TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Dissertation

APPLICATION OF C-H ACTIVATION AND NATURAL PRODUCT DERIVATIZATION FOR THE SYNTHESIS OF BIOACTIVE COMPOUNDS

ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Doktors der technischen Wissenschaften unter der Leitung von

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Think different.

STEVE JOBS

Front Matter

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Acknowledgements

First of all, I would like to thank my parents for the great support through all my life and especially throughout the years of my study. They supported me unconditionally for all of my imperfection. The same is true for my wife Đỗ Mai Hương who took over all the houseworks and helped me raise our daughter during the time I wrote up this dissertation.

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Abstract

In recent years, an advanced method has started to complement and even substitute cross-coupling chemistry, namely direct arylation methods, often referred to as C-H activation reactions. The advantage of this type of transformation is that either the organometallic species or the (pseudo)halide component can be substituted by substrates containing a reactive C-H bond instead. This method helped avoiding such pre-functionalization, shortening synthetic pathways significantly, which is more time-, resource-, and energy efficient.

Heterocycles are especially suitable for C-H activation chemistry since the different C-H bonds present are significantly different in reactivity due to the presence of the heteroatom(s). C-H activation reactions of several heterocycles have been described to contribute to the synthesis of many compounds which are potential biologically active. The application of C-H activation in the synthesis plan not only reduced reaction steps but also help the synthesis of variation products became much more convenient.

On the first project, a ligand free C-H activation on the thiazole scaffold was modified by using bromide coupling partners. Especially, a rare *N*-endo benzyl protected 2-aminothiazole was also submitted to directed arylation successfully by the new method. Structure of selective products of those arylations was confirmed indirectly due to the oxidative deprotection since their NMR profiles were unprecedent and unpredictable.

Next project, naringenin and hesperetin derivatives were synthesized by protection and reduction. Since the reduction was followed by de-protection hence the target was changed afterwards. Reduced bisprotected products were synthesized instead. 12 compounds were evaluated regarding their bioactivities on *E. amylovora* bacteria.

Move on to the third project, an efficient method of direct arylation on benzo[*b*]furan as well as benzo-fused heterocycles in general was developed. The method showed high regio-selectivity and good yields with readily palladium catalyst and phosphine ligands.

Last but not least, a scope of benzofuran neolignans was synthesized via both coupling reaction and C-H activation. 40 synthesized compounds (38 new ones) were screened for anti-inflammantory activities afterward. Up to 15 compounds displayed significant activity on NF-κB inhibition with IC_{50} values less than 10μM. 3 compounds showed promising activity on LXR-β activation. With 18 active compounds out of 40 tested scaffolds, the hit rate represents a remarkable 45%.

Kurzfassung

In den letzten Jahren hat eine fortschrittliche Methode begonnen, Kreuzkupplungreaktionen zu komplementiert und sogar zu ersetzt, nämlich direkte Arylierungsmethoden, die oft als CH-Aktivierungsreaktionen bezeichnet werden. Der Vorteil dieser Art von Transformation besteht darin, dass entweder die organometallische Spezies oder die (Pseudo-) Halogenidkomponente durch Substrate ersetzt werden kann, die stattdessen eine reaktive C-H Bindung enthalten. Diese Methode half, eine derartige Vorfunktionalisierung zu vermeiden und die Synthesewege signifikant zu verkürzen, und bietet somit eine zeit-, ressourcen- und energieeffizientere Alternative.

Heterocyclen sind besonders für die CH-Aktivierungschemie geeignet, da die verschiedenen vorliegenden C-H Bindungen aufgrund der Gegenwart des Heteroatoms (der Heteroatome) in der Reaktivität signifikant unterschiedlich sind. In der Literatur finden sich CH-Aktivierungsreaktionen unterschiedlicher Heterocyclen zur Synthese vieler potenziell biologisch aktiver Verbindungen. Die Anwendung der CH-Aktivierung in der Syntheseplanung reduzierte nicht nur die Anzahl der Reaktionsschritte, sondern half auch bei der Synthese von Variationsprodukten.

Im ersten Projekt wurde eine ligandenfreie CH-Aktivierung am Thiazolgerüst unter Verwendung von Bromidkupplungspartnern modifiziert. Insbesondere wurde ein seltenes N-*endo* benzyl-geschütztes 2-Aminothiazol auch erfolgreich einer gerichteten Arylierung durch das neue Verfahren unterzogen. Die Struktur der selektiven Produkte dieser Arylierungen wurde indirekt aufgrund der oxidativen Entschützung bestätigt, da ihre NMR-Profile beispiellos und nicht vorhersagbar waren.

Als nächstes Projekt wurden Naringenin- und Hesperetin-Derivate durch Schutzgruppeneinsatz und mittels Reduktion synthetisiert. Da auf die Reduktion eine Entschützung folgte, wurde das Ziel anschließend geändert. Reduzierte bis-geschützte Produkte wurden stattdessen synthetisiert. 12 Verbindungen wurden hinsichtlich ihrer Bioaktivitäten auf *E. amylovora* Bakterien untersucht.

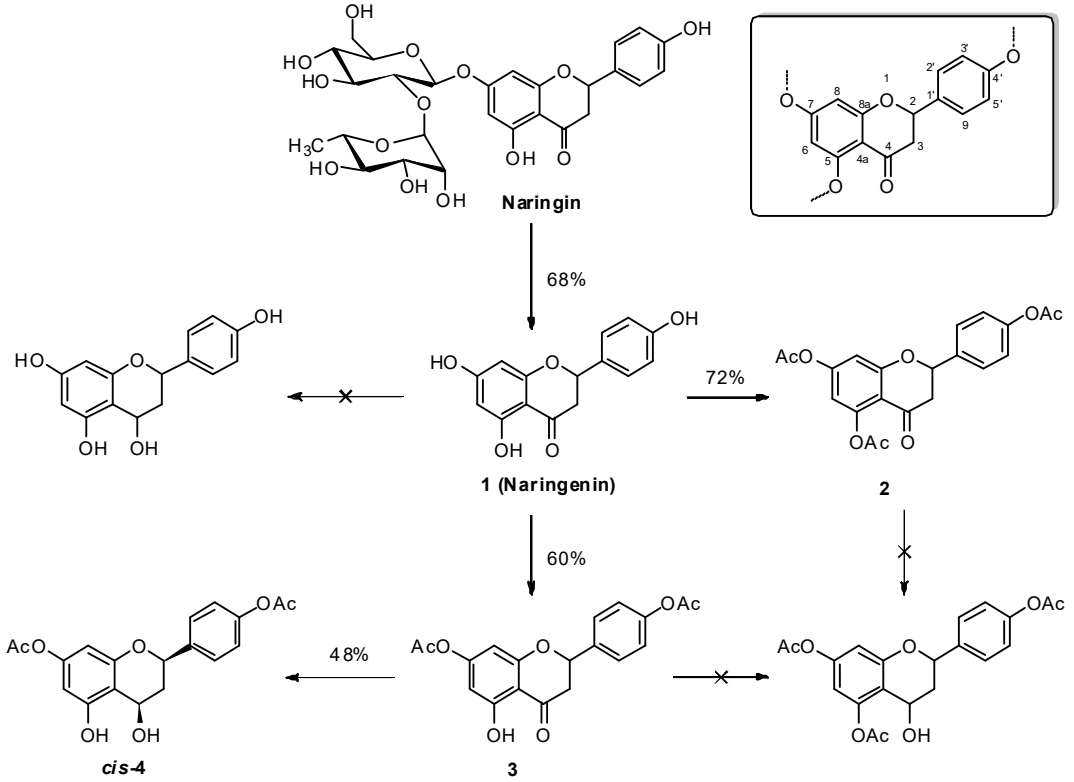
Im dritten Projekt wurde eine effiziente Methode der direkten Arylierung von Benzo[*b*]furan sowie von Benzo-anellierten Heterocyclen entwickelt. Das Verfahren zeigte hohe Regioselektivität und gute Ausbeuten mit leicht Palladiumkatalysator und Phosphinliganden.

Schließlich wurde eine Reihe von Benzofuran-Neolignanen sowohl über die Kopplungsreaktion als auch über die CH-Aktivierung synthetisiert. 40 synthetisierte Verbindungen (38 neue) wurden anschließend auf entzündungshemmende Aktivitäten untersucht. Bis zu 15 Verbindungen zeigten eine signifikante Aktivität zur NF-κB Hemmung mit IC_{50} Werten von weniger als 10μM. 3 Verbindungen zeigten vielversprechende Aktivität auf LXR-β Aktivierung. Mit 18 aktiven Verbindungen von 40 getesteten Gerüsten stellt die bemerkenswerte Trefferquote 45% dar.

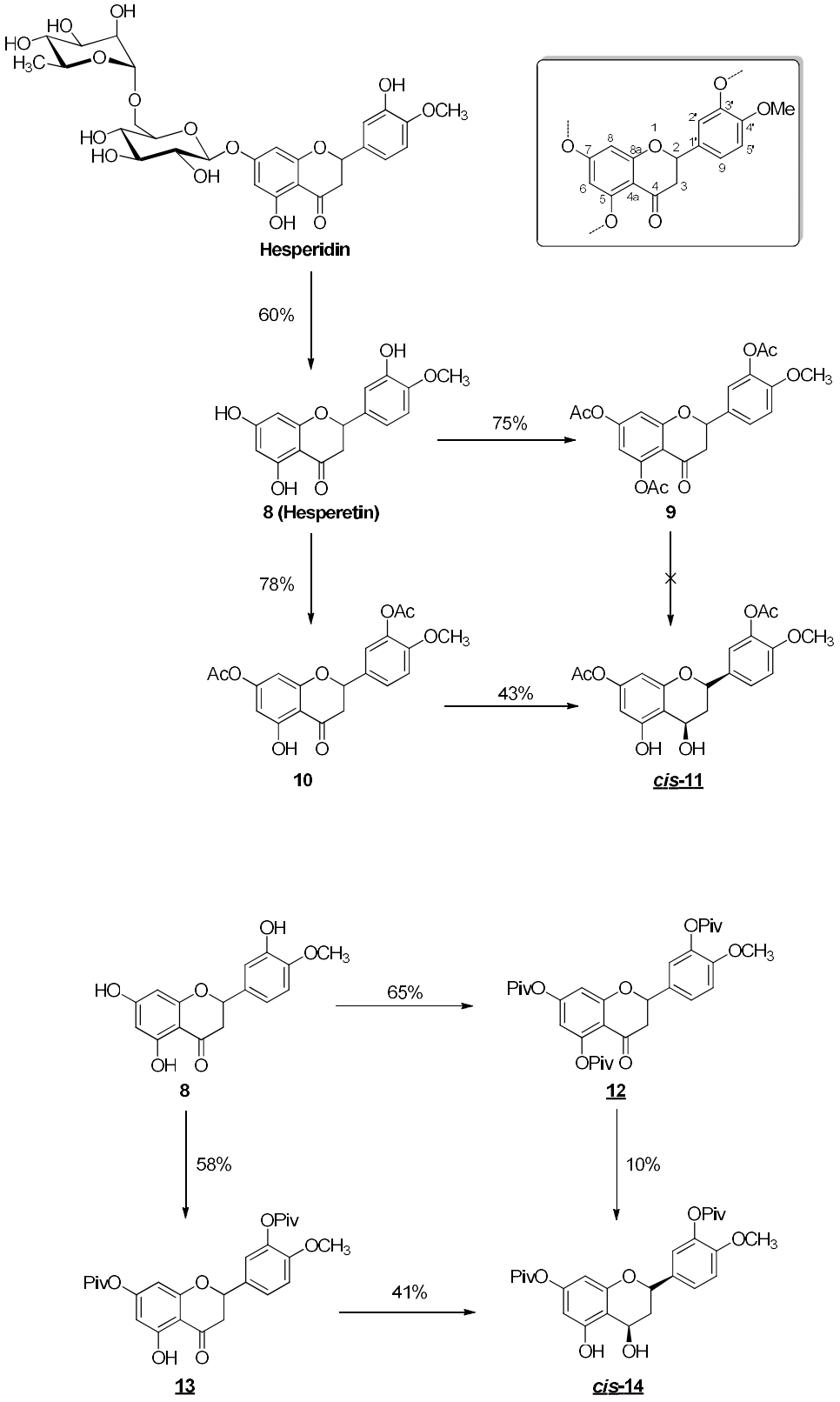
General schemes

All compounds prepared in this thesis are numbered in bold Arabic numerals. Compounds unknown to the literature are additionally underlined. Isomer of compounds was named in the same number with different Latin alphabet letter in suffix.

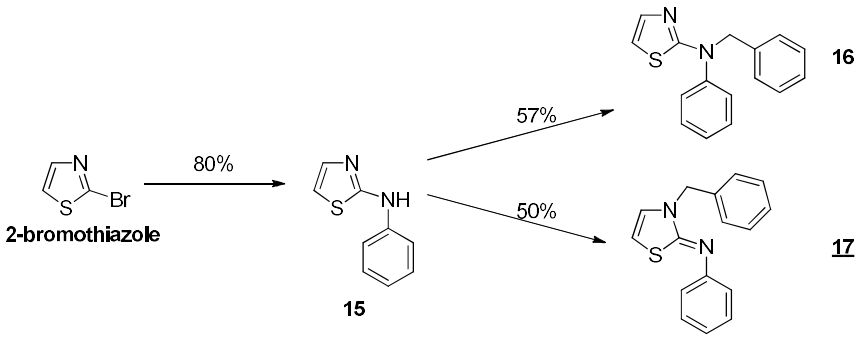
❖ Naringenin derivatives

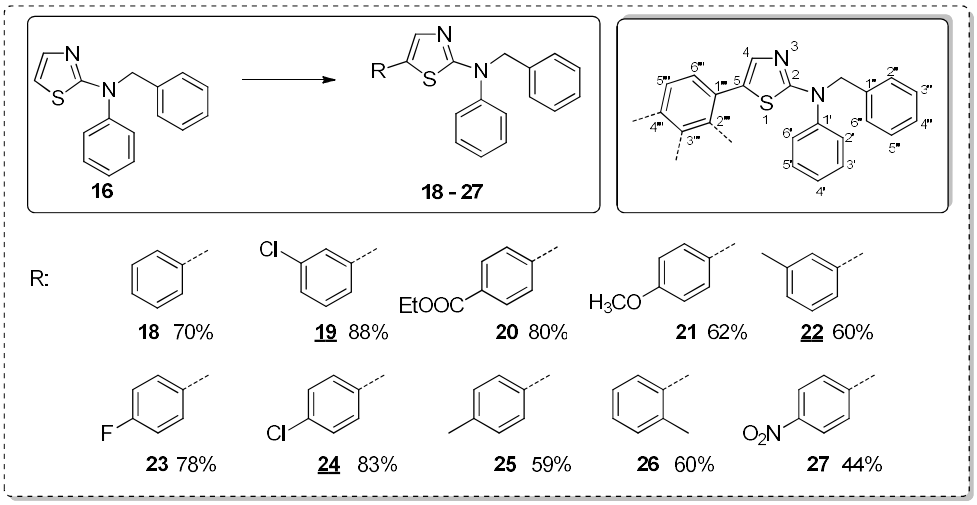


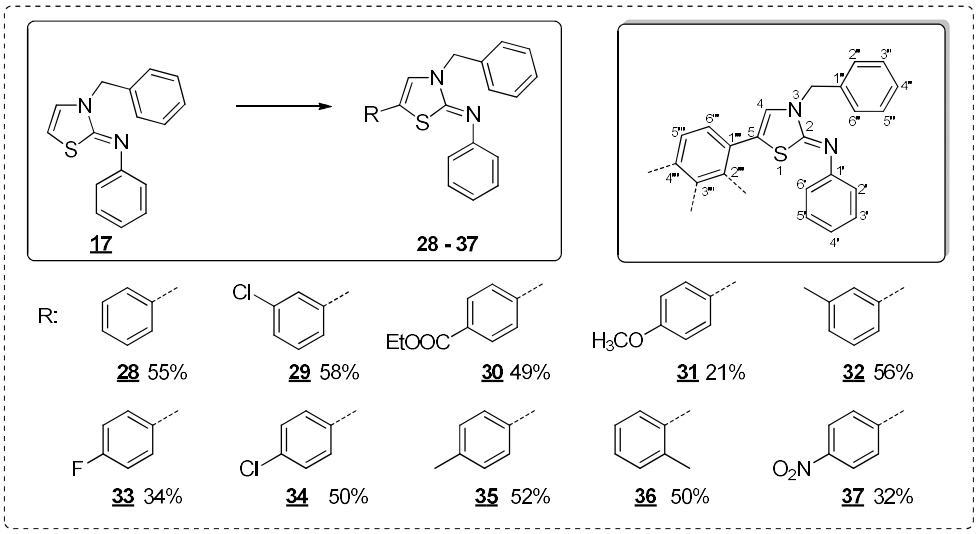
❖ Hesperetin derivatives

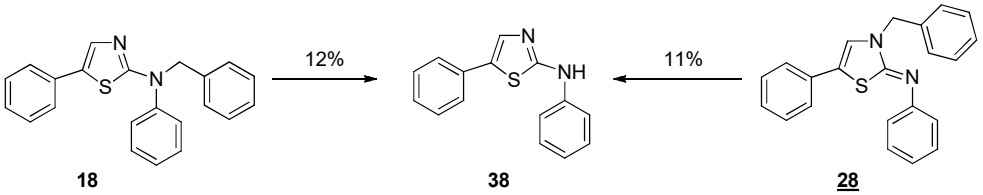


❖ Thiazole derivatives

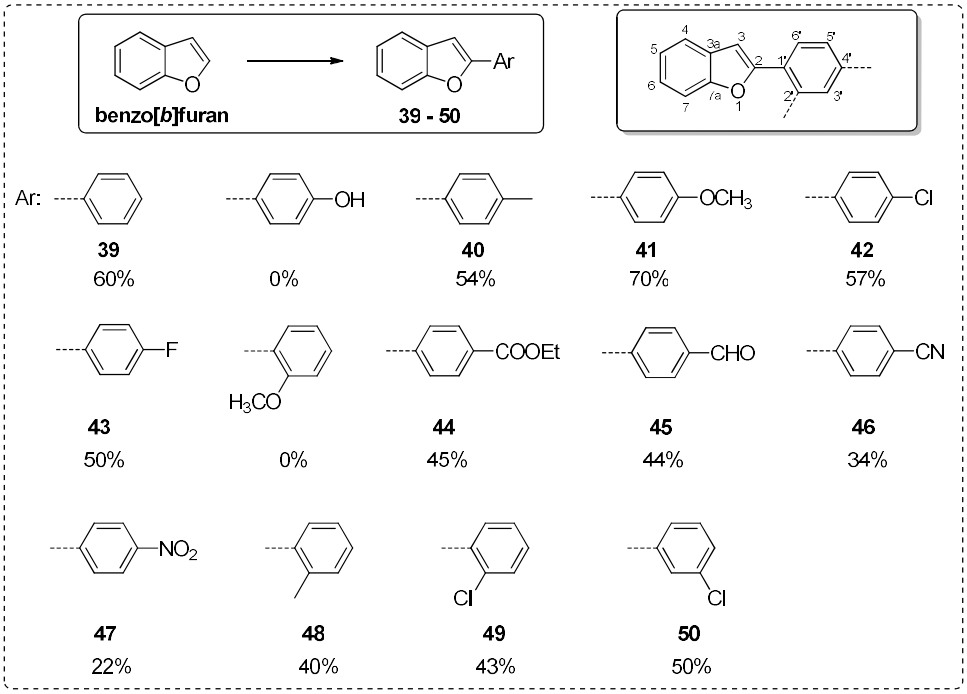


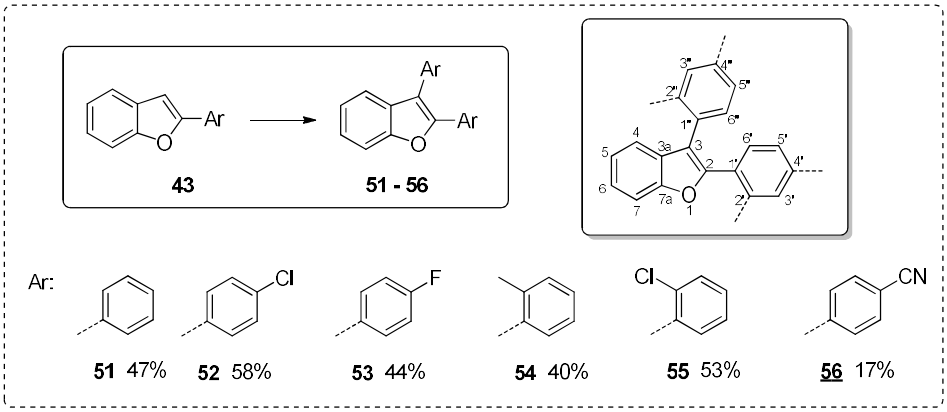


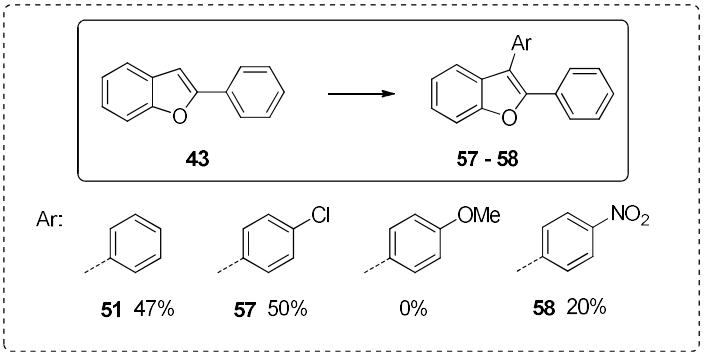


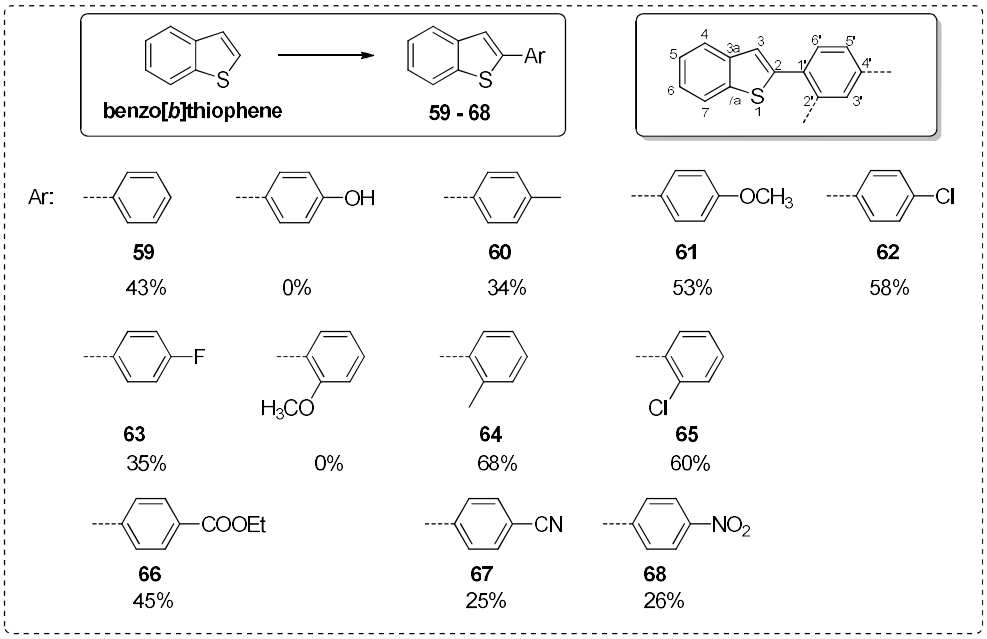


❖ C-H Activation on benzo-fused heterocycles








benzo[b]thiophene
59 - 68
Ar:
59
43%
OH
0%
60
34%
OCH3
61
53%
Cl
62
58%
F
63
35%
H3CO
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64
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Cl
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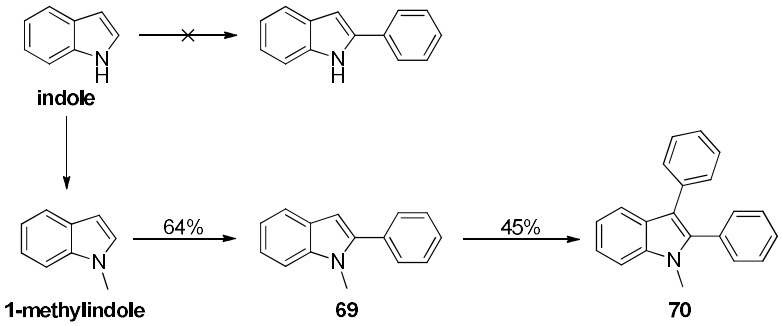
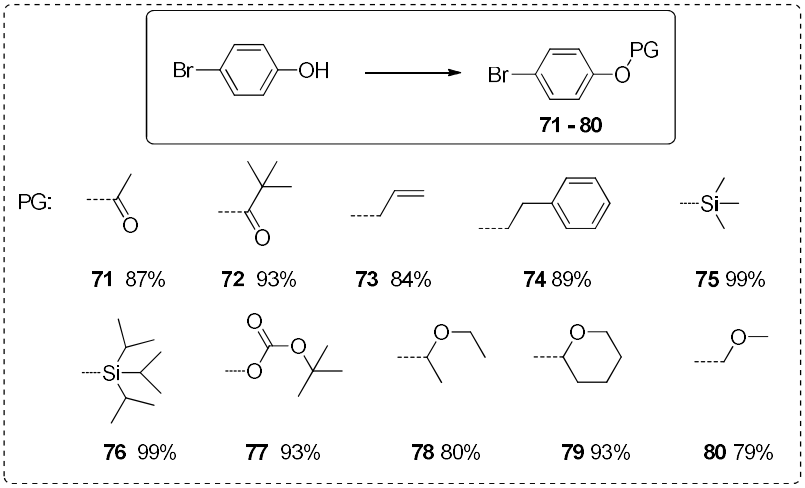
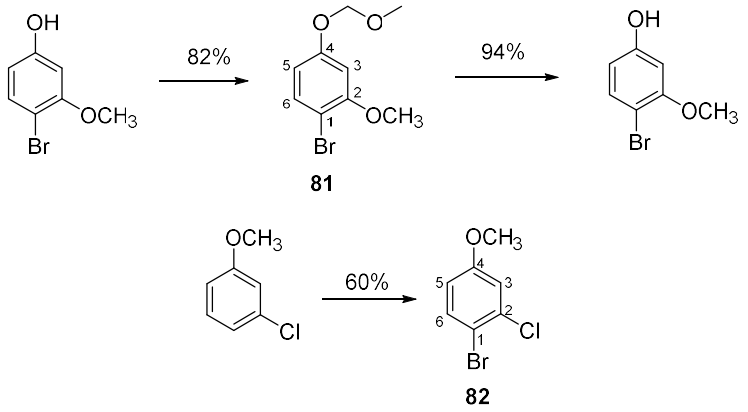
60%
COOEt
66
45%
CN
67
25%
NO2
68
26%

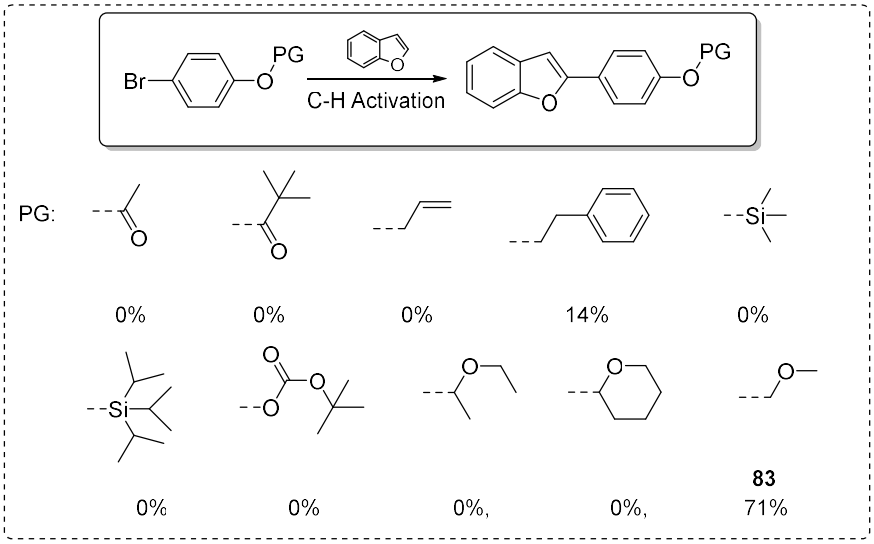

indole
64%
45%
1-methylindole
69
70

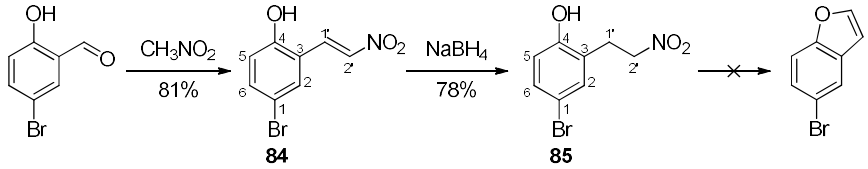
❖ Synthesis of aryl sources for total synthesis of neolignans

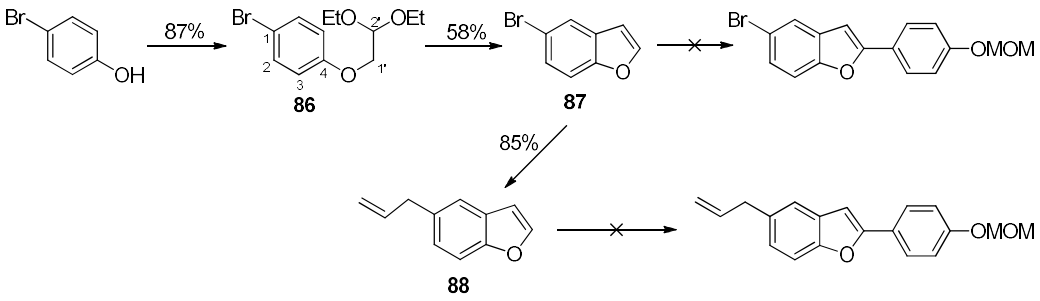


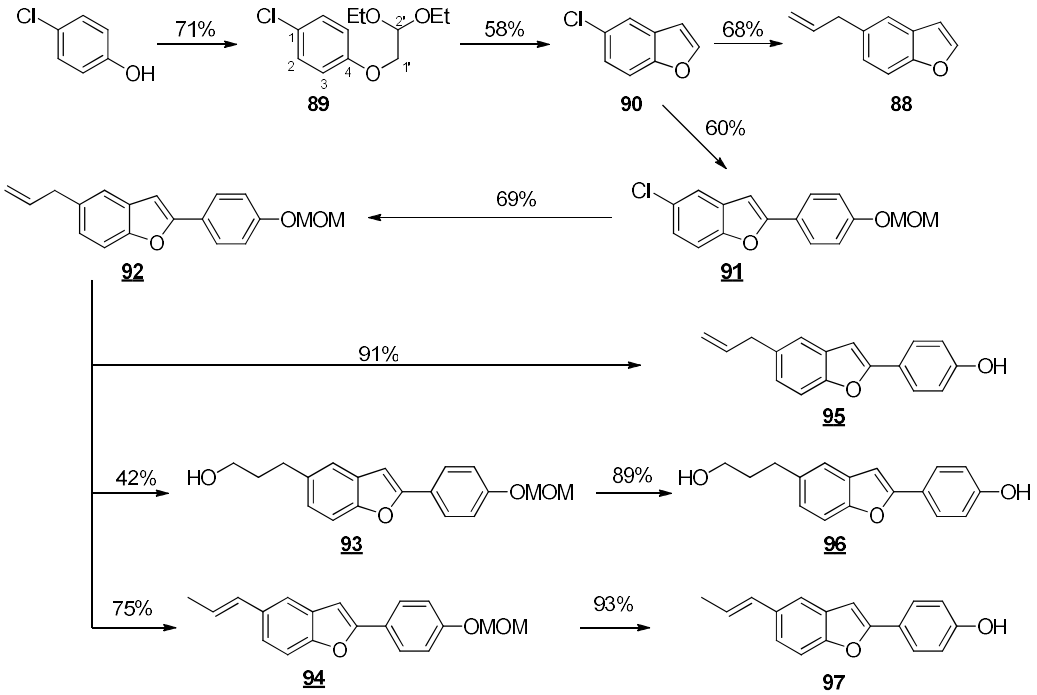


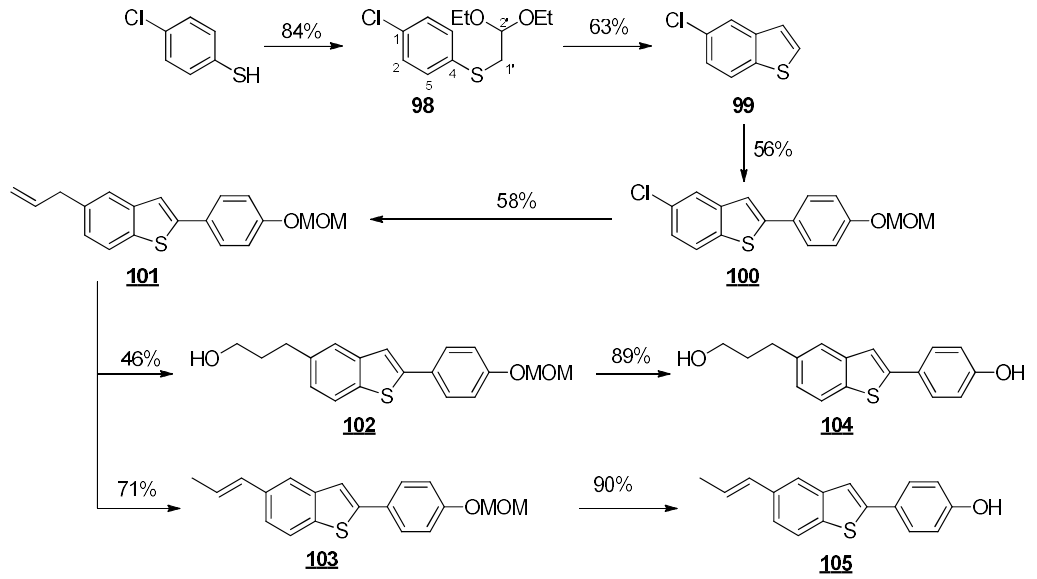
❖ Total synthesis of benzo-fused based neolignans








71%
58%
68%
60%
69%
91%
42%
89%
75%
93%
89
90
88
92
91
95
93
96
94
97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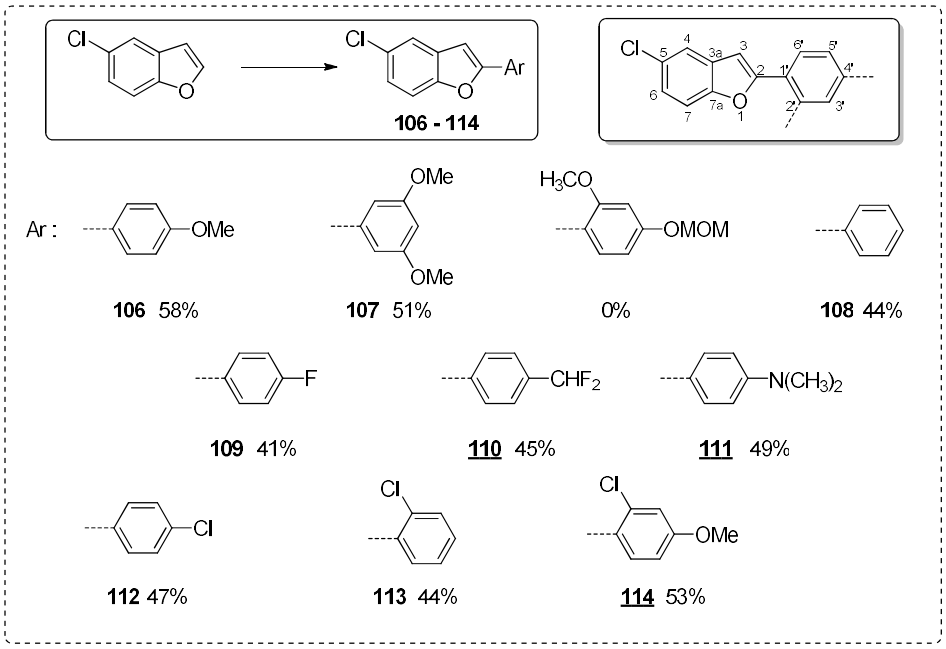
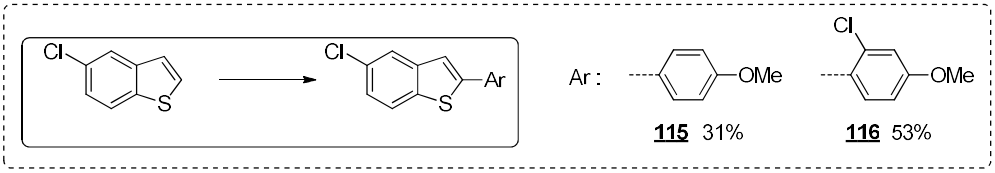
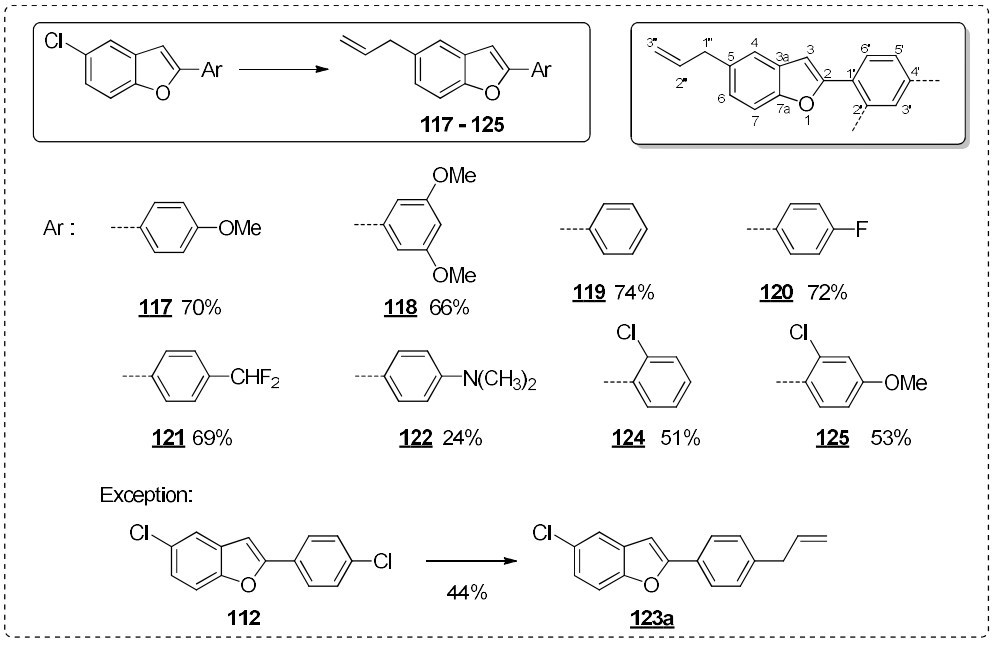
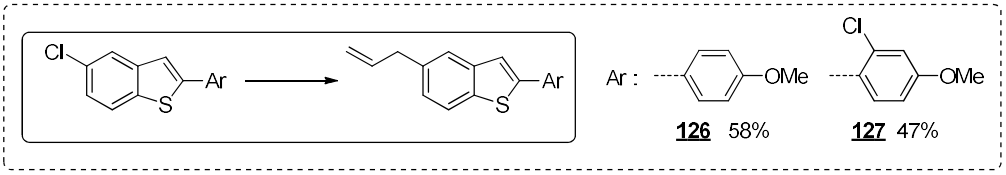
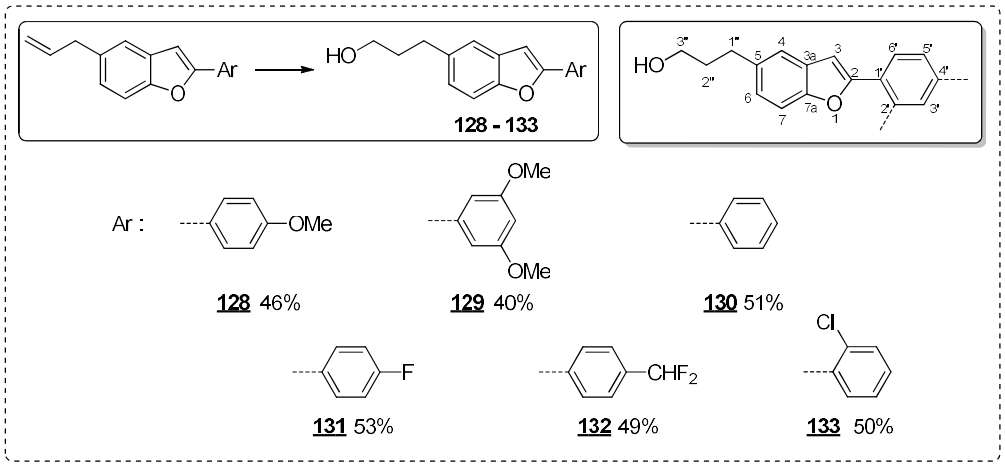
58%
46%
89%
71%
90%
98
99
101
100
102
104
103
105

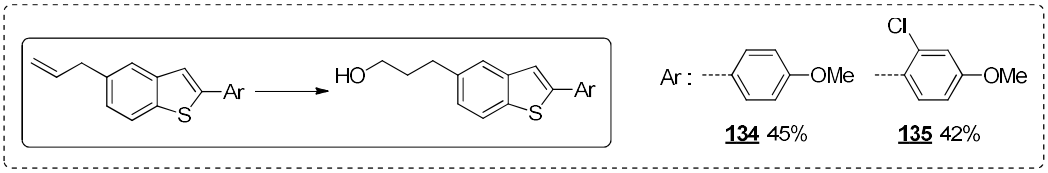

106 - 114
Ar :
OMe
OMe
OMe
H3CO
OMOM
F
CHF2
N(CH3)2
Cl
Cl
OMe
106 58%
107 51%
0%
108 44%
109 41%
110 45%
111 49%
112 47%
113 44%
114 53%

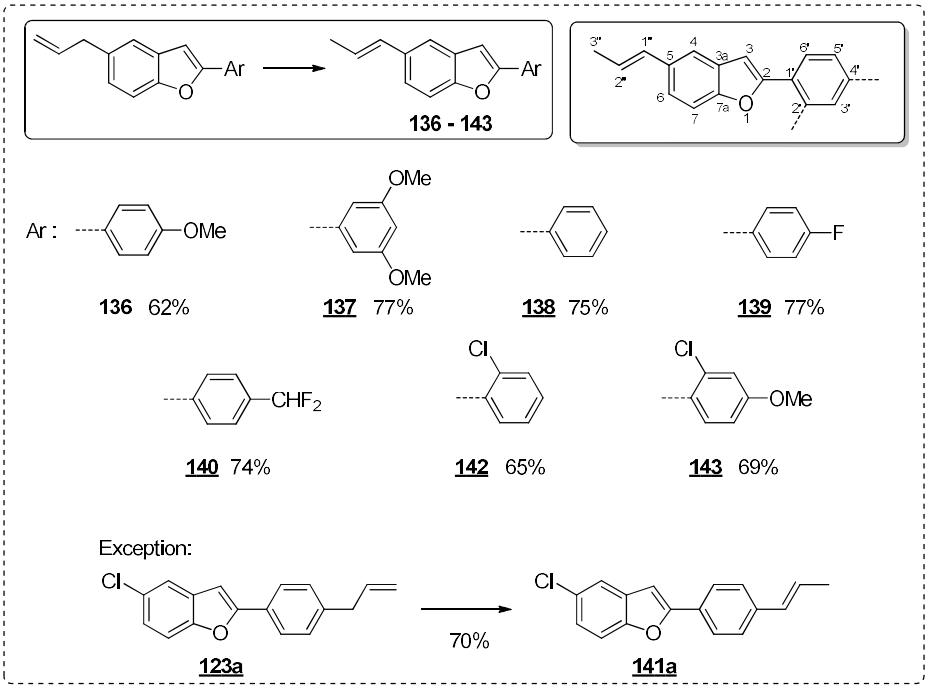

Cl
S
Ar
Ar :
OMe
OMe
115 31%
116 53%

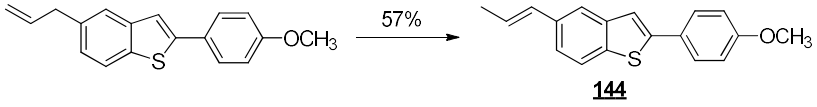

Cl
O
Ar
117 - 125
Ar :
OMe
OMe
F
CHF2
N(CH3)2
Cl
Cl
OMe
117 70%
118 66%
119 74%
120 72%
121 69%
122 24%
124 51%
125 53%
Exception:
Cl
Cl
44%
112
123a

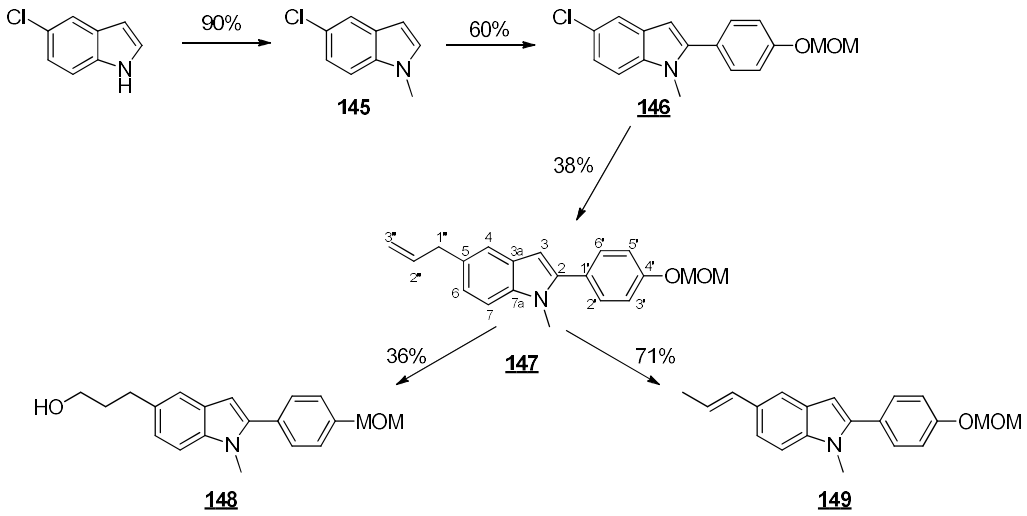

Cl
S
Ar
Ar :
OMe
OMe
126 58%
127 47%


Ar
HO
Ar
O
128 - 133
HO
3"
1"
2"
4
5
6
7
3a
7a
3
2
1
O
1'
2'
6'
5'
4'
3'
Ar :
OMe
OMe
OMe
128 46%
129 40%
130 51%
F
CHF2
Cl
131 53%
132 49%
133 50%


Ar
HO
Ar
S
Ar :
OMe
Cl
OMe
134 45%
135 42%


Ar
Ar
O
136 - 143
3"
1"
2"
4
5
6
7
3a
7a
3
2
1
O
1'
2'
6'
5'
4'
3'
Ar :
OMe
OMe
OMe
136 62%
137 77%
138 75%
F
139 77%
CHF2
Cl
Cl
OMe
140 74%
142 65%
143 69%
Exception:
Cl
O
123a
70%
Cl
O
141a


OCH3
S
57%
OCH3
S
144


Cl
N
H
90%
Cl
N
145
60%
Cl
N
OMOM
146
38%
3"
1"
2"
5
4
3a
3
6
7
7a
N
2
1'
6'
5'
4'
2'
3'
OMOM
147
36%
71%
HO
N
MOM
148
N
OMOM
149

A Development on naringenin and hesperetin to control Fireblight disease

A I Introduction

A I.1 Natural products with bioactivity and its application

Natural products (secondary metabolites) have been going along with human civilization for long time. They originate from a variety of sources such as plants, animals, fungies and microorganisms. These natural compounds were used as drugs or pesticides, based on experience, when people have not known anything about chemistry. Now a day, more than 50% of approved drug are related directly or indirectly to natural products.[1] These small molecules were used directly, were modified by semi-synthesis or became model for artifical active compounds.

In modern agriculture, with more and more caring about environment, natural compounds became interesting again to replace synthetic pesticides. One of the advantage of natural originated pesticides is that they do not have long half-lives because of their environmentally friendly sturture.[2]

Despite the development of medicine chemistry, there are a lot of natural compounds found and used for hundred years such as aspirin, morphine, quinine, nicotine and the family of anti-biotic penicillin.[3]

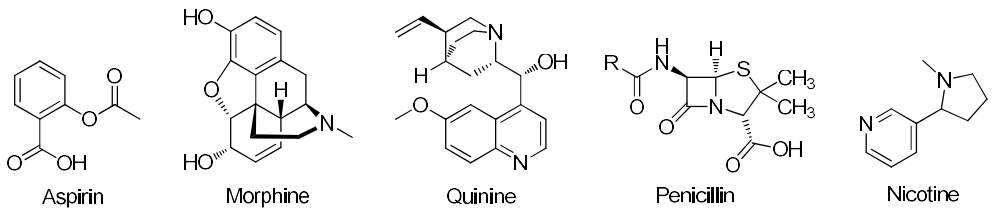


Figure A-1: Example of natural compounds with bioactivity

Recently, the isolation of new natural products and their bioassay still provide new clinical candidates and drugs. With the analysis of natural derived drugs from 1981 to 2014, Newman and Craig confirmed that they are still a significant source of new drugs, especially in the anticancer and antihypertensive therapeutic areas.[1b]

Back to 1928 when penicillin was first discovered by Fleming, the isolation and synthesis of penicillins opened a revolution in the drug discovery research. The success of penicillin led to the discovered of new anti-biotics occurred on large microorganism culture collections.

Natural product can not only be used directly but also lead to novel drugs using the semi-synthesis or total synthesis of similar structures. Using mechanism-based screening for bioassay-guided fractionation can make a noteworthy development in drug discovery.[3] β-Lactamase inhibitor clavulanic acid from *Streptomyces clavuligerus*[4] and the HMG-CoA reductase inhibitor mevastatin from *Penicillium citrinum*[5] were discovered using such mechanism-based screening method. Compacin from *Penicillium brevicompactum* containing

bioactivity as antifungal was later confirmed as mevastatin.[6] Hence, structure of mevastatin and lovastatin were the model for a series of similar compounds called "statins" which were used as antilipidemic drugs until now.[7]

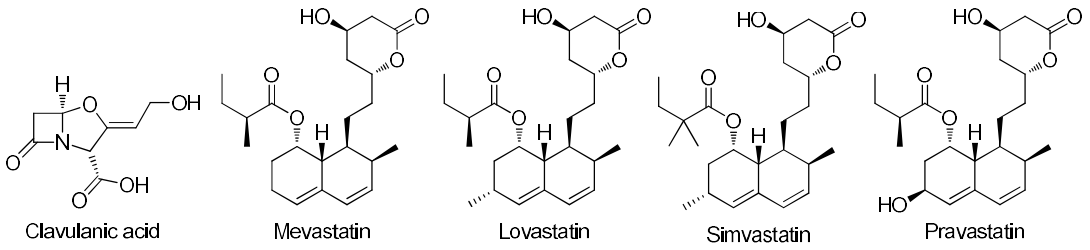


Figure A-2: Example of natural compounds with bioactivity

In addition, artemisinin, a sesquiterpene lactone containing an endoperoxide bridge (C-O-O-C) represents triggered research towards a novel series of antimalarial drugs. Artemisinin was first isolated from *Artemisia annua* Linn (Asteraceae), which was used traditionally by Chinese people for treating fevers.[8] Base on its structure, the endoperoxide bridge was determined to be the active centre of the compound since the disappearance of this moiety completely disable its antimalarial activity.[9] Therefore, many derivatives of artemisinin were semi-synthesized bearing such an endoperoxide bridge. They disply different advantages like less toxicity, solubility, longer half-life, slower release ability and so on.[10]

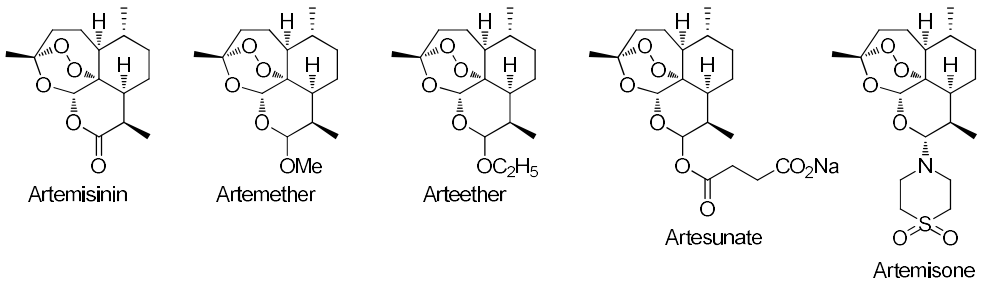


Figure A-3: Series of artemisinin derivatives was used as antimalarial drugs

Artemisinin derivatives are so far the strongest active antimalarial drugs and widely used throughout the world. The research on this series of drug is still invested in labs hence new compounds as well as new bioacitivity beside antimalarial were reported routinely.[10]

A I.2 About fireblight and its harassment

Fireblight is a plant disease comes from North America. Nowadays, it is still destroying crops in Western Europe and in the Mediterranean Sea area. The diease is caused by *Erwinia amylovora* bacteria, mostly on *Maloideae* family like apple, pear, etc. Only a few host plants belong to other subfamilies of the *Rosaceae*. Fireblight infections (Figure **A-4**) occur mostly during flowering. *E. amylovora* invades into plant tissues through opened wounds. The bacteria in moist can spread to nearby plants.

Figure A-4: Gala apple branch with "scorched" leaves after a severe fire-blight infection
(Photo by Peggy Greb http://www.ars.usda.gov/is/graphics/photos/mar07/k10805-2.jpg)

Fireblight is an unpredictable bacterial disease and can devastate apple and pear fields in a single season. It wipes out fields when they are still budding thus it is difficult to estimate the economic impact. A single severe epidemic could hold off the production for few years.

Firstly fire blight is still spreading geographically into new areas like Europe and Australia. Secondly, except for streptomycin, there was no registered product that can effectively control fire blight until 2000. Furthermore, the development of streptomycin-resistant strains of *Erwinia amylovora* is threatening the future use of this antibiotic in countries that still permitted the method. Finally, the new production methods, such as high-density planting, the use of rootstocks and of new cultivars, which are susceptible to fire blight, will also have an impact on the future economic importance of fire blight.[11]

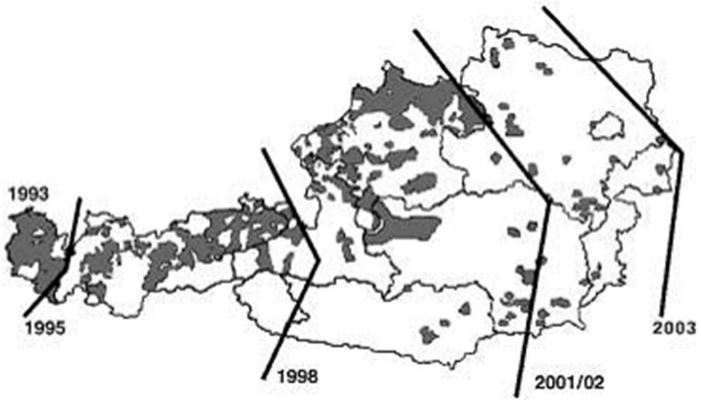


Figure A-5: Spread of fire blight in Austria from 1993 to 2003.
(graphic taken from reference 12)

In 1993, fireblight was detected for the first time in Austria, more particularly in Vorarlberg. During the following years, especially since 1998, a stepwise migration from the west to the east was observed despite that this country was considered as a fireblight protected zone in the European Union before.[12]

Chemical treatments have been limited for many years to a single copper oxychloride product but the use of the copper compounds is limited because of phytotoxicity, especially during spring, when most of the infections occur. In 2003, temporary application of the bioregulator *Regalis*[13] was authorized against secondary infections of *E. amylovora.* Only a few countries allow the use of the antibiotic streptomycin for

control of fireblight. These treatments can be very effective but strains resistant to streptomycin have been detected there. In some areas, the strict application of control measures has reduced the incidence of fireblight and possibly slowed down its progress. However these measures are not sufficient to protect against new, unexpected outbreaks.[11]

A I.3 Characteristics of *Erwinia amylovora* bacteria and the influence of flavanones

E. amylovora is the only bacterium inducing fire blight. It is a gram-negative bacterium belonging to the *Enterobacteriaceae* and its anatomy, physiology and serology have been well described[14]. During pathogenesis, the bacterium is exposed to a variety of plant-borne antimicrobial compounds. In plants of *Rosaceae*, many constitutively synthesized isoflavonoids affecting microorganisms were identified. In case of the infection, the plant self-defense mechanism was also mediated by bacterial multidrug efflux transporters which resist bacteria species as well as strange compounds. In *Escherichia coli*, *acrAB* of *E. amylovora* conferred resistance to hydrophobic and amphiphilic toxins.[15]

The *E. amylovora* outer membrane protein, TolC, might mediate a phytoalexin resistance process through its interaction with the multidrug efflux pump, *acrAB*.[16] A resistance mechanism to bypass the antimicrobial effects of secondary metabolites of the host defense has been studied for *E. amylovora*. Burse *et.* al. proved that the *E. amylovora* RND-family efflux pump *acrAB* was essential for resistance against plant-derived antimicrobial toxins, particularly against the apple phytoalexin, phloretin, and for a successful colonization of plant tissue.[17]

A I.4 Naringenin and hesperetin and their biological activities

Flavonoids, isoprenoids, and alkaloids compose three major classes of secondary metabolites synthesized by higher plants. These compounds are an essential part of adaptation to the life of plants. They are implicated in a broad range of physiological processes and have been considered to be important players in the protection of plants against potential pathogens. They may be preformed compounds present in healthy plant tissue or may be synthesized *de novo* in response to pathogen attack.[18] Only pathogens that can circumvent and, consequently, tolerate these plant inhibitors will further proliferate and continue to harm the plant.[19] Resistance strategies to combat antibiotics include enzymatic inactivation, alteration of the target structure, and reduced uptake.[20] In contrast to specific resistance mechanisms, a large number of so-called multidrug efflux transporters have been found to recognize and efficiently expel a broad range of structurally unrelated compounds from the invader cells. They are mediated by membrane-bound efflux pumps that enable to transfer cytotoxic compounds.[19, 21]

Hesperetin and naringenin are flavones obtained from the hydrolysis of hesperidin and naringin, respectively.[22] Hesperidin (hesperetin-7-rutinoside) and narirutin (naringenin-7-rutinoside) are the major flavonoids of oranges and mandarins. The main flavonoids of grapefruit are naringin (naringenin-7-neohesperoside) (70%) and narirutin (20%).[23] They cause the specific bitterness in taste of these citrus fruits because of their glycoside moiety.

Similar to other flavonoids, hesperetin and naringenin as well as their derivatives contain a plentiful of interesting biological activities. Hesperidin was reported as an active inhibitor of kinases and phosphodiesterases which are essential to cellular signal transduction and activation in an inflammation process.[24] Sakata *et* al. pointed out hesperidin as potential inhibitor of lipopolysaccharide (LPS) which induced overexpression of COX-2, inducible iNOS, overproduction of PGE-2 and nitric oxide (NO)[25] while Galati *et* al.

found that arachidonic acid and histamine release which are involved in inflammatory processes can also be inhibited by hesperetin.[26]

On the other hand, naringenin and its glycosides were reported with many anti-inflammatory activities, too. These flavanones are effective in the inhibition of pro-inflammatory cytokines induced by LPS in macrophages, that relate directly to periodontitis disease.[27] On another anti-inflammatory effect, they inhibit iNOS expression and nitric oxide production, help attenuating LPS/interferon (IFN)-γ, which induces TNF-α production in glial cells, originate to neuro-inflammatory injury.[28]

Moreover, hesperetin 7-glucuronide (Hp7G), a derivative of hesperetin, performed an influence on osteoblast differentiation. Therefore it could be a potential anticancer agent that could be used against carcinogenesis by minimizing DNA damage, tumor development and proliferation.[29]

Hesperetin plays another role as antiviral agent and was proved to be effective on fighting herpes simples, polio, parainfluenza, and syncytial viral infections, while naringin has no effect [30]. In a recent study, hesperetin showed a moderate antimicrobial activity against *Salmonella typhi* and *Salmonella typhimurium*.[31] With ability of inhibition of histamine release from pertinent mast cells in rats, hesperetin was suggested to have antiallergic activities.[32]

A I.5 Aim of study

Scanning a handful of flavanones, Weingart and Ullrich *et al.* found that naringenin significantly inhibited growth of the *acrAB* mutant in *E. amylovora* which plays an important role as a protein complex required for virulence of *E. amylovora* in resistance toward apple phytoalexins. The promoter activity of *acrR*, encoding a regulatory protein involved in *acrAB* expression, was increased by naringenin. [17]

E. amylovora is a gram negative bacterium so that to push active ingredients throught its membrane is a challenge. Naringenin and hesperetin need some modification to be able to get into the cell and perform their activities on the bacteria.

Gram negative bacteria are well protected by multilayer membranes which are highly lipophilic. Therefore, the free phenolic groups in naringenin and hesperetin must be protected to reduce the hydrophilicity. There are many protecting groups for phenolic hydroxyl but not many can be deprotected easily inside the cell by enzyms in order to act as “pro-drug”. We decided to use ester protective groups like acetyl and pivaloyl which can be deprotected by easterase enzymes. On the other hand, the carbonyl group at C-4 of naringenin and hesperetin are another obstacle for those compounds to get through the lipopolysaccharide outer membranes. Therefore, a reduction is required.

To be summed up, this work package was focused on a facile protocol to produce flavonoid substances that contain protected phenolic OH as well as reduction of the carbonyl group. Collection of the products was subsequently tested on *E. amylovora* bacteria by a collaboration partner at TU Wien (group of Prof. Stich) to evaluate their potential for the control of fireblight.

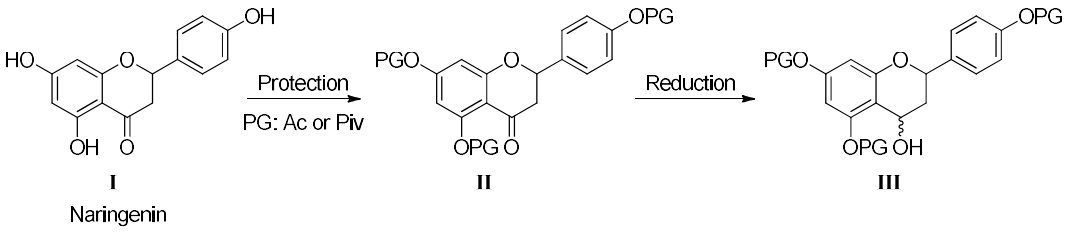
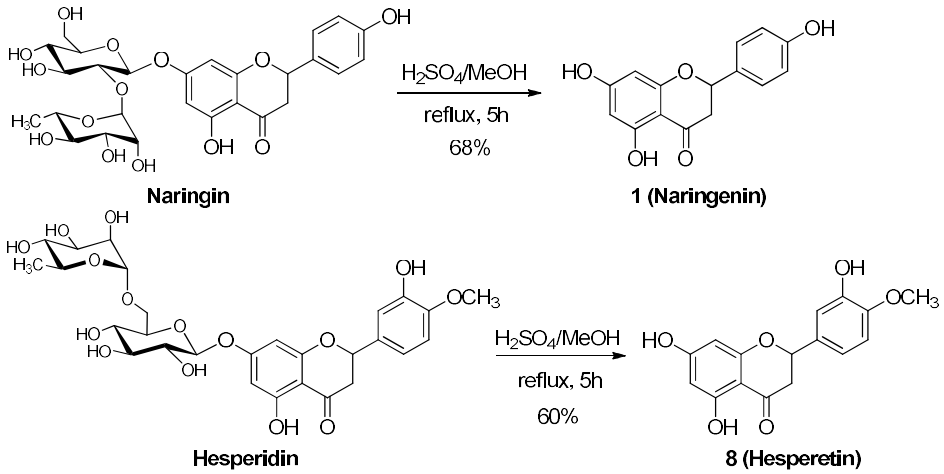


Figure A-6: Synthesis pathway sketch of the project

A II Results and discussion

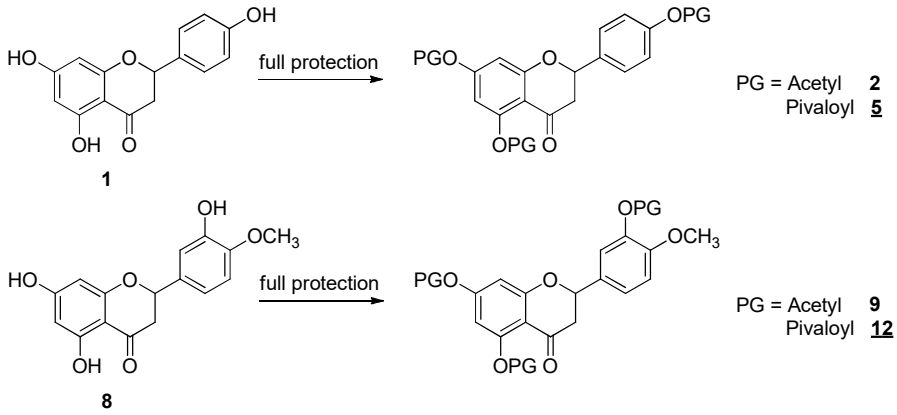
We decided to use naringin and hesperidin as starting material for the project. We collected naringin and hesperidin from student lab courses with about 90% purity isolated from orange peel. Hydrolysis in acidic pH occurred via procedure **A** (see Experimental Part) which was developed from the hydrolysis of hesperidin protocol from the group of Lahmer.[22]



Scheme A-1: Hydrolysis of naringin and hesperidin

Naringenin and hesperetin was obtained and purified from the hydrolysis reactions with good yields of 68% and 60% respectively.

There are many ways to put an acetyl protective group on phenolic hydroxyl groups.[33] One of the most common methods is using acid anhydrides in the presence of base and DMAP as catalyst [34].



Scheme A-2: Full protection of naringenin and hesperetin

This method worked well with naringenin and hesperetin and gave good yields of fully protected products (72% and 76% respectively for acetyl protection and 67% and 65% respectively for pivaloyl protection). The procedure used 4.0 equivalents of acid anhydrides (excess amount) in presence of 10 mol% of DMAP catalyst (procedure **B**, see Experimental Part) to warrant the protection on all 3 hydroxyl groups.

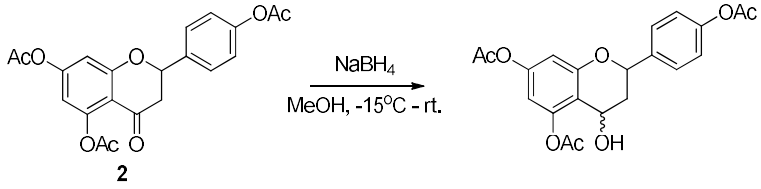
Table A-1: Full protection of naringenin and hesperetin

Starting material	Protecting group	Protected product	Yield
Naringenin (1)	Acetyl	**2**	72%
	Pivaloyl	**5**	67%
Hesperetin (8)	Acetyl	**9**	76%
	Pivaloyl	**12**	65%

isolated yield

Reduction of carbonyl group in flavones should not be a problem. Using of borohydride compounds to reduce carbonyl groups is well established for a long time.[35] At recent time, this method is still used for reduction of natural compounds such as flavones because of the mild condition and the commercial availability of the reducting agent.[36] In the literature, $NaBH_4$ was generally used without addition of any catalyst, in methanol or ethanol as solvent and at a temperature range of -15 °C to room temperature.

Therefore, reduction of **2** by $NaBH_4$ was tested in methanol at temperatures between -15 and room temperature. The reaction was monitored by TLC.



Scheme A-3: Reduction of 2 using $NaBH_4$ in MeOH

On TLC a new spot (**P1**) appeared at R_f = 0.25 in LP/EtOAc 2:1 lower than the starting material **2** (Figure **A-7**, **(a)**). This spot was found in blue color under UV lamp at 254nm and turned orange in acidic chromatic staining agent. However, in the efforts to isolate this new product, its NMR spectra were unclear and inconclusive. The same result was observed in the reduction of **9**. Surprisingly, the signal of a carbonyl carbon still showed up in ^{13}C-NMR, thus we assumed that the reduction was incomplete and a decomposition of the flavone ring system could probably happen under strong basic conditions.

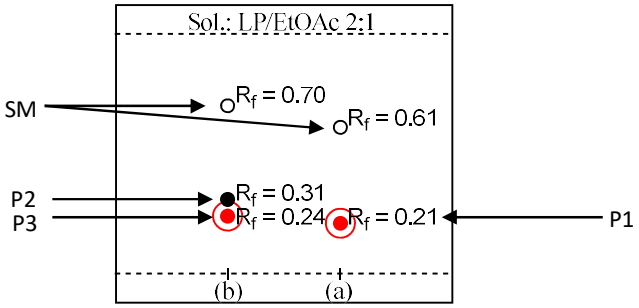
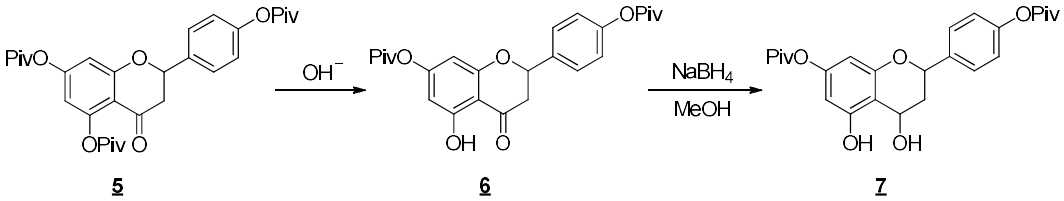


Figure A-7: TLC monitoring reductions
(a) Reduction of 2; (b) Reduction of 5

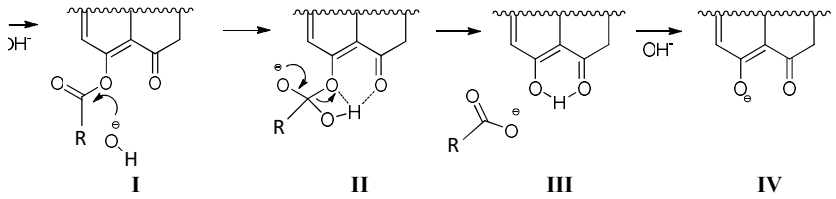
On another shot of the same reduction condition on **5**, 2 new spots (**P2**, **P3**) were found on TLC, below the starting material spot (Figure **A-7**, **(b)**). **P3** is actually not UV active but appeared as orange color when sprayed by acidic chromogenic reagent (TLC stain solution 2, see Experimental Part).

P2 and **P3** were isolated by column chromatography and identified by NMR methods. **P2** was measured as bis-protected naringenin (**6**) with peaks of 2 pivaloyl groups and a carbonyl carbon. **P3** is the reduced product of **P2** with a new peak of OH and the disappearance of the carbonyl carbon. (Scheme **A-3**)



Scheme A-4: Reactions in the reduction of compound 5 by $NaBH_4$

Compound **P2** was collected as major product of the reaction, telling that the reduction did not proceed in the expected way. The strong base of the reducing agent seems to easily hydrolyze the fully protected compound into the bis-protected one (**3** or **6**). The weakest ester group at C-5, due to strong intramolecular hydrogen bond in the CO(4) and OH(5) moiety of flavonoids, [37] will be the first group to be cut off to obtain keto-enol system (**III**) that is preferred. (Scheme **A-5**)

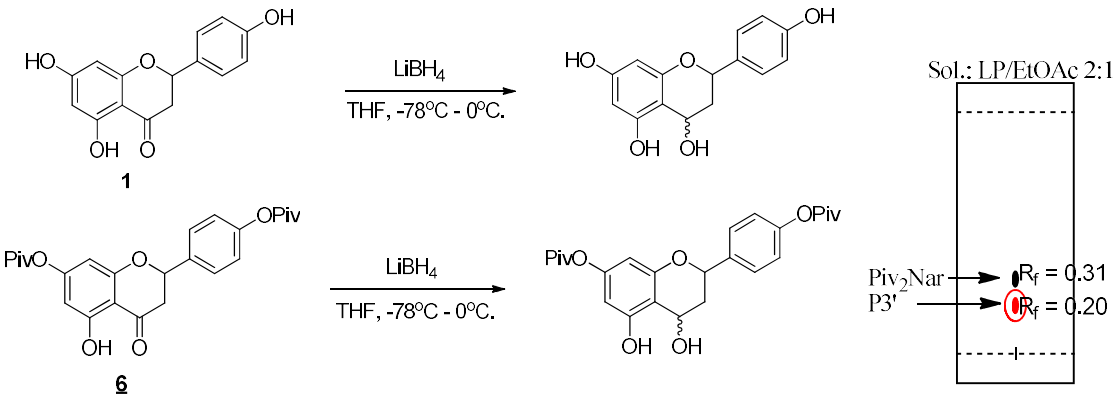


Scheme A-5: Proposed mechanism of flavonoid hydrolysis at C-5

The reduction of **5** hinted the propensity of the reaction on **2** because those two reactions must happen in similar ways. The TLC of the reaction (Figure **A-7**) showed a new spot which was actually UV active and then changed the color in acidic chromatic agent because there were two compounds **3** and its reduced product **4** at the same R_f.

As in our assumption, the reduction of **5** led to the hydrolysis of the starting material first because of the weakened bond at C-5 to obtain **6**. The basicity of $NaBH_4$ was not enough to cleave those bonds at C-7 and C-4' at -15 °C or even room temperature. Subsequently, the reduction took place on **6** but $NaBH_4$ is not reactive enough to fully convert the carbonyl at the same low temperature. Both **6** and **7** appeared as the by-products of the reaction. The reaction was once carried out at -78 °C (temperature of cooling bath) but compound **6** was already formed after 5 minutes while the reduction did not seem to proceed. A stronger reductive agent like $LiBH_4$ or even $LiAlH_4$ could be more effective but the more reductive it is since stronger basicity will apparently come along.[38]

Since the hydrolysis is inevitable with such boro-hydride complexes despite our effort to reproduce a protocol from the Deodhar group,[36c] we turned our focus on the reduction before the protection. Thus, naringenin and **6** were reacted with $LiBH_4$ in THF while increasing the temperature slowly from -78 °C to room temperature (Scheme **A-6**, procedure **C**). Naringenin showed no conversion even at room temperature but on the other hand, **6** gave full conversion after 4 hours at 0 °C (the reaction was monitored by TLC).

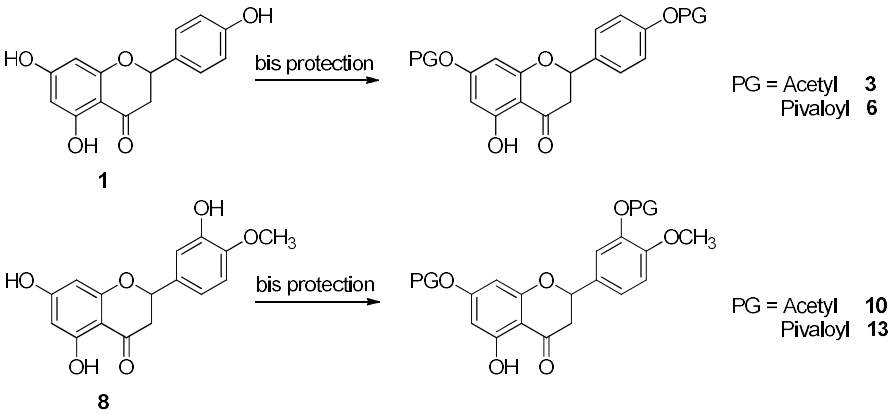


Scheme A-6: Reduction of 1 and 6 using $LiBH_4$ in THF

The reduction of **6** produced one product **P3'** (Scheme **A-6**). It was identified by NMR methods then compared to analytic results of the by-product obtained from the reduction of **5** before (P3, see Figure **A-7**). Although R_f of P3' is slightly lower than R_f of P3, NMR results of both products are the same. The difference of R_f could be explained by the difference of pH in the sample. Moreover, the reduction proceeded in good yield (44%), which is significantly higher than the reduction of the fully protected one **5**. This result once again emphasized the assumption that the reduction product is **7** which was already hydrolyzed.

The full conversion of the reaction suggests a good opportunity on the application of this procedure on **3** as well as **10** and **13**. But first of all, a protocol to synthesize **3** and **10** needed to be developed. Since the C-5 is the easiest position to hydrolyze, it is the most challenging one to esterify, even more difficult than phenolic groups that are already less nucleophilic than aliphatic hydroxyl groups. There are two reasons to explain it. This OH is hindered and less nucleophilic because of hydrogen bonding to the adjacent carbonyl group (see structure III, Scheme **A-7**). Procedure **B** used acid anhydrides as acyl sources but still required DMAP catalyst to promote the full protection. DMAP is stronger nucleophilic than an alcohol and the newly formed intermediate is less hindered, the acetyl group is still polarized and DMAP is a good leaving group.[39] All of these promote the reaction with hydroxyl groups.

The lack of DMAP could slow down or even restrain the reaction on the least reactive OH. Using only 2.5 equivalents of Ac_2O and 2.5 equivalents of pyridine in the absence of DMAP to react with naringenin (or hesperetin) in DMF turned out only bis-protected product in good yield (see procedure **B**).



Scheme A-7: Bis protection of naringenin and hesperetin

The reaction displayed the same outcome with Piv_2O and naringenin (or hesperetin). All results are shown in Table **A-2**.

Table A-2: Bis protection of naringenin and hesperetin

Starting material	Protecting group	Protected product	Yield
Naringenin (1)	Acetyl	**3**	60%
	Pivaloyl	**6**	53%
Hesperetin (8)	Acetyl	**10**	78%
	Pivaloyl	**13**	58%

isolated yield

The success in preparation of bis-protected naringenin and hesperetin led to a newly proposed synthesis route in which the last step is to protect the last phenolic OH (Figure **A-8**).

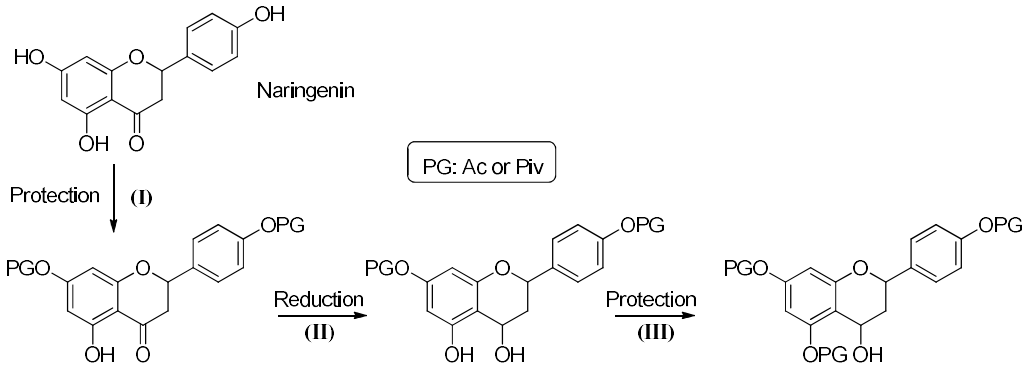


Figure A-8: New proposed synthesis route on naringenin

On step II, the reduction was subsequently carried out on all 4 bis-protected compounds. All results are shown in Table **A-3**.

Table A-3: Reduction on bis-protected naringenin/hesperetin

Starting material	Reduction product	Isolated Yield
2	**4**	48%
5	**7**	44%
9	**11**	43%
12	**14**	41%

The NMR spectra of compound **4** matched the precedent literature NMR spectra of (2*R*,4*R*)-4-(7-acetoxy-4,5-dihydroxychroman-2-yl)phenyl acetate.[40] This result can also be explained in Figure **A-9**. This pattern of ^{1}H-NMR were also found in all other reduction products **7**, **11**, **14** so we concluded that the reduction

of bis-protected naringenin and hesperetin were diastereoselective and led to the *cis* diastereomer products, only.

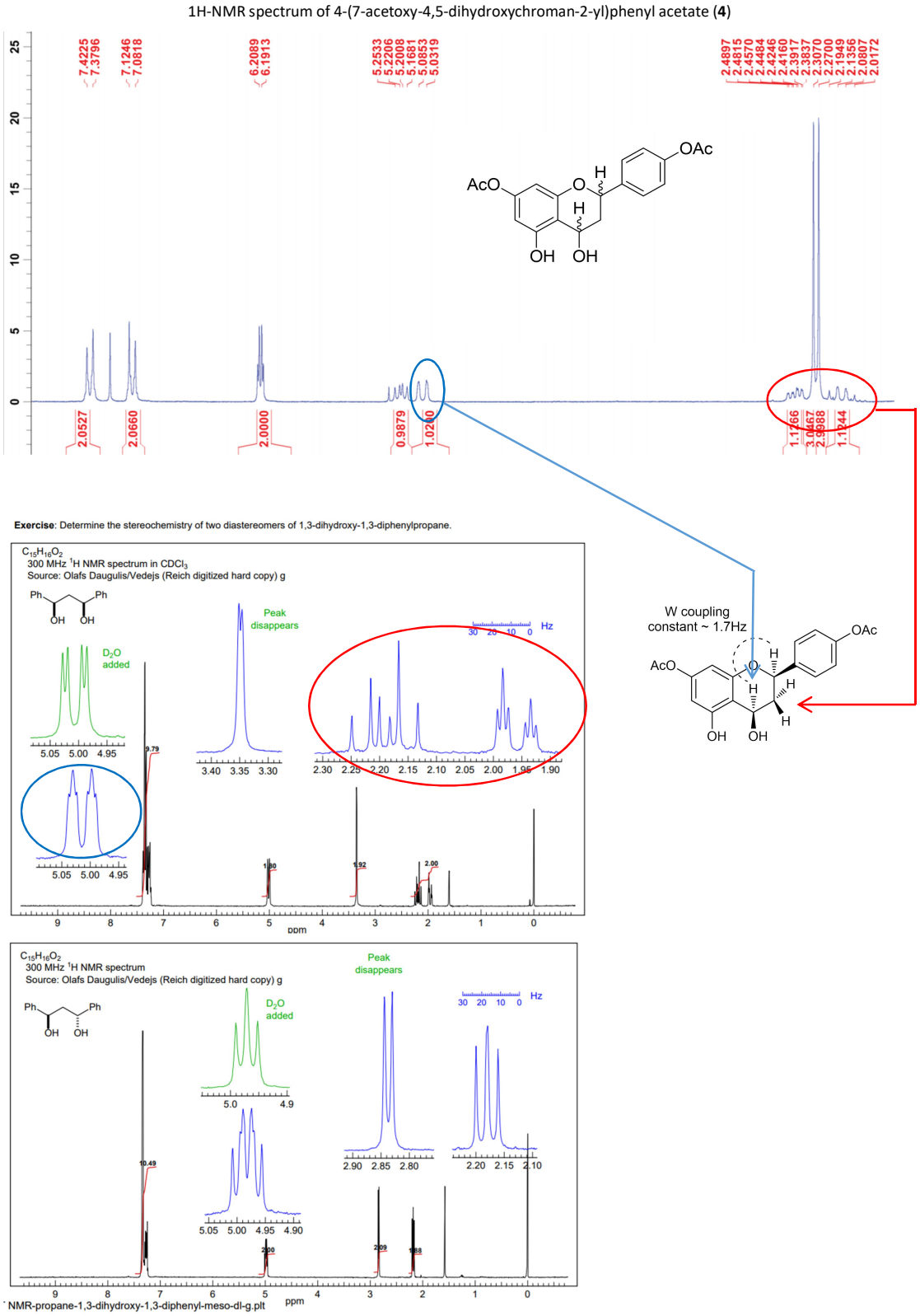
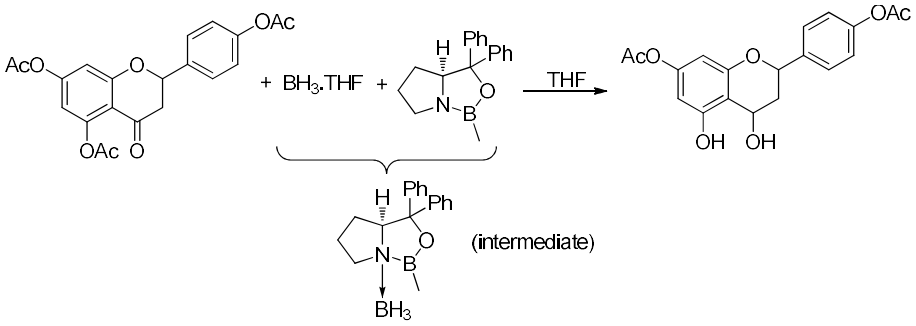


Figure A-9: Distinction of diastereomers on ^{1}H-NMR spectra

For step III, protection on compounds **4**, **7**, **11**, **14** using procedure **B** once again turned out to full protection on 4 OH groups that cannot be selectively cleaved off. There is only one way left to achieve the goal of the project which is to reduce the carbonyl on those flavones by another type of reductive agents without the hydrolysis.

The reduction by H_2 and Pd/C as catalyst was carried out under 5 atm overnight but no conversion was detected. There are many modern reduction methods applied on compounds similar to flavones, catalyzed by transition metal complex like Rh and Ru. [41] They looked very promising with good stereoselectivity even though those protocols have not been applied yet on either naringenin, hesperetin or any other flavone with a phenolic group at C-5. However, they are not as facile and practical as the goal of the project so we looked back to classical and popular methods which use less basic reducing agents.

Corey–Bakshi–Shibata (CBS) reduction uses BH_3.THF along with oxazaborolidine as catalyst (CBS catalyst), which mediate the enantioselective reduction of ketones. A reduction of Ac_3Nar (**2**) by 3 equiv. BH_3.THF and 0.3 equiv. S-(-)-2-methyl-CBS-oxazaborolidine in THF was tried. (Scheme **A-8**)



Scheme A-8: Reduction using CBS catalyst

The reaction was conducted at a temperature range from -20 °C to room temperature and stirring for 5 hours but no conversion was detected. The intermediate formed between BH_3 and CBS catalyst is seemingly too bulky to reach to the hindered carbonyl group at C-4.

Luche reduction also uses $NaBH_4$ reductive agent but a $CeCl_3$ catalyst could slightly reduce the basicity of the condition.[42] Ac_3Nar (**2**) was put in a reaction with 1 equiv. $NaBH_4$ and 1equiv. $CeCl_3.7H_2O$ in MeOH at -76 °C. There was no conversion until the temperature was increased to -10 °C. The reaction showed complete conversion after 4 hours. Products of the reaction were isolated and identified as the same as the result of the reduction with $NaBH_4$ or $LiBH_4$ before. The reduction and the hydrolysis probably happened at the same time.

Since the synthesis route in Figure **A-8** was so far the closest achievement to the goal of this project, derivatives of naringenin (compounds **2**-**7**) and of hesperetin (compounds **9**-**14**) were submitted to biological evaluation by the cooperation partner. Preliminary results did not confirm an improved activity of the novel compounds.

A III Conclusion

The hydrolysis side-reaction in the reduction using borohydride reactive agents is unexpected but inevitable. The overlap of products on TLC that cannot be detected on either GC-MS or TLC-MS are the most challenging that required a lot of time on determining whether the reduction did happen or not. However, it was finally solved and complete reductions were carried out on fully protected and bis-protected naringenin.

The desired end-products could not be synthesized but closely related derivatives; the carbonyl group is reduced in a practical and handy synthesis route with (*R*,*R*) diastereoselectivity (Figure **A-8**). Yields of total synthesis of compounds are shown in Table **A-4**.

Table A-4: Sum of the results

Starting material	Protected product	Yield	Reduction Product	Yield	Total Yield
Naringenin (1)	**2**	72%			
	3	60%	**4**	48%	**29%**
	5	67%			
	6	53%	**7**	44%	**23%**
Hesperetin (8)	**9**	76%			
	10	78%	**11**	43%	**34%**
	12	65%			
	13	58%	**14**	41%	**24%**

Isolated yield

Nevertheless, the presence of one non-protected phenolic OH group probably led to unexpected biology activities. More compounds with different protective groups or different procedures for reduction that can avoid the hydrolysis as well as more selective de-protections could be tried to improve the biological activities for such group of compounds.

B Thiazole

B I Heterocyclic compounds and their bioactivities

Synthetic organic small molecules have been extremely successful as bioactive compounds. In many of these substances an aromatic heterocyclic ring can be found, which again often contains nitrogen. Such heterocycles introduce rigidity in a structure and additionally they are able to interact with functional groups of an active site via their heteroatom(s). Amongst the many possible heterocycles, thiazole has proven to be of significant importance, occurring in a number of biologically relevant molecules such as thiamine (Vitamin B1)[43], ritonavir (an anti HIV protease inhibitor and one of the active compounds of the blockbuster drug Kaletra) or the cephalosporin antibiotic Cefdinir.[44]

B I.1 Animothiazole derivatives and their bioactivities

Amongst thiazole compounds, those carrying amine functionality seem to be of exceptional importance as can be seen from the examples in Figure **B-1**.[45] Actually, arylated thiazolamines seem to be privileged amongst bioactive thiazole containing scaffolds as NPY Y5 antagonists[45a], histone deacetylases inhibitors[45b], inducing autophagic cell death[45c], aurora kinase inhibition[45d], metabotropic glutamate receptor 1 (mGluR1) antagonist[45e], tyrosine kinase-3 inhibitor[45h], KDR kinase inhibitors[45i] or antifungal agents.[45j]

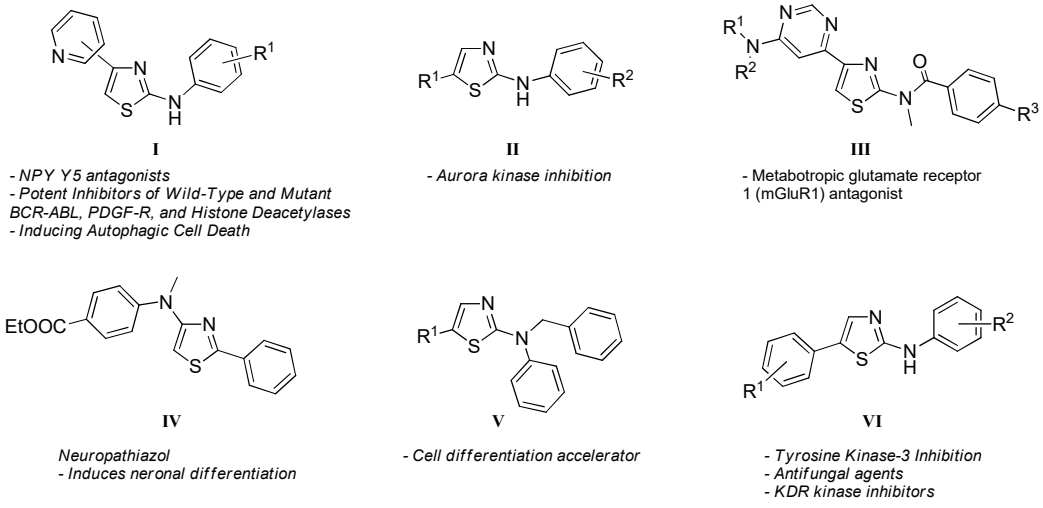


Figure B-1: Bioactive thiazolamine derivatives.

Two of the examples in Figure **B-1** show activity in the field of cell differentiation modulators (**IV** and **V**). This is of significant importance since employing synthetic small molecules (SySMs) for altering cell differentiation processes would be the preferred way to exploit this for therapeutic purposes as approval procedures for such compounds are well established. To date, intense research in this field is carried out and an increasing number of such compounds are being disclosed. [45f, 45g, 46]

In terms of bioactive thiazoles, Neuropathiazol **IV** was reported to induce a differentiation of multipotent adult hippocampal neural progenitor cells towards a neuronal phenotype. [45f] Within our group we synthesized *N*-benzyl-5-arylthiazol-2-amines of general structure **V** since their molecular geometry resembles that of Neuropathiazol to a certain extent and we were interested to study a prospectively similar biological activity. Interestingly, it was found that these compounds indeed influenced cell differentiation processes, however in a different way since those compounds showed good activity as differentiation accelerators [45g] of C2C12 skeletal muscle progenitor cells and not as neuronal differentiation modulators. Within this thesis an improved synthesis of compounds **V** is reported and also for the synthesis of regioisomers of these structures which carry the benzyl protecting group on the *endo*-cyclic nitrogen.

B I.2 Iminothiazole derivatives and their bioactivities

A selection of medicinally relevant compounds containing the iminothiazole scaffold is shown in Figure **B-2**. [47] These compounds and other members of the compound class have been reported to possess activity as platelet GPIIb/IIIa receptor antagonists,[47a] HIV-1 reverse transcriptase inhibitors, [47b, c] anti-inflammatory agents, kinase inhibitors, [47d-g] cytotoxic agents [47h, i] and a range of other activities. [47j-m] Moreover, pifithrin (Pft-α), a compound containing the 2-iminothiazole skeleton, has recently been identified as a potent inhibitor of p53 in vivo. This might be promising for the treatment of major neurodegenerative disorders (Parkinson's disease, Alzheimer's disease). [48]

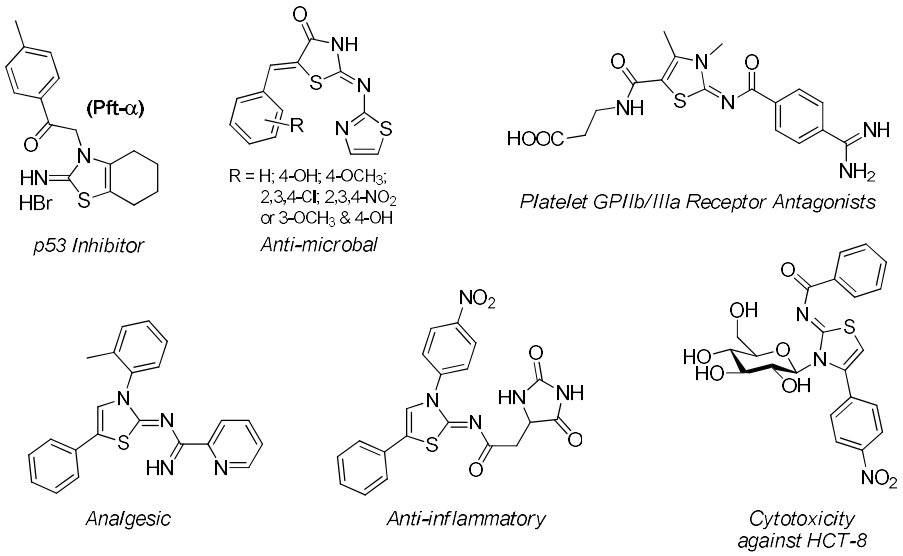
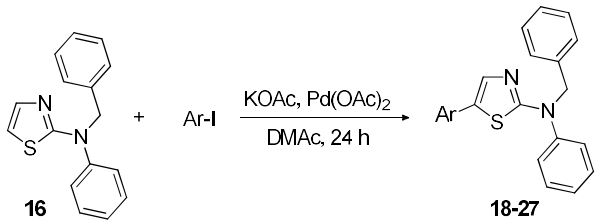


Figure B-2: Bioactive 2-iminothiazolines derivatives

B II Results and discussion

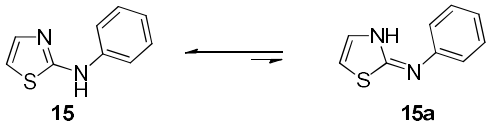
B II.1 Synthesis of aminothiazole and iminothiazol on demand

In our previous contribution[45g] we disclosed a new synthetic method for the preparation of compounds **18-27** involving direct arylation via C-H-activation as key step. Under palladium acetate catalysis, a range of substitueted 2-aminothiazoles reacted with aryl iodides in the presence of potassium acetate. No ligands were required for this reaction. In agreement with previous reports, the arylation took place selectively at the 5-position of the substrate. [49]



Scheme B-1: Direct arylation of *N*-benzyl-*N*-phenyl(thiazol-2-yl) amine by using aryl iodides as the aryl source

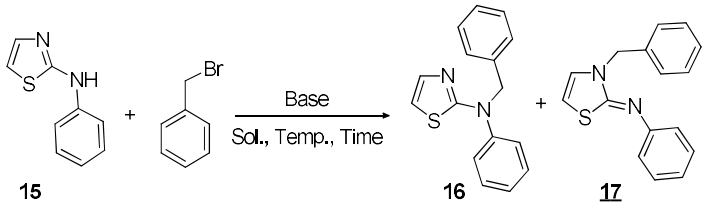
During the synthesis of starting material **16** we observed the formation of *endo*-cyclic benzylated compound **17** as a by-product (Table **B-1**). We explained the formation of this compound by considering that **15** is in equilibrium with its *exo*-cyclic imine form **15a** (Scheme **B-2**). Such an equilibrium has been reported previously for *N*-phenyl-(thiazol-2-yl)amine.[50] Both of these compounds can be deprotonated and subsequently benzylated, leading to the two regioisomeric products observed. As judged by their pK_a values, compound **15** (pK_a = 4.33) and **15a** (pK_a = 6.30) are reseasonably acidic, making triethylamine (pK_a = 10.7) sufficiently basic for their deprotonation.[51] Nevertheless, the type of base used for deprotonation seems to have a pronounced influence on the selectivity of the benzylation reaction.



Scheme B-2: Amine-imine equilibrium in 2-thiazolamines

We were interested in developing reaction conditions that lead to specific formation of either **16** or **17**. We found the best **16**/**17** selectivity of 5:1 to be obtained by using NaH as base in DMF at room temperature after 5 hours (Table **B-1**, entries 3-5). While maintaining the selectivity, the conversion of 66% (entry 3) was improved to 76% when 2 equivalents of NaH and a catalytic amount of NaI were applied (entry 4).

Table B-1: Synthesis of N-endo and N-exo benzyl thiazolamine in manner.

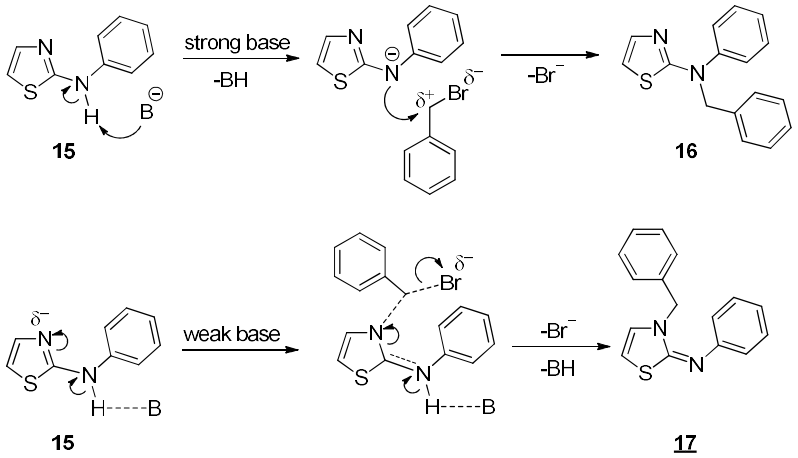


Entry	Base	Solvent	Temp.	Time	Conv.	Ratio 16:17
1[a]	Et_3N	Dioxane	120 °C	24h	76%	1:7
2[a]	Et_3N	Dioxane	120 °C	48h	78%	1:4
3[a]	NaH	DMF	rt.	5h	66%	5:1
4[b]	NaH	DMF	rt.	5h	75%	5:1
5[b]	NaH	DMF	rt.	7h	76%	5:1

[a] Substrate **15** (1equiv.), benzylbromide (1.3equiv.), base (1.3equiv.) as 0.3M solution in the respective solvent. Conversion and ratio of products was determined by GC with dodecane as internal standard. [b] 2.0 equiv. of base used and 0.1 equiv. of NaI added.

To invert the regioselectivity a change in base was most important: when the reaction was conducted at 120 °C in dioxane, using triethylamine as base, GC-analysis showed the formation of the products in a **16**/**17** ratio of 1:7 after 24 hours with a conversion of 76% (entry 1). Longer reaction times led to slightly increased conversion but also to an erosion of selectivity (**16**/**17** = 1:4 after 48 h) (entry 2), indicating that isomerization of the products can occur under the reaction conditions.

The outcome of these experiments can be rationalized by a switch in mechanism depending on the applied base. When NaH is used for deprotonation, benzylation might take place, whereas for deprotonation with triethylamine benzylthiazolium formation could precede deprotonation. This hypothesis is supported by the fact that the *endo*-cyclic nitrogen can be expected to have a lower nucleophilicity when compared with the corresponding anion and therefore requires higher temperatures to react.



Scheme B-3: Switch in mechanism depending on strong/weak base.

We were able to isolate both benzylation products **16** and **17** by column chromatography, although this was challenging because of their very similar R_f values in common mobile phases. Both **16** and **17** could be crystallized from their mixture with majority amount appearance in dichloromethane solution. To summarize, using different bases, we can produce mixtures of **16** and **17** in favor of either compound, which can then be separated via a final recrystallization step with yield of 50% and 57%, respectively.

B II.2 Development of direct arylation on aminothiazole

We have already reported the direct arylation of **16** using aryl iodides as aryl source. Before starting to investigate the direct arylation of **16**, we tested whether we could use the corresponding aryl bromides instead as more abundantly available reagents. In our original publication [45g] we noted that bromobenzene gave low conversion under the applied reaction conditions (KOAc 2 equiv., $Pd(OAc)_2$ 1 mol-%, dry DMAc, 120 °C).

We now revisited this procedure and quickly found that increasing the temperature to 140 °C was sufficient in order to get good yields of coupled products using only 1.5 equiv. aryl bromides within 24 h. In table **B-2** the results of the coupling protocol for both aryl halides are compared.

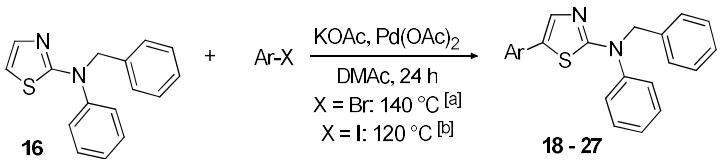
In case of substrate **16**, there is no clear trend whether bromides or iodides are the preferred aryl source. In several cases yields were significantly improved (Table 2, entries 3, 4, 6, 9) using aryl bromides but in others iodides proved to be superior (entries 1, 8).

Bromobenzene and iodobenzene gave product **18** in 70% and 85%, respectively (entry 1). Regarding the electronic nature of the substituents, electron donating and electron withdrawing groups were accepted in

both protocols. However, 4-iodoanisole required a higher catalyst loading of 10 mol-% indicating that the reaction is slower with electron-donating substituents. Furthermore, 4-bromo- and 4-iodonitrobenzene gave lower yields of **27** compared to the other examples, which can be explained by the ability of the nitro group to coordinate metal catalysts.[52] An ester functionality in *para*-position was well tolerated, irrespective of the halide leaving group (entry 3, **20**). Bromobenzenes bearing a chloro- or fluoro substituents also gave good yields in the reaction (entries 2, 6 & 7, compounds **19**, **23** & **24**).

Products **22**, **25** & **26** were obtained in essentially identical yields (59-60%) in the coupling of 2-, 3-, and 4-bromotoluene, which indicates that the reaction is not sensitive to sterically demanding reaction partners (entries 5,8, and 9). In case of o- and m-tolyl substituents, products **25** and **26** were obtained with the same yield within experimental error; however, reaction with the iodo-precursor was more efficient by about 20 % as compared to the bromotoluene series. Three examples were performed solely using aryl bromides (entries 2, 5, & 7) and gave generally good yields.

Table B-2: Result of direct arylation on 16.



Entry	R	Product	X = Br	X = I
1	phenyl	**18**	70%	85%
2	3-chlorophenyl	**19**	88%	n.i.[c]
3	4-ethylbenzoate ester	**20**	80%	60%
4	4-methoxyphenyl	**21**	62%	47%[d]
5	*m*-tolyl	**22**	60%	n.i.[c]
6	4-fluorophenyl	**23**	78%	71%
7	4-chlorophenyl	**24**	83%	n.i.[c]
8	*p*-tolyl	**25**	59%	77%
9	*o*-tolyl	**26**	60%	80%
10	4-nitrophenyl	**27**	44%	20%

[a] Reaction with ArBr: Substrate **2** (1.0 equiv.), ArBr (1.5 equiv.), KOAc (1.5 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 140 °C for 24 h. [b] Reaction with ArI: Substrate **2** (1.0 equiv.), ArI (2.0 equiv.), KOAc (2.0 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 120 °C for 24 h. [c] Reaction not investigated. [d] Protocol b but 10 mol-% catalyst loading.

B II.3 Regioselectivity of direct arylation of iminothiazole

We then set out to investigate the direct arylation of regioisomeric imine substrate **17**. 2-Iminothiazoles were previously synthesized by condensation of α-halo ketones and thiourea derivatives through the Hantzsch reaction[53] or Glaser–Hay oxidative coupling between aryl alkynes and an N-hydroxythiourea.[54] On the other hand, 2-iminothiazoles were observed in the methylation reaction of 2-anilinothiazoles[55] as well as in copper diacetate-catalyzed phenylation of 2-aminothiazole with triphenylbismuth diacetate.[56] The self-developed method of substitution turned out a more handy protocol to synthesize such compounds.

In a preliminary experiment, we found that, under the experimental conditions used for the Pd-catalyzed arylation, **17** also formed an arylated product with unknown regioselectivity. Due to the loss of aromaticity in **17**, the direct arylation can be considered as a Heck cross-coupling on the only double bond left on the thiazole ring. Both ends of the double bond are substituted with heteroatoms, which make prediction of the regiochemistry difficult; both **28** and **28a** are potential products (Figure **B-3**).

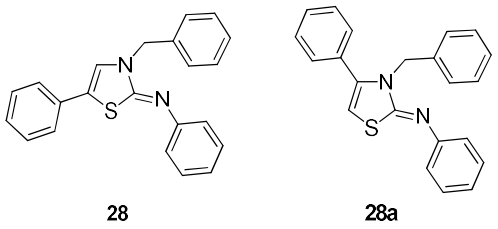
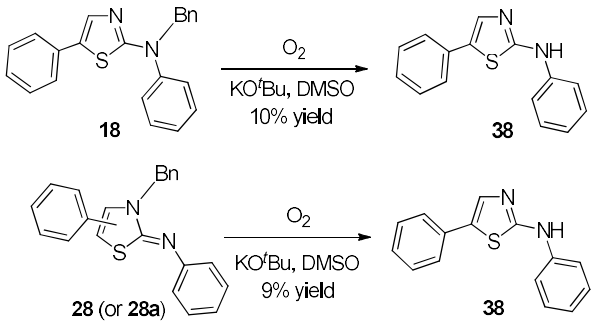


Figure B-3: Possibilities of arylation products of *endo*-N benzyl(thiazol-2-yl)amine

We subjected **17** to the direct arylation conditions and were very pleased to find that arylation of **17** occurred with similar efficiency as with **16** in spite of its non-aromatic character, giving 55% of product using bromobenzene and 79% using iodobenzene. However, assignment of regiochemistry was pending since arylation could either occur in position 5 to give **28** or in position 4 to give **28a** (Figure **B-3**). Therefore it was necessary to prove the structure of the obtained product unambiguously. Attempts to elucidate the structure by comparing of NMR spectra with predicted values or by 2D-NMR experiments were inconclusive. We therefore decided to cleave the benzyl group of **18** (product of aminothiazole arylation with proven regiochemistry) and **28**/**28a** and to compare the deprotected products. If the arylation of **17** had occurred in position 5, the same product should be obtained after deprotection.

Initially, reductive cleavage was attempted. However, **18** and **28**/**28a** were completely unreactive, even under high pressure (up to 100 bar H_2), high temperature (100 °C) or high loadings of the Pd/C catalyst in a continuous flow reactor. The reason is likely catalyst poisoning by the sulfur-containing thiazole moiety.[57] Alternatively, an oxidative method for N-debenzylation was applied: Treatment of compounds **18** and **28**/**28a** with potassium *tert*-butoxide and oxygen in DMSO at room temperature gave the deprotected compounds,[57b] albeit in low yield (10% starting from **18** and 9% starting from **28**/**28a**). (Scheme **B-4**)



Scheme B-4: De-protection of coupling products.

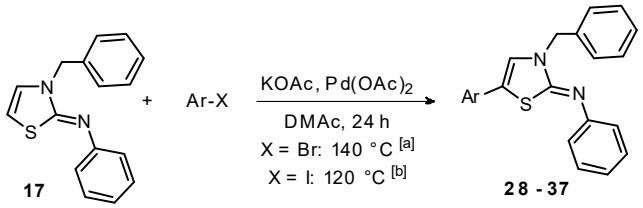
The rest of the starting materials were decomposed after the reaction. Since the sole purpose of these reactions was to prove the regioselectivity of arylation we did not further optimize the deprotection protocol. The GC/MS analysis, ^{1}H-NMR and ^{13}C-NMR spectra of the two deprotection products were compared and these turned out to be identical. Compound **38** was obtained in both cases, establishing that the direct arylation of **17** occurred in position 5 as well to give access to compounds of general structure **28**.

B II.4 Scope of direct arylation on iminothiazole

An arylation reaction such as this is, to our knowledge, unprecedented; hence, we investigated its substrate scope. In case of substrate **17**, aryl iodides gave considerably higher yields compared to the corresponding aryl bromides (Table **B-3**), yields were slightly lower compared with those of **16**, especially in the case of aryl bromides as reaction partners.

For some products, the differences in product yield were particularly pronounced. 1-Bromo-4-fluorobezene (**33**; 34% vs. 51% entry 7) and 4-bromoanisole (**31**; 21 vs. 41% entry 4) gave notably lower yield. The most striking difference was observed for the reaction of 4-iodonitrobenzene, for which a yield of 85% was obtained when compared with 41% for corresponding bromide reaction (**37**, entry 10). 2-Bromotoluene as a sterically demanding coupling partner gave 50% yield (entry 9), which is in the same range as for 3-bromo- and 4-bromotoluene (56%, **32** and 52%, **36**; entries 5 and 8). This indicates that steric bulk is not an issue in this coupling reaction.

Table B-3: Result of direct arylation on 17.



Entry	Ar	Product	X = Br	X = I
1	phenyl	**28**	55%	79%
2	3-chlorophenyl	**29**	58%	n.i.[c]
3	4- ethyl benzoate ester	**30**	49%	58%
4	4-methoxyphenyl	**31**	21%	41%
5	*m*-tolyl	**32**	56%	n.i.[c]
7	4-fluorophenyl	**33**	34%	51%
6	4-chlorophenyl	**34**	50%	n.i.[c]
8	*p*-tolyl	**35**	52%	68%
9	*o*-tolyl	**36**	50%	73%
10	4-nitrophenyl	**37**	41%	86%

[a] Reaction with ArBr: Substrate **3** (1.0 equiv.), ArBr (1.5 equiv.), KOAc (1.5 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 140 °C for 24 h. [b] Reaction with ArI: Substrate **3** (1.0 equiv.), ArI (2.0 equiv.), KOAc (2.0 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 120 °C for 24 h. [c] not investigated

Electron-deficient coupling partners, such as 4-nitro or 4-carboxyethyl-substituted benzenes were well tolerated (49%, **30** and 41%, **37**; entries 3 and 10). Finally, 1-bromo-3-chlorobenzene and 1-bromo-4-chlorobenzene worked as well as most other aryl bromides (58%, **29** and 50%, **34**; entries 2 and 6).

B III Conclusion

We have described an improved method for the direct arylation of *N*-benzyl-2-aminothiazole **16** employing aryl bromides as arylating reagent. Compared to our previously disclosed protocol using aryl iodides, the new method has the advantage of using less expensive and more readily available reagents. The aryl

bromide protocol is comparable in yield with no obvious drawbacks in the direct arylation of **16**. The same protocols could be used for the arylation of imino-thiazole **17** as well. In this case aryl iodides proved to be superior to aryl bromides. It was proven that arylation of **17** takes place in position 5 as well by means of deprotection of **18** and **28** which led to the same product **38**. Biological evaluation of compounds **28** – **37** was carried out in a previous PhD thesis.[58] Initial results suggest that they show similar activity as cell differentiation accelerators as compounds **18**.

C Benzofuran neolignan as potential inflammatory agents

C I Introduction of benzofuran project

C I.1 History of inflammation and aspirin

Long time ago, people indicated the phenomena of inflammation with 4 major signals: redness, heat, pain and swelling (*rubor*, *calor*, *dolor* & *tumor*). Lately, the fifth sign, the loss of tissue function (*functio laesa*), was added. In this time, using extract of willow leaves was one of the first solutions for the symptom. Ancient scientists observed bioactivity of willow bark as pain killer and fever reduction. Lately, in 1828, a German chemist, Johann Andreas Buchner successfully isolated an active compound from the extract of the willow bark and called it salicin. Chinese people used some other plants as their own cure of inflammation but they are actually salicylate-containing extract. [59]

The most successful derivative of salicylic acid is Aspirin™. This compound was first synthesized in 1899 but is still one of the most common medicines that are produced and consumed nowadays.[60] Aspirin was presumed to be acting as prodrug and the anti-inflammatory action caused by the liberation of salicylate.[61]

C I.2 General mechanism of inflammatory process

Recently, understanding about inflammatory mechanism is more and more deeply. Inflammation is the most obvious manifestation of immune defense. Inflammation is a response of vascularized tissues to the injury due to infections or damaged tissues. The process brings cells and mediator of immune system to the sites where the injury is, in order to eliminate the invaders. Inflammation symptoms are a side-effect when immune cells release specific mediators within the tissue to control invading factors.

Many of the chronic and uncured diseases that plague human populations are due to a dysfunctioning of the immune response. However, extensive inflammation can have a severe impact on the organism and can lead to other serious diseases. There are two types of inflammation: acute and chronic. The instant response to the infection and tissue damage is called acute inflammation. It typically happens in a short duration such as minutes or up to a few days. Its main characteristics are caused by the gathering of leukocytes at the injuried position, where tissues could be damaged by immune mediators itself to approach invading microorganisms. When the invaders are defeated or the injury is fixed; the reaction subsides; the acute inflammation is terminated by anti-inflammatory mediators. But if the response fails to clear the stimulus, the reaction can progress to a protracted phase that is called chronic inflammation.[62]

General mechanism of the inflammatory response can be summed into 5 steps:

- Recognition of the injurious agents
- Recruitment of leukocytes
- Removal of agents
- Regulation of the response
- Resolution (repair)

Recognition of the pathogen is mediated by many receptors, either soluble or membrane receptors. They can be classified in *cellular receptors* for microbes, amongst which the toll-like receptor (TLR) is the best studied.[63] Next important class is the *cell damage sensors* which are a specific set of cytosolic receptors that can recognize molecules released from the decomposition of the cell. These molecules include uric acid (product of DNA breakdown), ATP (released from damaged mitochondria), decreasing of intracellular K^+ concentration (reflecting loss of ions because of plasma membrane injury), etc. These receptors activate a multiprotein cytosolic complex called the *inflammasome*, which induces the production of the cytokine interleukin-1 (IL-1). The *inflammasome* has also been implicated in inflammatory reactions to urate crystals (the cause of *gout*), lipids (in metabolic syndrome), cholesterol crystals (in atherosclerosis), and even amyloid deposits in the brain (in Alzheimer disease). There are some other recognition machineries (*circulating proteins* can detect microbal sugar; *collectins* can bind and combat microbes; or others can find microbes coated with antibodies) which can also initiate inflammation and pathogen destruction. Upon pathogen recognition, mediators of inflammation are released, mainly from macrophages and mast cells.[62] (Figure **C-1**)

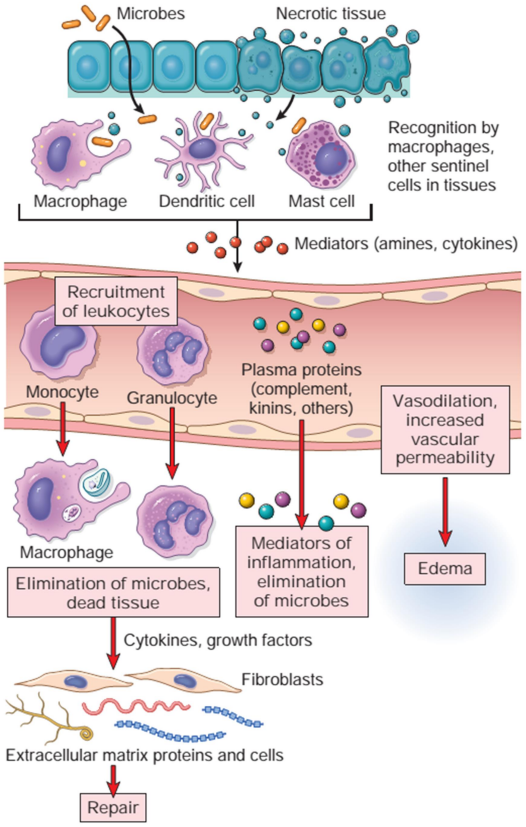


Figure C-1: Sequence of events in an inflammation reaction;
(graphic taken from reference 62)

After the recognition of the pathogen, blood vessels at the affected site undergo vasodilation. That leads to increase of vascular permeability and blood flow which allows the plasma proteins and leukocytes to pervade the damaged tissue. Such a vascular leakage of the fluid protein into the tissue together with the increased hydrostatic pressure leads to the typical signs of the inflammation such as erythema, heat and swelling.[62]

Recruitment of leukocytes is a multistep process, which includes leukocytes binding to and rolling on endothelium (thin cell layer in the interior of a blood vessel), passing of the leukocytes through the membrane. This process is mediated by several proteins like selectines or intergrins, ensuring the adhension, rolling and releasing of the leucocytes outside the vessel.

Cytokines produced by tissue macrophages and damaged tissue (TNF, IL-1) will promote selectins and intergrin ligands on endothelium, increase the attraction of intergrins. This activation could direct the migration of leukocytes. Getting through the vessel via the direction of intergrins and selectins channels, leukocytes start to eat microbes and eliminate death cells by phagocytosis. The destruction of invaders release cytokines TNF, IL-1 to continue the process cycle. (Figure **C-2**)

However, if the activation was too strong, those processes may induce tissue damage and prolonged inflammation because they do not only aim at destroying microbes and cleaning up necrotic tissues but also lead to injury of normal bystander host tissues. Anti-inflammatory mediators terminate the acute inflammatory reaction when it is no more necessary.[62]

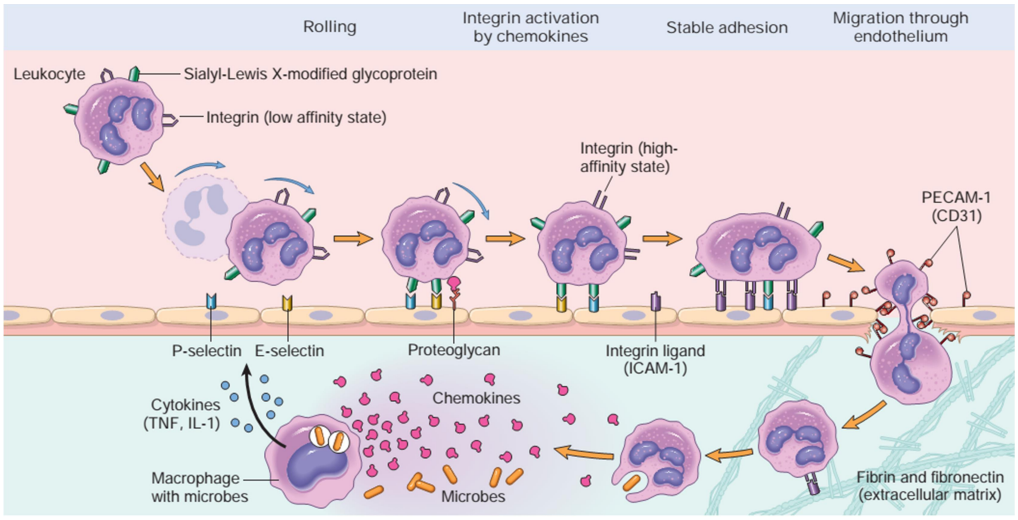


Figure C-2: The multistep process of leukocyte migration through blood vessels
(graphic taken from reference 62)

C I.3 Involvement of mediators and proteins on inflammtion

On a biochemical point of view, the recognition of pathogens liberates inflammatory mediators which are organic substances that initiate and regulate inflammatory reactions. Many mediators have been identified and targeted theurapically to limit inflammation. The most important mediators of acute inflammation are vasoactive amines, lipid products (prostaglandins, leukotrienes), cytokins (including chemokines) and products of complement activation. These mediators induce various components of inflammatory response typically by distinct mechanisms. The stimuli of these mediators can lead to the injury of normal host tissue. That is why many diseases can be connected to inflammation. Amongst them there are also some which were not considered of the inflammatory origin but rather some other origin e.g. metabolic or genetic.

Aspirin™ or some other non-steroid anti-inflammation drugs (NSAIDs) like ibuprofen™ were used to inhibit cyclooxygenase (both COX-1 and COX-2) and thus inhibit prostaglandin synthesis therefore control the pathogen of pain and fever. Nowadays, new classes of these drugs focused on agents inhibiting COX-2 selectively. COX-2 selective inhibitors could be potentially anti-inflammatory without side-effects related to gastric ulceration.

5-LO (5-lipoxygenase) is not affected by NSAIDs and many other inhibitors of the enzyme. Zileuton™, used to inhibit LOX, is useful in the treatment of asthema. Montelukast™ and similar drugs that can block leukotriene receptors and prevent action of leukotrienes are also used in the treatment of asthema. Corticosteroids were used as anti-inflammatory agents that reduce the transcription of genes encoding COX-2, phospholipase A2, proinflammatory cytokines and iNOS. Dietary lipids by increasing the consumption of fish oil such as polyunsaturated fatty acids are poor substrates for conversion to active metabolites by the cyclooxygenase and lipoxygenase pathways but are better substrates for the production of anti-inflammatory lipid products. [62]

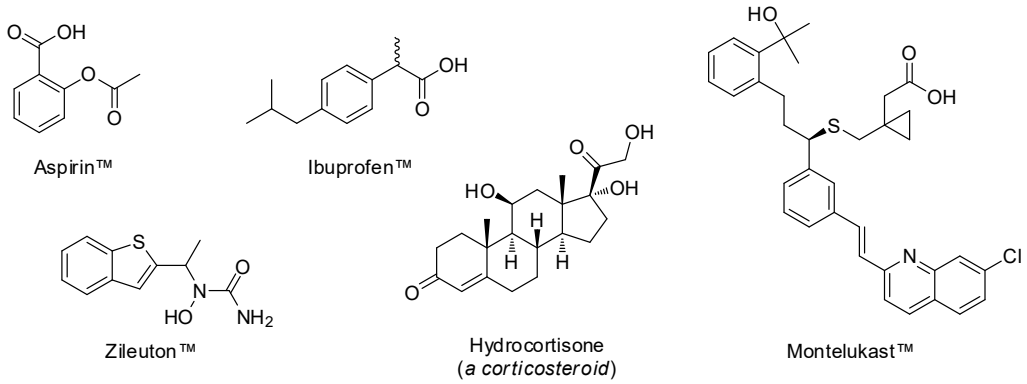


Figure C-3: Several small moleculars that are anti-inflammatory agents in used

TNF (tumor necrosis factor), produced by T lymphocytes and mast cell, and IL-1 (interleukin-I), produced by some epithelial cells, have crucial roles in leukocytes recruitment by promoting the combination of leukocytes to endothelium and their migration through vessels. Both TNF and IL-1 act on endothelium to increase the production of various mediators. TNF as well as IL-1 and IL-6 induce the systemic acute-phase responses associated with infection or injury, including fever. The production of TNF contributes to cachexia, which leads to weight loss and anorexia. The pathogen could even initiate some chronic infections or neoplastic diseases. TNF antagonists have been remarkably effective in the treatment of chronic inflammatory diseases, particularly rheumatoid arthritis and also psoriasis or some types of inflammatory bowel disease.[62]

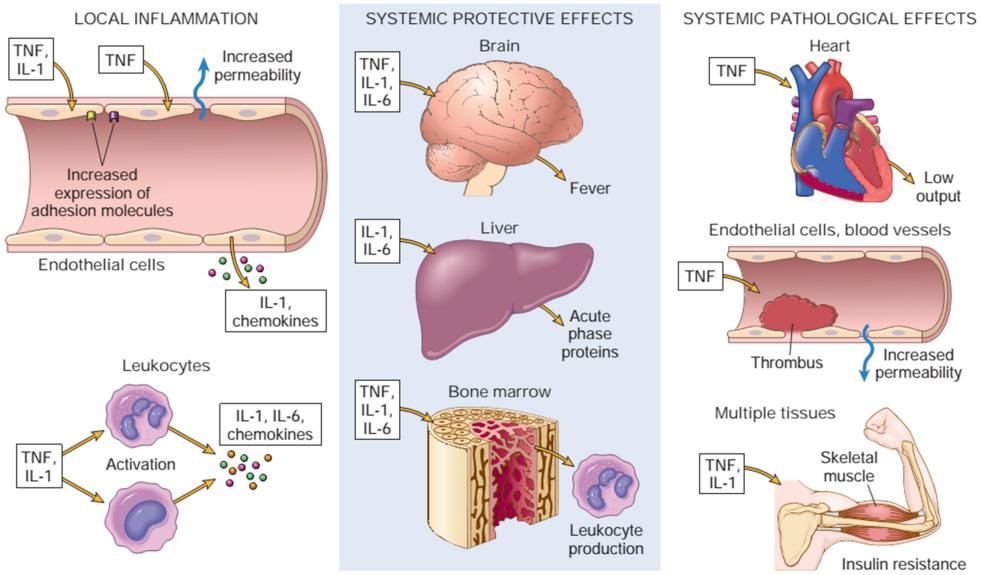


Figure C-4: Major roles of cytokines in acute inflammation
(graphic taken from reference 62)

NF-κB belongs to the nuclear transcription factor protein family, responsible for expression of genes essential in the inflammatory process. It also amplifies the inflammatory signal. NF-κB is directly activated by TNF and some other cytokines such as IL-1β. Upon the activation, it forms either homo or heterodimers and subsequently binds to the DNA binding domain and triggers gene transcription. Genes expressed upon the NF-κB stimuli encode proteins (COX, iNOS), cytokines (IL-2, IL-4, IL-5, IL-6, TNF) and other chemokines and adhesion proteins, all involved in inflammatory processes.[64] Therefore, it is not surprising that NF-κB

activation is found to be chronically active in many inflammatory diseases, such as inflammatory bowel disease, arthritis, sepsis, gastritis, asthma, atherosclerosis and others.

Some of the diseases are nowadays thought to originate or be linked to inflammatory dysfunction (Figure **C-5**). However, inhibiting or activating each proteins or mediators involved in the inflammatory processes has been exploited therapeutically.[65]

Figure C-5: Major roles of cytokines in acute inflammation
(graphic taken from reference 65)

C I.4 About Krameria species and its anti-inflammation neolignans

Krameria lappacea (Dombey), Krameriaceae, is a tropical perennial shrub growing across South America, mostly in Peru. Native people call it as Rhatany (or Rattany) and used its root (so called Peruvian rhatany) to clean and strengthen teeth.

The extract of Rhatany root was introduced into European medicine over 200 years ago as a remedy against stomach aches, diarrhoea, menstrual problems, nose bleeds and oropharyngeal inflammation. [66]

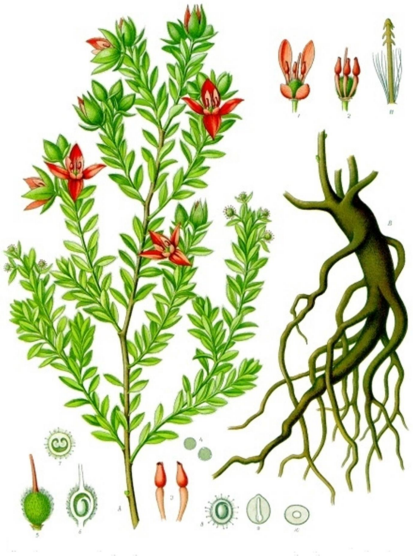


Figure C-6: *Krameria lappacea* plant
(Graphic by Franz Eugen Köhler, in *Köhler's Medizinal-Pflanzen*)

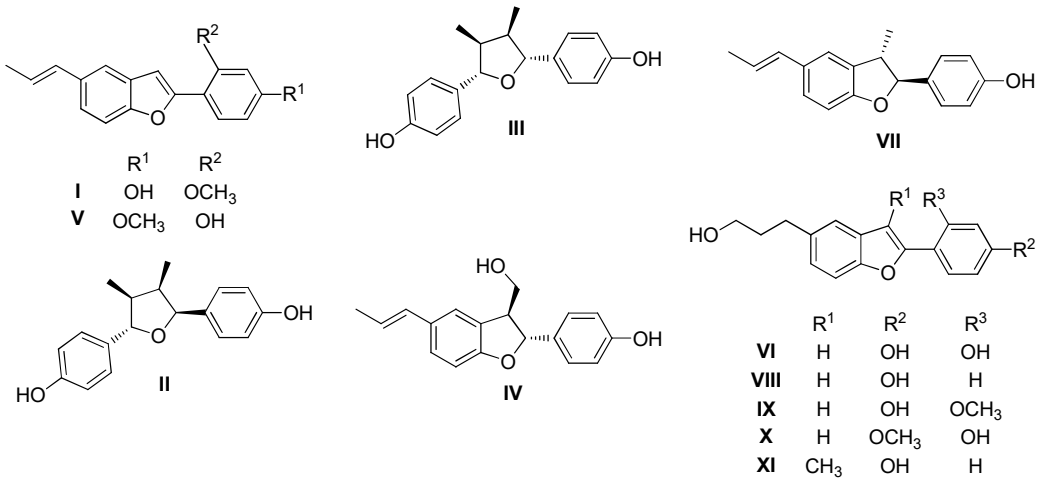


Figure C-7: Neolignans found in DCM extract of Rhatani root

In a study on the constituents of the Rhatany root, the group of Stuppner isolated 11 neolignans from the dichloromethane extract of the root (Figure **C-7**).[67] Amongst those benzofurans based neo-lignans, which are similar to what are found in other plants in the same *Krameriaceae* family, [67-68] only few display good activities against inflammation.

In further *in vivo* and *in vitro* studies on neolignans from *Krameria*, Baumgartner *et* al. addressed the most potent compounds that can inhibit acute inflammation in vivo and vitro.[69] Particularly, 2-(2-hydroxy-4-methoxyphenyl)-5-(3-hydroxypropyl)benzofuran and (+)-conocarpan (compound **V** and **VII** in Figure **C-6**) showed activity profiles similar to that of hydrocortisone regarding to time dependent edema development and leukocyte infiltration. For all neolignans ID_{50} values were measuerd and the inhibition of NF-κB, COX-1, COX-2, 5-LO, and mPGES-1 as well as antioxidant properties were demonstrated (in *vitro*). The studies revealed that the isolated lignan derivatives contribute strongly to the anti-inflammatory activity of this *K. lappacea* roots as a herbal drug.[69]

C II Results and discussion

C II.1 Structure analyst and synthesis route

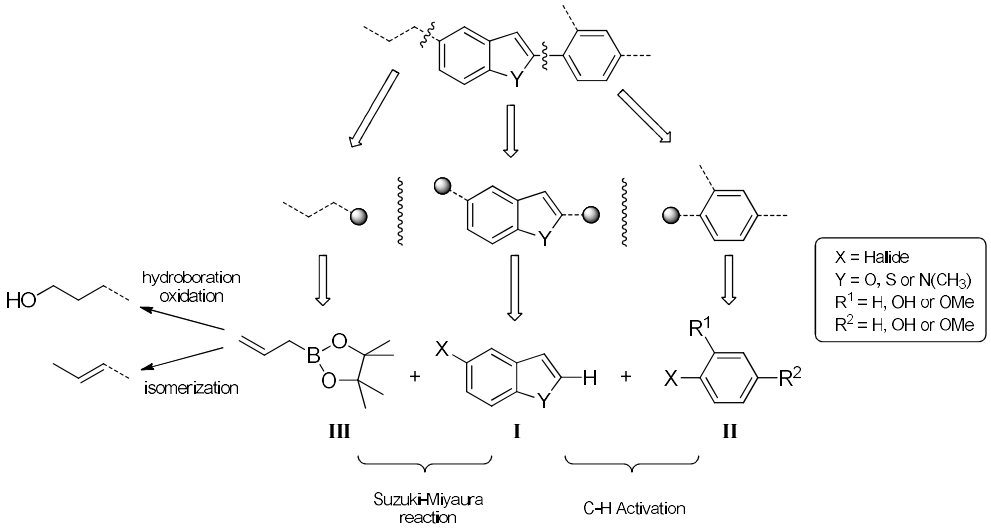


Figure C-8: **Structure analyst of neolignan type compounds**

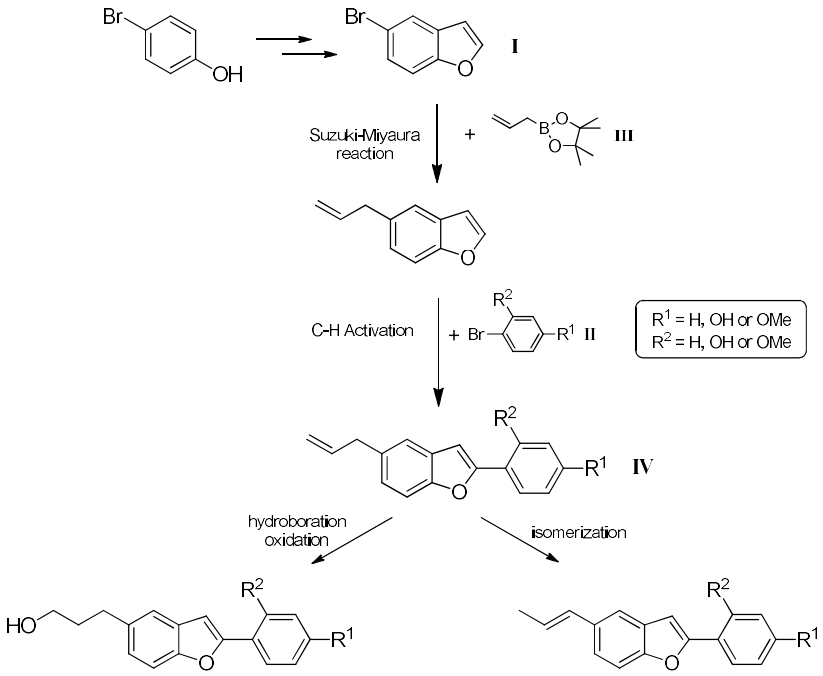
According to 11 neolignans isolated from DCM extract of Rhatany root the particularly active compounds were summed up into one lead structure in Figure **C-8**. This lead structure can be analyzed into 3 parts. These parts will be combined with each other by coupling reactions which are common choice nowadays with many advantages.

Building block **I** was designed as 5-halide benzo[*b*]furan (or other benzo-fused heterocycles). On one hand, H-2 and H-3 of benzo[*b*]furan were reported as one of the most reactive protons on such an electron-rich heterocycle. [70] A methodology for using C-H activation as selective coupling reaction at C-2 was envisioned to be developed. On the other hand, H-5 is less reactive and so a halide group at C-5 would avoid selectivity problems and direct Suzuki-Miyaura reactions better.

Building block **II** will be derivatives of benzene with a halide substituent to be a coupling partner for the C-H activation. Either R^1 or R^2 must be a phenolic OH which will definitely affect[49e, 71] the transition metal-catalyzed reactions. Thus, a protective group must be applied before the C-H activation.

Building block **III** is allylboronic acid pinacol ester which is a promising coupling partner for Suzuki-Miyaura reaction and readily commercial available. The allyl substituent can be transformed into 3-hydroxyl-propyl by hydroboration oxidation reaction[72] or 2-propenyl by isomerization reaction[73] as reported in the literatures.

In very first proposed synthesis route (Scheme **C-1**), benzo[*b*]furan was used as model compound to optimize the general route that can be applied for other benzo-fused heterocycles like benzothiophene and indole. Firstly, 5-bromobenzo[*b*]furan was considered as starting material. This compound was not readily available but could be synthesized in-house. Building block **III** will be combined into the benzofuran ring via Suzuki-Miyaura reaction before the C-H activation. The coupling reaction of 2 bromoaryls would not be easy to control if the C-H activation was handled first. Subsequently, C-H activation was applied on 5-allylbenzo[*b*]furan to attach the aryl building block to form key compound **IV**. This key compound can be easily transformed via hydroboration oxidation, isomerization or other reactions towards the target structures, if necessary.



Scheme C-1: General synthesis route for benzo[*b*]furan

C II.2 Methodology of C-H activation reaction on benzo-fused heterocylces

C II.2.1 Benzofuran and novel methods for bi-(hetero)aryl synthesis

2-Arylbenzo[*b*]furan derivatives are found regularly in natural products and synthetic compounds with high biological activity. For example, neolignins containing benzo[*b*]furan derivatives were reported to have good anti-inflammatory properties.[74] Some others are active as anti-bacterial or potential anti-cancer agents (Figure **C-9**).[75] Consequently, facile synthetic approaches to such compounds are of critical importance to further assess and refine the potential of this structural class as bioactive entities.

For decades, bi-(hetero)aryl motifs have been synthesized via de-novo synthesis using cyclization strategies.[76] This changed with the development of metal-catalyzed cross-coupling reactions, which were then the method of choice to synthesize such systems for many years.[77] In recent years, another method has started to complement and even substitute cross-coupling chemistry, namely direct arylation methods, often referred to as C-H activation reactions.[78] The advantage of this type of transformation is that it circumvents the requirement of two pre-functionalized coupling partners to be applied in the C-C bond forming step, since either the organometallic species (preferably) or the (pseudo)halide component can be substituted by substrates containing a reactive (i.e. activated) C-H bond instead. This helps to streamline synthesis and increase efficiency considerably, since it has to be taken into account that preparation of a functionalized substrate may require a multi-step synthesis, as well. Hence, avoiding such pre-functionalization shortens synthetic pathways significantly, which is more time-, resource-, and energy efficient. Additionally, the environmental burden can be reduced. All these factors often contribute to more economical processes, as well.[79] Therefore, many research groups, including ours, have focused attentions to the development of new methods for the direct arylation of heterocycles.[80]

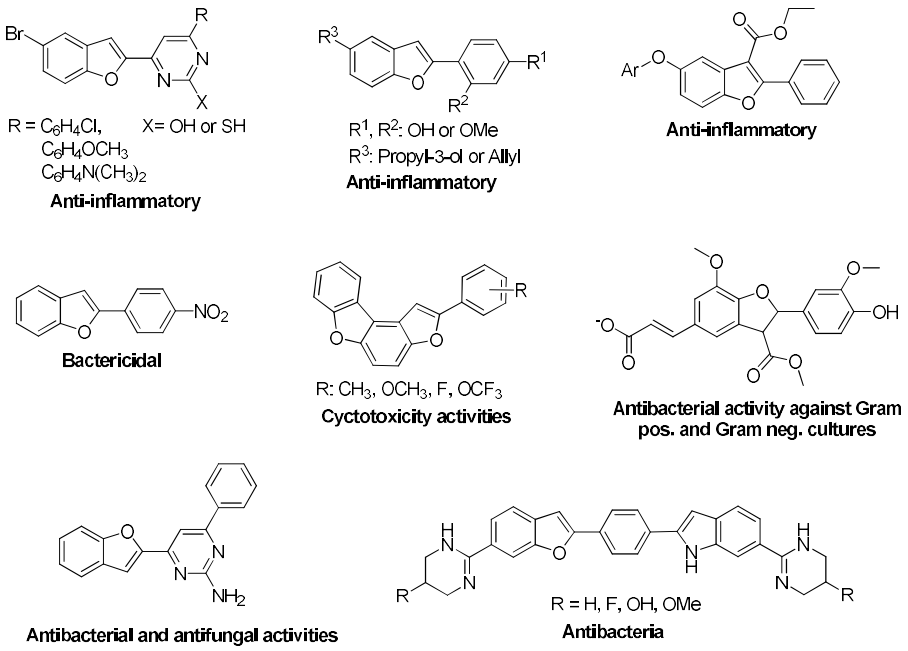


Figure C-9: Bioactive benzo[*b*]furan derivatives

Heterocycles are especially suitable for C-H activation chemistry since the different C-H bonds present are significantly different in reactivity due to the presence of one or more heteroatoms. To date, C-H activation reactions were successfully conducted on series of electron rich (benzo-fused) heterocycles, such as (benzo)thiophene,[81] indol,[82] (benzo)thiazole[83] or (benzo)furan,[49b, 70, 84] using palladium species as catalyst.

Interestingly, the direct arylation of benzo[*b*]furan has been largely neglected.[49b, 70, 84] Over the years, only a handful of examples were reported on this subject either with mediocre yields or under peculiar reaction conditions. The group of DeBoef disclosed a protocol for oxidative coupling between benzo[*b*]furan and benzene derivatives.[84a] However, benzene had to be used as solvent (> 80 equiv. as mixture with AcOH) and a complex catalytic system was required. Fagnou reported direct arylation of a series of heterocycles using a common protocol.[49b] One example was the arylation of benzo[*b*]furan with *o*-bromotoluene and in this case the yield was low with 29%. Also the groups of Bhanage[84b] and Kappe[84c] gave one example for benzo[*b*]furan arylation with aryl halides. Kappe followed essentially Fagnou's protocol and obtained 50% yield when benzo[*b*]furan was coupled with 3-bromoquinoline under microwave irradiation. Bhanage reacted benzo[*b*]furan with bromo- or iodobenzene using $Pd(TMHD)_2$ as catalyst (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedione) in good yields of 65% and 83% respectively. Substituted arylhalides were not investigated. The group of Horie used iodobenzene, 4-iodoanisol, and 4-iodobenzoic acid ethyl ester as coupling partners in the direct arylation of benzo[*b*]furan.[83a] For iodobenzene no isolated yield was given and only an NMR yield of 41% was reported without further comments. The other two coupling partners gave 41% and 53%, respectively. A more detailed investigation of the direct arylation of benzo[*b*]furan was reported by Ohta *et al.* already in 1990.[70b] They used simple $Pd(PPh_3)_4$ as catalyst, aryl bromides as coupling partners and KOAc as base in refluxing DMAc. From the ten aryl bromides tested, only six gave the coupling product but in low yields (typically ~20%). One exception was o-bromonitrobenzene which gave 50% of arylation product. The same group reported the direct arylation of benzo[*b*]furan with chloropyrazines.[70a] Hence, there is still demand for a general direct arylation protocol of benzo[*b*]furan.

Comparing the aromaticity of benzo[*b*]furan to benzo[*b*]-thiophene or furan, the C-2/C-3 bond on benzo[*b*]furan behaves chemically more like a localized olefinic double bond than an aromatic system, as it is the case in benzo[*b*]thiophene.[85] Consequently, arylation on C-2 of benzo[*b*]furan is not very selective.

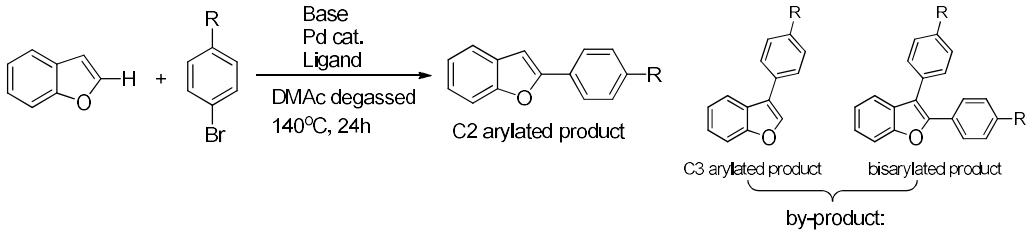
Normally, the C-2 arylated, C-3 arylated and bis-arylated products will be observed as mixture, making product isolation often difficult.[70] Therefore, in many recent reports, cyclization strategies were used still in order to synthesize benzo[*b*]furan derivatives, [86] especially 2-arylbenzo[*b*]furan.[87] Naturally, this requires more steps than a direct arylation approach and bears the possibility to face difficulties associated with the synthesis of required intermediates, stability or functional group tolerance. On the other hand, oxidative direct arylation is another option but not many functional groups can tolerate the required reaction conditions.[88]

In the following chapter, efforts to directly arylate benzo[*b*]furan are described taking advantage of a protocol which can be used for other benzo-fused heterocycles as well and allows coupling with a wide range of coupling partners carrying different functional groups.

C II.2.2 Optimization of C-H activation reaction on benzo[*b*]furan

We started our investigations by using the reaction conditions that we recently introduced for the successful C-5 arylation of N-protected thiazoleamines.[45g] There we used palladium acetate ($Pd(OAc)_2$) as catalyst without an additional ligand, potassium acetate (KOAc) as base and N,N-dimethylacetamide (DMAc) as solvent at 140 °C for 24 h. (Table **C-1**)

Table C-1: Scanning of amount of $Pd(OAc)_2$ for direct arylation of benzo[*b*]furan.[a]



Entry	$Pd(OAc)_2$	Conversion (%)	Yield (%)	C2 : C3 : Bisaryl
1	1 mol%	18	14	100:16:00
2	2 mol%	22	16	100:17:00
3	**4 mol%**	**27**	**22**	**100:17:00**
4	6 mol%	32	23[b]	100:15:00
5	8 mol%	36	22[b]	100:16:00
6	10 mol%	41	20[b]	100:17:00

[a] Reaction condition: benzo[*b*]furan (1 equiv.), 4-bromoanisole (1.5 equiv.), KOAc (1.5 equiv.), $Pd(OAc)_2$ as catalyst without ligand, 140 °C in 24 hours, 0.5M of substrate in solvent (degassed DMAc). The yield was determined by GC. [b] A byproduct stemming from homocoupling of 4-bromoanisole was observed.

In the case of the arylation of thiazole, aryl iodides served as the aryl source, whereas for the arylation of benzo[*b*]furan we wanted to focus on cheaper and more readily available bromides. As a model reaction we investigated the coupling of 4-bromoanisole with benzo[*b*]furan.

Initially, we started with a catalyst loading of 2 mol-% in the absence of any ligand, however, this gave only 16 % yield of the desired product (Table **C-1**, entry 2). Screening of various catalyst loadings (1–10 mol-%) (see Table **C-1**) revealed that 4 mol-% gave the highest but a still unsatisfactory yield, while higher catalyst loadings led to increased byproduct formation (debromination, and homocoupling of 4-bromoanisole).

We noted that 2 products with the same mass (based on GC/MS analysis) were observed at any loading of catalyst. These were the products from arylation at different positions, C-2 and C-3.[70] Using ^{1}H-NMR, the major product was identified as the desired C-2 arylated one, with a correlation of H-3 and H-4 (J_{H-H} = 0.8 Hz). Therefore the minor product is the C-3 arylated one. No *bis*-arylation was observed.

Table C-2: Optimization of the arylation of benzo[*b*]furan.

Entry	Base	Pd cat.	Ligand	Yield (%)	C2 : C3 : Bisaryl
1	KOAc	$Pd(OAc)_2$	*-No ligand-*	22	100:17:00
2	KOAc	$Pd(OAc)_2$	Tri-2-furylphosphine	15	100:22:00
3	KOAc	$Pd(OAc)_2$	Tris(p-chlorophenyl)phosphine	22	100:26:00
4	KOAc	$Pd(OAc)_2$	JohnPhos	10	100:19:00
5	KOAc	$Pd(OAc)_2$	XPhos	7	100:16:00
6	**KOAc**	**$Pd(OAc)_2$**	**SPhos**	**45**	**100:14:00**
7	KOAc	$Pd(OAc)_2$	CPhos	40	100:21:00
8	KOAc	$Pd(PPh_3)_2Cl_2$	SPhos	40	100:13:00
9	KOAc	$Pd(PPh_3)_4$	SPhos	44	100:29:00
10	K_2CO_3	$Pd(OAc)_2$	SPhos	13	100:12:00
11	Cs_2CO_3	$Pd(OAc)_2$	SPhos	25	100:09:00
12	CsOAc	$Pd(OAc)_2$	SPhos	19	100:24:00
13	KOPiv	$Pd(OAc)_2$	SPhos	65	100:08:00
14	**CsOPiv**	**$Pd(OAc)_2$**	**SPhos**	**72**	**100:05:00**
15	CsOPiv	$Pd(OAc)_2$	2,2'-bipyridine	34	*-nd-*
16	CsOPiv	$Pd(OAc)_2$	1,10-Phenanthroline	6	*-nd-*
17	CsOPiv	$Pd(OAc)_2$	4,4'-di-*tert*-butyl-2,2'-bipyridine	16	*-nd-*

Reaction condition: benzo[*b*]furan (1 equiv.), 4-bromoanisole (1.5 equiv.), KOAc (1.5 equiv.), $Pd(OAc)_2$ (4 mol%), ligand (8 mol%), 140°C in 24hours, 0.5M of substrate in solvent (degassed DMAc). The yield was determined by GC.

Because the addition of ligands has a significant influence on metal-catalyzed reactions (change in catalytic species and eventually oxidation state), we embarked on ligand screening with several commercially available ligands. [89] Because the addition of phosphine ligands changes the electronic and steric (vacant coordination sites blocked) environment of the catalytically active metal center, we chose to screen several commercially available phosphine ligands (Table **C-2**, entries 1-7 and 15-17). In this investigation only two systems (C-Phos and S-Phos, Figure **C-10**) displayed improved yields compared to conditions without an additional ligand (40 and 45 % yields, respectively; entries 6 and 7). It has to be mentioned that none of the investigated conditions led to full conversion. Variation of the palladium catalyst precursor species also did not affect the reaction efficiency significantly (entries 8 and 9).

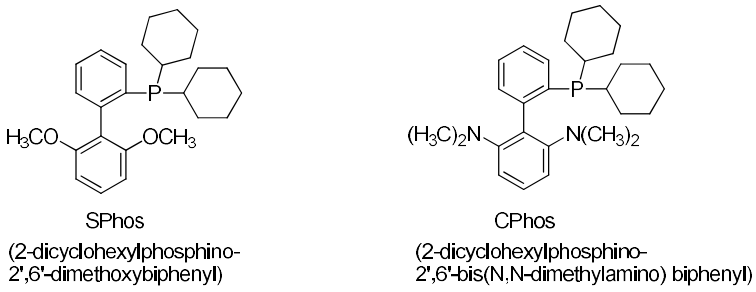
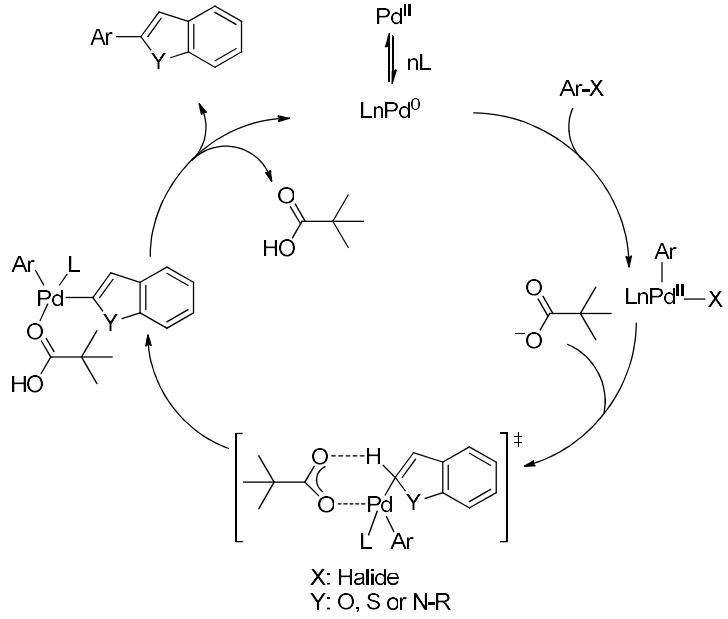


Figure C-10: Structures of phosphine ligands

Since there is strong evidence that the reaction proceeds through a concerted metalation/deprotonation (CMD) pathway, [90] we chose a carboxylate base for our screening efforts. This modification was inspired by the work of Fagnou and co-workers, who reported that pivalic acid (in situ becoming potassium pivalate due to the presence of stoichiometric amounts of K_2CO_3) acts as a co-catalyst to promote C–H cleavage and phosphine dissociation, ultimately preventing catalyst inhibition by excess phosphine.[49b, 90c] Speculating that the nature of the carboxylate base can also have a significant influence on the performance of a direct arylation process, we tested other carboxylate bases such as CsOAc, KOPiv, and CsOPiv. The proposed mechanism of this reaction is shown in Scheme **C-2**.



Scheme C-2: Proposed mechanism of direct arylation of benzo-fused heterocycles using pivalate specie as co-catalyst.

The reaction starts with the oxidative addition of the aryl bromide to the palladium catalyst. Then a pivalate ion from caesium pivalate coordinates to the catalyst. In the subsequent step a concerted metalation deprotonation takes place, as depicted in the transition state. Finally, dissociation of pivalic acid and reductive elimination delivers the desired product and regenerates the catalytically active palladium species.

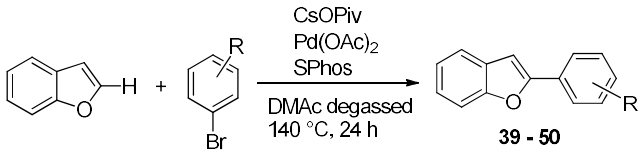
In contrast to the protocol by Fagnou and co-workers, we chose to use pivalate directly and use of either potassium pivalate (KOPiv) or caesium pivalate (CsOPiv) as base resulted in a significant increase in yield. Only when conducting the reactions in the presence of CsOPiv full conversion was observed (72 % yield, Table **C-2**, entry 14). In addition, a minor counter-ion effect was observed favoring Cs^+ over K^+ (65 %, entry 13). In both cases, the 3-arylated isomer was detected as a minor byproduct (~5 %) by GC–MS.

Having identified CsOPiv as the best-performing base we tested several N-based ligands in combination with this base, however, the conversions were significantly lower than those obtained with S-Phos (Table **C-2**, entry 15-17).

C II.2.3 Scope of the C-H activation at C-2 position of benzo[*b*]furan

As a result, the following reaction conditions were used to evaluate the substrate scope: Benzo[*b*]furan (1.0 equiv.) with aryl bromide (1.5 equiv.), CsOPiv (1.5 equiv.), $Pd(OAc)_2$ (4 mol-%), and SPhos (8 mol-%) in degassed DMAc (0.5M) at 140 °C for 24 h. Our results are summarized in Table **C-3**.

Table C-3: Scope of the direct arylation on C-2 of benzo[*b*]furan.



Entry	R	Product	Ratio C2 : C3 : bisaryl	Yield (%)
1	H	**39**	100 : 09 : 33	60
2	4-OH	-	-	0
3	4-CH_3	**40**	100 : 06 : 29	54
4	4-OCH_3	**41**	100 : 05 : 00	70
5	4-Cl	**42**	100 : 20 : 12	57
6	4-F	**43**	100 : 17 : 17	50
7	4-COOEt	**44**	100 : 11 : 00	45
8	4-CHO	**45**	100 : 04 : 00	44
9	4-CN	**46**	100 : 05 : 42	34
10	4-NO_2	**47**	100 : 00 : 00	22
11	2-OCH_3	-	-	0
12	2-CH_3	**48**	100 : 20 : 16	40
13	2-Cl	**49**	100 : 22 : 26	43
14	3-Cl	**50**	100 : 18 : 32	50

Reaction condition: benzo[*b*]furan (1 equiv.), arylbromide (1.5 equiv.), CsOPiv (1.5 equiv.), $Pd(OAc)_2$ (4 mol%), SPhos (8 mol%), 140 °C in 24 hours, 0.5M of substrate in solvent (degassed DMAc). Yields were isolated yields for C2-arylated product.

Benzo[*b*]furan was treated with a series of aryl bromides bearing various functional groups. In several cases, the bisarylated benzo[*b*]furan was observed as the major byproduct by GC–MS, and is responsible for decreased yields of the desired product due to associated separation problems.

To investigate the electronic effects of substituents on the arylbromide only para substituted derivatives were subjected to the established reaction conditions to eliminate steric interactions (Table **C-3**, entries 1-10).

It was found that electron-rich halides (**39**, **40** & **41** in entries 1, 3 & 4) upon coupling with benzo[*b*]furan generally result in better yields than electron-deficient substrates. Only in the case of 4-bromophenol no conversion was observed (entry 2), most likely due to the rather acidic phenolic OH group. For electron withdrawing substituents a significant trend was observed: increasing electron withdrawal by the substituent leads to decrease in the yields (see trend for entries 5-10).

In case of the 4-NO_2 substituent the conversion was especially low which accounts for the low yield even though the C2-arylated product was formed exclusively (**47**, entry 10). In this case homo-coupling product of the halide was observed in significant amount.

Next, we investigated the influence of the position of aryl functional groups on the halides (entries 11-14). A methyl group in ortho position was still tolerated, even though the yield dropped to 40% (**48**, entry 12). In contrast, a methoxy group in ortho position inhibits conversion completely, presumably due to chelating effects. Subsequent to oxidative addition into the C-Br bond, a relatively stable palladium complex may be formed due to the adjacent oxygen of the methoxy group; this results in coordination to the metal center via a lone pair, consequently inhibiting any further reaction at the metal center.

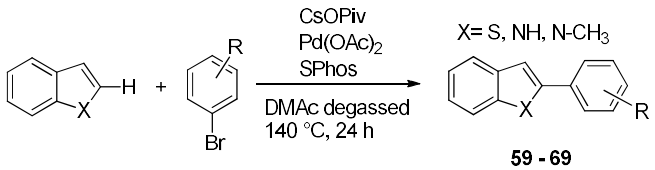
Additionally, we applied three different isomers of chloro-bromobenzene to the arylation protocol. Variation in reactivity showed that para substitution gave the highest yield (57%) and ortho substitution the lowest (40%). However this effect was not very pronounced (**42**, **49** & **50** in entries 5, 13 & 14). Notably, we never detected any product originating from a reaction at the chloride position rather than the bromide position. This absolute selectivity enables further transformations at the chloride position in future work.

C II.2.4 Scope of the C-H activation at C-2 position of other benzo-fused heterocycles

Next, we investigated whether the same reaction conditions can be translated to other benzo-fused heterocycles as well (Table **C-4**).

Benzo[*b*]thiophene was subjected to the established reaction conditions as next test system.[81i-l] Also in this case, bis-arylated benzo[*b*]thiophenes were observed in several cases but in low quantities (below 10%). In case of benzo[*b*]thiophene the byproduct did not impede isolation of the C-2 arylated product as observed for benzo[*b*]furan.[70b] The more pronounced difference in polarity of byproduct and desired product led to more facile purification as compared to the benzo[*b*]furan series. The results are quite similar to data obtained for benzo[*b*]furan. Again, a free OH or an *o*-methoxy group was not tolerated (entries 2 & 7) and electron withdrawing substituents had a negative effect on the reaction (**63**, **66**-**68** in entries 6, 10-12). It seems noteworthy, that *o*-bromotoluene and *o*-chloro-bromobenzene gave better yields than the corresponding para substituted isomers (entries 8 & 9 vs. 3 & 5).

Table C-4: Scope of direct arylation of other benzo-fuse heterocycles.



59 - 69

Entry	X	R	Product	Yield (%)
1	S	H	**59**	43*
2	S	4-OH	*-nd-*	0
3	S	4-CH_3	**60**	34*
4	S	4-OCH_3	**61**	53
5	S	4-Cl	**62**	58*
6	S	4-F	**63**	35*
7	S	2-OCH_3	*-nd-*	0
8	S	2-CH_3	**64**	68*
9	S	2-Cl	**65**	60*
10	S	4-COOEt	**66**	45
11	S	4-CN	**67**	25
12	S	4-NO_2	**68**	26
13	NH	H	*-nd-*	0
14	N-CH_3	H	**69**	64*

Reaction condition: benzo-fused heterocycle substrate (1 equiv.), arylbromide (1.5 equiv.), CsOPiv (1.5 equiv.), Pd(OAc)2 (4 mol%), SPhos (8 mol%), 140 °C in 24 hours, 0.5M of substrate in solvent (degassed DMAc). Yields were isolated yields.

* Bis arylated byproduct observed in GC.

Finally, we tested our conditions on indole, as well, even though direct arylation is well established on this heterocyclic system.[82] In this context, it was our aim to establish the scope and limitations of the developed protocol as a general method for direct arylation of benzo fused systems. Indole itself did not react, corroborating our above indicated hypothesis of a detrimental effect by acidic protons (entry 13). Blocking this position by employing 1-methylindole, the protocol again turned out as very robust to give a good isolated yield of the arylated product (64%, entry 14), again accompanied by minor amounts of bis-arylated side-product.

C II.2.5 Scope of C-H activation on C-3 of 2-arylbenzo[*b*]furan

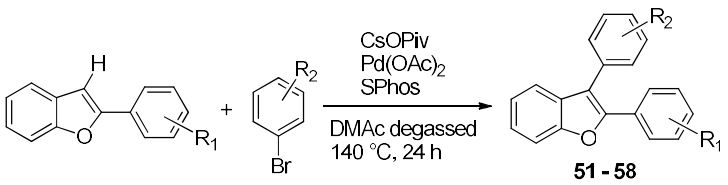
The formation of bis-arylated products as minor contaminant in a number of examples prompted us to exploit the protocol for the synthesis of 2,3-bis-arylated benzo-fused heterocycles as well, starting from C-2 arylated derivatives (Table **C-5**).

Initially, we introduced the same aryl residue in the second step at C-3 which was already attached to C-2 (Table C-5, entries **1-6**). Again, yields were in the same range (but slightly lower) confirming our previously observed trend regarding the electronic nature of substituents on the arylbromides. The lower yields for C-3 arylation can be rationalized by steric hindrance imposed by the aryl substituent in position 2 (compare entries 1-6 / Table **C-5** to entries 1, 5-9, 11 / Table **C-4**).

As a further logical extension of the method, we then introduced different aryls in position 3 than in position 2 (Table **C-5**, entries 7-9). Arylation with 4-chloro-bromobenzene proceeded with similar efficiency

compared to the reaction in position 2 (entry 8). 4-Bromoanisole on the other hand did not react at C-3 at all (entry 7). Coincidentally, no bis-arylated product was observed in case of C-2 arylation with 4-bromoanisole (entry 4 in Table **C-3**). The reason for the failure is not clear at the moment and may be subject of further investigations. Introduction of 4-nitrophenyl in position 3 resulted in a low yield of 20%, which was expected due to previous results obtained with that particular coupling partner.

Table C-5: Scope of the direct arylation on C-3 of 2-arylbenzo[b]furan.



51 - 58

Entry	R1	R2	Product	Yield (%)
1	H	H	**51**	47
2	4-Cl	4-Cl	**52**	58
3	4-F	4-F	**53**	44
4	2-Me	2-Me	**54**	40
5	2-Cl	2-Cl	**55**	53
6	4-CN	4-CN	**56**	17
7	H	4-OMe	-nd-	0*
8	H	4-Cl	**57**	50
9	H	4-NO_2	**58**	20

Reaction condition: 2-arylbenzo[b]furan substrate (1 equiv.), arylbromide (1.5 equiv.), CsOPiv (1.5 equiv.), Pd(OAc)2 (4 mol%), SPhos (8 mol%), 140 °C in 24 hours, 0.5M of substrate in solvent (degassed DMAc). Yields were isolated yields.

* Observed trace of product on GC.

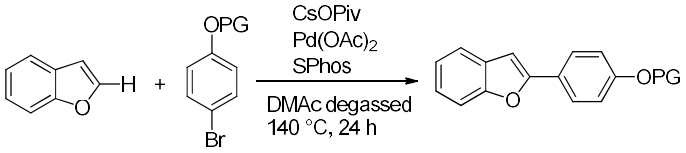
C II.2.6 Scope of protective groups on the C-H activation

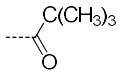
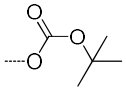
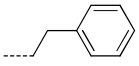
As predicted, entry 2 in Table **C-3** indicted no conversion because of the active proton on a phenolic hydroxyl group. A series of protective groups was screened for the tolerance under the basic environment of the C-H activation reaction condition. 4-Bromophenol was chosen to be model compound for this scanning. All the protection reactions of 4-bromophenol with several protective groups were described in Heading D.III.9 (Synthesis of bromide aryl coupling partners).[33]

4-Bromoanisole reacted well with benzo[*b*]furan with good yield that hinted at using ether protective groups. The active neolignans from *Rahtany* root extract have both OH and OCH_3 in the aryl moiety so another ether group to be selectively cleaved would be a challenge.

A series of other protective groups was put on the testing and the results were recorded in Table **C-6**.

Table C-6: Scope of protective groups on the C-H activation*



Entry	PG	Yield (%)	Entry	PG	Yield (%)
1	 (Ac)	0%	6	 (TIPS)	0%
2	 (Piv)	0%	7	 (Boc)	0%
3	 (Allyl)	0%	8	 (EVE)	0%
4	 (Bn)	14%	9	 (THP)	0%
5	 (TMS)	0%	10	 (MOM)	71%

Reaction condition: benzo[*b*]furan (1 equiv.), arylbromide (1.5 equiv.), CsOPiv (1.5 equiv.), $Pd(OAc)_2$ (4 mol%), SPhos (8 mol%), 140 °C in 24 hours, 0.5M of substrate in solvent (degassed DMAc). Yields were isolated yields.
*: Protection reactions of 4-bromophenol was describe in experimental part.

Ester (entry 1 & 2) and allyl (entry 3) protective groups were not tolerated using the established reaction condition. They are de-protected before the coupling reaction with 4-bromophenol and substrate were recovered from the reaction mixture. Ester might be hydrolyzed because of the basic environment and allyl group was isomerized before the hydrolysis.

Benzyl protective group was ether type so it can really survive in the basic condition but the conversion was surprisingly low (entry 4). Only 14% yield of product was isolated from the reaction mixture.

Silyl ether was reported as the one that can tolerate high pH, especially TIPS;[33] but both TMS and TIPS were also de-protected under the reaction condition (entry 5 & 6). The same thing happened with Boc which is normally removal under acidic condition only. The protected coupling partner was again de-protected before the reaction.

Diacetal type protective groups like EVE, THP and MOM are also included in the screening (entries 8, 9 & 10). However, only the MOM group gave satisfactory results. The conversion was good with 71% yield of protected product **83** was isolated after the reaction.

C II.2.7 Conclusion

In summary, we developed a generally applicable method to directly arylate benzo-fused heterocycles such as benzo[*b*]furan, benzo[*b*]thiophene, and *N*-methylindole. Even though yields are usually moderate, this protocol is very versatile and generally applicable producing highest yields for direct arylation of benzo[*b*]furan

compared to available literature procedures. [49b, 70, 84a-c] Both electron-rich and electron-poor arylbromides can be used as aryl sources, however, strong electron withdrawing substitutents have a limiting effect on the efficiency of the protocol.

As already indicated, the method can also be applied to benzo[*b*]thiophene and N-methylindole with similar results. The C2-arylated products were susceptible to undergo additional arylation at C-3 employing the same protocol, showing similar trends in reactivity as for C2-arylation. Investigations to translate this protocol to other heterocycles and application of other aryl sources (aryl iodides or chlorides) are currently under investigation in our laboratory.

On the other hand, reaction of 4-bromochlorobezene proved that the catalyst system reacted selectively on bromo group rather than chloro terminal on aryl coupling partner. The unreacted 4-bromoanisloe can be explained with active proton of the phenolic group. Many precedent literatures[49e, 71] reported that a trace of proton can shut down the catalytic circle. A protective group must be carried on before the coupling reaction.

Not many protective groups can tolerate the C-H activation condition (Table **C-6**) but MOM and ether group in general. MOM was chosen for the total synthesis plan of this project even though it was the last option because of the carcinogen properties of chloromethyl methyl ether.

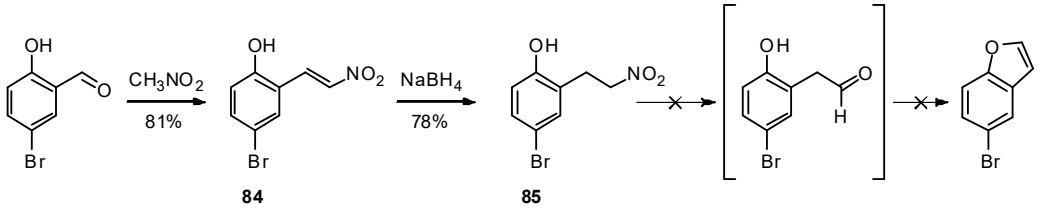
Last but not least, a substituent at *ortho* position of the arylbromide coupling partner can affect the C-H activation reaction. 2-Bromoanizole gave no conversion (entry 11, Table **C-3**) while 4-bromanisole reacted and did give good yield (entry 4, Table **C-3**). Such phenomenon did not happen with 1-bromo-2-chlorobenzene and 2-bromotoluene (entry 12 & 13, Table **C-3**).

C II.3 Synthetic access to benzo-fused-based neolignans

C II.3.1 Synthesis of benzofuran-based neolignan

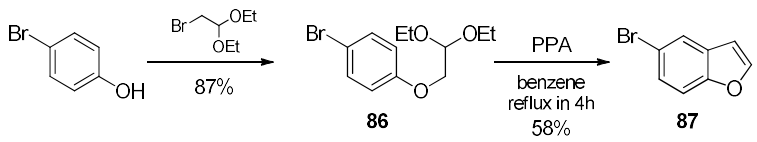
First of all, the synthesis of building block **I** (Scheme **C-1**) must be investigated. The formation of benzofuran ring system was well known but there are only handful methods for the synthesis of 5-bromobenzo[*b*]furan were published.[91]

B.-L. Zang *et al.* reported a new method starting from 5-bromo-2-hydroxybenzaldehyde, using Nef reaction to synthesize 5-bromobenzofuran. [91b] Follow this method (Scheme **C-3**), aldol addition product **84** was formed in 81% yield and the following reduction also gave good yield of **85** (78%). However, the Nef reaction did not perform well. No conversion was found even with long reaction time (24 hours).



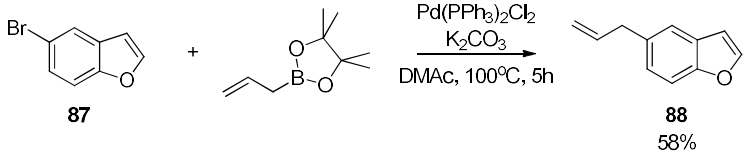
Scheme C-3: Synthesis of 5-bromobenzo[b]furan via Nef reaction

A. Taveras disclosed an older method starting from 4-bromophenol. [91d] This 2-step method was reported to be applied on the synthesis of the benzofuran derivatives with different substituents at C-5. At first step, 4-bromophenol was put into substitution with 2-bromo-1,1-diethoxyethane to obtain ether **86**. Afterward, a de-protection and ring closure in *situ* occurred in acidic condition of polyphosphoric acid. Desired product **87** was collected after distillation. This route turned out as quite robust.



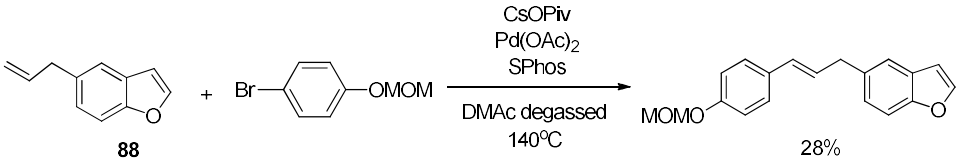
Scheme C-4: Synthesis of 5-bromobenzo[b]furan by Taveras' method

The subsequent reaction to add an allyl group into C-5 position was handled well under the condition with $Pd(PPh_3)_2Cl_2$ as catalyst, K_2CO_3 as base and in DMAc solvent. Product **88** was obtained in 58% yield.



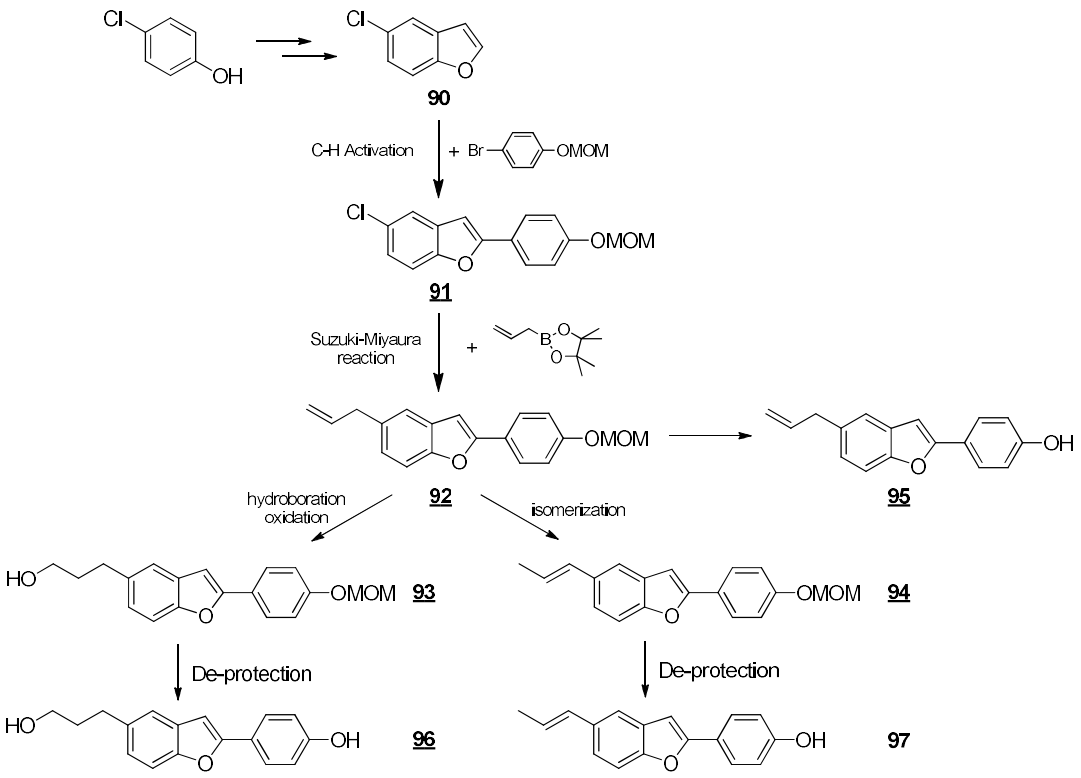
Scheme C-5: Suzuki-Miyaura reaction of 5-bromobenzo[*b*]furan

However, the C-H activation reaction of **88** did not give the desired result. The product of a Heck coupling reaction was found, instead.



Scheme C-6: Heck coupling reaction of 5-allylbenzo[*b*]furan

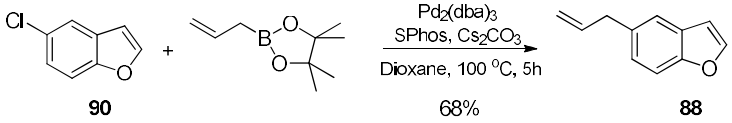
Notably, during the determination of the scope of C-H activation reaction on benzo[*b*]furan, chlorides as coupling partners were observed to be inert under the reaction conditions (entry 5, 13 & 14, Table **C-3**). This selectivity property turned out as actual advantage for outlining another approach to the desired products by starting from 5-chlorobenzo[*b*]furan (Scheme **C-7**).



Scheme C-7: New synthesis route for benzo[*b*]furan (Route A)

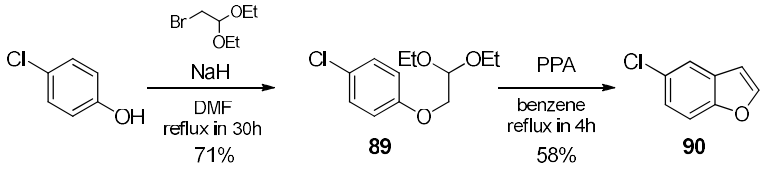
In this new route, the C-H activation and the Suzuku-Miyaura coupling will be swapped to avoid the Heck coupling reaction. Firstly, aryls moieties will be added selectively on C-2 of benzo[*b*]furan ring via C-H activation. Afterward, the chloride group at C-5 will still be substituted by a Suzuki-Miyaura reaction.

However, 5-chlorobenzo[*b*]furan did not react under former conditions using $Pd(PPh_3)Cl_2$ and K_2CO_3. Several stronger conditions for Suzuki-Miyaura reactions on chloride substrate have been reported,[92] but only the method of Thimmaiah *et.* al. used common catalysts and ligands.[92b] After a quick optimization, 5-allylbenzo[*b*]furan could be synthesized under conditions using $Pd_2(dba)_3$ as catalyst, SPhos as ligand, Cs_2CO_3 as base in dioxane, 100 °C and for 5 hours. The reaction gave 68% isolated yield to establish the principal reactivity for the coupling transformation. (Scheme **C-8**)



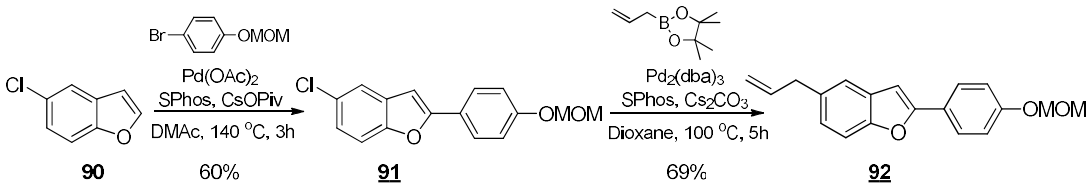
Scheme C-8: Suzuki-Miyaura reaction on 5-chlorobenzo[*b*]furan

For the preparation of 5-chlorobenzo[*b*]furan, the former pathway was still efficient. The yield of substitution reaction was slightly lower but the yield of the cyclization was still the same (Scheme **C-9**).



Scheme C-9: Synthesis of 5-chlorobenzo[*b*]furan (90)

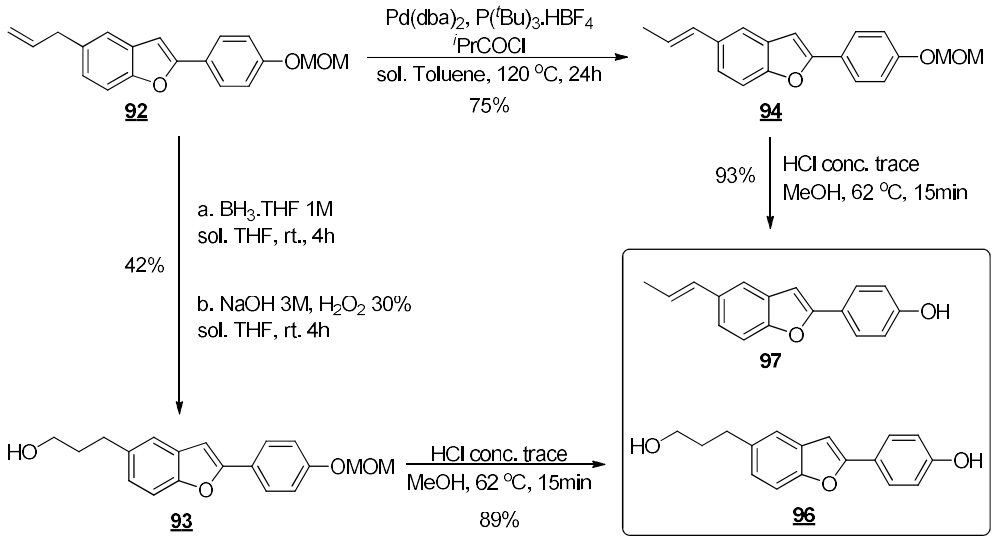
5-Chlorobenzo[*b*]furan reacted selectively with 1-bromo-4-(methoxymethoxy)benzene via certain C-H activation condition and no by-product was found. Product **91** was obtained with 60% yield after only 3h reation time. Compound **91** was subsequently submitted to the optimized Suzuki-Miyaura conditions to obtain product **92** in 69% yield (Scheme **C-10**). On the other hand, MOM protective group was sustainable under the Suzuki-Miyaura reaction condition as expected.



Scheme C-10: Synthesis of key compound 92

Product **92** represents a key compound for the synthesic route. From **92**, hydroboration oxidation reaction[72] using BH_3.THF 1M for the first step and NaOH, H_2O_2 in THF for the second step was utilizied in *situ* to obtain alcohol **93** with 42% isolated yield. MOM protective group was cleaved in methanol with traces of concentrated HCl afterwards to obtain the final product **96** (Scheme **C-11**).

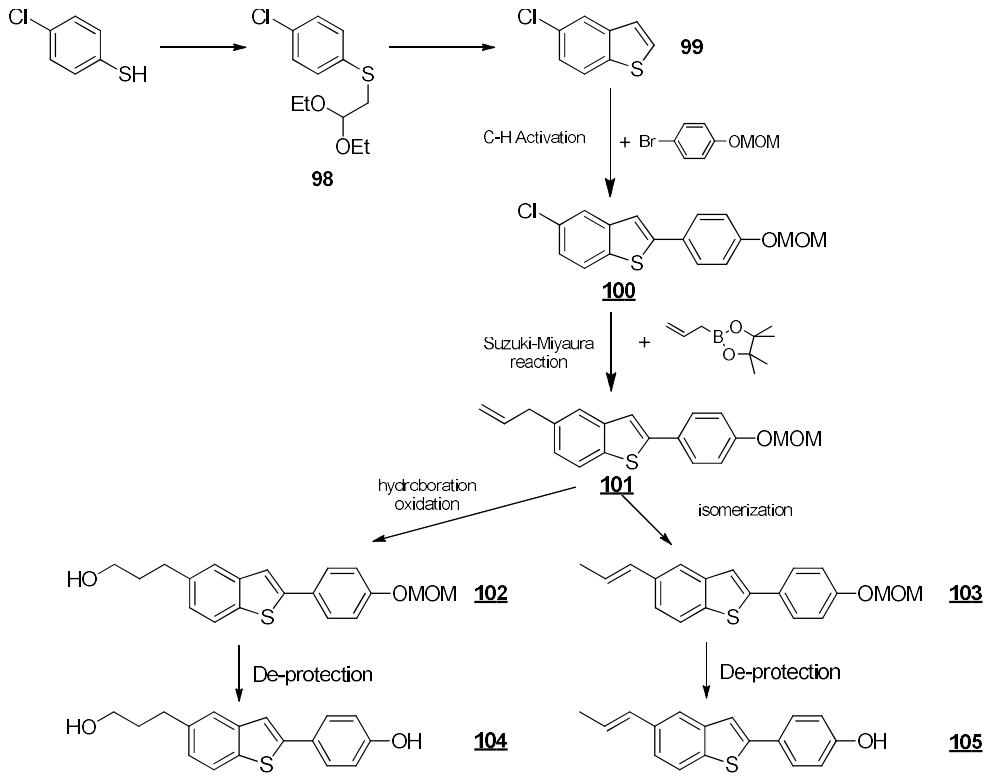
On the other hand, there are several different methods for isomerization of **92** using transition metal catalyst.[73] Only Gauthier *et.* al. used palladium catalyst with bulky ligand [73h] to migrate the double bond into conjugation with the aryl ring with very good stereoselectivity. The condition using $Pd(dba)_2$ as catalyst, $P(^tBu)_3.HBF_4$ as ligand was optimized separately on model compound 4-allylanisole. Product **94** was obtained in *E* configuration, with 75% yield. De-protection by concentrated HCl in methanol was occurred to remove MOM protective group to get final product **97**. (Scheme **C-11**)



Scheme C-11: Synthesis of final compounds 96 & 97

Total yield of the synthesis of **96** and **97** from 5-chlorobenzo[*b*]furan is 16% and 29% respectively after 4 steps which are acceptable for such total synthesis route in Scheme **C-8**. Other benzofused heterocycles will be applied to synthesize more neolignans.

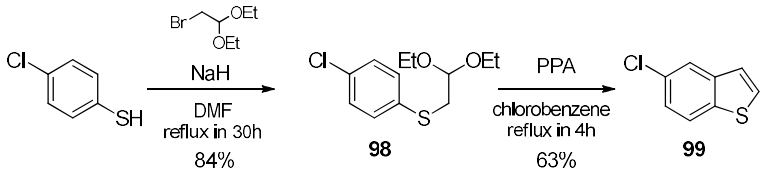
C II.3.2 Synthesis of benzothiophene-based neolignans



Scheme C-12: Synthesis route for benzothiophene (Route B)

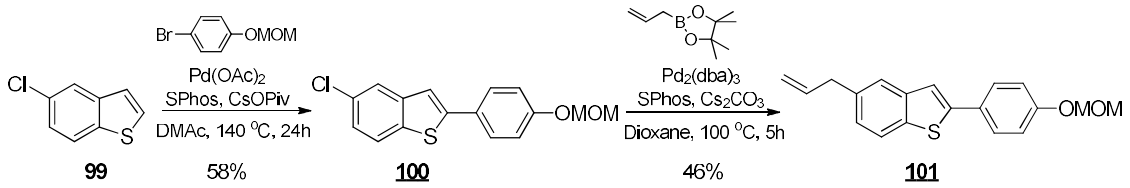
Firstly, a similar synthesis route applied on benzothiophene was proposed in Scheme **C-12**.

Starting material 5-chlorobenzothiophene was synthesized via 2-step method from 4-chlorobezenethiol.[93] The cyclization gave higher yield in chlorobenzene solvent compared to reaction of 4-chlorophenol in benzene (Scheme **C-13**).



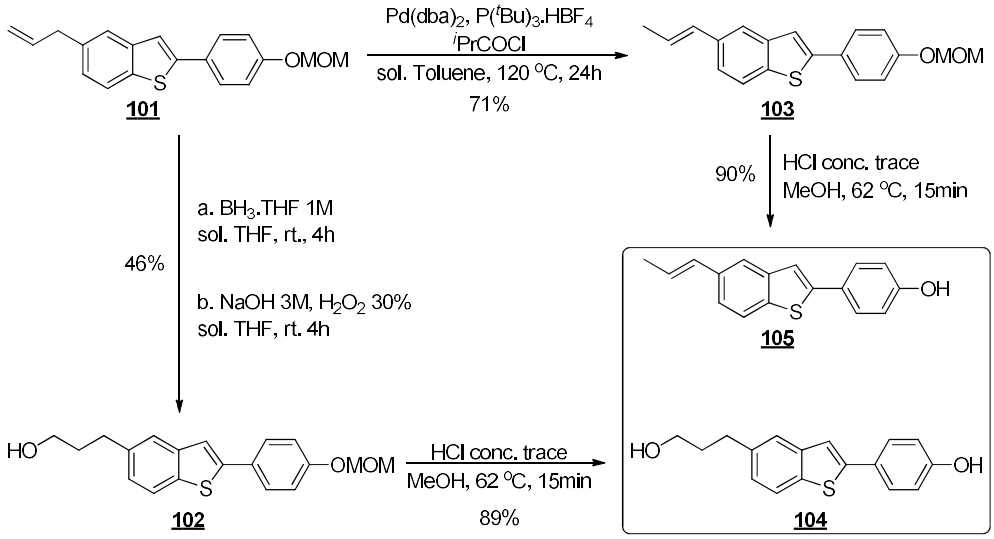
Scheme C-13: Synthesis of 5-chlorobenzothiophene

C-H activation reaction on 5-chlorobenzothiophene **99** was also selective. It gave slightly lower yield than the yield of the reaction on benzo[*b*]furan despite a prolonged reaction time of 24 hours. Suzuki-Miyaura reaction on **100** also gave lower yield, 46% compared to 69% in the same reaction on benzo[*b*]furan (Scheme **C-14**).



Scheme C-14: Synthesis of key compound 101

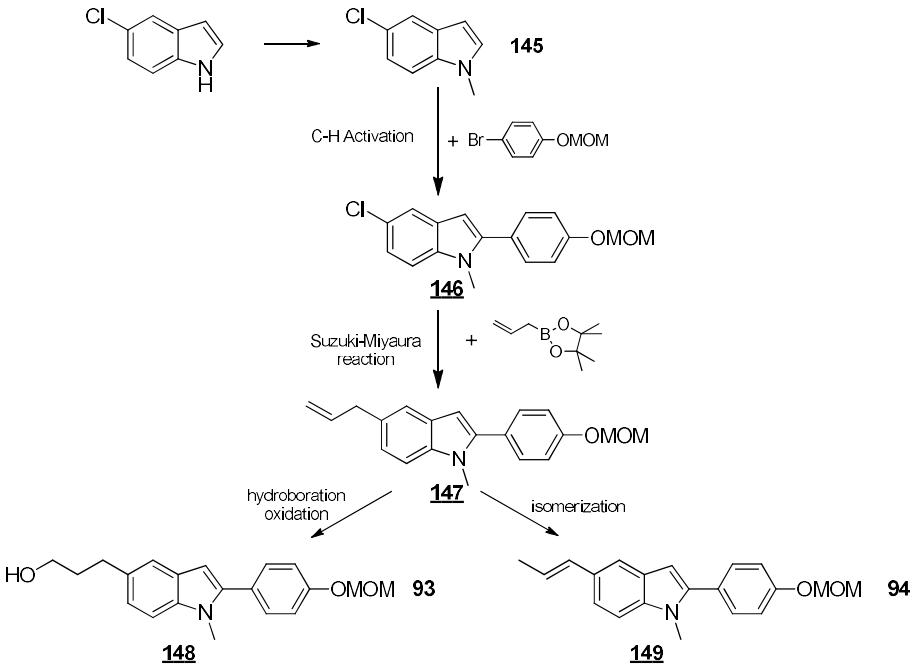
Final reactions were employed on benzothiophene compounds under identical conditions from the benzofuran series. Hydroboration oxidation reaction on **101** gave 46% isolated yield while isomerization reaction gave 71% yield. De-protection reaction on **102** and **103** proceeded in very good yield of 89% and 90%, respectively (Scheme **C-15**).



Scheme C-15: Synthesis of final compounds 104 & 105

Total yields of the synthesis of **104** and **105** from 5-chlorobenzothiophene (**99**) are 11% and 17% respectively.

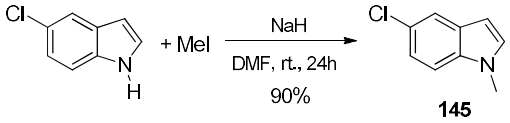
C II.3.3 Synthesis of indole-based neolignans



Scheme C-16: Synthesis route for indole (Route C)

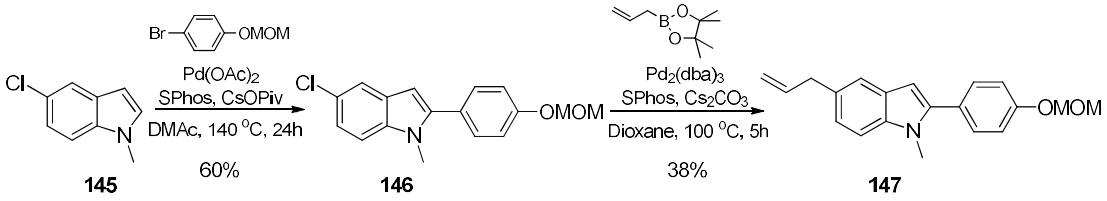
Since 5-chloroindole was commercially available, preparation of an indole starting material for the analogous reaction series required only an N-protection step with the intention to remove the activated N-H proton that can shut down the catalytic circle. Therefore, the synthesis route for indole was modified within the first steps only. (Scheme **C-16**)

5-Chloroindole was protected via methylation at the N-H group. The most common method is using MeI in the presence of NaH and DMF as solvent. The reaction was stirred at room temperature for 24 hours and gave 90% isolated yield.



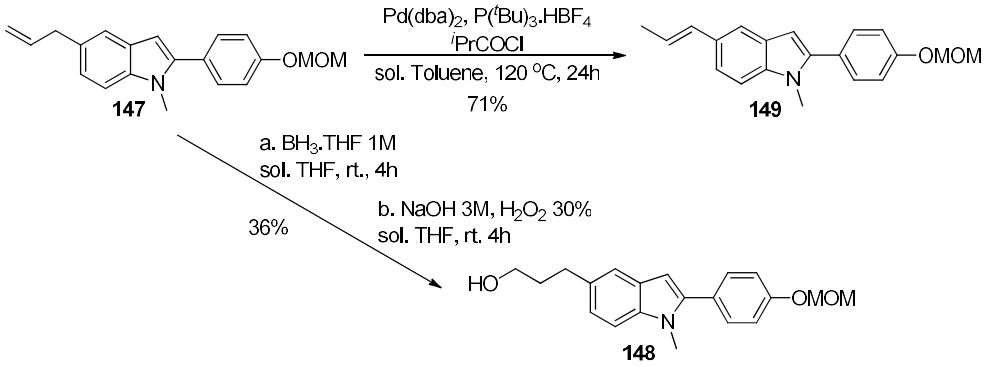
Scheme C-17: Preparation of starting material 5-chloro-N-methylindole (145)

C-H activation reaction performed well with indole compound **145** and gave 60% yield. Methyl protection group was sustainable under the reaction condition. On the other hand, Suzuki-Miyaura reaction on **146** was not very efficient because of the influence of the basicity of 1-methylindole itself. Suzuki reactions showed the sensitivity in basic or acidic substrate.[94] An additive can be applied to improve the yield. Key compound **147** was isolated in only 38% yield (Scheme **C-18**).



Scheme C-18: Synthesis of key compound 147

The key compound **147** was produced in low yield so subsequent final reactions were limited to hydroboration oxidation and isomerization reactions. Further experiments will be evaluated again in case biology testing results are promising. Both reactions gave similar yield compared to benzo[*b*]furan and benzothiophene. Compounds **148** and **149** were obtained in 36% and 71% yields respectively.



Scheme C-19: Synthesis of compound 148 and 149

C II.3.4 Synthesis of other neolignan derivatives

With a practical synthesis route for benzo[*b*]furan and benzothiophene compounds at hand, a group of neolignan-like compounds based on those heterocyclic rings were prepared to evaluate their biology properties as anti-inflammatory agents.

Table C-7: Series of C-H activation on 5-chloride benzo-fused heterocycle

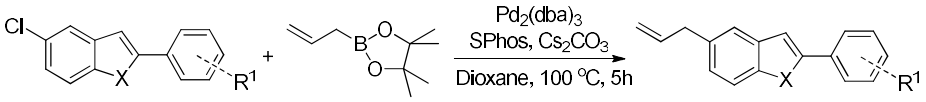
Entry	X	R^1	Product	Yield (%)
1	O	4-OMe	**106**	58%
2	O	3,5-dimethoxy	**107**	51%
3	O	2-OMe-4-OMOM	-	0%
4	O	H	**108**	44%
5	O	4-F	**109**	41%
6	O	4-CHF_2	**110**	45%
7	O	4-$N(CH_3)_2$	**111**	49%
8	O	4-Cl	**112**	47%
9	O	2-Cl	**113**	44%
10	O	2-Cl-4-OMe	**114**	53%
11	S	4-OMe	**115**	31%
12	S	2-Cl-4-OMe	**116**	53%

Reaction condition: see general procedure F. Yields were isolated yields.

Firstly, a series of C-H activation reactions was conducted (**table C-7**). In order to evaluate anti-inflammatory activities, a series of EDGs such as OMe, $N(CH_3)_2$ on the aryl moiety was designated on benzo[*b*]furan (entries 1, 2, 7 & 10) and benzothiophene (entries 11 & 12). Halides were also tried to determine the influences on the system (entries 5, 8, 9, 10 & 12). As mentioned before, entry 3 gave no conversion since the methoxy group at *ortho* position could block the interaction of the Pd catalyst across the C-Br bond. However, it did not happen with chloride substrates (entries 9, 10 & 12). Compounds **114** and **116** could be functionalized to exchange Cl into other groups at *ortho* position in a few steps.

Subsequently, Suzuki-Miyaura reactions were managed on C-H activation products (Table **C-8**). All compounds reacted and gave pretty good yields (47 – 72%) except **122** was isolated in only 24% yield (entry 6). Here, the basicity of the $N(CH_3)_2$ group could detrimentally affect the catalyst system.

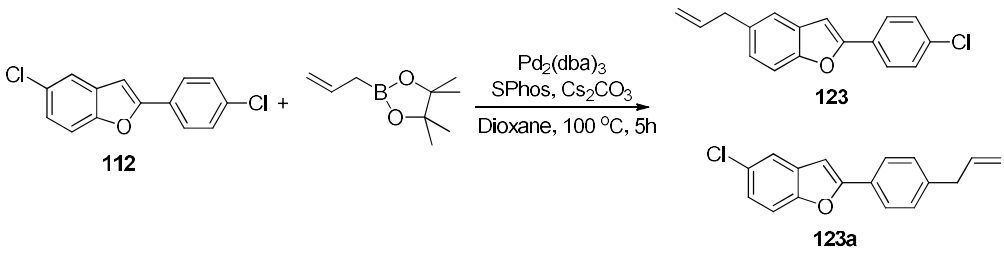
Table C-8: Series of Suzuki-Miyaura reaction in allyl addition step



Entry	X	R^1	Product	Yield (%)
1	O	4-OMe	**117**	70%
2	O	3,5-dimethoxy	**118**	66%
3	O	H	**119**	74%
4	O	4-F	**120**	72%
5	O	4-CHF_2	**121**	69%
6	O	4-$N(CH_3)_2$	**122**	24% [a]
7	O	4-Cl	**123**	44% [b]
8	O	2-Cl	**124**	51%
9	O	2-Cl-4-OMe	**125**	53%
10	S	4-OMe	**126**	58%
11	S	2-Cl-4-OMe	**127**	47%

Reaction condition: see general procedure G. Yields were isolated yields. [a]: using pre-conditioned silicagel with 1% TEA in purification. [b]: regioisomer isolated only

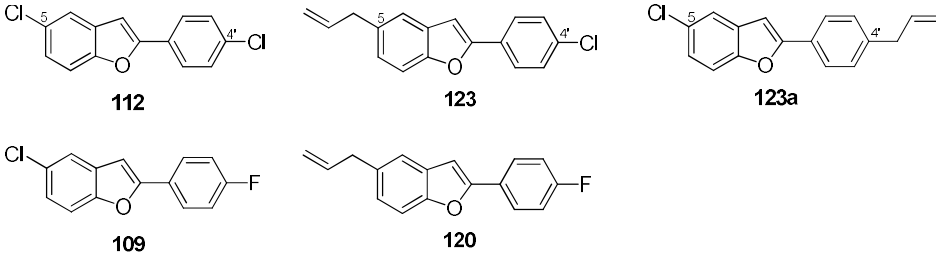
Another observation was found in entry 7. Starting material **112** contained 2 chloride substituents at C-5 and C-4' with potentially similar reactivities for the cross coupling step. Therefore, 2 possible products can be formed.



Scheme C-20: Suzuki-Miyaura reaction on compound 112

Both products **123** and **123a** are unprecedented so we used NMR comparison to define the structure of the product. Two substrates brought to the comparison were **109** (R^1 = 4-F) and **106** (R^1 = 4-OMe). Chemical shift of C-5 on **112**, **109** & **106** are similar since the affection from different substituents at C-4' are not trivial. However, chemical shift of C-5 on **123**/**123a** are different than that on **120**, **117** (allylation products of **109** and **106** respectively). Chemical shift of C-5 on **112** and its allylation product (**123** or **123a**) are pretty the same.

Table C-9: Comparison of NMR peak between substrate and product of Suzuki-Miyaura reaction



Compound	R^1	**C-5** (quaternary)		**C-4'** (quaternary)	
112 (substrate)	**Cl**	128.7	Δ = - 0.3 ppm	134.8	Δ = 6.4 ppm
123/123a (product)	**Cl**	128.4		141.2	
109 (substrate)	**F**	128.6	Δ = 6.2 ppm	163.1 (J_{C-F}^1)	Δ = - 0.2 ppm
120 (product)	**F**	134.8		162.9 (J_{C-F}^1)	

On the other hand, chemical shift of C-4' on **109** and **106** are not changed after the reaction with the same reason, the affection from different substituents at C-5 (allyl instead of chlor) are not considerable. This time, chemical shift of C-4' on **112** increased about 6 ppm after the allylation.

According to the comparison above, the substitution of **112** occurred at C-4' instead of C-5 since the chemical shift of C-4' was changed significantly. Chemical shift of C-4' of **112** increased 6.4 ppm after the reaction, similar to what happened to C-5 of **109** (6.2 ppm) and **106** (6.3 ppm). We concluded that compound **123a** was the one isolated from the reaction.

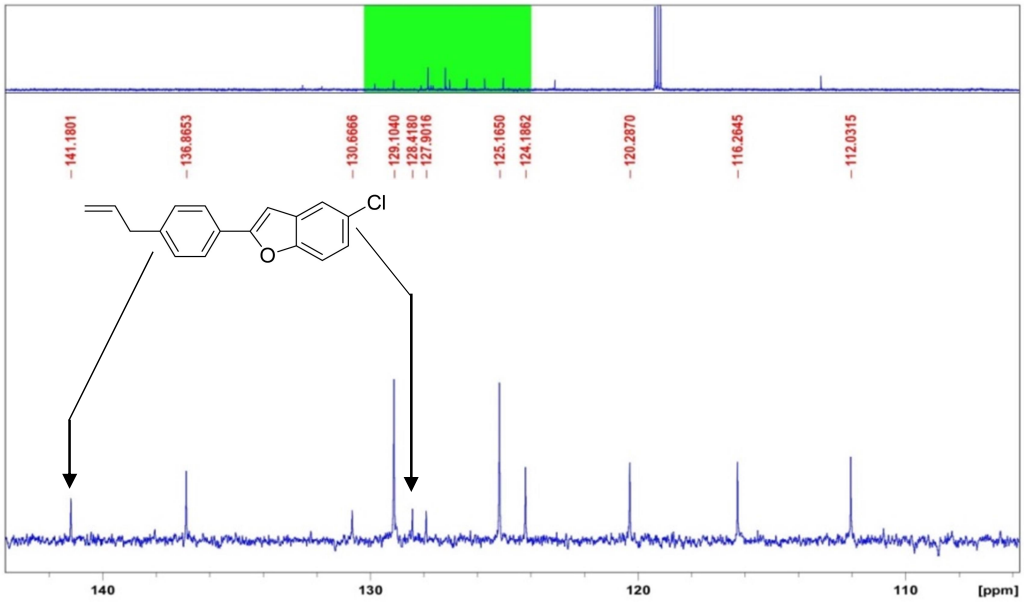
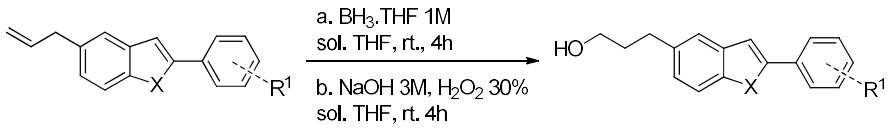


Figure C-11: Detail ^{13}C- NMR spectra of compound 123a

This result can be explained by using $Pd_2(dba)_3$ catalyst and SPhos ligand, an electron rich catalytic system. On the other hand, affected from benzo-fused system, electron density of the heterocycle moiety of substrate is higher than that in aryl moiety. Therefore, chloride group on the aryl side is more electrophile than

the other one on benzo[*b*]furan side. Thus, the Pd catalytic system prefers to attach to the one to form **123a** than to form **123**. This phenomenon was not found in the reaction of compounds containing chloride substitution at *ortho* position such as **113**, **114** & **116** (entries 8, 9 & 11, Table **C-8**) because of its hindered position.

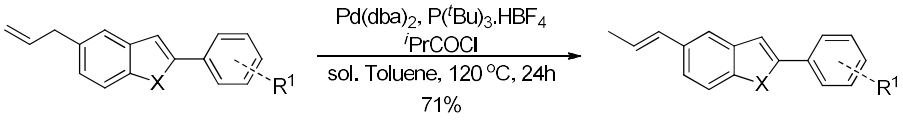
Table C-10: Series of hydroboration oxidation reactions



Entry	X	R^1	Product	Yield (%)
1	O	4-OMe	**128**	46%
2	O	3,5-dimethoxy	**129**	40%
3	O	H	**130**	52%
4	O	4-F	**131**	53%
5	O	4-CHF_2	**132**	49%
6	O	2-Cl	**133**	50%
7	S	4-OMe	**134**	45%
8	S	2-Cl-4-OMe	**135**	42%

Reaction condition: see general procedure H. Yields were isolated yields.

Table C-11: Series of isomerization reactions



Entry	X	R^1	Product	Yield (%)
1	O	4-OMe	**136**	62%
2	O	3,5-dimethoxy	**137**	77%
3	O	H	**138**	75%
4	O	4-F	**139**	77%
5	O	4-CHF_2	**140**	74%
6	O	2-Cl	**142**	65%
7	O	2-Cl-4-OMe	**143**	69%
8	S	4-OMe	**144**	57%

Reaction condition: see general procedure I. Yields were isolated yields.

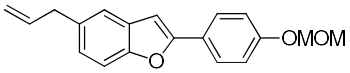
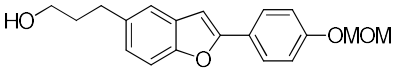
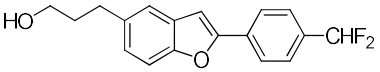
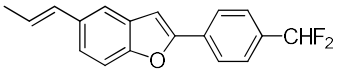
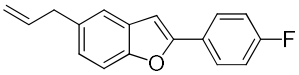
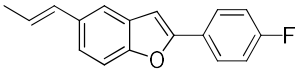
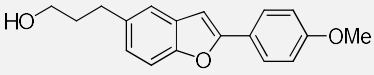
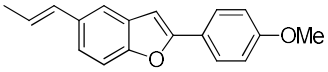
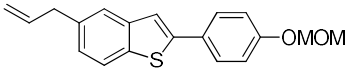
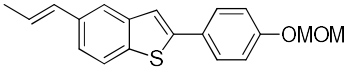
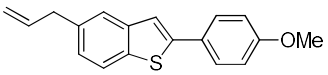
Products **117** – **127** were divided into 2 sets for 2 branches of the synthesis route. The first set was transformed within hydroboration oxidation reaction (Table **C-10**). All reactions gave moderate yields (42 – 53%) but enough material was obtained for biology testing. Compounds in the second set were isomerized with good yields (62 – 77%). (Table **C-11**)

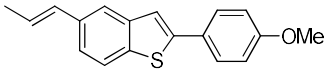
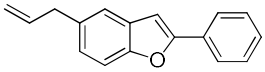
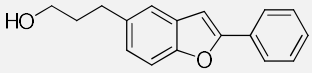
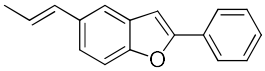
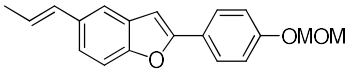
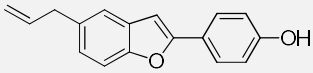
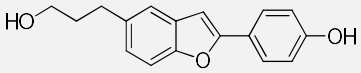
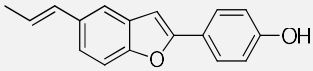
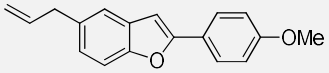
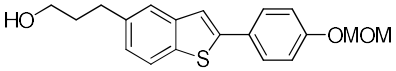
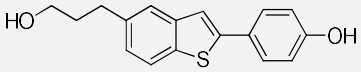
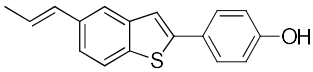
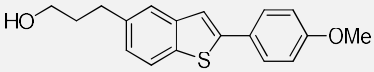
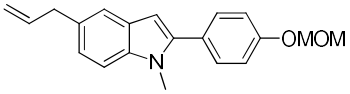
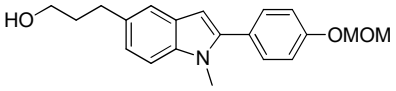
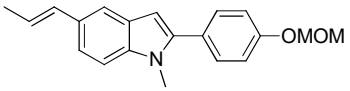
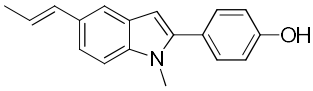
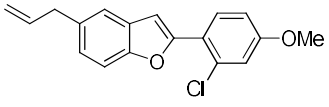
All benzo[*b*]furan-based neolignans (**92** – **97**), benzothiophene-based neolignan (**101** – **105**), indole-based neolignans (**147** – **149**) and products obtained in Table **C-10** & **C-11** (**128** – **144**) were submitted to biological testing, focussing on anti-inflammatory properties.

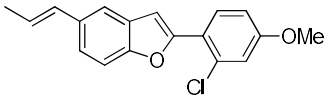
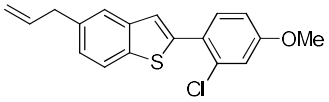
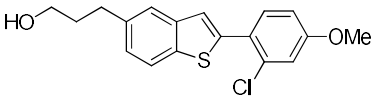
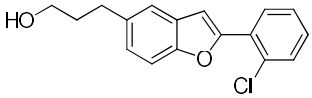
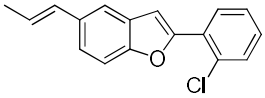
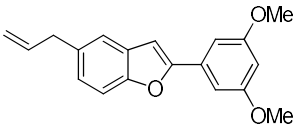
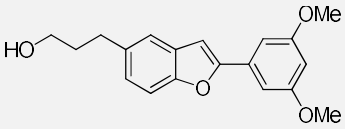
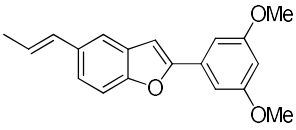
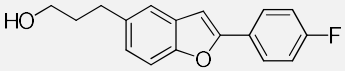
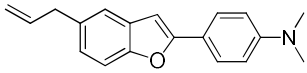
C II.4 Bioassay

In general, 18 compounds out of 40 neolignans tested were significantly active, which is a hit rate of 45 % (Table **C-12**). According to the table of biology testing results, it is necessary to find the molecular targets by which some of them inhibit NF-κB or activate LXR-β. Additionally, conducting further testing would enable us to gain the knowledge whether the conclusions that were drawn about their structure activity relationship can be applied to a greater number of neolignan-like derivatives.

Table C-12: Biology testing results

DNTI number	Compound	Structure	Fold activation NF-κB (at 10µM)	LXR-β activation	IC_{50} (NF-κB)
3143	**92**		**0.47**	**1.13**	n.d.
3144	**93**		**0.03**	**0.46**	**9.22 µM**
3145	**132**		**0.08**	**0.93**	**8.52 µM**
3146	**140**		**0.82**	**1.63**	n.d.
3148	**120**		**0.71**	**1.66**	n.d.
3149	**139**		**0.92**	**1.41**	n.d.
3150	**128**		**0.04**	**0.14**	**3.82 µM**
3151	**136**		**0.78**	**1.45**	n.d.
3152	**101**		**0.88**	**2.30**	n.d.
3153	**103**		**0.90**	**2.25**	n.d.
3154	**126**		**0.89**	**1.34**	n.d.

3155	**144**		**0.85**	**2.09**	n.d.
3156	**119**		**0.27**	**1.22**	n.d.
3232	**130**		**0.10**	n.d.	**1.46 µM**
3233	**136**		**0.66**	n.d.	n.d.
3234	**94**		**0.77**	n.d.	n.d.
3235	**95**		**0.06**	n.d.	**2.12 µM**
3236	**96**		**0.12**	n.d.	**1.24 µM**
3237	**97**		**0.15**	n.d.	**2.86 µM**
3238	**117**		**0.60**	n.d.	**3.60 µM**
3239	**102**		**0.96**	n.d.	n.d.
3240	**104**		**0.21**	n.d.	**4.74 µM**
3241	**105**		**0.78**	n.d.	**23.77 µM**
3242	**134**		**0.37**	n.d.	**6.59 µM**
3243	**147**		**0.79**	n.d.	n.d.
3244	**148**		**0.35**	n.d.	n.d.
3245	**149**		**1.10**	n.d.	n.d.
3246	**150**		**1.09**	n.d.	n.d.
3247	**125**		**1.17**	n.d.	n.d.

3248	**143**		**1.16**	n.d.	n.d.
3249	**127**		**1.18**	n.d.	n.d.
3250	**135**		**0.80**	n.d.	**13.69 µM**
3251	**133**		**1.08**	n.d.	n.d.
3252	**142**		**1.20**	n.d.	n.d.
3253	**118**		**0.54**	n.d.	n.d.
3254	**129**		**0.20**	n.d.	**1.92 µM**
3255	**137**		**0.94**	n.d.	n.d.
3256	**131**		**0.32**	n.d.	**2.20 µM**
3257	**122**		**0.30**	n.d.	n.d.

- Compounds were tested at 10µM in luciferase-based cell model (HEK293 cells) for NF-κB Inhibition and LXR beta activation. Table displays average fold induction/inhibition out of 3 independent experiments. (One-way ANOVA, Bonferroni post-test). DNTI numbers are compound numbers in DNTI comprehensive project.
- Fold activation on NF-κB lower than 0.5 was considered as significant activity.
- Activation on LXR-β higher than 2 fold was considered as significant activity.
- IC_{50} < 10 µM was considered as notable values.
- n.d.: not determined.

Firstly, hydroxylpropyl group (PrOH) at C-5 was found in majority of compounds that significantly inhibit NF-κB (**93**, **96**, **104**, **128** – **132**, **134** – **135** & **148**). None of them have good activity of LXR-β activation but some have notable IC_{50} values (**96**, **104**, **128** – **131** & **134**).

All 3 benzothiophene derivatives (**101**, **103** & **144**) displayed significant activities on LXR-β, but none of them were good NF-κB inhibitor. On the other hand, only 2 out of 11 benzothiophene derivatives were found as active compounds on NF-κB along with good IC_{50} values are (**104** & **134**).

Several benzothiophene-based neolignans are actually active inhibitors but they tend to have considerably high IC_{50} values. Compound **105**, a benzothiophene-based neolignan with 2-propenyl-1 at C-5 and

a hydroxyl group atn C-4', showed an IC_{50} value of 23.77 µM, which is about 10 times higher than that value of compound **97**, a benzo[b]furan derivative with exactly the same substituents. For other comparison of compounds with the same motif but different core, IC_{50} values of benzothiophene derivatives **104** (IC_{50} = 4.74 µM) and **134** (IC_{50} = 6.59 µM), which were considered as notably good inhibitors, are still about 2 times higher than IC_{50} of benzofuran derivatives **96** (IC_{50} = 1.24 µM) and **128** (IC_{50} = 3.82 µM).

Among the 12 halide containing compounds tested only 2 of them displayed good activities (**131** with CHF_2 and **132** with F), however, both of them have key group PrOH on the other side. Like halides, OMOM and OMe groups at C-4' showed no relation with the activity of tested compound. There is an exception with compound **129** which has 2 OMe groups at C-3' and C-5'. This is the only synthesized neolignan with substituents at this position so we cannot make sure whether activity of tested compound was defined by OMe at C-3' (and C-5') or no substituent at C-4' because compound **119** with no substituent is also a good inhibitor of NF-κB.

On the other hand, a phenolic hydroxyl group (OH) at C-4' displayed particular behavior despite of any substituent at C-5 since compound **95**, **96** and **97** all showed good inhibitor activity. Nevertheless, it was surprising that compound **96** containing both OH and PrOH is not better than compounds with only one of them separately (**93**, **132**, **128**, **130** with PrOH at C-5 and **95**, **97** with OH at C-4').

C III Conclusion

Active neolignans extracted from Rhatany's were successfully submitted to retro-synthetic analysis and a synthesis route was designed. Key steps of the synthesis route are transition-metal catalytic coupling reactions because of their advantages. One of those coupling reactions, a C-H activation was fully developed to directly introduce aryls to C-2 of benzo[*b*]furan selectively. The reaction also occurred successfully on benzothiophene and N-methylindole. The other coupling reaction was the Suzuki-Miyura reaction which was optimized for allylboronic acid pinacol ester and an aromatic chloride using common catalyst system.

By varying coupling partners for C-H activation, a group of neolignans based on benzofuran, benzothiophene and indole was synthesized. Even though neolignan with OH or OMe at C-2' was not produced, alternatively, an indicative compound with chloride at C-2' was prepared indeed. All those compounds did not display good activity on NF-κB inhibition but they pointed out a hint to further functionalization on this chloride moiety.

Subsequently, 40 synthesized compounds (38 absolutely new compounds) were tested for biological activities, focussing on anti-inflammatory properties. 15 compounds displayed significant activity on NF-κB inhibition, comparable to the positive control, parthenolide, with IC_{50} values less than 10μM. 3 compounds showed promising activity on LXR-β activation. With 18 active compounds were found out of 40 tested one, the hit rate is 45%.

Based on analysis of the neolignans bioassay, the relationship between structure and activities was presumed. Active proton might be a key factor for substituent when compounds have POH, OH or CHF_2 are the best inhibitors of NF-κB with low IC_{50} values. This conclusion is also in line with the report of Baumgartner *et.* al. about natural compounds.[69] It was reported that the most active compounds (IC_{50} ranging from 1.4 to 6.4 μM) always contain at least one phenolic hydroxyl at C-2' or C-5'.

D Experimental part

D I Materials and methods – chemical synthesis

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Reactions were followed via TLC (0.25 mm silica gel 60-F plates). Visualization was accomplished with UV light.

Table D-1: Recipes for TLC staining solutions used in this thesis.

TLC stain solution 1		TLC stain solution 2		TLC stain solution 3	
6 g	$KMnO_4$	10 g	phosphomolybdic acid hydrate	40 mg	bromocresol green
0.5 g	KOH	1 g	cerium ammonium nitrate	100mL	dry EtOH
40 g	K_2CO_3	20 g	H_2SO_4 conc.	0.1 M	NaOH until blue color appreas
600 mL	deion. H_2O	300 mL	EtOH		

Flash chromatographies were carried out on silica gel 40 – 63 µm by MPLC. All solvents for MPLC were distilled prior to use. Unless stated otherwise, a ratio of 1/100 crude material/silica gel was used for column chromatography. Pre-conditioned silicagel was prepared via stirring of silica in Et_3N/LP 10%, removal of the solvent in vacuo and storage of the dry material in a drying oven at 100 °C for 24 h.

Dimethylacetamide (DMAc) was distilled and subsequently degassed by bubbling argon through the solvent in an ultrasonic bath for 2 hours.

Nuclear Magnetic Resonance (^{1}H and ^{13}C-NMR) were recorded from deuterated solvents ($CDCl_3$, DMSO-d6, acetone-d6, etc.) solutions on a Bruker AC 200 or Bruker Advance UltraShield 400 (400 MHz) or Bruker Avance IIIHD (600 MHz). Chemical shifts (δ) are reported in parts per million (ppm) with tetramethylsilane (TMS) as internal standard. The abbreviations used to report the data are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad).

Gas Chromatography-Mass Spectrosopy (GC-MS) spectra were recorded either on a Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30 m x 0.25 mm ID) or a Thermo Trace 1300 / ISQ LT using a standard capillary column BGB 5 (30 m x 0.25 mm ID).

GC method:

- Joey_short: 100-280_ramp 20 in 15min

- Toan_20min: 120(2min), ramp 20, 280(3min)

- Toan_25min: 120(2min), ramp 20, 280(8min)

High Resolution Mass Spectroscopy: An Agilent 6230 LC TOFMS mass spectrometer equipped with an Agilent Dual AJS ESI-source was used for HR-MS analysis. The mass spectrometer was connected to a liquid chromatography system of the 1100/1200 series from Agilent Technologies, Palo Alto, CA, USA. The system

consisted of a 1200SL binary gradient pump, a degasser, column thermostat and an HTC PAL autosampler (CTC Analytics AG, Zwingen, Switzerland). A silica-based Phenomenex C-18 Security Guard Cartridge was used as stationary phase. Data evaluation was performed using Agilent MassHunter Qualitative Analysis B.07.00. Identification was based on peaks obtained from extracted ion chromatograms (extraction width ±20 ppm). Analyses were performed by Czollner Laszlo (IAS, VUT).

Melting points were determined using a Leica Galen III Kofler or a Buchi Melting Point B-545. Data is given in 0.5 °C intervals.

D II General procedures

This section gives general descriptions of repeatedly used protocols within this work.

D II.1 General procedure A for hydrolysis of naringin and hesperidin

Naringin and hesperidin was isolated by student lab courses due to precedence protocol [95] . They were found as beige fine powder, stored in desiccators and used without futher purification.

A 500 mL round bottom flask with magnetic stirring bar was charged with 200 mL of solution of 2 N methanolic sulfuric acid (2 mmol of H_2SO_4 in 1 mL methanol). Naringin (6 g, 10.3 mmol) or Hesperidin (6 g, 9.8 mmol) was suspended subsequently into the solution with the ratio of 30 mg substrate / 1 mL acid solution. A condenser was added and the reaction was heated at reflux for 5 hours. The resulting homogeneous solution was cooled and neutralized by saturated solution of Na_2CO_3 to pH not higher than 7. The hydrolysis product was extracted 3 times with 100 mL EtOAc. The organic phase was collected and washed for 3 times with 50 mL water and 1 last time with 50 mL brine. The solution of product was dried over Na_2SO_4 then all the solvent was evaporated (EtOAc) under reduced pressure. The crude product (naringenin or hesperetin) was dissolved again in minimum amount of acetic acid (7% solution in water) at 80 °C (1 g crude product can be dissolved in about 125 mL acid solution). The solution was cooled slowly to room temperature then left for crystallization overnight in the fridge. The precipitated crystals were collected by filtration and washed with cold water. The product was dried from water in a vacuum oven at 70 °C for 2 days.

D II.2 General procedure B for protection of naringenin or hesperetin

For full-protection, a 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with naringenin (272 mg, 1 mmol) or hesperetin (303 mg, 1 mmol), pyridine (320 µL, 317 mg, 4 mmol) and DMAP (12.2 mg, 0.1 mmol) dissolved in 2 mL DMF. Acid anhydride (Ac_2O (4 mmol) or Piv_2O (4 mmol)) was added subsequently. The solution was stirred and heated to 50 °C for 24h.

For bis-protection, similar procedure was applied with only 2.5 equiv. of acid anhydride (Ac_2O or Piv_2O), without DMAP catalyst and the reaction was occurred for 24h at room temperature only.

The reaction was worked-up by quenching with NH_4Cl saturated solution. Afterwards, a saturated solution of Na_2CO_3 was used to neutrualize the reaction mixture. The product was extracted with Et_2O (3 x 10 mL) then washed with H_2O (3 x 10 mL) and a last time with 10 mL brine. The organic phase was dried over Na_2SO_4 and all the solvent was evaporated under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc mixtures to obtain fully protected product.

D II.3 General procedure C for reduction of protected naringenin or protected hesperetin

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 0.4 mmol substrate (protected naringenin or hesperetin) dissolved in 2 mL dried THF. The mixture was cooled to -78 °C and maintained in a cooling bath filled with acetone and liquid nitrogen. An argon ballon was used to balance the pressure in the vial. $LiBH_4$ 0.5M in THF (0.8 mL, 0.4 mmol, 1 equiv.) was added slowly (in 15 min) to the reaction mixture at -78 °C (cooling bath temperature). Afterwards, the reaction was warmed slowly to 0 °C in an ice bath and then kept stirring for 4 hours at 0 °C. The reaction was worked-up by quenching with 20 mL saturated solution of NH_4Cl in water. The product was extracted with Et_2O (3 x 5 mL) then washed with H_2O (3 x 10 mL) and a last time with 10 mL brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc (ratio depends on polarity of products) to obtain the desired product.

D II.4 General procedure D for direct arylation of N-*exo* and N-*endo* benzylated 2-aminothiazole by aryl bromides

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with substrate *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine (**16**) or *N*-(3-benzylthiazol-2(3*H*)-ylidene)aniline (**17**) (0.5 mmol, 1.0 equiv.), aryl bromides (0.75 mmol, 1.5 equiv.), KOAc (74mg, 0.76 mmol, 1.5 equiv.), and $Pd(OAc)_2$ (1 mg, 0.005 mmol, 0.01 equiv.). The vial was closed with a septum, evacuated and flushed with argon 3 times. Then 3 mL of dry DMAc were added by syringe. The mixture was heated to 140 °C for 24 hours. Before work-up, the reaction mixture was cooled to room temperature and then diluted with 5 mL ethylacetate and filtered through a pad of Celite. The organic phase was washed with saturated NH_4Cl solution for 3 times and a last time with brine, then dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was conducted by MPLC on silica gel with LP/EtOAc mixtures (added 1% vol. of triethylamine). In several cases, some starting material was found as impurity in the product. In these cases, Kugelrohr distillation was employed for further purification.

D II.5 General procedure E for deprotection of N-*exo* and N-*endo* benzylated 5-phenyl-2-aminothiazole

In a 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar, 5-phenyl-*N*-protected-thiazolamine (34 mg, 0.1 mmol) was dissolved in 1.0 mL DMSO. Then, 0.70 mL of a 1M solution of KO^tBu in THF (0.7 mmol, 7 equiv.) was added dropwise into the reaction. O_2 was bubbled slowly through the reaction mixture at room temperature over 15 minutes. Afterwards, the reaction mixture was quenched with saturated Na_2CO_3 solution and then extracted with 10mL EtOAc. The organic phase was washed with brine for 3 times, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The purification was conducted by MPLC on silica gel with LP/EtOAc mixtures (added 1% vol. of triethylamine).

D II.6 General procedure F for C-H activation on benzo-fused heterocycles

A 7mL vial equipped with a screw cap with septum and a magnetic stirring bar was charged with benzo[*b*]furan or either benzothiophene, indole or 1-methyl indole (1.0 mmol, 1.0 equiv.), aryl bromide (1.5 mmol, 1.5 equiv.), cesium pivalate (350mg, 1.5 mmol, 1.5 equiv.), $Pd(OAc)_2$ (9mg, 0.04mmol, 0.04 equiv.) and SPhos (16.4 mg, 0.08 mmol, 0.08 equiv.). The vial was evacuated and flushed with argon 3 times. Then 2 mL of degassed DMAc were added via syringe. The mixture was heated to 140 °C for 24 hours. The reaction mixture

was cooled to room temperature and then diluted with 15mL diethylether or ethylacetate (depending on the polarity of the product) and filtered through a pad of celite. The organic phase was washed with saturated NH_4Cl solution for 3 times, once with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product), if mixed fractions of C2 & C3 arylated compounds were obtained, these fractions were recrystallized. For that purpose the product mixture was dissolved in the least amount of boiling LP. The solution was cooled to -5 – 0 °C and left to crystallize overnight. The crystals were collected by filtration and washed for 3 times with cold LP (-5 °C). The solid material was dried in vacuo.

The same procedure was used for C-3 arylation of 2-arylbenzo[*b*]furans.

D II.7 General procedure G for Suzuki-Miyaura coupling on chloro benzo-fused heterocycles

A 7mL vial equipped with a screw cap with septum and a magnetic stirring bar was charged with 5-chloro benzo-fused (1.0 mmol, 1.0 equiv.), allylboronic acid pinacol ester (1.5 mmol, 1.5 equiv.), cesium carbonate (486 mg, 1.5 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (45 mg, 0.05mmol, 0.05 equiv.) and SPhos (41 mg, 0.1 mmol, 0.1 equiv.). The vial was evacuated and flushed with argon 3 times. Then 2 mL of dried dioxane were added via syringe. The mixture was heated to 100 °C for 5 hours. The reaction mixture was cooled to room temperature and then diluted with 15mL diethylether or ethylacetate (depending on the polarity of the product) and filtered through a pad of celite. The organic phase was washed with saturated NH_4Cl solution for 3 times, once with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product).

D II.8 General procedure H for hydroboration - oxidation on allyl benzo-fused heterocycles

A 7mL vial equipped with a screw cap with septum and a magnetic stirring bar was charged with 5-allyl benzo-fused derivatives (0.5 mmol, 1.0 equiv.). The vial was evacuated and flushed with argon 3 times. 0.5 mL dry THF was added by syringe to dissolve the starting material then cooled to 0 °C. A 1M solution of BH_3.THF (0.5 mL, 0.5 mmol, 1.0 equiv.) was added slowly. Afterwards, the reaction solution was warmed to room temperature and stirred for 24 hours. On the other hand, a solution of 3M NaOH and H_2O_2 30% was mixed in ratio of 2 : 3 and then cooled to 0 °C. After 24 hours of reaction time, the reaction was cooled again to 0 °C and then the prepared solution of NaOH and H_2O_2 (1.20 mL, 1.2 mmol NaOH and 7.8 mmol H_2O_2) was added slowly. The reaction mixture was stirred at room temperature for 4 more hours, then diluted with 5 mL diethylether. The organic phase was washed with a saturated NH_4Cl solution for 3 times, once with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc mixtures.

D II.9 General procedure I for isomerization on allyl benzo-fused heterocycles

A 7mL vial equipped with a screw cap with septum and a magnetic stirring bar was charged with 5-allyl benzo-fused derivatives (0.5 mmol, 1.0 equiv.), $Pd(dba)_2$ (5.8 mg, 0.01mmol, 0.02 equiv.), $^tBu_3P.HBF_4$ (5.8 mg, 0.02 mmol, 0.04 equiv.) and ^{i}PrCOCl (10 µL, 10.6 mg, 0.1 mmol, 0.2 equiv.). The vial was evacuated and flushed with argon 3 times. Then 1 mL of degassed DMAc was added via syringe. The mixture was heated to 100 °C for 6 hours. The reaction mixture was cooled to room temperature and then diluted with 15mL ethylacetate and

filtered through a pad of celite. The organic phase was washed with a saturated NH_4Cl solution for 3 times, once with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product).

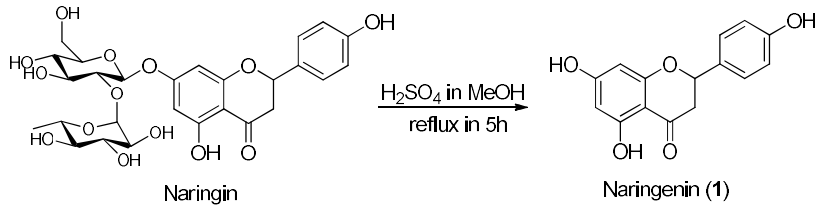
D II.10 General procedure J for deprotection of MOM

A 7mL vial equipped with a screw cap with septum and a magnetic stirring bar was charged with MOM protected substrate (0.1 mmol, 1.0 equiv.) dissolved in 0.5 mL MeOH. A 1N solution of HCl (50 µL, 0.05 mol, 0.5 equiv.) was added subsequently. The mixture was stirred at 65 °C for 30 minutes. The reaction mixture was cooled to room temperature and then diluted with 15mL Et_2O. The organic phase was washed with a saturated NH_4Cl solution for 3 times, once with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc 3:1 to obtain the desired product.

D III Experiments

D III.1 Hydrolysis of naringin and hesperidin

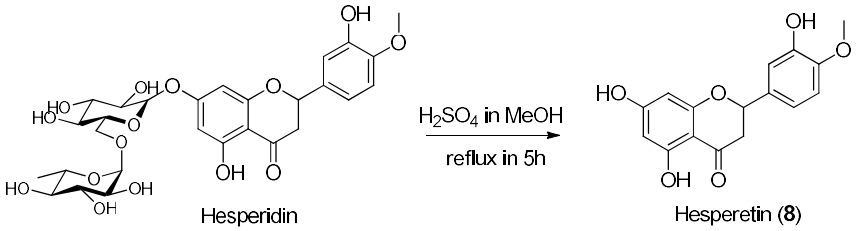
D III.1.1 Synthesis of naringenin (1)



Naringin — Naringenin (**1**)

General procedure	A
Reaction scale	3 g (5.17 mmol)
Substrate concentration	30 mg substrate in 1 mL acid solution
R_f	0.52 (LP/EtOAc 1:1)
Purification	Recrystalisation with acetic acid 7% solution in water
Yield	957 mg (68%) colorless crystalline needles
Molecular formular, m.w.	$C_{15}H_{12}O_5$, 272.25 g/mol
Melting point	245-247 °C (Lit. 247-250 °C) [96]
^{1}H-NMR (400 MHz, DMSO-d_6)	δ (ppm) = 2.68 (dd, *J* = 17.1, 3.0 Hz, 1H, H-3), 3.27 (dd, *J* = 17.1, 12.9 Hz, 1H, H-3), 5.44 (dd, *J* = 12.8, 2.9 Hz, 1H, H-2), 5.89 (s, 2H, H-6 + H-8), 6.78 – 6.82 (m, 2H, H-3' + H-5'), 7.30 – 7.34 (m, 2H, H-2' + H-6'), 9.60 (s, 1H, (C-4')OH), 10.80 (s, 1H, (C-7)OH), 12.16 (s, 1H, (C-5)OH).
^{13}C-NMR (100 MHz, DMSO-d_6)	δ (ppm) = 42.4 (t, CH_2, C-3), 78.9 (d, C-2), 95.4 (d, C-8), 96.2 (d, C-6), 102.2 (s, C-4a), 115.6 (d, 2C, C-3' + C-5'), 128.8 (d, 2C, C-2' + C-6'), 129.3 (s, C-1'), 158.2 (s, C-4'), 163.4 (s, C-8a), 164.0 (s, C-5), 167.1 (s, C-7), 196.9 (s, C-4),

D III.1.2 Synthesis of hesperetin (8)



Hesperidin — Hesperetin (**8**)

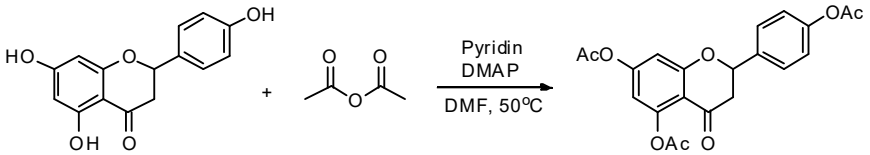
General procedure	A
Reaction scale	3 g (4.91 mmol)
Substrate concentration	30 mg substrate in 1 mL acid solution
R_f	0.47 (LP/EtOAc 1:1)
Purification	Recrystalisation with acetic acid (7% solution in water)
Yield	890 mg (60%) pale yellow crystalline needles
Molecular formular, m.w.	$C_{16}H_{14}O_6$, 302.28 g/mol
Melting point	222-225 °C (Lit. 224-225 °C)[96]
^{1}H-NMR (400 MHz, DMSO-d_6)	δ (ppm) = 2.71 (dd, *J* = 17.1, 3.0 Hz, 1H, H-3), 3.21 (dd, *J* = 17.1, 12.4 Hz, 1H, H-3), 3.78 (s, 3H, OCH_3), 5.44 (dd, *J* = 12.3, 3.0 Hz, 1H, H-2), 5.89 (dd, *J* = 5.5,

2.1 Hz, 2H, H-6 + H-8), 6.86 – 6.95 (m, 3H, H-2' + H-5' + H-6'), 9.12 (s, 1H, (C-3')OH), 10.81 (s, 1H, (C-7)OH), 12.14 (s, 1H, (C-5)OH).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm) = 42.5 (t, CH_2, C-3), 56.1 (q, OCH_3), 78.7 (d, C-2), 95.4 (d, C-8), 96.3 (d, C-6), 102.3 (s, C-4a), 112.4 (d, C-5'), 114.5 (d, C-2'), 118.1 (d, C-6'), 131.6 (s, C-1'), 146.9 (s, C-3'), 148.3 (s, C-4'), 163.3 (s, C-8a), 163.9 (s, C-5), 167.1 (s, C-7), 196.7 (s, C-4).

D III.2 Protection of naringenin and hesperetin

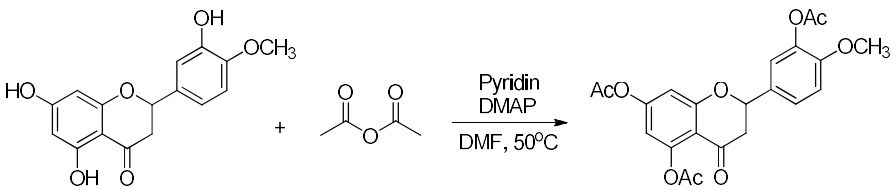
D III.2.1 Synthesis of 5,7,4'-*O*,*O*,*O*-triacetylnaringenin (2)



1 2

General procedure	B
Reaction scale	272 mg (1 mmol)
Reaction time	24 h
R_f	0.61 (LP/EtOAc 2:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	287 mg (72%) colorless solid
Molecular formular, m.w.	$C_{21}H_{18}O_8$, 398.36 g/mol
Melting point	130 – 133 °C (Lit. 125-126 °C)[97]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.30 (s, 3H, $OCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 2.38 (s, 3H, $OCOCH_3$), 2.77 (dd, *J* = 16.7, 3.0 Hz, 1H, H-3), 3.03 (dd, *J* = 16.7, 13.4 Hz, 1H, H-3), 5.48 (dd, *J* = 13.3, 2.8 Hz, 1H, H-2), 6.54 (d, *J* = 2.2 Hz, 1H, H-8), 6.78 (d, *J* = 2.2 Hz, 1H, H-6), 7.15 (d, *J* = 8.6 Hz, 2H, H-3' + H-5'), 7.46 (d, *J* = 8.6 Hz, 2H, H-2' + H-4').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.0 (q, CH_3), 21.1 (q, CH_3), 21.1 (q, CH_3), 45.0 (t, C-3), 79.0 (d, C-2), 109.0 (d, C-8), 110.6 (d, C-6), 111.7 (s, C-4a), 122.1 (d, 2C, C-3' + C-5'), 127.4 (d, 2C, C-2' + C-4'), 135.5 (s, C-1'), 150.9 (s, C-5/C-4'), 151.2 (s, C-4'/C-5), 155.6 (s, C-7), 162.8 (s, C-8a), 167.9 (s, C=O), 169.2 (s, C=O), 169.3 (s, C=O), 188.9 (s, C-4).

D III.2.2 Synthesis of 5,7,3'-*O*,*O*,*O*-triacetylhesperetin (9)

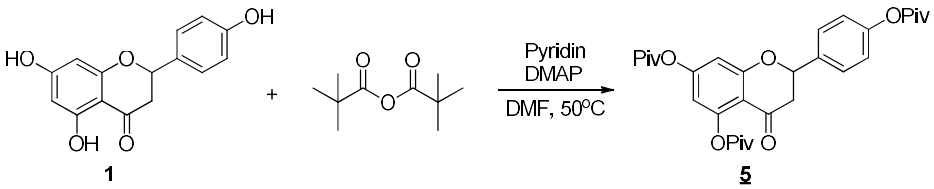


8 9

General procedure	B
Reaction scale	302 mg (1 mmol)
Reaction time	24 h

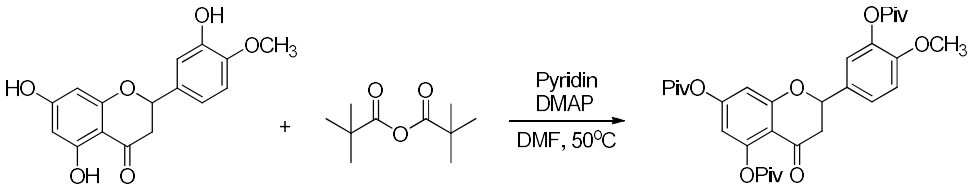
R_f	0.55 (LP/EtOAc 2:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	321 mg (75%) pale yellow solid
Molecular formular, m.w.	$C_{22}H_{20}O_9$, 428.39 g/mol
Melting point	142 – 145 °C (Lit. 143 – 144 °C) [98]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.30 (s, 3H, $OCOCH_3$), 2.33 (s, 3H, $OCOCH_3$), 2.38 (s, 3H, $OCOCH_3$), 2.76 (dd, *J* = 16.7, 3.0 Hz, 1H, H-3), 3.03 (dd, *J* = 16.7, 13.3 Hz, 1H, H-3), 3.86 (s, 3H, OCH_3), 5.42 (dd, *J* = 13.3, 2.9 Hz, 1H, H-2), 6.53 (d, *J* = 2.2 Hz, 1H, H-8), 6.77 (d, *J* = 2.2 Hz, 1H, H-6), 7.00 – 7.29 (m, 3H, H-2' + H-5' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 20.6 (q, CH_3), 21.0 (q, CH_3), 21.1 (q, CH_3), 44.1 (t, C-3), 55.8 (q, OCH_3), 78.7 (d, C-2), 109.0 (d, C-8), 110.5 (d, C-6), 111.6 (s, C-4a), 112.4 (d, C-5'), 121.0 (d, C-2'), 124.8 (d, C-6'), 130.4 (s, C-1'), 139.6 (s, C-3'), 151.1 (s, C-5/C-4'), 151.5 (s, C-4'/C-5), 155.6 (s, C-7), 163.0 (s, C-8a), 167.9 (s, C=O), 168.8 (s, C=O), 169.2 (s, C=O), 188.8 (s, C-4).

D III.2.3 Synthesis of 5,7,4'-*O*,*O*,*O*-triapivaloylnaringenin (5)



General procedure	B
Reaction scale	272 mg (1 mmol)
Reaction time	24 h
R_f	0.70 (LP/EtOAc 2:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	351 mg (67%) white solid
Molecular formular, m.w.	$C_{30}H_{36}O_8$, 524.60 g/mol
Melting point	163 – 167 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.34 (s, 9H, $C(CH_3)_3$), 1.36 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 2.77 (dd, *J* = 16.7, 3.0 Hz, 1H, H3), 3.02 (dd, *J* = 16.7, 13.3 Hz, 1H, H-3), 5.49 (dd, *J* = 13.2, 2.8 Hz, 1H, H-2), 6.47 (d, *J* = 2.2 Hz, 1H, H-8), 6.76 (d, *J* = 2.2 Hz, 1H, H-6), 7.12 (d, *J* = 8.5 Hz, 2H, H-3' + H-5'), 7.44 (d, *J* = 8.6 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.0 (q, 3C, CH_3), 27.1 (q, 3C, CH_3), 27.2 (q, 3C, CH_3), 39.1 (s, 2C, $\underline{C}(CH_3)_3$), 39.3 (s, $\underline{C}(CH_3)_3$), 45.4 (t, C-3), 79.0 (d, C-2), 108.9 (d, C-8), 110.5 (d, C-6), 112.2 (s, C-4a), 122.0 (d, 2C, C-3' + C-5'), 127.2 (d, 2C, C-2' + C-6'), 135.5 (s, C-1'), 151.4 (s, C-5/C-4'), 151.8 (s, C-4'/C-5), 156.4 (s, C-7), 163.1 (s, C-8a), 175.8 (s, C=O), 176.4 (s, C=O), 176.9 (s, C=O), 188.8 (s, C-4).

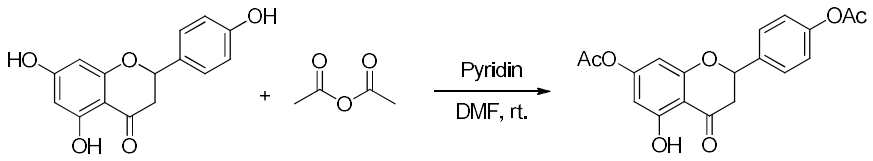
D III.2.4 Synthesis of 5,7,3'-*O*,*O*,*O*-tripivaloylhesperetin (12)



8 12

General procedure	B
Reaction scale	302 mg (1 mmol)
Reaction time	24 h
R_f	0.67 (LP/EtOAc 2:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	360 mg (65%) pale yellow solid
Molecular formular, m.w.	$C_{31}H_{38}O_9$, 554.63 g/mol
Melting point	214 – 217 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.33 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 2.75 (dd, *J* = 16.6, 2.9 Hz, 1H, H-3), 3.02 (dd, *J* = 16.6, 13.4 Hz, 1H, H-3), 3.83 (s, 3H, OCH_3), 5.42 (dd, *J* = 13.3, 2.8 Hz, 1H, H-2), 6.46 (d, *J* = 2.2 Hz, 1H, H-8), 6.74 (d, *J* = 2.2 Hz, 1H, H-6), 6.96 – 7.25 (m, 3H, H-2' + H-5' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.0 (q, 3C, CH_3), 27.2 (q, 6C, CH_3), 39.09 (s, 1C, $\underline{C}(CH_3)_3$), 39.11 (s, 1C, $\underline{C}(CH_3)_3$), 39.3 (s, $\underline{C}(CH_3)_3$), 45.2 (t, C-3), 56.0 (q, 1C, OCH_3), 78.8 (d, C-2), 108.9 (d, C-8), 110.4 (d, C-6), 112.1 (s, C-4a), 112.4 (d, C-5'), 120.8 (d, C-2'), 124.4 (d, C-6'), 130.7 (s, C-1'), 140.4 (s, C-3'), 151.6 (s, C5/C4'), 151.7 (s, C5/C4'), 156.3 (s, C-7), 163.1 (s, C-8a), 175.8 (s, C=O), 176.4 (s, C=O), 176.5 (s, C=O), 188.9 (s, C-4).

D III.2.5 Synthesis of 7,4'-*O*,*O*-diacetylnaringenin (3)

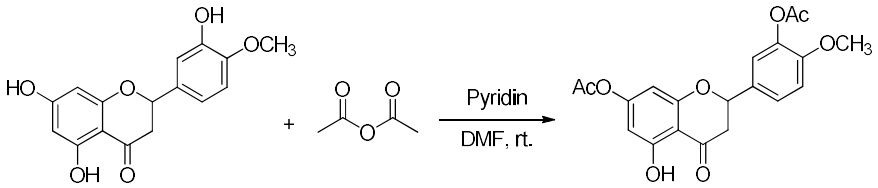


1 3

General procedure	B
Reaction scale	272 mg (1 mmol)
Reaction time	24 h
R_f	0.60 (LP/EtOAc 3:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	214 mg (60%) white solid
Molecular formular, m.w.	$C_{19}H_{16}O_7$, 356.33 g/mol
Melting point	147 – 150 °C (Lit. 141 – 142 °C) [99]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.29 (s, 3H, $OCOCH_3$), 2.32 (s, 3H, $OCOCH_3$), 2.87 (dd, *J* = 17.2, 3.3 Hz, 1H, H-3), 3.11 (dd, *J* = 17.2, 13.0 Hz, 1H, H-3), 5.46 (dd, *J* = 13.0, 3.1 Hz, 1H, H-2), 6.32 (d, *J* = 2.1 Hz, 2H, H-6 + H-8), 7.16 (d, *J* = 8.6 Hz, 2H, H-3' + H-5'), 7.47 (d, *J* = 8.6 Hz, 2H, H-2' + H-6'), 11.84 (s, 1H, ArOH).

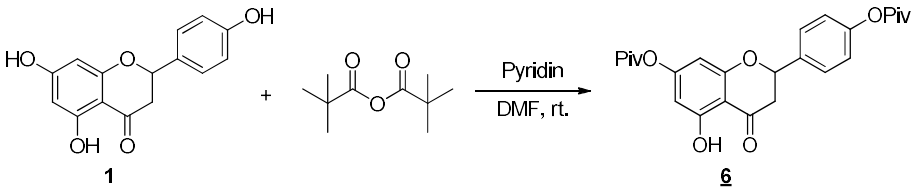
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 21.1 (q, CH_3), 21.2 (q, CH_3), 43.6 (t, C-3), 78.7 (d, C-2), 101.7 (d, C-8), 103.4 (d, C-6), 106.2 (s, C-4a), 122.1 (d, 2C, C-3' + C-5'), 127.3 (d, 2C, C-2' + C-6'), 135.5 (s, C-1'), 151.0 (s, C-4'), 158.4 (s, C-7), 162.1 (s, C-8a), 163.3 (s, C-5), 168.2 (s, C=O), 169.3 (s, C=O), 196.7 (s, C-4).

D III.2.6 Synthesis of 7,3'-*O*,*O*-diacetylhesperetin (10)



General procedure	B
Reaction scale	302 mg (1 mmol)
Reaction time	24 h
R_f	0.58 (LP/EtOAc 3:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	301 mg (78%) pale yellow solid
Molecular formular, m.w.	$C_{20}H_{18}O_8$, 386.35 g/mol
Melting point	132 – 135 °C (Lit. 102 – 103 °C)[100]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.26 (s, 3H, $OCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 2.82 (dd, *J* = 17.2, 3.0 Hz, 1H, H-3), 3.07 (dd, *J* = 17.2, 13.1 Hz, 1H, H-3), 3.83 (s, 3H, OCH_3), 5.35 (dd, *J* = 12.9, 2.9 Hz, 1H, H-2), 6.28 (dd, *J* = 4.9, 2.0 Hz, 2H, H-6 + H-8), 6.98 (d, *J* = 8.5 Hz, 1H, H-5'), 7.15 (d, *J* = 2.1 Hz, 1H, H-2'), 7.24 (dd, *J* = 8.4, 1.7 Hz, 1H, H-6'), 11.85 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 20.6 (q, CH_3), 21.1 (q, CH_3), 43.2 (t, C-3), 56.0 (q, OCH_3), 78.5 (d, C-2), 101.7 (d, C-8), 103.3 (d, C-6), 106.1 (s, C-4a), 112.5 (d, C-5'), 121.0 (d, C-2'), 124.8 (d, C-6'), 130.5 (s, C-1'), 139.9 (s, C-3'), 151.6 (s, C-4'), 158.3 (s, C-7), 162.2 (s, C-8a), 163.2 (s, C-5), 168.2 (s, C=O), 168.8 (s, C=O), 196.9 (s, C-4).

D III.2.7 Synthesis of 7,4'-*O*,*O*-triapivaloylnaringenin (6)

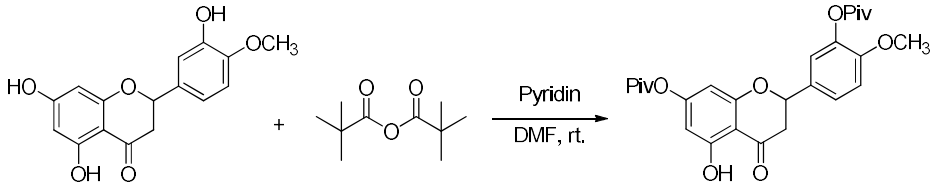


General procedure	B
Reaction scale	272 mg (1 mmol)
Reaction time	24 h
R_f	0.58 (LP/EtOAc 3:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 5% - 20% EtOAc) on 36 g silica 60
Yield	233 mg (53%) white solid
Molecular formular, m.w.	$C_{25}H_{28}O_7$, 440.49 g/mol
Melting point	174-177 °C

^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.37 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 2.63 (dd, *J* = 16.7, 3.0 Hz, 1H, H-3), 2.89 (dd, *J* = 16.7, 13.3 Hz, 1H, H-3), 5.32 (dd, *J* = 13.2, 2.8 Hz, 1H, H-2), 6.03 – 6.12 (m, 2H, H-6 + H-8), 7.07 (d, *J* = 8.5 Hz, 2H, H-3' + H-5'), 7.36 (d, *J* = 8.9 Hz, 2H, H-2' + H-6').

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 27.10 (q, 3C, CH_3), 27.16 (q, 3C, CH_3), 39.14 (s, 1C, $\underline{C}(CH_3)_3$), 39.17 (s, 1C, $\underline{C}(CH_3)_3$), 44.9 (t, C-3), 78.6 (d, C-2), 101.8 (d, C-8), 105.5 (d, C-6), 107.7 (s, C-4a), 121.9 (d, 2C, C-3' + C-5'), 127.4 (d, 2C, C-2' + C-6'), 136.0 (s, C-1'), 151.1 (s, C-4'), 152.2 (s, C-7), 163.3 (s, C-8a), 164.0 (s, C-5), 177.6 (s, C=O), 177.9 (s, C=O), 189.1 (s, C-4).

D III.2.8 Synthesis of 7,3'-*O*,*O*-tripivaloylhesperetin (13)

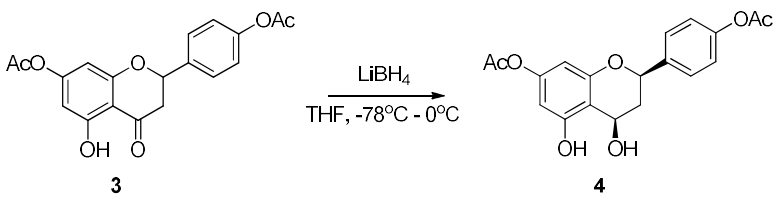


8 **13**

General procedure	B
Reaction scale	302 mg (1 mmol)
Reaction time	24 h
Purification	MPLC, LP/EtOAc (gradient ratio: 15% - 30% EtOAc) on 36 g silica 60
Yield	273 mg (58%) pale yellow solid
Molecular formular, m.w.	$C_{26}H_{30}O_8$, 470.51 g/mol
R_f	0.66 (LP/EtOAc 3:1)
Melting point	202 – 205 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.38 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 2.58 (dd, *J* = 16.7, 2.8 Hz, 1H, H-3), 2.88 (dd, *J* = 16.6, 13.6 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 5.22 (dd, *J* = 17.9, 7.1 Hz, 1H, H-2), 5.95 (d, J = 2.3 Hz, 1H, H-6), 6.08 (d, J = 2.3 Hz, 1H, H-8), 6.93 (d, *J* = 8.3 Hz, 1H, H-5'), 7.01 – 7.12 (m, 2H, H-2' + H-6'), 7.68 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.2 (q, 6C, CH_3), 39.13 (s, 1C, $\underline{C}(CH_3)_3$), 39.17 (s, 1C, $\underline{C}(CH_3)_3$), 44.8 (t, C-3), 56.0 (q, OCH_3), 78.6 (d, C-2), 101.7 (d, C-8), 105.4 (d, C-6), 107.7 (s, C-4a), 112.4 (d, C-5'), 120.9 (d, C-2'), 125.1 (d, C-6'), 131.0 (s, C-1'), 140.0 (s, C-3'), 151.4 (s, C-4'), 152.2 (s, C-7), 163.4 (s, C-8a), 164.0 (s, C-5), 177.7 (s, C=O), 177.8 (s, C=O), 189.1 (s, C-4).
MS analyst, m/z (Int.)	Does not fly over GC

D III.3 Reduction of protected naringenin and hesperetin

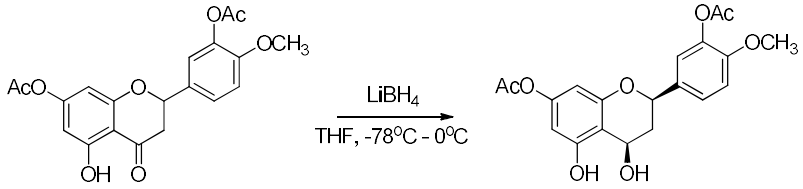
D III.3.1 Synthesis of (2*R*,4*R*)-4-(7-acetoxy-4,5-dihydroxychroman-2-yl)phenyl acetate (4)



3 **4**

General procedure	C
Reaction scale	142 mg (0.4 mmol)
Reaction time	4 h
R_f	0.25 (LP/EtOAc 1:1)
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	69 mg (48%) white solid
Molecular formular, m.w.	$C_{19}H_{18}O_7$, 358.34 g/mol
Melting point	95 – 99 °C [40]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.00 – 2.22 (m, 1H, H-3), 2.27 (s, 3H, $OCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 2.37 – 2.51 (m, 1H, H-3), 5.06 (d, *J* = 10.8 Hz, 1H, H-4), 5.21 (dd, *J* = 10.5, 6.5 Hz, 1H, H-2), 6.20 (dd, *J* = 5.8, 2.2 Hz, 2H, H-8 + H-6), 7.10 (d, *J* = 8.6 Hz, 2H, H-3' + H-5'), 7.40 (d, *J* = 8.6 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.1 (q, 2C, CH_3), 38.9 (t, C-3), 65.7 (d, C-4), 76.45 (d, C-2), 102.3 (d, C-6), 102.8 (d, C-8), 108.7 (s, C-4a), 121.8 (d, 2C, C-3' + C-5'), 127.3 (d, 2C, C-2' + C-6'), 137.4 (s, C-1'), 150.5 (s, C-4'), 151.6 (s, C-7), 155.8 (s, C-5), 157.5 (s, C-8a), 169.7 (s, C=O), 169.9 (s, C=O).

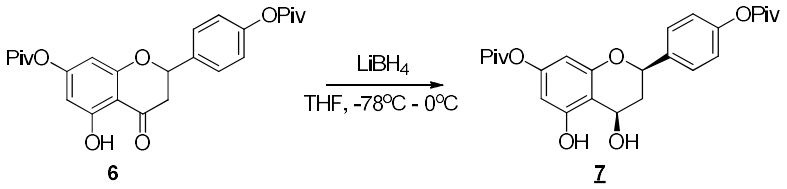
D III.3.2 Synthesis of 5-(7-acetoxy-4,5-dihydroxychroman-2-yl)-2-methoxyphenyl acetate (11)



10 → 11

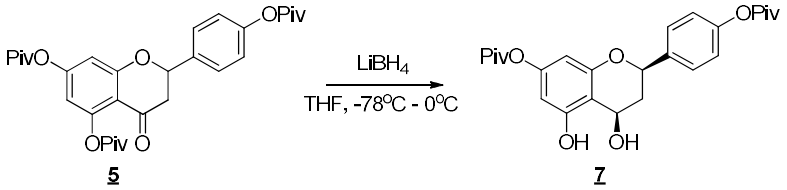
General procedure	C
Reaction scale	155 mg (0.4 mmol)
Reaction time	4 h
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	67 mg (43%) pale yellow solid
Molecular formular, m.w.	$C_{20}H_{20}O_8$, 388.37 g/mol
R_f	0.28 (LP/EtOAc 1:1)
Melting point	101 – 104 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.94 – 2.12 (m, 1H, H-3), 2.25 – 2.36 (m, 7H, 2x$OCOCH_3$ + H-3), 3.80 (m, 4H, OCH_3 + OH), 4.92 (d, *J* = 10.7 Hz, 1H, H-2), 5.11 (m, 1H, H-4), 6.15 (dd, *J* = 5.5, 2.2 Hz, 2H, H-6 + H-8), 6.91 – 7.21 (m, 3H, H-2' + H-5' + H-6'), 8.28 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 20.7 (q, CH_3), 21.1 (q, CH_3), 38.3 (t, C-3), 56.0 (q, OCH_3), 65.5 (d, C-4), 76.2 (d, C-2), 102.2 (d, C-6), 102.6 (d, C-8), 108.8 (s, C-4a), 112.3 (d, C-5'), 120.9 (d, C-2'), 124.9 (d, C-6'), 132.5 (s, C-1'), 139.6 (s, C-3'), 151.0 (s, C-4'), 151.4 (s, C-7), 155.8 (s, C-5), 157.4 (s, C-8a), 169.4 (s, C=O), 170.0 (s, C=O).

D III.3.3 Synthesis of 4,5-dihydroxy-2-(4-(pivaloyloxy)phenyl)chroman-7-yl pivalate (7)



6 7

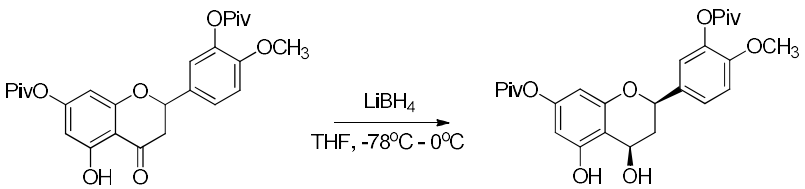
General procedure	C
Reaction scale	176 mg (0.4 mmol)
Reaction time	4 h
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	78 mg (44%) white solid



5 7

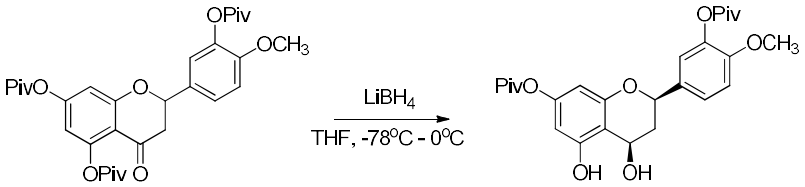
General procedure	C
Reaction scale	210 mg (0.4 mmol)
Reaction time	4 h
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	19 mg (11%) white solid
Molecular formular, m.w.	$C_{25}H_{30}O_7$, 442.50 g/mol
R_f	0.44 (LP/EtOAc 1:1)
Melting point	105 – 108 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.32 (s, 9H, $C(CH_3)_3$), 1.36 (s, 9H, $C(CH_3)_3$), 2.09 (dd, *J* = 23.4, 12.0 Hz, 1H, H-3), 2.41 (dd, *J* = 11.4, 6.6 Hz, 1H, H-3), 3.35 (d, *J* = 6.7 Hz, 1H, OH), 5.05 (d, *J* = 10.8 Hz, 1H, H-2), 5.11 – 5.26 (m, 1H, H-4), 6.16 (m, 2H, H-6 + H-8), 7.07 (d, *J* = 8.6 Hz, 2H, H-3' + H-5'), 7.39 (d, *J* = 8.5 Hz, 2H, H-2' + H-6'), 8.20 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.06 (q, 3C, $C(\underline{C}H_3)_3$), 27.11 (q, 3C, $C(\underline{C}H_3)_3$), 39.00 (t, C-3), 39.08 (s, 1C, $\underline{C}(CH_3)_3$), 39.10 (s, 1C, $\underline{C}(CH_3)_3$), 65.8 (d, C-4), 77.2 (d, C-2), 102.2 (d, C-6), 102.8 (d, C-8), 108.4 (s, C-4a), 121.7 (d, 2C, C-3' + C-5'), 127.2 (d, 2C, C-2' + C-6'), 137.3 (s, C-1'), 150.9 (s, C-4'), 152.1 (s, C-7), 155.7 (s, C-5), 157.5 (s, C-8a), 177.3 (s, C=O), 177.6 (s, C=O).

D III.3.4 Synthesis of 4,5-dihydroxy-2-(4-methoxy-3-(pivaloyloxy)phenyl)chroman-7-yl pivalate (14)



13 14

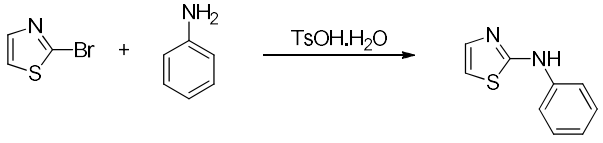
General procedure	C
Reaction scale	188 mg (0.4 mmol)
Reaction time	4 h
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	77 mg (41%) pale yellow solid



12 **14**

General procedure	C
Reaction scale	222 mg (0.4 mmol)
Reaction time	4 h
Purification	MPLC, LP/EtOAc (gradient ratio: 20% - 50% EtOAc) on 18 g silica 60
Yield	19 mg (10%) pale yellow solid
Molecular formular, m.w.	$C_{26}H_{32}O_8$, 472.53 g/mol
R_f	0.47 (LP/EtOAc 1:1)
Melting point	110 – 115 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.31 (s, 9H, $C(CH_3)_3$), 1.37 (s, 9H, $C(CH_3)_3$), 1.94 – 2.16 (m, 1H, H-3), 2.34 (dd, *J* = 12.5, 6.2 Hz, 1H, H-3), 3.57 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 4.96 (d, *J* = 10.8 Hz, 1H, H-2), 5.16 (m, 1H, H-4), 6.15 (m, 2H, H-6 + H-8), 6.90 – 7.26 (m, 3H, H-2' + H-5' + H-6'), 8.28 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.1 (q, 3C, $C(\underline{C}H_3)_3$), 27.2 (q, 3C, $C(\underline{C}H_3)_3$), 38.6 (t, C-3), 38.96 (s, 1C $\underline{C}(CH_3)_3$), 38.99 (s, 1C $\underline{C}(CH_3)_3$), 56.0 (q, 1C, OCH_3), 65.6 (d, C-4), 76.1 (d, C-2), 102.1 (d, C-6), 102.6 (d, C-8), 108.4 (s, C-4a), 112.3 (d, C-5'), 120.8 (d, C-2'), 124.4 (d, C-6'), 132.5 (s, C-1'), 140.1 (s, C-3'), 151.1 (s, C-4'), 152.0 (s, C-7), 155.7 (s, C-5), 157.5 (s, C-8a), 177.1 (s, C=O), 177.5 (s, C=O).

D III.4 Synthesis of N-phenylthiazol-2-amine



15

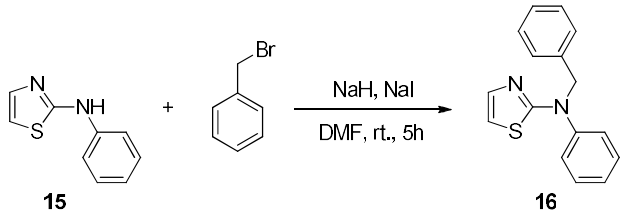
Aniline (2.70 mL, 2.75 g, 0.03 mol) and *p*-toluenesulfonic acid monohydrate (1.90 g, 0.01 mol) were charged into a 100 mL three-neck round-bottom flask equipped with a septum, magnetic stirring bar and a reflux condenser and dissolved in 20 mL of isopropanol at room temperature for 5 mins. 2-Bromothiazole (1.80 mL, 3.28 g, 0.02 mol) was added dropwise over 15 mins. The reaction was then heated to reflux (85 °C) for 48 hours. Before the work-up, the reaction mixture was cooled to room temperature and diluted by 20 mL of EtOAc and treated with an excess of saturated Na_2CO_3 solution. The organic phase was washed with brine for 3 times and then dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain 2.8 g of a brown solid (80% isolated yield). The product was used for subsequent reaction without any further purification as NMR indicated a purity of >98%.

Yield	2.8 g (80%) brown solid

Molecular formular, m.w.	$C_9H_8N_2S$, 176.24 g/mol
R_f	0.51 in LP/EtOAc = 4:1
Melting point	126 – 128 °C, (Lit.: 127 – 128 °C)[56]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 6.64 (d, *J* = 3.6 Hz, 1H, H-5), 7.08 (dd, *J* = 8.9, 4.5 Hz, 1H, H-4'), 7.30 (d, *J* = 3.6 Hz, 1H, H-4), 7.35 – 7.37 (m, 4H, H-2' + H-3' + H-5' + H-6'), 8.07 (s, 1H, NH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 107.2 (d, C-5), 118.1 (d, 2C, H-2' + H-6'), 122.9 (d, C-4'), 129.5 (d, 2C, C-3' + C-5'), 138.5 (d, C-4), 140.7 (s, C-1'), 166.0 (s, C-2).
GC retention time	8.07 min with Joey_short method
MS analyst, m/z (Int.)	176(100), 175(100, M^+), 150(16), 104(19), 77(31), 58(26).

D III.5 Protection of N-phenyl-2-aminothiazole

D III.5.1 Synthesis of *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine (16)

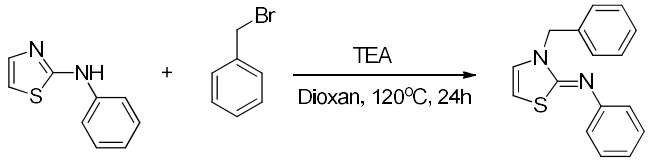


15 16

In a 7 mL vial equipped with a screw cap with septum and a magnetic stirring bar, *N*-phenyl(thiazol-2-yl)amine (1 g, 5.68 mmol), NaH 55% (0.48 g, 11 mmol) and NaI (85 mmg, 0.57 mmol) were dissolved in 5 mL DMF, then benzylbromide (0.88 mL, 7.39 mmol) was added dropwise into the mixture. The reaction mixture was stirred at room temperature for 5 h. The reaction was worked-up by adding H_2O and then extracted by 15 mL EtOAc. The organic phase was washed with saturated NH_4Cl solution for 2 times, a last time with saturated Na_2CO_3 and then dried over Na_2SO_4. All solvent was evaporated under reduced pressure to obtain 1.133 g of a product mixture containing *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine **16** and *N*-(3-benzylthiazol-2(3H)-ylidene)aniline **17** in a ratio of 5:1. The product mixture was dissolved again in the least amount of warm DCM (2-3 mL) then cooled to -5 °C and left to crystallize overnight. The crystalls were collected by filtration and washed for 3 times with cold LP (-5 °C) then dried under reduced pressure to obtain 861mg of *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine as yellow brown needle crystals (57% isolated yield).

Yield	861 mg (57%) beige needles
Molecular formular, m.w.	$C_{16}H_{14}N_2S$, 266.36 g/mol
R_f	0.20 in LP/EtOAc 5:2
Melting point	79 – 80 °C (Lit.: 79 – 80 °C)[45g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 5.19 (s, 2H, CH_2), 6.47 (d, *J* = 3.6 Hz, 1H, H-5), 7.21 – 7.33 (m, 11H, ArH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 56.5 (t, CH_2), 107.7 (d, C-5), 126.1 (d, 2C, C-2' + C-6'), 126.8 (d, C-4'), 127.2 (d, C-4''), 127.7 (d, 2C, C-2'' + C-6''), 128.5 (d, 2C, C-3'' + C-5''), 129.8 (d, 2C, C-3' + C-5'), 137.6 (s, C-1''), 139.3 (d, C-4), 145.3 (s, C-1'), 170.9 (s, C-2).
GC retention time	9.19 min with Joey_short method
MS analyst, m/z (Int.)	266(56, M+), 174(100), 167(30), 131(11), 91(16).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 267.0850, m/z (measured) = 267.0955, difference = 1.87 ppm.

D III.5.2 Synthesis of *N*-(3-benzylthiazol-2(3*H*)-ylidene)aniline (17)



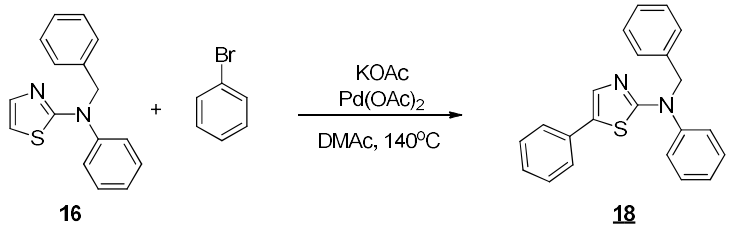
15 17

In a 50 mL round-bottom flask with a magnetic stirr bar and a reflux condenser, *N*-phenyl(thiazol-2-yl)amine (1 g, 5.68 mmol), benzylbromide (0.90 mL, 7.58 mmol) and triethylamine (0.80 mL, 5.68 mmol) were dissolved in 15 mL of 1,4-dioxane. The reaction mixture was heated to 120 °C for 24 hours. The reaction was worked-up by quenching with excess H_2O and then extracted by 15 mL EtOAc. The organic phase was washed with brine for 3 times then dried over Na_2SO_4. All solvent was evaporated under reduced pressure to obtain 1.178 g of a product mixture containing **16** and **17** in a ratio of 1:7. The product mixture was dissolved again in the least amount of warm dichlormethane (2 - 3 mL) then cooled to -5 °C and left to crystallize overnight. The crystalls were collected by filtration and washed for 3 times with cold LP (-5 °C) then dried under reduced pressure to obtain 831 mg of *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine as light brown needle crystals (55% isolated yield).

Yield	831 mg (55%) light brown needle crystal
Molecular formular, m.w.	$C_{16}H_{14}N_2S$, 266.36 g/mol
R_f	0.20 in LP/EtOAc = 5:2
Melting point	96 – 97 °C (Lit.: 94 – 95 °C) [45g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 5.06 (s, 2H, CH_2), 5.85 (d, *J* = 4.9 Hz, 1H, H-5), 6.50 (d, *J* = 4.9 Hz, 1H, H-4), 7.03 – 7.10 (m, 3H, ArH), 7.29 – 7.36 (m, 7H, ArH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 49.7 (t, CH_2), 97.6 (d, C-5), 121.4 (d, 2C, C-2' + C-6'), 122.9 (d, C-4'), 126.6 (d, C-4''), 127.8 (d, C-4), 128.1 (d, 2C, C-2'' + C-6''), 128.8 (d, 2C, C-3'' + C-5''), 129.4 (d, 2C, C-3' + C-5'), 136.7 (s, C-1''), 151.6 (s, C-1'), 158.6 (s, C-2).
GC retention time	10.21 min with Joey_short method
MS analyst, m/z (Int.)	266(42, M+), 167(100), 131(10), 91(18), 15(8).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 267.0950, m/z (measured) = 267.0954, difference = 1.50 ppm.

D III.6 Scope of direct arylation of *N*-protected *N*-phenyl-2-aminothiazole.

D III.6.1 Synthesis of *N*-benzyl-*N*,5-diphenyl(thiazol-2-yl)amine (18)

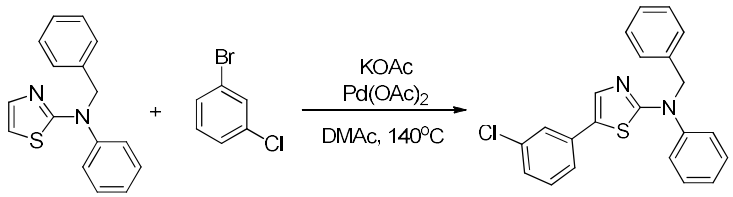


16 18

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient ratio: 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C

R_f	0.51 in LP/EtOAc 10:1
Yield	120 mg (70%) beige solid.
Molecular formular, m.w.	$C_{22}H_{18}N_2S$, 342.46 g/mol
Melting point	65 – 66 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.20 (s, 2H, CH_2), 7.26 – 7.39 (m, 15H, Ar-H), 7.46 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.2 (t, CH_2), 125.4 (d, 2C, C-2' + C-6'), 126.4 (d, 2C, C-2''' + C-6'''), 126.7 (d, C-4'), 127.1 (d, C-4''), 127.3 (d, C-4'''), 127.6 (s, C-5), 127.8 (d, 2C, C-2'' + C-6''), 128.5 (d, 2C, C-3'' + C-5''), 128.8 (d, 2C, C-3''' + C-5'''), 129.9 (d, 2C, C-3' + C-5'), 132.4 (s, C-1'''), 134.8 (d, C-4), 137.5 (C-1''), 145.0 (C-1'), 169.6 (C-2).
GC retention time	14.67 min with Toan_25min method
MS analyst, m/z (Int.)	343(9), 342(38, M+), 252(17), 251(85), 250(61), 219(16), 167(77), 134(20), 91(100).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 343.1263, m/z (measured) = 343.1281, difference = 5.25 ppm.

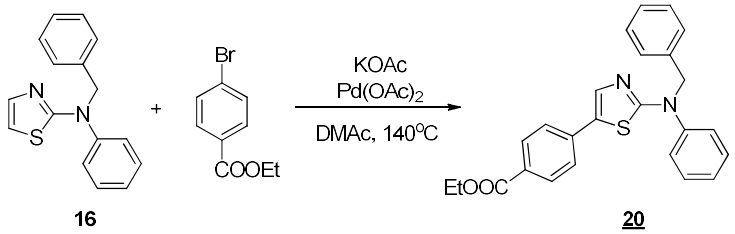
D III.6.2 Synthesis of *N*-benzyl-*N*,5-diphenyl(thiazol-2-yl)amine (19)



16 **19**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient ratio: 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.45 in LP/EtOAc = 10:1
Yield	166 mg (88%) light brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{22}H_{17}ClN_2S$, 376.90 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.20 (s, 2H, CH_2), 7.15 – 7.40 (m, 15H, Ar-H), 7.47 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 49.7 (t, CH_2), 123.3 (d, C-6'''), 125.2 (d, C-2'''), 125.9 (s, C-5), 126.5 (d, C-4'''), 126.6 (d, 2C, C-2' + C-6'), 127.4 (d, C-4'), 127.5 (d, C-4''), 127.8 (d, 2C, C-2'' + C-6''), 128.5 (d, 2C, C-3'' + C-5''), 128.5 (d, 1C, C-5'''), 129.9 (d, 2C, C-3' + C-5'), 134.1 (s, C-3'''), 134.7 (s, C-1'''), 135.7 (d, C-4), 137.2 (s, C-1''), 144.8 (s, C-1'), 170.1 (s, C-2).
GC retention time	17.71 min with Toan_25min method
MS analyst, m/z (Int.)	378(11), 376(30), 286(25), 285(50), 284(43), 167(83), 91(100), 77(24).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 376.9018, m/z (measured) = 376.7535, difference = 2.14 ppm.

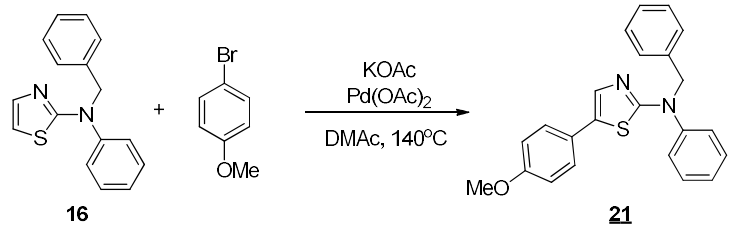
D III.6.3 Synthesis of ethyl 4-(2-(benzyl(phenyl)amino)thiazol-5-yl)benzoate (20)



16 20

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient ratio: 1% - 30% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.38 in LP/EtOAc = 10:1
Yield	166 mg (80%) brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{25}H_{22}N_2O_2S$, 414.52 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.38 (t, *J* = 7.1Hz, 3H, CH_2-C$\underline{H}_3$), 4.36 (q, *J* = 7.1Hz, 2H, C$\underline{H}_2$-CH_3), 5.21 (s, 2H, CH_2), 7.26 – 7.42 (m, 14H, Ar-H), 7.58 (s, 1H, H-4), 7.95 (d, *J* = 8.4Hz, 2H, H-3''' + H-5''').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 14.4 (q, CH_2-$\underline{C}H_3$), 56.3 (t, $\underline{C}H_2$-CH_3), 60.9 (t, CH_2), 124.3 (d, 2C, C-2' + C-6'), 126.1 (s, C-5), 126.3 (d, 2C, C-2'' + C-6''), 127.1 (d, C-4'), 127.2 (d, C-4''), 127.5 (d, 2C, C-3''' + C-5'''), 127.8 (s, C-1'''), 128.2 (d, 2C, C2''' + C-6'''), 129.7 (d, 2C, C-3'' + C-5''), 129.8 (d, 2C, C-3' + C-5'), 136.4 (d, C-4), 136.5 (s, C-1''), 136.9 (s, C-1'), 144.4 (s, C-4'''), 165.9 (s, C-2), 170.2 (s, C=O).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 415.1475, m/z (measured) = 415.1478, difference = 1.45 ppm.

D III.6.4 Synthesis of *N*-benzyl-5-(4-methoxyphenyl)-*N*-phenyl(thiazol-2-yl)amine (21)

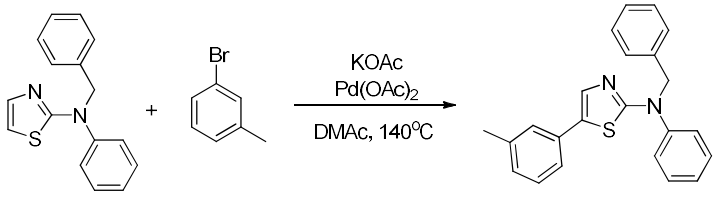


16 21

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.61 in LP/EtOAc = 10:1
Yield	115 mg (62%) beige oil
Molecular formular, m.w.	$C_{23}H_{20}N_2OS$, 372.48 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.80 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 6.82 – 6.86 (m, 2H, C-3''' + C-5'''), 7.26 – 7.36 (m, 15H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.3 (q, OCH_3), 56.2 (t, CH_2), 114.3 (d, 2C, C-2' + C-6'), 125.0 (s, C-5), 126.2 (d, 2C, C-2'' + C-6''), 126.8 (d, 2C, C-2''' + C-6'''), 127.0 (d, C-4'), 127.3 (d, C-4''), 127.6 (s, C-1'''), 127.7 (d, 2C, C-3''' + C-5'''), 128.5 (d, 2C, C-

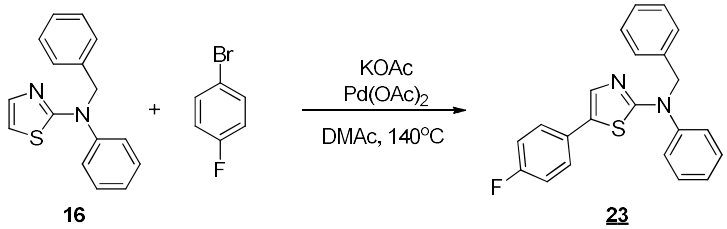
	3'' + C-5''), 129.9 (d, 2C, C-3' + C-5'), 133.5 (d, C-4), 137.6 (s, C-1''), 145.1 (s, C-1'), 158.7 (s, C-4'''), 169.0 (d, C-2).
GC retention time	19.34 min with Toan_25min method
MS analyst, m/z (Int.)	372(51), 282(24), 281(100), 280(38), 238(38), 207(24), 167(35), 91(48), 77(25).
HR-MS analyst	[M+H]+ m/z (predicted) = 373.1369, m/z (measured) = 373.1374, difference = 1.34 ppm.

D III.6.5 Synthesis of *N*-benzyl-*N*-phenyl-5-(*m*-tolyl)(thiazol-2-yl)amine (22)



General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.61 in LP/EtOAc = 10:1
Yield	115 mg (60%) beige solid
Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48 g/mol
Melting point	80-82 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.31 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 6.96 – 7.18 (m, 1H, H-4'), 7.23 – 7.38 (m, 13H, Ar-H), 7.44 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.4 (q, CH_3), 56.2 (t, CH_2), 122.5 (d, C-6'''), 126.2 (d, C-4'''), 126.4 (d, 2C, C-2' + C-6'), 127.1 (d, C-4') , 127.3(d, C-5'''), 127.6 (d, C-4''), 127.8 (d, 2C, C-2'' + C-6''), 127.8 (s, 1C, C-5), 128.5 (d, 2C, C-3' + C-5'), 128.7 (d, C-2'''), 129.9 (d, 2C, C-3'' + C-5''), 132.2 (s, C-1'''), 134.6 (d, C-4), 137.5 (s, C-1''), 138.5 (s, C-3'''), 145.0 (s, C-1'), 169.5 (s, C-2).
GC retention time	15.98 min with Toan_25min method
MS analyst, m/z (Int.)	357(12), 356(47, M+), 266(20), 265(100), 264(65), 167(63), 146(18), 91(61), 77(21).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1720, difference = 1.96 ppm.

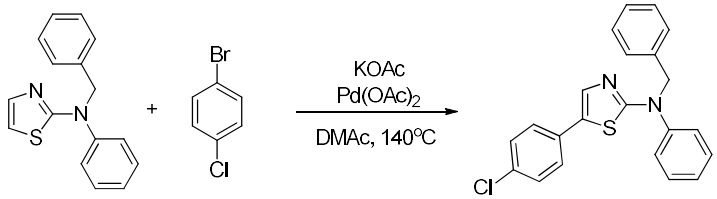
D III.6.6 Synthesis of *N*-benzyl-5-(4-fluorophenyl)-*N*-phenyl(thiazol-2-yl)amine (23)



General procedure	D
Reaction scale	133 mg (0.5 mmol)

Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.50 in LP/EtOAc 10:1
Yield	140 mg (78%) beige solid
Molecular formular, m.w.	$C_{22}H_{17}FN_2S$, 360.45 g/mol
Melting point	79-80 °C;
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.19 (s, 2H, CH_2), 6.93 – 7.02 (m, 2H, H-3''' + H-5'''), 7.24 – 7.38 (m, 13H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.2 (t, CH_2), 115.8 (d, $J^2_{C\text{-}F}$ = 21.8 Hz, 2C, C-3''' + C-5'''), 126.4 (d, 2C, C-2' + C-6'), 126.5 (s, C-5), 126.9 (d, C-4'), 127.1 (d, C-4''), 127.2 (d, $J^3_{C\text{-}F}$ = 7.9 Hz, 2C, C-2''' + C-6'''), 127.7 (d, 2C, C2'' + C-6''), 128.5 (d, 2C, C-3'' + C-5''), 128.6 (s, C-1'''), 129.9 (d, 2C, C-3' + C-5'), 134.7 (d, $J^6_{C\text{-}F}$ = 2.1 Hz, 1C, C-4), 137.5 (s, C-1''), 145.0 (s, C-1'), 161.7 (d, $J^1_{C\text{-}F}$ = 247 Hz, C-4'''), 169.9 (s, C-2).
GC retention time	14.12 min with Toan_25min method
MS analyst, m/z (Int.)	360(49, M+), 269(100), 167(72), 152(24), 91(32), 77(25).
HR-MS analyst	[M+H]+ m/z (predicted) = 362.1169, m/z (measured) = 361.1171, difference = 0.55 ppm.

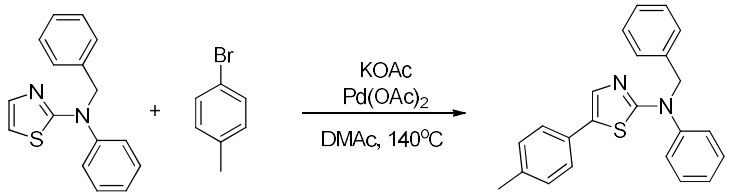
D III.6.7 Synthesis of *N*-benzyl-5-(4-chlorophenyl)-*N*-phenyl(thiazol-2-yl)amine (24)



16 **24**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.42 in EtOAc 10:1
Yield	156 mg (83%) pale brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{22}H_{17}ClN_2S$, 376.90 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.19 (s, 2H, CH_2), 7.25 – 7.39 (m, 14H, Ar-H), 7.43 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.2 (t, CH_2), 126.3 (s, C-5), 126.4 (d, 2C, C-2' + C-6'), 126.5 (d, 2C, C-2'' + C-6''), 127.3 (d, C-4'), 127.4 (d, C-4''), 127.8 (d, 2C, C-2''' + C-6'''), 128.5 (d, 2C, C-3''' + C-5'''), 128.9 (d, 2C, C-3'' + C-5''), 129.9 (d, 2C, C-3' + C-5'), 130.9 (s, C-1'''), 132.1 (s, C-4'''), 135.3 (d, C-4), 137.4 (s, C-1''), 144.9 (s, C-1'), 169.8 (s, C-2).
GC retention time	17.97 min with Toan_25min method
MS analyst, m/z (Int.)	378(11), 376(30, M+), 286(26), 285(61), 284(44), 168(21), 167(84), 91(100), 77(27).
HR-MS analyst	[M+H]+ m/z (predicted) = 376.9018, m/z (measured) = 376.9029, difference = 1.21 ppm.

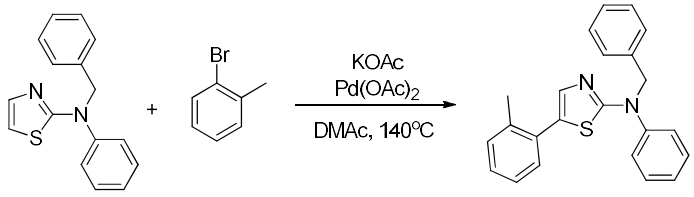
D III.6.8 Synthesis of *N*-benzyl-*N*-phenyl-5-(*p*-tolyl)(thiazol-2-yl)amine (25)



16 25

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.62 in LP/EtOAc = 10:1
Yield	105 mg (59%) beige solid
Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48 g/mol
Melting point	95 – 98 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.34 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 7.10 – 7.14 (m, 2H, H-3''' + H-5'''), 7.27 – 7.41 (m, 12H, Ar-H), 7.44 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.1 (q, CH_3), 56.2 (t, CH_2), 125.4 (d, 2C, C-2' + C-6'), 126.3 (d, 2C, C-3''' + C-5'''), 127.0 (d, C-4'), 127.3 (d, C-4''), 127.7 (d, 2C, C-2'' + C-6''), 127.8 (s, C-5), 128.5 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-2''' + C-6'''), 129.5 (s, C-1'''), 129.9 (d, 2C, C-3' + C-5'), 134.2 (d, C-4), 136.5 (s, C-4'''), 137.6 (s, C-1''), 145.1 (s, C-1'), 169.2 (s, C-2).
GC retention time	16.82 min with Toan_25min method
MS analyst, m/z (Int.)	356(36, M+), 265(100), 264(59), 167(62), 146(22), 91(75), 77(27).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1427, difference = 1.96 ppm.

D III.6.9 Synthesis of *N*-benzyl-*N*-phenyl-5-(*o*-tolyl)(thiazol-2-yl)amine (26)

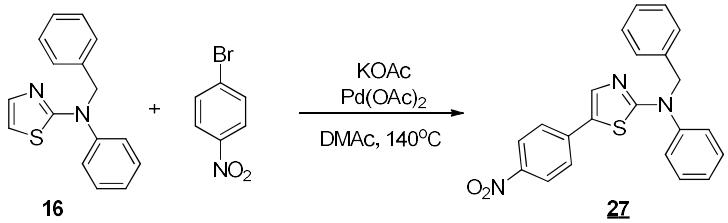


16 26

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.60 in LP/EtOAc = 10:1
Yield	107 mg (60%) beige solid
Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48 g/mol
Melting point	71 – 73 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.32 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 7.06-7.29 (m, 15H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.5 (q, CH_3), 56.2 (t, CH_2), 126.0 (d, C-6'''), 126.1 (s, C-5), 126.3 (d, 2C, C-2' + C-6'), 126.9 (d, C-4'), 127.3 (d, C-5'''), 127.4 (d, C-4''), 127.8 (d, 2C,

	C-2'' + C-6''), 128.5 (d, 2C, C-3'' + C-5''), 129.9 (d, 2C, C-3' + C-5'), 130.2 (d, 1C, C-4'''), 130.8 (d, C-3'''), 131.4 (s, C-1'''), 136.0 (d, C-4), 137.4 (s, C-2'''), 137.6 (s, C-1''), 145.1 (s, C-1'), 170.1 (s, C-2).
GC retention time	15.42 min with Toan_25min method
MS analyst, m/z (Int.)	356 (65, M^+), 167 (88), 147 (38), 115 (88), 91 (100), 65 (26).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1427, difference = 1.96 ppm.

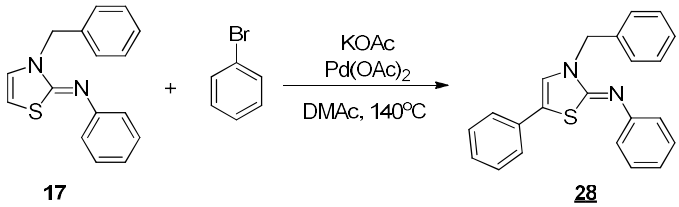
D III.6.10 Synthesis of *N*-benzyl-5-(4-nitrophenyl)-*N*-phenyl(thiazol-2-yl)amine (27)



16 27

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.26 in LP/EtOAc = 10:1
Yield	85 mg (44%) colorless solid
Molecular formular, m.w.	$C_{22}H_{17}N_3O_2S$, 387.45 g/mol
Melting point	197 – 200 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.21 (s, 2H, CH_2), 7.26 – 7.46 (m, 12H, Ar-H), 7.65 (s, 1H, H-4), 8.13 (d, *J* = 8 Hz, 2H, H-3''' + H-6''').
^{13}C NMR (50 MHz, DMSO-d_6)	δ (ppm) = 56.4 (t, CH_2), 124.2 (s, C-5), 124.4 (d, 2C, C-2' + C-6'), 124.9 (d, C-4'), 125.0 (d, 2C, C-2'' + C-6''), 125.9 (d, C-4''), 126.3 (d, 2C, C-3''' + C-5'''), 127.5 (s, C-1'''), 127.6 (d, 2C, C-3'' + C-5''), 128.4 (d, 2C, C-3' + C-5'), 128.6 (d, C-4), 130.1 (d, 2C, C-2''' + C-6'''), 137.1 (s, C-1''), 144.9 (s, C-4'''), 154.9 (s, C-1'), 169.9 (s, C-2).
HR-MS analyst	Could not be recorded, because of the insolubility of the compound in MeOH or *i*-PrOH.

D III.6.11 Synthesis of *N*-(3-benzyl-5-phenylthiazol-2(3*H*)-ylidene)aniline (28)

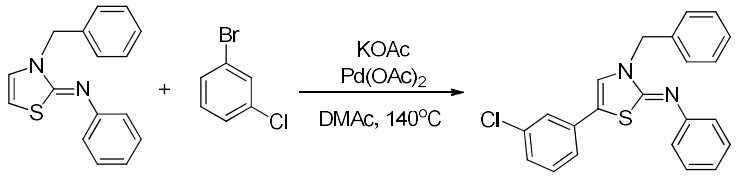


17 28

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.49 in LP/EtOAc = 10:1
Yield	94 mg (55%) beige solid

Molecular formular, m.w.	$C_{22}H_{18}N_2S$, 342.46
Melting point	65 – 66 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.14 (s, 2H, CH_2), 6.81 (s, 1H, H-4), 7.07 – 7.41 (m, 15H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 49.9 (t, CH_2), 115.3 (d, C-4), 121.6 (d, 2C, C-2' + C-6'), 121.8 (s, C-1'''), 123.3 (d, C-4'), 124.5 (d, 2C, C-3''' + C-5'''), 127.1 (d, C-4'''), 127.9 (d, C-4''), 128.1 (d, 2C, C-2'' + C-6''), 128.8 (d, 2C, C-2''' + C-6'''), 128.9 (d, 2C, C-3'' + C-5''), 129.4 (d, 2C, C-3' + C-5'), 131.6 (s, C-5), 136.5 (s, C-1''), 151.1 (s, C-1'), 157.7 (s, C-2).
GC retention time	16.40 min with Toan_25min method
MS analyst, m/z (Int.)	343(5), 342(20, M+), 251(41), 250(10), 219(8), 167(100), 91(42).
HR-MS analyst	[M+H]+ m/z (predicted) = 343.1263, m/z (measured) = 343.1271, difference = 2.33 ppm.

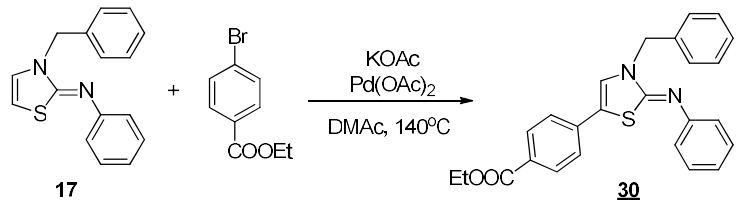
D III.6.12 Synthesis of *N*-(3-benzyl-5-(3-chlorophenyl)thiazol-2(3*H*)-ylidene)aniline (29)



17 **29**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.44 in LP/EtOAc = 10:1
Yield	109 mg (58%) pale brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{22}H_{17}ClN_2S$, 376.90 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.11 (s, 2H, CH_2), 6.83 (s, 1H, H-4), 7.05 – 7.40 (m, 14H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 49.9 (t, CH_2), 113.6 (d, C-4), 121.4 (d, 2C, C-2' + C-6'), 122.5 (d, C-6'''), 122.8 (d, C-2'''), 123.4 (d, C-4'), 124.2 (d, C-4'''), 126.8 (d, C-5'''), 128.0 (d, C-4''), 128.1 (d, 2C, C-2'' + C-6''), 128.9 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-3' + C-5'), 130.0 (s, C-5), 133.5 (s, C-1'''), 134.8 (s, C-3'''), 136.4 (s, C-1''), 151.1 (s, C-1'), 157.0 (s, C-2).
GC retention time	20.05 min with Toan_25min method
MS analyst, m/z (Int.)	378(4), 376(8, M+), 287(8), 285(16), 284(5), 168(16), 167(100), 91(78), 65(17).
HR-MS analyst	[M+H]+ m/z (predicted) = 376.9018, m/z (measured) = 376.9144, difference = 1.54 ppm.

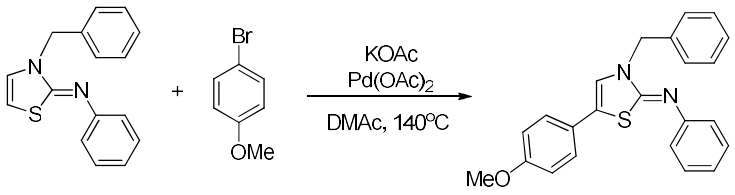
D III.6.13 Synthesis of ethyl 4-(3-benzyl-2-(phenylimino)-2,3-dihydrothiazol-5-yl)benzoate (30)



17 **30**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.36 in LP/EtOAc = 10:1
Yield	102 mg (49%) yellow oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{25}H_{22}N_2O_2S$, 414.52 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.37 (t, J = 7.1Hz, 3H, $CH_2\underline{CH_3}$), 4.34 (q, J = 7.1Hz, 2H, $\underline{CH_2}CH_3$), 5.13 (s, 2H, CH_2), 6.96 (s, 1H, H-4), 7.09 – 7.41 (m, 13H, Ar-H), 7.91 – 8.02 (m, 2H, H-3''' + H-5''').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 14.3 (q, $CH_2\underline{C}H_3$), 49.9 (t, $\underline{C}H_2CH_3$), 61.0 (t, CH_2), 114.0 (d, C-4), 121.4 (d, 2C, C-2' + C-6'), 123.4 (d, C-4'), 123.8 (d, 2C, C-2''' + C-6'''), 127.3 (d, C-4''), 128.1 (d, 2C, C-2'' + C-6''), 128.4 (s, C-4'''), 128.9 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-3' + C-5'), 130.1 (d, 2C, C-3''' + C-5'''), 130.6 (s, C-5), 136.0 (s, C-1'''), 136.4 (s, C-1''), 151.1 (s, C-1'), 156.9 (s, C-2), 166.1 (s, C=O).
HR-MS analyst	[M+H]+ m/z (predicted) = 415.1485, m/z (measured) = 415.1475, difference = 2.41 ppm.

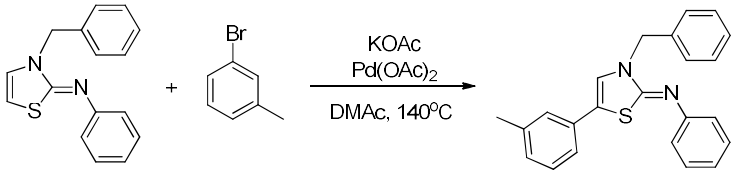
D III.6.14 Synthesis of *N*-(3-benzyl-5-(4-methoxyphenyl)thiazol-2(3*H*)-ylidene)aniline (<u>31</u>)



17 **<u>31</u>**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.46 in LP/EtOAc = 10:1
Yield	39 mg (21%) beige oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{23}H_{20}N_2OS$, 372.48 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.70 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2), 6.59 (s, 1H, H-4), 6.71 – 6.75 (m, 2H, H-3''' + H-5'''), 6.98 – 7.32 (m, 15H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 49.7 (t, CH_2), 55.3 (q, OCH_3), 114.3 (d, 2C, C-3''' + C-5'''), 115.0 (C-d, 4), 120.4 (s, C-1'''), 121.6 (d, 2C, C-2' + C-6'), 123.1 (d, C-4'), 124.4 (s, C-5), 125.8 (d, 2C, C-2''' + C-6'''), 127.9 (d, C-4''), 128.0 (d, 2C, C-2'' + C-6''), 129.0 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-3' + C-5'), 136.7 (s, C-1''), 151.4 (s, C-1'), 157.7 (s, C-2), 158.7 (s, C-4''').
GC retention time	22.51 min with Toan_25min method
MS analyst, m/z (Int.)	372(8, M+), 281(21), 207(100), 253(11), 167(17), 91(15).
HR-MS analyst	[M+H]+ m/z (predicted) = 373.1369, m/z (measured) = 373.1373, difference = 1.07 ppm.

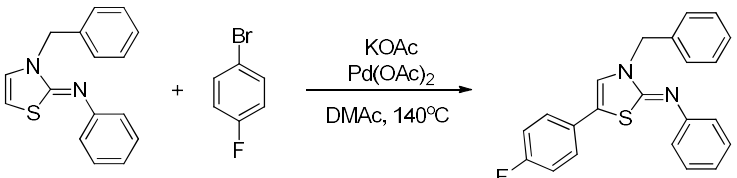
D III.6.15 Synthesis of *N*-(3-benzyl-5-(*m*-tolyl)thiazol-2(3*H*)-ylidene)aniline (32)



17 32

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
Rf	0.60 in LP/EtOAc = 10:1
Yield	100 mg (56%) beige solid
Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48
Melting point	63 – 64 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.28 (s, 3H, CH_3), 5.11 (s, 2H, CH_2), 6.79 (s, 1H, H-4), 7.01 – 7.39 (m, 13H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.4 (q, CH_3), 49.7 (t, CH_2), 115.2 (d, C-4), 121.4 (d, 2C, C-2' + C-6'), 122.9 (d, C-6'''), 123.1 (d, C-4'), 125.2 (d, C-2'''), 126.5 (d, C-4'''), 127.8 (d, C-4''), 128.0 (d, C-5'''), 128.1 (d, 2C, C-2'' + C-6''), 128.8 (d, 2C, C-3'' + C-5''), 129.4 (d, 2C, C-3' + C-5'), 131.6 (s, C-5), 136.7 (s, C-1''), 136.8 (s, C-1'''), 138.5 (s, C-3'''), 151.6 (s, C-1'), 157.5 (s, C-2).
GC retention time	18.40 min with Toan_25min method
MS analyst, m/z (Int.)	356(12), 265(32), 168(14), 167(100), 91(48), 65(17).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1428, difference = 2.24 ppm.

D III.6.16 Synthesis of *N*-(3-benzyl-5-(4-fluorophenyl)thiazol-2(3*H*)-ylidene)aniline (33)

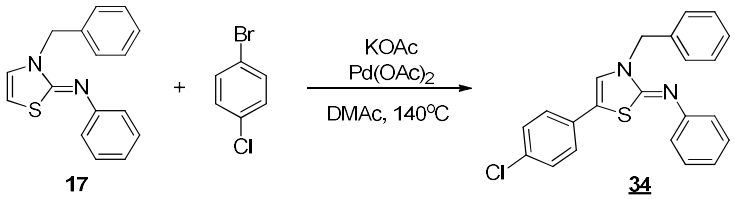


17 33

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
Rf	0.49 in LP/EtOAc
Yield	61 mg (34%) beige solid
Molecular formular, m.w.	$C_{22}H_{17}FN_2S$, 360.45 g/mol
Melting point	61 – 63 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.10 (s, 2H, CH_2), 6.71 (s, 1H), 6.91 – 7.40 (m, 14H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 49.9 (t, CH_2), 114.0 (s, C-4), 115.8 (d, $J^2_{C\text{-}F}$ = 21.8 Hz, 2C, C-3''' + C-5'''), 121.5 (d, 2C, C-2' + C-6'), 121.5 (d, $J^4_{C\text{-}F}$ = 1.4 Hz, 1C, H-1'''), 123.3 (d, C-4'), 126.1 (d, $J^3_{C\text{-}F}$ = 8.1Hz, 2C, C-2''' + C-6'''), 128.0 (d, C-4''), 128.1 (d, C-5),

	128.1 (d, 2C, C-2'' + C-6''), 128.9 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-3' + C-5'), 136.6 (s, C-1''), 151.4 (s, C-1'), 157.3 (s, C-2), 161.8 (d, $J^{1}_{C\text{-}F}$ = 249 Hz, 1C, C-4''').
GC retention time	15.70 min with Toan_25min method
MS analyst, m/z (Int.)	360(13, M+), 269(31), 268(10), 207(32), 167(100), 91(56).
HR-MS analyst	[M+H]+ m/z (predicted) = 362.1169, m/z (measured) = 361.1171, difference = 0.55 ppm.

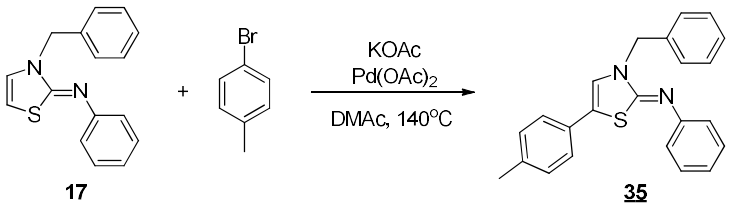
D III.6.17 Synthesis of *N*-(3-benzyl-5-(4-chlorophenyl)thiazol-2(3*H*)-ylidene)aniline (34)



17 34

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.39 in LP/EtOAc 10:1
Yield	94 mg (50%) brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{22}H_{17}ClN_2S$, 376.90 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.02 (s, 2H, CH_2), 6.70 (s, 1H, H-4), 7.01 – 7.32 (m, 14H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 50.1 (t, CH_2), 115.6 (d, C-4), 122.1 (d, 2C, C-2' + C-6'), 123.3 (d, C-4'), 125.3 (d, 2C, C-3''' + C-5'''), 126.7 (d, C-1'''), 127.6 (d, C-4''), 128.2 (d, 2C, C-2'' + C-6''), 128.6 (d, 2C, C-3'' + C-5''), 129.0 (d, 2C, C-3' + C-5'), 129.6 (d, 2C, C-2''' + C-6'''), 130.9 (s, C-5), 135.6 (s, C-4'''), 136.0 (s, C-1''), 151.6 (s, C-1'), 157.1 (s, C-2).
GC retention time	21.54 min with Toan_25min method
MS analyst, m/z (Int.)	378(4), 376(9, M+), 287(8), 286(7), 285(23), 284(6), 207(12), 168(21), 167(100), 91(71), 65(20).
HR-MS analyst	[M+H]+ m/z (predicted) = 376.9018, m/z (measured) = 377.1024, difference = 1.24 ppm.

D III.6.18 Synthesis of *N*-(3-benzyl-5-(*p*-tolyl)thiazol-2(3*H*)-ylidene)aniline (35)

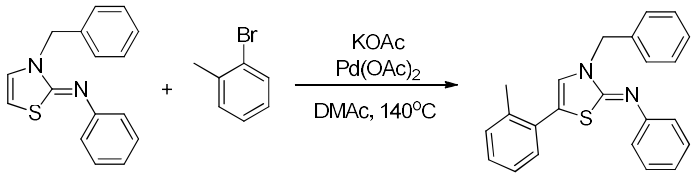


17 35

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.61 LP/EtOAc = 10:1
Yield	93 mg (52%) beige solid

Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48 g/mol
Melting point	79 – 80 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.29(s, 3H, CH_3), 5.10 (s, 2H, CH_2), 6.74 (s, 1H, H-4), 7.06 – 7.14 (m, 7H, Ar-H), 7.31 – 7.39 (m, 7H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.1 (q, CH_3), 49.7 (d, CH_2), 115.2 (d, C-4), 121.1 (s, C-5), 121.5 (d, 2C, C-2' + C-6'), 123.1 (d, C-4'), 124.4 (d, 2C, C-2''' + C-6'''), 127.9 (d, C-4''), 128.0 (d, 2C, C-2'' + C-6''), 128.9 (d, 2C, C-3'' + C-5''), 129.5 (d, 2C, C-3' + C-5'), 129.5 (d, 2C, C-3''' + C-5'''), 136.7 (d, C-1''), 136.9 (s, C-4'''), 151.5 (s, C-1'), 157.5 (s, C-2).
GC retention time	20.05 min with Toan_25min method
MS analyst, m/z (Int.)	356 (20, M+), 265(22), 207(19), 167(100), 115(34), 91(47).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1427, difference = 1.96 ppm.

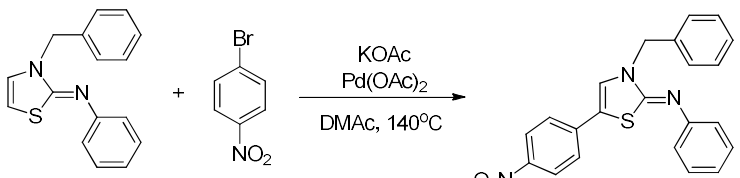
D III.6.19 Synthesis of *N*-(3-benzyl-5-(*o*-tolyl)thiazol-2(3*H*)-ylidene)aniline (36)



17 **36**

General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.57 in LP/EtOAc = 10:1
Yield	89 mg (50%) brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{23}H_{20}N_2S$, 356.48 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.25 (s, 3H, -CH_3), 5.04 (s, 2H, -CH_2), 6.42 (s, 1H, H-4), 6.93-7.30 (m, 15H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.7 (q, CH_3), 50.3 (t, CH_2), 114.5 (d, C-4), 122.0 (d, 2C, C-2' + C-6'), 123.5 (d, C-4'), 124.7 (d, C-5'''), 126.6 (d, C-6'''), 128.2 (d, C-4''), 128.3 (d, C-4'''), 128.6 (d, 2C, C-2'' + C-6''), 129.3 (d, 2C, C-3'' + C-5''), 129.8 (d, C-3'''), 129.9 (d, 2C, C-3' + C-5'), 130.2 (s, C-5), 131.4 (s, C-1'''), 136.4 (s, C-2'''), 137.1 (s, C-1''), 151.8 (s, C-1'), 158.5 (s, C-2).
GC retention time	15.90 min with Toan_25min method
MS analyst, m/z (Int.)	356 (20, M+), 265 (22), 207 (19), 167 (100), 115 (20), 91 (47).
HR-MS analyst	[M+H]+ m/z (predicted) = 357.1420, m/z (measured) = 357.1428, difference = 2.24 ppm.

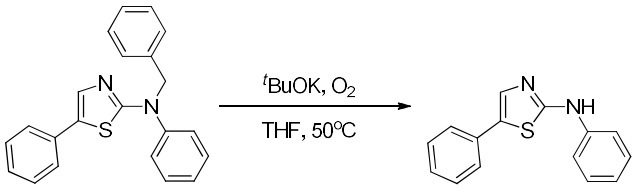
D III.6.20 Synthesis of *N*-(3-benzyl-5-(4-nitrophenyl)thiazol-2(3*H*)-ylidene)aniline (37)



17 **37**

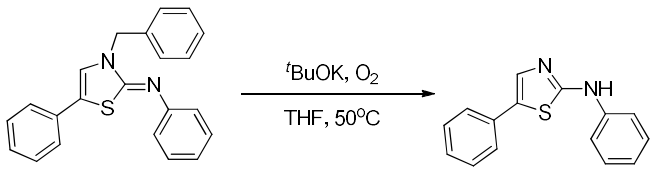
General procedure	D
Reaction scale	133 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc (gradient 1% - 20% EtOAc) with 1% TEA addition on 18 g silica 60 then washed by LP at 0 °C
R_f	0.25 in LP/EtOAc 10:1
Yield	62 mg (32%) dark orange oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{22}H_{17}N_3O_2S$, 387.45 g/mol
^{1}H NMR (200 MHz, DMSO-d_6)	δ (ppm) = 5.24 (s, 2H, CH_2), 7.25 – 7.47 (m, 10H, Ar-H), 7.65 (d, *J* = 8 Hz, 2H, H-2''' + H-6'''), 7.99 (s, 1H, H-4), 8.12 (d, *J* = 8 Hz, 2H, H-3''' + H-5''').
^{13}C NMR (50 MHz, Acetone-d_6)	δ (ppm) = 56.4 (t, CH_2), 112.6 (d, C-4), 122.0 (d, 2C, C-2' + C-6'), 124.2 (d, C-4'), 125.1 (d, 2C, C-2''' + C-6'''), 125.2 (d, 2C, C-2'' + C-6''), 127.8 (d, C-4''), 128.7 (s, C-5), 129.0 (d, 2C, C-3'' + C-5''), 129.1 (d, C-1'''), 129.6 (d, 2C, C-3' + C-5'), 130.3 (d, 2C, C-3''' + C-5'''), 138.2 (s, C-1''), 152.0 (s, C-1'), 156.6 (s, C-2), 163.2 (s, C-4''').
HR-MS analyst	[M+H]+ m/z (predicted) = 362.1114, m/z (measured) = 388.1118, difference = 1.03 ppm.

D III.7 De-protection of 5-phenyl-*N*-protected-thiazolamines.



18 38

General procedure	E
Reaction scale	68 mg (0.2 mmol)
Purification	MPLC, LP/EtOAc 9:1 (with 1% TEA addition), 9 g silica 60
Yield	6 mg (12%), brown oil, NMR indicated a purity of >98%



28 38

General procedure	E
Reaction scale	68 mg (0.2 mmol)
Purification	MPLC, LP/EtOAc 9:1 (with 1% TEA addition), 9 g silica 60
Yield	5.7 mg (11%), brown oil, NMR indicated a purity of >98%
Molecular formular, m.w.	$C_{15}H_{12}N_2S$, 252.33 g/mol[101]
Rf	0.64 in LP/EtOAc = 4:1
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 7.05 (s, 1H, H-4), 7.11 – 7.65 (m, 10H, Ar-H), 8.53 (s, 1H, N-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 118.4 (d, 2C, C-2' + C-6'), 120.5 (s, C-5), 123.2 (d, C-4'), 125.6 (d, 2C, C-2'' + C-6''), 129.0 (d, 2C, C-3'' + C-5''), 129.1 (d, C-4''), 129.6 (d, 2C, C-3' + C-5'), 131.9 (s, C-1''), 134.0 (d, C-4), 140.3 (s, C-1'), 164.7 (s, C-2).

GC retention time	10.80 min with Toan_25min method
MS analyst, m/z (Int.)	253(19), 252(100, M+), 251(36), 175(19), 150(57), 134(32), 121(42), 89(18), 77(30), 51(17).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 252.3342, m/z (measured) = 252.3981, difference = 1.68 ppm.

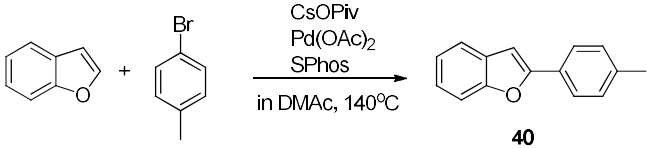
D III.8 Scope of direct arylation on benzo[*b*]furan.

D III.8.1 Synthesis of 2-phenylbenzo[*b*]furan (39)

39

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.63 in LP
Yield	58 mg (60%), colorless solid
Molecular formular, m.w.	$C_{14}H_{10}O$, 194.23 g/mol
Melting point	120-121°C (Lit. 121−122°C)[86d]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.03 (s, 1H, H-3), 7.14 – 7.69 (m, 8H, Ar-H), 7.80 – 7.95 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 101.3 (d, C-3), 111.2 (d, C-7), 120.9 (d, C-4), 122.9 (d, C-5), 124.3 (d, C-6), 124.9 (d, 2C, C-2' + C-6'), 128.6 (d, C-4'), 128.8 (d, 2C, C-3' + C-5'), 129.2 (s, C-3a), 130.5 (s, C-1'), 154.9 (s, C-7a), 155.9 (s, C-2).
GC retention time	9.64 min with Toan_20min method
MS analyst, m/z (Int.)	195(16), 194(100), 165(50), 97(9), 82(12).

D III.8.2 Synthesis of 2-(*p*-tolyl)benzo[*b*]furan (40)

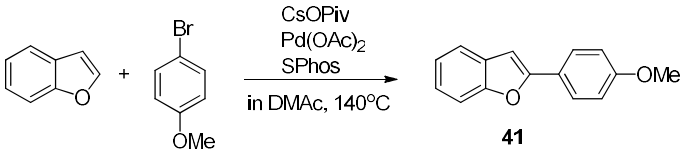


40

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.67 in LP
Yield	56 mg (54%), white solid
Molecular formular, m.w.	$C_{15}H_{12}O$, 208.25 g/mol
Melting point	125-127°C (Lit. 126−128°C)[102]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.38 (s, 3H, CH_3), 6.94 (d, *J* = 0.8 Hz, 1H, H-3), 7.16 – 7.30 (m, 4H, H-5 + H-6 + H-3' + H-6'), 7.48 – 7.57 (m, 2H, H-4 + H-7), 7.73 – 7.77 (m, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.4 (q, CH_3), 100.6 (d, C-3), 111.1 (d, C-7), 120.8 (d, C-4), 122.9 (d, C-5), 124.0 (d, C-6), 124.9 (d, 2C, C-3' + C-5'), 127.8 (s, C-1'), 129.4 (s, C-3a), 129.5 (d, 2C, C-2' + C-6'), 138.6 (s, C-4'), 154.8 (s, C-7a), 156.2 (s, C-2).

GC retention time	10.28 min with Toan_20min method
MS analyst, m/z (Int.)	209(17), 208(100), 207(29), 178(15), 165(16), 89(9).

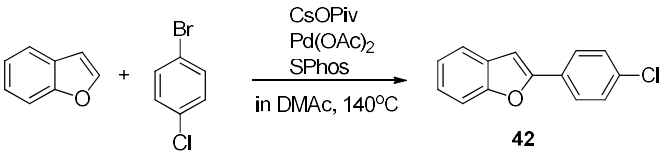
D III.8.3 Synthesis of 2-(4-methoxyphenyl)benzo[*b*]furan (41)



41

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 9:1, 18 g silica 60
R_f	0.74 in LP/EtOAc 9:1
Yield	78 mg (70%), white solid
Molecular formular, m.w.	$C_{15}H_{12}O_2$, 224.25 g/mol
Melting point	140-142°C (Lit. 148−150°C)[103]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.83 (s, 3H, OCH_3), 6.86 (d, *J* = 0.8 Hz, 1H, H-3), 6.94 – 6.98 (m, 2H, H-2' + H-6'), 7.15 – 7.29 (m, 2H, H-5 + H-6), 7.47 – 7.56 (m, 2H, H-4 + H-7), 7.76 – 7.81 (m, 2H, H-3' + H-5').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.4 (q, OCH_3), 99.7 (d, C-3), 111.0 (d, C-7), 114.3 (d, 2C, C-3' + C-5'), 120.6 (d, C-4), 122.8 (d, C-5), 123.4 (d, C-1'), 123.7 (d, C-6), 126.4 (d, 2C, C-2' + C-6'), 129.5 (s, C-3a), 154.7 (s, C-7a), 156.1 (s, C-2), 160.0 (s, C-4').
GC retention time	10.48 min with Toan_20min method
MS analyst, m/z (Int.)	225(16), 224(100), 210(12), 209(82), 207(29), 181(52), 152(34), 112(20), 76(12).

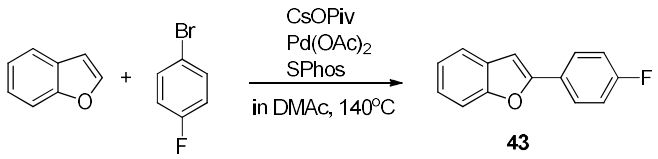
D III.8.4 Synthesis of 2-(4-chlorophenyl)benzo[*b*]furan (42)



42

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.65 in LP
Yield	64 mg (57%), white solid
Molecular formular, m.w.	$C_{14}H_9ClO$, 228.67 g/mol
Melting point	144-145°C (Lit. 148−149°C)[104]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.00 (s, 1H, H-3), 7.14 – 7.63 (m, 7H, Ar-H), 7.76 – 7.80 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 101.7 (d, C-3), 111.2 (d, C-7), 121.0 (d, C-4), 123.1 (d, C-5), 124.6 (d, C-6), 126.1 (d, 2C, C-3' + C-5'), 129.0 (s, C-1'), 129.0 (d, 2C, C-2' + C-6'), 129.0 (s, C-3a), 134.3 (s, C-4'), 154.8 (s, C-7a), 154.9 (s, C-2).
GC retention time	10.74 min with Toan_20min method
MS analyst, m/z (Int.)	230(32), 229(15), 228(100), 165(67), 164(18), 163(20), 115(16), 114(34), 82(30), 81(55), 63(12).

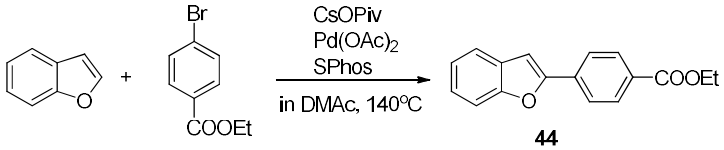
D III.8.5 Synthesis of 2-(4-fluorophenyl)benzo[*b*]furan (43)



43

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.68 in LP
Yield	53 mg (50%), white solid
Molecular formular, m.w.	$C_{14}H_9FO$, 212.22 g/mol
Melting point	120 – 122 °C (Lit. 124 °C)[105]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.95 (s, 1H, H-3), 7.09 – 7.33 (m, 4H, H-5 + H-6 + H-3' + H-5'), 7.49 – 7.59 (m, 2H, H-4 + H-7), 7.80 – 7.87 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 101.0 (d, C-3), 111.1 (d, C-7), 115.9 (d, J^2_{CF} = 20Hz, 2C, C-3' + C-5'), 120.9 (d, C-4), 123.0 (d, C-5), 124.3 (d, C-6), 126.7 (d, J^3_{CF} = 8Hz, 2C, C-2' + C-6'), 126.8 (s, C-1'), 129.2 (s, C-3a), 154.8 (s, C-7a), 155.0 (s, C-2), 162.8 (d, J^1_{CF} = 247Hz, 1C, C-4').
GC retention time	10.52 min with Toan_20min method
MS analyst, m/z (Int.)	213(13), 212(100), 183(69), 106(35), 91(26), 82(13).

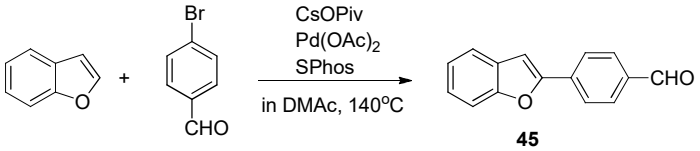
D III.8.6 Synthesis of ethyl 4-(benzo[*b*]furan-2-yl)benzoate (44)



44

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 95:5, 18 g silica 60
R_f	0.43 in LP/EtOAc 9:1
Yield	60 mg (45%), light yellow solid
Molecular formular, m.w.	$C_{17}H_{14}O_3$, 266.29 g/mol[77c]
Melting point	120 – 121 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.40 (t, *J* = 7.1 Hz, 3H, CH_3), 4.39 (q, *J* = 7.1 Hz, 2H, CH_2), 7.11 (d, *J* = 0.7 Hz, 1H, H-3), 7.19 – 7.35 (m, 2H, H-5 + H-6), 7.50 – 7.61 (m, 2H, H-4 + H-7), 7.87 – 7.91 (m, 2H, H-3' + H-5'), 8.08 – 8.12 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 14.4 (q, CH_3), 61.1 (t, CH_2), 103.4 (d, C-3), 111.3 (d, C-7), 121.3 (d, C-4), 123.2 (d, C-5), 124.5 (d, C-6), 125.0 (d, 2C, C-2' + C-6'), 128.9 (s, C-3a), 129.8 (s, C-1'), 130.1 (d, 2C, C-3' + C-5'), 134.4 (s, C-4'), 154.7 (s, C-7a), 155.1 (s, C-2), 166.2 (s, C=O).
GC retention time	11.98 min with Toan_25min method
MS analyst, m/z (Int.)	266(100), 238(69), 221(86), 193(24), 165(92), 164(30), 163(29), 139(18), 110(43), 83(42), 82(40), 69(20).

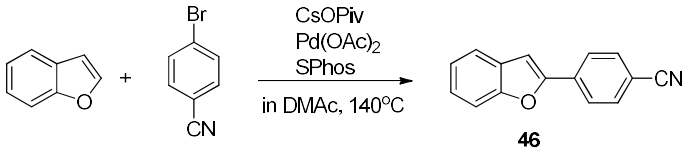
D III.8.1 Synthesis of 4-(benzo[*b*]furan-2-yl)benzaldehyde (45)



45

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 95:5, 18 g silica 60
R_f	0.51 in LP/EtOAc 9:1
Yield	57 mg (50%), white solid
Molecular formular, m.w.	$C_{15}H_{10}O_2$, 222.24 g/mol[106]
Melting point	125 – 126 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.18 (d, *J* = 0.8 Hz, 1H, H-3), 7.20 – 7.41 (m, 2H, H-5 + H-6), 7.48 – 7.67 (m, 2H, H-3' + H-5'), 7.88 – 8.06 (m, 4H, Ar-H), 10.01 (s, 1H, CH=O).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 104.3 (d, C-3), 111.4 (d, C-7), 121.4 (d, C-4), 123.3 (d, C-5), 125.1 (d, 2C, C-2' + C-6'), 125.4 (d, C-6), 128.8 (s, C-3a), 130.3 (d, 2C, C-3' + C-5'), 135.8 (s, C-1'), 135.8 (s, C-4'), 154.2 (s, C-7a), 155.3 (s, C-2), 191.5 (d, C=O).
GC retention time	10.35 min with Toan_20min method
MS analyst, m/z (Int.)	222(100), 221(48), 193(17), 165(57), 164(18), 163(17), 139(14), 96(39), 82(24), 69(16).

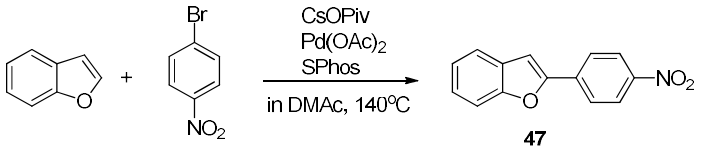
D III.8.2 Synthesis of 4-(benzo[*b*]furan-2-yl)benzonitrile (46)



46

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 95:5, 18 g silica 60
R_f	0.49 in LP/EtOAc 9:1
Yield	60 mg (45%), white solid
Molecular formular, m.w.	$C_{15}H_9NO$, 219.24 g/mol
Melting point	143-145°C (Lit 145-146°C)[107]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.17 (d, *J* = 0.8 Hz, 1H, H-3), 7.20 – 7.42 (m, 2H, H-5 + H-6), 7.51 – 7.64 (m, 2H, H-4 + H-7), 7.69 – 7.73 (m, 2H, H-3' + H-5'), 7.91 – 7.96 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 104.3 (d, C-3), 111.4 (d, C-7), 111.5 (s, C-4'), 118.7 (s, CN), 121.5 (d, C-4), 123.4 (d, C-5), 125.1 (d, 2C, C-2' + C-6'), 125.6 (d, C-6), 128.7 (s, C-3a), 132.6 (d, 2C, C-3' + C-5'), 134.4 (s, C-1'), 153.5 (s, C-7a), 155.2 (s, C-2).
GC retention time	10.70 min with Toan_20min method
MS analyst, m/z (Int.)	219(100), 204(14), 190(53), 164(12).

D III.8.3 Synthesis of 2-(4-nitrophenyl)benzo[*b*]furan (47)



47

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 9:1, 18 g silica 60
R_f	0.33 in LP/EtOAc 9:1
Yield	26 mg (22%), orange solid
Molecular formular, m.w.	$C_{14}H_9NO_3$, 239.23 g/mol
Melting point	182 – 184 °C (Lit. 182 – 183 °C)[77g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.22 (d, *J* = 0.6 Hz, 1H, H-3), 7.23 – 7.41 (m, 2H, H-5 + H-6), 7.53 – 7.66 (m, 2H, H-4 + H-7), 7.95 – 8.00 (m, 2H, H-2' + H-6'), 8.26 – 8.31 (m, 2H, H-3' + H-5').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 105.1 (d, C-3), 111.5 (d, C-7), 121.6 (d, C-4), 123.5 (d, C-5), 124.3 (d, 2C, C-3' + C-5'), 125.2 (d, 2C, C-2' + C-6'), 125.8 (d, C-6), 128.6 (s, C-3a), 136.2 (s, C-1'), 147.2 (s, C-4'), 153.2 (s, C-7a), 155.4 (s, C-2).
GC retention time	11.04 min with Toan_25min method
MS analyst, m/z (Int.)	239(100), 209(43), 193(26), 181(30), 165(97), 164(29), 163(35), 139(19).

D III.8.4 Synthesis of 2-(o-tolyl)benzo[*b*]furan (48)

48

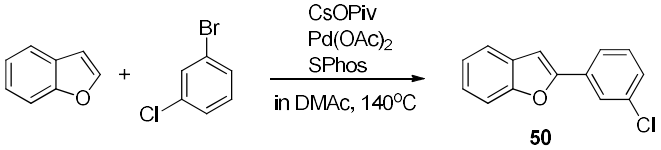
General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.68 in LP
Yield	41 mg (40%), oil
Molecular formular, m.w.	$C_{15}H_{12}O$, 208.25 g/mol[106]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.58 (s, 3H, CH_3), 6.88 (d, *J* = 0.8 Hz, 1H, H-3), 7.19 – 7.33 (m, 5H, Ar-H), 7.50 – 7.62 (m, 2H, Ar-H), 7.82 – 7.87 (m, 1H, H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 22.0 (q, CH_3), 105.1 (d, C-3), 111.1 (d, C-7), 120.9 (d, C-4), 122.8 (d, C-5), 124.3 (d, C-6), 126.1 (d, C-5'), 128.2 (d, C-6'), 128.5 (d, C-4'), 129.2 (s, C-3a), 130.0 (s, C-1'), 131.3 (d, C-3'), 135.8 (s, C-2'), 154.4 (s, C-7a), 155.7 (s, C-2).
GC retention time	8.68 min with Toan_20min method
MS analyst, m/z (Int.)	209(15), 208(100), 207(67), 189(13), 179(20), 178(30), 165(13), 152(14), 115(14), 89(16).

D III.8.5 Synthesis of 2-(2-chlorophenyl)benzo[*b*]furan (49)

49

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.68 in LP
Yield	49 mg (43%), white solid
Molecular formular, m.w.	$C_{14}H_9ClO$, 228.67 g/mol
Melting point	48 – 50 °C (Lit. 46 °C)[86c]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.20 – 7.40 (m, 4H, Ar-H), 7.46 – 7.54 (m, 3H, Ar-H), 7.60 – 7.64 (m, 1H, H-6'), 8.03 (dd, *J* = 7.8, 1.6 Hz, 1H, H-3').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 107.4 (d, C-3), 111.1 (d, C-7), 121.5 (d, C-4), 123.0 (d, C-5), 124.9 (d, C-6), 127.0 (d, C-5'), 129.0 (d, C-6'), 129.0 (s, C-3a), 129.1 (d, C-3'), 130.9 (d, C-4'), 131.3 (s, C-2'), 152.0 (s, C-7a), 154.2 (s, C-2).
GC retention time	9.54 min with Toan_20min method
MS analyst, m/z (Int.)	230(34), 229(15), 228(100), 165(64), 164(17), 163(18), 114(12), 82(13).

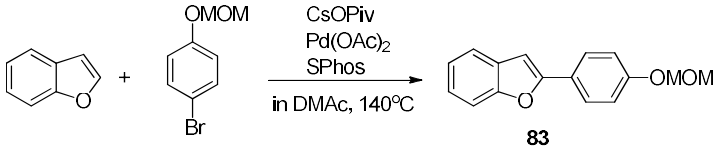
D III.8.6 Synthesis of 2-(3-chlorophenyl)benzo[*b*]furan (50)



50

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.65 in LP
Yield	57 mg (50%), white solid
Molecular formular, m.w.	$C_{14}H_9ClO$, 228.67 g/mol
Melting point	80 – 82 °C (Lit 85 °C)[108]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.05 (d, *J* = 0.7 Hz, 1H, H-3), 7.20 – 7.41 (m, 5H, Ar-H), 7.50 – 7.61 (m, 2H, H-4 + H-7), 7.73 (dt, *J* = 7.2, 1.6 Hz, H-6'), 7.85 – 7.86 (m, 1H, H-2').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 102.4 (d, C-3), 111.3 (d, C-7), 121.1 (d, C-4), 122.9 (d, C-6'), 123.1 (d, C-5), 124.8 (d, C-6), 124.9 (d, C-2'), 128.4 (d, C-4'), 128.9 (s, C-3a), 130.1 (d, C-5'), 132.2 (s, C-1'), 134.9 (s, C-3'), 154.3 (s, C-7a), 154.9 (s, C-2).
GC retention time	10.14 min with Toan_20min method
MS analyst, m/z (Int.)	230(32), 229(15), 228(100), 165(66), 164(18), 163(21), 115(17), 114(35), 83(33), 82(28), 81(20), 63(10).

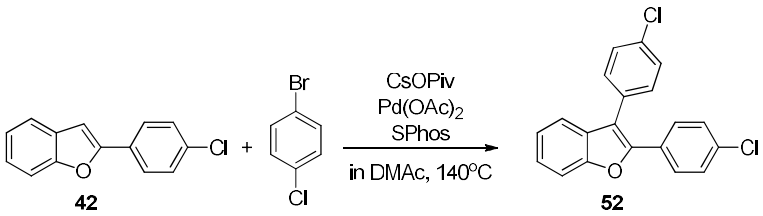
D III.8.7 Synthesis of 2-(4-(methoxymethoxy)phenyl)benzo[*b*]furan (83)



83

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 18 g silica 60
R_f	0.50 in LP/EtOAc 9:1
Yield	90 mg (71 %), white solid
Molecular formular, m.w.	$C_{16}H_{14}O_3$, 254.29 g/mol
Melting point	148 – 150 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.48 (s, 3H, OCH_3), 5.20 (s, 2H, OCH_2O), 6.87 (d, *J* = 0.6 Hz, 1H, H-3), 7.06 – 7.13 (m, 2H, H-3' + H-5'), 7.16 – 7.29 (m, 2H, H-5 + H-6), 7.47 – 7.56 (m, 2H, H-4 + H-7), 7.74 – 7.81 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 100.0 (d, C-4), 110.6 (d, C-7), 116.5 (d, 2C, C-3' + C-5'), 120.7 (d, C-4), 122.9 (s, C-1'), 123.9 (d, C-5), 124.5 (d, C-6), 126.4 (d, 2C, C-2' + C-6'), 129.5 (s, C-3a), 154.8 (s, C-7a), 155.9 (s, C-2), 157.6 (s, C-4').
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 255.1021, m/z (measured) = 255.1015, difference = 2.05 ppm.

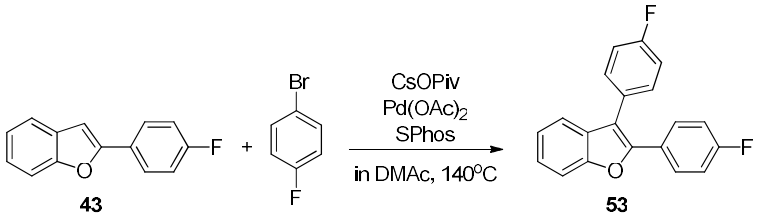
D III.8.8 Synthesis of 2,3-bis(4-chlorophenyl)benzo[*b*]furan (52)



42 52

General procedure	F
Reaction scale	57 mg (0.25 mmol)
Purification	MPLC, LP, 9 g silica 60
R_f	0.73 in LP
Yield	49 mg (58%), white solid
Molecular formular, m.w.	$C_{20}H_{12}Cl_2O$, 339.21 g/mol
Melting point	106 – 108 °C (Lit. 102 – 104 °C) [109]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.29 – 7.37 (m, 3H, Ar-H), 7.40 – 7.49 (m, 6H, Ar-H), 7.54 – 7.59 (m, 3H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.2 (d, C-7), 116.8 (s, C-3), 119.8 (d, C-4), 123.2 (d, C-5), 125.1 (d, C-6), 128.2 (d, 2C, C-2' + C-6'), 128.8 (d, 2C, C-2'' + C-6''), 129.0 (s, C-1'), 129.4 (d, 2C, C-3'' + C-5''), 129.7 (s, C-1''), 131.0 (d, 2C, C-3' + C-5'), 131.0 (s, C-3a), 133.8 (s, C-4'), 134.5 (s, C-4''), 149.6 (s, C-7a), 154.0 (s, C-2).
GC retention time	14.34 min with Toan_25min method
MS analyst, m/z (Int.)	340(69), 339(21), 338(100), 302(13), 268(50), 240(13), 239(56), 237(12), 207(10), 151(14), 134(40), 120(16), 119(19).

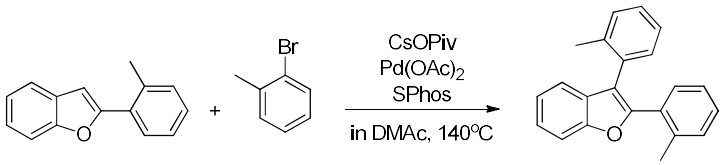
D III.8.9 Synthesis of 2,3-bis(4-fluorophenyl)benzo[*b*]furan (53)



43 53

General procedure	F
Reaction scale	53 mg (0.25 mmol)
Purification	MPLC, LP, 9 g silica 60
R_f	0.71 in LP
Yield	27 mg (44%), white solid
Molecular formular, m.w.	$C_{20}H_{12}F_2O$, 306.31 g/mol
Melting point	96 – 98 °C [110]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.98 – 7.07 (m, 2H, H-3'' + H-5''), 7.13 – 7.49 (m, 7H, Ar-H), 7.53 – 7.65 (m, 3H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 103.7 (s, C-3), 111.2 (d, C-7), 115.6 (d, J_{C-F} = 20Hz, 2C, C-3'' + C-5''), 116.2 (d, J_{C-F} = 20Hz, 2C, C-3' + C-5'), 119.8 (d, C-4), 123.1 (d, C-5), 124.9 (d, C-6), 126.7 (d, J_{C-F} = 3Hz, 1C, C-1'), 128.5(d, J_{C-F} = 3Hz, 1C, C-1''), 128.9 (d, J_{C-F} = 10Hz, 2C, C-2' + C-6'), 130.0 (s, C-3a), 131.4 (d, J_{C-F} = 10Hz, 2C, C-2'' + C-6''), 149.8 (s, C-7a), 153.9 (s, C-2), 162.4(d, J_{C-F} = 250Hz, 1C, C-4'), 162.7(d, J_{C-F} = 250Hz, 1C, C4'').
GC retention time	13.55 min with Toan_25min method
MS analyst, m/z (Int.)	307(21), 306(100), 277(23), 275(17), 257(14), 183(11), 143(11), 129(16).

D III.8.10 Synthesis of 2,3-di-o-tolylbenzo[*b*]furan (54)

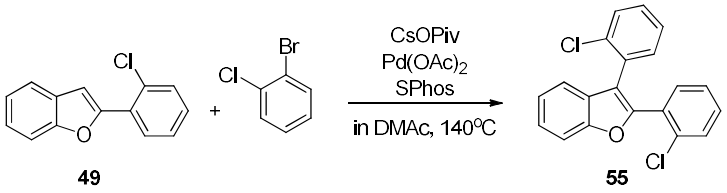


48 54

General procedure	F
Reaction scale	52 mg (0.25 mmol)
Purification	MPLC, LP, 9 g silica 60
R_f	0.73 in LP
Yield	24 mg (40%), white solid
Molecular formular, m.w.	$C_{22}H_{18}O$, 298.38 g/mol[111]
Melting point	71 – 73 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.04 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 7.01 – 7.44 (m, 10H, Ar-H), 7.48 – 7.67 (m, 2H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 20.0 (q, CH_3), 20.6 (q, CH_3), 111.2 (d, C-7), 118.3 (s, C-3), 120.4 (d, C-4), 122.7 (d, C-5), 124.3 (d, C-6), 125.5 (d, C-5'/C-6''), 125.9 (d, C-6''/C-5'), 127.7 (d, C-6'/C-5''), 128.9 (d, C-5''/C-6'), 129.7 (s, C-3a), 130.4 (d, C-4'/C-4''), 130.4 (s, C-1''), 130.5 (d, C-4''/C-4'), 130.7 (d, C-3'/C-3''), 130.9 (d, C-

	3''/C-3'), 131.8 (s, C-1'), 137.1 (s, C-2''), 137.5 (s, C-2'), 152.6 (s, C-7a), 154.3 (s, C-2).
GC retention time	11.34 min with Toan_25min method
MS analyst, m/z (Int.)	299(100), 298(94), 297(82), 283(16), 256(14), 252(16), 206(16), 192(22), 178(20), 134(24).

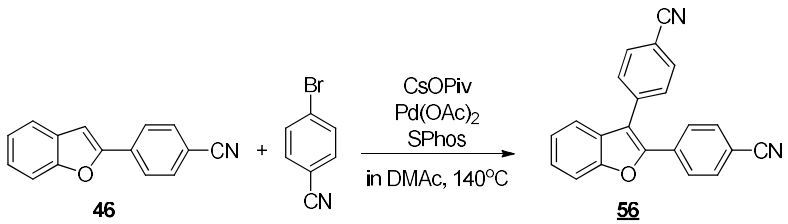
D III.8.11 Synthesis of 2,3-bis(2-chlorophenyl)benzo[*b*]furan (55)



49 55

General procedure	F
Reaction scale	57 mg (0.5 mmol)
Purification	MPLC, LP, 9 g silica 60
R_f	0.78 in LP
Yield	45 mg (53%), pale yellow solid
Molecular formular, m.w.	$C_{20}H_{12}Cl_2O$, 339.21 g/mol
Melting point	61 – 64 °C [110]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.23 – 7.37 (m, 6H, Ar-H), 7.41 – 7.53 (m, 5H, Ar-H), 7.61 – 7.65 (m, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.5 (d, C-7), 118.1 (s, C-3), 121.0 (d, C-4), 122.9 (d, C-5), 124.9 (d, C-6), 126.6 (d, C-5''), 126.9 (d, C-5'), 128.7 (s, C-3a), 129.2 (d, C-6''), 129.9 (s, C-2''), 130.0 (d, C-6'), 130.3 (d, C-3''), 130.4 (d, C-3'), 131.5 (s, C-2'), 132.2 (d, C-4''), 132.3 (d, C-4'), 134.0 (s, C-1''), 134.2 (s, C-1'), 150.4 (s, C-7a), 154.4 (s, C-2).
GC retention time	12.45 min with Toan_25min method
MS analyst, m/z (Int.)	340(46), 339(14), 338(67), 269(22), 268(100), 240(15), 239(56), 237(19), 134(32), 133(23), 120(29), 119(44), 118(23).

D III.8.12 Synthesis of 4,4'-(benzo[*b*]furan-2,3-diyl)dibenzonitrile (<u>56</u>)

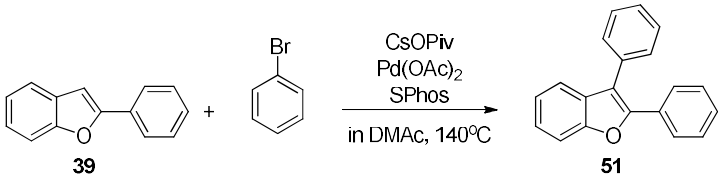


46 <u>56</u>

General procedure	F
Reaction scale	33 mg (0.15 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 9 g silica 60
R_f	0.58 in LP/EtOAc 4:1
Yield	8 mg (17%), pale yellow solid
Molecular formular, m.w.	$C_{22}H_{12}N_2O$, 320.34 g/mol
Melting point	178 – 183 °C

^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.33 (dd, *J* = 7.4, 1.1 Hz, 1H, H-7), 7.39 – 7.49 (m, 2H, H-5, H-6), 7.59 – 7.64 (m, 5H, Ar-H), 7.69 – 7.73 (m, 2H, Ar-H), 7.79 – 7.83 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.6 (d, C-7), 112.1 (s, C-4'), 112.1 (s, C-4''), 118.4 (s, C≡N), 118.5 (s, C≡N), 118.6 (s, C-3), 120.0 (d, C-4), 123.9 (d, C-5), 126.4 (d, C-6), 127.3 (d, 2C, C-2'' + C-6''), 128.9 (s, C-3a), 130.4 (d, 2C, C-2' + C-6'), 132.5 (d, 2C, C-3'' + C-5''), 133.1 (d, 2C, C-3' + C-5'), 134.1 (s, C-1'), 137.2 (s, C-1''), 148.9 (s, C-7a), 154.3 (s, C-2).
GC retention time	16.31 min with Toan_25min method
MS analyst, m/z (Int.)	321(21), 320(100), 291(13), 289(11), 264(12), 206(18), 190(10), 118(12).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 321.1028, m/z (measured) = 321.1039, difference = -3.83 ppm.

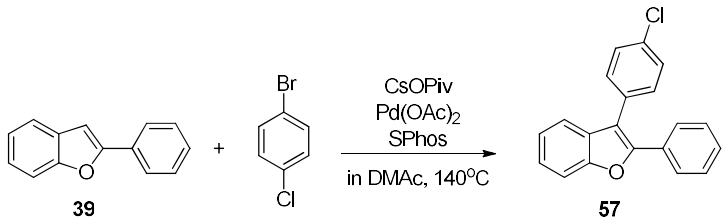
D III.8.13 Synthesis of 2,3-diphenylbenzo[*b*]furan (51)



39 51

General procedure	F
Reaction scale	48.5 mg (0.25 mmol)
Purification	MPLC, LP, 9 g silica 60
R_f	0.70 in LP
Yield	32 mg (47%), white solid
Molecular formular, m.w.	$C_{20}H_{14}O$, 270.32 g/mol
Melting point	122 – 123 °C (Lit. 121 °C)[112]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.18 – 7.59 (m, 12H, Ar-H), 7.59 – 7.72 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.1 (d, C-7), 117.5 (d, C-3), 120.0 (d, C-4), 122.9 (d, C-5), 124.7 (d, C-6), 127.0 (d, 2C, C-2' + C-6'), 127.6 (d, C-4'), 128.4 (d, C-4''), 128.4 (d, 2C, C-2'' + C-6''), 129.0 (d, 2C, C-3'' + C-5''), 129.8 (d, 2C, C-3' + C-5'), 130.3 (s, C-3a), 130.7 (s, C-1'), 132.9 (s, C-1''), 150.5 (s, C-7a), 154.0 (s, C-2).
GC retention time	12.68 min with Toan_25min method
MS analyst, m/z (Int.)	271(21), 270(100), 269(23), 255(12), 241(30), 239(31), 207(32), 165(10), 134(15), 119(15).

D III.8.14 Synthesis of 3-(4-chlorophenyl)-2-phenylbenzo[*b*]furan (57)

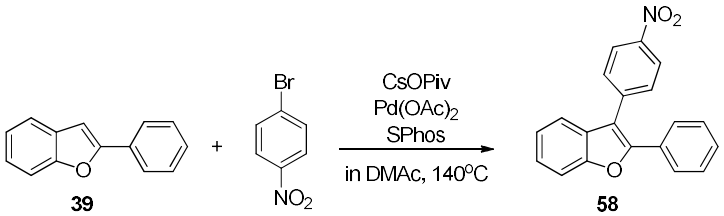


39 57

General procedure	F
Reaction scale	39 mg (0.2 mmol)
Purification	MPLC, LP, 9 g silica 60

Rf	0.70 in LP
Yield	31 mg (50%), white solid
Molecular formular, m.w.	$C_{20}H_{13}ClO$, 304.77 g/mol
Melting point	102 – 103 °C (Lit. 100 – 101 °C)[112]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.22 – 7.38 (m, 5H, Ar-H), 7.43 – 7.48 (m, 5H, Ar-H), 7.53 – 7.57 (m, 1H, H-4), 7.60 – 7.66 (m, 2H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.2 (d, C-7), 116.2 (d, C-3), 119.7 (d, C-4), 123.0 (d, C-5), 124.8 (d, C-6), 127.1 (d, 2C, C-2' + C-6'), 128.6 (d, 2C, C-2'' + C-6''), 128.6 (d, C-4'), 129.3 (d, 2C, C-3' + C-5'), 129.9 (s, C-3a), 130.4 (s, C-1'), 131.1 (d, 2C, C-3'' + C-5''), 131.4 (s, C-1''), 133.6 (s, C-4''), 150.8 (s, C-7a), 154.0 (s, C-2).
GC retention time	14.36 min with Toan_25min method
MS analyst, m/z (Int.)	306(33), 305(23), 304(100), 269(14), 268(33), 241(29), 240(16), 239(49), 207(33), 135(14), 134(46), 119(46), 118(24).

D III.8.15 Synthesis of 3-(4-nitrophenyl)-2-phenylbenzo[*b*]furan (58)



39 58

General procedure	F
Reaction scale	39 mg (0.2 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 18 g silica
Rf	0.46 in LP/EtOAc 9:1
Yield	13 mg (20%), pale yellow solid
Molecular formular, m.w.	$C_{20}H_{13}NO_3$, 315.32 g/mol
Melting point	140 – 141 °C (Lit. 135 – 138 °C)[112]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.25 – 7.42 (m, 5H, Ar-H), 7.49 – 7.63 (m, 4H, Ar-H), 7.66 – 7.71 (m, 2H, H-2' + H-6'), 8.29 – 8.34 (m, 2H, H-3'' + H-5'').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.5 (d, C-7), 115.4 (d, C-3), 119.5 (d, C-4), 123.5 (d, C-5), 124.3 (d, 2C, C-3'' + C-5''), 125.3 (d, C-6), 127.5 (d, 2C, C-2' + C-6'), 128.8 (d, 2C, C-2'' + C-6''), 128.9 (s, C-3a), 129.2 (d, C-4'), 129.8 (s, C-1'), 130.5 (d, 2C, C-3' + C-5'), 140.2 (s, C-1''), 147.1 (s, C-4''), 151.9 (s, C-7a), 154.2 (s, C-2).
MS analyst, m/z (Int.)	Does not fly over GC.

D III.8.16 Synthesis of 2-phenyl-benzo[*b*]thiophene (59)

59

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.53 in LP

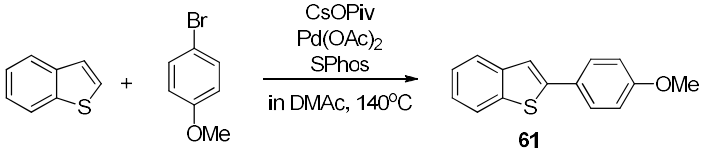
Yield	45 mg (43%), white solid
Molecular formular, m.w.	$C_{14}H_{10}S$, 210.29 g/mol
Melting point	160 – 161 °C (Lit. 164 – 168 °C)[113]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.29 - 7.46 (m, 5H, Ar-H), 7.53 (s, 1H, H-3), 7.67 - 7.84 (m, 4H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 119.5 (d, C-3), 122.3 (d, C-7), 123.6 (d, C-4), 124.3 (d, C-5), 124.5 (d, C-6), 126.5 (d, 2C, C-2' + C-6'), 128.3 (d, C-4'), 129.0 (d, 2C, C-3' + C-5'), 134.3 (s, C-1'), 139.5 (s, C-7a), 140.7 (s, C-3a), 144.3 (s, C-2).
GC retention time	9.55 min with Joey_shot_15min method
MS analyst, m/z (Int.)	211(16), 210(100), 209(12), 208(14), 178(12), 165(25).

D III.8.17 Synthesis of 2-(4-methylphenyl)-benzo[*b*]thiophene (60)

60

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.55 in LP
Yield	38 mg (34%), white solid
Molecular formular, m.w.	$C_{15}H_{12}S$, 224.32 g/mol
Melting point	164 – 165 °C (Lit. 166 – 168 °C)[76g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.38 (s, 3H, CH_3), 7.20 - 7.34 (m, 4H, Ar-H), 7.49 (s, 1H, H-3), 7.60 (d, *J* = 8.2 Hz, 2H, H-2' + H-6'), 7.72 - 7.83 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.3 (q, CH_3), 118.9 (d, C-3), 122.2 (d, C-7), 123.4 (d, C-4), 124.1 (d, C-5), 124.4 (d, C-6), 126.4 (d, 2C, C-3' + C-5'), 129.6 (d, 2C, C-2' + C-6'), 131.5 (s, C-1'), 138.3 (s, C-4'), 139.3 (s, C-7a), 140.8 (C-3a), 144.4 (s, C-2).
GC retention time	10.26 min with Joey_shot_15min method
MS analyst, m/z (Int.)	225(18), 224(100), 223(32), 221(13), 207(8), 178(7), 111(9).

D III.8.18 Synthesis of 2-(4-methoxyphenyl)-benzo[*b*]thiophene (61)

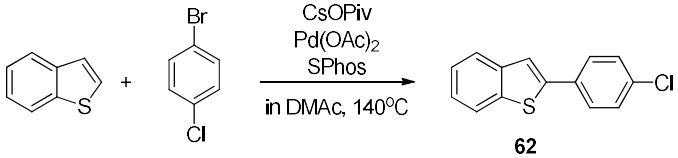


61

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc 95:5, 18 g silica 60
R_f	0.66 in LP/EtOAc 9:1
Yield	64 mg (53%), white solid
Molecular formular, m.w.	$C_{15}H_{12}OS$, 240.32 g/mol
Melting point	193 – 195 °C (Lit 188 – 190 °C)[113]

^{1}H-NMR (200 MHz, benzene-d6)	δ (ppm) = 3.85 (s, 3H, OCH_3), 6.95 (dd, J = 6.7, 2.1 Hz, 2H, H-3' + H-5'), 7.24 - 7.37 (m, 2H, H-5 + H-6), 7.42 (s, 1H, H-3), 7.62 - 7.82 (m, 4H, H4 + H-7 + H-2' + H-6').
^{13}C-NMR (100 MHz, benzene-d6)	δ (ppm) = 54.6 (q, OCH_3), 114.5 (d, 2C, C-3' + C-5'), 118.6 (d, C-3), 122.3 (d, C-7), 123.4 (d, C-4), 124.1 (d, C-5), 124.5 (d, C-6), 127.7 (s, C-1'), 127.9 (d, 2C, C-2' + C-6'), 139.5 (s, C-7a), 139.7 (s, C-3a), 141.3 (s, C-2), 160.1 (s, C-4').
GC retention time	11.06 min with Joey_shot_15min method
MS analyst, m/z (Int.)	240(100), 225(67), 197(46), 165(22), 152(16).

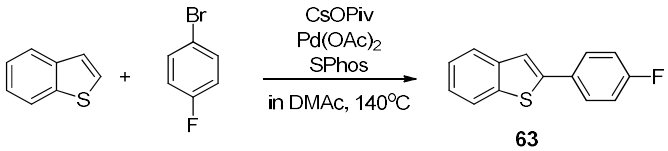
D III.8.19 Synthesis of 2-(4-chlorophenyl)-benzo[*b*]thiophene (62)



62

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.55 in LP
Yield	71 mg (58%), white solid
Molecular formular, m.w.	$C_{14}H_9ClS$, 244.74 g/mol
Melting point	200 – 201 °C (Lit. 190 – 192 °C)[76g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.23 - 7.39 (m, 4H, H-5 + H-6 + H-3' + H-5'), 7.49 (s, 1H, H-3), 7.60 (dd, J = 7.6, 2.1 Hz, 2H, H-2' + H-6'), 7.73 - 7.83 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 119.9 (d, C-3), 122.3 (d, C-7), 123.7 (d, C-4), 124.6 (d, C-5), 124.7 (d, C-6), 127.6 (d, 2C, C-2' + C-6'), 129.1 (d, 2C, C-3' + C-5'), 132.8 (s, C-1'), 134.1 (s, C-4'), 139.5 (s, C-7a), 140.6 (s, C-3a), 142.8 (s, C-2).
GC retention time	10.80 min with Joey_shot_15min method
MS analyst, m/z (Int.)	246(46), 244(100), 208(13), 165(16), 122(14), 104(10).

D III.8.20 Synthesis of 2-(4-fluorophenyl)-benzo[*b*]thiophene (63)



63

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.54 in LP
Yield	40 mg (35%), white solid
Molecular formular, m.w.	$C_{14}H_9FO$, 228.28 g/mol[114]
Melting point	183 – 184 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.08 - 7.18 (m, 2H, H-3' + H-5'), 7.28 - 7.41 (m, 2H, H-5 + H-6), 7.47 (s, 1H, H-3), 7.63 - 7.85 (m, 4H, H-4 + H-7 + H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 116.0 (d, J_{C-F} = 22Hz, 2C, C-3' + C-5'), 119.4 (d, C-3), 122.3 (d, C-7), 123.6 (d, C-4), 124.4 (d, C-5), 124.6 (d, C-6), 128.2 (d, J_{C-F} = 8Hz, 2C, C-2' + C-

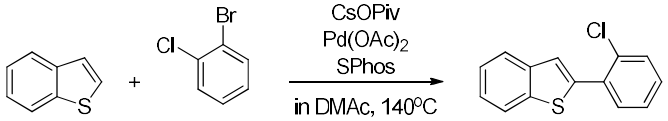
	6'), 130.6 (d, J_{C-F} = 3Hz, C-1'), 139.4 (s, C-7a), 140.7 (s, C-3a), 143.1 (s, C-2), 162.8 (d, J_{C-F} = 247 Hz, C-4').
GC retention time	9.40 min with Joey_shot_15min method
MS analyst, m/z (Int.)	229(16), 228(100), 196(13), 183(23), 114(14).

D III.8.21 Synthesis of 2-(2-methylphenyl)-benzo[*b*]thiophene (64)

64

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.53 in LP
Yield	76 mg (68%), white solid
Molecular formular, m.w.	$C_{15}H_{12}S$, 224.32 g/mol
Melting point	73 – 74 °C (Lit. 69 – 70 °C)[114]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.46 (s, 3H, CH_3), 7.21 - 7.43 (m, 6H, Ar-H), 7.46 - 7.48 (m, 1H, H-3), 7.73 - 7.85 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.1 (q, CH_3), 122.1 (d, C-3), 123.1 (d, C-7), 123.5 (d, C-4), 124.1 (d, C-5), 124.4 (d, C-6), 126.0 (d, C-6'), 128.4 (d, C-5'), 130.7 (d, C-4'), 130.8 (d, C-3'), 134.2 (s, C-1'), 136.5 (s, C-2'), 140.1 (s, C-7a), 140.2 (s, C-3a), 143.5 (s, C-2).
GC retention time	9.56 min with Joey_shot_15min method
MS analyst, m/z (Int.)	225(18), 224(100), 223(95), 221(19), 189(13).

D III.8.22 Synthesis of 2-(2-chlorophenyl)-benzo[*b*]thiophene (65)

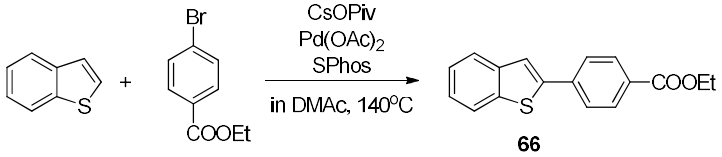


65

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60
R_f	0.58 in LP
Yield	73 mg (60%) white solid
Molecular formular, m.w.	$C_{14}H_9ClS$, 244.74 g/mol
Melting point	75 – 76 °C (Lit. 67.5 – 69 °C) [114]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.24 - 7.41 (m, 4H, Ar-H), 7.48 - 7.53 (m, 1H, Ar-H), 7.57 - 7.61 (m, 2H, H-3 + Ar-H), 7.79 - 7.87 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 122.0 (d, C-3) , 123.9 (d, C-7), 124.4 (d, C-4), 124.5 (d, C-5), 124.6 (d, C-6), 124.6 (d, C-5'), 127.0 (d, C-6'), 130.6 (d, C-3'), 131.9 (d, C-4'), 132.8 (s, C-2'), 133.2 (s, C-1'), 139.9 (s, C-7a), 140.2 (s, C-3a), 140.3 (s, C-2).
GC retention time	10.39 min with Joey_shot_15min method

MS analyst, m/z (Int.) 246(28), 244(100), 208(23), 165(40), 104(19).

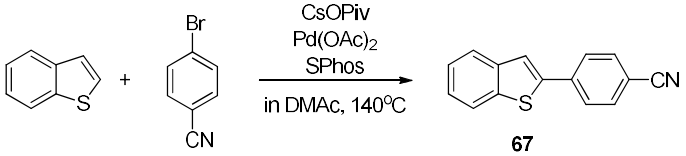
D III.8.23 Synthesis of ethyl 4-(benzo[*b*]thien-2-yl)-benzoate (66)



66

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 18 g silica 60
R_f	0.28 in LP/EtOAc 9:1
Yield	64 mg (45%), white solid
Molecular formular, m.w.	$C_{17}H_{14}O_2S$, 282.36 g/mol
Melting point	171 – 172 °C (Lit. 166 – 168 °C)[49b]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.42 (t, *J* = 7.1 Hz, 3H, CH_3), 4.41 (q, *J* = 7.1 Hz, 2H, CH_2), 7.33 - 7.38 (m, 2H, H-5 + H-6), 7.64 (s, 1H, H-3), 7.73 - 7.86 (m, 4H, Ar-H), 8.06 - 8.12 (m, 2H, H-3' + H-5').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 14.3 (q, CH_3), 61.1 (t, CH_2), 121.0 (d, C-3), 122.3 (d, C-7), 123.9 (d, C-4), 124.7 (d, C-5), 124.9 (d, C-6), 126.1 (d, 2C, C-3' + C-5'), 129.9 (s, C-1'), 130.2 (d, 2C, C-2' + C-6'), 138.4 (s, C-4'), 139.8 (s, C-7a), 140.5 (s, C-3a), 142.8 (s, C-2), 166.2 (s, C=O).
GC retention time	12.53 min with Joey_shot_15min method
MS analyst, m/z (Int.)	282(100), 254(27), 237(51), 208(38), 165(80), 119(10), 104(52).

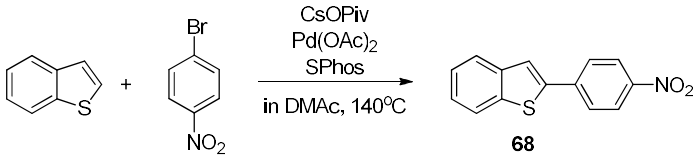
D III.8.24 Synthesis of 2-(4-cyanophenyl)-benzo[*b*]thiophene (67)



67

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 18 g silica 60
R_f	0.30 in LP/EtOAc 9:1
Yield	29 mg (25%), white solid
Molecular formular, m.w.	$C_{15}H_9NS$, 235.30 g/mol
Melting point	168 – 171 °C (Lit. 181 – 183 °C)[76g]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.33 - 7.43 (m, 2H, H-5 + H-6), 7.64 (s, 1H, H-3), 7.66 - 7.87 (m, 6H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 111.4 (s, C-4'), 118.7 (s, CN), 121.8 (d, C-3), 122.4 (d, C-7), 124.2 (d, C-4), 125.0 (d, C-5), 125.4 (d, C-6), 126.7 (d, 2C, C-2' + C-6'), 132.7 (d, 2C, C-3' + C-5'), 138.6 (s, C-1'), 140.0 (s, C-7a), 140.3 (s, C-3a), 141.7 (s, C-2).
GC retention time	11.57 min with Joey_shot_15min method
MS analyst, m/z (Int.)	236(19), 235(100), 203(10), 190(23), 118(12).

D III.8.25 Synthesis of 2-(4-nitrophenyl)-benzo[*b*]thiophene (68)



68

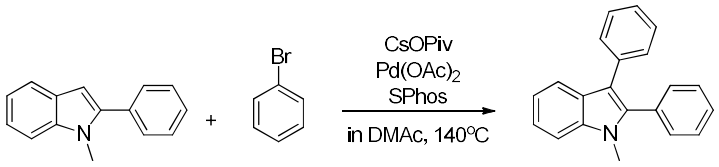
General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP/EtOAc = 9:1, 18 g silica 60
R_f	0.22 in LP/EtOAc 9:1
Yield	33 mg (26%), white solid
Molecular formular, m.w.	$C_{14}H_9ClO$, 255.29 g/mol
Melting point	213 – 214 °C (Lit. 201 – 202 °C)[84c]
^{1}H-NMR (200 MHz, DMSO)	δ (ppm) = 7.39 - 7.45 (m, 2H, H-5 + H-6), 7.89 - 7.94 (m, 1H, H4), 8.02 - 8.07 (m, 3H, H-7 + H-2' + H-6'), 8.15 (s, 1H, H-3), 8.29 - 8.33 (m, 2H, H-3' + H-5').
^{13}C-NMR (50 MHz, DMSO)	δ (ppm) = 122.6 (d, C-3), 123.5 (d, C-7), 124.5 (d, 2C, C-3' + C-5'), 124.5 (d, C-4), 125.2 (d, C-5), 125.7 (d, C-6), 126.8 (d, 2C, C-2' + C-6'), 139.4 (s, C-1'), 139.8 (s, C-7a), 140.1 (s, C-3a), 142.2 (s, C-2), 146.7 (s, C-4').
GC retention time	12.07 min with Joey_shot_15min method.
MS analyst, m/z (Int.)	255(100), 225(29), 209(21), 208 (50), 197 (17), 165 (48).

D III.8.26 Synthesis of 1-methyl-2-phenyl-1*H*-indole (69)

69

General procedure	F
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.78 in LP/EtOAc 9:1
Yield	66 mg (64%), light purple solid
Molecular formular, m.w.	$C_{15}H_{13}N$, 207.27 g/mol
Melting point	98 – 100 °C (Lit. 101 – 102 °C)[115]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.73 (s, 3H, N-CH_3), 6.56 (s, 1H, H-3), 7.10 – 7.28 (m, 2H, H-5 + H-6), 7.34 – 7.54 (m, 6H, Ar-H), 7.62 – 7.65 (m, 1H, H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 31.2 (q, N-CH_3), 101.7 (d, C-3), 109.6 (d, C-7), 119.9 (d, C-5), 120.5 (d, C-4), 121.7 (d, C-6), 127.9 (d, C-2), 128.0 (d, C-4'), 128.5 (d, 2C, C-2' + C-6'), 129.4 (d, 2C, C-3' + C-5'), 132.9 (s, C-3a), 138.4 (s, C-1'), 141.6 (s, C-7a).
GC retention time	12.61 min with Toan_25min method
MS analyst, m/z (Int.)	208(17), 207(100), 206(46), 165(12), 102(14).

D III.8.27 Synthesis of 1-methyl-2,3-diphenyl-1*H*-indole (70)

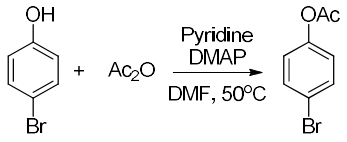


69 70

General procedure	F
Reaction scale	52 mg (0.25 mmol)
Purification	MPLC, LP, 18 g silica 60 then recrystallised in LP
R_f	0.8 in LP/EtOAc 9:1
Yield	32 mg (45%) light purple solid
Molecular formular, m.w.	$C_{21}H_{17}N$, 283.37 g/mol
Melting point	129 – 134 °C (Lit. 135 – 137 °C)[116]
Important information	Compound **70** can be decomposed quite easily under daylight. Its solution in chloroform is pink then become darker and darker purple in few hours.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.68 (s, 3H, N-CH_3), 7.15 – 7.43 (m, 13H, Ar-H), 7.79 (d, J = 8.0 Hz, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 30.9 (q, N-CH_3), 109.6 (d, C-7), 115.1 (d, C-3), 119.6 (d, C-5), 120.2 (d, C-4), 122.2 (d, C-6), 125.5 (d, C-4''), 127.0 (s, C-3a), 128.0 (d, C-4'), 128.2 (d, 2C, C-3'' + C-5''), 128.4 (d, 2C, C-3' + C-5'), 129.9 (d, 2C, C-2'' + C-6''), 131.2 (d, 2C, C-2' + C-6'), 131.9 (s, C-1'), 135.2 (s, C-1''), 137.3 (s, C-2), 137.7 (s, C-7a).
GC retention time	16.55 min with Toan_25min method
MS analyst, m/z (Int.)	284(20), 283(100), 267(25), 207(12), 133(23).

D III.9 Synthesis of bromide aryl coupling partners

D III.9.1 Synthesis of 4-bromophenyl acetate (71)



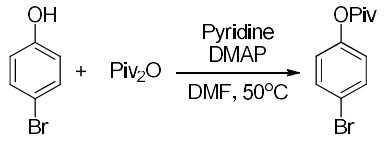
71

Using general method for esterization on phenolic compounds in the appearance of DMAP catalyst,[33] 4-bromophenol (173 mg, 1mmol), Ac_2O (110 µL, 119 mg, 1.16 mmol, 1.16 equiv.), pyridine (100 µL, 98 mg, 1.24 mmol, 1.24 equiv.) and DMAP (12 mg, 0.1 mmol, 0.1 equiv.) were dissolved in 2 mL DMF. The reaction mixture was stirred at 50 °C for 4 hours (consumption of starting material was monitored by TLC). The reaction was worked-up by quenching with saturated NH_4Cl solution to decompose DMF. Afterwards, a saturated Na_2CO_3 solution was used to neutrualize the reaction mixture. The product was extracted with Et_2O then washed for 3 times with 1M NaOH and 1 last time with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained without any further purification.

R_f	0.65 in LP/EtOAc = 9:1
Yield	187 mg (87%) colorless oil

Molecular formular, m.w.	$C_8H_7BrO_2$, 215.04 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 2.23 (s, 3H, CH_3), 6.95 (d, *J* = 8.8 Hz, 2H, H-2 + H-6), 7.44 (d, *J* = 8.8 Hz, 2H, H-3 + H-5).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 21.0 (q, CH_3), 118.8 (s, C-4), 123.5 (d, 2C, C-2 + C-6), 132.4 (d, 2C, C-3 + C-5), 149.7 (s, C-1), 169.0 (s, C=O).
GC analyst retention time	5.50 min with Joey_short method
MS analyst, m/z (Int.)	214(10), 172(100), 143(6), 93(22), 65(24).

D III.9.2 Synthesis of 4-bromophenyl pivalate (72)

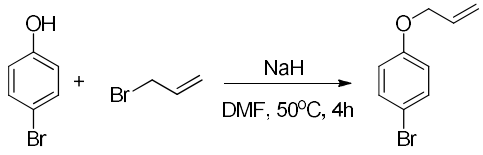


72

Similar to the esterization protocol in the synthesis of **71**, Piv_2O (300 µL, 275.4 mg, 1.48 mmol, 1.48 equiv.) was used instead as acyl source. The reaction mixture was stirred at 50 °C for 24 hours. The desired product was obtained after washing with 1M NaOH without any further purificatiton.

R_f	0.72 in LP/EtOAc = 9:1
Yield	478 mg (93%), colorless oil
Molecular formular, m.w.	$C_{11}H_{13}BrO_2$, 257.12 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.40 (s, 9H, $C(CH)_3$), 7.18 (dd, *J* = 6.7, 2.1 Hz, 2H, H-2 + H-6), 7.68 (dd, *J* = 6.7, 2.1 Hz, 2H, H-3 + H-5);
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 27.2 (q, 3C, $C(\underline{C}H_3)_3$), 38.1 (s, $\underline{C}(CH_3)_3$), 119.7 (s, C-4), 123.3 (d, 2C, C-2 + C-6), 131.5 (d, 2C, C-3 + C-5), 152.5 (s, C-1), 177.0 (s, C=O).

D III.9.3 Synthesis of 1-(allyloxy)-4-bromobenzene (73)



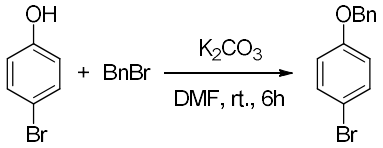
73

Allyl ether protective group was introduced by normal substitution reaction use NaH as base. [33] NaH 55% (52 mg, 1.2 mmol, 1.2 equiv.) was well stirred in 2 mL DMF. 4-Bromophenol (173 mg, 1mmol) was added to the suspension. Afterwards, allylbromide (0.1 mL, 140 mg, 1.16 mmol, 1.16 equiv.) was added dropwise. The reaction mixture was stirred at 50 °C for 4 hours (consumption of starting material was monitored by TLC) and then worked-up by quenching with saturated NH_4Cl solution. The product was extracted with EtOAc then washed for 3 times with 1M NaOH and 1 last time with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained without any further purification.

R_f	0.59 in LP
Yield	179 mg (84%), colorless oil
Molecular formular, m.w.	C_9H_9BrO, 213.07 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 4.50 (d, *J* = 5.3 Hz, 2H, H-1'), 5.28 (dd, *J* = 10.5, 2.1 Hz, 1H, H-3'), 5.40 (dd, *J* = 17.2, 2.1 Hz, 1H, H-3'), 5.98 – 6.06 (m, 1H, H-2'), 6.78 – 7.37 (m, 4H, ArH, H-2 + H-3 + H-5 + H-6);

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 68.9 (t, C-1'), 112.9 (s, C-4), 116.7 (d, 2C, C-2 + C-6), 118.0 (t, CH_2, C-3'), 131.5 (d, 2C, C-3 + C-5), 132.7 (d, C-2'), 157.6 (s, C-1).

D III.9.4 Synthesis of 1-(benzyloxy)-4-bromobenzene (74)



74

Benzyl ether protective group was introduced by normal substitution using potassium carbonate (K_2CO_3) as base. [33] 4-Bromophenol (173 mg, 1mmol), benzylbromide (170 µL, 244.5 mg, 1.43 mmol, 1.43 equiv.), K_2CO_3 (207 mg, 1.50 mmol, 1.50 equiv.) was mixed in 2 mL DMF. The reaction mixture was stirred at room temperature for 6 hours (consumption of starting material was monitored by TLC) then worked-up by quenching with NH_4Cl saturated solution. The product was extracted with EtOAc then washed for 3 times with 1M NaOH and 1 last time with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained without any further purification.

R_f	0.41 in LP
Yield	243 mg (89%), white solid
Molecular formular, m.w.	$C_{13}H_{11}BrO$, 263.13 g/mol
Melting point	60-64°C (Lit. 62 – 64)[117]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 5.02 (s, 2H, CH_2), 6.82 – 6.86 (m, 2H, H-3 + H-5), 7.34 – 7.40 (m, 7H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 70.2 (t, CH_2), 113.1 (s, C-1), 116.7 (d, 2C, C-3 + C-5), 127.5 (d, 2C, C2' + C-6'), 128.1 (d, C-4'), 128.7 (d, 2C, C-3' + C-5'), 132.3 (d, 2C, C-2 + C-6), 136.5 (s, C-1'), 157.8 (s, C-4).

D III.9.5 Synthesis of (4-bromophenoxy)trimethylsilane (75)

75

A substitution was used to introduce of sillyl ether protective groups on 4-bromophenol in appearance of imidazole. Mixture of 4-bromophenol (173 mg, 1mmol), imidazole (120 µL, 147.6 mg, 2.17 mmol, 2.17 equiv.), TMSCl (140 µL, 119.5 mg, 1.1 mmol, 1.1 equiv.) in 4 mL DCM was stirred under argon, at room temperature for 24 hours (consumption of starting material was monitored by TLC). The reaction was worked-up by quenching with saturated NH_4Cl solution. The product was extracted with EtOAc then washed for 3 times with 1M NaOH and 1 last time with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained without any further purification.

R_f	0.82 in LP
Yield	243 mg (99%) colorless liquid
Molecular formular, m.w.	$C_9H_{13}BrOSi$, 245.19 g/mol[33]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.15 (s, 9H, Si-CH_3), 6.72 (d, *J* = 8.7 Hz, 2H, H-3 + H-5), 7.04 (d, *J* = 8.7 Hz, 2H, H-2 + H-4).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 0.1 (3q, C, Si-$\underline{C}H_3$), 113.8 (s, C-1), 121.9 (d, 2C, C-3 + C-5), 132.3 (d, 2C, C-2 + C-6), 154.3 (s, C-4).

D III.9.6 Synthesis of (4-bromophenoxy)triisopropylsilane (76)

76

Similar to silyl ether protection protocol for **75**, TIPSOTf (300 µL, 342 mg, 1.12 mmol, 1.12 equiv.) was used in stead of TMSCl. The desired product was obtained after washing with 1M NaOH without any further purificatiton.

R_f 0.88 in LP

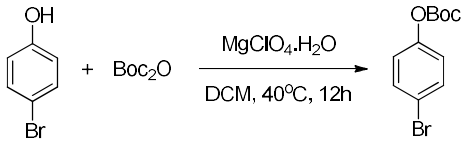
Yield 326 mg (99%) colorless liquid

Molecular formular, m.w. $C_{15}H_{25}BrOSi$, 329.35 g/mol[33]

^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.08 (d, *J* = 7.0 Hz, 18H, $(CH(C\underline{H}_3)_2)_3$), 1.15 – 1.29 (m, 3H, $(C\underline{H}(CH_3)_2)_3$), 6.75 (d, *J* = 9.0 Hz, 2H, H-3 + H-5), 7.30 (d, *J* = 9.0 Hz, 2H, H-2 + H-6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 12.6 (q, 6C, $(CH(\underline{C}H_3)_2)_3$), 17.9 (d, 3C, $(\underline{C}H(CH_3)_2)_3$), 113.2 (s, C-1), 121.7 (d, 2C, C-3 + C-5), 132.2 (d, 2C, C-2 + C-6), 155.3 (s, C-4).

D III.9.7 Synthesis of 4-bromophenyl tert-butyl carbonate (77)



77

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 4-bromophenol (173 mg, 1mmol), Boc_2O (501 mg, 2.3 mmol, 2.3 equiv.) and $Mg(ClO_4)_2.H_2O$ (24 mg, 0.1 mmol, 0.1 equiv.) in 4 mL DCM The reaction mixture was stirred at 40 °C for 12 hours (consumption of starting material was monitored by TLC). The reaction was worked-up by quenching with saturated NH_4Cl solution. The product was extracted with EtOAc then washed for 3 times with 1M NaOH and 1 last time with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained without any further purification.

R_f 0.68 in LP

Yield 254 mg (93%) white solid

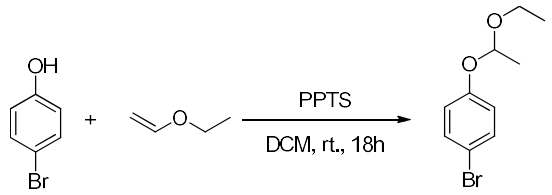
Molecular formular, m.w. $C_{11}H_{13}BrO_3$, 273.13 g/mol

Melting point 51 – 54 °C (Lit. 53 °C)[118]

^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.40 (s, 9H, $C(CH_3)_3$), 7.06 (dd, *J* = 8.7, 2.1 Hz, 2H, H-3 + H-5), 7.45 (dd, *J* = 8.7, 2.1 Hz, 2H, H-2 + H-6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) = 28.2 (q, 3C, $C(\underline{C}H_3)_3$), 84.4 (s, $\underline{C}(CH_3)_3$), 119.3 (s, C-1), 123.6 (d, 2C, C-3 + C-5), 132.9 (d, 2C, C-2 + C-6), 150.7 (s, C-4), 152.0 (s, C=O).

D III.9.8 Synthesis of 1-bromo-4-(1-ethoxyethoxy)benzene (78)

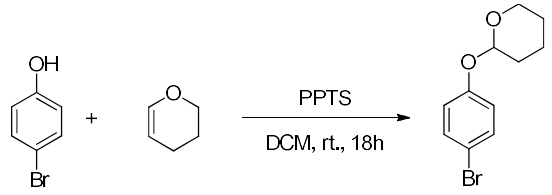


78

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 4-bromophenol (173 mg, 1 mmol) and pyridinium *p*-toluenesulfonate (25 mg, 0.1 mmol, 0.1 equiv.) in catalytic amount. The vial was evacuated and filled with argon (3 times). Dried DCM (2 mL) was added to dissolve the mixture and then ethyl vinyl ether (288 µL, 216 mg, 3.0 equiv.) was added slowly. The reaction was stirred at room temperature for 18 hours then diluted with Et_2O (15 mL) followed by the removal of excessive phenol using 3 times washing with aq 1M NaOH (3 x 10 mL). The organic phase was washed again with H_2O (3 x 10 mL) and a last time with 10 mL brine then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the desired product without any further purification procedure.

R_f	0.47 in LP/EtOAc 9:1
Yield	196 mg (80%) colorless oil
Molecular formular, m.w.	$C_{10}H_{13}BrO_2$, 245.11 g/mol[119]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.19 (t, 3H, CH_3), 1.48 (d, 3H, CH_3), 3.49 – 3.62 (m, 2H, OCH_2), 5.36(q, 1H, OCH), 6.89 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.37(dd, *J* = 8.7, 2.1 Hz, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 15.4 (q, $CH_2\underline{C}H_3$), 24.2 (q, $CH\underline{C}H_3$), 62.9 (t, CH_2), 106.8 (d, CH), 114.8 (s, C-1), 118.4 (2C, C-2 + C-6), 132.4 (2C, C-3 + C-5), 156.9 (C-4).

D III.9.9 Synthesis of 2-(4-bromophenoxy)tetrahydro-2H-pyran (79)

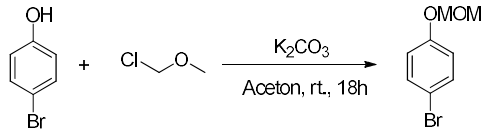


79

Similar to the synthesis protocol of **78**, 3,4-dihydropyran was used instead of ethyl vinyl ether. The desired product was obtained after washing with 1M NaOH without any further purificatiton.

R_f	0.43 in LP/EtOAc 9:1
Yield	239 mg (93%) white solid
Melting point	55 – 58 °C (Lit. 57 °C)[119]
Molecular formular, m.w.	$C_{11}H_{13}BrO_2$, 257.12 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.55 – 2.01 (m, 6H, H-5 + H-4 + H-3), 3.55 – 3.60 (m, 1H, H-6), 3.70 – 3.89 (m, 1H, H-6), 5.35 (t, *J* = 3.0 Hz, 1H, H-2), 6.92 (d, *J* = 8.9 Hz, 2H, H-3' + H-5'), 7.35 (d, *J* = 8.9 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.6 (t, C-4), 25.1 (t, C-5), 30.2 (t, C-3), 62.0 (t, C-6), 96.5 (d, C-2), 113.8 (s, C-4'), 118.3 (d, 2C, C-2' + C-6'), 132.2 (d, 2C, C-3' + C-5'), 156.1 (s, C-1').

D III.9.10 Synthesis of 1-bromo-4-(methoxymethoxy)benzene (80)

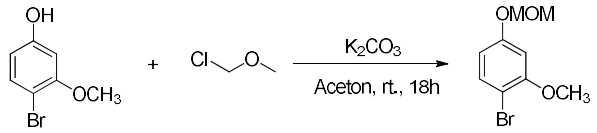


80

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 4-bromophenol (173 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv. The vial was evacuated and filled with argon (3 times). Dried acetone (2 mL) was added to dissolve the mixture, then MOM chloride (83 µL, 88 mg, 1.1 equiv.) was added slowly. The reaction was stirred at room temperature for 18 hours and then diluted by Et_2O (15 mL) followed by the removal of excessive phenol and MOM chloride using 3 times washing with aq 1M NaOH (3 x 10 mL). The organic phase was washed again with H_2O (3 x 10 mL) and a last time with 10 mL brine then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the desired product without any further purification procedure.

R_f	0.40 in LP/EtOAc 9:1
Yield	171 mg (79%) colorless oil
Molecular formular, m.w.	$C_8H_9BrO_2$, 217.06 g/mol[33]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.47 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2O), 6.94 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.0 (q, OCH_3), 94.5 (t, OCH_2O), 114.2 (s, C-1), 118.1 (d, 2C, C-2 + C-6), 132.3 (d, 2C, C-3 + C-5), 156.4 (s, C-4).

D III.9.11 Synthesis of 1-bromo-2-methoxy-4-(methoxymethoxy)benzene (81)

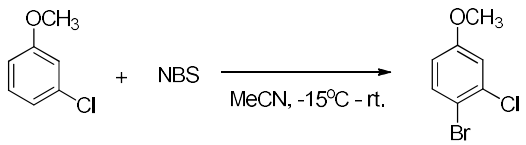


81

Similar to the synthesis of **80**, 4-bromo-3-methoxyphenol (203 mg, 1 mmol) was used as starting material. The desired product was obtained after washing with 1M NaOH without any further purificatiton.

R_f	0.38 in LP/EtOAc 9:1
Yield	202 mg (82%) colorless oil
Molecular formular, m.w.	$C_9H_{11}BrO_3$, 247.09 g/mol[33]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.47 (s, 3H, $OCH_2O\underline{C}H_3$), 3.86 (s, 3H, OCH_3), 5.15 (s, 2H, $O\underline{C}H_2OCH_3$), 6.55 (dd, *J* = 8.6, 2.7 Hz, 1H, H-5), 6.62 (d, *J* = 2.6 Hz, 1H, H-3), 7.39 (d, *J* = 8.7 Hz, 1H, H-6).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 56.1 (q, 2C, $OCH_2O\underline{C}H_3$ + OCH_3), 95.6 (t, $O\underline{C}H_2OCH_3$), 114.5 (s, C-1), 115.2 (d, C-3), 117.7 (d, C-5), 123.5 (d, C-6), 145.7 (s, C-4), 150.5 (s, C-2).

D III.9.12 Synthesis of 1-bromo-2-chloro-4-methoxybenzene (82)



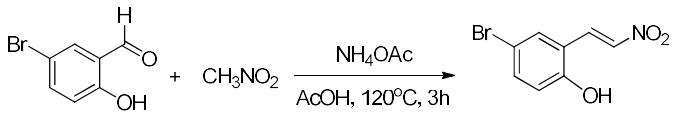
82

A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 3-methoxy chlorobenzene (245 µL, 285 mg, 2 mmol) dissolved in 4mL MeCN. The reaction vial was evacuated and filled with argon for 3 times. $HBF_4.Et_2O$ (300 µL, 356 mg, 2.2 mmol, 1.1 equiv.) was added subsequently. The reaction was stirred and cooled to -15 °C. Afterwards, NBS (356 mg, 2mmol, 1.0 equiv.) was added slowly into the reaction solution at -15 °C. Then the reaction was warmed to room temperature and stirred 4 more hours. The reaction was worked up by quenching with $NaHSO_3$ sat., and then it was extracted with EtOAc. The organic phase was washed again with H_2O (3 x 10 mL) and a last time with 10 mL brine then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification was performed on MPLC with eluent LP/EtOAc 98:2 to obtain the desired product.

R_f	0.61 in LP/EtOAc 9:1
Yield	266 mg (60%) colorless oil
Molecular formular, m.w.	C_7H_6BrClO, 221.48 g/mol[120]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.78 (s, 3H, OCH_3), 6.68 (dd, *J* = 8.8, 2.6 Hz, 1H, H-5), 7.00 (d, *J* = 2.6 Hz, 1H, H-3), 7.46 (d, *J* = 8.8 Hz, 1H, H-6).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.7 (q, OCH_3), 112.8 (s, C-1), 114.4 (d, C-5), 115.8 (d, C-3), 133.8 (s, C-2), 134.8 (d, C-6), 159.3 (s, C-4).
GC analyst retention time	7.83 min with Toan_20min method
MS analyst, m/z (Int.)	222(100), 220(78), 207(26), 205(20), 179(25), 177(20), 111(7), 63(9)

D III.10 Synthesis of 5-halo benzo-fused heterocycles.

D III.10.1 Synthesis of (*E*)-4-bromo-2-(2-nitrovinyl)phenol (84)

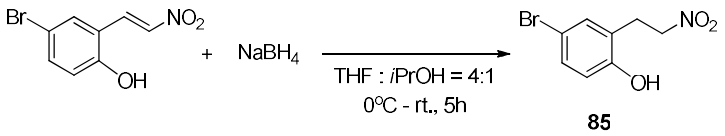


84

A 150 mL 3-neck round bottom flask with magnetic stirring bar was charged with 5-bromo-2-hydroxybenzaldehyde (2.01 g, 10.0 mmol) and ammonium acetate (1.54 g, 20.0 mmol, 2 equiv.), dissolved in 40 mL of glacial acetic acid. Nitromethane (5.36 mL, 6.11 mg, 100.0 mmol, 10 equiv.) was added slowly into the solution. A condenser was added and the reaction was heated at reflux (120 °C) for 2 hours. The resulting homogeneous solution was cooled and neutralized by a saturated solution of Na_2CO_3 to pH = 5. The obtained solution was extracted 3 times with 50 mL Et_2O. Organic phase was collected and washed for 3 times with 25 mL water and 1 last time with 25 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. Purification was performed on silica gel eluting with LP/Et_2O (8:2) mixtures. Product **84** appeared as yellow solid (1.98 g, 8.1 mmol) in 81% yield.

R_f	0.45 with LP/Et_2O 1:1
Molecular formular, m.w.	$C_8H_6BrNO_3$, 244.04 g/mol
Melting point	120 – 125 °C (Lit. 124 – 127 °C)[121]
^{1}H-NMR (200 MHz, DMSO)	δ (ppm) = 6.93 (d, *J* = 8.8 Hz, 1H, H-5), 7.41 (dd, *J* = 8.8, 2.4 Hz, 1H, H-6), 7.82 (d, *J* = 2.4 Hz, 1H, H-1'), 8.23 – 7.98 (m, 2H, H-2 + H-2'), 11.02 (s, 1H, OH).
^{13}C-NMR (50 MHz, DMSO)	δ (ppm) = 110.6 (s, C-1), 118.2 (s, C-3), 118.9 (d, C-5), 133.4 (d, C-2), 133.9 (d, C-6), 135.3 (d, C-2'), 138.2 (d, C-1'), 157.3 (s, C-4).
MS analyst, m/z (Int.)	Does not fly over GCMS

D III.10.2 4-Bromo-2-(2-nitroethyl)phenol (85)

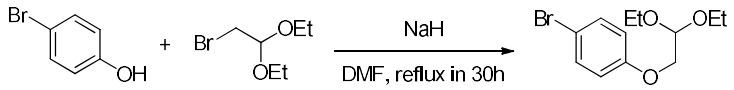


85

A 100 mL round bottom flask with magnetic stirring bar was charged with **84** (488 mg, 2.0 mmol), dissolved by 30 mL mixture solvent *i*-PrOH/THF (1:4). The solution was cooled to 0 °C in an ice bath. $NaBH_4$ (228 mg, 4.0 mmol, 2 equiv.) was added slowly while the temperature was not higher than 0 °C. Afterwards, the reaction was stirred for 4 more hours at 0 °C. The resulting solution was neutralized by an excess amount of saturated NH_4Cl solution. The obtained solution was extracted 3 times with 30 mL Et_2O. The organic phase was collected and washed for 3 times with 20 mL water and 1 last time with 20 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. Purification was performed on silica gel eluting with LP/Et_2O (8:2) mixtures. Product appeared as pale yellow solid (384 mg, 1.56 mmol) in 78% yield.

R_f	0.57 with LP:Et_2O 1:1
Molecular formular, m.w.	$C_8H_8BrNO_3$, 246.06 g/mol
Melting point	60 – 63 °C (Lit. 55 – 56 °C)[122]
^{1}H-NMR (200 MHz, $CDCl_3$)	3.26 (t, *J* = 7.1 Hz, 2H, H-1'), 4.64 (t, *J* = 7.1 Hz, 2H, H-2'), 6.62 (d, *J* = 8.6 Hz, 1H, H-5), 7.30 – 7.08 (m, 2H, H-2 + H-6), 7.36 (s, 1H, OH).
^{13}C-NMR (50 MHz, $CDCl_3$)	28.5 (t, C-1'), 74.3 (t, C-2'), 112.7 (s, C-1), 117.1 (d, C-6), 124.4 (d, C-5), 131.6 (s, C-3), 133.6 (d, C-2), 153.1 (s, C-4).

D III.10.3 Synthesis of 1-bromo-4-(2,2-diethoxyethoxy)benzene (86)

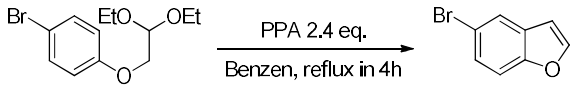


86

A 100 mL round bottom flask with magnetic stirring bar was charged with NaH 55% (0.567 g, 0.013 mmol, 1.3 equiv.) suspended in 20 mL DMF. 4-Bromophenol (1.73 g, , 0.01 mol) was added to the mixture subsequently. The solution was cooled to 0 °C in an ice bath. Bromoacetaldehyde diethyl acetal (2.56 g, 1.95 mL, 0.013 mmol, 1.3 equiv.) was added slowly maintaining the temperature below 0 °C. Afterwards, the reaction was refluxed for 24 more hours. The resulting solution was neutralized by excess amount of saturated solution of NH_4Cl. The obtained solution was extracted 3 times with 20 mL EtOAc. The organic phase was collected and washed for 3 times with 15 mL 1M NaOH and 1 last time with 15 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. Product **86** appeared as pale brown oil (2.53 g, 0.009 mol) in 87% yield, NMR indicated a purity of >98%.

R_f	0.65 with LP/EtOAc = 9:1
Molecular formular, m.w.	$C_{12}H_{17}BrO_3$, 289.17 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	1.23 (t, *J* = 7.1 Hz, 6H, CH_3), 3.53 – 3.82 (m, 4H, CH_2), 3.95 (d, *J* = 5.2 Hz, 2H, C-1'), 4.80 (t, *J* = 5.2 Hz, 1H, C-2'), 6.77 – 6.81 (m, 2H, H-3 + H-5), 7.33 – 7.37 (m, 2H, H-2 + H-6).
^{13}C-NMR (50 MHz, $CDCl_3$)	15.3 (q, 2C, CH_3), 62.6 (t, 2C, CH_2), 68.7 (d, C-2'), 100.4 (t, C-1'), 113.1 (s, C-1), 116.4 (d, 2C, C-2 + C-6), 132.2 (d, 2C, C-3 + C-5), 157.7 (s, C-4).
GC retention time	does not fly over GCMS

D III.10.4 Synthesis of 5-bromobenzo[*b*]furan (87)

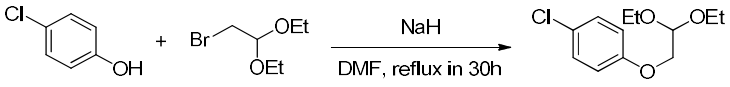


87

A 100 mL round bottom flask with magnetic stirring bar was charged with **86** (2.31 g, 0.008 mol) and PPA (1.92 g, 0.0192 mol, 2.4 equiv.), dissolved in 40 mL benzene. The reaction was refluxed for 5 hours. The resulting solution was neutralized by excess amount of saturated solution of Na_2CO_3. The obtained solution was extracted 3 times with 30 mL EtOAc. The organic phase was collected and washed for 3 times with 20 mL NH_4Cl sat. and 1 last time with 20 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The crude mixture was distilled under reduced pressure to obtain the desired product at 90 °C and 14 – 17 mBar. Product **87** appeared as colorless oil (914 mg, 4.64 mmol) in 58% yield.

R_f	0.58 with LP 100%
Molecular formular, m.w.	C_8H_5BrO, 197.03 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	6.72 (d, *J* = 2.2 Hz, 1H, H-3), 7.38 – 7.39 (m, 2H, H-4 + H-7), 7.62 (d, *J* = 2.2 Hz, 1H, H-2), 7.73 (m, 1H, H-6).
^{13}C-NMR (50 MHz, $CDCl_3$)	106.1 (d, C-3), 112.8 (d, C-7), 115.8 (s, C-5), 123.8 (d, C-4), 127.2 (d, C-6), 129.4 (s, C-3a), 146.1 (d, C-2), 153.7 (s, C-7a).
GC retention time	5.14 min with Joey_short method
MS analyst, m/z (Int.)	198(93), 197(10), 196(100), 117(38), 89(84), 63(32)

D III.10.5 Synthesis of 1-chloro-4-(2,2-diethoxyethoxy)benzene (89)

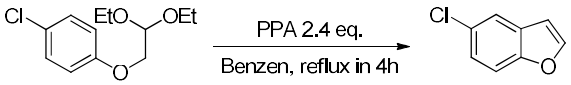


89

A 150 mL round bottom flask with magnetic stirring bar was charged with NaH 55% (2.27 g, 0.052 mol, 1.3 equiv.) suspended in 80 mL DMF. 4-Chlorophenol (3.91 mL, 5.14 g, 0.04 mol) was added to the mixture subsequently. The solution was cooled to 0 °C in an ice bath. Bromoacetaldehyde diethyl acetal (10.25 g, 7.8 mL, 0.052 mmol, 1.3 equiv.) was added slowly while the temperature was kept below 0 °C. Afterwards, the reaction was refluxed for 24 more hours. The resulting solution was neutralized by excess amount of saturated solution of NH_4Cl. The obtained solution was extracted 3 times with 50 mL EtOAc. The organic phase was collected and washed for 3 times with 30 mL 1M NaOH and 1 last time with 30 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The product appeared as brown oil (6.95 g, 0.028 mol), 71% yield, NMR indicated a purity of >98%.

R_f	0.58 with LP/EtOAc = 9:1
Molecular formular, m.w.	$C_{12}H_{17}ClO_3$, 244.72 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	1.24 (t, *J* = 7.1 Hz, 6H, CH_3), 3.55 – 3.84 (m, 4H, CH_2), 3.97 (d, *J* = 5.2 Hz, 2H, C-1'), 4.81 (t, *J* = 5.2 Hz, 1H, C-2'), 6.82 – 6.87 (m, 2H, H-2' + H-6'), 7.20 – 7.24 (m, 2H, H-3' + H-5').
^{13}C-NMR (50 MHz, $CDCl_3$)	15.3 (q, 2C, CH_3), 62.7 (t, 2C, CH_2), 68.8 (t, C-1'), 100.4 (d, C-2'), 115.9 (d, 2C, C-3 + C-5), 125.8 (s, C-1), 129.3 (d, 2C, C-2 + C-6), 157.2 (s, C-4).
GC retention time	7.38 min with Toan_20min method
MS analyst, m/z (Int.)	244(2), 199(2), 155(14), 153(39), 111(22), 103(100), 75(68).

D III.10.6 Synthesis of 5-chlorobenzo[*b*]furan (90)

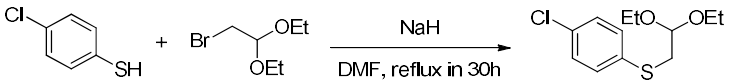


90

A 150 mL round bottom flask with magnetic stirring bar was charged with **89** (4.96 g, 0.02 mol), dissolved in 100 mL benzene. The solution was warmed to 40 – 50 °C in an oil bath, then PPA (5 g, 0.05 mol, 2.4 equiv.) was added. Afterwards, the reaction was refluxed for 18 more hours. The resulting solution was neutralized by excess amount of saturated solution of Na_2CO_3. The obtained solution was extracted 3 times with 50 mL EtOAc. The organic phase was collected and washed for 3 times with 30 mL NH_4Cl sat. and 1 last time with 30 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The crude mixture distillated under reduced pressure to obtain the desired product at 70 °C and 14 – 17 mBar pressure. Product appeared as transparent oil (1.77 g, 0.012 mol), 58% yield.

R_f	0.57 with LP
Molecular formular, m.w.	C_8H_5ClO, 152.58 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	6.70 – 6.71 (m, 1H, H-3), 7.24 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.41 (d, *J* = 8.7 Hz, 1H, H-7), 7.56 (d, *J* = 2.0 Hz, 1H, H-2), 7.62 (d, *J* = 2.1 Hz, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	106.3 (d, C-3), 112.4 (d, C-7), 120.8 (d, C-4), 124.5 (d, C-6), 128.3 (s, C-5), 128.8 (s, C-3a), 146.3 (d, C-2), 153.3 (s, C-7a).
GC retention time	3.937 min with Toan_20min method
MS analyst, m/z (Int.)	154(33), 152(100), 124(10), 89(41), 71(14), 57(20).

D III.10.7 Synthesis of (4-chlorophenyl)(2,2-diethoxyethyl)sulfane (98)

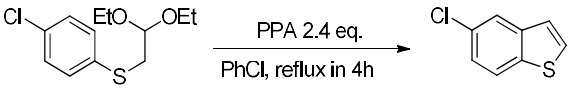


98

A 150 mL round bottom flask with magnetic stirring bar was charged with NaH 55% (2.27 g, 0.052 mol, 1.3 equiv.) suspended in 80 mL DMF. 4-Chlorobenzenthiol (5.78 g, 0.04 mol) was added to the mixture subsequently. The solution was cooled to 0 °C in an ice bath. Bromoacetaldehyde diethyl acetal (10.25 g, 7.8 mL, 0.052 mmol, 1.3 equiv.) was added slowly while the temperature was below 0 °C. Afterwards, the reaction was refluxed for 24 more hours. The resulting solution was neutralized by excess amount of saturated solution of NH_4Cl. The obtained solution was extracted 3 times with 50 mL EtOAc. The organic phase was collected and washed for 3 times with 30 mL 1M NaOH and 1 last time with 30 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The product appeared as brown oil (8.76 g, 0.034 mol), 84% yield, NMR indicated a purity of >98%.

R_f	0.57 with LP/EtOAc = 9:1
Molecular formular, m.w.	$C_{12}H_{17}ClO_2S$, 260.78 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	1.19 (t, 6H, *J* = 7 Hz, CH_3), 3.10 (d, 2H, *J* = 6 Hz, CH_2), 3.46-3.75 (m, 4H, H-1'), 4.63 (t, 1H, H-2'), 7.21-7.33 (m, 4H, Ar-H).

D III.10.8 Synthesis of 5-chlorobenzo[*b*]thiophene (99)

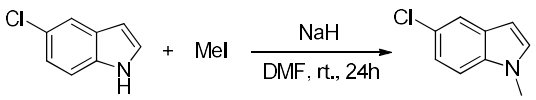


98 **99**

A 150 mL round bottom flask with magnetic stirring bar was charged with **98** (5.216 g, 0.02 mol), dissolved in 100 mL chlorobenzene. The solution was warmed to 40 – 50 °C in an oil bath then PPA (5 g, 0.05 mol, 2.4 equiv.) was added. Afterwards, the reaction was refluxed for 18 more hours. The resulting solution was neutralized by excess amount of saturated solution of Na_2CO_3. The obtained solution was extracted 3 times with 50 mL EtOAc. The organic phase was collected and washed for 3 times with 30 mL NH_4Cl sat. and 1 last time with 30 mL brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The crude mixture was distilled under reduced pressure to obtain the desired product at 85 °C and 14 – 17 mBar pressure. The product appeared as transparent oil (2.19 g, 0.013 mmol) in 63% yield.

R_f	0.51 with LP
Molecular formular, m.w.	C_8H_5ClS, 168.64 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.22-7.30 (m, 2H, H-2 + H-6), 7.46 (d, 1H, *J* = 6 Hz, H-3), 7.73-7.77 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 123.1 (d, C-4), 123.2 (d, C-3), 123.4 (d, C-7), 124.7 (d, C-6), 128.3 (d, C-2), 130.5 (s, C-5), 137.9 (s, C-7a), 140.8 (d, C-3a).
GC retention time	5.65 min with Joey_short method
MS analyst, m/z (Int.)	170 (35), 169 (11), 168 (100), 133 (19), 89 (13)

D III.10.9 Synthesis of 5-chloro-1-methyl-1*H*-indole (145)



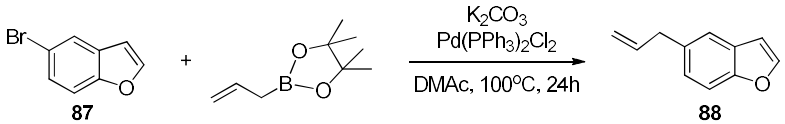
145

A 7 mL vial with magnetic stirring bar was charged with 5-chloro-1H-indole (302 mg, 2 mmol) and NaH 55% (113 mg, 2.6 mmol, 1.3 equiv.) dissolved in 4 mL chlorobenzene. MeI (160 µL, 366 mg, 2.6 mmol, 1.3 equiv.) was added slowly by syringe. The reaction was stirred at room temperature for 24 hours. The resulting solution was neutralized by excess amount of saturated solution of Na_2CO_3. The obtained solution was extracted 3 times with 50 mL EtOAc. The organic phase was collected and washed for 3 times with NH_4Cl sat. and 1 last time with brine. The solution of product was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. Purification was performed on MPLC with eluent LP/EtOAc 95:5. The product appeared as colorless oil (298 mg, 1.8 mol) in 90% yield.

Rf	0.53 with LP/EtOAc 9:1
Molecular formular, m.w.	C_9H_8ClN, 165.62 g/mol
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.78 (s, 3H, N-CH_3), 6.46 (d, *J* = 3 Hz, 1H, H-3), 7.09 (d, *J* = 3 Hz, 1H, H-2), 7.20 (d, J = 11 Hz, 2H, H-6 + H-7), 7.63 (s, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 33.0 (q, N-CH_3), 100.6 (d, C-3), 110.2 (d, C-7), 120.2 (d, C-4), 121.8 (d, C-6), 125.1 (s, C-5), 129.5 (s, C-3a), 130.2 (d, C-2), 135.1 (s, C-7a).
GC retention time	5.65 min with Joey_short method
MS analyst, m/z (Int.)	170 (35), 169 (11), 168 (100), 133 (19), 89 (13)

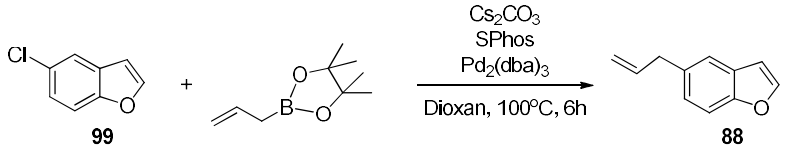
D III.11 Suzuki coupling on of 5-halidebenzo[*b*]furan.

D III.11.1 Synthesis of 5-allylbenzo[*b*]furan (88)



87 88

Procedure 1: A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with **87** (98 mg, 0.5 mmol), allyl-B(pin) (allylboronic acid pinacole ester) (126 mg, 140 µL, 0.75 mmol, 1.5 equiv.), K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv.) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol, 5 mol %). The vial was evacuated and filled with argon (3 times) then the mixture was dissolved in 1 mL DMAc and stirred at 100°C for 24h. The reaction mixture was then cooled to rt. and filtered through celite, washed with EtOAc (3 x 10 mL). The product was washed with saturated aqu. NH_4Cl (3 x 10 mL) and a last time with 10 mL brine then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain coupling product **88** (67 mg, colorless oil), 85% yield, NMR indicated a purity of >95%..

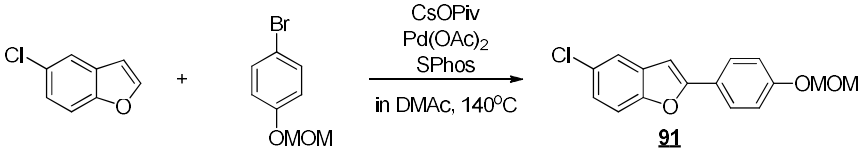


Procedure 2: A 7 mL vial equipped with a screw cap, septum and a magnetic stirring bar was charged with 5-chlorobenzo[*b*]furan (76 mg, 0.5 mmol), allyl-B(pin) (126 mg, 140 µL, 0.75 mmol, 1.5 equiv.), Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 equiv.), SPhos (21 mg, 0.05 mmol, 10 mol %) and $Pd_2(dba)_3$ (23 mg, 0.025 mmol, 5 mol %). The vial was evacuated and filled with argon (3 times) then the mixture was dissolved in 2 mL DMAc and stirred at 100°C for 6h. The reaction mixture was then cooled to rt. and filtered through celite and washed with EtOAc (3 x 10 mL). The product was washed with saturated aqu. NH_4Cl (3 x 10 mL) and a last time with 10 mL brine then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain coupling product **88** (54 mg, colorless oil) , 68% yield, NMR indicated a purity of >95%..

R_f	0.67 with LP
Molecular formular, m.w.	$C_{11}H_{10}O$, 158.20 g/mol[123]
^{1}H-NMR (200 MHz, $CDCl_3$)	3.51 (d, J = 6.7 Hz, 2H, H-1'), 5.08 – 5.17 (m, 2H, H-3'), 5.95 – 6.15 (m, 1H, H-2'), 6.73 – 6.75 (m, 1H, H-3), 7.16 (d, *J* = 8.6 Hz, 1H, H-6), 7.44 – 7.48 (m, 2H, H-4 + H-7), 7.62 (d, *J* = 2.1 Hz, 1H, H-2).
^{13}C-NMR (50 MHz, $CDCl_3$)	40.1 (t, C-1'), 106.4 (d, C-3), 111.1 (d, C-7), 115.6 (t, C-3'), 120.7 (d, C-4), 125.1 (d, C-6), 127.6 (s, C-3a), 134.5 (s, C-5), 138.0 (d, C-2'), 145.1 (d, C-2), 153.7 (s, C-7a).
GC retention time	4.77 min with Joey_short method
MS analyst, m/z (Int.)	158(100), 157(46), 129(82), 128(50), 115(18), 102(10), 89(10), 77(22), 63(15).

D III.12 C-H activation on 5-chloro benzo-fused heterocycles.

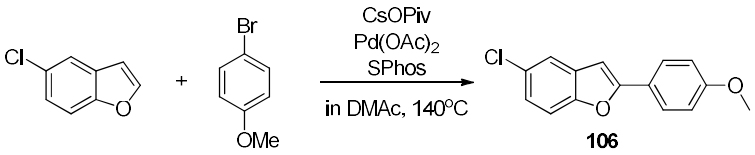
D III.12.1 Synthesis of 5-chloro-2-(4-(methoxymethoxy)phenyl)benzofuran (91)



General procedure	F
Reaction scale	153 mg (1.0 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	173 mg (60%) white solid
Molecular formular, m.w.	$C_{16}H_{13}ClO_3$, 288.73 g/mol

R_f	0.40 with LP/EtOAc 9:1
Melting point	138 – 141 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.50 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2O), 6.82 (s, 1H, H-3), 7.09 – 7.13 (m, 2H, H-3' + H-5'), 7.19 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.39 (d, *J* = 8.7 Hz, 1H, H-7), 7.50 (d, *J* = 2.1 Hz, 1H, H-4), 7.76 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) =56.1 (q, OCH_3), 94.3 (t, OCH_2O), 99.5 (d, C-3), 111.9 (d, C-7), 116.5 (d, , 2C, C-3' + C-5'), 120.1 (d, C-4), 123.8 (s, C-1'), 123.9 (d, C-6), 126.5 (d, , 2C, C-2' + C-6'), 128.4 (s, C-5), 130.8 (s, C-3a), 153.1 (s, C-7a), 157.4 (s, C-2), 157.9 (s, C-4').
GC Retention time	15.95 min with Toan_25min method
MS analyst, m/z (Int.)	290(37), 289(16), 288(100), 260(32), 258(97), 243(67), 217(20), 215(63), 152(100), 151(44), 125(13), 99(16), 63(28)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 289.0631, m/z (measured) = 289.0636, difference = -1.90 ppm.

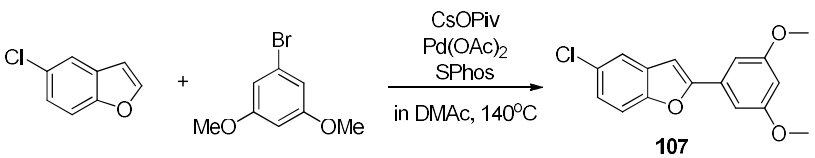
D III.12.2 Synthesis of 5-chloro-2-(4-methoxyphenyl)benzo[*b*]furan (106)



106

General procedure	F
Reaction scale	153 mg (1.0 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 5% EtOAc), 18 g silica 60 then recrystallised in LP
Yield	150 mg (58%), white solid
Molecular formular, m.w.	$C_{15}H_{11}ClO_2$, 258.70 g/mol[124]
R_f	0.73 with LP/EtOAc 9:1
Melting point	144 – 146 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.86 (s, 3H, OCH_3), 6.81 (s, 1H, H-3), 6.95 – 7.00 (m, 2H, H-3' + H-5'), 7.18 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.39 (d, *J* = 8.4 Hz, 1H, H-7), 7.50 (d, *J* = 2.1 Hz, 1H, H-4), 7.76 – 7.80 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.4 (q, OCH_3), 99.2 (d, C-3), 111.9 (d, C-7), 114.3 (d, 2C, C-3' + C-5'), 120.1 (d, C-4), 122.8 (d, C-6), 123.8 (s, C-1'), 126.6 (d, 2C, C-2' + C-6'), 128.3 (s, C-5), 130.9 (s, C-3a), 153.1 (s, C-7a), 157.5 (s, C-2), 160.3 (s, C-4').
GC Retention time	14.77 min with Toan_20min method
MS analyst, m/z (Int.)	260(30), 258(100), 245(24), 243(70), 215(46), 207(17), 152(40), 151(19), 126(12)

D III.12.3 Synthesis of 5-chloro-2-(3,5-dimethoxyphenyl)benzo[*b*]furan (107)

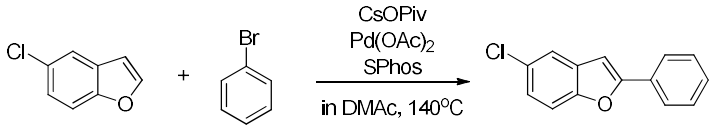


107

General procedure	F

Reaction scale	153 mg (1.0mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 5% EtOAc), 18 g silica 60 then recrystallised in LP
Yield	147 mg (51%), colorless oil
Molecular formular, m.w.	$C_{16}H_{13}ClO_3$, 288.73 g/mol[125]
R_f	0.54 with LP/EtOAc 9:1
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.86 (s, 6H, OCH_3), 6.48 (t, *J* = 2.3 Hz, 1H, H-4'), 6.93 (d, *J* = 0.8 Hz, 1H, H-3), 6.99 (d, *J* = 2.3 Hz, 2H, H-2' + H-6'), 7.23 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.42 (d, *J* = 8.7 Hz, 1H, H-7), 7.53 (d, *J* = 2.1 Hz, 1H, H-4).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 55.5 (q, 2C, OCH_3), 101.3 (d, C-4'), 101.4 (d, 2C, C-2' + C-6'), 103.2 (d, C-3), 112.1 (d, C-7), 120.5 (d, C-4), 124.5 (d, C-6), 128.5 (s, C-5), 130.5 (s, C-3a), 131.7 (s, C-1'), 153.2 (s, C-7a), 157.2 (s, C-2), 161.2 (s, 2C, C-3' + C-5').
GC Retention time	16.48 min with Toan_20min method
MS analyst, m/z (Int.)	290(33), 289(15), 288(100), 259(14), 231(13), 202(18), 152(12), 139(20), 125(13)

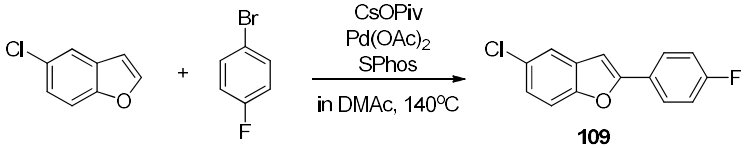
D III.12.4 Synthesis of 5-chloro-2-phenylbenzo[*b*]furan (108)



108

General procedure	F
Reaction scale	153 mg (1.0mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	100 mg (44%), white solid
Molecular formular, m.w.	$C_{14}H_9ClO$, 228.68 g/mol[126]
R_f	0.61 with LP
Melting point	125 – 128 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.96 (s, 1H, H-3), 7.20 – 7.55 (m, 6H, ArH, Ar-H), 7.81 – 7.87 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 100.8 (d, C-3), 112.1 (d, C-7), 120.4 (d, C-4), 124.4 (d, C-6), 125.0 (d, 2C, C-3' + C-5'), 128.5 (s, C–5), 128.8 (d, 2C, C-2' + C-6'), 129.0 (d, C-4'), 130.0 (s, C-1'), 130.6 (s, C-3a), 153.2 (s, C-7a), 157.4 (s, C-2).
GC Retention time	12.85 min with Toan_25min method
MS analyst, m/z (Int.)	230(33), 229(15), 228(100), 165(50), 164(14), 139(9), 114(13), 82(18)

D III.12.5 Synthesis of 5-chloro-2-(4-fluorophenyl)benzo[*b*]furan (109)

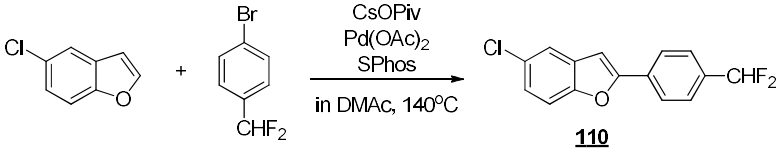


109

General procedure	F
Reaction scale	153 mg (1.0mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallised in LP

Yield	102 mg (41%), white solid
Molecular formular, m.w.	$C_{14}H_8ClFO$, 246.67 g/mol[127]
R_f	0.35 with *n*-heptane
Melting point	119 – 122 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.86 (s, 1H, H-3), 7.09 – 7.24 (m, 3H, H-6 + H-3' + H-5'), 7.38 – 7.52 (m, 2H, H-4 + H-7), 7.76 – 7.83 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 100.5 (d, J_{C-F} = 1.4 Hz, C-3), 112.1 (d, C-7), 116.0 (d, J_{C-F} = 21.9 Hz, 2C, C-3' + C-5'), 120.4 (d, C-4), 124.4 (d, C-6), 126.3 (d, J_{C-F} = 3.4 Hz, C-1'), 126.9 (d, J_{C-F} = 8.3 Hz, 2C, C-2' + C-6'), 128.6 (s, C-5), 130.5 (s, C-3a), 153.2 (s, C-7a), 156.5 (s, C-2), 163.1 (d, J_{C-F} = 247.9 Hz, C-4').
GC Retention time	12.72 min with Toan_25min method
MS analyst, m/z (Int.)	248(33), 247(15), 246(100), 183(35), 181(8), 123(10), 91(17)

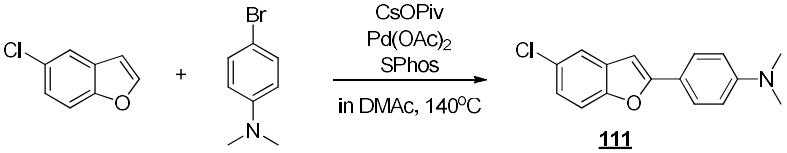
D III.12.6 Synthesis of 5-chloro-2-(4-(difluoromethyl)phenyl)benzo[*b*]furan (<u>110</u>)



<u>110</u>

General procedure	F
Reaction scale	153 mg (1.0mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallised in LP
Yield	126 mg (45%), white solid
Molecular formular, m.w.	$C_{15}H_9ClF_2O$, 278.68 g/mol
R_f	0.31 with *n*-heptane
Melting point	121 – 124 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.69 (t, J_{H-F} = 56.4 Hz, 1H, CHF_2), 7.02 (s, 1H, H-3), 7.26 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.44 (d, *J* = 8.7 Hz, 1H, H-7), 7.55 – 7.62 (m, 3H, H-4 + H-3' + H-5'), 7.90 – 7.93 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 102.1 (d, C-3), 112.2 (d, C-7), 114.4 (t, J_{C-F} = 237.6 Hz, 1C, CHF_2), 120.7 (d, C-4), 125.0 (d, C-6), 125.2 (d, 2C, C-2' + C-6'), 126.1 (t, J_{C-F} = 6.1 Hz, 2C, C-3' + C-5'), 128.7 (s, C-5), 130.3 (s, C-3a), 132.2 (t, J_{C-F} = 2.05 Hz, 1C, C-1'), 134.6 (t, J_{C-F} = 22.5 Hz, 1C, C-4'), 153.4 (s, C-7a), 156.1 (s, C-2).
GC Retention time	13.61 min with Toan_25min method
MS analyst, m/z (Int.)	280(33), 278(100), 228(13), 199(9), 163(11), 121(10), 107(18), 82(11).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 279.0388, m/z (measured) = 279.0392, difference = -1.62 ppm.

D III.12.7 Synthesis of 4-(5-chlorobenzo[*b*]furan-2-yl)-N,N-dimethylaniline (<u>111</u>)

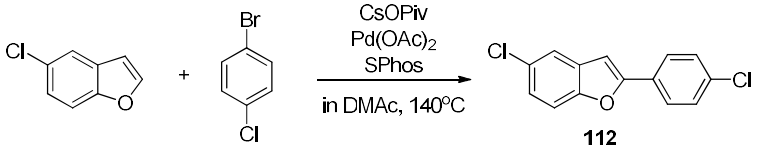


<u>111</u>

General procedure	F
Reaction scale	153 mg (1.0mmol)

Purification	MPLC with LP/EtOAc (gradient 2 – 10%), 18 g silica 60 then recrystallised in LP
Yield	134 mg (49%) white solid
Molecular formular, m.w.	$C_{16}H_{14}ClNO$, 271.74 g/mol
R_f	0.63 with LP/EtOAc 9:1
Melting point	129 – 132 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.04 (s, 6H, $N(CH_3)_2$), 6.73 – 6.79 (m, 3H, H-3 + H-2' + H-6'), 7.15 (dd, *J* = 8.6, 2.1 Hz, 1H, H-6), 7.38 (d, *J* = 8.6 Hz, 1H, H-7), 7.47 (d, *J* = 2.1 Hz, 1H, H-4), 7.70 – 7.74 (m, 2H, H-3' + H-5').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 38.1 (q, 2C, $N(CH_3)_2$), 95.3 (d, C-3), 109.4 (s, C-7), 109.9 (d, 2C, C-3' + C-5'), 117.5 (d, C-4), 120.9 (d, C-6), 124.1 (d, 2C, C-2' + C-6'), 126.0 (s, C-1'), 129.1 (s, C-5), 148.6 (s, C-3a) , 150.5 (s, C-7a), 150.7 (s, C-4'), 156.4 (s, C-2).
GC Retention time	17.25 min with Toan_25min method
MS analyst, m/z (Int.)	273(30), 271(100), 270(40), 255(16), 207(41), 163(11), 136(15), 135(36), 96(16).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 272.0842, m/z (measured) = 272.0839, difference = 1.01 ppm.

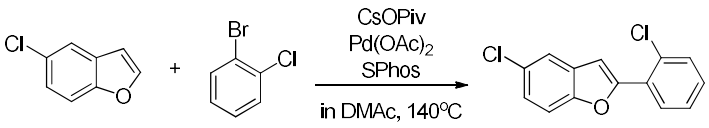
D III.12.8 Synthesis of 5-chloro-2-(4-chlorophenyl)benzo[*b*]furan (112)



112

General procedure	F
Reaction scale	153 mg (1.0mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	124 mg (47%), white solid
Molecular formular, m.w.	$C_{14}H_8Cl_2O$, 263.12 g/mol[127]
R_f	0.35 with *n*-heptane
Melting point	143 – 145 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 6.94 (d, *J* = 0.8 Hz, 1H, H-3), 7.24 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.41 – 7.44 (m, 3H, H-5 + H-3' + H-5'), 7.54 (d, *J* = 2.1 Hz, 1H, H-4), 7.75 – 7.79 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 101.2 (d, C-3), 112.1 (d, C-7), 120.5 (d, C-4), 124.7 (d, C-6), 126.3 (d, 2C, C-2' + C-6'), 128.5 (s, C-1'), 128.7 (s, C-5), 129.1 (d, 2C, C-3' + C-5'), 130.4 (s, C-3a), 134.8 (s, C-4'), 153.2 (s, C-7a), 156.3 (s, C-2).
GC Retention time	14.27 min with Toan_25min method
MS analyst, m/z (Int.)	264(63), 263(17), 262(100), 201(10), 199(31), 163(17), 131(8), 81(13)

D III.12.9 Synthesis of 5-chloro-2-(2-chlorophenyl)bqenzo[*b*]furan (113)

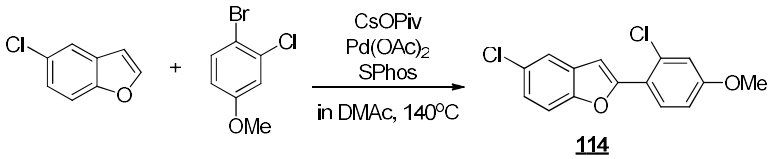


113

General procedure	F

Reaction scale	153 mg (1.0mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	58 mg (44%) colorless oil
Molecular formular, m.w.	$C_{14}H_8Cl_2O$, 263.12 g/mol[128]
R_f	0.54 with LP
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 7.26 – 7.54 (m, 6H, Ar-H), 7.61 (d, *J* = 1.9 Hz, 1H, H-3), 8.04 (dd, J = 7.7, 1.8 Hz, 1H, H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 106.8 (d, C-3), 112.0 (d, C-7), 120.9 (d, C-4), 125.1 (d, C-6), 127.0 (d, C-5'), 128.4 (s, C-5), 128.5 (d, C-6'), 129.0 (d, C-3'), 129.5 (s, C-1'), 130.4 (s, C-3a), 130.9 (d, C-4'), 131.5 (s, C-2'), 152.5 (s, C-7a), 153.4 (s, C-2).
GC Retention time	13.92 min with Toan_25min method
MS analyst, m/z (Int.)	264(66), 263(16), 262(100), 201(22), 199(65), 164(24), 163(40), 131(11), 99(17), 81(37)

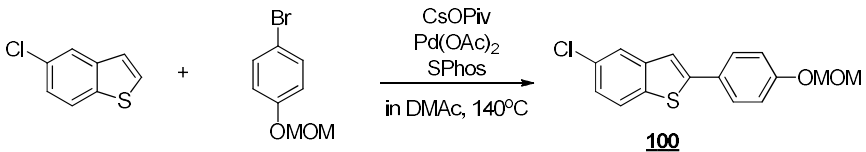
D III.12.10 Synthesis of 5-chloro-2-(2-chlorophenyl)benzo[*b*]furan (114)



114

General procedure	F
Reaction scale	153 mg (1.0mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	78 mg (53%), white solid
Molecular formular, m.w.	$C_{15}H_{10}Cl_2O_2$, 293.14 g/mol
R_f	0.31 with LP
Melting point	114 – 115 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.85 (s, 3H, OCH_3), 6.92 (dd, *J* = 8.9, 2.6 Hz, 1H, H-5'), 7.03 (d, *J* = 2.6 Hz, 1H, H-3'), 7.23 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 7.30 (s, 1H, H-3), 7.40 (d, *J* = 8.6 Hz, 1H, H-7), 7.55 (d, *J* = 2.1 Hz, 1H, H-4), 7.91 (d, *J* = 8.8 Hz, 1H, H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.6 (q, OCH_3), 105.1 (d, C-3), 111.8 (d, C-7), 113.3 (d, C-5'), 116.0 (d, C-3'), 120.6 (d, C-4), 121.3 (s, C-1'), 124.5 (d, C-6), 128.4 (s, C-5), 129.9 (d, C-6'), 130.7 (s, C-3a), 132.4 (s, C-2'), 152.3 (s, C-7a), 153.7 (s, C-2), 160.0 (s, C-4').
GC Retention time	15.94 min with Toan_25min method
MS analyst, m/z (Int.)	294(69), 293(17), 292(100), 251(25), 249(40), 214(16), 188(19), 186(50), 151(45), 146(16), 81(11), 75(26)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 293.0136, m/z (measured) = 293.0126, difference = 3.72 ppm.

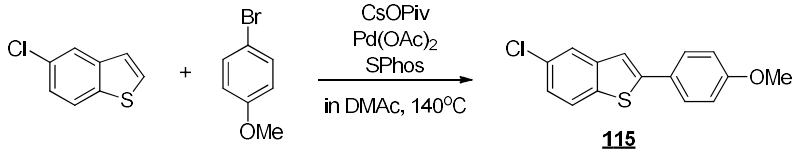
D III.12.11 Synthesis of 5-chloro-2-(4-(methoxymethoxy)phenyl)benzo[*b*]thiophene (100)



100

General procedure	F
Reaction scale	168 mg (1.0 mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	171 mg (56%), white solid
Molecular formular, m.w.	$C_{16}H_{13}ClO_2S$, 304.79 g/mol
R_f	0.53 with LP/EtOAc 9:1
Melting point	175 – 177 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.51 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2O), 7.09 – 7.12 (m, 2H, H-3' + H-5'), 7.25 (dd, *J* = 8.7, 2.0 Hz, 1H, H-6), 7.34 (s, 1H, H-3), 7.60 – 7.63 (m, 2H, H-2' + H-6'), 7.69 – 7.71 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 116.7 (d, 2C, C-3' + C-5'), 117.7 (d, C-3), 122.8 (d, C-4), 123.2 (d, C-7), 124.4 (d, C-6), 127.7 (s, C-1'), 127.8 (d, 2C, C-2' + C-6'), 130.7 (s, C-5), 137.3 (s, C-7a), 142.0 (s, C-3a), 146.1 (s, C-2), 157.7 (s, C-4').
GC Retention time	18.33 min with Toan_25min method
MS analyst, m/z (Int.)	306(37), 305(16), 304(100), 274(57), 259(31), 231(21), 207(29), 152(15), 104(17)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 305.0403, m/z (measured) = 305.0396, difference = 2.02 ppm.

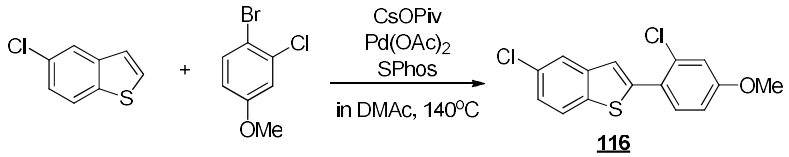
D III.12.12 Synthesis of 5-chloro-2-(4-methoxyphenyl)benzo[*b*]thiophene (115)



115

General procedure	F
Reaction scale	168 mg (1.0 mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	85 mg (31%) white solid
Molecular formular, m.w.	$C_{15}H_{11}ClOS$, 274.76 g/mol
R_f	0.65 with LP/EtOAc 9:1
Melting point	163 – 165 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.86 (s, 3H, OCH_3), 6.96 (d, *J* = 8.8 Hz, 2H, H-3' + H-5'), 7.21-7.26 (m, 1H, H-6), 7.34 (s, 1H, H-3), 7.63 (d, *J* = 8.7 Hz, 2H, H-2' + H-6'), 7.68-7.72 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 54.6 (q, OCH_3), 114.5 (d, 2C, C-3' + C-5'), 118.6 (d, C-3), 122.3 (d, C-7), 123.4 (d, C-4), 124.5 (d, C-6), 127.7 (s, C-1'), 127.9 (d, 2C, C-2' + C-6'), 130.6 (s, C-5), 137.4 (s, C-7a), 141.3 (s, C-3a), 146.4 (s, C-2), 160.1 (s, C-4').
GC Retention time	12.18 min with Joey_short method
MS analyst, m/z (Int.)	276 (34), 274 (100), 259 (59), 231 (35), 195 (29).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 275.0297, m/z (measured) = 275.0300, difference = -1.04 ppm.

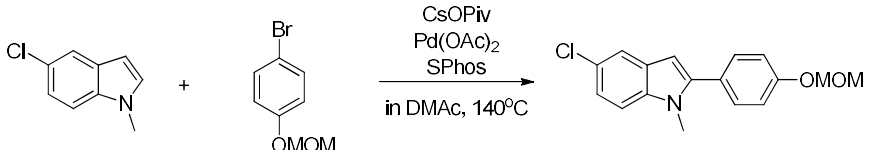
D III.12.13 Synthesis of 5-chloro-2-(2-chloro-4-methoxyphenyl)benzo[*b*]thiophene (116)



116

General procedure	F
Reaction scale	168 mg (1.0 mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	82 mg (53%), white solid
Molecular formular, m.w.	$C_{15}H_{10}Cl_2OS$, 309.20 g/mol
R_f	0.25 with LP
Melting point	125 - 127 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.85 (s, 3H, OCH_3), 6.87 (dd, *J* = 8.6, 2.6 Hz, 1H, H-5'), 7.05 (d, *J* = 2.6 Hz, 1H, H-3'), 7.29 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 7.42 (s, 1H, H-3), 7.48 (d, *J* = 8.6 Hz, 1H, H-6'), 7.72 – 7.76 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 55.7 (q, OCH_3), 113.3 (d, C-5'), 115.8 (d, C-3'), 122.9 (d, 2C, C-3 + C-4), 123.1 (d, C-7), 124.7 (d, C-6), 125.1 (s, C-1'), 130.6 (s, C-5), 132.5 (d, C-6'), 133.5 (s, C-2'), 138.1 (s, C-7a), 141.1 (s, C-3a), 142.5 (s, C-2), 160.1 (s, C-4').
GC Retention time	17.84 min with Toan_25min method
MS analyst, m/z (Int.)	310(70), 309(16), 308(100), 295(28), 293(40), 265(24), 229(24), 195(66), 186(12), 150(14), 97(14)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 308.9908, m/z (measured) = 308.9899, difference = 3.11 ppm.

D III.12.14 Synthesis of 5-chloro-2-(4-(methoxymethoxy)phenyl)-1-methyl-1*H*-indole (146)



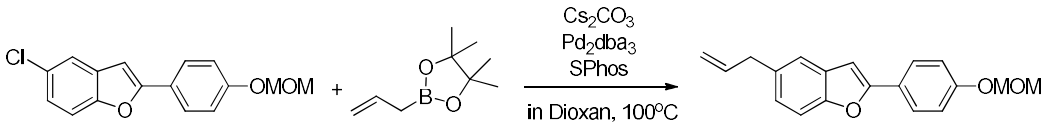
146

General procedure	F
Reaction scale	166 mg (1.0 mmol)
urification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	181 mg (60%), white solid
Molecular formular, m.w.	$C_{17}H_{16}ClNO_2$, 301.77 g/mol
R_f	0.30 with LP/EtOAc 9:1
Melting point	99 – 101 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.57 (s, 3H, OCH_3), 3.74 (s, 3H, N-CH_3), 5.28 (s, 2H, OCH_2O), 6.48 (s, 1H, H-3), 7.18 – 7.29 (m, 4H, H-3' + H-5' + H-6 + H-7), 7.44 – 7.46 (m, 2H, H-2' + H-6'), 7.62 (d, *J* = 1.7 Hz, 1H, H-4).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 31.2 (q, N-CH_3), 56.2 (q, O-CH_3), 94.4 (t, OCH_2O), 100.8 (d, C-3), 110.5 (d, C-7), 116.3 (d, 2C, C-3' + C-5'), 119.6 (d, C-4), 121.6 (d, C-6), 125.4

	(s, C-1'), 125.9 (s, C-5), 129.0 (s, C-3a), 130.6 (d, 2C, C-2' + C-6'), 136.6 (s, C-2), 142.7 (s, C-7a), 157.3 (s, C-4').
GC Retention time	18.15 min with Toan_25min method
MS analyst, m/z (Int.)	303(32), 301(100), 273(15), 271(45), 256(91), 228(13), 193(46), 191(26), 165(22), 102(12), 75(13)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 302.0948, m/z (measured) = 302.0956, difference = -2.66 ppm.

D III.13 Allylation on 5-chloro benzo-fused heterocycles derivatives.

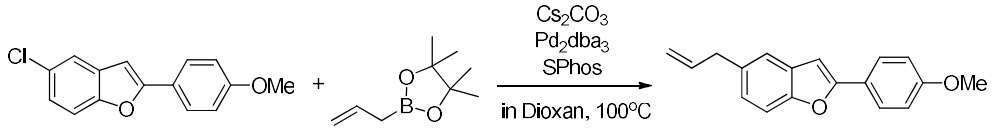
D III.13.1 Synthesis of 5-allyl-2-(4-(methoxymethoxy)phenyl)benzo[*b*]furan (92)



91 92

General procedure	G
Reaction scale	144 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	102 mg (69%), white solid
Molecular formular, m.w.	$C_{19}H_{18}O_3$, 294.35 g/mol
R_f	0.68 with LP/EtOAc 9:1
Melting point	126 – 129 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.47 – 3.51 (m, 5H, OCH_3 + H-1''), 5.07 – 5.23 (m, 4H, OCH_2O + H-3''), 6.04 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-2''), 6.85 (s, 1H, H-3), 7.07 – 7.14 (m, 3H, H-6 + H-3' + H-5'), 7.36 – 7.44 (m, 2H, H-2' + H-6'), 7.76 – 7.81 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 99.9 (d, C-3), 110.8 (d, C-7), 115.5 (t, C-3''), 116.5 (d, 2C, C-3' + C-5'), 120.2 (d, C-4), 124.5 (d, C-6), 124.7 (s, C-1'), 126.3 (d, 2C, C-2' + C-6'), 129.6 (s, C-3a), 134.6 (s, C-5), 138.1 (d, C-2''), 153.6 (s, C-7a), 156.1 (s, C-2), 157.5 (s, C-4').
GC Retention time	16.69 min with Toan_20min method
MS analyst, m/z (Int.)	295(22), 294(100), 264(63), 250(17), 249(71), 221(19), 194(21), 178(23), 165(38), 152(22), 128(15), 89(12).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 295.1329, m/z (measured) = 295.1323, difference = 2.1 ppm.

D III.13.2 Synthesis of 5-allyl-2-(4-methoxyphenyl)benzo[*b*]furan (117)

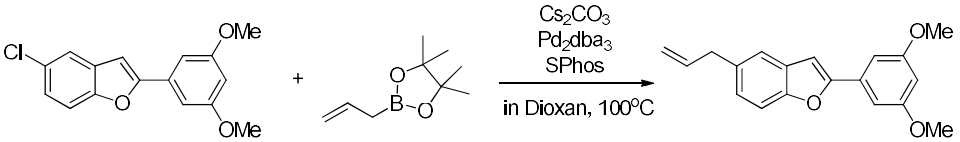


106 117

General procedure	G
Reaction scale	129 mg (0.5 mmol)

Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	92.5 mg (70%), white solid
Molecular formular, m.w.	$C_{18}H_{16}O_2$, 264.32 g/mol
R_f	0.47 with LP/EtOAc 20:1
Melting point	130 – 132 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.49 (d, *J* = 6.6 Hz, 2H, H-1''), 3.86 (s, 3H, OCH_3), 5.07 – 5.17 (m, 2H, H-1''), 6.05 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-3''), 6.84 (s, 1H, H-3), 6.93 – 7.00 (m, 2H, H-3' + H-5'), 7.09 (dd, *J* = 8.4, 1.7 Hz, 1H, H-6), 7.36 – 7.45 (m, 2H, H-2' + H-6'), 7.77 – 7.82 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 55.4 (q, OCH_3), 99.6 (d, C-3), 110.7 (d, C-7), 114.3 (d, 2C, C-3' +C-5'), 115.5 (t, C-3''), 120.2 (d, C-4), 123.5 (d, C-6), 124.6 (s, C-1'), 126.4 (d, 2C, C-2' + C-6'), 129.7 (s, C-3a), 134.6 (s, C-5), 138.1 (d, C-2''), 153.5 (s, C-7a), 156.3 (s, C-2), 160.0 (s, C-4').
GC Retention time	15.37 min with Toan_20min method
MS analyst, m/z (Int.)	265(20), 264(100), 249(36), 207(21), 165(11), 135(12)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 265.1223, m/z (measured) = 265.1221, difference = 0.93 ppm.

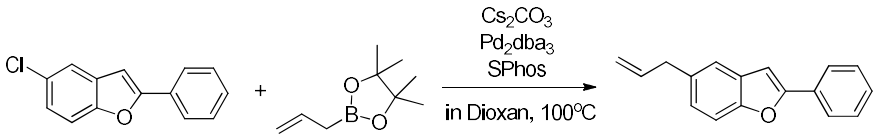
D III.13.3 Synthesis of 5-allyl-2-(3,5-dimethoxyphenyl)benzo[*b*]furan (<u>118</u>)



107 **<u>118</u>**

General procedure	G
Reaction scale	144 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	97 mg (66%), colorless oil
Molecular formular, m.w.	$C_{19}H_{18}O_3$, 294.35 g/mol
R_f	0.57 with LP/EtOAc 9:1
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.37 (d, *J* = 6.7 Hz, 2H, H-1''), 3.76 (s, 6H, OCH_3), 4.98 – 5.03 (m, 2H, H-1''), 5.92 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H. H-2''), 6.37 (t, *J* = 2.3 Hz, 1H, H-4'), 6.84 (d, *J* = 0.8 Hz, 1H, H-3), 6.91 (d, *J* = 2.3 Hz, 2H, H-2' + H-6'), 7.01 (dd, *J* = 8.4, 1.7 Hz, 1H, H-6), 7.27 – 7.34 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 55.5 (q, 2C, OCH_3), 101.2 (d, C-4'), 101.8 (d, C-3), 103.0 (d, 2C, C-2' + C-6'), 110.9 (d, C-7), 115.6 (t, C-3''), 120.5 (d, C-4), 125.3 (d, C-6), 129.3 (s, C-3a), 132.3 (s, C-1'), 134.8 (s, C-5), 138.0 (d, C-2''), 153.7 (s, C-7a), 155.0 (s, C-2), 161.1 (s, 2C, C-3' + C-5').
GC Retention time	17.43 min with Toan_20min method
MS analyst, m/z (Int.)	295(19), 294(100), 267(10), 235(11), 209(17), 178(11), 165(32), 152(14), 128(15).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 295.1329, m/z (measured) = 295.1328, difference = 0.17 ppm.

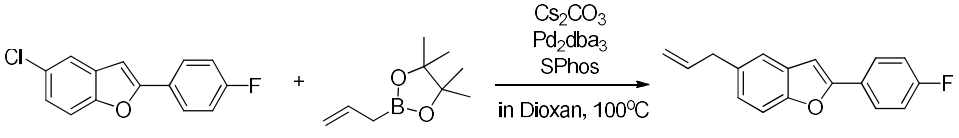
D III.13.4 Synthesis of 5-allyl-2-phenylbenzo[*b*]furan (119)



108 119

General procedure	G
Reaction scale	114 mg (0.5 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallised in LP
Yield	87 mg (74%), white solid
Molecular formular, m.w.	$C_{17}H_{14}O$, 234.30 g/mol
R_f	0.63 with LP
Melting point	118 – 120 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.37 (d, *J* = 6.5 Hz, 2H, H-1''), 4.96 – 5.04 (m, 2H, H-3''), 5.92 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-2''), 6.83 (s, 1H, H-3), 7.00 (d, *J* = 8.4 Hz, 1H, H-6), 7.21 – 7.35 (m, 5H, Ar-H), 7.72 – 7.75 (d, *J* = 7.2 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 101.2 (d, C-3), 110.9 (d, C-7), 115.6 (t, C-3''), 120.5 (d, C-4), 124.9 (d, 2C, C-2' + C-6'), 125.1 (d, C-6), 128.5 (d, C-4'), 128.8 (d, 2C, C-3' + C-5'), 129.5 (s, C-3a), 130.6 (s, C-1'), 134.7 (s, C-5), 138.1 (d, C-2''), 153.8 (s, C-7a), 156.2 (s, C-2).
GC Retention time	13.42 min with Toan_20min method
MS analyst, m/z (Int.)	234(100), 233(24), 215(14), 207(31), 190(11), 178(17), 129(20), 105(23), 89(20), 77(16)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 235.1117, m/z (measured) = 235.1119, difference = -0.8 ppm.

D III.13.5 Synthesis of 5-allyl-2-(4-fluorophenyl)benzo[*b*]furan (120)

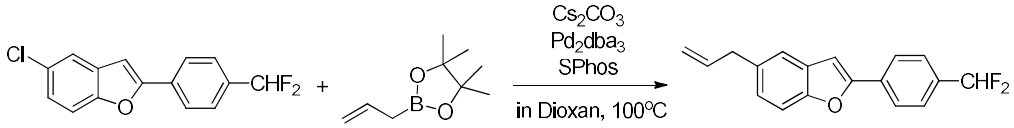


109 120

General procedure	G
Reaction scale	123 mg (0.5 mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallized in LP
Yield	91 mg (72%), white solid
Molecular formular, m.w.	$C_{17}H_{13}FO$, 252.29 g/mol
R_f	0.55 with *n*-heptane
Melting point	113 – 115 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.50 (d, *J* = 6.7 Hz, 2H, H-1''), 5.09 – 5.16 (m, 2H, H-3''), 6.05 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-2''), 6.90 (s, 1H, H-3), 7.11 – 7.16 (m, 3H, H-6 + H-3' + H-5'), 7.39 – 7.45 (m, 2H, H-2' + H-6'), 7.81 – 7.84 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 100.9 (d, J_{C-F} = 1.4 Hz, C-2), 110.9 (d, C-7), 115.6 (t, C-3''), 115.9 (d, J_{C-F} = 21.9 Hz, 2C, C-3' + C-5'), 120.5 (d, C-4), 125.2 (d, C-6), 126.7 (d, J_{C-F} = 8.5 Hz, 2C, C-2' + C-6'), 126.9 (d, J_{C-F} = 3.0), 129.4 (s, C-3a),

	134.8 (s, C-5), 138.0 (d, C-2''), 153.7 (s, C-7a), 155.3 (s, C-2), 162.9 (d, J_{C-F} = 248.7, C-4').
GC Retention time	13.23 min with Toan_20min method
MS analyst, m/z (Int.)	253(20), 252(100), 233(16), 225(32), 208(12), 196(26), 183(18), 170(11), 157(14), 129(45), 128(22), 123(41), 109(21), 98(16), 75(15)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 253.1023, m/z (measured) = 253.1034, difference = -4.4 ppm.

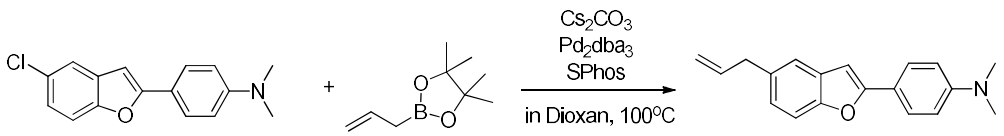
D III.13.6 Synthesis of 5-allyl-2-(4-(difluoromethyl)phenyl)benzo[*b*]furan (121)



110 121

General procedure	G
Reaction scale	139 mg (0.5 mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallized in LP
Yield	98 mg (69%), white solid
Molecular formular, m.w.	$C_{18}H_{14}F_2O$, 284.31 g/mol
R_f	0.35 with *n*-heptane
Melting point	116 – 118 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.50 (d, *J* = 6.6 Hz, 2H, H-3''), 5.08 – 5.17 (m, 2H, H-1''), 6.04 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H, H-2''), 6.68 (t, J_{H-F} = 56.4 Hz, 1H, CHF_2), 7.04 (s, 1H, H-3), 7.15 (dd, *J* = 8.4, 1.6 Hz, 1H, H-6), 7.41 – 7.60 (m, 4H, H-3' + H-5' + H-4 + H-7), 7.90 – 7.94 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.1 (t, C-1''), 102.6 (d, C-3), 111.0 (d, C-7), 114.5 (t, $^1J_{C-F}$ = 238.8 Hz, CHF_2), 115.7 (t, C-3''), 120.7 (d, C-4), 125.0 (d, 2C, C-2' +C-6'), 125.8 (d, C-6), 126.1 (t, $^3J_{C-F}$ = 6.1 Hz, 2C, C-3' + C-5'), 129.2 (s, C-3a), 132.8 (s, C-1'), 134.1 (t, $^2J_{C-F}$ = 22.4 Hz, C-4'), 135.0 (s, C-5), 137.9 (d, C-2''), 153.9 (s, C-7a), 154.9 (s, C-2).
GC Retention time	14.09 min with Toan_20min method
MS analyst, m/z (Int.)	284(100), 283(23), 257(20), 215(21), 207(48), 203(22), 189(11), 178(11), 155(16), 129(50), 128(29), 127(18), 115(11), 101(11), 89(11).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 285.1091, m/z (measured) = 285.1088, difference = 1.08 ppm.

D III.13.7 Synthesis of 4-(5-allylbenzo[*b*]furan-2-yl)-N,N-dimethylaniline (122)

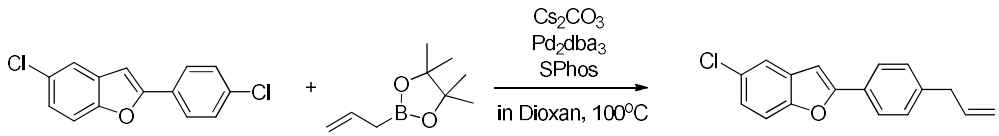


111 122

General procedure	G
Reaction scale	136 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP

Yield	33 mg (24%), yellow solid
Molecular formular, m.w.	$C_{19}H_{19}NO$, 277.37 g/mol
R_f	0.67 with LP/EtOAc 9:1
Melting point	125 – 127 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.02 (s, 6H, $N(CH_3)_2$), 3.47 (d, *J* = 6.7 Hz, 2H, H-1''), 5.06 – 5.13 (m, 2H, H-3''), 6.02 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H, H-2'), 6.74 – 6.80 (m, 4H, Ar-H), 7.03 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6), 7.32 (d, *J* = 1.2 Hz, 1H, H-4), 7.39 (d, *J* = 8.3 Hz, 1H, H-7), 7.72 – 7.74 (m, 2H, Ar-H).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.4 (t, C-1''), 40.4 (q, $N(CH_3)_2$), 98.0 (d, C-3), 110.5 (d, C-7), 112.2 (d, 2C, C-3' + C-5'), 115.4 (t, C-3''), 119.8 (d, C-4), 123.9 (d, C-6), 126.1 (d, 2C, C-2' + C-6'), 126.2 (s, C-1'), 130.1 (s, C-3a), 134.4 (s, C-5), 138.2 (d, C-2''), 150.6 (s, C-7a), 153.3 (s, C-2), 157.3 (s, C-4').
GC Retention time	18.10 min with Toan_20min method
MS analyst, m/z (Int.)	278(19), 277(100), 248(8), 208(14), 207(70), 124(15), 97(17), 57(17).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 278.1539, m/z (measured) = 278.1544, difference = -1.69 ppm.

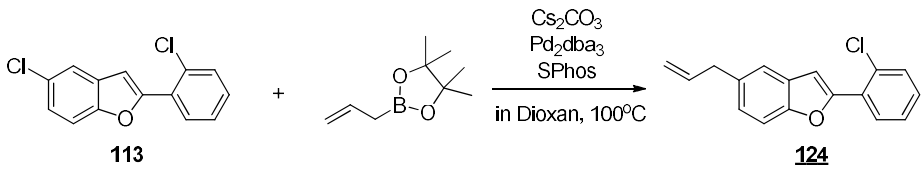
D III.13.8 Synthesis of 5-allyl-2-(4-chlorophenyl)benzo[*b*]furan (123a)



112 123a

General procedure	G
Reaction scale	132 mg (0.5 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallized in LP
Yield	59 mg (44%), white solid
Molecular formular, m.w.	$C_{17}H_{13}ClO$, 268.74 g/mol
R_f	0.55 with LP
Melting point	138 – 141 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.44 (d, *J* = 6.7 Hz, 2H, H-1''), 5.08 – 5.17 (m, 2H, H-3''), 5.98 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H, H-2''), 6.92 (s, 1H, H-3), 7.19 – 7.30 (m, 3H, H-6 + H-3' + H-5'), 7.40 – 7.53 (m, 2H, H-4 + H-7), 7.76 – 7.80 (m, 2H, H-2' + H-6')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 40.0 (t, C-1''), 100.3 (d, C-3), 112.0 (d, C-7), 116.3 (t, C-3''), 120.3 (d, C-4), 124.2 (d, C-6), 125.2 (d, 2C, C-2' + C-6'), 127.9 (s, C-1'), 128.4 (s, C-5), 129.1 (d, 2C, C-3' + C-5'), 130.7 (s, C-3a), 136.9 (d, C-2''), 141.2 (s, C-4'), 153.2 (s, C-7a), 157.5 (s, C-2).
GC Retention time	14.93 min with Toan_20min method
MS analyst, m/z (Int.)	270(24), 268(75), 243(5), 241(14), 208(19), 207(100), 128(16), 97(19), 57(15).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 269.0733, m/z (measured) = 269.0737, difference = -1.50 ppm.

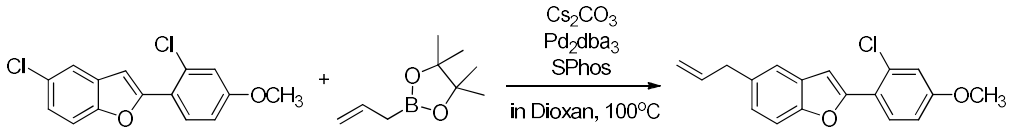
D III.13.9 Synthesis of 5-allyl-2-(2-chlorophenyl)benzo[*b*]furan (124)



113 124

General procedure	G
Reaction scale	132 (0.5 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallized in LP
Yield	68 mg (51%) colorless oil
Molecular formular, m.w.	$C_{17}H_{13}ClO$, 268.74 g/mol
R_f	0.57 with LP
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.57 (d, *J* = 6.2 Hz, 2H, H-1''), 4.90 – 5.03 (m, 2H, H-3''), 5.95 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H, H-2''), 6.74 (d, *J* = 0.7 Hz, 1H, H-3), 7.17 – 7.67 (m, 6H, Ar-H), 7.76 (d, *J* = 8.1. Hz, 1H, H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 38.3 (t, C-1''), 104.5 (d, C-3), 112.1 (d, C-7), 116.3 (t, C-3''), 120.5 (d, C-4), 124.4 (d, C-6), 126.6 (d, C-5'), 129.1 (d, C-6'), 129.2 (d, C-3'), 129.5 (s, C-1'), 129.9 (s, C-3a), 130.4 (s, C-5), 130.7 (d, C-4'), 136.8 (d, C-2''), 138.0 (s, C-2'), 153.0 (s, C-7a), 157.1 (s, C-2).
GC Retention time	13.83 min with Toan_20min method
MS analyst, m/z (Int.)	270(14), 268(43), 253(21), 218(38), 215(15), 128(100), 115(18), 101(19).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 269.0733, m/z (measured) = 269.0730, difference = 1.11 ppm.

D III.13.10 Synthesis of 5-allyl-2-(2-chloro-4-methoxyphenyl)benzo[*b*]furan (125)

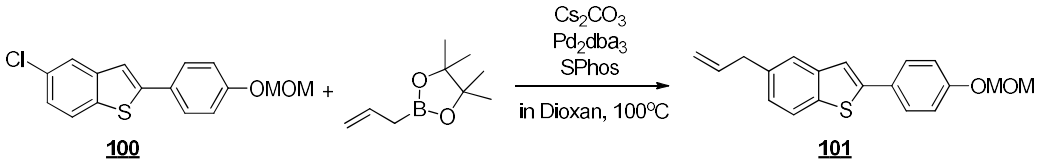


114 125

General procedure	G
Reaction scale	146 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc (gradient 2 – 10% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	79 mg (53%), white solid
Molecular formular, m.w.	$C_{18}H_{15}ClO_2$, 298.77 g/mol
R_f	0.35 with LP
Melting point	110 – 112 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.64 (d, *J* = 6.7 Hz, 2H, H-1''), 3.87 (s, 3H, OCH_3), 5.00 – 5.14 (m, 2H, H-3''), 6.00 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H, H-2'), 6.73 (s, 1H, H-3'), 6.87 – 6.90 (m, 2H, H-3 + H-5'), 7.20 – 7.72 (m, 5H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 38.4 (t, C-1''), 55.3 (q, OCH_3), 103.4 (d, C-3), 111.9 (d, C-7), 112.0 (d, C-5'), 115.9 (d, C-3'), 116.5 (t, C-3''), 120.2 (d, C-4), 122.3 (s, C-1'), 123.9 (d, C-6), 128.2 (s, C-3a), 130.5 (d, C-6'), 130.6 (s, C-5), 132.4 (s, C-2'), 136.5 (d, C-2''), 152.8 (s, C-7a), 157.2 (s, C-2), 160.2 (s, C-4').
GC Retention time	15.63 min with Toan_20min method
MS analyst, m/z (Int.)	300(16), 298(50), 283(22), 248(32), 189(24), 165(24), 158(100), 115(29).

HR-MS analyst	$[M+H]^+$ m/z (predicted) = 299.0833, m/z (measured) = 299.0833, difference = -0.02 ppm.

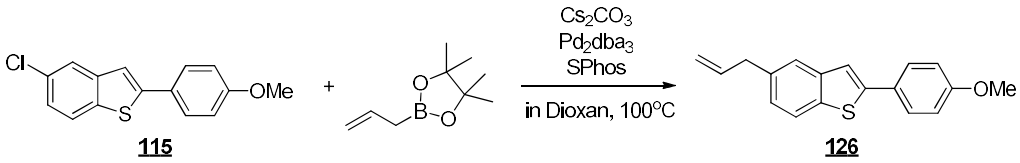
D III.13.11 Synthesis of 5-allyl-2-(4-(methoxymethoxy)phenyl)benzo[*b*]thiophene (101)



100 101

General procedure	G
Reaction scale	152 mg (0.5 mmol)
Reaction time	24 h
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	90 mg (58%), white solid
Molecular formular, m.w.	$C_{19}H_{18}O_2S$, 310.41 g/mol
R_f	0.57 with LP/EtOAc 9:1
Melting point	164 – 166 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.46 – 3.48 (m, 5H, OCH_3 + H-1''), 5.07 – 5.13 (m, 2H, H-3''), 5.19 (s, 2H, OCH_2), 6.01 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-2''), 7.06 – 7.13 (m, 3H, H-3' + H-5' + H-6), 7.35 (s, 1H, H-3), 7.53 (d, *J* = 0.7 Hz, 1H, H-4), 7.59 – 7.61 (m, 2H, H-2' + H-6'), 7.70 (d, *J* = 8.2 Hz, 1H, H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 115.8 (t, C-3''), 116.7 (d, 2C, C-3' + C-5'), 118.4 (d, C-3), 122.1 (d, C-4), 123.0 (d, C-7), 125.3 (d, C-6), 127.7 (d, 2C, C-2' + C-6'), 128.3 (s, C-1'), 136.5 (s, C-5), 137.2 (s, C-7a), 137.7 (d, C-2''), 141.3 (s, C-3a), 144.3 (s, C-2), 157.4 (s, C-4').
GC Retention time	19.51 min with Toan_20min method
MS analyst, m/z (Int.)	311(20), 310(10), 281(10), 280(44), 266(10), 265(41), 208(16), 171(12).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 311.1100, m/z (measured) = 311.1108, difference = -2.62 ppm.

D III.13.12 Synthesis of 5-allyl-2-(4-methoxyphenyl)benzo[*b*]thiophene (126)

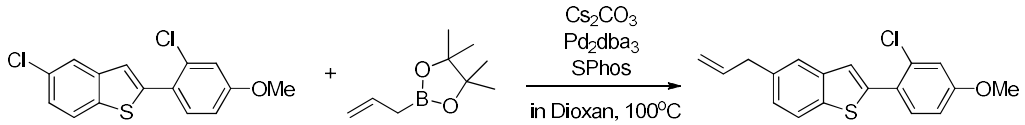


115 126

General procedure	G
Reaction scale	82 mg (0.3 mmol)
Reaction time	24 h
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	49 (58%), pale yellow solid
Molecular formular, m.w.	$C_{18}H_{16}OS$, 280.39 g/mol
R_f	0.67 with LP/EtOAc 9:1
Melting point	146 – 147 °C

^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 3.49 (d, *J* = 6.7 Hz, 2H, H-1''), 3.8 (s, 3H, OCH_3), 5.06 – 5.16 (m, 2H, H-3''), 6.02 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H, H-2''), 6.90 – 6.98 (m, 2H, H-3' + H-5'), 7.13 (dd, *J* = 8.2, 1.6 Hz, 1H, H-6), 7.36 (s, 1H, H-3), 7.54 (s, 1H, H-4), 7.63 (d, *J* = 8.8 Hz, 2H, H-2' + H-6'), 7.71 (d, *J* = 8.2 Hz, 1H, H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 40.2 (t, C-1''), 55.4 (q, OCH_3), 114.3 (d, 2C, C-3' + C-5'), 115.8 (t, C-3''), 118.0 (d, C-3), 122.0 (d, C-4), 122.9 (d, C-7), 125.1 (d, C-6), 127.2 (s, C-1'), 127.7 (d, 2C, C-2' + C-6'), 136.4 (s, C-5), 137.1 (s, C-7a), 137.7 (d, C-2''), 141.3 (s, C-3a), 144.4 (s, C-2), 159.8 (s, C-4').
GC Retention time	17.49 min with Toan_25min method
MS analyst, m/z (Int.)	281 (21), 280 (100), 279 (15), 265 (35), 171 (12).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 281.0995, m/z (measured) = 281.1000, difference = -1.98 ppm.

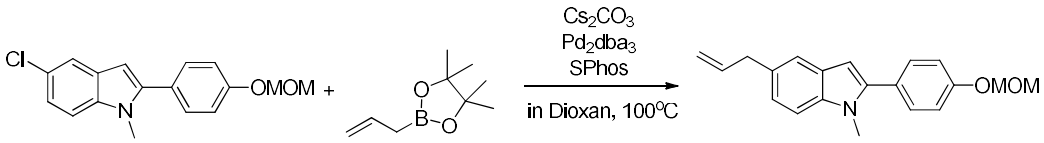
D III.13.13 Synthesis of 5-allyl-2-(2-chloro-4-methoxyphenyl)benzo[*b*]thiophene (127)



116 127

General procedure	G
Reaction scale	124 mg (0.4 mmol)
Reaction time	24 h
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	59 mg (47%), pale yellow solid
Molecular formular, m.w.	$C_{18}H_{15}ClOS$, 314.83 g/mol
R_f	0.72 with LP/EtOAc 9:1
Melting point	118 – 121 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.52 (2H, J = 6.5 Hz, H-1''), 3.85 (3H, OCH_3), 4.97 – 5.13 (m, 2H, H-3''), 5.89 – 6.08 (m, 1H, H-2''), 6.88 (dd, *J* = 8.7, 2.6 Hz, 1H, H-5'), 7.05 (d, *J* = 2.6 Hz, 1H, H-3'), 7.29 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 7.42 (s, 1H, H-3), 7.48 (d, *J* = 8.7 Hz, 1H, H-6'), 7.73 (d, *J* = 8.6 Hz, 1H, H-7), 7.76 (d, *J* = 2.0 Hz, 1H, H-4).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 37.9 (t, C-1''), 55.3 (q, OCH_3), 111.8 (d, C-5'), 115.6 (d, C-3'), 116.4 (t, C-3''), 122.1 (d, C-3), 122.9 (d, C-4), 123.0 (d, C-7), 124.3 (d, C-6), 126.1 (s, C-1'), 132.2 (d, C-6'), 133.9 (s, C-5), 134.6 (s, C-2'), 137.1 (d, C-2''), 138.2 (s, C-7a), 141.3 (C-3a), 142.3 (s, C-2), 159.9 (s, C-4').
GC Retention time	17.20 min with Toan_20min method
MS analyst, m/z (Int.)	316(33), 314(84), 299(35), 265(14), 264(76), 221(40), 209(10), 202(26), 189(10), 158(100), 139(19), 115(23)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 315.0605, m/z (measured) = 315.0602, difference = 0.8 ppm.

D III.13.14 Synthesis of 5-allyl-2-(4-(methoxymethoxy)phenyl)-1-methyl-1*H*-indole (147)

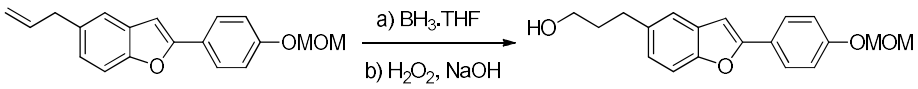


146 147

General procedure	G
Reaction scale	151 mg (0.5 mmol)
Reaction time	24 h
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 18 g silica 60 then recrystallized in LP
Yield	58 mg (38%), pale yellow solid
Molecular formular, m.w.	$C_{20}H_{21}NO_2$, 307.39 g/mol
R_f	0.46 with LP/EtOAc 9:1
Melting point	95 – 97 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 3.52 – 3.56 (m, 5H, OCH_3 + H-1''), 3.74 (s, 3H, N-CH_3), 5.06 – 5.18 (m, 2H, H-3''), 5.27 (s, 2H, OCH_2O), 6.09 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-2''), 6.49 (s, 1H, H-3), 7.09 – 7.19 (m, 3H, H-3' + H-5' + H-6), 7.28 (d, *J* = 7.1 Hz, 1H, H-7), 7.33 – 7.58 (m, 3H, H-2' + H-6' + H-4).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 31.1 (q, N-CH_3), 40.4 (t, C-1''), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 100.9 (d, C-3), 109.4 (d, C-7), 114.9 (t, C-3''), 116.2 (d, 2C, C-3' + C-5'), 119.8 (d, C-4), 122.6 (d, C-6), 126.6 (s, C-1'), 128.2 (s, C-3a), 130.6 (d, 2C, C-2' + C-6'), 131.4 (s, C-5), 137.0 (s, C-7a), 138.8 (d, C-2''), 141.5 (s, C-2), 157.0 (s, C-4').
GC Retention time	18.49 min with Toan_20min method
MS analyst, m/z (Int.)	308(23), 307(100), 276(10), 263(31), 262(84), 206(13), 192(12)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 308.1645, m/z (measured) = 308.1644, difference = 0.37 ppm.

D III.14 Hydroboration oxidation of 5-allyl benzo-fused heterocycles derivatives.

D III.14.1 Synthesis of 3-(2-(4-(methoxymethoxy)phenyl)benzo[*b*]furan-5-yl)propan-1-ol (93)

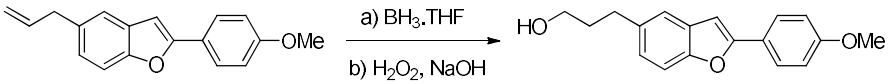


92 93

General procedure	H
Reaction scale	59 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	26 mg (42%) white solid
Molecular formular, m.w.	$C_{19}H_{20}O_4$, 312.37 g/mol
R_f	0.12 with LP/EtOAc 9:1
Melting point	155 – 156 °C

^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.33 (s, 1H, OH), 1.88 – 2.01 (m, 2H, H-2''), 2.81 (t, *J* = 7.3 Hz, 2H, H-1''), 3.51 (s, 3H, OCH_3), 3.70 (t, J = 6.4 Hz, 2H, H-3''), 5.23 (s, 2H, OCH_2O), 6.85 (s, 1H, H-3), 7.08 – 7.13 (m, 3H, H-3' + H-5' + H-6), 7.38 – 7.43 (m, 2H, H-4 + H-7), 7.78 (d, *J* = 8.7 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.8 (t, C-1''), 56.1 (q, OCH_3), 62.3 (t, C-3''), 94.4 (t, OCH_2O), 99.8 (d, C-3), 110.7 (d, C-7), 116.5 (d, 2C, C-3' + C-5'), 120.0 (d, C-4), 124.4 (d, C-6), 124.5 (s, C-1'), 126.3 (d, 2C, C-2' + C-6'), 129.6 (s, C-3a), 136.3 (s, C-5), 153.4 (s, C-7a), 156.1 (s, C-2), 157.5 (s, C-4').
GC Retention time	16.76 min with Toan_20min method
MS analyst, m/z (Int.)	312(11), 296(48), 266(24), 237(32), 223(12), 207(100), 194(30), 165(23), 132(21)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 313.1434, m/z (measured) = 313.1431, difference = 0.93 ppm.

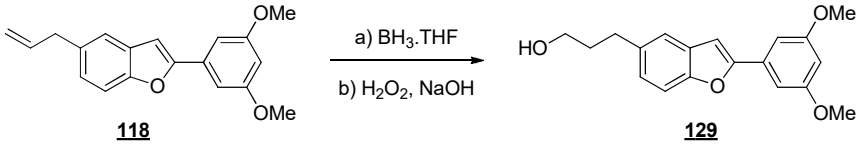
D III.14.2 Synthesis of 3-(2-(4-methoxyphenyl)benzo[*b*]furan-5-yl)propan-1-ol (128)



117 128

General procedure	H
Reaction scale	53 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	26 mg (46%), white solid
Molecular formular, m.w.	$C_{18}H_{18}O_3$, 282.34 g/mol
R_f	0.44 with LP/EtOAc 8:2
Melting point	150 – 152 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.41 (s, 1H, OH), 1.94 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.80 (t, *J* = 7.2 Hz, 2H, H-1''), 3.70 (t, *J* = 6.4 Hz, 2H, H-3''), 3.86 (s, 3H, OCH_3), 6.83 (d, *J* = 0.8 Hz, 1H, H-3), 6.95 – 7.00 (m, 2H, H-3' + H-5'), 7.09 (dd, *J* = 8.4, 1.8 Hz, 1H, H-6), 7.36 – 7.41 (m, 2H, H-4 + H-7), 7.76 – 7.80 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.8 (t, C-1''), 55.4 (t, OCH_3), 62.3 (t, C-3''), 99.5 (d, C-3), 110.7 (d, C-7), 114.2 (d, 2C, C-3' + C-5'), 119.9 (d, C-4), 123.5 (d, C-6), 124.4 (s, C-1'), 126.4 (d, 2C, C-2' + C-6'), 129.7 (s, C-3a), 136.3 (s, C-5), 153.4 (s, C-7a), 156.3 (s, C-2), 159.9 (s, C-4').
GC Retention time	15.41 min with Toan_20min method
MS analyst, m/z (Int.)	281(14), 266(93), 238(22), 237(100), 222(20), 207(53), 194(25), 165(18), 118(18), 97(12).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 283.1329, m/z (measured) = 283.1339, difference = -3.63 ppm.

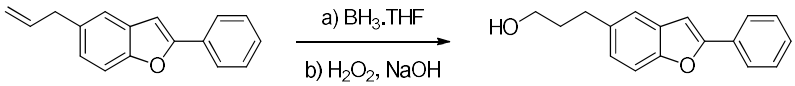
D III.14.3 Synthesis of 3-(2-(3,5-dimethoxyphenyl)benzo[*b*]furan-5-yl)propan-1-ol (129)



118 129

General procedure	H
Reaction scale	59 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	25 mg (40%) white solid
Molecular formular, m.w.	$C_{19}H_{20}O_4$, 312.37 g/mol
R_f	0.67 with LP/EtOAc 1:1
Melting point	66 – 68 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.43 (s, 1H, OH), 1.94 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.80 (t, *J* = 7.4 Hz, 2H, H-1''), 3.70 (t, *J* = 6.4 Hz, 2H, H-3''), 3.87 (s, 6H, OCH_3), 6.47 (t, *J* = 2.2 Hz, 1H, H-4'), 6.95 (s, 1H, H-3), 7.01 (d, *J* = 2.2 Hz, 2H, H-2' + H-5'), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H, H-6), 7.39 – 7.44 (m, 2H, H-4 + H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.7 (t, C-1''), 55.5 (q, 2C, OCH_3), 62.2 (t, C-3''), 101.0 (d, C-4'), 101.7 (d, C-3), 103.0 (d, 2C, C-2' + C-6'), 110.9 (d, C-7), 120.3 (d, C-4), 125.1 (d, C-6), 129.5 (d, C-3a), 132.3 (s, C-1'), 136.5 (s, C-5), 153.5 (s, C-7a), 155.9 (s, C-2), 161.1 (s, 2C, C-3' + C-5').
GC Retention time	17.48 min with Toan_20min method
MS analyst, m/z (Int.)	311(9), 297(16), 296(71), 268(22), 267(100), 209(49), 208(21), 207(79), 193(12), 165(15), 152(25), 134(29), 115(12), 96(15), 57(14)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 313.1434, m/z (measured) = 313.1430, difference = 1.32 ppm.

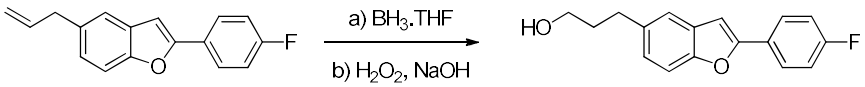
D III.14.4 Synthesis of 3-(2-phenylbenzo[*b*]furan-5-yl)propan-1-ol (130)



119 130

General procedure	H
Reaction scale	47 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	26 mg (51%) white solid
Molecular formular, m.w.	$C_{17}H_{16}O_2$, 252.31 g/mol
R_f	0.23 with LP/EtOAc 9:1
Melting point	128 – 129 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.39 (s, 1H, OH), 1.95 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.81 (t, *J* = 7.6 Hz, 2H, H-1''), 3.71 (t, *J* = 6.4 Hz, 2H, H-3''), 6.97 (d, *J* = 0.8 Hz, 1H, H-3), 7.13 (dd, *J* = 8.4, 1.8 Hz, 1H, H-6), 7.33 – 7.47 (m, 5H, Ar-H), 7.84 – 7.87 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.8 (t, C-1''), 62.3 (t, C-3''), 101.1 (d, C-3), 110.9 (d, C-7), 120.2 (d, C-4), 124.9 (d, 2C, C-2' + C-6'), 125.0 (d, C-6), 128.5 (d, C-4'), 128.8 (d, 2C, C-3' + C-5'), 129.4 (s, C-3a), 130.6 (s, C-1'), 136.5 (s, C-5), 153.6 (s, C-7a), 156.2 (s, C-2).
GC Retention time	13.47 min with Toan_20min method
MS analyst, m/z (Int.)	251(9), 236(91), 221(42), 220(100), 207(48), 194(27), 165(18)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 253.1223, m/z (measured) = 253.1220, difference = 1.05 ppm.

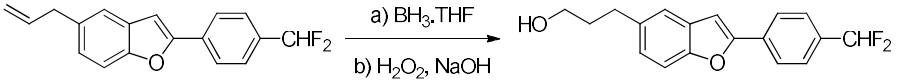
D III.14.5 Synthesis of 3-(2-(4-fluorophenyl)benzo[*b*]furan-5-yl)propan-1-ol (131)



120 131

General procedure	H
Reaction scale	50 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	29 mg (53%) white solid
Molecular formular, m.w.	$C_{17}H_{15}FO_2$, 270.30 g/mol
R_f	0.20 with LP/EtOAc 9:1
Melting point	124 – 126 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.41 (s, 1H, OH), 1.94 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2'), 2.81 (t, *J* = 7.6 Hz, 2H, H-1'), 3.72 (t, *J* = 6.4 Hz, 2H, H-3'), 6.89 (d, *J* = 0.4 Hz, 1H, H3), 7.11 – 7.15 (m, 3H, H-6 + H-3' + H-5'), 7.33 (m, 2H, H-4 + H-7), 7.80 – 7.84 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-1''), 34.8 (t, C-2''), 62.3 (t, C-3''), 100.9 (d, J_{C-F} = 1.2 Hz, C-3), 110.9 (d, C-7), 115.9 (d, J_{C-F} = 22.0 Hz, 2C, C-3' + C-5'), 120.2 (d, C-4), 125.0 (d, C-6), 126.7 (d, J_{C-F} = 8.2 Hz, 2C, C-2' + C-6'), 126.9 (d, J_{C-F} = 3.4 Hz, C-1'), 129.4 (s, C-3a), 136.6 (s, C-5), 153.6 (s, C-7a), 155.3 (s, C-2), 162.9 (d, J_{C-F} = 248.6 Hz, C-4').
GC Retention time	13.30 min with Toan_20min method
MS analyst, m/z (Int.)	269(12), 254(22), 252(100), 239(19), 220(36), 207(45), 194(27)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 295.1329, m/z (measured) = 295.1327, difference = 0.69 ppm.

D III.14.6 Synthesis of 3-(2-(4-(difluoromethyl)phenyl)benzo[*b*]furan-5-yl)propan-1-ol (132)

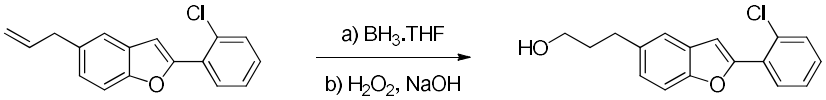


121 132

General procedure	H
Reaction scale	57 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	30 mg (49%) white solid
Molecular formular, m.w.	$C_{18}H_{16}F_2O_2$, 302.32 g/mol
R_f	0.19 with LP/EtOAc 9:1
Melting point	127 – 129 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.59 (s, 1H, OH), 1.95 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.82 (t, *J* = 7.6 Hz, 2H, H-1''), 3.71 (t, *J* = 6.4 Hz, 2H, H-3''), 6.68 (t, *J* = 56.4 Hz, 1H, CHF_2), 7.04 (s, 1H, H-3), 7.16 (dd, *J* = 8.4, 1.8 Hz, 1H, H-6), 7.41 – 7.45 (m, 2H, H-4 + H-7), 7.58 (d, *J* = 8.2 Hz, 2H, H-3' + H-5'), 7.92 (d, *J* = 8.5 Hz, 2H, H-2' + H-6').

^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.7 (t, C-1''), 62.2 (t, C-3''), 102.5 (d, C-3), 111.0 (d, C-7), 114.5 (t, J_{C-F} = 238.8 Hz, CHF_2), 120.5 (d, C-4), 125.0 (2C, C-2' + C-6'), 125.6 (d, C-6), 126.1 (t, J_{C-F} = 6.1 Hz, 2C, C-2' + C-6'), 129.1 (s, C-3a), 132.8 (s, C-1'), 134.1 (t, J_{C-F} = 22.4 Hz, 2C, C-4'), 136.8 (s, C-5), 153.8 (s, C-7a), 154.9 (s, C-2).
GC Retention time	14.10 min with Toan_20min method
MS analyst, m/z (Int.)	301(4), 287(11), 286(49), 258(19), 257(100), 208(15), 207(69), 178(13), 99(22), 57(23)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 303.1191, m/z (measured) = 303.1185, difference = 2.17 ppm.

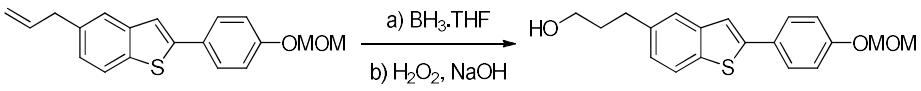
D III.14.7 Synthesis of 3-(2-(2-chlorophenyl)benzo[*b*]furan-5-yl)propan-1-ol (133)



124 **133**

General procedure	H
Reaction scale	54 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	29 mg (50%) colorless oil
Molecular formular, m.w.	$C_{17}H_{15}ClO_2$, 286.76 g/mol
R_f	0.67 with LP/EtOAc 4:1
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.39 (s, 1H, OH), 1.95 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.81 (t, *J* = 7.6 Hz, 2H, H-1''), 3.71 (t, *J* = 6.4 Hz, 2H, H-3''), 6.61 (d, *J* = 1.9 Hz, 1H, H-3), 7.26 – 7.54 (m, 6H, ArH, Ar-H), 8.04 (dd, J = 7.7, 1.8 Hz, 1H, H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 31.8 (t, C-2''), 36.0 (t, C-1''), 64.2 (t, C-3''), 104.1 (d, C-3), 113.3 (d, C-7), 120.4 (d, C-4), 124.0 (d, C-6), 127.4 (d, C-5'), 127.8 (d, C-6'), 128.4 (s, C-1'), 129.1 (d, C-3'), 129.1 (s, C-3a), 131.0 (d, C-4'), 132.5 (s, C-5), 134.3 (s, C-2'), 151.8 (s, C-7a), 153.5 (s, C-2).
GC Retention time	13.88 min with Toan_20min method
MS analyst, m/z (Int.)	285(7), 270(35), 268(100), 257(10), 255(27), 227(22), 207(41), 195(35), 165(18)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 287.0833, m/z (measured) = 287.0826, difference = 2.71 ppm.

D III.14.8 Synthesis of 3-(2-(4-(methoxymethoxy)phenyl)benzo[*b*]thiophen-5-yl)propan-1-ol (102)

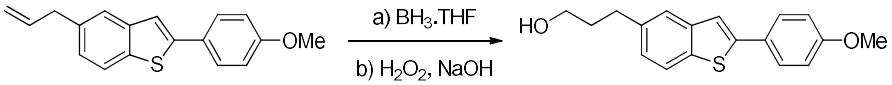


101 **102**

General procedure	H
Reaction scale	62 mg (0.2 mmol)

Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	30 mg (46%) white solid
Molecular formular, m.w.	$C_{19}H_{20}O_3S$, 328.43 g/mol
R_f	0.24 with LP/EtOAc 8:2
Melting point	170 – 172 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.44 (s, 1H, OH), 1.95 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.82 (t, *J* = 7.4 Hz, 2H, H-1''), 3.50 (s, 3H, OCH_3), 3.71 (t, *J* = 6.4 Hz, 2H, H-3''), 5.22 (s, 2H, OCH_2O), 7.07 – 7.16 (m, 3H, H-3' + H-5' + H-6), 7.38 (s, 1H, H-3), 7.57 (d, *J* = 0.9 Hz, 1H, H-4), 7.57 – 7.64 (m, 2H, H-2' + H-6'), 7.72 (d, *J* = 8.2 Hz, 1H, H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.5 (t, C-1''), 56.1 (q, OCH_3), 62.2 (t, C-3''), 94.4 (t, OCH_2O), 116.6 (d, 2C, C-3' + C-5'), 118.3 (d, C-3), 122.1 (d, C-4), 122.8 (d, C-7), 125.1 (d, C-6), 127.7 (d, 2C, C-2' + C-6'), 128.3 (s, C-1'), 137.0 (d, C-5), 138.2 (s, C-7a), 141.2 (s, C-3a), 144.3 (s, C-2), 157.4 (s, C-4').
GC Retention time	19.56 min with Toan_20min method
MS analyst, m/z (Int.)	327(10), 313(20), 312(100), 282(42), 252(67), 224(20), 208(16)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 329.1206, m/z (measured) = 329.1211, difference = -1.91 ppm.

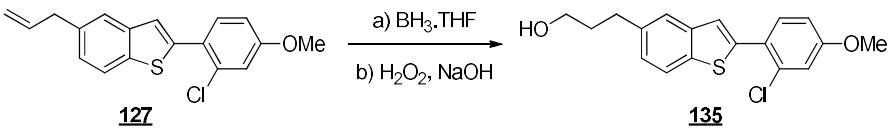
D III.14.9 Synthesis of 3-(2-(4-methoxyphenyl)benzo[*b*]thiophen-5-yl)propan-1-ol (134)



126 134

General procedure	H
Reaction scale	56 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	27 mg (45%)
Molecular formular, m.w.	$C_{18}H_{18}O_2S$, 298.40 g/mol
R_f	0.13 with LP/EtOAc 9:1
Melting point	151 – 153 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.29 (s, 1H, OH), 1.96 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.82 (t, *J* = 7.4 Hz, 2H, H-1''), 3.71 (t, *J* = 6.4 Hz, 2H, H-3''), 3.85 (s, 3H, OCH_3), 6.94 – 6.96 (m, 2H, H-3' + H-5'), 7.08 – 7.16 (m, 1H, H-6), 7.36 – 7.38 (m, 1H, H-4), 7.57 (s, 1H, H-3), 7.62 – 7.64 (m, 2H, H-2' + H-6'), 7.71 (d, *J* = 8.2 Hz, 1H, H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 32.0 (t, C-2''), 34.5 (t, C-1''), 55.4 (q, OCH_3), 62.3 (t, C-3''), 114.4 (d, 2C, C-3' + C-5'), 118.0 (d, C-3), 122.1 (d, C-4), 122.7 (d, C-7), 125.0 (d, C-6), 127.71 (s, C-1'), 127.72 (d, 2C, C-2' + C-6'), 136.9 (s, C-5), 138.2 (s, C-7a), 141.2 (s, C-3a), 144.4 (s, C-2), 159.8 (s, C-4').
GC Retention time	14.74 min with Toan_20min method
MS analyst, m/z (Int.)	297(5), 281(10), 240(20), 208(27), 207(100), 133(13), 97(20), 57(32)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 299.1100, m/z (measured) = 299.1072, difference = 9.57 ppm.

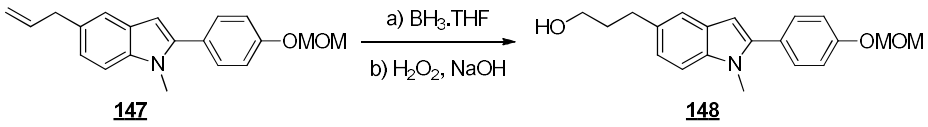
D III.14.10 Synthesis of 3-(2-(2-chloro-4-methoxyphenyl)benzo[*b*]thiophen-5-yl)propan-1-ol (135)



127 135

General procedure	H
Reaction scale	63 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	28 mg (42%)
Molecular formular, m.w.	$C_{18}H_{17}ClO_2S$, 332.84 g/mol
R_f	0.13 with LP/EtOAc 9:1
Melting point	127 – 129 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.47 (s, 1H, OH), 1.83 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.83 (t, *J* = 7.4 Hz, 2H, H-1''), 3.60 (t, *J* = 6.4 Hz, 2H, H-3''), 3.85 (s, 3H, OCH_3), 6.81 (dd, *J* = 8.5, 2.7 Hz, 1H, H-5'), 6.87 (d, *J* = 2.6 Hz, 1H, H-3'), 7.12 (s, 1H, H-3), 7.28 (dd, *J* = 8.5, 2.1 Hz, 1H, H-6), 7.35 (d, *J* = 8.5 Hz, 1H, H-6'), 7.72 (d, *J* = 8.5 Hz, 1H, H-7), 7.74 (d, *J* = 2.0 Hz, 1H, H-4).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 29.9 (t, C-2''), 34.1 (t, C-1''), 55.3 (q, OCH_3), 62.3 (t, CH_2OH, C-3''), 111.4 (d, C-5'), 115.3 (d, C-3'), 122.1 (d, C-4), 122.9 (d, C-3), 123.0 (d, C-7), 124.4 (d, C-6), 125.9 (s, C-1'), 132.4 (d, C-6'), 135.1 (s, C-5), 138.2 (s, C-7a), 141.2 (s, C-3a), 142.1 (s, C-2), 160.0 (s, C-4').
GC Retention time	17.04 min with Toan_20min method
MS analyst, m/z (Int.)	331(6), 316(20), 237(31), 209 (14), 207(28), 160(21), 159(100), 144(6)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 333.0711, m/z (measured) = 333.0715, difference = -1.42 ppm.

D III.14.11 Synthesis of 3-(2-(4-(methoxymethoxy)phenyl)-1-methyl-1*H*-indol-5-yl)propan-1-ol (148)



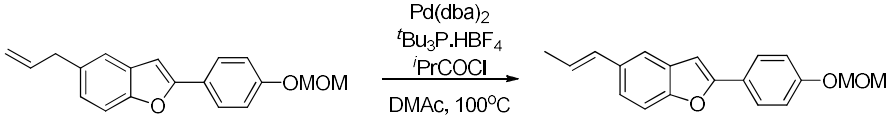
147 148

General procedure	H
Reaction scale	62 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 5 – 20% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	23 mg (36%), pink solid
Molecular formular, m.w.	$C_{20}H_{23}NO_3$, 325.41 g/mol
R_f	0.15 with LP/EtOAc 9:1
Melting point	101 – 103 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.34 (s, 1H, OH), 1.89 – 2.03 (m, 2H, H-2''), 2.83 (t, J = Hz, 2H, H-1''), 3.53 (s, 3H, OCH_3), 3.68 – 3.74 (m, 5H, N-CH_3 + H-3''), 5.24 (s, 2H, OCH_2O), 6.45 (s, 1H, H-3), 7.07 – 7.30 (m, 5H, Ar-H), 7.41 – 7.45 (m, 3H, Ar-H).1h too many

^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 31.1 (q, N-CH_3), 32.2 (t, C-2''), 35.0 (t, C-1''), 56.1 (q, OCH_3), 62.5 (t, C-3''), 94.4 (t, OCH_2O), 100.8 (d, C-3), 109.4 (d, C-7), 116.2 (d, C-4), 119.5 (d, 2C, C-3' + C-5'), 122.4 (d, C-6), 126.5 (s, C-1'), 128.2 (s, C-3a), 130.6 (d, 2C, C-2' + C-6'), 133.1 (s, C-5), 136.9 (s, C-7a), 141.5 (s, C-2), 157.0 (s, C-4').
GC Retention time	18.52 min with Toan_20min method
MS analyst, m/z (Int.)	324(7), 308(41), 277(17), 263(38), 206(88), 192(15)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 326.1751, m/z (measured) = 326.1755, difference = -1.25 ppm.

D III.15 Isomerization of 5-allyl benzo-fused heterocycles derivatives.

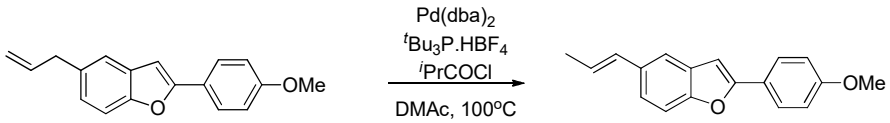
D III.15.1 Synthesis of (*E*)-2-(4-(methoxymethoxy)phenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (94)



92 94

General procedure	I
Reaction scale	59 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	44 mg (75%)
Molecular formular, m.w.	$C_{19}H_{18}O_3$, 294.35 g/mol
R_f	0.52 with LP/EtOAc 9:1
Melting point	151 – 153 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.90 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 3.50 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2O), 6.20 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.48 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1''), 6.85 (s, 1H, H-3), 7.09 – 7.12 (m, 2H, H-3' + H-5'), 7.25 – 7.27 (m, 1H, H-6), 7.39 – 7.47 (m, 2H, H-2' + H-6'), 7.76 – 7.79 (m, 2H, H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 100.1 (d, C-3), 110.9 (d, C-7), 116.5 (d, 2C, C-3' + C-5'), 117.7 (d, C-4), 122.1 (d, C-6), 124.4 (d, C-2''), 124.5 (s, C-1'), 126.3 (d, 2C, C-2' + C-6'), 129.7 (s, C-3a), 131.2 (d, C-1''), 133.2 (s, C-5), 154.1 (s, C-7a), 156.3 (s, C-2), 157.6 (s, C-4').
GC Retention time	17.47 min with Toan_20min method
MS analyst, m/z (Int.)	293(4), 292(22), 251(16), 250(100), 221(12), 207(16), 165(11), 121(19)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 295.1329, m/z (measured) = 295.1328, difference = 0.22 ppm.

D III.15.2 Synthesis of (*E*)-2-(4-methoxyphenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (136)

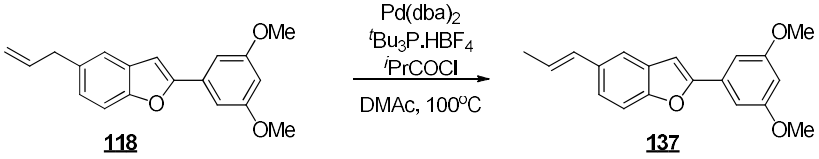


117 136

General procedure	I
Reaction scale	53 mg (0.2 mmol)

Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	33 mg (62%)
Molecular formular, m.w.	$C_{18}H_{16}O_2$, 264.32 g/mol[129]
R_f	0.73 with LP/EtOAc 9:1
Melting point	145 – 147 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.91 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 3.86 (s, 3H, OCH_3), 6.22 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.50 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1''), 6.83 (d, *J* = 0.6 Hz, 1H, H-3), 6.96 – 6.99 (m, 2H, H-3' + H-5'), 7.25 – 7.28 (m, 1H, H-6), 7.40 – 7.47 (m, 2H, H-4 + H-7), 7.77 – 7.79 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 55.4 (q, OCH_3), 99.7 (d, C-3), 110.9 (d, C-7), 114.3 (d, 2C, C-3' + C-5'), 117.7 (d, C-4), 122.0 (d, C-6), 123.4 (d, C-2''), 124.3 (s, C-1'), 126.4 (d, 2C, C-2' + C-6'), 129.8 (s, C-3a), 131.2 (d, C-1''), 133.2 (s, C-5), 154.1 (s, C-7a), 156.4 (s, C-2), 160.0 (s, C-4').
GC Retention time	16.28 min with Toan_20min method
MS analyst, m/z (Int.)	264(100), 249(33), 221(9), 191(7), 165(11), 135(13)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 265.1223, m/z (measured) = 265.1223, difference = -0.01 ppm.

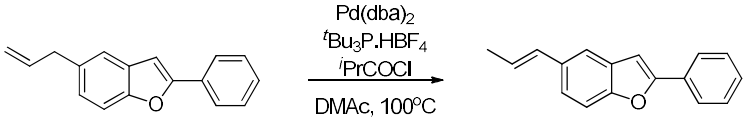
D III.15.3 Synthesis of (*E*)-2-(3,5-dimethoxyphenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (137)



118 137

General procedure	I
Reaction scale	59 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	45mg (77%), colorless oil
Molecular formular, m.w.	$C_{19}H_{18}O_3$, 294.35 g/mol
R_f	0.53 with LP/EtOAc 9:1
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.91 (d, *J* = 6.4 Hz, 3H, H-3''), 3.88 (s, 6H, OCH_3), 6.22 (dq, *J* = 15.9, 6.5 Hz, 1H, H-2''), 6.47 – 6.55 (m, 2H, H-1'' + H-3), 6.97 – 7.03 (m, 3H, H-4' + H-2' + H-6'), 7.27 – 7.50 (m, 3H, H-6 + H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.5 (C-3''), 55.5 (2C, OCH_3), 101.0 (C-4'), 101.9 (C-3), 102.9 (2C, C-2' + C-6'), 111.0 (C-7), 118.0 (C-4), 122.6 (C-6), 124.6 (C-2''), 129.4 (C-9), 131.1 (C-1''), 132.2 (C-1'), 133.3 (C-5), 154.1 (C-8), 156.1 (C-2), 161.1 (2C, C-3' + C-5').
GC Retention time	18.69 min with Toan_20min method
MS analyst, m/z (Int.)	295(18), 294 (100), 267(6), 235(7), 207(17), 179(7), 165(23), 146(14), 128(14).
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 313.1434, m/z (measured) = 313.1430, difference = 1.32 ppm.

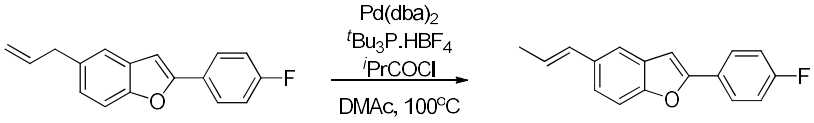
D III.15.4 Synthesis of (*E*)-2-phenyl-5-(prop-1-en-1-yl)benzo[*b*]furan (138)



119 138

General procedure	I
Reaction scale	47 mg (0.5 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallized in LP
Yield	35 mg (75%)
Molecular formular, m.w.	$C_{17}H_{14}O$, 234.30 g/mol
R_f	0.62 with LP
Melting point	126 – 128 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.92 (dd, *J* = 6.4, 1.8 Hz, 3H, H-3''), 6.22 (dq, *J* = 15.9, 6.5 Hz, 1H, H-2''), 6.51 (d, *J* = 15.9 Hz, 1H, H-1''), 7.00 (s, 1H, H-3), 7.27 – 7.52 (m, 6H, Ar-H), 7.87 (m, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) =18.5 (q, C-3''), 101.3 (d, C-2), 111.0 (d, C-7), 118.0 (d, C-4), 122.5 (d, C-6), 124.5 (d, C-4'), 124.9 (d, 2C, C-2' + C-6'), 128.5 (d, C-3''), 128.8 (d, 2C, C-3' + C-5'), 129.5 (s, C-3a), 130.5 (s, C-1'), 131.1 (d, C-1''), 133.3 (s, C-5), 154.2 (s, C-7a), 156.3 (s, C-2).
GC Retention time	14.04 min with Toan_20min method
MS analyst, m/z (Int.)	235(18), 234(100), 207(18), 189(12), 178(9), 129(17), 105(17), 89(12), 77(11)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 235.1117, m/z (measured) = 235.1123, difference = -2.28 ppm.

D III.15.5 Synthesis of (*E*)-2-(4-fluorophenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (139)

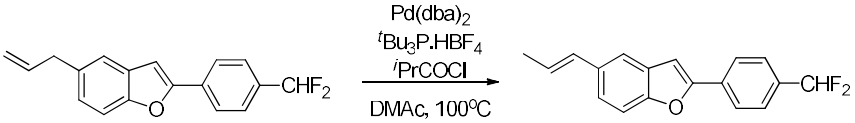


120 139

General procedure	I
Reaction scale	50 mg (0.2 mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallized in LP
Yield	39 mg (77%)
Molecular formular, m.w.	$C_{17}H_{13}FO$, 252.29 g/mol
R_f	0.45 with *n*-heptane
Melting point	123 – 125 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.91 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 6.22 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.50 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1'), 6.89 (s, 1H, H-3), 7.11 – 7.16 (m, 2H, H-3' + H-5'), 7.29 – 7.31 (dd, *J* = 8.6, 1.7 Hz, 1H, H-6), 7.41 – 7.49 (m, 2H, H-4 + H-7), 7.80 – 7.83 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 101.1 (d, J_{C-F} = 1.3 Hz, C-3), 111.0 (d, C-7), 115.9 (d, J_{C-F} = 21.8 Hz, 2C, C-3' + C-5'), 118.0 (d, C-4), 122.6 (d, C-6), 124.6 (d, C-2''), 126.7 (d, J_{C-F} = 8.3 Hz, 2C, C-2' + C-6'), 126.8 (d, J_{C-F} = 3.2 Hz, 1C, C-1'), 129.5

	(s, C-3a), 133.4 (s, C-5), 136.5 (d, C-1''), 154.2 (s, C-7a), 155.4 (s, C-2), 161.3 (d, J_{C-F} = 247.2 Hz, 1C, C-4').
GC Retention time	13.85 min with Toan_20min method
MS analyst, m/z (Int.)	253(21), 252(100), 225(10), 208(21), 207(74), 196(10), 183(10), 129(25), 109(12), 97(18), 57(20)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 253.1023, m/z (measured) = 253.1027, difference = -1.41 ppm.

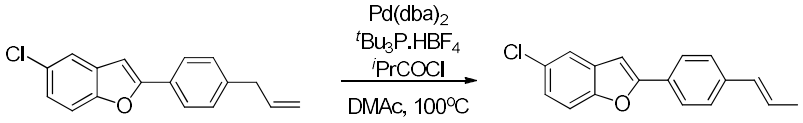
D III.15.6 Synthesis of (*E*)-2-(4-(difluoromethyl)phenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (140)



121 140

General procedure	I
Reaction scale	57 mg (0.2 mmol)
Purification	MPLC with *n*-heptane, 18 g silica 60 then recrystallized in LP
Yield	42 mg (74%)
Molecular formular, m.w.	$C_{18}H_{14}F_2O$, 284.31 g/mol
R_f	0.23 with *n*-heptane
Melting point	125 – 128 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.91 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 6.23 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.50 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1''), 6.68 (t, J_{H-F} = 56.4 Hz, 1H, CHF_2), 7.05 (s, 1H, H-3), 7.32 – 7.34 (m, 2H, H-6 + H-4), 7.51 – 7.59 (m, 3H, H-3' + H-5' + H-7), 7.92 (d, *J* = 8.4 Hz, 2H, H-2' + H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 102.7 (d, C-3), 111.2 (d, C-7), 114.5 (t, J_{C-F} = 237.3 Hz, 1C, CHF_2), 118.2 (d, C-4), 123.1 (d, C-6), 124.8 (d, C-2''), 125.0 (d, 2C, C-2' + C-6'), 126.1 (t, J_{C-F} = 6.2 Hz, 2C, C-3' + C-5'), 129.2 (d, C-3a), 131.0 (d, C-1''), 132.7 (s, C-5), 133.5 (s, C-1'), 134.1 (t, J_{C-F} = 22.4 Hz, 1C, C-4'), 154.4 (C-7a), 155.1 (s, C-2).
GC Retention time	14.70 min with Toan_20min method
MS analyst, m/z (Int.)	285(21), 284(100), 257(20), 207(37), 205(19), 155(22), 141(15), 129(68), 128(37), 97(17), 77(17), 57(20)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 285.1091, m/z (measured) = 285.1084, difference = 2.13 ppm.

D III.15.7 Synthesis of (*E*)-2-(2-chlorophenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (141a)

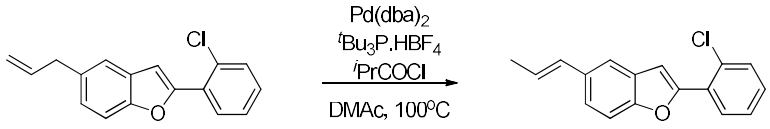


123a 141a

General procedure	I
Reaction scale	54 (0.2 mmol)
Purification	MPLC with LP, 9 g silica 60 then recrystallized in LP

Yield	38 mg (70%)
Molecular formular, m.w.	$C_{17}H_{13}ClO$, 268.74 g/mol
R_f	0.57 with LP
Melting point	142 – 143 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.92 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 6.33 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.45 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1''), 6.92 (d, *J* = 0.7 Hz, 1H, H-3), 7.22 (dd, *J* = 8.6, 2.1 Hz, 1H, H-6), 7.40 – 7.43 (m, 3H, H-3' + H-5' + H-7), 7.53 (d, *J* = 2.1 Hz, 1H, H-4), 7.76 – 7.78 (m, 2H, H-2' + H-6').
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 18.6 (q, C-3''), 100.4 (d, C-3), 112.0 (d, C-7), 120.3 (d, C-4), 124.2 (d, C-6), 125.2 (d, 2C, C-2' + C-6'), 126.2 (d, 2C, C-3' + C-5'), 127.0 (d, C-2''), 128.2 (s, C-1'), 128.5 (s, C-5), 130.5 (d, C-1''), 130.7 (s, C-3a), 138.7 (s, C-4'), 153.2 (s, C-7a), 157.4 (s, C-2).
GC Retention time	15.51 min with Toan_20min method
MS analyst, m/z (Int.)	270(29), 268(100), 255(13), 253(40), 227(10), 191(21), 165(11)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 269.0728, m/z (measured) = 269.0721, difference = 2.48 ppm.

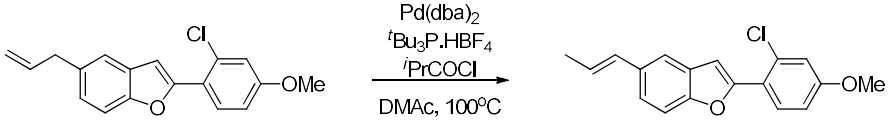
D III.15.8 Synthesis of (*E*)-2-(2-chlorophenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (142)



124 142

General procedure	I
Reaction scale	54 mg (0.2 mmol)
Purification	MPLC with LP, 18 g silica 60 then recrystallized in LP
Yield	35 mg (65%)
Molecular formular, m.w.	$C_{17}H_{13}ClO$, 268.74 g/mol
R_f	0.54 with LP
Melting point	66 – 68 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.94 (d, *J* = 6.5 Hz, 3H, H-3''), 6.33 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.45 (dd, *J* = 15.7, 1.3 Hz, 1H, H-1''), 6.67 – 6.77 (m, 2H, Ar-H), 7.47 – 7.75 (m, 5H, Ar-H), 8.04 – 8.11 (m, 1H, H-6').
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 14.6 (q, C-3''), 105.6 (d, C-3), 112.1 (d, C-7), 120.4 (d, C-4), 124.4 (d, C-6), 125.1 (d, C-2''), 127.0 (d, C-5'), 127.4 (d, C-3'), 128.3 (d, C-6'), 128.5 (d, C-4'), 128.9 (d, C-1''), 129.0 (s, C-1'), 129.1 (s, C-3a), 130.0 (s, C-5), 130.6 (s, C-2'), 153.0 (s, C-7a), 153.3 (s, C-2).
GC Retention time	14.32 min with Toan_20min method
MS analyst, m/z (Int.)	270(35), 268(100), 253(27), 233(23), 227(16), 218(20), 191(41), 165(13)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 269.0728, m/z (measured) = 269.0730, difference = -0.88 ppm.

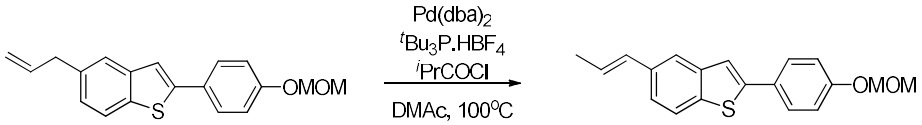
D III.15.9 Synthesis of (*E*)-2-(2-chloro-4-methoxyphenyl)-5-(prop-1-en-1-yl)benzo[*b*]furan (143)



125 143

General procedure	I
Reaction scale	60 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	41 mg (69%)
Molecular formular, m.w.	$C_{18}H_{15}ClO_2$, 298.77 g/mol
R_f	0.32 with LP
Melting point	112 – 115 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.93 (d, *J* = 6.5 Hz, 3H, H-3''), 3.86 (s, 3H, OCH_3), 6.19 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.67 – 6.77 (m, 2H, H-1'' + H-3), 6.85 – 7.02 (m, 2H, Ar-H), 7.18 – 7.71 (m, 4H, Ar-H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.7 (q, C-3''), 55.3 (q, OCH_3), 104.4 (d, C-3), 111.9 (d, C-7), 112.2 (d, C-5'), 112.9 (d, C-3'), 120.2 (d, C-4), 120.9 (s, C-1'), 123.9 (d, C-6), 128.2 (s, C-3a), 128.6 (d, C-2''), 129.8 (d, C-6'), 130.0 (d, C-1''), 130.7 (s, C-5), 134.4 (s, C-2'), 152.8 (s, C-7a), 156.7 (s, C-2), 160.1 (s, C-4').
GC Retention time	16.28 min with Toan_20min method
MS analyst, m/z (Int.)	300(35), 298(100), 269(15), 267(45), 252(24) 248(15), 226(33), 191(21), 135(14)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 299.0833, m/z (measured) = 299.0833, difference = 0.01 ppm.

D III.15.10 Synthesis of (*E*)-2-(4-(methoxymethoxy)phenyl)-5-(prop-1-en-1-yl)benzo[*b*]thiophene (103)

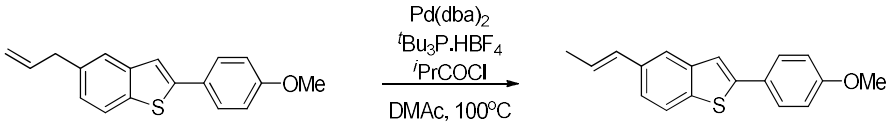


101 103

General procedure	I
Reaction scale	62 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	44 mg (71%)
Molecular formular, m.w.	$C_{19}H_{18}O_2S$, 310.41 g/mol
R_f	0.52 with LP/EtOAc 9:1
Melting point	173 – 174 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.91 (dd, *J* = 6.6, 1.5 Hz, 3H, H-3''), 3.50 (s, 3H, OCH_3), 5.21 (s, 2H, OCH_2O), 6.28 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.50 (dd, *J* = 15.8, 1.5 Hz, 1H, H-1''), 7.08 – 7.10 (m, 2H, H-3' + H-5'), 7.32 (dd, *J* = 8.4, 2.6 Hz, 1H, H-6), 7.39

	(s, 1H, H-3), 7.61 – 7.64 (m, 3H, H-2' + H-6' + H-4), 7.70 (d, *J* = 8.4 Hz, 1H, H-7).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 116.6 (d, 2C, C-3' + C-5'), 118.5 (d, C-3), 120.6 (d, C-4), 122.1 (d, 2C, C-7 + C-6), 125.3 (s, C-1'), 127.7 (d, 2C, C-2' + C-6'), 128.2 (d, C-2''), 131.1 (d, C-1''), 134.7 (s, C-5), 137.7 (s, C-7a), 141.3 (s, C-3a), 144.4 (s, C-2), 157.4 (s, C-4').
GC Retention time	20.21 min with Toan_25min method
MS analyst, m/z (Int.)	311(21), 310(100), 279(55), 265(21), 250(27), 208(13), 189(10), 158(87), 139(19)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 310.1022, m/z (measured) = 310.1025, difference = -1. 01 ppm.

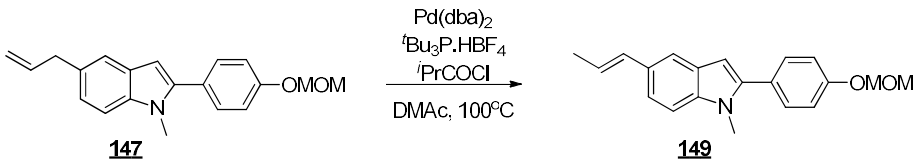
D III.15.11 Synthesis of (*E*)-2-(4-methoxyphenyl)-5-(prop-1-en-1-yl)benzo[*b*]thiophene (144)



126 144

General procedure	I
Reaction scale	56 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	32 mg (57%)
Molecular formular, m.w.	$C_{18}H_{16}OS$, 280.39 g/mol
R_f	0.67 with LP/EtOAc 9:1
Melting point	154 – 156 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.93 (d, *J* = 6.5 Hz, 3H, H-3''), 3.86 (s, 3H, OCH_3), 6.29 (dq, *J* = 15.6, 6.5 Hz, 1H, H-2''), 6.51 (d, *J* = 15.6 Hz, 1H, H-1''), 6.96 (d, *J* = 8.6 Hz, 2H, H-3' + H-5'), 7.27 – 7.39 (m, 2H, H-6 + H-3), 7.62 – 7.74 (m, 4H, H-2' + H-6' + H-4 + H-7).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, CH_3), 55.4 (q, OCH_3), 114.3 (d, 2C, C-3' + C-5'), 118.2 (d, C-3), 120.6 (d, C-4), 122.0 (d, C-7), 122.1 (d, C-6), 125.2 (d, C-2''), 127.1 (s, C-1'), 127.7 (d, 2C, C-2' + C-6'), 131.1 (d, C-1''), 134.6 (s, C-5), 137.6 (s, C-7a), 141.3 (s, C-3a), 144.5 (s, C-2), 159.8 (s, C-4')
GC Retention time	18.94 min with Toan_20min method
MS analyst, m/z (Int.)	281(20), 280(100), 265(36), 237(11), 221(10), 171(15), 151(11), 110(6)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 281.0995, m/z (measured) = 281.1004, difference = -3.48 ppm.

D III.15.12 Synthesis of (*E*)-2-(4-(methoxymethoxy)phenyl)-1-methyl-5-(prop-1-en-1-yl)-1*H*-indole (149)

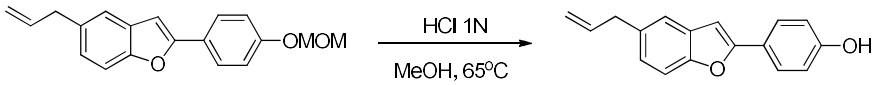


147 149

General procedure	I
Reaction scale	61 mg (0.2 mmol)
Purification	MPLC with LP/EtOAc (gradient 1 – 10% EtOAc), 9 g silica 60 then recrystallized in LP
Yield	44 mg (71%)
Molecular formular, m.w.	$C_{20}H_{21}NO_2$, 307.39 g/mol
R_f	0.40 with LP/EtOAc 9:1
Melting point	98 – 99 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.85 (dd, *J* = 6.6, 1.6 Hz, 3H, H-3''), 3.48 (s, 3H, N-CH_3), 3.53 (s, 3H, OCH_3), 5.24 (s, 2H, OCH_2O), 5.98 (dq, *J* = 15.6, 6.6 Hz, 1H, H-2''), 6.33 (dd, *J* = 15.8, 1.6 Hz, 1H, H-1''), 7.06 – 7.21 (m, 8H, Ar-H).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 18.5 (q, C-3''), 30.8 (q, N-CH_3), 56.1 (q, OCH_3), 94.4 (t, OCH_2O), 108.9 (d, C-3), 112.6 (s, C-1'), 115.9 (d, 2C, C-3' + C-5'), 117.5 (d, C-4), 119.3 (d, C-6), 121.9 (d, C-7), 125.7 (s, C-2) , 128.1 (d, C-2''), 129.0 (s, C-3a), 132.0 (d, 2C, C-2' + C-6'), 132.2 (d, C-1''), 136.5 (s, C-5), 137.6 (s, C-7a), 156.9 (s, C-4')
GC Retention time	19.14 min with Toan_20min method
MS analyst, m/z (Int.)	307(100), 276(12), 263(28), 262(78), 206(13), 192(12)
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 308.1645, m/z (measured) = 308.1647, difference = -0.62 ppm.

D III.16 MOM deprotection.

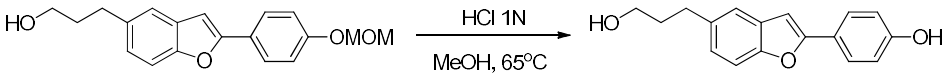
D III.16.1 Synthesis 4-(5-allylbenzo[*b*]furan-2-yl)phenol (95)



92 95

General procedure	J
Reaction scale	29 mg (0.1 mmol)
Purification	MPLC with LP/EtOAc 3:1, 9 g silica 60 then recrystallized in LP
Yield	23 mg (91%)
Molecular formular, m.w.	$C_{17}H_{14}O_2$, 250.30 g/mol
R_f	0.43 with LP/EtOAc 3:1
Melting point	165 – 168 °C
^{1}H-NMR (400 MHz, acetone-d6)	δ (ppm) = 3.33 (d, *J* = 6.7 Hz, 2H, H-1''), 4.88 – 4.99 (m, 2H, H-3''), 5.88 (ddt, *J* = 16.8, 10.4, 6.7 Hz, 1H, H-2''), 6.82 – 6.84 (m, 2H, H-3' + H-5'), 6.89 (s, 1H, H-3), 6.96 (dd, *J* = 8.5, 1.2 Hz, 1H, H-6), 7.26 – 7.31 (m, 2H, H-2' + H-6'), 7.63 – 7.65 (m, 2H, H-4 + H-7), 8.60 (s, 1H, ArOH).
^{13}C-NMR (100 MHz, acetone-d6)	δ (ppm) = 39.8 (t, C-1''), 99.1 (d, C-3), 110.4 (d, C-7), 114.7 (t, C-3''), 115.8 (d, 2C, C-3' + C-5'), 120.2 (d, C-4), 122.2 (s, C-1'), 124.5 (d, C-6), 126.4 (d, 2C, C-2' + C-6'), 129.9 (s, C-3a), 134.8 (s, C-5), 138.3 (d, C-2''), 153.4 (s, C-7a), 156.6 (s, C-2), 158.2 (s, C-4').
GC Retention time	does not fly over GC
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 251.1067, m/z (measured) = 251.1062, difference = 1.82 ppm.

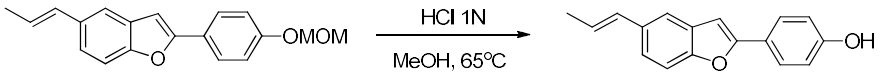
D III.16.2 Synthesis of 4-(5-(3-hydroxypropyl)benzo[*b*]furan-2-yl)phenol (96)



93 96

General procedure	J
Reaction scale	31 mg (0.1 mmol)
Purification	MPLC with LP/EtOAc 3:1, 9 g silica 60 then recrystallized in LP
Yield	24 mg (89%)
Molecular formular, m.w.	$C_{17}H_{16}O_3$, 268.31 g/mol
R_f	0.33 with LP/EtOAc 3:1
Melting point	194 – 196 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.89 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 2H, H-2''), 2.80 (t, *J* = 7.2 Hz, 2H, H-1''), 2.95 (s, 1H, OH), 3.62 (t, *J* = 6.4 Hz, 2H, H-3''), 6.95 – 6.97 (m, 3H, H-3 + H-3' + H-5'), 7.10 – 7.13 (m, 1H, H-6), 7.39 – 7.40 (m, 2H, H-4 + H-7), 7.75 – 7.77 (m, 2H, H-2' + H-6'), 8.66 (s, 1H, ArOH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 31.9 (t, C-1''), 35.1 (t, C-2''), 61.0 (t, C-3''), 99.1 (d, C-3), 110.3 (d, C-7), 115.7 (d, 2C, C-3' + C-5'), 119.9 (d, C-4), 122.2 (s, C-1'), 124.4 (d, C-6), 126.3 (d, 2C, C-2' + C-6'), 129.7 (s, C-3a), 137.0 (s, C-5), 153.2 (s, C-7a), 156.5 (s, C-2), 158.0 (s, C-4').
GC Retention time	does not fly over GC
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 269.1172, m/z (measured) = 269.1183, difference = -3.87 ppm.

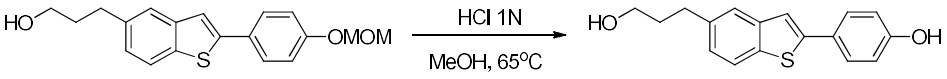
D III.16.3 Synthesis (*E*)-4-(5-(prop-1-en-1-yl)benzo[*b*]furan-2-yl)phenol (97)



94 97

General procedure	J
Reaction scale	29 mg (0.1 mmol)
Purification	MPLC with LP/EtOAc 3:1, 9 g silica 60 then recrystallized in LP
Yield	23 mg (93%)
Molecular formular, m.w.	$C_{17}H_{14}O_2$, 250.30 g/mol
R_f	0.40 with LP/EtOAc 3:1
Melting point	198 – 199 °C (Lit. 196 - 198 °C)[130]
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.87 (dd, *J* = 6.6, 1.2 Hz, 3H, H-3''), 6.26 (dq, *J* = 15.6, 6.6 Hz, 1H, H-2''), 6.51 (d, *J* = 15.8 Hz, 1H, H-1''), 6.98 – 7.02 (m, 3H, H-3 + H-3' + H-5'), 7.32 (dd, *J* = 8.6, 1.1 Hz, 1H, H-6), 7.44 (d, *J* = 8.5 Hz, 1H, H-7), 7.54 (s, 1H, H-4), 7.78 – 7.80 (m, 2H, H-2' + H-6'), 8.76 (s, 1H, Ar-OH)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 17.7 (q, C-3''), 99.3 (d, C-3), 110.6 (d, C-7), 115.8 (d, 2C, C-3' + C-5'), 117.7 (d, C-4), 121.9 (d, C-6), 122.1 (s, C-1'), 123.9 (d, C-2''), 126.5 (d, 2C, C-2' + C-6'), 130.0 (s, C-3a), 131.2 (d, C-1''), 133.3 (s, C-5), 153.9 (s, C-7a), 156.8 (s, C-2), 158.2 (s, C-4').
GC Retention time	does not fly over GC
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 251.1067, m/z (measured) = 251.1057, difference = 3.71 ppm.

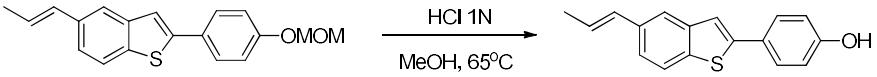
D III.16.4 Synthesis of 4-(5-(3-hydroxypropyl)benzo[*b*]thiophen-2-yl)phenol (104)



102 104

General procedure	J
Reaction scale	33 mg (0.1 mmol)
Purification	MPLC with LP/EtOAc 3:1, 9 g silica 60 then recrystallized in LP
Yield	25 mg (89%)
Molecular formular, m.w.	$C_{17}H_{16}O_2S$, 284.37 g/mol
R_f	0.29 with LP/EtOAc 3:1
Melting point	217 – 219 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ (ppm) = 1.74 (tt, *J* = 7.5, 6.2 Hz, 2H, H-2''), 2.67 (t, *J* = 7.6 Hz, 2H, H-1''), 2.73 (s, 1H, OH), 3.46 (t, *J* = 5.8 Hz, 2H, H-3''), 6.79 – 6.81 (m, 2H, H-3' + H-5'), 7.06 (dd, *J* = 8.2, 1.6 Hz, 1H, H-6), 7.38 (s, 1H, H-3), 7.47 – 7.65 (m, 4H, H-4 + H-7 + H-2' + H-6'), 8.54 (s, 1H, Ar-OH).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ (ppm) = 31.9 (t, C-2''), 34.9 (t, C-1''), 60.8 (t, C-3''), 115.9 (d, 2C, C-3' + C-5'), 117.8 (d, C-3), 121.8 (d, C-4), 122.7 (s, C-1'), 125.1 (d, C-7), 125.9 (d, C-6), 127.6 (d, 2C, C-2' + C-6'), 136.3 (s, C-5), 139.0 (s, C-7a), 141.5 (s, C-3a), 144.4 (s, C-2), 157.9 (s, C-4').
GC Retention time	does not fly over GS
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 285.0944, m/z (measured) = 285.0934, difference = 3.56 ppm.

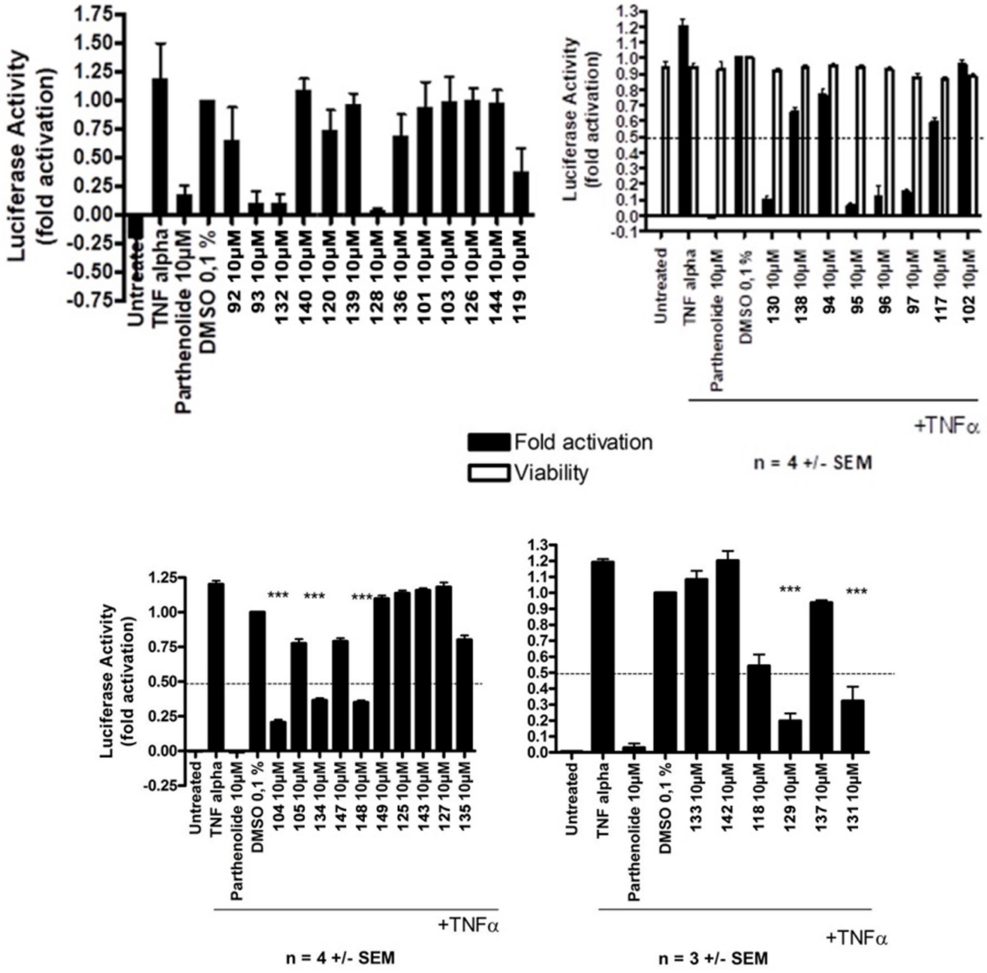
D III.16.5 Synthesis (*E*)-4-(5-(prop-1-en-1-yl)benzo[*b*]thiophen-2-yl)phenol (105)



103 105

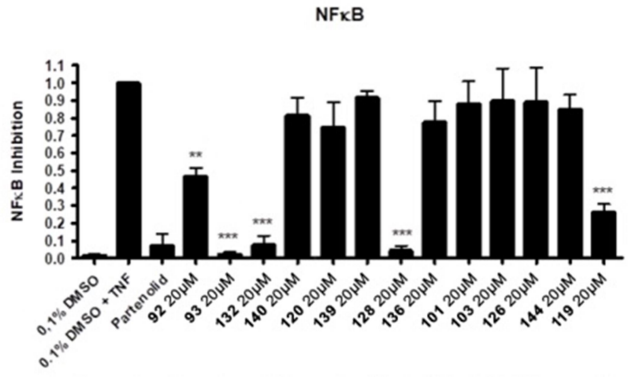
General procedure	J
Reaction scale	31 mg (0.5 mmol)
Purification	MPLC with LP/EtOAc 3:1, 9 g silica 60 then recrystallized in LP
Yield	24 mg (90%)
Molecular formular, m.w.	$C_{17}H_{14}OS$, 266.36 g/mol
R_f	0.38 with LP/EtOAc 3:1
Melting point	212 – 213 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ (ppm) = 1.74 (dd, *J* = 6.6, 1.6 Hz, 3H, H-3''), 6.21 (dq, *J* = 15.7, 6.6 Hz, 1H, H-2''), 6.38 (dd, *J* = 15.8, 1.5 Hz, 1H, H-1''), 6.79 – 6.81 (m, 2H, H-3' + H-5'), 7.23 (dd, *J* = 8.4, 1.7 Hz, 1H, H-6), 7.37 (s, 1H, H-3), 7.47 – 7.49 (m, 2H, H-2' + H-6'), 7.56 (d, *J* = 1.2 Hz, 1H, H-4), 7.63 (d, *J* = 8.4 Hz, 1H, H-7), 8.54 (s, 1H, Ar-OH).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ (ppm) = 17.8 (q, C-3''), 115.9 (d, 2C, C-3' + C-5'), 117.9 (d, C-3), 120.6 (d, C-4), 122.0 (s, C-1'), 124.8 (d, C-7), 125.7 (d, C-6), 127.61 (d, 2C, C-2' + C-6'), 127.66 (d, C-2''), 131.1 (d, C-1''), 134.8 (s, C-5), 137.3 (s, C-7a), 141.6 (s, C-3a), 144.8 (s, C-2), 158.0 (s, C-4').
GC Retention time	does not fly over GC
HR-MS analyst	$[M+H]^+$ m/z (predicted) = 267.0838, m/z (measured) = 267.0830, difference = 3.22 ppm.

D IV Biology testing results



n is number of independent experiments, means +/- SEM are shown, unpaired t-test for statistical analysis
***: p values < 0.001 statistical significance

Figure D-1: Results testing compounds for Luciferase activity



***: p values < 0.001 statistical significance

Figure D-2: Results testing compounds for NF-κB inhibition

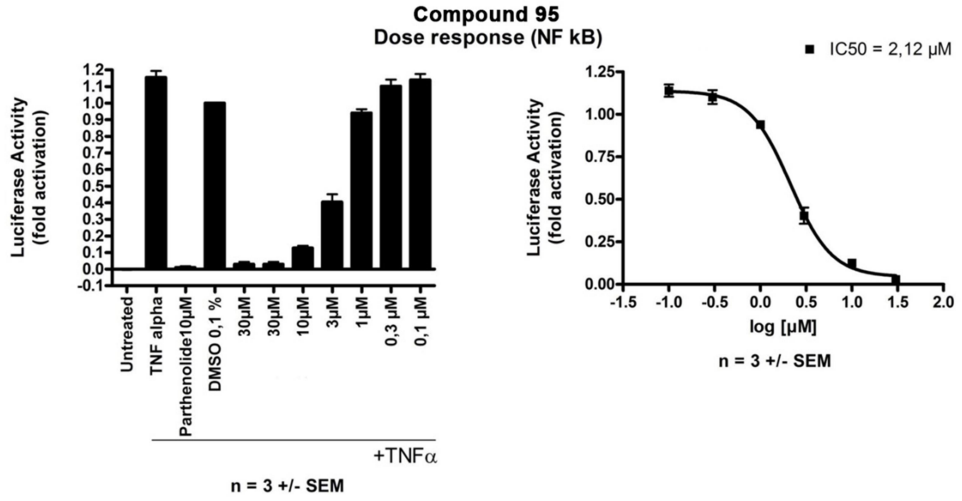


Figure D-3: Dose response curve of compound 95

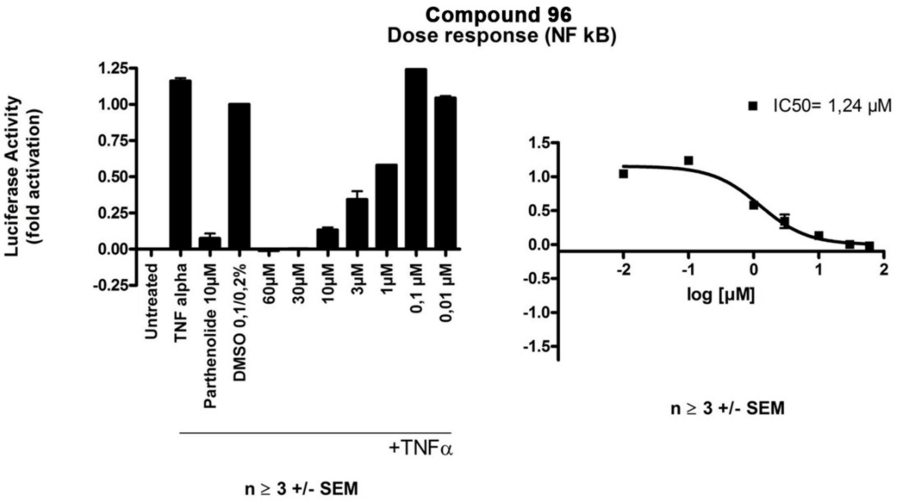


Figure D-4: Dose response curve of compound 96

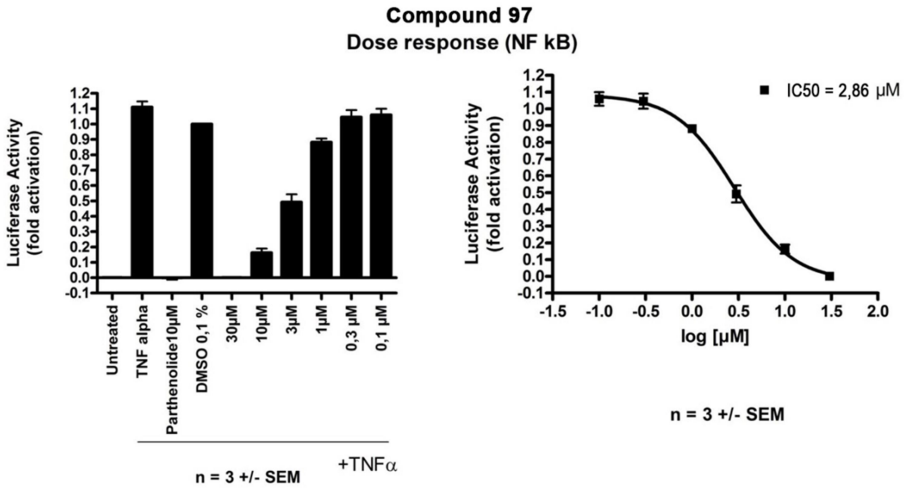


Figure D-5: Dose response curve of compound 97

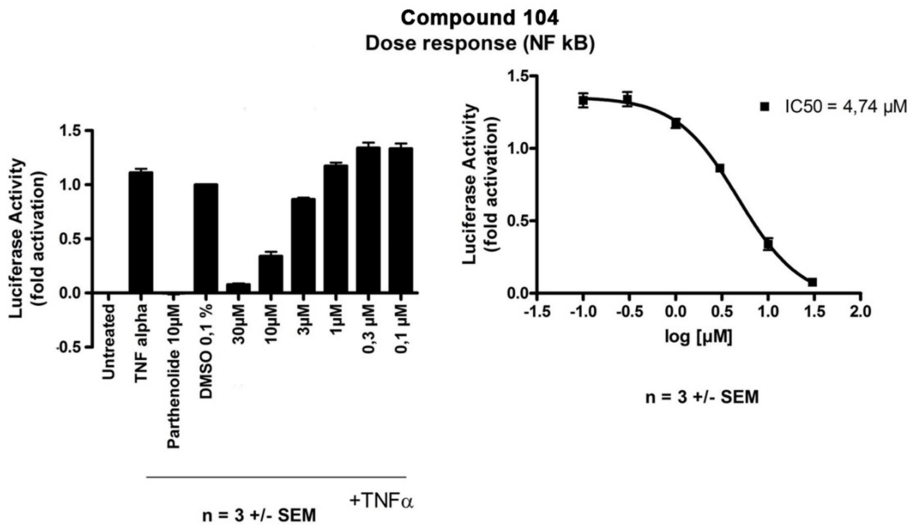


Figure D-6: Dose response curve of compound 104

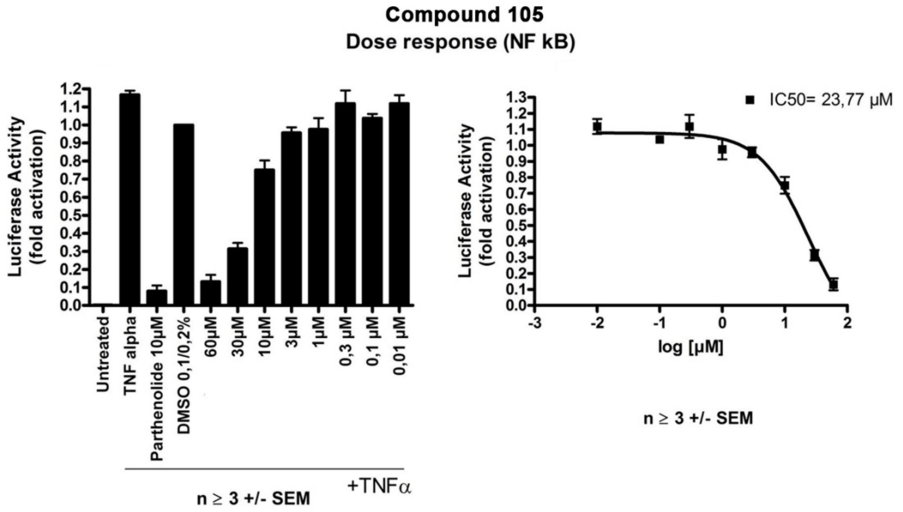


Figure D-7: Dose response curve of compound 105

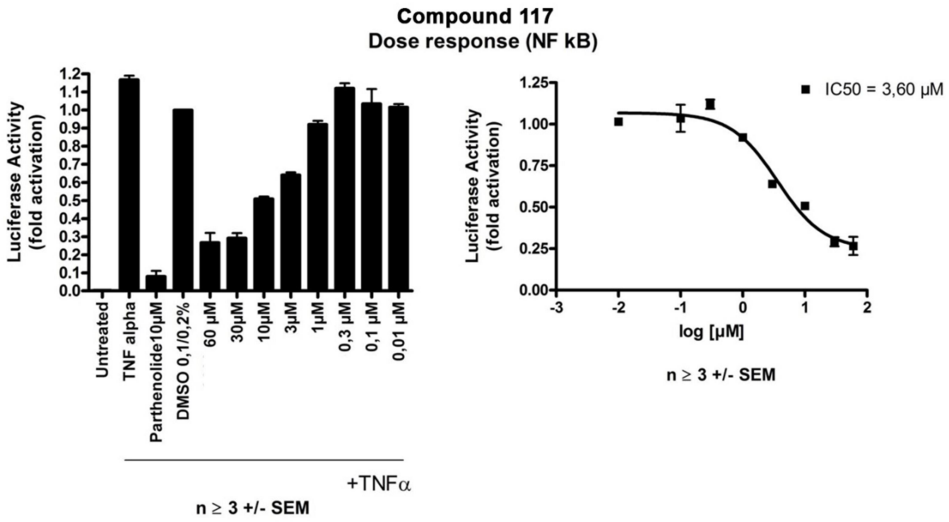


Figure D-8: Dose response curve of compound 117

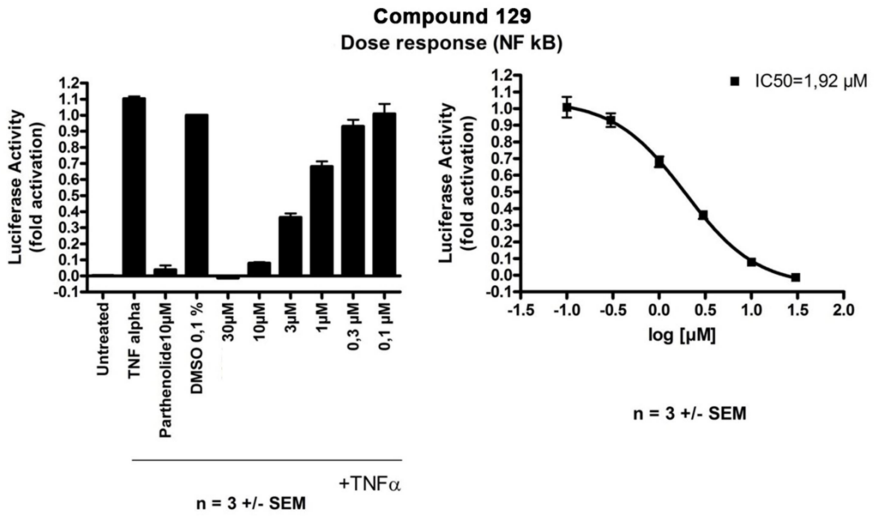


Figure D-9: Dose response curve of compound 129

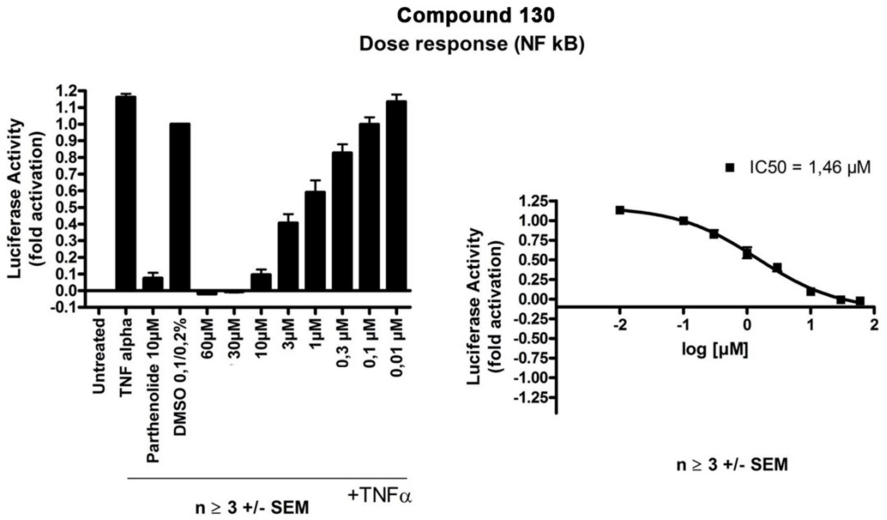


Figure D-10: Dose response curve of compound 130

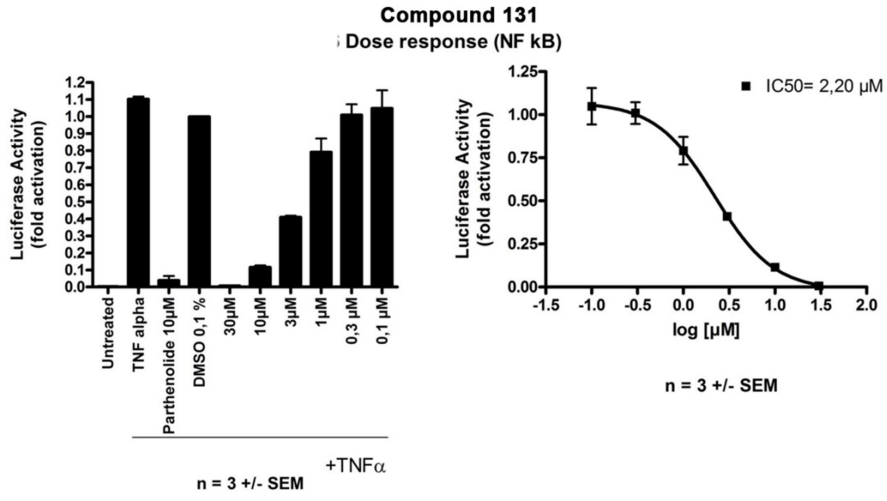


Figure D-11: Dose response curve of compound 131

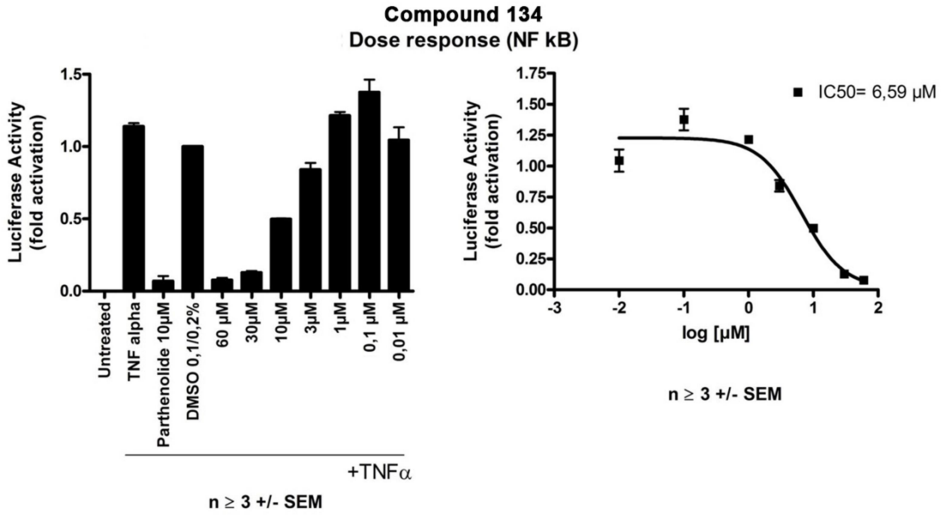


Figure D-12: Dose response curve of compound 134

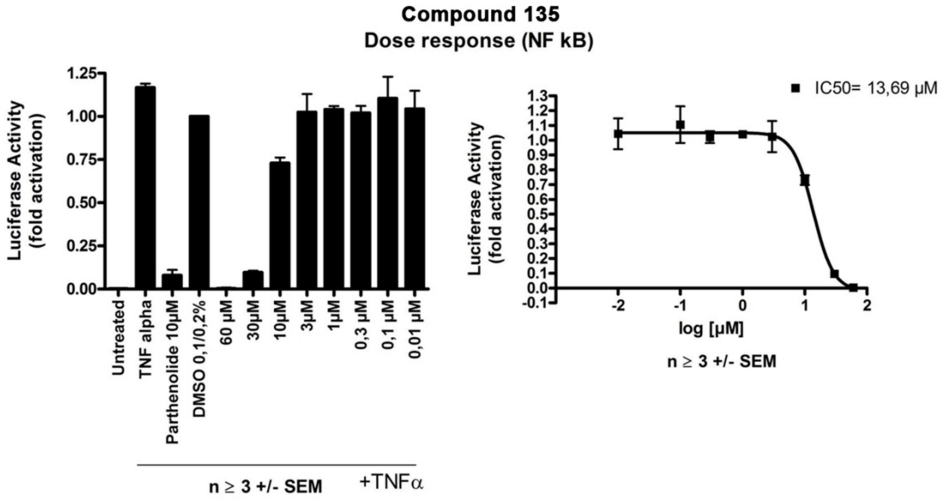


Figure D-13: Dose response curve of compound 135

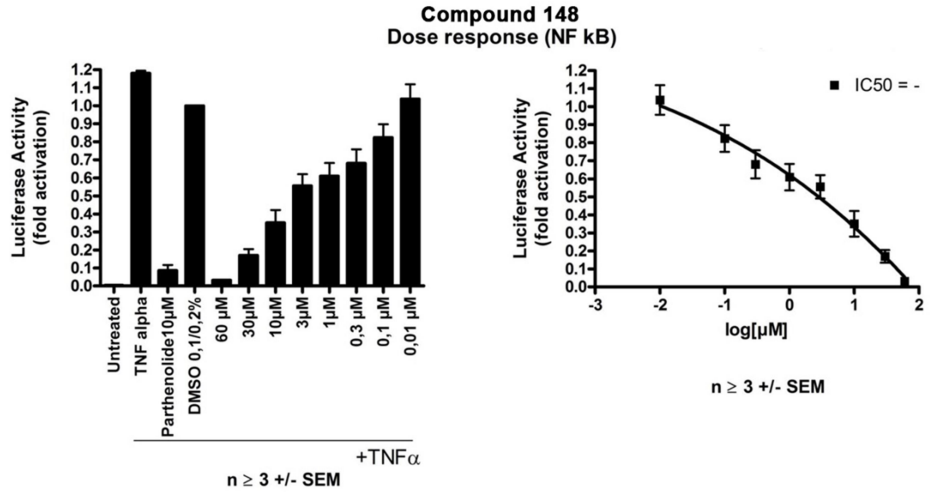


Figure D-14: Dose response curve of compound 148

D V Publications resulting from this thesis

1. T. Dao-Huy, B. J. Waldner, L. Wimmer, M. Schnuerch, M. D. Mihovilovic, "Synthesis of *endo*- and *exo*-*N*-Protected 5-Arylated 2-Aminothiazoles through Direct Arylation: An Efficient Route to Cell Differentiation Accelerators", Eur. J. Org. Chem. **2015**, 2015, 4765-4771.
2. T. Dao-Huy, M. Haider, F. Glatz, M. Schnuerch, M. D. Mihovilovic, "Direct Arylation of Benzo[*b*]furan and Other Benzo-Fused Heterocycles", *Eur. J. Org. Chem.* **2014**, *2014*, 8119-8125.

D VI Curriculum vitae

Toan Dao-Huy, MSc.

Born	04.04.1983
Nationality	Vietnam
Language	Vietnamese (native), English (C level), German (A2 level)

Education

2011 - Now	**Ph. D. Program: Techical Natrual Sciences**	**Vienna, Austria**
	Dissertation: *Application of C-H activation and natural product derivatization for the synthesis of bioactive compounds*	
	Supervisor: Prof. Marko D. Mihovilovic	
	Vienna University of Technology	
2010 - 2011	**Reseacher**	**Hanoi, Vietnam**
	Project: *Synthesis of quinoline derivatives with Anti-malaria activities*	
	Project Leader: Dr. Tran Khac Vu	
	Hanoi University of Science and Technology	
2009 – 2010	**Project Leader**	**Hanoi, Vietnam**
	Project: *Synthesis of the metal lignosulfonates to adhere to NPK fertilizer as a metal-source for plants*	
	Supervisor: Prof. Dao Van Hoang	
	Hanoi University of Science and Technology	
2006 - 2008	**Master Program: Organic and Petrochemical Engineering**	**Hanoi, Vietnam**
	Master thesis: *Synthesis of surfactant lignosulfonates used in modern agrichemical formulation*	
	Supervisor: Prof. Dao Van Hoang	
	Hanoi University of Science and Technology	
2001 - 2006	**Bachelor Program: Technology of Pharmaceutical and Pesticides Chemistry Engineering.**	**Hanoi, Vietnam**
	Bachelor thesis: *Synthesis of Microcrystalline Cellulose (MCC) from paper pulp and the application in pesticide formulation*	
	Supervisor: Dr. Nguyen Ba Xuan	
	Hanoi University of Science and Technology	
1998 - 2001	**Highschool**	**Hanoi, Vietnam**

Specialized Class of Chemistry.

Hanoi – Amsterdam Highschool

Work Experience

2008 - 2011	**HANOI UNIVERSITY OF SCIENCE AND TECHNOLOGY**	**Hanoi, Vietnam**
	Lecturer of Technology of Pharmaceutical and Pesticide Chemistry Dept., Hanoi University of Science and Technology.	
2006 - 2008	**HANOI UNIVERSITY OF SCIENCE AND TECHNOLOGY**	**Hanoi, Vietnam**
	Lecturer assistant of Technology of Pharmaceutical and Pesticide Chemistry Dept., Hanoi University of Science and Technology.	

Personal Archivements

2001 - 2006	**Student**
	University scholarships for excellent student in 5 years.
	Top 3 student of the faculty - GPA 8.49/10
	ASEAN University Games annual contest 2006 - Silver medal in Basketball
	University President's commendation for the best Class Monitor in study and Youth Union activities. (2005)
	- Building primary school for poor children (Phu Tho province) – Volunteer Teacher.
	- Water treatment process for poor farmers (Ha Tay province) – Volunteer Advisor.
	University Art Festival 2001 – First prize.
1995 - 2001	**Pupil**
	School scholarships for top pupil of the class – GPA 8.91/10
	Prudential Insurance Corporation scholarship for top student of the class (2001)
	3rd prize of Chemistry in National Excellent Pupil Contest (2001)
	1st prize in Festival of Young Yamaha organists (Northern provinces) – (1996)

Further Education & Skills

- Vietnam driving license B (< 9 seats, < 3.5T)
- Good skill in using computer and IT in general
- Good skill in playing Basketball and playing Keyboard & Piano

Hobbies & Fields of Interest

- Sport (basketball, table tennis, swimming)
- Travelling and Photography
- Reading and writing about basketball analyst
- Social activities

Conference Activities

Dec. 2015	**Institute of Applied Synthetic Chemistry (IAS) seminar**
	Oral Presentation
	Vienna, Austria
Sept. 2015	**16th Austrian Chemistry Day**
	Poster Presentation
	Innsbruck, Austria
Nov. 2014	**Nature Productes and Drug Discovery – Future Perspective**
	Poster Presentation
	Vienna, Austria
Jun. 2014	**2nd International Symposium on C-H Activation**
	Poster Presentation
	Rennes, France
Sept. 2013	**15th Austrian Chemistry Day**
	Poster Presentation
	Graz, Austria

Publications

1. C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, "A comprehensive overview on directing groups applied in metal catalyzed C-H functionalization chemistry", *Chem. Soc. Rev.* **2018**.
2. T. Dao-Huy, B. J. Waldner, L. Wimmer, M. Schnuerch, M. D. Mihovilovic, "Synthesis of endo- and exo-*N*-Protected 5-Arylated 2-Aminothiazoles through Direct Arylation: An Efficient Route to Cell Differentiation Accelerators", Eur. J. Org. Chem. **2015**, 2015, 4765-4771.
3. T. Dao-Huy, M. Haider, F. Glatz, M. Schnuerch, M. D. Mihovilovic, "Direct Arylation of Benzo[*b*]furan and Other Benzo-Fused Heterocycles", *Eur. J. Org. Chem.* **2014**, *2014*, 8119-8125.
4. T. T. Le, T. Dao-Huy, X. T. Hoang, K. V. Tran, *Tap Chi Hoa Hoc* **2011**, *49*, 401-404.

D VII List of abbreviations

General abbreviations

aqu.	Aqueous
Bp.	Boiling point
cat.	Catalyst
CMD	Concerted Metalation/Deprotonation
conc.	Concentrated
equiv.	Equivalent
GC/MS	Gas Chromatography/Mass Spectrometry
Mp.	Melting point
MPLC	Medium pressure liquid chromatography
MW	Microwave
rt.	Room temperature
sat.	Saturated
sol.	Solution
temp.	Temperature
TLC	Thin layer chromatography
SyMS	Synthetic small molecules

Abbreviations of biological names

AA	Arachidonic acid
ATP	adenosine triphosphate
COX	Cyclooxygenase
DNA	Deoxyribonucleic acid
HIV	Human immunodeficiency virus
IC_{50}	Half maximal inhibitory concentration
IL	Interleukin
KDR	Kinase insert domain receptor
5-LO	5-lipoxygenase
LPS	Lipopolysaccharide
LXR	Liver X receptor
NF-κB	Nuclear factor kappa B
NO	Nitric Oxide
iNOS	Nitric Oxide Synthase
NPY-Y5	Neuropeptide Y receptor Y 5
NSAIDs	Non-steroidal anti-inflammatory drug
RND	Resistance nodulation division
TNF	Tumor necrosis factor

Abbreviations of chemical names

Ac_3Nar	5,7,4'-*O*,*O*,*O*-Triacetylnaringenin
Ac_3Hes	5,7,3'-*O*,*O*,*O*-Triacetylhesperetin
Ac_2Nar	7,4'-*O*,*O*-Diacetylnaringenin
Ac_2Hes	7,3'-*O*,*O*-Diacetylhesperetin
boc	Tert-butyloxycarbonyl group
Bn	Benzyl group
CPhos	2-Dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl
CsOAc	Cesium acetate
CsOPiv	Cesium pivalate
dba	Dibenzylideneacetone
DCM	Dichloromethane
DMAP	4-Dimethylamineopyridine
DMAc	N,N-dimethylacetamide
DME	Dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	Dimethyl Sulfoxide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EVE	Ethyl vinyl ether group
EDGs	Electron donation groups
EWGs	Electron withdrawing groups
Hes	Hesperetin
MOM	Methoxymethyl group
Nar	Naringenin
NBS	N-Bromosuccinimide
Piv	Pivalate group
Piv_3Nar	5,7,4'-*O*,*O*,*O*-triapivaloylnaringenin
Piv_3Hes	5,7,3'-*O*,*O*,*O*-tripivaloylhesperetin
Piv_2Nar	7,4'-*O*,*O*-diapivaloylnaringenin
Piv_2Hes	7,3'-*O*,*O*-dipivaloylhesperetin
PE or LP	Petroleum ether
POH	Hydroxylpropyl group
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TEA	Triethylamine
TMS	Trimethylsiyl group
THF	Tetrahydrofuran
THP	Tetrahydropyranyl group
TIP	Triisopropyl group
p-TSA	para-Toluenesulfonic acid
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbophenyl

Abbreviations for NMR

^{13}CNMR	13-Carbon nuclear magnetic resonance
^{1}HNMR	1-Hydro nuclear magnetic resonance
COSY-NMR	Correlation Spectroscopy Nuclear Magnetic Resonance
Hz	Hertz
J	coupling constant
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
q	Quartet
at	Apperent triplet
dd	Dublet of dublets
dt	Dublet of triplets
br	Board signal

End.

D VIII References

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