Synthesis of Functionalized Naphthalenes, Coumarines, Quinolines, and Isoflavones by Chemo- and Site-Selective Palladium-Catalyzed Coupling Reactions

Dissertation

zur

Erlangung des akademischen Grades
doctor rerum naturalium (Dr. rer. nat.)
der Mathematisch-Naturwissenschaftlichen Fakultät
der Universität Rostock

vorgelegt von


Rostock

urn:nbn:de:gbv:28-diss2015-0137-3
Gutachter :

Gutachter 1. Prof. Dr. Dr. h.c mult. Peter Langer

Universität Rostock

Institut für Chemie

Gutachter 2. Prof. Dr. Bernd Schmidt

Universität Potsdam

Institut für Chemie

Datum der Einreichung 02. März 2015

Datum der Verteidigung 23. Juni 2015
Dedication

I feel a great pleasure to dedicate all of this work to Rostock University then to all of my colleagues in the department of chemistry of Rostock University and to my dear mother and all of my family.
Acknowledgments

I would like to thank my supervisor Prof. Dr. Dr. h.c. mult. Peter Langer for providing efficient guidance and energetic research environment during my whole Ph. D. I always found him ready to facilitate my research by effective discussion, reviving encouragements, unending trust, providing free hand in research and every possible facility.
I wish to express my special gratitude to Dr. Michalik and Dr. Hein and Dr. Feist for a numbers of nice talk about my work. Also to Dr. Vellinger for his professional and accurate X-ray crystallographic analyses. I would like to thank the members of the NMR, IR, MS, and X-ray laboratories of the University of Rostock.
I would like also to thank my colleagues at the University of Rostock Dr. Nadi Elya, Dr. Omer Akrawi, Mr. Aws Hamdy and finally a special thank from my Hearts for my uncle Dr. Ali Suleiman for all things what he did for me from the beginning of my Studying in Rostock and for my Family in Syria, who are waiting for me that I come back with my Ph.D.

Zien Khaddour……..
ABSTRACT IN ENGLISH

I studied the site-selectivity of Suzuki cross-coupling reactions of the bis(triflate) of naphthoates, coumarines, and isoflavones. In addition, the chemo-selectivity of Suzuki cross-coupling reactions of naphthoates and quinolones containing bromide and triflate leaving groups were studied. In this context, prepared various arylated pharmacologically relevant heterocycles which are not readily available by other synthetic methods.

ABSTRACT IN GERMAN

Main Contents

Chapter Two

Site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of methyl 3,7-dihydroxy-2-naphthoate

\[
\begin{align*}
\text{TfO} & \quad \text{O} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Tf}
\end{align*}
\]

\[
\begin{align*}
\text{Ar}^1 & \quad \text{B(OH)}_2 \\
\text{Ar}^2 & \quad \text{B(OH)}_2
\end{align*}
\]

Chapter Three

Chemoselective Suzuki–Miyaura cross-coupling reactions of methyl 4-bromo-3-(trifluoromethanesulfonyloxy)-2-naphthoate

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{Me} \\
\text{Br} & \quad \text{Tf}
\end{align*}
\]

\[
\begin{align*}
\text{Ar}^1 & \quad \text{B(OH)}_2 \\
\text{Ar}^2 & \quad \text{B(OH)}_2
\end{align*}
\]
Chapter Four
Site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of 4,7-dihydroxycoumarin

Chapter Five
Chemoselective Suzuki-Miyaura cross-coupling reactions of 5-bromo-quinolin-8-yl trifluoromethanesulfonate
Chapter Six

Site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of 5,7-dihydroxyisoflavone.
## DETAILED CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEDICATION</td>
<td>I</td>
</tr>
<tr>
<td>ACKNOWLEDGMENT</td>
<td>II</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>III</td>
</tr>
<tr>
<td>MAIN CONTENTS</td>
<td>IV</td>
</tr>
<tr>
<td><strong>CHAPTER ONE</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 General Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Palladium Chemistry</td>
<td>1</td>
</tr>
<tr>
<td>1.3 Palladium-Catalysed Suzuki-Miyaura Reaction</td>
<td>3</td>
</tr>
<tr>
<td>1.4 Applications of Suzuki Coupling Reactions</td>
<td>4</td>
</tr>
<tr>
<td>1.5 Heck Reaction</td>
<td>6</td>
</tr>
<tr>
<td>1.6 Applications of Heck Reaction</td>
<td>6</td>
</tr>
<tr>
<td><strong>CHAPTER TWO</strong></td>
<td>9</td>
</tr>
<tr>
<td>2 Site-selective Suzuki-Miyaura reactions of the bis(triflate) of Methyl 3,7-dihydroxynaphthoate</td>
<td>9</td>
</tr>
<tr>
<td>2.1 Introduction</td>
<td>9</td>
</tr>
<tr>
<td>2.2 Results and Discussion</td>
<td>10</td>
</tr>
<tr>
<td>2.3 Conclusion</td>
<td>13</td>
</tr>
<tr>
<td><strong>CHAPTER THREE</strong></td>
<td>14</td>
</tr>
<tr>
<td>3 Chemoselective Suzuki-Miyaura reactions of the Methyl 4-bromo-3-(trifluoromethanesulfonyloxy)-2-naphthoate</td>
<td>14</td>
</tr>
<tr>
<td>3.1 Introduction</td>
<td>14</td>
</tr>
<tr>
<td>3.2 Results and Discussion</td>
<td>15</td>
</tr>
<tr>
<td>3.3 Conclusion</td>
<td>19</td>
</tr>
<tr>
<td><strong>CHAPTER FOUR</strong></td>
<td>21</td>
</tr>
<tr>
<td>4 Site-Selective Suzuki–Miyaura reactions of the bis(triflate) of 4,7-dihydroxycoumarin</td>
<td>21</td>
</tr>
<tr>
<td>4.1 Introduction</td>
<td>21</td>
</tr>
<tr>
<td>4.2 Results and Discussion</td>
<td>22</td>
</tr>
<tr>
<td>4.3 Conclusion</td>
<td>26</td>
</tr>
<tr>
<td><strong>CHAPTER FIVE</strong></td>
<td>27</td>
</tr>
<tr>
<td>5 Chemoselective Suzuki-Miyaura Cross-Coupling Reactions of 5-Bromo-8-</td>
<td>27</td>
</tr>
</tbody>
</table>
(trifluorosulfonyloxy)quinoline

5.1 Introduction ........................................................................................................... 27
5.2 Results and Discussion ......................................................................................... 28
5.3 Conclusion .............................................................................................................. 32

CHAPTER SIX

6 Site-Selective Suzuki-Miyaura reactions of bis(triflate) of 5,7-
dihydroxyisoflavone ..................................................................................................... 33

6.1 Introduction ........................................................................................................... 33
6.2 Results and Discussion ......................................................................................... 34
6.3 Conclusion .............................................................................................................. 36

CHAPTER SEVEN

7 Experimental Section ................................................................................................ 37

7.1 Nuclear Magnetic Resonance Spectroscopy (NMR) ............................................. 37
7.2 Infrared Spectroscopy (IR) ................................................................................... 37
7.3 Mass Spectroscopy (MS) ...................................................................................... 37
7.4 High Resolution Mass Spectroscopy (HRMS) ...................................................... 37
7.5 Melting points ....................................................................................................... 37
7.6 X-ray Crystal Structure Analysis ......................................................................... 37
7.7 Chromatographic Methods .................................................................................. 38
7.7.1 Thin Layer Chromatography (TLC) ................................................................. 38
7.7.2 Column Chromatography ................................................................................ 38
7.8 Equipment, Chemicals and Work Technique ..................................................... 38
7.9 General Procedures and Spectroscopic Data ..................................................... 39

APPENDIX: CRYSTALLOGRAPHIC DATA ................................................................. 75

LIST OF ABBREVIATIONS .......................................................................................... 83
REFERENCES ............................................................................................................... 84
DECLARATION /ERKLÄRUNG .................................................................................. 93
LIST OF PUBLICATIONS ............................................................................................ 94
CURRICULUM VITAE ................................................................................................. 95
Chapter One

1.1 General Introduction

The formation of carbon-carbon bonds is one of the most important themes in synthetic organic chemistry. The diversity and complexity of several natural products and biological active compounds have created the demand to establish and develop efficient synthetic approaches for constructing C-C bond. As a result for this demand, several conventional synthetic methods have been successfully developed for constructing C-C bond such as Aldol, the Diels-Alder, Michael reactions and the Claisen ester condensation. The first vital synthetic method was discovered by Victor Grignard for constructing carbon-carbon bonds by using organomagnesium reagents. Later, a diverse array of organometallic reagents were developed, which allow to overcome the limitations of the synthetic scope of Grignard reagents. For example, cross-coupling reactions of aryl halides have been realized by a variety of transition metal catalysts. As a result of these developments, the synthesis of a high number of complex molecules and natural products has become viable in the last decades. This important development in organometallic chemistry has led to award Y. Chauvin, R. H. Grubbs (ruthenium catalysts), and R. R. Schrock (molybdenum catalyst) with the Nobel Prize in 2005 for developing the olefin metathesis reaction, and in (2010) to Ei-ichi Negishi and Richard Heck for establishing economic and environmentally-friendly approaches for building carbon-carbon bonds.

1.2 Palladium Chemistry

During recent decades, the so-called palladium-(0)-catalyzed reactions have been developed in large areas of organic chemistry, for example, in medical and pharmacological chemistry. There are different types of palladium-catalyzed cross-coupling reactions, which are known in organic synthesis, such as Suzuki, Heck, Stille, Sonogashira, Tsuji-Trost and Negishi reaction. Several groups have been working in the field of organometallic chemistry which developed many reagents based on the chemistry of palladium.
The general mechanism of palladium-catalyzed cross-coupling reactions consists of three key steps, which involves:

1. Oxidative addition, which includes formation of organometallic intermediate by addition of aryl electrophile to palladium, such as aryl halides or triflates (in this case the oxidation state of palladium-(0) species will be changed into palladium-(II) species).

2. Transmetallation process, where the organic moiety is transferred from a main group metal, such as Mg (Kumada reaction), Cu (Sonogashira reaction), Zn (Negishi reaction), B (Suzuki reaction) or Sn (Stille reaction), to a metal which is more electronegative, such as palladium to give a diorgano palladium complex.

3. Reductive elimination, where the product is formed and the catalyst is regenerated again. (Scheme 2).
Scheme 2 General catalytic cycles for Suzuki-Miyaura reaction.

1.3 Palladium-Catalyzed Suzuki-Miyaura Reaction

The coupling of aryl halides with organoboronic acids is one of the most important palladium-catalyzed cross-coupling reactions for both academic and industrial applications. This reaction may be defined as a reaction between aryl and vinyl-boronic acid with an aryl or vinyl-halide catalyzed by a Palladium-(0)-complex.\(^{12}\)

\[
R-X + R^1\text{-BY}_2 \xrightarrow{\text{Pd(0), base}} R-R^1
\]

- \(R=\) alkyl, vinyl, benzyl, aryl, alkenyl
- \(R^1=\) alkyl, alkinyl, aryl, vinyl
- \(X=\) Cl, Br, OTf, I

Scheme 3 Palladium-Catalyzed Suzuki coupling.

This reaction is widely used to synthesize poly-olefins, styrenes, and substituted biphenyls and the first work for this reaction was published in 1979 by Akira Suzuki and coworkers.\(^{13}\) The organoboranes and boronic acid in this reaction are very powerful partners. They are
commercially available, easy to handle, and relatively tolerant to air and to another functional
groups. The main advantages of this reaction are the low temperature, low pressure, high
yield, and the nontoxic by-products. Moreover, boron compounds are generally non-toxic.
Consequently, all of these mild conditions make this reaction very interesting in the
pharmaceutical and chemical industry.\textsuperscript{14}

1.4 Applications of Suzuki Coupling Reactions

The palladium-catalyzed cross-coupling reactions are important for the pharmacology and the
chemical industry, and also in a big area for the synthesis of many important natural products.
Thus, the palladium-catalyzed cross-coupling reactions are suitable for wide applications. In
the following I present some examples for the use of palladium-catalyzed cross coupling
reactions. The Suzuki reaction was used for preparing the antiviral brominated indole alkaloid
dragmacidin-F.\textsuperscript{15}

\textbf{Scheme 4} Synthesis of dragmacidin F via palladium-catalyzed Suzuki reaction.
Another application for the Suzuki reaction is the synthesis of the anti-cancer agent (+)-dynemicin A (Scheme 5).\textsuperscript{16}

![Scheme 5 Synthesis of (+)-dynemicin A via palladium-catalyzed Suzuki reaction.]

In the chemical industry, the Suzuki reaction could be used for the synthesis of industrial products, such as the drug Boscalid.\textsuperscript{17}

![Scheme 6 Synthesis of Boscalid via palladium-catalyzed Suzuki reaction.]

1.5 Heck reaction

Heck reaction is considered one of the most powerful synthetic tool which includes formation of C-C bond from coupling inactive C-H alkene bonds and (organ halides or triflates) by using palladium as a catalyst and in presence of a base (Scheme 7). \(^{17c}\)

\[
\begin{align*}
\text{R}^1\text{-X} + \text{H} & \quad \text{cat. Pd}^{(0)}/\text{Ligand} \\
\text{R}^2 & \quad \text{base} \\
\text{R}^3 & \quad \text{R}^4
\end{align*}
\]

organohalide       alkene       substituted alkene

\(\text{R}^1 = \text{alkyl, aryl, vinyl}\)
\(\text{X} = \text{Cl, Br, I, OTf}\)

**Scheme 7** Palladium catalyzed Heck coupling reaction.

1.6 Applications of Heck Coupling Reaction

The Heck reaction is one of the most important palladium-catalyzed cross-coupling reactions, which could be used for the synthesis of natural products, such as morphine. \(^{18}\)

**Scheme 8** Synthesis of morphine via palladium-catalyzed Heck reaction.
The Heck reaction has been used also in the chemical industry for the synthesis of several new products, such as fine chemicals\textsuperscript{19} as shown in Scheme 9.

\begin{equation}
\text{Heck reactions}
\end{equation}

\begin{equation}
\text{DVS-bis-BCB}
\text{(Monomer for high performance electronic resins (Cyclotene)}
\text{(Dow chemical 1989)}
\end{equation}

\textbf{Scheme 9} Synthesis of cyclotene via palladium-catalyzed Heck reaction.

In the last years Prof. Langer’s group has extensively studied selective Suzuki-Miyaura cross-coupling reactions preparing some unsymmetrical arylated pharmacologically relevant compounds. For example, the site-selective Suzuki coupling reaction of indole A was found to be in favor of the 2-position. This can be explained according to the sufficient difference in the electronic character of C-2 and C-3\textsuperscript{19a} Also, 2,3-dibromoindenone B gives an excellent site-selectivity, where the first attack occurred at position 3\textsuperscript{19b} (Scheme 10).

\begin{equation}
\text{A}
\end{equation}

\begin{equation}
\text{B}
\end{equation}

\textbf{Scheme 10} Site-selectivity of A and B.
Furthermore, the following reactions show examples of site-selective Suzuki coupling reactions. For example, the reactions of the bis(triflate) of 5,7-dihydroxyflavone C and of the bis(triflate) of 5,7-dihydroxycoumarine D proceed favorably at the 7-position.\textsuperscript{19c,19d} In both cases, the reason of the site-selectivity at position 7 in the coumarin and the flavone core structure can be explained by steric effects. The chemo-selective Suzuki coupling reaction of 5,7-dibromo-8-(trifluoromethanesulfonyloxy)quinoline, containing bromide groups in the presence of a triflate, proceeds favorably at the 5-position E\textsuperscript{19e}, because of the more electron deficient and sterically less hindered character of that particular position (Scheme 11).

\textbf{Scheme 11} Site-selectivity of Suzuki reactions of C and D and of the chemo-selectivity of the reactions of E.
CHAPTER TWO

2 Synthesis of arylated naphthoates by site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of methyl 3,7-dihydroxy-2-naphthoate

2.1 Introduction

Substituted naphthalenes are important lead structures in medicinal chemistry. They also act as intermediates in the synthesis of organic dyes and surfactants and as supporting agents in polymer industry. Naphthalenes derivatives exhibit a broad range of pharmacological activities, such as antimicrobial activity and activity as antibody inhibitors. Naphthalenes derivatives are found in a number of natural products. Examples include guieranone A which shows potent antifungal activity against Cladosporium cucumerinum (Figure 1). Michellamine A, isolated from Ancistrocladus korupensis, has attracted the scientific community primarily because of its interesting binaphthyl structure and its antimalaria and anti-HIV activity. In contrast, 5-(6-hydroxynaphth-2-yl)benzene-1,3-diol was found to be very active against human breast cancer cell line B. Konzik et al. reported that aryl substituents of naphthalenes have a strong influence on their fungistic activity. Therefore, arylated naphthalenes are of considerable pharmacological relevance.

Many methods have been used for the preparation of substituted naphthalenes. For example, 2-substituted naphthalenes were prepared by application of the Baylis–Hillman reaction, or by irradiation of 2-allylacylbenzenes in DMF. Other methods include transition-metal-catalyzed [2+2+2] alkyne cyclizations, Lewis acid catalyzed cyclizations of carbonyl compounds with alkynes and [4+2] cycloadditons. An alternative approach relies on the functionalization of naphthalenes by palladium catalyzed cross-coupling reactions. Recently, Prof. Langer's group has reported the synthesis of arylated naphthalene by chemo- and site-selective Suzuki-Miyaura reactions of naphthalene derivatives. Herein, I report what is, to the best of my knowledge, the first site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of methyl 3,7-dihydroxy-2-naphthoate.
Figure 1 Pharmacologically important naphthalene derivatives.

2.2 Results and discussion

Commercially available 3,7-dihydroxy-2-naphthoic acid (1) was transformed into methyl 3,7-dihydroxy-2-naphthoate (2) which was converted to bis(triflate) 3 in high yield (Scheme 1).

Scheme 1 Synthesis of 3. Conditions: \(i\), 1 (1.0 equiv.), \(\text{Me}_2\text{SO}_4\) (2.2 equiv.), DIPEA (1.1 equiv.), DMF, 85 °C, 1 h; \(ii\), 1) 2 (1.0 equiv.), pyridine (4.0 equiv.), \(\text{CH}_2\text{Cl}_2\), -78 °C, 10 min; 2) \(\text{Tf}_2\text{O}\) (2.4 equiv.), -78 → 0 °C, 4 h.

The Suzuki-Miyaura reaction of 3 with arylboronic acids 4a-i (1.2 equiv.), in the presence of \(\text{Pd(PPh}_3)_4\) (3 mol-%) and \(\text{K}_3\text{PO}_4\) (1.5 equiv.) (THF, 20 °C, 9 h), afforded the 7-aryl-3-(trifluoromethanesulfonyloxy)-2-naphthoates 5a-i in 70-85% yields (Scheme 13, Table 1). The reactions proceeded with very good site-selectivity in favor of position 6.
During the optimization, it proved to be important to carry out the reactions at 20 °C. Higher temperatures resulted in the formation of significant amounts of diarylated products. Very good yields were obtained for products derived from both electron poor and rich arylboronic acids. The structure of 5e was independently confirmed by X-ray crystal structure analysis (Figure 2).

Scheme 13 Synthesis of 5a-i. Conditions: i, 3 (1.0 equiv.), 4a-i (1.2 equiv.), Pd(PPh₃)₄ (3 mol-%), K₃PO₄ (1,5 equiv.), THF, 20 °C, 9 h.

Table 1 Synthesis of 5a-i

<table>
<thead>
<tr>
<th>4</th>
<th>5</th>
<th>Ar</th>
<th>(%(5))ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC₆H₃</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>b</td>
<td>3-MeC₆H₄</td>
<td>77</td>
</tr>
<tr>
<td>c</td>
<td>c</td>
<td>4-ClC₆H₄</td>
<td>80</td>
</tr>
<tr>
<td>d</td>
<td>d</td>
<td>4-EtC₆H₄</td>
<td>84</td>
</tr>
<tr>
<td>e</td>
<td>e</td>
<td>4-(MeO)C₆H₄</td>
<td>83</td>
</tr>
<tr>
<td>f</td>
<td>f</td>
<td>4-MeC₆H₄</td>
<td>78</td>
</tr>
<tr>
<td>g</td>
<td>g</td>
<td>4-(EtO)C₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>h</td>
<td>h</td>
<td>3-(MeO)C₆H₄</td>
<td>85</td>
</tr>
<tr>
<td>i</td>
<td>i</td>
<td>3-FC₆H₄</td>
<td>82</td>
</tr>
</tbody>
</table>

ᵃYields of isolated products
The one-pot reaction of 3 with two different arylboronic acids (sequential addition of the arylboronic acid) afforded 3,7-diaryl-2-naphthoate 6 in 45% yield. The reaction was carried out at 20 °C for the first step (to avoid double coupling) and at 105 °C in the second step. An additional amount of catalyst and base had to be added together with the second arylboronic acid.

Scheme 14 Synthesis of 7. Conditions: i, 1) 3 (1.0 equiv.), 4-(MeO)C₆H₄B(OH)₂ (1.0 equiv.), K₃PO₄ (1.5 equiv.), Pd(PPh₃)₄ (3 mol-%), THF, 20 °C, 9 h; 2) 4-MeC₆H₄B(OH)₂ (1.0 equiv.), K₃PO₄ (1.5 equiv.), Pd(PPh₃)₄ (3 mol-%), 1,4-dioxane, 105 °C, 8 h.
Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient and sterically less hindered position.\textsuperscript{3,34} Prof. Langer's group has previously reported that Suzuki-Miyaura reactions of the bis(triflate) of phenyl 1,4-dihydroxy-2-naphthoate proceed site-selectively at the more electron deficient, sterically more hindered position 1 located next to the ester group. Also Prof. Langer's group has reported that Suzuki-Miyaura reactions of the bis(triflate) of ethyl 3,5-dihydroxy-2-naphthoate (3.1a) proceed site-selectively at the more electron deficient, sterically more hindered position 3 located next to the ester group.\textsuperscript{35} The selectivity was explained by the electron-withdrawing effect of the ester group and by a catalyst-directing effect of the ester group (chelation control). In case of the bis(triflate) of methyl 3,7-dihydroxy-2-naphthoate (3), the reactions proceed with very good site-selectivity in favour of the less electron deficient, sterically less hindered position 7. Therefore, the results are, on the first glance, in contrast to my previous results on substrate 3.1a. However, the findings might be explained as follows: Position 7 of substrate 3 is less sterically hindered than position 5 of substrate 3.1a, due to the steric effect of the annulated ring (hydrogen atom at position 1). Therefore, in case of 3, the easy steric accessibility of position 7 seems to overrule the electron deficient character of position 3. In contrast, this is not possible for substrate 3.1a, because of the considerable steric demand of position 5.

![Scheme 15 Site-selectivity of Suzuki–Miyaura reactions of 3 and 3.1a.](image)

2.3 Conclusion

In conclusion, I have reported site-selective Suzuki-Miyaura reactions of the bis(triflate) of methyl 3,7-dihydroxy-2-naphthoate. These reactions provide a convenient approach to arylated naphthalene which are not readily available by other methods.
CHAPTER THREE

3 Synthesis of arylated naphthoates by chemo-selective Suzuki-Miyaura cross-coupling reactions of methyl 4-bromo-3-(trifluoromethanesulfonyloxy)-2-naphthoate

3.1 Introduction

Naphthalenes derivatives exhibit a broad range of pharmacological activities, occur in many natural products, for example, Azinomycin A and B (Figure 3) were isolated from Streptomyces exhibit promising activities against leukemia, Ehrlich carcinoma, Lewis lung carcinoma and Meth A fibrosarcoma. Substituted 2-naphthoates represent an important subgroup of naphthalene which show a wide range of pharmacological properties, such as cancerostatic activity. Several synthetic methods such as Baylis–Hillman reaction, transition-metal-catalyzed [2+2+2] alkyne cyclizations, Lewis acid catalyzed cyclizations and [4+2] cycloadditions have been developed for synthesizing substituted naphthalenes. Recently, Prof. Langer’s group has reported the synthesis of arylated 2-naphthoates by site-selective Suzuki–Miyaura reactions of bis(triflates) of dihydroxy-2-naphthoates. Prof. Langer’s group has started a program studying Suzuki–Miyaura reactions of several substrates containing a triflate and a bromide leaving group. These compounds generally reacted first at the bromide position. This was in agreement with earlier reports which showed that, in case of Suzuki–Miyaura reactions, aryl bromides are generally more reactive than aryl triflates, because of the stability of the boron–bromine bond formed during the reaction. As a part from the program, I studied the influence of some parameters, such as the structure of the substrate, on the chemo-selectivity Br/OTf. Herein, I report what is, to the best of my knowledge, the first Suzuki–Miyaura reactions of methyl 4-bromo-3-(trifluoromethylsulfonyloxy)-2-naphthoate. These reactions proceed with very good chemoselectivity in favor of the triflate rather than the bromide group. The change of the chemoselectivity from Br to OTf can be explained by additive electronic ortho effects.
3.2 Results and discussion

The DIPEA mediated reaction of 4-bromo-3-hydroxy-2-naphthoic acid (7) with dimethyl sulfate afforded methyl 4-bromo-3-hydroxy-2-naphthoate (8) which was transformed into methyl 4-bromo-3-(trifluoromethylsulfonyl)oxy)-2-naphthoate (9) by reaction with triflic anhydride (Scheme 16).

Scheme 16 Synthesis of 9. Conditions: (i) 7 (1.0 equiv), Me₂SO₄ (2.2 equiv), DIPEA (1.1 equiv), DMF, 85 °C, 1 h; (ii) 8 (1.0 equiv), pyridine (4.0 equiv), CH₂Cl₂, Tf₂O (2.4 equiv), 50 °C, 20 min.

The Suzuki–Miyaura reaction of 9 with arylboronic acids 4b–g, j (2.4 equiv) afforded methyl 3,4-diaryl-2-naphthoates 10a–g in 69–93% yield (scheme 17) and both electron-poor and electron-rich arylboronic acids were successfully employed, but the yields of the products derived from the (more nucleophilic) electron-rich arylboronic acids were higher (except...
for 10a). Very good yields were obtained under standard conditions, using Pd(PPh₃)₄ (6 mol %) as the catalyst, K₂CO₃ (2M, 2 mL) as the base, and 1,4-dioxane as the solvent (120 °C, 6 h). The use of 2-methylphenylboronic acid afforded the desired product which, however, could not be isolated in pure form (difficult chromatographic purification due to formation of side-products).

Scheme 17 Synthesis of 10a-g. Conditions: i, 9 (1.0 equiv), 4b–g, j (2.4 equiv), Pd(PPh₃)₄ (6 mol %), K₂CO₃ (2M, 2 mL), 1,4-dioxane, 120 °C, 6 h.

Table 2 Synthesis of 10a-g

<table>
<thead>
<tr>
<th>4</th>
<th>10</th>
<th>Ar</th>
<th>%(10)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>a</td>
<td>3-MeC₆H₄</td>
<td>72</td>
</tr>
<tr>
<td>c</td>
<td>b</td>
<td>4-ClC₆H₄</td>
<td>69</td>
</tr>
<tr>
<td>d</td>
<td>c</td>
<td>4-EtC₆H₄</td>
<td>81</td>
</tr>
<tr>
<td>e</td>
<td>d</td>
<td>4-(MeO)C₆H₄</td>
<td>86</td>
</tr>
<tr>
<td>f</td>
<td>e</td>
<td>4-MeC₆H₄</td>
<td>78</td>
</tr>
<tr>
<td>g</td>
<td>f</td>
<td>4-(EtO)C₆H₄</td>
<td>93</td>
</tr>
<tr>
<td>j</td>
<td>g</td>
<td>4-(CF₃)C₆H₄</td>
<td>73</td>
</tr>
</tbody>
</table>

ᵃYield of isolated products

The Suzuki–Miyaura reaction of 9 with 1.0 equiv of arylboronic acids 4b–f afforded 3-aryl-4-bromo-2-naphthoates 11a–e in 76–92% yield and the reactions proceeded with very good chemoselectivity in favor of the triflate group. During the optimization, it proved to be
important to use exactly 1.0 equiv of the arylboronic acid and to carry out the reaction at 60 °C instead of 120 °C to avoid double coupling. Both electron-poor and electron-rich arylboronic acids were successfully employed. The yields of the products derived from electron-rich arylboronic acids were again higher. The structures of the products were easily confirmed by the fact that, in the $^{13}$C NMR spectra, the characteristic quartet of the CF$_3$ group disappeared. The structure of 11d was independently confirmed by X-ray crystal structure analysis (Figure 4).

\[
\begin{align*}
\text{Scheme 18} & \quad \text{Synthesis of 11a-e. Conditions: } i, 9 \text{ (1.0 equiv), } 4b-f \text{ (1.0 equiv), } \\
Pd(PPh$_3$)$_4$ (3 mol%), K$_2$CO$_3$ (2M, 2 mL), 1,4-dioxane, 60 °C, 9 h.
\end{align*}
\]

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>11</td>
<td>Ar</td>
<td>% (11)$^a$</td>
</tr>
<tr>
<td>b</td>
<td>a</td>
<td>3-MeC$_6$H$_4$</td>
<td>83</td>
</tr>
<tr>
<td>c</td>
<td>b</td>
<td>4-ClC$_6$H$_4$</td>
<td>76</td>
</tr>
<tr>
<td>d</td>
<td>c</td>
<td>4-EtC$_6$H$_4$</td>
<td>88</td>
</tr>
<tr>
<td>e</td>
<td>d</td>
<td>4-(MeO)C$_6$H$_4$</td>
<td>92</td>
</tr>
<tr>
<td>f</td>
<td>e</td>
<td>4-MeC$_6$H$_4$</td>
<td>79</td>
</tr>
</tbody>
</table>

$^a$Yields of isolated
The one-pot reaction of 9 with two different arylboronic acids (sequential addition) afforded the methyl 3,4-diaryl-2-naphthoates 12a–c, containing two different aryl groups, in 71–86% yield and both electron-poor and electron-rich arylboronic acids were successfully employed. The best yield was obtained for product 12b derived from two electron-rich arylboronic acids. The lowest yield was obtained for product 12c where an electron-poor arylboronic acid was employed in the first step.

Scheme 19  Synthesis of 12a–c. Conditions: 1, (1) 9 (1.0 equiv), Ar¹B(OH), Pd(PPh₃)₄ (3 mol %), K₂CO₃ (2M, 2 mL), 1,4-dioxane, 60 °C, 9 h; (2) Ar²B(OH) (1.2 equiv), Pd(PPh₃)₄ (6 mol %), K₂CO₃ (2M, 2 mL), 1,4-dioxane, 120 °C, 6 h.
### Table 4 Synthesis of 12a-c

<table>
<thead>
<tr>
<th>4</th>
<th>12</th>
<th>Ar¹</th>
<th>Ar²</th>
<th>% (12)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>d, j</td>
<td>a</td>
<td>4-EtC₆H₄</td>
<td>4-(CF₃)C₆H₄</td>
<td>79</td>
</tr>
<tr>
<td>f, e</td>
<td>b</td>
<td>4-MeC₆H₄</td>
<td>4-(MeO)C₆H₄</td>
<td>86</td>
</tr>
<tr>
<td>c, d</td>
<td>c</td>
<td>4-ClC₆H₄</td>
<td>4-EtC₆H₄</td>
<td>71</td>
</tr>
</tbody>
</table>

²Yields of isolated Product.

### 3.3 Conclusion

In conclusion, I have reported that Suzuki–Miyaura reactions of methyl 4-bromo-3-(trifluoromethylsulfonyloxy)-2-naphthoate (9) proceeded by chemoselective attack to carbon atom C-3 attached to the triflate group. In contrast, Prof. Langer’s group reported earlier that Suzuki–Miyaura reactions of 2-acetyl-4-bromo-1-(trifluorosulfonyloxy)naphthalene (9.1a) proceeded by chemoselective attack to carbon atom C-4 attached to the bromine atom.⁴¹a

![Scheme 20 Chemoselectivity of Suzuki–Miyaura reactions of 9 and 9.1a.](image)

It was mentioned above that, in the case of Suzuki–Miyaura reactions, aryl bromides are usually more reactive than aryl triflates. It is known that palladium catalyzed cross-coupling reactions proceed selectively in favor of the sterically less hindered and electronically more deficient position.⁴², ⁴³
In addition, a carbonyl group can act as a catalyst-directing group (by chelation of the oxygen lone pairs to the metal). Carbon atoms C-3 and C-1 of substrates 9 and 9.1a, both attached to a triflate group, are more electron deficient than position C-4 of both substrates, because of the neighboring ester group, respectively. On the other hand, the ester carbonyl group can more efficiently chelate to the catalyst, due to the π-donating effect of the methoxy oxygen atom. Therefore, I believe that the chemoselectivity of the Suzuki–Miyaura reactions of 9 might be explained by additive electronic ortho effects, while the selectivity in case of 9.1a is a result of steric effects.
CHAPTR FOUR

4 Synthesis of arylated coumarins by site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of 4,7-dihydroxycoumarin

4.1 Introduction

Neoflavones (4-arylcoumarins) are of considerable pharmacological relevance and occur in several natural products and synthetic drugs. Natural and synthetic neoflavones have been reported to exhibit various kinds of pharmacological activities, such as anticancer, antimalarial, antibacterial, antiprotozoal, antivirus, antidiabetic, cytotoxic and anti-inflammatory activity. Merck developed a 7-substituted 4-arylcoumarin as a 5-lipoxygenase inhibitor for the treatment of inflammatory diseases such as asthma, chronic obstructive pulmonary disease and atherosclerosis (Figure 5). As a result of the promising biological and pharmacological activities of neoflavones, several strategies have been developed for the construction of the 4-arylcoumarin framework. Classically, neoflavones have been synthesized using the Pechmann, Perkin, Ponndorf, Houben-Hösch and Knoevenagel reactions. In recent years, transition metal catalyzed reactions have emerged as vital synthetic tools for the preparation of pharmacologically relevant heterocycles. Two synthetic strategies have been developed for the assembly of the neoflavone framework: the first one involves the formation of the pyrone ring by hydroarylation of alkynes, or by reaction of the alkenyl C-H bond with carbon dioxide. The second one relies on cross-coupling reactions of position 4 of activated coumarins with organometallic reagents. In recent years, site-selective cross coupling reactions of bis(halides) or bis(triflates) have been developed as a promising synthetic tool. In this context, palladium catalyzed cross-coupling reactions of coumarin derivatives have also been reported. Herein, I report what is, to the best of my knowledge, the first Suzuki-Miyaura coupling reaction of the bis(triflate) of 4,7-dihydroxycoumarin. The reactions, which proceed with excellent regioselectivity in favor of position 4, provide a convenient approach to various arylated coumarin derivatives which are not readily available by other methods.
Figure 5 A 5-lipoxygenase inhibitor developed by Merck.

4.2 Results and discussion

The reaction of 4,7-dihydroxycoumarin (13) with triflic anhydride gave bis(trflate) (Scheme 21).

Scheme 21 Synthesis of 14. Conditions: i, 13 (1.0 equiv.), pyridine (4.0 equiv.), CH₂Cl₂, Tf₂O (2.4 equiv.), 50°C, 4 h.

The Suzuki–Miyaura reaction of 14 with arylboronic acids 4a, e, g, k, l (2.4 equiv) afforded 4,7-diarylcoumarins 15a-e in 66-81% yield (Scheme 22, Table 5). Both electron rich and poor arylboronic acids were successfully employed.
Scheme 22 Synthesis of 15a-e. Conditions: \( i \), 14 (1.0 equiv.), 4a, e, g, k, l (2.4 equiv.), Pd(PPh\(_3\))\(_4\) (6 mol %), K\(_2\)CO\(_3\) (2M, 2 mL), 1,4-dioxane, 110 °C, 8 h.

Table 5 Synthesis of 15a-e

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>15</td>
<td>Ar</td>
</tr>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC(_6)H(_3)</td>
</tr>
<tr>
<td>e</td>
<td>b</td>
<td>4-(MeO)C(_6)H(_4)</td>
</tr>
<tr>
<td>g</td>
<td>c</td>
<td>4-(EtO)C(_6)H(_4)</td>
</tr>
<tr>
<td>k</td>
<td>d</td>
<td>C(_6)H(_5)</td>
</tr>
<tr>
<td>l</td>
<td>e</td>
<td>3,5-(MeO)C(_6)H(_3)</td>
</tr>
</tbody>
</table>

*Yields of isolated product.

The Suzuki–Miyaura reaction of 14 with one equivalent of arylboronic acids afforded the 4-aryl-7-(trifluormethanesulfonyloxy)-coumarins 16a-h in 64-82 % yield (Scheme 23, Table 6). The reactions proceeded by site-selectivity attack onto 4-position. During the optimization, it proved to be important to carry out the reaction at lower temperature (65 °C) as compared to the synthesis of the diarylated coumarins. In addition, the employment of toluene (instead of 1,4-dioxane) proved to be important to avoid formation of diarylated products. Again, both electron rich and poor arylboronic acids gave good yields. The structure of 16a was independently confirmed by X-ray crystal structure analyses (Figure 6).
Scheme 23 Synthesis of 16a-h. Conditions: $i$, 14 (1.0 equiv.), 4a, d-g, i, m, n (1.0 equiv.), Pd(PPh$_3$)$_4$ (3 mol%), K$_2$CO$_3$ (2M, 2 mL), toluene (3 mL), 65 °C, 6 h.

Table 6 Synthesis of 16a-h

<table>
<thead>
<tr>
<th>4</th>
<th>16</th>
<th>Ar</th>
<th>% (16)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC$_6$H$_3$</td>
<td>82</td>
</tr>
<tr>
<td>d</td>
<td>b</td>
<td>4-EtC$_6$H$_4$</td>
<td>73</td>
</tr>
<tr>
<td>e</td>
<td>c</td>
<td>4-(MeO)C$_6$H$_4$</td>
<td>71</td>
</tr>
<tr>
<td>f</td>
<td>d</td>
<td>4-MeC$_6$H$_4$</td>
<td>70</td>
</tr>
<tr>
<td>g</td>
<td>e</td>
<td>4-(EtO)C$_6$H$_4$</td>
<td>78</td>
</tr>
<tr>
<td>i</td>
<td>f</td>
<td>3-FC$_6$H$_4$</td>
<td>64</td>
</tr>
<tr>
<td>m</td>
<td>g</td>
<td>4-(OCF$_3$)C$_6$H$_4$</td>
<td>65</td>
</tr>
<tr>
<td>n</td>
<td>h</td>
<td>2,3,4-(MeO)C$_6$H$_2$</td>
<td>67</td>
</tr>
</tbody>
</table>

$^a$Yield of isolated products
The one-pot reaction of 14 with two different arylboronic acids (sequential addition) afforded the diarylated coumarin 17 in 84% yield (Scheme 24). A fresh portion of the catalyst and of solvent (1,4-dioxane) had to be added to the reaction mixture in the second step in order to obtain a good yield of diarylated coumarin 17.

**Scheme 24** Synthesis of 17. Conditions: *i*, 1) 14 (1.0 equiv.), 4-(MeO)C₆H₄B(OH)₂ (1.0 equiv.), Pd(PPh₃)₄ (3 mol%), K₂CO₃ (2M, 2 mL), toluene, 65 °C, 6 h.; 2) 4-MeC₆H₄B(OH)₂ (1.2 equiv.), Pd(PPh₃)₄ (6 mol%), K₂CO₃ (2M, 2 mL), 1,4-dioxane, 110 °C, 6 h.
4.3 Conclusion

In conclusion, I have reported the first Suzuki–Miyaura reactions of 4,7-bis(trifluoromethylsulfonyloxy)coumarin. These reactions provide a convenient access to a variety of arylated coumarins. The reactions proceeded with very good site-selectivity in favor of 4-position. Palladium catalyzed cross-coupling reactions of polyhalogenated substrates or of bis(triflates) usually proceed in favor of the sterically less hindered and electronically more deficient position. Position 4 is sterically more hindered than position 7, due to its location next to the annulated benzene ring. The selectivity can be explained by the highly electron deficient character of the 4-position of the coumarin moiety (electron-withdrawing effect of the carbonyl group).
CHAPTER FIVE

5 Synthesis of arylated quinolines by chemo-selective Suzuki-Miyaura cross-coupling reactions of 5-bromo-quinolin-8-yl-trifluoromethanesulfonate

5.1 Introduction

Arylated quinolines exhibit a wide range of pharmacological and biological activities, such as antiviral, antimalarial, antitumor and P-selecting antagonism. They are also promising agents for the treatment of acromegaly and diabetic retinopathy. As a result of their therapeutic value, many synthetic approaches have recently been developed. The classic condensation-type approaches for the synthesis of arylated quinolines include the Skraup, Doebner-Miller, Friedländer, Combes, Pfitzinger and Povarov reactions. Cross-coupling reactions have become an efficient synthetic tool in the synthesis of arylated quinolines and quinolines as well. Also, new transition metal catalytic systems have been developed for construction of arylated quinoline frameworks such as, Rh(III)-catalyzed oxidative annulations of pyridines, Pd-catalyzed hetero-Diels-Alder reactions between imines and olefins, Ru(I)-catalyzed coupling cyclizations of N-aryl imidoyl chloride with alkynes, Ru(II)-catalyzed Friedländer annulations and Pd-catalyzed regioselective hydroarylations of α-(2-aminoaryl)-α,β-alkynones with organoboron derivatives. Recent progress in Pd-catalyzed selective cross-coupling reactions have led to develop various protocols in the synthesis of some drugs and drug candidates in pharmaceutical industry. For example, a diverse range of 4-alkoxy-3,6-diarylquinolines as drug candidates have been synthesized by chemo-selective Suzuki reactions as the key step. The products exhibit potent and selective agonism of the somatostatin receptor subtype 2 (sst2) (Figure 7).
Figure 7 Selective Pd-catalyzed synthesis of 4-alkoxy-3,6-diarylquinolines (sst2), agonists protocol developed by Merck.

Previously, various regioselective Suzuki-Miyaura cross-reactions of dihalogenated pyridines and quinolines have been reported. Reactions of mixed triflates and halides are more rare. Some years ago, Prof. Langer’s group has reported reactions of quinolones containing a triflate and two bromine atoms. Prof. Langer’s group also reported chemoselective transformations of naphthalene derivatives containing triflate and bromide groups. In chapter 3 of this work such reactions are also described. Herein, I report what is, to the best of my knowledge, the first chemo-selective Suzuki-Miyaura reactions of 5-bromoquinolin-8-yl trifluoromethanesulfonate.

5.2 Results and discussion

Commercially available 5-bromo-8-hydroxyquinoline was converted to 5-bromoquinolin-8-yl trifluoromethanesulfonate 19 in high yield (Scheme 25).
The Suzuki-Miyaura reaction of 19 with arylboronic acids 4a, b, e, g (2.0 equiv.), in the presence of Pd(PPh$_3$)$_4$ (6 mol-%), K$_2$CO$_3$ (2 mL), 1,4-dioxane (3 mL), 110 °C, 10 h, gave 5,8-bis(aryl)quinolines 20a-d in 68-81% yields (Scheme 26, Table 7). The structure of compound 20c was independently confirmed by x-ray crystallography (Figure 8).

Scheme 26 Synthesis of 20a-d. Conditions: i, 19 (1.0 equiv.), 4a, b, e, g (2.0 equiv.), Pd(PPh$_3$)$_4$ (6 mol-%), K$_2$CO$_3$ (2 mL), 1,4-dioxane (3 mL), 110 °C, 10 h.

Table 7 Synthesis of 20a-d

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 20 Ar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC$_6$H$_3$</td>
</tr>
<tr>
<td>b</td>
<td>b</td>
<td>3-MeC$_6$H$_4$</td>
</tr>
<tr>
<td>e</td>
<td>c</td>
<td>4-(MeO)C$_6$H$_4$</td>
</tr>
<tr>
<td>g</td>
<td>d</td>
<td>4-(EtO)C$_6$H$_4$</td>
</tr>
</tbody>
</table>

$^\text{a}$ Yields of isolated products

Figure 8 X-ray crystal structure of 20c.
The Suzuki-Miyaura reaction of 19 with arylboronic acids 4a, c-g, o, p (1.0 equiv.), in the presence of Pd(PPh₃)₄ (3 mol-%), K₃PO₄ (1.0 equiv.), toluene (3 mL), 85 °C, 9 h, afforded 5-arylquinolin-8-yl trifluoromethanesulfonates 21a-h in 60-84% yields (Scheme 27, Table 8). The reactions proceeded with very good chemoselectivity in favor of position 5. During the optimization, it proved to be important to use exactly one equivalent of the arylboronic acid to carry out the reaction at lower temperature (85 °C) than the double-coupling. Very good yields were obtained for products derived from both electron poor and rich arylboronic acids. The structure of 21a was confirmed by 2D NMR correlation experiments (NOESY and COSY) (Figure 9).

![Scheme 27 Synthesis of 21a-h. Conditions: i, 19 (1.0 equiv.), 4a, c-g, o, p (1.0 equiv.), Pd(PPh₃)₄ (3 mol-%), K₃PO₄ (1.0 equiv.), toluene (3 mL), 85 °C, 9 h.]

<table>
<thead>
<tr>
<th>4</th>
<th>21</th>
<th>Ar</th>
<th>% (21)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC₆H₃</td>
<td>76</td>
</tr>
<tr>
<td>c</td>
<td>b</td>
<td>4-ClC₆H₄</td>
<td>60</td>
</tr>
<tr>
<td>d</td>
<td>c</td>
<td>4-EtC₆H₄</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>d</td>
<td>4-(MeO)C₆H₄</td>
<td>84</td>
</tr>
<tr>
<td>f</td>
<td>e</td>
<td>4-MeC₆H₄</td>
<td>81</td>
</tr>
<tr>
<td>g</td>
<td>f</td>
<td>4-(EtO)C₆H₄</td>
<td>69</td>
</tr>
<tr>
<td>o</td>
<td>g</td>
<td>4-FC₆H₄</td>
<td>63</td>
</tr>
<tr>
<td>p</td>
<td>h</td>
<td>2-(MeO)C₆H₄</td>
<td>79</td>
</tr>
</tbody>
</table>

ᵃ Yields of isolated product
The one-pot reaction of 19 with two different arylboronic acids (sequential addition of the arylboronic acids) afforded 5,8-diarlyquinoline 22 in 76% yield (Scheme 28). The reaction was carried out at 85 °C for the first step (to avoid double coupling) and at 110 °C in the second step (to ensure a complete reaction). An additional amount of catalyst and base had to be added together with the second arylboronic acid. In addition, 1,4-dioxane (3 mL) had to be added to complete the reaction, due to solubility reasons.

Scheme 28 Synthesis of 22. Conditions: i, 1) 4-MeC₆H₄B(OH)₂ (1.0 equiv.), Pd(PPh₃)₄ (3 mol-%), K₃PO₄ (1.0 equiv.), toluene, 85 °C, 9 h.; 2) 4-(MeO)C₆H₄B(OH)₂ (2.0 equiv.), Pd(PPh₃)₄ (6 mol-%), K₃PO₄ (1.0 equiv.), 1,4-dioxane, 110 °C, 10 h.
In general, aryl bromides undergo Suzuki-Miyaura reactions more rapidly than aryl triflates,\textsuperscript{76} because of the stability of the borane-halide bond. However, other parameters influence the selectivity as well.\textsuperscript{76e} The reactions of 19 proceed with very good chemoselectivity of the bromide group, despite the proximity of the triflate to the quinoline nitrogen which might exert a catalyst-directing effect based on participation of the nitrogen lone pairs.

5.3 Conclusion

In conclusion, I have reported chemoselective Suzuki-Miyaura reactions of 5-bromoquinolin-8-yl trifluoromethanesulfonate. The reactions proceeded with very good chemoselectivity in favor of the bromide group.
CHAPTER SIX

6 Synthesis of arylated isoflavones by site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of 5,7-dihydroxyisoflavone

6.1 Introduction

Isoflavones are heterocyclic compounds, which belong to flavonoids derivatives. The main body of isoflavone consists of a benzene and a ortho-pyrene moiety. Isoflavonoids are a subgroup of flavonoids mainly present in the species of Leguminosae (Figure 10). New syntheses of isoflavones have been developed in recent years. Syntheses rely on the cyclization of deoxybenzoin derivatives with suitable building blocks, using various reagents, such as ethoxalyl chloride or triethyl orthoformate. Furthermore, palladium catalyzed cross-coupling reactions have been used for the synthesis of isoflavones. Isoflavone derivatives show anticancer, and antibacterial, antimicrobial, and antiulcer activity. Isoflavones also play a role for the reduction of cholesterol. Isoflavones also possess antioxidant activity, inhibition of cancer cell proliferation, anti-inflammatory activity, and prevention of coronary heart diseases as well as osteoporosis.

![Figure 10 Species of Leguminosae.](image-url)
6.2 Results and discussion

Commercially available 5,7-dihydroxyisoflavone (23) was converted to 5,7-bis(trifluoromethanesulfonyloxy)isoflavone (24) in high yield 89% (Scheme 29).

![Scheme 29 Synthesis of 24. Conditions: i, 23 (1.0 equiv.), pyridine (4.0 equiv.) CH₂Cl₂, Tf₂O (2.4 equiv.), 50 °C, 4 h.](image)

The Suzuki-Miyaura reaction of 24 with arylboronic acids 4a, d, f (2.0 equiv.), in the presence of Pd(PPh₃)₄ (6 mole%), K₂CO₃ (1.5 mL), 1,4-dioxane (3 mL), 110 °C, 10 h., gave the 5,7-diaryl isoflavones 25a-c in 76-87% yields (Scheme 30, Table 9).

![Scheme 30 Synthesis of 25a-c. Conditions: i, 24 (1.0 equiv.), 4a, d, f (2.0 equiv.), Pd(PPh₃)₄ (6 mole%), K₂CO₃ (1.5 mL), 1,4-dioxane (3 mL), 110 °C, 10 h.](image)

<table>
<thead>
<tr>
<th>4</th>
<th>25</th>
<th>Ar</th>
<th>% of 25²</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-Me₆H₃</td>
<td>87</td>
</tr>
<tr>
<td>d</td>
<td>b</td>
<td>4-EtC₆H₄</td>
<td>81</td>
</tr>
<tr>
<td>f</td>
<td>c</td>
<td>4-MeC₆H₄</td>
<td>76</td>
</tr>
</tbody>
</table>

²Yields of isolated product
The Suzuki-Miyaura reaction of 24 with arylboronic acids 4a, d-f (1.0 equiv.), in the presence of Pd(PPh₃)₄ (3 mole%), K₃PO₄ (1.0 equiv.), THF (3 mL), 55 °C, 10 h, afforded the 5-arylisoflavone-7-trifluoromethanesulfonates 26a-d in 73-82% yields (Scheme 31, Table 10). The reactions proceeded with very good chemo-selectivity in favor of position 7. Very good yields were obtained for products derived from both electron poor and rich arylboronic acids. The structure of compound 26c, confirmed independently by x-ray (Figure 11).

![Scheme 31](image)

**Scheme 31** Synthesis of 26a-d. Conditions: i, 24 (1.0 equiv.), 4a, d-f (1.0 equiv.), Pd(PPh₃)₄ (3 mole%), K₃PO₄ (1.0 equiv.), THF (3 mL), 55 °C, 10 h.

**Table 10** Synthesis of 26a-d

<table>
<thead>
<tr>
<th>4</th>
<th>26</th>
<th>Ar</th>
<th>%(26)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>3,5-MeC₆H₃</td>
<td>73</td>
</tr>
<tr>
<td>d</td>
<td>b</td>
<td>4-EtC₆H₄</td>
<td>79</td>
</tr>
<tr>
<td>e</td>
<td>c</td>
<td>4-(MeO)C₆H₄</td>
<td>80</td>
</tr>
<tr>
<td>f</td>
<td>d</td>
<td>4-MeC₆H₄</td>
<td>82</td>
</tr>
</tbody>
</table>

aYields of isolated product
Figure 11 X-ray crystal structure of 26c.

6.3 Conclusion

In conclusion, I have reported site-selectivity Suzuki-Miyaura reactions of bis (triflate) of 5,7-dihydroxyisoflavone. The reactions proceeded with very good site-selectivity in favor of 5-position.
7 EXPERIMENTAL SECTION

7.1 NMR Spectroscopy
Burker AC 250, Burker ARX 300, Burker ARX 500. For NMR characterization the one-dimensional $^1$H NMR; Proton-decoupled $^{13}$C NMR, and DEPT 135 spectra were collected. If necessary, other techniques (NOESY, COSY, HMQC, and HMBC) were applied as well. All NMR spectra presented in this work were collected in CDCl$_3$ Solution. All chemical shifts are given in ppm. References ($^1$H NMR): TMS ($\gamma$ = 0.00) or residual CHCl$_3$ ($\gamma$ = 7.26) were taken as internal standard. References ($^{13}$C NMR): TMS ($\gamma$ = 0.00) or residual CHCl$_3$ ($\gamma$ = 77.0) were taken as internal standard. Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet. More complex patterns are represented by combinations of the respective symbols. Td indicates a triplet of doublets with the larger coupling constant associated with the first symbol (here, triplet).

7.2 Infra Red Spectroscopy (IR)
Nicolet 205 FT-IR, Nicolet Protégé 460 FT-IR. Peaks are given the following assignments: W = Weak, m = medium, s = strong, br = broad.

7.3 Mass Spectroscopy (MS)
AMD MS40, Varian MAT CH 7, MAT 731 (ET, 70 eV), Intecta AMD 402 (ET, 70 eV and Cl), Finnigan MAT 95 (Cl, 200 eV).

7.4 High Resolution Mass Spectrometry (HRMS)
Varian MAT 311, Intecta AMD 402.

7.5 Melting Points
Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus). Leitz Labolux 12 pol with heating table Mettler FP 90. Melting Points are uncorrected.

7.6 X-ray Structures
Burker X8Apex diffractometer with CCD camera (Mo Ka radiation and graphite monochromator, $\lambda$ = 0.71073 Å). The space group is determined by the XPREA program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method.
7.7 Chromatographic Methods

7.7.1 Thin Layer Chromatography (TLC)
Merck Kiessgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. As colourizing reagent the following mixtures were used: 1-2 100/ p-Anisaldehyde or vanillin, 10/100 glacial acetic, 5/100 sulphuric acid, 83-84/100 methanol.

7.7.2 Column Chromatography
Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.0200 mm, 70-320 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.

7.8 Equipment, Chemicals and work Technique
All solvents for using were distilled by standard methods. The coupling reactions were carried out in pressure tubes or Schlenck flask under inert atmosphere (Argon 4.6), oxygen and humidity exclusion. All of the chemicals are standard, commercially available from Merck, Aldrich, Arcos, and others. The order of the characterized connections effected numerically, but does not correspond to the order in the main part of dissertation.
7.9 Procedures and Spectroscopic Data

**Methyl 3,7-dihydroxy-2-naphthoate (2)**

To a solution of 3,7-dihydroxy-2-naphthoic acid 1 (2.0 g, 9.8 mmol) in DMF (30 mL), dimethyl sulfate (2.72 g, 21.56 mmol) and N,N-diisopropylethylamine (1.4 g, 10.78 mmol) were added. The reaction mixture was heated for 1 h at 85 °C. After cooling to room temperature, the mixture was poured into ice water. A white precipitate formed which was filtered off and the filtrate was concentrated in vacuo. The product 2 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a yellow solid (1.6 g, 77%); mp 101-102 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.95$ (s, 3H, OCH$_3$), 4.79 (s, 1H, OH), 7.04-7.05 (m, 1H, ArH), 7.08 (dd, $J = 2.4$, 8.8 Hz, 1H, ArH), 7.20 (s, 1H, ArH), 7.55 (d, $J = 8.9$ Hz, 1H, ArH), 8.25 (s, 1H, ArH), 10.19 (s, 1H, OH). $^{13}$C NMR (62.90 MHz, CDCl$_3$): = 52.5 (OCH$_3$), 110.1, 111.8 (CH), 114.6 (C), 121.6 (CH), 127.7 (C), 128.1, 130.3 (CH), 133.4, 151.7, 154.7 (C), 170.2 (CO). IR (KBr, cm$^{-1}$): $\nu = 3328$ (m), 3038, 3003, 2953 (w), 1681 (m), 1651, 1633, 1609, 1576, 1556 (w), 1531 (m), 1505, 1479, 1462 (w), 1441, 1392, 1345, 1263, 1214 (s), 1180, 1147, 1130, 1072 (m), 1012, 969 (w), 944, 903, (w), 860 (s), 836, 812 (m), 783 (s), 746 (w), 716 (s), 665, 620, 610 (w), 587, 550 (w). GC-MS (EI, 70 eV): m/z (%) = 218 ([M]+, 52), 187 (17), 186 (100), 185 (10), 159 (10), 158 (80), 130 (45), 102 (20). HRMS (EI, 70 eV) calced for C$_{12}$H$_{10}$O$_4$ [M]+: 218.0579; found: 218.0599.

**Methyl 3,7-bis(trifluoromethylsulfonyloxy)-2-naphthoate (3)**

To a CH$_2$Cl$_2$ solution (46 mL) of 2 (1.0 g, 4.6 mmol) was added pyridine (1.5 mL, 18.4 mmol) and the solution was stirred at 20 °C for 10 min under argon atmosphere. Then Tf$_2$O (1.8 mL, 11.0 mmol) was added at −78 °C and the reaction mixture was allowed to warm to room temperature and was stirred for 14 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The product 3 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a colourless solid (1.9 g, 87%); mp 75-77 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 4.06$ (s, 3H, OCH$_3$), 7.47-7.70 (m, 1H, ArH), 7.85 (s, 1H, ArH), 7.94 (d, $J = 2.3$ Hz, 1H, ArH), 8.03 (d, $J = 9.0$ Hz, 1H, ArH), 8.72 (s, 1H, ArH). $^{13}$C NMR (62.90 MHz, CDCl$_3$) = 52.99 (OCH$_3$), 117.7 (q, $J_{F,C} = 320.2$ Hz, CF$_3$), 117.9 (q, $J_{F,C} = 320.8$ Hz, CF$_3$), 120.4, 121.2, 123.6 (CH), 130.5 (C), 130.8 (CH), 131.8, 133.8 (C), 134.6 (CH), 145.5, 148.3 (C), 163.7 (CO). IR (KBr, cm$^{-1}$): $\nu = 3070$, 2963 (w), 1713 (s), 1678, 1633 (w), 1599 (m), 1502, 1461, 1443 (w), 1426, 1398 (s), 1365, 1309 (m), 1276 (s), 1249 (m), 1023, 1131, 1116, 1048 (s), 965.
Experimental Section

(w), 937, 909, 937, 909, 845, 813, 795 (s), 779, 766, 754, 739 (m), 697 (w), 676 (m), 650, 609, (s), 597, 582 (m), 565 (w). GC-MS (EI, 70 eV): m/z (%) = 482 ([M]+, 61), 451 (16), 350 (14), 349 (100), 257 (24), 129 (17). HRMS (ESI-TOF/MS) calcd for C_{14}H_{9}F_{6}O_{8}S_{2} [M+H]^+: 482.96375; found: 482.96348.

General procedure for the synthesis of 5a-i

A THF solution of 3 (0.145 mmol), K₃PO₄ (1.5 equiv), Pd(PPh₃)₄ (3 mol-%) and of arylboronic acid 4 (1.2 equiv.) was stirred at 20 °C for 9 h under argon atmosphere. To the reaction mixture were added H₂O (20 mL) and CH₂Cl₂ (25 mL). The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane / EtOAc = 100:5).

Methyl 7-(3,5-dimethylphenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5a)

Starting with 3 (70 mg, 0.145 mmol), 4a (26 mg, 0.174 mmol), Pd(PPh₃)₄ (5 mg, 3 mol-%), K₃PO₄ (46 mg, 0.22 mmol), and THF (4 mL), 5a was isolated as a white solid (45 mg, 70%); mp 102-104 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.35 (s, 6H, 2CH₃), 3.96 (s, 3H, OCH₃), 7.01 (s, 1H, ArH), 7.24 (br. s, 2H, ArH), 7.68-8.08 (m, 4H, ArH), 8.63 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.1. ¹³C NMR (75.5 MHz, CDCl₃): δ = 20.4 (2CH₃), 51.7 (OCH₃), 117.8 (q, J_C,F = 321.3 Hz, CF₃), 119.8 (CH), 121.2 (C), 124.3, 125.2, 125.6, 128.1, 128.8 (CH), 130.7, 132.9 (C), 134.0 (CH), 137.7, 138.7, 140.2, 143.6 (C), 164.4 (C=O). IR (KBr, cm⁻¹): ν = 3028, 3012, 2958, 2851 (w), 1721 (s), 1632 (w), 1596 (m), 1462 (w), 1420 (s), 1364, 1319, 1303, 1285, 1261, 1247 (w), 1198 (s), 1134, 1112, 1051, 1018, 946 (m). GC-MS (EI, 70eV): m/z (%) = 438 ([M]^+, 44), 305 (100), 275 (15), 247 (39), 219 (20), 202 (24). HRMS (EI, 70 eV): m/z calcd. for C_{21}H_{17}O_{5}F₃S [M]^+: 438.07433; found: 438.07419.

Methyl 7-(m-tolyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5b)

Starting with 3 (70 mg, 0.145 mmol), 4b (24 mg, 0.174 mmol), Pd(PPh₃)₄ (5 mg, 3 mol-%), K₃PO₄ (46 mg, 0.22 mmol), and THF (4 mL), 5b was isolated as a white solid (48 mg, 77%); mp 152-154 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.35 (s, 3H, CH₃), 3.96 (s, 3H, OCH₃), 7.00 (s, 1H, ArH), 7.18-7.24 (m, 3H, ArH),
7.68 (s, 1H, ArH), 7.87 (br. s, 2H, ArH), 8.10 (s, 1H, ArH), 8.63 (s, 1H, ArH). $^{19}$F NMR (282.4 MHz, CDCl$_3$): δ = -73.07. $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 21.4 (CH$_3$), 52.7 (OCH$_3$), 118.9 (q, $J_{C,F}$ = 320.9 Hz, CF$_3$), 119.8 (CH), 121.3 (C), 123.5, 125.6 (CH), 127.1 (C), 127.7 (CH), 127.9 (2CH), 128.1, 128.6 (CH), 130.7, 133.0 (C), 134.0 (CH), 137.8, 138.7, 144.6 (C), 163.9 (C=O). IR (KBr, cm$^{-1}$): ν = 3042, 3018, 2960, 2916 (w), 1721 (s), 1602, 1505, 1422, 1319, 1287, 1201 (m), 1134, 1085 (w), 1013 (s), 955, 944 (w). GC-MS (EI, 70eV): m/z (%) = 424 ([M]$^+$, 57), 292 (19), 291 (100), 263 (10), 261 (15), 233 (48), 205 (23). HRMS (ESI-TOF/MS): m/z calcd for C$_{20}$H$_{16}$O$_3$F$_3$S [M+H]$^+$: 425.05923; found: 425.05934.

**Methyl 7-(4-chlorophenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5c)**

Starting with 3 (70 mg, 0.145 mmol), 4c (27 mg, 0.174 mmol), Pd(PPh$_3$)$_4$ (5 mg, 3 mol-%), K$_3$PO$_4$ (46 mg, 0.22 mmol), and THF (4 mL), 5c was isolated as a white solid (52 mg, 80%); mp 98-100 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ = 3.95 (s, 3H, OCH$_3$), 7.18-7.33 (m, 1H, ArH), 7.38 (d, $J$ = 8.1 Hz, 2H, ArH), 7.55 (d, $J$ = 8.1 Hz, 2H, ArH), 7.69 (s, 1H, ArH), 7.76-7.90 (m, 1H, ArH), 8.04 (s, 1H, ArH), 8.62 (s, 1H, ArH). $^{19}$F NMR (282.4 MHz, CDCl$_3$): δ = -73.1. $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 52.8 (OCH$_3$), 118.3 (q, $J_{C,F}$ = 320.9 Hz, CF$_3$), 119.9 (CH), 121.8 (C), 125.6, 127.4, 127.6, 128.2, 128.3 (CH), 130.6, 133.0, 133.4 (C), 133.9 (CH), 137.2, 138.7, 143.8 (C), 163.3 (C=O). IR (KBr, cm$^{-1}$): ν = 3033, 3000, 2956, 1723 (s), 1632, 1604, 1490 (w), 1201 (s), 1134, 1091, 1050, 1011 (w), 963, 928 (m). GC-MS (EI, 70 eV): m/z (%) = 446 ([M], 37Cl$^+$, 24), 444 ([M], 35Cl$^+$, 61), 410 (40), 329 (15), 311 (100), 270 (10). HRMS (ESI-TOF): m/z calcd. for C$_{19}$H$_{13}$ClF$_3$O$_5$S ([M+H]$^+$, 37Cl$^+$): 445.01188; found: 445.01173; calcd for C$_{19}$H$_{13}$ClF$_3$O$_5$S ([M+H], 35Cl$^+$): 447.00951; found 447.00954.

**Methyl 7-(4-ethylphenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5d)**

Starting with 3 (70 mg, 0.145 mmol), 4d (26 mg, 0.174 mmol), Pd(PPh$_3$)$_4$ (5 mg, 3 mol-%), K$_3$PO$_4$ (46 mg, 0.22 mmol), and THF (4 mL), 5d was isolated as a white solid (54 mg, 84%); mp 66-68 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ = 1.21 (t, $J$ = 7.5 Hz, 3H, CH$_3$), 2.66 (q, $J$ = 7.5 Hz, 2H, CH$_2$), 3.95 (s, 3H, OCH$_3$), 7.27 (d, $J$ = 8.1 Hz, 2H, ArH), 7.55 (d, $J$ = 8.1 Hz, 2H, ArH), 7.68 (s, 1H, ArH), 7.87 (br. s, 2H, ArH), 8.07 (s, 1H, ArH), 8.62 (s, 1H, ArH). $^{19}$F NMR (282.4 MHz, CDCl$_3$): δ = -73.05. $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 15.5 (CH$_3$), 28.5 (CH$_2$), 52.7
(OCH₃), 119.7 (q, Jₑ,F = 322.1 Hz, CF₃), 119.8 (C), 125.3, 126.3, 126.7, 127.1, 127.6 (CH), 128.5 (C), 129.5 (CH), 132.8, 133.9 (C), 136.0 (CH), 139.9, 143.5, 143.6 (C), 163.4 (C=O). IR (KBr, cm⁻¹): ν = 3023, 2960, 2924, 2851 (w), 1716 (s), 1632, 1602, 1516, 1500 (w), 1423 (s), 1393, 1317, 1265, 1248 (w), 1204, 1136 (s), 1114, 1047, 963, 940 (w), 925, 896, 868, 840, 812, 796 (m), 719, 677, 632, 608, 591, 574 (w). GC-MS (EI, 70 eV): m/z (%) = 438 ([M]+, 100), 407 (4), 305 (44), 275 (14), 247 (35), 219 (13), 202 (19). HRMS (EI,70eV): m/z calcd for C₂₁H₁₇O₅F₃S ([M]+: 438.07433; found: 438.07418.

Methyl 7-(4-methoxyphenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5e)

Starting with 3 (70 mg, 0.145 mmol), 4e (26 mg, 0.174 mmol), Pd(PPh₃)₄ (5 mg, 3 mol-%), K₃PO₄ (46 mg, 0.22 mmol), and THF (4 mL), 5e was isolated as a white solid (53 mg, 83%); mp 142–144 °C. ¹H NMR (300 MHz, CDCl₃): δ = 3.81 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 6.97 (d, J = 8.7 Hz, 2H, ArH), 7.57 (d, J = 8.7 Hz, 2H, ArH), 7.67 (s, 1H, ArH), 7.86 (br. s, 2H, ArH), 8.04 (s, 1H, ArH), 8.61 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.09. ¹³C NMR (75.5 MHz, CDCl₃): δ = 52.7, 55.4 (OCH₃), 114.6 (CH), 117.6 (q, Jₑ,F = 320.8 Hz, CF₃), 120.8, 122.3 (C), 125.8, 128.1, 128.5, 129.4 (CH), 132.1, 133.6 (C), 134.1, 134.9 (CH), 140.6, 144.5, 159.8 (C), 164.4 (C=O). IR (KBr, cm⁻¹): ν = 3046, 3028 (w), 2958, 2919, 2849 (m), 2663, 1728 (w), 1722 (s), 1681, 1650, 1644 (m), 1604 (m), 1578, 1557, 1502 (m), 1460 (w), 1425, 1401, 1321 (s), 1282, 1268 (m), 1246, 1216, 1200 (s), 1115 (m). GC-MS (EI,70 eV): m/z (%) = 440 ([M]+, 50), 409 (4), 307 (100), 277 (13), 249 (23), 221 (15), 176 (14). HRMS (ESI-TOF): m/z calcd for C₂₀H₁₆O₆F₃S [M+H]+: 441.06142; found: 441.06173.

Methyl 7-(p-tolyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5f)

Starting with 3 (70 mg, 0.145 mmol), 4f (24 mg, 0.174 mmol), Pd(PPh₃)₄ (5 mg, 3 mol-%), K₃PO₄ (46 mg, 0.22 mmol) and THF (4 mL), 5f was isolated as a white solid (48 mg, 78%); mp: 133-135 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.36 (s, 3H, CH₃), 3.95 (s, 3H, OCH₃), 7.24 (d, J = 7.9 Hz, 2H, ArH), 7.52 (d, J = 8.0 Hz, 2H, ArH), 7.67 (s, 1H, ArH), 7.86 (br. s, 2H, ArH), 8.06 (s, 1H, ArH), 8.62 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.08. ¹³C NMR (75.5 MHz, CDCl₃): δ = 20.1 (CH₃), 51.7 (OCH₃), 118.8 (q, Jₑ,F = 320.7 Hz, CF₃), 119.8 (CH), 121.3 (C), 125.3, 126.2, 127.1, 128.5, 128.8 (CH), 130.7, 132.8 (C), 133.9 (CH), 135.8, 137.2, 139.9, 143.6 (C), 163.4 (C=O). IR (KBr, cm⁻¹): ν =
Experimental Section

3033, 3024, 3001 (w), 2985, 2978 (s), 2932, 2896 (m), 2862 (w), 2820 (s), 2764, 2719, 2680, 2655 (w), 2600, 2558 (s), 2552, 2520, 2487, 2430, 2390 (w), 2327, 1984, 1920 (s), 1690, 1620, 1570 (w), 1480, 1470, 1390, 1320 (s), 1290, 1245 (m).


Methyl 7-(4-ethoxyphenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5g)

Starting with 3 (70 mg, 0.145 mmol), 4g (29 mg, 0.174 mmol), Pd(PPh3)4 (5 mg, 3 mol-%), K3PO4 (46 mg, 0.22 mmol), and THF (4 mL), 5g was isolated as a white solid (54 mg, 82%); mp 105-108 °C. 1H NMR (300 MHz, CDCl3): δ = 1.38 (t, J = 7.2 Hz, 3H, CH3), 2.85 (s, 3H, OCH3), 3.96 (q, J = 7.2 Hz, 2H, OCH2), 6.88 (d, J = 8.9 Hz, 2H, ArH), 7.23 (d, J = 8.7 Hz, 2H, ArH), 7.40 (dd, J = 8.7, 2.5 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 8.28 (s, 1H, ArH). 13C NMR (75.5 MHz, CDCl3): δ = 20.1 (CH3), 55.4 (OCH3), 62.5 (OCH2), 113.2 (CH), 118.2 (q, J_C,F = 321.3 Hz, CF3), 118.7, 120.1 (C), 120.8, 128.3 (CH), 128.5 (C), 129.4, 129.6 (CH), 129.9 (C), 130.2, 135.6 (CH), 141.5, 143.7, 158.1 (C), 167.8 (C=O). IR (KBr, cm−1): ν = 3022, 3012, 2987 (w), 2925, 2912 (m), 1756, 1734 (s), 1722, 1686 (w), 1623 (m), 1605, 1592 (s), 1578, 1557, 1532 (m), 1517 (w), 1463, 1445, 1422, 1406 (m), 1361, 1333, 1328, 1312 (w), 1282 (m), 1278, 1245, 1232 (w), 1216 (s), 1175, 1132, 1128, 1116 (m). GC-MS (EI,70eV): m/z (%) = 454 ([M]+, 46), 322 (23), 321 (100), 293 (15), 265 (15), 234 (17), 205 (12). HRMS (ESI-TOF): m/z calcd for C21H18F3O6S [M+H]+: 455.07707; found: 455.07661.

Methyl 7-(3-methoxyphenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5h)

Starting with 3 (70 mg, 0.145 mmol), 4h (26 mg, 0.174 mmol), K3PO4 (46 mg, 0.22 mmol), Pd(PPh3)4 (5 mg, 3 mol-%), and THF (4 mL), 5h was isolated as a white solid (54 mg, 85%); mp: 82-83 °C. 1H NMR (300 MHz, CDCl3): δ = 3.83 (s, 3H, OCH3), 3.96 (s, 3H, OCH3), 6.89-6.93 (m, 1H, ArH), 7.14-7.22 (m, 3H, ArH), 7.36 (t, J = 7.9 Hz, 1H, ArH), 7.69 (br. s, 1H, ArH), 7.87-7.88 (m, 2H, ArH), 8.09 (br. s, 1H, ArH). 19F NMR (282.4 MHz, CDCl3): δ = -73.09. 13C NMR (75.5 MHz, CDCl3): δ = 52.7, 55.4 (OCH3), 113.3, 113.4 (CH), 117.9 (q, J_C,F = 319.3 Hz, CF3), 119.8, 120.8 (CH), 122.4 (C), 126.7, 128.2, 129.6, 130.1 (CH), 131.7, 134.1 (C), 135.0 (CH), 140.9, 141.2, 144.7,
Experimental Section

160.2 (C), 164.4 (C=O). IR (KBr, cm\(^{-1}\)): \(\nu = 3002, 2954, 2927, 2847\) (w), 1726 (s), 1632, 1599, 1509, 1488, 1459 (w), 1422 (s), 1402, 1370, 1314, 1286, 1263, 1249 (w), 1202, 1136 (s), 1052, 1031 (m), 969, 939 (w), 897, 853, 810, 792, 776, 722 (m), 696, 667, 643 (w), 609, 600 (m).

GC-MS (EI, 70 eV): \(m/z\) (%): 440 ([M]+, 59), 308 (20), 307 (100), 277 (15), 249 (50), 221 (18).

HRMS (EI, 70 eV): \(m/z\) calcd for C\(_{20}\)H\(_{15}\)O\(_6\)F\(_3\)S [M]+: 440.05359; found: 440.05333.

Methyl 7-(3-fluorophenyl)-3-(trifluoromethylsulfonyloxy)-2-naphthoate (5i)

Starting with 3 (70 mg, 0.145 mmol), 4i (24 mg, 0.174 mmol), Pd(PPh\(_3\))\(_4\) (5 mg, 3 mol-%), K\(_3\)PO\(_4\) (46 mg, 0.22 mmol), and THF (4 mL), 5i was isolated as a white solid (51 mg, 82%); mp 54-56 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 3.96\) (s, 3H, OCH\(_3\)), 7.25-7.41 (m, 3H, ArH), 7.70 (s, 1H, ArH), 7.79-7.92 (m, 3H, ArH), 8.07 (s, 1H, ArH), 8.64 (s, 1H, ArH). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta = 52.8\) (OCH\(_3\)), 114.2 (d, \(J_{CF} = 21.7\) Hz, CH), 114.9 (d, \(J_{CF} = 22.4\) Hz, CH), 115.2 (C), 119.4 (q, \(J_{CF} = 321.8\) Hz, CF\(_3\)), 120.9 (CH), 122.6 (C), 123.1, 126.9, 128.5, 129.3, 129.7 (CH), 130.7 (d, \(J_{CF} = 8.3\) Hz, CH), 131.7 (d, \(J_{CF} = 3.2\) Hz, CH), 134.7 (d, \(J_{CF} = 8.9\) Hz, C), 135.1 (CH), 142.0, 145.0 (C), 164.9 (d, \(J_{CF} = 245.2\) Hz, CF), 168.8 (C=O).

IR (KBr, cm\(^{-1}\)): \(\nu = 3079, 3038, 2956, 2918, 2849\) (w), 1720 (s), 1633, 1586, 1511, 1488 (w), 1420 (s), 1371, 1321, 1284, 1248 (w), 1201, 1135 (s).

The reaction was carried out in a pressure tube. To the THF suspension (4 mL) of 3 (70 mg, 0.145 mmol), arylboronic acid Ar\(^3\)B(OH)\(_2\) 4e (22 mg, 0.145 mmol), and Pd(PPh\(_3\))\(_4\) (5 mg, 3 mol%) was added K\(_3\)PO\(_4\) (46 mg, 0.22 mmol), and the resulting solution was degassed by bubbling argon through the solution for 10 min. The mixture was stirred at 20°C under an argon atmosphere for 9 h. Arylboronic acid Ar\(^2\)B(OH)\(_2\) 4f (20 mg, 0.145 mmol), Pd(PPh\(_3\))\(_4\) (3 mol-%), K\(_3\)PO\(_4\) (46 mg, 0.22 mmol) were added. The reaction mixtures were heated under an argon atmosphere at 105 °C for 8 h. They were diluted with H\(_2\)O and extracted with CH\(_2\)Cl\(_2\) (3 × 25 mL). The combined organic layers were dried
(Na$_2$SO$_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, heptane/EtOAc). 6 was isolated as a white solid (25 mg, 45%); mp 82-83°C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.36 (s, 3H, CH$_3$), 3.83 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 6.91 (d, $J$ = 8.8 Hz, 2H, ArH), 7.23-7.31 (m, 4H, ArH), 7.56 (d, $J$ = 8.8 Hz, 2H, ArH), 7.74 (s, 1H, ArH), 7.75-7.77 (m, 2H, ArH), 7.82 (s, 1H, ArH), 3.85%); mp 82-83°C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.36 (s, 3H, CH$_3$), 3.83 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 6.91 (d, $J$ = 8.8 Hz, 2H, ArH), 7.23-7.31 (m, 4H, ArH), 7.56 (d, $J$ = 8.8 Hz, 2H, ArH), 7.74 (s, 1H, ArH), 7.75-7.77 (m, 2H, ArH), 7.82 (s, 1H, ArH), 8.06 (s, 1H, ArH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 20.1 (CH$_3$), 52.7, 55.4 (OCH$_3$), 113.1, 119.8 (CH), 121.3 (C), 125.3, 126.2, 126.7, 127.1, 128.5, 128.8 (CH), 130.8, 132.9 (C), 133.9 (CH), 134.2, 134.6, 135.8, 137.2, 139.9, 143.6 (C), 164.3 (C=O).

IR (KBr, cm$^{-1}$): $\nu$ = 3002, 2954, 2927, 2847 (w), 1726 (s), 1632, 1599, 1509, 1488, 1459 (w), 1422 (s), 1402, 1370, 1314, 1286, 1263, 1249 (w), 1202, 1136 (s), 1052, 1031 (m), 969, 939 (w), 897, 853, 810, 792, 776, 722 (m), 696, 667, 643 (w), 609, 600 (m). GC-MS (EI, 70eV): m/z (%) = 382 ([M]$,^+$, 87), 367 (09), 311 (100), 281 (23), 207 (50), 198 (18). HRMS (ESI-TOF): m/z calcd. for C$_{26}$H$_{22}$O$_3$ [M+H]$^+$: 383.15678; found: 383.15623.

Methyl 4-bromo-3-hydroxy-2-naphthoate (8)

To a solution of 4-bromo-3-hydroxy-2-naphthoic acid 7 (1.0 g, 3.7 mmol) in DMF (15 mL), dimethyl sulfate (1.04 g, 8.3 mmol) and N,N-diisopropylethylamine (0.5 g, 4.1 mmol) were added. The reaction mixture was heated for 1 h at 85 °C. After cooling to room temperature, the mixture was poured into ice water. A white precipitate formed which was filtered off and the filtrate was concentrated in vacuo. The product 8 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a yellow solid (0.9 g, 87%); mp 88 - 95 °C. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 3.96 (s, 3H, OCH$_3$), 7.27-7.33 (m, 1H, ArH), 7.52-7.58 (m, 1H, ArH), 7.70 (d, $J$ = 8.2 Hz, 1H, ArH), 8.07 (d, $J$ = 8.5 Hz, 1H, ArH), 8.36 (s, 1H, ArH), 11.16 (s, 1H, OH).

$^{13}$C NMR (62.90 MHz, CDCl$_3$): = 52.0 (OCH$_3$), 106.0, 113.6 (C), 123.6, 124.8 (CH), 126.4 (C), 128.7, 129.5, 130.8 (CH), 135.1, 152.1 (C), 169.0 (CO). IR (KBr, cm$^{-1}$): $\nu$ = 3329 (m), 3039, 3004, 2955 (w), 1684 (m), 1652, 1634, 1609, 1574, 1557 (w), 1532 (m), 1504, 1479, 1464 (w), 1399, 1360, 1280, 1213, 1100 (s), 967, 901 (w), 830, 760, 680 (s). GC-MS (EI, 70 eV): m/z (%) = 282 ([M,$^{81}$Br]$^+$, 37), 280 ([M,$^{79}$Br]$^+$, 40), 250 (94), 248 (92), 251 (43), 194 (100), 192 (18). HRMS (EI, 70 eV) calcd. for C$_{12}$H$_9$BrO$_3$ [M,$^{81}$Br]$^+$: 281.98970; found: 281.98921; calcd for C$_{12}$H$_9$BrO$_3$ [M,$^{79}$Br]$^+$: 279.99351; found: 279.99354.
Methyl 4-bromo-3-(trifluoromethylsulfonyloxy)-2-naphthoate (9)

To a CH$_2$Cl$_2$ solution (50 mL) of 8 (1.0 g, 3.6 mmol) was added pyridine (1.1 mL, 14.2 mmol) and the solution was stirred at 20 °C for 10 min under argon atmosphere. Then Tf$_2$O (1.5 mL, 8.6 mmol) was added at 20 °C and the reaction mixture was heated at 50 °C for 20 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The product 9 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a colourless solid (1.33 g, 90 %); mp 90 - 92 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ = 3.96 (s, 3H, OCH$_3$), 7.59 - 7.64 (m, 1H, ArH), 7.70 - 7.75 (m, 1H, ArH), 7.91 (d, J = 8.1 Hz, 1H, ArH), 8.29 (d, J = 8.5 Hz, 1H, ArH), 8.47 (s, 1H, ArH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 53.0 (OCH$_3$), 117.7 (C), 118.5 (q, $J_{CF}$ = 317.4 Hz, CF$_3$), 123.8, 128.1 (CH), 128.6 (C), 129.5, 130.8, 131.6 (CH), 133.4, 134.2, 142.4 (C), 164.6 (CO). IR (KBr, cm$^{-1}$): v = 3071, 2962 (w), 1714 (s), 1676, 1630 (w), 1598 (m), 1503, 1462, 1441 (w), 1427 (w), 1345, 1233 (s), 1143, 1102, 985, (m), 865, 750, 701, 633 (w). GC-MS (EI, 70 eV): $m/z$ (%) = 414 ([M, $^{81}$Br]$^+$, 25), 412 ([M, $^{79}$Br]$^+$, 26), 281 (40), 279 (43), 251 (100), 248 (24), 223 (36), 221 (32). HRMS (EI, 70 eV) calcd for C$_{13}$H$_8$BrF$_3$O$_5$S [M, $^{81}$Br]$^+$: 413.99740; found: 413.99696; calcd for C$_{13}$H$_8$BrF$_3$O$_5$S [M, $^{79}$Br]$^+$: 411.98531; found: 411.98491.

General procedure for the synthesis of 10a-g

A solution of 9 (50 mg, 0.122 mmol), K$_2$CO$_3$ (2M, 2 mL), Pd(PPh$_3$)$_4$ (6 mmol-%) and arylboronic acid 4 (2.4 equiv.) in 1,4-dioxane (3 mL) was stirred at 120 °C for 6 h under argon atmosphere. To the reaction mixture H$_2$O (20 mL) and CH$_2$Cl$_2$ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

Methyl 3,4-bis(3-methylphenyl)-2-naphthoate (10a)

Starting with 9 (50 mg, 0.122 mmol), 4b (39 mg, 0.29 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mole %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 10a was isolated as a white solid (32 mg, 72 %); mp 95-97 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ = 2.12 (s, 3H, CH$_3$), 2.18 (s, 3H, CH$_3$), 3.53 (s, 3H, OCH$_3$), 6.74-6.84 (m, 5H, ArH), 6.92-6.98 (m, 2H, ArH), 7.02-7.08 (m, 1H, ArH), 7.35-7.50 (m, 3H, ArH), 7.89 (d, J = 8.51 Hz, 1H, ArH), 8.28 (s, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): δ = 21.2 (CH$_3$), 21.3
(CH$_3$), 53.4 (OCH$_3$), 126.3, 126.84, 126.88, 126.9, 127.1, 127.3, 127.6, 127.8, 128.0, 128.6 (CH), 129.2 (C), 129.4 (CH), 130.3 (C), 130.6 (CH), 131.6 (C), 131.7 (CH), 133.8, 136.3, 136.9, 137.0, 138.2, 139.9 (C), 169.2 (C=O). IR (KBr, cm$^{-1}$): $\nu$ = 3028, 2946, 2918, 2857, 2732 (w), 1727 (s), 1621, 1604, 1584, 1484 (w), 1436 (m), 1372, 1332 (w), 1301 (s), 1267 (m), 1226, 1202, 1190, 1163 (s), 1126 (m), 1101, 1087 (s), 1033, 1022 (m), 999, 970 (w).

**GC-MS (EI, 70 eV):** $m/z$ (%) = 366 ([M]$^+$, 100), 335 (32), 319 (10), 292 (13), 291 (12), 289 (14), 276 (14).

**HRMS (EI, 70 eV) calcd. for C$_{26}$H$_{22}$O$_2$:** [M]$^+$: 366.16143; found: 366.16095.

**Methyl 3,4-bis(4-chlorophenyl)-2-naphthoate (10b)**

Starting with 9 (50 mg, 0.122 mmol), 4c (45 mg, 0.29 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mole %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 10b was isolated as a white solid (34 mg, 69 %); mp 81-84 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.57 (s, 3H, OCH$_3$), 6.85-6.96 (m, 4H, ArH), 7.05-7.09 (m, 2H, ArH), 7.17-7.19 (m, 2H, ArH), 7.40-7.53 (m, 3H, ArH), 7.92 (d, $J$ = 7.5 Hz, 1H, ArH), 8.37 (s, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 52.15 (OCH$_3$), 126.6, 126.8, 127.5, 128.2, 128.5, 128.9 (CH), 129.6 (C), 130.6, 131.1 (CH), 131.8 (C), 132.2 (CH), 132.4, 133.0, 133.6, 135.9, 136.5, 138.3, 138.7 (C), 168.4 (C=O). IR (KBr, cm$^{-1}$): $\nu$ = 3057, 2961, 2925, 2855, 1716 (w), 1608, 1589 (m), 1536, 1482 (w), 1235, 1209 (m), 1137, 1117, 1095, 1070 (s). GC-MS (EI, 70 eV): $m/z$ (%) = 408 ([M, $^{37}$Cl]$^+$, 68), 406 ([M, $^{35}$Cl]$^+$, 100) 410 (12), 409 (18), 377 (24), 375 (37), 340 (17), 312 (24), 277 (18), 274 (18). HRMS (EI, 70 eV) calcd. for C$_{26}$H$_{16}$O$_2$Cl$_2$: [M, $^{35}$Cl]$^+$: 406.05219; found: 406.05154; calcd. for C$_{26}$H$_{16}$O$_2$Cl$_2$ [M, $^{73}$Cl]$^+$: 408.04924; found: 408.04910.

**Methyl 3,4-bis(4-ethylphenyl)-2-naphthoate (10c)**

Starting with 9 (50 mg, 0.122 mmol), 4d (43 mg, 0.29 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mole %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 10c was isolated as a white solid (39 mg, 81 %); mp 92-95 °C. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 1.12 (m, 6H, 2CH$_3$), 2.52 (dq, $J$ = 18.4, 7.6 Hz, 4H, 2CH$_2$), 3.51 (s, 3H, OCH$_3$), 6.84-6.92 (m, 6H, ArH), 6.99 (d, $J$ = 8.12 Hz, 2H, ArH), 7.35-7.52 (m, 3H, ArH), 7.88 (d, $J$ = 7.8 Hz, 1H, ArH), 8.26 (s, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ =14.4 (CH$_3$), 14.5 (CH$_3$), 27.4 (CH$_2$), 27.5 (CH$_2$), 51.9 (OCH$_3$), 125.3, 125.5 (C), 126.3, 126.6, 127.0, 127.1, 127.8, 128.7, 129.3, 129.8, 130.9 (CH), 133.0, 134.6,
136.0, 136.3, 138.9, 140.8, 141.4 (C), 168.3 (C=O). IR (KBr, cm\(^{-1}\)): \(v = 3059, 3022\) (w), 2965, 2945 (m), 2930, 2871 (w), 1720 (s), 1618, 1591 (w), 1513 (m), 1493, 1443, 1424, 1405 (m), 1370, 1334 (w), 1300, 1261, 1232, 1208 (s), 1179, 1149, 1127 (w), 1115 (m). GC-MS (EI, 70 eV): m/z (%) = 394 ([M\(^+\), 100], 347 (10), 305 (11), 289 (17), 276 (10). HRMS (EI, 70 eV) calcd. for C\(_{28}\)H\(_{26}\)O\(_2\) [M\(^+\)]: 394.19273; found: 394.19229.

**Methyl 3,4-bis(4-methoxyphenyl)-2-naphthoate (10d)**

Starting with 9 (50 mg, 0.122 mmol), 4e (44 mg, 0.29 mmol), Pd(PPh\(_3\))\(_4\) (8 mg, 6 mole %), K\(_2\)CO\(_3\) (2M, 2 mL) and 1,4-dioxane (3 mL), 10d was isolated as a white solid (42 mg, 86 %); mp 113 - 115 °C. \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta = 3.56\) (s, 3H, OCH\(_3\)), 3.68 (s, 3H, OCH\(_3\)), 3.73 (s, 3H, OCH\(_3\)), 6.63 (d, \(J = 8.8\) Hz, 2H, ArH), 6.73 (d, \(J = 8.8\) Hz, 2H, ArH), 6.87 (d, \(J = 8.7\) Hz, 2H, ArH), 6.92 (d, \(J = 8.8\) Hz, 2H, ArH), 7.35-7.51 (m, 3H, ArH), 7.89 (d, \(J =8.4\) Hz, 1H, ArH), 8.25 (br. s, 1H, ArH). \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)): \(\delta = 52.1, 55.0, 55.1\) (OCH\(_3\)), 112.7, 113.2, 126.3, 126.9, 127.8, 128.7, 129.3 (CH), 130.7, 130.8 (C), 130.9 (CH), 131.6 (C), 132.1 (CH), 132.5, 134.2, 136.8, 139.7, 157.8, 158.2 (C), 169.5 (C=O). IR (KBr, cm\(^{-1}\)): \(v = 3243, 3152, 2862, 2800, 2739\) (w), 1700 (m), 1655 (s), 1614, 1428, 1405 (m), 1377, 1315 (w), 1298 (m), 1233 (w), 1201, 1184, 1144, 1115 (s). GC-MS (EI, 70 eV): m/z (%) = 398 ([M\(^+\), 100], 367 (13), 256 (16). HRMS (EI, 70 eV) calcd. for C\(_{26}\)H\(_{22}\)O\(_4\) [M\(^+\)]: 398.15126; found: 398.15102.

**Methyl 3,4-bis(4-methylphenyl)-2-naphthoate (10e)**

Starting with 9 (50 mg, 0.122 mmol), 4f (39 mg, 0.29 mmol), Pd(PPh\(_3\))\(_4\) (8 mg, 6 mole %), K\(_2\)CO\(_3\) (2M, 2 mL) and 1,4-dioxane (3 mL), 10e was isolated as a white solid (35 mg, 78 %); mp 97 - 100 °C. \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta = 2.19\) (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 3.54 (s, 3H, OCH\(_3\)), 6.82-6.86 (m, 4H, ArH), 6.89 (d, \(J = 8.04\) Hz, 2H, ArH), 6.98 (d, \(J = 8.7\) Hz, 2H, ArH), 7.33-7.47 (m, 2H, ArH), 7.86-7.90 (m, 2H, ArH), 8.26 (br. s, 1H, ArH). \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)): \(\delta = 21.2\) (CH\(_3\)), 29.7 (CH\(_3\)), 55.2 (OCH\(_3\)), 126.3, 127.0, 127.8, 127.9, 128.3, 128.6, 129.4, 129.7 (CH), 130.6 (C), 130.9 (CH), 131.6, 134.0, 135.4, 135.5, 136.1, 136.9, 137.1, 139.9 (C), 169.3 (C=O). IR (KBr, cm\(^{-1}\)): \(v = 3043, 3022, 2952, 2918, 2849, 1900\) (w), 1716 (s), 1514, 1488, 1435 (m), 1417, 1408 (w), 1379 (m), 1333 (w), 1301, 1262, 1232, 1207, 1180 (s), 1144 (m), 1127 (w), 1115 (m).
Expermental Section

1153, 1128 (m). GC-MS (EI, 70 eV): m/z (%) = 366 ([M]$^+$, 100), 335 (29), 319 (12), 306 (12), 292 (16), 291 (13), 289 (18). HRMS (EI, 70 eV) calcd. for C$_{26}$H$_{22}$O$_2$ [M]$^+$: 366.16134; found: 366.16134.

Methyl 3,4-bis(4-ethoxyphenyl)-2-naphthoate (10f)

Starting with 9 (50 mg, 0.122 mmol), 4g (48 mg, 0.29 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mole %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 10f was isolated as a white solid (48 mg, 93%); mp 102 - 105 °C. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 1.28-1.35 (m, 6H, 2CH$_3$), 3.54 (s, 3H, OCH$_3$), 3.84-3.97 (m, 4H, 2OCH$_2$), 6.60 (d, $J$ = 8.6 Hz, 2H, ArH), 6.71 (d, $J$ = 8.6 Hz, 2H, ArH), 6.85 (d, $J$ = 8.6 Hz, 2H, ArH), 6.9 (d, $J$ = 8.8 Hz, 2H, ArH), 7.34-7.51 (m, 3H, ArH), 7.87 (d, $J$ = 7.4 Hz, 1H, ArH), 8.23 (br. s, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 14.9, 29.7 (2CH$_3$), 52.1 (OCH$_3$), 63.2, 63.3 (2OCH$_2$), 113.3, 113.7, 126.3, 127.0, 127.8, 128.7, 129.2 (CH), 130.6, 130.8 (C), 130.9 (CH), 131.7 (C), 132.1 (CH), 132.4, 134.2, 136.8, 139.8, 157.2, 157.6 (C), 169.5 (C=O). IR (KBr, cm$^{-1}$): $\nu$ = 3044, 2979, 2950, 2921, 2894, 2873, 2849 (w), 1721, 1715, 1608 (s), 1573 (w), 1512 (s), 1489, 1473, 1441, 1390, 1376 (m), 1331 (w), 1300 (s), 1284, 1258 (m), 1240, 1205, 1174 (s), 1129 (w), 1112 (s), 1097 (m), 1045 (s). GC-MS (EI, 70 eV): m/z (%) = 426 ([M]$^+$, 100), 281 (10), 252 (10). HRMS (EI, 70 eV) calcd. for C$_{28}$H$_{26}$O$_4$ [M]$^+$: 426.18256; found: 426.18189.

Methyl 3,4-bis(4-trifluoromethylphenyl)-2-naphthoate (10g)

Starting with 9 (50 mg, 0.122 mmol), 4j (55 mg, 0.29 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mole %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 10g was isolated as a white solid (42 mg, 73%); mp 94 - 97 °C. $^1$H NMR (300 MHz, CDC$_3$): $\delta$ = 3.56 (s, 3H, OCH$_3$), 7.08 (d, $J$ = 7.9 Hz, 2H, ArH), 7.13 (d, $J$ = 7.9 Hz, 2H, ArH), 7.34 (d, $J$ = 8.5 Hz, 3H, ArH), 7.43-7.48 (m, 3H, ArH), 7.53 (dd, $J$ = 8, 1.4 Hz, 1H, ArH), 7.95 (d, $J$ = 7.9 Hz, 1H, ArH), 8.46 (s, 1H, ArH). $^{19}$F NMR (282.4, MHz): $\delta$ = -62.52, -62.60. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 51.2 (OCH$_3$), 123.2 (q, $J_{C,F} = 3.9$ Hz, CH), 123.7 (CH), 123.8 (q, $J_{C,F} = 3.3$ Hz, CH), 124.0 (q, $J_{C,F} = 271$ Hz, CF$_3$), 124.1 (q, $J_{C,F} = 271$ Hz, CF$_3$), 125.4, 126.1 (C), 127.8, 128.0, 128.1, 129.1, 130.2 (CH), 130.9 (q, $J_{C,F} = 31$ Hz, C), 131.1 (q, $J_{C,F} = 35$ Hz, C), 132.4, 134.8, 137.5, 140.8, 142.5 (C), 167.2 (C=O). IR (KBr, cm$^{-1}$): $\nu$ = 3313, 3252 (w), 2962, 2870 (m), 2659, 1900 (w), 1785, 1754, 1673, 1576 (w), 1473, 1390, 1374, 1348, 1290, 1174 (s), 1129 (w), 1112 (s), 1097 (m), 1045 (s). GC-MS (EI, 70 eV): m/z (%) = 426 ([M]$^+$, 100), 281 (10), 252 (10). HRMS (EI, 70 eV) calcd. for C$_{28}$H$_{26}$O$_4$ [M]$^+$: 426.18256; found: 426.18189.
1608 (s), 1585, 1490, 1415 (w), 1328 (m), 1283, 1251 (s), 1154 (m). GC-MS (EI, 70 eV): m/z (% = 474 ([M]+, 100), 444 (14), 443 (57), 423 (13), 346 (23), 345 (10), 344 (13), 276 (22). HRMS (EI, 70 eV) calcd. for C26H16O2F6 [M]+: 474.10490; found: 474.10420.

**General procedure for the synthesis of 11a-e**

A 1,4-dioxan solution of 9 (50 mg, 0.122 mmol), K2CO3 (2M, 2 mL), Pd(PPh3)4 (3 mol-%) and of arylboronic acid 4 (1.0 equiv.) was stirred at 60 °C for 9 h under argon atmosphere. To the reaction mixture were added H2O (20 mL) and CH2Cl2 (25 mL). The organic and the aqueous layers were separated and the latter was extracted with CH2Cl2 (2 x 20 mL). The combined organic layers were dried (Na2SO4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane / EtOAc = 100:5).

**Methyl 4-bromo-3-(3-methylphenyl)-2-naphthoate (11a)**

Starting with 9 (50 mg, 0.122 mmol), 4b (17 mg, 0.122 mmol), Pd(PPh3)4 (4 mg, 3 mole %), K2CO3 (2M, 2 mL), and 1,4-dioxane (3 mL), 11a was isolated as a white solid (36 mg, 83 %); mp 105 - 108 °C.

1H NMR (300 MHz, CDCl3): δ = 2.34 (s, 3H, CH3), 3.53 (s, 3H, OCH3), 6.77 (s, 1H, ArH), 7.01 (d, J = 7.1 Hz, 2H, ArH), 7.14-7.16 (m, 1H, ArH), 7.24-7.29 (m, 1H, ArH), 7.51-7.56 (m, 1H, ArH), 7.64 (ddd, J = 8.5, 7, 1.3 Hz, 1H, ArH), 7.87 (d, J = 7.9 Hz, 1H, ArH), 8.33 (d, J = 8.7 Hz, 1H, ArH). 13C NMR (62.9 MHz, CDCl3): δ = 20.5 (CH3), 51.17 (OCH3), 125.3, 126.3, 126.6, 127.1, 127.2 (CH), 127.6 (C), 128.1, 128.6, 128.8, 128.9 (CH), 129.6, 131.5, 132.6, 136.2, 140.1 (C), 166.7 (C=O). IR (KBr, cm⁻¹): ν = 3050, 3023 (w), 2984, 2921 (m), 2845 (w), 1728 (s), 1621, 1545, 1512 (w), 1484, 1439 (m), 1375, 1322, 1303 (w), 1256, 1232, 1190 (s). GC-MS (EI, 70 eV): m/z (%) = 356 ([M, 81Br]+, 83), 354 ([M, 79Br]+, 83), 357 (17), 325 (19), 323 (19), 260 (10), 244 (100), 243 (18), 216 (21). HRMS (EI, 70 eV) calcd. for C19H15BrO2 [M, 79Br]+: 354.02499; found: 354.02481; calcd. for C19H15BrO2 [M, 81Br]+: 356.02295; found: 354.02303.
Methyl 4-bromo-3-(4-chlorophenyl)-2-naphthoate (11b)

Starting with 9 (50 mg, 0.122 mmol), 4c (19 mg, 0.122 mmol), Pd(PPh₃)₄ (4 mg, 3 mole %), K₂CO₃ (2M, 2 mL), and 1,4-dioxane (3 mL), 11b was isolated as a white solid (34 mg, 76 %); mp 88-91°C. ¹H NMR (250 MHz, CDCl₃): δ = 3.58 (s, 3H, OCH₃), 7.12-7.16 (m, 2H, ArH), 7.35 (d, J = 8.5 Hz, 2H, ArH), 7.53-7.70 (m, 2H, ArH), 7.88 (dd, J = 8.1 Hz, 1H, ArH), 8.33 (d, J = 8.9 Hz, 2H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 52.3 (OCH₃), 124.6, 126.4 (C), 127.6, 128.0, 128.1, 129.8, 130.4, 130.5 (CH), 131.5, 132.4, 132.5, 137.2, 138.7 (C), 166.2 (C=O). IR (KBr, cm⁻¹): v = 3100, 3083, 3051, 2997, 2947, 2918, 2849 (w), 1730, 1720 (s), 1621, 1596, 1555 (w), 1494, 1439, 1395, 1346, 1314 (m), 1263, 1227, 1208, 1140, 1099, 1083 (s), 1029 (w). GC-MS ( EI, 70 eV): m/z (%) = 376 ([M, ⁸¹Br, ³⁵Cl]⁺·100), 374 ([M, ⁷⁹Br, ³⁵Cl]⁺·75), 345 (28), 343 (22), 280 (14), 266 (26), 265 (19), 264 (77), 238 (10), 199 (13). HRMS (EI, 70 eV) calcld. for C₁₈H₁₂BrO₂Cl [M, ⁸¹Br, ³⁵Cl]⁺: 376.97032; found: 376.97039; calcld. for C₁₈H₁₂BrO₂Cl [M, ⁷⁹Br, ³⁵Cl]⁺: 375.96832; found: 375.96804.

Methyl 4-bromo-3-(4-ethylphenyl)-2-naphthoate (11c)

Starting with 9 (50 mg, 0.122 mmol), 4d (18 mg, 0.122 mmol), Pd(PPh₃)₄ (4 mg, 3 mole %), K₂CO₃ (2M, 2 mL), and 1,4-dioxane (3 mL), 11c was isolated as a white solid (39 mg, 88 %); mp 101-104 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.23 (m, 3H, CH₃), 2.67 (m, 2H, CH₂), 3.52 (s, 3H, OCH₃), 7.12 (d, J = 8.3 Hz, 2H, ArH), 7.18-7.22 (m, 3H, ArH), 7.50-7.55 (m, 1H, ArH), 7.63 (d, J = 8.5 Hz, 1H, ArH), 7.86 (d, J = 7.1 Hz, 1H, ArH), 8.32 (d, J = 8.50 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 15.3 (CH₃), 28.7 (CH₂), 52.2 (OCH₃), 125.5 (C), 127.2, 127.3, 128.1, 129.0, 129.1, 129.5, 129.8 (CH), 130.8, 132.4, 133.6, 138.4, 139.3, 143.4 (C), 167.8 (C=O). IR (KBr, cm⁻¹): v = 3050, 3020 (w), 2961, 2927, 2871, 2855 (m), 1729 (s), 1621, 1553 (w), 1515, 1484 (m), 1437 (s), 1409, 1373, 1346 (m), 1282, 1262, 1233, 1202 (s), 1145 (w), 1138, 1116 (s). GC-MS (EI, 70 eV): m/z (%) = 370 ([M, ⁸¹Br]⁺·56), 368 ([M, ⁷⁹Br]⁺·100), 314 (15), 251 (17), 149 (10). HRMS (EI, 70 eV) calcld. for C₂₀H₁₇BrO₂ [M, ⁷⁹Br]⁺: 368.04221; found: 368.04102; calcld. for C₂₀H₁₇BrO₂ [M, ⁸¹Br]⁺: 370.03921; found: 370.03100.
Experimental Section

Methyl 4-bromo-3-(4-methoxyphenyl)-2-naphthoate (11d)

Starting with 9 (50 mg, 0.122 mmol), 4e (19 mg, 0.122 mmol), Pd(PPh₃)₄ (4 mg, 3 mole %), K₂CO₃ (2M, 2 mL), and 1,4-dioxane (3 mL), 11d was isolated as a white solid (41 mg, 92 %); mp 107 - 110 °C. ¹H NMR (300 MHz, CDCl₃): δ = 3.56 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 6.91 (d, J = 8.69 Hz, 1H, ArH), 7.11 - 7.19 (m, 3H, ArH), 7.50 - 7.56 (m, 1H, ArH), 7.64 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, ArH), 7.86 (d, J = 7.93 Hz, 1H, ArH), 8.25 (s, 1H, ArH), 8.32 (d, J = 8.69 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 52.3, 55.2 (OCH₃), 113.2 (CH), 125.9 (C), 127.3, 128.1, 129.0, 129.5, 129.8, 130.5 (CH), 132.4, 133.5, 133.6, 137.8, 138.9, 142.2 (C), 167.9 (C=O). IR (KBr, cm⁻¹): ν = 3041, 3000, 2951, 2849, 2832, 2811 (w), 1729 (s), 1607, 1552 (w), 1513 (s), 1483 (w), 1455 (m), 1436 (s), 1346, 1314, 1304, 1285 (m), 1257, 1238, 1229, 1200, 1177, 1135, 1099, 1029 (s). GC-MS (EI, 70 eV): m/z (%) = 372 ([M, 81Br]+, 100), 370 ([M, 79Br]+, 100), 339 (11), 261 (16), 260 (68), 245 (22), 217 (10). HRMS (EI, 70 eV) calcd. for C₁₉H₁₅BrO₃ [M, 79Br]⁺: 370.01991; found: 370.01940; calcd. for C₁₉H₁₅BrO₃ [M, 81Br]⁺: 372.01786; found: 372.01693.

Methyl 4-bromo-3-(4-methylphenyl)-2-naphthoate (11e)

Starting with 9 (50 mg, 0.122 mmol), 4f (17 mg, 0.122 mmol), Pd(PPh₃)₄ (4 mg, 3 mole %), K₂CO₃ (2M, 2 mL), and 1,4-dioxane (3 mL), 11e was isolated as a white solid (34 mg, 79 %); mp 104 - 107 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.37 (s, 3H, CH₃), 3.55 (s, 3H, OCH₃), 6.85 - 6.91 (m, 1H, ArH), 7.10 (d, J = 8.12 Hz, 2H, ArH), 7.17 - 7.20 (m, 2H, ArH), 7.51 - 7.56 (m, 1H, ArH), 7.65 (ddd, J = 8.5, 7, 1.3 Hz, 1H, ArH), 7.87 (d, J = 7.93 Hz, 1H, ArH), 8.33 (d, J = 8.69 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 21.5 (CH₃), 52.23 (OCH₃), 127.4, 127.9, 128.1 (CH), 128.4 (C), 128.5, 129.1, 129.6, 129.9 (CH), 130.7, 132.5, 137.1, 138.3, 139.4, 139.9 (C), 167.9 (C=O). IR (KBr, cm⁻¹): ν = 3049, 3020, 2993, 2947 (w), 2920, 2853 (m), 1728 (s), 1621, 1591, 1554 (w), 1515, 1484 (m), 1438 (s), 1376, 1345 (w), 1322, 1300 (m), 1261, 1228, 1203, 1183 (s), 1150, 1138 (m), 1097 (s). GC-MS (EI, 70 eV): m/z (%) = 356 ([M, 81Br]⁺, 81), 354 ([M, 79Br]⁺, 81), 357 (17), 325 (16), 260 (11), 243 (17), 242 (100), 214 (11). HRMS (EI, 70 eV) calcd. for C₁₉H₁₅BrO₂ [M, 79Br]⁺: 354.02499; found: 354.02459; calcd. for C₁₉H₁₅BrO₂ [M, 81Br]⁺: 356.02295; found: 356.02276.
General procedure for the synthesis of 12a-c

A dioxan solution of 9 (50 mg, 0.122 mmol), Ar1B(OH)2 (1.0 equiv.), K2CO3 2M (2mL) and Pd(PPh3)4 (3 mol-%) was heated at 60 °C for 9 h under argon atmosphere. After cooling to 20 °C, Ar2B(OH)2 (1.2 equiv), Pd(PPh3)4 (6 mol-%) were added and the reaction mixture was heated at 120 °C for further 6 h. The reaction mixture was cooled again to 20 °C, H2O was added and the reaction mixture was extracted with CH2Cl2 (3 x 25 mL). The combined organic layers were dried (Na2SO4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc / heptanes).

Methyl 3-(4-ethylphenyl)-4-(4-trifluoromethylphenyl)-2-naphthoate (12a)

Starting with 9 (50 mg, 0.122 mmol), 4d (18 mg, 0.122 mmol), Pd(PPh3)4 (4 mg, 3 mole %), K2CO3 (2M, 2 mL), and 1,4-dioxane (3 ml), and 4j (28 mg, 0.146 mmol), Pd(PPh3)4 (8 mg, 6 mole %), K2CO3 (2M, 2 mL) and 1,4-dioxane (3 mL), 12a was isolated as a white solid (41 mg, 79%); mp 98-101 °C. 1H NMR (300 MHz, CDCl3): δ = 1.08 (t, J = 7.6, 2 Hz, 3H, CH3), 2.49 (q, J = 7.6, 3 Hz, 2H, CH2), 3.53 (s, 3H, OCH3), 6.81-6.88 (m, 4H, ArH), 7.13-7.18 (m, 3H, ArH), 7.37-7.49 (m, 4H, ArH), 7.92 (d, J = 7.9 Hz, 1H, ArH), 8.33 (s, 1H, ArH). 19F NMR (282.4 MHz): δ = -62.48. 13C NMR (62.9 MHz, CDCl3): δ = 14.3 (CH3), 27.4 (CH2), 51.0 (OCH3), 121.4 (C), 123.5 (q, Jc,F = 3.6 Hz, CH), 124.6 (q, Jc,F = 245 Hz, CF3), 126.8, 128.3, 128.9, 129.7, 130.2 (CH), 131.4 (q, Jc,F = 31 Hz, CF), 132.3, 135.6, 137.3, 141.4 (C), 167.8 (C=O). IR (KBr, cm⁻¹): v = 3451 (w), 3036, 2985, 2948, 2921 (w), 2856, 2744, 1962, 1935 (w), 1846, 1793 (m), 1732 (s), 1692 (w), 1576, 1534, 1478 (m), 1443, 1412 (w), 1376, 1344, 1317 (m), 1265, 1255 (s), 1232, 1201 (w), 1192 (s). GC-MS (EI, 70 eV): m/z (%) = 434 ([M]+, 100), 419 (21), 405 (11), 403 (16), 387 (12), 375 (12), 373 (10), 359 (10), 289 (15), 276 (17). HRMS (EI, 70 eV) calcd. for C27H21O2F3 [M]+: 434.14882; found: 434.14868.
Methyl 4-(p-methoxyphenyl)-3-(p-tolyl)-2-naphthoate (12b)

Starting with 9 (50 mg, 0.122 mmol), 4f (17 mg, 0.122 mmol), K$_2$CO$_3$ (2M, 2 mL), Pd(PPh$_3$)$_4$ (4 mg, 3 mol-%) and 4e (22 mg, 0.146 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mol %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 12b was isolated as a white solid (39 mg, 86 %); mp 87-88 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.21$ (s, 3H, CH$_3$), 3.54 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 6.73 (d, $J = 8.9$ Hz, 2H, ArH), 6.82-6.90 (m, 4H, ArH), 6.93 (d, $J = 8.7$ Hz, 2H, ArH), 7.35-7.45 (m, 2H, ArH), 7.47-7.50 (m, 1H, ArH), 7.88 (br. d, $J = 7.7$ Hz, 1H, ArH), 8.3 (s, 1H, ArH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 29.9$ (CH$_3$), 51.0, 54.2 (OCH$_3$), 112.1 (C), 113.1, 119.8 (CH), 125.3, 125.8 (C), 126.3 (CH), 126.9, 127.7 (C), 127.8, 127.9 (CH), 128.4, 128.7 (C), 128.9 (CH), 131.1 (C), 131.7, 132.1 (CH), 134.2 (C), 135.7 (CH), 169.4 (C=O). IR (KBr, cm$^{-1}$): $\nu = 3003$, 2956, 2928, 2849 (w), 1727 (s), 1634, 1598, 1507, 1489 (m), 1346, 1277, 1209, 1144 (s), 976, 944, 855, 820, 744 (m), 699, 640 (s). GC-MS (EI, 70 eV): m/z (%) = 382 ($[M]$+, 88), 370 (78), 311 (100), 298 (18), 245 (33), 198 (18). HRMS (EI, 70 eV) calcd. for C$_{26}$H$_{22}$O$_3$ [M]$^+$: 382.01653; found: 382.01693.

Methyl 3-(4-chlorophenyl)-4-(4-ethylphenyl)-2-naphthoate (12c)

Starting with 9 (50 mg, 0.122 mmol), 4c (19 mg, 0.122 mmol), Pd(PPh$_3$)$_4$ (4 mg, 3 mole %), K$_2$CO$_3$ (2M, 2 mL), and 1,4-dioxane (3 mL), and 4d (22 mg, 0.146 mmol), Pd(PPh$_3$)$_4$ (8 mg, 6 mol %), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 12c was isolated as a white solid (35 mg, 71 %); mp 112-115 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.20$ (m, 3H, CH$_3$), 2.57 (q, $J = 7.3$, 3 Hz, 2H, CH$_2$), 3.57 (s, 3H, OCH$_3$), 6.88-6.91 (m, 4H, ArH), 7.35 (s, 3H, OCH$_3$), 6.88-6.91 (m, 4H, ArH), 7.00-7.06 (m, 4H, ArH), 7.37-7.50 (m, 3H, ArH), 7.88-7.90 (m, 1H, ArH), 8.33 (s, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta = 14.3$ (CH$_3$), 27.4 (CH$_2$), 51.0 (OCH$_3$), 125.6, 126.1, 126.2, 126.3, 127.1, 127.7 (CH), 128.7 (C), 128.9, 129.7, 130.2 (CH), 130.8, 131.1, 133.1, 134.1, 134.7, 137.8, 139.2, 141.8 (C), 167.7 (C=O). IR (KBr, cm$^{-1}$): $\nu = 3422$, 3365 (w), 2964, 2902 (m), 2851, 2831, 2780 (w), 1983, 1934, 1868 (m), 1721 (s), 1650, 1577, 1562, 1492, 1445 (m), 1432 (s), 1388, 1376, 1322 (w), 1281, 1264, 1218 (s), 1194, 1163, 1114 (m). GC-MS (EI, 70 eV): m/z (%) = 402([M, $^{37}$Cl]$^+$, 35), 400([M, $^{35}$Cl]$^+$, 100), 369 (12), 304 (11), 291 (10), 290 (13), 289 (28), 277 (12), 276 (31). HRMS (EI, 70 eV) calcd. for C$_{26}$H$_{21}$O$_2$Cl [M, $^{35}$Cl]$^+$: 400.12246; found: 400.12207; calcd. for C$_{26}$H$_{21}$O$_2$Cl [M, $^{37}$Cl]$^+$: 402.11951; found: 402.12002.
Synthesis of 4,7-Bis-(trifluoromethylsulfonyloxy)-chromen-2-on (14)

To a CH₂Cl₂ solution (50 mL) of 13 (1.0 g, 5.6 mmol) was added pyridine (1.8 mL, 22.4 mmol) and the solution was stirred at 20 °C for 10 min under argon atmosphere. Then Tf₂O (2.3 mL, 13.5 mmol) was added at 20 °C and the reaction mixture was heated at 50 °C for 20 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The product 14 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a colourless solid (2.1 g, 85%); mp 79-77 °C. ¹H NMR (300 MHz, CDCl₃): δ = 6.51 (s, 1H, CH=CH), 7.27-7.32 (m, 2H, ArH), 7.74 (d, J = 8.7 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 105.6, 110.1, 111.6 (CH), 112.9 (C), 118.3 (q, J_C,F = 320.0 Hz, CF₃), 118.6 (q, J_F,C = 320.0 Hz, CF₃), 123.6 (CH), 151.4, 152.0, 154.9 (C), 157.3 (C=O). ¹⁹F NMR (282.4 MHz): δ = -72.5, -72.4. IR (KBr, cm⁻¹): v = 3171, 2988 (w), 1755 (s), 1698, 1643 (w), 1577 (m), 1550, 1499, 1475, 1433 (w). GC-MS (EI, 70 eV): m/z (%) = 441 ([M]⁺, 100), 356 (15), 276 (33), 234 (23), 195 (16), 168 (17). HRMS (EI, 70 eV) calcd. for C₃₁H₂₆O₈F₆S₂ [M]⁺: 441.93145; found: 441.93087.

General procedure for the synthesis of (15a-e)

A solution of 14 (0.045 mmol), K₂CO₃ (2M, 2 mL), Pd(PPh₃)₄ (6 mol%) and arylboronic acid (2.4 equiv.) in 1,4-dioxane (3 mL) was stirred at 110 °C for 8 h under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

4,7-Bis(3,5-dimethylphenyl)-chromen-2-on (15a)

Starting with 14 (20 mg, 0.045 mmol), 4a (16 mg, 0.11 mmol), Pd(PPh₃)₄ (3 mg, 6 mole%), K₂CO₃ (2M, 2 mL) and 1,4-dioxane (3 mL), 15a was isolated as a white solid (13 mg, 81%); mp: 127-130 °C. ¹H NMR (300 MHz, CDCl₃): δ =2.33 (s, 6H, 2CH₃), 2.34 (s, 6H, 2CH₃), 6.27 (s, 1H, ArH), 6.99-7.02 (m, 4H, ArH), 7.09 (s, 1H, ArH), 7.37-7.40 (m, 1H, ArH), 7.46-7.50 (m, 2H, ArH), 7.52-7.53 (m, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 21.3 (2CH₃), 21.4 (2CH₃), 114.3, 115.3 (CH), 117.9 (C), 122.9, 125.1, 126.2, 127.3, 130.2, 131.2 (CH), 135.3, 138.5, 138.6, 139.1, 145.2, 154.5, 155.8 (C), 161.0 (C=O). IR (KBr, cm⁻¹): ν = 3356, 3312, 2961, 1943 (m), 1902, 1831, 1805 (s), 1778, 1709 (w), 1688 (m), 1583, 1550, 1470
(s), 1419, 1352, 1315 (w), 1255, 1221, 1218 (s), 1157, 1144, 1103 (m). GC-MS (EI, 70 eV): m/z (%) = 354 ([M]+, 100), 340 (10), 339 (40), 327 (15), 326 (60), 162 (12). HRMS (EI, 70 eV) calcd. for C_{25}H_{22}O_{2} [M]+: 354.16143; found: 354.16190.

4,7-Bis(4-methoxyphenyl)-chromen-2-on (15b)

Starting with 14 (20 mg, 0.045 mmol), 4e (17 mg, 0.11 mmol), Pd(PPh_{3})_{4} (3 mg, 6 mole%), K_{2}CO_{3} (2M, 2 mL) and 1,4-dioxane (3 mL), 15b was isolated as a white solid (11 mg, 68 %); mp: 112-115 °C. \(^{1}\)H NMR (300 MHz, CDCl_{3}): \(\delta = 3.80\) (s, 3H, OCH_{3}), 3.83 (s, 3H, OCH_{3}), 6.26 (s, 1H, CH), 6.95 (d, \(J = 8.9\) Hz, 2H, ArH), 6.99 (d, \(J = 8.9\) Hz, 2H, ArH), 7.35-7.39 (m, 3H, ArH). \(^{13}\)C NMR (62.9 MHz, CDCl_{3}): \(\delta = 55.4, 55.7\) (2OCH_{3}), 110.3, 112.4, 113.0, 114.6 (CH), 117.8 (C), 122.4, 124.4, 127.6, 128.2 (CH), 131.7, 138.2, 143.2, 155.5, 156.9, 157.8, 159.7 (C), 161.0 (C=O). IR (KBr, cm\(^{-1}\)): \(\nu = 3377\) (m), 3012, 2961, 1921, 1850 (w), 1721, 1605 (s), 1578, 1529, 1510 (m), 1463, 1450, 1440, 1419, 1372, 1309 (w), 1295, 1278 (m), 1257, 1244 (s), 1197, 1179, 1164, 1131, 1110 (m), 1094 (w). GC-MS (EI, 70 eV): m/z (%) = 358 ([M]+, 100), 331 (10), 330 (43), 315 (30). HRMS (EI, 70 eV) calcd. for C_{25}H_{18}O_{4} [M]+: 358.11996; found: 358.11953.

4,7-Bis(4-ethoxyphenyl)-chromen-2-on (15c)

Starting with 14 (20 mg, 0.045 mmol), 4g (18 mg, 0.11 mmol), Pd(PPh_{3})_{4} (3 mg, 6 mole%), K_{2}CO_{3} (2M, 2 mL) and 1,4-dioxane (3 mL), 15c was isolated as a white solid (12 mg, 66 %); mp 114-117 °C. \(^{1}\)H NMR (300 MHz, CDCl_{3}): \(\delta = 1.36-1.43\) (m, 6H, 2CH_{3}), 3.99-4.09 (m, 4H, 2OCH_{2}), 6.25 (s, 1H, CH), 6.91-6.99 (m, 4H, ArH), 7.37 (d, \(J = 8.7\) Hz, 3H, ArH), 7.49-7.59 (m, 4H, ArH). \(^{13}\)C NMR (62.9 MHz, CDCl_{3}): \(\delta = 14.8\) (2CH_{3}), 63.6, 63.7 (2OCH_{2}), 113.7, 114.7, 114.8, 115.1 (CH), 117.5 (C), 122.4, 127.3 (CH), 127.4 (C), 128.3, 129.9 (CH), 131.2, 144.6, 154.8, 155.2, 159.6, 160.3 (C), 162.2 (C=O). IR (KBr, cm\(^{-1}\)): \(\nu = 3051, 3037, 2990, 2972, 2928, 2894, 2850\) (w), 1722, 1605 (s), 1576, 1569 (w), 1510 (m), 1476, 1455 (w), 1436 (m), 1397, 1386 (w), 1370 (m), 1308 (w), 1295 (m), 1257, 1242 (s). GC-MS (EI, 70 eV): m/z (%) = 386 ([M]+, 100), 358 (16), 330 (16), 329 (10), 302 (19), 273 (10). HRMS (EI, 70 eV) calcd. for C_{26}H_{22}O_{4} [M]+: 386.15126; found: 386.15104.
4,7-Bis(phenyl)-chromen-2-on (15d)

Starting with 14 (20 mg, 0.045 mmol), 4k (13 mg, 0.11 mmol), Pd(PPPh₃)₄ (3 mg, 6 mole%), K₂CO₃ (2M, 2mL) and 1,4-dioxane (3 mL), 15d was isolated as a white solid (11 mg, 79%); mp 131-133 °C. ¹H NMR (300 MHz, CDCl₃): δ = 6.31 (s, 1H, CH), 7.34-7.37 (m, 1H, ArH), 7.39-7.44 (m, 5H, ArH), 7.47-7.49 (m, 4H, ArH), 7.56-7.58 (m, 3H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 113.8, 114.4 (CH), 116.8 (C), 121.9, 126.2, 126.3 (CH), 126.5 (C), 127.4, 127.6, 127.9, 128.1, 128.7 (CH), 134.3, 138.0, 144.1, 153.6 (C), 162.1 (C=O). IR (KBr, cm⁻¹): ν = 3399, 3070, 3051, 2959, 2918, 2849, 1722, 1707, 1650, 1631, 1593 (w), 1573, 1535 (m), 1512, 1495 (w), 1446, 1428, 1402 (m), 1315, 1290 (w), 1285 (s), 1227 (w), 1163, 1156 (m), 1123, 1076, 1012 (s). GC-MS (EI, 70 eV): m/z (%) = 298 ([M⁺], 100), 297 (17), 271 (20), 241(28), 240 (11), 239 (32). HRMS (EI, 70 eV) calcd. for C₂₁H₁₄O₂ [M⁺]: 298.09883; found: 298.09803.

4,7-Bis(3,5-dimethoxyphenyl)-chromen-2-on (15e)

Starting with 14 (20 mg, 0.045 mmol), 4l (18 mg, 0.11 mmol), Pd(PPPh₃)₄ (3 mg, 6 mole%), K₂CO₃ (2M, 2mL) and 1,4-dioxane (3 mL), 15e was isolated as a white solid (13 mg, 69%); mp 111-114 °C. ¹H NMR (300 MHz. CDCl₃): δ = 3.02 (s, 6H, 2OCH₃), 3.04 (s, 6H, 2OCH₃), 5.56 (s, 1H, CH), 5.70 (s, 1H, ArH), 5.75-5.79 (m, 3H, ArH), 5.92-5.93 (m, 2H, ArH), 6.60-6.63 (m, 1H, ArH), 7.76-7.78 (m, 2H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 53.4 (2OCH₃), 55.5 (2OCH₃), 99.9, 100.5, 101.4, 105.4, 110.7, 116.6, 122.6 (CH), 123.8 (C), 130.0 (CH), 132.5, 135.7, 150.2, 156.4, 157.5, 160.5, 160.9 (C), 161.2 (C=O). IR (KBr, cm⁻¹): ν = 3377 (m), 3012, 2961, 1921, 1850 (w), 1721, 1605 (s), 1578, 1529, 1510 (m), 1463, 1450, 1440, 1419, 1372, 1309 (w), 1295, 1278 (m), 1257, 1244 (s), 1197, 1179, 1164, 1131, 1110 (m), 1094 (w). GC-MS (EI, 70 eV): m/z (%) = 418 ([M⁺], 100), 390 (28), 369 (13). HRMS (EI, 70 eV) calcd. for C₂₅H₂₂O₆ [M⁺]: 418.14313; found: 418.14202.
**General procedure for the synthesis of 16a-h**

A solution of 14 (0.045 mmol), K₂CO₃ (2M, 2 mL), Pd(PPh₃)₄ (3 mole%) and arylboronic acid (1.0 equiv.) in toluene (3 mL) was stirred at 65 °C. for 6 h. under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over (Na₂SO₄), filtered and the filtrate was concentrated in vacuo.

The residue was purified by column chromatography (silica gel, heptane/EtOAc).

**4-(3,5-Methylphenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-one (16a)**

Starting with 14 (20 mg, 0.045 mmol), 4a (7 mg, 0.045 mmol), Pd(PPh₃)₄ (1.5 mg, 3 mole%), K₂CO₃ (2M, 2 mL), and toluene (3 mL), 16a was isolated as a white solid (15 mg, 82 %); mp 93-96 °C.

**1H NMR** (300 MHz, CDCl₃): δ = 2.43 (s, 6H, 2CH₃), 6.33 (s, 1H, CH), 6.96 (s, 2H, ArH), 7.07-7.11 (m, 2H, ArH), 7.26-7.27 (m, 1H, ArH), 7.55 (d, J = 8.9 Hz, 1H, ArH). 

**19F NMR** (282.4 MHz): δ = -72.51.

**13C NMR** (62.9 MHz, CDCl₃): δ = 21.3 (2CH₃), 110.6, 115.6, 117.3 (CH), 118.1 (q, J_C,F = 320.6 Hz, CF₃), 119.3 (C), 125.9, 128.9, 131.7 (CH), 134.3, 150.7, 154.6, 154.9, 159.9 (C), 161.8 (C=O). 

**IR (KBr, cm⁻¹):** v = 3085, 3059, 3028, 2956 (w), 2921 (m), 2852 (w), 1650, 1624, 1600 (s), 1545 (m), 1488 (w), 1444 (m), 1428, 1412, 1400, 1376 (s), 1317 (m), 1269 (w), 1247, 1226 (m), 1204, 1190 (s), 1160 (m), 1141 (s), 1087, 1075, 1052 (w). GC-MS (EI, 70 eV): m/z (%) = 398 ([M]+, 100), 397 (16), 384 (19), 265 (14), 250 (11), 238 (11), 237 (65), 209 (48), 181 (12), 166 (32), 165 (45), 152 (10). 

**HRMS (EI, 70 eV) calcd. for C₁₈H₁₃O₅F₃S [M]+: 398.04303; found: 398.04260.**

**4-(Ethylphenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-one (16b)**

Starting with 14 (20 mg, 0.045 mmol), 4d (7 mg, 0.045 mmol), Pd(PPh₃)₄ (1.5 mg, 3 mole%), K₂CO₃ (2M, 2 mL), and toluene (3 mL), 16b was isolated as a white solid (13 mg, 73 %); mp 81-84 °C. 

**1H NMR** (300 MHz. CDCl₃): δ = 1.24 (t, J = 7.5 Hz, 3H, CH₃), 2.69 (q, J = 7.4 Hz, 2H, CH₂), 6.35 (s, 1H, CH), 7.09 (d, J = 8.5 Hz, 1H, ArH), 7.19 (s, 1H, ArH), 7.30 (s, 4H, ArH), 7.58 (d, J = 9.0 Hz, 1H, ArH). 

**19F NMR** (282.4, MHz): δ = -72.52. 

**13C NMR** (62.9 MHz, CDCl₃): δ = 15.7 (CH₃), 28.7 (CH₂), 110.7, 115.1, 115.3, 117.2 (CH), 118.6 (q, J_C,F = 321.2 Hz, CF₃), 119.3, 126.4 (C), 128.9, 129.9 (CH), 150.8, 154.3, 154.8, 159.7 (C), 160.6 (C=O). 

**IR (KBr, cm⁻¹):** v = 3371 (m), 3124, 3081, 3059, 2968, 2919, 2880, 2850 (w), 1715, 1606 (s), 1555, 1509, 1507, 1489, 1416 (w),
4-(Methoxyphenyl)-7-(trifluoromethylsulfonyloxy)chromen-2-one (16c)

Starting with 14 (20 mg, 0.045 mmol), 4e (7 mg, 0.045 mmol), Pd(PPh$_3$)$_4$ (1.5 mg, 3 mole%), K$_2$CO$_3$ (2M, 2 mL), and toluene (3 mL), 16c was isolated as a white solid (13 mg, 71 %); mp 86-88 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.83 (s, 3H, OCH$_3$), 6.33 (s, 1H, CH), 6.95 (d, $J$ = 8.7 Hz, 2H, ArH), 7.10 (dd, $J$ = 8.9, 2,3 Hz, 1H, ArH), 7.24 (d, $J$ = 2.3 Hz, 1H, ArH), 7.33 (d, $J$ = 8.7 Hz, 2H, ArH), 7.59 (d, $J$ = 8.9 Hz, 1H, ArH). $^{19}$F NMR (282.4 MHz): $\delta$ = -72.5. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 55.51 (OCH$_3$), 110.8, 114.3, 114.6, 117.3 (CH), 118.3 (q, $J_{C,F}$ = 320.0 Hz, CF$_3$), 119.3, 126.6 (C), 128.9, 129.9 (CH), 150.6, 153.0, 154.8, 159.7 (C), 161.2 (C=O). IR (KBr, cm$^{-1}$): $v$ = 3039, 2967, 2929 (w), 1756, 1699, 1675, 1596 (s), 1557, 1528, 1512, 1503, 1474, 1453 (w), 1435 (m), 1396, 1378, 1353 (m), 1295, 1259, 1243, 1209, 1196 (w), 1136 (m), 1084, 1072, 1029, 999 (w), 960 (m), 907 (w), 868, 848, 816, 777 (m), 760 (s), 731 (w), 705, 692 (s), 676, 630, 618, 565, 553, 546 (w). GC-MS (EI, 70 eV): m/z (%) = 400 ([M]$^+$, 100), 240 (15), 211 (33), 183 (23), 168 (19). HRMS (EI, 70 eV) calcd. for C$_{18}$H$_{13}$F$_3$O$_5$S [M]$^+$: 400.02197; found: 400.02229.

4-(Methylphenyl)-7-(trifluoromethylsulfonyloxy)chromen-2-one (16d)

Starting with 14 (20 mg, 0.045 mmol), 4f (6 mg, 0.045 mmol), Pd(PPh$_3$)$_4$ (1.5 mg, 3 mole%), K$_2$CO$_3$ (2M, 2 mL), and toluene (3 mL), 16d was isolated as a white solid (12 mg, 70 %); mp 79-82 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.13 (s, 3H, CH$_3$), 6.31 (s, 1H, CH), 6.99 (d, $J$ = 8.7 Hz, 2H, ArH), 7.08 (dd, $J$ = 8.9, 2,3 Hz, 1H, ArH), 7.27 (d, $J$ = 2.5 Hz, 1H, ArH), 7.33 (d, $J$ = 8.7 Hz, 2H, ArH), 7.59 (d, $J$ = 8.9 Hz, 1H, ArH). $^{19}$F NMR (282.4 MHz): $\delta$ = -72.5. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 21.2 (CH$_3$), 110.8, 114.3, 115.8, 117.6 (CH), 118.3 (q, $J_{C,F}$ = 320.3 Hz, CF$_3$), 119.5, 125.6 (C), 128.3, 129.0 (CH), 150.8, 152.8, 155.8, 159.7 (C), 163.4 (C=O). IR (KBr, cm$^{-1}$): $v$ = 3139, 2967, 2729 (w), 1756, 1699, 1675, 1596 (s), 1557, 1528, 1512, 1503, 1484, 1453 (w), 1405, 1396, 1378, 1353 (m), 1265, 1239, 1213, 1209, 1156 (w), 1112 (m), 1084, 1072 (s), 1009, 980,
960 (m), 907 (w), 888, 854, 832 (m), 777, 760 (s), 731 (w), 705, 692 (s), 696, 640, 607, 553, 546 (w). GC-MS (EI, 70 eV): m/z (%) = 384 ([M]^+, 100), 335 (17), 295 (22), 265 (17), 237 (17), 152 (15). HRMS (EI, 70 eV) calcd. for C_{17}H_{11}O_5F_3S [M]^+: 384.03225; found: 384.0342.

4-(Ethoxyphenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-on (16e)

Starting with 14 (20 mg, 0.045 mmol), 4g (8 mg, 0.045 mmol), Pd(PPh_3)_4 (1.5 mg, 3 mole%), K_2CO_3 (2M, 2 mL), and toluene (3 mL), 16e was isolated as a white solid (15 mg, 78%); mp 88-91 °C. \(^1^H\) NMR (300 MHz, CDCl_3): δ = 1.40 (t, J = 7.0 Hz, 3H, CH_3), 4.05 (q, J = 7.1 Hz, 2H, OCH_2), 6.33 (s, 1H, CH), 6.95-7.00 (m, 2H, ArH), 7.10 (dd, J = 8.9, 2.5 Hz, 1H, ArH), 7.27 (s, 1H, ArH), 7.30-7.33 (m, 2H, ArH), 7.61 (d, J = 8.9 Hz, 1H, ArH). \(^1^9^F\) NMR (282.4 MHz): δ = -72.54. \(^{13}\)C NMR (62.9 MHz, CDCl_3): δ = 14.8 (CH_3), 63.8 (OCH_2), 110.7, 115.1, 115.3, 117.2 (CH), 117.9 (q, J_{C,F} = 321.1 Hz, CF_3), 119.3, 126.4 (C), 128.9, 129.8 (CH), 150.8, 154.3, 154.8, 159.7 (C), 160.6 (C=O). IR (KBr, cm\(^{-1}\)): ν = 3069, 3052, 2977, 2958, 2924, 2872 (s), 1692, 1679, 1666, 1649, 1642 (w), 1606 (m), 1573, 1565 (m), 1553 (w), 1512 (m), 1475 (w), 1428 (s), 1394 (w), 1366 (m), 1293 (w), 1261 (m), 1243, 1214, 1199, 1179, 1140, 1107 (s). GC-MS (EI, 70 eV) calc. for C_{17}H_{11}O_5F_3S [M]^+: 384.03794; found: 384.03693.

4-(3-Fluorophenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-on (16f)

Starting with 14 (20 mg, 0.045 mmol), 4i (6 mg, 0.045 mmol), Pd(PPh_3)_4 (1.5 mg, 3 mole%), K_2CO_3 (2M, 2 mL), and toluene (3 mL), 16f was isolated as a white solid (11 mg, 64%); mp 65-68 °C. \(^1^H\) NMR (300 MHz, CDCl_3): δ = 5.61 (s, 1H, CH), 6.31-6.39 (m, 3H, ArH), 6.43 (s, 1H, ArH), 6.53-6.55 (m, 1H, ArH), 6.72-6.75 (m, 2H, ArH). \(^1^9^F\) NMR (282.4 MHz): δ = -111.34, -73.14. \(^{13}\)C NMR (62.9 MHz, CDCl_3): δ = 110.9 (CH), 115.7 (d, J_{C,F} = 23 Hz, CH), 116.3 (CH), 117.3 (d, J_{C,F} = 21 Hz, CH), 117.6 (CH), 118.3 (q, J_{C,F} = 321.1 Hz, CF_3), 124.1 (d, J_{C,F} = 3.3 Hz, CH), 128.5 (CH), 131.1 (d, J_{C,F} = 8 Hz, CH), 136.4 (d, J_{C,F} = 7.7 Hz, CF), 151.0, 153.1 (C), 153.2 (d, J_{C,F} = 1.0 Hz, CF), 154.7 (C), 159.1 (C=O), 164.4 (d, J_{C,F} = 249 Hz, CF). IR (KBr, cm\(^{-1}\)): ν = 3086, 3062, 2957, 2918, 2849 (w), 1711, 1605 (s), 1584, 1563, 1483 (m), 1411 (s), 1371 (m), 1326, 1307, 1278, 1255 (w), 1239, 1200 (s), 1161 (m), 1136, 1125, 1110 (s), 1079 (m), 990, 978, 859 (s). GC-MS (EI, 70 eV): m/z (%) = GC-MS
(EI, 70 eV): m/z (%) = 388 ([M]+, 100), 296 (24), 228 (14), 225 (25), 199 (43). HRMS (EI, 70 eV) calcd. for C16H8O5F4S [M]+: 388.00231; found: 388.00187.

4-(Trifluoromethoxyphenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-on (16g)

Starting with 14 (20 mg, 0.045 mmol), 4m (9 mg, 0.045 mmol), Pd(PPh3)4 (1.5 mg, 3 mole%), K2CO3 (2M, 2 mL), and toluene (3 mL), 16g was isolated as a white solid (13 mg, 65 %); mp 61-64 °C. 1H NMR (300 MHz, CDCl3): δ = 6.37 (s, 1H, ArH), 7.10-7.14 (m, 1H, ArH), 7.29-7.30 (m, 1H, ArH), 7.34 (d, J = 8.12 Hz, 2H, ArH), 7.41-7.49 (m, 3H, ArH). 19F NMR (282.4 MHz): δ = -72.52, -57.74. 13C NMR (62.9 MHz, CDCl3): δ = 109.9, 115.4, 116.5 (CH), 117.8 (C), 118.8 (q, JCF = 320.4 Hz, CF3), 120.5 (CH), 123.4 (q, JCF = 259 Hz, CF), 127.5, 129.0 (CH), 149.4 (q, JCF = 2 Hz, CF), 150.0, 152.1, 153.7 (C), 158.1 (C=O). IR (KBr, cm⁻¹): ν = 3102, 2961, 2923, 2851 (w), 1739 (s), 1620 (m), 1608 (s), 1565, 1507 (m), 1493 (w), 1425 (s), 1411, 1367 (m), 1323 (w), 1256, 1235, 1198, 1162, 1137, 1099, 1028, 987 (s). GC-MS (EI, 70 eV): m/z (%) = 454 ([M]+, 86), 362 (21), 294 (17), 293 (100), 237 (25), 152 (23). (ESI-TOF/MS) calcd. for C17H9F6O6S [M+H]+: 455.00185; found: 455.00181.

4-(2, 3, 4-Trimethoxyphenyl)-7-(trifluoromethylsulfonyloxy)-chromen-2-on (16h)

Starting with 14 (20 mg, 0.045 mmol), 4n (10 mg, 0.045 mmol), Pd(PPh3)4 (1.5 mg, 3 mole%), K2CO3 (2M, 2 mL), and toluene (3 mL), 16h was isolated as a white solid (14 mg, 67 %), mp: 97-100 °C. 1H NMR (300 MHz, CDCl3): δ = 3.68 (s, 3H, OCH₃), 3.87 (s, 6H, 2OCH₃), 6.34 (s, 1H, CH), 6.72 (d, J = 8.5 Hz, 1H, ArH), 6.85-6.87 (m, 1H, ArH), 7.05 (dd, J = 8.9, 2.5 Hz, 1H, ArH), 7.53-7.66 (m, 2H, ArH). 19F NMR (282.4 MHz, CDCl3): δ = -72.06. 13C NMR (62.9 MHz, CDCl3): δ = 56.9 (OCH₃), 61.0, 61.5 (2OCH₃), 107.6, 116.7 (CH), 117.1 (C), 118.3 (q, JCF = 321.1 Hz, CF3), 121.0, 122.9 (C), 124.2, 128.5, 129.2, 132.1 (CH), 142.4, 150.6, 152.4, 154.2, 155.4 (C), 159.7 (C=O). IR (KBr, cm⁻¹): ν = 3075, 2917, 2848 (w), 1733 (s), 1607 (w), 1573, 1539, 1494, 1463 (w), 1414 (m), 1369, 1325, 1296, 1259 (w), 1237, 1209, 1137 (m), 1095 (s). GC-MS (EI, 70 eV): m/z (%) = 460 ([M]+, 100), 355 (10), 281 (10), 207 (11), 165 (13), 139 (71), 137 (21), 135 (13). HRMS (EI, 70 eV) calcd. for C19H15O₈F₃S [M]+: 460.04342; found 460.04260.
Experimental Section

4-(Methoxyphenyl)-7-(methylphenyl)-chromen-2-on (17)

Starting with 14 (20 mg, 0.045 mmol), 4e (7 mg, 0.045 mmol), Pd(PPh₃)₄ (1.5 mg, 3 mole%), K₂CO₃ (2M, 2 mL) and toluene (3 mL), and 4f (7 mg, 0.054 mmol), Pd(PPh₃)₄ (3 mg, 6 mole%), K₂CO₃ (2M, 2 mL) and 1,4-dioxane (2 mL), 17 was isolated as a white solid (13 mg, 84%); mp 104-107 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.38 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 6.28 (s, 1H, C=CH), 7.01 (d, J = 8.7 Hz, 2H, ArH), 7.28 - 7.33 (m, 1H, ArH), 7.37 - 7.41 (m, 6H, ArH), 7.53 (d, J = 8.00 Hz, 2H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 21.3 (CH₃), 55.5 (OCH₃), 114.2 (C), 114.4, 115.5 (CH), 118.0 (C), 122.9, 124.4 (CH), 127.6 (C), 127.9, 129.0, 129.3, 129.9 (CH), 138.8, 145.2, 152.5, 154.7, 155.2 (C), 161.2 (C=O). IR (KBr, cm⁻¹): v = 3012, 2878, 2822 (w), 1966, 1844 (s), 1744, 1696 (m), 1601, 1578, 1522, 1504 (w), 1487, 1454, 1412 (m). GC-MS (EI, 70 eV): m/z (%) = 342 ([M⁺], 100), 318 (23), 280 (16), 234 (10), 187 (19). HRMS (EI, 70 eV) calcd. for C₂₃H₁₈O₃ [M⁺]: 342.12505; found: 342.12459.

5-Bromo-quinolin-8-yl trifluoromethanesulfonate (19)

To a CH₂Cl₂ solution (20 mL) of 18 (1.0 g, 4.5 mmol) was added pyridine (0.45 mL, 5.4 mmol) and the solution was stirred at 20 °C for 10 min under argon atmosphere. Then Tf₂O (0.9 mL, 5.4 mmol) 2 was added at 20 °C and the reaction mixture was heated at 50 °C for 20 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The product 19 was isolated by column chromatography (flash silica gel, heptanes/EtOAc) as a colourless solid (1.35 g, 85%); mp 89-91 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.45 (d, J = 8.31 Hz, 1H, ArH), 7.59 (dd, J = 8.59, 4.25 Hz, 1H, ArH), 7.80 (d, J = 8.31 Hz, 1H, ArH), 8.51 (dd, J = 8.69, 1.51 Hz, 1H, ArH), 9.01 (dd, J = 4.15, 1.51 Hz, 1H, ArH). ¹⁹F NMR (282.4 MHz): δ = -73.6. ¹³C NMR (62.9 MHz, CDCl₃): δ = 118.9 (q, JCF = 321.3 Hz, CF₃), 121.4 (CH), 121.8 (C), 123.7 (CH), 129.0 (C), 129.4, 135.7 (CH), 141.6, 145.6 (C), 152.2 (CH). IR (KBr, cm⁻¹): v = 3171, 2959, 2845 (w), 1753, 1733 (s), 1666, 1632, 1588 (m), 1541 (s), 1480, 1476, 1422 (w), 1366 (s), 1244, 1198, 1170 (m), 1085 (s). GC-MS (EI, 70 eV): m/z (%) = 357 ([M, ⁸¹Br⁺], 31) 355 ([M, ⁷⁹Br⁺], 34), 304 (28), 283 (51), 239 (100), 198 (11), 173 (14). HRMS (EI, 70 eV): calcd. for C₁₀H₅BrF₃NO₃S [M⁺]: 356.91051; found: 356.90991; calcd. for C₁₀H₅BrF₃NO₃S [M, ⁷⁹Br⁺]: 354.91256; found: 354.91241.
General procedure for the synthesis of 20a-d

A solution of 19 (0.056 mmol), K₂CO₃ (2M, 2 mL), Pd(PPh₃)₄ (6 mmol%) and arylboronic acid (2.0 equiv.) in 1,4-dioxane (3 mL) was stirred at 110 °C for 10 h. under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

5,8-Bis(3,5-dimethylphenyl)quinoline (20a)

Starting with 19 (20 mg, 0.056 mmol), a₄ (17 mg, 0.112 mmol), Pd(PPh₃)₄ (4 mg, 6 mole%), K₂CO₃ (2M, 2 mL) and 1,4-dioxane (3 mL), 20a was isolated as a white solid (15 mg, 81%); mp 105-107 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.34 (br. s, 12H, 4CH₃), 6.98 (br. s, 1H, ArH), 7.04 (br. s, 3H, ArH), 7.21-7.30 (m, 3H, ArH), 7.44 (d, J = 7.37 Hz, 1H, ArH), 7.64 (d, J = 7.37 Hz, 1H, ArH), 8.23 (dd, J = 8.59, 1.79 Hz, 1H, ArH), 8.86 (dd, J = 4.15, 1.70 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 20.3, 20.4 (4CH₃), 120.7 (CH), 125.7 (C), 126.7 (CH), 126.9 (C), 127.9, 128.4, 129.1, 129.2, 129.7, 134.7 (CH), 136.3, 136.9, 138.4, 138.5, 139.1, 145.4 (C), 149.9 (CH). IR (KBr, cm⁻¹): v = 3011, 2955, 2917, 2850, 2730 (w), 1727, 1683, 1596, 1576, 1500, 1455, 1392 (m), 1373, 1355, 1325, 1290, 1259 (w), 1227, 1200, 1184, 1167, 1155 (m), 1093, 1035 (s). GC-MS (EI, 70 eV): m/z (%) = 337 ([M]+, 67), 336 (100), 322 (78), 232 (12). HRMS (ESI-TOF/MS): calcd for C₂₅H₂₄N [M+H]+: 338.19033; found: 338.19043.
Experimental Section

5,8-Bis(3-methylphenyl)quinoline (20b)

Starting with 19 (20 mg, 0.056 mmol), 4b (15 mg, 0.112 mmol), Pd(PPh$_3$)$_4$ (4 mg, 6 mole%), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 20b was isolated as a white solid (14 mg, 77%); mp 79-80 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.38 (s, 6H, 2CH$_3$), 7.15-7.24 (m, 3H, ArH), 7.32-7.34 (m, 1H, ArH), 7.39-7.46 (m, 3H, ArH), 7.56-7.60 (m, 2H, ArH), 7.80 (d, $J$ = 8.3 Hz, 1H, ArH), 8.19 (dd, $J$ = 8.7, 1.7 Hz, 1H, ArH), 8.99 (dd, $J$ = 4.72, 1.7 Hz, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 20.3 (2CH$_3$), 120.3, 121.4 (CH), 121.8 (C), 123.7, 126.2, 127.0 (CH), 128.2 (C), 128.5, 129.0, 129.4, 130.6, 134.6, 135.7 (CH), 137.9, 138.5, 141.1, 141.4, 145.2, 145.6 (C), 151.3, 152.2 (CH). IR (KBr, cm$^{-1}$): $\nu$ = 3042, 2956, 2924, 2854 (w), 1727, 1593 (m), 1573, 1562 (w), 1499, 1491, 1463 (m), 1422 (s), 1382, 1352, 1308, 1293 (w), 1246 (m), 1205, 1138 (s). GC-MS (EI, 70 eV): m/z (%) = 309 ([M]+, 54), 289 (81), 247 (100), 211 (21), 177 (18), 163 (09). HRMS (ESI-TOF/MS): calcd for C$_{23}$H$_{20}$N [M+H]$^+$: 310.15175; found: 310.15139.

5,8-Bis(p-methoxyphenyl)quinoline (20c)

Starting with 19 (20 mg, 0.056 mmol), 4e (17 mg, 0.112 mmol), Pd(PPh$_3$)$_4$ (4 mg, 6 mole%), K$_2$CO$_3$ (2M, 2 mL) and 1,4-dioxane (3 mL), 20c was isolated as a white solid (13 mg, 68%); mp 119-120 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.82 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 6.99 (br. d, $J$ = 8.5 Hz, 4H, ArH), 7.28 (dd, $J$ = 8.7, 4.2 Hz, 1H, ArH), 7.36 (d, $J$ = 8.9 Hz, 2H, ArH), 7.45 (d, $J$ = 7.6 Hz, 1H, ArH), 7.62 (d, $J$ = 8.9 Hz, 2H, ArH), 7.67 (d, $J$ = 7.4 Hz, 1H, ArH), 8.23 (dd, $J$ = 8.6, 1.8 Hz, 1H, ArH), 8.88 (dd, $J$ = 4.2, 1.7 Hz, 1H, ArH). $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 55.3, 55.4 (OCH$_3$), 113.6, 113.9, 120.7, 126.9 (CH), 127.3 (C), 129.5, 131.1, 131.7 (CH), 131.9, 132.0 (C), 134.6 (CH), 139.3, 139.4, 146.3 (C), 149.8 (CH), 159.1, 159.3 (C). IR (KBr, cm$^{-1}$): $\nu$ = 2989 (w), 2967, 2855, 2821 (m), 1788, 1756 (s), 1689, 1644, 1632, 1619, 1589, 1576 (w), 1512 (s), 1477, 1435, 1412, 1344, 1312 (m), 1298, 1276, 1254 (s), 1176, 1144, 1132, 1117, 1098 (m). GC-MS (EI, 70 eV): m/z (%) = 341 ([M]$^+$, 86), 340 (100), 326 (16), 297 (7), 254 (10), 234 (11). HRMS (ESI-TOF/MS): calcd for C$_{23}$H$_{20}$NO$_2$ [M+H]$^+$: 342.14886; found: 342.14897.
Starting with 19 (20 mg, 0.056 mmol), 4g (19 mg, 0.112 mmol), Pd(PPh₃)₄ (4 mg, 6 mole%), K₂CO₃ (2M, 2 mL) and 1,4-dioxane (3 mL), 20d was isolated as a white solid (15 mg, 72 %); mp 127-129 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.37-1.44 (m, 6H, 2CH₃), 4.02-4.10 (m, 4H, 2OCH₂), 6.96-6.99 (m, 4H, ArH), 7.27 (dd, J = 8.6, 4.1 Hz, 1H, ArH), 7.34 (d, J = 7.8 Hz, 2H, ArH), 7.45 (d, J = 7.3 Hz, 1H, ArH), 7.6 (d, J = 8.7 Hz, 2H, ArH), 7.67 (d, J = 7.3 Hz, 1H, ArH), 8.24 (dd, J = 8.7, 1.7 Hz, 1H, ArH), 8.87 (dd, J = 4.2, 1.7 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 28.6, 29.9 (2CH₃), 62.4, 62.5 (2OCH₂), 113.1, 113.4, 119.6, 125.9 (CH), 126.2 (C), 128.4, 130.1, 130.7 (CH), 130.8 (C), 133.6 (CH), 138.2, 128.4, 142.3, 145.2 (C), 148.7 (CH), 157.4, 157.5 (C). IR (KBr, cm⁻¹): v = 3041, 2957 (w), 2885, 2842 (m), 1713 (s), 1574 (m), 1512 (s), 1490 (w), 1472 (m), 1431, 1410 (w), 1299, 1282 (m), 1258 (w), 1239 (s), 1175 (m), 1151, 1131 (w), 1110. 1098 (m). GC-MS (EI, 70 eV): m/z (%) = 369 ([M]+, 100), 368 (98), 341 (10), 340 (45), 312 (11), 283 (11), 282 (14). HRMS (ESI-TOF/MS): calcd for C₂₅H₂₄NO₂ [M+H]+: 370.18016; found: 370.18022

**General procedure for the synthesis of 21a-h**

A solution of 19 (0.056 mmol), K₃PO₃ (1.0 equiv.), Pd(PPh₃)₄ (3 mmol%) and arylboronic acid (1.0 equiv.) in toluene (3 mL) was stirred at 85 °C for 9 h under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).
**5-(3,5-Methylphenyl)-quinolin-8-yl trifluoromethanesulfonate (21a)**

Starting with 19 (20 mg, 0.056 mmol), 4a (8 mg, 0.056 mmol), Pd(PPh₃)₄ (2 mg, 3 mole%), K₃PO₄ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21a was isolated as a white solid (16 mg, 76 %); mp 97-99 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.35 (s, 6H, 2CH₃), 6.98 (br. s, 2H, ArH), 7.05 (br. s, 1H, ArH), 7.39-7.43 (m, 2H, ArH), 7.57 (d, J = 7.9 Hz, 1H, ArH), 8.21 (dd, J = 8.69, 1.70 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 20.3 (2CH₃), 118.3, 119.3, 121.4, 125.2 (CH), 126.5 (C), 126.7, 128.8 (CH), 132.3 (C), 133.7 (CH), 136.9, 137.3, 140.1, 140.6 (C), 150.2 (CH). IR (KBr, cm⁻¹): v = 2961 (m), 2922, 2853, 1594, 1499 (w), 1423 (m), 1257 (s), 1222, 1209 (w), 1078 (m), 1008 (s). GC-MS (EI, 70 eV): m/z (%) = 381 ([M]+, 37), 249 (19), 248 (100), 221 (13), 220 (78), 204 (32). HRMS (EI, 70 eV) calcld for C₁₈H₁₄F₃NO₃S [M]+: 381.06381; found: 381.06410.

**5-(4-Chloro)-quinolin-8-yl trifluoromethanesulfonate (21b)**

Starting with 19 (20 mg, 0.056 mmol), 4c (9 mg, 0.056 mmol), Pd(PPh₃)₄ (2 mg, 3 mole%), K₃PO₄ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21b was isolated as a white solid (13 mg, 60 %); mp 143-145 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.32 (d, J = 8.5 Hz, 2H, ArH), 7.42-7.46 (m, 4H, ArH), 7.59 (d, J = 7.9 Hz, 1H, ArH), 8.13 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 9.01 (dd, J = 4.5, 1.5 Hz, 1H, ArH). ¹⁹F NMR (282.4 MHz): δ = -73.7. ¹³C NMR (62.9 MHz, CDCl₃): δ = 119.1 (q, Jₐᵣ₀,₉ = 320.4 Hz, CF₃), 119.4, 121.6, 126.5 (CH), 127.0 (C), 127.9, 130.2, 133.2 (CH), 133.6, 135.3, 138.8, 140.2, 146.5 (C), 150.5 (CH). IR (KBr, cm⁻¹): v = 3070, 3050, 2959, 2929, 2873, 2850 (w), 1731 (m), 1597 (w), 1501, 1467 (m), 1424 (s), 1400, 1309 (w), 1258, 1243, 1208, 1172 (m), 1139, 1123, 1082, 1043, 1024, 1013 (s). GC-MS (EI, 70 eV): m/z (%) = 389 ([M,³⁷Cl]+, 14), 387 ([M,³⁵Cl]+, 36), 256 (34), 255 (17), 254 (99), 228 (34), 227 (17), 226 (100). HRMS (EI, 70 eV) calcld for C₁₆H₁₄O₃NClF₃S ([M,³⁵Cl]+): 386.99341; found: 386.99383; calcld for ([M,³⁷Cl]+): 388.99088; found: 388.990297.
5-(4-Ethylphenyl)-quinolin-8-yl trifluoromethanesulfonate (21c)

Starting with 19 (20 mg, 0.056 mmol), 4d (8 mg, 0.056 mmol), Pd(PPh$_3$)$_4$ (2 mg, 3 mole%), K$_3$PO$_4$ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21c was isolated as a white solid (16 mg, 75%); mp 106-108 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.26 (t, $J = 7.5$ Hz, 3H, CH$_3$), 2.71 (q, $J = 7.6$ Hz, 2H, ArH), 7.29 (br. s, 4H, ArH), 7.39-7.44 (m, 2H, ArH), 7.58 (d, $J = 8.2$ Hz, 1H, ArH), 8.22 (dd, $J = 8.7$, 1.7 Hz, 1H, ArH), 8.99 (dd, $J = 4.2$, 1.5 Hz, 1H, ArH). $^{19}$F NMR (282.4 MHz): $\delta$ = -73.6. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 15.5 (CH$_3$), 30.9 (CH$_2$), 119.1 (q, $J_{C,F} = 320.8$ Hz, CF$_3$), 120.4, 122.4, 126.3 (CH), 127.3 (C), 128.2, 129.8, 134.7 (CH), 135.3, 141.2, 141.4, 144.5, 145.2 (C), 151.3 (CH). IR (KBr, cm$^{-1}$): $\nu$ = 2959 (w), 2917, 2849 (s), 1736, 1711, 1611, 1592, 1569, 1513, 1495 (w), 1467, 1464 (m), 1421 (s), 1401, 1382, 1357, 1306, 1260 (w), 1244, 1202 (s), 1170 (m), 1140 (s). GC-MS (EI, 70 eV): m/z (%) = 381 ([M]$^+$, 35), 250 (23), 249 (22), 248 (100), 222 (11), 221 (10), 220 (44), 205 (22), 204 (12), 193 (29). HRMS (EI, 70 eV): calcd for C$_{18}$H$_{14}$F$_3$NO$_3$S [M]$^+$: 381.06465; found: 381.06449.

5-(4-Methoxyphenyl)-quinolin-8-yl trifluoromethanesulfonate (21d)

Starting with 19 (20 mg, 0.056 mmol), 4e (9 mg, 0.056 mmol), Pd(PPh$_3$)$_4$ (2 mg, 3 mole%), K$_3$PO$_4$ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21d was isolated as a white solid (18 mg, 84%); mp 108-110 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.82 (s, 3H, OCH$_3$), 6.99 (d, $J = 8.9$ Hz, 2H, ArH), 7.39-7.43 (m, 2H, ArH), 7.45 (d, $J = 8.9$ Hz, 2H, ArH), 7.57 (d, $J = 7.9$ Hz, 1H, ArH), 8.21 (dd, $J = 8.7$, 1.7 Hz, 1H, ArH), 8.98 (dd, $J = 4.2$, 1.5 Hz, 1H, ArH). $^{19}$F NMR (282.4 MHz): $\delta$ = -73.7. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 55.4 (OCH$_3$), 114.2 (CH), 118.5 (q, $J_{C,F} = 322.5$ Hz, CF$_3$), 120.4, 122.4, 126.2 (CH), 131.0 (C), 131.1 (CH), 133.1 (C), 134.6 (CH), 135.9, 139.2, 143.7 (C), 151.2 (CH), 159.7 (C). IR (KBr, cm$^{-1}$): $\nu$ = 3189, 2974, 2966 (w), 2898, 2876, 2833 (m), 1798 (s), 1783, 1766 (m), 1723, 1693, 1665, 1622 (w), 1584, 1566 (s), 1532, 1487, 1466 (w), 1411, 1382, 1354, 1334, 1312 (m), 1276 (s), 1273, 1244 (w), 1212, 1167, 1154, 1134, 1089 (m). GC-MS (EI, 70 eV): m/z (%) = 383 ([M]$^+$, 23), 251 (14), 250 (100), 222 (63), 179 (20), 178 (22). HRMS (EI, 70 eV): calcd for C$_{17}$H$_{12}$F$_3$NO$_4$S [M]$^+$: 383.04336; found: 383.04323.
5-(p-Tolyl)-quinolin-8-yl trifluoromethanesulfonate (21e)

Starting with 19 (20 mg, 0.056 mmol), 4f (8 mg, 0.056 mmol), Pd(PPh₃)₄ (2 mg, 3 mole %), K₃PO₄ (1.0 equiv) (12 mg, 0.056 mmol), and toluene (3 mL), 21e was isolated as a white solid (17 mg, 81%); mp 102-104 °C. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) = 2.40 (s, 3H, CH₃), 7.27 (br. s, 4H, ArH), 7.38 - 7.44 (m, 2H, ArH), 7.58 (d, \(J = 7.9\) Hz, 1H, ArH), 8.21 (dd, \(J = 8.6, 1.6\) Hz, 1H, ArH), 8.99 (dd, \(J = 4.2, 1.5\) Hz, 1H, ArH). \(^{19}\)F NMR (282.4 MHz): \(\delta\) = -73.7. \(^{13}\)C NMR (62.9 MHz, CDCl₃): \(\delta\) = 21.2 (CH₃), 117.7 (q, \(J_{C,F} = 321.5\) Hz, CF₃), 120.5, 122.3 (CH), 126.2 (C), 128.2, 129.4, 134.5 (CH), 135.1, 138.2, 141.2, 141.3, 145.2 (C), 151.2 (CH). IR (KBr, cm\(^{-1}\)): \(v\) = 3058, 3018, 2952, 2920, 2850 (w), 1722, 1671, 1587 (m), 1500 (w), 1454, 1423 (s), 1395, 1379, 1354 (m), 1242, 1208 (s), 1171 (w), 1157, 1139 (m). GC-MS (EI, 70 eV): m/z (%) = 367 ([M]+, 37), 235 (16), 234 (100), 207 (15), 206 (88), 205 (10), 204 (28), 191 (11). HRMS (EI, 70 eV) calcld for C₁₇H₁₂F₃NO₃S [M]+: 367.04845; found: 367.04755.

5-(4-Ethoxyphenyl)-quinolin-8-yl trifluoromethanesulfonate (21f)

Starting with 19 (20 mg, 0.056 mmol), 4g (9 mg, 0.056 mmol), Pd(PPh₃)₄ (4 mg, 3 mole %), K₃PO₄ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21f was isolated as a white solid (15 mg, 69%); mp 113-114 °C. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) = 1.41 (t, \(J = 7.0\) Hz, 3H, CH₃), 4.06 (q, \(J = 7.1\) Hz, 2H, OCH₂), 6.97 (d, \(J = 8.7\) Hz, 2H, ArH), 7.28 (d, \(J = 8.9\) Hz, 2H, ArH), 7.38-7.42 (m, 2H, ArH), 7.57 (d, \(J = 7.9\) Hz, 1H, ArH), 8.21 (dd, \(J = 8.7, 1.70\) Hz, 1H, ArH), 8.98 (dd, \(J = 4.2, 1.5\) Hz, 1H, ArH). \(^{19}\)F NMR (282.4 MHz): \(\delta\) = -73.6. \(^{13}\)C NMR (62.9 MHz, CDCl₃): \(\delta\) = 14.8 (CH₃), 63.6 (OCH₂), 114.7 (CH), 119.2 (q, \(J_{C,F} = 320.9\) Hz, CF₃), 120.4, 122.3, 126.2 (CH), 128.3, 130.1 (C), 131.0, 134.6 (CH), 137.2, 141.0, 144.3 (C), 151.2 (CH), 159.1 (C). IR (KBr, cm\(^{-1}\)): \(v\) = 3042, 2994, 2917, 2849 (w), 1606 (s), 1591, 1572 (w), 1514 (s), 1493, 1475, 1461 (m), 1443 (w), 1420 (s), 1405, 1395, 1381 (m), 1354, 1342 (w), 1303 (m), 1290, 1255, 1227, 1206, 1179, 1130, 1117, 1083, 1044 (s). GC-MS (EI, 70 eV): m/z (%) = 397 ([M]+, 28), 265 (19), 264 (100), 236 (14), 209 (10), 152 (11). HRMS (EI, 70 eV) calcld for C₁₈H₁₄F₃NO₄S [M]+: 397.05901; found: 397.5842.
5-(4-Fluorophenyl)-quinolin-8-yl trifluoromethanesulfonate (21g)

Starting with 19 (20 mg, 0.056 mmol), 4o (8 mg, 0.056 mmol), Pd(PPh3)4 (2 mg, 3 mole%), K3PO4 (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21g was isolated as a white solid (13 mg, 63 %); mp 134-136 °C. 1H NMR (300 MHz, CDCl3): δ = 7.15 (d, J = 8.7 Hz, 2H, ArH), 7.32-7.38 (m, 2H, ArH), 7.41-7.46 (m, 2H, ArH), 7.59 (d, J = 7.9 Hz, 1H, ArH), 8.14 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 9.00 (dd, J = 4.2, 1.5 Hz, 1H, ArH). 19F NMR (282.4 MHz): δ = -113.4, -73.8. 13C NMR (62.9 MHz, CDCl3): δ = 115.8 (d, JCF = 21.5 Hz, CH), 118.6 (q, JCF = 321.2 Hz, CF3), 120.4, 122.7, 126.5 (CH), 128.0, 128.2, 130.7 (C), 131.6 (d, JCF = 8.7 Hz, CH), 133.9 (C), 134.2 (CH), 145.4 (C), 151.4 (CH), 163.4 (d, JCF = 245.7 Hz, CH). IR (KBr, cm⁻¹): ν = 2955, 2918, 2849, 1738 (w), 1605 (m), 1573 (w), 1511 (s), 1495 (w), 1468 (m), 1420, 1403 (s), 1381, 1356, 1335, 1309, 1274 (w), 1243, 1225, 1210 (s), 1172, 1165 (m), 1134 (s), 1085 (m). GC-MS (EI, 70 eV): m/z (%) = 371 ([M]+, 28), 239 (12), 211 (15), 210 (100), 128 (75). HRMS (EI, 70 eV) calcd for C16H9O3NF4S [M]+: 371.02338; found: 371.02351.

5-(2-Methoxyphenyl)-quinolin-8-yl trifluoromethanesulfonate (21h)

Starting with 19 (20 mg, 0.056 mmol), 4p (9 mg, 0.056 mmol), Pd(PPh3)4 (2 mg, 3 mole%), K3PO4 (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL), 21h was isolated as a white solid (17 mg, 79 %); mp 85-87 °C. 1H NMR (300 MHz, CDCl3): δ = 3.36 (s, 3H, OCH3), 6.98-7.06 (m, 2H, ArH), 7.17-7.21 (m, 1H, ArH), 7.34-7.44 (m, 3H, ArH), 7.58 (d, J = 7.9 Hz, 1H, ArH), 7.87 (dd, J = 8.6, 1.6 Hz, 1H, ArH), 8.96 (dd, J = 4.1, 1.4 Hz, 1H, ArH). 19F NMR (282.4 MHz): δ = -72.8. 13C NMR (62.9 MHz, CDCl3): δ = 55.4 (OCH3), 111.0 (CH), 119.3 (q, JCF = 318.9 Hz, CF3), 120.4, 120.9, 122.6, 126.5 (CH), 128.0, 128.2, 129.1 (C), 131.5, 131.6 (CH), 133.9 (C), 135.1 (CH), 145.4 (C), 151.2 (CH), 156.9 (C). IR (KBr, cm⁻¹): ν = 3062, 2958, 2918, 2849, 1931, 1901, 1737, 1618 (w), 1600 (m), 1579 (w), 1502, 1493, 1471, 1435 (m), 1416, 1402 (s), 1388, 1362, 1312 (w), 1290, 1263 (m), 1236, 1208, 1201 (s), 1173, 1164 (m), 1140, 1121 (s). GC-MS (EI, 70 eV): m/z (%) = 383 ([M]+, 53), 251 (18), 250 (100), 222 (20), 220 (10), 206 (15), 204 (12), 194 (26), 193 (10), 191 (11), 178 (12), 151 (10). HRMS (ESI-TOF/MS): calcd for C17H13F3NO4S [M+H]+: 384.05119; found: 384.05153.
5-(p-Methylphenyl)-8-(p-methoxyphenyl)quinoline (22)

Starting with 19 (20 mg, 0.056 mmol), 4f (8 mg, 0.056 mmol), Pd(PPh₃)₄ (2 mg, 3 mol-%), K₃PO₄ (1.0 equiv.) (12 mg, 0.056 mmol), and toluene (3 mL) and 4e (17 mg, 0.112 mmol), Pd(PPh₃)₄ (4 mg, 6 mole %), K₃PO₄ (1.0 equiv.) (12 mg, 0.056 mmol) and 1,4-dioxane (3 mL), 22 was isolated as a white solid (14 mg, 76%), mp: 118-119 °C.¹H NMR (300 MHz, CDCl₃): δ = 2.37 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 6.99 (d, J = 8.5 Hz, 2H, ArH), 7.23-7.29 (m, 3H, ArH), 7.36 (d, J = 8.8 Hz, 2H, ArH), 7.46 (d, J = 7.3 Hz, 1H, ArH), 7.56 (d, J = 7.9 Hz, 2H, ArH), 7.68 (d, J = 7.3 Hz, 1H, ArH), 8.23 (dd, J = 8.5, 1.9 Hz, 1H, ArH), 8.87 (dd, J = 4.1, 1.9 Hz, 1H, ArH). ¹³C NMR (62.9 MHz, CDCl₃): δ = 20.3 (CH₃), 54.4 (OCH₃), 112.9, 119.7 (CH), 124.6 (C), 125.9 (CH), 126.2 (C), 127.8, 128.5, 129.5, 130.2 (CH), 130.5, 130.9 (C), 133.5 (CH), 135.9, 139.5, 139.9 (C), 148.8 (CH), 158.2 (C). IR (KBr, cm⁻¹): v = 3034, 2973 (w), 2878 (m), 1986, 1964 (s), 1875, 1844, 1776 (m), 1722, 1702 (w), 1656, 1634, 1612 (m), 1587, 1564, 1532 (w), 1455, 1412 (m), 1376, 1347 (s), 1289, 1244 (m), 1167, 1133 (w), 1057, 988 (m). GC-MS (EI, 70 eV): m/z (%) = 325 ([M]+, 66), 324 (100), 310 (20), 281 (11), 266 (10), 218 (11), 140 (10), 133 (24). HRMS (ESI-TOF/MS): calcd. for C₂₃H₁₉NO [M+H]+: 326.15394; found: 326.15404.

5,7-Bis(trifluoromethanesulfonyloxy)isoflavone (24)

To a CH₂Cl₂ solution (30 mL) of 23 (1.0 g, 3.9 mmol) was added pyridine (1.3 mL, 15.7 mmol) and the solution was stirred at 20 °C for 10 min under argon atmosphere. Then Tf₂O (1.6 mL, 9.4 mmol) was added at 50 °C and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The product 24 was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a colourless solid (1.8 g, 89%); mp 75-77 °C.¹H NMR (300 MHz, CDCl₃): δ = 7.09 (s, 1H, ArH), 7.35-7.39 (m, 3H, ArH), 7.42-7.47 (m, 3H, ArH), 7.92 (s, 1H, ArH).¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.10, -72.19. ¹³C NMR (75.5 MHz, CDCl₃): δ = 111.3, 112.3 (CH), 117.3 (C), 117.6 (q, J_{CF} = 321.9 Hz, CF₃), 117.7 (q, J_{CF} = 321.9 Hz, CF₃), 126.4 (C), 127.7 (CH), 128.0 (2CH), 128.9, 147.3, 149.7 (C), 151.3 (CH), 156.3 (C), 172.0 (CO). IR (KBr, cm⁻¹): v = 3095, 2961, 2918, 2849 (w), 1645, 1619 (s), 1578, 1569, 1497, 1469 (w), 1424 (s), 1377, 1364, 1316 (w), 1243 (m), 1203, 1173, 1137, 1099 (s). GC-MS (EI, 70 eV): m/z (%) = 518 ([M+H]+, 100), 384 (12), 293 (36), 224 (34). HRMS (EI, 70 eV) calcd. for C₁₇H₉₀₈S₆F₂ [M+H]+: 518.96375; found: 518.96486.
General procedure for the synthesis of 25a-c
A solution of 24 (0.039 mmol), K$_2$CO$_3$ (2 M, 1.5 mL), Pd(PPh$_3$)$_4$ (6 mmol%) and arylboronic acid (2.0 equiv.) in 1,4-dioxane (3 mL) was stirred at 110 °C for 10 h. under argon atmosphere. To the reaction mixture H$_2$O (20 mL) and CH$_2$Cl$_2$ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

5,7-Bis(3,5-dimethylphenyl)-3-phenyl-4H-chromen-4-one (25a)

Starting with 24 (20 mg, 0.039 mmol), 4a (12 mg, 0.078 mmol), Pd(PPh$_3$)$_4$ (2.7 mg, 6 mole%), K$_2$CO$_3$ (1.5 mL), and 1,4-dioxane (3 mL), 25a was isolated as a white solid (14 mg, 87%); mp 111-113 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.27 (s, 6H, 2CH$_3$), 2.32 (s, 6H, 2CH$_3$), 6.89 (s, 2H, ArH), 6.92 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.21-7.31 (m, 5H, ArH), 7.34 (d, $J$ = 1.7 Hz, 1H, ArH), 7.39 (d, $J$ = 1.9 Hz, 1H, ArH), 7.90 (s, 1H, ArH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 21.4 (2CH$_3$), 21.5 (2CH$_3$), 115.2 (CH), 118.4 (C), 125.2, 126.3, 127.6, 127.9, 128.3, 128.8, 129.2, 130.3 (CH), 136.2, 138.7, 141.9, 144.4, 145.3, 150.85 (C), 151.8 (CH), 152.9, 154.4, 157.2 (C), 172.2 (CO). IR (KBr, cm$^{-1}$): $\nu$ = 3092, 3053, 3026 (w), 2919, 2850 (m), 2725, 1710 (w), 1637 (s), 1619 (m), 1608, 1599 (s), 1553 (m), 1487, 1455, 1445 (w), 1375 (m), 1329, 1312, 1293 (w), 1259, 1217 (m), 1118, 1083 (w). GC-MS (EI, 70 eV): m/z (%) = 429 ([M-H]$^+$, 100), 412 (12). HRMS (EI, 70 eV) calcd. for C$_{31}$H$_{25}$O$_2$ [M-H]$^+$: 429.18491; found: 429.18478.

5,7-Bis(4-ethylphenyl)-3-phenyl-4H-chromen-4-one (25b)

Starting with 24 (20 mg, 0.039 mmol), 4d (12 mg, 0.078 mmol), Pd(PPh$_3$)$_4$ (2.7 mg, 6 mole%), K$_2$CO$_3$ (1.5 mL), and 1,4-dioxane (3 mL), 25b was isolated as a white solid (13.5 mg, 81%); mp 101-103 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.19-1.24 (m, 6H, 2CH$_3$), 2.60-2.68 (m, 4H, 2CH$_2$), 7.14-7.18 (m, 2H, ArH), 7.20-7.29 (m, 7H, ArH), 7.38 (d, $J$ = 1.9 Hz, 1H, ArH), 7.41-7.44 (m, 2H, ArH), 7.55 (d, $J$ = 8.2 Hz, 2H, ArH), 7.60 (d, $J$ = 1.9 Hz, 1H, ArH), 7.88 (s, 1H, ArH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 15.2 (CH$_3$), 15.5 (CH$_3$), 28.6 (CH$_2$), 29.7 (CH$_2$), 115.0 (CH), 116.0 (CH), 125.2, 126.3, 127.6, 127.9, 128.3, 128.8, 129.2, 130.3 (CH), 136.2, 138.7, 141.9, 144.4, 145.3, 150.85 (C), 151.8 (CH), 152.9, 154.4, 157.2 (C), 172.2 (CO).
Experimental Section

120.5, 126.4 (C), 127.1, 127.3, 127.6, 127.9, 128.3, 128.6, 128.7, 129.3 (CH), 132.0, 136.0, 139.1, 142.8, 144.3, 145.1, 145.2 (C), 151.8 (CH), 157.9 (C), 175.9 (CO). IR (KBr, cm⁻¹): ν = 3052, 3024 (w), 2961, 2923, 2869, 2850 (m), 1902, 1789, 1713 (w), 1647, 1605 (s), 1548, 1514, 1493, 1445 (m), 1423 (w), 1384, 1372, 1360 (s), 1304 (m), 1244 (s), 1187 (m), 1157 (w).

Starting with 24 (20 mg, 0.039 mmol), 4f (11 mg, 0.078 mmol), Pd(PPh₃)₄ (2.7 mg, 6 mole%), K₂CO₃ (1.5 mL), and 1,4-dioxane (3 mL), 25c was isolated as a white solid (12 mg, 76%); mp 107-110 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.19 (m, 6H, 2CH₃), 7.11-7.14 (m, 2H, ArH), 7.18-7.21 (m, 3H, ArH), 7.24-7.29 (m, 4H, ArH), 7.37 (d, J = 1.9 Hz, 1H, ArH), 7.41-7.44 (m, 2H, ArH), 7.52 (d, J = 8.1 Hz, 2H, ArH), 7.60 (d, J = 1.9 Hz, 1H, ArH), 7.89 (s, 1H, ArH). ¹³C NMR (75.5 MHz, CDCl₃): δ = 29.7 (2CH₃), 115.0 (CH), 115.7 (C), 116.9 (CH), 126.8 (C), 127.2 (CH), 127.5, 128.0 (C), 128.2 (2CH), 128.3, 128.4, 129.3, 129.9 (CH) 130.1, 130.3, 131.5, 134.8, 141.2, 145.2 (C), 153.1 (CH), 173.0 (CO). IR (KBr, cm⁻¹): ν = 3047, 3025, 2953 (w), 2918 (s), 2850 (m), 1902, 1799, 1736 (w), 1657 (s), 1621 (m), 1606 (s), 1577, 1549, 1516, 1494, 1461, 1446, 1431, 1418, 1400 (w), 1375, 1371 (m), 1314, 1306, 1295 (w) 1247, 1239 (w), 1212, 1195, 1185, 1160, 1109, 1096 (w), 1073 (m), 1045, 1038 (w), 1017 (m). GC-MS (EI, 70 eV): m/z (%) = 401 ([M-H]⁺, 100), 402 (48), 403 (10). HRMS (EI, 70 eV) calcd. for C₂₉H₂₁O₂ [M-H]⁺: 401.15361; found: 401.15322.

5,7-Bis(p-tolyl)-3-phenyl-4H-chromen-4-one (25c)

General procedure for the synthesis of 26a-d

A solution of 24 (0.039 mmol), K₃PO₄ (0.039 mmol), Pd(PPh₃)₄ (3 mmol%) and arylboronic acid (1.0 equiv.) in THF (3 mL) was stirred at 55 °C for 10 h. under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

Starting with 24 (20 mg, 0.039 mmol), 4f (11 mg, 0.078 mmol), Pd(PPh₃)₄ (2.7 mg, 6 mole%), K₂CO₃ (1.5 mL), and 1,4-dioxane (3 mL), 25c was isolated as a white solid (12 mg, 76%); mp 107-110 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.19 (m, 6H, 2CH₃), 7.11-7.14 (m, 2H, ArH), 7.18-7.21 (m, 3H, ArH), 7.24-7.29 (m, 4H, ArH), 7.37 (d, J = 1.9 Hz, 1H, ArH), 7.41-7.44 (m, 2H, ArH), 7.52 (d, J = 8.1 Hz, 2H, ArH), 7.60 (d, J = 1.9 Hz, 1H, ArH), 7.89 (s, 1H, ArH). ¹³C NMR (75.5 MHz, CDCl₃): δ = 29.7 (2CH₃), 115.0 (CH), 115.7 (C), 116.9 (CH), 126.8 (C), 127.2 (CH), 127.5, 128.0 (C), 128.2 (2CH), 128.3, 128.4, 129.3, 129.9 (CH) 130.1, 130.3, 131.5, 134.8, 141.2, 145.2 (C), 153.1 (CH), 173.0 (CO). IR (KBr, cm⁻¹): ν = 3047, 3025, 2953 (w), 2918 (s), 2850 (m), 1902, 1799, 1736 (w), 1657 (s), 1621 (m), 1606 (s), 1577, 1549, 1516, 1494, 1461, 1446, 1431, 1418, 1400 (w), 1375, 1371 (m), 1314, 1306, 1295 (w) 1247, 1239 (w), 1212, 1195, 1185, 1160, 1109, 1096 (w), 1073 (m), 1045, 1038 (w), 1017 (m). GC-MS (EI, 70 eV): m/z (%) = 401 ([M-H]⁺, 100), 402 (48), 403 (10). HRMS (EI, 70 eV) calcd. for C₂₉H₂₁O₂ [M-H]⁺: 401.15361; found: 401.15322.

General procedure for the synthesis of 26a-d

A solution of 24 (0.039 mmol), K₃PO₄ (0.039 mmol), Pd(PPh₃)₄ (3 mmol%) and arylboronic acid (1.0 equiv.) in THF (3 mL) was stirred at 55 °C for 10 h. under argon atmosphere. To the reaction mixture H₂O (20 mL) and CH₂Cl₂ (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel, heptane/EtOAc).
7-(3,5-Methylphenyl)-4-oxo-3-phenyl-4H-chromen-5-yl trifluoromethanesulfonate (26a)

Starting with 24 (20 mg, 0.039 mmol), 4a (6 mg, 0.039 mmol), Pd(PPh₃)₄ (1.4 mg, 3 mole%), K₃PO₄ (8.2 mg, 0.039 mmol), and THF (3 mL), 26a was isolated as a white solid (13 mg, 73%); mp 96-100 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.36 (s, 6H, 2CH₃), 7.07 (s, 1H, ArH), 7.15 (s, 2H, ArH), 7.32-7.40 (m, 4H, ArH), 7.47-7.51 (m, 2H, ArH), 7.64 (d, J = 1.7 Hz, 1H, ArH), 7.91 (s, 1H, ArH). ¹³F NMR (282.4 MHz, CDCl₃): δ = -73.10. ¹³C NMR (75.5 MHz, CDCl₃): δ = 21.4 (2CH₃), 116.6 (CH), 117.9 (C), 118.3 (q, J_C,F = 320.8 Hz, CF₃), 125.1 (CH), 126.4 (C), 126.6, 126.7 (CH), 129.2 (2CH), 130.8 (C), 131.4 (CH), 137.2, 139.2, 147.2, 147.5 (C), 152.2 (CH), 157.4 (C), 174.0 (CO). IR (KBr, cm⁻¹): v = 3058, 3028, 2955 (w), 2922 (m), 2852, 2733 (w), 1727 (m), 1650, 1623 (s), 1600 (m), 1545, 1487, 1444 (w), 1429 (s), 1411 (w), 1400, 1375, 1365 (m), 1316, 1287, 1269 (w), 1247, 1225 (m), 1204, 1190 (s), 1159 (m), 1141 (s), 1074, 1051 (w). GC-MS (EI, 70 eV): m/z (%) = 474 ([M]+, 100), 342 (51), 326 (21), 313 (22). HRMS (EI, 70 eV) calcd. for C₂₄H₁₈O₅F₃S [M+H]+: 475.08216; found: 475.08218.

7-(4-Ethylphenyl)-4-oxo-3-phenyl-4H-chromen-5-yl trifluoromethanesulfonate (26b)

Starting with 24 (20 mg, 0.039 mmol), 4d (6 mg, 0.039 mmol), Pd(PPh₃)₄ (1.4 mg, 3 mole%), K₃PO₄ (8.2 mg, 0.039 mmol), and THF (3 mL), 26b was isolated as a white solid (15 mg, 79%); mp 99-101 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.23 (t, J = 7.6 Hz, 3H, CH₃), 2.67 (q, J = 7.6 Hz, 2H, CH₂), 7.30 (d, J = 8.2 Hz, 2H, ArH), 7.33-7.38 (m, 4H, ArH), 7.47-7.50 (m, 4H, ArH), 7.65 (d, J = 1.7 Hz, 1H, ArH), 7.91 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.27. ¹³C NMR (75.5 MHz, CDCl₃): δ = 15.4 (CH₃), 29.7 (CH₂), 115.2 (C), 116.3, 117.7 (CH), 118.1 (q, J_C,F = 321.3 Hz, CF₃), 125.8 (C), 127.2 (CH), 128.6 (2CH), 129.0, 129.1 (CH), 129.8, 133.5, 145.3, 145.8, 146.5, (C), 152.2 (CH), 156.5 (C), 172.3 (CO). IR (KBr, cm⁻¹): v = 3056, 3026 (w), 2959, 2922, 2851, 2817 (m), 1911, 1816, 1728, 1691 (w), 1646, 1626 (s), 1543, 1521, 1494, 1461, 1446 (w), 1426 (s), 1401, 1376, 1367 (m), 1313, 1281 (w), 1256 (m), 1243, 1208 (s). GC-MS (EI, 70 eV): m/z (%) = 474 ([M]+, 100), 342 (51), 326 (21), 313 (22). HRMS (EI, 70 eV) calcd. for C₂₄H₁₇O₅F₃S [M]+: 474.07433; found: 474.07343.
7-(4-Methoxyphenyl)-4-oxo-3-phenyl-4H-chromen-5-yl trifluoromethanesulfonate (26c)

Starting with 24 (20 mg, 0.039 mmol), 4e (6 mg, 0.039 mmol), Pd(PPh₃)₄ (1.4 mg, 3 mole%), K₃PO₄ (8.2 mg, 0.039 mmol), and THF (3 mL), 26c was isolated as a white solid (15 mg, 80%); mp 85-87 °C. ¹H NMR (300 MHz, CDCl₃): δ = 3.82 (s, 3H, OCH₃), 6.98 (d, J = 8.6 Hz, 2H, ArH), 7.33-7.37 (m, 4H, ArH), 7.48-7.53 (m, 4H, ArH), 7.61 (d, J = 1.7 Hz, 1H, ArH), 7.90 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.28. ¹³C NMR (75.5 MHz, CDCl₃): δ = 55.5 (OCH₃), 113.9, 114.7 (CH), 115.3 (C), 116.3 (CH), 117.9 (q, J_C,F = 321.3 Hz, CF₃), 125.7 (C), 127.1, 128.5, 128.6 (CH), 129.8 (C), 131.0 (CH), 131.2, 145.4, 146.6 (C), 151.2 (CH), 156.5, 160.0 (C), 172.9 (CO). IR (KBr, cm⁻¹): ν = 3072, 3057, 3020 (w), 2955, 2917, 2849 (m), 1728 (m), 1650, 1627, 1601 (s), 1580, 1545 (w), 1519 (m), 1493, 1462 (w), 1427 (s), 1403, 1373, 1364, 1292 (w), 1257, 1243, 1202, 1179, 1141, 1117 (s), 1071, 1043 (m). GC-MS (EI, 70 eV): m/z (%) = 476 ([M]+, 100), 475 (18), 344 (44), 328 (20), 315 (18). HRMS (EI, 70 eV) calcd. for C₂₃H₁₆O₆F₃S [M]+: 476.07433; found: 476.07343.

7-(4-Methylphenyl)-4-oxo-3-phenyl-4H-chromen-5-yl trifluoromethanesulfonate (26d)

Starting with 24 (20 mg, 0.039 mmol), 4f (5 mg, 0.039 mmol), Pd(PPh₃)₄ (1.4 mg, 3 mole%), K₃PO₄ (8.2 mg, 0.039 mmol), and THF (3 mL), 26d was isolated as a white solid (15 mg, 82%); mp 101-102 °C. ¹H NMR (300 MHz, CDCl₃): δ = 2.37 (s, 3H, CH₃), 7.26 (d, J = 7.9 Hz, 2H, ArH), 7.33-7.38 (m, 4H, ArH), 7.44-7.47 (m, 4H, ArH), 7.64 (d, J = 1.7 Hz, 1H, ArH), 7.90 (s, 1H, ArH). ¹⁹F NMR (282.4 MHz, CDCl₃): δ = -73.23. ¹³C NMR (75.5 MHz, CDCl₃): δ = 21.2 (CH₃), 116.2 (CH), 116.6 (C), 117.7 (CH), 118.4 (q, J_C,F = 320.8 Hz, CF₃), 126.8 (C), 127.1 (CH), 128.6 (2CH), 129.1, 130.2 (CH), 130.8, 134.3, 140.1, 146.8, 147.6 (C), 152.2 (CH), 157.5 (C), 174.0 (CO). IR (KBr, cm⁻¹): ν = 3074, 2955, 2923, 2815, 1732 (w), 1640 (m), 1624 (s), 1575, 1568, 1557, 1542, 1506, 1496, 1472, 1455, 1447 (w), 1424 (s), 1398, 1380, 1372 (m), 1320, 1286, 1274 (w), 1256, 1244 (m), 1200, 1138 (s). GC-MS (EI, 70 eV): m/z (%) = 460 ([M]+, 100), 459 (54), 395 (13), 327 (16), 228 (12). HRMS (ESI/TOF) calcd. for C₂₃H₁₆O₅F₃S [M+H]+: 461.06651; found: 461.06672.
X-Ray Crystal Data

Crystal data and structure refinement for 5e

Identification code  N1-Mono-4OMe

Empirical formula  C_{20}H_{15}F_{3}O_{6}S

Formula weight  440.38

Temperature  173 (2) K

Wavelength  0.71073 Å

Crystal system  monoclinic

Space group (H.-M.)  P 21/n

Space group (Hall)  -P 2yn

Unit cell dimensions  
\[ a = 8.1302(19) \text{ Å} \]  \( a = 90.00 \) 
\[ b = 5.3259(13) \text{ Å} \]  \( \beta = 94.470(15) \) 
\[ c = 42.899(10) \text{ Å} \]  \( \gamma = 90.00 \)

Volume  1851.9(8) Å³

Z  4

Density (calculated)  1.580 Mg m⁻³

Absorption coefficient  0.222 mm⁻¹

F(000)  904

Crystal size  0.34 × 0.10 × 0.02 mm

\( \Theta \) range for data collection  \( \theta = 1.90-24.30^\circ \)

Index ranges  -9≤h≤9, -6≤k≤6, -48≤l≤49

Reflections collected  15118

Independent reflections  2952 [R(int) = 0.0672]
Completeness to $\Theta = 24.30^\circ$ 97.8%

Absorption correction  Semi-empirical from equivalents

Max. and min. transmission 0.9222 and 0.9952

Refinement method Full-matrix least-squares on F2

Data/ restraints / parameters 2952/0/ 273

Goodness-of-fit on F2 1.016

Final R indices [I>2$\sigma$(I)] $R_1 = 0.0450$, $wR_2 = 0.0913$

R indices (all data) $R_1 = 0.0888$, $wR_2 = 0.1075$

Largest diff. peak and hole 0.243 and -0.406 e Å$^{-3}$

Crystal data and structure refinement for 11d

Identification code  N2-Mono-4OMe

Empirical formula  C$_{19}$ H$_{15}$ Br O$_3$

Formula weight  371.22

Temperature 173 (2) K

Wavelength 0.71073 Å

Crystal system monoclinic

Space group (H.-M.) C 2/c

Space group (Hall) -C 2yc

Unit cell dimensions

\[a = 19.8135(6) \text{ Å} \quad \alpha = 90.00\]
\[b = 8.6733(2) \text{ Å} \quad \beta = 112.5630(10)\]
\[c = 20.2861(5) \text{ Å} \quad \gamma = 90.00\]

Volume 3219.30 (15) Å
$Z$ 8

Density (calculated) 1.532 Mg m$^{-3}$

Absorption coefficient 2.566 mm$^{-1}$

$F(000)$ 1504

Crystal size 0.38 $\times$ 0.22 $\times$ 0.15 mm

$\Theta$ range for data collection 2.98-32.50

Index ranges $-29 \leq h \leq 29, -12 \leq k \leq 13, -29 \leq l \leq 30$

Reflections collected 22818

Independent reflections 5824[$R$(int) = 0.0256]

Completeness to $\Theta = 32.50^\circ$ 99.8%

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.4422 and 0.6995

Refinement method Full-matrix least-squares on F2

Data/ restraints / parameters 5824/0/210

Goodness-of-fit on F2 1.011

Final R indices [$I>2\sigma(I)$] $R1 = 0.0313$, $wR2 = 0.0714$

R indices (all data) $R1 = 0.0495$, $wR2 = 0.0775$

Largest diff. peak and hole 0.47 and $-0.23$ e Å$^{-3}$
Crystal data and structure refinement for 16a

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>K-Mono-3,5.Me</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C₁₈H₁₃F₅O₅S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>398.34</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 (2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group (H.-M.)</td>
<td>P 21/c</td>
</tr>
<tr>
<td>Space group (Hall)</td>
<td>-P 2ybc</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>(a) = 15.7620(7) Å</td>
<td>(a = 90.00)</td>
</tr>
<tr>
<td>(b) = 7.7357(4) Å</td>
<td>(\beta = 115.035(2))</td>
</tr>
<tr>
<td>(c) = 15.5226(6) Å</td>
<td>(\gamma = 90.00)</td>
</tr>
<tr>
<td>Volume</td>
<td>1714.85(13) Å²</td>
</tr>
<tr>
<td>(Z)</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.543 Mg m⁻³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.248 mm⁻¹</td>
</tr>
<tr>
<td>(F(000))</td>
<td>816</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.85 × 0.37 × 0.02 mm</td>
</tr>
<tr>
<td>(\Theta) range for data collection</td>
<td>(\theta = 2.63-29.06)</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-20 \leq h \leq 21, -10 \leq k \leq 10, -21 \leq l \leq 91)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>20048</td>
</tr>
</tbody>
</table>
Absorption correction  Semi-empirical from equivalents

Refinement method  Full-matrix least-squares on F2

Data/ restraints / parameters  4477/15/ 268

Goodness-of-fit on F2  1.031

Final R indices [I>2σ(I)]  R1 = 0.0532, wR2 = 0.1182

R indices (all data)  R1 = 0.0983, wR2 = 0.1382

Largest diff. peak and hole  0.268 and -0.384 e Å\(^{-3}\)

Crystal data and structure refinement for 20c

Identification code  Chin-D-OMe

Empirical formula  C\(_{23}\)H\(_{19}\)N\(_2\)O\(_2\)

Formula weight  341.39

Temperature  173 (2) K

Wavelength  0.71073 Å

Crystal system  Monoclinic

Space group (H.-M.)  P 2\(_1\)/n

Space group (Hall)  -P 2yn

Unit cell dimensions  
\[ \begin{align*}
a &= 21.2098(11) \text{ Å} \\
b &= 5.9382(3) \text{ Å} \\
c &= 26.9576(12) \text{ Å}
\end{align*} \]

\[ \begin{align*}
\alpha &= 90.00 \\
\beta &= 93.634(3)° \\
\gamma &= 90.00
\end{align*} \]

Volume  3388.4(3) Å\(^3\)
Z 8
Density (calculated) 1.338 Mg m$^{-3}$
Absorption coefficient 0.085 mm$^{-1}$
F(000) 1440
Crystal size 0.99 × 0.43 × 0.05 mm
$\Theta$ range for data collection $\theta = 1.19-19.00^\circ$
Index ranges $-28 \leq h \leq 27, -8 \leq k \leq 7, -36 \leq l \leq 36$
Reflections collected 45074
Independent reflections 8958 [R(int) = 0.0424]
Completeness to $\Theta = 30.00^\circ$ 99.7%
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9204 and 0.9958
Refinement method Full-matrix least-squares on F2
Data/ restraints / parameters 8958/0/475
Goodness-of-fit on F2 1.003
Final R indices [I>2$\sigma$(I)] \(R_1 = 0.0489, \text{wR}^2 = 0.1084\)
R indices (all data) \(R_1 = 0.1110, \text{wR}^2 = 0.1410\)
Largest diff. peak and hole 0.287 and -0.242 e Å$^{-3}$
Crystal data and structure refinement for 26c

Identification code  Isoflavone-Mono-4OMe

Empirical formula  C_{23} H_{15} F_{3} O_{6} S

Formula weight  476.41

Temperature  173 (2) K

Wavelength  0.71073 Å

Crystal system  monoclinic

Space group (H.-M.)  C 2/c

Space group (Hall)  C 2yc

Unit cell dimensions
\[a = 24.0109(9) \text{ Å} \quad \alpha = 90°\]
\[b = 9.9045(4) \text{ Å} \quad \beta =113.994(2)°\]
\[c = 18.7132(8) \text{ Å} \quad \gamma = 90°\]

Volume  4065.7(3) Å³

Z  8

Density (calculated)  1.557 Mg m⁻³

Absorption coefficient  0.227 mm⁻¹

F(000)  1952

Crystal size  0.270 × 0.150 × 0.060 mm

Θ range for data collection  0 = 2.26- 22.86°

Index ranges  -33≤h≤33, -13≤k≤13, -25≤l≤25

Reflections collected  25514

Independent reflections  5704[R(int) = 0.0613]

Completeness to Θ = 31.00°  99.8%
<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9839 and 0.9125</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>5704/0/299</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.092</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ(I)]</td>
<td>R1 = 0.0460, wR2 = 0.1158</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0696, wR2 = 0.1251</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.337 and -0.479e Å⁻³</td>
</tr>
</tbody>
</table>
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOAc</td>
<td>Ethylacetate</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>Trifluoromethanesulfonic Anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofurane</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Ethyldiisopropylamine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>EI</td>
<td>Electronic Impact</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray Ionization</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>HZ</td>
<td>Hertz</td>
</tr>
</tbody>
</table>
References


References


References


Declaration

Here by I declare that this work has so far neither submitted to the Faculty of Mathematics and Natural Sciences at the University of Rostock nor to any other scientific Institution for the purpose of doctorate. Furthermore, I declare that I have written this work by myself and that I have not used any other sources, other than mentioned earlier in this work.

I hereby apply irrevocably to take oral examination in the form of a private viva voce and a public presentation.

Erklärung

Hiermit erkläre ich, daß diese Arbeit bisher von mir weder an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock noch einer anderen wissenschaftlichen Einrichtung zum Zwecke der Promotion eingereicht wurde.

Ferner erkläre ich, dass ich diese Arbeit selbständig verfasst und keine anderen als die darin angegebenen Hilfsmittel benutzt habe.
List of Publications


CURRICULUM VITAE

Personel Particular

<table>
<thead>
<tr>
<th>Name</th>
<th>Zien Suleiman Khaddour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth</td>
<td>01.09.1984</td>
</tr>
<tr>
<td>Nationality</td>
<td>Syrian</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Marital Status</td>
<td>Single</td>
</tr>
<tr>
<td>Languages</td>
<td>Arabic (Mother Tongue)</td>
</tr>
<tr>
<td>E-mail address</td>
<td><a href="mailto:Zien.khaddour@yahoo.de">Zien.khaddour@yahoo.de</a></td>
</tr>
</tbody>
</table>

Educational Background

2. B.Sc. Degree in Chemistry, from Department of Chemistry, College of Science, University of Damascus, Damascus-Syria 2006.
3. M.Sc. Degree in Organic Chemistry, Department of Chemistry, College of Science, University of Rostock, Rostock-Germany 2012
4. Since March 2012 till now promotion study program at the University of Rostock.