UNIVERSITÄT ROSTOCK

Regioselective Palladium(0)-Catalyzed Cross-Coupling Reactions of Brominated Furans, Thiophenes, Pyrroles and Selenophenes and Synthesis of N,O-Heterocycles by Cyclocondensations of Hydrazone and Oxime Dianions

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“Dedicated to my **Parent** and my uncle, **Vu Van Chung**”

With my love and appreciation !

Who of you by worrying can add a single hour to his life?

Matthew 6:27

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I thank all those who contributed to the success of this work and who supported me during my time as a Ph.D. student.

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I owe all of them in my life!

MAIN CONTENTS

DETAIL CONTENTS

SUMMARY

A significant part of this dissertation has already been published (see the detail list of publication at the end) and submitted. Each chapter contains the content of a publication or shortcommunication and full paper. Text, tables and synthetic schemes from these publications were directly used while writing thesis. The work presented in this dissertation was divided into two parts as following:

Part one: Regioselective Palladium(0)-catalyzed cross-coupling reactions of bromosubstituted furan, pyrrole, selenophene and thiophene

1. *Synthesis of 2-(2-Arylethenyl)-5-arylfurans by Regioselective Palladium(0)-Catalyzed Coupling Reactions of 2-(2-Bromo-2-nitroethenyl)-5-bromofuran.* The Suzuki reaction of 2-(2-bromo-2-nitroethenyl)-5-bromofuran, readily available from furfural, resulted in regioselective attack onto the furan moiety. The first regioselective suzuki cross-coupling reactions occurs at the bromo substituted furan to give 2-(2-bromo-2-nitroethenyl)-5-arylfuran. The alkenyl moiety could be functionalized in a second Suzuki reaction. These reactions represent a valuable synthetic method for the synthesis of pharmacologically relevant products and of useful intermediates for further synthetic transformations.

2. *Regioselective Synthesis of Functionalized Pyrroles based on the first Palladium(0)-Catalyzed Cross-Coupling Reactions of N-Methyltetrabromopyrrol.* Pyrrole is the core of many natural products having a rich pharmacological and medicinal potential, such as Ningaline A, Lamellarin, Lukianol A, and Storniamide. In this chapter I report a new methodology for the functionalization of pyrroles. Regioselective Suzuki cross-coupling reactions of 2,3,4,5-tetrabromo-1-methylpyrrole allow a convenient synthesis of functionalized pyrroles.

3. *Regioselective Sonogashira Reactions of N-Methyltetrabromo-pyrrole. First Synthesis of Tri- and Tetra(1-alkynyl)pyrroles.* Hydrocarbons bearing multiple alkynyl groups have received considerable attention due to their interesting physicochemical properties, as synthetic building blocks of new and interesting arenes, and due to their æsthetic attraction. Recently, studies related to the synthesis and characterization of hexaethynylbenzene and tetra(1-alkynyl)thiophene based on Sonogashira coupling reactions were published. In this

chapter, *N*-methyl-2,3,4,5-tetrabromopyrrole is transformed into a variety of alkylnyl-substituted pyrroles by regioseletive Sonogashira cross-coupling reactions. In addition, the synthesis of the first tri-, and tetra(1-alkylnyl)pyrrole is reported.

4. *Efficient Synthesis of Substituted Selenophenes based on the First Palladium(0)-Catalyzed Cross-Coupling Reactions of Tetrabromoselenophene.* Selenium represents an essential element for higher organisms and is of considerable pharmacological relecance. This includes antiviral activity, inhibitory activity against human myelogenous leukemia K562 cells, cytotoxicity against HT-29, HeLa, ACHN and 5637 cells, and muscarinic antagonist activity. Therefore, the synthesis of functionalized selenophenes is important for pharmacological and medicinal applications. Regioselective Suzuki cross-coupling reactions of tetrabromoselenophene allow a convenient synthesis of various aryl-substituted selenophenes. High yields were obtained using a novel biaryl monophosphine ligand. The first tetra(1-alkynyl)selenophene was prepared in one step by a Sonogashira reaction of tetrabromoselenophene.

5. *Regioselective Palladium(0)-Catalyzed Cross-Coupling Reactions and Metal-Halide Exchange Reactions of Tetrabromothiophene.* Thiophenes possess many applications in medicinal chemistry and in material sciences (light-emission, electroluminescenc, redox activity etc.). The Suzuki reaction of tetrabromothiophene with arylboronic acids provides a regioselective approach to various 5-aryl-2,3,4-tribromothiophenes, symmetrical 2,5-diaryl-3,4-dibromothiophenes, and tetraarylthiophenes. Unsymmetrical 2,5-diaryl-3,4-dibromothiophenes are prepared by Suzuki reaction of 5-aryl-2,3,4-tribromothiophenes. Tetraarylthiophenes containing two different types of aryl groups are obtained by Suzuki reactions of 2,5-diaryl-3,4-dibromothiophenes. During the optimization of the conditions of each individual reaction, the solvent, the catalyst and the temperature played an important role. In several cases, classical conditions (use of $Pd(PPh_3)_4$ as the catalyst) gave excellent yields. The yields of those transformations which failed or proceeded sluggishly could be significantly improved by application of a new biaryl monophosphine ligand developed by Buchwald and coworkers. Regioselective metal-halide-exchange reactions of tetrabromothiophene provide a convenient approach to various 2,5-substituted 3,4-dibromothiophenes. 5-Alkyl-2-trimethylsilyl-3,4-dibromothiophenes could be prepared in a one-pot protocol by sequential addition of trimethylchlorosilane and alkyl bromides. The reaction of tetrabromothiophene with methyl chloroformiate and subsequent Suzuki reactions

afforded 3,4-diaryl-2,5-bis(methoxycarbonyl)thiophenes. These products were transformed into sulphur-analogues of pyrrole natural products, such as ningaline A.

Part two: Oriented Synthesis of N,O-Heterocycles by Cyclization Reactions of Hydrazone with Diethyl Acetate and Arylkenyl-Oxime

6. *Synthesis of Pyrazole-3-carboxylates and Pyrazole-1,5-Dicarboxylates by One-Pot Cyclization of Hydrazone Dianions with Diethyl Oxalate.* Pyrazole-5-carboxylic acid derivatives represent important building blocks in organic and medicinal chemistry due to their pharmacological properties. For example, pyrazole-5-carboxylic acids and pyrazolo[1,5-*c*]quinazoline-2-carboxylates are nicotinic acid receptor agonists and excitatory amino acid antagonists, respectively. Ethyl 5-propyl-1*H*-pyrazole-3-carboxylate is a key intermediate for the synthesis of viagra. Herein I reported a new and convenient approach to synthesize pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by one-pot cyclization of hydrazone dianions with diethyl oxalate.

7. *Regioselective Synthesis of 6-Halomethyl-5,6-dihydro-4H-1,2-oxazines based on Cyclizations of Arylalkenyl-oximes.* 1,2-Oxazines are of pharmacological relevance and represent useful synthetic building blocks as intermediates during the synthesis of glycosidase inhibitor analogues and of functionalized pyrroles. They have been prepared by other methods, for example, hetero-Diels-Alder reactions of alkenes with ene-nitroso compounds derived from α-haloximes, hetero-Diels-Alder reactions of dienes with nitroso compounds and base-mediated cyclizations of γ-chloroximes and γ-sulfonyloximes. In this chapter I report that 6-iodo- and 6-bromomethyl-5,6-dihydro-4*H*-1,2-oxazines were prepared by condensation of dilithiated acetophenone-oximes with allylbromide and subsequent regioselective iodine- or NBS-mediated cyclization.

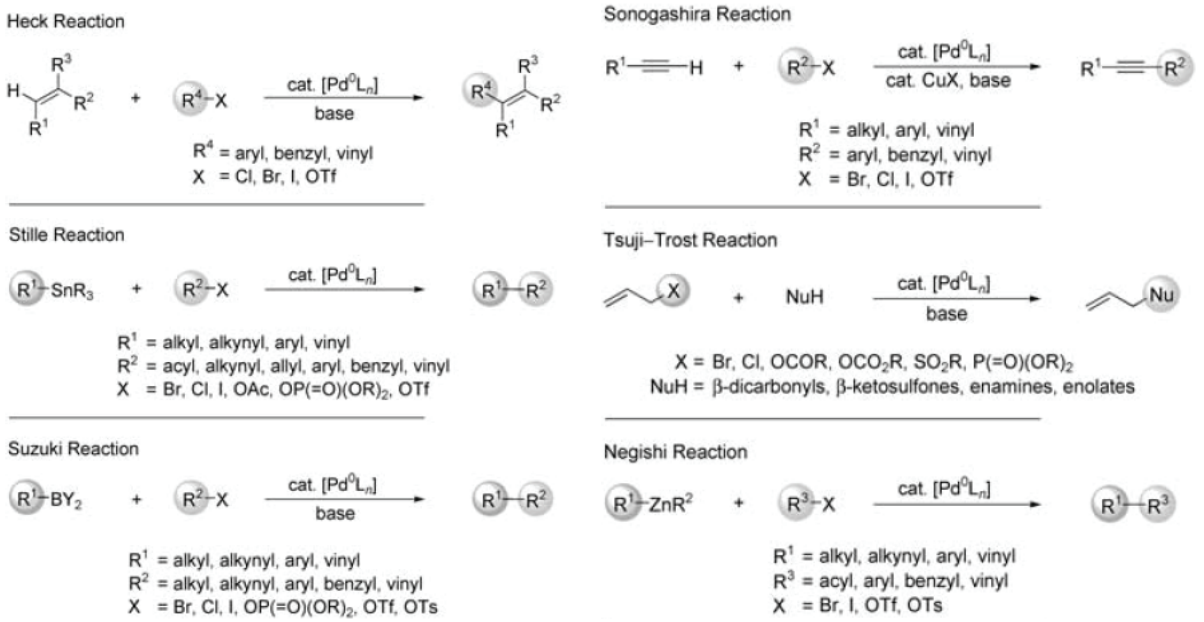
Experimental section

Experimental section. The experimental procedures and spectrocopic data and full characterization of all new products are described.

Part 1 Regioselective Palladium(0)-Catalyzed Coupling Reactions of Bromosubstituted Furans, Thiophenes, Pyrroles, Selenophenes

Introduction

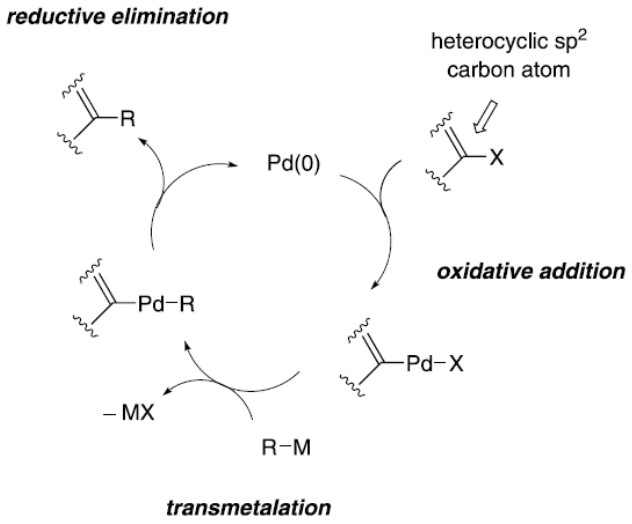
The formation of carbon-carbon and carbon-heteroatom bonds is always of interest for chemists from past until now. It provides a convenient approach to construct complicated molecules from simple precusors. Up to date there are many useful methodologies for making bonds. One of them relies on transition metal-catalyzed reactions, particularly palladium(0)-catalyzed carbon-carbon bond forming reactions.[1] The application of palladium-catalyzed cross-coupling reactions is tremendously successful in chemistry such as total synthesis, nanotechnology, synthesis of advanced materials, biological, medicinal and pharmacological chemistry. The cross-coupling bond forming reactions between sp^2 carbon atom with various hybridized carbon (sp, sp^2, sp^3) [2,3] are well-know as the Heck, Stille, Suzuki, Sonogashira, Tsuji-Trost and Negishi reactions (Scheme 1).



Scheme 1: The most commonly utilized palladium-catalyzed cross-coupling reactions. (This scheme was copied from *Angew. Chem. Ind. Ed.* **2005**, *44*, 4442)

A short look at the mechanistic picture[1] for a typical cross-coupling reactions reveals three key steps in generally catalytic cycle (Scheme 2). Different substrates and reagents lead to the

particularly useful reactions. The first step is the oxidative addition of organic halides or pseudo-halides to the Pd(0) complex to form organopalladium halides. The following step is transmetallation with nucleophilic compounds to give a diorganopalladium complex. This complex undergoes a reductive elimination to create carbon-carbon bond and regeneration of the catalyst.



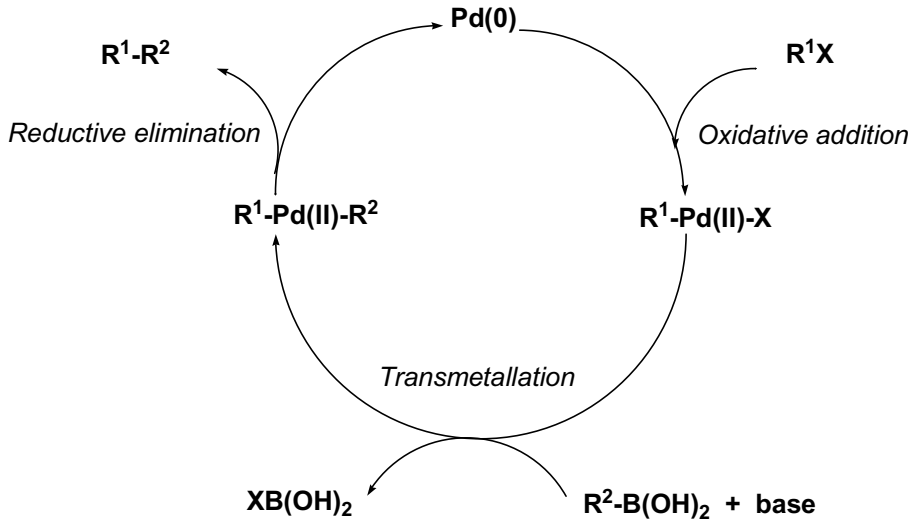
Scheme 2. General mechanism for palladium-catalyzed cross-coupling reaction (This scheme was copied from *Tetrahedron*, **2005**, *61*, 2245)

Suzuki reaction

In 1981, a very useful palladium-catalyzed carbon-carbon formation was reported by Suzuki and Miyaura which involves the palladium-mediated coupling of aryl or akenyl halides and triflates with organoboron compounds in the presence of base, a process known today as Suzuki reaction.[4] The success of the Suzuki reaction relies on its cheracteristic features. 1) commercial availability of a large number of boronic acids and esters, 2) the stability to heat, air and moisture, 3) the tolerance to a broad range of functional groups, 4) mild reaction conditions, 5) low toxicity of the reagents, 6) and easy separation of inorganic by-products from the reaction mixture.

A general catalytic cycle for the cross-coupling of organic halides or triflates with organometallic reagents is shown in (Scheme 3).[1] It involves the oxidative addition of organic halides or triflates to the Pd(0) complex to form a organopalladium halide (R^1-Pd(II)-X). This

step is followed by transmetallation with a boronic acid derivative or a borane to give a diorganopalladium complex (R^1-Pd-R^2). This complex undergoes a reductive elimination with carbon-carbon bond formation and regeneration of the catalyst.

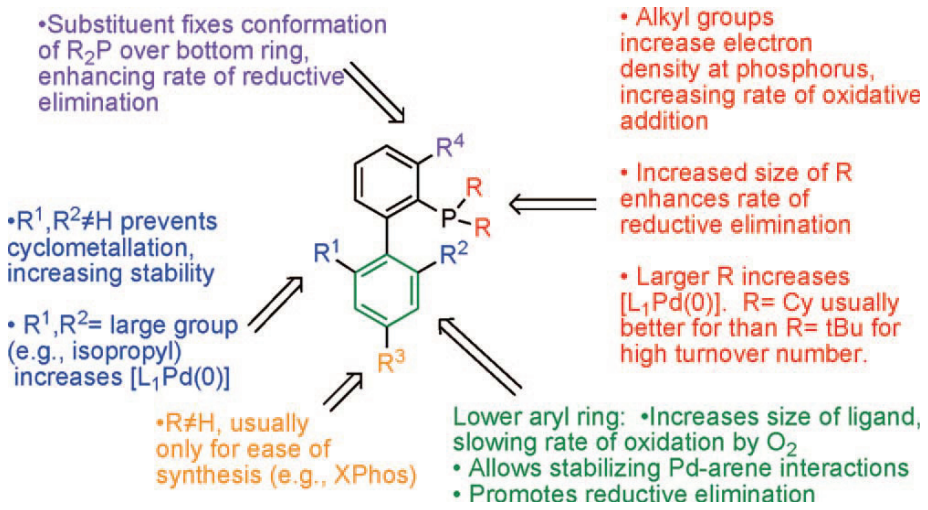


Scheme 3. Catalytic cycle in Suzuki reaction

The rate of Suzuki reaction mainly relies on the oxidative addition and transmetallation. The oxidative addition step is dependent on the reactivity of the substrate according to the order Ar-I> Ar-Br > Ar-Cl > Ar-OTf. The transmetalation is accelerated by the presence of base. This can be explained by the increase of the nucleophilicity of the organoborane compound by formation of an organoborate containing a tetravalent borom atom. The solvent plays an important role in Suzuki reaction. Often the use of DMF gives good results.

The choice of the catalysts is also very important for the success of the reaction. The common palladium sources employed include, for example, $Pd(OAc)_2$, $PdCl_2$, $Ph(PPh_3)_2Cl_2$, and $Pd(dba)_2$. The use of bulky electron-rich ligands is often the key for a successful transformation. The ferrocenylphosphine[5], N-heterocyclic carbenes[6], $P(t\text{-}Bu)_3$ [7], $P(Cy)_3$ often give a good yield. Recently the innovation of ligands has been developed strongly by Prof. Mathias Beller. He has developed some nowadays comercially available ligands, such as dibutyl-1-adamatylphosphine[8] and phosphino subsituted *N*-aryl pyrroles.[9] These ligands are applied in the palladium-catalyzed coupling of variety of aryl and heteroaryl chlorides with arylboronic acid showing high turnover numbers at mild reaction temperatures. Another famous ligand was reported by Prof. Buchwald and co-workers.[10] They have developed electron-rich, bulky biphenylphosphine ligands, such as S-Phos (2,6-dimethoxybiphenyl-dicyclohexylphosphine), X-Phos, Dave-Phos, and others. The application of these ligands

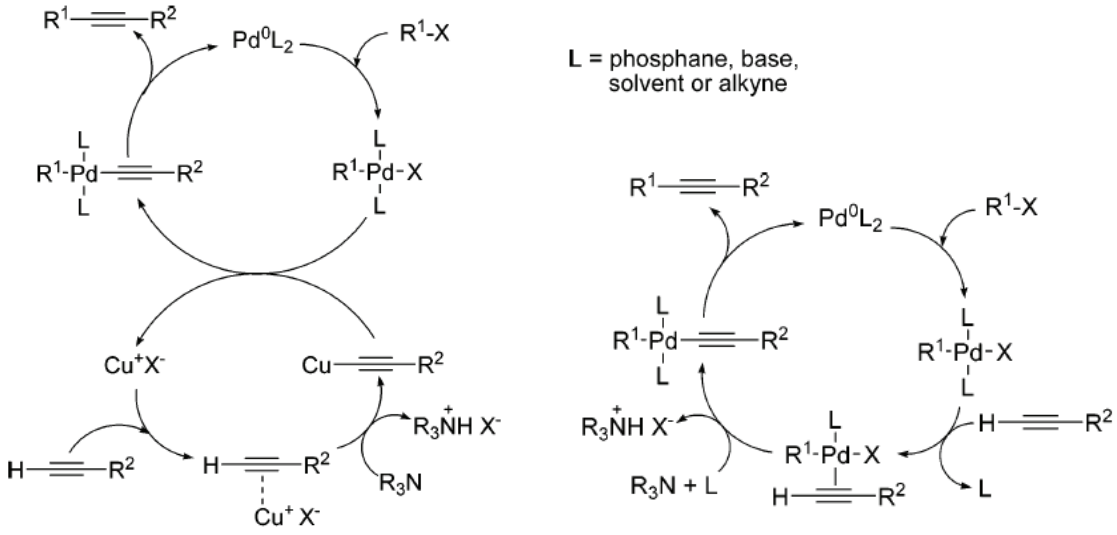
gave excellent yields for aryl chlorides and heteroaryl chlorides with arylboronic and heteroarylboronic acids. In my research, S-Phos ligand was employed for most of the Suzuki reactions.



Scheme 4. Structural features of the dialkylbiarylphosphines and their impact on the efficacy of catalysts using these ligands.[11] (This scheme was copied from *Acc. Chem. Res*. **2008**, *41* (11) 1461)

Sonogashira reaction

The palladium-catalyzed coupling of terminal akynes with vinyl or aryl halides was first reported independently and simultaneously by the groups of Cassar[12] anh Heck[13] in 1975. A few months later, Sonogashira and co-workers demonstrated that, in many cases, this cross-coupling reaction could be accelerated by the addition of cocatalytic Cu^I salts to the reaction mixture.[14,15] The protocol for Sonogashira reaction has been improved a lot. Nowadays, the Sonogashira reaction proceeds under mild conditions, sometimes even at room temperature, with high turnover number. The classical conditions of the Sonogashira coupling relies on the use of copper salts as cocatalysts. Modern variants can be carried out under copper-free conditions.



Scheme 5. Two mechanisms of the Sonogashira reaction (This scheme was copied from Chem. Rev. **2007**, *107*, 874)

The different mechanism of different variants of the Sonogashira reaction leads to different invidual protocols. The in situ generation of copper alkylides under the reaction conditions often generates homocoupling products (so-called Glaser coupling).[16] This side reaction is an important problem. The addtion of copper salts as cocatalysts have drawbacks. The mechanism of the copper-free Sonogashira reaction is not well-known. The oxidative addtion of R^1-X to the palladium(0) complex is the initial step. The second step is still under debate. Some authors supposed that the alkyne replaces one ligand to give an intermediate complex and the ligated alkyne would be more easily deprotonated by the amine to form a new complex $R_1Pd(-CCR_2)L_2$, which subsequently gives rise to the formation of the coupling product by reductive elimination. In this copper-free mechanism, the way of adding the alkyne plays an important role. Buchwald and cowoker have reported that a slow addition of the alkyne at 70-90 °C using a syringe pump in a pressure tube gives best results.[17]

The general reactivity order of the sp^2 species is vinyl iodide > vinyl triflate > vinyl bromide > aryl iodide > aryl triflate > aryl bromide >> aryl chloride; therefore the Sonogashira process usually runs smoothly when the more expensive and unstable aryl or vinyl iodides are used.[1]

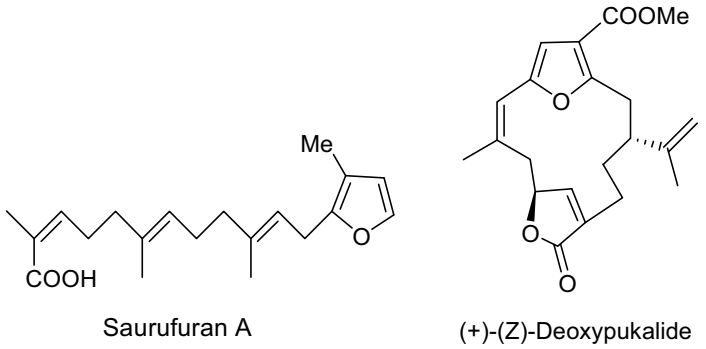
Several catalysts and ligands for Sonogashira reaction have been developed. Typical reactions are performed using a palladium(0)-phosphane complex in the presence of a cocatalytic amount of a copper (I) salt and an amine (used as a solvent or in large excess) under

homogeneous conditions. The classically used catalysts are triphenylphosphane-related complexes, such $Pd(Ph_3)_4$, $Pd(Ph_3)_2Cl_2$, $Pd(dppe)Cl_2$, Pd-$(dppp)Cl_2$ or $Pd(dppf)Cl_2$. Most frequently used loadings of palladium are in the range of 5 mol-%. Larger amounts of the copper(I) salt are often employed and the use of THF as the solvent[18] was highly recommended. For copper-free Sonogashira reactions more electron-rich phosphane ligands are used because of the easier oxidative insertion of the palladium(0) species to the aryl halides. The palladium sources[1] mainly employed are $Pd(OAc)_2$, $Pd_2(PhCN)_2$, $Pd_2(CH_3CN)_2$, $Pd_2(dba)_3$ and $Pd(\eta^3\text{-}C_3H_5)Cl_2$,[19] and ligands, such as, $P(t\text{-}Bu)_3$,[20] $P(Cy)_3$, electron-rich o-biphenylphosphane (X-Phos)[17], multidentate ferrocenyl phosphane[21b], and tetraphosphanes. The Sonogashira reaction provides a valuable method for synthesis of conjugated acetylenic systems, which are used in a diverse array of important applications from natural products and pharmaceutical to designed molecules of interest in biotechnology and nanotechnology.[1]

1.1 Synthesis of 2-(2-Arylethenyl)-5-arylfurans by Regioselective Palladium(0)-Catalyzed Coupling Reactions of 2-(2-Bromo-2-nitroethenyl)-5-bromofuran

1.1.1 Introduction

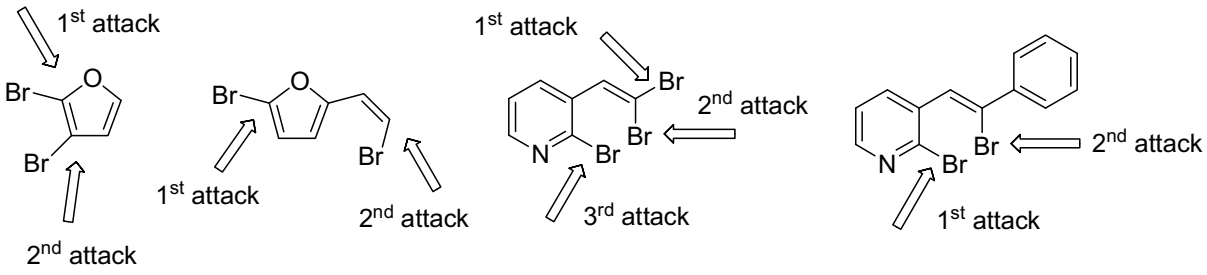
Furans are of considerable pharmacological relevance and occur in a variety of natural products.[22,23] Some natural products containing the furan ring have an intense odour, e.g. 2-furylmethanethiol, a component of coffee aroma, Rose furan, a component of rose oil, Menthofuran, which occurs in peppermint oil.[24] Recently, (+)-(Z)-Deoxypukalide[25] was isolated from the Pacific Octocoral *Leptogorgia sp.* and Saurufuran A, B[26] isolated from the *Saururus chinenesis* (Scheme 6).



Scheme 6. Some natural products containing furan moieties.

A number of synthetic approaches to furans have been reported.[27] Bach and coworkers reported an interesting approach to 2,3-disubstituted furans by regioselective palladium(0)-catalyzed coupling reactions of 2,3-dibromofurans.[28] The success of these transformations relies on the fact that the oxidative addition of the palladium(0) complex onto carbon atom C-2 of the furan is faster than onto C-3 (Scheme 7).[29] Herein, I wish to report what are, to the best of my knowledge, the first regioselective palladium(0)-catalyzed coupling reactions of 2-(2-bromoalkenyl)-5-bromofurans which contain both a furyl and an alkenyl bromide function (Scheme 7). A similar idea of 2-(2-bromophenyl)-2-bromopyridine[5] was published later than. The oxidative addition of the palladium(0) complex to the C-Br bond attached to carbon C-2 of pyridine is faster than to the C-alkenyl moiety. However, if there are two bromine atoms located at the alkenyl group, the oxidative addition of the palladium(0) complex was reversed (Scheme 7). These reactions should be of considerable interest, since the starting materials are readily available and the products are pharmacologically relevant and represent useful

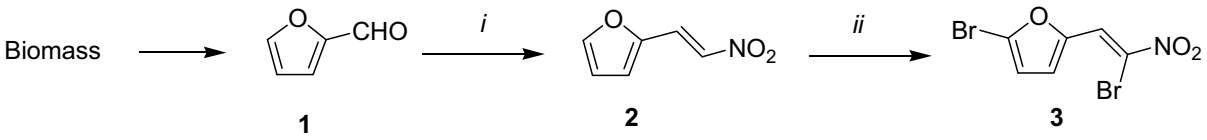
intermediates for further synthetic transformations (e. g. electrocyclic ring-closure reactions).[30]



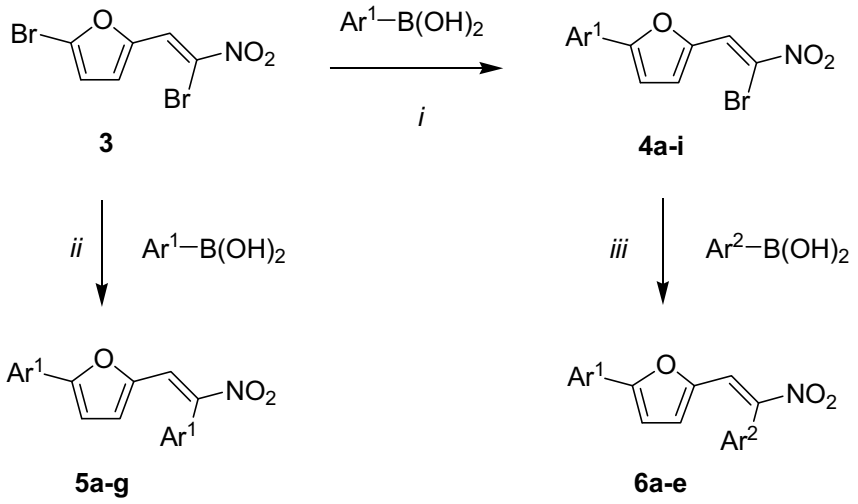
Scheme 7. Regioselectivity of palladium(0)-catalyzed coupling reactions

1.1.2 Results and Discussion

As a starting point for my studies I chose (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran **3** which is readily available by Henry reaction of furfural with nitromethane and subsequent bromination (Scheme 8).[31] It has been shown that compound **3** possesses interesting biological activity and its derivatization is, therefore, of considerable interest.[31e] Furfural represents an inexpensive, *green* starting material which is produced in large scale by acid-mediated hydrolysis of plant-derived polysaccharides (sustainable development).



Scheme 8. Synthesis of (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran (**3**); *conditions*: *i*, CH_3NO_2, NaOH, H_2O; *ii*, 1) Br_2, AcOH; 2) pyridine



Scheme 9. Suzuki reactions of **3**; *conditions*: *i*, **3** (1.2 equiv.), $Ar^1B(OH)_2$ (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_3PO_4 (2.0 equiv.), solvent (see Table 1); *ii*, **3** (1.0 equiv.), $Ar^1B(OH)_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), solvent (see Table 2); *iii*, **4a-i** (1.0 equiv.), $Ar^2B(OH)_2$ (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_3PO_4 (2.0 equiv.), solvent (see Table 3)

The Suzuki reaction of **3** (1.2 equiv.) with various boronic acids (1.0 equiv.) resulted in regioselective coupling of the furan rather than the alkenyl moiety to give the 2-(2-bromo-2-nitroethenyl)-5-arylfurans **4a-i** (Scheme 9). The reaction proceeded without *E/Z*-isomerization of the double bond. The structure and configuration of the products was proved by spectroscopic methods and by X-ray crystal structure analyses. During the optimization, the stoichiometry, temperature, solvent, and the presence of water played an important role (Table 1). The reaction of **3** (1.0 equiv.) with 2.0 equiv. of boronic acids resulted in double coupling and formation of the 2-(2-aryl-2-nitroethenyl)-5-arylfurans **5a-e** containing two identical aryl groups (Table 2). The Suzuki reaction of **4a** (1.0 equiv.) with various arylboronic acids (1.0 equiv.) allowed the synthesis of 2-(2-aryl-2-nitroethenyl)-5-phenylfurans **6a-f** which contain two different aryl groups (Table 3). The formation of **5a-e** and **6a-f** proceeded, as expected for Suzuki reactions, without *E/Z*-isomerization of the double bond.

Table 1. Synthesis of 2-(2-bromo-2-nitroethenyl)-5-arylfurans **4a-i**

entry	**4**	Ar[1]	Solvent/H_2O (6:1)	*T* (°C)	% (**4**)[a]
1	**a**	Ph	Toluene	90	90
2	**a**	Ph	Toluene	20	76
3	**a**	Ph	THF	20	73
4	**a**	Ph	1,4-Dioxane [b]	90	70
5	**a**	Ph	1,4-Dioxane	90	78
6	**b**	4-(HO)C_6H_4	1,4-Dioxane	90	83
7	**b**	4-(MeO)C_6H_4	1,4-Dioxane	90	69
8	**b**	4-(MeO)C_6H_4	Toluene	90	38
9	**c**	2-(MeO)C_6H_4	1,4-Dioxane	90	64
10	**d**	3,5-$Me_2C_6H_3$	Toluene	90	93
11	**d**	3,5-$Me_2C_6H_3$	1,4-Dioxane	90	56
12	**e**	4-(EtO)C_6H_4	1,4-Dioxane	90	67
13	**f**	1-Naphtyl	1,4-Dioxane	90	52
14	**f**	1-Naphtyl	Toluene	90	75
15	**g**	3,4,5-$(MeO)_3C_6H_2$	1,4-Dioxane	90	77
16	**h**	2-Thienyl	1,4-Dioxane	90	87
17	**i**	4-MeC_6H_4	Toluene	90	84

[a] Isolated yields; [b] without addition of H_2O.

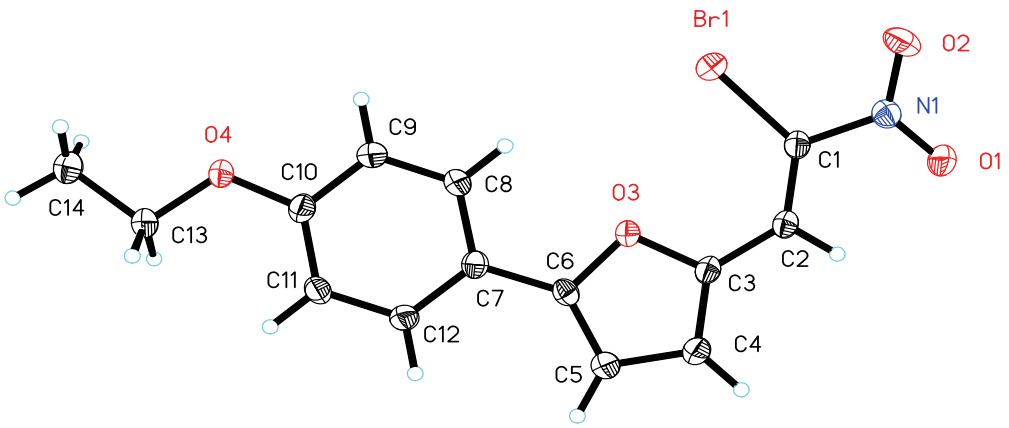


Figure 1. X-Ray crystal structure of compound **5e**

Table 2. Synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans **5a-g**

5	Ar^1	Solvent/H_2O (6:1)	% (**5**) [a]
a	Ph	Toluene	67
b	4-(MeO)C_6H_4	1,4-Dioxane	69
c	2-(MeO)C_6H_4	1,4-Dioxane	64
d	3,5-$Me_2C_6H_3$	1,4-Dioxane	86
e	4-(EtO)C_6H_4	Toluene	87
f	4-MeC_6H_4	Toluene	82
g	2-Thienyl	1,4-Dioxane	42

[a] Isolated yields (all reactions were carried out at 90 °C)

Table 3. Synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans **6a-e**

6	Ar^1	Ar^2	Solvent/H_2O (6:1)	% (**6**) [a]
a	Ph	1-Naphthyl	Toluene	63
b	Ph	3,5-$Me_2C_6H_3$	Toluene	74
c	Ph	4-MeC_6H_4	Toluene	79
d	Ph	4-(MeO)C_6H_4	1,4-Dioxane	75
e	Ph	2-Thienyl	Toluene	57

[a] Isolated yields (all reactions were carried out at 90 °C)

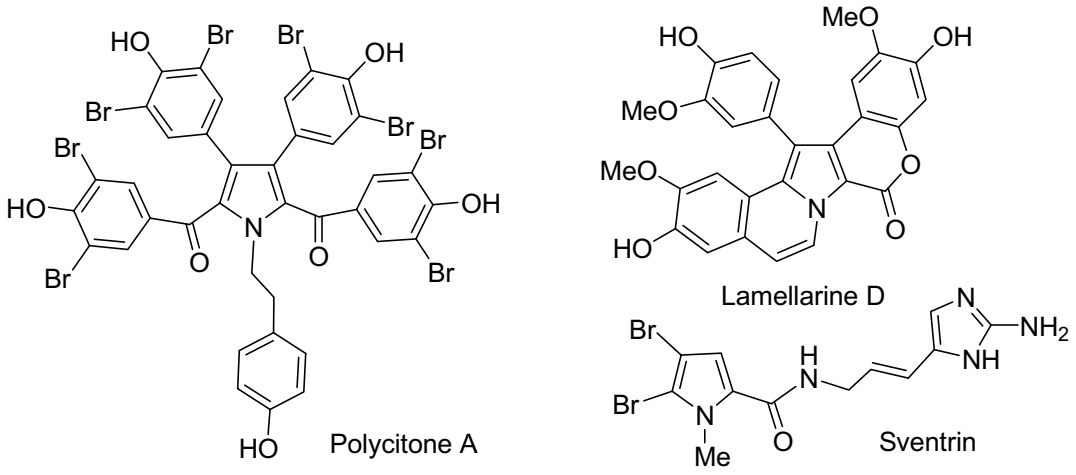
1.1.3 Conclusion

The Suzuki reaction of 2-(2-bromo-2-nitroethenyl)-5-bromofuran, readily available from furfural, resulted in regioselective attack onto the furan moiety. The first regioselective Suzuki cross-coupling reaction occurs at the bromo-substituted furan to give 2-(2-bromo-2-nitroethenyl)-5-arylfuran. The alkenyl moiety could be functionalized in a second Suzuki reaction. The products are formed without *E/Z*-isomerization of the double bond.

1.2 Regioselective Suzuki Cross-Coupling Reactions of 2,3,4,5-Tetrabromo-1-methylpyrrole

1.2.1 Introduction

Pyrroles are of considerable pharmacological relevance. They occur in a number of synthetic drugs (e. g. zomepirac and atorvastatin) and natural products (e. g. in the tetrapyrrole pigments Porphobilinogen, Bilirubin, Polycitone A, Lamellarin D, Sventrin, etc.) (Scheme 10).[32,33,34] Oligopyrroles proved to be important as organic materials (e. g. as synthetic metals).[35] Heterocycles have been widely functionalized by palladium(0)-catalyzed cross-coupling reactions.[36] In recent years, it has been shown that polyhalogenated heterocycles may be regioselectively functionalized in such reactions by selective activation of a single halogen atom – a process which is controlled by electronic and steric parameters.[37] Recently, I reported the synthesis of tetraarylthiophenes based on regioselective Suzuki reactions of tetrabromothiophene.[38] Despite their potential synthetic utility, regioselective functionalization reactions of polyhalogenated pyrroles have only scarcely been reported to date. Bach and Schröter recently reported regioselective Suzuki reactions of ethyl 2,3,4-tribromopyrrole-5-carboxylate and of 2,3-dibromo-5-nitropyrrole.[39] Herein, I disclose my preliminary results related to Suzuki cross-coupling reactions of 2,3,4,5-tetrabromo-1-methylpyrrole. Palladium(0)-catalyzed cross-coupling reactions of tetrahalopyrroles have, to the best of my knowledge, not been reported to date. In general, reactions of tetrahalogenated pyrroles are rather rare which can be explained by the unstable nature of these compounds.[40]



Scheme 10. Some natural products containing pyrrole moieties.

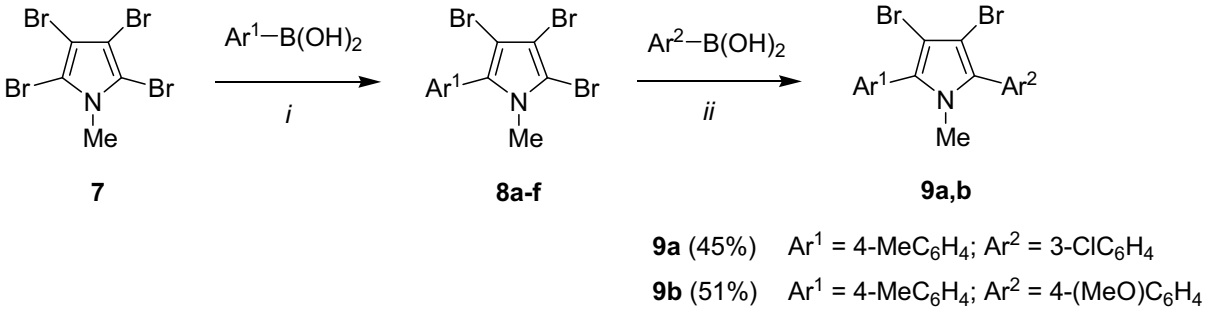
1.2.2 Results and Discussion

2,3,4,5-Tetrabromo-1-methylpyrrole (**7**) was prepared by NBS-mediated bromination of *N*-methylpyrrole. The published procedure[41] for the synthesis of **7** was modified, as I were not able to isolate the pure product by the original protocol. The reaction was carried out at −78 °C for 8 h. It proved to be helpful for the separation of succinimide to add heptane to the reaction mixture which results in precipitation of succinimide and of side-products. The yellowish crude product was purified by repeated washing with cold ethyl acetate to give the pure material in the form of colourless crystals. Noteworthy, impure product fails to undergo the desired Suzuki reactions and also more rapidly decomposes. The solid can be stored under argon at −18 °C for a few weeks. After a few weeks the compound starts to become slightly yellow and the quality is not sufficient anymore for Suzuki reactions.

The Suzuki reaction of **7** with various boronic acids (1.1 equiv.) afforded the 5-aryl-2,3,4-tribromopyrroles **8a-f** in good yields and with very good regioselectivity (Scheme 4, Table 4). During the optimization, it proved to be important to suppress the formation of 2,5-diaryl-3,4-dibromopyrroles, as their separation from the desired products proved to be difficult and tedious. The stoichiometry, temperature, solvent, and the presence of water proved to play an important role in terms of yield (Table 4). Noteworthy, the employment of benzyl-, carbamate-, and sulfonyl-protected pyrroles was unsuccessful (decomposition). The reaction of **8e** with 1.1 equiv. of (3-chlorophenyl)- and (4-methoxyphenyl)boronic acid resulted in regioselective formation of 2,5-diaryl-3,4-dibromopyrroles **9a** and **9b**, respectively (Scheme 11).

The Suzuki reaction of **7** with 2.5 equiv. of various arylboronic acids afforded the 2,5-diaryl-3,4-dibromopyrroles **10a-f** in good yields and with very good regioselectivity (Scheme 12, Table 5).[12] The solvent proved again to be a very important parameter during the optimization of the yield. The reaction of **10c** with (4-methoxyphenyl)- and (4-chlorophenyl)boronic acid gave tetraarylpyrroles **12a** and **12b**, respectively, containing two different types of aryl groups. Tetraarylpyrroles **11a,b**, containing four identical aryl groups, were prepared by reaction of **7** with (4-ethylphenyl)- and (3.chlorophenyl)boronic acid (5.0 equiv.). The best yields of **11a,b** and **12a,b** were obtained when the reactions were carried out using a ternary solvent mixture (toluene/EtOH/H_2O = 5:1:1) and an increased amount of catalyst and reagents. Considerable amounts of 2,3,5-triaryl-4-bromopyrroles were formed when the

amounts of reagents and catalyst were too low. Noteworthy, the bromide groups of 2,5-diaryl-3,4-dibromopyrroles **10a-f** proved to be considerably less reactive than those of 2,5-diaryl-3,4-dibromothiophenes.[38] This must be explained by electronic reasons, as the steric hindrance is similar for both types of substrates. The conditions developed for the synthesis of **11a,b,c** and **12a,b** could be successfully applied to the synthesis of related tetraarylpyrroles.



7 **8a-f** **9a,b**

9a (45%) Ar^1 = 4-MeC_6H_4; Ar^2 = 3-ClC_6H_4

9b (51%) Ar^1 = 4-MeC_6H_4; Ar^2 = 4-$(MeO)C_6H_4$

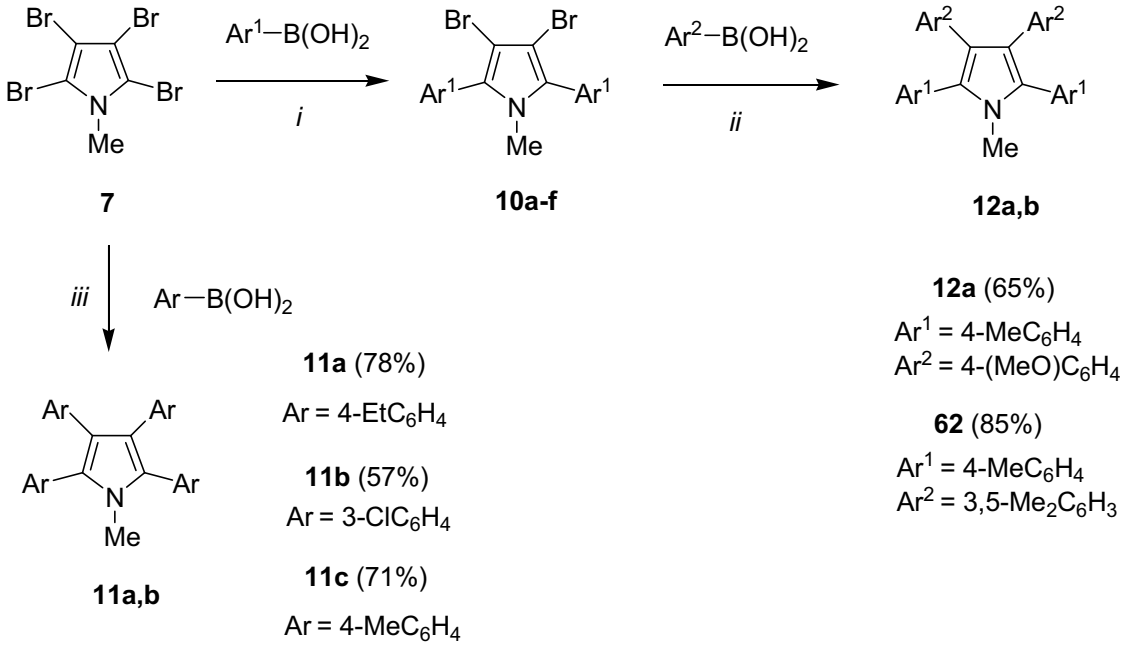
Scheme 11. Synthesis of 5-aryl-2,3,4-tribromopyrroles **8a-f** and of 2,5-diaryl-3,4-dibromopyrroles **9a,b**; *conditions*: *i*, **7** (1.0 equiv.), $Ar^1B(OH)_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (6 mol-%), K_3PO_4 (4.0 equiv.), solvent (see Table 4), 90 °C, 12 h; *ii*, **2c** (1.0 equiv.), $Ar^2B(OH)_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (4.0 equiv.), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, 48 h

Table 4. Synthesis of **8a-f**

8	Ar	solvent [a]	% [b]
a	3-PhC_6H_4	Toluene/H_2O	66
b	3-ClC_6H_4	Toluene/H_2O	71
c	4-EtC_6H_4	Toluene/H_2O	75
d	2-$(MeO)C_6H_4$	1,4-Dioxane/H_2O	70
e	4-MeC_6H_4	1,4-Dioxane/H_2O	81
f	3,5-$Me_2C_6H_3$	1,4-Dioxane/H_2O	72

[a] Solvent/H_2O = 4:1; [b] yields of isolated products

All products were characterized by spectroscopic methods. The structure of **8e** and **10b** was independently confirmed by X-ray crystal structure analysis (Figure 2, 3).



Scheme 12. Synthesis of 2,5-diaryl-3,4-dibromopyrroles **10a-f** and of tetraarylpyrroles **11a,b** and **12a,b**; *conditions*: *i*, **7** (1.0 equiv.), $Ar^1B(OH)_2$ (2.5 equiv.), $Pd(PPh_3)_4$ (6-10 mol-%), K_3PO_4 (4.0 equiv.), solvent (see Table 5), 90 °C, 12 h; *ii*, **10c** (1.0 equiv.), $Ar^2B(OH)_2$ (3.0 equiv.), $Pd(PPh_3)_4$ (20 mol-%), K_3PO_4 (4.0 equiv.), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, (**12a**: 48 h, **12b**: 96 h); *iii*, **7** (1.0 equiv.), $ArB(OH)_2$ (5.0 equiv.), $Pd(PPh_3)_4$ (20 mol-%), K_3PO_4 (5.0 equiv.), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, 96 h

Table 5. Synthesis of **10a-f**

10	Ar^1	solvent	% [a]
a	3-ClC_6H_4	Toluene/H_2O (5:1)	57
b	4-EtC_6H_4	Toluene/H_2O (5:1)	52
c	4-MeC_6H_4	Toluene/H_2O (5:1)	79
d	4-ClC_6H_4	1,4-Dioxane/H_2O (5:1)	67
e	4-(MeO)C_6H_4	1,4-Dioxane /H_2O (5:1)	79
f	Thien-2-yl	Toluene/MeOH/H_2O (2:2:1)	50

[a] Yields of isolated products

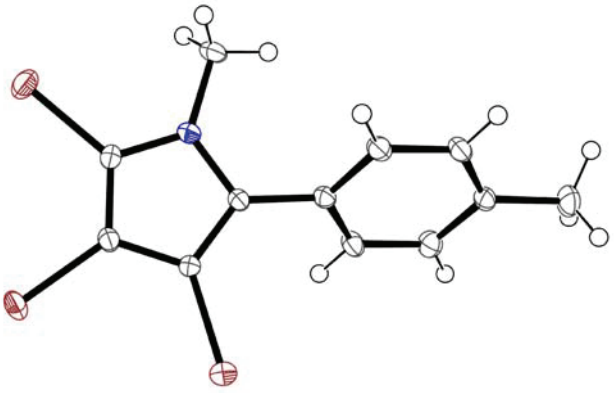


Figure 2. Ortep plot of **8e** (50% probability level)

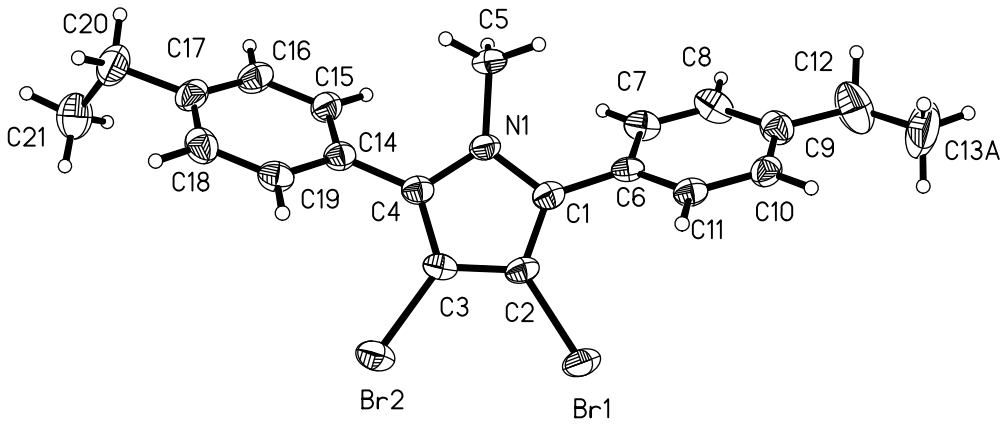


Figure 3. Ortep plot of **10b** (50% probability level)

1.2.3 Conclusion

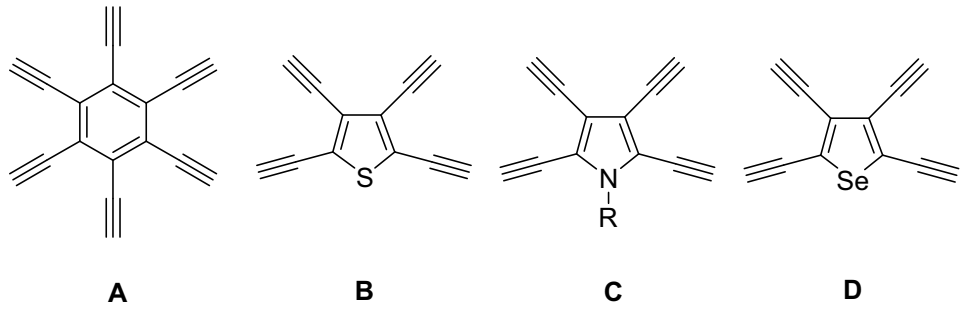
In conclusion, I have reported a new strategy for the synthesis of 5-aryl-2,3,4-tribromopyrroles, 2,5-diaryl-3,4-dibromopyrroles and tetraarylpyrroles based on regioselective Suzuki cross-coupling reactions of *N*-methyltetrabromopyrrole.

1.3 Regioselective Sonogashira Reactions of *N*-Methyl-Tetrabromopyrrole. First Synthesis of Tri- and Tetra-(1-alkynyl)pyrroles

1.3.1 Introduction

Hydrocarbons bearing multiple alkynyl groups have received considerable attention, due to their interesting physicochemical properties, as synthetic building blocks of new and interesting arenes, and because of their æsthetic attraction (Scheme 13).[42] For example, Vollhardt and coworkers reported the synthesis and characterization of hexaethynylbenzene **A** and its application to the first synthesis of the so-called archimedanes containing only benzene and cyclobutane moieties.[43] In contrast to their hydrocarbon counterparts, multiple-alkynylated heterocycles are relatively rare. Whitesides *et al.* reported the synthesis of tetra(1-alkynyl)thiophenes **B** based on regioselective Sonogashira couplings of tetraiodothiophene.[44] Later, related reactions of tetrabromothiophene were reported.[45]

Pyrroles constitute an important class of heterocycles which are present in natural products (e. g. in the tetrapyrrole pigments porphobilinogen and bilirubin)[46] and in various synthetic drugs (e. g. zomepirac and atorvastatin).[34] Pyrroles and oligopyrroles show promising properties as new materials (e.g., as synthetic metals).[35] In recent years, syntheses of 2,5-[47] and 3,4-di(1-alkynyl)pyrroles[48] have been reported. These molecules have been used for the synthesis of polymers and fused heterocycles. The synthesis of tri- and tetra(1-alkynyl)pyrroles **C** has, to the best of my knowledge, not been reported to date.



Scheme 13. Molecules with multiple alkynyl groups

Heterocycles have been widely functionalized by palladium(0)-catalyzed cross-coupling reactions.[49] In recent years, it has been shown that polyhalogenated heterocycles may be

regioselectively functionalized in such reactions by selective activation of a single halogen atom – a process which is controlled by electronic and steric parameters.[37] Bach and Schröter reported regioselective Sonogashira reactions of ethyl 2,3,4-tribromopyrrole-5-carboxylate and of 2,3-dibromo-5-nitropyrrole.[39] Recently, I reported the synthesis of aryl-substituted thiophenes[38] and pyrroles[50] by Suzuki reactions of tetrabromothiophene and tetrabromo-*N*-methylpyrrole, respectively. Herein, I disclose my preliminary results related to what are, to the best of my knowledge, the first Sonogashira cross-coupling reactions of tetrabromo-*N*-methylpyrrole. These reactions allow a convenient synthesis of a variety of novel alkynylated pyrroles. In this context, I report what are, to the best of my knowledge, the first syntheses of tri- and tetra(1-alkynyl)pyrroles.

1.3.2 Results and Discussion

The reaction of *N*-methylpyrrole with *N*-bromosuccinimide (NBS) afforded tetrabromo-*N*-methylpyrrole (**7**). The synthesis was carried out following the procedure of Gilow and Burton,[51] but with some variations (related to the temperature, reaction time, and amount of NBS). Notably, I observed that it is crucial to isolate **7** in analytically pure form as colourless crystals. The oily form is generally slightly impure, tends to be considerably less stable and decomposes within a few days. The presence of impurities results in a failure of Pd(0)-catalyzed cross-coupling reactions. In contrast, the crystalline solid can be stored under argon atmosphere at −18 °C (in the dark) for a few weeks. Then, the compound starts to slightly darken and it cannot be successfully used anymore in Pd(0)-catalyzed reactions.

In general, the Sonogashira cross-coupling reactions reported herein only proved to be possible when tetrabromo-*N*-methylpyrrole was employed. The employment of benzyl-, carbamate-, and sulfonyl-protected tetrabromopyrroles was unsuccessful and resulted in the formation of complex mixtures and decomposition. In most of the Sonogashira reactions reported herein, the best yields were obtained when (freshly prepared) $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), and (rigorously dried and freshly distilled) *i*Pr_2NH were employed. The yields dramatically decrease when traces of water are present. The temperature and the reaction time also proved to be important parameters (*vide infra*). The yields of most products reported herein could be slightly increased when 20 rather than 10 mol-% of catalyst was employed. The best yields were generally obtained for non-volatile alkynes, due to the high reaction temperatures.

The Sonogashira reaction of **7** with various alkynes (1.1 equiv.) regioselectively afforded the novel 5-(1-alkynyl)-2,3,4-tribromopyrroles **13a-e** (Scheme 14, Table 6). The formation of a 4-(1-alkynyl)-2,3,5-tribromopyrrole was *not* observed. The relatively low yields of **13a-e** can be explained by the formation of considerable amounts of 2,5-di(1-alkynyl)-3,4-dibromopyrroles. Therefore, it proved to be important during the optimization to use not more than 1.1 equiv. of the alkyne and to stirr the solution at 90 °C for not more than 1 h. Stirring for 3 h resulted in the formation of a mixture of 2,5-di(1-alkynyl)-3,4-dibromopyrroles and starting material (**7**). Likewise, the yields of **13a-e** decreased when the reactions were carried out at temperatures lower than 90 °C. The yields could be slightly increased when 20 rather than 10 mol-% of catalyst was employed.

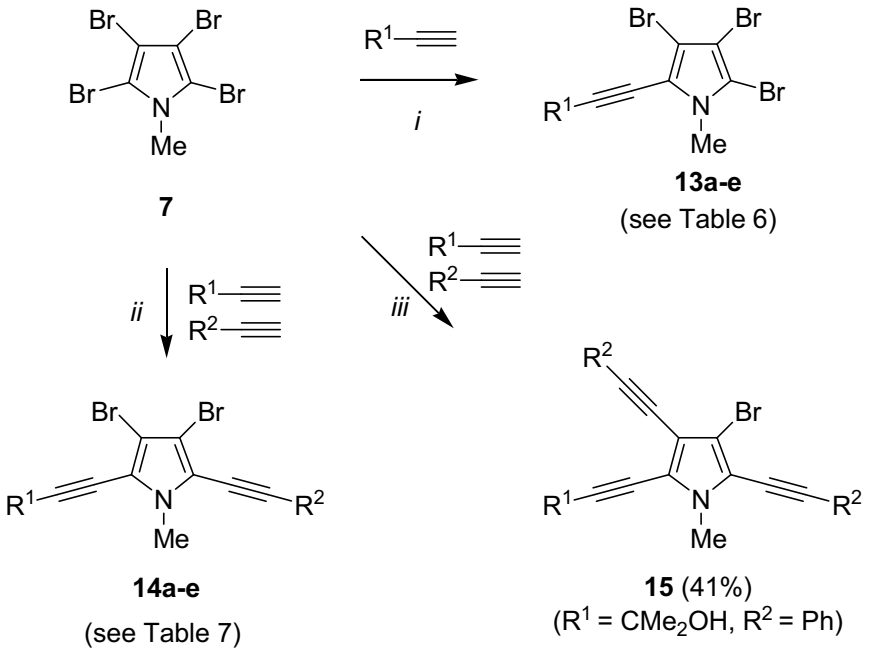
The Sonogashira reaction of **7** with two *different* alkynes (1.05 equiv. each) afforded the unsymmetrical 2,5-(1-alkynyl)-3,4-tribromopyrroles **3a-e** (Scheme 14, Table 7). During the optimization, it proved to be important that alkynes of considerably different reactivity are employed. In addition, it was crucial to add both alkynes at the same time to avoid the formation of symmetrical 2,5-di(alkynyl)pyrroles.

The reaction of **7** with 2-methylbut-3-yn-2-ol and phenylacetylene (1.05 equiv. each) and, subsequently, with phenylacetylene (1.05 equiv.) afforded the 2,4,5-tri(1-alkynyl)-3-bromopyrrole **4**.

Table 6. Synthesis of **13a-e**

13	R^1	% [a]
a	*n*Pr	30
b	CMe_2OH	32
c	$(CH_2)_3OH$	30
d	$CH_2CH(OH)Me$	35
e	4-MeC_6H_4	40

[a] yields of isolated products



Scheme 14. Synthesis of **13a-e**, **14a-e**, and **15**; *conditions*: *i*, **7** (1.0 equiv.), $R^1C{\equiv}CH$ (1.2 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), iPr_2NH, 90 °C, 1 h; *ii*, **7** (1.0 equiv.), $R^1C{\equiv}CH$ and $R^2C{\equiv}CH$ (1.05 equiv. each, addition at the same time), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), iPr_2NH, 90 °C, 6-8 h; *iii*, 1) **7** (1.0 equiv.), $R^1C{\equiv}CH$ and $R^2C{\equiv}CH$ (1.05 equiv. each, addition at the same time), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), iPr_2NH, 100 °C, 6-8 h; 2) $R^2C{\equiv}CH$ (1.05 equiv.), 12-16 h

Table 7. Synthesis of **14a-e**

14	R^1	R^2	% [a]
a	4-MeC_6H_4	$CH_2CH(OH)Me$	40
b	4-MeC_6H_4	$(CH_2)_3OH$	40
c	4-MeC_6H_4	CMe_2OH	44
d	4-MeC_6H_4	*n*Hex	41
e	CMe_2OH	*n*Hex	37

[a] yields of isolated products

The Sonogashira reaction of **7** with 2.5 equiv. of various alkynes afforded the symmetrical 2,5-di(1-alkynyl)-3,4-dibromopyrroles **16a-k** in good yields and with very good

regioselectivity (Scheme 15, Table 8). Products **16a,b,d,g-k** were obtained in good yields when the reaction was carried out using $PdCl_2(CH_3CN)_2$, PPh_3 and $HNiPr_2$ (procedure A). The best yields were obtained when the reaction mixture was stirred at 100 °C for 6-8 h. Longer and shorter reaction times resulted in a decrease in yield, due to decomposition and uncomplete conversion, respectively. However, product **16b** could be isolated in equally good yield after stirring for only 3 h when the reaction was carried out in an autoclave (at 90 °C). The yields of products **16a,b** could be improved when $Pd(OAc)_2$, the novel ligand **L** and Cs_2CO_3 were employed (procedure C). This method was also successfully applied to the synthesis of **16c,e,f**. The yields of **16a,b,i** considerably decreased when the (freshly prepared) carbene-ligated catalyst **7** (5 mol-%) was employed (procedure B).

The structure of **16b** was independently confirmed by X-ray crystal structure analysis (Figure 4).[73]

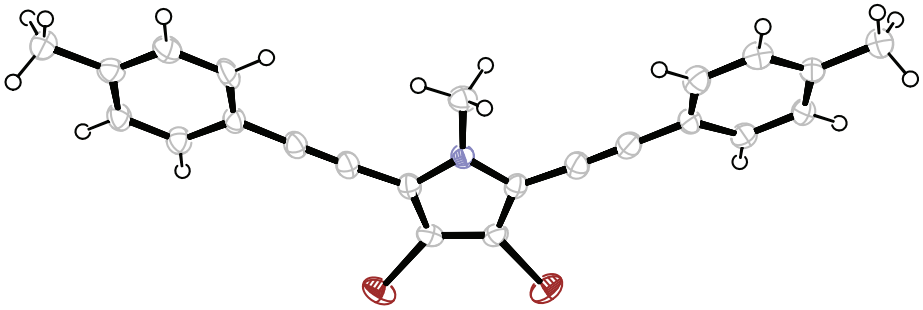
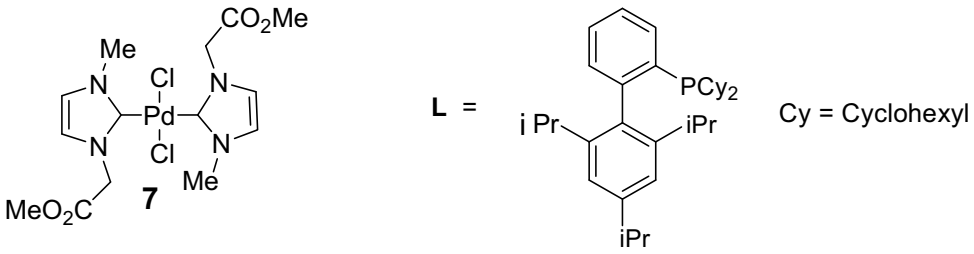
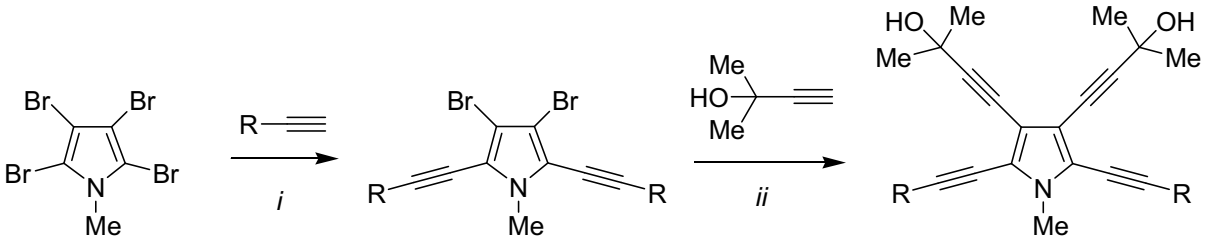


Figure 4. Ortep plot of **16b** (50% probability level)



The Sonogashira reaction of **16a,b** with 2-methylbut-3-yn-2-ol (4.0 equiv.) afforded the tetra(1-alkynyl)pyrroles **17a,b** containing two different types of alkynyl substituents.



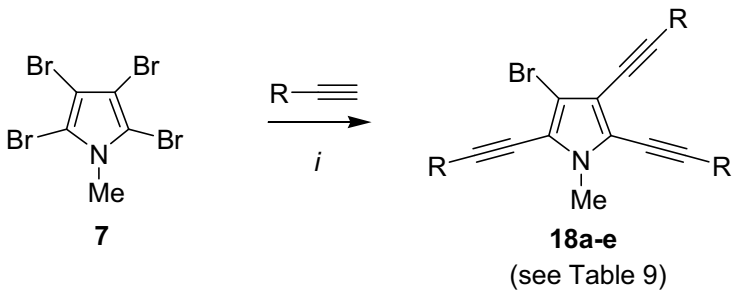
Scheme 15. Synthesis of **16a-h** and **17a,b**; *conditions*: *i*, procedure A: **7** (1.0 equiv.), RC≡CH (2.5 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), *i*Pr_2NH, 100 °C, 6-8 h; procedure B: **7** (1.0 equiv.), **7** (5 mol-%, structure see below), PPh_3 (5 mol-%), CuI (10 mol%), Cs_2CO_3 (1.5 equiv.), DMF; procedure C: $Pd(OAc)_2$ (5 mol-%), **L** (15 mol-%), Cs_2CO_3 (3.0 equiv.), CH_3CN, reflux, 6 h; *ii*, **16a,b** (1.0 equiv.), RC≡CH (4.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), *i*Pr_2NH, 100 °C, 20 h

Table 8. Synthesis of **16a-h**

16	Ar	% (A) [a]	% (B) [a]	% (C) [a]
a	Ph	59	17	84
b	4-MeC_6H_4	71	19	79
c	4-FC_6H_4			47
d	*n*Pr	45		
e	*n*Pent			67
f	*n*Oct			72
g	*n*Undec	65		
h	$(CH_2)_3OH$	61		
i	$CH_2CH(OH)Me$	70	15	
j	CMe_2OH	74		
k	$SiMe_3$	67		

[a] yields of isolated products using procedures A, B, and C (see Scheme 14)

2,4,5-Tri(1-alkynyl)-3-bromopyrroles **18a-e**, containing three identical alkynyl groups, were selectively prepared by Sonogashira reaction of **7** with 3.3 equiv. of various alkynes (Scheme 16, Table 9).[16,21] The best yields were obtained when the reaction mixture was stirred at 100 °C for 12-16 h. The success of these transformations relies on the fact that the formation of the fourth carbon-carbon bond is significantly slower than the formation of the third one. In fact, no competing formation of a tetra(1-alkynyl)pyrrole was observed.



Scheme 16. Synthesis of **18a-e**; *conditions*: *i*, **7** (1.0 equiv.), RC≡CH (3.3 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), *i*Pr_2NH, 100 °C, 12-16 h

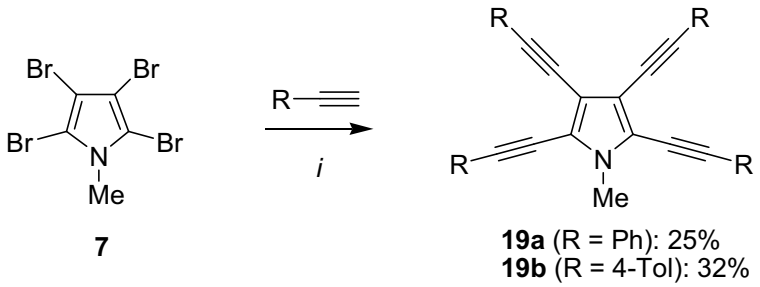
Table 9. Products and yields

18	R	% [a]
a	Ph	36
b	4-MeC_6H_4	42
c	CMe_2OH	40
d	$(CH_2)_3OH$	40
e	$CH_2CH(OH)Me$	44

[a] yields of isolated products

Tetra(1-alkynyl)pyrroles **19a** and **19b**, containing four identical alkynyl groups, were prepared by reaction of **7** with an excess (6.0 equiv.) of phenylacetylene and 4-tolylacetylene, respectively (Scheme 17). The best yields were obtained when the reaction mixture was stirred at 100 °C for 20 h. Although the yields of **19a,b** are relatively low, it should be taken into account that four carbon-carbon bonds are formed in one reaction. A theoretical yield of 71% for each C-C bond formation would result in a 25% overall yield. Notably, products derived from alkyl-substituted alkynes proved to be rather unstable and could not be isolated

in pure form. We have not yet tried to prepare the unsubstituted parent compound, tetraethynyl-*N*-methylpyrrole, as its thiophene analogue has been reported to be highly explosive.[44]



Scheme 17. Synthesis of **19a,b**; *conditions*: *i*, **7** (1.0 equiv.), RC≡CH (6.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol-%), CuI (10 mol-%), PPh_3 (20 mol-%), *i*Pr_2NH, 100 °C, 20 h

1.3.3 Conclusion

In conclusion, I have studied the synthesis of a variety of alkynyl-substituted pyrroles based on regioselective Sonogashira cross-coupling reactions of tetrabromo-*N*-methylpyrrole. In this context, the synthesis of what are, to the best of my knowledge, the first tri- and tetra(1-alkynyl)pyrroles has been reported. The Sonogashira reactions of tetrabromo-*N*-methylpyrrole first occur at carbon atoms C2 and C5 which are more electron deficient than C3 and C4. The formation of 2,5-di(1-alkynyl)pyrroles is relatively fast. Therefore, the best yields were obtained for the synthesis of the symmetrical di(alkynyl)pyrroles **16**. In contrast, the synthesis of the mono-alkynylated pyrroles **13** was more difficult and required a thorough optimization of the reaction time. Unsymmetrical di(alkynyl)pyrroles **14** could be directly prepared from **7** when two alkynes of different reactivity were employed and added at the same time. The first tri(1-alkynyl)pyrroles were prepared. For their successful synthesis it proved to be important that the formation of the fourth carbon-carbon bond is significantly slower than the formation of the third one. Finally, I reported the synthesis of the first tetra(1-alkynyl)pyrroles.

1.4 Efficient Synthesis of Substituted Selenophenes based on the First Palladium(0)-Catalyzed Cross-Coupling Reactions of Tetrabromoselenophene

1.4.1 Introduction

Selenium represents an essential element for higher organisms.[52] In this context, the selenium containing enzymes *Glutathioneperoxidase* and *5'-Deiodase type 1* play an important role. In fact, a number of diseases can result from selenium deficiency.[53,54] In addition, selenium containing molecules are of considerable pharmacological relevance.[55] A prominent example is the antitumor and antiviral active C-glycosyl selenazole selenazofurin.[56] Selenophenes have also been reported to be of considerable pharmacological relevance. For example, they act as muscarinic antagonists,[57] show antiviral activity,[58] inhibitory activity against human myelogenous leukemia K562 cells, cytotoxicity against HT-29, HeLa, ACHN and 5637 cells,[59] and in vitro antiproliferative activity against human acute B-lymphoblastic leukemia and human acute T-lymphoblastic leukemia.[60] In addition, selenophenes promote the polymerization of tubulin and stabilize microtubules.[61] Selenophene containing porphyrines have been shown to possess activity against murine colon carcinoma Colo-26 cells.[62] Selenophenes also exhibit antifungal activity[63] and cytotoxic against human cervical cancer KB cells and human hepatocellular carcinoma HepG2 cells cells.[64]

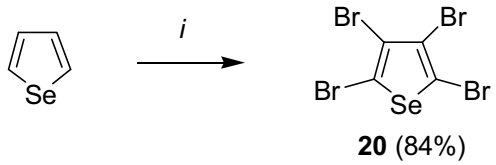
Unfortunately, selenium compounds are in most cases less stable than their corresponding sulfur analogues. In addition, the methods and conditions available for the synthesis of organosulfur compounds can often not be applied to selenium. Therefore, the development of new methods for the synthesis of organoselenium compounds is of considerable current interest. Substituted selenophenes[65] have been mostly prepared so far based on cyclocondensation reactions. For example, 2,5-diarylselenophenes and tetraarylselenophenes are available by cyclocondensation of alkynes (2 equiv.) with selenium in the presence of lithium metal.[66] However, these reactions often suffer from the harsh reaction conditions. Kirsch and coworkers reported[67] the synthesis of 2,5-diarylselenophes by β-Aryl-β-chloro acroleins, easily prepared from substituted acetophenones and Vilsmaier-Haack reagent, are condensed with appropriate benzylbromide derivatives to give the title compounds Heterocycles have been widely functionalized by palladium(0)-catalyzed cross-coupling reactions.[68] However, syntheses of functionalized selenophenes by such reactions are

relatively rare. 2,5-Diarylselenophenes were prepared by Suzuki reactions of 2,5-dihaloselenophenes.[69] The Sonogashira reaction of 2-bromo- and 2-iodoselenophene with alkynes has been reported to give (1-alynyl)selenophenes.[70] The reaction of 2,5-diiodoselenophene with two equivalents of an alkyne has been reported to give 2,5-di(1-alkynyl)selenophenes. The synthesis of tri- and tetra(1-alkynyl)selenophenes has, to the best of my knowledge, not been reported to date.

In recent years, it has been shown that polyhalogenated heterocycles can be regioselectively functionalized in palladium(0)-catalyzed cross-coupling reactions by selective activation of a single halogen atom. The regioselectivity is controlled by electronic and steric parameters.[37] Recently, I have reported the synthesis of tetraarylthiophenes[50] and –pyrroles[71] based on regioselective Suzuki reactions of tetrabromothiophene and tetrabromo-*N*-methylpyrrole, respectively. Herein, I disclose my preliminary results related to Suzuki reactions of tetrabromoselenophene. These reactions allow a convenient and regioselective approach to aryl-substituted selenophenes which are not readily available by other methods. In addition, I report the synthesis of what is, to the best of my knowledge, the first tetra(1-alkynyl)selenophene by a Sonogashira reaction of tetrabromoselenophene.

1.4.2 Results and Discussion

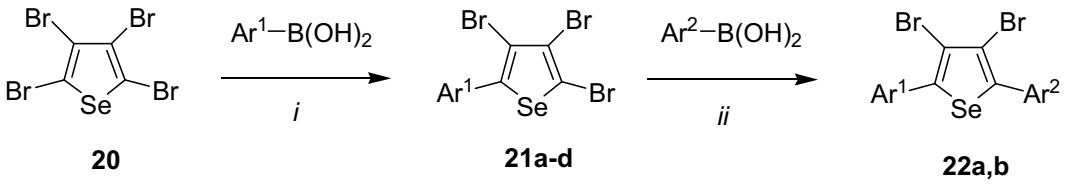
Helmholdt and coworkers have recently reported the synthesis of tetrabromoselenophene (**20**) in 39% yield by reflux of a $CHCl_3$ solution of selenophene with an excess of bromine.[72] We have been able to improve the yield to 84% by some modifications (Scheme 18). The solvent $CHCl_3$ was replaced by CH_2Cl_2. Due to the lower boiling point of CH_2Cl_2, the amount of bromine present in solution (and not in the gas phase) could be increased. The reaction time had to be extended from 12 to 72 h in order to make sure that the bromination is complete. Considerable amounts of di- and tribrominated selenophenes were formed when the reaction time was too short. Tetrabromoselenophene was isolated as a crystalline solid which can be stored under argon at −18 °C for several weeks.



20 (84%)

Scheme 18. Synthesis of tetrabromoselenophene (**20**); *conditions*: *i*, 1) Br_2 (7.0 equiv.), 0 °C, CH_2Cl_2; 2) reflux, 3 d; 3) NaOH, H_2O (2 M), reflux, 6 h

The Suzuki reaction of **20** with various boronic acids (1.1 equiv.) afforded the 5-aryl-2,3,4-tribromoselenophenes **21a-d** in good yields and with very good regioselectivity (Scheme 19, Table 21). During the optimization, it was important to suppress the formation of 2,5-diaryl-3,4-dibromoselenophenes, as their separation from the desired products proved to be difficult. Therefore, the stoichiometry was an important parameter and only a slight excess of the boronic acid should be used. Products **21a,c,d** were best prepared using $Pd(PPh_3)_4$ (5 mol-%) in dioxane/toluene/H_2O (2:2:1) (procedure A). For the reaction of **20** with sterically encumbered 3,5-dimethylphenylboronic acid (to give product **21b**) the application of procedure A gave unsatisfactory results (formation of a complex mixture). The problem was solved by employment of the new ligand **L** (Chart 1) which has been recently introduced by Buchwald and coworkers. The reaction of a dioxane/toluene solution (1:1) of **20** with 3,5-dimethylphenylboronic acid, in the presence of $Pd(OAc)_2$ (5 mol-%) and **L** (10 mol-%), afforded **21b** in 85% yield (procedure B). The reaction of **21a,b** with 1.2 equiv. of (4-tolyl)boronic acid, following procedure B, resulted in regioselective formation of the unsymmetrical 2,5-diaryl-3,4-dibromoselenophenes **22a,b** (Scheme 19).



20 **21a-d** **22a,b**

22a (Ar^1 = 3,5-$Me_2C_6H_3$; Ar^2 = 4-MeC_6H_4): 76%
22b (Ar^1 = 4-EtC_6H_4; Ar^2 = 4-MeC_6H_4): 80%

Scheme 19. Synthesis of 5-aryl-2,3,4-tribromoselenophenes **21a-d** and of 2,5-diaryl-3,4-dibromoselenophenes **22a,b**; *conditions*: *i*, procedure A: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene/H_2O (2:2:1), reflux, 8 h; procedure B: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (1.1 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h; *ii*, **21a,b** (1.0 equiv.), (4-MeC_6H_4)$B(OH)_2$ (1.1 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h

Table 10. Products and yields

21	Ar^1	% (**2**) [a,b]
a	4-EtC_6H_4	50 (A)
b	3,5-$Me_2C_6H_3$	85 (B)
c	4-$(MeO)C_6H_4$	68 (A)
d	3-PhC_6H_4	47 (A)

[a] Isolated yields; in brackets: [b] procedure (see legend of Scheme 19)

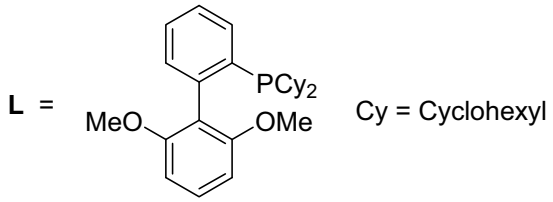
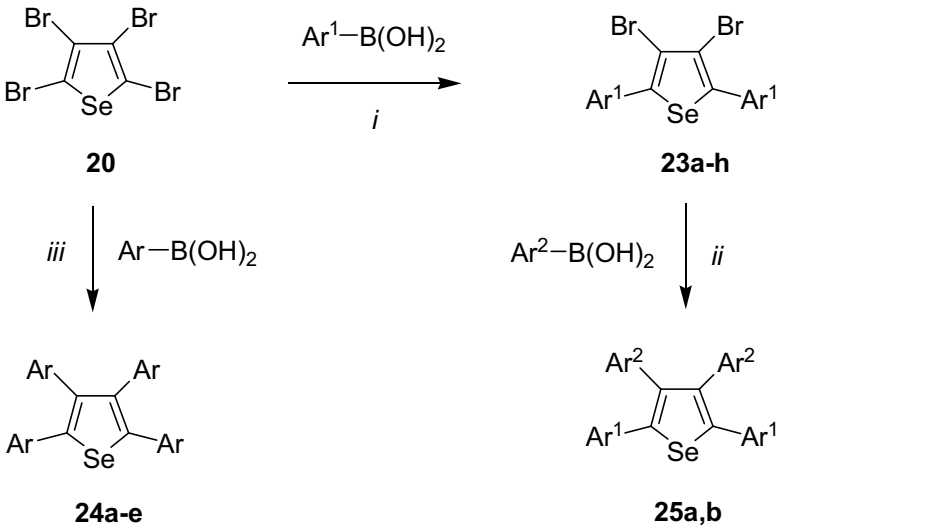


Chart 1. Biaryl monophosphine ligand developed by Buchwald and coworkers (ref. 73)

The Suzuki reaction of **20** with 2.5 equiv. of various arylboronic acids afforded the symmetrical 2,5-diaryl-3,4-dibromoselenophenes **23a-h** in good yields and with very good regioselectivity (Scheme 20, Table 11). The best yields of products **23b,c** were obtained by application of procedure B (using $Pd(OAc)_2$ / **L**). In contrast, procedure A (using $Pd(PPh_3)_4$) gave better yields for halogenated arylboronic acids (products **23f,g**). This can be explained by the assumption that $Pd(OAc)_2$ / **L** catalyzes a homo-coupling of the halogenated arylboronic acid which competes with the desired cross-coupling reaction.

The reaction of **23b** with (4-methoxyphenyl)boronic acid (3.0 equiv.) gave tetraarylselenophene **25a,b** containing two different types of aryl groups (Scheme 12). Tetraarylselenophene **24a-e**, containing four identical aryl groups, was prepared by reaction of **20** with various arylboronic acid (5.0 equiv.) (Table 12). The sterically encumbered tetraarylselenophenes **24a-e** and **25a,b** were isolated in very good yields when a) procedure B was employed, b) an excess of the respective boronic acid was employed and c) the amount catalyst was increased (10 rather than 5 mol-%). Considerable amounts of 2,3,5-triaryl-4-bromoselenophenes were formed when the amounts of boronic acid and catalyst were too low.



25a (79%): Ar^1 = 4-(MeO)C_6H_4, Ar^2 = 4-EtC_6H_4
25b (82%): Ar^1 = 4-(MeO)C_6H_4, Ar^2 = 3,5-$Me_2C_6H_4$

Scheme 20. Synthesis of 2,5-diaryl-3,4-dibromoselenophenes **23a-h** and tetraarylselenophenes **24a-e** and **25a,b** ; *conditions*: *i*, procedure A: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (2.5 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene/H_2O (2:2:1), reflux, 14 h; procedure B: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (2.1 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h; *ii*, **23b** (1.0 equiv.), (4-(MeO)$C_6H_4B(OH)_2$ (3.0 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h; *iii*, procedure A: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (5.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene/H_2O (2:2:1), reflux, 14 h; procedure B: **20** (1.0 equiv.), $Ar^1B(OH)_2$ (5.0 equiv.), $Pd(OAc)_2$ (10 mol-%), **L** (see Chart 1, 20 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h

Table 11. Synthesis of **23a-h**

23	Ar^1	% (**4**) [a,b]
a	4-MeC_6H_4	83 (A)
b	4-EtC_6H_4	69 (A), 83 (B)
c	3,5-$Me_2C_6H_3$	65 (A), 79 (B)
d	4-(MeO)C_6H_4	82 (B)
e	2-(MeO)C_6H_4	42 (A), 68 (B)
f	3-ClC_6H_4	45 (A), 15 (B)
g	4-BrC_6H_4	55 (A)
h	3-PhC_6H_4	48 (A)

[a] Isolated yields; in brackets: procedure (see legend of Scheme 19)

Table 12. Synthesis of **24a-e**

24	Ar[1]	% (**5**) [a]
a	Ph	55 (A), 79 (B)
b	4-MeC_6H_4	89 (B)
c	4-EtC_6H_4	98 (B)
d	3,5-$Me_2C_6H_3$	74 (A)
e	4-$(MeO)C_6H_4$	89 (B)

[a] Isolated yields; in brackets: procedure (see legend of Scheme 19)

All products were characterized by spectroscopic methods. The structures of **23d** and **24d** were independently confirmed by X-ray crystal structure analyses (Figures 5 and 6).[74]

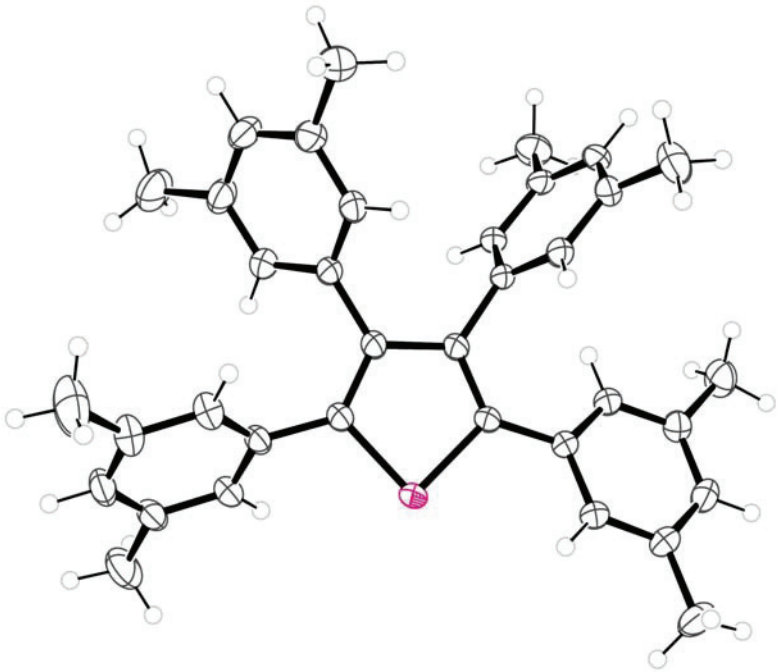


Figure 5. Ortep plot of **24d** (50% probability level)

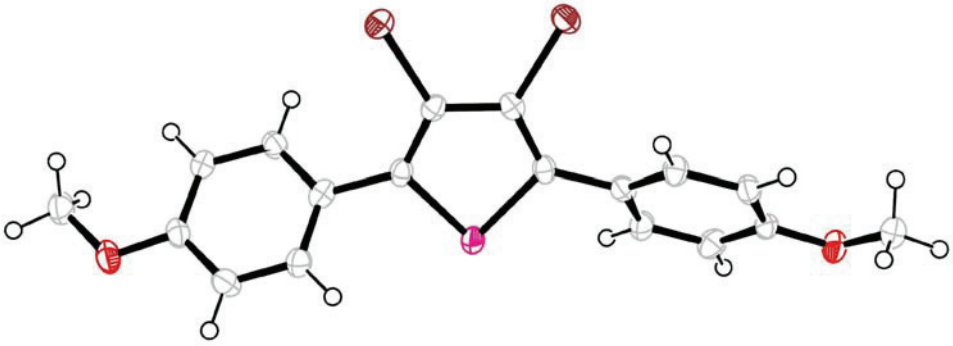
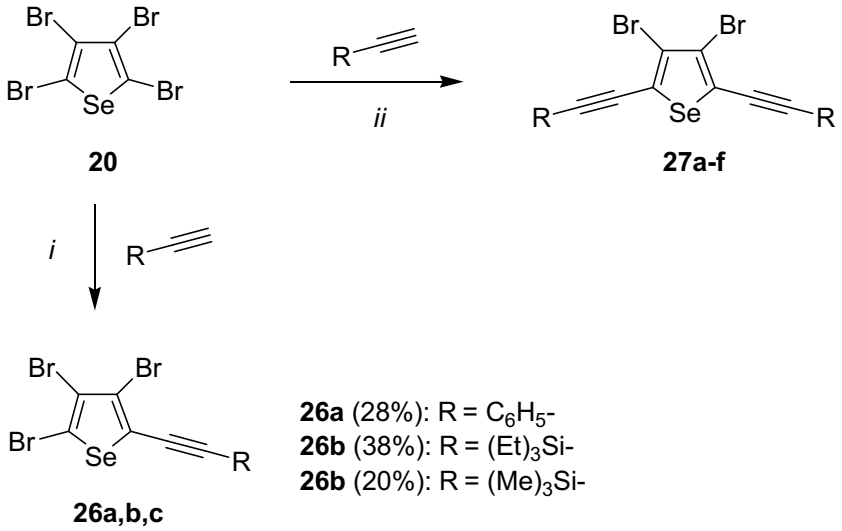


Figure 6. Ortep plot of **23d** (50% probability level)



Scheme 21. Synthesis of **7**; *conditions*: *i*, **20** (1.0 equiv.), alkyne (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), CuI (5 mol-%), iPr_2NH, 100 °C, 12 h; *ii*, **20** (1.0 equiv.), alkyne (2.3 equiv.), $Pd(CH_3CN)_2Cl_2$ (5 mol-%), $P(t\text{-}Bu)_3$ (10 mol-%), CuI (5 mol-%), iPr_2NH, 100 °C, 12 h

Firstly, the Sonogashira coupling of **20** (1.0 equiv.) with alkyne (1.1 equiv.) gave the products **26a,b,c** with low yield when tetrakis was used as catalysts (Scheme 14). The optimization of Sonogashira reaction of **20** was screened by some procedures. The Sonogashira coupling of **20** with 2.3 equiv. phenylacetylene under different kinds of ligand, base, solvent and temperature was shown in table 13. The best yield was obtained when procedure (**d**) was used. The catalytic system (**d**) was applied for synthesis of di(1-alkynyl)selenophene. The results of product **27a-f** were shown in table 14. The di(1-alkynyl)selenophene **27d,f** were obtained with high yield.

The structures of **26a** was independently confirmed by X-ray crystal structure analyses (Figure 7).[74]

Table 13. The screening of some procedures [a]

C_6H_5	Catalysts – 5 mol %	Solvent - base	T°C	%
a	$Pd(Ph_3)_4$	DMF – NEt_3	Room temperature	-
b	$Pd(Ph_3)_4$	Toluene : EtOH – $HN(iPr)_2$	100°C	53
c	$Pd(CH_3CN)_2Cl_2$–$P(t\text{-}Bu)_3$	1,4-Dioxane - $HN(iPr)_2$	Room temperature	86
d	$Pd(CH_3CN)_2Cl_2$–$P(t\text{-}Bu)_3$	1,4-Dioxane - $HN(iPr)_2$	100°C	91
e	$Pd(OAc)_2$	$N(C_2H_5OH)_3$	100°C	66

[a] : CuI 2 mol-% **b**: 4 mL Toluene : EtOH (2:2); **c, d**: ligand $P(t\text{-}Bu)_3$ (10 mol-%), 4 mL 1,4-Dioxane; **e**: 4 mL $N(C_2H_5OH)_3$: acts as ligand, base and solvent.

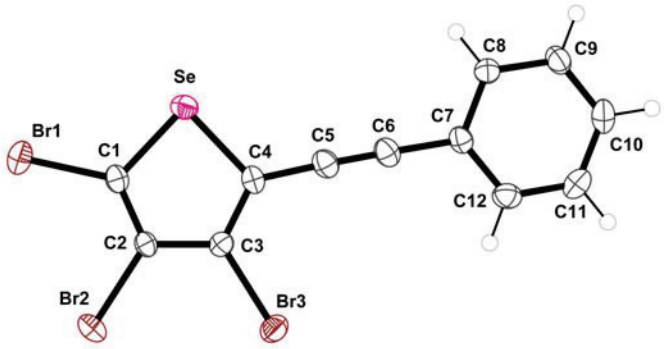


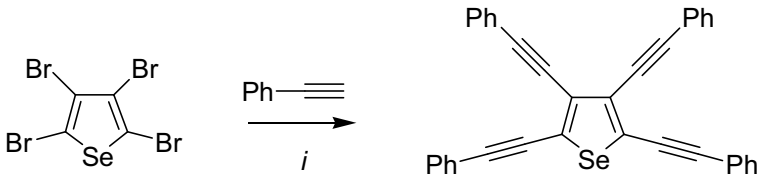
Figure 7. Ortep plot of **26a** (50% probability level)

Table 14. Synthesis of **27a-f**

27	R	% (**27**) [d]
a	p-tolyl	83
b	4-$(MeO)C_6H_4$	40
c	trimethylsiyl	65
d	m-tolyl	98
e	4-FC_6H_4	46
f	C_6H_5	91

[d] : procedure d was employed.

The Sonogashira coupling of **20** with phenylacetylene afforded tetra(1-alkynyl)selenophene 2**8** in 77% yield (Scheme 22). During the optimization, the employment of an excess of alkyne (6.0 equiv.), a relatively high temperature (100 °C) and a long reaction time (14 h) proved to be important. The best results were obtained when $Pd(PPh_3)_4$ (10 mol-%) was used as the catalyst. The use of an excess of CuI allowed to significantly improve the yield compared to the use of only 10 mol-%. Diisopropylamine was used as the solvent. To the best of my knowledge, the synthesis of a tetra(1-alkynyl)selenophene has not been reported to date.



20 **28** (77%)

Scheme 22. Synthesis of **28**; *conditions*: *i*, **20** (1.0 equiv.), PhC≡CH (6.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), CuI (4.0 equiv.), *i*Pr_2NH, 100 °C, 14 h

1.4.3 Conclusion

In conclusion, I have reported a new strategy for the synthesis of 5-aryl-2,3,4-tribromoselenophenes, 2,5-diaryl-3,4-dibromoselenophenes, and tetraarylselenophenes based on regioselective Suzuki reactions of tetrabromoselenophene. The first tetra(1-alkynyl)selenophene was prepared by Sonogashira reaction of tetrabromoselenophene with phenylacetylene.

1.5 Regioselective Palladium(0)-Catalyzed Cross-Coupling Reactions and Metal-Halide Exchange Reactions of Tetrabromothiophene

1.5.1 Introduction

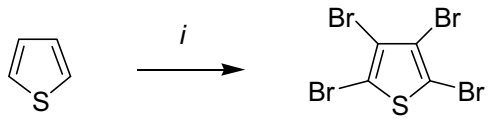
Regioselective functionalizations of polyhalogenated heterocycles play an increasingly important role in organic synthesis.[37] Such reactions rely on the higher reactivity of more electron-deficient carbon atoms while the other reactive positions remain unattacked. This concept has been applied to regioselective palladium(0)-catalyzed cross-coupling reactions based on different rates of oxidative additions of palladium(0) species to different carbon-halide bonds of the substrate. Thiophene-containing compounds constitute an important class of materials which show intrinsic electronic properties such as luminescence, redox activity, nonlinear optical chromism and electron-transport.[75] Thiophenes are also present in pharmacologically relevant natural products. This includes, for example, dibenzothiophenes,[76] [2,2';5',2'']terthiophenes,[77] and thienyl-diynes.[78]

2,3-Dibromothiophene has been functionalized by regioselective Sonogashira coupling of carbon atom C-2.[79] A very good C-2 regioselectivity was observed also for the Kumada cross coupling of 2,3- and 2,4-dibromothiophene.[80] 2,5-Disubstituted thiophenes were prepared by regioselective Sonogashira coupling reactions of tetraiodothiophene[81] and tetrabromothiophene.[82] Recently, I reported the synthesis of *symmetrical* 2,3,4,5-tetraaryl- and 2,5-diaryl-3,4-dibromothiophenes by regioselective Suzuki reactions of tetrabromothiophene.[38] In my initial study, 'classical' conditions (use of 10-20 mol-% of $Pd(PPh_3)_4$) were employed. Although these conditions gave excellent yields in a number of cases, several other reactions failed or proceeded sluggishly in only moderate or low yields. Herein, I report that the yields could be significantly improved by application of a new biaryl monophosphine ligand developed by Buchwald and coworkers. With respect to my preliminary studies, I herein report for the first time the selective synthesis of 5-aryl-2,3,4-tribromothiophenes and their transformation into *unsymmetrical* 2,5-diaryl-3,4-dibromothiophenes. These reactions were not possible at all under classical conditions. In addition, I report regioselective metal-halide exchange reactions of tetrabromothiophene. Although a few isolated examples of such reactions have been previously reported,[83] I studied the preparative scope and synthetic applications. For example, the combination of metal-halide exchange reactions with Suzuki reactions provides a new and convenient strategy for

the synthesis of ningaline A analogues and related target molecules. In addition, I report for the first time a one-pot protocol for the sequential reaction of tetrabromothiophene with two different electrophiles.

1.5.2 Results and Discussion

Tetrabromothiophene (**30**) was prepared by bromination of thiophene (following a modified literature procedure) (Scheme 23).[84] During the optimization, it proved to be important to dropwise add an excess of bromine (dissolved in chloroform) to a chloroform solution of thiophene at 0 °C. A saturated aqueous solution of NaOH was added and the mixture was stirred under reflux for 6 h. The product was recrystallized from a 1:1 solution of chloroform and methanol. The crude product (red to brownish crystals) was washed with cold ethyl acetate for several times to give pure **30** as colourless crystals (87%). Notably, I observed that it is crucial to isolate **30** in analytically pure form as colourless crystals. The oily form is generally slightly impure, tends to be considerably less stable and decomposes within a few days. The presence of impurities results in a failure of Pd(0)-catalyzed cross-coupling reactions. In contrast, the crystalline solid can be stored under argon atmosphere at −18 °C (in the dark) for a few weeks. Then, the compound starts to slightly darken and it cannot be successfully used anymore in Pd(0)-catalyzed reactions.

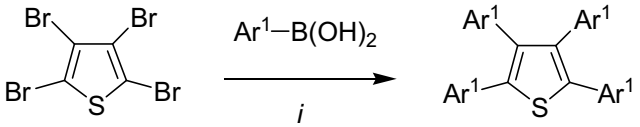


30 (87%)

Scheme 23. Synthesis of tetrabromoselenophene (**30**); *conditions*: *i*, 1) Br_2 (7.0 equiv., slow addition), 0 °C, $CHCl_3$, 2) reflux, 3 h; 3) NaOH, H_2O (2 M), reflux, 6 h

The tetraarylthiophenes **31a-g**, containing four identical aryl groups, were successfully prepared by Suzuki reaction[85] of **30** (1.0 equiv.) with 5.0 equiv. of various boronic acids (Scheme 24, Table 14). All reactions were carried out based on optimization studies of Suzuki reactions carried out in my laboratory.[86] The protocol is defined as 'procedure A' in the present manuscript. Tetrakis(triphenylphoshane)palladium(0) and potassium phosphate were used as catalyst and base, respectively. The stoichiometry of the reagents, the temperature, the solvent, and the presence of water proved to be important parameters. Oxygen-containing boronic acids showed a better solubility in 1,4-dioxane than in toluene. On the other hand, the

higher boiling point of toluene proved to be advantageous in many cases. All reactions were carried out in the presence of water (solvent/water = 4:1) which proved to be very important in order to obtain good yields.[87] While products **31b** and **31d-g** were formed in excellent yields, **31a** and **31c** could be isolated in only moderate yields. The synthesis of tetra(thien-2-yl)thiophene (**31h**) completely failed. Products **31a**, **31c** and **31h** were prepared in good yields by the application of $Pd(OAc)_2$ as the catalyst and the new biaryl monophosphine ligand **L** (Chart 1) developed by Buchwald and coworkers.



30 **31a-h**

Scheme 24. Synthesis of tetraarylthiophenes **31a-h**. Conditions: *i*, procedure A: **17** (1.0 equiv.), $Ar^1B(OH)_2$ (5.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (8.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 1); procedure B: **17** (1.0 equiv.), $Ar^1B(OH)_2$ (6.0 equiv.), $Pd(OAc)_2$ (5 mol-%), L (10 mol-%, see Chart 1), K_3PO_4 (8.0 equiv.), dioxane/toluene (1:1), 100 °C, 8 h

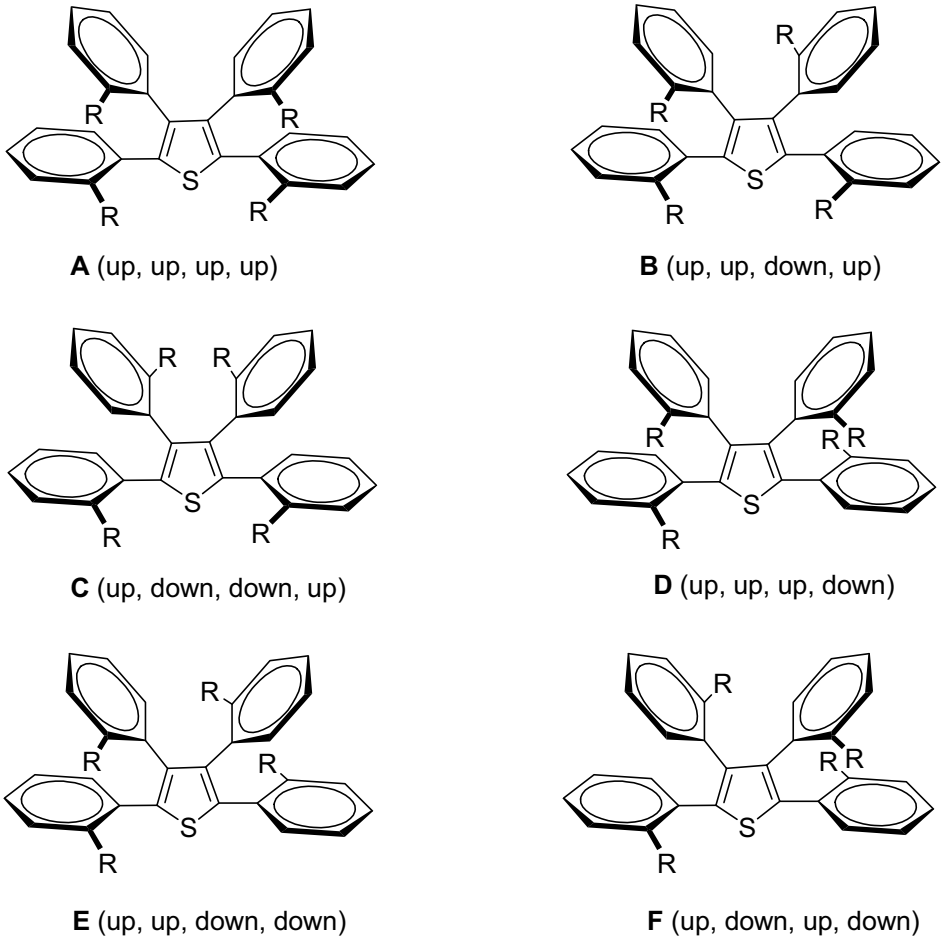
Table 14. Synthesis of 2,3,4,5-tetraarylthiophenes **31a-h**

31	Ar^1	Solvent	% (A) [a]	% (B) [b]
a	Ph	Toluene	37 [c]	70
b	4-(MeO)C_6H_4	1,4-Dioxane	94 [d]	
c	2-(MeO)C_6H_4	1,4-Dioxane	38 [d]	65
d	1-Naphthyl	Toluene	65 [d]	
e	4-MeC_6H_4	Toluene	87 [c]	
f	4-ClC_6H_4	Toluene	89 [d]	
g	4-FC_6H_4	Toluene	93 [d]	
h	2-Thienyl	Toluene	0	81

[a] Isolated yields, procedure A (see Scheme 24); [b] isolated yields, procedure B (see Scheme 24); [c] reaction time: 12 h; [d] reaction time: 24 h

Detailed inspection of the ^1H and ^{13}C NMR spectra and dynamic NMR studies (variable temperature NMR etc.) of tetrakis(2-methoxyphenyl)thiophene (**31c**) show that the rotation of

the aryl-groups is sterically hindered and that two (out of theoretically possible six) rotamers are present at room temperature (Scheme 25). However, the structure of the rotamers could not be unambigiously assigned.



31c (R = OMe)

Scheme 25. Possible rotameric structures of **31c**

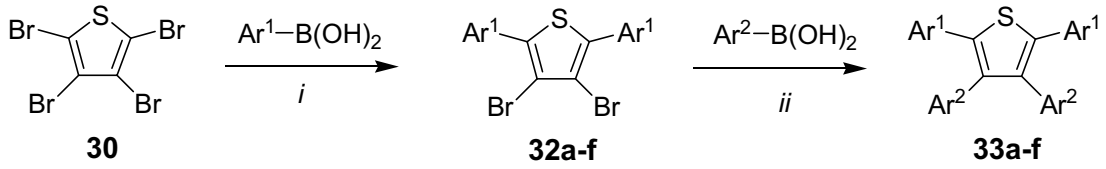
Since it is not possible to assign the rotational isomers of **31c** unambiguously on the basis of both ^{1}H and ^{13}C NMR spectra, I (in collaboration with Dr. H. Jiao, Leibniz-Institute of Catalysis, Rostock) have carried out B3LYP density functional theory calculations to get the energetic order of these six possible isomers (**A**-**F**).[88] At first I have optimized **A**-**F** at the B3LYP/6-31G(d) level and they are found to energy minimums by frequency calculations (without imaginary frequencies). We also have carried out single-point energy calculations at the B3LYP level by using the more flexible 6-311+G(d,p) basis set and the B3LYP/6-31G(d) optimized geometries for energetic comparison. As given in Table 15, isomer **F** is most stable, tightly followed by isomers **D** and **E** within less than 1 kcal/mol (0.72 and 0.83 kcal/mol,

respectively). Isomer **B** is higher in energy by 1.12 kcal/mol, while isomers **A** and **C** are much higher in energy by 3.06 2.42 kcal/mol, respectively. These energetic differences indicate that **F** is the most stable isomer, and also major part of the isomeric mixture; **D** and **E** are minor part of the mixture. Probably isomer **B** will have some trace contribution, but the contribution of isomer **A** and **C** could be ruled out.

Table 15. The computed total electronic energies (E_{tot}, au) and relative energies (ΔE, kcal/mol)

Structure	E_{tot} [a]	E_{tot} [b]	ΔE [b]
A (31c)	–1935,29952	–1935.72280	3.06
B (31c)	–1935,30356	–1935.72589	1.12
C (31c)	–1935,30189	–1935.72382	2.42
D (31c)	–1935,30407	–1935.72654	0.72
E (31c)	–1935,30359	–1935.72635	0.83
F (31c)	–1935,30571	–1935.72768	0.00
G (31b)	–1699.90610	–1700.28558	1.22

[a] B3LYP/6-31G* (full optimization); [b] B3LYP/6-311+G**//B3LYP/6-31G* (single-point energy calculation)



30 **32a-f** **33a-f**

Scheme 26. Synthesis of symmetrical 2,5-diaryl-3,4-dibromothiophenes **32a-f** and of tetraarylthiophenes **33a-f**. *Conditions*: *i*, procedure A: **30** (1.0 equiv.), $Ar^1B(OH)_2$ (2.2 equiv.), $Pd(PPh_3)_4$ (6 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 2); procedure B: **30** (1.0 equiv.), $Ar^1B(OH)_2$ (2.1 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h; *ii*, **32a,b** (1.0 equiv.), $Ar^2B(OH)_2$ (3.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 17)

The reaction of **30** (1.0 equiv.) with 2.2 equiv. of boronic acids allowed the regioselective synthesis of the 2,5-diaryl-3,4-dibromothiophenes **32a-f** (Scheme 26, Table 16). The

application of procedure A ($Pd(PPh_3)_4$) allowed to prepare the products in moderate yields (except for **32b** which was isolated in good yield). The yields of **32a** and **32c-f** were significantly improved by application of method B ($Pd(OAc)_2$, **L**). Products **32a,b** (1.0 equiv.) could be further functionalized by Suzuki-reaction with 3.0 equiv. of various arylboronic acids to give the tetraarylthiophenes **33a-f** which contain two different types of aryl groups (Scheme 26, Table 17). The products were isolated in good yields. During the optimization, the solvent played an important role. For oxygen-containing boronic acids, the use of a mixture of toluene and dioxane proved to be advantageous (vide supra).

Table 16. Synthesis of symmetrical 2,5-diaryl-3,4-dibromo-thiophenes **32a-f**

32	Ar^1	Solvent	% (A) [a]	% (B) [b]
a	Ph	Toluene	32 [c]	88
b	4-MeC_6H_4	Toluene	77 [c]	
c	4-$(MeO)C_6H_4$	1,4-Dioxane	43 [d]	85
d	2-$(MeO)C_6H_4$	1,4-Dioxane	35 [d]	79
e	3,5-$Me_2C_6H_3$	Toluene	54 [d]	91
f	2-Thienyl	Toluene	54 [d]	71

[a] Isolated yields, procedure A (see Scheme 23); [b] isolated yields Isolated yields, procedure B (see Scheme 23); [c] reaction time: 12 h; [d] reaction time: 24 h

Table 17. Synthesis of tetraarylthiophenes **33a-f**

33	Ar^1	Ar^2	Solvent	% (A) [a]
a	Ph	4-MeC_6H_4	Toluene	86 [b]
b	4-MeC_6H_4	Ph	Toluene	51 [b]
c	4-MeC_6H_4	4-$(MeO)C_6H_4$	Dioxane/Toluene (1:1)	76 [c]
d	4-MeC_6H_4	4-$(EtO)C_6H_4$	Dioxane/Toluene (1:1)	93 [c]
e	4-MeC_6H_4	4-$(HO)C_6H_4$	Dioxane/Toluene (1:1)	82 [c]
f	4-MeC_6H_4	4-ClC_6H_4	Toluene	91 [c]

[a] Isolated yields; [b] reaction time: 12 h; [c] reaction time: 24 h

The structures of all products were established by spectroscopic methods. The structure of **32b** was independently confirmed by an X-ray crystal structure analysis (Figure 8).[89]

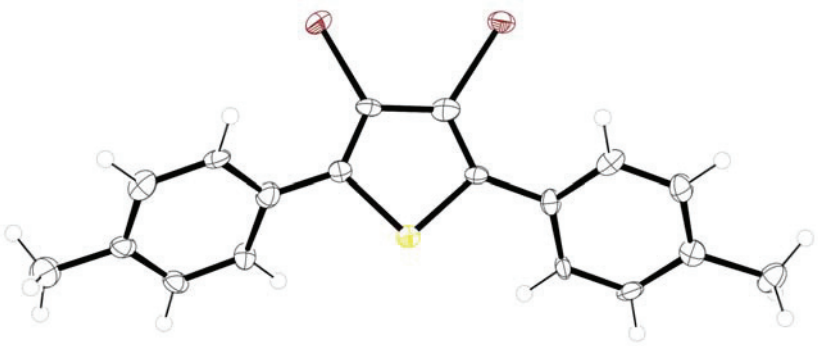


Figure 8. Ortep plot of **32b** (50% probability level)

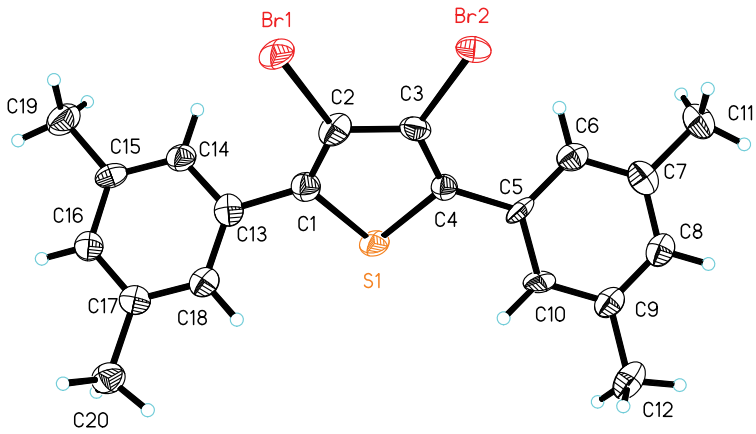
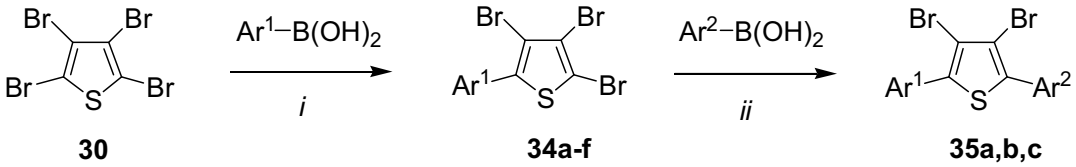


Figure 9. Ortep plot of **32e** (50% probability level)

The Suzuki reaction of **30** with various boronic acids (1.1 equiv.) afforded the 5-aryl-2,3,4-tribromothiophenes **34a-f** in good yields and with very good regioselectivity (Scheme 27, Table 18). The reactions were carried out by application of procedure B ($Pd(OAc)_2$, **L**). The application of method A proved to be unsuccessful. During the optimization, it was important to suppress the formation of 2,5-diaryl-3,4-dibromothiophenes, as their separation from the desired products proved to be difficult. The structure of **34f** was independently confirmed by an X-ray crystal structure analysis (Figure 9).[74] The reaction of **34b** with 1.2 equiv. of arylboronic acids, following again procedure B, resulted in regioselective formation of the unsymmetrical 2,5-diaryl-3,4-dibromothiophenes **35a-c** (Scheme 27).



35a (Ar^1 = 4-(MeO)C_6H_4, Ar^2 = 4-EtC_6H_4): 72%
35b (Ar^1 = 4-(MeO)C_6H_4, Ar^2 = 3,5-$Me_2C_6H_3$): 67%
35c (Ar^1 = 4-(MeO)C_6H_4, Ar^2 = 3-PhC_6H_4): 69%

Scheme 27. Synthesis of 5-aryl-2,3,4-tribromothiophenes **34a-f** and of unsymmetrical 2,5-diaryl-3,4-dibromothiophenes **35a-c**; *conditions*: *i*, **30** (1.0 equiv.), $Ar^1B(OH)_2$ (1.2 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h; *ii*, **34b** (1.0 equiv.), $Ar^2B(OH)_2$ (1.2 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane/toluene (1:1), reflux, 8 h

Table 18. Products and yields

34	Ar^1	% (**5**) [a]
a	2-(MeO)C_6H_4	75
b	4-(MeO)C_6H_4	80
c	3-PhC_6H_4	77
d	2-Naph	69
e	4-EtC_6H_4	87
f	Ph	61 [b]

[a] Isolated yields (procedure B)

[b] Isolated yields (procedure A)

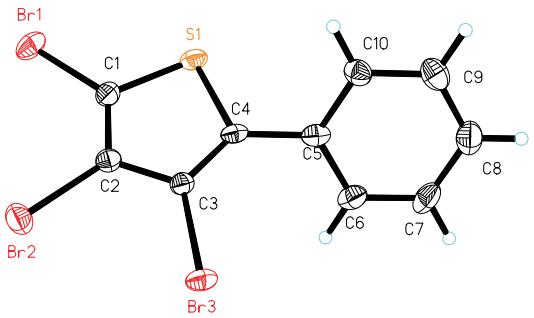
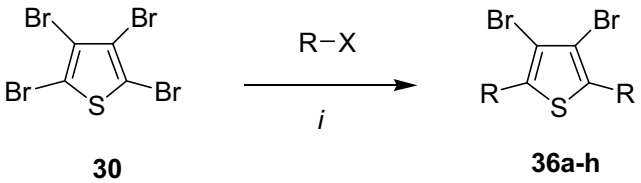


Figure 10. Ortep plot of **34f** (50% probability level)

The addition of *n*-butyllithium (2.5 equiv.) to a THF solution of tetrabromothiophene (**30**) (1.0 equiv.) and subsequent addition of alkyl halides (3.0 equiv.) afforded the 2,5-dialkyl-3,4-dibromothiophenes **36a-d** (Scheme 28, Table 19). This approach is preparatively useful, since the Suzuki reaction of tetrabromothiophene with alkylboronic acids failed. All attempts to prepare 3,4-dibromo-2,5-dihexylthiophene from **30** under Suzuki conditions using a variety of different ligands (e. g., dppf, $P(tBu)_3$, PPh_3, BINAP) failed. 3,4-Dibromo-2,5-bis(trimethylsilyl)thiophene (**36e**) was prepared in good yield from **30** and trimethylchlorosilane. The reaction of dilithiated **30** with dimethyl disulfide afforded thiophene **36f**. Thiophenes **36g** and **36h** were prepared by reaction of dilithiated **30** with methyl chloroformate and benzoyl chloride, respectively. During the optimization of the reactions, the stoichiometry (excess of base and electrophile) played an important role. The structure of the products was established by spectroscopic methods. The structure of **36g** was independently confirmed by an X-ray crystal structure analysis (Figure 11).[74]



Scheme 28. Synthesis of symmetrical 3,4-dibromothiophenes **36a-h**. Conditions: *i*, 1) *n*BuLi (2.5 equiv.), −78 °C, 1 h; 2) RX (3.0 equiv.), −78 → 20 °C, 16 h

Table 19. Synthesis of symmetrical 3,4-dibromothiophenes **36a-h**

36	R	X	% [a]
a	Me	Br	56
b	nBu	I	94
c	isoPent	Br	77
d	nDodec	Br	89
e	$SiMe_3$	Cl	82
f	SMe	SMe	55
g	CO_2Me	Cl	52
h	COPh	Cl	68

[a] Isolated yields

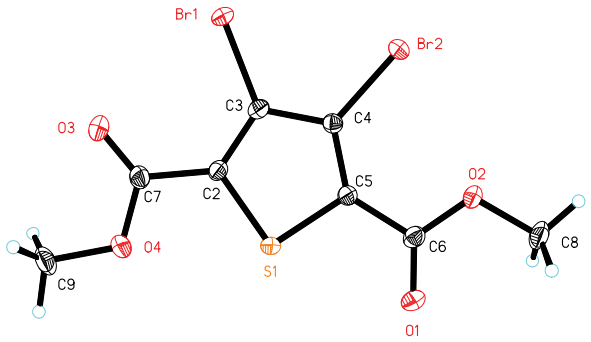
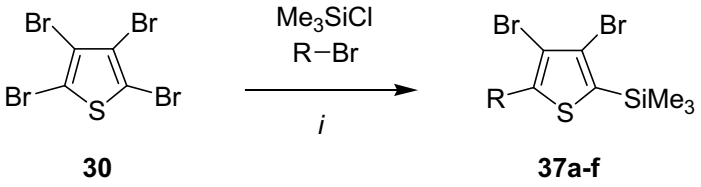


Figure 11. Ortep plot of **36g**

The addition of *n*-butyllithium (2.5 equiv.) to a THF solution of tetrabromothiophene (**30**) (1.0 equiv.) and subsequent addition of trimethylchlorosilane (1.0 equiv.) and subsequent addition of alkyl bromides (1.2 equiv.) afforded the 5-alkyl-3,4-dibromo-2-trimethylsilylthiophenes **37a-f** in a one-pot protocol (Scheme 29, Table 20). However, the application of this strategy to the synthesis of 2,5-dialkylthiophenes containing two different alkyl groups proved to be successful.[90]



30 **37a-f**

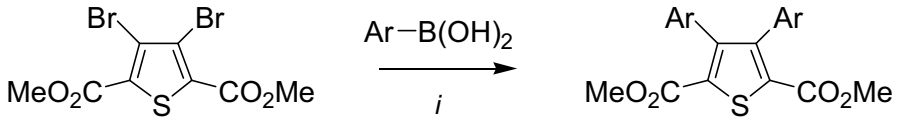
Scheme 29. Synthesis of 5-alkyl-2-trimethylsilyl-3,4-dibromothiophenes **37a-f**. Conditions: *i*, 1) **30** (1.0 equiv.), *n*BuLi (2.5 equiv.), TMEDA (2.5 equiv.), −78 °C, 30 min; 2) Me_3SiCl (1.0 equiv., addition during 3 h), 30 min, −78 °C; 4) RBr (1.2 equiv.), −78 °C, 4 h

Table 20. Synthesis of unsymmetrical 3,4-dibromothiophenes **37a-f**

37	R	% [a]
a	Et	65
b	nBu	61
c	iPent	60
d	nHex	60
e	nHept	55
f	nUndec	51

[a] Isolated yields

The double Suzuki reaction of diester **36g** with arylboronic acids afforded the 3,4-diarylthiophenes **38a-d** (Scheme 30, Table 21). Products **38a-c** were prepared by application of procedure A. The best results were obtained, similar to the experiments outlined above, when dioxane was used for boronic acids containing oxygen (products **38b,c**). The yield of 9b was much improved by application of protocol B. Likewise, product **9d** was prepared in good yield by application of protocol B.



36g **38a-d**

Scheme 30. Synthesis of 3,4-diarylthiophenes **38a-d**. Conditions: *i*: Procedure A: **36g** (1.0 equiv.), $ArB(OH)_2$ (3.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 19). Procedure B: **7g** (1.0 equiv.), $ArB(OH)_2$ (2.5 equiv.), $Pd(OAc)_2$ (5 mol-%), **L** (see Chart 1, 10 mol-%), K_3PO_4 (4.0 equiv.), dioxane, reflux, 8 h

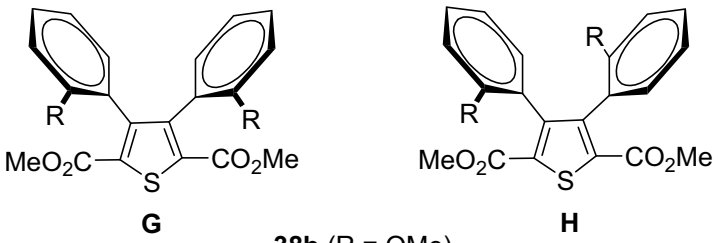
Table 21. Synthesis of 3,4-diarylthiophenes **38a-d**

38	Ar	% (A) [a]	% (B) [b]
a	4-ClC_6H_4	42 [c]	
b	2-(MeO)C_6H_4	45 [d]	85 [c]
c	2-(HO)C_6H_4	49 [d]	
d	4-(HO)C_6H_4		71 [e]

[a] Isolated yields (procedure A); [b] isolated yields (procedure B); [c] solvent: toluene; [d] solvent: toluene / dioxane = 1:1; [e] solvent: dioxane

Detailed inspection of the ^1H and ^{13}C NMR spectra and dynamic NMR studies (variable temperature NMR etc.) for 3,4-di(2-methoxyphenyl)thiophene **38b** show that two atropisomers are present at room temperature, due to the hindered rotation of the aryl groups (Scheme 31). In contrast, only one set of signals is observed for 3,4-di(2-hydroxyphenyl)thiophene **38c**. This might be explained by the higher rotation barrier in case

of the methoxy derivative **38b** (and fast equilibration for **38c** at 20 °C) or, alternatively, by the selective formation of one atropisomer in case of **38c**.



Scheme 31. Possible rotameric structures of **38b,c**

In addition I have also computed the relative energies of the two isomers (**G** and **H**) for **38b** (R = OMe) and **38c** (R = OH). At the same level of theory for **38b**, isomer **H** is more stable than isomer **G** by 1.22 kcal/mol. Therefore, **38b** is a mixture of isomers with **H** as the major isomer and **G** as the minor isomer, and this is in agreement with the experimental observation. For **38c** (R = OH), the situation becomes somewhat more complicated due to the possibility of the formation of hydrogen bonding interaction between the O–H group at the phenyl ring and the carboxylic C=O group. For isomer **G** with two O–H groups at the same side of the thiophene ring, there are three possible structures; one (**G-1**) does not have hydrogen bonding interaction (with O–H group in the phenyl ring plane); and the second one (**G-2**) has one set of hydrogen bonding interaction and the B3LYP/6-31G(d) optimized O–H···O=C distance is 1.791 Å; and the third one (**G-3**) has two sets of hydrogen bonding interaction with the O–H···O=C distance of 1.885 Å. For isomer **H**, due to the appropriate orientation of the O–H group at the phenyl ring and the carboxylic C=O group it is possible to form two sets of hydrogen bonding interaction, and the B3LYP/6-31G(d) optimized O–H···O=C distance is 1.803 Å. As given in Table 22, isomer **H** is most stable, and isomers **G-a**; **G-b** and **G-c** are higher in energy by 5.35, 2.99, and 4.88 kcal/mol kcal/mol, respectively. The large energy difference between **H** and **G** identifies **H** as the only one isomer in the solution (>99%); and this is also in agreement with the experimental finding. Compared this result with that for **38b**, it is interesting to know the driving force for this enhanced stability for isomer **H** over isomer **G** of **38c**. Apart from the hydrogen bonding interaction, the appropriate conrotatory orientation of the phenyl groups in isomer **H** reduces their repulsive interaction and strengths at the same time the hydrogen bonding interaction. Although both **G-b** and **G-c** also have hydrogen bonding interaction, the disrotatory orientation of the phenyl groups will increase

the repulsive interaction with the increased hydrogen bonding interaction. Consequently, isomer **H** is considerably more stable than isomer **G** for **38c**. This explains perfectly the findings from the ^{1}H and ^{13}C NMR spectra. In case of of **38c**, only one atropisomer, namely **H**, is selectively formed. In case of of **38b**, both atropisomers are formed and are detetced (slow equilibrium at 20 °C on the NMR time scale).

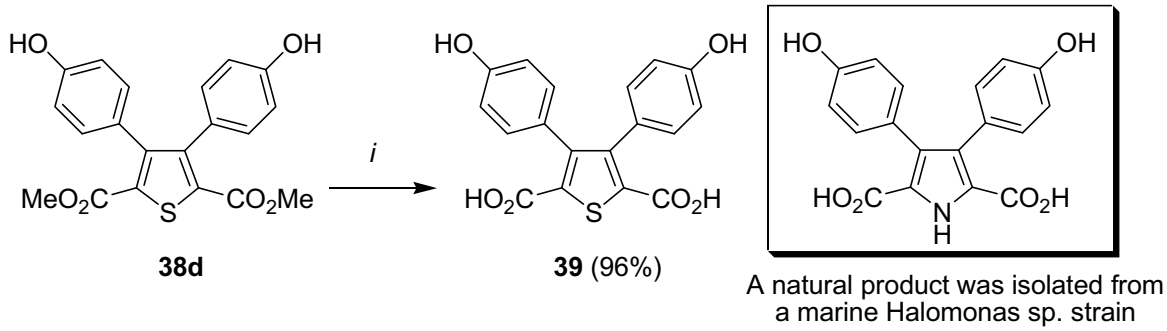
Table 22. The computed total electronic energies (E_{tot}, au) and relative energies (ΔE, kcal/mol)

Structure	E_{tot}[a]	E_{tot}[b]	ΔE[b]
G (38b)	–1699.90610	–1700.28558	1.22
H (38b)	–1699.90772	–1700.28753	0.00
G-1 (38c)	–1621.29328	–1621.66814	5.35
G-2 (38c)	–1621.29880	–1621.67191	2.99
G-3 (38c)	–1621.29659	–1621.66889	4.88
H (38c)	–1621.30484	–1621.67667	0.00

a) B3LYP/6-31G* (full optimization)

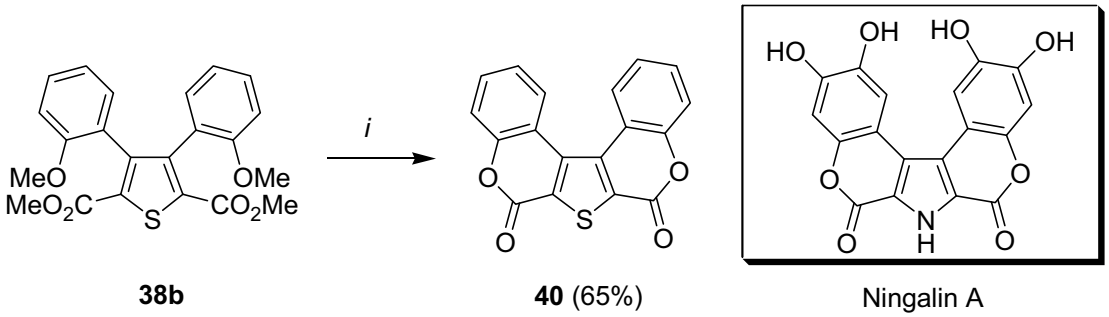
b) B3LYP/6-311+G**//B3LYP/6-31G* (single-point energy calculation)

Recently, 3,4-bis(4′-hydroxyphenyl)pyrrole-2,5-dicarboxylic acid was isolated from a new marine Halomonas sp. strain.[91] This compound shows potent anti-tumor-promoting activities. The sulfur analogue **39** of this natural product was prepared by base-mediated hydrolysis of **38d** (Scheme 32).



Scheme 32. Synthesis of **39**. Conditions: *i*: aq. KOH (30%), EtOH, reflux, 2.5 h

Recently, the natural product ningaline A, a pyrrole-based bis-lactone, was isolated.[92] This compound also exhibits a strong anti-proliferatuve activity. The sulfur analogue **40** of ningaline A was prepared by treatment of **38b** with BBr_3 and subsequent addition of potassium tert-butanolate (Scheme 33).



38b **40** (65%) Ningalin A

Scheme 33. Synthesis of **40**. Conditions: *i*: 1) BBr_3 (8.0 equiv.), CH_2Cl_2, 20 °C, 4 d; 2) KO*t*Bu, H_2O

1.5.3 Conclusion

In conclusion, I have reported Suzuki reactions of tetrabromothiophene with arylboronic acids which provide a regioselective approach to various 5-aryl-2,3,4-tribromothiophenes, symmetrical 2,5-diaryl-3,4-dibromothiophenes, and tetraarylthiophenes. Unsymmetrical 2,5-diaryl-3,4-dibromothiophenes are prepared by Suzuki reaction of 5-aryl-2,3,4-tribromothiophenes. Tetraarylthiophenes containing two different types of aryl groups are obtained by Suzuki reactions of 2,5-diaryl-3,4-dibromothiophenes. During the optimization of the reaction conditions, the solvent and the catalyst played an important role. In several cases, classical conditions ($Pd(PPh_3)_4$) gave excellent yields. The yields of those transformations which completely failed or proceeded sluggishly could be significantly improved by application of a new biaryl monophosphine ligand developed by Buchwald and coworkers. Regioselective metal-halide-exchange reactions of tetrabromothiophene provide a convenient approach to 2,5-dialkyl-3,4-dibromothiophenes. 2-Trimethylsilyl-5-alkyl-3,4-dibromothiophenes could be prepared in a one-pot protocol by sequential addition of trimethylchlorosilane and alkyl bromides. The reaction of tetrabromothiophene with methyl chloroformiate and subsequent Suzuki reactions afforded 3,4-diaryl-2,5-bis(methoxycarbonyl)thiophenes. Based on this strategy, sulphur-analogues of the natural products ningaline A and 3,4-bis(4′-hydroxyphenyl)pyrrole-2,5-dicarboxylic acid were prepared.

Part 2 Synthesis of N,O-Heterocycles based on Cyclocondensation Reactions of Hydrazone and Oxime Dianions

Introduction

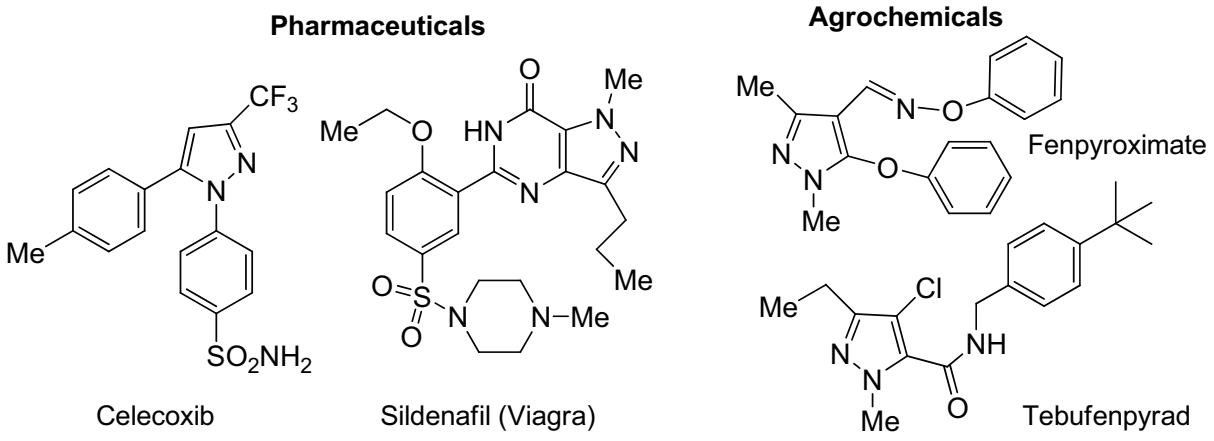
Besides catalysis, the development of new synthetic strategies and building blocks represents an important challenge in organic chemistry.[93,94] The development of new cyclization reactions of dianions and dianion equivalents, which lead to biologically relevant ring systems, is a current field of research in the group of Prof. Langer. In his review about dianion chemistry,[95] Prof. Langer defined dianions more specifically as species that (a) posses a lithium, sodium, potassium or magnesium counterion and (b) undergo at least one carbon-carbon bond formation in their reaction with electrophiles. The generation of dianions often requires the use of a strong base, such as lithium diisopropylamide (LDA) or butyllithium (*n*BuLi). Dianions can be generated by deprotonation, reduction or metal-haldide exchange.[95,96]

The work outlined in the second part of this thesis is a contribution to the chemistry of 1,4-*C,N*-dianions. The reactions developed allow a facile synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by cylization of hydrazone dianions with diethyl oxalate (chapter 6). In addition, a regioselective synthesis of 6-halomethyl-5,6-dihydro-4*H*-1,2-oxazines based on cyclizations of arylalkenyl-oximes is reported (chapter 7).

1.6 Synthesis of Pyrazole-3-carboxylates and Pyrazole-1,5-Dicarboxylates by One-Pot Cyclization of Hydrazone Dianions with Diethyl Oxalate

1.6.1 Introduction

Pyrazole-5-carboxylic acid derivatives represent important building blocks in organic and medicinal chemistry. In addition, they are of interest in their own right, due to their pharmacological properties. For example, pyrazole-5-carboxylic acids and pyrazolo[1,5-*c*]quinazoline-2-carboxylates are nicotinic acid receptor agonists[97] and excitatory amino acid antagonists, respectively.[98] It was shown that related bis(benzo[*g*]indazole-3-carboxamides) exhibit antiproliferative activity against various cancer cell lines.[99] Ethyl 5-propyl-1*H*-pyrazole-3-carboxylate is a key intermediate for the synthesis of viagra.[100] Celecoxib is the first-to-market drug of a number of selective cyclo-oxygenase 2 (COX-2) inhibitors which are promising anti-inflammatory and analgetic agents (without the undesirable side effects associated with other non-steroidal anti-inflammatories).[101] Recently, Nicolaou *et al.*[102] reported that a pyrazole-substituted epothilone derivative shows a strong antitumor activity through the stabilization of microtubules by binding with tubulin. In fact, it is considered to be the most potent epothilone derivative reported to date. The pyrazole moiety is also present in many agrochemically important compounds, such as Fenpyroximate, Tebufenpyrad, Tolfenpyrad, etc (Scheme 34).[103]



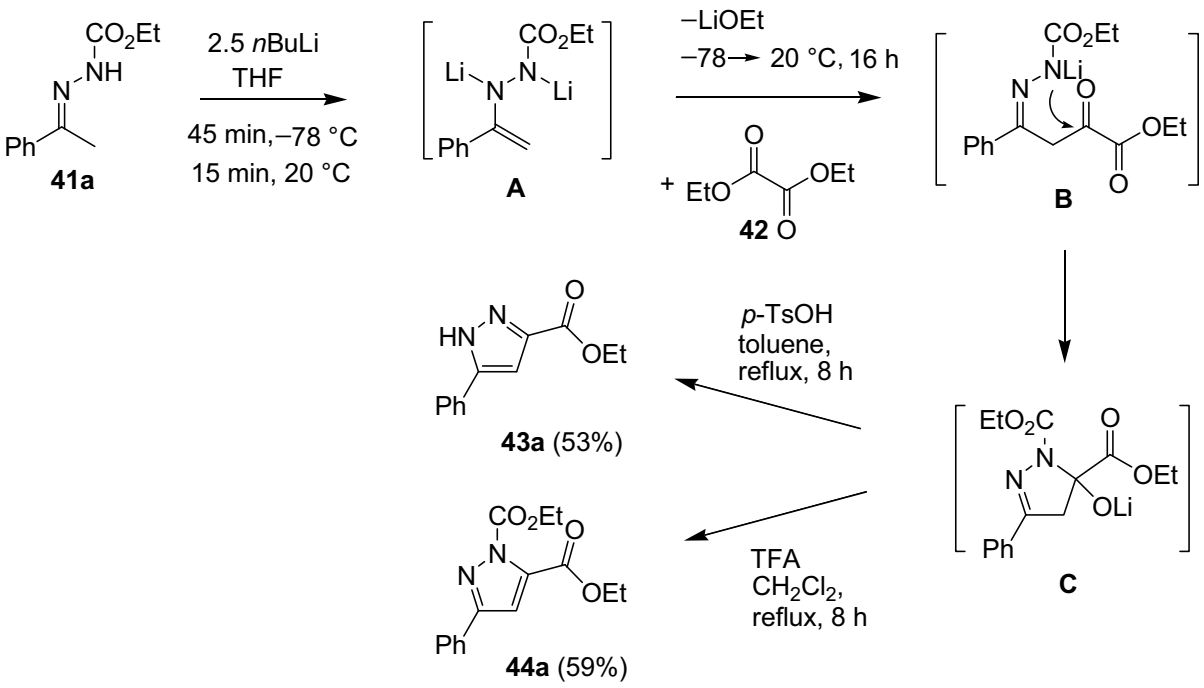
Scheme 34: some natural products containing pyrazole moieties.

Pyrazoles are available by 1,3-dipolar cycloaddition reactions of diazoalkanes with alkynes and related transformations.[104] Other syntheses rely on cyclizations of 1,3-diketones with

hydrazine[105] and on Michael reactions of hydrazines with α,β-unsaturated ketones.[106] An interesting approach to pyrazoles relies on the cyclization[107] of hydrazone dianions, generated by means of *n*BuLi, with esters,[108] acid chlorides[109] and nitriles.[110] Pyrazolines were prepared by cyclization of dilithiated hydrazones with α-haloketones.[111] Recently, the synthesis of pyrazole-3-carboxylates by reaction of hydrazines with propiolates and Weinreb amides was reported.[112] Ranatunge reported[113] the synthesis of 3-aryl-pyrazole-5-carboxylates based on the condensation of hydrazines with 4-aryl-2,4-dioxoesters. The products were transformed into nitrate-substituted oximes which represent potent and selective COX-1 and COX-2 inhibitors. We reported the cyclization of oxime and hydrazone dianions with epibromohydrin to give 1,2-oxazines and oxazolo[3,4-*b*]pyridazin-7-ones, respectively.[114] We also reported the cyclization of oxime dianions with diethyl oxalate which provides a convenient access to isoxazole-5-carboxylates.[115] Recently, I reported a new and convenient approach to pyrazole-3-carboxylates by one-pot cyclizations of hydrazone dianions with diethyl oxalate.[116] Herein, I report full details of these studies. In addition to my preliminary communication,[74] I also report the synthesis of pyrazole-1,5-dicarboxylates (protected pyrazole-5-carboxylates) from the same starting materials.

1.6.2 Results and Discussion

The reaction of a THF solution of diethyl oxalate (**42**) with the dianion of acetophenone hydrazone **41a**, generated by *n*-butyllithium (2.5 equiv.), and subsequent reflux of a toluene solution of the crude product in the presence of *p*-toluenesulfonic acid (PTSA) afforded pyrazole-3-carboxylate **43a** in up to 53% yield (Scheme 35). The best results were obtained when the reaction mixture was allowed to slowly warm from −78 to 20 °C. The solvent was removed *in vacuo* without aqueous work-up and a toluene solution of the residue was simply refluxed in the presence of PTSA for 8 h. Notably, the use of oxalyl chloride or ethyl oxalyl chloride resulted in polymerization. The use of a hydrazone containing a tosyl protective group was not successful (formation of complex mixtures).

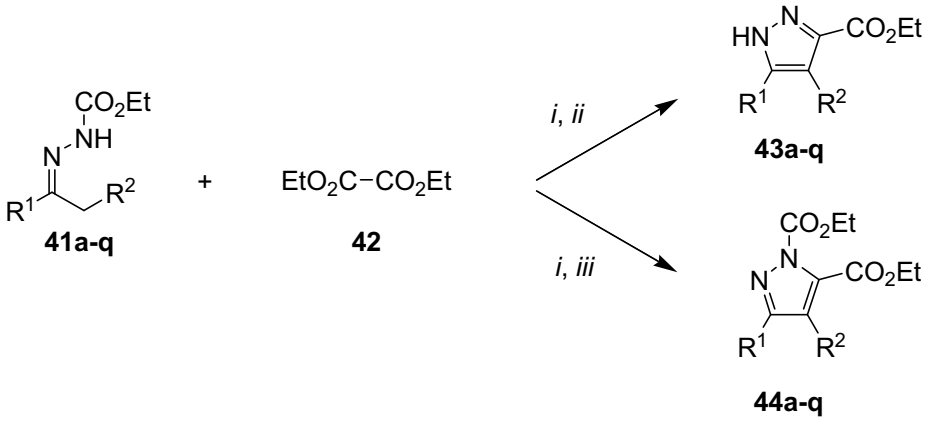


Scheme 35. Mechanism of the formation of pyrazole-5-carboxylate **43a** and of pyrazole-1,5-dicarboxylate **44a**

The formation of **43a** can be explained by attack of the carbon atom of the dianion **A** onto the ester group (intermediate **B**), subsequent cyclization by attack of the nitrogen atom onto the keto group (intermediate **C**), aromatization upon addition of the acid, and subsequent acid-mediated decarboxylation. Notably, reflux of a CH_2Cl_2 solution of the crude product in the presence of trifluoroacetic acid (TFA) afforded the pyrazole-1,5-dicarboxylate **44a** in up to 59% yield. Noteworthy, both protected and non-protected pyrazole-carboxylates can be prepared from the same starting materials. The results can be explained by the higher acidity of PTSA compared to TFA.

The cyclization of the dianions of hydrazones **41a-j** with diethyl oxalate and subsequent dehydration with PTSA afforded the aryl-substituted pyrazole-5-carboxylates **43a-j** (Table 23). Likewise, pyrazole-1,5-dicarboxylates **44a-j** were obtained when TFA was employed. The cyclization of diethyl oxalate with the dilithiated hydrazone of *p*-nitroacetophenone was unsuccessful. The cyclization of diethyl oxalate with the dianions of hydrazones **41k** and **41l**, prepared from 3-methylbutane-2-one and pentane-2-one, afforded the alkyl-substituted pyrazole-5-carboxylates **43k** and **43l** and pyrazole-1,5-dicarboxylates **44k** and **44l** in good yields, respectively. Pyrazoles **43m** and **44m**, containing a phenyl and a methyl substituent, were prepared based on the cyclization of diethyl oxalate with propiophenone-derived

hydrazone **41m**. The structure of **43b** was independently confirmed by crystal structure analysis.[117] The cyclization of diethyl oxalate with the dianions of tetralone hydrazone **41n** and of cycloalkanone-derived hydrazones **41p-r** afforded, after dehydration with PTSA, the pyrazole-5-carboxylates **43n-r**. The pyrazole-1,5-dicarboxylates **44n-r** were isolated when the dehydration was carried out using TFA. The yields of pyrazole-1,5-dicarboxylates **44** were in most cases slightly better than those of pyrazole-5-carboxylates **43**.



Scheme 36. Synthesis of pyrazole-5-carboxylates **43a-q** and pyrazole-1,5-dicarboxylates **44a-q**. *i*: 1) *n*BuLi (2.5 equiv.), THF, 45 min, −78 °C, 2) 15 min, 20 °C, 3) **42**, −78 → 20 °C, 16 h, 4) removal of THF; *ii*: *p*-TsOH (4.0 equiv.), toluene, reflux, 8 h; *iii*: TFA, CH_2Cl_2, reflux 8 h.

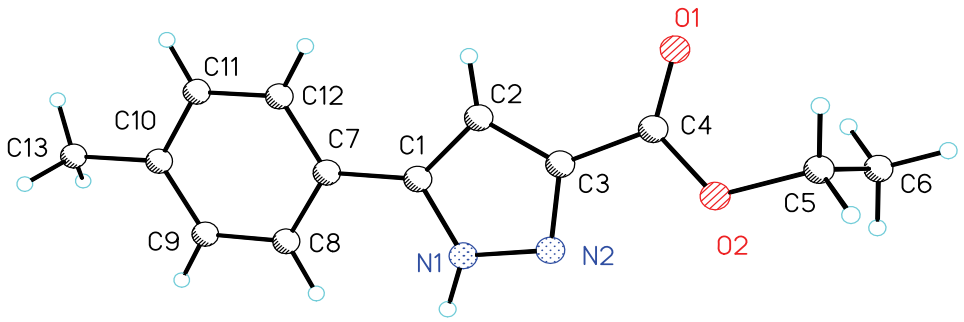


Figure 12. Ortep plot of **43b**

The structure of products **43b,i** were independently confirmed by X-ray crystal structure analysis (Figures 12, 13).[74]

Table 23. Synthesis of **43a-q** and **44a-q**

43	R^1	R^2	% (**43**) [a]	% (**44**) [a]
a	C_6H_5	H	53	59
b	4-MeC_6H_4	H	57	61
c	3-MeC_6H_4	H	61	48
d	4-$(MeO)C_6H_4$	H	45	47
e	2-$(MeO)C_6H_4$	H	-	42
f	1-Naphthyl	H	45	-
g	2-Naphthyl	H	38	-
h	4-ClC_6H_4	H	42	54
i	4-FC_6H_4	H	47	41
j	*i*Pr	H	69	72
k	*n*Pr	H	72	70
l	C_6H_5	Me	62	69
m	$C_6H_4(CH_2)_2$		54	49
n	$(CH_2)_4$		43	44
o	$(CH_2)_5$		40	47
p	$(CH_2)_6$		38	42
q	$(CH_2)_{10}$		31	65

[a] Yields of isolated products

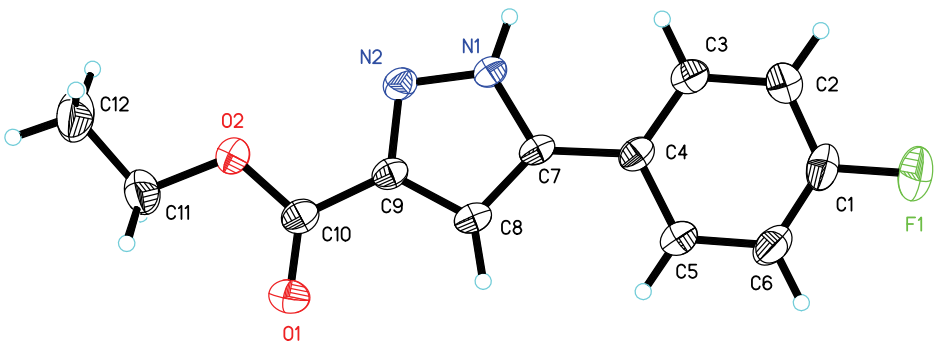


Figure 13. Ortep plot of **43i**

1.6.3 Conclusion

In conclusion, I have reported a convenient and regioselective synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboylates by cyclization of hydrazone dianions with diethyl oxalate.

1.7 Regioselective Synthesis of 6-Halomethyl-5,6-dihydro-4*H*-1,2-oxazines based on Cyclizations of Arylalkenyl-oximes

1.7.1 Introduction

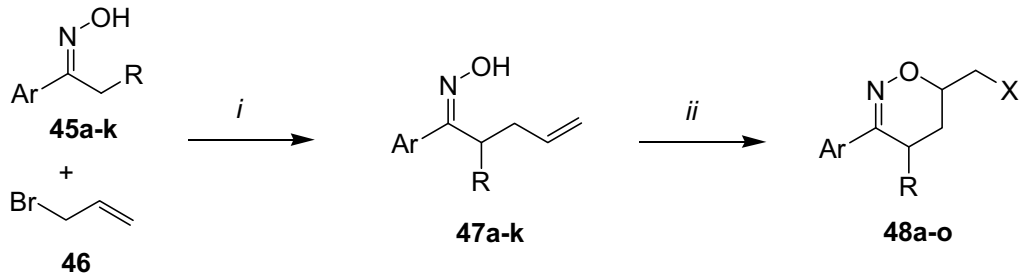
1,2-Oxazines are of pharmacological relevance and represent useful synthetic building blocks. They have been used, for instance, as intermediates during the synthesis of glycosidase inhibitor analogues[118] and of functionalized pyrroles.[119] 1,2-Oxazines have been prepared, for example, by hetero-Diels-Alder reactions of alkenes with ene-nitroso compounds derived from α-haloximes[120] and by hetero-Diels-Alder reactions of dienes with nitroso compounds.[121] 1,2-Oxazines are also available by NBS-,[122] diphenyldiselenide-,[123] acid-,[124] and UV-mediated[125] cyclization of alkenyl-substituted oximes. 1,2-Oxazines have also been prepared by base-mediated cyclizations of γ-chloroximes[9] and γ-sulfonyloximes.[126] Other synthetic approaches to 1,2-oxazines rely on Lewis-acid catalyzed reactions of allenoximes,[127] acid-catalyzed cyclization of cyclopropyloximes,[128] and on cyclizations of γ-nitroketones.[129] Recently, I have reported[130] the synthesis of 1,2-oxazines by cyclization[131] of oxime dianions with epibromohydrin. Herein, I report what are, to the best of my knowledge, the first syntheses of 6-iodomethyl-5,6-dihydro-4*H*-1,2-oxazines by condensation of oxime dianions with allylbromide and subsequent *O*-regioselective iodine-mediated cyclization.

1.7.2 Results and Discussion

The reaction of the dianions of oximes **45a-k**, generated by means of *n*BuLi (2.5 equiv.), afforded the arylalkenyl-oximes **47a-k** in good yields (Scheme 37, Table 24). The reaction of the latter with iodine afforded the 6-iodomethyl-5,6-dihydro-4*H*-1,2-oxazines **48a-k** in moderate to excellent yields. The best yields were obtained when the reaction was carried out in dichloromethane using a saturated aqueous solution of sodium bicarbonate as the base. The reaction of **47e,f,j,k** with *N*-bromosuccinimide (NBS) afforded the 6-bromomethyl-5,6-dihydro-4*H*-1,2-oxazines **48l-o**. The tricyclic oxazine **48p** was prepared in high yield from tetralone (**45p**) (Scheme 38). The structure of all products was established by spectroscopic methods. The structures of **48d**, **48f** and **48j** were independently confirmed by X-ray crystal structure analyses (Figures 14-16).[74] Products **48j,k** and **48n-p** were isolated as 1:1 mixtures of diastereomers. In case of **48j**, one of the two diastereomers could be separated by crystallization (Figure 16).

The regioselectivity of cyclization requires some discussion. Oximes are ambident nucleophiles which can react with electrophiles either at the oxygen or at the nitrogen atom. Grigg and coworkers showed that the regioselectivity is controlled by the *E*/*Z*-configuration of the oxime and by the rate of *E/Z*-isomerization with respect to the *N*- or *O*-nucleophilic attack.[132,133,134] The intramolecular reaction of oximes with halonium ions has been reported to result in *N*-alkylation and formation of nitrones. For example, treatment of a CH_2Cl_2-solution of alkenyl-oxime **49** with iodine and anhydrous potassium carbonate quantitatively afforded nitrone **50** which was trapped by a subsequent [3+2] cycloaddition (Scheme 39).[134] Similar results were obtained for the oxime of ethyl 2-homoallyl-cyclohexanone-2-carboxylate. The *N*-regioselectivity was explained by a rapid *Z*→*E* isomerization and subsequent attack of the nitrogen atom onto the iodonium ion. The reaction of **5** with *N*-bromosuccinimide (NBS) was reported to give a 2:1-mixture of nitrone and 1,2-oxazine which reflects the *E/Z*-ratio of **5**.[122] In this reaction, the *E/Z*-isomerization was slow compared to the *N*- and *O*-cyclization. Similar results have been reported for diphenyl diselenide-mediated cyclizations.[123]

In contrast to **49**, the aryl-substituted oximes **47a-l** contain an *E*-configured C=N group, due to the steric effect of the aryl group.[135] The excellent *O*-regioselectivity of the formation of 1,2-oxazines **48a-p** can be explained by the assumption that the *E*→*Z* isomerization is slow compared to the *O*-regioselective 1,2-oxazine formation.



Scheme 37: Synthesis of 1,2-oxazines **48a-o**. Reagents and conditions: *i*, 1) **45** (1.0 equiv), *n*BuLi (2.5 equiv), THF, 1 h, –78 °C, then 10 min, 20 °C, 2) **2** (2.0 equiv), –78 → 20 °C, 16 h; *ii*, **48a-k**: I_2 (2.0 equiv), CH_2Cl_2, $NaHCO_3$ (sat. aqueous solution), 20 °C, 12 h, **48l-o**: NBS (1.0 equiv), CH_2Cl_2, 20 °C, 2 h

Table 24. Products and yields

45,47	**48**	X	R	Ar	% (**3**) [a]	% (**4**) [a]
a	**a**	I	H	Ph	85	95
b	**b**	I	H	4-MeC_6H_5	69	83
c	**c**	I	H	3-(MeO)C_6H_5	68	66
d	**d**	I	H	4-(MeO)C_6H_5	71	67
e	**e**	I	H	2-(EtO)C_6H_5	64	96
f	**f**	I	H	4-(EtO)C_6H_5	69	61
g	**g**	I	H	4-FC_6H_5	67	81
h	**h**	I	H	4-ClC_6H_5	60	52
i	**i**	I	H	1-Naphthyl	65	66
j	**j**	I	Me	Ph	63	50 [b]
k	**k**	I	Me	4-(MeO)C_6H_5	60	43 [b]
e	**l**	Br	H	2-(EtO)C_6H_5	64	57
f	**m**	Br	H	4-(EtO)C_6H_5	69	87
j	**n**	Br	Me	Ph	63	73 [b]
k	**o**	Br	Me	4-(MeO)C_6H_5	60	25 [b]

[a] Yields of isolated product; [b] dr = 1:1

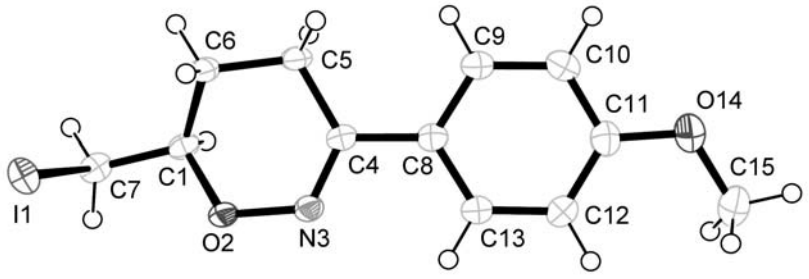


Figure 14. Ortep plot of **48d** (50% probability level)

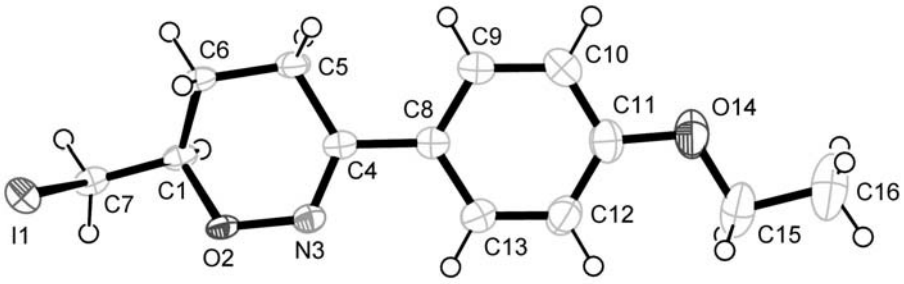


Figure 15. Ortep plot of **48f** (50% probability level)

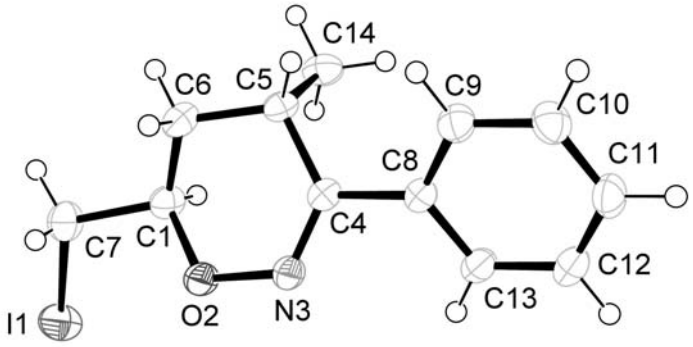
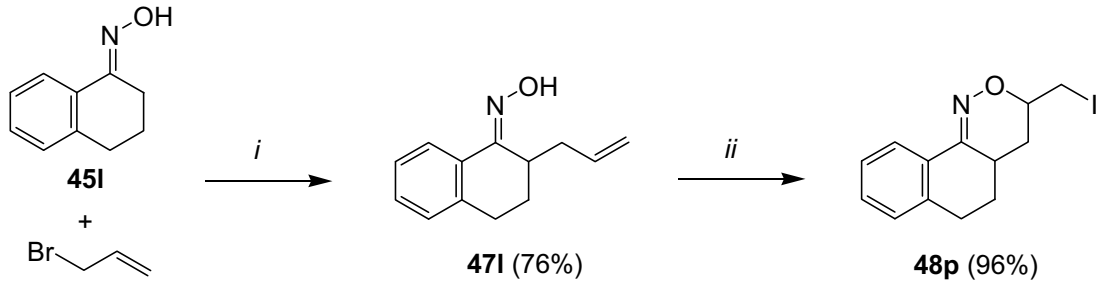
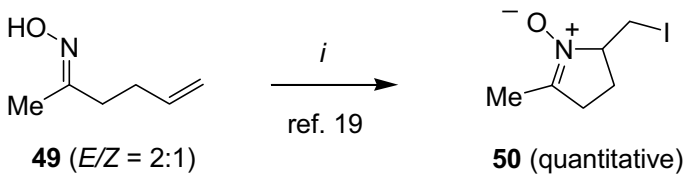


Figure 16. Ortep plot of **48j** (50% probability level)



Scheme 38. Synthesis of 1,2-oxazine **48p**. Reagents and conditions: *i*, 1) **45** (1.0 equiv), *n*BuLi (2.5 equiv), THF, 1 h, −78 °C, then 10 min, 20 °C, 2) **2** (2.0 equiv), −78 → 20 °C, 16 h; *ii*, I_2 (2.0 equiv), CH_2Cl_2, $NaHCO_3$ (sat. aqueous solution), 20 °C, 12 h, dr = 1:1



(**50** was trapped by [3+2] cycloaddition
with *N*-methylmaleimide)

Scheme 39. Synthesis of nitrone **50** by Grigg *et al.* (ref. 133). Reagents and conditions: *i*, I_2 (2.0 equiv), CH_2Cl_2, K_2CO_3 (anhydrous), 25 °C, 12 h

1.7.3 Conclusion

In conclusion, 6-iodo- and 6-bromomethyl-5,6-dihydro-4*H*-1,2-oxazines were prepared by condensation of dilithiated acetophenone-oximes with allylbromide and subsequent regioselective iodine- or NBS-mediated cyclization. The results reported herein show that oxazines are available from alkenyl-oximes containing sterically demanding substituents.

Experimental Section

1.8 Material and Methods

1.8.1 General Remarks

Reactions were carried out under inert atmosphere (Argon 4.6) in order to simultaneously exclude oxygen and water when appropriate. Schlenck techniques were applied. Solvents for reactions were dried and destilled by standard methods or purchased from Merck, Aldrich, Acros Organics, and others whenever exclusion of water was desired. Solvents for liquid chromatography and extraction were always destilled prior to use and partly reused after fractionating destillation (*n*-heptane, ethyl acetate).

1.8.2 Methods for Compound Characterization and Analysis

NMR Spectroscopy

Bruker AC 250, Bruker ARX 300, Bruker ARX 500, Bruker Avance 600. For NMR characterization the one-dimensional ^{1}H NMR, proton-decoupled ^{13}C NMR, and DEPT 135 spectra were collected. If necessary, other techniques (APT, NOESY, COSY, 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 ($\delta = 0.00$) or residual $CHCl_3$ ($\delta = 7.26$) were taken as internal standard. When these reference peaks were superimposed by signals belonging to the compound under investigation a small amount of CH_2Cl_2 ($\delta = 5.30$) was added and taken as reference instead.

References (^{13}C NMR): TMS ($\delta = 0.0$) or residual $CHCl_3$ ($\delta = 77.0$) were taken as internal standard.

Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad signal. More complex coupling patterns are represented by combinations of the respective symbols. For example, td indicates a triplet of doublets with the larger coupling constant associated with the first symbol (here: triplet).

Infrared Spectroscopy (IR)

Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR. Peaks are given the following assignments: w = weak, m = medium, s = strong, br = broad.

Mass Spektrometry (MS)

AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV).

High Resolution Mass Spectrometry (HRMS)

Varian MAT 311, Intecta AMD 402.

Elemental Analysis

LECO CHNS-932, Thermoquest Flash EA 1112.

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.

Rotation Angles

LμP (IBZ Meßtechnik, Na^D = 589 nm).

X-ray Structures

Bruker X8Apex diffractometer with CCD camera (Mo K_α radiation and graphite monochromator, λ = 0.71073 Å). The space group is determined by the XPREP program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method.

1.8.3 Chromatographic Methods

Thin Layer Chromatography (TLC)

Merck Kieselgel 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 acid, 5/100 sulphuric acid, 83-84/100 methanol.

Column Chromatography

Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.200 mm, 70-230 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.

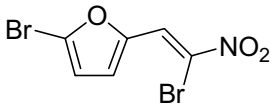
High Performance Liquid Chromatography (HPLC)

For separation of enantiomers an analytical column type CHIRALCEL OD-H was used. Purification of diastereomers was carried out on a Knauer LiChrosorb RP 18 column.

1.9 General Procedures

1.9.1 Synthesis of functionalized furans based on suzuki coupling reactions of 2-(2-bromoethenyl)-5-furan

Synthesis of 2-(2-bromoethenyl)-5-bromofuran (3)

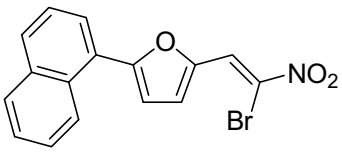


^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.53 (d, ^3J = 3.8 Hz, 1 H, furan), 7.28 (d, ^3J = 3.8 Hz, 1 H, furan), 8.41 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.5 (CH), 120.9, 122.7 (CH, furan), 123.9, 128.4, 147.4 (C).

1.9.1.1 Synthesis of 2-(2-bromo-2-nitroethenyl)-5-arylfurans

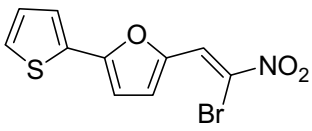
General procedure for the synthesis of 2-(2-bromo-2-nitroethenyl)-5-arylfurans (4a-i): To a toluene solution (3 ml) of **3** (0.356 g, 1.2 mmol) was added $Pd(PPh_3)_4$ (0.042 g, 3 mol %) at 20 °C. After stirring for 30 min, the arylboronic acid (1.0 mmol), K_3PO_4 (2.0 mmol) and water (0.5 ml) were added. The mixture was stirred at 90 °C for 8 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, *n*-heptane / EtOAc = 20:1→5:1).

Synthesis of 2-((*Z*)-2-bromo-2-nitrovinyl)-5-(1-naphtyl)furan (4f):



Starting with **3** (0.356 g, 1.2 mmol) and 4-hydroxyphenylboronic acid (1.0 mmol), **4f** was isolated (0.241 g, 75 %) as a red solid. Mp: 122-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (d, ^3J = 3.8 Hz, 1 H, furan), 7.52-7.59 (m, 4 H, Ar), 7.86 (d, ^3J = 8.7 Hz, 1 H, Ar), 7.91 (d, ^3J = 8.7 Hz, 1 H, Ar), 7.96 (t, ^3J = 8.7 Hz, 2 H, Ar), 8,43 (d, ^3J = 3.8 Hz, 1 H, furan), 8.69 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.0 (CH), 122.9, 124.6, 125.3, 126.4, 127.2, 127.3, 130.5 (CH, Ar), 123.7, 126.6 (CH, furan), 123.5, 126.6, 128.7, 134.0, 146.1, 159.3 (C). IR (KBr, cm-1): $\tilde{\nu}$ = 3428 (s), 2241 (w), 2111 (w), 1649 (w), 1045 (s), 1017 (s), 1004 (s), 823(s), 765 (s), 627 (s). MS (EI, 70 eV): *m/z* (%) = 345 (M^+, [^{81}Br], (11), 343 (M^+, [^{79}Br], (15), 85 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_{10}O_3NBr$ (M^+, [^{79}Br]): 342.9844; found: 342.9849.

Synthesis of 2-((*Z*)-2-bromo-2-nitrovinyl)-5-(2-thienyl)furan (4h):

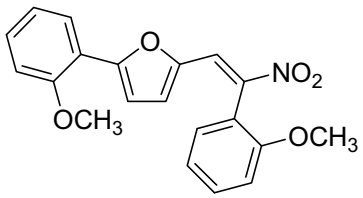


Starting with **3** (0.297 g, 1.0 mmol) and (2-thienyl)boronic acid (2.2 mmol), **4h** was isolated (0.261 g, 42%) as a red solid. Mp: 70-71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (d, ^{3}J = 3.8 Hz, 1 H, furan), 7.13 (t, ^{3}J = 4.01 Hz, 1 H, thiophene), 7.38, 7.42, 7.49 (d, ^{3}J = 3.8 Hz, 2 H, furan, d, ^{3}J = 4.01 Hz, 1 H, thiophene), 8.57 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.7 (CH), 123.3, 125.8, 127.4, 128.3 (CH, 4CH, furan and thiophene), 124.2, 131.8, 140.2, 154.6 (C). IR (KBr, cm-1): $\tilde{\nu}$ = 3412 (s), 2243 (w), 2131 (w), 1655 (w), 1051 (s), 1019 (s), 1002 (s), 827(s), 768 (s), 625(s). MS (EI, 70 eV): *m/z* (%) = 301 (M^+, [^{81}Br], 5), 299 (M^+, [^{79}Br], (10), 285 (22), 235 (12), 219 (10), 189 (18), 169 (100), 147 (28), 119 (20). HRMS (EI, 70 eV): calcd for $C_{10}H_6O_3NBrS$ (M^+, [^{79}Br]): 289.92518; found: 289.92511.

1.9.1.2 Synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans (5a-g)

General procedure for the synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans (5a-g). To a toluene solution (3 ml) of **3** (0.297 g, 1.0 mmol) was added $Pd(PPh_3)_4$ (0.070 g, 5 mol%) at 20 °C. After stirring for 30 min, the arylboronic acid (2.2 mmol), K_3PO_4 (2.0 mmol) and water (0.5 ml) were added. The mixture was stirred at 90 °C for 8 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by columnchromatography (silica gel, *n*-heptane / EtOAc = 20:1→5:1).

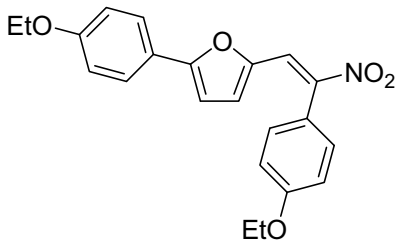
Synthesis of 2-((*Z*)-2-methoxyphenyl-2-nitrovinyl)-5-(2-methoxyphenyl)furan (5c):



Starting with **3** (0.297 g, 1.0 mmol) and 4-methoxyphenyl boronic acid (2.2 mmol), **5c** was isolated (0.224 g, 64%) as a red solid. Mp: 116-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.68, 6.96 (d, ^{3}J = 3.8 Hz, 1 H, furan), 6.80, 6.85, 7.05, 7.10 (d, ^{3}J = 8.7 Hz, 4 CH, Ar), 6.94, 7.12, 7.19, 7.53 (t, ^{3}J = 8.7 Hz, 4 CH, Ar), 8.14 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4, 55.7 (OCH_3), 112,2 (CH), 111.2, 111.3, 120.5, 120.9, 122.2, 122.5, 131.1, 131.3 (8 CH, Ar), 126.6, 129.4 (CH, furan), 118.1, 142.9, 145.6, 145.9, 154.6, 156.1, 157.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3439 (w), 2826 (w), 2612 (w), 1640 (s), 1503 (s), 1288 (s), 1243 (s), 1021 (s), 965 (s), 748 (s). MS (EI, 70 eV): *m/z* (%) = 351 (M^+, 83), 321 (19), 293 (93), 290 (31), 247 (24), 202 (40), 189 (100),

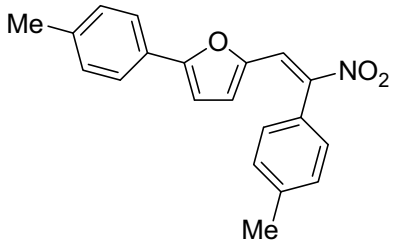
187 (45), 145 (27), 135 (27). HRMS (EI, 70 eV): calcd for $C_{20}H_{17}O_5N$ (M^+): 351.11012; found: 351.10931.

Synthesis of 2-((*Z*)-4-ethoxyphenyl-2-nitrovinyl)-5-(4-ethoxyphenyl)furan (5e):



Starting with **3** (0.297 g, 1.0 mmol) and (4-methoxyphenyl)boronic acid (2.2 mmol), **5e** was isolated (0.242 g, 69%) as a red solid. Mp: 94-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38, 1.42 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.98, 402 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 6.45, 7.16 (d, ^3J = 3.8 Hz, 1 H, furan), 6.75, 6.88, 6.98, 7.14 (d, ^3J = 8.7 Hz, 4 H, Ar), 8.12 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 14.9 (CH_3), 63.6, 63.7 (CH_2), 105.9 (CH), 114.9, 115.0, 125.8, 126.1 (CH, Ar), 124.0, 131.8 (CH, furan), 123.6, 145.0, 145.1, 146.4, 158.3, 159.7, 160.1 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3441 (w), 2829 (w), 2622 (w), 1645 (s), 1517 (s), 1272 (s), 1252 (s), 1021 (s), 965 (s), 747 (s). MS (EI, 70 eV): *m/z* (%) = 379 (M^+, 38), 349 (18), 347 (42), 321 (52), 249 (14), 216 (71), 203 (60), 188 (45), 187 (25), 119 (100), 29 (18). HRMS (EI, 70 eV): calcd for $C_{22}H_{21}O_5N$ (M^+): 379.14142; found: 379.14150.

Synthesis of 2-((*Z*)-4-tolyl-2-nitrovinyl)-5-(4-tolyl)furan (5f):



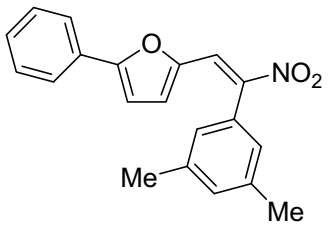
Starting with 3 (0.297 g, 1.0 mmol) and (4-tolyl)boronic acid (2.2 mmol), 5f was isolated (0.262 g, 82%) as a red solid. Mp: 111-112 °C. 1H NMR (300 MHz, CDCl3): δ = 2.23, 2.40 (s, 3 H, CH3), 6.43, 6.49 (d, 3J = 3.8 Hz, 1 H, furan), 7.00, 7.04, 7.19, 7.23 (d, ^3J = 8.7 Hz, 4 H, Ar), 8.00 (s, CH). 13C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.5 (CH_3), 106.9 (CH), 124.3, 125.1, 129.4, 129.7 (CH, Ar), 122.0, 129.5 (CH, furan), 126.4, 128.2, 139.2, 139.7, 141.4, 146.4, 158.3 (C). IR (KBr, cm-1): $\tilde{\nu}$ = 3439 (s), 2250 (w), 2124 (w), 1659 (w), 1056 (s), 1028 (s), 1008 (s), 823(s), 761 (s), 625(s). MS (EI, 70 eV): m/z (%) = 319 (M^+, 24), 261 (54), 229 (21), 215 (28), 186 (17), 173 (100), 129 (30), 128 (18), 32 (27). HRMS (EI, 70 eV): calcd for $C_{20}H_{17}O_3N$ (M^+): 319.12084; found: 319.12069.

1.9.1.3 Synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans (6a-e)

General procedure for the synthesis of 2-(2-aryl-2-nitroethenyl)-5-arylfurans (6a-e). To a toluene solution (3 ml) of **4a** (0.294 g, 1.0 mmol) was added $Pd(PPh_3)_4$ (0.042 g, 3 mol %) at 20 °C. After stirring for 30 min, the arylboronic acid (1.2 mmol), K_3PO_4 (2.0 mmol) and

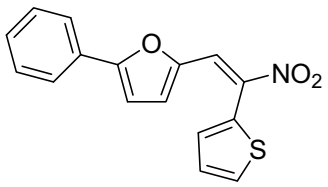
water (0.5 ml) were added. The mixture was stirred at 90 °C for 8 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, *n*-heptane / EtOAc = 20:1→5:1).

Synthesis of 2-((*Z*)-3,5-dimethylphenyl-2-nitrovinyl)-5-phenylfuran (6d):



Starting with **4a** (0.294 g, 1.0 mmol) and (3,5-dimethylphenyl)boronic acid (1.2 mmol), **6d** was isolated (0.327 g, 74%) as a red solid. Mp: 115-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 6 H, $2CH_3$), 6.43, 7.35 (d, ^3J = 3.8 Hz, 1 H, furan), 6.95 (s, 2 H, Ar), 7.06 (s, 1 H, Ar), 7.13 (m, 5 CH, Ar), 8.01 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 108.1 (CH), 124.3, 127.8, 128.4 (2CH, Ar), 122.6, 128.4 (CH, Ar), 122.2, 130.3 (CH, furan), 138.3, 138.4, 138.7, 147.9, 156.1, 157.8 (C). IR (KBr, cm-1): $\tilde{\nu}$ = 3439 (s), 2255 (w), 2119 (w), 1661 (w), 1048 (s), 1018 (s), 1014 (s), 823(s), 761 (s), 627(s). MS (EI, 70 eV): *m/z* (%) = 319 (M^+, 57), 289 (30), 262 (17), 261 (88), 258 (22), 215 (31), 159 (100), 131 (12), 115 (19). HRMS (EI, 70 eV): calcd for $C_{22}H_{17}O_3N$ (M^+): 319.12029; found: 319.12002.

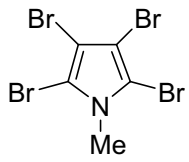
Synthesis of 2-((*Z*)-2-thienyl-2-nitrovinyl)-5-phenylfuran (6e):



Starting with **4a** (0.294 g, 1.0 mmol) and 2-thienyl boronic acid (2.2 mmol), **6e** was isolated (0.148 g, 57%) as a orange solid. Mp: 106-108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83, 7.39 (d, ^3J = 3.8 Hz, 1 H, furan), 7.17 (t, ^3J = 4.01 Hz, 1 H, thiophene), 7.68, 7.71 (d, ^3J = 4.01 Hz , 1 H, thiophene), 7.29-7.37 (m, 5 CH, Ar), 8.50 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.9 (CH), 123.5, 124.5, 128.7, 128.8, 129.7 (CH, furan & thiophene), 125.0, 129.1 (2 CH, Ar), 129,6 (CH, Ar), 138.3, 138.4, 138.7, 147.8, 159.8 (C). IR (KBr, cm-1): $\tilde{\nu}$ = 3427 (s), 2247 (w), 2110 (w), 1648 (w), 1041 (s), 1011 (s), 1001 (s), 823(s), 755 (s), 622 (s). MS (EI, 70 eV): *m/z* (%) = 297 (M^+, 12), 295 (18), 293 (18), 214 (100), 198 (12), 183 (14), 168 (55), 139 (63), 115 (62), 77 (24), 63 (18). HRMS (EI, 70 eV): calcd for $C_{16}H_{11}O_3NS$ (M^+): 297.32844; found: 297.32839.

1.9.2 Synthesis of functionalized pyrroles based on suzuki coupling reactions of tetrabromopyrrole

Synthesis of 2,3,4,5-tetrabromo-1-methylpyrrole (7):

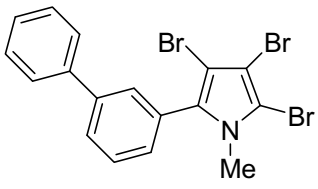


To a THF solution (700 mL) of 1-methylpyrrole (40.5 g, 44.5 mL, 0.5 mol) was added *N*-bromosuccinimide (504 g, 2.5 mol) at –78 °C and the solution was stirred at this temperature for 8 h. To the mixture was added *n*-heptane (500 mL) and the tetrahydrofuran was subsequently removed under reduced pressure to give a colourless precipitate of succinimide. The precipitate was filtered off and the solvent of the filtrate was removed in vacuo. To the residue added a saturated aqueous solution of NaOH and the solution was heated under reflux for 6 h. The aqueous and the organic layer were separated. The latter was dired (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was recrystallized from a 1:1-solution of chloroform and methanol at –18 °C. The crude product (in the form of yellow crystals) was washed with very cold ethyl acetate for several times times to give **7** as colourless crystals (174.7 g, 88%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.65 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0 (CH_3), 101, 103.5 (CBr).

1.9.2.1 Synthesis of 5-aryl-2,3,4-tribromo-1-methylpyrroles (8a-f)

General procedure for synthesis of 5-diaryl-2,3,4-tribromo-1-methylpyrroles: To a solution (4 mL) (see table 4 for each individual compounds) of **7** (0.199 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.035 g, 6 mol-%) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (1.1 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred under relux for 12 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

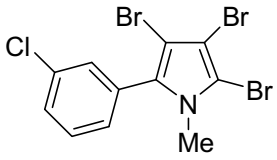
Synthesis of 5-(3-bisphenyl)-2,3,4-tribromo-1-methylpyrrole (8a):



Starting with **7** (0.199 g, 0.5 mmol) and 3-bisphenyl boronic acid (0.109 g, 1.1 mmol), **8a** was isolated (0.135 g, 66%) as a yellow solid, mp = 164–165 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.57 (s, 3 H, CH_3), 7.30-7.86 (m, 9 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.8 (CH_3), 98.4, 101.4, 104.7 (CBr), 126.20, 126.24, 127.3, 127.4, 129.2 (CH, Ar), 127.2,

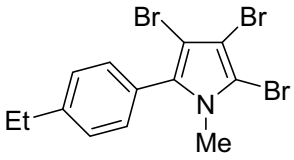
128.8 (2 CH, Ar), 131.0, 133.6, 140.3, 141.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 2911 (w), 1661 (m), 1585 (s), 1569 (m), 1518 (s), 1419 (m), 1284 (m), 1254 (s), 1149 (s), 1037 (s), 800 (s), 743 (m), 699 (m). MS (EI, 70 eV): *m/z* (%) = 473 (M^+, [^{81}Br,^{81}Br,^{81}Br], 49), 471 (M^+, [^{81}Br,^{81}Br,^{79}Br], 100), 469 (M^+, [^{81}Br,^{79}Br,^{79}Br], 45), 467 (M^+, [^{79}Br,^{79}Br,^{79}Br], 50). HRMS (EI, 70 eV): calcd for $C_{17}H_{12}Br_3N$ (M^+, [^{81}Br ,^{81}Br ,^{79}Br]): 470.84789; found: 470.84780; (M^+, [^{81}Br ,^{79}Br ,^{79}Br]): 468.84994; found: 468.84986.

Synthesis of 5-(3-chloro)-2,3,4-tribromo-1-methylpyrrole (8b):



Starting with **7** (0.199 g, 0.5 mmol) and 3-chlorophenyl boronic acid (0.080 g, 1.1 mmol), **8b** was isolated (0.152 g, 71%) as a yellow solid, mp = 139–141 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.53 (s, 3 H, CH_3), 7.26 (t, ^3J = 8.2 Hz, 1 H, Ar), 7.35 (s, 1 H, Ar), 7.40 (d, ^3J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.8 (CH_3), 98.8, 101.5, 105.4 (CBr), 128.6, 128.9, 129.8, 130.4 (CH, Ar), 131.9, 132.0, 134.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2919 (w), 1669 (m), 1579 (s), 1565 (m), 1519 (s), 1423 (m), 1289 (m), 1259 (s), 1169 (s), 1026 (s), 801 (s), 768 (m), 695 (m). MS (EI, 70 eV): *m/z* (%) = 433 (M^+, [^{81}Br,^{81}Br,^{81}Br,^{37}Cl], 31), 431 (M^+, [^{81}Br, ^{81}Br,^{79}Br,^{37}Cl], 52), 429 (M^+, [^{81}Br,^{79}Br,^{79}Br,^{37}Cl], 45), 427 (M^+, [^{79}Br,^{79}Br,^{79}Br,^{37}Cl], 47), 425 (M^+, [^{79}Br,^{79}Br,^{79}Br,^{35}Cl], 56). HRMS (EI, 70 eV): calcd for $C_{11}H_7Br_3ClN$ (M^+, [^{81}Br , ^{79}Br ,^{79}Br,^{37}Cl]): 428.77762; found: 428.77752; (M^+, [^{79}Br ,^{79}Br,^{79}Br,^{37}Cl]): 426.77967; found: 428.77961; (M^+, [^{79}Br ,^{79}Br ,^{79}Br,^{37}Cl]): 424.78171; found: 424.78170.

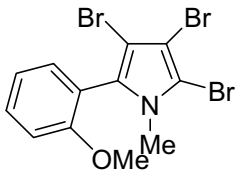
Synthesis of 5-(4-ethylphenyl)-2,3,4-tribromo-1-methylpyrrole (8c):



Starting with **7** (0.199 g, 0.5 mmol) and 4-ethylphenyl boronic acid (0.083 g, 1.1 mmol), **8c** was isolated (0.158 g, 75%) as a yellow solid, mp = 147–150 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.65 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 3.58 (3 H, pyrrole-CH_3), 7.20, 7.22 (d, ^3J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 28.7 (CH_2), 35.7 (pyrrole-CH_3), 98.0, 101.1, 104.2 (CBr), 128.0, 130.3 (2 CH, Ar), 126.9, 133.8, 144.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1700 (w), 1491 (w), 1453 (w), 1373 (w), 1329 (m), 1183 (w), 1115 (w), 1087 (w), 1016 (w), 974 (w), 819 (s), 7.65 (w), 715 (w), 607 (m). MS (EI, 70 eV): *m/z* (%) = 425 (M^+, [^{81}Br,^{81}Br,^{81}Br], 50), 423 (M^+, [^{81}Br,^{81}Br,^{79}Br], 100), 421 (M^+, [^{81}Br,^{79}Br,^{79}Br], 41), 419 (M^+, [^{79}Br,^{79}Br,^{79}Br], 54). HRMS (EI, 70 eV): calcd for

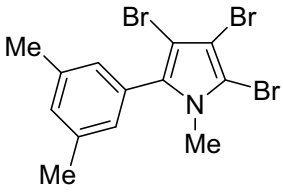
$C_{13}H_{12}Br_3N$ (M^+, [^{81}Br ,^{81}Br ,^{79}Br]): 422.84789; found: 422.84781; (M^+, [^{81}Br ,^{79}Br ,^{79}Br]): 420.84994; found: 420.84979.

Synthesis of 5-(2-methoxylphenyl)-2,3,4-tribromo-1-methylpyrrole (8d):



Starting with **7** (0.199 g, 0.5 mmol) and 2-methoxylphenyl boronic acid (0.084 g, 1.1 mmol), **8d** was isolated (0.147 g, 75%) as a yellowish solid, mp = 150–153 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, OCH_3), 3.58 (3 H, pyrrole-CH_3), 6.67, 7.03 (d, ^3J = 8.2 Hz, 1 H, Ar), 7.25, 7.41 (t, ^3J = 8.2 Hz, 1 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4 (pyrrole-CH_3), 55.5 (OCH_3), 98.4, 100.5, 103.9 (CBr), 111.1, 120.7, 130.9, 133.1 (CH, Ar), 119.3, 130.0, 157.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1733 (w), 1501 (w), 1470 (w), 1393 (w), 1340 (m), 1193 (w), 1129 (w), 1099 (w), 1019 (w), 979 (w), 831 (s), 761 (w), 727 (w), 600 (m). MS (EI, 70 eV): *m/z* (%) = 427 (M^+, [^{81}Br,^{81}Br,^{81}Br], 39), 425 (M^+, [^{81}Br,^{81}Br,^{79}Br], 100), 423 (M^+, [^{81}Br,^{79}Br,^{79}Br], 50), 421 (M^+, [^{79}Br,^{79}Br,^{79}Br], 47). HRMS (EI, 70 eV): calcd for $C_{12}H_{10}Br_3NO$ (M^+, [^{81}Br ,^{81}Br ,^{79}Br]): 424.82716; found: 424.82705; (M^+, [^{81}Br ,^{79}Br ,^{79}Br]): 422.82921; found: 422.82911.

Synthesis of 5-(3,5-dimethylphenyl)-2,3,4-tribromo-1-methylpyrrole (8f):



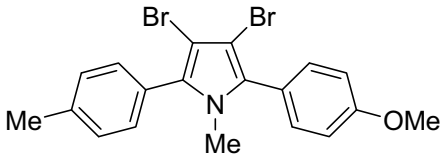
Starting with **7** (0.199 g, 0.5 mmol) and 3,5-dimethylphenyl boronic acid (0.083 g, 1.1 mmol), **8f** was isolated (0.151 g, 72%) as a yellowish solid, mp = 160–162 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.37 (s, 6 H, CH_3), 3.55 (3 H, pyrrole-CH_3), 6.98 (s, 2 CH, Ar), 7.20 (s, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 35.7 (pyrrole-CH_3), 97.9, 101.0, 104.2 (CBr), 125 (CH, Ar), 128 (2 CH, Ar), 128.7, 134.0, 141.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1709 (w), 1497 (w), 1467 (w), 1361 (w), 1322 (m), 1180 (w), 1111 (w), 1080 (w), 1009 (w), 972 (w), 817 (s), 7.55 (w), 713 (w), 600 (m). MS (EI, 70 eV): *m/z* (%) = 425 (M^+, [^{81}Br,^{81}Br,^{81}Br], 29), 423 (M^+, [^{81}Br,^{81}Br,^{79}Br], 100), 421 (M^+, [^{81}Br,^{79}Br,^{79}Br], 52), 419 (M^+, [^{79}Br,^{79}Br,^{79}Br], 31). HRMS (EI, 70 eV): calcd for $C_{13}H_{12}Br_3N$ (M^+, [^{81}Br ,^{81}Br ,^{79}Br]): 422.84789; found: 422.84775; (M^+, [^{81}Br ,^{79}Br ,^{79}Br]): 420.84994; found: 420.84973.

1.9.2.2 Synthesis of asymmetric 3,4-dibromo-2,5-diaryl-1-methylpyrroles (9a,b)

General procedure for synthesis of asymmetric 3,4-dibromo-2,5-diaryl-1-methylpyrroles: To a DMF:toluene:EtOH:H_2O solution (4:1:1:1 mL) of **8e** (0.203 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.058 g, 10 mol-%) at 20 °C under argon atmosphere. After

stirring for 30 min, the arylboronic acid (1.1 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred under relux for 48 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of 3,4-dibromo-2-(4-methoxyphenyl)-5-di(4-tolyl)-1-methylpyrrole (9b):

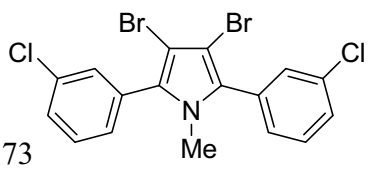


Starting with **8e** (0.199 g, 0.5 mmol) and 4-methoxyphenyl boronic acid (0.084 g, 1.1 mmol), **9b** was isolated (0.11 g, 51%) as a yellow solid, mp = 109–111 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.37 (s, 3 H, CH_3), 3.70 (s, 3 H, pyrrole-CH_3), 3.81 (s, 3 H, OCH_3), 6.42, 6.79, 7.05, 7.19 (d, ^3J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 33.6 (pyrrole-CH_3), 55.2 (OCH_3), 113.5, 113.9 (CBr), 121.0 (C-pyrrole, overlap), 127.8, 129.1, 129.9, 131.3 (4CH, Ar), 135.7, 136.0, 156.3, 157.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2920 (m), 2848 (w), 1666 (m), 1597 (s), 1572 (m), 1509 (s), 1420 (m), 1289 (m), 1251 (s), 1165 (s), 1021 (s), 802 (s), 769 (m), 697 (m). MS (EI, 70 eV): *m/z* (%) = 437 (M^+, [^{81}Br,^{81}Br], 18), 435 (M^+, [^{81}Br,^{79}Br], 100), 437 (M^+, [^{79}Br,^{79}Br], 31). HRMS (EI, 70 eV): calcd for $C_{19}H_{17}Br_2NO$ (M^+, [^{81}Br ,^{79}Br]): 434.96564, found: 434.96555; (M^+, [^{79}Br ,^{79}Br]): 432.96769; found: 432.96759.

1.9.2.3 Synthesis of symmetric 3,4-dibromo-2,5-diaryl-1-methylpyrroles (10a-f)

General procedure for synthesis of 3,4-dibromo-2,5-diaryl-1-methylpyrroles: To a solution (4 mL) (see table 5 for each individual compounds) of **7** (0.199 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.058 g, 10 mol-%) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (2.5 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred under relux for 24 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

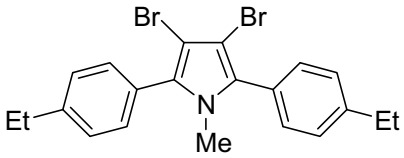
Synthesis of 3,4-dibromo-2,5-di(3-chlorophenyl)-1-methylpyrrole (10a):



Starting with **7** (0.199 g, 0.5 mmol) and 3-chlorophenylboronic acid (0.182 g, 2.5 mmol), **10a** was isolated (0.130 g, 57%) as a

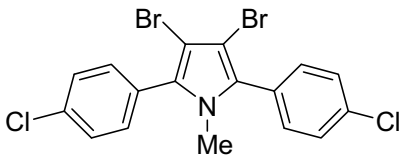
brownish solid, mp = 129–131 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.47 (s, 3 H, CH_3), 6.91 (t, ^{3}J = 8.2 Hz, 1 H, Ar), 7.10 (d, ^{3}J = 8.2 Hz, 2 H, Ar), 7.21 (s, 1 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.9 (CH_3), 99.5 (CBr), 105.5 (C-pyrrole), 126.8, 128.4, 129.2, 130.6 (2 CH, Ar), 133.7, 135.3 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1928 (w), 1922 (w), 1559 (w), 1520 (w), 1466 (m), 1439 (w), 1359 (m), 1257 (w), 1120 (w), 1015 (w), 979 (w), 830 (m), 814 (m), 777 (w), 701 (w). MS (EI, 70 eV): *m/z* (%) = 465 (M^+, [^{81}Br,^{81}Br,^{37}Cl,^{37}Cl], 14), 463 (M^+, [^{81}Br, ^{79}Br,^{37}Cl,^{37}Cl], 22), 461 (M^+, [^{79}Br,^{79}Br,^{37}Cl,^{37}Cl], 100), 459 (M^+, [^{79}Br,^{79}Br,^{35}Cl,^{37}Cl], 55), 457 (M^+, [^{79}Br,^{79}Br,^{35}Cl,^{35}Cl], 34). HRMS (EI, 70 eV): calcd for $C_{17}H_{11}Br_2Cl_2N$ (M^+, [^{79}Br , ^{79}Br ,^{37}Cl,^{37}Cl]): 460.85853; found: 460.85839; (M^+, [^{79}Br ,^{79}Br,^{35}Cl,^{37}Cl]): 458.86148; found: 458.86139; (M^+, [^{79}Br ,^{79}Br ,^{35}Cl,^{35}Cl]): 456.86353; found: 456.86341.

Synthesis of 3,4-dibromo-2,5-di(4-ethoxyphenyl)-1-methylpyrrole (10b): Starting with **7** (0.199 g, 0.5 mmol) and 4-ethoxyphenylboronic acid (0.187g, 2.5 mmol), **10b** was isolated (0.116 g, 52%) as a yellowish solid, mp = 124–128 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (t, ^{3}J = 7.2 Hz, 6 H, $2CH_3$), 2.72 (q, ^{3}J = 7.2 Hz, 4 H, $2OCH_2CH_3$), 3.38 (3 H, pyrrole-CH_3), 7.32, 7.36 (d, ^{3}J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 28.7 (CH_2), 34.9 (pyrrole-CH_3), 98.7 (CBr), 127.9, 130.4 (4 CH, Ar), 128.2 (C-pyrrole), 132.7, 144.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1929 (w), 1919 (w), 1551 (w), 1529 (w), 1483 (m), 1441 (w), 1310 (m), 1221 (w), 1110 (w), 1031 (w), 979 (w), 823 (m), 800 (m), 771 (w), 712 (w). MS (EI, 70 eV): *m/z* (%) = 449 (M^+, [^{81}Br,^{81}Br], 25), 447 (M^+, [^{81}Br, ^{79}Br],100), 445 (M^+, [^{79}Br,^{79}Br], 51). HRMS (EI, 70 eV): calcd for $C_{21}H_{21}Br_2N$ (M^+, [^{81}Br , ^{79}Br]): 447.00203; found: 447.00189; (M^+, [^{79}Br ,^{79}Br]): 445.00407; found: 445.0035.



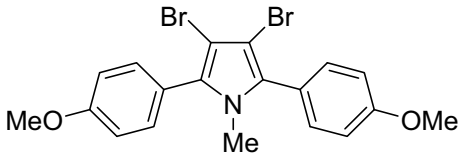
Synthesis of 3,4-dibromo-2,5-di(4-chlorophenyl)-1-methylpyrrole (10d):

Starting with **7** (0.199 g, 0.5 mmol) and 4-chlorophenyl boronic acid (0.170 g, 2.5 mmol), **10d** was isolated (0.166 g, 79%) as a colourless solid, mp = 139–142 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.36 (s, 3 H, CH_3), 7.38, 7.43 (d, ^{3}J = 8.2 Hz, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5 (CH_3), 99.6 (CBr), 128.9, 131.7 (4 CH, Ar), 129.1 (C-pyrrole), 131.9, 134.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1922 (w), 1920 (w), 1555 (w), 1529 (w), 1466 (m), 1439 (w), 1359 (m), 1256 (w), 1129 (w), 1012 (w), 988 (w), 834 (m), 814 (m), 777 (w), 701 (w). MS (EI, 70 eV): *m/z* (%) = 465 (M^+, [^{81}Br,^{81}Br,^{37}Cl,^{37}Cl], 19), 463



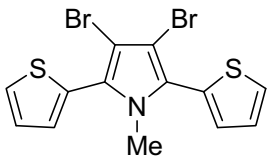
(M^+, [^{81}Br, ^{79}Br,^{37}Cl,^{37}Cl], 27), 461 (M^+, [^{79}Br,^{79}Br,^{37}Cl,^{37}Cl], 100), 459 (M^+, [^{79}Br,^{79}Br,^{35}Cl,^{37}Cl], 47), 457 (M^+, [^{79}Br,^{79}Br,^{35}Cl,^{35}Cl], 26). HRMS (EI, 70 eV): calcd for $C_{17}H_{11}Br_2Cl_2N$ (M^+, [^{79}Br , ^{79}Br ,^{37}Cl,^{37}Cl]): 460.85853; found: 460.85837; (M^+, [^{79}Br ,^{79}Br,^{35}Cl,^{37}Cl]): 458.86148; found: 458.86138; (M^+, [^{79}Br ,^{79}Br ,^{35}Cl,^{35}Cl]): 456.86353; found: 456.86344.

Synthesis of 3,4-dibromo-2,5-di(4-methoxyphenyl)-1-methylpyrrole (10e):



Starting with **7** (0.199 g, 0.5 mmol) and 4-methoxyphenyl boronic acid (0.190 g, 2.5 mmol), **10e** was isolated (0.178 g, 79%) as a colourless solid, mp = 159–160 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.34 (s, 3 H, pyrrole-CH_3), 3.86 (s, 6 H, 2OCH_3), 7.00, 7.36 (d, ^3J = 8.2 Hz, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.7 (pyrrole-CH_3), 55.3 (OCH_3), 98.5 (CBr), 113.9, 131.8 (4CH, Ar), 123.3 (C-pyrrole), 132.2, 159.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1931 (w), 1925 (w), 1561 (w), 1532 (w), 1479 (m), 1454 (w), 1370 (m), 1251 (w), 1134 (w), 1029 (w), 977 (w), 829 (m), 807 (m), 778 (w), 710 (w). MS (EI, 70 eV): *m/z* (%) = 453 (M^+, [^{81}Br,^{81}Br], 29), 451 (M^+, [^{81}Br,^{79}Br], 100), 449 (M^+, [^{79}Br,^{79}Br], 38), 244 (24). HRMS (EI, 70 eV): calcd for $C_{19}H_{17}Br_2NO_2$ (M^+, [^{81}Br ,^{79}Br]): 450.96056, found: 450.96042; (M^+, [^{79}Br ,^{79}Br]): 448.96260; found: 448.96251.

Synthesis of 3,4-dibromo-2,5-di(2-thienyl)-1-methylpyrrole (10f):

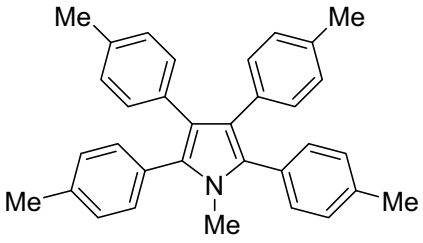


Starting with **7** (0.199 g, 0.5 mmol) and 2-thienyl boronic acid (0.160 g, 2.5 mmol), **10f** was isolated (0.1 g, 50%) as a brownish solid, mp = 112–114 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, pyrrole-CH_3), 7.01 (t, ^3J = 4.01 Hz, 2 H, thiophene), 7.17, 7.21 (d, ^3J = 4.01 Hz , 2 H, thiophene). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9 (CH_3), 100.9 (CBr), 103.5 (C-pyrrole), 123.7, 124.3, 127.7 (2 CH, thiophene), 137.3 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1934 (w), 1911 (w), 1538 (w), 1524 (w), 1475 (m), 1456 (w), 1369 (m), 1242 (w), 1127 (w), 1016 (w), 970 (w), 856 (m), 828 (m). MS (EI, 70 eV): *m/z* (%) = 405 (M^+, [^{81}Br,^{81}Br], 15), 403 (M^+, [^{81}Br,^{79}Br], 100), 401 (M^+, [^{79}Br,^{79}Br], 45). HRMS (EI, 70 eV): calcd for $C_{13}H_9Br_2NS_2$ (M^+, [^{81}Br ,^{79}Br]): 402.85227, found: 402.85222; (M^+, [^{79}Br ,^{79}Br]): 400.85432; found: 400.85421.

1.9.2.4 Synthesis of tetraaryl-1-methylpyrroles (11a,b,c)

General procedure for synthesis of 3,4-dibromo-2,5-diaryl-1-methylpyrroles: To a DMF:toluene:EtOH solution (4:1:1 mL) of **7** (0.199 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.116 g, 20 mol-%) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (5 mmol), K_3PO_4 (5.0 mmol) and water (1.0 mL) were added. The mixture was stirred under relux for 48 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of tetratolyl-1-methylpyrrole (11c):

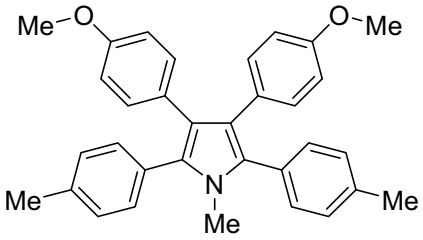


Starting with **7** (0.199 g, 0.5 mmol) and tolylboronic acid (0.34 g, 5 mmol), **11c** was isolated (0.157 g, 71%) as a yellow solid, mp = 176–180 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.13, 2.29 (6 H, CH_3), 3.30 (3 H, pyrrole-CH_3), 6.79 (m, 8 H, Ar), 7.02, 7.15 (d, ^3J = 8.2 Hz, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 21.0 (CH_3), 32.7 (pyrrole-CH_3), 127.9, 128.6, 130.5, 131.0 (4 CH, Ar), 121.6, 129.8, 131.3, 132.6, 134.1, 136.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 2862 (w), 1520 (w), 1496 (w), 1360 (w), 1112 (w), 1020 (w), 835 (m), 819 (m), 804 (m), 746 (m), 721 (m). MS (EI, 70 eV): *m/z* (%) = 441 (M^+, 100), 366 (4), 309 (2), 239 (1), 91 (12). HRMS (EI, 70 eV): calcd for $C_{33}H_{31}N$ (M^+): 441.24510; found: 441.245085.

1.9.2.5 Synthesis of tetraaryl-1-methylpyrroles (12a,b)

General procedure for synthesis of 3,4-dibromo-2,5-diaryl-1-methylpyrroles: To a DMF:toluene:EtOH solution (4:1:1 mL) of **10c** (0.208 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.116 g, 20 mol-%) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (3 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred under relux for 96 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of 2,5-ditolyl-3,4-di(4-methoxyphenyl)-1-methylpyrrole (12a):



Starting with **10c** (0.209 g, 0.5 mmol) and 4-methoxyphenyl boronic acid (0.228 g, 3 mmol), **12a** was isolated (0.153 g, 65%) as a yellow solid, mp = 172–174 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.35 (6 H, CH_3), 3.4 (3 H, pyrrole-CH_3), 3.71 (6 H, OCH_3), 6.63, 6.87, 7.14, 7.19 (d, ^3J = 8.2 Hz, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.25 (CH_3), 32.9 (pyrrole-CH_3), 54.9 (OCH_3), 112.9, 128.8, 311.2, 131.8 (4 CH, Ar), 121.9, 128.2, 130.1, 131.3, 136.7, 157.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2915 (w), 2849 (w), 1529 (w), 1486 (w), 1359 (w), 1112 (w), 1020 (w), 835 (m), 820 (m), 802 (m), 755 (m), 722 (m). MS (EI, 70 eV): *m/z* (%) = 473 (M^+, 100), 444 (5), 353 (3), 211 (1), 112 (12), 97 (11), 69 (5). HRMS (EI, 70 eV): calcd for $C_{33}H_{31}NO_2$ (M^+): 473.23548; found: 473.23534.

1.9.3 Synthesis of functionalized pyrroles based on alkynylation of tetrabromopyrroles

General procedure for Sonogashira reactions:

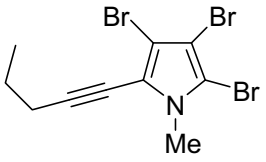
Tetrabromo-*N*-methylpyrole (**7**) (750 mg, 1.87 mmol), triphenylphosphane (98 mg, 20 mol%), $PdCl_2(CH_3CN)_2$ (49 mg, 10 mol-%) and CuI (36 mg, 10 mol-%) were added to an oven dry Schlenk flask, evacuated for 10 min, and then flushed with argon. To the mixture was added thoroughly dried, freshly distilled and oxygen-free diisopropylamine (20 mL). The clear yellow solution was stirred for 15 min at 20 °C for the generation of the catalyst. The solution was subsequently cooled to 0 °C and the alkyne was dropwise added by syringe. The solution was stirred for 1 h at 0 °C and for 3 h at 20 °C. The dark brown mixture was heated at the indicated temperature (90°C) indicated period of time. The solution was allowed to cool to ambient temperature, filtered and the filtrate was concentrated in vacuo. To the residue was added CH_2Cl_2 and the solution was extracted with water. The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (neutral silica gel, *n*-hexane). For the synthesis of products **3**, the two alkynes were added at the same time.

General procedure for Sonogashira reactions (Procedure C) : a pressure tube was evacuated and backfilled argon and then charged under positive pressure of argon with $PdCl_2(CH_3CN)_2$ (5% mol, 6.5 mg) ,**L** (20%mol, 44.6 mg), Cs_2CO_3 (5 eq, 0.815 g), followed by anhydrous acetonitrile (1 mL), and tetrabromo-N-pyrrole (0.5 mol – 0.191 g). The slightly

yellow suspension was stirred for 25 min. The alkyne (2.5 mmole) was injected . The pressure tube was seald by Teflon vavle, and the mixture of reaction was stirred at the desired temperature (100°C) for the indicated period of time. The organic layer was isolated from suspension by funnel, and washed the solid residue several times by ethylacetate. The organic layer was concentrated and purified by flash chromatography on fine silicagel to provide the desired product.

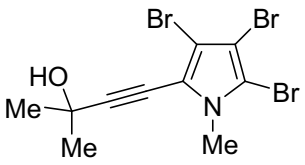
1.9.3.1 Synthesis of 5-alkynyl-2,3,4-tribromo-1-methylpyrroles

Synthesis of 5-pentylnyl-2,3,4-tribromo-1-methylpyrrole (13a):



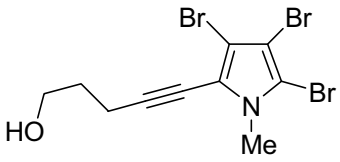
Starting with tetrabromopyrole (500 mg, 1.25 mmol) and 2-pentyne (1.3 mmol), **13a** was isolated (134 mg, 30%) as a brownish highly viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^{3}J = 7.5 3H, Me), 1.64 (sextet, ^{3}J = 7.2 Hz, 2H, CH_2), 2.47 (t, ^{3}J = 7.0 Hz, 2H, CH_2), 3.64 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 21.6, 22.0 (CH_2), 35.6 (NMe), 70.1, 98.8 (C≡C), 100.4, 102.93, 104.19, 118.34 (C, pyrrole). IR (KBr, cm^{-1}): δ = 3436 (br, s), 2958 (s), 2932 (m), 2872 (m), 2228 (w), 1717 (m), 1529 (m), 1456 (s), 1431 (m), 1378 (m), 1330 (s), 1092 (m). MS (EI, 70 eV, 85 °C): *m/z* (%) = 387 (12) [M^+, ^{81}Br, ^{81}Br, ^{81}Br], 385 (13) [M^+, ^{79}Br, ^{81}Br, ^{81}Br], 383 (48) [M^+, ^{79}Br, ^{79}Br, ^{81}Br], 381 (19) [M^+, ^{79}Br, ^{79}Br, ^{79}Br], 356 (67), 354 (58), 275 (14), 224 (54), 194 (60), 115 (100). HRMS (EI, 70 eV): calcd for $C_{10}H_{10}Br_3N$ ([M^+, ^{79}Br, ^{79}Br, ^{79}Br]): 380.83579, found 380.83501.

Synthesis of 5-(2-methylbut-2-ol-3-ylnyl)-2,3,4-tribromo-1-methylpyrrole (13b):



Starting with tetrabromopyrole (500 mg, 1.25 mmol), 2-methyl-3-pentyne-2-ol (0.15 mL, 1.5 mmol), **13b** was isolated (160 mg, 32 %) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 6H, 2Me), 3.64 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.32 (2Me), 35.71 (NMe), 65.78 (C, CMe_2OH), 71.65 (C≡C), 100.76 (C, pyrol), 104.09 (C≡C), 102.14 (C, pyrrole), 105.49 (C, pyrrole), 116.79 (C, pyrrole). IR (KBr, cm^{-1}): δ = 3443 (m), 3014 8 (w), 2983 (s), 2936 (w), 2250 (w), 1723 (s), 1454 (s), 1379 8 (m), 1329 (s), 1216 (m), 1163 (m), 908 (s), 759 (m), 734 (m). MS (EI, 70 eV, 85 °C): *m/z* (%) = 401 (51) [M^+, ^{81}Br, ^{81}Br],, 399 (50) [M^+, ^{79}Br, ^{81}Br], 397 (19) [M^+, ^{79}Br, ^{79}Br] 388 (33) 386 (90), 384 (100) [M^+-CH_3], 382 (42), 320 (23), 193 (18), 145 (22).

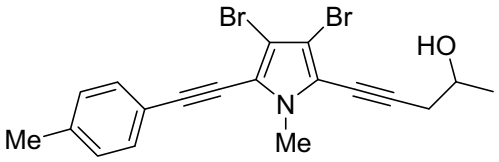
Synthesis of 5-(pent-1-ol-4-ylnyl)-2,3,4-tribromo-1-methylpyrrole (13d):



Starting with tetrabromopyrole (500 mg, 1.26 mmol), 4-pentyne-1-ol (1.32 mmol), **13d** was isolated (145 mg, 29 %) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (pentet, ^{3}J = 7.1 2H, CH_2), 2.05 (br S, 1H OH), 2.62 (t, ^{3}J = 6.9 Hz, 2H, CH_2), 3.64 (s, 3H, NCH_3), 3.82 (br t, ^{3}J = 6.0 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.25 (CH_2), 31.16 (CH_2), 35.67 (NMe), 61.4 (CH_2OH) 70.40 (C≡C), 97.95 (C, pyrrole), 100.38 (C, pyrrole), 103.11 (C, pyrrole), 104.43 (C≡C), 118.02 (C, pyrrole). IR (KBr, cm^{-1}): δ = 3411 (br, s), 2944 (s), 2873 (m), 1717 (m), 1636 (w), 1479 (m), 1455 (s), 1434 (s), 1377 (m), 1330 (s), 1186 (m), 1094 (s), 1060 (s), 919 (m), 748 (s), 692 (s), 520 (s), 509 (s). HRMS (EI, 70 eV): calcd for $C_{10}H_{10}NOBr_3$ [Br^{79}]; 396.83070, found 396.830504.

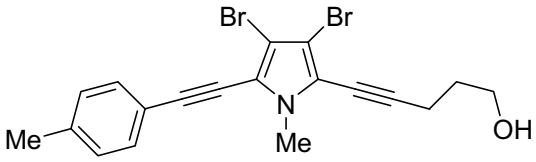
1.9.3.2 Synthesis of asymmetric 3,4-tribromo-2,5-dialkynyl-1-methylpyrroles

Synthesis of 3,4-tribromo- 2-(pent-2-ol-4-ylnyl)-5-tolylacetylyl-1-methylpyrrole (14a):



Starting with tetrabromopyrole (500 mg, 1.26 mmol), 4-pentyne-2-ol (1.38 mmol) *p*-tolyl acetylene (1.38 mmol), **14a** was isolated (216 mg, 40 %) as a red solid. The two alkynes were added at the same time. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3H, Me), 2.36 (s, 3H, Me-tolyl) 2.68 (d, ^{3}J = 6.9 Hz, 2H, CH_2), 3.71 (s, 3H, NCH_3), 4.07 (m, 1H, CH), 7.15 (d, ^{3}J = 7.8 Hz, 2H, tolyl), 7.40 (d, ^{3}J = 8.1 Hz, 2H, tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.05 (Me, tolyl), 22.41 (Me), 30.13 (CH_2), 35.66 (NMe), 60.33 (CH), 66.29 (C≡C), 72.27 (C≡C), 97.27 (C, pyrrole), 103.57 (C, pyrrole), 103.76 (C≡C), 117.29 (C, pyrrole), 117.65 (C, pyrrole), 119.07 (C, *p*-tolyl), 129.12 (CH, *p*-tolyl), 131.27 (CH, *p*-tolyl), 139.99 (C, *p*-tolyl). IR (KBr, cm^{-1}): δ = 3455 (br, s), 2972 (s), 2927 (s), 2252 (s), 2212 (w), 1727 (s), 1728 (s), 1656 (s), 1446 (s), 1377 (s), 1341 (m), 1250(m), 1120 (m), 908 (br, s), 816 (s), 733 (br, s).

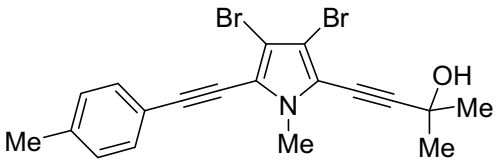
Synthesis of 3,4-tribromo- 2-(pent-1-ol-4-ylnyl)-5-tolylacetylyl-1-methylpyrrole (14b):



Starting with tetrabromopyrole (500 mg, 1.26 mmol), 4-pentyne-1-ol (1.38 mmol) *p*-tolylacetylene (1.38 mmol), **14b** was isolated (213 mg, 39 %) as a red solid. The two alkynes were added at the same time. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (m, 2H, CH_2), 2.38 (s, 3H, Me-

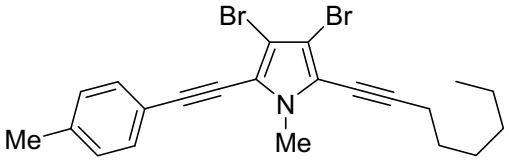
olyl) 2.63 (t, ^{3}J = 6.9 Hz, 2H, CH_2), 3.72 (s, 3H, NCH_3), 3.84 (t, ^{3}J = 6.9 Hz, 2H, CH_2), 7.15 (d, ^{3}J = 8.1 Hz, 2H, tolyl), 7.42 (d, ^{3}J = 7.5 Hz, 2H, tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.26 (CH_2), 22.60 (Me, tolyl), 31.14 (CH_2), 30.13 (CH_2), 34.43 (NMe), 61.46 (CH_2), 68.52 (C≡C), 70.49 (C≡C), 97.89 (C, pyrrole), 98.00 (C, pyrrole), 103.23 (C≡C), 103.41 (C≡C), 117.10 (C, pyrrole), 117.98 (C, pyrrole), 119.18 (C, *p*-tolyl), 129.16 (CH, *p*-tolyl), 131.33 (CH, *p*-tolyl), 139.00 (C, *p*-tolyl).

Synthesis of 3,4-tribromo- 2-(2-methylbut-2-ol-3-ylnyl)-5-tolylacetylyl-1-methylpyrrole (14c):



Starting with tetrabromopyrole (500 mg, 1.25 mmol), 2-methyl-3-pentyne-2-ol (1.3 mmol) and p-tolylacetylene (1.3 mmol), 14c was isolated (238 mg, 44%) as a red to brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 6 H, CH3), 2.36 (s, 3H, Me-tolyl), 3.72 (s, 3H, CH3), 7.16 (d, 3J = 8.1 Hz, 2H, tolyl), 7.43 (d, 3J = 8.1 Hz, 2H, tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH3, tolyl), 31.3 (CH3), 34.4 (NCH3), 65.9 (C, CMe2OH), 71.7, 71,6 (C≡C), 97.5, 97.7 (C, pyrrole), 102.2, 103.9 (C≡C), 116.9, 117.9 (C, pyrrole), 119.1, 131.4 (CH, p-tolyl), 139.2 (C, p-tolyl). IR (KBr, cm-1): δ = 3324 (br, s), 2983 (s), 2929 (s), 2865 (w), 2249 (m), 1906 (w), 1728 (s), 1534 (m), 1509 (m), 1440 (s), 1232 (s), 1160 (br, s), 910 (s), 815 (s), 730 (br, s). MS (EI, 70 eV, 110 °C): m/z (%) = 437 [M^+, ^{81}Br, ^{81}Br] (49), 435 [M^+, ^{79}Br, ^{81}Br] (100), 433 [M^+, ^{79}Br, ^{79}Br] (49), 422 (30), 420 (65), 418 (40), 417 (11), 405 (17) 377 (18), 356 (15), 354 (14). HRMS (EI, 70 eV): calcd for $C_{17}H_{19}NOBr_2$ [Br^{79}]: 432.96769, found 432.96751.

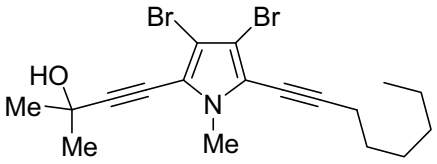
Synthesis of 3,4-tribromo- 2-octylyl-5-tolylacetylyl-1-methylpyrrole (14d):



Starting with tetrabromopyrole (600 mg, 1.51 mmol), *p*-tolylacetylene (1.66 mmol), 1-Octyne (1.66 mmol), **14d** was isolated (285 mg, 41%) as a red solid. The two alkynes were added at the same time. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (tr, ^{3}J = 6.9 Hz, 3H, Me), 1.32 (br m, 4H, $2CH_2$), 1.47 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.36 (s, 3H, Me-tolyl), 2.49 (tr, ^{3}J = 6.9 Hz, 2H, CH_2), 3.72 (s, 3H, NCH_3). 7.15 (d, ^{3}J = 8.0 Hz, 2H, tolyl), 7.42 (d, ^{3}J = 8.1 Hz, 2H, tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06 (Me), 19.73 (CH_2), 21.56 (Me-tolyl), 22.57 (CH_2), 28.48 (CH_2), 28.50 (CH_2), 31.29 (CH_2), 34.41 (NMe), 70.03 (C≡C), 78.05 (C≡C), 97.13 (C≡C), 99.13 (C,

pyrrole), 103.14 (C, pyrrole), 103.66 (C≡C), 116.96 (C, pyrrole), 118.36 (C, pyrrole), 119.30 (C, *p*-tolyl), 129.18 (CH, *p*-tolyl), 131.33 (CH, *p*-tolyl), 138.96 (C, *p*-tolyl).

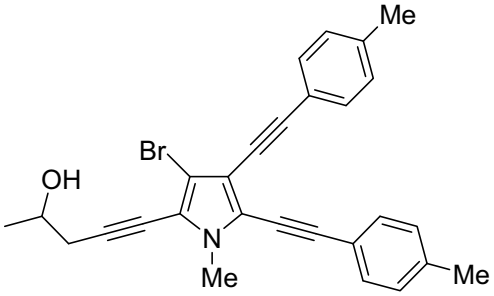
Synthesis of 3,4-tribromo- 2-octylyl-5-(2-methylbut-2-ol-3-ylnyl)-1-methylpyrrole (14e):



Starting with tetrabromopyrole (700 mg, 1.76 mmol), 2-methyl-3-pentyne-2-ol (1.94 mmol), 1-Octyne (1.94 mmol), **14e** was isolated (280 mg, 37 %) as a red brown solid. The two alkynes were added at the same time. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (tr, ^{3}J = 6.9 Hz, 3H, Me), 1.29 (br m, 6H, $3CH_2$), 1.47 (m, 2H, CH_2), 1.64 (s, 6H, 2Me), 2.49 (tr, ^{3}J = 7.0 Hz, 2H, CH_2), 3.63 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.02 (Me), 19.65 (CH_2), 22.52 (CH_2), 28.41 (CH_2), 28.44 (CH_2), 31.24 (CH_2), 31.34 ((2Me), 34.30 (NMe), 65.80 (C, CMe_2OH), 69.83 (C≡C), 71.80 (C≡C), 99.00 (C, pyrrole), 101.61 (C, pyrrole), 101.85 (C≡C), 103.80 (C≡C), 115.96 (C, pyrrole), 118.30 (C, pyrrole). IR (KBr, cm^{-1}): δ = 3411 (br, s), 2931 (s), 2929 (s), 2859 (s), 2249 (m), 2223 (m), 1726 (m), 1525 (m), 1378 (s), 1345 (s), 1233 (s), 1159 (s), 908 (br, s), 9734 (br s).

1.9.3.3 Synthesis of 3-bromo-2,4,5-trialkynyl-1-methylpyrroles

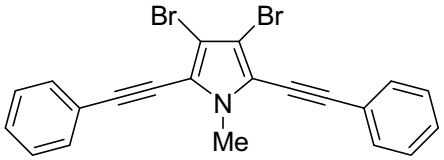
Synthesis of 3-bromo-2-(pent-2-ol-4-ylnyl)-4,5-ditolylecetylnyl-1-methylpyrrole (15):



Starting with tetrabromopyrole (500 mg, 1.26 mmol), 2-methyl-3-butyne-2-ol (1.38 mmol) phenylacetylene (1.38 mmol), **15** was isolated (228 mg, 41%) as a red solid. The two alkynes were added at the same time. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 6 H, 2Me), 3.77 (s, 3H, NCH_3), 7.35 (br, dd, ^{3}J = 6.3, ^{4}J = 3.6 Hz, 6H, Ph), 7.52 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.55, (2Me), 34.07 (NMe), 65.78 (C, CMe_2OH), 74.29 (C≡C), 78.52 (C≡C), 78.74 (C≡C), 97.20 (C, pyrrole), 97.73 (C, pyrrole), 98.82 (C≡C), 104.95 (C≡C), 111.32 (C≡C), 117.56 (C, pyrrole), 120.56 (C, pyrrole), 122.24 (Ph), 122.29 (Ph), 128.44 (Ph), 128.53 (Ph), 131.34 (Ph), 131.39 (Ph), 131.94 (Ph), 131.99 (Ph). IR (KBr, cm^{-1}): δ = 3466 (br, s), 3294 (br, s), 3056 (m), 2980 (s), 2930 (m), 2201 (s), 2065 (br, s), 1597 (s), 1440 (m), 1363 (s), 1120 (s), 908 (s), 815 (s), 732 (br, s), 689 (s). HRMS (EI, 70 eV): calcd for $C_{26}H_{20}NOBr$ [Br^{79}]: 441.07228, found 441.07232.

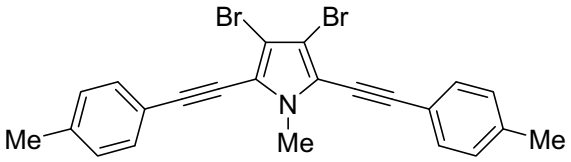
1.9.3.4 Synthesis of symmetric 3,4-tribromo-2,5-dialkynyl-1-methylpyrroles

Synthesis of 3,4-tribromo- 2,5-diphenylacetylnyl-1-methylpyrrole (16a):



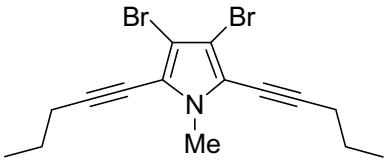
Starting with tetrabromopyrole (750 mg, 1.90 mmol), phenylacetylene (1.5 mmol), **16a** was isolated (492 mg, 59%) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, NCH_3), 7.36 (m, 6H, Ph), 7.53 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.62 (NMe), 78.50 (C≡C), 97.56 (C, pyrrole) 104.46 (C≡C), 117.88 (C, pyrrole), 122.21 (C, Ph), 128.45 (Ph), 128.82 (Ph), 131.46 (Ph). (EI, 70 eV, RT °C): *m/z* (%) = 441 (61) [M^+ ^{81}Br, ^{81}Br], 439 (100) [M^+ ^{79}Br, ^{81}Br], 437 (58) [M^+ ^{79}Br, ^{79}Br], 279 (13), 278 (26), 202 (16), 151 (96), 149 (34), 137 (45), 135 (38), 127 (10). IR (KBr, cm^{-1}): δ = 3430 (br, s), 2980 (m), 2932 (m), 2360 (w), 1723 (s), 1631 (s), 1434 (s), 1380 (s), 1256 (m), 1160 (m), 994 (m), 881 (m). HRMS (EI, 70 eV): calcd for $C_{21}H_{13}Br_2N$ [Br^{79}]: 436.94093, found 436.940105.

Synthesis of 3,4-tribromo- 2,5-ditolylacetylnyl-1-methylpyrrole (16b):



Starting with tetrabromopyrole (750 mg, 1.87 mmol) and *p*-tolylacetylene (0.6 mL, 4.67 mmol), **16b** (620 mg, 71%) was isolated as a white crysaline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 6H, CH_3, *p*-tolyl), 3.77 (s, 3H, NCH_3), 7.14 (d, ^{3}J = 8.1 Hz, 4H, *p*-tolyl), 7.56 (d, ^{3}J = 8.1 Hz, 4H, *p*-tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3, *p*-tolyl), 34.6 (NCH_3), 77.9 (C≡C), 97.7 (C, pyrrol), 104.1 (C≡C), 117.9 (C, pyrrol), 119.1 (C, *p*-tolyl), 129.2 (CH, *p*-tolyl), 131.3 (CH, *p*-tolyl), 139.1 (C, *p*-tolyl). IR (KBr, cm^{-1}): δ = 3435 (br, m), 3023 (m), 2717 (s), 2206 (w), 1537 (s), 1441 (s), 1377 (s), 1345 (s), 817 (s), 809 8s), 535 (s), 520 (s). MS (EI, 70 eV, 320 °C): *m/z* (%) = 469.5 [M^+, ^{81}Br, ^{81}Br] (50), 470 (12), 467.6 [M^+, ^{79}Br, ^{81}Br] (100), 466.8 (17), 465.6 [M^+, ^{79}Br, ^{79}Br] (51), 403 (16), 306.5 (10), 292.5 (14), 277 (42). HRMS (EI, 70 eV): calcd for $C_{23}H_{17}Br_2N$ [Br^{79}]: 464.97223, found 464.97163.

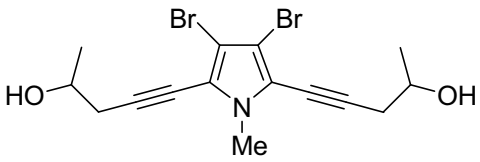
Synthesis of 3,4-tribromo- 2,5-dipentylnyl-1-methylpyrrole (16d):



Starting with tetrabromopyrole (600 mg, 1.51 mmol), 1-pentyne (3.8 mmol), **16d** was isolated (252 mg, 45 %) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^{3}J = 7.5 Hz, 6H, 2Me), 1.63 (hept, ^{3}J = 7.2 Hz 2H, CH_2), 2.46

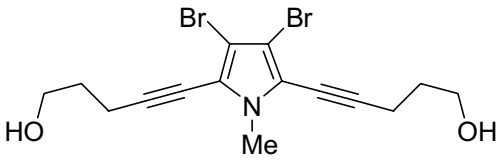
(t, ^{3}J = 6.9 Hz, 2H, CH_2), 3.63 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.48 (Me), 21.68, 22.05 ($2CH_2$), 34.27 (NMe), 70.24 (C≡C), 98.24 (C, pyrrole), 102.61 (C≡C), 117.38 (C, pyrrole). (EI, 70 eV, 170 °C): *m/z* (%) = 374 (55), 372 [M^+, ^{81}Br, ^{81}Br] (100), 370[M^+, ^{81}Br, ^{79}Br] (55), 345 (49), 341 (53), 314 (11), 262 (12), 211 (11), 182 (26), 152 (24). IR (KBr, cm^{-1}): δ = 3468 (br, m), 2963, 2934, 2872 (s), 2833 (m), 2228 (w), 1717 (m), 1526 (w), 1456 (s), 1442 (s), 1379 (s), 1343 (s), 1197 (m), 950 (m), 908 (m), 758 (br, s). HRMS (EI, 70 eV): calcd for $C_{15}H_{17}Br_2N$ [Br^{79}]: 368.97223, found 368.972072.

Synthesis of 3,4-tribromo- 2,5-di(pent-2-ol-4-ylnyl)-1-methylpyrrole (16i):



Starting with tetrabromopyrrole (700 mg, 1.76 mmol), 4-pentyne-2-ol (4.4 mmol), **16i** was isolated (496 mg, 70 %) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 6H, 2Me), 2.23 (br s, 2OH) 2.68 (d, ^{3}J = 5.4 Hz, 4H, CH_2), 3.66 (s, 3H, NCH_3), 4.07 (m, 2H, CH), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.42 (Me), 30.15 (CH_2), 34.45 (NMe), 66.30 (CH), 72.24 (C≡C), 94.68 (C, pyrrole), 103.34 (C≡C), 117.12 (C, pyrrole). (EI, 70 eV, 170 °C): *m/z* (%) = 406 [M^+, ^{81}Br, ^{81}Br] (56), 404 [M^+, ^{81}Br, ^{79}Br] (100), 402 [M^+, ^{79}Br, ^{79}Br] (54), 461 (32), 357 (29), 314 (30), 321 (18), 280 (28), 278 (27), 234 (23). IR (KBr, cm^{-1}): δ = 3366 (br, s), 2947 (s), 2920 (s), 2898 (2), 2360 (w), 1634 (m), 1442 (s), 1343 (s), 1199 (m), 1107 (s), 1086 (s), 939 (s), 657 (br, s). HRMS (EI, 70 eV): calcd for $C_{15}H_{17}NBr_2O_2$ [Br^{79}]: 400.96206, found 400.96088.

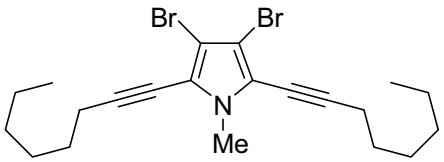
Synthesis of 3,4-tribromo- 2,5-di(pent-1-ol-4-ylnyl)-1-methylpyrrole (16h):



Starting with tetrabromopyrrole (500 mg, 1.26 mmol), 4-pentyne-1-ol (3.15 mmol), **16h** was isolated (309 mg, 61 %) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (pentet, ^{3}J = 7.1 Hz, 4H, $2CH_2$), 2.27 (br s, 2H, 2OH), 2.58 (m, 4H, $2CH_2$), 3.46 (s, 3 H, NCH_3), 3.81 (br t, ^{3}J = 6.8 Hz, 4H, $2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.28 (CH2), 31.13 (CH2), 50.71 (CH2), 33.82 (NMe), 70.98 (C≡C), 97.15 (C, pyrrole), 102.86 (C≡C), 117.26 (C, pyrrole). (EI, 70 eV, 150 °C): *m/z* (%) = 405 [M^+, ^{81}Br, ^{81}Br] (6), 403 [M^{+} ^{79}Br, ^{81}Br], (8) 401 [M^{+} ^{79}Br, ^{79}Br] (5), 279 (10), 278 (48), 277 (100), 276 (4), 202 (5), 201 (28), 199 (37), 196 (8), 185 (16), 183 (29), 171 (6), 170 (7), 152 (23), 105 (9). IR (KBr, cm^{-1}): δ = 3391 (br, s), 2947 (s), 2836 (s), 2228 (w), 1648 (s), 1438 (s), 1378 (m), 1362 (m), 1179 (w), 1120 (m), 1026 (s), 924

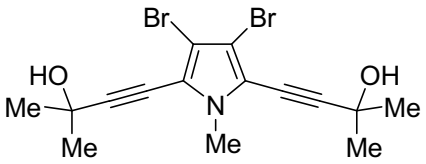
(w), 724 (br, s). HRMS (EI, 70 eV): calcd for $C_{15}H_{17}NO_2Br_2$ [Br^{79}]: 400.96040, found 400.96126.

Synthesis of 3,4-tribromo- 2,5-dioctylnyl-1-methylpyrrole (16g):



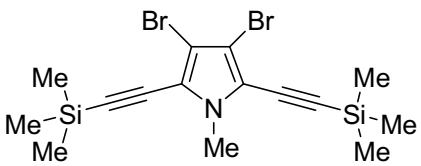
Starting with tetrabromopyrole (700 mg, 1. 76 mmol), 1-Octyne (4.4 mmol), **16g** was isolated (520 mg, 65%) as a red brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (tr, ^3J = 6.9 Hz, 3H, Me), 1.30 (br m, 8H, $4CH_2$), 1.49 (m, 2H, $2CH_2$), 1.61 (m, 4H, $2CH_2$), 2.48 (tr, ^3J = 6.9 Hz, 2H, CH_2), 3.64 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06 (Me), 19.22 (CH_2), 22.56 (CH_2), 28.51 (CH_2), 28.54 (CH_2), 31.32 (CH_2), 35.60 (NMe), 77.50 (C≡C), 98.43 (C, pyrrole), 103.00 (C≡C), 117.37 (C, pyrrole). (EI, 70 eV, 120 °C): *m/z* (%) = 457 (28) [M^+, ^{81}Br, ^{81}Br], 455 (55) [M^+, ^{79}Br, ^{81}Br], 453 (28) [M^+, ^{79}Br, ^{79}Br], 427 (35), 418 (45), 425 (39), 384 (46), 356 (56), 354 (45), 307 (40), 305 (55), 304 (18), 295 (82), 280 (45), 277 (60), 275 (41), 267 (100), 265 (65). HRMS (EI, 70 eV): calcd for $C_{21}H_{29}Br_2N$ [Br^{79}]: 453.06566, found 453.06613.

Synthesis of 3,4-tribromo- 2,5-di(2-methylbut-2-ol-3-ylnyl)-1-methylpyrrole (16h):



Starting with tetrabromopyrole (500 mg, 1.25 mmol) and 2-methyl-3-pentyne-2-ol (0.4 mL, 4.12 mmol), **16h** was isolated (370 mg, 74%) as a brownish solid. ^{1}H-NMR (250 MHz, DMSO-d_6): δ = 1.45, 1.48 (2 s, 18H, CH_3), 3.60 (s, 3H, NCH_3), 5.42, 5.60, 5.61 (3 s, 3OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.35, 31.38, 31.8, (6 CH_3), 33.8 (NCH_3), 63.8, 63.9, (C, *C*Me_2OH), 69.8, 70.0, 72.4, (C≡C), 100.1, 102.6, 103.7 (C, pyrrole), 104.1, 110.0 (C≡C), 116.8 (C, pyrrole). IR (KBr, cm^{-1}): δ = 3435 (br, s), 2980 (s), 2933 (s), 2226 (w), 1634 (m), 1452 (m), 1374 (s), 1374 (s), 1238 (s), 1164 (s), 1137 (s), 989 (w), 938 (s), 939 (m), 892 (w), 841 (m). MS (EI, 70 eV, 130 °C): *m/z* (%) = 407 (100) [M^+, ^{81}Br, ^{81}Br], 405 (99) [M^+, ^{79}Br, ^{81}Br], 403 (16) [M^+, ^{79}Br, ^{79}Br], 390 (14), 388 (28), 374 (65), 372 (71), 278 (40), 235 (23). HRMS (EI, 70 eV): calcd for $C_{20}H_{24}BrNO_3$ [Br^{79}]: 405.09341, found 405.09328.

Synthesis of 3,4-tribromo- 2,5-ditrimethylsilylacetylnyl-1-methylpyrrole (16k):

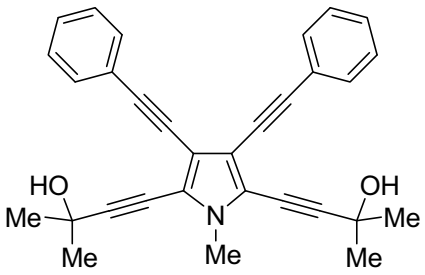


Starting with tetrabromopyrole (600 mg, 1.51 mmol), trimethylsilaneacetylene (3.8 mmol), **16k** was isolated (436 mg, 67%) as a red brown solid. ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 0.27 (s, 18H, $2SiMe_3$), 3.66 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.15 ($SiMe_3$), 34.60 (NMe), 70.98 (C≡C), 93.32 (C, pyrrole), 104.05 (C≡C), 117.88 (C, pyrrole). (EI, 70 eV, 60 °C): *m/z* (%) = 433 (60) [M^+, ^{81}Br, ^{81}Br], 431 (100) [M^+, ^{79}Br, ^{81}Br], 429 (56) [M^+, ^{79}Br, ^{79}Br], 419 (11), 418 (45), 417 (22), 416 (74), 414 (40), 359 (63), 357 (33), 346 (34), 344 (59), 200 (45). HRMS (EI, 70 eV): calcd for $C_{15}H_{21}Br_2NSi_2$ [Br^{79}]: 428.957318, found 428.957075.

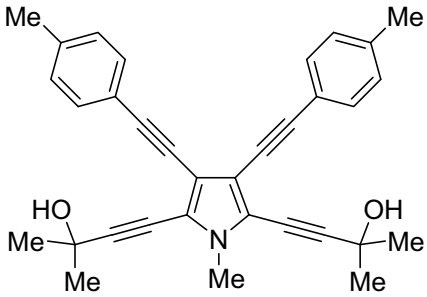
1.9.3.5 Synthesis of tetraalkynyl-1-methylpyrroles

Synthesis of 3,4-diphenylacetylnyl- 2,5-di(2-methyl-2-ol-3-ylnyl)-1-methylpyrrole (17a):



Compound **16h** (500 mg, 1.26 mmol), phenylacetylene (5.0 mmol), **17a** was isolated (182 mg, 33%) as a red brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65, (s, 6H, 2Me), 2.37 (s, 6 H, 2Me), 3.76 (s, 3H, NCH_3), 7.17 (br d, ^3J = 8.1, Hz, 4H, Ph), 7.42 (m, 6H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 31.6 (4Me), 34.08 (NMe), 65.84 (C, CMe_2OH), 74.43 (C≡C), 77.97 (C≡C), 78.20 (C≡C), 97.34 (C≡C), 98.00, (C, pyrol), 98.63 (C, pyrol), 104.66 (C≡C), 111.32 (C, pyrrole), 111.00 (C≡C), 117.63 (C, pyrrole), 119.23, 119.28 (C, Ph), 120.92 (C≡C), 129.20, 129.25 (Ph), 131.35, 131.38 (Ph), 139.03, 139.06 (Ph). IR (KBr, cm^{-1}): δ = 3441 (br, s), 2983 (s), 2982 (s), 29.25 (s), 2866 (w), 2249 (s), 1905 (w), 1729 (s), 1540 (m), 1502 (s), 1453 (s), 1437 (s), 1364 (s), 1256 (m), 1156 (m), 908 (s), 816 (s), 730 (br, s).

Synthesis of 3,4-tolyl- 2,5-di(2-methyl-2-ol-3-ylnyl)-1-methylpyrrole (17b):

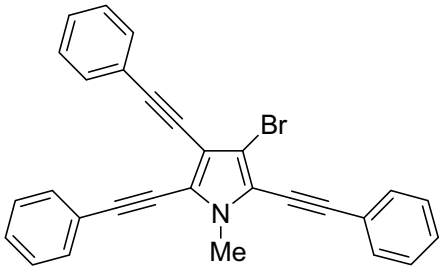


Starting with compound **16h** (500 mg, 1.26 mmol), *p*-tolylacetylene (5.0 mmol), **17b** was isolated (88 mg, 15 %) as a red brown solid. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.48 (s, 12H, 2Me), 1.98, 2.32 (2 Me), 3.63 (s, 3H, NCH_3), 7.23 (d, ^3J = 8.1 Hz, 4H, tolyl), 7.34 (d, ^3J = 8.1 Hz, 4H, tolyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.05 (4Me, tolyl), 31.33 (2Me), 33.92 (NMe), 59.73 (C, CMe_2OH), 70.03 (C≡C), 80.98 (C≡C), 101.74 (C, pyrrole), 102.63 (C, pyrrole), 103.91 (C≡C), 104.61 (C≡C), 109.89 (C, pyrrole), 120.00 (C, pyrol), 119.42 (C, *p*-tolyl), 129.39 (CH, *p*-tolyl), 130.88 (CH, *p*-tolyl), 138.35 (C, *p*-tolyl). IR (KBr, cm^{-1}): δ = 3401 (br, s), 2911 (s), 2982 (m), 2833 (s), 2821(w), 2189 (s),

1895 (m), 1745 (s), 1580 (m), 1533 (s), 1472 (s), 1410 (s), 1354 (m), 1285 (s), 1160 (m), 903 (s), 801 (s), 729 (br, s).

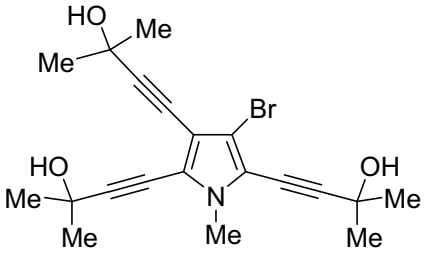
1.9.3.6 Synthesis of 3-bromo-2,4,5-trialkynyl-1-methylpyrroles

Synthesis of 3-bromo-2,4,5-tritolyl-1-methylpyrrole (18a):



Starting with tetrabromopyrole (500 mg, 1.26 mmol), phenylacetyylene (4.16 mmol), **18a** was isolated (208 mg, 36 %) as a red to brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, NCH_3), 7.34 (m, 9H, Ph), 7.55 (m, 6H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.16 (NMe), 78.6, 78.94, 81.61 (3C≡C), 94.25, 97.31 (2C, pyrrole), 99.00, 105.03 (2C≡C), 111.97 (C≡C), 117.83, 120.78 (2C, pyrrole), 122.33, 122.39, 123.56 (C, Ph), 128.03, 128.25, 128.46, 128.76 (Ph), 131.44, 131.47, 131.53 (Ph). IR (KBr, cm^{-1}): δ = 3435 (br s), 3060 (m), 3031 (m), 2206 (s), 1596 (s), 1479 (s), 1440 (s), 1367 (s), 1258 (m), 1068 (m), 1025 (m), 911 (m), 753 (s), 687 (s), 521 (m). (EI, 70 eV, 85 °C): *m/z* (%) = 460 [M^+, Br^{79}] (100), 462 (97), 480 (100), 378 (12), 351 (5), 338 (6), 238 (16), 237 (12), 142 (18). HRMS (EI, 70 eV): calcd for $C_{28}H_{18}NBr$ [Br^{79}]: 459.06171, found 459.061708.

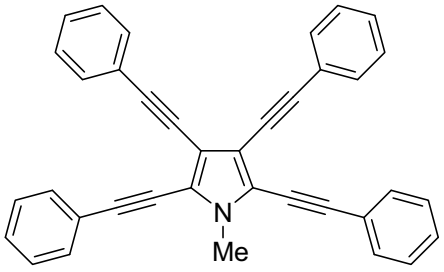
Synthesis of 3-bromo-2,4,5-tri(2-methylbut-2-ol-3-ylnyl)-1-methylpyrrole (18c):



Starting with tetrabromopyrole (500 mg, 1.25 mmol), 2-methyl-3-pentyne-2-ol (0.4 mL, 4.12 mmol), 18c was isolated (198 mg, 39 %) as a brown crystalline solid. 1H-NMR (250 MHz, DMSO-d_6): δ = 1.45, (s, 12H, 4CH3), 1.48 (s, 6H, 2CH3), 3.60 (s, 3H, NCH3), 5.42, 5.60, 5.61 (3 s, 3OH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 31.35, 31.38, 31.8, (6 CH3), 33.8 (NCH3), 63.8, 63.9, (C, CMe2OH), 69.8, 70.0, 72.4, (C≡C), 100.1, 102.6, 103.7 (C, pyrrole), 104.1, 110.0 (C≡C), 116.8 (C, pyrrole), 119.9 (C, pyrrole). IR (KBr, cm-1): δ = 3435 (br, s), 2980 (s), 2933 (s), 2226 (w), 1634 (m), 1452 (m), 1374 (s), 1374 (s), 1238 (s), 1164 (s), 1137 (s), 989 (w), 938 (s), 939 (m), 892 (w), 841 (m). MS (EI, 70 eV, 130 °C): m/z (%) = 407 (100) [M^+, ^{81}Br], 405 (99) [M^+, ^{79}Br], 403 (16), 390 (14), 388 (28), 374 (65), 372 (71), 278 (40), 235 (23). HRMS (EI, 70 eV): calcd for $C_{20}H_{24}BrNO_3$ ([M^+, ^{79}Br]): 405.09341, found 405.09328.

1.9.3.7 Synthesis of tetraalkynyl-1-methylpyrroles

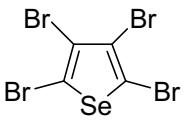
Synthesis of tetraphenylacetylnyl-1-methylpyrrole (19a):



Starting with tetrabromopyrole (500 mg, 1.25 mmol) and phenylacetylene (0.82 mL, 7.5 mmol), 1**9a** was isolated (150 mg, 25%) as an orange to red oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.81 (s, 3H, NCH_3), 7.32 (br s, 4H, Ph), 7.35 (m, 8H, Ph), 7.56 (m, 8H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.8 (NCH_3), 79.2, 82.3, 94.3 (C≡C), 112.7 (C, pyrrole), 120.6 (C, pyrrole), 122.5 (C, Ph), 123.9 (C, Ph), 127.9, 128.3, 128.46, 128.7, 131.46, 131.52 (CH, Ph). IR (KBr, cm^{-1}): δ = 3435 (m), 3058 (w), 2959 (s), 2927 (s), 2871 (m), 2204 (s), 1728 (s), 1597 (s), 1478 (s), 1454 (s), 1376 (m), 1255 (m), 1067 (m), 910 (m), 754 (s), 688 (s). MS (EI, 70 eV, 85 °C): *m/z* (%) = 482 (10), 481 (39) [M^+], 480 (100), 476 (6), 401 (4), 338 (6), 239 (22), 230 (2). HRMS (EI, 70 eV): calcd for $C_{37}H_{23}N$: 481.18301, found 481.18276.

1.9.4 Synthesis of functionalized selenophene by suzuki-cross coupling reactions of tetrabromoselenophenes

Synthesis of tetrabromoselenophene, C_4Br_4Se (20):



Selenophene (2.50 g, 0.019 mol) was dissloved in CH_2Cl_2 (10 mL). This solution was cooled to 0 °C in an ice bath and subsequently an excess of bromine (13.00 g, 0.13 mol) was added dropwise during 2 h. The solution was stirred under reflux for 3 days. To the residue was added a saturated aqueous solution of NaOH and the solution was heated under reflux for 6 h. The aqueous layer and the organic layer were separated. The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The product was recrystallized from a 1:1-solution of chloroform and methanol at -18 °C. The product (in the form of yellow crystals) was washed with very cold ethyl acetate for several times to give the product as slightly yellow crystals (84%), mp. = 97-98 °C. ^{13}C NMR (75 MHz: $CDCl_3$): δ = 112.2, 117.9 (CBr).

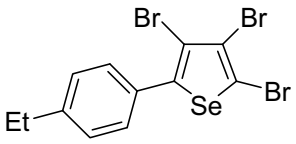
General procedure A for the synthesis of substituted arylselenophene: To a (1:1, 4 mL) toluene/dioxane solution of tetrabromoselenophene (**20**) (0.134 g, 0.3 mmol) was added $Pd(PPh_3)_4$ at 20 °C. After stirring for 30 min, the arylboronic acid, K_3PO_4 and water (1 mL)

were added. The mixture was stirred and heated under reflux for 8 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (fine flash silica gel, n-heptane).

Gerneral procedure B for the synthesis of substitutedaryl selenophene: An oven-dried Schlenk flask was charged with $Pd(OAc)_2$, ligand **L**, tetrabromoselenophene (**20**), boronic acid and powdered, anhydrous K_3PO_4. The Schlenk flask was capped with a rubber septum and then evacuated and filled with argon. A (1:1, 4 mL) toluene/dioxane mixture was added by syringe through a septum. The septum was replaced by a condenser in an argon stream. The reaction mixture was stirred at 100 °C for 6 h under argon. The solution was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated and the latter was dried (Na_2SO_4). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (fine flash silica gel, n-heptane).

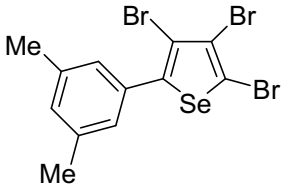
1.9.4.1 Synthesis of 5-aryl-2,3,4-tribromoselenophenes (21a-d)

Synthesis of 5-(4-ethylphenyl)-2,3,4-tribromoselenophene (21a):



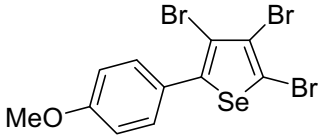
Employed method A. Starting with **20** (0.134 g, 0.3 mmol), 4-ethylphenylboronic acid (1.0 eq, 0.33 mmol, 0.050 g), and $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **21a** (50%, 0.07 g) was isolated as a slightly yellow solid, mp. = 60-62 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, CH_3), 2.70 (q, 2 H, CH_2), 7.25, 7.44 (d, ^3J = 8.2 Hz, 2 H, 2 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.7 (CH_2), 128.2, 129.0 (CH, Ar), 110.2, 111.3, 119.5 (C, CBr), 131.7, 144.8, 145.5 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 3037 (w), 3019 (w), 2966 (w), 2925 (w), 2847 (w), 1905 (w), 1885 (w), 1660 (w), 1607 (w), 828 (w). MS (EI, 70 eV): *m/z* (%) = 475 (M^+, [^{81}Br, ^{81}Br, ^{81}Br], 11), 473 (M^+, [^{81}Br, ^{81}Br, ^{79}Br], 16), 472 (100), 471 (M^+, [^{81}Br, ^{79}Br, ^{79}Br], 19), 469 (M^+, [^{79}Br, ^{79}Br, ^{79}Br], 13). HRMS (EI, 70 eV): calcd for $C_{12}H_9Br_3Se$ (M^+, [^{81}Br, ^{81}Br, ^{79}Br]): 473.73732; found: 473.73826, (M^+, [^{81}Br, ^{79}Br, ^{79}Br]): 471.73936, found : 471.73943, (M^+, [^{79}Br, ^{79}Br, ^{79}Br]): 469.74141, found: 469.74065.

Synthesis of 5-(3,5-dimethylphenyl)-2,3,4-tribromoselenophene (21b).



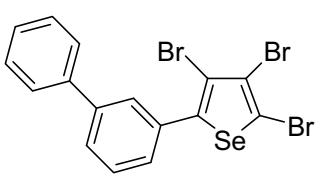
Employed method B. Starting with **20** (0.134 g, 0.3 mmol) and 3,5-dimethylphenylboronic acid (1.1 eq, 0.33 mmol, 0.050 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12.3 mg, 10 mol-%), reflux 8h, **21b** (85%, 0.12 g) was isolated as a white solid, mp. = 130-132 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.36 (s, 6 H, $2CH_3$), 7.04 (s, 1 H, CH, Ar), 7.12 (s, 2 H, 2 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 126.8, 130.8 (CH, Ar), 110.2, 111.4, 119.4 (C, CBr), 134.1, 138.4, 145.1 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2909 (w), 2851 (w), 2721 (w), 1796 (w), 1769 (w), 1746 (w), 1722 (w), 1592 (w), 1453 (w), 1229 (w), 848 (w), 722 (w), 690 (m). MS (EI, 70 eV): *m/z* (%) = 475 (M^+, [^{81}Br, ^{81}Br, ^{81}Br], 10), 473 (M^+, [^{81}Br, ^{81}Br, ^{79}Br], 17), 472 (100), 471 (M^+, [^{81}Br, ^{79}Br, ^{79}Br], 19), 469 (M^+, [^{79}Br, ^{79}Br, ^{79}Br], 13). HRMS (EI, 70 eV): calcd for $C_{12}H_9Br_3Se$ (M^+, [^{81}Br, ^{81}Br, ^{79}Br]): 473.73732; found: 473.73824, (M^+, [^{81}Br, ^{79}Br, ^{79}Br]): 471.73936, found: 471.73962, (M^+, [^{79}Br, ^{79}Br, ^{79}Br]): 469.74141, found: 469.74110.

Synthesis of 5-(4-methoxyphenyl)-2,3,4-tribromoselenophene (21c):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and 4-methoxyphenylboronic acid (1.1 eq, 0.33 mmol, 0.051 g), and $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **2c** (68%, 0.96 g) was isolated as a yellow solid, mp. = 125-127 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 6.94, 7.44 (d, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (CH_3), 114.1, 130.4 (d, ^3J = 8.2 Hz, CH, Ar), 110.0, 110.9, 119.4 (C, CBr), 126.7, 144.6, 160.2 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3026 (w), 2953 (w), 2895 (w), 2830 (w), 2546 (w), 2090 (w), 1884 (w), 1601 (w), 1492 (w), 1245 (w), 1029 (w), 826 (w), 690 (m). MS (EI, 70 eV): *m/z* (%) = 477 (M^+, [^{81}Br, ^{81}Br, ^{81}Br], 7), 475 (M^+, [^{81}Br, ^{81}Br, ^{79}Br], 14), 474 (100), 473 (M^+, [^{81}Br, ^{79}Br, ^{79}Br], 18), 471 (M^+, [^{79}Br, ^{79}Br, ^{79}Br], 12). HRMS (EI, 70 eV): calcd for $C_{11}H_7Br_3OSe$ (M^+, [^{81}Br, ^{79}Br, ^{79}Br]): 473.71863, found: 473.72001, (M^+, [^{79}Br, ^{79}Br, ^{79}Br]): 471.72068, found: 471.72235.

Synthesis of 5-(3-biphenyl)-2,3,4-tribromoselenophene (21d):



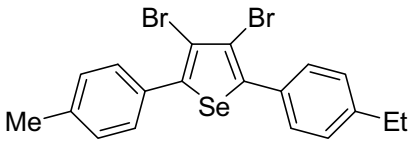
Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and 4-methoxyphenylboronic acid (1.1 eq, 0.33 mmol, 0.065 g), and $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2

mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **21d** (47%, 0.73 g) was isolated as a yellow solid, mp. = 90-93 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38-7.74 (m, 9 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.21, 127.91, 128.93 (CH, 2CH, Ar), 127.79, 127.85, 129.2 (CH, 1 CH, Ar), 110.9, 111.9, 119.7 (C, CBr), 134.8, 140.2, 141.8, 144.5 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 3024 (w), 1926 (w), 1874 (w), 1798 (w), 1693 (w), 1568 (w), 1468 (w), 1233 (w), 745 (w), 689 (w), 619 (w), 588 (m). MS (EI, 70 eV): *m/z* (%) = 523 (M^+, [^{81}Br, ^{81}Br, ^{81}Br], 6), 521 (M^+, [^{81}Br, ^{81}Br, ^{79}Br], 10), 519 (M^+, [^{81}Br, ^{79}Br, ^{79}Br], 9), 517 (M^+, [^{79}Br, ^{79}Br, ^{79}Br], 7). HRMS (EI, 70 eV): calcd for $C_{16}H_9Br_3Se$ (M^+, [^{81}Br, ^{81}Br, ^{79}Br]): 521.73732; found: 521.73765, (M^+, [^{81}Br, ^{79}Br, ^{79}Br]): 519.73936, found: 519.73924, (M^+, [^{79}Br, ^{79}Br, ^{79}Br]): 517.74141, found: 517.74031.

1.9.4.2 Synthesis of unsymmetrical-2,5-diaryl-3,4-dibromoselenophenes

General procedure B for synthesis of unsymmetrical 2,5-diaryl-3,4-dibromoselenophenes (22a,b): An oven-dried Schenk flask was charged with $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%), **22a, b** (0.3 mmol), the boronic acid (1.1 equiv., 0.33 mmol) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g). The Schlenk flask was evacuated and subsequently flushed with argon. A mixture of toluene and dioxane (1:1, 4 mL) was added by syringe. The reaction mixture was heated under reflux for 6 h. The mixture was allowed to cool to ambient temperature and water (5mL) was added. The aqueous and the organic layer were separated. The latter was dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (fine silica gel, heptanes).

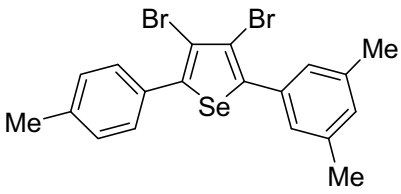
Synthesis of 2-ethylphenyl-5-(*p*-tolyl)-3,4-dibromoselenophene (22a):



Employed method B. Starting with **21b** (0.141 g, 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g) and 4-methylphenylboronic acid (1.0 eq, 0.33 mmol, 0.041 g, reflux 8h, **22a** (76%, 0.11 g) was isolated as an orange highly viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.67 (q, 2 H, CH_2), 7.19, 7.25, 7.42, 7.47 (d, ^{3}J = 8.2 Hz, 2 H, 2 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 21.1 (CH_3), 28.5 (CH_2), 126.79, 126.90, 128.2, 129.4 (CH, Ar), 132.06, 132.28, 136.7, 138.6, 143.0, 145.0 (C, Ar), 112.0 (overlap of two CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3020 (w), 2961

(w), 2927 (w), 2968 (w), 1901 (w), 1605 (w), 1490 (m), 940 (w), 817 (m), 799 (m), 718 (w). MS (EI, 70 eV): *m/z* (%) = 485 (M^+, [^{81}Br, ^{81}Br], 11), 484 (100), 483 (M^+, [^{81}Br, ^{79}Br], 19), 481 (M^+, [^{79}Br, ^{79}Br], 22). HRMS (EI, 70 eV): calcd for $C_{19}H_{16}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]): 485.87425; found: 485.87411, (M^+, [^{81}Br, ^{79}Br]): 483.87635, found: 483.87642, (M^+, [^{79}Br, ^{79}Br]): 481.87840, found: 481.87849.

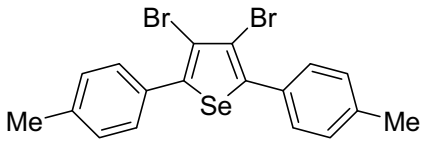
Synthesis of 3,5-dimethylphenyl-5-(p-tolyl)-3,4-dibromoselenophene (22b):



Employed method B. Starting with **21b** (0.141 g, 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g) and 4-methylphenylboronic acid (1.1 eq, 0.33 mmol, 0.041 g), reflux 8h, **22b** (80%, 0.116 g) was isolated as an orange highly viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (s, 6 H, 2CH_3), 1.30 (s, 3 H, CH_3), 7.19, 7.28 (d, ^3J = 8.2 Hz, 2 H, 2 CH, Ar), 7.51 (s, 1 H, CH, Ar), 7.59 (s, 2 H, 2 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.4 (CH_3), 125.1 (C, 1 CH, Ar), 126.8, 129.1, 129.4 (C, 2 CH, Ar), 132.1, 136.7, 138.1, 138.8, 141.4, 142.9 (C, Ar), 112.1 (overlap of two CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3019 (w), 2914 (w), 2857 (w), 2729 (w), 1666 (w), 1597 (m), 1490 (m), 1239 (m), 840 (m), 799 (m), 693 (w). MS (EI, 70 eV): *m/z* (%) = 485 (M^+, [^{81}Br, ^{81}Br], 12), 484 (100), 483 (M^+, [^{81}Br, ^{79}Br], 21), 481 (M^+, [^{79}Br, ^{79}Br], 22). HRMS (EI, 70 eV): calcd for $C_{19}H_{16}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]) : 485.87425; found : 485.87431, (M^+, [^{81}Br, ^{79}Br]) : 483.87635, found : 483.87649, (M^+, [^{79}Br, ^{79}Br]) : 481.87840, found : 481.87836.

1.9.4.3 Synthesis of symmetrical 2,5-diaryl-3,4-dibromoselenophenes (23a-h)

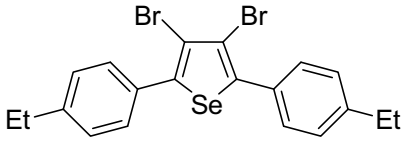
Synthesis of 2,5-ditolyl-3,4-dibromoselenophene (23a):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and *p*-tolylboronic acid (2.2 eq, 0.66 mmol, 0.09 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **23a** (83%, 0.117 g) was isolated as a yellow solid, mp. = 98-102 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 6 H, 2CH_3), 7.22, 7.39 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 129.5, 129.8 (CH, Ar), 132.1, 138.8, 142.9 (C, Ar), 112.1 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3019 (w), 2914 (w), 2725 (w), 1894 (w), 1565 (w), 1488 (m), 1246 (w), 1178 (w), 1021 (w), 957 (w), 809 (m), 719 (m), 637 (m). MS (EI, 70 eV): *m/z* (%)

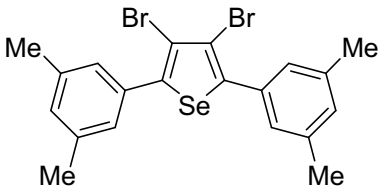
= 471 (M^+, [^{81}Br, ^{81}Br], 20), 469 (M^+, [^{81}Br, ^{79}Br], 23), 470 (100), 467 (M^+, [^{79}Br, ^{79}Br], 19). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]): 471.85811; found: 471.85951, (M^+, [^{81}Br, ^{79}Br]): 469.86015, found: 469.86074, (M^+, [^{79}Br, ^{79}Br]): 467.86220, found: 467.86196.

Synthesis of 2,5-diethylphenyl-3,4-dibromoselenophene (23b):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and *p*-ethylphenylboronic acid (2.2 eq, 0.66 mmol, 0.099 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h. Employed method B. Starting with **20** (0.134 g, 0.3 mmol) and *p*-ethylphenylboronic acid (2.2 eq, 0.66 mmol, 0.099 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), reflux 8h, **23b** (method A : 69%, 0.103 g ; method B : 0.124 g) was isolated as a yellow solid, mp. = 68-72 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (t, 6 H, $2CH_3$), 2.56 (q, 4 H, $2CH_2$), 7.12, 7.41 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.6 (CH_2), 128.2, 129.1 (CH, Ar), 132.2, 143.0, 145.0 (C, Ar), 112.1 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2926 (w), 2867 (w), 1906 (w), 1668 (w), 1607 (w), 1522 (w), 1490 (m), 1453 (w), 834 (m), 796 (m), 769 (m), 688 (m). MS (EI, 70 eV): *m/z* (%) = 499 (M^+, [^{81}Br, ^{81}Br], 21), 498 (100), 497 (M^+, [^{81}Br, ^{79}Br], 23), 495 (M^+, [^{79}Br, ^{79}Br], 19). HRMS (EI, 70 eV): calcd for $C_{20}H_{18}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]): 499.88941; found: 499.88998, (M^+, [^{81}Br, ^{79}Br]): 497.89145, found: 497.89169, (M^+, [^{79}Br, ^{79}Br]): 495.89350, found: 495.89277.

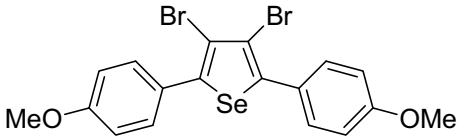
Synthesis of 2,5-(3,5-dimethylphenyl)-3,4-dibromoselenophene (23c):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and 3,5-dimethylboronic acid (2.2 eq, 0.66 mmol, 0.099 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h. Employed method B. Starting with **20** (0.134 g, 0.3 mmol) and 3,5-dimethylboronic acid (2.2 eq, 0.66 mmol, 0.099 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), reflux 8h, **23c** (method A : 65%, 0.097 g ; method B : 79%, 0.118 g) was isolated as a yellow solid, mp. = 162-164 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 12 H, $4CH_3$), 6.97 (s, 2 H, 2 CH, Ar), 7.12 (s, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.3 (CH_3), 126.9, 130.4 (CH, Ar), 134.8, 138.2, 143.1 (C, Ar),

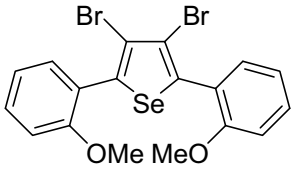
112.0 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2995 (w), 2911 (w), 2857 (w), 2725 (w), 1737 (w), 1595 (w), 1444 (w), 1228 (m), 888 (w), 843 (m), 784 (m), 691 (m). MS (EI, 70 eV): *m/z* (%) = 499 (M^+, [^{81}Br, ^{81}Br], 21), 498 (100), 497 (M^+, [^{81}Br, ^{79}Br], 25), 495 (M^+, [^{79}Br, ^{79}Br], 20). HRMS (EI, 70 eV): calcd for $C_{20}H_{18}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]): 499.88941; found: 499.89033 (M^+, [^{81}Br, ^{79}Br]): 497.89145, found: 497.89246, (M^+, [^{79}Br, ^{79}Br]): 495.89350, found: 495.89365.

Synthesis of 2,5-(p-methoxyphenyl)-3,4-dibromoselenophene (23d):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and p-methoxyphenylboronic acid (2.2 eq, 0.66 mmol, 0.09 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), reflux 8h, **23d** (82%, 0.123 g) was isolated as a yellow solid, mp. = 157-161 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.75 (s, 6 H, 2OCH_3), 6.84, 7.45 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 114.0, 130.4 (CH, Ar), 127.3, 142.3, 159.9 (C, Ar), 111.7 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2983 (w), 2965 (w), 2832 (w), 1605 (m), 1491 (m), 1242 (m), 1174 (m), 1028 (m), 827 (m), 783 (w), 728 (w), 685 (w), 656 (w), 631 (m). MS (EI, 70 eV): *m/z* (%) = 503 (M^+, [^{81}Br, ^{81}Br], 11), 502 (100), 501 (M^+, [^{81}Br, ^{79}Br], 21), 500 (100), 499 (M^+, [^{79}Br, ^{79}Br], 17). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2O_2Se$ (M^+, [^{81}Br, ^{81}Br]): 503.84794; found: 503.84884, (M^+, [^{81}Br, ^{79}Br]): 501.84998, found: 501.84986, (M^+, [^{79}Br, ^{79}Br]): 499.85203, found: 499.85235.

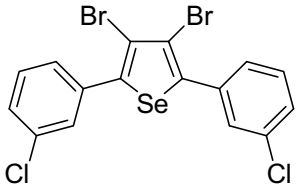
Synthesis of 2,5-(o-methoxyphenyl)-3,4-dibromoselenophene (23e):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and o-methoxyphenylboronic acid (2.2 eq, 0.66 mmol, 0.09 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h. Employed method B. Starting with **20** (0.134 g, 0.3 mmol) and o-methoxyphenylboronic acid (2.2 eq, 0.66 mmol, 0.09 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), reflux 8h, **23e** (method A : 42%, 0.063 g; method B : 68%, 0.102 g) was isolated as a yellow solid, mp. = 85-87 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.76 (s, 6 H, 2OCH_3), 6.89, 6.98 (t, ^3J = 8.2 Hz, 2 H, 2 CH, Ar), 7.29, 7.35 (d, ^3J = 8.2 Hz, 2 H, 2 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 111.2, 120.3, 130.3, 131.8 (CH, Ar), 123.8, 139.2, 156.5 (C, Ar), 113.6 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3011 (w), 2936 (w),

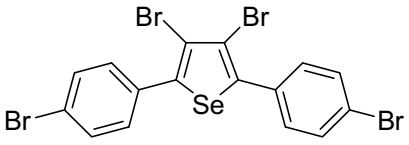
2833 (w), 1472 (m), 1428 (m), 1256 (m), 1237 (m), 1113 (m), 1017 (m), 805 (w), 747 (w), 681 (w), 565 (w), 537 (m). MS (EI, 70 eV): *m/z* (%) = 503 (M^+, [^{81}Br, ^{81}Br], 14), 502 (100), 501 (M^+, [^{81}Br, ^{79}Br], 23), 500 (100), 499 (M^+, [^{79}Br, ^{79}Br], 19). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2O_2Se$ (M^+, [^{81}Br, ^{81}Br]): 503.84794; found: 503.84889, (M^+, [^{81}Br, ^{79}Br]): 501.84998, found: 501.84990, (M^+, [^{79}Br, ^{79}Br]): 499.85203, found: 499.85213.

Synthesis of 2,5-(m-chlorophenyl)-3,4-dibromoselenophene (23f):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and m-chlorophenylboronic acid (2.2 eq, 0.66 mmol, 0.103 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h. Employed method B. Starting with **20** (0.134 g, 0.3 mmol) and m-chlorophenylboronic acid (2.2 eq, 0.66 mmol, 0.103 g), $Pd(OAc)_2$ (3.4 mg, 5 mol-%), **L** (12,3 mg, 10 mol-%) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), reflux 8h, **23f** (method A : 45%, 0.069 g; method B : 15%, 0.023 g) was isolated as a white solid, mp. = 170-171 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.37, 7.39 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar), 7.46 (t, ^3J = 8.2 Hz, 2 H, 2 CH, Ar), 7.58 (s, 2H, 2CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.4, 129.0, 129.2, 129.9 (CH, Ar), 134.6, 136.3, 141.8 (C, Ar), 113.4 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3154 (w), 3097 (w), 3045 (w), 1942 (w), 1874 (w), 1802 (w), 1757 (w), 1693 (w), 1590 (m), 1557 (m), 1545 (m), 878 (m), 767 (m), 688 (m). MS (EI, 70 eV): *m/z* (%) = 515 (M^+, [^{81}Br, ^{81}Br, ^{37}Cl, ^{37}Cl], 6), 513 (M^+, [^{81}Br, ^{79}Br, ^{37}Cl, ^{37}Cl], 32), 511 (M^+, [^{79}Br, ^{79}Br, ^{37}Cl, ^{37}Cl], 77), 509 (M^+, [^{79}Br, ^{79}Br, ^{35}Cl, ^{37}Cl], 100), 507 (M^+, [^{79}Br, ^{79}Br, ^{35}Cl, ^{35}Cl], 65). HRMS (EI, 70 eV): calcd for $C_{16}H_8Br_2Cl_2Se$ (M^+, [^{81}Br, ^{81}Br, ^{35}Cl, ^{35}Cl]): 511.74886; found: 511.74944, (M^+, [^{81}Br, ^{79}Br, ^{37}Cl, ^{37}Cl]): 509.75091, found: 509.75133, (M^+, [^{79}Br, ^{79}Br, ^{35}Cl, ^{35}Cl]): 507.75295, found: 507.75284.

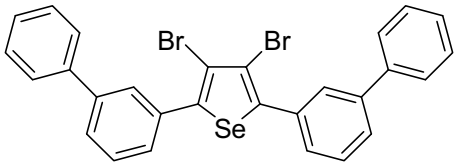
Synthesis of 2,5-(p-bromophenyl)-3,4-dibromoselenophene (23g):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and p-bromophenylboronic acid (2.2 eq, 0.66 mmol, 0.185 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **23g** (55%, 0.099 g) was isolated as a white solid, mp. = 207-209 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47, 7.56 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.71, 131.89, (CH, Ar), 123.2, 133.6, 142.0 (C, Ar), 113.2 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ =

3083 (w), 3044 (w), 3017 (w), 2923 (w), 2295 (w), 1895 (w), 1584 (w), 1472 (m), 1391 (m), 1071 (m), 1008 (m), 820 (m), 733 (m). MS (EI, 70 eV): *m/z* (%) = 603 (M^+, [^{81}Br, ^{81}Br, ^{81}Br, ^{81}Br], 10), 601 (M^+, [^{79}Br, ^{81}Br, ^{81}Br, ^{81}Br], 17), 599 (M^+, [^{79}Br, ^{79}Br, ^{81}Br, ^{81}Br], 19), 597 (M^+, [^{79}Br, ^{79}Br, ^{79}Br, ^{81}Br], 16), 595 (M^+, [^{79}Br, ^{79}Br, ^{79}Br, ^{79}Br], 9). HRMS (EI, 70 eV): calcd for $C_{16}H_8Br_4Se$ (M^+, [^{79}Br, ^{81}Br, ^{81}Br, ^{81}Br]): 601.64578; found: 601.64663, (M^+, [^{79}Br, ^{79}Br, ^{81}Br, ^{81}Br]): 599.64783, found: 599.64887, (M^+, [^{79}Br, ^{79}Br, ^{79}Br, ^{79}Br]): 595.65192, found: 595.65151.

Synthesis of 2,5-(3-biphenyl)-3,4-dibromoselenophene (23h):



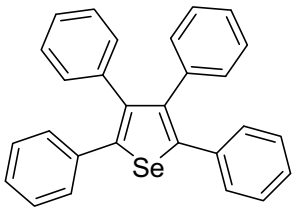
Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and 3-biphenylboronic acid (2.2 eq, 0.66 mmol, 0.131 g), $Pd(PPh_3)_4$ (5 mol-%, 17 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 8h, **23h** (48%, 0.085 g) was isolated as a yellow solid, mp. = 90-93 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.87 (m, 18 H, 18 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.2, 125.5, 125.7, 125.0, 126.9, 127.1 (CH, Ar), 133.3, 138.4, 139.7, 141.1 (C, Ar), 110.7 (CBr, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 3027 (w), 2961 (w), 1945 (w), 1878 (w), 1799 (w), 1594 (m), 1467 (m), 1261 (m), 1238 (m), 904 (m), 749 (m), 692 (m). MS (EI, 70 eV): *m/z* (%) = 595 (M^+, [^{81}Br, ^{81}Br], 24), 593 (M^+, [^{81}Br, ^{79}Br], 24), 591 (M^+, [^{79}Br, ^{79}Br], 19). HRMS (EI, 70 eV): calcd for $C_{28}H_{18}Br_2Se$ (M^+, [^{81}Br, ^{81}Br]): 595.88941; found: 595.89002, (M^+, [^{81}Br, ^{79}Br]): 593.8914, found: 593.89108, (M^+, [^{79}Br, ^{79}Br]): 591.89350, found : 591.89212.

Synthesis of tetraarylselenophenes

1.9.4.4 Synthesis of tetraarylselenophenes

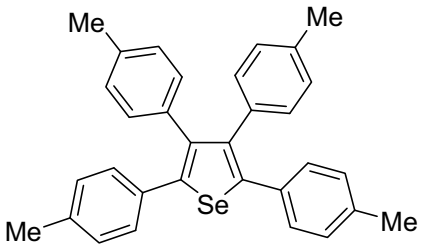
General procedure for synthesis of tetraarylselenophenes (24a-e): An oven-dried Schenk flask was charged with $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%), **20** (0.3 mmol), the boronic acid (5 equiv., 1. 5 mmol) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g). The Schlenk flask was evacuated and subsequently flushed with argon. A 1:1-mixture (4 mL) of toluene and dioxane was added by syringe. The reaction mixture was heated under reflux for 8 h. The mixture was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated. The latter was dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (fine silica gel, heptanes).

Synthesis of tetraphenylselenophene (24a):



Employed method A. Starting with **20** (0.134 g, 0.3 mmol) and phenylboronic acid (5.0 eq, 1.5 mmol, 0.183 g), $Pd(PPh_3)_4$ (10 mol-%, 34 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 14h. Method B. Starting with **20** (0.134 g, 0.3 mmol) and phenylboronic acid (5.0 eq, 1.5 mmol, 0.183 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **24a** (method A : 55%, 0.072 g; method B : 79%, 0.103 g) was isolated as a yellow solid, mp. = 158-162 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.94-7.21 (m, 20 H, 12 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.4, 125.0, 125.7, 126.2, 127.4, 128.9 (CH, Ar), 124.2, 135.9, 139.7, 142.6 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 3020 (w), 2962 (w), 1948 (w), 1876 (w), 1806 (w), 1596 (m), 1440 (m), 1068 (m), 1025 (m), 789 (m), 758 (m), 690 (m). MS (EI, 70 eV): *m/z* (%) = 435 (M^+, 11), 434 (52), 434 (19), 433 (15), 150 (12). HRMS (EI, 70 eV): calcd for $C_{28}H_{20}Se$ (M^+): 436.07302; found : 436.07311.

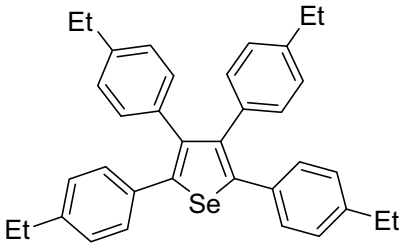
Synthesis of tetratolylselenophene (24b):



Employed B. Starting with **20** (0.134 g, 0.3 mmol) and tolylboronic acid (5.0 eq, 1.5 mmol, 0.205 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **24b** (89%, 0.131 g) was isolated as a yellow solid, mp. = 240-244 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.26, 2.31 (s, 6 H, $2CH_3$), 6.86, 6.90, 7.03, 7.10 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.13, 21.22 (CH_3), 128.4, 128.9, 129.3, 130.7 (CH, Ar), 133.6, 135.2, 135.7, 136.6, 141.4, 144.0 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3021 (w), 2917 (w), 2860 (w), 1907 (w), 1738 (w), 1511 (m), 1495 (m), 1181 (m), 1110 (m), 857 (m), 831 (m), 813 (m), 731 (m). MS (EI, 70 eV): *m/z* (%) = 491 (M^+, 15), 490 (47), 489 (17), 488 (15), 206 (9). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}Se$ (M^+): 492.13507; found: 492.13510.

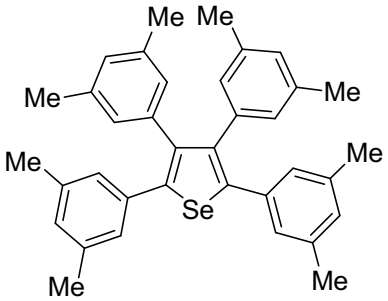
Synthesis of tetra(*p*-ethylphenyl)selenophene (24c):

Employed B. Starting with **20** (0.134 g, 0.3 mmol) and *p*-ethylphenylboronic acid (5.0 eq, 1.5 mmol, 0.225 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered,



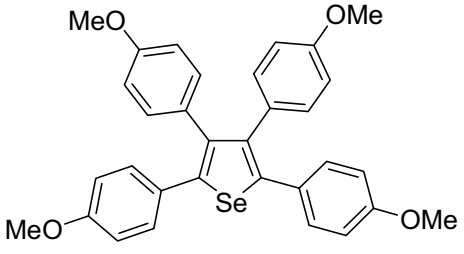
anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **24c** (0.98%, 0.161 g) was isolated as a yellow solid, mp. = 101-103 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20, 1.25 (t, 6 H, $2CH_3$), 2.57, 2.64 (q, 4 H, $2CH_2$), 6.90, 6.93, 7.06, 7.14 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar), ^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.16, 15.27 (CH_3), 28.43 (overlap of two carbons) (CH_2), 127.0, 127.6, 129.3, 130.8 (CH, Ar), 133.9, 135.5, 141.6, 142.0, 142.8, 144.0 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2961 (m), 2930 (w), 2871 (w), 1903 (w), 1789 (w), 1510 (m), 1494 (m), 1453 (m), 1019 (m), 830 (m), 800 (m), 680 (m), 546 (m). MS (EI, 70 eV): *m/z* (%) = 547 (M^+, 13), 546 (50), 547 (14), 546 (19), 262 (13). HRMS (EI, 70 eV): calcd for $C_{36}H_{36}Se$ (M^+): 548.49767; found: 548.19767.

Synthesis of tetra-(3,5-dimethylphenyl)selenophene (24d):



Employed A. Starting with **20** (0.134 g, 0.3 mmol) and 3,5-dimethylphenylboronic acid (5.0 eq, 1.5 mmol, 0.225 g), $Pd(PPh_3)_4$ (10 mol-%, 34 mg) and powdered, anhydrous K_3PO_4 (1.2 mmol, 4.0 equiv., 0.254 g), water (1 mL), reflux 14h, **24d** (74%, 0.122 g) was isolated as a yellow solid, mp. = 158-160 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.11, 2.19 (s, 12 H, $4CH_3$), 6.72, 6.81 (s, 2 H, 2 CH, Ar), 6.61, 6.86 (s, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.2 (CH_3), 127.2, 128.7, 136.6, 137.3 (CH, Ar), 127.7 (overlap of two quatery carbon), 128.5, 138.1, 142.1, 143.7 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (w), 2947 (w), 2915 (w), 2858 (w), 1593 (m), 1463 (m), 1375 (m), 847 (m), 810 (m), 693 (m). MS (EI, 70 eV): *m/z* (%) = 547 (M^+, 13), 546 (51), 547 (13), 546 (20), 262 (12). HRMS (EI, 70 eV): calcd for $C_{36}H_{36}Se$ (M^+): 548.49767; found: 548.19747.

Synthesis of tetra(*p*-methoxyphenyl)selenophene (24e):

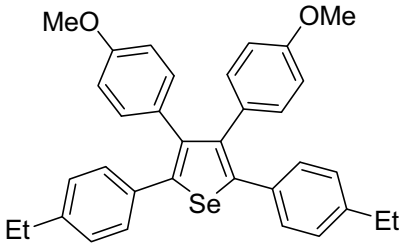


Employed B. Starting with **20** (0.134 g, 0.3 mmol) and *p*-ethylphenylboronic acid (5.0 eq, 1.5 mmol, 0.228 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **24e** (89%, 0.148 g) was isolated as a yellow solid, mp. = 188-193 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.72, 3.76 (s, 6 H, OCH_3), 6.66, 6.75, 6.83, 7.10 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ =

54.9, 55.1 (CH_3), 113.1, 113.6, 130.5, 132.0 (CH, Ar), 129.0, 130.6, 140.7, 143.1, 157.9, 158.4 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3002 (w), 2955 (w), 2838 (w), 1891 (w), 1601 (m), 1494 (m), 1281 (m), 1236 (m), 1110 (m), 1027 (m), 830 (m), 779 (m), 547 (m). MS (EI, 70 eV): *m/z* (%) = 555 (M^+, 18), 554 (51), 553 (21), 542 (16), 539 (10), 223 (15), 195 (15), 152 (11), 44 (20). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}O_4Se$ (M^+): 556.11339; found: 556.11393.

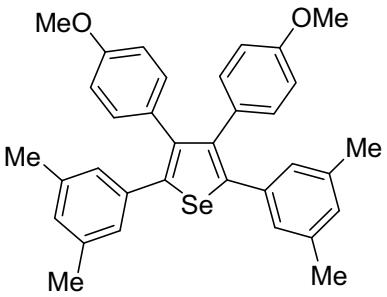
General procedure for synthesis of tetraarylselenophenes (25a,b): An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%), **23b,c** (0.3 mmol), the boronic acid (3 equiv., 0.9 mmol) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g). The Schlenk flask was evacuated and subsequently flushed with argon. A mixture (1:1, 4 mL) of toluene and dioxane was added by syringe. The reaction mixture was heated under reflux for 8 h. The mixture was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated. The latter was dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (fine silica gel, heptanes).

Synthesis of 2,5-di(*p*-ethylphenyl-3,4-di(*p*-methoxyphenyl)selenophene (25a):



Employed method B. Starting with **23b** (0.149 g, 0.3 mmol) and *p*-methoxyboronic acid (3 eq, 0.9 mmol, 0.137 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **25a** (79%, 0.13 g) was isolated as a yellow solid, mp. = 182-185 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, 6 H, $2CH_3$), 2.60 (q, 4 H, $2CH_2$), 3.73 (s, 6 H, OCH_3), 6.66, 6.84, 7.04, 7.10 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar), ^{13}C NMR (75 MHz, $CDCl_3$), δ = 15.2, 55.0 (CH_3), 28.4 (CH_2), 113.1, 127.7, 129.3, 132.0 (CH, Ar), 130.7, 133.9, 141.1, 142.7, 143.9, 157.9 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2930 (w), 2834 (w), 2058 (w), 1894 (w), 1604 (m), 1506 (m), 1493 (m), 1241 (m), 1029 (m), 807 (m), 779 (m), 554 (m). MS (EI, 70 eV): *m/z* (%) = 551 (M^+, 16), 550 (47), 549 (11), 549 (16), 266 (17). HRMS (EI, 70 eV): calcd for $C_{34}H_{32}O_2Se$ (M^+): 552.15620; found: 552.15502.

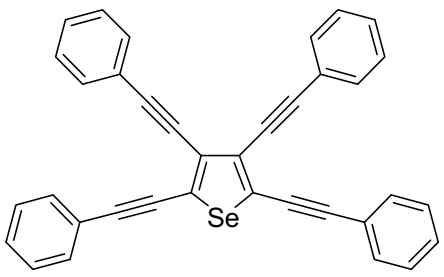
Synthesis of 2,5-di(3,5-dimethylphenyl)-3,4-di(*p*-methoxyphenyl)selenophene (25b):



Employed B. Starting with **23c** (0.149 g, 0.3 mmol) and *p*-methoxyboronic acid (3.0 eq, 0.9 mmol, 0.137 g), $Pd(OAc)_2$ (6.8 mg, 10 mol-%), **L** (24.6 mg, 20 mol-%) and powdered, anhydrous K_3PO_4 (2.4 mmol, 8.0 equiv., 0.508 g), reflux 8h, **25b** (82%, 0.135 g) was isolated as a yellow solid, mp. = 238-240 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 12 H, $4CH_3$), 3.73 (s, 6 H, $2OCH_3$), 6.66, 6.81 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar), 6.83 (s, 4 H, 4CH, Ar), 6.87 (s, 2 H, 2 CH, Ar), ^{13}C NMR (75 MHz, $CDCl_3$), δ = 21.2 (CH_3), 55.1(OCH_3), 130.1, 127.7, 128.7, 131.9 (CH, Ar), 130.8, 136.4, 141.2, 144.1, 157.8, 158.0 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2913 (w), 2836 (w), 2532 (w), 1727 (w), 1599 (m), 1495 (m), 1462 (m), 1242 (m), 1105 (m), 1032 (m), 1011 (m), 800 (m). MS (EI, 70 eV): *m/z* (%) = 551 (M^+, 15), 550 (49), 549 (10), 549 (18), 266 (12). HRMS (EI, 70 eV): calcd for $C_{34}H_{32}O_2Se$ (M^+): 552.15620; found: 552.15655.

1.9.4.5 Synthesis of tetraalylnylselenophenes

General procedure for the synthesis of tetra(phenylethynyl)selenophene (26): An oven-dried Schenk flask was charged with $Pd(Ph_3)_4$ (35 mg, 10 mol-%), **20** (0.3 mmol), phenyacetylene (5.0 equiv., 1.5 mmol, 153 mg) and CuI (1.2 mmol, 4.0 equiv., 229 mg). The Schlenk flask was evacuated and subsequently flushed with argon. To the mixture 12 mL of *i*Pr_2NH was added by syringe. After cooling to 0 °C for 4 h, the reaction was heated under reflux for 8 h. The mixture was allowed to cool to ambient temperature and the solvent was removed in vacuo. The residue was purified by flash column chromatography (fine silica gel, heptanes). Product **26** (77%, 0.123 g) was isolated as a yellow solid, mp. = 80-81 °C. ^{1}H

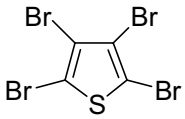


NMR (250 MHz, $CDCl_3$): δ = 7.33, 7.36 (t, ^3J = 8.2 Hz, 4 H, 4 CH, Ar), 7.38, 7.39 (t, ^3J = 8.2 Hz, 2 H, 2 CH, Ar), 7.52, 7.55 (d, ^3J = 8.2 Hz, 4 H, 4 CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.4, 128.5, 129.2, 1231.6, 132.5 (overlap of two CH) (CH, Ar), 73.9, 81.6, 83.3, 100.8 (C, acetylene), 119.6, 122.1, 132.9 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2913 (w), 2836 (w), 2532 (w), 1727 (w), 1599 (m), 1495 (m), 1462 (m), 1242 (m), 1105 (m), 1032 (m), 1011 (m), 800 (m). MS (EI, 70 eV): *m/z* (%) = 531 (M^+, 15), 530

(100), 529 (37), 528 (22), 452 (17), 389 (15). HRMS (EI, 70 eV): calcd for $C_{36}H_{20}Se$ (M^+): 532.07302; found: 532.070312.

1.9.5 Synthesis of functionalized thioephenes based on suzuki-cross coupling and metal-halide exchange reactions of tetrabromothiophene

Synthesis of tetrabromothiophene (30):



To a chloroform solution (10 mL) of thiophene (25 mL) a chloroform solution (20 mL) of bromine (60 mL) was dropwise added within 45 minutes at 0 °C. The reaction mixture was warmed to room temperature and an additional amount of bromine (10 mL) was added and the reaction mixture was subsequently stirred under reflux for three hours. A saturated aqueous solution of NaOH was added and the mixture was stirred under reflux for 6 h to remove the bromine. The solvent and the excess of bromine was removed in vacuo. The product was recrystallized from a 1:1 solution of chloroform and methanol. The crude product (red to brownish crystals) was washed with cold ethyl acetate for several times to give pure **3** as colourless crystals (87%). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.3, 116.9; MS (EI, 70 eV): *m/z* (%) = 400 (M^+, 100), 321 (65), 240 (34), 161 (41).

1.9.5.1 Synthesis of tetraarylthiophenes

General procedure A for the synthesis of 31a-h:

To a solution (for the solvents, see the individual procedures given below) of **30** was added $Pd(PPh_3)_4$ (10 mol-%) at 20 °C. After stirring for 30 min, the arylboronic acid, K_3PO_4 (8.0 mmol) and water (1.0 mL) were added. The mixture was stirred for the indicated period of time at the indicated temperature. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane). The solvents and the amounts are given in the individual procedures (see below).

General procedure B for the synthesis of 31a-h:

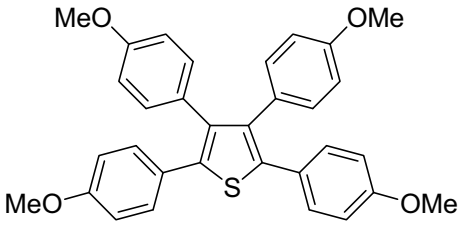
An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (5 mol-%), ligand **L** (10 mol-%), the starting material **30**, the boronic acid (6.0 eq) and powered, anhydrous K_3PO_4 (8.0 eq). The Schlenk flask was filled with argon. The solvent was added by syringe through a septum. The

septum was replaced by a condenser in an argon stream. The reaction mixture was stirred and refluxed for the indicated period of time at the indicated temperature. The solution was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated and the latter was dried Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (fine flash silica gel, heptanes). The solvents and the amounts are given in the individual procedures (see below).

General procedure A for the synthesis of 2,3,4,5-tetraarylthiophenes (33a-f):

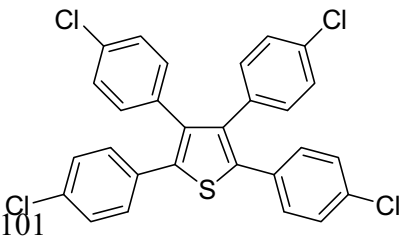
To a solution of 3,4-dibromothiophene **32** (1.0 mmol) was added $Pd(PPh_3)_4$ (0.116 g, 10 mol-%) at 20 °C. After stirring for 30 min, the arylboronic acid (3.0 mmol), K_3PO_4 (4.0 mmol) and water (2.0 mL) were added. The mixture was stirred at 90 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of tetra(4-methoxyphenyl)thiophene (31b):



Procedure A: dioxane:H_2O = 4:1 (5 mL), reflux 24 h, 100 °C. Starting with **30** (0.400 g, 1.0 mmol) and (4-methoxyphenyl)boronic acid (0.759 g, 5.0 mmol), $Pd(PPh_3)_4$ (0.115 g, 10 mol-%), K_3PO_4 (1.7 g, 8.0 mmol), **31b** was isolated (0.477 g, 94%) as a colourless solid; mp 183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65, 3.72 (s, 12 H, 2×2OCH_3), 6.59, 6.69, 6.82, 7.09 (d, 4×4H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.00, 56.06 (C, OCH_3), 114.8, 116.0, 130.2, 131.9 (CH, Ar), 127. 0, 129.0, 137.1, 138.3, 158.0, 158.6 (C, ArC). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3431 (w), 3031 (m), 3003 (m), 2957 (m), 2924 (m), 2840 (m), 1607 (m), 1511 (s), 1495 (s), 1286 (s), 1175 (s), 1031 (s), 834 (s), 799 (m). MS (EI, 70 eV): *m/z* (%) = 508 (M^+, 100), 255 (31), 178 (15), 172 (29), 160 (26), 96 (10). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}O_4S$ (M^+): 508.6273; found: 508.6277.

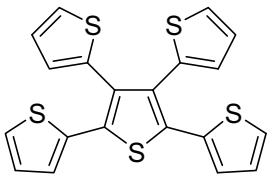
Synthesis of tetra(4-chlorophenyl)thiophene (31f):



Procedure A: toluene:H_2O = 4:1 (5 mL), reflux 24 h, 100 °C. Starting with **30** (0.400 g, 1.0 mmol) and 4-chlorophenylboronic acid (0.782 g, 5.0 mmol), $Pd(PPh_3)_4$

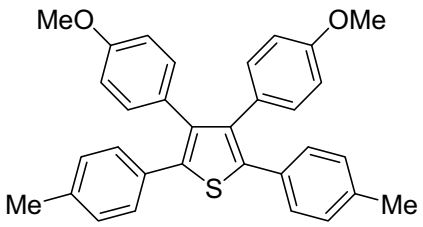
(0.115 g, 10 mol-%), K_3PO_4 (1.7 g, 8.0 mmol), **31f** was isolated (0.468 g, 89%) as a colourless solid; mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75, 7.05, 7.08, 7.09 (d, 8×2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.5, 128.7, 130.3, 131.9 (CH, Ar), 130.3, 131.8, 131.9, 132.4, 137.3, 147.3 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (m), 3066 (w), 1492 (s), 1480 (s), 1093 (s), 1086 (s), 834 (s), 806 (s), 769 (m), 526 (m), 520 (w), 501 (w), 487 (w). MS (EI, 70 eV): *m/z* (%) = 530 (M^+, [^{37}Cl,^{37}Cl,^{37}Cl,^{35}Cl], 13), 528 (M^+, [^{37}Cl,^{37}Cl,^{35}Cl,^{35}Cl], 51), 526 (M^+, [^{37}Cl,^{35}Cl,^{35}Cl,^{35}Cl], 100), 524 (M^+, [^{35}Cl,^{35}Cl,^{35}Cl,^{35}Cl], 71). HRMS (EI, 70 eV): calcd for $C_{28}H_{16}Cl_4S$ ((M^+, [^{37}Cl,^{35}Cl,^{35}Cl,^{35}Cl]): 526.3026; found: 526.3022.

Synthesis of tetra(thien-2-yl)thiophene (31h):



Procedure B: 5 mL of toluene, reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and (thien-2-yl)boronic acid (6.0 equiv., 0.383 g, 0.6 mmol), $Pd(OAc)_2$ (11 mg, 5 mol-%), **L** (41 mg, 10 mol-%), K_3PO_4 (1.7 g, 8.0 mmol), **31h** was isolated (0.166g, 81%) as a yellow solid. mp. = 110-112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.90, 7.10, 7.19, 7.30 (d, 2 H, 4 CH, thienyl), 6.94, 6.96 (t, 2 H, CH, thienyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.4, 126.3, 126.4, 126.8, 127.1, 128.4 (2 CH, thienyl), 132.4, 133.3, 135.3, 135.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3096 (w), 2959 (w), 2922 (w), 2851 (w), 1259 (w), 1216 (w), 1060 (w), 1036 (w), 1024 (w), 816 (w), 695 (m). MS (EI, 70 eV): *m/z* (%) = 412 (M^+, 100), 378 (M^+, 8), 367 (M^+,9), 346 (M^+,6), 285 (M^+,4), 283 (M^+,4). HRMS (EI, 70 eV): calcd for $C_{20}H_{12}S_5$ (M^+): 411.95371, found: 411.95369.

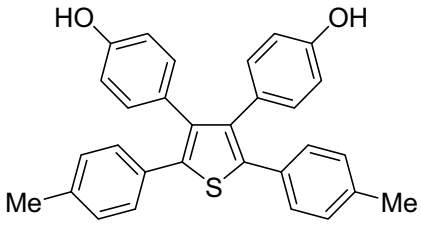
Synthesis of 3,4-di(4-methoxyphenyl)-2,5-di(4-tolyl)thiophene (33c):



Procedure A: Toluene:dioxane:H_2O = 2:2:1 (5 mL), reflux 24 h, 100 °C. Starting with **32b** (0.42 g, 1.0 mmol) and (4-methoxyphenyl)boronic acid (0.455 g, 3.0 mmol), $Pd(PPh_3)_4$ (0.115 g, 10 mol-%), K_3PO_4 (0.848 g, 4.0 mmol), **33c** was isolated (0.361 g, 76%) as a colourless solid; 230–231 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 3.62 (s, 3 H, OCH_3), 6.53, 6.75, 6.97, 7.06 (m, 16 H, 4×4CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.25 (C, CH_3), 55.10 (C, OCH_3), 113.37, 129.07, 129.09, 132.00 (CH, Ar), 129.00, 131.88, 136.84, 138.44, 139.86, 158.18 (C, ArC). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3446 (m), 2999 (m), 2962 (m), 2835 (m), 1608 (s), 1513 (s), 1290 (s), 1245 (s), 1034 (s), 841 (s), 809 (s), 563 (w). MS (EI, 70 eV): *m/z* (%) =

476 (M^+, 100), 83 (10), 71 (10), 69 (13), 57 (17), 43 (22), 40 (13). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}O_2S$ (M^+): 476.6258; found: 476.6255.

Synthesis of 3,4-bis(4-hydroxyphenyl)-2,5-di(4-tolyl)thiophene (33e):

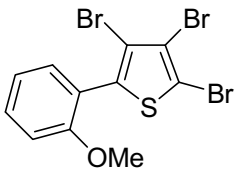


Procedure A: Toluene:dioxane:H_2O = 2:2:1 (5 mL), reflux 24 h, 90 °C. Starting with **32b** (0.42 g, 1.0 mmol) and (4-hydroxyphenyl)boronic acid (0.433 g, 3.0 mmol), $Pd(PPh_3)_4$ (0.115 g, 10 mol-%), K_3PO_4 (0.848 g, 4.0 mmol), **33e** was isolated (0.367 g, 82%) as a colourless solid; mp 186–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, CH_3), 6.49, 6.67, 6.92, 7.06 (d, 16 H, 4×4CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (C, CH_3), 128.7, 128.9, 131.7, 131.8 (CH, Ar), 127.3, 127.9, 136.8, 137.2, 139.6, 156.2 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3383 (m), 3062 (w), 2921 (m), 1609 (m), 1513 (s), 1263 (s), 1210 (s), 815 (s), 559 (w). MS (EI, 70 eV): *m/z* (%) = 449 (M^+, 57), 448 (100), 364 (23), 362 (20), 283 (15), 69 (13), 57 (14), 43 (12), 40 (11). HRMS (EI, 70 eV): calcd for $C_{30}H_{24}O_2S$ (M^+): 448.5754; found: 448.5752.

1.9.5.2 Synthesis of 2,3,4-tetrabromo-5-arylthiophenes

General procedure B for the synthesis of 34a-e: An oven-dried Schlenk flash was charged with $Pd(OAc)_2$ (5 mol-%), ligand **L** (10 mol-%), the starting material, the boronic acid (1.0 equiv.) and powered, anhydrous K_3PO_4 (4 equiv.). The Schlenk flask was filled with argon. The solvent was added by syringe through a septum. The septum was replaced by a condenser in an argon stream. The reaction mixture was stirred and refluxed for the indicated period of time at the indicated temperature. The solution was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated and the latter was dried Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (fine flash silica gel, heptanes). The solvents and the amounts are given in the individual procedures (see below).

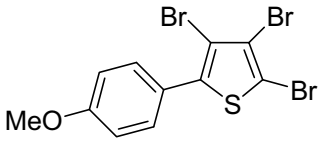
Synthesis of 2,3,4-tribromo-5-(2-methoxyphenyl)thiophene (34a):



Procedure B: toluene:dioxane = 1:1 (4 mL), reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and (2-methoxyphenyl)boronic acid (0.091 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **34a** was isolated (0.158 g, 75%) as a white solid. mp. = 72-78 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OMe), 6.98, 7.03 (d, 1

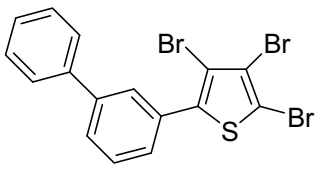
H, CH, Ar), 7.34, 7.44 (t, 1 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (OMe), 110.5, 112.6, 117.3 (CBr), 111.3, 120.5, 131.0, 131.9 (CH, Ar), 120.9, 136.3, 157.0 (C). IR (KBr, $\tilde{cm}^{-1}$): $\tilde{\nu}$ = 3077 (w), 3008 (w), 2933 (m), 2831 (m), 2487 (w), 2042 (w), 1903 (w), 1579 (s), 1246 (s), 1022 (s), 744 (s), 723 (s). MS (EI, 70 eV): *m/z* (%) = 430 (M^+, [^{81}Br,^{81}Br,^{81}Br], 35), 428 (M^+, [^{81}Br,^{81}Br,^{79}Br], 99), 426 (M^+, [^{81}Br,^{79}Br,^{79}Br], 100), 424 (M^+, [^{79}Br,^{79}Br,^{79}Br], 33). HRMS (EI, 70 eV): calcd for $C_{11}H_7Br_3S$ (M^+, [^{81}Br,^{81}Br,^{81}Br]): 429.77009, found: 429.77005; (M^+, [^{81}Br,^{81}Br,^{79}Br]): 427.77213, found: 427.77182; (M^+, [^{81}Br,^{79}Br,^{79}Br]): 425.77418, found: 425.77375; (M^+, [^{79}Br,^{79}Br,^{79}Br]): 423.77622, found: 423.77569.

Synthesis of 2,3,4-tribromo-5-(4-methoxyphenyl)thiophene (34b):



Procedure B: toluene:dioxane = 1:1 (4 mL), reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and (4-methoxyphenyl)boronic acid (0.091 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **34b** was isolated (0.17 g, 80%) as a white solid. mp. = 124-125 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OMe), 6.96, 7.49 (d, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (OMe), 109.3, 109.9, 118.3 (CBr), 114.2, 130.3 (2 CH, Ar), 124.6, 140.0, 160.3 (C). IR (KBr, $\tilde{cm}^{-1}$): $\tilde{\nu}$ = 3028 (w), 3005 (w), 2954 (w), 2895 (w), 2830 (w), 1879 (w), 1603 (w), 1489 (m), 1248 (m), 1177 (m), 1031 (m), 832 (m). MS (EI, 70 eV): *m/z* (%) = 430 (M^+, [^{81}Br,^{81}Br,^{81}Br], 35), 428 (M^+, [^{81}Br,^{81}Br,^{79}Br], 97), 426 (M^+, [^{81}Br,^{79}Br,^{79}Br], 100), 424 (M^+, [^{79}Br,^{79}Br,^{79}Br], 33). HRMS (EI, 70 eV): calcd for $C_{11}H_7Br_3S$ (M^+, [^{81}Br,^{81}Br,^{81}Br]): 429.77009, found: 429.76984; (M^+, [^{81}Br,^{81}Br,^{79}Br]): 427.77213, found: 427.77152; (M^+, [^{81}Br,^{79}Br,^{79}Br]): 425.77418, found: 425.77363; (M^+, [^{79}Br,^{79}Br,^{79}Br]): 423.77622, found: 423.77564.

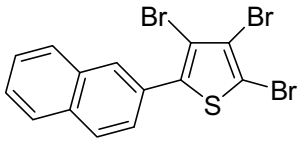
Synthesis of 2,3,4-tribromo-5-(3-biphenyl)thiophene (34c). Procedure B: 5 mL of toluene, reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and 3-biphenylboronic acid (0.119 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **34c** was isolated (0.181 g, 77%) as a yellow solid. mp. = 116-117 °C.



^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38-7.79 (m, 9 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.3, 110.6, 118.6 (CBr), 127.2, 129.9 (2CH, Ar), 127.7, 127.8, 127.9, 129.2 (CH, Ar), 132.7, 139.9, 140.2, 141.9 (C). IR (KBr, $\tilde{cm}^{-1}$): $\tilde{\nu}$ = 3077 (w), 3056 (w), 3024 (w), 1595 (w), 1567 (w), 1468 (w), 1273 (w), 786 (m), 748 (m), 691 (m). MS (EI, 70 eV): *m/z* (%) = 476

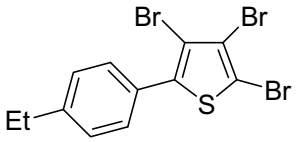
(M^+, [^{81}Br,^{81}Br,^{81}Br], 36), 474 (M^+, [^{81}Br,^{81}Br,^{79}Br], 97), 472 (M^+, [^{81}Br,^{79}Br,^{79}Br], 100), 470 (M^+, [^{79}Br,^{79}Br,^{79}Br], 33). HRMS (EI, 70 eV): calcd for $C_{16}H_9Br_3S$ (M^+, [^{81}Br,^{81}Br,^{81}Br]): 475.79082, found: 475.79034; (M^+, [^{81}Br,^{81}Br,^{79}Br]): 473.79287, found: 473.79226; (M^+, [^{81}Br,^{79}Br,^{79}Br]): 471.79491, found: 471.79506; (M^+, [^{79}Br,^{79}Br,^{79}Br]): 469.79696, found: 469.79689.

Synthesis of 2,3,4-tribromo-5-(naphth-2-yl)thiophene (34d):



Procedure B: 5 mL of toluene, reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and (naphtha-2-yl)boronic acid (0.103 g, 0.7 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **34d** was isolated (0.153 g, 69%) as an orange viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47-7.97 (m, 7 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.9, 113.7, 117.6 (CBr), 125.0, 125.5, 126.4, 127.0, 128.5, 129.4, 130.2 (CH, Ar), 129.5, 131.5, 133.5, 138.2 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3050 (w), 2962 (w), 2848 (w), 1926 (w), 1875 (w), 1814 (w), 1501 (w), 1434 (m), 1386 (m), 1261 (m), 793 (s), 796 (s) 729 (m). MS (EI, 70 eV): *m/z* (%) = 450 (M^+, [^{81}Br,^{81}Br,^{81}Br], 17), 448 (M^+, [^{81}Br,^{81}Br,^{79}Br], 48), 446 (M^+, [^{81}Br,^{79}Br,^{79}Br], 48), 444 (M^+, [^{79}Br,^{79}Br,^{79}Br], 16). HRMS (EI, 70 eV): calcd for $C_{14}H_7Br_3S$ (M^+, [^{81}Br,^{81}Br,^{79}Br]): 447.77777, found: 447.77769; (M^+, [^{81}Br,^{79}Br,^{79}Br]): 445.77981, found: 445.77989.

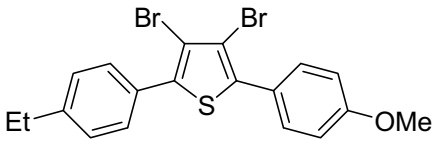
Synthesis of 2,3,4-tribromo-5-(4-ethylphenyl)thiophene (34e):



Procedure B: 5 mL of toluene, reflux 8 h, 100 °C. Starting with **30** (0.200 g, 0.5 mmol) and (4-ethylphenyl)boronic acid (0.090 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **34e** was isolated (0.183 g, 87%) as a light yellow solid; mp 58-63 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, CH_3), 2.62 (q, 2 H, CH_2), 7.20, 7.40 (d, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.7 (2 H, CH_2), 109.7, 110.0, 118.4 (CBr), 128.3, 128.8 (2 CH, Ar), 129.6, 140.2, 145.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2965 (m), 2923 (w), 2874 (w), 2836 (w), 1901 (w), 1888 (w), 1608 (w), 1484 (w), 1433 (w), 1409 (w), 1268 (m), 824 (m). MS (EI, 70 eV): *m/z* (%) = 428 (M^+, [^{81}Br,^{81}Br,^{81}Br], 34), 426 (M^+, [^{81}Br,^{81}Br,^{79}Br], 96), 424 (M^+, [^{81}Br,^{79}Br,^{79}Br], 97), 422 (M^+, [^{79}Br,^{79}Br,^{79}Br], 33). HRMS (EI, 70 eV): calcd for $C_{12}H_9Br_3S$ (M^+, [^{81}Br,^{81}Br,^{81}Br]): 427.79082, found: 427.79059; (M^+, [^{81}Br,^{81}Br,^{79}Br]): 425.79287, found: 425.79277; (M^+, [^{81}Br,^{79}Br,^{79}Br]): 423.79491, found: 423.79458; (M^+, [^{79}Br,^{79}Br,^{79}Br]): 421.79696, found: 421.79606.

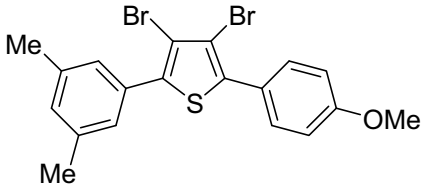
1.9.5.3 Synthesis of unsymmetrical 3,4-dibromo-2,5-diarylthiophenes

Synthesis of 3,4-dibromo-2-(4-methoxyphenyl)-5-(4-ethylphenyl)thiophene (35a):



Procedure B: toluene:dioxane = 1:1 (4 mL), reflux 8 h, 100 °C. Starting with **34b** (0.212 g, 0.5 mmol) and (4-ethylphenyl)boronic acid (0.090 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **35b** was isolated (0.163 g, 72%) as an orange solid; mp 61-76 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, CH_3), 2.76 (q, 2 H, CH_2), 3.89 (s, 3 H, OMe), 7.02, 7.34, 7.62, 7.65 (d, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.6 (CH_2), 55.3 (OMe), 111.57, 111.63 (CBr), 114.0, 128.1, 128.9, 130.3 (CH, Ar), 125.9, 127.6, 137.6, 137.7, 145.0, 159.0 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (w), 2960 (w), 2929 (w), 2871 (w), 2047 (w), 1905 (w), 1603 (w), 1486 (m), 1248 (m), 1028 (m), 827 (m), 800 (m). MS (EI, 70 eV): *m/z* (%) = 454 (M^+, [^{81}Br,^{81}Br], 53), 452 (M^+, [^{81}Br,^{79}Br], 100), 450 (M^+, [^{79}Br,^{79}Br], 50), 439 (M^+, 22), 437 (M^+, 40), 435(M^+, 21). HRMS (EI, 70 eV): calcd for $C_{19}H_{16}Br_2SO$ (M^+, [^{81}Br,^{81}Br]): 453.92422, found: 453.92399, (M^+, [^{81}Br,^{79}Br]): 451.92627, found: 451.92589; (M^+, [^{79}Br,^{79}Br]): 449.92831, found: 449.92798.

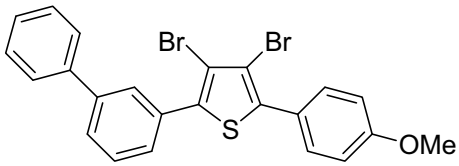
Synthesis of 3,4-dibromo-2-(4-methoxyphenyl)-5-(3,5-dimethylphenyl)thiophene (35b).



Procedure B: tolulene:dioxane = 1:1 (4 mL), reflux 8 h, 100 °C. Starting with **34b** (0.212 g, 0.5 mmol) and (3,5-dimethylphenyl)boronic acid (0.090 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **35b** was isolated (0.150 g, 67%) as an orange solid; mp 85-89 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 (s, 6 H, CH_3), 3.77 (s, 3 H, OCH_3), 6.89, 7.51 (d, 2 H, CH, Ar), 6.96 (d, H, CH, Ar), 7.18 (s, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.3 (O CH_3), 111.5, 111.7 (CBr), 114.2, 126.8, 131.4 (2 CH, Ar), 131.2 (CH, Ar), 114.3, 125.3, 132.7, 137.7, 138.2, 160.0 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2994 (w), 2931 (w), 2912 (w), 2832 (w), 2545 (w), 2077 (w), 1880 (w), 1599 (m), 1530 (m), 1469 (m), 1248 (m), 1033 (m), 824 (m), 796 (m), 739 (m), 689 (m). MS (EI, 70 eV): *m/z* (%) = 454 (M^+, [^{81}Br,^{81}Br], 53), 452 (M^+, [^{81}Br,^{79}Br], 100), 450 (M^+, [^{79}Br,^{79}Br], 49), 439 (M^+, 17), 437 (M^+, 32), 435(M^+, 16). HRMS (EI, 70 eV): calcd for $C_{19}H_{16}Br_2SO$ (M^+, [^{81}Br,^{81}Br]): 453.92422, found:

453.92398, (M^+, [^{81}Br,^{79}Br]): 451.92627, found: 451.92577; (M^+, [^{79}Br,^{79}Br]): 449.92831, found: 449.92776.

Synthesis of 3,4-dibromo-2-(4-methoxyphenyl)-5-(3-biphenyl)thiophene (35c):



Procedure B: toluene:dioxane = 1:1 (4 mL), reflux 8 h, 100 °C. Starting with **34b** (0.212 g, 0.5 mmol) and 3-biphenylboronic acid (0.119 g, 0.6 mmol), $Pd(OAc)_2$ (5,6 mg, 5 mol-%), **L** (20.5 mg, 10 mol-%), K_3PO_4 (0.424 g, 4.0 mmol), **35c** was isolated (0.171 g, 69%) as an orange solid; mp 60-62 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.99 (d, 2 H, CH, Ar), 7.33-7.65 (m, 11 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (O CH_3), 111.8, 112.2 (CBr), 114.1, 127.2, 128.9, 130.3 (2 CH, Ar), 127.2, 127.6, 127.7, 127.8, 129.1 (CH, Ar), 125.2, 133.4, 137.3, 138.2, 140.5, 141.7, 160.1 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 3029 (w), 3003 (w), 2929 (w), 2833 (w), 1873 (w), 1604 (w), 1474 (m), 1450 (m), 1253 (m), 1179 (m), 1033 (m), 821 (m), 747 (m), 961 (m). MS (EI, 70 eV): *m/z* (%) = 502 (M^+, [^{81}Br,^{81}Br], 14), 500 (M^+, [^{81}Br,^{79}Br], 30), 498 (M^+, [^{79}Br,^{79}Br], 13), 497 (M^+, 66), 486 (M^+, 12), 484 (M^+, 24). HRMS (EI, 70 eV): calcd for $C_{23}H_{16}Br_2SO$ (M^+, [^{81}Br,^{81}Br]): 501.92422, found: 501.92450, (M^+, [^{81}Br,^{79}Br]): 499.92627, found: 499.92610; (M^+, [^{79}Br,^{79}Br]): 497.92831, found: 497.92959.

1.9.5.4 Synthesis of dimethyl 3,4-diarylthiophene-2,5-dicarboxylate

General procedure A for the synthesis of 38a-d:

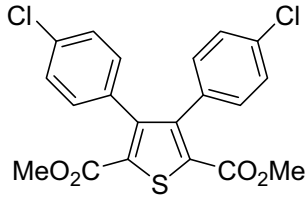
To a solution (for the solvents, see the individual procedures given below) of starting material was added $Pd(PPh_3)_4$ (10 mol-%) at 20 °C. After stirring for 30 min, the arylboronic acid, K_3PO_4 (8.0 mmol) and water (1.0 mL) were added. The mixture was stirred for the indicated period of time at the indicated temperature. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane). The solvents and the amounts are given in the individual procedures (see below).

General procedure B for the synthesis of 38a-d:

An oven-dried Schlenk flash was charged with $Pd(OAc)_2$ (10 mol-%), ligand **L** (20 mol-%), the starting material, the boronic acid and powered, anhydrous K_3PO_4 (8 equiv.). The Schlenk

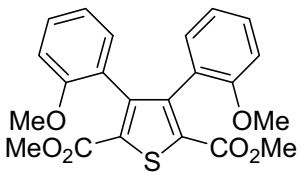
flask was filled with argon. The solvent was added by syringe through a septum. The septum was replaced by a condenser in an argon stream. The reaction mixture was stirred and refluxed for the indicated period of time at the indicated temperature. The solution was allowed to cool to ambient temperature and water (5 mL) was added. The aqueous and the organic layer were separated and the latter was dried Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (fine flash silica gel, heptanes). The solvents and the amounts are given in the individual procedures (see below).

Synthesis of dimethyl 3,4-di(4-chlorophenyl)thiophene-2,5-dicarboxylate (38a):



Procedure A: toluene:H_2O = 4:1 (5 mL), reflux 24 h, 100 °C. Starting with **36g** (0.358 g, 1.0 mmol) and (4-chlorophenyl)boronic acid (0.469 g, 3 mmol), $Pd(PPh_3)_4$ (0.060 g, 5 mol-%), K_3PO_4 (0.848 g, 4.0 mmol), **38a** was isolated (0.176 g, 42%) as a white solid; mp 149–151 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 6H, 2OCH_3), 7.14, 7.51 (d, ^3J = 8.2 Hz, 2H, CH, Ar), 7.31 (d, ^3J = 8.2 Hz, 4H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.56 (C, OCH_3), 127.56, 129.07, 129.85, 132.42 (CH, Ar), 141.30, 159.19 113.73, 141.85 (C, Ar), 160.09 (C, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3429 (m), 2950 (m), 1899 (w), 1721 (s), 1593 (w), 1522 (w), 1437 (s), 1095 (m), 1016 (m), 829 (m), 807 (s), 761 (m). MS (EI, 70 eV): *m/z* (%) = 421 (M^+, 35), 350 (100), 240 (16), 210 (10), 191 (11), 149 (9), 112 (7), 97 (9), 83 (12), 81 (19), 44 (7). HRMS (EI, 70 eV): calcd for $C_{30}H_{22}O_4Cl_2S$ (M^+): 421.2938; found: 421.2936.

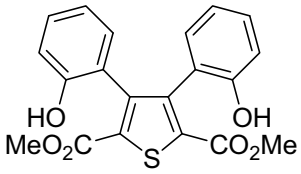
Synthesis of dimethyl 3,4-di(2-methoxyphenyl)thiophene-2,5-dicarboxylate (38b):



Procedure B: 5 mL of dioxane, reflux 8 h, 100 °C. Starting with **36g** (0.358 g, 1.0 mmol) and (2-methoxyphenyl)boronic acid (0.299 g, 2.2 mmol), $Pd(OAc)_2$ (11.2 mg, 5 mol-%), **L** (41 mg, 10 mol-%), K_3PO_4 (0.848 g, 4.0 mmol), **38b** was isolated (0.185 g, 45%) as a colourless solid; mp 205–207 °C. A doubling of some signals in the ^{1}H and ^{13}C NMR spectra is observed, due to the presence of two atropisomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43, 3.51 (2 x s, 6 H, OCH_3), 3.67, 3.68 (2 x s, 6 H, CO_2CH_3), 6.61, 6.72 (d, ^3J = 8.2 Hz, 2 H, CH, Ar), 6.83, 7.18 (t, ^3J = 8.2 Hz, 2 H, CH, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0 (C, OCH_3), 55.0, 55.1 (CH_3, $OCOCH_3$), 110.0, 110.1, 119.4, 119.5, 129.0, 129.1, 130.5, 130.8 (CH, Ar), 132.0, 132.1, 145.3, 146.0 (C, Ar), 123.8, 124.1, 156.6 (C, thiophene), 161.8, 161.9 (C=O). IR

(KBr, $\tilde{\nu}$ [cm^{-1}]): $\tilde{\nu}$ = 3433 (br, w), 3065 (w), 3029 (w), 3001 (w), 2953 (s), 2833 (s), 1724 (s), 1601 (m), 1583 (s), 1508 (s), 1468 (s), 1289 (s), 1158 (m), 1079 (m), 1048 (m), 762 (s), 750 (s). MS (EI, 70 eV): *m/z* (%) = 412 (M^+, 98), 382 (25), 381 (100), 322 (10), 321 (46), 307 (16), 305 (9), 287 (19). HRMS (EI, 70 eV): calcd for $C_{22}H_{20}O_6S$ (M^+): 412.0975; found: 412.0971.

Synthesis of dimethyl 3,4-di(2-hydroxyphenyl)thiophene-2,5-dicarboxylate (38c):

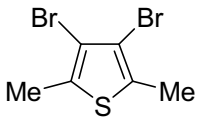


Procedure A: toluene:dioxane:H_2O = 2:2:1 (5 mL). Starting with **36g** (0.358 g, 1.0 mmol) and (2-hydroxyphenyl)boronic acid (0.443 g, 3 mmol), $Pd(PPh_3)_4$ (0.060 g, 5 mol-%), K_3PO_4 (0.848 g, 4.0 mmol), **38c** was isolated (0.188 g, 49%) as a colourless solid; mp 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 6 H, 2OCH_3), 7.31, 9.00 (d, ^3J = 8.2 Hz, 2 H, CH, Ar), 7.39, 7.51 (t, ^3J = 8.2 Hz, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.7, 118.0, 123.1, 124.4 (CH, Ar), 112.7, 130.7, 140.6, 155.9 (C, Ar), 160.2 (C, CO). IR (KBr, $\tilde{\nu}$ [cm^{-1}]): $\tilde{\nu}$ = 3333 (br, s), 3062 (m), 3023 (m), 2921 (m), 2900 (m), 1688 (m), 1670 (s), 1596 (s), 1523 (s), 1494 (s), 1236 (s), 1142 (m), 1100 (m), 1010 (m), 833 (s), 816 (s). MS (EI, 70 eV): *m/z* (%) = 384 (M^+, 26), 364 (35), 322 (10), 321 (46), 307 (16), 305 (9), 287 (19), 283 (100). HRMS (EI, 70 eV): calcd for $C_{20}H_{16}O_6S$ (M^+): 384.4024; found: 384.4028.

1.9.5.5 Synthesis of 3,4-dibromothiophenes

General procedure for the synthesis of 3,4-dibromothiophenes 36a-h: To a THF solution of tetrabromothiophene (**30**) (0.400 g, 1.0 mmol) was added 1 mL of *n*-butyllithium (2.5 M in heptane) at –78 °C. After stirring for 60 min at –78 °C, the electrophile (3.0 mmol) was added at –78 °C. After warming of the mixture to 20 °C within 16 h, a saturated aqueous solution of NH_4Cl (30 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (fine silica gel, *n*-heptane).

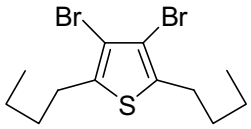
Synthesis of 3,4-dibromo-2,5-dimethylthiophene (36a):



Starting with tetrabromothiophene (**30**) (0.400 g, 1.0 mmol) and iodomethane (0.426 g, 3.0 mmol), **36a** was isolated (0.151 g, 56%) as a

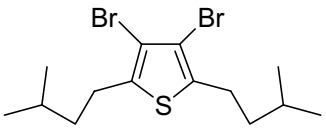
colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (s, 6 H, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (C, CH_3), 112.2, 131.7 (C, ArC). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2965 (m), 2928 (m), 2879 (w), 1515 (w), 1448 (m), 1445 (w), 1315 (w). MS (EI, 70 eV): *m/z* (%) = 272 (M^+, [^{81}Br,^{81}Br], 52), 270 (M^+, [^{81}Br,^{79}Br], 100), 268 (M^+, [^{79}Br,^{79}Br], 51), 191 (93), 189 (93), 95 (12), 51 (16). Anal. Calcd for $C_6H_6Br_2S$: C 26.69, H 2.24, S 11.88; found: C 26.65, H 2.26, S 11.88.

Synthesis of 3,4-dibromo-2,5-dibutylthiophene (36b):



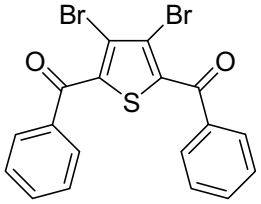
Starting with tetrabromothiophene (**30**) (0.400 g, 1.0 mmol) and 1-iodobutane (0.546 g, 3.0 mmol), **36b** was isolated (0.333 g, 94%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, ^{3}J = 7.2 Hz, 6H, $2CH_3$), 1.22-1.32 (m, 4H, $2CH_2$, CH_2CH_3), 1.40-1.55 (m, 4H, $2CH_2$, $CH_2CH_2CH_3$), 2.69 (t, ^{3}J = 7.2 Hz, 4H, $2CH_2$, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (C, CH_3), 22.4, 29.7, 32.3 (C, CH_2), 118.8, 137.3 (C, ArC). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (s), 2926 (m), 2869 (m), 1466 (m), 1384 (w), 1366 (w), 1360 (w). MS (EI, 70 eV): *m/z* (%) = 356 (M^+, [^{81}Br,^{81}Br], 14), 354 (M^+, [^{81}Br,^{79}Br], 26), 352 (M^+, [^{79}Br,^{79}Br], 13), 313 (52), 311 (100), 309 (51), 269 (13), 255 (17), 231 (14), 194 (12). Anal. Calcd for $C_{12}H_{18}Br_2S$: C, 40.70, H, 5.12, S, 9.05; found: C, 40.74, H, 5.12, S, 9.05.

Synthesis of 3,4-dibromo-2,5-di(isopentyl)thiophene (36c):



Starting with tetrabromothiophene (**30**) (0.400 g, 1.0 mmol) and 1-bromo-3-methylbutane (0.453 g, 3.0 mmol), **36c** was isolated (0.294 g, 77%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, ^{3}J = 7.2 Hz, 12H, 2×$2CH_3$), 1.64 (m, 4H, $2CH_2$, $CH_2(CH_3)_2$), 1.73 (m, 2H, 2CH), 2.90 (m, 4H, $2CH_2$, $CH_2CH_2(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (C, CH_3), 27.6, 30.0 (C, CH_2), 39.4 (C, CH), 119.8 , 137.2 (C, ArC). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (s), 2926 (m), 2869 (m), 1466 (m), 1384 (w), 1366 (w), 1360 (w). MS (EI, 70 eV): *m/z* (%) = 384 (M^+, [^{81}Br,^{81}Br], 11), 382 (M^+, [^{81}Br,^{79}Br], 21), 380 (M^+, [^{79}Br,^{79}Br], 10), 327 (17), 323 (17), 271 (20), 269 (38), 267 (19), 255 (17), 248 (12), 247 (99), 245 (100), 57 (13). Anal. Calcd for $C_{14}H_{22}Br_2S$: C, 44.00, H, 5.80, S, 8.39; found: C, 44.05, H, 5.72, S, 8.33.

Synthesis of 2,5-dibenzoyl-3,4-dibromothiophene (36h):



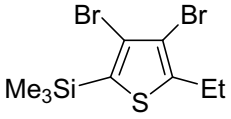
Starting with tetrabromothiophene (**30**) (0.400 g, 1.0 mmol) and benzoyl chloride (2.2 mmol), **36h** was isolated (0.306 g, 68%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (m, 4H, 2CH, Ar), 7.61 (m, 2H, 2CH, Ar), 7.79 (m, 4H, 2CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.5, 131.4, 135.4 (CH, Ar), 120.5, 140.6, 141.5 (C, ArC), 187.9 (C, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 2940 (m), 2917 (m), 2862 (w), 1755 (s), 1644 (s), 1600 (m), 1444 (m), 1440 (m), 1298 (s), 1266 (s), 1076 (m), 772 (s), 689 (m). MS (EI, 70 eV): *m/z* (%) = 452 (M^+, [^{81}Br,^{81}Br], 18), 450 (M^+, [^{81}Br,^{79}Br], 42), 448 (M^+, [^{79}Br,^{79}Br], 70), 354 (100), 310 (16), 267 (18), 178 (15), 165 (6), 121 (9), 77 (8). HRMS (EI, 70 eV): calcd for $C_{18}H_{10}Br_2O_2S$ (M^+, [^{81}Br,^{79}Br]): 450.1438; found: 450.1441.

1.9.5.6 Synthesis of 3,4-dibromo-5-alkyl-2-trimethylsiylthiophenes

General procedure for the synthesis of 3,4-dibromothiophenes 37a-f:

To a THF solution (15 mL) of *n*BuLi (2.5 M in *n*-hexane, 1.05 mL, 2.5 mmol) and TMEDA (0.775 mL, 2.5 mmol) was added tetrabromothiophene (**30**) (0.200 g, 0.5 mmol) at -78 °C under Argon atmosphere and the mixture was stirred for 30 min. To the stirred solution was dropwise added a THF solution (5 mL) of TMSCl (0.063 mL, 0.5 mmol) over a period of 3 h. The reaction mixture was stirred for further 30 min and, subsequently, the 1-bromoalkane (0.75 mmol) was added. After stirring for 4 h, to the solution was added a saturated aqueous solution of Na_2SO_4 (10 mL). The aqueous and the organic layer were separated. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

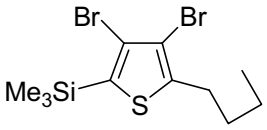
Synthesis of 3,4-dibromo-5-ethyl-2-trimethylsilylthiophene (37a):



Starting with **30** (0.200 g, 0.5 mmol) and 1-bromoethane (0.6 mmol, 0.09 mL), **37a** was isolated (0.112 g, 65%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.44 (s, 9 H, $Si(CH_3)_3$), 1.33 (t, 3 H, CH_3), 2.89 (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.7 (CH_3, $Si(CH_3)_3$) , 15.0 (CH_3), 23.4 (CH_2), 110.5, 113.7 (CBr), 131.7, 146.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2931 (w), 2896 (w), 2872 (w), 1248 (s), 1004 (s), 996 (s), 832 (s), 756 (s), 696 (s), 632 (m). MS (EI, 70 eV): *m/z* (%) = 344 (M^+, [^{81}Br,^{81}Br], 17), 342 (M^+, [^{81}Br,^{79}Br], 30), 340 (M^+, [^{79}Br,^{79}Br], 15), 329 (M^+, 55), 327 (M^+, 100), 325 (M^+, 50). HRMS (EI, 70 eV): calcd for $C_9H_{14}Br_2SSi$ (M^+,

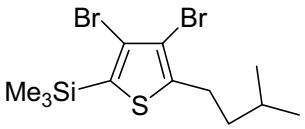
[^{81}Br,^{81}Br]): 343.89058, found: 343.89041, (M^+, [^{81}Br,^{79}Br]): 341.89263, found: 341.89283; (M^+, [^{79}Br,^{79}Br]): 339.89467, found: 339.89459.

Synthesis of 5-butyl-3,4-dibromo-2-trimethylsilylthiophene (37b):



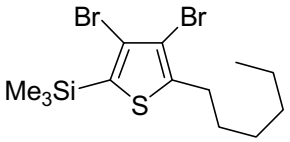
Starting with **30** (0.200 g, 0.5 mmol) and 1-bromobutane (0.6 mmol, 0.06 mL), **37b** was isolated (0.113 g, 61%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.45 (s, 9 H, $Si(CH_3)_3$), 0.98 (t, 3 H, CH_3), 1.37-1.54 (m, 4 H, CH_2), 2.67 (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.4 (CH_3, $Si(CH_3)_3$), 13.8 (CH_3), 22.4, 30.6, 32.7 (CH_2), 110.8, 114.0 (CBr), 138.7, 149.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 2897 (w), 2859 (w), 1248 (s), 1052 (s), 1005 (s), 913 (w), 831 (s), 756 (s), 695 (m), 638 (m), 538 (m). MS (EI, 70 eV): *m/z* (%) = 372 (M^+, [^{81}Br,^{81}Br], 32), 370 (M^+, [^{81}Br,^{79}Br], 32), 368 (M^+, [^{79}Br,^{79}Br], 16), 357 (M^+, 57), 355 (M^+, 100), 353 (M^+, 49), 327 (M^+, 18). HRMS (EI, 70 eV): calcd for $C_{11}H_{18}Br_2SSi$ (M^+, [^{81}Br,^{79}Br]): 369.92448, found: 369.92439; (M^+, [^{79}Br,^{79}Br]): 367.92652, found: 367.92648.

Synthesis of 3,4-dibromo-5-isopentyl-2-trimethylsilylthiophene (37c):



Starting with **30** (0.200 g, 0.5 mmol) and 1-bromo-3-methylbutane (0.6 mmol, 0.08 mL), **37c** was isolated (0.115 g, 60%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.37 (s, 9 H, $Si(CH_3)_3$), 0.93, 0.96 (t, 3 H, CH_3), 1.66 (m, H, CH), 1.51 (q, 2 H, CH_2), 2.81 (t, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3 (CH_3, $Si(CH_3)_3$), 23.2 (CH_3), 28.6 (CH), 29.9, 40.3 (CH_2), 115.1, 120.6 (CBr), 132.9, 146.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2925 (m), 2869 (w), 1248 (s), 993 (s), 835 (s), 756 (s), 696 (m), 620 (m), 555 (m). MS (EI, 70 eV): *m/z* (%) = 386 (M^+, [^{81}Br,^{81}Br], 22), 384 (M^+, [^{81}Br,^{79}Br], 40), 382 (M^+, [^{79}Br,^{79}Br], 19), 371 (M^+, 54), 370 (M^+, 18), 369 (M^+, 98), 367 (M^+, 48), 327 (M^+, 29), 249 (M^+, 100). HRMS (EI, 70 eV): calcd for $C_{12}H_{20}Br_2SSi$ (M^+, [^{81}Br,^{81}Br]): 385.93753, found: 385.93628; (M^+, [^{81}Br,^{79}Br]): 383.93958, found: 383.93849; (M^+, [^{79}Br,^{79}Br]): 381.94162, found: 381.94032.

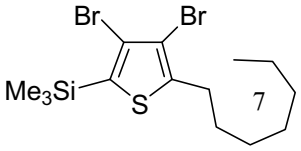
Synthesis of 3,4-dibromo-5-hexyl-2-trimethylsilylthiophene (37d):



Starting with **30** (0.200 g, 0.5 mmol) and 1-bromohexane (0.6 mmol, 0.09 mL), **37d** was isolated (0.119 g, 60%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.38 (s, 9 H, $Si(CH_3)_3$), 0.89 (t, 3 H, CH_3), 1.33-1.42 (m, 6 H, CH_2), 1.62 (q, 2 H, CH_2), 2.80 (q, 2 H,

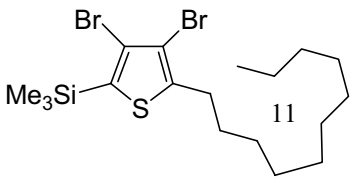
CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3 (CH_3, $Si(CH_3)_3$), 14.4 (CH_3), 23.2, 30.4, 30.5, 30.9, 32.0 (CH_2), 115.1, 120.6 (CBr), 132.8, 146.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2925 (m), 2855 (w), 1248 (s), 994 (s), 834 (s), 756 (s), 696 (m), 637 (m), 557 (m). MS (EI, 70 eV): *m/z* (%) = 400 (M^+, [^{81}Br,^{81}Br], 19), 398 (M^+, [^{81}Br,^{79}Br], 34), 396 (M^+, [^{79}Br,^{79}Br], 16), 385 (M^+, 56), 384 (M^+, 18), 383 (M^+, 100), 381 (M^+, 49), 327 (M^+, 26), 327 (M^+, 26). HRMS (EI, 70 eV): calcd for $C_{13}H_{22}Br_2SSi$ (M^+, [^{81}Br,^{81}Br]): 399.95318, found: 399.95288, (M^+, [^{81}Br,^{79}Br]): 397.95523, found: 397.95562; (M^+, [^{79}Br,^{79}Br]): 395.95727, found: 395.95728.

Synthesis of 3,4-dibromo-5-heptyl-2-trimethylsilylthiophene (37e):



Starting with **30** (0.200 g, 0.5 mmol) and 1-bromoheptane (0.6 mmol, 0.09 mL), **37e** was isolated (0.113 g, 55%) as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.39 (s, 9 H, $Si(CH_3)_3$), 0.78 (t, 3 H, CH_3), 1.18-1.39 (m, 8 H, CH_2), 1.73 (q, 2 H, CH_2), 3.25 (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.4 (CH_3, $Si(CH_3)_3$), 14.6 (CH_3), 22.6, 28.5, 28.6, 31.3, 31.6, 33.0, 33.8 (CH_2), 115.0, 120.3 (CBr), 136.5, 140.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2925 (m), 2855 (w), 1248 (s), 994 (s), 834 (s), 756 (s), 696 (m), 637 (m), 557 (m). MS (EI, 70 eV): *m/z* (%) = 414 (M^+, [^{81}Br,^{81}Br], 16), 412 (M^+, [^{81}Br,^{79}Br], 35), 410 (M^+, [^{79}Br,^{79}Br], 22), 385 (M^+, 54), 384 (M^+, 19), 383 (M^+, 100), 381 (M^+, 51), 327 (M^+, 31), 327 (M^+, 21). HRMS (EI, 70 eV): calcd for $C_{14}H_{24}Br_2SSi$ (M^+, [^{81}Br,^{79}Br]): 412.29886, found: 412.29874; (M^+, [^{79}Br,^{79}Br]): 409.97347, found: 409.97339.

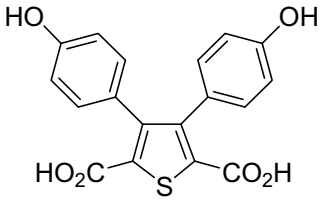
Synthesis of 3,4-dibromo-2-trimethylsilyl-5-undecylthiophene (37f):



Starting with **30** (0.200 g, 0.5 mmol) and 1-bromoundecane (0.6 mmol, 0.27 mL), **37f** was isolated (0.119 g, 51%) as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.39 (s, 9 H, $Si(CH_3)_3$), 0.78 (t, 3 H, CH_3), 1.18-1.39 (m, 16 H, CH_2), 1.73 (q, 2 H, CH_2), 3.25 (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.4 (CH_3, $Si(CH_3)_3$), 14.6 (CH_3), 22.9, 28.7, 28.9, 29.41, 29.46, 29.49, 25.32, 25.39, 32.1, 32.7 (CH_2), 115.0, 120.3 (CBr), 136.5, 140.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2925 (m), 2855 (w), 1248 (s), 994 (s), 834 (s), 756 (s), 696 (m), 637 (m), 557 (m). MS (EI, 70 eV): *m/z* (%) = 470 (M^+, [^{81}Br,^{81}Br], 21), 468 (M^+, [^{81}Br,^{79}Br], 28), 466 (M^+, [^{79}Br,^{79}Br], 21), 383 (M^+, 100), 381 (M^+, 39), 327 (M^+, 32), 327 (M^+, 19). HRMS (EI, 70 eV): calcd for $C_{18}H_{32}Br_2SSi$ (M^+, [^{81}Br,^{79}Br]): 468.40518, found: 468.40510; (M^+, [^{79}Br,^{79}Br]): 466.03607, found: 466.03600.

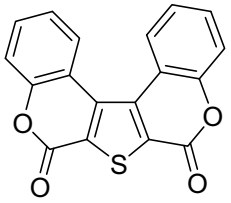
1.9.5.7 Synthesis of natural analog products

Synthesis of 3,4-di(4-hydroxyphenyl)thiophene-dicarboxylic acid (39):



Compound **38d** (0.115 g, 0.3 mmol) was dissolved in a mixture of EtOH (5 mL) and of an aqueous solution of KOH (10 mL, 30%) and the solution was refluxed for 2.5 h. The mixture was extracted several times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The crude product was washed to give **39** as a brownish solid (0.111 g, 96%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.5, 7.4 (d, 2 H, 2 CH, Ar), 7.25 (s, 2 H, OH), 8.14 (b, 2 H, COOH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.0, 132.3 (CH, Ar), 128.2, 132.8, 150.0, 157.5, 162.8 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3417 (w), 3071 (w), 2920 (m), 2850 (m), 2721 (w), 1722 (s), 1601 (s), 1401 (s), 1342 (s), 1187 (s), 1055 (s), 744 (s). MS (EI, 70 eV): *m/z* (%) = 356 (M^+, 55), 312 (M^+, 100), 293 (M^+, 15), 268 (M^+, 26), 64 (M^+, 74), 247 (M^+, 13), 220 (M^+, 50), 203 (M^+, 14), 128 (M^+, 23), 44 (M^+, 43). HRMS (EI, 70 eV): calcd for $C_{18}H_{12}O_6S$ (M^+): 356.03546, found: 356.03539.

Synthesis of the sulphur analogue 40 of ningaline A:



To a CH_2Cl_2 solution (2.5 mL) of **38b** (75 mg, 0.2 mmol) was added BBr_3 (1.6 mmol, 0.881 g) at 0 °C. The solution was allowed to warm to 20 °C during 4 days. To the solution was added an aqueous solution of KO*t*Bu (10 mL, 0.1 M), and the solution was stirred for 30 min. The organic layer was separated, dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The product was purified by chromatography (silica gel) and isolated as a yellow solid (49 mg, 65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.58, 8.40 (d, 2 H, CH, Ar), 7.41, 7.62 (t, 2 H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.4, 124.4, 125.2, 131.2 (CH, Ar), 117.1, 133.26, 140.3, 152.7, 156,8 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3417 (w), 3071 (w), 2920 (m), 2850 (m), 2721 (w), 1722 (s), 1601 (s), 1401 (s), 1342 (s), 1187 (s), 1055 (s), 744 (s). MS (EI, 70 eV): *m/z* (%) = 321 (M^+, 19), 320 (M^+, 100), 319 (M^+, 17), 263 (M^+, 4), 208 (M^+, 13), 163 (M^+, 13). HRMS (EI, 70 eV): calcd for $C_{18}H_8O_4S$ (M^+): 320.01378, found: 320.01316.

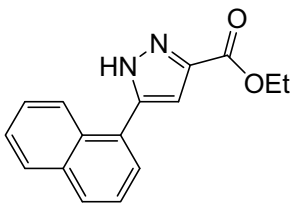
1.9.6 Synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by one-pot cyclization of hydrazone dianions with diethyl oxalate

1.9.6.1 Synthesis of pyrazole-3-carboxylates

Typical procedure for the synthesis of pyrazole-3-carboxylates 3a-q:

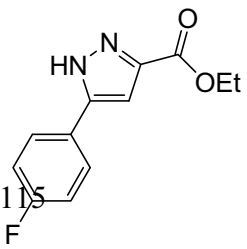
To a THF solution of hydrazone **41a-q** (2.0 mmol) was added *n*-butyllithium (2 mL, 2.5 M solution in hexane) at –78 °C. After stirring for 45 min at –78 °C, the mixture was stirred for 15 min at 20 °C and, subsequently, diethyl oxalate (2.2 mmol) was added at –78 °C. After warming of the reaction mixture to 20 °C within 16 h, the solvent (THF) was removed *in vacuo*. To the residue were added *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene. The mixture was stirred under reflux for 8 h. After cooling to 20 °C, a saturated aqueous solution (20 mL) of $NaHCO_3$ was added and the mixture was stirred for 15 min at 20 °C. The organic layer was separated, dried (Na_2SO_4), and filtered. The solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc = 10:1-2:1).

Ethyl 5-(naphth-1-yl)-1*H*-pyrazole-3-carboxylate (43f):



Starting with a THF solution (20 mL) of hydrazone **41f** (2.0 mmol, 0.568 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **43f** (45%, 239 mg) was isolated as a yellow solid, mp. 172-174°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 4.39 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 7.17 (s, 1H, C*H*), 7.57 (m, 3H, NaphH), 7.72 (d, 1H, NaphH), 7.96 (d, 2H, NaphH), 8.02 (s, 1H, NaphH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.9 (OCH_2CH_3), 65.6 (OCH_2CH_3), 114.0 (CH), 130.5, 130.6, 131.2, 131.8, 132.4, 133.5, 134.1 (CH), 135.0, 148.6, 149.1 (3C), 150.3, 159.0 (C, pyrazole), 160.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3138 (m), 3058 (m), 2979 (m), 1732 (s), 1560 (m), 1382 (s), 1262 (s), 1244 (s), 1144 (s), 1100 (s), 1024 (s), 802 (s), 777 (s), 659 (m), 570 (m). MS (EI, 70 eV): *m/z* (%) = 266 (M^+, 19), 221 (100), 193 (26), 139 (25), 127 (56), 73 (35), 45 (16). HRMS (EI, 70 eV): calcd for $C_{16}H_{14}O_2N_2$ (M^+): 266.1055, found: 266.1048.

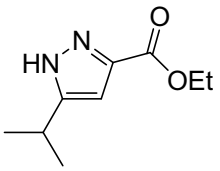
Ethyl 5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate (43i):



Starting with a THF solution (20 mL) of hydrazone **41i** (2.0 mmol, 0.448 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30

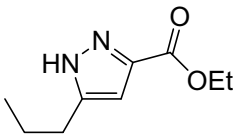
mL of toluene, **43i** (47%, 228 mg) was isolated as a yellow solid, mp. 188-189 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^{3}J = 7.2 Hz, 3H, OCH_2CH_3), 4.18 (q, ^{3}J = 7.2 Hz, 2H, OCH_2CH_3), 6.86 (s, 1H, C*H*), 7.00 (t, ^{3}J = 8.4 Hz, 2H, Ar*H*), 7.60 (t, ^{3}J = 8.4 Hz, 2H, Ar*H*), 9.50 (s, br, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 61.3 (OCH_2CH_3), 105.1 (CH), 115.7, 116.1 (d, $^{3}J_{CF}$= 95, CH, Ar), 127.5, 127.6 (d, $^{2}J_{CF}$ = 109 Hz, CH, Ar), 126.6 (C, Ar), 160.7, 160. (d, $^{1}J_{CF}$ = 240 Hz, CF, Ar), 140.0, 137.6 (C, pyrazole), 164.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437 (w), 3193 (m), 3133 (m), 3058 (m), 2985 (w), 1727 (s), 1612 (w), 1508 (s), 1449 (w), 1411 (m), 1275 (s), 1246 (s), 1197 (s), 994 (s), 840 (s), 824 (s), 779 (s), 615 (m). MS (EI, 70 eV): *m/z* (%) = 234 [M^+, (73)], 189 (15), 188 (18), 134 (9), 133 (16), 132(100). HRMS (EI, 70 eV): calcd for $C_{12}H_{11}O_2N_2F$ (M^+): 234.0799, found: 234.0797.

Ethyl 5-isopropyl-1*H*-pyrazole-3-carboxylate (43j):



Starting with a THF solution (20 mL) of hydrazone **41j** (2.0 mmol, 0.334 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **43j** (72%, 262 mg) was isolated as a yellow solid, mp. 61-63 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (m, ^{3}J =7.2 Hz, 9H, $3CH_3$), 3.27 (m, ^{3}J = 7.2 Hz, 1H, $(CH_3)_2CH$), 4.48 (q, ^{3}J = 7.2 Hz, 2H, OCH_2CH_3), 6.70 (s, 1H, C*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.5, 22.3 ($(CH_3)_2CH$), 32.2 (OCH_2CH_3), 61.0 (OCH_2CH_3), 104.6, 105.9 (*CH*), 142.0, 153.4 (C, Pyrazole), 162.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (m), 2968 (m), 2835 (m), 1809 (s), 1759 (s), 1534 (w), 1468 (s), 1386 (s), 1231 (s), 1219(s), 1011 (s), 1000 (m), 969 (m), 778 (m). MS (EI, 70 eV): *m/z* (%) = 182 (M^+, 27), 121 (100), 107 (23), 79 (24), 67 (17), 29 (21). HRMS (EI, 70 eV): calcd for $C_9H_{14}O_2N_2$ (M^+): 182.1055, found: 182.1052.

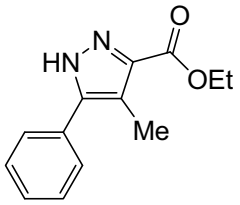
Ethyl 5-*n*-propyl-1*H*-pyrazole-3-carboxylate (43k):



Starting with a THF solution (20 mL) of hydrazone 4**1k** (2.0 mmol, 0.334 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **43k** (63%, 228 mg) was isolated as a yellow solid, mp. 67-69 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, ^{3}J =7.2 Hz, 3H, $CH_2CH_2CH_3$), δ = 1.19 (t, ^{3}J =7.2 Hz, 3H, OCH_2CH_3), 1.52 (m, ^{3}J =7.2 Hz, 2H, $CH_2CH_2CH_3$), 2.54 (t, ^{3}J =7.2 Hz, 2H, $CH_2CH_2CH_3$), 4.20 (q, ^{3}J = 7.2 Hz, 2H, OCH_2CH_3), 6.45 (s, 1H, C*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.9 ($CH_2CH_2CH_3$), 14.5 (OCH_2CH_3), 22.7, 29.4 ($2CH_2$), 62.4 (OCH_2CH_3), 106.4 (CH), 142.4, 147.3 (C, pyrazole), 162.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2999

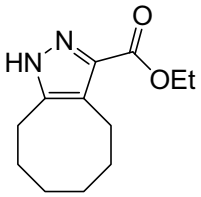
(m), 2964 (m), 2831 (m), 1803 (s), 1765 (s), 1523 (w), 1478 (s), 1389 (s), 1236 (s), 1212(s), 1019 (s), 1003 (m), 969 (m), 778 (m). MS (EI, 70 eV): *m/z* (%) = 182 (M^+, 18), 121 (100), 108 (51), 107 (23), 79 (14), 43 (15), 29 (11). HRMS (EI, 70 eV): calcd for $C_9H_{14}O_2N_2$ (M^+): 182.1055, found: 182.1051.

Ethyl 4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (43l):



Starting with a THF solution (20 mL) of hydrazone **41l** (2.0 mmol, 0.438 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **43l** (62%, 251 mg) was isolated as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, ^3J =7.2 Hz, 3H, OCH_2CH_3), 2.54 (s, 3H, CH_3) 4.25 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 7.48 (m, 3H, Ar*H*), 7.63 (d, ^3J = 8.2 Hz, 2H, Ar*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 10.1 (CH_2CH_3), 14.5 (CH_3), 60.8 (OCH_2CH_3), 128.0, 128.4, 129.0, 130.2, 130.8 (CH, ArH), 133.7 (C, Ar), 117.4, 138.3, 145.0 (C, pyrazole), 161.21 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3221 (w), 3123 (m), 3099 (m), 3025 (m), 2956 (w), 1861 (s), 1821 (s), 1399 (s), 1365 (s), 1332 (s), 1299 (s), 1251 (s), 1989 (s), 1005 (s), 986 (s), 865 (m), 779 (m), 763 (m), 699 (m). MS (EI, 70 eV): *m/z* (%) = 231 (M^+, 13), 230 (90), 185 (18), 184 (26), 183 (29), 129 (13), 128 (100), 77 (18). HRMS (EI, 70 eV): calcd for $C_{13}H_{14}O_2N_2$ (M^+): 203.1055, found: 203.1057.

Ethyl 4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*c*]pyrazole-3-carboxylate (43p):



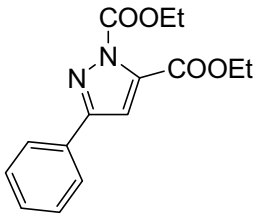
Starting with a THF solution (20 mL) of hydrazone **41p** (2.0 mmol, 0.426 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g), 30 mL of toluene, **43p** (38%, 168 mg) was isolated as a yellow solid, mp. 121-123 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.25-1.40 (m, 4H, $2CH_2$), 1.50-1.60 (m, 4H, CH_2), 2.68, 2.75 (mm, 4H, $2CH_2$), 4.19, 4.30 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.9 (OCH_2CH_3), 20.4, 23.7, 24.5, 24.6, 27.4, 28.9 ($6CH_2$), 59.6 (OCH_2CH_3), 121.9, 134.6, 146.9 (3C), 160.9 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3183 (m), 3125 (m), 2928 (m), 2853 (m), 1717 (s), 1456 (s), 1445 (s), 1270 (s), 1245 (s), 1151 (s), 1095 (s), 1043 (s), 948(m), 865 (m), 779 (m), 732 (m). MS (EI, 70 eV): *m/z* (%) = 222 (M^+, 46), 194 (14), 193 (86), 177 (12), 176 (25), 175 (100), 149 (13), 147 (12), 121 (12), 120 (12). HRMS (EI, 70 eV): calcd for $C_{12}H_{18}O_2N_2$ (M^+): 222.1362, found: 222.1358.

1.9.6.2 Synthesis of pyrazole-1,5-dicarboxylates

Typical procedure for the synthesis of pyrazole-1,5-carboxylates 44a-q:

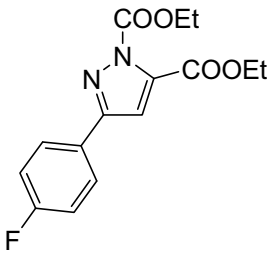
To a THF solution of hydrazone **41a-q** (2.0 mmol) was added *n*-butyllithium (2 mL, 2.5 M solution in hexane) at –78 °C. After stirring for 45 min at –78 °C, the mixture was stirred for 15 min at 20 °C and, subsequently, diethyl oxalate (2.2 mmol) was added at –78 °C. After warming of the reaction mixture to 20 °C within 16 h, the solvent (THF) was removed *in vacuo*. To the residue were added TFA (1 mL) and 30 mL of CH_2Cl_2. The mixture was stirred under reflux for 8 h. After cooling to 20 °C, a saturated solution (20 mL) of $NaHCO_3$ was added and the mixture was stirred for 15 min at 20 °C. The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc = 10:1-2:1).

Diethyl phenylpyrazole-1,5-dicarboxylate (44a):



Starting with a THF solution (20 mL) of hydrazone **41a** (2.0 mmol, 0.412 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44a** (59%, 339 mg) was isolated as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28-1.39 (tt, ^3J =7.2 Hz, 6H, 2OCH$_2$C*H*$_3$), 4.29-4.59 (qq, ^3J = 7.2 Hz, 4H, 2OC*H*$_2$CH$_3$), 7.06 (s, 1H, C*H*), 7.39 (m, 3H, Ar*H*), 7.87 (d, ^3J = 8.2 Hz, 2H, Ar*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 14.7 (2CH$_2$*CH*$_3$), 62.0, 65.6 (2O*CH*$_2$CH$_3$), 110.4 (CH, pyrazole), 126.8, 127.1, 128.4, 129.1, 129.8 (CH, ArH), 130.9 (C, Ar), 138.8, 149.4 (C, pyrazole), 154.4, 160.6 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3201 (m), 3012 (s), 2956 (m), 2931 (w), 1798 (s), 1731 (s), 1615 (m), 1565 (m), 1538 (m), 1465 (s), 1321 (s), 1254 (s), 935 (s), 865 (m), 732 (m). MS (EI, 70 eV): *m/z* (%) = 288 (M$^+$, 56), 171 (100), 170 (15), 142 (23), 114 (29), 104 (8), 89 (29), 77 (18). HRMS (EI, 70 eV): calcd for $C_{15}H_{16}O_4N_2$ (M$^+$): 288.1110, found: 288.1115.

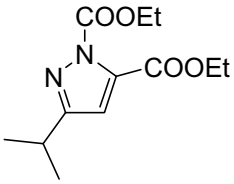
Diethyl 3-(4-fluorophenyl)pyrazole-1,5-dicarboxylate (44i):



Starting with a THF solution (20 mL) of hydrazone **41i** (2.0 mmol, 0.448 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44i** (41%, 250 mg) was isolated as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.22-1.38 (tt, ^3J = 7.2 Hz, 6H, 2OCH$_2$C*H*$_3$),

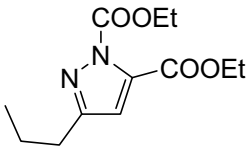
4.26-4.49 (qq, ^3J = 7.2 Hz, 4H, 2OCH_2CH$_3$), 6.89 (s, 1H, C*H*), 7.00 (t, ^3J = 8.3 Hz, 2H, Ar*H*), 7.70 (t, ^3J = 8.3 Hz, 2H, Ar*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 14.4 (2CH_3), 62.7, 65.4 (2CH_2), 110.1 (CH), 116.1, 116.3(d, $^3J_{CF}$ = 95, CH, Ar), 127.5, 127. 8 (d, $^2J_{CF}$ = 109 Hz, CH, Ar), 127.5 (C, Ar), 153.4, 160.4 (d, ^1J = 240 Hz, CF, Ar), 138.9, 149.3 (C, pyrazole), 162.2, 165.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3139 (w), 3067 (w), 2985 (s), 2940 (m), 2908 (w), 1763 (s), 1739 (s), 1608 (s), 1455 (s), 1433 (s), 1371 (s), 1244 (s), 1159 (s), 949 (s), 831 (s), 770 (s). MS (EI, 70 eV): *m/z* (%) = 306 [M^+, (45)], 235 (10), 234 (75), 233 (26), 189 (47), 188 (39), 162 (23), 134 (16), 133 (25), 132 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}O_4N_2F$ (M^+): 306.1016, found: 306.1011.

Diethyl isopropylpyrazole-1,5-dicarboxylate (44j):



Starting with a THF solution (20 mL) of hydrazone **41j** (2.0 mmol, 0.344 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44j** (72%, 365 mg) was isolated as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, ^3J =7.2 Hz, 6H, (CH_3)$_2$CH), δ = 1.22-1.34 (tt, ^3J =7.2 Hz, 6H, 2OCH$_2$CH_3), 2.95 (m, ^3J =7.2 Hz, 1H, (CH$_3$)$_2$*CH*), 4.19-4.43 (qq, ^3J = 7.2 Hz, 4H, 2OCH_2CH$_3$), 6.49 (s, 1H, C*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2, 28.0 (2OCH$_2$$CH_3$), 22.2 (($CH_3$)$_2$CH), 62.4, 65.7 (2C$H_2$), 110.1, 110.2 (2CH), 149.3, 160.8 (C, pyrazole), 138.2, 162.1 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2973 (m), 2938 (w), 2876 (w), 1776 (s), 1739 (s), 1657 (s), 1479 (s), 1373 (s), 1292 (s), 1235(s), 1064 (s), 1017 (m), 981 (m), 771 (m). MS (EI, 70 eV): *m/z* (%) = 254 (M^+, 38), 209 (12), 182 (16), 181 (62), 167 (30), 137 (38), 136 (26), 135 (70), 121 (100), 67 (12), 29 (31). HRMS (EI, 70 eV): calcd for $C_{12}H_{18}O_4N_2$ (M^+): 254.1261, found: 254.1258.

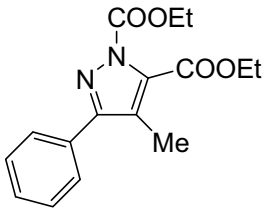
Diethyl *n*-propylpyrazole-1,5-dicarboxylate (44k):



Starting with a THF solution (20 mL) of hydrazone **41k** (2.0 mmol, 0.344 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44k** (70%, 365 mg) was isolated as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 7.2 Hz, 3H, CH$_2$CH$_2$CH_3): δ = 1.24-1.40 (tt, ^3J =7.2 Hz, 6H, 2OCH$_2$CH_3), 1.61 (m, ^3J =7.2 Hz, 2H, CH$_2$$CH_2CH_3$), 2.55 (t, ^3J =7.2 Hz, 2H, CH_2CH$_2$CH$_3$), 4.24-4.48 (qq, ^3J = 7.2 Hz, 4H, 2OCH_2CH$_3$), 6.49 (s, 1H, C*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH$_2$CH$_2$$CH_3$), 22.6, 30.7 (2OCH$_2$$CH_3$), 62.5, 65.3 (2C$H_2$), 111.7 (CH), 149.2, 160.8 (C, pyrazole), 132.9, 158.3 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2964 (m), 2936 (m), 2874 (m), 1775

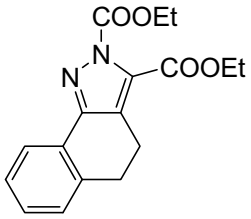
(s), 1739 (s), 1558 (w), 1471 (s), 1374 (s), 1297 (s), 1237(s), 1064 (s), 1018 (m), 986 (m), 770 (m). MS (EI, 70 eV): *m/z* (%) = 254 (M^+, 4), 226 (27), 209 (10), 182 (21), 154 (83), 137 (42), 136 (17), 121 (24), 108 (100), 107 (14), 79 (21). HRMS (EI, 70 eV): calcd for $C_{12}H_{18}O_4N_2$ (M^+): 254.1261, found: 254.1264.

Diethyl 4-methyl-5-phenylpyrazole-1,5-dicarboxylate (44l):



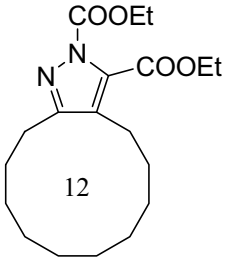
Starting with a THF solution (20 mL) of hydrazone **41l** (2.0 mmol, 0.412 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44l** (69%, 416 mg) was isolated as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30-1.40 (tt, ^3J =7.2 Hz, 6H, 2OCH$_2$C*H*$_3$), 2.20 (s, 3H, C*H*$_3$), 4.30-4.59 (qq, ^3J = 7.2 Hz, 4H, 2OC*H*$_2$CH$_3$), 7.30 (m, 3H, Ar*H*), 7.59 (d, ^3J = 8.2 Hz, 2H, Ar*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 9.8, 14.5 (2CH$_2$*CH*$_3$), 15.6 (C*H*$_3$), 62.9, 65.4 (2O*CH*$_2$CH$_3$), 128.7, 128.9, 129.3 (CH, ArH), 131.9 (C, Ar), 120.8, 136.1, 149.5 (C, pyrazole), 155.0, 161.6 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 2982 (m), 2964 (m), 2953 (m), 2873 (w), 1771 (s), 1758 (s), 1444 (s), 1371 (s), 1345 (s), 1302 (s), 1244 (s), 1216 (s), 1083 (s), 1047 (s), 860 (m), 774 (m), 763 (m), 700 (m). MS (EI, 70 eV): *m/z* (%) = 302 (M^+, 60), 230 (47), 229 (23), 207 (13), 185 (47), 184 (45), 128 (100), 104 (22), 77 (22), 29 (26). HRMS (EI, 70 eV): calcd for $C_{16}H_{18}O_4N_2$ (M^+): 302.1261, found: 302.1263.

Diethyl 4,5-dihydrobenzo[*g*]indazole-1,5-carboxylate (44m):



Starting with a THF solution (20 mL) of hydrazone **41m** (2.0 mmol, 0.464 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **44m** (49%, 339 mg) was isolated as a yellow solid, mp. 131-133 .^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.36-1.51 (tt, ^3J = 7.2 Hz, 6H, 2OCH$_2$C*H*$_3$), 2.94 (m, 4H, CH$_2$), 4.20-4.58 (qq, ^3J = 7.2 Hz, 4H, 2OC*H*$_2$CH$_3$), 7.29 (m, 3H, ArH), 8.03 (m, 1H, ArH), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.152 (2OCH$_2$*CH*$_3$), 29.4, 31.9 (2CH$_2$), 62.0, 64.9 (2O*CH*$_2$CH$_3$), 124.0, 127.1, 128.5, 129.5 (CH), 127.4, 137.6 (2C), 127.4, 129.5, 151.4 (3C, pyrazole), 149.5, 160.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (w), 3412 (m), 3142 (m), 2956 (m), 1856 (s), 1567 (w), 1354 (s), 1198(s), 1101 (w), 899 (w), 856 (s), 785 (m). MS (EI, 70 eV): *m/z* (%) = 314 (M^+, 100), 242 (36), 241 (20), 213 (37), 196 (49), 195 (65), 169 (80), 168 (59), 140 (88), 139 (63), 115 (35). HRMS (EI, 70 eV): calcd for $C_{17}H_{18}O_4N_2$ (M^+): 314.1261, found: 314.1262.

Diethyl 4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[*c*]pyrazole-1,5-dicarboxylate (4q):



Starting with a THF solution (20 mL) of hydrazone 3**1q** (2.0 mmol, 0.536 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2, **4q** (65%, 227,5 mg) was isolated as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.36, 1.37 (t, ^3J = 7.2 Hz, 6H, 2OCH$_2$C*H*$_3$), 1.32-1.54 (m, 12H, 6*CH*$_2$), 1.63, 1.79 (m, 4H, *CH*$_2$), 2.51, 2.68 (t, 4H, 2C*H*$_2$), 4.39, 4.49 (q, ^3J = 7.2 Hz, 4H, 2OC*H*$_2$CH$_3$), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9 (2OCH$_2$*CH*$_3$), 20.1, 22.7, 22.8, 23.0, 24.7, 24.9, 25.5, 25.6, 27.4, 27.9 (10CH$_2$), 61.68, 64.39 (2O*CH*$_2$CH$_3$), 125.9, 134.61, 149.0 (3C), 156.8, 161.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3485 (w), 2989 (m), 2927 (s), 2855 (m), 1749 (s), 1736 (s), 1485 (s), 1459 (s), 1381 (s), 1374 (s), 1235 (s), 1157 (s), 1049 (s), 969(w), 862 (m), 831 (m), 765 (m). MS (EI, 70 eV): *m/z* (%) = 350 (M$^+$, 22), 278 (19), 277 (100), 240 (17), 231 (21), 205 (11), 121 (10). HRMS (EI, 70 eV): calcd for $C_{15}H_{22}O_4N_2$ (M$^+$): 350.2200 found: 350.2195.

1.9.7 Synthesis of 6-halomethyl-5,6-dihydro-4H-1,2-oxazines

General procedure for the preparation of oximes 47:

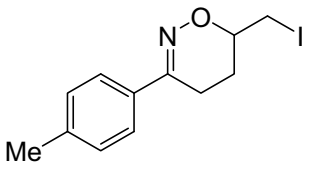
To a THF solution (20 mL) of oxime **45** (2.0 mmol) was added *n*-butyllithium (5.0 mmol, 2.5 M) at −78 °C. After stirring for 1 h at −78 °C, the mixture was warmed to 20 °C and stirred for 10 min. Subsequently, allylbromide (0.484 g, 4.0 mmol) was added at −78 °C. After warming of the mixture to 20 °C for 16 h, a saturated aqueous solution of NH_4Cl (30 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 5:1).

General procedure for the synthesis of 1,2-oxazines 48a-k and 48p: To a CH_2Cl_2 solution (15 mL) of **47a-k,l** (0.81 mmol) and of I_2 (0.406 g, 1.6 mmol) was added a saturated aqueous solution of $NaHCO_3$ (16 mL) and the solution was stirred for 12 h at 20 °C. The excess of iodine was removed by addition of a saturated aqueous solution of Na_2SO_3 (40 mL). The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the

filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane → *n*-heptane/EtOAc = 4:1).

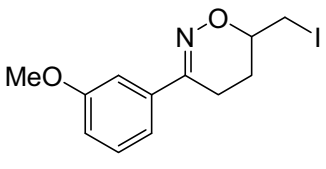
General procedure for the synthesis of 1,2-oxazines 48l-o: To a CH_2Cl_2 solution (10 mL) of **47e,f,j,k** (2.0 mmol) was portionwise added NBS (0.356 g, 2.0 mmol) over 15 min at 0 °C. The resultant solution was stirred for 2 h at room temperature. The residue was purified by column chromatography (silica gel, *n*-heptane → *n*-heptane/EtOAc = 4:1).

6-Iodomethyl-3-*p*-tolyl-5,6-dihydro-4*H*-[1,2]oxazine (48b):



Starting with 1-(3-tolyl)pent-4-en-1-one oxime **47b** (0.342 g, 1.80 mmol), I_2 (0.914 g, 3.60 mmol), and a saturated aqueous solution of $NaHCO_3$ (18 mL) in CH_2Cl_2 (30 mL), **48b** was isolated as a colourless solid (0.471 g, 83%); mp 120-122 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.85 (m, 1H, CH_2), 2.32 (m, 1H, CHC*H*$_2$), 2.36 (s, 3H, $C_{Ar}CH_3$), 2.68 (m, 2H, CC*H*$_2$), 3.25 (dd, ^2J = 10.5 Hz, ^3J = 7.3 Hz, 1H, CHC*H*$_2$I), 3.41 (dd, ^2J = 10.5 Hz, ^3J = 5.0 Hz, 1H, CHC*H*$_2$I), 3.84 (m, 1H, OC*H*CH$_2$), 7.18 (d, ^3J = 8.1 Hz, 2H, CH_{Ar}), 7.57 (d, ^3J = 8.1 Hz, 2H, CH_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 5.5 (CH_2I), 21.3 ($C_{Ar}CH_3$), 21.6, 24.3 (CHC*H*$_2$C*H*$_2$C), 74.0 (*C*HO), 125.3 (CH_{Ar}), 129.2 (CH_{Ar}), 132.3 (C), 139.8 (C), 154.8 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3431 (br, w), 3034 (m), 2935 (br, w), 2910 (w), 1611 (w), 1592 (w), 1510 (w), 1418 (w), 1407 (m), 1380 (m), 1335 (s), 1297 (m), 1233 (m), 1198 (s), 1163 (w), 1111 (w), 1088 (w), 1062 (w), 1013 (s), 936 (w), 915 (s), 812 (s), 760 (w), 710 (w). MS (GC/MS, 70 eV): *m/z* (%) = 315 (M^+, 100), 188 (9), 174 (20), 143 (14), 132 (32), 117 (33), 105 (9), 91 (40), 77 (7), 65 (17). HRMS (EI): calculated for $C_{12}H_{14}NOI$ (M^+): 315.01146, found 315.01158.

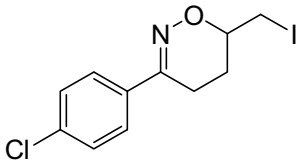
6-Iodomethyl-3-(3-methoxyphenyl)-5,6-dihydro-4*H*-[1,2]oxazine (48c):



Starting with 1-(4-methoxyphenyl)pent-4-en-1-one oxime **47c** (0.205 g, 1 mmol), I_2 (0.508 g, 2 mmol), and a saturated aqueous solution of $NaHCO_3$ (5 mL) in CH_2Cl_2 (10 mL), **48c** was isolated as a brown oil (0.219 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76, 2.22 (m, 2 H, CH_2), 2.55 (m, 2 H, CH_2), 3.19, 3.35 (t, 2 H, CH_2), 3.75 (m, 1 H, CH), 7.85, 7.25 (s, 1 H, Ar), 7.12, 7.15 (d, ^3J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.7, 22.0, 24.5 (3C, CH_2), 55.4 (C, CH_3), 74.1 (C, CH), 110.4, 116.3, 119.5, 129.6 (4C, ArCH), 136.6, 154.6 (2C, ArC), 159.6 (C, CN); IR (KBr, cm^{-1}); $\tilde{\nu}$ = 3067 (w), 2994 (w), 2954

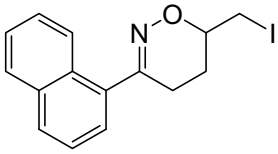
(w), 2932 (w), 2832 (w), 1597 (m), 1568 (m), 1425 (m), 1287 (m), 1234 (m), 1175 (m), 1038 (s), 924 (m), 823 (m), 779 (m), 688 (m). MS (EI, 70 eV): *m/z* (%) = 332 (M^+, 14), 331 (100), 204 (14), 190 (21), 187 (16), 186 (18), 178 (20), 133 (23). HRMS (EI, 70 eV): calcd for $C_{12}H_{14}NO_2I$ (M^+): 331.00637; found: 331.00608.

3-(4-Chlorophenyl)-6-iodomethyl-5,6-dihydro-4*H*-[1,2]oxazine (48h):



Starting with 1-(4-chlorophenyl)pent-4-en-1-one oxime **47h** (0.209 g, 1.0 mmol), I_2 (0.508 g, 2.0 mmol), and a saturated aqueous solution of $NaHCO_3$ (5 mL) in CH_2Cl_2 (10 mL), **48h** was isolated as a brownish oil (0.172 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82, 2.22 (m, 2 H, CH_2), 2.65 (q, 2 H, CH_2), 3.19, 3.31 (t, 2 H, CH_2), 3.75 (m, 1 H, CH), 7.25, 7.46 (d, ^3J = 8.2 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.4, 23.0, 26.0 (3C, CH_2), 74.4 (C, CH), 127.7, 129.3 (4C, ArCH), 134.0, 136.0 (2C, ArC), 153.7 (C, CN); IR (KBr, cm^{-1}); $\tilde{\nu}$ = 3049 (w), 3005 (w), 2928 (w), 1548 (m), 1456 (m), 1349(m), 1075 (m), 924 (s), 819 (s), 752 (m). MS (EI, 70 eV): *m/z* (%) = 336 (M^+, [^{37}Cl], 7), 334 (M^+, [^{35}Cl], 19), 192 (55), 180 (100), 177 (38), 143 (61), 137 (29), 112 (35), 101 (19). HRMS (EI, 70 eV): calcd for $C_{11}H_{11}INOCl$ (M^+, [^{35}Cl]): 334.95738; found: 334.95742.

6-Iodomethyl-4-(naphthalen-1-yl)-5,6-dihydro-4*H*-[1,2]oxazine (48i):



Starting with 1-(1-naphthyl)pent-4-en-1-one oxime **47i** (0.225 g, 1.0 mmol), I_2 (0.508 g, 2.0 mmol), and a saturated aqueous solution of $NaHCO_3$ (5 mL) in CH_2Cl_2 (10 mL), **48i** was isolated as a brownish oil (0.232 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92, 2.31 (m, 2 H, CH_2), 2.61 (t, 2 H, CH_2), 2.35, 2.41 (t, 2 H, CH_2), 3.94 (m, 1 H, CH), 7.31 (t, ^3J = 8.2 Hz, 2 H, Ar), 7.38 (d, ^3J = 8.2 Hz, 2 H, Ar), 7.73, 7.79 (d, ^3J = 8.2 Hz, 2 H, Ar), 7.87 (t, ^3J = 8.2 Hz, 1 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.6, 24.6, 26.3 (3C, CH_2), 125.0, 125.1, 125.7, 126.1, 126.8, 128.5, 129.6 (7C, ArCH), 131.3, 133.8, 133.9 (3C, ArC), 158.0 (C, CN); IR (KBr, cm^{-1}); $\tilde{\nu}$ = 3044 (w), 2953 (w), 2932 (m), 2852 (m), 1673 (m), 1506 (m), 1368 (m), 1280 (m), 1127 (m), 999 (m), 895 (s), 772 (s). MS (EI, 70 eV): *m/z* (%) = 351 (M^+, 100), 350 (11), 224 (15), 206 (15), 165 (15), 153 (46), 152 (33), 127 (38). HRMS (EI, 70 eV): calcd for $C_{15}H_{14}NO_2I$ (M^+): 351.01146; found: 351.01165.

Appendix

1.10 Crystallographic Data

Ethyl 5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate

Table 1. Crystal data and structure refinement for **43i**.

Identification code	tung36	
Empirical formula	$C_{12}H_{11}FN_2O_2$	
Formula weight	234.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/n$	
Space group (Hall)	-P 2yn	
Unit cell dimensions	a = 14.176(3) Å	α = 90°.
	b = 5.0195(8) Å	β = 106.664(4)°.
	c = 16.533(3) Å	γ = 90°.
Volume	1127.0(4) $Å^3$	
Z	4	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	488	
Crystal size	0.74 x 0.22 x 0.05 mm^3	
Θ range for data collection	3.00 to 28.30°.	
Index ranges	-18≤h≤18, -6≤k≤3, -22≤l≤22	
Reflections collected	11338	
Independent reflections	2689 [R(int) = 0.0415]	
Completeness to Θ = 28.30°	95.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9947 and 0.9252	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2689 / 0 / 158	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2σ(I)]	R1 = 0.0428, wR2 = 0.0958	
R indices (all data)	R1 = 0.0755, wR2 = 0.1114	
Largest diff. peak and hole	0.169 and -0.205 $e.Å^{-3}$	

Abbreviations

Ac	Acetyl
Anal.	Elemental Analysis
APT	Attached Proton Test
bp.	Boiling point
calcd	Calculated
CI	Chemical Ionization
COSY	Correlated Spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron Impact
Et_2O	Diethyl ether
EtOH	Ethanol
GC	Gas Chromatography
GP	General Procedure
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared Spectroscopy
LDA	Lithium diisopropylamide
Me_3SiCl	Chlorotrimethylsilane
Me_3SiOTf	Trimethylsilyl trifluoromethanesulfonate
MS	Mass Spectrometry
mp	Melting point
NaOEt	Sodium ethanolate
*n*BuLi	*n*-Butyllithium
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser and Exchange Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate
Ph	Phenyl
ppm	Parts per million
R_f	Retention factor
SET	Single electron transfer
Tf_2O	Trifluoromethanesulfonic anhydride (triflic anhydride)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Tol	Tolyl (*p*-MeC_6H_4)
Tos	Tosyl (*p*-$MeC_6H_4SO_2$

Erklärung

Ich versichere hiermit an Eides statt, daß ich die vorliegende Arbeit selbständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, February 2009.

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POSTER PRESENTATION IN INTERNATIONAL CONFERENCES

1. **Tung Thanh Dang**, Tuan Thanh Dang, Farman Ullah, Narir Rasool, Rasheed Ahmad, Peter Langer*. Regioselective Palladium-Catalyzed Reactions of Tetrabromo-thiophene, -selenophene, -*N*-methylpyrrole. Poster Presentation in 2th EuCheMS (European Association for Chemical and Molecular Sciences) Chemistry Congress – 16-20th September **2008** in Torino – Italy
2. Tuan Thanh Dang, **Tung Thanh Dang**, Uwe Albrecht, Katrin Gerwien, Melanie Siebert, Peter Langer*. One-pot cyclization of dilithiated oximes and hydrazones with epibromohydrin and diethyl oxalate. Poster Presentation in 11th Belgian Organic Synthesis Symposium July **2008** (BOSS-11) - Belgium

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1. **Thanh Tung Dang,** Tuan Thanh Dang, Alexander Villinger, Haijun Jaio, Christine Fischer, Peter Langer*. Regioselective Palladium(0)-Catalyzed Cross-Coupling Reactions and Metal-Halide Exchange Reactions of Tetrabromothiophene: Optimization, Scope and Limitations. ***Submitted in Adv.Synth.Catal.***
2. Munawar Hussain, **Dang Thanh Tung**, Serge-Mithérand Tengho Toguem, Alexander Villinger, Christine Fischer, Peter Langer* Synthesis of Carbazoles and 1,2-Dihydrocarbazoles by Domino ′Twofold Heck / 6π-Electrocyclization′ Reactions of Di-, Tri- and Tetrabromo-*N*-methylindoles. ***Sumitted in Synlett.***

3. Farman Ullah, **Tung Thanh Dang**, Joachim Henicke, Alexander Villinger, Peter Langer*. Regioselective Sonogashira reactions of *N*-metyltetrabromopyrolle. First synthesis of Tri- and Tetra(1-alkylnyl)pyrroles. ***Accepted in Synlett.***
4. **Thanh Tung Dang,** Alexander Villinger, Peter Langer*. Efficient Synthesis of Substituted Selenophenes based on the First Palladium(0)-Catalyzed Cross-coupling reactions of tetrabromoselenophene**.** ***Advanced Synthesis & Catalysis*** **2008**, *350*, 2109-2117.
5. Vahuni Karapetyan, Satenik Mkrtchyan, **Tung Thanh Dang**, Helmut Reinke, and Peter Langer*. Regioselective Synthesis of 6-Halomethyl-5,6-dihydro-4*H*-1,2-oxazines based on Cyclizations of Arylalkenyl-oximes. ***Tetrahedron*** **2008,** *64*, 8010-8015.
6. **Tung Thanh Dang**, Tuan Thanh Dang, Christine Fischer, Helmar Goerls, Peter Langer*. Synthesis of Pyrazole-3-carboxylates and Pyrazole-1,5-Dicarboxylates by One-Pot Cyclization of Hydrazone Dianions with Diethyl Oxalate. ***Tetrahedron*** **2008,** *64*, 2207-2215.
7. **Thanh Tung Dang**, Rasheed Ahmed, Tuan T. D, Helmut Reinke and Peter Langer*. Regioselective Suzuki cross-coupling reactions of tetrabromo-1-methylpyrrole. ***Tetrahedron Lett*** **2008**, *49,* 1698-1700.
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