

Chapter 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: cannabins 48, isolated from the fruits of *Cannabis sativa* [1]. 6,7-dehydrosempervivrol 49 [2], isolated from the roots of *Salvia apiana* and negundin B 50 [3], 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 [4–6]. Dihydronaphthalene derivatives are used as fluorescent ligands for the estrogen receptor [7] and exhibit activity as Hepatitis C NS5B polymerase inhibitors [8]. Recently, dihydronaphthalenes were found to be potent and selective inhibitors of aldosterone synthase (CYP11B2) for the treatment of congestive heart failure and myocardial fibrosis Fig. 2.1 [9].

As dihydronaphthalene derivatives are useful starting materials for the synthesis of biologically active cyclic molecules [10], numerous traditional synthetic approaches to these compounds have been reported [11–13, 45]. Among them the dearomatization of naphthalene derivatives by the nucleophilic addition of certain organometallic reagents is one of the most useful and convenient methods [14–18]. 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 [7, 19–27]. They can undergo bromination [28], cyclopropanation [29, 30], dipolar cycloaddition [31, 32] and epoxidation [33] reactions to afford

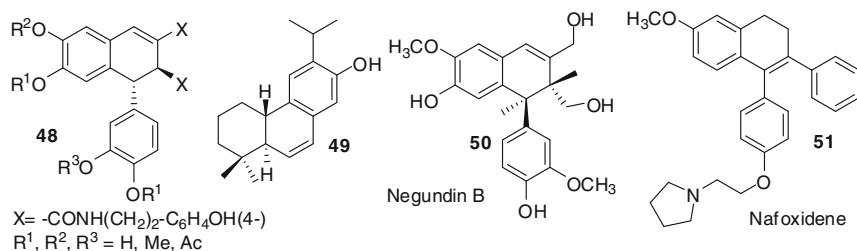
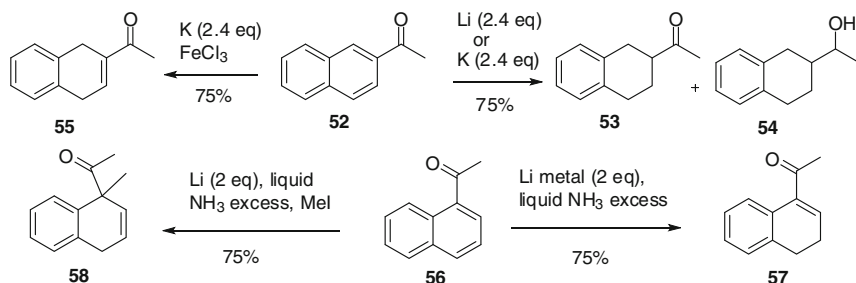


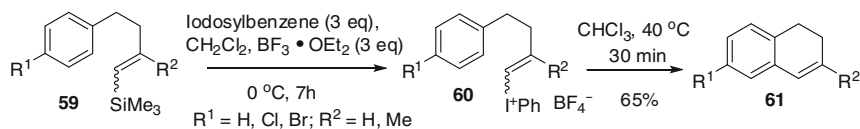
Fig. 2.1 Dihydronaphthalene natural products



Scheme 2.1 The Birch reduction

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 [34, 35]. The conversion of α - and β -tetralone into dihydronaphthalenes was accomplished by palladium-catalysed coupling of Grignard reagents with in situ-generated enol phosphates [36]. The gold(I)-catalysed intramolecular rearrangement of vinylidenecyclopropanes also gives dihydronaphthalenes [37]. The metal-ammonia reduction of naphthalene and its derivatives has also been extensively investigated [38, 39]. 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 2.1) [40]. However, anhydrous ferric chloride has been found to limit the reduction to the dihydro-stage with 2-acetylnaphthalene.

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



Scheme 2.2 Hypervalent iodine-mediated synthesis of dihydronaphthalene **61**

0.5 h in a sealed tube and provided dihydronaphthalene **61** in 65 % yield (Scheme 2.2) [41].

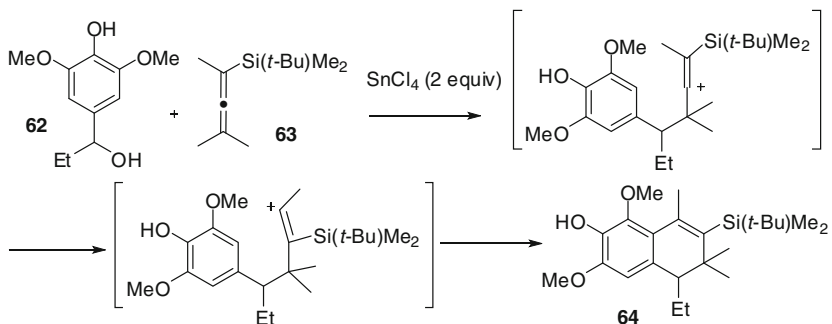
1,2-Dihydronaphthalenes can also be prepared in moderate yields from allenylsilanes and benzylic cations by a one-step intermolecular cyclisation. For example, treatment of alcohol **62** with an excess of allenylsilane **63** and 2.0 equivalents of tin(IV) chloride in dichloromethane at 0 °C afforded 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 2.3) [42].

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 2.4) [43].

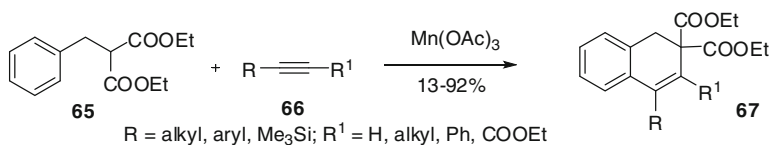
In 2002, Harrowven [44] reported the conversion of 4-arylalk-1-en-1-yl methyl ethers **68** to dihydronaphthalenes under catalytic reaction condition. Cyclisation is accomplished by warming a toluene solution of the substrate **68** with 1,2-ethanediol and catalytic *para*-toluenesulfonic acid at 80 °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 2.5).

Suzuki and co-workers [45] 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 2.6). 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.

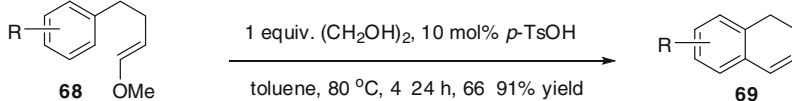
Yamamoto [46] described the preparation of 1,2-dihydronaphthalene **75** by the reaction of *o*-(alkynyl)benzaldehydes or *o*-(alkynyl)phenyl ketones **73** with olefins **74** using 10 mol % Cu(OTf)₂ at 80 °C in THF. This Cu(OTf)₂-catalysed cycloaddition reaction affords dihydronaphthalene derivatives **75** bearing a ketone



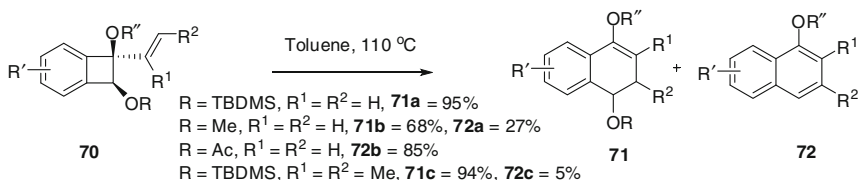
Scheme 2.3 Synthesis of dihydronaphthalene **64** from benzylic alcohol **62**



Scheme 2.4 Manganese mediated synthesis of dihydronaphthalene **67**



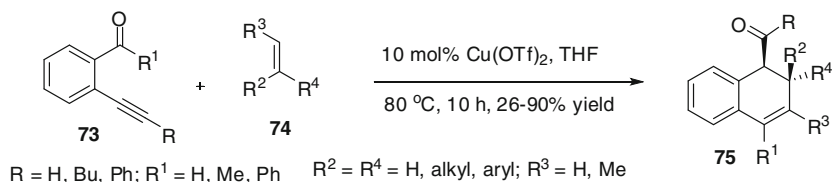
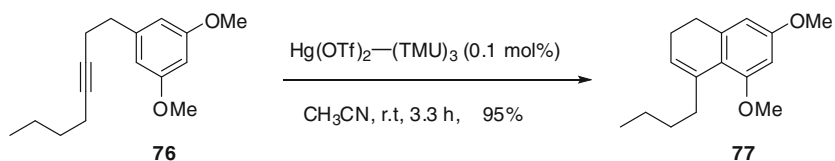
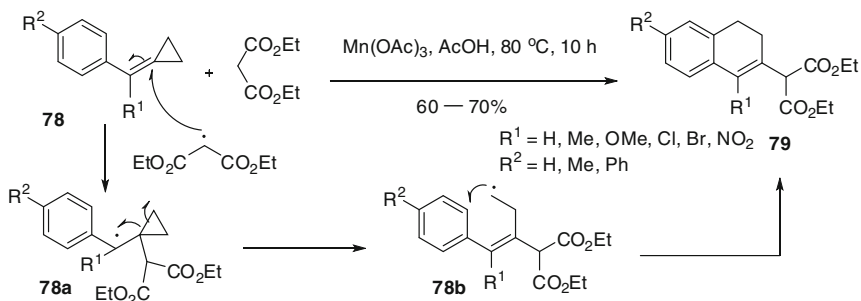
Scheme 2.5 Acid-catalysed cyclisation of **68** to dihydronaphthalene **69**



Scheme 2.6 Thermal ring expansion of **70** into dihydronaphthalenes

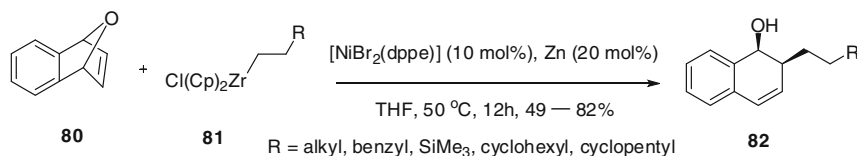
function at the 1-position in 26–90 % yields. The process is reasonably general with regard to the types of substituents on the olefin that can be employed and alkyne can also be used with a range of substitution patterns (Scheme 2.7).

The formation of dihydronaphthalene derivatives from ω -aryllalkyne **76** can be catalysed by the use of 0.1 mol % $\text{Hg}(\text{OTf})_2$ - $(\text{TMU})_3$ ($\text{TMU} = \text{tetramethylurea}$) 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 2.8) [47].

**Scheme 2.7** Cu(OTf)_2 -catalysed [4 + 2] cycloaddition of *o*-alkynylbenzenes with alkenes**Scheme 2.8** Mercuric triflate-(TMU)₃-catalysed cyclisation of ω-aryllalkyne**Scheme 2.9** Manganese acetate mediated free-radical cyclisation reaction of alkylencyclopropanes

Chen and co-workers [48] 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 2.9).

The regio- and stereoselective ring-opening addition of alkyl- or allylzirconium reagents to 7-oxabenzonorbornadienes **80** as described in Scheme 2.10 is catalysed by 10 mol % $\text{NiBr}_2(\text{dppe})$ and 20 mol % Zn powder in dry THF at $50 \text{ }^\circ\text{C}$ [49]. 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



Scheme 2.10 Synthesis of dihydronaphthalene **82** by nickel-catalysed addition of alkyl zirconium reagents **81** to oxabenzonorbornadienes

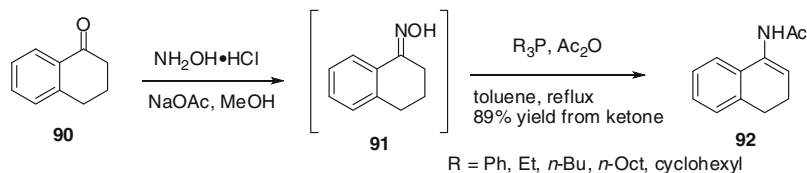
initial coordination of 7-oxabenzonorbornadiene (via the *exo* face of the carbon-carbon double bond) to the Ni center in **81b** followed by the addition of the organonickel species into the double bond resulting in the formation of intermediate **81c**. Subsequent β -oxy elimination leads to intermediate **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 2.11).

Ichikawa and co-workers [50] 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 $\text{Me}_3\text{SiB}(\text{OTf})_4$]. 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 -fluorocarocation **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 2.12).

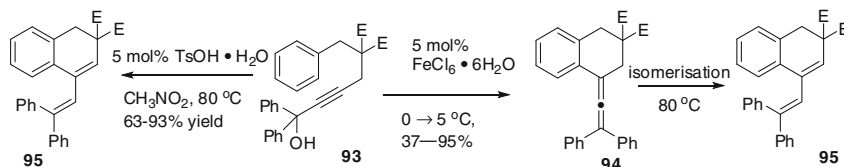
Alternatively, 1,2-disubstituted-3,4-dihydronaphthalenes **89** are formed in 36–90 % yields by the cycloaddition reaction of vinylarenes **87** with electron-deficient alkynes **88** such as diethyl acetylenedicarboxylate and methyl phenylpropiolate [51]. These reactions were conducted at 110 °C in the presence of DMF-DMA (*N,N*-dimethylformamide dimethyl acetal) as an organocatalyst (Scheme 2.13). This organocatalysed methodology exhibits the advantages of substrate versatility and mild reaction conditions.

A new synthesis of dihydronaphthalene from α -tetralone was disclosed by Singh and co-workers [52]. 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 2.14) [52].

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 [53]. 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



Scheme 2.14 Synthesis of dihydronaphthalene **92** from α -tetralone **90**

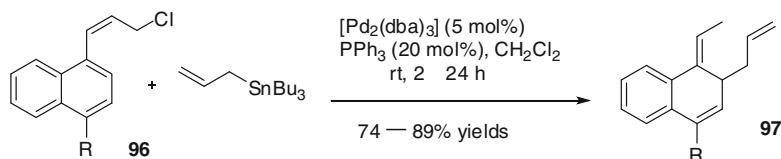


Scheme 2.15 Synthesis of **95** from aryl-substituted propargylic alcohols **93**

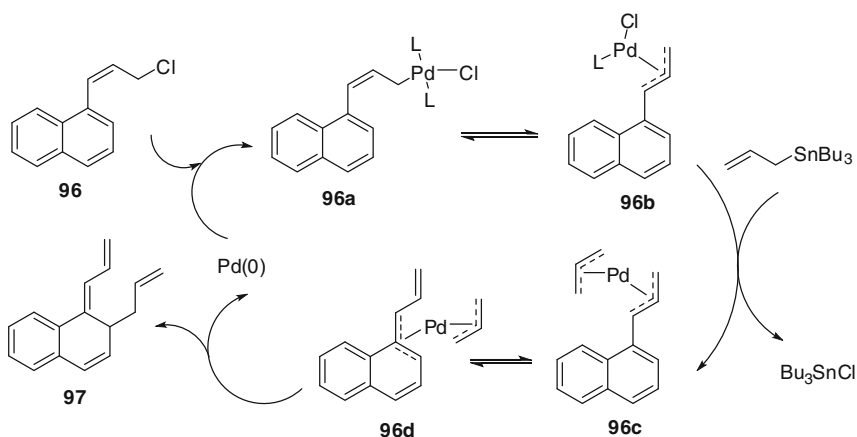
intramolecular Friedel–Crafts reaction followed by successive isomerisation in moderate to excellent yields, depending on the nucleophilicity of the aryl nucleus involved and the nature of substituents at the propargylic position. Selective preparation of **95** could be achieved by using $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ 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 $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ at 80 °C (Scheme 2.15).

A range of dihydronaphthalenes was accomplished by the palladium-catalysed de-aromatisation reaction of naphthalene derivatives with allyltributylstannane (Scheme 2.16) [54]. The allylative de-aromatisation reactions of naphthalene derivatives **96** with allyltributylstannane have been performed in the presence of $[\text{Pd}_2(\text{dba})_3]$ (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 2.17).

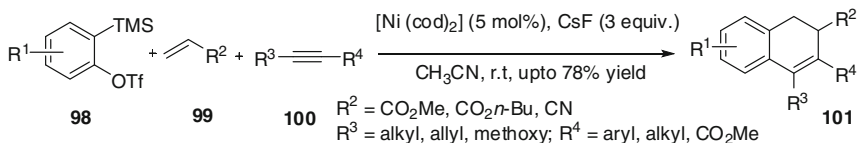
Nickel can efficiently catalyse the cyclisation of alkenes, and alkynes to afford a series of substituted dihydronaphthalenes that cannot be prepared from the readily available starting materials [55]. In 2009, Xie and Qiu described the preparation of wide range of dihydronaphthalenes in good yields from nickel-catalysed three-component [2 + 2 + 2] carboannulation reaction of arynes, activated alkenes, and alkynes [56]. This work offers an exceptionally efficient route to 1,2-dihydronaphthalenes from readily available starting materials. Various alkynes were



Scheme 2.16 Synthesis of **97** by palladium-catalysed de-aromatisation of naphthalene derivatives with allyltributylstannane



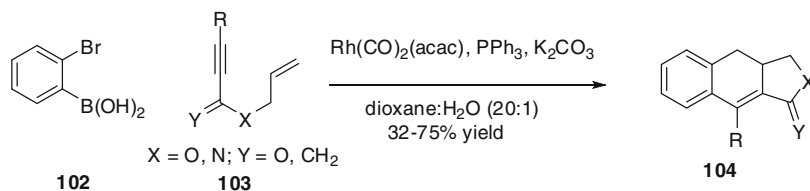
Scheme 2.17 Mechanism for the de-aromatisation of **96** (all charges are omitted)



Scheme 2.18 Nickel-catalysed synthesis of **101** via a multi-component reaction

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 % $[\text{Ni}(\text{cod})_2]$ 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 2.18).

In 2009, the rhodium-catalysed reaction of 1,6-enynes **103** with 2-bromophenylboronic acids **102** has been utilized by Tong et al. [57]. To construct a multi-substituted dihydronaphthalene scaffold. A screen of reaction conditions revealed that 5 mol % $\text{Rh}(\text{CO})_2(\text{acac})$, triphenylphosphine, potassium carbonate in a dioxane and water mixture at 100 °C for 3–5 h afforded dihydronaphthalene



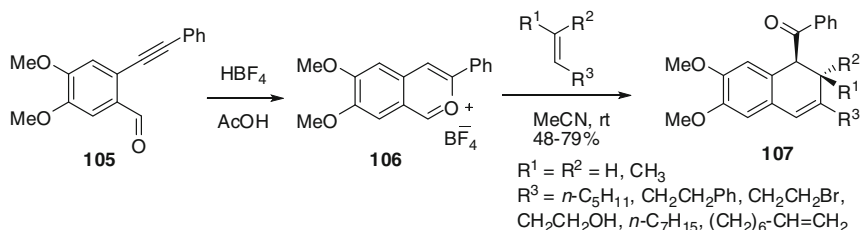
Scheme 2.19 Rhodium-catalysed synthesis of dihydronaphthalene scaffold **104**

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 2.19).

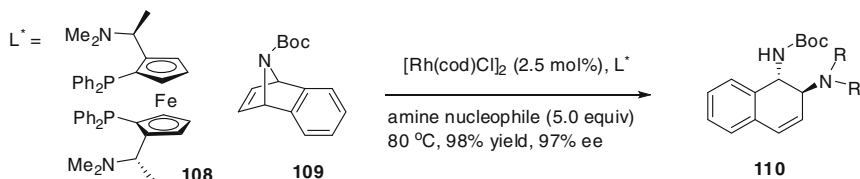
In 2009, Yao and co-workers [58] exploited scope of isochromenylium tetrafluoroborates as precursors of various dihydronaphthalenes. Direct metal-free treatment of isochromenylium tetrafluoroborate **106** with alkenes in acetonitrile at either 25 or 60 °C afforded a diverse range of dihydronaphthalenes **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 2.20).

In an attempt to induce chirality on dihydronaphthalene ring systems, Cho and co-workers used chiral (S,S') - (R,R') -C₂-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 2.21) [59].

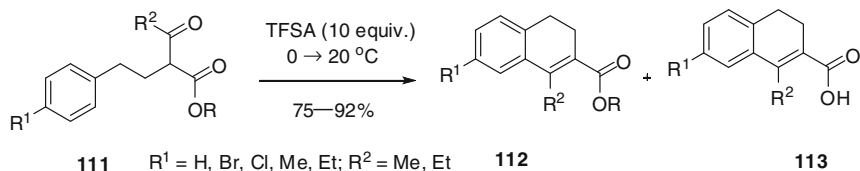
In 2010, Ohwada and co-workers [60] disclosed the acid-catalysed cyclisation of arylacetoacetates to afford 3,4-dihydronaphthalene derivatives in Brønsted superacids. For example, methyl 2-aceto-4-phenylbutyrate **111** underwent the cyclisation in the presence of 10 equivalents trifluoromethyl sulfonic 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 2.22) [60].



Scheme 2.20 Synthesis of **107** from isochromenylium tetrafluoroborate **106**



Scheme 2.21 Rhodium-catalysed synthesis of **110** using ferrocene ligands



Scheme 2.22 Synthesis of dihydronaphthalenes 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 [61–65], kinafluorenone **114** [66], stealthins [67] **115**, kinobscurinone [68], seongomycin [69] and cysfluoretin [70] (Fig. 2.2) 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* [67] 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 [71, 72]. Benzofluorenes found application as estrogen receptor antagonists [73] and have utility in blue organic electroluminescent devices [74].

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 [65, 75–85] and non-natural [45, 86–90, 97] aromatic benzo[*b*]fluorenes have been developed.

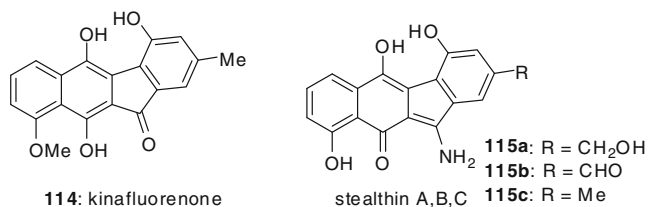
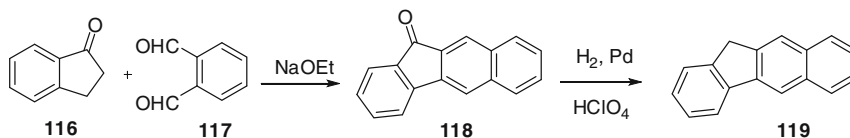


Fig. 2.2 Benzofluorene-based natural products



Scheme 2.23 The synthesis of benzofluorene **119** by condensation of **116** and **117**

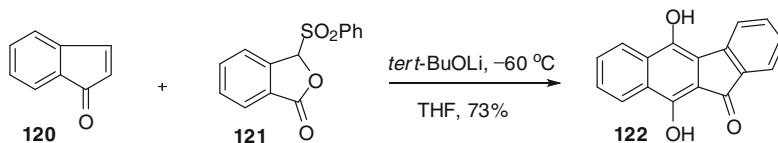
Typically, methods based on [4 + 2] cycloaddition, Suzuki coupling, oxidative free radical cyclisation or Heck coupling have been employed.

In 1980, Bestmann described the preparation of 11*H*-benzo[*b*]fluorenone **118** by the reaction of hexaphenylcarbodiphosphorane with phthalaldehyde [91, 92]. An alternative approach towards the 11*H*-benzo[*b*]fluorenone and related benzofluorenes was also reported by Streitwieser (Scheme 2.23). 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** [93].

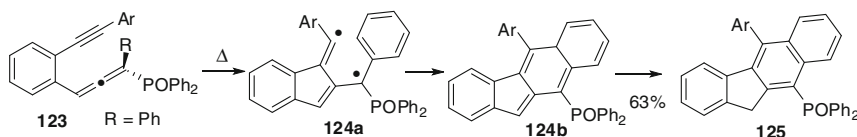
An alternative strategy targeting the Kinafluorenone scaffold was reported by Mal [94] in their formal synthesis of Kinamycin antibiotics. Treatment of the phthalide sulfone anion, prepared by deprotonation of **121** by *tert*-BuOLi at -60 °C, with a solution of **121** in THF, followed by acidic work-up resulted in a red amorphous solid of quinol **122** in 73 % yield (Scheme 2.24).

The thermal cyclisation of enyne allenes **123** to the corresponding benzofluorene **125** has been described by Schmittel and co-workers (Scheme 2.25). 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 C₂–C₆ cyclisation, giving rise to formal ene and Diels–Alder products **125** via an unexpected biradical intermediate **124a** as depicted in Scheme 2.25. 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 [95].

Echavarren and co-workers [96] demonstrated the cyclisation of trimethylsilyl alkynes connected to allenes by preferential [4 + 2] cycloaddition to form



Scheme 2.24 Synthesis of benzofluorenone by annulation of indenone **120** with phthalide sulfone **122**



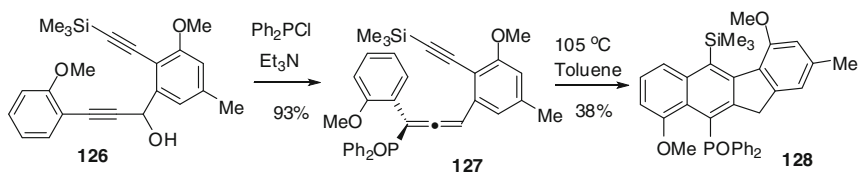
Scheme 2.25 Synthesis of benzofluorene **125** by intramolecular Diels–Alder reaction of enyne allenes **123**

tetracyclic derivatives. Phosphorylation of **126** with Ph_2PCl and Et_3N followed by [2, 3] sigmatropic rearrangement under typical reaction conditions (THF, -70 to $-40\text{ }^\circ\text{C}$) 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 2.26).

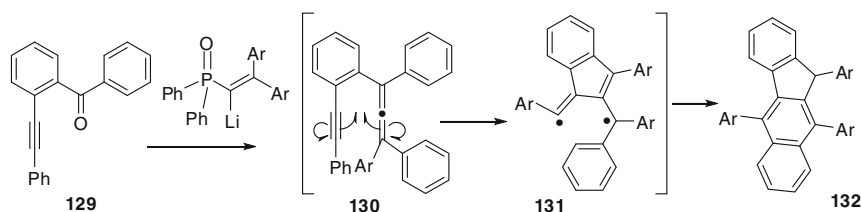
The use of the thermally-induced isomerisation reactions of organic molecules to generate the carbon-centered biradicals has several potential advantages over the conventional chemical or photochemical methods. This chemistry was subsequently employed for the synthesis of benzofluorenes by Wang and co-workers [97]. 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 2.27.

Domínguez and Saá [98] 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 2.28).

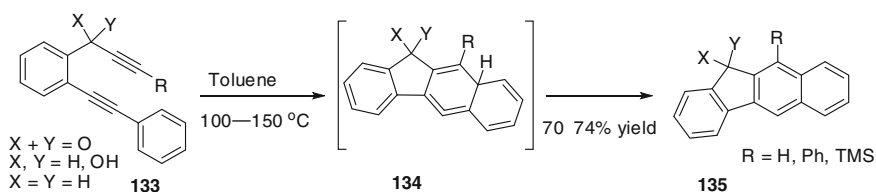
The Sonogashira reaction between 2-ethynyl-2'-methoxy-1,1'-In an attempt to induce chirality-binaphthyl and 1-iodo-2-[(trimethylsilyl)ethynyl]benzene and



Scheme 2.26 The synthesis of **128** by an arylalkyne-allene cycloaddition

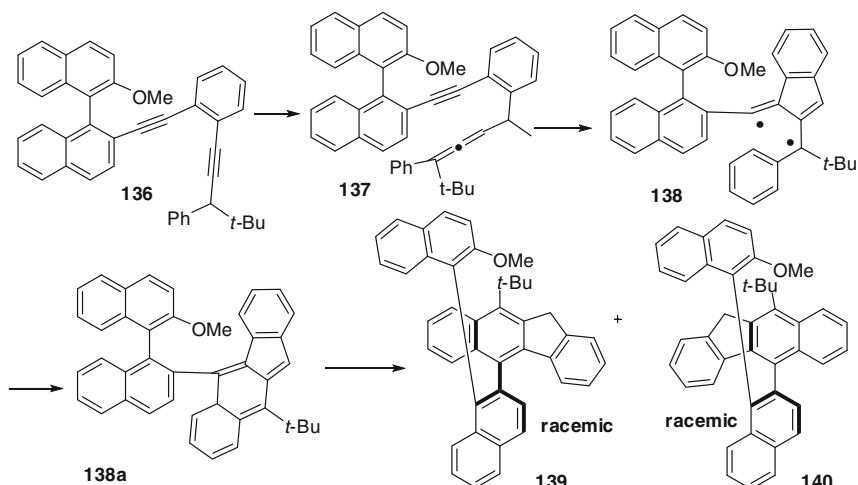


Scheme 2.27 Thermolysis of benzoenyne-allenes to form biradicals and subsequent formation of benzofluorene **132**



Scheme 2.28 Synthesis of benzo[*b*]fluorene derivatives **135** by intramolecular [4 + 2] cycloaddition reactions of diarylacetylenes

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 2.29). A subsequent Schmitt 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 [99].

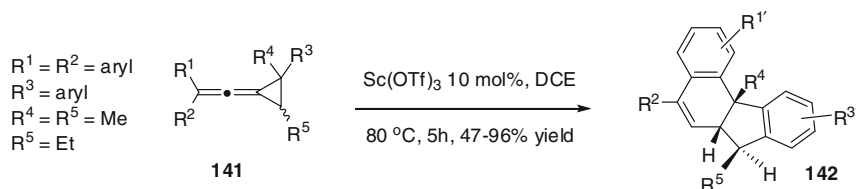


Scheme 2.29 Synthesis of the atropisomers of 2-(5-benzo[*b*]fluorenyl)-20-hydroxy-1,10-binaphthyl and related compounds

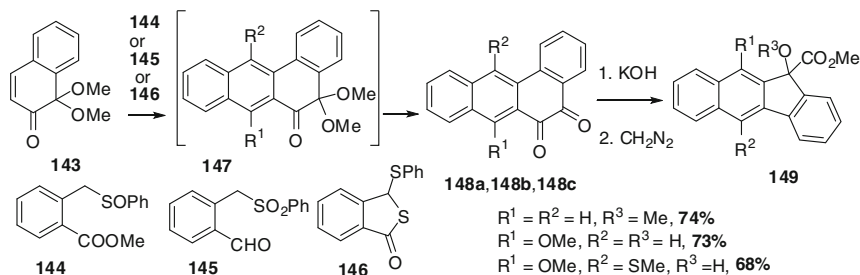
Shi and co-workers [100] reported the use of the aryl-substituted allenes of type **141** as precursors to naphthalene derivatives via interesting rearrangements. They have also shown that the Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes **141** is tolerant of substituents on the 1- and 2-positions of the cyclopropane ring in the synthesis of 6*aH*-benzo[*c*]fluorene. The treatment of arylvinylidenecyclopropanes **141** with 10 mol % scandium triflate in dry dichloroethane afforded 6*aH*-benzo[*c*]fluorene derivatives **142** in 47–96 % yields. The Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes of type **141** provides a useful route to 6*aH*-benzo[*c*]fluorene derivatives via a double intramolecular Friedel–Crafts reaction (Scheme 2.30).

Mal and co-workers [101] described the synthesis of several benzofluorenes and benzofluorenes 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 $-60\text{ }^{\circ}\text{C}$), 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 2.31). Subsequent conversion into benzo[*b*]fluorenone was also achieved by refluxing with chromium trioxide (CrO_3) in acetic acid.

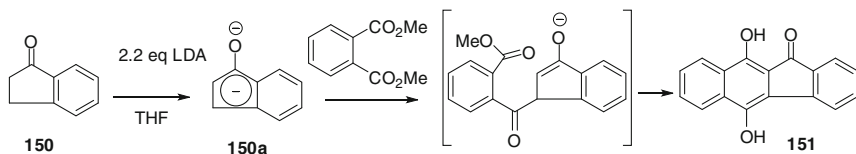
A rapid approach to benzo[*b*]fluorenes **151** via the reaction of 1-indanone dianions **150a** with phthalate diesters is described by Birman and co-workers [102]. In the same communication, Birman also reported a concise synthesis of



Scheme 2.30 Lewis acid-catalysed rearrangement of arylvinylidenecyclopropanes **141**



Scheme 2.31 Synthesis of benzo[*b*]fluorenes via ring contraction by benzil-benzic acid rearrangement of benz[*a*]anthracene-5,6-diones **148**

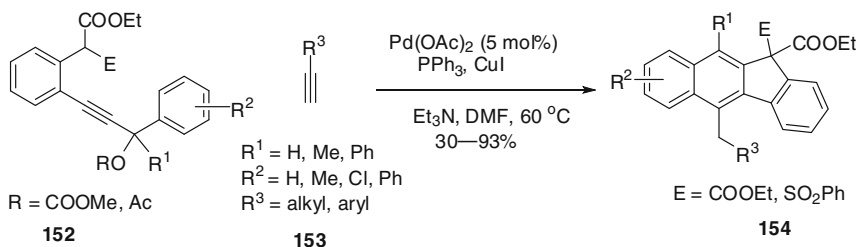


Scheme 2.32 Synthesis of benzo[*b*]fluorene **151** via indanone dianion annulation **150a**

prekinamycin and its unnatural analogues. This approach provides a convenient synthetic access to benzo[*b*]fluorene derivatives (Scheme 2.32).

Liang and co-workers [103] 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 2.33 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.

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



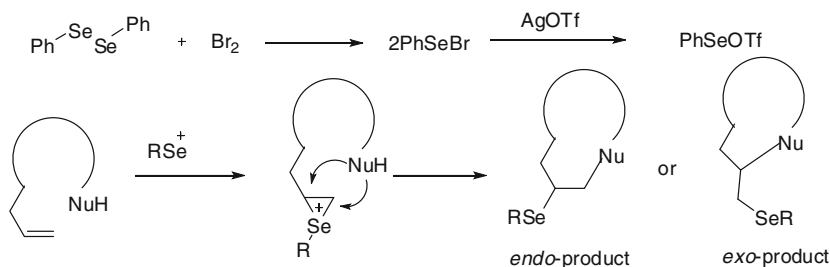
Scheme 2.33 Palladium-catalysed synthesis of benzofluorenes **154** from propargylic compounds with terminal alkynes via a biscyclisation process

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



Scheme 2.34 Activation of alkenes by a selenium electrophile and subsequent addition of an internal nucleophile

required for the substrate deprotonation. We felt that both of these problems could be resolved by employing an appropriate substrate (Scheme 2.34).

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 (Fig. 2.3).

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 electron 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 Fig. 2.4 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.

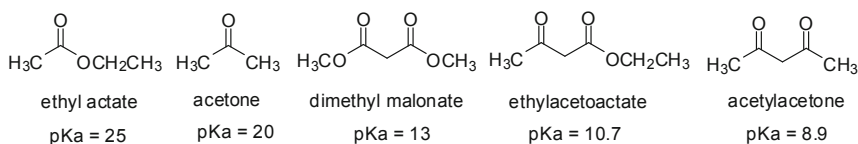


Fig. 2.3 pKa values of different carbonyl compounds

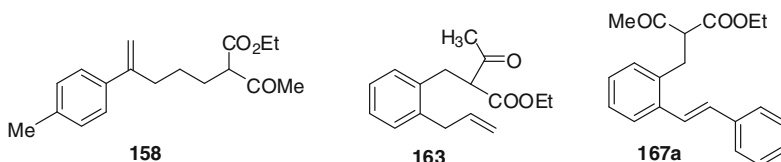


Fig. 2.4 Substrates bearing enolisable carbon that can act as a carbon nucleophile

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 (Fig. 2.4).

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 (Fig. 2.5).

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 compound to effect a double intramolecular cyclisation. The advancement of such methodologies should diminish the effort generally needed to access such structurally diverse molecules.

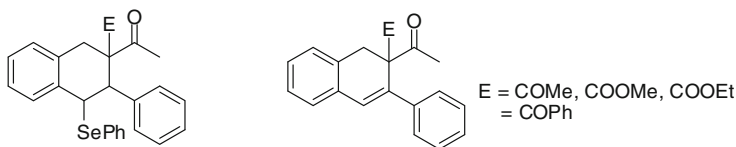
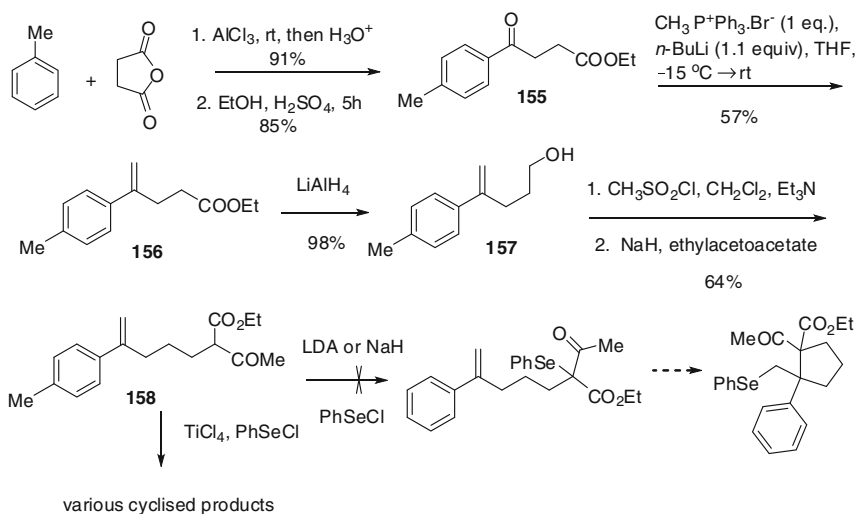


Fig. 2.5 Tetrahydronaphthalene and dihydronaphthalene derivatives



Scheme 2.35 Synthesis of **158** and subsequent attempts toward carbocyclisation

2.4 Results and Discussion

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

Literature procedures [104] were used for the synthesis of the substrate **158**. 4-(4'-Methylphenyl)-4-oxobutanoic acid ethyl ester **155** was prepared in good yield under Friedel–Crafts reaction conditions (Scheme 2.35). 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.

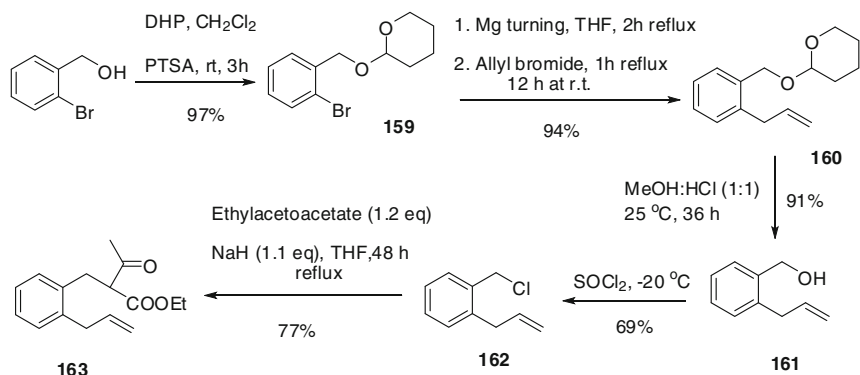
To test the reactivity of selenium for the proposed electrophilic carbocyclisation strategy, the reaction of the proposed substrate **158** with a selenium electrophile in dichloromethane at $-78\text{ }^{\circ}\text{C}$ was investigated. Exposure of the substrate to electrophiles without the addition 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, $-78\text{ }^{\circ}\text{C}$), 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 ^1H 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**

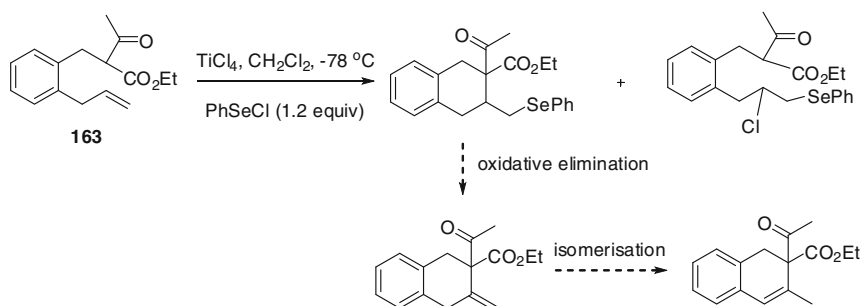
Our key task was the development of a carbocyclisation process for the synthesis of dihydronaphthalenes from alkenes containing carbon nucleophiles. The nature of the substrate **158** precludes its use in selenium-mediated cyclisation. However, substrate **163** is capable of being transformed into 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 dihydropyran 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 $\text{S}_{\text{N}}2$ 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 2.36).

We attempted to cyclise substrate **163** to tetrahydronaphthalene using titanium tetrachloride and phenylselenenyl chloride at $-78\text{ }^{\circ}\text{C}$ as described in Scheme 2.37 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 $-78\text{ }^{\circ}\text{C}$. In addition, phenylselenenyl triflate proved to be unsatisfactory for



Scheme 2.36 Synthesis of substrate **163**



Scheme 2.37 Attempts towards 6-*exo-trig* carbocyclisation

cyclisation under variety of conditions such as those shown in Scheme 2.37. However, all chosen reaction conditions failed to effect selective carbon–carbon bond formation. Some alternative conditions for this reaction, such as use of $\text{BF}_3 \cdot \text{OME}_2$ 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.

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 2.37). This may

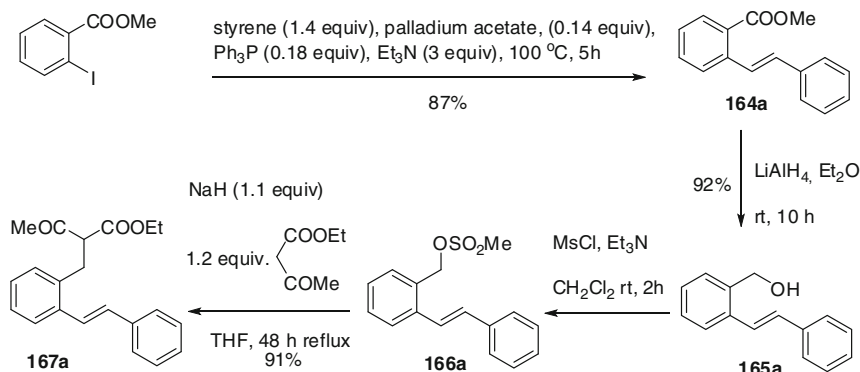
be because the substrate chain length is not appropriate to provide the selective formation of a six membered ring. In addition, the allyl group is more prone to form the addition product than cyclisation; however a mixture of products is formed from this substrate under various conditions. As a result it was not possible to synthesise benzoannulated products using selenium electrophiles.

2.4.4 Modification of Substrate and Successful Cyclisation

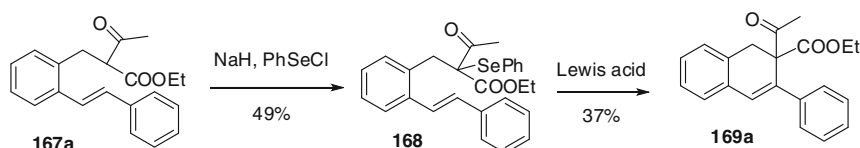
Unfortunately, problems were encountered with previous substrates **158** and **163** to effect carbocyclisation. It was decided that attention should be directed towards design of alternative substrates that may promote the desired reactions. Alkenes containing a functional group that can act as an 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 [105] of methyl 2-iodobenzoate with styrene, using palladium acetate [Pd(OAc)₂], triphenylphosphine (Ph₃P), and triethylamine at 100 °C for 5 h. The yield of this process is quite high and can readily accommodate considerable functionality (Scheme 2.38). 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 2.38).

The presence of an acetyl group lowering the pK_a 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 % yields 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



Scheme 2.38 Synthesis of target substrate **167a**



Scheme 2.39 New mode of carbocyclisation

forward (Scheme 2.39). The newly formed intermediate can be readily transformed into the cyclic product upon treatment with a Lewis acid as shown in Scheme 2.39. 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 2.1, entry 1).

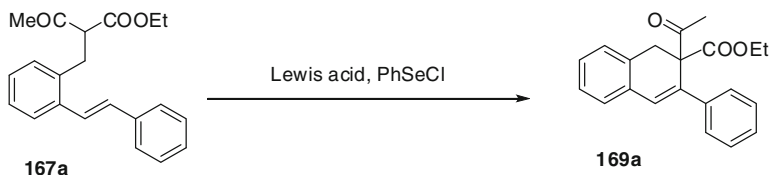
The cleavage of the selenium-carbon bond mediated by the Lewis acid could lead to the in situ formation of a selenium electrophile, which would subsequently activate the double bond for the carbocyclisation. Although the overall yields are quite low, the synthetic utility of this reaction could be markedly 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 2.40.

Table 2.1 Optimisation of reaction conditions

Entry	Substrate	Reagents	Time (h)	Yield (%)
	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 • OMe ₂ (2.0 equiv.), PhSeCl (1.1 equiv.)	22	90

**Scheme 2.40** Direct synthesis of dihydronaphthalene **169a** from **167a**

Treatment of stilbene substrate **167a** with phenylselenenyl chloride in the presence of TiCl₄ afforded dihydronaphthalene **169a** in 86 % yield via a cyclisation/elimination one-pot sequence without formation of the intermediate **168** as shown in Scheme 2.40 (Table 2.1, entry 4). The reaction was monitored by TLC, after 3 h stirring at -78 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 h. 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 2.39). 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 notprecedented. The cyclisation does not occur in the absence of the selenium electrophile and only starting material was recovered quantitatively (Table 2.1, entry 3). The combination of boron trifluoride dimethyl etherate and phenylselenenyl chloride (Table 2.1, 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 (Fig. 2.6, see detail in Appendix 2.1).

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

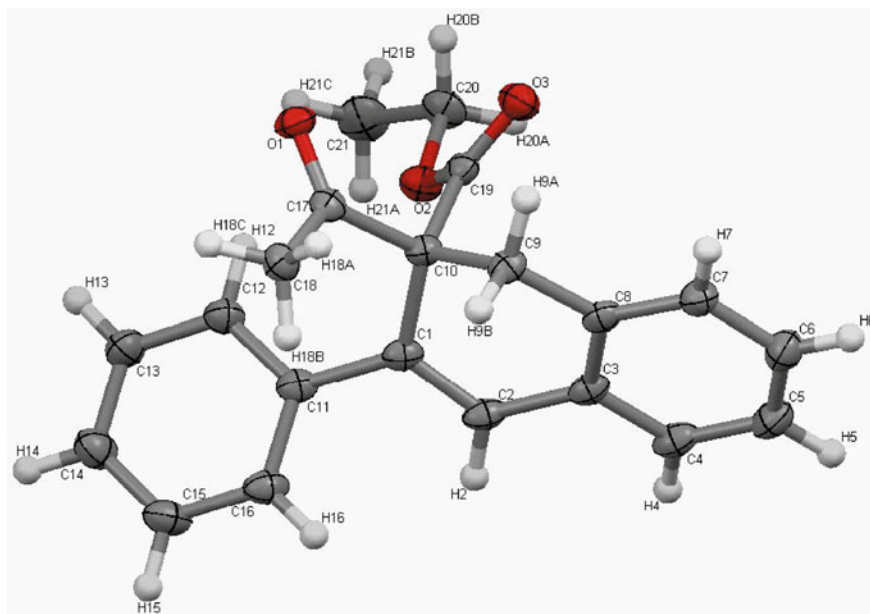
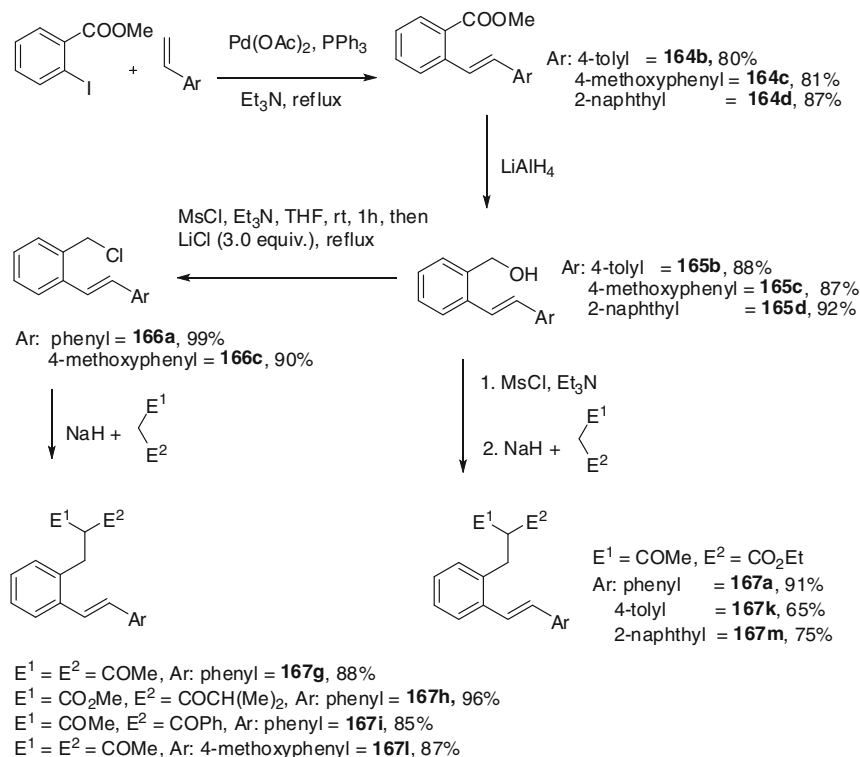


Fig. 2.6 Crystal structure of dihydronaphthalene **169a**

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 2.41). 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 2.41).

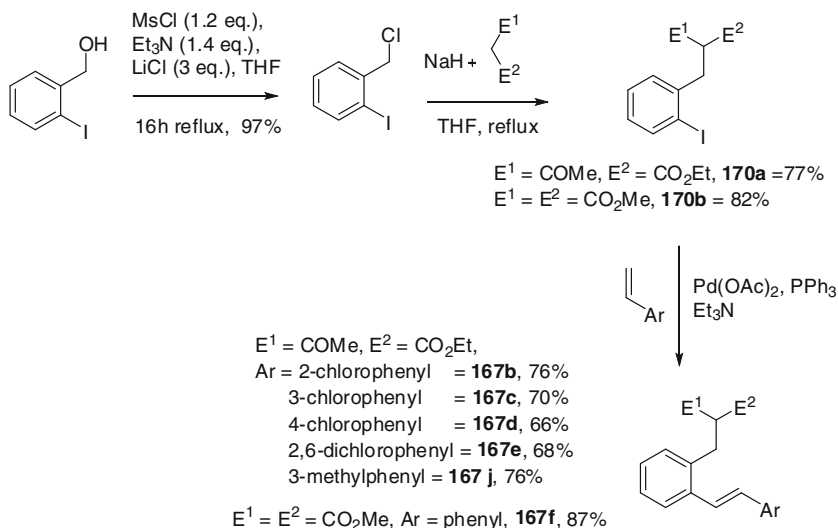
Further investigations regarding the synthesis of substrates were undertaken, and an easy synthetic route was started from 2-iodobenzyl alcohol, establishing another independent route to target substrates **167e**, **167f**, **167g**, **167h** and **167i** (Scheme 2.42). Conversion of 2-iodobenzyl alcohol to the corresponding chloride was achieved by treating the alcohol with MsCl in the presence of lithium chloride



Scheme 2.41 Synthesis of substrates **167**

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.

The stilbene substrates are then subjected to carbocyclisation, and the resulting dihydronaphthalene is generally isolated in good to excellent yields as shown in Table 2.2. For example, treatment of chlorosubstituted stilbene **167b** with 2.0 equivalents of Lewis acid and 1.2 equivalents of phenylselenenyl chloride at -78 °C, gave the corresponding dihydronaphthalene **169b** essentially as a single product in 74 % yield (Table 2.2, 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 2.2. Upon treatment of the diester-substituted stilbene **167f** with phenyl selenenyl chloride and $\text{BF}_3 \cdot \text{OMe}_2$, the standard protocol failed entirely to give the desired product (Table 2.2, entry 5). However, after exposure of stilbene **167f** to selenium electrophile under strong Lewis acid conditions for 36 h at room temperature, the corresponding dihydronaphthalene **169f** was isolated in 50 % yield along with 41 % recovery of starting



Scheme 2.42 Alternative synthetic route to substrates **167**

material (Table 2.2, 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 2.2, entry 5).

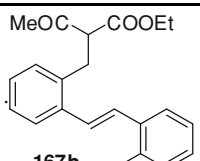
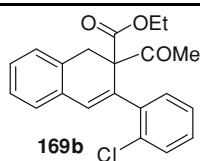
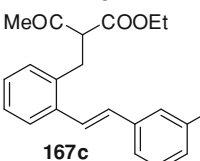
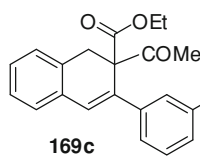
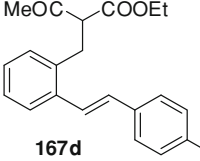
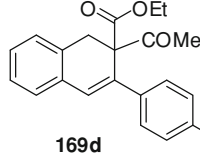
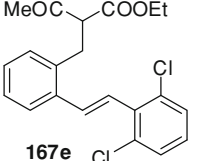
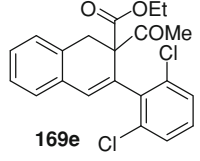
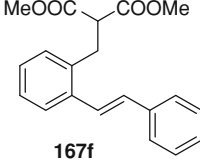
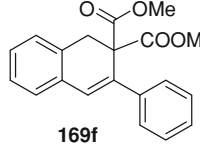
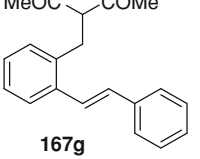
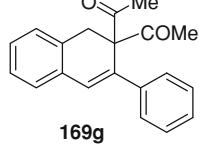
The diacetyl-substituted stilbene **167g** was found to be more reactive under the optimised reaction conditions and the reaction of the Ti-enolate derived from stilbene **167g** with phenyl selenenyl chloride resulted in the corresponding dihydronaphthalene **169g** within three hours reaction time in 73 % yield (Table 2.2, entry 6). Varying the Lewis acids SnCl_4 to TiCl_4 led to only a negligible increase in yield (Table 2.2, 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 2.43).

The carbocyclisation of stilbene **167i** with a bulky group using standard protocols proved troublesome at first; however by maintaining the reaction temperature at $-78\text{ }^\circ\text{C}$ for 1 h the corresponding dihydronaphthalene was formed in 59 % yield (Scheme 2.44). 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.

An interesting feature of this approach is the fact that selenium-mediated carbocyclisation using a various stilbenes as precursors of dihydronaphthalenes were used successfully for the construction of dihydronaphthalene units via

Table 2.2 Synthesis of dihydronaphthalenes **169b–169g**

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

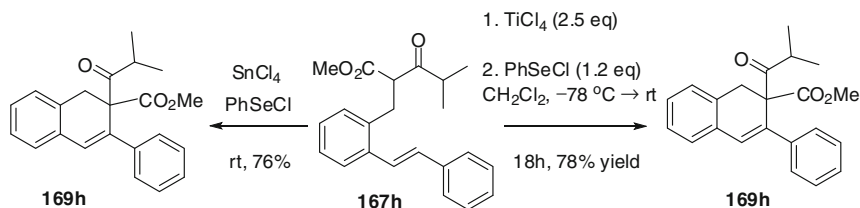
Reaction conditions: $\text{BF}_3 \cdot \text{OME}_2$ or SnCl_4 (2 equiv), -60°C , 15 min, then PhSeCl (1.2 equiv.), $-60^\circ\text{C} \rightarrow \text{RT}$

^a $\text{BF}_3 \cdot \text{OME}_2$, 20°C , 15 min, then PhSeCl (2.0 equiv.)

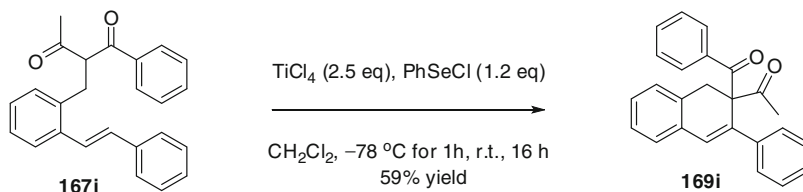
^b SnCl_4 or TiCl_4 , -60°C , 15 min, then PhSeCl (1.2 equiv.), $-60^\circ\text{C} \rightarrow \text{RT}$

^c SnCl_4 or TiCl_4 , -60°C , 15 min, then PhSeCl (2 equiv.), $-60^\circ\text{C} \rightarrow \text{RT}$

addition/elimination sequence under very mild reaction conditions. Stilbene substrates (Table 2.2, entries 1–5) tolerated substitution at any position of the aromatic ring, and both electron-donating and electron-withdrawing functionalities were compatible.



Scheme 2.43 Isopropyl carbonyl substituted synthesis of dihydronaphthalene

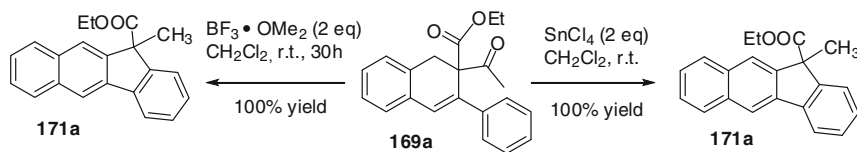


Scheme 2.44 Benzoyl substituted dihydronaphthalene **169i**

2.4.5.2 Further Manipulation of Dihydronaphthalenes Ring into Benzofluorenes

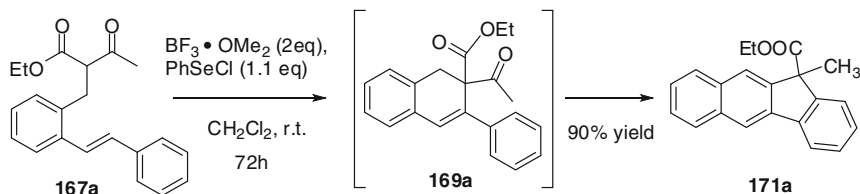
The resulting dihydronaphthalenes were then used as the starting materials for further elaboration because acetyl containing products can be further diversified by using a number of subsequent Lewis acid-catalysed Friedel–Crafts acylation processes. After the successful synthesis of dihydronaphthalenes with acetyl functional groups, as strongly electrophilic species, acetyl functional group can also participate in Friedel–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 $-78\text{ }^\circ\text{C}$ for 30 h, 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 2.45).

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 2.46).



Scheme 2.45 Use of the intramolecular Friedel–Crafts reaction for the synthesis of benzofluorene **171a**

Upon the addition of boron trifluoride dimethyl etherate at $-60\text{ }^{\circ}\text{C}$ and subsequent addition of phenylselenenyl chloride, compound **167a** was converted into dihydronaphthalene **169a**, as observed by ^1H NMR analysis of the crude reaction mixture after 12 h 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 2.46). 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 2.45. 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 2.3. 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 2.3, entry 5). Irreversible electrophilic substitutions on naphthalene tend to occur in the 1-position, consistent with this result [106, 107]. 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 Fig. 2.7 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



Scheme 2.46 Selenium and Lewis acid-mediated tandem reaction to benzofluorene

contributors are greater in number and can delocalise charge more effectively than the electrophile attack at position three. The majority of $S_{E}Ar$ products are kinetic products (not thermodynamic): the reactions are usually not reversible, since the reverse reaction is usually very unfavorable [106, 107]. That means that the structure of the product is determined by the free energy of activation, but not by the stability of the product.

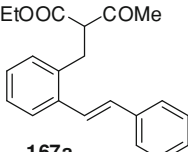
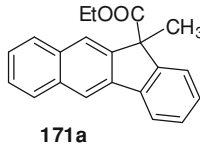
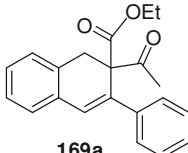
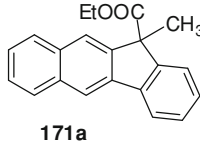
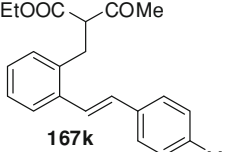
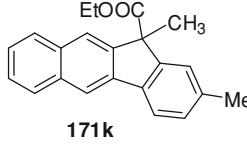
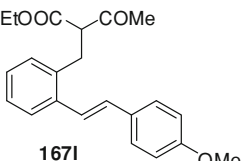
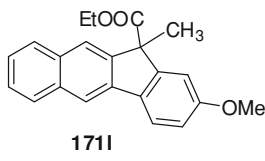
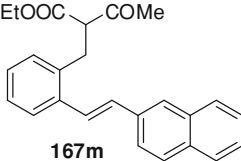
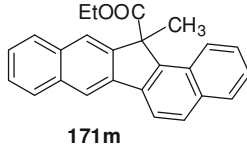
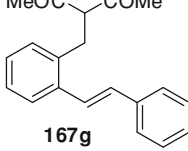
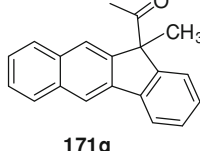
The formation of the tetracyclic compounds **171** shows that this tandem reaction involves a novel rearrangement process by activation of the double bond, which results in a total of three C–C bond formations, and a C–C and C–O bond cleavage, leading to the formation of tetracyclic compounds **171**. The structure of **171m** was additionally confirmed by X-ray crystallographic analysis (Fig. 2.8, see detail in Appendix 2.2).

We also observed the formation of benzo[*b*]fluorene **171i** 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 2.3, 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 2.3, 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 2.3, 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 2.47), the possibility for regioisomeric products existed because two different nucleophilic sites of the aromatic ring are active towards a Friedel–Crafts reaction.

Table 2.3 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 SnCl₄ or BF₃ • OMe₂ used as the Lewis acid, 1.2 equivalents PhSeCl, -60 °C → room temperature

^a Conversion given, only 0.3 equivalents of BF₃ • OMe₂ used

^b 2 equivalents of SnCl₄ used instead of BF₃ • OMe₂ as the Lewis acid

^c Product **171m** obtained as only one regioisomer

^d 2 equivalents of TiCl₄ used instead of BF₃ • OMe₂ as the Lewis acid

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** (Fig. 2.9). 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

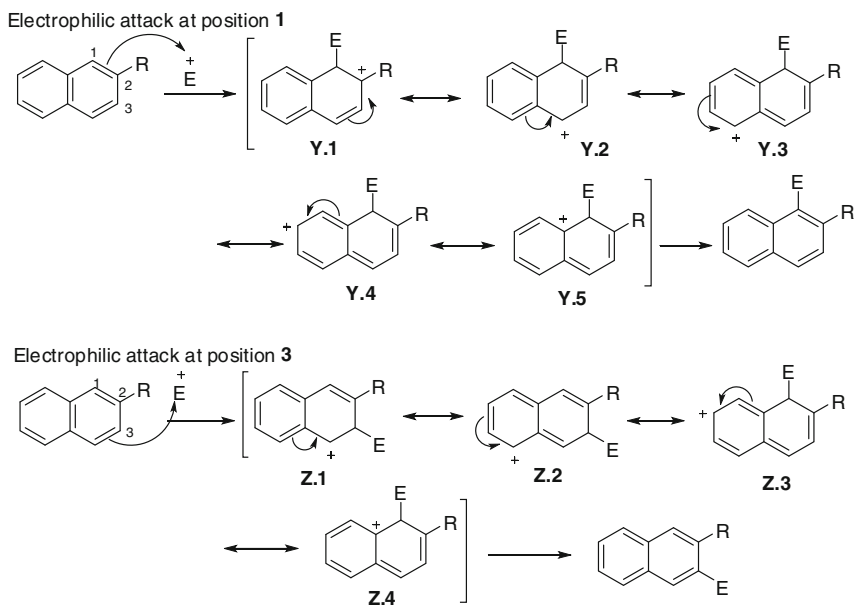


Fig. 2.7 Explanation for the formation of 171m

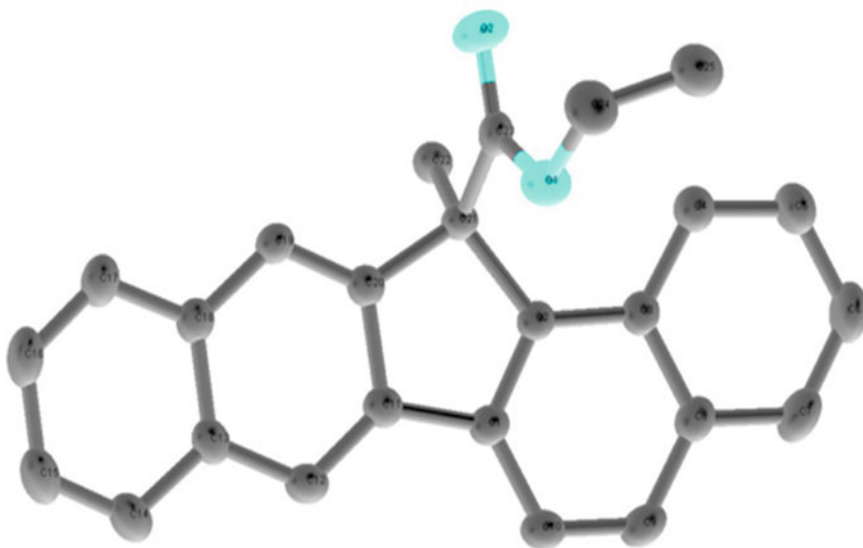
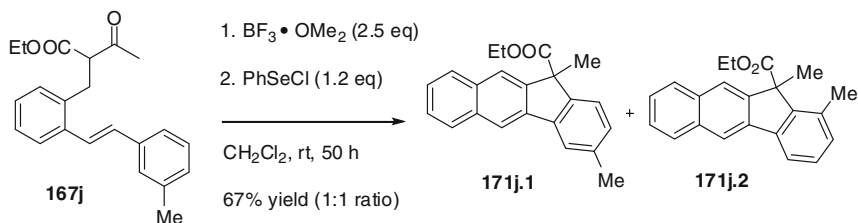


Fig. 2.8 Crystal structure of benzofluorene 171m



Scheme 2.47 Formation of regioisomers of benzofluorene from substrate **167j**

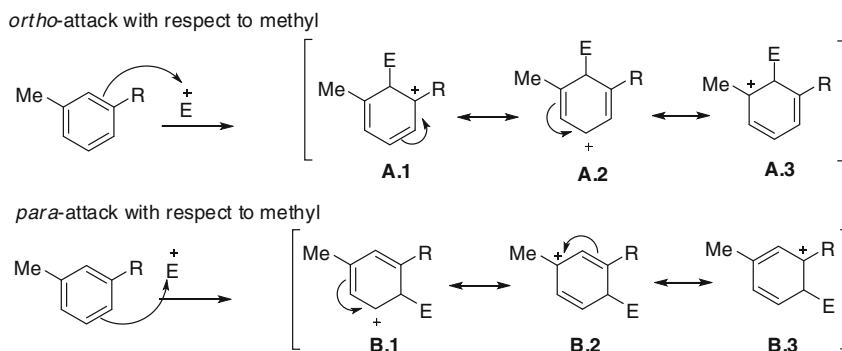


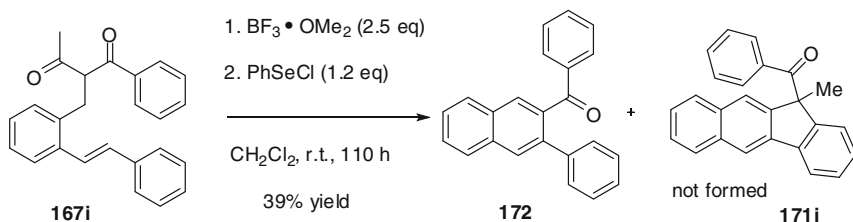
Fig. 2.9 Explanation for the formation of regioisomers **171j.1** and **171j.2**

three resonance contributors. The difference between arenium ions **A** and **B** is very small resulting in no regioselectivity in the Friedel–Crafts reaction.

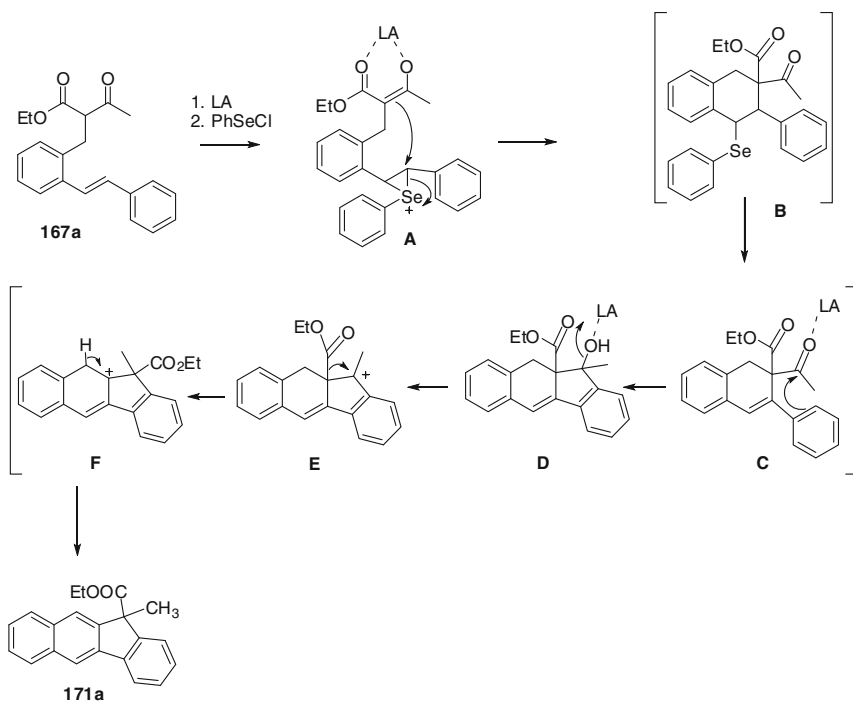
Accordingly, we carried out the cascade reaction with different substrates while further investigating this type of rearrangement in order to probe the generality and diversity of this tandem process as depicted in Scheme 2.48. Compound **167i** including a benzoyl group was subjected to the standard 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 2.48. However, the reaction protocol failed to induce benzoyl migration and subsequent formation of benzofluorene.

2.4.5.3 Proposed Mechanism

A mechanism that accounts for the formation of dihydronaphthalenes and benzofluorenes is depicted in Scheme 2.49. 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



Scheme 2.48 Unexpected formation of naphthalene derivative **172**



Scheme 2.49 Mechanistic proposal for selenium and Friedel–Crafts mediated cascade reaction for the synthesis of benzofluorenes involving a new rearrangement

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 2.49) 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.

Similar 1,2-migrations of ester moieties under the assistance of Lewis acids have been reported in literature [108]. 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 phenylselenenyl 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.

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