Synthesis of Sterically Encumbered Biaryls by [3+3] Cyclocondensation Reactions and Synthesis of Arylated Pyrazoles, Bis(diaryl)sulfones, and Bis(alkenyl)pyridines by Pd(0)-Catalysed Cross-Coupling Reactions

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Dekan : Prof, Dr Hendrick Schubert

1. Gutachter: Prof Dr Andreas Kirschning
University of Hannover, Germany

2. Gutachter: Prof. Dr Peter Langer,
Institut für Chemie, Albert Einstein Str.3a,
8059 Rostock, Germany

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Affectionately dedicated to

My parents, sweet brothers and sisters.

CONTENTS

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Abbreviations

Ar	Aromatic
APT	Attached Proton Test
ATCC	American Type Culture Collection
*n*BuLi	*n*-Butyl lithium
DEPT	Distortion less Enhancement by Polarisation Transfer
EI	Electronic Impact
ESI	Electro spray Ionization
EtOAc	Ethyl acetate
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
MS	Mass Spectrometry
Ph	Phenyl
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Correlated Spectroscopy
NOESY	Nuclear Over Hauser and Exchange Spectroscopy
Me_3SiOTf	Trimethylsilyl-trifluoromethanesulfonate
Me_3SiCl	Trimethylsilylchloride
Mp	Melting Point
RCM	Ring Closing Metathesis
TBAI	Tetra butyl Ammonium Iodide
TFA	Trifluoroacetic Acid
Tf_2O	Trifluoromethanesulfonic Anhydride
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
UV	Ultraviolet spectroscopy

0. General Introduction and Task of the Thesis

The main focus of chemists is to synthesize both natural products and compounds that do not exist in nature and to study their physical, chemical and biological properties. This is accompanied by a deep understanding of the fundamental principles of chemical structure and reactivity and lead to the development of modern pharmaceutical and chemical industries. Natural products play an important role in the discovery and development of pharmacologically relevant compounds (drug-like compounds) and drugs which are actually used in the clinic. In this context, it is important to find new lead structures for drug discovery and to develop new synthetic methods or strategies for their assembly.[1] Besides natural products, synthetic compounds, which do not resemble natural products, also play a key role in pharmacology. In recent times, the tremendous improvements in synthetic methodology have provided a convenient access to a great variety of synthetic substances like antibiotic, anti-infective, anti-cancer and cardio-vascular agents etc.

Natural products often represent lead structures in drug discovery.[2] Various natural products have been reported to show antibiotic activity. Since the discovery of penicillin, a large number of antibiotics have been isolated from of microorganisms.[3] Anti-infective compounds are obtained from both animals and plants. The development of new drugs includes synthetic and semi-synthetic studies, microbial transformations, the biological screening and the study of the mechanism of action.[4] The effort to design better anti-malaria agents for prophylaxis has also led to the discovery of a class of synthetic products, such as Malarone.

Natural products have provided a great contribution to the chemotherapy of cancer. A number of anticancer drugs are isolated from plants or microorganisms.[5] This includes bleomycin, doxorubicin, mitomycin, paclitaxel (Taxol^{TM}); examples of semi-synthetic derivatives of natural products, which are important anticancer drugs are, Ironotecan (a camptothecin derivative), etoposide or tenoposide (a podophyllotoxin derivative). Currently, both a semi-synthetic derivative with improved water solubility, docetaxel (Taxotene^{TM}) and paclitaxel (Taxol^{TM}) are approved and used clinically in the treatment of ovarian breast cancers. In this context, it is important to note, that the biological activity of synthetically modified natural products is often better than the activity of the natural products themselves.

The combination of medicinal chemistry and synthetic chemistry is a good tool for the development of new drugs. In this context, the generation of compound libraries by combinatorial chemistry and parallel synthesis provides a pool for screening.[6]

Task of my thesis

My own studies, which are outlined in this thesis, are focused on the development of new and reliable synthetic strategies and their application to the preparation of pharmacologically relevant carba- and heterocycles.

In the first chapter, I had the task to develop a new application of formal [3+3] cyclization reactions which have been extensively studied before in the group of Prof. Langer. The plan was to develop an approach to sterically encumbered biaryls by combination of a recently developed Cu-catalyzed coupling reactions of 1,3-diketones with aryl halides with formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes.

Chapters 2, 3, and 4 of my thesis deal with new synthetic applications of palladium(0)-catalyzed cross-coupling reactions. In recent years, the group of Prof. Langer has been studying Pd(0)-catalyzed cross coupling reactions of polyhalogenated arenes and heterocycles. In this context, the issue of site-selectivity (regioselectivity) plays an important role. I have studied the synthesis of arylated pyrazoles, bis(diaryl)sulfones, and di(alkenyl)pyridines by Suzuki and Heck reactions of tribrominated pyrazoles, bis(triflates) of 2'-4-dihydroxy-diphenylsulfone and dibrominated pyridines, respectively.

Summary

A significant part of the present dissertation has been recently published. Therefore, parts of the content of the publications were used for the present thesis. The thesis can be summarized as follows:

1. *Synthesis of sterically encumbered biaryls based on a Cu(1)-catalysed arylation / [3+3] cyclocondensation strategy.* This chapter deals with synthesis of sterically encumbered biaryls by combination of CuI / proline-catalyzed arylation to give 3-arylpentan-2,4-diones. The [3+3] cyclocondensation of the silyl enol ethers of the latter with 1,3-bis(trimethylsilyloxy)-1,3-dienes afforded the sterically encumbered, functionalized biaryls.

2. *Synthesis of arylated pyrazoles by site-selective Suzuki-Miyaura reactions of N-protected tribromopyrazoles.* This chapter deals with the synthesis of 3,4,5-triarylpyrazoles, 3,5-diaryl-4-bromopyrazoles, and 5-aryl-3,4-dibromopyrazoles by reaction of N-protected 3,4,5-tribromopyrazoles with one, two and three equivalents of arylboronic acids by Suzuki-Miyaura reactions.

3. *Synthesis of bis(diaryl)sulfones by Suzuki-Miyaura reactions of 2,4-bis(trifluoromethylsulfonyloxy)diphenylsulfone.* This chapter deals with synthesis of 2,4-bis(aryl)diphenylsulfones by reaction of 2,4-bis(trifluoromethylsulfonyloxy)diphenylsulfone with two equivalents of aryl boronic acids. One equivalent of boronic acid gives 2-(trifluorosulfonyloxy)-4-arylsulfones.

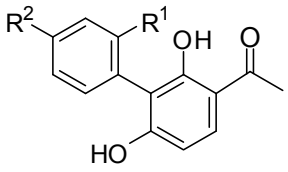
4 This chapter deals with the synthesis of novel bis(alkenyl)pyridines by double Heck cross coupling reactions of dibrominated pyridines. The Heck reaction of 2,5-dibromopyridine unexpectedly afforded 5,5′-bis(alkenyl)-2,2′-bipyridines by palladium-catalyzed dimerization to give 5,5′-dibromo-2,2′-bipyridine and subsequent twofold Heck reaction.

1 Synthesis of Sterically Encumbered Biaryls based on a Copper(I)-Catalyzed Arylation / [3+3] Cyclocondensation′ Strategy

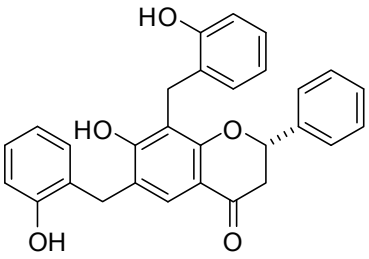
1.1 Introduction

Sterically encumbered biaryls are found in several natural products. These biaryls are of considerable importance in pharmacology. The simple biaryl cynandione A was isolated from *Cynachum wilfordii*. Cynandione A was shown to protect cultured cortical neurons from toxicity of H_2O_2, L-glutamate and kainate.[7] Cynandione A-C are effective against hepatocytes, human bladder carcinoma T-24 cells, epidermoid carcinoma KB cells, and human hepatoma PLC/PRF/5 cells.[8] 3-Arylbenzoates are also present in many flavones (e.g. 2,3-dihydroamentoflavone, obtained from *selagenella tamariscina*, which is active against type-2 diabetes and obesity.[9a] Bartramiaflavone,[9b] robustaflavone, obtained from *selagenella dicatula*, is effective against hepatitis B.[9c] Dichamanetin, obtained from *U. chamae*, is effective against gram positive bacteria.[9d,e] For some derivatives, inhibition of the human liver cathepsin B and K has been reported.[9f,g] Anastatin A, which was isolated from *anastatica heirochuntica*,[10] possesses a benzofuran moiety and shows hepativeprotective activity.[11] Many pharmacologically active biaryl natural products, such as picropodophyllone, can be formally regarded as sterically encumbered 4-arylphenols.[12] Others, such as dioncophylleine A, contain a naphthalene and an isoquinoline moiety.[13] Flavidine may be regarded as a complex bridged biaryl derivative.[14]

Sterically encumbered biaryls are readily available by Pd(0)-catalyzed cross-coupling reactions (e.g., Suzuki reactions).[15] Despite the usefulness of this approach, the synthesis of sterically encumbered and functionalized products can be sometimes difficult. Recently, a number of new ligands have been developed which allow to tackle these problems.[16] But the regioselective preparation of the corresponding aryl halides, which have to be usedf as educts, is still a difficult problem in many cases. Arenes are alternatively available by using dienes in cyclisation reactions. For example, Chan *et al.* developed[17] a convenient approach to salicylates by [3+3] cyclizations[18] of with 3-trimethylsilyloxy-2-en-1-ones with 1,3-bis(trimethylsilyloxy)-1,3-dienes.[19] I have studied the synthesis of sterically encumbered and functionalized biaryls by a combination of CuI-proline-catalyzed arylation reactions and [3+3] cyclizations.



Cynandione A



Dichamanetin

1.2 Results and discussion

The CuI-proline-catalyzed arylation[20] of 1,3-diketone **1a** with aryl iodides **2a-c** afforded the 2-aryl-1,3-diketones **3a-c** in 85-90% yield (Scheme 1, Table 1). Aryl iodides **2a-c** were prepared by a method reported by He *et al.*.[21] The silylation of **3a-c** gave the 3-silyloxy-2-en-1-ones **4a-c**. The known 1,3-bis(silyloxy)-1,3-dienes **5a-l** were prepared in two steps from the corresponding β-ketoesters.[10] The $TiCl_4$-mediated [3+3] cyclocondensation of 2-aryl-3-silyloxy-2-en-1-ones **4a-c** with **5a-l** afforded the biaryls **6a-z** (Scheme 2, Table 2). During the optimization, it turned out that the reactions proceed very well in a highly concentrated solution. The reaction of **4a** with 1,3-bis(silyloxy)-1,3-butadienes derived from acetylacetone and benzoylacetone proved to be unsuccessful. This can be explained their lower reactivity compared to dienes derived from β-ketoesters. The nature of the aryl group of enones has a small influence on the yield of the cyclization reactions. N-Butyl substituted enones gave comparatively lower yield.

The substitution pattern of dienes has a strong influence on the yields. The best yields were obtained for products derived from non-substituted diene **5a** which is derived from methyl acetoacetate. This might be explained by cleavage of the benzyl ester moiety by $TiCl_4$. Since both dienes are closely related with respect to their structure, this result indicates that the individual quality of the diene and reagents employed also have a strong influence.

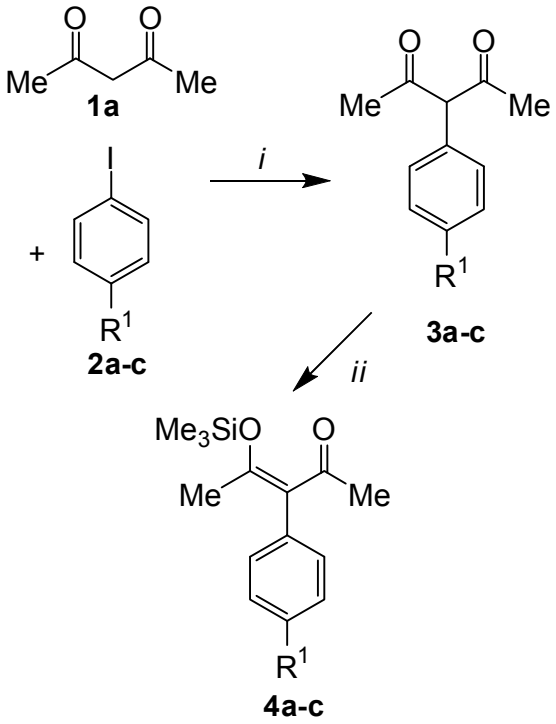
a) The dienes electrophiles must be entirely pure and distilled.

b) The dienes must be free of polymeric impurities and monosilyl enol ether.

c) The $TiCl_4$ employed must not be old.

Chromatographic purification also plays an important role. The yields of the products derived from 4-substituted dienes are often slightly lower than the yields of the products derived from **5a**.

The structures of **6b** and **6v** were independently confirmed by X-ray crystal structure analyses (Figures 1 and 2).[22] The two aryl moieties are twisted out of plane. An intramolecular hydrogen bond O–H···O is present in all structures.

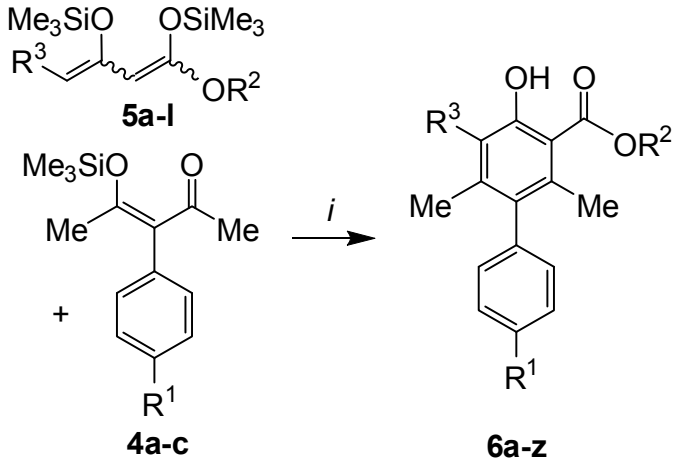


Scheme 1. Synthesis of **4a-c**, *i*: K_2CO_3, CuI 10 mol %, L-proline 20 mol%, DMSO, 90 °C, 6-12 h; *ii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h

Table 1: Synthesis of 3-aryl-1,3-diketones **3a-c** and 3-silyloxy-2-en-1-ones **4a-c**

1	**2**	**3,4**	R^1	% (**3**) [a]	% (**4**) [a]
a	**a**	**a**	H	76	90
a	**b**	**b**	Me	82	88
a	**c**	**c**	*n*Bu	83	85

[a]Yields of isolated products



Scheme 2. Synthesis of **6a-z**; *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h

Table 2. Synthesis of biaryls **6a-z**

4	**5**	**6**	R^1	R^2	R^3	% (**6**)[a]
a	**a**	**a**	H	Me	H	61
a	**b**	**b**	H	Et	H	40
a	**c**	**c**	H	CH_2Ph	H	35
a	**d**	**d**	H	Me	Me	48
a	**e**	**e**	H	Me	Et	53
a	**f**	**f**	H	Me	$(CH_2)_2Ph$	38

a	**g**	**g**	H	Me	*n*Pent	50
a	**h**	**h**	H	Me	*n*Hex	46
a	**i**	**i**	H	Me	$(CH_2)_2CH=CH_2$	48
a	**j**	**j**	H	Me	Cl	37
b	**a**	**k**	Me	Me	H	54
b	**b**	**l**	Me	Et	H	40
b	**d**	**m**	Me	Me	Me	41
b	**e**	**n**	Me	Me	Et	46
b	**f**	**o**	Me	Me	$(CH_2)_2Ph$	36
b	**h**	**p**	Me	Me	*n*Hex	42
c	**a**	**q**	*n*Bu	Me	H	52
c	**b**	**r**	*n*Bu	Et	H	45
c	**c**	**s**	*n*Bu	CH_2Ph	H	38
c	**d**	**t**	*n*Bu	Me	Me	58
c	**e**	**u**	*n*Bu	Me	Et	55
c	**f**	**v**	*n*Bu	Me	$(CH_2)_2Ph$	37
c	**h**	**x**	*n*Bu	Me	nHex	48
c	**k**	**w**	*n*Bu	Me	*n*Non	42
c	**l**	**y**	*n*Bu	Me	Allyl	55
c	**i**	**z**	*n*Bu	Me	$(CH_2)_2CH=CH_2$	53

[a]yields of isolated products

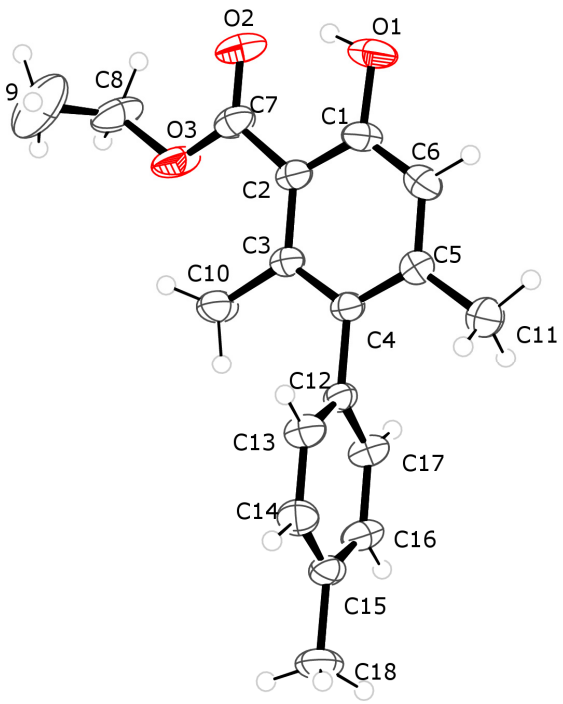


Figure 1. Ortep plot of **6b** (50% probability).

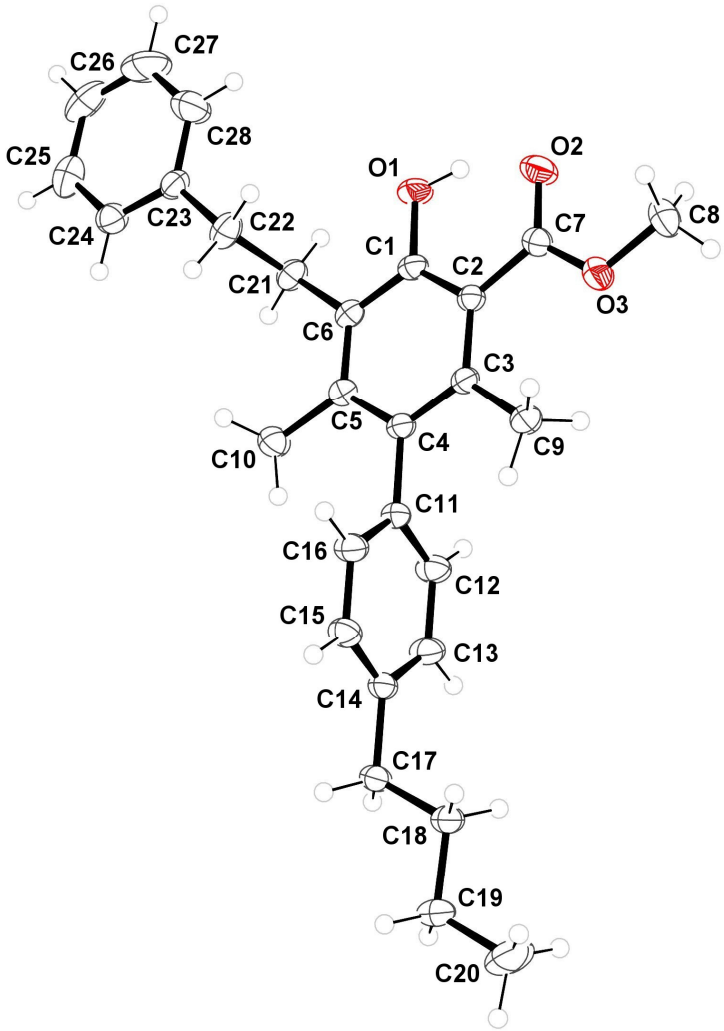


Figure 2. Ortep plot of **6v** (50% probability)

1.3 CONCLUSIONS

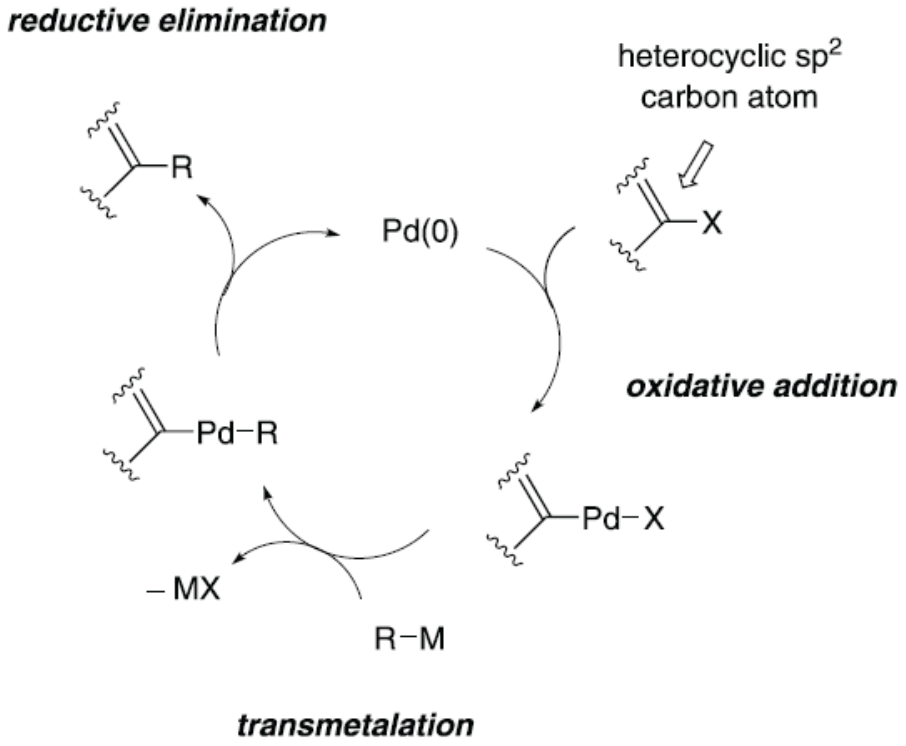
In short, I prepared various sterically encumbered biaryls by CuI-proline catalysed reactions followed by [3+3] cyclocondensation reactions.

2. Syntheses of Arylated Pyrazoles by Site-Selective Suzuki- Miyaura Reactions of *N*-Protected 3,4,5-Tribromo-1-*H*-pyrazoles

2.1 Introduction to palladium(0)-catalyzed reactions

Palladium (Pd) is one of the most versatile and useful metals in modern organic synthesis.[23,24] Palladium-catalyzed reactions have been applied to the synthesis of natural products, polymers, agrochemicals, and pharmaceuticalsImportant Pd(0)-catalyzed reactions include the Heck reaction, Suzuki-Miyaura reaction, Stille reaction, the Buchwald-Hartwig reaction, and the Tsuji-Trost allylation. The well-known Wacker reaction is a Pd(II) catalyzed process.[25]

The mechanism of the Suzuki and of the Stille reaction is depicted in Scheme 3. [27] It includes an oxidative addition, transmetallation and reductive elimination. For Suzuki reactions, boronic acids or esters are used as the reagent R-M. For Stille reactions, organotin compounds are employed.



Scheme 3. General mechanism for Suzuki and Stille cross-coupling reaction (this scheme was copied from *Tetrahedron*, **2005**, *61*, 2245).

The Suzuki reaction was first reported by Akira Suzuki and his group in 1979.[26] The broad applicability of Suzuki reaction relies on the following facts.

(1) Commercial availability of large number of boronic acids.
(2) Mild reaction conditions.
(3) Low toxicity of reagents.
(4) Easy separation of inorganic by-products from reaction mixture.
(5) Tolerance to a broad range of functional group.

The rate of Suzuki reaction depends upon the oxidative addition and transmetallation. The oxidative addition depends upon the reactivity of substrate. The order of reactivity of substrate is Ar-I> Ar-Br = Ar-OTf > Ar-Cl. The rate of transmetallation is increased by base. This can be explained by the increase in nuleophilicity of organoborane compounds by the formation of organoborate which contains a tetravalent boron atom.

The catalyst plays an important role in Suzuki reactions. Very often $Pd(OAc)_2$, $PdCl_2$, $Ph(PPh_3)Cl_2$, and $Pd(dba)_2$ are employed. Bulky electron-rich ligands often give excellent results, such as ferrocenylphos[28], N-heterocyclic carbenes,[29] $P(tBu)_3$[30], $P(Cy)_3$ and others.

Suzuki reaction have been applied to several physically or biologically relevant systems, such as NLO-active 1,8-diarylnapthalenes,[31] non-natural amino acids,[32] anti HIV compounds,[33] potent antibiotics such as vancomycin,[34] carbon nanotubes,[3] and even solar cells.[36]

The Heck reaction was developed by Mizoroki and Heck in the early 1970s. The Heck reaction is the palladium catalysed cross-coupling reaction of organohalides or triflates with alkenes in the presence of a base.[37, 38] Generally the rate of reaction of more substituted olefins is slower than the rate of reaction of less substituted olefins. Typically the order of reaction of organohalides is as follows $I > Br \sim OTf >> Cl$

The mechanism of the Heck reaction is similar to the Suzuki reaction, but the C-C bond formation is established by carbapalladation of the alkene instead of transmetallation.[39, 40, 41]

2.2 Introduction to pyrazole syntheses

Five-membered heterocyclic compounds are of synthetic relevance, due to their biological properties. Pyrazoles show a variety of pharmacological effects which include anti-inflammatory[42], antiobiotic[43], alcohol dehydrogenase inhibitory activity,[44] activity as nicotinic acid receptor agonists,[45a] and activity as excitory amino acid antagonists.[45b, 45c] The drug celecoxib, which exhibits anti-inflammatory properties, is used to treat arthritis, minstrel cramps and colonic polyps.[45d,e] Recently, Nicolaou and coworkers[45f] studied the anticancer activity of epothilone A and B, which also contain a pyrazole moiety.

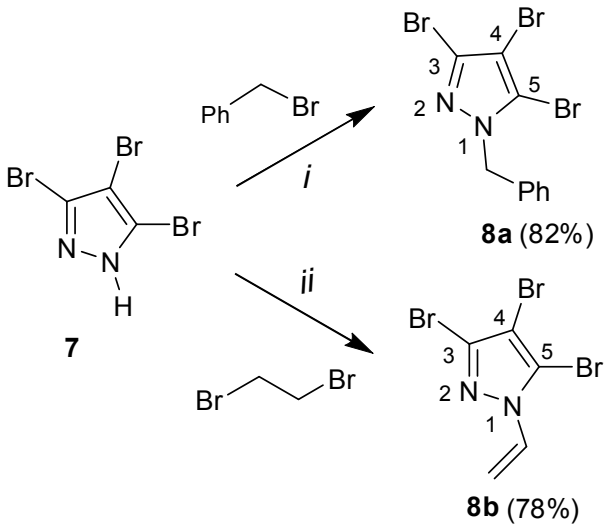
Pyrazoles are synthetically available by 1,3-dipolar cycloaddition reactions of diazoalkanes with alkynes and related transformations.[46] A classic approach to pyrazoles relies on the cyclisation of hydrazines with 1,3-diketones or α,β-unsaturated ketones.[47] lternatively, hydrazone dianions have been cyclized with various carboxylic acid derivatives.[48] Noteworthy, some COX-1 and COX-2 inhibitors were prepared by reaction of hydrazine with 4-aryl-2,4-dioxoesters.[49]

2.3 Results and discussion

The field of site-selective palladium catalysed cross-coupling reactions of polyhalogenated heterocycles is of great interest nowadays because these reactions often provide a facile and site-selective approach to highly substituted heterocycles.[50,51] This approach relies on substitution reactions of the heterocyclic core rather than on its assembly as described in the introduction (see above). When I started my work, palladium-catalyzed cross-coupling reactions of polyhalogenated pyrazoles had, to the best of my knowledge, not been reported. Recently, metal-halide exchange reactions of *N*-vinyl-tribromopyrazole were reported.[52] Together with my colleagues R. A. Khera and M. Hussain, I have developed Suzuki-Miyaura reactions of *N*-vinyl- and *N*-benzyl-tribromopyrazole. The results of my own efforts in this field are described in this thesis. The products, triaryl-pyrazoles, 3,5-diaryl-4-

bromopyrazoles, and 5-aryl-3,4-dibromopyrazoles, are of considerable pharmacological relevance.[53] Previous syntheses of these molecules are not straightforward and mainly include derivatives containing the same type of aryl moiety.

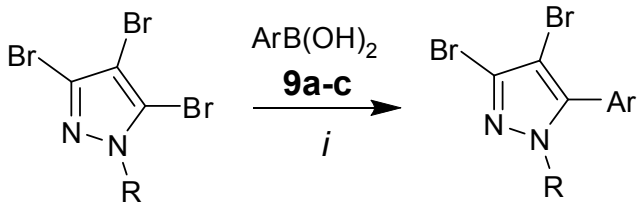
N-Benzyl-tribromopyrazole (**8a**) was prepared from commercially available tribromopyrazole by modification of a known procedure (Scheme 4).[54] Instead of benzylchloride, which was used in the original procedure, I have used benzylbromide. *N*-Vinyl-tribromopyrazole (**8b**) was prepared, again following a reported procedure,[52] by reaction of commercially available tribromopyrazole with dibromoethane.



Scheme 4. Synthesis of **8a,b**. *Reagents and conditions: i*, (1.0 equiv), benzylbromide (1.0 equiv), NEt_3 (1.1 equiv), CH_2Cl_2 (5 mL per mmol of **7**), 20 °C, 4 h. *ii*, **7** (1.0 equiv), 1, 2-dibromoethane (1.2 equiv), NEt_3 (5 mL per mmol), CH_3CN (5 mL per mmol of **7**), 70 °C, 7 h

The Suzuki-Miyaura reaction of **8a** and **8b** with arylboronic acids **9a-c** (1.0 equiv.) afforded the 5-aryl-3,4-dibromopyrazoles **10a-c** in 66-73% yield (Table 3, Scheme 5). A good yield was obtained even for sterically hindered boronic acids. During the optimization, the best yields were obtained when $Pd(PPh_3)_4$ was used as the catalyst (3 mol %) and when K_3PO_4 (1.5 equiv.) was used as the base. The use of $Pd(OAc)_2$ in

the presence of XPhos[55] gave less yield. The use of exactly one equivalent of the boronic acid was crucial to avoid multiple coupling. The reactions were carried out in a 4:1 mixture of dioxane and water. The use of toluene was less efficient because of the low solubility of the boronic acids in toluene. The temperature (100 °C) and the reaction time (12 h) also played an important role. The formation of **10a-c** proceded, like the metal-halide exchange,[50] with excellent site-selectivity in favour of position 5.



8a,b **10a-c**

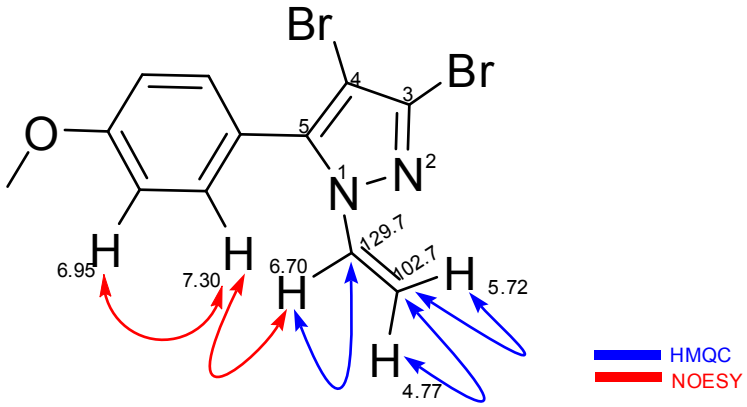
Scheme 5. Synthesis of 5-aryl-3,4-dibromopyrazoles **10a-c**. *Reagents and conditions: i*, **8** (1.0 equiv), $ArB(OH)_2$ (1.0 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane / H_2O (4:1), 100 °C, 12 h.

Table 3. Synthesis of 5-aryl-3,4-dibromopyrazoles **10a-c**

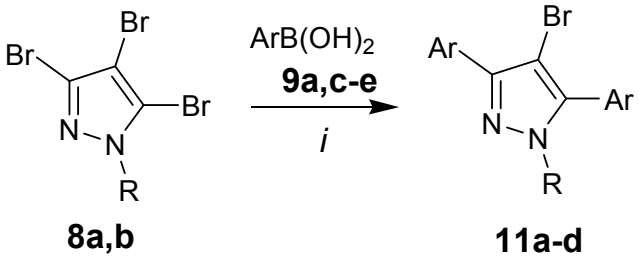
8	**9**	**10**	R	Ar	%(**10**)[a]
b	**a**	**a**	Vinyl	4-(MeO)C_6H_4	66
b	**b**	**b**	Vinyl	2-(MeO)C_6H_4	69
b	**c**	**c**	Vinyl	2,6$(MeO)_2C_6H_3$	71

[a] Yields of isolated compounds

The structure of compound **10a** was established by 2D NMR using H-H (NOESY) and H-C (HMQC) correlations. The vinylic proton attached to carbon C-129.7 showed a clear correlation through space with the phenyl proton located at δ 7.30 which confirmed that the 4-methoxyphenyl is attached at C-5 of the pyrazole moiety (see structure below).



The Suzuki-Miyaura reaction of **8a** and **8b** with arylboronic acids **9c-d** (2.0 equiv.) gave the 3,5-diaryl-4-bromopyrazoles **11a-d** in 40-74% yield (Table 4, Scheme 6). A good yield was obtained even for the sterically hindered boronic acid **9d**. A slightly increased amount of the catalyst (5 mol %), exactly two equivalents of the boronic acid, and the double amount of base (3.0 equiv.) were used. The yields slightly decreased for product **11d** derived from the electron-poor boronic acid **9d** and for product **11b** derived from the sterically hindered boronic acid **9d**. The structure of **11a** was independently confirmed by X-ray crystal structure analysis (Figure 3). As expected, the heterocyclic moiety is flat. The aryl groups are slightly twisted out of plane, presumambly due to steric reasons.



Scheme 6. Synthesis of 5-aryl-3,4-dibromopyrazoles **11a-d**. *Reagents and conditions: i*, **8** (1.0 equiv), $ArB(OH)_2$ (2.0 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (5 mol-%), 1, 4-dioxane / H_2O (4:1), 100 °C, 12 h.

Table 4. Synthesis of 3,5-diaryl-4-bromopyrazoles **11a-d**

8	**9**	**11**	R	Ar	%(**11**)[a]
b	**a**	**a**	Vinyl	4-(MeO)C_6H_4	40
b	**c**	**b**	Vinyl	2,6-$(MeO)_2C_6H_3$	62
b	**d**	**c**	Vinyl	3,5-$(MeO)_2C_6H_3$	74
a	**e**	**d**	Benzyl	4-FC_6H_4	66

[a]Yields of isolated compounds

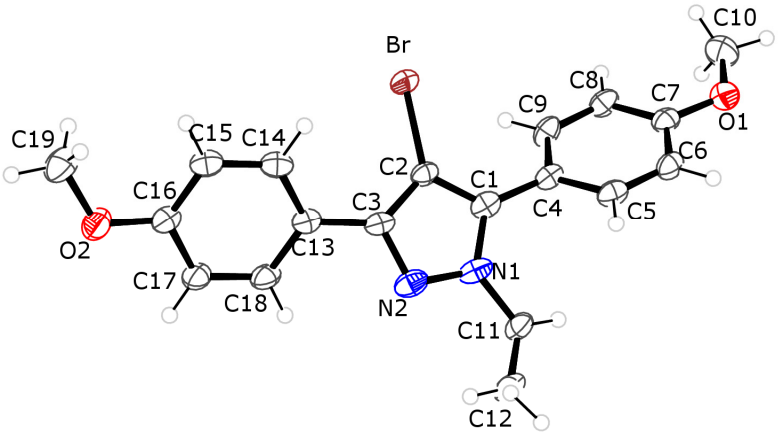
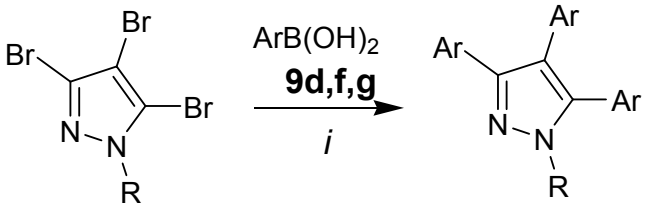


Figure 3. Ortep plot of **11a** (50% probability)

The Suzuki-Miyaura reaction of **8a** and **8b** with an excess of arylboronic acids **9d,f,g** (3.5 equiv.) afforded the 3,4,5-triaryl-pyrazoles **12a-c** in 50-76% yield (Table 5, Scheme 7). The use of 10 mol% of catalyst, excess of boronic acid (3.5 equiv) and

base (4.5 equiv) gave excellent results during optimization. The yields slightly decreased for product **12b** derived from the electron-poor boronic acid **9b**.



8a,b **12a-c**

Scheme 7. Synthesis of 3,4,5-triaryl-pyrazoles **12a-c**. *Reagents and conditions: i*, **8** (1.0 equiv), $ArB(OH)_2$ (3.5 equiv), K_3PO_4 (4.5 equiv), $Pd(PPh_3)_4$ (10 mol-%), 1,4-dioxane / H_2O (4:1), 100 °C, 12 h.

Table 5. Synthesis of 3,4,5-triaryl-pyrazoles **12a-c**

8	**12**	**9**	R	Ar	% (**12**)[a]
b	**a**	**d**	Vinyl	3,5-$(OMe)_2C_6H_3$	74
a	**b**	**f**	Benzyl	4-ClC_6H_4	50
a	**c**	**g**	Benzyl	4-EtC_6H_4	58

[a] Yields of isolated compounds

2.4 Conclusion

In conclusion, I reported site-selective Suzuki-Miyaura reactions of *N*-protected tribromopyrazoles. The reaction of the latter with three, two or one equivalents of arylboronic acids gave 3,4,5-triaryl-pyrazoles, 3,5-diaryl-4-bromopyrazoles, or 5-aryl-3,4-dibromopyrazoles, respectively. The products are not readily available by other methods.

3 Synthesis of Bis(diaryl)sulfones by Suzuki-Miyaura Reactions of 2,4′-Bis(trifluoromethylsulfonyloxy)-diphenylsulfone

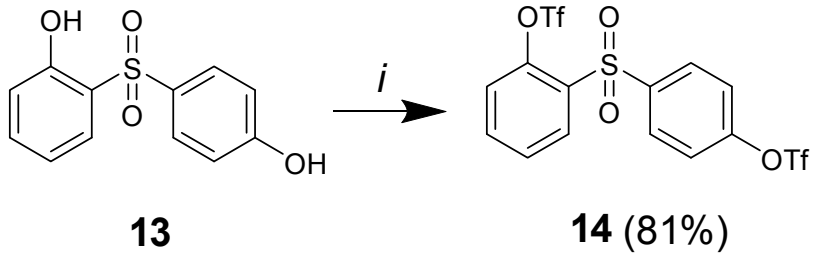
3.1 Introduction

Diarylsulfones constitute a pharmacologically important molecular entity. Reported activities include antimicrobial activity,[56] various enzyme inhibitions[57, 58, 59] hypolipidemic,[60] cytotoxic,[61] neuropetide receptor binding,[62], anti HIV[63], anticholestermic,[64] muscuarinic receptor binding,[65] histamine H_3 receptor antagonistic,[66] antiprotozoal,[67] neuroblastemic cellbinding,[68] and cannabinoid CB1 receptor binding activity.[69]

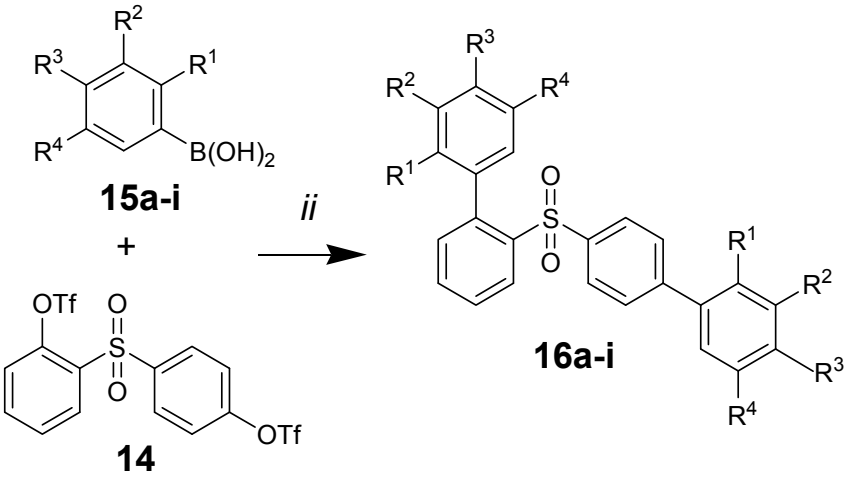
Diaryl sulfones are classically available by oxidation of diaryl sulfides,[70] Friedel-Crafts acylation of methoxybenzene with arylsulfoniyl chlorides,[71] or by condensation of phenols with benzenesulfonic acid.[72] These methods usually require drastic conditions and proceed with low o,p-regioselectivities. Diaryl sulfones have been prepared by CuI/proline-mediated reaction of aryl iodides with sodium benzenesulfinate.[73] In addition, the Suzuki reaction of phenylsulfonic acid chloride with 4-methoxybenzeneboronic acid,[74] and the $Cu(OAc)_2$-catalyzed reaction of 4-methoxybenzeneboronic acid with sodium benzenesulfinate have been reported.[75] Diaryl sulfones have also been prepared by cyclization reactions of sulfone-containing building blocks.[76] In my thesis, I have developed a new approach to bis(diaryl)sulfones by Suzuki-Miyaura reactions of the bis(triflate) of 2,4′-bis(dihydroxy)diphenylsulfone. The issue of site-selectivity for these transformations has not been addressed by myself, but by a different student, due to lack of time.

3.2 Results and discussion

Commercially available 2,4′-bis(hydroxy)-diphenylsulfone (**13**) was transformed into its bis(triflate) **14** in 81% yield (Scheme 8). The Suzuki reaction of **14** with arylboronic acids **15a-i** (2.6 equiv.) afforded the novel 2,4′-bis(aryl)-diphenylsulfones **16a-i** in good yields (Scheme 9, Table 6). The reactions were carried out using $Pd(PPh_3)_4$ (6 mol-%) as the catalyst. The employment of other catalysts, such as $PdOAc)_2$/ XPhos, resulted in a decreased yield (formation of complex mixtures which are difficult to be separated). A slight excess (2.6 equiv.) of the boronic acid was used. Potassium phosphate (K_3PO_4) was used as the base. 1,4-Dioxane (110 °C, 4 h) was used as the solvent.



Scheme 8. Synthesis of **14**. *Reagents and conditions: i*, CH_2Cl_2, **13** (1.0 equiv), -78 °C, pyridine (4.0 equiv), Tf_2O (2.4 equiv), -78 → 0 °C, 4 h.



Scheme 9. Synthesis of **16a-i**. *Reagents and conditions: i*, **14** (1.0 equiv.), **15a-i** (2.6 equiv.), K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%), 1,4-dioxane (5 mL per 1 mmol of **14**), 110 °C, 4 h

Table 6. Synthesis of 2,4′-bis(aryl)diphenylsulfones **16a-i**

14,16	R^1	R^2	R^3	R^4	%(**16**)[a]
a	H	H	Me	H	70
b	H	CF_3	H	H	60
c	OMe	H	H	H	62
d	H	H	CF_3	H	65
e	H	H	*t*Bu	H	70
f	H	H	F	H	55
g	H	H	Vinyl	H	65
h	H	Me	H	Me	60
i	H	OMe	H	OMe	72

[a]Yields of isolated products

The structure of **16e** was independently confirmed by X-ray crystal structure analysis (Figure 4). All four phenyl groups are slightly twisted out of plane, due to steric reasons.

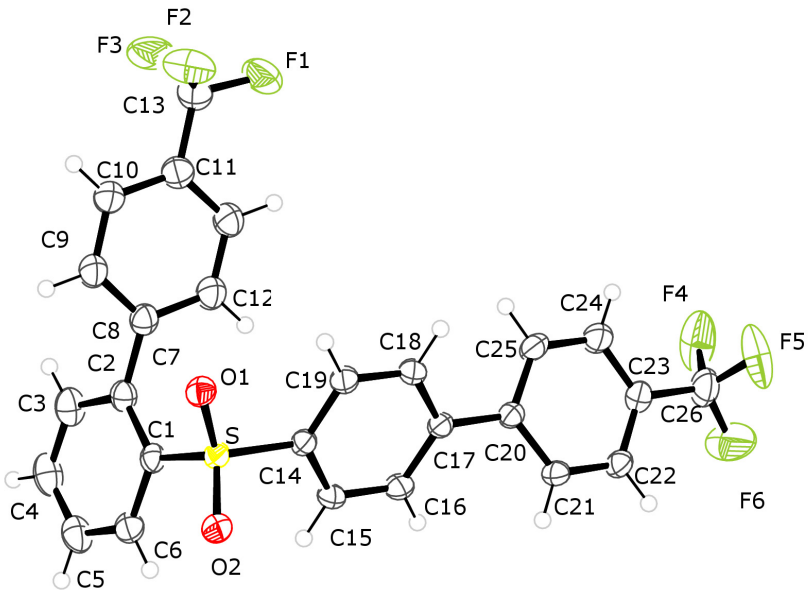


Figure 4. Ortep plot of **16e** (50% probability).

3.2 Conclusions

In conclusion, I have reported a new synthesis of 2,4′-bis(aryl)diphenylsulfones by palladium(0)-catalyzed cross-coupling reactions of the bis(triflate) of 2,4′-bis(hydroxy)-diphenylsulfone. The reactions proceed with very good site-selectivity.

4 First double Heck cross-coupling reactions of dibromopyridines

4.1 Introduction

Pyridines are of relevance in medicinal chemistry and occur in a number of natural products. A prominent example is nicotinic acid and its derivatives, vitamin B_6 and various other molecules.[77,78] The research group of Prof. P. Langer has reported the synthesis and biological evaluation of 2-sulfonylpyridines[79] and 4-hydroxy-4-(pyridyl)alk-3-en-2-ones[80] which exhibit anti-microbial activity. The class method of preparation of pyridine derivatives relies on base-mediated cyclocondensation reactions, e. g., the Hantzsch reaction.[78,81,82]. Although these methods have great utilities but in case of specific substitution pattern and labile functionalities these methods are not so successful. To overcome these problems palladium-catalyzed cross-coupling reactions to halogenated pyridines can be advantageous. As mentioned in chapter 3, various site-selective reactions of polyhalogenated heterocycles have been previously studied.[83,] Cross-coupling reactions of halogenated pyridines have also been reported. 2,5-Dibromopyridine has been used in aminations,[84] and in Stille,[85] Suzuki,[86] Negishi,[87] Sonogashira,[88] and Kumada couplings.[89] In all cases, the first reaction occured at the more electron-deficient position C-2. In most studies, single coupling reactions were carried out. Recently, Handy and coworkers reported the first double Suzuki couplings of 2,5- and 2,3-dibromopyridine.[90] Single Heck coupling reactions of 2-chloro- and 2-bromopyridine have been studied in recent years.[91] In my thesis, I have studied double Heck reactions of various dibrominated pyridines.

4.2 Results and discussion

The Heck reaction of 2,3-dibromopyridine (**17a**) with acrylates **18a-e** afforded the 2,3-di(alkenyl)pyridines **19a-e** (Table 7). The reaction of **17a** with styrenes **18f-i** gave products **19f** and **19h-i** (**19g** could not be isolated, due to decomposition during the reaction). All products **19a-i** were isolated in 60-84% yield and contain exclusively *E*-configured double bonds. The reaction of **18f** and **18i** with 2,3-dichloropyridine (**17b**) instead of **17a** afforded **19f** and **19i**, albeit, in only poor yields. The reaction conditions were thoroughly optimized for the synthesis of **19c** and **19f** (Scheme 10, Table 10). The best yields were obtained when the reactions were carried out using **17a**, $Pd(OAc)_2$ (5 mol-%) and the biaryl monophosphine ligands SPhos (L_1, for **19a-g,i**) or XPhos (L_2, for **19h**) (10 mol-%) which were both recently developed by Buchwald and coworkers. The use of tricyclohexylphosphane (L_4) gave slightly lower yields. The employment of $Pd(PPh_3)_4$ resulted in considerably lower yields. Trietylamine was used as the base in all reactions. The application of other bases (K_2CO_3) did not result in an increase of the yield. The reactions were carried out in DMF at 120 °C. A relatively long reaction time (48 h) was necessary to achieve a complete conversion. Recently, Li and Wang reported[92] that triethanolamine (L_3) represents an efficient and reusable combined base, ligand, and solvent for Heck reactions. However, only traces of product could be isolated when these conditions were applied.

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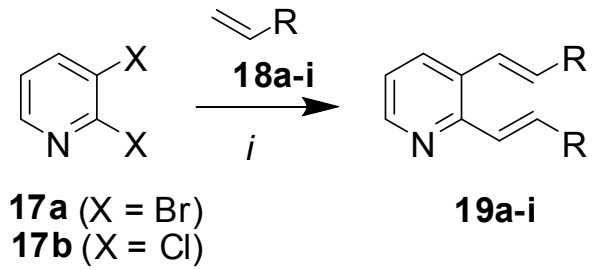
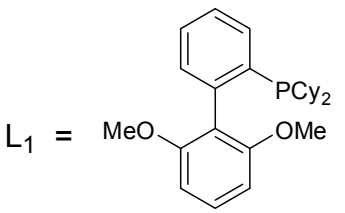


Scheme 10. Conditions: *i*, Pd $(OAc)_2$ (5 mol-%), $\mathbf{L_1}$ (10 mol-%), NEt_3, DMF, 120 ˚C, 48 h

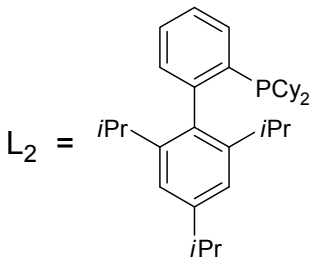
Table 7. Synthesis of 2,3-di(alkenyl)pyridines **19a-i**

17	18	R	%(19)[a]
a	**a**	CO_2Me	63
a	**b**	CO_2Et	71
a	**c**	CO_2iBu	82
a	**d**	CO_2tBu	84
a	**e**	CO_2CO_2[b]	60
a	**f**	CO_2R[b]	72
b	**f**	Ph	11
a	**g**	Ph	0[c]
a	**h**	4-(*t*BuO)C_6H_4	79
a	**i**	4-(MeO)C_6H_4	65
b	**i**	4-MeC_6H_4	9

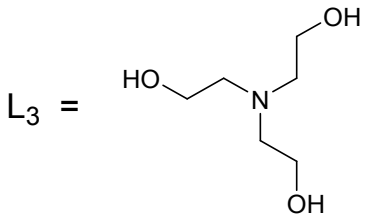
[a] yields of isolated products; [b] 2-ethylhexyl; [c] decomposition



SPhos
Cy = Cyclohexyl



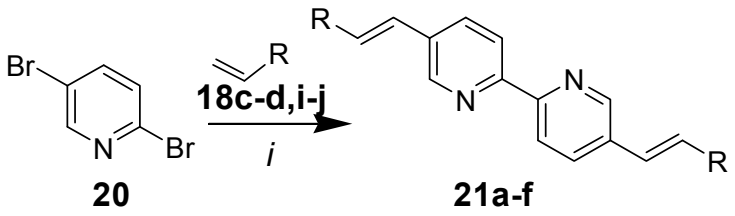
XPhos



$L_4 = P(Cy)_3$

The Heck reaction of 2,5-dibromopyridine (**20**) with acrylates **18c-e,i-k** gave the 5,5′-di(alkenyl)-2,2′-bipyridines **21a-f** in 60-84% yields instead of the expected bis(alkenyl)pyridines (Table 8). The best yields were obtained using $Pd(OAc)_2$ and L_2. The synthesis of 2,5-di(alkenyl)pyridines by double Heck reaction was not possible under various conditions (different catalysts and temperatures). The formation of **21a-f** can be explained by palladium-catalyzed dimerization to give 5,5′-dibromo-2,2′-bipyridine and subsequent twofold Heck reaction. The palladium-catalyzed dimerization seems to be faster than the Heck reaction. The formation of 2,2′-bipyridine as a side product in Heck reactions of 2-bromopyridine has been previously noted.

The structure of **21d** was independently confirmed by X-ray crystal structure analysis (Figure 5). The bipyridyl moiety is only slightly twisted out of plane.



Scheme 11. Conditions: *i*, $Pd(OAc)_2$ (5 mol-%), $\mathbf{L_2}$ (10 mol-%), NEt_3, DMF, 120 ˚C, 48 h.

Table 8. Synthesis of 5,5′-di(alkenyl)-2,2′-bipyridines **21a-f**

18	**21**	R	% (**21**)[a]
j	**a**	CO_2nBu	83
k	**b**	CO_2nHex	71
e	**c**	CO_2R [b]	82
d	**d**	CO_2tBu	84
c	**e**	CO_2iBu	77
i	**f**	4-MeC_6H_4	60

[a]Yields of isolated products.

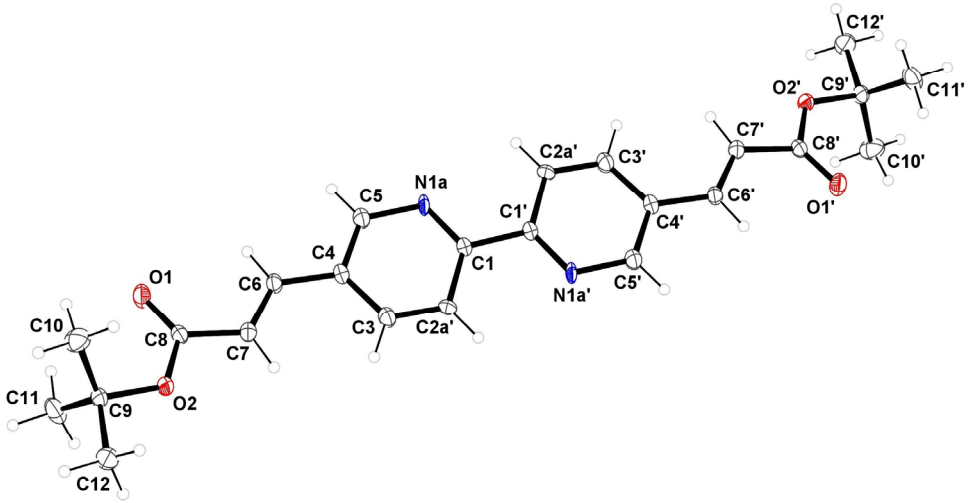
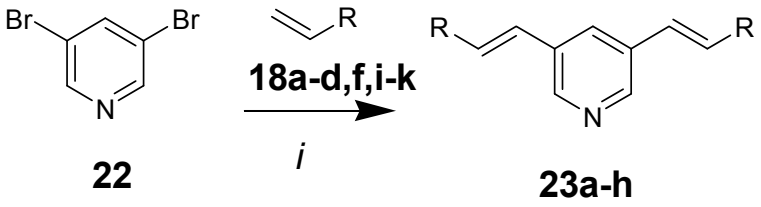


Figure 5. Ortep plot of **21d** (50% probability).

The double Heck reaction of 3,5-dibromopyridine (**22**) with acrylates **18a-d,f,i-k**, using $Pd(OAc)_2$ and L_4, afforded the 3,5-di(alkenyl)pyridines **23a-h** in 69-84% yields (Scheme 12, Table 9). Similar yields were obtained using ligands L_4 and L_1 (Table 10). Therefore, the cheaper ligand L_4 was employed.



Scheme 12. Conditions: *i*, $Pd(OAc)_2$ (5 mol-%), **L_4** (10 mol-%), NEt_3, DMF, 120 ˚C, 48 h

Table 9. Synthesis of 3,5-di(alkenyl)pyridines **23a-h**

18	**23**	R	% (**23**) [a]
a	**a**	CO_2Me	69
b	**b**	CO_2Et	71
j	**c**	CO_2nBu	82
c	**d**	CO_2iBu	84
k	**e**	CO_2nHex	77
d	**f**	CO_2tBu	81
f	**g**	Ph	72
i	**h**	4-MeC_6H_4	76

[a]Yields of isolated products.

Table 10. Optimization of the synthesis of 3,5-di(alkenyl)pyridines **23c,f**

Conditions	% (**23c**) [a]	% (**23f**)[a]
$Pd(PPh_3)_4$ (5 mol-%), NEt_3, DMF, 120 ˚C, 48 h	38	49
$Pd(OAc)_2$ (5 mol-%), PCy_3(10 mol-%), NEt_3, DMF, 120 ˚C,48h	72	63
$Pd(OAc)_2$ (5 mol-%), L_1 (10 mol-%), NEt_3, DMF, 120 ˚C, 48 h	82	72
$Pd(OAc)_2$ (5 mol-%), L_2 (10 mol-%), NEt_3, DMF, 120 ˚C, 48 h	80	69
$Pd(OAc)_2$ (5 mol-%), $N(CH_2CH_2OH)_3$ (3 mL), 120 ˚C, 48 h	2	10

[a] Yields of isolated products

4.3 Conclusions

In conclusion, I have reported the first double Heck cross-coupling reactions of 2,3- 2,5- and 3,5-dibromopyridine with various alkenes. These reactions afforded the corresponding bis(alkenyl)-pyridines. The Heck reaction of 2,5-dibromopyridine gave 5,5′-bis(alkenyl)-2,2′-bipyridines by palladium-catalyzed dimerization and subsequent twofold Heck reaction of 5,5′-dibromo-2,2′-bipyridine thus formed.

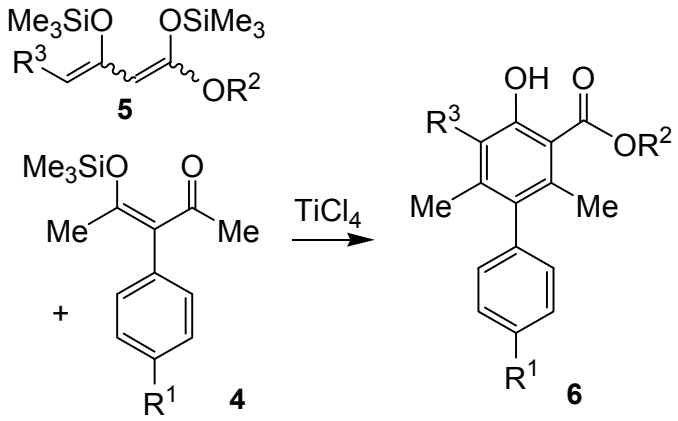
5. Abstract

Sterically encumbered biaryls were prepared by combination of [3+3] cyclocondensation reactions with the arylation of acetylaceton in the presence of catalytic amounts of CuI and L-proline (Scheme I).

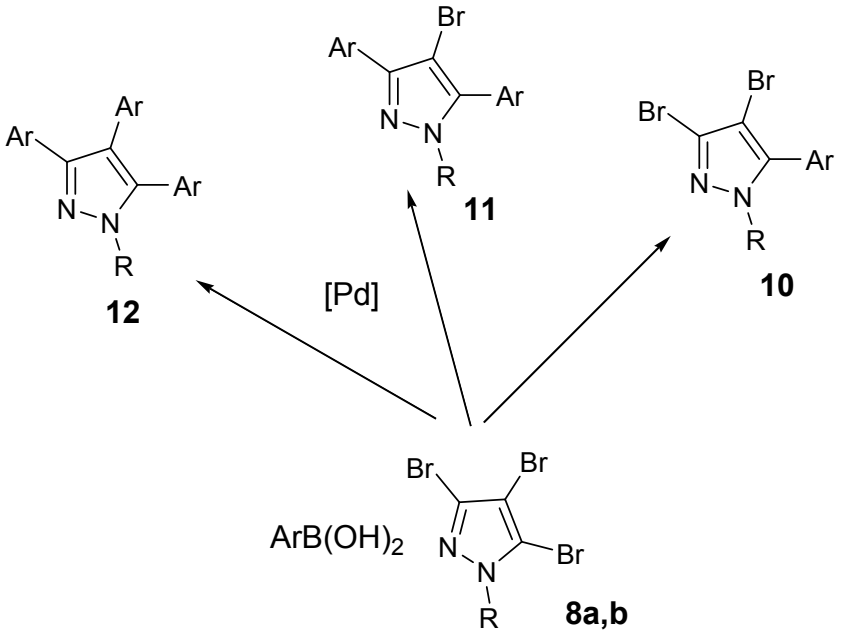
3,4,5-Triarylpyrazoles, 3,5-diaryl-4-bromopyrazoles and 5-aryl-3,4-dibromopyrazoles were prepared by the Suzuki-Miyaura reactions of *N*-protected 3,4,5-tribromopyrazoles. The reactions proceeded with very good site-selectivity (Scheme II).

Bis(diaryl)sulfones were prepared by Suzuki reaction of the bis(triflate) of 2,4-bis(hydroxyl)-diphenylsulfone (Scheme III).

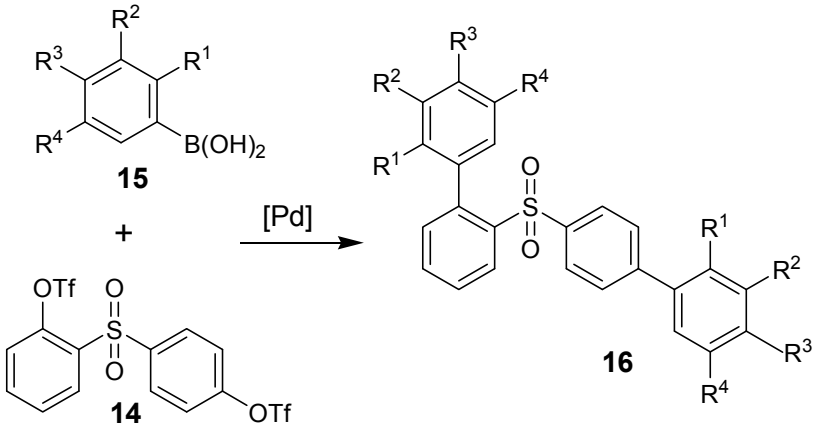
Heck cross-coupling reactions of 2,3- and 3,5-dibromopyridine with various alkenes afforded the corresponding novel bis(alkenyl)pyridines (Scheme IV). The Heck reaction of 2,5-dibromopyridine unexpectedly afforded 5,5′-bis(alkenyl)-2,2′-bipyridines by palladium-catalyzed dimerization to give 5,5′-dibromo-2,2′-bipyridine and subsequent twofold Heck reaction.



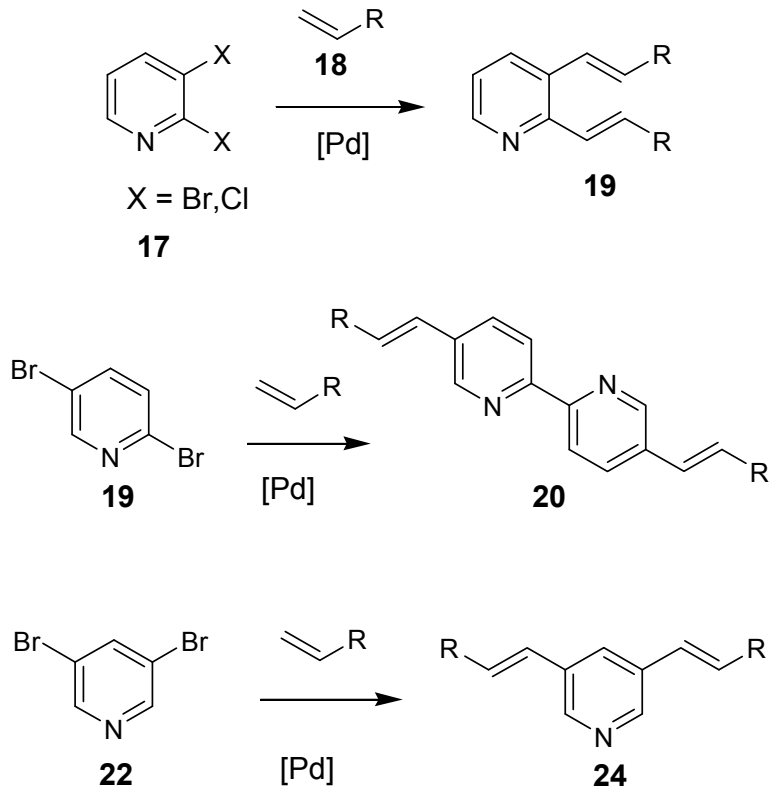
Scheme I. Synthesis of biaryls



Scheme II. Suzuki reactions of tribromopyrazole



Scheme III. Synthesis of bis(diaryl)sulfones



Scheme IV. Heck reactions of dibrominated pyridines

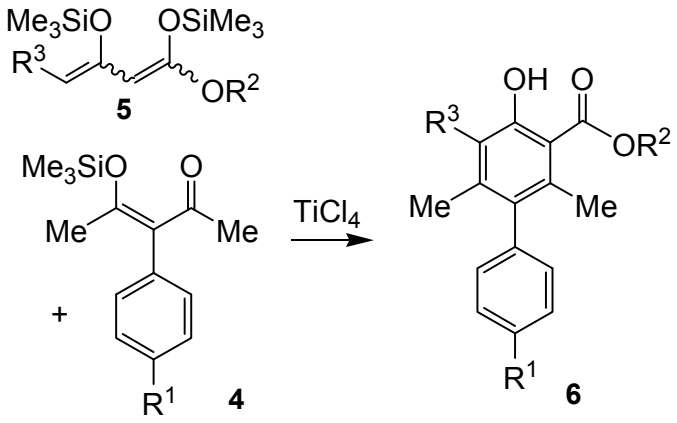
Abstract in German

Sterisch gehinderte Biaryle wurden durch Kombination von [3+3] Cyclocondensation mit der Arylierung von Acetylaceton in Gegenwart katalytischer Mengen von CuI und L-Prolin (Schema I).

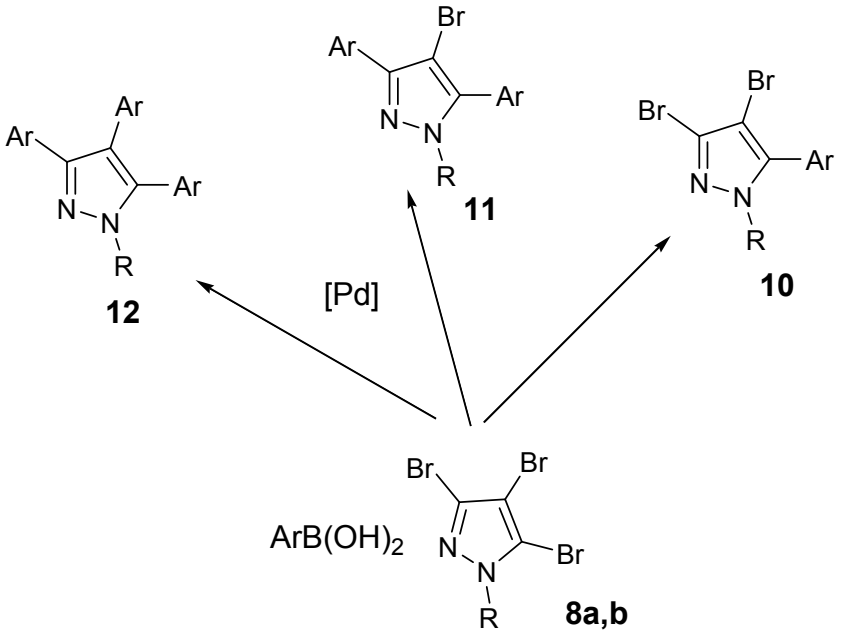
3,4,5-Triarylpyrazole, 3,5-Diaryl-4-bromopyrazole und 5-Aryl-3,4-dibromopyrazole wurden durch Suzuki-Miyaura Reaktionen von *N*-geschützten 3,4,5-Tribromopyrazolen hergestellt. Die Reaktionen laufen mit sehr gutter Regioselektivität ab (Schema II).

Bis(diaryl)sulfone wurden durch Suzuki Reaktionen von Bis(triflaten) von 2,4-Bis(hydroxyl)-diphenylsulfonen hergestellt (Schema III).

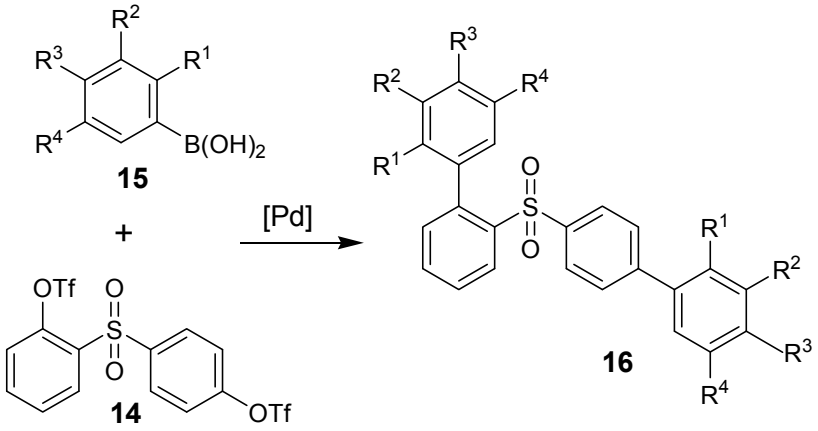
Die Heck Kreuzkupplung von 2,3- und 3,5-Dibromopyridinen mit verschiedenen Alkenen lieferte die entsprechenden Bis(alkenyl)pyridine (Schema IV). Die Heck Reaktion von 2,5-Dibromopyridin lieferte überraschend 5,5′-Bis(alkenyl)-2,2′-bipyridine durch Palladium-katalysierte Dimerisierung und anschließende Heck-eaktion.



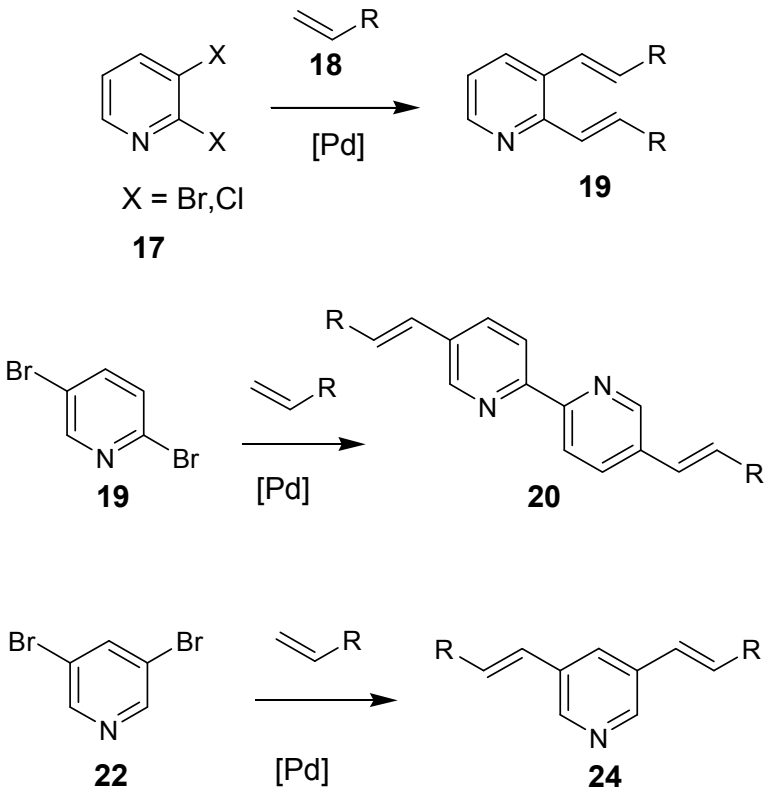
Scheme I. Synthese von Biarylen



Scheme II. Suzuki Reaktionen von Tribrompyrazolen



Scheme III. Synthese von Bis(diaryl)sulfonen



Scheme IV. Heck Reaktionen dibrominierter Pyridine

6 Experimental Section

6.1 General: Equipment, chemicals and work technique

^{1}H NMR Spectroscopy:

Bruker: AM 250, Bruker ARX 300, Bruker ARX 500; δ = 0.00 ppm for Tetramethylsilane; δ = 2.04 ppm for acetone-d_6; δ = 7.26 ppm for ($CDCl_3$); 2.50 ppm for DMSO- d_6; characterization of the signal multiplicity: s = singlet, d = doublet, dd = double of doublet, ddd = doublet of a double doublet, t = triplet, q = quartet, quint = quintet; sext = Sextet, sept = Septet, m = multiplet, br = broadly. Spectra were evaluated according to first order rule. All coupling constants are indicated as (*J*).

^{13}C NMR Spectroscopy

Bruker: AM 250, (62.9 MHz); Bruker: ARX 300, (75 MHz), Bruker: ARX 500, (125 MHz) Ref: 29.84 ± 0.01 ppm and 206.26 ± 0.13 ppm for $(CD_3)_2CO$. δ = 128.00 ppm for acetone-d_6; δ = 77.00 ppm for CDCl3. The multiplicity of the carbon atoms was determined by the DEPT 135 and APT technique (APT = Attached Proton Test) and quoted as CH_3, CH_2, CH and C for primary, secondary, tertiary and quaternary carbon atoms. Characterization of the signal fragmentations: quart = quartet the multiplicity of the signals was determined by the DEPT recording technology and/or the APT recording technology.

Mass Spectroscopy

AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731.

High Resolution mass spectroscopy

Finnigan MAT 95 or Varian MAT 311; Bruker FT
CIR, AMD 402 (AMD Intectra).

Infrared spectroscopy (IR):
Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart Orbit (ATR); KBr, KAP, Nujol, and ATR; Abbreviations for signal allocations: w = weak, m = medium, s = strong, br = broad.

Elementary analysis

LECO CHNS-932, Thermoquest Flash EA 1112.

X-ray crystal structure analysis

Bruker X8Apex Diffractometer with CCD-Kamera (Mo-K_a und Graphit Monochromator, $\lambda = 0.71073$ Å).

Melting points

Micro heating table HMK 67/1825 Kuestner (Büchi apparatus); Melting
Points are uncorrected.

Column chromatography

Chromatography was performed over Merck silica gel 60 (0,063 -0,200 mm, 70 - 230 mesh) as normal and/or over mesh silica gel 60 (0,040 - 0,063 mm, 200 -400 mesh) as Flash Chromatography. All solvent were distilled before use.

TLC

Merck DC finished foils silica gel 60 F_{254} on aluminum foil and Macherey finished Foils Alugram® Sil G/UV_{254}. Detection under UV light with 254 nm and/or 366 nm without dipping reagent, as well as with anisaldehyde sulfuric acid reagent (1 mL anisaldehyde consisting in 100 mL stock solution of 85% methanol, 14% acetic acid and 1% sulfuric acid).

Chemicals and work technique

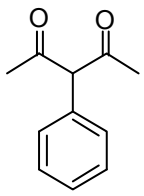
All solvents for using were distilled by standard methods. All reactions were carried out under an inert atmosphere, oxygen and humidity exclusion. All of the chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others. The order of the characterized connections effected numerically, but does not correspond to the order in the main part of dissertation.

6.2 Procedures and spectroscopic data

Typical procedure for the synthesis of 2-aryl-1,3-diones (3a-c)

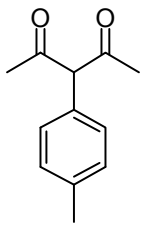
A DMSO solution (2 mL) of **1a** (1.5 mmol), **2a-c** (0.5 mmol), K_2CO_3 (2.0 mmol), CuI (0.05 mmol), L-proline (1.0 mmol) was stirred at 90-120 °C under Argon atmosphere for 6-12 h. The cooled solution was poured into 1.0 M HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc) to afford **3a-c**. All products mainly reside in their enol tautomeric form.

3-Phenylpentane-2,4-dione (3a)



Starting with **1a** (7.7 mL, 75.0 mmol), **2a** (2.7 mL, 25.0 mmol), K_2CO_3 (13.8 g, 100.0 mmol), CuI (0.47 g, 10 mol%), L-proline (0.57 g, 20 mol%) and 100 mL of DMSO (heating for 6 h at 90 °C), **3a** was obtained as a pale yellow oil (3.18 g, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$, enol): δ = 1.93 (s, 6H, CH_3), 6.99 (d (br.), 2H, J = 6.8 Hz, H_{Ar}), 7.23-7.34 (m, 3H, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_3), 114.3 (C, enol form), 125.5 (CH_{Ph}), 127.3 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 134.2 (C_{Ar}), 190.8 (C=O).

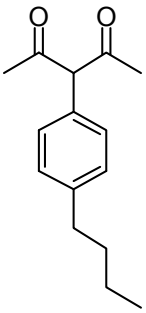
3-*p*-Tolylpentane-2,4-dione (3b)



Starting with **1a** (7.7 mL, 75.0 mmol), **2b** (5.4 g, 25.0 mmol), K_2CO_3 (13.8 g, 100.0 mmol), CuI (0.47 g, 10 mol%), L-proline (0.57 g, 20 mol%) in 100 mL of DMSO (heating for 9 h at 90 °C), **3b** was obtained as a colorless solid (3.86 g, 82%). ^{1}H-NMR (300 MHz, $CDCl_3$, enol): δ = 1.99 (s, 6H, CH_3), 7.08 (d (br.), 2H, J = 7.7 Hz, H_{Ar}), 7.17 (d (br.), 2H, J

= 7.7 Hz, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.7, 24.2 (CH_3), 114.7 (C, enol form), 129.2 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 135.1, 136.2 (C_{Ar}), 191.4 (C=O).

3-(4-Butylphenyl)pentane-2,4-dione (3c)



Starting with **1a** (9.4 mL, 92.22 mmol), **2c** (5.1 mL, 30.75 mmol), K_2CO_3 (17.04 g, 123.03 mmol), CuI (0.585 g, 10 mol%), L-proline (0.708 g, 20 mol%) in 123 mL of DMSO (heating for 10 h at 120 °C), **3c** was obtained as a viscos yellowish oil (5.93 g, 83%). ^{1}H-NMR (300 MHz, $CDCl_3$, enol): δ = 0.88 (t, 3H, *J* = 7.1 Hz, CH_3), 1.31 (sextet, 2H, *J* = 7.2 Hz, CH_2), 1.58 (quintet, 2H, *J* = 7.8 Hz, CH_2), 1.91 (s, 6H, CH_3), 2.58 (t, 2H, *J* = 7.6 Hz, CH_2), 6.85 (d, 2H, *J* = 8.2 Hz, H_{Ar}), 7.11 (d, 2H, *J* = 8.2 Hz, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.4 (CH_2), 24.1 (CH_3), 33.5, 35.3 (CH_2), 115.0 (C, enol form), 128.7 ($2CH_{Ar}$), 130.8 ($2CH_{Ar}$), 134.0, 142.1 (C_{Ar}), 191.0 (C=O).

General procedure for the synthesis of silyl enol ethers (4a-c).

To stirred benzene solution (2.5 mL per 1.0 mmol of **3a-c**) of **3a-c** (1.0 equiv.) was added triethylamine (1.6 equiv.). After stirring for 2 h, trimethylchlorosilane (1.8 equiv.) was added. The solution was stirred for 72 h and, subsequently, the solvent was removed in vacuo and hexane (1.5 mL per 1.0 mmol of starting material) was added to the residue to give a suspension. The latter was filtered under argon atmosphere. The filtrate was concentrated in vacuo to give silyl enol ethers **4a-c**, which were used without further purification. Due to the unstable nature of the products, MS and analytical data could not be obtained. All products were obtained as mixtures of *E*/*Z*-isomers.

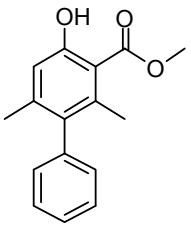
3-Phenyl-4-(trimethylsilyloxy)pent-3-en-2-one (4a): Starting with benzene (42.5 mL), **3a** (3.0 g, 17.02 mmol), triethylamine (3.2 mL, 27.2 mmol) and trimethylchlorosilane (4.5 mL, 30.6 mmol), **4a** was isolated as a yellowish oil (3.80 g, 90%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.21 (s, 9H, Si[CH_3]$_3$), 2.00 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.99 (d (br.), 2H, ^{3}J = 6.8 Hz, H_{Ar}), 7.23-7.34 (m, 3H, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 0.4 (Si[CH_3]$_3$), 21.7, 23.7 (CH_3), 114.6 (=C), 125.5 (CH_{Ph}), 127.3 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 134.2 (C_{Ar}), 186.1 (COSi), 191.2 (C=O).

3-*p*-Tolyl-4-(trimethylsilyloxy)pent-3-en-2-one (4b): Starting with benzene (31.5 mL), **3c** (2.4 g, 12.6 mmol), triethylamine (2.4 mL, 20.1 mmol) and trimethylchlorosilane (3.38 mL, 22.7 mmol), **4b** was isolated as a slight yellowish oil (2.9 g, 88%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.21 (s, 9H, Si[CH_3]$_3$), 1.93 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.08 (d (br.), 2H, *J* = 7.7 Hz, H_{Ar}), 7.17 (d (br.), 2H, *J* = 7.7 Hz, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 0.4 (Si[CH_3]$_3$), 21.5, 23.8, 24.1 (CH_3), 114.7 (=C), 129.2 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 136.3 (C_{Ar}), 186.3 (COSi), 191.0 (C=O).

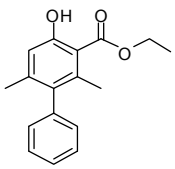
3-(4-Butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one (4c): Starting with benzene (50 mL), **3c** (4.4 g, 18.9 mmol), triethylamine (3.5 mL, 30.2 mmol) and trimethylchlorosilane (5.0 mL, 34.2 mmol), **4c** was isolated as a yellowish oil (4.8 g, 85%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.21 (s, 9H, Si[CH_3]$_3$), 0.88 (t, 3H, *J* = 7.1 Hz, CH_3), 1.31 (sextet, 2H, *J* = 7.2 Hz, CH_2), 1.58 (quintet, 2H, *J* = 7.8 Hz, CH_2), 1.87 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.58 (t, 2H, *J* = 7.6 Hz, CH_2), 6.85 (d, 2H, *J* = 8.2 Hz, H_{Ar}), 7.11 (d, 2H, *J* = 8.2 Hz, H_{Ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 0.4 (Si[CH_3]$_3$), 13.9 (CH_3), 22.4 (CH_2), 23.9, 24.2 (CH_3), 33.5, 35.3 (CH_2), 114.8 (=C), 128.7 ($2CH_{Ar}$), 130.8 ($2CH_{Ar}$), 134.0, 142.2 (C_{Ar}), 186.4 (COSi), 191.0 (C=O).

General procedure for the synthesis of 4-hydroxybiphenyl-3-carboxylates (6a-z). To a CH_2Cl_2 solution (2 mL / 1.0 mmol of **5**) of **5** (1.0 equiv.) was added **4** (1.0 equiv.) and subsequently $TiCl_4$ (1.0 equiv.) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added a saturated aqueous solution of sodium bicarbonate (10 mL) and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane / EtOAc) to give product **6**.

Methyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate(6a): Starting with 1,3-bis(silyl enol ether) **5a (**600 mg, 2.30 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (571 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **6a** was obtained as a light yellow solid (360 mg, 61%), mp = 80-82 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.76 (s, 1H, H_{Ar}), 7.05 (d (br.), 2H, ^3J = 7.0 Hz, H_{Ar}), 7.31-7.41 (m, 3H, H_{Ar}), 11.01 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.9 (CH_3), 52.1 (OCH_3), 110.8 (C_{Ar}), 116.2 (CH_{Ar}), 126.8 (CH_{Ph}), 128.6 ($2CH_{Ph}$), 129.7 ($2CH_{Ph}$), 135.2, 138.5, 140.9, 144.0, 161.1 (C_{Ar}), 172.3 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3060, 3004, 2953, 2852 (w), 1655, 1597 (m), 1441 (s), 1356 (m), 1318, 1228 (s), 1092 (m), 990 (w), 881, 810 (m), 701 (s); MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 77), 225 (61), 224 (100), 196 (40), 181 (10), 167 (18), 165 (14), 153 (17), 152 (22); HRMS (EI): calcd. for $C_{16}H_{16}O_3$ $[M]^+$: 256.10940; found: 256.10877.

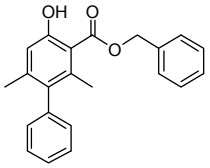


Ethyl 4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6b): Starting with 1,3-bis(silyl enol ether) **5b** (600 mg, 2.18 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (542 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6b** was obtained as a colorless solid (236 mg, 40%), mp = 78-79 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, 3H, ^3J = 7.0 Hz, CH_3), 1.90 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.36 (q, 2H, ^3J = 7.0 Hz, OCH_2), 6.73 (s, 1H, H_{Ar}), 7.03 (d (br.), 2H, ^3J = 6.9 Hz, H_{Ar}), 7.28-7.37 (m, 3H, H_{Ar}), 11.06 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 20.9, 21.9

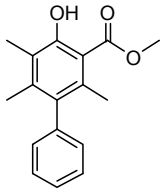


(CH_3), 61.5 (OCH_2), 111.0 (C_{Ar}), 116.2 (CH_{Ar}), 126.8 (CH_{Ph}), 128.6 ($2CH_{Ph}$), 129.8 ($2CH_{Ph}$), 135.1, 138.6, 140.9, 143.8, 161.1 (C_{Ar}), 171.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057, 3005, 2983, 2873 (w), 1648 (s), 1597, 1462, 1371, 1315 (m), 1224, 1091 (s), 1008, 857, 802 (m), 707 (s); MS (EI, 70 eV): *m/z* (%) = 270 (M^+, 84), 225 (79), 224 (100), 196 (43), 181 (12), 167 (20), 165 (18), 153 (21), 152 (24); HRMS (EI): calcd. for $C_{17}H_{18}O_3$ $[M]^+$: 270.12505; found: 270.12507.

Benzyl 4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6c): Starting with 1,3-bis(silyl enol ether) **5c** (600 mg, 1.78 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (442 mg, 1.78 mmol) and $TiCl_4$ (0.19 mL, 1.78 mmol), **6c** was obtained as a light yellow solid (207 mg, 35%), mp = 59-60 °C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 5.32 (s, 2H, OCH_2), 6.71 (s, 1H, H_{Ar}), 6.98-7.34 (m, 10H, 2Ph), 10.97 (s, 1H, OH); ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 21.2, 21.9 (CH_3), 67.3 (OCH_2), 110.8 (C_{Ar}), 116.2 (CH_{Ar}), 126.8 (CH_{Ph}), 128.5 ($2CH_{Ph}$), 128.6 ($3CH_{Ph}$), 128.7 ($2CH_{Ph}$), 129.8 ($2CH_{Ph}$), 135.2, 137.0, 138.7, 140.8, 144.1, 161.2 (C_{Ar}), 171.6 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3059, 2964, 1950, 1879, 1726 (w), 1649 (s), 1595, 1495, 1449 (m), 1375, 1311, 1221 (s), 1153 (m), 1089 (s), 1026, 985, 934, 884, 802 (m), 751, 694 (s), 639, 576 (m); MS (EI, 70 eV): *m/z* (%) = 332 (M^+, 25), 314 (4), 225 (11), 224 (55), 223 (5), 165 (5), 152 (6), 91 (100), 65 (5); HRMS (EI): calcd. for $C_{22}H_{20}O_3$ $[M]^+$: 332.14070; found: 332.14053.

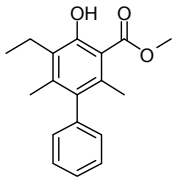


Methyl 4-hydroxy-2,5,6-trimethylbiphenyl-3-carboxylate (6d): Starting with 1,3-bis(silyl enol ether) **5d** (500 mg, 1.82 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (452 mg, 1.82 mmol) and $TiCl_4$ (0.20 mL, 1.82 mmol), **6d** was obtained as a colorless solid (236 mg, 48%), mp = 99-101 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.98 (d (br.), 2H, ^3J = 6.9 Hz, H_{Ar}), 7.23-7.35 (m, 3H, H_{Ar}), 11.20 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.0, 18.8, 20.9 (CH_3), 52.0 (OCH_3), 110.2 (C_{Ar}), 126.6 (CH_{Ph}), 127.5 (C_{Ar}), 128.5 ($2CH_{Ph}$), 129.9 ($2CH_{Ph}$), 135.1, 136.9, 141.9, 142.2, 159.0 (C_{Ar}), 172.9 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3074, 3020, 2926, 2857 (w), 1652, 1600, 1537, 1403 (m), 1326, 1223 (s), 1141, 1068, 983 (m), 911 (w), 806, 765 (m), 702 (s),



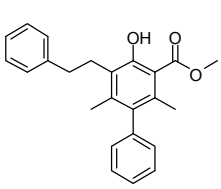
609, 556 (m); GC-MS (EI, 70 eV): *m/z* (%) = 271 (8), 270 (M^+, 46), 239 (25), 238 (100), 237 (27), 210 (31), 196 (11), 195 (55), 165 (30), 152 (15), 77 (5); HRMS (EI): calcd. for $C_{17}H_{18}O_3$ $[M]^+$: 270.12505; found: 270.12488.

Methyl 5-ethyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6e): Starting with



1,3-bis(silyl enol ether) **5e** (600 mg, 2.07 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (514 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **6e** was obtained as a colorless solid (312 mg, 53%), mp = 125-126 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, 3H, ^3J = 7.4 Hz, CH_3), 1.87 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.67 (q, 2H, ^3J = 7.4 Hz, CH_2), 3.86 (s, 3H, OCH_3), 6.99 (d (br.), 2H, ^3J = 6.8 Hz, H_{Ar}), 7.22-7.34 (m, 3H, H_{Ar}), 11.18 (s, IH, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.2, 16.9 (CH_3), 18.8 (CH_2), 19.8 (CH_3), 50.9 (OCH_3), 109.4 (C_{Ar}), 125.5 (CH_{Ph}), 127.3 (C_{Ar}), 127.4 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 134.0, 134.2, 140.4, 140.9, 157.8 (C_{Ar}), 171.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 2971, 2876, 1650, 1599 (m), 1493 (w), 1435, 1364, 1321 (m), 1221 (s), 1142, 1067, 1001, 952 (m), 853 (w), 808, 705 (s), 650, 580 (m); GC-MS (EI, 70 eV): *m/z* (%) = 284 (M^+, 73), 253 (30), 252 (100), 251 (69), 224 (96), 209 (43), 196 (10), 195 (40), 178 (12), 166 (21), 165 (47), 152 (13); HRMS (EI): calcd. for $C_{18}H_{20}O_3$ $[M]^+$: 284.14070; found: 284.140870.

Methyl 4-hydroxy-2,6-dimethyl-5-phenethylbiphenyl-3-carboxylate (6f): Starting



with 1,3-bis(silyl enol ether) **5f** (500 mg, 1.37 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (340 mg, 1.37 mmol) and $TiCl_4$ (0.15 mL, 1.37 mmol), **6f** was obtained as a colorless solid (187 mg, 38%), mp = 109-111 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.63 (t, 2H, ^3J = 5.0 Hz, CH_2), 2.78 (t, 2H, ^3J = 5.0 Hz, CH_2), 3.78 (s, 3H, OCH_3), 6.84 (d (br.), 2H, ^3J = 6.8 Hz, H_{Ar}), 7.03-7.23 (m, 8H, H_{Ar}), 11.17 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 19.3, 22.1 (CH_3), 30.3, 36.3 (CH_2), 53.2 (OCH_3), 111.7 (C_{Ar}), 127.0 (CH_{Ph}), 127.2 (C_{Ar}), 127.8 (CH_{Ph}), 129.4 ($2CH_{Ph}$), 129.7 ($2CH_{Ph}$), 129.8 ($2CH_{Ph}$), 131.0 ($2CH_{Ph}$), 136.3, 136.8, 143.0, 143.1, 143.7, 160.4 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3081, 3025, 2950, 2865 (w), 1650, 1596, 1494, 1438 (m), 1325, 1219 (s), 1163, 1082, 1033, 987, 912, 804 (m), 700 (s); MS (EI, 70 eV): *m/z* (%) = 360 (M^+, 28), 328 (5), 270 (6), 269 (39), 238

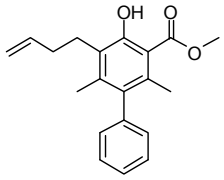
(24), 237 (100), 166 (7), 165 (11); HRMS (EI): calcd. for $C_{24}H_{24}O_3$ $[M]^+$: 360.17200; found: 360.17109

Methyl 4-hydroxy-2,6-dimethyl-5-pentylbiphenyl-3-carboxylate (6g): Starting with 1,3-bis(silyl enol ether) **5g** (700 mg, 2.11 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (524 mg, 2.11 mmol) and $TiCl_4$ (0.23 mL, 2.11 mmol), **6g** was obtained as a light yellow solid (345 mg, 50%), mp = 102-104 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71 (t, 3H, ^3J = 7.6 Hz, CH_3), 1.09-1.31 (m, 6H, $3CH_2$), 1.75 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.52 (t, 2H, ^3J = 7.4 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.89 (d (br.), 2H, ^3J = 6.8 Hz, H_{Ar}), 7.13-7.24 (m, 3H, Ph), 11.05 (s, 1H, OH); ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 15.2, 19.3, 22.0 (CH_3), 23.8, 27.8, 29.9, 33.4 (CH_2), 53.1 (OCH_3), 111.6 (C_{Ar}), 127.7 (CH_{Ph}), 128.4 (C_{Ar}), 129.7 ($2CH_{Ph}$), 131.0 ($2CH_{Ph}$), 136.2, 136.3, 142.8, 143.2, 160.2 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2953 (m), 2857, 1933 (w), 1702, 1655, 1595, 1438, 1377, 1326 (m), 1213 (s), 1142, 1048, 1003 (m), 903 (w), 839 (s), 772 (m), 702 (s), 627, 579 (w); GC-MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 76), 294 (33), 277 (63), 265 (25), 251 (22), 239 (19), 238 (100), 237 (81), 210 (30), 195 (24), 166 (25), 165 (54), 152 (10); HRMS (EI): calcd. for $C_{21}H_{26}O_3$ $[M]^+$: 326.18765; found: 326.18798.

Methyl 5-hexyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6h): Starting with 1,3-bis(silyl enol ether) **5h** (500 mg, 1.45 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (360 mg, 1.45 mmol) and $TiCl_4$ (0.16 mL, 1.45 mmol), **6h** was obtained as a light yellowish solid (227 mg, 46%), mp = 105-107 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71 (t, 3H, ^3J = 7.1 Hz, CH_3), 1.09-1.34 (m, 8H, $4CH_2$), 1.75 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.52 (t, 2H, ^3J = 7.2 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.89 (d (br.), 2H, ^3J = 6.8 Hz, H_{Ar}), 7.12-7.25 (m, 3H, Ph), 11.06 (s, 1H, OH); ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 15.3, 19.3, 22.0 (CH_3), 23.8, 27.8, 30.2, 30.9, 32.9 (CH_2), 53.1 (OCH_3), 111.5 (C_{Ar}), 127.7 (CH_{Ph}), 128.4 (C_{Ar}), 129.6 ($2CH_{Ph}$), 131.0 ($2CH_{Ph}$), 136.2, 136.3, 142.7, 143.2, 160.2 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955 (m), 2852 (w), 1652, 1597, 1537, 1405 (m), 1328, 1217 (s), 1141, 1065 (m), 983 (m), 903 (w), 835 (s), 770 (m), 702 (s), 609, 556 (m); GC-MS (EI, 70 eV): *m/z*

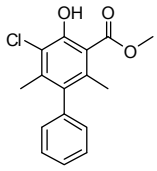
(%) = 340 (M^+, 65), 308 (30), 293 (43), 291 (53), 279 (33), 265 (25), 251 (20), 239 (20), 238 (100), 237 (76), 210 (26), 195 (21), 165 (43), 152 (9); HRMS (EI): calcd. for $C_{22}H_{28}O_3$ $[M]^+$: 340.20330; found: 340.20341.

Methyl 5-(but-3-enyl)-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6i):



Starting with 1,3-bis(silyl enol ether) **5i** (600 mg, 1.90 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (472 mg, 1.90 mmol) and $TiCl_4$ (0.20 mL, 1.90 mmol), **6i** was obtained as a light yellowish solid (283 mg, 48%), mp = 112-114 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.07-2.13 (m, 2H, CH_2), 2.63 (t, 2H, ^3J = 7.8 Hz, CH_2), 3.78 (s, 3H, OCH_3), 4.77-4.92 (m, 2H, $=CH_2$), 5.69-5.83 (m, 1H, =CH), 6.89 (d, 2H, ^3J = 6.8 Hz, H_{Ar}), 7.11-7.25 (m, 3H, Ph), 11.09 (s, 1 H, OH); ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 19.4, 22.0 (CH_3), 27.4, 34.2 (CH_2), 53.2 (OCH_3), 111.6 (C_{Ar}), 115.6 ($=CH_2$), 127.7 (CH_{Ph}), 128.6 (C_{Ar}), 129.7 ($2CH_{Ph}$), 131.0 ($2CH_{Ph}$), 136.3, 136.7 (C_{Ar}), 139.9 (=CH), 142.9, 143.1, 160.2 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057, 2952 (w), 1708, 1651, 1597, 1493, 1404, 1325 (m), 1215 (s), 1142, 1071, 1000, 908, 763, 763 (m), 701 (s), 609, 555 (m); GC-MS (EI, 70 eV): *m/z* (%) = 310 (M^+, 11), 270 (5), 269 (24), 238 (17), 237 (100), 166 (9), 165 (18), 152 (3); HRMS (EI): calcd. for $C_{20}H_{22}O_3$ $[M]^+$: 310.15635; found: 310.15668.

Methyl 5-chloro-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6j):



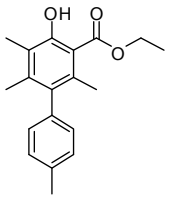
Starting with 1,3-bis(silyl enol ether) **5j** (600 mg, 2.03 mmol), 3-phenyl-4-(trimethylsilyloxy)pent-3-en-2-one **4a** (504 mg, 2.03 mmol) and $TiCl_4$ (0.22 mL, 2.03 mmol), **6j** was obtained as a colorless solid (218 mg, 37%), mp = 98-99 °C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 7.06 (d, 2H, ^3J = 6.9 Hz, H_{Ar}), 7.32-7.43 (m, 3H, H_{Ar}), 11.40 (s, 1H, OH); ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 19.4, 20.7 (CH_3), 52.5 (OCH_3), 115.2 (C_{Ar}), 127.4 (CH_{Ph}), 128.7 (C_{Ar}), 129.6 ($2CH_{Ph}$), 131.0 ($2CH_{Ph}$), 136.4, 136.9, 140.6, 141.4, 156.1 (C_{Ar}), 171.9 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3023 (m), 2958, 2851, 1731 (w), 1657 (s), 1595, 1493, 1437 (m), 1363 (s), 1285 (m), 1225 (s), 1072, 995 (m), 910 (w), 804 (s), 736 (m), 702 (s), 602, 558 (m); GC-MS (EI, 70 eV): *m/z* (%) = 292 (M^+, ^{37}Cl, 8), 290 (M^+, ^{35}Cl, 22), 260 (36), 259 (25), 258 (100), 167

(9), 166 (7), 165 (17), 152 (13); HRMS (EI): calcd. for $C_{16}H_{15}ClO_3$ $[M]^+$: 290.07042; found: 290.07071.

Methyl 4-hydroxy-2,4',6-trimethylbiphenyl-3-carboxylate (6k): Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), 3-p-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (603 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **6k** was obtained as white solid (335 mg, 54%), mp = 112-114 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 6.79 (s, 1H, H_{Ar}), 6.97 (d (br.), 2H, ^3J = 8.1 Hz, H_{Ar}), 7.21 (d (br.), 2H, ^3J = 8.1 Hz, H_{Ar}), 11.01 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.2, 21.9 (CH_3), 52.0 (OCH_3), 110.7 (C_{Ar}), 116.1 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 135.1, 136.2, 137.7, 138.6, 144.2, 160.9 (C_{Ar}), 172.2 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3408, 2952, 1808 (w), 1708, 1664, 1605, 1512, 1438, 1351, 1319 (m), 1222 (s), 1156 (s), 1090 (m), 994, 899, 805, 733, 654, 564 (m); GC-MS (EI, 70 eV): *m/z* (%) = 270 (M^+, 36), 239 (23), 238 (100), 210 (12), 209 (5), 165 (14), 152 (9); HRMS (EI): calcd. for $C_{17}H_{18}O_3$ $[M]^+$: 270.12505; found: 270.12516.

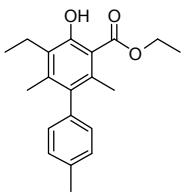
Ethyl 4-hydroxy-2,4',6-trimethylbiphenyl-3-carboxylate (6l): Starting with 1,3-bis(silyl enol ether) **5b** (600 mg, 2.18 mmol), 3-*p*-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (572 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6l** was obtained as a white solid (248 mg, 40%), mp = 117-119 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, 3H, ^3J = 7.1 Hz, CH_3), 1.95 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.40 (q, 2H, ^3J = 7.1 Hz, OCH_2), 6.76 (s, 1H, H_{Ar}), 6.95 (d (br.), 2H, ^3J = 8.0 Hz, H_{Ar}), 7.18 (d (br.), 2H, ^3J = 8.0 Hz, H_{Ar}), 11.07 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2, 20.9, 21.2, 21.9 (CH_3), 61.4 (OCH_2), 111.0 (C_{Ar}), 116.2 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1, 136.2, 137.9, 138.7, 144.0, 161.0 (C_{Ar}), 171.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3049, 2919, 2860 (w), 1645, 1595, 1514, 1463, 1392 (m), 1314 (s), 1224 (m), 1103 (w), 1061, 994, 920 (m), 813 (s), 723, 653, 551 (m); GC-MS (EI, 70 eV): *m/z* (%) = 284 (M^+, 30), 239 (24), 238 (100), 210 (13), 195 (6), 165 (14), 152 (8); HRMS (EI): calcd. for $C_{18}H_{20}O_3$ $[M]^+$: 284.14070; found: 284.14118.

Methyl 4-hydroxy-2,4',5,6-tetramethylbiphenyl-3-carboxylate carboxylate (6m):



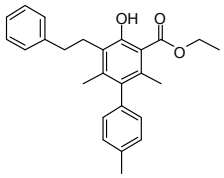
Starting with 1,3-bis(silyl enol ether), **5d** (600 mg, 2.18 mmol), 3-*p*-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (572 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6m** was obtained as a white solid (254 mg, 41%), mp = 143-145 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.89 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.92 (d (br.), 2H, ^3J = 7.9 Hz, H_{Ar}), 7.21 (d (br.), 2H, ^3J = 7.9 Hz, H_{Ar}), 11.28 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.0, 18.8, 20.9, 21.2 (CH_3), 52.0 (OCH_3), 110.2, 122.2 (C_{Ar}), 129.2 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 134.8, 135.2, 136.1, 138.8, 142.4, 158.9 (C_{Ar}), 172.9 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3012, 2953, 2864, 1711 (w), 1651, 1597, 1514, 1404 (m), 1327 (s), 1294 (m), 1222 (s), 1141, 1060, 987, 919, 857 (m), 804 (s), 736, 698, 551 (m); GC-MS (EI, 70 eV): *m/z* (%) = 284 (M^+, 42), 253 (23), 252 (100), 251 (16), 237 (15), 224 (22), 210 (9), 209 (43), 181 (13), 166 (13), 165 (25), 152 (5), 126 (7); HRMS (EI): calcd. for $C_{18}H_{20}O_3$ $[M]^+$: 284.14070; found: 284.14063.

Methyl 5-ethyl-4-hydroxy-2,4',6-trimethylbiphenyl-3-carboxylate (6n): Starting



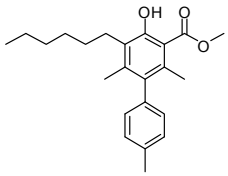
with 1,3-bis(silyl enol ether) **5e** (600 mg, 2.07 mmol), 3-p-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (543 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **6n** was obtained as a white solid (284 mg, 46%), mp = 137-138 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, 3H, ^3J = 7.4 Hz, CH_3), 1.77 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.56 (q, 2H, ^3J = 7.4 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.78 (d (br.), 2H, ^3J = 7.8 Hz, H_{Ar}), 7.03 (d (br.), 2H, ^3J = 7.8 Hz, H_{Ar}), 11.05 (s, IH, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.2, 17.9 (CH_3), 19.8 (CH_2), 20.8, 21.2 (CH_3), 51.9 (OCH_3), 110.4, 128.2 (C_{Ar}), 129.1 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 135.0, 135.3, 136.0, 138.8, 141.6, 158.7 (C_{Ar}), 172.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3009 (w), 2953 (m), 2873 (w), 1650, 1597, 1514, 1434, 1358, 1290 (m), 1221 (s), 1141, 1066, 987 (m), 855 (w), 807 (s), 695 (m), 590 (w), 529 (m); GC-MS (EI, 70 eV): *m/z* (%) = 298 (M^+, 87), 267 (30), 266 (100), 265 (55), 251 (85), 238 (80), 223 (44), 209 (42), 195 (11), 179 (22), 165 (34); HRMS (EI): calcd. for $C_{19}H_{22}O_3$ $[M]^+$: 298.15635; found: 298.15990.

Methyl 4-hydroxy-2,4',6-trimethyl-5-phenethyl-biphenyl-3-carboxylate (6o):



Starting with 1,3-bis(silyl enol ether) **5f** (600 mg, 1.64 mmol), 3-p-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (430 mg, 1.64 mmol) and $TiCl_4$ (0.18 mL, 1.64 mmol), **6o** was obtained as a white solid (221 mg, 36%), mp = 122-124 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.66 (t, 2H, ^3J = 5.0 Hz, CH_2), 2.79 (t, 2H, ^3J = 5.0 Hz, CH_2), 3.76 (s, 3H, OCH_3), 6.79 (d (br.), 2H, ^3J = 7.9 Hz, H_{Ar}), 7.04 (d (br.), 2H, ^3J = 7.9 Hz, H_{Ar}), 11.16 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 19.3, 22.1, 22.4, (CH_3), 30.4, 36.3 (CH_2), 53.2 (OCH_3), 111.6 (C_{Ar}), 127.0 (CH_{Ar}), 127.1 (C_{Ar}), 129.4 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 130.4 ($2CH_{Ar}$), 136.2, 137.0, 137.3, 140.0, 143.2, 143.8, 160.2 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3025, 2947, 2862, 1699 (w), 1650, 1600, 1513, 1440, 1406 (m), 1325, 1225 (s), 1145, 1085, 990, 920, 872 (m), 807 (s), 753, 698 (m), 632 (w), 549 (m); MS (EI, 70 eV): *m/z* (%) = 374 (M^+, 29), 342 (5), 283 (28), 252 (22), 251 (100), 180 (5), 165 (9), 91 (4); HRMS (EI): calcd. for $C_{25}H_{26}O_3$ $[M]^+$: 374.18765; found: 374.18782.

Methyl 5-hexyl-4-hydroxy-2,4',6-trimethylbiphenyl-3-carboxylate (6p): Starting



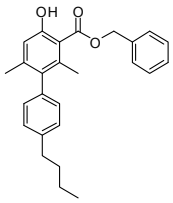
with 1,3-bis(silyl enol ether) **5h** (600 mg, 1.74 mmol), 3-*p*-tolyl-4-(trimethylsilyloxy)pent-3-en-2-one **4b** (457 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **6p** was obtained as white solid (259 mg, 42%), mp = 105-107 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71 (t, 3H, ^3J = 7.2 Hz, CH_3), 1.09-1.34 (m, 8H, $4CH_2$), 1.76 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.51 (t, 2H, ^3J = 7.1 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.77 (d (br.), 2H, ^3J = 7.8 Hz, H_{Ar}), 7.03 (d (br.), 2H, ^3J = 7.8 Hz, H_{Ar}), 11.03 (s, IH, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.3, 19.4, 22.0, 22.5 (CH_3), 23.8, 27.9, 30.2, 30.9, 32.9 (CH_2), 51.1 (OCH_3), 111.5, 128.3 (C_{Ar}), 130.6 ($2CH_{Ar}$), 132.1 ($2CH_{Ar}$), 136.1, 136.5, 138.3, 140.1, 143.0, 160.0 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2953, 2855, 1933 (w), 1702, 1655, 1593 (m), 1513 (w), 1437, 1378, 1325 (m), 1216 (s), 1141 (m), 1051, 987 (m), 902 (w), 841 (s), 765, 696 (m), 628, 557 (w); GC-MS (EI, 70 eV): *m/z* (%) = 354 (M^+, 45), 322 (19), 307 (53), 305 (37), 293 (24), 279 (21), 253 (26), 252 (100), 251 (61), 224 (19), 209 (31), 207 (56), 165 (11); HRMS (EI): calcd. for $C_{23}H_{30}O_3$ $[M]^+$: 354.21895; found: 354.21973.

Methyl 4'-butyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6q): Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (700 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **6q** was obtained as a colorless solid (373 mg, 52%), mp = 66-68 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, ^3J = 7.3 Hz, CH_3), 1.32 (sextet, 2H, ^3J = 7.3 Hz, CH_2), 1.57 (quintet, 2H, ^3J = 7.7 Hz, CH_2), 1.88 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.58 (t, 2H, ^3J = 7.6 Hz, CH_2), 3.86 (s, 3H, OCH_3), 6.69 (s, 1H, H_{Ar}), 6.88 (d, 2H, ^3J = 8.1 Hz, H_{Ar}), 7.14 (d, 2H, ^3J = 8.1 Hz, H_{Ar}), 10.91 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.8, 21.9 (CH_3), 22.4, 33.5, 35.4 (CH_2), 52.0 (OCH_3), 110.7 (C_{Ar}), 116.1 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 135.2, 137.9, 138.7, 141.3, 144.3, 160.9 (C_{Ar}), 172.3 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2953, 2856, 1730 (w), 1657 (s), 1599, 1512, 1437, 1376, 1318 (m), 1220 (s), 1113, 1061, 993, 858, 803, 736 (m), 653 (w), 575 (m); GC-MS (EI, 70 eV): *m/z* (%) = 312 (M^+, 24), 281 (25), 280 (100), 237 (12), 209 (11), 166 (5), 165 (12), 152 (3); HRMS (EI): calcd. for $C_{20}H_{24}O_3$ $[M]^+$: 312.17200; found: 312.17167.

Ethyl 4'-butyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6r): Starting with 1,3-bis(silyl enol ether) **5b** (600 mg, 2.18 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (664 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6r** was obtained as a colorless solid (320 mg, 45%), mp = 73-75 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88-0.98 (m, 6H, $2CH_3$), 1.34 (sextet, 2H, ^3J = 7.2 Hz, CH_2), 1.58 (quintet, 2H, ^3J = 7.3 Hz, CH_2), 1.89 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.59 (t, 2H, ^3J = 7.6 Hz, CH_2), 4.41 (q, 2H, ^3J = 7.2 Hz, OCH_2), 6.71 (s, 1H, H_{Ar}), 6.90 (d, 2H, ^3J = 8.0 Hz, H_{Ar}), 7.14 (d, 2H, ^3J = 8.0 Hz, H_{Ar}), 11.01 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.1, 20.9, 21.9 (CH_3), 22.4, 33.5, 35.3 (CH_2), 61.4 (OCH_2), 110.9 (C_{Ar}), 116.0 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 135.1, 138.7, 141.2, 142.1, 144.1, 160.9 (C_{Ar}), 171.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956, 2858, 1809 (w), 1708 (m), 1654 (s), 1574 (m), 1510 (w), 1462, 1395 (m), 1314, 1221 (s), 1178, 1091, 1012 (m), 931 (w), 859, 802, 737, 653, 573 (m); GC-MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 24), 281 (26), 280

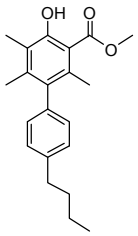
(100), 252 (4), 237 (10), 209 (10), 166 (4), 165 (9), 152 (3); HRMS (EI): calcd. for $C_{21}H_{26}O_3$ $[M]^+$: 326.18765; found: 326.18752.

Benzyl 4'-butyl-4-hydroxy-2,6-dimethylbiphenyl-3-carboxylate (6s): Starting with



1,3-bis(silyl enol ether) **5c** (500 mg, 1.45 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (442 mg, 1.45 mmol) and $TiCl_4$ (0.16 mL, 1.45 mmol), **6s** was obtained as a yellowish solid (215 mg, 38%), mp = 64-66 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3H, ^3J = 7.3 Hz, CH_3), 1.31 (sextet, 2H, ^3J = 7.3 Hz, CH_2), 1.57 (quintet, 2H, ^3J = 7.8 Hz, CH_2), 1.89 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.57 (t, 2H, ^3J = 7.5 Hz, CH_2), 5.33 (s, 2H, OCH_2), 6.70 (s, 1H, H_{Ar}), 6.91-7.33 (m, 9H, H_{Ar}), 10.93 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.9, 21.2, 21.9 (CH_3), 22.4, 33.5, 35.3 (CH_2), 67.3 (OCH_2), 110.6 (C_{Ar}), 116.1 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 135.2, 137.8, 138.8, 141.3, 142.1, 144.4, 161.0 (C_{Ar}), 171.6 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3032, 2955, 2857, 1760 (w), 1709 (m), 1655 (s), 1573 (m), 1498 (w), 1416, 1344,1289 (m), 1216, 1156 (s), 1088, 1028, 947, 835, 737, 653, 570 (m); GC-MS (EI, 70 eV): *m/z* (%) = 388 (M^+, 54), 346 (25), 282 (41), 281 (28), 280 (100), 254 (18), 237 (13), 208 (68), 165 (16), 133 (35); HRMS (EI): calcd. for $C_{26}H_{27}O_3$ $[M-H]^+$: 387.19657; found: 387.19655.

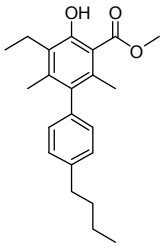
Methyl 4'-butyl-4-hydroxy-2,5,6-trimethylbiphenyl-3-carboxylate (6t): Starting



with 1,3-bis(silyl enol ether) **5d** (500 mg, 1.82 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (554 mg, 1.82 mmol) and $TiCl_4$ (0.20 mL, 1.82 mmol), **6t** was obtained as a colorless solid (344 mg, 58%), mp = 68-70 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, ^3J = 7.5 Hz, CH_3), 1.32 (sextet, 2H, ^3J = 7.4 Hz, CH_2), 1.58 (quintet, 2H, ^3J = 7.8 Hz, CH_2), 1.84 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.58 (t, 2H, ^3J = 7.6 Hz, CH_2), 3.85 (s, 2H, OCH_3), 6.87 (d, 2H, ^3J = 8.2 Hz, H_{Ar}), 7.13 (d, 2H, ^3J = 8.2 Hz, H_{Ar}), 11.21 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.0, 13.9, 18.7, 20.8 (CH_3), 22.4, 33.6, 35.3 (CH_2), 52.0 (OCH_3), 110.2, 122.1 (C_{Ar}), 128.4 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 134.9, 135.2, 138.9, 141.1, 142.2, 159.8 (C_{Ar}), 172.9 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3038 (w), 2955 (m), 2860, 1689 (w), 1649, 1597, 1511, 1431 (m), 1326, 1219 (s), 1141, 1097, 1029 (m), 940 (w), 860 (m), 805 (s), 748,

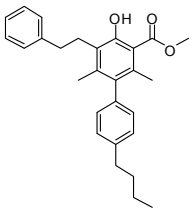
708, 653, 594, 547 (m); GC-MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 31), 295 (25), 294 (100), 293 (8), 266 (6), 251 (21), 237 (14), 223 (10), 209 (10), 179 (7), 165 (13), 152 (2); HRMS (EI): calcd. for $C_{21}H_{26}O_3$ $[M]^+$: 326.18765; found: 326.18774.

Methyl 4'-butyl-5-ethyl-4-hydroxy-2,6-dimethyl-biphenyl-3-carboxylate (6u):



Starting with 1,3-bis(silyl enol ether) **5e** (600 mg, 2.07 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (630 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **6u** was obtained as a colorless solid (387 mg, 55%), mp = 81-83 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, ^3J = 7.3 Hz, CH_3), 1.05 (t, 3H, ^3J = 7.5 Hz, CH_3), 1.31 (sextet, 2H, ^3J = 7.4 Hz, CH_2), 1.58 (quintet, 2H, ^3J = 7.8 Hz, CH_2), 1.87 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.58 (t, 2H, ^3J = 7.6 Hz, CH_2), 2.66 (q, 2H, ^3J = 7.5 Hz, CH_2), 3.85 (s, 1H, OCH_3), 6.88 (d, 2H, ^3J = 8.2 Hz, H_{Ar}), 7.12 (d, 2H, ^3J = 8.2 Hz, H_{Ar}), 11.15 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.2, 13.9, 18.0 (CH_3), 19.8 (CH_2), 20.9 (CH_3), 22.4, 33.5, 35.4 (CH_2), 51.9 (OCH_3), 110.4, 128.2 (C_{Ar}), 128.4 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1, 135.4, 139.0, 141.0, 141.7, 158.7 (C_{Ar}), 172.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955 (m), 2871, 1730 (w), 1653 (s), 1593 (m), 1512 (w), 1438, 1376, 1320 (m), 1212 (s), 1141, 1065, 987, 808, 756, 705, 649, 578 (m); GC-MS (EI, 70 eV): *m/z* (%) = 340 (M^+, 54), 309 (30), 308 (74), 307 (17), 281 (10), 280 (40), 265 (28), 252 (17), 251 (100), 237 (15), 179 (16), 165 (16); HRMS (EI): calcd. for $C_{22}H_{28}O_3$ $[M]^+$: 340.20330; found: 340.20332.

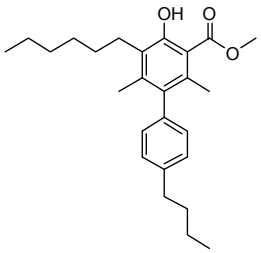
Methyl 4'-butyl-4-hydroxy-2,6-dimethyl-5-phenethyl-biphenyl-3-carboxylate (6v):



Starting with 1,3-bis(silyl enol ether) **5f** (500 mg, 1.37 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (417 mg, 1.37 mmol) and $TiCl_4$ (0.15 mL, 1.37 mmol), **6v** was obtained as a colorless solid (211 mg, 37%), mp = 69-71 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, ^3J = 7.2 Hz, CH_3), 1.32 (sextet, 2H, ^3J = 7.4 Hz, CH_2), 1.58 (quintet, 2H, ^3J = 7.8. Hz, CH_2), 1.78 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.58 (t, 2H, ^3J = 7.5 Hz, CH_2), 2.74 (t, 2H, ^3J = 4.8 Hz, CH_2), 2.92 (t, 2H, ^3J = 4.8 Hz, CH_2), 3.87 (s, 3H, OCH_3), 6.86 (d, 2H, ^3J = 7.9 Hz, H_{Ar}), 7.11-7.23 (m, 7H, H_{Ar}), 11.24 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.1, 20.9 (CH_3), 22.4, 29.1, 33.6, 35.1, 35.3 (CH_2), 52.0 (OCH_3), 110.4 (C_{Ar}), 125.7 (CH_{Ar}), 125.9

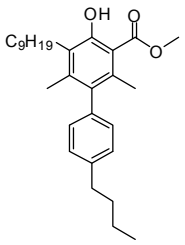
(C_{Ar}), 128.2 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1, 135.8, 138.9, 141.1, 142.0, 142.6, 159.0 (C_{Ar}), 172.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3024 (w), 2951 (m), 2859 (w), 1707, 1650, 1599, 1512, 1452, 1405, 1354,1293 (m), 1220 (s), 1160, 1083, 1029, 949, 870, 804, 743 (m), 696 (s), 614, 567 (m); EI-MS (EI, 70 eV): *m/z* (%) = 416 (M^+, 24), 385 (16), 325 (42), 283 (28), 252 (35), 251 (100), 237 (10), 180 (19), 165 (11), 152 (12), 91 (8); HRMS (EI): calcd. for $C_{28}H_{33}O_3$ $[M+H]^+$: 417.24242; found: 417.24261.

Methyl 4'-butyl-5-hexyl-4-hydroxy-2,6-dimethyl-biphenyl-3-carboxylate (6w):



Starting with 1,3-bis(silyl enol ether) **5g** (600 mg, 1.74 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (530 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **6z** was obtained as a yellowish solid (331 mg, 48%), mp = 84-85 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71 (t, 3H, ^3J = 7.2 Hz, CH_3), 0.78 (t, 3 H, ^3J = 7.3 Hz, CH_3), 1.09-1.59 (m, 12 H, $6CH_2$), 1.76 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3), 2.47-2.52 (m, 4 H, $2CH_2$), 3.75 (s, 3H, OCH_3), 6.78 (d, 2H, ^3J = 7.9 Hz, H_{Ar}), 7.02 (d, 2 H, ^3J = 7.9 Hz, H_{Ar}), 11.04 (s, 1 H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2, 15.3, 19.4, 22.1 (CH_3), 23.6, 23.8, 27.9, 30.2, 30.9, 32.9, 34.7, 36.5 (CH_2), 53.0 (OCH_3), 111.5, 128.3 (C_{Ar}), 129.6 ($2CH_{Ar}$), 130.8 ($2CH_{Ar}$), 135.2, 136.3, 140.3, 142.2, 143.0, 160.0 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2953, 2855 (m), 1933 (w), 1703 (m), 1654 (s), 1593 (m), 1512 (w), 1438, 1377, 1325 (m), 1213 (s), 1141, 1057, 987 (m), 901 (w), 840, 752, 696, 651, 578 (m) cm-1MS (EI, 70 eV): *m/z* (%) = 396 (M^+, 42), 365 (25), 335 (35), 294 (100), 293 (54), 251 (18), 237 (29), 209 (19), 165 (11); HRMS (EI): calcd. for $C_{26}H_{37}O_3$ $[M+H]^+$: 397.27372; found: 397.27411.

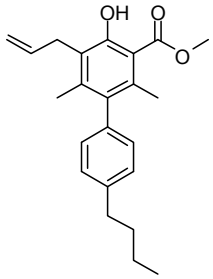
Methyl 4'-butyl-4-hydroxy-2,6-dimethyl-5-nonyl-biphenyl-3-carboxylate (6x):



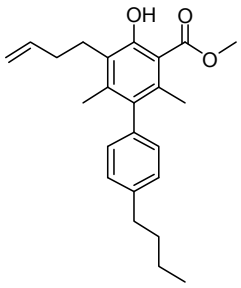
Starting with 1,3-bis(silyl enol ether) **5k** (600 mg, 1.55 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (472 mg, 1.55 mmol) and $TiCl_4$ (0.17 mL, 1.55 mmol), **6x** was obtained as a yellowish solid (285 mg, 42%), mp = 66-68 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.69 (t, 3H, ^3J = 6.7 Hz, CH_3), 0.78 (t, 3H, ^3J = 7.2 Hz, CH_3), 1.09-1.58 (m, 18H, $9CH_2$), 1.76 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.45-2.53 (m, 4H, $2CH_2$), 3.75 (s, 3H, OCH_3), 6.78 (d, 2H, ^3J = 8.0 Hz, H_{Ar}), 7.03 (d, 2H, ^3J = 8.0

Hz, H_{Ar}), 11.03 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2, 15.3, 19.4, 22.1 (CH_3), 22.8, 23.6, 23.7, 27.8, 30.2, 30.5, 30.7, 30.8, 31.1, 34.8, 36.6 (CH_2), 53.1 (OCH_3), 111.5, 128.2 (C_{Ar}), 129.6 ($2CH_{Ar}$), 130.8 ($2CH_{Ar}$), 136.2, 136.5, 140.2, 142.2, 143.0, 160.0 (C_{Ar}), 174.0 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2953, 2853 (m), 1731 (w), 1654 (s), 1593 (m), 1512 (w), 1438 (m), 1325, 1212 (s), 1140, 1058, 987 (m), 887 (w), 807, 752, 651, 578 (m); GC-MS (EI, 70 eV): *m/z* (%) = 438 (M^+, 38), 406 (22), 391 (30), 389 (32), 349 (56), 335 (51), 295 (20), 294 (100), 293 (50), 251 (14), 237 (22), 209 (15), 165 (15); HRMS (EI): calcd for $C_{29}H_{42}O_3$ $[M]^+$: 438.64583; found: 438.64927.

Methyl 5-allyl-4'-butyl-4-hydroxy-2,6-dimethyl-biphenyl-3-carboxylate (6y):



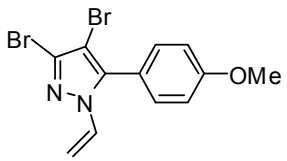
Starting with 1,3-bis(silyl enol ether) **5l** (600 mg, 1.99 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (606 mg, 1.99 mmol) and $TiCl_4$ (0.21 mL, 1.99 mmol), **6y** was obtained as a yellowish solid (386 mg, 55%), mp = 74-76 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, 3H, ^3J = 7.2 Hz, CH_3), 1.18 (sextet, 2H, ^3J = 7.3 Hz, CH_2), 1.45 (quintet, 2H, ^3J = 7.6 Hz, CH_2), 1.75 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.47 (t, 2H, ^3J = 7.4 Hz, CH_2), 3.32 (d, 2H, ^3J = 5.7 Hz, CH_2), 3.75 (s, 3H, OCH_3), 4.76-4.98 (m, 2H, $=CH_2$), 5.72-5.85 (m, 1H, =CH), 6.78 (d, 2H, ^3J = 8.1 Hz, H_{Ar}), 7.03 (d, 2H, ^3J = 8.1 Hz, H_{Ar}), 11.09 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.1, 19.4, 22.1 (CH_3), 23.5, 30.8, 34.7, 36.5 (CH_2), 53.2 (OCH_3), 111.7 (C_{Ar}), 115.7 ($=CH_2$), 124.8 (C_{Ar}), 129.6 ($2CH_{Ar}$), 130.8 ($2CH_{Ar}$), 135.2, 136.4 (C_{Ar}), 137.0 (=CH), 140.0, 142.3, 143.8, 159.9 (C_{Ar}), 173.9 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955, 2926 (m), 2856 (w), 1656, 1595 (m), 1512 (w), 1438, 1325, 1287 (m), 1219 (s), 1139, 1059, 993, 911, 833, 750, 654, 565 (m); GC-MS (EI, 70 eV): *m/z* (%) = 353 (19), 352 (M^+, 88), 320 (88), 305 (65), 292 (100), 263 (48), 249 (61), 235 (35), 203 (32), 179 (25), 165 (10), 152 (11), 129 (31); HRMS (EI): calcd. for $C_{23}H_{28}O_3$ $[M]^+$: 352.20330; found: 352.20362.

Methyl 5-(but-3-enyl)-4'-butyl-4-hydroxy-2,6-dimethyl-biphenyl-3-carboxylate (6z): 

Starting with 1,3-bis(silyl enol ether) **5i** (500 mg, 1.58 mmol), 3-(4-butylphenyl)-4-(trimethylsilyloxy)pent-3-en-2-one **4c** (481 mg, 1.58 mmol) and $TiCl_4$ (0.17 mL, 1.58 mmol), **6z** was obtained as a yellowish solid (306 mg, 53%), mp = 76-78 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, 3H, ^3J = 7.2 Hz, CH_3), 1.20 (sextet, 2H, ^3J = 7.3 Hz, CH_2), 1.44 (quintet, 2H, ^3J = 7.6 Hz, CH_2), 1.76 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.10-2.13 (m, 2H, CH_2), 2.46 (t, 2H, ^3J = 7.4 Hz, CH_2), 2.62 (t, 2H, ^3J = 7.6 Hz, CH_2), 3.75 (s, 3H, OCH_3), 4.77-4.92 (m, 2H, $=CH_2$), 5.69-5.83 (m, 1H, =CH), 6.78 (d, 2H, ^3J = 8.0 Hz, H_{Ar}), 7.02 (d, 2H, ^3J = 8.0 Hz, H_{Ar}), 11.07 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.3, 20.9 (CH_3), 22.4, 26.2, 33.0, 33.6, 35.3 (CH_2), 52.0 (OCH_3), 110.4 (C_{Ar}), 114.4 ($=CH_2$), 126.0 (C_{Ar}), 128.4 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1, 135.7 (C_{Ar}), 138.8 (=CH), 139.0, 141.1, 142.1, 158.9 (C_{Ar}), 172.8 (C=O); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2858, 2667, 1786 (w), 1710, 1655, 1606 (m), 1511 (w), 1438, 1377, 1324, 1286 (m), 1216 (s), 1157, 1058, 991, 906, 807 (m), 751, 700 (s), 634 (w), 576 (m); GC-MS (EI, 70 eV): *m/z* (%) = 367 (33), 366 (M^+, 100), 335 (25), 333 (12), 305 (9), 293 (24), 277 (11), 249 (11), 235 (29), 203 (10), 179 (9), 165 (9), 152 (6), 115 (9); HRMS (EI): calcd. for $C_{24}H_{30}O_3$ $[M]^+$: 366.21895; found: 366.21880.

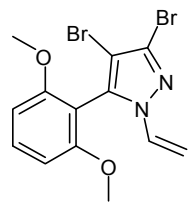
General procedure for syntheses of 3,4-dibromo-5-arylpyrazoles: To a 1,4-dioxane solution (4 mL) of **8a,b** (0.5 mmol) was added $Pd(PPh_3)_4$ (3-10 mol %) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (1.0-1.2 equiv. per bromine atom of the substrate), K_3PO_4 (1.5 equiv. per bromine atom of the substrate) and water (1.0 mL) were added. The mixture was heated for 12 h at 100 °C. After cooling to 20 °C, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3 x 25 mL), dried (Na_2SO_4), and filtered. The solvent of the filtrate was concentrated in *vacuo* and the residue was purified by column chromatography (heptanes/EtOAc).

3,4-Dibromo-5-(4-methoxyphenyl)-1-vinyl-1*H*-pyrazole (10a): Following the



General procedure compound **10a** was prepared from **8b** (165 mg, 0.50 mmol), $Pd(PPh_3)_4$ (18 mg, 3 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (159 mg, 0.75 mmol) and 4-methoxyphenylboronic acid (76 mg, 0.50 mmol) as a white solid (117 mg, 66%), m.p 145-147°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 4.77 (d, 1H, *J* = 8.7 Hz, vinyl), 5.72 (d, 1H, *J* = 15.2 Hz, vinyl), 6.7 (dd, 1H, *J* = 15.2, 8.7 Hz vinyl CH), 6.95 (d, 2H, *J* = 8.8 Hz, ArH), 7.25 (d, 2H, *J* = 8.8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 55.4 (OCH_3), 98.2 (C), 102.7 (CH_2), 114.3 (CH), 119.0 (C), 129.7 (CH), 130.5 (C), 131.5 (CH), 142.4, 160.7 (C). IR (KBr): *v* = 3002, 2936, 2835, 1730 (w), 1641 (m), 1574 (w), 1488 (s), 1432 (m), 1392 (w), 1355 (m), 1332 (s), 1290 (m), 1249 (s), 1196 (w), 1174 (s), 1110 (m), 1030 (s), 984 (s), 888 (m), 833 (s), 801 (m), 725 (w), 602 (m), 551 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 358 ([M, ^{79}Br, ^{81}Br]$^+$, 100), 356 ([M, ^{79}Br, ^{79}Br]$^+$, 70) 343 (13), 327 (22), 277 (39), 246 (22), 198 (23). HRMS (EI, 70 eV): calcd for $C_{12}H_{10}N_2Br_2O$ [M, ^{79}Br, ^{79}Br]$^+$: 355.91544; found 355.915354.

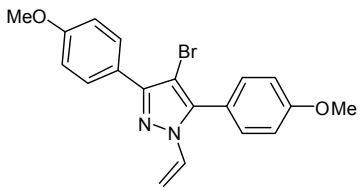
3,4-Dibromo-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole (**10b**): Following the *General*



procedure compound **10b** was prepared from **8b** (165 mg, 0.50 mmol), $Pd(PPh_3)_4$ (18 mg, 3 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (159 mg, 0.75 mmol) and 2,6-dimethoxyphenylboronic acid (91 mg, 0.50 mmol) as a colourless oil (136 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69 (s, 6H, $2OCH_3$), 4.65 (d, 1H, *J* = 8.6 Hz, vinyl), 5.66 (d, 1H, *J* = 15.2 Hz, vinyl), 6.47 (dd, 1H, *J* = 15.2, 8.6 Hz, vinyl CH), 6.57 (d,

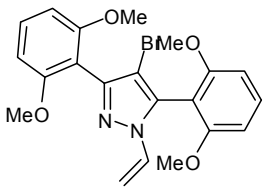
2H, *J* = 8.8 Hz, ArH), 7.33-7.39 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.9 ($2OCH_3$), 100.0 (C), 101.2 (CH_2), 103.9 (CH), 104.3, 130.0 (C), 130.2, 132.5 (CH), 137.0, 158.8 (C). IR (KBr): ν = 3093, 2928, 2838, 1726 (w), 1643 (m), 1537 (w), 1474 (s), 1431 (m), 1389 (w), 1356 (m), 1332 (s), 1297 (w), 1253 (s), 1187, 1173 (w), 1253 (s), 1150 (w), 1107 (s), 1030 (w), 985 (s), 886 (w), 763 (m), 588 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 390 ([M, ^{81}Br, ^{81}Br]$^+$, 40), 388 ([M, ^{79}Br, ^{81}Br]$^+$, 77), 386 ([M, ^{79}Br, ^{79}Br]$^+$, 39), 357 (100), 276 (26), 265 (13), 228 (42). HRMS (ESI^+): calcd for $C_{13}H_{13}N_2Br_2O$ [M+1, ^{79}Br, ^{81}Br]$^+$: 388.9918; found 388.9326, calcd for $C_{13}H_{13}N_2Br_2O$ [M+1, ^{79}Br, ^{79}Br]$^+$: 386.9338; found 386.9344.

4-Bromo-3,5-bis(4-methoxyphenyl)-1-vinyl-1*H*-pyrazole (11a): Following the



General procedure compound **11a** was prepared from **8b** (165 mg, 0.50 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (318 mg, 1.5 mmol) and 4-methoxyphenylboronic acid (152 mg, 1.0 mmol) as a white crystalline solid, m.p 140-142°C. (77 mg, 40%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.75 (d, 1H, *J* = 8.5 Hz, vinyl), 5.75 (d, 1H, *J* = 15.4 Hz, vinyl), 6.78 (dd, 1H, *J* = 8.8, 15.3 Hz, vinyl CH), 6.92 (d, 2H, *J* = 8.9 Hz, ArH), 6.96 (d, 2H, *J* = 8.8 Hz, ArH), 7.30 (d, 2H, *J* = 8.8 Hz, ArH), 7.86 (d, 2H, *J* = 8.9 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.3, 55.4 (OCH_3), 94.2 (C), 101.6 (CH_2), 113.7, 114.2 (CH), 120.1, 124.5 (C), 129.4, 130.3, 131.7 (CH), 142.2, 149.3, 159.9, 160.4 (C). IR (KBr): ν = 3090, 2996, 2834, 1789 (w), 1638 (m), 1574 (w), 1489 (s), 1436 (m), 1307 (w), 1207 (m), 1250, 1178 (s), 1161, 1111 (m), 1029 (s), 1114 (m), 975 (s), 943 (m), 834 (s), 795 (w), 736 (m), 635 (w), 528 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 386 (M, ^{81}Br], 384 ([M, ^{79}Br]$^+$, 100), 365 (08), 332 (07), 281 (13), 207 (100), 175 (9), 135 (4). HRMS (ESI^+): calcd for $C_{19}H_{18}N_2BrO_2$ [M+1, ^{81}Br]$^+$: 387.05278; found 387.05244, calcd for $C_{19}H_{18}N_2BrO_2$ [M+1, ^{79}Br]$^+$: 385.05462; found 385.05434.

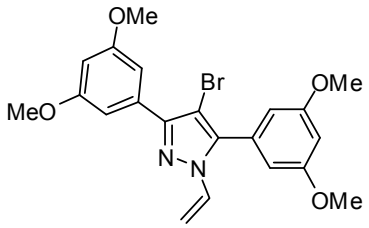
4-Bromo-3,5-bis(2,6-dimethoxyphenyl)-1-vinyl-1*H*-pyrazole (11b): Following the



General procedure compound **11b** was prepared from **8b** (165 mg, 0.50 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (318 mg, 1.5 mmol) and

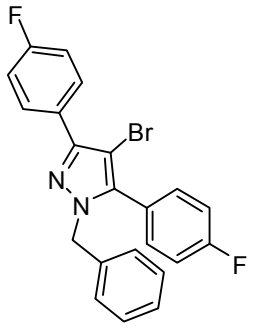
2,6-dimethoxyphenylboronic acid (182 mg, 1 mmol) as a colourless oil. (137 mg, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.62 (s, 6 H, $2OCH_3$), 3.63 (s, 6H, $2OCH_3$), 4.52 (d, 1H, *J* = 8.7 Hz, vinyl), 5.55 (d, 1H, *J* = 15.5 Hz, vinyl), 6.47-6.57 (m, 5H), 7.11-7.29 (m, 2H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 56.0 ($2OCH_3$), 56.1 ($2OCH_3$), 99.7 (CH_2), 100.2 (C), 104.1, 104.2 (CH), 105.7, 109.9 (C), 130.4, 131.0, 131.9 (CH), 135.1, 145.9, 159.0, 159.3 (C). IR (KBr): *v* = 3086, 2957, 2837, 1645 (w), 1558 (m), 1472 (s), 1431 (m), 1384 (w), 1334 (m), 1277 (w), 1248 (s), 1174 (w), 1107 (s), 1082, 977, 822 (m), 773, 729, 636 (s), 589 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 444 ($[M]^+$, ^{79}Br, 24), 415 (04), 365 (100), 319 (04), 223 (03), 190 (05). HRMS (EI, 70 eV): calcd for $C_{21}H_{21}N_2BrO_4$ [M, $^{79}Br]^+$:]$^+$: 444.06846; found 444.06837.

4-Bromo-3,5-bis(3,5-dimethoxyphenyl)-1-vinyl-1*H*-pyrazole(11c): Following the



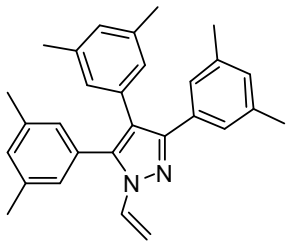
General procedure compound **11c** was prepared from **8b** (165 mg, 0.50 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (318 mg, 1 mmol) and 3,5-dimethoxyphenylboronic acid (182 mg, 1 mmol) as a white solid, m.p 151-152°C. (165 mg, 74%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.68 (s, 12H, $4OCH_3$), 4.58 (d, 1H, *J* = 8.7 Hz, vinyl), 5.60 (d, 1H, *J* = 15.5 Hz, vinyl), 6.52-6.62 (m, 5H), 7.16-7.34 (m, 2H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.0 ($2OCH_3$), 56.1 ($2OCH_3$), 99.7 (CH_2), 100.2 (C), 104.1, 104.2 (CH), 105.7, 109.9 (C), 130.4, 131.0, 131.9 (CH), 135.1, 145.9, 159.0, 159.3 (C). IR (KBr): *v* = 3086, 2957, 2837, 1645 (w), 1601 (m), 1584, 1472 (s), 1431, 1334 (m), 1277 (w), 1248 (s), 1174 (w), 1107 (s), 1082, 977, 882 (m), 773, 729, 636 (s), 590 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 446 ([M, ^{81}Br], 24), 444 ([M, $^{79}Br]^+$, 24), 415 (04), 365 (100), 319 (04), 223 (03), 190 (05). HRMS (EI, 70 eV): calcd for $C_{21}H_{21}N_2BrO_4$ [M, $^{79}Br]^+$: 444.06843; found 444.06830.

1-Benzyl-4-bromo-3,5-bis(4-fluorophenyl)-1*H*-pyrazole (11d): Following the



General procedure compound was prepared from **8a** (198 mg, 0.50 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (318 mg, 1.5 mmol) and 4-fluorophenylboronic acid (140 mg, 1 mmol) as a colourless oil (140 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20 (s, 2H, CH_2), 6.95-6.98 (m, 2H, ArH), 7.03-7.09 (m, 4H, ArH), 7.17-7.23 (m, 5H, ArH), 7.84-7.89 (m, 2H, ArH). ^{19}F NMR (300 MHz, $CDCl_3$): δ = -113.5, -110.8. ^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 53.9 (CH_2), 114.3 (d, $J_{F,C}$ = 21.5 Hz, CH), 115.0 (d, $J_{F,C}$ = 21.8 Hz, CH), 123.7 (CH), 1123.9 (C), 126.8 (CH), 127.5 (d, $J_{F,C}$ = 8.1 Hz, CH), 128.6 (CH), 126.8 (C), 131.9 (d, $J_{F,C}$ = 8.4 Hz, CH), 135.6, 141.3, 146.6, 160.3 (C), 163.7 (d, $J_{F,C}$ = 249.0 Hz, CF), 164.3 (d, $J_{F,C}$ = 248.6 Hz, CF). IR (KBr): v = 3061, 2956, 1900, 1667, 1590 (w), 1486 (s), 1446 (m), 1348 (w), 1222 (s), 1177 (w), 1156 (s), 1012 (m), 948 (w), 840 (s), 787 (m), 722 (s), 650 (m), 575 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 424 ([M]$^+$, ^{79}Br, 49), 349 (06), 329 (11), 225 (38), 91 (100). HRMS (EI, 70 eV): calcd for $C_{22}H_{15}N_2BrF_2$ [M, ^{79}Br]$^+$: 424.03812; found 424.037441.

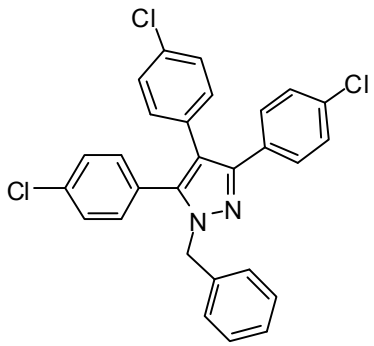
3,4,5-Tris(3,5-dimethylphenyl)-1-vinyl-1*H*-pyrazole (12a): Following the *General*



procedure compound **12a** was prepared from **8b** (152 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 10 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (477 mg, 2.25 mmol) and 3,5-dimethylphenylboronic acid (263 mg, 1.75 mmol) as a light yellow oil (116 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 6H, $2CH_3$), 2.10 (s, 6H, $2CH_3$), 2.15 (s, 6H, $2CH_3$), 4.69 (d, 1H, J = 8.7 Hz, vinyl), 5.78 (d, 1H, J = 15.3 Hz, vinyl), 6.61- 6.90 (m, 8H), 7.09 (brs, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.2, 21.3 (CH_3), 100.5 (CH_2), 120.5 (C), 126.2, 128.1, 128.2, 128.5 (CH), 129.2 (C), 129.3, 130.3, 130.4 (CH), 132.6, 133.0, 137.0, 137.4, 137.8, 141.8, 150.4 (C). IR (KBr): v = 3002, 2915, 2859 (w), 1738, 1642 (m), 1600 (s), 1550 (w), 1444 (m), 1373 (s), 1303, 1268 (w), 1237 (s), 1203, 1154, 1110, 1096 (w), 1093 (m), 996, 900, 881 (w), 848 (s), 789 (w), 691 (m), 542 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 406 ([M]$^+$, 100), 391 (26), 375 (02), 259 (04), 203 (03),

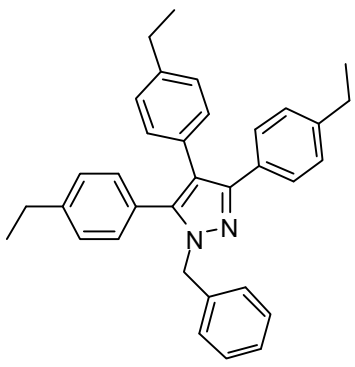
180 (02), 132 (04). HRMS (EI, 70 eV): calcd for $C_{29}H_{30}N_2$ $[M]^+$: 406. 24090; found: 406. 240571

1-Benzyl-5-(3-chlorophenyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole(12b):



Following the *General procedure* compound was prepared from **8a** (198 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 10 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (477 mg, 2.25 mmol) and 4-chloromethoxyphenylboronic acid (273 mg, 1.75 mmol) as a white solid (122 mg, 50%), m.p 155-157°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20 (s, 2H, CH_2), 684-6.87 (m, 2H, ArH), 6.92-6.95 (m, 2H, ArH), 7.00-7.08 (m, 4H, ArH), 7.17-7.22 (m, 7H, ArH), 7.31-7.34 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.2 (CH_2), 127.1, 127.7 (CH), 128.0 (C), 128.6, 128.8, 128.9, 129.0, 129.5(CH), 130.9, 131.2, 131.4(C), 131.5, (CH), 132.7, 133.6, 135.1, 136.9, 141.4, 147.8 (C). IR (KBr): v = 3089, 3031, 1913, 1601, 1496 (w), 1441 (m), 1391, 1268 (w), 1152 (m), 1089 (s), 1031 (w), 1008, 980 (s), 956 (w), 841 (s), 784 (w), 734 (s), 609 (w), 542 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 490 ([M, ^{35}Cl, ^{35}Cl, ^{37}Cl]$^+$, 96), 488 ([M, ^{35}Cl, ^{35}Cl, ^{35}Cl]$^+$, 100), 343 (13), 327 (22), 277 (39), 246 (22), 198 (23). HRMS (EI, 70 eV): calcd for $C_{28}H_{19}N_2Cl_3$ [M, ^{35}Cl, ^{35}Cl, ^{37}Cl]$^+$: 490.05788; found 490.057812, calcd for $C_{28}H_{19}N_2Cl_3$ [M, ^{35}Cl, ^{35}Cl, ^{35}Cl]$^+$: 488.91544; found 488.915354.

1-Benzyl-5-(3-ethylphenyl)-3,4-bis(4-ethylphenyl)-1*H*-pyrazole(12c): Following the *General procedure* compound **12c** was prepared from **8a** (198 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 10 mol%), 1,4-dioxane/H_2O (4:1, 5 mL), K_3PO_4 (477 mg, 2.25 mmol) and 4-Ethylphenylboronic acid (262 mg, 1.75 mmol) as a colourless oil (136 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.08-1.17 (m, 9H, $3CH_3$), 2.46-2.58 (m, 6H, $3CH_2$), 5.20 (s, 2H, CH_2), 689-7.05 (m, 12H, ArH), 7.13-7.19 (m, 3H, ArH), 7.33-7.36 (m, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.1, 15.2, 15.4 (CH_3), 28.4, 28.5, 28.6, 53.2 (CH_2), 127.1, 127.3, 127.4(CH), 127.5(C), 127.6(CH), 127.8(C), 128.1, 128.4, 130.2, 130.3 (CH), 130.7,

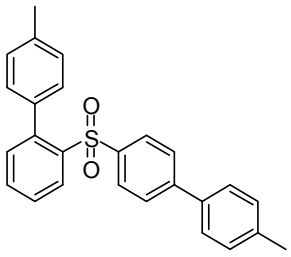


131.1, 137.8, 141.8, 142.4, 143.1, 144.4, 148.9 (C). IR (KBr): ν = 3063 (w), 2962 (m), 2871, 1910, 1524 (w), 1494, 1452 (s), 1373 (m), 1253, 1155, 1062, 981 (w), 957 (m), 837 (s), 792 (m), 724, 694 (s), 595, 536 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 470 ($[M]^+$, 02), 446 (16), 366 (100), 351 (08), 289 (12), 261 (12). HRMS (EI, 70 eV): calcd for $C_{34}H_{34}N_2$ $[M]^+$: 470.27215; found 470.27208.

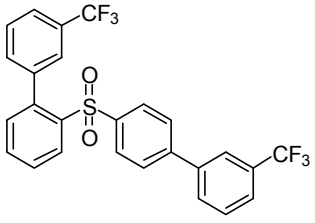
General procedure for the synthesis of 16 a-i

A 1,4-dioxane solution of the arylboronic acid, K_3PO_4, $Pd(PPh_3)_4$ and **14** was stirred at 110 °C for 4 h under argon atmosphere. After cooling to 20 °C, a saturated aqueous solution of NH_4Cl was added. The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in *vacuo*. The residue was purified by column chromatography.

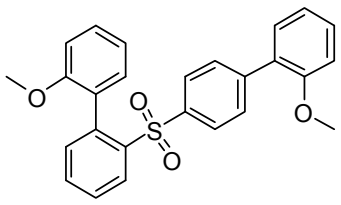
2',4''-Sulfonyl-bis(4-methylbiphenyl) (16a): Starting with **14** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 4-methylphenylboronic acid (135 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16a** was isolated as a white solid (111 mg, 70%), m.p 131 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.77-6.80 (m, 2H, ArH), 6.89-6.92 (m, 2H, ArH), 7.11-7.20 (m, 7H, ArH), 7.26-7.33 (m, 2H, ArH), 7.44-7.48 (m, 2H, ArH), 8.31-8.35 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.2, 21.3 (CH_3), 126.6, 127.1, 127.6, 127.8, 128.2, 128.5, 129.8, 130.0, 132.8, 132.9 (CH), 135.4, 136.5, 137.4, 138.5, 139.3, 140.1, 142.3, 145.3 (C). IR (KBr): ν = 3058, 2921, 2854,1731 (w), 1613, 1484, 4163, 1404, 1392 (m), 1313 (s), 1247 (w), 1151 (s), 1091, 959 (w), 820 (m), 757 (s), 670 (m), 585 (s), 532 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 398 ($[M]^+$, 100), 366 (02), 318 (22), 215 (06), 198 (04), 183 (22), 165 (46), 155 (07), 152 (38), 115 (06). HRMS (EI, 70 eV): calcd for $C_{26}H_{22}O_2S$ $[M]^+$: 398.13350; found 398.133551.



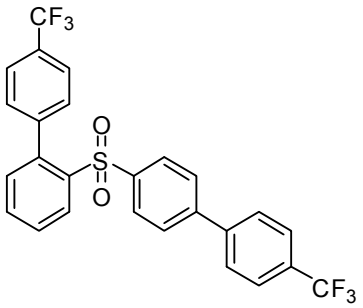
2',4''-Sulfonyl-bis(3-(trifluoromethyl)biphenyl) (16b): Starting with **14** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 3-(trifluoromethyl)phenylboronic acid (190 mg,



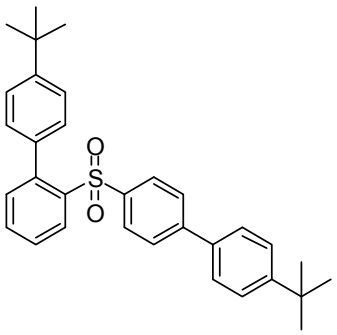
1.0 mmol) and 1,4-dioxane (2 mL), **16b** was isolated as a white solid (121 mg, 60%), m.p 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17-7.25 (m, 3H, ArH), 7.32-7.65 (m, 12H, ArH), 8.39-8.42 (m, 1H, ArH). ^{19}F NMR (300 MHz, $CDCl_3$): δ = -113.5, -110.8. ^{13}CNMR (62.9 MHz, $CDCl_3$): 121.6 (C), 124.1 (q, $J_{F,C}$ = 3.7 Hz, CH), 124.6 (q, $J_{F,C}$ = 3.7 Hz, CH), 125.2 (q, $J_{F,C}$ = 3.6 Hz, CH), 126.2 (q, $J_{F,C}$ = 3.8 Hz, CH), 126.9 (d, $J_{F,C}$ = 278.2 Hz, CF_3), 127.3 (CH), 127.5 (d, $J_{F,C}$ = 279.2 Hz, CF_3), 127.9, 128.2, 128.5, 128.9, 129.5 (CH), 130.0 (C), 130.5, 132.4, 133.3, 134.2 (CH), 138.7, 139.6, 139.9, 140.2, 140.4, 144.4 (C). IR (KBr): ν = 3064, 2922, 2852,1565, 1470 (w), 1330 (s), 1260 (m), 1225 (w), 1147, 1075 (s), 1022 (m), 955, 901 (w), 803, 755 (s), 729 (w), 699 (s), 677 (m), 618 (w), 591 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 506 ([M]$^{+}$, 100), 487 (14), 442 (23), 401 (10), 372 (11), 269 (38), 237 (45), 201 (58), 152 (38). HRMS (EI, 70 eV): calcd for $C_{26}H_{16}F_6O_2S$ [M]$^{+}$: 506.07697; found 506.077006.

2',4''-Sulfonyl-bis(2-methoxybiphenyl) (16c): Starting with **14** (205 mg, 0.4 mmol), 
K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 2-methoxyphenylboronic acid (152 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16c** was isolated as a white solid (106 mg, 62%), m.p 141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.54 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 6.77-6.93 (m, 8H, ArH), 7.21-7.34 (m, 5H, ArH), 7.53-7.61 (m, 2H, ArH), 7.82-7.87 (m, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$) : δ =55.4, 55.5 (OCH_3), 110.0, 111.4, 119.1, 120.8, 121.0, 121.2 (CH), 123.8 (C), 126.6 (CH), 128.3 (C), 129.2, 130.0, 130,5, 130.7, 132.8, 136.1, 136.8 (CH), 139.5, 141.3, 143.2, 155.9, 156.4, 164.6 (C). IR (KBr): ν = 3052, 2924, 2836, 1720 (w), 1599 (m), 1500 (w), 1465, 1393, 1293, 1231 (m), 1127 (s), 1051 (m), 954 (w), 884 (w), 834 (m), 751 (s), 690 (m), 595 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 430 ([M]$^{+}$, 100), 399 (08), 337 (17), 258 (03), 181 (42), 168 (70), 152 (15), 139 (30) cm^{-1}. HRMS (EI, 70 eV): calcd for $C_{26}H_{22}O_4S$ [M]$^{+}$: 430.12333; found 430.123164**.**

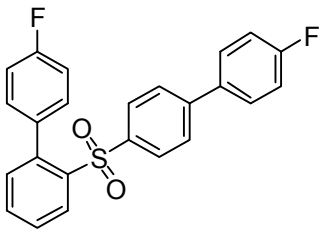
2',4''-Sulfonyl-bis(4-(trifluoromethyl)biphenyl) (16d): Starting with **14** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 4-(trifluoromethyl)phenylboronic acid (190 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16d** was isolated as a white solid (121 mg, 60%), m. p 151 °C.[1]H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.0 Hz, 2H, ArH), 7.11-7.16 (m, 1H, ArH), 7.21-7.24 (m, 2H, ArH), 7.30-7.34 (m, 4H, ArH), 7.51-7.65 (m, 6H, ArH), 8.35-8.40 (m, 1H, ArH). [13]CNMR (62.9 MHz, $CDCl_3$): 126.1 (q, $J_{F,C}$ = 3.7 Hz, CH), 124.1 (q, $J_{F,C}$ = 3.8 Hz, CH), 126.1 (q, $J_{F,C}$ = 272.1 Hz, CF_3), 126.2 (q, $J_{F,C}$ = 271.4 Hz, CF_3), 127.2, 127.6, 128.2, 128.5, 128.6 (CH), 129.8 (C), 130.5 (CH), 130.9 (C), 132.1, 133.3 (CH), 139.7, 140.2, 140.4, 141.8 (q, $J_{F,C}$ = 1.2 Hz, C), 142.5 (d, $J_{F,C}$ = 1.0 Hz, C), 1441 (C). IR (KBr): v = 3060, 2923, 2851, 1915, 1740 (w), 1592 (m), 1490, 1389 (w) 1323 (s), 1249, 1187 (w), 1155, 1070 (s), 1004 (m), 967, 881 (w), 819 (s), 763 (m), 742 (s), 719 (m), 677 (w), 570 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 506 ($[M]^+$, 100), 487 (19), 441 (48), 401 (21), 372 (23), 357 (09), 283 (12), 269 (48), 237(41), 201 (84), 152 (82). HRMS (EI, 70 eV): calcd for $C_{26}H_{16}O_2SF_6$ $[M]^+$: 506.07697 found; 506.076877.



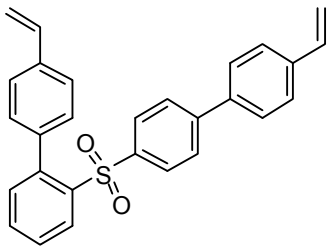
2',4''-Sulfonyl-bis(4-tert-butylbiphenyl) (16e): Starting with **14** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 4-tertiaryphenylboronic acid (178 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16e** was isolated as a white solid (135 mg, 70%), m. p 160 °C.[1]H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9H, $3CH_3$), 1.25 (s, 9H, 3 CH_3), 6.81-6.83 (m, 2H, ArH), 7.07-7.25 (m, 9H, ArH), 7.35 (brs, 2H, ArH), 7.42-7.46 (m, 2H, ArH), 8.34-8.37 (m, 1H, ArH). [13]C NMR (75.5 MHz, $CDCl_3$): δ = 31.4, 31.6 ($3CH_3$), 34.4, 34.6 (C), 114.9 (CH), 126.0, 126.5, 126.9, 127.5, 128.3, 128.5, 129.9, 132.7, 132.9 (CH), 135.2, 136.4, 139.2, 140.1, 142.3, 145.0, 150.8, 151.8 (C). IR (KBr): v = 3060, 2950, 2863, 1608, 1566, 1486, 1434 (w), 1311 (m), 1245, 1180 (w), 1156 (s), 1093 (m), 1040 (w), 1001, 831 (m), 815, 765, 722 (s). 640 (w), 610, 556 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 482 ($[M]^+$, 58), 467 (100), 411



(02), 257 (06), 226 (35), 198 (12), 165 (17). HRMS (EI, 70 eV): calcd for $C_{32}H_{34}O_2S$ $[M]^+$: 482.22786; found 482.22779.

2',4''-Sulfonyl-bis(4-fluorobiphenyl) (16f): Starting with **14** (205 mg, 0.4 mmol), 

K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 4-fluorophenylboronic acid (140 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16f** was isolated as a colourless oil. (114 mg, 70%), m. p 131 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 6.75-6.89 (m, 4H, ArH), 7.07-7.11 (m, 3H, ArH), 7.19-7.22 (m, 2H, ArH), 7.27-7.3 (m, 2H, ArH), 7.37-7.41 (m, 2H, ArH), 7.49-7.52 (m, 2H, ArH) 8.34-8.37 (m, 1H, ArH). ^{13}CNMR (75.5 MHz, $CDCl_3$): 113.1 (d, $J_{F,C}$ = 22.1 Hz, CH), 115.0 (d, $J_{F,C}$ = 23.0 Hz, CH), 125.7, 126.9, 127.1, 127.5, 128.0 (d, $J_{F,C}$ = 8.3 Hz, CH), 130.7 (d, $J_{F,C}$ = 8.0 Hz, CH), 131.7, 132.0 (CH), 133.0 (d, $J_{F,C}$ = 3.0 Hz, C), 134.2 (d, $J_{F,C}$ = 3.0 Hz, C), 138.4, 138.9, 140.0, 143.5 (C), 161.4 (d, $J_{F,C}$ = 249.0 Hz, CF), 162. 0 (d, $J_{F,C}$ = 249.2 Hz, CF). IR (KBr): ν = 3060, 2950, 2863, 1608, 1566, 1486, 1434 (w), 1311 (m), 1245, 1180 (w), 1156 (s), 1093 (m), 1040 (w), 1001, 831 (m), 815, 765, 722 (s), 640 (w), 610, 556 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 406 ($[M]^+$, 100), 342 (21), 321 (20), 233 (05), 219 (17), 187 (41), 170 (82), 159 (17), 133 (09). HRMS (EI, 70 eV): calcd for $C_{24}H_{16}O_2SF_2$ $[M]^+$: 406.08389; found 406.08378.

2',4''-Sulfonyl-bis(4-vinylbiphenyl) (16g): Starting with **14** (205 mg, 0.4 mmol), 

K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 4-vinylphenylboronic acid (148 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16g** was isolated as a colourless oil (110 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.21 (d, *J* = 10.8 Hz, 2H, Vinylic CH), 5.69 (dd, *J* = 12.2, 17.5 Hz, 2H, Vinylic CH_2), 6.64 (dd, *J* = 10.8, 17.5 Hz, 2H, Vinylic CH_2), 6.85 (d, *J* = 8.2 Hz, 2H, ArH), 7.07-7.10 (m, 3H, ArH), 7.13-7.38 (m, 8H, ArH), 7.47-7.49 (m, 2H, ArH), 8.32-8.35 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 114.5, 114.8 (CH_2), 125.1, 126.6, 126.9, 127.4, 127.7, 128.3, 128.5, 130.2, 132.5, 132.9, 136.1, 136.4 (CH), 136.9, 137.7, 137.8, 138.5, 139.3, 140.1, 141.8, 144.9 (C). IR (KBr): ν = 3086, 2922, 2852, 1921, 1627 (w), 1589 (m), 1512 (w), 1466 (m), 1430 (w), 1392 (m), 1314

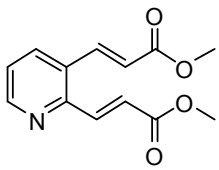
(s), 1249 (w), 1152 (s), 1092 (m), 1333, 968 (w), 822 (s), 756 (s), 666 (m), 586 (s), 539 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 422 ($[M]^+$, 100), 387 (04), 357 (12), 328 (07), 255 (05), 195 (13), 178 (44), 151 (15), 117 (06). HRMS (EI, 70 eV): calcd for $C_{28}H_{22}O_2S$ $[M]^+$: 422.13350; found 422.133839.

2',4''-Sulfonyl-bis(3,5-dimethylbiphenyl) (16h): Starting with **14** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$, (6 mol%), 3,4-Dimethylphenylboronic acid (150 mg, 1.0 mmol) and 1,4-dioxane (2 mL), **16h** was isolated as a white solid (102 mg, 60%), m. p 135 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 6H, $2CH_3$), 2.26 (s, 6H, $2CH_3$), 6.44 (s, 2H, ArH), 6.82 (s, 1H, ArH), 6.29 (s, 1H, ArH), 7.03-7.09 (m, 3H, ArH), 7.17-7.19 (m, 2H, ArH), 7.27-7.30 (m, 2H, ArH), 7.42-7.46 (m, 2H, ArH), 8.32-8.35 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.2 ($2CH_3$), 21.4 ($2CH_3$), 125.2, 126.8, 127.5 (CH), 127.6 (C), 127.8, 128.3, 128.5, 129.1, 130.1, 132.5, 132.8 (CH), 136.8, 138.0, 138.5, 139.4, 139.6, 140.0, 142.5 (C). IR (KBr): *v* = 3085, 2917, 2855 (w),1589 (m), 1556 (w), 1467 (m), 1388 (w), 1302 (s), 1249 (w), 1151 (s), 1125 (m), 995 (w), 853 (m), 831 (s), 777, 699 (m), 586 (s), 562 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 426 ($[M]^+$, 100), 408 (16), 347 (31), 317 (11), 281 (05), 197 (10), 165 (52), 115 (07). HRMS (EI, 70 eV): calcd for $C_{28}H_{26}O_2S$ $[M]^+$: 426.16480; found 426.164819.

General procedure for double Heck cross-coupling reactions.

In a pressure tube (glass bomb) a DMF suspension (5 mL) of Pd $(OAc)_2$ (12 mg, 0.05 m mol, 2.5 mol% per Br) and dicyclohexyl (2', 4', 6'-triisopropylbiphenyl-2-yl) phosphine (L_2) (47 mg, 0.10 m mol), or of the same amount of the other ligand Indicated, was purged with argon and stirred at 20 °C to give a yellowish or brownish transparent solution. To the stirred solution were added the dibromopyridine (199 mg, 1.0 m mol), NEt_3 (1.1 mL, 8.0 m mol) and the acryl ate or styrene (1.25 equiv. per Br). The reaction mixture was stirred at 120 °C for 48 h. The solution was cooled to 20 °C, poured into H_2O and CH_2Cl_2 (25 mL each), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes/EtOAc).

***(2E,2'E)*-Dimethyl 3,3'-(pyridine-2,3-diyl)diacrylate (19a).**

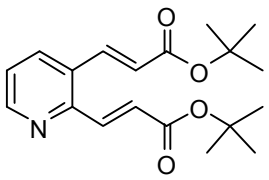


Compound **19a** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow oil (175 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.34 (d, J = 15.2 Hz, 1H, CH), 7.01 (d, J = 15.6 Hz, 1H, CH), 7.22-7.26 (m, 1H, ArH), 7.77 (dd, J = 1.5, 8.2 Hz, 1H, ArH), 7.93 (d, J = 15.4 Hz, 1H, CH), 8.00 (d, J = 15.4 Hz, 1H, CH), 8.56 (dd, J = 1.7, 4.6 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 51.8, 51.9 (OCH_3), 123.0, 124.3, 124.6 (CH), 130.1 (C), 134.9, 138.6, 139.2, 150.7 (CH), 150.9, 166.2, 167.0 (C). IR (KBr): ν = 2955, 2929, 2852 (w), 1722, 1709 (s), 1634 (m), 1580, 1555 (w), 1434 (s), 1361(w), 1300, 1275, 1194, 1161 (s), 1086, 1064, 1010, 990 (w), 970, (m), 932, 870, 778 (m), 732, 720, 702, 605, 582, 568, 544 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 247 ([M]$^+$, 2), 216 (19), 188 (100), 156 (28), 144 (24), 78 (6). HRMS (EI, 70 eV): calcd for $C_{13}H_{13}O_4N$ ([M]$^+$, 247.08391; found 247.08462.

***(2E,2'E)*-Diethyl 3,3'-(pyridine-2,3-diyl)diacrylate (19b).** Compound **19b** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a white solid (195 mg, 71%), m.p = 145-147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3H, CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3), 4.19 (q, *J* = 7.1, 14.3 Hz, 2H, CH_2O), 4.22 (q, *J* = 7.1, 14.3 Hz, 2H, CH_2O), 6.30 (d, *J* = 15.2 Hz, 1H, CH), 6.99 (d, *J* = 15.2 Hz, 1H, CH), 7.20-7.25 (m, 1H, ArH), 7.76 (dd, *J* = 1.4, 8.1 Hz, 1H, ArH), 7.89-7.99 (m, 2H, ArH), 8.53 (dd, *J* = 1.6, 4.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 ($2CH_3$), 60.7, 60.8 (CH_2O), 123.5, 124.3, 125.1 (CH), 130.1 (C), 134.9, 138.4, 150.7 (CH), 150,8 (C), 165.8, 166.5 (CO). IR (KBr): *v* = 1705, 1631 (s), 1580, 1552, 1473, 1446 (w), 1423, 1364 (m), 1295 (s), 1228 (m), 1661 (s), 1112, 1065 (w), 1027, 971, 892, 872, 808, 782 (s), 722, 709, 602, 580, 546 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 275 ([M]$^+$, 3), 246 (02), 230 (30), 202 (100), 174 (48), 156 (33), 130 (71), 77 (9). HRMS (EI, 70 eV): calcd for $C_{15}H_{17}O_4N$ [M]$^+$: 275.11521; found: 275.11549

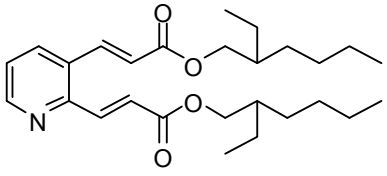
(2*E*,2'*E*)-Di*iso*butyl 3,3'-(pyridine-2,3-diyl)diacrylate (19c). Compound **19c** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow semisolid (271 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, 6H, *J* = 6.8 Hz, $2CH_3$), 0.93 (d, 6H, *J* = 6.7 Hz, $2CH_3$), 1.90-2.00 (m, 2H), 3.93 (d, 2H, *J* = 6.7 Hz, CH_2), 3.96 (d, 2H, *J* = 6.7 Hz, CH_2), 6.33 (d, H, *J* = 15.6 Hz), 7.01 (d, H, *J* = 15.9 Hz), 7.20-7.25 (m, H, ArH), 7.80 (dd, H, *J* = 1.5, 8.0 Hz, ArH), 7.95 (d, H, *J* = 15.2 Hz, H), 8.00 (d, H, *J* = 15.8 Hz, H), 8.55 (dd, H, *J* = 1.6, 4.5 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.1 (CH_3), 27.8 (CH), 70.8, 71.0 (CH_2O), 123.5, 124.3, 125.2 (CH), 130.1 (C), 135.0, 138.4, 139.0, 150.6 (CH), 150.8, 165.1, 165.8(C). IR (KBr): *v* = 2960, 2874 (m), 1712 (s), 1635, 1469, 1424, 1376, 1369 (m), 1305, 1292, 1276, 1256, 1158, 1010, 973 (s), 802, 780, 702, 606, 590 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 331 ([M]$^+$, 02), 258 (46), 230 (100), 202 (29), 174 (81), 156 (19), 129 (38). HRMS (EI, 70 eV): calcd for $C_{19}H_{25}O_4N$ [M]$^+$: 331.11778; found: 331.17745.

***(2E,2'E)*-Di(*tert*-butyl) 3,3'-(pyridine-2,3-diyl)diacrylate (19d).** Compound **19d**



was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow solid (278 mg, 84%), m.p = 137-138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9H, $3CH_3$), 1.44 (s, 9H, $3CH_3$), 6.22 (d, *J* = 15.2 Hz, 1H, CH), 6.90 (d, *J* = 15.9 Hz, 1H, CH), 7.17-7.22 (m, 1H, CH ArH), 7.73 (dd, *J* = 1.7, 8.0 Hz, 1H, ArH), 7.84 (d, *J* = 15.2 Hz, 1H, CH), 7.86 (d, *J* = 15.8 Hz, 1H, CH), 8.50 (dd, *J* = 1.7, 4.6 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.0 ($3CH_3$), 28.1 ($3CH_3$), 80.7, 81.0 (C), 124.0, 125.3, 127.0 (CH), 130.1 (C), 134.9, 137.6, 138.0, 150.4 (CH), 150.9 (CH), 164.9, 165.7 (CO). IR (KBr): *v* = 3004, 2978, 2930, 2871 (w), 1698 (s), 1634, 1578, 1552, 1471, 1456 (w), 1422, 1392, 1365, 1392 (m), 1365, 1309, 1254, 1138 (s), 1086, 1062, 1039 (w), 971 (s), 922, 889, 845, 805, 763, 731, 598, 538 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 331 ([M]$^{+}$, 1), 275 (1), 230 (23), 202 (39), 174 (99), 130 (100), 102 (10), 57 (91). HRMS (EI, 70 eV): calcd for $C_{19}H_{25}O_4N$ [M]$^{+}$: 331.17781; found 331.17840.

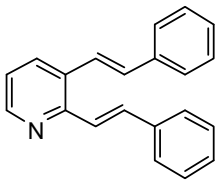
***(2E,2'E)*-Di(2-ethylhexyl) 3,3'-(pyridine-2,3-diyl)diacrylate (19e).** Compound **19e**



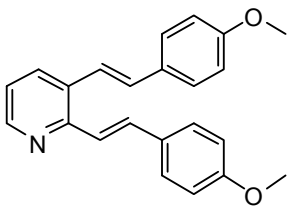
was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellowish oil (265 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82–0.87 (m, 12 H, $4CH_3$), 1.27-1.31 (m, 12H, $6CH_2$), 1.28-1.31 (m, 4H, $2CH_2$), 1.33-1.60 (m, 2H, CH), 4.06-4.09 (m, 4H, $2CH_2O$), 6.31 (d, 15.2 Hz, 1H, CH), 7.01 (d, *J* = 15.2, 1H, CH), 7.20-7.25 (m, 1H, ArH), 7.78 (dd, *J* = 1.5, 8.0 Hz, 1H, ArH), 7.92 (d, *J* = 15.2 Hz, 1H, CH), 7.97 (d, *J* = 15.2 Hz, 1H, CH), 8.55 (dd, *J* = 1.8, 4.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.9, 11.0, 14.0 (CH_3), 22.9, 23.8 28.9, 30.4 (CH_2), 38.7, 38.8 (CH), 67.1, 67.4 (CH_2O), 123.6, 124.2, 125.2 (CH), 138.3 (C), 135.0, 138.4, 138.9, 150.6 (CH), 150.9 (C), 165.9, 166.6 (CO). IR (KBr): *v* = 2957, 2927, 2872, 2869 (m), 1713 (s), 1636, 1580, 1554, 1460, 1425, 1380 (w), 1296, 1260 (m), 1220, 1204 (w), 1163 (s), 1085, 1063, 1027, 1014 (w), 974 (m), 918, 869, 801 (w), 780 (m), 729, 703, 606 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) =

443 ([M]$^+$, 2), 398 (04), 332 (42), 286 (100), 202 (48), 70 (16), 57 (29). HRMS (EI, 70 eV): calcd for $C_{27}H_{41}O_4N$ [M]$^+$: 443.30301; found 443.30301.

2,3-Di(2-phenylethenyl)pyridine (19f). Compound **17f** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow solid (204 mg, 72%), m.p = 130-132 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88 (d, J = 15.2 Hz, 1H, CH), 7.06 (dd, J = 7.9, 4.5 Hz, 1H, ArH), 7.21-7.31 (m, 6H, ArH), 7.36-7.45 (m, 4H, ArH), 7.49-7.52 (m, 2H, ArH), 7.69-7.74 (m, 2H, ArH), 8.44 (dd, J = 1.8, 4.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 122.3, 124.2, 124.4, 126.8, 127.3, 128.3, 128.4, 128.7, 128.9, (CH), 131.4 (C), 133.1, 134.4, 134.7 (CH), 137.0, 148.4, 152.5 (C). IR (KBr): ν = 3078, 3055, 3024, 2929, 1732, 1699, 1628, 1597, 5174 (w), 1492, 1448, 1419 (m), 1371, 1323, 1300, 1271, 1240, 1203, 1179, 1162, 1072, 1045, 1027 (w), 958 (s), 915, 847 (w), 770, 744, 687 (s), 543 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 283 ([M]$^+$, 100), 206 (42), 180 (07), 134 (06), 91 (04), 77 (03). HRMS (EI, 70 eV): calcd for $C_{21}H_{16}N$ [M-1]$^+$: 282.12783; found 282.12783.



2,3-Di[2-(4-methoxyphenyl)ethenyl]pyridine (19g). Compound **19g** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow crystalline solid (271 mg, 79%), m.p = 123-124 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.81-6.88 (m, 5H, ArH), 7.03-7.07 (m, 1H, ArH), 7.30 (d, J = 15.7 Hz, 1H, CH), 7.31 (d, J = 15.2 Hz, 1H, CH), 7.39-7.49 (m, 4H, ArH), 7.64 (d, J = 15.2 Hz, 1H, CH), 7.72 (dd, J = 1.6, 8.0 Hz, 1H, ArH), 8.42 (dd, J = 1.5, 4.6 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.3, 55.3 (OCH_3), 114.1, 114,2 , 121.9, 122.1, 122.3, 127.9, 128.6, (CH), 129.3, 130.3 (C), 132.3, 133.9, 134.1, 148.0 (CH), 156.0, 159.7, 159.9 (C). IR (KBr): ν = 3045, 3000, 2668, 2932, 2836, 1692, 1626(w), 1600, 1572 (m), 1550 (w), 1508 (s), 1464, 1455, 1439, 1426 (m), 1344, 1332 (w), 1245, 1170 (s), 1023, 967 (m), 936, 856 (w), 818 (s), 791, 775 (m), 715, 688, 612 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z*



(%) = 343 ([M]$^+$, 100), 236 (72), 222 (09), 121 (31), 77 (2). HRMS (EI, 70 eV): calcd for $C_{23}H_{21}O_2N$ [M]$^+$: 343.15668; found 343.15642.

2,3-Di[2-(4-methylphenyl)ethenyl]pyridine (19h). Compound **19h** was prepared starting with 2,3-dibromopyridine (**17**), (237 mg, 1.0 mmol) as a light yellow semisolid (202 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.85 (d, J = 15.2 Hz, 1H, CH), 7.03-7.14 (m, 5H, ArH), 7.32-7.43 (m, 6H, ArH), 7.64-7.72 (m, 2H, ArH), 8.42 (dd, J = 1.5, 4.5 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 21.4 (CH_3), 122.0, 123.3, 123.5, 126.6, 127.2, 129.4 (CH), 129.5 (C), 129.6 (CH), 131.5 (C), 132.8, 134.2 (CH), 134.3 (C), 134.5 (CH), 138.2, 138.4 (C), 148.2 (CH), 152.6 (C). IR (KBr): v = 3031, 2919, 2853, 2727, 1693, 1626, 1605, 1573, 1550, 1450 (w), 1422 (m), 1324, 1298, 1200, 1182, 1109, 1082, 1039, 1018 (w), 959 (s), 867 (w), 805 (s), 706, 635, 613, 548 (w), 533 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 311 ([M]$^+$, 60), 310 (100), 220 (45), 147 (06), 105 (09). HRMS (EI, 70 eV): calcd for $C_{23}H_{21}N$ [M]$^+$: 311.15903 found 311.15912.

***(2E,2'E)*-Dibutyl 3,3'-(2,2'-bipyridine-5,5'-diyl)diacrylate (21a).** Compound **20a** was prepared starting with 2,5-dibromopyridine (**20**), (237 mg, 1.0 mmol) as a white solid (169 mg, 83%), m.p = 225-227 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.33-1.45 (m, 4H, $2CH_2$), 1.57-1.69 (m, 4H, $2CH_2$), 4.18 (t, J = 6.7 Hz, 4H, $2CH_2O$), 6.45 (d, J = 15.2 Hz, 2H, 2CH), 7.61 (d, J = 15.2 Hz, 2H, 2CH), 7.88 (dd, J = 2.2, 8.4 Hz, 2H, ArH), 8.39 (d, J = 8.3 Hz, 2H, ArH), 8.70 (d, J = 1.9 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.6 (CH_3), 19.2, 29.7 (CH_2), 64.7 (CH_2O), 120.6, 121.3 (CH), 130.5 (C), 135.0, 140.0, 149.4 (CH), 156.4, 166.4 (C). IR (KBr): v = 3055, 2957, 2933, 2872 (w), 1714, 1635, 1469, 1377, 1303 (s), 1250, 1200 (m), 1168, 1140, 1117 (s), 1056, 1020, 989, 976, 953, 925, 900, 862 (m), 833 (s), 723, 707, 652, 532 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 408

([M]$^+$, 100), 363 (24), 336 (65), 279 (70), 178 (11). HRMS (EI, 70 eV): calcd for $C_{24}H_{28}O_4N_2$ [M]$^+$: 408.20436; found 408.20450.

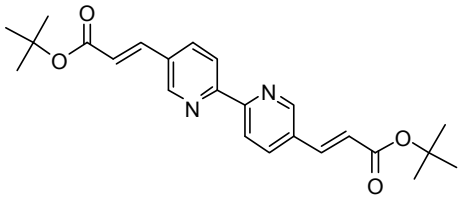
***(2E,2'E)*-Dihexyl 3,3'- (2,2'-bipyridine-5,5'-diyl)diacrylate (21b).** Compound **21b** was prepared starting with 2,5-dibromopyridine (**20**), (165 mg, 1.0 mmol) as a white solid (329 mg, 71%), m.p = 215-217 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t J = 6.57 Hz, 6H, $2CH_3$), 1.17-1.35 (m, 12H, $6CH_2$), 1.59-1.69 (m, 4H, $2CH_2$), 4.15 (t, J = 6.7 Hz, 4H, $2CH_2O$), 6.49 (d, J = 15.2 Hz, 2H, 2CH), 7.63 (d, J = 15.2 Hz, 2H, 2CH), 7.89 (d, J = 8.3 Hz, 2H, ArH), 8.40 (d, J = 8.3 Hz, 2H, ArH), 8.70 (brs, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.5, 25.6, 28.6, 31.4 (CH_2), 65.0 (CH_2O), 120.6, 121.3 (CH), 130.5 (C), 135.0, 140.4, 149.3 (CH), 156.3 (C), 166.4 (CO). IR (KBr): ν = 2952, 2928, 2870 (m), 1714, 1635 (s),1592,1544 (w), 1468, 1376 (m), 1304 (s), 1273, 1250, 1214, 1199 (w), 1171, 1139 (s), 1067, 1013 (w), 990, 975 (m), 931, 899, 879, 863 (w), 834 (m), 815 (w), 724, 708, 652 (m), 599, 538, 529 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 464([M]$^+$,73), 407 (17), 363 (100), 336 (91), 324 (34), 279 (65), 205 (14), 57 (13). HRMS (EI, 70 eV): calcd for $C_{28}H_{36}N_2O_4$ [M]$^+$, 464.27380 found 464.27481.

***(2E,2'E)*-Di(2-ethylhexyl)3,3'-(2,2'-bipyridine-5,5'-diyl)-diacrylate(21c).**

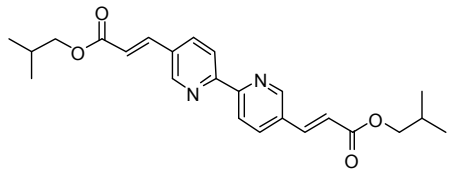
Compound **21c** was prepared starting with 2,5-dibromopyridine (**20**), (237 mg, 1.0 mmol), following the *general procedure*, as a white solid (213 mg, 82 %), m.p = 255-257 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82-0.90 (m, J = 12H, $4CH_3$), 1.18-1.39 (m, 16H, $10CH_2$), 1.59-1.69 (m, 2H, 2CH), 4.08-4.10 (m, 4H, $2CH_2O$), 6.51 (d, J = 15.2 Hz, 2H, 2CH), 7.64 (d, J = 15.2 Hz, 2H, 2CH), 7.91 (dd, J = 2.2, 8.4 Hz, 2H, ArH), 8.39 (d, J = 8.3 Hz, 2H, ArH), 8.72 (brs, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.0, 14.0 (CH_3), 23.0, 23.8, 28.9, 30.4 (CH_2), 38.8 (CH), 67.2 (CH_2O), 120.6, 121.3 (CH), 130.5 (C), 135.0, 140.4, 149.4 (CH), 156.4 (C), 166.5 (CO). IR (KBr):ν = 2957,

2926, 2858, 1709, 1633 (s), 1568, 1468, 1379 (m), 1302 (s), 1254 (m), 1162(s), 1135 (m), 1050, 1005 (w), 839 (m), 767, 748, 729, 709, 546 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 520 ($[M]^+$, 21), 491 (6), 408 (14), 391 (37), 364 (22), 296 (100), 205 (7). HRMS (EI, 70 eV): calcd for $C_{32}H_{44}N_2O_4$: 520.33011; found 520.33045.

***(2E,2'E)*-Di(*tert*-butyl) 3,3'-(2,2'-bipyridine-5,5'-diyl)-diacrylate (21d)**. Compound **21d** was prepared starting with 2,5-dibromopyridine (**20**), (237 mg, 1.0 mmol) as a white solid (342 mg, 84%), m.p = 237-238 °C ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 18H, $6CH_3$), 6.43 (d, *J* = 15.2 Hz, 2H, 2CH), 7.56 (d, *J* = 15.2 Hz, 2H, 2CH), 7.89 (dd, *J* = 2.2, 8.4 Hz, 2H, ArH), 8.39 (d, *J* = 8.3 Hz, 2H, ArH), 8.71 (d, *J* = 2.0 Hz, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (CH_3), 81.0 (C), 121.3, 122.5 (CH), 130.7 (C), 135.0, 139.3, 149.2 (CH), 156.1 (C), 156.5 (CO). IR (KBr): *v* = 3006, 2976, 2928, 2855 (w), 1699 (s), 1667 (w), 1634 (m), 1555, 1544 (w), 1468, 1455, 1363, 1315, 1251, 1208 (m), 1146 (s), 1054, 1023 (m), 993, 981, 835 (s), 765, 750, 738, 710, 650 (m), 589 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 408 ($[M]^+$, 24), 352 (27), 296 (100), 205 (10), 279 (40), 252 (80), 205 (10). HRMS (EI, 70 eV): calcd for $C_{24}H_{28}N_2O_4$ $[M]^+$: 408.20436; found 408.20549.

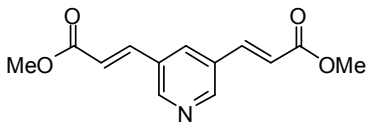


***(2E,2'E)*-Di(*iso*butyl) 3,3'-(2,2'-bipyridine-5,5'-diyl)diacrylate (21e).** Compound **21e** was prepared starting with 2,5-dibromopyridine (**20**), (157 mg, 1.0 mmol) as a white solid (314 mg, 77%), m.p = 231-232 °C ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 12H, $4CH_3$), 1.89-1.97 (m, 2H, 2CH), 3.94 (d, *J* = 6.7 Hz, 4H, $2CH_2O$), 6.53 (d, *J* = 15.2 Hz, 2H, 2CH), 7.65 (d, *J* = 15.2 Hz, 2H, 2CH), 7.91 (d, *J* = 2.1, 8.4 Hz, 2H, ArH), 8.39 (d, *J* = 8.3, Hz, 2H, ArH), 8.33 (brs, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.1 (CH_3), 26.8 (CH), 69.9 (CH_2O), 119.6, 120.3 (CH), 129.5 (C), 134.0, 139.5, 148.4 (CH), 155.4 (C), 165.4 (CO). IR (KBr): *v* = 2959, 2929, 2873,

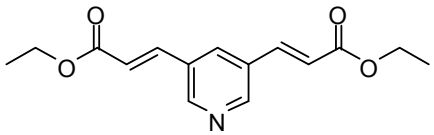


(m), 1728 (s), 1679, 1641, 1632, 1590 (w), 1462, 1378 (m), 1235, 1169 (s), 1092, 984, 945, 800, 784 (m), 648 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 408 ($[M]^+$, 56), 352 (17), 296 (100), 205(11), 131 (06). HRMS (EI, 70 eV): calcd for $C_{24}H_{28}N_2O_4[M]^+$: 408.2041; found 408.20451.

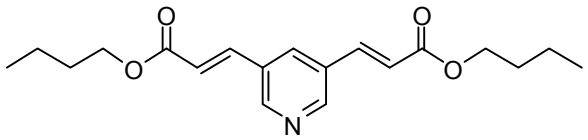
***(2E,2'E)*-Dimethyl -3,3'-(pyridine-3,5-diyl)diacrylate (23a).** Compound **23a** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (170 mg, 69%), m.p = 156-158 °C ^1H NMR (300 MHz, $CDCl_3$): δ= 3.76 (s, 6H, $2CH_3O$), 6.46 (d, *J* = 16.1 Hz, 2H, 2CH), 7.62 (d, *J* = 16.1 Hz, 2H, 2CH), 7.86 (brs, 1H, ArH), 8.66 (s, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ= 60.0 (CH_3O), 121.1, 132.2 (CH), 132.6 (C), 140.3, 150.3 (CH), 166.4 (CO). IR (KBr): ν = 2954, 2921, 2851 (m), 1722, 1716, 1642 (s), 1433, 1329, 1316, 1329, 1315 (m), 1292, 1278 (w), 1244, 1189 (m), 1169 (s), 1025, 1014, 999 (w), 977, 854 (m), 785, 738, 727, 704 (w), 688 (m), 600 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 247 ($[M]^+$, 70), 232 (64), 216 (100), 200 (30), 184 (72), 156 (46), 128 (31). HRMS (EI, 70 eV): calcd for $C_{13}H_{13}O_4N$ $[M]^+$, 247.08448 found 247.08498.



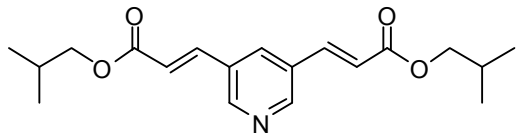
***(2E,2'E)*-Diethyl 3,3'-(pyridine-3,5-diyl)diacrylate (23b).** Compound **23b** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (195 mg, 71%), m.p = 162-163 °C ^1H NMR (300 MHz, $CDCl_3$): δ= 1.27 (t, *J* = 7.0 Hz, 6H, $2CH_3$), 4.22 (q, *J* = 7.1, 14.3 Hz, 4H, $2CH_2O$), 6.48 (d, *J* = 16.1 Hz, 2H, 2CH), 7.60 (d, *J* = 16.1 Hz, 2H, 2CH), 7.88 (s, 1H, ArH), 8.66 (s, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ= 14.2, (CH_3), 60.9 (CH_2O), 121.5 (CH), 130.5 (C), 132.4, 140.0, 150.2 (CH), 156.9(CO). IR (KBr): ν = 2982, 2934, 2904, 2874 (w), 1699 (s), 1639 (m), 1592, 1567 (w), 1420, 1368, 1321, 1239 (m), 1167 (s), 1094 (m), 977 (s), 911(w), 854 (s), 810 (w), 686 (m), 605, 587, 541 (w) cm^{-1}. GC-MS (EI, 70eV): *m/z* (%) = 275 ($[M]^+$, 51), 246 (61), 230 (100), 200 (44), 184 (42), 128 (14), 51 (7). HRMS (EI, 70 eV): calcd for $C_{15}H_{17}O_4N$ $[M]^+$: 275.11521; found 275.11571.



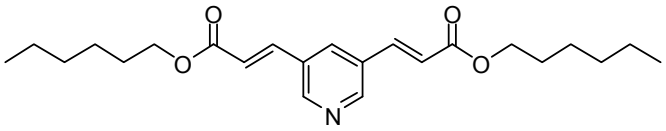
***(2E,2'E)*-Dibutyl 3,3'-(pyridine-3,5-diyl)diacrylate (23c).** Compound **23c** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (271 mg, 82%), m.p = 148-149 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.89 (t, *J* = 7.4 Hz, 6H, $2CH_3$), 1.30-1.42 (m, 4H, $2CH_2$), 1.57-1.67 (m, 4H, $2CH_2$), 4.15 (t, *J* = 6.7 Hz, 4H, $2CH_2O$), 6.49 (d, *J* = 16.1 Hz, 2H, 2CH), 7.63 (d, *J* = 16.1 Hz, 2H, 2CH), 7.89 (s, 1H, ArH), 8.66 (s, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 13.6 (CH_3), 19.1, 30.7 (CH_2), 64.8 (CH_2O), 121.4 (CH), 130.4 (C), 132.3, 139.9, 150.3 (CH), 166.0 (CO). IR (KBr): *v* = 2957, 2933, 2872, 1708 (s), 1638 (m), 1567, 1465, 1448, 1432, 1382, 1355, 1342 (w), 1312, 1285, 1258, 1239 (m), 1168 (s), 1062 (m), 978 (s), 901 (w), 858 (s), 735, 702 (w), 683 (m), 602, 589 cm^{-1}. GC-MS (EI, 70eV): *m/z* (%) = 331 ($[M]^+$, 12), 258 (100), 230 (22), 202 (53), 184 (35), 156 (22), 128 (17). HRMS (EI, 70 eV): calcd for $C_{19}H_{25}O_4N$ $[M]^+$, 331.17781 found 331.17819.



***(2E,2'E)*-Di(isobutyl) 3,3'-(pyridine-3,5-diyl)diacrylate (23d).** Compound **23d** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (278 mg, 84%), m.p = 147-148 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.90 (d, *J* = 6.8 Hz, 12H, $4CH_3$), 1.88-2.00 (m, 2H, 2CH), 3.92 (d, *J* = 6.7 Hz, 4H, $2CH_2O$), 6.51 (d, *J* = 16.1 Hz, 2H, 2CH), 7.60 (d, *J* = 16.1 Hz, 2H, 2CH), 7.92 (s, 1H, ArH), 8.68 (s, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 19.0, (CH_3), 27.8 (CH), 70.9 (CH_2O), 121.4, (CH), 130.6 (C), 132.3, 140.0, 150.3 (CH), 166.0 (CO). IR (KBr): *v* = 2956, 2872 (m), 1708, 100 (s), 1638 (m), 1573, 1558 (w), 1470, 1435, 1375, 1312, 1293, 1273, 1256, 1240 (m), 1170, 1020, 980, 858 (s), 799, 732, 706 (w), 682 (s), 590, 552, 534 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 331 ($[M]^+$, 06), 276 (27), 258 (100), 220 (61), 202 (30), 184 (20), 156 (13), 56 (10). HRMS (EI, 70 eV): calcd for $C_{19}H_{25}O_4N$ $[M]^+$: 331.40610; found 331.40611.

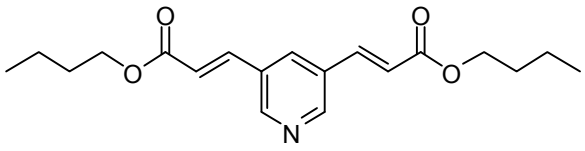


***(2E,2'E)*-Dihexyl 3,3'-(pyridine-3,5-diyl)diacrylate (23e).** Compound **23e** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid



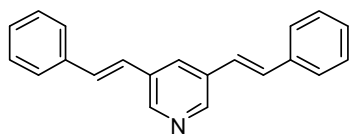
(299 mg, 77%), m.p = 130-132 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, J = 6.8 Hz, 6H, $2CH_3$), 1.16-1.35 (m, 12H, $6CH_2$), 1.58-1.65 (m, 4H, $2CH_2$), 4.14 (t, 4H, $2CH_2O$), 6.49 (d, J = 16.1 Hz, 2H, 2CH), 7.59 (d, J = 16.1 Hz, 2H, 2CH), (brs, 1H, ArH), 8.65 (s, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 13.2 (CH_3), 21.5, 24.6, 27.6, 30.4 (CH_2), 63.6 (CH_2O), 120.5 (CH), 129.3 (C), 131.3, 139.0, 149.3 (CH), 165.0 (CO). IR (KBr): v = 2954, 2927, 2857 (m), 1712 (s), 1644 (m), 1589, 1566, 1464, 1421, 1343 (w), 1316 (m), 1258 (s), 1227 (m), 1166 (s), 1068, 1040, 1023 (m), 993, 980 (s), 903, 866, 857, 794, (m), 613, 603, 545 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 387 ($[M]^+$, 08), 330 (08), 304 (50), 286 (100), 258 (30), 220 (88), 202 (51), 184 (26). HRMS (EI, 70 eV): calcd for $C_{23}H_{33}O_4N$ $[M]^+$: 387.24041; found 387.240367.

***(2E,2'E)*-Di(*tert*-butyl) 3,3'-(pyridine-3,5-diyl)diacrylate (23f).** Compound **23f** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (268 mg, 81%)

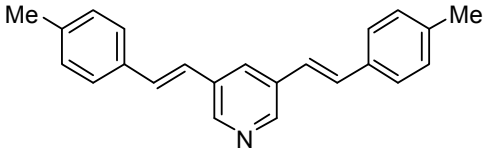


m.p = 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.47 (s, 18H, $6CH_3$), 6.41 (d, J = 16.1 Hz, 2H, 2CH), 7.49 (d, J = 16.1 Hz, 2H, 2CH), 7.84 (brs, 1H, ArH), 8.62 (s, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ= 28.0 (CH3), 81.06 (C-O), 123.3 (CH), 130.5 (C), 132.1, 139.0, 150.1 (CH), 165.2 (CO). IR (KBr): v = 2974, 2929, 2871 (m), 1698 (s), 1644 (m), 1573, 1454, 1433 (w), 1391, 1365, 1328, 1295, 1279, 1256 (m), 1147 (s), 1040, 1025 (w), 970 (s), 857, 848 (m), 807, 782, 761, 724 (w), 687 (m), 605, 591, 540 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 331 ($[M]^+$, 20), 275 (20), 258 (88), 220 (99), 202 (60), 173 (33), 57(100). HRMS (EI, 70 eV): calcd for $C_{19}H_{25}O_4N$ 331.17781 found 331.17831.

3,5-Di(2-phenylethenyl)pyridine (23g). Compound **23g** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (204 mg, 72%), m.p = 115-116 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (d, J = 16.4 Hz, 2H, 2CH), 7.08 (d, J = 16.4 Hz, 2H, 2CH), 7.17-7.31 (m, 6H, ArH), 7.39-7.44 (m, 4H, ArH), 7.78 (s, 1H, ArH), 8.51 (s, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.7, 126.8, 128.25, 128.8, 129.4, 131.1 (CH), 133.1, 136.7 (C), 147.2 (CH). IR (KBr): ν = 3098, 3080, 3052, 3023, 2926, 2850 (w), 1446 (m), 1414, 1340, 1309, 1239, 1230, 1178, 1155, 1107, 1023, 999, 983 (w), 962 (s), 919, 892, 825, 833, 797, 779 (w), 745, 691 (s), 545, 526 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 283 ([M]$^{+}$, 62), 282 (100), 204 (4), 156 (4), 133 (8). HRMS (EI, 70 eV): calcd for $C_{21}H_{17}N$ [M]$^{+}$: 283.13610; found 283.13699.



3,5-Di[2-(4-methylphenyl)ethenyl]pyridine (23h). Compound **23h** was prepared starting with 3,5-dibromopyridine (**22**), (237 mg, 1.0 mmol) as a white solid (236 mg, 76%), m.p = 118-119 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 6H, 2CH_3), 6.93 (d, J = 16.1 Hz, 2H, 2CH), 7.09-7.14 (m, 6H), 7.37 (d, J = 8.1, 4H, ArH), 7.85 (brs, 1H, ArH), 8.50 (s, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 123.6, 126.7, 129.4, 129.6, 131.1 (CH), 133.2, 133.8, 138.3 (C), 146.6 (CH). IR (KBr): ν = 3038, 3020, 2998, 2912, 2854, 2725 (m), 1603, 1583, 1510, 1462, 1434, 1414, 1371, 1327, 1303, 1241, 1212, 1180, 1112, 1041, 1017 (w), 966 (s), 950 (m), 889 (w), 849, 841 (m), 799 (s), 667, 626 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 311 ([M]$^{+}$, 72), 310 (100), 294 (10), 170 (6), 154 (12). HRMS (EI, 70 eV): calcd for $C_{23}H_{20}N$ [M-1]$^{+}$: 310.15903; found 310.15921.



References

1. Soejarto, D. D.; Farnswoth, N. R. *Perspect.Biol.Med*. **1989**, *32*, 244.
2. Krohn, K.; Michel, A.; Bahramsari, R.; Floerke, U.; Aust, H. J.; Dreger, S.; Schulz, B.; Wray, V. *Nat. Prod. Lett*. **1996**, *8*, 43.
3. Berdy, J. (eds.), *Handbook of Antibiotic*s, Little, Brown, Boston **1988**.
4. (a) Trigg, P. I. *In Economic and Medicinal Plant Research*, Vol. 3, Wagner, H.; Hikino, H.; Farnswoth, N. R. (Eds), *Academic Press*, London **1989**, 19. (b) Wu, Y.L.; Li. Y.; *Med. Chem. Res. 5*, **1995**, 569. (c) Lee, I. -S.; Hufford, C. D. *Pharmacol. Ther.* **1990**, *48*, 345.
5. Loo, T. L.; Freireich, E. J.; "*Cancer chemo therapeutic drugs" In Principles of Pharmacology: Basic Concepts and Clinical Applications*, Munson, P. L.; Mueller, R. A.; Breese G. R.; (eds), **1995**, 1475, Chapman and Hall, New York.
6. Topliss, J. G.; Clark, A. M.; Ernst, E.; Hufford, C. D.; Johnston, G. A. R.; Rimoldi, J. M; Weimann, B. J. *Pure App. Chem.* **2002**, *74*, 1957.
7. Lee, M. K.; Kim, J.; Markelonis, G.J.; Oh, T.H.; Y, C, *J. Neurosci. Res.* **2000**, *59*, 259.
8. Cynodiones A-C: (a) Lin, Y. L.; Wu, Y. M.; Kuo, Y. H. *Phytochemistry* **1997**, *45*,1057. (b) Huang, P. L.; Won, S. J.; Day, S. H.; Lin, C. N. *Helv. Chim. Acta* **1999**, *82*, 1716. (c) Lin, Y. L.; Lin, T. C.; Kuo, Y. H. *J. Nat. Prod*. **1997**, *60*, 368. (d) Buchanan, M. S.; Gill, M.; Yu, J. *J. Chem. Soc., Perkin Trans*. **1997**, 919.
9. 2,3-Dihydroamentoflavone: (a) Das, B.; Mahendar, G.; Rao,Y. K.; Prabhakar, A.; Jagadesh, B. *Chem. Pharm. Bull*. **2005**, *53*, 135. Bartramiaflavone: (b) Basile, A.; Sorbo, S.; Lopez-Saez, J. A.; Cobianchi, R. C. *Phytochemistry* **2003**, *62*, 1145. Rubastaflavone: (c) Chen, J. J.; Duh, C.Y.; Chen, J. F. *Planta Med*. **2005**, *71*, 659. Dichamanetin: (d) Anam, E. M.; Ekpa, O. D.; Gariboldi, P.V.; Morah, F. N. I.; Dosunmu, M. I. *Indian J. Chem. Sect. B* **1993**, *32*, 1051. (e) Dasgupta, B.; Burke, B. A.; Stuartt, K. L. *Phytochemistry* **1981**, *20*, 153. (f) G. Z.; Tan, N. H.; Hao, X. J.; Mu, Q. Z.; Li, R.T. *Bioorg. Med. Chem*, *Lett*.**2006**, 16, 6178. (g) Zeng, G. Z.; Pan, X. L.; Tan, N. H.; Xiong, J.; Zhang, Y. M. *Eur. J. Med. Chem. Ther*. **2006**, *41*, 1247.
10. Yshikawa, M.; Xu, F.; Morkawa, Ninimiya, K.; Matsudah. *Biorg. Med. Chem. Lett*. **2003**, *13*, 1045.

11. Anastatin A.; Yoshikawa, M.; Xu, F.; Morikawa, T.; Ninomiya, K.; Matsuda, H. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1045.

12. (a) Tanoguchi, M.; Arimoto, M.; Saika, H.; Yamaguchi, H. *Chem. Pharm. Bull*. **1987**, *35*, 4162. (b) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun*. **1980**, 354. (c) Wang, C. L. J.; Ripka, W. C. *J. Org .Chem*. **1983**, *48*, 2555. (d) Tuchinda, P.; Kumkao, A.; Pohmakotr, M.; Sophasan, S.; Santisuk, T.; Reutraku, V. *Planta Med.* **2006,** *72*, 60.

13. (a) Bringmann, G.; Dreyer, M.; Kopff, H.; Rischer, H.; Wohlfarth, M.; Hadi, H. A.; Brun, R.; Meimberg, H.; Heubl, G. *J. Nat. Prod*. **2005**, *68*, 686. (b) Ponte-sucre, A.; Faber, J. H.; Guider, T.; Kajahn, I.; Pederson, S. E. H.; Schultheis. M.; Bringmann, G.; Moll, H. *Antimicrob. Agents. Chemother*. **2007**, *51*, 188.

14. Jayaprakasha, G. K.; Rao, l. J.; Sakariah, K. K. *Bioorg. Med. Chem*. **2004**, *12*, 5141.

15. *Metal-Catalysed Cross-Coupling Reactions* (eds: de Meijere, A.; Diederich, F.), Wiley- VCH, Weinheim **2004**.

16. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. R. *J. Am. Chem. Soc*. **2005**, *127*, 4685.

17. (a) Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc*. **1980**, *102*, 3534. (b) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem*. **1983**, *61*, 688.

18. Review of [3+3] Cyclisations: Feist, H.; Langer, P. *Synthesis*. **2007**, 327.

19. Review of 1,3- bis(trimethylsilyloxy)-1,3-dienes: Langer, P. *Synthesis* **2002**, 441.

20. For a review of copper-assisted nucleophilic substitution reactions of aryl halides, see: (a) Lindley, J. *Tetrahedron.* **1984**, *40*, 1433. For seleceted examples see: (b) Okuro, K.; Furuune, M.; Miura, M.; Nomura. M. *J. Org. Chem*. **1993**, *58*, 7606. (c) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

21. Jiang, Y.; Wu, N.; Wu, H.; He, M. *Synlett* **2005**, 2731.

22. CCDC-xxx contain all crystallographic details of this publication which are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax:(+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

23. (a) Becalli, E. M.; G.; Brogeni, G.; Maltinelli, S. *Chem. Rev*. **2007**, *107*, 5318. (b) Muzart, J. *J. Mol. Catal. A* **2007**, *276*, 62. (c) Zeni, G.; Larock. R. C. *Chem. Rev*. **2006**, *106*, 4644. (d) Buchwald, S. l.; Mauger, C.; Mignani, G.; Scholz, U. *Ad. Synth. Catal*. **2006**, *348*, 23. (e) Cacchi, S.; fabrizi, G. *Chem. Rev*. **2005**, *105*, 2873.

24. (a) *Handbook of organopalladium chemistry for organic synthesis*, Negishi, E, ed., Wiley-inerscience: New York, **2002**. (b) Tsujji, J: *Palladium reagents and catalysts. Innovations in organic synthesis*, Wiley: New York, **1995**.

25. For recent review, see: Punniyamurthy, s.; Iqbal, J. *Chem. Rev*. **2005**, 2329.

26 Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437.

27. (a) *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Hermann. W. A., Ed.; Wiley-VCH: Wieheim, **1996**. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi. E.; de Meijere, A., Eds. Wiley: New York **2002**. (c) *Cross-coupling Reactions*; Miyaura, N., ed.; Springer: Berlin, **2000**. (d) *Metal catalysed cross coupling reactions,* 2nd ed.; Diedrich, F., de Meijere, A., eds.; Wiley-VCH: Weiheim, **2004**. (e) *Transition Metals for Organic Synthesis; Building Blocks and fine chemicals*, 2nd eds.; Beller, M.; Bolm, C., Eds; Wiley-VCH: Weinheim, **2004**. (f) Tsuji, J. *Palladium reagents and catalysis, innovations in organic synthesis*; Wiley: New York, **1995**.

28. Noriyashu, K.; Quinetta, S.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem***. 2002**, *67*, 5553.

29. (a) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett*. **2008**, *10*, 1333. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc*., **2006**, *128*, 4101.

30. Netherton, M. R.; Fu, G. C. *Org. Lett*. **2001**, *3*, 4295.

31. Bhal, A.; Grahn, W.; Stadler, S.; Freiner, F.; Brauchle, C.; Reisner, A.; Jones, P. G. *Angew. Chem., Int. Ed. Engl*.**1995**, *34*, 1485.

32. Sabat, M.; Johnson, C. R. *Org. Lett*. **2000**, *8*, 1089.

33. Bringmann, G.; Götz, R.; Keller, P. A.; Walter, R.; Boyd, M. R.; Lang, F.; Garcia, A.; Walsh, J. J.; Tellito, I.; Bhaskar, K. V.; Kelly, T. R. *J. Org. Chem*. **1998**, *63*, 100.

.

34. Nicolaou, K. C.; Ramanjulu, J. M.; Natarajan, S.; Brase, S.; Li, H.; Boddy, C. N. C.; Rubsam, F. *Chem. Commun*. **1977**, 1899.

35. Cheng, F.; Adronov, A. *Chem. Mater*. **2006**, *18*, 5389.

36. Bluin, N.; Michaud, A.; Gendron, D.; Wakim, S.; Blair, E.; Neagu-Plesu, R.; Belletete, M.; Drocher, G.; Tao, Y.; Lecrec, M. *J. Am. Chem. Soc.* **2008**, *130*, 732.

37. Beletskaya, Irina P.; Cheprakkov, Andrei V. *Chem. Rev.* **2000**, *100*, 3009.

38. Kurti, L.; Czako, B. *Strategies and Applications of Named Reactions in Organic Synthesis*, Burlington, M. A. Elsevier, Inc., **2005**, 196.

39. Cabri, W.; Candiani, I.; DeBernardis, S.; Francalanci, F.; Penco, S. *J. Org. Chem*. **1991**, *56*, 5796.

40. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113,* 1417.

41. Amatore, Christian; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

42. Penning T. D.; Talley J. J.; Bertenshaw S. R.; Carter J. S.; Collins P. W.; Docter S.; Graneto M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins W. E.; Seibert K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997,** *40*, 1347.

43. Rinaldi-Carmona, M.; Barth, F.; Héaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Néliat, G.; Caput, D.; Ferrara, P.; Soubrieé, P.; Breliére, J. C.; Le Fur, G. *FEBS Lett.* **1994,** *350*, 240.

44. Baud, F. J.; Bismuth, C.; Garnier, R.; Galliot, M.; Astier, A.; Maistre, G.; Soffer, M. *Clin. Toxicol.* **1986**, *24*, 463.

45. (a) Van Herk, T.; Brusse, J.; van den Nieuwendijk, A. M. C. H.; van der Klein, P. Oxford Univeristy Press: Oxford, **2000.** (b) Dannhardt, G.; Laufer, S. *Curr. Med. Chem***. 2000**, *7*, 1101. (c) Carty, T. J.; Marfat, A. *Curr. Opin. Antoinflamm. Immunomod. Invest. Drugs* **1999**, *1*, 89. (d) Niclolaou, K. C.; Pratt, B. A.; Arseniyadis, S.; Wartmann, M.; O, Brate, A.; Giannakakaou, P. *ChemMedChem*. **2006**, 1, 41.

46. (a) *The Chemistry of Heterocyclic Compounds*, Grunanger, P.; Vita-Finzi, P., eds, JhonWilley, New York, **1991**, vol. *49*, Part 1. (b) Aggarwal, V. K.; de Vincente, J.; Bonnert, R. V. *J. Org. Chem*. **2003**, *68*, 5381. (c) Deng, X.; Mani, N .S. *Org .Lett*. **2006**, *8*, 3505.

47. *Handbook of Heterocyclic Chemistry*, Katritzky, A. R.; Pozharskii, A. F., eds, Pergamon, 2000. (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675. (c) Humphries, P. A.; Finefield, J. M. *Tetrahedron Lett.* **2006**, *47*, 2443. (d) Bishop, B. C. *Synthesis* **2004**, 43. (e) Ahmed, S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487.

48. For a review of cyclisation reactions of dianions in organic synthesis, see: (a) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125. For original papers, see: (b) Matsumura, N.; Kunigihara, A.; Yoneda, S. *Tetrahedron Lett*. **1983**, *24*, 3239. (c) Matsumura, N.; Kunigihara, A.; Yoneda, S. *Tetrahedron Lett*. **1984**, *25*, 4529. (d) Duncan, D. C.; Trumbo, T. A.; Almquist, C. D.; lentz, T. A.; Beam, C. F. *J. Heterocyclic Chem*. **1987**, *24*, 555. (e) Beam, C. F.; Reames, D. C.; Harris, C. E.; Dasher, I. W.; Hollinger, W. M.; Shealy, N. L.; Sandifer, R. M.; Perkin, M.; C. R. *J. Org. Chem*. **1975**, *40*, 514. (f) Presson, T.; Nielson, J. *Org. Lett*. **2006**, *8*, 3219. (g) Dang, T. T.; Dang, T. T.; Rienke, H.; Fischer, C.; Langer, P. *Tetrahedron*. **2008**, *64*, 2207.

49. Ranatunge, R. R.; Augustiniak, M.; Bandarage, U. K.; R. A.; Ellis, J. L.; Garvey,D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Schroder, J. D.; Shumway, M. J.; Tam, S. W.; Trocha, A. M.; Young, D. V. *J. Med. Chem*. **2004**, *47*, 2180.

50. For the review of cross-coupling reactions of polyhalogenated heterocycles, see (a) Shroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, 61, 2245. (b) Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

51. For studies from our laboratories, see: (a) Dang, T. T.; Ahmad, R.; Reinke, H.; Langer, P. *Tetrahedron Lett*. **2008**, *49*,1698. (b) Dang, T. T.; Villinger, A.; Langer, P. *Adv. Synth. Catal*. **2008**, *350*, 2109. (c) Hussain, M.; Nguyen, T. H.; Langer, P. *Tetrahedron Lett*. **2009**, *50*, 3929. (d) Tengho Toguem, S. M.; Hussain, M.; Villinger, A.; Langer, P. *Tetrahedron Lett*. **2009**, *50*, 4962. (e) Dang, T. T.; Rasool, N.; Villinger, A.; Langer, P. *Adv. Synth. Catal*. **2009**, *351*, 1595.

52. Iddon, B.; Toender, J. E.; Hosseini, M.; Begtrup, M. *Tetraedron*. **2007**, *63*, 56.

53. For pharmacological relevant 3,4,5-tribromopyrazoles, see: (a) Meanweel, N. A.; Rosenfel, M. J.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. *J. Med. Chem*. **1992**, *35*, 389. For pharmalogical relevant 3,5-diaryl-4-bromopyrazoles,

see: (b) Bondavalli, F.; Bruno, O.; Ranise, A.; Schenone, P. *Farmaco* **1988**, *43*, 725. Only 5-aryl-3,4-dibromopyrazoles have been reported so far: (c) Trofimenko, S.; Yap, G. P. A.; Jove, F. A.; Claramunt, R. M.; Garcia, M. A.; Santa Maria, M. D.; Alkorta, I.; Elguero, J. *Tetrahedron* **2007**, *63*, 8104.

54. Grandberg, A. *J. Gen. Chem. USSR (Engl. Transl)* **1963**, *33*, 503; *Zhurnal Obshchei Khimii* **1963**, *33*, 511.
55. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 3358.
56. (a) Shrimali, S. S.; Joshi, B. C.; Kishore, D. *J. Indian Chem. Soc.* **1988,** *65*, 438. (b) Upadhyay, P. S.; Vansdadia, R. S.; Baxi, A. J *Indian J. Chem., Sect. B* **1990,** *29*, 793.
57. Teshirogi, I.; Matsutani, R.; Shirahase, K.; Fujii, K.; Yoshida, T. *J. Med. Chem.* **1996**, *39,* 5183.
58. Paulini, R.; Lerner, C.; Diederich, F.; Jakob-Roetne, R.; Zuercher, G.; Borroni. E. *Helv. Chim. Acta* **2006**, *89*, 1856.
59. (a) de Benedetti, P. G.; Iarossi, D.; Menziani, C.; Caiolfa, V.; Frassineti, C.; Cennamo, C. *J. Med. Chem.* **1987,** *30*, 459 (b) de Benedetti, P. G.; Iarossi, D.; Folli, U.; Frassineti, C.; Menziani, M. C.; Cennamo. C. *J. Med. Chem.* **1989**, *32*, 2396.
60. Sircar, I.; Hoefle, M.; Maxwell, R. E.; *J. Med. Chem.* **1983,** *26,* 1020.
61. Markley, L. D.; Tong, Y. C.; Dulworth, D. L.; Steward, C. D.;Goralski. *J. Med. Chem.* **1986**, *29*, 427.
62. Wright, J.; Bolton, G.; Creswell, M.; Downing, D.; Georgic, L. *Bioorg. Med. Chem. Lett.* **1996**, *6,* 1809.
63. (a) Neamati, N.; Mazumde,. A.; Zhao, H.; Sunder, S.; Burke, Jr. T. R.; Schultz, R. J.; Pommier, Y. *Antimicrob. Agents Chemother.* **1997,** *41*, 385. (b) Chan, J. H.; Hong, J. S.; Hunter, R. N.; Orr, G. F.; Cowan, J. R.; Sherman, D. B.; Sparks, S. M.; Reitter, B. E.; Andrews, C. W.; Hazen, A.; Richard, J.; Clair, M. S. *J. Med. Chem.* **2001,** *44,*1866 (c) Tagat, J. R.; McCombie, S. W.; Steensma, R. W.; Lin, S. I.; Nazareno, D. V.; Baroudy, B.; Vantuno, N.; Xu, S.; Liu, J. *Bioorg. Med. Chem. Lett.* **2001**,*11,* 2143.
64. Stanton, J. L.; Cahill, E.; Dotson, R.; Tan, J.; Tomaselli, H. C.; Wasvary, J. M.; Stephan, Z. F.; Steele, R. E. *Bioorg. Med. Chem. Lett.* **2000,** *10*, 1661.

65. (a) Kozlowski, J. A.; Zhou, G.; Tagat, J. R.; Lin, S. I.; McCombie, S. W. ; Ruperto, V. B.; Duffy, R. A.; McQuade, R. A.; Crosby, G.; Taylor, L. A.; Billard, W. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 791.

66. Sasse, A.; Ligneau, X. ; Sadek, B. ; Elz, S. ; Pertz, H. H. ; Ganellin, C. R. ; Arrang, J. M.; Schwartz, J. C.; Schunack, W.; Stark, S.; *Arch. Pharm. (Weinheim Ger.)* **2001**, *33*, 45.

67. Langler, R. F.; Paddock, R. L.; Thompson, D. B.; Crandall, I.; Ciach, M.; Kain, K. C. *Aust. J. Chem.* **2003,** *56*, 1127.

68. Clark, R. D.; Jahangir, A.; Severance, D.; Salazar, R.; Chang, T.; Chang, D.; Jett, M. F.; Smith, S.; Bley, K. *Bioorg. Med. Chem. Lett.* **2004,** *14,* 1053.

69. Lavey, B. J.; kozlowski, J. A.; Hipkin, R. W.; Gonsiork, W.; Lundell, D. J.; Piwinski, J. J.; Narula, S.; Lunn, C. A. *Bioorg. Med. Chem. Lett*. **2005**, *15,* 783.

70. Joseph, J. K.; Jain, S. L.; Sain, B. *Synth. Commum*. **2006**, *36*, 2743.

71. (a) Chen, D. W.; Kubiak, R. J.; Ashley, J. A.; Janda, K. D. *J. Chem. Soc. Perkin Trans.1.* **2001**, *21*, 2796. (b) Marquie, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurse, J. R. *J. Org. Chem*.**2001**, *66*, 421. (c) Rephchet, S.; Roux, C. Le.; Dubac, J. *Tetrahedron Lett*. **1999**, *40*, 9233. (d) Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Pourmousavi, S. A.; Mirjalili, B. B. F.; Ruoho, A. E. *Phosphorous, Sulfure, Silicon Relat. Elem*. **2005**, *180*, 2029.

72. Woroshzow, V.; Kutschkarow, V. *Zh. Obshch. Khim*. **1994**, *19*, 1943; *Chem. Abstr*. **1950**, 1922.

73. Zhu, W.; Ma, D. *J. Org. Chem*. **2005**, *70*, 2696.

74. Bandgar, B. P.; Bettigeri, S. V.; Phopase, *J. Org. Lett*. **2004**, *6*, 2105.

75. Huang, F.; Batey, R. A. *Tetrahedron* **2007**, *63*, 7667.

76. (a) Erian, A. W.; Issac, Y.; Sherif, S. M.; Mahmoud, F. F. *J. Chem. Soc., Perkin Trans.1* **2000**, 3686 (b) Ogura, K.; Takeda, M.; Xie, J. R.; Akazome, M.; Matsumoto, S. *Tetrahedron Lett*. **2001**, *42*, 1923. (c) Matsumoto, S.; umazawa, K.; Ogura, K. *Bull. Chem. Soc. Jpn*. **2003**, *76*, 2179. (d) Bianchi, L.; Dellerba, C.; Maccagno, M.; Magnoli, A.; Novi, M.; Petrillo, G.; Sancassan, F.; Tavani, C. *J. Org .Chem*. **2003**, *68*, 5254.

77. *Römpp Lexikon Naturstoffe* (W. Steglich, B. Fugmann, S. Lang-Fugmann, eds.), Thieme, Stuttgart: **1997**.

78. (a) Gilchrist, T. L.Heterocyclic Chemistry; Longman: Harlow, **1997**; (b) Li. J. J. *Name Reactions in Heterocyclic Chemistry*; John Wiley & Sons: Hoboken, **2005**.

79. Hussain. I.; Yawer, M. A.; Lalk, M.; Lindequist, U.; Villinger, A.; Fischer, C.; Langer. P. *Bioorg. Med. Chem.* **2008**, *16*, 9898.

80. Riahi, A.; Wurster, M.; Lalk, M.; Lindequist, U.; Langer, P. *Bioorg. Med. Chem.* **2009**, *17*, 4323.

81. Scriven, E. F.; V. *Pyridines and their Benzo Derivatives: (ii) Reactivity at Ring Atoms*, *Vol. 2*, Part 2A, Chapt. 2.05 (Boulton. A. J, McKillop. A, eds.) in *Comprehensive Heterocyclic Chemistry* (Katritzky. A. R, C. W Rees, eds.); Elsevier Science, Oxford, **1984**, 165.

82. For recent pyridine syntheses, see: (a) Dash, J.; Lechel, T.; Reissig, H. U. *Org. Lett* **2007**, *9*, 5541, and references cited therein. (b) Andersson. H, Almqvist. F, Olsson. R. *Org. Lett.* **2007**, *9*, 1335.

83. For reviews of cross-coupling reactions of polyhalogenated heterocycles, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Schnürch, M.; Khan. A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

84. (a) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681; (b) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251; (c) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351; (d) Ji, J.; Li. T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611; (e) Jiang, W.; Guan, J.; Macielag, M. J.; Zhang, S.; Qui, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2005**, *48*, 2126; (f) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

85. (a) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem.* **2002**, *67*, 443; b) Haino, T.; Araki, H.; Yamanaka, Y.; Fukazawa, Y. *Tetrahedron Lett.* **2001**, *42*, 3203.

86. (a) Sandee, A. J.; Williams, C. K.; Evans, N. R.; Davies, J. E.; Boothby, C. E.; Koehler, A.; Friend, R. H.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 7041. (b) Vice, S.; Bara, Bauer. T.; Evans, S.; Ford, C. A. L; Josien, H.; McCombieMiller, S. M.; Nazareno, D.; Palani, A.; Tagat, J. *J. Org. Chem.* **2001**, *66*, 2487. (c) Couve-Bonnaire, S.; Carpentier, J. f.; Mortreux, A. ;

Castanet, Y. *Tetrahedron Lett.* **2001**, *42*, 3689. (d) Frampton, M. J.; Namdas, E. B.; Lo, S. C.; Burn, P. L.; Samuel, I. C. W. *J. Mater. Chem.* **2004**, *14,* 2881. (e) Palucki, M.; Hughes, D. L. ; Yasuda, N.; Yang, C.; Reider, P. J.; *Tetrahedron Lett.* **2001**, *42*, 6811. (f) Simoni, D.; Giannini, G. ; Baraldi, P. G.; Romagnoli, R.; Roberti, M.; Rondanin, R.; Baruchello, R.; Grisolia, G.; Rossi, M.; Mirizzi, D. F.; Invidiata, F. P.; Grimaudo, P.; Tolomeo, M. *Tetrahedron Lett.* **2003**, *44,* 3005.

87. (a) Fang, Y. Q.; Hanan, G. S. *Synlett* **2003**, 852. (b) Tilley, J. W.; Zawaoiski, S. *J. Org. Chem.* **1988**, *53*, 386. (c) Simkovsky, N. M.; Ermann, M.; Roberts, S. M.; Parry, D. M.; Baxter. A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1847.
88. (a) Nakano, Y.; Ishizuka, K.; Muraoka, K.; Ohtani, H.; Takayama, Y.; Sato, F. *Org. Lett.* **2004**, *6*, 2373. (b) Gelman, D.; Tsvelikhovsky, D, G. A.; Molander, J. Blum. *J. Org. Chem.* **2002**, *67*, 6287. (c) Hartner, F.W.; Hsiao, Y.; Eng, K.K.; Rivera, N.R.; Palucki, M.; Tan, L.; Yasuda, N.; Hughes, D.L.; Weissman, D. Zewge, T. King, D. Tschaen, R. P. Volante, *J. Org. Chem.* **2004**, *69*, 8723.
89. (a) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, J. *Tetrahedron* **2002**, *58*, 4429. (b) Dumouchel, S.; Mongin, F.; Trecourt, F.; Queguiner, G. *Tetrahedron Lett.* **2003**, *44*, 3877.
90. Handy, S. T.; Wilson, T.; Muth. A. *J. Org. Chem.* **2007**, *72*, 8496.
91. (a) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981. (b) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2002**, *344*, 172. (c) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495. (d) Iyer, S.; Kulkarni, G. M.; Ramesh, C. *Tetrahedron* **2004**, *60*, 2163. (e) Parrain, J. L.; Duchene, A.; Quintard, J. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 187. (f) Berthiol, F.; Feuerstein, M.; Doucet, H. ; Santelli, M. *Tetrahedron Lett.* **2002**, *43,* 5625. (g) Li, J. H.; Wang, D. P.; Xie, Y. X.; *Synthesis* **2005**, 2193. (h) Cui, X.; Li, Z.; Tao, C. Z.; Xu, Y.; Li, J.; Liu, L.; Guo, Q. X. *Org. Lett.* **2006**, *8*, 2467. (i) Polshettiwar, V.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron* **2007**, *63*, 6784.
92. Li, H. J.; Wang, L. *Eur. J. Org. Chem*. **2006**, 5099.

Data for compound 6b Chapter 1:

Identification code	AS-107	
Empirical formula	$C_{12}H_{14}O_2$	
Formula weight	190.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$^{-}P2_1/m^{-}$	
Space group (Hall)	-P 2yb	
Unit cell dimensions	a = 506(3) Å	α = 90°.
	b = 6.638(5) Å	β = 108.88(3)°.
	c = 11.126(5) Å	γ = 90°.
Volume	524.5(5) $Å^3$	
Formula Unit (Z)	2	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F (000)	204	
Crystal size	0.37 x 0.28 x 0.28 mm^3	
Reflections collected	4929	
Independent reflections	999 [R(int) = 0.0754]	
Absorption correction	Multiscan	
Absorption coefficient (μ)	.081 mm^{-1}	
Final R indices [I>2σ(I)]	R1 = 0.0656, wR2 = 0.1543	
R indices (all data)	R1 = 0.0525, wR2 = 0.1447	

Data for compound 6v Chapter 1:

Identification code	AS-106
Empirical formula	$C_{18}H_{20}O_3$
Formula weight	284.34
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	$^{-}C2_1/c^{-}$
Space group (Hall)	-C2yc
Unit cell dimensions	a = 21.224(5) Å

		$\alpha = 90°$.
	b = 7.7457(17) Å	$\beta = 100.535(14)°$.
	c = 18.668(5) Å	$\gamma = 90°$.
Volume	3017.3(12) $Å^3$	
Formula Unit (Z)	8	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F (000)	1216	
Crystal size	0.51 x 0.21 x 0.18 mm^3	
Reflections collected	25656	
Independent reflections	9657 [R (int) = 0.0754]	
Absorption correction	Multiscan	
Goodness-of-fit on F^2	1.068	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0581, wR2 = 0.1302	
R indices (all data)	R1 = 0.0443, wR2 = 0.1218	

Data for compound 11a Chapter 2:

Identification code	AS-284(b)	
Empirical formula	$C_{19}H_{17}O_2BrN_2$	
Formula weight	385.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c^-$	
Space group (Hall)	P 2ybc-	
Unit cell dimensions	a = 9.7394(5) Å	$\alpha = 90°$.
	b = 19.122(11) Å	$\beta = 96.902(3)°$.
	c = 9.6321(5) Å	$\gamma = 90°$.
Volume	1715.06(16) $Å^3$	
Formula Unit (Z)	4	
Density (calculated)	1.282 Mg/m^3	
F (000)	784	
Crystal description	Block	
Crystal colour	Colourless	
Crystal size	0.25 x 0.20 x 0.8 mm^3.	
Reflections collected	19267	

Independent reflections	4975 [R(int) = 0.0754]
Absorption correction	Multiscan
Absorption coefficient (μ)	2.410 mm^{-1}
Final R indices [I>2σ(I)]	R1 = 0.0765, wR2 = 0.0962
R indices (all data)	R1 = 0.0409, wR2 = 0.0866

Data for compound 16e Chapter 3:

Identification code	AS-236
Empirical formula	$C_{26}H_{16}O_2F_6S_2$
Formula weight	506.45
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	P-1-
Space group (Hall)	P- 1
Unit cell dimensions	a = 6.984(3) Å α = 107.228°(7). b = 12.824(7) Å β = 103.169(10)°. c = 13.600(5) γ = 100.03(15)°.
Volume	1094(9) $Å^3$
Formula Unit (Z)	2
Density (calculated)	1.282 Mg/m^3
Absorption coefficient	0.222 mm^{-1}
F (000)	516
Crystal description	Block
Crystal colour	Colorless
Crystal size	0.85 x 0.35 x 0.13 mm^3
Reflections collected	200371
Independent reflections	5639 [R(int) = 0.0754]
Absorption correction	Multiscan
Absorption coefficient (μ)	.081 mm^{-1}
Goodness-of-fit on F^2	1.045
Final R indices [I>2σ(I)]	R1 = 0.0522, wR2 = 0.1229
R indices (all data)	R1 = 0.0426, wR2 = 0.1175

Data for compound 21d Chapter 4:

Identification code	AS-201	
Empirical formula	$C_{22}H_{28}N_2O_4$	
Formula weight	408.48	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	-P-1	
Space group (Hall)	-P-1	
Unit cell dimensions	a = 5.761(3) Å	α=87.926°(15).
	b = 9.751(5) Å	β=79.371°(17).
	c = 10.180(5) Å	γ = 78.22°(3).
Volume	550.2(5) $Å^3$	
FormulaUnit (Z)	1	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient (μ)	0.084 mm^{-1}	
F(000)	218	
Crystal size	0.33 x 0.19 x 0.05 mm^3	
Reflections collected	10031	
Independent reflections	2495 [R (int) = 0.0754]	
Absorption correction	Tmin 9728, Tmax9958	
Final R indices [I>2σ(I)]	R1 = 0.0655, wR2 = 0.1181	
R indices (all data)	R1 = 0.0441, wR2 = 0.1109	

Asad Ali

Date/Place of Birth: Febraury 20, 1982 / Mardan (Pakistan)

Publications:

1. ***Asad Ali***, Ihsan Ullah, Muhammad Sher, Alexander Villinger, Peter Langer*, *Tetrahedron Lett.* **2009**, *50*, 118-120. Synthesis of Sterically Encumbered Biaryls based on a ′Copper(I)-Catalyzed Arylation / [3+3] Cyclocondensation′ Strategy.
2. Ihsan Ullah, Muhammad Sher, **Asad Ali**, Mohannad Shakoor, Christine Fischer, Peter Langer. Chelation control in formal 3+3 cyclisation reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-ones. One pot synthesis of 3-aryl-3,4-Dihydroisocumarines. *Tetrahdron* **2010**, *66,* 1874-1884.

3. ***Asad Ali***, Rasheed Ahmad Khera, Farooq Ebad, Munawar Hussain, Peter Langer. Synthesis of bis(diaryl)sulfones by site selective Suzuki-Miyaura reactions of 2,4-bis(trifluoromethanesulfonyloxy)diphenylsufone. *Synlett*. **2010**, 731-734.

4. ***Asad Ali*,** Munawar Hussain, Imran Malik, Peter Langer. Heck cross-coupling reactions of dibrominated pyridines. *Helv. Chem. Acta*. **2010**, accepted.

5. Rasheed Ahmad Khera, ***Asad Ali***, Jovana Tatar, Farooq Ibad, Peter Langer. Synthesis of arylated pyrazoles by site-selective Suzuki-Miyaura reactions of 3,4,5-tribromo-1-*H*-pyrazole. *Synlett* **2010**, accepted.

6. Farooq Ibad, Munawar Hussain, Obaid-Ur-Rehman, ***Asad Ali***, Peter Langer. One-pot synthesis of unsymmetrical 2,3-diarylindoles by site selective Suzuki Miyaura reactions of *N*-methyl 2,3-dibromoindole**.** *Synlett* **2010**, *3* 411-414.

7. Muhammad Sher, ***Asad Ali***, Villinger, Peter Langer. Synthesis of 3-aryl -3,3-dihydrisocuomarines by regioselective domino 3+3 cyclisation/lactonisation reactions of 1,3 bis(silyloxy)-1,3 butadienes with 1-hydroxy-5-silyloxy-4-ene-3-ones. *Tetrahedron Lett.* **2008**, *49,* 37.
8. Obaid-Ur-Rahman, Farooq Ibad, Muhammad Nawaz, ***Asad Ali***, Peter Langer. Synthesis of 2,4-diarylnaphthoates by site-selective Suzuki-Miyaura reaction. *Tetrahedron Lett*. **2010**, *51*, 1541-1544.
9. Imran Malik, Munawar Hussain, ***Asad Ali***, Christine Fischer, Peter Langer. Synthesis of disubstituted pyrazines and quinoxilines by Heck cross coupling reaction of 2,3-dichloropyrazines and 2,3-dichloroquinoxalines. Infuence of temperature on the product distribution. *Tetrahedron* **2010**, *66,* 1637-1642.
10. Ihsan Ullah, Muhammad Sher, ***Asad Ali***, Rasheed Ahmad Khera, Muhammad Nawaz, Mohanad Shakoor,Inam Iqbal, Muhammad Imran, Alexander Villinger, Christine Fischer, Peter Langer. Synthesis of sterically encumberd biaryls based on Copper(1)- Catalysed arylation/[3+3] cyclocondensation strategy. *Tetrahedron*. **2010**, *66*, 3824-3835.

Declaration/Erklärung

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

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

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

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

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Asad Ali