did not improve the results, giving a disappointing 25% yield (Table 1, Entry 2). We also examined the Ziegler method (Scheme 7) which was found to perform similarly (15% yield) (Table 1, Entry 4) with our substrate.




**Scheme 6: Ullmann coupling of 3-bromo and 3-iodothiophenes**




**Scheme 7: Ziegler's method for Ullmann coupling**

2. Optimisation of the reaction

Careful scrutiny of the NMR spectra of the products from these preliminary experiments showed two things: 1) in some cases the substrate is not reactive enough and mostly starting material is recovered, or 2) dehalogenated starting material (**307** or **332,** Scheme 6) is obtained in considerable conversion meaning the halothiophene undergoes oxidative addition with the copper but the coupling does not happen, perhaps because more vigourous conditions are needed or because impurities prevent the reaction from happening.

For these reasons, the problem of low yields was initially addressed using a microwave reactor, the coupling of iodoimine **326** gave interesting results with a conversion improved to 48% (Table 2, Entry 4). However, it rapidly became apparent (Table 2) that careful purification of the CuTC was crucial to obtain good results, and after further examination of reaction conditions to control competing dehalogenation (Scheme 6), using the iodoimine **326** we obtained desired product **331** in 55% conversion (Table 2, Entry 6). In view of this slow progress with attempts to improve the yield of the coupling in the iodo series, and since it would save two steps, we turned instead to explore our new microwave

method with the original bromoimine **324**. It turned out to give a surprisingly large improvement. Microwave irradiation at 90 °C gave dialdehyde **320** in a 67% conversion (but only 55% isolated yield, Table 2, Entry 8). Also, driven by our interest in a large scale synthesis, we found that simply heating bromoimine **324** at 90 °C using 2.2 equivalents of CuTC, for 17 hours gave dialdehyde **320** in an improved 68% isolated yield (e.g. Table 2, Entry 9).

| Entry | Substrate | Conditions | Yield [%] of dialdehyde | Yield [%] of dehalogenated SM |
|---|---|---|---|---|
| 1 | **326** (Y = I) | RT, 48 hrs, CuTC (3.5 eq) | **331** (20[a]) | **332** (23[a,c]) |
| 2 | **326** (Y = I) | 60 °C, 60 hrs , CuTC (3 eq), $N_2$ | **331** (29[a]) | **332** (60[a,c]) |
| 3 | **326** (Y = I) | RT, 60 hrs, CuTC (3 eq), $N_2$ | **331** (43[b]) | **332** (37[b]) |
| 4 | **326** (Y = I) | 60 °C, μW, 20 min, CuTC (3 eq), $N_2$ | **331** (48[b]) | **332** (26[b]) |
| 5 | **326** (Y = I) | 90 °C, μW, 15 min, CuTC (3 eq), Ar | **331** (51[b]) | **332** (33[b]) |
| 6 | **326** (Y = I) | 60 °C, μW, 30 min, CuTC (3 eq), $N_2$ | **331** (55[b]) | **332** (21[b]) |
| 7 | **324** (Y = Br) | 90 °C, μW, 15 min, CuTC (2.2 eq), Ar | **320** (62[b,d]) | **307** (19[a,b]) |
| 8 | **324** (Y = Br) | 90 °C, μW, 25 min, CuTC (2.2 eq), Ar | **320** (67[b,e]) | **307** (17[b]) |
| 9 | **324** (Y = Br) | 90 °C, 17 hrs, CuTC (2.2 eq), Ar | **320** (68[f]) | - |

[a] based on NMR of crude bis aldehyde; [b] based on NMR of crude bis imine; [c] catalyst not pure enough; [d] 52% isolated yield; [e] 55% isolated yield; [f] isolated yield.

**Table 2: Control of dehalogenation in the coupling of halo-thiophenes.**

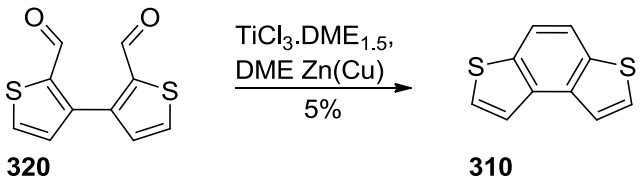
c) Ring closing

i) McMurry coupling

The intermolecular version of this reaction is widely used, transforming carbonyl compounds into alkenes via a low-valent titanium catalysed homo-coupling. There is no general rule for the formation of *cis* and *trans* alkenes (despite extended studies),[26] however experience has shown us that when using 2-carbonylthiophenes, aldehydes give (*E*)-alkenes whereas ketones give opposite (*Z*) configuration. In the case of 2,2'-diformyl-3,3'-bithiophene **320**, the situation is somewhat different as the reaction would be intramolecular, and can only give the (*Z*) product (the more unlikely intermolecular dimerisation arising from a double intermolecular coupling was not expected to compete).

Being familiar with the general / most common conditions for the coupling, our first attempt was carried out using $TiCl_4$ and Zn and refluxing in THF our di-aldehyde substrate with the preformed low-valent titanium species. Unfortunately, the reaction did not give

any product and starting material was recovered. Careful study of the literature suggested that the most reactive system for intramolecular cyclisation could be $TiCl_3.DME_{1.5}$ with Zn(Cu) couple as the reducing agent.[27,15c] However, when 2,2'-diformyl-3,3'-bithiophene is submitted to these conditions, and despite several attempts, the yield did not exceed 5% (Scheme 8).



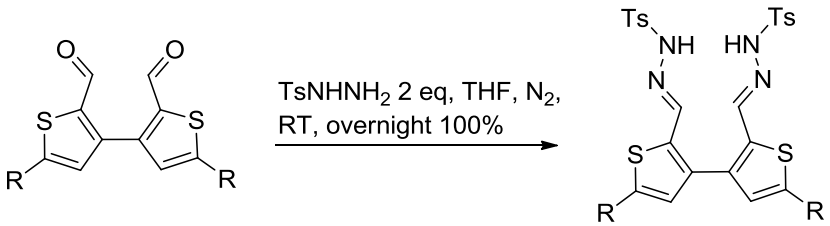

**320** **310**

**Scheme 8: McMurry coupling using $TiCl_3.DME_{1.5}$ with Zn(Cu)**

One thing has to be added; the literature quoted earlier also mentions the benefits of running the reaction with a slow addition of the aldehyde substrate, however we made no attempt to verify this. Also, as stated in this paragraph, 2-formylthiophenes tend to give *trans* alkenes, which might disfavour the **BDT** formation and explain why Rajca successfully ring-closed the diketone equivalent in the conditions we used.

ii) Bis-hydrazone route

We moved on to examine the cyclisation of a bis-tosylhydrazone formed in the double condensation reaction of diadehydes **320** and **331**. First, the condensation reaction affording bis-hydrazones was studied and after struggling slightly to separate the bis-hydrazone products and remaining tosylhydrazide, we found that simply stirring at room temperature a mixture of one equivalent aldehyde and exactly two equivalents of tosylhydrazide gave the desired bis-hydrazones **321** and **334** with full conversion without any need for purification (Scheme 9).




**320** (R = H)
**331** (R = TMS)

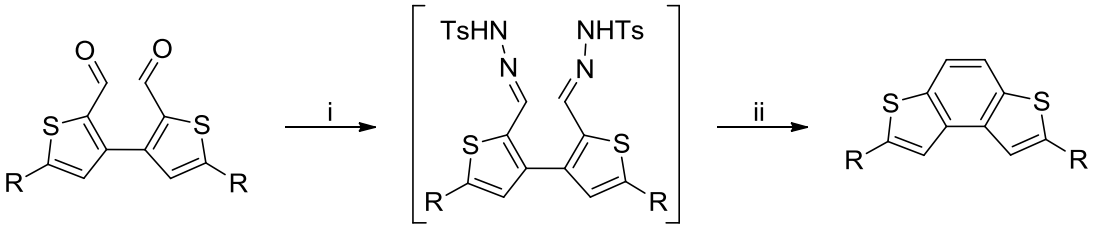
**321** (R = H)
**334** (R = TMS)

**Scheme 9: Bis hydrazones synthesis**

We then concentrated on the ring closing step which is an alternative to the McMurry coupling of aldehydes and has shown good potential for the synthesis of phenanthrene (80% yield).[20a] Although the Jung *et al.* publication[20a] does not really give clear details of the conditions used, our first attempts at the cyclisation of bis hydrazone **321** using sodium hydride as the base gave **BDT** in encouraging yields up to 37%. The reaction was also carried out with bis TMS-hydrazone **334**, however now when using sodium hydride, partial desilylation was observed, therefore *n*-BuLi was used and di-TMS-**BDT 335** was obtained in 32% yield.

Several optimisations were attempted. Jung had commented[20a] that the addition of CuI-$P(OEt)_3$ following the treatment of bis-hydrazones with *n*-BuLi helped to increase the yield of phenanthrene from 29% to 80%, however no such improvement was observed in our case. Changing the base to potassium *t*-butoxide was inefficient, and modification of the amount of usual bases used (2.5 eq NaH, 1.05 eq *n*-BuLi) did not improve the yields previously obtained. Nonetheless, one thing can be noted, performing the reaction with a bis hydrazone concentration over five grams per litre affects the yield negatively. We also tried different hydrazides (2,4,6-triisopropylbenzenesulfonylhydrazide and 2,4,6-trimethylbenzenesulfonylhydrazide), as they have shown higher abilities to form diazoalkanes in Bamford-Stevens reaction,[28] but results obtained with the classic tosylhydrazide were not improved. Moreover, we even tried the harsher Baker *et al.* conditions using hydrazine and acetic acid,[20b] but without success.

Thus the most favourable conditions that we have found so far for this reaction are the "one pot" process with the formation of the bis-hydrazone (**321** and **334**) in tetrahydrofuran *in situ*, subsequent drying over sodium sulfate, and addition of base at low temperature followed by heating at reflux for a few hours (Scheme 10).




**320** (R = H)
**331** (R = TMS)

**321** (R = H)
**334** (R = TMS)

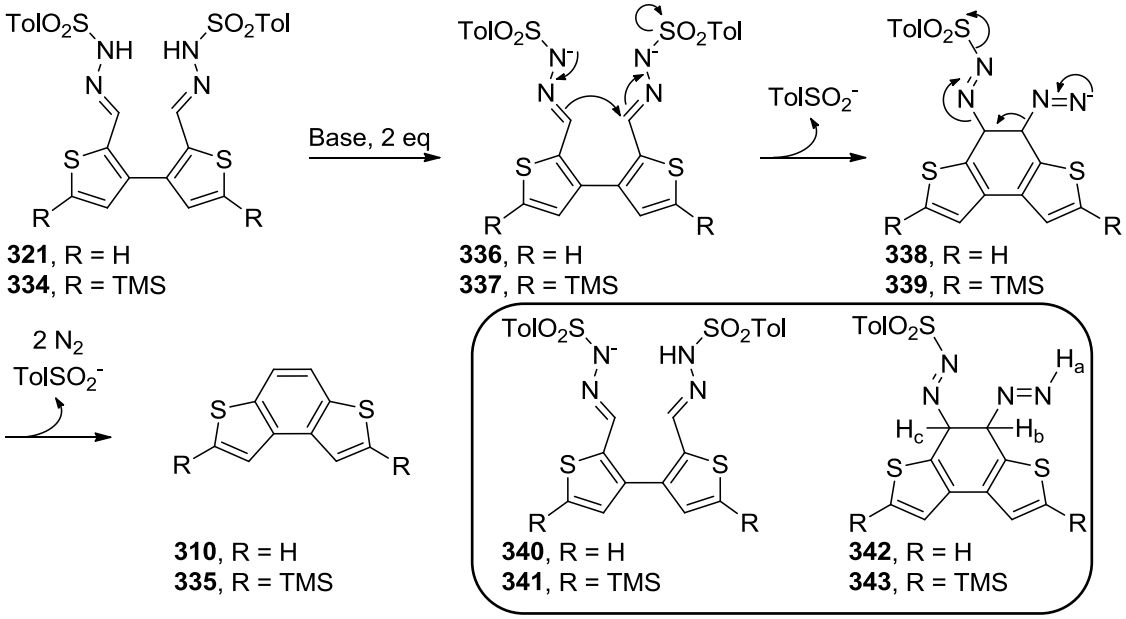
**310** (R = H)
**335** (R = TMS)

i) 1) $TsNHNH_2$ 2 eq, THF, RT, 2) $NaSO_4$; ii) R = H: NaH 2.5 eq, 0 °C then reflux 3 hrs, $N_2$, THF, 37%; R = TMS: *n*-BuLi 1.05 eq, -78 °C then reflux 5 hrs, $N_2$, THF, 32%

**Scheme 10: One pot synthesis of BDT derivatives from bis aldehyde**

The conditions used to form **BDT** resemble those for the Bamford–Stevens reaction,[29] but the use of *n*-BuLi in the preparation of di-TMS-**BDT** (**335**) is more typical of a Shapiro reaction.[30] Both the Bamford–Stevens and Shapiro procedures employ arylsulfonylhydrazones and are generally considered to begin by deprotonation of the NH-$SO_2Ar$,[31] and exploit the chemistry of arylsulfinate ($ArSO_2^-$) leaving groups, and the elimination of $N_2$ to provide a powerful driving force. Under aprotic conditions the Bamford–Stevens reaction is believed to proceed by formation of a carbene,[30c] but with the bis-hydrazones (**321** and **334**) shown in Scheme 10 it seems probable that the initial dianion (**336** and **337**) cyclises as shown in Scheme 11 by intramolecular nucleophile addition to the hydrazone and elimination of an arylsulfinate (**338** and **339**).[20a] Subsequent loss of two molecules of nitrogen and the second arylsulfinate (**340** and **341**) completes the benzo[1,2-b:4,3-b′]dithiophene ring (**310** and **335**).

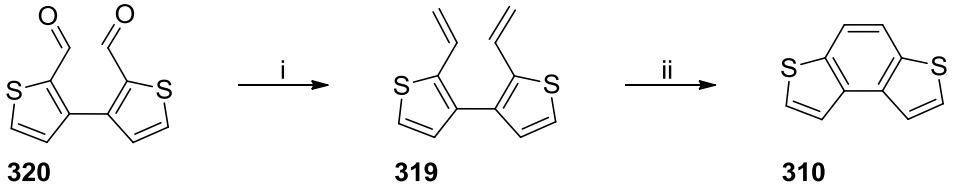
Alternatively we could suggest the formation of a monoanion intermediate (see Scheme 11, box, **340** and **341**) in the cyclisation reaction, when 1.05 equivalents of n-butyllithium is employed. However, it seems unlikely that the second deprotonation can be effected by the toluenesulfinate anion (pKa about 2), whether you deprotonate the diazene proton (Scheme 11, box, **342** and **343,** $H_a$) or one of the proton alpha to one of the -N=N- group (Scheme 11, box, **342** and **343,** $H_b$ or $H_c$). Considering that the formation of the desired **BDT** has only been observed when heating the reaction to reflux after the initial deprotonation step, perhaps the reaction proceeds through an electrocyclic reaction of the mono- or dianion (**342**, **343** or **336**, **337**).




**Scheme 11: Possible mechanism for the ring closing of bis-hydrazones under basic conditions**

iii) Alkene metathesis

The persistent difficulties with low yields that were encountered in the two previous routes, lead us to turn next to the usually efficient ring-closing metathesis (RCM) approach. From dialdehyde **320**, a simple Wittig reaction produced 2,2'-divinyl-3,3'-bithiophene (**319**) in 77% yield. This compound had to be used immediately for the next step as it is fully decomposed after a week (polymerisation), even when stored in the dark at –18 °C. The RCM step using the Iuliano conditions[19a] with the 1st generation Grubbs catalyst $Ru(PCy_3)_2(CHPh)Cl_2$ has been reported to give 100% yield in the preparation of phenanthrene in the divinylbiphenyl case. This does indeed appear to be a very efficient and general RCM method, and in our case we achieved 90% yield at a 5 mol % catalyst loading, which can be improved to 96% yield using the catalyst at 10 mol % (Scheme 12).

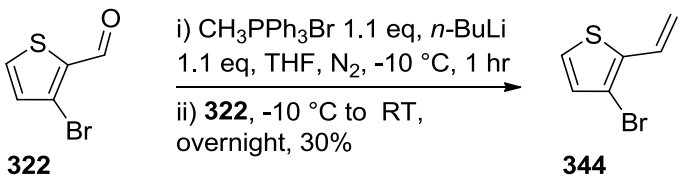



**320** **319** **310**

i) $CH_3PPh_3Br$ 2.2 eq, *n*-BuLi 2.2 eq, THF, $N_2$, -10 °C to RT overnight, 77%;
ii) DCM, $[Ru(Pcy_3)_2(CHPh)Cl_2]$, 0.1 eq, RT, 8 hrs, Ar, 96%.

**Scheme 12: Ring closing metathesis route.**

Also, since the highest yielding route to **BDT** (**310**) was achieved by the RCM reaction, we considered the possibility of coupling of 3-bromo-2-vinylthiophene (**344**) to make 2,2'-divinyl-3,3'-bithiophene (**319**) more directly from 3-bromothiophene (**323**) in just three steps. Wittig methylenation of **322**, however, proceeded in only 30% yield. It is possible that the ease of dimerisation and polymerisation of the reactive vinyl group in 3-bromo-2-vinylthiophene limits the efficiency of this reaction. Thus Ullmann coupling prior to Wittig methylenation is the better approach.




**322** **344**

**Scheme 13: Synthesis of 3-bromo-2-vinylthiophene**

d) Conclusion

In conclusion, we have shown that benzo[1,2-b:4,3-b']dithiophene (**310**) is accessible in 48% overall yield in 5 steps from 3-bromothiophene (**323**) by Ullmann coupling of the cyclohexylimine **324**, methylenation of dialdehyde **320** and ring-closing metathesis in a simple reaction sequence that avoids the use of photochemical conditions. Concerning the less costly alternatives, the bis-hydrazone route was found less effective affording **BDT** in only 24% yield for 4 steps whereas the McMurry route gave **BDT** in only 3% yield. However, the latter might be the route worthwhile improving by more careful use of reagents and slow addition of dialdehyde **320**. Also, in the context of atom economy, developing the low temperature Ullmann coupling of the hydrazone of 3-bromo-2-formylthiophene could ultimately provide a possible 'greener' improvement to the present route.

III) Tetrathia[7]helicene synthesis

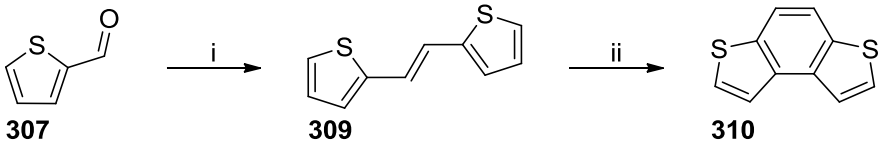
1) 7,8-Dipropyltetrathia[7]helicene (**8**)

7,8-Dipropyltetrathia[7]helicene was initially chosen because the synthesis has already been reported,[2] facilitating our access to helicene. Moreover, it has been published by a group friendly to ours, Licandro and Maiorana established in Milan, and funding was available in the grant supporting the project for a short study visit to their department to gain experience with the large scale photochemical procedure which uses a potentially hazardous 500 Watt UV lamp. An identical lamp and reaction vessel was purchased for use in Norwich. The Licandro and Maiorana approach to the synthesis of the tetrathia[7]helicenes is different to the one mentioned in earlier in the thesis. The overall synthesis includes two photochemical steps and the key intermediate is benzo[1,2-b:4,3-b']thiophene (**310**) for which we reported the chemical synthesis.[13]

a) BDT photochemical synthesis

The first step of the synthesis is an intermolecular McMurry coupling of 2-formylthiophene (**307**), simplifying previously reported Wittig reaction that requires the preparation of two different molecules. This first reaction afforded the *trans* alkene **309** in good 85% yield (a mixture of *cis* and *trans* **309** is observed in the crude NMR spectrum, however after recrystallization pure *trans* **309** is obtained). Photodehydrocyclisation of **309** gave desired **BDT** (**310**) in 83% yield after long UV irradiation of 35 hours. This method

for the synthesis of **BDT** compares well with the chemical synthesis giving the product in just two steps and 71% yield (Scheme 14), however it requires highly specialised equipment and is limited in scale as the photochemical reaction is performed preferably with a concentration below 10 mmol $L^{-1}$. Also when **BDT** (**310**) is isolated, even traces of starting material can have a negative effect on the following reaction if the batch is not used rapidly. Indeed, when the **BDT** obtained is not 100% pure, light seems to induce some decomposition (the white powder can become black after a few months) which will affect the next reaction.




**307** **309** **310**

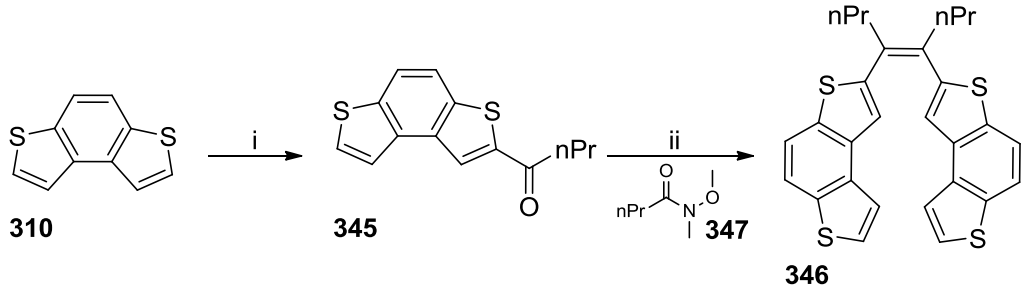
i) 1) $TiCl_4$ 1.2 eq, Zn 2.2 eq, THF, reflux 2 hrs, Ar; 2) Pyridine 1 eq, reflux 30 min; 3) **307** reflux 18 hrs, 85%, ii) hυ, PhMe, $I_2$ 0.05eq, Air, 35 hrs, 83%.

**Scheme 14: Photochemical synthesis of BDT**

b) 7,8-Dipropyltetrathia[7]helicene synthesis

i) McMurry

In principle, the most simple and archetypal substrate to develop our proposed new methodology would be the 'parent' unsubstituted tetrathia[7]helicene (**2**), which would be constructed from simple disubstituted alkenes. However, reports show that the disubstituted alkenes have a poor solubility in toluene (and even in benzene) due to pi-stacking phenomena.[2b] This problem can be overcome by the introduction of bulky groups on the thiophene rings (ideally TIPS groups) which helps to solubilise the alkene precursor for photocyclisation.[2b] Nonetheless, the introduction and removal of silyl groups adds an extra two steps; therefore the alternative of using tetrasubstituted alkenes was chosen. For this, BDT (**310**) is transformed into the corresponding propylketone **345** in good 75% yield by quenching lithio-**BDT** with propyl Weinreb amide **347**; the ketone was submitted to McMurry coupling conditions giving *cis*-tetrasubstituted alkene **346** in excellent 93% yield (Scheme 15).

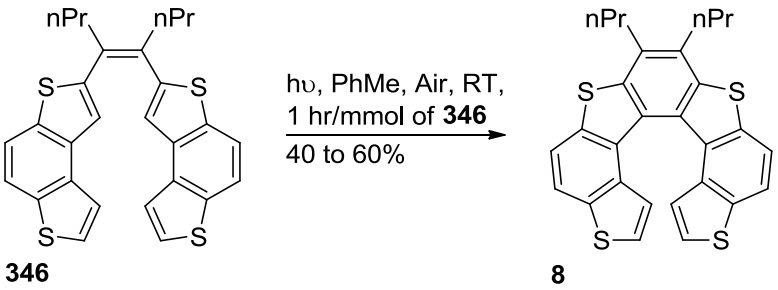



i) 1) *n*-BuLi, 1.1 eq, THF, -78 °C to 0 °C, 1 hr; 2) **347**, -78 °C, 30 min then RT 2.5 hrs, 75%, ii) $TiCl_4$ 1.3 eq, Zn 2.3 eq, THF, 0 °C then reflux, Ar, 3 hrs, 93%

**Scheme 15: Synthesis of tetrasubstituted alkene precursor for photocyclisation**

ii) Photodehydrocyclisation

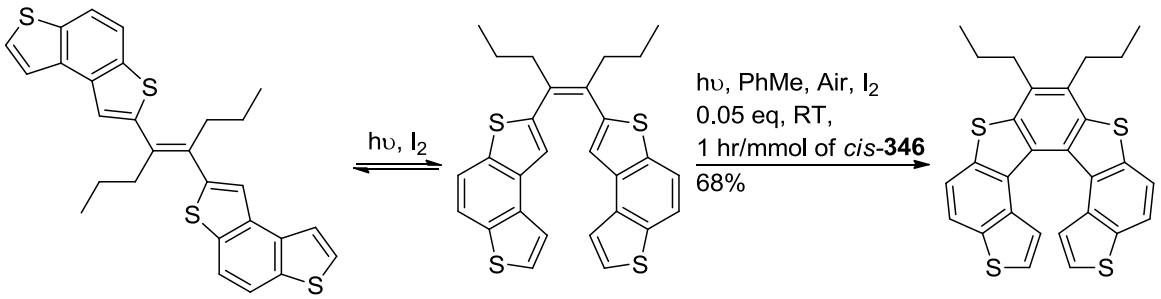
The synthesis is completed with the crucial photodehydrocyclisation step. In fact, there are two advantages of using tetrasubstituted alkene precursors (*i.e.* **346**), first their solubility is far greater than the solubility of disubstituted alkenes allowing for a faster reaction, and also the additional substituents cause the McMurry reaction to give mostly *cis*-alkenes which are in the right configuration for an easier cyclisation. Despite these advantages, one issue can still affect the final yield: the presence of *trans*-alkene (*trans*-**346**). Indeed, some *trans*-**346** (about 7%) is also formed in the McMurry reaction and it is crucial to try to remove as much of it as possible because in the reaction conditions used for the final step, the *trans*-alkene does not have time to be fully isomerised to *cis*. This would not be a problem if it could easily be separated from helicene, however both silica gel chromatography and recrystallization failed to give efficient separation. With this information in mind, our preferred method is now to separate the *cis* and *trans*-alkenes and use only the *cis* isomer in the photcyclisation, which proceeds so rapidly that the far slower *cis* to *trans* photoisomerisation does not produce a noticeable amount of the unwanted *trans* alkene in the helicene product.




**Scheme 16: Maiorana's condition for photocyclisation**

The cyclisation reaction was then performed using Maiorana's conditions[2] giving helicene **8** in decent 40 to 60% yield (Scheme 16), however, despite several attempts (with concentrations as low as $5 \times 10^{-4}$ M and up to $1 \times 10^{-2}$ M) results could not match the 68% reported.

We suspected that helicene **8** was not so stable in the reaction conditions and that once reaching a high conversion the kinetics were more favourable for a destruction of **8** than for ring closing of remaining *cis*-alkene **346**; so if prolonged reaction times were used to attempt to achieve a higher conversion the result would be that the yield would start dropping towards the end of the reaction. Also, Maiorana[2] reports that the cyclisation is just as efficient when using a less powerful UV lamp (*i.e.* 125W UV lamp successfully cyclises a solution of $2.56 \times 10^{-3}$ M *cis*-alkene) indicating that the higher energy is not required. We addressed this situation by adding a catalytic amount of iodine which might shield some of the UV energy. Also, it was anticipated that the addition of iodine would facilitate the *trans*/*cis* isomerisation and therefore might allow the cyclisation of remaining traces of *trans*-alkene making the purification of helicene product easier. Agreeably, the reaction performed in those conditions gave reproducible results with yields reaching 68% and averaging 65%; also traces (when less than 2-3% of *trans*-**346** is present in cis-**346** SM) of *trans*-alkene **346** were no more present in the helicene obtained (Scheme 17). Overall, 7,8-dipropyltetrathia[7]helicene (**8**) is obtained in 33% over 5 steps.




**Scheme 17: Improved method for photocyclisation reaction**

One might argue that the *cis/trans* equilibrium should be in favour of the more thermodynamically stable *trans* product, therefore the composition of the *cis/trans* mixture should not matter to obtain cyclisations with no remaining *trans*-alkene. However experiments showed no sign of this, indeed, when pure *cis*-alkene is submitted to the cyclisation conditions (catalytic iodine, Air, hυ) pure helicene is obtained, whereas in the same conditions pure *trans*-alkene gives a mixture of helicene and starting material. This

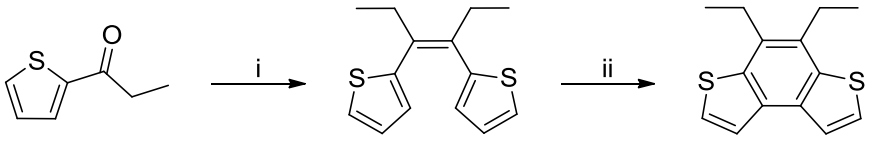
proves that the equilibrium between *cis* and *trans*-alkene is much slower than the actual photodehydrocyclisation otherwise *trans*-alkene would also be obtained in the experiment using pure *cis*-alkene. This might also explain why traces of *trans*-alkene (up to 1 or 2%) are fully transformed in those conditions whereas larger amounts (the McMurry reaction produces roughly 7% of *trans*-alkene) are not.

2) Hexasubstituted tetrathia[7]helicenes

I suggested earlier in this chapter that the difficulties encountered with the photocyclisation steps were mostly caused by the usage of *trans*-alkene. Knowing that the McMurry reaction of 2-ketylthiophenes gives the *cis*-alkene as the major product, it seemed advantagous to build helicenes using this feature. In order not to complicate the assignment of NMR signals it was decided to build helicenes bearing the same substitutent at all the positions around the core which gives hexaalkyltetrathia[7]helicenes.

a) 4,5,7,8,10,11-Hexaethyltetrathia[7]helicene (**360**)

We applied this strategy using 2-propionylthiophene (**348**); the McMurry coupling gave *cis*-alkene **349** in isolated 43% yield (a small quantity of *trans*-alkene was separated). This product was readily cyclised giving diethyl-**BDT 350** in 69% yield (Scheme 18). The low yield of the first reaction is due to experimental errors and could easily be improved to the usual standards of the McMurry reaction (*i.e.* about 75% yield).

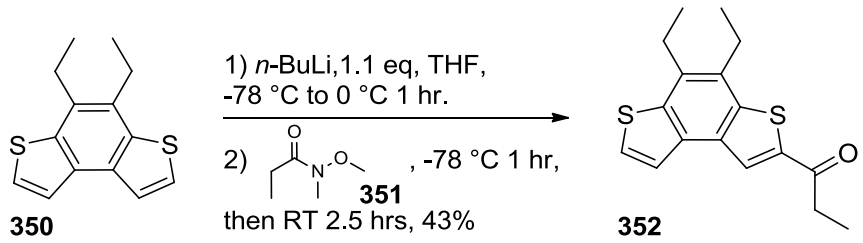



**348** **349** **350**

i) 1) $TiCl_4$ 1.3 eq, Zn 2.3 eq, THF, 0 °C then reflux 5 hrs, Ar, 43%;
ii) hυ, PhMe, $I_2$ 0.05 eq, Air, 6 hrs, 69%.

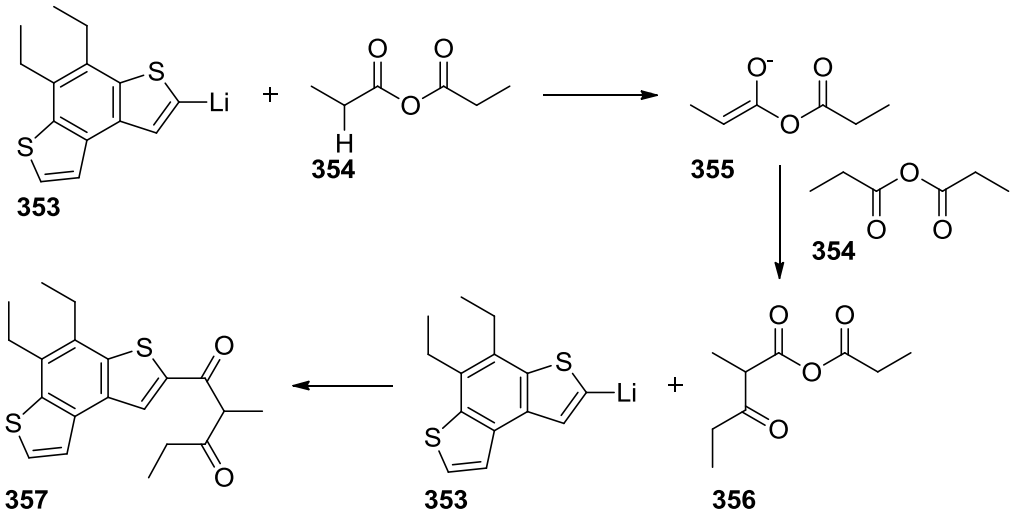
**Scheme 18: Synthesis of dipropyl-BDT 350**

Diethyl-**BDT 350** was treated with *n*-BuLi and subsequent quench with ethyl Weinreb amide **351** gave ethyl ketone **352** in 43% yield and 19% recovered starting material. The low yield obtained was explained by possible decomposition of diethyl-**BDT 350** (in the same fashion as the parent **BDT 310**) which would account for the almost 40% missing material (Scheme 19).



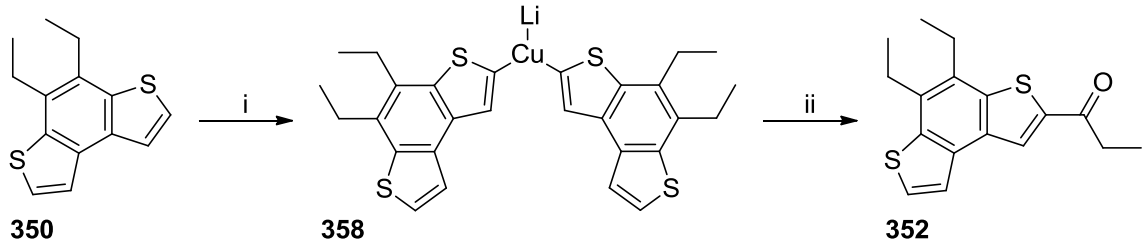

**Scheme 19: Synthesis of ketone 352**

Also, it seems relevant to say that reacting lithiated diethyl-**BDT 353** with commercially available propionic anhydride (**354**) was not successful, giving an unidentified mixture of products. This was quite likely due to deprotonation of propionic anhydride by the lithiated diethyl-**BDT** to produce enolate **355** which would undergo a condensation reaction with another molecule of propionic anhydride. The condensation product **356** could then either undergo further condensation reactions, or react with lithiated diethyl-**BDT** (**357**, Scheme 20). There is some evidence for such compounds from the presence of doublets in the 1-2 ppm region of the crude $^{1}$H NMR spectrum, characteristic of $CH_3$-$CHR_2$ groups.




**Scheme 20: Rationale for failed reaction using propionic anhydride**

An alternative reaction was attempted using propionic anhydride; the lithiated diethyl-**BDT 353** was converted into the Gilman cuprate **358** using CuI. Subsequent quench with propionic anhydride gave desired ketone **352** in 40% yield but no starting material was recovered (Scheme 21).

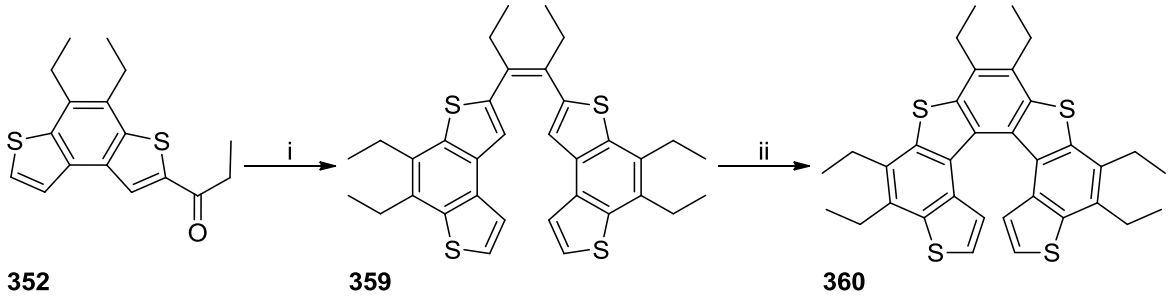



**350** **358** **352**

i) 1) *n*-BuLi,1.1 eq, THF, -78 °C to 0 °C, 1 hr; 2) CuI 0.5 eq, -78 °C then -60 °C, 2 hrs; ii) propionic anhydride, 1.5 eq, -60 °C, then warm up to -20 °C over 2 hrs, 40%

**Scheme 21: Synthesis of ketone 352 via a Gilman cuprate reagent 358**

The synthesis was completed with usual McMurry coupling and photocyclisation, affording 4,5,7,8,10,11-hexaethyltetrathia[7]helicene (**360**) in 34% over two steps (Scheme 22) but in a disappointing 4.4% over 5 steps.



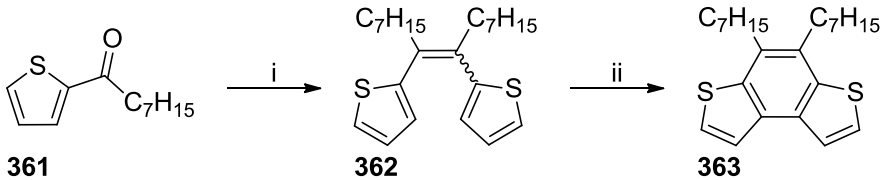

**352** **359** **360**

i) $TiCl_4$ 1.3 eq, Zn 2.3 eq, THF, 0 °C then reflux, Ar, 3 hrs, 51%; ii) hυ, PhMe, Air, $I_2$ 0.05eq, RT, 1 hr/mmol of **359**, 68%.

**Scheme 22: Synthesis of 4,5,7,8,10,11-hexaethyltetrathia[7]helicene (360)**

b) 4,5,7,8,10,11-Hexahepthyltetrathia[7]helicenes (**368**)

Using the same reaction sequence as for the previous helicene, we synthesised 4,5,7,8,10,11-hexahepthyltetrathia[7]helicene. Starting with 2-octanoylthiophene (**361**), McMurry coupling gave the alkene **362** in 76% yield as a mixture of *cis* and *trans* isomers (85/15). In this case, we found that the mixture of *cis* and *trans*-alkenes could be used conveniently in the photodehydrocyclisation, giving pure dihepthyl-**BDT 363** in 86% yield (Scheme 18).

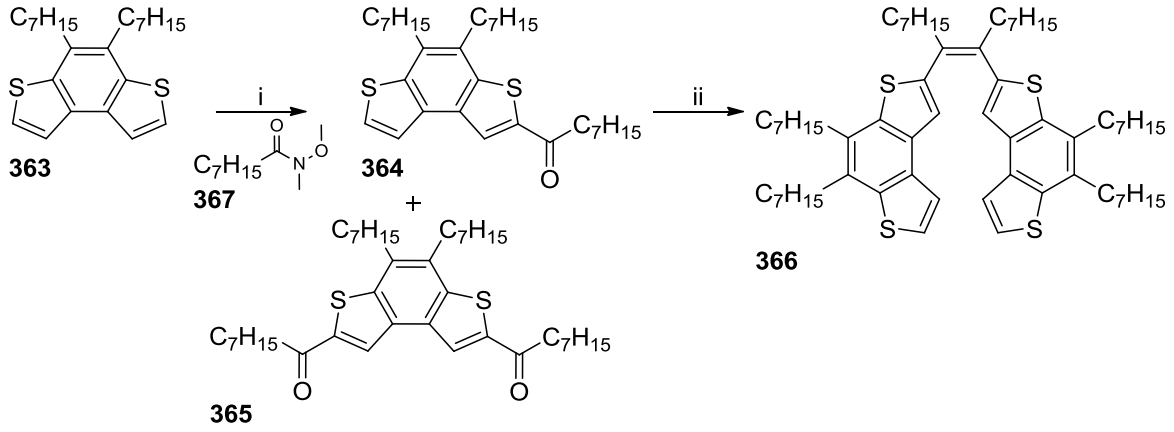



**361** **362** **363**

i) 1) $TiCl_4$ 1.3 eq, Zn 2.3 eq, THF, 0 °C then reflux 3 hrs, Ar, 76%,
ii) hυ, PhMe, $I_2$ 0.05 eq, Air, 5 hrs, 86%.

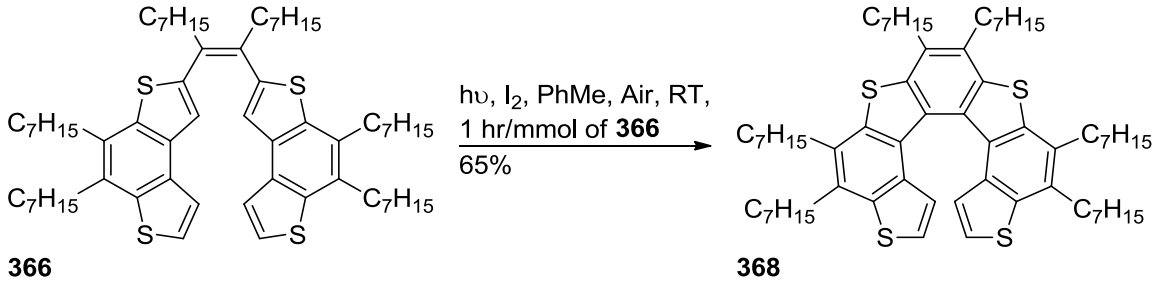
**Scheme 23: Synthesis of dihepthyl-BDT 363**

Dihepthyl-**BDT 363** was treated with *n*-BuLi and subsequent quench with hepthyl Weinreb amide **367** to give the heptyl ketone **364** in 77% yield. Some bis ketone **365** was also formed in this reaction which turned out to be hard to separate despite repeated chromatographic efforts. It was decided to perform the next step without completely separating mono and bis ketones (12% of bis ketone **365**), but unfortunately several by-products were formed and the difficultly of the subsequent separation limited the yield of the McMurry coupling to 38% (Scheme 24).




**Scheme 24: Synthesis of dihepthylalkene 366**

The synthesis was now completed with usual photocyclisation, affording 4,5,7,8,10,11-hexahepthyltetrathia[7]helicene **368** in 65% yield (Scheme 25) and 12.4% over 5 steps.




**Scheme 25: Synthesis of 4,5,7,8,10,11-hexahepthyltetrathia[7]helicene 368**

IV) Conclusion

Herein are reported the syntheses of three different tetrathia[7]helicene. 7,8-dipropyltetrathia[7]helicene (**8**) has been synthesised by two different routes which intersect at a common **BDT** (**310**) intermediate. The standard route follows Licandro and

Maiorana's work[2] using two photodehydrocyclisation steps and gave helicene **8** in 33% over five steps. For the alternative route, we developed[13] a fully chemical synthesis of the **BDT (310)** intermediate, obtained in 48% over five steps. Overall, helicene **8** is obtained in 23% yield over 8 steps.

For the synthesis of 4,5,7,8,10,11-hexaethyltetrathia[7]helicene **360** and 4,5,7,8,10,11-hexaethyltetrathia[7]helicene **368**, Licandro and Maiorana's method was adapted, **360** and **368** were respectively obtained in 4.4% and 12.4% yield over five steps. The yields obtained for these hexasubstituted helicenes are low in comparison with the 33% yield obtained for **8**. However, this can be easily explained, 7,8-dipropyltetrethia[7]helicene (**8**) being at the core of the project, every single step has been finely tuned from several runs, whereas yields obtained for helicenes **360** and **368** are unoptimised and could be easily improved if needed, by simple repetition of the reaction sequence. In addition we can also comment that the scale of the reaction sequence is only limited by the photochemical steps that can be carried out up to 5 g per batch, giving an easy access to large quantities of helicenes.

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# Chapter 2:
# Synthesis of chiral auxiliaries for the KR of tetrathia[7]helicenes

## I) Introduction

This chapter will describe the synthesis of chiral reagents used for the kinetic resolution of tetrathia[7]helicenes. As presented in the introduction, the products of the kinetic resolution should be suitable targets to be easily transformed into push-pull systems. For this, we are interested in preparing enantiomerically pure 2-formyl- and 2,13-diformyl-thiahelicenes which would be good intermediates for the synthesis of chiral push-pull systems. Therefore, it was necessary to develop methods that could achieve that, and two main strategies could be identified. In the first, asymmetric lithiation with a chiral auxiliary like (–)-sparteine or other chiral diamines followed by quench with a conventional achiral formyl donor like DMF or *N*-formylpiperidine seemed to be a good approach which is well precedented in the many chiral-diamine-mediated asymmetric transformations in the literature. On the other end, direct asymmetric formylation of aromatic systems was clearly an unexplored area, where the identification of a new strategy was necessary to design efficient chiral formylating compounds.

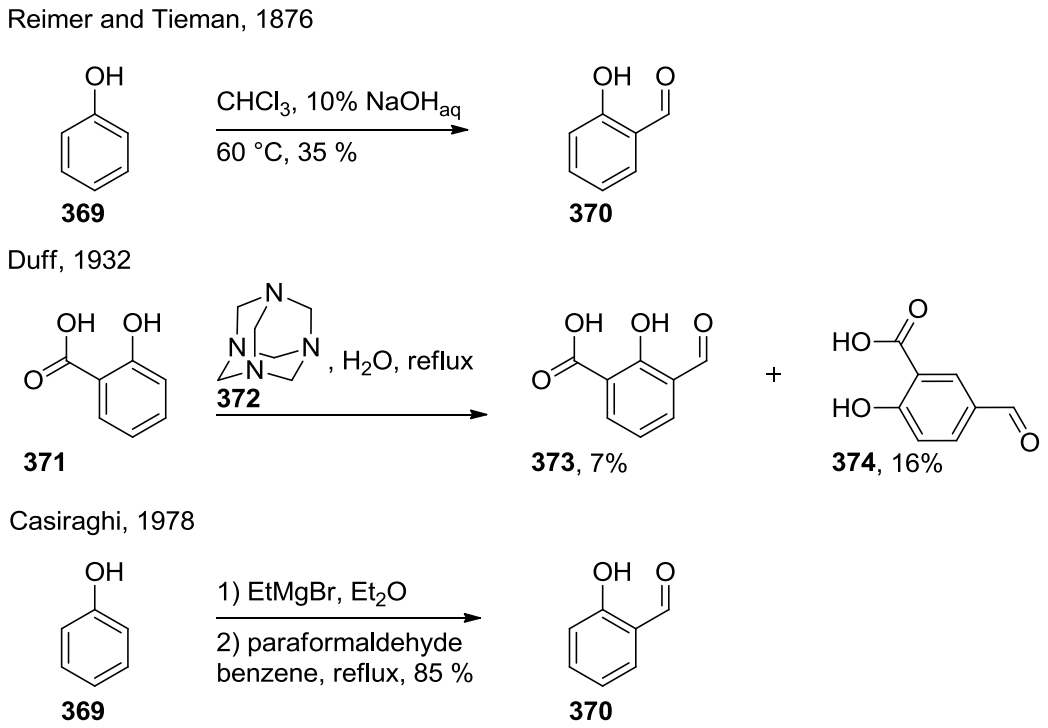
## II) Synthesis of chiral formamides

### 1) Formylation of aromatic substrates: generalities

Many procedures are available to introduce an aldehyde group onto aromatic structures based on two distinct strategies: electrophilic aromatic substitution reactions (Vilsmeier-Haack,[1] Reimer-Tieman,[2] Duff,[3] Casiraghi,[4] Gattermann-Koch[5] and Gattermann aldehyde synthesis[6], Rieche formylation,[7] Friedel Craft equivalent with formic acid derivatives), nucleophilic reactions with formyl donors such as DMF or *N*-formylpiperidine.

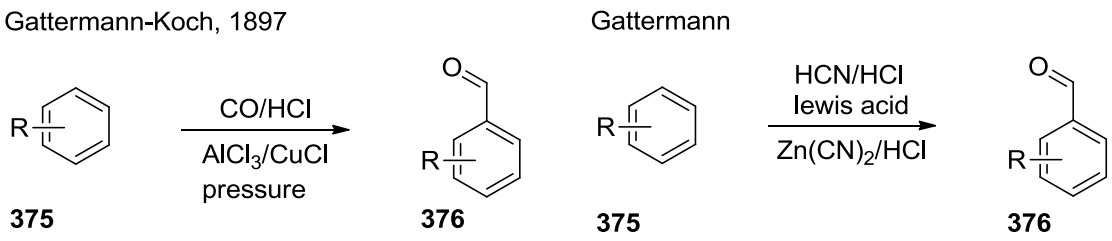
#### a) Electrophilic aromatic substitution ($S_EAr$)

Of the available methods (see above) some are very substrate-dependent and would not be suitable for our purpose. This is the case for the Reimer-Tieman, Duff and Casiraghi reactions that work with phenolic substrates which direct the formylation in ortho or para positions (Scheme 1).




**Scheme 1: Formylation of phenolic systems**

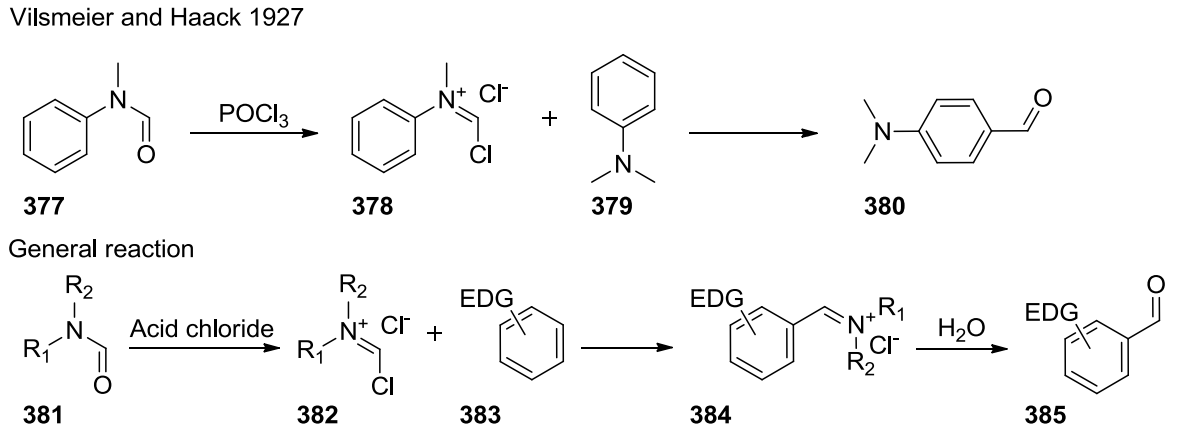
There are other methods of electrophilic aromatic substitution where the formic acid derivatives that were originally used have been replaced by alternative reagents improving the feasibility of the reaction. Indeed, the Gattermann Koch reaction reported in 1897 uses a CO/HCl mixture with CuCl (*in situ* formation of formyl chloride) in Friedel-Crafts conditions to introduce the aldehyde onto an aromatic ring. The Gattermann reaction when initially performed with an HCN/HCl mixture, requires conditions that are far too harsh for our purpose, but the Adams modification that uses of $Zn(CN)_2$/HCl instead (Scheme 2) should be more suitable.[6]




**Scheme 2: Gattermann-Koch and Gattermann formylation**

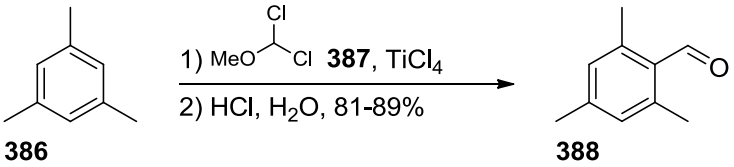
Among all formylation techniques, the Vilsmeier-Haack formylation reported in 1927 is one of the most famous ones. The electrophile of this reaction, the Vilsmeier reagent

chloromethyliminium salt (**378** or **382**) can be prepared in situ from any *N*,*N*-disubstituted formamide by reacting it with an acid chloride, generally $POCl_3$, $SOCl_2$, oxalyl chloride. The electrophilic aromatic substitution gives an iminium salt that is hydrolysed producing the desired aldehyde (Scheme 3).




**Scheme 3: Vilsmeier-Haack formylation**

The Rieche formylation reported in 1960 uses dichloromethyl methyl ether (**388**) as electrophile activated by $TiCl_4$, followed by an acidic work up giving the desired aromatic aldehydes (Scheme 4).




**Scheme 4: The Rieche formylation**

Since then, several different electrophiles have been developed to perform electrophilic aromatic substitutions under more friendly conditions.[8] Indeed, triformamide (**389**), tris(diformylamino)methane (**390**), *N*,*N*,*N*',*N*'-tetraformylhydrazine (**391**), tris(dichloromethyl)amine (**392**) have proved to be very efficient electrophiles, affording a large variety of aromatic aldehydes in good yields.

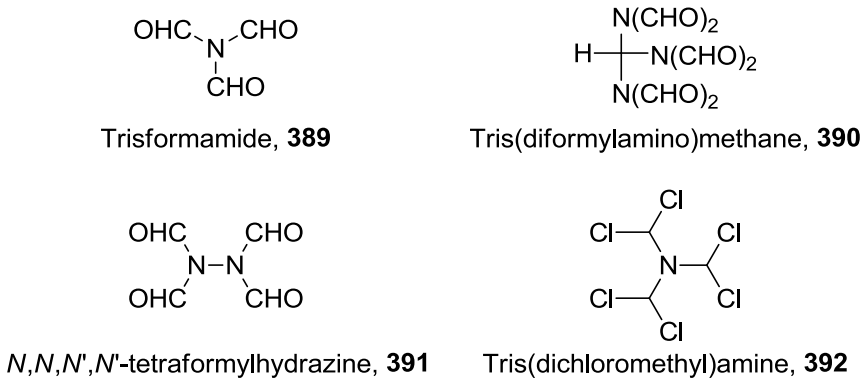
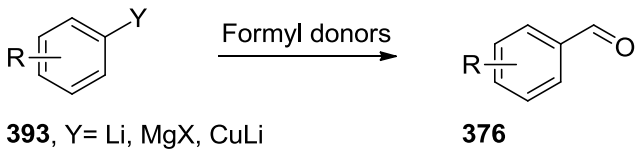



**Figure 1: Efficient electrophiles for $S_EAr$**

b) Nucleophilic additions

The other alternative in general use is the nucleophilic addition of aryllithium, arylcuprates or aryl grignard reagents (**393**) onto formyl donors like DMF or *N*-formylpiperidine (Scheme 5). This strategy is particularly interesting when metallation of the aromatic moiety is selective to one position which is the case, for example, with aryl halides and several heterocycles.




**Scheme 5: Nucleophilic addition of metallated aryls on formyl donors**

2) Asymmetric formylation

Asymmetric formylation of olefins largely relies on hydroformylation, where a wide range of catalysts and ligands can provide enantioenriched aliphatic aldehydes.[9] Asymmetric formylation of aromatic substrates could seem pointless as you cannot directly introduce any chirality on an aromatic ring. For this reason asymmetric formylation of aryl has not been studied, even though three classes of specialised aromatic compounds could be interesting substrates: biaryl structures (axial chirality), paracyclophanes and metallocenes (planar chirality), and helicenes (axial chirality).

For the asymmetric synthesis of formylhelicenes, very few of the reactions presented in the first part of this chapter can be transposed in an asymmetric manner, namely Vilsmeier-Haack and the reaction of metallated aryls with formyl donors. Of those, the latter seems

the more attractive especially as thiahelicenes are selectively lithiated at the position adjacent to the sulfur. Also, this method and the Vilsmeier-Haack reaction have in common the use of formamides, therefore the chiral reagents used for the asymmetric version of one reaction could also be used for the other. Thus, our approach to transform these reactions into asymmetric ones was the synthesis of chiral formamides, that would be used in the kinetic resolution of tetrathia[7]helicenes.

3) Synthesis of chiral formamides

a) Chiral secondary amines

i) Commercially available secondary amines

Our starting point was to use or synthesise chiral secondary amines and to introduce the formyl group onto the nitrogen via one of the reported methods.[16,17,18] Conveniently, a range of chiral secondary amines is commercially available (Figure 2) in enantiopure form.

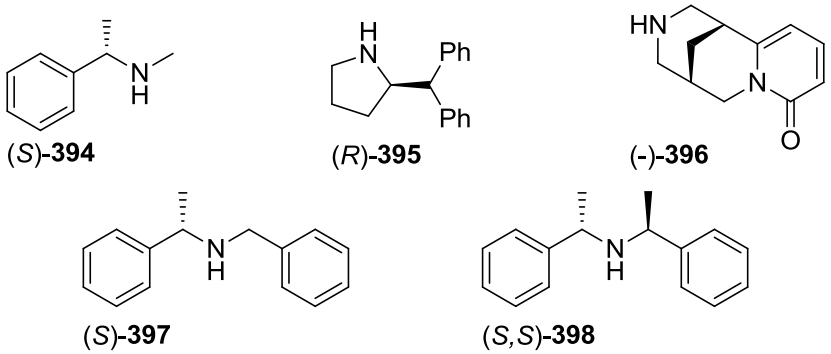
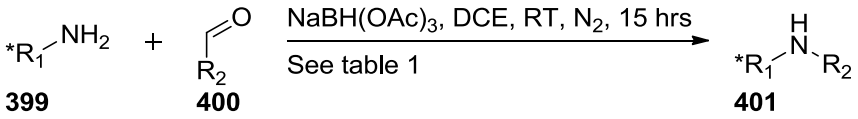



**Figure 2: A few relevant commercially available secondary amines**

ii) Reductive amination

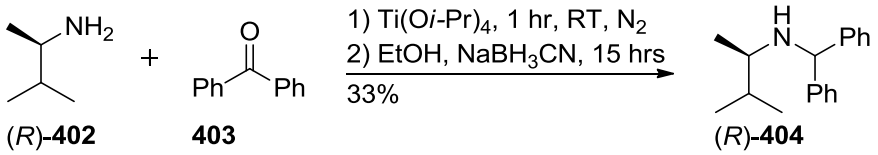
Although, several chiral secondary amines are available, it was decided to access a wider range of structures by simple reductive amination of aldehydes or ketones with chiral primary amines (**399**). Methods for reductive amination have largely been described, therefore allowing the synthesis of chemically varied examples.[10] For the reductive amination of aldehydes (**400**), a single and widely applicable method has been chosen for all the target structures. For this, the amine, an aldehyde and sodium triacetoxyborohydride are stirred at room temperature in 1,2-dichloroethane (DCE) (Scheme 6); results are reported in Table 1. This is a nice and mild method where the borohydride reagent reduces the imine in situ, driving the equilibrium toward the formation of product (**401**). It should

be added that starting materials (amine and aldehydes) were directly used in the state that they were kept with no further purification, which sometime has altered the yields of the reductive amination step.

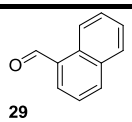
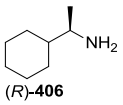
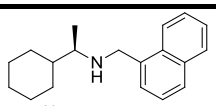
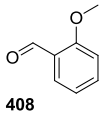
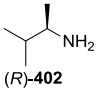
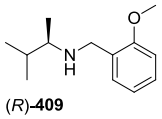


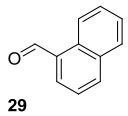
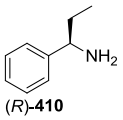
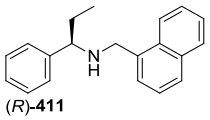
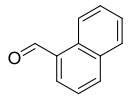
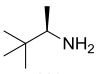
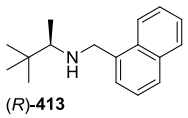
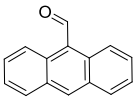
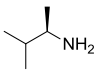
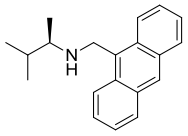
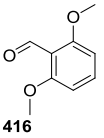
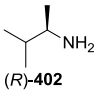
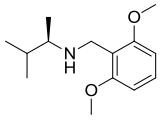
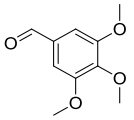
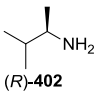
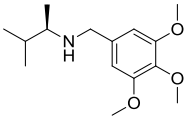
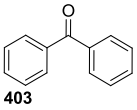
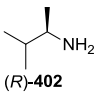
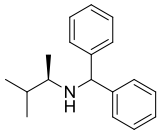
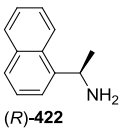
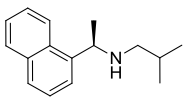

**Scheme 6: Reductive amination of aldehydes**

The reductive amination of aryl ketones is known to be more difficult because the imine is not readily formed for steric and electronic reasons. Using benzophenone, the same conditions used for aldehydes were tried and unsurprisingly, no product was observed. Harsher conditions had to be used.[11] We found that using a stepwise procedure, where first amine and ketone are mixed in neat titanium(IV) isopropoxide to produce an intermediate that was then reduced with sodium cyanoborohydride in ethanol, gave the desired product in a low but acceptable 33% yield. It should be noted that Mattson *et al.*[11] have reported that the intermediate formed in the first step is in fact a carbinol rather than an iminium ion. The reductive amination of dibenzosuberone was also attempted using this same method, but no secondary amine product was observed.




**Scheme 7: Reductive amination of benzophenone**

| Entry | Aldehyde | amine | Yield | Amine |
|---|---|---|---|---|
| 1 |  **29** |  (*R*)-**406** | 71 |  (*R*)-**407** |
| 2 |  **408** |  (*R*)-**402** | 50 |  (*R*)-**409** |

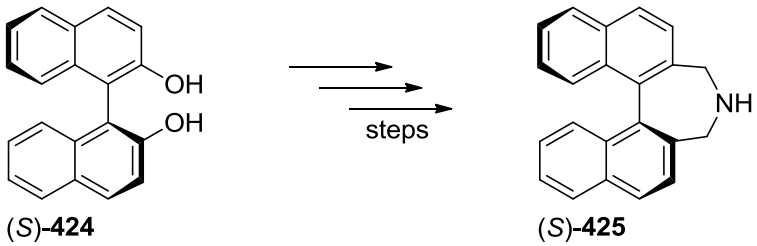
| | | | | |
|---|---|---|---|---|
| 3 |  **29** |  (*R*)-**410** | 63 |  (*R*)-**411** |
| 4 |  **29** |  (*R*)-**412** | 77 |  (*R*)-**413** |
| 5 |  **414** |  (*R*)-**402** | 75[a] |  (*R*)-**415** |
| 6 |  **416** |  (*R*)-**402** | 45 |  (*R*)-**417** |
| 7 |  **418** |  (*R*)-**402** | 52 |  (*R*)-**419** |
| 8 |  **403** |  (*R*)-**402** | 33 |  (*R*)-**420** |
| 9 |  **421** |  (*R*)-**422** | 25[b] |  (*R*)-**423** |

[a] 95% pure product, difficulties to remove impurity; [b] impurities in naphthylamine.

**Table 1: Results of reductive aminations**

iii) Other amines

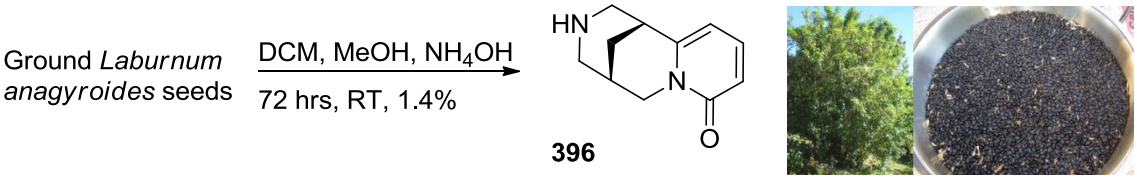
More specialised amines were also chosen for study. An amine presenting a binaphtyl core [(*S*)-**425**, Scheme 8] has been synthesised at the UEA by the Page group[12] and was made available to us.




(*S*)-**424** (*S*)-**425**

**Scheme 8: Chiral azepine (*S*)-425**

Another convenient possibility, because it is an intermediate to the widely used '(+)-sparteine surrogate' (see Chapter III) is the natural product (–)-cytisine (**396**), which although commercially available, is expensive, but is easily extracted from cytisus seeds (*Laburnum anagyroides*) according to the reported procedure.[13] Seeds were directly collected from a tree in the garden of my parents, powdered, and stirred in a DCM/MeOH/$NH_4OH$ mixture for 72 hours. After acidic aqueous extraction, the aqueous layer was basified and extracted with DCM. The crude product was then recrystallized from acetone yielding (–)-cytisine (**396**) in 1.4% of the initial mass (Scheme 9).




**Scheme 9: Extraction of (–)-cytisine**

b) Synthesis of chiral formamides

i) Reported methods

Some chiral formamides have already been reported (Figure 3),[14] although they have not been used for asymmetric formylation.

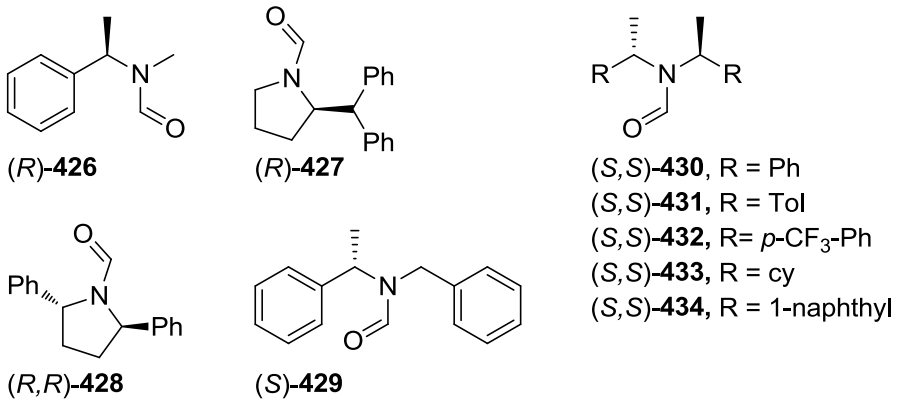


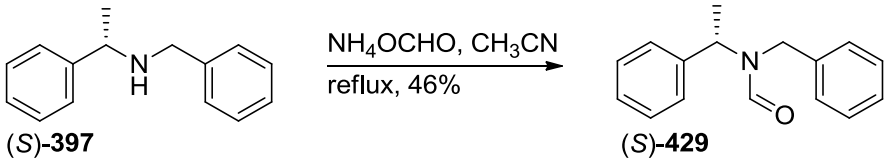

**Figure 3: Some previously reported chiral formamides**

These reported formamides have all been obtained from the corresponding secondary amines. Several methods have been reported in the literature for the *N*-formylation of amines, the most common one being the use of acetic formic anhydride.[15] Other methods using formamide/NaOMe,[14a] ammonium formate in refluxing acetonitrile,[14c] formic acid in

toluene with Dean Stark apparatus,[16] or even formic acid and acetic anhydride to form in-situ acetic formic anhydride[17] have been described.

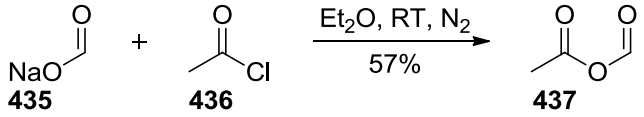
ii) Results

For our first attempt, commercially available (*R*)-**397** and ammonium formate were refluxed in acetonitrile and gave formamide (*R*)-**429** in 46% yield (Table 2, Entry 1). The same reaction was tried on amine (*R*,*R*)-**398**, but no product was observed.



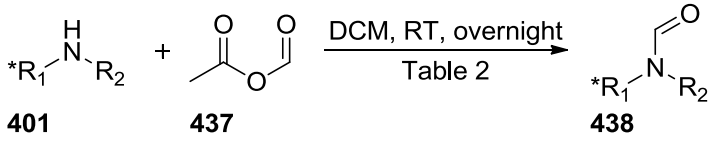

**Scheme 10: *N*-formylation of (*R*)-397 using ammonium formate**

It was then decided to use acetic formic anhydride, and although in some methods it is generated *in situ*, it was decided to synthesise acetic formic anhydride (**437**) according to the Krimen preparation (Scheme 11)[15] where acetyl chloride is added to a diethyl ether suspension of sodium formate while keeping the temperature below 27 °C. After 5.5 hours the solution is filtered and solvent is removed under reduced pressure, and acetic formic anhydride is distilled under reduced pressure, at low temperature.




**Scheme 11: Synthesis of acetic formic anhydride**

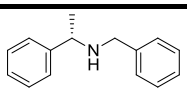
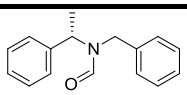
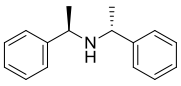
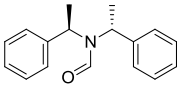
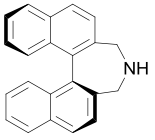
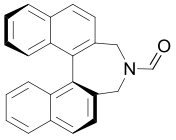
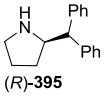
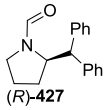
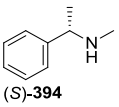
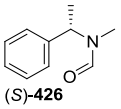
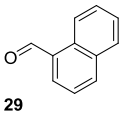
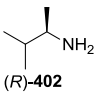
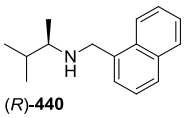
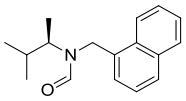
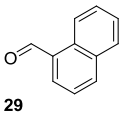
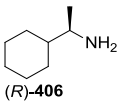
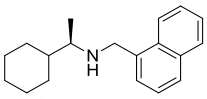
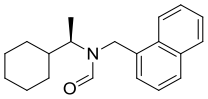
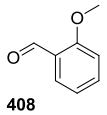
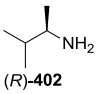
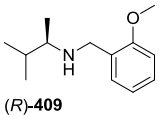
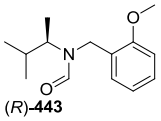
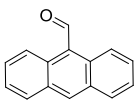
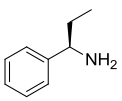
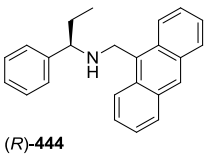
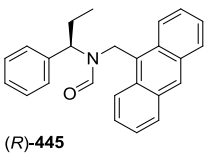
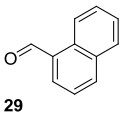
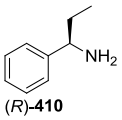
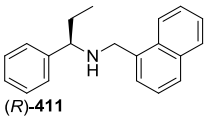
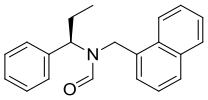
With the acetic formic anhydride now available on a substantial scale, we turned to the preparation of the chiral formamides, which were obtained in excellent yields from both the commercially available and synthesised chiral secondary amines by simple treatment with formic acetic anhydride, at room temperature in DCM (Scheme 12, Table 2).




**Scheme 12: Synthesis of chiral formamides**

iii) Comments on the synthesis of chiral formamides

In cases where the crude material obtained from the reductive amination seemed clean enough, the amine was not isolated, and the *N*-formylation was performed directly on the crude material.

| Entry | Aldehyde | amine | Yield (%) of **401** | Amine | Yield (%) of **438** | Formamide |
|---|---|---|---|---|---|---|
| 1 | | | |  (*S*)-**397** | 46[a] |  (*S*)-**429** |
| 2 | | | |  (*R*,*R*)-**398** | 100 |  (*R*,*R*)-**398** |
| 3 | | | |  (*S*)-**425** | 99 |  (*S*)-**439** |
| 4 | | | |  (*R*)-**395** | 90 |  (*R*)-**427** |
| 5 | | | |  (*S*)-**394** | 89 |  (*S*)-**426** |
| 6 |  **29** |  (*R*)-**402** | - |  (*R*)-**440** | 73[e] |  (*R*)-**441** |
| 7 |  **29** |  (*R*)-**406** | 71 |  (*R*)-**407** | 77 |  (*R*)-**442** |
| 8 |  **408** |  (*R*)-**402** | 50 |  (*R*)-**409** | 77 |  (*R*)-**443** |
| 9 |  **414** |  (*R*)-**410** | -[b] |  (*R*)-**444** | 26[b,e] |  (*R*)-**445** |
| 10 |  **29** |  (*R*)-**410** | 63 |  (*R*)-**411** | 79 |  (*R*)-**446** |

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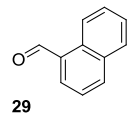
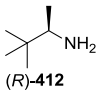
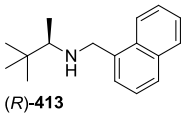
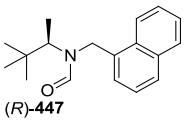
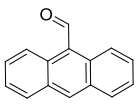
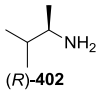
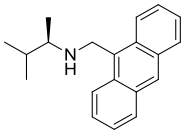
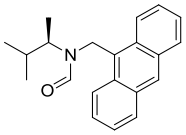
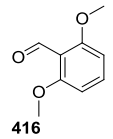
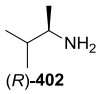
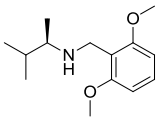
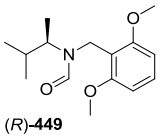
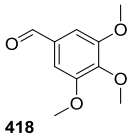
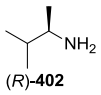
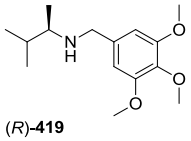
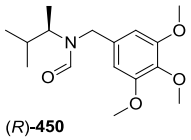
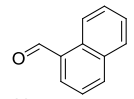
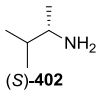
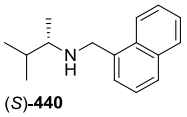
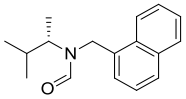
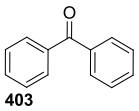
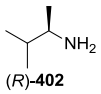
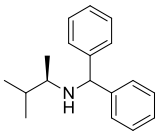
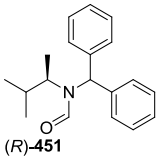
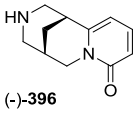
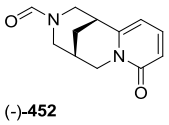
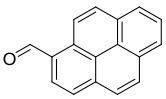
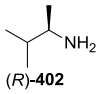
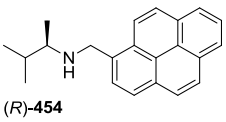
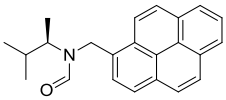
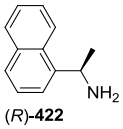
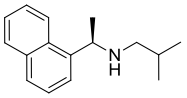
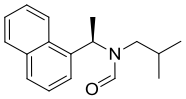
|---|---|---|---|---|---|---|
| 11 |  **29** |  (*R*)-**412** | 77 |  (*R*)-**413** | 63 |  (*R*)-**447** |
| 12 |  **414** |  (*R*)-**402** | 75[c] |  (*R*)-**415** | 99[d] |  (*R*)-**448** |
| 13 |  **416** |  (*R*)-**402** | 45 |  (*R*)-**417** | 71 |  (*R*)-**449** |
| 14 |  **418** |  (*R*)-**402** | 52 |  (*R*)-**419** | 100 |  (*R*)-**450** |
| 15 |  **29** |  (*S*)-**402** | - |  (*S*)-**440** | 65[e] |  (*S*)-**441** |
| 16 |  **403** |  (*R*)-**402** | 33 |  (*R*)-**420** | 89 |  (*R*)-**451** |
| 17 | - | - | - |  (-)-**396** | 79 |  (-)-**452** |
| 18 |  **453** |  (*R*)-**402** | - |  (*R*)-**454** | 55[e] |  (*R*)-**455** |
| 19 |  **421** |  (*R*)-**422** | 25[f] |  (*R*)-**423** | 74 |  (*R*)-**456** |

[a] formylation of amine using ammonium formate [b] good conversion to the amine but difficulties to purify so used semi-crude material for formylation step; [c] impure amine; [d] from pure amine; [e] over two steps (amine not isolated); [f] naphthylamine impure lower yield.

**Table 2: Synthesis of chiral secondary amines and chiral formamides**

An important advantage of using non-commercial starting materials for this part of the project is that a range of carefully selected chiral formamides could be built up during their

use in the kinetic resolution experiments. The rationale for their design will be discussed later in the kinetic resolution chapter (Chapter 3).

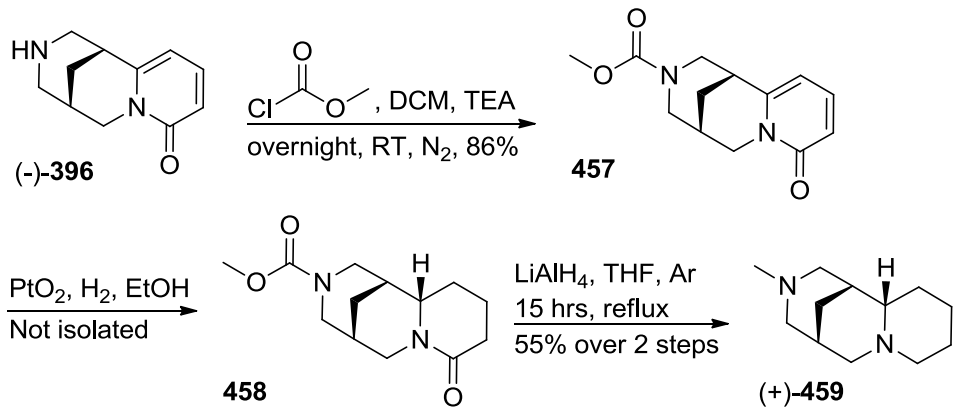
III) Synthesis of chiral diamines

1) Generalities

Asymmetric lithiation largely relies on chiral auxiliaries that generally are chiral diamines,[18] and amongst them (–)-sparteine is definitely the leader. This alkaloid occurs naturally in the (–)-enantiomer form, but although there is an alternative synthesis of the (+)-enantiomer,[19] it requires a huge amount of work and resources. (–)-Sparteine is available to us in quantities large enough to fulfil the project aims, however, for reasons relevant to the kinetic resolutions we became interested in the (+)-sparteine surrogate (+)-**459** reported by O'Brien *et al.*[20]

2) (+)-Sparteine surrogate synthesis.

The starting material for this synthesis is (–)-cytisine (see above). Its extraction from *Laburnum anagyroides* seeds has been described earlier in this chapter. From this compound, a three-step synthesis affords the (+)-sparteine surrogate **459** in good yield. In the first step, (–)-cytisine (**396**) is converted into its *N*-methyl carboxylate **457** using methyl chloroformate. Then the pyridone ring is hydrogenated using catalytic platinum oxide under a hydrogen atmosphere before reducing the carbonyl groups with lithium aluminium hydride (Scheme 13). Finally, the surrogate (+)-**459** is obtained after distillation under reduced pressure.




**Scheme 13: Synthesis of (+)-sparteine surrogate (+)-459**

## IV) Conclusion

The synthesis of various chiral formamides has been achieved with good success. The *N*-formylation gave products with full conversion of the secondary amine starting material and yields often greater than 90%. Secondary amine products were in most cases obtained by reductive amination of aldehydes, and gave products in good yields when starting materials used for the reaction were pure enough. The reductive amination of ketones proved to be more challenging, however we report the synthesis of one chiral formamide derived from benzophenone. Moreover, (+)-sparteine surrogate **459** was obtained in three steps from hand-picked *Laburnum anagyroides* seeds, in decent yields considering that these strongly basic amines are somewhat sensitive compounds and prone to degradation.

This range of new formamides was synthesised with the aim of performing the kinetic resolutions of tetrathia[7]helicenes; moreover, a clear rationale behind the synthesis of these compounds will be presented in the following chapter presenting the kinetic resolution results. Although using conventional and well-established reaction procedures, the work described in this chapter has made available for the first time a library of simple chiral auxiliaries which have previously been overlooked because their typical applications do not directly introduce chirality into the product structures. Besides our intended use in helicene synthesis, however, the compounds should also be of value in desymmetrisation reactions of prochiral bis-arenes and in the kinetic resolution of other classes of chiral aromatics, for examples binapthyls.

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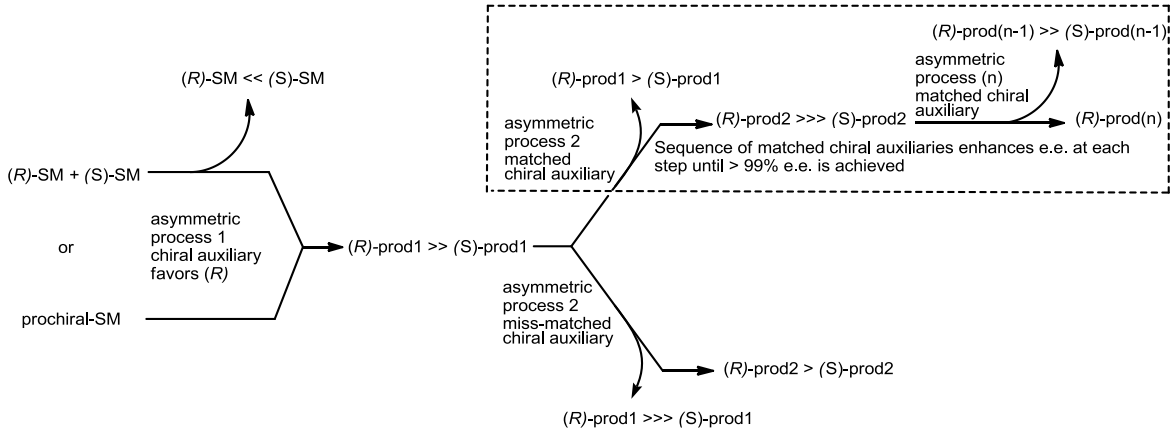
# Chapter 3:
# Multiple KR of
# 7,8-dipropyltetrathia[7]helicene

# I) Introduction

## 1) Multiple kinetic resolution approach (multi-KR).

The multi-KR approach aims at analysing a synthetic route to identify key points at which an asymmetric bias can be introduced, and selects those points most likely to be efficient for initial investigation. Because of the series of kinetic resolutions, the e.e. of the product is progressively improved as the route approaches its ultimate target (Scheme 1). The advantage of this novel approach is that no major effort is needed to take any one step to >90% efficiency, but, once practical access to an enantiopure product has been achieved (e.g. by recrystallization after the final KR step), further improvements in chiral recognition in each KR serve to improve the overall yield of the whole synthesis.




**Scheme 1: Illustration of multi-KR for a sequence of three asymmetric processes [*i.e.* n = 3 in this example].**

## 2) Strategy for the multi-KR of tetrathia[7]helicenes

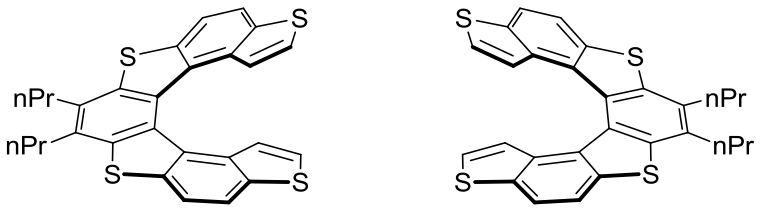
In view of the well-established difficulty of approaches based on asymmetric induction in the general construction of helicene and heterohelicene cores, we have opted for a novel multi-kinetic resolution procedure starting from racemic tetrathia[7]helicene. To the best of our knowledge, the concept of di- and multi-KR strategies in synthesis design is elucidated here for the first time. Some related examples however amount to di-[1] or multi-KR sequences, but do not define the concept. Because of the C2 symmetry of helicenes, this class of targets is especially suitable for the multi-KR method of synthesis because the stereochemical environment is the same at each end of the molecule. The matched chiral auxiliary at one end will also will also be matched if the same reaction is performed at the other end.

As explained in chapter 2, two strategies have been selected to perform enantioselective formylation of racemic tetrathia[7]helicene: direct asymmetric formylation and asymmetric lithiation. For this, a range of chiral auxiliaries (presented in chapter 2) will first be evaluated in the single kinetic resolution of tetrathia[7]helicene. This KR screening producing enantio-enriched products, should allow us to decide on the strategy for the synthesis of enantiopure tetrathia[7]helicene derivatives (2-formyl- and 2,13-diformyltetrathia-[7]-helicene) via an optimised number of kinetic resolution steps by identifying the best points to apply KR in the synthetic route.

3) Chiral analysis

For the analysis of tetrathia[7]helicenes, a 25 cm ChiralPak IA column with 3 μm particles was used. The attribution of HPLC signals to the *M* and *P* enantiomers of 7,8-dipropyltetrathia[7]helicene (**8**) (Scheme 2) was made by correlation between HPLC data and signs of specific rotation, according to published literature (Maiorana and Licandro established in two of their publications that (*P*)-**8** elutes first when using ChiralPak IA HPLC columns).[2] Moreover, a generally accepted feature of helicenes (both from theoretical or experimental evidence) is that (+)-helicenes and (+)-heterohelicenes possess the absolute configuration of a right-handed helix (*P* configuration). A similar reasoning was used for the attribution of HPLC signals of products of the kinetic resolutions. First, knowing that there is no possible epimerisation of the helicene, the product of a KR should have an opposite sign of specific rotation to that of the recovered starting material. Once this was established, peaks in the chromatogram corresponding to the product of the KR were attributed accordingly.

In practice, (*P*)-(+)-**8** (SM) comes first in the chromatogram, therefore if a KR gives (*P*)-(+)-**8** (SM) as the major enantiomer, products of this KR would be mainly of the (*M*)-configuration (with the second peak being the largest).




(*M*)-(-)-**8** (*P*)-(+)-**8**

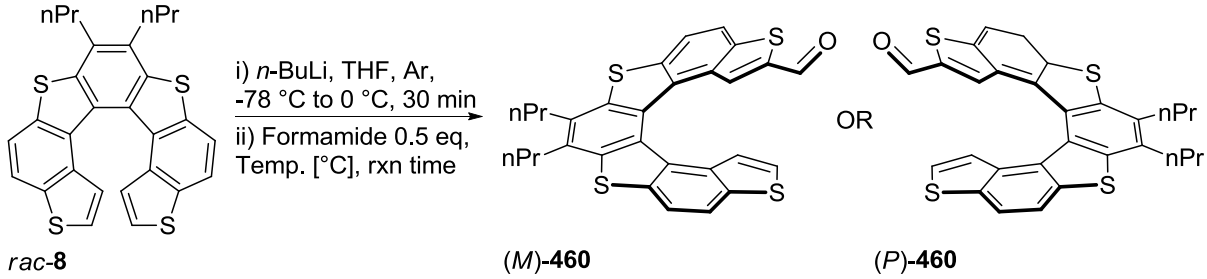
**Scheme 2: (*M*) and (*P*)-7,8-dipropyltetrathia[7]helicene**

II) Single kinetic resolution: use of chiral formamides

1) Introduction

As explained in chapter 2, we opted for a method where lithiated helicene is quenched with a chiral formamide, especially being aware that the non-asymmetric equivalent using DMF gives good yields for the synthesis of racemic 7,8-dipropyl-2-formyltetrathia[7]helicene (**460**).[3] Although we synthesised three different helicenes (**8**, **360** and **368**), screening of chiral auxiliaries was performed using helicene **8** for two main reasons. First, both enantiomers of this particular helicene have been charaterised[2a,c] which allows for an easy attribution of absolute configurations of the enantiomers obtained in kinetic resolution experiments, and also it facilitated our collaboration with Licandro's group.

The reactions needed to be carried out in a reproducible way. In our standard procedure, lithiation of the helicene is effected with *n*-BuLi at –78 °C at a set concentration in THF, the reaction mixture is allowed to warm up to 0 °C over 30 minutes, and after cooling back to –78 °C, a solution of 0.5 equivalents of the chiral formamide, in a set volume of THF, is added dropwise (Scheme 3). These parameters were not modified unless otherwise specified, and the reaction was then allowed to continue for a time and a temperature reported in the result tables.



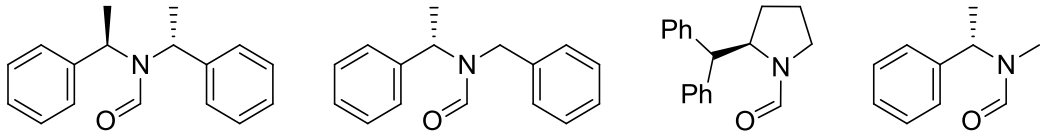

**Scheme 3: Screening of chiral formamides**

2) Asymmetric formylation: results

a) Preliminary results

Our first was approach was based on screening some of the most accessible formamides [(*R*,*R*)-**430**, (*S*)-**429**, (*R*)-**427**, (*S*)-**426]**, obtained from commercially available chiral amines (Figure 1). These first experiments allowed us to improve our knowledge of the reaction as well as our skills. It was promptly recognised that the conditions used for formamide (*R*,*R*)-**430** (Table 1, Entry 1) were not suitable to obtain a maximised selectivity. In fact, this first example showed that the reactivity was poorer than expected. Subsequently, we found out

that these chiral formamides were not particularly reactive when the reaction was performed at low temperatures. Indeed, at –78 °C, the reaction of (*S*)-**429** and (*R*)-**427** (Table 1, Entries 2 and 3) used up only about half the amount of formamide giving the product in respectively 22% and 29% yields, despite leaving the reaction for extended time of 6 hours. Concerning the selectivities, no great result was obtained, the best result being achieved with (*S*)-**429** (Table 1, Entry 2) affording product with only 14% e.e. Although we did not expect (*S*)-**426** to improve the results (Table 1, Entry 4), we ensured that at moderately low temperatures, the reaction could go to completion.




(*R,R*)-**430** (*S*)-**429** (*R*)-**427** (*S*)-**426**

**Figure 1: Most accessible formamides**

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e.[a] [%] of 460 | e.e.[a] [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R,R*)-**430** | –78 to RT | 1 + 1 | 35 | 2.5 (*M*) | 2 (*P*) |
| 2 | (*S*)-**429** | –78 | 6 | 29 | 14 (*M*) | 4 (*P*) |
| 3 | (*R*)-**427** | –78 | 6 | 22 | 7 (*P*) | 1 (*M*) |
| 4 | (*S*)-**426** | –43 | 3 | 50 | 2 (*P*) | *rac* |

[a] measured by HPLC

**Table 1: KR results with most accessible formamides**

b) Use of second generation formamides

It was decided to synthesise more formamides based on the structure of (*S*)-**429** that gave the best preliminary results (Figure 2, (*R*)-**445** and (*R*)-**446**). As well as formamides bearing two aromatic moieties it was decided to synthesise some mixed ones bearing both a chiral aliphatic and an aromatic moiety (Figure 2, (*R*)-**441**, (*R*)-**442**, (*R*)-**443** and (*R*)-**447**). Moreover, we screened other non-related structures (Figure 2, (*S*)-**439** and (–)-**452**), in order to show if a trend could be established for the most efficient auxiliaries.

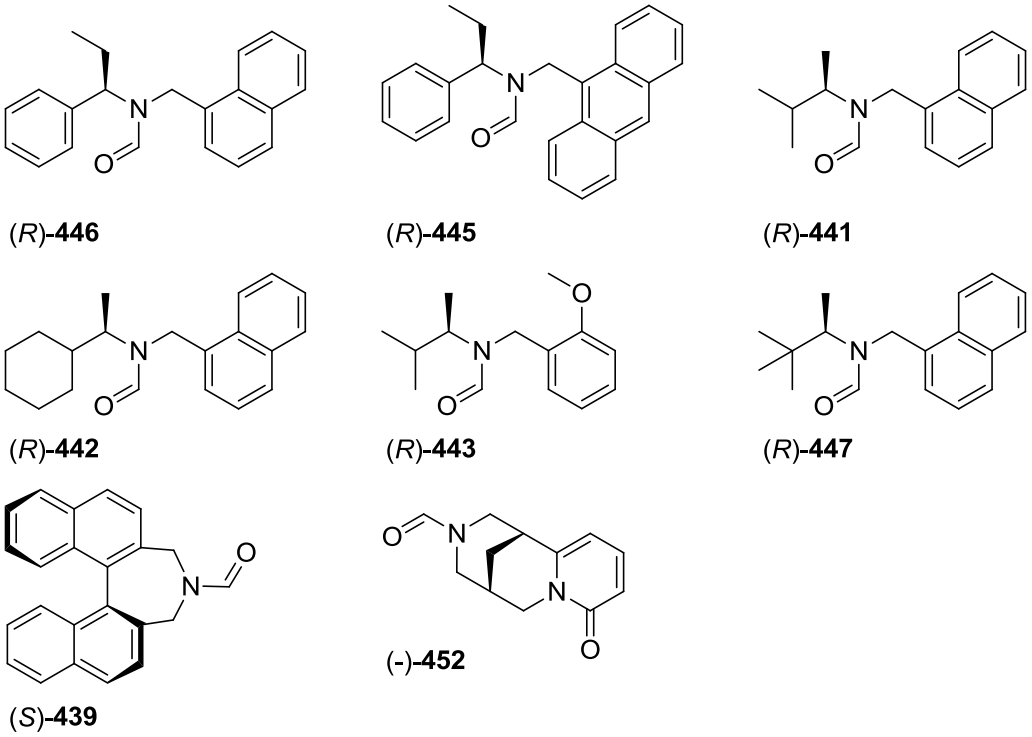



**Figure 2: Second generation formamides**

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e.[a] [%] of 460 | e.e.[a] [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**446** | –78 | 7 | 19 | 13 (*M*) | 5.5 (*P*) |
| 2 | (*R*)-**445** | –78 | 6 | 15 | 9 (*M*) | 1 (*P*) |
| 3 | (*R*)-**441** | –78 | 6 | 23 | 42 (*M*) | 8 (*P*) |
| 4 | (*R*)-**442** | –78 | 6 | 34 | 29 (*M*) | 7 (*P*) |
| 5 | (*R*)-**443** | –78 | 6 | 15 | 25 (*M*) | 5 (*P*) |
| 6 | (*R*)-**447** | –78 | 6 | 29 | 17 (*M*) | 3 (*P*) |
| 7 | (*S*)-**439** | –78 | 7 | 26 | 13 (*M*) | 5 (*P*) |
| 8 | (–)-**452** | –78 | 18 | 41 | *rac* | *rac* |

[a] measured by HPLC.

**Table 2: KR results with second generation formamides**

The attempts made with structures closely related to (*R*)-**429** (Table 2, Entries 1 and 2) culminating at 13% e.e. did not improve on the results previously obtained. The breakthrough came with formamides bearing a chiral aliphatic moiety on one side and an aromatic moiety on the other side. Indeed, formamides (*R*)-**441**, (*R*)-**442**, (*R*)-**443** and (*R*)-**447** afforded the desired formyl-helicene **460** in higher enantiomeric excesses than all

previously examined formamides (Table 2, Entries 3 to 6). Comparing formamides (*R*)-**441**, (*R*)-**442** and (*R*)-**447** (Table 2, Entries 3, 4 and 6) allowed us to establish that of the aliphatic moieties represented (only these three are easily accessed from commercially available primary amines) the isopropyl derivatised (*R*)-**441** is the most efficient one, giving the product in 42% e.e. Also, comparing Table 2, Entries 3 and 5 showed that the 1-naphthyl moiety of (*R*)-**441** that gave 42% e.e. is more suitable than the 2-methoxyphenyl of (*R*)-**443** that only gave 25% e.e. In order to make sure that the trend observed with these formamides represented the most favourable opportunity for further tuning and optimisation of the structure, we also performed the KR using some formamides with very different structures, (*S*)-**439** and (–)-**452** (Figure 2). To our surprise, these compared very poorly with any of the chiral aliphatic series, giving 13% e.e. for binaphthyl azepine (*S*)-**439** and racemic material for (–)-cytisine derived (–)-**452**.

It was therefore concluded that optimisations of formamide structures using the same chiral 3-methylbutan-2-amine motif and varying the aromatic side held the key to further improvements of the KR results. However, there are a few limitations to the usage of these aliphatic/aromatic formamides. First, further optimisation of the chiral aliphatic moiety is restricted as it relies on the access to commercially available chiral primary amines. Secondly, the reaction of the successful chiral formamides in the kinetic resolution conditions still did not provide the product with full conversions (i.e. to 50% yield) despite long reaction times (initially ~ 6-7 hours; part way through the project, the availability of a chiller made overnight reactions possible).

c) Third generation formamides

In order to further improve the selectivity of the kinetic resolution, and additional series of formamides were synthesised based on the structure of (*R*)-**441** (Figure 3). The idea behind the synthesis of these formamides was to introduce bulk at different positions on the aromatic moiety in order to study the effect on the selectivity of the KR.

First, the kinetic resolution using formamide (*R*)-**441** was repeated but left to react overnight. A similar result to that previously observed was obtained (Table 3, Entry 1) giving formylhelicene **460** in 41% e.e. but showing an increased yield of 30% (for a 6 hour-reaction, product had been obtained in 23% yield and 42% e.e.; see Table 2, Entry 3).

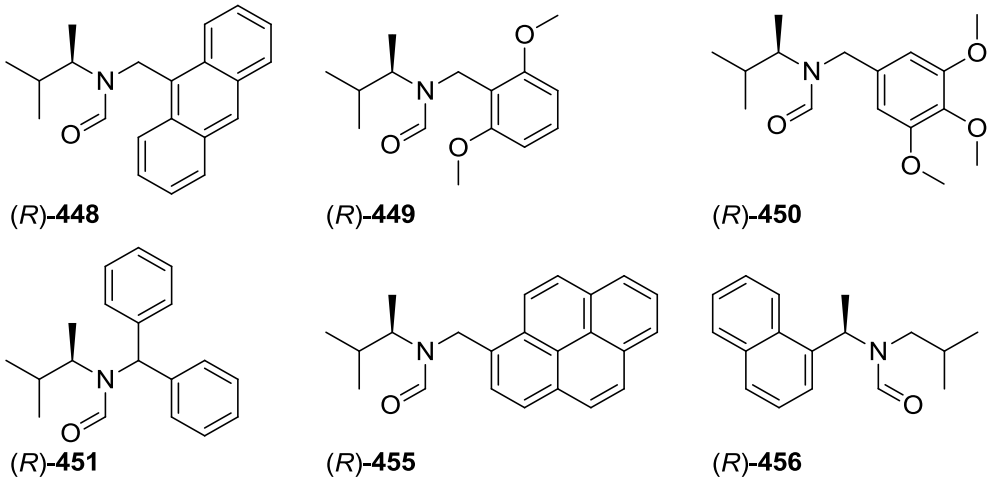



**Figure 3: Third generation formamides**

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e.[a] [%] of 460 | e.e.[a] [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** | –78 | 18 | 30 | 41 (*M*) | 10 (*P*) |
| 2 | (*R*)-**448** | –78 | 18 | 20 | 3 (*P*) | 1 (*M*) |
| 3 | (*R*)-**450** | –78 | 6 | 9 | 28 (*M*) | 3 (*P*) |
| 4 | (*R*)-**449** | –78 | 6 | NR | - | - |
| 5 | (*R*)-**451** | –78 | 18 | NR | - | - |
| 6 | (*R*)-**455** | –78 | 18 | 32 | 42 (*M*) | 11 (*P*) |
| 7 | (*R*)-**456** | –78 | 18 | 35 | 7 (*P*) | 2.5 (*M*) |

[a] measured by HPLC.

**Table 3: KR results with third generation formamides**

Unfortunately, none of the third generation formamides improved the 42% e.e. mark achieved with (*R*)-**441**. The best result was obtained with (*R*)-**456** bearing a pyrene moiety, and performed in the same way as (*R*)-**441** giving product in 32% yield and 42% e.e. (Table 3, Entry 6). Interestingly, this example shows that the approach of the lithiated helicene towards the formamide is not influenced by the introduction of steric bulk on its outer side. Turning to trimethoxyformamide (*R*)-**450** (Table 3, Entry 3), the reaction proceeded in similar fashion as with methoxyformamide (*R*)-**443** (Table 2, Entry 5), giving desired product in 9% yield and 29% e.e. Surprisingly, anthracenoformamide (*R*)-**448** performed very poorly, giving expected aldehyde in only 3% e.e. Although no clear mechanistic insight could be gained from this experiment, the three dimensional structure of naphthyl formamide (*R*)-**441** must be severely altered by the addition of the extra

benzene ring for the KR to proceed with such poor selectivity when using (*R*)-**448**. This could mean that the design of the aromatic side of the formamide must be dissymmetric to force the formamide in the correct conformation.

Next, we found out that the use of formamides where steric hindrance is introduced directly in the vicinity of the reactive site ((*R*)-**449**and (*R*)-**451**, Figure 3) completely disabled the reaction and only starting material was recovered (Table 3, Entries 4 and 5).

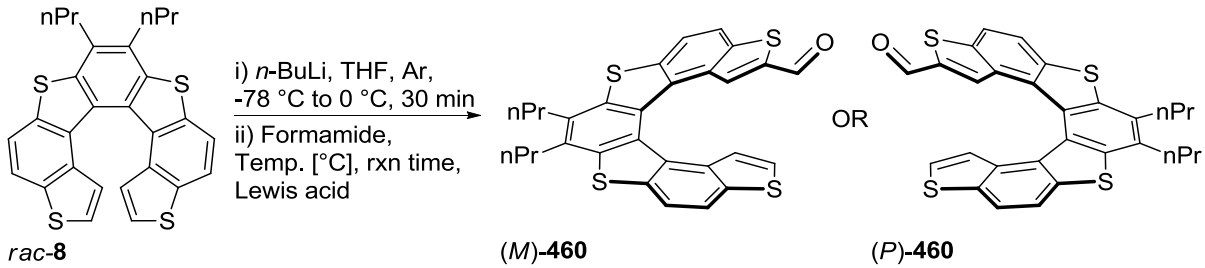
Finally, we thought it would be worth checking that a reversed structure with a naphthyl group next to the chiral centre and an achiral isopropyl moiety on the other side ((*R*)-**456**, Figure 3) would not out-perform formamide (*R*)-**441**; however when using (*R*)-**456**, formylhelicene was obtained in 35% yield with only 7% e.e.

Although none of these results improved on the ones obtained at the outset, interesting information was gathered that should be helpful for further development and fine tuning of the chiral formamide approach. At the moment, more formamides are being developed in our labs based on the observations made with the second and third generation of chiral auxiliaries.

3) Modification of reaction conditions

Despite considerable efforts put into developing an improved structure of (*R*)-**441**, no success was obtained. Nonetheless, we thought that tuning the reaction conditions could provide some improvements. There were two clear targets: improving the conversion towards formylhelicene and improving the selectivity of the reaction. In the most favourable situation, we could hope for improvements of both aspects, although getting higher yields while retaining the selectivity or enhancing the enantiomeric excess of the product alone would still be considered as a success.

a) Temperature, Lewis acid and formamide




*rac*-**8** (*M*)-**460** (*P*)-**460**

**Scheme 4: KR using chiral formamides in modified conditions**

| Entry | Formamide (eq) | Lewis acid | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e.[a] [%] of 460 | e.e.[a] [%] of 8 |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** (0.5) | - | –78 | 18 | 30 | 41 (*M*) | 10 (*P*) |
| 2 | (*R*)-**441** (0.5) | - | –63 | 2 | 9 | 34 (*M*) | 7 (*P*) |
| 3 | (*R*)-**441** (0.35) | - | –40 | 2 | 29 | 25 (*M*) | 9 (*P*) |
| 4 | (*R*)-**441** (1) | - | –78 | 6 | 29 | 17 (*M*) | 5 (*P*) |
| 5 | (*S*)-**441** (0.5) | $BF_3$•$Et_2O$ | –78 | 18 | 37 | 10 (*P*) | 6 (*M*) |
| 6 | (*R*)-**451** (0.5) | $BF_3$•$Et_2O$ | –78 | 18 | 20 | 4.5 (*P*) | 1.5 (*M*) |

[a] measured by HPLC.

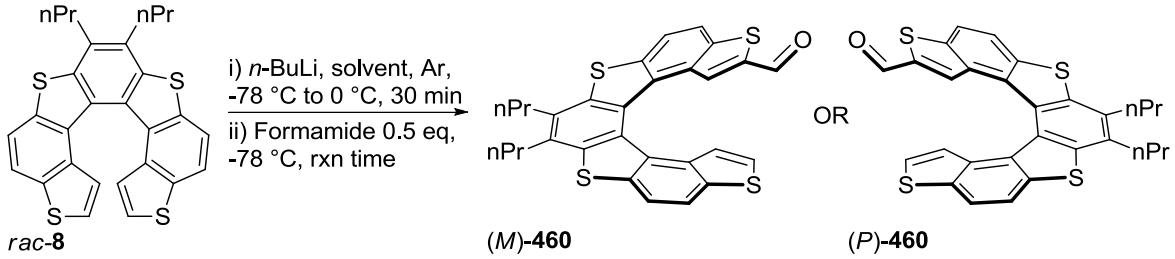
**Table 4: Kinetic resolution results using modified reaction conditions**

Unsurprisingly, all attempts made to improve the yield of the reaction by helping the reactivity of the lithiohelicene towards the formamide, resulted in decrease of selectivity. Increasing the temperature to –63 °C and –42 °C (Table 4, Entries 2 and 3), gave the desired product, **460**, with 34% e.e. and 25% e.e., respectively. Having observed this drop of selectivity, no attempt was made to run these reactions for longer times. Using one equivalent of formamide gave an even more disappointing 17% e.e. (Table 4, Entry 4), and the Lewis acid mediated reaction ($BF_3$.$Et_2O$ was stirred at 0 °C with chiral formamide before adding dropwise to lithiohelicene solution) gave even an poorer 10% e.e. and 37% yield (Table 4, Entry 5). However, the latter experiment did prove to be somewhat useful as it enabled the reaction to be performed with previously unreactive formamides allowing us to compare its efficiency with formamide (*R*)-**441**. It turned out that (*R*)-**451** (Table 4, Entry 5) gave the desired product in only 20% yield and 4.5% e.e., showing not only that steric bulk slows down the reaction but also that it does not necessarily make it more selective. As it appeared unlikely that the use of $BF_3$•$Et_2O$ would promote the reaction with a higher selectivity that had been already obtained (Table 4, Entry 1), the kinetic resolution with other unreactive formamides was not attempted under those conditions.

b) Solvent

Among the possible modifications that could be made to the reaction conditions, using different solvents was surely one of the most significant ones. First, we were hoping to improve the results previously obtained, and also, as the second part of the kinetic resolution study will rely on (–)-sparteine-mediated asymmetric lithiation, we needed a

solvent system compatible with both types of chiral auxiliaries [(–)-sparteine is famously known for not working efficiently in THF[4]], so this was a key objective.




**Scheme 5: Kinetic resolution: solvent screening**

| Entry | Formamide | Solvent | Rxn time [hrs] | Yield [%] | e.e.[a] [%] of 460 | e.e.[a] [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** | THF | 18 | 30 | 41(*M*) | 10 (*P*) |
| 2 | (*R*)-**441** | $Et_2O$/Toluene | 18 | 35 | 3 (*M*) | 1.5 (*P*) |
| 3 | (*R*)-**455** | 2-MeTHF | 18 | 26 | 16 (*M*) | 5 (*P*) |
| 4 | (*R*)-**441** | DME/THF | 18 | 28 | 30 (*M*) | 7 (*P*) |
| 5 | (*R*)-**441** | MTBE | 18 | 32 | 1 (*P*) | 0.15 (*M*) |

[a] measured by HPLC.

**Table 5: Kinetic resolution: solvent screening results**

Along with THF, $Et_2O$ is possibly the most common solvent used for reactions of organolithium reagents. However, due to the low solubility of 7,8-dipropyltetrathia[7]helicene in $Et_2O$, the reaction was not really feasible. Using a co-solvent that would help the solubilisation but would not actively participate in the reaction seemed to be the best compromise. Knowing that toluene efficiently solubilises our helicene (the last step of its synthesis is carried out in toluene) and that it is generally a poor solvent for organolithium reagents, the KR was performed in a 1:4 mixture of $Et_2O$ and toluene at –78 °C but gave formyl-helicene **460** in 35% yield and disappointing 3% e.e. (Table 5, Entry 2). Although this was surprising, the discrepancy in selectivities was attributed to the differences in coordination abilities of the solvents. Indeed, $Et_2O$ is known for being weekly coordinating toward the lithium cation compared to other ethers (for the same exact reason $Et_2O$ is a good solvent for (–)-sparteine chemistry). Unsurprisingly, MTBE which is known to be a good substitute for $Et_2O$ (and also solubilised helicene **8**), performed poorly and product was obtained in 1% e.e. (Table 5, Entry 5), whereas, when

using more coordinating 2-MeTHF, product was obtained in an improved 16% e.e. (Table 5, Entry 3) verifying our hypothesis about the importance of the coordination ability.

For this reason, the next objective was to use a solvent with even higher coordinating abilities than THF, and with a low enough freezing point. A publication from O'Brien *et al.*[5] suggested that 1,2-dimethoxyethane (DME) is more coordinating than THF which itself is much more coordinating than 2-MeTHF. Considering that DME's melting point is –58 °C, it could easily be brought down to –78 °C upon addition of toluene or THF as an additive. Since DME was more coordinating than THF, the KR was performed in a 2:1 mixture of DME and THF affording formylhelicene **460** in 28% yield and 30% e.e. (Table 5, Entry 4). No clear explanation for this was found, besides the possibility that the geometry of the THF solvate of lithiohelicene much favoured a higher selectivity than the corresponding DME solvate.

#### 4) Conclusion

The screening of several formamides has allowed us to discover a preferred type of structure with a chiral 3-methylbutan-2-amine moiety on one side and a dissymmetric aromatic moiety on the other side of the formamide. Although considerable efforts have been put towards further optimisation of the structure, none of the latest generation of chiral formamides, nor the alternative conditions screened, improved the results obtained with (*R*)-**441** in THF. Nonetheless, the insight gathered from these attempts to optimise the reaction should prove useful for further tuning of the conditions. Future work in this area should involve attempts of kinetic resolution at below –78 °C, the synthesis of new formamides closely related to (*R*)-**441**, and a deeper study of the role of solvation and the effect of the solvent.

### III) Single kinetic resolution: chiral diamine promoted asymmetric lithiation

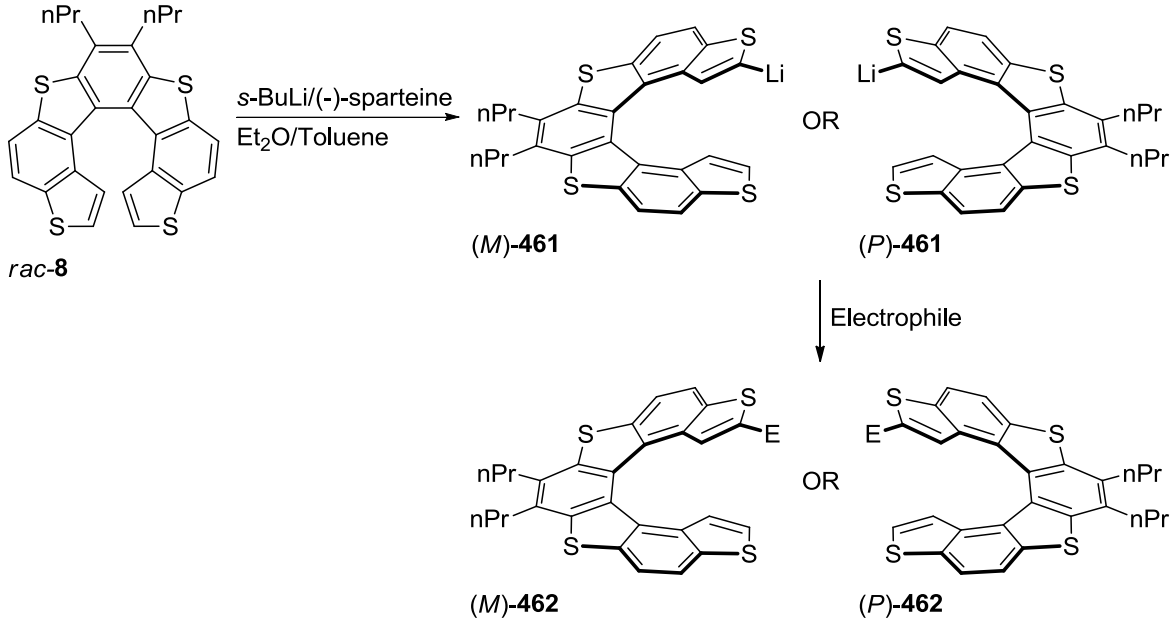
#### 1) Introduction

Two main strategies were accessible in order to perform asymmetric lithiations. The use of chiral diamines, in particular (–)-sparteine, clearly represented our best opportunity. However, an alternative consisting in using a type of chiral LDA reagent (i.e., mixing chiral secondary amines and *n*-BuLi) was also considered. Unfortunately, preliminary experiments showed that LDA does not deprotonate 7,8-dipropyltetrathia[7]helicene even at room temperature. This latter idea was then abandoned, and we concentrated on the use

of chiral diamines, and more particularly towards the archetypal chiral auxiliary (–)-sparteine.

Using *s*-BuLi in the presence of (–)-sparteine, then quenching with an electrophile, was chosen as a quick way to gain initial experience with the production of enantioenriched 2-lithiotetrathia[7]helicene (**461**) (Scheme 6).

Concerning solvents, diethylether, commonly used for (–)-sparteine chemistry, could not be used on its own for solubility reasons (as explained previously in this chapter) and so was mixed with toluene.



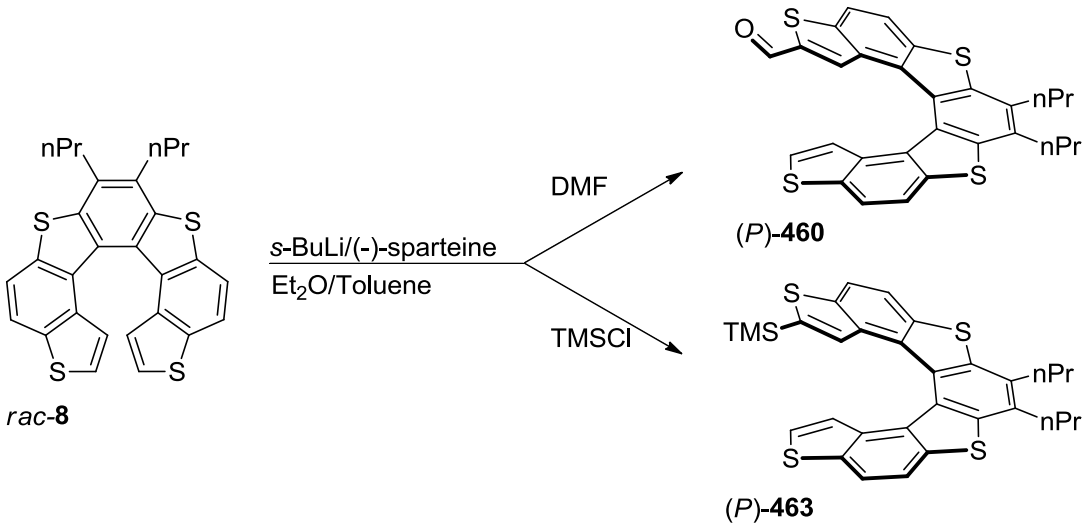

**Scheme 6: Asymmetric lithiation**

2) Preliminary results

We started with formylhelicene **460** as the synthetic target and DMF was chosen as the first electrophile. The first attempts at this reaction were unsuccessful and only starting material was recovered. Following this initial struggle, more practical conditions were used, where *s*-BuLi/(–)-sparteine mixture was mixed at 0 °C and added dropwise using a syringe (Table 6, Entries 1, 2 and 3) giving formylhelicene (*P*)-**460** at best in 11% e.e. (Table 6, Entries 3).

Being assured that this method could proceed in an enantioselective manner, more efforts were put into developing a technique where the addition of *s*-BuLi/(–)-sparteine at –78 °C would give the desired formylhelicene **460**. However, based on our experience with chiral formamides, we knew that formylation at –78 °C proceeds slowly; therefore we moved on

to a faster reaction, by quenching lithiated species with a more reactive electrophile, chlorotrimethylsilane. Premixing *s*-BuLi and (–)-sparteine at –78 °C for 30 minutes, followed by cannulating this mixture into a solution of helicene **8** that had been previously cooled to –78 °C afforded lithiohelicene **461** and subsequent quenching with TMSCl gave TMS-helicene (*P*)-**463** (Scheme 7), albeit at a low 9% yield and 7% e.e. (Table 6, Entry 4). Also, traces of dilithiated helicene were identified from small amounts of the di-TMS-helicene observed in the crude product, but not enough material was available to perform chiral analyses.




**Scheme 7: Kinetic resolution: preliminary reactions**

| Entry | *s*-BuLi [eq] | (–)-sparteine / *s*-BuLi ratio | Lithiation time [hrs] | Rxn time[a] [hrs] | Yield [%] | e.e. [%] of product[c] | e.e. [%] of 8[c] |
|---|---|---|---|---|---|---|---|
| 1 | 0.7 | 1:1 | 0.5 | 18 | **460**, 25 | 7 (*P*) | 2.5 (*M*) |
| 2 | 0.5 | 2:1 | 1 | 18 | **460**, 20 | 5 (*P*) | 0.4 (*M*) |
| 3 | 0.5 | 1:1 | 0.5 | 18 | **460**, 10 | 11 (*P*) | 1 (*M*) |
| 4[b] | 0.5 | 1:1 | 0.5 | 2 | **463**, 9 | 7 (*P*) | 1.7 (*M*) |

[a] time for the reaction after addition of the electrophile; [b] SM and products were not separated on column chromatography, and conversion was measured by integration of HPLC signals (calibrations were done showing that **8** and **463** have similar enough UV responses to measure the conversion directly by integration of the HPLC signals) [c] measured by HPLC.

**Table 6: KR: preliminary results using (–)-sparteine**

Although we are particularly interested in formylhelicene **460** and diformylhelicene **468** because they are intermediate in the synthesis of chiral push-pull systems, the synthesis of

TMS-helicene **463** or di-TMS-helicene **466** has also some advantages. The trimethylsilyl groups can easily be reomoved or transformed into the corresponding halo-helicenes by simple treatment with bromine or iodine monochloride[6] which should allow for greater functionalization possibilities.

3) Improved results

a) Rationale for the low conversion and selectivities

Preliminary results (Table 6) showed poor yields and selectivity, despite several attempts under various conditions. If asymmetric lithiation is efficient, for a KR experiment, the quantity of butyllithium should be chosen to convert about half the starting material into 2-lithiotetrathiahelicene (**461**). In practice, it was difficult to distinguish whether the low overall conversion was a consequence of incomplete lithiation or inefficient reactivity towards the electrophile. Indeed, formylation proved to be quite a slow reaction at the low temperatures (–78 °C) required for good stereoselectivity, and therefore we modified our approach to exploit the convenience of using the more reactive chlorotrimethylsilane which ensures that all the lithiated material is used efficiently in the reaction.

However, more so than the low yields, the lack of selectivity represented a greater challenge and further optimisation of the chiral recognition between the (–)-sparteine•*s*-BuLi and helicene **8** was clearly still necessary. Literature reports several studies on the aggregation of (–)-sparteine with several organolithium reagents, either based on NMR spectroscopy[7] or crystallisation experiments.[8]

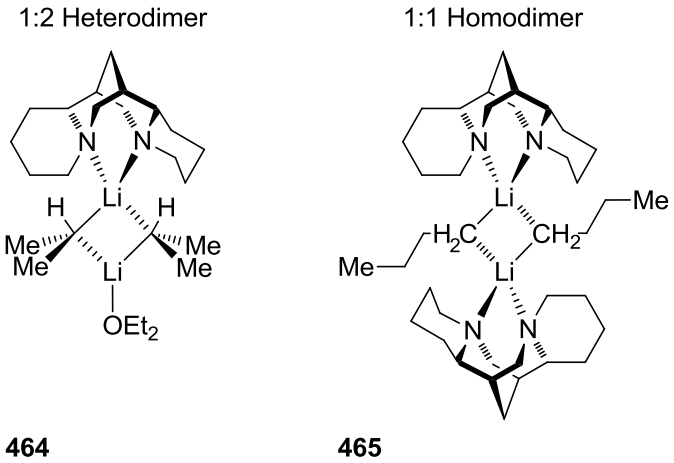


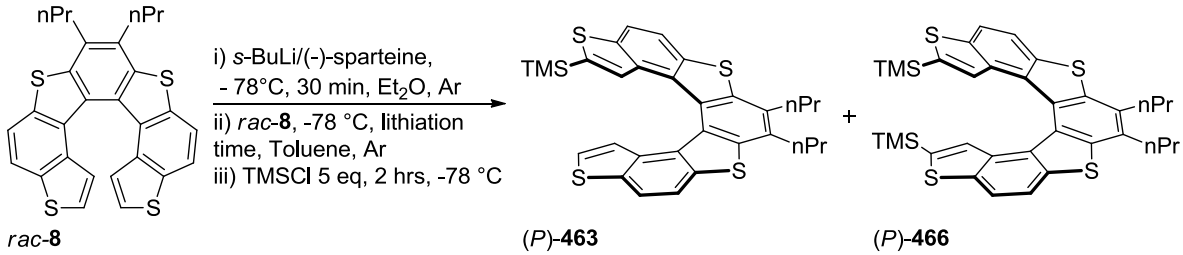

**Figure 4: (–)-Sparteine aggregates formed with *n*-BuLi and *i*-PrLi[7ab,8b]**

However, no direct study of (–)-sparteine•*s*-BuLi aggregates can be found, because of the complication that the chirality of *s*-BuLi generates, as several diastereomeric complexes could be observed. Nonetheless, many reports detail the behaviour of *n*-BuLi and *i*-PrLi, and generally, it is accepted that *i*-PrLi is a good surrogate for *s*-BuLi. Crystal structure studies show that *i*-PrLi and (–)-sparteine form a (–)-sparteine•(*i*-PrLi)$_2$ aggregate **464** as a 1:2 heterodimer,[7a,8b] whereas *n*-BuLi and (–)-sparteine form a [(–)-sparteine]$_2$•(*n*-BuLi)$_2$ aggregate **465** as a tetrameric 1:1 complex (Figure 4), often referred to as a '1:1 homodimer' in the literature.[7b8b]

In line with these suggestions that sparteine aggregates may play an important part in this chemistry, we postulated that whichever (–)-sparteine•*s*-BuLi complex is responsible for the asymmetric lithiation (the *s*-BuLi equivalent of **464** or **465**), it may not be very reactive and also might not be formed efficiently in the conditions we had been using. Therefore increasing the ratio (–)-sparteine/*s*-BuLi should be an appropriate method to provide efficiently a complex [whether a 1:1 or 1:2 (–)-sparteine•*s*-BuLi aggregate] which should be expected to be more efficient at asymmetric lithiation. Using larger quantities of *s*-BuLi should also solve the problems encountered with low conversions.

b) Results

To make a direct comparison, we used the normal 0.5 equivalents of *s*-BuLi relative to the helicene **8** but substantially increased the (–)-sparteine/*s*-BuLi ratio, and ultimately, by using a 20:1 ratio (Table 7, Entry 1), we observed immediate improvement, obtaining **463** in a promising 55% e.e., albeit at a low conversion. This supported our view that the (–)-sparteine/*s*-BuLi ratio was important to control aggregation, so further experiments were performed in which we adjusted the proportions of (–)-sparteine/*s*-BuLi and the amounts of *s*-BuLi relative to **8** with a view to improving the overall formation of the product.




*rac*-**8** (*P*)-**463** (*P*)-**466**

**Scheme 8: Kinetic resolution: synthesis of TMS-helicene derivatives**

| Entry | *s*-BuLi [eq] | (–)-Sparteine /*s*-BuLi ratio | Lithiation time [hrs] | Conversion 466 [%][a] | e.e. [%] of 466[b] | Conversion 463 [%][a] | e.e. [%] of 463[b] | e.e. [%] of 8[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.5 | 20:1 | 0.5 | - | - | 6 | 55 (*P*) | 3.3 (*M*) |
| 2 | 1.5 | 6.6:1 | 0.5 | 2 | >90 (*P*) | 22 | 60 (*P*) | 17.5 (*M*) |
| 3 | 2 | 5:1 | 0.75 | 2.5 | >90 (*P*) | 27 | 72 (*P*) | 28 (*M*) |
| 4 | 2 | 5:1 | 4 | 1 | >90 (*P*) | 23 | 74 (*P*) | 21 *(M)* |
| 5 | 2 | 5:1 | 4 | 5 | >90 (*P*) | 35 | 84 (*P*) | 58 (*M*) |
| 6 | 2 | 1:1 | 4 | 4 | 87 (*P*) | 23 | 51 (*P*) | 21.5 (*M*) |
| 7 | 4 | 5:1 | 0.75 | 2.6 | >90 (*P*) | 35 | 85 (*P*) | 66 (*M*) |
| 8 | 4 | 5:1 | 2 | 36 | 81 (*P*) | 33 | 62 (*M*)[c] | 69 (*M*) |
| 9 | 1 | 5:1 | 4 | 1.5 | >90 (*P*) | 18 | 65 (*P*) | 14 (*M*) |
| 10 | 1 | 3:1 | 4 | 0.3 | >90 (*P*) | 12 | 62 (*P*) | 9.4 (*M*) |
| 11 | 3 | 5:1 | 4 | 9 | >90 (*P*) | 38 | 68 (*P*) | 67 (*M*) |
| 12 | 3 | 5:1 | 4 | 14 | >90 (*P*) | 30 | 39 (*P*) | 80 (*M*) |
| 13[d] | 2 | 5:1 | 4 | 1.8 | >90 (*P*) | 21 | 84 (*P*) | 33 (*M*) |
| 14[d] | 2 | 5:1 | 4 | 1 | >90 (*P*) | 20 | 71 (*P*) | 24 (*M*) |

[a] SM and products were not separated on column chromatography, and conversion was measured by integration of HPLC signals (calibrations were done showing that **8**, **463** and **466** have similar enough UV responses to measure the conversion directly by integration of the HPLC signals) [b] measured by HPLC. [c] mono TMS is mostly the *M* enantiomer because all the *P* thiahelicene has been used up by forming the disilylated product.[d] MTBE was used as solvent.

**Table 7: KR results using *s*-BuLi/(–)-sparteine**

This produced some unexpected results (for kinetic resolutions), showing eventually that the use of three equivalents of *s*-BuLi was required to reach 50% conversion (Table 7, Entries 11 and 12) and that this was possible without significant losses of selectivity (Table 7, compare Entries 1 and 11). The most favourable conditions to form the mono-silylated product **463** with high selectivity were found to be two equivalents of *s*-BuLi relative to helicene **8** and a 5:1 ratio of (–)-sparteine/*s*-BuLi, which gave our best result; **463** was formed in 84% e.e. at 35% conversion (Table 7, Entry 5). This result, however, proved hard to reproduce, and generally experiments using a 5:1 ratio and two equivalents of *s*-BuLi, gave reproducibly TMS-helicene **463** with 70-75% e.e. (Table 7, Entries 3 and 4), independently of the lithiation time. Indeed, after 45 minutes of lithiation time (Table 7, Entry 3), both yield and enantioselectivity seem to plateau, as results obtained after 4 hours lithiation (Table 7, Entry 4) are almost equivalent to the 45 minute-result. Also, we found that similar selectivities could be accessed by performing the reaction solely in MTBE (Table 7, Entries 13 and 14), using two equivalents of *s*-BuLi, obtaining **463** with 84% e.e. and 71% e.e. However, the conversions obtained were lower compared to the equivalent

experiment in $Et_2O$/toluene (for example compare Table 7, Entries 4 and 13), therefore using MTBE as solvent was not continued.

### c) Asymmetric lithiation: mechanistic insights

Our original postulate that high ratios of (–)-sparteine/*s*-BuLi were necessary to form an efficient lithiating species was supported by these results, but it remained unclear whether (–)-sparteine•(*s*-BuLi)$_2$ or [(–)-sparteine]$_2$•(*s*-BuLi)$_2$ complexes were responsible for efficient asymmetric recognition, or even, whether it was one of the many higher aggregates speculated on in the literature (no higher aggregates have been proposed for sparteine/*s*-BuLi systems, but many higher aggregates have been reported for other systems).[9]

#### i) Higher aggregates

It is possible that the explanation for the large amount of (–)-sparteine used in our more efficient examples may arise from the need to generate a particular highly reactive and very chirally discriminating aggregate which is present only as a relatively small proportion of the sparteine-modified organolithium species formed in solution under our reaction conditions. Indeed, since a three-fold (Table 7, Entries 11 and 12) or four-fold (Table 7, Entries 7 and 8) excess of *s*-BuLi fails to produce complete silylation (or disilylation), it is reasonable to conclude that only about 25% (allowing for partial disilylation) of the *s*-BuLi added to the reaction is actually present in the reactive form, perhaps even less if the reactive aggregate is replenished by equilibrium with other less reactive aggregates as the reaction progresses. However, if a constant supply of the reactive aggregate was made available by an equilibrium, longer lithiation times would give much higher yields, which is not the case as the conversion seems to plateau out between 45 minutes and 4 hours (compare Table 7, Entries 3 and 4, and Table 7, Entries 7 and 8).

#### ii) Dissociation of the standard/predicted aggregates

Alternatively, if one of the aggregates **464** and **465** (Figure 4) is also the reactive aggregate when *s*-BuLi is used, additional (–)-sparteine is needed to ensure that the equilibrium controlling the dissociation of the aggregates remains in favour of the required aggregated species at all stages of the reaction. Otherwise, when lower amounts of (–)-sparteine are

used, partial dissociation of the aggregate would become possible, meaning that 'free' *s*-BuLi is present in solution. Therefore, the low selectivities observed in those cases (e.g. below 11% e.e., Table 6) are probably caused by 'free' *s*-BuLi itself rather than by the poor chiral recognition by any other aggregate present in solution. Moreover, knowing that the aggregates are poorly reactive compared to *s*-BuLi, even little / slow dissociation of *s*-BuLi can be responsible for the low enantioselectivities, which would also explain why, although low selectivities were observed in preliminary studies, the yields were poor too (which would not be the case if large amounts of 'free' *s*-BuLi were present in solution). The experiment reported in Table 7, Entry 6, using 2 equivalents of *s*-BuLi but only a 1:1 ratio can easily be seen to support what is being explained here. Indeed, in theory / practically, a 1:1 ratio is sufficient to ensure to formation of aggregates **464** or **465** (Figure 4), but the lack of extra (–)-sparteine which allows for partial dissociation of the aggregate is responsible for the lower selectivity observed in this experiment.

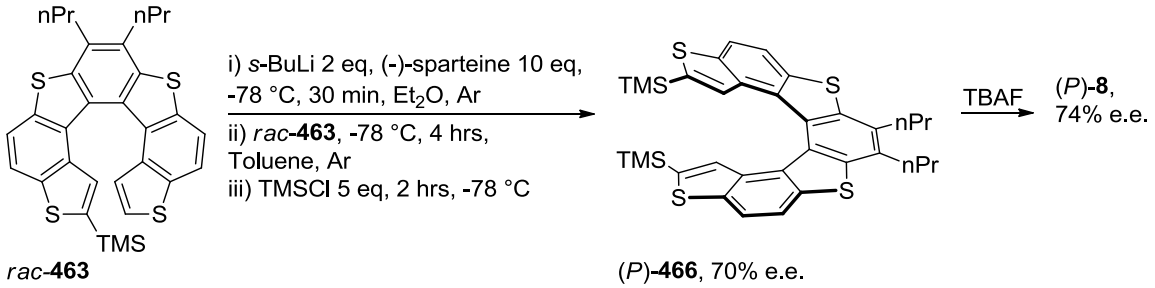
d) KR: recovery of enantiopure starting material

Results presented in Table 7 also suggest that in principle, the *s*-BuLi/sparteine/chlorotrimethylsilane procedure could be used to obtain enantiomerically pure recovered helicene **8**. Indeed, **8** could be recovered in reasonable yields if the conversion in the KR was taken over 50% by using larger excesses of the lithiating species, or in theory, if longer reaction times were employed (in fact, experience shows that conversion plateaus before four hours of lithiation). This, however, would be unlikely to be a practical procedure, and in fact since monolithiation is always accompanied by dilithiation in these reactions, optimisation of the production of di-TMS-helicene **466** and subsequent desilylation offers a better approach (*vide infra*). In view of these considerations, we have not pursued further attempts to use even greater excesses of *s*-BuLi to obtain enantiopure SM **8**, which was obtained in about 65-80 % e.e. by this approach (Table 7, entries 7, 8, 11 and 12).

4) KR of TMS-helicene **463**

As noted above (see also Table 7) the initial monolithiated species **461** is capable of undergoing a second lithiation step, so when the reaction is quenched with chlorotrimethylsilane, a mixture of mono and disilylated products are formed, reducing the yield of the monosilylated helicene. An alternative, starting with racemic TMS-helicene

**463** (Scheme 9), was also examined (in this case it would be the recovered starting material that would be the target to take onward in the reaction sequence). Using two equivalents of *s*-BuLi relative to the helicene and a 5:1 ratio of (–)-sparteine/*s*-BuLi, di-TMS-helicene (*P*)-**466** was obtained in 15% conversion and 70% e.e. and the recovered SM **463** was obtained in 15% e.e. Desilylation (TBAF) of **466** (70% e.e.) gave (*P*)-**8** (74% e.e.), confirming with accuracy the enantiomeric excess measured for (*P*)-**466**.



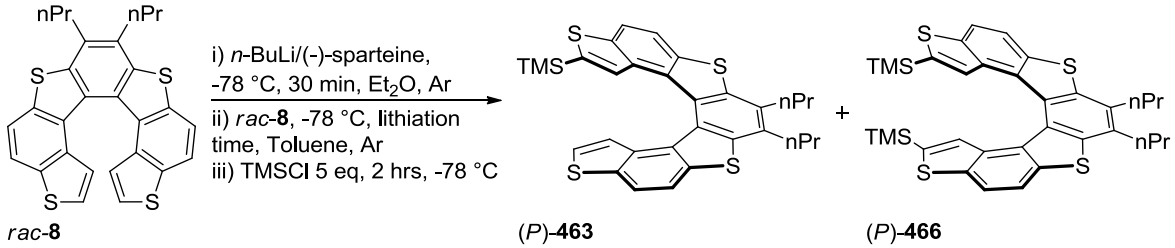

**Scheme 9: KR reaction using racemic TMS-helicene 463**

We have not reported values for the selectivity factor (*S*) (see the KR section of the introductory chapter), because these lithiation reactions do not always proceed with complete recovery of all the material introduced in the reaction, making *S* values imprecise because they rely on the accurate measurement of the conversion. Also, the standard lithiation of helicene **8** gives two products making the calculation of *S* even more meaningless. However this particular example, using TMS-helicene **463**, only produces one product and the HPLC analysis of the mixture of product **466** and SM **8** gives a chromatogram where the integration of peaks corresponding to the (*P*)-enantiomers is equivalent to the one of the (*M*)-enantiomers, meaning that no material has been lost. In this case, *S* value can be calculated accurately. Using the Goodman applet,[10] a selectivity factor of 12 was obtained for this last reaction, meaning that it should be possible to obtain enantiopure recovered (*M*)-**463** by a single KR of racemic TMS-helicene **463** at over 65% conversion.

5) Kinetic resolution using *n*-BuLi

The choice of alkyllithium reagent is an important consideration in the optimisation of the KR process, since this should influence the reactivity of each aggregate and the proportions of the aggregates formed. Table 8 presents results obtained using *n*-BuLi. Despite its lower selectivity, conversions were considerably higher when using *n*-BuLi (two times higher

than with *s*-BuLi; compare Table 7, entries 4 and 5 with Table 8, entry 1, for example), and it proved possible to reduce the excess of (–)-sparteine needed for an efficient KR (table 2, entry 2). (*P*)-**463** was obtained in 51% e.e. at 33% conversion and (*P*)-**466** was formed in 84% e.e. in this experiment.




*rac*-**8** (*P*)-**463** (*P*)-**466**

**Scheme 10: Kinetic resolution using *n*-BuLi**

| Entry | *n*-BuLi [eq] | (–)-Sparteine /*n*-BuLi ratio | Lithiation time [hrs] | Conversion 466 [%][a] | e.e. [%] of 466[b] | Conversion 463 [%][a] | e.e. [%] of 463[b] | e.e. [%] of 8[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 5:1 | 4 | 16 | 86 (*P*) | 45 | 30 (*P*) | 68 (*M*) |
| 2 | 2 | 1.1:1 | 4 | 7 | 84 (*P*) | 33 | 51 (*P*) | 40 (*M*) |
| 3 | 1 | 5:1 | 4 | 0.5 | >90 (*P*) | 13.5 | 53 (*P*) | 12 (*M*) |
| 4 | 2 | 1:1 | 4 | 8 | 87 (*P*) | 34 | 44 (*P*) | 43 (*M*) |

[a] SM and products were not separated on column chromatography, and conversion was measured by integration of HPLC signals (calibrations were done showing that **8**, **463** and **466** have similar enough UV responses to measure the conversion directly by integration of the HPLC signals) [b] measured by HPLC.

**Table 8: KR results using *n*-BuLi**

Interestingly, these results shed some light on the formation of aggregates, showing that the 1:1 homodimer **465** (see Figure 4) reported for *n*-BuLi, is probably formed efficiently when a only 1:1 ratio is used (compare Table 8, Entry 1 and Entry 4). On this basis, one would expect that using *i*-PrLi, the (–)-sparteine•(*i*-PrLi)$_2$ 1:2 heterodimer **464** (see Figure 4) would be formed if a 1:2 ratio of (–)-sparteine / *i*-PrLi is employed. It is generally thought that *i*-PrLi and *s*-BuLi behave similarly, but in fact when using a 1:1 ratio with *s*-BuLi (which is in theory twice as much as what is needed to form the 1:2 dimer), the selectivities were lower than when the ratio was 5:1. In contrast, when *n*-BuLi was used with a 1:1 ratio, it gave the same results as those observed for a 5:1 ratio. This means that with *n*-BuLi the aggregate is always 1:1 regardless of the excess of the (–)-sparteine, whereas with *s*-BuLi, the aggregation state varies when more (–)-sparteine is employed. This suggests that the 1:2 heterodimer, although probably formed in substantial amounts, may not necessarily be the important chiral base determining the stereocontrol of the

formation of the lithiohelicene. It could also be the case that *s*-BuLi, like *n*-BuLi, prefers to form a 1:1 dimer, but because of steric hinderance, more (–)-sparteine is needed to progress substantially from the 1:2 structure to the 1:1 form.

### 6) Introduction to multiple kinetic resolution

Of all of these asymmetric lithiation experiments, the second lithiation of the partially kinetically resolved 2-lithiotetrathia[7]helicene **461** is itself a kinetic resolution, so the production of di-TMS-helicene **466**, reported in Table 7 and Table 8, corresponds to a double-KR process. In view of this, it is perhaps not surprising that in every case, far higher e.e.s (i.e. almost completely enantiomerically pure **466**) were observed for **466** than for the monosilyl product **463** from the same experiment. Because of the $C_2$ symmetry of the thiahelicene starting material **8**, the preferred combination of (–)-sparteine•BuLi aggregate and (*M*)/(*P*) helicene for the initial lithiation step (e.g. at C-2) is also the stereochemically advantageous combination at C-13. The production of very highly enantioenriched di-TMS-helicene (*P*)-**466** has provided us with our first example of a stereochemically efficient double-KR process. Desilylation of (*P*)-**466** provides the most practical access to the enantiopure starting material (*P*)-**8** as very highly enantioenriched **8** can be recrystallized to optical purity (from e.e. > 90% to e.e. > 99%). Following on from this first example and proof of principle, this thesis will describe several other multi-KR strategies that can afford enantiopure helicene derivatives.

## IV) Multiple kinetic resolution: results

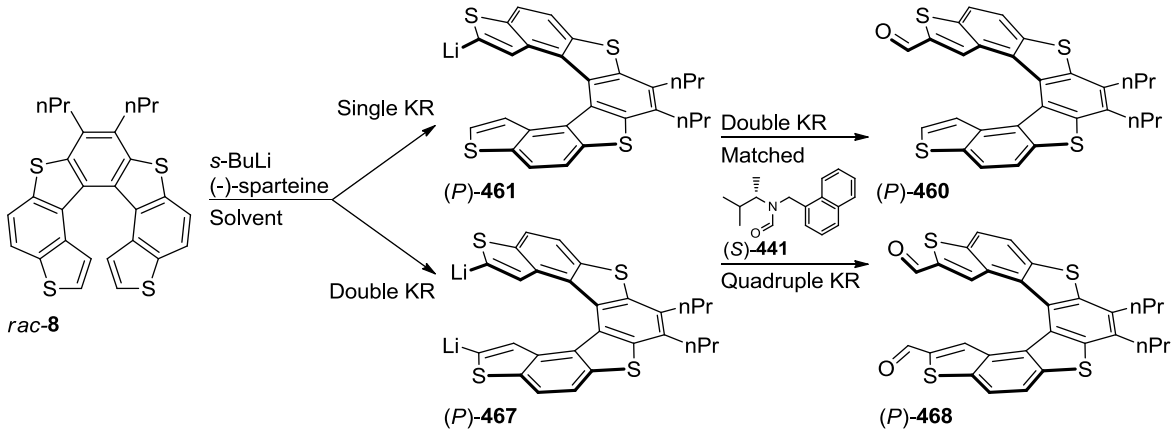
### 1) Initial approach

#### a) (–)-Sparteine / chiral formamide (*R*)-**441**

At the outset of this research, our initial strategy for the multi-KR synthesis of 2-formyl- and 2,13-diformyltetrathia[7]helicenes (**460** and **468**) was to employ (–)-sparteine-mediated asymmetric lithiation of racemic tetrathia[7]helicene, followed by a novel asymmetric formylation using chiral formamides in the matched configuration, in the same step (Scheme 11).

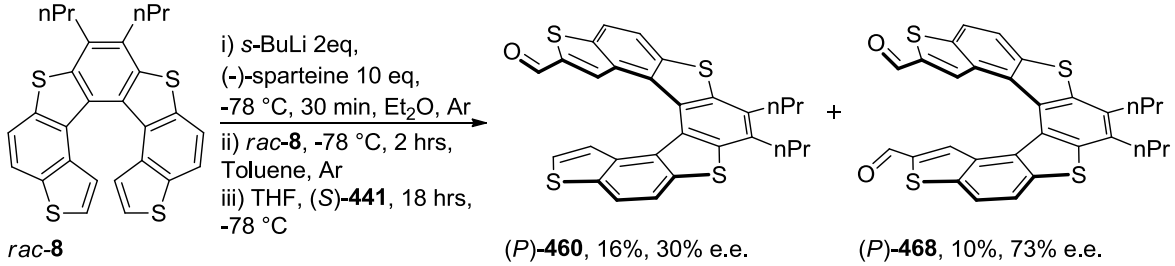
However, finding a compatible solvent for both steps turned out to be problematic. As shown by the results of single kinetic resolutions, the formamides can only really be used in THF, and the lithiation with chiral auxiliary (–)-sparteine is known not to be efficient in THF (THF is a stronger ligand for organolithium reagents than $Et_2O$ and (–)-sparteine).

Considering that the better step by far is the lithiation step, improving significantly the enantioselectivity in a second step using formamides, could only be done in conditions most favourable to the asymmetric formylation.




**Scheme 11: Initial strategy for the multi-KR**

Consequently, for our first attempts at double KR in the formylhelicene **460** synthesis, we tried combining positive solvent effects for each step of the reaction. We generated the non-racemic lithiohelicene (*P*)-**461** in $Et_2O$/toluene before adding a solution of chiral formamide (*R*)-**441** in THF. Unfortunately, the desired formylhelicene **460** was identified by HPLC in only 30% e.e. (some diformylhelicene **468** was observed in 73% e.e.) (Scheme 12).

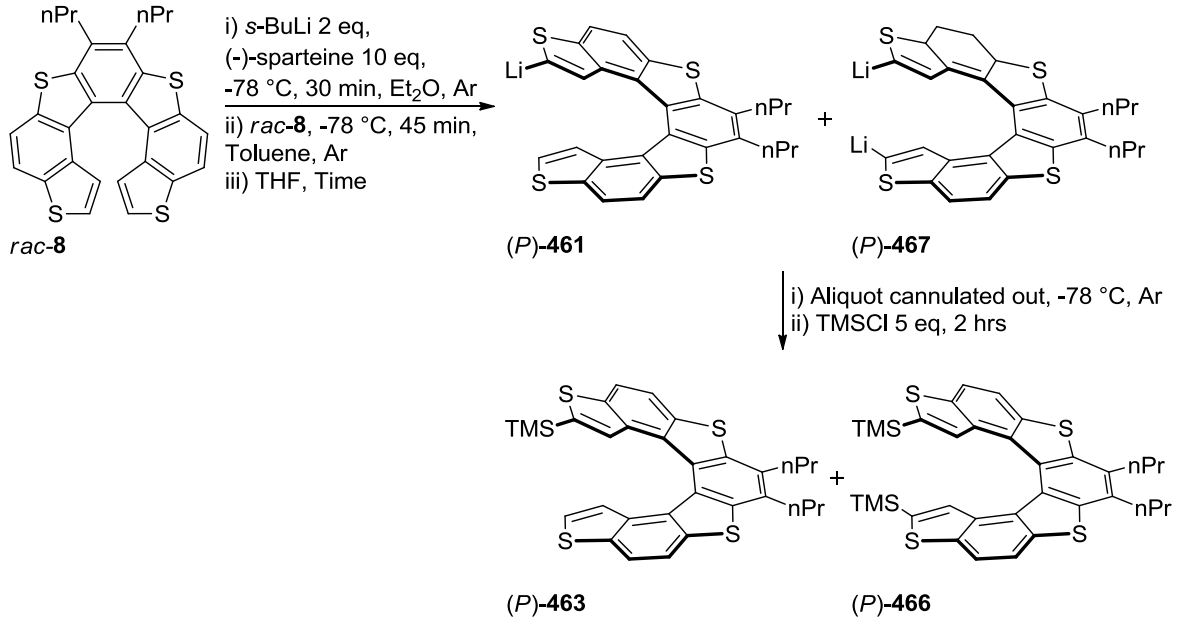



**Scheme 12: Attempt at double KR**

There were no big expectations for this strategy, and the poor results can simply be explained by the possibility that upon addition of THF, dissociation of the (–)-sparteine•*s*-BuLi aggregates 'frees' *s*-BuLi generating more lithiohelicene **461** in a non-asymmetric manner. Consequently low enantioselectivity of lithiohelicene **461** can be expected, and

formylhelicene **460** cannot be formed in high enantioselectivities. Furthermore, considering that the reaction of lithiohelicene **461** with the chiral formamide is much slower that the lithiation of SM **8** by *s*-BuLi, this reaction could never be successful.

This view can be supported by the following experiment. Using the standard efficient lithiation process promoted by a 5:1 ratio of (–)-sparteine/*s*-BuLi, a 2-lithiohelicene **461** solution was prepared and after addition of THF, aliquots were taken at regular intervals and quenched by addition of excess chlorotrimethylsilane (Scheme 13). The enantiomeric excesses of the resulting samples of TMS-helicene **463** were measured by HPLC and the data is showed in Table 9.




**Scheme 13: KR of helicene 8 followed by addition of THF**

| Entry | Time [hrs] after THF added | Conversion into 466 [%][b] | e.e. [%] of 466[c] | Conversion into 463 [%][b] | e.e. [%] of 463[c] | e.e. [%] of 8[c] |
|---|---|---|---|---|---|---|
| 1 | 0 | 3 | 82 *(P)* | 28 | 53 (*P*) | 30 (*M*) |
| 2[a] | 0.5 | 3 | 6 (*P*) | 23 | 9 (*M*) | 1 (*M*) |
| 3 | 3 | 31 | 1 (*M*) | 48 | 8 (*M*) | 10 (*P*) |
| 4 | 17 | 20 | 10 (*M*) | 61 | 5 (*M*) | 5 (*P*) |

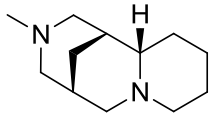
[a] same conditions but different reaction; [b]SM and products were not separated on column chromatography, and conversion was measured by integration of HPLC signals (calibrations were done showing that **8**, **463** and **466** have similar enough UV responses to measure the conversion directly by integration of the HPLC signals) [c] measured by HPLC.

**Table 9: KR results: influence of the addition of THF after the asymmetric lithiation**

Although these results have to be taken cautiously because taking out the aliquots in a representative manner has proven to be quite challenging, the data collected in Table 9 show that non-asymmetric lithiation is occurring readily after the addition of THF, proving that addition of a chiral formamide solution in THF cannot be successful in the same conditions as those for efficient asymmetric lithiation.

b) Use of (+)-sparteine surrogate (+)-**459**

O'Brien's work[11] has established a possible alternative to (–)-sparteine, the '(+)-sparteine surrogate' (+)-**459** (Figure 1) which forms aggregates with organolithium reagents even in THF.[12] However, repeated asymmetric lithiation attempts performed with the (+)-**459** in THF failed to afford enantioenriched material. This was surprising, and the most likeky explanation was that aggregates were formed but there was no chiral recognition of helicene **8**. In order to explore this more fully, the surrogate was used in the exact same conditions that gave successful results with (–)-sparteine (i.e. in $Et_2O$/toluene and the 5:1 ratio), and despite repeated efforts, TMS-helicene **463** obtained showed no e.e.s greater than 5%.




(+)-**459**

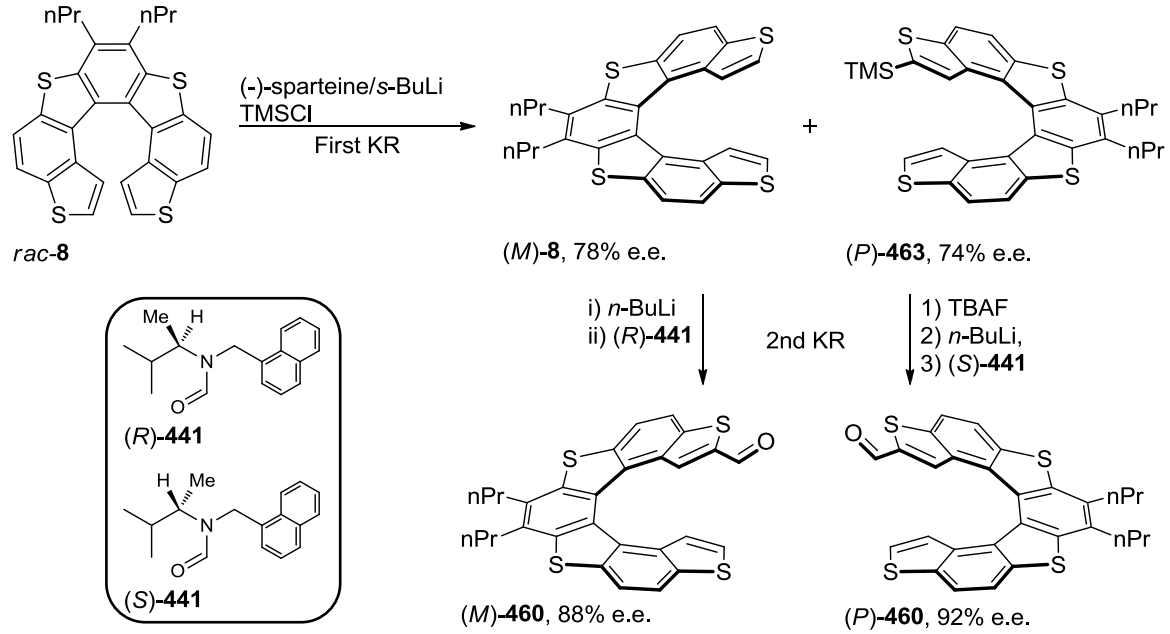
**Figure 5: (+)-Sparteine surrogate (+)-459**

2) Stepwise multi-KR

a) Formation of enantiopure formylhelicene **460**

Our attention now turned towards performing the asymmetric lithiation and the asymmetric formylation in two separate chemical steps. In this way, the contribution of each asymmetric bias to the overall progress towards enantiomeric purity would be more easily studied than in the procedurally more rapid one-pot version of the double-KR process discussed above. First, the *s*-BuLi/(–)-sparteine/chlorotrimethylsilane procedure afforded (from two distinct experiments), after separation by column chromatography, highly enantioenriched recovered helicene (*M*)-**8** and TMS-helicene (*P*)-**463**. (*P*)-**463** was desylilated and then both (*M*)-**8** and (*P*)-**8** were examined in asymmetric formylation with chiral formamide **441** in the matched configuration. This two-step protocol (Scheme 14) allows a different solvent (THF in our case) to be used in the second step which proved to

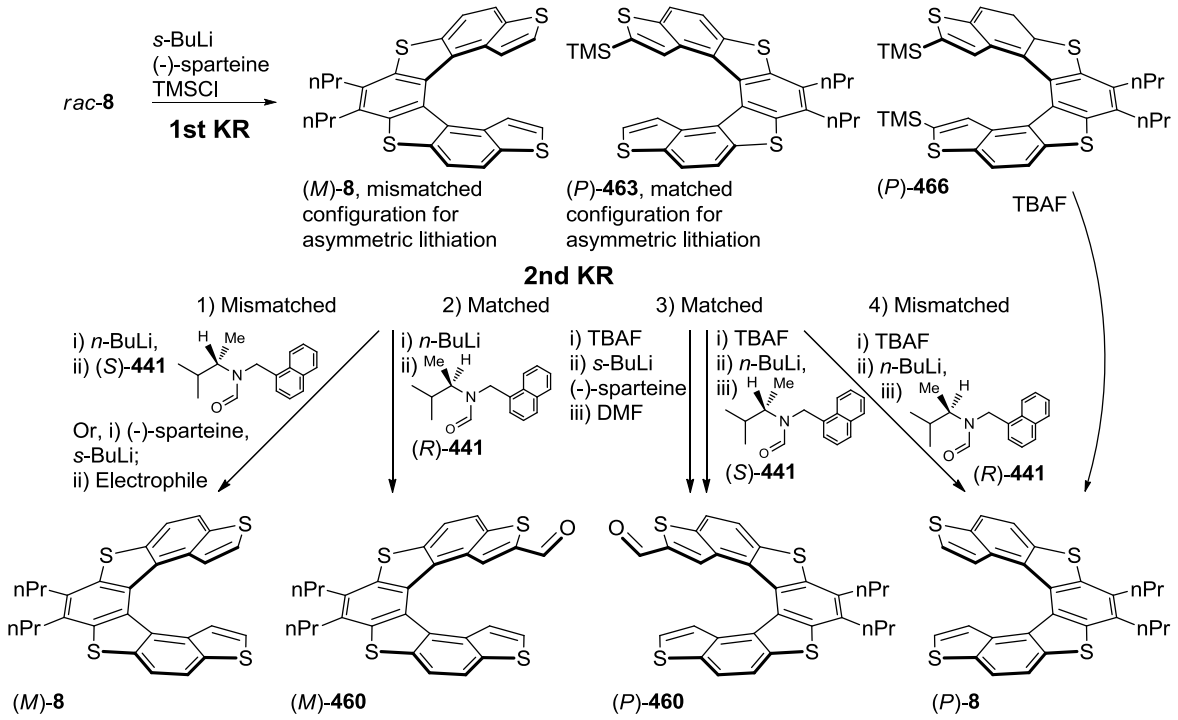
be a considerable practical advantage as (*M*)-**460** and (*P*)-**460** were obtained respectively in 88% (Table 10, Entry 2) and 92% e.e. (Table 10, Entry 7). Another advantage of this approach is that using a single enantiomer of sparteine, both enantiomers of the formylhelicene **460** could be obtained as enantiopure products (in practice the highly enantioenriched samples from the double-KR would then be recrystallized to gain enantiopurity).




**Scheme 14: Double kinetic resolution**

b) Other double kinetic resolutions

Clearly, even for this simple two-step process, many alternative multi-KR strategies are available, combining matched and mismatched asymmetric lithiation [using (–)-sparteine] and asymmetric formylation (using the appropriate enantiomer of the chiral formamides). The *s*-BuLi/(–)-sparteine/chlorotrimethylsilane procedure should always be used first as it allows regeneration of parent helicene (after desylilation) and is much more efficient. Based on this principle, Scheme 15 presents: 1) two mismatched-mismatched strategies; 2) one mismatched-matched strategy (already presented in the previous paragraph); 3) two matched-matched strategies (one is already presented in the previous paragraph); 4) one matched-mismatched strategy.




**Scheme 15: Comparison of double KR strategies**

| Entry | Conditions [a] for $KR_1$ | Conversion of $KR_1$ | $KR_1$: e.e. of product | Conditions [a] for $KR_2$ | Conversion of $KR_2$ | $KR_2$: e.e. of product | Overall conversion $KR_1$*$KR_2$ |
|---|---|---|---|---|---|---|---|
| 1 | B | **466**, 14%[b] | 93% (*P*) | - | - | - | 14% |
| 2 | B | **8**, 56%[b] | 64% (*M*) | B | **8**, 83%[b]<br>**466**, 5%[b] | 93% (*M*)<br>>90% (*P*) | 47%[b]<br>3%[b] |
| 3 | B | **8**, 56%[c] | 78% (*M*) | C | **460**, 10%[b] | 88% (*M*) | 5.6% |
| 4 | B | **8**, 56%[c] | 77% (*M*) | E | **8**, 69% | 84% (*M*) | 39% |
| 5 | B | **8**, 56%[c] | 74% (*M*) | A | **8**, 76% | 88% (*M*) | 43% |
| 6 | A | **463**, 22% | 67% (*P*) | D | **466**, 11%[d] | 84% (*P*) | 2.4% |
| 7 | A | **463**, 23% | 74% (*P*) | C | **460**, 10%[b] | 92% (*P*) | 2.3% |
| 8 | B | **463**, 30% | 43% (*P*) | A | **466**, 15%<br>**463**, 45% | >90% (*P*)<br>76% (*P*) | 4.5%<br>14.5% |

[a] Conditions: A: 2 eq *s*-BuLi, 5:1 ratio (–)-sparteine/*s*-BuLi, 4 hrs lithiation, 2 hrs reaction time after electrophile addition; B: 3 eq *s*-BuLi, 5:1 ratio (–)-sparteine/*s*-BuLi, 4 hrs lithiation, 2 hrs reaction time after electrophile addition; C: 1 eq *n*-BuLi, no (–)-sparteine, 1 hr lithiation, 18 hrs reaction after matched chiral formamide addition; D: 6 eq *s*-BuLi to the mismatched helicene, 5:1 ratio (–)-sparteine/*s*-BuLi, 4 hrs lithiation, 2 hrs reaction time after electrophile addition; E: 1 eq *n*-BuLi, no (–)-sparteine, 1 hr lithiation, 18 hrs reaction after mismatched chiral formamide addition; F: 2 eq *n*-BuLi, no (–)-sparteine, 1 hr lithiation, 18 hrs reaction after mismatched chiral formamide addition; [b] isolated yields (in the other cases the overall conversion was calculated by integration of the HPLC signals); [c] Initially **8** came from the same reaction in 56% conversion, however the e.e.s are different because the material with 78% e.e. was used for a KR and recovered SM showed 77% e.e, which was used again and recovered SM showed 74% e.e.; [d] asymmetric lithiation performed on enantioenriched **463** giving **466** as the product

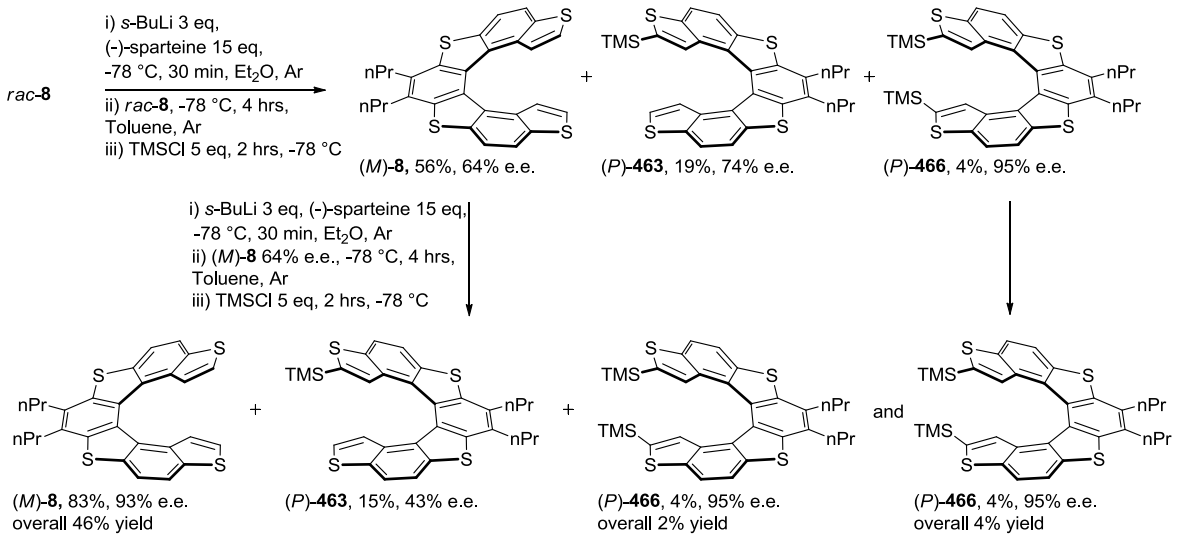
**Table 10: Results of double KR**

These results showed that in practice, the mismatched-mismatched strategy using twice the asymmetric lithiation method (with three equivalents of *s*-BuLi and a 5:1 (–)-sparteine/*s*-BuLi ratio) is the most powerful, giving the parent helicene **8** in high 47% yield and 93% e.e. (Table 10, Entry 2, see also below Scheme 16). Alternatively, using a chiral formamide for the second mismatched step gave **8** in 39% conversion and 84% e.e. (Table 10, Entry 4).

Concerning the matched-matched strategies, yields obtained are lower, and although they could be improved, kinetic resolution by nature is limiting them. For example, when a second KR step is performed in the matched condition, if one wants to perform the reaction in conditions as similar as possible to the racemic case, the amount of resolving agent has to be added according to the amount of the minor enantiomer. Taking Table 10, Entry 7 as an example, in order to perform the second step with helicene **8** at 74% e.e. (equivalent to e.r. of 87:13), only 0.13 equivalents of the chiral formamide can be used when seeking a stereodifferentiation effect at the same level as that obtained when starting with racemic helicene **8**. For this reason, matched-matched strategies will only proceed with a poor conversion of the initial starting material. Although the asymmetric lithiation is much more efficient than the asymmetric formylation, the use of two asymmetric lithiation steps, whether they are two distinct steps (Table 10, Entries 6 and 8) or one single dilithiation, (Table 10, Entry 1) will also give low conversions. Interestingly, the one-step dilithiation double KR (Table 10, Entry 1), although proceeding at a low conversion, it is in fact a much higher conversion (**466**, 14%) than the stepwise triple KR (Table 10, Entry 8) that converts only 4.5% the initial SM **8**.

3) Best example of a double KR

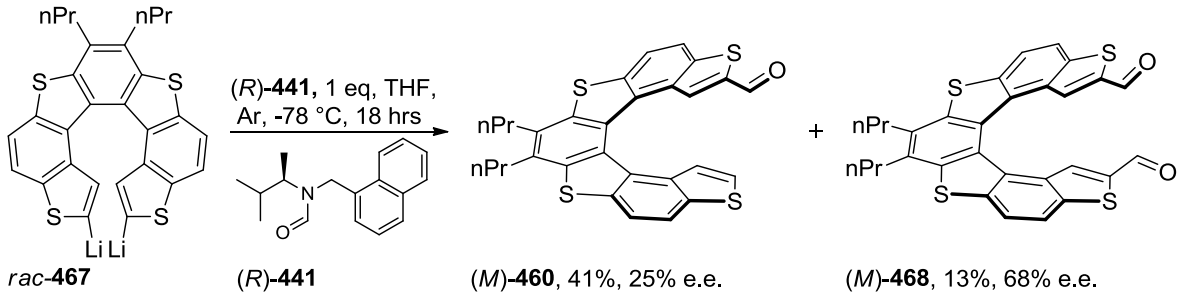
In order to summarise results obtained, emphasis will be given to the sequence of KR steps that employs two distinct asymmetric lithiations. It allows the resolution of 52% of the racemic helicene **8**, (46% of (*M*)-**8** and 6% of (*P*)-**466**) at enantiomeric excesses greater than 90% in an only two-step process (Scheme 16). This adequately demonstrates the power of KR by (–)-sparteine-mediated chiral recognition of 7,8-dipropyltetrathia[7]helicene (**8**), and establishes the principle of the multi-KR approach.




**Scheme 16: Most efficient double KR sequence**

4) Double KR by asymmetric diformylation

In view of our target, 2,13-diformyl-7,8-dipropyltetrathia[7]helicene (**468**), we examined the alternative of performing a double KR using asymmetric diformylation. Upon treatment of racemic parent helicene **8** with two equivalents of *n*-BuLi, racemic 2,13-dilithiohelicene **467** was generated and a subsequent quench with formamide (*R*)-**441** gave a mixture of formylhelicene (*M*)-**460** and diformyl-helicene (*M*)-**468** (Scheme 17). The latter was obtained in 13% yield and 68% e.e. This compares positively with the single KR of parent helicene **8** using formamide (*R*)-**441**, that gave formylhelicene (*M*)-**460** in only 42% e.e.




**Scheme 17: Double KR by asymmetric diformylation**

V) Conclusion

The preliminary studies on the single KR whether using asymmetric lithiation or asymmetric formylation allowed us to get a deeper understanding of the helicene's

behaviour under the conditions used. The examination of asymmetric formylation identified the most suitable type of target (i.e. a formamide with a secondary amine scaffold bearing an aliphatic chiral moiety and an aromatic moiety). Among this class of compounds, formamide (*R*)-**441** bearing a naphthyl moeity, gave formylhelicene (*M*)-**460** in 30% yield and 41% e.e. The examination of asymmetric lithiation using a *s*-BuLi/(–)-sparteine system gave surprising results for a kinetic resolution, as we found that the most favourable conditions required two or three equivalents of the organolithium reagent. The detailed study of the *s*-BuLi/(–)-sparteine system described in this chapter revealed that the control of aggregation was the key to promote efficient asymmetric inductions. Although the aggregation state of *s*-BuLi/(–)sparteine obtained in the case of the most successful examples is not clearly identified, either a 1:1 dimer (–)-sparteine•*s*-BuLi, or a slightly higher aggregation state, is most likely to be the reactive species. Ensuring the control of the aggregation state by using large excesses of (–)-sparteine (limiting the dissociation of *s*-BuLi or causing the formation of higher aggregates that are more chirally discriminating) was found to be essential to the success of the KR experiments. Using two equivalents of *s*-BuLi with a 5:1 ratio of (–)-sparteine/*s*-BuLi followed by the subsequent quench with chlorotrimethylsilane gave TMS-helicene **463**, in 35% conversion and with 84% e.e.

For our study of the multiple kinetic resolution, several strategies based on the combination of two matched or mismatched steps were developed. However, the stepwise sequence of two asymmetric lithiations was found to be the most effective technique allowing for the resolution of more than 50% of the initial stating material at over 90% e.e., as shown in Scheme 16. Since highly enantioenriched 7,8-dipropyltetrathia[7]helicene can be recrystallized from hexane to the enantiopure form (from 90% e.e. to enantiopure), the levels of chiral discrimination achieved, even at this early stage, validate our methodology as a practical access to both enantiomers of enantiopure tetrathia[7]helicene. At this stage, we have demonstrated for the first time the principle of multi-KR methods in enantioselective synthesis, by the successful preparation of enantiomerically pure parent 7,8-dipropyl-tetrathia[7]helicene (**8**). The techniques used are suitable for enantioselective preparation of formyl and diformylhelicenes **460** and **468** required for studies of nonlinear optics and TPCD effects with D-(chiral-π)-A chromophores.

Of course, in future work, more progress can be expected, whether it is via the development of more efficient chiral formamides, or by finer tuning / deeper understanding of the conditions used for the asymmetric lithiation (or both). This continued in-depth

study, and the extension of these methods to a range of helicenes, will prepare the way for a far broader application of the multi-KR method as a general synthetic procedure for targets that combine, for example, pharmacophores with stereogenic centres. This doctoral study has launched a new approach to the design of enantioselective synthetic routes, and the application of the methodology with other helicenes and related C2 symmetric starting materials (e.g. biaryls) would be decisive steps in illustrating the wider applicability of the procedures described here for the first time in this thesis.

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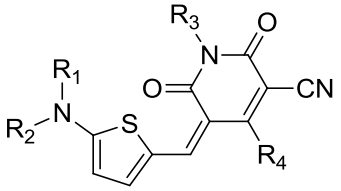
# Chapter 4:
# Synthesis of chiral push-pull systems

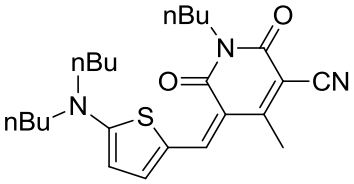
# I) Push-pull systems

## 1) General characteristics

'Push-pull systems' contain an electron donor (D), an electron acceptor (A) spaced out by a π system, constituting D-π-A molecules. These molecules exhibit strong nonlinear optical properties, which can be optimised either by increasing the length of the conjugation or by increasing the strength of the donor and acceptor groups. Thiophene-based organic high performance chromophores[1] are an important class of push-pull systems. Among these organic dyes based on a thiophene scaffold,[2] ATOP dyes (aminothienyl-oxopyridine) (Figure 1) have shown important NLO properties,[3] and it was decided at the outset of our research to build our thiahelicene push-pull systems based on the model of the ATOP-1 dye (**470**).




ATOP dyes, R = alkyl, **469**




ATOP-1, **470**

**Figure 1: ATOP dyes**

## 2) Our push-pull systems

The strategy of 'decorating' our helicenes with substituents that have proved to be efficient in creating NLO effects was motivated by recent studies[4] estimating that tetrathiahelicenes are interesting candidates for nonlinear optics especially for the direct observation of Two Photon Circular Dichroism (TPCD).[5] For this, our aim was to synthesise push-pull systems with a stereochemically defined 7,8-dipropyltetrathia[7]helicene core bearing the ATOP dye end groups. Figure 2 presents two of our targets. (*M*)-**471** is a D-(chiral-π)-A example, whereas (*M*)-**472** is an A-(chiral-π)-A example, which could be regarded as an A-(chiral-π)-D-(chiral-π)-A structure if the helicene core with the two propyl chains on the central ring takes the role of the electron donor.

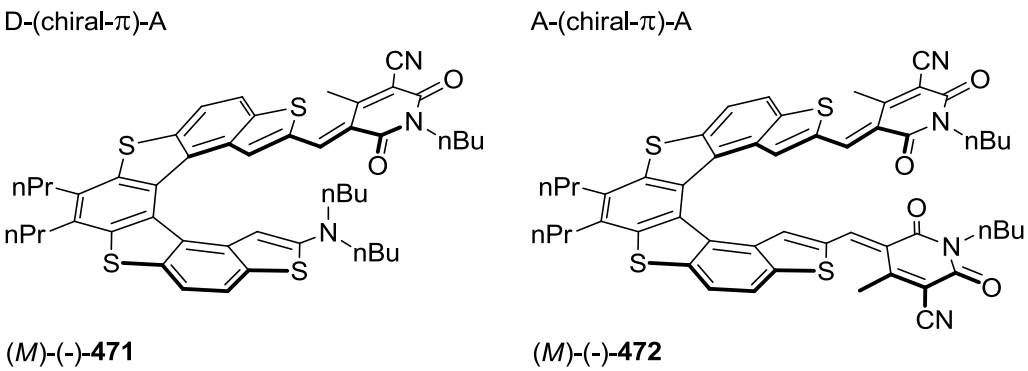



**Figure 2: Push-pull systems targets (here in *M* configuration)**

Some intermediates in the synthesis of the targets presented in Figure 2, can also be interesting compounds to study the nonlinear optical effects described earlier. Indeed, di-formylhelicene **468**, or amino-formylhelicene **473** (Figure 3) are respectively decent A-(chiral-π)-A and D-(chiral-π)-A systems.

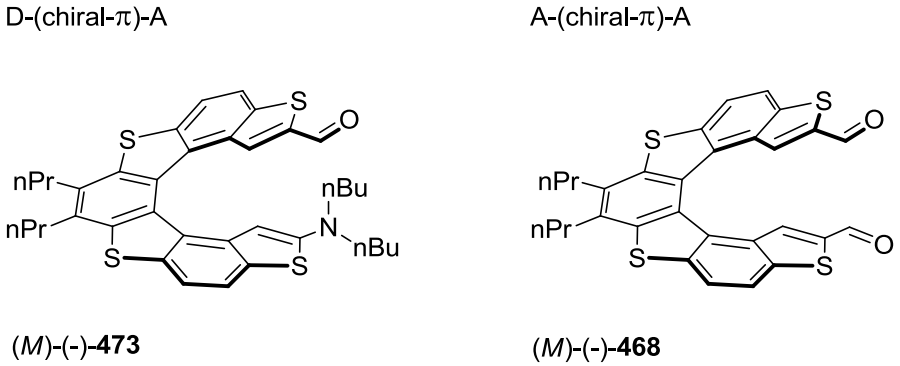



**Figure 3: Alternative push-pull systems (here in the *M* configuration)**

When the project started, the thiahelicene core itself was potentially a good target to observe TPCD, however the technological status at the time lacked the sensitivity needed for the direct observation of TPCD phenomena. Since then, technological improvements have been made, and even enantiopure 7,8-dipropyltetrathia[7]helicene (**8**) itself, could possibly allow the observation of TPCD, and this is currently being examined by our collaborators in Leuven (Pr. Thierry Verbiest).

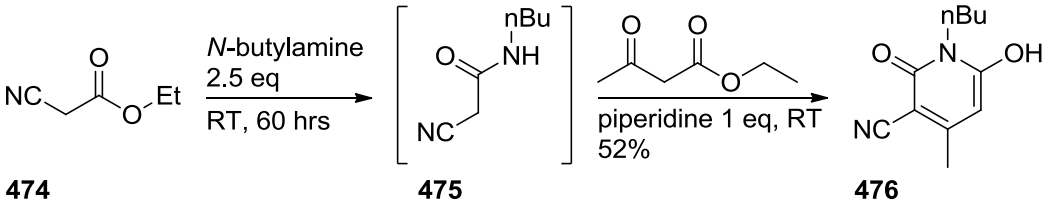
Although in previous chapters we have presented strategies to obtain enantiopure helicene material, discussions with Pr. Verbiest made it clear that enantiopure material will not necessarily outperform simply enantioenriched helicene. Nonlinear optical experiments on

helicene at varying e.e.s from racemic to enantiopure forms will establish what level of enantiopurity is optimal for the NLO response.

II) Synthesis of D-(chiral-π)-A and A-(chiral-π)-A systems

1) Synthesis of the pyridone acceptor group

Pyridone acceptor groups are found in ATOP dyes, but also in many other dyes. Pyridone **476** was synthesised according to the published literature.[6] Ethyl cyanoacetate (**474**) was added dropwise to *N*-butylamine forming a non-isolated intermediate 2-cyano-*N*-butylacetamide (**475**), which was then reacted with ethyl acetoacetate forming desired pyridone **476** in 52% yield (Scheme 1).



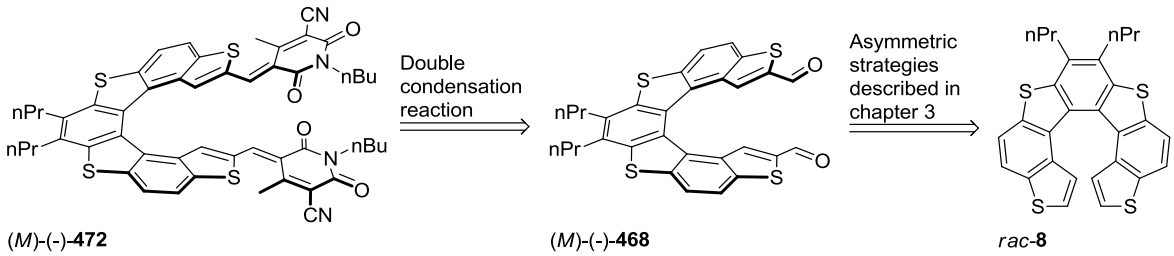

**474** **475** **476**

**Scheme 1: Synthesis of pyridone 476**

2) A-(chiral-π)-A systems

a) Retrosynthetic analysis

Of the two types of push-pull systems presented above, A-(chiral-π)-A molecules are by far the easier ones to synthesise as only one type of functionality has to be installed. Our case requires introducing pyridine-dione moieties; they can be obtained by a straightforward double condensation reaction of dialdehyde **468** and pyridone **476**, as shown on the retrosynthetic analysis (Scheme 2). The required aldehyde intermediate, **468**, can be obtained in enantioenriched forms using one of the asymmetric strategies described in chapter 3.




(*M*)-(-)-**472** (*M*)-(-)-**468** *rac*-**8**

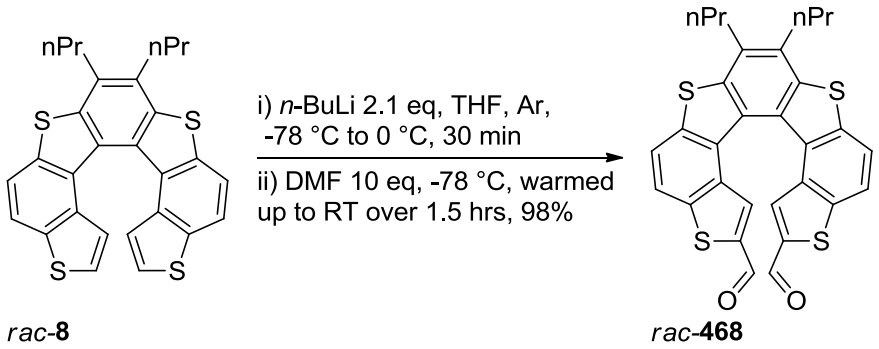
**Scheme 2: Retrosynthetic strategy for the synthesis of A-(chiral-π)-A system 472**

Although the representation in Scheme 2 shows the helicene in the *M* configuration, both enantiomers are potential targets.

b) Synthesis

i) Racemic series

In order to get familiar with the chemistry, all target molecules were first synthesised as racemic versions. After dilithiation of racemic helicene **8** using an excess of *n*-BuLi, subsequent quenching with DMF gave the known[7] racemic dialdehyde **468** in 98% yield (Scheme 3).

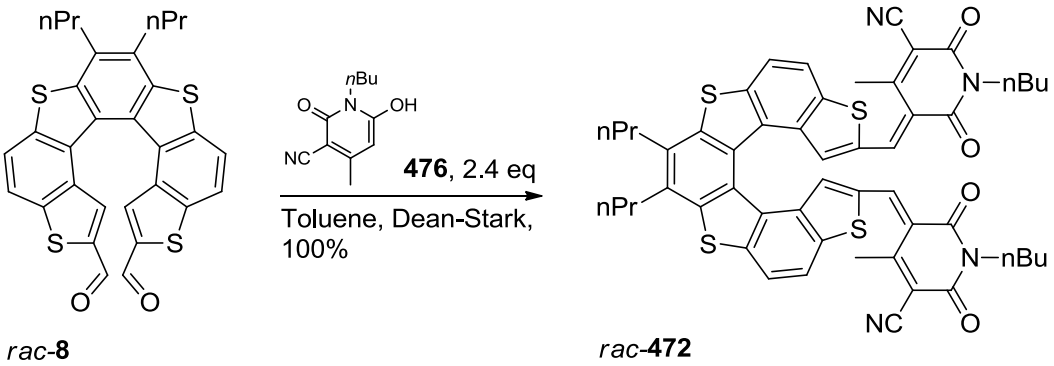



*rac*-**8** *rac*-**468**

**Scheme 3: Synthesis of racemic dialdehyde 468**

The double condensation reaction was then examined. The literature about the synthesis of ATOP dyes[3] that we were following indicates that the condensation reaction is performed in the absence of solvent and simply using acetic anhydride (5.5 eq, 0.5 mL per mmol) as a drying agent that drives the equilibrium of the condensation reaction forward. However, this procedure was seen as unpractical in the case of our helicenes where the amount of product used is most likely to be below one millimole. Therefore, we decided to perform this reaction in toluene, in a reaction vessel equipped with a Dean-Stark trap in order to remove the water produced. One equivalent of dialdehyde **468** and 2.4 equivalents (although used in excess, no trace of **476** is observed in the crude NMR) of pyridone **476** were refluxed in toluene for two hours giving the deep-red pyridine-dione **472** in quantitative yield (Scheme 4). Although many different solvents were tried for recrystallization of **472**, the formation crystals was not observed. Unfortunately, these attempts resulted in the rearrangement of **472** into an unidentified product. NMR spectral data ($^{1}$H and $^{13}$C NMR) seems to indicate that the product is still symmetrical (unsymmetrically substituted helicenes show more complex $^{1}$H NMR data), but possesses one extra proton signal and two extra carbon signals (one tertiary and one quaternary

carbon). The spectra for this product are included in this thesis in Appendix B, and since this experiment was performed in the final weeks of the research period, at the time of submission samples of this intriguing and puzzling product had be sent to the EPSRC Mass Spectrometry Service at Swansea to gain molecular ion data.




**Scheme 4: Synthesis of racemic A-(chiral-π)-A 472**

ii) Enantioenriched series

Before attempting the synthesis in the enantioenriched series, a careful study of the conditions used for recrystallization and storage of the novel racemic dye **472** needs to be done in order to assess the stability of the compound. When this is established, future work will focus on synthesising enantiopure **472**.

As stated previously in this chapter, dialdehyde **468** can also be an interesting target for the study of the TPCD phenomenon. Although its synthesis in an enantiopure version has not been described in this thesis, many different strategies presented in the multi-KR chapter would readily give the enantiopure dialdehyde **468**.

3) D-(chiral-π)-A

a) Retrosynthetic analysis

The synthesis of D-(chiral-π)-A systems, in particular aminohelicene-pyridine-dione **471**, is more complex than the synthesis of previously described A-(chiral-π)-A systems because it requires the introduction of two different groups in a stepwise sequence. The best combination remains to be established (Scheme 5). One thing is clear, however; the synthesis of amino-formyl intermediate **473** (Scheme 5) should be the focus of our attention in this retrosynthetic analysis, as it can easily be transformed into D-(chiral-π)-A **471** by a simple condensation reaction.

i) $S_NAr$

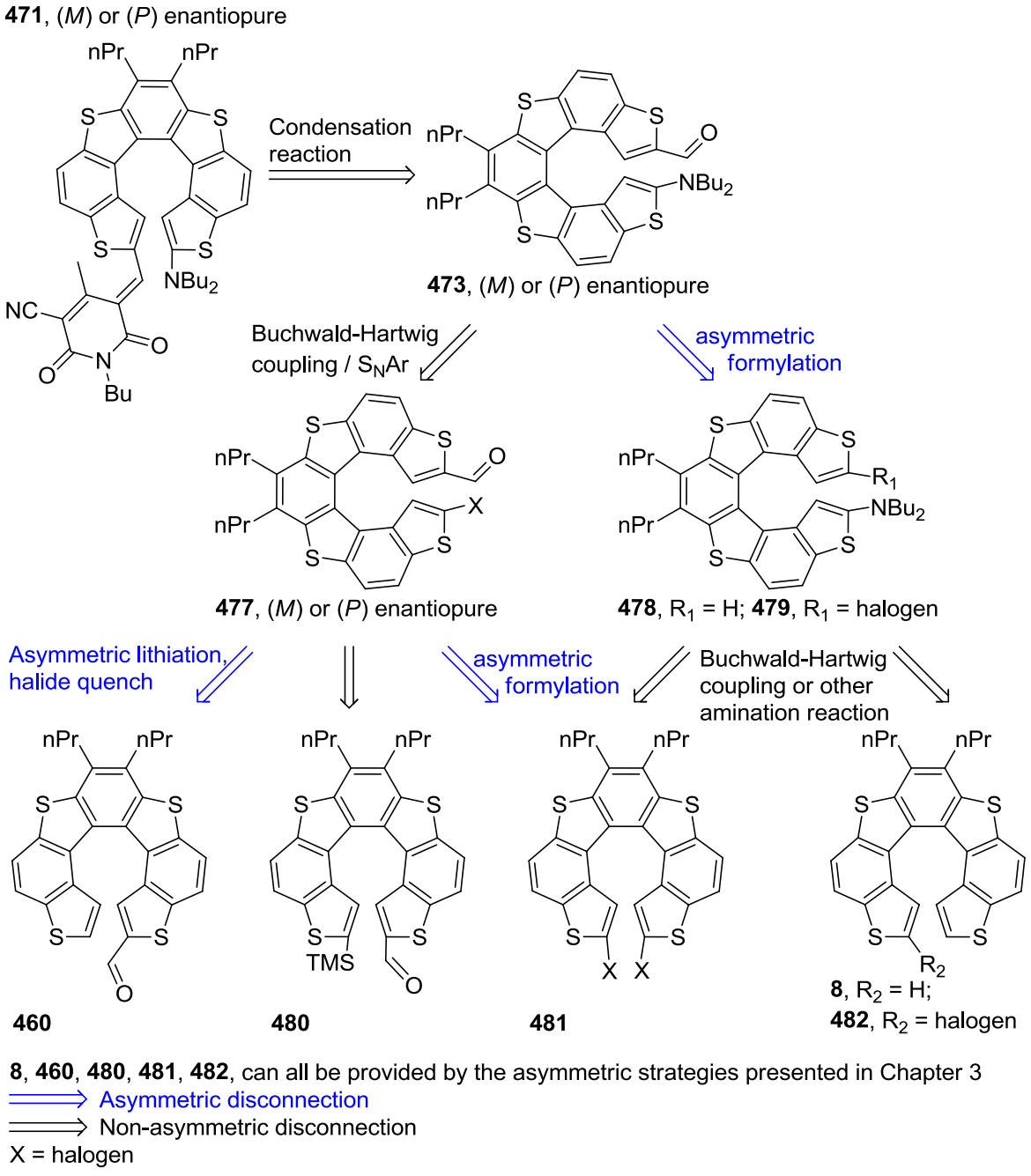
The strategy existing for the synthesis of ATOP dyes is based on the introduction of dialkylamines groups via a nucleophilic aromatic substitution reaction between 5-bromothiophene-2-carboxaldehyde and dialkylamines.[3,6] This reaction works because the C-5 position bearing the bromo substitutent is activated by the aldehyde which acts as an efficient electron withdrawing group that is essential for the reaction. However, in the case of helicenes, it was anticipated that the electron withdrawing effect of the aldehyde might be too low, in this extended aromatic structure, to influence the electrophilicity needed the carbon bearing the bromine substituent. For the further development of this strategy, the synthesis of fluoro- or chloro-**477** by means presented in Scheme 5 would be preferable to the synthesis of bromo- or iododerivatives as the reactivity for nucleophilic aromatic substitution is well-known to go in the following order for aryl halides: F > Cl > Br > I.

i) Buchwald-Hartwig coupling

A possible alternative for the introduction of the tertiary amine group is the Buchwald-Hartwig palladium mediated coupling of aryl halides and secondary amines. This would be a suitable strategy for the synthesis of aminohelicene **478**, amino-halohelicene **479** and amino-formylhelicene **473** (Scheme 5). However, 2-substituted thiophenes are known for being relatively bad substrates for Buchwald-Hartwig[8] coupling especially when using electron rich dialkylamines.

ii) Strategies for the synthesis of amination precursors

Amination precursors halo-helicene **482**, dihalohelicene **481** and halo-formylhelicene **477** can be synthesised by asymmetric protocols, or in racemic form, as shown in Scheme 5. The asymmetric methods will not be described here, but TMS-helicene **463**, di-TMS-helicene **466** and TMS-formylhelicene **480** can be obtained in enantioenriched forms using strategies described in chapter 3, and could be subsequently transformed into the iodo- or bromo-equivalents by treatment respectively with iodine monochloride or bromine.



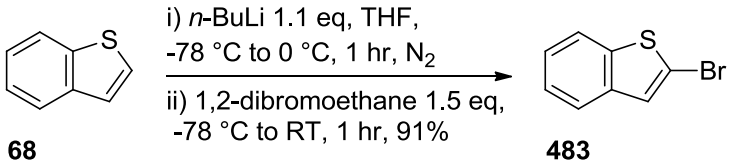

**Scheme 5: Retrosynthetic strategy for the synthesis of D-(chiral-π)-A system 471**

b) Synthesis

Concerning the introduction of the tertiary amine group, the $S_NAr$ method was not selected for the reasons explained earlier, and the Buchwald-Hartwig reaction was instead chosen as it was thought to be more suitable (as well as being possibly transformed to an asymmetric reaction as a multi-KR option).

i) Optimisation of Buchwald-Hartwig conditions

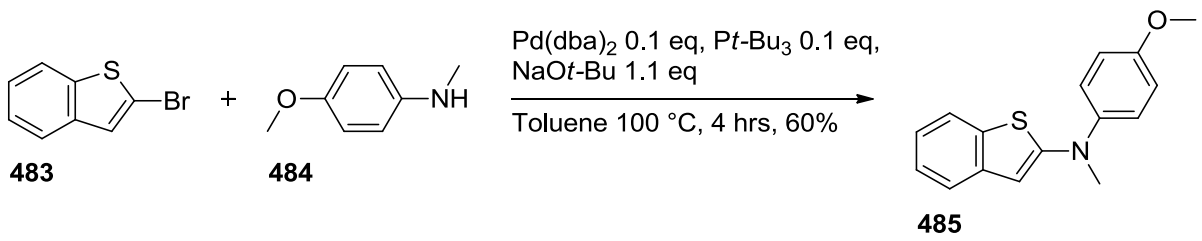
Before attempting the reaction with bromohelicene derivatives, we examined the reaction on 2-bromobenzo[b]thiophene (**483**) in order to find suitable conditions. Coupling precursor **483** was obtained in 91% yield by quenching 2-lithiobenzo[b]thiophene with 1,2-dibromoethane (Scheme 6).




**Scheme 6: Synthesis of 2-bromobenzo[b]thiophene (483)**

Following the literature[8,9] for Buchwald-Hartwig coupling reactions, we screened a range of possible conditions for the reaction of 2-bromobenzo[b]thiophene (**483**) and di-*N*-butylamine. Different palladium sources were used, Pd(P*t*-$Bu_3)_2$, $Pd(dba)_2$ and $Pd_2(dba)_3$ as well as BINAP and $Pcy_3$ ligands. Unfortunately, no desired product was observed; some reactions returned mostly starting material whereas others gave small amounts of the homocoupling product 2,2'-bibenzo[b]thiophene. Alternatively, we tried a copper mediated coupling which has been reported[10] to work for the coupling of 2-iodothiophene and pyrolidine using copper powder in DEANOL, however the formation of the desired product was not observed.

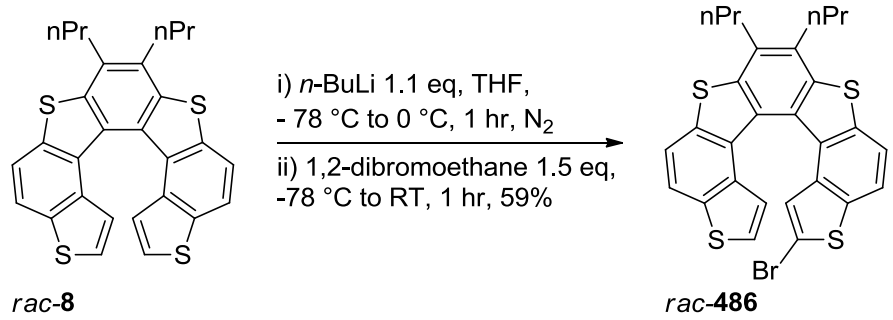
Subsequently, we turned towards more reactive aromatic secondary amines that would still be decent electron donors. *N*-methyl-*p*-anisidine **484** was chosen, and performing the coupling with what was described as the best reaction conditions,[8] using $Pd(dba)_2$ and P*t*-$Bu_3$ in equimolar amounts (although $Pd(dba)_2$ would accept two phosphine ligands, Buchwald comments that the catalytic species when using these conditions could be $Pd^I$(P*t*-$Bu_3$)Br, therefore 1:1 ratio is preferred) gave the desired amino-benzo[b]thiophene **485** in 60% yield (Scheme 7). Conscious that the improvements made to the method might generate positive results with the less reactive secondary amines too, the reaction was attempted again with di-*N*-butylamine (in dioxane and in toluene) but unfortunately no desired product was observed. It seems that the use of the more reactive aromatic secondary amines is essential.




**Scheme 7: Buchwald-Hartwig coupling of 2-bromobenzo[b]thiophene (483)**

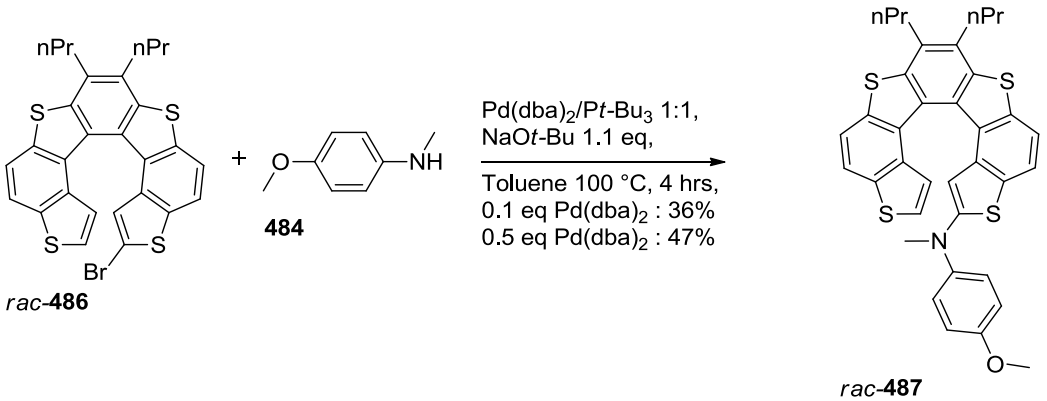
ii) Buchwald-Hartwig reaction with 2-bromohelicene **486**

Racemic helicene **8** was lithiated using *n*-BuLi and subsequent quench with 1,2-dibromoethane gave racemic 2-bromohelicene **486** in 59% yield (41% of starting material was also recovered) (Scheme 8).




**Scheme 8: Synthesis of 2-bromohelicene 486**

Using the optimised conditions described in the previous paragraph, the Buchwald-Hartwig coupling of 2-bromohelicene **486** with *N*-methyl-*p*-anisidine (**484**) gave desired product **487** but in only 36% yield (16% as a pure product, and 20% as a 90%-pure mixture). By using 0.5 equivalents of palladium catalyst, yields were improved to 47 % (14% as a pure product and 33% as a 70%-pure mixture) (Scheme 9).



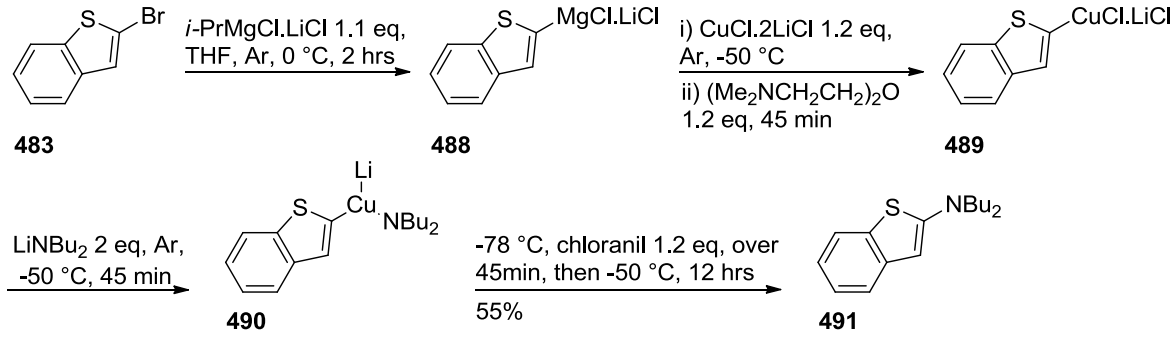

**Scheme 9: Buchwald-Hartwig coupling of 2-bromohelicene 486**

Although the outcome of this reaction could still be improved, the difficulties of purification, added to the fact that it was not our original target, convinced us to find an alternative amination method.

iii) Alternative amination technique

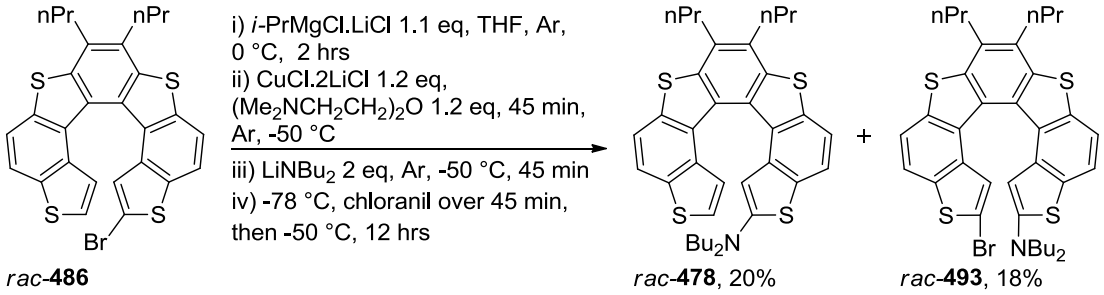
Having in mind the ability of thiahelicenes to give selectively C-2 metallation products, we thought that finding amination method where the nitrogen of the secondary amine is electrophilic could be convenient. Extensive scrutiny of the literature drew our attention to a few methods where the reaction of aryl Grignard reagents[11] or arylcuprates[12] with amine derivatives achieve the formation of the desired C-N bond. After a few unsuccessful attempts, particular attention was paid to Knochel's work. His seminal contribution is well-established in the field of organo-cuprate and organo-magnesium chemistry. Indeed, he reported[13] the modification of several standard Grignard-mediated or cuprate-mediated reactions using unusual reagents. In particular, he showed that arylcuprates could be coupled with lithium amides forming C-N bonds.

First, we evaluated the potential of his approach using our test substrate, 2-bromobenzo[b]thiophene with di-*N*-butylamine. The experimental procedure is quite tricky requiring the addition of a long list of chemicals. The first step is the formation of Grignard reagent **488** by reacting arylbromide **483** with 'Turbo Grignard' (*i*-PrMgCl•LiCl) at –50 °C. Then, this Grignard intermediate is transformed into the corresponding arylcuprate **489** by adding CuCl•$(LiCl)_2$ at –50 °C. This is then followed by the addition of lithium di-*N*-butylamide at –78 °C (forming arylcuprateamide **490**) and finally an oxidant, chloranil, is added at –78 °C (and stirred overnight at –50 °C) to form the C-N bond. Following this procedure the desired amino-benzo[b]thiophene **491** was obtained in 55% yield (Scheme 10), with a small quantity of the homocoupling product.



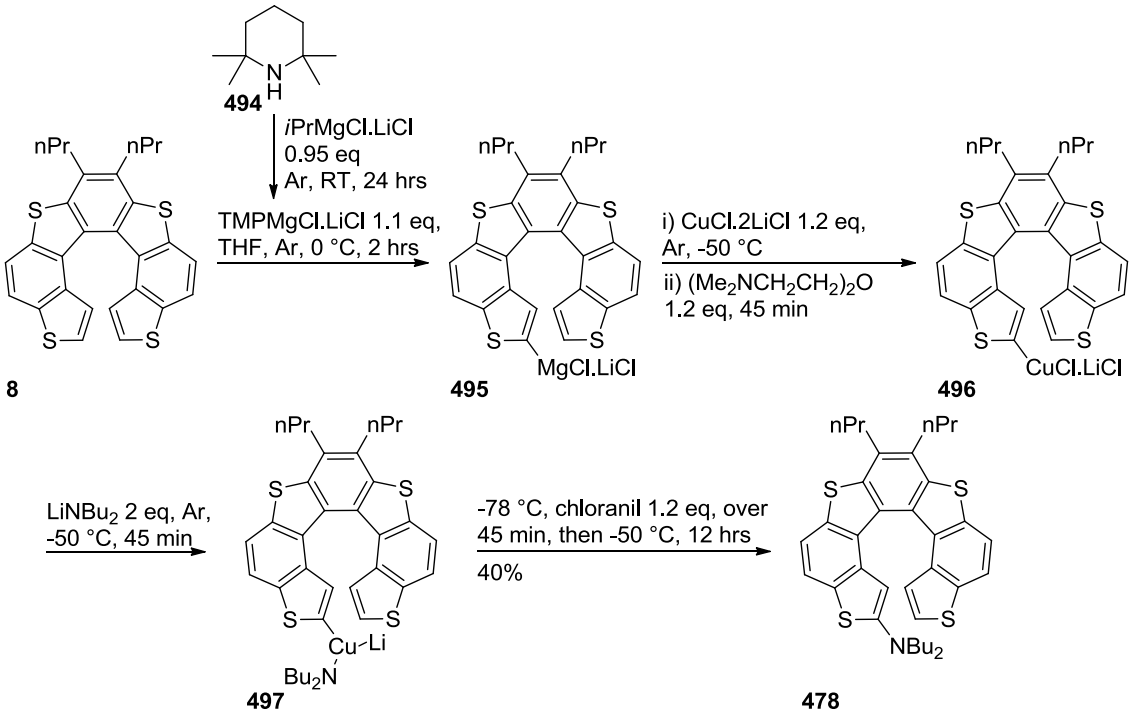

**Scheme 10: Knochel amination method**

The method was then used with 2-bromohelicene **486**, and gave surprising results. Two products were obtained. The desired 2-aminohelicene **478** was isolated in 20% yield but 2-bromo-13-aminohelicene **492** was also formed in 18% yield (Scheme 11). This result can easily be explained by the fact that the proton at the C-13 position is relatively acidic, therefore it can be deprotonated by *i*-PrMgCl•LiCl and subsequently transformed into the Grignard reagent.




**Scheme 11: Amination of 2-bromohelicene 486**

We immediately thought of using this to our advantage drawing on more results obtained by Knochel[14] as our inspiration. Knochel reports that Grignard reagents can be formed directly from an aryl species when it possesses protons that are acidic enough, using TMPMgCl•LiCl (Scheme 12). When applying this strategy to the parent helicene **8**, we were agreeably surprised to obtain the desired product in 40% yield.

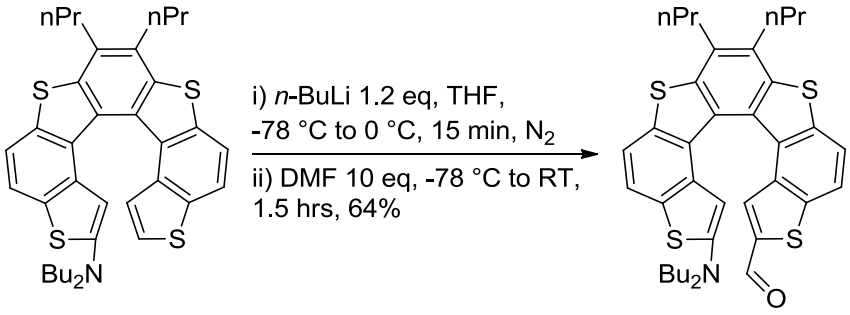



**Scheme 12: Modified amination reaction using parent helicene 8**

Unfortunately, despite several attempts, this result could not be improved, and when performed on a large scale the yield fell to only about 5%. Several biproducts were observed, and although they could not be clearly identified, they showed characteristic $^{1}H$ NMR signals of thiahelicenes and more particularly of aminated thiahelicenes. Considering that the reaction with 2-bromobenzo[b]thiophene (**483**) did not produce any degraded biproducts, and since quinone oxidations (chloranil is tetrachloro-1,4-benzoquinone) are known to proceed via radical mechanisms, it seems likely that a radical source is responsible for the degradation of the aminohelicene product. Moreover, chloranil is possibly the most oxidising molecule of this class of compounds, therefore further improvements of the reaction might be possible by using alternatives of oxidising agents. There was not, at this stage, time remaining in the project to explore this further.

iv) D-(chiral-π)-A systems

Dibutylaminohelicene **478** was lithiated using *n*-BuLi and a subsequent quench with DMF gave aminoformylhelicene **473** in 64% yield (Scheme 13). However, the final condensation reaction has not yet been attempted. Also, it seems that dibutylaminohelicene **473** is not very stable at room temperature if unprotected from UV light, which probably explains why the amination reaction is so low yielding. Nonetheless, when kept in the dark at –18 °C in a freezer, no sign of degradation is seen, even after three months.




**478** **473**

**Scheme 13: Synthesis of D-(chiral-π)-A 473**

c) Future work

Once a reliable synthetic pathway for the synthesis of aminohelicene derivatives has been developed, it will be easier to establish a clear strategy for the synthesis of both racemic and enantioenriched D-(chiral-π)-A systems (whether they are aminoformylhelicene **473** or

aminohelicene-pyridine dione **471**). At the moment, on the basis that the Knochel amination technique will prove, in the near future, to be the most suitable, the preferred route now seems to be the racemic synthesis of aminohelicene **478**, followed by either a double kinetic resolution with (–)-sparteine/*s*-BuLi and a chiral formyl donor or a conventional kinetic resolution, quenching with TMSCl to provide highly enantioenriched recovered aminohelicene starting material.

III) General conclusions and future work

Throughout these almost four years of doctoral research, three different tetrathia[7]helicenes (**8**, **360** and **368**) have been synthesised. The kinetic resolution of 7,8-dipropyltetrathia[7]helicene (**8**) has been performed using newly synthesised chiral formamides and by developing an efficient (–)-sparteine-mediated asymmetric lithiation protocol. Combining the asymmetric induction obtained from a single KR in a longer multi-KR sequence has allowed us to obtain enantiopure 7,8-dipropyltetrathia[7]helicene derivatives via several distinct routes. These derivatives will be useful intermediates in the synthesis of D-(chiral-π)-A and A-(chiral-π)-A push-pull systems, once a clear and efficient synthetic route in the racemic series has been established.

The results presented in this thesis provide a firm foundation for the onward development of the wide range of prospective applications of enantiopure thiahelicenes. It is expected that the main focus at first, will be to develop efficient routes towards the push-pull systems that are described in this chapter, and, depending on the photo-physics results, other structures with different end groups (donor or acceptor) could also become of interest.

The generalisation of the multi-KR strategy to other helicenes which we have synthesised (**360** and **368** initially, and then perhaps more advanced targets), and later as a method for use with other substrates, will be important future steps. Additionally, the easy access to enantiopure helicene **8** developed in this doctoral study can be useful to gain similarly efficient access to chiral helical catalysts and ligands for application in asymmetric synthesis. The principles of double- and multi-KR that have been set out for the first time in this thesis have the potential to impact in the future on the fundamentals of synthesis design in much the same way as Masamune's insight into double stereodifferentiation[15] and Kagan's discovery of nonlinear effects in asymmetric induction[16] have done in previous decades.

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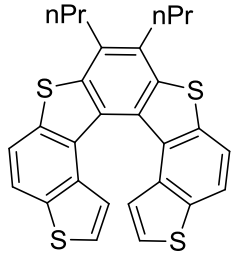
# Chapter 5:
# Experimental section

**General Methods.** Chemicals of reagent grade were used as purchased unless stated otherwise. When mentioned as distilled, THF, $Et_2O$, DME, 2-MeTHF, MTBE were freshly distilled from sodium benzophenone ketyl. DCM, (–)-sparteine, *N*,*N*-dibutylamine and acetonitrile were distilled from calcium hydride. Toluene and xylene were distilled from sodium. All non-aqueous reactions were carried out under oxygen-free nitrogen or argon using flame-dried glassware. Organolithium reagents were titrated according to the procedure reported by Burchat,[1] using *N*-benzylbenzamide. Photochemical experiments were carried out using a 500 W high pressure Hg lamp (model UV-50F) powered by a GR.E 500W power unit from Helios Italquartz. Flash column chromatography was carried out using Davisil LC60A 40-63 micron silica (amorphous silicon dioxide). Thin layer chromatography was carried out using commercially available Macherey-Nagel pre-coated TLC-sheets (ALUGRAM® SIL G/$UV_{254}$ silica plates). Microwave experiments were run with a Biotage Initiator Robot Sixty. Proton and carbon NMR spectra were recorded on a Varian UNITYplus 400 MHz spectrometer with a 5 mm Inverse detect broad band z-gradient probe, a Bruker Avance III nanobay 400 MHz spectrometer with a 5 mm broad band observe $BBFO^{plus}$ probe fitted with an actively shielded z-gradient coil and Bruker Avance III 500 MHz spectrometer with a 5 mm broad band observe $BBFO^{plus}$ smart probe™ fitted with an actively shielded z-gradient coil (500 MHz). NMR signals were measured using the residual non-deuteriated NMR solvent signal as a reference (for $^1H$ NMR, $CHCl_3$ at 7.27 ppm and DMSO at 2.50 ppm). For $^{13}C$ NMR, $CDCl_3$ at 77.0 ppm and DMSO-d6 at 39.51 ppm were used. HPLC chromatograms were recorded with two different systems designated as A and B in the appendix. A is a Varian instrument comprising a VWR organizer, a VWR UV detector L-2400, a VWR column oven L-2300, a VWR autosampler L-2200 and a VWR pump L-2130. B is a Shimadzu instrument comprising a LC-20AB prominence liquid chromatograph, a SIL-20A prominence autosampler and a SDP-M20A prominence diode array detector; this was used with a Gilson CE4600 column oven. Melting points were measured on a Buchi melting point B-545 apparatus. Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. The specific rotations were measured on a ADP 440 polarimeter from Bellingham + Stanley, and were measured in $CHCl_3$ at 15 mg $mL^{-1}$ unless otherwise stated. Specific rotations presented for formamides were measured on a mixture of rotamers. Chemical ionisation and high resolution mass spectra were measured at the EPSRC Mass Spectrometry Centre at the University of Wales, Swansea.

Experimental data of chapter 1

**7,8-Dipropyltetrathia[7]helicene[2] (8):**




Chemical Formula: $C_{28}H_{22}S_4$

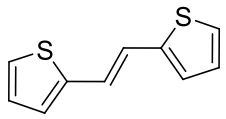
Molecular Weight: 486.7343

A solution of (*Z*)-**2,2'-(oct-4-ene-4,5-diyl)bis(benzo[1,2-b:4,3-b']dithiophene** (**346**, 2.35 g, 4.81 mmol, 1 eq) and iodine (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 7 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (25 g silica, hexanes) affording **7,8-dipropyltetrathia[7]helicene** (**8**, 1.6 g, 68%) as a pale (light yellow) solid.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.01 (d, 2H, $^3J$ = 8.4 Hz), 7.96 (d, 2H, $^3J$ = 8.4 Hz), 6.89 (d, 2H, $^3J$ = 5.5 Hz), 6.75 (d, 2H, $^3J$ = 5.5 Hz), 3.07-3.20 (m, 4H), 1.82-1.95 (m, 4H,), 1.18 (t, 6H, $^3J$ = 7.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 139.6 (2C, C), 136.5 (2C, C), 135.97 (2C, C), 135.95 (2C, C), 132.2 (2C, C), 131.5 (2C, C), 128.2 (2C, C), 125.2 (2C, CH), 124.0 (2C, CH), 120.8 (2C, CH), 118.5 (2C, CH), 34.4 (2C, $CH_2$), 23.3 (2C, $CH_2$), 14.7 (2C, $CH_3$).

**(*E*)-1,2-di(thiophen-2-yl)ethene[3] (309):**




Chemical Formula: $C_{10}H_8S_2$

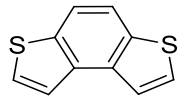
Molecular Weight: 192.30

In a 1-L three-necked RBF flame dried under argon, to distilled THF (500 mL) stirred at 0 °C, $TiCl_4$ (60.93 g, 321.4 mmol, 35.22 mL, 1.2 eq) was added dropwise over 15 min and the resulting yellow mixture was stirred another 5 min. Zinc dust (40.83 g, 589.2 mmol,

2.2 eq) was then added in 5 portion under vigorous stirring, and resultant reaction mixture was refluxed for 2 hrs. Then, pyridine (21.21 g, 21.7 mL, 267.84 mmol, 1 eq) was added before refluxing for another 30 min. The reaction mixture was cooled to RT, and thiophene-2-carboxaldehyde (**307**, 24.96 mL, 30.3 g, 267.84 mmol, 1 eq) was added carefully before refluxing for 18 hrs. Reaction mixture was cooled down to RT, and then concentrated to 100 mL. $H_2O$ (500 mL) was added to the black sludge which was extracted with DCM (5 x 500 mL). The combined organic layers were dried over $MgSO_4$ and evaporated affording 25 g crude product. The crude solid was recrystallized in hexanes (impurities insoluble in boiling hexane were separated) affording **(*E*)-1,2-bis(thien-2-yl)ethene** (**309**, 21.8 g, 85%) as a yellow solid.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ(ppm) 7.19 (br. d, 2H, $^3J$ = 5.0 Hz), 7.06 (s, 2H), 7.05 (dd, 2H, $^3J$ = 3.5 Hz, $^4J$ = 1.1 Hz), 7.00 (dd, 2H, $^3J$ = 5.0 Hz, $^3J$ = 3.5 Hz).

**benzo[1,2-b:4,3-b']dithiophene[4] (310):**




Chemical Formula : $C_{10}H_6S_2$

Molecular Weight: 190.28

**Method A**

In a 1-L RBF, **[3,3'-bithiophene]-2,2'-dicarbaldehyde** (**320**, 8.78 g, 39.5 mmol, 1 eq) and tosylhydrazide (14.71 g, 79 mmol, 2 eq) were dissolved in distilled THF (800 mL) and stirred at RT overnight. The THF solution was dried over $Na_2SO_4$, and transferred to a 2-L 3-necked RBF flame dried under nitrogen, and distilled THF (1 L) was added. The reaction mixture was cooled to 0 °C and NaH (95%, 2.49 g, 98.8 mmol, 2.5 eq) was added in portions. The reaction mixture was then allowed to reach RT and was refluxed for 3 hrs. The reaction mixture was allowed to cool down and was concentrated to 300 mL, sat. aq $NH_4Cl$ (300 mL) was added and the mixture was extracted with EtOAc (2 x 400 mL). The combined organic layers were dried over $MgSO_4$, and evaporated to obtain 10.5 g of brown solid. The crude material was purified by column chromatography (100 g silica, hexanes) affording **benzo[1,2-b:4,3-b']dithiophene** (**310**, 2.5 g, 33%) as a white solid.

**Method B**

In a 100-mL three-necked RBF, flame dried under nitrogen, was added ***N'*,*N''*-([3,3'-bithiophene]-2,2'-diylbis(methanylylidene))bis(4-methylbenzenesulfonohydrazide)**

(**321**, 325 mg, 0.58 mmol, 1 eq) in distilled THF (40 mL). Then, NaH (60% in mineral oil, 46 mg, 1.16 mmol, 2 eq) was added in one portion, under nitrogen, and reaction mixture was refluxed for 2 hrs. The reaction mixture was allowed to cool down and a few drops of sat. aq $NH_4Cl$ were added, before being evaporated to obtain 0.42 g of brown solid. The crude material was purified by column chromatography (10 g silica, hexanes) affording **benzo[1,2-b:4,3-b']dithiophene** (**310**, 42 mg, 37%) as a white solid.

**Method C** *(From the bis TMS-BDT)*

In a 250-mL three-necked RBF, to a solution of **2,7-bis(trimethylsilyl)benzo[1,2-b:4,3-b']dithiophene** (**335**, 1.36 g, 4.06 mmol, 1 eq) in distilled THF (150 mL) at RT, under nitrogen, was added dropwise TBAF (1M in THF, 8.12 mL, 8.12 mmol, 2 eq). After stirring 5 min at RT the reaction was complete. $H_2O$ (100 mL) was added and the mixture was extracted with EtOAc (2 x 100 mL), the combined organic layers were dried over $MgSO_4$ and evaporated to give 1.4 g of crude material, which was then purified by column chromatography (10 g silica, hexanes) affording **benzo[1,2-b:4,3-b']dithiophene** (**310**, 830 mg, 75%) as a white solid.

**Method D** (photochemistry)

A solution of **(*E*)-1,2-bis(thien-2-yl)ethene** (**309**, 5.1 g, 26.5 mmol, 1 eq) and $I_2$ (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 35 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (100 silica, hexanes) affording **benzo[1,2-b:4,3-b']dithiophene** (**310**, 4.2 g, 83%) as a white solid.

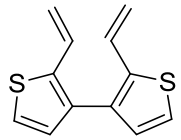
**Method E**

In a 100-mL RBF, flame dried under argon, Grubbs catalyst 1$^{st}$ generation (30 mg, 0.036 mmol, 0.1 eq) was added to a solution of **2,2'-divinyl-3,3'-bithiophene** (80 mg, 0.36 mmol, 1 eq) in dry DCM (25mL). The reaction mixture was stirred at RT for 8 hrs. After removing the solvent under reduced pressure, the crude product was purified by column chromatography (2 g silica, hexanes), affording **benzo[1,2-b:4,3-b']dithiophene** (**310**, 67 mg, 96%) as a white solid.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.84 (s, 2H), 7.73 (d, 2H, $^3J$ = 5.7 Hz), 7.58 (d, 2H, $^3J$ = 5.7 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 136.4 (2C, C), 134.6 (2C, C), 126.4 (2C, CH), 121.9 (2C, CH), 118.7 (2C, CH).

**2,2′-Divinyl-3,3′-bithiophene (319)**:



Chemical Formula: $C_{12}H_{10}S_2$

Molecular Weight: 218.3378

To a suspension of methyltriphenylphosphonium bromide (1.7 g, 4.75 mmol, 2.2 eq) in distilled THF (50 mL), *n*-BuLi (1.6 M in hexanes, 2.96 mL, 4.75 mmol, 2.2 eq) was added dropwise at –10 °C under nitrogen. The deep-orange solution was stirred at RT for 30 min, then a solution of **[3,3′-bithiophene]-2,2′-dicarbaldehyde** (**320**, 460 mg, 2.16 mmol, 1 eq) in distilled THF (10 mL) was added dropwise. The mixture was stirred at RT under nitrogen for 17 hrs, then the reaction was quenched with sat. aq. $NH_4Cl$ (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography (10 g silica, hexanes), to afford **2,2′-divinyl-3,3′-bithiophene** (**319**, 350 mg, 77%) as a viscous oil. The product was kept in the freezer in the dark, and used as soon as possible.

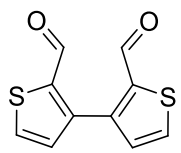
**IR (ATR):** ν ($cm^{-1}$) 3103, 3066, 3005, 2957, 2925, 2869, 1800, 1616.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.19 (dd, 1H, $^3J$ = 5.3 Hz, $^5J$ = 0.8 Hz), 6.94 (d, 1H, $^3J$ = 5.3 Hz), 6.66 (ddd, 1H, $^3J$ = 17.3 Hz, $^3J$ = 11.0 Hz, $^5J$ = 0.8 Hz), 5.58 (d, 1H, $^3J$ = 17.3 Hz), 5.13 (d, 1H, $^3J$ = 11.0 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 139.1 (1C, C), 134.2 (1C, C), 130.1 (1C, CH), 129.2 (1C, CH), 123.1 (1C, CH), 113.7 (1C, $CH_2$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}S_2$: 219.0299; found: 219.0297.

**[3,3'-bithiophene]-2,2'-dicarbaldehyde[5] (320)**:



Chemical Formula: $C_{10}H_6O_2S_2$

Molecular Weight: 222.2834

*Method A: palladium coupling*

Anhydrous DMSO (50 mL) was degassed under nitrogen for 30 min, then **3-bromothiophene-2-carbaldehyde** (**322**, 2 g, 10.5 mmol, 1 eq) was added and nitrogen gas was bubbled through the resulting solution for 10 min. $Pd(PPh_3)_4$ (1.21 g, 1.05 mmol, 0.1 eq) and copper powder (2 g, 31.5 mmol, 3 eq) were added and the solution was stirred and heated to 100 °C, under nitrogen for 15 hrs and then at 120 °C for 8 hrs. The solution was cooled to RT before addition of EtOAc (200 mL) and filtration through a pad of kieselghur. The filtrate was washed with $H_2O$ (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and evaporated to give a brown oil that was purified by chromatography (silica, hexanes/EtOAc gradient 95:5 to 3:1 v/v) to afford **[3,3'-bithiophene]-2,2'-dicarbaldehyde** (**320**, 405 mg, 35%) as a yellow powder.

*Method B (large scale)*

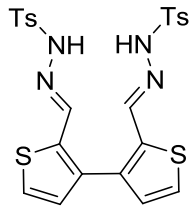
In a 2-L three-necked RBF, ***N*-((3-bromothiophen-2-yl)methylene)cyclohexanamine** (**324**, 60.5 g, 222 mmol, 1 eq) was dissolved in dry NMP (1.5 L) under argon. CuTC (93 g, 490 mmol, 2.2 eq) was added in several portions (in order to achieve a good mixing of the solution). The resultant mixture was stirred 14 hrs, under argon, at 90 °C. The reaction mixture was filtered on a pad of kiesielghur which washed with EtOAc (1 L) until the filtrate was colourless. The filtrate was washed with 15% aq. $NH_3$ (1.5 L) producing a clear deep blue aqueous layer. The organic layer was separated, and the aqueous layer was then extracted with EtOAc (3 x 1 L). The combined organic layers were washed with brine (4 x 3 L) (to remove as much NMP as possible), dried over $MgSO_4$, and evaporated. Resultant brown oil was dissolved in DCM (1 L) and 15% aq. AcOH (700 mL) was added before the mixture was stirred overnight at RT. The organic layer was separated and the aqueous layer was extracted with DCM (300 mL). The combined organic layers were washed with brine (4 x 500 mL), filtered through a $MgSO_4$ / neutral alumina pad, and evaporated to give a solution of crude product in NMP (despite the washing, the NMP was not removed completely). The resultant brown oil was taken in $H_2O$ (200 mL) and shaken until the product crushes out. The mixture was then filtered, resultant solid was then taken in DCM (100 mL), dried over $MgSO_4$, and evaporated. The solid residue was washed with a mixture of hexanes and EtOAc (8:1 v/v, 3 x 250 mL) and dried under vacuum affording **[3,3'-bithiophene]-2,2'-dicarbaldehyde** (**320**, 16.8 g, 68%) as a yellow solid.

*General method: microwave*

A dried 20-mL microwave vial was flushed with argon. To a solution ***N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine** (**324**, 1 g, 3.67 mmol, 1 eq) in NMP (15 mL), CuTC (1.54 g, 8.1 mmol, 2.2 eq) was added with stirring. The microwave vial was then sealed, vacuum was applied, and then the vial was filled again with argon. The reaction mixture was irradiated (see Table 2, Chapter 1), then diluted with EtOAc and 15% aq. $NH_3$ was added to produce a clear deep-blue aqueous layer. The organic layer was separated and retained and the aqueous layer was extracted with EtOAc. The organic layers were combined and evaporated and the resultant crude product (green oil) was dissolved in $Et_2O$. This solution was washed with brine, dried over $MgSO_4$, filtered, and evaporated to leave a brown oil, which was dissolved in DCM (50 mL), 15% aq. AcOH was added and mixture was stirred overnight at RT. The organic layer was separated and retained and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to give a brown oil. The oil was purified by column chromatography (silica; hexanes/EtOAc gradient 100:0 to 2:1 v/v) affording **[3,3′-bithiophene]-2,2′-dicarbaldehyde** (**320**) as a yellow solid (for yields, see Table 2, Chapter 1).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.81 (d, 2H, $^5J$ = 1.1 Hz), 7.85 (dd, 2H, $^3J$ = 5.0 Hz, $^5J$ = 1.1 Hz), 7.26 (d, 2H, $^3J$ = 5.0 Hz).

***N′*,*N′′*-{[3,3′-bithiophene]-2,2′-diylbis(methanylylidene)}bis(4-methylbenzenesulfonylhydrazone) (321)**:




Chemical Formula: $C_{24}H_{22}N_4O_4S_4$

Molecular Weight: 558.7159

**[3,3′-Bithiophene]-2,2′-dicarbaldehyde** (**320**, 1.05 g, 4.7 mmol, 1 eq) and tosylhydrazide (1.75 g, 9.4 mmol, 2 eq) were dissolved in distilled THF (300 mL) and stirred at RT overnight. The reaction mixture was dried over $MgSO_4$, filtered and evaporated to give ***N′*,*N′′*-{[3,3′-bithiophene]-2,2′-diylbis(methanylylidene)}bis(4-methylbenzenesulfonylhydrazone** (**321**, 2.62 g, 100%) as a bright orange solid foam.

**Mp.**: 128-131 °C.

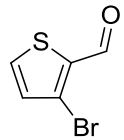
**IR (ATR):** ν ($cm^{-1}$) 3176, 2958, 2923, 2867, 1645, 1594.

**$^{1}$H NMR (DMSO-d6, 400 MHz):** δ (ppm) 11.33 (s, 2H), 7.77 (d, 2H, $^{5}J$ = 0.9 Hz), 7.69 (dd, 2H, $^{3}J$ = 5.1 Hz, $^{5}J$ = 0.7 Hz), 7.67 (d, 4H, $^{3}J$ = 8.4 Hz) 7.40 (dd, 4H, $^{3}J$ = 8.1 Hz, $^{4}J$ = 0.6 Hz), 7.03 (d, 2H, $^{3}J$ = 5.1 Hz), 2.36 (s, 6H).

**$^{13}$C NMR (DMSO-d6, 100 MHz):** δ (ppm) 143.7 (2C, C), 140.7 (2C, CH), 136.4 (2C, C), 136.0 (2C, C), 134.7 (2C, C), 130.3 (2C, CH), 129.8 (4C, CH), 128.7 (1C, CH), 127.2 (4C, CH), 21.1 (2C, $CH_3$).

**HRMS (ESI)**: *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_4S_4$: 559.0597; found: 559.0587.

**3-bromothiophene-2-carbaldehyde[6] (322):**




Chemical Formula: $C_5H_3BrOS$

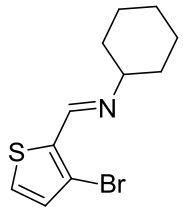
Molecular Weight: 191.05

In a 2-L three-necked RBF, to a solution of diisopropylamine (49.7 g, 491 mmol, 1.05 eq) in dry THF (1 L), was added dropwise *n*-BuLi (1.6 M in hexanes, 307 mL, 491 mmol, 1.05 eq) at –10 °C, with a pressure equalized dropping funnel, over 30 min. After stirring 45 min at 0 °C, 3-bromothiophene (76.3 g, 468 mmol, 1 eq) was added dropwise. Then, the solution stirred another 1 hr at 0 °C before *N*-formylpiperidine (55.6 g, 491 mmol, 1.05 eq) was added dropwise and solution was stirred at RT for 2.5 hrs. Then, sat. aq. $NH_4Cl$ (700 mL) was added, organic layer was separated, aqueous layer was extracted with $Et_2O$ (2 x 500 mL). The separated THF solution was evaporated, and resulting oil was dissolved with $Et_2O$ layers, combined organic layers were concentrated to 500 mL, then washed with brine (400 mL), dried over $MgSO_4$ and evaporated to get 113 g of dark orange oil. Crude material was then purified by column chromatography (700 g silica, hexanes/EtOAc gradient 100/0 to 1/1 v/v) affording **3-bromothiophene-2-carbaldehyde** (**322**, 87 g, 97%) as an orange oil.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.99 (d, 1H, $^{5}J$ = 1.4 Hz), 7.73 (dd, 1H, $^{3}J$ = 5.1 Hz, $^{5}J$ = 1.4 Hz), 7.16 (d, 1H, $^{3}J$ = 5.1 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 182.9 (1C, C), 136.7 (1C, C), 134.8 (1C, CH), 131.9 (1C, CH), 120.3 (1C, C).

***N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine (324)**:




Chemical Formula: $C_{11}H_{14}BrNS$

Molecular Weight: 272.20

In a 1-L three-necked RBF, equipped with a Dean–Stark trap, a solution of **3-bromo-2-formylthiophene** (**322**, 84.15 g, 0.44 mol, 1 eq) and cyclohexylamine (54.6 g, 0.55 mol, 1.25 eq) in toluene (700 mL) was refluxed under nitrogen for 16 hrs. The solution was then evaporated to afford ***N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine** (**324**, 120 g, 100%) as an orange oil which was used directly in the next step.

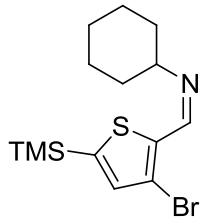
**IR (ATR):** ν ($cm^{-1}$) 3075, 2925, 2851, 1623.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.44 (s, 1H), 7.34 (dd, 1H, $^{3}J$ = 5.3 Hz, $^{5}J$ = 1.1 Hz), 7.00 (d, 1H, $^{3}J$ = 5.3 Hz), 3.19-3.25 (m, 1H), 1.51–1.85 (m, 7H), 1.18–1.41 (m, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 151.0 (1C, C), 144.4 (1C, C), 140.5 (1C, C), 136.5 (1C, CH), 114.5 (1C, C), 70.0 (1C, CH), 34.1 (2C, $CH_2$), 25.5 (1C, $CH_2$) 24.7 (2C, $CH_2$), –0.6 (3C, $CH_3$).

**HRMS (GC, CI$^-$):** *m*/*z* $[M-H]^-$ calcd for $C_{11}H_{13}BrNS$: 269.9947; found: 269.9947.

***N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine (325)**:




Chemical Formula = $C_{14}H_{22}BrNSSi$

Molecular Weight = 344.39

*n*-BuLi (1.6 M in hexanes, 53 mL, 84.5 mmol, 1.15 eq) was added dropwise to a solution of diisopropylamine (12 mL, 8.5 g, 84.5 mmol, 1.15 eq) in anhydrous THF (600 mL) at 0 °C under nitrogen. After stirring for 45 min at 0 °C, ***N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine** (**324**, 20 g, 73.5 mmol, 1 eq) in anhydrous THF (50 mL) was added dropwise over 10 min. After stirring for a further 45 min at 0 °C under nitrogen, the reaction mixture was cooled to –78 °C and TMSCl (10.7 mL, 9.2 g, 84.5 mmol, 1.15

eq) was added dropwise. After stirring for 1 hr at –78 °C, the reaction mixture was allowed to warm to RT, sat. aq. $NH_4Cl$ (700 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 400 mL) and the combined organic layers were washed with brine (500 mL), filtered through a $MgSO_4$ / basic alumina pad, and evaporated to give ***N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine** (**325**, 25.2 g, 99%) as an orange oil.

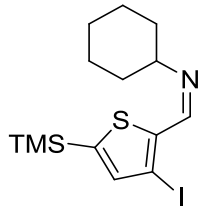
**IR (ATR):** ν ($cm^{-1}$) 2927, 2853, 1624.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.43 (s, 1H), 7.10 (s, 1H), 3.19-3.25 (m, 1H), 1.22–1.87 (m, 10H), 0.31 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 151.0 (1C, CH), 144.4 (1C, C), 140.5 (1C, C), 136.5 (1C, CH), 114.5 (1C, C), 70.0, 34.1, 25.5, 24.7 (, –0.6 (3C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{14}H_{23}BrNSSi$: 344.0498; found: 344.0503.

***N*-{[3-iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexanamine (326):**




Chemical Formula = $C_{14}H_{22}INSSi$

Molecular Weight = 391.39

A solution of ***N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine** (**325**, 6.94 g, 20.2 mmol, 1 eq) in anhydrous THF (350 mL) was cooled to –78 °C, under nitrogen. *n*-BuLi (1.6 M in hexanes, 13.9 mL, 22.2 mmol, 1.1 eq) was added dropwise. The mixture was stirred for 30 min at –78 °C and a solution of iodine (7.7 g, 30.3 mmol, 1.5 eq) in anhydrous THF (25 mL) was added dropwise until the red iodine colour persisted. After 15 min at –78 °C, the reaction mixture was allowed to warm to RT, $H_2O$ (350 mL) was added and the mixture was extracted with DCM (3 × 250 mL). The combined organic layers were concentrated to 300 mL, washed with sat. aq. $Na_2SO_3$ (2 × 300 mL), dried over $MgSO_4$, filtered, and evaporated to give ***N*-{[3-iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexanamine** (**10**, 7.12 g, 90%) as a brown oil, that crystallised upon standing.

**Mp.**: 59 °C.

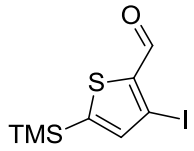
**IR (ATR)**: ν ($cm^{-1}$) 2928, 2851, 1618.

**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ (ppm) 8.34 (s, 1H), 7.20 (s, 1H), 3.20-3.26 (m, 1H), 1.57-1.85 (m, 7H), 1.38–1.23 (m, 3H), 0.31 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ (ppm) 153.2 (1C, CH), 145.4 (1C, C), 143.7 (1C, C), 141.4 (1C, CH), 85.1 (1C, C), 69.9 (1C, CH), 34.2 (2C, $CH_2$), 25.5 (1C, $CH_2$) 24.7 (2C, $CH_2$), –0.5 (3C, $CH_3$).

**HRMS (ESI)**: *m/z* $[M - H]^-$ calcd for $C_{14}H_{21}NISSi$: 390.0203; found: 390.0203.

**3-Iodo-5-(trimethylsilyl)thiophene-2-carbaldehyde (327):**




Chemical Formula: $C_8H_{11}IOSSi$

Molecular Weight: 310.2273

To a solution of ***N*-{[3-iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexanamine** (**326**, 3 g, 7.7 mmol, 1 eq) in DCM (200 mL), was added a 30% v/v solution of acetic acid and $H_2O$ (200 mL), and was vigorously stirred overnight. The organic layer was separated, and washed with brine (5 x 200 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (35 g silica, hexanes/EtOAc gradient 100/0 to 95/5 v/v) affording **3-iodo-5-(trimethylsilyl)thiophene-2-carbaldehyde** (**327**, 2.09 g, 88%) as a yellow solid.

**Mp.:** 47-49 °C.

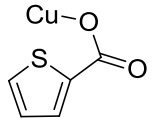
**IR (ATR):** ν ($cm^{-1}$) 2955, 2896, 2844, 1649.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.81 (s, 1H), 7.34 (s, 1H), 0.36 (s, 9H)

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 184.8 (1C, **C**H), 153.2 (1C, C), 142.78 (1C, C), 142.75 (1C, **C**H), 90.9 (1C, C), –0.7 (3C, $CH_3$)

**HRMS (ESI):** *m/z* $[M]^+$ calcd. for $C_8H_{11}IOSSi$: 309.9335, found: 309.9336.

**Copper(I) thiophene-2-caboxylate[7] (CuTC, 330)**

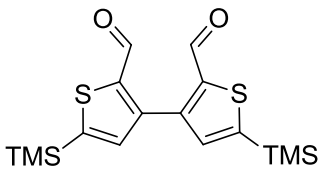



Chemical Formula: $C_5H_3CuO_2S$

Molecular Weight: 190.6871

In a 250-mL three-necked RBF, equipped with a Dean-Stark trap and a condenser, was added thiophene-2-carboxylic acid (40 g, 0.31 mol, 4 eq), $Cu_2O$ (11g, 78 mmol, 1eq), and toluene (150 mL). The mixture was refluxed overnight, under nitrogen. Then, the red-brown sludge was filtered on a sinter, under a flow of nitrogen, and then washed with deoxygenated MeOH (200 mL), and then with diethyl ether, and a small amount of hexanes, until filtrate was colour free (it is important to ensure that eluent is colour free and not light green prior to any use). The brown powder was then dried under vacuum, affording **CuTC** (**330**, 23g, 77%). The powder when dry is stable in air, but it is recommended to repeat the washing process before any use, in order to maximise the yield.

**5,5'-Bis(trimethylsilyl)-[3,3'-bithiophene]-2,2'-dicarbaldehyde (331):**




Chemical Formula: $C_{16}H_{22}O_2S_2Si_2$

Molecular Weight: 366.6457

*Method A (Ziegler method)*

A solution of ***N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine** (**325**, 1 g, 2.9 mmol, 1 eq) in distilled THF (100 mL) was cooled to –78 °C, under nitrogen. *n*-BuLi (1.6 M in hexanes, 1.93 mL, 3.1 mmol, 1.05 eq) was added dropwise and stirred at –78 °C for 30 min. Then CuI-$P(OEt)_3$ (1.55g, 4.4 mmol, 1.5 eq) was added in one portion and was stirred another 30 min at –78 °C before a solution of ***N*-{[3-iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexanamine** (**326**, 1.13 g, 2.9 mmol, 1 eq) in distilled THF (5 mL) was added dropwise. The reaction mixture was then allowed to warm up, and was stirred 60 hrs at RT. The reaction mixture was then diluted with DCM (150 mL) and 15% aq. AcOH (700 mL) was added and the resulting mixture was at stirred RT overnight. The organic layer was separated and the aqueous layer was extracted with DCM (150 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over a pad of $MgSO_4$ and neutral alumina, filtered and evaporated. The crude material was purified by column chromatography (35 g silica, hexanes/EtOAc gradient 100/0 to 2/1), affording **5,5'-bis(trimethylsilyl)-[3,3'-bithiophene]-2,2'-dicarbaldehyde** (**331**, 80 mg, 15%) as a yellow solid (see Table 1, entry 4; Chapter 1).

*General method: microwave*

A dried 20-mL microwave vial was flushed with argon. To a solution ***N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine** (**326**; 1 g, 2.7 mmol, 1 eq) in NMP (15 mL), CuTC (1.54 g, 8.1 mmol, 3 eq) was added with stirring. The microwave vial was then sealed, vacuum was applied, and then the vial was filled with argon. The reaction mixture was irradiated (see Table 2, Chapter 1), then diluted with EtOAc and 15% aq. $NH_3$ was added to produce a clear deep-blue aqueous layer. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, evaporated, and the resultant crude product (green oil) was dissolved in $Et_2O$. This solution was washed with brine, dried over $MgSO_4$, filtered, and evaporated to leave a brown oil, which was dissolved in DCM (50 mL), 15% aq. AcOH (50 mL) was added and mixture was stirred overnight at RT. The organic layer was separated and retained and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to give a brown oil. The oil was purified by column chromatography (15 silica; hexanes/EtOAc gradient 100:0 to 2:1 v/v) affording **5,5'-bis(trimethylsilyl)-[3,3'-bithiophene]-2,2'-dicarbaldehyde** (**331**) as a yellow solid (for yields, see Table 2, Chapter 1).

**Mp.:** 185-187 $^{o}$C.

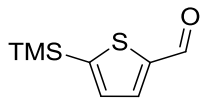
**IR (ATR):** $\nu$ ($cm^{-1}$) 3071, 2959, 2875, 1644.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** $\delta$ (ppm) 9.78 (s, 2H), 7.30 (s, 2H), 0.40 (s, 18H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** $\delta$ (ppm) 182.5 (2C, C), 152.2 (2C, C), 144.7 (2C, C), 142.6 (2C, C), 137.5 (2C, CH), –0.5 (6C, $CH_3$).

**HRMS (ESI)**: *m/z* $[M + H]^+$ calcd. for $C_{12}H_{11}S_2$: 366.0594, found: 366.0597.

**5-(Trimethylsilyl)thiophene-2-carbaldehyde (332):**




Chemical Formula: $C_8H_{12}OSSi$

Molecular Weight: 184.3308

Under some reaction conditions for coupling reactions of **331** (see Table 2, Chapter 1), a competing dehalogenation process formed significant amounts of the side product **5-(trimethylsilyl)thiophene-2-carbaldehyde** (**332**) which was also eluted during chromatography.

**Mp.:** 35-36°C.

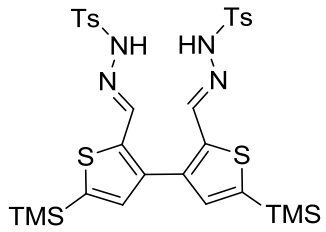
**IR (ATR):** ν ($cm^{-1}$) 2960, 2896, 2855, 2801, 1657.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.95 (s, 1H), 7.80 (d, 1H, , $^{3}J$ = 3.8 Hz), 7.32 (d, 1H, $^{3}J$ = 3.8 Hz), 0.37 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ(ppm) 182.5 (1C, C), 152.7 (1C, C), 148.2 (1C, C), 136.7 (1C, CH), 134.5 (1C, CH), –0.4 (3C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_8H_{13}OSSi$: 185.0451, found: 185.0451.

***N′,N′′*-{[5,5′-bis(trimethylsilyl)-(3,3′-bithiophene)-2,2′-diyl]bis(methanylylidene)} bis(4-methylbenzenesulfonylhydrazone) (334)**:




Chemical Formula: $C_{30}H_{38}N_4O_4S_4Si_2$

Molecular Weight: 703.0781

**5,5′-Bis(trimethylsilyl)-(3,3′-bithiophene)-2,2′-dicarbaldehyde** (**331**; 2 g, 5.45 mmol, 1 eq) and tosylhydrazide (2.03 g, 10.9 mmol, 2 eq) were dissolved in distilled THF (250 mL) and the mixture was stirred at RT overnight, dried over $MgSO_4$, and evaporated to afford ***N′,N′′*-{[5,5′-bis(trimethylsilyl)-(3,3′-bithiophene)-2,2′-diyl]bis(methanylylidene)}bis (4-methylbenzenesulfonylhydrazone)** (**334**, 3.83 g, 100%) as a bright orange solid foam.

**Mp.:** 155-157 °C.

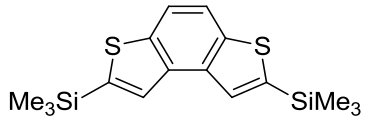
**IR (ATR):** ν ($cm^{-1}$) 3190, 3065, 2955, 2926, 2898, 2856, 1597.

**$^{1}$H NMR (DMSO-d6, 400 MHz):** δ (ppm) 11.38 (s, 2H), 7.74 (s, 2H), 7.67 (d, 4H, $^{3}J$ = 8.2 Hz), 7.40 (dd, 4H, $^{3}J$ = 8.2 Hz, $^{4}J$ = 0.7 Hz), 7.16 (s, 2H), 2.36 (s, 6H), 0.30 (s, 18H).

**$^{13}$C NMR (DMSO-d6, 100 MHz):** δ (ppm) 143.5 (2C, C), 142.5 (2C, C), 140.2 (2C, C), 139.2 (2C, C), 137.3 (2C, C), 137.0 (2C, C), 136.1 (2C, C), 129.7 (4C, CH), 127.0 (4C, CH), 20.99 (2C, $CH_3$), –0.46 (6C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{30}H_{39}N_4O_4S_4Si_2$: 703.1387; found: 703.1387.

**2,7-Bis(trimethylsilyl)benzo[1,2-*b*:4,3-*b′*]dithiophene (335)**:




Chemical Formula: $C_{16}H_{22}S_2Si_2$

Molecular Weight: 334.6469

**5,5′-Bis(trimethylsilyl)-[3,3′-bithiophene]-2,2′-dicarbaldehyde** (**331**; 2.62 g, 7.15 mmol, 1 eq) and tosylhydrazide (2.66 g, 15.30 mmol, 2 eq) were dissolved in distilled THF (450 mL) and stirred at RT overnight. The THF solution was dried over $Na_2SO_4$, and transferred to a 500-mL three-necked RBF that had been flame-dried under nitrogen. The reaction mixture was cooled to –78 °C, *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol, 1.05 eq) was added dropwise and the mixture was stirred for 5 min at –78 °C. The reaction mixture was allowed to warm to RT, then heated at reflux for 5 hrs. After cooling, sat. aq. $NH_4Cl$ (200 mL) was added and the mixture was extracted with EtOAc (200 mL). The organic layer was concentrated under reduced pressure to 100 mL, diluted with $Et_2O$ (200 mL), washed with brine (2 × 250 mL), dried over $MgSO_4$, filtered, and evaporated to leave a brown solid (5.1 g). The crude material was purified by column chromatography (50 g silica, hexanes) affording **2,7-Bis(trimethylsilyl)benzo[1,2-*b*:4,3-*b′*]dithiophene** (**335**, 770 mg, 32%) as a white solid.

**Mp.:** 127-130 °C.

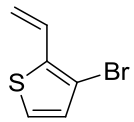
**IR (ATR):** ν ($cm^{-1}$) 3053, 2985, 2959, 2897.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.88 (s, 2H), 7.80 (s, 2H), 0.44 (s, 18H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 142.3 (2C, C), 140.4 (2C, C), 135.9 (2C, C), 128.7 (2C, CH), 118.4 (2C, CH), –0.2 (6C, $CH_3$).

HRMS (ESI): *m*/*z* $[M]^+$ calcd. for $C_{16}H_{22}S_2Si_2$: 334.0696; found: 334.0696.

**3-Bromo-2-vinylthiophene[8] (344):**




Chemical Formula: $C_6H_5BrS$

Molecular Weight: 189.0729

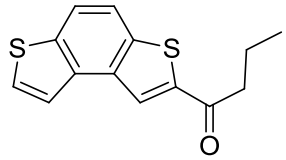
To a suspension of methyltriphenylphosphonium bromide (4.1 g, 11.4 mmol, 1.1 eq) in distilled THF (60 mL), *n*-BuLi (1.6 M in hexane, 7.2 mL, 11.4 mmol, 1.1 eq) was added

dropwise at –10 °C, under nitrogen. Then, the deep orange solution was stirred at RT for 30 min before a solution of **3-bromothiophene-2-carbaldehyde** (**322**, 2 g, 10.4 mmol, 1 eq) in distilled THF (10 ml) was added dropwise. The mixture was stirred at RT for 24 hrs under nitrogen, and was then quenched with sat. aq. $NH_4Cl$ (50 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography (15 g silica, Hexanes) affording 3-**bromo-2-vinylthiophene** (**344**, 600 mg, 30%) as a colourless oil. (not stable at RT)

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ(ppm) 7.15 (dd, 1H, $^3J$ = 5.2 Hz, $^5J$ = 1.0 Hz), 6.95 (d, 1H, $^3J$ = 5.2 Hz), 6.88 (ddd, 1H, $^3J$ = 17.1 Hz, $^3J$ = 11.0 Hz, $^5J$ = 1.0 Hz), 5.64 (d, 1H, $^3J$ = 17.1 Hz), 5.28 (d, 1H, $^3J$ = 11.0 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ(ppm) 137.2 (1C, C), 130.7 (1C, C), 128.3 (1C, CH), 124.1 (1C, CH), 115.3 (1C, CH), 110.5 (1C, $CH_2$).

**1-(Benzo[1,2-b:4,3-b']dithiophen-2-yl)butan-1-one[2] (345):**




Chemical Formula: $C_{14}H_{12}OS_2$

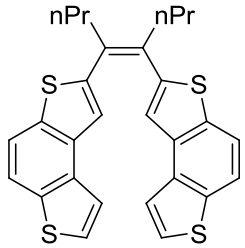
Molecular Weight: 260.37

In a three-necked RBF, flame dried under nitrogen, to a solution of **benzo[1,2-b:4,3-b']dithiophene** (**310**, 7 g, 37.4 mmol, 1 eq) in distilled THF (400 mL) cooled at –78 °C, was added dropwise *n*-BuLi (1.6 M in hexanes, 25.7 mL, 41.1 mmol, 1.1 eq) under nitrogen. After stirring 45 min at –78 °C and 10 min at –10 °C, the reaction mixture was cooled –78 °C and ***N*-methoxy-*N*-methylbutanamide** (**347**, 5.39 g, 41.1 mmol, 1.1 eq) was added dropwise. The solution was stirred at –78 °C for 30 min and then was allowed to warm to RT and the solution was stirred at RT for another 2.5 hrs. Then sat. aq. $NH_4Cl$ (300 mL) was added, the organic layer was separated and the aqueous layer extracted with EtOAc (3 x 150 mL). The combined organic layers were dried and evaporated to give 8.5 g of crude material which was then purified by column chromatography (100 g silica, hexanes/DCM gradient 20/1 to 5/1 v/v) affording **1-(benzo[1,2-b:4,3-b']dithiophen-2-yl)butan-1-one** (**345**, 7.3 g, 75%) as a pale yellow solid and **benzo[1,2-b:4,3-b']dithiophene** (**310**, 0.7 g, 10%).

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.32 (s, 1H), 7.94 (dd, 1H, $^3J$ = 8.8 Hz, $^5J$ = 0.8 Hz), 7.81 (d, 1H, $^3J$ = 8.8 Hz), 7.77 (d, 1H, $^3J$ = 5.5 Hz), 7.67 (d, 1H, $^3J$ = 5.5 Hz), 3.05 (t, 2H, $^3J$ = 7.5 Hz), 1.83-1.92 (m, 2H), 1.08 (t, 3H, $^3J$ = 7.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 194.6 (1C, C), 143.6 (1C, C), 139.9 (1C, C), 136.8 (1C, C), 135.8 (1C, C), 134.2 (1C, C), 127.8 (1C, CH), 126.3 (1C, CH), 122.0 (1C, CH), 121.6 (1C, CH), 118.8 (1C, CH), 41.3 (1C, $CH_2$), 18.2 (1C, $CH_2$), 13.9 (1C, $CH_3$).

**(*Z*)-2,2'-(oct-4-ene-4,5-diyl)bis(benzo[1,2-b:4,3-b']dithiophene[2] (346):**




Chemical Formula: $C_{28}H_{24}S_4$

Molecular Weight: 488.75

In a 500-mL three-necked RBF, flame dried under nitrogen, to a solution of **1-(benzo[1,2-b:4,3-b']dithiophen-2-yl)butan-1-one** (**345**, 6.89g, 26.5mmol, 1eq) in distilled THF (300 mL) cooled at 0 °C under argon, $TiCl_4$ (3.74 mL, 34.4 mmol, 1.3 eq) was added dropwise. After stirring 5 min at 0 °C, zinc powder (3.98 g, 60.9 mmol, 2.3 eq) was added in 5 portions over 15 min, and the reaction mixture was refluxed for 3 hrs under argon. After cooling the mixture at RT, ice-water (400 mL) was added and then the mixture was diluted with DCM (300 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 300 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography (100 g silica, cyclohexane until no more *trans* then hexanes/EtOAc 50/1 v/v) affording **(*Z*)-2,2'-(oct-4-ene-4,5-diyl)bis(benzo[1,2-b:4,3-b']dithiophene** [(*Z*)-**346**, 6.0 g, 93%] as a bright yellow foam, and **(*E*)-2,2'-(oct-4-ene-4,5-diyl)bis(benzo[1,2-b:4,3-b']dithiophene** [(*E*)-**346**, 320 mg, 5%) as a white solid.

*Cis*

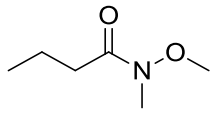
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.68 (dd, 2H, $^3J$ = 8.8 Hz, $^5J$ = 0.8 Hz), 7.58 (d, 2H, $^3J$ = 8.8 Hz), 7.56 (dd, 2H, $^3J$ = 5.5 Hz, $^5J$ = 0.8 Hz), 7.49 (d, 2H, $^5J$ = 0.8 Hz), 7.48 (d, 2H, $^3J$ = 5.5 Hz), 2.70-2.75 (m, 4H), 1.53-1.59 (m, 4H), 1.02 (t, 6H, $^3J$ = 7.5 Hz)

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 145.5 (2C, C), 136.9 (2C, C), 136.2 (2C, C), 134.5 (2C, C), 134.4 (2C, C), 134.2 (2C, C), 126.1 (2C, CH), 121.9 (2C, CH), 121.5 (2C, CH), 118.4 (2C, CH), 118.3 (2C, CH), 37.8 (2C, $CH_2$), 21.9 (2C, $CH_2$), 14.1 (2C, $CH_3$).

*Trans*

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.83 (dd, 2H, $^3J$ = 8.6 Hz, $^5J$ = 0.7 Hz), 7.80 (d, 2H, $^3J$ = 8.6 Hz), 7.73 (dd, 2H, $^3J$ = 5.5 Hz, $^5J$ = 0.7 Hz), 7.60 (d, 2H, $^3J$ = 5.5 Hz), 7.55 (s, 2H), 2.53-2.58 (m, 4H), 1.46-1.53 (m, 4H), 0.85 (t, 6H, $^3J$ = 7.5 Hz).

***N*-methoxy-*N*-methylbutanamide[9] (347):**



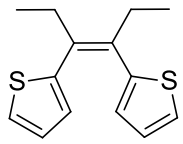

Chemical Formula: $C_6H_{13}NO_2$

Molecular Weight: 131.17

In a 1-L RBF, butyryl chloride (10.65 g, 100 mmol, 1 eq) and *N*,*O*-dimethylhydroxylamine hydrochloride (10.73 g, 110 mmol, 1.1 eq) were dissolved in DCM (600 mL), and stirred at RT for 20 min. Then, the solution was cooled to 0 °C, pyridine (17.4 g, 220 mmol, 2.2 eq) was added and the solution was stirred at RT for 1 hr and then evaporated. The residue is taken in a 1:1 mixture of $Et_2O$ and DCM (200 mL) and brine (200 mL). The organic layer was separated, dried with $MgSO_4$ and evaporated, affording 13 g of crude material which was purified by distillation (45 mbar, 90 °C) affording ***N*-methoxy-*N*-methylbutanamide (347,** 10.5g, 80%) as a pale liquid.

**$^1$H NMR ($CDCl_3$, 400MHz):** δ(ppm) 3.68 (s, 3H), 3.18 (s, 3H), 2.40 (t, 2H, $^3J$ = 7.5 Hz), 1.63-1.68 (m, 2H), 0.97 (t, 3H, $^3J$ = 7.2 Hz).

**(*Z*)-2,2'-(hex-3-ene-3,4-diyl)dithiophene (349):**




Chemical Formula: $C_{14}H_{16}S_2$

Molecular Weight: 248.4068

In a 1-L RBF, flame dried under argon, to a solution of 2-propionylthiophene (12.5 g, 89.2 mmol, 1 eq) in distilled THF (500 mL) cooled at 0 °C under argon, $TiCl_4$ (12.7 mL, 21.6 g, 115.9 mmol, 1.3 eq) was added dropwise. After stirring 5 min at 0 °C zinc powder (13.4 g,

205.1 mmol, 2.3 eq) was added in 10 portions over 15min, and reaction mixture was refluxed for 5 hrs under argon. After cooling the mixture at RT, ice-water (500 mL) was added and then the mixture was diluted with DCM (150 mL). The organic layer was separated and the aqueous layer was extracted with DCM (6 x 200 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. Crude material was then purified by column chromatography (150 g silica, hexanes) affording [**(*Z*)-349**, 4.96 g, 45%) as a colourless oil.

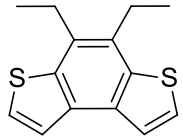
**IR (ATR):** ν ($cm^{-1}$) 3104, 3070, 2965, 2930, 2871.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.16 (dd, 2H, $^3J$ = 5.1 Hz, $^4J$ = 1.2 Hz), 6.87 (dd, 2H, $^3J$ = 5.1 Hz, $^3J$ = 3.5 Hz), 6.75 (dd, 2H, $^3J$ = 3.5 Hz, $^4J$ = 1.2 Hz), 2.58 (q, 4H, $^3J$ = 7.5 Hz), 1.09 (t, 6H, $^3J$ = 7.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 144.6 (2C, C), 133.7 (2C, C), 126.5 (2C, C), 126.3 (2C, C), 125.0 (2C, C), 28.6 (2C, $CH_2$), 13.3 (2C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{14}H_{16}S_2$: 249.0766; found: 249.0763.

**4,5-Diethylbenzo[1,2-b:4,3-b']dithiophene (350):**




Chemical Formula: $C_{14}H_{14}S_2$

Molecular Weight: 246.3910

A solution of **2,2'-(hex-3-ene-3,4-diyl)dithiophene** [**(*Z*)-349** 96:4, 4.7 g, 18.9 mmol, 1 eq] and $I_2$ (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 6 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (55 g silica, hexanes) affording **4,5-diethylbenzo[1,2-b:4,3-b']dithiophene** (**350**, 3.23 g, 69%) as a white powder.

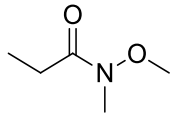
**Mp.:** 131-133 °C.

**IR (ATR):** ν ($cm^{-1}$) 3100, 3074, 2970, 2931, 2869.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.71 (d, 2H, $^3J$ = 5.4 Hz), 7.50 (d, 2H, $^3J$ = 5.4 Hz), 3.08 (q, 4H, $^3J$ = 7.5 Hz), 1.40 (t, 6H, $^3J$ = 7.5 Hz)

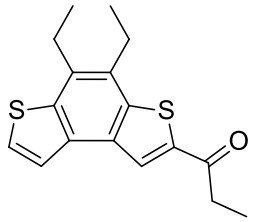
**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 138.3 (2C, C), 132.8 (2C, C), 131.2 (2C, C), 125.0 (2C, CH), 122.5 (2C, CH), 25.2 (2C, $CH_2$), 14.3 (2C, $CH_3$).
**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{14}S_2$: 247.0611; found: 247.0610.

***N*-methoxy-*N*-methylpropionamide[9] (351):**



Chemical Formula: $C_5H_{11}NO_2$
Molecular Weight: 117.1463
In a 1-L RBF, propionyl chloride (1.39 g, 15 mmol, 1 eq) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.61 g, 16.5 mmol, 1.1 eq) were dissolved in DCM (100 mL), and stirred at RT for 20 min. Then, the solution was cooled to 0 °C, pyridine (2.61 g, 33 mmol, 2.2 eq) was added and the solution was stirred at RT for 1 hr and then evaporated. The residue is taken in a 1:1 mixture of $Et_2O$ and DCM (50 mL) and brine (50 mL). The organic layer was separated, dried with $MgSO_4$ and evaporated, affording ***N*-methoxy-*N*-methylpropionamide** (**351**, 1.76 g, 100%) as a pale liquid.
**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 3.68 (s, 3H), 3.18 (s, 3H), 2.45 (t, 2H, $^3J$ = 7.5 Hz), 0.97 (t, 3H, $^3J$ = 7.5 Hz).

**1-(4,5-diethylbenzo[1,2-b:4,3-b']dithiophen-2-yl)propan-1-one (352):**



Chemical Formula: $C_{17}H_{18}OS_2$
Molecular Weight: 302.4542
Method A
In a 100-mL three-necked RBF, flame dried under nitrogen, to a solution of **4,5-diethylbenzo[1,2-b:4,3-b']dithiophene** (**350**, 1.6 g, 5.48 mmol, 1 eq) in distilled THF (50 mL) cooled at –78 °C, was added dropwise *n*-BuLi (2.2 M in hexanes, 2.6 mL, 5.75 mmol, 1.05 eq) under nitrogen. After stirring 45 min at –78 °C and 10 min at –10 °C, reaction mixture was cooled –78 °C and a solution of ***N*-methoxy-*N*-methylpropionamide** (**351**,

0.7 g, 6.03 mmol, 1.1 eq) was added dropwise. The solution was stirred at –78 °C for 1 hr and was then allowed to reach RT and was stirred at RT for another 2.5 hrs. Then sat. aq. $NH_4Cl$ (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 60mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (30 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording **1-(4,5-diethylbenzo[1,2-b:4,3-b']dithiophen-2-yl)propan-1-one** (**352**, 720 mg, 43%) as a yellow solid, 19% of starting material was recovered as well.

Method B:

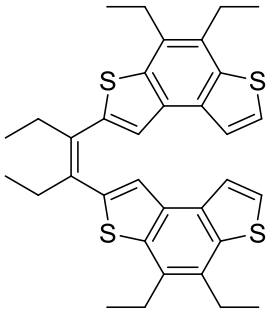
In a 250-mL three-necked RBF, flame dried under nitrogen, to a solution of **4,5-diethylbenzo[1,2-b:4,3-b']dithiophene** (**350**, 530 mg, 2.15 mmol, 1 eq) in distilled THF (100 mL) cooled at –78 °C, was added dropwise *n*-BuLi (1.4 M in hexanes, 1.7 mL, 2.3 mmol, 1.05 eq) under nitrogen. After stirring 10 min at –78 °C the temperature was brought to –10 °C for 10 min, and the reaction mixture was cooled again at –78 °C. Then CuI (204 mg, 1.07 mmol, 0.5 eq) was added, the temperature was raised to –60 °C for 2 hrs and propionic anhydride (0.3 mL, 2.3 mmol, 1.05 eq) was added dropwise and the solution was warmed up to –20 °C and stirred for 2 hrs. Then sat. aq. $NH_4Cl$ (50 mL) was added, the mixture was extracted with EtOAc (2 x 150mL) and the combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (30 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording **1-(4,5-diethylbenzo[1,2-b:4,3-b']dithiophen-2-yl)propan-1-one** (**352**, 250 mg, 40%) as a yellow solid.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 8.30 (s, 1H), 7.72 (d, 1H, $^3J$ = 5.4 Hz), 7.57 (d, 1H, $^3J$ = 5.4 Hz), 3.11 (q, 2H, $^3J$ = 7.3 Hz), 3.02-3.13 (m, 4H), 1.36-1.41 (m, 6H), 1.32 (t, 3H, $^3J$ = 7.3 Hz).

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ (ppm) 195.1 (1C, C), 141.9 (1C, C), 141.8 (1C, C), 138.8 (1C, C), 134.9 (1C, C), 134.0 (1C, C), 132.5 (1C, C), 131.3 (1C, C), 127.0 (1C, CH), 126.2 (1C, CH), 122.2 (1C, CH), 32.5 (1C, $CH_2$), 25.5 (1C, $CH_2$), 24.9 (1C, $CH_2$), 14.1 (1C, $CH_3$), 14.0 (1C, $CH_3$), 8.7 (1C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{17}H_{18}OS_2$: 303.0872; found: 303.0871.

**(*Z*)-2,2'-(hex-3-ene-3,4-diyl)bis(4,5-diethylbenzo[1,2-b:4,3-b']dithiophene) (359):**



Chemical Formula: $C_{34}H_{36}S_4$

Molecular Weight: 572.9096

In a 100-mL three-necked RBF, flame dried under nitrogen, to a solution of **1-(4,5-diethylbenzo[1,2-b:4,3-b']dithiophen-2-yl)propan-1-one** (**352**, 1.2 g, 3.98 mmol, 1 eq) in distilled THF (60 mL) cooled at 0 °C under nitrogen, $TiCl_4$ (30.57 mL, 0.98 g, 5.16 mmol, 1.3 eq) was added dropwise. After stirring 5 min at 0 °C zinc powder (0.6 g, 9.14 mmol, 2.3 eq) was added in 5 portions over 15min, and the reaction mixture was refluxed for 3 hrs under nitrogen. After cooling the mixture at RT, ice-water (50 mL) was added and then the mixture was diluted with DCM (100mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 100mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography (10 g silica, hexanes/EtOAc gradient 100/0 to 95/5 v/v) affording **(*Z*)-2,2'-(hex-3-ene-3,4-diyl)bis(4,5-diethylbenzo[1,2-b:4,3-b']dithiophene)** (**359**, 580 mg, 51%) as a bright yellow oil.

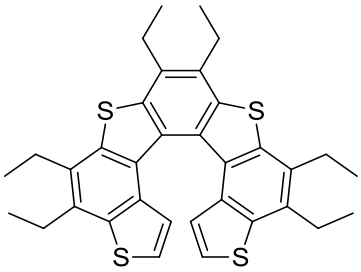
**IR (ATR):** ν ($cm^{-1}$) 3100, 3074, 2967, 2931, 2871.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.50 (d, 2H, $^3J$ = 5.4 Hz), 7.43 (s, 2H), 7.38 (d, 2H, $^3J$ = 5.4 Hz), 2.98 (q, 4H, $^3J$ = 7.6 Hz), 2.87 (q, 4H, $^3J$ = 7.6 Hz), 2.75 (q, 4H, $^3J$ = 7.6 Hz), 1.33 (t, 6H, $^3J$ = 7.6 Hz), 1.15-1.22 (m, 12H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 143.7 (2C, C), 138.5 (2C, C), 138.0 (2C, C), 135.2 (2C, C), 132.8 (2C, C), 132.5 (2C, C), 130.9 (2C, C), 130.7 (2C, C), 124.5 (2C, CH), 122.6 (2C, CH), 122.2 (2C, CH), 28.7 (2C, $CH_2$), 25.2 (2C, $CH_2$), 25.0 (2C, $CH_2$), 14.2 (2C, $CH_3$), 14.0 (2C, $CH_3$), 13.5 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{34}H_{36}S_4$: 572.1694; found: 572.1684.

**3,4,7,8,11,12-Hexaethyltetrathia[7]helicene (360):**



Chemical Formula: $C_{34}H_{34}S_4$

Molecular Weight: 570.8938

A solution of **(*Z*)-2,2'-(hex-3-ene-3,4-diyl)bis(4,5-diethylbenzo[1,2-b:4,3-b']dithiophene)** (**359**, 580 mg, 1.01 mmol, 1 eq) and $I_2$ (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 2 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (15 g silica, hexanes) affording **3,4,7,8,11,12-hexaethyltetrathia[7]helicene** (**360**, 395 mg, 68%) as a white foam.

**Mp.:** 201-202 °C.

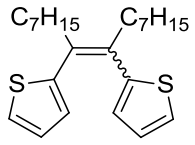
**IR (ATR):** ν ($cm^{-1}$) 3091, 2966, 2931, 2871.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 6.80 (d, 2H, $^3J$ = 5.7 Hz), 6.77 (d, 2H, $^3J$ = 5.7 Hz), 3.12-3.26 (m, 12H), 1.54 (t, 6H, $^3J$ = 7.9 Hz), 1.44-1.49 (m, 12H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 138.4 (2C, C), 138.1 (2C, C), 137.5 (2C, C), 134.2 (2C, C), 133.3 (2C, C), 132.6 (2C, C), 130.8 (2C, C), 130.0 (2C, C), 129.0 (2C, C), 126.1 (2C, CH), 122.2 (2C, CH), 25.5 (2C, $CH_2$), 25.3 (2C, $CH_2$), 25.2 (2C, $CH_2$), 14.5 (2C, $CH_3$) 14.40 (2C, $CH_3$), 14.39 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{34}H_{34}S_4$: 570.1538; found: 570.1535.

**2,2'-(Hexadec-8-ene-8,9-diyl)dithiophene (362):**



Chemical Formula: $C_{24}H_{36}S_2$

Molecular Weight: 388.6726

In a 250-mL three-necked RBF, flame dried under nitrogen, to a solution of 2-octanoyllthiophene (5.44 g, 25.8 mmol, 1 eq) in distilled THF (150 mL) cooled at 0 °C under argon, $TiCl_4$ (3.69 mL, 6.37 g, 33.5 mmol, 1.3 eq) was added dropwise. After stirring 5 min at 0 °C zinc powder (3.88 g, 59.3 mmol, 2.3 eq) was added in 5 portions over 15 min, and reaction mixture was refluxed for 3 hrs under argon. After cooling the mixture at RT, ice-water (150 mL) was added and then the mixture was diluted with DCM (150mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 150mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude material was then purified by column chromatography (50 g silica, hexanes) affording **2,2'-(hexadec-8-ene-8,9-diyl)dithiophene** (**362**, 3.8 g, 76%) in a mixture of *cis* and *trans* isomers (*cis/trans*, 78:22) as a colourless oil.

**IR (ATR):** ν ($cm^{-1}$) 2955, 2925, 2855.

*Cis* isomer

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.14 (dd, 2H, $^3J$ = 5.1 Hz, $^4J$ = 1.1 Hz), 6.85(dd, 2H, $^3J$ = 5.1 Hz, $^3J$ = 3.5 Hz), 6.72 (dd, 2H, $^3J$ = 3.5 Hz, $^4J$ = 1.1 Hz), 2.51-2.54 (m, 4H), 1.41-1.46 (m, 4H), 1.30-1.35 (m, 16H), 0.89 (t, 6H, $^3J$ = 6.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 144.0 (2C, C), 134.2 (2C, C), 126.6 (2C, C), 125.6 (2C, C), 124.3 (2C, C), 37.0 (2C, $CH_2$), 31.7 (2C, $CH_2$), 29.4 (2C, $CH_2$), 29.1 (2C, $CH_2$), 29.0 (2C, $CH_2$), 22.6 (2C, $CH_2$), 14.1 (2C, $CH_3$).

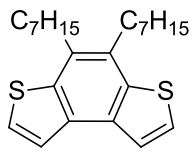
*Trans* isomer

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.28 (dd, 2H, $^3J$ = 5.1 Hz, $^4J$ = 1.3 Hz), 7.03 (dd, 2H, $^3J$ = 5.1 Hz, $^3J$ = 3.5 Hz), 6.88 (dd, 2H, $^3J$ = 3.5 Hz, $^4J$ = 1.3 Hz), 2.34-2.38 (m, 4H), 1.31-1.35 (m, 4H), 1.20-1.25 (m, 4H), 1.16-1.19 (m, 12H), 0.85 (t, 6H, $^3J$ = 7.0 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 145.1 (2C, C), 132.9 (2C, C), 126.4 (2C, C), 126.3 (2C, C), 124.9 (2C, C), 35.7 (2C, $CH_2$), 31.8 (2C, $CH_2$), 29.6 (2C, $CH_2$), 29.2 (2C, $CH_2$), 28.6 (2C, $CH_2$), 22.6 (2C, $CH_2$), 14.1 (2C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{24}H_{36}S_2$: 389.2331; found: 389.2322.

**4,5-Diheptylbenzo[1,2-b:4,3-b']dithiophene (363):**




Chemical Formula: $C_{24}H_{34}S_2$

Molecular Weight: 386.6568

A solution of **2,2'-(hexadec-8-ene-8,9-diyl)dithiophene** (**362**, *cis*/*trans* 85:15) (4.26 g, 11.0 mmol, 1 eq) and $I_2$ (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 5 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (70 g silica, hexanes) affording **4,5-diheptylbenzo[1,2-b:4,3-b']dithiophene** (**363**, 3.65 g, 86%) as a white viscous oil.

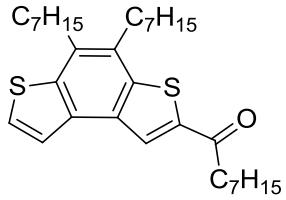
**IR (ATR):** ν ($cm^{-1}$) 2955, 2925, 2855.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.69 (d, 2H, $^3J$ = 5.3 Hz), 7.49 (d, 2H, $^3J$ = 5.3 Hz), 2.98-3.02 (m, 4H), 1.73-1.78 (m, 4H), 1.49-1.53 (m, 4H), 1.39-1.43 (m, 4H), 1.30-1.35 (m, 8H), 0.92 (t, 6H, $^3J$ = 6.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 138.7 (2C, C), 132.7 (2C, C), 130.3 (2C, C), 124.9 (2C, CH), 122.4 (2C, CH), 32.3 (2C, $CH_2$), 31.8 (2C, $CH_2$), 30.1 (2C, $CH_2$), 29.8 (2C, $CH_2$), 29.1 (2C, $CH_2$), 22.7 (2C, $CH_2$), 14.1 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{24}H_{34}S_2$: 387.2175; found: 387.2172.

**1-(4,5-Diheptylbenzo[1,2-b:4,3-b']dithiophen-2-yl)octan-1-one (364):**




Chemical Formula: $C_{32}H_{48}OS_2$

Molecular Weight: 512.8529

In a 250-mL three-necked RBF, flame dried under nitrogen, to a solution of **4,5-diheptylbenzo[1,2-b:4,3-b']dithiophene** (**363**, 3.6 g, 9.3 mmol, 1 eq) in distilled THF (150 mL) cooled at –78 °C, was added dropwise *n*-BuLi (2.2 M in hexanes, 4.4 mL, 9.7 mmol, 1.05 eq) under nitrogen. After stirring 45 min at –78 °C and 10 min at –10 °C, the reaction mixture was cooled –78 °C and ***N*-methoxy-*N*-methyloctanamide** (**367**, 1.92 g, 10.2 mmol, 1.1 eq) was added dropwise. The solution was stirred at –78 °C for 1 hr, then was allowed to reach RT and the solution was stirred at RT for another 2.5 hrs. Then sat. aq. $NH_4Cl$ (100mL) was added, organic layer separated, aqueous layer extracted with

EtOAc (2 x 100 mL), dried and evaporated. The crude material was then purified by column chromatography (90 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording **1-(4,5-diheptylbenzo[1,2-b:4,3-b']dithiophen-2-yl)octan-1-one** (**364**, 4.22 g, 77%) as a yellow oil which solidifies containing 12% of bisketone **365**. (12% of **365** from NMR), 7% of starting material **363** was recovered as well.

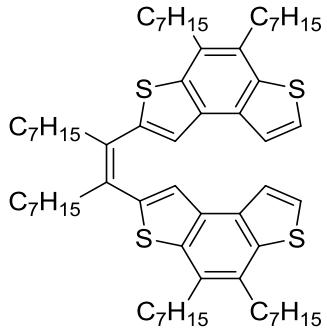
**IR (ATR):** ν ($cm^{-1}$) 2955, 2926, 2855, 1662.

**$^{1}$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.28 (s, 1H), 7.72 (d, 1H, $^{3}J$ = 5.4 Hz), 7.56 (d, 1H, $^{3}J$ = 5.4 Hz), 3.05 (t, 2H, $^{3}J$ = 7.3 Hz), 2.95-3.03 (m, 4H), 1.80-1.85 (m, 2H), 1.72-1.76 (m, 4H), 1.31-1.50 (m, 24H), 0.89-0.93 (m, 9H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 194.9 (1C, C), 142.4 (1C, C), 142.1 (1C, C), 139.4 (1C, C), 134.0 (1C, C), 133.9 (1C, C), 132.4 (1C, C), 130.5 (1C, C), 127.0 (1C, CH), 126.2 (1C, CH), 122.2 (1C, CH), 39.3 (1C, $CH_2$), 32.6 (1C, $CH_2$), 32.1 (1C, $CH_2$), 31.81 (1C, $CH_2$), 31.77 (1C, $CH_2$), 31.7 (1C, $CH_2$), 30.1 (2C, $CH_2$), 29.8 (1C, $CH_2$), 29.7 (1C, $CH_2$), 29.3 (1C, $CH_2$), 29.11 (2C, $CH_2$), 29.06 (1C, $CH_2$), 25.0 (1C, $CH_2$), 22.7 (3C, $CH_2$), 14.1 (3C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{32}H_{48}OS_2$: 513.3219; found: 513.3205.

**(*Z*)-2,2'-(hexadec-8-ene-8,9-diyl)bis(4,5-diheptylbenzo[1,2-b:4,3-b']dithiophene) (366):**




Chemical Formula: $C_{64}H_{96}S_4$

Molecular Weight: 993.7070

In a 250-mL RBF, flame dried under nitrogen, to a solution of **1-(4,5-diheptylbenzo[1,2-b:4,3-b']dithiophen-2-yl)octan-1-one** (**364**, 3.67 g, 7.17 mmol, 1 eq) in distilled THF (200 mL) cooled at 0 °C under argon, $TiCl_4$ (1.02 mL, 1.75 g, 9.3 mmol, 1.3 eq) was added dropwise. After stirring 5 min at 0 °C zinc powder (2.03 g, 18.9 mmol, 2.3 eq) was added in 5 portions over 15 min, and the reaction mixture was refluxed for 6 hrs under argon. After cooling the mixture at RT, ice-water (150 mL) was added and then the mixture was diluted with DCM (300 mL). The organic layer was separated and the aqueous layer was

extracted with DCM (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography (70 g silica, hexanes/EtOAc gradient 100/0 to 95/5 v/v) affording **(*Z*)-2,2'-(hexadec-8-ene-8,9-diyl)bis(4,5-diheptylbenzo[1,2-b:4,3-b']dithiophene)** (**366**, 1.35 g, 38%) as a bright yellow oil.

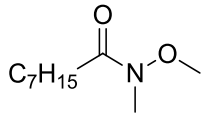
**IR (ATR):** ν ($cm^{-1}$) 2955, 2925, 2855.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.48 (d, 2H, $^3J$ = 5.4 Hz), 7.40 (s, 2H), 7.36 (d, 2H, $^3J$ = 5.4 Hz), 2.88-3.03 (m, 4H), 2.75-2.80 (m, 4H), 2.68-2.72 (m, 4H), 1.66-1.71 (m, 4H) 1.16-1.56 (m, 60H), 0.86-0.90 (m, 18H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 144.1 (2C, C), 138.9 (2C, C), 138.3 (2C, C), 134.3 (2C, C), 132.7 (2C, C), 132.4 (2C, C), 130.0 (2C, C), 129.7 (2C, C), 124.4 (2C, CH), 122.5 (2C, CH), 122.0 (2C, CH), 35.7 (2C, $CH_2$), 32.3 (2C, $CH_2$), 32.0 (2C, $CH_2$), 31.83 (2C, $CH_2$), 31.79 (4C, $CH_2$), 30.1 (2C, $CH_2$), 30.0 (2C, $CH_2$), 29.8 (2C, $CH_2$), 29.7 (2C, $CH_2$), 29.6 (2C, $CH_2$), 29.2 (2C, $CH_2$), 29.1 (2C, $CH_2$), 28.9 (2C, $CH_2$), 28.7 (2C, $CH_2$), 22.7 (4C, $CH_2$), 22.6 (2C, $CH_3$), 14.13 (2C, $CH_3$), 14.09 (4C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{64}H_{96}S_4$: 992.6389; found: 992.6372.

***N*-methoxy-*N*-methyloctanamide[10] (367):**



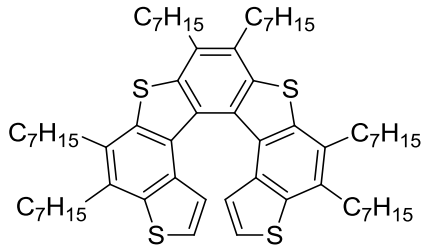

Chemical Formula: $C_{10}H_{21}NO_2$

Molecular Weight: 187.2792

In a 500-mL RBF, octanoyl chloride (3 g, 18.4 mmol, 1 eq) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.98 g, 20.3 mmol, 1.1 eq) were dissolved in DCM (300 mL) and stirred at RT for 20 min. Then, the solution was cooled to 0 °C, pyridine (3.2 g, 40.5 mmol, 2.2 eq) was added and the solution was stirred at RT for 1 hr and then evaporated. The residue is taken in a 1:1 mixture of $Et_2O$ and DCM (100 mL) and brine (100 mL). The organic layer was separated, dried with $MgSO_4$ and evaporated, affording ***N*-methoxy-*N*-methyloctanamide** (**367,** 3.29 g, 95%) as a pale liquid.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 3.69 (s, 3H), 3.19 (s, 3H), 2.42 (t, 2H, $^3J$ = 7.5 Hz 1.60-1.65 (m, 2H), 1.29-1.34 (m, 8H), 0.89 (t, 3H, $^3J$ = 6.9 Hz).

**3,4,7,8,11,12-Hexaheptyltetrathia[7]helicene (368)**:



Chemical Formula: $C_{64}H_{94}S_4$

Molecular Weight: 991.6912

A solution of (*Z*)-**2,2'-(hexadec-8-ene-8,9-diyl)bis(4,5-diheptylbenzo[1,2-b:4,3-b']dithiophene)** (**366**, 1.35 g, 1.36 mmol, 1 eq) and $I_2$ (50 mg) in toluene (3 L) was irradiated in a 3-L photochemical reaction vessel equipped with a quartz jacket using a 500 W UV lamp. The solution was irradiated for 3 hrs at RT with air bubbling into the solution. The solvent was then evaporated and the residue was dissolved in DCM (100 mL), washed with sat. aq. $Na_2SO_3$ (100 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (25 g silica, hexanes) affording **3,4,7,8,11,12-hexaheptyltetrathia[7]helicene** (**368**, 865 mg, 65%) as an orange wax.

**Mp.:** 85-87 °C.

**IR (ATR):** ν ($cm^{-1}$) 2955, 2925, 2855.

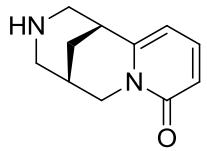
**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 6.77 (d, 2H, $^3J$ = 5.7 Hz), 6.73 (d, 2H, $^3J$ = 5.7 Hz), 3.06-3.20 (m, 12H), 1.78-1.94 (m, 12H), 1.32-1.63 (m, 48H), 0.91-0.96 (m, 18H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 138.7 (2C, C), 138.5 (2C, C), 137.8 (2C, C), 134.1 (2C, C), 132.4 (2C, C), 131.7 (2C, C), 129.88 (2C, C), 129.86 (2C, C), 128.8 (2C, C), 126.0 (2C, CH), 122.0 (2C, CH), 32.6 (2C,$CH_2$), 32.4 (2C, $CH_2$), 32.2 (2C, $CH_2$), 31.88 (2C, $CH_2$), 31.87 (2C, $CH_2$), 31.84 (2C, $CH_2$), 30.3 (2C, $CH_2$), 30.2 (2C, $CH_2$), 30.1 (2C, $CH_2$), 30.0 (4C, $CH_2$), 29.9 (2C, $CH_2$), 29.2 (2C, $CH_2$), 29.14 (2C, $CH_2$), 29.13 (2C, $CH_2$), 22.74 (2C, $CH_2$), 22.72 (2C, $CH_2$), 22.70 (2C, $CH_2$), 14.2 (2C, $CH_3$), 14.1 (4C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{64}H_{94}S_4$: 990.6233; found: 990.6221.

Experimental section for chapter 2

**(–)-cytisine[11] [(–)-396]:**




Chemical Formula: $C_{11}H_{14}N_2O$

Molecular Weight: 190.2417

Ground *Laburnum anagyroides* seeds (1.2 kg), DCM (2 L), MeOH (600 mL) and $NH_4OH$ (200 mL) were stirred in a 5-L reaction vessel for 72 hrs. The reaction mixture was filtered, and the solids were washed with DCM (1 L). The filtrate was acidified with HCl (3N) until pH 1. The aqueous layer was separated, basified with $NH_4OH$ (28%) until pH 11-12 and extracted with DCM (10 x 1 L). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude solid obtained was triturated in acetone, and after filtration the resulting solid was dried under vacuum affording **(–)-cytisine** [**(–)-396**, 16.55 g, 1.4%] as a yellow solid.

**Mp.:** 153-155°C.

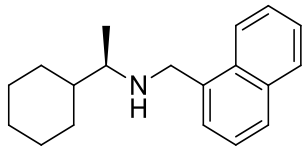
$[\alpha]_D = -55°$.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 7.29 (dd, 1H, $^3J$ = 9.1 Hz, $^3J$ = 7.0 Hz), 6.44 (dd, 1H, $^3J$ = 9.1 Hz, $^4J$ = 1.6 Hz), 5.99 (dd, 1H, $^3J$ = 7.0 Hz, $^4J$ = 1.6 Hz), 4.1 (d, 1H, $^2J$ = 15.7 Hz), 3.89 (ddd, 1H, $^2J$ = 15.7 Hz, $^3J$ = 6.6 Hz, $^5J$ = 1.0 Hz), 3.08 (br. d, 1H, $^2J$ = 12.6 Hz), 3.04 (dd, 1H, $^2J$ = 12.6 Hz, $J$ = 2.5 Hz), 2.98 (br. d, 2H, $^2J$ = 12.6 Hz), 2.89 (br. s, 1H), 2.31 (br. s, 1H), 1.92-1.97 (m, 4H).

**General procedure for reductive amination of aldehydes:**

Amine (1 eq) and aldehyde (1 eq) were mixed in 1,2-dichloroethane (about 5 mL/mmol of amine) before sodium triacetoxyborohydride (1.4 eq) was added. The mixture was stirred at RT under nitrogen overnight. Then, sat. aq. $NaHCO_3$, was added and the mixture was extracted with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the crude material which was generally purified by silica gel column chromatography. In cases where the crude was pure enough, it was treated directly with formic acetic anhydride affording the corresponding formamide.

**(*R*)-1-cyclohexyl-*N*-(naphthalen-1-ylmethyl)ethanamine [(*R*)-407]:**



Chemical Formula: $C_{19}H_{25}N$

Molecular Weight: 267.4085

The product was obtained as a light yellow oil.

$[\alpha]_D = -21.3°$.

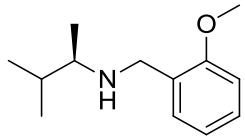
**IR (ATR):** $\nu$ ($cm^{-1}$) 3046, 2920, 2849.

**$^1$H NMR ($CDCl_3$, 400 MHz):** $\delta$ (ppm) 8.14 (d, 1H, $^3J$ = 8.2 Hz), 7.86 (d, 1H $^3J$ = 8.0 Hz), 7.76 (d, 1H, $^3J$ = 8.0 Hz), 7.35-7.56 (m, 4H), 4.28 (d, 1H, $^2J$ = 12.8 Hz), 4.15 (d, 1H, $^2J$ = 12.8 Hz), 2.62-2.66 (m, 1H), 1.69-1.73 (m, 5H), 1.40-1.44 (m, 2H), 0.99-1.30 (m, 8H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** $\delta$ (ppm) 136.6 (1C, C), 133.8 (1C, C), 131.9 (1C, C), 128.7 (1C, CH), 127.6 (1C, CH), 126.03 (1C, CH), 125.97 (1C, CH), 125.5 (1C, CH), 125.4 (1C, CH), 123.8 (1C, CH), 58.2 (1C, CH), 49.6 (1C, $CH_2$), 43.0 (1C, CH), 29.9 (1C, $CH_2$), 28.2 (1C, $CH_2$), 26.8 (1C, $CH_2$), 26.7 (1C, $CH_2$), 26.5 (1C, $CH_2$), 16.9 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{19}H_{25}N$: 268.2053; found: 268.2060.

**(*R*)-*N*-(2-methoxybenzyl)-3-methylbutan-2-amine [(*R*)-409]:**



Chemical Formula: $C_{13}H_{21}NO$

Molecular Weight: 207.3119

The product was obtained as a colourless oil.

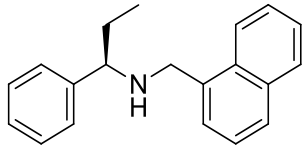
$[\alpha]_D = -39°$.

**IR (ATR):** $\nu$ ($cm^{-1}$) 2956, 2870, 2834.

**$^1$H NMR ($CDCl_3$, 400 MHz):** $\delta$ (ppm) 7.21-7.27 (m, 2H), 6.91 (td, 1H, $^3J$ = 7.4 Hz, $^4J$ = 0.9 Hz), 6.86 (br. d, 1H, $^3J$ = 7.9 Hz), 3.85 (s, 3H), 3.84 (d, 1H, $^2J$ = 13.2 Hz), 3.73 (d, 1H, $^2J$ = 13.2 Hz), 2.40-2.45 (m, 1H), 1.68-1.72 (m, 2H), 1.00 (d, 3H, $^3J$ = 6.4 Hz), 0.89 (d, 3H, $^3J$ = 6.8 Hz), 0.87 (d, 3H, $^3J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 157.7 (1C, C), 129.8 (1C, CH), 128.8 (1C, C), 128.0 (1C, CH), 120.3 (1C, CH), 110.1 (1C, CH), 57.2 (1C, CH), 55.2 (1C, $CH_3$), 47.0 (1C, $CH_2$), 32.2 (1C, CH), 19.3 (1C, $CH_3$), 17.4 (1C, $CH_3$), 16.0 (1C, $CH_3$).
**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{21}NO$: 208.1696; found: 208.1695.

**(*R*)-*N*-(naphthalen-1-ylmethyl)-1-phenylpropan-1-amine [(*R*)-411]:**



Chemical Formula: $C_{20}H_{21}N$

Molecular Weight: 275.3874

The product was obtained as a colourless oil.

$[\alpha]_D$ = +55°.

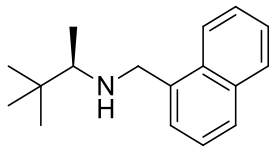
**IR (ATR):** ν ($cm^{-1}$) 3058, 2959, 2927, 2872.

**$^1$H NMR ($CDCl_3$, 400MHz):** δ(ppm) 8.00-8.03 (m, 1H), 7.84-7.86 (m, 1H), 7.76-7.78 (m, 1H), 7.48-7.50 (m, 2H), 7.40-7.44 (m, 6H), 7.30-7.32 (m, 1H), 4.10 (d, 1H, $^2J$ = 13 Hz), 3.98 (d, 1H, $^2J$ = 13 Hz), 3.66 (dd, 1H, $^3J$ = 7.7 Hz, $^3J$ = 6.0 Hz), 1.66-1.82 (m, 3H), 0.83 (t, 3H, $^3J$ = 7.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 100MHz):** δ(ppm) 144.3 (1C, C), 136.5 (1C, C), 134.1 (1C, C), 132.1 (1C, C), 128.8 (1C, CH), 128.6 (2C, CH), 127.9 (1C, CH), 127.8 (2C, CH), 127.3 (1C, CH), 126.4 (1C, CH), 126.2 (1C, CH), 125.8 (1C, CH), 125.6 (1C, CH), 124.1 (1C, CH), 65.4 (1C, CH), 49.8 (1C, $CH_2$), 31.4 (1C, $CH_2$), 11.1 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{20}H_{21}N$: 276.1747; found: 276.1750.

**(*R*)-3,3-dimethyl-*N*-(naphthalen-1-ylmethyl)butan-2-amine [(*R*)-413]:**



Chemical Formula: $C_{17}H_{23}N$

Molecular Weight: 241.3712

The product was obtained as a colourless oil.

$[\alpha]_D$ = –60°.

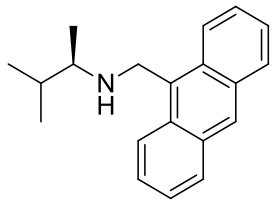
**IR (ATR):** ν ($cm^{-1}$) 3045, 2954, 2847.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.19 (d, 1H, $^3J$ = 8.4 Hz), 7.86 (br. d, 1H, $^3J$ = 7.7 Hz), 7.77 (d, 1H, $^3J$ = 8.0 Hz), 7.42-7.57 (m, 4H), 4.37 (d, 1H, $^2J$ = 12.8 Hz), 4.08 (d, 1H, $^2J$ = 12.8 Hz), 2.44 (q, 1H, $^3J$ = 6.4 Hz), 1.33 (br. s, 1H), 1.13 (d, 3H, $^3J$ = 6.4 Hz), 0.89 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 136.8 (1C, C), 133.8 (1C, C), 132.0 (1C, C), 128.6 (1C, CH), 127.6 (1C, CH), 126.2 (1C, CH), 125.8 (1C, CH), 125.5 (1C, CH), 125.3 (1C, CH), 124.2 (1C, CH), 62.3 (1C, CH), 50.9 (1C, $CH_2$), 34.5 (1C, C), 26.5 (3C, $CH_3$), 14.8 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{17}H_{23}N$: 242.1903; found: 242.1904.

**(*R*)-*N*-(anthracen-9-ylmethyl)-3-methylbutan-2-amine [(*R*)-415]:**




Chemical Formula: $C_{20}H_{23}N$

Molecular Weight: 277.4033

The product was obtained as a yellow oil.

$[\alpha]_D = -14°$.

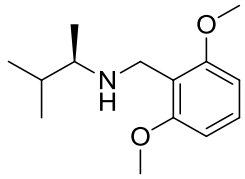
**IR (ATR):** ν ($cm^{-1}$) 3056, 2958, 2926, 2873.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 8.42 (s, 1H), 8.38 (dd, 2H, $^3J$ = 8.8 Hz, $^4J$ = 1.0 Hz), 8.03 (dd, 2H, $^3J$ = 8.5 Hz, $^4J$ = 0.6 Hz), 7.57 (ddd, 2H, $^3J$ = 9.1 Hz, $^3J$ = 6.6 Hz, $^4J$ = 1.6 Hz), 7.49 (ddd, 2H, $^3J$ = 8.2 Hz, $^3J$ = 6.3 Hz, $^4J$ = 1.0 Hz), 4.77 (d, 1H, $^2J$ = 11.9 Hz), 4.65 (d, 1H, $^2J$ = 11.9 Hz), 2.81-2.86 (m, 1H), 1.89-1.93 (m, 1H), 1.31 (br. s, 1H), 1.22 (d, 3H, $^3J$ = 6.3 Hz), 0.99 (d, 6H, $^3J$ = 6.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ(ppm) 132.3 (1C, C), 131.6 (2C, C), 130.3 (2C, C), 129.1 (2C, CH), 127.0 (1C, CH), 126.0 (2C, CH), 124.9 (2C, CH), 124.3 (2C, CH), 59.8 (1C, $CH_2$), 44.2 (1C, CH), 32.3 (1C, CH), 19.5 (1C, $CH_3$), 17.5 (1C, $CH_3$), 16.5 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{20}H_{23}N$: 278.1903; found: 278.1905.

**(*R*)-*N*-(2,6-dimethoxybenzyl)-3-methylbutan-2-amine [(*R*)-417]:**



Chemical Formula: $C_{14}H_{23}NO_2$

Molecular Weight: 237.3379

The product was obtained as a colourless oil.

$[\alpha]_D = -35°$.

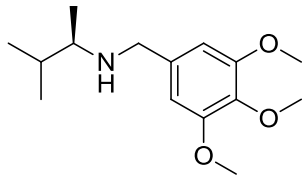
**IR (ATR):** ν ($cm^{-1}$) 2956, 2870, 2835.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.17 (t, 1H, $^3J$ = 8.4 Hz), 6.54 (d, 2H, $^3J$ = 8.4Hz), 3.86 (d, 2H, $^5J$ = 1.3Hz), 3.82 (s, 6H), 2.31-2.36 (m, 1H), 2.05 (br. s, 1H), 1.68-1.73 (m, 1H), 1.0 (d, 3H, $^3J$ = 6.4 Hz), 0.86 (d, 3H, $^3J$ = 6.8 Hz), 0.84 (d, 3H, $^3J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 158.7 (2C, C), 128.1 (1C, CH), 116.2 (1C, C), 103.5 (2C, CH), 57.0 (1C, CH), 55.6 (2C, CH3), 39.0 (1C, $CH_2$), 32.0 (1C, CH), 19.2 (1C, $CH_3$), 17.6 (1C, $CH_3$), 15.9 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{23}NO_2$: 238.1802; found: 238.1805.

**(*R*)-3-methyl-*N*-(3,4,5-trimethoxybenzyl)butan-2-amine [(*R*)-419]:**



Chemical Formula: $C_{15}H_{25}NO_3$

Molecular Weight: 267.3639

The product was obtained as a colourless oil.

$[\alpha]_D = -29°$.

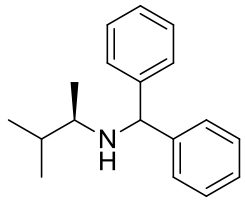
**IR (ATR):** ν ($cm^{-1}$) 2956, 2835.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 6.60 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.83 (d, 1H, $^2J$ = 13.2 Hz), 3.68 (d, 1H, $^2J$ = 13.2 Hz), 2.50-2.55 (m, 1H), 1.72-1.76 (m, 1H), 1.48 (br. s, 1H), 1.02 (d, 3H, $^3J$ = 6.4 Hz), 0.92 (d, 3H, $^3J$ = 7.0 Hz), 0.90 (d, 3H, $^3J_{H\text{-}H}$ = 7.0 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 153.4 (2C, CH), 136.9 (1C, C), 136.6 (1C, C), 104.7 (2C, CH), 60.8 (1C, CH), 57.3 (1C, $CH_2$), 56.0 (2C, $CH_3$), 51.7 (1C, $CH_3$), 32.2 (1C, CH), 19.3 (1C, $CH_3$), 17.3 (1C, $CH_3$), 15.9 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{25}NO_3$: 268.1907; found: 268.1913.

**(*R*)-*N*-benzhydryl-3-methylbutan-2-amine [(*R*)-420]:**



Chemical Formula: $C_{18}H_{23}N$

Molecular Weight: 253.3819

The product was obtained as a colourless oil.

$[\alpha]_D = -38°$

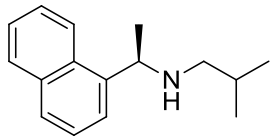
**IR (ATR):** ν ($cm^{-1}$) 3085, 3063, 3027, 2959, 2927, 2871.

**$^1$H NMR ($CDCl_3$, 500MHz):** δ(ppm) 7.41 (br. d, 4H), 7.28-7.31 (m, 4H), 7.19-7.21 (m, 2H), 4.98 (s, 1H), 2.40-2.45 (m, 1H), 1.71-1.76 (m, 1H), 1.28 (br. s, 1H), 0.99 (d, 3H, $^3J$ = 6.3 Hz), 0.89 (d, 3H, $^3J$ = 6.9 Hz), 0.89 (d, 3H, $^3J$ = 6.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 120MHz):** δ(ppm) 145.1 (1C, C), 144.5 (1C, C), 128.4 (2C, CH), 128.3 (2C, CH), 127.6 (2C, CH), 127.3 (2C, CH), 126.8 (2C, CH), 64.1 (1C, CH), 54.9 (1C, CH), 35.5 (1C, CH), 19.2 (1C, $CH_3$), 17.5 (1C, $CH_3$), 16.0 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{18}H_{23}N$: 268.1907; found: 268.1913.

**(*R*)-2-methyl-*N*-(1-(naphthalen-1-yl)ethyl)propan-1-amine [(*R*)-423]:**



Chemical Formula: $C_{16}H_{21}N$

Molecular Weight: 227.3446

The product was obtained as a yellow oil.

$[\alpha]_D$ = don't have the compound anymore.

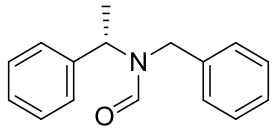
**IR (ATR):** ν ($cm^{-1}$) 3053, 2963, 2924, 2854.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.18 (d, 1H, $^3J$ = 8.5 Hz), 7.89 (dd, 1H, $^3J$ = 8.2 Hz, $^4J$ = 1.6 Hz), 7.77 (d, 1H, $^3J$ = 8.5 Hz), 7.69 (d, 1H, $^3J$ = 7.3 Hz), 7.47-7.54 (m, 3H), 4.69 (q, 1H, $^3J$ = 6.6 Hz), 2.48 (ddd, 1H, $^2J$ = 11.3 Hz, $^3J$ = 6.3 Hz, $^4J$ = 2.2 Hz), 2.35 (ddd, 1H, $^2J$ = 11.3 Hz, $^3J$ = 6.3 Hz, $^4J$ = 2.2 Hz), 1.87 (s, 1H), 1.78-1.83 (m, 1H), 1.54 (dd, 3H, $^3J$ = 6.6 Hz, $^4J$ = 1.9 Hz), 0.92 (dd, 3H, $^3J$ = 6.6 Hz, $^4J$ = 1.9 Hz), 0.89 (dd, 3H, $^3J$ = 6.9 Hz, $^4J$ = 1.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 141.4 (1C, C), 134.0 (1C, C), 131.4 (1C, C), 128.9 (1C, CH), 127.0 (1C, CH), 125.71 (1C, CH), 125.67 (1C, CH), 125.2 (1C, CH), 123.0 (1C, CH), 122.7 (1C, CH), 56.1 (1C, CH), 53.8 (1C, CH), 28.7 (1C, $CH_2$), 23.6 (1C, $CH_3$), 20.8 (1C, $CH_3$), 20.7 (1C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{16}H_{21}N$: 228.1747; found: 228.1744.

**(*S*)-*N*-benzyl-*N*-(1-phenylethyl)formamide[12] [(*S*)-429]:**




Chemical Formula: $C_{16}H_{17}NO$

Molecular Weight: 239.3123

In a flame dried 50-mL RBF, (*S*)-*N*-benzyl-*N*-(1-phenylethyl)amine (2.5g, 11.8 mmol, 1 eq), and $NH_4CO_2H$ (1.12 g, 17.7 mmol, 1.5 eq) were refluxed in distilled acetonitrile (20 mL) for 15 hrs. After cooling down to RT, the solution was evaporated, the residue was dissolved in EtOAc (40 mL) and washed with $H_2O$ (50 mL), the organic layer was separated, dried over $MgSO_4$, and evaporated. The crude material was purified by column chromatography (50 g silica, hexanes/EtOAc 6:1, v/v) affording **(*S*)-*N*-benzyl-*N*-(1-phenylethyl)formamide** [**(*S*)-429**, 1.31 mg, 46%] as a colourless oil.

$[\alpha]_D$ = +48°.

**IR (ATR):** ν ($cm^{-1}$) 3061, 3029, 2977, 2935.

Major rotamer: 70%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.53 (s, 1H), 7.15-7.35 (m, 10H), 4.62 (q, 1H, $^3J$ = 7.1 Hz), 4.45 (d, 1H, $^2J$ = 15.2 Hz), 4.28 (d, 1H, $^2J$ = 15.2 Hz), 1.51 (d, 3H, $^3J$ = 7.1 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.5 (1C, CH), 140.4 (1C, **C**), 137.4 (1C, **C**), 128.8 (2C, **C**H), 128.5 (2C, **C**H), 128.0 (2C, **C**H), 127.3 (2C, **C**H), 126.8 (2C, **C**H), 56.7 (1C, **C**H), 45.3 (1C, **C**$H_2$), 20.2 (1C, **C**$H_3$).

Minor rotamer: 30%

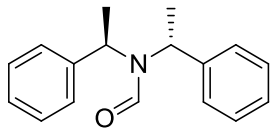
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.31 (s, 1H), 7.15-7.35 (m, 8H), 7.04 (br. d, 2H, $^{3}J$ = 7.5 Hz), 5.74 (q, 1H, $^{3}J$ = 7.1 Hz), 4.25 (d, 1H, $^{2}J$ = 15.2 Hz), 4.02 (d, 1H, $^{2}J$ = 15.2 Hz), 1.35 (d, 3H, $^{3}J$ = 7.1 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.5 (1C, CH), 139.7 (1C, C), 137.6 (1C, C), 128.6 (2C, CH), 128.5 (2C, CH), 127.9 (2C, CH), 127.8 (2C, CH), 127.70 (1C, CH), 127.65 (1C, CH), 50.6 (1C, CH), 48.3 (1C, $CH_2$), 17.0 (1C, $CH_3$).

**General procedure for the *N*-formylation of secondary amines:**

To a solution of secondary amine in DCM under nitrogen, was added formic acetic anhydride (2.5 eq). The resulting solution was stirred overnight at RT. Then sat. aq. $NaHCO_3$ was added and the organic layer was then separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and evaporated. Crude material was then purified by silica gel column chromatography affording the desired formamide.

***N*,*N*-bis((*R*)-1-phenylethyl)formamide[13] [(*R*,*R*)-398]:**




Chemical Formula: $C_{17}H_{19}NO$

Molecular Weight: 253.3389

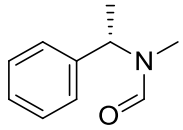
The product was obtained as a white solid.

$[\alpha]_D$ = +167°.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.33 (s, 1H), 7.26-7.29 (m, 5H), 7.13-7.17 (m, 3H), 6.78-6.82 (m, 2H), 5.71 (q, 1H, $^{3}J$ = 7.1 Hz), 4.49 (q, 1H, $^{3}J$ = 7.1 Hz), 1.71 (d, 3H, $^{3}J$ = 7.1 Hz), 1.68 (d, 3H, $^{3}J$ = 7.1 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.6 (1C, CH), 141.0 (1C, C), 139.8 (1C, C), 128.31 (2C, CH), 128.28 (2C, CH), 128.1 (2C, CH), 127.6 (1C, CH), 127.4 (1C, CH), 126.7 (2C, CH), 52.9 (1C, CH), 50.7 (1C, CH), 22.4 (1C, $CH_3$), 17.0 (1C, $CH_3$).

**(*S*)-*N*-methyl-*N*-(1-phenylethyl)formamide[14] [(*S*)-426]:**



Chemical Formula: $C_{10}H_{13}NO$

Molecular Weight: 163.2163

The product was obtained as a colourless oil.

$[\alpha]_D = -123°$.

Major rotamer 66%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.39 (s, 1H), 7.25-7.40 (m, 5H), 4.80 (q, 1H, $^3J$ = 7.1 Hz), 2.66 (s, 3H), 1.65 (d, 3H, $^3J$ = 7.1 Hz).

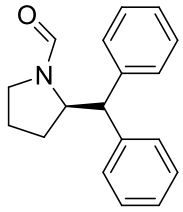
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.4 (1C, CH), 139.5 (1C, C), 128.7 (2C, CH), 127.9 (1C, CH), 126.7 (2C, CH), 56.6 (1C, CH), 26.1 (1C, $CH_3$), 17.9 (1C, $CH_3$).

Minor rotamer 34%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ(ppm) 8.13 (s, 1H), 7.25-7.40 (m, 5H), 5.82 (q, 1H, $^3J$ = 7.1 Hz), 2.66 (s, 3H, $CH_3$), 1.54 (d, 3H, $^3J$ = 7.1 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.6 (1C, CH), 139.4 (1C, C), 128.5 (2C, CH), 127.5 (1C, CH), 127.3 (2C, CH), 48.8 (1C, CH), 29.5 (1C, $CH_3$), 15.3 (1C, $CH_3$).

**(*R*)-2-benzhydrylpyrrolidine-1-carbaldehyde [(*R*)-427]:**



Chemical Formula: $C_{18}H_{19}NO$

Molecular Weight: 265.3496

The product was obtained as a white solid.

Major rotamer 87%

$[\alpha]_D = -178°$.

**Mp.:** 124-126 °C.

**IR (ATR):** ν ($cm^{-1}$) 3061, 3041, 3022, 2949, 2890, 1654.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.19-7.36 (m, 11H), 4.50-4.55 (m, 1H), 3.87 (d, 1H, $^{3}J$ = 10.5 Hz), 3.64-3.68 (m, 1H), 3.37-3.41 (m, 1H), 1.89-2.07 (m, 3H), 1.81-1.86 (m, 1H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 161.6 (1C, CH), 141.5 (1C, C), 141.4 (1C, C), 128.9 (2C, CH), 128.8 (2C, CH), 128.6 (2C, CH), 128.3 (2C, CH), 127.2 (1C, CH), 126.9 (1C, CH), 61.8 (1C, CH), 56.1 (1C, CH), 43.1 (1C, $CH_2$), 29.8 (1C, $CH_2$), 22.1 (1C, $CH_2$).

Minor rotamer 13%

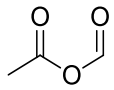
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ(ppm) 8.18 (s, 1H), 7.19-7.36 (m, 10H), 4.98-5.03 (m, 1H), 4.51-4.55 (m, 1H), 3.45-3.49 (m, 1H), 3.07-3.11 (m, 1H), 1.89-2.07 (m, 2H), 1.70-1.75 (m, 1H), 1.50-1.55 (m, 1H).

**$^{13}$C NMR* ($CDCl_3$, 100 MHz):** δ(ppm) 161.3 (1C, CH), 129.5 (2C, CH), 128.7 (2C, CH), 128.1 (2C, CH), 126.7 (1C, CH), 126.4 (1C, CH), 57.6 (1C, CH), 52.4 (1C, CH), 46.2 (1C, $CH_2$), 28.0 (1C, $CH_2$), 23.1 (1C, $CH_2$).

***$^{13}$C NMR:** 2 **C**H aromatic missing, no quaternary carbons

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{18}H_{19}NO$: 266.1539; found: 266.1542.

**Acetic formic anhydride[15] (437):**



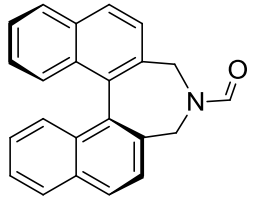
Chemical Formula: $C_3H_4O_3$

Molecular Weight: 88.0621

To a solution of sodium formate (25 g, 0.37 mol, 1.2 eq) in dry $Et_2O$ (80 mL) acetyl chloride (24.5 g, 0.31 mol, 1 eq) was added, keeping the temperature below 27 °C and was stirred overnight under nitrogen. The solids were filtered and the solvent was removed under reduced pressure at low temperature. Then, the liquid obtained was distilled (15 mbar, 35 °C) affording **acetic formic anhydride** (**437**, 15.7 g, 57%).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.11 (s, 1H), 2.28 (s, 3H).

**(*S*)-3H-dinaphtho[2,1-c:1',2'-e]azepine-4(5H)-carbaldehyde [(*S*)-439]:**



Chemical Formula: $C_{23}H_{17}NO$

Molecular Weight: 323.3872

The product was obtained as a light yellow waxy solid.

$[\alpha]_D$ = +9°.

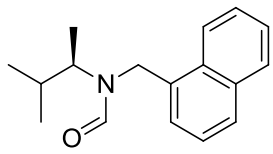
**IR (ATR):** ν ($cm^{-1}$) 3050, 2957, 2923, 2863, 1657.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.27 (s, 1H), 8.00-8.02 (m, 2H), 7.97 (d, 2H, $^3J$ = 8.2 Hz), 7.63 (d, 1H, $^3J$ = 8.2 Hz), 7.56 (d, 1H, $^3J$ = 8.2 Hz), 7.50-7.52 (m, 2H), 7.43 (d, 1H, $^3J$ = 8.4 Hz), 7.40 (d, 1H, $^3J$ = 8.6 Hz), 7.29-7.31 (m, 2H), 5.24 (d, 1H, $^2J$ = 13.6 Hz), 4.44 (d, 1H, $^2J$ = 13.0 Hz), 4.06 (d, 1H, $^2J$ = 13.0 Hz), 3.59 (d, 1H, $^2J$ = 13.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 160.4 (1C, CH), 135.4 (1C, C), 134.9 (1C, C), 133.44 (1C, C), 133.38 (1C, C), 131.7 (1C, C), 131.44 (2C, C), 131.37 (1C, C), 129.6 (1C, CH), 129.5 (1C, CH), 128.4 (2C, CH), 127.6 (1C, CH), 127.5 (1C, CH), 127.3 (1C, CH), 126.4 (1C, CH), 126.3 (1C, CH), 126.21 (1C, CH), 126.16 (1C, CH), 126.0 (1C, CH), 50.0 (1C, $CH_2$), 45.0 (1C, $CH_2$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{23}H_{17}NO$: 324.1383; found: 324.1378.

**(*R*)-*N*-(3-methylbutan-2-yl)-*N*-(naphthalen-1-ylmethyl)formamide [(*R*)-441]:**



Chemical Formula: $C_{17}H_{21}NO$

Molecular Weight: 255.35

The product was obtained as a light yellow oil.

$[\alpha]_D$= –10°.

**IR (ATR):** ν ($cm^{-1}$) 3048, 2963, 2872, 1659.

Major rotamer: 82%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.38 (s, 1H), 8.10 (br. d, 1H, $^3J$ = 8.0 Hz), 7.87 (br. d, 1H, $^3J$ = 8.0 Hz), 7.81 (d, 1H, $^3J$ = 8.0 Hz), 7.37-7.60 (m, 4H), 5.09 (d, 1H, $^2J$ = 15.0 Hz), 4.92 (d, 1H, $^2J$ = 15.0 Hz), 3.08-3.13 (m, 1H), 1.80-1.85 (m, 1H), 1.06 (d, 3H, $^3J$ = 6.8 Hz), 0.89 (d, 3H, $^3J$ = 6.5 Hz), 0.78 (d, 3H, $^3J$ = 6.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.6 (1C, CH), 133.8 (1C, C), 132.4 (1C, C), 131.5 (1C, C), 128.7 (1C, CH), 128.4 (1C, CH), 126.9 (1C, CH), 126.5 (1C, CH), 125.9 (1C, CH), 125.1 (1C, CH), 123.7 (1C, CH), 59.9 (1C, CH), 43.8 (1C, CH), 32.6 (1C, CH), 20.0 (1C, $CH_3$), 19.5 (1C, $CH_3$), 18.0 (1C, $CH_3$).

Minor rotamer 18%*

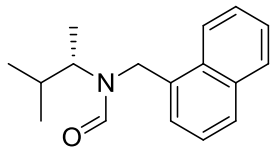
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.28 (s, 1H), 7.96 (br. d, 1H, $^3J$ = 8.0 Hz), 7.91 (br. d, 1H, $^3J$ = 8.0 Hz), 7.83-7.85 (m, 1H), 7.37-7.60 (m, 4H), 4.86 (d, 1H, $^2J$ = 15.8 Hz), 4.79 (d, 1H, $^2J$ = 15.8 Hz), 3.98-4.03 (m, 1H), 1.99-2.04 (m, 1H), 1.12 (d, 3H, $^3J$ = 7.0 Hz), 0.94 (d, 3H, $^3J$ = 6.8 Hz), 0.91 (d, 3H, $^3J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 164.1 (1C, CH), 129.1 (1C, CH), 126.7 (1C, CH), 126.3 (1C, CH), 126.1 (1C, CH), 125.3 (1C, CH), 122.4 (1C, CH), 55.7 (1C, CH), 46.7 (1C, CH), 31.2 (1C, CH), 20.2 (1C, $CH_3$), 19.9 (1C, $CH_3$), 16.1 (1C, $CH_3$).

***** Carbon data not complete all 3 quaternary carbons missing, 1 aromatic CH missing.

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{17}H_{21}NO$: 256.1696; found: 256.1691.

**(*S*)-*N*-(3-methylbutan-2-yl)-*N*-(naphthalen-1-ylmethyl)formamide [(*S*)-441]:**

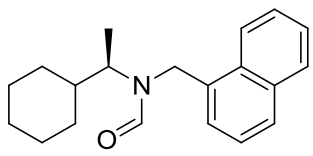



The product was obtained as a light yellow oil.

$[\alpha]_D$ = +10.5°

Same spectral data as **(*R*)-441**

**(*R*)-*N*-(1-cyclohexylethyl)-*N*-(nαphthalen-1-ylmethyl)formamide [(*R*)-442]:**



Chemical Formula: $C_{20}H_{25}NO$

Molecular Weight: 295.42

The product was obtained as a light yellow oil.

$[\alpha]_D$= –18.4°.

**IR (ATR):** ν ($cm^{-1}$) 3048, 2922, 2860, 1660.

Major rotamer 82%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.34 (s, 1H), 8.10 (d, 1H, $^3J$ = 8.6 Hz), 7.86 (br. d, 1H $^3J$ = 8.0 Hz), 7.80 (d, 1H, $^3J$ = 7.9 Hz), 7.31-7.60 (m, 4H), 5.12 (d, 1H, $^2J$ = 15.2 Hz), 4.85 (d, 1H, $^2J$ = 15.2 Hz), 3.12-3.17 (m, 1H), 1.62-1.71 (m, 5H), 1.36-1.40 (m, 1H), 1.04 (d, 3H, $^3J$ = 6.9 Hz), 0.67-1.20 (m, 5H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 162.7 (1C, CH), 133.7 (1C, C), 132.5 (1C, C), 131.5 (1C, C), 128.7 (1C, CH), 128.4 (1C, CH), 126.9 (1C, CH), 126.4 (1C, CH), 125.9 (1C, CH), 125.1 (1C, CH), 123.7 (1C, CH), 58.9 (1C, CH), 43.9 (1C, $CH_2$), 42.1 (1C, CH), 30.3 (1C, $CH_2$), 29.9 (1C, $CH_2$), 26.1 (1C, $CH_2$), 26.0 (1C, $CH_2$), 25.8 (1C, $CH_2$), 17.9 (1C, $CH_3$).

Minor rotamer 18%*****

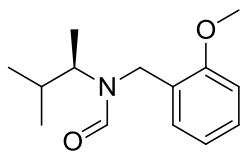
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.28 (s, 1H), 7.96 (br. d, 1H, $^3J$ = 8.0 Hz), 7.91 (br. d, 1H, $^3J$ = 8.0 Hz), 7.83-7.85 (m, 1H), 7.37-7.60 (m, 4H), 4.85 (d, 1H, $^2J$ = 15.8 Hz), 4.76 (d, 1H, $^2J$ = 15.8 Hz), 4.03-4.07 (m, 1H), 1.62-1.71 (m, 5H, cyclohexyl), 1.36-1.40 (m, 1H), 1.11 (d, 3H, $^3J$ = 7.0 Hz), 0.67-1.20 (m, 5H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 164.1 (1C, CH), 129.1 (1C, CH), 128.7 (1C, CH), 126.7 (1C, CH), 126.4 (1C, CH), 126.1 (1C, CH), 125.3 (1C, CH), 122.5 (1C, CH), 53.4 (1C, CH), 46.9 (1C, $CH_2$), 40.4 (1C, CH), 30.2 (1C, $CH_2$), 26.2 (1C, $CH_2$), 15.8 (1C, $CH_3$)

*****3 Cyclohexyl $CH_2$ missing, all 3 quaternary carbons missing

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{20}H_{25}NO$: 296.2003; found: 296.2009.

**(*R*)-*N*-(2-methoxybenzyl)-*N*-(3-methylbutan-2-yl)formamide [(*R*)-443]:**




Chemical Formula: $C_{14}H_{21}NO_2$

Molecular Weight: 235.3220

The product was obtained as a colourless oil.

$[\alpha]_D = -2.4°$.

**IR (ATR):** ν ($cm^{-1}$) 2962, 2872, 1663.

Major rotamer 60%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.31 (s, 1H), 7.19-7.32 (m, 2H), 6.81-6.96 (m, 2H), 4.57 (d, 1H, $^2J$ = 15.8 Hz), 4.48 (d, 1H, $^2J$ = 15.8 Hz), 3.85 (s, 3H), 3.11-3.16 (m, 1H), 1.80-1.85 (m, 1H), 1.15 (d, 3H, $^3J$ = 7.0 Hz), 0.93 (d, 3H, $^3J$ = 6.8 Hz), 0.84 (d, 3H, $^3J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.2 (1C, CH), 156.7 (1C, C), 129.2 (1C, CH), 128.2 (1C, CH), 125.6 (1C, C), 120.6 (1C, CH), 110.1 (1C, CH), 61.0 (1C, CH), 55.2 (1C, $CH_3$), 39.4 (1C, $CH_2$), 32.3 (1C, CH), 20.1 (1C, $CH_3$), 19.6 (1C, $CH_3$), 17.8 (1C, $CH_3$).

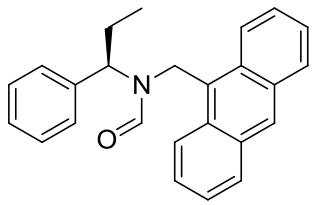
Minor rotamer 40%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.26 (s, 1H), 7.19-7.32 (m, 2H), 6.81-6.96 (m, 2H), 4.35 (d, 1H, $^2J$ = 15.4 Hz), 4.30 (d, 1H, $^2J$ = 15.4 Hz), 3.85 (s, 3H), 3.76-3.80 (m, 1H), 1.90-1.94 (m, 1H), 1.06 (d, 3H, $^3J$ = 6.8 Hz), 0.89 (d, 3H, $^3J$ = 6.6 Hz), 0.79 (d, 3H, $^3J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 164.4 (1C, CH), 157.7 (1C, C), 129.9 (1C, CH), 129.4 (1C, CH), 125.2 (1C, C), 120.4 (1C, CH), 110.4 (1C, CH), 56.1 (1C, CH), 55.2 (1C, $CH_3$), 45.5 (1C, $CH_2$), 30.9 (1C, CH), 20.1 (1C, $CH_3$), 20.0 (1C, $CH_3$), 16.42 (1C, $CH_3$)

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{14}H_{21}NO_2$: 236.1645; found: 236.1640.

**(*R*)-*N*-(anthracen-9-ylmethyl)-*N*-(1-phenylpropyl)formamide [(*R*)-445]:**




Chemical Formula: $C_{25}H_{23}NO$

Molecular Weight: 353.46

The product was obtained as an orange solid.

$[\alpha]_D = -23°$.

**Mp.:** 135-137 °C.

**IR (ATR):** ν ($cm^{-1}$) 3061, 3023, 2963, 2931, 1655.

Major rotamer: 66%

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.63 (s, 1H), 8.47 (s, 1H), 8.10-8.13 (m, 2H), 7.97-8.01 (m, 3H), 7.45-7.49 (m, 3H), 7.19-7.23 (m, 3H), 6.80-6.83 (m, 2H), 5.97 (d, 1H, $^2J$ = 15.1 Hz), 5.18 (d, 1H, $^2J$ = 15.1 Hz), 3.80 (t, 1H, $^3J$ = 8.4 Hz), 1.72-1.77 (m, 2H), 0.44 (t, 3H, $^3J$ = 7.3 Hz).

Minor rotamer: 34%

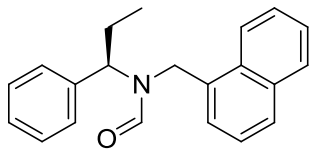
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.46 (s, 1H), 7.35-7.60 (m, 14H), 5.90 (dd, 1H, $^3J$ = 8.8 Hz, $^3J$ = 7.0 Hz), 5.15 (d, 1H, $^2J$ = 13.3 Hz), 4.80 (d, 1H, $^2J$ = 13.3 Hz), 2.33-2.37 (m, 2H), 1.21 (t, 3H, $^3J$ = 7.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)*:** δ (ppm) 162.4 (1C, CH minor rotamer = b), 161.9 (1C, CH major rotamer = a), 140.1 (1C, a), 138.9 (1C, b), 131.4 (2C, a), 131.3 (2C, a), 131.3 (1C, C), 131.2 (1C, C), 130.0 (1C, CH), 129.12 (2C, CH, a), 129.09 (1C, CH), 128.78 (1C, CH), 128.75 (1C, CH), 128.53 (1C, CH), 128.48 (2C, CH, a), 128.2 (1C, CH), 127.6 (1C, CH), 127.05 (1C, CH), 126.9 (1C, CH), 126.7 (2C, CH, a), 126.4 (2C, CH, a), 125.2 (1C, CH), 125.1 (2C, CH, a), 124.3 (2C, CH, a), 123.0 (1C, CH), 61.8 (1C, CH, a), 56.1 (1C, CH, b), 53.4 (1C, $CH_2$, b), 39.6 (1C, $CH_2$, b) 38.3 (1C, $CH_2$, a), 27.8 (1C, $CH_2$, a), 22.1 (1C, $CH_2$, b), 11.4 (1C, $CH_3$, b), 10.9 (1C, $CH_3$, a).

* Data from both rotamers, some quaternary carbons might be missing. Because the ratio is close to 2:1 and that many of the anthracene carbon signals account for 2 protons it was difficult to distinguish whether the signal could be attributed to a carbon of the major rotamer integrating for 1 or to a carbon of the minor rotamer integrating for 2.

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{25}H_{23}NO$: 354.1852; found: 354.1856.

**(*R*)-N-(naphthalen-1-ylmethyl)-*N*-(1-phenylpropyl)formamide [(*R*)-446]:**




Chemical Formula: $C_{21}H_{21}NO$

Molecular Weight: 303.40

The product was obtained as a light yellow oil.

$[\alpha]_D = -5°$.

**IR (ATR):** ν ($cm^{-1}$) 3048, 2966, 2932, 2876, 1656.

Major rotamer 79%

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.60 (s, 1H), 7.99-8.01 (m, 1H), 7.76-7.79 (m, 2H), 7.20-7.50 (m, 7H), 7.06-7.09 (m, 2H), 5.26 (d, 1H, $^{2}J$ = 14.8 Hz), 4.41 (d, 1H, $^{2}J$ = 14.8 Hz), 4.09 (t, 1H, $^{3}J$ = 7.9 Hz), 1.80-1.84 (m, 2H), 0.62 (t, 3H, $^{3}J$ = 7.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 161.9 (1C, CH), 139.4 (1C, C), 133.7 (1C, C), 132.0 (1C, C), 131.6 (1C, C), 128.7 (2C, CH), 128.62 (1C, CH), 128.57 (1C, CH), 127.9 (1C, CH), 127.6 (1C, CH), 127.1 (2C, CH), 126.5 (1C, CH), 126.0 (1C, CH), 125.0 (1C, CH), 123.9 (1C, CH), 62.9 (1C, CH), 43.7 (1C, $CH_2$), 26.7 (1C, $CH_2$), 11.2 (1C, $CH_3$).

Minor rotamer 21%*

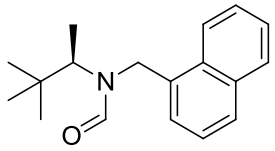
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.15 (s, 1H), 7.76-7.80 (m, 2H), 7.20-7.50 (m, 10H), 5.53 (t, 1H, C**H**, $^{3}J$ = 7.9 Hz), 4.62 (d, 1H, $^{2}J$ = 15.2 Hz), 4.55 (d, 1H, $^{2}J$ = 15.2 Hz), 1.94-1.98 (m, 2H), 0.87 (t, 3H, $^{3}J$ = 7.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.7 (1C, CH), 128.9 (1C, CH), 128.54 (2C, CH), 128.49 (2C, CH), 127.8 (1C, CH), 127.0 (1C, CH), 126.5 (1C, CH), 125.1 (1C, CH), 122.6 (1C, CH), 57.1 (1C, CH), 45.7 (1C, $CH_2$), 23.2 (1C, $CH_2$), 13.8 (1C, $CH_3$).

***** Carbon data not complete all 4 quaternary carbons missing, 2 aromatic CH missing

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{21}H_{21}NO$: 304.1696; found: 304.1695.

**(*R*)-*N*-(3,3-dimethylbutan-2-yl)-*N*-(naphthalen-1-ylmethyl)formamide [(*R*)-447]:**




Chemical Formula: $C_{18}H_{23}NO$

Molecular Weight: 269.3813

The product was obtained as a yellow solid.

$[\alpha]_D$= –46.5°.

**Mp.:** 87-89 °C.

**IR (ATR):** ν ($cm^{-1}$) 3050, 2962, 2870, 1658.

Major rotamer: 90%

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.46 (s, 1H), 8.02 (d, 1H, $^{3}J$ = 8.0 Hz), 7.88 (br. d, 1H, $^{3}J$ = 8.0 Hz), 7.81 (d, 1H, $^{3}J$ = 8.3 Hz), 7.42-7.57 (m, 3H), 7.34 (d, 1H, $^{3}J$ = 7.0 Hz),

5.60 (br. d, 1H, $^{2}J$ = 14.5 Hz), 4.60 (d, 1H, $^{2}J$ = 14.5 Hz), 3.21 (q, 1H, $^{3}J$ = 7.3 Hz), 1.05 (d, 3H, $^{3}J$ = 7.3 Hz), 0.99 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.2 (1C, CH), 133.8 (1C, C), 132.1 (1C, C), 131.4 (1C, C), 128.7 (1C, CH), 128.3 (1C, CH), 126.6 (1C, CH), 126.4 (1C, CH), 125.9 (1C, CH), 125.1 (1C, CH), 123.4 (1C, CH), 61.2 (1C, CH), 46.2 (1C, $CH_2$), 36.3 (1C, C), 27.3 (3C, $CH_3$), 15.7 (1C, $CH_3$).

Minor rotamer 10%*

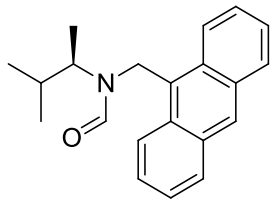
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.25 (s, 1H), 7.91-7.95 (m, 3H), 7.40-7.60 (m, 4H), 4.98 (d, 1H, $^{2}J$ = 15.5 Hz), 4.91 (d, 1H, $^{2}J$ = 15.5 Hz), 1.05 (d, 3H, $^{3}J$ = 6.5 Hz), 1.06 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 129.1 (1C, CH), 128.2 (1C, CH), 126.0 (1C, CH), 125.4 (1C, CH), 122.0 (1C, CH), 27.6 (3C, $CH_3$).

*** $^{1}$H NMR** C**H**-NRCHO missing**, $^{13}$C NMR:** most of carbons missing

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{18}H_{23}NO$: 270.1852; found: 270.1854.

**(*R*)-*N*-(anthracen-9-ylmethyl)-*N*-(3-methylbutan-2-yl)formamide [(*R*)-448]:**




Chemical Formula: $C_{21}H_{23}NO$

Molecular Weight: 305.4134

The product was obtained as an orange solid.

$[\alpha]_D$ = –22°.

**IR (ATR):** ν ($cm^{-1}$) 3048, 2965, 2932, 2871, 1666.

**Mp.:** 133-135°C.

Major rotamer: 77%

**$^{1}$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.49 (s, 1H), 8.40 (s, 1H), 8.32 (dd, 1H, $^{3}J$ = 8.8 Hz, $^{4}J$ = 0.8 Hz), 8.04 (br. d, 1H, $^{3}J$ = 8.3 Hz), 7.57 (ddd, 2H, $^{3}J$ = 8.8 Hz, $^{3}J$ = 6.6 Hz, $^{4}J$ = 1.6 Hz), 7.50-7.53 (m, 2H), 5.84 (d, 1H, $^{2}J$ = 15.1 Hz), 5.47 (d, 1H, $^{2}J$ = 15.1 Hz), 2.64-2.69 (m, 1H), 1.74-1.79 (m, 1H), 0.83 (d, 3H, $^{3}J$ = 7.2 Hz), 0.70 (d, 3H, $^{3}J$ = 6.6 Hz), 0.64 (d, 3H, $^{3}J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 161.8 (1C, **C**H), 134.1 (1C, C), 131.4 (2C, C), 131.3 (2C, C), 129.3 (2C, **C**H), 128.5 (1C, **C**H), 126.6 (2C, **C**H), 125.1 (2C, **C**H), 124.0 (2C, **C**H), 58.1 (1C, **C**H), 38.6 (1C, **C**$H_2$), 33.4 (1C, **C**H), 19.8 (1C, $CH_3$), 19.3 (1C, $CH_3$), 18.7 (1C, $CH_3$).

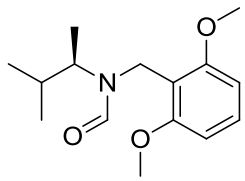
Minor rotamer 23%

**$^{1}$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.54 (s, 1H), 8.14 (dd, 1H, $^{3}J$ = 8.8 Hz, $^{4}J$ = 0.8 Hz), 8.06 (br. d, 1H), 7.70 (s, 1H), 7.48-7.61 (m, 4H), 5.26 (d, 1H, $^{2}J$ = 13.8 Hz), 5.21 (d, 1H, $^{2}J$ = 13.8 Hz), 4.06-4.08 (m, 1H), 2.24-2.29 (m, 1H), 1.46 (d, 3H, $^{3}J$ = 6.9 Hz), 1.08 (d, 3H, $^{3}J$ = 6.6 Hz), 1.04 (d, 3H, $^{3}J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 162.4 (1C, CH), 133.5 (1C, C), 131.4 (2C, C), 131.2 (2C, C), 129.5 (1C, CH), 129.2 (1C, CH), 127.2 (2C, CH), 125.2 (2C, CH), 123.1 (2C, CH), 55.6 (1C, CH), 41.2 (1C, $CH_2$), 30.6 (1C, CH), 20.5 (1C, $CH_3$), 20.2 (1C, $CH_3$), 16.3 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{21}H_{23}NO$: 306.1852; found: 306.1854.

**(R)-*N*-(2,6-dimethoxybenzyl)-*N*-(3-methylbutan-2-yl)formamide [(*R*)-449]:**




Chemical Formula: $C_{15}H_{23}NO_3$

Molecular Weight: 265.3480

The product was obtained as a colourless oil.

$[\alpha]_D = -8°$.

**IR (ATR):** ν ($cm^{-1}$) 2960, 2941, 2879, 2838, 1659.

Major rotamer 80%

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.21 (s, 1H), 7.25 (t, 1H, $^{3}J$ = 8.4 Hz), 6.54 (d, 2H, $^{3}J$ = 8.4Hz), 4.37 (s, 2H), 3.83 (s, 6H), 3.65-3.69 (m, 1H), 1.95-2.00 (m, 1H), 1.12 (d, 3H, $^{3}J$ = 7.0 Hz), 0.86 (d, 3H, $^{3}J$ = 6.8 Hz), 0.73 (d, 3H, $^{3}J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 164.4 (1C, CH), 158.9 (2C, C), 129.6 (1C, CH), 112.6 (1C, C), 103.6 (2C, CH), 56.2 (1C, CH), 55.6 (2C, CH3), 38.7 (1C, $CH_2$), 30.5 (1C, CH), 20.3 (1C, $CH_3$), 19.9 (1C, $CH_3$), 16.3 (1C, $CH_3$).

Minor rotamer 20*%

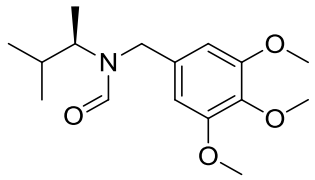
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.22 (s, 1H), 7.23 (t, 1H, $^{3}J$ = 8.4 Hz), 6.54 (d, 2H, $^{3}J$ = 8.4 Hz), 4.84 (d, 1H, $^{2}J$ = 13.7 Hz), 4.54 (d, 1H, $^{2}J$ = 13.7 Hz), 3.82 (s, 6H), 2.77-2.81 (m, 1H), 1.75-1.80 (m, 1H), 1.07 (d, 3H, $^{3}J$ = 7.0 Hz), 0.83 (d, 3H, $^{3}J$ = 6.8 Hz), 0.76 (d, 3H, $^{3}J$ = 6.8 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 161.7 (1C, CH), 159.3 (2C, C), 129.2 (1C, CH), 103.5 (2C, CH), 59.0 (1C, CH), 55.6 (2C, CH3), 34.9 (1C, $CH_2$), 33.0 (1C, CH), 19.68 (1C, $CH_3$), 19.66 (1C, $CH_3$), 18.3 (1C, $CH_3$).

*$^{13}$C NMR data, 1 quaternary carbon missing.

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{15}H_{23}NO_3$: 266.1751; found: 266.1744.

**(*R*)-*N*-(3-methylbutan-2-yl)-*N*-(3,4,5-trimethoxybenzyl)formamide [(*R*)-450]:**




Chemical Formula: $C_{16}H_{25}NO_4$

Molecular Weight: 295.3740

The product was obtained as a white solid.

$[\alpha]_D = -4°$.

**IR (ATR):** ν ($cm^{-1}$) 2996, 2966, 2937, 2838, 1650.

**Mp.:** 80-82°C.

Major rotamer 78%

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.29 (s, 1H), 6.53 (s, 2H), 4.48 (d, 1H, $^{2}J$ = 15.0 Hz), 4.40 (d, 1H, $^{2}J$ = 15.0 Hz), 3.85 (s, 6H), 3.83 (s, 3H), 3.09-3.13 (m, 1H), 1.80-1.85 (m, 1H), 1.20 (d, 3H, $^{3}J$ = 6.8 Hz), 0.94 (d, 3H, $^{3}J$ = 6.6 Hz), 0.84 (d, 3H, $^{3}J$ = 6.6Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.1 (1C, CH), 153.2 (2C, C), 137.2 (1C, C), 133.6 (1C, C), 105.1 (2C, CH), 61.0 (1C, CH or $CH_3$), 60.8 (1C, CH or $CH_3$), 56.1 (2C, CH3), 45.5 (1C, $CH_2$), 32.4 (1C, CH, iPr), 20.2 (1C, $CH_3$), 19.6 (1C, $CH_3$), 18.5 (1C, $CH_3$).

Minor rotamer* 22%

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ(ppm) 8.29 (s, 1H), 6.45 (s, 2H), 4.29 (s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 1.88-1.93 (m, 1H), 1.12 (d, 3H, $^{3}J$ = 6.8 Hz), 0.93 (d, 3H, $^{3}J$ = 6.6 Hz), 0.89 (d, 3H, $^{3}J$ = 6.6 Hz).

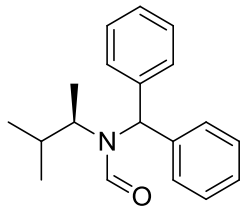
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ(ppm) 163.7 (1C, **C**H), 153.5 (2C, C), 137.6 (1C, C), 133.2 (1C, C), 104.5 (2C, **C**H), 60.9 (1C, CH or **C**$H_3$), 56.2 (2C, **C**H3), 56.0 (1C, CH or $CH_3$), 49.9 (1C, **C**$H_2$), 31.1 (1C, **C**H), 20.2 (1C, $CH_3$), 19.9 (1C, $CH_3$), 16.9 (1C, $CH_3$).

*$^{1}$H NMR C**H**-NRCHO missing

$^{13}$C NMR data, 1 quaternary carbon missing

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{16}H_{25}NO_4$: 296.1856; found: 296.1859.

**(*R*)-*N*-benzhydryl-*N*-(3-methylbutan-2-yl)formamide [(*R*)-451]:**




Chemical Formula: $C_{19}H_{23}NO$

Molecular Weight: 281.3920

The product was obtained as a white solid.

$[\alpha]_D$ = +34°.

**Mp.:** 62-64 °C.

**IR (ATR):** ν ($cm^{-1}$) 3087, 3062, 3029, 2974, 2875, 1663.

Major rotamer: 82%

**$^{1}$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.31 (s, 1H), 7.29-7.38 (m, 6H), 7.18-7.22 (m, 4H), 5.68 (s, 1H), 4.12-4.16 (m, 1H), 2.00-2.05 (m, 1H), 1.14 (d, 3H, $^{3}J$ = 7.2 Hz), 0.96 (d, 3H, $^{3}J$ = 6.6 Hz), 0.90 (d, 3H, $^{3}J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 164.4 (1C, CH), 140.7 (1C, C), 140.1 (1C, C), 128.9 (2C, CH), 128.74 (2C, CH), 128.71 (2C, CH), 128.0 (2C, CH), 127.9 (1C, CH), 127.7 (1C, CH), 63.0 (1C, CH), 56.4 (1C, CH), 31.7 (1C, CH), 20.7 (1C, $CH_3$), 20.0 (1C, $CH_3$), 16.6 (1C, $CH_3$).

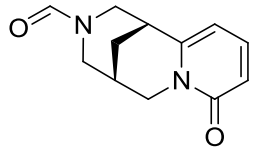
Minor rotamer 18%

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.40 (s, 1H), 7.25-7.38 (m, 10H), 6.25 (s, 1H), 3.30-3.34 (m, 1H), 1.49-1.53 (m, 1H), 1.35 (d, 3H, $^3J$ = 6.9 Hz), 0.86 (d, 3H, $^3J$ = 6.6 Hz), 0.64 (d, 3H, $^3J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 162.7 (1C, CH), 139.5 (1C, C), 139.4 (1C, C), 130.1 (2C, CH), 128.3 (2C, CH), 128.2 (2C, CH), 128.0 (2C, CH), 127.7 (1C, CH), 127.0 (1C, CH), 61.7 (1C, CH), 59.1 (1C, CH), 32.4 (1C, CH), 20.4 (1C, $CH_3$), 17.87 (1C, $CH_3$), 17.07 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{19}H_{23}NO$: 282.1852; found: 282.1850.

**(1*R*,5*S*)-8-oxo-4,5,6,8-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine-3(2H)-carbaldehyde [(–)-452]:**




Chemical Formula: $C_{12}H_{14}N_2O_2$

Molecular Weight: 218.2518

The product was obtained as a pale solid.

$[\alpha]_D$ = –127°.

**Mp.:** 164-166 °C.

**IR (ATR):** ν ($cm^{-1}$) 2938, 2867, 1652.

Major rotamer: 57%

**$^1$H NMR ($CDCl_3$, 500MHz):** δ (ppm) 7.91 (s, 1H), 7.29 (dd, 1H, $^3J$ = 6.9 Hz, $^4J$ = 1.0 Hz), 6.46 (br t, 1H, $^3J$ = 6.6 Hz), 6.08 (dd, 1H, $^3J$ = 6.9 Hz, $^4J$ = 1.0 Hz), 4.44-4.46 (m, 1H), 4.08 (d, 1H, $^3J$ = 6.0 Hz), 3.90 (ddd, 1H, $^2J$ = 17.0 Hz, $^3J$ = 6.6 Hz, $^4J$ = 1.3 Hz), 3.64-3.69 (m, 1H), 3.46 (dd, 1H, $^2J$ = 12.9 Hz, $^3J$ = 2.2 Hz), 3.11 (br. s, 1H), 2.95 (dd, 1H, $^2J$ = 12.9 Hz, $^3J$ = 2.5 Hz), 2.55 (broad s, 1H), 2.07-2.11 (m, 2H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.4 (1C, C), 161.1 (1C, CH), 147.8 (1C, C), 139.0 (1C, CH), 117.7 (1C, CH), 105.9 (1C, CH), 52.1 (1C), 48.6 (1C), 47.1 (1C), 33.9 (1C), 27.1 (1C), 26.4 (1C) .

Minor rotamer 43%

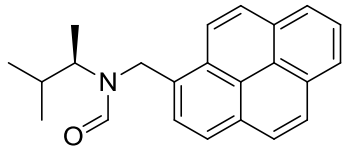
**$^1$H NMR ($CDCl_3$, 500MHz):** δ (ppm) 7.68 (s, 1H), 7.28 (dd, 1H, $^3J$ = 6.9 Hz, $^4J$ = 1.0 Hz), 6.44 (broad t, 1H, $^3J$ = 6.9 Hz,), 6.02 (dd, 1H, $^3J$ = 6.9 Hz, $^4J$ = 1.0 Hz), 4.54-4.56 (m, 1H),

4.11 (d, 1H, $^3J$ = 6.0 Hz), 3.87 (ddd, 1H, $^2J$ = 17.0 Hz, $^3J$ = 6.6 Hz, $^4J$ = 1.3 Hz), 3.53-3.57 (m, 1H), 3.41-3.45 (m, 1H), 3.11 (br. s, 1H), 2.89-2.93 (m, 1H), 2.55 (br. s, 1H), 2.11-2.15 (m, 2H).

**$^{13}$C NMR ($CDCl_3$, 120MHz):** δ (ppm) 163.2 (1C, C), 161.2 (1C, CH), 148.0 (1C, C), 138.6 (1C, CH), 118.1 (1C, CH), 105.0 (1C, CH), 53.4 (1C), 48.8 (1C), 46.1 (1C), 34.6 (1C), 26.7 (1C), 26.4 (1C).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{14}N_2O_2$: 219.1128; found: 219.1124.

**(*R*)-*N*-(3-methylbutan-2-yl)-*N*-(pyren-1-ylmethyl)formamide [(*R*)-455]:**




Chemical Formula: $C_{23}H_{23}NO$

Molecular Weight: 329.4348

The product was obtained as a pale solid.

$[\alpha]_D = -23°$.

**Mp.:** 129-131 °C.

**IR (ATR):** ν ($cm^{-1}$) 3041, 2967, 2872, 1664.

Major rotamer: 85%

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.44 (s, 1H), 8.37 (d, 1H, $^3J$ = 9.1 Hz), 8.14-8.24 (m, 4H), 8.01-8.11 (m, 3H), 7.95 (d, 1H, $^3J$ = 7.6 Hz), 5.39 (d, 1H, $^2J$ = 15.1 Hz), 5.20 (d, 1H, $^2J$ = 15.1 Hz), 3.09-3.13 (m, 1H), 1.80-1.84 (m, 1H), 1.02 (d, 3H, $^3J$ = 7.2 Hz), 0.86 (d, 3H, $^3J$ = 6.6 Hz), 0.77 (d, 3H, $^3J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 162.6 (1C, CH), 131.3 (1C, C), 131.0 (1C, C), 130.8 (1C, C), 130.4 (1C, C), 129.8 (1C, C), 128.1 (1C, CH), 127.5 (1C, CH), 127.4 (1C, CH), 127.3 (1C, CH), 126.0 (1C, CH), 125.3 (2C, CH), 124.9 (1C, C), 124.7 (1C, C), 124.6 (1C, CH), 123.1 (1C, CH), 60.1 (1C, CH), 43.7 (1C, $CH_2$), 32.6 (1C, CH), 20.1 (1C, $CH_3$), 19.5 (1C, $CH_3$), 18.2 (1C, $CH_3$).

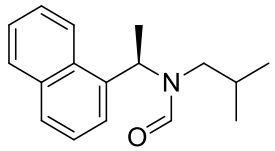
Minor rotamer 15%

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 8.42 (s, 1H), 8.24-8.14 (m, 5H), 7.96-8.11 (m, 4H), 5.12 (d, 1H, $^2J$ = 15.7 Hz), 5.05 (d, 1H, $^2J$ = 15.7 Hz), 3.96-4.00 (m, 1H), 2.03-2.07 (m, 1H), 1.10 (d, 3H, $^3J$ = 6.9 Hz), 0.93 (d, 3H, $^3J$ = 5.3 Hz), 0.92 (d, 3H, $^3J$ = 5.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.9 (1C, CH), 131.3 (1C, C), 131.2 (1C, C), 130.6 (1C, C), 129.7 (1C, C), 128.7 (1C, C), 128.5 (1C, CH), 127.7 (1C, CH), 127.3 (1C, CH), 126.6 (1C, CH), 126.2 (1C, CH), 125.7 (1C, CH), 125.4 (1C, CH), 124.9 (1C, C), 124.8 (1C, CH), 124.7 (1C, C), 121.7 (1C, CH), 56.0 (1C, CH), 47.0 (1C, $CH_2$), 31.1 (1C, CH), 20.3 (1C, $CH_3$), 20.0 (1C, $CH_3$), 16.3 (1C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{23}H_{23}NO$: 330.1852; found: 330.1853.

**(*R*)-*N*-isobutyl-*N*-(1-(naphthalen-1-yl)ethyl)formamide [(*R*)-456]:**




Chemical Formula: $C_{17}H_{21}NO$

Exact Mass: 255.1623

The product was obtained as a light yellow oil.

$[\alpha]_D$= +169°.

**IR (ATR):** ν ($cm^{-1}$) 3050, 2960, 2870, 1663.

Major rotamer: 79%

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.14 (s, 1H), 7.99 (d, 1H, $^3J$ = 8.5 Hz), 7.85-7.87 (m, 1H), 7.84 (d, 1H, $^3J$ = 8.5 Hz), 7.59 (d, 1H, $^3J$ = 7.2 Hz), 7.45-7.56 (m, 3H), 6.44 (q, 1H, $^3J$ = 7.2 Hz), 2.70 (dd, 1H, $^2J$ = 14.8 Hz, $^3J$ = 7.2 Hz), 2.49 (dd, 1H, $^2J$ = 14.8 Hz, $^3J$ = 7.2 Hz), 1.70 (d, 3H, $^3J$ = 6.9 Hz), 1.01-1.05 (m, 1H), 0.60 (d, 3H, $^3J$ = 6.6 Hz), 0.48 (d, 3H, $^3J$ = 6.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.0 (1C, CH), 134.7 (1C, C), 133.5 (1C, C), 132.0 (1C, C), 128.9 (1C, CH), 128.6 (1C, CH), 126.8 (1C, CH), 126.0 (1C, CH), 124.8 (1C, CH), 124.6 (1C, CH), 123.5 (1C, CH), 52.3 (1C, CH), 46.5 (1C, CH), 27.9 (1C, $CH_2$), 19.8 (1C, $CH_3$), 19.5 (1C, $CH_3$), 17.2 (1C, $CH_3$).

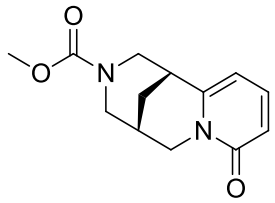
Minor rotamer: 21%

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.67 (s, 1H), 7.95 (d, 1H, $^3J$ = 8.5 Hz), 7.91 (dd, 1H, $^3J$ = 7.9 Hz, $^4J$ = 1.6 Hz), 7.84 (d, 1H, $^3J$ = 8.5 Hz), 7.46-7.59 (m, 4H), 5.49 (q, 1H, $^3J$ = 7.2 Hz), 3.31 (dd, 1H, $^2J$ = 13.5 Hz, $^3J$ = 7.9 Hz), 2.70 (dd, 1H, $^2J$ = 13.5 Hz, $^3J$ = 7.9 Hz), 1.82 (d, 3H, $^3J$ = 6.9 Hz), 1.61-1.66 (m, 1H), 0.74 (d, 3H, $^3J$ = 6.6 Hz), 0.69 (d, 3H, $^3J$ = 6.9 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.1 (1C, CH), 135.7 (1C, C), 133.9 (1C, C), 131.1 (1C, C), 129.2 (1C, CH), 128.8 (1C, CH), 126.7 (1C, CH), 125.9 (1C, CH), 125.3 (1C, CH), 123.6 (1C, CH), 122.2 (1C, CH), 53.7 (1C, CH), 49.6 (1C, CH), 27.2 (1C, $CH_2$), 20.8 (1C, $CH_3$), 20.1 (1C, $CH_3$), 20.0 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{17}H_{21}NO$: 256.1696; found: 256.1697.

**(1*R*,5*R*)-methyl 8-oxo-4,5,6,8-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine-3(2H)-carboxylate[11] (457) :**



Chemical Formula: $C_{13}H_{16}N_2O_3$

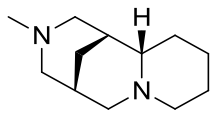
Molecular Weight: 248.2777

Methyl chloroformate (4.0 mL, 51.7 mmol, 10.3 eq) was added dropwise over 10 min to a stirred solution of (–)-cytisine [(–)-**396**, 960 mg, 5.0 mmol, 1 eq] and $Et_3N$ (7.1 mL, 51.7 mmol, 10.3 eq) in distilled DCM (40 mL) at 0 °C under nitrogen. The resulting mixture was stirred at RT for 3.5 hrs, then the solvent was evaporated under reduced pressure. EtOAc (15 mL) was added to the residue and the solids were removed by filtration. The filtrate was evaporated under reduced pressure and the residue was then purified by column chromatography (4 g silica, DCM/MeOH 9:1 v/v) affording **(1*R*,5*R*)-methyl 8-oxo-4,5,6,8-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine-3(2H)-carboxylate** (**457**, 1.14 g, 88%) as a colourless gum.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 7.29-7.31 (m, 1H), 6.47-6.49 (m, 1H), 6.07 (br. s, 1H), 4.21 (br. s, 2H), 4.15 (d, 1H, $^2J$ = 15.8 Hz), 3.87 (dd, 1H, $^2J$ = 15.8 Hz, $^3J$ = 6.8 Hz), 3.57 (br. s, 3H), 3.05 (br. s, 3H), 2.47 (br. s, 1H), 2.01 (d, 1H, $^2J$ = 13.2 Hz), 1.93 (d, 1H, $^2J$ = 13.2 Hz).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 163.4 (1C), 156.1 (1C), 148.8 (1C), 139.0 (1C), 111.3 (1C), 105.8 (1C), 52.8 (1C), 51.1 (1C), 50.2 (1C), 49.0 (1C), 34.5 (1C), 27.2 (1C), 25.8 (1C).

**(1*R*,5*S*,11a*S*)-3-methyldecahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine[16] [(+)-459] :**




Chemical Formula: $C_{12}H_{22}N_2$

Molecular Weight: 194.3165

A suspension of pyridone **457** (3.53 g, 14.2 mmol, 1 eq) and platinum (IV) oxide (322 mg, 0.42mmol, 0.1 eq) in dry EtOH (50 mL) was stirred at RT under a $H_2$ atmosphere ($H_2$ balloon) for 5 hrs. The solids were removed by filtration through kiesielghur and the filter cake was washed with 9:1 DCM/MeOH (200 mL). The filtrate was evaporated under reduced pressure to give the crude product **458** as a white solid. To a solution of **458** in THF (85 mL) stirred at 0 °C under nitrogen was added $LiAlH_4$ (3.2 g, 85.2 mmol, 6 eq) in one portion. The resulting suspension was refluxed for 16 hrs. After cooling to 0 °C, $Et_2O$ (10 mL) was added followed by the dropwise addition of sat. aq. $Na_2SO_4$ until effervescence ceased. The solids were removed by filtration through kiesielghur and the filter cake was washed with 9:1 DCM/MeOH (100 mL). The filtrate was dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave (+)-sparteine surrogate (+)-**459** (1.52 g, 55%) as a colourless oil.

$[\alpha]_D$ = +23° (0.13 g $mL^{-1}$ in EtOH, litt. $[\alpha]_D$ = +26°, c 0.1 in EtOH).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 3.01 (br. t, 2H, $^2J$ = 11.0 Hz), 2.87-2.91 (m, 2H), 2.25 (br. d, 1H, $^2J$ = 10.1 Hz), 2.17 (br. s, 4H), 1.98 (br. d, 1H, $^2J$ = 9.4 Hz), 1.90 (br. d, 1H, $^2J$ = 10.6 Hz), 1.48-1.84 (m, 9H), 1.29-1.33 (m, 2H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 66.5 (1C), 60.54 (1C), 60.48 (1C), 57.7 (1C), 56.4 (1C), 47.5 (1C), 35.3 (1C), 34.0 (1C), 30.9 (1C), 25.7 (1C), 25.2 (1C).

Experimental section for chapter 3

**General procedure for the asymmetric formylation of 7,8-dipropyltetrathia[7]helicene (8), using chiral formamides:**

In a 10-mL RBF, flame dried under argon, to a solution of **7,8-dipropyltetrathia[7]helicene** (**8**, 70 mg, 0.143 mmol, 1 eq) in distilled solvent (5 mL) cooled at –78 °C, was added dropwise *n*-BuLi ( 0.143 mmol, 1 eq). After stirring 5 min at –78 °C, the yellow solution was allowed to reach 0 °C over 30 min, and then was cooled again at –78 °C. Then, a solution of chiral formamide (0.71 mmol, 0.5 eq) in distilled solvent (1 mL) was added dropwise (when using Lewis acid, $BF_3$•$Et_2O$ is added dropwise to the formamide solution at 0 °C and stirred for 15 min at 0 °C before adding dropwise to the lithiohelicene) before stirring at the temperature and for the time reported in chapter 3, table 1, 2, 3, 4 and 5. Then sat. aq. $NH_4Cl$ (1 mL) was added, and the resulting mixture was extracted with EtOAc (2 x 20 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (4 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording **7,8-dipropyl-2-formyltetrathia[7]helicene**, (**460**, yields and e.e.s are reported in chapter 3, tables 1, 2, 3, 4 and 5).

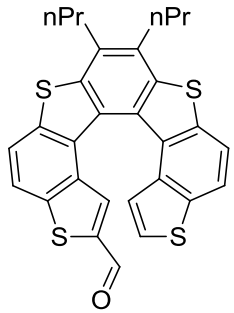
**General procedure for the asymmetric lithiation of 7,8-dipropyltetrathia[7]helicene (8):**

In a 10-mL RBF, flame dried under argon (flame dried first and then a sequence of vacuum and flushing with argon is applied 3 times), a solution of **7,8-dipropyltetrathia[7]helicene** (**8**, 70 mg, 0.143 mmol, 1 eq) in distilled toluene (5 mL) was cooled at –78 °C. In a 2-mL vial, flame dried under Ar (flame dried first and then a sequence of vacuum and flushing with argon is applied 3 times), was prepared a solution of (–)-sparteine in $Et_2O$ (0.8 mL), and *s*-BuLi was added at –78 °C under Ar (the amounts are specified in chapter 3, tables 6, 7, 8 and 10 as well as in schemes 9, 12,[17] 13 and 16). After stirring 30 min at –78 °C, the content of the vial was cannulated over to the solution of helicene **8** kept at –78 °C, and was stirred at temperatures and for times reported in chapter 3 (tables 6, 7, 8 and 10 as well as in schemes 9, 12,[18] 13 and 16) (the solution starts yellow, and goes greener and greener up to almost brown as lithiation is happening). Then, TMSCl (90 μL, 0.72 mmol, 5 eq) was added, and the reaction mixture was stirred for another 2 hrs at –78 °C. Then the reaction mixture was quenched with sat. aq. $NH_4Cl$ (1 mL) at –78 °C and let to warm up to RT. Then HCl (1N, 15 mL) was added and the mixture was extracted with DCM (2 x 30 mL),

dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography (4 g silica, hexanes) affording a mixture of 7**,8-dipropyltetrathia[7]helicene (8), 7,8-dipropyl-2-trimethylsilyltetrathia[7]helicene (463)** and **2,13-Bis(trimethylsilyl)-7,8-dipropyltetrathia[7]helicene (466)**, that was not separated and was analysed by chiral HPLC.

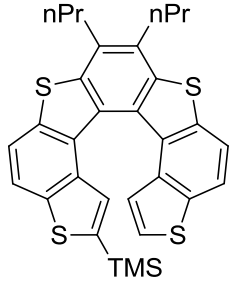
Alternatively the quench was done with DMF (110 μL, 1.43 mmol, 10 eq) and the reaction mixture was stirred at –78 °C for 18 hrs. Then the reaction mixture was quenched with sat. aq. $NH_4Cl$ (1 mL) at –78 °C and let to warm up to RT. Then HCl (1N, 15 mL) was added and the mixture was extracted with DCM (2 x 30 mL), dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography (4 g silica, hexanes) affording separately **7,8-dipropyltetrathia[7]helicene** (**8**), **7,8-dipropyl-2-formyltetrathia[7]helicene** (**460**) and **2,13-Bis(formyl)-7,8-dipropyltetrathia[7]helicene** (**468**), that were analysed by chiral HPLC.
The acidic aqueous layer is kept for recovery of (–)-sparteine, when enough has been gathered.

**7,8-dipropyl-2-formyltetrathia[7]helicene[2] (460):**




Chemical Formula: $C_{29}H_{22}OS_4$
Molecular Weight: 514.7444
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 9.25 (s, 1H), 8.13 (d, 1H, $^3J$ = 8.6 Hz), 8.05 (dd, 1H, $^3J$ = 8.4 Hz, $^5J$ = 0.8 Hz), 8.01 (d, 1H, $^3J$ = 8.4 Hz), 8.00 (dd, 1H, $^3J$ = 8.6 Hz, $^5J$ = 0.7 Hz), 7.33 (d, 1H, $^5J$ = 0.8 Hz), 6.94 (d, 1H, $^3J$ = 5.5 Hz), 6.65 (dd, 1H, $^3J$ = 5.5 Hz, $^5J$ = 0.7Hz), 3.09-3.23 (m, 4H), 1.88-1.99 (m, 4H), 1.18 (t, 6H, $^3J$ = 7.2 Hz).

**7,8-dipropyl-2-trimethylsilyltetrathia[7]helicene (463):**




Chemical Formula: $C_{31}H_{30}S_4Si$

Molecular Weight: 558.9154

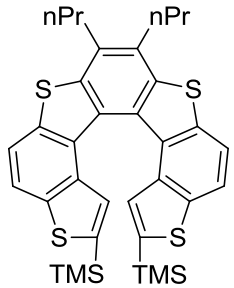
The product was obtained as a white solid.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.00 (dd, 2H, $^3J$ = 8.5 Hz, $^5J$ = 0.9 Hz), 7.97 (d, 1H, $^3J$ = 8.5 Hz), 7.93 (d, 1H, $^3J$ = 8.5 Hz), 6.88 (d, 1H, $^5J$ = 0.9 Hz), 6.87 (d, 1H, $^3J$ = 5.6 Hz), 6.73 (dd, 1H, $^3J$ = 5.6 Hz, $^5J$ = 0.6 Hz), 3.10-3.15 (m, 4H), 1.86-1.90 (m, 4H), 1.14-1.17 (m, 6H), –0.05 (s, 9H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 140.7 (1C, C), 140.1 (1C, C), 139.7 (1C, C), 139.6 (1C, C), 137.1 (1C, C), 136.6 (1C, C), 136.1 (1C, C), 135.9 (1C, C), 135.7 (1C, C), 132.2 (1C, C), 132.09 (1CH), 132.08 (1C, C), 131.6 (1C, C), 131.3 (1C, C), 128.3 (1C, C), 128.2 (1C, C), 125.4 (1C, CH), 123.8 (1C, CH), 120.6 (1C, CH), 120.5 (1C, CH), 118.7 (1C, CH), 118.4 (1C, CH), 34.38 (1C, $CH_2$), 34.37 (1C, $CH_2$), 23.29 (1C, $CH_2$), 23.27 (1C, $CH_2$), 14.70 (1C, $CH_3$), 14.69 (1C, $CH_3$), –0.7 (3C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{31}H_{30}S_4Si$: 559.1072; found: 559.1062.

**2,13-Bis(trimethylsilyl)-7,8-dipropyltetrathia[7]helicene[19] (466)**:




Chemical Formula: $C_{34}H_{38}S_4Si_2$

Molecular Weight: 631.0965

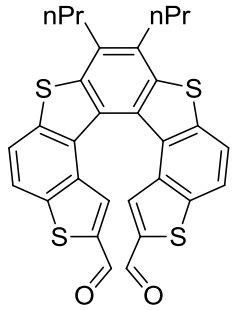
The product was obtained as a white solid.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ (ppm) 8.00 (dd, 2H, $^3J$ = 8.5 Hz, $^5J$ = 0.9 Hz), 7.94 (d, 2H, $^3J$ = 8.5 Hz), 6.85 (d, 2H, $^5J$ = 0.9 Hz), 3.10-3.15 (m, 4H), 1.86-1.91 (m, 4H), 1.14-1.17 (m, 6H), –0.06 (s, 18H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ (ppm) 140.8 (2C, C), 139.7 (2C, C), 139.6 (2C, C), 137.1 (2C, C), 135.7 (2C, C), 132.3 (2C, CH), 132.1 (2C, C), 131.4 (2C, C), 128.3 (2C, C), 120.4 (2C, CH), 118.5 (2C, CH), 34.4 (2C, $CH_2$), 23.3 (2C, $CH_2$), 14.7 (2C, $CH_3$), -0.6 (3C, TMS).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{34}H_{38}S_4Si_2$: 630.1389; found: 630.1376.

**2,13-Bis(formyl)-7,8-dipropyltetrathia[7]helicene[2] (468):**




Chemical Formula: $C_{30}H_{22}O_2S_4$

Molecular Weight: 542.7545

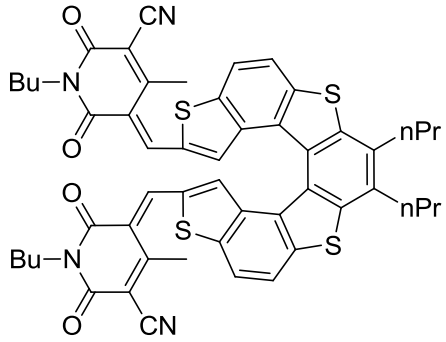
In a 50-mL RBF, flame dried under argon, to a solution of **7,8-dipropyltetrathia[7]helicene** (**8**, 300 mg, 0.62 mmol, 1 eq) in distilled THF (12 mL) cooled at –78 °C, was added dropwise *n*-BuLi (2.5 M in hexanes, 0.52 mL, 1.29 mmol, 2.1 eq). After stirring 5 min at –78 °C, the yellow solution was allowed to reach 0 °C over 30 min, and then was cooled again at –78 °C. Then, DMF (0.48 mL, 6.2 mmol, 10 eq) was added dropwise and the temperature was allowed to reach RT over 1.5 hrs. Then sat. aq. $NH_4Cl$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (2 x 50 mL), dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (10 g silica, hexanes/EtOAc gradient 100/0 to 3/1 v/v) affording **2,13-bis(formyl)-7,8-dipropyltetrathia[7]helicene** (**468**, 330, 98%) as a bright yellow solid.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 9.22 (d, 1H, $^4J$ = 3 Hz), 8.12 (dd, 2H, $^3J$ = 8.5 Hz, $^5J$ = 2.2 Hz), 7.99 (dd, 2H, $^3J$ = 8.5 Hz, $^5J$ = 2.2 Hz), 7.15 (d, 2H, $J$ = 4.4 Hz), 3.11-3.23 (m, 4H), 1.88-1.93 (m, 4H), 1.16 (t, 6H, $^3J$ = 7.4 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 183.4, (2C, CH), 141.1 (2C, C), 140.8 (2C, C), 140.1 (2C, C), 137.0 (2C, C), 134.7 (2C, CH), 134.1 (2C, C), 133.3 (2C, C), 131.8 (2C, C),

127.3 (2C, C), 122.9 (2C, CH), 121.2 (2C, CH), 34.4 (2C, $CH_2$), 23.3 (2C, $CH_2$), 14.7 (2C, $CH_3$).

**5,5'-[7,8-Dipropyltetrathia[7]helicene-2,13-diylbis(methanylylidene)]bis(1-butyl-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile) (472):**




Chemical Formula: $C_{52}H_{46}N_4O_4S_4$
Molecular Weight: 919.2060

In a 25-mL RBF equipped with a Dean-Stark trap, **7,8-dipropyl-2,13-diformyltetrathia[7]helicene** (**8**, 54 mg, 0.1 mmol, 1 eq) and **1-butyl-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile** (**476**, 50 mg, 0.24 mmol, 2.4 eq) were dissolved in toluene (20 mL). The suspension was refluxed for 1.5 hrs and the resulting dark red solution was evaporated under reduced pressure affording bis-pyridine-dione **472** (100 mg, 99%), as a red/black solid.

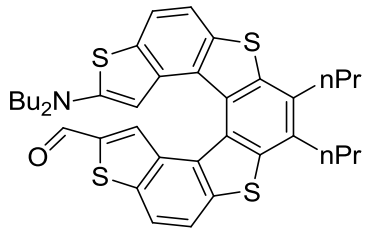
**Mp.:** 254-256 °C.

**IR (ATR):** ν ($cm^{-1}$) 2959, 2931, 2870, 2223, 1693, 1649.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 8.23 (d, 2H, $^3J$ = 8.5 Hz), 8.07 (dd, 2H, $^3J$ = 8.5 Hz, $^5J$ = 0.9 Hz), 7.21 (s, 2H), 7.07 (s, 2H), 3.84-3.88 (m, 4H), 3.18-3.23 (m, 4H), 2.37 (s, 6H), 1.88-1.93 (m, 4H), 1.48-1.53 (m, 4H), 1.34-1.38 (m, 4H), 1.20 (t, 6H, $^3J$ = 7.2 Hz), 0.94 (t, 6H, $^3J$ = 7.3 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 162.3, (2C, C), 159.9 (2C, C), 157.6 (2C, C), 144.9 (2C, C), 144.4 (2C, CH), 143.8 (2C, CH), 141.4 (2C, C), 137.2 (2C, C), 135.3 (2C, C), 133.7 (2C, C), 133.3 (2C, C), 130.7 (2C, C), 127.4 (2C, C), 124.4 (2C, CH), 120.0 (2C, CH), 118.6 (2C, C), 114.4 (2C, C), 105.1 (2C, C), 40.1 (2C, $CH_2$), 34.5 (2C, $CH_2$), 29.7 (2C, $CH_2$), 23.3 (2C, $CH_2$), 20.1 (2C, $CH_2$), 18.7 (2C, $CH_3$), 14.7 (2C, $CH_3$), 13.7 (2C, $CH_3$).

***N*,*N*-dibutyl-7,8-dipropyl-13-formyltetrathia[7]helicen-2-amine (473):**




Chemical Formula: $C_{37}H_{39}NOS_4$

Molecular Weight: 641.9717

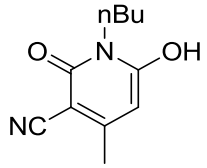
In a 10-mL RBF, flamed dried under vacuum and flushed with argon (cycle repeated 3 times), to a solution of ***N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine** (**478**, 24 mg, 39 μmol, 1 eq) in distilled THF (3 mL), cooled at –78 °C was added *n*-BuLi (2.5 M in hexanes, 19 μL, 1.2 eq) under argon. After stirring 15 min at –78 °C, the solution was allowed to warm up to 0 °C over 15 min. The solution was then cooled back down to –78 °C, DMF (25 μL, 0.39 mmol, 10 eq) was added and the solution was allowed to reach RT over 1.5 hrs. Then, sat. aq. $NH_4Cl$ (5 mL) was added, and the resulting mixture was extracted with DCM (2 x 25mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was then purified by column chromatography (5 g silica, hexanes/EtOAc gradient 100:0 to 50:1, v/v) affording ***N*,*N*-dibutyl-7,8-dipropyl-13-formyltetrathia[7]helicen-2-amine** (**473**, 16 mg, 64%) as an orange solid.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 9.42 (s, 1H), 8.09 (d, 1H, $^3J$ = 8.5 Hz), 7.93 (dd, 1H, $^3J$ = 8.5 Hz, $^5J$ = 0.9 Hz), 7.71 (dd, 1H, $^3J$ = 8.5Hz, $^5J$ = 0.7 Hz), 7.65 (d, 1H, $^3J$ = 8.5Hz), 7.60 (d, 1H, $^5J$ = 0.7 Hz), 5.32 (s, 1H), 3.10-3.15 (m, 4H), 2.80-2.85 (m, 2H), 2.64-2.68 (m, 2H), 1.86-1.91 (m, 4H), 1.20-1.24 (m, 4H), 1.16-1.19 (m, 6H), 1.05-1.09 (m, 4H), 0.80 (t, 6H, $^3J$ = 7.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 184.4 (1C, CH), 155.7 (1C, C), 140.2 (1C, C), 140.0 (1C, C), 139.9 (1C, C), 139.3 (1C, C), 137.5 (1C, C), 136.9 (1C, CH), 136.7 (1C, C), 136.5 (1C, C), 135.6 (1C, C), 133.0 (1C, C), 132.9 (1C, C), 131.5 (1C, C), 128.7 (1C, C), 127.9 (1C, C), 127.3 (1C, C), 127.2 (1C, C), 122.7 (1C, CH), 120.5 (1C, CH), 120.2 (1C, CH), 113.8 (1C, CH), 100.3 (1C, CH), 53.1 (2C, $CH_2$), 34.43 (1C, $CH_2$), 34.36 (1C, $CH_2$), 28.6 (2C, $CH_2$), 23.2 (2C, $CH_2$), 20.0 (2C, $CH_2$), 14.7 (2C, $CH_3$), 13.6 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{37}H_{39}NOS_4$: 642.1987; found: 642.1971.

**1-Butyl-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile[20] (476):**



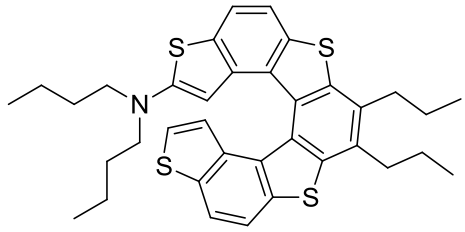

Chemical Formula: $C_{11}H_{14}N_2O_2$

Molecular Weight: 206.2411

Ethyl cyanoacetate (3.33 g, 29.4 mmol, 1.eq) was added dropwise (over 15 min) to the respective *N*-butylamine (5.38 g, 73.6 mmol, 2.5 eq), and the reaction mixture was stirred at RT for 60 hrs, affording 2-cyano-*N*-butylacetamide (**475**). Then ethyl acetoacetate (3.82g, 29.4 mmol, 1 eq) and piperidine (3 mL) were added, and the mixture was stirred at 100 °C for 20 hrs. The solvent was evaporated, and the pH was adjusted to 1 with 32% aqueous HCl. After precipitation at room temperature, the product was filtered and washed with $H_2O$ (100 mL) and $Et_2O$ (50 mL) affording **1-butyl-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (476**, 3.15g, 52%) as a beige solid.

**$^1$H NMR (DMSO-d6, 500 MHz):** δ (ppm) 5.6 (s, 1H), 3.86-3.90 (m, 2H), 2.20 (s, 3H), 1.47-1.53 (m, 2H), 1.23-1.30 (m, 2H), 0.88 (t, 3H, $^3J$ = 7.6 Hz).

***N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine (478):**




Chemical Formula: $C_{36}H_{39}NS_4$

Molecular Weight: 613.9616

A 25-mL RBF, flame dried under vacuum flushed with argon (3 times) was charged with **2-bromo-7,8-dipropyltetrathia[7]helicene** (**486**, 187 mg, 0.33 mmol, 1 eq) and distilled THF (2 mL) was added. The solution was cooled to 0 °C and *i*-PrMgCl·LiCl (1.3 M in THF; 0.28 mL, 0.37 mmol, 1.1 eq) was added dropwise and the mixture was stirred at 0 °C for 2 hrs to afford the Grignard reagent. This solution was cooled to –50 °C before CuCl•2LiCl (1.0 M in THF; 0.4 mL, 0.40 mmol, 1.2 eq) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (77 μL, 0.4 mmol, 1.2 eq) were added dropwise and the mixture was stirred for 45 min. A solution of lithium dibutylamide was prepared by adding

dropwise *n*-BuLi (2.5 M in hexanes, 0.26 mL, 0.66 mmol, 2 eq) to di-*N*-butylamine (113 μL, 2 mmol, 2 eq) in distilled THF (1 mL), at –78 °C under argon; the solution was stirred 15 min at –78 °C and 15 min at 0 °C. To the so formed aryl cuprate, was added dropwise the solution of lithium dibutylamide and the mixture was further stirred for 45 min at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of chloranil (98 mg, 0.4 mmol, 1.2 eq), in THF (3.5 mL), was added slowly over a period of 45 min. The reaction mixture was then allowed to reach –50 °C and stirred for 18 hrs. Then $Et_2O$ (10 mL) was added to the crude reaction mixture which was filtered through kiesielghur and washed with $Et_2O$ thoroughly. The combined filtrates were washed with aq. $NH_4OH$ (28%, 2 x 10 mL), the organic layer was separated, the aqueous layer was extracted with $Et_2O$ (2 x 10 mL), combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography (10 g silica, hexanes) affording ***N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine (478**, 41 mg, 20%) as a bright yellow oil and **13-bromo-*N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine (493**, 40 mg, 21%) as a yellow oil.

Alternatively the Grignard reagent can be formed by adding TMPMgCl•LiCl[21] (1.2 M in THF, 132 μL, 1.1 eq) to a solution of **7,8-dipropyltetrathia[7]helicene (8**, 0.143 mmol, 1 eq) in distilled THF (2 mL) at RT, and stirring overnight. Using this method, and following the rest of the procedure, ***N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine (478**, 28 mg, 32%) was obtained as a bright yellow oil and some SM **8** (26 mg, 37%) was recovered.

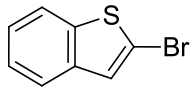
**IR (ATR):** ν ($cm^{-1}$) 2956, 2928, 2868, 1548, 1526.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.94 (s, 2H), 7.68 (d, 1H, $^3J$ = 8.2 Hz), 7.62 (d, 1H, $^3J$ = 8.2 Hz), 7.02 (d, 1H, $^3J$ = 5.6 Hz), 7.00 (d, 1H, $^3J$ = 5.6 Hz), 5.42 (s, 1H), 3.04-3.17 (m, 4H), 2.78-2.83 (m, 2H), 2.62-2.67 (m, 2H), 1.83-1.92 (m, 4H), 1.20-1.26 (m, 4H), 1.13-1.19 (m, 6H), 1.04-1.12 (m, 4H), 0.80 (t, 6H, $^3J$ = 7.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 155.8 (1C, C), 139.2 (1C, C), 139.0 (1C, C), 138.2 (1C, C), 136.7 (1C, C), 136.34 (1C, C), 136.31 (1C, C), 135.8 (1C, C), 132.0 (1C, C), 131.9 (1C, C), 131.2 (1C, C), 129.0 (1C, C), 128.6 (1C, C), 127.9 (1C, C), 127.1 (1C, C), 125.8 (1C, CH), 123.3 (1C, CH), 120.3 (1C, CH), 119.9 (1C, CH), 118.5 (1C, CH), 113.4 (1C, CH), 99.5 (1C, CH), 52.7 (2C, $CH_2$), 34.36 (1C, $CH_2$), 34.33 (1C, $CH_2$), 28.9 (2C, $CH_2$), 23.24 (1C, $CH_2$), 23.22 (1C, $CH_2$), 20.0 (2C, $CH_2$), 14.7 (2C, $CH_3$), 13.8 (2C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{36}H_{39}NS_4$: 614.2038; found: 614.2031.

**2-Bromobenzo[b]thiophene[22] (483):**




Chemical Formula: $C_8H_5BrS$

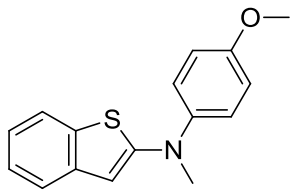
Molecular Weight: 213.0943

In a 250-mL RBF, flame dried under nitrogen, to a solution of benzo[b]thiophene (5 g, 37 mmol, 1 eq) in distilled THF (200 mL), cooled at –78 °C was added dropwise *n*-BuLi (2.2 M in hexanes, 18.6 mL, 1.1 eq). The reaction mixture was stirred at –78 °C for 30 min and was then allowed to warm to 0 °C over 1 hour. It was then cooled back down to –78 °C, 1,2-dibromoethane (4.8 mL, 55.5 mmol, 1.5 eq) was added dropwise and reaction mixture was allowed to warm up to RT over 1 hr. Then, sat. aq. $NH_4Cl$ (2 mL) was added and the crude mixture was evaporated under reduced pressure. The crude product was taken in DCM (50 mL), washed with brine (2 x 50 mL), dried over $MgSO_4$ and evaporated affording 7.9 g of a brown oil which solidifies. The crude material was then purified by column chromatography (80 g silica, hexanes) affording **2-bromobenzo[b]thiophene** (**483**, 4.76 g, 60%) as a white solid and (2.97 g, 31%) as an impure white solid containing 16% of SM.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.73-7.75 (m, 1H), 7.69-7.71 (m, 1H), 7.30-7.35 (m, 3H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 140.9 (1C, C), 139.5 (1C, C), 126.5 (1C, CH), 124.7 (1C, CH), 124.4 (1C, CH), 122.7 (1C, CH), 121.6 (1C, CH), 115.4 (1C, C).

***N*-(4-methoxyphenyl)-*N*-methylbenzo[b]thiophen-2-amine (485):**




Chemical Formula: $C_{16}H_{15}NOS$

Molecular Weight: 269.3614

**2-Bromobenzo[b]thiophene** (**483**, 100 mg, 0.47 mmol, 1 eq), *N*-methyl-*p*-anisidine (65 mg, 0.47 mmol, 1 eq), NaO*t*-Bu (51 mg, 0.52 mmol, 1.1 eq), $Pd(dba)_2$ (27 mg, 0.047

mmol, 0.1 eq), and P(*t*-Bu)$_3$ (1 M in toluene, 47 μL, 0.047 mmol, 0.1 eq) were charged to a 5-mL vial flame dried under argon. Toluene (4 mL) was added and the suspension was heated at 100 °C for 4 hrs. The reaction mixture was cooled to RT, $H_2O$ (2 mL) was added, the mixture was extracted with DCM (2 x 15 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was then purified by column chromatography (3 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording ***N*-(4-methoxyphenyl)-*N*-methylbenzo[b]thiophen-2-amine** (**385**, 76 mg, 60%) as pale orange crystals.

**Mp.:** 100-102 °C.

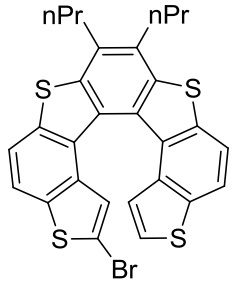
**IR (ATR):** ν ($cm^{-1}$) 3060, 2948, 2932, 2897, 2832, 2815, 1529, 1507.

**$^1$H NMR ($CDCl_3$, 500MHz):** δ (ppm) 7.54 (d, 1H, $^3J$ =7.9 Hz), 7.45 (d, 1H, $^3J$ = 7.9 Hz), 7.26-7.28 (m, 2H), 7.23-7.25 (m, 1H), 7.07-7.09 (m, 1H), 6.93-6.95 (m, 2H), 6.24 (br. s, 1H), 3.85 (s, 3H), 3.39 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 157.1 (1C, C), 156.0 (1C, C), 141.7 (1C, C), 140.7 (1C, C), 133.0 (1C, C), 125.4 (2C, CH), 124.4 (1C, CH), 121.4 (1C, CH), 121.1 (1C, CH), 120.5 (1C, CH), 114.6 (2C, CH), 100.6 (1C, CH), 55.5 (1C, $CH_3$), 42.3 (1C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{16}H_{15}NOS$: 270.0947; found: 270.0950.

**2-Bromo-7,8-dipropyltetrathia[7]helicene (486):**




Chemical Formula: $C_{28}H_{21}BrS_4$

Molecular Weight: 565.6303

To a solution of **7,8-dipropyltetrathia[7]helicene** (**8**, 290g, 0.60 mmol, 1 eq) in distilled THF (15 mL), cooled at –78 °C under a nitrogen atmosphere was added dropwise *n*-BuLi (2.5 M in hexanes, 250 μL, 0.63 mmol, 1.05 eq). The reaction mixture was stirred at –78 °C for 30 min and was then allowed to warm to 0 °C over 1 hr. It was then cooled back down to –78 °C, 1,2-dibromoethane (0.52 mL, 5.95 mmol, 10 eq) was added dropwise and the reaction mixture was allowed to warm up to RT over 2 hrs. Then, sat. aq. $NH_4Cl$ (10 mL) was added and the mixture was extracted with DCM (3 x 40 mL), dried over $MgSO_4$,

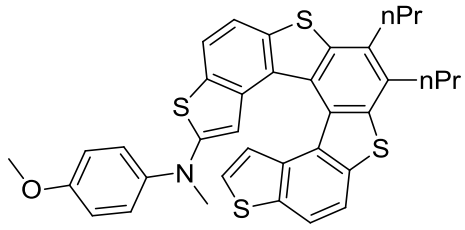
evaporated, and purified by column chromatography (10 g silica, hexanes) affording **2-bromo-7,8-dipropyltetrathia[7]helicene** (**486**, 200 mg, 59 %) as a white solid. Some starting material **8** was also recovered (120 mg, 41%).

**$^{1}$H NMR ($CDCl_3$, 500MHz):** δ(ppm) 8.06 (dd, 1H, $^{3}J$ = 8.5 Hz, $^{5}J$ = 0.7Hz), 7.98 (d, 1H, $^{3}J$ = 8.5 Hz), 7.94 (d, 1H, $^{3}J$ = 8.5 Hz), 7.83 (dd, 1H, $^{3}J$ = 8.5 Hz, $^{5}J$ = 0.7 Hz), 7.04 (d, 1H, $^{3}J$ = 5.5 Hz), 6.76 (dd, 1H, $^{3}J$ = 5.6 Hz, $^{5}J$ = 0.7 Hz), 6.75 (d, 1H, $^{5}J$ = 0.7 Hz), 3.10-3.17 (m, 4H), 1.85-1.91 (m, 4H), 1.14-1.18 (m, 6H).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 139.7 (1C, C), 139.6 (1C, C), 137.5 (1C, C), 136.8 (1C, C), 136.4 (1C, C), 136.0 (1C, C), 135.7 (1C, C), 135.6 (1C, C), 132.5 (1C, C), 132.2 (1C, C), 131.1 (1CH), 130.4 (1C, C), 128.6 (1C, CH), 128.0 (1C, C), 127.8 (1C, C), 124.7 (1C, CH), 124.5 (1C, CH), 121.1 (1C, CH), 119.6 (1C, CH), 118.8 (1C, CH), 118.6 (1C, CH), 113.2 (1C, C), 34.39 (1C, $CH_2$), 34.36 (1C, $CH_2$), 23.3 (2C, $CH_2$), 14.70 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M]^+$ calcd. for $C_{28}H_{21}BrS_4$: 563.9704; found: 563.9699.

***N*-(4-methoxyphenyl)-*N*-methyl-7,8-dipropyltetrathia[7]helicen-2-amine (487):**




Chemical Formula: $C_{36}H_{31}NOS_4$

Molecular Weight: 621.8974

**2-Bromo-7,8-dipropyltetrathia[7]helicene** (57 mg, 0.1 mmol, 1 eq), *N*-methyl-p-anisidine (13.7 mg, 0.1 mmol, 1 eq), NaO*t*-Bu (10 mg, 0.11 mmol, 1.1 eq), $Pd(dba)_2$ (27.5 mg, 0.05 mmol, 0.5 eq), and P(*t*-Bu)$_3$ (1 M in toluene, 50 μL, 0.05 mmol, 0.5eq) were charged to a 5-mL vial flame dried under argon. Toluene (4 mL) was added and the suspension was heated at 100 °C for 4 hrs. The reaction mixture was cooled to RT, $H_2O$ (2 mL) was added, the mixture was extracted with DCM (2 x 15 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was then purified by column chromatography (3 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording ***N*-(4-methoxyphenyl)-*N*-methyl-7,8-dipropyltetrathia[7]helicen-2-amine** (9 mg, 14%) as pale orange solid and (29 mg as a 70% pure mixture, 33%).

**Mp.:** 76-78 °C.

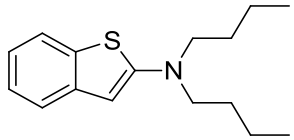
**IR (ATR):** ν ($cm^{-1}$) 2956, 2927, 2867, 1547, 1523, 1507.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.95 (dd, 1H, $^3J$ = 8.5 Hz, $^5J$ = 0.7 Hz), 7.92 (d, 1H, $^3J$ = 8.5 Hz), 7.70 (d, 1H, $^3J$ = 8.5 Hz), 7.64 (d, 1H, $^3J$ = 8.5 Hz), 7.05 (d, 1H, $^3J$ = 5.4 Hz), 6.99 (dd, 1H, $^3J$ = 5.4 Hz, $^5J$ = 0.7 Hz), 6.90-6.92 (m, 2H), 6.77-6.79 (m, 2H), 5.72 (s, 1H), 3.80 (s, 3H), 3.06-3.14 (m, 4H), 2.63 (s, 3H), 1.83-1.89 (m, 4H), 1.16 (t, 3H, $^3J$ = 7.2 Hz), 1.15 (t, 3H, $^3J$ = 7.2 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 156.8 (1C, C), 155.1 (1C, C), 141.5 (1C, C), 139.3 (1C, C), 139.2 (1C, C), 137.1 (1C, C), 136.6 (1C, C), 136.3 (1C, C), 136.2 (1C, C), 135.9 (1C, C), 132.1 (1C, C), 131.8 (1C, C), 131.5 (1C, C), 129.3 (1C, C), 128.8 (1C, C), 128.7 (1C, C), 127.9 (1C, C), 126.0 (1C, CH), 124.9 (2C, CH), 123.4 (1C, CH), 120.4 (1C, CH), 120.1 (1C, CH), 118.5 (1C, CH), 115.0 (1C, CH), 114.4 (2C, CH), 104.7 (1C, CH), 55.4 (1C, $CH_3$), 41.7 (1C, $CH_3$), 34.4 (1C, $CH_2$), 34.3 (1C, $CH_2$), 23.2 (2C, $CH_2$), 14.70 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{36}H_{31}NOS_4$: 622.1361; found: 622.1356.

***N*,*N*-dibutylbenzo[b]thiophen-2-amine (491):**




Chemical Formula: $C_{16}H_{23}NS$

Molecular Weight: 261.4255

A 25-mL RBF, flame dried under vacuum flushed with argon (3 times) was charged with **2-bromobenzo[b]thiophene** (**483**, 213 mg, 1 mmol, 1 eq) and distilled THF (2 mL) was added. The solution was cooled to 0 °C and *i*-PrMgCl·LiCl (1.3 M in THF; 0.85 mL, 1.1 mmol, 1.1 eq) was added dropwise and the mixture was stirred at 0 °C for 2 hrs to afford the Grignard reagent. This solution was cooled to –50 °C before CuCl•2LiCl (1.0 M in THF; 1.2 mL, 1.2 mmol, 1.2 eq) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2 eq) were added dropwise and the mixture was stirred for 45 min. A solution of lithium dibutylamide was prepared by adding dropwise *n*-BuLi (2.5 M in hexanes, 0.8 mL, 2 mmol, 2 eq) to di-*N*-butylamine (0.34 mL, 2 mmol, 2 eq) in distilled THF (1 mL), at –78 °C under argon; the solution was stirred 15 min at –78 °C and 15 min at 0 °C. To the so formed aryl cuprate, was added dropwise the solution of lithium dibutylamide and the mixture was further stirred for 45 min at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of chloranil (295 mg, 1.2 mmol, 1.2 eq), in THF (7 mL), was added

slowly over a period of 45 min. The reaction mixture was then allowed to reach –50 °C and stirred for 18 hrs. Then $Et_2O$ (10 mL) was added to the crude reaction mixture which was filtered through kiesielghur and washed with $Et_2O$ thoroughly. The combined filtrates were washed with aq. $NH_4OH$ (28%, 2 x 10 mL), the organic layer was separated, the aqueous layer was extracted with $Et_2O$ (2 x 10 mL), combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography (10 g silica, hexanes) affording ***N,N*-dibutylbenzo[b]thiophen-2-amine** (**491**, 144 mg, 55%) as a colourless oil.

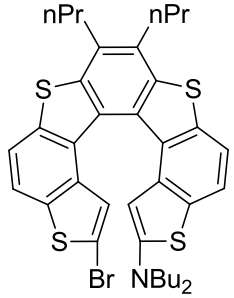
**IR (ATR):** ν ($cm^{-1}$) 3061, 2957, 2931, 2870, 1563, 1542.

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ(ppm) 7.55 (dm, 1H, $^3J$ = 7.9 Hz), 7.39 (dm, $^3J$ = 7.9 Hz), 7.20-7.22 (m, 1H), 6.99-7.01 (m, 1H), 5.92 (br s, 1H), 3.31 (br t, 4H, $^3J$ = 7.5 Hz), 1.65-1.69 (m, 4H), 1.38-1.42 (m, 4H), 0.99 (t, 6H, $^3J$ = 7.5 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ(ppm) 156.1 (1C, C), 141.7 (1C, C), 131.5 (1C, C), 124.4 (1C, CH), 121.2 (1C, CH), 119.7 (1C, CH), 119.5 (1C, CH), 94.8 (1C, CH), 53.1 (2C, $CH_2$), 29.3 (2C, $CH_2$), 20.3 (2C, $CH_2$), 13.9 (2C, $CH_3$).

**HRMS (ESI):** *m/z* $[M + H]^+$ calcd. for $C_{16}H_{23}NS$: 262.1624; found: 262.1626.

**13-Bromo-*N*,*N*-dibutyl-7,8-dipropyltetrathia[7]helicen-2-amine (493):**




Chemical Formula: $C_{36}H_{38}BrNS_4$

Molecular Weight: 692.8576

**$^1$H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.90 (d, 1H, $^3J$ = 8.5 Hz), 7.76 (d, 1H, $^3J$ = 8.5 Hz), 7.73 (d, 1H, $^3J$ = 8.5 Hz), 7.63 (d, 1H, $^3J$ = 8.5 Hz), 7.01 (s, 1H), 5.41 (s, 1H), 3.08-3.16 (m, 4H), 2.84-2.90 (m, 2H), 2.70-2.76 (m, 2H), 1.83-1.89 (m, 4H), 1.28-1.33 (m, 4H), 1.15 (m, 6H), 1.08-1.12 (m, 4H), 0.80 (t, 6H, $^3J$ = 7.6 Hz).

**$^{13}$C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 155.9 (1C, C), 139.2 (1C, C), 139.0 (1C, C), 137.9 1C, C), 137.3 (1C, C), 136.5 (1C, C), 136.34 (1C, C), 136.30 (1C, C), 132.4 (1C, C), 132.3 (1C, C), 131.2 (1C, C), 130.9 (1C, C), 129.2 (1C, CH), 128.84 (1C, C), 128.78 (1C, C),

127.5 (1C, C), 120.1 (1C, CH), 119.0 (1C, CH), 118.7 (1C, CH), 113.5 (1C, CH), 112.3 (1C, C), 98.9 (1C, CH), 52.9 (2C, $CH_2$), 34.38 (1C, $CH_2$), 34.33 (1C, $CH_2$), 28.7 (2C, $CH_2$), 23.2 (2C, $CH_2$), 20.0 (2C, $CH_2$), 14.7 (2C, $CH_3$), 13.8 (2C, $CH_3$).

**HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd. for $C_{36}H_{38}BrNS_4$: 692.1143; found: 692.1141.

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[17] In that case the starting material was not **8**, it was **460**.

[18] In that case the starting material was not **8**, it was **460**.

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# Appendix A:

# HPLC data

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e. [%] of 460 | e.e. [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**430** | –78 to RT | 1 + 1 | 35 | 2.5 (*M*) | 2 (*P*) |
| 2 | (*S*)-**429** | –78 | 6 | 29 | 14 (*M*) | 4 (*P*) |
| 3 | (*R*)-**427** | –78 | 6 | 22 | 7 (*P*) | 1 (*M*) |
| 4 | (*S*)-**426** | –43 | 3 | 50 | 2 (*P*) | *rac* |

**Chapter 3: Table 1**

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e. [%] of 460 | e.e. [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**446** | –78 | 7 | 19 | 13 (*M*) | 5.5 (*P*) |
| 2 | (*R*)-**445** | –78 | 6 | 15 | 9 (*M*) | 1 (*P*) |
| 3 | (*R*)-**441** | –78 | 6 | 23 | 42 (*M*) | 8 (*P*) |
| 4 | (*R*)-**442** | –78 | 6 | 34 | 29 (*M*) | 7 (*P*) |
| 5 | (*R*)-**443** | –78 | 6 | 15 | 25 (*M*) | 5 (*P*) |
| 6 | (*R*)-**447** | –78 | 6 | 29 | 17 (*M*) | 3 (*P*) |
| 7 | (*S*)-**439** | –78 | 7 | 26 | 13 (*M*) | 5 (*P*) |
| 8 | (–)-**452** | –78 | 18 | 41 | *rac* | *rac* |

**Chapter 3: Table 2**

| Entry | Formamide | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e. [%] of 460 | e.e. [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** | –78 | 18 | 30 | 41 (*M*) | 10 (*P*) |
| 2 | (*R*)-**448** | –78 | 18 | 20 | 3 (*P*) | 1 (*M*) |
| 3 | (*R*)-**450** | –78 | 6 | 9 | 28 (*M*) | 3 (*P*) |
| 4 | (*R*)-**449** | –78 | 6 | NR | - | - |
| 5 | (*R*)-**451** | –78 | 18 | NR | - | - |
| 6 | (*R*)-**455** | –78 | 18 | 32 | 42 (*M*) | 11 (*P*) |
| 7 | (*R*)-**456** | –78 | 18 | 35 | 7 (*P*) | 2.5 (*M*) |

**Chapter 3: Table 3**

| Entry | Formamide (eq) | Lewis acid | Temp. [°C] | Rxn time [hrs] | Yield [%] | e.e. [%] of 460 | e.e. [%] of 8 |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** (0.5) | - | –78 | 18 | 30 | 41 (*M*) | 10 (*P*) |
| 2 | (*R*)-**441** (0.5) | - | –63 | 2 | 9 | 34 (*M*) | 7 (*P*) |
| 3 | (*R*)-**441** (0.35) | - | –40 | 2 | 29 | 25 (*M*) | 9 (*P*) |
| 4 | (*R*)-**441** (1) | - | –78 | 6 | 29 | 17 (*M*) | 5 (*P*) |
| 5 | (*S*)-**441** (0.5) | $BF_3$•$Et_2O$ | –78 | 18 | 37 | 10 (*P*) | 6 (*M*) |
| 6 | (*R*)-**451** (0.5) | $BF_3$•$Et_2O$ | –78 | 18 | 20 | 4.5 (*P*) | 1.5 (*M*) |

**Chapter 3: Table 4**

| Entry | Formamide | Solvent | Rxn time [hrs] | Yield [%] | e.e. [%] of 460 | e.e. [%] of 8 |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**441** | THF | 18 | 30 | 41(*M*) | 10 (*P*) |
| 2* | (*R*)-**441** | $Et_2O$/Toluene | 6 | 9 | 5 (*M*) | 1 (*P*) |
| 3 | (*R*)-**455** | 2-MeTHF | 18 | 26 | 16 (*M*) | 5 (*P*) |
| 4 | (*R*)-**441** | DME/THF | 18 | 28 | 30 (*M*) | 7 (*P*) |
| 5 | (*R*)-**441** | MTBE | 18 | 32 | 1 (*P*) | 0.15 (*M*) |

**Chapter 3: Table 5**

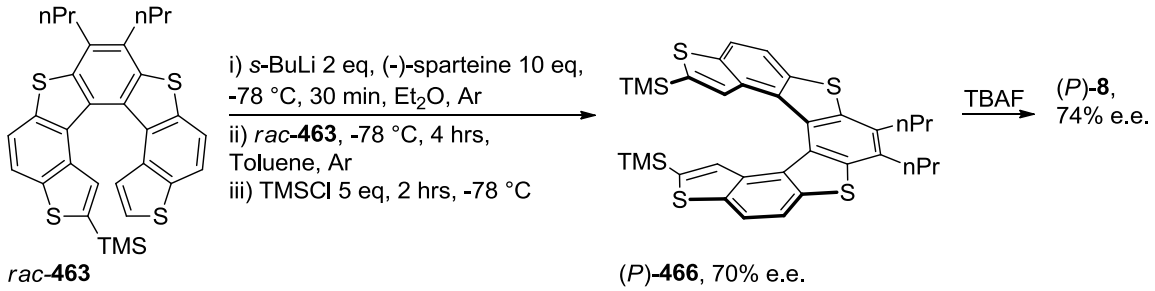
| Entry | *s*-BuLi [eq] | (–)-sparteine / *s*-BuLi ratio | Lithiation time [hrs] | Rxn time[a] [hrs] | Yield [%] | e.e. [%] of product[c] | e.e. [%] of 8[c] |
|---|---|---|---|---|---|---|---|
| 1 | 0.7 | 1:1 | 0.5 | 18 | **460**, 25 | 7 (*P*) | 2.5 (*M*) |
| 2 | 0.5 | 2:1 | 1 | 18 | **460**, 20 | 5 (*P*) | 0.4 (*M*) |
| 3 | 0.5 | 1:1 | 0.5 | 18 | **460**, 10 | 11 (*P*) | 1 (*M*) |
| 4[b] | 0.5 | 1:1 | 0.5 | 2 | **463**, 9 | 7 (*P*) | 1.7 (*M*) |

**Chapter 3: Table 6**

| Entry | *s*-BuLi [eq] | (–)-Sparteine / *s*-BuLi ratio | Lithiation time [hrs] | Conversion into 466 [%][a] | e.e. [%] of 466[b] | Conversion into 463 [%][a] | e.e. [%] of 463[b] | e.e. [%] of 8[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.5 | 20:1 | 0.5 | - | - | 6 | 55 (*P*) | 3.3 (*M*) |
| 2 | 1.5 | 6.6:1 | 0.5 | 2 | >90 (*P*) | 22 | 60 (*P*) | 17.5 (*M*) |
| 3 | 2 | 5:1 | 0.75 | 2.5 | >90 (*P*) | 27 | 72 (*P*) | 28 (*M*) |
| 4 | 2 | 5:1 | 4 | 1 | >90 (*P*) | 23 | 74 (*P*) | 21 *(M)* |
| 5 | 2 | 5:1 | 4 | 5 | >90 (*P*) | 35 | 84 (*P*) | 58 (*M*) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 | 2 | 1:1 | 4 | 4 | 87 (*P*) | 23 | 51 (*P*) | 21.5 (*M*) |
| 7 | 4 | 5:1 | 0.75 | 2.6 | >90 (*P*) | 35 | 85 (*P*) | 66 (*M*) |
| 8 | 4 | 5:1 | 2 | 36 | 81 (*P*) | 33 | 62 (*M*)[c] | 69 (*M*) |
| 9 | 1 | 5:1 | 4 | 1.5 | >90 (*P*) | 18 | 65 (*P*) | 14 (*M*) |
| 10 | 1 | 3:1 | 4 | 0.3 | >90 (*P*) | 12 | 62 (*P*) | 9.4 (*M*) |
| 11 | 3 | 5:1 | 4 | 9 | >90 (*P*) | 38 | 68 (*P*) | 67 (*M*) |
| 12 | 3 | 5:1 | 4 | 14 | >90 (*P*) | 30 | 39 (*P*) | 80 (*M*) |
| 13[d] | 2 | 5:1 | 4 | 1.8 | >90 (*P*) | 21 | 84 (*P*) | 33 (*M*) |
| 14[d] | 2 | 5:1 | 4 | 1 | >90 (*P*) | 20 | 71 (*P*) | 24 (*M*) |

**Chapter 3: Table 7**

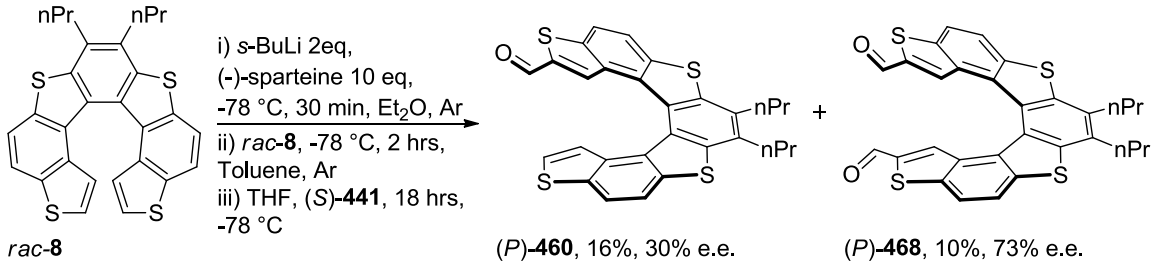



*rac*-**463** (*P*)-**466**, 70% e.e.

**Chapter 3: Scheme 9**

| Entry | *n*-BuLi [eq] | (–)-Sparteine / *n*-BuLi ratio | Lithiation time [hrs] | Conversion into 466 [%][a] | e.e. [%] of 466[b] | Conversion into 463 [%][a] | e.e. [%] of 463[b] | e.e. [%] of 8[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 5:1 | 4 | 16 | 86 (*P*) | 45 | 30 (*P*) | 68 (*M*) |
| 2 | 2 | 1.1:1 | 4 | 7 | >90 (*P*) | 33 | 51 (*P*) | 40 (*M*) |
| 3 | 1 | 5:1 | 4 | 0.5 | >90 (*P*) | 13.5 | 53 (*P*) | 12 (*M*) |
| 4 | 2 | 1:1 | 4 | 8 | >90 (*P*) | 31 | 44 (*P*) | 39 (*M*) |

**Chapter 3: Table 8**

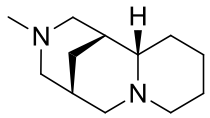



*rac*-**8** (*P*)-**460**, 16%, 30% e.e. (*P*)-**468**, 10%, 73% e.e.

**Chapter 3: Scheme 12**

| Entry | Time [hrs] after THF added | Conversion into 466 [%][b] | e.e. [%] of 466[c] | Conversion into 463 [%][b] | e.e. [%] of 463[c] | e.e. [%] of 8[c] |
|---|---|---|---|---|---|---|
| 1 | 0 | 3 | 82 *(P)* | 28 | 53 (*P*) | 30 (*M*) |
| 2[a] | 0.5 | 3 | 6 (*P*) | 23 | 9 (*M*) | 1 (*M*) |
| 3 | 3 | 31 | 1 (*M*) | 48 | 8 (*M*) | 10 (*P*) |
| 4 | 17 | 20 | 10 (*M*) | 61 | 5 (*M*) | 5 (*P*) |

**Chapter 3: Table 9**

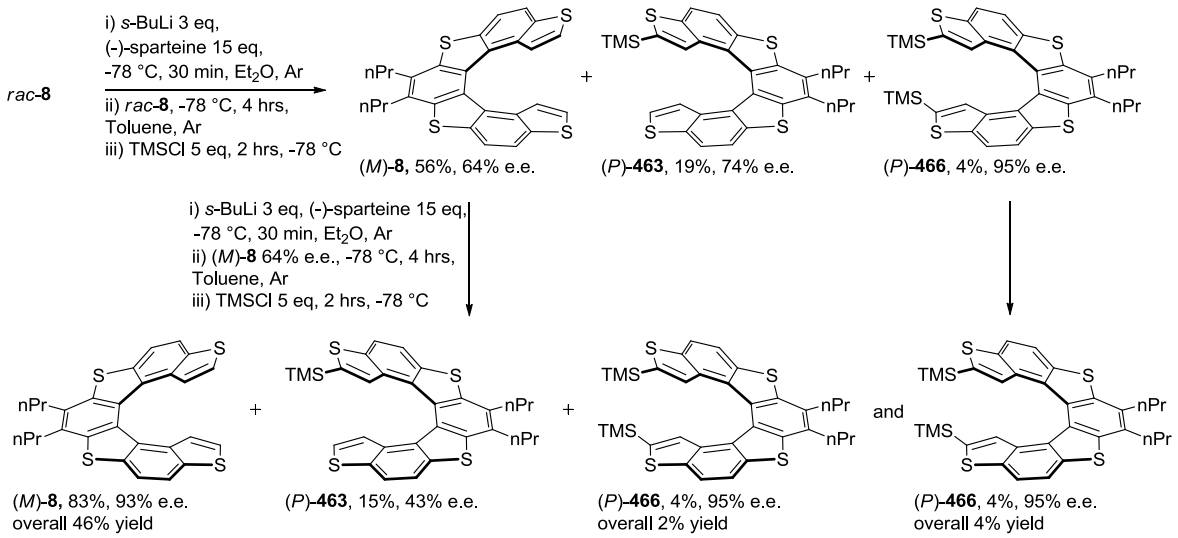



(+)-**459**

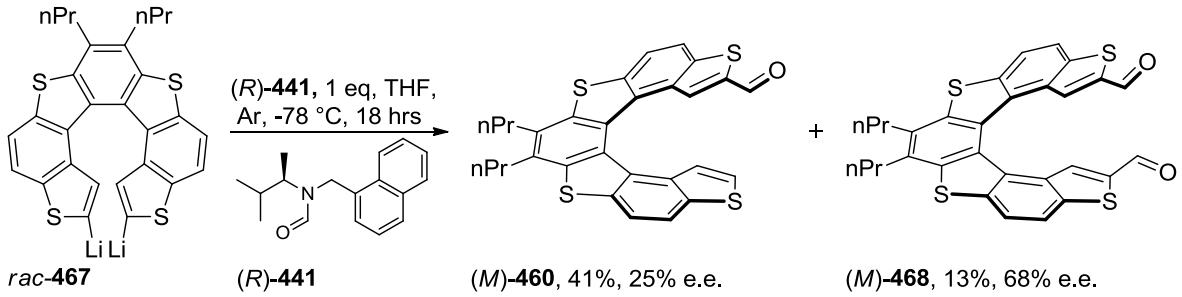
**Chapter 3: Figure 5**

| Entry | Conditions[a] for $KR_1$ | Conversion of $KR_1$, product | $KR_1$: e.e. of product | Conditions[a] for $KR_2$ | Conversion of $KR_2$, product | $KR_2$: e.e. of product | Overall conversion $KR_1$*$KR_2$ |
|---|---|---|---|---|---|---|---|
| 1 | B | **466**, 14%[b] | 93% (*P*) | - | - | - | 14% |
| 2 | B | **8**, 56%[b] | 64% (*M*) | B | **8**, 83%[b]<br>**466**, 5%[b] | 93% (*M*)<br>>90% (*P*) | 47%[b]<br>3%[b] |
| 3 | B | **8**, 56%[c] | 78% (*M*) | C | **460**, 10%[b] | 88% (*M*) | 5.6% |
| 4 | B | **8**, 56%[c] | 77% (*M*) | E | **8**, 69% | 84% (*M*) | 39% |
| 5 | B | **8**, 56%[c] | 74% (*M*) | A | **8**, 76% | 88% (*M*) | 43% |
| 6 | A | **463**, 22% | 67% (*P*) | D | **463**, 11% | 84% (*P*) | 2.4% |
| 7 | A | **463**, 23% | 74% (*P*) | C | **460**, 10%[b] | 92% (*P*) | 2.3% |
| 8 | B | **463**, 30% | 43% (*P*) | A | **466**, 15%<br>**463**, 45% | >90% (*P*)<br>76% (*P*) | 4.5%<br>14.5% |

**Chapter 3: Table 10**




**Chapter 3: Scheme 16**




**Chapter 3: Scheme 17**

**HPLC conditions:**

**A: Varian HPLC, hexane/IPA 99.5:0.5, 0.5 mL min$^{-1}$ 20 °C.**

**B: Shimadzu HPLC, hexane/IPA 99.5:0.5, 0.5 mL min$^{-1}$ 20 °C.**

**C: Shimadzu HPLC, hexane/IPA 99.7:0.3, 0.5 mL min$^{-1}$ 20 °C.**

**D: Shimadzu HPLC, hexane/IPA 93:7, 0.5 mL min$^{-1}$ 20 °C.**

**E: Shimadzu HPLC, hexane/IPA 97:3, 0.5 mL min$^{-1}$ 20 °C.**

| Table or Scheme | Entry | HPLC conditions | Compound | Retention time for *P* [min] | Retention time for *M* [min] | Ratio *M/P* | e.e. [%] |
|---|---|---|---|---|---|---|---|
| - | *rac* | B | **8** | 11.75 | 13.66 | 50/50 | 0 |
| - | *rac* | C | **8** | 15.35 | 18.57 | 50/50 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| - | *rac* | A | **460** | 16.82 | 19.72 | 50/50 | *0* |
| - | *rac* | E | **460** | 16.20 | 19.83 | 50/50 | 0 |
| - | *rac* | C | **463** | 10.25 | 12.19 | 50/50 | 0 |
| - | *rac* | C | **466** | 8.15 | 8.60 | 50/50 | 0 |
| - | *rac* | D | **468** | 24.99 | 28.98 | 50/50 | 0 |
| 1 | 1 | B | **8** | 12.39 | 14.20 | 50.98/49.02 | 2 (*P*) |
| 1 | 1 | A | **460** | 17.56 | 20.81 | 48.79/51.21 | 2.5 (*M*) |
| 1 | 2 | B | **8** | 11.95 | 13.58 | 47.24/52.76 | 5 (*M*) |
| 1 | 2 | A | **460** | 17.84 | 21.29 | 52.13/42.87 | 14 (*P*) |
| 1 | 3 | B | **8** | 12.33 | 14.13 | 49.59/50.41 | 1 (*M*) |
| 1 | 3 | A | **460** | 18.47 | 23.37 | 53.32/46.68 | 7 (*P*) |
| 1 | 4 | B | **8** | 11.44 | 13.98 | 49.75/50.24 | 0.5 (*M*) |
| 1 | 4 | A | **460** | 17.57 | 21.58 | 51.31/48.69 | 3 (*P*) |
| 2 | 1 | B | **8** | 12.42 | 14.05 | 52.85/47.15 | 5.5 (*P*) |
| 2 | 1 | A | **460** | 19.52 | 24.15 | 43.28/56.72 | 13 (*M*) |
| 2 | 2 | B | **8** | 12.55 | 14.27 | 49.60/50.4 | 1 (*M*) |
| 2 | 2 | A | **460** | 20.10 | 24.50 | 52.45/47.55 | 5 (*P*) |
| 2 | 3 | B | **8** | 12.71 | 14.64 | 52.63/47.37 | 8 (*P*) |
| 2 | 3 | A | **460** | 17.85 | 20.94 | 29.18/70.82 | 42 (*M*) |
| 2 | 4 | B | **8** | 12.09 | 13.60 | 53.52/46.48 | 7 (*P*) |
| 2 | 4 | A | **460** | 18.02 | 21.99 | 35.35/63.65 | 27 (*M*) |
| 2 | 5 | B | **8** | 12.30 | 13.97 | 52.47/47.53 | 5 (*P*) |
| 2 | 5 | A | **460** | 17.74 | 21.84 | 37.41/62.59 | 25 (*M*) |
| 2 | 6 | B | **8** | 12.39 | 14.21 | 51.36/48.64 | 3 (*P*) |
| 2 | 6 | A | **460** | 17.46 | 20.93 | 41.40/58.60 | 17 (*M*) |
| 2 | 7 | B | **8** | 12.33 | 14.15 | 52.67/47.33 | 5 (*P*) |
| 2 | 7 | A | **460** | 17.11 | 19.98 | 43.64/56.36 | 13 (*M*) |
| 2 | 8 | B | **8** | 11.71 | 13.76 | 49.99/50.01 | *rac* |
| 2 | 8 | E | **460** | 14.11 | 16.35 | 49.85/50.15 | *rac* |
| 3 | 1 | B | **8** | 11.81 | 13.29 | 54.96/45.04 | 10 (*P*) |
| 3 | 1 | E | **460** | 14.91 | 17.56 | 29.76/70.24 | 41 (*M*) |
| 3 | 2 | B | **8** | 11.60 | 13.87 | 49.3/50.7 | 1 (*M*) |
| 3 | 2 | E | **460** | 14.20 | 16.40 | 51.11/48.89 | 3 (*P*) |
| 3 | 3 | B | **8** | 12.43 | 14.14 | 51.62/48.38 | 3 (*P*) |
| 3 | 3 | A | **460** | 19.26 | 23.41 | 35.98/64.02 | 28 (*M*) |
| 3 | 6 | B | **8** | 10.70 | 12.44 | 55.37/44.63 | 11 (*P*) |
| 3 | 6 | E | **460** | 14.11 | 16.34 | 28.89/71.11 | 42 (*M*) |
| 3 | 7 | B | **8** | 10.04 | 11.48 | 48.71/51.28 | 2.5 (*M*) |
| 3 | 7 | E | **460** | 14.57 | 16.73 | 53.45/46.55 | 7 (*P*) |
| 4 | 1 | Same as | Table 3 | Entry 1 | | | |
| 4 | 2 | B | **8** | 13.01 | 14.93 | 53.53/46.47 | 7 (*P*) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 | 2 | A | **460** | 16.06 | 19.73 | 32.82/67.18 | 34 (*M*) |
| 4 | 3 | B | **8** | 12.30 | 13.87 | 54.91/45.09 | 9 (*P*) |
| 4 | 3 | A | **460** | 17.34 | 21.42 | 37.37/62.63 | 25 (*M*) |
| 4 | 4 | B | **8** | 12.49 | 14.29 | 55.03/44.97 | 10 (*P*) |
| 4 | 4 | A | **460** | 15.17 | 16.98 | 41.43/58.57 | 17 (*P*) |
| 4 | 5 | B | **8** | 11.02 | 12.83 | 46.88/53.12 | 6 (*M*) |
| 4 | 5 | E | **460** | 15.38 | 17.98 | 54.80/45.20 | 10 (*P*) |
| 4 | 6 | B | **8** | 11.69 | 13.79 | 49.14/50.86 | 2 (*M*) |
| 4 | 6 | E | **460** | 15.77 | 18.70 | 52.22/47.78 | 5 (*P*) |
| 5 | 1 | Same as | Table 3 | Entry 1 | | | |
| 5 | 2 | B | **8** | 11.60 | 13.90 | 49.23/50.77 | 1 (*M*) |
| 5 | 2 | E | **460** | 14.32 | 16.33 | 51.52/48.48 | 3 (P) |
| 5 | 3 | B | **8** | 13.67 | 15.83 | 52.55/47.45 | 5 (*P*) |
| 5 | 3 | E | **460** | 14.26 | 16.44 | 41.92/58.08 | 16 (*M*) |
| 5 | 4 | B | **8** | 10.76 | 12.51 | 53.50/46.5 | 7 (*P*) |
| 5 | 4 | E | **460** | 14.39 | 16.70 | 35.1/64.9 | 30 (*M*) |
| 5 | 5 | B | **8** | 11.73 | 13.68 | 49.89.50.10 | *rac* |
| 5 | 5 | E | **460** | 16.22 | 19.84 | 50.48/49.52 | 1 (*P*) |
| 6 | 1 | B | **8** | 11.56 | 13.46 | 51.28/48.72 | 2.5 (*P*) |
| 6 | 1 | E | **460** | 15.01 | 17.78 | 46.50/53.50 | 7 (*M*) |
| 6 | 2 | B | **8** | 12.81 | 14.69 | 50.21/49.79 | 0.4 (*P*) |
| 6 | 2 | E | **460** | 14.96 | 17.63 | 47.64/52.35 | 5 (*P*) |
| 6 | 3 | B | **8** | 11.31 | 12.95 | 50.21/49.79 | 0.4 (*P*) |
| 6 | 3 | E | **460** | 15.03 | 17.88 | 44.70/55.30 | 11 (*M*) |
| 6 | 4 | B | **8** | 12.86 | 15.00 | 45.21/45.64 | 1.7 (*M*) |
| 6 | 4 | C | **463** | 9.04 | 10.18 | 4.93/4.22 | 7 (*P*) |
| 7 | 1 | B | **8** | 10.9 | 12.81 | 45.04/48.26 | 3 (*M*) |
| 7 | 1 | C | **463** | 8.24 | 9.09 | 5.06/1.46 | 55 (*P*) |
| 7 | 2 | C | **8** | 14.31 | 17.88 | 30.97/44.10 | 17 (*M*) |
| 7 | 2 | C | **463** | 9.54 | 11.15 | 18.12/4.42 | 60 (*P*) |
| 7 | 2 | C | **466** | 7.72 | - | 2.18 | > 90 (*P*) |
| 7 | 3 | C | **8** | 14.20 | 17.71 | 25.25/44.68 | 28 (*M*) |
| 7 | 3 | C | **463** | 9.50 | 10.99 | 23.66/3.94 | 72 (*P*) |
| 7 | 3 | C | **466** | 7.73 | - | 2.48 | > 90 (*P*) |
| 7 | 4 | C | **8** | 12.93 | 15.48 | 29.90/46.19 | 21 (*M*) |
| 7 | 4 | C | **463** | 9.25 | 10.34 | 19.74/2.90 | 74 (*P*) |
| 7 | 4 | C | **466** | 7.73 | - | 1.26 | > 90 (*P*) |
| 7 | 5 | C | **8** | 17.03 | 20.06 | 12.94/48.20 | 58 (*M*) |
| 7 | 5 | C | **463** | 10.91 | 12.83 | 31.43/2.82 | 84 (*P*) |
| 7 | 5 | C | **466** | 8.63 | - | 4.40 | > 90 (*P*) |
| 7 | 6 | C | **8** | 17.77 | 21.93 | 28.44/44.01 | 21.5 (*M*) |

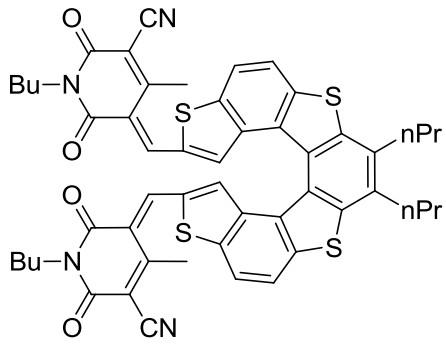
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 7 | 6 | C | **463** | 10.86 | 13.34 | 17.65/5.84 | 51(*P*) |
| 7 | 6 | C | **466** | 8.38 | 8.79 | 3.78/0.26 | 87 (*P*) |
| 7 | 7 | C | **8** | 16.34 | 19.63 | 10.35/50.75 | 66 (*M*) |
| 7 | 7 | C | **463** | 10.62 | 12.53 | 33.96/2.77 | 85(*P*) |
| 7 | 7 | C | **466** | 8.42 | - | 2.17 | > 90 (*P*) |
| 7 | 8 | C | **8** | 16.26 | 20.73 | 4.27/23.58 | 69 (*M*) |
| 7 | 8 | C | **463** | 10.39 | 12.44 | 5.79/24.68 | 66 (*M*) |
| 7 | 8 | C | **466** | 8.21 | 8.53 | 37.79/3.89 | 81 (*P*) |
| 7 | 9 | C | **8** | 15.22 | 18.18 | 34.63/46.14 | 14 (*M*) |
| 7 | 9 | C | **463** | 10.25 | 11.47 | 14.66/3.10 | 65 (*P*) |
| 7 | 9 | C | **466** | 8.30 | - | 1.46 | > 90 (*P*) |
| 7 | 10 | C | **8** | 15.12 | 18.68 | 39.86/48.12 | 9 (*M*) |
| 7 | 10 | C | **463** | 10.30 | 11.88 | 9.60/2.06 | 62 (*P*) |
| 7 | 10 | C | **466** | 8.33 | - | 0.35 | > 90 (*P*) |
| 7 | 11 | C | **8** | 13.41 | 15.86 | 8.59/44/10 | 67 (*M*) |
| 7 | 11 | C | **463** | 9.49 | 10.69 | 32.22/6.08 | 68 (*P*) |
| 7 | 11 | C | **466** | 7.85 | - | 9.01 | > 90 (*P*) |
| 7 | 12 | C | **8** | 16.47 | 20.64 | 5.57/50.26 | 80 (*M*) |
| 7 | 12 | C | **463** | 10.43 | 12.59 | 21.72/8.85 | 39 (*P*) |
| 7 | 12 | C | **466** | 8.20 | 8.58 | 12.93/0.39 | 93 (*P*) |
| 7 | 13 | C | **8** | 17.20 | 20.43 | 25.73/50.96 | 33 (*M*) |
| 7 | 13 | C | **463** | 11.00 | 12.99 | 19.84/1.68 | 84 (*P*) |
| 7 | 13 | C | **466** | 8.67 | - | 1.78 | > 90 (*P*) |
| 7 | 14 | C | **8** | 16.89 | 20.37 | 30.66/48.90 | 24 (*M*) |
| 7 | 14 | C | **463** | 10.86 | 13.06 | 17.17/2.90 | 71 (*P*) |
| 7 | 14 | C | **466** | 8.46 | - | 0.86 | > 90 (*P*) |
| Scheme 9 | - | C | **463** | 9.53 | 11.08 | 36.04/48.88 | 15 (*M*) |
| Scheme 9 | - | C | **466** | 7.74 | 7.99 | 12.85/2.23 | 70 (*P*) |
| Scheme 9 | - | B | **8** | 11.43 | 12.87 | 87.13/12.87 | 74 (*P*) |
| 8 | 1 | C | **8** | 15.66 | 19.26 | 6.24/32.79 | 68 (*M*) |
| 8 | 1 | C | **463** | 10.13 | 11.99 | 28.99/15.55 | 30 (*P*) |
| 8 | 1 | C | **466** | 8.07 | 8.39 | 15.23/1.19 | 86 (*P*) |
| 8 | 2 | C | **8** | 17.18 | 21.82 | 18.29/42.28 | 40 (*M*) |
| 8 | 2 | C | **463** | 10.55 | 12.83 | 25.6/8.13 | 51 (*P*) |
| 8 | 2 | C | **466** | 8.24 | 8.59 | 5.23/0.47 | 84 (*P*) |
| 8 | 3 | C | **8** | 16.27 | 20.9 | 37.75/48.02 | 12 (*M*) |
| 8 | 3 | C | **463** | 10.28 | 12.33 | 10.57/3.23 | 53 (*P*) |
| 8 | 3 | C | **466** | 8.08 | - | 0.43 | > 90 (*P*) |
| 8 | 4 | C | **8** | 16.91 | 20.61 | 16.07/39/90 | 43 (*M*) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | 4 | C | **463** | 10.66 | 12.90 | 25.48/9.91 | 44 (*P*) |
| 8 | 4 | C | **466** | 8.29 | 8.72 | 8.12/0.52 | 86 (*P*) |
| Scheme 12 | - | B | **8** | 10.89 | 12.50 | 44.55/55.45 | 10 (*M*) |
| Scheme 12 | - | B | **460** | 15.63 | 18.10 | 63.63/33.37 | 30 (*P*) |
| Scheme 12 | - | D | **468** | 27.12 | 32.17 | 86.57/13.42 | 86 (*P*) |
| 9 | 1 | C | **8** | 15.33 | 17.67 | 23.24/43.50 | 30 (*M*) |
| 9 | 1 | C | **463** | 10.20 | 11.71 | 23.09/7.0 | 53 (*P*) |
| 9 | 1 | C | **466** | 8.20 | 8.44 | 2.81/0.28 | 82 (*P*) |
| 9 | 2 | C | **8** | 15.77 | 18.31 | 36.44/36.94 | 1 (*M*) |
| 9 | 2 | C | **463** | 10.37 | 11.96 | 10.56/12.58 | 9 (*M*) |
| 9 | 2 | C | **466** | 8.29 | 8.62 | 1.84/1.62 | 6 (*P*) |
| 9 | 3 | C | **8** | 15.01 | 17.34 | 9.80/8.17 | 10 (*P*) |
| 9 | 3 | C | **463** | 10.04 | 11.44 | 23.67/27.42 | 8 (*M*) |
| 9 | 3 | C | **466** | 8.11 | 8.40 | 15.32/15.60 | 1 (*M*) |
| 9 | 4 | C | **8** | 13.72 | 15.7 | 8.68/7.79 | 5 (*P*) |
| 9 | 4 | C | **463** | 9.59 | 10.69 | 29.86/32.74 | 5 (*M*) |
| 9 | 4 | C | **466** | 7.93 | 8.13 | 9.62/11.09 | 10 (*M*) |
| Figure 5 | - | C | **8** | 16.97 | 21.33 | 39.43/39.54 | *rac* |
| Figure 5 | - | C | **463** | 10.65 | 12.92 | 10.65/9.56 | 5 (*P*) |
| Figure 5 | - | C | **466** | 8.33 | 8.82 | 0.44/0.41 | *rac* |
| 10 | 1 | C | **466** | 8.20 | 8.58 | 12.93/0.39 | 93 (*P*) |
| 10 | 2 | C | **8** | 12.90 | 15.63 | 12.17/57.17 | 64 (*M*) |
| 10 | 2 | C | **8** | 18.23 | 22.32 | 1.44/78.36 | 93 (*M*) |
| 10 | 2 | C | **466** | 8.59 | - | 3.99 | > 90 (*P*) |
| 10 | 3 | C | **8** | 17.15 | 21.04 | 10.79/89.21 | 78 (*M*) |
| 10 | 3 | B | **460** | 13.93 | 16.14 | 5.95/94/05 | 88 (*M*) |
| 10 | 4 | B | **8** | 10.66 | 12.71 | 11.5/88.5 | 77 (*M*) |
| 10 | 4 | B | **8** | 11.05 | 12.98 | 8.13/91.87 | 84 (*M*) |
| 10 | 5 | B | **8** | 11.74 | 14.09 | 13.13/86.87 | 74 (*M*) |
| 10 | 5 | C | **8** | 14.48 | 17.25 | 4.67/77.20 | 88 (*P*) |
| 10 | 6 | C | **463** | 9.53 | 11.08 | 83.61/16.39 | 67 (*P*) |
| 10 | 6 | C | **466** | 7.94 | 8.29 | 10.05/0.87 | 84 (*P*) |
| 10 | 7 | B | **8** | 11.34 | 13.23 | 87.67/12.32 | 74 (*P*) |
| 10 | 7 | B | **460** | 14.38 | 16.82 | 96.11/3.89 | 92 (*P*) |
| 10 | 8 | B | **8** | 11.03 | 12.90 | 71.11/28.89 | 43 (*P*) |
| 10 | 8 | C | **463** | 9.70 | 10.72 | 39.99/5.53 | 76 (*P*) |
| 10 | 8 | C | **466** | 8.23 | - | 15.13 | > 90 (*P*) |
| Scheme 16 | - | C | **8** | 12.90 | 15.63 | 12.17/57.17 | 64 (*M*) |
| Scheme 16 | | C | **463** | 9.40 | 10.39 | 23.18/3.46 | 74 (*P*) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Scheme 16 | - | C | **466** | 7.96 | - | 4.00 | > 90 (*P*) |
| Scheme 16 | | C | **8** | 18.23 | 22.32 | 1.44/78.36 | 93 (*M*) |
| Scheme 16 | - | C | **463** | 11.21 | 13.81 | 11.44/4.76 | 43 (*P*) |
| Scheme 16 | | C | **466** | 8.59 | - | 3.99 | > 90 (*P*) |
| Scheme 17 | - | B | **8** | 10.73 | 12.77 | 63.61/36.39 | 27 (*P*) |
| Scheme 17 | - | B | **460** | 14.47 | 17.02 | 36.68/61.31 | 25 (*M*) |
| Scheme 17 | - | D | **468** | 25.70 | 30.69 | 16.20/83.80 | 68 (*M*) |

# Appendix B: NMR spectra for unknown structure.

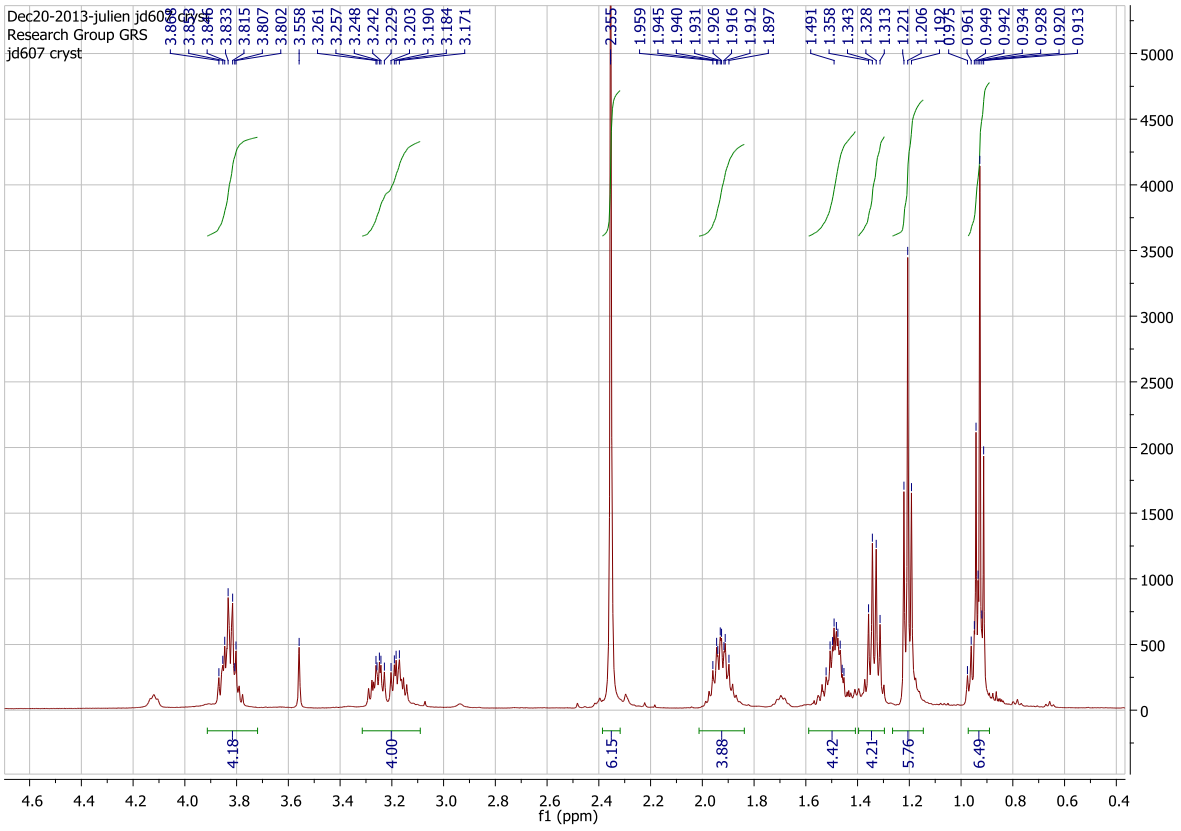
Structure of the non-degraded compound **476**

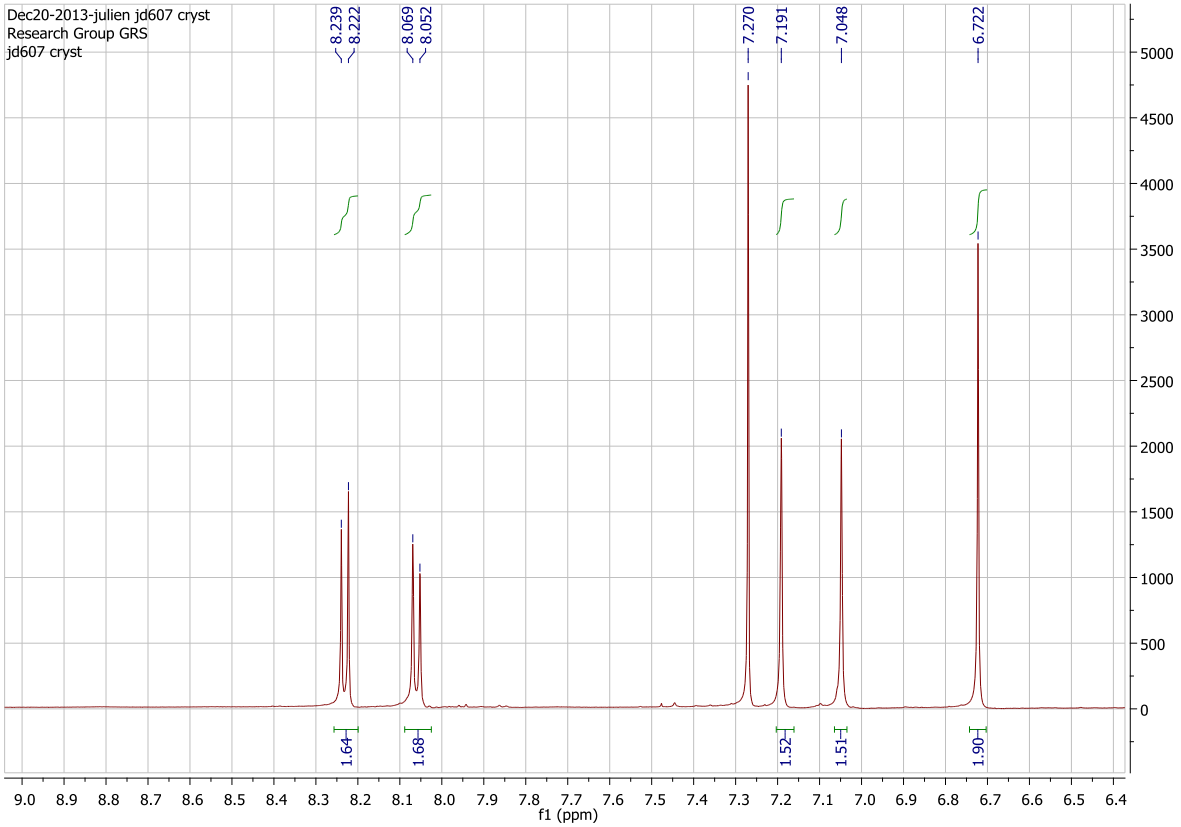



Chemical Formula: $C_{52}H_{46}N_4O_4S_4$

Molecular Weight: 919.2060

**Mp.:** 246-248 °C (for the degraded compound)

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Research Group GRS
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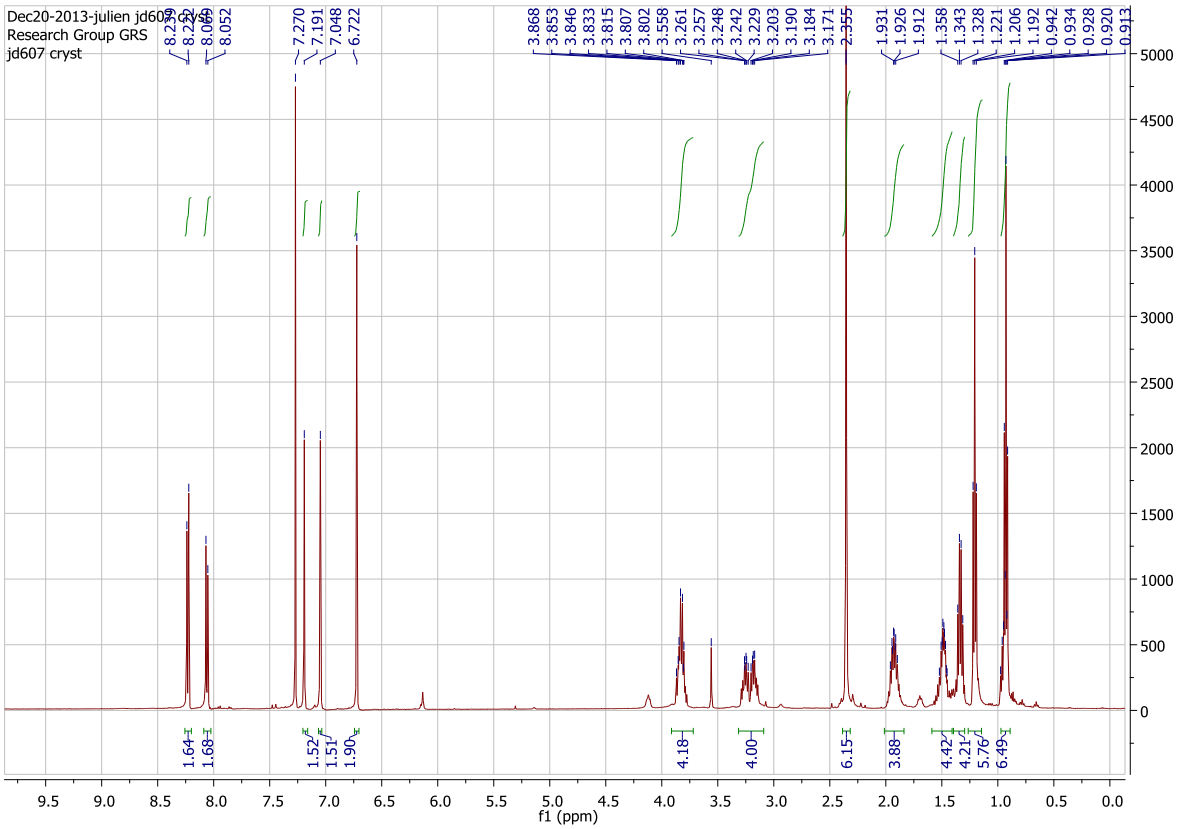
1.52
1.51
1.90
f1 (ppm)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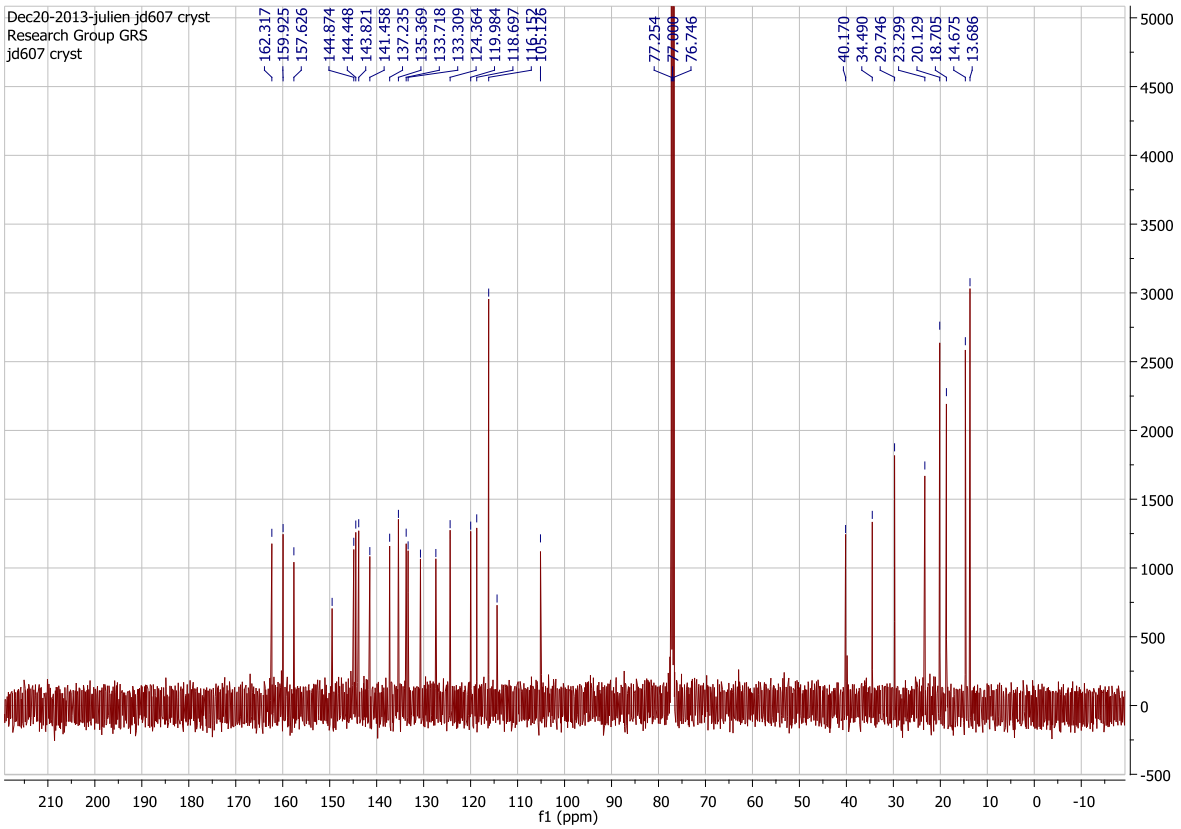
Research Group GRS
jd607 cryst
f1 (ppm)


Dec20-2013-julien jd607 cryst
Research Group GRS
jd607 cryst
162.317
159.925
157.626
144.874
144.448
143.821
141.458
137.235
135.369
133.718
133.309
124.364
119.984
118.697
116.152
105.126
77.254
77.000
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40.170
34.490
29.746
23.299
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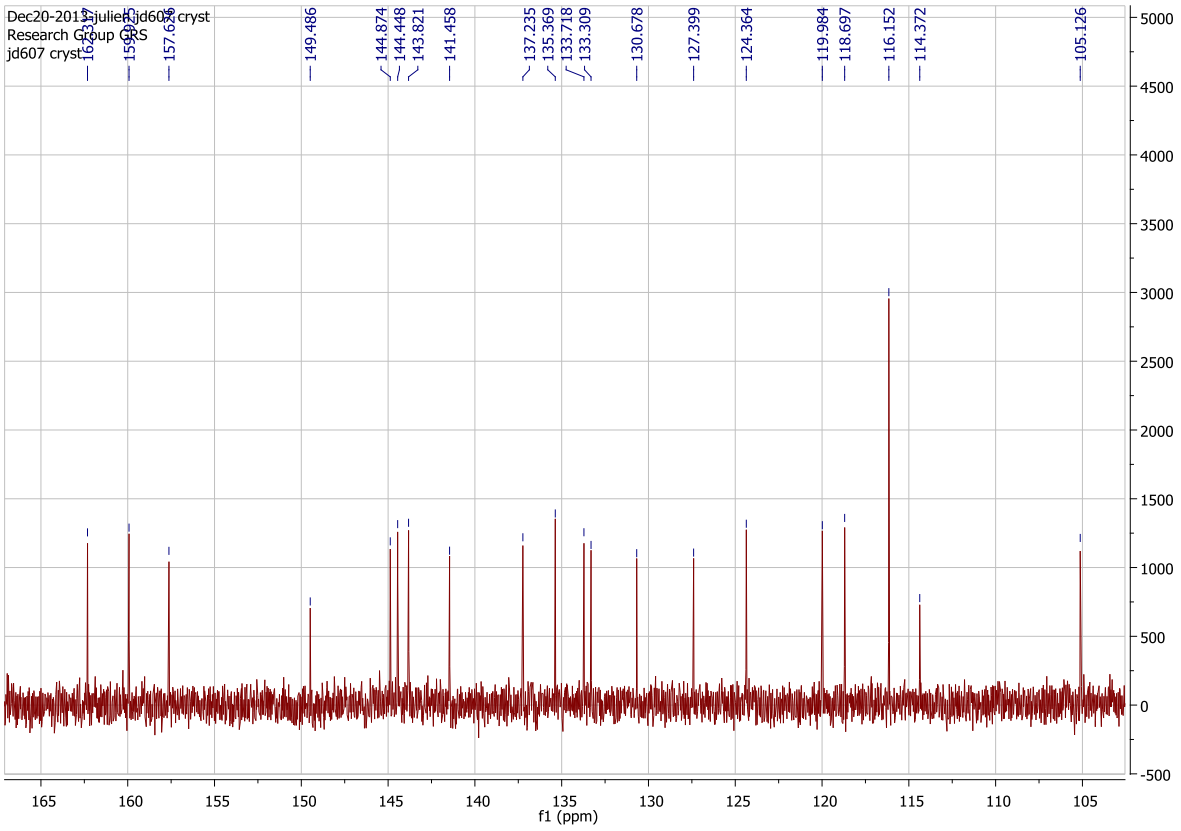
18.705
14.675
13.686
f1 (ppm)


Dec20-2013-julien jd607 cryst
Research Group GRS
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141.458
137.235
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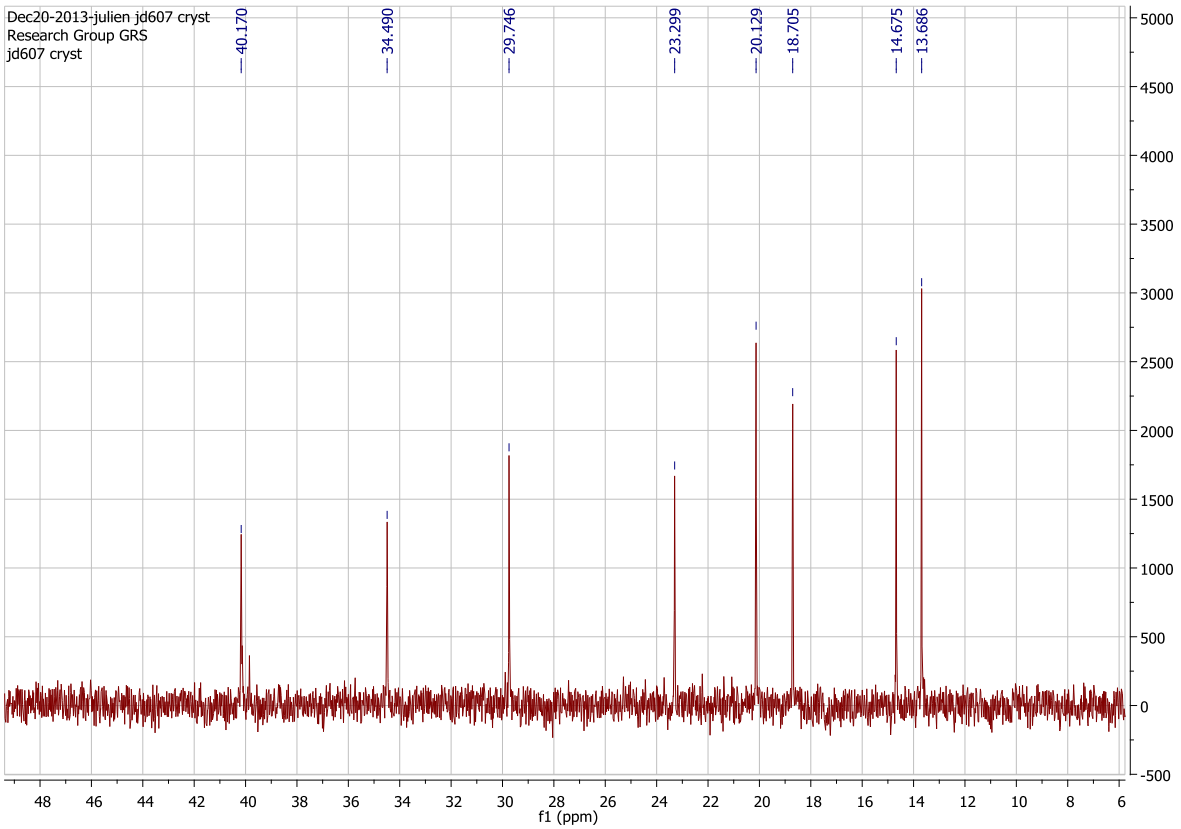
114.372
105.126
f1 (ppm)


Dec20-2013-julien jd607 cryst
Research Group GRS
jd607 cryst
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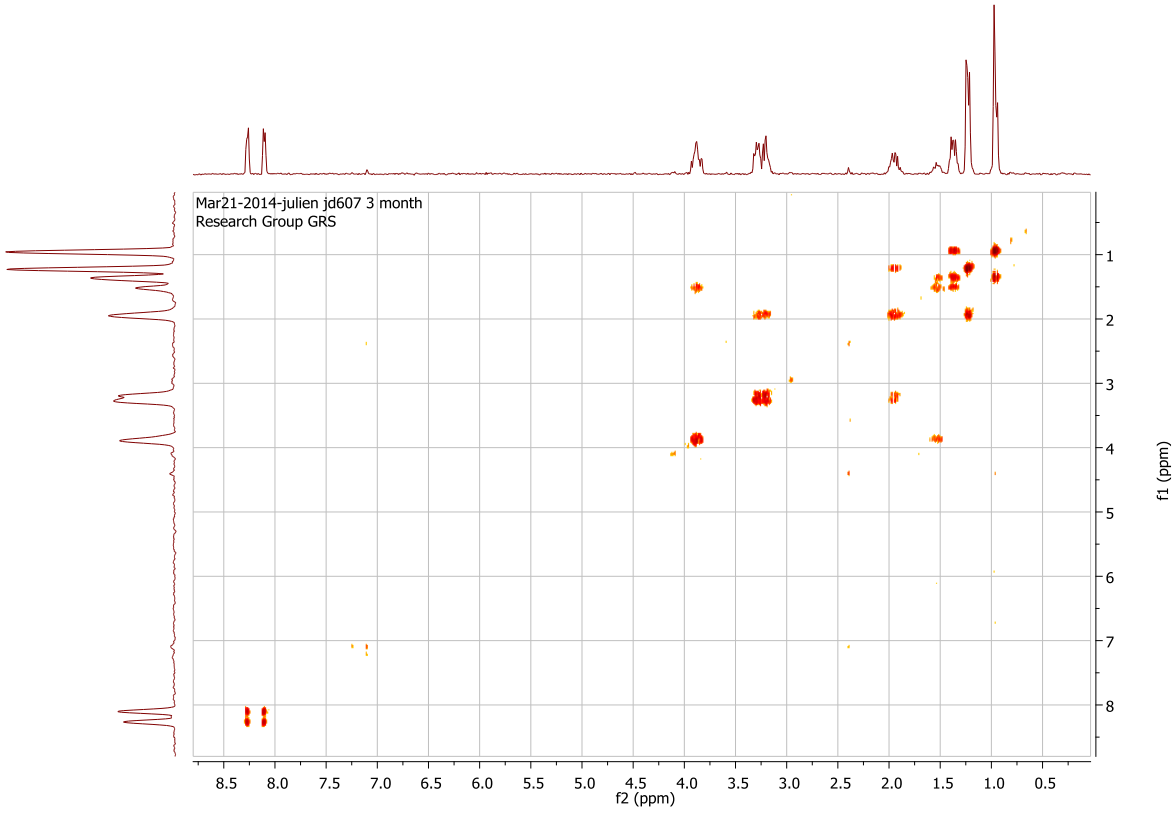
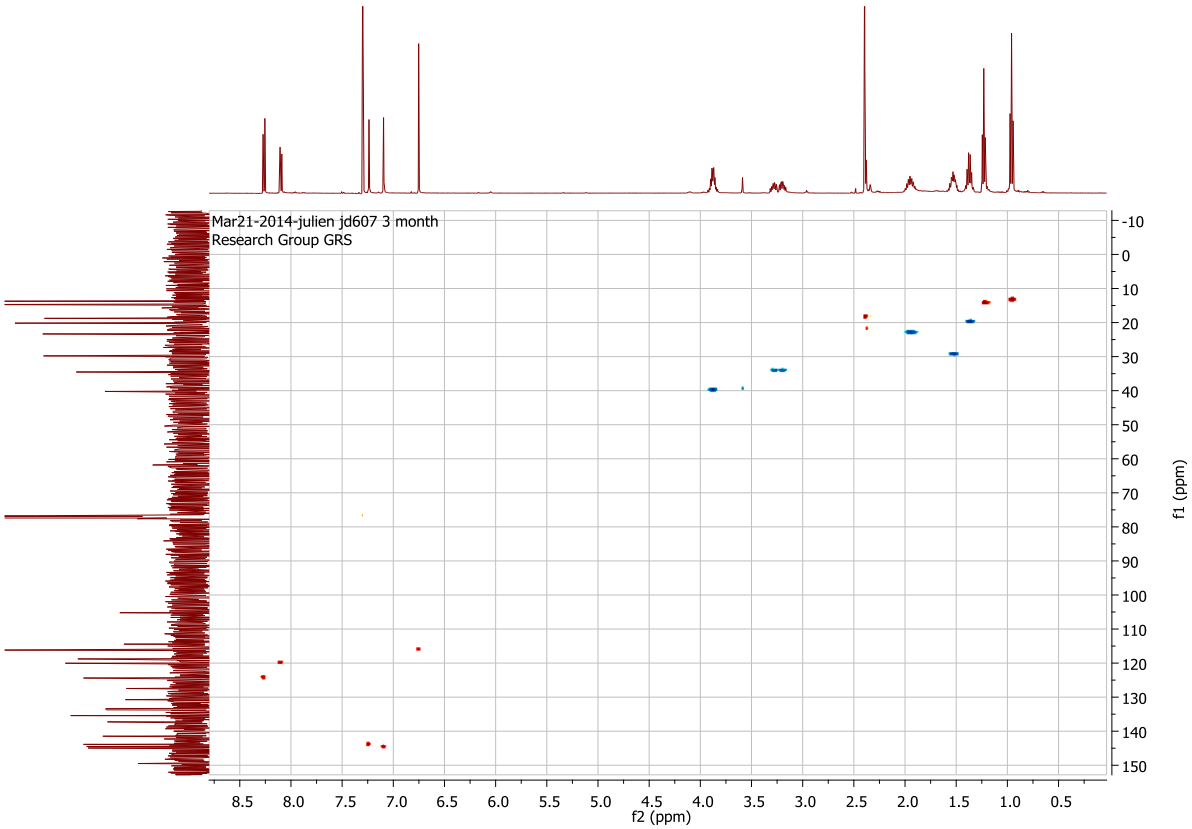
34.490
29.746
23.299
20.129
18.705
14.675
13.686
f1 (ppm)


Mar21-2014-julien jd607 3 month
Research Group GRS
f2 (ppm)
f1 (ppm)

Appendix B: NMR spectra for unknown structure



# Appendix C:

# Comparison of Ullmann/RCM and Ullmann/Bis-hydrazone Coupling Reactions; New Access to Benzodithiophenes for Dye-Sensitized Solar Cell and Thiahelicene Applications

# Comparison of Ullmann/RCM and Ullmann/Bis-hydrazone Coupling Reactions; New Access to Benzodithiophenes for Dye-Sensitized Solar Cell and Thiahelicene Applications

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**Abstract:** The use of CuTC (Liebeskind's catalyst), followed by methylenation and ring-closing metathesis, or bis-hydrazone coupling reactions is described. This approach establishes an alternative non-photochemical synthesis of the strategically important 1,2-*b*:4,3-*b*′ BDT regioisomer, which has previously been underused in applications such as dye-sensitized solar cells and nonlinear optics because of the difficulty of synthesis on a large scale.

**Key words:** benzodithiophene, Liebeskind's catalyst, bis-hydrazone coupling, alkene metathesis, non-photochemical synthesis

The combination of thiophenes and benzene rings in high-performance chromophores has proved to be a powerful strategy[1] because of the lower aromatic resonance energy of thiophene compared to benzene.[2] Linear and fused-ring structures, of which the simplest (examples are shown in Figure 1) are benzothiophenes (BTs), benzodithiophenes (BDTs, e.g. **1**,**2**,**3**) and benzothienobenzothiophenes (BTBTs, e.g. **4**). These have found significant commercial applications in organic field-effect transistors[3] (OFETs), organic light-emitting diodes[4] (OLEDs) and solar cells.[5] In practice, isomers **2** and **3** are by far the most widely studied, and are of growing importance,[6] however, recent papers describing applications in dye-sensitized solar cells (DSCs) point out that the symmetrical isomer **1** is underused.[7] For our own interests in tetrathia[7]helicenes as components in nonlinear optics [8,9] and in novel chelating diphosphine ligands,[10] regioisomer **1** is a well-established key intermediate which, of the available BTDs, has a unique role because its extension (by incorporating additional fused rings) is ideal for helix formation.[11] The most efficient access[12] to tetrathia[7]helicenes employs a photochemical electrocyclic reaction of **5** combined with oxidative rearomatisation as the final step. Currently, this type of photochemical cyclisation is also used for the preparation of regioisomer **1**, but this approach is slow and inconvenient in the unsubstituted series because the *Z*-isomer of the alkene is required for photocyclisation. In most cases, applications have involved substituted examples, which are easier to prepare.[13]

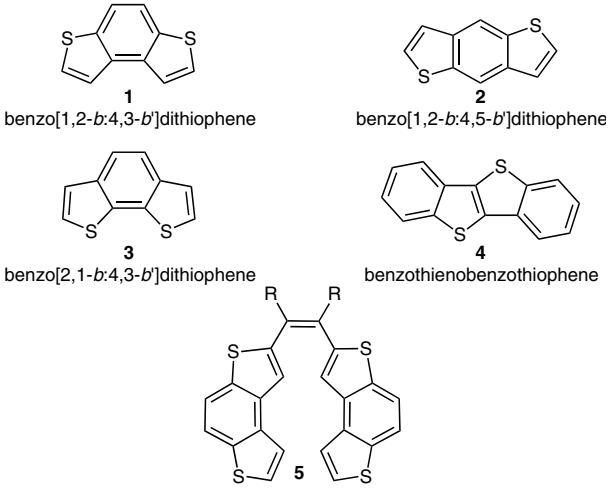


**Figure 1** Structures of thiophene-based cores of high-performance chromophores **1**–**4** and the tetrathia[7]helicene precursor **5**

We describe here chemical syntheses[14] of benzo[1,2-*b*:4,3-*b*′]dithiophenes that will not only make **1** more easily available for tetrathia[7]helicene synthesis, but will also open up opportunities for more rapid development for commercial applications, where previous reliance on photochemical steps cause complications in production chemistry that has held back evaluation of the 1,2-*b*:4,3-*b*′ isomer series.

Development of the two strategies shown in Scheme 1 both required diformyl bithiophene **12a** (Scheme 2), which we approached by using the Liebeskind modification[15] of Ullmann coupling or the mild copper(I) iodide triethylphosphite method of Ziegler.[16] The standard dimerisation method involving (2-formyl-3-thienyl)boronic acid gave the product in only 18% yield[17] and required three steps from 3-bromo-2-formylthiophene (**9**). From **12a**, formation of the bis-hydrazone[18] or dimethylenation should give easy access to precursors for the cyclisation step. The novel intermediate 2,2′-divinyl-3,3′-bithiophene (**6**) was also expected to be important for the formation of BDT by alkene metathesis, which should be an efficient strategy because the corresponding metathesis reaction of 2,2′-divinylbiphenyl to form phenanthrene is known to work well.[19]

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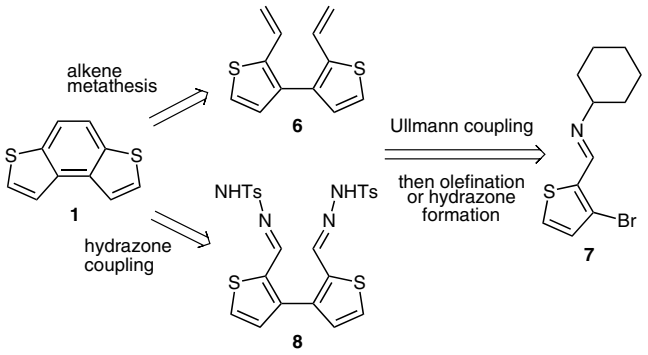
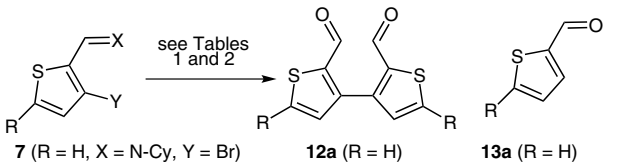
Advanced online publication: 05.02.2014
DOI: 10.1055/s-0033-1340667; Art ID: ST-2013-D0987-L




**Scheme 1** Strategies for the non-photochemical preparation of benzo[1,2-*b*:4,3-*b*′]dithiophene **1**




**7** (R = H, X = N-Cy, Y = Br)
**9** (R = H, X = O, Y = Br)
**10** (R = $SiMe_3$, X = N-Cy, Y = I)
**11** (R = $SiMe_3$, X = O, Y = I)

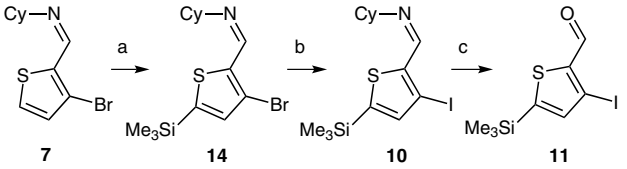
**12a** (R = H)
**12b** (R = $SiMe_3$)

**13a** (R = H)
**13b** (R = $SiMe_3$)

**Scheme 2** Ullmann coupling of 3-bromo- and 3-iodothiophenes

To gain access to the bis-formyl derivatives **12**, we explored coupling chemistry using compounds **7**, **9**, **10**, and **11** (Scheme 2). The *N*-formylpiperidine method could be used to convert 3-bromothiophene into **9**, improving the yield from 72–86%[20] to 97%, which is also an improved yield over more common alternatives that use DMF[21] or *N*-formyl-*N*-methylaniline,[22] or the Vilsmeier–Haack process.[23] The required imine **7** was easily made in quantitative yield by heating **9** to reflux in toluene with cyclohexylamine using a Dean–Stark trap.[24]

Our first attempt at the Ullmann coupling (Scheme 2) of cyclohexylimine **7** with Liebeskind catalyst in *N*-methyl-2-pyrrolidinone (NMP) at room temperature[25] gave a disappointing 25% yield (Table 1, entry 2). To prepare the more reactive 3-iodothiophene analogue (Scheme 3), we first protected the 5-position of **7** with a trimethylsilyl group to give **14**[26] through selective C-5 lithiation, which proceeded in the presence of the 3-bromo substituent by using LDA.[27] This was followed by bromine–lithium exchange and quenching with $I_2$ to form **10**.[28] Unfortunately, the Ullmann coupling was not significantly improved by using iodoimine derivative **10**, and the required product was obtained in only 29% yield (Table 1, entry 3). The silyl-protected aldehyde intermediate **11** was also examined in the Ullmann step (14% yield; Table 1, entry 5). This was compared with the Ziegler method,[16] which was found to perform similarly (15% yield; Table 1, entry 4) with our substrate.[29] The direct palladium-catalyzed coupling[30] of the 3-bromo-2-formylthiophene starting material **9** was also investigated because it would save a step, and this gave the required product in 35% yield (Table 1, entry 1).[31]




**7** **14** **10** **11**

**Scheme 3** Preparation of iodothiophenes **10** and **11**. *Reagents and conditions*: (a) LDA, $Me_3SiCl$, THF, $N_2$, 99%; (b) *n*-BuLi, $I_2$, THF, $N_2$, 90%; (c) AcOH, $CH_2Cl_2$, $H_2O$, 88%.

The problem of low yields was initially addressed by using a microwave reactor[32] (using **7** and **10**), and it soon became apparent that careful purification of the CuTC was crucial for obtaining good results (Table 2). Further examination of reaction conditions to control competing dehalogenation allowed **12a** to be obtained in a satisfactory 67% isolated yield (Table 2, entry 8). On a large scale, however, we found that simply heating **7** at 90 °C for 17 hours gave **12a** in 68% isolated yield (e.g., Table 2, entry 9).

The BDT synthesis was completed by a simple Wittig reaction to produce 2,2′-divinyl-3,3′-bithiophene (**6**),[33] followed by a ring-closing metathesis (RCM) step. For the RCM step, we chose to use Iuliano conditions[19] with the 1st generation Grubbs catalyst [$Ru(Pcy_3)_2(CHPh)Cl_2$], which has been reported[19a] to give 100% yield in the preparation of phenanthrene in the case of divinylbiphenyl. Gratifyingly, this does indeed appear to be a very efficient and general RCM method, and in our case we achieved 90% yield of **1** at 5 mol% catalyst loading, which was im-

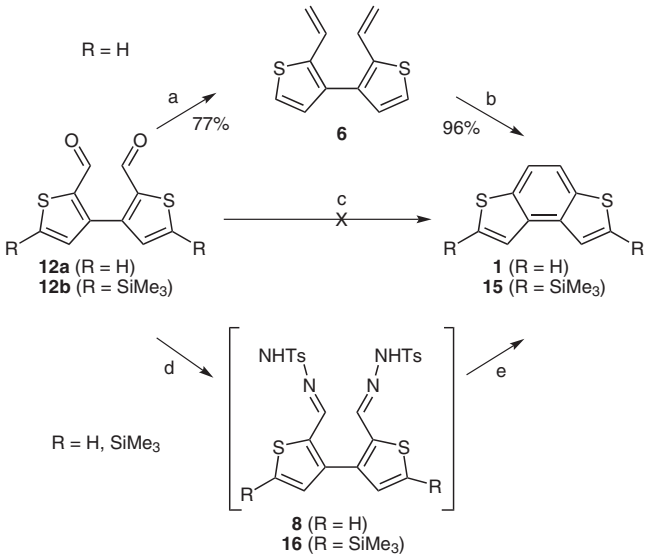
**Table 1** Coupling Reactions to 2,2′-Diformyl-3,3′-bithiophenes **12a** and **12b**

| Entry | Substrate | Catalyst (equiv) | Solvent | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **9** | Cu (10) / $Pd(PPh_3)_4$ (0.1) | DMSO | 100 | 15 | 35[a] |
| 2 | **7** | CuTC (2.2) | NMP | r.t. | 60 | 25[b] |
| 3 | **10** | CuTC (3.0) | NMP | r.t. | 60 | 29[b] |
| 4 | **10** | CuI-$P(OEt)_3$ (1.5) | THF | –78 to r.t. | 60 | 15[b] |
| 5 | **11** | CuTC (3.0) | NMP | r.t. | 60 | 14[b] |

[a] Isolated yield.
[b] Based on NMR analysis of the crude bis-aldehyde **12a** or **12b**.

proved to 96% yield by using 10 mol% catalyst (Scheme 4).[34]




**Scheme 4** Cyclisation reactions to form benzo[1,2-*b*:4,3-*b*′]dithiophenes. *Reagents and conditions*: (a) *n*-BuLi, $MePPh_3Br$, THF, $N_2$, 77%; (b) $CH_2Cl_2$, $[Ru(Pcy_3)_2(CHPh)Cl_2]$ (0.1 equiv), r.t., 8 h, Ar, 96%; (c) $TiCl_3(DME)_{1.5}$/Zn(Cu), DME, 5%; (d) tosylhydrazide (2 equiv), THF, **8**: 100%, **16**: 100%; (e) **8**, NaH, $N_2$, THF, 37% or **16**, *n*-BuLi, $N_2$, THF, 32%.

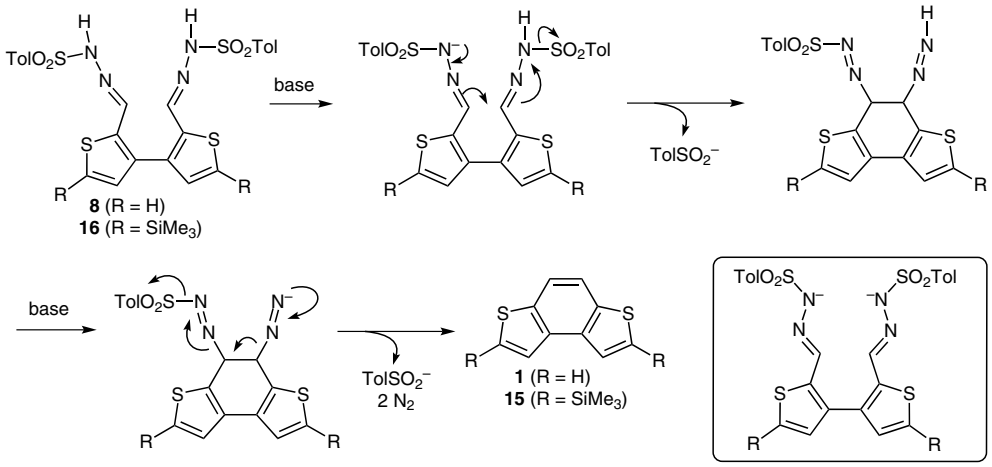
We also examined the formation of a bis-tosylhydrazone in the double condensation reaction of 2,2′-diformyl-3,3′-bithiophene (**12a**).[35] This alternative[18] to the McMurry coupling[36] of aldehydes gives direct access to the benzo[1,2-*b*:4,3-*b*′]dithiophene ring system in 32–37% yield and was successful both for **1** itself[37] and the 2,7-di(trimethylsilyl)-protected derivative **15**,[38] which was obtained from **16** by bis-hydrazone coupling of **12b**.[39] The conditions used to form **1** resemble those for the Bamford–Stevens reaction,[40] but the use of *n*-butyllithium in the preparation of **11** is more typical of a Shapiro reaction.[41] Both the Bamford–Stevens and Shapiro procedures employ arylsulfonylhydrazones and are generally considered to begin by deprotonation of the NH-$SO_2Ar$,[42] and exploit the chemistry of arylsulfinate ($ArSO_2^-$) leaving groups, and the elimination of $N_2$ to provide a powerful driving force. Under aprotic conditions the Bamford–Stevens reaction is believed to proceed by formation of a carbene,[43,44] but with the bis-hydrazones shown in Scheme 4 it seems probable that the initial anion[45] cyclises as shown in Scheme 5 by intramolecular nucleophile addition to the hydrazone and elimination of an arylsulfinate.[46] Subsequent loss of two molecules of $N_2$ and the second arylsulfinate completes the benzo[1,2-*b*:4,3-*b*′]dithiophene ring. The bis-hydrazone coupling reaction is useful, but requires further optimisation, perhaps by the use of more modern bases[47] which have become popular in the Shapiro reaction.

Finally, because the highest yielding route to BDT **1** was achieved by the application of the RCM reaction, we considered the possibility of coupling of 3-bromo-2-vinylthiophene to make 2,2′-divinyl-3,3′-bithiophene (**6**) more directly from **9** in just two steps. Wittig methylenation of **9**, however, proceeded in only 30% yield. It is possible that the ease of dimerisation and polymerisation of the reactive vinyl group in 3-bromo-2-vinylthiophene limits the efficiency of this reaction. Thus, Ullmann coupling prior to Wittig methylenation is the better approach.

**Table 2** Control of Dehalogenation in the Coupling of Halothiophenes

| Entry | Substrate | Conditions | Yield (%) | |
|---|---|---|---|---|
| | | | **12** | **13** |
| 1 | **10** | r.t., 48 h, CuTC (3.5 equiv) | **12b** (20[a]) | **13b** (23[a,c]) |
| 2 | **10** | 60 °C, 60 h, CuTC (3 equiv), $N_2$ | **12b** (29[a]) | **13b** (60[a,c]) |
| 3 | **10** | r.t., 60 h, CuTC (3 equiv), $N_2$ | **12b** (43[b]) | **13b** (37[b]) |
| 4 | **10** | 60 °C, MW, 20 min, CuTC (3 equiv), $N_2$ | **12b** (48[b]) | **13b** (26[b]) |
| 5 | **10** | 90 °C, MW, 15 min, CuTC (3 equiv), Ar | **12b** (51[b]) | **13b** (33[b]) |
| 6 | **10** | 60 °C, MW, 30 min, CuTC (3 equiv), $N_2$ | **12b** (55[b]) | **13b** (21[b]) |
| 7 | **7** | 90 °C, MW, 15 min, CuTC (2.2 equiv), Ar | **12a** (62[b,d]) | **13a** (19[a,b]) |
| 8 | **7** | 90 °C, MW, 25 min, CuTC (2.2 equiv), Ar | **12a** (67[b,e]) | **13a** (17[b]) |
| 9 | **7** | 90 °C, 17 h, CuTC (2.2 equiv), Ar | **12a** (68[f]) | – |

[a] Based on NMR analysis of crude bis-aldehyde.
[b] Based on NMR analysis of crude bis-imine.
[c] Catalyst not pure.
[d] 52% isolated yield.
[e] 55% isolated yield.
[f] Isolated yield.




**Scheme 5** Possible mechanism for the bis-hydrazone cyclisation. The monoanion formed by the first deprotonation step will be in equilibrium with the dianion (see box) when one equivalent of base is used,[38] but with an excess of base[37] the dianion is likely to be formed before loss of the first *p*-toluenesulfinate.[45]

In conclusion, we have shown that benzo[1,2-*b*:4,3-*b*′]dithiophene (**1**) is accessible in 50% overall yield in four steps from 3-bromo-2-formylthiophene by Ullmann coupling of the cyclohexylimine, methylenation, and ring-closing metathesis in a simple reaction sequence that avoids the use of photochemical conditions. The less costly alternative, bis-hydrazone route was found to be less effective than the metathesis route.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) **Preparation of *N*-[(3-Bromothiophen-2-yl)methylene]cyclohexylimine (7)**: In a 1-L three-necked round-bottom flask, equipped with a Dean–Stark trap, a solution of 3-bromo-2-formylthiophene **9** (84.15 g, 0.44 mol, 1 equiv) and cyclohexylamine (54.6 g, 0.55 mol, 1.25 equiv) in toluene (700 mL) was heated at reflux under nitrogen for 16 h. The solution was then evaporated to afford an orange oil (120 g, 100%) which was used directly in the next step. IR (ATR): 3075, 2925, 2851, 1623 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ = 8.44 (s, 1 H), 7.34 (dd, *J* = 5.3, 1.1 Hz, 1 H), 7.00 (d, *J* = 5.2 Hz, 1 H), 3.22 (m, 1 H), 1.51–1.85 (m, 7 H), 1.18–1.41 (m, 3 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 151.0, 136.5, 130.5, 128.4, 113.5, 69.8, 34.1, 25.5, 24.7. HRMS (GC, CI+): *m/z* $[M–H]^-$ calcd for $C_{11}H_{13}BrNS$: 269.9947; found: 269.9947.
(25) **General Procedure**: *N*-[(3-Bromothiophen-2-yl)methylene]cyclohexylimine (**7**; 1 equiv) was dissolved in anhydrous NMP under argon, CuTc (2.2 equiv) was added in several portions (to achieve good mixing), and the reaction mixture was stirred at 90 °C under argon for 17 h. After cooling, the mixture was filtered through a pad of kieselguhr, which was then washed with EtOAc until no more brown colour was released from the filter cake. The filtrate was washed with 15% aqueous ammonia, producing a clear deep-blue aqueous layer. The organic layer was separated and retained, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine to remove as much NMP as possible, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The brown oily residue was dissolved in $CH_2Cl_2$ and 15% aqueous AcOH was added and mixture was at stirred r.t. overnight. The organic layer was separated and retained, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, filtered through a $MgSO_4$/neutral alumina pad, and evaporated under reduced pressure to give a solution of crude product in NMP (despite the washing, the NMP was not removed completely). The

resultant brown oil was taken up in $H_2O$ and shaken until the product precipitated. The mixture was then filtered and the residue was washed with $H_2O$ and dissolved in $CH_2Cl_2$, dried over $MgSO_4$, filtered and evaporated. The solid residue was washed with a mixture of hexanes and EtOAc (8:1 v/v) and dried under vacuum to give [3,3′-bithiophene]-2,2′-dicarboxaldehyde **12a**; for yields, see Table 1 and Table 2.

(26) **Preparation of *N*-{[3-Bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine (14)**: A solution of *n*-BuLi (1.6 M in hexanes, 53 mL, 84.5 mmol, 1.15 equiv) was added dropwise to diisopropylamine (12 mL, 8.5 g, 84.5 mmol, 1.15 equiv) in anhydrous THF (600 mL) at 0 °C under nitrogen. After stirring for 45 min at 0 °C, *N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine (**7**; 20 g, 73.5 mmol, 1 equiv) in anhydrous THF (50 mL) was added dropwise over 10 min. After stirring for a further 45 min at 0 °C under nitrogen, the reaction mixture was cooled to –78 °C and trimethylsilyl chloride (10.7 mL, 9.2 g, 84.5 mmol, 1.15 equiv) was added dropwise. After stirring for 1 h at –78 °C, the reaction mixture was allowed to warm to r.t., sat. aq $NH_4Cl$ (700 mL) was added, and the organic layer was separated and retained. The aqueous layer was extracted with EtOAc (2 × 400 mL) and the combined organic layers were washed with brine (500 mL), filtered through a $MgSO_4$/basic alumina pad, and evaporated to give **14** (25.2 g, 99%) as an orange oil. IR (ATR): 2927, 2853, 1624 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ = 8.43 (s, 1 H), 7.10 (s, 1 H), 3.22 (m, 1 H), 1.22–1.87 (m, 10 H), 0.31 (s, 9 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 151.0, 144.4, 140.5, 136.5, 114.5, 70.0, 34.1, 25.5, 24.7, –0.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{23}BrNSSi$: 344.0498; found: 344.0503.

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(28) **Preparation of *N*-{[3-Iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine (10)**: A solution of *N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine (**14**; 6.94 g, 20.2 mmol, 1 equiv) in anhydrous THF (350 mL) was cooled to –78 °C, under nitrogen. *n*-BuLi (1.6 M in hexanes, 13.9 mL, 22.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 30 min at –78 °C and a solution of iodine (7.7 g, 30.3 mmol, 1.5 equiv) in anhydrous THF (25 mL) was added dropwise until the red iodine colour persisted. After 15 min at –78 °C, the reaction mixture was allowed to warm to r.t., $H_2O$ (350 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 250 mL). The combined organic layers were concentrated to 300 mL, washed with sat. aq sodium sulfite (2 × 300 mL), dried over $MgSO_4$, filtered, and evaporated to give **10** (7.12 g, 90%) as a brown oil, that crystallised upon standing. Mp 59 °C. IR (ATR): 2928, 2851, 1618 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ = 8.34 (s, 1 H), 7.20 (s, 1 H), 3.24 (br. m, 1 H), 1.85–1.57 (m, 7 H), 1.38–1.23 (m, 3 H), 0.31 (s, 9 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 153.2, 145.4, 143.7, 141.4, 85.1, 69.9, 34.2, 25.5, 24.7, –0.5. HRMS (ESI): *m/z* $[M–H]^-$ calcd for $C_{14}H_{21}NISSi$: 390.0203; found: 390.0203.

(29) **General Procedure**: A solution of *N*-{[3-bromo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine **14** (1 equiv) in anhydrous THF was cooled to –78 °C under nitrogen. *n*-BuLi (1.05 equiv) was added dropwise and the mixture was stirred at –78 °C for 30 min. Then CuI-$P(OEt)_3$ (1.5 equiv) was added in one portion and the mixture was stirred for a further 30 min at –78 °C before a solution of *N*-{[3-iodo-5-(trimethylsilyl)thiophen-2-yl]methylene}cyclohexylimine **10** in anhydrous THF was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred at r.t. for 60 h. The reaction was quenched with $H_2O$ and the reaction mixture was diluted with $CH_2Cl_2$, and 15% aqueous AcOH was added. The mixture was at stirred r.t. overnight, then the organic layer was separated and retained and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, filtered through a $MgSO_4$/neutral alumina pad and evaporated under reduced pressure. Crude material was purified by column chromatography (silica; hexanes–EtOAc, 100:0 to 2:1 v/v) to give 5,5′-bis(trimethylsilyl)-[3,3′-bithiophene]-2,2′-dicarbaldehyde (**12b**); for yields, see Table 1.

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(31) **Preparation of [3,3′-Bithiophene]-2,2′-dicarboxaldehyde (12a)**: Anhydrous DMSO (50 mL) was degassed under nitrogen for 30 min, then 3-bromo-2-formylthiophene (**9**; 1 equiv) was added and nitrogen gas was bubbled through the resulting solution for 10 min. $Pd(PPh_3)_4$ (0.1 equiv) and copper powder (3 equiv) were added and the solution was stirred and heated to 100 °C, under nitrogen for 15 h and then at 120 °C for 8 h. The progress of the reaction was monitored by TLC (hexanes–EtOAc, 3:1 v/v). The solution was cooled to r.t. before adding EtOAc (200 mL) and filtration through a pad of kieselghur. The filtrate was washed with $H_2O$ (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a brown oil that was purified by chromatography (silica; hexanes–EtOAc, 95:5 to 3:1 v/v) to afford **12a** (405 mg, 35%) as a yellow powder.

(32) **General Procedure**: A dried 20-mL microwave vial was flushed with argon. To a solution *N*-[(3-bromothiophen-2-yl)methylene]cyclohexylimine (**7**; 1 equiv) in NMP (15 mL), CuTC (2.2 equiv) was added with stirring. The microwave vial was then sealed, vacuum was applied, and then the vial was filled with argon. The reaction mixture was irradiated (see Table 2), then diluted with EtOAc and 15% aqueous ammonia was added to produce a clear deep-blue aqueous layer. The organic layer was separated and retained and the aqueous layer was extracted with EtOAc. The organic layers were combined and evaporated and the resultant crude product (green oil) was dissolved in $Et_2O$. This solution was washed with brine, dried over $MgSO_4$, filtered, and evaporated to leave a brown oil, which was dissolved in $CH_2Cl_2$ (50 mL), 15% aqueous AcOH (50 mL) was added and mixture was stirred overnight at r.t. The organic layer was separated and retained and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated (first under reduced pressure on a rotary evaporator and then under high vacuum using a vacuum line) to give a brown oil. The oil was purified by column chromatography (silica; hexanes–EtOAc, 100:0 to 2:1 v/v) to afford [3,3′-bithiophene]-2,2′-dicarbaldehyde **12a** as a yellow solid (for yields, see Table 2).

(33) **Preparation of 2,2′-Divinyl-3,3′-bithiophene (6)**: To a suspension of methyltriphenylphosphonium bromide (1.7 g, 4.75 mmol, 2.2 equiv) in distilled THF (50 mL), *n*-BuLi (1.6 M in hexanes, 2.96 mL, 4.75 mmol, 2.2 equiv) was added dropwise at –10 °C under nitrogen. The deep-orange solution was stirred at r.t. for 30 min, then a solution of [3,3′-bithiophene]-2,2′-dicarbaldehyde (**12a**; 460 mg, 2.16 mmol, 1 equiv) in distilled THF (10 mL) was added dropwise. The mixture was stirred at r.t. under nitrogen for 17 h, then the reaction was quenched with sat. aq $NH_4Cl$ (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The crude product was



 

purified by column chromatography (silica; hexanes), to afford **6** (350 mg, 77%) as a viscous oil. The product was kept in the freezer in the dark, and used as soon as possible. IR (ATR): 3103, 3066, 3005, 2957, 2925, 2869, 1800, 1616 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.19 (dd, *J* = 5.3, 0.8 Hz, 1 H), 6.94 (d, *J* = 5.3 Hz, 1 H), 6.66 (ddd, *J* =17.3, 11.0, 0.8 Hz, 1 H), 5.58 (d, *J* = 17.3 Hz, 1 H), 5.13 (d, *J* = 11.0 Hz, 1 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 139.1, 134.2, 130.1, 129.2, 123.1, 113.7. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{11}S_2$: 219.0299; found: 219.0297.

(34) **Preparation of Benzo[1,2-*b*:4,3-*b*′]dithiophene (1) by RCM**: Under argon, Grubbs' 1st generation catalyst $[Ru(Pcy_3)_2(CHPh)Cl_2]$ (30 mg, 0.1 equiv) was added to a solution of 2,2′-divinyl-3,3′-bithiophene (**6**; 80 mg, 0.36 mmol, 1 equiv) in anhydrous $CH_2Cl_2$ (25 mL). The reaction mixture was stirred at r.t. for 8 h, then the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica; hexanes), to afford **1** (67 mg, 96%).

(35) **Preparation of *N*′,*N*″-{[3,3′-Bithiophene]-2,2′-diylbis(methanylylidene)}bis(4-methylbenzenesulfonylhydrazone) (8)**: [3,3′-Bithiophene]-2,2′-dicarbaldehyde **12a** (1.05 g, 4.7 mmol, 1 equiv) and tosylhydrazide (1.75 g, 9.4 mmol, 2 equiv) were dissolved in distilled THF (300 mL) and stirred at r.t. overnight. The reaction mixture was dried over $MgSO_4$, filtered and evaporated to give **8** (2.62 g, 100%) as a bright-yellow-orange solid foam. Mp 129 °C. IR (ATR): 3176, 2958, 2923, 2867, 1645, 1594 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.33 (s, 2 H), 7.77 (d, *J* = 0.9 Hz, 2 H), 7.69 (dd, *J* = 5.1, 0.7 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 4 H), 7.40 (dd, *J* = 8.1, 0.6 Hz, 4 H), 7.03 (d, *J* = 5.1 Hz, 2 H), 2.36 (s, 6 H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 143.7, 140.7, 136.4, 136.0, 134.7, 130.3, 129.8, 128.7, 127.2, 21.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{23}N_4O_4S_4$: 559.0597; found: 559.0587.

(36) The intramolecular McMurry cyclisation of **12a** was unsuccessful under a variety of conditions [e.g., $TiCl_4$/Zn and $TiCl_3(DME)_{1.5}$/Zn(Cu)], despite its use as an intermolecular coupling reaction to obtain the 1,2-dithiophenylethene starting material for the photochemical route. For typical reaction conditions, see: (a) Yoshida, S.; Fujii, M.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Org. Chem.* **1994**, *59*, 3077. (b) See also ref. 15c.

(37) **Preparation of Benzo[1,2-*b*:4,3-*b*′]dithiophene (1) by Bis-hydrazone Coupling**: [3,3′-Bithiophene]-2,2′-dicarbaldehyde (**12a**; 4 g, 18 mmol, 1 equiv) and tosylhydrazide (6.59 g, 36 mmol, 2 equiv) were dissolved in distilled THF (850 mL), and the mixture was stirred at r.t. overnight, dried over $Na_2SO_4$, and transferred to a 1 L three-necked round-bottom flask that has been flame-dried under nitrogen. The reaction mixture was cooled to 0 °C and NaH (95%; 1.08 g, 45 mmol, 2.5 equiv) was added in portions. The reaction mixture was allowed to warm to r.t. and then heated at reflux for 3 h under nitrogen. After cooling, the solution was concentrated under reduced pressure to 100 mL, and sat. aq $NH_4Cl$ (300 mL) was added. The mixture was extracted with EtOAc (2 × 400 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to leave a brown solid (4 g). The crude product was purified by column chromatography (silica; hexanes) to afford **1** (1.21 g, 37%) as colourless crystals.

(38) **Preparation of 2,7-Bis(trimethylsilyl)benzo[1,2-*b*:4,3-*b*′]dithiophene (15) by Bis-hydrazone Coupling**: 5,5′-Bis(trimethylsilyl)-[3,3′-bithiophene]-2,2′-dicarbaldehyde (**12b**; 2.62 g, 7.15 mmol, 1 equiv) and tosylhydrazide (2.66 g, 15.30 mmol, 2 equiv) were dissolved in distilled THF (450 mL) and stirred at r.t. overnight. The THF solution was dried over $Na_2SO_4$, and transferred to a 500-mL three-necked round-bottom flask that had been flame-dried under nitrogen. The reaction mixture was cooled to –78 °C, *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol, 1.05 equiv) was added dropwise and the mixture was stirred for 5 min at –78 °C. The reaction mixture was allowed to warm to r.t., then heated at reflux for 5 h. After cooling, sat. aq $NH_4Cl$ (200 mL) was added and the mixture was extracted with EtOAc (200 mL). The organic layer was concentrated under reduced pressure to 100 mL, diluted with $Et_2O$ (200 mL), washed with brine (2 × 250 mL), dried over $MgSO_4$, filtered, and evaporated to leave a brown solid (5.1 g). Crude material was purified by column chromatography (silica; hexanes) to afford **15** (770 mg, 32%) as colourless crystals. Mp 128 °C. IR (ATR): 3053, 2985, 2959, 2897 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.88 (s, 2 H), 7.80 (s, 2 H), 0.44 (s, 18 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 142.3, 140.4, 135.9, 128.7, 118.4, –0.2. HRMS (ESI): *m*/*z* $[M]^+$ calcd. for $C_{16}H_{22}S_2Si_2$: 334.0696; found: 334.0696.

(39) **Preparation of *N*′,*N*″-{[5,5′-Bis(trimethylsilyl)-(3,3′-bithiophene)-2,2′-diyl]bis(methanylylidene)}bis(4-methylbenzenesulfonylhydrazone) (16)**: Using the method employed for the synthesis of **8** (see ref. 35) 5,5′-bis(trimethylsilyl)-(3,3′-bithiophene)-2,2′-dicarbaldehyde (**12b**; 2 g, 5.45 mmol, 1 equiv) and tosylhydrazide (2.03 g, 10.9 mmol, 2 equiv) were dissolved in distilled THF (250 mL) and the mixture was stirred at r.t. overnight, dried over $MgSO_4$, and evaporated to afford **16** (3.83 g, 100%) as a bright-yellow-orange solid foam. Mp 156 °C. IR (ATR): 3190, 3065, 2955, 2926, 2898, 2856, 1597 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ = 11.38 (s, 2 H), 7.74 (s, 2 H), 7.67 (d, *J* = 8.2 Hz, 4 H), 7.40 (dd, *J* = 8.2, 0.7 Hz, 4 H), 7.16 (s, 2 H), 2.36 (s, 6 H), 0.30 (s, 18 H). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ = 143.5, 142.5, 140.2, 139.2, 137.3, 137.0, 136.1, 129.7, 127.0, 21.0, –0.5. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{30}H_{39}N_4O_4S_4Si_2$: 703.1387; found: 703.1387.

(40) (a) Bamford, W. R.; Stevens, T. S. M. *J. Chem. Soc.* **1952**, 4735. (b) Chamberlain, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1.

(41) (a) Shapiro, R. H.; Duncan, J. H.; Clopton, J. C. *J. Am. Chem. Soc.* **1967**, *89*, 471. (b) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. (c) Aldington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(42) (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) Miranda, R.; Hernandez, A.; Angeles, E.; Cabrera, A.; Salmon, M.; Joseph-Nathan, P. *Analyst* **1990**, *115*, 1483.

(43) Chamberlin, A. R.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 154.

(44) Carbene intermediates have also been proposed for the Shapiro reaction, see ref. 41c.

(45) A referee has suggested that the dianion (see Scheme 5, box) is the intermediate in the cyclisation reaction, which is entirely reasonable, especially in the sodium hydride procedure (see ref. 37) in which the base was used in excess, but when 1.05 equiv butyllithium is employed (see ref. 38), the second deprotonation is probably effected by the toluenesulfinate anion in a reversible step that is driven, ultimately, by the irreversible loss of nitrogen, and the reaction then probably follows the mechanism drawn in Scheme 5.

(46) Jung tentatively proposes (see ref. 18a) that when the base is sodium hydride, both tosylhydrazones deprotonate and eliminate the tosylsulphinate, before ring closure occurs.

(47) Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. *Org. Lett.* **2012**, *14*, 2250.

# Appendix D:

## A non-photochemical route to synthesize simple benzo[1,2-b:4,3-b’]dithiophenes: $FeCl_3$-mediated cyclization of dithienyl ethenes

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# A non-photochemical route to synthesize simple benzo[1,2-*b*:4,3-*b*′]dithiophenes: $FeCl_3$-mediated cyclization of dithienyl ethenes†

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**The $FeCl_3$-mediated cyclization of α,α′-disubstituted *Z*-alkenes 1 is reported as a general and non-photochemical route to synthesize benzo[1,2-*b*:4,3-*b*′]dithiophene (BDT) derivatives 2, achievable in good yields starting from cheap and easily available materials. The influence of the temperature and the nature of the substituents on the scope and limitations of this methodology is also reported.**

Thiophene-containing fused, aromatic compounds represent an interesting class of π-conjugated systems in functional organic materials.[1] Among them, five isomeric tricyclic β-fused benzodithiophenes have stimulated a lot of interest thanks to their use as monomers or co-monomers for the synthesis of conductive materials used in electronic devices.[2] A role of increasing importance is going to be acquired by one of these isomers, namely benzo[1,2-*b*:4,3-*b*′]dithiophene (**BDT**) and its derivatives, which have been studied as repeating units of mono- and polydisperse oligomers in the field of materials science,[3] and, more recently, as π-spacers in push–pull organic chromophores for photovoltaic applications.[4] Moreover, **BDT** represents a key intermediate in the synthesis of inherently chiral helical systems such as tetrathia[7]helicenes (7-TH),[5] which are an extremely attractive class of conjugated molecules, with unique physicochemical properties provided by their helix-like structure.[6] On the basis of the above considerations, **BDT** can be identified as a key starting molecule that, through a judicious functionalization of the α-positions of the thiophene rings, can allow access to more complex and interesting systems.[3,4,7] Despite all these potential advantages, convenient synthetic methodologies to prepare **BDT** are still scarce,[8] and normally involve the oxidative photochemical cyclization of dithienyl ethenes as the key step.[9] However, this reaction requires specific photochemical equipment and highly dilute solutions, takes several hours, and, to a significant extent, can limit the scale-up of the synthesis of **BDT**.

Within this context, and in view of potential wider and industrial applications, a simple, reliable, reproducible and economic synthesis of **BDT** which avoids the use of photochemical pathways is highly desirable. In the course of our research projects in which we use **BDT** as a relevant precursor for the construction of both thiahelicenes[5a,b,10] and push–pull chromophores,[4b] we faced this synthetic problem and we focused our attention on the $FeCl_3$-mediated oxidative intramolecular cyclization of dithienyl ethenes *via* C–C bond formation between the β-positions of thiophene rings. In fact, iron(III) chloride is an economical and commercially available salt that has found widespread application as a Lewis acid[11] but also as a mild and selective oxidising agent, and is therefore particularly useful for C–C coupling reactions involving arenes and heteroarenes.[12] In this way, complex polycyclic aromatic compounds, containing the **BDT** framework as part of an *ortho*-condensed aromatic system, have been prepared.[13] In contrast, no synthesis of the simple tricyclic **BDT** scaffold has so far been reported using the $FeCl_3$ mediated oxidative coupling.

Herein, we report the first results of our investigations on the $FeCl_3$-mediated oxidative intramolecular cyclization of α,α′-disubstituted (*Z*)-dithienyl ethenes **1** to afford benzodithiophene derivatives **2**.[14] In this study we focused our attention on (*Z*)-dithienyl ethenes **1** bearing two *n*-propyl chains on the double bond, which improve the solubility of the **BDT** derivatives **2** in organic solvents.[4b] (*Z*)-Alkene **1a**, obtained as the major isomer from the corresponding *n*-propyl thienyl ketone by means of a McMurry coupling, was the starting compound for the synthesis of new α,α′-disubstituted (*Z*)-dithienyl ethenes **1b–f**, prepared according to Scheme 1. It is interesting to underline that, under the McMurry reaction conditions, we isolated **1a** as a 9 : 1 mixture of the *Z* and *E* isomers.[15] This is a fundamental stereochemical

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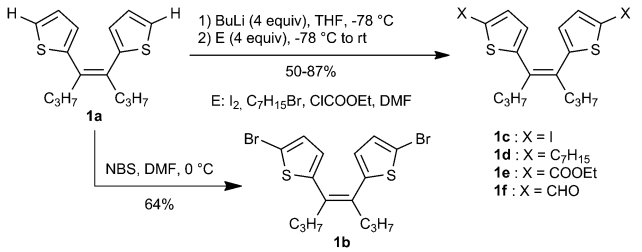
† Electronic supplementary information (ESI) available: Experimental details of **1a–f**, **2a–f**, **3** and **4**. Crystal data for **3**. CCDC 967135. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3nj01567j




Scheme 1 Synthesis of (*Z*)-dithienyl ethenes **1b–f**.

prerequisite for the further $FeCl_3$-mediated cyclization, which proceeds only with the *Z* isomer.[13b] Dibromo alkene **1b** was obtained in 64% yield by means of regioselective bromination of **1a** with NBS in DMF at 0 °C, whereas all of other α,α′-disubstituted (*Z*)-dithienyl ethenes **1c–f** were prepared in 50–87% yield, by deprotonation of the two alpha positions of the thiophene rings of **1a** with BuLi at −78 °C, followed by reaction with an appropriate electrophile (Scheme 1). The oxidative cyclization of **1a–f** was then investigated using $FeCl_3$ as an oxidant.

In order to assess the best conditions for the oxidative cyclization of **1a–f** to the corresponding **BDT** derivatives **2a–f**, preliminary screening has been performed to evaluate the influence of the amount of $FeCl_3$ on the cyclization of the α,α′-dibromo ethene **1b**, used as a model alkene, in $CH_2Cl_2$ at room temperature (Table 1).

In particular, the addition of a stoichiometric amount of $FeCl_3$ (2 equiv.)[16] to a solution of **1b** in $CH_2Cl_2$ at room temperature gave the expected product **2b** in 60% yield after 30 minutes (entry 1, Table 1). The use of twice the stoichiometric amount of $FeCl_3$ (4 equiv.) resulted in the formation of **2b** in higher yield (76%, entry 2, Table 1). This result is in accordance with the literature. In fact, even if the stoichiometric ratio of $FeCl_3$–alkene to perform the cyclization is 2 : 1, quite often the use of a higher ratio is necessary to obtain higher reaction yield.[13c,m,17] However, in our case, the use of a much larger excess of $FeCl_3$ (12 equiv.) did not result in an improvement of the reaction yield (72%, entry 3, Table 1). Moreover, an experiment performed with a catalytic amount of $FeCl_3$ (10 mol%) in combination with a stoichiometric amount of *m*-CPBA (1 equiv.)[18] as an oxidant resulted in a significant decrease of the yield, and compound **2b** was isolated in only

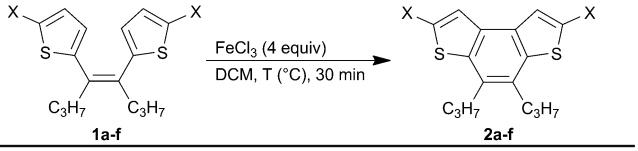
Table 1 $FeCl_3$-mediated cyclization of **1b**: the effect of the $FeCl_3$–**1b** ratio

**1b** —$FeCl_3$ (equiv), DCM, r. t., 30 min→ **2b**

| Entry[a] | $FeCl_3$ (equiv.) | Yield of **2b** (%) |
|---|---|---|
| 1 | 2 | 60 |
| 2 | 4 | 76 |
| 3 | 12 | 72 |
| 4 | 0.1[b] | 13 |
| 5[c] | 4 | 60 |

[a] Unless otherwise noted, an appropriate amount of $FeCl_3$ was added to a solution of **1b** (0.25 mmol) in dry $CH_2Cl_2$ (20 mL), and stirred for 30 minutes under a nitrogen atmosphere. [b] *meta*-Chloroperbenzoic acid (*m*-CPBA, 1 equiv.) was used as an oxidant. [c] A mixture of $CH_2Cl_2$–$MeNO_2$ (9/1) was used as solvent.

Table 2 $FeCl_3$-mediated intramolecular cyclization of **1a–f**




| | Reagent | | Products | Isolated yield (%) | | | |
|---|---|---|---|---|---|---|---|
| Entry[a] | **1** | X | **2** | r.t. | 0 °C | 40 °C | 80 °C[b] |
| 1 | **1a** | H | **2a** | —[c] | —[c] | | |
| 2 | **1b** | Br | **2b** | 76 | 79 | 57 | 60[d] |
| 3 | **1c** | I | **2c** | 10 | 32 | 74[e] | [f] |
| 4 | **1d** | $C_7H_{15}$ | **2d** | —[c] | 66 | [f] | [f] |
| 5 | **1e** | COOEt | **2e** | 66 | [f] | 87 | 89 |
| 6 | **1f** | CHO | **2f** | <10 | [f] | <10 | 40 |

[a] Unless otherwise noted, $FeCl_3$ (4 equiv.) was added to a solution of **1** (0.25 mmol) in $CH_2Cl_2$ (20 mL), and stirred for 30 min under nitrogen. [b] Solvent: $ClCH_2CH_2Cl$ (DCE). [c] The starting alkene decomposed completely after a few minutes. [d] Tribromo derivative **3** was isolated in 10% yield. [e] A solution of **1c** (0.25 mmol) in $CH_2Cl_2$ (5 mL) was added to a slurry of $FeCl_3$ (4 equiv.) in $CH_2Cl_2$ (20 mL) at 40 °C. [f] Not performed.

13% yield (entry 4, Table 1). Although $FeCl_3$-mediated cyclodehydrogenations are often carried out employing $CH_2Cl_2$ in combination with nitromethane as co-solvent,[12] in our case the use of a mixture of $CH_2Cl_2$ and $MeNO_2$ as solvent in the reaction of **1b** with 4 equiv. of $FeCl_3$ did not improve the efficiency, affording **2b** in lower yield (60%, entry 5, Table 1). Finally, the same reaction run in acetonitrile as solvent gave a complex mixture in which the expected **2b** was present in low amounts. Based on these results, we then ran the cyclization reactions of **1a–f** with 4 equiv. of $FeCl_3$ in $CH_2Cl_2$, evaluating the influence of the temperature on the outcome of these reactions (Table 2).

As expected, when a solution of **1a** in $CH_2Cl_2$ was treated with $FeCl_3$ at room temperature or 0 °C, a complex mixture of polymerization products was obtained after a few minutes (entry 1, Table 2). In this case, the known higher spin density of the thiophene radical cation at the 2-position favours the formation of polymers[13b,c] instead of the required benzodithiophene **2a**. In contrast, when alkenes **1b–f** with substituents on the alpha positions of the thiophenes were used, the polymerization was prevented and the corresponding disubstituted **BDT** derivatives **2b–f** were obtained. As reported in entry 2 of Table 1, while the cyclization of **1b** at room temperature gave **2b** in 76% yield, a slightly higher yield (79%) of **2b** was obtained at 0 °C (entry 2, Table 2). In contrast, increasing the temperature (up to 40 or 80 °C) was found to produce **2b** in lower yields, together with tribromo derivative **3** (Fig. 1a), which was isolated in 10% yield at 80 °C. The structure of tribromide **3** was confirmed by the X-ray analysis. The ORTEP view of **3** shows that the molecule is essentially planar neglecting the two *n*-propyl chains, which extend on two opposite sites of the mean plane of the benzodithiophene unit (Fig. 1b). The formation of **3** could be rationalized by taking into account that thiophenes brominated in the α-positions readily undergo debromination and/or rearrangement reactions through heating in the presence of catalytic amounts of strong acids.[19]

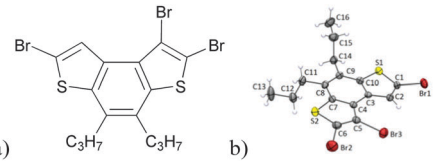
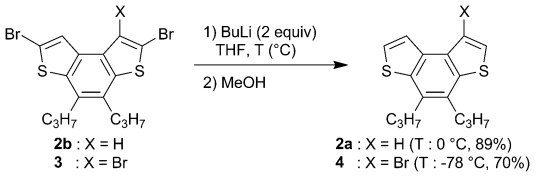



Fig. 1 (a) Chemical structure of **3**. (b) ORTEP view of the crystal structure of **3** (ellipsoids are drawn at their 30% probability level).




Scheme 2 Debromination of bromo **BDT** derivatives **2b** and **3**.

These processes, which generally involve the loss of brominating species, could also occur in the $FeCl_3$-mediated cyclization of **1b** at 80 °C. In fact, the hydrogen chloride generated during the cyclization of **1b** could catalyze the loss, from **2b**, of a "brominating" species, which then could be able to brominate **2b** to furnish the tribromo **BDT 3**. The fate of the resulting debrominated **2b** is not known because, as already stated above, α-unsubstituted **BDT**s decompose under these conditions. We found that heating the dibromo **BDT 2b**, in the presence of 4 equiv. of $FeCl_3$ in DCE at 80 °C, resulted in the formation of **3** in 40% yield after 1 hour, besides the recovery of 5% of **2b**. In this case, it could be that catalytic amounts of HCl arising from $FeCl_3$ partially decompose **2b** thus generating the brominating species which affords **3**. In contrast to bromide **1b**, the iodide **1c** gave the cyclized product **2c** in only 10% and 32% yields at room temperature and at 0 °C, respectively (entry 3, Table 2). Moreover, **2c** decomposed completely and very quickly when the reaction mixture was warmed to 40 °C, with evident loss of iodine, presumably due to the carbon–iodine bond lability.[13b] We found, however, that the order of addition of the reagents played a crucial role in the cyclization of **1c**. In fact, when a solution of **1c** in DCM was dropped into a slurry of $FeCl_3$ (4 equiv.) in DCM at reflux, **2c** was isolated in 74% yield. This could be the consequence of a faster cyclization of **1c** in the presence of excess of $FeCl_3$ at 40 °C relative to its decomposition. In addition, we found that the substrate **1d**, bearing two alkyl chains in the α-positions, underwent fast degradation at room temperature, while a lower reaction temperature (0 °C) allowed us to obtain the required product **2d** in 66% yield (entry 4, Table 2). Different results were obtained with (*Z*)-dithienyl ethenes **1e** and **1f**, substituted in the α-positions with the electron-withdrawing groups COOEt and CHO, respectively. In particular, the oxidative coupling of **1e** efficiently occurred at room temperature, 40 °C and 80 °C, providing **2e** in 66%, 87% and 89% yields, respectively (entry 5, Table 2). These results indicate that **2e** is stable under these oxidative conditions, and that higher temperatures favour its cyclization. On the other hand, the more electron-poor substrate **1f** remained practically unreactive, affording only traces of **2f**, both at room temperature and 40 °C (entry 6, Table 2). However, by increasing the temperature from 40 °C to 80 °C, **2f** could be isolated in 40% yield along with 10% **1f**. Most likely, the presence of the electron-withdrawing formyl substituents on the thiophene rings of **1f** makes it difficult to generate the supposed radical cation intermediate,[13m] and, in this case, the temperature plays a crucial role in promoting the intramolecular cyclization. The synthesis of functionalized benzodithiophene derivatives **2b–f** has important implications for the development of new and more complex molecular architectures. In fact, further modifications exploiting the reactivity of the substituents in the α-positions of the thiophene rings appear just as useful. Among these, the possibility of the debromination of **BDT 2b** was explored by treating it with BuLi–MeOH at 0 °C (Scheme 2).

From this reaction we isolated, in 89% yield, unsubstituted **2a**, which as already stated above, cannot be obtained by means of the $FeCl_3$-mediated cyclization of **1a**. More interestingly, the analogous regioselective debromination of the two α-positions of **3** also occurred using two equivalents of BuLi–MeOH at −78 °C, providing the β-bromo substituted **BDT** derivative **4** in 70% yield. The latter compound represents a potential new key intermediate for the synthesis of an interesting class of chiral atropoisomeric molecules, from which enantiomerically pure thiahelicenes could be prepared.[8a] In summary, a non-photochemical methodology for the synthesis of **BDT** scaffolds through the $FeCl_3$-mediated oxidative cyclization of 1,2-dithienylethenes **1b–f** has been set up. This work has demonstrated the feasibility of achieving α,α′-disubstituted **BDT** without the need to be inserted into more complex polyaromatic systems. The presence of two functional groups in the α,α′ positions of alkenes **1b–f** efficiently prevents polymerization under the oxidative conditions of cyclization, and allows further functionalization of the final **BDT**s. For these reasons, we believe that the establishment of this methodology can promote renewed and increased interest in the [1,2-*b*:4,3-*b*′] **BDT** scaffold and consequently the development of new applications, for example in conductive organic polymers and DSSCs. In addition, new investigations aimed at exploring the synthesis of enantiopure thiahelicenes from 3-bromo **BDT** derivative **4** are currently in progress in our laboratory.

## Experimental

### General procedure for the $FeCl_3$-mediated cyclization of alkenes 1b–f

To a solution of alkenes **1b–f** (0.25 mmol) in dry DCM (20 mL), constantly sparged with nitrogen at an appropriate temperature (0, rt, 40 or 80 °C), $FeCl_3$ (1 mmol, 4 eq.) was added. The resulting mixture was stirred under a nitrogen purge for 30′, and then treated with methanol (*ca.* 50 mL) for 1 h. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel. The chromatographic fractions containing the required compound were collected and concentrated to give the corresponding **2b–f** as pale yellow solids in 40–89% yield (entries 2–6, Table 2).

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