Synthesis of PAH-metabolites to be used in Environmental Research

by

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Stavanger, February 28th, 2013

Abstract

As environmental pollutants, polycyclic aromatic hydrocarbons (PAHs) are well known to form metabolites which can react with DNA and proteins to cause mutagenesis and create cancer. For chrysene the metabolite (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol has been found to be the most carcinogenic. In order to better understand the metabolism of PAHs and the absolute stereochemistry for PAH metabolites formed *in vivo*, the pure enantiomer of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol is needed for further research. The synthetic strategy for the total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol involves the formation of a general chiral bulding block, which can be incorporated as a building-block to form the target molecule, and other PAH metabolites. The key step in the synthesis of the building block is the Shi-epoxidation introducing the chiral centers in the formation of a *trans*-diol. The *trans*-diol is further elaborated in order to generate (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol.

Polycyclic aromatic hydrocarbons can be formed from a directed *ortho* metalation (DoM) reaction, followed by a Suzuki-Miyaura cross-coupling reaction and a directed remote metalation reaction (DreM). This methodology was used in the synthesis of chrysen-5-ol and the attempted synthesis of chrysen-6-ol. The unexpected results in the attempted synthesis of chrysen-6-ol led to a study of the birayl rotational barrier study which included several *ortho*-tolyl amides. However, the rotational barrier could not explain the failed directed remote metalation (DreM) reaction for the synthesis of chrysen-6-ol.

From PAHs with a directing group attached a directed *ortho* metalation (DoM) can be carried out in order to form larger PAHs. The directed *ortho* metalation was studied for four chrysenyl diethylcarbamates. These reactions resulted in good to excellent yield of the *ortho*-metalated products.

Abbreviations

AIBN	azobisisobutyronitrile
Am	*N*,*N*-diethylamide
BH_3-THF	borane tetrahydrofurane complex
$Cp_2Zr(H)Cl$	bis(cyclopentadienyl)zirconium(IV) chloride hydride
CYP 450	cytochrome P450
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMM	dimethoxymethane
D*o*M	directed *ortho* metalation
DreM	directed remote metalation reaction
ee	*enantiomeric excess*
EXSY	exchange spectroscopy
GC	gas chromatography
HPLC	high performance liquid chromatography
Hz	herz
K	Kelvin
k_c	rate constant for exchanging signals
KHMDS	potassium hexamethyldisilazid
LDA	lithium diisopropylamine
Me	methyl
MeOH	methanol
MHz	megaherz
MS	mass spectrometry
MsOH	methane sulphonic acid
m/z	mass-to-charge ratio
NaH	sodium hydride
NBS	*N*-bromosuccinimine
n-BuLi	*n*-butyl lithium
$Ni(acac)_2$	nickel(II) acetylacetonate
$NiCl_2$(dppe)	1,2-bis(diphenylphosphino)ethane nickel(II) dichloride

$NiCl_2(PCy_3)$	bis(tricyclohexylphosphine)nickel(II) dichloride
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser spectroscopy
NOE	nuclear overhauser effect
Oxone	potassium peroxymonosulfate
PAH	polycyclic aromatic hydrocarbon
PCC	pyridinium chlorochromate
$PdCl_2$(dppf)	[1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PPh_3	triphenyl phosphine
s-BuLi	*sec*-butyl lithium
$SOCl_2$	thionyl chloride
TBDMS	*tert*-butyl dimethyl silyl
TBDPS	*tert*-butyl diphenyl silyl
t-BuOK	potassium *tert*-butoxide
T_c	coalescence temperature
THF	Tetrahydrofurane
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
tris(HCl)	tris(hydroxymethyl)aminomethane hydrochloride

Contents

Chapter 1

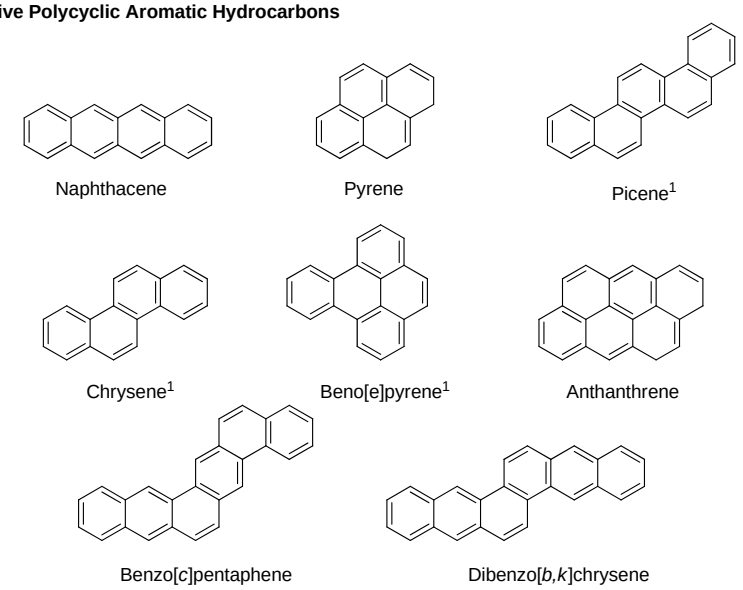
Introduction

1.1 Polycyclic aromatic hydrocarbons (PAHs)

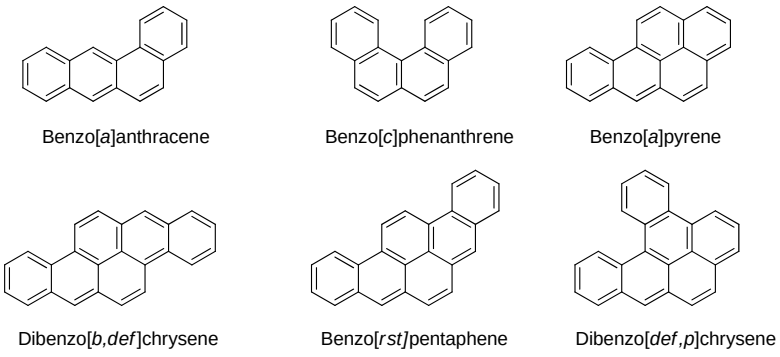
Polycyclic aromatic hydrocarbons (PAHs) are compounds consisting of two or more aromatic rings. These aromatic rings can also consist of nitrogen[1] or sulphur.[2] The polycyclic aromatic hydrocarbons can be divided into two broad classes, petrogenic or pyrogenic PAH`s, depending on how they are formed. Petrogenic PAHs includes the polycyclic aromatic hydrocarbons that can be found naturally in coal tars and oil, while pyrogenic PAH`s on the other hand are formed from burned or incomplete combustion of organic material[3]. Tobacco smoke,[4] burned meat[5] and wood fuel burning[6] are all known pyrogenic PAHs which can induce cancer.

Polycyclic aromatic hydrocarbons can be found in many forms and sizes and some have been found to be more toxic, carcinogenic and mutagenic than others, especially benz[*a*]anthracene, benzo[*c*]phenanthrene and benzo[*a*]pyrene among others.[7] A few of the inactive compounds, such as chrysene, picene and benzo[*e*]pyrene have been found to have tumour-initiating activity, as shown in Figure 1.

Inactive Polycyclic Aromatic Hydrocarbons



Carcinogenic Polycyclic Aromatic Hydrocarbons



[1] Tumor-initiating activity

Figure 1: Inactive and carcinogenic polycyclic aromatic hydrocarbons

Coal tars and oils were found to have carcinogenic activity already in the nineteenth century[8] and early research noted that the active compounds in the initiation of cancer were the aromatic hydrocarbons.[9] Later research established that the more active compounds were the metabolites which were formed *in vivo* during metabolism and cellular detoxification.[10]

Regarding the aquatic environment many of the carcinogenic and tumor-initiating polycyclic aromatic hydrocarbons can be found naturally in oil reservoirs from offshore installations.[11] These hydrophobic hydrocarbons can enter the sea water from oils spills and can either be solved in the water or found as oil droplets in a dispersed form[3]. For bottom-dwelling fish a high incident of liver tumour has been reported[12] and, naturally, because of their mutagenic and carcinogenic properties these compounds are of concern for the whole aquatic environment. Some PAH have been found to be more important when it comes to analysis and monitoring oils spills, and these includes chrysene, phenanthrene, benzo[*a*]pyrene and benzo[*a*]antrachene.[13]

1.2 Metabolism of PAHs

Due to their lack of polar functional groups the aromatic hydrocarbons are highly hydrophobic. When these compounds are digested by mammals and fish they can accumulate in fatty tissues such as the liver. From the fatty tissues these compounds can penetrate the cells by passive diffusion were they can be oxidized by enzymes to form more water-soluble and more active compound. The vast majority of the oxidized hydrocarbons are excreted in the bile fluid and are of no harm to mammals or fish.[3,14] However, when dihydrodiols are formed these metabolites can be further oxidized to dihydrodiol-epoxides which then can react with proteins and nucleic acids in cells to form mutagenic adducts,[10] as shown in Figure 2.

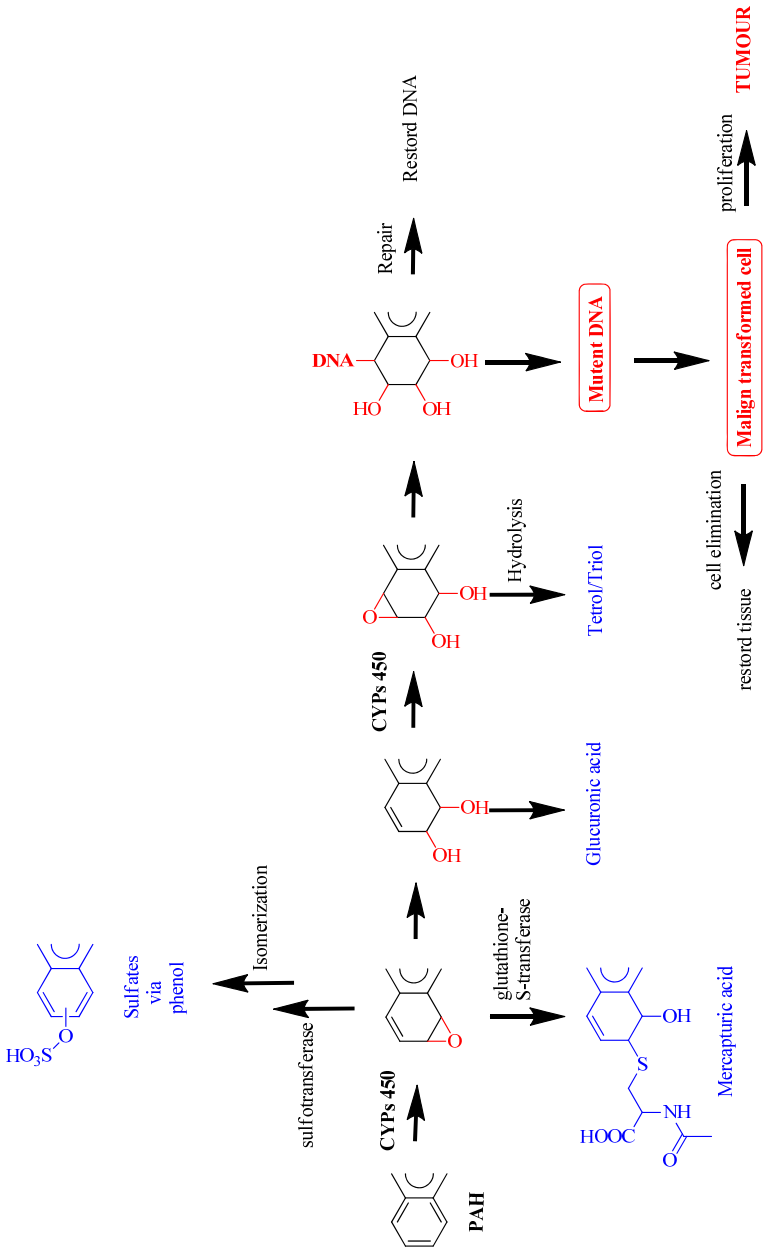


Figure 2: Metabolism of polycyclic aromatic hydrocarbons[10]

In order for the polycyclic aromatic hydrocarbons to have any carcinogenic activity they have to go through a two-stage activation with cytochrome P450 (CYP) monooxygenase. In the first stage the PAH`s are activated by cytochrome P450 (CYP) monooxygenase (phase I metabolism) to form epoxides. This epoxide can be transformed by either sulfontransferase or glutathione-S-transferase to form sulfates or mercapturic acids. These sulfates and mercapturc acids are excreted in the bile fluids and are of no harm to organisms.[10,14] However, when this epoxide is transformed by epoxide hydrolase to dihydrodiols (phase II) a second activation with cytochrome P450 monooxygenase can take place. The formed dihydrodiol-epoxide has been found to have a high affinity for nucleic acids and proteins in cells,[15,16] and when nucleic acids and proteins binds covalently to these PAH-metabolites DNA- or protein adducts can be formed.[17] If the cell is not repaired and restored these adducts can eventually lead to a mutagenic cell forming tumor.[10]

As for most other enzymes, cytochrome P450 monooxygenase can be found in many forms as different isozymes. Different isozymes can be found in different metabolic systems, resulting in a different mixture of *trans*-diols and other metabolites. The cytochrome P450 monooxygenase can also activate different sites on the aromatic hydrocarbons.[18] In some metabolic systems, like for example Bullehead liver microsomes, 58% of the most tumour-initiating stereoisomer (-)-(1*R*,2*R*)-1,2-dihydro-1,2-diol chrysene, shown in Figure 3, is formed after activation by CYP1A and epoxide hydrolase,[12] while 24% of 3,4-dihydro-3,4-diol is formed. In rat liver microsomes, however, the amount of 1,2-dihydro-1,2-diol **1** and 3,4-dihydro-3,4-diol **3** are formed in approximately the same amount.[19] Very little of 5,6-dihydro-5,6-diol **2** is formed in any of these metabolic systems.

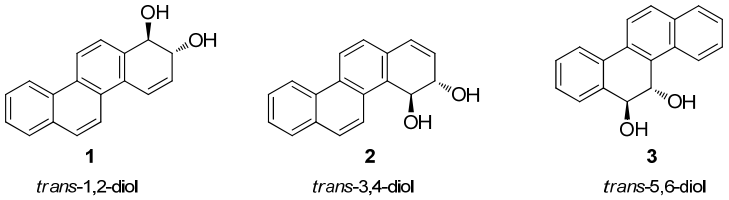


Figure 3: *trans*-diols that are formed during metabolism of chrysene

As for chrysene the CYP450 monooxygenase can activate different sites on most polycyclic aromatic hydrocarbons. In Figure 4 six different polycyclic aromatic hydrocarbons are given for were the most likely position for the oxidation to take place with the CYP1A P450 monooxygenase found in fish.[3,18]

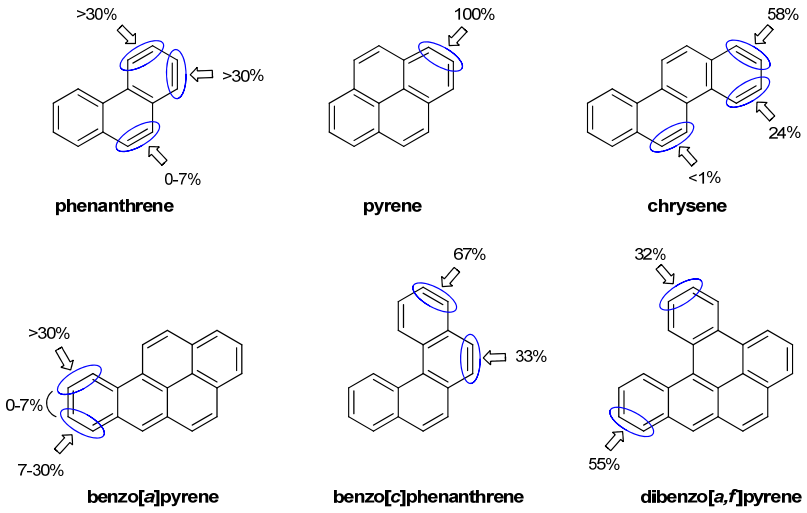


Figure 4: The position where the oxidation is most likely to take place for fish CYP1A monooxygenase[3,18]

1.3 Toxicity of PAHs

As mention above, CYP450 monooxygenase can activate different sites on polycyclic aromatic hydrocarbons for the formation of dihydrodiols. The different dihydrodiols formed have various carcinogenic and toxic effects, and the position of the dihydrodiol have been found to be essential in order for their metabolites to exert their effect. Especially the position of the epoxide after the second activation with CYP450 monooxygenase for the formation of dihydrodiol-epoxide has been reported to be important. In Figure 5 the most carcinogenic dihydrodiol-epoxide of different polycyclic aromatic hydrocarbons are given.

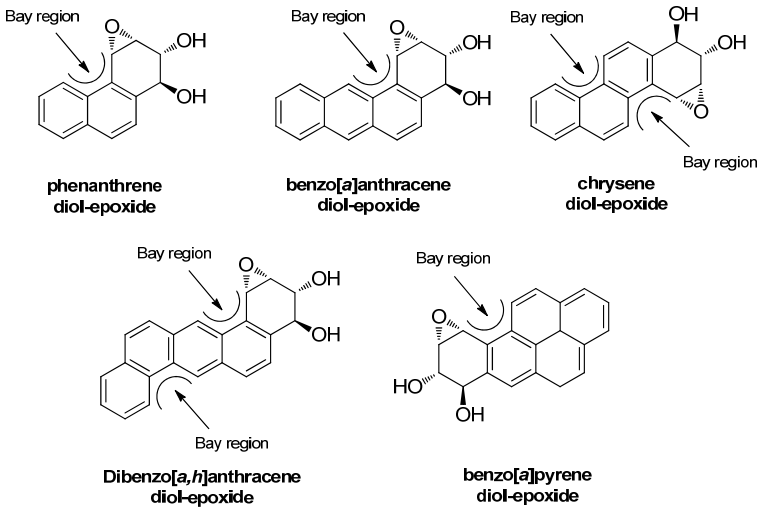


Figure 5: The most toxic regio- and stereoisomer PAH for the parent compounds

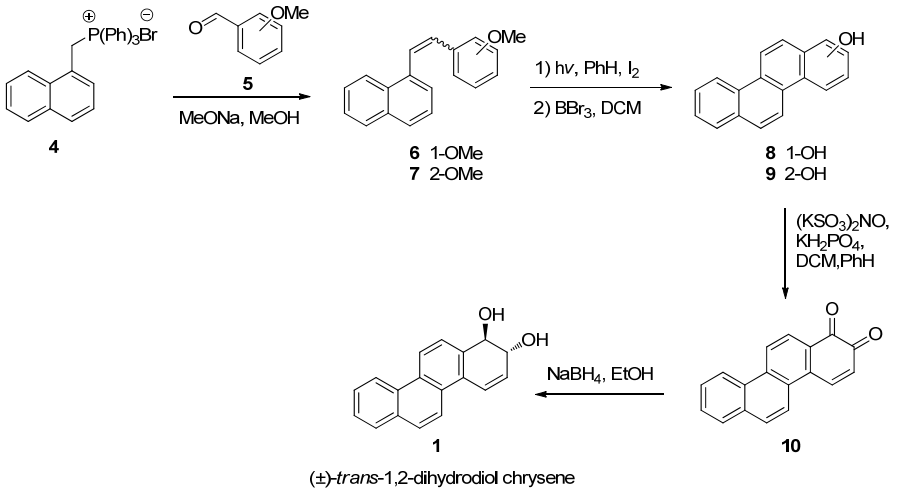
For polycyclic aromatic hydrocarbons it has been reported that when the epoxide is positioned at the bay region of the molecule the amount of tumor is higher than when it is position in a non-bay region. When substituents are bound in a way that blocks the bay region, particularly in the case of benzo[*a*]anthracene, these derivatives prevent the carcinogenic effect of these compounds. Molecular orbital calculation has also predicted a greater ease for carbocations to be formed at the benzylic carbon atom of bay-region epoxides and dihydrodiol-epoxides then for their corresponding non-bay-region epoxides and dihydrodiol-epoxides. The affinity for nucleic acids and proteins to covalently bind to aromatic hydrocarbons are higher at the bay-region of the molecules then in the non-bay region.[16]

1.4 Synthesis of PAH-metabolites

Robert Harvey and coworkers has been the pioneer in the synthesis of polycyclic aromatic hydrocarbon metabolites, especially the synthesis of *trans*-1,2-dihydrochrysene-1-2-diol **1**. In his publications several different routes has been reported for the formation of the *trans*-1,2-dihydrochrysene-1,2-diol **1**. However, in all routes the *trans*-dihydrodiol **1** was formed in a rasemic mixture, either from chrysene-quinones[20,21] or by addition of silverbenzoate to a suitable olefin.[22] The enantiomeric pure (1*R*,2*R*)-*trans*-1,2-dihydrochrysene-1-2-diol (**1**) was obtained either by converting the *trans*-dihydrodiol to corresponding diasteromeric esters by chiral acids followed by separation by flash coloum chromatography,[23] or by a separation of the rasemic *trans*-dihydrodiol by HPLC using a chiral coloum.[24]

The most classical formation of *trans*-1,2-dihydro-1,2-diol chrysene **1** includes a Wittig reaction followed by a photocyclization reaction,[20] as shown in Scheme 1.

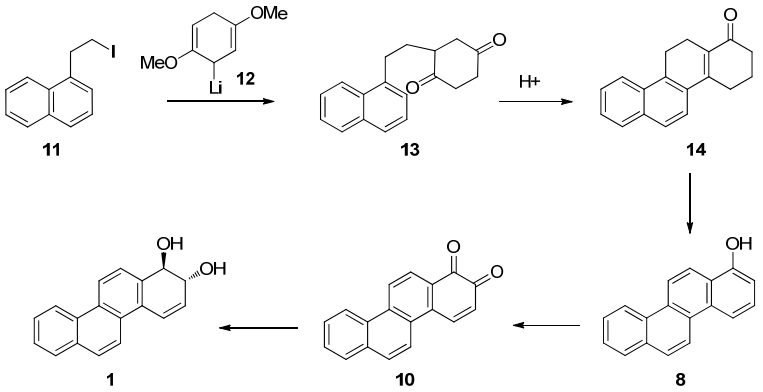
Scheme 1: Harvey`s synthesis towards *trans*-1,2-dihydrodiol chrysene



After the photocyclization reaction, 1-, or 2-chrysenol were formed by a deprotection of the methoxy-group with BBr_3. Chrysene-1,2-diketone was formed by an oxidation reaction with Fremy`s salt ([(KSO3)NO]), followed by reducing of the diketone with $NaBH_4$, thus affording *trans*-1,2-dihydrochrysene-1,2-diol **1**. By using the same route Harvey *et al*. also synthesized 6-methyl- and 5-mehyl-*trans*-1,2-dihydrochrysene-1,2-diol.

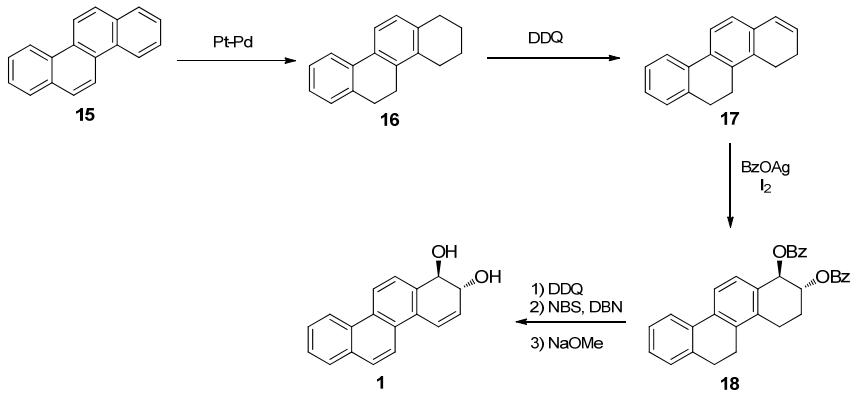
Another example of reduction of chysene-1,2-diketone in the formation of *trans*-1,2-dihydro-1,2-diol chrysene is given in Scheme 2. Chrysen-1-ol was formed from an alkylation of lithium 1,4-dimethoxycyclohexane-1,4-diene (**12**) with 1-(1-iodoethyl)naphthalene (**11**) followed by cyclization to yield the chrysene skeleton.[21] Also here, 6-methyl-, and 5-methyl *trans*-1,2-dihydro-1,2-diol chrysene were synthesized by the same approach.

Scheme 2: Synthesis of *trans*-1,2-dihydro-1,2-diol chrysene



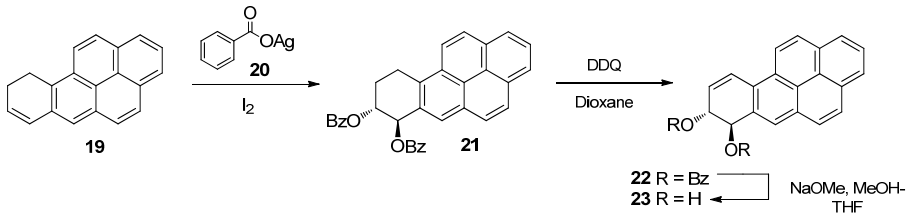
As mention above, the *trans*-1,2-dihydrochrysene-1,2-diol **1** can also be made from the addition of silver benzoate to olefin. The synthesis started with a partial saturation of chrysene with Pt-Pd. After a regiospesific dehydrogenation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) the *trans*-diol was generated by an addition of silver benzoate to the newly formed olefin.[22] DDQ was used to dehydrogenate the 5,6-protons, while the bromination/dehydrodebromination had to be used to dehydrogenate the 3,4-protons, as shown in Scheme 3.

Scheme 3: Synthesis of trans-1,2-dihydro-1,2-diol using silver benzoate



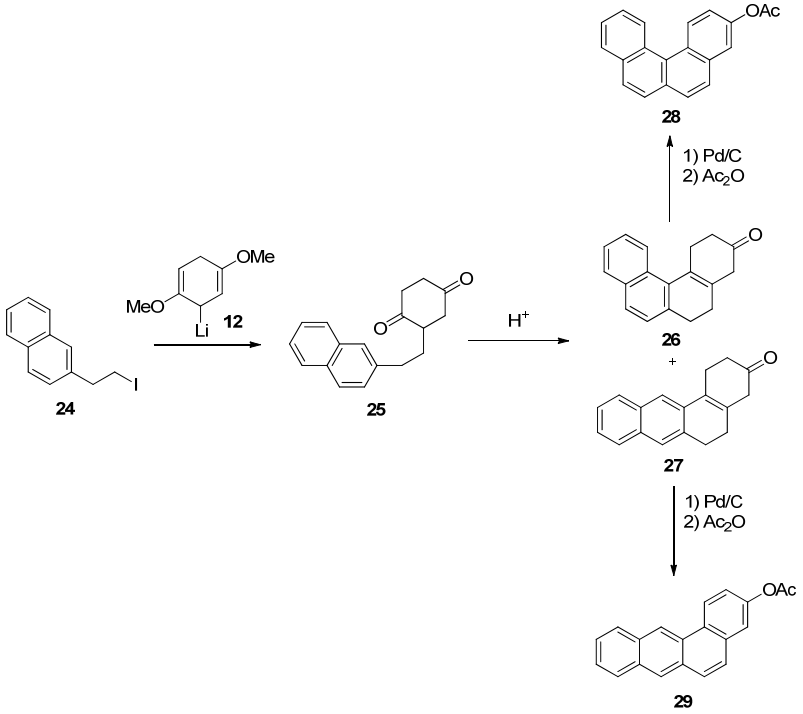
Silver benzoate can not only be used to form *trans*-1,2-dihydrochrysene-1,2-diol **1** but it was also applied as a reagent in the synthesis of *trans*-7,8-dihydro-7,8-diol benzo[*a*]pyrene 23,[25] shown in Scheme 4. After the addition of silver benzoate the 9,10-protons was dehydrogenated with DDQ.

Scheme 4: Synthesis of 7,8-dihydro-7,8-diol BaP using silver benzoate



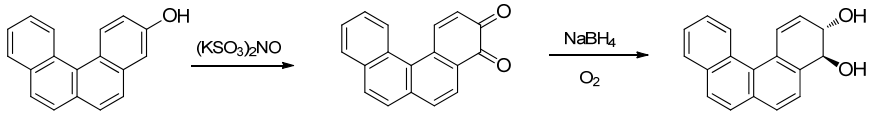
The synthesis of benzo[*c]*phenanthrene- and, benzo[*a*]anthracene-metabolites[26] are outlined in Scheme 5. 2-(2-(naphthalen-2-yl)ethyl)cyclohexane-1,4-dione (**25**) was formed from an alkylation of **12** with 2-(2-iodoethyl)naphthalene (**24**). From a Friedel-Craft cyclization reaction using polyposhoric acid both 1,2,5,6-tetrahydrobenzo[*c*]phenanthren-3(4H)-one (**26**) and 1,2,5,6-tetrahydrotetraphen-3(4H)-one (**27**) was formed. Dehydrogenation with Pd/C after separation of the two compounds gave the desired PAH-acetates.

Scheme 5: Synthesis of benzo[*c*]phenanthrene-, benzo[*a*]anthracene-metabolites



The *trans*-1,2-dihydro-1,2-diol of benzo[*c*]phenanthrene was formed by hydrolysis of the acetate, followed by oxidation with Fremy`s salt [$(KSO_3)_2NO$], and reduction with $NaBH_4$,[26] as shown in Scheme 6.

Scheme 6: Oxidation and reduction in the formation of 1,2-dihydro-1,2-diol benzo[a]phenanthrene

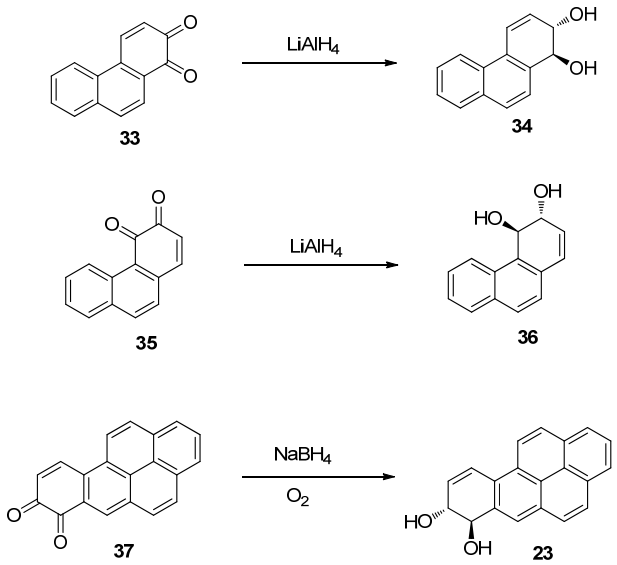


30 **31** **32**

The oxidation using Fremy`s salt often gave a mixture of diketons. Hypervalent iodine has been found to be a more promising reagent for regio-controlled oxidation of phenols. *o*-iodoxybenzoic acid, which is a mild oxidant, is more soluble in organic solvents than Fremy`s salt, and widely employed for oxidations of alcohol. This reagent has been used in the oxidation of several PAH-phenols.[27]

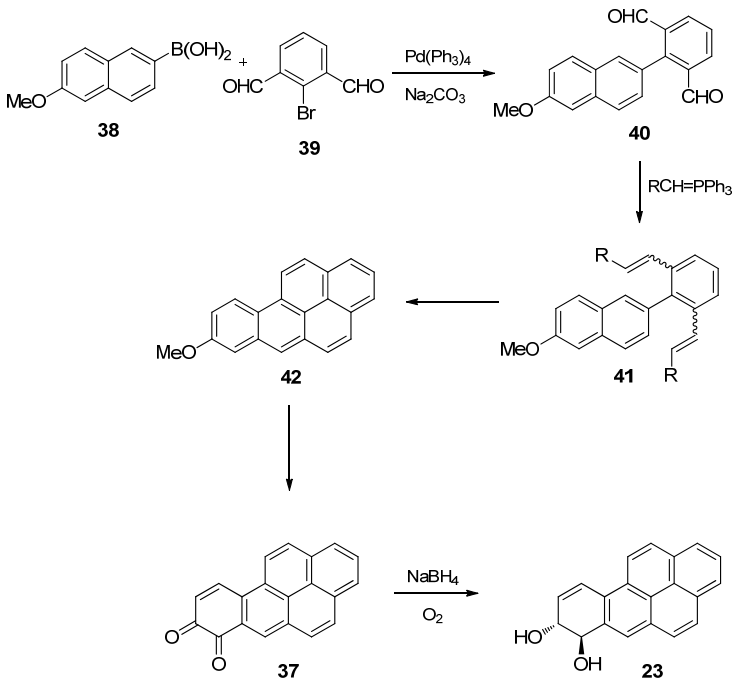
Reduction of diketones for the formation of *trans*-diols has been applied for many polycyclic aromatic hydrocarbons,[28] as shown in Scheme 7.

Scheme 7: Reduction of a few quinones with either $NaBH_4$ or $LiAlH_4$



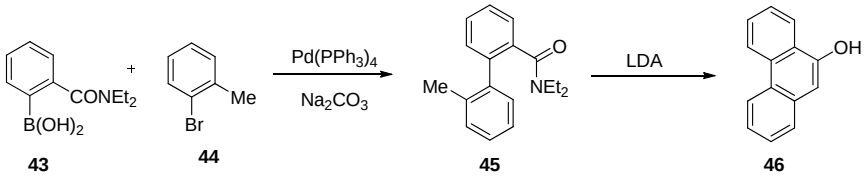
Suzuki-Miyaura cross-coupling reactions have in recent years been applied for the synthesis of PAH-metabolites. One example is the synthesis of *trans*-7,8-dihydro-7,8-diol benzo[*a*]pyrene **23** starting with a Suzuki-Miyaura cross-coupling reaction followed by a Wittig reaction, and a photochemical reaction which upon oxidation and reduction afforded the *trans*-diol **23**, as outlined in Scheme 8.[29]

Scheme 8: Synthesis of *trans*-7,8-dihydro-7,8-diol benzo[a]pyrene with Suzuki coupling



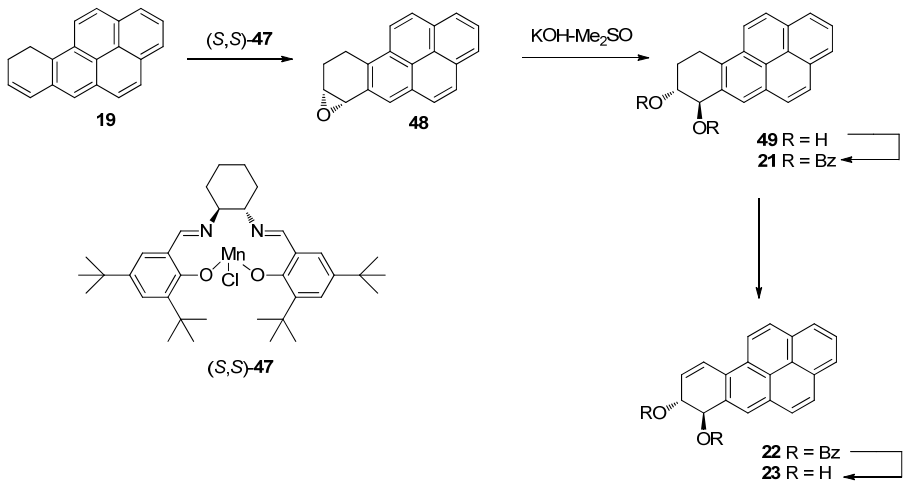
A combined Suzuki-Miyaura cross-coupling reaction and directed remote metalation reaction (DreM) has also been applied in the synthesis of PAH-metabolites. One example of this is the synthesis of 9-phenanthrol **46**, shown in Scheme 9.[30]

Scheme 9: Synthesis of 9-phenanthrol by Suzuki-Miyaura cross-coupling reaction and DreM



However, in most of the synthesis of the PAH-metabolites the *trans*-diol is formed in a rasemic mixture. In 1995 Huang *et. al*, was the first to synthesized enantiomeric pure *trans*-7,8-dihydro-7,8-diol benzo[*a*]pyrene **23**. From the olefin **19** an asymmetric epoxidaiton using Jacobsens catalyst (*S*,*S*-**47**) afforded the tetrahydrobenzo[1,12]tetrapheno[8,9]oxirene **48**. The epoxide **48** was then opened to *trans*-diol **49** using KOH-Me_2SO,[31] shown in Scheme 10.

Scheme 10: Asymmetric synthesis of *trans*-7,8-dihydro-7,8-diol benzo[*a*]pyrene **23**



Chapter 2

Total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol

2.1 Introduction

As mentioned in chapter 1, (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) has been found to be the most carcinogenic of all *trans*-diols formed during metabolism of chrysene.[32] In some metabolic system, like for example the Brown Bullhead liver microsomes (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol is formed in a higher amount compared to the other *trans*-diols.[12] Compared to benzo[*a*]pyrene,[8] very little is known about the type of adducts that is formed when *trans*-diol epoxide of chrysene binds covalenly to DNA.

As described in chapter 1, Harvey and coworker have made *trans*-1,2-dihydrochrysene-1,2-diol **1** using different synthetic strategies. However, the synthesis resulted in the rasemic mixture of *trans*-dihydrodiol **1** in all cases. The enantiomeric pure *trans*-dihydrodiol was first available after either chromatographic purification of the corresponding diasteromers, or after preperative, chiral HPLC.

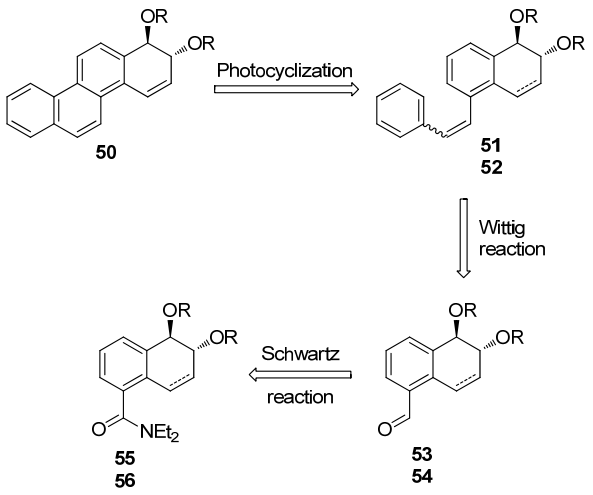
In this chapter the total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) will be discussed. In the first section the retrosynthetic analysis for the formation of *trans*-dihydrodiol **1** will be outlined. A retrosynthetic analysis in the formation of other PAH-metabolites will also be included in this section.

2.2 Retrosynthetic analysis

The strategy for the generation of chrysene metabolite is to first make a general chiral building block, which can not only be used to form the chrysene metabolite but also to form other PAH-metabolites. Two alternative approaches for the transformation from the general chiral building block to the chrysene-metabolites are outlined in the following section.

In the first alternative approach the general chiral building block can be transformed to its corresponding aldehyde in an amide reduction using Schwartz reagent ($Cp_2Zr(H)Cl$),[33] as shown in Scheme 11. From aldehyde **53**/**54** *Z* and *E*-stilbene can be formed from a typical Wittig reaction[34] and from a photocyclization Mallory reaction[35] the chrysene metabolite will be formed. It is believed that the double bond in 3,4-position can either be introduce before the amide reduction or after the photocyclization reaction.

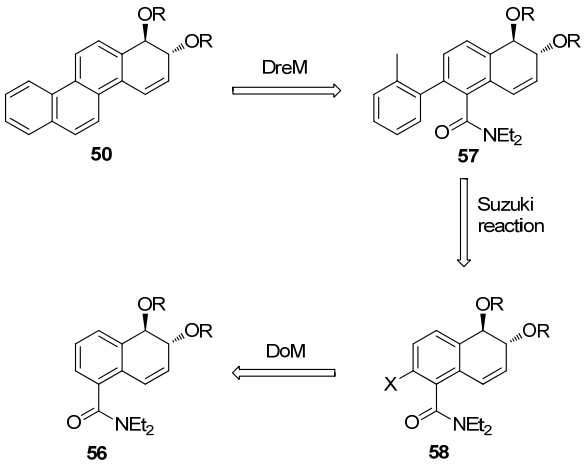
Scheme 11: First alternative approach[a]



[a] **51**, **53** and **55** without double bond
52, **54** and **56** with double bond

The second alternative starts by a directed *ortho* metalation reaction (DoM), were either boronic acid or a halogen are introduced *ortho* to the amide-group in the general chiral building block **56**. Compound **58** can then be transformed to the corresponding biaryl **57** by a Suzuki-Miyaura cross-coupling reaction.[36] Substrate **57** can then be converted to the chrysene skeleton by a directed remote metalation reaction (DreM).[30,37] This alternative approach can then be completed by a cleavage of the formed alcohol group protected as a carbamate group.[38]

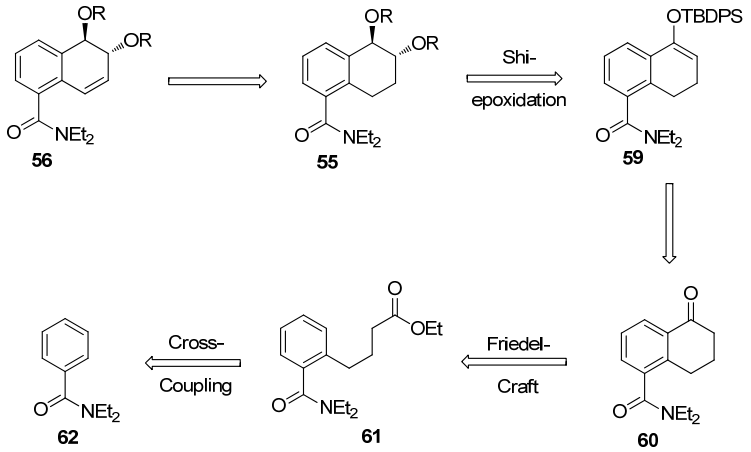
Scheme 12: Second alternative approach



It is believed that the general chiral bulding block can be formed from readily available *N*,*N*`-diethylbenzamide (**62**). By a Negishi cross-coupling reaction *N*,*N*`-diethylbenzamide (**62**) can be cross-coupled with ethyl-4-bromobutyrate to form compound **61**. After a hydrolization reaction of the ester the corresponding acid can be transformed to tetralone **60** by a Friedel-Craft cyclization reaction. The tetralone can then be transformed to its corresponding *tert*-butyldiphenylsilyl enol ether **59**, which in a Shi-epoxidation reaction affords the *trans*-diol monosilyl ether.[39] After protection

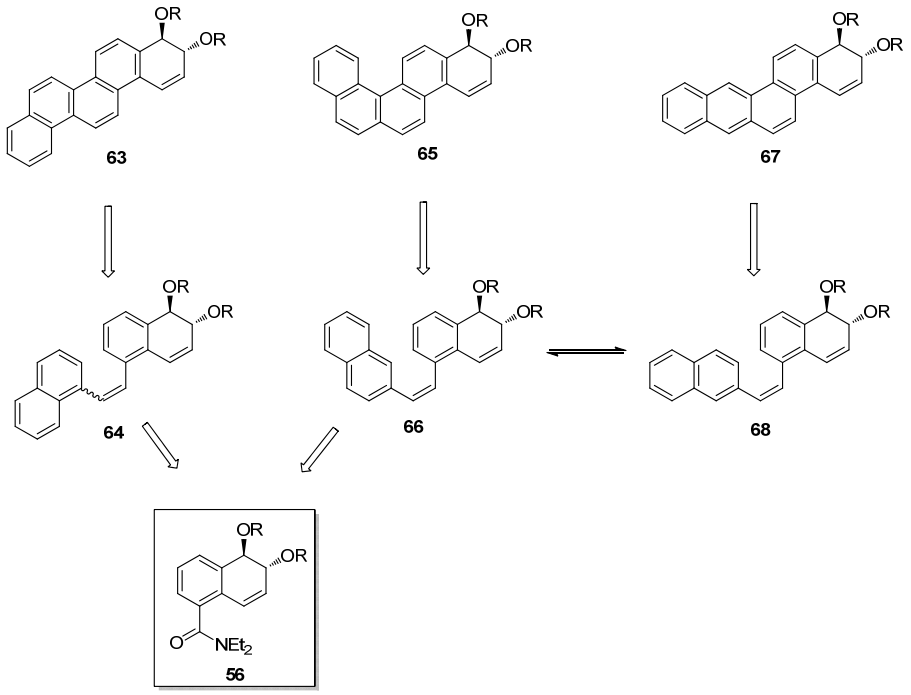
of the free alcohol-group, and a dehydrogenation reaction the general chiral building block **56** can be generated.

Scheme 13: Strategy for the generation of the general chiral building block



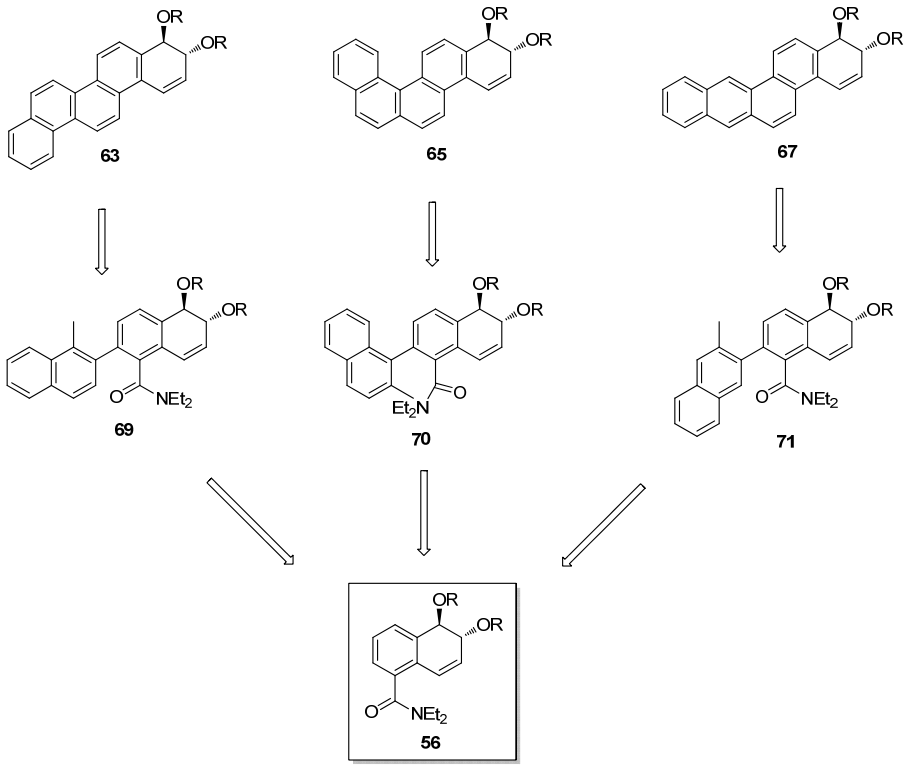
As mention above, the general chiral building block **56** can not only be used to formed (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) but also other PAH-metabolites such as (3*R*,4*R*)-3,4-dihydropicene-3,4-diol (**63**), (9*R*,10*R*)-9,10-dihydrobenzo[*c*]chrysene-9,10-diol (**65**) and (1*R*,2*R*)-1,2-dihydrobenzo[*c*]tetraphene-1,2-diol (**67**). The retrosynthetic analysis in the formation of these metabolites employing the first alternative approach is outlined in Scheme 14.

Scheme 14: Different PAH-metabolites which can be generated from the general chiral building block **56** using the first alternative approach



As for *trans*-dihydrochrysene-diol, (3*R*,4*R*)-3,4-dihydropicene-3,4-diol (**63**), (9*R*,10*R*)-9,10-dihydrobenzo[*c*]chrysene-9,10-diol (**65**) and (1*R*,2*R*)-1,2-dihydrobenzo[*c*]tetraphene-1,2-diol (**67**) can also be formed from the second alternative approach, as shown in Scheme 15.

Scheme 15: Different PAH-metabolites which can be formed from general chiral building block



2.3 Results and discussion

In this section the results obtained in the total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) will be discussed.

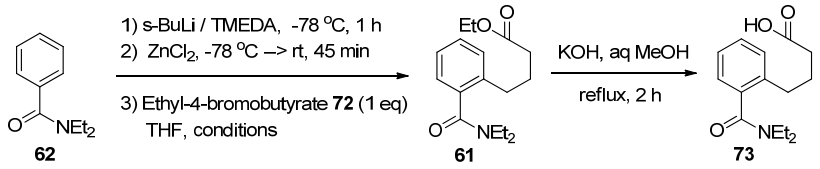
2.3.1 Negishi cross-coupling reaction

The total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) starts by coupling readily available *N*,*N*`-diethylbenzamide (**62**) with ethyl-4-bromobutyrate (**72**) utilizing a Negishi cross-coupling reaction. *N*,*N*`-diethylbenzamide (**62**) was *ortho* lithiated with *sec*-butyl lithium (*s*-BuLi),[40] followed by a transmetalation with zinc chloride ($ZnCl_2$), and an *in situ* cross-coupling with ethyl-4-bromobutyrate (**72**).[41] In the first attempt to cross-couple substrate **72** and benzamide **62** tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (Entry 1, Table 1) was used as catalyst in refluxing THF. Unfortunately, only starting material could be recovered from the reaction mixture. For [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2(dppf)$) (Entry 2, Table 1), which proved to be a great catalyst for the Suzuki-Miyaura reaction[36] (see chapter 3 for details), no cross-coupling of compound **62** and **72** occurred. However, starting material could be recovered from the reaction mixture. Reducing the palladium (II) catalyst to palladium (0) using diisobutylaluminum hydride (DIBALH) (Entry 3, Table 1) did not improve the reaction in any way.

Fortunately, when changing the metal from palladium to nickel using nickel(II) acetylacetonate ($Ni(acac)_2$) and triphenyl phosphine (PPh_3) (Entry 4, Table 1) as catalyst cross-coupling product was isolated after running the reaction at 0 °C to room temperature overnight.[42] Worth mention, is that in all the reaction were the cross-coupling of ethyl-4-bromobutyrate (**72**) and *N*,*N*`-diethylbenzamide (**62**) occurred there was always a small amount of unreacted benzamid **62** in a mixture with the cross-coupling product **61** after chromatographic purification. The ester **61** was, therefore, hydrolyzed with potassium hydroxide in methanol for 2 hours at reflux. After basic and acidic

extraction the butanoic acid **73** was obtain in the respective yields shown in Table 1.

Table 1: Negishi cross coupling reaction and ester hydrolysation



Entry	Catalyst (mol%)	Additive (mol%)	Temperature (°C)	Time (h)	Yield (%)[a] (2 steps)
1	$Pd_2(dba)_3$	-	reflux	19	nr
2	$Pd(dppf)Cl_2$ (5)	-	reflux	19	nr
3	$Pd(dppf)Cl_2$(5),	DIBALH (10)	reflux	19	nr
4	$Ni(acac)_2$ (5)	PPh_3, (5)	0 → rt	19	23[b]
5	$Ni(acac)_2$ (5)	PPh_3, (5)	50	2	40[c]
6	**$Ni(acac)_2$(5)**	**PPh_3, (5)**	**reflux**	**2**	**67**
7	$Ni(acac)_2$(5)	PPh_3, (10)	reflux	2	44
8	$NiCl_2(PCy_3)_2$ (2)	-	reflux	2	61
10	$NiCl_2$(dppe) (5)	DIBALH (10)	reflux	2	20[e]

[a] yields after ester hydrolization; [b] 40% homocoupling product isolated; [c] homocoupling product observed by TLC but not isolated; [d] 38% homocoupling product isolated

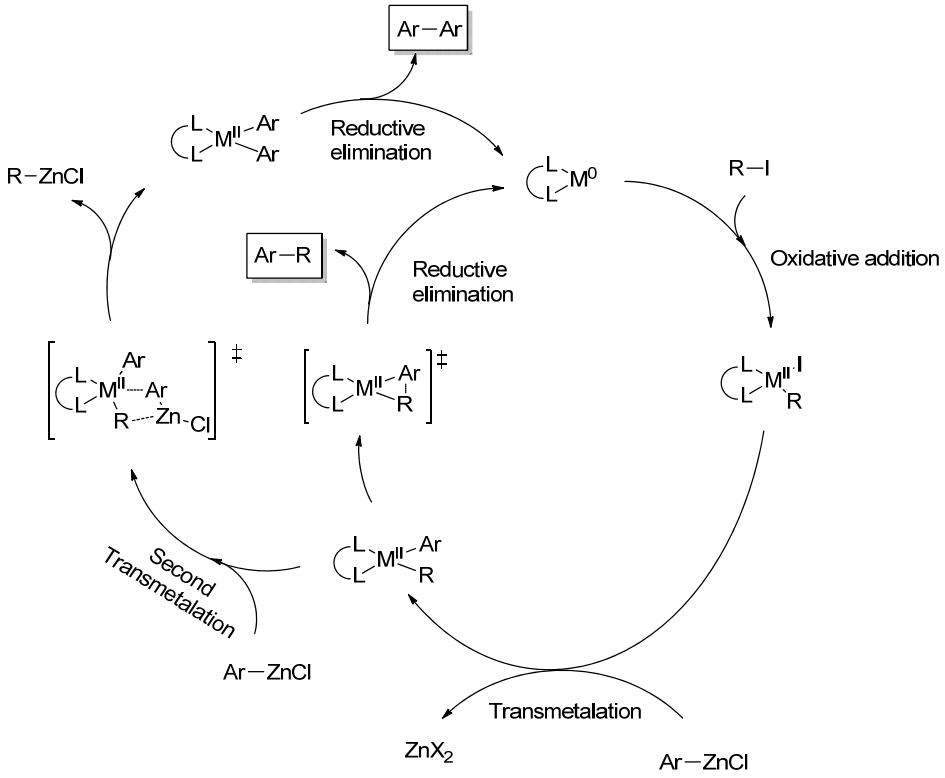
As indicated in Table 1, 40% of $N^2,N^2,N^{2'},N^{2'}$-tetraethyl-[1,1'-biphenyl]-2,2'-dicarboxamide, which is the homocoupled product of *N*,*N*`-diethylbenzamide, was isolated along with the cross-coupling product **61** after running the reaction at room temperature. When increasing the temperature to 50 °C (Entry 5, Table 1) higher yield of the cross-coupling product **61** was obtained, but also here some of the homocoupled benzamide was observed by TLC analysis. However, when running the reaction at reflux (Entry 6, Table 1) no homocoupling of benzamide **62** was observed and the cross-coupling

product was obtained in 67% isolated yield after hydrolization. In an attempt to increase the yields further other catalyst were tested. When using bis(tricyclohexylphosphine)nickel(II) dichloride ($NiCl_2(PCy_3)$) (Entry 8, Table 1) 61% of the cross-coupling product after hydrolization was isolated using only 2 mol% of the catalyst.
Unfortunately, when utilizing 1,2-bis(diphenylphosphino)ethane nickel(II) dichloride ($NiCl_2$(dppe)) (entry 9) 38% of homocoupled benzamide and only 20% of the cross-coupling product after hydrolization was isolated.

Before 1995 there were few publications found on the cross-coupling of unactivated, β-H-containing alkyl electrophiles,[43] and there are several reasons for that. Since alkyl electrophiles are more electron rich compared to vinyl and aryl electrophiles they have less tendency to undergo oxidative addition with especially low-valent transition metal-complexes. If alkyl electrophiles are able to undergo oxidative addition with metal-complexes relatively active species are formed due to low stabilization by electronic interactions with the metal. This active specie can then suffer from side reaction such as β-H elimination, which is a fast and thermodynamically stable reaction, or halide exchange reaction. Since also the reductive elimination of the coupling product is relatively slow side reactions are even more likely.[43,44]

As discussed above, one of the side product that was isolated in the Negishi cross-coupling of ethyl-4-bromobutyrate (**72**) and *N*,*N*`-diethylbenzamide (**62**) was the homocoupled product of benzamide. As mentioned, when alkyl electrophiles are to be cross-coupled the reductive elimination step can be relatively slow. When this occurs a competing second transmetalation can take place,[45] eventually leading to an alkyl zinc specie and a homocoupled product of aryl, as outlined in Scheme 16.

Scheme 16: Proposed mechanism for the formation of homocoupled benzamide[45]



When *N*,*N*-diethylbenzamide (**62**) and ethyl-4-bromobutyrate (**72**) were cross-coupled at low temperature using $Ni(acac)_2/PPh_3$ as catalyst a high amount of homocoupling of benzamide was isolated (Entry 4 and 5, Table 1). It is believed that at low temperature the reductive elimination step of the aryl-alkyl-metal complex is relatively slow. This can lead to, as shown in Scheme 16, to a competing second transmetalation reaction, resulting in a zink-specie and a more stable aryl-aryl-metal complex. The more stable aryl-aryl-metal complex will upon reductive elimination give the homocoupled product of benzamide. However, when the temperature is raised the rate of the

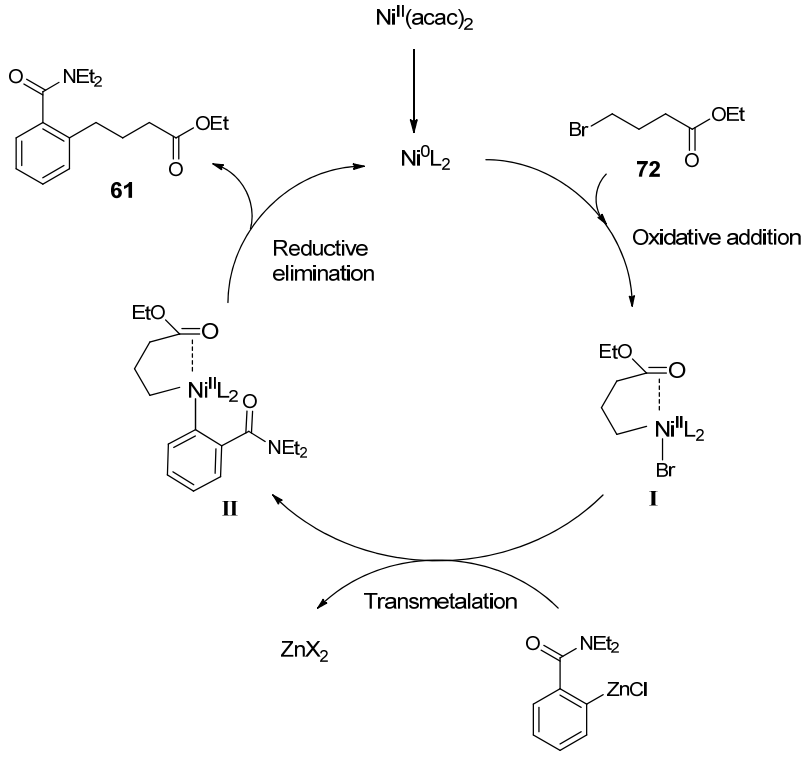
reductive elimination process increases thereby reducing the chance of the second transmetalation reaction to occur. Fortunately, this leads to higher yield of the desired cross-coupling product as described above.

For $NiCl_2$(dppe) (Entry 10, Table 1), the relatively electron deficient ligand dppe can increase the electron density around the nickel catalyst. When the electron density around the nickel catalyst increases a relatively unstable aryl-alkyl-metal complex can occur, which can lead to the formation of the more stable aryl-aryl-metal complex in a second transmetalation reaction. The aryl-aryl-metal complex will upon reductive elimination result in the homocoupled product of aryl. This was observed in the cross-coupling of benzamide **62** and bromobutyrate **72** utilizing the $NiCl_2$(dppe) (Entry 10, Table 1).[43,44]

Interestingly, when using 10 mol% of PPh_3 and 5 mol% of $Ni(acac)_2$ a lower yield of the cross coupling product was obtain (Entry 8, Table 2). This might be explained by the higher electron density around nickel when two triphenyl phosphines are bond compared to only one, as described earlier in this chapter. However, since no side product was isolated or observed the oxidative addition of ehyl-4-bromobutyrate might be slower than for the other conditions and nickel catalyst that was tested in this reaction. With longer reaction time the yield could perhaps be higher.

It has been proposed that nickel-catalyzed Negishi cross coupling reaction can undergo different mechanisms depending on what ligands are bound to the metal and which substrate that are to be coupled.[44a] Knochel proposed a mechanism for alkyl electrophiles having a double bond or a carbonyl-group in the 4- or 5-position were the π-bound coordinated to nickel. The acidity of the π-bond has the possibility to reduce the electron density around nickel and thereby facilitate the reductive elimination process. In Scheme 17 the proposed mechanism for the cross-coupling of *N*,*N*-diethylbenzamide (**62**) and ethyl-4-bromobutyrate (**72**) is outlined, which is based on the mechanism originally proposed by Knochel.[46]

Scheme 17: Proposed mechanism for the Negishi cross-coupling reaction of benzamide **62** and ethylbromobutyrate **72**[46]



2.3.2 Friedel-Craft cyclization reaction

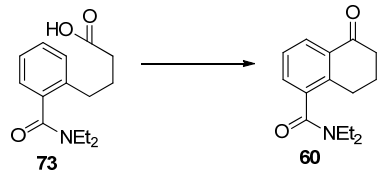
Butanoic acid **73** could be converted to tetralone **60** via an intramolecular Friedel-Craft acylation reaction.[47] In the first attempt butanoic acid **73** was first transformed to its corresponding acyl chloride by thionyl chloride ($SOCl_2$). The newly formed acyl chloride was attempted to be cyclisized to tetralone **60** by a catalytically amount of aluminium trichloride ($AlCl_3$) dissolved in 1,2-dichloroethane (Entry 1, Table 2). However, only trace amount of product was observed and nothing of the starting material could be recovered.

Methane sulphonic acid (MsOH) has shown to be able to directly transform carboxylic acids to tetralones.[48] However, when applying this to butanoic acid **73** no reaction occurred (Entry 2, Table 2), but fortunately starting material could be recovered. Eaton`s reagent (7.7 w% of $P_2O_5$ in MsOH) has also shown promising results in the direct transformation of carboxylic acids to tetralones.[49] Unfortunately, when butanoic acid **73** dissolved in Eaton`s reagent was stirred at room temperature overnight, no reaction occurred (Entry 3, Table 2), but also here starting material could be recovered. However, when increasing the temperature to 60 °C using Eaton`s reagent tetralone **60** could be obtain in 26% isolated yield after 6 hours of stirring (Entry 4, Table 2). After 19 hours of stirring tetralone **60** was isolated in 39% yield (Entry 5, Table 2). Unfortunately, when stirring the reaction mixture for 3 days at 60 °C the yield of tetralone **60** decreased to 30% (Entry 6, Table 2).

In order to improve the reaction the temperature was raised to 100 °C. After stirring the reaction mixture for 2 hours at 100 °C, tetralone **60** could be isolated in 61% yield (Entry 10, Table 2). The decrease in yield after longer reaction time was also observed at 100 °C. When butanoic acid **73** in Eaton`s reagent was stirred at 100 °C for 3 days, tetralone **60** was only obtained in 13% isolated yield (Entry 12, Table 2). The decrease in yield upon longer reaction time probably occurs because amides can be reduced to nitriles in the present of drying agents such as diphosphor pentaoxide (P_2O_5).[50] Raising the temperature further, to 120 °C, did not improve the reaction in any way. Tetralone **60** was afforded in 54% isolated yield after 1.5 hour of stirring (Entry 15, Table 2).

Interestingly, for this Friedel-Craft cyclization reaction 2 equivalent of P_2O_5 was necessary in order to obtain 61% yield (Entry 9, Table 2). If only 1 equivalent was used tetralone **60** was only obtain in 31 or 37% yield after 3 or 1 hour at 100 °C (Entry 12 and 13, respectively). Also here the yield decreased with longer reaction time, as observed for other conditions.

Table 2: Friedel craft acylation of butanoic acid **73**

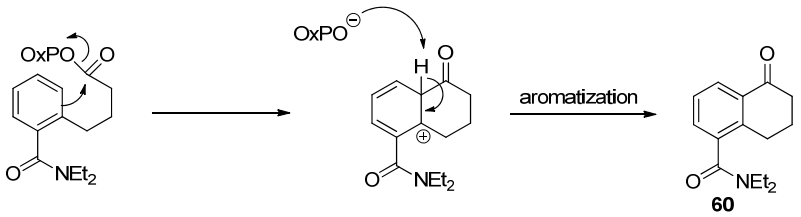


Entry	Reagent	Temperature (°C)	Time (h)	Yield (%)
1	$SOCl_2$ / $AlCl_3$, $(CH_2)_2Cl_2$	75 / 85	2 / 19	trace
2	MsOH	70	19	nr
3	Eaton`s reagent	r.t	19	nr
4	Eaton`s reagent	60	6	26
5	Eaton`s reagent	60	19	39
6	Eaton`s reagent	60	72	30
7	Eaton`s reagent	80	1.5	45
8	Eaton`s reagent	80	4	52
9	Eaton`s reagent	100	1.5	54
10	Eaton`s reagent	**100**	**2**	**61**
11	Eaton`s reagent	100	3	59
12	Eaton`s reagent	100	67	13
13	Eaton`s reagent[a]	100	1	37
14	Eaton`s reagent[a]	100	3	31
15	Eaton`s reagent	120	1.5	54

Eaton`s reagent = 7.7 w% of P_2O_5 dissolved in MsOH;
2 equivalent of P_2O_5 was used if not otherwise specified.
[a] 1 equivalent of P_2O_5

A proposed mechanism for the Friedel-Craft cyclization reaction using Eaton`s reagent is outlined in Scheme 18. The transformation from carboxylic acid to the tetralone using phosphorious reagents has been proposed to involve the formation of a mixed phosphoric-carboxylic acid anhydride.[51]

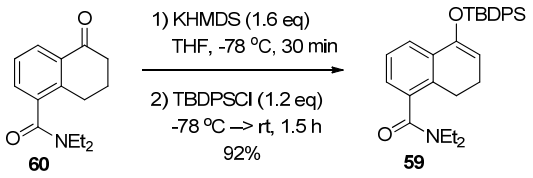
Scheme 18: Proposed mechanism for the Friedel-Craft cyclization using P_2O_5



2.3.3 Shi-epoxidation reaction

From tetralone **60** the silyl enol ether was generated by a deprotonation with potassium hexamethyldisilazid (KHMDS) and *in situ* trapping of the formed enol with *tert*-butyldiphenylsilyl chloride (TBDPSCl). By following literature procedure[39] *tert*-butyldiphenylsilyl enol ether **59** was obtained in 92% isolated yields.

Scheme 19: Formation of tert-butyldiphenylsilyl enol ether

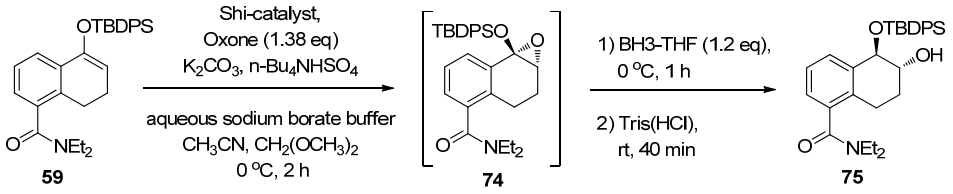


With *tert*-butyldiphenylsilyl enol ether **59** in hand, the key step in the total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**), which was the Shi-epoxidation reaction,[39,52] could be performed. In this reaction a silyloxy epoxide was first formed from silyl enol ether and then transformed to *trans*-diol monosilyl ether by a regio- and stereospecific addition of hydride. This

transformation from tetralone has been shown to give *trans*-diols in high yields and high *enantiomeric excess*.[39]

In a typical Shi-epoxidation reaction Oxone- and potassium carbonate-solution was added slowly to a mixture of silyl enol ether **59** and Shi-catalyst in dimethoxymethane (DMM) and acetonitrile at 0 °C. After workup the crude silyloxy epoxide **74** was subjected to treatment with BH_3-THF at 0 °C, followed by a careful quenching with tris(hydroxymethyl)aminomethane hydrochloride (tris(HCl)). Normal workup procedures afforded *trans*-diol monosilyl ether **75**, as shown in Scheme 20.

Scheme 20: Shi-epoxidation reaction of enol ether **59**



A) Shi-catalyst (0.3 eq), K_2CO_3 (5.8 eq) - 48%, 85% ee
B) Shi-catalyst (0.3 eq), K_2CO_3 (8 eq) - 70%, 83% ee
C) Shi-catalyst (0.5eq), K_2CO_3 (8 eq) - 76%, 83% ee

The Shi-epoxidation reaction is a relatively sensitive reaction, and the outcome of the reaction is depended on the temperature, reaction time, solvent and especially the pH of the reaction mixture.[52] When following the literature procedure,[39] *trans*-diol monosilyl ether **75** was only obtain in 48% yield. However, the pH was measured to be only 9, when this reaction under ideal conditions should be carried out at pH 10.5 or higher.[52] Fortunately, by increasing the amount of potassium carbonate to 8 equivalents instead of 5.8 equivalents, *trans*-diol monosilyl ether **75** could be obtained in 70% isolated yield. In order to see if the yield could be increased any further, the reaction was performed with 0.5 equivalents of Shi-catalyst, but the yield of *trans*-diol monosilyl ether only increased slightly, to 76%. The *enantiomeric excess* was

shown to be 85% when the low yield was obtained and 83% at higher yields. The HPLC chromatograph is given in Figure 6. Two components were detected; the minor enantiomer at t_R 13.2 and the major enantiomer at t_R 16.6.

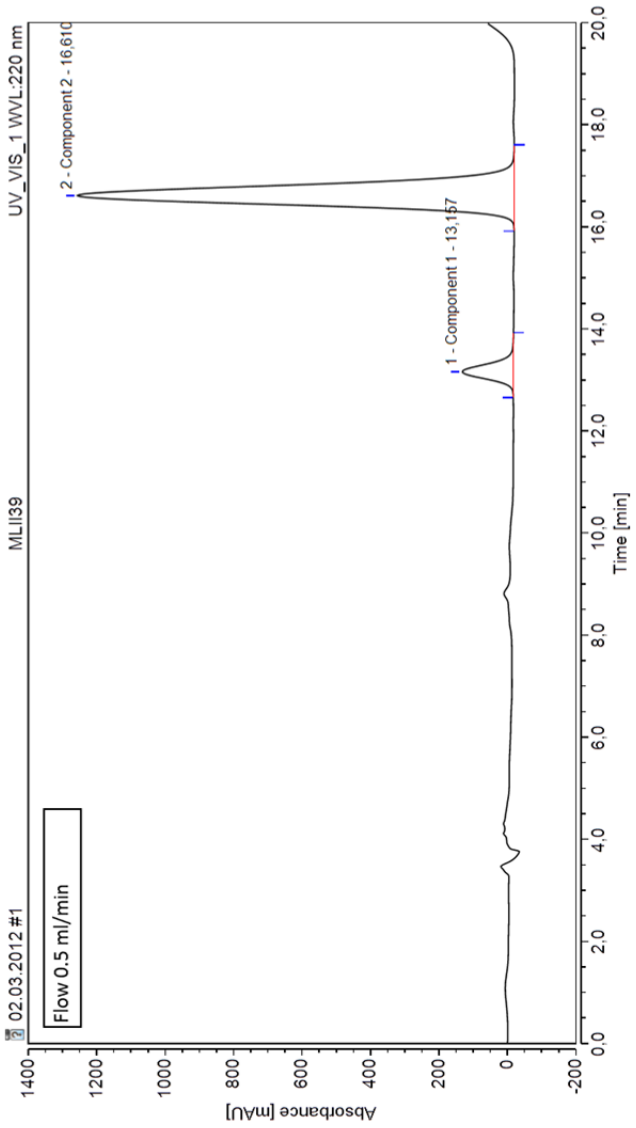
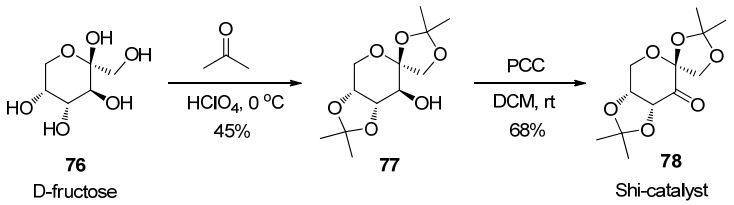


Figure 6: HPLC chromatogram of *trans*-monosilyl diol ether **75**

The catalyst that was used in this asymmetric epoxidation was formed from D-fructose in two simple steps utilizing literature procedure.[52] D-fructose **76** was subjected to treatment with perchloric acid ($HClO_4$) and acetone to afford the protected D-fructose **77** in 45% yield after recrystallization. The free hydroxyl-group in turn was oxidized with pyridinium chlorochromate (PCC) at room temperature, and after chromatographic purification the Shi-catalyst **78** was obtained in 68% yield, as shown in Scheme 21.

Scheme 21: Formation of the Shi-catalyst



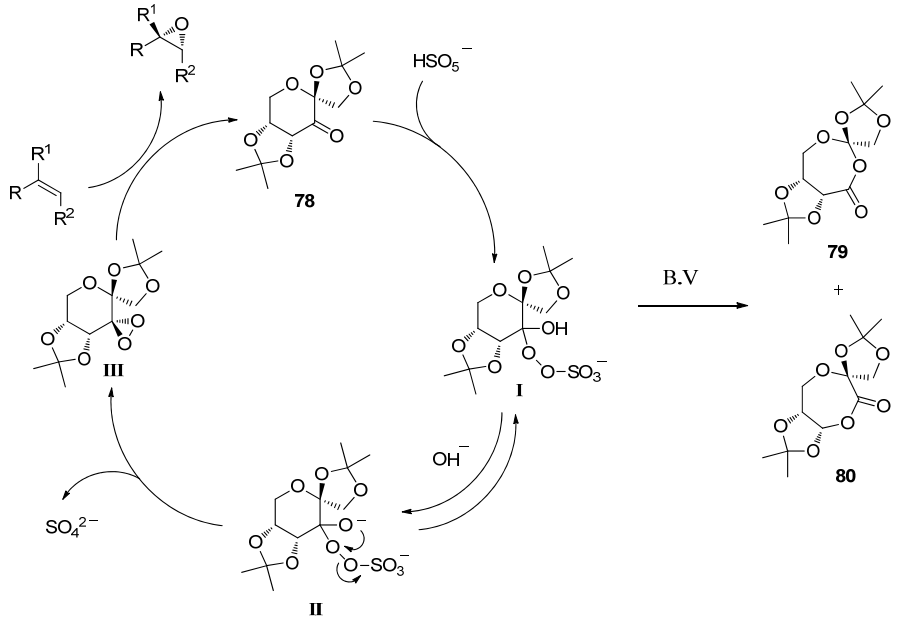
76
D-fructose

77

78
Shi-catalyst

The D-fructose derived catalyst **78** goes through a catalytical cycle as outlined in Scheme 22. When Oxone is slowly added to the reaction mixture it reacts with the ketone and under basic conditions forms anion **I** which in turn generates the dioxirane **III** *in situ*. When the chiral dioxirane **III** is generated the silyl enol ether can be transformed to a silyloxy epoxide asymmetrically. Several other di- or trisubstituted olefins has shown to also be able to be transformed to its respective epoxides with excellent yields and *enantiomeric excess*.[39,52]

Scheme 22: Catalytical cycle for the Shi-epoxidation reaction



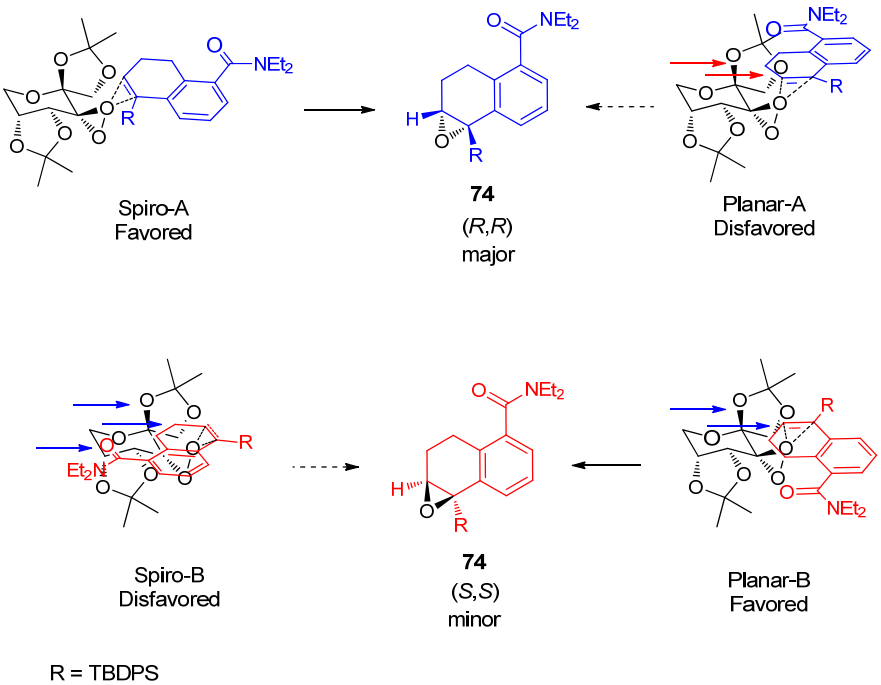
As mentioned earlier in this chapter, high pH is very important for this reaction, especially for the formation of anion **II** which is essential in the formation of the chiral dioxirane **III**. At low pH (7-8) the affinity for the formation of anion **II** is low. The catalyst can then go through a Baeyer Villiger reaction to form a decomposed catalyst (**79** and **80**), which has no catalytical activity. At higher pH (>10) Oxone has been known to go through an autodecomposition. However, at higher pH the ketone is sufficiently reactive to compete with the decomposition of Oxone, and the higher nucleophilicity of Oxone facilitates the formation of anion **II** that is essential in the formation of the chiral dioxirane **III**. The higher nucleophilicity of Oxone also decrease the chance for the catalyst to go through a Baeyer Villiger reaction.[52]

For the D-fructose derived catalyst the reaction center where the substrate and the catalyst approach each other is close to a stereogenic center. This results in an efficient stereochemical communication between the

substrate and the catalyst, where one face of the catalyst is stereogenically blocked. This again limits competing approaches resulting in the formation of epoxides in high *enantiomeric excess*.[39,52]

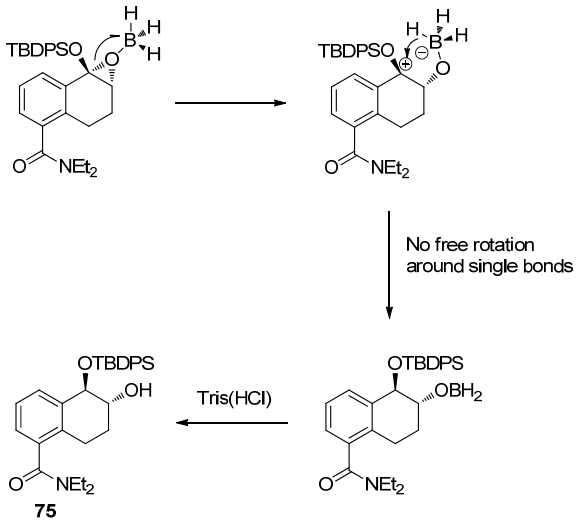
There are several ways for the substrate to approach the catalyst. Four transition states are outlined in Scheme 23, were two of them results in the formation of (*R*,*R*)-entantiomer, while the other two results in the formation of the (*S*,*S*)-enantiomer. These transition states include two mechanistic extremes which is the spiro and planar transition state. In order for the substrate to form the (*R*,*R*)-entantiomer it has to approach the catalyst in such a way that generates either a spiro-A or planar-A transition state, while spiro-B and planar-B transition state results in the formation of the (*S*,*S*)-enantiomer. The spiro-A transition state generate less energy difference compare to all other approaches, hence forming the (*R*,*R*)-enantiomer in high *enantiomeric excess*.[52a]

Scheme 23: Four alternative approaches for the catalyst



As mentioned above, crude epoxide **74** was subjected to treatment with BH_3-THF in the formation of *trans*-diol monosilyl ether **75** in 48-76% yield. As Scheme 24 illustrate, BH_3 coordinates to the oxygen in the epoxide and binds covalently when the epoxide is open up by forming a cationic center and a hydride. Since there is no free rotation around single bonds, due to the fused 6-membered ring, epimerization is not very likely at either site. The hydride will therefore attack the cationic center from the same side as the epoxide was formed. Since it is not likely that the compound epimerizes the enantioselectivity must come from the Shi-epoxidation reaction, in keeping with Shi`s prior observations,[52] as Lim *et al*. pointed out.[39]

Scheme 24: Formation of *trans*-diol monosilyl ether **75** from epoxide **74**



The oxygen-boron bond was cleaved by Tris(HCl) resulting in the formation of *trans*-monosilyl enol ether **75** as a *ca* 3:2 mixture of rotamers determined by ^{1}H NMR experiments (Figure 7).

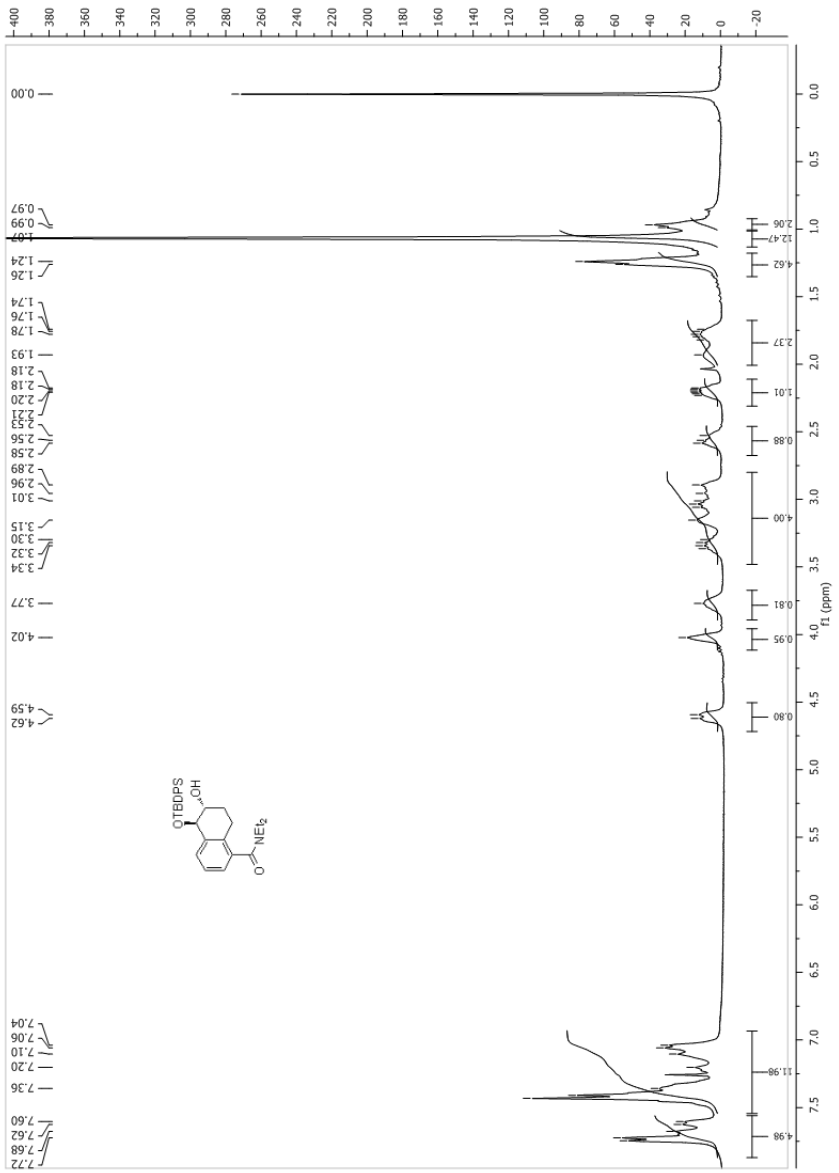
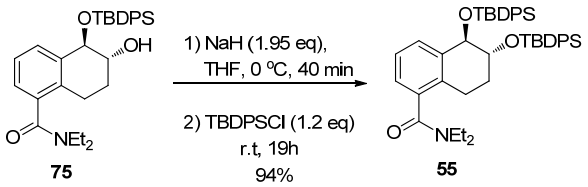


Figure 7: 300 MHz ^{1}H NMR spectrum of *trans*-diol monosilyl ether **75**

The free hydroxyl in *trans*-diol monosilyl ether **75** was deprotonated by sodium hydride (NaH) and trapped *in situ* with *tert*-butyldiphenylsilyl chloride (TBDPSCl), as shown in Scheme 25. This gave the *trans*-diol disilyl ether **55** in 94% yield after purification by flash coloum chromatography.

Scheme 25: Protection of the *trans*-diol monosilyl ether **75**



The long reaction time (19 hours) for the *in situ* trapping of the oxide with *tert*-butyldiphenylsilyl chloride (TBDPSCl) was observed to be very essential. With shorter reaction time compound **55** was only obtained in 49-78% yield. Fortunately, in all cases were the yield was less than 94% *trans*-diol monosilyl ether **75** could be recovered, and after a second deprotection and *in situ* trapping of the oxide with TBDPSCl *trans*-diol disilyl ether **55** was formed in quantitative yields. As indicated in Figure 8 the product gave a *ca* 3:2 mixture of rotamers as judged by ^{1}H NMR spectrometry.

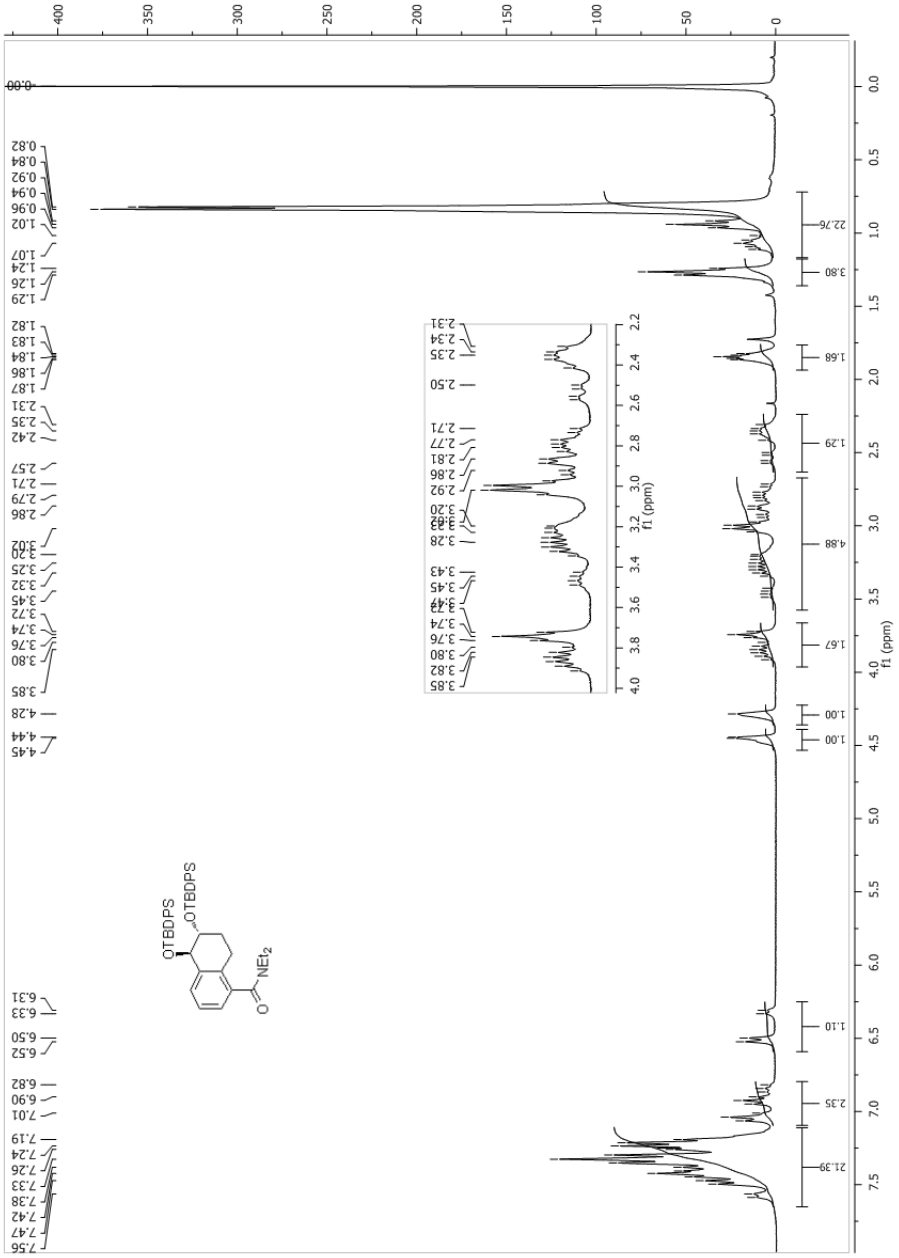


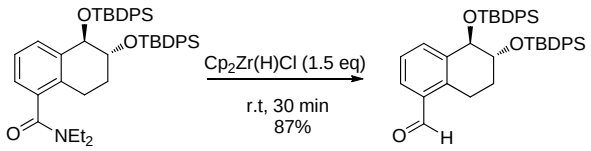
Figure 8: 300 MHz ^{1}H NMR spectrum of *trans*-diol disilyl ether **55**

2.3.4 First attempt towards the synthesis of (1R,2R)-1,2-dihydrochrysene-1,2-diol

In 2000, White *et al*. reported a fast and efficient reduction of tertiary amides to aldehydes by using Schwartz reagent, $Cp_2Zr(H)Cl$. Both aromatic and aliphatic tertiary amides could easily be reduced to aldehydes, and the conditions tolerated a wide range of functionalities to be present in the substrate.[33a]

Subjecting *trans*-diol disilyl ether **55** to these conditions by adding a solution of compound **55** in THF to a suspension of $Cp_2Zr(H)Cl$ in THF at room temperature converted the white suspension to a clear, light yellow solution after a few minutes, indicating that the reaction was finished. However, the solution was stirred for 30 min, concentrated *in vacuo* and purified by flash coloum chromatography, thus giving aldehyde **53** in 87% isolated yield (Scheme 26).

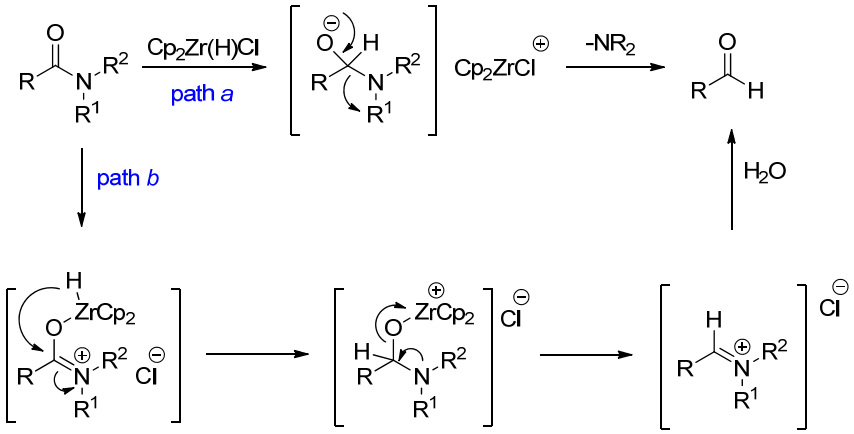
Scheme 26: Amide reduction of *trans*-diol disilyl ether **55**



55 **53**

Georg and his coworkers proposed that the mechanism for the amide reduction either to go through path *a* or path *b*, as shown in Scheme 27. After labeling experiments with H_2O^{18} followed by NMR analysis they suggested that the proposed reaction path *b* to be more likely than path *a*. In path *b* zirconium coordinates to the oxygen of the carbonyl-group in the formation of an imine salt. The hydride attacks the imine in the formation of amine, followed by a new imine-formation with $OZrCp_2$ as leaving group. The aldehyde is first formed in the present of water during work-up and chromatographic purification.[33]

Scheme 27: Proposed mechanism for the amide reduction[33]



The ^{1}H NMR spectrum of compound **53** shows the characteristic aldehyde proton at 10.33 ppm (Figure 9). The CH_2-group adjacent to the benzaldehyde is detected as two multiplets, one ranging from 2.39-2.30 ppm and the other ranging from 1.96-1.89 ppm. There are no mixture of rotamers, thus the benzaldehyde protons are detected as one dublet at 7.69 ppm, a triplet at 7.00 ppm and a dublet at 6.61 ppm.

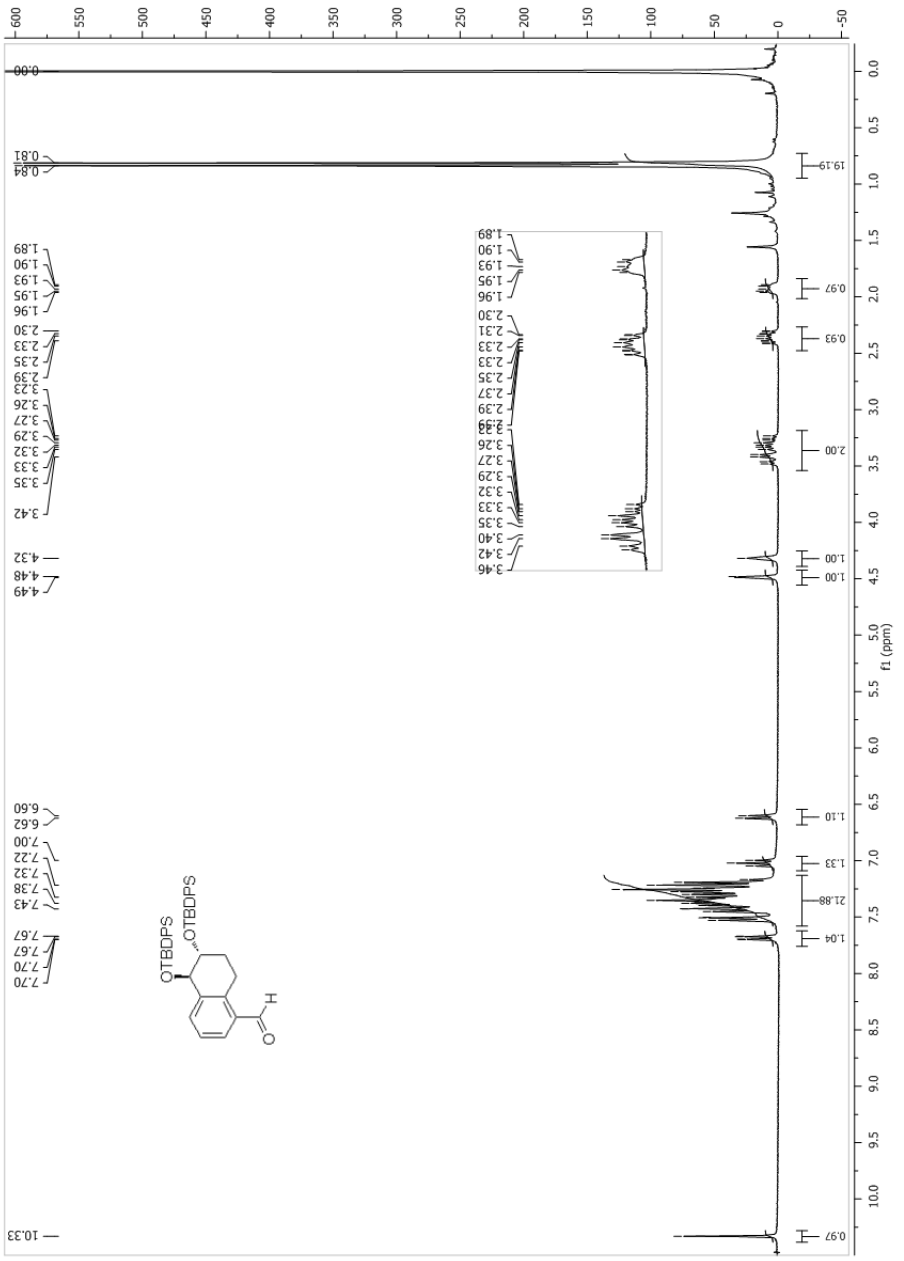
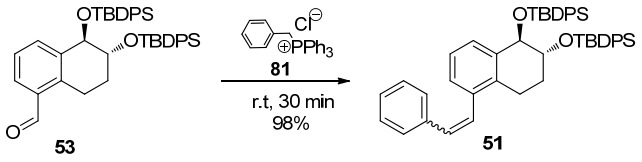


Figure 9: 300 MHz ^{1}H NMR spectrum of aldehyde **53**

Stilbenes can easily be generated from aldehydes.[34] In a typical Wittig reaction aldehyde **53** was transformed to stilbene **51** upon treatment with a mixture of benzyltriphenylphosphonium chloride (**81**) (Wittig salt) and sodium hydroxide (50% solution) in DCM at room temperature.[35c] The yellow reaction mixture turned orange after the addition of sodium hydroxide-solution, and turned yellow again after stirring for 30 min, indicating that the reaction was finished. After chromatographic purification a mixture of *E*- and *Z*-stilbene **51** was obtained in 98% yield, as shown in Scheme 28.

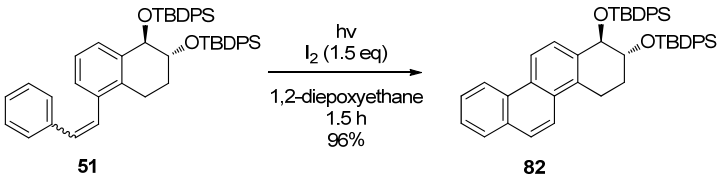
Scheme 28: Wittig reaction



The *E*- and *Z*-relationship was determined to be *ca* 2:1, however, due to overlapping signals it was difficult to determined which isomer was formed in a higher amount than the other. The *E*- and *Z*-stilbene were not separated from one another by flash coloum chromatography, since *E*-stilbene isomerizes to the *Z*-stilbene under irradiation.[53] Only the *Z*-stilbene is able to ringcyclisize to the chrysene skeleton. The mechanism for both the isomerization and photocyclization will be outlined later in this chapter.

In the photocylization reaction *E*- and *Z*-stilbene was dissolved in toluene, and iodine (1.1 equiv.) was added. The resulting pink reaction mixture was irradiated for 2 hours with a 400 w medium pressure Mercury-lamp.[35c] Normal workup procedure followed by flash coloum chromatography afforded compound **82** in 96% isolated yield, as shown in Scheme 29.

Scheme 29: Photocyclization reaction for the formation of compound **82**



51 **82**

In the ^{1}H NMR spectrum, given in Figure 10, the characteristic chrysene signals can be detected between 8.65-6.80 ppm.

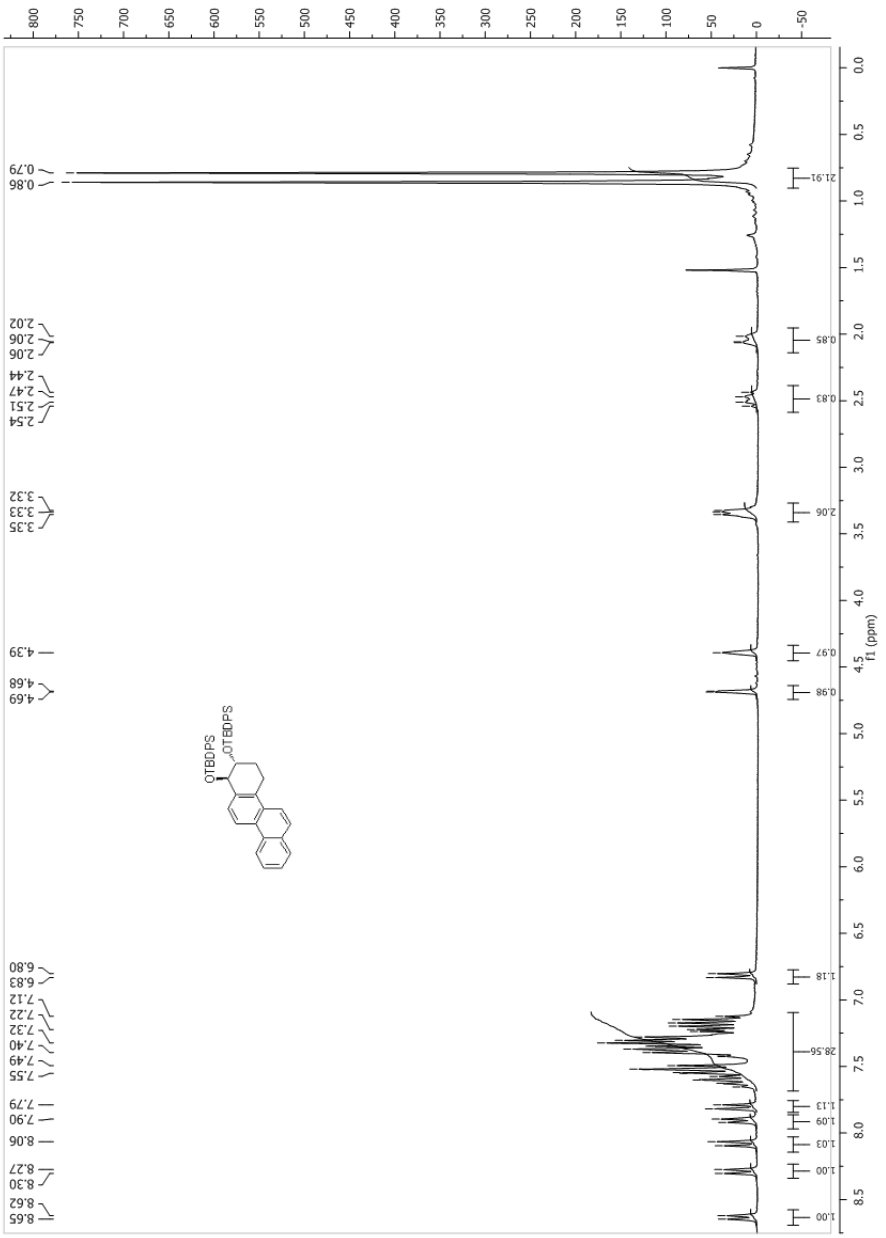
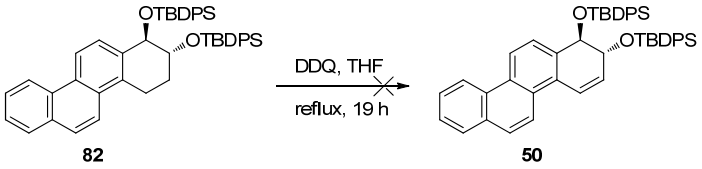


Figure 10: 300 MHz ^{1}H NMR spectrum of compound **82**

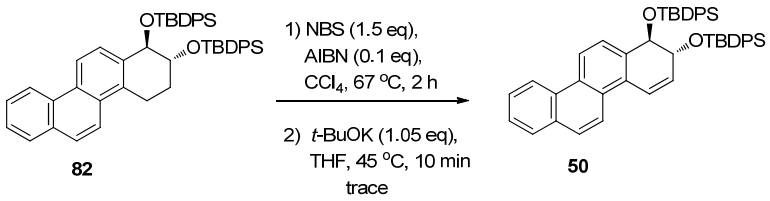
From substrate **82** the double bond was attempted introduced by doing a dehydrogenation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry THF. This transformation has been well established for the dehydrogenation of benzo[*a*]pyrene.[25,54] Unfortunately, when applying this to **82** no product was formed; only starting material could be recovered. Interestingly, Harvey and his coworkers also observed this for their chrysene-metabolite precursor.[22] This might be explained by the relatively steric hindrance due to the large protecting group of the adjacent hydroxyl-group.

Scheme 30: Dehydrogenation with DDQ



Since the dehydrogenation approach with DDQ failed a more typical bromination-dehydrobromination approach was carried out in order to afford **50**. *N*-bromosuccinimine (NBS) and catalytical amount of azobisisobutyronitrile (AIBN) was added to a solution of compund **82** in tetrachloromethane.[22,55] Unfortunately, the reaction mixture gave a range of products which were not possible to separate by coloum chromatography. Continuing with the dehydrobromination using potassium *tert*-butoxide resulted in a mixture of two main products and trace amount of the wanted *trans*-diolchrysene **50** as evident from ^{1}H NMR analysis. In spite of all the effort put into trying to separate these compounds by flash coloum chromatography these products were not separable from one another on silica gel.

Scheme 31: Bromination and dehydrobromination of compound **82**

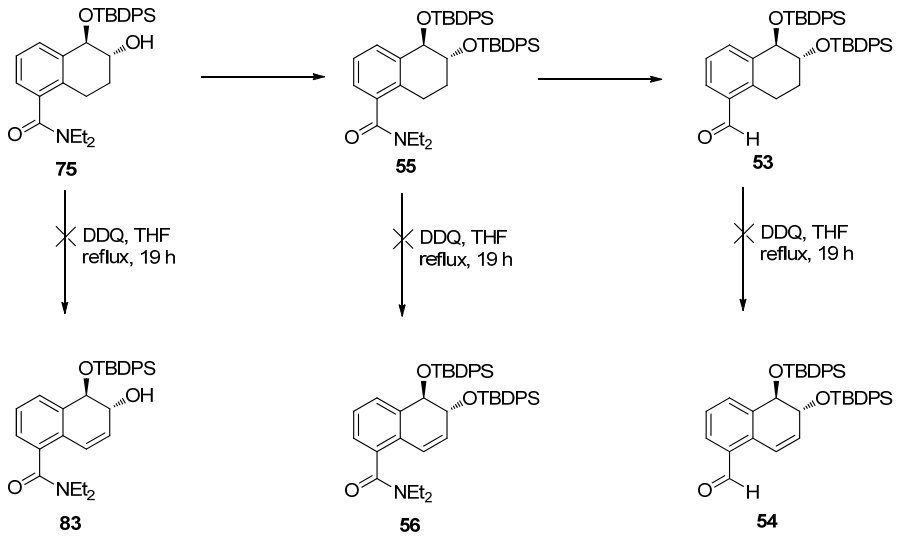


The two main products were deprotected with TBAF. As mentioned, only trace amount of the desired product was isolated along with the mixture. The other two products seem to arise from an addition of bromine to compound **82** from the bromination reaction. Some deprotection of *trans*-diol after the bromination was also observed, but due to difficulty of separating all compounds formed in the complex mixture these products were not isolated or recovered. Due to the complex mixture of products afforded after the bromination reaction this was thought to not be a good strategy for the formation of *trans*-dihydrodiol **1**.

2.3.5 Second attempt towards the synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol

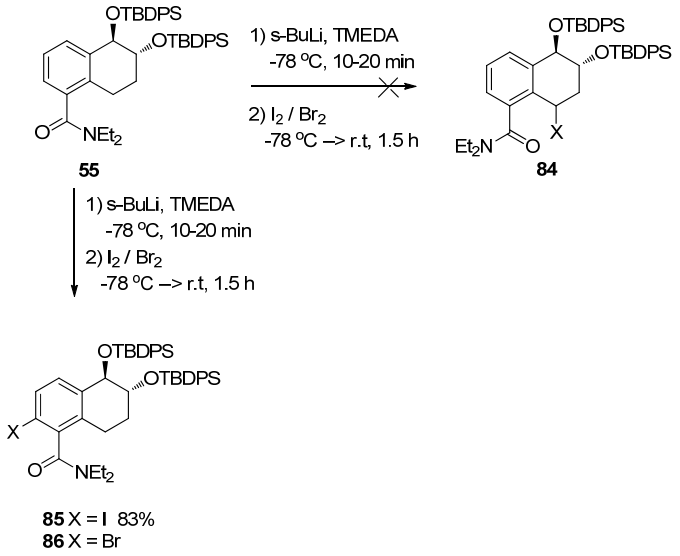
In the second attempt towards the synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol (**1**) the dehydrogenation step using DDQ was attempted on the *trans*-diol monosilyl ether **75**, on the *trans*-diol disilyl ether **55** and on the aldehyde **53** (Scheme 32). Unfortunately, DDQ failed to react in all these reactions, and only starting material could be recovered. A reason for why this failed, especially for compound **75** and **55** can be because of the steric hindrance from both the amide group and the TBDPS protecting group.

Scheme 32: Attempted dehydrogenation of compound **75**, **55** and **53**



Since dehydrogenation with DDQ failed the double bond was attempted to be introduced by a metalation reaction. Due to the amide directing group and the relatively acidic benzylic proton it was believed that a halogen could be introduced in the benzylic position using organolithium reagents,[56] and *in situ* trapping of the lithium specie with either iodine or bromine. Both LDA and *n*-BuLi were tested in this reaction, but there was no indication that the reaction proceeded, and after work-up procedures only starting material could be recovered. However, when amide **55** was added to a solution of *s*-BuLi and TMEDA a deep purple color appeared. This deep purple color is a relatively strong indication that the benzylic proton had been deprotonated. Unfortunately, after chromatographic purification the *ortho*-metalated product **85**/**86** was isolated, as can be seen in Scheme 33. This product is formed from the general directed *ortho*-metalation (D*o*M) reaction, which will be discussed in more detail in chapter 3.

Scheme 33: Attempted metalation reaction in the formation of **84**



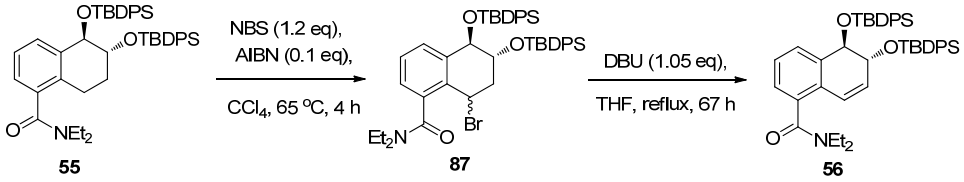
Since both DDQ and the metalation strategy failed the more typical bromination,[22,55] followed by dehydrobromination of compound **55** was attempted. NBS and catalytically amount of AIBN was added to a solution of compound **55** in tetrachloromethane. After 1.5-2 hours stirring the light yellow solution went orange, indicating the formation of bomine (Br_2). After yet another 2 hours the orange solution went yellow again, indicating that the reaction had reached completion. After chromatographic purification the benzyl bromide **87** was obtained in 67% isolated yield, and from this reaction 26% of starting material could also be recovered. Trace amounts of impurities was also observed by TLC analysis, however, these were not attempted isolated.

With the benzyl bromide **87** in hand, a dehydrobromination/ elimination reaction could be performed. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added to a solution of benzyl bromide **87** in THF. After stirring the reaction mixture at reflux for three days compound **56** was obtain in 74% yield after chromatographic purification. The long reaction time is believed to

arise from the relatively large steric hindrance of the protons adjacent to the protected hydroxyl-group, due to the size of the protecting groups, in addition to the size of DBU.

Potassium *tert*-butoxide (*t*-BuOK) could also be used as base in the elimination reaction, and the reaction was finished after only one hour. By such means the desired compound **56** was obtained in 66% isolated yield after chromatographic purifications. Using *t*-BuOK a small amount of deprotected product was also observed by TLC analysis, however, this was not attempted isolated.

Scheme 34: Bromination and dehydrobromination of **55** in the formation of **56**



The ^{1}H NMR spectrum of *trans*-diol disilyl ether **56** is given in Figure 11.

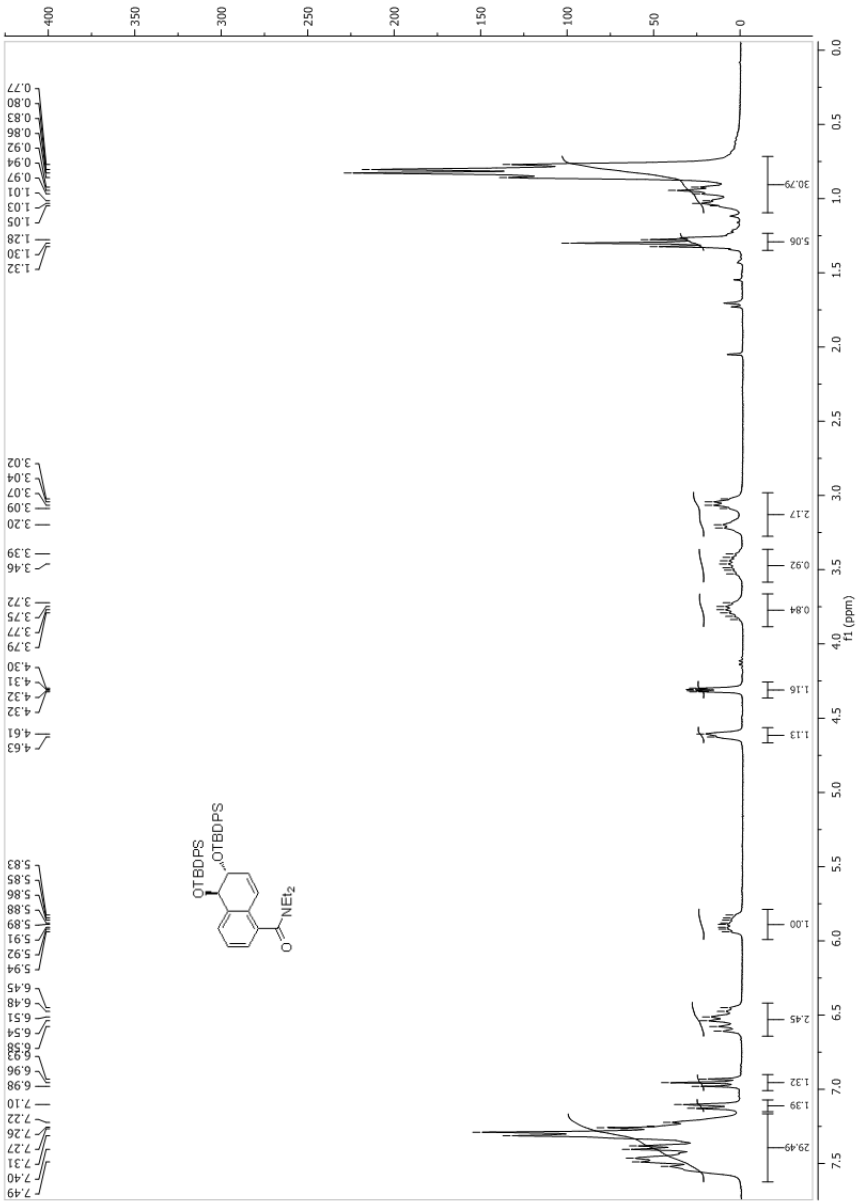
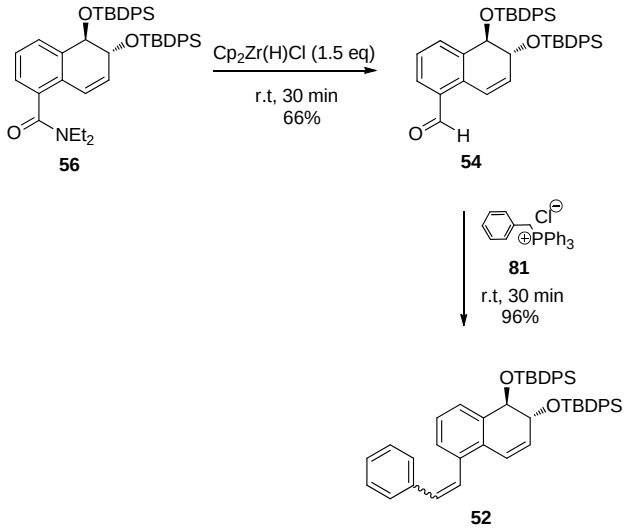


Figure 11: 300 MHz ^{1}H NMR spectrum of compound **56**

From amide **56** an amide reduction using Schwartz reagent was performed.[33a] In a typical amide reduction *trans*-diol disilyl ether **56** in THF was added to a suspension of $Cp_2Zr(H)Cl$ in THF at room temperature and the resulting light yellow solution was stirred for 20 min, before a few drops of water was added. After chromatographic purification aldehyde **54** was obtained in 66% isolated yield. Compared to compound **53** discussed earlier in this chapter the yield of aldehyde **54** was lower, which mostly can be explained by the double bond that is present in compound **54**. Zirconium hydride is well known to add to alkenes and alkynes and used further in cross-coupling reactions.[57]

Scheme 35: Amide reduction of **56**, followed by a Wittig reaction in the formation of stilbene **52**

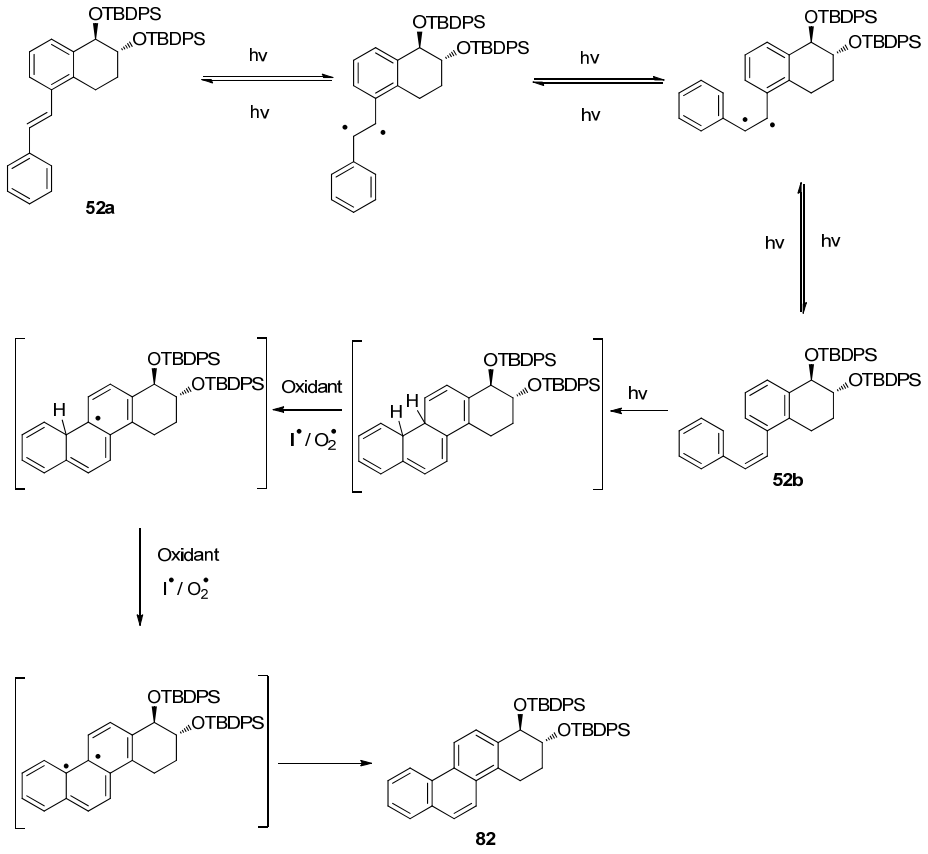


Aldehyde **54** was transformed to stilbene **52** by subjecting it to a Wittig reaction[34] utilizing the same conditions[35c] as discussed earlier in this

chapter. After normal workup procedures and chromatographic purification a mixture of *E*- and *Z*-stilbene **52** was isolated in 96% yield.

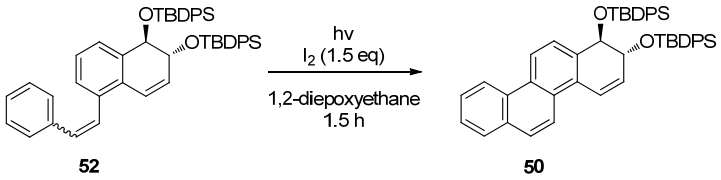
As described earlier in this chapter *E*- and *Z*-stilbene was not separated from one another, since in the photochemical reaction the *E*-stilbene isomerizes to the *Z*-stilbene[53] which then ringcyclizises to the chrysene skeleton in the photocyclization reaction. The proposed mechanism for the photochemical Mallory reaction[35] is illustrated in Scheme 36. A radical is believed to be involved in both the *E*/*Z* isomerization and the ring cyclization reaction. The oxidant in this reaction can either be Iodine (I_2) or oxygen (O_2).

Scheme 36: Proposed mechanism for the photocyclization reaction



The *E*- and *Z*-stilbene was dissolved in toluene, iodine (1.1 equiv) was added and the mixture was irradiated for 2 hours.[35c] Unfortunately, after chromatographic purification a complex mixture of product was isolated. These products were not separable from one another, but from the mixture trace amount of product was detected by ^{1}H NMR analysis. After GC-MS analysis one product with a mass of 864 Dalton was detected, indicating that iodine had been added somewhere in the chrysene molecule.

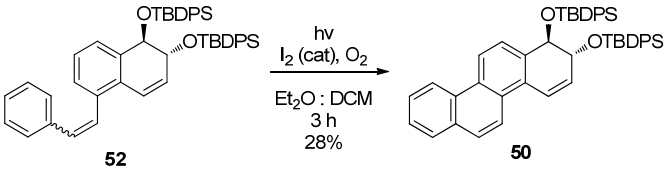
Scheme 37: Photocyclization reaction of stilbene **52**



52 **50**

Since iodine was shown to be a problem the photocyclization reaction was tested with catalytically amount of iodine. *Trans*- and *cis*-stilbene was solved in diethyl ether and dichloromethane (7:1) and the reaction mixture was saturated with air by bobbling air into the solution for 5 min. Catalytically amount of iodine was added and the mixture was irradiated for 3 hours.[58] After chromatographic purification **50** was obtained in 28% isolated yield.

Scheme 38: Photocyclization reaction of stilbene **52**



Also in this reaction a complex mixture of products was isolated along with the desired product. It seems like either solvent or oxygen had attacked the product somewhere in the molecule. However, it is believed that with shorter reaction time higher yields of the product might be obtain. Hopefully, the reaction may also be improved by changing the solvent to toluene.

The ^{1}H NMR spectrum of 1,2-dihydrochrysene-1,2-disilyl ether **50** is given in Figure 12. The characteristic chrysene signals can be detected between 8.62-6.95 ppm. The double dublet at 5.96 ppm couples with the double dublet at 4.42 ppm. These signals represent the H-3 and the H-2 protons, respectively.

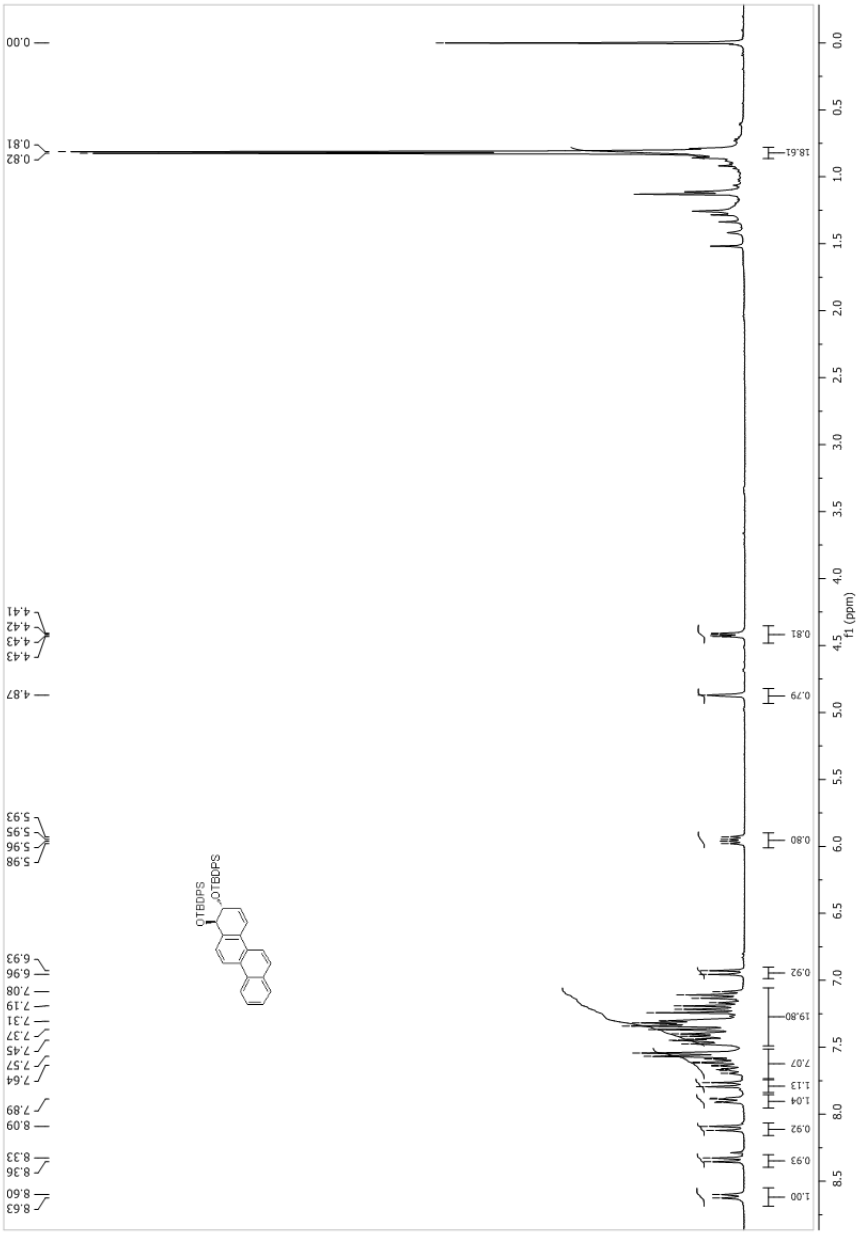
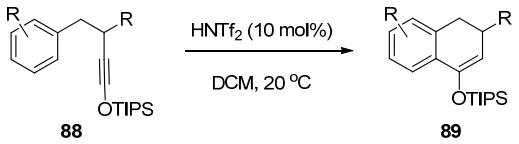


Figure 12: 300 MHz ^{1}H NMR spectrum of compound **50**

2.3.6 Attempted alternative synthesis towards the silyl enol ether

A different strategy was attempted in the formation of silyl enol ether **59** starting from readily available *N*,*N*-diethylbenzamide (**62**). Zhang *et al*.[59] published in 2004 a catalytic ringcyclization reaction of siloxyalkynes using Brønsted-acid triflimide $HNTf_2$ (Scheme 39). The R-group in the compounds were either hydrogen, propyl or methyl.

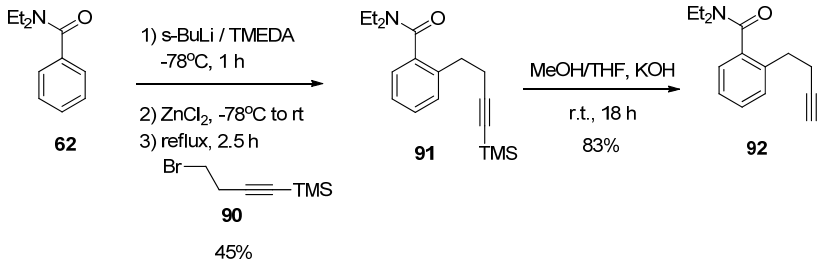
Scheme 39: Brønsted-acid promoted cyclization of siloxyalkynes



88 **89**

In a Negishi cross-coupling reaction the TMS-protected alkyne **91** was formed by *ortho*-lithiation of *N*,*N*-diethylbenzamide (**62**) using *s*-BuLi, followed by transmetalation with $ZnCl_2$ and finally a cross-coupling with (4-bromobut-1-yn-1-yl)trimethylsilane (**90**) to afford the TMS-protected alkyne **91**, as shown in Scheme 40. From this reaction 45% yield of the desired product **91** could be isolated in addition to 39% recovery of unreacted benzamide **62**. The TMS-protected alkyne **91** was deprotected with potassium hydroxide (KOH) in a solution of MeOH/THF to afford alkyne **92** in 83% isolated yield.

Scheme 40: Formation of alkyne **92**

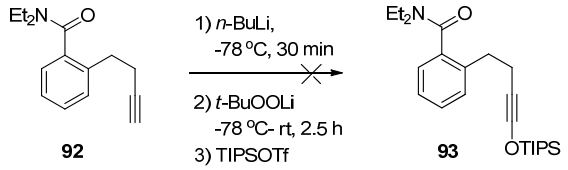


62 **90** **91** **92**

45%

From alkyne **92** the synthesis of siloxyalkyne **93** was attempted utilizing literature procedures.[59] However, this reaction was proven to be more difficult than envisioned, and the product was not obtained even after several attempts.

Scheme 41: Attempted synthesis of siloxyalkyne **93**



Due to the difficulty of forming the siloxyalkyne **93** this strategy was abandoned.

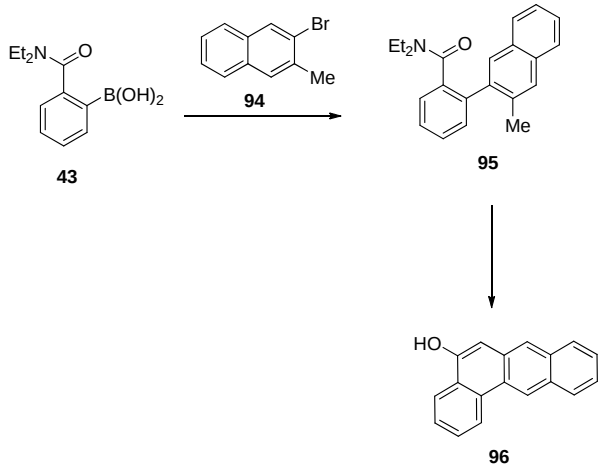
Chapter 3

Directed remote metalation and directed *ortho* metalation reactions for the formation of PAHs

3.1 Introduction

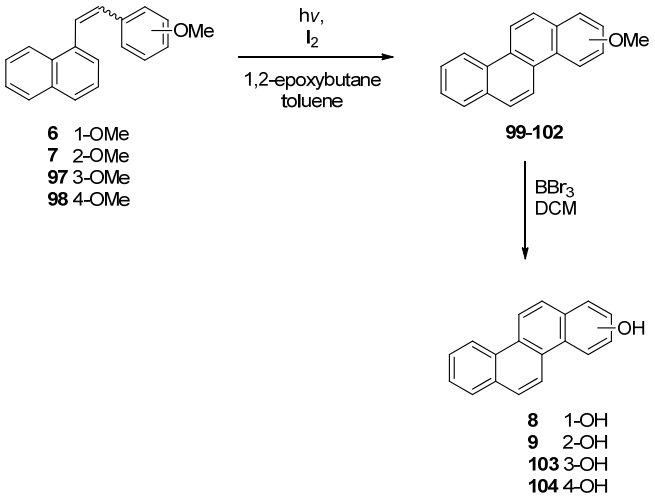
Directed *ortho* metalation (D*o*M),[40,60] followed by a Suzuki-Miyaura cross-coupling and a directed remote metalation reaction (DreM) has been applied in the synthesis of many polycyclic aromatic hydrocarbons, especially for three and four ring aromatic hydrocarbons.[30,37] In chapter 1 the synthesis of 9-phenantrol was shown. Another example of the combined D*o*M, Suzuki-Miyaura and DreM reaction is the synthesis of tetraphen-5-ol (**96**), shown in Scheme 42.

Scheme 42: Formation of tetraphen-5-ol (**96**)



It was envisioned that chrysene-5-ol and chrysene-6-ol could be formed by the combined DoM, Suzuki-Miyaura and DreM strategy. The synthesis of chrysene-5-ol and the attempted synthesis of chrysene-6-ol will be discussed in this chapter. In addition the directed *ortho* metalation reaction (D*o*M) of chrysenyl diethylcarbamates will be discussed. The chrysenyl diethylcarbamates was formed from the already available chrysenols,[35c] shown in Scheme 43.

Scheme 43: Available chrysenols[35c]



3.2 Results and discussion

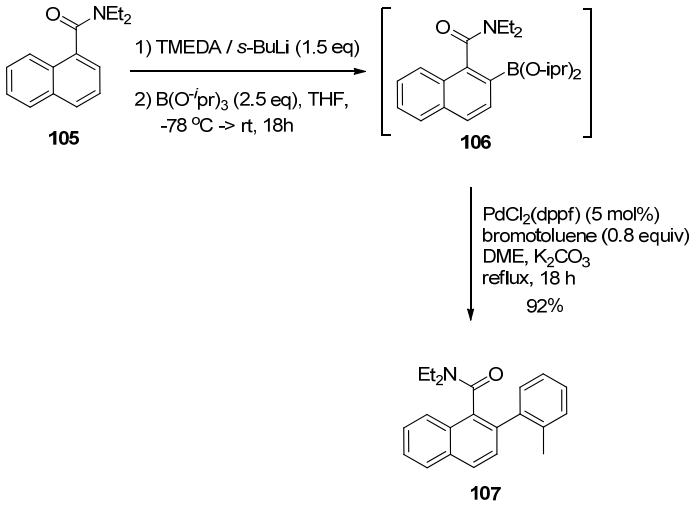
In this section the results obtained in the synthesis of chrysenol, and the directed *ortho* metalation of chrysenyl diethylcarbamates will be discussed.

3.2.1 Directed remote metalation (DreM) of biphenyls for the formation of chrysenols and chrysenyl diethylcarbamates

In order to form chrysene-5-ol by a directed remote metalation reaction, *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (**107**) had to be prepared first. By a directed *ortho* metalation reaction (D*o*M),[40,60] followed by a Suzuki-Miyaura cross-coupling[36] reaction *N*,*N*-diethyl-1-naphthamide (**105**) was transformed to biphenyl **107**. In the Suzuki-Miyaura cross-coupling reaction two borolates, triisopropyl borate and dioxaborolane, was tested.

In a typical D*o*M reaction *N*,*N*-diethyl-1-naphthamide (**105**) was subjected to a solution of *s*-BuLi and TMEDA in THF at -78 °C. The formed *ortho* lithiated specie was trapped *in situ* with triisopropyl borate ($B(O\text{-}^{i}pr)_3$) and the reaction mixture warmed to room temperature overnight. After normal work-up procedures (extraction) the crude naphtyl-borate **106** in DME was cross-coupled with 0.8 equivalent of 2-bromotoluene (**44**) in a typical Suzuki-Miyaura reaction using 5 mol% of $PdCl_2$(dppf) as catalyst (Scheme 44). After chromatographic purification *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (**107**) was obtained in 92% isolated yield.

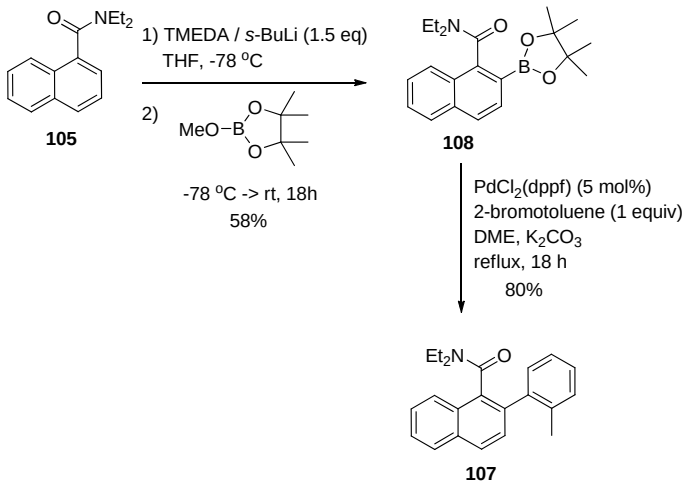
Scheme 44: Formation of biphenyl from *N*,*N*-diethyl-1-naphthamide



By a directed *ortho* metalation reaction *N*,*N*-diethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthamide (**108**) could also be formed from naphthamide **105.** Naphthamide **105** was subjected to *s*-BuLi at -78 °C and the formed *ortho* lithiated specie was trapped *in situ* with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. By TLC analysis it looked like the reaction had gone to completion, however, after chromatographic purification only 58% yield of naphyl-dioxoborolane **108** was obtained.

Naphtyl-dioxoborolane **108** was cross-coupled with 1 equivalent of 2-bromotoluene (**44**) by Suzuki-Miyaura reaction using 5 mol% of $PdCl_2$(dppf) as catalyst. After chromatographic purification biphenyl **107** was obtained in 80% isolated yield. This gave an overall yield of 46%, which was much lower than what was obtained when using triisopropylborolane. Due to the extra purification step this was not thought as a good borolane to be used for this specific compound.

Scheme 45: Formation of biphenyl via dioxaborolanyl-naphtamide



The ^{1}H NMR spectrum of *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (**107**) is shown in Figure 13. As for many other *ortho*-substituted amides prepared in this thesis biphenul **107** is detected as a *ca* 3:2 mixture of rotamers. The amide group display separate signals for the individual protons of the CH_2-groups. These protons are detected as broad multiplets between 4-2.5 ppm. Two signals can also be detected for the methyl-group at 2.26 ppm and 2.19 ppm

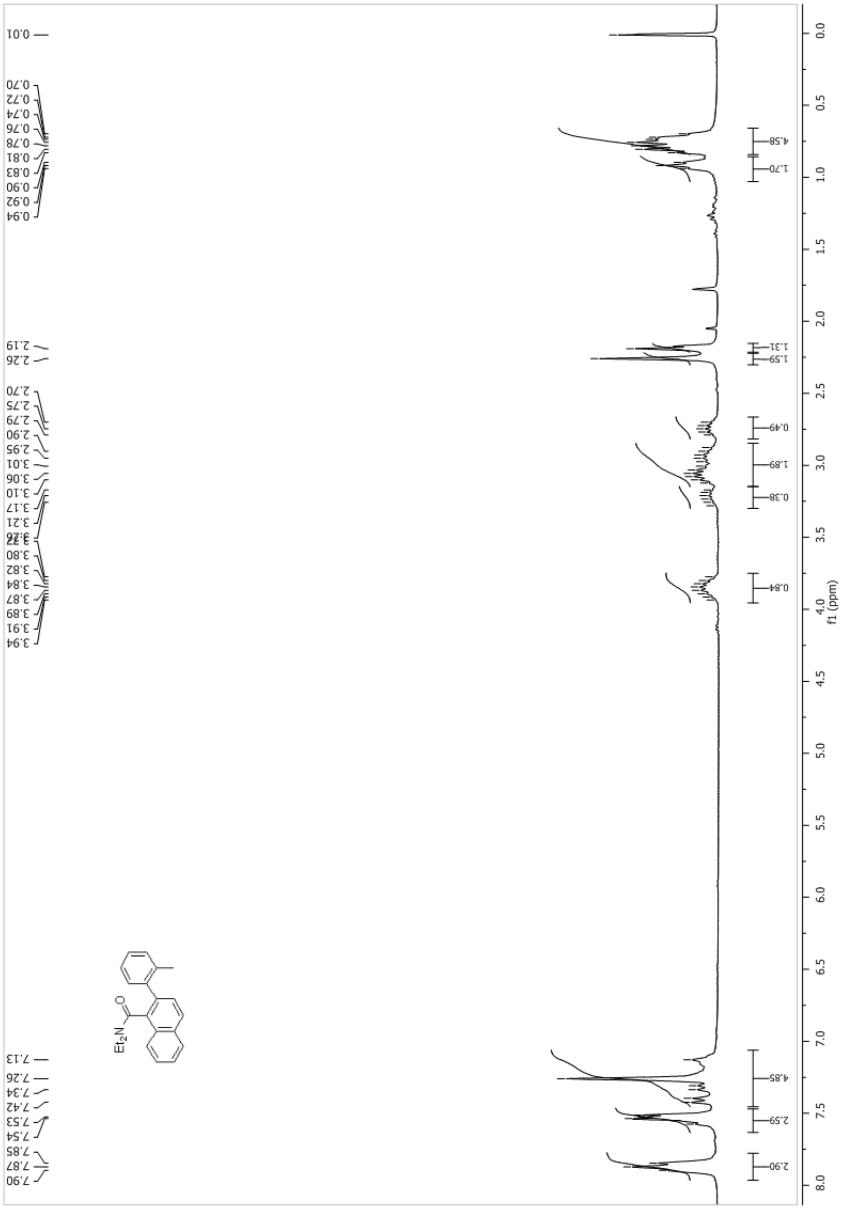
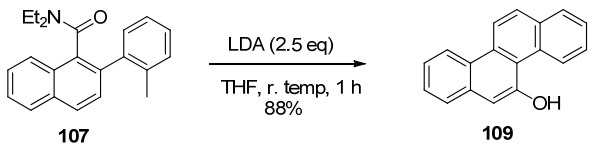


Figure 13: 300 MHz ^{1}H NMR spectrum of compound **107**

In a typical directed remote metalation reaction (DreM) *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (**107**) was subjected to treatment with lithium diisopropylamine (LDA) at 0 °C. Upon addition of LDA the reaction mixture turned red, but after stirring for 1 hour at room temperature the mixture turned yellow. The yellow color indicated that the reaction had reached completion and after chromatographic purification, chrysene-5-ol (**109**) was obtained in 88% isolated yield, as Scheme 46 illustrate.

Scheme 46: Directed remote metalation reaction for the formation of chrysen-5-ol (**109**)

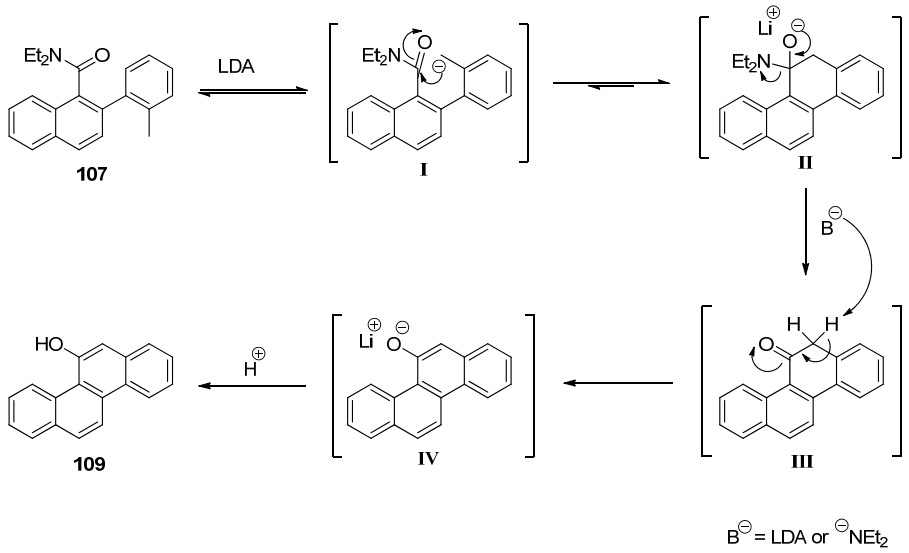


Chrysen-5-ol (**109**) was found to be relatively unstable in air and on silica gel during purification. Therefore, under work-up procedures chrysen-5-ol was kept under an atmosphere of nitrogen to a large extent as possible. During purification of chrysene-5-ol the silica gel became yellow and red, which is a relatively strong indication that chrysene-5-ol is relatively unstable. After purification the solution of chrysene-5-ol was also covered and kept under a nitrogen atmosphere as much as possible in order to minimize oxidation.

The mechanism for the DreM reaction is outlined in Scheme 47. As for the directed *ortho* metalation[60] LDA is believed to first coordinate to the directing group in the directed remote metalation reaction and deprotonates the methyl-proton in the adjacent aromatic ring.[30] After LDA has deprotonated the methyl-proton in the adjacent aromatic ring this lithiated methyl further attacks the carbonyl of the directing group forming chrysen-5(6H)-one **II**. After a second deprotonation with either LDA or NEt_2 chrysen-

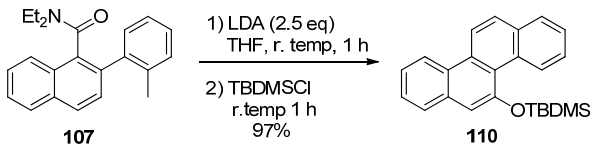
5-olate **IV** is then formed. During extraction the chrysen-5-olate extracts a proton, resulting in the formation of chrysen-5-ol (**109**).

Scheme 47: Mechanism for DreM, specific for the formation of chrysen-5-ol



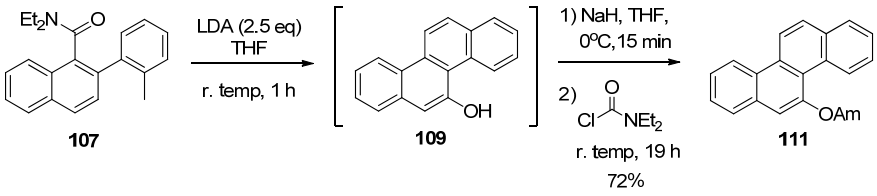
As mentioned above, chrysen-5-ol (**109**) was found to be relatively unstable. Therefore, after DreM reaction chrysene-5-olate **IV** was protected by an *in situ* trapping with *tert*-butyl dimethylsilyl chloride (TBDMSCl). In one-pot *tert*-butyl(chrysen-5-yloxy)dimethylsilane (**110**) was obtained in 97% isolated yield from biphenyl **107** (Scheme 48).

Scheme 48: Formation of *tert*-butyl(chrysen-5-yloxy)dimethylsilane (**110**) from biphenyl **107**



In spite of all the efforts chrysen-5-yl diethylcarbamate (**111**) could not be formed via a DreM reaction, followed by *in situ* trapping of the oxide with diethylcarbamoyl chloride in one-pot. However, when chrysene-5-ol (**109**) after work-up procedures was deprotonated with NaH in a crude mixture and the newly formed oxide was trapped *in situ* with diethylcarbamoyl chloride chrysen-5-yl diethylcarbamate (**111**) could be isolated in 72% overall yield. As mentioned earlier, chrysene-5-ol (**109**) was kept under an atmosphere of nitrogen to a large extend as possible during work-up procedures.

Scheme 49: Formation of chrysen-5-yl diethylcarbamate (**111**)



In the ^{1}H NMR spectrum, shown in Figure 14, a singlet can be detected at 7.69 ppm.

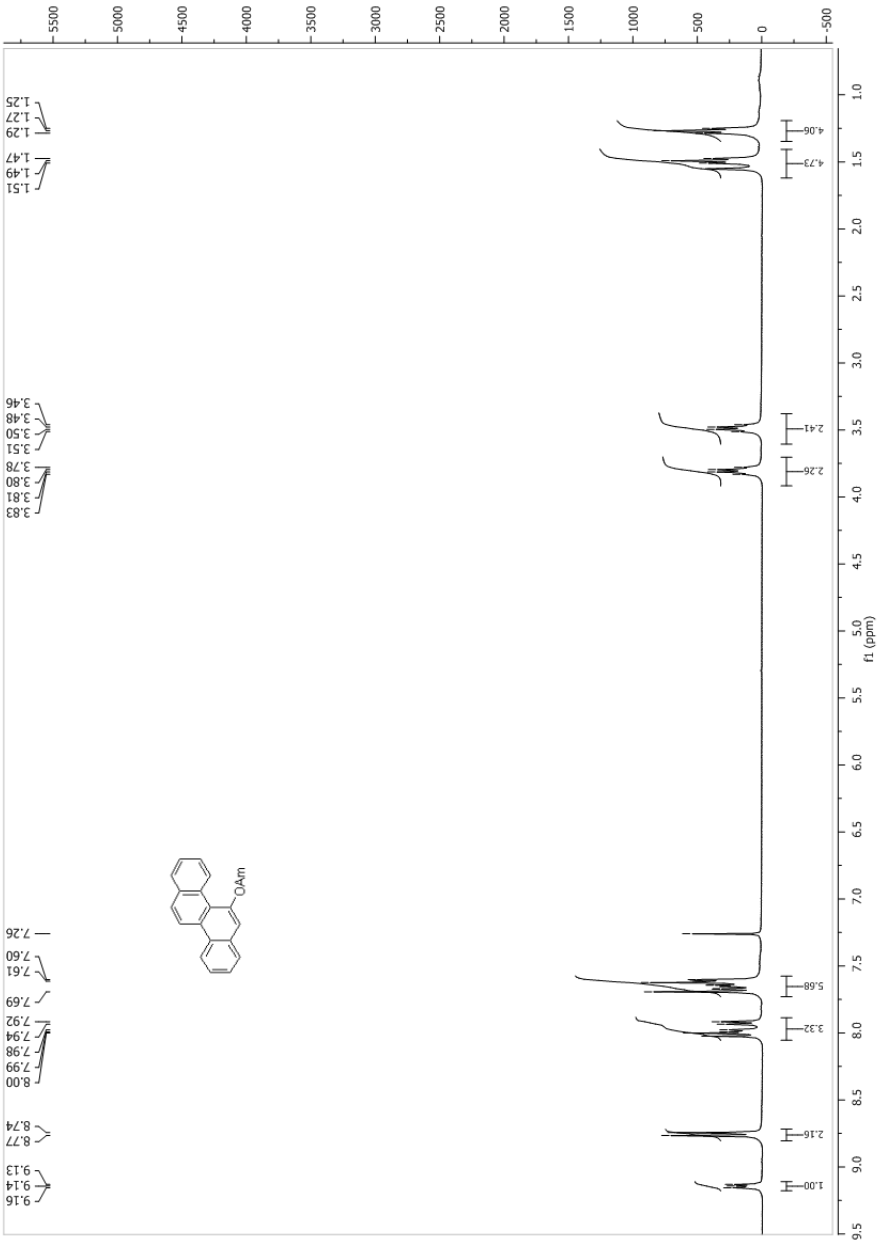
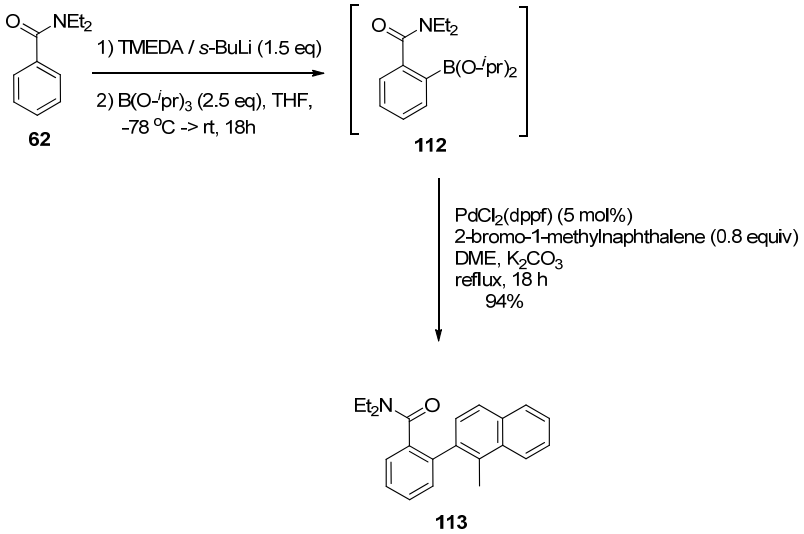


Figure 14: 400 MHz ^{1}H NMR spectrum of compound **111**

By a typical DreM reaction it was envisioned that chrysen-6-ol and chrysen-6-yl diethylcarbamate could be formed from *N,N*-diethyl-2-(1-methylnaphthalen-2-yl)benzamide (**113**). Biphenyl **113** was first formed by a typical D*o*M reaction, where *N,N*-diethylbenzamide (**62**) was subjected to a solution of *s*-BuLi and TMEDA in THF at -78 °C and the formed *ortho* litihiated specie trapped *in situ* with triisopropyl borate ($B(O\text{-}^{i}pr)_3$). After a simple work-up procedure, crude phenyl-boronate **112** was cross-coupled with 0.8 equivalent of 2-bromo-1-methylnaphtlaene in a Suzuki-Miyaura cross-coupling reaction using 5 mol% of $PdCl_2$(dppf) as catalyst (Scheme 50). After chromatographic purification biphenyl **113** was obtained in 94% yield.

Scheme 50: Formation of biphenyl from *N,N*-diethylbenzamide



In Figure 15 the ^{1}H NMR spectrum of *N,N*-diethyl-2-(1-methylnaphthalen-2-yl)benzamide (**113**) is given. The CH_2-protons of amide are detected as five broad peaks ranging from 3.58-2.35 ppm. Also the CH_3-protons are detected as broad signals at 0.61 ppm and 0.51 ppm, except from one triplet at 0.92 ppm. Only one methyl-signal is detected at 2.71 ppm.

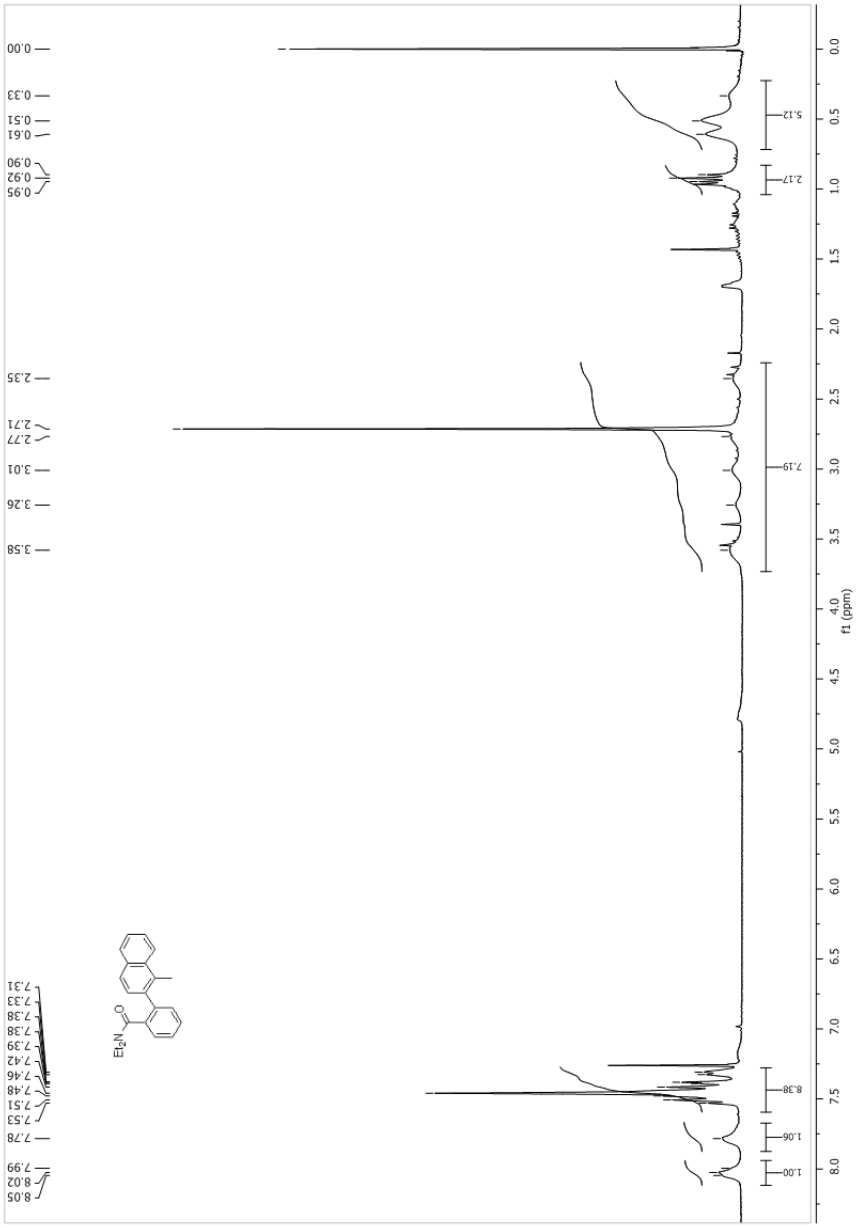
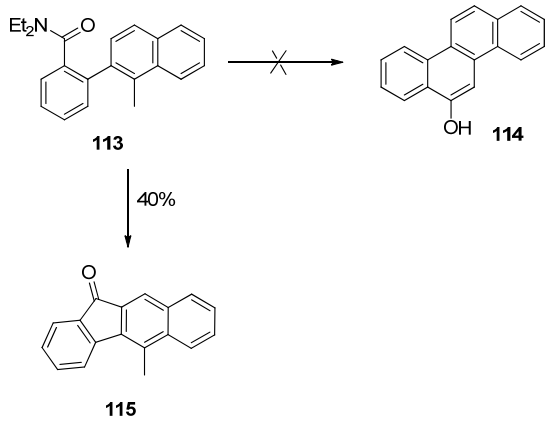


Figure 15: 300 MHz ^{1}H NMR spectrum of biphenyl **113**

By a directed remote metalation reaction chrysen-6-ol (**114**) was attempted synthesized from biphenyl **113**. Lithium diisopropylamine (LDA) was added to a precooled solution of biphenyl **113** in THF at 0 °C. After stirring the reaction mixture at room temperature for 1.5 hours *tert*-butyldimethylsilyl chloride (TBDMSCl) was added. Unfortunately, chrysen-6-ol (**114**) was not formed when subjecting biphenyl **113** to LDA in a DreM reaction. However, from this reaction 5-methyl-11H-benzo[*b*]fluoren-11-one (**115**) was isolated in 40% yield (Scheme 51), along with a complex and intractable mixture of products.

Scheme 51: Directed remote metalation reaction of biphenyl **113**



In Figure 16 the ^{1}H NMR spectrum of 5-methyl-11H-benzo[*b*]fluoren-11-one (**115**) is given. In this spectrum 9 protons can be detected in the aromatic area, along with the methyl-signal at 2.63 ppm. In the ^{13}C NMR a typical ketone signal around 194.4 ppm was also detected, which is a strong indication that the fluorenone **115** had been formed. The mass was measured to be 245.09 *m/z* by high resolution MS analysis, which is in accordance of what is expected for 5-methyl-11H-benzo[*b*]fluoren-11-one (**115**).

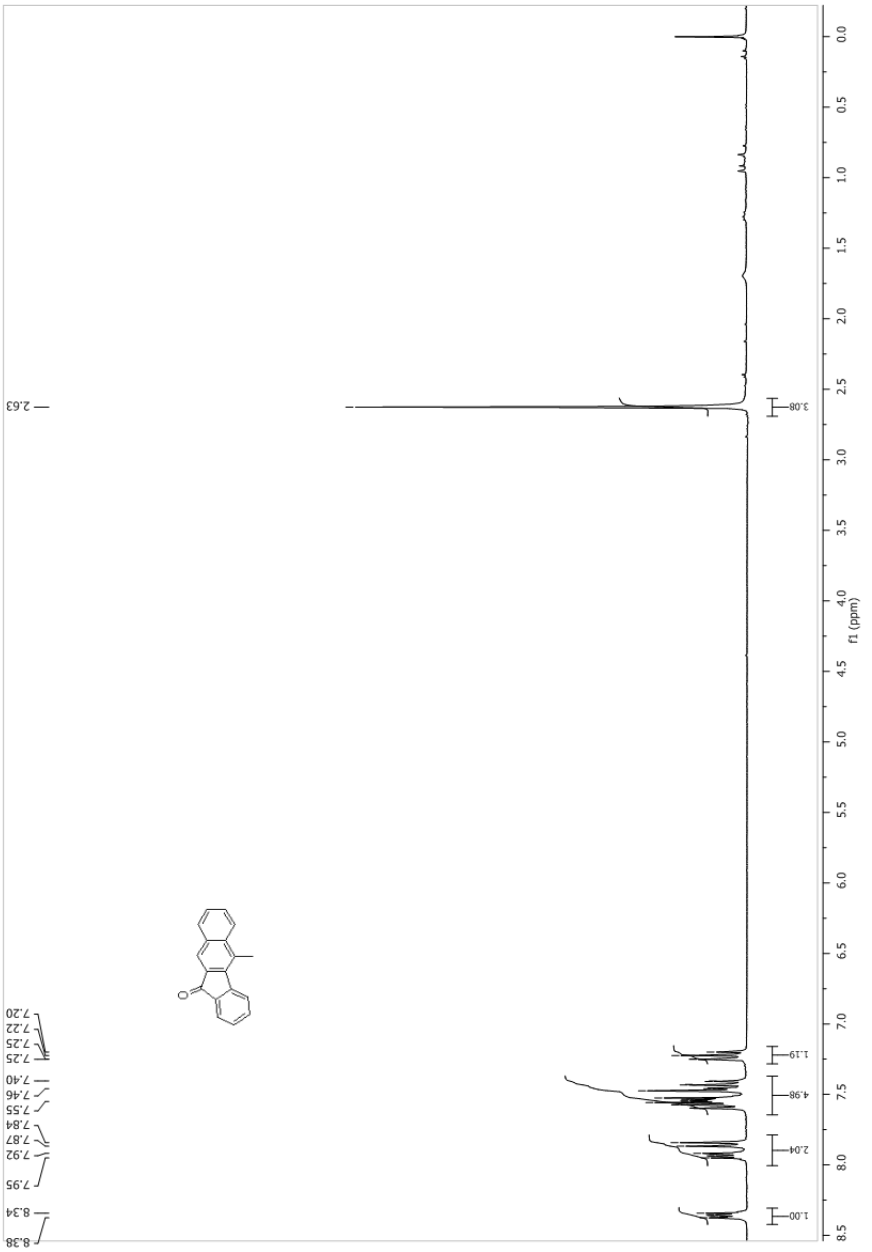
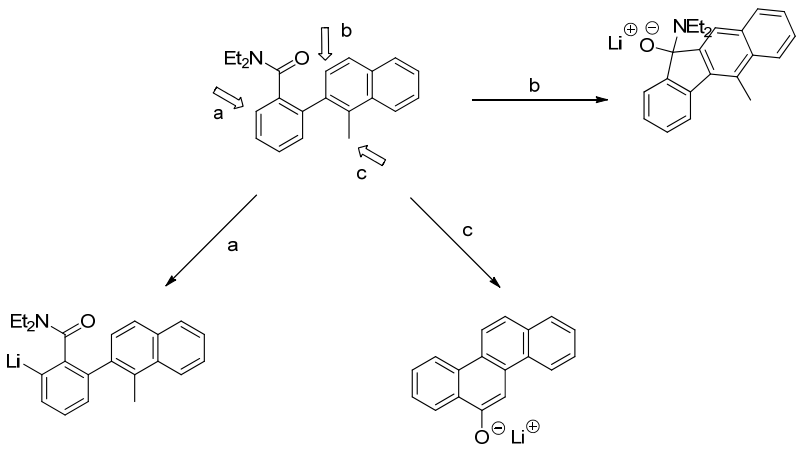


Figure 16: 300 MHz ^{1}H NMR spectrum of compound **115**

The directed remote metalation reaction is dependent on several factors.[61] The rigidity of the starting material, the acidity of protons (either the benzylic- or the aromatic proton), the stability of the lithiated/metalated products and the rate of the reaction are all important factors that need to be considered. For *N,N*-diethyl-2-(1-methylnaphthalen-2-yl)benzamide (**113**) there are three different site were LDA can deprotonate, as Scheme 52 illustrates, resulting in three different products. If LDA deprotonates *ortho* to the amide (route a) the general directed *ortho*-lithiated/metalated specie will be formed. If LDA deprotonates either the aromatic hydrogen (route b) or the methyl hydrogen (route c) the directed remote metalation give rise to either fluoerenone **115** or the chrysene-6-ol **114**, respectively.

Scheme 52: Different product formation for biphenyl **113**



A reason for why the reaction failed in the formation of chrysene-6-ol might be because the molecule is not able to align in such a way for the corrodinated LDA[62] to be able to deprotonate the methyl-group of the adjacent aromatic group. Thus, coordinated LDA can then deprotonates the nearest aromatic proton in the fomation of the fluorenone. It was believed that

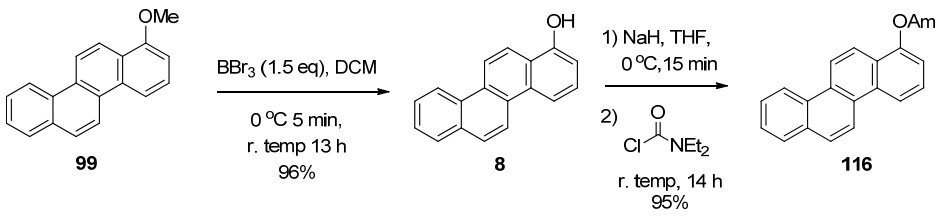
chrysene-6-ol could not be formed due to high activation energy of rotation around the biphenyl-bond of biphenyl **113**. An electron effect might also be a factor for why the fluorenone **115** is formed instead of chrysen-6-ol (**114**).

3.2.2 Formation of chrysenyl diethylcarbamates from methoxychrysenes

Chrysenyl diethylcarbaamtes **116**, **117** and **118** were formed from their respective methoxychrysenes by deprotection with boron tribromide (BBr_3)[35c], followed by a deprotonation and the formed oxide trapped *in situ* by diethylcarbamoyl chloride. Chrysen-1-ol and chrysen-3-ol were purified and isolated before further reaction with diethylcarbamoyl chloride, while chrysenyl-2-diethylcarbamate was formed from the crude chrysen-2-ol.

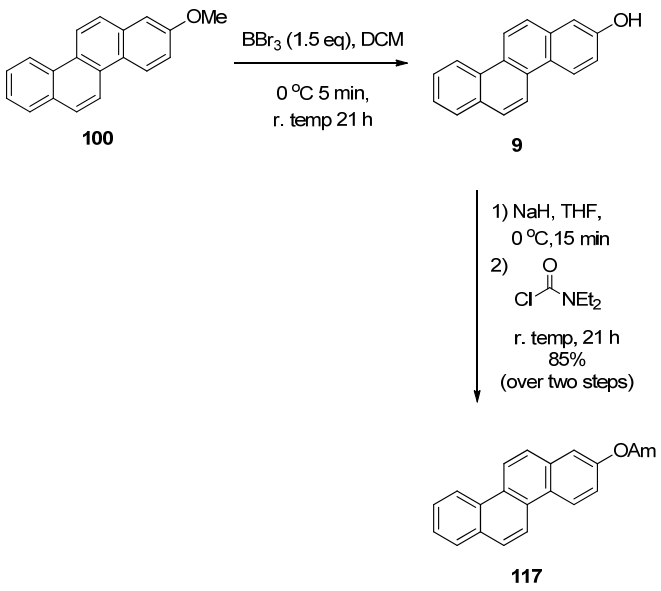
In a typical methoxy-deprotection[35c] reaction BBr_3 was added to a solution of 1-metoxhychrysene (**99**) in DCM at 0 °C and stirred at room temperature for 13 hours. After chromatographic purification chrysen-1-ol (**8**) was afforded in 96% isolated yield. Chrysen-1-ol (**8**) in turn was deprotonated by sodium hydride (NaH), and the resulting chrysene-1-olate was trapped *in situ* by diethylcarbamoyl chloride to afford chrysen-1-yl diethylcarbamate (**116**) in 95% isolated yield (Scheme 53).

Scheme 53: Formation of chrysen-1-yl diethylcarbamate (**116**)



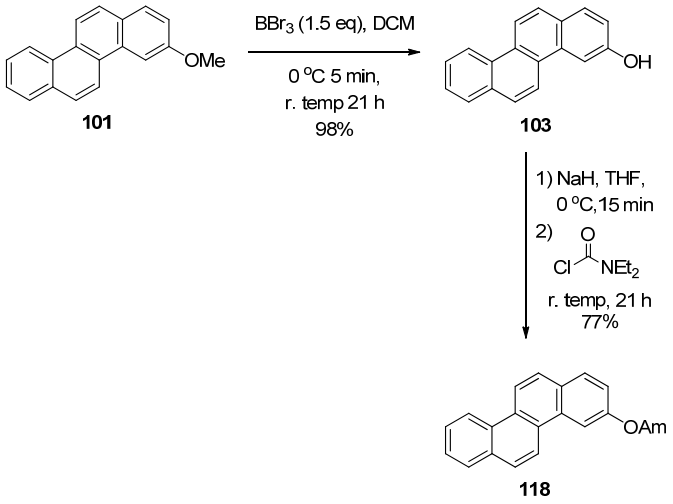
For 2-metoxhychrysene (**100**) the deprotection with BBr_3 had to be performed at room temperature with twice the amount of dichloromethane (DCM) compared to 1- and 3-methoxychrysene, due to lower solubility of substrate **100** in DCM. BBr_3 was added to a solution of 2-methoxychrysene (**100**) at room temperature[35c] and the resulting mixture was stirred for 21 hours. According to TLC analysis the reaction had gone to completion and after work-up procedures, the crude chrysen-2-ol (**9**) was subjected to treatment with NaH. The resulting chrysen-2-olate was trapped *in situ* by diethylcarbamoyl chloride to afford chrysen-2-yl diethylcarbamate (**117**) in 85% isolated yield over two steps (Scheme 54).

Scheme 54: Formation of chrysen-2-yl diethylcarbamate (**117**)



3-Methoxychrysene (**101**) was subjected to treatment with BBr_3 at 0 °C and the mixture stirred for 13 hours.[35c] After chromatographic purification chrysen-3-ol (**103**) was afforded in 98% isolated yield. Chrysen-3-ol (**103**) in turn was deprotonated by sodium hydride (NaH) and the resulting chrysen-3-olate was trapped *in situ* by diethylcarbamoyl chloride to afford chrysenyl-3-diethylcarbamate (**118**) in 77% isolated yield (Scheme 55). From this reaction chrysen-3-ol was also recovered in a mixture with a small amount of product **118**. The mixture was attempted separated three times by flash coloum chromatography, but it was difficult to separate the small amount of product **118** from chrysen-3-ol (**103**).

Scheme 55: Formation of chrysen-3-yl diethylcarbamate (**118**)



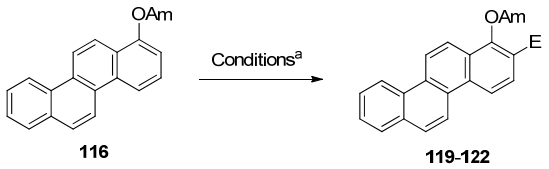
In a second attempt, chrysen-3-ol (**103**) was not purified after the methoxy-deprotection, and the crude chrysen-3-ol (**103**) was deprotonated with NaH and reacted with diethylcarbamoyl chloride. After chromatographic purification chrysene-3-yl diethylcarbamate (**118**) was obtained in 90% isolated yield over two steps.

3.2.3 Directed *ortho* metalation of chrysenyl diethylcarbamates

In this section the directed *ortho* metalation of chrysenyl diethylcarbamates will be discussed.

Chrysen-1-yl diethylcarbamate (**116**) was *ortho*-lithiated with *s*-BuLi/TMEDA (-78 °C, 30-60 min) and trapped *in situ* with trimethylsilyl chloride (TMSCl), iodine (I_2) bromine (Br_2) or hexachloroethane (Cl_3CCCl_3), as outlined in Table 3.

Table 3: Directed *ortho* metalation of chysen-1-yl dietylcarbamate



116 **119-122**

Entry	E^+ / E	Yield (%)
1	TMSCl / TMS [b]	93
2	I_2 / I	94
3	Br_2 / Br	86
4	Cl_3CCCl_3 / Cl	96

[a] 1) *s*-BuLi / TMEDA (1.1 equiv), -78 °C, 30-60 min; 2) E^+, -78 °C – rt, 5-16 h

[b] *in situ* quench, -78 °C, 1.5 h

When TMSCl was used as electrophile (Entry 1, Table 3) it was added to the solution of chrysen-1-yl diethylcarbamate (**116**) and TMEDA before *s*-BuLi was added. This afforded 2-(trimethylsilyl)chrysen-1-yl diethylcarbamate (**119**) in 93% yield. Idodine (Entry 2, Table 3) and hexachloroethane (Entry 4) was in a solution of THF added to the lithiated chrysen-1-yl diethylcarbamate to afford 2-iodochrysen-1-yl diethylcarbamate (**120**) and 2-chlorochrysen-1-yl diethylcarbamte (**122**) in 94% and 96% isolated yield respectively. Bromine (Entry 3, Table 3) was added neat to the

reaction mixture. Due to the high density and small amount of bromine used it was difficult to do a slow addition. Usually, the electrophile is added slowly and the temperature kept between -78--73 °C, but due to the fast addition of bromine the temperature increased to -52 °C relatively fast. When electrophiles are added too fast some rearrangement of carbamates can occur. However, no rearrangement product was observed and 2-bromochrysen-1-yl diethylcarbamate (**121**) was isolated in 86% yield.

In Figure 17 the ^{1}H NMR spectrum of 2-(trimethylsilyl)chrysen-1-yl diethylcarbamate (**119**) is given. For this the CH_2 of carbamate is detected as a broad signal between 3.87-3.41 ppm. This broad signal was evident for most of the *ortho*-metalated chrysen-1-yl diethylcarbamates outlined in Table 3, especially for TMS and idodo.

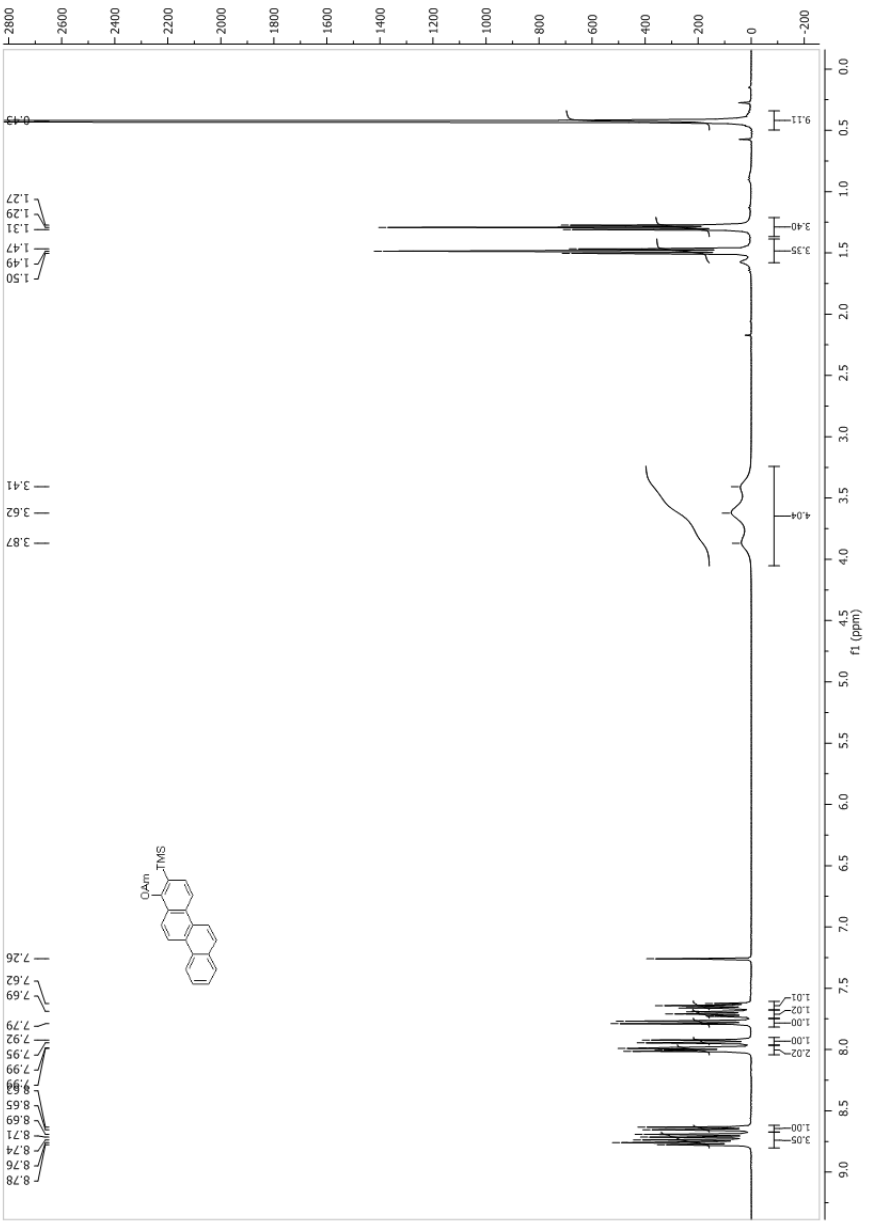
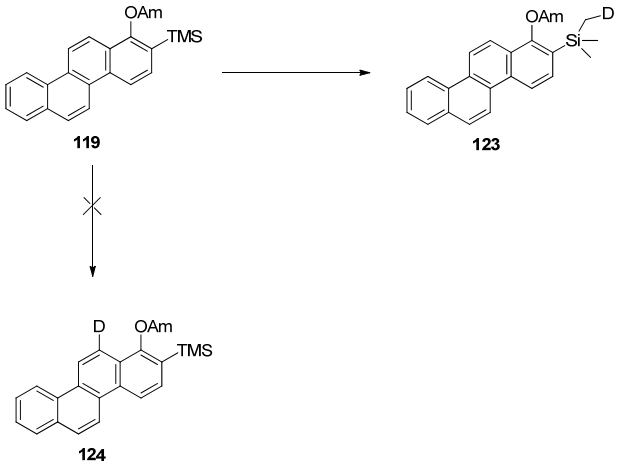


Figure 17: 400 MHz ^{1}H NMR spectrum of compound **119**

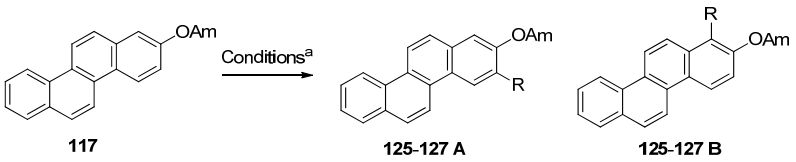
2-(trimethylsilyl)chrysen-1-yl diethylcarbamate (**119**) was subjected to treatment with *s*-BuLi in a second directed *ortho* metalation reaction. In this second D*o*M reaction it was believed that the peri-hydrogen, H-12, could be lithiated and quenched to afford a peri-metalated product.[63] Unfortunately, this did not occur, as shown in Scheme 56. Instead it seemsed like one of the methyl-group of TMS was deuterated. However, this is just assumption based on the ^{1}H NMR analysis, where it seemsed like the TMS-group integrated for only 8 protons.

Scheme 56: 2-(trimethylsilyl)chrysen-1-yl diethylcarbamate (**119**) in a second D*o*M reaction



Chrysen-2-yl diethylcarbamate (**117**) was *ortho*-lithiated with *s*-BuLi/TMEDA (-78 °C, 30-60 min) and quenched *in situ* with trimethylsilyl chloride (TMSCl), iodine (I_2) bromine (Br_2) or hexachloroethane (Cl_3CCCl_3), as outlined in Table 4.

Table 4: Directed *ortho* metalation of chrysen-2-yl diethylcarbamate



117 **125-127 A** **125-127 B**

Entry	E^+ / E	Yield (%)	A:B[c]
1	TMSCl / TMS[b]	trace	-
2	I_2 / I	68	43:57
3	Br_2 / Br	67	44:56
4	Cl_3CCCl_3 / Cl	96	41:59

[a] 1) *s*-BuLi / TMEDA (1.1 equiv), -78 °C, 30-60 min;
2) E^+, -78 °C – rt, 5-16 h

[b] *in situ* quench, -78 °C, 1.5 h; [c] measured by ^{1}H NMR

When TMSCl was used as electrophile (Entry 1, Table 4) it was added to the solution of chrysen-2-yl diethylcarbamate (**117**) and TMEDA before *s*-BuLi was added for an *in situ* quench. This was done to see if the selectivity would be any different from what was observed for iodine (Entry 2, Table 4), bromine (Entry 3, Table 4) and hexachloroethane (Entry 4, Table 4). Unfortunately, only trace amount of (trimethylsilyl)chrysen-2-yl diethylcarbamate was detected by TLC and ^{1}H NMR analysis. Iodine (Entry 2, Table 4) and hexachloroethane (Entry 4, Table 4) was dissolved in THF prior to addition, and after work-up and chromatographic purifications the halogenated product was obtained in 68% and 96%, respectively. Bromine (Entry 3, Table 4), however, was added neat, and after normal work-up procedure and purification the brominated product **126A** and **126B** was

obtained in 67% yield. For the reaction with iodine (Entry 2, Table 4) and bromine (Entry 3, Table 4) starting material could also be recovered.

As Table 4 indicates, the directed *ortho* metalation reaction of chrysen-2-yl diethylcabamate (**117**) affords regioisomers. In all reaction the regioselectivity was approximately the same. Regioisomer **B** was always formed in a higher amount (56-59%) compared to regioisomer **A** (41-44%). These regioisomers were not separable from each other on silica gel. However, the regioselectivity was determined by ^{1}H NMR analysis, were the two expected singlets in regioisomer **A** was found to have smaller integration compared to other signals. This was evident for all the compounds formed in the directed *ortho* metalation of chrysen-2-yl diethylcarbamate given in Table 4.

In Figure 18 the ^{1}H NMR spectrum of the chlorinated products **127A** and **127B**, in a mixture, is given. One of the expected singlet at 8.70 ppm overlaps with other peaks. However, for the other expected singlet at 7.83 ppm, it is easier to detect that this peak is smaller than for example the adjacent dublet at 7.88 ppm. Thus, the two isomers are formed in a *ca* 41:59 mixture.

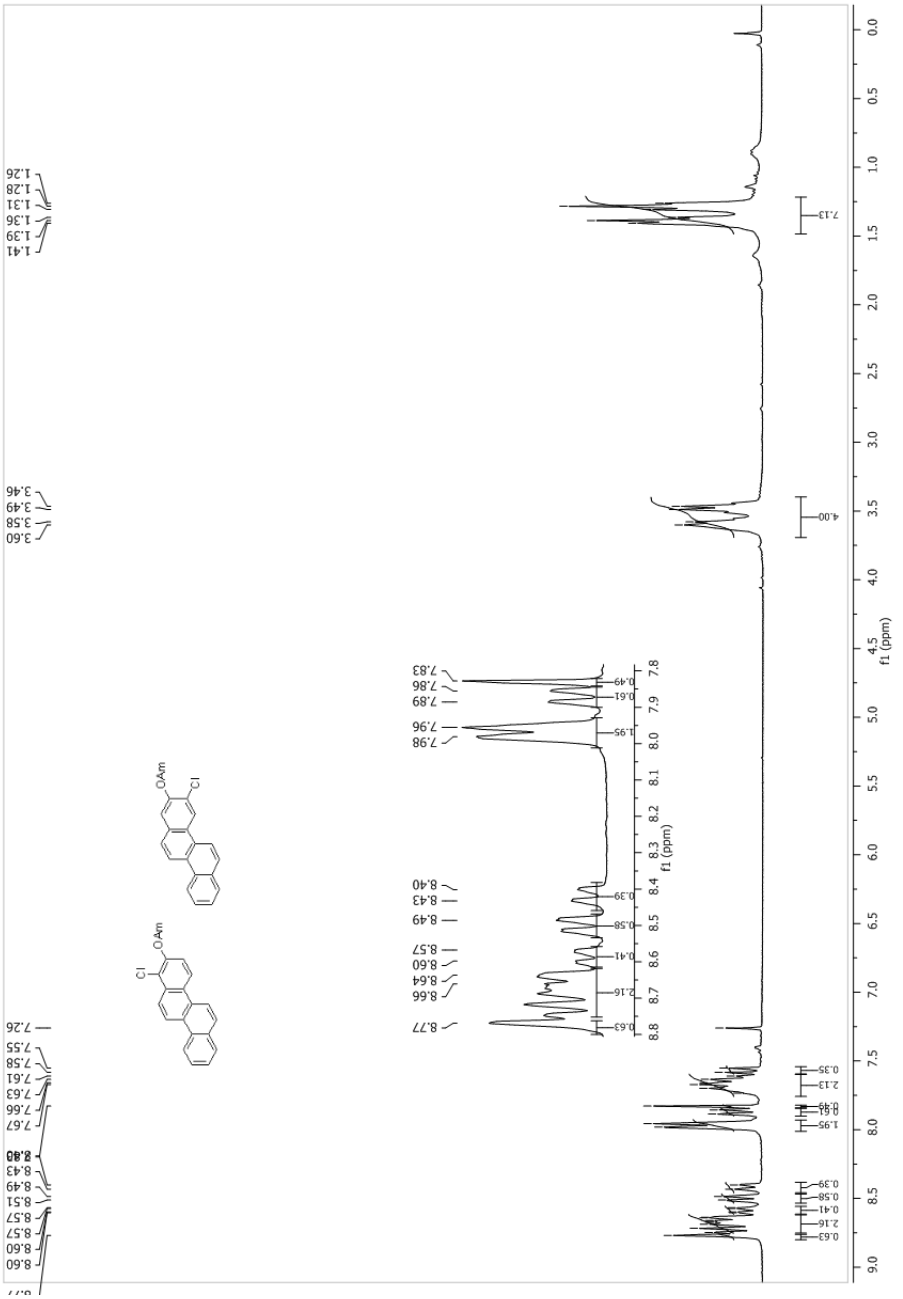
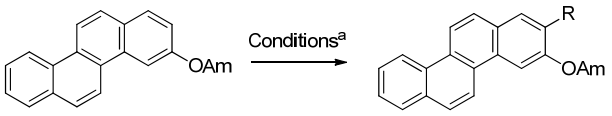


Figure 18: 300 MHz ^{1}H NMR spectrum of **127A** and **127B**

Chrysen-3-yl diethylcarbamate (**118**) was *ortho*-lithiated with *s*-BuLi/TMEDA (-78 °C, 30-60 min) and trapped *in situ* with trimethylsilyl chloride (TMSCl), iodine (I_2) or hexachloroethane (Cl_3CCCl_3) as outlined in Table 5.

Table 5: Directed *ortho* metalation of chrysen-3-yl diethylcarbamate



118 **128-130**

Entry	E^+ / E	Yield (%)
1	TMSCl / TMS[b]	89
2	I_2 / I	91
3	Cl_3CCCl_3 / Cl	70[c]

[a] 1) *s*-BuLi / TMEDA (1.1 equiv), -78 °C, 30-60 min; 2) E^+, -78 °C – rt, 5-16 h

[b] *in situ* quench, -78 °C, 1.5 h; [c] NMR-yield

As for chrysen-1-yl diethylcarbamate (**116**) and chrysen-2-yl diethylcarbamate (**117**), an in situ quench of TMSCl was performed in the directed *ortho* metalation of chrysen-3-yl diethylcarbamate (**118**) (Entry 1, Table 5). After normal work-up and chromatographic purification 2-(trimethylsilyl)chrysen-3-yl diethylcarbamate (**128**) was obtained in 89% yield. Iodine (Entry 2, Table 5) and hexachloroethane (Entry 4, Table 5) was dissolved in THF before the addition to the reaction mixture. After work-up and purification 2-iodochrysen-3-yl diethylcarbamate (**129**) and 2-chlorochrysen-3-yl diethylcarbamate (**130**) was obtained in 91% and 70% yield, respectively. For 2-chlorochrysen-3-yl diethylcarbamate (**130**) the yield was determined by ^{1}H NMR analysis based on the starting material. The product and the unreacted starting material were not separable from each other on silica gel.

For all reaction carried out for chrysen-3-yl diethylcarbamate (**118**), only one regioisomer was isolated or observed. It is believed that the H-5 proton blocks the lithiation of the H-4 proton, due to steric hindrance. The lithiation will therefore take place at the least hindered proton, which is the H-2 proton.

The ^{1}H NMR spectrum of 2-(trimethylsilyl)chrysen-3-yl diethylcarbamate (**128**) is shown in Figure 19. Here the two singlets at 8.37 and 8.08 ppm is a strong indication that only the 2-substituted specie is formed in the reaction. No product from metalation on the 4-position was observed in the reaction mixture.

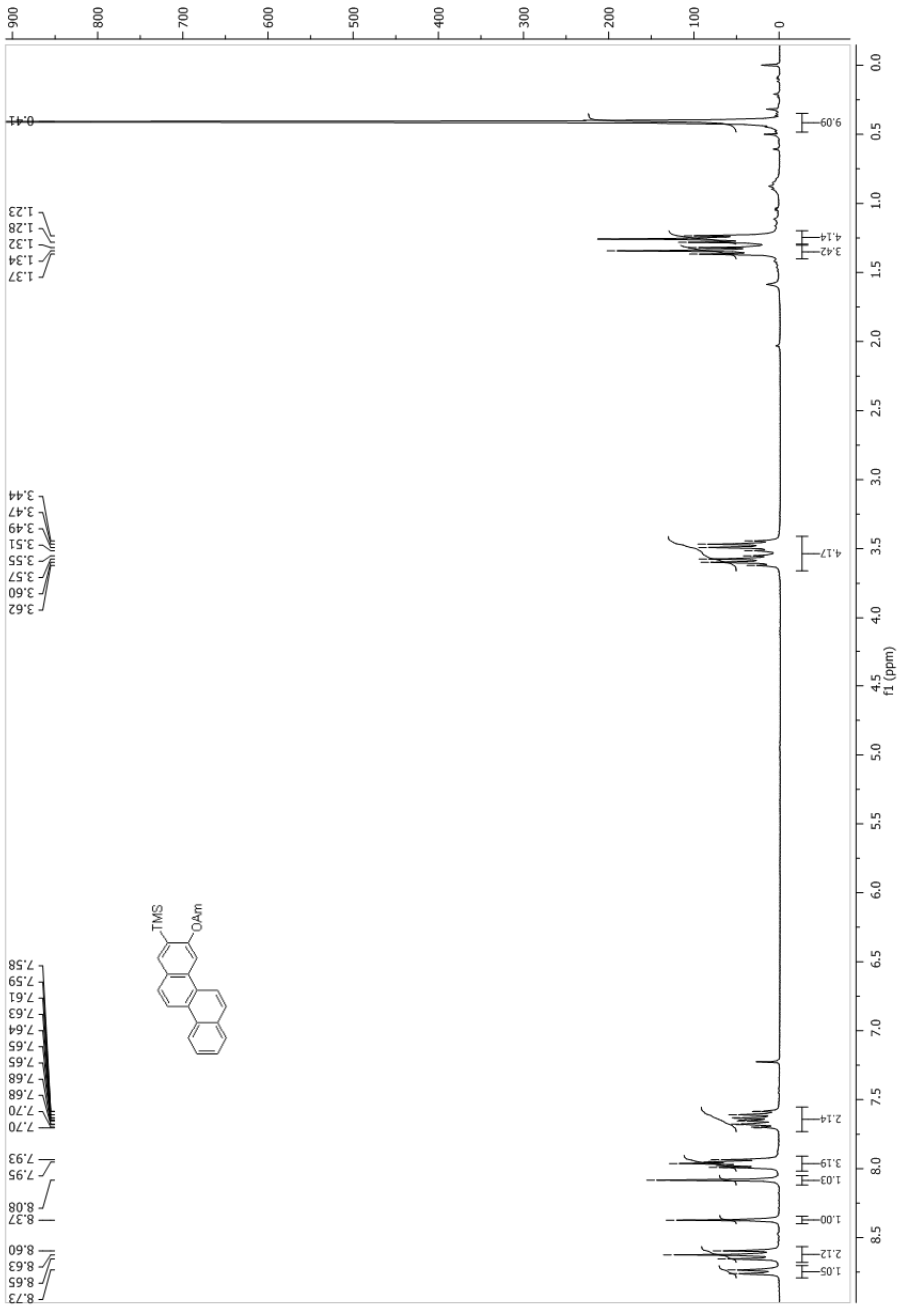
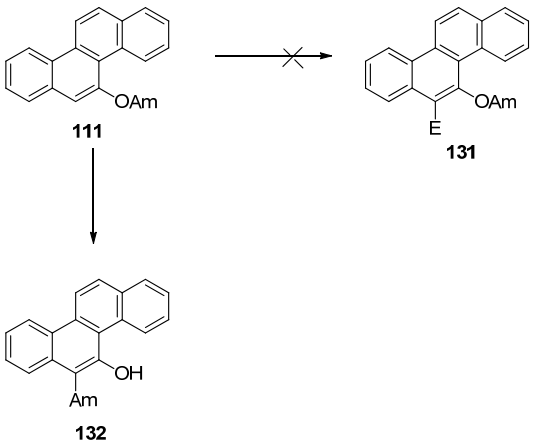


Figure 19: 300 MHz ^{1}H NMR spectrum of compound **128**

For chrysen-5-yl diethylcarbamate (**111**) directed *ortho* metalation was not possible, due to *ortho* Fries rearrangement[64] that occurred instantly when carbamate **111** was subjected to *s*-BuLi, as Table 6 illustrate. Even at -100 °C and with an *in situ* quench of trimethylsilyl chloride the *ortho*-fries product **132** was formed, probably due to steric hindrance from the C-4 hydrogen and release of steric strain for the rearranged product.

Table 6: Directed *ortho* metalation of chrysen-5-yl diethylcarbamate



Entry	E^+ / E	Temperature (°C)	Yield (%)[b]
1	TMSCl / TMS[d]	-78	75
2	-	-100	79[c]
3	Br_2 / Br[e]	-100	71

[a] 1.1 equiv *s*-BuLi / TMEDA; [b] Fries rearrangement product
[c] after 1 hour stirring; [d] *in situ* quench;
[e] added 10 min after *s*-BuLi

When *s*-BuLi was added to the solution of chrysenyl-5-diethylcarbamate (**111**) the yellow solution turned immediately green, which was an indication of the formation of the *ortho*-lithiated product. In the first attempt an *in situ* quench of TMSCl was carried out (Entry 1, Table 6). After the addition of *s*-BuLi the reaction mixure turned green, and quickly turned to light yellow. The quick change of color was believed to arise from the *in situ* trapping of TMSCl. However, as Table 6 indicates, only the *ortho*-Fries product was obtained in 75% yield.

In the next attempt, the reaction mixture was carried out at -100 °C (hexane/liquid nitrogen) (Entry 2, Table 6). The reaction was monitored by TLC analysis. In this reaction the color stayed green for 20 min after *s*-BuLi had been added to the solution at -100 °C, until it turned yellow again. After one hour of stirring most starting material had rearranged to the *ortho*-Fries product. After warming the reaction mixture up to room temperature, there was no change of the amount of Fries rearrangement product, and the product was obtained in 79% yield. Starting material could also be recovered from this reaction.

In the next attempt bromine (Entry 3, Table 6) was added only 10 min after *s*-BuLi had been added at -100 °C. Unfortunately, only the *ortho*-Fries rearrangement product could be isolated in 71% yield, along with recovery of starting material.

An *in situ* quench of TMSCl was not attempted at -100 °C. However, since bromine quench after only 10 min, and an *in situ* quench of TMSCl at -78 °C both gave the rearrangement product, it was believed that lower temperature would not improve the reaction in any way.

In Figure 20 the ^{1}H NMR spectrum of 6-pentylchrysen-5-ol (**132**) is given. Here a triplet can be detected at 7.50 ppm, and at 7.20 ppm. Also two overlapping triplets can be seen between 7.39-7.35 ppm. Both the CH_2 and CH_3 signals are detected as a broad singlet, probably due to the relatively strict rotation around the C-N bond. The OH signal is detected at 10.13 ppm, also this as a broad signal.

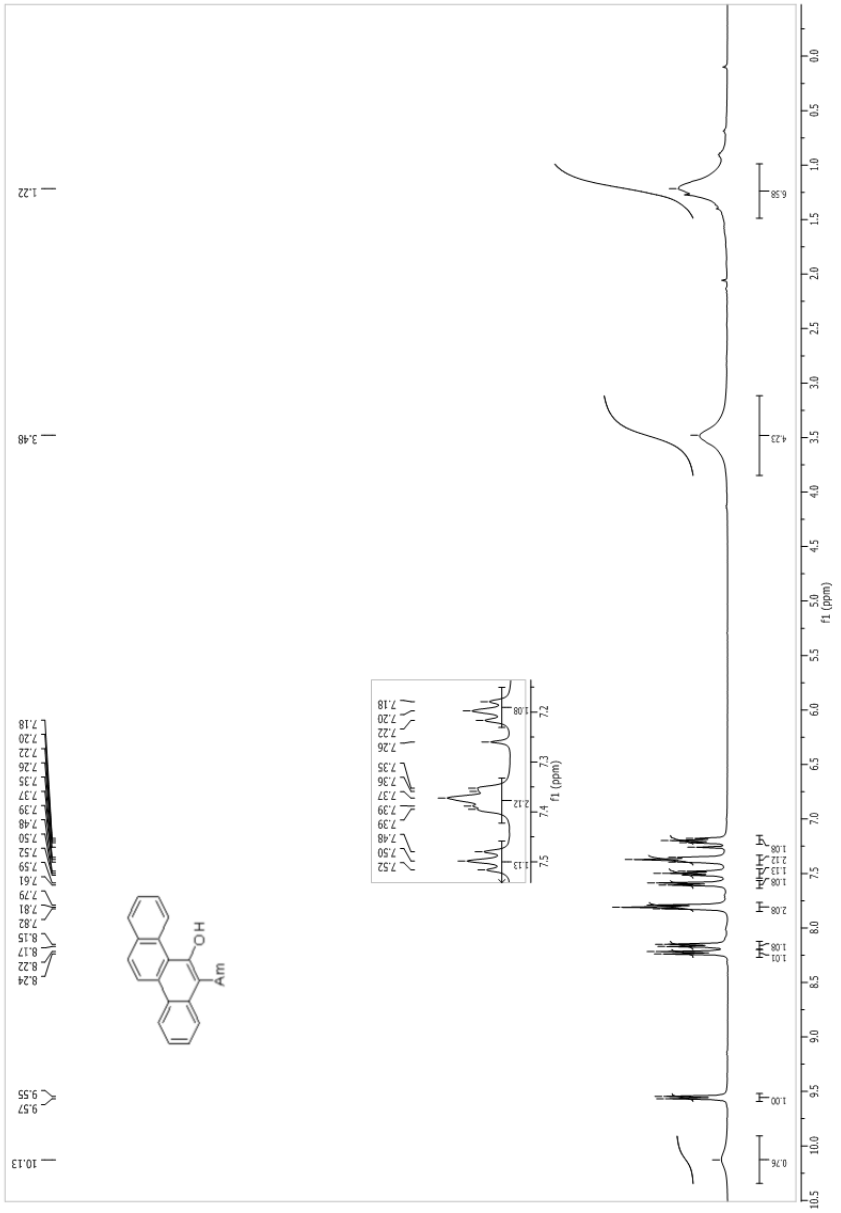


Figure 20: 400 MHz ^{1}H NMR spectrum of the *ortho*-Fries product **132**

Chapter 4

Rotational barrier studies of *ortho*-tolyl amides

4.1 Introduction

As mentioned in chapter 3, it was believed that chrysene-6-ol (**114**) could not be formed in a directed remote metalation reaction due to a high activation energy of rotation around biphenyl bond of *N*,*N*-diethyl-2-(1-methylnaphthalen-2-yl)benzamide (**113**). The suggestion that a high rotational barrier could be the reason for the reaction to fail, led to a rotational barrier study that included 5(6) more *ortho*-tolyl amides which were available from a previous project.[65] Also *N*,*N*-diethyl-2-(*o*-tolyl)-1-naphthamide (**107**), discussed in chapter 3, was included in this study (Figure 21)

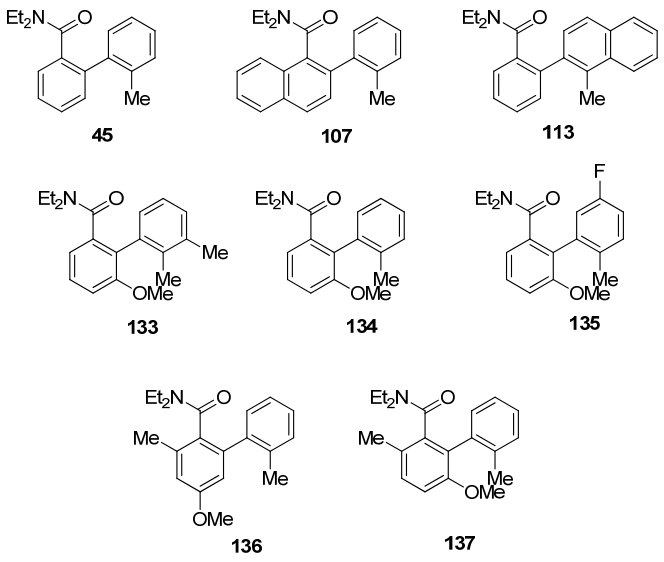


Figure 21: *ortho*-tolyl amides included in the rotational barrier study

All compounds included in this study were generated from a directed *ortho* metalation reaction, followed by a Suzuki-Miyaura cross-coupling reaction,[65] as previously described in chapter 3.

Rotational energy barriers from restricted rotation of sterically hindered groups have been studied experimentally by various spectroscopical methods such as chiral HPLC,[66] dynamic GC[67] and variable temperature NMR (VT NMR).[68] Some studies relevant for the rotational barrier study of *ortho*-tolyl amides are reviewed her.

By experimental VT NMR or VT HPLC measurements Clayden and coworkers investigated the strict rotation around the Ar-CO bond in different napthamides, both with an *ortho* substituent and without a substituent present,[69] as shown in Figure 22. In this study Ar-CO rotation in napthamides with no substituents present were found to have an activation energy of rotation between 15.0-17.9 kcal/mol. For napthamides with an *ortho* substituent the barrier increased to between 21.0-25.4 kcal/mol, which were found to be surprisingly high, depending on the substituent.

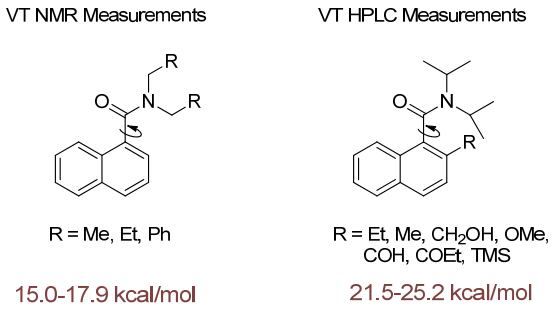


Figure 22: VT NMR and VT HPLC measurements of different naphtamides

By dynamic gas chromatography the activation energy of rotation for biphenyls with different *ortho* substituents on both phenyl rings has been investigated by Wolf *et al.*[67] The activation energy of rotation varied from 23.1-27.5 kcal/mol, depending on the substituents, as outlined in Figure 23.

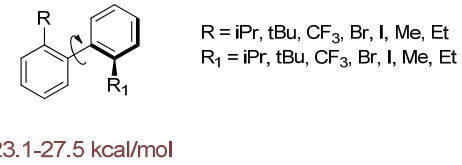


Figure 23: Activation energy barrier of rotation for different biphenyls

For biphenyls with *ortho* substituents on both phenyl rings there has been observed a strong substituents effect, especially for compounds containing methoxy-group, as Figure 24 indicate. The activation energy of rotation was decreased by 2-6 kcal/mol when the methoxy-group was present. It was rationalized that the lower activation energy was a result of stabilization by resonance structures and that the lower van der vaals radius of methoxy compared to the other groups was also a part of the reason.[68b]

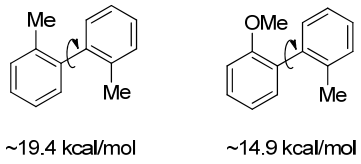


Figure 24: Activation energy barrier for compounds containing a methoxy-group compared to a methyl-group

4.2 Results and discussion

In this rotational barrier study variable temperature NMR (VT NMR) was carried out with temperature ranging from 190 Kelvin (-83 °C) to 332 Kelvin (59 °C). The VT NMR experiments of all compounds were recorded on a 400 MHz Bruker NMR using d_8-toluene as solvent and the VT NMR probe used in these experiments was calibrated by an ethylene glycol solution in order to set the correct temperature. For low temperature experiments a flow of dry nitrogen was passed through liquid nitrogen in order to reach the low temperature of choice.

In this study all compounds, except compound **107** (298 K) and **113** (190 K), were cooled down to 250 Kelvin before ^{1}H NMR, NOESY and COSY was recorded. The low temperature was necessary in order to record the maximum chemical shift different ($\Delta\upsilon$, in herz) between the two methyl-peaks which were monitored by variable temperature. From $\Delta\upsilon$, the rate constant, k_c, which is the time one rotamer converts to the other rotamer at coalescence temperature, T_c, was calculated by from the Gutowsky-Holm equation;[68c,70,71]

$$k_c = \pi\Delta\upsilon / \sqrt{2} = \sim 2.22\Delta\upsilon \ s^{-1} \qquad (1)$$

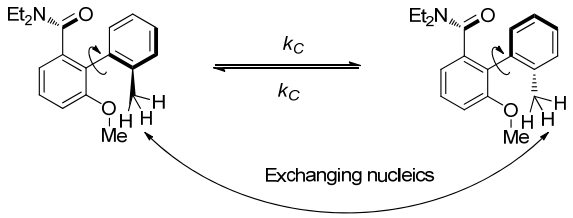
It must be pointed out that a complete line-shape analysis[74] was not carried out in order to find the exchange rate, k, since it has been shown that it is often sufficient to find the rate constant, k_c, at low temperature using the Gutowsky-Holm equation.[68c,73]

After the two methyl peaks were detected the temperature was raised until the coalescence of the two peaks was reached. From the coalescence temperature, T_c, and the rate constant, k_c, the activation energy of rotation (ΔG_{Tc}) was calculated using the Eyring equation, were R is the gas constant, 1.986 kcal/mol:[68c,71,74]

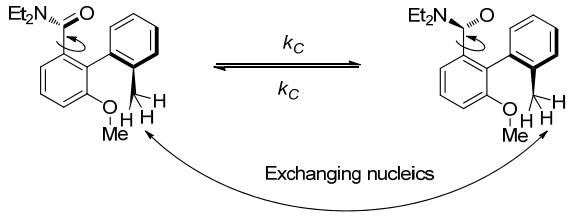
$$\Delta G_{Tc} = RT_c[23.76 - \ln(k_c/T_c)] \qquad (2)$$

In the NOESY experiment a clear exchange between the methyl-protons of the two rotamers were easily detected for most compounds. This exchange between signals is better known as EXSY (**Ex**change **S**pectroscop**y**) experiment.[71] The exchange of signals detected by NMR analysis is especially evident for compounds with a slow exchange at low temperature, and comes from the conversion of for example one rotamer to the other rotamer. For *ortho*-tolyl-amides two rotations, either the Ar-Ar rotation or the Ar-CO rotation can occur resulting in exchanging signals as illustrated in Scheme 57 and Scheme 58.

Scheme 57: Conversion of one rotamer to the other, due to rotation around Ar-Ar bond, resulting in exchanging signals



Scheme 58: Conversion of one rotamer to the other, due to rotation around Ar-CO bond, resulting in exchanging signals



As mentioned earlier, the rate constant k_C represents the time it takes for one rotamer to convert to the other rotamer. In Figure 25 the expanded region for the NOESY experiment of *N*,*N*-diethyl-6-methoxy-2'-methyl-[1,1'-biphenyl]-2-carboxamide **134** is given. In this figure the diagonal peak from the methyl-signal at 2.39 ppm and 2.15 ppm has a clear exchange with the methyl-peak at 2.15 ppm and 2.39 ppm, respectively. Exchanging signals are detected as a positive (red) NOE signal and with the same sign as the diagonal peak (red), as shown in Figure 25.

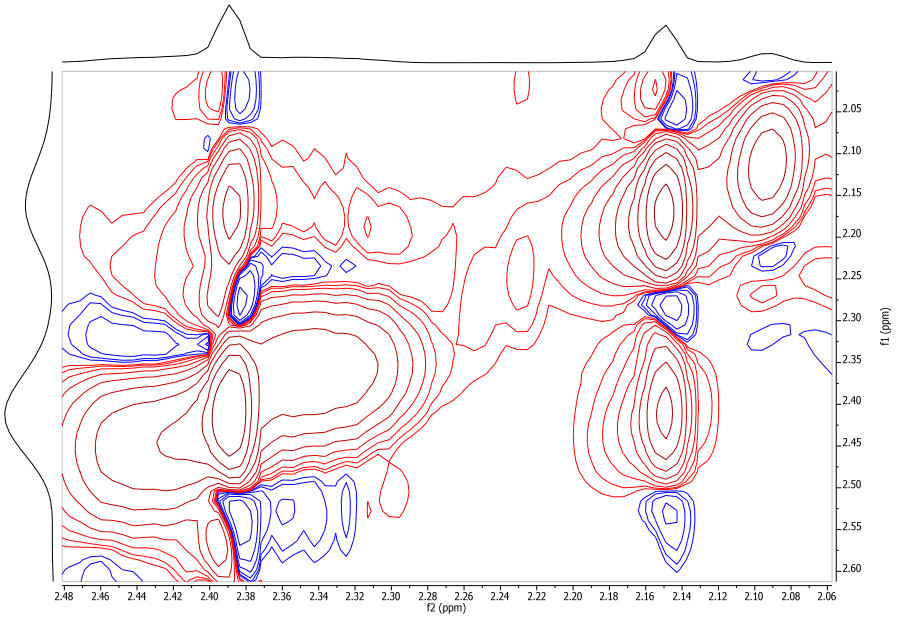


Figure 25: Exchanging methyl-proton in the NOESY spectrum of compound **134**

For the compounds that did not have a clear exchange between the two methyl-signals, the two peaks of interest were detected from COSY correlation and NOE interaction with adjacent protons. For adjacent protons a COSY-related interaction/correlation can be observed in the NOESY spectrum. Also nucleic/proton interactions through space can be detected. In Figure 26 all of these interactions are outlined, specific for substrate **134**.

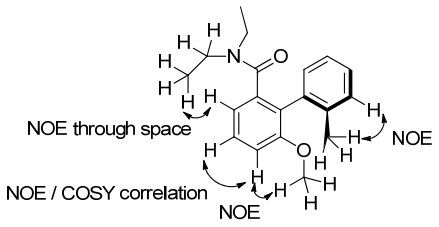


Figure 26: Different NOE-interactions found in compound **134**

In the NOESY spectrum of compound **134**, a NOE interaction can be detected between the methoxy-protons at 3.13 ppm and its adjacent aromatic proton at 6.49 ppm. This aromatic proton has a NOE interaction or a COSY like correlation with its adjacent aromatic proton at 7.09 ppm, which again correlates /interacts with the adjacent proton at 6.87 ppm. From this proton a NOE interaction through space with the CH_3-group of amide at 0.7 ppm can be detected. Other through space NOE interactions can be detected for the CH_2-group for both rotamers. This is, however, more difficult to verify due to the overlapping aromatic peaks. A NOE is also detected for the methyl-protons to the adjacent proton in the tolyl-group in both rotamers. For one rotamer the methyl-proton detected at 2.39 ppm interacts with its adjacent proton at 7.12 ppm, and for the other rotamer the methyl-proton at 2.15 ppm with its adjacent proton at 7.06 ppm. All of these interactions are visual as a negative (blue) NOE to the diagonal peak (red), as shown in the NOESY spectrum in Figure 27.

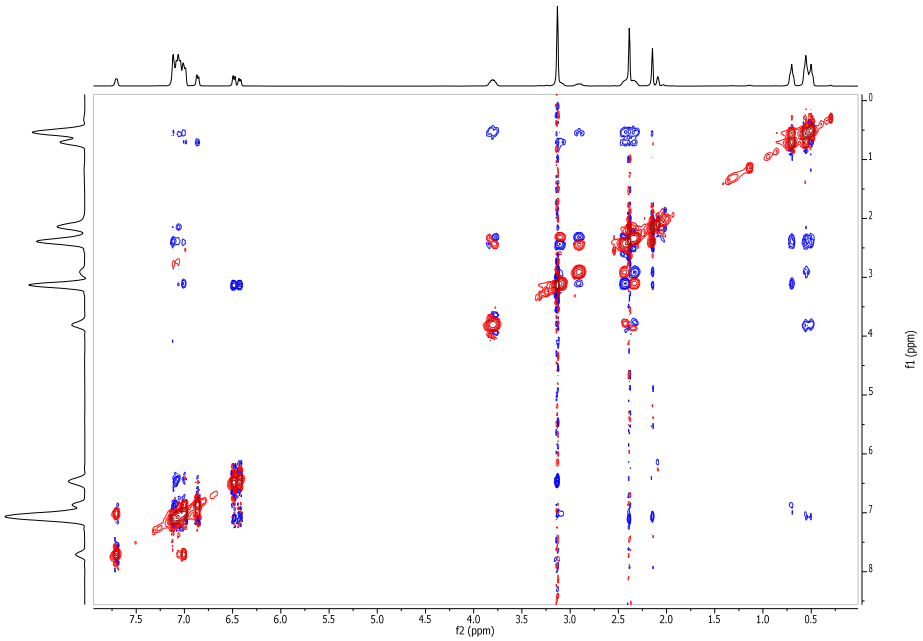


Figure 27: NOESY spectrum of biphenyl **134** at 250 Kelvin

After detecting the right methyl-peaks the temperature was raised for each compound until the coalescence of the two peaks was reached. For substrate **134** the two peaks at 2.39 ppm and 2.15 ppm merged together to one peak at 2.25 ppm. As shown in Figure 28 the two peaks had started to melt together at 310 K. However, at both 310 K and 312 K a bump was detected on the merging peaks, and the temperature was raised further until the bump was not observable. At 314 K no bump on the merging peak was detected, meaning that the coalescence had been reached.

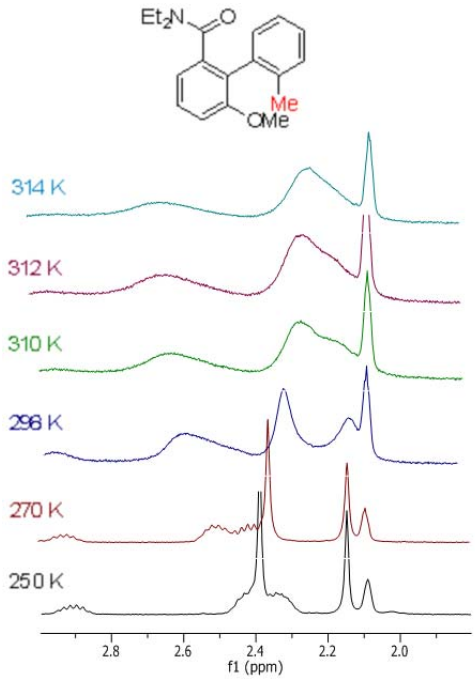


Figure 28: VT NMR measurements of biphenyl **134** to obtain coalescence

With a coalescence temperature at 314 Kelvin the activation energy for the rotational barrier was calculated to be 15.1 kcal/mol using the Eyring equation.

Another example of two methyl-peaks merging together in coalescence is given for *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide **107**. In the NOESY spectrum the two methyl-peaks at 2.33 ppm and 2.15 ppm had a clear exchange. In Figure 29 the expanded region of the two methyl-peaks of the NOESY spectrum is given.

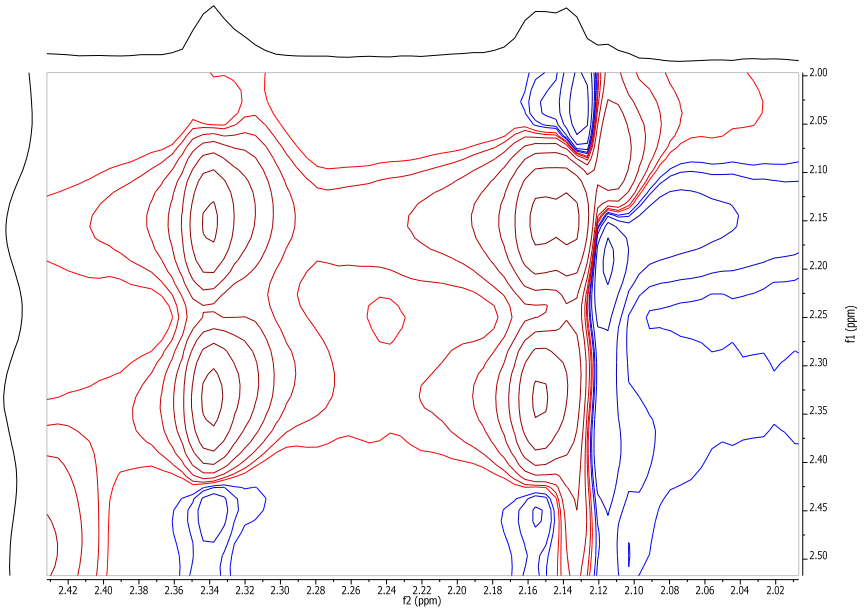


Figure 29: Expanded NOESY spectrum of compound **107** at 298 K

The two peaks at 2.33 ppm and 2.15 ppm merge together at 332 Kelvin to one peak at 2.24 ppm, as shown in Figure 30. The two peaks had already started to melt in together at 330 Kelvin, but still a "shoulder" could be detected at this temperature, and also a small bump was observed at 331 Kelvin. However, at 332 Kelvin no bump was observed and therefore this was the coalescence temperature.

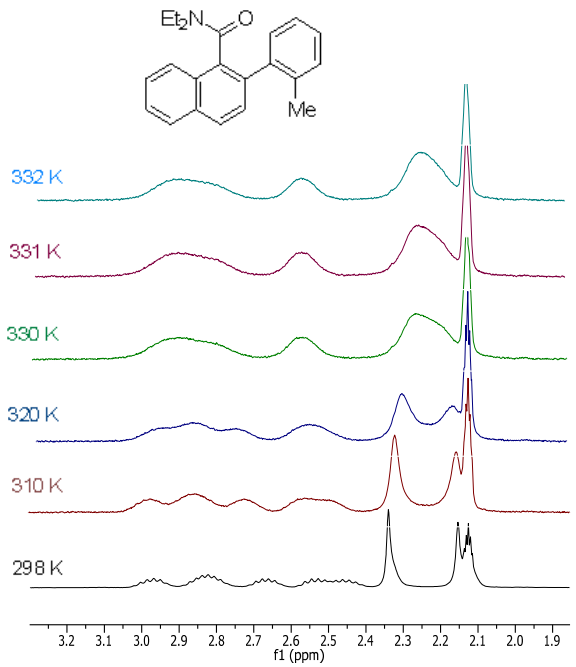
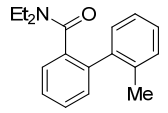


Figure 30: VT NMR measurements of biphenyl **107**

With a coalescence temperature of 332 K, the activation energy of rotation (ΔG_{Tc}) was estimated to be 16.1 kcal/mol by employing the Eyring equation.

In Table 7 the activation energy barrier of rotation (ΔG_{Tc}) for all compounds measured in this study are summarized, along with their shift values (δ), shift different in herz (Δv), rate constant, (k_c) and coalescence temperature in kelvin (T_c).

Table 7: Rotational barriers from VT-NMR measurements[a,b]



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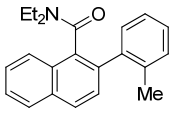
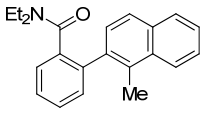
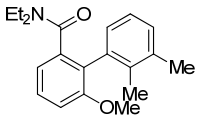


107

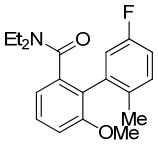


113

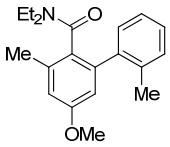


133

134



135



136

Entry	Compound	δ (ppm)	Δv^c (Hz)	k_c^d (s^{-1})	T_c (K)	$\Delta G_{Tc}^{e,f}$ (kcal/mol)
1	**45**	2.35, 2.08	106.9	237.4	284	13.5
2	**107**	2.30, 2.12	74.4	165.2	332	16.1
3	**113**	2.46, 2.35	42.8	95.06	283	14.0
4	**133**	2.26, 2.04	89.4	198.4	313	15.1
5	**134**	2.39, 2.15	96.6	214.4	314	15.1
6	**135**	2.24, 2.02	88.8	197.2	301	14.5
7	**136**	2.43, 2.13	117.1	259.9	325	15.5

[a] 400 MHz NMR; [b] Lowest temperature reach 190 K; [c] Δv obtained from the methyl-peak in exchange at low temperature; [d] $k_c = 2.22\Delta v$; [e] estimated margin of error ± 0.2 kcal/mol; [f] It is assumed that ΔS_{Tc} is zero;

For *ortho*-tolyl-amide **45** the activation energy for rotation was measured to be 13.5 kcal/ mol. Compared to the other compounds included in this study compound **45** has no substituents and it was expected that compound **45** would have the lowest rotational barrier, as was observed. The highest activation energy for rotation was measured for *ortho*-tolyl-amide **107**, with an energy barrier measured to be 16.1 kcal/mol. The higher barrier compared to compound **45** is believed to arise from the peri-hydrogen of naphtalene. This hydrogen is believed to interrupt the transition state of the rotation resulting in higher activation energy of rotation. This peri-hydrogen has no ability to rotate and the strict hindrance results in the amide functionality not being able to align in the right position in order for the biphenyl to rotate. For *ortho*-tolyl-amide **136**, the activation energy of rotation was measured to be 15.5 kcal/mol. This was higher than what was observed for substrate **45**, but lower than what was measured for compound **107**. It is believed that since the methyl-group *ortho* to the amide-group has the ability to rotate in an eclipsed alignment to the amide, the amide has better chance to align in the right position in order for the biphenyl to rotate, resulting in lower activation energy of rotation compared to substrate **107**.

For *ortho*-tolyl-amide **113**, which we believed could not form chrysene-6-ol (**114**) in a directed remote metalation due to strict rotation around biphenyl bond, the activation energy of rotation was measured to be 14.0 kcal/mol. This was surprisingly low, and due to the low activation energy measured the failed reaction could not be explained by a large rotational barrier.

One interesting feature which was observed was when a substituent (methoxy) was present *ortho* to the biphenyl, as for compound **133**, **134** and **135**, the activation energy of rotation was measured to be 15.1, 15.1 and 14.5 kcal/mol, respectively. The substituent did not influence the barrier in any way. However, as mentioned in the introduction, it has been reported in the literature that compounds with a methoxy-group *ortho* to the biphenyl has a 2-6 kcal/mol decreased activation energy of rotation compared to methyl- and carboxyl-groups.[68b] This decrease in activation energy was believed to arise from the ability of the methoxy-group to stabilize the biphenyl-bond by resonance during the transition state of the rotation. The smaller van der vaals

radius of methoxy compared to other groups was also believed to influence the rotational barrier.

In Figure 31 the calculated values for both the rotation around the Ar-CO bond (purple) and Ar-Ar bond (blue), along with the experimental value (black), described above, are given. The computational calculations were made by Indrek Kalvet, a Master Student from the University of Tartu, Estonia, visiting the group of Prof. Snieckus at Queen`s University in 2012. The computational calculations were describes as followed: ´the calculations were performed in gas phase using B97D density functional theory method with cc-pVDZ basis set. The structures were optimized and frequency calculations were performed until the number of imaginary frequencies was 0 for local minima and 1 for transition states. To confirm that the obtained transition state connect the correct minima, intrinsic reaction coordinate (IRC) calculation were performed´.[75]

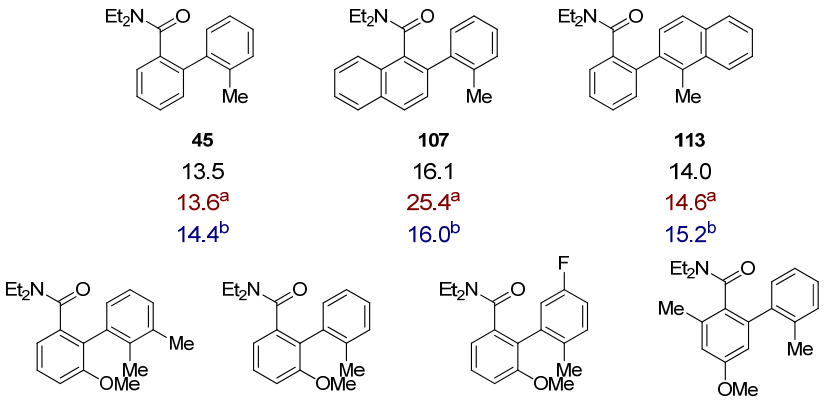
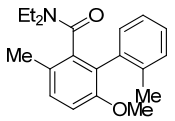


Figure 31: Experimental and calculated rotational energy barrier for the *ortho*-tolyl-amides

From the computational calculations it was observed that when a substituent *ortho* to the amide-group was present the Ar-CO rotation was significantly higher (25.4 kcal/mol for *ortho*-tolyl-amide **107**, and 23.0 kcal/mol for compound **136**) compared to those compounds with no substituent (13.6 – 15.0 kcal/mol for compounds **45**, **113** and **133-135**). However, when a substituent *ortho* to the biphenyl-bond was present the Ar-Ar rotation was calculated to be significantly higher (25.9 – 28.5 kcal/mol for compounds **133-135**) compared to those without a substituent (substrates **45**, **107** and **136**). For compounds **45** and **113**, with no substituent at either site the calculated activation energy barrier of rotation for both Ar-CO and Ar-Ar rotation was approximately the same.

The activation energy of rotation for *N*,*N*-diethyl-6-methoxy-2',3-dimethyl-[1,1'-biphenyl]-2-carboxamide **137** was estimated to be 26.7 kcal/mol for the Ar-CO rotation and 25.5 kcal/mol for the Ar-Ar rotation by computational calculations, as shown in Figure 32.



137
26.7[a]
25.5[b]
[a] Ar-CO rotation
[b] Ar-Ar rotation

Figure 32: Calculated barrier for Ar-CO and Ar-Ar rotation for compound **137**

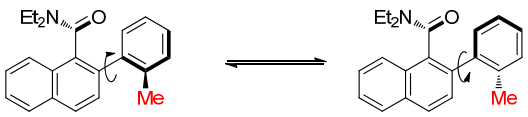
Preliminary result for substrate **137** has shown that the activation energy of the rotation was >19 kcal/mol from experimental VT NMR measurements. In d_8-toluene the coalescence of the two methyl-signals was not obtainable, and the solvent needed to be change for the VT NMR experiment. For the VT NMR measurements the compound will at a later

stage be recorded in d_6-DMSO instead, to see if it is possible to reach coalescence using this solvent.

When comparing the results from the VT NMR experimental measurements to the computational calculated results, a relatively clear cooperative rotation can be observed. Either the experimental measurements matches the calculated rotational barrier around the Ar-Ar bond (**107** and **136**), or it matches the calculated rotational barrier around the Ar-CO bond (**133**, **134** and **135**). For *ortho*-tolyl-amides **45** and **113** the Ar-CO and the Ar-Ar rotation are approximately the same. However, the calculated Ar-CO rotations for compound **45** and **113** are slightly lower than what were calculated for the Ar-Ar rotation. It is therefore believed that the most likely rotation measured in the VT NMR experiments for substrates **45** and **113** are the Ar-CO rotation.

For *N*,*N*-diethyl-2-(*o*-tolyl)-1-naphthamide (**107**) the barrier of rotation was estimated to be 16.1 kcal/mol by VT NMR measurements. The calculated Ar-CO rotational barrier was estimated to be 25.4 kcal/mol, while the calculated Ar-Ar rotation was estimated to be 16.0 kcal/mol. Here the calculated value of the Ar-Ar rotation was in closer proximity with the experimental measurements than for the Ar-CO rotation. For substrate **107** it was therefore believed that the rotation monitored in the VT NMR experiments was the Ar-Ar rotation, as shown in Scheme 59.

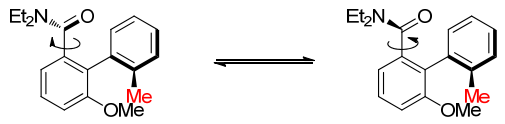
Scheme 59: Rotation around the Ar-Ar bond



For *N*,*N*-diethyl-6-methoxy-2'-methyl-[1,1'-biphenyl]-2-carboxamide (**134**) the rotational barrier was measured to be 15.1 kcal/mol from VT-NMR experiments. The calculated Ar-Ar rotation was estimated to be 26.7 kcal/mol,

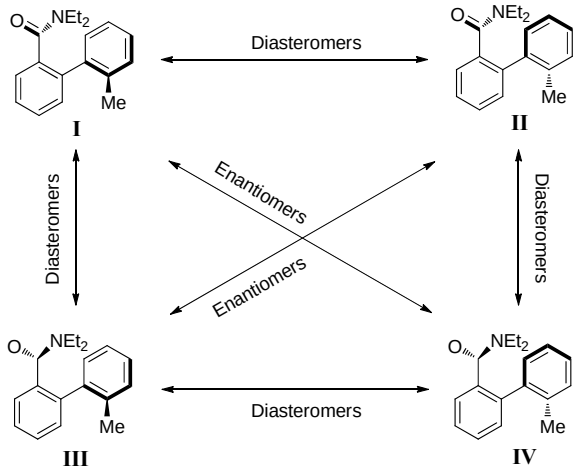
while the Ar-CO rotation was estimated to be 14.4 kcal/mol. The measured rotation from the VT-NMR experiments was for this molecule believed to arise from the Ar-CO rotation as shown in Scheme 60.

Scheme 60: Rotation around Ar-CON bond



When combining these two rotamers, the Ar-CO and Ar-Ar rotation, shown in Scheme 61, enantiotropic and diastereotropic rotamers can be observed. The enantiotropic rotamer will of course not be visual in the NMR spectrum, only the diastereotropic rotamer. So if only the Ar-CO rotation occur (or only the Ar-Ar rotation) the different signals, due to the diastereotropic rotamers, will be detected in the NMR spectrum.

Scheme 61: Cooperative rotation resulting in diastereotropic and enantiotropic rotamers



The different enantiotropic and diastereotropic rotamers were calculated for all compounds to see if there were any thermodynamically different between the rotamers. However, no major energy different were observed. The two enantiotropic rotamers **I** and **IV** were calculated to be equal in energy, also the enantiotropic **II** and **III**. An average of 0.5 kcal/mol difference was found for **I** and **IV** compare to their diastereotropic rotamer **II** and **III**. The former (**I** and **IV**) was found to be more thermodynamically stable then the latter (**II** and **III**).[75]

4.3 Conclusion

Based on the computational calculations and VT NMR measurements it is believed that if the rotation around Ar-CO bond is higher than the rotation around the Ar-Ar bond, due to steric hindrance from *ortho*-substituents to the amide-group, the Ar-Ar rotation will occur. However, if the Ar-Ar rotation is higher than the Ar-CO rotation, due to steric hindrance from substituents *ortho* to the biaryl bond, the Ar-CO rotation will take place.

The explanation for the different reactivity in the DreM reaction for compound **107** and **113** can probably not be explained from the rotational barriers.

Chapter 5

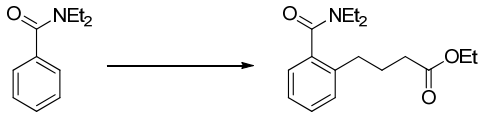
Experimental

5.1 General:

Tetrahydrofurane (THF) was distilled under nitrogen atmosphere from Na/benzophenone. *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) was distilled and stored over potassium hydroxide (KOH). Glove box was used when necessary. All reactions were carried out under nitrogen atmosphere if not otherwise specified. The photochemical reactions were performed by using a Photochemical Reactor Ltd. equipped with a 400 w medium pressure Mercury-lamp in a 350 ml quartz immersion well reactor fitted with a no. 3408 pyrex glass filter sleeve. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 254 nm and 5% alcoholic molybdophosphoric acid for detection. Normalsil 60, 40-63μm silica gel was used for flash chromatography. ^{1}H NMR and ^{13}C NMR was recorded on a Varian Mercury 300 MHz (UiS, Norway), or a BRUKER ADVANCE-400 (automatic sample changer, BB auto tuning; Queens University, Kingston, Canada), all at room temperature. D_1-chloroform was used as solvent, unless otherwise specified. Chemical shift was reported in ppm compared to TMS (δ 0, singlet, for ^{1}H NMR), or for ^{13}C resonance signal to $CDCl_3$ (δ 77.0, triplet). The splitting pattern was recorded as a singlet, s; dublet, d; triplet, t; double dublet, dd; double triplet, dt; quartet, q; multiplet, m; broad, br. IR was recorded on a Perkin Elmer FT-IR spectrometer, version 3.02.01. Melting points was determined on a Stuart Scientific melting point apparatus SMP3. Enantiomeric excess was determine using chiral Ultimate 300 HPLC with a Lux 3u Cellulose-2 coloum (150 x 4.60 mm, Phenomex Inc.), RS pump, Autosampler and a Diode Array detector at 220 nm.

5.2 Total synthesis of (1*R*,2*R*)-1,2-dihydrochrysene-1,2-diol

5.2.1 Synthesis of ethyl 4-(2-(*N*,*N*'-diethylcarbamoyl)phenyl)butanoate (61)

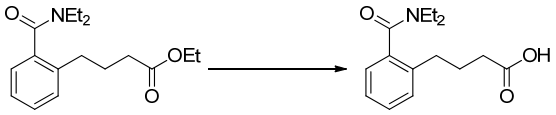


N,*N*'-diethylbenzamide (1.68 g, 9.48 mmol) in THF (10 ml) was added to a solution of *s*-BuLi (8.4 ml, 10.42 mmol, 1.4 M solution in cyclohexane), TMEDA (1.56 ml, 10.41 mmol) and THF (14 ml) at -78 °C. After stirring for 1 hour a solution of zinc chloride (1.43 g, 10.45 mmol.) in THF (10 ml) was added and the mixture was allowed to warm to 11 °C over 35 min.

A second round bottomed flask containing nickel (II) acetylacetenoat (124 mg, 0.48 mmol, 5 mol%) and PPh_3 (128 mg, 0.49 mmol, 5 mol%) in THF (15 ml) was warmed to reflux before ethyl-4-brombutyrate (1.4 ml, 9.69 mmol) was added. After stirring the resulting reaction mixture for 10 min arylzinc chloride was added slowly over a period of 15 min and the mixture was stirred at reflux for 2 hours. After allowing the mixture to cool down it was quenched with saturated ammonium chloride (50 ml) and extracted with diethyl ether (3 x 70ml). The organic layer was dried over magnesium sulphate, filtered and concentrated to give a yellow oil. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 1:1) to afford a *ca*. 9:1 mixture of product and benzamide **62** (2.04 g) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (s, 4H, benzamide **62**), 7.30-7.14 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (app s, 1H), 3.58 (app. s, 2H, benzamide **62**), 3.35 (app s, 1H), 3.48 (q, *J* = 7.0 Hz, 2H), 2.66-2.58 (br. m, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.99-1.92 (m, 2H), 1.28-1.22 (m, 6H), 1.11 (app. s, 3H, benzamide **62**), 1.04 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2 (**C**OOEt), 170.5 (**C**ON), 137.5 (C), 136.7 (C), 129.3 (**C**H), 128.6 (**C**H), 126.0

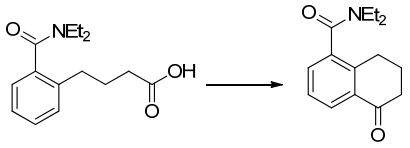
(**C**H), 125.5 (**C**H), 60.1 O**C**$H_2$$CH_3$), 42.7 (N**C**$H_2$), 38.5 (N**C**$H_2$), 33.8 (**C**$H_2$), 32.1 (**C**$H_2$), 25.8 (**C**$H_2$), 14.1 (NC$H_2$**C**$H_3$), 13.8 (OC$H_2$**C**$H_3$), 12.6 (NC$H_2$**C**$H_3$)

5.2.2 4-(2-(*N*,*N*'-diethylcarbamoyl)phenyl)butanoic acid (73)



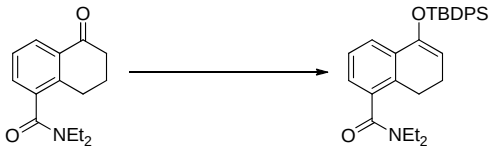
To a solution of phenylbutanoate **61** (2.04 g) in methanol (65 ml) and water (5 ml) was added potassium hydroxide (0.79 g, 14.15 mmol). The reaction mixture was heated at reflux for 2 hour, before concentrated *in vacuo*. The yellow residue was dissolved in water (50 ml), added 2M NaOH-solution (2 ml) and extracted with diethyl ether (2 x 60ml). The water layer was adjusted to pH 0 by the addition of 6M HCl (4 ml) and extracted a second time with diethyl ether (3 x 60ml). The latter organic layer was dried over magnesium sulphate, filtered and concentrated to afford 1.68 g (67% from benzamide **62**) of the product **73** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.14 (m, 4H), 3.78 (app. s, 1H), 3.35 (app. s, 1H), 3.12 (q, *J* = 6.9 Hz, 2H), 2.66 (app. s, 1H), 2.57 (app. s, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.94 (app. hep, *J* = 7.3 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.0 (**C**OOH), 170.9 (**C**ON), 137.4 (C), 136.5 (C), 129.5 (**C**H), 128.8 (**C**H), 126.1 (**C**H), 125.6 (**C**H), 42.9 (N**C**H_2), 38.8 (N**C**H_2), 33.6 (**C**H_2), 32.0 (**C**H_2), 25.1 (**C**H_2), 13.8 (NCH_2**C**H_3), 12.6 (NCH_2**C**H_3); IR (KBr) 2974 (m), 2936 (m), 1731 (s), 1630 (m), 1591 (s), 1498 (w), 1460 (m), 1439 (m), 1383 (w), 1364 (w), 1292 (w), 1220 (w), 1150 (w), 1117 (w), 1085 (w), 946 (w), 752 (w); Mass spectrometry *m/z* (relative intensity %) 286.1 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{15}H_{21}O_3N$ + Na: 286.1414, Found 286.1412

5.2.3 *N*,*N*'-diethyl-5-oxo-5,6,7,8-tetrahydronaphthalene-1-carboxamide (60)



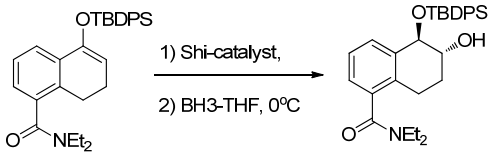
To butanoic acid **73** (300 mg, 1.141 mmol) was added Eaton`s reagent (7.7 w% P_2O_5 in MsOH, 6.2 ml) and quickly warmed to 100 °C and stirred for 2 hours. The dark brown mixture was cooled to room temperature and poured over ice (40 ml). After the ice had melted the yellow water solution was extracted with dichloromethane (3 x 60 ml). The organic layer was washed with saturated sodium bicarbonate-solution (100 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a dark brown oil. The crude product was purified by flash coloum chromatography (petroleum ether: ethyl acetate 1:1) to afford 170 mg (61%) of product **60** as a white solid. Mp 96.1-96.6 °C (diethyl ether); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09-8.06 (m, 1H), 7.39-7.29 (m, 2H), 3.76 (app. s, 1H), 3.43 (app. s, 1H), 3.14 (q, *J* = 7.2 Hz, 2H), 3.06 (app. s, 1H), 2.73 (app. s, 1H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.14 (app. d, *J* = 6.9 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.7 (**C**O), 169.6 (**C**ON), 140.4 (**C**), 136.8 (**C**), 133.1 (**C**), 130.2 (**C**H), 127.7 (**C**H), 126.7 (**C**H), 42.8 (N**C**H_2), 39.0 (N**C**H_2), 38.9 (**C**H_2), 26.4 (**C**H_2), 22.7 (**C**H_2), 14.1 (NCH_2**C**H_3), 12.9 (NCH_2**C**H_3); IR (KBr) 2981 (w), 2943 (m), 2874 (w), 1683 (s), 1624 (s), 1584 (m), 1478 (m), 1457 (m), 1432 (m), 1366 (w), 1327 (w), 1296 (m), 1278 (s), 1215 (m), 1192 (w), 1131 (m), 1088 (m), 950 (w), 905 (w), 829 (m), 802 (m), 736 (w), 669 (w), 548 (w); Mass spectrum *m/z* (relative intensity %) 268.1 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{15}H_{19}O_2N$ + Na: 268.1308, Found 268.1309

5.2.4 5-((*tert*-butyldiphenylsilyl)oxy)-*N*,*N*-diethyl-7,8-dihydronaphthalene-1-carboxamide (59)



A solution of potassium hexamethyldisilazide (213 mg, 1.07 mmol) in THF (3 ml) was added dropwise to a stirred solution of tetralone **60** (161 mg, 0.66 mmol) in THF (8 ml) at -78°C. The brown solution was stirred for 35 min before *tert*-butyldiphenylsilyl chloride (0.2 ml, 0.77 mmol) was added dropwise. After stirring for 5 min at -78 °C, the flask was removed from the cooling bath and allowed to warm to room temperature. The mixture was stirred at room temperature for 1 hour, and concentrated *in vacuo*. The brown oil was dissolved in pentane (30 ml) and filtered through celite. The yellow filtrate was concentrated and purified by flash chromatography (petroleum ether: ethyl acetate 2:1) to afford 292 mg (92%) of product **59** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (app. d, J = 6.8 Hz, 3H), 7.72 (app. d, J = 6.3 Hz, 2H), 7.41 (app. s, 6H), 7.30 (t, J = 7.7 Hz, 1H), 7.10 (dd, J = 1.0, 7.6 Hz, 1H), 4.79 (t, J = 4.7 Hz, 1H), 3.78-3.71 (m, 1H), 3.43-3.37 (m, 1H), 3.16 (q, J = 7.1 Hz, 2H), 2.73-2.65 (m, 1H), 2.51-2.43 (m, 1H), 2.10-1.99 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.10 (app. s, 9H), 1.04 (t, J = 7.1 Hz, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6 (**C**O), 147.4 (**C**), 135.5 (**C**Hx4), 134.0 (**C**), 133.0 (**C**), 132.9 (**C**), 132.3 (**C**), 129.8 (**C**H), 127.7 (**C**Hx4), 126.3 (**C**H), 124.6 (**C**Hx2), 122.0 (**C**H), 106.3 (**C**H=), 42.7 (N**C**H_2), 38.7 (N**C**H_2), 26.6 (**C**H_3x3), 24.6 (**C**H_2), 21.6 (**C**H_2), 19.5 (**C**), 14.2 (NCH_2**C**H_3), 12.9 (NCH_2**C**H_3); IR (KBr) 3072 (w), 2891 (w), 2932 (m), 2858 (w), 1635 (s), 1473 (w), 1428 (m), 1362 (w), 1344 (w), 1286 (w), 1255 (m), 1220 (w), 1196 (w), 1149 (m), 1113 (m), 955 (w), 921 (w), 823 (w), 736 (w), 701 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.2.5 *Trans*-(5*R*,6*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-*N*,*N*-diethyl-6-hydroxy-5,6,7,8-tetrahydronaphthalene-1-carboxamide (75)[39]

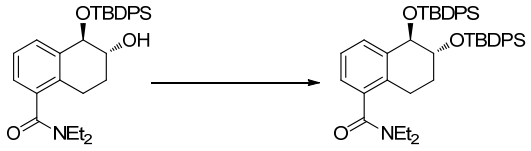


Oxone (519 mg, 0.844 mmol, 1.38 eq) in aqueous EDTA solution[39] (4.9 ml), and potassium carbonate (674 mg, 4.88 mmol, 8 eq) in water (4.9 ml) was added simultaneously (syringe drive, 0.053 ml/min) over a period of 90 min to a precooled mixture of silyl enol ether **59** (295 mg, 0.61 mmol), Shi-catalyst (51 mg, 0.197 mmol, 0.3 eq), tetrabutylammonium bisulphate (5 mg, 0.015 mmol, 0.04 eq), acetonitrile (3.7 ml), 1,2-dimetoxymethane (7.4 ml) and aqueous sodium borate-EDTA solution[39] (7.4 ml) at 0 °C. After stirring for additional 30 min at 0°C, the reaction mixture was diluted with ice-cold pentane (70 ml), and ice-cold water (40 ml). The layers were separated and the aqueous layer was extracted with ice-cold pentane (2 x 70 ml). The organic layer was washed with brine (150 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a transparent oil.

To a precooled solution of crude product in THF (12 ml) was added BH_3-THF (0.91 ml, 0.91 mmol, 1M in THF) at 0 °C. The reaction mixture was stirred at 0 ºC for 90 min, before septum was removed and the mixture diluted with diethyl ether (10 ml). Tris(hydroxymethyl)aminomethane hydrochloride (1.0 M, 10 ml) was added carefully, and the solution was warmed to room temperature and stirred for 30 min. Water (10 ml) was added, the layers were separated, and the aqueous layer extracted with ethyl ether (3 x 30 ml). The organic layer was washed with brine (75 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 1:1) to afford 215 mg (70%) of product **75** as a fluffy white foamy oil. 83% *ee* by using Lux 3u Cellulose-2 coloum (10% iPrOH in hexane, 220 nm, 0,5 ml/min) t_R 13.2 (minor), t_R 16.6 (major); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.62 (m, 4H), 7.47-7.37 (m, 6H), 7.21-7.05 (m, 3H), 4.62 (app. d, J = 8.5 Hz,

1H), 4.02 (app. s, 1H), 3.77 (app. s, 1H), 3.36-2.89 (m, 4H), 2.58-2.53 (m, 1H), 2.23-2.18 (m, 1H), 1.93 (app. s, 1H), 1.83-1.74 (m, 1H), 1.26-1.22 (br. m, 4H), 1.07 (s, 9H), 0.99-0.95 (br. m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6 (**C**O), 137.5 (**C**), 136.3 (**C**H), 136.2 (**C**H), 135.9 (**C**H), 135.7 (**C**H), 134.2 (**C**), 133.0 (**C**), 132.4 (**C**), 132.2 (**C**), 129.9 (**C**H), 129.8 (**C**H), 127.9 (**C**Hx2), 127.6 (**C**Hx2), 125.9 (**C**H), 125.8 (**C**H),124.5 (**C**H), 75.1 (**C**H-OSi), 71.2 (**C**H-OSi), 42.5 (N**C**H_2), 38.6 (N**C**H_2), 27.1 (**C**H_3x3), 26.2 (**C**H_2), 22.6 (**C**H_2), 19.5 (**C**), 14.0 (NCH$_2$**C**H_3), 12.8 (NCH$_2$**C**H_3); IR (KBr) 3393 (br, w), 3070 (w), 2932 (m), 2857 (m), 1614 (s), 1460 (w), 1427 (s), 1292 (w), 1217 (w), 1110 (s), 1069 (s, br), 853(w), 821 (w), 788 (w), 741 (w), 703 (m), 609 (w); Mass spectrum *m/z* (relative intensity %) 524.3 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{31}H_{39}O_3NSi$ + Na: 524.2591, Found 524.2591

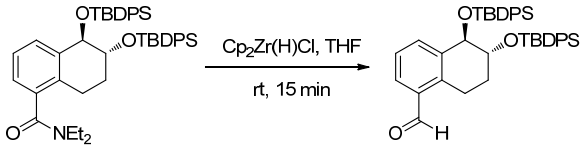
5.2.6 (5*R*,6*R*)-5,6-bis((*tert*-butyldiphenylsilyl)oxy)-*N*,*N*-diethyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (55)



To a suspension of NaH (56 mg, 1.40 mmol) in THF (4 ml) was added *trans*-diol monosilyl ether **75** (365 mg, 0.728 mmol) in THF (9 ml) at 0 ºC. The reaction mixture was warmed to room temperature, and stirred for 30 min before *tert*-butyldiphenylsilyl chloride (0.23 ml, 0.886 mmol) was added dropwise. After stirring overnight (19 hours) the reaction mixture was quenched with saturated ammonium chloride (15 ml) and extracted with diethyl ether (3 x 30 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash coloum chromatography (petroleum ether: ethyl acetate 2:1) to afford 508 mg (94%) of product **55** as fluffy white foamy oil as a *ca*. 2:3 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59-7.19 (m, 20H), 7.04 (t, *J* = Hz, 1H), 6.92 (t, *J* = Hz, 1H – major rotamer), 6.84 (t, *J* = Hz, 1H – minor rotamer), 6.51 (d, *J* = Hz, 1H – major rotamer), 6.32 (d, *J* = Hz, 1H – minor

rotamer), 4.45 (app. d, *J* = Hz, 1H), 4.28 (app. s, 1H), 3.91-3.72 (m, 1.5H), 3.49-2-71 (m, 4H), 2.57-231 (m, 1H), 1.87-1.82 (m, 1.5H), 1.29-1.24 (m, 3H), 1.11-1.02 (m,1H – minor rotamer), 0.94 (t, *J* = 6.9 Hz, 2H – minor rotamer) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9 (**C**O), 136.6 (**C**), 136.3 (**C**), 135.9 (**C**Hx2), 135.8 (**C**Hx2), 135.7 (**C**Hx2), 135.5 (**C**Hx2), 133.8 (**C**), 133.7 (**C**), 133.5 (**C**), 132.9 (**C**), 131.7(**C**), 129.6 (**C**H), 129.5 (4) (**C**H), 129.5 (0) (**C**H), 129.3 (**C**H), 127.5 (**C**Hx4), 127.4 (**C**Hx4), 127.3 (**C**H), 125.3 (**C**H), 124.5 (**C**H), 71.7 (**C**H-OSi, minor rotamer), 71.4 (**C**H-OSi, major rotamer), 70.3 (**C**H-OSi, major rotamer), 67.9 (**C**H-OSi, minor rotamer), 42.7 (N**C**H_2, minor rotamer), 42.4 (N**C**H_2, major rotamer), 38.7 (N**C**H_2, minor rotamer), 38.5 (N**C**H_2, major rotamer), 26.7 (**C**H_3x6), 24.1 (**C**H_2, minor rotamer), 23.5 (**C**H_2, major rotamer), 21.1 (**C**H_2, minor rotamer), 20.4 (**C**H_2, major rotamer), 19.1 (**C**), 14.0 (NCH_2**C**H_3), 12.8 (NCH_2**C**H_3); IR (KBr) 3071 (w), 2931 (m), 2857 (m), 1637 (s), 1590 (w), 1473 (w), 1460 (w), 1427 (m), 1290 (w), 1221 (w), 1111 (s), 1080 (m, br), 1008 (w), 822 (w), 740 (w), 701 (s), 609 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

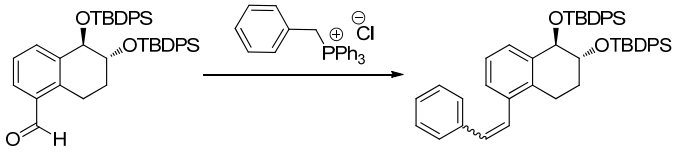
5.2.7 (5*R*,6*R*)-5,6-bis((*tert*-butyldiphenylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-1-carbaldehyde (53)[33a]



Amide **55** (282 mg, 0.38 mmol) in THF (4 ml) was added to a suspension of $Cp_2Zr(H)Cl$ (148 mg, 0.57 mmol) in THF (2 ml) at room temperature. After 30 min off stirring the yellow solution was concentrated *in vacuo* and the orange residue was purified by flash coloum chromatography (petroleum ether: ethyl acetate 4:1) to afford 221 mg (87%) of product **53** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.33 (s, 1H), 7.69 (d, *J* = 6.4 Hz, 1H), 7.53-7.17 (m, 20H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 6.7 Hz, 1H), 4.49 (app. d, *J* = 2.8 Hz, 1H), 4.32 (s, 1H), 3.48-3.23 (m, 2H), 2.41-2.31 (m, 1H), 1.95-1.90 (m, 1H), 0.84 (s, 9H), 0.81 (s, 9H); ^{13}C NMR ($CDCl_3$,

75 MHz): δ 193.1 (**C**O), 140.0 (**C**), 137.4 (**C**H), 137.2 (**C**), 135.8 (**C**Hx4), 135.6 (**C**Hx2), 135.5 (**C**Hx2), 133.9 (**C**), 133.6 (**C**), 133.4 (**C**x2), 133.3 (**C**), 132.2 (**C**H), 129.7 (**C**H), 129.6 (**C**H), 129.5 (**C**H), 129.4 (**C**H), 127.7 (**C**Hx2), 127.6 (**C**Hx2), 127.5 (**C**Hx2), 127.3 (**C**Hx2), 125.5 (**C**H), 71.5 (**C**H-OSi), 69.7 (**C**H-OSi), 26.7 (**C**H_3x6), 23.4 (**C**H_2), 21.2 (**C**H_2), 19.2 (Cx2); IR (KBr) 3071 (w), 2931 (m), 2857 (m), 1698 (m), 1590 (w), 1472 (w), 1427 (m), 1184 (w), 1113 (s), 1079 (s, br), 1008 (w), 822 (w), 740 (w), 701 (s), 610 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

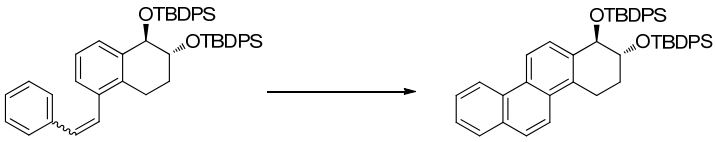
5.2.8 (((1*R*,2*R*)-5-styryl-1,2,3,4-tetrahydronaphthalene-1,2-diyl)bis(oxy))bis(*tert*-butyldiphenylsilane) (51)[35c]



To a solution of aldehyde **53** (179 mg, 0.27 mmol) in dichloromethane (8 ml) was added wittig salt **81** (146 mg, 0.38 mmol) and a 50% -solution of NaOH (0.8 ml). The yellow reaction mixture was stirred at room temperature for 2.5 hours. Water (20 ml) was added and the water layer was extracted with dichloromethane (3 x 20 ml). The organic layer was washed with brine (40 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash coloum chromatography (2% ethyl acetate in petroleum ether) to afford 195 mg (98%) of product **51** as a fluffy white foamy oil as *ca* 2:1 mixture of *Z* and *E* isomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.18 (m, 25H), 7.02-6.88 (m, 2H), 6.76-6.59 (m, 2H), 6.45 (d, *J* = 7.6 Hz, 1H, minor isomer), 6.36 (d, *J* = 7.6 Hz,1H, major isomer), 4.50 (app. s, 1H), 4.30 (app. s, 1H), 3.08-2.76 (m, 2H), 2.41-2.31 (m, 1H), 1.89-1.84 (m, 1H), 0.85 (s, 9H), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.0 (**C**), 136.6 (**C**), 136.0 (**C**H), 135.9 (**C**Hx2), 135.8 (**C**Hx2), 135.6 (**C**Hx2), 135.2 (**C**), 134.1 (**C**), 134.0 (**C**), 133.9 (**C**), 133.8 (4) (**C**), 133.8 (0) (**C**), 131.3 (**C**), 130.7 (**C**H), 130.2 (**C**H), 129.9 (**C**H),

129.8 (**C**), 129.5 (**C**Hx2), 129.4 (**C**H), 129.3 (**C**H), 129.0 (**C**Hx2), 128.7 (**C**H), 128.1 (**C**H), 128.0 (**C**Hx2), 127.5 (4) (**C**Hx2), 127.5 (1) (**C**H), 127.4 (**C**Hx2), 127.2 (**C**Hx2), 126.9 (**C**H), 126.6 (**C**), 126.5 (**C**H), 125.3 (**C**), 125.1 (**C**H), 124.7 (**C**), 72.0 (**C**H-OSi – minor isomer), 71.9 (**C**H-OSi – major isomer), 70.4 (**C**H-OSi – major isomer), 70.2 (**C**H-OSi – minor isomer), 26.8 (**C**H_3x3), 26.7 (**C**H_3x3), 24.0 (**C**H_2), 22.0 (**C**H_2), 19.2 (3) (**C**x2 – major isomer), 19.2 (0) (**C**x2 – minor isomer); IR (KBr) 3070 (m), 2930 (s), 2857 (m), 1660 (w), 1589 (w), 1472 (m), 1427 (s), 1390 (w), 1362 (w), 1189 (w), 1112 (s), 1075 (br, s), 1007 (m), 910 (w), 858 (w), 822 (m), 790 (w), 738 (m), 701 (s), 610 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

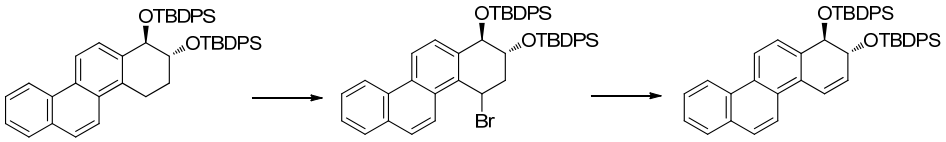
5.2.9 (((1R,2R)-1,2,3,4-tetrahydrochrysene-1,2-diyl)bis(oxy))bis(tert-butyldiphenylsilane) (82)[35c]



To a solution of stilbene **51** (173 mg, 0.23 mmol) in degassed toluene (350 ml) was added iodine (68 mg, 0.27 mmol) and 1,2-diepoxybutane (7 ml). The pink mixture was irradiated for 1.5 hours before concentrated to a volume of 50 ml. The residue was washed with 10% aqueous sodium thiosulphate solution (20 ml) and brine (20 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash coloum chromatography (5% ethyl acetate in petroleum ether) to afford 166 mg (96%) of product **82** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.63 (d, *J* = 7.9 Hz, 1H), 8.29 (d, *J*= 8.5 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.63-7.49 (m, 4H), 7.42-7.12 (m, 18H), 6.82 (d, *J* = 8.5 Hz, 1H), 4.69 (app. d, *J* = 1.9 Hz, 1H), 4.39 (app. s, 1H), 3.35-3.32 (m, 2H), 2.51-2.47 (m, 1H), 2.06-2.01 (m, 1H), 0.86 (s, 9H), 0.79 (s, 9H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9 (**C**Hx2), 136.0 (**C**Hx2), 135.6 (2) (**C**Hx2), 135.6 (0) (**C**Hx2), 134.1 (**C**), 134.0 (**C**), 133.8

(2) (**C**), 133.8 (0) (**C**), 133.7 (**C**), 133.2 (**C**), 131.6 (**C**), 130.7 (**C**), 130.1 (**C**H), 129.6 (**C**H), 129.5 (**C**H), 129.4 (**C**Hx2), 129.3 (**C**H), 128.4 (**C**H), 127.6 (**C**Hx2), 127.5 (**C**Hx2), 127.4 (**C**Hx2), 127.2 (**C**Hx2), 126.4 (**C**H), 126.2 (**C**H), 123.0 (**C**H), 122.5 (**C**H), 120.1 (**C**H), 72.1 (**C**H-OSi), 70.4 (**C**H-OSi), 26.8 (**C**H_3x3), 26.7 (**C**H_3x3), 24.1 (**C**H_2), 21.4 (**C**H_2), 19.3 (**C**x2), 19.2 (**C**x2); IR (KBr) 3070 (m), 2930 (s), 2857 (m), 1589 (w), 1471 (m), 1427 (m), 1390 (w), 1361 (m), 1189 (w), 1112 (s), 1085 (br, s), 1068 (br, s), 1007 (m), 908 (m), 841 (m), 822 (m), 790 (w), 771 (w), 739 (m), 701 (s), 610 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis

5.2.10 (((1*R*,2*R*)-1,2-dihydrochrysene-1,2-diyl)bis(oxy))bis(*tert*-butyldiphenylsilane) (50)

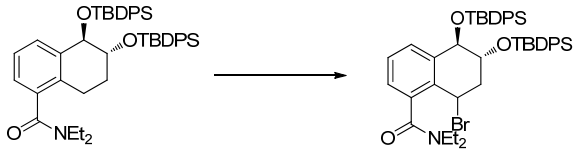


To a solution of compound **82** (399 mg, 0.54 mmol) in tetrachloromethane (CCl_4) (10 ml) was added *N*-Bromosuccinimide (NBS) (144 mg, 0.81 mmol) and azobisisobutyronitrile (AIBN) (12 mg, 0.06 mmol). The solution was quickly warmed to reflux, stirred for 2 hours before it was allowed to cool down. *N*-succinimine was filtered of, and the filtrate was diluted in dichloromethane (100 ml), washed with brine (70 ml), dried over magnesium sulphate, filtered and concentrated to a yellow oil. The crude product was purified by flash coloum chromatography (2% ethyl acetate in petroleum ether) to afford an intractable mixture of products.

To a solution of benzyl bromide (306 mg) in THF (5 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.6 ml,0.54 mmol) at room temperature. The solution was stirred for 1 hour, quenched with ammonium chloride (10 ml), extracted into diethyl ether (3 x 15 ml), washed with brine (30 ml), dried over over magnesium sulphate, filtered and concentrated. The

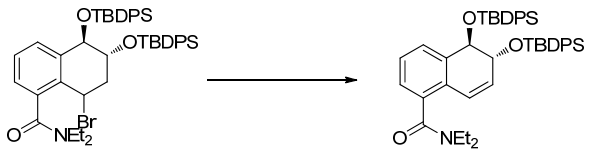
crude product was purified by flash coloum chromatography (5% ethyl acetate in petroleum ether) to afford an intractable mixture of products.

5.2.11 (5*R*,6*R*)-8-bromo-5,6-bis((*tert*-butyldiphenylsilyl)oxy)-*N*,*N*-diethyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (87)



NBS (53 mg, 0.299 mmol) and AIBN (3 mg, 0.012 mmol) was added to a solution of amide **55** (188 mg, 0.254 mmol) in CCl_4 (7 ml). The reaction mixture was warmed to 65 °C, stirred for 4 hours and cooled down before the succinimide was filtered off. The filtrate was diluted in dichloromethane (50 ml), washed with brine (30 ml), dried over magnesium sulphate, filtered and concentrated. The concentrate was purified by flash coloum chromatography (petroleum ether: ethyl acetate 4:1) to afford 136 mg (67%) of product **87** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54-7.15 (m, 20H), 7.05 (d, *J* = Hz, 1H), 6.84 (t, *J* = Hz, 1H), 6.23 (d, *J* = Hz, 1H), 6.14 (t, *J* = Hz, 1H), 4.46 (app. d, *J* = Hz, 1H), 4.21 (app. s, 1H), 3.84-3.73 (m, 1H), 3.40-3.33 (m, 2H), 3.25-3.06 (m, 2H), 2.64-2.57 (m, 1H), 1.30 (t, *J* = Hz, 3H), 1.21 (t, *J* = Hz, 3H), 0.88 (s, 9H), 0.77 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7 (**C**O), 137.9 (**C**), 137.1 (**C**), 135.9 (**C**Hx2), 135.8 (**C**Hx2), 135.6 (0) (**C**Hx2), 135.5 (**C**Hx2), 135.2 (**C**), 134.8 (**C**Hx2), 133.6 (**C**x2), 133.5 (**C**), 133.3 (**C**), 131.5 (**C**H), 129.8 (**C**H), 129.6 (**C**Hx2), 129.3 (**C**H), 127.7 (**C**Hx4), 127.5 (**C**H), 127.3 (**C**H), 127.1 (**C**H), 126.9 (**C**H), 126.0 (**C**H), 72.0 (**C**H-OSi), 71.6 (**C**H-OSi), 43.5 (3) (N**C**H_2), 43.5 (0) (N**C**H_2), 38.5 (N**C**H_2), 37.4 (**C**HBr), 26.7 (**C**H_3x3), 26.6 (**C**H_3x3), 19.2 (**C**CH_3), 19.0 (**C**CH_3), 13.5 (NCH_2**C**H_3), 11.8 (NCH_2**C**H_3); IR (KBr) 3071 (w), 2959 (m), 2931 (m), 2893 (m), 2857 (m), 1617 (br. m), 1590 (m), 1472 (m), 1461 (m), 1382 (w), 1363 (m), 1285 (w), 1214 (w), 1190 (w), 1156 (w), 1113 (br. s), 1007 (w), 998 (w), 983 (w), 908 (w), 854 (w), 822 (m), 791 (w), 731 (m), 701 (s), 609 (m), 504 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

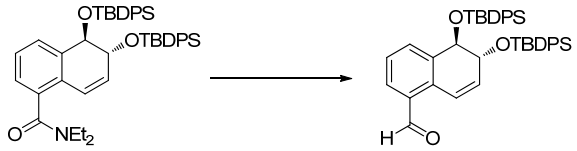
5.2.12 (5*R*,6*R*)-5,6-bis((*tert*-butyldiphenylsilyl)oxy)-*N*,*N*-diethyl-5,6-dihydronaphthalene-1-carboxamide (56)



1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.035 ml, 0.231mmol) was added to a solution of benzyl bromide **87** (136 mg, 0.166 mmol) in THF (4 ml) at room temperature. The reaction mixture was warmed to reflux, and stirred for 67 hours, cooled down, quenched with saturated ammonium chloride (15 ml) and extracted with diethyl ether (3 x 30 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated. The concentrate was purified by flash coloum chromatography (petroleum ether: ethyl acetate 3:1) to afford 92 mg (73%) of product **56** as a fluffy white foamy oil as a *ca.* 3:2 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52-7.22 (m, 20H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 9.4 Hz, 1H, H-7 – major rotamer), 6.52 (d, *J* = 7.7 Hz, 1H, H-4), 6.46 (d, *J* = 7.5 Hz, 1H, H-7 – minor rotamer), 5.94-5.82 (m, 1H, H-3), 4.61 (app. s, 1H, H-1), 4.31 (dd, *J* = 1.8, 4.8 Hz, 1H, H-2), 3.82-3.72 (m, 1H), 3.53-3.39 (m, 1H), 3.21 (app. d, *J* = 6.2 Hz, 2H – minor rotamer), 3.05 (app. d, *J* = 7.0 Hz, 2H – major rotamer), 1.30 (t, *J* = 7.0 Hz, 3H), 1.05-1.01 (br. m, 3H – minor rotamer), 0.97-0.92 (br. m, 3H – major rotamer), 0.86 (s, 9H – minor rotamer), 0.83 (s, 9H – major rotamer), 0.80 (s, 9H – major rotamer), 0.77 (s, 9H – minor rotamer); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (**C**O), 135.7 (**C**Hx6), 135.6 (**C**Hx2), 135.4 (**C**), 135.1 (**C**), 134.3 (**C**), 133.9 (**C**), 133.7 (**C**), 133.3 (**C**), 130.2 (**C**H, C-4 - major rotamer) , 130.0 (**C**H , C-4 - minor rotamer), 129.6 (**C**Hx2), 129.4 (**C**), 129.3 (**C**), 128.9 (**C**H, C-3 - major rotamer), 128.7 (**C**H , C-3- minor rotamer), 128.6 (**C**), 127.6 (**C**Hx6), 127.5 (**C**Hx2), 127.3 (**C**Hx2), 127.0 (**C**H), 125.8 (**C**H), 125.7, 125.5 (**C**H, C-7 - major rotamer), 125.0 (**C**H, C-7 - minor rotamer), 73.0 (**C**H-OSi, C-1 - minor rotamer), 72.6 (**C**H-OSi, C-1 - major rotamer), 68.7 (**C**H-OSi, C-2 - minor rotamer), 68.3 (**C**H-OSi, C-2 - major rotamer), 42.9 (N**C**H_2), 39.0 (N**C**H_2), 26.6 (**C**H_3x6), 19.2 (**C**CH_3), 19.0 (**C**CH_3), 14.0 (NCH_2**C**H_3), 13.1

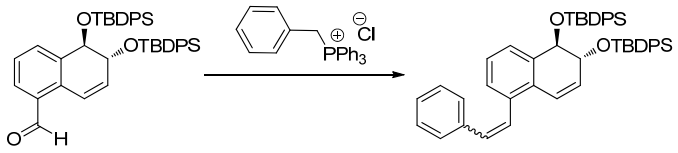
($NCH_2\mathbf{C}H_3$); IR (KBr) 3071 (w), 3048 (w), 2961 (m), 2931 (m), 2857 (m), 1634 (s), 1589 (w), 1473 (m), 1462 (m), 1428 (s), 1381 (w), 1362 (m), 1290 (w), 1216 (w), 1112 (s), 1073 (s, br.), 1007 (w), 910 (w), 887 (w), 822 (m), 771 (w), 738 (m), 701 (s), 610 (m), 504 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.2.13 (5*R*,6*R*)-5,6-bis((*tert*-butyldiphenylsilyl)oxy)-5,6-dihydronaphthalene-1-carbaldehyde (54)



Amide **56** (110 mg, 0.149 mmol) in THF (3 ml) was added to a suspension of $Cp_2Zr(H)Cl$ (57 mg, 0.221 mmol) in THF (2 ml) at room temperature. After 20 min off stirring, one drop of water along with silica was added to the yellow solution before concentrated *in vacuo* and purified by flash coloum chromatography (petroleum ether: ethyl acetate 10:1) to afford 65 mg (66%) of product **54** a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.23 (s, 1H), 7.59 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.52 (d, *J* = 9.9 Hz, 1H), 7.47-7.18 (m, 19H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 5.94 (ddd, *J* = 1.2, 5.5, 9.9 Hz, 1H), 4.60 (app. q, *J* = 1.2 Hz, 1H), 4.27 (dd, *J* = 2.4,5.5 Hz, 1H), 0.76 (s, 9H), 0.73 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.3 (**C**HO), 136.0 (**C**), 135.8 (**C**Hx2), 135.6 (**C**Hx4), 135.4 (**C**H), 133.9 (**C**), 133.7 (**C**), 133.6 (**C**), 133.5 (**C**), 133.4 (**C**), 131.7 (**C**H), 131.1 (**C**H), 130.7 (**C**), 129.7 (**C**Hx2), 129.6 (**C**H), 129.4 (**C**H), 127.7 (**C**Hx2), 127.6 (**C**Hx2), 127.5 (**C**Hx2), 127.3 (**C**Hx2), 127.0 (**C**H), 123.7 (**C**H), 72.8 (**C**H-OSi), 67.9 (**C**H-OSi), 26.7 ($\mathbf{C}H_3$x3), 26.6 ($\mathbf{C}H_3$x3), 19.2 (**C**), 19.1 (**C**); IR (KBr) 3070 (w), 2930 (m), 2856 (m), 1697 (m), 1590 (w), 1569 (w), 1471 (w), 1427 (m), 1390 (w), 1361 (w), 1195 (w), 1112 (s), 1074 (s, br), 886 (w), 821 (w), 780 (w), 739 (m), 701 (s), 611 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

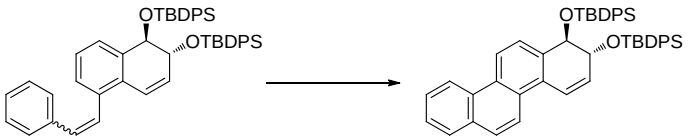
5.2.14 (((1*R*,2*R*)-5-styryl-1,2-dihydronaphthalene-1,2-diyl)bis(oxy))bis(*tert*-butyldiphenylsilane) (52)



To a solution of aldehyde **54** (91 mg, 0.137 mmol) in dichloromethane (4 ml) was added wittig salt **81** (75 mg, 0.193 mmol) and a 50% -solution of NaOH (0.4 ml). The orange reaction mixture was stirred at room temperature for 30 min (till the mixture went yellow). Water (10 ml) was added and the water layer was extracted with dichloromethane (3 x 20 ml). The organic layer was washed with brine (25 ml), dried over magnesium sulphate, filtered and concentrated. The crude product was purified by flash coloum chromatography (2% ethyl acetate in petroleum ether) to afford 97 mg (96%) of product **52** as a transparent oil as a *ca*. 2:3 mixture of *Z* and *E* isomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.40 (m, 8H), 7.37-7.12 (m, 16H), 7.09-7.01 (m, 3H), 6.95-6.84 (m, 2H), 6.76-6.57 (m, 2H), 6.45 (d, J = Hz, 1H – minor isomer), 6.37 (d, J = Hz, 1H – major isomer), 5.76-5.65 (m, 1H), 4.59-4.58 (m, 1H – minor isomer), 4.56-4.55 (m, 1H – major isomer), 4.24-4.21 (m, 1H), 0.78 (s, 9H – major isomer), 0.77 (s, 9H – minor isomer), 0.75 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6 (**C**), 136.7 (**C**), 135.9 (**C**Hx2), 135.7 (4) (**C**Hx2), 135.7 (9) (**C**Hx2), 135.3 (**C**), 135.2 (**C**), 134.7 (**C**), 134.2 (**C**), 133.9 (**C**H), 133.8 (**C**), 131.4 (**C**H), 131.0 (**C**H), 130.3 (**C**), 130.0 (**C**), 129.7 (**C**H), 129.6 (**C**H), 129.4 (**C**H), 129.3 (**C**H), 129.2 (**C**H), 129.1 (1) (**C**H), 129.1 (0) (**C**H), 128.7 (**C**H), 128.6 (**C**H), 128.1 (**C**H), 127.6 (**C**Hx4), 127.4 (**C**Hx2), 127.3 (**C**H), 127.2 (**C**H), 127.1 (**C**H), 127.0 (4) (**C**H), 127.0 (0) (**C**H), 126.5 (**C**H), 126.3 (**C**H – major isomer), 126.2 (**C**H – minor isomer), 125.7 (**C**H – major isomer), 125.4 (**C**H – minor isomer), 73.5 (**C**H-OSi, minor), 73.3 (**C**H-OSi, major), 68.7 (**C**H-OSi, minor), 68.5 (**C**H-OSi, major), 26.7 (2) ($\mathbf{C}H_3$x6, minor), 26.7 (0) ($\mathbf{C}H_3$x6, minor), 19.2 (**C**x2, minor), 19.1 (**C**x2, major); IR (KBr) 3069 (w), 2930 (m), 2856 (m), 1472 (w), 1427 (m), 1361 (w), 1112 (s), 1075 (br, s), 888 (w), 822 (w), 769 (m), 739 (m), 701

(s), 611 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

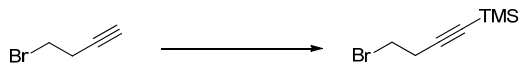
5.2.15 (((1*R*,2*R*)-1,2-dihydrochrysene-1,2-diyl)bis(oxy))bis(*tert*-butyldiphenylsilane) (50)



Air was bubbled through a solution of stilbene **52** (84 mg, 0.113 mmol) in diethyl ether (245 ml) and dichloromethane (7 ml) for 5 min. A catalytically amount of iodine (2 mg) was added to the solution and the reaction mixture was irradiated for 3 hours before washed with 10% aqueous sodium thiosulphate solution (100 ml) and brine (250 ml), dried over magnesium sulphate, filtered and concentrated. The crude product was purified by flash coloum chromatography (2% ethyl acetate in petroleum ether) to afford 23 mg (28%) of product **50** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.62 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 7.9 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.78 (d, *J* = 9.3 Hz, 1H), 7.69-7.08 (m, 23H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.96 (dd, *J* = 5.4, 9.8 Hz, 1H), 4.87 (app. s, 1H), 4.42 (dd, *J* = 2.2, 5.4 Hz, 1H), 0.82 (s, 9H), 0.81 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9 (**C**Hx2), 135.7 (4) (**C**Hx2), 135.7 (1) (**C**Hx2), 135.7 (0) (**C**Hx2), 134.2 (**C**) , 134.0 (**C**), 133.9 (**C**), 133.6 (**C**), 133.3 (**C**x2), 131.5 (**C**), 130.6 (**C**), 130.5 (**C**), 129.6 (1) (**C**H), 129.6 (0) (**C**H), 129.4 (**C**H), 129.3 (**C**H), 128.7 (**C**H), 128.5 (**C**), 128.4 (**C**H), 128.0 (**C**H), 127.6 (**C**Hx4), 127.3 (**C**Hx2), 127.2 (**C**Hx2), 126.8 (**C**H), 126.6 (**C**H), 126.5 (**C**H), 124.6 (**C**H), 122.6 (**C**H), 121.7 (3) (**C**H), 121.7 (0) (**C**H), 73.7 (**C**H-OSi), 68.7 (**C**H-OSi), 26.7 (1) (**C**H_3x3), 26.7 (0) (**C**H_3x3), 19.3 (**C**), 19.1 (**C**); IR (KBr) 3071 (w), 3049 (w), 2930 (m), 2857 (m), 1718 (w), 1589 (w), 1472 (m), 1428 (m), 1389 (w), 1361 (w), 1190 (w), 1112 (s), 1074 (s), 999 (w), 908 (m), 891 (w), 822 (m), 751 (m), 736 (m), 701 (s), 611 (m), 506 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.3 Attempted alternative synthesis towards silyl enol ether

5.3.1 Synthesis of (4-bromobutynyl)trimethylsilane (90)



To a stirring solution of 4-bromobutyn (0.7 ml, 7.5 mmol) in THF (20 ml) was added *n*-BuLi (3.3 ml,8.25 mmol, 2.5 M in cyclohexane) at -78ºC. The mixture was stirred at -78ºC before trimethyl silylchloride (1.04 ml, 8.25 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature over 30 min, and stirred at room temperature for additional 30 min before diluted with pentane (60 ml), extracted with ammonium chloride (35 ml), water (35 ml) and brine (35 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo* to give 1.395 g (91%) of product **90** as a light yellow solution. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.43 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 103.2, 87.0, 29.2, 24.3, -0.1 which is in accordance with literature.[59]

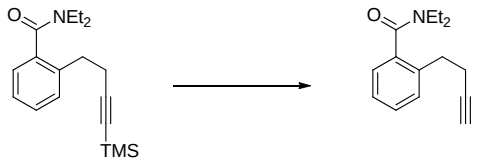
5.3.2 Synthesis of *N*,*N*'-diethyl-2-(4-(trimethylsilyl)but-3-ynyl)benzamide (91)

A solution of *N*,*N*'-diethylbenzamide (459 mg, 2.59 mmol) in THF (5 ml) was added slowly to a solution of *s*-BuLi (2.65 ml, 2.86 mmol, 1.08 M solution in cyclohexane) and TMEDA (0.43 ml, 2.87 mmol) in THF (10 ml) at -78 °C. After stirring for 1 hour at -78 °C a solution of $ZnCl_2$ (491 mg, 3.6

mmol) in THF (10 ml) was added, and the mixture was warmed to room temperature over 30 min.

In another bottle $Ni(acac)_2$ (33 mg, 0.130 mmol) and PPh_3 (34 mg, 0.130 mmol) was dissolved in THF (10 ml) and warmed to reflux, before (4-bromobutyl)trimethylsilane (**90**) (545 mg, 2.64 mmol) was added. After stirring for 10 min arylzinc chloride was added dropwise and the mixture was stirred at reflux for 2.5 hours. After allowing the mixture to cool down it was quenched with ammonium chloride (15 ml), and extracted with diethyl ether (3 x15ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo* to give yellow oil. The oil was separated by flash chromatography with (petroleum ether: ethyl acetate 1:1) as an eluent to afford 352 mg (45%) of product **91** as a transparent oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.15 (m, 4H), 3.76 (app. s, 1H), 3.39 (app. s, 1H), 3.13 (q, J = 6.9 Hz), 2.8 (app. d, J = 6.6 Hz), 2.52 (app. s, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 6.9 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5 (**C**O), 136.7 (**C**), 136.5 (**C**), 129.8 (**C**H), 128.5 (**C**H), 126.4 (**C**H), 125.5 (**C**H), 106.5 (**C**≡), 85.3 (**C**≡), 42.8 (N**C**H_2CH_3), 38.6 (N**C**H_2CH_3), 32.2 (**C**H_2), 21.2 (**C**H_2), 13.9 (NCH_2**C**H_3), 12.7 (NCH_2**C**H_3), 0.03 (Si(**C**H_3)$_3$); IR (KBr) 2964 (m), 2175 (m), 1634 (s), 1493 (m), 1428 (m), 1348 (w), 1290 (m), 1249 (m), 1222 (w), 1116 (w), 1082 (m), 1043 (m), 996 (w), 842 (s), 759 (m), 698 (w); Mass spectrum *m/z* (relative intensity %) 324.2 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{18}H_{27}ONSi$ + Na: 324.1754, Found 324.1757

5.3.3 Synthesis of 2-(but-3-ynyl)-*N*,*N*'-diethylbenzamide (92)

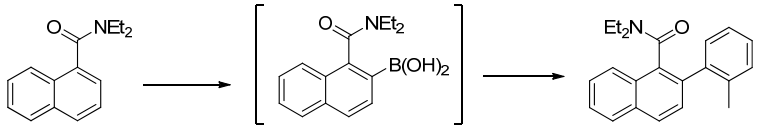


To a solution of alkyne **91** (320 mg, 1.06 mmol) dissolved MeOH (6 ml), was added a 2M solution of KOH (0.5 ml) and THF (4 ml).The reaction mixture was stirred for 17 hours at room temperature, diluted in pentane (50

ml), extracted with water (4 x 20 ml) and brine (20 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give 202 mg (83%) of product **92** as a light yellow oil.^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.16 (m, 4H), 3.75 (app. s, 1H), 3.93 (app. s, 1H), 3.13 (q, J = 6.9 Hz, 2H), 2.82 (app. t, J = 7.2 Hz), 2.51 (app. s, 2H), 1.96 (app. t, J = 2.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4 (**C**O), 136.8 (**C**), 136.4 (**C**), 129.6 (**C**H), 128.6 (**C**H), 126.5 (**C**H), 125.6 (**C**H), 83.7 (**C**≡), 68.9 (≡**C**H), 42.8 (N**C**H_2), 38.6 (N**C**H_2), 32.1 (**C**H_2), 19.8 (**C**H_2), 14.0 (NCH_2**C**H_3), 12.7 (NCH_2**C**H_3); IR (KBr): 3294 (m), 3239 (m), 2974 (m), 2936 (m), 2117 (w), 1628 (s), 1494 (m), 1429 (s), 1382 (m), 1365 (m), 1291 (m), 1221 (m), 1082 (m), 944 (w), 881 (w), 781 (m), 753 (m), 666 (w), 630 (m); Mass spectrum *m/z* (relative intensity %) 252.1 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{15}H_{19}ON$ + Na: 252.1359, Found 252.1359

5.4 Directed remote metalation reaction in the formation of chrysenol and chrysenyl diethylcabamate

5.4.1 Synthesis of *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (107)

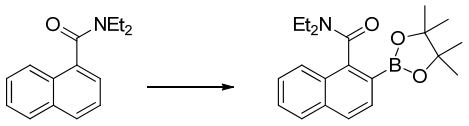


N,*N*'-diethyl-1-naphthoylamide (0.781 g, 3.44 mmol) in THF (10 ml) was added to a solution of *s*-BuLi (3.7 ml, 5.17 mmol, 1.4 M solution in cyclohexane), TMEDA (0.77 ml, 5.16 mmol) and THF (10 ml) at -78 °C. After stirring for 1 hour triisopropyl borate (1.97 ml, 8.59 mmol) was added, and the mixture stirred at -78 °C for 1.5 hour and warmed to room temperature overnight (18 hours). The reaction mixture was quenched with ammonium chloride (15 ml) and extracted with diethyl ether (3 x 15ml). The

organic layer was washed with water (2 x 45 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give brown oil.

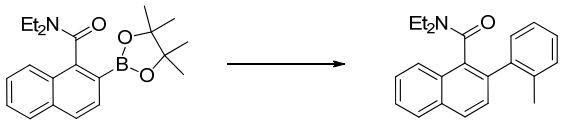
All solutions were degassed prior to use. A mixture of $PdCl_2$(dppf) (118 mg, 0.14 mmol, 5 mol%) and 2-bromotoluene (0.35 ml, 2.91 mmol) in DME (6 ml) was stirred at room temperature for 15 min. The solution of (1-(diethylcarbamoyl)naphthalen-2-yl)boronic acid (3.44 mmol,) in DME (4 ml) was added, followed by 2M sodium carbonate-solution (6 ml), at room temperature. The mixture was heated at reflux for 18 hours, cooled, and extracted with diethyl ether (3 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate 2:1) to afford 0.85 g (92%) of brown oil as a *ca* 3:2 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87-7.85 (app. m, 3H), 7.57-7.51 (m, 3H), 7.42-7.13 (m, 4H), 3.89-3.82 (m, 1H), 3.26-2.70 (m, 3H), 2.26 and 2.19 (s, 3H), 0.94-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9 (**C**O), 139.9 (**C**), 138.6 (**C**), 137.8 (**C**), 134.9 (**C**), 133.9 (**C**), 132.5 (**C**H), 131.2 (**C**H), 130.0 (04) (**C**H), 130.0 (0) (**C**H), 128.2 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 127.7 (**C**Hx2), 127.5 (**C**H), 126.9 (**C**Hx2), 126.2 (**C**H), 125.6 (**C**H), 125.5 (**C**x2), 124.5 (**C**x2), 42.7 (N**C**H_2 - minor rotamer), 42.1 (N**C**H_2 - major rotamer), 37.7 (N**C**H_2 - major rotamer), 37.5 (N**C**H_2 - minor rotamer), 20.4 (**C**H_3 - minor rotamer), 20.3 (**C**H_3 - major rotamer), 13.9 (2) (NCH_2**C**H_3 - minor rotamer), 13.9 (0) (NCH_2**C**H_3 - major rotamer), 11.9 (NCH_2**C**H_3 - major rotamer), 11.6 (NCH_2**C**H_3 - minor rotamer); IR (KBr): 3055 (w), 2974 (m), 2933 (m), 2873 (w), 2238 (w), 1628 (s), 1492 (m), 1473 (m), 1434 (s), 1381 (m), 1280 (m), 1267 (m), 1221 (m), 1128 (m), 828 (m), 761 (m), 728 (m); Mass spectrum *m/z* (relative intensity %) 340.2 $[M + Na]^+$ (100); HRMS (ESI) Calc. for $C_{22}H_{23}ON$ + Na: 340.1672, Found 340.1671

5.4.2 Synthesis of *N*,*N*-diethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthamide (108)



N,*N*'-diethyl-1-naphthoylamide (764 mg, 3.36 mmol) in THF (10 ml) was added to a solution of *s*-BuLi (3.6 ml, 5.04 mmol, 1.4 M solution in cyclohexane), TMEDA (0.76 ml, 5.07 mmol) and THF (10 ml) at -78 °C. After stirring for 1 hour 2-metoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborolane (1.10 ml, 6.72 mmol) was added, and the reaction mixture stirred at -78 °C for 1.5 hour before warmed to room temperature overnight (15 hours). The mixture was quenched with ammonium chloride (15 ml) and extracted with diethyl ether (3 x 15ml). The organic layer was washed with water (2 x 45 ml), dried over magenisum sulphate, filtered and concentrated to give brown oil. The oil was separated by flash chromatography with Petroleum ether: Ethyl acetate (3:2) to afford 676 mg (58%) of product **108**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (m, 3H), 7.50 (m, 2H), 3.82 (app. t, *J* = 6.9 Hz, 1H), 3.61 (app. t, *J* = 6.9 Hz), 3.07 (m, 2H), 1.42 (t, *J* = 6.9 Hz, 3H), 1.34 (s, 12H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2 (**C**O), 142.9 (**C**), 134.8 (**C**), 130.78 (**C**H), 129.4 (**C**), 127.9 (**C**H), 127.1 (**C**H), 126.4 (**C**H), 125.8 (**C**H), 43.2 (**C**H_2), 38.9 (**C**H_2), 24.8 (4x**C**H_3), 13.7 (**C**H_3), 12.8 (**C**H_3)

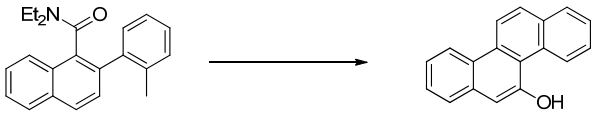
5.4.3 Synthesis of *N*,*N*-diethyl-2-(o-tolyl)-1-naphthamide (107)



All solutions were degassed prior to use. A mixture of $PdCl_2$(dppf) (79 mg, 0.097 mmol) and 2-bromotoluene (0.23 ml, 1.91 mmol) in DME (6 ml) was stirred at room temperature for 15 min under N_2-atmosphere. The

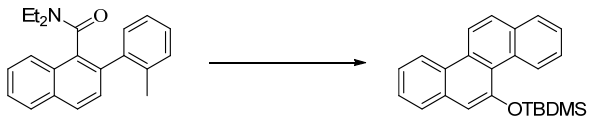
solution of boronaphtaleneamide (676 mg, 1.90 mmol) in DME (4 ml) was added, followed by 2M sodium carbonate-solution (6 ml), at room temperature. The mixture was heated at reflux for 18 hours, cooled, and extracted with diethyl ether (3 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate 2:1) to afford 485 mg (80%) of product **107** as a brown oil.

5.4.4 Synthesis of chrysene-5-ol (109)



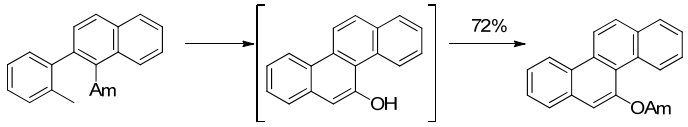
Lithium diisopropylamine (2.75 ml, 3.82 mmol, 1.39 M solution in THF) was added to a precooled solution of biphenyl **107** (0.485 g, 1.528 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, quenched with ammonium chloride (10 ml) and extracted with diethyl ether (3 x 10 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated. The crude product was separated by flash coloum chromatography (petroleum ether: ethyl acetate 3:1) to give 327 mg (88%) of chrysene-5-ol (**109**). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.05 (app. dd, J = 9.3, 1.8 Hz, 1H), 8.88 (d, J = 9.3 Hz, 1H), 8.81 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H), 8.07-8.04 (m, 1H), 7.83 (app. dd, J = 9.3, 1.8 Hz, 1H), 7.71-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.0 (**C**x2), 133.9 (**C**x2), 131.9 (**C**), 131.8 (**C**), 130.0 (**C**H), 129.3 (**C**H), 129.0 (**C**H), 127.7 (**C**H), 127.1 (**C**H), 126.9 (1) (**C**H), 126.9 (0) (**C**H), 124.8 (**C**H), 124.3 (**C**H), 122.3 (**C**H), 122.0 (**C**), 110.0 (**C**H)

5.4.5 Synthesis of *tert*-butyl(chrysen-5-yloxy)dimethylsilane (110)



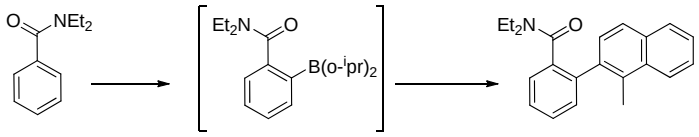
Lithium diisopropylamine (LDA) (4.65 ml, 6.46 mmol, 1.39 M solution in THF) was added to a precooled solution of biphenyl **107** (820 mg, 2.58 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, before *tert*-butyldimethyl silyl chloride (1M, 5.9 ml, 5.9 mmol) was added. The reaction mixture was stirred overnight (18 hours), quenched with ammonium chloride (20 ml) and extracted into diethyl ether (3 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated in vaccue. The crude mixture was separated by flash coloum chromatography (petroleum ether: ethyl acetate 9:1) to afforded 0.90 g (97%) of product **110** as a beige solid. Mp: 119.4-120.2 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.83 (dd, *J* = 3.9 and 6.3 Hz, 1H), 8.72-8.67 (m, 2H), 7.8-7.94 (m, 2H), 7.81 (dd, *J* = 3.0 and 6.3 Hz, 1H), 7.62-7.54 (m, 4H), 7.38 (s, 1H), 1.10 (s, 9H), 0.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.4 (**C**O), 132.8 (**C**x2), 132.6 (**C**x2), 130.9 (**C**), 130.4 (**C**), 129.0 (**C**H), 128.2 (**C**H), 128.0 (**C**H), 126.6 (4) (**C**H), 126.6 (2) (**C**H), 126.0 (**C**H), 125.6 (**C**H), 124.5 (**C**H), 123.1 (**C**H), 121.2 (**C**H), 114.5 (**C**H), 100.1 (**C**) 26.2 ($\mathbf{C}H_3$x3), 18.8 (Si**C**$(CH_3)_3$), -3.7 (Si($\mathbf{C}H_3)_2$); IR (KBr): 3053 (w), 2953 (m), 2857 (m), 1594 (m), 1517 (w), 1438 (m), 1330 (m), 1308 (m), 1250 (m), 1203 (m), 1130 (m), 1065 (m), 1005 (m), 879 (m), 826 (s), 761 (s); Mass spectrum *m/z* (relative intensity %) 359.2 $[M + 1]^+$ (100); HRMS (ESI) Calc. for $C_{24}H_{27}OSi$: 359.1826, Found 359.1822

5.4.6 Synthesis of Chrysen-5-yl diethylcarbamate (111)



To a solution of diisopropylamine (DIPA) (1.26 ml, 8.99 mmol) in THF (15 ml) was added *n*-BuLi (4.26 ml, 8.95 mmol) at -5 ºC. Biphenyl **107** (1.22 g, 3.85 mmol) in THF (8 ml) was added dropwise, and the reaction mixture stirred for 70 min at room temperature. Normal workup gave the 5-hydroxychrysene as a yellow solid in complete reaction according to TLC. 5-hydroxychrysene (3.85 mmol) was added to a suspension of NaH (0.258 g, 6.45 mmol) in THF (7 ml) at 0 ºC. Diethylcarbamoyl chloride (0.5 ml, 3.95 mmol) was added at room temperature, and the reaction mixture stirred at room temperature for 18 hours. Normal workup followed by flash chromatography (hexane:ethyl acetate 6:1) afforded 953 mg (72%) of product **111**. Mp (°C) 142.8-143.3 (ethyl acetate); ^{1}H NMR (400 MHz) δ 9.16-9.13 (m, 1H), 8.76 (d, *J* = 9.0 Hz, 2 H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.99 (d, *J* = 6.2 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.67-7.60 (m, 4H), 3.81 (q, *J* = 7.0 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 154.1 (**C**O), 147.6 (**C**), 133.0 (**C**), 132.0 (**C**), 131.0 (**C**), 129.6 (**C**), 128.9 (**C**), 128.7 (**C**H), 128.4 (**C**H), 127.8 (**C**H), 126.8 (**C**H), 126.6 (**C**H), 126.4 (**C**H), 126.2 (**C**H), 126.2 (**C**H), 123.5 (**C**), 123.3 (**C**H), 121.3 (**C**H), 120.5 (**C**H), 42.2 (N**C**H$_2$), 41.9 (N**C**H$_2$), 14.5 (NCH$_2$**C**H$_3$), 13.4 (NCH$_2$**C**H$_3$); IR (KBr) 2979 (w), 2932 (w), 1702 (s), 1522 (w), 1474 (w), 1422 (m), 1380 (w), 1272 (m), 1243 (m), 1221 (w), 1185 (w), 1164 (m), 1097 (w), 972 (w), 881 (w), 812 (w), 759 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.4.7 Synthesis of *N*,*N*-diethyl-2-(1-methylnaphthalen-2-yl)benzamide (113)

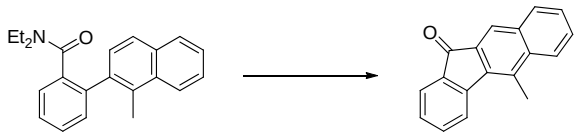


N,*N*'-diethylbenzamide (612 mg, 3.45 mmol) in THF (10 ml) was added to a solution of *s*-BuLi (3.7 ml, 5.18 mmol, 1.4 M solution in cyclohexane), TMEDA (0.77 ml, 5.16 mmol) and THF (10 ml) at -78 °C. After stirring for 1 hour triisopropyl borate (1.97 ml, 8.59 mmol) was added, and the mixture stirred at -78 °C for 1.5 hour and warmed to room temperature overnight (18 hours). The reaction mixture was quenched with ammonium chloride (15 ml), and extracted with diethyl ether (3x15ml). The organic layer was washed with water (2x45 ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a brown oil.

All solutions were degassed prior to use. A mixture of $PdCl_2$(dppf) (116 mg, 0.14 mmol, 5 mol%) and 2-bromo-1-methylnaphthalene (638 mg, 2.89 mmol) in DME (6 ml) was stirred at room temperature for 15 min under N_2-atmosphere. The solution 2-(*N*,*N*-Diethylcarboxamido)phenylboronic acid (3.45 mmol) in DME (4 ml) followed by 2M sodium carbonate-solution (6 ml) was added at room temperature and the mixture was heated at reflux for 18 hours. After allowing the mixture to cool down it was extracted with diethyl ether (3 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 2:1) afforded 862 mg (94%) of product **113** as a viscous, brown/red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (app s, 1H), 7.78 (app. s, 1H), 7.50-7.30 (m, 8H), 3.58-2.35 (5 peaks app. s, 4H), 2.71 (s, 3H), 1.28-1.11 (m, 3H), 0.60-0.5 (app. d, *J* = Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0 (**C**O), 137.2 (**C**), 134.2 (**C**), 131.5 (**C**), 129.0 (**C**H), 128.3 (**C**Hx2), 127.8 (**C**), 127.6 (**C**Hx2), 126.9 (**C**), 126.2 (**C**Hx2), 125.8 (**C**H), 125.5 (**C**Hx2), 124.6 (**C**); IR (KBr): 3064 (w), 2973 (m), 2933 (m), 2872 (w), 1630 (s), 1513 (w), 1458 (m), 1426 (m), 1381 (m), 1288 (m), 1221 (w), 1098 (m), 1078 (w), 871 (w), 836 (w), 784 (w), 764 (m),

480 (m), 471 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

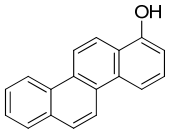
5.4.8 Directed remote metalation reaction of biphenyl 113



Lithium diisopropylamine (LDA) (4.65 ml, 6.46 mmol, 1.39 M in THF) was added to a precooled solution of biphenyl **113** (661 mg, 2.08 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, before *tert*-butyldimethylsilyl chloride (1M, 5.7 ml, 5.7 mmol) was added. The reaction mixture was stirred overnight (18 hours), quenched with ammonium chloride (20 ml) and extracted with diethyl ether (3 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude mixture was separated by flash chromatography (petroleum ether: ethyl acetate 9:1) to afforded 201 mg (40%) of 5-methyl-11H-benzo[b]fluoren-11-one **115** as an orange solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38-8.34 (m, 1H), 7.95-7.92 (m, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.60-7.40 (m, 5H), 7.22 (t, J = 7.8 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 194.7 (**C**O), 145.1 (**C**), 141.0 (**C**), 136.7 (**C**), 136.4 (**C**), 134.3 (**C**H), 131.2 (**C**), 128.8 (**C**), 128.2 (**C**H), 128.0 (**C**H), 127.1 (**C**H), 125.6 (**C**H), 126.4 (**C**H), 123.8 (**C**H), 122.9 (**C**H), 120.5 (**C**H), 19.9 (**C**H_3); IR (KBr): 3049 (w), 2981 (w), 1709 (s), 1621 (w), 1606 (w), 1583 (m), 1468 (w), 1424 (m), 1400 (m), 1272 (w), 1195 (w), 1114 (w), 1086 (w), 928 (w), 851 (w), 780 (m), 754 (m), 710 (m), 666 (w); Mass spectrum *m/z* (relative intensity %) 245.1 $[M+1]^+$ (100); HRMS (ESI) Calc. for $C_{18}H_{189}O$: 245.0961, Found 245.0959

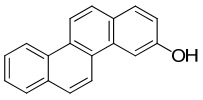
5.5 Formation of chrysenyl diethylcarbamates from methoxychrysenes

5.5.1 1-hydroxychrysene (8)



To a solution of 1-methoxychrysene (0.767 g, 2.969 mmol) in DCM (24 ml) was added BBr_3 (4.45 ml, 4.45 mmol) at 0 °C. After stirring for 13 hours, the reaction mixture was quenched with water (15 ml), and concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 x 40 ml), and the organic layer was dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:hexane 1:5) to afford 694 mg (96%) of 1-hydroxychrysene as a white solid: ^{1}H NMR (400 MHz) δ 9.19 (s, 1H), 8.91 (d, J = 8.4 Hz, 1H), 8.80 (app t, J = 8.4 Hz, 2H), 8.50 (d, J = 9.2 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.74 (t, J = 6.8 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H) in accordance with literature.[35c]

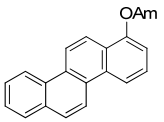
5.5.2 3-hydroxychrysene (103)



To a solution of 3-methoxychrysene (339 mg, 1.31 mmol) in DCM (12 ml) was added BBr_3 (1.95 ml, 1.95 mmol) at 0 °C. After stirring for 13 hours, the reaction mixture was quenched with water (7 ml) and concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 15ml) and

the organic layer was dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:hexane 1:5) to afford 316 mg (98%) of chrysene-3-ol as a white solid. ^{1}H NMR (400 MHz) δ 9.19 (s, 1H), 8.91 (d, *J* = 8.4 Hz, 1H), 8.80 (app t, *J* = 8.4 Hz, 2H), 8.50 (d, *J* = 9.2 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.74 (t, *J* = 6.8 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H) in accordance with literature.[35c]

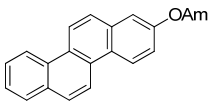
5.5.3 Chrysen-1-yl diethylcarbamate (116)



Chrysen-1-ol (668 mg, 2.73 mmol) in THF (8 ml) was added to a suspension of NaH (167 mg, 4.18 mmol) in THF (8 ml) at 0 °C. After stirring for 15 min the mixture was warmed to room temperature before *N*,*N*'-diethylcarbamoyl chloride (0.37 ml, 2.92 mmol) was added, and the reaction mixture stirred overnight (13 h), quenched with ammonium chloride (20 ml), and extracted into diethyl ether (3 x 25 ml). The organic layer was washed with brine (70 ml), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:hexane 1:5) to afford 886 mg (95%) of product **116** as a white shiny powder. Mp (°C) 172.2-172.8 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.74 (d, *J* = 7.8 Hz, 1H), 8.72 (d, *J* = 9.3 Hz, 1H), 8.65 (d, *J* = 9.3 Hz, 1H), 8.60 (d, *J* = 9.0 Hz, 1H), 8.10 (d, *J* = 9.3 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.71-7.59 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 1H), 3.65 (app. d, *J* = 6.9 Hz, 2H), 3.48 (app. d, *J*= 6.9 Hz, 2H), 1.41 (t, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz) δ 154.3 (**C**O), 148.0 (**C**), 132.3 (**C**), 132.1 (**C**), 130.5 (**C**), 128.6 (**C**H), 128.2 (**C**), 128.2 (**C**), 127.6 (**C**H), 126.8 (**C**H), 126.5 (**C**H), 126.3 (**C**H), 126.1 (**C**), 123.2 (**C**H), 121.7 (**C**H), 121.5 (**C**H), 120.5 (**C**H), 120.3 (**C**H), 118.9 (**C**H), 42.4 (N**C**H$_2$), 42.1 (N**C**H$_2$), 14.6 (NCH$_2$**C**H$_3$), 13.5 (NCH$_2$**C**H$_3$); IR (KBr) 2976 (w), 2936 (w), 1716 (s), 1596 (m), 1409 (m),

1273 (m), 1259 (m), 1234 (m), 1221 (m), 1175 (m), 1157 (s), 969 (m), 815 (m), 765 (s); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

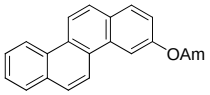
5.5.4 Chrysen-2-yl diethylcarbamate (117)



To a solution of 2-methoxychrysene (833 mg, 3.23 mmol) in DCM (30 ml) was added BBr_3 (4.84 ml, 4.84 mmol) at 0 °C. After stirring for 21 hours, the reaction mixture was quenched with water (14 ml), and concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 30 ml), and the organic layer dried over magnesium sulphate and concentrated *in vacuo*. Chrysen-2-ol (3.23 mmol) in THF (15 ml) was added to a suspension of NaH (193 mg, 4.83 mmol) in THF (10 ml) at 0 °C. After stirring for 15 min the mixture was warmed to room temperature before *N*,*N*'-diethylcarbamoyl chloride (0.42 ml, 3.31 mmol) was added, and the reaction mixture was stirred overnight (21 h), quenched with ammonium chloride (20 ml, and concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (3x 30 ml) and the organic layer was dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether : ethyl acetate 2:1, with 10% DCM) to afford 936 mg (85% - two step) of product **117** as a white shiny powder: Mp (°C) 189.3-189.7 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.74 (d, *J* = 8.7 Hz, 2H), 8.69 (d, *J* = 9.3 Hz, 1H), 8.65 (d, *J* = 9.0 Hz, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1 H), 7.94 (d, *J* = 9.3 Hz, 1 H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.61 (t, *J* = 6.9 Hz, 1H), 7.49 (dd, *J* = 2.4, 9.0 Hz, 1H), 3.53-3.43 (m, 4H), 1.34-1.25 (m, 6H); ^{13}C NMR (75 MHz) δ 154.3 (**C**O), 149.8 (**C**), 132.9 (**C**), 131.9 (**C**), 128.5 (**C**), 128.1 (**C**H), 128.0 (**C**), 127.8 (**C**), 127.5 (**C**), 126.9 (**C**H), 126.7 (**C**H), 126.3 (**C**H), 124.5 (**C**H), 123.0 (**C**H), 121.8 (**C**H), 232.7 (**C**H), 121.2 (**C**H), 119.4 (**C**H), 42.3 (N**C**H_2), 42.0 (N**C**H_2), 14.3 (NCH$_2$**C**H_3), 13.4 (NCH$_2$**C**H_3); IR (KBr) 2978 (w), 1703

(s), 1522 (w), 1474 (w), 1422 (m), 1364 (w), 1272 (m), 1260 (m), 1243 (m), 1221 (w), 1185 (w), 1164 (m), 1097 (w), 972 (w), 881 (w), 812 (w), 776 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.5.5 Chrysen-3-yl diethylcarbamate (118)



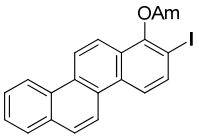
Chrysen-3-ol (369 mg, 1.51 mmol) in THF (7 ml) was added to a suspension of NaH (94 mg, 2.35 mmol) in THF (7 ml) at 0 °C. After stirring for 15 min the mixture was warmed to room temperature before *N*,*N*'-diethylcarbamoyl chloride (0.20 ml, 1.58 mmol) was added. The reaction mixture stirred overnight (14 h), quenched with ammonium chloride (20 ml) and extracted into diethyl ether (3 x 30 ml). The organic layer was washed with brine (60 ml), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:hexane 1:5, with 10% DCM) to afford 400 mg (77%) of product **118** as a white shiny powder: Mp (°C) 121.8-122.3 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.74 (d, *J* = 7.4 Hz, 1H), 8.64 (d, *J* = 9.3 Hz, 1H), 8.59 (d, *J* = 9.3 Hz, 1H), 8.47 (s, 1H), 7.95 (d, *J* = 9 Hz, 4H), 7.70-7.58 (m, 2H), 3.54-3.44 (m, 4H), 1.35-1.23 (m, 6H); ^{13}C NMR (75 MHz) δ 154.4 (**C**O), 150.2 (**C**), 132.2 (**C**), 131.4 (**C**), 130.4 (**C**), 129.7 (**C**), 129.54 (**C**H), 128.5 (**C**H), 128.4 (**C**), 127.8 (**C**), 127.1 (**C**H), 126.8 (**C**H), 126.6 (**C**H), 126.4 (**C**H), 123.2 (**C**H), 121.6 (**C**H), 121.4 (**C**H), 120.6 (**C**H), 115.0 (**C**H), 42.3 (N**C**H_2), 42.0 (N**C**H_2), 14.3 (NCH$_2$**C**H_3), 13.4 (NCH$_2$**C**H_3); IR (KBr) 2975 (m), 1715 (s), 16.18 (w), 1596 (w), 1470 (m), 1456 (m), 1418 (s), 1376 (m), 1313 (w), 1272 (m), 1248 (m), 1225 (w), 1192 (s), 1168 (m), 1150 (s), 1093 (m), 966 (m), 926 (w), 882 (m), 847 (m), 818 (m), 749 (m), 679 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.6 Directed *ortho* metalation of chrysenyl diethylcarbamates

5.6.1 General procedure for the DoM

To a solution of chrysenyl diethylcarbamate (1 mmol) and TMEDA (1.1 mmol) in THF (3 ml) was added *sec*-butyl lithium (1.1 mmol, 0.72-1.2 M solution in cyclohexane) at -78 ºC. After stirring for 30 min electrophile (1.5-2 mmol) was added, and the reaction mixture was warmed to room temperature overnight (18 hours). Normal workup followed by flash chromatography afforded the desired product.

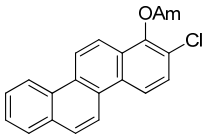
5.6.2 2-iodochrysen-1-yl diethylcarbamate (120)



According to general procedure chrysen-1-yl diethylcarbamate (102 mg, 0.30 mmol) in THF (2.2 ml) was metalated with *s*-BuLi (0.26 ml, 0.33 mmol), TMEDA (0.05 ml, 0.33 mmol) and Iodine in THF (1M, 0.6 ml, 0.6 mmol) at -78 °C, and warmed to room temperature over 5.5 hours. Normal workup, followed by flash coloum chromatography (hexane:ethyl acetate 6:1) afforded 131 mg (94 %) of product **120** as a beige solid. Mp (°C) 221.1-221.6 (ethyl acetate); ^{1}H NMR (400 MHz) δ 8.77 (d, *J* = 9.1 Hz, 2H), 8.65 (d, *J* = 9.1 Hz, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 2H), 8.02-8.00 (m, 2H), 7.74 (t, *J* = 7.0 Hz, 1H), 7.67 (t, *J* = 7.0 Hz, 1H), 3.82-3.50 (br m, 4H), 1.53 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 152.8 (**C**O), 148.9 (**C**), 135.4 (**C**H), 132.3 (**C**), 131.8 (**C**), 130.4 (**C**x2), 128.6 (**C**H), 128.3 (**C**), 128.0 (**C**H), 127.4 (**C**), 126.9 (**C**H), 126.7 (**C**H), 123.2 (**C**H), 122.7 (**C**H), 122.4 (**C**H), 121.1 (**C**H), 120.5 (**C**H), 89.3 (**C**), 42.6 (N**C**H_2), 42.3 (N**C**H_2), 14.7 (NCH_2**C**H_3), 13.5 (NCH_2**C**H_3); IR (KBr) 2972 (w), 1723 (s), 1587 (w), 1469 (w), 1419 (m), 1392 (m), 1367 (m), 1270 (s), 1206 (m), 1179 (w), 1148 (s), 1119 (m), 1097 (w), 1062 (w), 1037 (w), 965

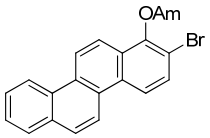
(m), 915 (w), 815 (w), 798 (m), 774 (m), 748 (m), 684 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.6.3 2-chlorochrysen-1-yl diethylcarbamate (122)



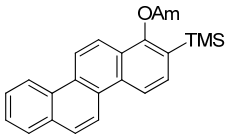
According to general procedure chrysen-1-yl diethylcarbamate (100 mg, 0.29 mmol) in THF (2.2 ml) was metalated with *s*-BuLi (0.25 ml, 0.31 mmol), TMEDA (0.05 ml, 0.33 mmol) and Cl_3CCCl_3 (139 mg, 0.59 mmol) in THF (1 ml) at -78 °C, and warmed to room temperature over 6 hours. Normal workup, followed by flash coloum chromatography (hexane : ethyl acetate 6:1) afforded 108 mg (96%) of product **122** as a white solid. Mp (°C) 218.9-219.4 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.73 (d, *J* = 8.1 Hz, 1H), 8.70 (d, *J* = 6.9 Hz, 1H), 8.55 (d, *J* = 10.2 Hz, 1H), 8.51 (d, *J* = 10.8 Hz, 1H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.71-7.60 (m, 3H), 3.68 (q, *J* = 7.5 Hz, 2H), 3.49 (q, *J* = 7.5 Hz, 2H), 1.46 (t, *J* = 6.9 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 153.0 (**C**O), 143.9 (**C**), 132.2 (**C**), 130.3 (1) (**C**), 130.3 (0) (**C**), 128.5 (**C**H), 128.1 (**C**), 127.9 (4) (**C**H), 127.9 (0) (**C**), 127.7 (**C**), 127.3 (**C**H), 126.9 (**C**H), 126.6 (**C**H), 124.9 (**C**), 123.1 (**C**H), 122.8 (**C**H), 121.7 (**C**H), 121.0 (**C**H), 120.0 (**C**H), 42.6 (N**C**H_2), 42.3 (N**C**H_2), 14.5 (NCH$_2$**C**H_3), 13.4 (NCH$_2$**C**H_3); IR (KBr) 2976 (w), 2933 (w), 1724 (s), 1594 (w), 1471 (w), 1419 (m), 1397 (m), 1382 (m), 1268 (m), 1232 (w), 1210 (m), 1180 (w), 1150 (m), 1063 (w), 966 (m), 923 (w), 867 (w), 817 (w), 798 (m), 775 (m), 751 (m), 702 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.6.4 2-bromochrysen-1-yl diethylcarbamate (121)



According to general procedure chrysen-1-yl diethylcarbamate (141 mg, 0.41 mmol) in THF (2.8 ml) was metalated with *s*-BuLi (0.39 ml, 0.46 mmol), TMEDA (0.07 ml, 0.47 mmol) and Br_2 (19.25 M, 0.03 ml, 0.58 mmol) at -78 °C, and warmed to room temperature over 16 hours. Normal workup, followed by flash coloum chromatography (hexane : ethyl acetate 5:1) afforded 149 mg (86%) of product **121** as a beige solid. Mp (°C) 211.0-211.6 (ethyl acetate ^{1}H NMR (300 MHz) δ 8.71 (d, *J* = 9.9 Hz, 1H), 8.70 (d, *J* = 7.8 Hz, 1H), 8.55 (d, *J* = 8.7 Hz, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.71-7.60 (m, 2H), 3.69 (app. d, *J* = 6.9 Hz, 2H), 3.49 (app. d, *J* = 5.7 Hz, 2H), 1.47 (t, *J* = 6.9 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz) δ 152.8 (**C**O), 145.4 (**C**), 132.2 (**C**), 130.9 (**C**), 130.3 (**C**), 129.9 (**C**H), 128.5 (**C**H), 128.2 (**C**), 127.9 (**C**H), 127.9 (**C**), 127.8 (**C**), 126.9 (**C**H), 126.6 (**C**H), 123.1 (**C**H), 122.8 (**C**H), 122.0 (**C**H), 121.0 (**C**H), 120.2 (**C**H), 114.6 (**C**), 42.6 (N**C**H_2), 42.3 (N**C**H_2), 14.5 (NCH$_2$**C**H$_3$), 13.4 (NCH$_2$**C**H$_3$);); IR (KBr) 2975 (w), 1725 (s), 1591 (w), 1471 (w), 1417 (m), 1394 (m), 1267 (m), 1209 (m), 1149 (s), 1125 (m), 965 (m), 916 (w), 866 (w), 817 (w), 798 (m), 775 (m), 749 (m), 695 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

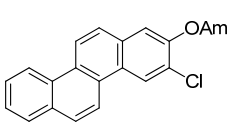
5.6.5 2-(trimethylsilyl)chrysen-1-yl diethylcarbamate (119)

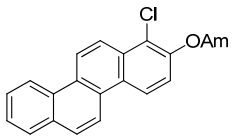


According to general procedure chrysen-1-yl diethylcarbamate (187 mg, 0.54 mmol) in THF (3 ml) was metalated with *s*-BuLi (0.51 ml, 0.60

mmol), TMEDA (0.09 ml, 0.60 mmol) and TMSCl (0.10 ml, 0.79 mmol) at -78 °C for 1.5 hours. Normal workup, followed by flash coloum chromatography (hexane : ethyl acetate 6:1) afforded 209 mg (93%) of product **119** as a beige solid. Mp (°C) 158.2-159.1 (ethyl acetate); ^{1}H NMR (400 MHz) δ 8.77 (d, *J* = app. 6.4 Hz, 1H), 8.75 (d, *J* = 9.1 Hz, 1H), 8.70 (d, *J* = 9.1 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.71 (dt, *J* = 2.0, 7.0 Hz, 1H), 7.64 (t, *J* = 7.0 Hz, 1H), 3.86-3.40 (m, 4H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 154.4 (**C**O), 153.2 (**C**), 133.0 (**C**), 132.3 (**C**), 131.42 (**C**H), 130.4 (**C**), 129.0 (**C**), 128.5 (**C**H), 128.3 (**C**), 128.1 (**C**), 127.5 (**C**H), 126.7 (**C**H), 126.5 (**C**H), 126.0 (**C**), 123.2 (**C**H), 121.8 (**C**H), 121.5 (**C**H), 120.4 (**C**H), 120.4 (**C**H), 42.0 (N**C**H$_2$), 41.8 (N**C**H$_2$), 14.5 (NCH$_2$**C**H$_3$), 13.3 (NCH$_2$**C**H$_3$), -0.7 (Si(**C**H)$_3$); IR (KBr) 2971 (w), 1709 (s), 1615 (w), 1584 (w), 1474 (w), 1418 (m), 1390 (w), 1349 (w), 1270 (s), 1247 (w), 1206 (m), 1177 (m), 1156 (s), 1097 (w), 1065 (w), 968 (w), 871 (w), 838 (m), 806 (m), 750 (m), 642 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.6.6 1-chlorochrysen-2-yl diethylcarbamate (127B) and 3-chlorochrysen-2-yl diethylcarbamate (127A)

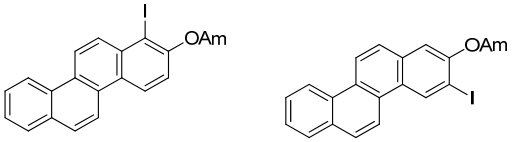




According to general procedure chrysen-2-yl diethylcarbamate (130 mg, 0.38 mmol) in THF (6 ml) was metalated with *s*-BuLi (0.44 ml, 0.0.44 mmol), TMEDA (0.07 ml, 0.46 mmol) and Cl_3CCCl_3 (1 M, 0.57 ml, 0.57 mmol) at -78 °C, and warmed to room temperature over 16 hours. Normal workup, followed by flash coloum chromatography (petroleum ether : ethyl acetate 2:1) afforded 138 mg (96%) of product **127A** and **127B** as a white solid. Mp (°C) 184.6-185.5 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.77-8.62

(m, 3 + 2H), 8.58 (d, *J* = 9.2 Hz, 1H - minor), 8.49 (d, *J* = 9.1 Hz, 1H - major), 8.41 (d, *J* = 9.4 Hz, 1H - minor), 7.96 (d, *J* = 7.5 Hz, 2 + 2H), 7.86 (d, *J* = 9.1 Hz, 1H - major), 7.81 (s, 1H - minor), 7.72-7.59 (m, 2 + 1H), 7.56 (d, *J* = 9.1 Hz, 1H - minor), 3.57 (q, *J* = 6.7 Hz, 2 + 2H), 3.46 (q, *J* = 6.8 Hz, 2 + 2H), 1.36 (t, *J* = 6.9 Hz, 3 + 3H), 1.26 (t, *J* = 7.3 Hz, 3 + 3H); **127B (major)** ^{13}C NMR (75 MHz) δ 153.3 (**C**O), 145.7 (**C**), 132.1 (**C**x2), 131.4 (**C**), 130.3 (**C**), 128.8 (**C**), 128.5 (**C**H), 128.2 (**C**), 127.8 (**C**H), 127.1 (**C**), 126.8 (**C**H), 126.6 (**C**H), 126.3 (**C**H), 124.7 (**C**H), 123.0 (**C**H), 122.1 (**C**H), 122.0 (**C**H), 120.9 (**C**H), 42.5 (N**C**H_2), 42.2 (N**C**H_2), 14.2 (NCH_2**C**H_3), 13.4 (NCH_2**C**H_3); **127A(minor)** ^{13}**C** NMR (75 MHz) δ 153.3 (**C**O), 145.9 (**C**), 132.1 (**C**x2), 131.4 (**C**), 130.4 (**C**), 130.2 (**C**), 129.2 (**C**), 128.5 (**C**H), 127.9 (4) (**C**H), 127.9 (0) (**C**), 126.9 (**C**H), 126.6 (**C**H), 123.1 (**C**H), 122.9 (**C**H), 122.6 (**C**H), 122.5 (**C**H), 121.1 (**C**H), 42.5 (N**C**H_2), 42.2 (N**C**H_2), 14.2 (NCH_2**C**H_3), 13.4 (NCH_2**C**H_3); IR (KBr) 2978 (w), 2934 (w), 1731 (s), 1472 (w), 1419 (m), 1381 (w), 1274 (w), 1250 (s), 1220 (m), 1194 (w), 1170 (w), 1151 (m), 1100 (w), 1050 (m), 998 (w), 892 (w), 850 (w), 802 (w), 775 (w), 751 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

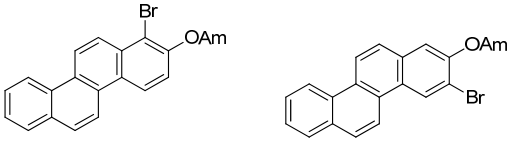
5.6.7 1-iodochrysen-2-yl diethylcarbamate (125B) and 3-iodochrysen-2-yl diethylcarbamate (125A)



According to general procedure chrysen-2-yl diethylcarbamate (139 mg, 0.41 mmol) in THF (10 ml) was metalated with *s*-BuLi (0.43 ml, 0.43 mmol), TMEDA (0.07 ml, 0.46 mmol) and Iodine (0.6 ml, 0.6 mmol, 1M in THF) at -78 °C, and warmed to room temperature over 5.5 hours. Normal workup, followed by flash coloum chromatography (hexane : ethyl acetate 6:1) afforded 130 mg (68 %) of product **125A** and **125B** as a beige solid. Mp (°C) 171.8-172.8 (ethyl acetate); ^{1}H NMR (300 MHz) δ 9.21 (s, 1H – minor isomer), 8.75 (d, *J* = 9.3 Hz, 2H), 8.71-8.62 (m, 1+1H), 8.56 (d, *J* = 9.3 Hz, 1H – minor isomer), 8.37 (d, *J* = 9.3 Hz, 1H – major isomer), 7.99 (d, *J* = 9.3

Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 1H – minor isomer), 7.80 (s, 1H – minor isomer), 7.75-7.63 (m, 2H), 7.52 (d, *J* = 9.3 Hz, 1H – major isomer), 3.66-3.61 (m, 2H), 3.47 (q, *J* = 6.3 Hz, 2H), 1.44-1.37 (m, 3H), 1.28 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz) δ 153.2 (**C**O), 151.0 (**C**), 149.1 (**C**), 134.7 (**C**H), 134.2 (**C**), 132.7 (**C**), 132.1 (**C**), 130.9 (**C**H), 130.3 (2) (**C**), 130.3 (0) (**C**), 129.7 (**C**), 129.0 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.0 (**C**Hx2), 127.9 (**C**H), 126.9 (2) (**C**H), 129.9 (0) (**C**H), 126.8 (**C**), 126.7 (**C**H), 126.5 (**C**H), 124.8 (**C**H), 123.5 (**C**H), 123.1 (**C**H), 123.0 (**C**H), 122.5 (**C**H), 122.1 (**C**H), 121.1 (**C**H), 120.9 (**C**H), 120.8 (**C**H), 96.0 (**C**I), 90.7 (**C**I), 42.4 (N**C**H$_2$), 42.2 (N**C**H$_2$), 14.5 (NCH$_2$**C**H$_3$), 138 (NCH$_2$**C**H$_3$); IR (KBr) 2978 (w), 2933 (w), 1713 (s), 1591 (w), 1473 (m), 1416 (s), 1380 (w), 1313 (w), 1272 (m), 1245 (s), 1217 (m), 1187 (m), 1153 (s), 1097 (w), 1048 (w), 988 (m), 925 (w), 886 (w), 800 (m), 774 (w), 749 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

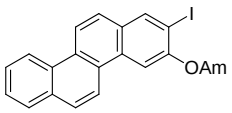
5.6.8 1-bromoochrysen-2-yl diethylcarbamate (126B) and 3-bromochrysen-2-yl diethylcarbamate (126A)



According to general procedure chrysen-2-yl diethylcarbamate (89 mg, 0.26 mmol) in THF (6 ml) was metalated with *s*-BuLi (0.38 ml, 0.27 mmol), TMEDA (0.04 ml, 0.27 mmol) and Br_2 (0.04 ml, 0.77 mmol) at -78 °C, and warmed to room temperature over 5 hours. Normal workup, followed by flash coloum chromatography (hexane : ethyl acetate 4:1) afforded 73 mg (67%) of product **126A** and **126B** as a beige solid. Mp (°C) 198.8-199.8 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.94 (s, 1H – minor isomer), 8.77-8.65 (m, 3 + 2H), 8.59 (d, *J* = 9.2 Hz, 1H – minor isomer), 8.51 (d, *J* = 9.2 Hz, 1H – major isomer), 8.42 (d, *J* = 9.4 Hz, 1H – minor isomer), 7.97 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 9.1 Hz, 1H – major isomer), 7.81 (s, 1H – minor isomer), 7.74-7.59 (m, 2H), 7.55 (d, *J* = 9.1 Hz, 1H – minor isomer), 3.64-3.55 (m, 2H), 3.46 (q, *J* = 6.9 Hz, 2H), 1.41-1.37 (m, 3H), 1.29-1.24 (m, 3H); ^{13}C

NMR (75 MHz) δ 153.2 (**C**O), 147.5 (**C**), 132.1 (**C**x2), 131.9 (**C**), 131.6 (**C**), 130.3 (**C**), 130.2 (**C**), 129.3 (**C**), 129.2 (**C**), 128.5 (4) (**C**H), 128.5 (0) (**C**H), 128.0 (3) (**C**H), 128.0 (0) (**C**H), 127.9 (**C**H), 127.8 (**C**H), 127.5 (**C**), 126.9 (**C**H), 126.8 (**C**H), 126.7 (**C**H), 126.6 (**C**H), 126.4 (**C**H), 126.2 (**C**), 125.6 (**C**H), 124.4 (**C**), 123.5 (**C**H), 123.1 (3) (**C**H), 123.1 (0) (**C**H), 122.6 (**C**H), 122.3 (**C**H), 121.8 (**C**H), 121.1 (**C**H), 120.9 (**C**H), 119.3 (**C**), 116.3 (**C**), 42.4 (N**C**H_2), 42.1 (N**C**H_2), 14.3 (NCH_2**C**H_3), 13.4 (NCH_2**C**H_3); IR (KBr) 2978 (w), 2933 (w), 1726 (s), 1472 (w), 1417 (m), 1381 (w), 1273 (m), 1249 (s), 1219 (m), 1186 (w), 1151 (m), 1094 (w), 1043 (w), 993 (w), 926 (w), 866 (w), 824 (w9, 801 (m), 775 (w), 751 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

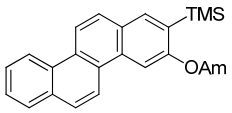
5.6.9 2-iodochrysen-2-yl diethylcarbamate (129)



According to general procedure chrysen-3-yl diethylcarbamate (117 mg, 0.34 mmol) in THF (5 ml) was metalated with *s*-BuLi (0.36 ml, 0.40 mmol), TMEDA (0.06 ml, 0.40 mmol) and Iodine in THF (0.5 M, 1.0 ml, 0.5 mmol) at -78 °C, and warmed to room temperature over 18 hours. Normal workup, followed by flash coloum chromatography (petroleum ether : ethyl acetate 2:1) afforded 145 mg (91 %) of product **129** as a beige solid. Mp (°C) 200.8-201.3 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.71 (d, *J* = 8.2 Hz, 1H), 8.63 (d, *J* = 9.1 Hz, 1H), 8.54 (d, *J* = 10.3 Hz, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.71-7.60 (m, 2H), 3.64 (q, *J* = 7.1 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz) δ 153.4 (**C**O), 149.5 (**C**), 139.1 (**C**H), 132.4 (**C**), 131.4 (**C**), 131.3 (**C**), 130.3 (**C**), 128.6 (**C**H), 128.5 (**C**), 127.7 (**C**), 127.5 (**C**H), 126.8 (**C**H), 126.7 (**C**H), 125.6 (**C**H), 123.2 (**C**H), 121.7 (**C**H), 121.1 (**C**H), 116.8 (**C**H), 90.2 (**C**I), 42.4 (N**C**H_2), 42.2 (N**C**H_2), 14.5 (NCH_2**C**H_3), 13.4 (NCH_2**C**H_3); IR (KBr) 2973 (w), 1723 (s), 1469 (w), 1417 (m), 1380

(w), 1318 (w), 1275 (m), 1248 (w), 1195 (m), 1171 (w), 1151 (m), 1087 (w), 1040 (w), 969 (w), 894 (w), 810 (w), 746 (m), 691 (w); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

5.6.10 2-(trimethylsilyl)chrysen-3-yl diethylcarbamate (128)



According to general procedure chrysen-3-yl diethylcarbamate (134 mg, 0.39 mmol) in THF (2.5 ml) was metalated with *s*-BuLi (0.37 ml, 0.43 mmol), TMEDA (0.07 ml, 0.46 mmol) and TMSCl (0.07 ml, 0.55 mmol) at -78 °C for 1.5 hours. Normal workup, followed by flash coloum chromatography (petroleum ether : ethyl acetate 4:1) afforded 144 mg (89%) of product **128** as a beige solid. Mp (°C) 106.2-107.0 (ethyl acetate); ^{1}H NMR (300 MHz) δ 8.76 (d, *J* = 8.2 Hz, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.62 (d, *J* = 8.8 Hz, 1H), 8.37 (s, 1H), 8.08 (s, 1H), 7.99-7.93 (m, 3H), 7.68 (t, *J* = 6.3 Hz, 1H), 7.61 (t, *J* = 6.8 Hz, 1H), 3.59 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.41 (s, 9H); ^{13}C NMR (75 MHz) δ 154.6 (**C**O), 154.5 (**C**), 136.3 (**C**H), 132.3 (3) (**C**), 132.3 (0) (**C**), 131.9 (**C**), 130.4 (**C**), 129.4 (**C**), 128.5 (4), (**C**), 128.5 (0) (**C**H), 127.7 (**C**), 127.0 (2) (**C**H), 127.0 (0) (**C**H), 126.5 (**C**H), 126.4 (**C**H), 123.2 (**C**H), 121.6 (**C**H), 120.5 (**C**H), 115.5 (**C**H), 42.0 (N**C**H_2), 41.6 (N**C**H_2), 14.3 (NCH$_2$**C**H_3), 13.3 (NCH$_2$**C**H_3), -0.8 (Si**C**H_3); IR (KBr) 2961 (w), 1699 (s), 1467 (m), 1420 (m), 1310 (w), 1271 (m), 1248 (m), 1185 (m), 1157 (s), 1100 (m), 1066 (m), 985 (m), 956 (w), 898 (w), 838 (m), 811 (m), 759 (m); Mass spectrum *m/z* (relative intensity %) sample sent for analysis.

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