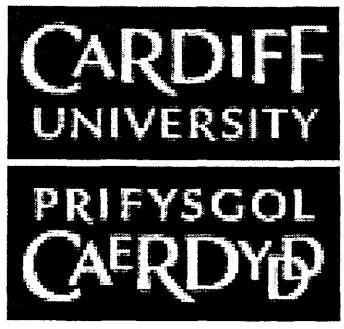
Novel Selenium-Mediated Cyclisations



Sohail Anjum Shahzad

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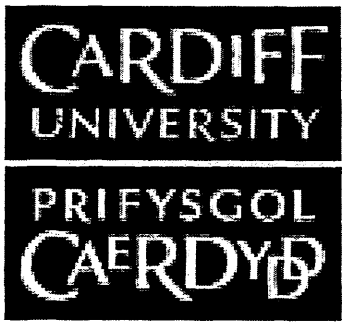

A thesis submitted for the degree of Doctor of Philosophy

at Cardiff University

By

Sohail Anjum Shahzad

July 2010

Declaration

This work has no previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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Date.....October 19, 2010.....

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This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD

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Statement 2

This thesis is the result of my own independent investigations, except where stated otherwise. Other sources are acknowledged by explicit references.

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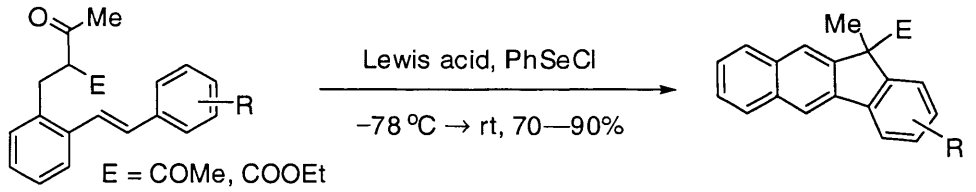
Sohail Anjum Shahzad

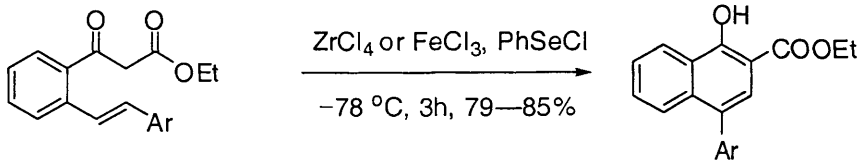
Abstract

The present work describes the selenium-mediated cyclofunctionalisations of alkenes. Three different areas are reported herein.

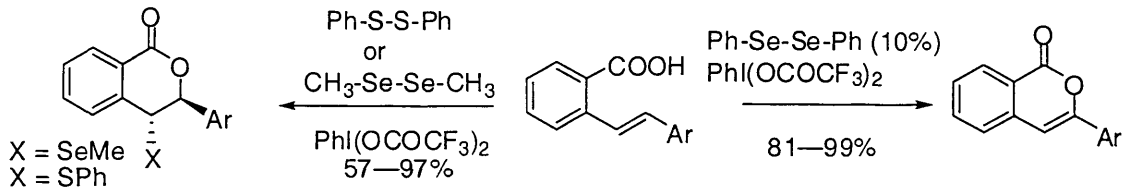
Chapter 2 reports syntheses of several substrates for carbocyclisation reactions and use of selenium and Lewis acids resulting in various dihydronaphthalenes. These dihydronaphthalenes then acted as substrates for second ring forming reactions. This novel tandem double cyclisation comprises a carboannulation, a Friedel-Crafts reaction and a rearrangement. This cascade sequence has been proven to be a useful tool in the selective synthesis of dihydronaphthalenes and benzofluorenes from easily accessible stilbenes and provides fast access to polycyclic ring systems in a single step.



Chapter 3 describes electrophilic selenium-mediated reactions which have been used to cyclise a range of *β*-keto esters to corresponding biaryl compounds under very mild conditions. The products were formed by a carboannulation via addition/elimination sequence and a subsequent rearrangement of range of alkyl and aryl groups. The key starting materials stilbene *β*-keto esters were readily prepared by Heck coupling and hydrolysis followed by condensation with potassium ethyl malonate.



Chapter 4 describes work on catalytic selenium reagents with stoichiometric amount of hypervalent iodine to convert a range of stilbene carboxylic acids into their corresponding isocoumarins. The work also describes the selective synthesis of dihydroisocoumarins using diphenyl disulfide and dimethyl diselenide.



List of Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	*azo-bis*-isobutyronitrile
Ar	aryl group
δ	chemical shift
°C	degree (s) Celsius
Δ	reflux
BOC	*t*-butoxycarbonyl
br	broad
Bu	butyl
calc.	calculated
$CDCl_3$	deuterated chloroform
cod	1,5-cyclooctadienyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet
dba	dibenzylidene acetone
DCE	1,2-dichloroethane
DHP	dihydropyran
DMAD	dimethylacetylene dicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	deuterated dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
Dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI^+	electron impact (mass spectrometry)
ESI	electrospray ionisation (mass spectrometry)
equiv.	equivalent
Et_3N	triethylamine

Et	ethyl
h	hours
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mp	melting point
Ms	methanesulfonyl
n-	normal (linear alkyl group)
NMR	nuclear magnetic resonance (spectroscopy)
Nu	nucleophile
o-	*ortho*
p-	*para*
Ph	phenyl
Pr	propyl
p-Tol	4-methylphenyl
N-PSP	*N*-(phenylseleno)phthalimide
q	quartet
qn	quintet
R	general (alkyl) group
rt	room temperature
sec	secondary
tert- or *t*-	tertiary
THF	tetrahydrofuran
THP	tetrahydropyran(yl)
TLC	thin layer chromatography
TMU	tetramethylurea
Z or EWG	electron withdrawing group

List of Contents

Chapter 1

1 General Introduction on Selenium

1.1 History of Selenium

Selenium was discovered by Jöns Jacob Berzelius, a Swedish chemist, in the year 1817. He believed the element that was contaminating the sulphuric acid being produced at a factory in Sweden was tellurium. He realized he had found a new element. Berzelius suggested naming the element selenium; from the Greek word *selene,* for "moon".

1.2 Properties of Selenium

Selenium is a chemical element in group 16 of the periodic table, represented by the chemical symbol Se which rarely occurs in its elemental state in nature. Selenium is a naturally occurring mineral element. It is distributed widely in nature in most rocks and soils. When pure, it exists as metallic grey to black hexagonal crystals. Among several isolated allotropic forms, three are generally known. Crystalline monoclinic selenium is deep red and crystalline hexagonal selenium, the most stable form, is grey. It has a minimum of 29 isotopes, out of which six are stable isotopes: ^{74}Se (0.89%), ^{76}Se (9.37%), ^{77}Se (7.63%), ^{78}Se (23.77%), ^{80}Se (49.61%), and ^{82}Se (8.73%).

1.3 Sources of Selenium

Selenium is most commonly obtained from selenide in many sulfide ores, such as those of copper, silver or lead. It is obtained as a by-product of processing these ores from the anode mud of copper refineries and the mud from lead chambers of sulphuric acid plants. These muds can be processed by different ways to obtain the rare free selenium.[1]

1.4 Uses of Selenium

The element selenium has many industrial uses. Most notable is the use of selenium for photovoltaic and photoconductive purposes. This makes it valuable for use in photoelectric cells and exposure meters for photographic purposes. It also used in the

glass industry where it is used to remove colour from glass and also impart a red colour in the form of CdSe to glass and enamels.[1]

1.5 Health Effects

Selenium has some rather interesting nutritional roles. It is essential in very small amounts for the health in both plants and animals. Animals that do not have enough selenium in their diets may develop weak muscles. But large doses of selenium are dangerous. Exposure to selenium mainly takes place through food, as selenium is naturally present in grains, cereals and meat. Adults need to absorb 70 μg of selenium daily in order to maintain good health and is proven to be an essential trace element. Elemental selenium is known to be practically non-toxic. However, hydrogen selenide and other organoselenium reagents are extremely toxic. Over-exposure to selenium may cause fluid on the lungs, garlic breath, bronchitis, nausea, headaches, sore throat and many other health problems including death.[1]

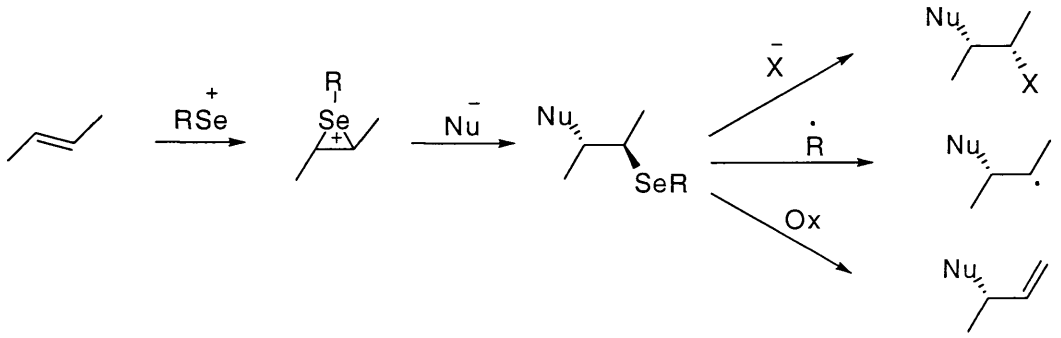
1.6 Development of Organoselenium Chemistry

In the early 1970s only selenium dioxide and elemental selenium were in (general) use in laboratories. The *syn*-selenoxide elimination reaction, which was discovered in the 1970s, was found to be a powerful and effective olefin forming method.[2] The required selenoxides were readily available from the oxidation of the corresponding selenides. The chemistry of selenium compounds bears a resemblance to that of sulphur and tellurium analogues. Selenium-based methods in organic chemistry have developed rapidly over the past years and organoselenium chemistry is now a very useful tool in the hands of synthetic chemists.[3-4] In addition, certain features of chiral selenium-containing compounds make these reagents particularly valuable for efficient stereoselective reactions.[5] The ability of selenium to functionalise non-activated alkenes, alkynes, activated C—H bond and for catalysis provides unique opportunities to achieve synthetic targets.[6-8]

Certain features make selenium compounds particularly valuable, for example, the C—Se bond is weaker (234 kJ/mol) than C—S bond (272 kJ/mol) and the Se=O bond in the selenoxide functionality is more strongly polarised than the sulfoxide counterpart. Therefore, the selenoxide elimination can occur rapidly below room temperature whereas the sulphur analogues require heating to over 100 °C. The poor π overlap in

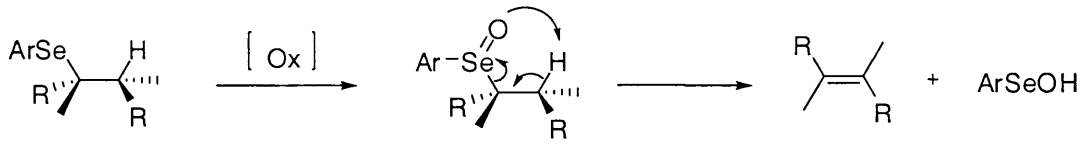
C=Se bonds makes them more reactive than C=S bonds, for example, in cycloadditions. It was found that the seleninate ($RSeO_2^-$) group functions as an excellent leaving group whereas sulfinates are relatively poor leaving groups. Selenium compounds such as selenium dioxide are useful oxidants for a variety of functional groups. These compounds can also be used catalytically in several oxidation reactions.[7]

Selenium halides are often used as electrophilic selenium reagents. They are easily prepared from the corresponding diselenides by addition of molecular bromine or thionyl chloride. Addition of selenium electrophiles to double bonds are most frequently used as part of synthetic sequences as shown in Scheme 1. Applications of selenium functional group that is most attractive in organic synthesis is the ability to replace a selenium moiety with an amazing array of different functional groups. Selenides can be attacked by nucleophiles or converted into radicals by homolytic cleavage of the carbon-selenium bond which then undergo further radical reactions as shown in Scheme 1.[8a-c]



Scheme 1: Reactions of organoselenium compounds.

Oxidation to the selenoxide and subsequent β-elimination allows the stereospecific formation of double bonds as shown in Scheme 2.[8b-c]



Scheme 2: Selenoxide *syn*-elimination reaction

Synthesis of enantiopure organoselenium reagents and their application in asymmetric synthesis are of current interest in many research groups. Wirth *et al.* have developed a range of chiral selenium reagents, which are accessible in only a few steps[9] where previously long routes were known. It has been found that a heteroatom-containing functional group in the *ortho*-position is essential for the stereoselectivity as intramolecular coordination of the heteroatom lone pair to the positively charged selenium results in a fixed conformation as shown in Figure 1. This then draws the chiral centre closer to the reaction centre making the transfer of chirality is more efficient.

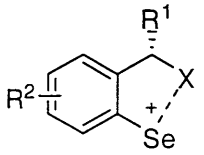
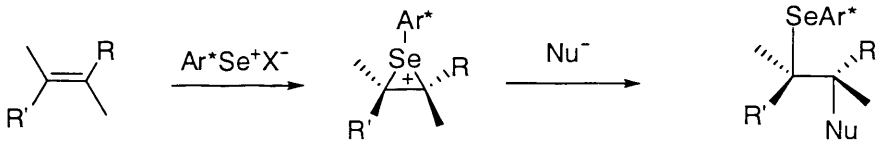


Figure 1: Chelation of selenium (Se) cation by γ-heteroatoms

Wirth *et al.* have developed another area of organoselenium chemistry the functionalisation of alkenes using chiral and achiral selenium electrophiles. The selenenylation reaction is initiated by the selenium electrophiles to form the seleniranium ion. The nucleophile then attacks the substrate from the backside in an S_N2 reaction, leading to the *anti* addition product. The attack of the nucleophile occurs on the carbon atom that has the more stable positive charge, usually the most substituted carbon atom (Scheme 3).

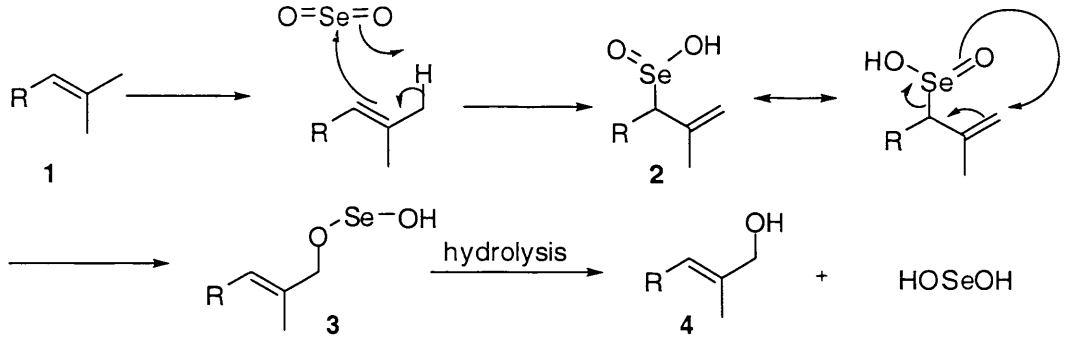


Scheme 3: Electrophilic selenenylation of alkenes

1.7 Allylic Oxidation Using Selenium Dioxide

Selenium dioxide-mediated oxidation[8d] is an important organic reaction for the oxidation of allylic positions of alkenes. Catalytic amounts of selenium dioxide in the presence of a stoichiometric oxidant could be used to enhance the rate of olefin oxidation. This type of reaction involves a reaction of selenium dioxide with an alkene by a similar mechanism to an ene reaction. An allylic seleninic acid is formed by

transferring the allylic proton to the selenium oxide. An allylic seleninic acid **2** undergoes a [2,3]-sigmatropic rearrangement to give an unstable compound **3** that rapidly decomposes to an allylic alcohol **4** (Scheme 4).



Scheme 4: Selenium dioxide-mediated allylic oxidation of alkenes

1.8 The Use of Selenium in Carbocyclisations

In spite of the tremendous advances in modern organic synthesis, development of synthetic methods continues to play a pivotal role in expanding organic synthetic capabilities. The efficient formation of carbon-carbon bonds forms the backbone of synthetic organic chemistry. Introduction of new functional groups and the compatibility of reactions with existing functional groups pose a major challenge in any synthetic plan. As an introduction, the major reactions that build new carbon-carbon bonds have been classified into four major types: electrophilic, nucleophilic, pericyclic, and radical reactions. Carbocyclisations of alkenes and alkynes are extremely important reactions for the syntheses of a variety of carbocyclic compounds. Many carbocyclisations are promoted by transition metals or their complexes. In most cases the nucleophilic carbon is an organometallic derivative where the metal is magnesium, lithium, sodium, potassium, or a transition metal. The term "electrophile mediated carbocyclisation" has been used to describe a cyclisation process involving carbon-carbon bond formation by electrophilic activation of a double or triple bond. The electrophile-promoted carbocyclisation is one of the important basic process that involves electrophilic species as activators of double or triple bonds.

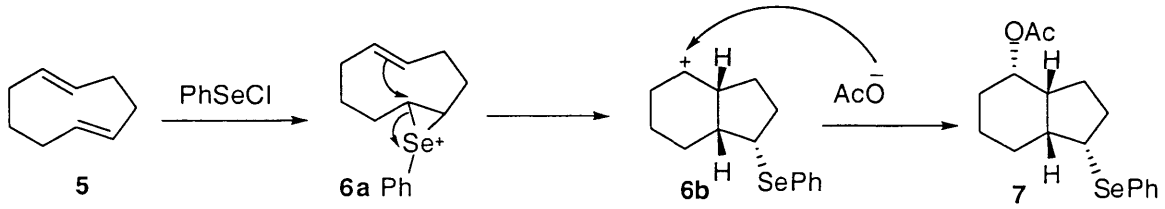
Electrophile-mediated reactions are some of the most powerful bond forming transformations, and the synthetic flexibility of alkenes and alkynes is remarkable. Selenium-mediated reactions constitute a powerful strategy toward the stereoselective

synthesis of organic compounds. The ability of selenium to behave as a powerful electrophile provides unique opportunities for cyclofunctionalisation of alkenes. This includes reactions initiated by the interaction of electrophiles with double bonds resulting in the formation of seleniranium ions, followed by intramolecular attack of either heteroatom or carbon nucleophiles. Although much progress has been made in the development of O–C and N–C bond forming reactions, few methods exist for the cyclisation by C–C bond forming reactions mediated by selenium electrophiles. Some selenium-mediated carbocyclisations are decribed below.

1.9 Literature Examples of Selenium-Mediated Carboyclisations

1.9.1 Cyclisations of Diolefins

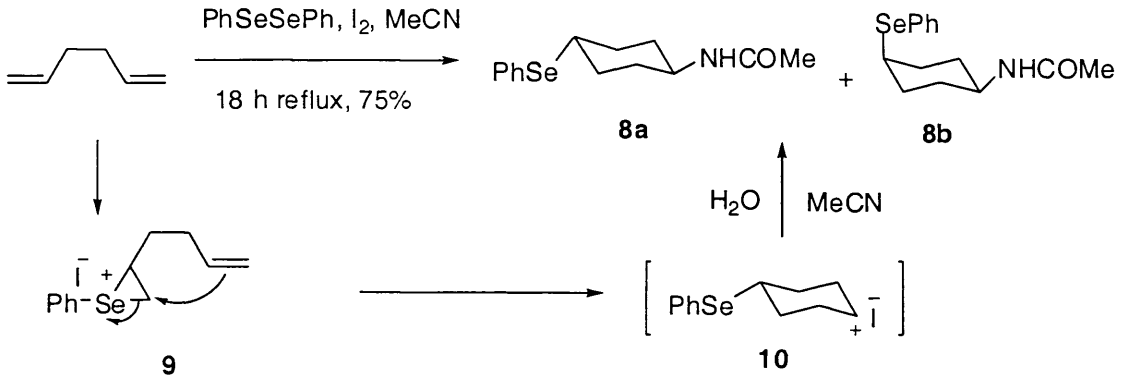
Carbocyclic compounds can be formed by the attack of internal nucleophile onto a seleniranium intermediate. The resulting carbonium ion **6** can react with another nucleophile or with the solvent. The first examples of such carbocyclisation reactions were observed with dienes. Clive[10] reported that the reaction of the diene **5** with phenylselenenyl chloride in acetic acid afforded the intermediate **6b** which reacts with acetic acid in the presence of sodium acetate to give the bicyclic compound **7** (Scheme 5).



Scheme 5: Cyclisation of cyclonona-1,5-diene

Phenylselenenyl iodide has shown unique reactivity in the cyclisation of certain diolefins. The reaction of phenylselenenyl iodide with diolefins in acetonitrile results in carbon-carbon bond formation. Carbocyclisation of diolefin substrates were efficiently promoted by phenylselenenyl iodide produced from diphenyl diselenide and iodine. As indicated in Scheme 6, Toshimitsu[11a] reported that the reaction of 1,5-hexadiene with diphenyl diselenide and iodine in acetonitrile followed by treatment with water

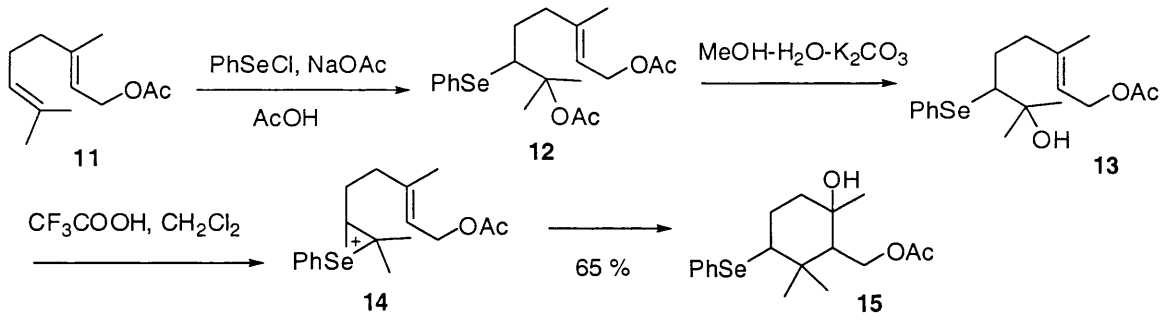
afforded the acetamido cyclohexane derivative **8**. The product 1-phenylseleno-4-acetomido cyclohexane was obtained in 75% yield with a 83:17 ratio of *trans* **8a** and *cis* **8b** isomers. When phenyl selenenyl iodide and diolefins were used in equimolar amounts, the total yield of **8a** and **8b** was only 12%. Mechanistically, cyclohexane derivative **8** derived from cyclisation of the seleniranium intermediate **9** followed by the reaction of the carbocation **10** with acetonitrile in a Ritter-type reaction. These products are obtained in very poor yield when phenylselenenyl chloride or bromide are used under similar conditions.



Scheme 6: Cyclisation of 1,5-hexadiene by PhSeI

1.9.2 Cyclisation of the Olefinic β-hydroxy Selenide

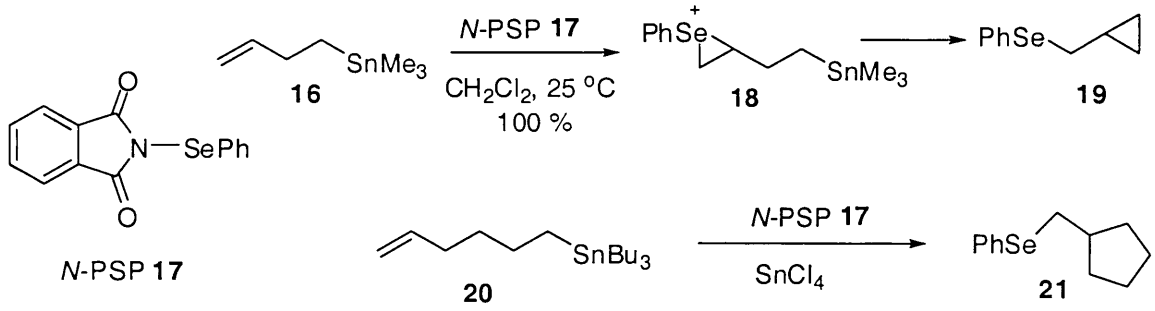
In several cases, carbocyclisation reactions can be conveniently initiated by independently generating the seleniranium intermediates. A simple procedure involves reaction of trifluoromethanesulfonic acid with β-hydroxyselenides, which can be easily obtained from the nucleophilic opening of epoxides with sodium phenylselenolate.[11b] In a related study, Kametani[12] showed that the cyclisation of β-hydroxyselenide **13** to a 6-membered carbocycle is a two-step process. The reaction of selenide **13** with acid leads to the formation of seleniranium intermediate **14** and subsequent cyclisation gave product **15** in 65% yield (Scheme 7).



Scheme 7: Acid-catalysed formation of a six-membered carbocycle from diene

1.9.3 Carbocyclisation of unsaturated organotin derivative

N-(Phenylseleno)phthalimide (*N*-PSP) **17** was developed as a valuable reagent for the introduction of the phenylselenenyl group to various substrates. An interesting carbocyclisation process was observed when alkenyl stannanes were treated with electrophilic selenenylating reagents. Nicolaou *et al.* showed that compound **16** reacted with *N*-(phenylseleno)phthalimide to form intermediate **18** which afforded the cyclopropane **19** (Scheme 8).[13] Further examples were reported by Herndon.[14] In the presence of tin tetrachloride, stannane **20** was converted to cyclopentane derivative **21**. This cyclisation reaction proved to be quite general with respect to a variety of substitution patterns, but it appears to be restricted to the formation of three- and five-membered rings.

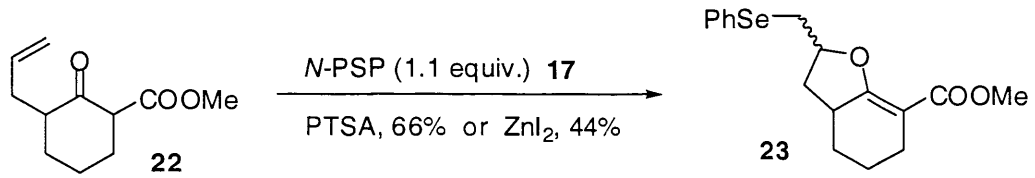


Scheme 8: Carbocyclisation of alkenyl stannanes

1.9.4 Cyclisation of Unsaturated β-Dicarbonyl Compounds

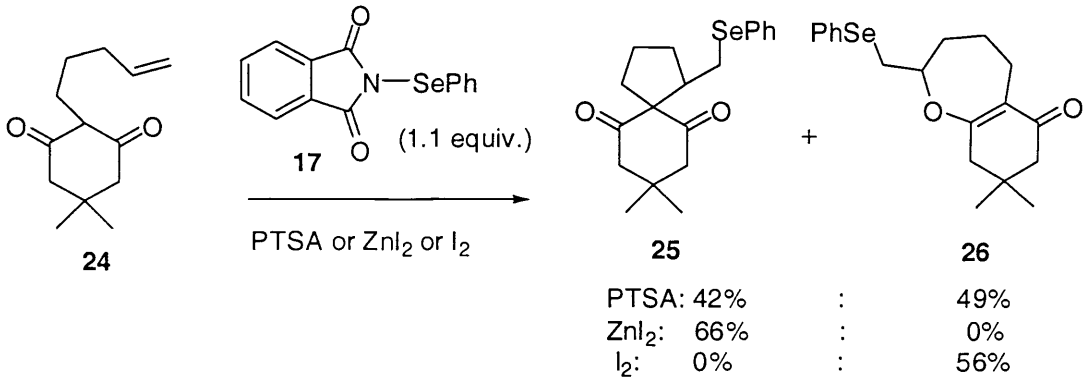
Ley and co-workers reported that *N*-PSP is an excellent reagent for the formation of carbocyclic rings from appropriately substituted unsaturated precursors.[15–16] The *N*-PSP promoted transformation of β-dicarbonyl compounds to the corresponding cyclised products deserves comment. The reaction of alkenyl-substituted β-dicarbonyl species

with *N*-phenylselenophthalimide has been shown to be a useful cyclising reagent for certain alkenyl-substituted 1,3-dicarbonyl compounds. At room temperature in dichloromethane, compound **22** was treated with *N*-PSP under different conditions to give cyclised product **23** (Scheme 9).



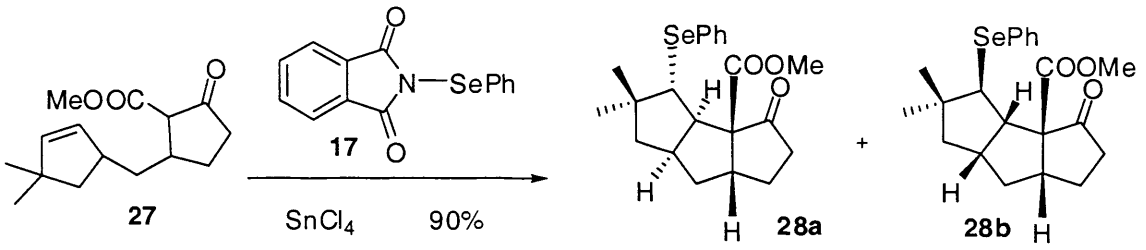
Scheme 9: *N*-PSP- mediated *O*-cyclisation

Interestingly, when the pentenyl-substituted dimedone **24** was treated with *N*-PSP in the presence of a catalytic amount of iodine, the oxygen-cyclised product **26** was obtained. Under Brønsted acidic conditions, both the carbon- and oxygen-cyclised products **25** and **26** were produced; while in the presence of ZnI_2, **25** appeared to be the only product (Scheme 10). The reasons for these changes in the reaction pathway are not yet fully understood.



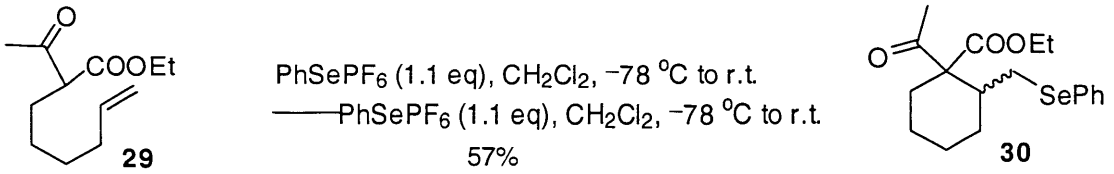
Scheme 10: Cyclisation of alkenyl-substituted *β*-dicarbonyl compounds using *N*-(phenylseleno)phthalimide

That *N*-PSP-mediated carbocyclisation is also able to cope with high molecular complexity is illustrated by the synthesis of hirsutene precursor **28** (Scheme 11).[16] *N*-PSP-mediated procedure has been recently employed by Ley to effect the conversion of the alkenyl *β*-keto lactone into tricyclic selenides **28a** and **28b** which are key intermediates in the preparation of compounds with antifeedant activity.[17]



Scheme 11: Synthesis of hirsutene precursor **26** using *N*-(phenylseleno)phthalimide

Phenylselenating agents, in which the counter-ion is non-nucleophilic[18] (such as SbF_6^-, or PF_6^-) react with certain alkenylsubstituted *β*-ketoesters to afford cyclised products. Literature shows only a few examples of cyclisation of alkenyl-substituted *β*-dicarbonyl compounds using *N*-(phenylseleno)phthalimide (*N*-PSP). However, this approach was not applicable in all cases. Treatment of the *β*-dicarbonyl species **29** with $PhSePF_6$, gave product **30** resulting from a 6-*exo-trig* cyclisation that could not be achieved using *N*-PSP (Scheme 12).

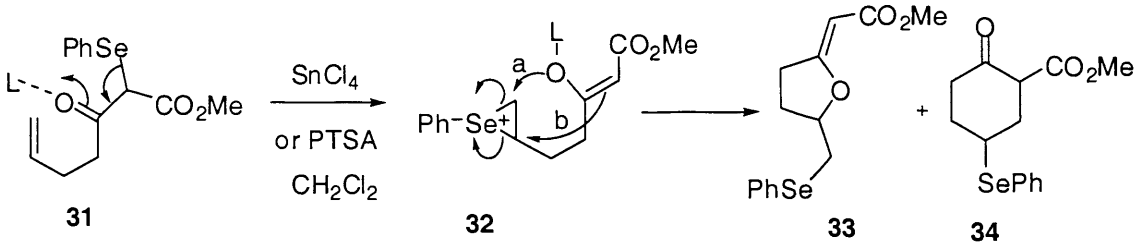


Scheme 12: $PhSePF_6$ mediated-carbocyclisation

1.9.5 Seleno-transfer carbocyclisation of α-phenylseleno ketones

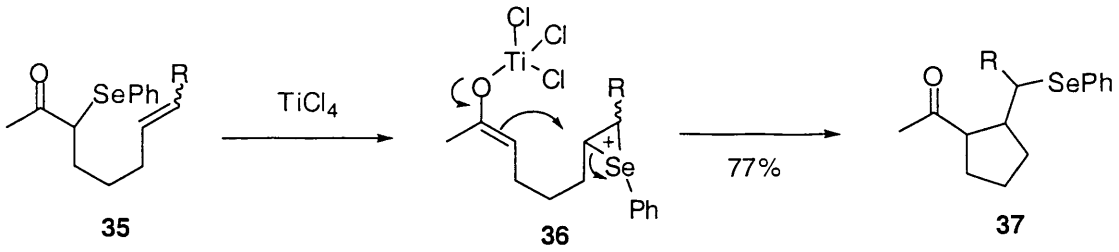
Selective carbocyclisation of alkenyl-substituted *β*-dicarbonyl compounds was further investigated by Ley *et al.* as shown in Scheme 13. Phenylseleno alkenyl *β*-ketoesters **31** could be selectively converted into either **33** or **34** depending on the reaction conditions.[19] Upon treatment with PTSA at room temperature in dichloromethane, reactant **31** gave the cyclised product **33**. In the seleniranium intermediate **32** (derived from the *β*-ketoester **31**) cyclisation through the oxygen atom to afford **33** is kinetically favoured. This reaction, however, is reversible. After prolonged reaction times in the presence of strong Lewis acids such as $SnCl_4$ the carbocyclisation product **34** is formed. Phenylseleno alkenyl *β*-ketoester **31** was readily prepared by quenching the anions of the corresponding alkenyl *β*-ketoesters with *N*-(phenylseleno)phthalimide (Scheme 13).[13] From this reaction, it is clear that one can achieve a selective cyclisation *via* either the central carbon atom of the *β*-ketoester unit (*C*-cyclisation) or

via the enol oxygen atom (*O*-cyclisation). In general, *O*-cyclisation can be achieved with *p*-toluenesulphonic acid as catalyst or if the reaction is worked up after a short time (kinetic product). Carbocyclisation is favoured if strong Lewis acids (e.g. $SnCl_4$) are used and the reaction performed for longer times (thermodynamic product).



Scheme 13: Acid dependent carbocyclisation

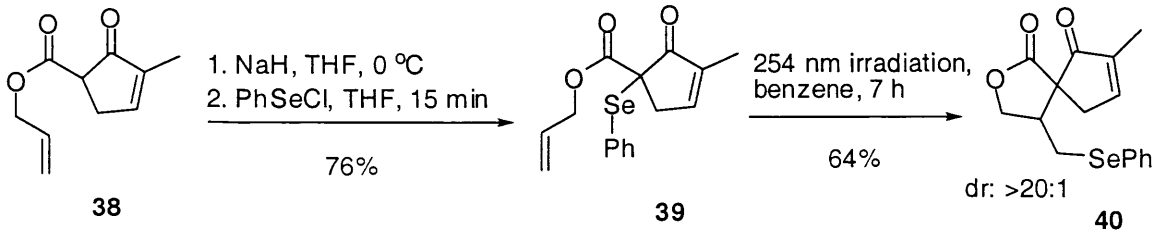
In a related investigation, Toru[20] described carbocyclisation reactions that occur by titanium tetrachloride-promoted transfer of the phenylseleno group in α-phenylseleno alkenyl ketones. As indicated in Scheme 14, treatment of α-phenylseleno ketones **35** bearing an alkenyl substituent with titanium tetrachloride induces enolisation of the carbonyl group to generate a titanium enolate and a phenylselenenyl cation that can react with the alkene to form a seleniranium ion **36**. The intermediate **36** then undergoes a cyclisation to afford the cyclopentane **37**. The net result of this process is phenylseleno group transfer with intramolecular carbon-carbon bond formation. Similar reaction conditions can also used to cyclise different α-phenylseleno alkenyl ketones to spiro compounds with high stereoselectivities and yields. This approach provides easy access to five- and six-membered rings as well as spiro carbocycles.



Scheme 14: Seleno-transfer carbocyclisations of phenyl seleno ketones

1.9.6 Radical Cyclisation

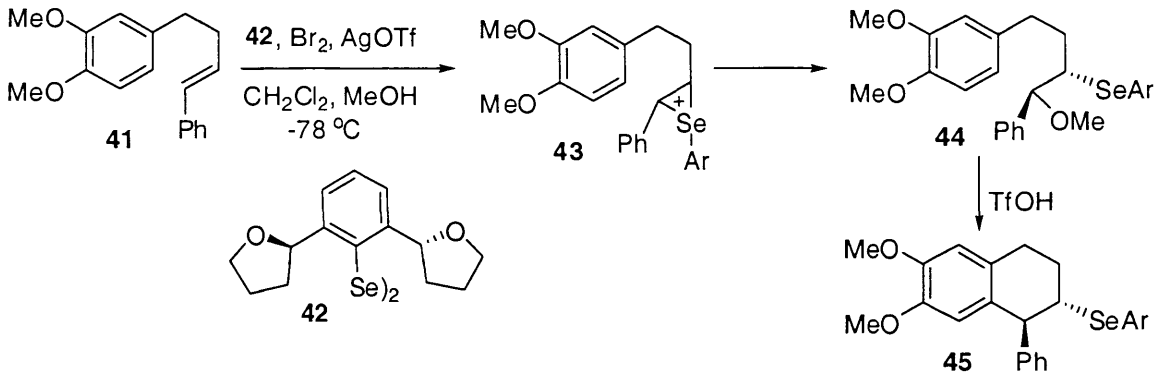
Radical cyclisations to generate spiro lactone moieties was reported by Back *et al.*[21] Spiro lactone **40** is obtained by photolysis of an appropriately substituted allyl α-phenylseleno-β-keto ester. Selenenylation of β-keto ester **38** with phenylselenenyl chloride to afford α- phenylseleno-β-keto ester **39** in 76% yield. Irradiation for several hours with UV light at 254 *nm* in benzene, or for 1 h with a 275 Watt sunlamp, resulted in ring-closure to give spiro lactone **40** as a pair of diastereomers in a ratio of >20:1 (Scheme 15).



Scheme 15: Free radical cyclisation

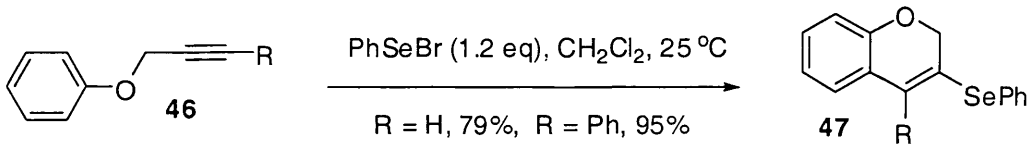
1.9.7 Intramolecular Arene–Olefin Cyclisations

Addition of carbon-based nucleophiles to olefins is a process that is efficiently activated by selenium-electrophiles. This process is especially useful for the construction of carbocyclic systems in which the nucleophile is an aromatic ring. Deziel[22] has reported that the reaction of alkene **41** (Scheme 16) with the chiral aryl selenenyl triflate derived from diselenide **42** afforded a 1:1 mixture of compounds **44** and **45**. These compounds are derived from the capture of intermediate seleniranium ion **43** by methanol or by the aromatic ring, respectively. The addition product **44** can be transformed into cyclisation product **45** via the seleniranium intermediate **43** by treatment with trifluoromethanesulfonic acid. Tetrahydronaphthalene **45** was obtained in 70% yield and with 98% diastereomeric excess (Scheme 16).



Scheme 16: Arene-alkene cyclisation mediated by chiral organoselenium reagent

The electrophilic cyclisation of substituted propargyl aryl ethers by phenylselenenyl bromide produces 3,4-disubstituted 2*H*-benzopyrans in good yields (Scheme 17).[23] This methodology results in C–C bond formation under mild reaction conditions but only two examples are reported. 3,4-Disubstituted 2*H*-benzopyrans were obtained in good yields using I_2 or ICl when the substituent on the alkyne was a simple phenyl or an alkenyl group. An alkyl-substituted alkyne terminus gave no desired product on tratment with iodine (I_2) or iodine monochloride (ICl) but worked with phenylselenenyl bromide.



Scheme 17: Synthesis of substituted 2*H*-benzopyrans by electrophilic cyclisation of propargylic aryl ethers

In summary, previous selenium-based methods for the formation of carbocycles require expensive selenium reagents and are highly sensitive to the nature of the substrate. Low yields are obtained in these reactions due to the formation of side products. This makes them either undesirable or impractical in a number of synthetic applications. The application of selenium electrophiles to carbocyclisation reactions is relatively unexplored. To expand the scope of selenium electrophile in carbocyclisation reactions, it was decided to further explore its chemical reactivity of these systems to obtain a better understanding of selenium-carbocyclisations. It is believed that after further investigation, such reactions could find many applications in organic synthesis.

Chapter 2

2 The Synthesis of Novel Dihydronaphthalenes and Benzofluorenes

This chapter is concerned with the synthesis and applications of dihydronaphthalenes and benzofluorenes. This chapter describes literature methods for the preparation of dihydronaphthalenes and benzofluorenes. Efforts to discover new synthetic methods for the synthesis of dihydronaphthalenes and benzofluorenes are then described.

2.1 Introduction to Dihydronaphthalenes

The 1,2-dihydronaphthalene ring system is present in various natural products of therapeutic importance including: cannabisins **48**, isolated from the fruits of Cannabis sativa.[24] 6,7-dehydrosempervirol **49**,[25] isolated from the roots of Salvia apiana and negundin B **50**,[26] isolated from the roots of Vitex negundo. Nafoxidene **51** is a class of biologically active dihydronaphthalene and its analogues can be prepared from 1-(4-benzyloxyphenyl)-6-methoxy-2-phenyl-3,4-dihydronaphthalene.[27] Dihydronaphthalene derivatives are used as fluorescent ligands for the estrogen receptor[28] and exhibit activity as Hepatitis C NS5B polymerase inhibitors.[29] Recently, dihydronaphthalenes were found to be potent and selective inhibitors of aldosterone synthase (CYP11B2) for the treatment of congestive heart failure and myocardial fibrosis.[30]

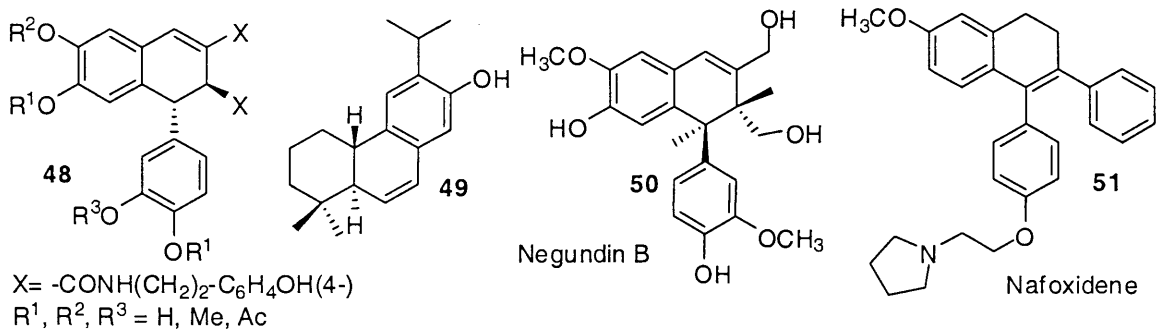
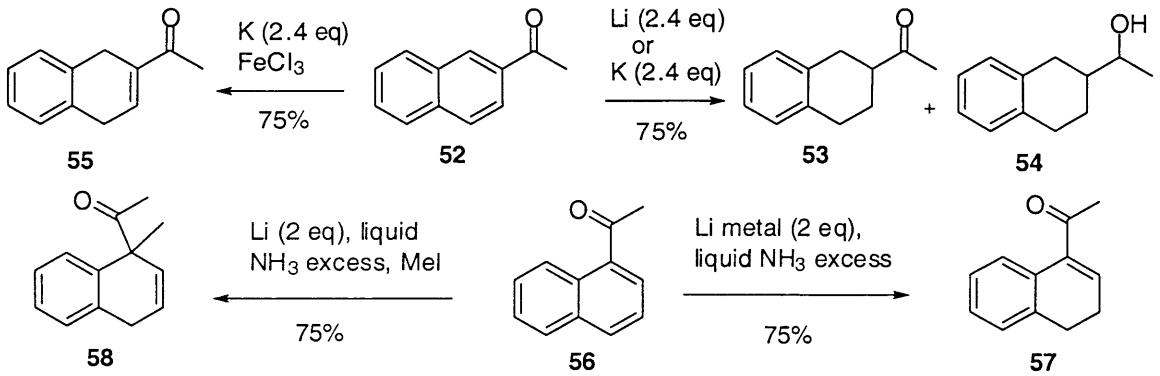


Figure 2: Dihydronaphthalene natural products

As dihydronaphthalene derivatives are useful starting materials for the synthesis of biologically active cyclic molecules,[31] numerous traditional synthetic approaches to these compounds have been reported.[32,49] Among them the dearomatisation of

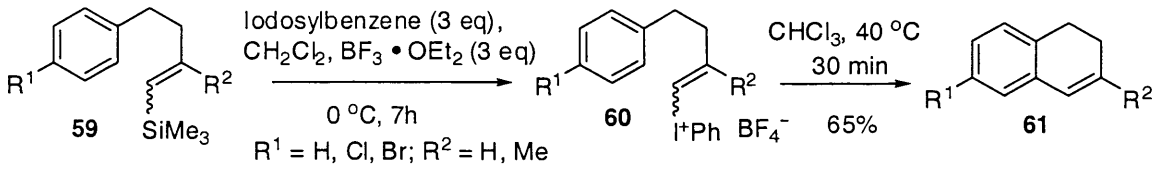
naphthalene derivatives by the nucleophilic addition of certain organometallic reagents is one of the most useful and convenient methods.[33] A drawback of the nucleophilic addition method is the difficulty in application to a wide range of substrates. Dihydronaphthalenes are known as useful building blocks in organic synthesis.[28,34] They can undergo bromination,[35] cyclopropanation,[36,37] dipolar cycloaddition[38] and epoxidation[39] reactions to afford useful products. Rhodium- and palladium-catalysed asymmetric ring-opening reactions of oxabenzonorbornadienes by various alcohol, amine and alkyl nucleophiles afford dihydronaphthalene derivatives in good yields.[40] The conversion of α- and β-tetralone into dihydronapthalenes was accomplished by palladium-catalysed coupling of Grignard reagents with *in situ*-generated enol phosphates.[41] The gold(I)-catalysed intramolecular rearrangement of vinylidenecyclopropanes also gives dihydronaphthalenes.[42] The metal-ammonia reduction of naphthalene and its derivatives has also been extensively investigated.[43] Additional metal-catalysts have also been used in the formation of dihydronaphthalenes, such as those used in the Birch reduction and the reductive methylation of 1- and 2-acetylnaphthalenes into dihydronaphthalenes as described by Rao and Sundar. It has been found that 1-acetylnaphthalene is reduced to the 3,4-dihydronaphthalene **57** whilst the 2-acetylnaphthalene gives the corresponding 1,2,3,4-tetrahydronaphthalene **53** (Scheme 18).[44] However, anhydrous ferric chloride has been found to limit the reduction to the dihydro-stage with 2-acetylnaphthalene.



Scheme 18: The Birch reduction

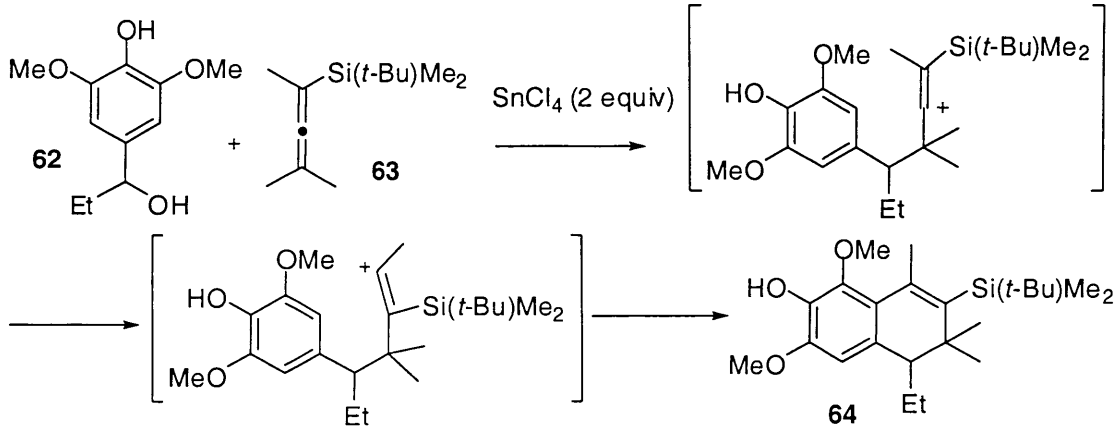
1,2-Dihydronaphthalene derivatives have been synthesised by the thermal cyclisations of alkenyliodonium tetrafluoroborates. The required alkenyliodonium salts **60** possessing an aromatic group were prepared from alkenylsilanes **59** using iodosylbenzene in the presence of boron trifluoride-diethyl ether at 0 °C followed by quenching with aqueous sodium tetrafluoroborate, affording a 77% yield of the

vinyliodonium tetrafluoroborate **60**. Intramolecular aromatic vinylation of the iodonium salts **60** was found to occur smoothly on gentle heating at 40 °C for 0.5 h in a sealed tube and provided dihydronaphthalene **61** in 65% yield (Scheme 19).[45]



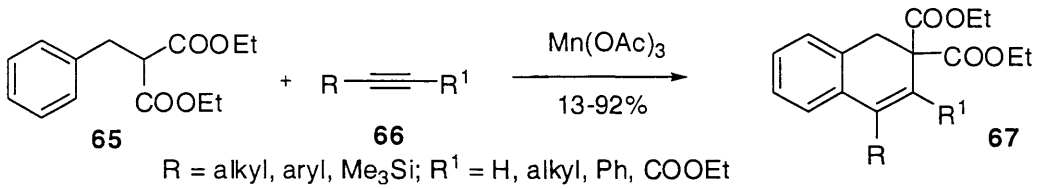
Scheme 19: Hypervalent iodine-mediated synthesis of dihydronaphthalene **61**

1,2-Dihydronaphthalenes can also be prepared in moderate yields from allenylsilanes and benzylic cations by a one-step intermolecular cyclisation. For example, treatment of alcohol **62** with an excess of allenylsilane **63** and 2.0 equivalents of tin(IV) chloride in dichloromethane at 0 °C afforded dihydronaphthalene **64** in 65% yield. The reaction can also be carried out using an excess of benzylic alcohol, for example, treating 2.0 equivalents of alcohol **62** with allene **63** afforded dihydronaphthalene **64** in 79% yield. The use of an excess of one of the reactants is a drawback. Another drawback is that substitution on the aromatic ring controls whether dihydronaphthalene or spirodecatrienone products are formed (Scheme 20).[46]



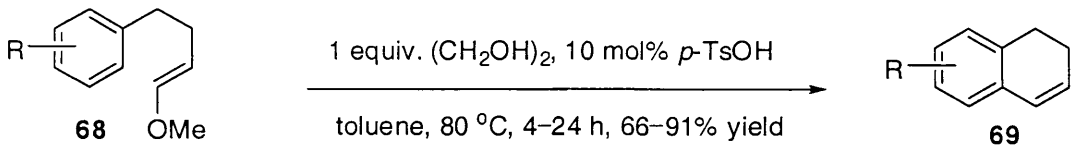
Scheme 20: Synthesis of dihydronaphthalene **64** from benzylic alcohol **62**

The transition metal-promoted insertion of carbonyl compounds to carbon-carbon triple bonds can provide useful route to dihydronaphthalenes. Oxidation of diethyl α-benzylmalonate **65** by manganese(III)acetate in acetic acid at 70 °C in the presence of alkynes **66** leads to dihydronaphthalene derivatives **67** in low to good yields (Scheme 21).[47]



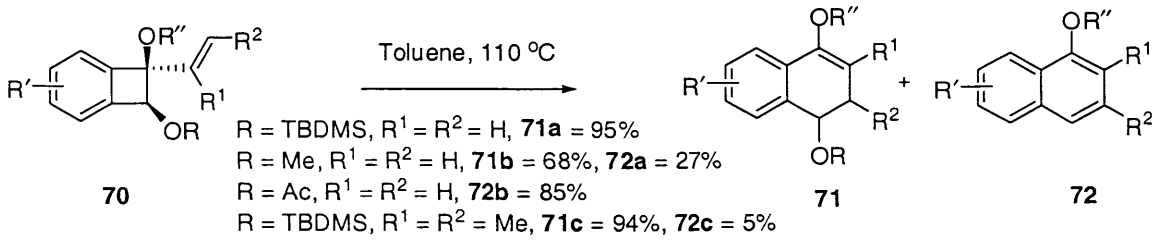
Scheme 21: Manganese mediated synthesis of dihydronaphthalene **67**

In 2002, Harrowven[48] reported the conversion of 4-arylalk-1-en-1-yl methyl ethers **68** to dihydronaphthalenes under catalytic reaction condition. Cyclisation is accomplished by warming a toluene solution of the substrate **68** with 1,2-ethanediol and catalytic *para*-toluenesulfonic acid at 80 °C which proceeds via *in situ* formation of a 1,3-dioxolane. Reactions generally give good yields (66—91%) and have been successful with electron rich, unsubstituted and halogenated arenes, the latter requiring extended reaction times (Scheme 22).



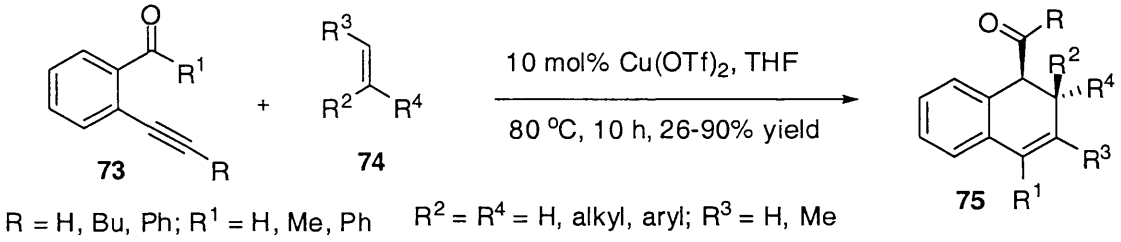
Scheme 22: Acid-catalysed cyclisation of **68** to dihydronaphthalene **69**

Suzuki and co-workers[49] described the thermal ring expansion of various alkenylbenzocyclobutenol derivatives into dihydronaphthalenes. The reactions were carried out at 110 °C in toluene. Thermolysis of **70** showed a reactivity dependence on the R group (Scheme 23). The relative propensity to form either dihydronaphthalene **71** or naphthalene derivative **72** is dependent upon the nature of the substrate. Substrates with silyl or methyl ether groups underwent smooth rearrangement to give the dihydronaphthalene **71**. When R is an acetyl, the naphthalene **72b** was obtained as the main product. The stereochemistry of the thermal conversion of alkenylbenzocyclobutenol into either *cis*-dihydronaphthalene or *trans*-dihydronaphthalene was also studied.



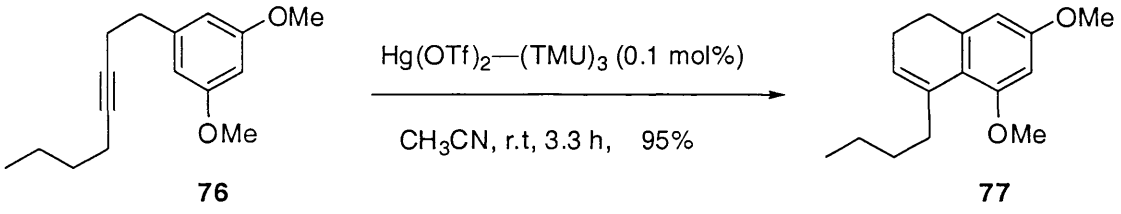
Scheme 23: Thermal ring expansion of **70** into dihydronaphthalenes

Yamamoto[50] described the preparation of 1,2-dihydronaphthalene **75** by the reaction of *o*-(alkynyl)benzaldehydes or *o*-(alkynyl)phenyl ketones **73** with olefins **74** using 10 mol% $Cu(OTf)_2$ at 80 °C in THF. This $Cu(OTf)_2$-catalysed cycloaddition reaction affords dihydronaphthalene derivatives **75** bearing a ketone function at the 1-position in 26—90% yields. The process is reasonably general with regard to the types of substituents on the olefin that can be employed and alkyne can also be used with a range of substitution patterns (Scheme 24).



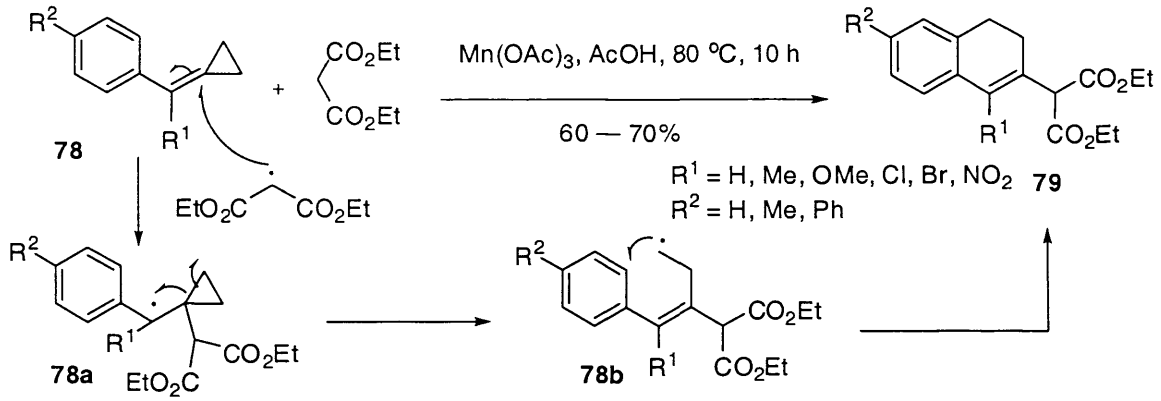
Scheme 24: $Cu(OTf)_2$-catalysed [4+2] cycloaddition of *o*-alkynylbenzenes with alkenes

The formation of dihydronaphthalene derivatives from *ω*-arylalkyne **76** can be catalysed by the use of 0.1 mol% $Hg(OTf)_2$-$(TMU)_3$ (TMU = tetramethylurea) complex in acetonitrile at room temperature. Under these conditions, various dihydronaphthalene derivatives are formed in good yields along with smaller amounts of by-products. However, the choice of substitution pattern on the substrate is crucial for the success of this process (Scheme 25).[51]



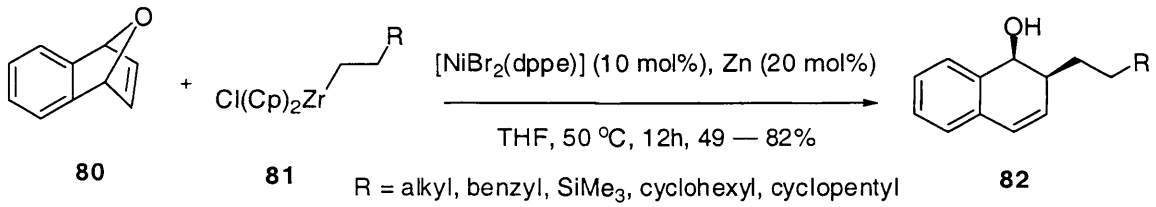
Scheme 25: Mercuric triflate-$(TMU)_3$-catalysed cyclisation of *ω*-arylalkyne

Chen and co-workers[52] reported a convenient synthesis of 3,4-dihydronaphthalen-2-yl-malonic esters **79** in moderate yield by the reaction of arylidene cyclopropanes **78** with diethyl malonate in the presence of $Mn(OAc)_3$. The reaction is proposed to proceed by the β-scission of the C—C bond in the cyclopropane ring in **78a** to generate **78b**. Subsequent intramolecular radical cyclisation of **78b** produces cyclic product **79** with the loss of a proton and oxidation in the presence of another molecule of $Mn(OAc)_3$ (Scheme 26).

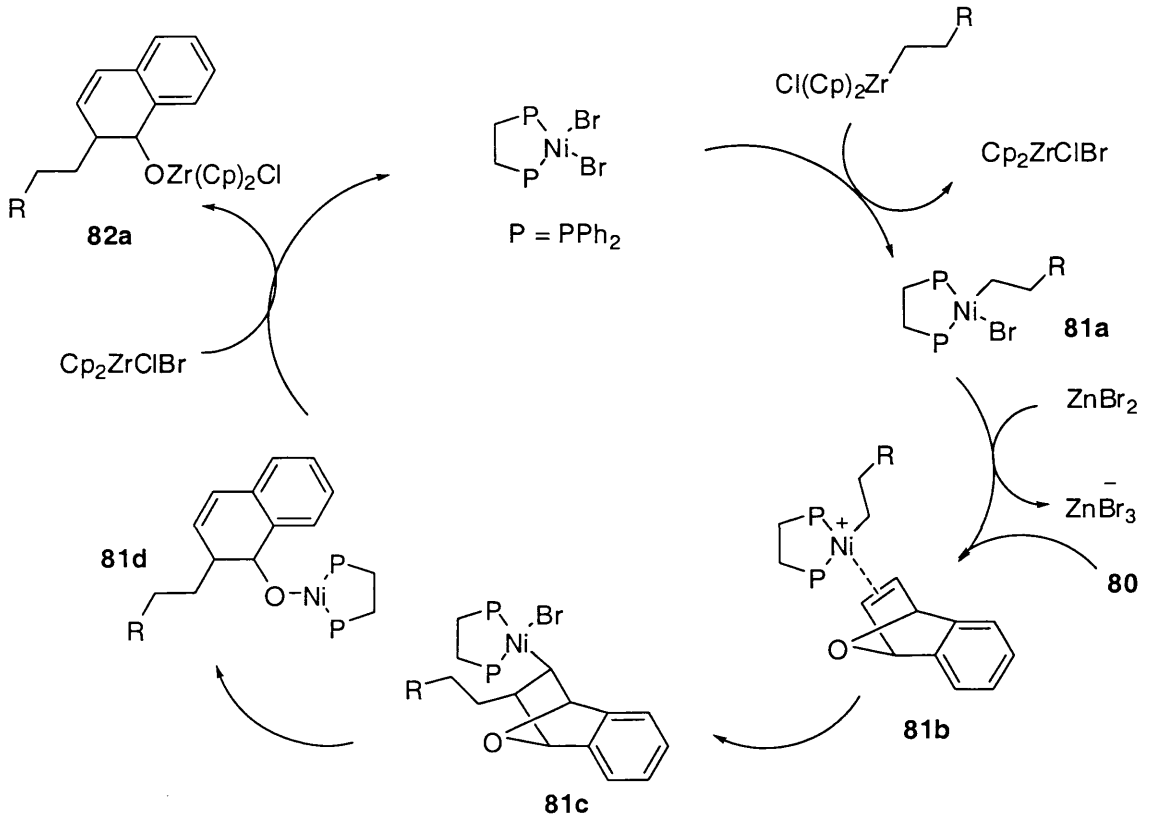


Scheme 26: Manganese acetate mediated free-radical cyclisation reaction of alkylenecyclopropanes

The regio- and stereoselective ring-opening addition of alkyl- or allylzirconium reagents to 7-oxabenzonorbornadienes **80** as described in Scheme 27 is catalysed by 10 mol% $NiBr_2$(dppe) and 20 mol% Zn powder in dry THF at 50 °C.[53] Under these conditions, a wide range of *cis*-2-alkyl- or allyl-1,2-dihydronaphthalenes **82** are formed in good yields (49–82%). The nickel-catalysed transmetalation of alkylzirconium reagents to form nickel(II) alkyl intermediate **81c** is postulated to proceed through the formation of a π alkene nickel complex **81b**. The catalytic cycle involves initial coordination of 7-oxabenzonorbornadiene (*via* the exo face of the carbon-carbon double bond) to the Ni center in **81b** followed by the addition of the organonickel species into the double bond resulting in the formation of intermediate **81c**. Subsequent β-oxy elimination leads to intermediate **81d**, and transmetalation with $Cp_2ZrClBr$ gives the nickel(II) catalyst and zirconium alkoxide **82a**. The latter is converted to the final desired alkyl product **82** by protonation after workup (Scheme 28).



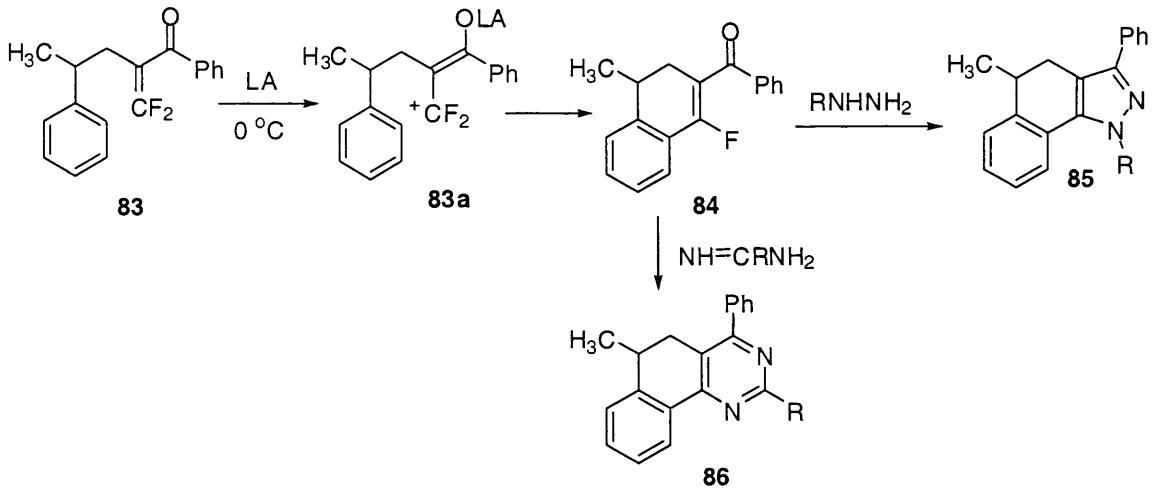
Scheme 27: Synthesis of dihydronaphthalene **82** by nickel-catalysed addition of alkyl zirconium reagents **81** to oxabenzonorbornadienes



Scheme 28: Proposed catalytic cycle for the preparation of **82**

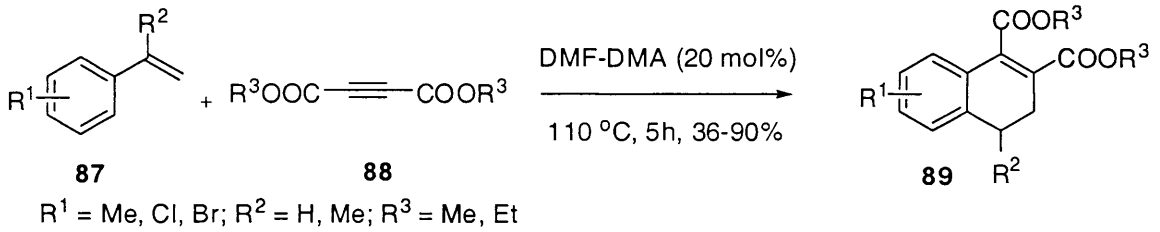
Ichikawa and co-workers[54] have shown that 2,2-difluorovinyl ketones bearing an aryl group can be cyclised to 4-fluorinated 3-acyl-1,2-dihydronaphthalenes using 1 equivalent trimethylsilylating agent [Me_3SiOTf or $Me_3SiB(OTf)_4$]. The resulting dihydronaphthalene **84** is subjected to a substitution-cyclodehydration process or a Nazarov-type cyclisation to construct fused polycyclic systems. The process is believed to proceed through the generation of the α-fluorocarbocation **83a** followed by Friedel-Crafts cyclisation. For example, 4-fluorinated 3-acyl-1,2-dihydronaphthalene **84** was formed in 84% yield via a Friedel-Crafts-type alkylation accompanied by the loss of a fluoride ion. 4,5-Dihydrobenzo[g]indazoles **85** and 5,6-dihydrobenzo[h]quinazolines **86**

have been obtained in good yields by the reaction of **84** with both hydrazines and amidines as bifunctional nucleophiles in benzene at reflux, respectively (Scheme 29).



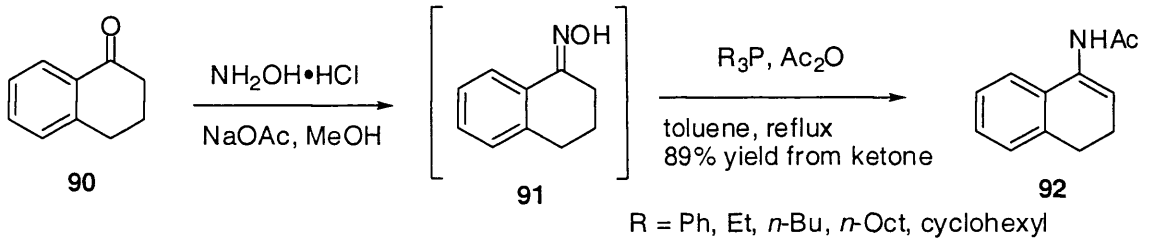
Scheme 29: Synthesis of dihydronaphthalene and its application to fused heterocycles

Alternatively, 1,2-disubstituted-3,4-dihydronaphthalenes **89** are formed in 36—90% yields by the cycloaddition reaction of vinylarenes **87** with electron-deficient alkynes **88** such as diethyl acetylenedicarboxylate and methyl phenylpropiolate.[55] These reaction were conducted at 110 °C in the presence of DMF-DMA (*N,N*-dimethylformamide dimethyl acetal) as an organocatalyst (Scheme 30). This organocatalysed methodology exhibits the advantages of substrate versatility and mild reaction conditions.



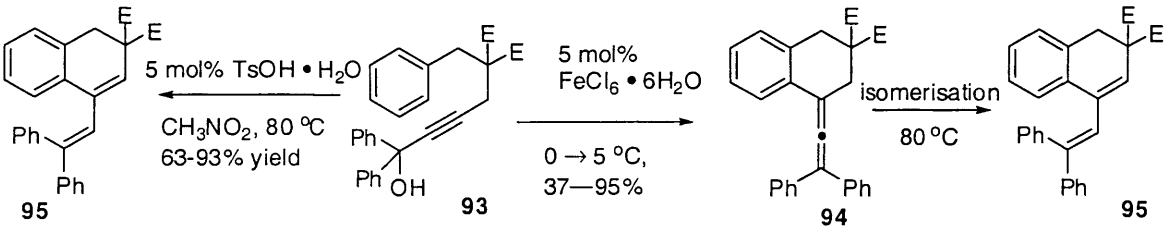
Scheme 30: Synthesis of dihydronaphthalene by cycloaddition reaction of **87** with **88**

A new synthesis of dihydronaphthalene from α-tetralone was disclosed by Singh and co-workers.[56] When ketoxime **91** was treated with (stoichiometric) triphenylphosphine and acetic anhydride in toluene at reflux, complete conversion to product **92** was observed. This methodology involves a phosphine-mediated reductive acylation of oximes and the resulting dihydronaphthalene **92** bearing enamide is isolated in good yields (up to 89%) with excellent purity (Scheme 31).[56]



Scheme 31: Synthesis of dihydronaphthalene **92** from α-tetralone **90**

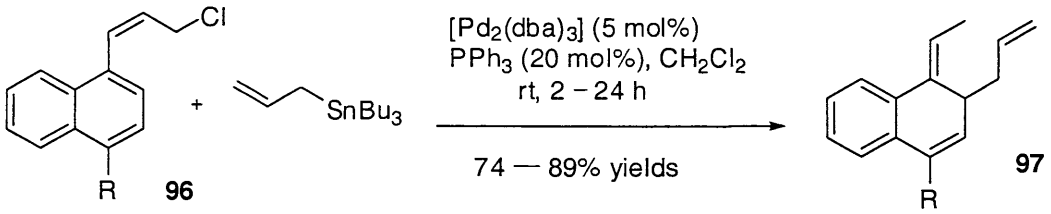
Reactions of arylsubstituted propargylic alcohols catalysed by a simple Lewis or Brønsted acid have been developed for the selective synthesis of di- and tetrahydronaphthalene systems.[57] Treatment of a variety of aryl substituted propargylic alcohols **93** with toluenesulfonic acid in nitromethane at 80 °C afforded the corresponding 1,2-dihydronaphthalenes **95** formed through the intramolecular Friedel-Crafts reaction followed by successive isomerisation in moderate to excellent yields, depending on the nucleophilicity of the aryl nucleus involved and the nature of substituents at the propargylic position. Selective preparation of **95** could be achieved by using $FeCl_3 \cdot 6\ H_2O$ at 0—5 °C. It was also feasible to isolate **94** in good yields using TsOH as a catalyst if the reaction was carried out at room temperature. Remarkably, both **93** and **95** were converted to spiro-skeletons, when using $FeCl_3 \cdot 6\ H_2O$ at 80 °C (Scheme 32).



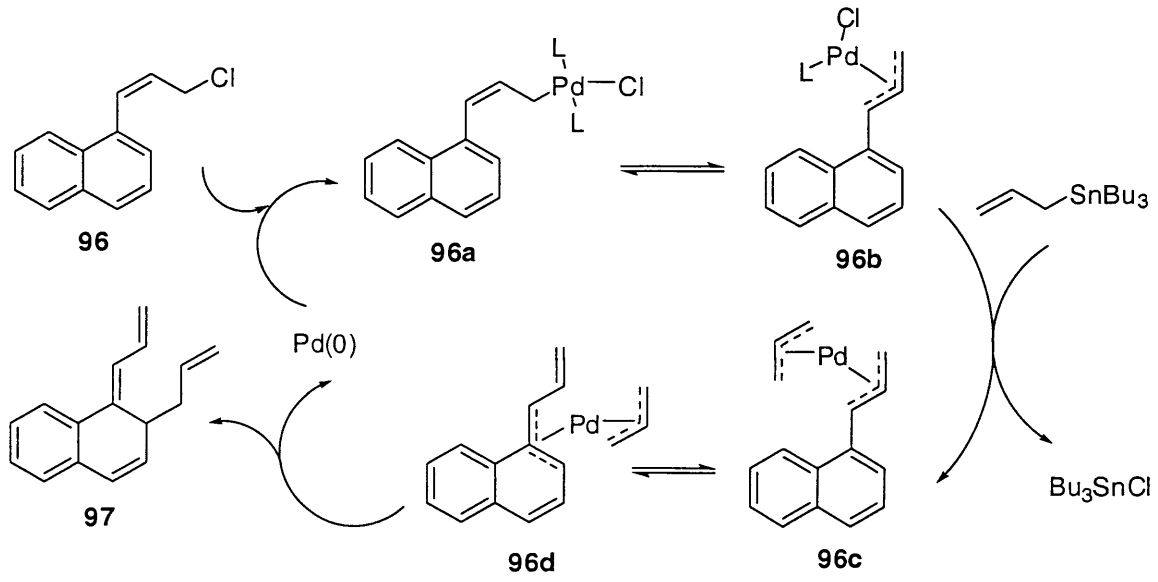
Scheme 32: Synthesis of **95** from aryl-substituted propargylic alcohols **93**

A range of dihydronaphthalenes was accomplished by the palladium-catalysed de-aromatisation reaction of naphthalene derivatives with allyltributylstannane (Scheme 33).[58] The allylative de-aromatisation reactions of naphthalene derivatives **96** with allyltributylstannane have been performed in the presence of $[Pd_2(dba)_3]$ (5 mol%) and PPh_3 (20 mol%). The simple substrates **96** underwent the de-aromatisation reaction smoothly to afford **97** in high yields (74—87%) Neither the electron-donating group nor the electron-withdrawing group on the aromatic ring exerted a strong influence on the reaction (except in terms of the reaction times). The proposed mechanism involves the

formation of η^3-allylpalladium chloride intermediate **96b** by oxidative addition of **96a** to a Pd(0) species, followed by reaction with allyltributylstannane to generate a bis(η^3-allyl)palladium intermediate **96c** upon ligand exchange. Isomerisation of **96c** would occur to give a bis(η^3-allyl)palladium intermediate **96d**. The resulting allyl-Pd complex undergoes reductive elimination to form the dearomatised product **97** and regenerate the Pd(0) catalyst (Scheme 34).



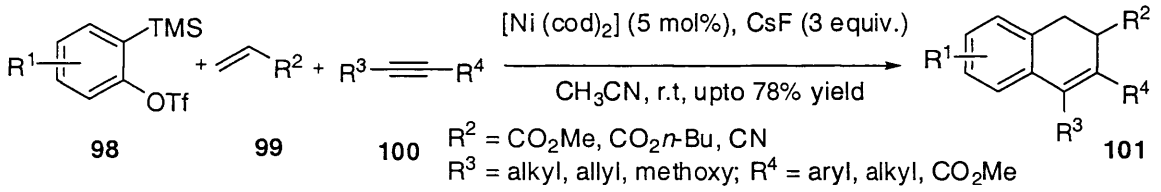
Scheme 33: Synthesis of **97** by palladium-catalysed de-aromatisation of naphthalene derivatives with allyltributylstannane



Scheme 34: Mechanism for the de-aromatisation of **96** (all charges are omitted)

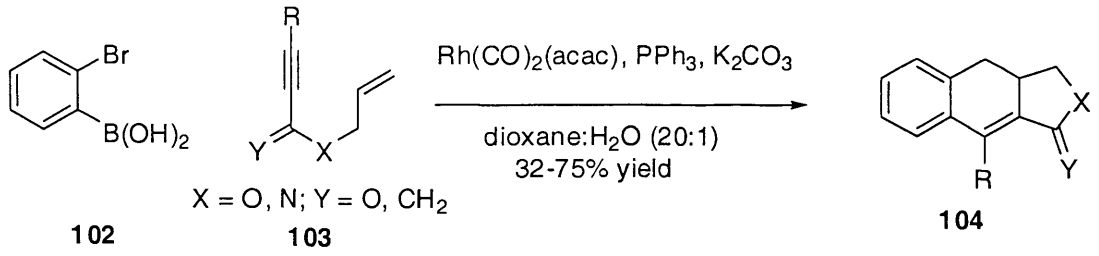
Nickel can efficiently catalyse the cyclisation of alkenes, and alkynes to afford a series of substituted dihydronaphthalenes that cannot be prepared from the readily available starting materials.[59] In 2009, Xie and Qiu described the preparation of wide range of dihydronaphthalenes in good yields from nickel-catalysed three-component [2+2+2] carboannulation reaction of arynes, activated alkenes, and alkynes.[60] This work offers an exceptionally efficient route to 1,2-dihydronaphthlenes from readily available starting materials. Various alkynes were compatible with this nickel-catalysed

carboannulation reaction and gave the desired dihydronaphthalenes **101** in very good yields. The best results were obtained using 5 mol% $[Ni(cod)_2]$ and 3 equivalents cesium fluoride in acetonitrile at room temperature. If unactivated alkenes were used, none of the desired products **101** were detected. Functionalised aryne precursors with electron-donating groups were less effective, producing dihydronaphthalene derivatives **101** in moderate yields (Scheme 35).



Scheme 35: Nickel-catalysed synthesis of **101** via a multi-component reaction

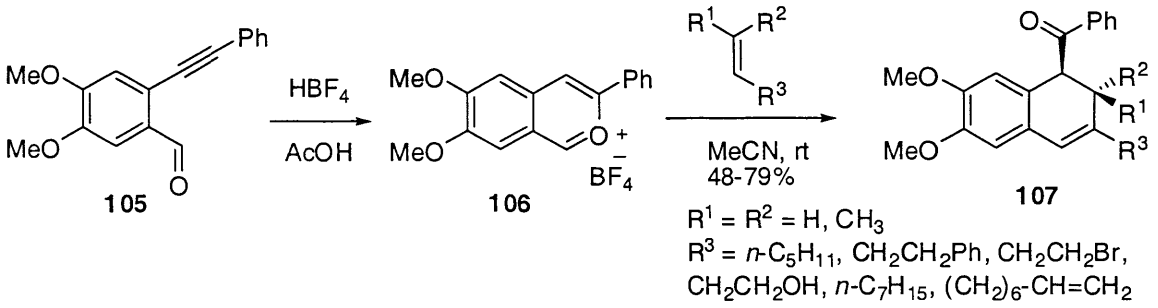
In 2009, the rhodium-catalysed reaction of 1,6-enynes **103** with 2-bromophenylboronic acids **102** has been utilized by Tong *et al.*[61] to construct a multi-substituted dihydronaphthalene scaffold. A screen of reaction conditions revealed that 5 mol% $Rh(CO)_2(acac)$, triphenylphosphine, potassium carbonate in a dioxane and water mixture at 100 °C for 3–5 h afforded dihydronaphthalene scaffold **104** in good yields for most substrates. This [2+2+2] cycloaddition of 1,6-enynes with 2-bromophenylboronic acids involves the Rh-catalysed regioselective insertion of an alkyne into an arylrhodium(I) species and the oxidative addition of C–Br bonds in the adjacent phenyl ring to the resulting vinylrhodium(I) species as key steps (Scheme 36).



Scheme 36: Rhodium-catalysed synthesis of dihydronaphthalene scaffold **104**

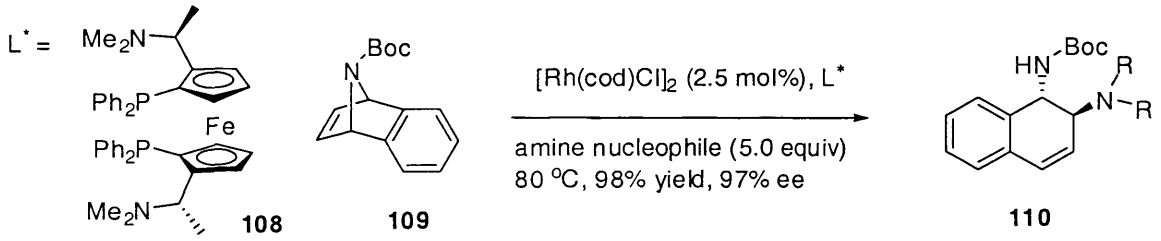
In 2009, Yao and co-workers[62] exploited scope of isochromenylium tetrafluoroborates as precursors of various dihydronaphthalenes. Direct metal-free treatment of isochromenylium tetrafluoroborate **106** with alkenes in acetonitrile at either 25 or 60 °C afforded a diverse range of dihydronaphthalenes **107** via mild cascade reactions. Reaction of **106** with the monosubstituted, disubstituted, and trisubstituted olefins as

well as with cyclic alkenes delivered desired products **107** successfully in 48—79% yields (Scheme 37).



Scheme 37: Synthesis of **107** from isochromenylium tetrafluoroborate **106**

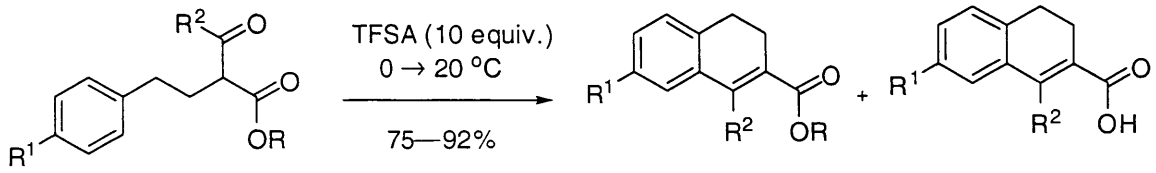
In an attempt to induce chirality on dihydronaphthalene ring systems, Cho and co-workers used chiral (*S,S'*)-(*R,R'*)-C_2-ferriphos **108** as ligand and $[Rh(cod)Cl]_2$ as a catalyst in tetrahydropyrane at 80 °C. In the presence of a rhodium catalyst generated *in situ* from $[Rh(cod)Cl]_2$ and (*S,S'*)-(*R,R'*)-C2-ferriphos **108**, the asymmetric ring-opening reaction of azabenzonorbornadienes **109** with various aliphatic and aromatic amines proceeded with high enantioselectivity (up to 99% ee) to give the corresponding 1,2-diamine substituted dihydronaphthalene derivatives **110** in high yields. Experiments revealed that the nature of the chiral ligand has the significant impact on the reactivity of the catalyst and the use of excess (2.2 equiv. to Rh) of the chiral ligand plays an important role to increase the enantioselectivity in the ring-opening reactions of azabenzonorbornadienes with amine nucleophiles (Scheme 38).[63]



Scheme 38: Rhodium-catalysed synthesis of **110** using ferrocene ligands

In 2010, Ohwada and co-workers[64] disclosed the acid-catalysed cyclisation of arylacetoacetates to afford 3,4-dihydronapthhalene derivatives in Brønsted superacids. For example, methyl 2-aceto-4-phenylbutyrate **111** underwent the cyclisation in the presence of 10 equivalents trifluoromethyl sulfonic acid (TFSA) to afford 1-methyl-2-carbomethoxy-3,4-dihydronaphthalene **112** and 1-methyl-3,4-dihydronaphthalene-2-

carboxylic acid **113** in 87% combined yield. In the same communication, they also reported thermochemical data on the acid-catalysed cyclisation of arylacetoacetates. Thermochemical data shows that activation of arylacetoacetates toward cyclisation by a strong acid, and the electron-withdrawing nature of the *O*-protonated ester functionality significantly increases the electrophilicity of the ketone moiety (Scheme 39).[64]



Scheme 39: Synthesis of dihydronapththalenes by acid-catalysed cyclisation of **111**

2.2 Introduction to Benzofluorenes

Benzo[*b*]fluorene subunits have, in recent years, achieved significant importance because of their occurrence in many bioactive natural products. The secondary metabolites prekinamycin,[65-66] kinafluorenone **114**,[67] stealthins[68] **115**, kinobscurinone,[69] seongomycin[70] and cysfluoretin[71] (Figure 3) have all been found in extracts from Streptomyces murayamaensis. In 1992, the Seto group reported the isolation of stealthin A and B as potent radical scavengers from Streptomyces viridochromogenes[68] and showed that their radical-scavenging activities were 20–30 times higher than those of vitamin E. The Gould group synthesised stealthin C and demonstrated its existence in kinamycin biosynthesis.[72-73] Benzofluorenes found application as estrogen receptor antagonists[74] and have utility in blue organic electroluminescent devices.[75]

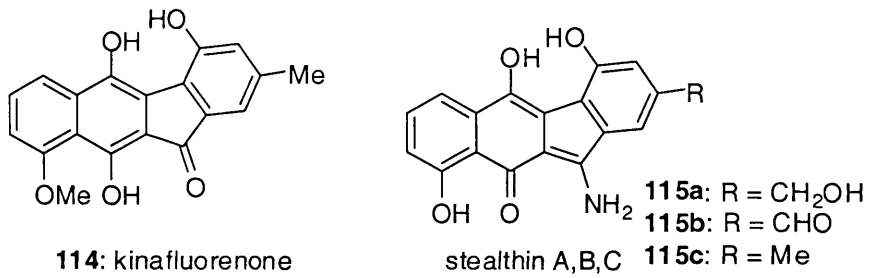
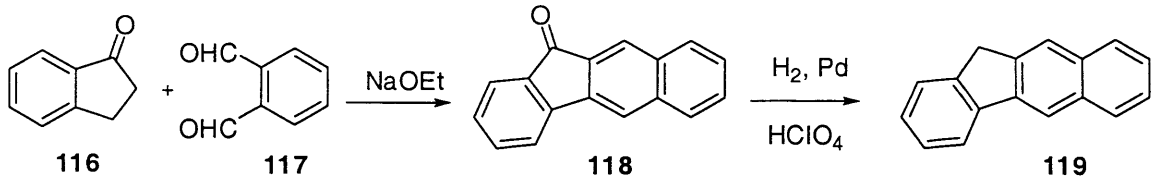


Figure 3: Benzofluorene-based natural products

The wide range of biological activities of these antibiotics as well as their mode of action has made them important synthetic targets. In recent years, several routes to the

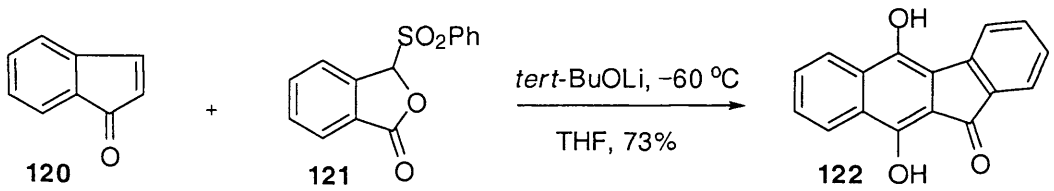
synthesis of naturally occurring benzo[*b*]fluorenes[66,76,77,78] and non-natural[49,79,85] aromatic benzo[*b*]fluorenes have been developed. Typically, methods based on [4+2] cycloaddition, Suzuki coupling, oxidative free radical cyclisation or Heck coupling have been employed.

In 1980, Bestmann described the preparation of 11*H*-benzo[b]fluorenone **118** by the reaction of hexaphenylcarbodiphosphorane with phthalaldehyde.[80] An alternative approach towards the 11*H*-benzo[b]fluorenone and related benzofluorenes was also reported by Streitwieser (Scheme 40). Despite slight differences in the precursor, condensation of 1-indanone **116** with phthalaldehyde **117** in the presence of sodium ethoxide at room temperature afforded 11*H*-benzo[*b*]fluorenone **118** in 50% yield. Subsequent hydrogenation of **118** with 5% palladium on carbon and 1 atmosphere hydrogen led to the corresponding benzofluorene **119**.[81]



Scheme 40: The synthesis of benzofluorene **119** by condensation of **116** and **117**

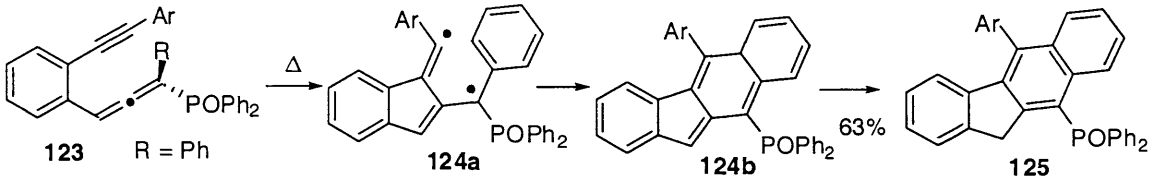
An alternative strategy targeting the Kinafluorenone scaffold was reported by Mal[82] in their formal synthesis of Kinamycin antibiotics. Treatment of the phthalide sulfone anion, prepared by deprotonation of **121** by *tert*-BuOLi at −60 °C, with a solution of **121** in THF, followed by acidic work-up resulted in a red amorphous solid of quinol **122** in 73% yield (Scheme 41).



Scheme 41: Synthesis of benzofluorenone by annulation of indenone **120** with phthalide sulfone **122**

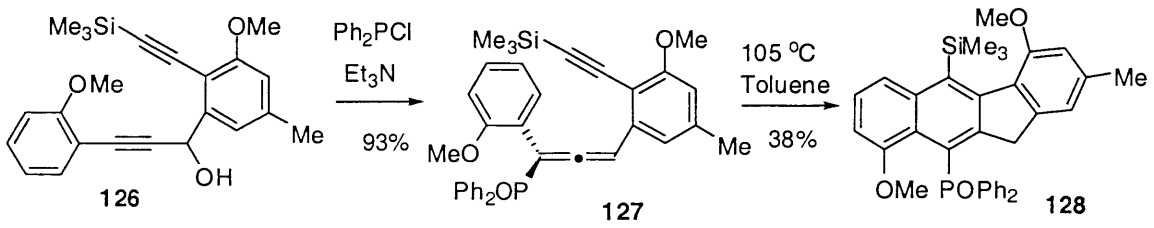
The thermal cyclisation of enyne allenes **123** to the corresponding benzofluorene **125** has been described by Schmittel and co-workers (Scheme 42). Numerous derivatives of

enyne allenes with various substitution patterns, which on heating generally furnish the expected Myers-Saito cyclisation products, have already been studied. However, the attachment of an aryl group to the alkyne terminus of the enyne allenes redirects the reaction course to a novel C_2—C_6 cyclisation, giving rise to formal ene and Diels–Alder products **125** via an unexpected biradical intermediate **124a** as depicted in Scheme 42. It was found that enyne allene type substrates **123** could easily lead to ene- and Diels-Alder-type products depending on the nature of group R.[83]



Scheme 42: Synthesis of benzofluorene **125** by intramolecular Diels–Alder reaction of enyne allenes **123**

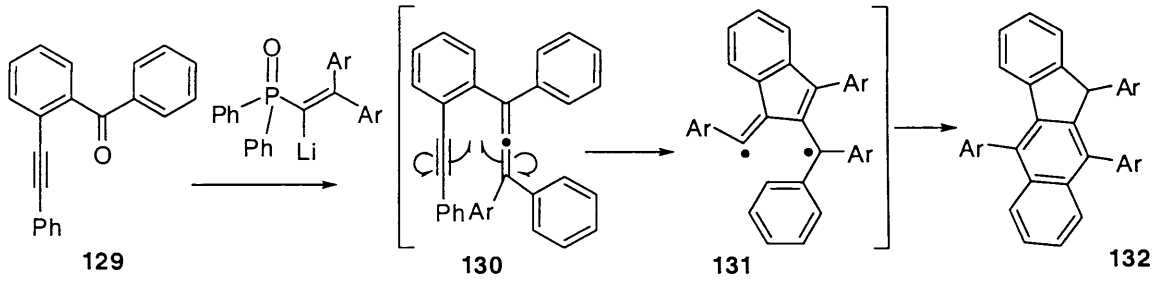
Echavarren and co-workers[84] demonstrated the cyclisation of trimethylsilyl alkynes connected to allenes by preferential [4+2] cycloaddition to form tetracyclic derivatives. Phosphorylation of **126** with Ph_2PCl and Et_3N followed by [2,3] sigmatropic rearrangement under typical reaction conditions (THF, −70 to −40 °C) gave the stable allene **127**, which could be purified by flash column chromatography (93% yield). Subsequent heating of **127** and excess 1,4-cyclohexadiene in toluene under reflux gave **128** in 38% yield (Scheme 43).



Scheme 43: The synthesis of **128** by an arylalkyne-allene cycloaddition

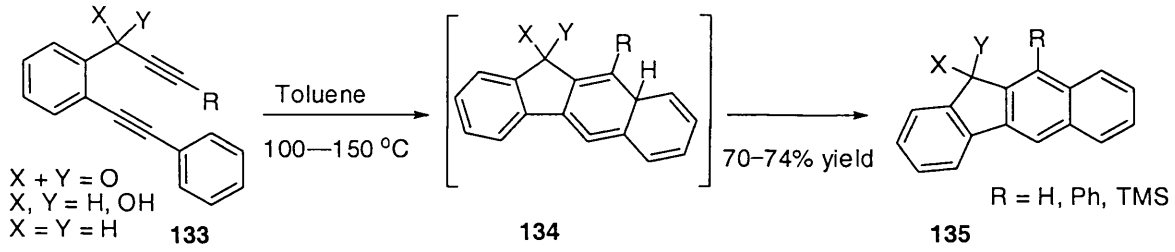
The use of the thermally-induced isomerisation reactions of organic molecules to generate the carbon-centered biradicals has several potential advantages over the conventional chemical or photochemical methods. This chemistry was subsequently employed for the synthesis of benzofluorenes by Wang and co-workers.[85] 2-(Phenylethynyl)benzophenone **129** was synthesised by the reaction of 2-(phenylethynyl)benzaldehyde with aryl magnesium bromide followed by oxidation

with PCC. The treatment of alkynyl benzophenone **129** with phosphinoxy carbanion produces 11*H*-benzo[*b*]fluorenes **132** under mild thermal conditions. This pathway is proposed to proceed by cycloaromatisation of ethyne allene **130** *via* biradical **131** is the real deriving force to form new carbon–carbon bonds. This transformation ultimately rendered 11*H*-benzo[*b*]fluorenes **132** efficiently through one-pot annulations as shown in Scheme 44.



Scheme 44: Thermolysis of benzoenyne-allenes to form biradicals and subsequent formation of benzofluorene **132**

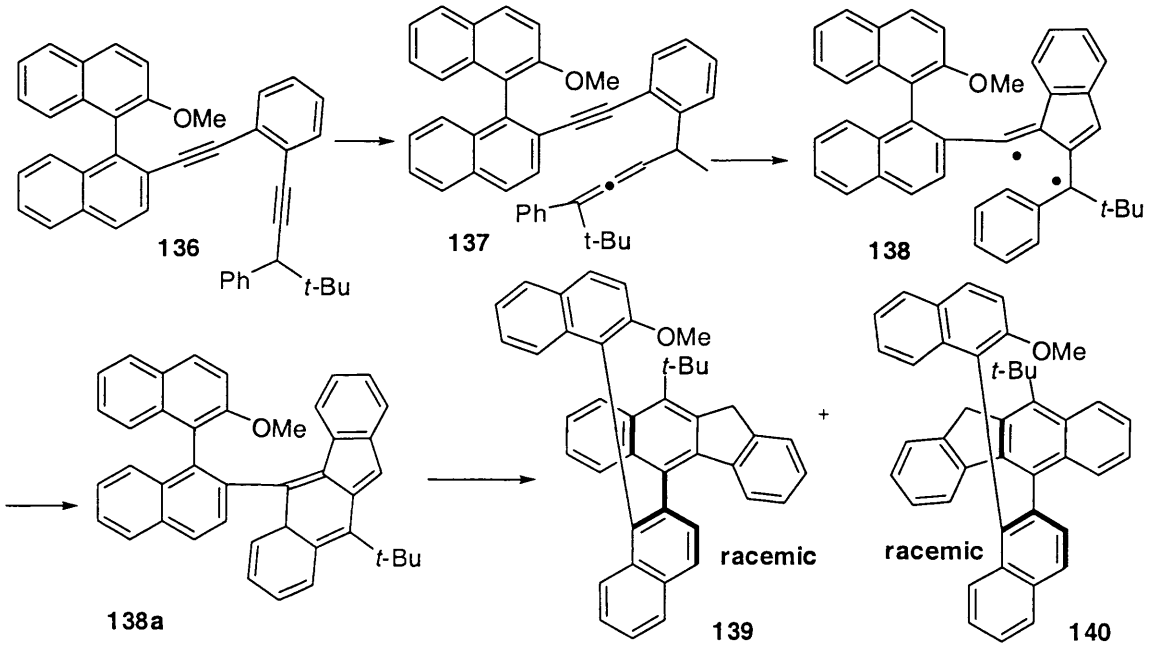
Domínguez and Saá[86] reported the thermal cyclisation of 2-propynyldiarylacetylenes **133** to benzo[*b*]fluorene derivatives **135** via a formal intramolecular [4 + 2] cycloaddition. The most striking feature was the hybridisation effect of the tether connecting alkynes **133** on the course of the reaction. They also studied the mechanism in detail by using theoretical calculations and isotopic labeling experiments. Overall, the reaction sequence involves the initial formation of a 1,4-vinyl biradical which then undergoes fast intramolecular coupling to a strained cyclic allene intermediate which then evolves into benzo[*b*]fluorene derivatives **135** (Scheme 45).



Scheme 45: Synthesis of benzo[*b*]fluorene derivatives **135** by intramolecular [4 + 2] cycloaddition reactions of diarylacetylenes

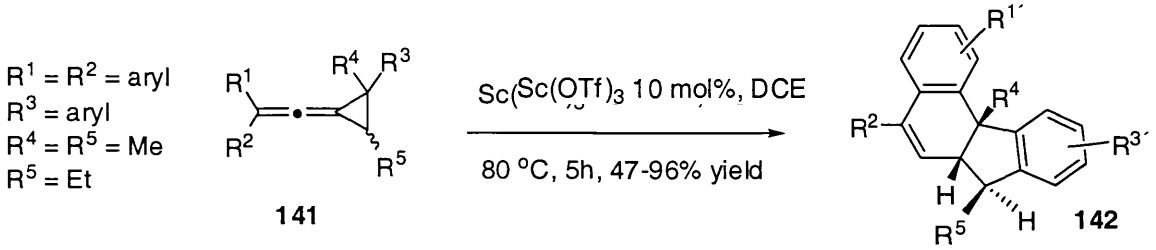
The Sonogashira reaction between 2-ethynyl-2′-methoxy-1,1′-binaphthyl and 1-iodo-2-[(trimethylsilyl)ethynyl]benzene and subsequent condensation with pivalophenone

followed by reduction with triethylsilane in the presence of trifluoroacetic gave the benzannulated enediyne substrate **136**. Treatment of **136** with potassium *tert*-butoxide in refluxing toluene for 5 h then produced an essentially 1:1 mixture of the two atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-methoxy-1,1′-binaphthyl, the *syn* atropisomer **139** (racemic) with the methoxyl group and the five-membered ring of the benzo[*b*]fluorenyl moiety *syn* to each other and the corresponding *anti* atropisomer **140** (racemic). Presumably, the transformation from **136** to **139** and **140** involved an initial 1,3-prototropic rearrangement to form the benzannulated enyne-allene **137** (Scheme 46). A subsequent Schmittel cyclisation reaction then generated biradical **138** for an intramolecular radical-radical coupling followed by prototropic rearrangement to produce **139** and **140**. The 5-benzo[*b*]fluorenyl substituent in **139** and **140** lacks symmetry elements and its two faces are heterotopic, making it possible to form the two atropisomers **139** and **140**. Treatment of the mixture of **139** and **140** with boron tribromide (BBr_3) furnished the corresponding demethylated products as well.[87]



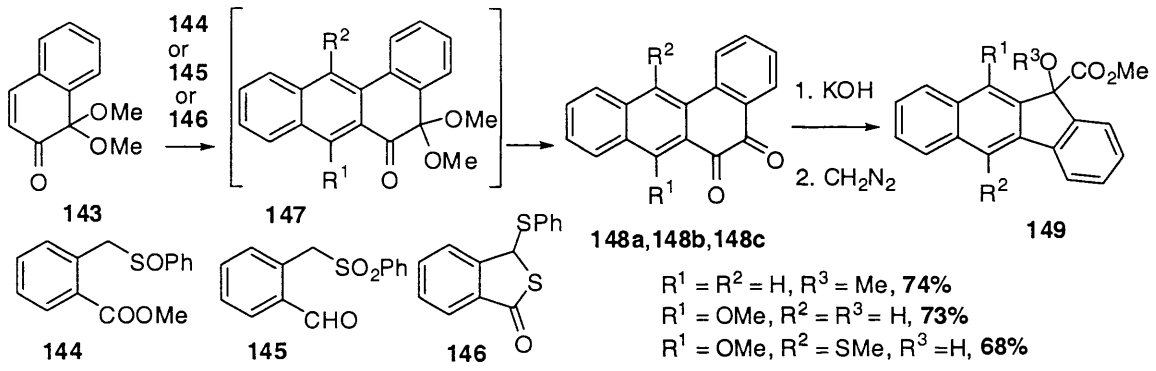
Scheme 46: Synthesis of the atropisomers of 2-(5-benzo[*b*]fluorenyl)-20-hydroxy-1,10-binaphthyl and related compounds

Shi and co-workers[88] reported the use of the aryl-substituted allenes of type **141** as precursors to naphthalene derivatives via interesting rearrangements. They have also shown that the Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes **141** is tolerant of substituents on the 1- and 2-positions of the cyclopropane ring in the synthesis of 6a*H*-benzo[*c*]fluorene. The treatment of arylvinylidenecyclopropanes **141** with 10 mol% scandium triflate in dry dichloroethane afforded 6a*H*-benzo[*c*]fluorene derivatives **142** in 47–96% yields. The Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes of type **141** provides a useful route to 6a*H*-benzo[*c*]fluorene derivatives via a double intramolecular Friedel-Crafts reaction (Scheme 47).



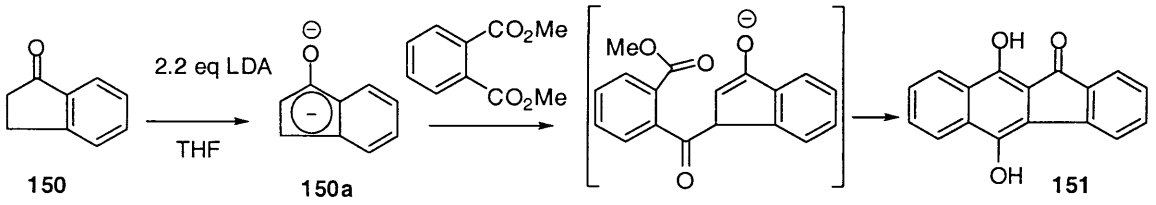
Scheme 47: Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes **141**

Mal and co-workers[89] described the synthesis of several benzofluorenes and benzofluorenones by annulation of **144**, **145** and **146** with naphthoquinone monoketal **143**. Condensation of **143** with **144** provided compound **148a** in 75% yield. Annulation of the compound **145** with quinone monoketal **143** was achieved under typical reaction conditions (lithium *tert*-butoxide in THF at –60 °C), followed by methylation and deketalisation gave compound **148b** in 73% yield. Similarly, thiophthalide **146** was condensed with quinone ketal **143**, treated with iodomethane and hydrolysed to provide benz[*a*]anthracene-5,6-dione **148c** in 68% yield. Reaction of compounds **148** with powdered potassium hydroxide in dioxane followed by treatment with diazomethane furnished the carboxylic ester **149** (Scheme 48). Subsequent conversion into benzo[*b*]fluorenone was also achieved by refluxing with chromium trioxide (CrO_3) in acetic acid.



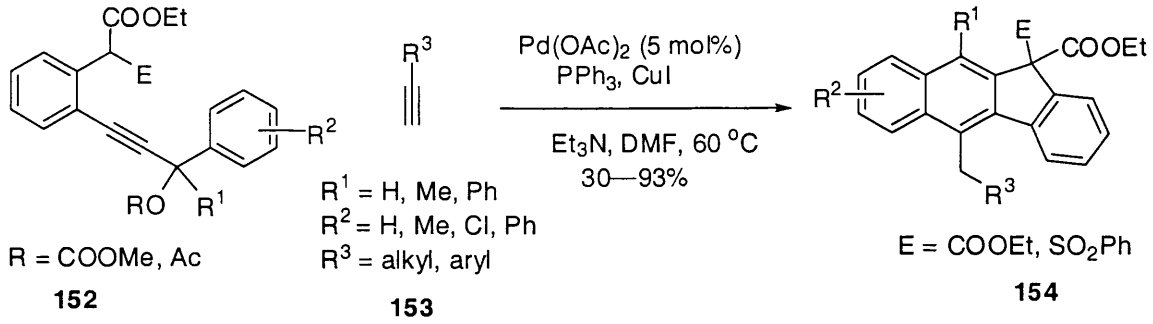
Scheme 48: Synthesis of benzo[*b*]fluorenones *via* ring contraction by benzil-benzilic acid rearrangement of benz[*a*]anthracene-5,6-diones **148**

A rapid approach to benzo[*b*]fluorenones **151** via the reaction of 1-indanone dianions **150a** with phthalate diesters is described by Birman and co-workers.[90] In the same communication, Birman also reported a concise synthesis of prekinamycin and its unnatural analogues. This approach provides a convenient synthetic access to benzo[*b*]fluorene derivatives (Scheme 49).



Scheme 49: Synthesis of benzo[*b*]fluorene **151** *via* indanone dianion annulation **150a**

Liang and co-workers[91] reported the palladium-catalysed reaction of propargylic compounds **152** with terminal alkynes **153**, which afforded a simple and efficient route to polycyclic aromatic compounds. The reaction described in Scheme 50 is catalysed by 5 mol% palladium acetate in dimethylformamide at 60 °C. Under these conditions, various benzo[*b*]fluorene derivatives **154** are formed in low to good yields (30—93%). Various propargylic derivatives and alkynes having a variety of substituents have been subjected to cyclisation and the corresponding benzofluorenes were found to be the exclusive products formed in good yields. This reaction involved a sequence of carboannulation, coupling, CH activation and C–C bond formation processes.



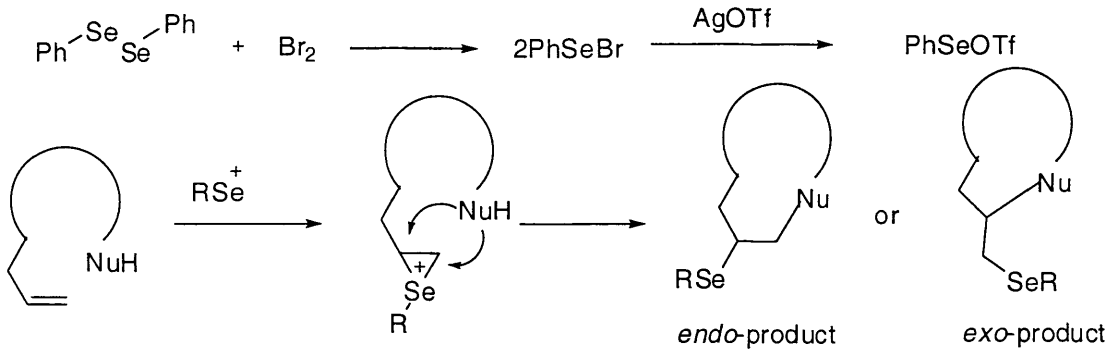
Scheme 50: Palladium-catalysed synthesis of benzofluorenes **154** from propargylic compounds with terminal alkynes via a biscyclisation process

In summary, this chapter demonstrated various approaches to achieving a variety of cyclisation reactions for the preparation of dihydronaphthalene and benzofluorene ring systems but this is limited to either transition metal or more traditional strategies such as an intramolecular aldol type reactions and rearrangements. Furthermore, dihydronaphthalenes and benzofluorenes have been synthesised from relatively expensive and difficult starting materials. The synthesis of some of these compounds has suffered low yields due to the formation of side products. Some good yields were obtained, however high temperature conditions were required to facilitate the reactions. Typically, different cyclisation strategies were employed to install various functional groups. Moreover, there have been no examples reported for the synthesis of dihydronaphthalenes and benzofluorenes using selenium electrophiles.

2.3 Aims of the Project

It has been well established that carbocyclisations can be achieved using various standard electrophiles. It is important to understand the chemical properties of organoselenium reagents, particularly selenium electrophiles, and note their behaviour in carbocyclisation reactions. The increasing number of publications within this field strongly reflects the high potential of selenium-mediated transformations and their usefulness in organic synthesis. Furthermore, despite the numerous reports about selenium-mediated transformations, few experimental investigations have been carried out to construct carbocycles using electrophilic selenium species.

Because of our keen interest in selenium-mediated cyclisations, a study published by Ley and coworkers in the 1980s on the remarkably efficient transformation of alkenyl β-ketoester into the corresponding carbocycles and heterocycles caught our attention. Dihydronaphthalenes are important intermediates for many synthetic targets and, therefore, our efforts were directed to accomplish the synthesis of dihydronaphthalene ring systems. In planning the synthesis of dihydronaphthalene, we identified two problems that required special consideration: one was the formation of a mixture of products in the presence of a Lewis acid; the other was a constraint through the need for basic reaction conditions required for the substrate deprotonation. We felt that both of these problems could be resolved by employing an appropriate substrate.



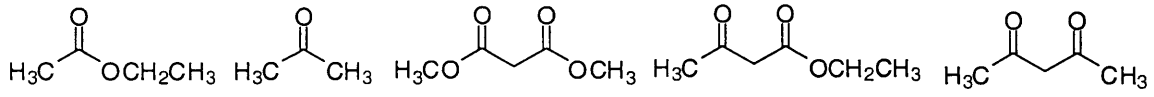
Scheme 51: Activation of alkenes by a selenium electrophile and subsequent addition of an internal nucleophile

To avoid the addition product, a selenium electrophile with non-nucleophilic counter-ion such as triflate was proposed. Addition of a selenium electrophile to the double bond would form the seleniranium ion and then intramolecular addition of the internal

carbon nucleophile to the seleniranium ion can produce *exo* and/or *endo* products. The formation of these products could be selective under kinetic or thermodynamic control. The preferential formation of the 6-membered over the 5-membered product by a selenium electrophile could control the selectivity as well.

2.3.1 Concept and Design of Substrates

The presence of an electron withdrawing group on a C–H moiety enhances the acidity of that hydrogen. The carbonyl group is a typical electron withdrawing group and the ability to increase the acidity of proton is shown to follow the pKa order (Figure 4.1).



ethyl actate	acetone	dimethyl malonate	ethylacetoactate	acetylacetone
pKa = 25	pKa = 20	pKa = 13	pKa = 10.7	pKa = 8.9

Figure 4.1: pKa values of different carbonyl compounds

Under basic or acidic conditions, α-carbon of the carbonyl group can serve as an internal nucleophile attacking the electron deficient alkene-selenium complex. It would be very attractive synthetically to design a substrate having a double bond along with a carbon that would be enolisable. Removal of that proton by a base generates a carbanion, and the more synthetically useful carbanions are usually stabilised by an adjacent eletron withdrawing group such as a carbonyl group (ketones, aldehydes, esters). Strong bases such as organolithium reagents are usually required to generate the carbanion. With the enhancement in acidity induced by the presence of two carbonyl groups, much weaker bases can be used for deprotonation. It is notable that many of the substrates shown in Figure 4.2 contain an element of "bifunctionality", where the role of the electrophilic selenium reagent is coupled with a potential carbon–carbon double bond activator and the subsequent attack of an internal nucleophile. This observation has been critical in designing appropriate substrates for this process.

Intramolecular cyclisation is a powerful method for the construction of carbocycles. We proposed that an intramolecular cyclisation of alkenyl β-dicarbonyl substrates, using selenium electrophiles, would produce a range of smaller carbocyclic ring systems. In the proposed reaction, the selenium functionality would be attached by

employing a combination of base and selenium electrophile. Alkenyl 1,3-dicarbonyl substrates could react to form either the carbocyclisation product or the addition product (Figure 4.2).

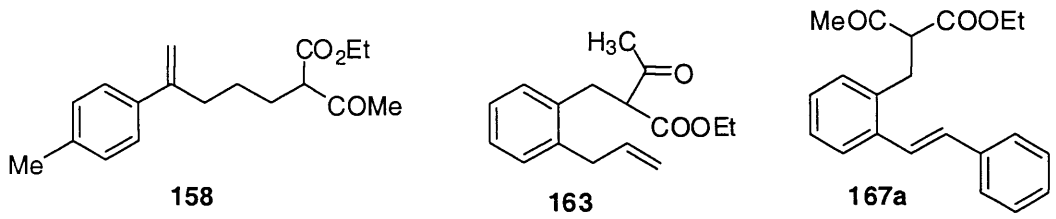


Figure 4.2: Substrates bearing enolisable carbon that can act as a carbon nucleophile

By employing a stilbene derivative as a precursor, the formation of a 6-membered ring would be easier than in the corresponding styrene. The seleniranium ion derived from the styrene would electronically direct the formation of a 5-membered ring. The extra aryl group in the stilbene should overcome this effect allowing product selection to be determined only by ring-size factors. The close proximity of the aryl group to the acetyl moiety can allow an intramolecular Friedel-Crafts type reaction. The intramolecular cyclisation of stilbenes generates a range of dihydronaphthalenes using an enolate as the internal nucleophile. The resulting dihydronaphthalenes would be used as substrates for a second ring forming reaction (Figure 4.3).

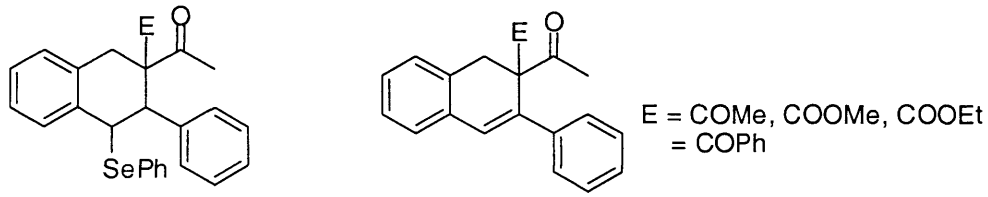


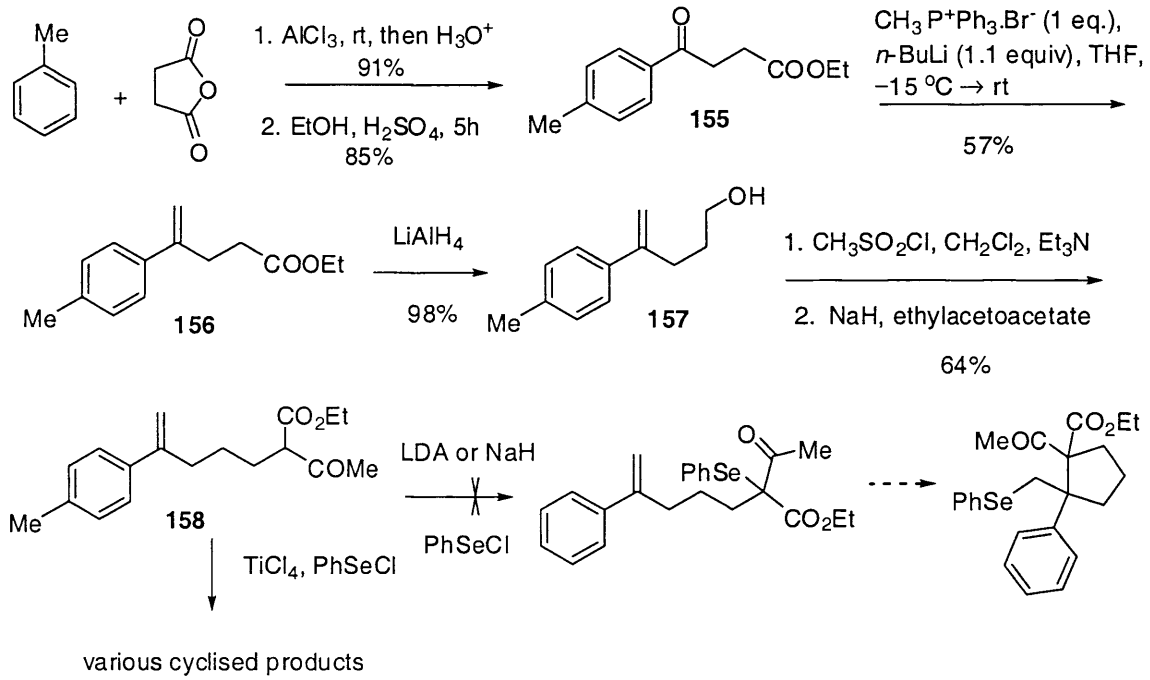
Figure 4.3: Tetrahydronaphthalene and dihydronaphthalene derivatives

Following up on this path-finding strategy we began to explore selenium chemistry into a straightforward synthesis of carbocycles. Use of Lewis acid-mediated enolisation and selenium electrophilic activation of alkenes might allow the construction of carbocycles. Dihydronaphthalene bearing acetyl functional groups could possibly participate in intramolecular Friedel-Crafts reaction with electron-rich aromatic rings also present in the compond to effect a double intramolecular cyclisation. The advancement of such methodologies should diminish the effort generally needed to access such structurally diverse molecules.

2.4 Results and Discussion

2.4.1 Synthesis of Dimethyl 2-(4-*p*-tolylpent-4-enyl)malonate and Attempt Towards Cyclisation

Literature procedures[92] were used for the synthesis of the substrate **158**. 4-(4′-Methylphenyl)-4-oxobutyric acid ethyl ester **155** was prepared in good yield under Friedel-Crafts reaction conditions (Scheme 52). Transformation of the ketone group of compound **155** into a methylene double bond was achieved by treatment with methylenetriphenylphosphorane (Wittig reaction) to furnish **156** in 57% yield. Reduction of the ester with lithium aluminium hydride in diethylether yielded the corresponding alcohol **157**, which was then converted into a good leaving group by treatment with methanesulfonyl chloride at room temperature to give the mesylate. Subsequent reaction of the mesylate with the sodium salt of the malonic ester furnished **158** as a yellow oil in 64% yield after flash chromatography.



Scheme 52: Synthesis of **158** and subsequent attempts toward carbocyclisation

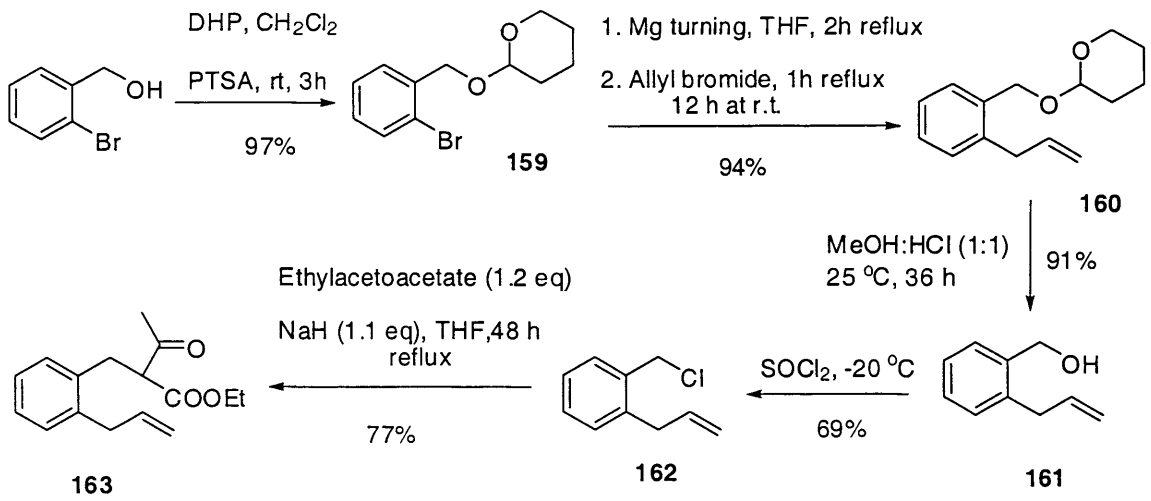
To test the reactivity of selenium for the proposed electrophilic carbocyclisation strategy, the reaction of the proposed substrate **158** with a selenium eletrophile in dichloromethane at −78 °C was investigated. Exposure of the substrate to electrophiles without the addition of base usually resulted in starting material being recovered along

with a quantitative yield of diphenyl diselenide – selenenylation of the α-carbon of a 1,3-dicarbonyl was unsuccessful when phenylselenium triflate was used. This suggests that the triflate counterion is not sufficiently basic to deprotonate the α-carbon. To achieve the selenenylation, the enolate would need to be produced using a base before exposure to the selenium electrophile. Sodium hydride and lithium diisopropylamide seem to be basic enough to abstract acidic protons from **158** and can furnish selenenylation. However, under these reaction conditions (NaH or LDA, PhSeCl, −78 °C), selenenylation was unsuccessful. With this in mind, we briefly screened Lewis acid-mediated reactions for the carbocyclisation reaction and found that it can proceed in combination with phenylselenenyl chloride. The substrate **158** was treated with phenylselenenyl chloride in the presence of titanium tetrachloride; the formation of a mixture of cyclised products was detected by ^{1}H NMR. These Lewis acid-mediated reaction conditions provided various cyclic products that were difficult to isolate.

2.4.2 Synthesis of Ethyl 2-(2-Allylbenzyl)-3-oxobutanoate 163

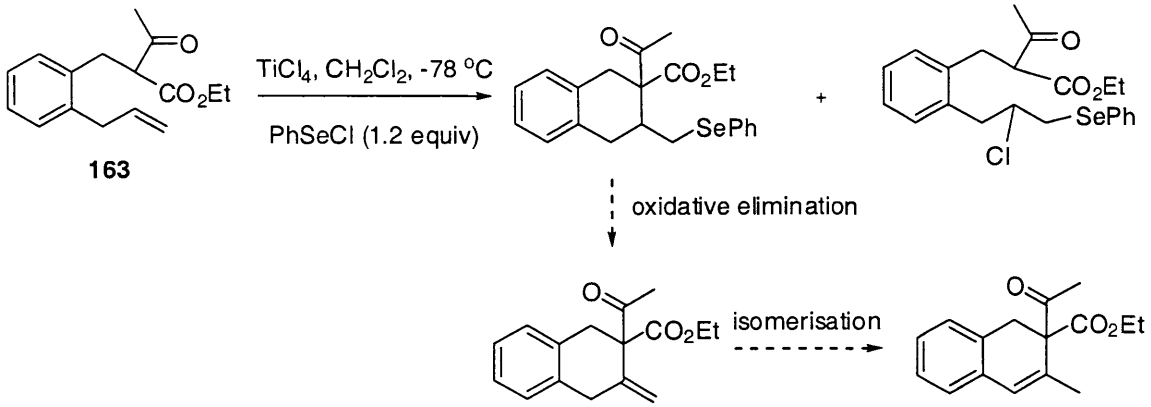
Our key task was the development of a carbocyclisation process for the synthesis of dihydronaphthalenes from alkenes containing carbon nucleophiles. The nature of the substrate **158** precludes its use in selenium-mediated cyclisation. However, substrate **163** is capable of being transformed into a 6-membered carbocycle because formation of the 7-membered ring is kinetically difficult.

In the synthesis of the allyl substituted substrate **163**, the hydroxy group of 2-bromo benzylalcohol was protected with a THP protecting group in order to perform the safe preparation of the Grignard reagent. The alcohol was reacted with dihydropyrane in the presence of *p*-toluenesulfonic acid to give the THP derivative **159** in very good yield. Treatment of **159** with Mg turnings in THF under reflux resulted in the corresponding Grignard reagent and subsequent S_N2 reaction with allyl bromide furnished coupling product **160** in quite good yield. The removal of the THP protecting group under mild acidic conditions at room temperature gave 2-allyl benzyl alcohol **161** in 91% yield, which upon treatment with methanesulfonyl chloride and triethylamine in the presence of lithium chloride under reflux provided 2-allyl benzylchloride **162** in a one pot manner. The reaction of 2-allyl benzylchloride with ethylacetoacetate in the presence of sodium hydride under reflux afforded desired substrate **163** in 77% yield (Scheme 53).



Scheme 53: Synthesis of substrate **163**

We attempted to cyclise substrate **163** to tetrahydronaphthalene using titanium tetrachloride and phenylselenenyl chloride at –78 °C as described in Scheme 54 but none of the desired cyclised product was isolated. Unfortunately, the reaction of **163** with phenylselenenyl triflate proved to be vigorous and lead to decomposition even at –78 °C. In addition, phenylselenenyl triflate proved to be unsatisfactory for cyclisation under variety of conditions such as those shown in Scheme 54. However, all chosen reaction conditions failed to effect selective carbon-carbon bond formation. Some alternative conditions for this reaction, such as use of $BF_3 \bullet OMe_2$ and phenylselenyl chloride led to formation of various products. The reaction generally favors carbon—carbon bond formation at the more substituted carbon of the alkene (the branched product) although several factors can reverse this trend. The use of a Lewis acid in conjunction with the selenium electrophile yields a mixture of cyclised products but the utility of this cyclisation was greatly reduced due to difficulty in chromatographic separation of the desired product from unidentified byproducts.



Scheme 54: Attempts towards 6-*exo-trig* carbocyclisation

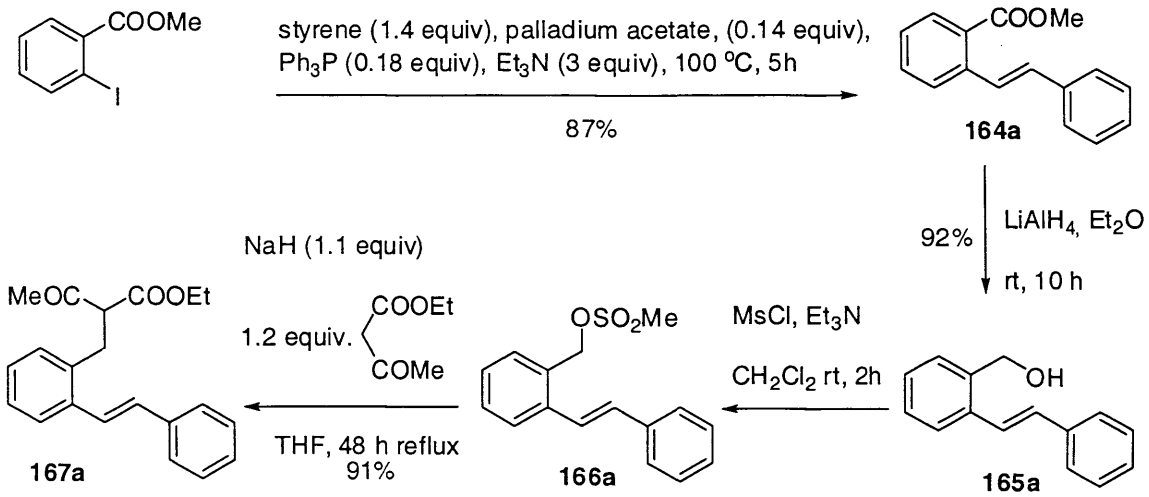
2.4.3 Conclusion

During the course of investigation of the electrophilic cyclisation of alkenyl dicarbonyl type substrate **163**, it was unfortunately discovered that the above reaction was unsuccessful for the synthesis of 6-membered carbocycles (Scheme 54). This may be because the substrate chain length is not appropriate to provide the selective formation of a six membered ring. In addition, the allyl group is more prone to form the addition product than cyclisation; however a mixture of products is formed from this substrate under various conditions. As a result it was not possible to synthesise benzoannulated products using selenium electrophiles.

2.4.4 Modification of Substrate and Successful Cyclisation

Unfortunately, problems were encountered with previous substrates **158** and **163** to effect carbocyclisation. It was decided that attention should be directed towards design of alternative substrates that may promote the desired reactions. Alkenes containing a functional group that can act as an internal nucleophile at an appropriate distance from the carbon–carbon double bond should undergo intramolecular cyclisations to generate a wide variety of dihydronaphthalenes. The choice of reaction conditions and selection of the substrate is crucial for the success of this process. Incorporation of an ethylacetoacetate moiety adds one more carbon to the substrate chain length. In addition, the central carbon of the 1,3-dicarbonyl functionality is versatile enough to act as a nucleophile and many functional group transformations are possible allowing access to a diverse range of products.

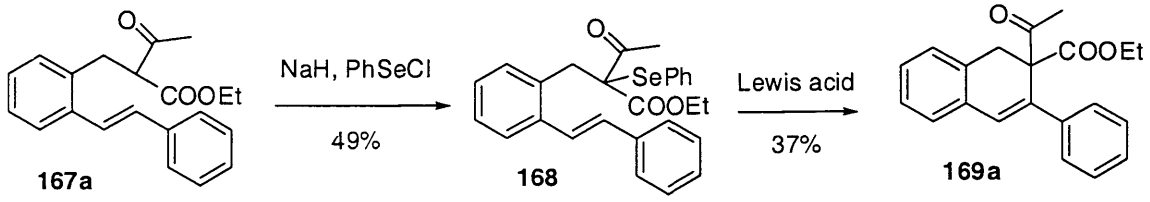
Synthesis of a new precursor, **167a**, started by preparing methyl 2-styrylbenzoate by Heck coupling[93] of methyl 2-iodobenzoate with styrene, using palladium acetate [$Pd(OAc)_2$], triphenylphosphine (Ph_3P), and triethylamine at 100 °C for five hours. The yield of this process is quite high and can readily accommodate considerable functionality (Scheme 55). The reduction of methyl 2-styrylbenzoate **164a** with lithium aluminium hydride provided the corresponding alcohol **165a** in good yield without the concomitant reduction of the stilbene double bond. The alcohol **165a** was converted to the mesylate followed by subsequent condensation of the mesylate with the sodium salt of ethyl acetoacetate under reflux furnishing the desired stilbene substrate **167a** in good yield (Scheme 55).



Scheme 55: Synthesis of target substrate **167a**

The presence of an acetyl group lowering the pKa value of proton attached to the α-carbon of the carbonyl group in substrate **167a** makes this substrate slightly more reactive towards deprotonation and subsequent selenenylation. Deprotonation of stilbene **167a** was accomplished with sodium hydride, and subsequent treatment with phenylselenenyl chloride led to the formation of the desired precursor **168** in 49% yield along with recovery of starting material **167a**. The use of sodium hydride in conjunction to phenyl selenenyl chloride with the stilbene substrate **167a** proved that these reaction conditions were able to promote the attachment of the selenium functionality to the α-carbon of the carbonyl group in the stilbene substrate. Unfortunately, decomposition into starting material and diphenyldiselenide was observed when intermediate **168** is allowed to stand at room temperature or even at 0 °C, however the mixture could not be separated at this point and thus was carried

forward (Scheme 56). The newly formed intermediate can be readily transformed into the cyclic product upon treatment with a Lewis acid as shown in Scheme 56. This intermediate underwent selective *6-endo-trig* cyclisation using 1.5 equivalents titanium tetrachloride followed by an elimination, cyclic product dihydronaphthalene **169a** being readily isolated by flash chromatography in 37% yield (Table 1, entry 1).

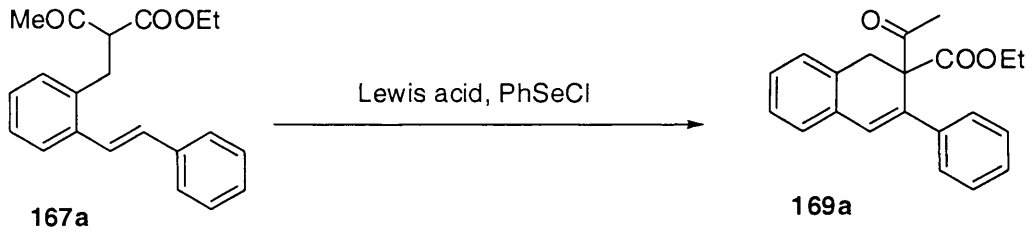


Scheme 56: New mode of carbocyclisation

The cleavage of the selenium-carbon bond mediated by the Lewis acid could lead to the *in situ* formation of a selenium electrophile, which would subsequently activate the double bond for the carbocyclisation. Although the overall yields are quite low, the synthetic utility of this reaction could be markedly enhanced if the preparation of the enolate and its subsequent *6-endo-trig* carbocyclisation could be carried out as a one-pot process from the stilbene substrate.

2.4.5 Optimisation of One Pot Synthesis of Dihydronaphthalene

At this stage, substrate **167a** was used as a model system for further optimisation of the reaction conditions. A new strategy was adapted to improve the yields; therefore we focussed on a direct approach for the synthesis of dihydronaphthalene **169a** without preparing the intermediate **168** as shown in Scheme 57.



Scheme 57: Direct synthesis of dihydronaphthalene **169a** from **167a**

Table 1: Optimisation of reaction conditions

Entry	Substrate	Reagents	Time [h]	Yield [%]
1	**168**	$TiCl_4$ (1.5 equiv.)	16	37
2	**168**	$SnCl_4$ (2.0 equiv.)	16	35
3	**167a**	$SnCl_4$ (2.0 equiv.)	144	0
4	**167a**	$TiCl_4$ (2 equiv), PhSeCl (1.1 equiv.)	16	86
5	**167a**	$SnCl_4$ (2 equiv), PhSeCl (1.1 equiv.)	16	77
6	**167a**	$BF_3 \bullet OMe_2$ (2.0 equiv.), PhSeCl (1.1 equiv.)	22	90

Treatment of stilbene substrate **167a** with phenylselenenyl chloride in the presence of $TiCl_4$ afforded dihydronaphthalene **169a** in 86% yield *via* a cyclisation/elimination one-pot sequence without formation of the intermediate **168** as shown in Scheme 57 (Table 1, entry 4). The reaction was monitored by TLC, after 3 hours stirring at −78 °C to 0 °C the presence of starting material was still observed. The cooling bath was removed and the reaction was stirred at room temperature for a further 12 hours. The only product was separated by column chromatography in 86% yield and its structure was characterised as dihydronaphthalene **169a** (for details see experimental section). The sample from the one-pot sequence exhibiting spectral characteristics identical to that obtained from the previous reaction sequence (see Scheme 56). The direct synthesis of dihydronaphthalene is consequently highly valuable from the standpoint of atom economy and the direct use of a Lewis acid and selenium electrophile in carbocyclisation is not precedented. The cyclisation does not occur in the absence of the selenium electrophile and only starting material was recovered quantitatively (Table 1, entry 3). The combination of boron trifluoride dimethyl etherate and phenylselenenyl chloride (Table 1, entry 6) was found to be the optimal reaction conditions leading to the expected dihydronaphthalene compound **169a** in 90% yield. The structure of **169a** was additionally confirmed by X-ray crystallographic analysis (Figure 5, see detail in Appendix 2.1).

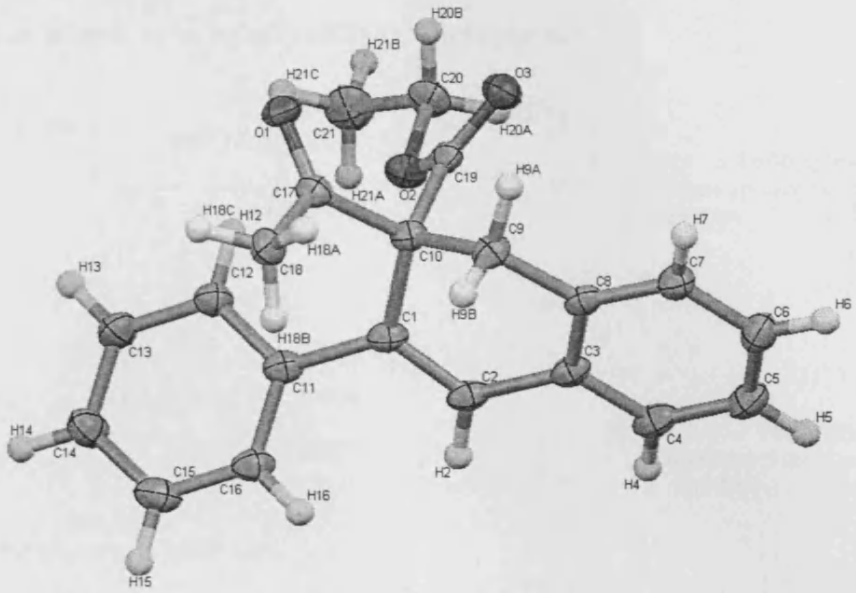
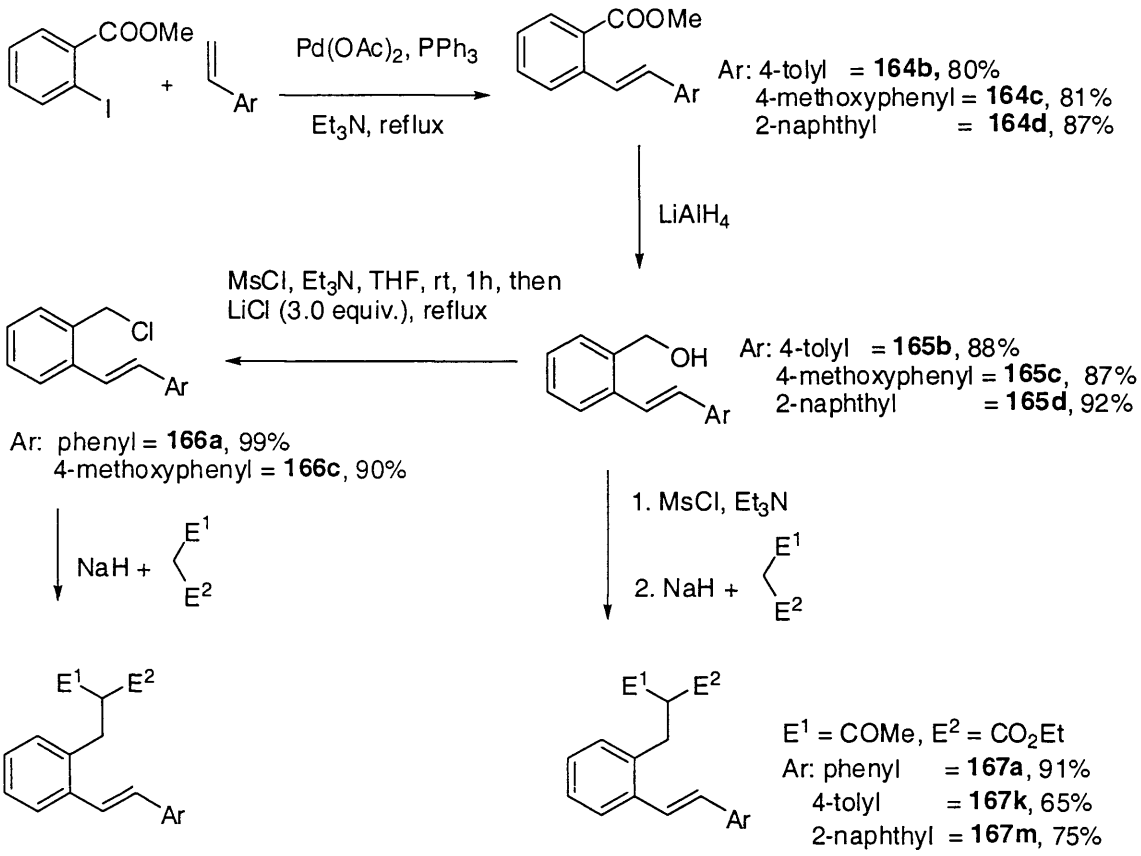


Figure 5: Crystal structure of dihydronaphthalene **169a**

2.4.5.1 Scope of the Reaction

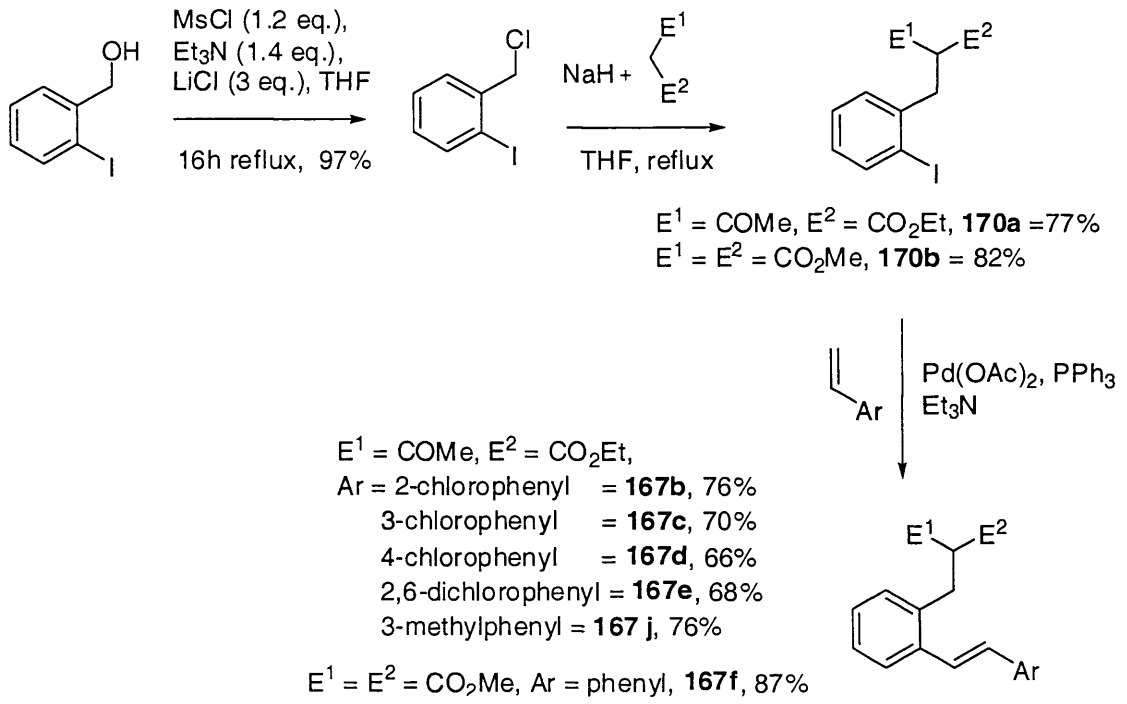
Having found suitable conditions, the effect of the substituents on the cyclisations was further explored. In an effort to cover other functional groups containing stilbenes, several substituted stilbenes have been synthesized using a Heck coupling strategy. The general scheme employed by us for the synthesis of substrates involves the Heck coupling of substituted styrenes with methyl 2-iodobenzoate (Scheme 58). The resulting esters were reduced to alcohols using lithium aluminium hydride and subsequent mesylation was achieved by the treatment of alcohols with methanesulfonyl chloride in the presence of triethylamine. The condensation of the mesylate with the sodium salt of ethylacetoacetate or methyl malonate under reflux provided the desired substrate in good yields. Unfortunately, in the case of alcohol **165c**, we obtained a mixture of mesylate and alcohol in a 2:3 ratio after extraction with diethyl ether followed by washing with water. Under usual work-up conditions, the mesylate was hydrolysed to the corresponding alcohol probably due to the lower stability of the mesylate. We therefore changed our reaction sequence; the alcohol was reacted with methanesulfonyl chloride in the presence of triethylamine in THF as solvent, followed by the addition of lithium chloride and reaction mixture was heated at reflux for 20 h

resulting in the corresponding chloride in a one-pot reaction. Finally, compound **167h–167j** were prepared in 85–96% yield in a similar way to **167a**, **167b**, **167d** and the reaction proved to be equally efficient (Scheme 58).



Scheme 58: Synthesis of substrates **167**

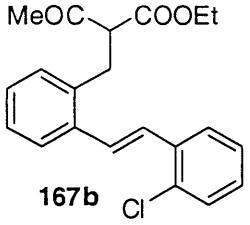
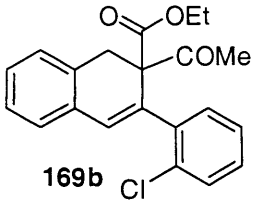
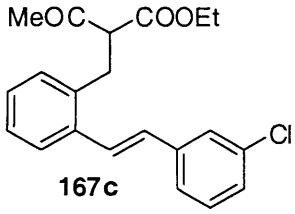
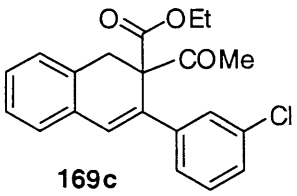
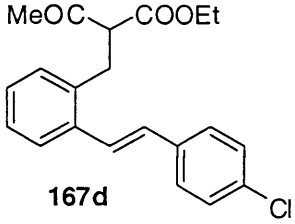
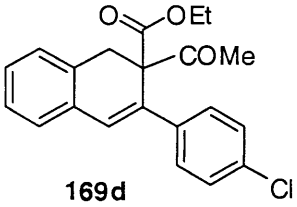
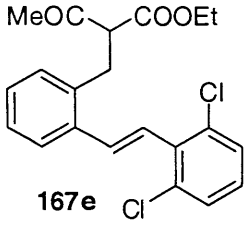
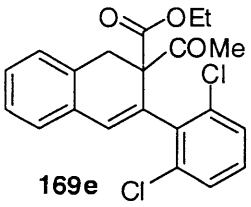
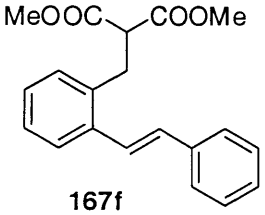
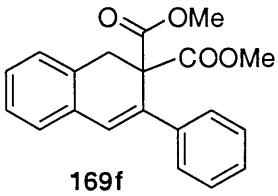
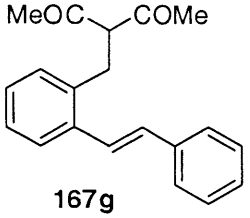
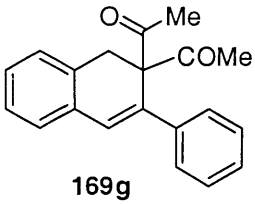
Further investigations regarding the synthesis of substrates were undertaken, and an easy synthetic route was started from 2-iodobenzyl alcohol, establishing another independent route to target substrates **167e**, **167f**, **167g**, **167h** and **167i** (Scheme 59). Conversion of 2-iodobenzyl alcohol to the corresponding chloride was achieved by treating the alcohol with MsCl in the presence of lithium chloride under reflux for 16 h, affording 2-iodobenzyl chloride in 98% yield. Ethyl 2-(2-iodobenzyl)-3-oxobutanoate was then obtained by the reaction of the sodium salt of ethylacetoacetate with 2-iodobenzyl chloride in THF under reflux. Treatment of ethyl 2-(2-iodobenzyl)-3-oxobutanoate with different styrenes in a Heck coupling reaction at 90 °C furnished desired substrates **167e–167i** in 66–87% yield.



Scheme 59: Alternative synthetic route to substrates **167**

The stilbene substrates are then subjected to carbocylisation, and the resulting dihydronaphthalene is generally isolated in good to excellent yields as shown in Table 2. For example, treatment of chlorosubstituted stilbene **167b** with 2.0 equivalents of Lewis acid and 1.2 equivalents of phenylselenyl chloride at −78 °C, gave the corresponding dihydronaphthalene **169b** essentially as a single product in 74% yield (Table 2, entry 1). Various other substrates of type **167** have been cyclised in such a selenium-mediated reaction and dihydronaphthalene derivatives **169b–169g** have been obtained as shown in **Table 2**. Upon treatment of the diester-substituted stilbene **167f** with phenyl selenenyl chloride and $BF_3 \bullet OMe_2$, the standard protocol failed entirely to give the desired product (Table 2, entry 5). However, after exposure of stilbene **167f** to selenium electrophile under strong Lewis acid conditions for 36 hours at room temperature, the corresponding dihydronaphthalene **169f** was isolated in 50% yield along with 41% recovery of starting material (Table 2, entry 5). Upon increasing the amount of phenylselenenyl chloride up to 2.0 equivalents; the yield could be further improved to 70%, albeit at the expense of an extended reaction time (Table 2, entry 5).

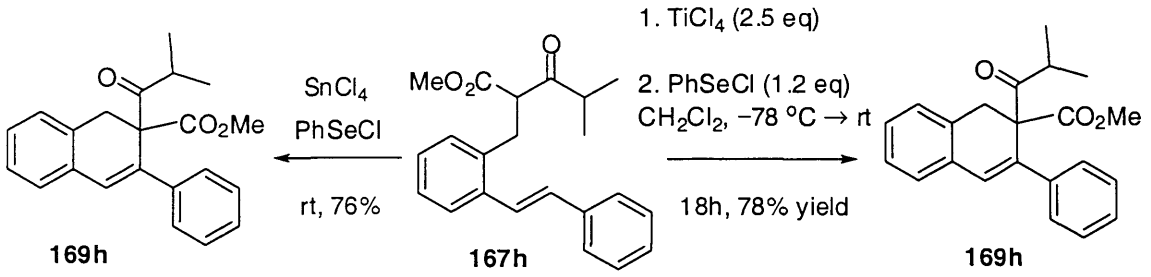
Table 2: Synthesis of dihydronaphthalenes **169b–169g**

Entry	Substrate [4]	Product [6]	Time [h]	Yield [%]
1	 **167b**	 **169b**	16	74
2	 **167c**	 **169c**	16	68
3	 **167d**	 **169d**	22	78
4	 **167e**	 **169e**	16	82
5	 **167f**	 **169f**	50 36 40	0[a] 50[b] 70[b]
6	 **167g**	 **169g**	3h	73[b]

Reaction conditions: $BF_3.OMe_2$ or $SnCl_4$ (2 equiv), –60 °C, 15 min, then PhSeCl (1.2 equiv.), –60 °C → RT. (a) $BF_3.OMe_2$, 20 °C, 15 min, then PhSeCl (2.0 equiv.). (b) $SnCl_4$ or $TiCl_4$, –60 °C, 15 min, then PhSeCl (1.2 equiv.), –60 °C → RT. (c) $SnCl_4$ or $TiCl_4$, –60 °C, 15 min, then PhSeCl (2 equiv.), –60 °C → RT.

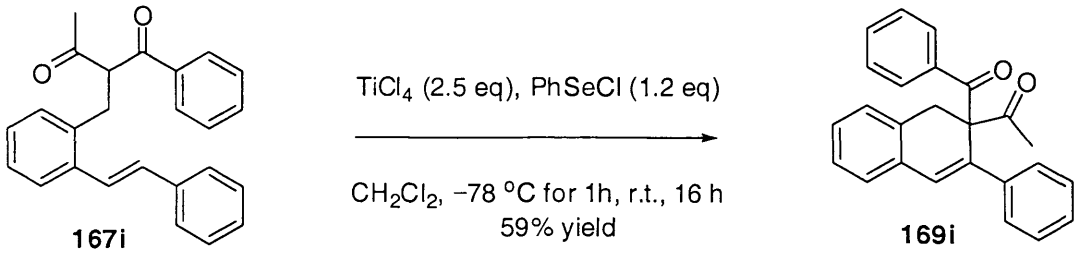
The diacetyl-substituted stilbene **167g** was found to be more reactive under the optimised the reaction conditions and the reaction of the Ti-enolate derived from stilbene **167g** with phenyl selenenyl chloride resulted in the corresponding dihydronaphthalene **169g** within three hours reaction time in 73% yield (Table 2, entry 6). Varying the Lewis acids $SnCl_4$ to $TiCl_4$ led to only a negligible increase in yield (Table 2, Entry 1–2, 4–5).

As it could be expected from the optimisation studies, isopropyl carbonyl-substituted stilbene **167h** was appropriate for selective *6-endo-trig* carbocyclisation which also underwent carbocyclisation on treatment with phenyl selenenyl chloride to give corresponding dihydronaphthalene **167h** in 78% yield (Scheme 60).



Scheme 60: Isopropyl carbonyl substituted synthesis of dihydronaphthalene

The carbocyclisation of stilbene **167i** with a bulky group using standard protocols proved troublesome at first; however by maintaining the reaction temperature at –78 °C for one hour the corresponding dihydronaphthalene was formed in 59% yield (Scheme 61). As an alternative, a number of reaction conditions were surveyed, starting with the standard protocol, which afforded the desired dihydronaphthalene **169i** in relatively low yield along with the recovery of starting material and other unknown by-products. In the presence of benzoyl functionality, the cyclisation mode was significantly exacerbated and the overall yield decreased significantly.

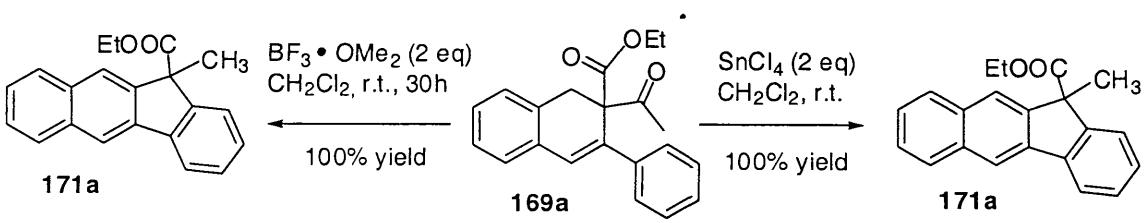


Scheme 61: Benzoyl substituted dihydronaphthalene **169i**

An interesting feature of this approach is the fact that selenium-mediated carbocyclisation using a various stilbenes as precursors of dihydronaphthalnes were used successfully for the construction of dihydronaphthalene units via addition/elimination sequence under very mild reaction conditions. Stilbene substrates (Table 2, entries 1–5) tolerated substitution at any position of the aromatic ring, and both electron-donating and electron-withdrawing functionalities were compatible.

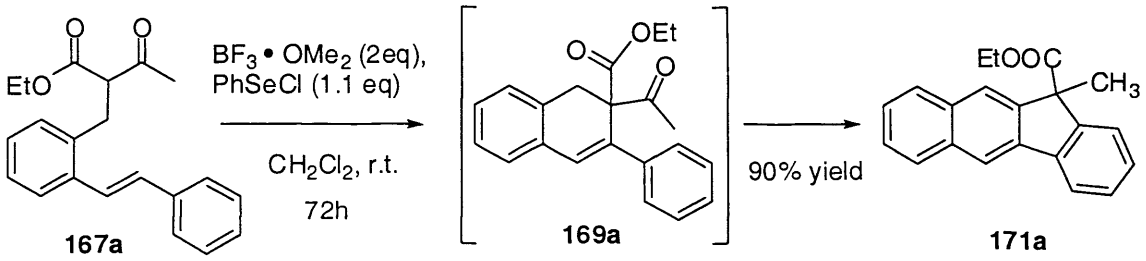
2.4.5.2 Further Manipulation of Dihydronaphthalenes Ring into Benzofluorenes

The resulting dihydronaphthalenes were then used as the starting materials for further elaboration because acetyl containing products can be further diversified by using a number of subsequent Lewis acid-catalysed Friedel-Crafts acylation processes. After the successful synthesis of dihydronaphthalenes with acetyl functional groups, as strongly electrophilic species, acetyl functional group can also participate in Friedal-Crafts acylation reaction with electron-rich aromatic rings. Accordingly, the C10—C11 bond formation could take place in an intramolecular fashion from the corresponding dihydronaphthalene. Therefore, treatment of the dihydronaphthalene with a Lewis acid should conveniently allow accessing a new carbocycle. With the methodology to access the dihydronaphthalene in hand, the treatment of dihydronaphthalene derivative **169a** with tin tetrachloride in dichloromethane at −78 °C for 30 hours, followed by quenching of the reaction mixture with water afforded benzofluorene **171a** in quantitative yield as a single product after flash chromatography. Similarly, when exposed to boron trifluoride dimethyl etherate for a longer time, we observed that dihydronaphthalene **169a** underwent a subsequent Friedel-Crafts-type cyclisation through a novel rearrangement and we were pleased to isolate the desired tandem product (Scheme 62).



Scheme 62: Use of the intramolecular Friedel-Crafts reaction for the synthesis of benzofluorene **171a**

At this juncture our attention switched to the use of one-pot reaction sequence for which same course of reaction may offer benzofluorene **171**. Therefore, we began our modification in the above-mentioned methodology by treating a stilbene **167a** as precursors to the same dihydronaphthalene **169a**, with phenyl selenenyl chloride in the presence of tin tetrachloride resulting in the formation of tetracyclic ring system **171a** (Scheme 63).



Scheme 63: Selenium and Lewis acid-mediated tandem reaction to benzofluorene

Upon the addition of boron trifluoride dimethyl etherate at −60 °C and subsequent addition of phenylselenenyl chloride, compound **167a** was converted into dihydronaphthalene **169a**, as observed by ^{1}H NMR analysis of the crude reaction mixture after 12 hours of stirring at room temperature. If the compound **167a** is exposed for a longer time (3 days) to boron trifluoride dimethyl etherate at room temperature, the rearrangement to a tetracyclic compound occurred and was isolated in good yields (Scheme 63). The reaction time is critical for obtaining the products from a double carbocyclisation process. For an additional investigation into the mechanism of the tandem double cyclisation reaction, dihydronaphthalene **169a** was treated with boron trifluoride dimethyl etherate and led to the tetracyclic product in quantitative yield as shown in Scheme 62. With dihydronaphthalene **169f**, however, the same reaction protocol failed to afford the tetracyclic product even after a reaction time of one week. It seems that the subsequent reaction cascade is sensitive to the electronic properties of the molecule; dihydronaphthalenes **169b–169f** also did not form any tetracyclic products. The difference in reactivity amongst stilbenes illustrates the impact of electron donating substituents can have on this method. This reaction could be however extended to other electron-rich stilbene derivatives. The treatment of compounds **167g**, **167k–167m** with boron trifluoride dimethyl etherate or other Lewis acids, and using phenyl selenenyl chloride as the selenium electrophile allowed the

straightforward synthesis of benzo[*b*]fluorenes **171** in good yields as shown in Table 3. The reaction using stilbene **167m** displayed remarkable regioselectivity. While the possibility for the formation of two different regioisomeric products exists, **171m** was the only product observed, the structure of which was verified by NMR and X-ray crystallography, a result consistent with the only indicated structure (Table 3, entry 5). Irreversible electrophilic substitutions on naphthalene tend to occur in the 1-position, consistent with this result.[94a-b] This could be explained by drawing **Y**-type carbocations, and **Z**-type carbocations. The relative stabilities of the **Y** and **Z** carbocations enable us to determine the preferred pathway of the reaction, because the more stable the carbocation, the more stable the transition state for the formation will be, and therefore the more rapidly product will be formed. **Y**-type carbocations are stabilised by allylic resonance and benzenoid character of the other ring is maintained in **Y.1** and **Y.2**. When attack is at C-3, the benzenoid character of the other ring is sacrificed. The resonance contributors **Y.1**, **Y.2** and **Z.1** that are shown in Figure 6 are the most stable. In those contributors, the relative stabilities of the carbocations formed from the electrophilic substitution of the naphthalene determine the preferred reaction pathway. 1-Substituted naphthalenes are easier to form since their resulting resonance contributors are greater in number and can delocalise charge more effectively than the electrophile attack at position three. The majority of S_EAr products are kinetic products (not thermodynamic): the reactions are usually not reversible, since the reverse reaction is usually very unfavorable.[94a-b] That means that the structure of the product is determined by the free energy of activation, but not by the stability of the product.

The formation of the tetracyclic compounds **171** shows that this tandem reaction involves a novel rearrangement process by activation of the double bond, which results in a total of three C—C bond formations, and a C—C and C—O bond cleavage, leading to the formation of tetracyclic compounds **171**. The structure of **171m** was additionally confirmed by X-ray crystallographic analysis (Figure 7, see detail in Appendix 2.2).

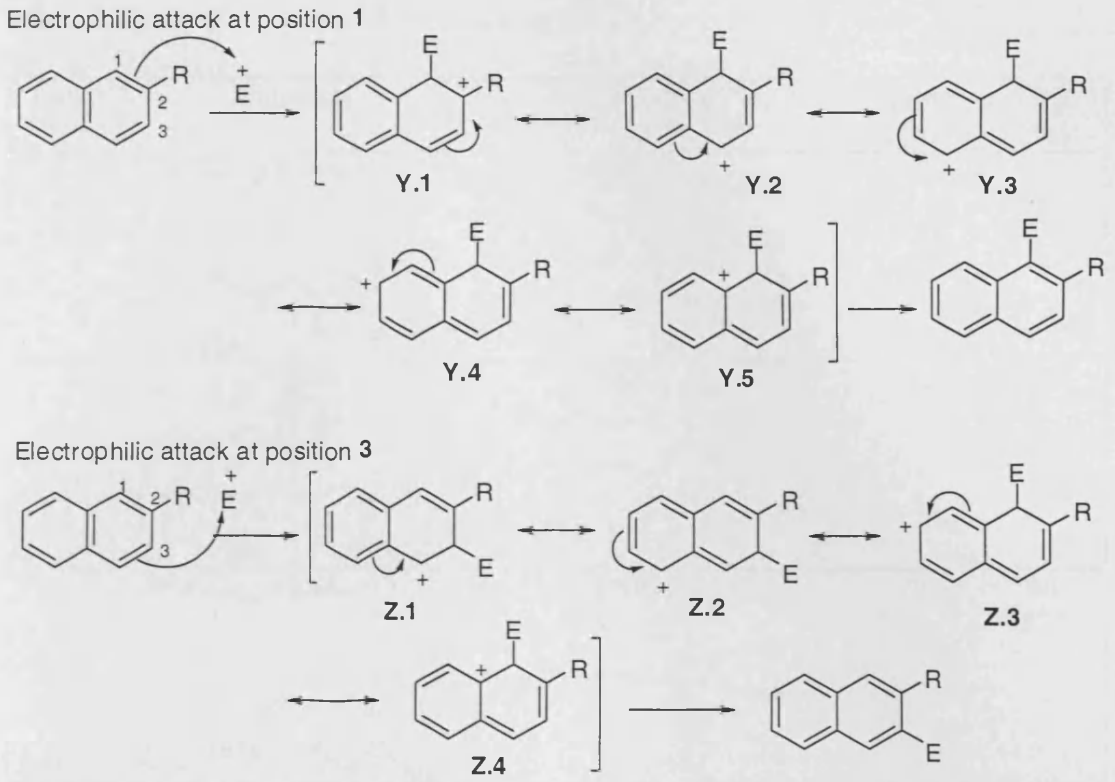


Figure 6: Explainations for the formation of **171m**

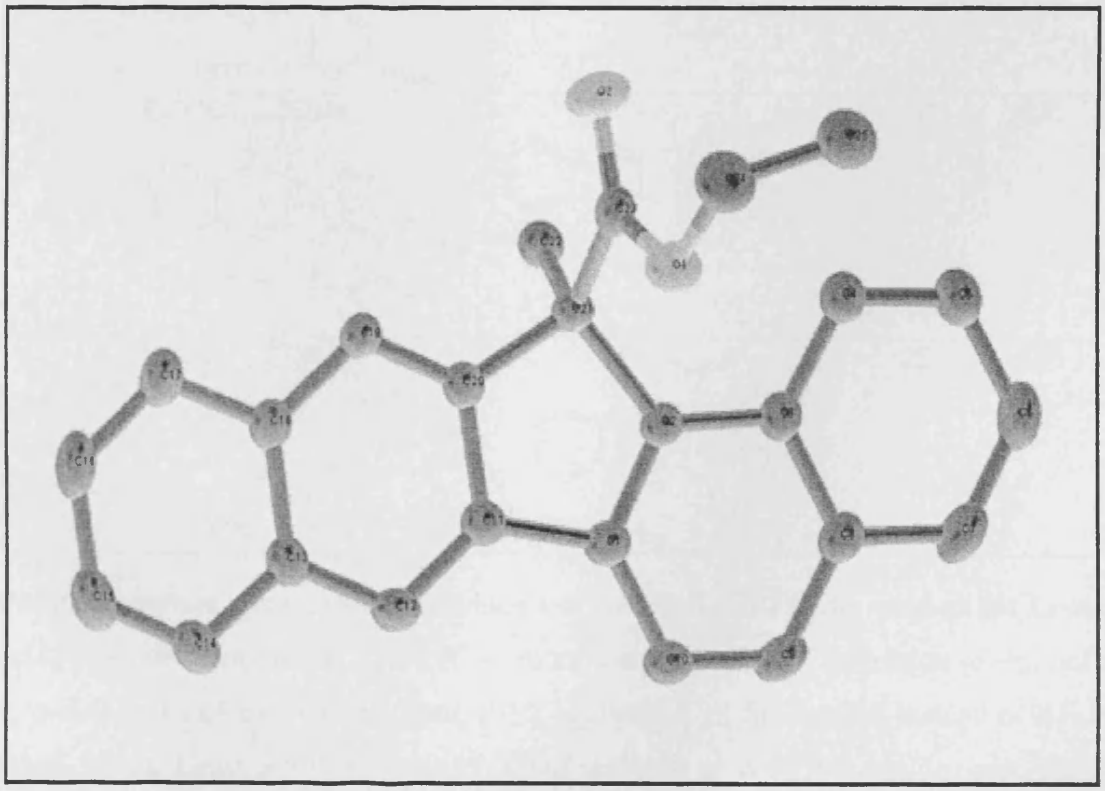
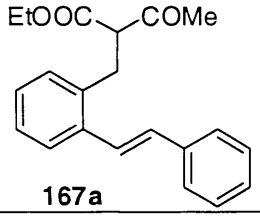
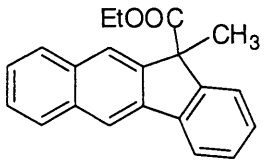
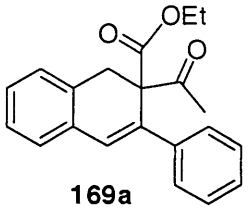
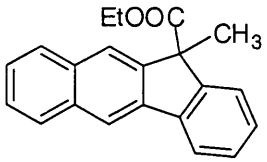
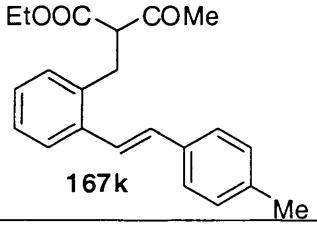
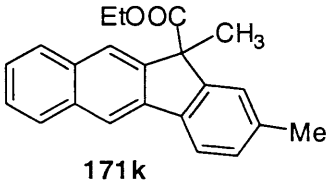
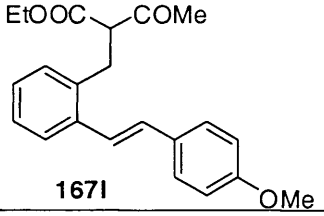
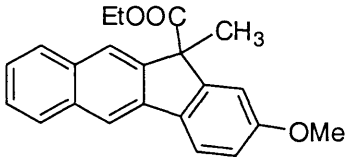
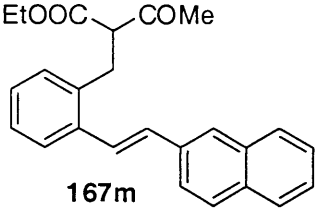
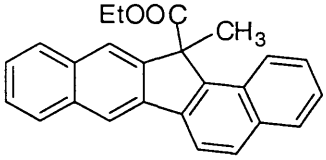
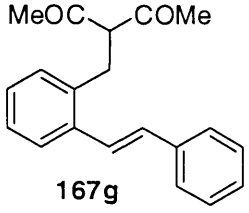
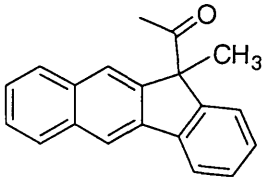


Figure 7: Crystal structure of benzofluorene **171m**

Table 3: Synthesis of novel benzofluorenes **171**

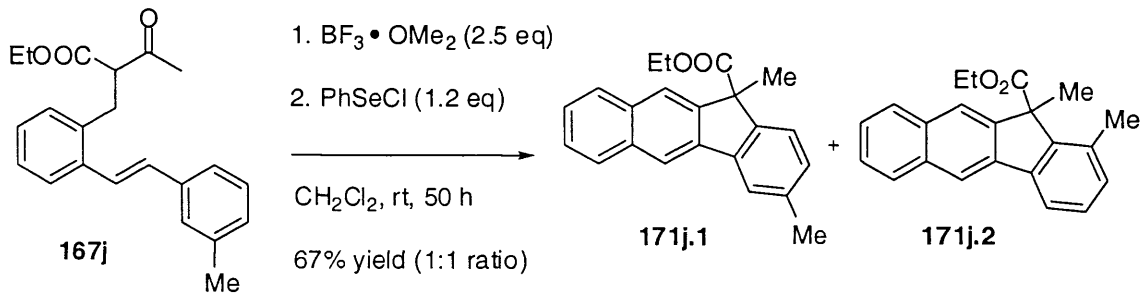
Entry	Substrate	Product	Time [h]	Yield [%]
1	 **167a**	 **171a**	72	90
2	 **169a**	 **171a**	70	30[a]
3	 **167k**	 **171k**	60	80 87[b]
4	 **167l**	 **171l**	69	67
5	 **167m**	 **171m**	50	82[c]
6	 **167g**	 **171g**	25	85[d]

Standard reaction conditions: 2 equivalents of $SnCl_4$ or $BF_3 \cdot OMe_2$ used as the Lewis acid, 1.2 equivalents PhSeCl, –60 °C→ room temperature. [a] Conversion given, only 0.3 equivalents of $BF_3 \cdot OMe_2$ used. [b] 2 equivalents of $SnCl_4$ used instead of $BF_3 \cdot OMe_2$ as the Lewis acid. [c] Product **171m** obtained as only one regioisomer. [d] 2 equivalents of $TiCl_4$ used instead of $BF_3 \cdot OMe_2$ as the Lewis acid.

We also observed the formation of benzo[*b*]fluorene **171l** in low yields when Lewis acids ($TiCl_4$, $SnCl_4$) were used at room temperature instead of low reaction temperatures. The presence of electron-donating substituents R on the aromatic moiety of **167** seems to be crucial for the success of the double cyclisation process. In an effort to probe the amount of Lewis acid, substrate **169a** was subjected to a set of standard reaction conditions with only 0.3 equivalents of boron trifluoride dimethyl etherate, the yield drops significantly and only 30% conversion is observed (Table 3, entry 2). Longer reaction times do not improve the conversion. Stoichiometric amounts of the Lewis acid are therefore required in this reaction. The generation of equimolar amounts of water in this cyclisation leads to an inactivation of the Lewis acid, therefore stoichiometric amounts are required.

Interestingly, substrate **167g** (Table 3, entry 6), containing two methylketone moieties, showed that the migration of an acetyl functional group is also possible under the standard reaction conditions and the product **171g** was isolated in 85% yield. Introducing the two acetyl groups enhances the rate of the reaction and the corresponding tandem product was obtained with rearrangement of the acetyl functional group even if reaction was performed for a shorter period of time (Table 3, entry 6). There is significant difference in rate between the substrate with an ester and substrate with an acetyl group: the acetyl group rearranges faster than the ester group.

When a methyl group was located at the *meta*-position (Scheme 64), the possibility for regioisomeric products existed because two different nucleophilic sites of the aromatic ring are active towards a Friedel-Crafts reaction.



Scheme 64: Formation of regioisomers of benzofluorene from substrate **167j**

To understand why a substituent directs an incoming electrophile to either position, we must look at the stability of the carbocations (arenium ions) **A** and **B** (Figure 8). When

the methyl group is at position 3, the carbocations formed by putting the incoming electrophile on the *ortho-* and *para*-positions, each have a three resonance contributors. The difference between arenium ions **A** and **B** is very small resulting in no regioselectivity in the Friedel-Crafts reaction.

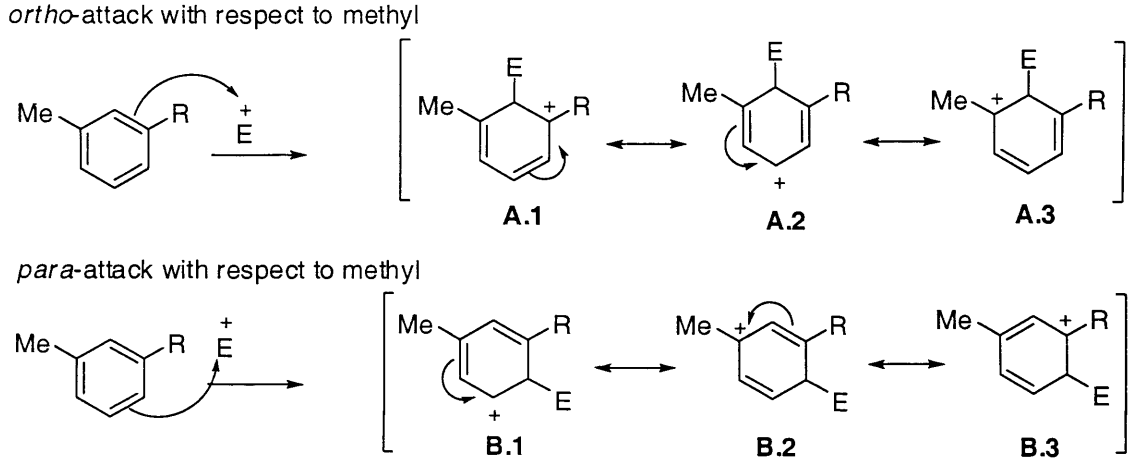
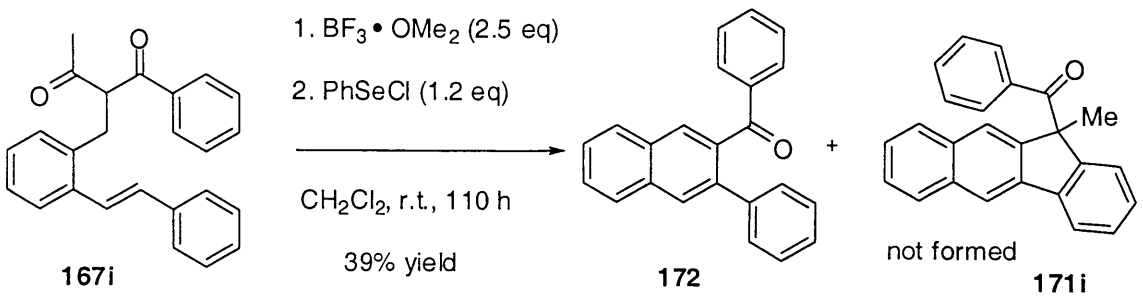


Figure 8: Explaination for the formation of regioisomers **171j.1** and **171j.2**

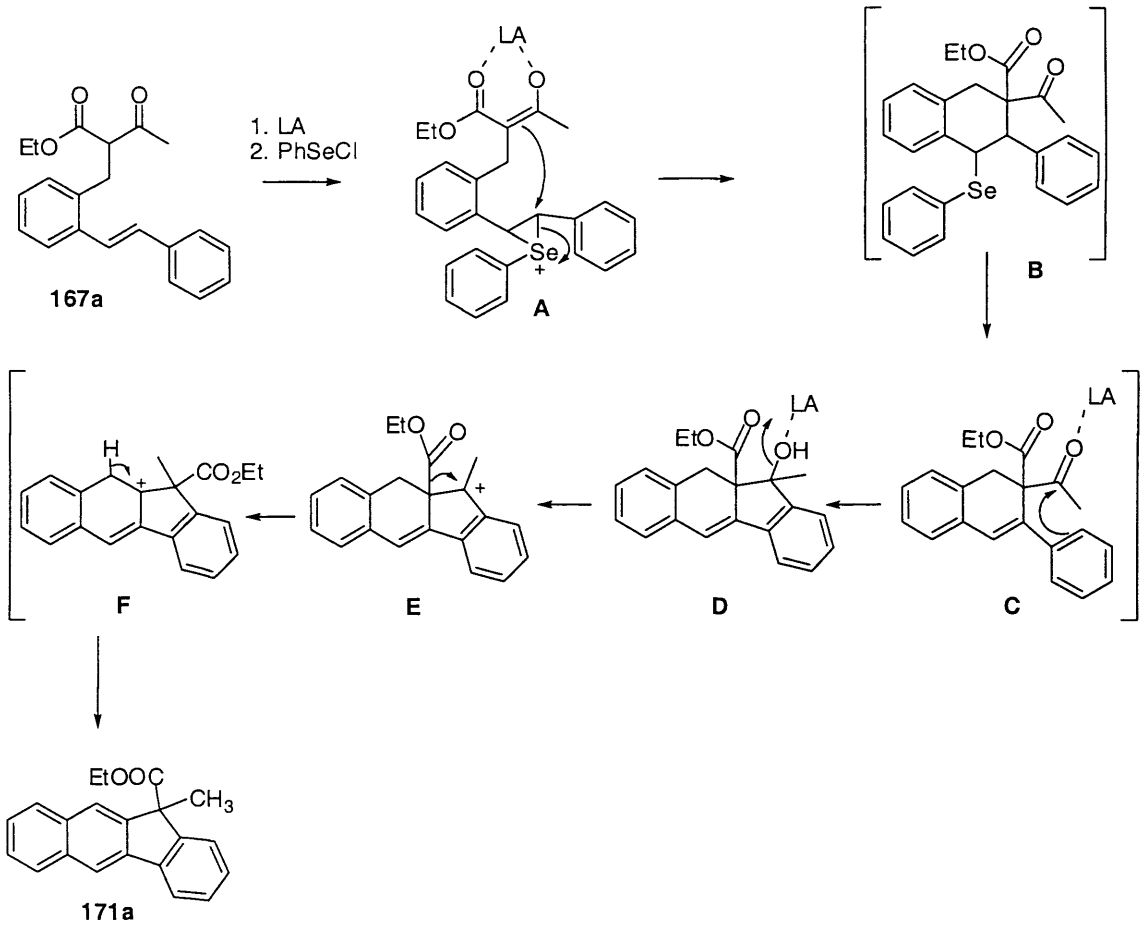
Accordingly, we carried out the cascade reaction with different substrates while further investigating this type of rearrangement in order to probe the generality and diversity of this tandem process as depicted in Scheme 65. Compound **167i** including a benzoyl group was subjected to the standard reaction conditions hoping to achieve a benzoyl migration. Unfortunately, a mixture of products resulted, one of which, **172**, was isolated in 39% yield. It is unclear how the loss of the acetyl group occurs in this case. Out of the conditions surveyed for cyclisation, the best were that outlined in Scheme 65. However, the reaction protocol failed to induce benzoyl migration and subsequent formation of benzofluorene.



Scheme 65: Unexpected formation of naphthalene derivative **172**

2.4.5.3 Proposed Mechanism

A mechanism that accounts for the formation of dihydronaphthalenes and benzofluorenes is depicted in Scheme 66. Binding of the carbonyl groups of stilbene **167a** with Lewis acid leads to enolate formation and subsequent alkene activation gives enolate **A**. The enolate in **A** acts as a carbon nucleophile towards the activated alkene with the indicated regiocontrol. As a result, formation of the new C—C bond within this organized environment would lead to a cyclic product. The initial product of the reaction is the phenylseleno-substituted tetrahydronaphthalene **B** which undergoes the subsequent elimination of a selenium moiety under the reaction conditions to deliver the dihydronaphthalene. It is surprising that the selenium moiety was so prone to elimination. While we cannot rule out that the Lewis acid could induce elimination directly after cyclisation of the stilbene, the heightened propensity of the selenium moiety to eliminate suggests that the selenium functional group is sensitive to the elimination even without oxidation. This premise is consistent with the fact that the stability of dihydronaphthalene also favours elimination at least in a thermodynamic sense. This issue is further convoluted by the fact that it is unclear whether Lewis acid mediation is involved in this elimination. The mechanism below (Scheme 66) assumes Lewis acid mediated activation of the acetyl group gives the reactive electrophilic carbon species which is captured by the electron rich aromatic ring in an intramolecular Friedel-Crafts reaction; aromaticity is then re-established via proton transfer to give an intermediate **D**. Perhaps, subsequent extrusion of the hydroxyl functional group would release carbocation **E**. Migration of the ester gives more stable carbocation **F** and subsequent aromatisation that provides additional driving force to this rearrangement process and thereby tandem sequence, completing the synthesis of benzo[*b*]fluorene derivative **171a** as the thermodynamically most stable product.



Scheme 66: Mechanistic proposal for selenium and Friedel-Crafts mediated cascade reaction for the synthesis of benzofluorenes involving a new rearrangement.

Similar 1,2-migrations of ester moieties under the assistance of Lewis acids have been reported in literature.[94c] The elimination of an equimolar quantity of water in this tandem carbocyclisation results in an inactivation of the Lewis acid, therefore stoichiometric amounts of Lewis acids are indispensable.

This tandem approach gave us quick access to benzofluorenes with quite good yields; the reaction mixtures were virtually free of organic side products facilitating the isolation of the products. Overall, this cascade reaction comprising ring closure via addition/elimination sequence, intramolecular Friedel-Crafts and ester and acetyl functional group rearrangement all of which paved the way to the tetracyclic ring system of benzofluorene in one pot under standard reaction conditions.

2.4.6 Summary

In conclusion, we have developed a flexible synthetic route, which establishes new carbon-carbon bond forming process in 6-*endo-trig* fashion for the first time. The key selenium-mediated cyclisation to yield dihydronaphthalenes was compatible with different functional groups. We have also developed a tandem double carbocyclisation of stilbenes with a phenyselenenyl chloride in the presence of a Lewis acid, which afforded various novel benzofluorenes in a one-pot reaction from simple starting materials that provided the desired chemical targets in a more expedient way under very mild reaction conditions than previously reported approaches. This work represents the first example of carbocyclisation promoted by electrophilic selenium reagent to dihydronaphthalenes which are subsequently transformed to benzofluorenes through an unprecedented Lewis acid mediated cascade cyclisation reaction sequence involving a new rearrangement of ester and acetyl functional groups.

The key selenium-mediated cyclisation to yield dihydronaphthalene is the first example of an electrophile-mediated reaction in which the tandem sequence is controlled by the electronic bias of the phenyl ring. This implementation extends the methodology to tetracyclic ring systems, a motif found in many natural products. Finally, effective use of Heck-coupling, reduction, and condensation all contributed to the overall success of this synthetic endeavor. This synthesis confirmed the "educated guess" that was made when we began our synthesis. It is believed that a wide range of carbocycles could be prepared by this general strategy. Natural products close in similarity to dihydronaphthalene, and many other unknown natural products could be approached. Each specific case would lead to a slightly different implementation of this method. The success of this project is a testament to the power of selenium in the carbon–carbon bond forming process. Further studies to apply and improve upon this strategy in the synthesis of other carbocycles could be considered in order to further understanding of this missing area of selenium chemistry.

Chapter 3

3 The Synthesis of Naphthalenes and Biaryls

3.1 Introduction

This chapter initially outlines the literature methods for the synthesis of naphthalene and biaryl ring systems, then describes our synthetic efforts towards the synthesis of biaryl and naphthalene derivatives. The reactions of a range of β-keto ester substituted stilbenes with phenylselenenyl chloride and several Lewis acids are described, obtaining biaryls in good to excellent yields.

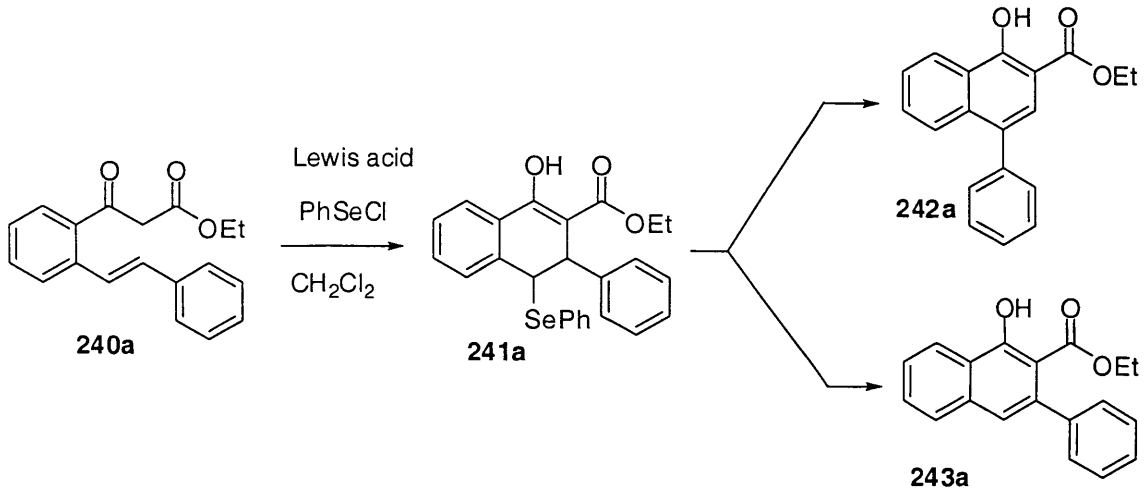
3.2 Aims of the Project

The compounds illustrated in Figures 9 and 10 (pages 61–62) are of interest from a structural viewpoint, but they also have a range of potentially useful biological properties. Biaryl derivatives have stimulated considerable interest within the synthetic chemistry community as a result of their widespread occurrence in nature and their associated biological activities. Despite the presence of some literature procedures, there continues to be a demand for novel methods for biaryl synthesis while there is little literature precedence for the synthesis of 4-arylnaphthol derivatives.

With an aim to develop a practical carbon-carbon bond forming process, we describe the concept of a novel C–C bond formation and its application in the synthesis of carbocycles. Our development of a chemical synthesis of these compounds using a wide range of stilbene substrates has been described in chapter 2. This enables us to extend the scope to other carbocycles. The aim of this project was the selenium-mediated synthesis of challenging biaryls (Scheme 67). We proposed linear 1,3-dicarbonyl stilbenes as precursors which would allow the synthesis of biologically important analogues of naphthalenes and biaryls using a combination of a selenium electrophile and a Lewis acid. Upon changing the substitution pattern on the stilbene, we could enhance the reactivity and selectivity in these reactions to deliver the desired cyclic products. Thus, selenium electrophile-mediated cyclisation reactions of β-keto ester substituted alkenes of type **240** could generate the desired products **242** and **243**. This scenario assumes a one-pot process involving the activation of the alkene and the attack of the internal nucleophile. Because of its cationic character, the seleniranium

intermediate could be attacked by the internal carbon nucleophile to generate the 6-*endo* cyclic product **241**.

In planning the synthesis of naphthalenes and biaryls, we focussed attention on the cyclisation of the *β*-keto ester substituted stilbenes **240**. Once appropriate reaction conditions are found for the cyclisation and elimination of the selenium functionality will give rise to corresponding cyclised product **243a**. Alternatively, elimination of selenium functional group and formation of benzylic carbocation, the homo-benzylic carbocation could be formed by migration of an aryl group. Subsequent aromatisation could offer biaryls of type **242**. It was also hoped that by replacing the aryl moiety in the substrate alkene **240** by a methyl group, the cyclisation would be possible.



Scheme 67: Synthesis of naphthalene-based biaryl derivatives

Once a suitable procedure is found, a range of *β*-keto ester stilbenes could be used as precursors for cyclisations and could offer good prospects for the development of a C—C bond forming process. The recycling of the selenium electrophile in these reactions is essential for both environmental and economic reasons.

3.3 Motifs of Natural Products and Their Applications

Polysubstituted naphthalenes have been used in many applications such as pharmaceuticals, plant protection agents and dyes. In addition, some natural products that contain naphthalene often exhibit biological activities.[95] Naphthalene derivatives have been found to be inhibitors of the Human Immunoglobulin E Antibody production.[96] Additionally, liquid crystal properties are associated with the naphthalene core of these compounds.[97] Naphthalene derivatives isotorachrysone **173** and isotorachrysone peracetate **174** were isolated from the stem bark of *Rhamnus nakaharai* and showed antiplatelet properties.[98] Other related natural naphthalenes **175** and **176** were isolated from the root bark of *Rhamnus nakaharai* (Rhamnaceae).[99] A naphthalene carboxylic acid methyl ester **177** which is related to juglone was isolated from the branches of *Rhoiptelea chiliantha*.[100] Antiprotozoal and cytotoxic naphthalene derivatives such as **178** were isolated from Diospyros assimilis.[101] 1-Hydroxy-5-methoxynaphthalene **179**, 1-hydroxy-5-methoxy-2-nitronaphthalene **180**, 1,5-dimethoxy-4-nitronaphthalene **181**, 1-hydroxy-5-methoxy-2,4-dinitronaphthalene **182** and 1,5-dimethoxy-4,8-dinitronaphthalene **183** were isolated from an endophytic fungus, *Coniothyrium* sp. These nitronaphthols showed considerable antibacterial, antifungal, and antialgal (algicidal) properties.[102]

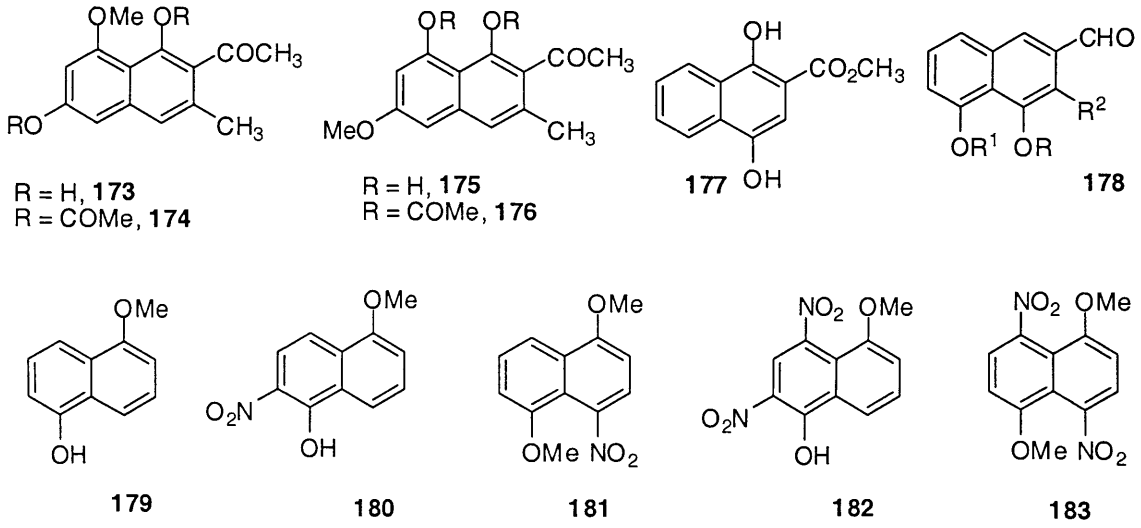


Figure 9: Naphthalene-containing natural products

The analysis of the leaf extract of *Aloe plicatilis* identified natural naphthalene derivatives of type **184** which are designated as plicataloside.[103] A naphthalene glycoside **185** was isolated from callus cultures of *Diospyros kaki*[104] while many other

naphthalene glycosides such as **186** and **187** were isolated from the roots of *Rumex patientia* (Polygonaceae).[105] Two derivatives, 2-acetyl-4-chloro-1,8-dihydroxy-3-methylnaphthalene-8-*O*-β-D-glucopyranoside **188** and 2,4-dichloro-1,8-dihydroxy-3-methylnaphthalene-8-*O*-β-D-glucopyranoside **189** were isolated from the roots of *Rumex patientia.*[106] Recently, naphthalene containing glycosides were isolated from stem bark of *Diospyros angustifolia.*[107]

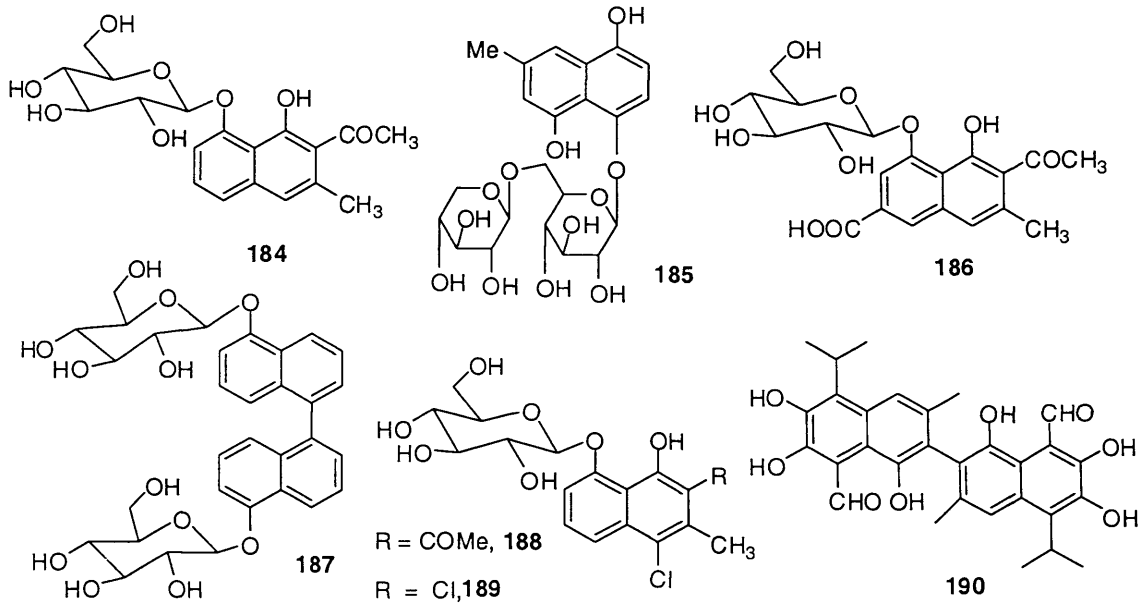


Figure 10: Naphthalene and biaryl glycosides

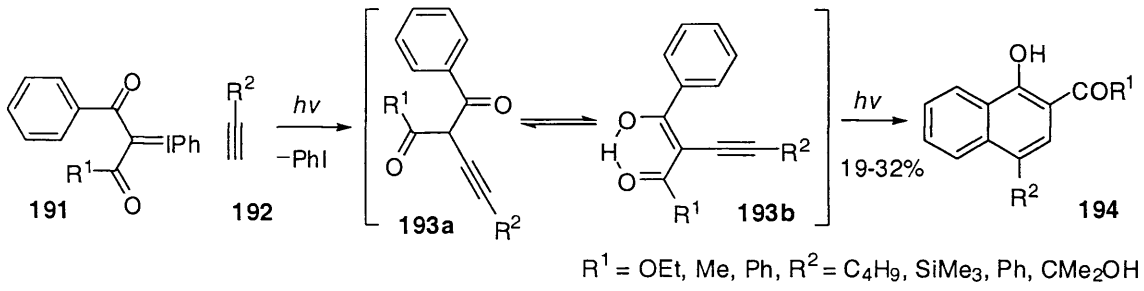
In 1886, racemic gossypol **190**, a natural toxin, was isolated from cotton seeds and its structure was elucidated some 50 years later.[108] This polyphenolic compound comprises of two identical naphthalene units linked by a biaryl axis. Restricted rotation about this axis imparts chirality to the molecule. Pharmacologically it is known to be an oral antifertility agent in men and male animals, and it shows potential for the treatment of HIV infections, diabetic complications and cancer. Of interest, though, are the observations that (*R*)-gossypol is more effective than its atropisomer (*S*)-gossypol **190** against tumour cells and HIV-1, while the opposite is true for activity against herpes simplex virus, influenza and parainfluenza virus. Apart from their interesting biological activity, the naphthalene ring system is an important intermediate in the syntheses of many natural products.[109] They also serve as versatile chiral reagents and ligands in synthetic chemistry[110] which make their preparation of great interest in organic synthesis.[111] In addition, their metal complexes have found a wide range of applications such as asymmetric hydrogenation and industrial applications.[112] (1,1'-Binaphthyl)-2,2'-

diol (BINOL) and its derivatives are widely used in asymmetric synthesis either as ligands or as chiral auxiliaries and are capable of catalysing a variety of reactions.[113]

3.4 Literature Reports on the Synthesis of Naphthalenes and Biaryls

3.4.1 Photochemical Reactions

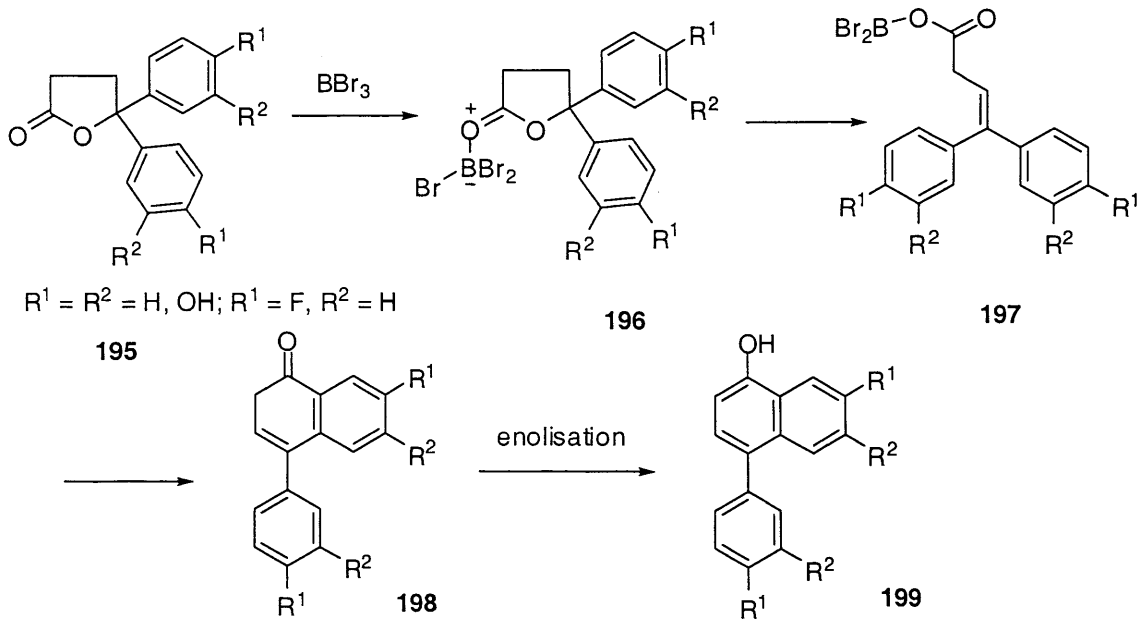
Kalogiannis and Spyroudis[114] found that irradiation of phenyliodonium ylides of acyclic β-dicarbonyl compounds bearing at least one benzoyl group with terminal alkynes affords 2,4-disubstituted naphthol derivatives **194**. Mechanistically, the naphthalene ring formation arises from the cyclisation of the enolic form of the ethynylated compounds **193b** and is favoured by the S-*cis* configuration of the benzene ring and the triple bond in **193b** (Scheme 68).



Scheme 68: The photochemical reaction of phenyliodonium ylides with alkynes

3.4.2 The Use of Friedel–Crafts Reaction Sequence for the Synthesis of Biaryls

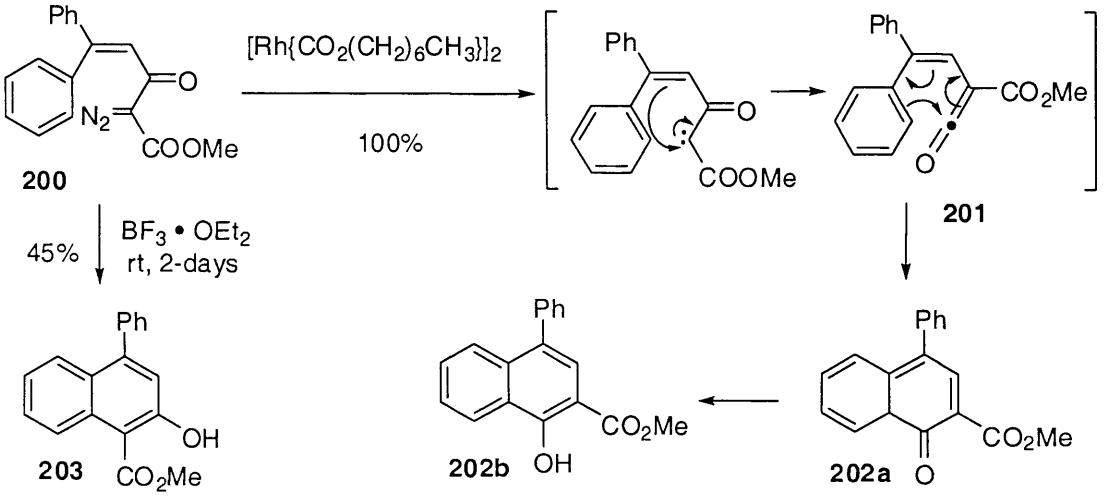
It has been reported that 4-arylnaphthalen-1-ols **199** were synthesized by an intramolecular Friedel-Crafts reaction of lactones **195** upon treatment with boron tribromide. The intramolecular acylation of lactones **195** is thought to involve elimination of HBr from the activated lactone-BBr_3 complex **196**. Subsequent electrophilic attack of the boron ester in **197** on an aromatic ring leads to rapid cyclisation forming **198**. Subsequent aromatisation led to biaryl **199** (Scheme 69).[115]



Scheme 69: The synthesis of biaryl compounds from lactones by using BBr_3

3.4.3 Rhodium-Mediated Cyclisations

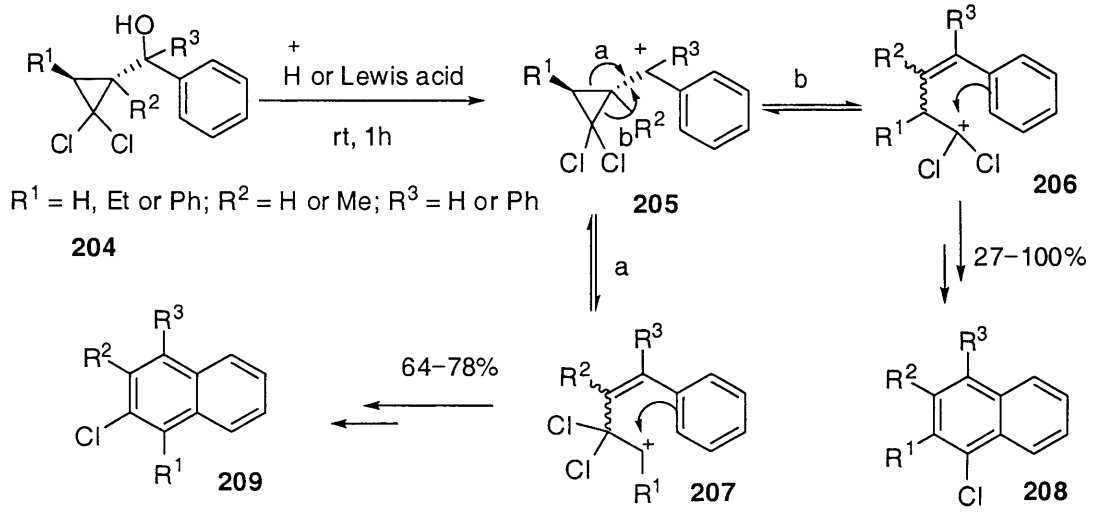
The group of Karady and Reamer[116] found that the rhodium-catalysed decomposition of diazoketone **200** afforded almost quantitative yields of naphthol **202b**. This result was rationalised as having occurred by a Wolff rearrangement, followed by electrocyclisation of the ketene intermediate **201** and subsequent aromatisation of **202a**. The same group also found that a Lewis-acid promoted ring closure of diazoketone **200** gave regioisomeric naphthol **203** in moderate yields (Scheme 70).



Scheme 70: Lewis acid mediated ring-closure and rhodium catalysed synthesis of *β*-naphthols by a Wolff rearrangement pathway

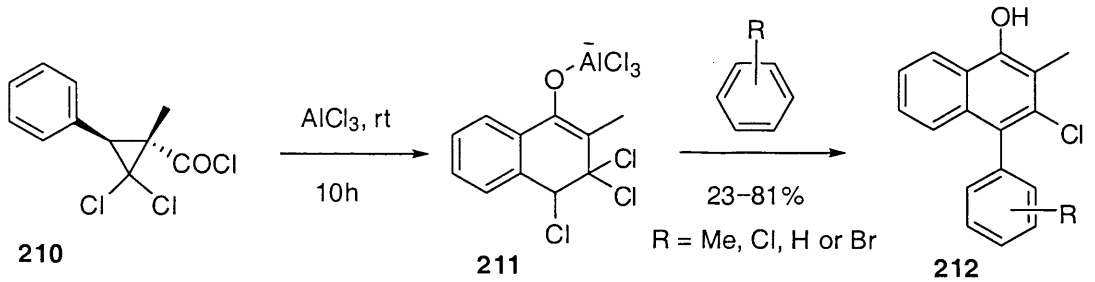
3.4.4 Rearrangement of Cyclopropanes

Tanabe *et al.*[117] have described the synthesis of halogenated naphthalenes and naphthols from suitably substituted cyclopropanes. Their synthesis of halogenated naphthalenes was brought about by the acid catalysed ring opening of aryl(2,2-dihalocyclopropyl)methanols **204**, as outlined in Scheme 71. One of two possible cyclopropylmethyl cation rearrangements in **205** occurs, depending on the stability of the resulting carbocations **206** or **207**. The cation then undergoes an intramolecular Friedel-Crafts reaction to afford isomeric naphthalene products **208** or **209**. Yields of a wide variety of functionalised naphthalenes **208–209** were moderate to excellent.



Scheme 71: Synthesis of naphthalenes from Lewis acid-mediated rearrangment

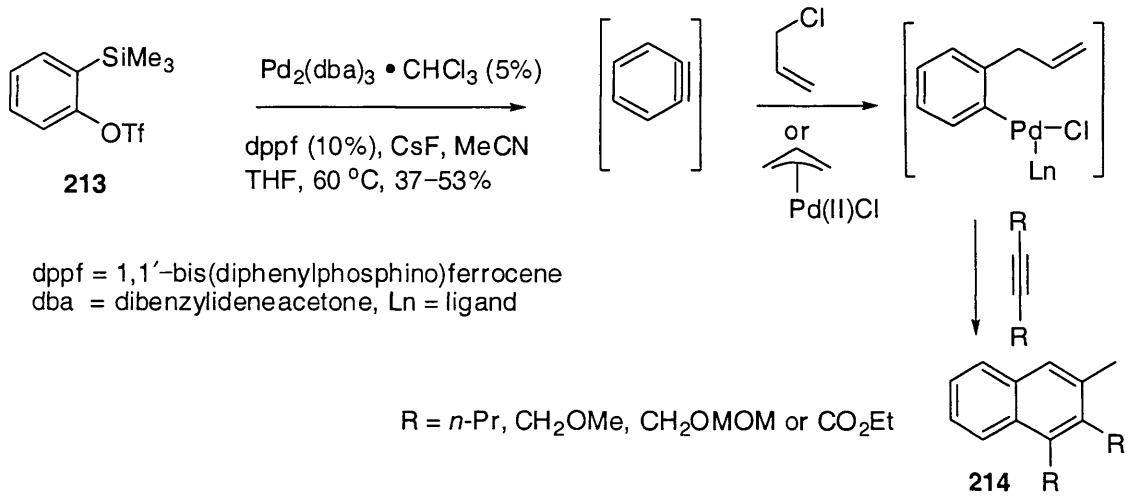
In a related transformation, the synthesis of naphthols has been achieved by two sequential Friedel-Crafts reactions of 3-aryl-2,2-dihalocyclopropanecarbonyl chlorides such as **210**.[118] An intramolecular cyclisation similar to that shown in the previous Scheme afforded intermediate **211**. This was followed by a intermolecular Friedel-Crafts coupling reaction to yield naphthols **212** in moderate yields (Scheme 72).



Scheme 72: Synthesis of biaryls from Friedel-Crafts coupling sequence

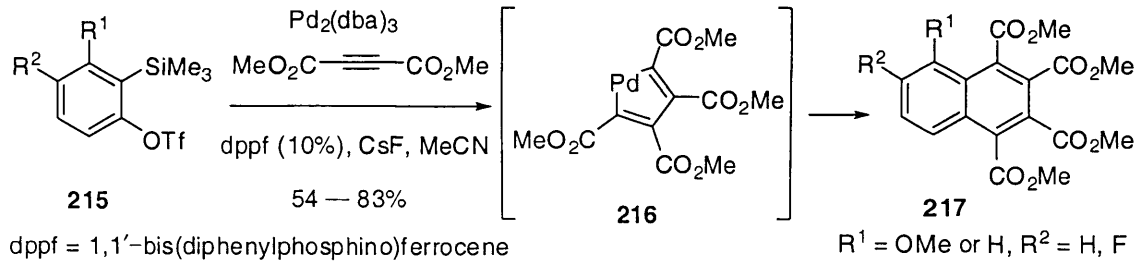
3.4.5 Palladium-Catalysed Cyclisations

The synthesis of functionalised naphthalenes by a palladium-catalysed reaction of arynes with alkynes has been reported by two groups. Yamamoto and co-workers[119] generated benzyne from triflate **213** by reaction with cesium fluoride, followed by a controlled carbopalladation with allyl chloride and functionalised alkynes to afford naphthalenes **214** in moderate yields. The key steps of this reaction are depicted in Scheme 73.



Scheme 73: A palladium catalysed-synthesis of naphthalenes from **213**

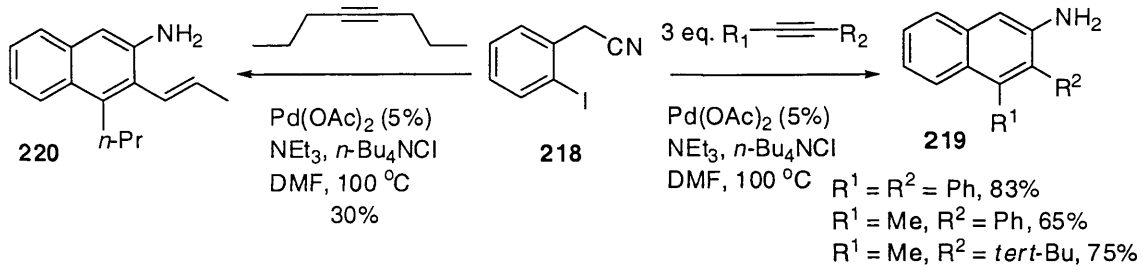
Pérez and co-workers generated benzynes in a similar fashion from **215** which underwent subsequent palladium-catalysed cocyclisation of the benzynes with alkynes gave naphthalenes **217** in good yields (54—83%), probably by formation of intermediate **216** (Scheme 74).[120]



Scheme 74: Palladium-catalysed cyclisation of benzynes with alkynes

An interesting route to functionalised 2-aminonaphthalenes was discovered by the Larock group when (2-iodophenyl)acetonitrile **218** was treated with internal alkynes and a palladium catalyst (Scheme 75).[121] The 2-naphthylamines **219** were isolated in generally good yields, and only the reaction with 4-octyne resulted in a surprising

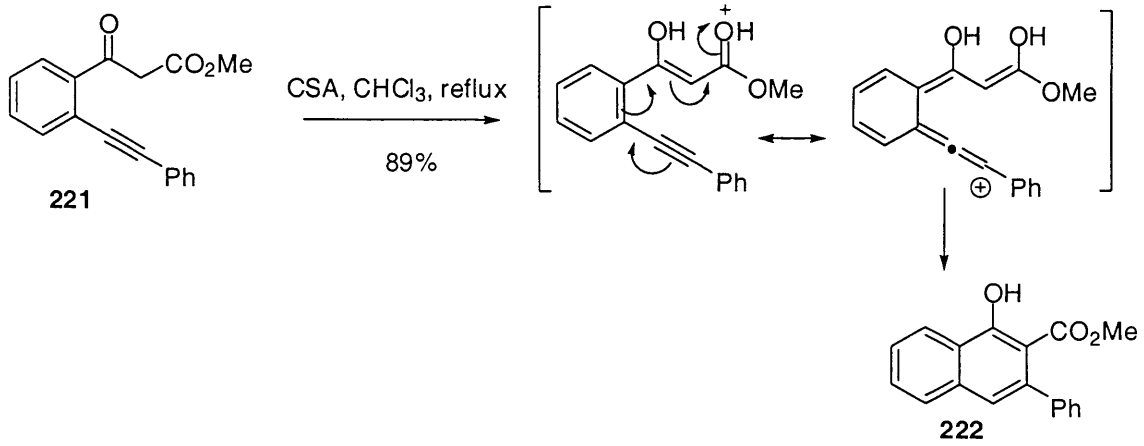
product, 2-amino-3-(1-propenyl)-4-*n*-propylnaphthalene **220**, albeit in a rather disappointing yield. Larock and co-workers have also published other related approaches to naphthalenes (Scheme 75).[122]



Scheme 75: Palladium catalysed synthesis of naphthalenes from 2-iodobenzonitrile **218**

3.4.6 Acid-Catalysed Cyclisations

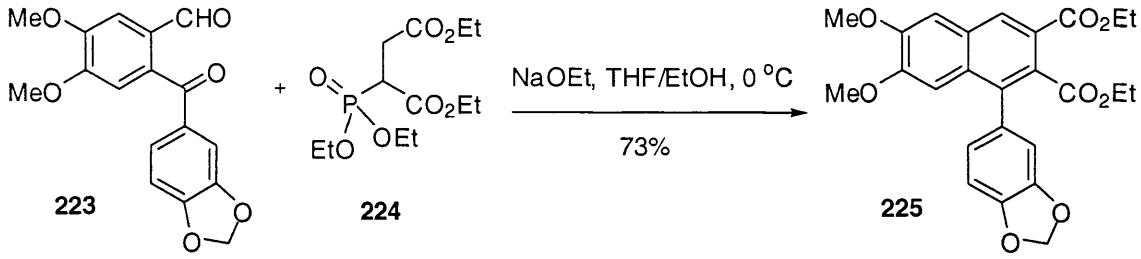
Another interesting synthesis of naphthalenes, which is acid catalysed, involves the treatment of phenyl substituted substrate of type **221** with camphorsulfonic acid in hot chloroform to afford naphthol **222** (Scheme 76).[123] This work has been applied to a number of substrates to afford 2,3-disubstituted-1-naphthols **222**. The mechanism of this reaction is yet not clear, but it seems plausible that cyclisation may commence with protonation of the ester carbonyl of the enol tautomer of the starting ketoester **221**. The carbonyl group should be significantly more basic than the triple bond and its protonation would activate the molecule toward cyclisation through the electrocyclic process shown in Scheme 76.



Scheme 76: Acid mediated *6-endo dig* intramolecular cyclisation

3.4.7 Claisen Condensation

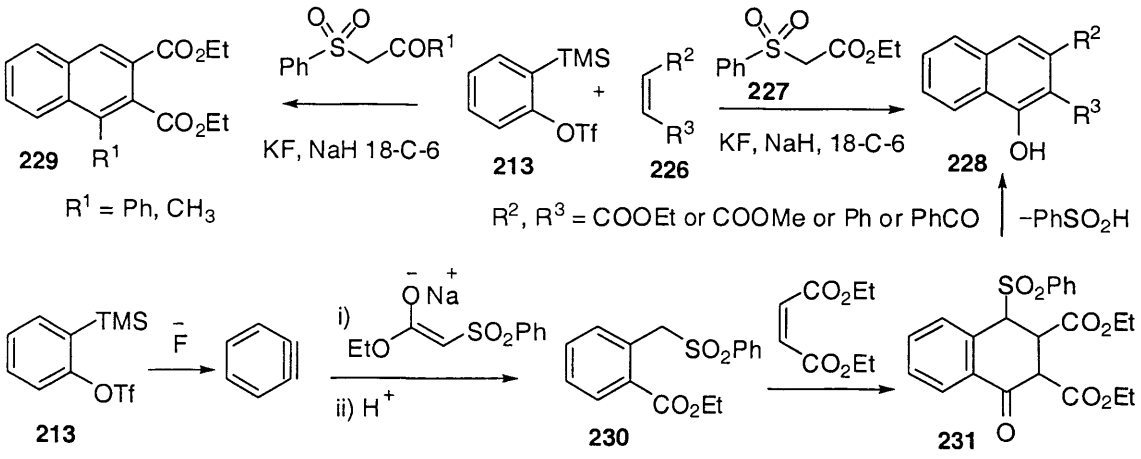
A Horner-Emmons reaction between ketoaldehyde **223** and phosphonate **224**, followed by a Claisen condensation was used by Harrowven and co-workers (Scheme 77)[124] to assemble the lignan framwork **225** of justicidin B and retrojusticidin B (Scheme 77).



Scheme 77: The use of Horner-Emmons and Claisen condensation sequence

3.4.8 The Synthesis of Biaryls by Multi-Component Reactions

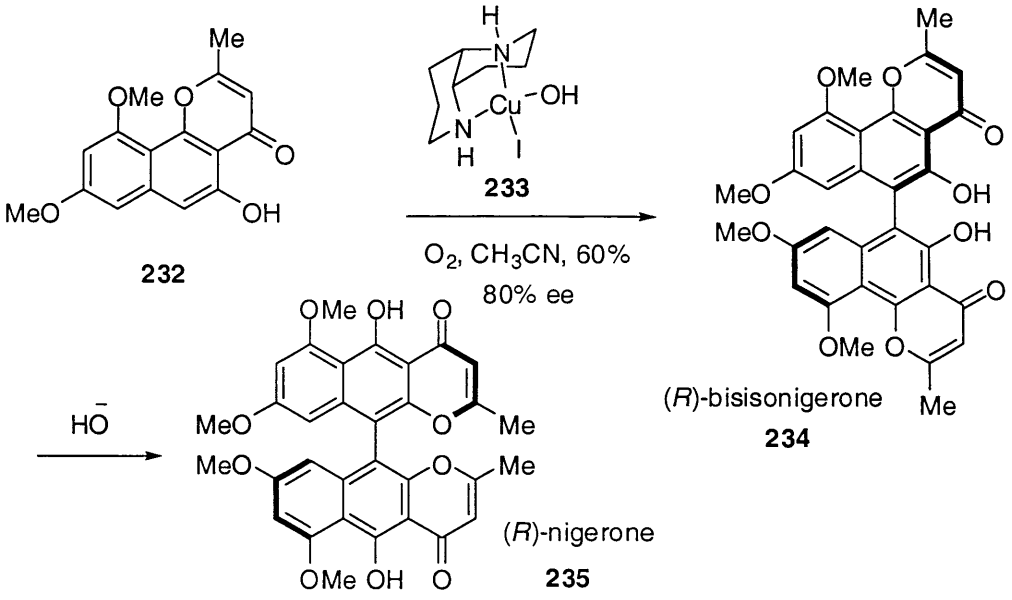
A multi-component reaction of arynes, β-keto sulfones, and Michael acceptors has been described by Huang for the synthesis of polysubstituted naphthols and naphthalenes. The insertion of β-keto sulfones to arynes was achieved by treatment of 2-(trimethylsilyl)phenyl triflate **213** with β-sulfonylacetate **227** in the presence of 2 equiv. of potassium fluoride and 18-crown-6 in THF at room temperature, the corresponding insertion product **230** was obtained in 85% yield. Subsequent annulation of **230** with Michael acceptors such as maleic esters, fumaric esters, or ethyl acrylate gave a range of polysubstituted naphthols **228**, presumably through intermediate **231**. (Scheme 78).[125]



Scheme 78: Synthesis of naphthols *via* a multi-component reaction sequence

3.4.9 The Use of Copper Catalysis

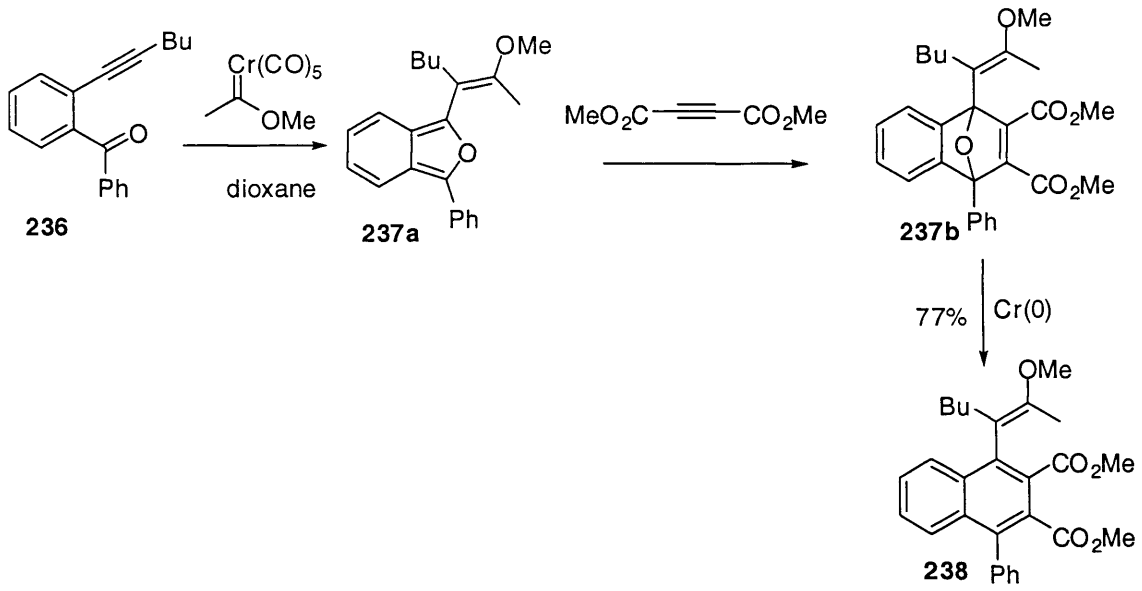
Recently, an enantioselective synthesis of the chiral bisnaphthopyrone natural product nigerone **235** was reported by Kozlowski and co-workers (Scheme 79).[126] The key isomerisation of **234** via a sequence of eight conjugate addition/elimination reactions was found to give nigerone **235**. The isomerisation precursor **234** was prepared by an asymmetric oxidative biaryl-coupling of an advanced intermediate **232** with a 1,5-diaza-*cis*-decalin copper catalyst **233**.



Scheme 79: Copper catalysed synthesis of biaryl **235**

3.4.10 Chromium–Mediated Synthesis of Biaryls

Chromium-containing Fischer carbenes react with enyne-aldehydes or ketones such as **236** in the presence of dimethylacetylene dicarboxylate (DMAD) to afford naphthalenes such as **238** (Scheme 80).[127] It has been shown that the reaction proceeds by the way of the intermediate isobenzofuran **237a** which undergoes a Diels-Alder reaction with dimethylacetylene dicarboxylate (DMAD). The Diels-Alder adduct **237b** is then reduced to naphthalene **238** by cromium(0).

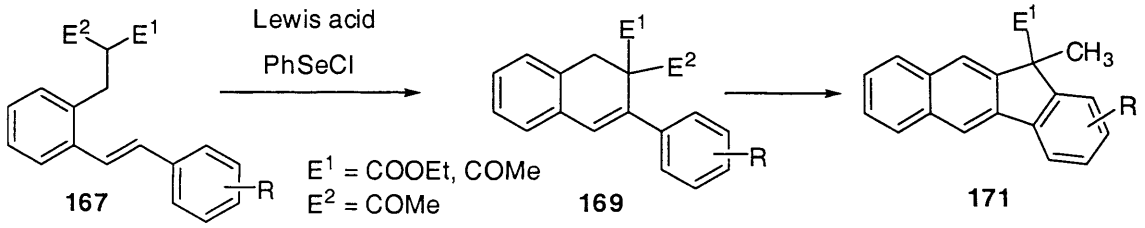


Scheme 80: Chromium carbene promoted synthesis of biaryls **238** from enyne-ketone **236**

In summary transition metal-mediated cyclisations (palladium coupling reactions, rhodium mediated rearrangements and chromium containing Fischer carbene initiated annulations) provide useful routes for the synthesis of naphthalene and biaryl ring systems. Acid-catalysed reaction conditions have also been used to synthesise naphthalene derivatives and to mediate multi-component and Friedel-Crafts reaction sequences. However, most of the reaction conditions are vigrous, inconvenient or expensive. Therefore, selenium-mediated protocols along with mild reaction conditions could be advantageous more useful for the synthesis of these products.

3.5 Background of the Project

As described earlier in Chapter 2, a series of β-keto ester stilbene derivatives **167** with different substituents were treated with phenylselenenyl chloride in the presence of Lewis acids under very mild reaction conditions as shown in Scheme 81. This method afforded dihydronaphthalene derivatives **169** in good yields (Chapter 2, Table 2, page no. 47). Furthermore, the conversion of these dihydronaphthalenes and stilbenes into benzofluorenes through a Friedel-Crafts reaction was found to proceed with the migration of ester and acetyl functional groups (Scheme 62 & Table 3, pages no. 49–53).[128]



Scheme 81: Use of stilbenes **167** for the synthesis of dihydronaphthalenes and benzofluorenes

A range of benzofluorenes has also been synthesised in good yield from the reaction of β-keto ester substituted stilbenes with phenylselenenyl chloride through a cascade biscarbocyclisation process (Chapter 2, Table 3). The proposed mechanism for the reaction is shown in Scheme 66 (page no. 56–57). The cascade of events is initiated by the nucleophilic attack of the benzene on the electrophilic carbonyl which is activated by Lewis acid. Chapter 2 describes further the development of this chemistry including the fact that the new annulation chemistry can be conducted with the combination of Lewis acids and selenium electrophiles. Furthermore, we intended to extend the scope of this annulation reaction to other carbocycles.

Previous methods for the formation of naphthalenes and biaryls usually require either complex reaction conditions or give low yields due to the formation of side products. This makes them either undesirable or impractical in a number of synthetic applications. It was decided to explore whether this new reaction would allow the synthesis of naphthalenes and biaryls in higher yields from easily available starting materials.

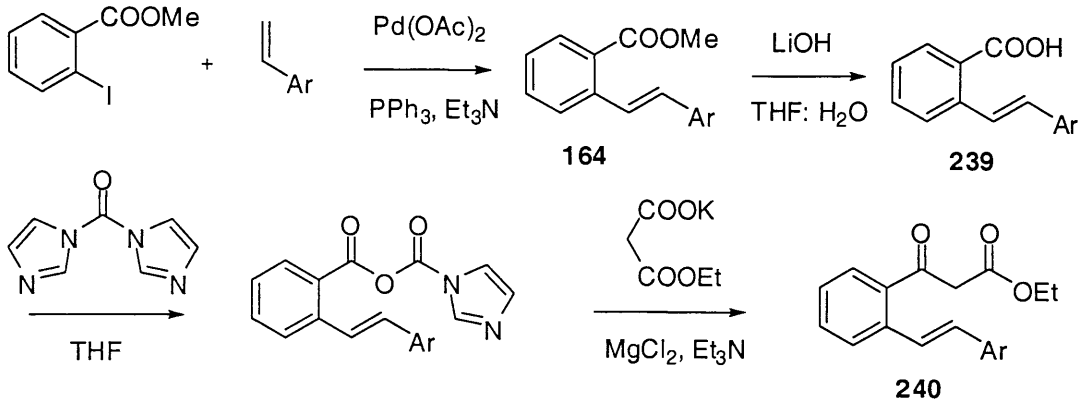
3.6 Results and discussion

3.6.1 Our Proposed Methodology

To study the scope of the novel annulation chemistry described in Chapter 2. We proposed linear β-keto-dicarbonyl stilbenes as precursors of target carbocycles. A range of β-keto ester substituted stilbenes were obtained from commercially available methyl 2-iodobenzoate. The scope of this methodology has been further explored by reacting a range of β-keto ester substituted stilbenes with phenylselenenyl chloride to get the envisioned cyclic products.

3.6.2 Synthesis of the Starting Compounds

The synthesis of the stilbene starting materials is based on known reaction sequences which involve Mizoroki-Heck reactions, ester hydrolysis, and subsequent condensation steps. The palladium-catalysed cross-coupling reaction of methyl 2-iodobenzoate with different styrene derivatives afforded esters **164** in good yields. The resulting esters were hydrolysed to the corresponding carboxylic acids **239** almost quantitatively with lithium hydroxide (Scheme 82). Condensation of the carboxylic acid with potassium ethyl malonate in the presence of 1,1′-carbonyldiimidazole, triethylamine and magnesium chloride afforded the β-keto ester derivatives **240**.[129] NMR investigations revealed that the stilbene β-keto esters **240** are in equilibrium with their corresponding enol forms with the equilibrium largely shifted toward the keto form. Yields of all products are summarized in Table 4.



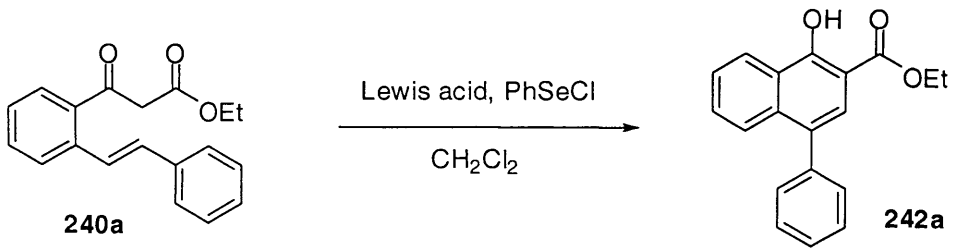
Scheme 82: Synthesis of target substrates **240a–h**

Table 4: Yields of esters (**164**), acids (**239**) and substrates (**240**)

Entry	Aryl	(Esters-164) [yield %]	(Acids-239) [yield %]	(Substrates-240) [yield %]
1	phenyl	(**164a**) 87	(**239a**) 87	(**240a**) 83
2	4–tolyl	(**164b**) 82	(**239b**) 88	(**240b**) 98
3	4–methoxyphenyl	(**164c**) 85	(**239c**) 97	(**240c**) 95
4	2–naphthyl	(**164d**) 87	(**239d**) 95	(**240d**) 83
5	1–naphthyl	(**164e**) 93	(**239e**) 98	(**240e**) 95
6	2–chlorophenyl	(**164f**) 88	(**239f**) 100	(**240f**) 58
7	3–chlorophenyl	(**164g**) 81	(**239g**) 100	(**240g**) 80
8	4–chlorophenyl	(**164h**) 80	(**239h**) 99	(**240h**) 94

3.6.3 The Use of Phenylselenenyl Chloride for Selective C–C Bond Formation

The same reagent combination (phenylselenenyl chloride and Lewis acids) is now used for the cyclisation of *β*-keto ester substituted stilbenes **240**. The treatment of *β*-keto ester **240a** with phenylselenenyl chloride and titanium tetrachloride resulted in 6-*endo* cyclisation and phenyl migration to give **242a** (Scheme 83).



240a **242a**

Scheme 83: Optimisation of new synthetic pathway for biaryl **242a**

Table 5: Optimisation of reaction conditions

Entry	Lewis acid	PhSeCl	Reaction Time [h]	Temperature [°C]	Yields 242a [%]
1	$TiCl_4$ (2.5 eq.)	1.5 equiv.	10	–78	61
2	$SnCl_4$ (2.5 eq.)	1.5 equiv.	10	–78	59
3	$AlCl_3$ (2.5 eq.)	1.5 equiv.	1	–78	70
4	BF_3•OMe_2 (2.5eq.)	1.5 equiv.	4	20	75
5	$FeCl_3$ (2.5 eq.)	1.8 equiv.	0.5	–78	79
6	$FeCl_3$ (1.1 eq.)	2.0 equiv.	0.5	–78	82
7	BF_3•OMe_2 (2.5eq.)	–	48	20	traces
8	$FeCl_3$ (2.5 eq.)	–	50	20	40
9	$ZrCl_4$ (1.1 eq.)	2.0 equiv.	2	–78	80
10	$ZrCl_4$ (1.1 eq.)	1.0 equiv.	2	–78	45[a]
11	$ZrCl_4$ (2.5 eq.)	–	48	–78	No reaction
12	–	2.0 equiv.	2	–78	No reaction

[a] conversion measured by ^{1}H NMR on crude reaction product

The selenium moiety was eliminated under the reaction conditions as we have observed in other examples,[128] and the naphthol derivative **242a** was isolated in 61% yield. Careful analysis of the product **242a** also revealed that a migration of the phenyl group had taken place as this was found in the 4-position. The spectroscopic data of **242a** are in agreement with literature values.[130] The structural assignment of biaryl **242a** is based on their IR and ^{1}H, ^{13}C and DEPT NMR spectra. The IR absorption for the carbonyl function of ester in **242a** appears at ca. 1661 cm^{-1}, while it appears at 1656 cm^{-1} in the un-rearranged product.[123] The ^{1}H NMR spectra of the biaryl **242a** shows that the distinctive aromatic methylene and phenolic group appear at 7.66 (1 H, singlet) and 12.01 (1 H, singlet), respectively. The aromatic and non-aromatic carbons were clearly assigned by ^{13}C and DEPT NMR spectroscopy. High resolution mass spectrometric results also support the formation of cyclic product but final proof of the structure was provided by an X-ray analysis obtained from crystals of compound **242a** (Figure 11, see detail in Appendix 2.3).

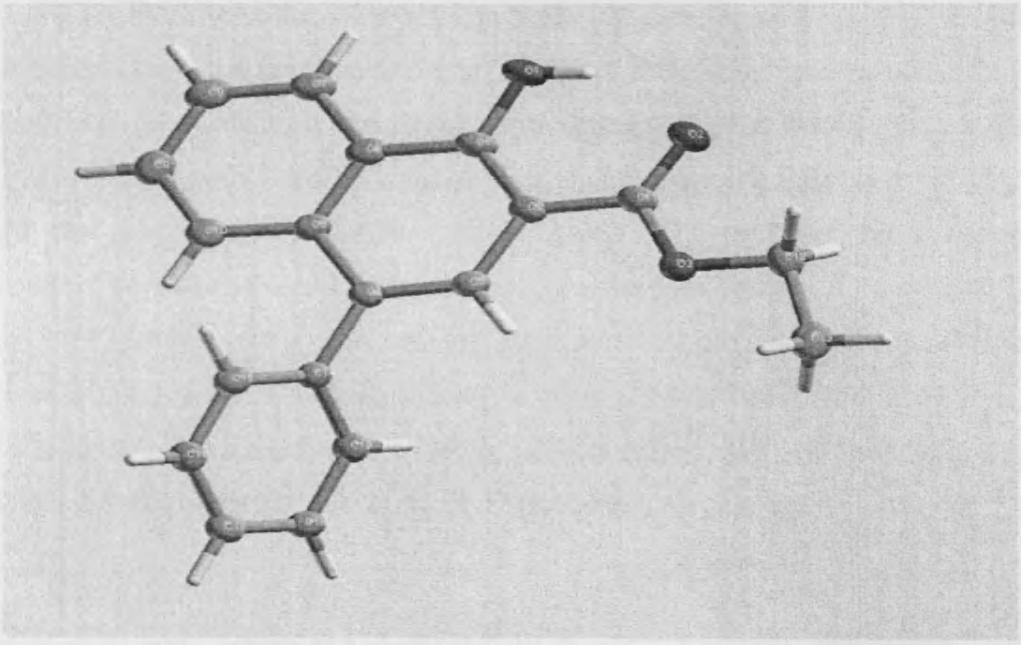
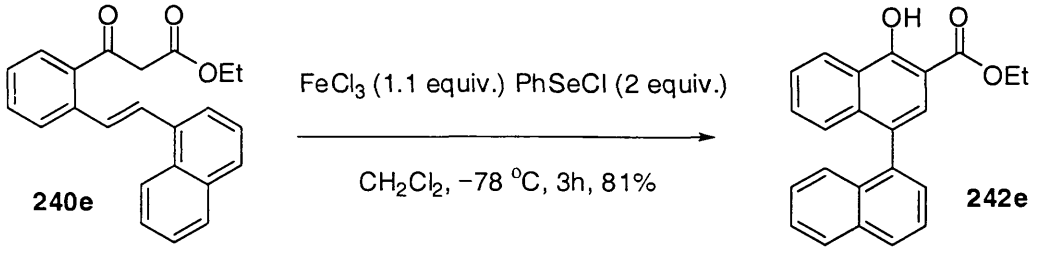


Figure 11: Single crystal X-ray analysis of **242a**

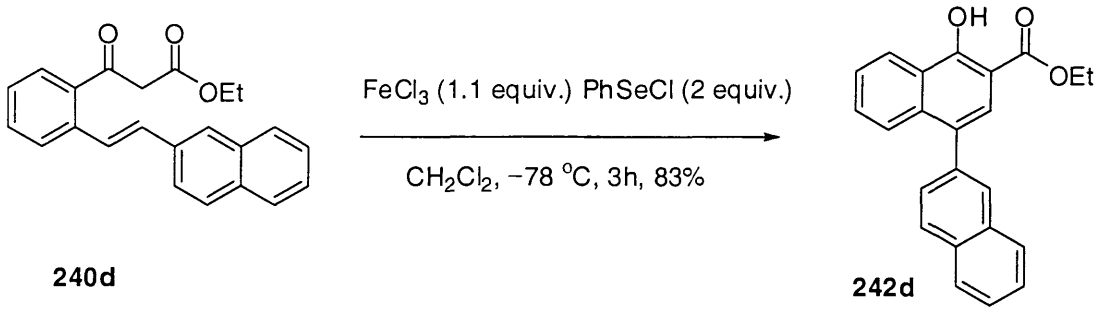
Other Lewis acids and reaction conditions were screened which resulted in different yields of **242a**; some of these results are shown in Table 5. The Lewis acids $FeCl_3$ and $ZrCl_4$ provided the highest yield in this reaction with short reaction times under very mild reaction conditions (Table 5, entries 6 and 9). Experiments revealed that the optimal combination is $FeCl_3$ with PhSeCl as a very good yield is obtained in only 30 min reaction time (entry 6). When $BF_3 \bullet OMe_2$ (2.5 equiv) was used in the presence of PhSeCl, the product was obtained within 4 h in 75% yield (entry 4). The combination of phenyl selenenyl chloride with many Lewis acids are more or less effective for this C—C bond formation, and the corresponding substituted naphthalene **242a** was obtained after rearrangement of the aryl substituent. Less reactive Lewis acids such as $BF_3 \bullet OMe_2$ can be used at room temperature. To test the feasibility of this carbocyclisation without PhSeCl, stilbene **240a** was reacted with either $BF_3 \bullet OMe_2$ (2.5 equiv) or $ZrCl_4$ (2.5 equiv), but even after prolonged time (2 days) no reaction was observed (Table 5, entries 7 and 11). However, using stronger Lewis acids, the carbon nucleophile can add to the alkene (activated by Lewis acid) to afford the same cylic 6-*endo* product with rearrangement in reduced yield. For example, when only iron (III) chloride (2.5 equiv) was used for the cyclisation, the yield dropped to 40% (Table 5, entry 8). In addition, it was found that 1.1 equiv of the Lewis acid was sufficient (Table 5, entries 5 and 6).

Adopting the conditions described in Table 5, entry 6 as the optimal reaction conditions for cyclisation and rearrangement, the generality of the method was demonstrated by evaluating a variety of substrates. For example naphthyl sustituted β-keto ester stilbene **240e** was treated with iron(III) chloride and phenylselenenyl chloride at −78 °C to afford the *6-endo-trig* cyclisation product **242e**. As a result of the *6-endo-trig* cyclisation, ethyl 4-hydroxy-1,1′-binaphthyl-3-carboxylate **242e** was formed in 81% yield (Scheme 84). However, the same reaction protocol at room temperature failed to produce a good yield of **242e**. Similarly, a poor yield of **242e** was obtained when reaction time was extended up to 20 hours. This reaction could also serve as an entry into the synthesis of various substituted 1,1′-binaphthyl derivatives.



Scheme 84: Synthesis of ethyl 4-hydroxy-1,1′-binaphthyl-3-carboxylate **242e**

After the successful thermal rearrangement of a 1-naphthyl group at very low temperature −78 °C encouraged us to establish a reliable method for the preparation of interesting biaryl derivatives. The treatment of 2-naphthyl-substituted stilbene substrate **240d** with phenylselenenyl chloride in the presence of iron(III) chloride induced a similar 6-*endo* cyclisation with rearrangement to the corresponding cyclic product **242d** in very good yield (Scheme 85). From this reaction, cyclisation and rearrangement of 2-naphthyl group was accomplished under very mild reaction conditions and provided a noteworthy case to prepare 1,2′-biaryl of type **242d**.

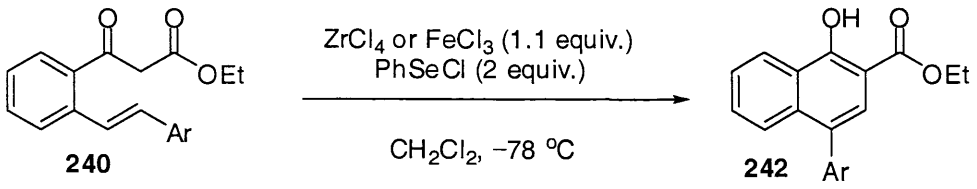


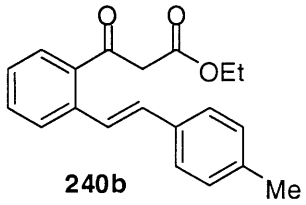
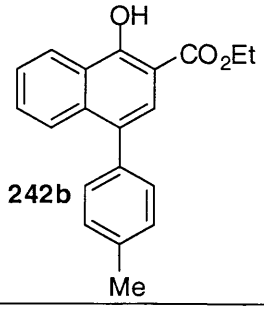
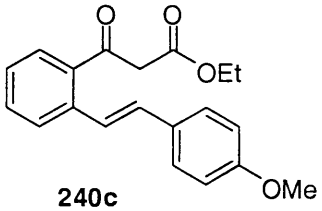
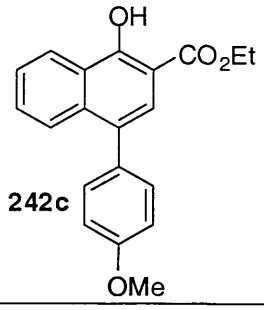
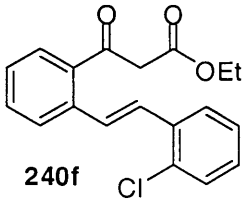
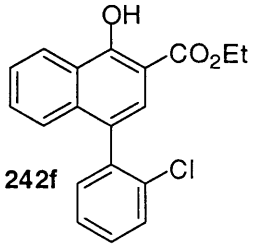
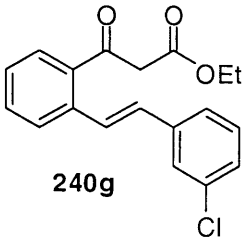
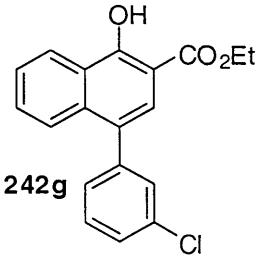
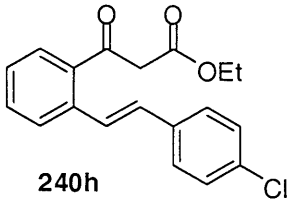
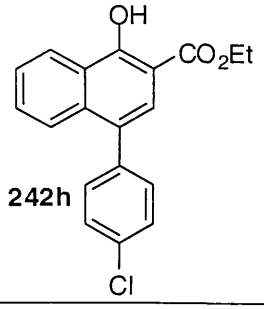
Scheme 85: Synthesis of ethyl 4-hydroxy-1,2′-binaphthyl-3-carboxylate **242d**

The results in Table 6 demonstrate that the reaction proceeds smoothly with various substituted stilbenes to afford 4-substituted naphthalen-1-ols in good yields (Table 6, entries 1–5). For example, *β*-keto ester substituted stilbenes bearing a chlorine substituent on the aromatic ring can also be cyclised with rearrangement in good yields by using of phenylselenenyl chloride and anhydrous $FeCl_3$ at −78 °C (Table 6, entry 3–5). Using $ZrCl_4$ as a Lewis acid and selenium in this reaction also provides corresponding 6-*endo-trig* cyclisation products with rearrangement in good yields. The 2- and 3-chlorophenyl substituted stilbenes were transformed into the corresponding cyclised products in 81% and 68% yield respectively within 1.5 h, (Table 6, entry 3–4). However, the rate of transformation of 4-chlorophenyl substituted stilbene into the corresponding product was relatively slow and the product was obtained in 69% yield after 5 h stirring at −78 °C (Table 6, entry 5).

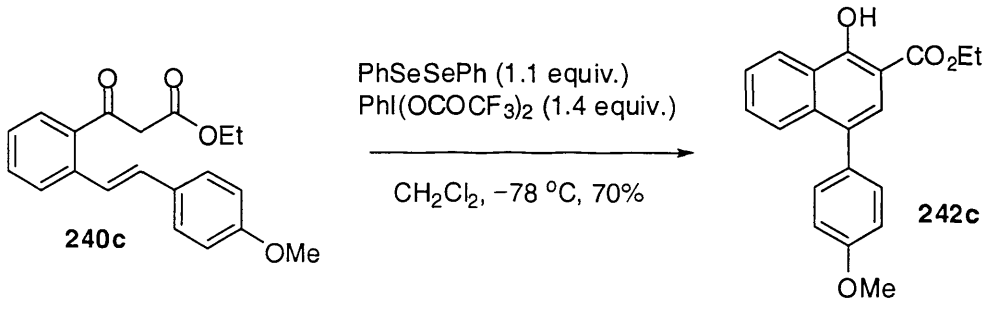
Substrates with electron-donating groups, such as **240b** and **240c** were much more reactive in this transformation. Cyclisation and subsequent rearrangement was achieved in good yields in a shorter period of time with a range of Lewis acids such as $FeCl_3$, $ZrCl_4$ and phenylselenenyl chloride (Table 6, entry 1–2). It was also found that the reaction tolerates a variety of substituents on aryl ring. With aromatic substituents R, the substrates **240a–240i** underwent facile cyclisation and migration of the aryl moiety R to the neighboring sp^2-hybridized carbon atom. It is necessary to maintain the temperature at −78 °C to obtain good yields. These results are particularly significant when considering that all synthetic routes to 4-arylsubstituted naphthalen-1-ol derivatives are long and complicated. In addition, Lewis acids such as $BF_3{\bullet}OMe_2$, $FeCl_3$, $ZrCl_4$, $TiCl_4$, $SnCl_4$ and $AlCl_3$ in combination with phenylselenenyl chloride are capable of achieving the described benzannulation reactions (Table 6). Electron-poor aryl groups afforded slightly lower yields, but electron-rich moieties (Table 6, entry 1–2) gave facile migration of the aryl group to produce aryl-substituted naphthalen-1-ols in high yield.

Table 6: Synthesis of biaryls **242** from a range of β-keto ester stilbenes **240**



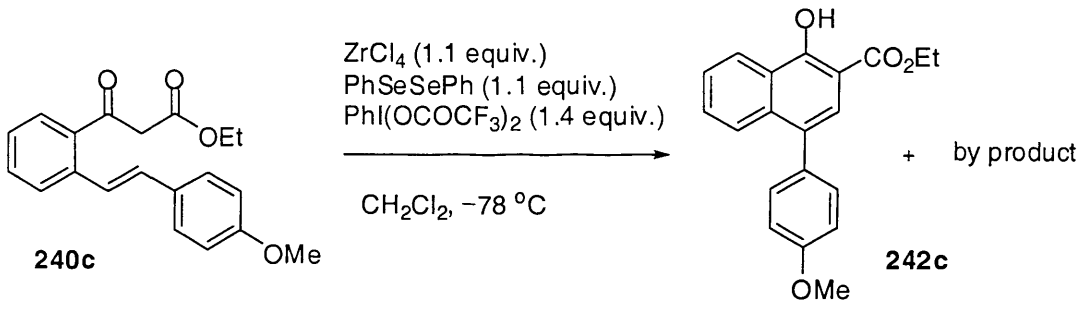
Entry	Substrate 240	Product 242	Time [h]	Yield [%]
1	 **240b**	 **242b**	1	80
2	 **240c**	 **242c**	1	96
3	 **240f**	 **242f**	1.5	81
4	 **240g**	 **242g**	1.5	68
5	 **240h**	 **242h**	5	69

Wirth *et al* have already shown that [bis(trifluoroacetoxy)iodo]benzene and catalytic amounts of diphenyl diselenide is an effective reagent combination for the synthesis of butenolides.[160] A similar logic, using a PhSeSePh rather than phenylselenenyl chloride as the source of electrophile was used in these carbocyclisation reactions. As expected, this transformation is compatible with a range of substrates. For the carbocyclisation of **240c**, however, only the combination of [bis(trifluoroacetoxy)iodo]benzene with stoichiometric amounts of diphenyl diselenide led to product formation probably *via* phenylselenenyl trifluoroacetate as the reactive selenium electrophile (Scheme 86). When only the hypervalent iodine reagent was used without diphenyl diselenide, only small amounts of the product **242c** are formed together with side products.



Scheme 86: Diphenyldiselenide and [bis(trifluoroacetoxy)iodo]benzene mediated carbocyclisation

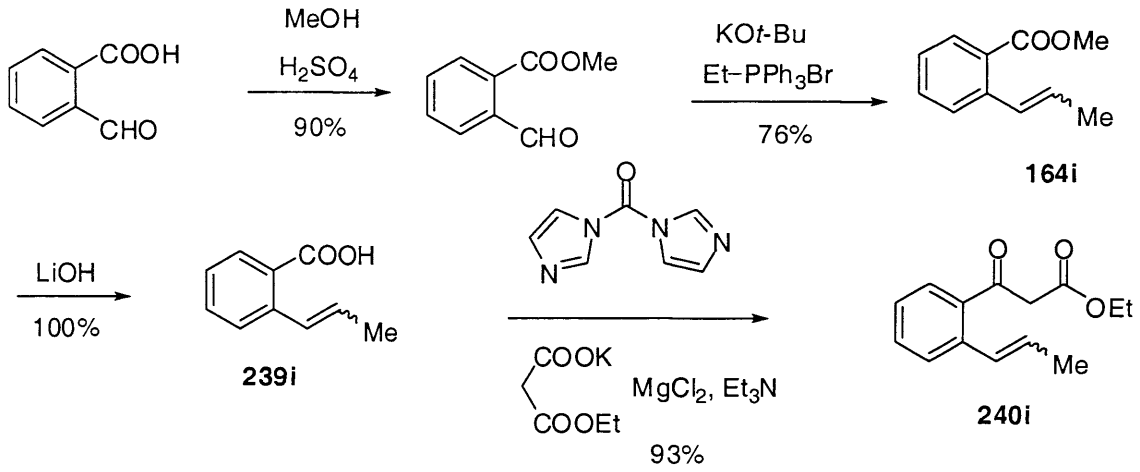
The treatment of β-keto ester substituted stilbene **240c** with Lewis acid in the presence of diphenyldiselenide and [bis(trifluoroacetoxy)iodo]benzene led to the formation of the desired product along with unidentifiable by products. However, separation of these products is quite difficult. From this reaction, it was found that the use of Lewis acid was unnecessary, since **242c** was formed in a good yield upon treatment with diselenide plus hypervalent iodine such as [bis(trifluoroacetoxy)iodo]benzene without subsequent addition of Lewis acid (Scheme 87).



Scheme 87: The use of diphenyl diselenide, hypervalent iodine reagent and Lewis acids to effect carbocyclisation

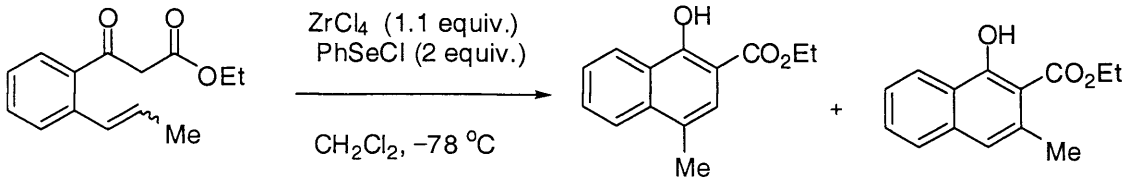
3.6.4 Synthesis of an Alkene and Subsequent Cyclisation Reaction

After the successful cyclisations with aryl substituted starting materials, we investigated alkyl substituted substrates as alternative cyclisation precursors. Therefore substrate **240i** was prepared in good yield as shown in Scheme 88. The methyl-substituted β-keto ester substituted alkene **240i** was prepared from commercially avaliable 2-formyl benzoic acid. Synthesis of **240i** began by esterification of 2-formyl benzoic acid followed by standard Wittig protocol[92] which gave **164i** as a 1:5.5 mixture of (*E* : *Z*) diastereomers. Sequential hydrolysis of the ester allowed us to introduce the β-keto function by means of a condensation of acid **239** with potassium salts of mono ethylmalonate. The above mentioned synthetic sequence and reaction conditions giving methyl 2-(prop-1-en-1-yl)benzoate **240i** as a 1:5.5 mixture of *E* and *Z* isomers in 93% yield (Scheme 88).



Scheme 88: The synthesis of methyl susbstituted β-keto ester alkene **240i** from 2-formyl benzoic acid

Notably, when *E* and *Z* (1:5.5) mixture of the methyl substituted β–keto ester alkene **240i** was subjected to selenium electrophilic cyclisation by employing similar reaction conditions, a 50% yield of cyclised products **242i** and **243i** was formed upon reaction with selenium electrophile and $ZrCl_4$ in a 2:1 ratio that was inseparable by flash chromatography (Scheme 89). All attempts to separate these two products failed. It appears that migration of the methyl group is less favourable than that of the aryl groups. It is known that groups less able to accomodate a positive charge migrate more slowly in cationic rearrangements.[132a] The role of a phenonium ion can also facilitate the migration of phenyl groups in such reactions.



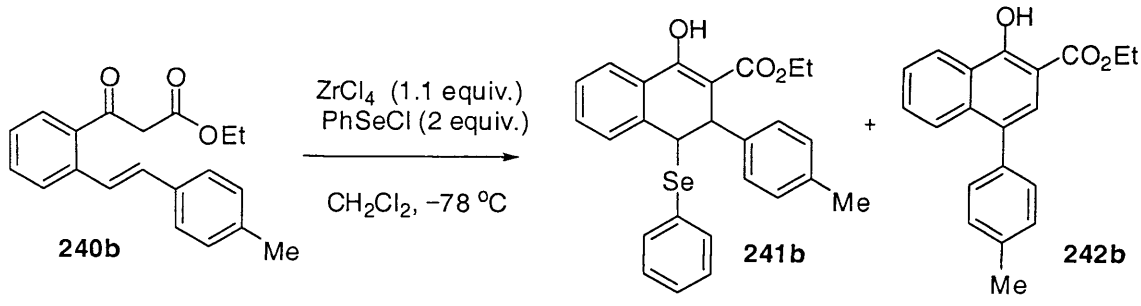
240i 242i 243i

Scheme 89: Methyl substituted synthesis of naphthalene **242i** with partial rearrangement of a methyl group

3.6.5 Computational Study and Mechanistic Insight

The study on the use of Lewis acid without the selenium electrophile showed a poor conversion of substrate **240a** into product **242a** when strong Lewis acids $FeCl_3$ and $TiCl_4$ are employed (Table 5, entry 8). This raises questions about the precise roles of the selenium electrophile and the Lewis acid in this carbocyclisation. The need for both the Lewis acid and the selenium electrophile to obtain carbocylisation products in good yield suggests that they act together in the dominant mechanism. Further experiments revealed more mechanistic detail.

Quenching the reaction after 15 min allowed isolation of the key intermediate **241b**, by preparative TLC and its characterisation by ^{1}H, ^{13}C and ^{77}Se NMR spectroscopy (Scheme 90). Seleno-dihydronaphthalene **241b** initially forms but then disappears, whilst biaryl **242b** appears with the passage of time when monitored by TLC, suggesting that seleno-dihydronaphthalene **241b** is an intermediate in the formation of biaryl **242b**.

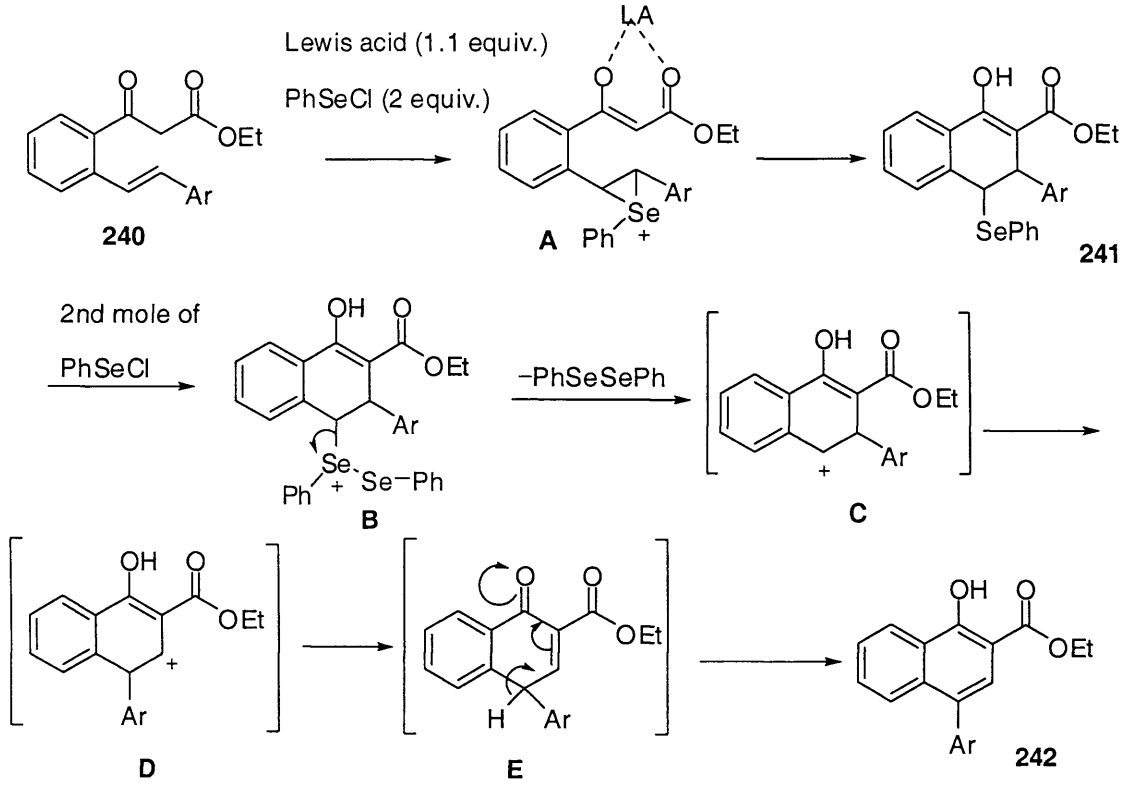


240b 241b 242b

Scheme 90: Isolation of key intermediate **241b**

The reaction is proposed to proceed by the activation of the double bond to generate seleniranium ion **A**. The carbon nucleophile from the corresponding enolate then reacts

with the seleniranium ion intermediate to form cyclic dihydronaphthalene product **241**. The subsequent activation of the selenide moiety **B** by a second selenium electrophile (supported by the recovery of PhSeSePh in quantitative yield) produces the carbocationic intermediate **C**, which then rearranges to **D** and, after rearomatisation, generates **242** as single reaction product (Scheme 91).



Scheme 91: The proposed mechanism for selenium-mediated cyclisation of **240**

This observation was rationalised by performing computational studies[131] on these carbocations which support the proposed mechanism for the synthesis of carbocycles **242**. The carbocations **C** and **D** with Ar = Ph (from **240a**) and also by replacement of this aryl group with a methyl (from **240i**) were calculated as methyl esters instead of ethyl esters. The ab initio calculations were performed using the Gaussian 03 program.[133] Geometries were fully optimized at B3LYP/6–31G(d) level using the PCM solvent model for dichloromethane, and the obtained energy minimum structures were characterized by frequency calculation at the same calculation level. It was found that both cations **D** (Ar = Ph and Ar = Me) are more stable than the cations **C** by approximately 14.5 kcal/mol. Attempts to locate a phenonium ion intermediate as observed by us in other cyclisations failed.[132b]

3.6.6 Summary

In conclusion, we have shown that various carbocyclic ring systems can be prepared by cyclisation of *β*-keto ester substituted stilbenes using selenium electrophiles in the presence of Lewis acids. The resulting 4-substituted naphthalen-1-ols are obtained through cyclisation and subsequent 1,2-rearrangement of aryl groups under very mild reaction conditions. Of particular interest is our finding that the course of aryl rearrangements is dictated by the formation of a homo-benzylic cation and the nature of substituents on the alkene. When the aryl ring carries a powerful electron-donating group, conversion of the substrate and rearrangement was observed much faster than those substrates having electron-withdrawing groups. In other cases the strong Lewis acid is also capable to induce 6-*endo* cyclisation without selenium electrophile, which leads to an identical product albeit in lower overall yield.

It is envisioned that this reaction would find applications in the synthesis of natural products, and this methodology will serve as a fast and convenient access to interesting naphthalene and biaryl compounds. Due to their reactivity, *β*-keto ester substituted stilbenes are convenient starting materials for the synthesis of biaryls. The electrophilic selenium approach worked well over a range of substrates, forming products in good yield with a rearrangement that can be further manipulated. This opens attractive possibilities for C—C bond formation in typical organic reactions falling into the otherwise extremely rare categories of seleno-carbocyclisations. Moreover, with rearrangement of aryl and alkyl groups from the designed substrates, reactions can be performed in a regioselective fashion, allowing for the construction of carbocycles.

From a synthetic perspective, the high yields, low cost of substrate synthesis and safe recovery of selenium in quantitative yield are the key advantages of the transformations described in this chapter. Our methodology is complimentary to existing approaches to naphthalene and biaryls and should prove a valuable addition to the existing toolbox available for the synthesis of such carbocycles.

Chapter 4

4 Synthesis of Isocoumarins and Dihydroisocoumarins

This chapter initially reviews methods for the preparation of isocoumarin derivatives and describes some previous synthetic methods. A new selenium-catalysed synthesis of isocoumarins is discussed and its application for preparation of a range of isocoumarins by reaction of stilbene carboxylic acids with diphenyl diselenide and a hypervalent iodine reagent is described. It was also discovered that dimethyldiselenide and diphenyl disulfide can be used in place of diphenyl diselenide. Using this modification the method was extended to prepare more challenging dihydroisocoumarins.

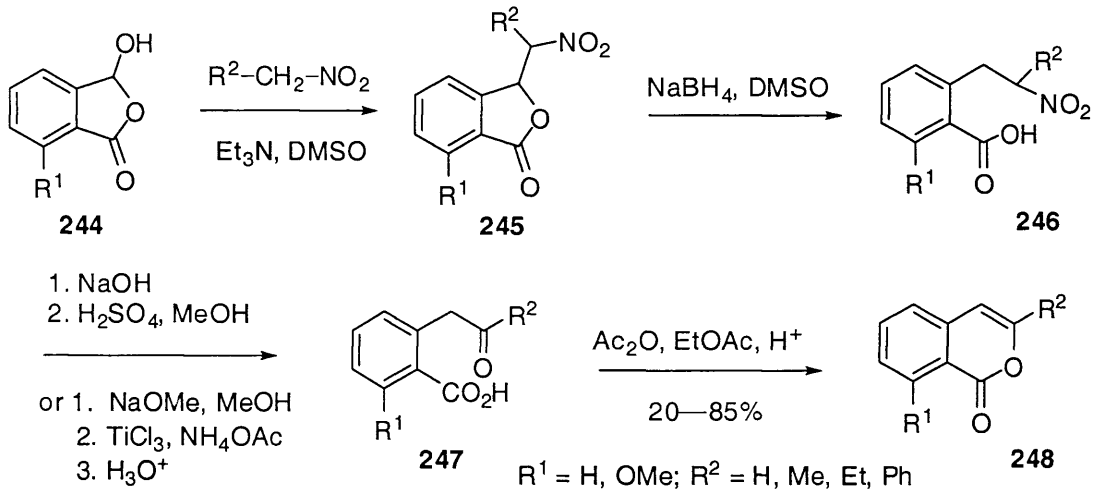
4.1 Applications of Isocoumarins and Dihydroisocoumarins

The isocoumarin skeleton is part of many naturally occurring lactones which display a wide range of biological and pharmacological activities.[134-135] 3,4-Dihydroisocoumarins and their derivatives are compounds that widely exist in nature and serve as key intermediates in the synthesis of biologically active molecules. As these compounds are known to have a wide range of interesting activities such as antifungal, antiallergenic, antiulcer, and antimalarial activities, they are regarded as highly attractive molecules in organic chemistry.[135] 3-Aryl-isocoumarin derivatives constitute a pharmacologically important chemical entity which occurs in several natural products. These include thunberginol C, D, and E and hydrangenol.[136a-b] Pharmacological activities of these natural products include the promotion of the adipogenesis of murine 3T3-L1 cells[136a] and antiproliferative activity against mouse splenocytes.[136b] Other 3-aryl-3,4-dihydroisocoumarins[136c] show antifungal activity,[136d] inhibition of rat basophilic leukaemia RBL-2H3 cells,[136e] antiproliferative activity against C57/BL6 mouse splenocytes,[136b] antiallergic activity,[136f] induction of steroidogenesis,[136g] phagocytic activity,[135c] immunomodulatory activity on spleen lymphocyte proliferation (activated by lipopolysaccharide, concanavalin A and phytohaemagglutinin in mice)[136h] and antimicrobial activity.[136i-k,137] In a number of natural products, one of the hydroxyl groups in the 3-aryl-3,4-dihydroisocoumarin core is glycosylated; this includes, for example, (−)-hydrangenol 4′-O-glucoside[135c] and phyllodulcin 8-O-glucoside.[136a,136j]

4.2 Previous Synthesis of Isocoumarins and Dihydroisocoumarins

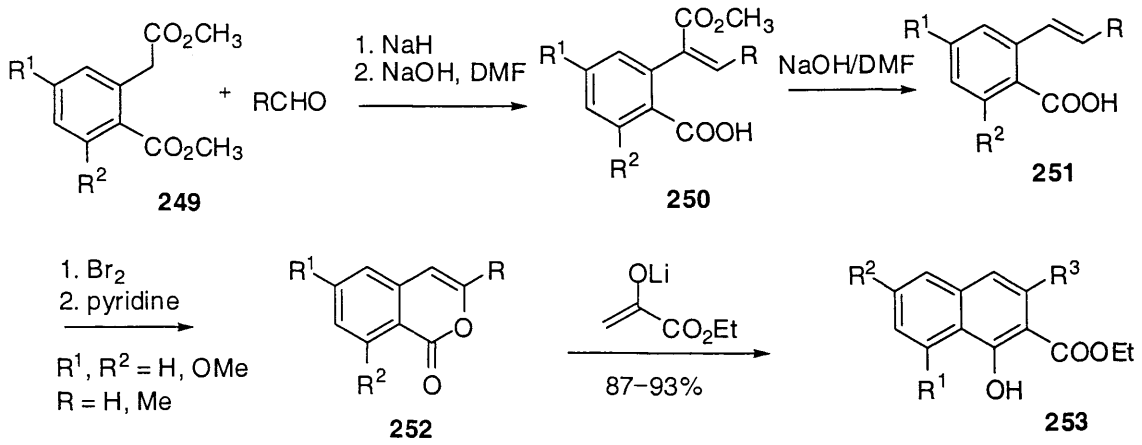
4.2.1 Regiospecific Syntheses of Benzopyran-1-ones

In 1988, Hauser and co-workers[138a] reported the synthesis of benzopyran-1-ones **248** from phthalaldehydic acids **244** and nitroalkanes (Scheme 92). The sequence permits a straightforward variation of both the 3-substituent and the pattern of functionalisation on the aromatic ring of the benzopyran ring system. The nitroalkyl isobenzofuranones **245** (obtained from condensation of **244** and nitroalkanes with triethylamine in DMSO) are treated with sodium borohydride in dimethyl sulfoxide providing the (nitroalkyl)benzoic acids **246** in 70–95% yield. The benzopyran-1-ones **248** were obtained by the Nef reaction of **246** followed by intramolecular cyclisation of the resulting **247** and subsequent dehydration (Scheme 92).



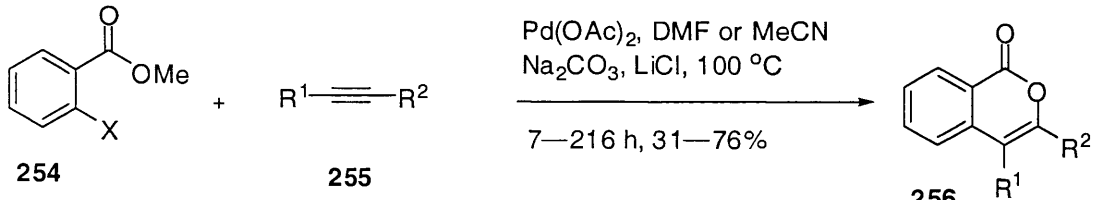
Scheme 92: Synthesis of isocoumarins **248** from phthalaldehydic acids **244**

Stobbe condensations of homophthalates **249** with aldehydes have also been widely employed for the synthesis of benzopyran-1-ones **252** as shown in Scheme 93. Reactions of the homophthalate **249** with aromatic aldehydes gave good yields of the styryl half esters **250**; however, the corresponding reaction with aliphatic aldehydes gave low yields. The additional steps necessary to convert **250** to **251** are harsh, and the overall yields of products using this approach are rather modest, especially for benzopyranones containing a 3-alkyl group **252**. Isocoumarins can be used as precursors of carbocycles as shown in Scheme 93. The lithium enolate of ethyl acetate reacts smoothly with benzopyran-1-ones **252** to give naphthoates **253** in high yield.[138b-c]



Scheme 93: The synthesis of isocoumarins and their synthetic utility in carbocycle synthesis

Larock and co-workers described the synthesis of the 3,4-disubstituted isocoumarins **256** in good yields by treating the 2-halobenzoate esters **254** with internal alkynes **255** in the presence of a palladium catalyst (Scheme 94).[139] Synthetically, this methodology provides a convenient regioselective route to isocoumarins containing aryl, silyl, ester, *tert*-alkyl, and other hindered groups.

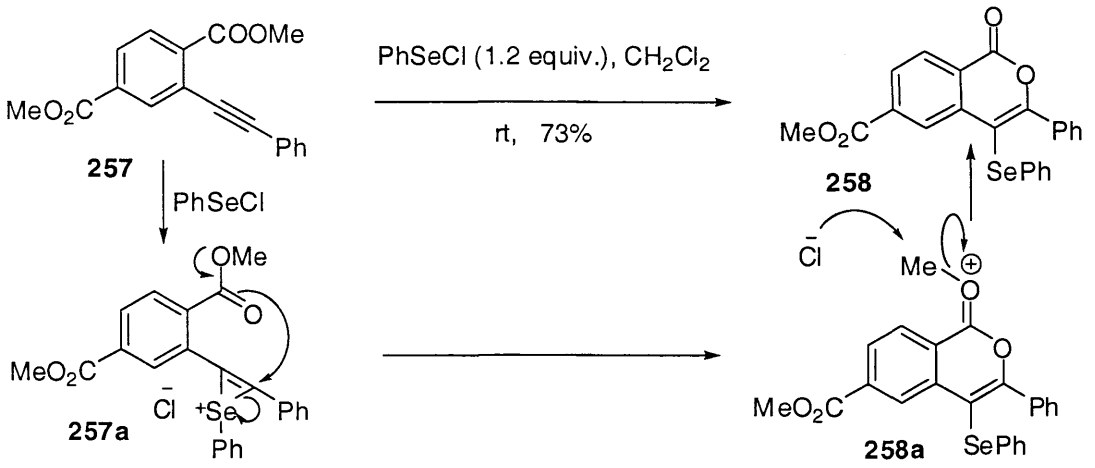


R^1 = Me, Et, *n*-Bu; R^2 = Me_3C, MeCOH, Ph, Me_3Si, *i*-Pr_3Si; X = I, Br

Scheme 94: The synthesis of **256** by palladium-catalysed coupling of **254** with alkynes

4.2.2 Synthesis of Isocoumarins via Electrophilic Cyclisation

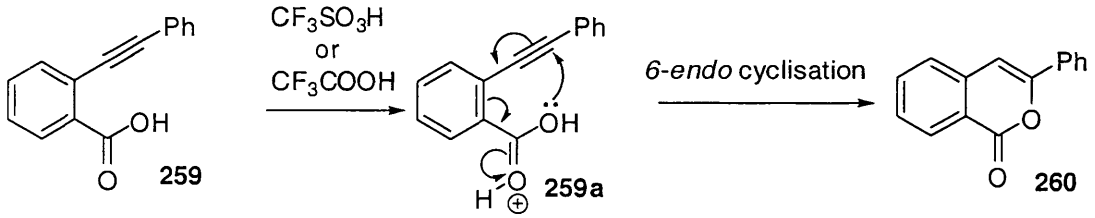
A two-step approach to isocoumarins has been examined by Larock *et al.*[140] This approach involves the preparation of *o*-(1-alkynyl)benzoates **257** by a Sonagashira coupling reaction using 2 mol% $PdCl_2(PPh_3)_2$ followed by an electrophilic cyclisation (Scheme 95). A variety of substituted isocoumarins **258** were prepared in good yields under mild reaction conditions by the reaction of *o*-(1-alkynyl)benzoates **257** with ICl, I_2, phenylselenenyl chloride, 4-nitrophenylsulfinyl chloride, and HI. In a couple of cases, five-membered lactones are also formed. However, few examples are reported for the synthesis of isocoumarins using selenium electrophiles. Overall, this methodology accommodates various alkynyl esters by employing a range of electrophiles.



Scheme 95: Synthesis of isocoumarins by intramolecular electrophilic cyclisation

4.2.3 Acid catalysed Cyclisations of 2-(Phenylethynyl)benzoic acid

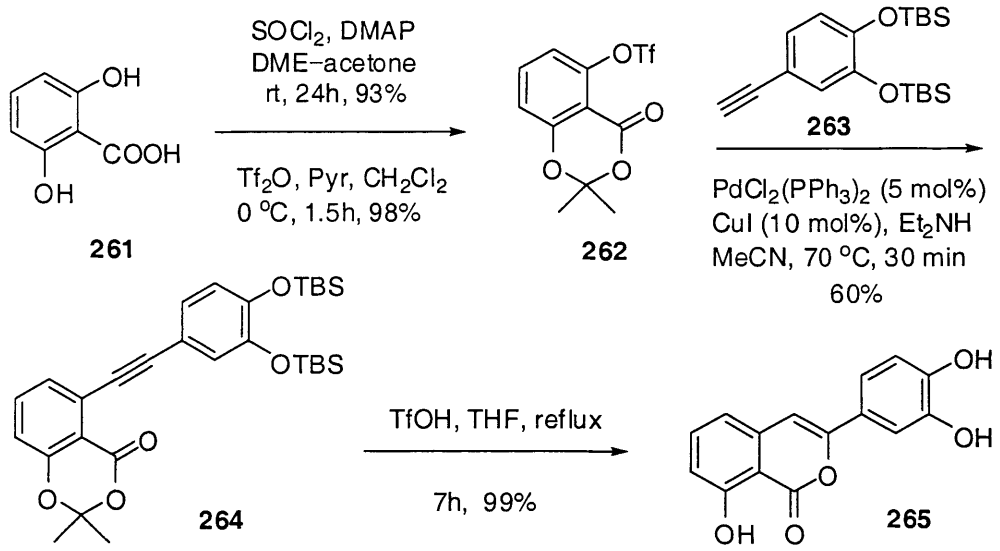
Uchiyama and co-workers described the selective cyclisation of an enynecarboxylic acid **259** to isocoumarin **260**, based on the activation of the carbon-carbon triple bond (**259a**) by acid catalyst and its application to the synthesis of thunberginol A.[141]



Scheme 96: Regiocontrolled intramolecular cyclisations of **259**

Thunberginols were isolated from *Hydrangea bacrophylla* SERINGE var. *thunbergii* MAKINO by Yoshikawa in 1992. They are known for having unique biological activities such as antiallergic and antimicrobial activities.[136i-k,142] Among several syntheses of thunberginol A **265**, Rossi reported the construction of the pyran-2(2*H*)-one system via two successive reactions: the cyclisation of the acetylenic ester mediated by iodine, followed by reductive removal of the iodine atom catalysed by a palladium complex.[143] In 2006, Uchiyama[141] described the synthesis of thunberginol A **265** from commercially available **261** and **263** as starting materials. Cyclisation and deprotection steps were achieved simultaneously under acidic conditions (Scheme 97). The phenolic hydroxyl group and the carboxylate of 2,6-dihydroxybenzoic acid **261** were protected as the acetal, and the resulting hydroxyl group was converted to the triflate in **262** in good overall yield. The Sonogashira coupling reaction between **262** and **263** afforded **264** in 60% yield. Finally, the cyclisation and deprotection steps were

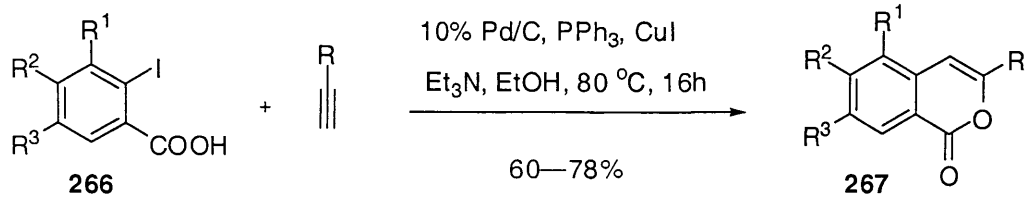
accomplished in the same reaction with TfOH in refluxing THF to furnish thunberginol A **265** (99%).



Scheme 97: Palladium-catalysed synthesis of Thunberginol A **265**

4.2.4 Palladium on Charcoal Catalysed Synthesis of Isocoumarins

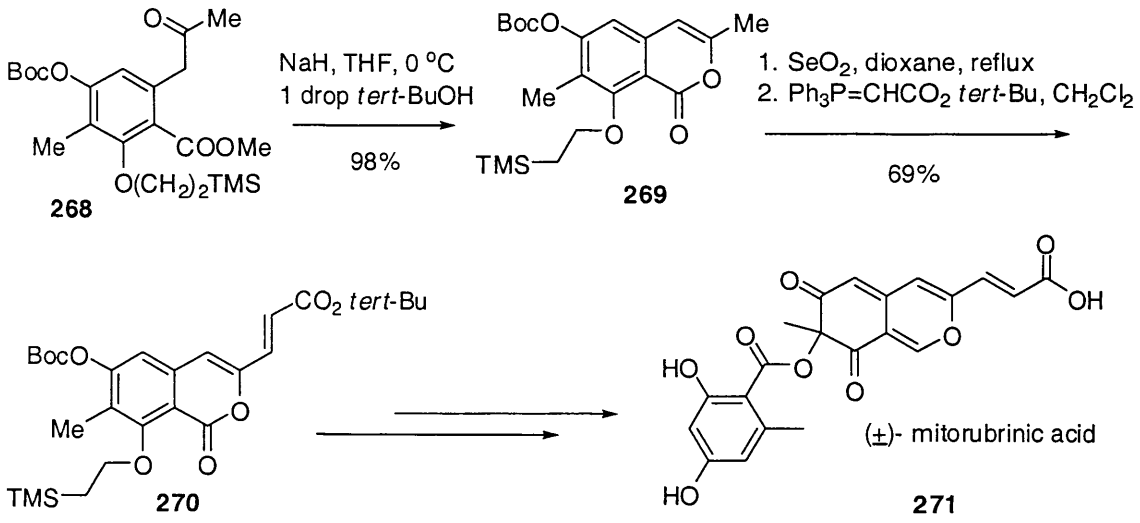
The Pd-catalysed cyclisation of alkynes bearing an oxygen nucleophile is a powerful method for the construction of various oxygen-containing heterocycles. For example, Pal and co-workers[144] reported that 6-membered lactones **267** can be obtained in good yields by the Pd-catalysed intermolecular cyclisation of *o*-iodobenzoic acid **266** with terminal alkynes using a catalyst system of 10% Pd/C-Et_3N-CuI-PPh_3. 3-Substituted isocoumarins were formed in good yields (60–78%) and with good regioselectivity when the reaction was performed in ethanol (Scheme 98).



Scheme 98: Palladium-catalysed coupling of benzoic acid derivatives with alkynes

4.2.5 The use of Isocoumarins as Precursors in the total Synthesis of Mitorubrinic Acid

Pettus and co-workers[145] have shown that keto ester **268** can readily be converted to the corresponding isocoumarin **269** at 0 °C using NaH and *tert*-BuOH. The simple addition of base promoted the enolisation and cyclisation of **268** to afford the isocoumarin **269** in 98% yield. In this example, isocoumarin was used as an advanced synthetic intermediate for the twelve step synthesis of (±)-Mitorubrinic acid **271**, a member of the azaphilone family of natural products, as shown in Scheme 99. Key aspects of the synthesis include elaboration and oxidative dearomatisation of an isocoumarin **269** to provide the azaphilone nucleus with a disubstituted, unsaturated carboxylic acid side chain. Starting from isocoumarin **269**, allylic oxidation with selenium dioxide in anhydrous dioxane affords the corresponding 3-formyl isocoumarin. Homologation using (*tert*-butoxycarbonylmethylene)triphenylphosphorane in dichloromethane gives a 69% overall yield of (*E*)-*tert*-butyl ester **270**.

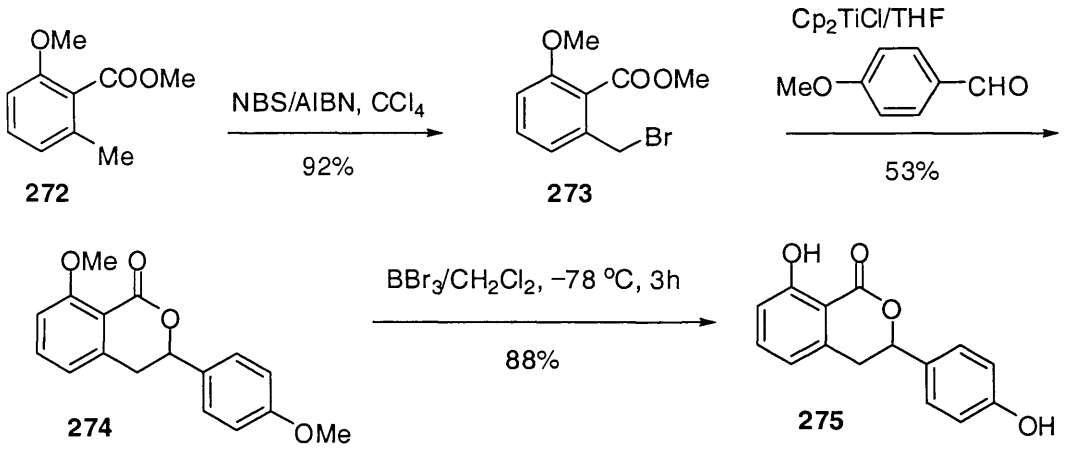


Scheme 99: Synthesis and use of isocoumarin **269** in the total synthesis of mitorubrinic acid **271**

4.2.6 Radical-Induced Synthesis of 3,4-Dihydroisocoumarins

The total synthesis of naturally occurring dihydrocoumarins such as hydrangenol, phyllodulcin, macrophyllol and thunberginol G has been accomplished using titanocene(III) chloride (Cp_2TiCl) as a radical initiator.[146] Cp_2TiCl was prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn-dust. For example, compound **272** was brominated with NBS in the presence of the radical

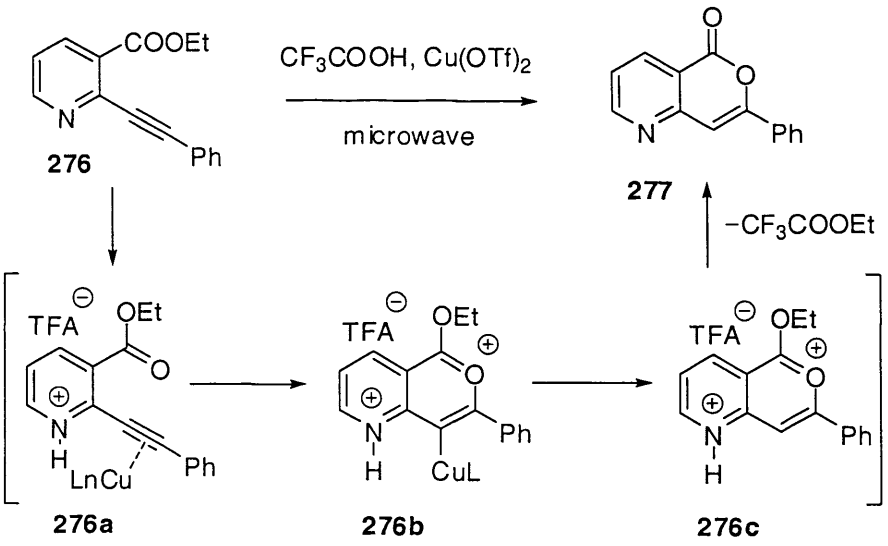
initiator AIBN yielding **273** in 92%. Bromide **273**, on treatment with Cp_2TiCl in the presence of 4-methoxybenzaldehyde, afforded lactone **274** in 53% yield as a crystalline solid. Demethylation of **274** with boron tribromide in CH_2Cl_2 afforded hydrangenol **275** in 88% yield as colourless crystals (Scheme 100).



Scheme 100: Titanocene(III) chloride mediated radical-induced synthesis of hydrangenol **275**

4.2.7 The Use of Lewis Acids in the Presence of Brønsted acids

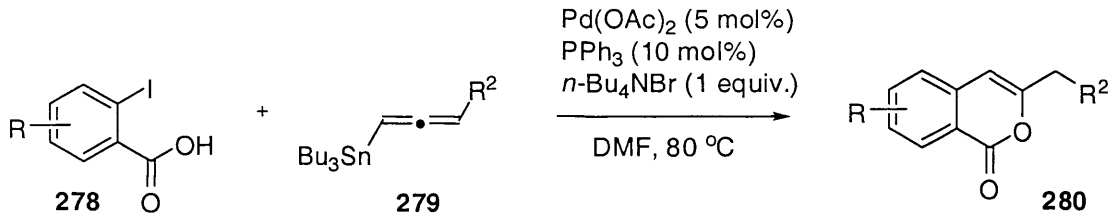
Recently, Bihel and co-workers[147] reported a regiocontrolled *6-endo-dig* cyclisation of 2-(2-arylethynyl)heteroaryl esters **276** to the corresponding lactones **277** by employing Brønsted acids in the presence of a catalytic amount of Lewis acids such as $Cu(OTf)_2$, $AuCl_3$, or $(CF_3CO_2)Ag$ under microwave heating at 100 °C. This chemistry has been used to prepare heterocyclic 6-membered lactone **277** in 98% yield by the reaction of **276** with trifluoroacetic acid and copper triflate (5 mol%). A plausible mechanism for the lactone forming reaction is shown in Scheme 101. Under strong acidic conditions (TFA as solvent), protonation of the pyridine moiety was observed by ^1H NMR spectroscopy. Therefore, the copper catalyst can coordinate with the triple bond, giving **276a**, thus enhancing the electrophilicity of the alkyne. The resulting pyridinium moiety acts as an electron-withdrawing group, leading to an electronic bias on carbons of the alkyne, favoring Michael-type (6-*endo*) cyclisation. The nucleophilic attack of the carbonyl oxygen atom on the electron-deficient alkyne provides cupricate complex **276b** which, after a protonolysis provides lactone **277**, while regenerating the copper catalyst (Scheme 101).



Scheme 101: 6-*endo-dig* Cyclisation of heteroarylester substituted alkynes promoted by a Lewis acid catalyst in the presence of a Brønsted acid

4.2.8 Synthesis of Isocoumarins *via* Tandem Stille Reaction

A general route to 3-substituted isocoumarins from 2-iodobenzoic acids **278** has been described by Cherry and co-workers.[148] Treatment of 2-iodobenzoic acids **278** with various allenyltributyltin reagents **279** in the presence of palladium acetate, triphenylphosphine, and tetrabutylammonium bromide in dimethylformamide provided good yields of the corresponding 3-substituted isocoumarins **280** via a tandem Stille reaction and 6-*endo-dig* oxacyclisation (Scheme 102).

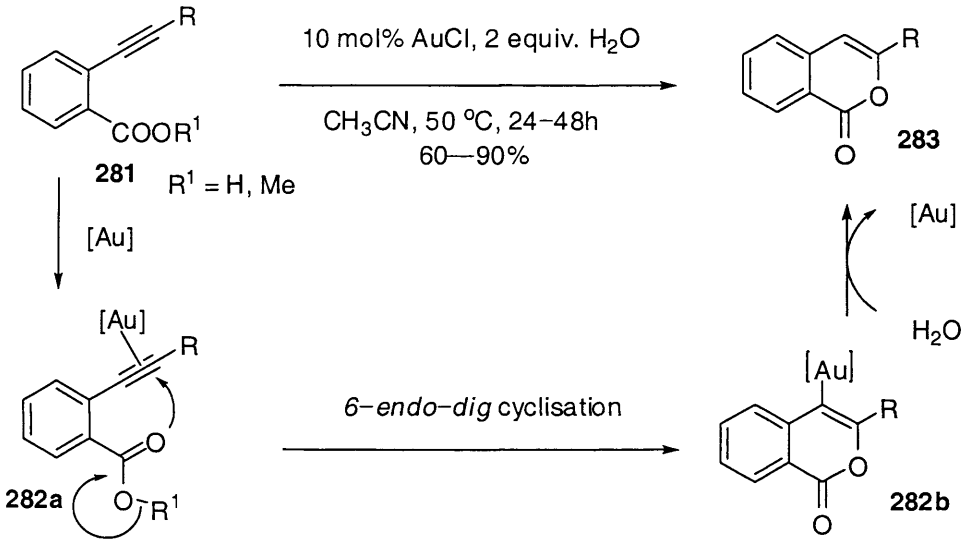


Scheme 102: Synthesis of isocoumarins by utilizing of the tandem Stille reaction

4.2.9 Gold(I) Chloride Catalysed Synthesis of Isocoumarins

Weghe and co-workers[149] investigated a gold(I)-catalysed intramolecular cyclisation of γ-alkynic acids **281** to various alkylidene lactones **283**. The electronic effects of the R group and bulky substituents on the alkyne strongly modify the reactivity. The formation of isocoumarins from the cycloisomerisation of *o*-alkynylbenzoic methyl esters is catalysed by 10 mol% AuCl in the presence of 2 equivalents of water. Under

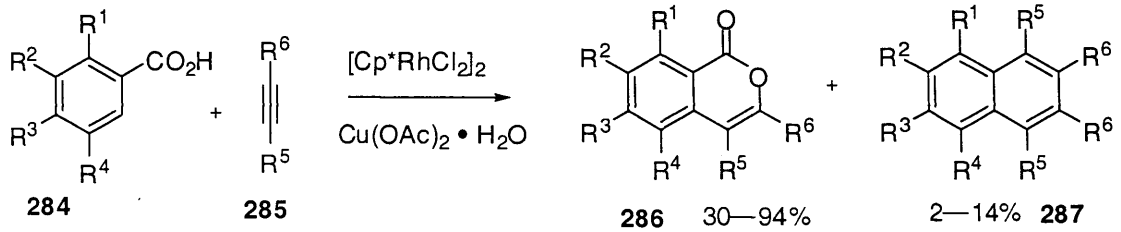
these conditions, several lactone rings **283** are formed in 60—83% yield. A plausible mechanism has also been proposed for the gold-catalysed cyclisation of acetylenic acids and esters (Scheme 103).[149] In the case of the cycloisomerisation of acetylenic acids (R^1=H), the mechanism involved the initial formation of a carboxylate by deprotonation of the acid with K_2CO_3. The nucleophilic attack of the carboxylate on the gold-activated ethylene **282a** led probably to the gold complex **282b**. Protonolysis of **282b** regenerated the gold(I) catalyst furnishing the lactone **283**.



Scheme 103: Cycloisomerisation of γ-acetylenic acids catalysed by gold(I) chloride

4.2.10 Rhodium-Catalysed Synthesis of Isocoumarins

In the context of rhodium mediated catalytic coupling of benzoic acid derivatives, Miura and co-workers[150] have described the rhodium-catalysed direct oxidative coupling of benzoic acids with internal alkynes. This leads to the formation of 6-membered lactones **286** as the major products and naphthalene derivatives **287** as by products (Scheme 104). This process affords a range of isocoumarins **286** in 30—94% yield by the use of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ as catalyst and oxidant, respectively. The reaction of **284** with dialkylacetylenes proceeded efficiently to produce 3,4-dialkylisocoumarins in good yields. Using unsymmetrical alkylphenylacetylenes, 4-alkyl-3-phenylisocoumarins **286** were predominantly formed in 84—89% yields, along with minor amounts of their regioisomers.

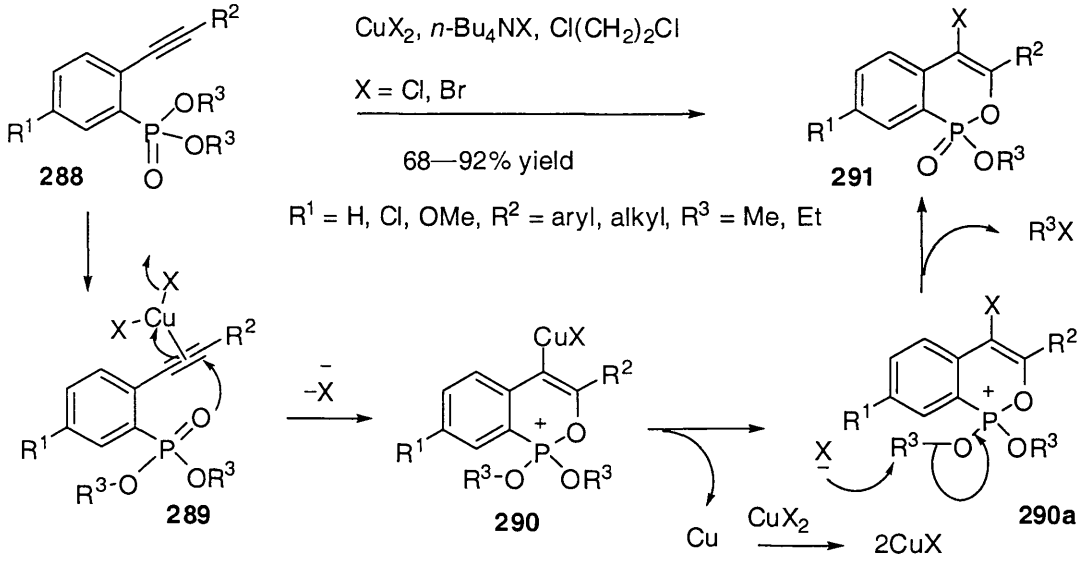


$R^1 = R^2 = H$, Me, OMe; $R^3 = H$, Me, OH, Cl, CF_3; $R^4 = H$, OMe
$R^5 = n$-Pr, n-Bu, n-C_7H_{15}, Me, Ph; $R^6 = n$-Pr, n-C_7H_{15}, Ph

Scheme 104: Rhodium-catalysed oxidative coupling of benzoic acids with alkynes

4.2.11 Synthesis of Phosphaisocoumarins

More recently, a series of 4-halophosphaisocoumarins **291** were formed in good yields by direct halocyclisation of 2-(1-alkynyl)phenylphosphonic acid diesters.[151] Optimal conditions for this cyclisation utilize a catalytic amount of CuX_2 (X = Br, Cl) in dichloroethane with the addition of n-Bu_4NX or/and AgI. Mechanistically, coordination of CuX_2 with the alkynyl moiety of **288** forms the π-complex **289**. Subsequently, regioselective nucleophilic attack of phosphonyl oxygen on to activated triple bond in the *endo* mode gives intermediate **290** (Scheme 105).

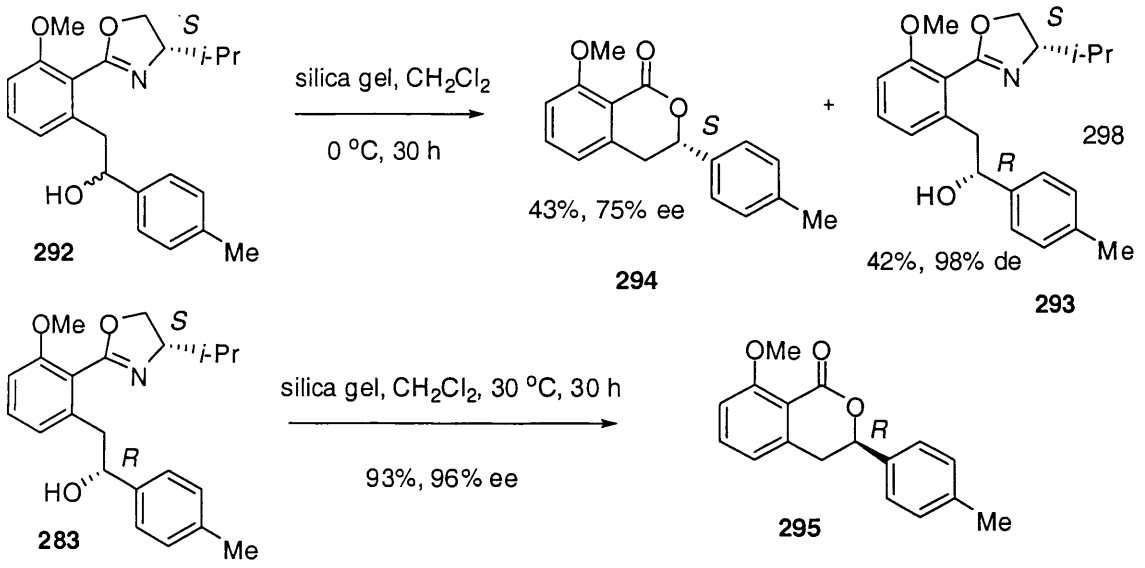


Scheme 105: Synthesis of **291** via CuX_2-mediated direct halocyclisation of **288**

4.2.12 Asymmetric Synthesis of 8-Hydroxy-3,4-dihydroisocoumarins

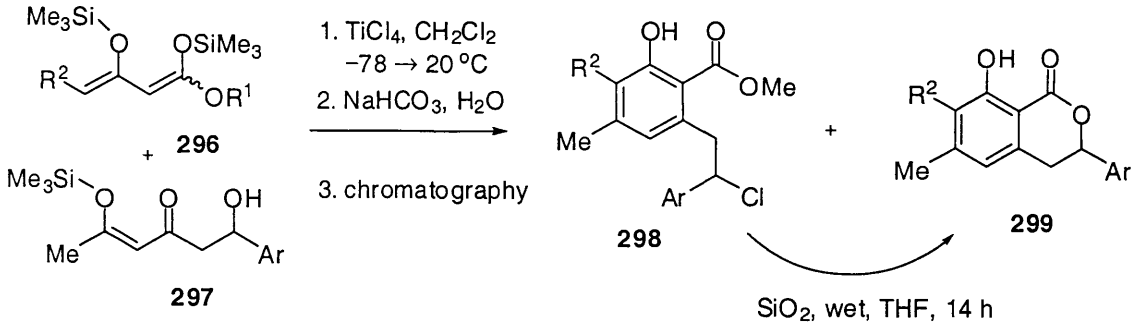
Iwao and co-workers[152] have reported a simple, direct method for the synthesis of dihydroisocoumarin **294** by the reaction of oxazoline **292** and silica gel in dichloromethane at 0 °C (Scheme 106). The (*S*,*S*)-diastereomer of **292** cyclised to the

corresponding 3,4-dihydroisocoumarin faster than the (*S*,*R*)-product on silica gel, allowing access to both enantiomers of 8-methoxy-3-*p*-tolyl)-3,4-dihydroisocoumarin **294** in 75% ee (*S*-enantiomer) and **295** in 96% ee (*R*-enantiomer).



Scheme 106: Asymmetric synthesis of dihydro-isocoumarins **294** and **295**

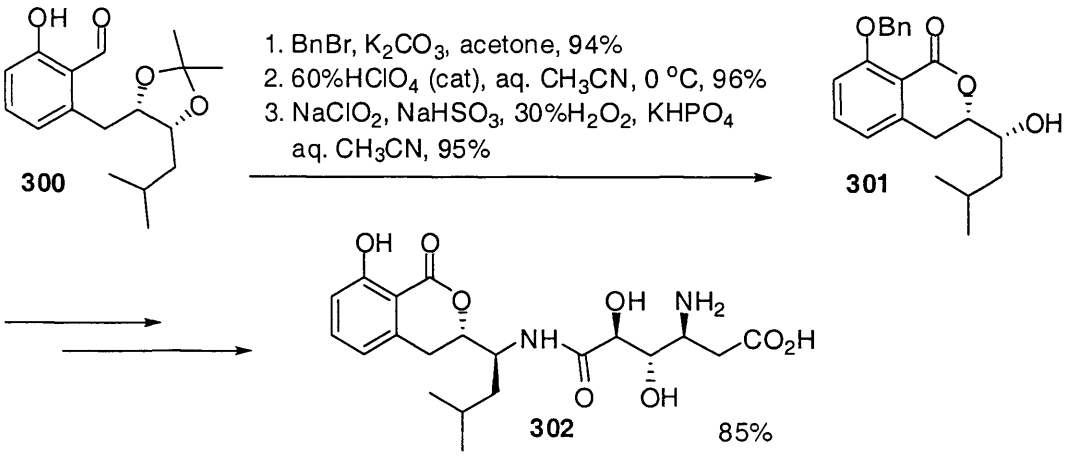
[3+3] cyclisation of 1,3-bis(silyloxy)-1,3-butadienes **296** with 1-hydroxy-5-silyloxy-hex-4-en-3-ones **297** resulted in the one-pot formation of 3-aryl-3,4-dihydroisocoumarins **299** (Scheme 107).[153] The reactions proceeded by regioselective cyclisation to give 6-(2-aryl-2-chloroethyl)salicylates **298**, which underwent a silica gel-mediated lactonisation giving lactones **299**.



Scheme 107: Silical gel-mediated synthesis of **299**

4.2.13 An Enantioselective Total Synthesis of AI-77-B

The AI-77s such as **302** are a group of 3,4-dihydroisocoumarin antibiotics that have been isolated from a culture broth of *Bacillus pumilus* AI-77.[154-155] AI-77-B **302**, has been found to exhibit potent gastroprotective activity without anticholinergic, antihistaminergic, or central suppressive effects.[156] Its synthesis is straightforward as shown in Scheme 108. Protection of **300** as its benzyl ether followed by deprotection of an acetonide function gave a diol (present as a form of hemiacetal), which was further oxidized with $NaClO_2/NaHSO_3$ and 30% H_2O_2 under carefully controlled conditions to afford lactone **301**. Dihydroisocoumarin **301** was then transformed to AI-77-B **302**.[157]



Scheme 108: Total synthesis of AI-77-B

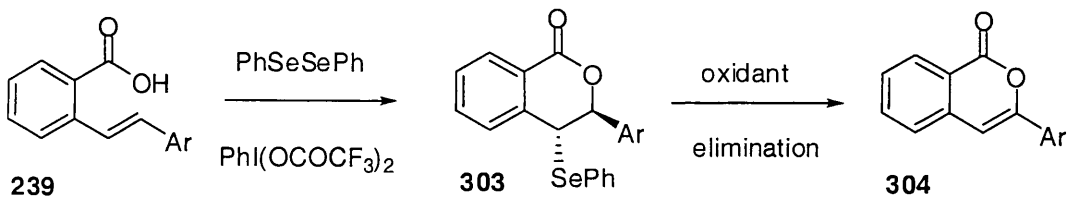
In conclusion, this chapter has reviewed the most fundamental and important literature methods in the synthesis of isocoumarins, along with some applications of such molecules into complex products. Literature methods invovling electrophilic cyclisations for the synthesis of isocoumarins are known to be efficient reactions which proceed under mild reaction conditions and exhibit a broad scope in terms of the functional groups compatibility. However, there are, to date, no selenium-catalysed methods reported for the synthesis of isocoumarins.

4.3 Aims of the Project

Cyclofunctionalisation reactions have proven useful in the synthesis of target molecules. However, the high temperatures and expensive catalysts often required to achieve good conversion discourage their use use in organic synthesis. Organoselenium reagents are conveniently used in organic synthesis to introduce new functional groups into organic substrates under mild reaction conditions. Over the years, many research groups have described the synthesis of non-chiral and chiral deselenides, which can be transformed *in situ* into electrophilic selenenylating reagents. The reactions of these intermediates with alkenes in the presence of an internal nucleophile result in cyclisation reactions.

Isocoumarins and dihydroisocoumarins are compounds that widely exist in nature as key intermediates in the synthesis of biologically active molecules. However, the direct synthesis of such compounds by traditional methods using either catalytic or stoichiometric amounts is often fraught with low yields and high reaction temperatures. Phenylselenenyl chloride or bromide are generally expensive electrophiles and removal of selenium moiety is often accomplished by using oxidation processes in a separate chemical step. A solution to this problem is to carry out a reaction employing the diselenide as a pre-catalyst and a stoichiometric oxidising agent to generate the electrophile. Following the *in situ* formation of the electrophile the intramolecular cyclisation-elimination sequence would furnish the required heterocycles. Our synthetic efforts aimed at the implementation of convenient catalytic conditions to address the issues of expensive reagents and high temperatures and lower yields are reported herein.

4.3.1 Cyclisation Reactions with Internal Nucleophiles



239 303 304

Scheme 109: Diphenyldiselenide catalysed synthesis of isocoumarins **304**

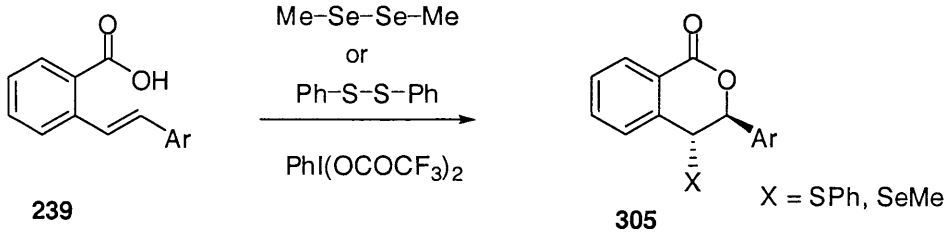
The intramolecular selenenylation-deselenenylation reaction allows a range of isocoumarins to be formed using a carboxylic acid as an internal nucleophile. The

process can occur due to the acid moiety in the *ortho*-position of the starting material and the presence of a hydrogen atom β- to the selenide in **303**. Once the selenium electrophile has added to the alkene and the cyclisation has occured, the presence of an oxidant allows the selenide to convert to either the selenoxide or a good leaving group, which can undergo elimination processes called selenoxide elimination or deselenenylation (Scheme 109).

4.3.2 Elimination of Selenium Moiety

In the presence of a β-proton, a selenide will give an elimination reaction after oxidation leading to an alkene and diphenyl diselenide. Regeneration of the diselenide in the presence of an oxidising agent, such as hypervalent iodine reagent would facilitate re-entery into the catalytic cycle. Oxidising agents that have been used previously are hydrogen peroxide, ammonium persulfate, *m*CPBA and hypervalent iodine reagents. Previously, this type of reaction has been used to achieve the synthesis of butenolides in good yields.[159-160] The purpose of this section of work involves investigating the reaction conditions for the preparation of isocoumarins using only catalytic amounts of selenium reagents.

An additional focus was that the protocol needs to be sufficiently mild so that functional groups elsewhere in the molecule would be unaffected. Moreover, a general procedure for achieving a selective synthesis of dihydroisocoumarins from the stilbene carboxylic acids **239** has not yet been reported. Selenium also shares many chemical properties with sulfur. Therefore, we also decided to use diphenyl disulfide in the selective synthesis of dihydroisocoumarins. We could demonstrate that the use of different dichalcogenides also allows the simple conversion of stilbene carboxylic acids into the dihydroisocoumarins **305**, without formation of isocoumarins (Scheme 110).



239 **305**

Scheme 110: New proposed synthesis of dihydroisocumarins **305**

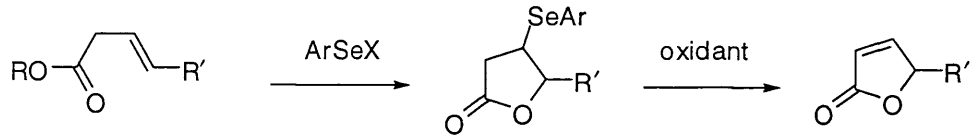
Mild reaction conditions are required to implement a useful protocol for the formation of the sulphur electrophile. The use of a disulfide is a relatively new concept to produce

a sulphur electrophile by employing hypervalent iodine reagents. The reactivity will then be tested with stilbenes to determine if dihydroisocoumarins are formed.

4.4 Catalytic Use of Selenium Electrophiles in Cyclisations

In recent years, selenium reagents have attracted much interest for their application in organic synthesis. Selenium dioxide is well known and traditionally used as an oxidising agent for alkenes, ketones and other substrates, but it was not until 1977 that Umbriet and Sharpless[158] found that only catalytic amounts of selenium dioxide could be used to enhance the rate of oxidation of olefins. Firstly, it was found that hydrogen peroxide in the presence of catalytic selenium dioxide oxidised the highly reactive β-pinene smoothly via allylic oxidation. The increasing work in this area contributes to a better understanding of organoselenium chemistry.

In 1993, Tiecco and co-workers[159] found that butenolides can be prepared from the reaction of β,γ-unsaturated acids with catalytic amounts of diphenyl diselenide and excess ammounium persulfate as a stoichiometric oxidant. The carboxyl group acts as an internal nucleophile and produces reasonable yields of product (Scheme 111).



306 307 308

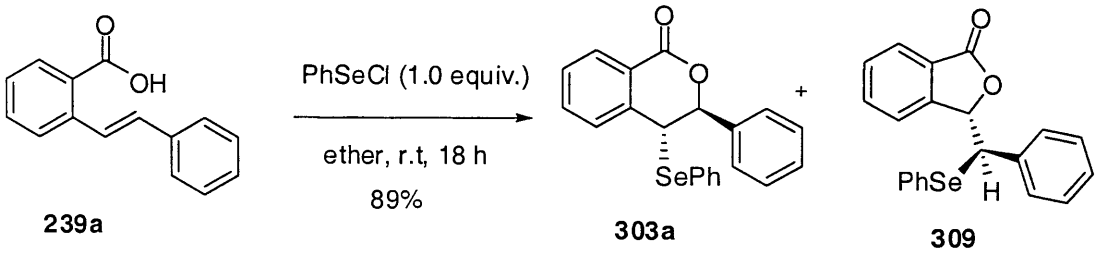
Scheme 111: Selenium catalysed synthesis of butenolides

In 2007, Wirth and co-workers[160] have developed a novel method for the synthesis of butenolides from the reaction of the easily available β,γ-unsaturated acids with catalytic amounts of diphenyl diselenide and stoichiometric hypervalent iodine reagent. It was found that the best oxidant for the reaction was [bis(trifluoroacetoxy)iodo]benzene and selenium based catalysts were the most efficient. However, this protocol has not been applied to other biologically important heterocyclic compounds. Therefore, we decided to utilise the previous reaction conditions to convert different stilbene derivatives to the corresponding isocoumarins.

4.5 Results and Discussion

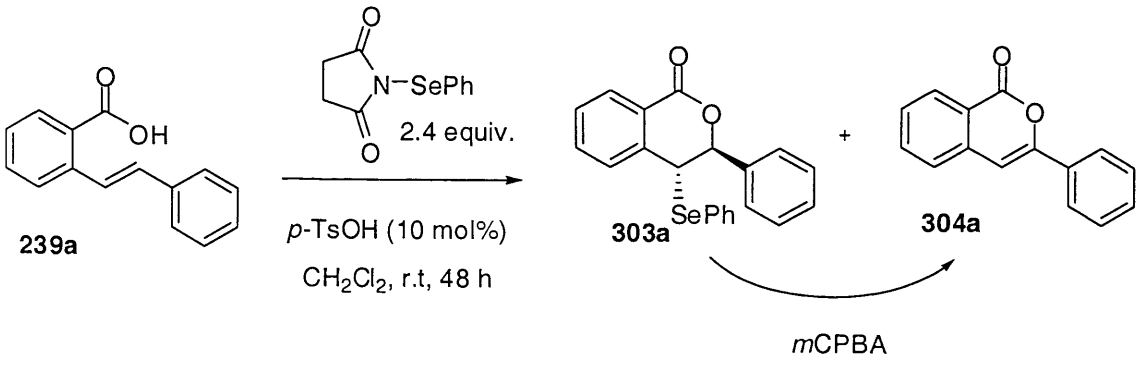
The use of hypervalent iodine compounds as oxidants for a facile *in situ* formation of selenium electrophiles from diselenides was already reported by Wirth *et al.* but this protocol has not been yet applied to the synthesis of isocoumarins. The key difference between the previous and present examples is the elimination step. Elimination was facilitated by an acidic proton present after initial selenocyclisation of the *β,γ*-butenoic acids. In sharp contrast, there is no active methylene group in stilbenes **239** bearing carboxylic acid functionality.

Clive *et al.* reported that the reaction of 2-styryl benzoic acid **239a** (Ar = Ph) with phenylselenenyl chloride afforded a mixture of dihydroisocoumarin **303a** and a five-membered lactone **309** in a 1.0:1.5 ratio (Scheme 112).[161]



Scheme 112: Selenium catalysed synthesis of butenolides

The cyclisation of **239a** using an excess (2.4 equiv.) of *N*-(phenylseleno)succinimide (*N*-PSS) as a different selenium electrophile was reported to give a mixture of **303a** and **304a**, compound **303a** was converted into **304a** by oxidative elimination using *m*CPBA (Scheme 113).[162]

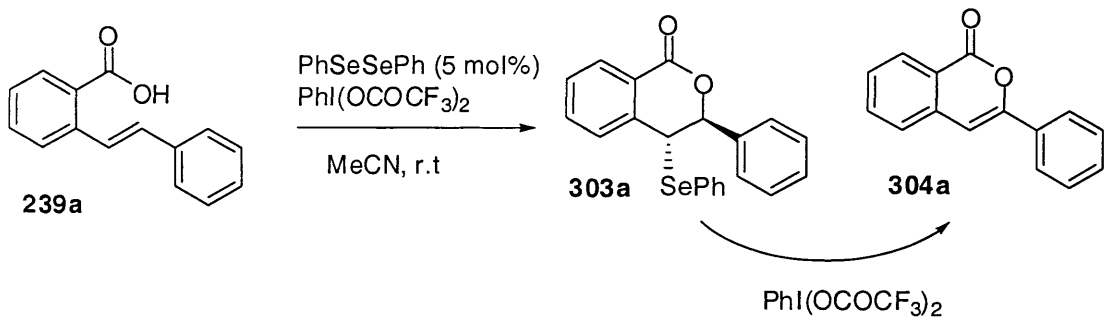


Scheme 113: Selenium catalysed synthesis of butenolides

Because of the overstoichiometric amounts of *N*-PSS as an expensive reagent, we developed a rapid catalytic method for the synthesis of isocoumarins from precursors **239**.

4.5.1 Cyclisation by a Selenenylation-Elimination

Phenylselenolactonisation is known as a means of functionalising unsaturated carboxylic acids, which undergo cyclisation when treated with an electrophile produced from diphenyl diselenide. Selenium containing reagents can be used as catalysts or ligands in various stereoselective reactions. The initial addition to the alkene involves the electrophilic addition of the selenenyl cation and nucleophilic addition of the carboxy function. 2-Styryl benzoic was chosen to test the reaction conditions. When 2-styryl benzoic acid was treated with 5 mol% diphenyl diselenide and stoichiometric [bis(trifluoroacetoxy)iodo]benzene in acetonitrile, the corresponding cyclic lactones were formed in low yield (Scheme 114).



Scheme 114: The synthesis of isocoumarin **304a** *via* dihydroisocoumarin **303a** by using catalytic amounts of diphenyl diselenide

4.5.2 Optimisation of Reaction Conditions

In order to find appropriate conditions to effect the transformation depicted in Scheme 114, various conditions were screened and are summarised in Table 7.

Table 7: Optimisation of selenium-catalysed cyclisations

Entry	Ph-Se-Se-Ph	$PhI(OCOCF_3)_2$ [equiv.]	Time [h]	**304a** Yield [%]
1	5 mol %	1.2	1	30
2	5 mol %	2.1	1	30
3	10 mol %	1.2	1	92
4	15 mol %	1.2	1	92
5	–	2.1	10	0

Employing the reaction conditions developed previously, 2-styryl benzoic acid **239a** was cyclised using 5 mol% diphenyl diselenide and 1.2 equiv. of [bis(trifluoroacetoxy)iodo]benzene as oxidant leading to lactone **304a** along with traces of **303a** but the rate of the overall reaction was low (Table 7, entry 1). If the reaction is stopped after 5 minutes, small amounts of dihydroisocoumarin **303a** can be identified with isocoumarin **304a**, both in low yield, as determined by ^{1}H NMR spectroscopy. In order to improve the yield of cyclised products, the amount of the catalyst was examined. An increase to 10 mol% is sufficient to obtain the reaction product in 92% yield (Table 7, entry 3) while larger amounts did not further raise the yield. No reaction was observed in the absence of diphenyl diselenide and only starting material was recovered (Table 7, entry 5).

4.5.3 Scope of Catalytic Reaction

Because the highest yields have been observed using [bis(trifluoroacetoxy)iodo]benzene in acetonitrile, these conditions were chosen in all subsequent experiments. The scope of the reaction was investigated further by using a range of different substituted stilbene carboxylic acids in the catalytic cycle. The starting materials for the reaction were prepared by Heck coupling reactions with different styrenes.

4.5.4 Starting Materials for Cyclisation Reactions

During the development of a new approach towards the synthesis of isocoumarins and dihydroisocoumarins, stilbene carboxylic acids were synthesized by coupling of styrenes with methyl 2-iodobenzoate using a Mizoroki-Heck reaction providing

stilbene esters **167** in good yields. The subsequent hydrolysis with lithium hydroxide in the presence of aqueous methanol provided the corresponding carboxylic acids **239** in high yields (Figure 12).

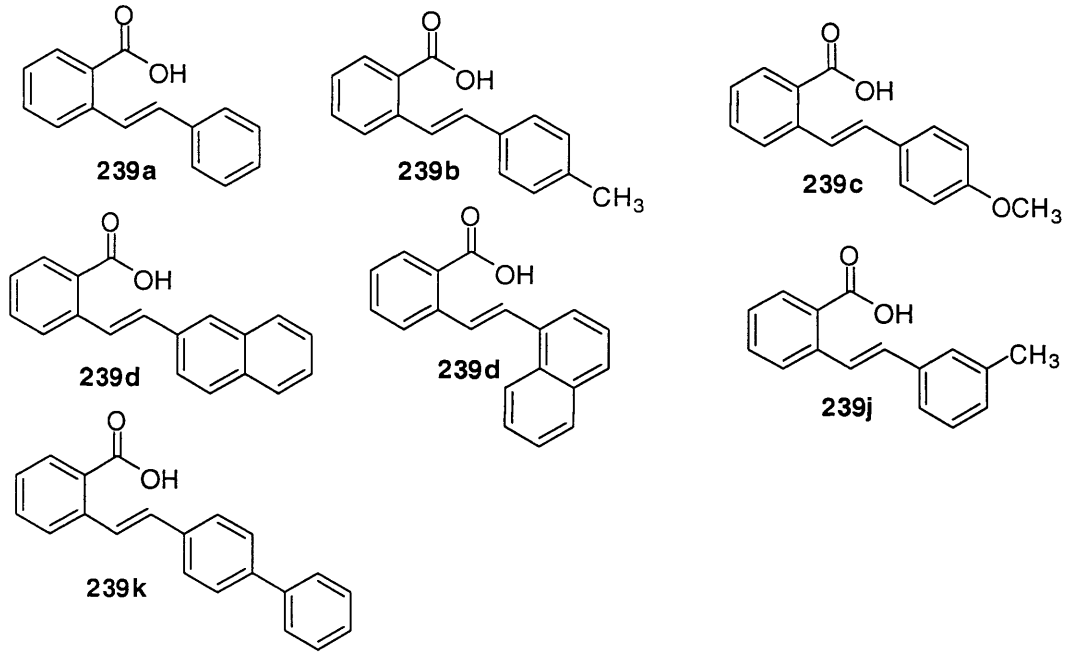
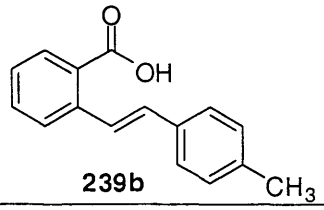
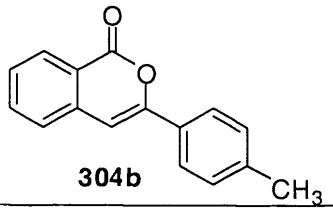
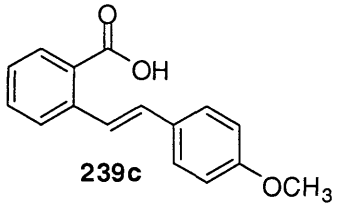
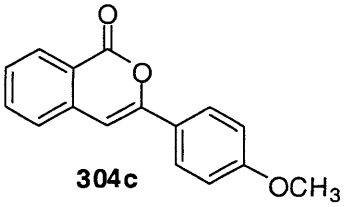
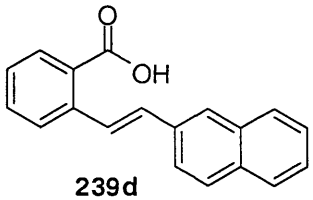
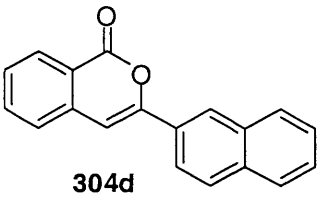
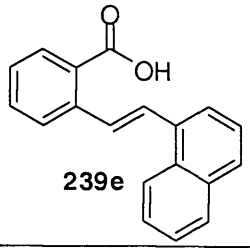
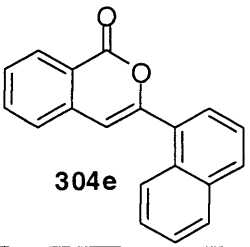
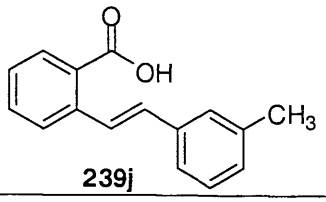
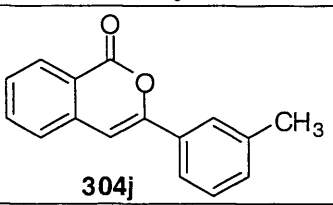
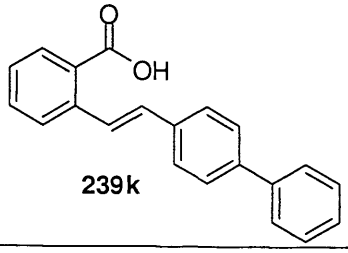
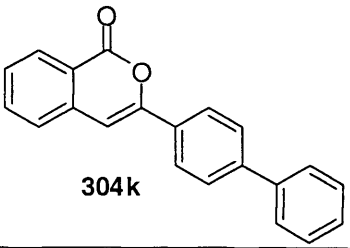


Figure 12: Starting materials **239** for the synthesis of isocoumarins derivatives

Using the optimised conditions, the protocol was extended to other stilbene derivatives **239** as shown in Table 8. The reaction of stilbene carboxylic acids bearing naphthyl **239d/239e**, tolyl **239b/239j**, 4-methoxyphenyl **239c** and biphenyl **239k** substituents gave the corresponding isocoumarins **304** in high yields. In some cases the dihydroisocoumarin derivatives **303** are obtained as minor side products. With electron-rich substrates such as **239c** very rapid conversion took place at room temperature and the corresponding isocoumarin **304c** was obtained as single product using only 10 mol% diphenyl diselenide and the hypervalent iodine reagent (Table 8, entry 2). It was found that longer reaction times were required to accomplish the synthesis of isocoumarins **304d**, **304e** and **304j**. Under the standard reaction conditions it appears that conversion of dihydroisocoumarins **303d**, **303e**, and **303j** to isocoumarins **304d**, **304e**, and **304j** is slow, taking up to 16 hours (Table 8, entries 3–5). The corresponding dihydroisocoumarins can also be isolated by preparative TLC if the reaction is stopped after a short period (5–20 minutes). The dihydroisocoumarins **303a, 303d** and **303j** have an *anti*-relation of the substituents due to the *anti*-addition to the *E*- configured double bond.[161]

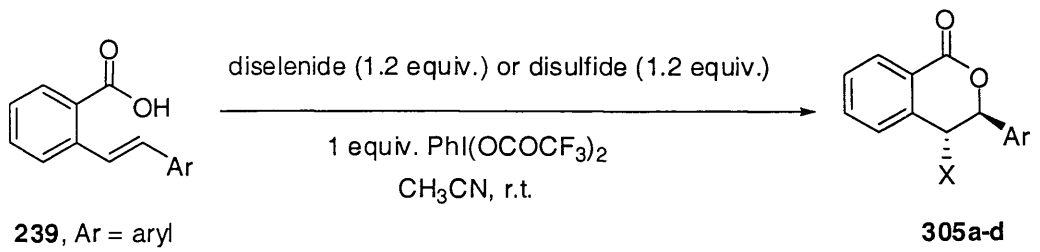
Table 8: Diphenyl diselenide catalysed cyclisation of stilbene carboxylic acids **239** to isocoumarins **304**

Entry	Starting material 239	Product 304	Time [h]	Yield [%]
1	 **239b**	 **304b**	1	88[c]
2	 **239c**	 **304c**	1	96[c]
3	 **239d**	 **304d**	16	94[a, c]
4	 **239e**	 **304e**	16	99[c]
5	 **239j**	 **304j**	1	81[b]
6	 **239k**	 **304k**	1	99[c]

Standard reaction conditions: PhSeSePh (10 mol%), $PhI(OCOCF_3)_2$ (1.2 equiv.), r.t.
(a) 4% dihydroisocoumarin **303d** was also isolated (b) 4.4% dihydroisocoumarin **303j** was also isolated (c) diphenyldiselenide is recovered as yellow crystals in quantitative yield.

4.5.5 Synthesis of Seleno- and Thio-Dihydroisocoumarins

A range of different dichalcogen compounds was used to test the efficiency and selectivity of the corresponding electrophile for the synthesis of dihydroisocoumarins (Scheme 115).



239, Ar = aryl **305a-d**

Scheme 115: Synthesis of dihydroisocoumarins **305** from **239**

Table 9: Seleno- and thio-dihydroisocoumarins

Entry	Reagent (1.2 equiv.)	Time [min]	Substrate	X	Product yield [%]
1	Me-Se-Se-Me	5	**239c** Ar = 4-Me-C_6H_4	Se-Me	**305a** 97
2	Ph-S-S-Ph	60	**239a** Ar = Ph	S-Ph	**305b** 75
3	Ph-S-S-Ph	60	**239a** Ar = Ph	S-Ph	**305b** 5[a]
4	Ph-S-S-Ph	60	**239e** Ar = 1-Naphthyl	S-Ph	**305c** 66
5	Ph-S-S-Ph	60	**239k** Ar = 4-Ph-C_6H_4	S-Ph	**305d** 57

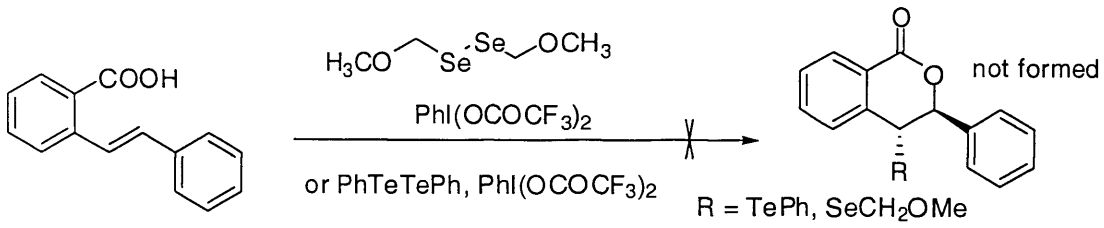
[a] $PhI(OCOCF_3)_2$ (2.0 equiv.), no characterisable product isolated

A selective reaction to dihydroisocoumarins **305** can be performed by selecting different electrophiles while maintaining the hypervalent iodine reagent as oxidant. When the reaction was carried out using dimethyl diselenide instead of diphenyl diselenide, the dihydroisocoumarin derivative **305a** was the only product formed in almost quantitative yield under very mild reaction conditions within five minutes (Table 9, entry 1). This indicates that the substituent on the selenium atom strongly influences the subsequent reactivity of the selenide. Longer reaction times have no influence on the elimination of the selenium moiety and the product is enough stable to store at room temperature. However, traces of the corresponding isocoumarin **304b**

were found in the methyl seleno-dihydroisocoumarin sample **305a** upon standing at room temperature for six months in air.

The use of hypervalent iodine reagents as the only electrophile to activate the double bond was unsuccessful and resulted in decomposition. In order to extend the scope of this method and the structural variety of the dihydroisocoumarin derivatives **305**, we also investigated diphenyl disulfide and hypervalent iodine compounds as reagent combination to perform such cyclisations. The sulfur electrophiles led to a selective 6-*endo-trig* cyclisation and formation of dihydroisocoumarins **305**. The reaction of three stilbene carboxylic acids **239a**, **239c** and **239k** was examined using diphenyl disulfide and [bis(trifluoroacetoxy)iodo]benzene and good yields of the new dihydroisocoumarin derivatives **305** were obtained (Table 9, entries 2, 4–5). Furthermore, the results in Table 9, entry 3 also suggest that an excess of hypervalent iodine is detrimental for the cyclisation. Under these conditions, extensive decomposition is observed. This is probably the result of oxidation of the thio-dihydroisocoumarin by the excess oxidant, or might be due to further oxidation of the sulfur electrophile before it can react with the starting material.

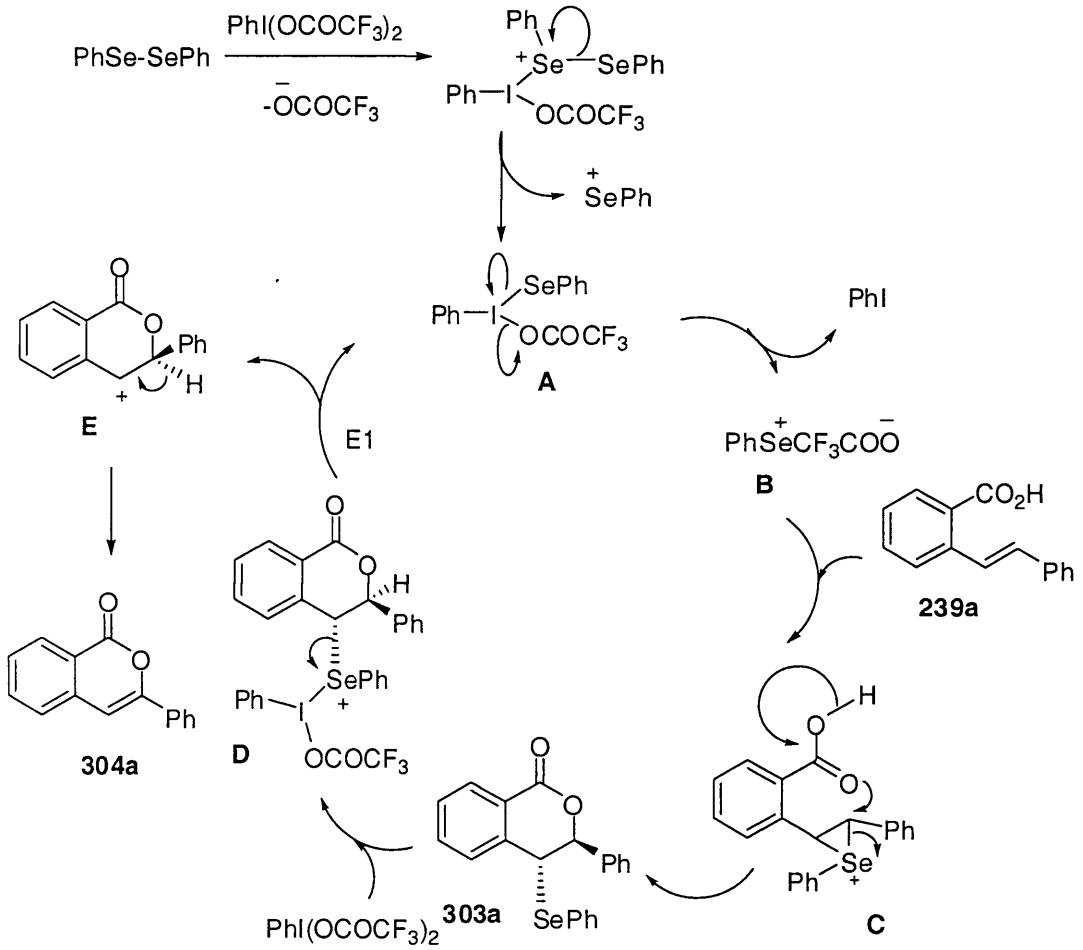
However, dimethoxymethyl diselenide and diphenyl ditelluride failed to provide the desired cyclisation (Scheme 116). The effect of substitution on the selenium atom can be thought to be either steric or electronic in nature. It means that the substitution on the selenium atom has a large influence on the reactivity of the diselenide. Molecular iodine-mediated reaction conditions were tested with substrate **239a** in order to access similar cyclisation results. Moreover, iodine-mediated cyclisation was unsuccessful at producing the desired product and this electrophile displayed a slow rate of reaction and showed side reactions.



Scheme 116: Failure of dimethoxymethyldiselenide and diphenylditelluride in cyclisation

4.5.6 The Proposed Catalytic Cycle

The catalytic cycle is initiated by the oxidation of diphenyl diselenide with the hypervalent iodine reagent to form phenylselenenyl trifluoroacetate *via* formation of seleno-hypervalent iodine species **A** (Scheme 118). Electrophile **B** (phenylselenenyl trifluoroacetate) then reacts with the stilbene carboxylic acid **239a** in a cyclisation reaction to yield compound **303a** *via* assumed intermediate **C**. The selenide in lactone **303a** is then activated by [bis(trifluoroacetoxy)iodo]benzene and intermediate **D** eliminates by an E1 mechanism through carbocation **E** and regenerating the intermediate **A**. Eliminination of a proton from the carbocation **E** gave isocoumarin **304a.** In this way the catalytic cycle is completed by regenerating diphenyl diselenide**.** The mechanistic investigations of this catalytic cycle have already been performed in the synthesis of butenolides.[160]



Scheme 118: Proposed catalytic cycle for the generation of selenium electrophilic specie via addition-elimination mechanism

4.5.7 Conclusion

In summary, a simple and inexpensive catalytic method has been developed to effect the conversion of stilbene carboxylic acids to the corresponding isocoumarins as well as seleno- and thio-dihydroisocoumarins. The use of a hypervalent iodine oxidant to form selenium electrophiles has shown unique reactivity in the synthesis of isocoumarins. The cyclisation is accomplished by mixing a solution of the substrate with diphenyl diselenide (10 mol%) and [bis(trifluoroacetoxy)iodo]benzene. Several dihydroisocoumarin derivatives have also been synthesised. The preparation of seleno-dihydroisocoumarin has also been achieved almost in quantitative yields from the reaction of stilbenes and dimethyl diselenide with [bis(trifluoroacetoxy)iodo]benzene. The substrate scope of this new method has been shown by using a range of stilbene carboxylic acids. It has been observed that the size and nature of the substituents on the selenium atom play an important role in controlling the reactivity and selectivity of the product. It was also found that the catalyst could be reused many times without decrease in yields. Other catalysts such as diphenyl ditelluride and dimethoxymethyl diselenide failed to effect the cyclisation. When iodine (I_2) is used as electrophile, a different side reaction took place along with the desired product.

This methodology offers very mild reaction conditions for the selective synthesis of seleno- and thio-dihydroisocoumarins as well. The scope of this methodology has been further explored by reacting a range of stilbene carboxylic acids with the diselenide or disulfide and hypervalent iodine to afford seleno-dihydroisocoumarin and thio-dihydroisocoumarins. This methodology could be used for the synthesis of various natural products analogues. The clean reaction products and high yields showing the diversity of the reaction conditions. The methodology is straightforward, the reaction conditions are mild and the products are formed in good yields.

Chapter 5

5 Experimental Section

5.1 General Methods

Most reactions were carried out using standard laboratory equipment. Inert reactions conditions were applied by vacuum dried or oven dried (120 °C) apparatus under argon atmosphere. Non-sensitive reactions were performed open to air or in loosely stoppered vessels. All reactions were continually agitated with magnetic stirring unless otherwise stated. Reactions requiring constant temperature were performed using hotplates with temperature probe control in silicon oil or dry heating blocks. The solvent evaporation was performed with Büchi B-461, B-481, B-490 rotary evaporator (vacuum down to approx. 15 mbar). Further drying was obtained under high vacuum at approx. 0.05 mbar. Kugelrohr distillation was performed in a Büchi GKR-50 Kugelrohr distillation apparatus. Anhydrous solvents were freshly distilled: THF and diethyl ether were distilled over sodium and benzophenone under inert atmosphere. Toluene was distilled over sodium. Acetonitrile and dichloromethane were distilled over calcium hydride. All other high purity solvents employed in reactions were purchased from Aldrich, Alfa Aesar, Fluka or Acros in septum bottles and handled under argon. The temperature –78 °C for certain reaction was achieved by preparing a cooling bath with dry ice and acetone, while 0 °C was achieved by ice and water.

Physical Data

^{1}H NMR spectra were recorded at Bruker DPX 500 (500 MHz), Bruker DPX 400 (400 MHz) or Bruker DPX 250 (250 MHz). The chemical shifts δ are given in parts per million (ppm) downfield of tetramethylsilane. The compounds are dissolved in deuterated chloroform or dimethylsulfoxide ($CDCl_3$ or DMSO-d6) unless otherwise stated. All coupling constants J are reported in Hz. The multiplicity of a signal is designated: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, Ar = aromatic ring protons which could not be assigned.

^{13}C NMR spectra were recorded on Bruker UltraShield 500 (125 MHz), Bruker DPX 400 (100 MHz) or Bruker DPX 250 (63 MHz).The chemical shift δ is given in ppm downfield of tetramethylsilane. The peak at (δ 77.0 t) is assigned to the solvent $CDCl_3$.

^{77} Se NMR spectrum was recorded on *Jeol Eclipse 300* ^{77}Se NMR (57.3 MHz). The chemical shifts are referenced to the solvent used.

Infrared spectra were recorded on Perkin Elmer 1600 FTIR Spectrometer and wave numbers quoted in cm^{-1}. Samples were measured either neat or as KBr disc. Melting points were determined on an electrothermal melting point apparatus (Gallenkamp variable heater) in open capillary tubes and values are uncorrected.

Mass Spectromery

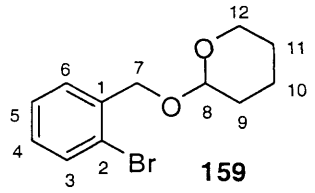
Rob Jenkins, Robin Hicks or Dave Walker performed the analysis at the mass spectrometry laboratory at Cardiff University. Ions were generated by the atmospheric pressure ionisation techniques voltage applied corana discharge pin (APCI), voltage on a tip (ES) or electrochemical ionisation (EI). In all cases the mass fragments are given in atomic mass units per elementary charge (m/z). The intensity relative to the strongest signal is quoted in brackets using percentages. High-resolution mass spectrometry of the compounds was carried out either at Cardiff University or EPSRC NMSSC Swansea. All molecular formulae are values quoted for either molecular ions ($M^{\bullet+}$), molecular + hydrogen ($M + H^+$), molecular + ammonium ion ($M + NH_4^+$), molrcular + sodium ($M + Na^+$) or molecular + potassium ($M + K^+$).

Chromatography

Flash column chromatography was performed using Merck Kieselgel 60 silica (230–400 mesh). Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with ceric ammonium molybdate, aqueous basic potassium permanganate or vanillin.

5.2 Synthesis of ethyl 2-(2-allylbenzyl)-3-oxobutanoate

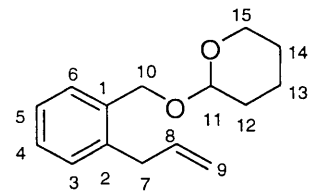
2-Bromobenzyl tetrahydropyranyl ether 159[163]



159

This compound was prepared by the usual protecting method.[163] To a mixture of 2-bromobenzyl alcohol (5.0 g, 26.7 mmol) and a catalytic amount of *p*- toluene sulfonic acid (*p*-TsOH, 0.7 g) in dichloromethane (100 mL) was added dropwise a solution of 3,4-dihydro-2*H*-pyran (2.6 g, 30.3 mmol) in dichloromethane (50 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was then poured into sodium hydrogen carbonate solution (30 mL) and extracted with diethyl ether (3x15 mL). The combined organic extracts were washed with water (10 mL) and concentrated in vacuo. The resulting residue was purified by column chromatogaphy (eluent: dichloromethane) to give the title compound **159** in 97% yield (7.0 g, 25.9 mmol) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.0 (m, 4H, H-3, H-4, H-5, H-6), 4.93-4.47 (m, 3H, H-7, H-8), 3.8-3.5 (m, 2H, H-12), 2.15-1.25 (m, 6H, H-9, H-10, H-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 137.9 (C-1), 132.5 (CH-3), 129.1 (CH-6), 128.8 (CH-4), 127.4 (CH-5), 122.7 (C-2), 98.4 (CH-8), 68.6 (CH_2-7), 62.2 (CH_2-12), 30.6 (CH_2-9), 25.5 (CH_2-11), 19.4 (CH_2-10) ppm. The spectroscopic data are in agreement with literature.[163]

Preparation of 2-allylbenzyl tetrahydropyranyl ether 160[163–164]

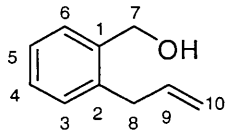


160

Grignard reagent was prepared by slow, dropwise addition of a solution of the THP ether **159** (26 mmol, 6.73 g) in THF (10 ml) to magnesium turnings (27 mmol, 0.64 g) immersed in stirred THF (10 ml), followed by reflux of the mixture for 3 h under

nitrogen. Allyl bromide was added to a stirred, cooled (0 °C) solution of Grignard reagent. The mixture was allowed to warm to room temperature and refluxed for 30 minutes. After 20 h, saturated ammonium chloride was added portionwise over 5 minutes. Filtration through plug of celite to remove salt and the aqueous layer was extracted with dichloromethane, and the extract was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with dichloromethane as eluent to give the product THP ether **160** as a colourless oil (5.67 g, 24.4 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (dd, 1H, J = 8.5 Hz, 1.8 Hz, H-6), 7.30-7.23 (m, 3H, H-3, H-4, H-5), 6.08-5.98 (m, 1H, H-8), 5.12-5.03 (m, 2H, cis and trans H-9), 4.87 (d, 1H, $J_{geminal}$ = 12.1 Hz, H-10_a), 4.75 (t, 1H, J = 3.5 Hz, H-11), 4.56 (d, 1H, $J_{geminal}$ = 12.1 Hz, H-10_b), 4.00-3.94 (m, 1H, H-15), 3.63-3.58 (m, 1H, H-15), 3.51 (dd, 2H, J = 7.8 Hz, 1.4 Hz, H-7), 1.94-1.55 (m, 6 H, H-12, H-13, H-14) ppm. The spectroscopic data are in agreement with literature.[164]

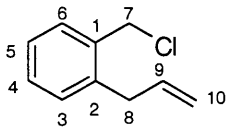
Preparation of 2-allylbenzyl alcohol 161 [164]



161

A solution of 2-allylbenzyl tetrahydropyranyl ether (26 mmol, 5.94 g) in methanol : HCl (1:1) was stirred for 36 hours at room temperature. Product was extracted with diethylether (3x20 ml) and washed with aqueous sodium hydrogen carbonate (20 ml). Solvent was evaporated under reduced pressure. The crude product was purified by chromatography (silica gel; dichloromethane) to give the title compound **161** (3.5 g, 23.6 mmol, 91%) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (dd, 1H, J = 7.2, 1.7 Hz, H-6), 7.15-7.07 (m, 3H, H-3, H-4, H-5), 5.92-5.82 (m, 1H, H-9), 4.98-4.94 (m, 1H, cis-H-10), 4.91-4.86 (m, 1 H, trans-H-10), 4.52 (s, 2 H, H-7), 3.33 (dt, 2 H, H-8), 2.30 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.7 (C-1), 137.8 (C-2), 137.4 (CH-9), 129.9 (CH), 128.4 (CH), 128.1 (CH), 126.7 (CH), 115.9 (CH_2-10), 63.2 (CH_2-7), 36.8 (CH_2-8) ppm. HRMS (ESI): m/z $[M + NH_4]^+$ calcd. for $C_{10}H_{12}O$: 166.1226; found: 166.1226. The spectroscopic data are in agreement with literature.[164]

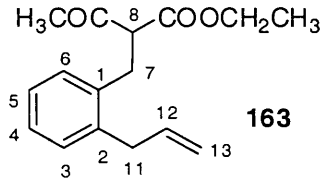
Preparation of 2-allylbenzyl chloride 162 [164]



162

A sample of alcohol **161** (5.5 g, 37 mmol) in CH_2Cl_2 was treated with $SOCl_2$ (10 g, 84 mmol). Reaction mixture was stirred for 4 hours at room temperature. The alcohol was extracted with ether and washed with aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, dissolved in pentane. Flash chromatography of the residue over silica gel, using hexane as eluent, gave a colorless liquid in 69% yield (4.2 g, 25.3 mmol). ^1H NMR (400 MHz, $CDCl_3$,) δ = 7.27 (d, 1H, J = 7.4 Hz, H-6), 7.21 (dd, 1H, J = 7.4 Hz, 2.4 Hz, H-3), 7.15 (t, 2H, J = 7.4 Hz, H-4, H-5), 5.97-5.87 (m, 1 H, H-9), 5.05-5.01 (m, 1H, J = 1.5, 10.5, 1.8 Hz, *cis*-H-10), 4.98-4.92 (m, 1 H, J = 1.5, 16.4, 1.8 Hz, *trans*-H-10), 4.55 (s, 2 H, H_2-7), 3.46 (d of m, J = 1.5, 6.1 Hz, 2 H, CH_2-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.7 (C-1), 136.7 (CH-9), 135.6 (C-2), 130.3 (CH-3), 130.2 (CH-6), 129.1 (CH-4), 126.9 (CH-5), 116.2 (CH_2-10), 44.2 (CH_2-7), 36.7 (CH_2-8); HR GCMS (EI): *m/z* $[M]^+$ calcd. for $C_{10}H_{11}Cl$: 166.0544; found: 166.0543. The spectroscopic data are in agreement with literature.[164]

Preparation of ethyl 2-(2-allylbenzyl)-3-oxobutanoate 163[164b]

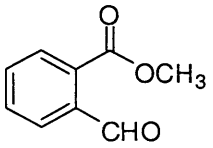


163

Solution of NaH (60% in mineral oil, 5.5 mmol, 0.22 g) and ethylacetoacetate (5.0 mmol, 0.63 ml) in THF (20ml) were added 2-allylbenzyl chloride **15** (4.8 mmol, 0.8 g), then the reaction mixture was stirred at reflux for three days. The mixture was poured into 10% HCl and extracted with ether. The ether extract were dried over $MgSO_4$ and evaporated to dryness. Finally, the residue was purified by column chromatography (EtOAc: Hexane, 1:4) and obtained as colourless oil in 77% yield (0.95 g, 3.65 mmol). ^1H NMR (250 MHz, $CDCl_3$,) δ = 7.10-7.04 (m, 4 H, Ar-H), 5.95-5.84 (m, 1 H, H-12), 5.09 (dd, 1H, J = 10.5, 1.8, 1.5 Hz, *cis* H-13), 5.03 (m, 1 H, J = 16.4, 1.8, 1.5, Hz, *trans*

H-13), 4.12-4.03 (m, 2 H, OCH_2CH_3), 3.70 (t, 1H, J = 7.1, H-8), 3.37 (d of m, 2 H, J = 1.5, 6.1 Hz, H-11), 3.12 (m, 2H, H-7), 2.12 (s, 3H, CO-CH_3), 1.11 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 201.4 (C=O), 168.3 (C=O), 136.7 (C), 136.0 (CH-12), 135.3 (C-2), 129.1 (CH), 128.6 (CH), 126.0 (CH), 125.5 (CH), 115.0 (CH_2-13), 60.4 (OCH_2), 59.3 (CH-8), 36.0 (CH_2-11), 29.6 (CH_2-7), 28.6 (CO-CH_3), 13.0 (OCH_2CH_3) ppm. IR (KBr): ν = 3075, 2980, 2938, 1738, 1717, 1637, 1490, 1451, 1432, 1367, 1359, 1261, 1213, 1149, 1096, 1025, 915, 754 cm^{-1}. HRMS (ESI): m/z [M + NH_4]$^+$ calcd. for $C_{16}H_{20}O_3$: 278.1751; found: 278.1754.

Methyl 2-formylbenzoate[165]



To a solution of K_2CO_3 (17.0 g, 123 mmol) and 2-formylbenzoic acid (6.0 g, 40 mmol) in acetone (100 mL), methyl iodide (6.2 g, 44 mmol) was added at room temperature. The mixture was refluxed under nitrogen for 4 h. After cooling to room temperature, the mixture was filtrated and concentrated. Then, the residue was extracted with ether (3 x 50 mL), and the combined organic layers were washed with brine (2 x 15 mL), and then dried over anhydrous Na_2SO_4. After removing the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10/1) to give the methyl 2-formylbenzoate (5.9 g, 36 mmol, 90%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.57 (s, 1H, CHO), 7.94-7.87 (m, 2H, Ar-H), 7.62-7.60 (m, 2H, Ar-H), 3.93 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1 (C=O), 166.7 (C=O), 137.0 (C), 132.9 (CH), 132.4 (CH), 132.0 (C), 130.3 (CH), 128.3 (CH), 52.7 (OCH_3). The spectroscopic data are in agreement with literature.[165]

1-Vinylnaphthalene

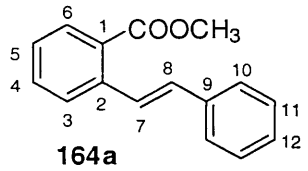
A mixture of CH_3PPh_3Br (12.9 mmol, 4.61 g) and KOtBu (14 mmol, 1.57 g) in dry toluene (30 mL) stirred at 0 °C for 30 min and at r.t. for 4h. The reaction mixture was cooled to 0 °C followed by addition of 1-naphthaldehyde (11.8 mmol, 1.84 g). The reaction mixture was stirred overnight at r.t. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using hexane as

eluent to yield 1-vinylnaphthalene in quantitative yield (11.8 mmol, 1.81 g) as colorless oil. The spectroscopic data are in agreement with literature.[166]

5.3 General procedure (GP1) for the synthesis of stilbene esters[93] 164

A mixture of methyl 2-iodo benzoate (15 mmol, 4.0 g), styrene (18 mmol, 2.1 mL), triethylamine (32 mmol, 4.4 mL), palladium acetate (0.48 mmol, 323 mg) and triphenylphosphine (0.96 mmol, 251 mg) were heated under reflux at 100 °C for 5 h. Solid products were isolated by diluting the reaction mixtures with 200 ml of 10% hydrochloric acid with stirring to dissolve the salts and excess amine. Finally, the residue was purified by column chromatography (EtOAc/hexane, 1/12) to give products **164a-164k** in good yields.

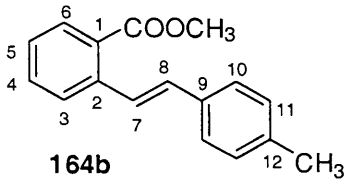
(*E*)-Methyl 2-styrylbenzoate 164a



164a

According to GP1 compound **164a** was obtained as yellow oil in 87% yield (13.07 mmol, 3.11 g) after purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, 1H, *J* = 16.2 Hz, H-7), 7.97 (dd, 1H, *J* = 7.9, 1.3 Hz, H-6), 7.76 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.60 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 7.55 (td, 1H, *J* = 7.5, 1.1 Hz, Ar-*H*), 7.41 (t, 2H, *J* = 7.8, Ar-*H*), 7.36 (td, 1H, *J* = 7.8, 1.1 Hz, Ar-*H*), 7.33-7.32 (m, 1H, Ar-*H*), 7.06 (d, *J* = 16.2 Hz, 1H, H-8), 3.97 (s, 3H, COO*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9 (C=O), 139.3 (C-1), 137.5 (C-2), 132.2 (CH), 131.5 (CH), 130.7 (CH), 128.7 (2xCH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.9 (2xCH, C-9), 52.2 ppm. IR (KBr): *v* = 3061, 3024, 2949, 2839, 1718, 1598, 1584, 1565, 1495, 1480, 1447, 1433, 1293, 1271, 1250, 1189, 1131, 1077, 1016, 964, 761, 743, 705, 691 cm^{-1}. HRMS (ES): *m/z* $[M + NH_4]^+$ calcd. for $C_{16}H_{14}O_2 \bullet NH_4$: 256.1332; found: 256.1331. The spectroscopic data are in agreement with literature.[167]

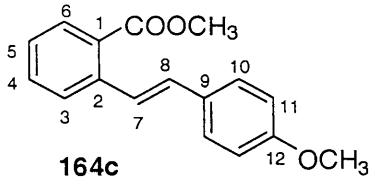
(*E*)-Methyl 2-(4-methylstyryl)benzoate 164b



164b

According to GP1 compound **164b** was obtained as colorless crystals in 82% yield (12.3 mmol, 3.1 g) after purification. M.p.: 79-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 1H, *J* = 16.2 Hz, H-7), 7.81 (d, 1H, *J* = 8.0 Hz, H-10), 7.60 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.37 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.34 (d, 2H, *J* = 7.9 Hz, H-6), 7.18 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 7.05 (d, 2H, *J* = 7.9 Hz, H-11), 6.88 (d, 1H, *J* = 16.2 Hz, 1H, H-8), 3.80 (s, 3H, COO*CH*$_3$), 2.25 (s, 3H, Ar*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C=O), 139.5 (C), 137.8 (C), 134.8 (C), 132.2 (CH), 131.5 (CH), 130.7 (CH), 129.5 (2xCH), 128.5 (C), 127.0 (CH), 126.9 (3xCH), 126.4 (CH), 52.1 (OCH_3), 21.4 (CH_3) ppm. IR (KBr): *v* = 3077, 2957, 2915, 2843, 1713, 1598, 1512, 1466, 1436, 1271, 1249, 1192, 1128, 1080, 964, 806, 797, 749, 710 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{17}O_2$: 253.1223; found: 253.1224.

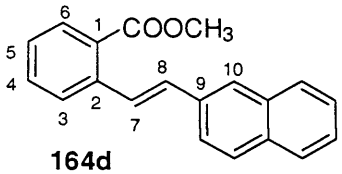
(*E*)-Methyl 2-(4-methoxystyryl)benzoate 164c



164c

According to GP1 compound **164c** was obtained as colorless crystal in 85% yield (12.8 mmol, 3.42 g). M.p.: 80-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 1H, *J* = 7.9 Hz, H-6), 7.90 (d, 1H, *J* = 16.3 Hz, H-7), 7.74 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.54-7.50 (m, 3H, Ar-*H*), 7.32 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.01 (d, 1H, *J* = 16.3 Hz, H-8), 6.93 (d, 2H, *J* = 8.4 Hz, H-11), 3.95 (s, 3H, COO*CH*$_3$), 3.85 (s, 3H, O*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C=O), 159.6 (C), 139.5 (C), 132.1 (CH), 131.0 (CH), 130.7 (CH), 130.3 (C), 128.4 (C), 128.2 (2xCH), 126.7 (2xCH), 125.3 (CH), 114.2 (2xCH), 55.4 (OMe), 52.1 (OMe) ppm. IR (KBr): *v* = 3065, 3000, 2950, 2905, 2833, 1717, 1603, 1592, 1512, 1432, 1301, 1277, 1250, 1176, 1129, 1078, 1030, 971, 767, 755, 721 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{17}O_3$: 269.1172; found: 269.1175.

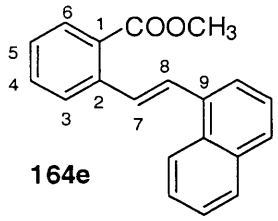
(*E*)-Methyl 2-(2-(naphthalen-2-yl)vinyl)benzoate 164d



164d

According to GP1 compound **164d** was obtained as colorless crystals in 87% yield (13.06 mmol, 3.76 g). M.p.: 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, 1H, *J* = 16.2 Hz, H-7), 7.89 (dd, 1H, *J* = 7.9, 1.3 Hz, Ar-*H*), 7.82 (s, 1H, H-10), 7.78-7.71 (m, 5H, Ar-*H*), 7.48 (dt, 1H, *J* = 7.7 Hz, 1.1 Hz, Ar-*H*), 7.41-7.38 (m, 2H, Ar-*H*), 7.28 (t, 1H, *J* = 7.7 Hz, Ar-*H*), 7.12 (d, 1H, *J* = 16.2 Hz, H-8), 3.89 (s, 3H, COO*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9 (C=O), 139.3 (C-1), 135.0 (C-2), 133.7 (C-5), 133.2 (C), 132.2 (CH), 131.6 (CH), 130.8 (CH), 128.6 (C), 128.4 (CH), 128.1 (CH), 127.7 (2xCH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.3 (CH), 126.0 (CH), 123.9 (CH), 52.2 (O*CH*$_3$) ppm. IR (KBr): *v* = 3055, 2949, 1717, 1627, 1596, 1566, 1482, 1432, 1266, 1242, 1130, 1077, 961, 814, 741 cm^{-1}. HRMS (ES): *m/z* $[M + NH_4]^+$ calcd. for $C_{20}H_{16}O_2 \bullet NH_4$: 306.1489; found: 306.1493.

(*E*)-Methyl 2-(2-(naphthalen-1-yl)vinyl)benzoate 164e

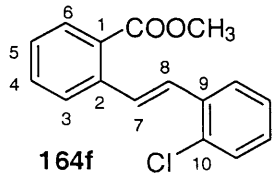


164e

According to GP1 compound **164e** was obtained as light yellow viscous oil in 93% yield (14 mmol, 4.03 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.91 (d, 1H, *J* = 15.9 Hz, H-7), 7.88 (dd, 1H, *J* = 8.1 Hz, 1.2 Hz, Ar-*H*), 7.79-7.71 (m, 4H, Ar-*H*), 7.68 (d, 1H, *J* = 15.9 Hz, H-8), 7.49-7.40 (m, 4H, Ar-*H*), 7.28 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 3.84 (s, 3H, COO*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9 (C=O), 139.6 (C), 135.0 (C), 133.8 (C), 132.3 (CH), 131.5 (C), 130.7 (CH), 130.6 (CH), 128.8 (C), 128.7 (CH), 128.5 (2xCH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 125.8 (CH), 124.2 (CH), 123.8 (CH), 52.2 (O*CH*$_3$) ppm. IR (KBr): *v* = 3061, 2947, 1718, 1596, 1568, 1480, 1432, 1282, 1259, 1246, 1130, 1076, 963, 795,

775 cm^{-1}. HRMS (ES): *m/z* $[M + NH_4]^+$ calcd. for $C_{20}H_{16}O_2 \bullet NH_4$: 306.1489; found: 306.1491.

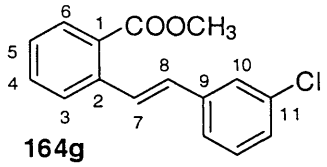
(*E*)-Methyl 2-(2-chlorostyryl)benzoate 164f



164f

According to GP1 compound **164f** was obtained as colorless solid in 88% yield (13.2 mmol, 3.61 g). M.p.: 68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, 1H, *J* = 16.4 Hz, H-7), 7.99 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.80 (d, 2H, *J* = 7.9 Hz, Ar-*H*), 7.57 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 7.46-7.36 (m, 3H, H-8 & Ar-*H*), 7.31 (d, 1H, *J* = 7.3 Hz, Ar-*H*), 7.23 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 3.95 (s, 3H, $COOCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 167.8 (C=O), 139.1 (C), 135.5 (C), 133.6 (C), 132.4 (CH), 130.8 (CH), 130.1 (CH), 129.8 (CH), 128.8 (CH), 128.6 (C), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 52.2 (OCH_3). IR (KBr): *v* = 3061, 2950, 1718, 1598, 1568, 1483, 1431, 1295, 1267, 1245, 1216, 1125, 1078, 1034, 958, 755, 716 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{14}Cl^{35}O_2$: 273.0677; found: 273.0679.

(*E*)-Methyl 2-(3-chlorostyryl)benzoate 164g

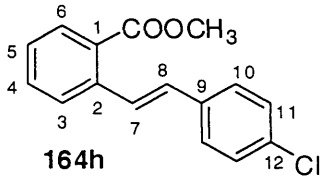


164g

According to GP1 compound **164g** was obtained as colorless solid in 81% yield (12.2 mmol, 3.32 g). M.p.: 70-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, 1H, *J* = 16.2 Hz, H-7), 7.98 (dd, 1H, *J* = 7.9, 1.2 Hz, Ar-*H*), 7.71 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 7.56-7.52 (m, 2H, Ar-*H*), 7.44 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 7.39-7.35 (m, 1H, Ar-*H*), 7.33-7.25 (m, 2H, Ar-*H*), 6.94 (d, 1H, *J* = 16.2 Hz, H-8), 3.96 (s, 3H, $COOCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7 (C=O), 139.4 (C), 138.9 (C), 134.7 (C), 132.3 (CH), 130.8 (CH), 130.0 (CH), 129.9 (CH), 129.0 (CH), 128.6 (C), 127.8 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 125.0 (CH), 52.2 (OCH_3). IR (KBr): *v* = 3064, 2947,

1717, 1591, 1568, 1483, 1433, 1293, 1266, 1245, 1131, 1076, 962, 779, 750, 703 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{14}Cl^{35}O_2$: 273.0677; found: 273.0680.

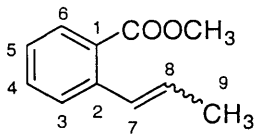
(*E*)-Methyl 2-(4-chlorostyryl)benzoate 164h



164h

According to GP1 compound **164h** was obtained as colorless crystals in 80% yield (12.04 mmol, 3.28 g) after purification. M.p.: 81 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, 1H, *J* = 16.2 Hz, H-7), 7.87 (dd, 1H, *J* = 7.8, 1.3 Hz, Ar-*H*), 7.63 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.45 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.41 (d, 2H, *J* = 8.4 Hz, H-10), 7.28-7.25 (m, 3H, H-11 & Ar-*H*), 6.88 (d, 1H, *J* = 16.2 Hz, H-8), 3.86 (s, 3H, COO*CH3*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8 (C=O), 139.0 (C), 136.0 (C), 133.5 (C), 132.3 (CH), 130.8 (CH), 130.1 (CH), 128.9 (2xCH), 128.5 (C), 128.2 (CH), 128.0 (2xCH), 127.4 (CH), 127.0 (CH), 52.2 (OCH_3) ppm. IR (KBr): *v* = 3061, 2950, 1719, 1491, 1435, 1267, 1256, 1135, 1078, 969, 910, 813, 748 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{14}Cl^{35}O_2$: 273.0677; found: 273.0681.

Methyl 2-(prop-1-enyl)benzoate 164i [92]

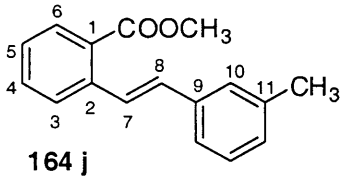


164i

A mixture of $CH_3CH_2PPh_3Br$ (15 mmol, 5.57 g) and KOtBu (16.5 mmol, 1.85 g) in dry THF (30 mL) stirred at 0 °C for 30 min and at r.t. for 4h. The reaction mixture was cooled to 0 °C followed by addition of methyl 2-formylbenzoate (15 mmol, 2.46 g). The reaction mixture was stirred overnight at r.t. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using ethylacetate/hexane (1:10) as eluent to furnish product **164i** in 76% yield (11.5 mmol, 2.02 g) as colorless oil. The spectroscopic data are in agreement with literature.[168]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 1H, *J* = 7.9 Hz, H-6 of *Z*-isomer), 7.86 (d, 1H, *J* = 7.9 Hz, H-6 of *E*-isomer), 7.55-7.43 (m, 3H, Ar-*H* of *E* &*Z*-isomer), 7.34-7.25 (m, 3H, Ar-*H* of *E* & *Z*-isomer), 7.18 (dd, 1H, *J* = 15.6, 1.5 Hz, H-7 of *E*-isomer in 1.0 ratio), 6.92 (dd, 1H, *J* = 11.6, 1.5 Hz, H-7 of *Z*-isomer in 2.0 ratio), 6.22-6.13 (m, 1H, H-8 of *E*-isomer), 5.90-5.82 (m, 1H, *Z*-H-8), 3.92 (s, 3H, COO*CH*$_3$ of *E*-isomer), 3.89 (s, 3H, COO*CH*$_3$ of *Z*-isomer), 1.94 (dd, 1H, *J* = 6.6, 1.7 Hz, H-9 of *E*-isomer in 1.0 ratio), 1.76 (dd, 1H, *J* = 7.1, 1.8 Hz, H-9 of *Z*-isomer in 2.0 ratio) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 168.07 (C=O), 167.76 (C=O), 139.68 (C), 138.82 (C), 131.93 (CH), 131.47 (CH), 130.88 (CH), 130.43 (CH), 130.26 (CH), 129.65 (2xCH), 129.34 (C), 128.64 (CH), 128.05 (C), 127.17 (CH), 126.57 (CH), 126.45 (CH), 126.25 (CH), 51.99 (COO*CH*$_3$), 51.93 (COO*CH*$_3$), 18.81 (*E*-CH_3-9 in 1.0 ratio), 14.28 (*Z*-CH_3-9 in 2.0 ratio). IR (KBr): *v* = 3068, 3028, 2954, 1723, 1598, 1568, 1482, 1433, 1294, 1261, 1132, 1077, 965, 762, 744, 706 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{11}H_{13}O_2$: 177.0910; found: 177.0908.

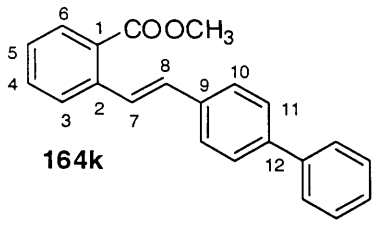
(*E*)-Methyl 2-(3-methylstyryl)benzoate 164j



164 j

According to GP1 compound **164j** was obtained as light yellow viscous oil in 79% yield (11.9 mmol, 3.0 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 1H, *J* = 16.2 Hz, H-7), 7.85 (d, 1H, *J* = 7.9 Hz, H-6), 7.64 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.43 (dt, 1H, *J* = 7.9, 1.0 Hz, Ar-*H*), 7.29-7.22 (m, 3H, Ar-*H*), 7.17 (t, 1H, *J* = 8.6 Hz, Ar-*H*), 7.01 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 6.91 (d, 1H, *J* = 16.2 Hz, H-8), 3.85 (s, 3H, COO*CH*$_3$), 2.30 (s, 3H, Ar-*CH*$_3$) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 167.9 (C=O), 139.4 (C-1), 138.2 (C-2), 137.4 (C-9), 132.2 (CH), 131.7 (CH), 130.7 (CH), 128.7 (CH), 128.6 (C-11 & CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 124.2 (CH), 52.2, 21.5 ppm. IR (KBr): *v* = 3061, 3021, 2948, 1718, 1601, 1487, 1433, 1294, 1274, 1252, 1130, 1077, 962, 779 cm^{-1}. HRMS (AP): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{17}O_2$: 253.1229; found: 253.1236.

(*E*)-Methyl 2-(2-(biphenyl-4-yl)vinyl)benzoate 164k



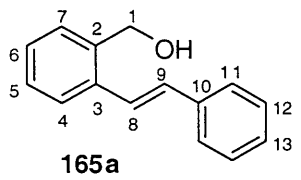
164k

According to GP1 compound **164k** was obtained as colourless crystal in 84% yield (12.6 mmol, 3.96 g). M.p.: 138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, 1H, *J* = 16.2 Hz, H-7), 7.99 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.79 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.68-7.66 (m, 6H, Ar-*H*), 7.56 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.50 (t, 2H, *J* = 7.5 Hz, Ar-*H*), 7.41-7.36 (m, 2H, Ar-*H*), 7.10 (d, 1H, *J* = 16.2 Hz, H-8), 3.99 (s, 3H, COO*CH*$_3$) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 167.9 (C=O), 140.7 (C), 140.6 (C), 139.3 (C), 136.6 (C), 132.2 (CH), 131.0 (CH), 130.8 (CH), 128.9 (2xCH), 128.6 (C), 127.5 (CH), 127.4 (5xCH), 127.2 (CH), 127.0 (3xCH), 52.2 (CH_3) ppm. IR (KBr): ν = 3071, 3032, 2947, 1719, 1566, 1487, 1432, 1266, 1248, 1129, 1077, 971, 832, 765, 721, 700 cm^{-1}. HRMS (ESP): *m/z* $[M + NH_4]^+$ calcd. for $C_{22}H_{22}NO_2$: 332.1645; found: 332.1647.

5.4 General procedure (GP2) for the synthesis of alcohols 165 [92,169]

A solution of **164** (9 mmol) in dry diethyl ether (20 mL) was added to suspension of $LiAlH_4$ (10.8 mmol, 410 mg) in dry diethyl ether (100 mL) at 0 °C. After stirring for 2 h, the reaction was quenched with aqueous Na_2SO_4 solution (20 mL) and the residue was purified by flash chromatography with petroleum ether/ethyl acetate (4:1) as eluent to give a white solid as product **165** in good yields.

(*E*)-(2-Styrylphenyl)methanol 165a

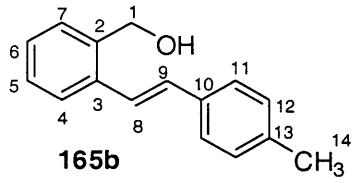


165a

According to GP2, the reaction of ester **164a** (2.2 g, 9 mmol) with $LiAlH_4$ (0.41 g, 10.8 mmol) gave 92 % yield (8 mmol, 1.74 g) of **165a** as white crystals. M.p.: 103 °C (lit. m.p.: 145 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 1H, *J* = 7.5 Hz, H-7), 7.56 (d,

2H, J = 7.5 Hz, Ar-*H*), 7.46 (d, 1H, J = 16.2 Hz, H-8), 7.42-7.30 (m, 6H, Ar-*H*), 7.05 (d, 1H, J = 16.2 Hz, H-9), 4.87 (s, 2H, H-1) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9 (C), 137.4 (C), 136.4 (C), 131.3 (C), 128.7 (2xCH), 128.6 (CH), 128.3 (CH), 127.87 (CH), 127.79 (CH), 126.7 (2xCH), 126.0 (CH), 125.4 (CH), 63.7 (CH_2-1) ppm. The spectroscopic data are in agreement with literature.[170]

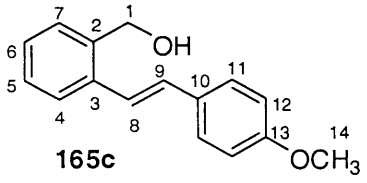
(*E*)-(2-(4-Methylstyryl)phenyl)methanol 165b



165b

According to GP2, the reaction of ester **164b** (2.2 g, 9 mmol) with $LiAlH_4$ (0.41 g, 10.8 mmol) gave 88 % yield (7.9 mmol, 1.78 g) of pure **165b** as white crystals. M.p.: 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 1H, J = 7.4 Hz, H-7), 7.36 (d, 2H, J = 7.9 Hz, H-11), 7.31-7.19 (m, 4H, H-8, Ar-*H*), 7.10 (d, 2H, J = 7.9 Hz, H-12), 6.96 (d, 1H, J = 16.1 Hz, H-9), 4.75 (s, 2H, H-1), 2.29 (s, 3H, H-14) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.80 (C-2), 137.75 (C-3), 136.6 (C-10), 134.6 (C-13), 131.2 (CH), 129.4 (2xCH-11), 128.6 (CH), 128.3 (CH), 127.6 (CH), 126.6 (2xCH-12), 125.9 (CH), 124.3 (CH), 63.7 (CH_2-1), 21.3 (CH_3-14) ppm. IR (KBr): ν = 3345, 3014, 2908, 1509, 1476, 1436, 1370, 1047, 968, 802, 750, 710 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{16}H_{20}NO$: 242.1539; found: 242.1536.

(*E*)-(2-(4-Methoxystyryl)phenyl)methanol 165c



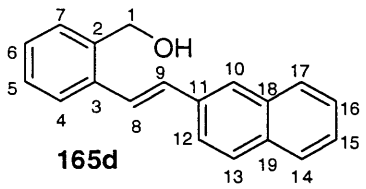
165c

According to GP2, the reaction of ester **164c** (2.60 g, 9.7 mmol) with $LiAlH_4$ (0.44 g, 12 mmol) gave 87 % yield (8.4 mmol, 2.01 g) of pure **165c** as white crystals.

M.p.: 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 1H, J = 7.5 Hz, H-7), 7.41 (d, 2H, J = 6.7 Hz, H-11), 7.32-7.19 (m, 4H, H-8, Ar-*H*), 6.95 (d, 1H, J = 16.2 Hz, H-9), 6.83 (d, 2H, J = 6.7 Hz, H-12), 4.77 (s, 2H, H-1), 3.77 (s, 1H, H-14) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 159.5 (C-13), 137.6 (C-2), 136.7 (C-10), 130.8 (CH), 130.2 (C-3), 128.6 (CH), 128.3 (CH), 128.0 (2xCH-11), 127.4 (CH), 125.8 (CH), 123.2 (2xCH-12), 114.2 (2xCH-12), 63.7 (CH_2-1), 55.4 (CH_3-14) ppm. IR (KBr): ν = 3257, 3011, 2959, 1606, 1599, 1507, 1250, 1172, 1023, 962, 818 cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{16}H_{16}NaO_2$: 263.1043; found: 263.1041; HRMS (ESI): *m/z* [2M + Na]$^+$ calcd. for $C_{32}H_{32}Na_2O_4$: 503.2193; found: 503.2183.

(*E*)-(2-(2-(Naphthalen-2-yl)vinyl)phenyl)methanol 165d



165d

According to GP2, the reaction of ester **164d** (1.875 g, 6.51 mmol) with $LiAlH_4$ (494 mg, 13 mmol) gave 92 % yield (6.0 mmol, 1.56 g) of pure **165d** as white crystals.

M.p.: 140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1H, H-7), 7.88-7.84 (m, 3H, Ar-*H*), 7.79 (d, 1H, *J* = 8.6 Hz, Ar-*H*), 7.75 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.62 (d, 1H, *J* = 16.1 Hz, H-8), 7.53-7.47 (m, 2H, Ar-*H*), 7.44 (d, 1H, *J* = 7.4 Hz, Ar-*H*), 7.40 (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.33 (t, 1H, *J* = 7.4 Hz, Ar-*H*), 7.26 (d, 1H, *J* = 16.1 Hz, H-9), 4.91 (s, 2H, H-1), 1.65 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9 (C), 136.4 (C), 134.9 (C), 133.7 (C), 133.2 (C), 131.3 (CH), 128.7 (CH), 128.40 (CH), 128.38 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 126.9 (CH), 126.4 (CH), 126.04 (CH), 126.0 (CH), 125.6 (CH), 123.7 (CH), 63.8 (CH_2-I) ppm. IR (KBr): ν = 3264, 3033, 1622, 1593, 1483, 1369, 1043, 959, 816, 740 cm^{-1}. HRMS (ESI): *m/z* [M + NH_4]$^+$ calcd. for $C_{19}H_{20}NO$: 278.1539; found: 278.1541.

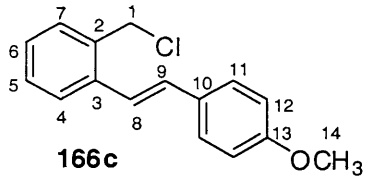
5.4.1 Synthesis of substituted styryl benzyl chlorides 166 [171]

(*E*)-1-(Chloromethyl)-2-styrylbenzene 166a

Alcohol **165a** (1.70 g, 7.1 mmol) was dissolved in THF (25 mL), Et_3N (13 mmol, 1.85 mL) and methanesulfonyl chloride (12 mmol, 0.92 mL) was added at 0 °C. After stirring for 10 min at rt, lithium chloride (25 mmol, 1.06 g) was added into reaction mixture and refluxed for 16 h. (*E*)-1-(chloromethyl)-2-styrylbenzene **166a** was

obtained by flash chromatography (hexane as eluent) in 81% yield (5.8 mmol, 1.32 g) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, 1H, *J* = 7.3 Hz, H-7), 7.64-7.61 (m, 2H, Ar-*H*), 7.55 (d, 1H, *J* = 16.1 Hz, H-8), 7.48-7.33 (m, 6H, Ar-*H*), 7.15 (d, 1H, *J* = 16.1 Hz, H-9), 4.79 (s, 2H, H-1) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 137.3 (C-2), 137.1 (C-3), 134.6 (C-10), 131.9 (CH), 130.4 (CH), 129.3 (CH), 128.8 (2xCH-11), 128.1 (CH), 127.9 (CH), 126.9 (2xCH-12), 126.4 (CH), 124.9 (CH), 44.7 (CH_2-1) ppm. The spectroscopic data are in agreement with literature.[172]

(*E*)-1-(Chloromethyl)-2-(4-methoxystyryl)benzene 166c



166c

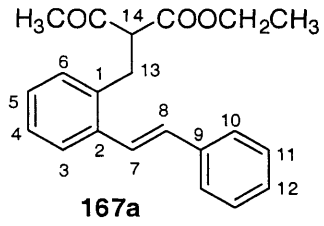
Compound **166c** was synthesised similar to **166a** in 90% yield (6.3 mmol, 1.64 g) as viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, 1H, *J* = 7.9 Hz, H-7), 7.43 (d, 2H, *J* = 8.6 Hz, H-11), 7.29-7.15 (m, 4H, H-8, H-8, Ar-*H*), 6.96 (d, 1H, *J* = 16.1 Hz, H-9), 6.84 (d, 2H, *J* = 8.6 Hz, H-12), 4.65 (s, 2H, H-1), 3.77 (s, 1H, H-14) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C-13), 137.4 (C-1), 134.3 (C-10), 131.3 (CH), 130.3 (CH), 130.1 (C), 129.2 (CH), 128.1 (2xCH-11), 127.5 (CH), 126.1 (CH), 122.7 (CH), 114.2 (2xCH-12), 55.4 (CH_3-14), 44.7 (CH_2-1) ppm. IR (KBr): ν = 3046, 2936, 1653, 1598, 1500, 1453, 1248, 1173, 1028, 958, 818, 743, 663 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{16}ClO$: 259.0884; found: 259.0890.

5.5 General procedure (GP3) for the synthesis of substrates 167[169]

Mesyl chloride (7 mmol, 0.54 mL) was added in one portion to solution of the alcohol **165** (5.0 mmol) and triethylamine (8 mmol, 1.12 mL) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then for 24 h at rt, after which it was poured to water (100 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were collected, dried over $MgSO_4$, and filtered. The solvent was removed in vacuum, yielding the crude products, which were used without further purification. A solution of NaH (60 % in mineral oil, 5.5 mmol, 0.22 g) and ethylacetoacetate (6 mmol, 0.76 mL) in THF (20 mL) were added to the mesylated

residue (5 mmol), then the reaction mixture was refluxed for 3 d. The mixture was poured into 10% HCl (15 mL) and extracted with ether (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated to dryness, the residue was chromatographed (12:1 hexane/EtOAc) to give **167** as a light yellow oils.

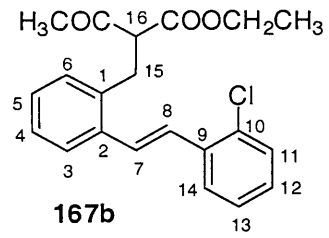
(*E*)-Ethyl 3-oxo-2-(2-styrylbenzyl)butanoate 167a



167a

Alcohol **165a** (1.47 g, 5 mmol) was subjected to GP3 yielding **167a** as a yellow oil (1.47 g, 4.56 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, 1H, *J* = 7.6 Hz, H-6), 7.59-7.57 (m, 2H, Ar-*H*), 7.44-7.39 (m, 3H, Ar-*H*, H-7), 7.34-7.27 (m, 2H, Ar-*H*), 7.23-7.22 (m, 2H, Ar-*H*), 7.05 (d, 1H, *J* = 16.1 Hz, H-8), 4.20 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 3.87 (t, *J* = 7.3 Hz, 1H, H-14), 3.40-3.30 (m, *J* = 7.3 Hz, 2H, H-13), 2.18 (s, 3H, $COCH_3$), 1.17 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.4 (CO), 169.3 (CO), 137.4 (C-1), 136.3 (C-2), 136.0 (C-9), 131.2 (CH), 130.4 (CH), 128.8 (2xCH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.7 (2xCH), 126.2 (CH), 125.6 (CH), 61.6 (OCH_2), 60.4 (CH-14), 31.5 ($COCH_3$), 29.8 (C-13), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 3021, 2990, 1736, 1711, 1450, 1351, 1147, 961, 757, 695 cm^{-1}. HRMS (CI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{22}O_3$: 340.1907; found: 340.1911.

(*E*)-Ethyl 2-(2-(2-chlorostyryl)benzyl)-3-oxobutanoate 167b

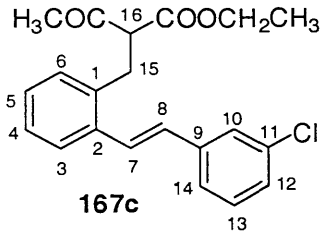


167b

A mixture of ethyl α-acetyl-2-iodo-benzenepropanoate **170a** (4 mmol, 1.41 g), 2-chlorostyrene (5 mmol, 0.64 mL), triethylamine (12.5 mmol, 1.7 mL), palladium

acetate (0.63 mmol, 0.19 g) and triphenylphosphine (0.85 mmol, 0.222 g) were refluxed at 100 °C for 5 h. Solid products were isolated by diluting the reaction mixtures with 10% HCl (200 mL) with stirring to dissolve the salts and excess amine. The residue was chromatographed (13:1 hexane/EtOAc) to give **167b** as a light yellow oil in 76 % yield (3 mmol, 1.08 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (dd, 1H, *J* = 7.8, 1.4 Hz, Ar-*H*), 7.57 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.32-7.11 (m, 8H, H-7, H-8 & Ar-*H*), 4.06-4.04 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 3.69 (t, 1H, *J* = 7.3 Hz, H-16), 3.30-3.20 (m, 2H, H-15), 2.01 (s, 3H, $COCH_3$), 1.10 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 202.4 (C=O), 169.3 (C=O), 136.2 (C-1), 136.1 (C-2), 135.5 (C-10), 133.5 (C-9), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 126.6 (CH), 61.6 (OCH_2), 60.5 (CH-16), 31.4 (CH_2-15), 29.8 (CO-CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 2978, 1733, 1716, 1655, 1560 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{22}Cl^{35}O_3$: 357.1257; found: 357.1243.

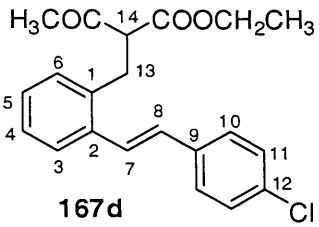
(*E*)-Ethyl 2-(2-(3-chlorostyryl)benzyl)-3-oxobutanoate 167c



167c

Compound **167c** was synthesised similar to **167b**. Yellow oil, yield 70% (2.8 mmol, 0.99 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.43 (m, 1H, *J* = 3.4 Hz, 1.7 Hz, H-10), 7.33 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.30 (d, 1H, *J* = 16.1 Hz, H-7), 7.23 (t, 1H, *J* = 7.7 Hz, Ar-*H*), 7.20-7.12 (m, 4H, Ar-*H*), 6.87 (d, 1H, *J* = 16.1 Hz, H-8), 4.06 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 3.67 (t, 1H, *J* = 7.3 Hz, H-16), 3.31-3.20 (m, 2H, H-15), 2.09 (s, 3H, $COCH_3$), 1.12 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.2 (C=O), 169.2 (C=O), 139.3 (C-1), 136.2 (C-11), 135.8 (C-2), 134.7 (C-9), 130.4 (CH), 130.0 (CH), 129.7 (CH), 128.1 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 124.8 (CH), 61.6 (OCH_2CH_3), 60.4 (CH_2-15), 31.3 (CH_2-16), 29.7 (CO-CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 2977, 1736, 1713, 1588, 1555, 1483 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{25}Cl^{35}NO_3$: 374.1517; found: 374.1515.

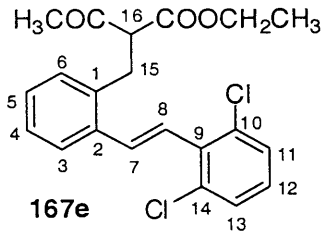
(*E*)-Ethyl 2-(2-(4-chlorostyryl)benzyl)-3-oxobutanoate 167d



167d

Compound **167d** was synthesised similar to **167b**. Yellow oil, yield 66% (2.6 mmol, 0.94 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, 1H, *J* = 7.5 Hz, H-6), 7.38 (d, 2H, *J* = 8.5 Hz, H-10), 7.25 (d, 2H, *J* = 8.5 Hz, H-11), 7.17-7.10 (m, 4H, Ar-H, H-7), 6.87 (d, 1H, *J* = 16.0 Hz, H-8), 4.07-4.03 (m, 2H, OCH_2CH_3), 3.64 (t, 1H, *J* = 7.3 Hz, H-14), 3.29-3.18 (m, 2H, H-13), 2.07 (s, 3H, $COCH_3$), 1.10 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.3 (C=O), 169.3 (C=O), 136.1 (C-9), 136.0 (C-1), 135.9 (C-2), 133.4 (C-12), 130.3 (CH), 129.7 (CH), 128.9 (2xCH-10), 128.0 (CH), 127.9 (2xCH-11), 127.3 (CH), 126.2 (CH), 126.1 (CH), 61.6 (OCH_2CH_3), 60.5 (CH-14), 31.4 (CH-13), 29.8 ($CO-CH_3$), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 2975, 1736, 1712, 1655, 1493 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{25}Cl^{35}NO_3$: 374.1517; found: 374.1522.

(*E*)-Ethyl 2-(2-(2,6-dichlorostyryl)benzyl)-3-oxobutanoate 167e

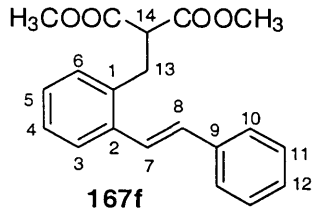


167e

Compound **167e** was synthesised similar to **167b**. Yellow oil, yield 68% (2.7 mmol, 1.06 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, 1H, *J* = 7.6 Hz, H-6), 7.31 (d, 1H, *J* = 16.4 Hz, H-7), 7.29 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.21-7.04 (m, 5H, Ar-*H*), 6.94 (d, 1H, *J* = 16.4 Hz, H-8), 4.05 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 3.81 (t, 1H, *J* = 7.5 Hz, H-16), 3.26-3.19 (m, 2H, H-15), 2.07 (s, 3H, $COCH_3$), 1.11 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 202.4 (C=O), 169.1 (C=O), 136.2 (C-1), 136.1 (C-2), 134.5 (2xC-10), 134.3 (C-9), 130.5 (CH), 128.6 (2xCH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 126.6 (CH), 125.3 (CH), 61.5 (OCH_2CH_3), 60.3 (CH-16), 31.5

(CH_2-15), 29.9 (CO-CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 2975, 1735, 1713, 1655, 1555 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{24}Cl_2NO_3$: 408.1128; found: 408.1127.

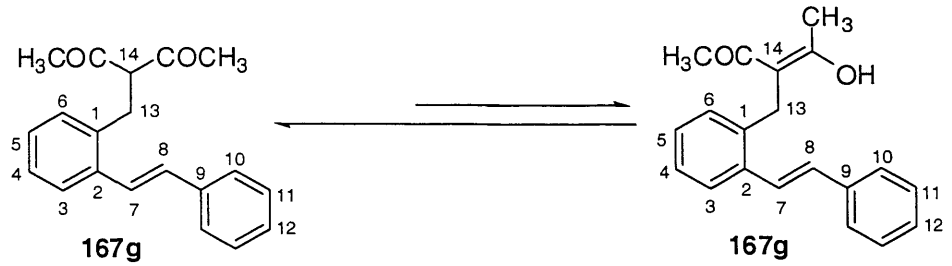
(*E*)-Dimethyl 2-(2-styrylbenzyl)malonate 167f



167f

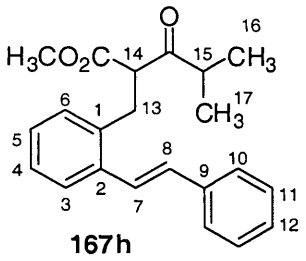
A mixture of dimethyl 2-(2-iodobenzyl)malonate **170b** (4 mmol, 1.37 g), styrene (5 mmol, 0.55 mL), triethylamine (12.5 mmol, 1.7 mL), palladium acetate (0.63 mmol, 0.19 g) and triphenylphosphine (0.85 mmol, 0.222 g) were heated under reflux at 100 °C for 5 h. The resulting residue was chromatographed (14:1 hexane/EtOAc) to give **167f** as a light yellow oil in 87 % yield (3.43 mmol, 1.11 g). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, 1H, *J* = 7.6 Hz, H-6), 7.48-7.47 (m, 2H, Ar-*H*), 7.34-7.30 (m, 3H, H-7, Ar-*H*), 7.23-7.19 (m, 3H, Ar-*H*), 7.14-7.13 (m, 2H, Ar-*H*), 6.96 (d, 1H, *J* = 16.1 Hz, H-8), 3.64-3.61 (m, 7H, H-14, 2 × $COOCH_3$), 3.34 (d, 2H, *J* = 7.6 Hz, H-13) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (2xC=O), 137.4 (C-1), 136.4 (C-2), 135.5 (C-9), 131.2 (CH), 130.2 (CH), 128.7 (2xCH-10), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.7 (2xCH-11), 126.1 (CH), 125.4 (CH), 52.9 (CH-14), 52.6 (2xOCH_3), 32.3 (CH_2-13) ppm. IR (KBr): ν = 3022, 2944, 2840, 1739, 1595, 1491, 1436, 1341, 1280, 1228, 1155, 1025, 965, 762, 693 cm^{-1}. HMRS (ES): *m/z* $[M + NH_4]^+$ calcd. for $C_{20}H_{24}NO_4$: 342.1700; found: 342.1702.

(*E*)-3-(2-Styrylbenzyl)pentane-2,4-dione 167g



Literature procedure[171] was used to prepare the compound **167g**. A solution of NaH (60 % in mineral oil, 5.5 mmol, 0.22 g) and acetylacetone (6 mmol, 0.6 mL) in THF (20 mL) were added to the (*E*)-1-(chloromethyl)-2-styrylbenzene **166a** (4.4 mmol, 1.0 g), then the reaction mixture was refluxed for 3 d. The mixture was poured into 10% HCl (15 mL) and extracted with ether (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated to dryness, the residue was chromatographed (12:1 hexane/EtOAc) to give **167g** as a light yellow oil in 88% yield (3.87 mmol, 1.13 g). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (t, 1H, *J* = 7.4 Hz, Ar-*H*), 7.48-7.44 (m, 2H, Ar-*H*), 7.35 (d, 1H, *J* = 16.1 Hz, H-7), 7.30 (t, 2H, *J* = 7.6 Hz, Ar-*H*), 7.25-7.10 (m, 4H, Ar-*H*), 7.05 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 6.97-6.92 (m, 1H, H-8 of keto-enol form), 3.92 (t, *J* = 7.2 Hz, 1H, H-14), 3.66 (s, 2H, H-13 of enol form in 0.85 ratio), 3.21 (d, *J* = 7.2 Hz, 2H, H-13 of keto form in 1.0 ratio), 2.01 (br. s, 3H, CO-C*H*$_3$ of keto form), 1.95 (br. s, 3H, CO-C*H*$_3$ of enol form in 0.85 ratio) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 203.7 (2xC=O), 192.2 (C-OH, C=O of enol form), 137.4 (C), 137.2 (C), 136.6 (C), 136.5 (C), 136.2 (C), 135.8 (C), 131.40 (CH), 131.37 (CH), 130.2 (CH), 128.9 (2xCH), 128.8 (2xCH), 128.1 (C), 128.02 (CH), 127.98 (CH), 127.96 (CH), 127.4 (CH), 126.8 (C), 126.7 (3xCH), 126.41 (C), 126.37 (CH), 126.2 (C), 125.6 (C), 125.4 (CH), 107.3 (C-14 of enol form), 68.7 (CH-14 of keto form), 31.9 (CH_2-13 of keto-enol form), 30.3 ($COCH_3$ of enol form), 30.1 (2xCO-C*H*$_3$ of keto form), 23.2 (CH_3) ppm. IR (KBr): ν = 3404, 3058, 3028, 2925, 1725, 1700, 1598 cm^{-1}. HRMS (ES^+): *m/z* $[M + NH_4]^+$ calcd. for $C_{20}H_{24}NO_2$: 310.1807; found: 310.1805.

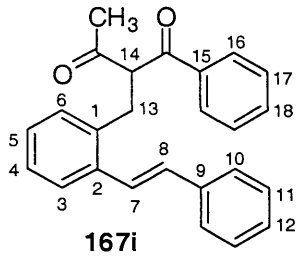
(*E*)-Methyl 4-methyl-3-oxo-2-(2-styrylbenzyl)pentanoate 167h



167h

Synthesis procedure is similar as mentioned for **167g** using (*E*)-1-(chloromethyl)-2-styrylbenzene **166a** (4.9 mmol, 1.1 g) and methyl isobutyrl acetate (5.6 mmol, 0.81 mL). Product **167h** was obtained as light yellow oil in 96 % yield (4.7 mmol, 1.59 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 7.59-7.57 (m, 2H, Ar-*H*), 7.43-7.42 (m, 2H, Ar-*H*), 7.39 (d, 1H, *J* = 5.7 Hz, Ar-*H*), 7.34-7.26 (m, 2H, Ar-*H*), 7.21-7.17 (m, 2H, Ar-*H*), 7.06 (d, 1H, *J* = 16.1 Hz, H-8), 4.01 (dd, 1H, *J* = 6.6, 6.6 Hz, H-14), 3.71 (s, 3H, $COOCH_3$), 3.40-3.38 (m, 2H, H-13), 2.57 (m, 1H, *J* = 6.9 Hz, H-15), 1.04 (d, 3H, *J* = 6.9 Hz, H-16), 0.81 (d, 3H, *J* = 6.9 Hz, H-17) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.4 (C=O), 169.6 (C=O), 137.4 (C-1), 136.2 (C-2), 136.1 (C-9), 131.1 (CH), 130.7 (CH), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.7 (CH), 126.1 (CH), 125.6 (CH), 57.2 ($COOCH_3$), 52.5 (CH-14), 41.5 (CH-15), 32.0 (CH_2-13), 17.6 (CH_3-16), 17.5 (CH_3-17) ppm. IR (KBr): *v* = 3059, 3025, 2972, 2934, 2874, 1747, 1717, 1599, 1577, 1495, 1448, 1435, 1384, 1339, 1264, 1211, 1160, 1100, 1026, 965, 762 cm^{-1}. HRMS (ES^+): *m/z* $[M + NH_4]^+$ calcd. for $C_{22}H_{24}NO_3NH_4$: 354.2064; found: 354.2067.

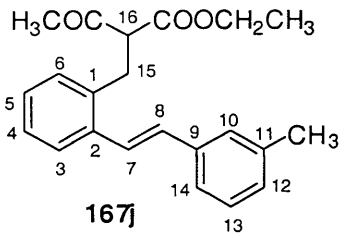
(*E*)-1-Phenyl-2-(2-styrylbenzyl)butane-1,3-dione167i



167i

Synthesis procedure is similar as mentioned for **167g** using (*E*)-1-(chloromethyl)-2-styrylbenzene **166a** (5.3 mmol, 1.2 g) and benzoyl acetone (4.8 mmol, 0.78 g) and NaH (5.0 mmol, 0.20 g). Product **167i** was obtained as light yellow semi-solid in 85 % yield (4.5 mmol, 1.59 g). However, white solid appeared from compound **167i** upon standing at room temperature for several days. M.p.: 95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 2H, Ar-*H*), 7.59 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.55-7.52 (m, 3H, Ar-*H*), 7.42-7.32 (m, 6H, Ar-*H*), 7.24-7.17 (m, 3H, Ar-*H*), 7.03 (d, 1H, *J* = 16.0 Hz, H-8), 4.83 (t, 1H, *J* = 7.0 Hz, H-14), 3.55-3.44 (m, 2H, H-13), 2.13 (s, 3H, CO-*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8 (C=O), 196.2 (C=O), 137.3 (C), 136.5 (C), 136.3 (C), 136.2 (C), 133.7 (CH), 131.4 (CH), 130.5 (CH), 128.8 (CH), 128.73 (CH), 128.65 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.7 (CH), 126.3 (CH), 125.8 (CH), 63.4 (CH-14), 32.5 (CH_2-13), 29.0 (CH_3) ppm. IR (KBr): *v* = 3082, 3051, 3023, 2982, 2940, 1703, 1679, 1597, 1581, 1497, 1450, 1413, 1359, 1279, 1215, 1150, 1053, 989, 959, 766 cm^{-1}. HRMS (ES$^+$): *m/z* [M + NH_4]$^+$ calcd. for $C_{25}H_{22}NO_2NH_4$: 372.1958; found: 372.1959.

(*E*)-Ethyl 2-(2-(3-methylstyryl)benzyl)-3-oxobutanoate 167j

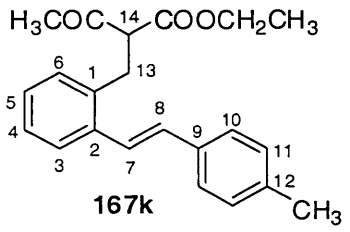


167j

Compound **167j** was synthesised similar to **167b**. Yellow oil, yield 76% (3.04 mmol, 1.02 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.28-7.25 (m, 3H, H-10, Ar-*H*), 7.21-7.17 (m, 2H, Ar-*H*), 7.11-7.10 (m, 2H, Ar-*H*), 7.03 (d, 1H, *J* =

7.4 Hz, Ar-*H*), 6.92 (d, 1H, *J* = 16.0 Hz, H-8), 4.08-4.04 (m, 2H, OC*H*$_2$CH$_3$), 3.70 (t, 1H, *J* = 7.3 Hz, H-16), 3.31-3.21 (m, 2H, H-15), 2.32 (s, 3H, Ar-C*H*$_3$), 2.08 (s, 3H, CO-C*H*$_3$), 1.11 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 202.4 (C=O), 169.3 (C=O), 138.4 (C-1), 137.3 (C-2), 136.4 (C-9), 135.9 (C-11), 131.3 (CH), 130.3 (CH), 128.7 (2xCH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 125.3 (CH), 123.8 (CH), 61.5 (O*C*H$_2$CH$_3$), 60.3 (CH-16), 31.5 (CH$_2$-15), 29.8 (CO-*C*H$_3$), 21.5 (Ar-*C*H$_3$), 14.0 (OCH$_2$*C*H$_3$) ppm. IR (KBr): ν = 3799, 1740, 1717, 1541, 1489, 1457, 781, 755, 691 cm^{-1}. HRMS (ESI): *m/z* [M + NH$_4$]$^+$ calcd. for $C_{22}H_{28}NO_3$: 354.2064; found: 354.2061.

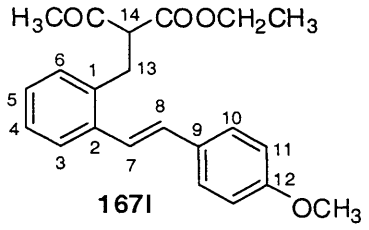
(*E*)-Ethyl 2-(2-(4-methylstyryl)benzyl)-3-oxobutanoate167k



167k

Alcohol **165b** (1.51 g, 5 mmol) was subjected to GP3 yielding **167k** in 65% yield as a light yellow oil (1.1 g, 3.3 mmol). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.51 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.35 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.22 (d, 1H, *J* = 16.1 Hz, H-7), 7.17-7.15 (m, 1H, Ar-H), 7.12-7.08 (m, 4H, Ar-H), 6.91 (d, 1H, *J* = 16.1 Hz, H-8), 4.07-4.02 (q, 2H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.69 (t, 1H, *J* = 7.3 Hz, H-14), 3.27-2.23 (m, 2H, H-13), 2.29 (s, 3H, ArC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 1.11 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 202.4 (C=O), 169.3 (C=O), 137.8 (C-1), 136.5 (C-2), 135.9 (C-9), 134.6 (C-12), 131.1 (CH), 130.4 (CH), 129.5 (2xCH-10), 127.6 (CH), 127.3 (CH), 126.6 (2xCH-11), 126.1 (CH), 124.5 (CH), 61.5 (O*C*H$_2$CH$_3$), 60.3 (CH-14), 31.5 (CH$_2$-13), 29.8 (CO-*C*H$_3$), 21.3 (Ar-*C*H$_3$), 14.0 (OCH$_2$*C*H$_3$) ppm. IR (KBr): ν = 3071, 2922, 1736, 1711, 1513, 1444, 1358, 1209, 1144, 961, 800, 751 cm^{-1}. HRMS (ES): *m/z* [M + NH$_4$]$^+$ calcd. for $C_{22}H_{28}NO_3$: 354.2064; found: 354.2068.

(*E*)-Ethyl 2-(2-(4-methoxystyryl)benzyl)-3-oxobutanoate 167l

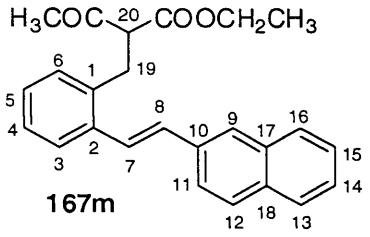


167l

To a solution of NaH (60% dispersion in mineral oil, 7 mmol, 0.28 g) and ethylacetoacetate (8.6 mmol, 1.09 mL) in THF (20 mL), 1-(chloromethyl)-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]benzene (5.4 mmol, 1.41 g) was added. The reaction mixture was stirred at reflux for 16 h. The mixture was poured into 10% HCl (15 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography on silica gel to afford **167l** as yellow oil in 87% yield (4.7 mmol, 1.66 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.50 (d, 2H, *J* = 6.8 Hz, H-10), 7.29-7.19 (m, 4H, H-3, Ar-*H*), 7.00 (d, 1H, *J* = 16.0 Hz, H-8), 6.95 (d, 2H, *J* = 6.8 Hz, H-11), 4.18-4.14 (m, 2H, OCH_2CH_3), 3.87 (s, 1H, OCH_3), 3.80 (t, 1H, *J* = 7.3 Hz, H-14), 3.38-3.33 (m, 2H, H-13), 1.22 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5 (C=O), 169.3 (C=O), 159.5 (C-12), 136.6 (C-1), 135.7 (C-2), 130.6 (CH), 130.3 (CH), 130.2 (C-9), 127.9 (2xCH-10), 127.4 (CH), 127.3 (CH), 125.9 (CH), 123.4 (CH), 114.2 (2xCH-11), 61.5 (OCH_2), 60.3 (CH-14), 55.4 (OCH_3), 31.5 (CH_2-13), 29.8 (CO-CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 3053, 2992, 2833, 1736, 1713, 1607, 1508, 1455, 1361, 1293, 1247, 1175, 1028, 959, 820 cm^{-1}. HRMS (HESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{22}H_{28}NO_4$: 370.2013; found: 370.2013.

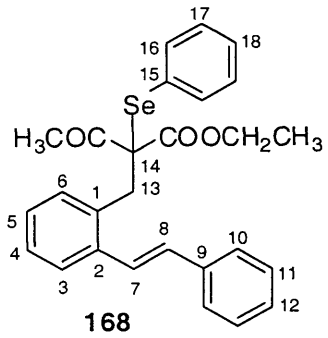
(*E*)-Ethyl 2-(2-(2-(naphthalen-2-yl)vinyl)benzyl)-3-oxobutanoate 167m



167m

Alcohol **165d** (1.51 g, 5 mmol) was subjected to GP3 yielding **167m** as light yellow oil (1.39 g, 3.7 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80-7.70 (m, 5H, H-7, Ar-*H*), 7.59 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.43-7.39 (m, 3H, Ar-*H*), 7.20 (s, 1H, Ar-*H*), 7.14-7.10 (m, 3H, H-8, Ar-*H*), 4.09-4.04 (m, 2H, OCH_2CH_3), 3.73 (t, 1H, *J* = 7.7 Hz, H-20), 3.36-3.25 (m, 2H, H-19), 2.10 (s, 3H, CO-CH_3), 1.12 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.4 (C=O), 169.3 (C=O), 136.3 (C), 136.1 (C), 134.9 (C), 133.7 (C), 133.2 (C), 131.2 (CH), 130.4 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 126.4 (CH), 126.1 (CH), 126.0 (CH), 125.9 (CH), 123.5 (CH), 61.6 (OCH_2), 60.4 (CH-20), 31.5 (CH_2-19), 29.8 (CO-CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 3055, 2979, 1737, 1715, 1596, 1357, 1210, 1147, 745 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{25}H_{28}NO_3$: 390.2064; found: 390.2067.

(*E*)-Ethyl 3-oxo-2-(phenylselanyl)-2-(2-styrylbenzyl)butanoate 168



168

The reaction of **167a** (161 mg, 0.5 mmol) with NaH (60% in mineral oil, 20 mg, 0.5 mmol) in THF (10 mL) was stirred for 15 min and then PhSeCl (0.5 mmol, 96 mg) was added at room temperature to give **168** in 49% yield (0.24 mmol, 117 mg).

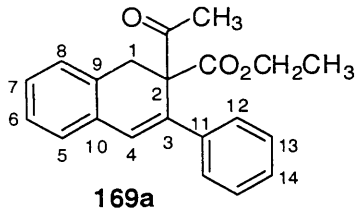
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, 1H, *J* = 7.6 Hz, 1.6 Hz, H-6), 7.46-7.43 (m, 2H, Ar-*H*), 7.41-7.38 (m, 3H, Ar-*H*), 7.33-7.27 (m, 3H, Ar-*H*), 7.25-7.10 (m, 6H, H-7,

Ar-*H*), 6.85 (d, 1H, *J* = 16.0 Hz, H-8), 3.99-3.84 (m, 2H, OC*H*$_2$CH$_3$), 3.54 (d, 1H, *J* = 15.6 Hz, H-13), 3.32 (d, 1H, *J* = 15.6 Hz, H-13), 2.30 (s, 3H, COC*H*$_3$), 0.94 (t, 3H, *J* = 7.2 Hz, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6 (C=O), 169.0 (C=O), 137.4 (C-1), 136.4 (C-2), 135.9 (C-9), 133.4 (2xCH), 131.1 (CH), 130.7 (CH), 129.2 (2xCH), 128.8 (C-15), 128.7 (2xCH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.8 (2xCH)), 126.1 (CH), 125.7 (CH), 61.7 (OCH$_2$), 57.0 (C-14), 36.2 (CH$_2$-13), 31.9 (CO-*CH*$_3$), 14.0 (OCH$_2$*CH*$_3$) ppm.

5.6 General Procedure (GP4) for the Synthesis of Dihydronaphthalenes 169

A mixture of substrate **167** (0.5 mmol) and $SnCl_4$ (1.0 mmol, 0.12 mL) or $BF_3 \cdot OMe_2$ (1 mmol, 0.091 mL) in dry dichloromethane under argon was stirred at –60 °C for 10 to 15 minutes. Phenylselenenyl chloride (0.55 mmol, 0.105 g) was added to reaction mixture and stirred over night while warming up to rt. The crude product was poured into cold water, extracted with diethyl ether (3 × 10 mL), washed with water (10 mL) and dried over anhydrous magnesium sulfate. The filtered solution was evaporated, the residue was chromatographed on silica gel (EtOAc:hexane, 1:12) to give products **169**.

Ethyl 2-acetyl-3-phenyl-1,2-dihydronaphthalene-2-carboxylate 169a

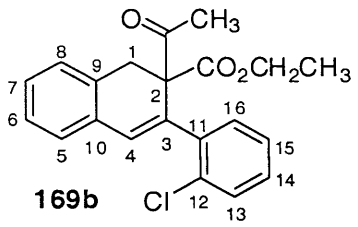


169a

According to GP4 compound **169a** was obtained as colourless solid (86%, 0.43 mmol, 138 mg). M.p.: 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.36 (m, 2H, Ar-*H*), 7.27-7.20 (m, 4H, Ar-*H*), 7.13-7.08 (m, 3H, Ar-*H*), 6.73 (s, 1H, H-4), 4.04-3.89 (m, 2H, OC*H*$_2$CH$_3$), 3.55 (d, *J* = 15.3 Hz, 1H, H-1), 3.39 (d, 1H, *J* = 15.3 Hz, H-1), 2.02 (s, 3H, COC*H*$_3$), 0.93 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.7 (C=O), 171.2 (C=O), 140.1 (C-3), 138.2 (C-11), 133.1 (C-9), 131.4 (C-10), 129.2 (CH), 128.3 (2xCH), 128.1 (CH), 127.7 (CH), 127.5 (3xCH), 127.3 (CH), 127.0 (CH), 66.3 (C-2), 61.6 (OCH$_2$), 36.8 (CH$_2$-1), 28.0 (CO-*CH*$_3$), 13.7 (OCH$_2$*CH*$_3$), ppm. IR (KBr): ν = 3027, 2972, 1733, 1710, 1596, 1491, 1450, 1354, 1290, 1244, 1194,

1066, 755, 697 cm^{-1}. LRMS (CI^+): *m/z* $[M + NH_4]^+$ 338 (100), 321(90); HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{24}NO_3$: 338.1751; found: 338.1747.

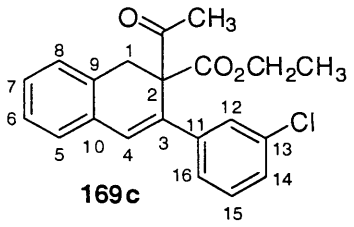
Ethyl 2-acetyl-3-(2-chlorophenyl)-1,2-dihydronaphthalene-2-carboxylate 169b



169b

According to GP4 compound **169b** was obtained as light yellow oil, yield 74% (0.37 mmol, 131 mg). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (dd, 1H, *J* = 7.2, 2.3 Hz, Ar-*H*), 7.33 (dd, 1H, *J* = 7.2 Hz, 1.7 Hz, Ar-*H*), 7.17-7.12 (m, 5H, Ar-*H*), 7.08-7.07 (m, 1H, Ar-*H*), 6.62 (s, 1H, H-4), 3.91-3.84 (m, 2H, OCH_2CH_3), 3.68 (d, 1H, *J* = 15.7 Hz, H-1), 3.43 (d, 1H, *J* = 15.7 Hz, H-1), 2.02 (s, 3H, $COCH_3$), 0.86 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.8 (C=O), 170.6 (C=O), 138.7 (C-3), 133.8 (C-11), 133.6 (C-10), 133.1 (C-9), 132.2 (CH), 131.9 (C-12), 131.0 (CH), 129.5 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.4 (CH), 66.1 (C-2), 61.7 (OCH_2), 36.3 (CH_2-1), 27.4 (CO-CH_3), 13.5 (OCH_2CH_3) ppm. IR (KBr): ν = 2970, 1729, 1711, 1648, 1245 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{20}O_3$: 355.1095; found: 355.1099; HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{23}Cl^{35}NO_3$: 372.1361; found: 372.1363.

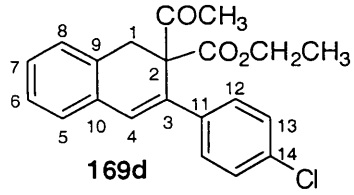
Ethyl 2-acetyl-3-(3-chlorophenyl)-1,2-dihydronaphthalene-2-carboxylate 169c



169c

According to GP4 compound **169c** was obtained as light yellow oil, yield 68% (0.34 mmol, 121 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, 1H, *J* = 2.3 Hz, H-12), 7.25-7.08 (m, 7H, Ar-*H*), 6.74 (s, 1H, H-4), 4.05-3.92 (m, 2H, OCH_2CH_3), 3.58 (d, 1H, *J* = 15.4 Hz, H-1), 3.38 (d, 1H, *J* = 15.4 Hz, H-1), 2.06 (s, 3H, $COCH_3$), 0.96 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.4 (C=O), 171.1 (C=O), 142.0 (C-3), 137.0 (C-11), 134.2 (C-10), 132.9 (C-9), 131.4 (C-13), 130.1 (CH), 129.5 (CH), 128.5 (CH), 127.70 (CH), 127.67 (CH), 127.64 (CH), 127.29 (CH), 127.25 (CH), 125.7 (CH), 66.2 (C-2), 61.8 (OCH_2), 36.8 (CH_2-1), 28.1 (CO-CH_3), 13.7 (OCH_2CH_3) ppm. IR (KBr): ν = 2958, 1723, 1711, 1590 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{21}H_{23}Cl^{35}NO_3$: 372.1361; found: 372.1363.

Ethyl 2-acetyl-3-(4-chlorophenyl)-1,2-dihydronaphthalene-2-carboxylate 169d

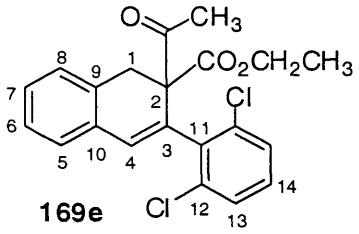


169d

According to GP4 compound **169d** was obtained as colorless oil, yield 78% (0.39 mmol, 138 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, 2H, *J* = 8.4 Hz, H-12), 7.22 (d, 2H, *J* = 8.4 Hz, H-13), 7.14-7.08 (m, 4H, Ar-*H*), 6.71 (s, 1H, H-4), 4.04-3.91 (m, 2H, OCH_2CH_3), 3.56 (d, 1H, *J* = 15.3 Hz, H-1), 3.38 (d, 1H, *J* = 15.3 Hz, H-1), 2.04 (s, 3H, $COCH_3$), 0.96 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.6 (C=O), 171.2 (C=O), 138.6 (C-3), 137.1 (C-11), 133.6 (C-9), 132.9 (C-10), 131.3 (C-14), 129.7 (CH), 128.9 (2xCH-12), 128.5 (2xCH-13), 128.4 (CH), 128.6 (CH), 127.3 (CH), 127.2 (CH), 66.3 (C-2), 61.8 (OCH_2), 36.8 (CH_2-1), 28.0 (CO-CH_3),

13.8 (OCH_2CH_3) ppm. IR (KBr): ν = 2980, 1729, 1710, 1489 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{20}Cl^{35}O_3$: 355.1095; found: 355.1099.

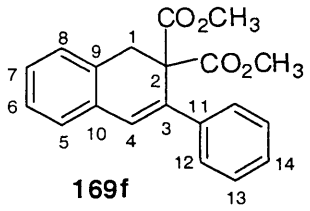
Ethyl 2-acetyl-3-(2,6-dichlorophenyl)-1,2-dihydronaphthalene-2-carboxylate 169e



169e

According to GP4 compound **169e** was obtained as light yellow oil, yield 82% (0.41 mmol, 160 mg). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29-7.26 (m, 2H, Ar-*H*), 7.16-7.11 (m, 5H, Ar-*H*), 6.58 (s, 1H, H-4), 3.91-3.79 (m, 2H, OCH_2CH_3), 3.77 (d, 1H, *J* = 16.2 Hz, H-1), 3.32 (d, 1H, *J* = 16.2 Hz, H-1), 2.00 (s, 3H, $COCH_3$), 0.83 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0 (C=O), 169.8 (C=O), 139.1 (C), 135.9 (C), 135.5 (C), 133.9 (CH), 133.13 (CH), 133.10 (CH), 131.7 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 64.5 (C-2), 61.5 (OCH_2), 36.7 (CH_2-1), 27.3 (CO-CH_3), 13.4 (OCH_2CH_3) ppm. IR (KBr): ν = 1729, 1711, 1648, 1554, 1425, 1245 cm^{-1}. LRMS (AP): *m/z* $[M]^+$ 389 (30%), 371 (30%), 317 (44%), 315 (73%); HRMS (AP): *m/z* $[M]^+$ calcd. for $C_{21}H_{19}Cl_2{}^{35}O_3$: 389.0711; found: 389.0716.

Dimethyl 3-phenyl-1,2-dihydronaphthalene dicarboxylate 169f



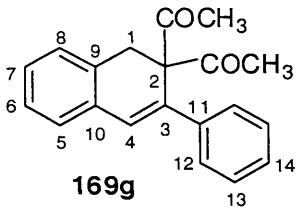
169f

A mixture of substrate **167f** (0.5 mmol, 0.130 g) and $SnCl_4$ (1.0 mmol, 0.126 mL) in dry dichloromethane under argon was stirred at –60 °C for 10 to 15 minutes. Phenylselenenyl chloride (0.55 mmol, 0.105 g) was added to reaction mixture, warmed up to rt and stirred for 36 h. The crude product was poured into cold water, extracted with diethyl ether (3 × 20 mL) and dried over anhydrous magnesium sulfate. The

filtered solution was evaporated, the residue was chromatographed on silica gel (EtOAc:hexane, 1:13) to give **169f** as white solid in 50% yield (0.25 mmol, 80 mg).

M.p.: 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.41 (m, 2H, Ar-*H*), 7.27-7.21 (m, 3H, Ar-*H*), 7.14-7.09 (m, 4H, Ar-*H*), 6.70 (s, 1H, H-4), 3.53 (s, 2H, H-1), 3.50 (s, 6H, 2 × COOC*H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (2xC=O), 140.0 (C), 137.7 (C), 132.8 (C), 131.8 (C), 128.9 (CH), 128.1 (3xCH), 127.6 (CH), 127.5 (2xCH), 127.4 (2xCH), 127.0 (CH), 60.4 (C-2), 52.8 (2xOCH_3), 37.5 (CH_2-1) ppm. IR (KBr): ν = 3032, 2946, 1731, 1426, 1284, 1236, 1093, 1060, 960, 899, 770, 699 cm^{-1}. HRMS (HNES): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}O_4$: 323.1278; found: 323.1281.

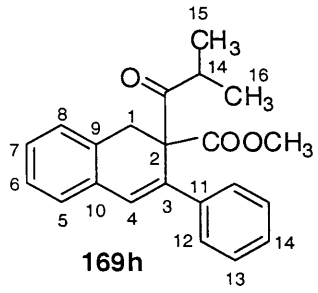
1,1′-(3-Phenyl-1,2-dihydronaphthalene-2,2-diyl)diethanone 169g



169g

According to GP4 compound **169g** was obtained as colorless solid in a 73 % yield (106 mg) after purification. M.p.: 161–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28-7.20 (m, 5H, Ar-*H*), 7.13-7.08 (m, 4H, Ar-*H*), 6.81 (s, 1H, H-4), 3.46 (s, 2H, H-1), 2.02 (s, 6H, 2xCO-*CH*$_3$) ppm. ^{13}C NMR (125 MHz & DEPT, $CDCl_3$): δ = 208.1 (2xC=O), 140.0 (C-3), 138.6 (C-11), 133.6 (C-9), 130.4 (C-10), 129.4 (CH), 128.7 (2xCH-12), 128.3 (CH), 127.9 (2xCH-13), 127.3 (CH), 127.14 (CH), 127.11 (2xCH), 71.9 (C-2), 36.6 (CH_2-1), 28.9 (2xCH_3) ppm. IR (KBr): *v* = 3060, 3022, 2960, 1716, 1699, 1599, 1489, 1495, 1453, 1422, 1355, 1293, 1199, 1163, 891, 779, 761, 701 cm^{-1}. HRMS (ES^+): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}NO_2$: 291.1380; found: 291.1381.

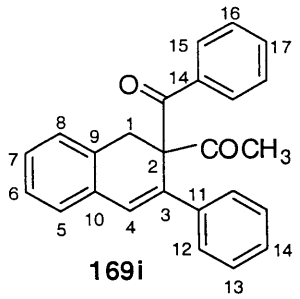
Methyl 2-isobutryl-3-phenyl-1,2-dihydronaphthalene-2-carboxylate 169h



169h

According to GP4 compound **169h** was obtained as solid in a 78 % yield (3.9 mmol, 130 mg) after purification. M.p.: 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.35 (m, 2H, Ar-*H*), 7.27-7.20 (m, 3H, Ar-*H*), 7.14-7.09 (m, 4H, Ar-*H*), 6.73 (s, 1H, H-4), 3.53 (s, 3H, COO*CH*$_3$), 3.51 (d, 2H, *J* = 7.0 Hz, H-1), 2.86 (m, 1H, H-14), 0.95 (d, 3H, *J* = 6.6 Hz, H-15 or H-16), 0.42 (d, 3H, *J* = 6.6 Hz, H-15 or H-16) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 212.6 (C=O), 171.9 (C=O), 140.4 (C), 137.8 (C), 133.0 (C), 131.5 (C), 129.6 (CH), 128.4 (2xCH), 128.2 (CH), 128.0 (2xCH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 67.6 (C-2), 52.6 (OCH_3), 38.1 (CH-14), 36.5 (CH_2-1), 21.2 (CH_3), 19.2 (CH_3) ppm. IR (KBr): *v* = 3061, 3020, 2982, 2937, 2903, 2974, 1735, 1700, 1597, 1494, 1453, 1428, 1380, 1346, 1281, 1257, 1247, 1217, 1105, 1092, 1048, 972, 936, 895, 876, 841, 766 cm^{-1}. HRMS (EI$^+$): *m/z* [M$^+$] calcd. for $C_{22}H_{22}NO_3NH_4$: 335.1647; found: 335.1651.

1-(2-Benzoyl-3-phenyl-1,2-dihydronaphthalen-2-yl)ethanone 169i

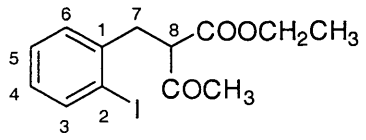


169i

According to GP4 compound **169i** was obtained as very light solid in a 59 % yield (3.3 mmol, 116 mg) after purification. M.p.: 128-130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (dd, 2H, *J* = 8.2 Hz, 1.1 Hz, Ar-*H*), 7.34-7.30 (m, 3H, Ar-*H*), 7.21 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 7.16-7.13 (m, 4H, Ar-*H*), 7.09-7.07 (m, 2H, Ar-*H*), 6.98 (d, 1H, *J* = 7.4 Hz, Ar-*H*), 6.90 (s, 1H, H-4), 3.86 (d, 1H, *J* = 16.0 Hz, H-1), 3.45 (d, 1H, *J* = 16.0 Hz, H-

1), 2.23 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1 (C=O), 202.0 (C=O), 140.2 (C-3), 139.0 (C), 135.6 (C), 133.5 (C), 132.6 (CH), 131.0 (C), 129.7 (2xCH), 129.2 (CH), 128.4 (2xCH), 128.3 (CH), 128.0 (2xCH), 127.7 (CH), 127.64 (CH), 127.60 (2xCH), 127.4 (CH), 127.1 (CH), 70.2 (C-2), 37.9 (CH_2-1), 29.4 (CH_3) ppm. IR (KBr): ν = 3055, 3025, 2966, 2927, 1719, 1657, 1593, 1577, 1493, 1447, 1353, 1287, 1231, 1181, 1150, 1071, 1002, 888, 856, 759 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{21}O_2$: 353.1536; found: 353.1539.

5.7 Synthesis of ethyl α-acetyl-2-iodo-benzenepropanoate[173] 170a

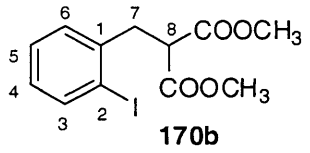


170a

2-Iodobenzyl chloride (4.8 mmol, 0.8 g) was added to a solution of NaH (60 % in mineral oil, 5.5 mmol, 0.22 g) and ethyl acetoacetate (5 mmol, 0.63 mL) in THF (20 mL) and stirred at reflux for 24 h. The mixture was poured into 10% HCl (10 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated to dryness. Finally, the residue was chromatographed (12:1 hexane/EtOAc) to give **170a** as a colorless oil in 77% yield (2.7 mmol, 0.95 g).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.82 (d, *J* = 7.8 Hz, 1H, H-3), 7.26-7.25 (m, 2H, H-4, H-5), 6.94-6.91 (m, 1H, H-6), 4.19-4.13 (m, 2H, OCH_2CH_3), 3.96 (t, *J* = 7.4 Hz, 1H, H-8), 3.27 (d, *J* = 7.4 Hz, 2H, H-7), 2.26 (s, 3H, $COCH_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0 (CO of ketone), 168.7 (CO of ester), 140.7 (C-1), 139.7 (CH-3), 130.9 (CH-6), 128.6 (CH-4), 128.4 (CH-5), 100.4 (C-2), 61.5 (OCH_2), 59.1 (CH-8), 38.5 (CH_2-7), 29.8 (CO-CH_3), 14.1(OCH_2CH_3) ppm. IR (KBr): ν = 2980, 1741, 1717, 1467, 1439, 1358, 1213, 1147, 1012, 752 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{13}H_{19}INO_3$: 364.0404; found: 364.0410.

2-[(2-Iodophenyl)methyl]propanedioic acid 1,3-dimethyl ester[174] 170b



170b

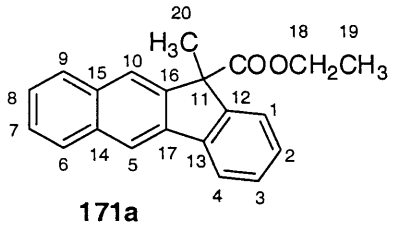
2-Iodobenzyl chloride (11 mmol, 2.85 g) was added to a solution of NaH (60 % in mineral oil, 15.0 mmol, 0.60 g) and dimethylmalonate (17 mmol, 1.94 mL) in THF (30 mL), then the reaction mixture was refluxed for 6 h. The mixture was poured into 10% HCl (15 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (12:1 hexane/EtOAc) to give **170b** as a colorless oil in 82% yield (9 mmol, 3.13 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84-7.83 (d, 1H, *J* = 8.0 Hz, H-3), 7.28-7.24 (m, 2H, H-5, H-6), 6.95-6.92 (t, 1H, *J* = 8.0 Hz, H-4), 3.88 (t, 1H, *J* = 7.8 Hz, H-8), 3.72 (s, 6H, 2 × $COOCH_3$), 3.36-3.34 (d, 2H, *J* = 7.8 Hz, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (2xCO), 140.2 (C-1), 139.8 (CH-3), 130.5 (CH-6), 128.8 (CH-5), 128.4 (CH-4), 100.4 (C-2), 52.6 (2xOCH_3), 51.6 (CH-8), 39.4 (CH_2-7) ppm. IR (KBr): ν = 2951, 1735, 1467, 1434, 752 cm^{-1}.

5.8 General procedure (GP5) for the synthesis of benzo[*b*]fluorene derivatives 171

A solution of stilbene compound **167** (0.5 mmol) in dichloromethane (5 mL) was cooled to –60 °C and $BF_3 \cdot OMe_2$ (1.5 mmol, 0.138 mL) was added dropwise to give a dark brown solution. After being stirred for 10-15 minutes, phenyl selenenyl chloride (0.55 mmol, 105 mg) was added in one portion. The stirring was continued for 60 h at room temperature. The resulting mixture was quenched by addition of H_2O (10 mL) and then extracted with diethylether (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The solvent was removed in vacuo yielding the crude product, which was purified on silica gel with ethylacetate/hexane (1:10) as eluent to yield products **171**.

Ethyl 11-methyl-11*H*-benzo[*b*]fluorene-11-carboxylate 171a



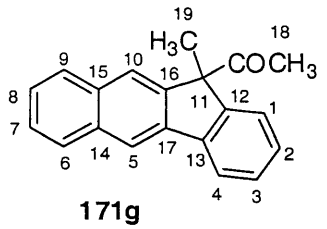
171a

Prepared according to GP5, light yellow viscous oil obtained in 90 % yield (0.45 mmol, 136 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H, H-5), 7.89 (s, 1H, H-10), 7.85-7.79 (m, 3H, Ar-*H*), 7.79 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 7.41-7.35 (m, 3H, Ar-*H*), 7.31 (dd, 1H, *J* = 7.5 Hz, 1.3 Hz, Ar-*H*), 4.04-3.95 (m, 2H, OCH_2CH_3), 1.78 (s, 3H, CH_3), 1.01 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0 (C=O), 148.0 (C), 145.6 (C), 139.8 (C), 138.8 (C), 133.7 (C), 133.4 (C), 128.32 (CH), 128.26 (CH), 128.21 (CH), 128.20 (CH), 126.0 (CH), 125.7 (CH), 124.4 (CH), 122.9 (CH), 120.7 (CH), 118.3 (CH), 61.3 (OCH_2), 56.8 (C), 25.0 (CH_3), 14.0 (CH_3) ppm.

HSQC NMR Experiment		
^{13}C shift [ppm]	^{1}H shift [ppm]	Functionality
128.3, 128.25, 128.19, 128.18, 126.0, 125.7, 124.4, 122.9, 120.7, 118.3	8.07-7.31 (multiplets)	10xCH_{Ar}
61.3	4.02-3.95 (multiplet)	-OCH_2CH_3
25.0	1.78 (singlet)	CO-CH_3
14.0	1.01 (triplet)	OCH_2CH_3

IR (KBr): 3049, 2969, 1726, 1501, 1436, 1228, 1103, 1018, 883, 748 cm^{-1}. LRMS (ESI): *m/z* $[M+H]^+$ 303 (100%), 230 (22%), 229 (100%), 202 (18%). HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{19}O_2$: 303.1390; found: 303.1385.

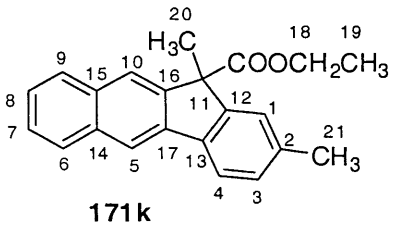
1-(11-methyl-11*H*-benzo [*b*] fluoren-11-yl)ethanone 171g



171g

A mixture of substrate **167g** (0.5 mmol, 146 mg) and $TiCl_4$ (1.0 mmol, 0.24 mL) in dry dichloromethane (5 mL) was stirred at –60 °C for 15 minutes. Phenylselenenyl chloride (0.55 mmol, 0.105 g) was added to the reaction mixture and stirred for 27 hours at rt. The crude product was poured into cold water, extracted with diethyl ether (3 × 10 mL) and dried over anhydrous magnesium sulfate. The filtered solution was evaporated, the residue was chromatographed on silica gel (EtOAc:hexane, 1:12) to give **171g** as white solid (85%, 0.43 mmol, 116 mg). M.p.: 137–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (s, 1H, H-5), 7.91-7.88 (m, 2H, Ar-*H*), 7.79 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.71 (s, 1H, H-10), 7.47-7.41 (m, 3H, Ar-*H*), 7.33-7.32 (m, 2H, Ar-*H*), 1.66 (s, 3H, CH_3), 1.44 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.3 (C=O), 148.0 (C), 145.5 (C), 140.7 (C), 139.4 (C), 133.7 (C), 133.5 (C), 128.7 (CH), 128.5 (CH), 128.27 (CH), 128.25 (CH), 126.3 (CH), 126.0 (CH), 123.9 (CH), 122.7 (CH), 121.2 (CH), 118.8 (CH), 63.7 (C-11), 25.2 (CH_3), 21.2 (CH_3) ppm. IR (KBr): ν = 3055, 2976, 2928, 1703, 1501, 1349, 1203, 1086 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{20}H_{16}O$: 272.1201; found: 272.1201.

Ethyl 2,11-dimethyl-11*H*-benzo[*b*]fluorene-11-carboxylate 171k



171k

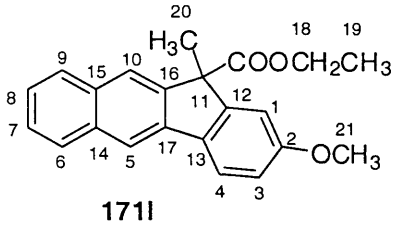
Prepared according to GP5, light yellow oil, yield 80% (0.4 mmol, 127 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (s, 1H, H-5), 7.97 (s, 1H, H-10), 7.93 (d, 1H, *J* = 7.3 Hz, H-6 or H-9), 7.90 (d, 1H, *J* = 7.3 Hz, H-6 or H-9), 7.80 (d, 1H, *J* = 7.7 Hz, H-3), 7.51-7.48 (m, 2H, H-5, H-10), 7.40 (d, *J* = 0.5 Hz, 1H, H-1), 7.29 (dd, *J* = 7.7, 0.5 Hz, 1H,

H-3), 4.11 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 2.49 (s, 3H, Ar-CH_3), 1.87 (s, 3H, CH$_3$), 1.13 (t, 3H, J = 7.0 Hz, OCH$_2$CH_3) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 174.1 (C=O), 148.2 (C), 145.8 (C), 138.9 (C), 138.4 (C), 137.2 (C), 133.7 (C), 133.2 (C), 129.1 (CH), 128.3 (CH), 128.1 (CH), 126.0 (CH), 125.5 (CH), 124.9 (CH), 122.8 (CH), 120.5 (CH), 117.8 (CH), 61.3 (CH$_2$), 56.7 (C), 25.0 (CH$_3$), 21.8 (CH$_3$), 14.0 (CH$_3$) ppm.

HSQC NMR Experiment			
^{13}C shift [ppm]	^{1}H shift [ppm]	Multiplicity	Functionality
122.8	8.13	singlet	CH-5
117.7	7.97	singlet	CH-10
128.3, 128.1	7.93, 7.90	Two doublet	CH-6, CH-9
125.9, 125.4	7.51-7.48	multiplet	CH-7, CH-8
124.9	7.40	doublet	CH-1
129.1	7.29	Doublet of doublet	CH-3
120.5	7.80	doublet	CH-4
61.3	4.11	quartet	OCH$_2$CH$_3$
25.0	1.87	singlet	CH$_3$
14.0	1.01	triplet	OOCH$_2$CH$_3$

IR (KBr): ν = 3056, 2976, 2916, 1723, 1503, 1443, 1363, 1233, 1103, 1018, 883, 818, 743 cm^{-1}. LRMS (EI): *m/z* [M, 316]$^+$ 244 (16%), 243 (100%), 228 (34%); HRMS (ESI): *m/z* [M + NH$_4$]$^+$ calcd. for $C_{22}H_{24}NO_2$: 334.1802; found: 334.1798.

Ethyl 2-methoxy-11-methyl-11*H*-benzo[*b*]fluorene-11-carboxylate 171l



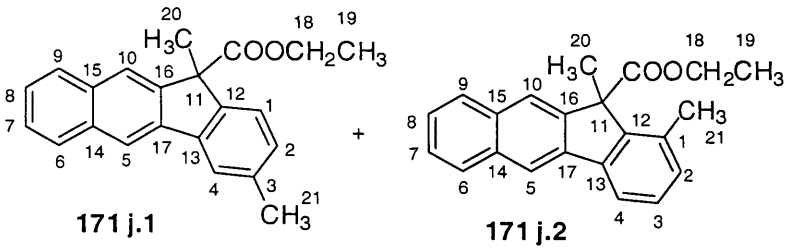
171l

Prepared according to GP5, light yellow oil, yield 67% (0.33 mmol, 111 mg). Using TiCl$_4$ as Lewis acid resulted in 60% yield of **171l** (0.3 mmol, 99 mg). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.96 (s, 1H, H-5), 7.84 (s, 1H, H-10), 7.82 (d, J = 7.7 Hz, 1H, H-6 or H-9), 7.78 (dd, J = 7.4, 1.3 Hz, 1H, H-6 or H-9), 7.72 (d, J = 8.4 Hz, 1H, H-4), 7.42-7.35 (m, 2H, H-7,8), 7.01 (d, 1H, J = 2.4 Hz, H-1), 6.93 (dd, 1H, J = 8.4, 2.4 Hz, H-3), 4.03-3.99 (m, 2H, OCH_2CH$_3$), 3.82 (s, 3H, OCH_3), 1.76 (s, 3H, CH_3), 1.03 (t, J = 7.1

Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0 (C=O), 160.3 (C), 149.8 (C), 145.7 (C), 138.8 (C), 133.8 (C), 132.8 (C), 132.7 (C), 128.3 (CH), 128.0 (CH), 126.0 (CH), 125.3 (CH), 122.7 (CH), 121.6 (CH), 117.0 (CH), 114.5 (CH), 109.7 (CH), 61.3 (OCH_2), 56.8 (C), 55.6 (OCH_3), 25.1 (CH_3), 14.0 (OCH_2CH_3) ppm. IR (KBr): ν = 3003, 2932, 1721, 1653, 1279, 1240, 1100, 1050, 1029 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{22}H_{20}O_3$: 332.1412; found: 332.1409.

Ethyl 3,11-dimethyl-11*H*-benzo[b]fluorene-11-carboxylate 171j.1

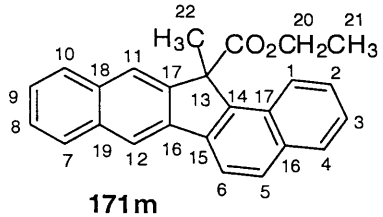
Ethyl 1,11-dimethyl-11*H*-benzo[b]fluorene-11-carboxylate 171j.2



171 j.1 + **171 j.2**

Viscous oil, combined yield 91% (0.46 mmol, 145 mg), **171j.1** and **171j.2** not separable by column chromatography. Both diastereomers listed in NMR data. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, H-5), 8.05 (s, 1H, H-10) 7.87 (s, 1H, Ar-*H*), 7.85-7.83 (m, 2H, Ar-*H*), 7.81 (s, 1H, Ar-*H*), 7.79-7.77 (m, 2H, Ar-*H*), 7.68 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.63 (s, 1H, Ar-*H*), 7.42-7.36 (m, 5H, Ar-*H*), 7.29 (t, 1H, *J* = 7.1 Hz, Ar-*H*), 7.13 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.09 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 4.09-3.88 (m, 2H, H-18), 2.41/2.33 (s, 3H, Ar-CH_3), 1.78/1.75 (s, 3H, CH_3), 1.02/0.98 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.24 (C=O), 174.18 (C=O), 146.5 (C), 146.3 (C), 146.1 (C), 145.3 (C), 140.2 (C), 139.9 (C), 138.9 (2xC), 138.0 (C), 134.5 (C), 133.8 (C), 133.7 (C), 133.42 (C), 133.39 (C), 130.4 (CH), 129.3 (CH), 128.3 (CH), 128.23 (2xCH), 128.19 (2xCH), 126.01 (CH), 125.97 (CH), 125.7 (CH), 125.6 (CH), 124.1 (CH), 122.9 (CH), 121.6 (CH), 121.3 (CH), 118.4 (CH), 118.3 (CH), 118.1 (CH), 61.3 (2xCH_2-18), 56.9 (C), 56.5 (C), 25.1 (CH_3-20), 22.7 (CH_3-20), 21.6 (CH_3-21), 18.8 (CH_3-21), 14.0 (2xCH_3-19) ppm. IR (KBr): ν = 3041, 2984, 2927, 2851, 1725, 1655, 1561, 1457, 1370, 1233, 1098, 1021, 878, 744 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{22}H_{20}O_2$: 316.1463; found: 316.1465.

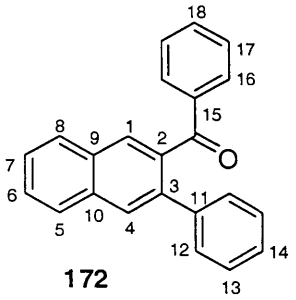
Ethyl-13-methyl-13*H*-dibenzo[*a,h*]fluorene-13-carboxylate 171m



171m

A mixture of substrate **167m** (0.5 mmol, 186 mg) and $TiCl_4$ (1.0 mmol, 0.24 mL) [or $BF_3 \bullet OMe_2$ (1.0 mmol, 0.091 ml)] in dry dichloromethane (5 mL) was stirred at –60 °C for 10 to 15 minutes. Phenylselenenyl chloride (0.55 mmol, 0.105g) was added to the reaction mixture and stirred for 50 hours at rt. The crude product was poured into cold water, extracted with diethyl ether (3 × 20 mL) and dried over anhydrous magnesium sulfate. The filtered solution was evaporated, the residue was chromatographed on silica gel (EtOAc:hexane, 1:12) to give **171m** as white solid (82%, 0.41 mmol, 144 mg). M.p.: 211 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (s, 1H, H-5), 7.97 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 7.90-7.88 (m, 4H, Ar-*H*), 7.83 (t, 2H, *J* = 8.6 Hz, Ar-*H*), 7.49 (t, 1H, *J* = 7.0 Hz, Ar-*H*), 7.44-7.41 (m, 3H, Ar-*H*), 4.03-3.85 (m, 2H, H-20), 1.92 (s, 3H, H-22), 0.84 (dt, 3H, *J* = 7.1 Hz, 0.8 Hz, H-21) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (C=O), 147.2 (C), 143.8 (C), 139.3 (C), 137.7 (C), 134.2 (C), 133.8 (C), 133.3 (C), 129.6 (C), 129.4 (2 × CH), 128.3 (CH), 128.2 (CH), 126.8 (CH), 126.1 (CH), 125.7 (CH), 125.6 (CH), 124.0 (CH), 121.5 (CH), 119.0 (CH), 118.3 (CH), 61.4 (CH_2-20), 57.1 (C-13), 24.2 (CH_3-22), 13.9 (CH_3-21) ppm. IR (KBr): ν = 3056, 2986, 1723, 1458, 1368, 1243, 1093 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{25}H_{24}NO_2$: 370.1802; found: 370.1807; HRMS (ESI): *m/z* $[2M + NH_4]^+$ calcd. for $C_{50}H_{44}NO_4$: 722.3265; found: 722.3272.

2-Benzoyl-3-phenylnaphthalene 172



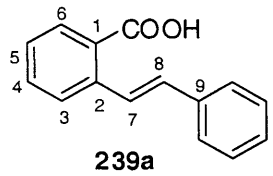
172

A mixture of substrate **167i** (0.5 mmol) and $BF_3 \bullet OMe_2$ (1.3 mmol, 0.115 mL) in dry dichloromethane under argon was stirred at at –60 °C for 10 to 15 minutes. Phenylselenenyl chloride (0.55 mmol, 0.105 g) was added to reaction mixture and stirred for 7-days. The crude product was poured into cold water, extracted with diethyl ether (3 x 10 mL), washed with water (10 mL) and dried over anhydrous magnesium sulfate. The filtered solution was evaporated; the residue was purified on preparative TLC (EtOAc:hexane, 1:16) to give product **172** in 32 % yield (49 mg, 0.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1H, H-1), 7.88-7.83 (m, 3H, Ar-*H*), 7.65-7.62 (m, 2H, Ar-*H*), 7.57-7.45 (m, 2H, Ar-*H*), 7.40-7.34 (m, 1H, Ar-*H*), 7.30-7.11 (m, 7H, Ar-*H*) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.4 (C=O), 140.4 (C-2), 138.5 (C-15), 137.7 (C-3), 137.4 (C), 134.1 (C), 132.9 (CH), 131.6 (C), 130.1 (2xCH), 129.4 (CH), 129.2 (CH), 129.1 (2xCH), 128.5 (CH), 128.3 (2xCH), 128.2 (2xCH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 126.9 (CH) ppm. LS (EI): *m/z* $[M]^+$ 308 (100), 292 (80), 231(91), 202 (53). The spectroscopic data are in agreement with literature.[175]

5.9 General Procedure (GP6) for the Synthesis of Stilbene Carboxylic Acids 239a

To a mixture of **164** (8.4 mmol) in 60 mL of THF:MeOH:H_2O (4:1:l, v:v:v) LiOH (600 mg, 25.2 mmol) was added at room temperature. The reaction mixture was then heated to 70 °C for 12 hours. After the reaction mixture was allowed to cool to room temperature, reaction mixture was neutralised up to pH 6 using 1M HCl. The product was extracted with ethyl acetate (2 x 20 mL), washed with water and brine. The extract was dried over anhydrous $MgSO_4$, evaporated under reduced pressure and then recrystallised from ethanol to give the corresponding stilbene carboxylic acids **239** in very good yields.

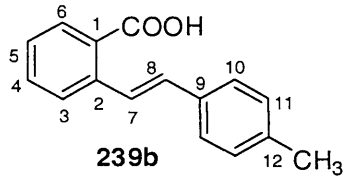
(*E*)-2-Styrylbenzoic acid 239a



239a

According to GP6 compound **239a** was obtained as colorless solid in 87% yield (7.2 mmol, 1.64 g). M.p.: 151-152 °C (literature[162] m.p.: 159-161 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04-7.98 (m, 2H, H-6, H-7), 7.66 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.49-7.47 (m, 3H, Ar-*H*), 7.31-7.27 (m, 3H, Ar-*H*), 7.22-7.16 (m, 1H, Ar-*H*), 6.95 (d, 1H, *J* = 16.2 Hz, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.3 (C=O), 140.3 (C-1), 137.4 (C), 133.2 (C), 131.9 (CH), 131.7 (CH), 128.8 (3xCH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.0 (2xCH) ppm. IR (KBr): *v* = 3330-2745, 3061, 1685, 1601, 1565, 1495, 1447, 1406, 1301, 1275, 1253, 1078, 963, 913, 759, 744 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{13}O_2$: 225.0910; found: 225.0912. The spectroscopic data are in agreement with literature.[176]

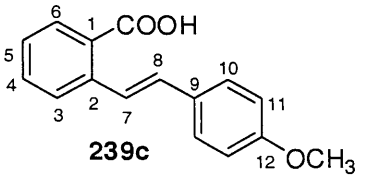
(*E*)-2-(4-Methylstyryl)benzoic acid 239b



239b

According to GP6 compound **239b** was obtained as colorless crystals in 88% yield (7.4 mmol, 1.76 g). M.p.: 158-159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (dd, 1H, *J* = 5.9 Hz, 1.2 Hz, H-6), 8.07 (d, 1H, *J* = 16.2 Hz, H-7), 7.78 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.60 (dt, 1H, *J* = 8.5 Hz, 1.1 Hz, Ar-*H*), 7.50 (d, 2H, *J* = 8.0 Hz, H-10), 7.39 (dt, 1H, *J* = 8.5 Hz, 1.1 Hz, Ar-*H*), 7.22 (d, 2H, *J* = 8.0 Hz, H-11), 7.06 (d, 1H, *J* = 16.2 Hz, H-8), 2.41 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2 (C=O), 140.4 (C-1), 137.9 (C), 134.6 (C), 133.1 (CH), 131.8 (CH), 131.7 (CH), 129.5 (2xCH), 127.3 (CH), 127.2 (C), 127.1 (CH), 126.9 (2xCH), 126.5 (CH), 21.3 (CH_3) ppm. IR (KBr): *v* = 3064-2647, 1682, 1594, 1570, 1511, 1481, 1412, 1306, 1277, 1253, 1079, 957, 934, 853, 802, 748 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{15}O_2$: 239.1067; found: 239.1069.

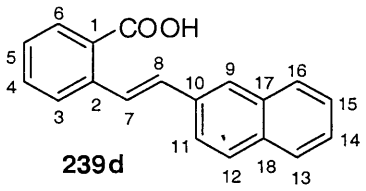
(*E*)-2-(4-Methoxystyryl)benzoic acid 239c



239c

According to GP6 compound **239c** was obtained as colorless crystals in 97% yield (8.4 mmol, 2.14 g). M.p.: 192 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85-7.82 (m, 2H, Ar-*H*), 7.79 (d, 1H, *J* = 16.4 Hz, H-7), 7.56 (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.50 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.36 (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.13 (d, 1H, *J* = 16.4 Hz, H-8), 3.79 (s, 1H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7 (C=O), 159.2 (C-12), 138.1 (C-1), 131.8 (CH), 130.3 (CH), 130.2 (CH), 129.8 (C), 129.5 (C), 127.9 (2xCH-10), 126.9 (CH), 126.3 (CH), 124.7 (CH), 114.3 (2xCH-11), 55.2 (OCH_3) ppm. IR (KBr): *v* = 3100-2517, 1688, 1604, 1562, 1508, 1405, 1298, 1076, 1026, 966, 901, 749 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{15}O_3$: 255.1016; found: 255.1018.

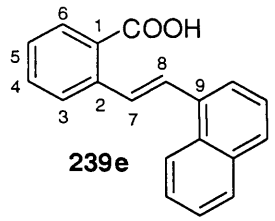
(*E*)-2-(2-(Naphthalen-2-yl)vinyl)benzoic acid 239d



239d

According to GP6 compound **239d** was obtained as colorless crystals in 95% yield (7.9 mmol, 2.16 g). M.p.: 219-220 °C (lit.[177] m.p.: 211-212 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.30 (d, 1H, *J* = 16.3 Hz, H-7), 8.06-8.04 (dd, 1H, *J* = 7.8, 1.2 Hz, H-6), 8.02 (s, 1H, H-9), 7.96-7.90 (m, 4H, Ar-*H*), 7.87-7.85 (dd, 1H, *J* = 8.6, 1.7 Hz, Ar-*H*), 7.64 (dt, *J* = 7.4, 1.0 Hz, 1H, Ar-*H*), 7.55-7.49 (m, 2H, Ar-*H*), 7.44 (dt, 1H, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.38 (d, 1H, *J* = 16.3 Hz, H-8) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.8 (C=O), 140.0 (C-1), 136.2 (C-2), 134.8 (C), 134.2 (C), 133.1 (CH), 131.9 (CH), 131.7 (CH), 130.0 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 124.6 (CH) ppm. IR (KBr): *v* = 3103-2517, 1675, 1627, 1598, 1565, 1485, 1410, 1305, 1249, 1165, 1141, 1080, 964, 930, 903, 845, 822, 800, 742, 702, 663 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{15}O_2$: 275.1067; found: 275.1071.

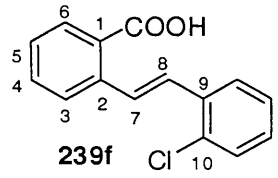
(*E*)-2-(2-(Naphthalen-1-yl)vinyl)benzoic acid 239e



239e

According to GP6 compound **239e** was obtained as colorless crystals in 98% yield (8.2 mmol, 2.25 g). M.p.: 160-162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, 1H, *J* = 8.4 Hz, H-6), 8.06 (dd, 1H, *J* = 7.9 Hz, 1.2 Hz, Ar-*H*), 8.01 (d, 1H, *J* = 16.0 Hz, H-7), 7.80-7.78 (m, 2H, Ar-*H*), 7.74 (d, 2H, *J* = 7.4 Hz, Ar-*H*), 7.70 (d, 1H, *J* = 16.0 Hz, H-8), 7.55 (td, 1H, *J* = 7.5 Hz, 1.0 Hz, Ar-*H*), 7.48-7.39 (m, 3H, Ar-*H*), 7.33 (td, 1H, *J* = 8.5 Hz, 1.1 Hz, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6 (C=O), 140.6 (C), 134.9 (C), 133.8 (C), 133.2 (CH), 131.7 (CH), 131.4 (C), 130.7 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.4 (C), 126.2 (CH), 125.84 (CH), 125.80 (CH), 124.4 (CH), 123.8 (CH); IR (KBr): *v* = 3223-2513, 1675, 1598, 1564, 1482, 1402, 1403, 1266, 1171, 1145, 1086, 964, 925, 794, 745, 664 cm^{-1}. HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd. for $C_{19}H_{14}O_2 \bullet NH_4$: 292.1332; found: 292.1335

(*E*)-2-(2-Chlorostyryl)benzoic acid 239f

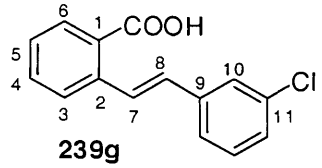


239f

According to GP6 compound **239f** was obtained as colorless crystals in quantitative yield (8.4 mmol, 2.18 g). M.p.: 178 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.04-7.97 (m, 2H, Ar-*H*), 7.78-7.76 (m, 2H, Ar-*H*), 7.59-7.55 (m, 1H, Ar-*H*), 7.41-7.37 (m, 3H, Ar-*H*), 7.33-7.29 (m, 1H, Ar-*H*), 7.26-7.23 (m, 1H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, CD_3OD & DEPT 135): δ = 170.8 (C=O), 140.1 (C-1), 136.9 (C-2), 134.5 (C-10), 133.4 (CH), 131.9 (CH), 131.7 (CH), 130.8 (C-9 & CH), 130.0 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH) ppm. IR (KBr): *v* = 3070-2556, 3066, 2878, 2648, 1691, 1598, 1569, 1485, 1441, 1409, 1307, 1274, 1249, 1079, 1049, 1036, 956,

915, 747, 711, 662 cm^{-1}. HRMS (ESP): *m/z* $[M + NH_4]^+$ calcd. for $C_{15}H_{11}Cl^{35}O_2 \bullet NH_4$: 276.0786; found: 276.0791.

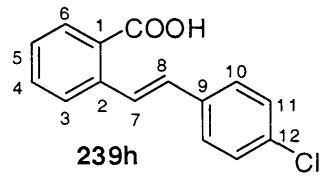
(*E*)-2-(3-Chlorostyryl)benzoic acid 239g



239g

According to GP6 compound **239g** was obtained as colorless crystals in 100% yield (0.0084 mol, 2.16 g). M.p.: 149-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 1H, *J* = 7.7 Hz, H-6), 8.09 (d, 1H, *J* = 16.2 Hz, H-7), 7.74 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.62 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.55 (s, 1H, Ar-*H*), 7.47-7.40 (m, 2H, Ar-*H*), 7.34-7.27 (m, 2H, Ar-*H*), 6.97 (d, 1H, *J* = 16.2 Hz, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 172.6 (C=O), 139.8 (C-1), 139.3 (C), 134.7 (C), 133.3 (CH), 131.8 (CH), 130.4 (CH), 129.9 (CH), 129.1 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.3 (C), 127.0 (CH), 125.0 (CH) ppm. IR (KBr): *v* = 3300-2700, 3061, 2870, 1686, 1594, 1567, 1483, 1415, 1301, 1268, 1167, 1144, 1078, 956, 782 cm^{-1}. HRMS (ESP): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{11}Cl^{35}O_2Na$: 281.0340; found: 281.0343.

(*E*)-2-(4-Chlorostyryl)benzoic acid 239h

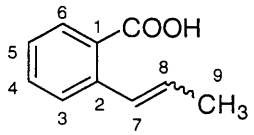


239h

According to GP6 compound **239h** was obtained as colorless crystals in 99% yield (8.4 mmol, 2.16 g). M.p.: 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, 1H, *J* = 7.9 Hz, 1.3 Hz, H-6), 7.97 (d, 1H, *J* = 16.2 Hz, H-7), 7.66 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.52 (dt, 1H, *J* = 7.7 Hz, 1.2 Hz, Ar-*H*), 7.41 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.32 (dt, 1H, *J* = 7.7 Hz, 1.2 Hz, Ar-*H*), 7.26 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 6.90 (d, 1H, *J* = 16.2 Hz, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 172.1 (C=O), 139.9 (C-1), 135.9 (C), 133.6 (C), 133.2 (CH), 131.7 (CH), 130.5 (CH), 128.9 (CH), 128.2 (CH), 128.1(CH), 127.5 (CH), 127.4 (CH), 127.2 (C) ppm. IR (KBr): *v* = 3071-2631, 1683, 1568, 1490,

1404, 1267, 1245, 1090, 1077, 1011, 969, 819, 748 cm^{-1}; HRMS (ES): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{11}Cl^{35}O_2Na$: 281.0340; found: 281.0341.

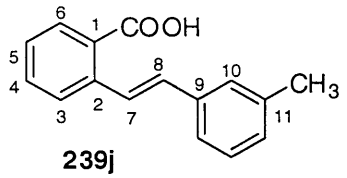
2-(Prop-1-enyl)benzoic acid 239i



239i

According to GP6 compound **239i** (*E/Z* mixture 1:5.5) was obtained as colorless crystals in 100% yield (8.4 mmol, 1.36 g). M.p.: 71-73 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 1H, *J* = 7.5 Hz, H-6 of *Z*-isomer), 8.05 (d, 1H, *J* = 7.7 Hz, H-6 of *Z*-isomer), 7.59-7.52 (m, 1H, Ar-*H* of *Z* or *E* isomer), 7.39-7.33 (m, 2H, Ar-*H* of *Z* and *E* isomer), 7.00 (d, 1H, *J* = 11.6 Hz, H-7), 6.24-6.19 (m, 1H, *E*-H-8), 5.94-5.86 (m, 1H, *Z*-H-8), 1.98 (br d, 3H, *J* = 6.6 Hz, *E*-H-9), 1.79 (dd, 3H, *J* = 7.0, 1.4 Hz, *Z*-H-9) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 173.6 (C=O), 173.1 (C=O), 140.7 (C-1), 139.7 (2xC), 133.0 (CH), 132.5 (CH), 131.5 (CH), 131.3 (CH), 131.2 (CH), 129.9 (CH), 129.8 (CH), 129.1 (CH), 128.1 (C), 127.5 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 18.9 (*E*-CH_3), 14.4 (*Z*-CH_3) ppm. MS (EI) (relative intensity) *m/z*: 162 (M^+, 65), 147 (100), 134 (12), 117 (17), 116 (33), 115 (92), 105 (20), 91 (33), 77 (21). IR (KBr): *v* = 3260-2566, 3068, 2976, 2930, 2647, 1679, 1598, 1568, 1485, 1451, 1409, 1308, 1280, 1137, 1078, 958, 914, 793, 755, 702, 664 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{10}H_{10}O_2$: 162.0675; found: 162.0673.

(*E*)-2-(3-Methylstyryl)benzoic acid 239j

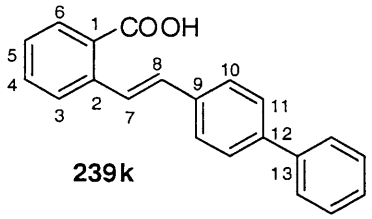


239j

According to GP6 compound **239j** was obtained as colourless crystals in 81% yield (6.8 mmol, 1.62 g). M.p.: 163-164 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (dd, 1H, *J* = 7.8 Hz, 1.3 Hz, H-6), 7.97 (d, 1H, *J* = 16.2 Hz, H-7), 7.67 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.50 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 7.30-7.27 (m, 3H, Ar-*H*), 7.20-7.17 (m, 1H, Ar-*H*), 7.03

(d, 1H, J = 7.6 Hz, Ar-*H*), 6.93 (d, 1H, J = 16.2 Hz, H-8), 2.30 (s, 3H, Ar-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6 (C=O), 140.3 (C-1), 138.3 (C-2), 137.3 (C-3), 133.1 (CH), 132.1 (CH), 131.7 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.2 (C-11 & CH), 124.1 (CH), 21.5 (CH_3) ppm. IR (KBr): v = 3069-2511, 1689, 1595, 1581, 1566, 1484, 1415, 1303, 1278, 1261, 1166, 1143, 1077, 957, 934, 777, 754, 733, 702 cm^{-1}. HRMS (ES): m/z $[M + NH_4]^+$ calcd. for $C_{16}H_{18}NO_2$: 256.1332; found: 256.1334.

(*E*)-2-(2-(Biphenyl-4-yl)vinyl)benzoic acid 239k



239k

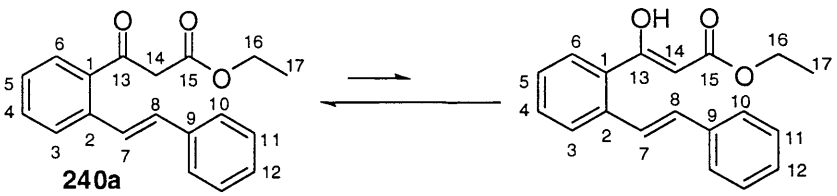
According to GP6 compound **239k** was obtained as colourless crystals in 92% yield (7.7 mmol, 2.31 g). M.p.: 180-183 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.99 (d, 1H, J = 16.4 Hz, H-7), 7.88 (d, 2H, J = 8.0 Hz, Ar-*H*), 7.72 (t, 4H, J = 8.0 Hz, Ar-*H*), 7.66 (d, 2H, J = 8.3 Hz, Ar-*H*), 7.60 (t, 1H, J = 8.0 Hz, Ar-*H*), 7.49 (t, 2H, J = 7.9 Hz, Ar-*H*), 7.42-7.37 (m, 2H, Ar-*H*), 7.24 (d, 1H, J = 16.4 Hz, H-8) ppm. ^{13}C NMR (125 MHz & DEPT 135, DMSO-d_6): δ = 168.6 (C=O), 139.6 (C-1), 139.5 (C-2), 137.8 (C-9), 136.4 (C), 131.9 (CH), 130.3 (CH), 130.1 (CH), 129.8 (C), 129.0 (2xCH), 127.5 (CH), 127.4 (CH), 127.20 (2xCH), 127.15 (CH), 127.0 (2xCH), 126.6 (CH), 126.5 (2xCH), ppm. IR (KBr): v = 3100-2540, 1683, 1627, 1602, 1565, 1485, 1452, 1409, 1305, 1272, 1247, 1139 1073, 965, 917, 823, 764, 744, 718, 697, 558 cm^{-1}. HRMS (ES): m/z $[M + H]^+$ calcd. for $C_{21}H_{17}O_2$: 301.1223; found: 301.1225.

5.10 General procedure (GP7) for the synthesis of stilbene benzoylacetates[129] 240

Step A: A solution of stilbene carboxylic acids **239a** (1.66 g, 7.4 mmol) and 1,1'-carbonyldiimidazole (1.19 g, 7.4 mmol) in anhydrous tetrahydrofuran (10 mL) was stirred at room temperature overnight. Step B: To a suspension of potassium ethyl malonate (2.5 g, 15 mmol), anhydrous acetonitrile (27 mL), and triethyl amine (3.1 mL, 0.022 mol) was added portionwise magnesium chloride (1.75 g, 0.018 mol) while

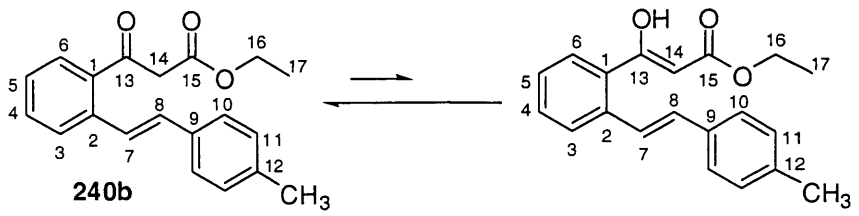
maintaining the temperature below 20 °C. The reaction mixture B was stirred at room temperature for 4 h then cooled in an ice bath. The solution A was added dropwise, and the suspension stirred at room temperature overnight. The solvent was removed in vacuo, the residue was taken up in toluene (30 mL), cooled in ice bath, and aqueous HCl (12%, 12 mL) was slowly added. The mixture was warmed to room temperature and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with hexane/ether to give **240a** (1.81 g, 83%) along with recovery of traces of starting material **239a**.

(*E*)-Ethyl 3-oxo-3-(2-styrylphenyl)propanoate 240a



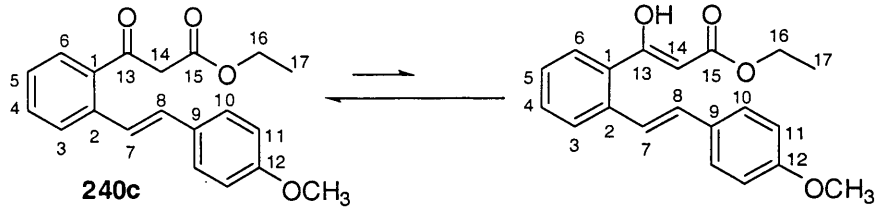
According to GP7 compound **240a** was obtained as yellow oil in 83 % yield (6.2 mmol, 1.81 g) after purification (keto:enol 2.5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.68 (m, 2H, Ar-*H*), 7.57-7.53 (m, 4H, Ar-*H*), 7.49-7.36 (m, 3H, Ar-*H*), 7.34-7.30 (m, 1H, Ar-*H*), 7.09-7.01 (m, 1H, Ar-*H*), 5.37 (s, 1H, H-14 of enolic form), 4.28 (q, 2H, *J* = 7.1 Hz, H-16 of enol form), 4.22 (q, 2H, *J* = 7.1 Hz, H-16 of keto form), 4.00 (s, 2H, H-14 of keto form), 1.35 (t, 3H, *J* = 7.1 Hz, H-17 of enol form), 1.25 (q, 2H, *J* = 7.1 Hz, H-17 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 196.28 (C-13 of keto form), 173.60 (C-13 of enol form), 172.81 (C-15 of keto form), 167.37 (C-15 of enol form), 138.00 (C), 137.35 (C), 137.17 (C), 136.29 (C), 136.19 (C), 133.68 (C), 132.29 (CH), 132.20 (CH), 130.71 (CH), 130.36 (CH), 128.97 (CH), 128.79 (CH), 128.70 (4xCH), 128.04 (CH), 127.87 (CH), 127.61 (CH), 127.45 (CH), 127.29 (CH), 127.01 (CH), 126.97 (4xCH), 126.83 (CH), 126.43 (CH), 93.08 (CH-14 of enol), 61.48 (CH_2-16 of keto form), 60.45 (CH_2-16 of enol form), 48.59 (CH_2-14 of keto form), 14.32 (CH_3-17 of enol), 14.09 (CH_3-17 of keto form) ppm. IR (KBr): ν = 3058, 3028, 2981, 1740, 1684, 1624, 1476, 1447, 1408, 1316, 1266, 1196, 1027, 961, 759, 690 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{19}O_3$: 295.1329; found: 295.1332.

(*E*)-Ethyl 3-(2-(4-methylstyrylphenyl)-3-oxopropanoate 240b



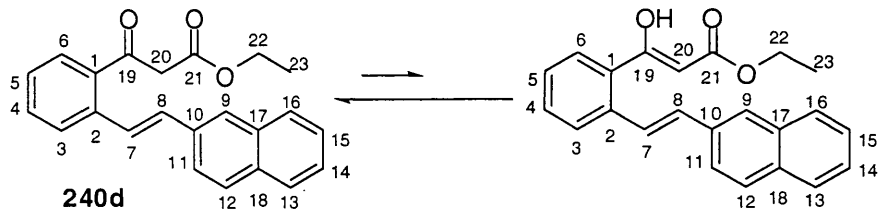
According to GP7 compound **240b** was obtained as light yellow oil in 98% yield (7.3 mmol, 2.24 g) after purification (keto: enol 2.5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, 1H, *J* = 7.9 Hz, H-6), 7.57-7.52 (dd ovelapped, 2H, *J* = 16.1, 6.6 Hz, H-7 & Ar-*H*), 7.44-7.41 (m, 1H, Ar-*H*), 7.37-7.32 (m, 2H, Ar-*H*), 7.28- 7.20 (m, 1H, Ar-*H*), 7.09 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 6.92 (t, 1H, *J* = 16.1 Hz, H-8 of keto & enol form), 5.26 (s, 1H, H-14 of enolic form), 4.19 (q, 2H, *J* = 7.1 Hz, H-16 of enol form), 4.11 (q, 2H, *J* = 7.1 Hz, H-16 of keto form), 3.88 (s, 2H, H-14 of keto form), 2.28 (s, 3H, Ar-*CH*$_3$), 1.25 (t, 3H, *J* = 7.1 Hz, H-17 of enol form), 1.15 (q, 2H, *J* = 7.1 Hz, H-17 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 196.4 (C=O), 173.6 (C-13 of enol form), 172.8 (C-15 of keto form), 167.4 (C-15 of enol form), 138.1 (C), 138.0 (C), 137.8 (C), 136.5 (C), 136.2 (C), 134.6 (C), 134.4 (C), 133.6 (C), 132.3 (CH), 132.1 (CH), 130.6 (CH), 130.3 (CH), 129.4 (4xCH), 128.9 (CH), 128.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.9 (3xCH), 126.8 (CH), 126.3 (CH), 125.9 (CH), 125.8 (CH), 93.0 (CH-14 of enol form), 61.5 (CH_2-16 keto form), 60.4 (CH_2-16 enol form), 48.6 (CH_2-14 of keto form), 21.3 (CH_3 of keto & enol form), 14.3 (CH_3-17 enol form), 14.1 (CH_3-17 keto form) ppm. IR (KBr): *v* = 3058, 3022, 2981, 2936, 2870, 1742, 1683, 1626, 1562, 1514, 1476, 1445, 1410, 1196, 1032, 964, 805, 754 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{21}O_3$: 309.1485; found: 309.1488.

(*E*)-Ethyl 3-(2-(4-methoxystyryl)phenyl)-3-oxopropanoate 240c



According to GP7 compound **240c** was obtained as light yellow oil in 95% yield (7.0 mmol, 2.28 g) after purification (keto:enol 2.8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 1H, *J* = 7.9 Hz, H-6), 7.66 (d, 1H, *J* = 6.8 Hz, Ar-*H*), 7.56 (d, 1H, *J* = 16.1 Hz, H-7), 7.52-7.45 (m, 3H, Ar-*H*), 7.39- 7.31 (m, 1H, Ar-*H*), 7.01 (t, 1H, *J* = 16.1 Hz, H-8 of keto & enol form), 6.94-6.91 (m, 2H, Ar-*H*), 5.37 (s, 1H, H-14 of enol form), 4.30 (q, 2H, *J* = 7.1 Hz, H-16 of enol form in 1.0 ratio), 4.21 (q, 2H, *J* = 7.1 Hz, H-16 of keto form), 3.99 (s, 2H, H-14 of keto form), 3.86 (s, 3H, O*CH*$_3$), 1.35 (t, 3H, *J* = 7.1 Hz, H-17 of enol form), 1.25 (q, 2H, *J* = 7.1 Hz, H-17 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.45 (C-13 of keto form), 173.78 (C-13 of enol form), 172.83 (C-15 of keto form), 167.38 (C-15 of enol form), 159.7 (C-12 of keto form), 159 (C-12 of enol form), 138.21 (C), 136.59 (C), 136.09 (C), 133.4 (C), 132.1 (CH), 132.0 (CH), 130.3 (CH), 130.2 (C & CH), 130.0 (C), 128.9 (CH), 128.8 (CH), 128.2 (4xCH-10 of keto-enol form), 128.1 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.2 (CH), 124.7 (CH), 114.2 (4xCH-11 of keto-enol form), 92.97 (CH-14 of enol form), 61.42 (CH_2-16 of keto form), 60.40 (CH_2-16 of enol form), 55.36 (OCH_3), 48.65 (CH_2-14 of keto form), 14.32 (CH_3-17 of enol form), 14.09 (CH_3-17 of keto form) ppm. ^{13}C DEPT 135 NMR (125 MHz, $CDCl_3$): 132.1 (CH), 132.0 (CH), 130.3 (CH), 130.2 (CH), 128.9 (CH), 128.8 (CH), 128.2 (4xCH), 128.1 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.2 (CH), 124.7 (CH), 114.16 (4xCH), 92.98 (CH-14 of enol form), 61.45 (CH_2-16 keto form), 60.42 (CH_2-16 enol form), 55.36 (OCH_3), 48.4 (CH_2-14 of keto form), 14.33 (CH_3-17 of enol form), 14.10 (CH_3-17 of keto form) ppm. IR (KBr): *v* = 3061, 2982, 2936, 2836, 1740, 1683, 1625, 1605, 1594, 1511, 1409, 1250, 1196, 1174, 1032, 964, 820 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{21}O_4$: 325.1434; found: 325.1439.

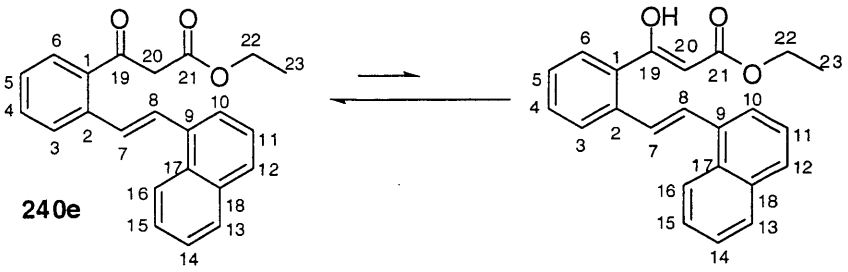
(*E*)-Ethyl 3-(2-(2-naphthalene-2-yl)vinyl)phenyl)-3-oxopropanoate 240d



240d

According to GP7 compound **240d** was obtained as yellow solid in 83% yield (6.15 mmol, 2.12 g) after purification (keto:enol 2.9:1). M.p.: 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79-7.66 (m, 6H, Ar-*H*), 7.64-7.59(m, 1H, Ar-*H*), 7.53 (d, 1H, *J* = 16.2 Hz, H-7), 7.48-7.44 (m, 1H, Ar-*H*), 7.42-7.35 (m, 2H, Ar-*H*), 7.31-7.25 (m, 1H, Ar-*H*), 7.12 (t, 1H, *J* = 15.2 Hz, H-8), 5.30 (s, 1H, H-20 of enol form), 4.20 (q, 2H, *J* = 7.2 Hz, H-22 of enol form), 4.12 (q, 2H, *J* = 7.2 Hz, H-22 of keto form), 3.92 (s, 2H, H-20 of keto form), 1.25 (t, 3H, *J* = 7.1 Hz, H-23 of enol form), 1.15 (q, 2H, *J* = 7.1 Hz, H-23 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 196.32 (C-19 of keto form), 173.63 (C-19 of enol form), 172.84 (C-21 of keto form), 167.40 (C-21 of enol form), 138.05 (C), 136.33 (C), 136.15 (C), 134.88 (C), 134.72 (2xC), 133.71 (C), 133.60 (C), 133.27 (C), 133.17 (C), 132.40 (CH), 132.25 (CH), 130.82 (CH), 130.40 (CH), 129.05 (2xCH), 128.86 (CH), 128.38 (2xCH), 128.13 (CH), 128.09 (CH), 127.75 (2xCH), 127.59 (CH), 127.50 (CH), 127.33 (CH), 127.29 (CH), 127.18 (CH), 126.97 (CH), 126.37 (3xCH), 126.11 (CH), 126.06 (CH), 123.89 (CH), 123.79 (CH), 93.13 (CH-20 of enol form), 61.51 (CH_2-22 of keto form), 60.46 (CH_2-22 of enol form), 48.60 (CH_2-20 of keto form), 14.33 (CH_3-23 of enol form), 14.11 (CH_3-23 of keto form) ppm. IR (KBr): *v* = 3045, 2982, 1736, 1682, 1622, 1592, 1408, 1314, 1268, 1191, 1146, 1036, 961, 812, 752 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{23}H_{21}O_3$: 345.1485; found: 345.1491.

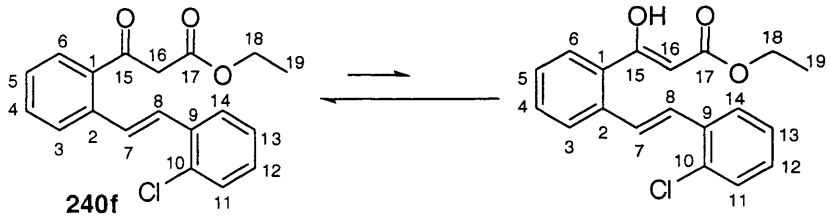
(*E*)-Ethyl 3-(2-(2-naphthalene-1-yl)vinyl)phenyl)-3-oxopropanoate 240e



240e

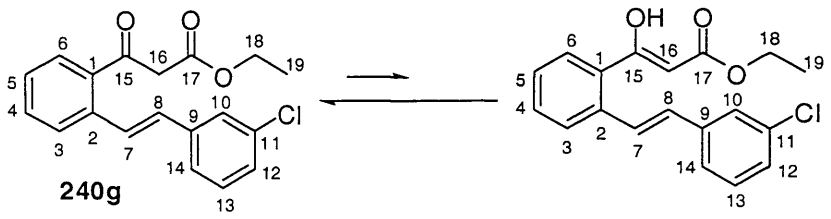
According to GP7 compound **240e** was obtained as light yellow oil in 95% yield (7 mmol, 2.42 g) after purification (keto:enol 2.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 1H, *J* = 8.1 Hz, H-6), 7.80-7.72 (m, 4H, Ar-*H*), 7.68-7.61 (m, 2H, Ar-*H*), 7.51-7.40 (m, 5H, Ar-*H*), 7.34-7.28 (m, 1H, Ar-*H*), 5.30 (s, 1H, H-20 of enol form), 4.18 (q, 2H, *J* = 7.1 Hz, H-22 of enol form), 4.09 (q, 2H, *J* = 7.1 Hz, H-22 of keto form), 3.91 (s, 2H, H-20 of keto form), 1.23 (t, 3H, *J* = 7.1 Hz, H-23 of enol form), 1.12 (q, 2H, *J* = 7.1 Hz, H-23 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 196.16 (C-19 of keto form), 173.6 (C-19 of enol form), 172.8 (C-21 of keto form), 167.37 (C-21 of enol form), 138.37 (2xC-1 keto-enol form), 136.57 (C), 136.26 (C), 134.95 (C), 134.67 (2xC), 133.82 (C), 133.75 (2xC), 132.31 (CH), 131.39 (CH), 130.43 (CH), 130.10 (CH), 129.85 (CH), 129.21 (CH), 129.03 (CH), 128.85 (CH), 128.69 (2xCH), 128.41 (CH), 128.27 (CH), 128.01 (CH), 127.80 (CH), 127.61 (CH), 127.45 (CH), 126.78 (CH), 126.18 (2xCH), 125.88 (CH), 125.83 (CH), 125.78 (CH), 124.30 (CH), 124.08 (CH), 123.80 (CH), 123.69(CH), 93.15 (CH-20 of enol form), 61.49 (CH_2-22 of keto form), 60.45 (CH_2-22 of enol form), 48.58 (CH_2-20 of keto form), 14.31(CH_3-23 of enol form), 14.07 (CH_3-23 of keto form) ppm. IR (KBr): *v* = 3059, 2980, 2936, 1741, 1683, 1625, 1593, 1563, 1509, 1477, 1445, 1409, 1316, 1258, 1191, 1033, 960, 795, 775 cm^{-1}; HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{23}H_{21}O_3$: 345.1485; found: 345.1489.

(*E*)-Ethyl 3-(2-(2-chlorostyryl)phenyl)-3-oxopropanoate 240f



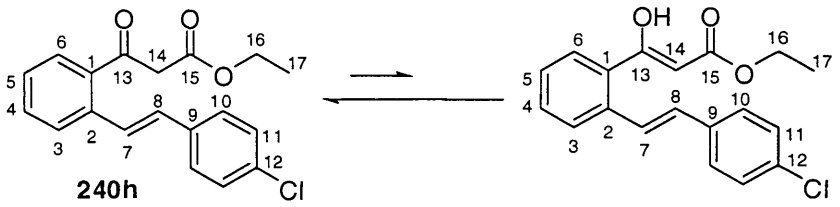
According to GP7 compound **240f** was obtained as colorless oil in 58 % yield (4.3 mmol, 1.41 g) after purification (keto: enol 2.6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.64 (m, 2H, Ar-*H*), 7.61-7.57 (m, 2H, Ar-*H*), 7.47-7.42 (m, 1H, Ar-*H*), 7.38-7.35 (m, 1H, Ar-*H*), 7.33-7.25 (m, 2H, Ar-*H*), 7.19-7.09 (m, 2H, Ar-*H*), 5.25 (s, 1H, H-16 of enol form), 4.18 (q, 2H, *J* = 7.2 Hz, H-18 of enol form), 4.10 (q, 2H, *J* = 7.2 Hz, H-18 of keto form), 3.89 (s, 2H, H-16 of keto fom), 1.23 (t, 3H, *J* = 7.2 Hz, H-19 of enol form), 1.13 (q, 2H, *J* = 7.2 Hz, H-19 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.9 (C-15 of keto form), 173.5 (C-15 of enol form), 172.8 (C-17 of keto form), 167.4 (C-17 of enol form), 137.97 (C), 136.01 (C), 135.97 (C), 135.40 (C), 135.28 (C), 133.83 (C), 133.54 (2xC), 132.46 (CH), 130.48 (CH), 129.83 (CH), 129.79 (CH), 129.74 (CH), 129.35 (CH), 129.10 (CH), 128.91 (CH), 128.81 (2xCH), 128.05 (CH), 127.94 (CH), 127.86 (CH), 127.68 (CH), 127.15 (CH), 127.04 (2xCH), 126.91 (CH), 126.85 (CH), 126.67 (CH), 93.14 (CH-16 of enol form), 61.51 (CH_2-18 of keto form), 60.48 (CH_2-18 of enol form), 48.44 (CH_2-16 of keto form), 14.33 (CH_3-19 of enol form), 14.10 (CH_3-19 of keto form) ppm. ^{13}C DEPT 135 NMR (125 MHz, $CDCl_3$): 132.50 (CH), 130.50 (CH), 129.84 (CH), 129.79 (CH), 129.75 (CH), 129.33 (CH), 129.13 (CH), 128.92 (CH), 128.80 (CH), 128.07 (CH), 127.93 (CH), 127.88 (CH), 127.70 (CH), 127.15 (CH), 127.05 (CH), 126.90 (CH), 126.85 (CH) , 126.65 (CH), 93.2 (CH-16 of enol form), 61.5 (CH_2-18 keto form), 60.5 (CH_2-18 enol form), 48.4 (CH_2-16 of keto form), 14.3 (CH_3-19 enol form), 14.1 (CH_3-19 keto form) ppm. IR (KBr): *v* = 3063, 2982, 2934, 2905, 1742, 1683, 1626, 1562, 1484, 1438, 1412, 1318, 1259, 1194, 1034, 995, 966, 813, 757, 689 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{18}Cl^{35}O_3$: 329.0939; found: 329.0939.

(*E*)-Ethyl 3-(2-(3-chlorostyryl)phenyl)-3-oxopropanoate 240g



According to GP7 compound **240g** was obtained as colorless oil in 80% yield (0.0059 mol, 1.95 g) after purification (keto:enol 2.6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63-7.59 (m, 2H, Ar-*H*), 7.48-7.38 (m, 3H, Ar-*H*), 7.34-7.26 (m, 2H, Ar-*H*), 7.24-7.16 (m, 2H, Ar-*H*), 6.87 (t, 1H, *J* = 16.2 Hz, H-8 of keto-enol form), 5.26 (s, 1H, H-16 of enol form), 4.21 (q, 2H, *J* = 7.1 Hz, H-18 of enol form), 4.13 (q, 2H, *J* = 7.1 Hz, H-18 of keto form), 3.91 (s, 2H, H-16 of keto form), 1.27 (t, 3H, *J* = 7.1 Hz, H-19 of enol form), 1.16 (q, 2H, *J* = 7.1 Hz, H-19 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.0 (C-15 of keto form), 173.4 (C-15 of enol form), 172.8 (C-17 of keto form), 167.4 (C-17 of enol form), 139.3 (C), 139.0 (C), 137.6 (C), 136.0 (C), 135.8 (C), 134.6 (2xC), 133.8 (C), 132.4 (CH), 130.6 (CH), 130.5 (CH), 129.9 (2xCH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (2xCH), 127.74 (2xCH), 127.68 (CH), 126.8 (CH), 126.7 (CH), 126.5 (CH), 125.1 (CH), 125.0 (CH), 93.1 (CH-16 of enol form), 61.5 (CH_2-18 of enol form), 60.5 (CH_2-18 keto form), 48.4 (CH_2-16 of enol form), 14.3 (CH_3-19 enol form), 14.1 (CH_3-19 keto form) ppm. ^{13}C DEPT 135 NMR (125 MHz, $CDCl_3$): 132.4 (CH), 130.6 (CH), 130.5 (CH), 129.9 (2xCH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (2xCH), 127.74 (2xCH), 127.69 (CH), 126.8 (CH), 126.6 (CH), 128.5 (CH), 125.1 (CH) , 125.0 (CH), 93.2 (CH-16 of enol form), 61.5 (CH_2-18 enol form), 60.5 (CH_2-18 keto form), 48.4 (CH_2), 14.3 (CH_3-19 enol form), 14.1 (CH_3-19 keto form) ppm. IR (KBr): *v* = 3063, 2981, 2937, 1742, 1683, 1626, 1592, 1566, 1481, 1410, 1367, 1317, 1262, 1196, 1095, 1030, 961, 682 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{18}Cl^{35}O_3$: 329.0939; found: 329.0945.

(*E*)-Ethyl 3-(2-(4-chlorostyrylphenyl)-3-oxopropanoate 240h



According to GP7 compound **240h** was obtained as yellow oil in 94 % yield (6.94 mmol, 2.28 g) after purification (keto:enol 2.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63-7.56 (m, 2H, H-6, H-7 of keto-enol form), 7.47-7.43 (m, 1H, Ar-*H*), 7.40-7.34 (m, 3H, Ar-*H*), 7.30-7.23 (m, 3H, Ar-*H*), 6.88 (t, 1H, *J* = 16.1 Hz, H-8 of keto-enol form), 5.25 (s, 1H, H-14 of enol form), 4.20 (q, 2H, *J* = 7.1 Hz, H-16 of enol form), 4.12 (q, 2H, *J* = 7.1 Hz, H-16 of keto form), 3.90 (s, 2H, H-14 of keto form), 1.25 (t, 3H, *J* = 7.1 Hz, H-17 of enol form), 1.15 (q, 2H, *J* = 7.1 Hz, H-17 of keto form) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 196.1 (C-13 of keto form), 173.54 (C-13 of enol form), 172.78 (C-15 of keto form), 167.35 (C-15 of enol form), 137.81 (C), 136.00 (C), 135.94 (C), 135.86 (C), 135.73 (C), 133.73 (C), 133.62 (C), 133.46 (C), 132.32 (CH), 130.79 (CH), 130.40 (CH), 129.34 (CH), 129.09 (CH), 128.86 (5xCH), 128.1 (3xCH), 127.97 (CH), 127.77 (CH), 127.67 (CH), 127.63 (CH), 127.50 (CH), 127.46 (CH), 126.39 (CH), 93.07 (CH-14 of enol form), 61.51 (CH_2-16 enol form), 60.49 (CH_2-16 keto form), 48.5 (CH_2-14 of keto form), 14.3 (CH_3-17 enol form), 14.1 (CH_3-17 keto form) ppm. IR (KBr): *v* = 3063, 2982, 2937, 1742, 1683, 1626, 1592, 1491, 1405, 1316, 1263, 1196, 1089, 1030, 1011, 963, 811, 756 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{18}Cl^{35}O_3$: 329.0939; found: 329.0944.

Ethyl 3-oxo-3-(2-(prop-1-enyl)phenyl)propanoate 240i

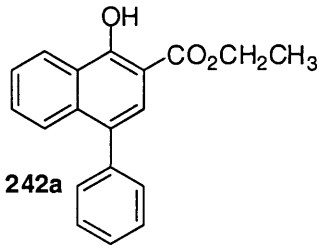
According to GP7 compound **240i** (E/Z mixture 1:5.5) was obtained as light yellow oil in 93 % yield (6.9 mmol, 1.60 g) after purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (dd, 1H, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.62 (dd, 1H, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.57 (dd,

1H, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.51-7.37 (m, 2H, Ar-H), 7.35-7.30 (m, 2H, Ar-H), 6.88 (dd, 1H, *J* = 15.6, 1.6 Hz, H-7 of keto-enol form of *E*-isomer), 6.73 (dd, 1H, *J* = 11.5, 1.6 Hz, H-7 of keto form of *Z*-isomer), 6.61 (dd, 1H, *J* = 11.5, 1.6 Hz, H-7 of enol form of *Z*-isomer), 6.21-6.12 (m, 1H, H-8 of keto-enol form of *E*-isomer), 5.92-5.82 (m, 1H, H-8 of keto-enol form of *Z*-isomer), 5.41 (s, 1H, *Z*-isomer of H-11 of enol form), 5.30 (s, 1H, *E*-isomer of H-11 of enol form), 4.30-4.24 (m, 2H, H-13 enol form of *E*-isomer), 4.21-4.16 (m, 2H, H-13 keto form of *Z*-isomer), 3.93 (s, 2H, H-11 keto form of *Z*-isomer), 3.92 (s, 2H, H-11 keto form of *E* isomer), 1.92-1.89 (m, 3H, H-9 of keto-enol form of *E*-isomer), 1.80-1.79 (dd, 3H, *J* = 7.1, 1.8 Hz, H-9 of enol form of *Z*-isomer), 1.73-1.71 (dd, 3H, *J* = 7.1, 1.8 Hz, H-9 of keto form of *Z*-isomer), 1.35-1.31 (m, 3H, H-14 keto-enol form of *E* isomer), 1.25-1.22 (m, 3H, H-14 keto-enol form of *Z*-isomer) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.62 (C-10 keto form of *E*-isomer), 196.14 (C-10 keto form of *Z*-isomer), 173.92 (C-10 enol form of *E*-isomer), 173.00 (C-10 enol form of *Z*-isomer), 172.86 (C-13 keto form of *Z*-isomer), 172.80 (C-13 keto form of *E*-isomer), 167.43 (C-12 enol of Z-isomer), 167.37 (C-12 enol of *E*-isomer), 138.23, 137.17, 137.03, 136.75, 135.91, 135.87, 133.68, 132.77, 131.88 (CH), 131.60 (CH), 130.93 (CH) , 130.39 (CH), 130.14 (CH), 129.75 (CH), 129.66 (CH), 129.28 (CH), 129.14(CH), 129.08 (CH), 129.04(CH), 128.92 (2xCH), 128.49 (CH), 128.33 (CH), 128.01 (CH), 127.92 (CH), 127.69 (CH), 127.17 (CH), 126.86 (CH), 126.79 (CH), 126.67 (CH), 126.59 (CH), 126.41 (CH), 92.67 (CH-11 enol form of *E*-isomer), 92.53 (CH-11 enol form of *Z*-isomer), 61.34 (CH_2-13 keto form of *E*-isomer), 61.29 (CH_2-13 keto form of *Z*-isomer), 60.31 (CH_2-13 enol form of *E* & *Z*-isomer), 48.63 (CH_2-11 keto form of *E*-isomer), 48.55 (CH_2-11 keto form of *Z*-isomer), 18.76 (CH_3-9 keto-enol form of *Z*-isomer), 18.71 (CH_3-9 keto-enol form of *E*-isomer), 14.40 (CH_3-14 enol form of *E*-isomer), 14.36 (CH_3-14 keto form of *E*-isomer), 14.30 (CH_3-14 enol form of *Z*-isomer), 14.06 (CH_3-14 keto form of *Z*-isomer) ppm. IR (KBr): *v* = 3062, 3022, 2980, 2938, 2912, 1742, 1689, 1624, 1595, 1564, 1478, 1444, 1410, 1367, 1317, 1260, 1193, 1030, 770 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{17}O_3$: 233.1172; found: 233.1169.

5.11 General Procedure (GP8) for the Synthesis of Biaryls 242

A mixture of substrate **240** (1.0 mmol) and $FeCl_4$ (1.1 mmol, 178.2 mg) or $ZrCl_4$ (1.1 mmol, 256.3 mg) or $BF_3 \bullet OMe_2$ (1.1 mmol, 0.10 mL) in dry dichloromethane under argon was stirred at –78 °C for three minutes. Phenylselenenyl chloride (2.0 mmol, 383 mg) was added to the reaction mixture and stirred for the time indicated in the manuscript (Table 2) with the temperature at –78 °C throughout the reaction. The crude product was poured into cold water, extracted with diethyl ether (3 x 15 mL), washed with water (15 mL) and dried over anhydrous magnesium sulfate. The filtrate was evaporated under reduced pressure and residue was chromatographed on silica gel (EtOAc:hexane, 1:12) to give products **242**.

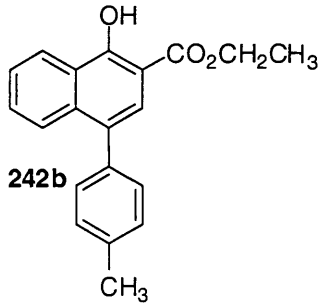
2-Ethoxycarbonyl-4-phenyl-l-naphthol 242a



242a

According to GP8 compound **242a** was obtained as white solid in 85% yield (0.85 mmol, 248 mg). M.p.: 115–116 °C (literature[178] m.p.: 115–117 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.01 (s, 1H, OH), 8.43-8.41 (m, 1H, Ar-*H*), 7.74-7.72 (m, 1H, Ar-*H*), 7.66 (s, 1H, Ar-*H*), 7.47-7.45 (m, 2H, Ar-*H*), 7.41-7.34 (m, 5H, Ar-*H*), 4.36 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 1.34 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 90, 135): δ = 171.1 (CO), 160.4 (C), 140.2 (C), 135.5 (C), 131.2 (C), 130.2 (2xCH), 129.4 (CH), 128.4 (2xCH), 127.2 (CH), 125.9 (CH), 125.7 (CH), 125.0 (C), 124.9 (CH), 124.2 (CH), 105.4 (C) , 61.5 (CH_2), 14.3 (CH_3) ppm. IR (KBr): *v* = 3074-2905, 2982, 1661, 1629, 1598, 1580, 1507, 1477, 1450, 1266, 1233, 1152, 1092, 1020 cm^{-1}. LRMS (EI): *m/z* $[M]^+$ 292 (44), 246 (100), 189 (59); HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{17}O_3$: 293.1172; found: 293.1171. The spectroscopic data are in agreement with literature.[178]

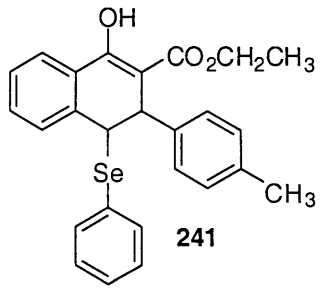
Ethyl 1-hydroxy-4-*p*-tolyl-2-naphthoate 242b



242b

According to GP8 compound **242b** was obtained as white solid in 80% yield (0.80 mmol, 245 mg) after purification. M.p.: 109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.99 (s, 1H, OH), 8.43-8.41 (m, 1H, Ar-*H*), 7.76-7.74 (m, 1H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 7.48-7.44 (m, 2H, Ar-*H*), 7.28 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 7.22 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 4.37 (q, *J* = 7.2 Hz, 2H, $COOCH_2CH_3$), 2.38 (s,3H, CH_3), 1.34 (t, 3H, *J* = 7.2 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.1 (CO), 160.3 (C), 137.3 (C), 136.9 (C), 135.6 (C), 131.1 (C), 130.1 (2xCH), 129.3 (CH), 129.1 (2xCH), 126.0 (CH), 125.6 (CH), 125.0 (C), 124.9 (CH), 124.1 (CH), 105.4 (C), 61.5 (CH_2), 21.3 (CH_3), 14.3 ($COOCH_2CH_3$) ppm. IR (KBr): *v* = 3309-2865, 3001, 2978, 1659, 1630, 1601, 1580, 1516, 1461, 1449, 1402, 1343, 1296, 1263, 1234, 1154, 1089, 1012, 826, 802, 775 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}O_3$: 307.1329; found: 307.1333.

Isolation of ethyl 1-hydroxy-4-(phenylselanyl)-3-*p*-tolyl-3,4-dihydronaphthalene-2-carboxylate intermediate 241

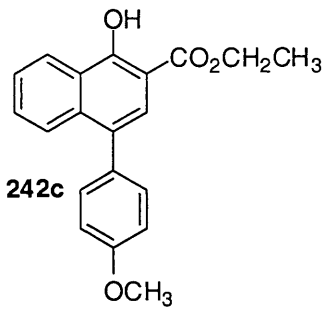


241

Reaction is performed according to GP8 but reaction is worked up after 15 minutes and compound **241** was isolated by preparative TLC as viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.62 (s, 1H, OH), 7.82 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.45 (d, 2H, *J* = 6.8 Hz, Ar-*H*), 7.29 (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.26-7.20 (m, 3H, Ar-*H*), 7.14 (dt, 1H, *J* = 7.5,

1.3 Hz, Ar-*H*), 6.83 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 6.80 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 6.69 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 4.57 (bs, 1H, CH), 4.19 (bs, 1H, CH), 4.17-3.97 (m, 2H, *J* = 7.2 Hz, COO*CH*$_2$CH$_3$), 2.14 (s,3H, CH$_3$), 1.12 (t, 3H, *J* = 7.1 Hz, COOCH$_2$*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 172.5 (CO), 164.7 (C), 139.1 (C), 137.1 (C), 136.6 (2xCH), 136.4 (C), 130.8 (CH), 129.3 (C), 129.1 (2xCH), 129.0 (2xCH), 128.9 (C) 128.7 (CH), 128.5 (CH), 127.7 (CH), 127.0 (2xCH), 124.8 (CH) , 98.2 (C_{Ar}), 60.7 (CH_2), 48.5 (CH), 43.3 (CH), 21.0 (CH_3), 14.1 (COOCH$_2$*CH*$_3$) ppm. ^{77}Se NMR (57.3 Hz, $CDCl_3$): δ = 496.40 ppm. HRMS (AP$^+$): *m/z* $[M]^+$ calcd. for $C_{26}H_{25}O_3Se^{80}$: 465.0969; found: 465.0978.

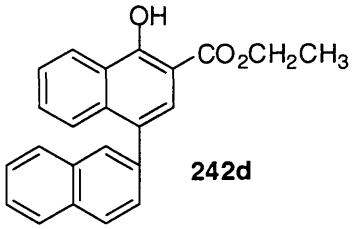
Ethyl 1-hydroxy-4-(4-methoxyphenyl)-2-naphthoate 242c



242c

According to GP8 compound **242c** was obtained as colorless solid in 96 % yield (0.96 mmol, 309 mg) after purification. M.p.: 145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.11 (s, 1H, OH), 8.55-8.53 (m, 1H, Ar-*H*), 7.87-7.85 (m, 1H, Ar-*H*), 7.76 (s, 1H, Ar-*H*), 7.59-7.57 (m, 2H, Ar-*H*), 7.42 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.06 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 4.49 (q, *J* = 7.2 Hz, 2H, COO*CH*$_2$CH$_3$), 3.93 (s, 3H, OCH_3), 1.47 (t, 3H, *J* = 7.2 Hz, COOCH$_2$*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.1 (CO), 160.2 (C), 159.0 (C), 135.8 (C), 132.6(C), 131.2 (2xCH), 130.8 (C), 129.3 (CH), 126.0 (CH), 125.6 (CH), 125.0 (C), 124.8 (CH), 124.1 (CH), 113.8 (2xCH), 105.4 (C), 61.5 (CH_2), 55.4 (OCH_3), 14.3 (CH_3) ppm. IR (KBr): *v* = 3071-2833, 3001, 2976, 1792, 1666, 1627, 1577, 1515, 1463, 1386, 1290, 1233, 1089, 1035, 899, 838, 802, 776 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}O_4$: 323.1278; found: 323.1282.

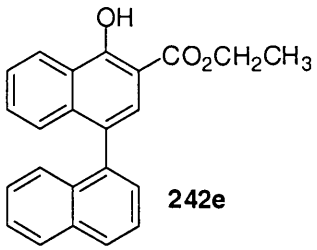
Ethyl 4-hydroxy-1,2′-binaphthyl-3-carboxylate 242d



242d

According to GP8 compound **242d** was obtained as white solid in 83% yield (0.83 mmol, 283 mg) after purification. M.p.: 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.1 (s, 1H, OH), 8.57 (t, 1H, *J* = 6.4, 5.2 Hz, Ar-*H*), 7.99-7.88 (m, 5H, Ar-*H*), 7.87 (s, 1H, Ar-*H*), 7.63 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 7.60-7.57 (m, 4H, Ar-*H*), 4.50 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 1.46 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.12 (CO), 160.53 (C), 137.78 (C), 135.64 (C), 133.52 (C), 132.58 (C), 131.08 (C), 129.51 (CH), 128.79 (CH), 128.59 (CH), 128.01 (CH), 127.78 (CH), 127.75 (CH), 126.37 (CH), 126.07 (CH), 125.98 (CH), 125.75 (CH), 125.26 (CH), 125.07 (C), 124.21 (CH), 105.48 (C), 61.56 (CH_2), 14.31 (CH_3) ppm. IR (KBr): *ν* = 3058, 2983, 1660, 1627, 1581, 1507, 1373, 1260, 1238, 1153, 1092, 769, 747 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{23}H_{19}O_3$: 343.1329; found: 343.1333.

Ethyl 4-hydroxy-1,1'-binaphthyl-3-carboxylate 242e

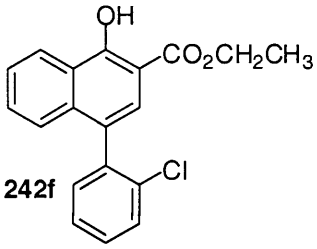


242e

According to GP8 compound **242e** was obtained as white solid in 81% yield (0.81 mmol, 278 mg) after purification. M.p.: 167 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.21 (s, 1H, OH), 8.57 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 7.99-7.97 (m, 2H, Ar-*H*), 7.85 (s, 1H, Ar-*H*), 7.62 (t, 1H, *J* = 7.9, 7.2 Hz, Ar-*H*), 7.60-7.50 (m, 3H, Ar-*H*), 7.46-7.44 (m, 2H, Ar-*H*), 7.35-7.31 (m, 2H, Ar-*H*), 4.46 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 1.41 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.16 (CO), 160.71(C), 137.83 (C), 136.68 (C), 133.60(C), 133.13 (C), 129.44 (CH), 129.15 (C), 128.25 (2xCH), 128.04 (CH), 126.49 (2xCH), 126.09 (CH), 125.88 (CH),

125.81 (CH), 125.71 (CH), 125.50 (CH), 124.80 (C), 124.03 (CH), 105.49 (C), 61.55 (CH_2), 14.27 (CH_3) ppm. IR (KBr): ν = 1664, 1581, 1377, 1235, cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{23}H_{19}O_3$: 343.1329; found: 343.1334.

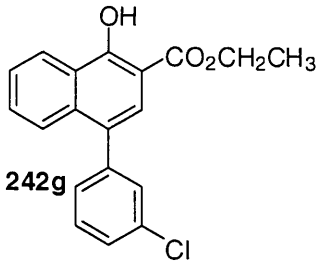
Ethyl 4-(2-chlorophenyl)-1-hydroxy-2-naphthoate 242f



242f

According to GP8 compound **242f** was obtained as white solid in 81% yield (0.81 mmol, 265 mg) after purification. M.p.: 111-112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.07 (s, 1H, OH), 8.43-8.41 (dd, 1H, *J* = 6.2, 2.7 Hz, Ar-*H*), 7.62 (s, 1H, Ar-*H*), 7.48-7.44 (m, 3H, Ar-*H*), 7.32-7.28 (m, 4H, Ar-*H*), 4.37 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 1.35 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.01, 160.92 (C), 138.77 (C), 135.47 (C), 134.62 (C), 132.50 (CH), 129.59 (CH), 129.55 (CH), 129.05 (CH), 128.33 (C), 126.76 (CH), 125.81 (CH), 125.75 (CH), 125.28 (CH), 124.80 (C), 124.16 (CH), 105.33 (C), 61.55 (CH_2), 14.27 (CH_3) ppm. IR (KBr): ν = 3065, 2980, 1662, 1630, 1582, 1508, 1451, 1342, 1281, 1250, 1236, 1154, 1094, 1021, 803, 768, 754 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{16}Cl^{35}O_3$: 327.0782; found: 327.0787.

Ethyl 4-(3-chlorophenyl)-1-hydroxy-2-naphthoate 242g

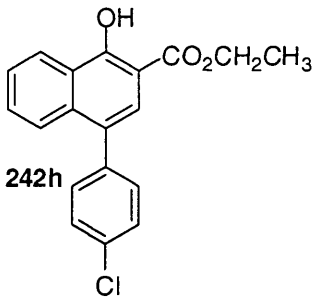


242g

According to GP8 compound **242g** was obtained as white solid in 68% yield (0.68 mmol, 222 mg) after purification. M.p.: 141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.16 (s, 1H, OH), 8.54-8.52 (dd, 1H, *J* = 7.6, 2.5 Hz, Ar-*H*), 7.80-7.78 (dd, 1H, *J* = 7.6, 2.2 Hz, Ar-*H*), 7.74 (s, 1H, Ar), 7.63-7.57 (m, 2H, Ar-*H*), 7.49 (s, 1H, Ar-*H*), 7.44-

7.43(m, 2H, Ar-*H*), 7.38-7.36 (m, 1H, Ar-*H*), 4.49 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 1.47 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.26 (CO), 161.02 (C), 142.32 (C), 135.46 (C), 134.55 (C), 130.50 (CH), 129.98 (CH), 129.94 (C), 129.86 (CH), 128.75 (CH), 127.65 (CH), 126.15 (CH), 125.81 (CH), 125.37 (CH), 125.32 (C), 124.54 (CH), 105.65 (C), 61.9 (CH_2), 14.6 (CH_3) ppm. IR (KBr): *v* = 3068, 2980, 1655, 1624, 1595, 1474, 1374, 1341, 1256, 1238, 1156, 1096, 799, 767, 710 cm^{-1}. HRMS (ES): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{16}Cl^{35}O_3$: 327.0782; found: 327.0786.

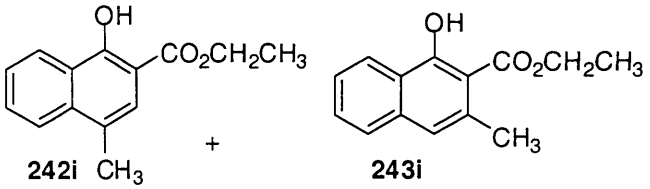
Ethyl 4-(4-chlorophenyl)-1-hydroxy-2-naphthoate 242h



According to GP8 compound **242h** was obtained as white solid in 69% yield (0.69 mmol, 225 mg) after purification. M.p.: 114 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.02 (s, 1H, OH), 8.42-8.40 (dd, 1H, *J* = 6.3, 2.7 Hz, Ar-*H*), 7.67-7.65 (m, 1H, *J* = 7.1, 3.3 Hz Ar-*H*), 7.61 (s, 1H, Ar-*H*), 7.48-7.46 (m, 2H, Ar-*H*), 7.37 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.30 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 4.37 (q, *J* = 7.2 Hz, 2H, $COOCH_2CH_3$), 1.35 (t, 3H, *J* = 7.2 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ & DEPT 135): δ = 171.0 (CO), 160.6 (C), 138.6 (C), 135.3 (C), 133.3 (C), 131.5 (2xCH), 129.8 (C), 129.6 (CH), 128.6 (2xCH), 125.8 (CH), 125.6 (CH), 125.1 (C), 125.0 (CH) , 124.3 (CH), 105.4 (C), 61.6 (CH_2), 14.3 (CH_3) ppm. IR (KBr): *v* = 3072-2937, 2983, 1663, 1628, 1600, 1580, 1509, 1491, 1472, 1447, 1402, 1373, 1340, 1267, 1240, 1154, 1090, 1024, 1014, 925, 896 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{19}H_{15}Cl^{35}O_3$: 326.0710; found: 326.0708.

Ethyl 1-hydroxy-4-methyl-2-naphthoate 242i

Ethyl 1-hydroxy-3-methyl-2-naphthoate 243i



242i : **243i**

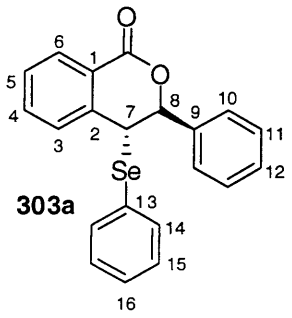
1 : 3.5

The title compounds **242i** and **243i** was obtained according to GP8 as white solid in 50% combined yield (0.5 mmol, 115 mg). The compounds could not be separated. M.p.: 54 °C (mixture). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.76 (s, 1H, OH), 12.40 (s, 1H, OH), 8.34 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 8.28 (d, 1H, 8.1 Hz, Ar-*H*), 8.15 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 7.61 (t, 1H, *J* = 8.3 Hz, Ar-*H*), 7.55 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.48 (dt, 1H, *J* = 8.1, 1.1 Hz, Ar-*H*), 7.36 (t, 1H, *J* = 8.1 Hz, Ar-*H*), 7.23 (s, 1H, Ar-*H*), 7.22-7.21 (m, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 4.39 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 3.93 (s, 3H, OCH_3), 2.69 (s, 3H, CH_3 in 1.0 ratio), 2.57 (s, 3H, CH_3 in 3.5 ratio), 1.38 (t, 3H, *J* = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 171.9, 162.6, 160.5, 136.1, 135.1, 133.7, 133.6, 133.4, 133.3, 133.2, 130.6, 129.6, 126.4, 125.8, 124.9, 124.5, 124.3, 124.0, 123.7, 120.7, 106.4, 62.1, 61.6, 24.7, 20.5, 14.3, 14.2 ppm. IR (KBr): ν = 3061, 2977, 1643, 1592, 1406, 1369, 1325, 1264, 1202, 1158, 1082, 962, 825 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ 230 (10), 185 (9), 184 (50), 128 (21), 86 (77), 83 (100). HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{14}H_{14}O_3$: 230.0943; found: 230.0943.

5.12 General Procedure (GP9) for the Synthesis of Isocoumarin Derivatives 303 and 304

Stilbene carboxylic acid **239** (0.22 mmol) was added to a solution of diphenyl diselenide (0.022 mmol, 6.9 mg, 10 mol%) in acetonitrile (5 mL) followed by [bis(trifluoroacetoxy)iodo]benzene (112 mg, 0.26 mmol) and the mixture was stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was evaporated under reduced pressure and the residue purified immediately by flash chromatography eluting with ethyl acetate:hexane (1:4) to yield the cyclisation products (first elution with hexane gave diphenyl diselenide, second elution with ethyl aetate/hexane gave cyclised product **304**, and the seleno-substituted products **303** could be isolated on preparative TLC if the reaction was stopped after 5-20 minutes).

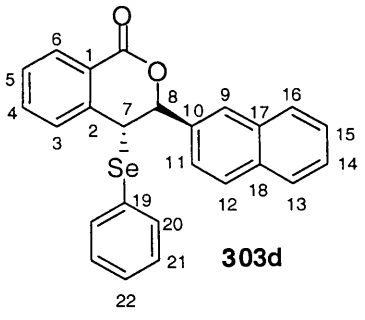
3,4-Dihydro-3-phenyl-4-(phenylseleno)isocoumarin 303a



303a

According to GP9 compound **303a** was obtained as colourless crystals in 20% yield (0.044 mmol, 16.6 mg). M.p.: 123-125 °C (lit.[161-162] m.p.: 124-125 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, 1H, *J* = 7.8 Hz, H-6), 7.46-7.44 (m, 2H, Ar-*H*), 7.37 (dt, 1H, *J* = 7.6, 1.4 Hz, Ar-*H*), 7.30-7.25 (m, 2H, Ar-*H*), 7.20 (t, 2H, *J* = 7.6 Hz, Ar-*H*), 7.14-7.11 (m, 4H, Ar-*H*), 7.02-7.00 (m, 2H, Ar-*H*), 5.76 (d, 1H, *J* = 2.3 Hz, H-8), 4.78 (d, 1H, *J* = 2.3 Hz, H-7) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 163.5 (C=O), 138.3 (C-1), 138.0 (C-9), 136.6 (2xCH), 133.9 (CH), 130.1 (CH), 129.4 (2xCH), 129.1 (CH), 128.6 (2xCH), 128.4 (CH), 128.2 (2xCH), 127.7 (C-2), 125.9 (2xCH), 124.9 (C-13), 82.3 (CH-4), 43.8 (CH-3) ppm. IR (KBr): *v* = 3058, 2927, 1732, 1598, 1474, 1437, 1234, 1065, 767, 737, 689 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{17}O_2Se^{80}$: 381.0394; found: 381.0402. The spectroscopic data are in agreement with literature.[161-162]

3,4-Dihydro-3-(2′-naphthyl)-4-(phenylseleno)isocoumarin 303d

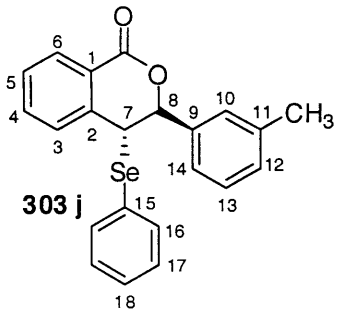


303d

According to GP9 compound **303d** was obtained as white solid in 4% yield (9.3 μmol, 4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (dd, 1H, *J* = 7.8 Hz, *J* = 1.2 Hz, H-6), 7.67-7.65 (m, 1H, Ar-*H*), 7.63 (br d, 2H, *J* = 8.9 Hz, Ar-*H*), 7.48-7.46 (m, 3H, Ar-*H*), 7.37-7.35 (m, 3H, Ar-*H*), 7.31-7.24 (m, 2H, Ar-*H*), 7.20 (t, 2H, *J* = 7.6 Hz, Ar-*H*), 7.13-7.10 (m, 2H, Ar-*H*), 5.92 (d, 1H, *J* = 2.3 Hz, H-8), 4.90 (d, 1H, *J* = 2.3 Hz, H-7)

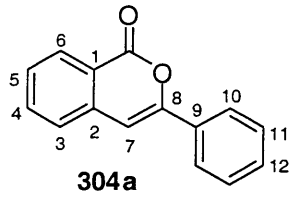
ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C=O), 138.0 (C-1), 136.6 (2xCH), 135.5 (C-10), 133.9 (CH), 132.88 (C), 132.85 (C), 130.1 (CH), 129.4 (2xCH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (C), 127.5 (CH), 126.5 (2xCH), 125.3 (CH), 124.9 (C), 123.3 (CH), 82.4 (CH-8), 43.8 (CH-7) ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{19}O_2Se^{80}$: 431.0545; found: 431.0546.

3,4-Dihydro-3-(3′-methylphenyl-4-(phenylseleno)isocoumarin 303j



According to GP9 compound **303j** was obtained as orange-yellow solid. M.p.: 192–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 1H, *J* = 6.8 Hz, H-6), 7.45-7.43 (m, 2H, Ar-*H*), 7.38 (dt, 1H, *J* = 7.6, 1.4 Hz, Ar-*H*), 7.31-7.25 (m, 2H, Ar-*H*), 7.21 (t, 2H, *J* = 7.6 Hz, Ar-*H*), 7.13 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.02 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 6.93 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 6.83 (s, 1H, H-10), 6.79 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 5.73 (d, 1H, *J* = 2.4 Hz, H-8), 4.79 (d, 1H, *J* = 2.4 Hz, H-7), 2.16 (s, 3H, Ar-*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.6 (C=O), 138.4 (C-1), 138.2 (C-9), 138.1 (C-2), 136.6 (2xCH), 133.9 (C-15 & CH), 130.1 (CH), 129.3 (2xCH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.6 (CH), 124.9 (C-11), 122.9 (CH), 82.3 (CH-8), 43.8 (CH-7), 21.4 (CH_3) pm. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{22}H_{18}O_2Se^{80}$: 392.0480; found: 392.0493.

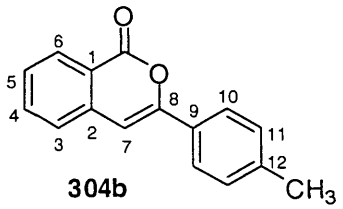
3-(Phenyl)isocoumarin 304a



304a

According to GP9 compound **304a** was obtained as colourless soild in 92% yield (0.20 mmol, 45.1 mg). M.p.: 90–92 °C (literature[179] m.p.: 90–91 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, 1H, *J* = 8.2 Hz, H-6), 7.84-7.81 (m, 2H, Ar-*H*), 7.66 (dt, 1H, *J* = 7.6, 1.3 Hz, Ar-*H*), 7.46-7.36 (m, 5H, Ar-*H*), 6.90 (s, 1H, H-7) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 162.3 (C=O), 153.7 (C-8), 137.6 (C-1), 134.9 (CH), 132.0 (C-2), 130.0 (CH), 129.7 (CH), 128.9 (2xCH), 128.2 (CH), 126.0 (CH), 125.3 (2xCH), 120.6 (C-9), 101.8 (CH-7) ppm. IR (KBr): *v* = 3062, 3030, 2962, 2922, 1732, 1635, 1483, 1234, 1066, 766 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{11}O_2$: 223.0754; found: 223.0753. The spectroscopic data are in agreement with literature.[179]

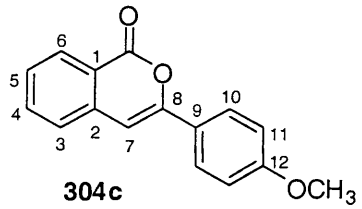
3-(4'-Methylphenyl)isocoumarin 304b



304b

According to GP9 compound **304b** was obtained as colourless crystals in 95% yield (0.21 mmol, 49 mg). M.p.: 114-115 °C (literature[180] m.p.: 108-110 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, 1H, *J* = 8.2 Hz, H-6), 7.70 (d, 2H, *J* = 8.1 Hz, H-10), 7.63 (dt, 1H, *J* = 8.2 Hz, *J* = 1.3 Hz, Ar-*H*), 7.41-7.38 (m, 2H, Ar-*H*), 7.19 (d, 2H, *J* = 8.1 Hz, H-11), 6.83 (s, 1H, H-7), 2.33 (s, 3H, *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.4 (C=O), 153.9 (C-8), 140.3 (C-1), 137.8 (C-2), 134.8 (CH), 129.7 (CH), 129.6 (2xCH), 129.2 (C-9), 127.9 (CH), 125.9 (CH), 125.2 (2xCH), 120.5 (C-12), 101.1 (CH-7), 21.4 (CH_3) ppm. IR (KBr): *v* = 3032, 2921, 1731, 1630, 1604, 1559, 1512, 1477, 1458, 1343, 1308, 1235, 1107, 1067, 1008, 847, 817, 751, 711, 688 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{13}O_2$: 237.0910; found: 237.0911. The spectroscopic data are in agreement with literature.[180]

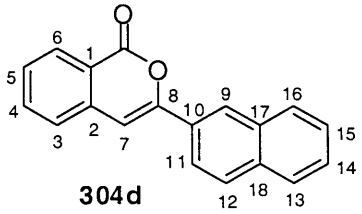
3-(4'-Methoxyphenyl)isocoumarin 304c



304c

According to GP9 compound **304c** was obtained as colourless crystals in 96% yield (0.21 mmol, 53 mg). M.p.: 112-113 °C (literature[180] m.p.: 111-113 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, 1H, *J* = 8.3 Hz, H-6), 7.76 (d, 2H, *J* = 8.9 Hz, H-10), 7.63 (dt, 1H, *J* = 7.6 Hz, *J* = 1.3 Hz, Ar-*H*), 7.40-7.38 (m, 2H, Ar-*H*), 6.90 (d, 2H, *J* = 8.9 Hz, H-11), 6.76 (s, 1H, H-7), 3.80 (s, 3H, *OCH$_3$*) ppm. ^{13}C & DEPT 90, 135 NMR (125 MHz, $CDCl_3$): δ = 162.5 (C=O), 161.1 (C-12), 153.8 (C-8), 137.9 (C-1), 134.8 (CH), 129.7 (CH), 127.7 (CH), 126.9 (2xCH), 125.7 (CH), 124.6 (C-2), 120.2 (C-9), 114.3 (2xCH), 100.3 (CH-7), 55.4 (OCH_3) ppm. IR (KBr): *v* = 3036, 2999, 2958, 2844, 1738, 1632, 1562, 1514, 1480, 1457, 1344, 1309, 1290, 1264, 1237, 1200, 1177, 1114, 1064, 1022, 925, 880, 837, 820, 790, 752, 687, 668 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{13}O_3$: 253.0859; found: 253.0858. The spectroscopic data are in agreement with literature.[180]

3-(Naphthalen-2-yl)isocoumarin 304d

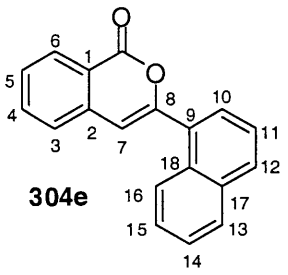


304d

According to GP9 a mixture of stilbene carboxylic acid **239d** (60 mg, 0.22 mmol) and PhSeSePh (6.9 mg, 0.022 mmol) was reacted with [bis(trifluoroacetoxy)iodo]benzene (113 mg, 0.26 mmol). Product **304d** was obtained as colourless crystals in 94% yield (0.21 mmol, 57 mg). M.p.: 157 °C (literature[181] m.p.: 161-163 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (s, 1H, H-9), 8.28 (d, 1H, *J* = 7.9 Hz, H-6), 7.89-7.78 (m, 4H, Ar-*H*), 7.68 (dt, 1H, *J* = 7.9 Hz, 1.3 Hz, Ar-*H*), 7.48-7.45 (m, 4H, Ar-*H*), 7.03 (s, 1H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.4 (C=O), 153.6 (C-8), 137.6 (C-1), 134.9 (CH), 133.9 (C), 133.2 (C), 129.8 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH),

128.2 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 126.1 (CH), 125.4 (CH), 122.0 (CH), 120.7 (C), 102.3 (CH-7) ppm. IR (KBr): ν = 3108, 3058, 1717, 1635, 1608, 1562, 1367, 1331, 1221, 1191, 1074, 851, 818, 746, 682 cm^{-1}. HRMS (AP): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{13}O_2$: 273.0916; found: 273.0909 The spectroscopic data are in agreement with literature.[181]

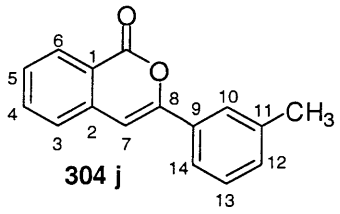
3-(1-Naphthyl)isocoumarin 304e



304e

According to GP9 compound **304e** was obtained as colourless crystals in 99% yield (0.22 mmol, 59 mg). M.p.: 147 °C (literature[180] m.p.: 120-122 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, 1H, *J* = 7.9 Hz, H-6), 8.16-8.14 (m, 1H, Ar-*H*), 7.85 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.83-7.81 (m, 1H, Ar-*H*), 7.68-7.65 (m, 2H, Ar-*H*), 7.48-7.41 (m, 5H, Ar-*H*), 6.71 (s, 1H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6 (C=O), 154.8 (C-8), 137.5 (C-1), 134.9 (CH), 133.8 (C), 130.84 (C), 130.77 (C), 130.6 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 127.7 (CH), 127.1 (CH), 126.3 (CH), 125.9 (CH), 125.2 (CH), 125.1 (CH), 120.6 (CH), 107.1 (CH-7) ppm. IR (KBr): ν = 3091, 3042, 1717, 1640, 1606, 1566, 1509, 1487, 1453, 1397, 1352, 1310, 1241, 1200, 1179, 1154, 1117, 1066, 1053, 1026, 993, 956, 922, 882, 847, 790, 770, 748, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{13}O_2$: 273.0910; found: 273.0907. The spectroscopic data are in agreement with literature.[180]

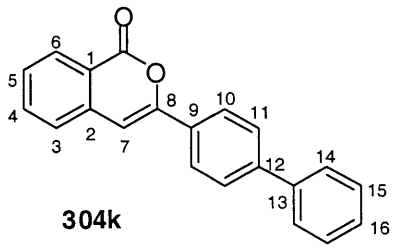
3-(3'-Methylphenyl)isocoumarin 304j



304 j

According to GP9 mixture of stilbene carboxylic acid **239j** (5 mg, 0.021 mmol) and PhSeSePh (0.7 mg, 0.0021 mmol) was reacted with [bis(trifluoroacetoxy)iodo]benzene (10.8 mg, 0.0252 mmol). Product **304j** was obtained as colourless crystals in 81% yield (0.017 mmol, 4 mg). M.p.: 90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, 1H, *J* = 8.2 Hz, H-6), 7.68-7.64 (m, 2H, Ar-*H*), 7.62 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.45-7.42 (m, 2H, Ar-*H*), 7.29 (t, 1H, *J* = 7.8 Hz, Ar-*H*), 7.19 (s, 1H, H-10), 6.89 (s, 1H, H-7), 2.37 (s, 3H, *CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.4 (C=O), 153.9 (C-8), 138.6 (C-1), 137.7 (C), 134.9 (CH), 132.0 (C), 130.8 (CH), 129.7 (CH), 128.7 (CH), 128.1 (CH), 125.9 (2xCH), 122.4 (CH), 120.6 (C), 101.7 (CH-7), 21.5 (CH_3) ppm. HRMS (AP): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{13}O_2$: 237.0916; found: 237.0917.

3-(Biphenyl)isocoumarin 304k



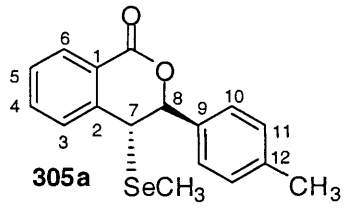
304k

According to GP9 mixture of stilbene carboxylic acid **239k** (100 mg, 0.33 mmol) and PhSeSePh (10.3 mg, 0.033 mmol) was reacted with [bis(trifluoroacetoxy)iodo]benzene (170 mg, 0.4 mmol). Product **304k** was obtained as colourless crystals in 99% yield (0.325 mmol, 97 mg). M.p.: 173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, 1H, *J* = 8.3 Hz, H-6), 7.88 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 7.65-7.61 (m, 3H, Ar-*H*), 7.57 (m, 2H, Ar-*H*), 7.43 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 7.39 (t, 2H, *J* = 7.5 Hz, Ar-*H*), 7.33-7.29 (m, 1H, Ar-*H*), 6.92 (s, 1H, H-7) ppm. ^{13}C & DEPT 90, 135 NMR (125 MHz, $CDCl_3$): δ = 162.3 (C=O), 153.5 (C-8), 142.7 (C-12), 140.1 (C-13), 137.6 (C-1), 134.9 (CH), 130.8 (C), 129.7 (CH), 128.9 (2xCH), 128.2 (CH), 127.9 (CH), 127.5 (2xCH), 127.1 (2xCH),

126.0 (CH), 125.7 (2xCH), 120.6 (C), 101.8 (CH-7), IR (KBr): ν = 3098, 3061, 3032, 1719, 1639, 1602, 1486, 1408, 1239, 1071, 836, 764, 687 cm^{-1}. HRMS (ESP): *m/z* [M + H]$^+$ calcd. for $C_{21}H_{15}O_2$: 299.1067; found: 299.1070.

5.12.1 Selective Synthesis of Seleno-Dihydroisocoumarin

3,4-Dihydro-3-(4′-methylphenyl)-4-(methylseleno)isocoumarin 305a



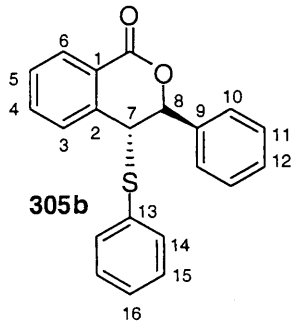
305a

Stilbene carboxylic acid **239b** (59.5 mg, 0.25 mmol), was added to a solution of dimethyl diselenide (2.65 ml, 5.2 mg, 0.028 mmol) in acetonitrile (5 mL), followed by [bis(trifluoroacetoxy)iodo]benzene (112 mg, 0.26 mmol) and the mixture stirred under argon at room temperature for 5 minutes. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate:light petroleum (1:4) to yield **305a** in 97% yield (80 mg, 0.22 mmol) as light yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (dd, 1H, *J* = 7.6 Hz, 1.3 Hz, H-6), 7.47 (dt, 1H, *J* = 7.6 Hz, 1.3 Hz, Ar-*H*), 7.36 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.31 (dt, 1H, *J* = 7.6 Hz, 1.0 Hz, Ar-*H*), 7.09 (d, 2H, *J* = 8.1 Hz, H-10), 7.03 (d, 2H, *J* = 8.1 Hz, H-11), 5.73 (d, 1H, *J* = 4.3 Hz, H-8), 4.46 (d, 1H, *J* = 4.3 Hz, H-7), 2.22 (s, 3H, *CH*$_3$), 1.85 (s, 3H, Se*CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ =164.0 (C=O), 139.0 (C-1), 138.4 (C-2), 135.3 (C-9), 134.2 (CH), 130.2 (CH), 129.3 (2xCH), 128.3 (CH), 128.2 (CH), 126.3 (2xCH), 125.0 (C-12), 83.8 (CH-8), 39.6 (CH-7), 21.1 (CH_3) and 4.8 (Se*CH*$_3$). IR (KBr): ν = 3030, 2924, 1726, 1634, 1601, 1515, 1455, 1371, 1282, 1259, 1234, 1109, 1088, 1047, 913, 817, 783, 760, 700 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{17}O_2Se^{80}$: 333.0405; found: 333.0394.

5.12.2 General Procedure (GP10) for the Synthesis of Thio-Substituted Dihydroisocoumarins 305

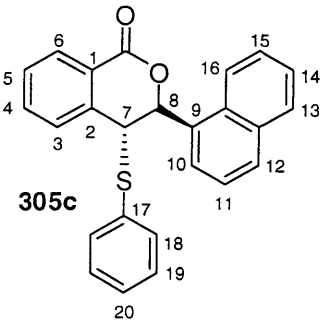
To a stirred solution of **239** (0.45 mmol), PhSSPh (0.45 mmol, 98 mg) in CH_3CN (10 mL) [bis(triflouroacetoxy)iodo]benzene (0.44 mmol, 189 mg,) was added at room temperature. The mixture was stirred at room temperature for 1 hour. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate:hexane (1:4) to yield the cyclisation products **305b**, **305c** and **305d** (first elution with hexane gave diphenyl disulfide, second elution with ethyl acetate:hexane gave cyclised product).

3-Phenyl-4-(phenylthio)isochroman-1-one 305b



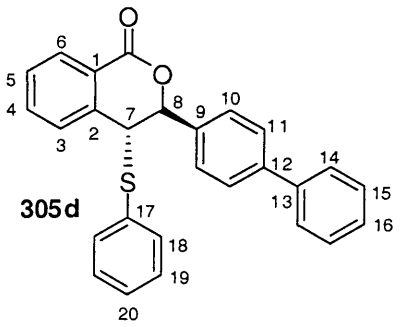
According to GP10 compound **305b** was obtained as colourless solid in 75% yield (0.34 mmol, 112.5 mg). M.p.: 218 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, 1H, *J* = 7.6 Hz, H-6), 7.53 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 7.45-7.41 (m, 3H, Ar-*H*), 7.36-7.32 (m, 4H, Ar-*H*), 7.25-7.24 (m, 3H, Ar-*H*), 7.14-7.13 (m, 2H, Ar-*H*), 5.78 (d, 1H, *J* = 3.2 Hz, H-8), 4.72 (d, 1H, *J* = 3.2 Hz, H-7) ppm. ^{13}C NMR & DEPT 135 (125 MHz, $CDCl_3$): δ = 163.6 (C=O), 137.7 (C-1), 137.2 (C-9), 134.5 (2xCH), 134.0 (CH), 132.4 (C-2), 130.2 (CH), 129.3 (2xCH), 128.9 (2xCH), 128.6 (2xCH), 128.5 (CH), 128.4 (CH), 126.1 (2xCH), 125.1 (C-13), 81.7 (CH-8), 50.8 (CH-7) ppm. IR (KBr): ν = 3059, 3027, 2988, 1708, 1601, 1461, 1439, 1377, 1331, 1302, 1241, 1113, 1098, 1077, 1029, 748, 742, 728, 715, 692 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{21}H_{17}O_2S$: 333.0944; found: 333.0935.

3-(1-Naphthyl)-4-(phenylthio)isochroman-1-one 305c



According to GP10 compound **305c** was obtained as colourless crystals in 66% yield (0.30 mmol, 114 mg). M.p.: 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, 1H, *J* = 7.4, 1.5 Hz, H-6), 7.73 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.61 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.50-7.48 (m, 2H, Ar-*H*), 7.39-7.35 (m, 4H, Ar-*H*), 7.32-7.29 (m, 4H, Ar-*H*), 7.14 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.07-7.04 (m, 1H, Ar-*H*), 7.01 (d, 1H, *J* = 7.3 Hz, Ar-*H*), 6.51 (d, 1H, *J* = 1.7 Hz, H-8), 4.69 (d, 1H, *J* = 1.7 Hz, H-7) ppm. ^{13}C NMR & DEPT 135 (125 MHz, $CDCl_3$): δ = 163.9 (C=O), 137.0 (C-1), 136.0 (2xCH), 134.1 (CH), 133.8 (C-9), 132.5 (C-2), 131.9 (C-17), 130.1 (CH), 129.8 (C), 129.5 (CH), 129.4 (2xCH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 126.8 (CH), 125.9 (CH), 124.9 (CH), 124.8 (C), 124.1 (CH), 122.2 (CH), 79.4 (CH-8), 50.2 (CH-7) ppm. IR (KBr): ν = 3065, 2970, 1714, 1598, 1460, 1439, 1389, 1329, 1290, 1243, 1120, 1092, 1023, 787, 774, 754, 748, 714, 693 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{19}O_2S$: 383.1100; found: 383.1102.

3-Bisphenyl-4-(phenylthio)isochroman-1-one 305d



According to GP10 compound **305d** was obtained as colourless crystals in 57% yield (0.26 mmol, 106 mg). M.p.: 132-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, 1H, *J* = 7.6 Hz, H-6), 7.46 (dt, 1H, *J* = 7.6, 1.4 Hz, Ar-*H*), 7.41 (d, 2H, *J* = 7.1 Hz, Ar-*H*), 7.37-7.30 (m, 8H, Ar-*H*), 7.27-7.22 (m, 4H, Ar-*H*), 7.11 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 5.72 (d, 1H, *J* = 3.6 Hz, H-8), 4.66 (d, 1H, *J* = 3.6 Hz, H-7) ppm. ^{13}C NMR & DEPT 135 (125 MHz, $CDCl_3$): δ = 163.6 (C=O), 141.3 (C-1), 140.2 (C-9), 137.3 (C-2), 136.6 (C-12), 134.4 (2xCH), 134.1 (CH), 132.4 (C-13), 130.3 (CH), 129.3 (2xCH), 128.8 (4xCH), 128.5 (CH), 127.6 (CH), 127.3 (2xCH), 127.0 (3xCH), 126.7 (CH), 125.2 (C-17), 81.7 (CH-8), 50.8 (CH-7) ppm. IR (KBr): ν = 3057, 3030, 2955, 2918, 1712, 1601, 1583, 1487, 1457, 1439, 1409, 1369, 1333, 1302, 1237, 1113, 1088, 1047, 1028, 757, 747, 742, 708, 687 cm^{-1}. HRMS (ESP): *m/z* $[M + H]^+$ calcd. for $C_{27}H_{21}O_2S$: 409.1257; found: 409.1256.

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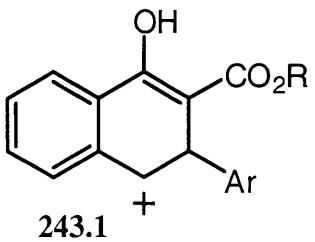
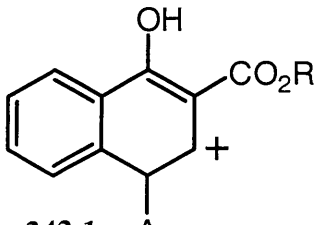
7. Appendix

Appendix 1: Computional Calculations for **243.1** and **242.1**



243.1



242.1

b3lyp/6-31G(d) pcm solvent model for CH_2Cl_2

	abs H / hartree	DeltaH / kcal.mol^{-1}
Phenyl substituent, carboxylic acid		
243.1A (Ar=Ph, R=H) benzylic cation	−880,872176	
242.1A (Ar=Ph, R=H) homobenzylic cation	−880,895927	-14,9

Attempts to locate phenonium ion led to minimisation to the homobenzylic cation

Methyl substituent, carboxylic acid		
243.1B (Ar=Me, R=H) benzylic cation	−689,190787	
242.1B (Ar=Me, R=H) homobenzylic cation	−689,213994	-14,6

b3lyp/6-31G(d) pcm solvent model for CH_2Cl_2

	abs H / hartree	DeltaH / kcal.mol-1
Phenyl substituent, carboxylic acid methyl ester		
243.1C (Ar=Ph, R=Me) benzylic cation	−920,140848	
242.1C (Ar=Ph, R=Me) homobenzylic cation	−920,163950	-14,5

Methyl substituent, carboxylic acid methyl ester		
243.1D (Ar=Me, R=Me) benzylic cation	−728,459523	
242.1D (Ar=Me, R=Me) homobenzylic cation	−728,482296	-14,3

All b3lyp/6-31G(d), PCM model for CH_2Cl_2 as implemented in Gaussian03, atomic coordinates in angstroms

243.1A (Ar=Ph, R=H) Carboxylic acid, phenyl substituent, benzylic cation

1	C	1.706519	-1.074769	-0.560990
2	C	2.571496	-2.205292	-0.681564
3	C	3.851384	-2.151024	-0.173477
4	C	4.292902	-0.974607	0.466380
5	C	3.470537	0.147893	0.601530
6	C	2.172717	0.120352	0.095766
7	H	2.198838	-3.099095	-1.180513
8	H	4.519836	-3.004515	-0.261714
9	H	5.305055	-0.936797	0.867685
10	H	3.841612	1.038424	1.099480
11	C	0.423392	-1.107351	-1.082304
12	C	-0.531526	0.003298	-0.956786
13	H	0.071074	-2.007244	-1.590134
14	C	-1.769800	-0.618448	-0.248349
15	C	0.011121	1.241486	-0.309909
16	C	-0.810171	2.456596	-0.240950
17	C	1.289803	1.279109	0.200185
18	O	1.826277	2.339495	0.800636
19	H	1.132409	3.057070	0.811043
20	O	-1.977053	2.357873	-0.875493
21	O	-0.448495	3.489140	0.334528
22	H	-2.465243	3.219179	-0.773484
23	C	-1.701590	-0.954407	1.109977
24	C	-2.807017	-1.529698	1.738893
25	C	-3.973733	-1.784176	1.013684
26	C	-4.034728	-1.460000	-0.344478
27	C	-2.932938	-0.883574	-0.978352
28	H	-0.799401	-0.751642	1.684901
29	H	-2.753291	-1.779937	2.796740
30	H	-4.834583	-2.232527	1.506157
31	H	-4.943909	-1.648092	-0.912542
32	H	-2.984705	-0.622860	-2.034105
33	H	-0.863726	0.243627	-1.986422

SCF energy = −881.145243735 Eh
Absolute enthalpy = −880.872176 Eh

242.1A (Ar=Ph, R=H) Carboxylic acid, phenyl substituent, homobenzylic cation

1	C	0.019854	1.297933	-0.531670
2	C	0.771627	2.464867	-0.682486
3	C	0.248135	3.696941	-0.296539
4	C	-1.040549	3.792949	0.254542
5	C	-1.804511	2.651350	0.414142
6	C	-1.281876	1.395915	0.021069
7	H	1.774231	2.409355	-1.101490
8	H	0.848737	4.596119	-0.423797
9	H	-1.436093	4.761098	0.553362
10	H	-2.804261	2.707969	0.835440

11	C	0.587762	-0.033200	-0.962539
12	C	-0.334720	-1.184671	-0.790386
13	H	0.788686	0.021593	-2.050386
14	C	1.929974	-0.388497	-0.292235
15	C	-1.576348	-1.091390	-0.244165
16	C	-2.460157	-2.274662	-0.066847
17	C	-2.072988	0.207197	0.172285
18	O	-3.255733	0.321412	0.689529
19	H	-3.688683	-0.596991	0.725156
20	O	-1.934776	-3.412971	-0.479270
21	O	-3.586717	-2.180653	0.425522
22	H	-2.589520	-4.150224	-0.321844
23	C	2.022503	-0.456026	1.104870
24	C	3.231488	-0.801471	1.709183
25	C	4.352310	-1.087877	0.924594
26	C	4.260542	-1.026315	-0.467409
27	C	3.051619	-0.680066	-1.075921
28	H	1.155789	-0.231583	1.725264
29	H	3.296442	-0.848346	2.794662
30	H	5.294656	-1.357040	1.398062
31	H	5.130300	-1.244415	-1.084345
32	H	2.983209	-0.632646	-2.162021
33	H	0.036329	-2.155069	-1.117231

SCF energy = -881.169437213 Eh
Absolute enthalpy = -880.895927 Eh

243.1B (Ar=Me, R=H) Carboxylic acid, methyl substituent, benzylic cation

1	C	0	-0.249680	-0.956078	0.051188
2	C	0	1.148530	-0.546143	0.023515
3	C	0	1.481335	0.840298	-0.188616
4	C	0	0.466194	1.768709	-0.322183
5	C	0	-0.955913	1.430854	-0.222614
6	C	0	-1.258725	-0.028234	-0.097615
7	C	0	2.179858	-1.471893	0.176303
8	C	0	3.508663	-1.045520	0.116271
9	C	0	3.850870	0.307037	-0.097140
10	C	0	2.852061	1.242665	-0.246798
11	C	0	-1.546955	2.290079	0.965279
12	C	0	-2.642764	-0.514230	-0.166283
13	O	0	-2.956541	-1.697582	0.000824
14	O	0	-0.447906	-2.263277	0.204389
15	O	0	-3.541737	0.434239	-0.433518
16	H	0	3.082328	2.295075	-0.407900
17	H	0	4.897272	0.600992	-0.139301
18	H	0	4.303600	-1.780632	0.237082
19	H	0	1.950504	-2.520373	0.339640
20	H	0	0.720100	2.820589	-0.471277
21	H	0	-1.432544	-2.422688	0.203171
22	H	0	-4.443358	0.012265	-0.458746

23	H	0	-2.625574	2.136595	0.997502
24	H	0	-1.102445	1.977356	1.913371
25	H	0	-1.341388	3.350729	0.798683
26	H	0	-1.439868	1.837777	-1.133630

SCF energy = -689.408624754 Eh
Absolute enthalpy = -689.190787 Eh

242.1B (Ar=Me, R=H) Carboxylic acid, methyl substituent, homobenzylic cation

1	C	-1.400061	0.623167	-0.198276
2	C	-2.776747	0.836128	-0.303950
3	C	-3.669227	-0.228274	-0.193996
4	C	-3.208532	-1.536680	0.026429
5	C	-1.850310	-1.776619	0.123542
6	C	-0.936929	-0.701777	0.007185
7	H	-3.159110	1.839319	-0.481453
8	H	-4.738070	-0.040393	-0.281853
9	H	-3.916443	-2.357841	0.113712
10	H	-1.475335	-2.783796	0.281658
11	C	-0.436721	1.778251	-0.294297
12	C	0.993349	1.392393	-0.284594
13	H	-0.606058	2.299409	-1.256684
14	C	-0.673285	2.845343	0.822321
15	C	1.438799	0.121572	-0.103345
16	C	2.886586	-0.220680	-0.067271
17	C	0.474985	-0.950434	0.067557
18	O	0.874897	-2.167243	0.266638
19	H	1.890863	-2.183502	0.267717
20	O	3.693939	0.807291	-0.248202
21	O	3.280348	-1.374116	0.118601
22	H	4.640345	0.491949	-0.205167
23	H	1.718243	2.196711	-0.408953
24	H	0.011795	3.687968	0.690208
25	H	-1.697617	3.220411	0.764674
26	H	-0.513538	2.407972	1.812025

SCF energy = -689.432245073 Eh
Absolute enthalpy = -689.213994 Eh

243.1C (Ar=Ph, R=Me) Methyl ester, phenyl substituent, benzylic cation

1	C	-2.411135	-1.720448	-0.933551
2	C	-1.380968	-1.098446	-0.218006
3	C	-1.204721	-1.374759	1.143680
4	C	-2.084441	-2.240543	1.794581
5	C	-3.124133	-2.848059	1.086708
6	C	-3.285697	-2.586279	-0.277159
7	C	-0.393727	-0.142563	-0.968260
8	C	0.746308	-1.038497	-1.202156
9	C	2.004005	-0.829676	-0.652318
10	C	2.256825	0.377602	0.090672

11	C	1.186247	1.357181	0.264604
12	C	-0.071594	1.127362	-0.246466
13	C	3.530861	0.592552	0.612131
14	C	4.535859	-0.357683	0.406737
15	C	4.303858	-1.541365	-0.321571
16	C	3.050821	-1.779117	-0.846609
17	C	-1.102912	2.157622	-0.074485
18	O	-0.915631	3.207212	0.548322
19	O	1.537054	2.456702	0.929287
20	O	-2.255488	1.841031	-0.669096
21	H	2.838914	-2.685889	-1.411805
22	H	5.109057	-2.258582	-0.464061
23	H	5.526432	-0.173955	0.821220
24	H	3.742538	1.496583	1.174783
25	H	0.563907	-1.932620	-1.800838
26	H	0.731064	3.041245	0.984918
27	C	-3.364335	2.763375	-0.573317
28	H	-0.401164	-0.903108	1.704658
29	H	-1.953138	-2.440897	2.856224
30	H	-3.808349	-3.523803	1.596395
31	H	-4.098714	-3.051123	-0.831736
32	H	-2.541507	-1.511705	-1.994502
33	H	-0.871418	0.080194	-1.937526
34	H	-3.037419	3.711354	-0.146827
35	H	-3.745769	2.901767	-1.586504
36	H	-4.128633	2.301423	0.056196

SCF energy = -920.444014037 Eh
Absolute enthalpy = -920.140848 Eh

242.1C (Ar=Ph, R=Me) Methyl ester, phenyl substituent, homobenzylic cation

1	C	2.758609	-1.686035	-1.071950
2	C	1.828143	-1.001564	-0.282912
3	C	1.863851	-1.140041	1.111397
4	C	2.830949	-1.949190	1.708330
5	C	3.763273	-2.628284	0.918754
6	C	3.725982	-2.495026	-0.470701
7	C	0.748297	-0.122346	-0.945345
8	C	0.803880	1.329736	-0.533140
9	C	-0.328902	1.978061	0.019391
10	C	-1.548035	1.238995	0.193892
11	C	-1.651425	-0.154993	-0.198755
12	C	-0.571477	-0.772596	-0.746636
13	C	-0.267023	3.341699	0.393879
14	C	0.907474	4.049428	0.215228
15	C	2.029588	3.408466	-0.335800
16	C	1.978267	2.065490	-0.703040
17	C	-2.953065	-0.849485	0.005197
18	O	-3.929427	-0.271451	0.487397

19	O	-2.565390	1.854060	0.710800
20	O	-2.945926	-2.107434	-0.388889
21	H	2.859341	1.584889	-1.122784
22	H	2.953696	3.966376	-0.477770
23	H	0.962137	5.097864	0.499641
24	H	-1.144849	3.822053	0.816727
25	H	0.936741	-0.171307	-2.035920
26	H	-3.347728	1.208804	0.765518
27	C	-4.160064	-2.895188	-0.252307
28	H	1.144338	-0.612641	1.735810
29	H	2.854523	-2.049574	2.791863
30	H	4.517286	-3.258701	1.386380
31	H	4.451163	-3.018133	-1.091327
32	H	2.731335	-1.584083	-2.156110
33	H	-0.649639	-1.813792	-1.056064
34	H	-4.976126	-2.277310	0.120623
35	H	-4.383942	-3.291053	-1.243906
36	H	-3.932260	-3.707556	0.439960

SCF energy = -920.467612073 Eh
Absolute enthalpy = -920.16395 Eh

243.1D (Ar=Me, R=Me) Methyl ester, methyl substituent, benzylic cation

1	C	3.200842	1.238366	-0.302820
2	C	1.831255	0.838198	-0.207524
3	C	1.501751	-0.546974	0.021190
4	C	2.536520	-1.472571	0.154236
5	C	3.863491	-1.048029	0.059925
6	C	4.202102	0.302843	-0.170681
7	C	0.813497	1.766786	-0.323315
8	C	-0.604657	1.433651	-0.172477
9	C	-0.908565	-0.025920	-0.038799
10	C	0.104309	-0.955397	0.083782
11	O	-0.088792	-2.263260	0.240793
12	C	-1.133565	2.285829	1.051353
13	C	-2.296289	-0.510961	-0.065356
14	O	-3.196762	0.445783	-0.303277
15	O	-2.608466	-1.694362	0.096771
16	H	3.428279	2.289385	-0.476470
17	H	5.247435	0.595502	-0.239694
18	H	4.660227	-1.783392	0.166747
19	H	2.309987	-2.519840	0.328884
20	H	1.065177	2.816841	-0.488783
21	H	-1.072752	-2.422856	0.257508
22	C	-4.581101	0.027360	-0.360849
23	H	-2.209457	2.132158	1.134062
24	H	-0.644189	1.966154	1.974782
25	H	-0.935802	3.347741	0.882904
26	H	-1.131772	1.849750	-1.053222

27	H	-4.878845	-0.417013	0.591357
28	H	-5.144598	0.938366	-0.557954
29	H	-4.719072	-0.697170	-1.166400

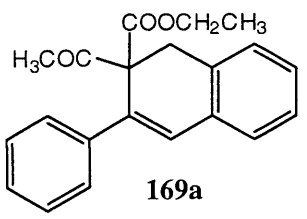
SCF energy = -728.708324691 Eh
Absolute enthalpy = -728.459523 Eh

242.1D (Ar=Me, R=Me) Methyl ester, methyl substituent, homobenzylic cation

1	C	0.067766	-0.988392	0.084404
2	C	-1.333141	-0.686356	0.006086
3	C	-1.743460	0.655099	-0.202993
4	C	-0.735678	1.772808	-0.280900
5	C	0.678045	1.332900	-0.256239
6	C	1.074017	0.046221	-0.072578
7	C	-2.287887	-1.726188	0.108385
8	C	-3.634616	-1.435083	-0.007113
9	C	-4.042804	-0.110040	-0.231879
10	C	-3.109435	0.920180	-0.327227
11	C	-0.945286	2.838893	0.843892
12	C	2.508480	-0.353508	-0.021587
13	O	2.857138	-1.520241	0.169471
14	O	0.416405	-2.220733	0.287771
15	O	3.352590	0.644480	-0.198705
16	H	-3.450989	1.937376	-0.508405
17	H	-5.102482	0.117839	-0.334676
18	H	-4.373998	-2.229160	0.069229
19	H	-1.953723	-2.747000	0.270299
20	H	-0.874274	2.308646	-1.239780
21	H	1.428616	-2.279823	0.302301
22	C	4.767032	0.316544	-0.162558
23	H	1.433510	2.109316	-0.371350
24	H	-0.224482	3.653944	0.730312
25	H	-1.952590	3.255513	0.773908
26	H	-0.818605	2.385460	1.831051
27	H	4.999509	-0.400803	-0.952041
28	H	5.278198	1.263041	-0.330308
29	H	5.024041	-0.100870	0.813003

SCF energy = -728.731679562 Eh
Absolute enthalpy = -728.482296 Eh

Appendix 2.1: X-ray crystal data for dihydronaphthalene **169a**



169a

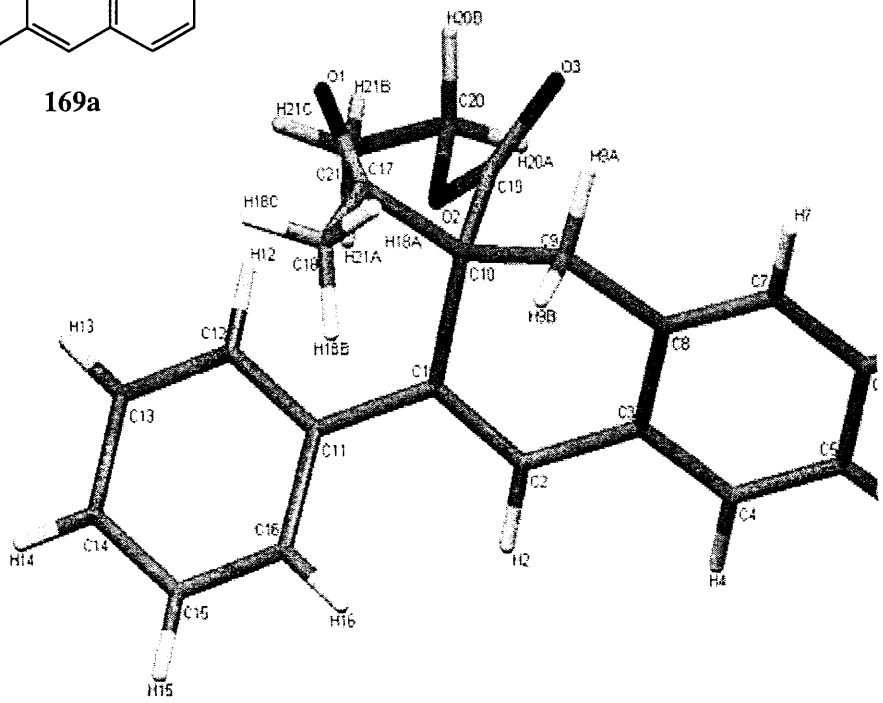


Table 1. Crystal data and structure refinement for **169a**: CCDC-713446 these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Empirical formula	$C_{21}H_{20}O_3$	
Formula weight	320.37	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 8.1491(5) Å	α = 86.372(3)°
	b = 9.5844(4) Å	β = 79.630(2)°
	c = 10.9652(6) Å	γ = 85.915(4)°
Volume	839.19(8) Å^3	
Z	2	
Density (calculated)	1.268 Mg / m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	340	
Crystal	Fragment; Colourless	
Crystal size	0.24 × 0.22 × 0.20 mm^3	

θ range for data collection	3.22 – 27.48°
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 12$, $-14 \leq l \leq 14$
Reflections collected	15007
Independent reflections	3851 [R_{int} = 0.0698]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9834 and 0.9802
Refinement method	Full-matrix least-squares on F^2
Data/ restraints / parameters	3851 / 0 / 219
Goodness-of-fit on F^2	1.108
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0630, $wR2$ = 0.1393
R indices (all data)	$R1$ = 0.1080, $wR2$ = 0.1597
Largest diff. peak and hole	0.404 and –0.445 e Å^{-3}

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	10588(2)	12249(2)	6121(2)	22(1)	1
C2	10023(3)	12978(2)	5175(2)	24(1)	1
C3	10963(3)	13066(2)	3913(2)	23(1)	1
C4	10536(3)	14061(2)	3015(2)	28(1)	1
C5	11378(3)	14042(2)	1804(2)	30(1)	1
C6	12631(3)	13019(2)	1470(2)	31(1)	1
C7	13084(3)	12031(2)	2351(2)	26(1)	1
C8	12273(3)	12061(2)	3570(2)	23(1)	1
C9	12658(3)	10969(2)	4544(2)	23(1)	1
C10	12379(2)	11570(2)	5844(2)	21(1)	1
C11	9551(3)	12105(2)	7371(2)	23(1)	1
C12	10213(3)	12137(2)	8464(2)	26(1)	1
C13	9208(3)	11959(2)	9615(2)	31(1)	1
C14	7525(3)	11738(2	9715(2)	34(1)	1
C15	6850(3)	11719(2)	8644(2)	33(1)	1
C16	7845(3)	11898(2)	7494(2)	27(1)	1
C17	12703(3)	10365(2)	6786(2)	23(1)	1
C18	11717(3)	9099(2)	6854(2)	28(1)	1
C19	13706(3)	12624(2)	5872(2)	23(1)	1
C20	14315(3)	14619(2)	6875(2)	31(1)	1
C21	13643(3)	15233(3)	8094(2)	42(1)	1
O1	13789(2)	10431(1)	7402(1)	28(1)	1
O2	13147(2)	13600(1)	6683(1)	26(1)	1
O3	15079(2)	12549(2)	5251(1)	30(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.345(3)	C12–C13	1.383(3)
C1–C11	1.480(3)	C12–H12	0.9500
C1–C10	1.541(3)	C13–C14	1.387(3)
C2–C3	1.457(3)	C13–H13	0.9500
C2–H2	0.9500	C14–C15	1.386(3)
C3–C4	1.399(3)	C14–H14	0.9500
C3–C8	1.401(3)	C15–C16	1.379(3)
C4–C5	1.381(3)	C15–H15	0.9500
C4–H4	0.9500	C16–H16	0.9500
C5–C6	1.381(3)	C17–O1	1.213(2)
C5–H5	0.9500	C17–C18	1.493(3)
C6–C7	1.389(3)	C18–H18A	0.9800
C6–H6	0.9500	C18–H18B	0.9800
C7–C8	1.381(3)	C18–H18C	0.9800
C7–H7	0.9500	C19–O3	1.201(2)
C8–C9	1.506(3)	C19–O2	1.331(2)
C9–C10	1.545(3)	C20–O2	1.461(2)
C9–H9A	0.9900	C20–C21	1.491(3)
C9–H9B	0.9900	C20–H20A	0.9900
C10–C19	1.537(3)	C20–H20B	0.9900
C10–C17	1.541(3)	C21–H21A	0.9800
C11–C16	1.400(3)	C21–H21B	0.9800
C11–C12	1.403(3)	C21–H21C	0.9800
C2–C1–C11	121.92(18)	C6–C7–H7	120.0
C2–C1–C10	116.86(18)	C7–C8–C3	120.09(18)
C11–C1–C10	121.23(17)	C7–C8–C9	121.96(18)
C1–C2–C3	123.47(18)	C3–C8–C9	117.78(17)
C1–C2–H2	118.3	C8–C9–C10	111.68(15)
C3–C2–H2	118.3	C8–C9–H9A	109.3
C4–C3–C8	118.97(19)	C10–C9–H9A	109.3
C4–C3–C2	122.33(18)	C8–C9–H9B	109.3
C8–C3–C2	118.57(17)	C10–C9–H9B	109.3
C5–C4–C3	120.58(19)	H9A–C9–H9B	107.9
C5–C4–H4	119.7	C19–C10–C17	106.04(16)
C3–C4–H4	119.7	C19–C10–C1	112.20(15)
C6–C5–C4	119.78(19)	C17–C10–C1	112.99(16)
C6–C5–H5	120.1	C19–C10–C9	109.10(16)
C4–C5–H5	120.1	C17–C10–C9	108.00(15)
C5–C6–C7	120.5(2)	C1–C10–C9	108.39(16)
C5–C6–H6	119.8	C16–C11–C12	117.52(19)
C7–C6–H6	119.8	C16–C11–C1	119.82(18)
C8–C7–C6	120.0(2)	C12–C11–C1	122.65(19)
C8–C7–H7	120.0	C13–C12–C11	120.8(2)

C13–C12–H12	119.6	C17–C18–H18C	109.5
C11–C12–H12	119.6	H18A–C18–H18C	109.5
C12–C13–C14	120.8(2)	H18B–C18–H18C	109.5
C12–C13–H13	119.6	O3–C19–O2	124.92(19)
C14–C13–H13	119.6	O3–C19–C10	123.62(18)
C15–C14–C13	119.1(2)	O2–C19–C10	111.45(17)
C15–C14–H14	120.4	O2–C20–C21	106.98(17)
C13–C14–H14	120.4	O2–C20–H20A	110.3
C16–C15–C14	120.4(2)	C21–C20–H20A	110.3
C16–C15–H15	119.8	O2–C20–H20B	110.3
C14–C15–H15	119.8	C21–C20–H20B	110.3
C15–C16–C11	121.4(2)	H20A–C20–H20B	108.6
C15–C16–H16	119.3	C20–C21–H21A	109.5
C11–C16–H16	119.3	C20–C21–H21B	109.5
O1–C17–C18	121.81(18)	H21A–C21–H21B	109.5
O1–C17–C10	120.13(18)	C20–C21–H21C	109.5
C18–C17–C10	117.96(17)	H21A–C21–H21C	109.5
C17–C18–H18A	109.5	H21B–C21–H21C	109.5
C17–C18–H18B	109.5	C19–O2–C20	117.64(16)
H18A–C18–H18B	109.5		

Symmetry transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

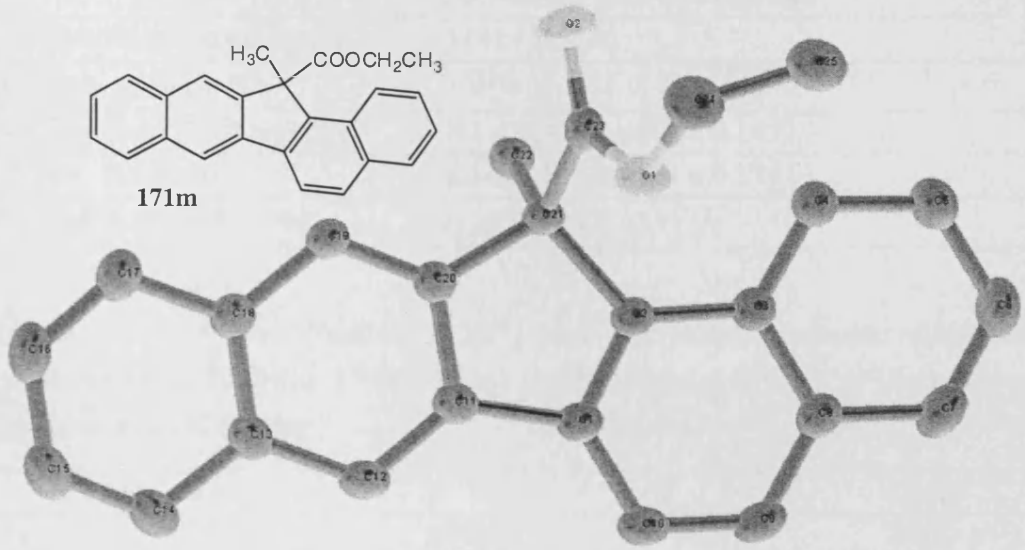
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	21(1)	20(1)	26(1)	−7(1)	−7(1)	0(1)
C2	23(1)	23(1)	30(1)	−9(1)	−11(1)	5(1)
C3	25(1)	19(1)	27(1)	−5(1)	−12(1)	−1(1)
C4	30(1)	21(1)	35(1)	−2(1)	−15(1)	2(1)
C5	34(1)	27(1)	32(1)	4(1)	−15(1)	−2(1)
C6	35(1)	32(1)	27(1)	2(1)	−10(1)	−4(1)
C7	24(1)	28(1)	28(1)	0(1)	−6(1)	0(1)
C8	22(1)	22(1)	27(1)	−3(1)	−11(1)	−2(1)
C9	26(1)	18(1)	25(1)	−2(1)	−7(1)	3(1)
C10	20(1)	21(1)	23(1)	−2(1)	−6(1)	0(1)
C11	23(1)	20(1)	27(1)	−7(1)	−6(1)	3(1)
C12	23(1)	27(1)	28(1)	−4(1)	−7(1)	−2(1)
C13	29(1)	41(1)	26(1)	−4(1)	−8(1)	−4(1)
C14	28(1)	43(1)	31(1)	−8(1)	0(1)	−5(1)
C15	22(1)	41(1)	38(1)	−12(1)	−6(1)	−2(1)
C16	23(1)	30(1)	31(1)	−11(1)	−8(1)	4(1)
C17	21(1)	23(1)	23(1)	−3(1)	2(1)	3(1)
C18	29(1)	25(1)	30(1)	1(1)	−6(1)	−5(1)
C19	24(1)	22(1)	23(1)	3(1)	−9(1)	−1(1)
C20	29(1)	27(1)	37(1)	−3(1)	−7(1)	−11(1)

C21	44(2)	45(1)	41(2)	−12(1)	−11(1)	−17(1)
O1	24(1)	29(1)	32(1)	2(1)	−12(1)	0(1)
O2	25(1)	23(1)	32(1)	−5(1)	−6(1)	−5(1)
O3	24(1)	32(1)	33(1)	0(1)	−3(1)	−4(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	8953	13460	5339	29	1
H4	9660	14755	3240	33	1
H5	11095	14731	1202	36	1
H6	13189	12991	632	37	1
H7	13951	11333	2115	32	1
H9A	13834	10603	4322	27	1
H9B	11933	10179	4562	27	1
H12	11365	12282	8414	31	1
H13	9677	11988	10346	37	1
H14	6844	11602	10508	41	1
H15	5695	11581	8702	40	1
H16	7362	11882	6769	33	1
H18A	12257	8464	6215	42	1
H18B	10582	9384	6716	42	1
H18C	11664	8620	7675	42	1
H20A	14405	15361	6200	37	1
H20B	15438	14155	6884	37	1
H21A	12511	15650	8087	62	1
H21B	14366	15958	8239	62	1
H21C	13610	14496	8758	62	1

Appendix 2.2: Crystal data for benzofluorene **171m**



171m

Table 6. Crystal data and structure refinement for **171m**: CCDC-713447 these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Empirical formula	$C_{25}H_{20}O_2$	
Formula weight	352.41	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 14.2710(7) Å	$\alpha = 90°$
	b = 7.8800(4) Å	$\beta = 105.779(2)°$
	c = 16.7080(10) Å	$\gamma = 90°$
Volume	1808.10(17) $Å^3$	
Z	4	
Density (calculated)	1.295 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	744	
Crystal size	0.26 x 0.18 x 0.04 mm^3	
Theta range for data collection	2.53 to 27.50°	
Index ranges	−18<=h<=18,−10<=k<=9, −21<=l<=21	
Reflections collected	6856	
Independent reflections	4131 [R(int) = 0.0702]	

Completeness to theta = 27.50°	99.4 %
Max. and min. transmission	0.9968 and 0.9793
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4131 / 0 / 246
Goodness-of-fit on F^2	1.016
Final R indices [I >2 sigma(I)]	R1 = 0.0720, wR2 = 0.1451
R indices (all data)	R1 = 0.1401, wR2 = 0.1741
Largest diff. peak and hole	0.297 and –0.233 e.$Å^{-3}$

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **171m**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1537(2)	966(3)	7981(2)	26(1)
C(2)	997(2)	1701(3)	8457(1)	24(1)
C(3)	–37(2)	1773(3)	8179(2)	26(1)
C(4)	–638(2)	2534(3)	8627(2)	32(1)
C(5)	–1626(2)	2573(4)	8314(2)	39(1)
C(6)	–2074(2)	1844(4)	7540(2)	46(1)
C(7)	–1516(2)	1099(4)	7087(2)	39(1)
C(8)	–492(2)	1031(3)	7386(2)	29(1)
C(9)	90(2)	247(3)	6924(2)	31(1)
C(10)	1082(2)	211(3)	7204(2)	29(1)
C(11)	2578(2)	1127(3)	8404(1)	25(1)
C(12)	3384(2)	572(3)	8186(2)	29(1)
C(13)	4327(2)	990(3)	8700(2)	27(1)
C(14)	5183(2)	485(3)	8490(2)	33(1)
C(15)	6082(2)	953(4)	8972(2)	39(1)
C(16)	6171(2)	1925(4)	9690(2)	40(1)
C(17)	5361(2)	2413(4)	9924(2)	35(1)
C(18)	4417(2)	1968(3)	9435(2)	26(1)
C(19)	3562(2)	2465(3)	9660(2)	27(1)
C(20)	2670(2)	2046(3)	9158(2)	25(1)
C(21)	1658(2)	2344(3)	9286(2)	25(1)
C(22)	1541(2)	1273(3)	10023(2)	29(1)
C(23)	1521(2)	4215(3)	9436(2)	28(1)
C(24)	1130(2)	6900(3)	8778(2)	43(1)
C(25)	64(2)	7175(4)	8675(2)	44(1)
O(1)	1346(1)	5095(2)	8733(1)	34(1)
O(2)	1567(2)	4821(3)	10106(1)	47(1)

Table 8. Bond lengths [Å] and angles [°] for **171m**.

C(1)-C(2)	1.377(3)	C(24)-H(24A)	0.9700
C(1)-C(10)	1.415(3)	C(24)-H(24B)	0.9700
C(1)-C(11)	1.466(3)	C(25)-H(25A)	0.9600
C(2)-C(3)	1.422(3)	C(25)-H(25B)	0.9600
C(2)-C(21)	1.535(3)	C(25)-H(25C)	0.9600
C(3)-C(4)	1.415(4)	C(2)-C(1)-C(10)	121.1(2)
C(3)-C(8)	1.431(3)	C(2)-C(1)-C(11)	109.8(2)
C(4)-C(5)	1.365(4)	C(10)-C(1)-C(11)	129.0(2)
C(4)-H(4)	0.9300	C(1)-C(2)-C(3)	121.5(2)
C(5)-C(6)	1.401(4)	C(1)-C(2)-C(21)	110.9(2)
C(5)-H(5)	0.9300	C(3)-C(2)-C(21)	127.6(2)
C(6)-C(7)	1.370(4)	C(4)-C(3)-C(2)	124.6(2)
C(6)-H(6)	0.9300	C(4)-C(3)-C(8)	118.4(2)
C(7)-C(8)	1.412(4)	C(2)-C(3)-C(8)	117.0(2)
C(7)-H(7)	0.9300	C(5)-C(4)-C(3)	121.2(3)
C(8)-C(9)	1.419(4)	C(5)-C(4)-H(4)	119.4
C(9)-C(10)	1.366(4)	C(3)-C(4)-H(4)	119.4
C(9)-H(9)	0.9300	C(4)-C(5)-C(6)	120.6(3)
C(10)-H(10)	0.9300	C(4)-C(5)-H(5)	119.7
C(11)-C(12)	1.370(3)	C(6)-C(5)-H(5)	119.7
C(11)-C(20)	1.428(3)	C(7)-C(6)-C(5)	119.9(3)
C(12)-C(13)	1.425(3)	C(7)-C(6)-H(6)	120.1
C(12)-H(12)	0.9300	C(5)-C(6)-H(6)	120.1
C(13)-C(14)	1.417(3)	C(6)-C(7)-C(8)	121.5(3)
C(13)-C(18)	1.426(4)	C(6)-C(7)-H(7)	119.3
C(14)-C(15)	1.366(4)	C(8)-C(7)-H(7)	119.3
C(14)-H(14)	0.9300	C(7)-C(8)-C(9)	121.8(2)
C(15)-C(16)	1.400(4)	C(7)-C(8)-C(3)	118.5(2)
C(15)-H(15)	0.9300	C(9)-C(8)-C(3)	119.8(2)
C(16)-C(17)	1.372(4)	C(10)-C(9)-C(8)	121.9(2)
C(16)-H(16)	0.9300	C(10)-C(9)-H(9)	119.1
C(17)-C(18)	1.417(4)	C(8)-C(9)-H(9)	119.1
C(17)-H(17)	0.9300	C(9)-C(10)-C(1)	118.6(2)
C(18)-C(19)	1.425(3)	C(9)-C(10)-H(10)	120.7
C(19)-C(20)	1.360(3)	C(1)-C(10)-H(10)	120.7
C(19)-H(19)	0.9300	C(12)-C(11)-C(20)	120.9(2)
C(20)-C(21)	1.534(3)	C(12)-C(11)-C(1)	131.2(2)
C(21)-C(23)	1.517(4)	C(20)-C(11)-C(1)	107.9(2)
C(21)-C(22)	1.539(3)	C(11)-C(12)-C(13)	119.3(2)
C(22)-H(22A)	0.9600	C(11)-C(12)-H(12)	120.3
C(22)-H(22B)	0.9600	C(13)-C(12)-H(12)	120.3
C(22)-H(22C)	0.9600	C(14)-C(13)-C(18)	119.0(2)
C(23)-O(2)	1.202(3)	C(14)-C(13)-C(12)	121.4(2)
C(23)-O(1)	1.327(3)	C(18)-C(13)-C(12)	119.6(2)
C(24)-O(1)	1.461(3)	C(15)-C(14)-C(13)	120.8(3)
C(24)-C(25)	1.500(4)	C(15)-C(14)-H(14)	119.6

C(13)-C(14)-H(14)	119.6	C(20)-C(21)-C(22)	109.81(19)
C(14)-C(15)-C(16)	120.4(3)	C(21)-C(22)-H(22A)	109.5
C(14)-C(15)-H(15)	119.8	C(21)-C(22)-H(22B)	109.5
C(16)-C(15)-H(15)	119.8	H(22A)-C(22)-H(22B)	109.5
C(17)-C(16)-C(15)	120.7(3)	C(21)-C(22)-H(22C)	109.5
C(17)-C(16)-H(16)	119.6	H(22A)-C(22)-H(22C)	109.5
C(15)-C(16)-H(16)	119.6	H(22B)-C(22)-H(22C)	109.5
C(16)-C(17)-C(18)	120.6(3)	O(2)-C(23)-O(1)	124.4(2)
C(16)-C(17)-H(17)	119.7	O(2)-C(23)-C(21)	124.2(2)
C(18)-C(17)-H(17)	119.7	O(1)-C(23)-C(21)	111.4(2)
C(17)-C(18)-C(19)	121.9(2)	O(1)-C(24)-C(25)	110.8(2)
C(17)-C(18)-C(13)	118.6(2)	O(1)-C(24)-H(24A)	109.5
C(19)-C(18)-C(13)	119.5(2)	C(25)-C(24)-H(24A)	109.5
C(20)-C(19)-C(18)	119.7(2)	O(1)-C(24)-H(24B)	109.5
C(20)-C(19)-H(19)	120.2	C(25)-C(24)-H(24B)	109.5
C(18)-C(19)-H(19)	120.1	H(24A)-C(24)-H(24B)	108.1
C(19)-C(20)-C(11)	120.9(2)	C(24)-C(25)-H(25A)	109.5
C(19)-C(20)-C(21)	129.4(2)	C(24)-C(25)-H(25B)	109.5
C(11)-C(20)-C(21)	109.6(2)	H(25A)-C(25)-H(25B)	109.5
C(23)-C(21)-C(2)	113.2(2)	C(24)-C(25)-H(25C)	109.5
C(23)-C(21)-C(20)	109.9(2)	H(25A)-C(25)-H(25C)	109.5
C(2)-C(21)-C(20)	101.24(19)	H(25B)-C(25)-H(25C)	109.5
C(23)-C(21)-C(22)	110.7(2)	C(23)-O(1)-C(24)	117.1(2)
C(2)-C(21)-C(22)	111.5(2)		

Symmetry transformations used to generate equivalent atoms.

Table 9. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	32(1)	20(1)	25(1)	0(1)	7(1)	0(1)
C(2)	29(1)	18(1)	24(1)	−1(1)	5(1)	1(1)
C(3)	29(1)	19(1)	29(1)	1(1)	5(1)	0(1)
C(4)	32(2)	29(1)	34(2)	−2(1)	7(1)	0(1)
C(5)	29(2)	43(2)	45(2)	−5(1)	10(1)	0(1)
C(6)	24(1)	57(2)	52(2)	−3(2)	2(1)	−3(2)
C(7)	36(2)	43(2)	33(2)	−1(1)	−1(1)	−10(1)
C(8)	31(1)	25(1)	28(1)	1(1)	4(1)	−4(1)
C(9)	41(2)	25(1)	24(1)	−2(1)	4(1)	−6(1)
C(10)	38(2)	23(1)	27(1)	−2(1)	11(1)	0(1)
C(11)	31(1)	21(1)	24(1)	3(1)	9(1)	1(1)
C(12)	38(2)	26(1)	24(1)	2(1)	11(1)	4(1)
C(13)	30(1)	24(1)	28(1)	8(1)	10(1)	5(1)
C(14)	37(2)	33(2)	33(2)	10(1)	16(1)	9(1)
C(15)	33(2)	47(2)	39(2)	15(2)	15(1)	12(1)
C(16)	26(1)	51(2)	40(2)	12(2)	4(1)	2(1)
C(17)	32(2)	39(2)	31(2)	7(1)	3(1)	4(1)
C(18)	30(1)	26(1)	24(1)	7(1)	7(1)	2(1)

C(19)	30(1)	26(1)	23(1)	0(1)	4(1)	1(1)
C(20)	29(1)	22(1)	24(1)	4(1)	7(1)	4(1)
C(21)	28(1)	26(1)	21(1)	−1(1)	6(1)	3(1)
C(22)	30(1)	33(2)	26(1)	1(1)	9(1)	4(1)
C(23)	24(1)	30(2)	28(1)	0(1)	2(1)	2(1)
C(24)	55(2)	20(1)	52(2)	0(1)	14(2)	0(1)
C(25)	56(2)	32(2)	46(2)	2(1)	15(2)	7(1)
O(1)	49(1)	22(1)	34(1)	1(1)	13(1)	1(1)
O(2)	69(1)	39(1)	30(1)	−9(1)	5(1)	8(1)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **171m**.

	x	y	z	U(eq)
H(4)	−353	3018	9144	38
H(5)	−2006	3087	8618	47
H(6)	−2748	1866	7333	55
H(7)	1819	627	6572	47
H(9)	−214	−256	6417	37
H(10)	1452	−299	6890	35
H(12)	3317	−71	7706	35
H(14)	5133	−172	8017	40
H(15)	6637	623	8823	47
H(16)	6785	2244	10012	48
H(17)	5433	3042	10408	42
H(19)	3613	3072	10147	32
H(22A)	1942	1736	10533	44
H(22B)	1736	125	9962	44
H(22C)	872	1290	10035	44
H(24A)	1326	7506	8344	51
H(24B)	1500	7351	9310	51
H(25A)	−301	6738	8146	66
H(25B)	−62	8367	8703	66
H(25C)	−127	6596	9111	66

Appendix 2.3: X-ray crystal data for biaryl **242a**

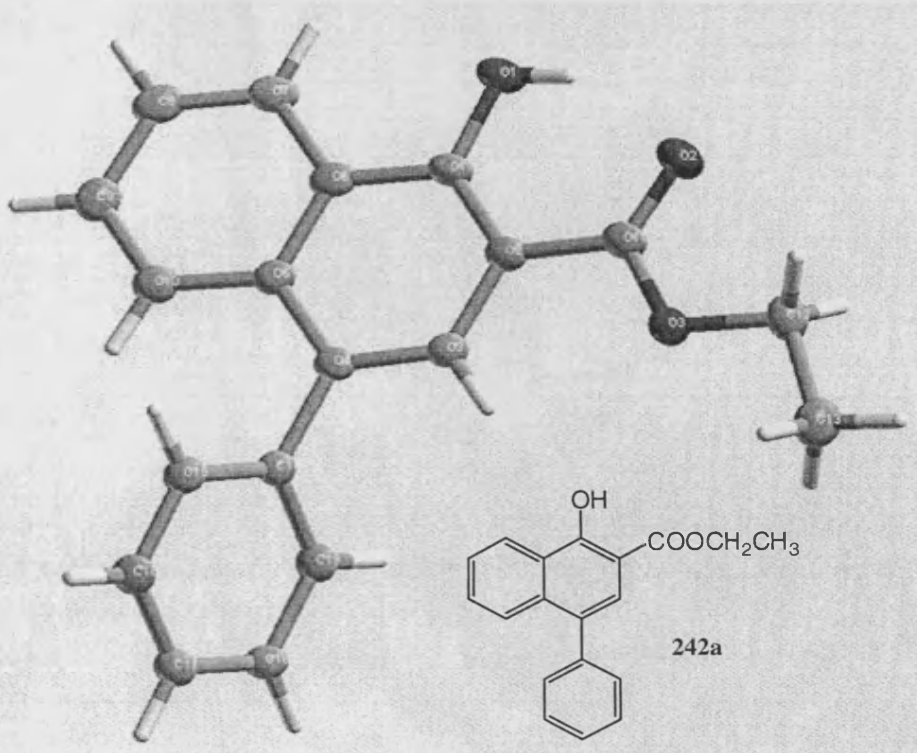


Table 11. Crystal data and structure refinement for **242a**: CCDC-760701 contains the supplementary crystallographic data for **242a**. These data can be obtained free of charge via www.ccdc-.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB21 EZ, UK.

Empirical formula	$C_{19}H_{16}O_3$	
Formula weight	292.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 5.8790(2) Å	α = 90°
	b = 21.0830(11) Å	β = 92.597(3)°
	c = 11.9310(5) Å	γ = 90°
Volume	1477.29(11) $Å^3$	
Z	4	
Density (calculated)	1.314 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	616	
Crystal size	0.40 x 0.08 x 0.08 mm^3	
Theta range for data collection	2.58 to 27.11°	
Index ranges	−7<=h<=7,−24<=k<=26,	

	−15<=l<=15
Reflections collected	5468
Independent reflections	3216 [R(int) = 0.0513]
Completeness to theta = 27.11°	98.6 %
Absorption correction	Empirical
Max. and min. transmission	0.9930 and 0.9655
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3216 / 0 / 202
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1327
R indices (all data)	R1 = 0.1041, wR2 = 0.1529
Extinction coefficient	0.044(6)
Largest diff. peak and hole	0.226 and −0.219 e.$Å^{-3}$

Table 12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4475(4)	1828(1)	2863(2)	32(1)
C(2)	3115(3)	1405(1)	2252(2)	31(1)
C(3)	3660(3)	751(1)	2287(2)	31(1)
C(4)	5518(3)	518(1)	2880(2)	29(1)
C(5)	6982(3)	953(1)	3501(2)	29(1)
C(6)	6443(4)	1612(1)	3500(2)	32(1)
C(7)	7880(4)	2038(1)	4118(2)	38(1)
C(8)	9784(4)	1823(1)	4700(2)	41(1)
C(9)	10329(4)	1176(1)	4705(2)	39(1)
C(10)	8951(4)	751(1)	4122(2)	34(1)
C(11)	1152(4)	1639(1)	1580(2)	33(1)
C(12)	−1980(4)	1387(1)	326(2)	39(1)
C(13)	−2970(4)	799(1)	−218(2)	45(1)
C(14)	5971(3)	−179(1)	2870(1)	29(1)
C(15)	7895(3)	−431(1)	2393(2)	33(1)
C(16)	8222(3)	−1083(1)	2349(2)	34(1)
C(17)	6641(3)	−1489(1)	2783(2)	34(1)
C(18)	4730(4)	−1247(1)	3267(2)	34(1)
C(19)	4396(4)	−594(1)	3308(2)	32(1)
O(1)	4052(3)	2459(1)	2887(1)	42(1)
O(2)	596(3)	2199(1)	1513(1)	43(1)
O(3)	−5(2)	1185(1)	1015(1)	36(1)

Table 13. Bond lengths [Å] and angles [°].

C(1)-O(1)	1.354(2)	O(1)-C(1)-C(2)	122.85(18)
C(1)-C(2)	1.383(3)	O(1)-C(1)-C(6)	116.55(17)
C(1)-C(6)	1.430(3)	C(2)-C(1)-C(6)	120.60(18)
C(2)-C(3)	1.414(3)	C(1)-C(2)-C(3)	119.17(18)
C(2)-C(11)	1.461(3)	C(1)-C(2)-C(11)	119.67(18)
C(3)-C(4)	1.365(3)	C(3)-C(2)-C(11)	121.17(17)
C(3)-H(3)	0.9500	C(4)-C(3)-C(2)	122.76(18)
C(4)-C(5)	1.440(3)	C(4)-C(3)-H(3)	118.6
C(4)-C(14)	1.494(3)	C(2)-C(3)-H(3)	118.6
C(5)-C(10)	1.411(3)	C(3)-C(4)-C(5)	118.89(18)
C(5)-C(6)	1.425(3)	C(3)-C(4)-C(14)	119.27(17)
C(6)-C(7)	1.418(3)	C(5)-C(4)-C(14)	121.84(16)
C(7)-C(8)	1.368(3)	C(10)-C(5)-C(6)	118.13(17)
C(7)-H(7)	0.9500	C(10)-C(5)-C(4)	122.40(18)
C(8)-C(9)	1.401(3)	C(6)-C(5)-C(4)	119.47(17)
C(8)-H(8)	0.9500	C(7)-C(6)-C(5)	119.39(19)
C(9)-C(10)	1.375(3)	C(7)-C(6)-C(1)	121.51(18)
C(9)-H(9)	0.9500	C(5)-C(6)-C(1)	119.09(17)
C(10)-H(10)	0.9500	C(8)-C(7)-C(6)	120.5(2)
C(11)-O(2)	1.227(2)	C(8)-C(7)-H(7)	119.8
C(11)-O(3)	1.338(2)	C(6)-C(7)-H(7)	119.8
C(12)-O(3)	1.456(2)	C(7)-C(8)-C(9)	120.50(19)
C(12)-C(13)	1.504(3)	C(7)-C(8)-H(8)	119.7
C(12)-H(12A)	0.9900	C(9)-C(8)-H(8)	119.7
C(12)-H(12B)	0.9900	C(10)-C(9)-C(8)	120.2(2)
C(13)-H(13A)	0.9800	C(10)-C(9)-H(9)	119.9
C(13)-H(13B)	0.9800	C(8)-C(9)-H(9)	119.9
C(13)-H(13C)	0.9800	C(9)-C(10)-C(5)	121.3(2)
C(14)-C(19)	1.393(3)	C(9)-C(10)-H(10)	119.3
C(14)-C(15)	1.394(3)	C(5)-C(10)-H(10)	119.3
C(15)-C(16)	1.390(3)	O(2)-C(11)-O(3)	121.85(18)
C(15)-H(15)	0.9500	O(2)-C(11)-C(2)	124.19(18)
C(16)-C(17)	1.381(3)	O(3)-C(11)-C(2)	113.96(17)
C(16)-H(16)	0.9500	O(3)-C(12)-C(13)	106.65(17)
C(17)-C(18)	1.384(3)	O(3)-C(12)-H(12A)	110.4
C(17)-H(17)	0.9500	C(13)-C(12)-H(12A)	110.4
C(18)-C(19)	1.391(3)	O(3)-C(12)-H(12B)	110.4
C(18)-H(18)	0.9500	C(13)-C(12)-H(12B)	110.4
C(19)-H(19)	0.9500	H(12A)-C(12)-H(12B)	108.6
O(1)-H(1)	0.8400	C(12)-C(13)-H(13A)	109.5

C(12)-C(13)-H(13B)	109.5	C(15)-C(16)-H(16)	119.9
H(13A)-C(13)-H(13B)	109.5	C(16)-C(17)-C(18)	120.10(18)
C(12)-C(13)-H(13C)	109.5	C(16)-C(17)-H(17)	119.9
H(13A)-C(13)-H(13C)	109.5	C(18)-C(17)-H(17)	119.9
H(13B)-C(13)-H(13C)	109.5	C(17)-C(18)-C(19)	119.82(19)
C(19)-C(14)-C(15)	118.60(18)	C(17)-C(18)-H(18)	120.1
C(19)-C(14)-C(4)	119.56(18)	C(19)-C(18)-H(18)	120.1
C(15)-C(14)-C(4)	121.79(17)	C(18)-C(19)-C(14)	120.76(19)
C(16)-C(15)-C(14)	120.60(19)	C(18)-C(19)-H(19)	119.6
C(16)-C(15)-H(15)	119.7	C(14)-C(19)-H(19)	119.6
C(14)-C(15)-H(15)	119.7	C(1)-O(1)-H(1)	109.5
C(17)-C(16)-C(15)	120.11(19)	C(11)-O(3)-C(12)	116.77(15)
C(17)-C(16)-H(16)	119.9		

Symmetry transformations used to generate equivalent atoms.

Table 14. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	40(1)	22(1)	34(1)	−1(1)	4(1)	−1(1)
C(2)	34(1)	25(1)	34(1)	−1(1)	5(1)	0(1)
C(3)	32(1)	27(1)	33(1)	−2(1)	3(1)	−3(1)
C(4)	30(1)	26(1)	31(1)	2(1)	5(1)	1(1)
C(5)	32(1)	28(1)	28(1)	0(1)	5(1)	−4(1)
C(6)	38(1)	30(1)	29(1)	0(1)	5(1)	−7(1)
C(7)	50(1)	30(1)	34(1)	0(1)	2(1)	−6(1)
C(8)	49(1)	39(1)	33(1)	−2(1)	−1(1)	−13(1)
C(9)	37(1)	45(1)	33(1)	1(1)	−3(1)	−5(1)
C(10)	38(1)	33(1)	32(1)	1(1)	1(1)	−2(1)
C(11)	38(1)	27(1)	36(1)	0(1)	6(1)	2(1)
C(12)	38(1)	44(1)	36(1)	3(1)	−4(1)	5(1)
C(13)	45(1)	54(2)	37(1)	2(1)	−5(1)	−2(1)
C(14)	30(1)	27(1)	29(1)	1(1)	−3(1)	−1(1)
C(15)	31(1)	32(1)	36(1)	1(1)	1(1)	−2(1)
C(16)	34(1)	32(1)	36(1)	−3(1)	2(1)	2(1)
C(17)	38(1)	28(1)	35(1)	−2(1)	−5(1)	2(1)
C(18)	37(1)	28(1)	38(1)	3(1)	−1(1)	−5(1)
C(19)	32(1)	31(1)	35(1)	−1(1)	1(1)	1(1)
O(1)	54(1)	22(1)	50(1)	−1(1)	−4(1)	1(1)
O(2)	49(1)	29(1)	50(1)	0(1)	−3(1)	7(1)
O(3)	36(1)	30(1)	42(1)	−1(1)	−5(1)	2(1)

Table 15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(3)	2693	463	1882	37
H(7)	7518	2477	4128	46
H(8)	10744	2114	5103	49
H(9)	11653	1030	5113	46
H(10)	9332	313	4138	41
H(12A)	−1522	1692	−252	47
H(12B)	−3112	1593	795	47
H(13A)	−1821	595	−666	68
H(13B)	−4293	913	−705	68
H(13C)	−3443	504	364	68
H(15)	8992	−155	2095	39
H(16)	9536	−1250	2019	41
H(17)	6867	−1935	2749	40
H(18)	3648	−1526	3571	41
H(19)	3079	−430	3638	39
H(1)	2914	2542	2461	63

List of Publications

1. "Diselenides and Disulfide Mediated Efficient Synthesis of Isocoumarins"
   S. A. Shahzad, C. Venin, T. Wirth, *Eur. J. Org. Chem.* **2010**, 3465–3472.

2. "Selenium-Mediated Synthesis of Biaryls through Rearrangement"
   S. A. Shahzad, C. Vivant, T. Wirth, *Org. Lett.* **2010**, *12*, 1364–1367.

3. "Fast Synthesis of Benzofluorenes by Selenium Mediated Carbocyclizations"
   S. A. Shahzad, T. Wirth, *Angew. Chem.* **2009**, *121*, 2626–2628; *Angew. Chem. Int. Ed.* **2009**, *48*, 2588–2591.

4. "Recent Advances in Organoselenium Chemistry"
   D. M. Freudendahl, **S. A. Shahzad**, T. Wirth, *Eur. J. Org. Chem.* **2009**, 1649–1664.

5. "Green Chemistry with Selenium Reagents: Development of Efficient Catalytic Reactions"
   D. M. Freudendahl, S. Santoro, **S. A. Shahzad**, C. Santi, T. Wirth, *Angew. Chem.* **2009**, *125*, 8559–8562; *Angew. Chem. Int. Ed.* **2009**, *48*, 8409–8411.

6. "Dimethylaluminum Methylselenolate"
   S. A. Shahzad, T. Wirth, *Electronic Encyclopedia of Reagents for Organic Synthesis*, Ed. L. A. Paquette, John Wiley & Sons, **2009**.

7. "Diphenylselenium Bis(trifluoroacetate)"
   S. A. Shahzad, T. Wirth, *Electronic Encyclopedia of Reagents for Organic Synthesis*, Ed. L. A. Paquette, John Wiley & Sons, **2008**.