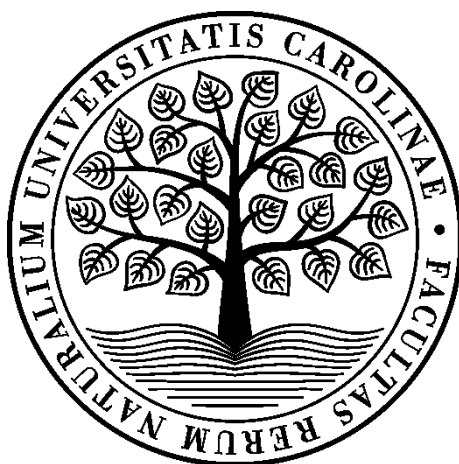**Charles University**

Faculty of Science

Study programme: Chemistry

Branch of study: Medicinal Chemistry

Ema Bažíková

Syntéza polycyklických sloučenin s aromatickým kruhem s využitím Heckovy reakce

Using Heck reaction for aromatic ring formation in the synthesis of polycyclic compounds

Bachelor's thesis

Supervisor: PharmDr. Eliška Matoušová, Ph.D.

Prague, 2020

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 7. 6. 2020   Ema Bažíková

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Abstrakt

Tato bakalářská práce se zabývá syntézou polykarbocyklické sloučeniny s naftalenovým jádrem a její následnou oxidací na příslušný *ortho*-naftochinon. Naftalenový i naftochinonový skelet se vyskytují v mnoha přírodních látkách se zajímavými biologickými vlastnstmi. Tato práce rozšiřuje rozsah metody navržené naší skupinou pro syntézu přirozeně se vyskytujících *ortho*-naftochinonů. Klíčovým krokem syntézy bylo vytvoření aromatického kruhu pomocí Heckovy reakce.

Klíčová slova: syntéza, polycyklické sloučeniny, naftaleny, katalýza, Heckova reakce

Abstract

This bachelor's thesis focuses on the synthesis of a polycarbocyclic compound with naphthalene core and the following oxidation to the corresponding *ortho*-naphthoquinone. The naphthalene and naphthoquinone skeleton can be found in many natural products with interesting biological properties. This thesis extends the scope of a method developed by our group for the synthesis of naturally occurring *ortho*-naphthoquinones. The key step of the synthesis was to form an aromatic ring using the Heck reaction.

Keywords: synthesis, polycyclic compounds, naphthalenes, catalysis, Heck reaction

Table of Contents

Abbreviations

Ac   acetyl

Ar   aryl

Bu   butyl

DCM   dichloromethane

DMA   dimethylacetamide

DMAP   4-dimethylaminopyridine

DMF   dimethylformamide

DMPU   *N,N'*-dimethylpropyleneurea

dppf   1,1'-bis(diphenylphosphino)ferrocene

Et   ethyl

equiv   equivalent

IR   infrared spectroscopy

LDA   lithium diisopropylamide

LiHMDS   lithium bis(trimethylsilyl)amide

Me   methyl

Ms   methanesulphonate

MS   mass spectrometry

NMP   *N*-methyl-2-pyrrolidone

NMR   nuclear magnetic resonance

Ph   phenyl

Piv   pivaloyl

TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TEA	triethylamine
Tf	trifluoromethanesulphonate
THF	tetrahydrofuran
TLC	thin layer chromatography
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

1. Introduction

1.1 Naturally occurring compounds with naphthalene moiety

Naphthalene skeleton is present in various natural products produced by plants, microorganisms or insects.[1] Due to the wide diversity of moieties attached to the naphthalene core, a broad spectrum of bioactivities has been unravelled including anticancer, antifungal, antiviral, antibacterial etc.[2] Therefore, these naturally occurring naphthalene derivatives hold great promise for becoming potential novel medicines.

One of the structural motifs found in natural products is naphthoresorcinol motif. Three examples of compounds with this structural core are depicted in Figure 1.1. Guieranone A **1** is a leaf constituent of a shrub *Guiera senegalensis* growing on the west coast of Africa. It exhibited antifungal activity against *Cladosporium cucumerinum*, which is a pathogen causing scab on some cultivated plants.[3] Flavasperone **2**, produced by fungi, was found to selectively inhibit ACAT2, a protein responsible for cholesteryl ester synthesis, thus might serve as an antiatherosclerotic agent.[4] Another substituted naphthalene derivative of natural origin can induce apoptosis of epithelial cancer cells. Extracted from a plant *Aegle marmelos*, marmelin **3** activates tumour necrosis factor-α and caspases and inhibits proliferation in HCT-116 colon and HEp-2 alveolar cancer cell lines.[5]
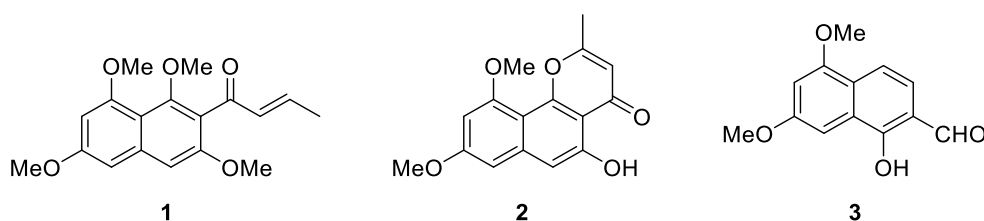

Figure 1.1. Naturally occurring compounds with naphthoresorcinol motif

Natural arylnaphthalene lignans (Figure 1.2) have also drawn attention due to their variety of biological activities. Justiprocumin B **4** was isolated from an Asian plant *Justicia gendarussa*. This natural product was screened for its anti-HIV activity and showed strong inhibition against four HIV-1 strains.[6] Another compound with similar structure extracted from *Justicia patentiflora*, patentiflorin A **5**, was tested against cancer cell lines. It showed *in vitro* cytotoxic activity against HCT-116 colon and MCF 7 breast carcinomas.[7] Helioxanthin

6 was found to inhibit human hepatitis B virus by suppressing viral gene expression and replication in hepatocellular carcinoma.[8]
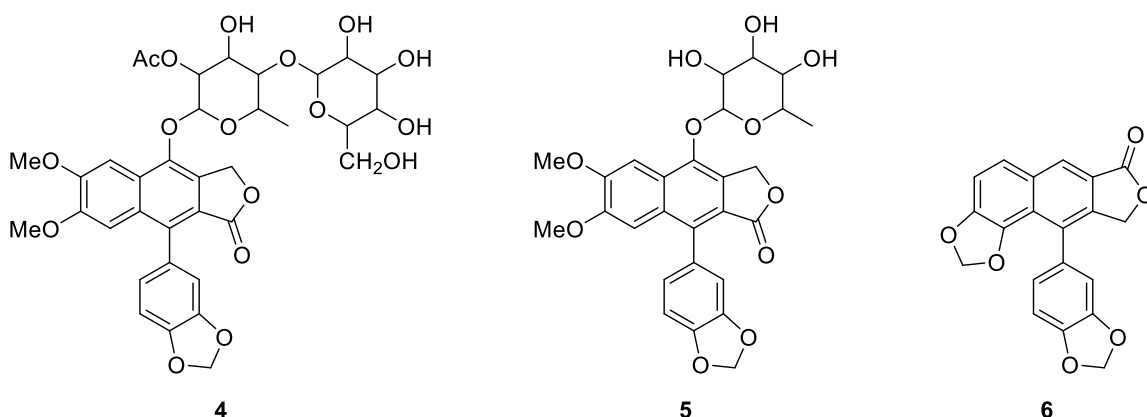

Figure 1.2. Naturally occurring arylnaphthalene lignans

Extraction of compound MK 3018 **7** from a fungus *Tetraploa aristata* in 1989 led to a discovery of a new type of biologically active secondary metabolites – spirodioxynaphthalenes (Figure 1.3), isolated predominantly from fungi. Pioneering compound **7** showed antibacterial properties against various bacterial strains.[9] Another fungal metabolite CJ-12,371 **8** also exhibited antibacterial activity, primarily on Gram-positive bacteria by inhibition of DNA gyrase.[10] Bioactive compound deoxypreussomerin A **9** extracted from *Microsphaeropsis sp.* was found to have moderate antimycobacterial and antiplasmodial activity. Furthermore, its action on farnesyl-protein transferase caused the growth inhibition of mammalian cells.[11]
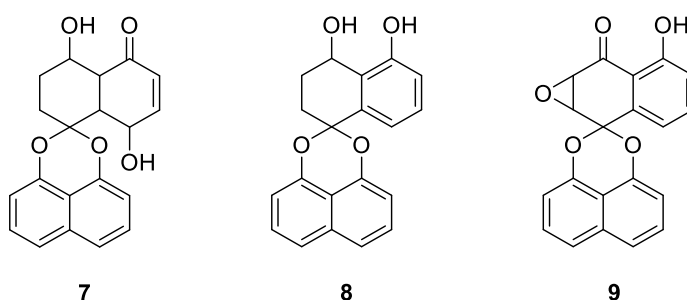

Figure 1.3. Naturally occurring spirodioxynaphthalenes

The natural products mentioned in this section are apparently only a minute fraction of the total number of so far identified metabolites with naphthalene core. A number of other naturally occurring naphthalenes have been discovered and have showed various interesting

biological activities, such as nitronaphthalenes,[12] phenalenones,[13] naphthylisoquinolines,[14] naphthohydroquinones[15] and more.

1.2 Natural products with naphthoquinone moiety

Other very interesting naphthalene derivatives of natural origin are naphthoquinones. These natural products have drawn attention due to their pharmacological properties, e.g. antibacterial, anti-inflammatory and antimalarial. Owing to their cytotoxicity, they are also known as anticancer agents which act on different types of cancer through different mechanisms while maintaining low toxicity.[16]

The majority of naphthoquinones have been extracted from the families Bignoniaceae, Verbenaceae and Proteaceae. They occur as two isomers – 1,4-naphthoquinones and 1,2-naphthoquinones.[16] Some examples of naturally occurring *para*-naphthoquinones with biological activities with the known mechanism of action are depicted in Figure 1.4. Plumbagin **10** up-regulates tumour suppressor in human brain cancer cells and activates caspases in liver cancer cells as well.[17,18] Shikonin **11** is a case in which apoptosis induced by endoplasmic reticulum stress (ERS) is observed in human prostate carcinoma cell lines.[19] Furthermore, shikonin **11** triggers off several other pro-apoptotic cascades in human cervical and breast cancer cells.[20]
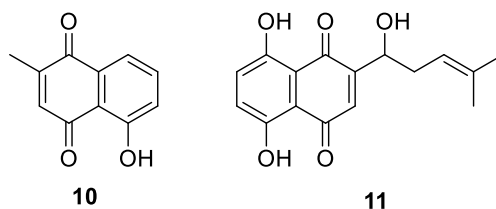

Figure 1.4. Naturally occurring *para*-naphthoquinones

In our group, we tried to synthesise 1,2-naphthoquinone-based compounds structurally similar to natural products, specifically to miltirone **12** and mansonone D **13** (Figure 1.5). *Ortho*-naphthoquinones are less prevalent in nature than *para*-naphthoquinones. The mechanism by which *ortho*-naphthoquinones act against various cancer cell lines is reported to be mainly connected with the generation of reactive oxygen species (ROS) which cause DNA or other macromolecular damages.[16] Examples of naturally occurring *ortho*-naphthoquinones, which are further described, are depicted in Figure 1.5.

Miltirone **12** is a 1,2-naphthoquinone found in the roots of *Salvia miltiorrhiza.* It was first isolated and characterised in 1970.[21] It shows anticancer effects on colon cancer cells (ROS-mediated apoptosis) and hepatoma cells (ROS-mediated activation of mitogen-activated protein kinases and p-glycoprotein inhibition).[22,23] Zhou et al. published an article with *in vivo* studies of miltirone's anti-leukemic activity.[24] They reported a 51% tumour weight reduction and found out that it triggered the ROS generation in human leukaemia cells. In addition, miltirone might serve as an antioxidant, prevention against thrombotic disorders and it employs anti-inflammatory effects.[25–27]

Mansonone D **13** is a constituent of plants *Mansonia altissima* and *Hibiscus tiliaceus*. It exhibited cytotoxicity against human breast adenocarcinoma (ROS generation) and inhibited toxicity of some plant and bacterial toxins.[28] Furthermore, it showed strong interaction with radicals at low concentration, thus might be used as an antioxidant.[29]

β-lapachone **14** is a 1,2-naphthoquinone which was first isolated from a lapacho tree (*Tabebuia avellanedae*) found in South America. It is one of the most studied *ortho*-naphthoquinones with published mechanisms and multiple biological activities. It exhibits cytotoxicity on multiple cancer cell lines - prostate cancer cells, pancreatic cancer cells and leukaemia cells. Also, it has noteworthy anti-proliferative and anti-metastatic effects in case of breast cancer.[30] It was observed that NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme was overexpressed in cancer cells. In these NQO1 overexpressed cells, β-lapachone was found to increase generation of ROS.[31] Moreover, it was observed to form ROS which then inhibited enzymes responsible for DNA damage repair.[16]
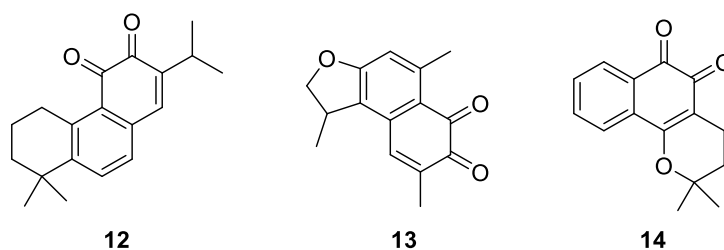

Figure 1.5. Naturally occurring *ortho*-naphthoquinones

1.3 The Heck reaction used for the aromatic ring formation in reported publications

The initial exploration of palladium as a catalyst dates back to the second half of the 20th century. When Smidt et al. published oxidation of ethylene into acetaldehyde using Pd(II) as a catalyst, the well-known industrial Wacker process,[32] it inspired other scientists to further research palladium catalysis in organic chemistry. This led to a discovery of new reactions for the formation of C–C bonds, including the versatile methodology known as the Heck reaction. The Heck reaction, in its original form, is the palladium-catalysed cross-coupling of aryl or alkenyl halides with olefins in the presence of a base. The reaction was independently discovered by Mizoroki and Heck in the early 1970s and later on developed further by Heck. The mechanism proposed by Heck and Dieck in 1974 for reactions catalysed by Pd(OAc)$_2$ with monophosphine ligands was summarised in equations and can be drawn as a catalytic cycle (Scheme 1.1).[33,34] It involves the oxidative addition, migratory *syn* insertion, β-hydride elimination and reductive elimination.
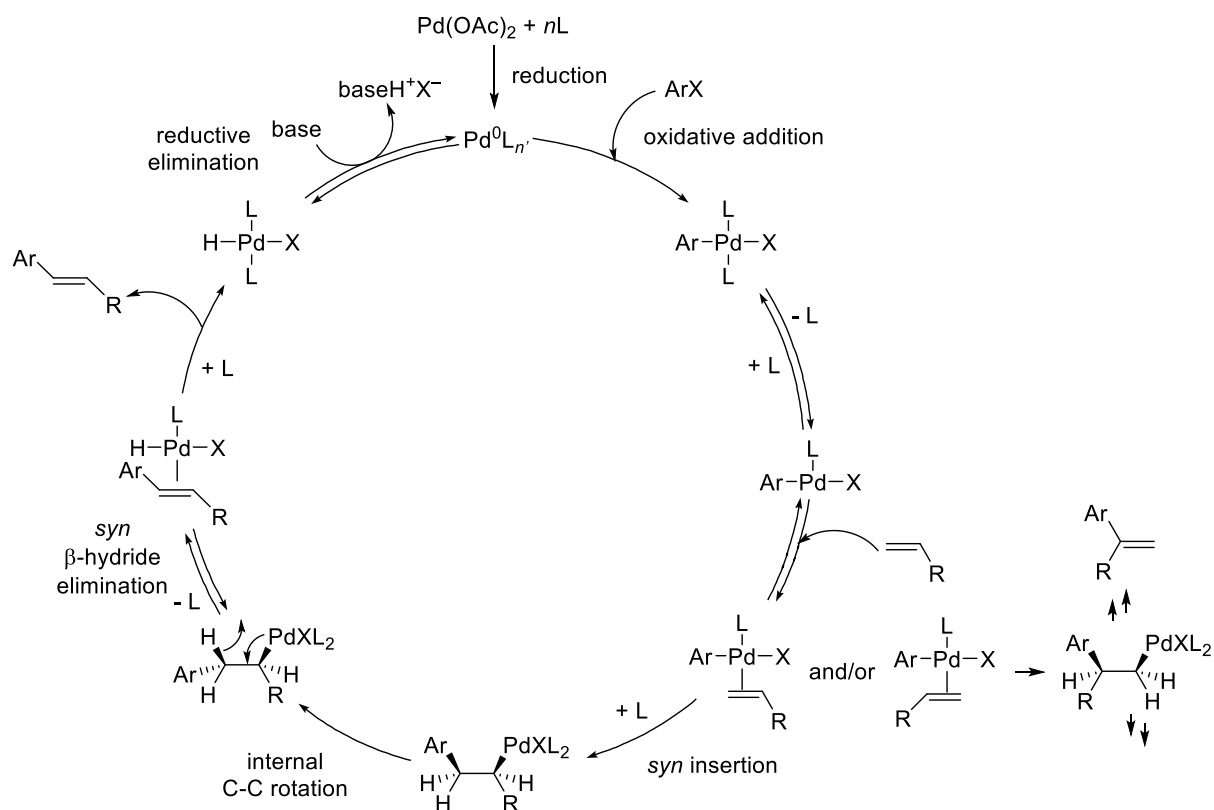
Scheme 1.1. Mechanism proposed by Heck and Dieck with Pd(OAc)$_2$ and monophosphine ligands L

These main steps of the catalytic cycle were confirmed to be correct, however, the palladium intermediates can vary depending on different reagents, ligands, catalytic precursors and additives. The Heck reaction has gained popularity in the syntheses of pharmaceuticals, polymers, dyes, etc. Owing to its flexibility and unlimited scope, both the inter- and intramolecular versions of the Heck reaction have found applications in the syntheses of various carbocycles and heterocycles.[35]

The intramolecular Heck reaction can be a useful tool for the benzene ring synthesis. In this thesis, the Heck reaction was suggested for the key aromatic ring formation in the synthesis of polycyclic compounds with naphthalene core. The cyclic Heck reaction of an aryl halide or vinyl halide to the conjugated 1,3-diene system to form a benzene ring had not been investigated until 2001. The very first uses of intramolecular Heck reaction employed for such benzannulation were reported by Mizufune and his co-workers.[36] A regiospecific synthesis of helioxanthin **16** from α,β-bisbenzylidene-γ-lactone **15** was achieved with a 60% isolated yield (Scheme 1.2). The reaction was performed using Pd(OAc)$_2$ and K$_2$CO$_3$ in NMP.
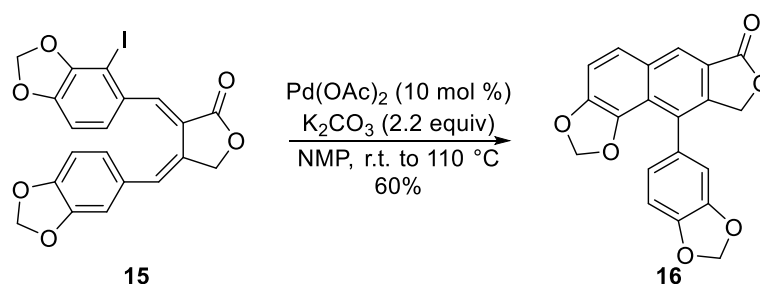

Scheme 1.2. Benzannulation using the Heck reaction by Mizufune et al.

Later in 2006, Mizufune's group extended their library of other arylnaphthalene lignan compounds using the same methodology. The benzannulation of bisbenzylidenesuccinic acid derivatives gave the highest yields of up to 80% applying Pd(OAc)$_2$ (10 mol %) and TEA in DMF at 100–110 °C.[37]

In the synthesis of naphthocarbazoles developed by Routier et al., naphthyl triflate **17** underwent the Heck reaction to obtain a cyclised product **18** using Pd(OAc)$_2$ and PPh$_3$ as a catalytic system, NaOAc as a base and Bu$_4$NCl as a transfer agent (Scheme 1.3).[38] The results showed that the coupling reaction did not proceed at all with a free indolic nitrogen. However, even with the sulphonyl-protected substrate **17**, the yields were very low when up to 30 mol % of palladium catalyst was used. A dramatic rise of the yield was only observed

using a non-catalytical 1 equivalent of palladium species. The yield of **19** after two steps, the Heck reaction and subsequent deprotection, was in this case 91%.
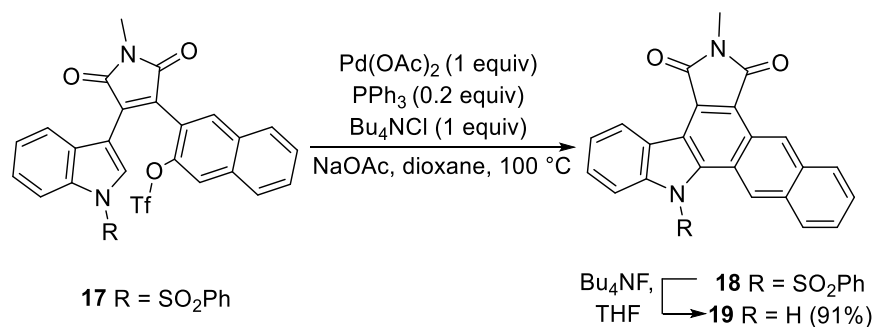
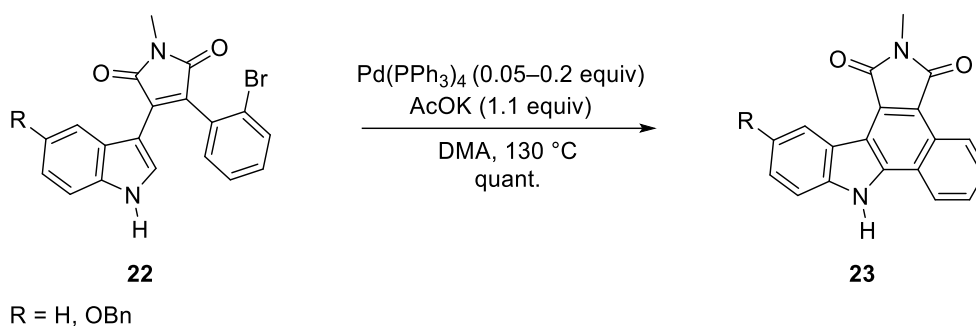Scheme 1.3. The synthesis of naphthocarbazoles

The use of catalytical amounts of palladium complex in another synthesis of carbazoles was reported by Sanchez-Martinez and co-workers.[39] The final benzannulation reaction of substrate **20** was performed using optimised conditions: Pd(PPh₃)₄ as a catalyst, AcOK as a base in DMA at 130 °C (Scheme 1.4). Aryl- and heterorarylpyrrolocarbazoles **21** were generated in 26–75% yields. It is worth mentioning that while photooxidation of 2-naphthyl indolyl maleimide gave a mixture of two regioisomers, applying the Heck conditions resulted in a formation of only one isomer.
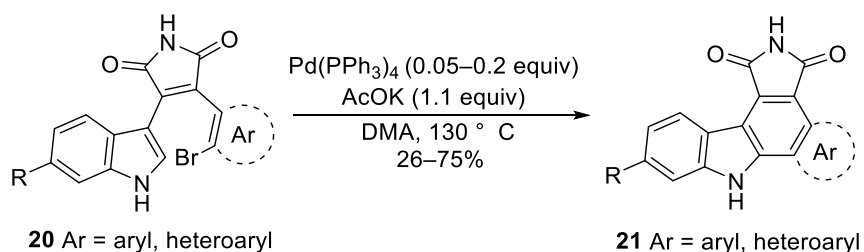
Scheme 1.4. The synthesis of aryl- and heteroarylpyrrolocarbazoles

Inspired by the work of Sanchez-Martinez, Routier published an improved strategy for the intramolecular Heck reaction using catalytical amounts of palladium species in the synthesis of phenylcarbazoles.[40] In their first attempt, phenyl triflate underwent the Heck reaction. However, in comparison with their previous work with naphthyl triflates, no insertion of palladium into C–OTf bond was observed. Therefore, bromophenyl substrates **22** were synthesised instead and were subjected to the Heck reaction. Applying the conditions Pd(PPh₃)₄, AcOK in DMA at 130 °C, the reaction afforded the cyclised products **23** in quantitative yields (Scheme 1.5). The difference in the reactivity was observed between

protected and deprotected indoles. While in the previous report cleaving the benzenesulphonyl group prevented the cyclisation, deprotection in this case showed to be very beneficial. When the protecting benzenesulphonyl group was cleaved before the intramolecular Heck reaction, it resulted in the quantitative yield of the cross-coupling products **23**. On the contrary, when the deprotection was done after the Heck reaction, the yield of the cyclised Heck product dropped to 15% (for R = H).
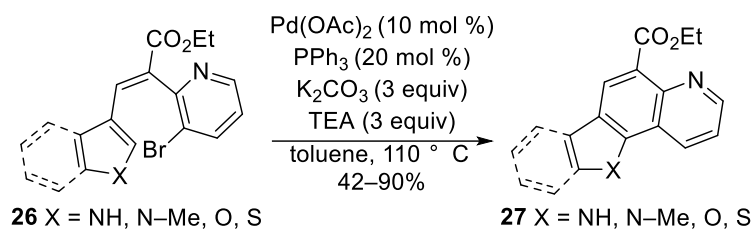

Scheme 1.5. The synthesis of phenylcarbazoles

In a research group of Fan, 2-alkenylindole **24** was subjected to the Heck reaction and gave product **25** in the yield of 82% (Scheme 1.6).[41] In comparison to the reactions mentioned above, the conditions differed in a few extra additives. One equivalent of pivalic acid and one equivalent of tetrabutylammonium bromide was used along with Pd(OAc)$_2$ and PPh$_3$ as a catalytic system and K$_2$CO$_3$ as a base in DMF at 90 °C.
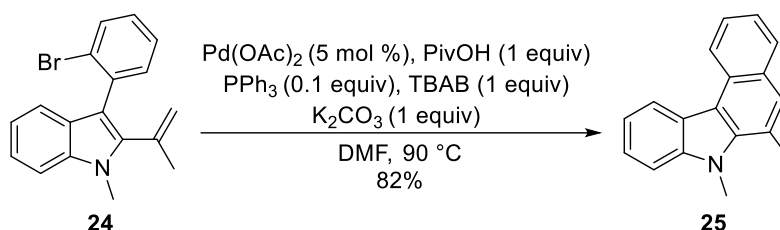

Scheme 1.6. The use of 2-alkenylindole in the Heck reaction

Yang and Miao reported the Heck reaction of heteroaromatic bromides **26**. The reaction was catalysed by Pd(OAc)$_2$ and PPh$_3$ and provided multiple pyridocarbazole derivatives **27** in up to 90% yield (Scheme 1.7).[42]

Scheme 1.7. The synthesis of pyridocarbazole derivatives

Moving away from different carbazoles, in 2012, substituted benzo[α]phenazines **29** were prepared by the Heck closure (Scheme 1.8).[43] Compounds **28** were treated with Pd(PPh$_3$)$_4$, Ag$_2$SO$_4$ as an additive and TEA in DMA at 140 °C. The reaction gave products **29** in isolated yields of 77–86%.
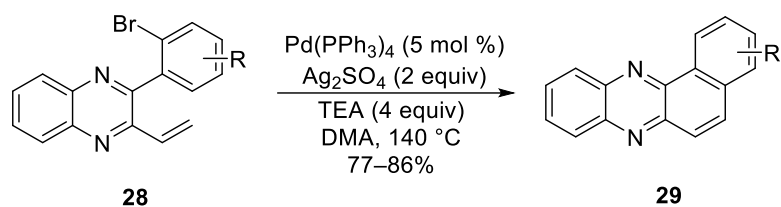
Scheme 1.8. The synthesis of substituted benzo[α]phenazines

Compound **30**, prepared by the iron(III)-catalysed Claisen rearrangement/aerobic dehydrogenative cyclisation domino reaction, underwent the Heck reaction as reported by Jiang et al. (Scheme 1.9).[44] Choosing Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ as a catalytic system and NaOH as a base in toluene afforded product **31** in 72% yield.
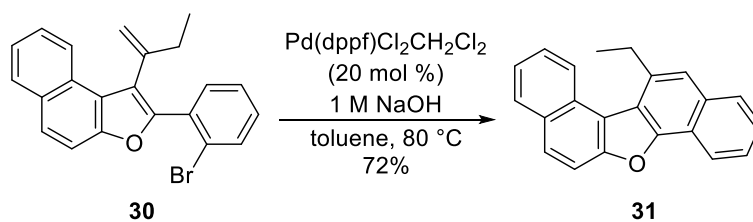

Scheme 1.9. The use of **30** in the Heck reaction

2. Aim of Work

The main aim of the thesis was to synthesise a polycyclic compound containing naphthalene core using the Heck reaction to form an aromatic ring and its oxidation to a corresponding naphthoquinone. This work intended to broaden the scope of a method developed by our group in the synthesis of polycyclic compounds structurally similar to naturally occurring *ortho*-naphthoquinones. The synthesis can be divided into 4 sections:

- Preparation of starting material
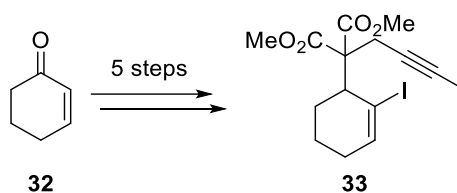
- Preparation of bromide **34** using tandem cyclisation/Suzuki cross-coupling reaction
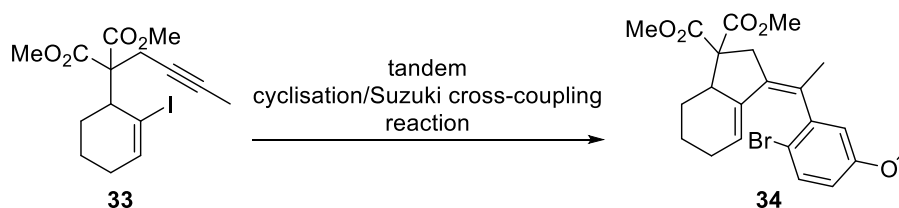
- Formation of the aromatic ring using the key Heck reaction

- Oxidation to *ortho*-naphthoquinone

3. Results and Discussion

3.1 Synthesis of a polycyclic naphthalene with fused 5-membered carbocycle

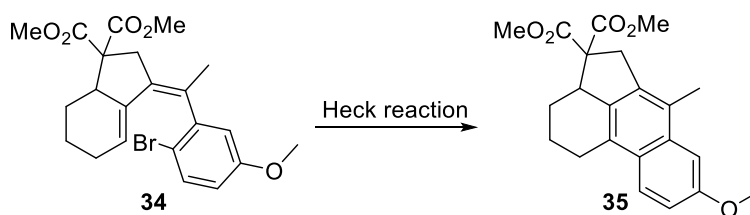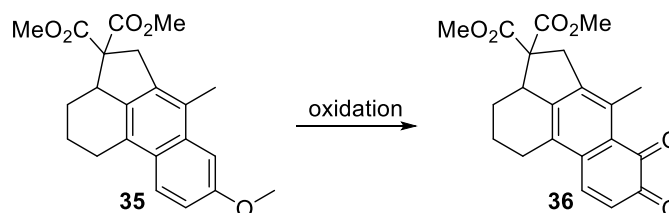To synthesise the desired carbocyclic derivative with naphthalene skeleton and 5-membered ring, a method developed earlier by our group was suggested (Scheme 3.1). The method had worked well with *O*-heterocyclic derivative **37** which was converted to naphthalene **38**, therefore it was proposed to apply the same procedure to this project as well. The plan was to first synthesise starting material **33** from cyclohex-2-ene-1-one **32** which would undergo tandem cyclisation/Suzuki cross-coupling reaction followed by the key Heck reaction to form naphthalene **35**.
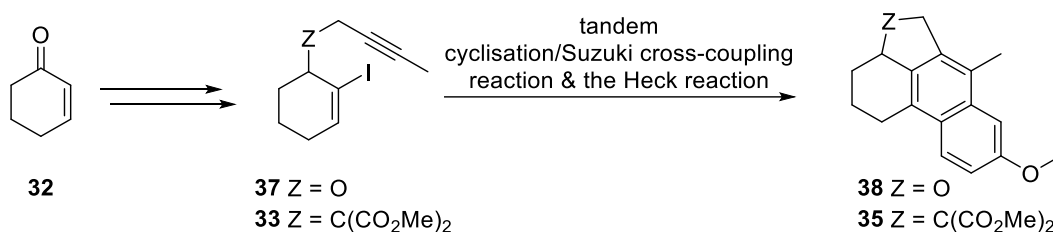
Scheme 3.1. A method developed by our group

The synthesis started with a commercially available cyclohex-2-ene-1-one **32** which underwent alpha-iodination under reported conditions[45] with the modified amount of DMAP. Since we could not achieve the same yields following the published procedure, the amount of DMAP was increased to 0.5 equivalents which eventually gave higher yields. Overall, it included the use of iodine, DMAP, K_2CO_3 in THF/H_2O solvent system and afforded the iodinated product **39** in up to 99% yield (Scheme 3.2). Then the Luche reduction was carried out (NaBH$_4$, CeCl$_3$·7H$_2$O in MeOH) and the product **40** was obtained as crude in up to 95%. Since the reaction proceeded cleanly, there was no need to purify it by the column chromatography.
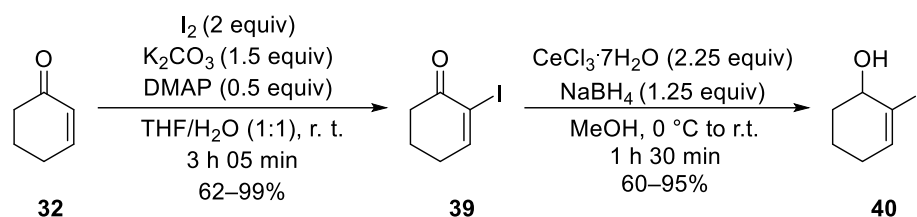
Scheme 3.2. Alpha-iodination of **32** followed by the Luche reduction

Using methanesulphonyl chloride and triethylamine in DCM, the hydroxy group was converted into a better leaving group to be able to alkylate dimethyl malonate in the next step (Scheme 3.3). The reaction afforded mesylate **41** as well as chloride **42** since some of the mesylate was converted into more stable chloride. There were some problems with monitoring the reaction by TLC due to the same retention factors of alcohol **40** and mesylate **41**. The reaction was stopped after 1.5 h according to the previous experience of our group. The formed mixture showed to be rather unstable. In the first experiment, it decomposed during the night when stored under nitrogen atmosphere, and the second time it decomposed after extraction and evaporation within a few minutes under air. Therefore, mesylate should be neither stored nor purified before applying to the following step. During the next experiments, the mixture was only extracted, evaporated and immediately subjected to another step.
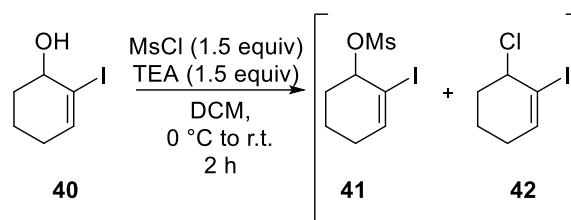
Scheme 3.3. Mesylation of **40**

Then one-pot double alkylation of dimethyl malonate was tried as reported with a similar substrate in the previous work of our group.[46] The mixture of **41** and **42** reacted with enolate of dimethyl malonate in THF and after cooling to 0 °C another portion of NaH and 1-bromobut-2-yne were added for the second alkylation. Nevertheless, with my substrate, a mixture of desired alkylated product **33** as well as a disubstituted malonate was observed. Thus, we decided to separate the mentioned steps. Firstly, dimethyl malonate was alkylated with the crude mesylate mixture (**41** and **42**) using NaH in THF at 70 °C and purified (Scheme 3.4). Formed malonate derivative **43** was isolated in yields up to 61%. Subsequently,

the second alkylation was performed with the use of TBAI, 1-bromobut-2-yne and NaH in THF at room temperature and lead to the expected starting material **33** in 88–95% yields (Scheme 3.4).
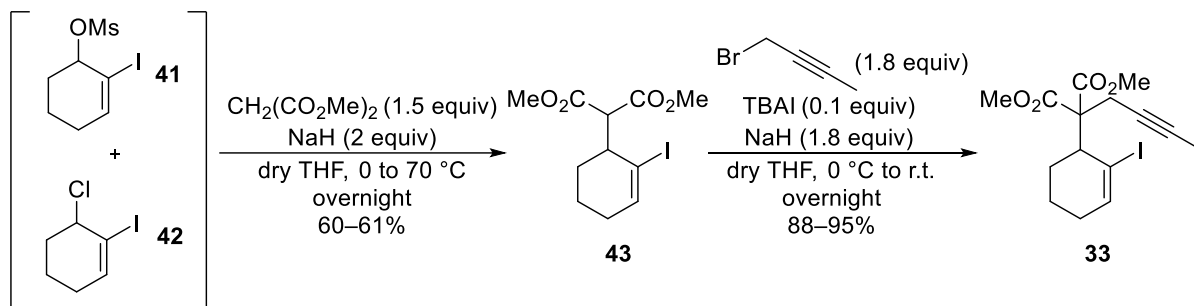
Scheme 3.4. Formation of malonate derivative **43** which underwent alkylation to form **33**

The next step involved tandem cyclisation/Suzuki cross-coupling reaction in order to synthesise a carbocyclic substrate **34** for the key step. The tandem reaction proceeded smoothly using conditions optimised in our group (Pd(PPh$_3$)$_4$ (4 mol %), Cs$_2$CO$_3$ (2 equivalents) and boronic acid (1.5 equivalent) in THF/H$_2$O at 70 °C) (Scheme 3.5).[47] The reaction afforded the desired product **34** in the yields up to 65%, and with *Z* configuration on the newly formed double bond. No *E*-isomer was isolated.
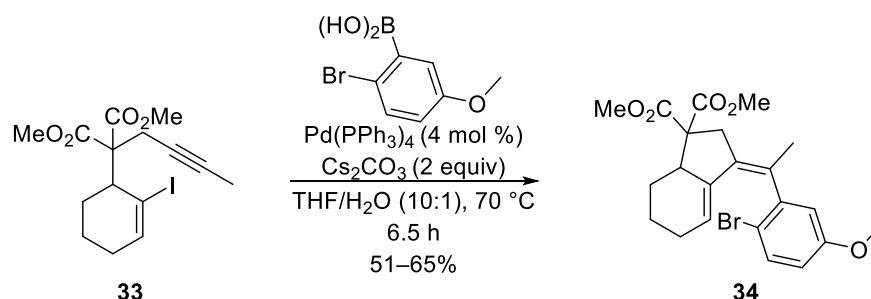
Scheme 3.5. Tandem Heck/Suzuki cross-coupling yielding **34**

To form the naphthalene product, the Heck reaction was performed. Substrate **34** was subjected to the Heck conditions which were used previously in our group. It included the use of Pd(OAc)$_2$ (10 mol %), XPhos (20 mol %) as a ligand, K$_2$CO$_3$ (2 equivalents) as a base in DMF/H$_2$O (4:1) at 110 °C (Table 3.1, entry 1). Precipitation of palladium was observed within 30 minutes, so 2 additional amounts of 10 mol % of Pd(OAc)$_2$ were added later. Although TLC showed that no starting material was left in the end, it did not form our desired product **35**. Different conditions were screened (Table 3.1) including the use of XPhos Pd G2 instead of Pd(OAc)$_2$ (entry 2), or Pd(PPh$_3$)$_4$ with (entry 3) or without (entry 4) ligand XPhos.

Unfortunately, the result was always the same, palladium went black after 30–40 minutes and despite having no starting material left according to TLC, crude ^{1}H NMR spectra showed compound to be decomposed.

Table 3.1. Screening of the Heck reaction conditions
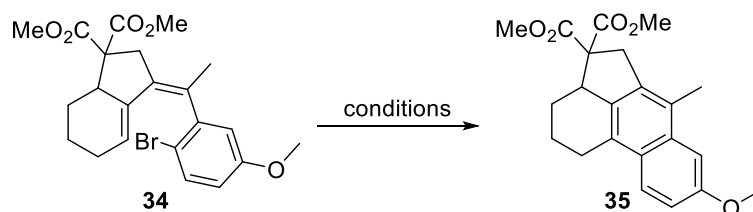
Entry	Catalyst [mol %]	Ligand [mol %]	Base [equiv]	Solvent	Temperature [°C]	Reaction time [h]	Yield [%]
1	Pd(OAc)$_2$ [3 × 10]	XPhos [20]	K$_2$CO$_3$ [2]	DMF/H$_2$O (4:1)	110	22	0
2	XPhos Pd G2 [10]	XPhos [20]	K$_2$CO$_3$ [2]	DMF/H$_2$O (4:1)	110	1.75	0
3	Pd(PPh$_3$)$_4$ [10]	XPhos [20]	K$_2$CO$_3$ [2]	DMF/H$_2$O (4:1)	110	2	0
4	Pd(PPh$_3$)$_4$ [10]	–	K$_2$CO$_3$ [2]	DMF/H$_2$O (4:1)	110	1.5	0

3.2 Synthesis of a polycyclic naphthalene with fused 6-membered carbocycle

Since the Heck reaction did not work with the carbocyclic substrate with a 5-membered ring, we came up with an alternative. We decided to use a starting material with a longer chain. Then, subjecting it to tandem carbocyclisation/Suzuki reaction would lead to a formation of a carbocyclic compound with a 6-membered ring which could undergo the benzannulation using the Heck conditions.

The same procedures were applied for the preparation of malonate derivative **43** which was subsequently alkylated with 4-bromobut-1-yne instead of 1-bromobut-2-yne using the above-mentioned conditions (TBAI, NaH in THF at room temperature; Table 3.2, entry 1). Trying to follow the same path, we came across a problem with obtaining the alkylated product **44**. Different solvent systems were examined and even increased temperature was tried (Table 3.2, entries 2–4). However, none afforded product **44**. Either there was mostly starting material left and the rest was decomposed (entries 1–3) or no conversion was observed on TLC at all (entry 4).

Table 3.2. Screening of the alkylation reaction using TBAI, NaH
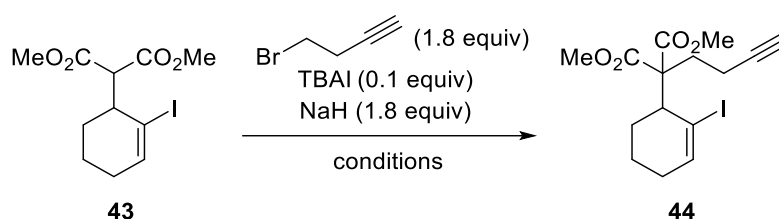
Entry	Solvent	Temperature [°C]	Reaction time [h]	Yield [%]
1	THF	0 to r.t.	21	0
2	DMF	0 to r.t.	24	0
3	THF/DMF (3:1)	0 to r.t.	23	0
4	THF	0 to 60	20	0

After failing to synthesise **44**, the steps of alkylation reactions were swapped. Firstly, dimethyl malonate was alkylated with 4-bromobut-1-yne using NaH in DMF following the reported procedure[48] to form **45** in isolated yield in up to 56% (Scheme 3.6). The rest was unreacted dimethyl malonate.
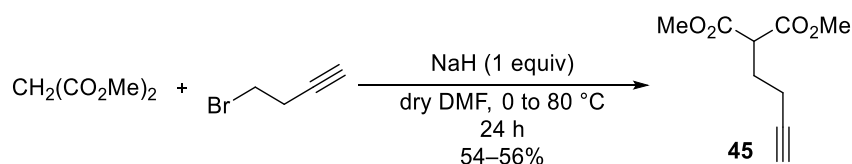
Scheme 3.6. Alkylation of dimethyl malonate to form **45**

Compound **45** reacted further with the crude mixture of mesylate **41** and chloride **42** (Scheme 3.7). The second alkylation afforded product **44** in 59% yield.
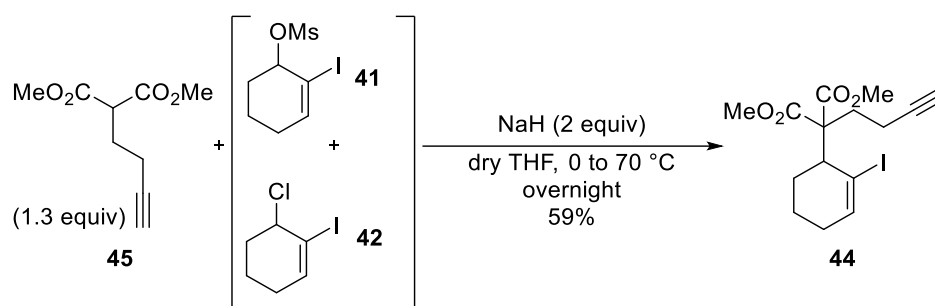
Scheme 3.7. Alkylation of **45** to form **44**

The next step was to methylate the triple bond before performing the tandem reaction. However, no methylated product **46** was obtained when **44** was treated with LiHMDS and methyl iodide in THF at -78 °C (Table 3.3, entry 1). Since this procedure was not successful, other conditions were screened which are depicted in Table 3.3. Even increased amount of methyl iodide and the base (entry 2) did not afford the desired product. Using modified procedure from the literature,[49] 1.5 equivalent of LDA and 5 equivalents of methyl iodide (entry 3) did not lead to any satisfactory result either. Finally, following another procedure found in the literature[50] with DMPU (2 equivalents) and LDA (1.2 equivalent) (entry 4) afforded a potential product **46**. Even though the column chromatography did not provide a pure product, ^{1}H NMR spectrum looked promising and mass spectra showed [M+Na]$^+$ peak. Changing base to LiHMDS (1.2 equivalent), addition of DMPU (2 equivalents) and increased amount of methyl iodide to 10 equivalents (entry 5) gave a small amount of impure product **46**, too.

Table 3.3. Screening conditions of methylation
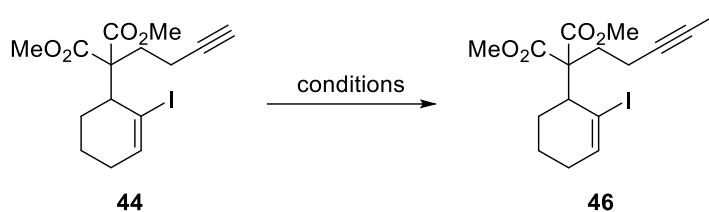
Entry	Base [equiv]	CH$_3$I [equiv]	Additive [equiv]	Solvent	Temperature [°C]	Reaction time [h]	Result
1	LiHMDS [1.1]	1.05	–	THF	-78 to r.t.	19.5	no product
2	LiHMDS [1.5]	5	–	THF	-78 to r.t.	5	no product
3	LDA [1.5]	5	–	THF	0 to r.t.	25.25	no product
4	LDA [1.2]	5	DMPU [2]	THF	-78 to r.t.	18.75	impure product
5	LiHMDS [1.2]	10	DMPU [2]	THF	-78 to r.t.	20	impure product

We decided to try the next tandem cyclisation/Suzuki reaction even with the impure compound **46**, to see if the reaction works using the same conditions as was mentioned above (Scheme 3.8). Even though column chromatography did not provide pure fractions, one of them showed signals in [^1]H NMR that could correspond to desired product **47**. Hence, further investigation has to be done to characterise the major product completely and to be able to continue with the synthesis.
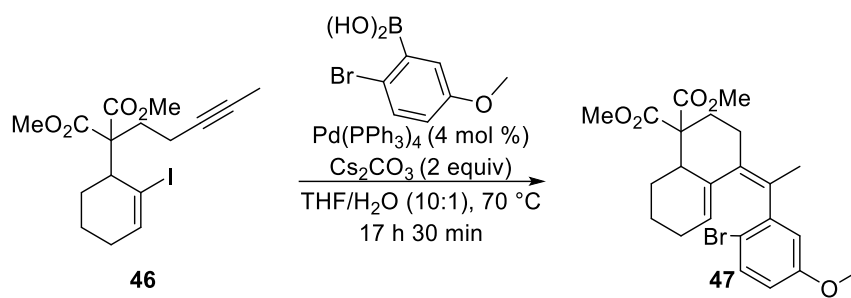
Scheme 3.8. Tandem Heck/Suzuki cross-coupling of **46**

4. Experimental Section

4.1 General

All commercially available reagents were purchased and used without further purification. Solvents were purified and dried by distillation as follows: tetrahydrofuran (THF) from sodium/benzophenone. Ethyl acetate, hexane and dichloromethane (DCM) were distilled prior to their use. *N,N*-Dimethylformamide (DMF) was purchased dry from Lach-Ner and used without purification.

The reactions were monitored using analytical thin layer chromatography (TLC) which was performed on Merck Silica gel 60 F_{254} coated aluminium plates. Eluted plates were visualised under a UV lamp (254 nm) and treated with a suitable dip followed by heating. The used dips include anisaldehyde dip: CH_3COOH (99%) (6 ml), anisaldehyde (8 ml), CH_3CH_2OH (400 ml), H_2SO_4 (20 ml); cerium phosphomolybdate dip: $Ce(SO_4)_2 \cdot 4H_2O$ (2 g), $H_3[P(Mo_3O_{10})_4]$ (4 g), H_2SO_4 (10 ml), H_2O (200 ml).

Column chromatography was performed on Acros Silica gel 60A (35–70 μm).

NMR spectra were recorded on Bruker AVANCE III HD 400 spectrometer. NMR spectra were measured in $CDCl_3$ at room temperature. Chemical shifts were referenced to a residual $CDCl_3$ signal (^1H, δ = 7.26; ^{13}C, δ = 77.16). Coupling constants *J* are given in Hz and multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or the combination of all above-mentioned.

Infrared spectra were recorded with Thermo Nicolet AVATAR 370 FT-IR spectrometer on KBr tablets of the compounds via DRIFT method and are reported in wave numbers (cm^{-1}).

Mass spectra were recorded on LTQ Orbitrap XL, Shimadzu QP 2010 or VG-Analytical ZAB-SEQ instruments.

4.2 Syntheses of starting materials

2-Iodocyclohex-2-en-1-one (39)
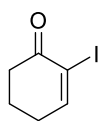
Starting cyclohex-2-ene-1-one (0.68 ml, 7.00 mmol) was dissolved in THF (17.5 ml) and distilled water (17.5 ml). K_2CO_3 (1.45 g, 10.50 mmol), iodine (3.55 g, 14.00 mmol) and DMAP (0.428 g, 3.50 mmol) were added to a stirred solution. The mixture was left to react at room temperature for 4 h 10 min. Then it was quenched by $Na_2S_2O_3$ (6 ml), extracted between EtOAc (70 ml) and saturated brine solution (2 × 70 ml), the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (8/2 hexane/EtOAc). The product **39** was a yellow-orange solid compound (1.49 g, 96%). The reaction was repeated multiple times and gave isolated yields in the range of 62–99%. The recorded spectral data were in agreement with previously reported data.[51]
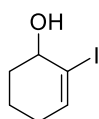
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (t, J = 4.4 Hz, 1H), 2.68 – 2.64 (m, 2H), 2.44 (td, J = 6.0, 4.4 Hz, 2H), 2.13 – 2.05 (m, 2H).

2-Iodocyclohex-2-en-1-ol (40)

Prepared 2-iodocyclohex-2-en-1-one **39** (1.49 g, 6.71 mmol) and $CeCl_3 \cdot 7H_2O$ (5.63 g, 15.10 mmol) were dissolved in methanol (70 ml). After the mixture was cooled to 0 °C, NaBH$_4$ (0.317 g, 8.39 mmol) was added portionwise. Reaction proceeded at 0 °C for 1h 40 min. Then it was quenched with distilled water (7 ml) and left to stir for additional 15 min. After methanol was evaporated, suspension was extracted between saturated brine solution (2 × 50 ml) and EtOAc (50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **40** was obtained as an orange liquid and was used for another step without purification (1.32 g, 88%). This reaction was repeated multiple times and gave yields of the crude products in the range of 60–95%. The recorded spectral data were in agreement with previously reported data.[52]

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.52 – 6.49 (m, 1H), 4.22 – 4.16 (m, 1H), 2.18 – 1.94 (m, 4H), 1.92 – 1.83 (m, 41H), 1.82 – 1.63 (m, 2H).

The crude mixture with alcohol **40** (0.605 g, 2.70 mmol) was dissolved in DCM (20 ml) and the solution was cooled to 0 °C. Triethylamine (0.56 ml, 4.05 mmol) and methanesulphonyl chloride (0.31 ml, 4.05 mmol) were added. After stirring at 0 °C for 30 min, the mixture was warmed up to room temperature and stirred for additional 2 h. Then it was quenched with saturated aqueous solution of NH_4Cl (20 ml) and extracted between distilled water (25 ml) and DCM (2 × 25 ml). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture of mesylate **41** and chloride **42** was neither purified nor characterized by spectral data due to its instability and was used as crude in the next steps.

Dimethyl 2-(2-iodocyclohex-2-en-1-yl)malonate (43)
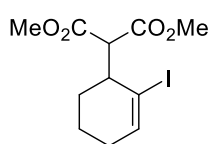
Sodium hydride (0.160 g of a 60% dispersion in mineral oil, 4.00 mmol) was placed in a dry flask under argon atmosphere and dry THF (7 ml) was added. The suspension was cooled to 0 °C. After adding dimethyl malonate (0.34 ml, 3.00 mmol) dropwise, the crude mixture of mesylate **41** and chloride **42** dissolved in dry THF (2 ml) was added. The reaction mixture was heated to reflux at 70 °C and left to react overnight. Then it was quenched with saturated aqueous solution of NH_4Cl (7.5 ml), extracted between brine (2 × 20 ml) and EtOAc (20 ml), the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexane $\rightarrow$ 92/8, hexane/EtOAc). Obtained product **43** was a colourless liquid (0.415 g, 61%). The reaction was repeated several times and the isolated yields were in a range of 60–61%.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.57 (ddd, J = 5.2, 3.3, 2.0 Hz, 1H), 4.06 (d, J = 4.9 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.10 – 3.02 (m, 1H), 2.19 – 1.97 (m, 3H), 1.92 – 1.83 (m, 1H), 1.75 – 1.57 (m, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.1, 168.4, 142.3, 100.5, 56.1, 52.8, 52.4, 44.7, 29.3, 26.4, 20.2; **IR** (KBr) v_{max} 2950, 1733, 1622, 1434, 1281, 1251, 1222, 1192, 1159, 1138, 988 cm^{-1}; **MS** (ESI) m/z (%) 361.0 (100, M$^{+\cdot}$); **HRMS** (ESI) m/z calcd for C$_{11}$H$_{15}$O$_4$INa [M+Na]$^+$ 360.99078, found 360.99072.

Dimethyl 2-(but-2-yn-1-yl)-2-(2-iodocyclohex-2-en-1-yl)malonate (33)
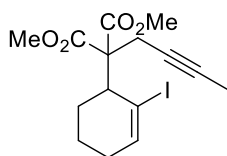
Compound **43** (0.507 g, 1.50 mmol) and tetrabutylammonium iodide (0.055 g, 0.15 mmol) were placed to a dry flask under argon atmosphere and were dissolved in dry THF (4.5 ml). 1-Bromobut-2-yne (0.24 ml, 2.70 mmol) was added, followed by a portionwise addition of NaH (0.108 g of a 60% dispersion in mineral oil, 2.70 mmol) at 0 °C. The mixture was stirred for 15 min at 0 °C and then left to react overnight at room temperature. Then the mixture was quenched with saturated aqueous solution of NH_4Cl (5 ml) and extracted between brine (2 × 40 ml) and EtOAc (40 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexane → 8/2, hexane/EtOAc). An orange sticky liquid **33** was obtained (0.517 g, 88%). The reaction was repeated twice, and the yields were 88 and 95%.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.67 (ddd, J = 5.1, 3.3, 1.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.59 – 3.52 (m, 1H), 2.97 (dq, J = 16.8, 2.6 Hz, 1H), 2.84 (dq, J = 16.9, 2.6 Hz, 1H), 2.13 – 1.94 (m, 3H), 1.93 – 1.83 (m, 1H), 1.77 (t, 3H), 1.76 – 1.68 (m, 1H), 1.64 – 1.51 (m, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.4, 170.1, 144.3, 96.4, 78.6, 74.9, 61.3, 52.8, 52.7, 46.9, 29.5, 27.4, 24.3, 20.0, 3.9; **IR** (KBr) v_{max} 2950, 2911, 2190, 1736, 1434, 1266, 1237, 1207, 1087 cm^{-1}; **HRMS** (EI) m/z calcd for $C_{15}H_{19}O_4I$ 390.0328, found 390.0329.

Dimethyl 2-(but-3-yn-1-yl)malonate (45)
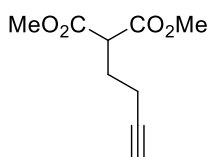
The reaction was done according to reported procedure.[48] Sodium hydride (0.120 g of a 60% dispersion in mineral oil, 3.00 mmol) and dry DMF (3.6 ml) were added to a flask. Dimethyl malonate (0.343 ml, 3.00 mmol) dissolved in dry DMF (0.6 ml) was added dropwise under argon atmosphere at 0 °C. The mixture was stirred for one hour before a dropwise addition 4-bromobut-1-yne (0.282 ml, 3.00 mmol) dissolved in dry DMF (0.6 ml) at 0 °C. The mixture was left to stir for 24 h at 80 °C. Then the mixture was quenched with saturated aqueous solution of NaCl (5 ml) and extracted between brine (2 × 10 ml) and EtOAc (10 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexane → 8/2, hexane/EtOAc). A colourless oil of compound **45** was obtained (0.306 g, 56%). The reaction was repeated

twice, and the yields were 54 and 56%. The recorded spectral data were in agreement with previously reported data.[48]

¹H NMR (400 MHz, CDCl₃) δ 3.75 (s, 6H), 3.62 (t, J = 7.4 Hz, 1H), 2.30 (td, J = 7.0, 2.6 Hz, 2H), 2.16 – 2.09 (m, 2H), 2.00 (t, J = 2.6 Hz, 1H).

Dimethyl 2-(but-3-yn-1-yl)-2-(2-iodocyclohex-2-en-1-yl)malonate (44)
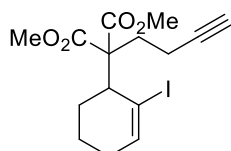
Sodium hydride (0.200 g of a 60% dispersion in mineral oil, 5.00 mmol) and dry THF (8.3 ml) were added to a flask under argon atmosphere. The suspension was cooled to 0 °C. Then a solution of compound **45** dissolved in dry THF (2 ml) and a solution of a mixture of mesylate **41** and chloride **42** were added dropwise. The mixture was heated to reflux at 70 °C and left to react overnight. Then the mixture was quenched with saturated aqueous solution of NH₄Cl (10 ml) and extracted between brine (2 × 25 ml) and EtOAc (25 ml). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexane → 8/2, hexane/Et₂O). A white solid compound **44** was obtained (0.573 g, 59%).

¹H NMR (400 MHz, CDCl₃) δ 6.65 (ddd, J = 5.2, 3.7, 1.6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.42 – 3.35 (m, 1H), 2.50 (dddd, J = 15.9, 11.4, 4.5, 2.6 Hz, 1H), 2.38 (ddd, J = 13.4, 11.2, 4.5 Hz, 1H), 2.21 – 2.11 (m, 2H), 2.10 – 1.99 (m, 2H),1.98 (t, J = 2.6 Hz, 1H), 1.87 – 1.52 (m, 4H); **IR** (KBr) ν_{max} 3294, 2950, 2932, 2119, 1727, 1428, 1290, 1230, 1198, 1090 cm⁻¹; **MS** (ESI) m/z (%) 413.0 (100, [M+Na]⁺), 391.0 (13, [M+H]⁺); **HRMS** (ESI) m/z calcd for C₁₅H₁₉O₄INa 413.0220, found 413.0219.

Dimethyl 2-(2-iodocyclohex-2-en-1-yl)-2-(pent-3-yn-1-yl)malonate (46)
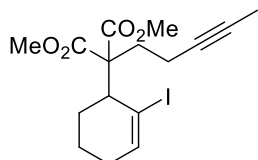
Published procedure was followed to synthesise **46**.[50] Alkyne **44** (0.117 g, 0.30 mmol) was dissolved in dry THF (1 ml) and the mixture was cooled to –78 °C. Then LDA (0.2 ml, 0.36 mmol) was added and the mixture was stirred for 30 min at –78 °C. DMPU (0.073 ml, 0.60 mmol) and CH₃I (0.093 ml, 1.5 mmol) were added before the mixture was warmed to room temperature and left to react overnight. When the reaction was complete, the mixture was extracted between 1N Na₂SO₄ (2 × 10 ml) and EtOAc (10 ml). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude

product was subjected to column chromatography on silica gel (8/2, hexane/Et$_2$O) but compound **46** could not be separated from side products. However, mass spectrum showed a [M+Na]$^+$ peak.

MS (ESI) *m/z* (%) 427.07 (80, [M+Na]$^+$).

4.3 Tandem Heck/Suzuki reaction

Dimethyl (*Z*)-3-(1-(2-bromo-5-methoxyphenyl)ethylidene)-2,3,5,6,7,7a-hexahydro-1*H*-indene-1,1-dicarboxylate (34)
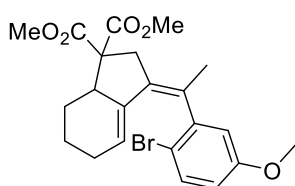
Alkyne **33** (0.483 g, 1.24 mmol) was dissolved in THF (13 ml). Cs$_2$CO$_3$ (0.808 g, 2.48 mmol), 2-bromo-5-methoxyphenylboronic acid (0.429 g, 1.86 mmol) and distilled water (1.3 ml) were added. Then the mixture was degassed by evacuating and backfilling the flask with argon. After the addition of Pd(PPh$_3$)$_4$ (0.057 g, 0.050 mmol), the mixture was degassed three more times. The reaction mixture was stirred at 70 °C under argon atmosphere for 6.5 h. Then it was extracted between brine (2 × 40 ml) and EtOAc (40 ml), the organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5, hexane/EtOAc). The product **34** was a yellow liquid (0.364 g, 65%). The reaction was repeated several times and gave yields in the range of 51–65%.

¹H NMR (400 MHz, CDCl$_3$; mixture of atropoisomers, signals of both atropoisomers are listed) δ 7.45 (d, *J* = 8.7 Hz, 1H$^\#$), 7.42 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 3.1 Hz, 1H), 6.70 – 6.64 (m, 1H, 1H$^\#$), 6.61 (d, *J* = 3.1 Hz, 1H$^\#$), 4.84 – 4.79 (m, 1H), 4.79 – 4.74 (m, 1H$^\#$), 3.79 (s, 3H), 3.78 (s, 3H, 3H$^\#$), 3.76 (s, 3H$^\#$), 3.70 (s, 3H), 3.68 (s, 3H$^\#$), 3.26 – 3.16 (m, 1H, 1H$^\#$), 3.14 – 3.01 (m, 1H, 1H$^\#$), 2.72 – 2.61 (m, 1H, 1H$^\#$), 2.18 – 2.08 (m, 1H, 1H$^\#$), 1.96 (s, 3H$^\#$), 1.94 (s, 3H), 1.88 – 1.76 (m, 2H, 2H$^\#$), 1.75 – 1.66 (m, 1H, 1H$^\#$), 1.53 – 1.33 (m, 1H, 1H$^\#$), 1.05 – 0.90 (m, 1H, 1H$^\#$); **¹³C NMR** (101 MHz, CDCl$_3$; mixture of atropoisomers, signals of both atropoisomers are listed) δ 172.5$^\#$, 172.4, 171.5, 171.2$^\#$, 159.6$^\#$, 159.2, 146.2$^\#$, 145.7, 137.6, 137.0$^\#$, 133.8, 133.4, 133.3$^\#$, 133.0$^\#$, 128.5$^\#$, 128.0, 123.2$^\#$, 122.6, 115.5, 114.6$^\#$, 114.3, 114.2$^\#$, 113.7$^\#$, 112.5, 60.8$^\#$, 60.6, 55.6 (1C, 1C$^\#$), 52.6$^\#$, 52.6, 52.2$^\#$, 52.1, 47.7$^\#$, 47.4, 39.3$^\#$, 39.2, 25.8, 25.8$^\#$, 25.7$^\#$, 25.5, 22.5, 22.3$^\#$, 22.0$^\#$, 22.0 (#atropoisomer signals – the signals are in pairs, one signal of the pair which appears to have lower intensity is marked by #);

IR (KBr) ν_{max} 2947, 2857, 1736, 1592, 1437, 1251, 1225, 1204, 1036, 1015, 812 cm^{-1};
HRMS (EI) *m/z* calcd for $C_{22}H_{25}O_5Br$ 448.0885, found 448.0880.

4.4 Heck reaction

Dimethyl 8-methoxy-6-methyl-2,3,3a,5-tetrahydroacephenanthrylene-4,4(1*H*)-dicarboxylate (35)
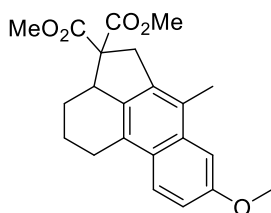
Along with the starting material **34** (46.3 mg, 0.103 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol), XPhos (9.8 mg, 0.021 mmol) and K$_2$CO$_3$ (28.5 mg, 0.206 mmol) were placed into a flask. Then the mixture was degassed by evacuating and backfilling the flask with argon and dissolved in DMF (0.8 ml) and distilled water (0.2 ml). The mixture was degassed, filled with argon three more times and then heated to 110 °C. After 3 h, another portion of Pd(OAc)$_2$ (23 mg, 0.010 mmol) was added and left overnight to react. The next day, after 19 h, a third portion of Pd(OAc)$_2$ (23 mg, 0.010 mmol) was added and the reaction was stopped after 22 h. Using this procedure, it did not lead to our desired product **35**.

5. Conclusion

In conclusion, the starting material **33** was prepared from commercially available cyclohex-2-en-1-one in 5 steps. The substrate for the key Heck reaction **34** was successfully obtained by the tandem cyclisation/Suzuki cross-coupling reaction, which afforded exclusively *Z*-isomer of product **34** in up to 65% yield, while no *E*-isomer was isolated. Unfortunately, the Heck reaction did not provide our desired product with naphthalene core, even after screening of different catalytic systems. In order to attempt the Heck reaction with a different substrate, starting material **46** with longer chain was prepared in 6 steps. In the alkylation of dimethyl malonate, optimisation was needed and included the changed sequence of alkylation steps. Unfortunately, when the triple bond was methylated, we achieved neither satisfactory yields nor pure product. Thus far, the following tandem cyclisation/Suzuki cross-coupling reaction was performed only once and with impure substrate **46**. According to NMR, product **47** was most likely to be obtained, however, it could not be isolated as a pure compound. Therefore, further investigation is needed in order to completely characterise the formed product, so it can be applied to the next Heck reaction to form desired naphthalene **48** followed by oxidation to the corresponding *ortho*-naphthoquinone.

33 n = 1	**34** n = 1	**35** n = 1
46 n = 2	**47** n = 2	**48** n = 2
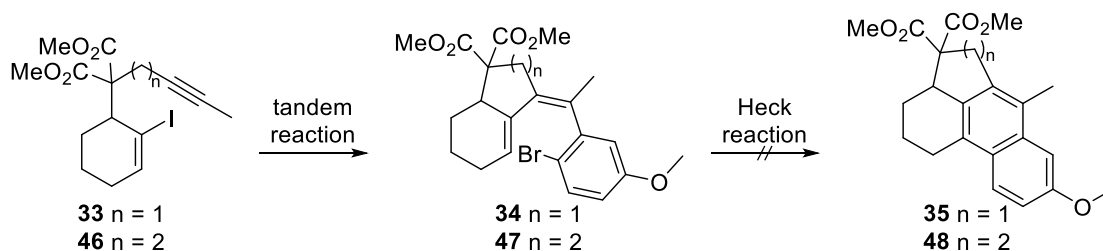
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