

# **Transition Metal-Catalyzed Nucleophilic Substitution at Thiophene Halides**

## **Dissertation**

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*“Die Theorie ist eine Vermutung mit Hochschulbildung.”*

James “Jimmy” Earl Carter

*Im Gedenken an meinen Großvater,  
der immer an meine Fähigkeiten geglaubt hat  
(\*31.12.1924 †01.10.2007),  
und meinen geliebten Bruder.  
(\*30.03.1968 †11.11.2008).*



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**Abbreviations**

$\mu$ w	Microwave
AIBN	Azabisisobutyronitrile
AM1	Amplitude modulation
APCI	Atmospheric pressure chemical ionization
BCO	Bis(cyclohexanone)oxalyldihydrazone
BenzoEDOT	Benzo[ <i>e</i> ]thieno[3,4- <i>b</i> ][1,4]dioxine
BINAP	2,2'-Bis-diphenylphosphanyl-[1,1']binaphthalenyl
Boc	<i>tert</i> -Butyl oxycarbonyl
CI	Chemical ionization
CNB	2-Chloronitrobenzene
CPMV	Cowpea mosaic virus
CV	Cyclic voltammetry
DABCO	1,4-Diazabicyclo-[2.2.2]-octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethylazadicarboxylate
DEE	Diethylether
DFBN	3,4-Difluorobenzonitrile
DIAD	Di- <i>iso</i> -propyldiazacarboxylate
DIEA	Di- <i>iso</i> -propylethylamine
DMA	<i>N,N</i> -Dimethylacetamide
DME	Dimethoxyethane
DMEDA	<i>N,N'</i> -Dimethylethylenediamine
DMF	<i>N,N</i> -Dimethylformamide
DMPU	Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DPA	9,10-Diphenylanthracene
dpePhos	2,2'-Oxibis(2,1-phenylene)bis(diphenylphosphine)

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DPPA	Diphenylphosphorylazide
dppBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
dppEn	1,2-Bis(diphenylphosphino)ethene
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
DPV	Difference potential voltammetry
EDOT	2,3-Dihydrothieno[3,4- <i>b</i> ][1,4]dioxine
EE	Ethylacetate
EI	Electronical ionization
ESI	Electrospray ionization
ESR	Electron spin resonance
Fc/Fc <sup>+</sup>	Ferrocene/ferricinium couple
FID	Flame-ionization detector
GC	Gas chromatography
GPC	Gel permeation chromatography
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethyl-phosphoric triamide
HMPT	Hexamethyl-phosphorous triamide
HOMO	Highest occupied molecular orbital
HRMS	High-resolution mass spectrometry
ICT	Intramolecular charge transfer
IR	Infrared spectrum
LUMO	Lowest unoccupied molecular orbital
m.p.	Melting point
MALDI	Matrix-assisted laser desorption/ ionization
MS	Mass spectrometry
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MTBE	Methyl <i>tert</i> -butyl ether
NBS	<i>N</i> -Bromosuccinimide
NMP	<i>N</i> -Methylpyrrolidone

---

NMR	Nuclear magnetic resonance
ODN	Oligodeoxyribonucleotide
OLED	Organic light emitting diode
PCR	Polymerase chain reaction
PEDOT	Poly-2,3-dihydrothieno[3,4- <i>b</i> ][1,4]dioxine
PEG	Polyethyleneglycole
$pK_a$	Acidity constant
ProDOT	3,4-Dihydro-2 <i>H</i> -thieno[3,4- <i>b</i> ][1,4]dioxepine
PSS	Polystyrenesulfonic acid
<i>p</i> -TSA	<i>para</i> -Toluenesulfonic acid
r.t.	Room temperature
RNA	Ribonucleic acid
ROMP	Ring opening metathesis polymerization
SAM	Self-assembled monolayer
TBAB	Tetrabutylammoniumbromide
TBAHPF	Tetrabutylammonium hexafluorophosphate
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBTA	Tris((1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl)amine
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMHD	2,2,6,6-Tetramethyl-3,5-heptadion
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TOF	Time of flight
TON	Turn over number
UV/vis	Ultra-violet/visible spectrum

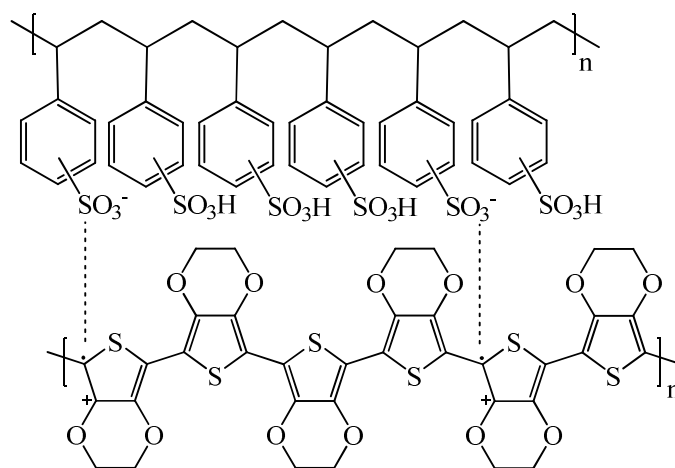
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# Chapter 1

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## **Introduction and Aim of this Thesis**

Shirakawa, MacDiarmid and Heeger discovered in 1977 polyacetylene, which shows after doping high electrical conductivity.<sup>1</sup> This invention was honoured with the Nobel-prize for chemistry in 2000. Since the late seventies a lot of developments were undertaken to build up a conducting polymer, which is processable, stable and produced in simple way. One of the most successful materials was developed by Bayer company in 1989.<sup>2</sup> The polymerization of 3,4-ethylenedioxythiophene (EDOT) yielded a polymer, which changes from semiconducting to conducting state at very low potentials.<sup>3</sup> Electrochemical polymerization in aqueous polystyrenesulfonate (PSS) gave the most stable PEDOT (Chart 1.1) with a conductivity up to 500 S/cm.<sup>4</sup> The dark blue suspension can be used as antistatic, in condensers, electrochromics and OLED's.<sup>5</sup> After drying a transparent, highly conducting and stable film is formed. The colloidal suspension can be purchased in several grades for different applications.

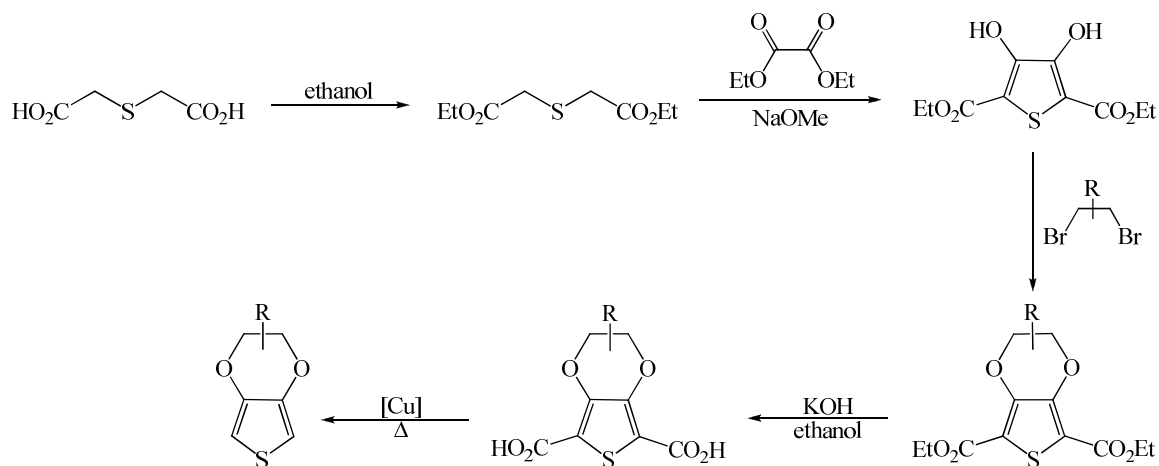


**Chart 1.1** PEDOT:PSS as Clevios P®

To synthesize EDOT several methods were published in the last decades. For nucleophilic substitution the activation of the thiophene ring is necessary. By Williamson ether synthesis of diethyl 3,4-dihydroxythiophene 2,5-dicarboxylate with 1,2-dibromoethanes EDOT derivatives can be produced (Scheme 1.1). Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate was synthesized by Hinsberg.<sup>6</sup> In 1994 Holzer and co-workers applied sodium ethanolate as base in ethanol.<sup>7</sup> However, with potassium carbonate higher yields were obtained.<sup>8</sup> An improvement was made by Heinze *et al.*, who used triethyl amine as base in DMF.<sup>9</sup> After saponification under basic conditions<sup>8, 10</sup> and

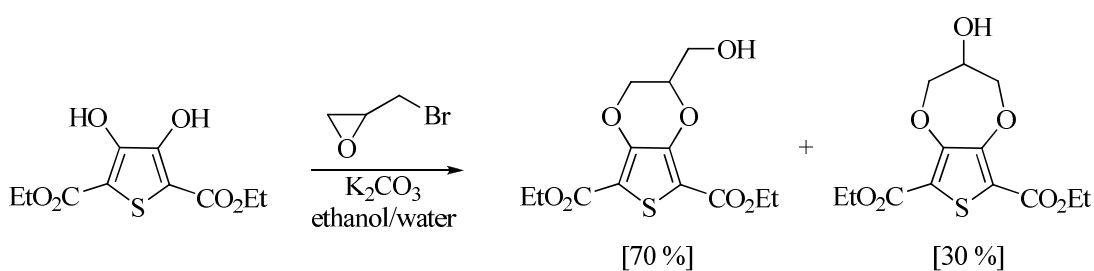


decarboxylation with copper(-salts) at elevated temperatures<sup>8, 10</sup> deactivated monomers were obtained.



**Scheme 1.1** Synthesis of EDOT via Hinsberg thiophene synthesis, Williamson ether synthesis, saponification and decarboxylation.

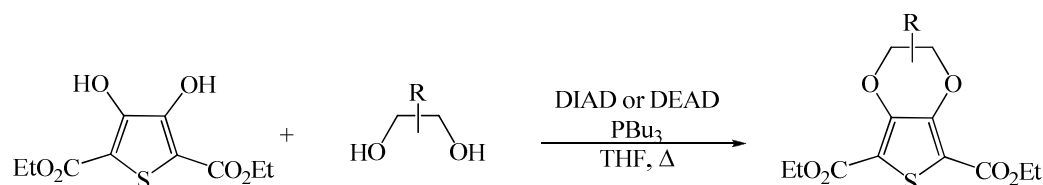
The conversion of diethyl 3,4-dihydroxythiophene 2,5-dicarboxylate with a brominated epoxide led to two different products.<sup>11</sup> Therefore, EDOT was obtained together with propylenedioxythiophene (ProDOT) (Scheme 1.2). After ring closure again harsh conditions are requested for the cleavage of the ester groups.



**Scheme 1.2** EDOT- synthesis with Chevrot's procedure containing epoxide ring-opening.<sup>11</sup>

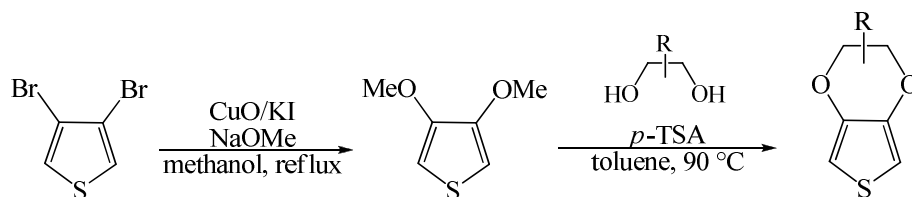
In 2002, Bäuerle *et al.*<sup>12</sup> and Reynolds *et al.*<sup>13</sup> published independently the conversion of diethyl 3,4-dihydroxythiophene 2,5-dicarboxylate with glycols under Mitsunobu conditions (Scheme 1.3). Both di-*iso*-propyldiazocarboxylate (DIAD) and diethyldiazocarboxylate (DEAD) were sufficient as Mitsunobu reagents in THF. Betaine was built using tributylphosphine, which was shown to be more efficient than

triphenylphosphine.<sup>13</sup> Also higher temperatures facilitated the reaction. Reynolds and co-workers obtained diethyl 3,4-ethylenedioxythiophene 2,5-dicarboxylate in 95 % yield after 12 hours. For the first time the synthesis of chiral EDOT derivatives was described by Bäuerle *et al.*



**Scheme 1.3** EDOT derivatives synthesized by Mitsunobu protocol.

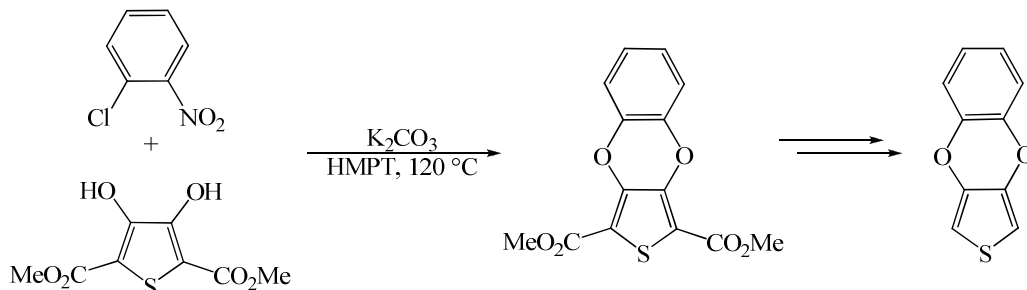
All the methods described above for the formation of EDOT's require activation of the thiophene ring through ester functionality in  $\alpha$ -position. However, harsh conditions are utilized for the cleavage of the ester groups. To overcome this disadvantage Reynolds and Meijer *et al.*<sup>14</sup> developed a transesterification protocol for the synthesis of ProDOT's. In 2004 Bäuerle *et al.*<sup>15</sup> and Hellberg *et al.*<sup>16</sup> used this procedure to obtain EDOT derivatives under mild reaction conditions (Scheme 1.4).<sup>17</sup> 3,4-Dimethoxythiophene was coupled to glycols using *para*-toluene sulfonic acid (*p*-TSA) as catalyst. Also chiral glycols were applied to obtain the corresponding EDOT's without remarkable loss of enantiomeric excess. However, 3,4-dimethoxythiophene prepared from 3,4-dibromothiophene under copper-catalyzed conditions requires long reaction times.<sup>18</sup>



**Scheme 1.4** Preparation of EDOT's with transesterification protocol.

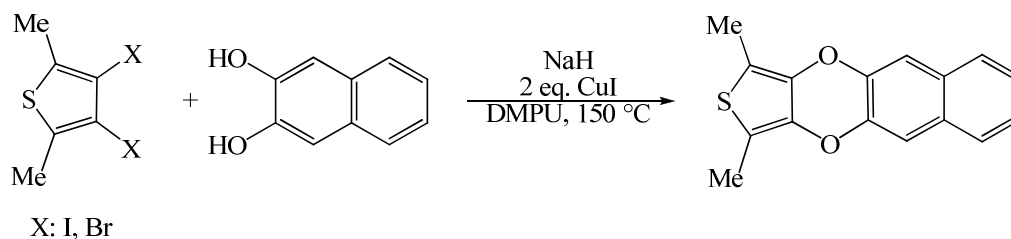
Another efficient polymer contains benzoEDOT as monomeric unit.<sup>19</sup> The synthesis of the monomers is as time-consuming as for EDOT. The conversion of dimethyl 3,4-dihydroxythiophene 2,5-dicarboxylate by nucleophilic substitution with 2-nitrochlorobenzene in HMPT led to the cyclized product in only 40 % (Scheme 1.5).<sup>20</sup> The

following saponification and decarboxylation yielded in 50 % of benzoEDOT. With 3,4-difluorobenzonitrile as nucleophile, benzoEDOT derivatives could be obtained in 65 %. Oxidation of the cyano group gave the acid functionality.



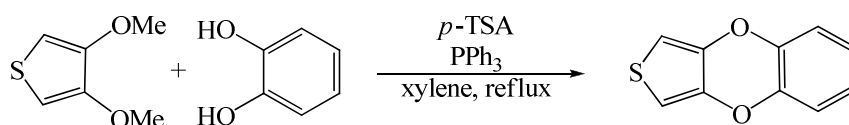
**Scheme 1.5** Synthesis of benzoEDOT developed by Ritter *et al.*<sup>20</sup>

Copper-catalyzed nucleophilic substitution of 2,5-dimethyl-3,4-diiodide and bromide with naphthalene-2,3-diol gave the corresponding naphthalenic dioxinothiophene in only 9 % (Scheme 1.6).<sup>21</sup> Dimethylpropyleneurea (DMPU) was used as non-carcinogenic alternative to HMPA with copper(I)-iodide as catalyst.



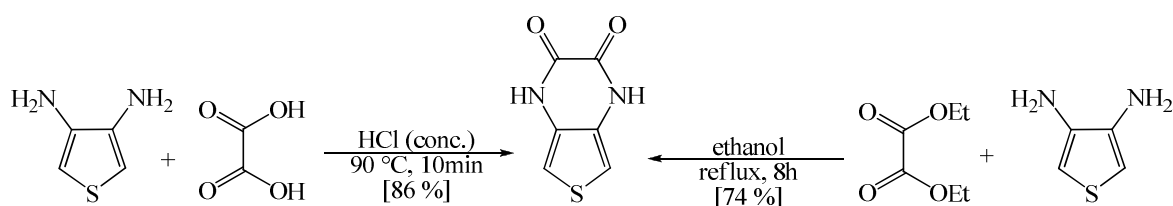
**Scheme 1.6** Copper(I)-catalyzed synthesis of 1,3-dimethylnaphtho[2,3-*e*]thieno[3,4-*b*][1,4]dioxine.<sup>21</sup>

However, in Bayer company benzoEDOT is produced by transesterification protocol from 3,4-dimethoxythiophene and pyrocatechol in 26 % yield (Scheme 1.7).<sup>19</sup> Also several derivatives were synthesized and polymerized.



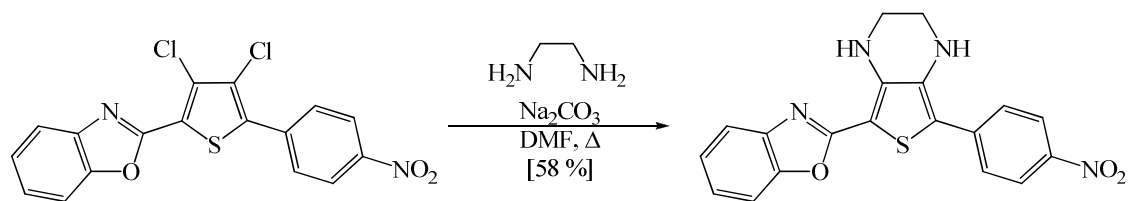
**Scheme 1.7** Synthesis of benzoEDOT established by Bayer researchers.<sup>19</sup>

To tune the electrochemical properties of (semi-)conducting polymers also *N*-analogous EDOT derivatives were investigated. Paulmier *et al.* described the ring closure of 3,4-diaminothiophene with oxalic acid using hydrochloric acid as additive (Scheme 1.8).<sup>22</sup> The use of diethyl oxalate in ethanol gave the same product in slightly lower yield in much longer reaction time. However, aminothiophenes are highly sensitive to air and some effort is necessary to synthesize 3,4-diaminothiophene stabilized as hydrochloric acid salt.<sup>23</sup>



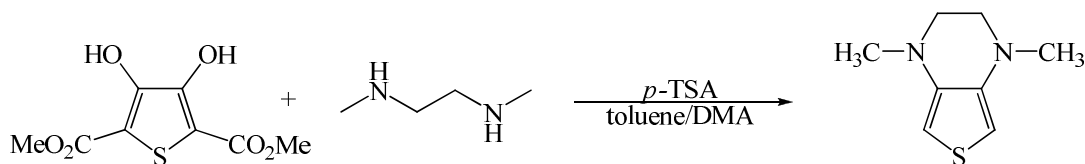
**Scheme 1.8** Synthesis of thieno[3,4-*b*]pyrazine-2,3(1*H*,4*H*)-dione from 3,4-diaminothiophene.

In 1991, Rangnekar *et al.* described the formation of an 3,4-ethylene-diaminothiophene from an activated 3,4-dichlorothiophene.<sup>24</sup> A protocol similar to Williamson ether synthesis was used with sodium carbonate as base (Scheme 1.9). The  $\alpha$ -positions are blocked, therefore, no polymers can be obtained.



**Scheme 1.9** Williamson ether type synthesis of *N*-analogous EDOT derivative.<sup>24</sup>

Another method was patented by Jonas and co-workers (Agfa comp.) using a procedure similar to transesterification protocol.<sup>25</sup> Dimethyl 3,4-dihydroxythiophene 2,5-dicarboxylate was reacted with *N,N'*-dimethyl-1,2-diaminoethane in the presence of *para*-toluene sulfonic acid as catalyst (Scheme 1.10). After acidic work up the already decarboxylated 1,4-dimethyl-1,2,3,4-tetrahydrothieno[3,4-*b*]pyrazine was obtained in 16 % yield.



**Scheme 1.10** Amination protocol for the formation of 1,4-dimethyl-1,2,3,4-tetrahydrothieno[3,4-*b*]pyrazine.<sup>25</sup>

All of the methods described so far require long reaction times and several reaction steps. Because PEDOT derivatives are used in many applications, an effective reaction to synthesize monomers is of interest for industry. Therefore, there is a demand on high yields in as few reaction steps as possible. Also up-scaling to industrial scale is necessary.

Transition metal catalysis is used to facilitate the nucleophilic substitution even on electron-rich aryl halides. Most popular are Buchwald-Hartwig reactions using palladium-catalysts and Ullmann-type couplings with copper complexes as catalyst.

The aim of this thesis is the nucleophilic substitution of (di-)halogenothiophenes to *N*- and *O*-nucleophiles using palladium- and copper-catalysts. These methods should be applied to the synthesis of EDOT derivatives and *N*-analogues in high yields in only one reaction step starting from 3,4-dibromothiophene.

In stepwise grown polymers with alternating donor- and acceptor substituted thiophenes a high degree of intramolecular charge transfer (ICT) was observed, which led into a low band gap.<sup>26</sup>

Concerning the copper-mediated regioselective formation of 1,4-disubstituted 1,2,3-*H*-triazoles from azides and terminal alkynes described by Sharpless *et al.*<sup>27</sup> and Meldal *et al.*<sup>28</sup> a similar donor-acceptor co-polymer should be built up. Therein, triazole serves as acceptor and thiophene as donor. The azide functionality should be introduced *via* an Ullmann-type C-N cross-coupling. Electrochemical characterization of the striven triazole-thiophene co-oligomers and polymers should give structure-property relationships which would help to establish well-defined materials for electronic devices, such as solar cells or OLED's.

## 1.1 References

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## **Chapter 2**

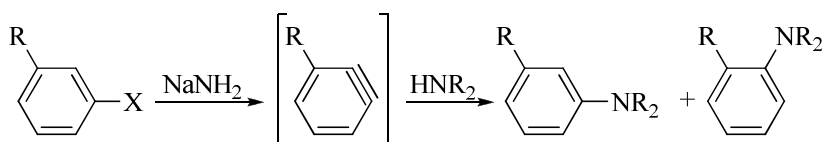
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### **Transition Metal-Catalyzed C-N and C-O Cross-Coupling**

## 2.1 Buchwald-Hartwig Reaction

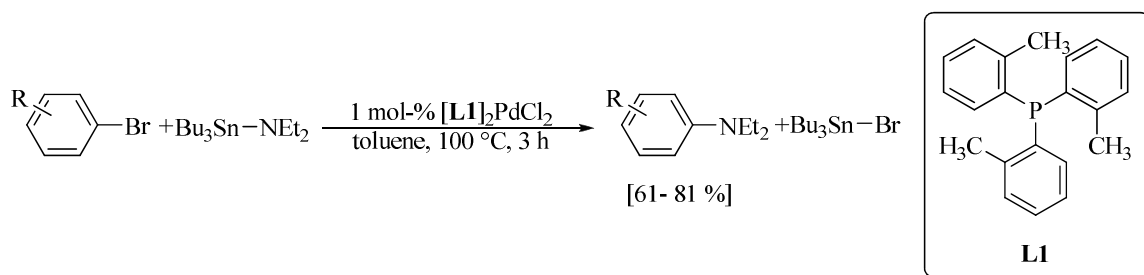
### 2.1.1 Amination Reactions

For first time, Ullmann described in 1903 the *ipso*-substitution of aryl halides with copper catalysts.<sup>1</sup> The aryne chemistry allowed the conversion of an expanded scope of aryl halides into amines.<sup>2</sup> However, the functional group compatibility was low and two regio isomers can be formed by this protocol (Scheme 2.1).



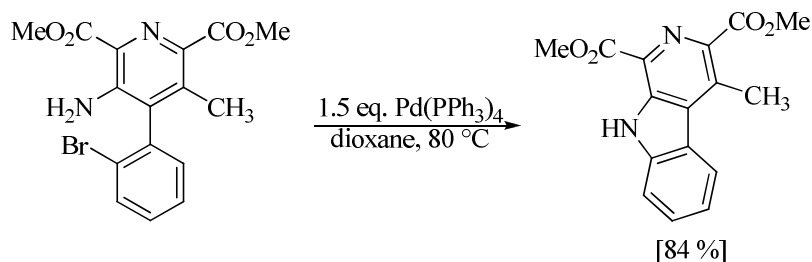
**Scheme 2.1** Amination *via* reduction/ addition procedure.

The first palladium-catalyzed amination starting from aryl halides and stannic amides was published by Migita *et al.* in 1983 (Scheme 2.2).<sup>3</sup> The reaction was limited due to the temperature, water sensitivity and toxic tin reagents. Electron-neutral aryl bromides, vinyl bromides and aryl bromides bearing electron-donating or -withdrawing groups were converted in only low yields. However, this paper was unreferenced for a decade.



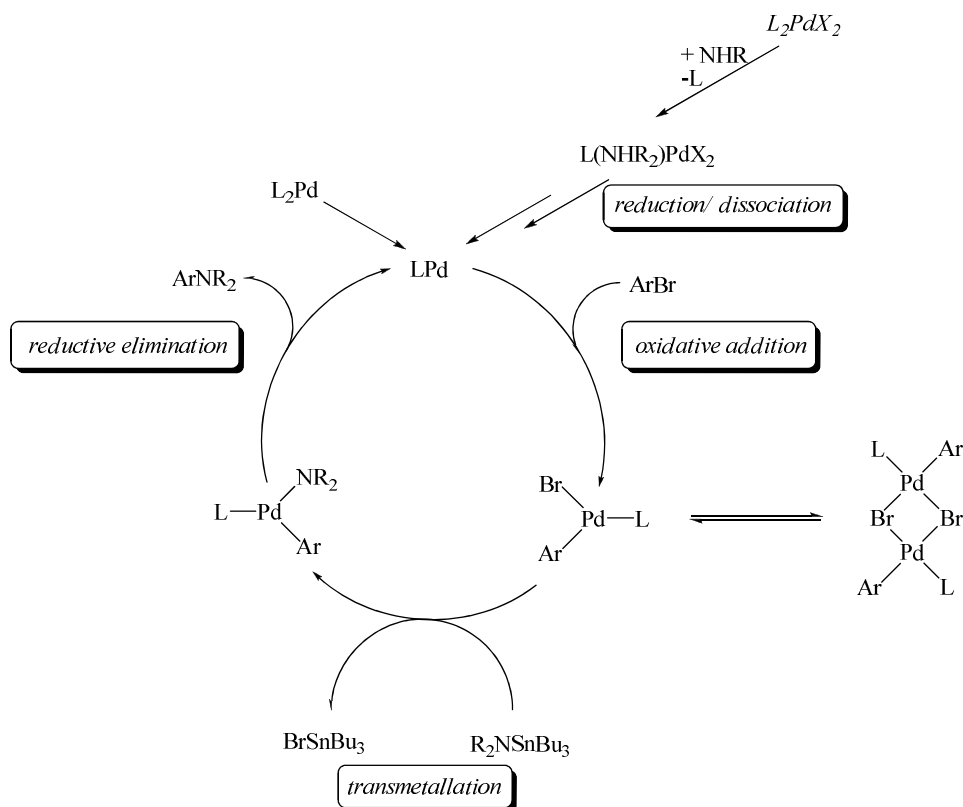
**Scheme 2.2** Palladium-catalyzed amination of aryl halides using tin organyles.<sup>3</sup>

One year later an intramolecular amination using an equimolar amount of palladium catalyst was performed by Booger and Panek (Scheme 2.3).<sup>4</sup> Unfortunately, no reaction occurred with low catalyst loading.



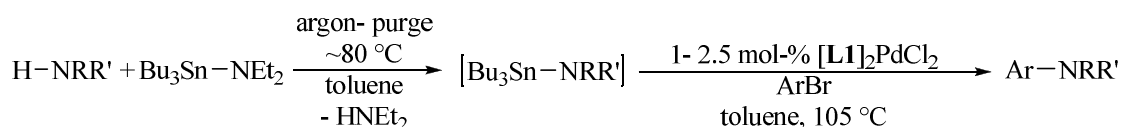
**Scheme 2.3** Intramolecular amination using a palladium complex.<sup>4</sup>

In 1994, Hartwig and co-workers took up again the idea to form aromatic amines starting from aryl halides and stannic amides.<sup>5</sup> A catalytic cycle was supposed, which is shown in Scheme 2.4. Due to phosphine inhibition monophosphine palladium(0) was assumed to be the active species. As in Stille couplings tin transmetallation appears to be the rate-limiting step. In the presence of stannic amides the catalyst dimer is suspected to irreversibly dissociate to monomeric form. The dimer was isolated and characterized by X-ray.



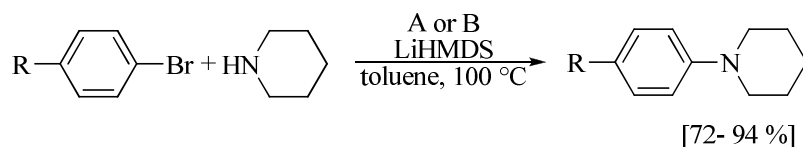
**Scheme 2.4** Catalytic cycle confirmed by Hartwig.<sup>5</sup>

A further development was the *in situ* generation of the stannic amide as described by Buchwald *et al.*<sup>6</sup> Diethylamine formed was exhausted with the argon stream. By this protocol also aromatic amines could be coupled (Scheme 2.5).



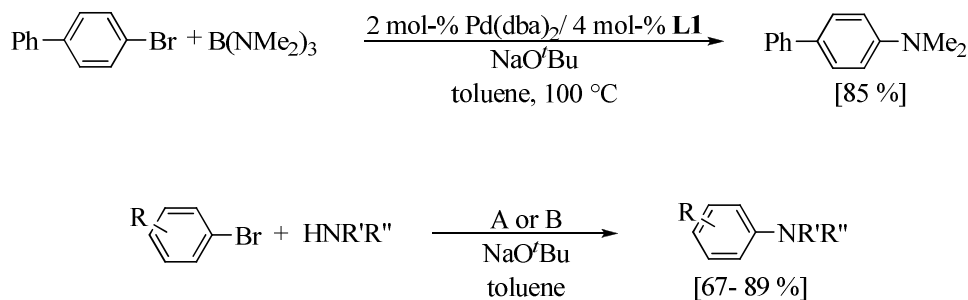
**Scheme 2.5** Palladium-catalyzed amination starting from aryl bromide and amines.<sup>6</sup>

Only one year later Hartwig and co-workers developed the arylation of numerous amines with aryl halides using palladium(0) or palladium(II) catalysts with *ortho*-tolyl phosphine (**L1**) as ligand (Scheme 2.6).<sup>7</sup> For the success of a reaction the electronic and sterical properties of the ligand are important. Until now the ligand design is subject of investigations.



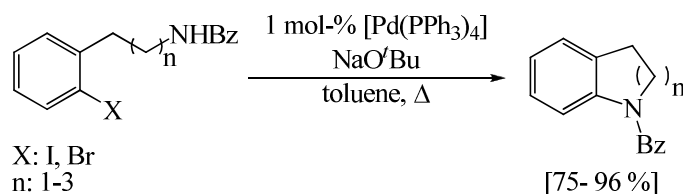
**Scheme 2.6** Direct amination of aryl bromides using 5 mol-% [**L1**]<sub>2</sub>Pd<sup>II</sup>Cl<sub>2</sub> (A) or [**L1**]<sub>2</sub>Pd<sup>0</sup> (B).<sup>7</sup>

Again Buchwald and co-workers published first results of amination based on Suzuki-type bond formation using aminoboranes.<sup>8</sup> The transfer of other amines to tris(dimethylamino)borane gave arylated amines in good yields (Scheme 2.7). The addition of base formed the sodium amide. Also direct arylation of amines was possible by the addition of a base.



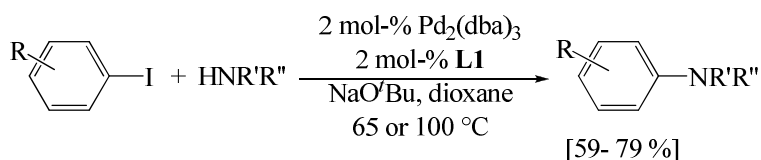
**Scheme 2.7** Amination of aryl bromides using 2 mol-% Pd(dba)<sub>3</sub>/ 4 mol-% L1 at 65 °C (A) or 2 mol-% [L1]<sub>2</sub>PdCl<sub>2</sub> at 100 °C (B) as catalyst.<sup>8</sup>

Intramolecular amination led to five- to seven-membered rings (Scheme 2.8). Several catalysts, bases and temperatures were tested. For cyclization [Pd(PPh<sub>3</sub>)<sub>4</sub>] gave higher yields than [PdCl<sub>2</sub>(L1)<sub>2</sub>] at lower catalyst loadings (Scheme 2.8).



**Scheme 2.8** Intramolecular amination using palladium(0) or palladium(II) sources.<sup>8</sup>

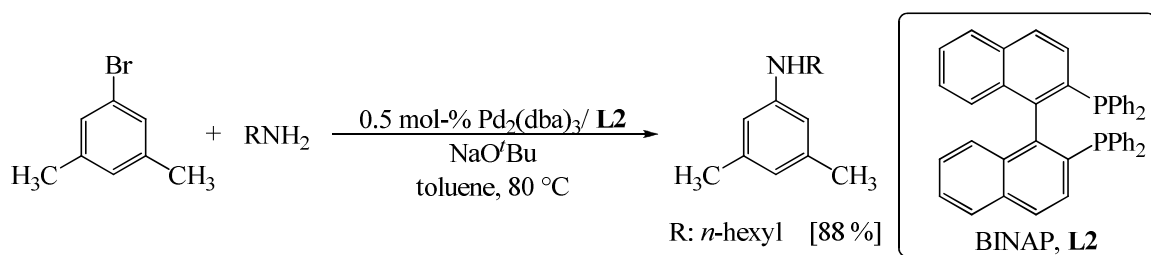
In 1996, Buchwald *et al.* described the synthesis of amines starting from aryl iodides and secondary amines (Scheme 2.9).<sup>9</sup> However, primary amines gave only low yields, also when coupled to sterically unhindered aryl iodides.



**Scheme 2.9** Direct amination of aryl iodides with secondary amines.<sup>9</sup>

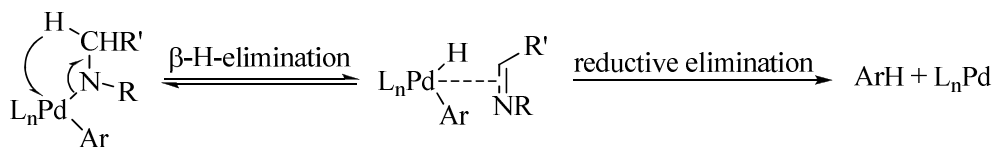
Independently, Hartwig *et al.*<sup>10</sup> and Buchwald *et al.*<sup>11</sup> changed reaction conditions for amination of aryl halides by using bis(phosphine) ligands. Buchwald and co-workers

established 2,2'-bis-diphenylphosphanyl-[1,1']binaphthalenyl (BINAP, **L2**) as ligand (Scheme 2.10). The yields and substrate generality increased dramatically and the catalyst loading could be reduced. For the example displayed in Scheme 2.10 only 35 % yield were obtained using **L1** as ligand instead of **L2**. In 2000, it was shown that also palladium(II) acetate instead of palladium(0) dibenzylidenacetone ( $\text{Pd}_2(\text{dba})_3$ ) is an efficient catalyst precursor.<sup>12</sup>



**Scheme 2.10** New catalyst developed for amination.<sup>10</sup>

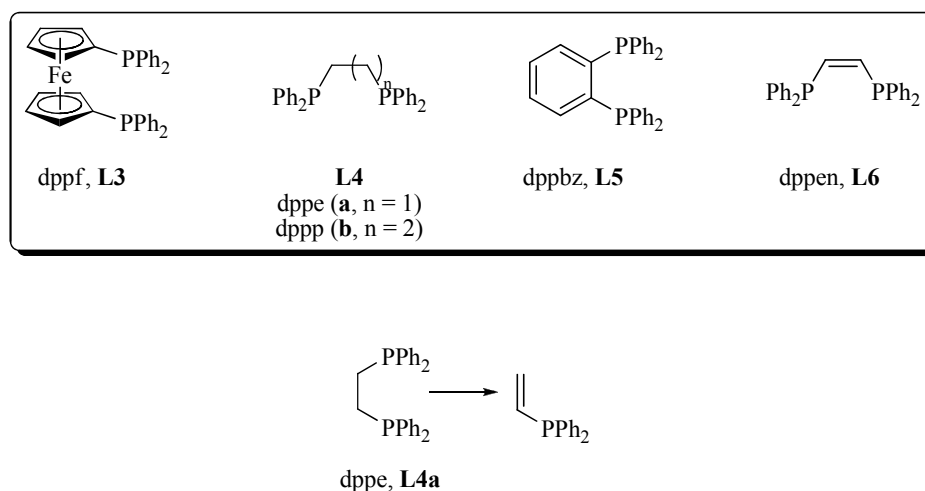
A main problem of palladium-catalyzed amination reaction is the  $\beta$ -H-elimination.<sup>13</sup> It is a common side reaction especially for electron-rich aryl halides and sulfonates. In Scheme 2.11, a possible process is discussed. If the  $\beta$ -H-elimination is reversible a palladium(II) imin complex is formed. Through reductive elimination the reduced arene was obtained. If the re-chelatisation becomes faster than the  $\beta$ -H-elimination the side reaction can be suppressed. When a bidentate phosphine ligand is applied the free coordination side at the palladium centre is blocked. Therefore, the  $\beta$ -H-elimination can be neglected.



**Scheme 2.11**  $\beta$ -H-elimination postulated by Hartwig.<sup>13</sup>

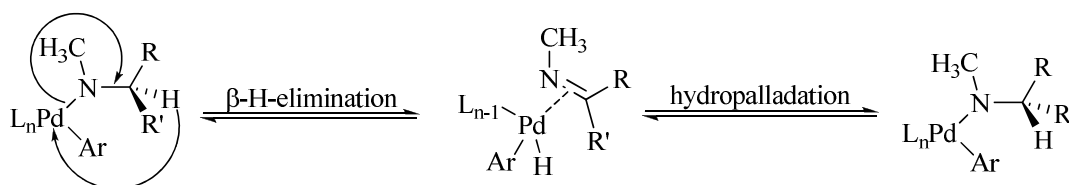
Hartwig and co-workers established a bidentate phosphine ligand (1,1'-bis(diphenylphosphine)-ferrocene, dppf, **L3**) for the coupling of primary amines to

electron-deficient aryl halides.<sup>10</sup> The catalytic cycle contains a bis(phosphine) intermediate, therefore no sterical demanding phosphine is necessary for intermolecular amination of aryl halides. By this protocol reductive elimination predominates the  $\beta$ -H-elimination. Other bis(diphenylphosphine) ligands (dppp – **L4**, dppbz – **L5**, dppen – **L6**) tested by Hartwig *et al.* decomposed due to C-P bond destruction (Chart 2.1). **L3** was efficient for the amination of aryl bromides and iodides, bearing both electron-donating and -withdrawing substituents, even in *ortho*-position, with primary alkyl- and aromatic amines.



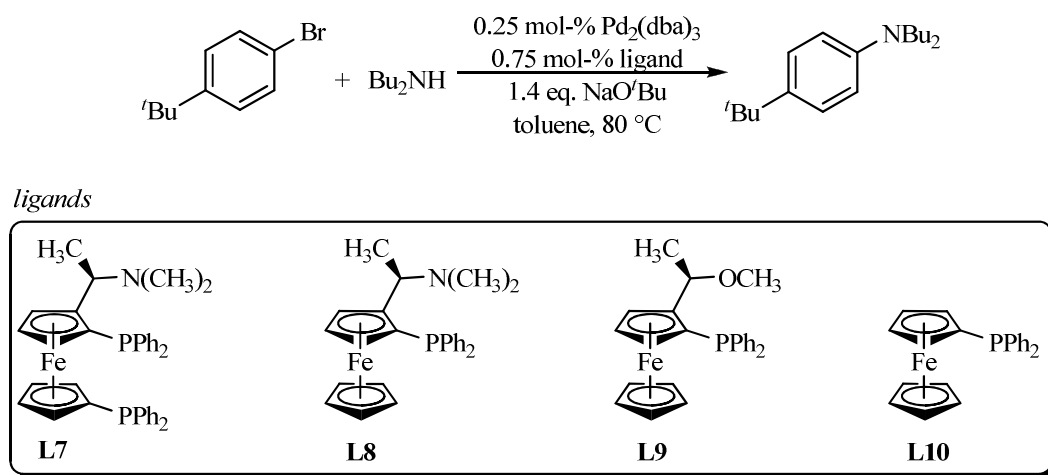
**Chart 2.1** Ligands developed by Hartwig *et al.* for amination reactions.<sup>10</sup>

In 1999, Buchwald *et al.* showed that even intramolecular amination of chiral substrates is possible.<sup>14</sup> For six- and seven-membered metallacycles  $\beta$ -H-elimination is difficult. In intermolecular couplings the degradation of the enantiomeric excess of  $\alpha$ -chiral substrates can occur if  $\beta$ -H-elimination is fast and reversible (Scheme 2.12).<sup>15</sup> With a bidentate phosphine ligand (e.g. **L2**) this behaviour was efficiently suppressed.



**Scheme 2.12** Degradation of enantiomeric excess due to a  $\beta$ -H-elimination/ hydropalladation sequence.<sup>15</sup>

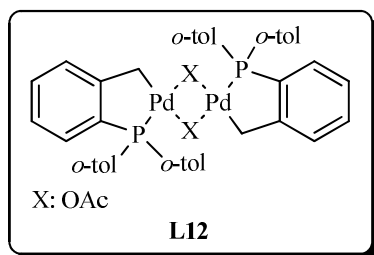
For C-N cross-coupling of secondary acyclic amines Buchwald and co-workers developed a series of ferrocene-derived mono- and bidentate phosphine ligands (Scheme 2.13).<sup>16</sup>



**Scheme 2.13** Ligand screening by Buchwald *et al.*<sup>16</sup>

Apart from aryl halides also triflates can be coupled to cyclic and acyclic primary and secondary amines. Buchwald *et al.* applied palladium(II) acetate (2 mol-%), **L2** or tol-BINAP (**L11**) with sodium *tert*-butanolate in toluene as catalytic system.<sup>17</sup> Hartwig and co-workers used similar reaction conditions with BINAP or dppf as ligand.<sup>18</sup>

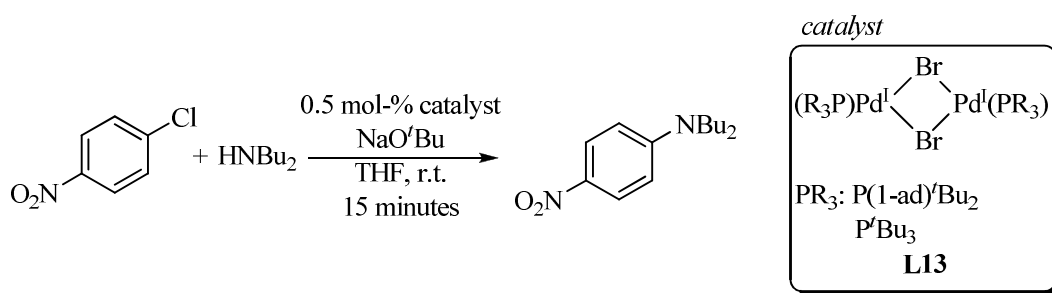
In 1998, Beller *et al.* described for the first time the amination of activated aryl chlorides.<sup>19</sup> A palladacycle served as catalyst (Scheme 2.14). Crucial for the successful coupling of aryl chlorides is the use of potassium *tert*-butanolate as base at elevated temperatures. Also aryl bromides and iodides were aminated with primary and secondary amines and anilines.



**Scheme 2.14** Palladacycle used by Beller *et al.* for amination of aryl chlorides.<sup>19</sup>

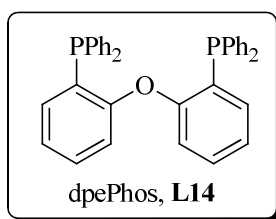


Also Hartwig and co-workers used preformed palladium catalysts for the amination of aryl chlorides (Scheme 2.15).<sup>20</sup> The elongation of reaction time didn't lead to higher yields. The high turnover number (TON) observed goes around with the instability of the complex. The conversion of chloroarenes with dialkyl amines tolerates a lot of functional groups due to short reaction times. However, no reaction of *para*-chlorotoluene with diphenylamine or primary amines was observed. On the other hand, unactivated aryl bromides were aminated successfully.



**Scheme 2.15** C-N cross-coupling of aryl chlorides using a pre-synthesized catalyst.<sup>20</sup>

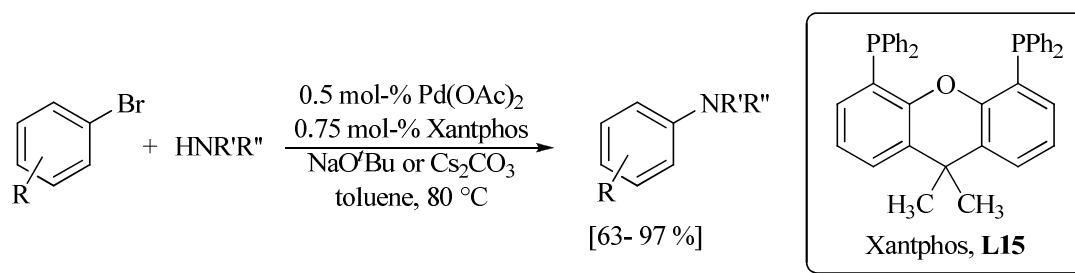
A new bidentate phosphine ligand (dpePhos, **L14**, Chart 2.2) for C-N cross-coupling was introduced by Buchwald *et al.*<sup>21</sup> As precatalyst palladium(II) acetate (0.5 to 5 mol-%) was used in toluene with sodium *tert*-butanolate or cesium carbonate as base. Also electron-rich aryl bromides could be coupled to electron-deficient anilines. These reaction conditions tolerate sterical bulkiness at both aryl and amine substrate. The new ligand is as efficient as BINAP and even more reactive than dppf.



**Chart 2.2** New bidentate ligand developed by Buchwald.<sup>21</sup>

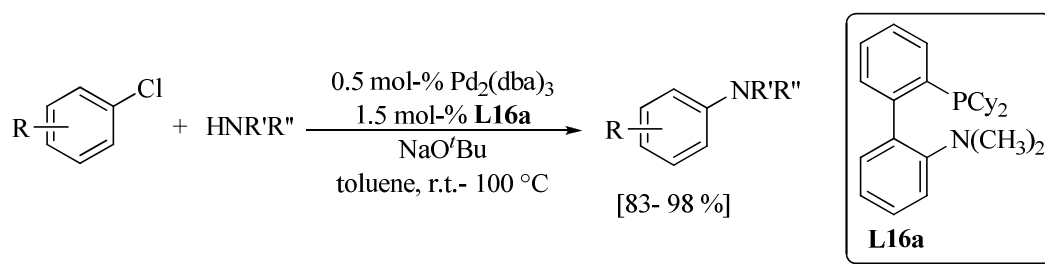
In 1999, van Leeuwen and co-workers improved **L14** as ligand by a dimethylmethylene bridge, which forces the two phosphine substituents into plane.<sup>22</sup> The

new ligand shown in Scheme 2.16 (Xantphos, **L15**) was used for the coupling of electron-rich and electron-deficient aryl bromides with primary and secondary aliphatic amines and anilines. Even sterically crowded substrates showed good reactivity.



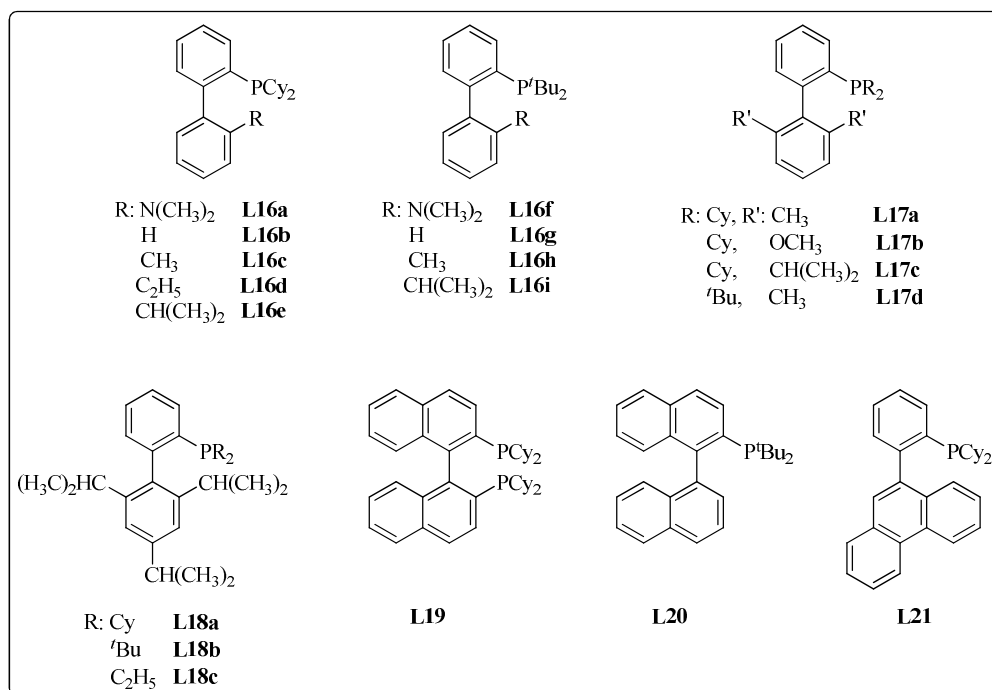
**Scheme 2.16** Amination using Xantphos as ligand as described by vanLeeuwen *et al.*<sup>22</sup>

A big improvement for the amination of unactivated aryl chlorides was the introduction of bidentate, monophosphine electron-rich biphenyls as ligands by Buchwald *et al.* (Scheme 2.17).<sup>23</sup> Mechanistic investigations led to the assumption that the oxidative addition is the rate-limiting step. For aryl chlorides this is more sluggish. To facilitate this step more electron-rich ligands were explored. These types of ligands were also useful for Suzuki-type C-C cross-coupling of aryl chlorides even at room temperature.



**Scheme 2.17** Amination of aryl chlorides described by Buchwald *et al.*<sup>23</sup>

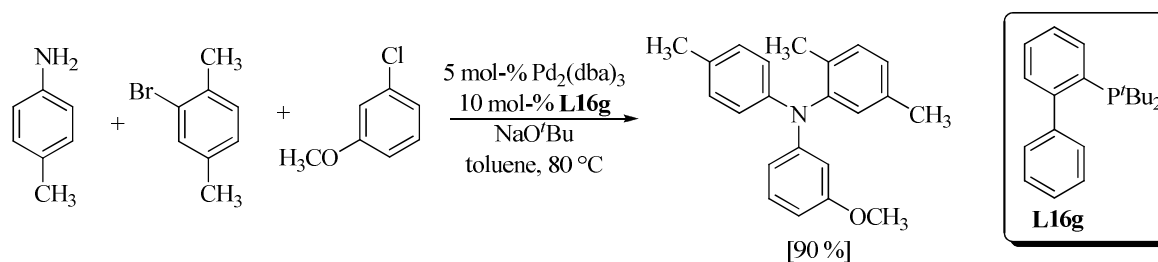
Further investigations showed that bidentate binding of the ligand to the metal center is unnecessary.<sup>24</sup> Buchwald and co-workers established sterically demanding and electron-rich biphenyl phosphines as ligands (Chart 2.3) for the coupling of cyclic amines to aryl bromides at room temperature. Also aryl chlorides and triflates were converted into corresponding amines. However, generality is still not simple.



**Chart 2.3** Ligands investigated in the amination reaction of aryl halides.<sup>24</sup>

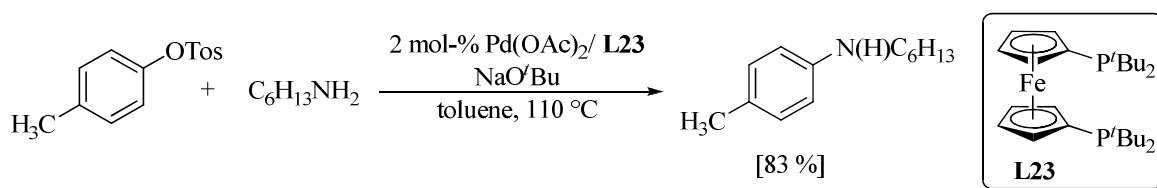
In 2003, Buchwald *et al.* broadened the scope of these ligands by the amination of aryl tosylates and benzene sulfonates.<sup>25</sup> For the first time amides and carbamates were coupled to tosylates, including *N*-Boc protected amines. The addition of catalytic quantity of phenyl boronic acid was necessary to ensure complete reduction of Pd(II) to Pd(0).

An effective one-pot synthesis of unsymmetrical triaryl amines with anilines, aryl bromides and aryl chlorides as precursors was published in 2000 using a monodentate biphenyl ligand (Scheme 2.18).<sup>26</sup> Due to the reactivity gradient first the aryl bromide was coupled to the primary amine. Afterwards the aryl chloride was aminated by the secondary amine.



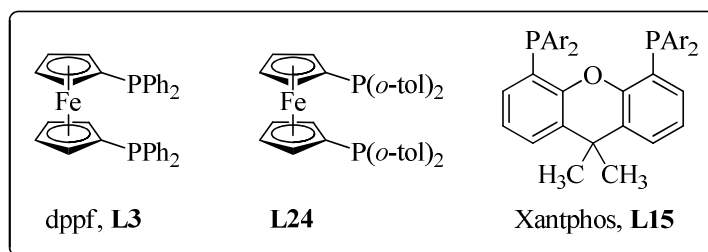
**Scheme 2.18** Synthesis of unsymmetrical triaryl amines in a one-pot procedure.<sup>26</sup>

Hartwig *et al.* found the dppf derivative, with sterically more demanding *tert*-butyl groups instead of phenyl substituents (Scheme 2.19), to be more general and effective than dppf.<sup>27</sup> Even the C-N cross-coupling of aryl tosylates to amines was successful. Also tri-*tert*-butylphosphine ( $P^tBu_3$ , **L22**) was found to be a remarkably active ligand. The functional group compatibility was increased by the use of  $K_3PO_4$  or  $Cs_2CO_3$  as bases.



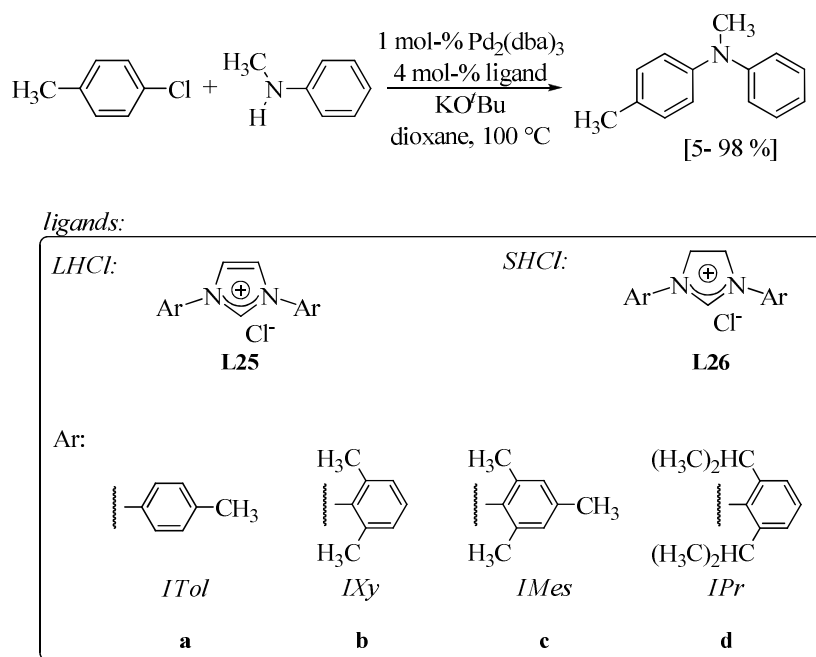
**Scheme 2.19** Conversion of tosylates as described by Hartwig *et al.*<sup>27</sup>

Further systematic studies on ligand effects with respect to steric, electronic, and geometric perturbations followed.<sup>27</sup> With a small set of model reactions and ligand sets it was proofed that an enlarged ligand size led to an increased rate of dehydrohalogenation and  $\beta$ -H-elimination. This effect was postulated to be due to partial dissociation to a three-coordinate complex. For the largest bidentate ligands in  $^{13}\text{P}$ -NMR complexes were observed, wherein one of the ligands was partially dissociated to form such a three-coordinate complex. Furthermore, the addition of electron-withdrawing groups to the ligand aryl group didn't help to favour the reductive elimination. An increased bite angle accelerated the dehydrohalogenation through the increased  $\beta$ -H-elimination.



**Chart 2.4** Some ligands tested in amination reactions.<sup>27</sup>

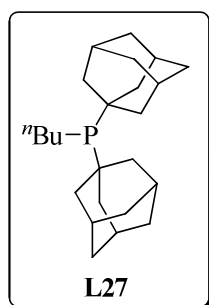
In 1999, Nolan and co-workers established with carbenes a new ligand generation for the Buchwald-Hartwig amination (Scheme 2.20).<sup>28</sup> Both, Pd(0) and Pd(II) salts can serve as catalyst precursors. Potassium *tert*-butanolate and sodium hydroxide were tested as bases. The catalytic system worked out was general for the coupling of aryl iodides, bromides and chlorides to amines. Iodides and bromides were converted even at room temperature. Also sterically hindered aryl chlorides could be coupled to primary and secondary alkylamines. Both, electron-rich and -deficient aryl chlorides were used. The electron-donor property of carbene facilitates activation of aryl chlorides. Additionally, the bulky substituents in *ortho*-position of carbene aryl group accelerate the reductive elimination. For the coupling of *p*-chlorotoluene with *N*-methylaniline using 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (**L25d**) as ligand the product was obtained in 98 % (Scheme 2.20). Less reactive indoles were converted to *N*-arylimidazoles with aryl bromides using more donating 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-imidazolium chloride (**L26d**) as ligand with Pd(OAc)<sub>2</sub> and NaOH as base.



**Scheme 2.20** Amination of aryl chlorides using carbenes as ligands.<sup>28</sup>

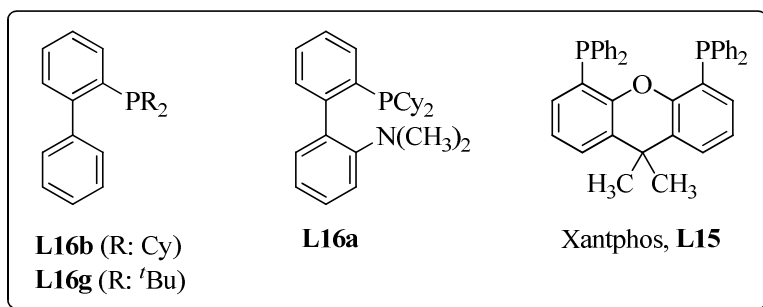
For the coupling of unactivated aryl chlorides to amines Beller *et al.* used a sterically demanding phosphine (Chart 2.5) with palladium(II) acetate in toluene as catalyst.<sup>29</sup>

Several phosphine ligands, phosphine/palladium ratios, and catalytic amounts were tested. Remarkable results were obtained for the C-N cross-coupling of sterically crowded aryl chlorides to hindered amines.



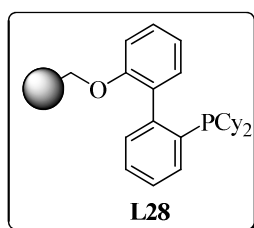
**Chart 2.5** Sterical demanding phosphin ligand for the amination of aryl chlorides.<sup>29</sup>

Buchwald and co-workers optimized the reaction conditions according to ligand, base ( $\text{NaOtBu}$ ,  $\text{Cs}_2\text{CO}_3$ ), solvent (dioxane, dioxane/ *tert*-butanol, THF, NMP, DMA), and temperature.<sup>30</sup> Cesium carbonate was used as base for the coupling of substrates bearing base-sensitive functional groups. The amination of aryl iodides was usually less effective than corresponding bromides. Ligand **L16g**, suitable for the conversion of aryl bromides and chlorides, was not efficient. However, **L16b** gave higher yields. The arylation of each amine was optimized using **L16b**, **L16a** and **L15** as ligands, dioxane, dioxane/ *tert*-butanol mixture or neat THF as solvent at different temperatures. BINAP (**L2**), ferrocene- and *tert*-butyl biphenylphosphine derivatives were less reactive. Highly polar solvents like NMP, DMA or DMSO led in significant reduction of the aryl iodide. The conversion was slower in unpolar solvents.



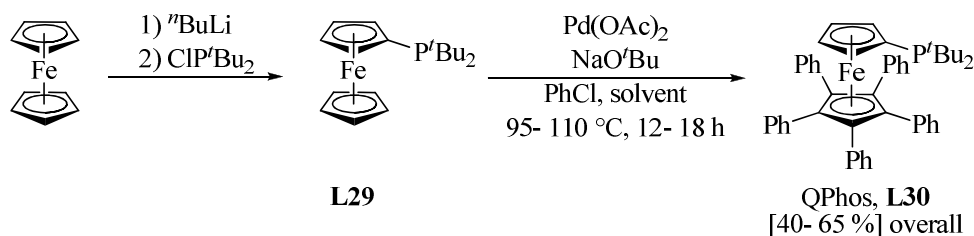
**Chart 2.6** Ligands applied for the amination of aryl iodides by Buchwald *et al.*<sup>30</sup>

Also polymer-supported dialkylphosphino biphenyl ligands (Chart 2.7) were effective for C-N cross-couplings of unactivated aryl iodides, bromides and chlorides.<sup>31</sup> After filtration the product can be isolated *via* a simplified aqueous work-up. The removed polymer supported catalyst can be recycled four times without loss of activity during amination reactions. The degradation of the catalyst reactivity might be caused by decomposition of the phosphine ligand during the reaction cycles.



**Chart 2.7** Polymer-supported phosphine biphenyl ligand.<sup>31</sup>

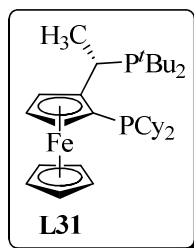
During cross-coupling with phenyl bromide using ferrocenyl di-*tert*-butylphosphine (**L29**) Hartwig *et al.* observed the phenylation of the ligand.<sup>32</sup> This new derivative (QPhos, **L30**) shown in Scheme 2.21 is even more effective than the parent ligand. Electron-rich and -deficient aryl bromides and chlorides could be coupled to acyclic and cyclic secondary alkyl- and aromatic amines and primary alkyl- and aromatic amines. In scope and limitation experiments  $\text{Pd}_2(\text{dba})_3$  and  $\text{Pd}(\text{OAc})_2$  were used as precursors. A proper choice of base was important. For example sodium *tert*-butanolate in toluene or potassium phosphate in DME were used to obtain the desired amines in good to excellent yields. Also C-C and C-O cross-couplings were investigated using QPhos.



**Scheme 2.21** Formation of QPhos as described by Hartwig *et al.*<sup>32</sup>

In 2002, Hartwig *et al.* investigated the use of aqueous potassium hydroxide in the palladium-catalyzed amination.<sup>33</sup> Aryl halides were converted in high yields with  $\text{Pd}[\text{P}^t\text{Bu}_3]_2$  as catalyst and cetyltrimethyl ammonium bromide ( $\text{C}_{16}\text{H}_{33}\text{N}(\text{CH}_3)_3\text{Br}$ ) as phase-transfer catalyst. A wide range of aryl chlorides and bromides were coupled to aliphatic and aromatic amines. With this new system further functional groups were tolerated, which were problematic with sodium *tert*-butanolate, such as esters, enolizable ketones, nitriles and nitro groups. Also 1,3-dimesityl-imidazolium tetrafluoroborate (**L25c**) and **L16g** were investigated as ligands. However, best results were obtained with  $\text{Pd}[\text{P}^t\text{Bu}_3]_2$ , which is air and moisture stable and commercially available.

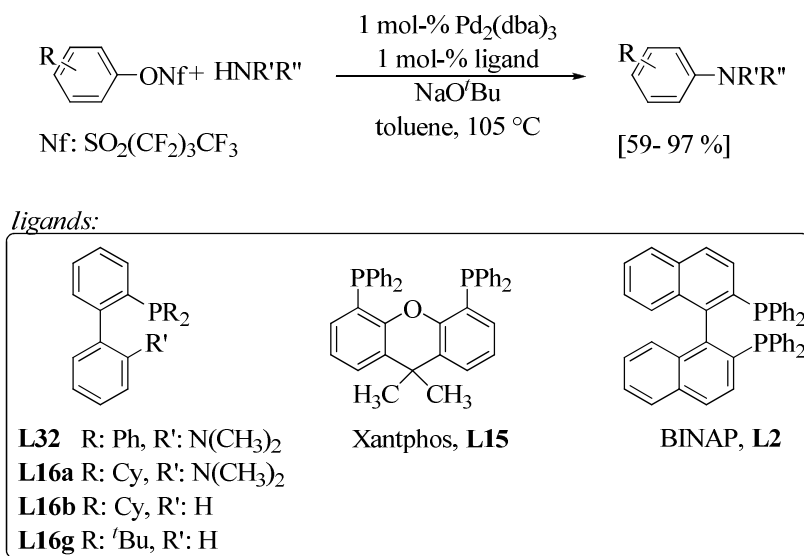
A novel ferrocene bisphosphine ligand (Chart 2.8) was established for the conversion of aryl and heteroaryl chlorides<sup>34</sup> and aryl tosylates<sup>35</sup> with primary amines in good yields under mild conditions. Even a very low catalyst loading of 10 to 50 ppm with Pd/ ligand ratio of 1:1 was sufficient.



**Chart 2.8** Novel bidentate ferrocenyl bisphosphine ligand.<sup>34, 35</sup>

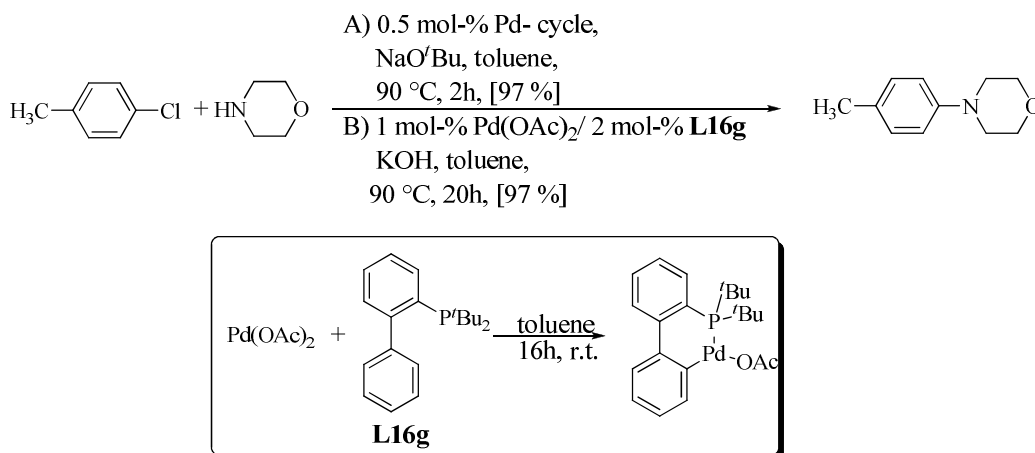
A further progress was made by Buchwald and co-workers, who converted electron-rich and -deficient aryl nonaflates with primary and secondary amines (Scheme 2.22).<sup>36</sup> In haloaryl nonaflates the nonaflate group was preferably substituted. This leaving group is an effective alternative to triflates. They showed an increased stability under the reaction conditions of Buchwald-Hartwig amination. Best results were obtained with Xantphos (**L15**) as ligand.





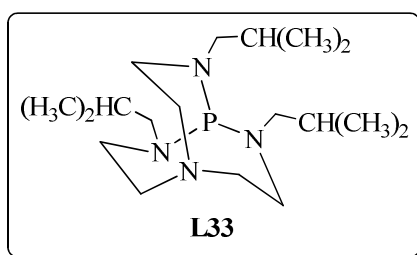
**Scheme 2.22** Amination of aryl nonaflates under non-aqueous conditions.<sup>36</sup>

When primary alkoxides were used as bases with dppf (**L3**) as ligand remarkable reduction of the aryl halides was observed. Buchwald *et al.* developed an air, moisture and thermally stable palladacycle for the amination of aryl chlorides.<sup>37</sup> The catalyst was easily prepared and with sodium methoxide as base an improved level of functional group compatibility was reached. Reduction was no more observed. For the conversion of anilines the addition of triethylamine was necessary, otherwise no reaction took place. The amine reduces Pd(II) to Pd(0). As shown in Scheme 2.23 the use of the palladacycle accelerates the conversion of aryl chlorides to corresponding amine.



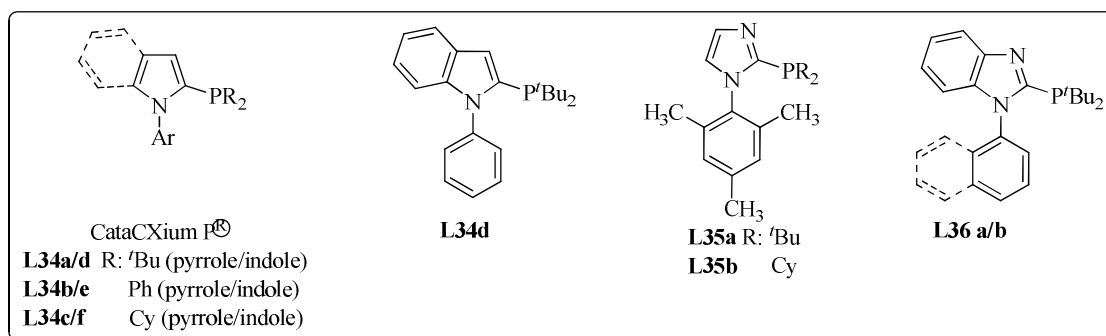
**Scheme 2.23** Amination of *p*-chloro toluene and synthesis of the palladacycle.<sup>37</sup>

Another spacious ligand for the amination of aryl bromides and iodides was published by Verkade *et al.* in 2003 (Chart 2.9).<sup>38</sup> Palladium(II) acetate served as catalyst precursor.



**Chart 2.9** Effective ligand for C-N cross-coupling of aryl bromides and iodides.<sup>38</sup>

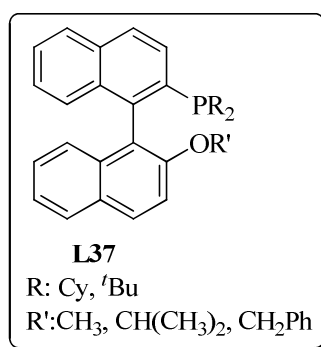
Beller and co-workers screened a ligand library containing monodentate (benzo-)indoles and imidazoles (Chart 2.10).<sup>39</sup> Both C-N and Suzuki-type C-C cross-couplings were investigated. As catalyst precursors  $\text{Pd}_2(\text{dba})_3$  and  $\text{Pd}(\text{OAc})_2$  were used with  $\text{K}_3\text{PO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{NaOAc}$ ,  $\text{Cs}_2\text{CO}_3$  as bases. Certainly, due to high sterical demand ligands with *tert*-butyl substituents gave best results. In scope and limitation experiments (hetero-)aryl chlorides were coupled to primary and secondary alkyl- and aromatic amines.



**Chart 2.10** New ligand class developed by Beller group and Degussa.<sup>39</sup>

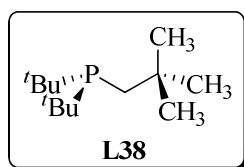
In 2006, Zhang *et al.* investigated easily preparable ligands, which are moisture and air stable both in solid and solution state.<sup>40</sup> The C-N cross-coupling revealed the crucial role of sterical bulkiness of the substituents on the phosphorous atom. For primary amines a high sterical demand, e.g. in *tert*-butyl or *iso*-propyl group (Chart 2.11), improved the

reaction rate. On the other hand, less bulky ligands ( $R = \text{Cy}$ ,  $R' = \text{Me}$ ) were more effective in the conversion of secondary amines. They are bulkier than primary amines and require more space at the binding site at the palladium centre.



**Chart 2.11** MOP-type ligands developed by Zhang.<sup>40</sup>

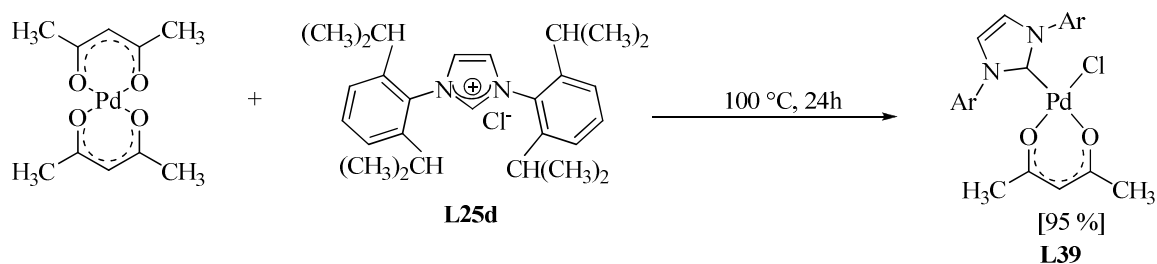
Dixon and Shaughnessy *et al.* improved the compatibility and activity of  $\text{P}^t\text{Bu}_3$  by exchange one substituent by a neopentyl group (Chart 2.12), which increases the cone angle of the phosphine.<sup>41</sup> On the other hand,  $\text{P}^t\text{Bu}_3$  is a stronger electron donor, which led to higher yields when chlorides were converted. A second neopentyl group led to less efficiency. Primary and secondary aromatic amines were coupled using  $\text{Pd}_2(\text{dba})_3$  as pre-catalyst, and sodium *tert*-butanolate as base in toluene at room temperature. For the arylation of alkylamines palladium(II) acetate was applied at 50 °C. Aryl chlorides were coupled to amines at elevated temperatures, ranging from 50 to 140 °C.



**Chart 2.12** New neopentyl-bis(*tert*-butyl)phosphine ligand for amination reactions.<sup>41</sup>

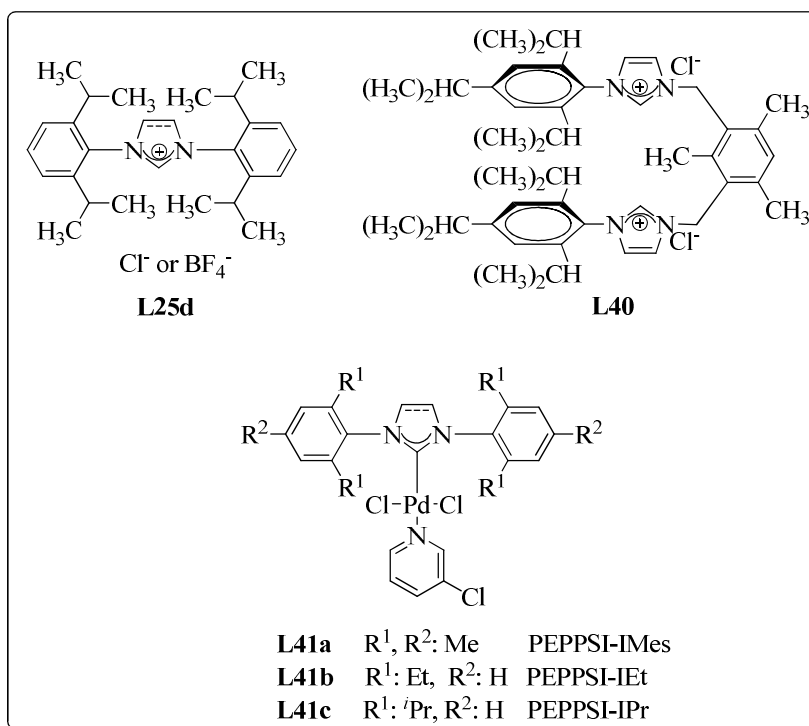
Nolan and co-workers synthesized a new palladium(II) catalyst from commercially available starting materials.<sup>42</sup> Reacting palladium(II) acetylacetonate with 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (**L25d**) resulted in the complex

(**L25d**)Pd<sup>II</sup>(acac)Cl displayed in Scheme 2.24. In scope and limitation experiments the complex was proven to be highly effective. Also unactivated, sterically hindered, heterocyclic aryl chlorides were aminated.



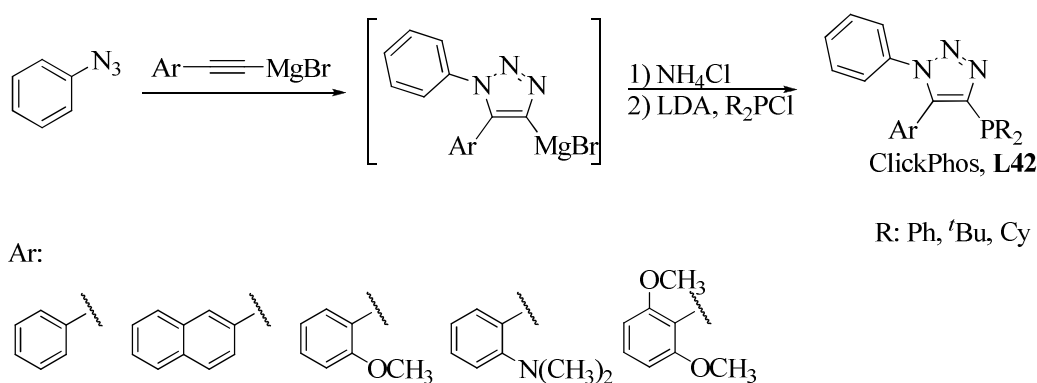
**Scheme 2.24** Preparation of the palladium catalyst developed by Nolan *et al.*<sup>42</sup>

An overview about NHC-ligands developed for C-C and C-N cross-coupling reactions was given by Organ *et al.* (Chart 2.13).<sup>43</sup> The electronical and chemical properties were investigated. As bases served potassium or sodium *tert*-butanolate in DME or 1,4-dioxane. The reactions were performed at room or elevated temperatures, up to 100 °C. With these carbenes as ligands aryl halides were coupled with aromatic and aliphatic amines as well as NH-containing heterocycles. The arylation of primary alkylamines was always problematic and required higher temperatures and catalyst loadings with large excess of amine. With the preformed palladium catalyst (PEPPSI, **L41**) a variety of unactivated, sterically hindered or heterocyclic halides were coupled to primary and secondary amines.



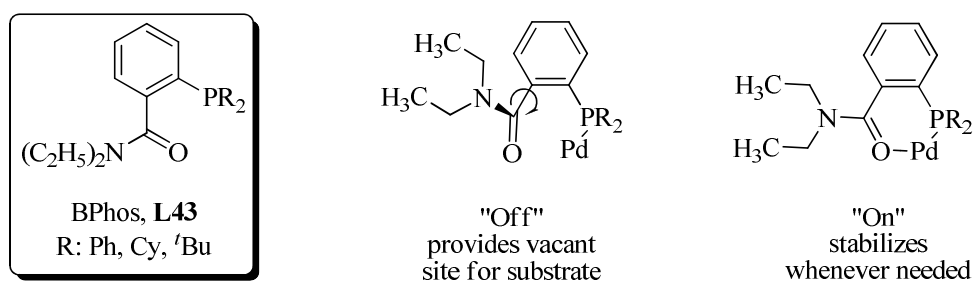
**Chart 2.13** Some examples for NHC-ligands and the newly developed PEPPSI-precatalysts.<sup>43</sup>

A new class of ligands was introduced by Zhang *et al.*<sup>44</sup> Using triazole-phosphines (ClickPhos, **L42**, Scheme 2.25) aryl chlorides were effectively aminated. Best results in Buchwald-Hartwig aminations showed the *tert*-butyl substituted phosphine with 2-methoxyphenylene in 5-position of the triazole ring. As catalyst, precursor Pd<sub>2</sub>(dba)<sub>3</sub> was used with sodium *tert*-butanolate as base in toluene. With this protocol aryl chlorides were coupled to primary and secondary amines and anilines in good to excellent yields.



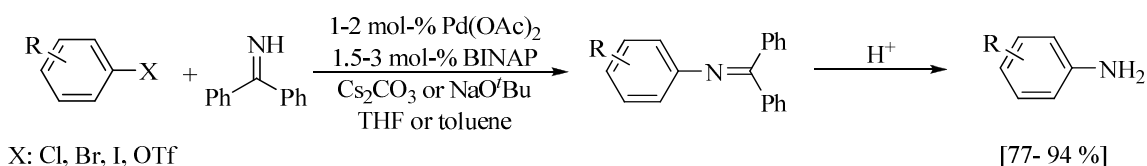
**Scheme 2.25** Triazole-based phosphine ligands established for effective C-C and C-N cross-coupling.<sup>44</sup>

A further effective ligand for the C-N cross-coupling of aryl- and heteroaryl chlorides was presented by Kwong *et al.* in 2007.<sup>45</sup> The benzamide phosphine ligands are easy to prepare and hemilabile. The free rotation of the amide group can stabilize the palladium complex due to palladium-oxygen coordination or can provide free vacancy at the phosphine group (Scheme 2.26).



**Scheme 2.26** Benzamide phosphine ligands with hemilabile side groups.<sup>45</sup>

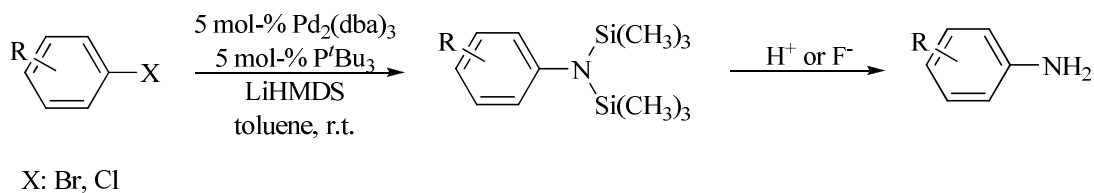
The formation of anilines is always problematic. Buchwald and co-workers described in 1997 the conversion of aryl halides to imines.<sup>46</sup> The following acidic work-up produced the corresponding anilines (Scheme 2.27).



**Scheme 2.27** Formation of benzophenone imines followed by hydrolysis to yield anilines.<sup>46</sup>

A similar approach was published by Nolan *et al.*<sup>47</sup> They synthesized benzophenone imines, which were reduced by acidic hydrolysis to form the amine. For the conversion of the aryl halides into imines NHC-ligands (**L25**, **L26**) were used.

In the same year Hartwig and co-workers investigated the conversion of aryl halides with lithium bis(trimethylsilyl)amide (LiHMDS).<sup>48</sup> The intermediate arylamide was treated with acids or fluoride ions to yield the desired aniline (Scheme 2.28). However, no *ortho*-substituents were tolerated.

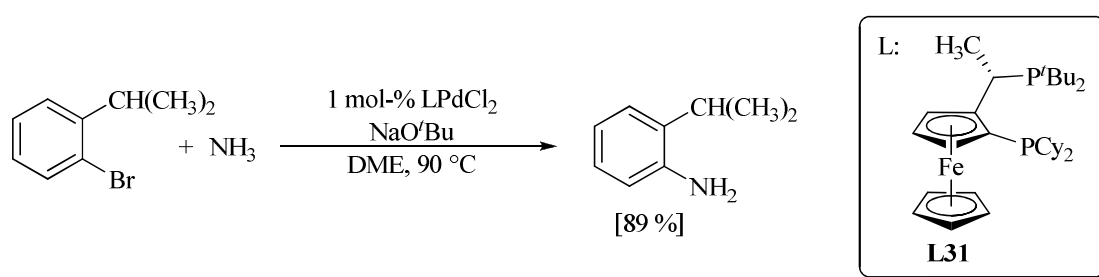


**Scheme 2.28** Synthesis of aniline derivatives with LiHMDS as precursor.<sup>48</sup>

Buchwald *et al.* applied 2-[bis(cyclohexyl)phosphine]-biphenyl (**L16b**) as ligand instead of tri(*tert*-butyl) phosphine (**L22**).<sup>49</sup> Under these conditions also *ortho*-substituted aryl bromides could be converted into the aniline. For example 2-*iso*-propyl-bromobenzene was transformed into corresponding aniline in 90 % yield.

Also zinc trimethylsilylamide could be used as precursor for the aniline formation.<sup>50</sup> Starting from aryl bromide, chloride or triflate the aniline was synthesized using lithium chloride as additive. In contrast to the protocol of Hartwig and co-workers  $\text{Zn}(\text{HMDS})_2$  in combination with lithium chloride tolerates also base-sensitive functionalities.

In 2006, Hartwig *et al.* published the direct synthesis of aniline derivatives by using a ferrocene-ligand and gaseous ammonia (Scheme 2.29).<sup>51</sup> However, the lithium amide is a better amine source and more practical than gaseous ammonia. The procedure could be extended to aryl chlorides.



**Scheme 2.29** Direct synthesis of aniline derivatives using ammonia.<sup>51</sup>

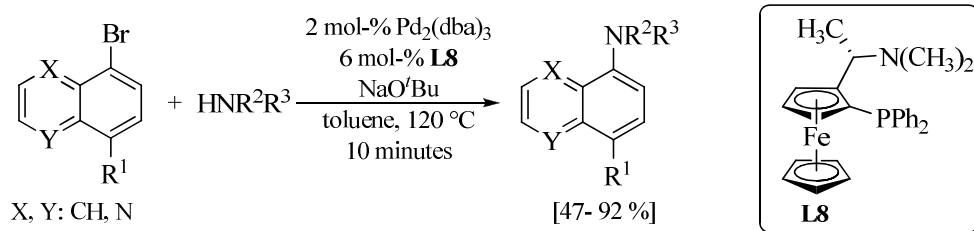
With the introduction of the microwave technique as a heating method in synthetic chemistry also Buchwald-Hartwig aminations were carried out with this method. Under experts a lively discussion is going on to explain the fastening of reaction and/ or the increase of yields. A so-called hot-spot is discussed for the transition-metal centre. The

metals have a big dipole moment, which can be excited by microwave irradiation. In comparison with “conventional” heating a much higher energy at the metal centre can be achieved. Because the reaction proceeds much faster less side products were expected.

In 2002, Alterman and co-workers coupled electron-rich, -deficient and -neutral phenyl bromides with primary and secondary aliphatic and aromatic amines in good yields.<sup>52</sup> A four-fold excess of amine was arylated with palladium(II) acetate (5 mol-%) and BINAP (**L2**, 5 mol-%) as catalyst and potassium *tert*-butanolate as base in DMF. No inert conditions were necessary. The reaction proceeded in four minutes at 130 °C.

Maes *et al.* converted activated and non-activated azaheteroaryl chlorides and non-activated aryl chlorides into amines.<sup>53</sup> The products were obtained in 75 to 91 % within ten minutes. Only 0.5 to 2 mol-% of palladium(II) acetate were necessary as catalyst with 1 to 4 mol-% 2-[bis(cyclohexyl)phosphine]-biphenyl (**L16b**) as ligand, sodium *tert*-butanolate as base in toluene at 150 to 200 °C.

For the amination of aryl bromides Wang and co-workers used a ferrocenyl-phosphine derivative as ligand (Scheme 2.30).<sup>54</sup> Under microwave heating the products were obtained in moderate to excellent yields.

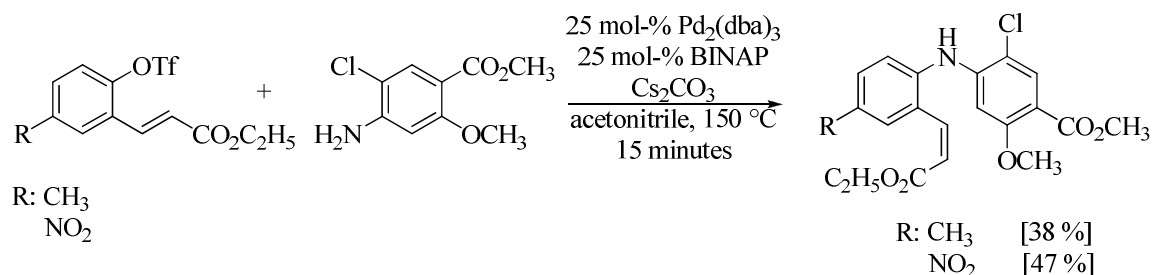


**Scheme 2.30** Amination of aryl bromides in good to excellent yields.<sup>54</sup>

With carbene ligands (hetero)aryl chlorides were coupled to primary and secondary amines with Pd<sub>2</sub>(dba)<sub>3</sub> as catalyst precursor.<sup>55</sup> Potassium *tert*-butanolate served as base in DMF or DME as solvent. Also Pd(OAc)<sub>2</sub> was used with 2-[bis(cyclohexyl)phosphine]-biphenyl (**L16b**) as ligand. In this catalyst system sodium *tert*-butanolate was used in toluene at 150 to 200 °C. The desired arylated amines were obtained within five to ten minutes.

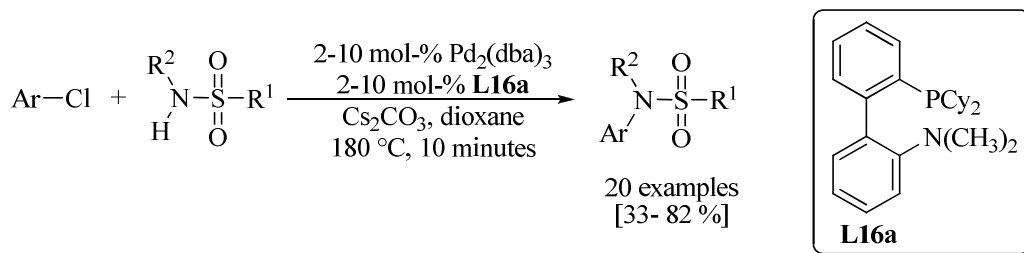


Ullrich *et al.* reported the conversion of aryl triflates to corresponding amines.<sup>56</sup> Also sterically crowded substrates could be converted (Scheme 2.31).



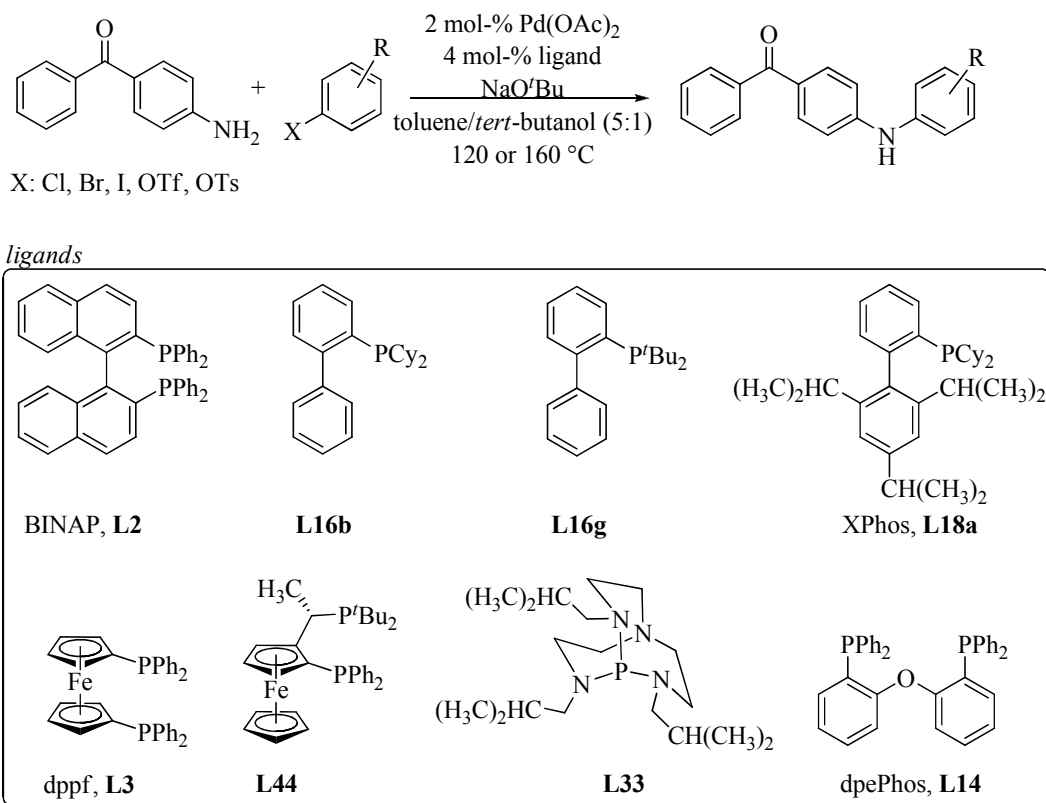
**Scheme 2.31** C-N cross-coupling of triflates and aromatic amines.<sup>56</sup>

Also *N*-arylsulfonamides were synthesized under microwave irradiation starting from aryl chlorides (Scheme 2.32).<sup>57</sup>



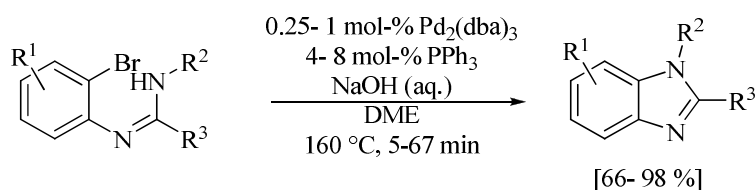
**Scheme 2.32** Formation of *N*-aryl sulfonamides under microwave irradiation.<sup>57</sup>

Skjaerbaek *et al.* screened various ligands for the arylation of several anilines with aryl bromides with a variety of functional groups.<sup>58</sup> Even iodides, chlorides, triflates and tosylates were aminated in good to excellent yields. Best results were obtained using XPhos (**L18a**) as ligand (Scheme 2.33).



**Scheme 2.33** Optimization of palladium-catalyzed amination reaction under microwave irradiation.<sup>58</sup>

Intramolecular amination was performed in moderate yields with Pd<sub>2</sub>(dba)<sub>3</sub> and triphenylphosphine as catalyst (Scheme 2.34).<sup>59</sup>

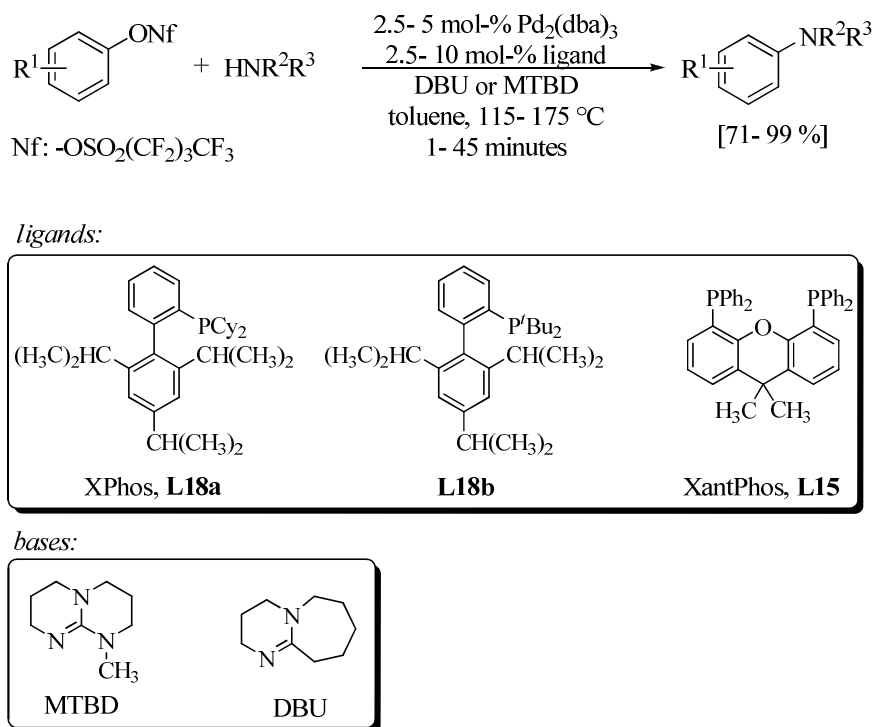


**Scheme 2.34** Intramolecular amination under microwave irradiation.<sup>59</sup>

A catalyst-free conversion of electron-rich aryl halides with secondary amines was presented by Tu *et al.* Only potassium *tert*-butanolate was added as base in DMSO.<sup>60</sup>

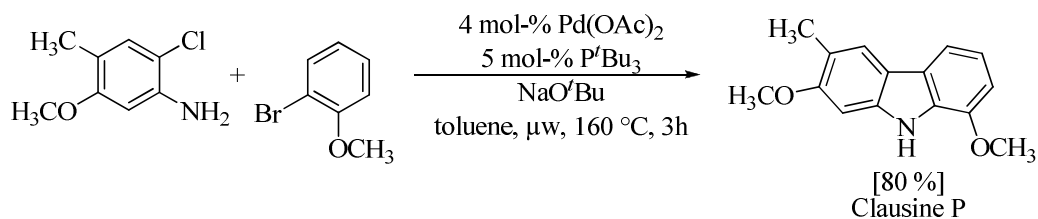
Also Wang and co-workers reported about the catalyst-free C-N cross-coupling of electron-rich and -deficient aryl triflates.<sup>61</sup> Additionally no base was necessary in NMP. Halogenated aryl triflates were converted chemoselectively to halogenated anilines.

In 2006, Buchwald *et al.* screened organic bases (TEA, DBU, DABCO, TMP, MTBD) in different solvents for the coupling of nonaflates to amines (Scheme 2.35).<sup>62</sup>



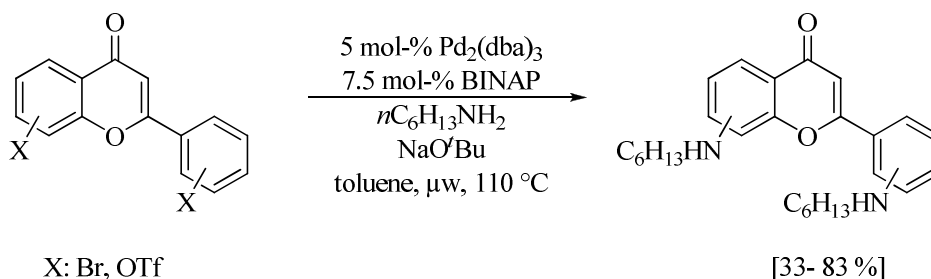
**Scheme 2.35** Optimization of C-N cross-coupling under microwave irradiation with organic bases.<sup>62</sup>

A new protocol for the synthesis of *N*-H carbazoles starting from 2-chloroaniline and bromoarene was established by Bedford *et al.* in 2006.<sup>63</sup> The sequence of Buchwald-Hartwig amination and C-H activation was performed in a one-pot procedure (Scheme 2.36). As catalyst palladium(II) acetate and tri(*tert*-butyl)phosphine (**L22**) were applied with sodium *tert*-butanolate in toluene at 160 °C.



**Scheme 2.36** Palladium-catalyzed formation of *N*-H carbazoles in a one-pot procedure.<sup>63</sup>

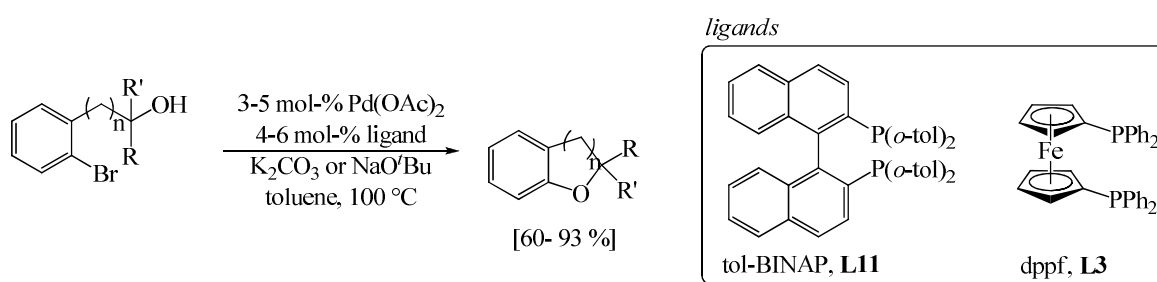
Dihaloflavones were diaminated using microwave irradiation.<sup>64</sup> As ligand BINAP was used in combination with  $\text{Pd}_2(\text{dba})_3$  as precursor (Scheme 2.37).



**Scheme 2.37** Amination of halogenated flavones by palladium-catalyzed protocol.<sup>64</sup>

### 2.1.2 Etherification

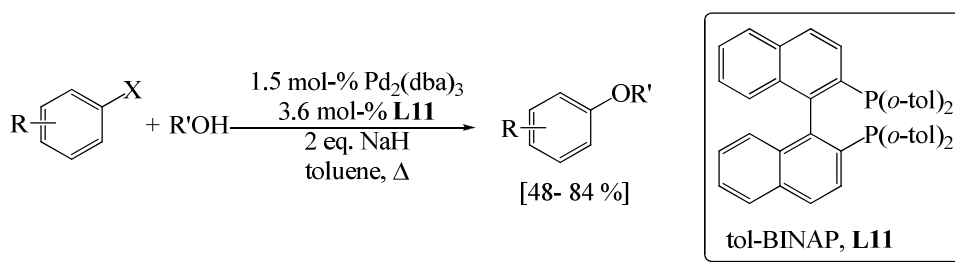
The development of palladium-catalyzed etherification is similar to C-N cross-coupling.<sup>65</sup> The substrate scope expands with ligand improvement. For the coupling of aryl halides to alcohols chelating ligands are necessary, otherwise no reaction was observed. Tertiary alcohols were converted in good yields, however, secondary alcohols gave only low yields. Buchwald and co-workers described the synthesis of 5-, 6- and 7-membered rings in good to excellent yields (Scheme 2.38).



**Scheme 2.38** Intramolecular etherification by Buchwald-Hartwig procedure.<sup>65</sup>

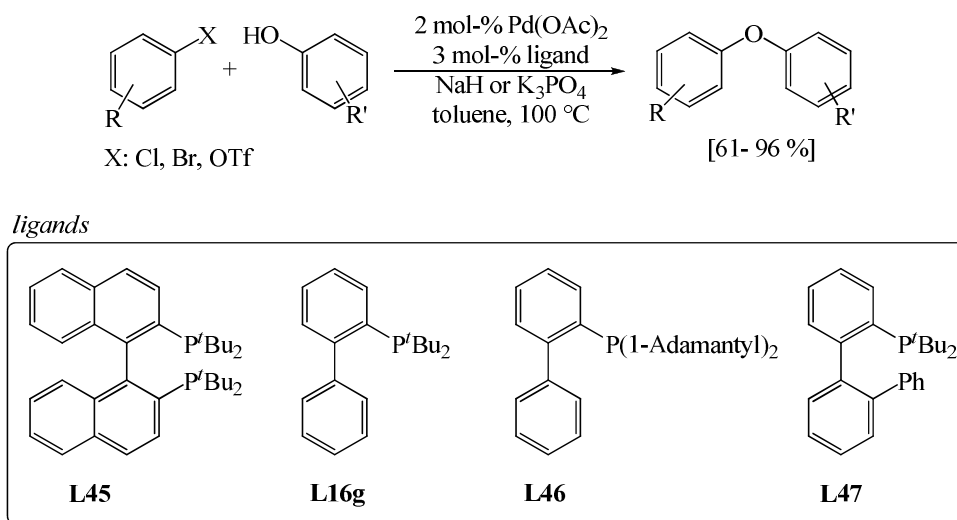
In parallel Hartwig *et al.* discussed the first intermolecular palladium-catalyzed C-O cross-coupling.<sup>66</sup> Electron-deficient aryl bromides were etherified with *tert*-butanolate using  $\text{Pd}_2(\text{dba})_3$  or  $\text{Pd}(\text{PPh}_3)_4$  (10 mol-%), dppf (**L3**, 12 mol-%) in toluene at 100 °C.

One year later, in 1997, Buchwald and co-workers presented an effective coupling of primary, secondary and tertiary alcohols to electron-deficient aryl bromides (Scheme 2.39).<sup>67</sup> Electron-rich and -neutral aryl bromides could only be converted, when tertiary or cycloalkanoles were used. With palladium(II) acetate a higher amount of reduction of the halogenoarene was observed.



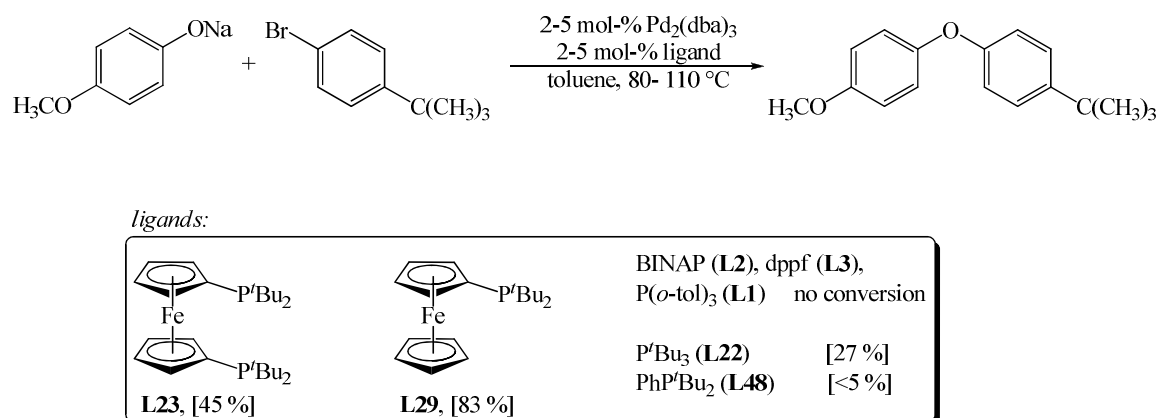
**Scheme 2.39** Inter-molecular etherification by Buchwald-Hartwig procedure.<sup>67</sup>

The variety of aryl halides was broadened to aryl chlorides, bromides and triflates.<sup>68</sup> For the formation of diaryl ethers several ligands were screened (Scheme 2.40). Also electron-neutral and -rich aryl halides and triflates were coupled in good yields with high functional group tolerance. The lack of this procedure was low yields observed for aryl halides bearing electron-withdrawing groups in *ortho*-position. However, phenols with bulky substituents gave good yields.



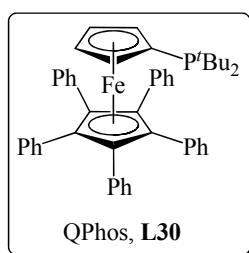
**Scheme 2.40** Formation of diaryl ethers through palladium catalysis.<sup>68</sup>

The formation of diaryl and *tert*-butoxyethers from sodium alcoholates was investigated by Hartwig and co-workers.<sup>69</sup> Aryl bromides and chlorides were converted using several ligands (Scheme 2.41). The monophosphine substituted ferrocenyl ligand gave remarkably higher yields than the corresponding diphosphinyl derivative.



**Scheme 2.41** Ligand screening for diaryl ether synthesis as described by Hartwig *et al.*<sup>69</sup>

The pentaphenylated ferrocenyl phosphine ligand **L30** (Chart 2.14) developed for C-N cross-coupling was also useful for the formation of aryl ethers.<sup>32, 70</sup> Electron-deficient and -neutral aryl halides were coupled to sodium alkoxides. Tertiary and aromatic alcoholates were arylated in good yields. Only low yields were obtained for primary and secondary alcohols. Also intermolecular aryl and alkyl ether formation was described.

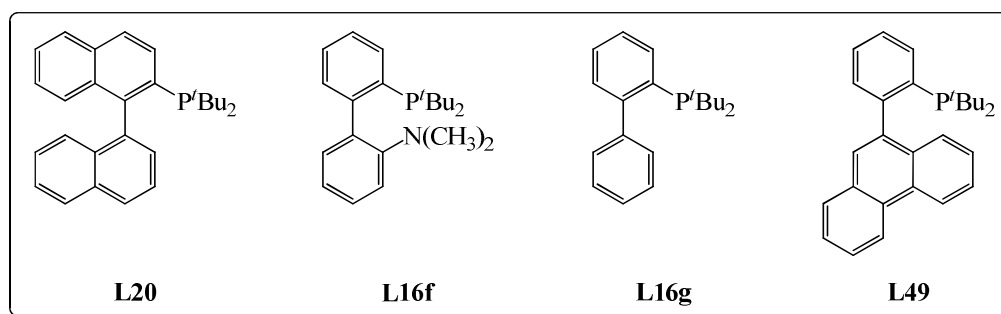


**Chart 2.14** Catalyst developed for etherification by Hartwig and co-workers.<sup>70</sup>

The intramolecular etherification led to 5-, 6- and 7-membered rings.<sup>71</sup> Bromides were coupled more rapidly and cleanly than chlorides and primary alcohols cyclized more

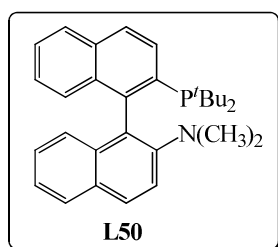
easily than secondary ones. For the conversion of secondary alcohols higher catalyst loadings and temperatures were required.

With biphenylphosphines (Chart 2.15) also electron-rich aryl bromides were coupled to *tert*-butanol.<sup>72</sup> The corresponding ethers served as precursors for diaryl ether formation. The ligands applied are air stable.



**Chart 2.15** Ligands used for the intramolecular etherification.<sup>72</sup>

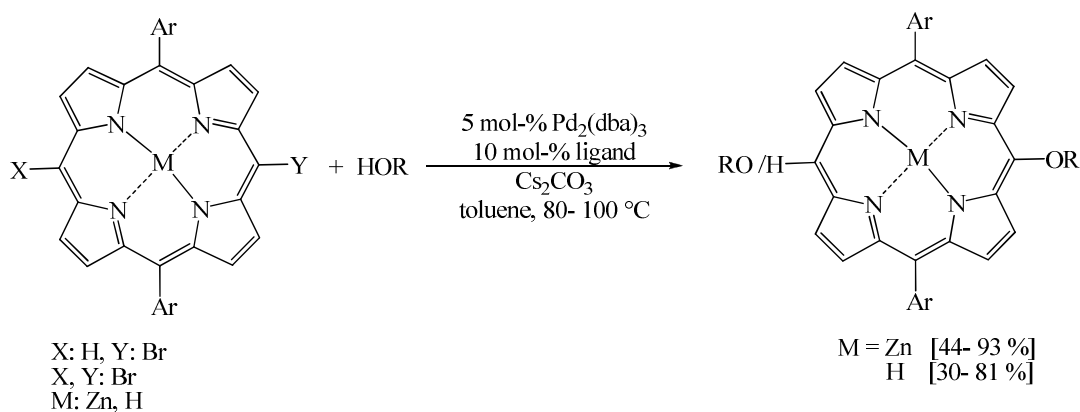
Buchwald *et al.* investigated the binaphthyl ligand **L50** for the C-O cross-coupling of primary alcohols.<sup>73</sup> Both electron-deficient and -neutral aryl halides gave good yields and also electron-rich aryl halides bearing *ortho*-alkyl substituents worked well. Additionally, other ligands were tested. For **L50** (Chart 2.16) the lowest ratio of reduction/ coupling was observed.



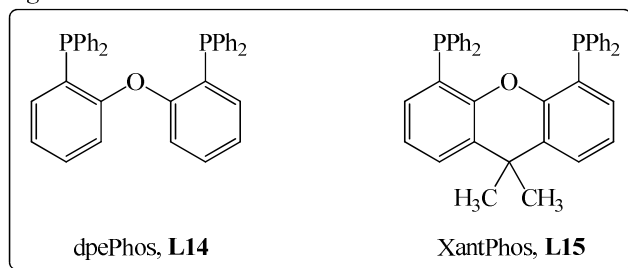
**Chart 2.16** Ligand developed by Buchwald and co-workers for the C-O cross-coupling of primary alcohols.<sup>73</sup>

In 2003, Zhang *et al.* published the etherification at the porphyrin periphery (Scheme 2.42).<sup>74</sup> Also sterically demanding phenols were coupled. Electron-rich and -deficient phenols gave the desired products in good yields. The double etherification was also

investigated at aliphatic alcohols (primary, secondary, cyclic and acyclic). Zinc as protective group for the NH-group at the porphyrine ring was unnecessary. Best results were obtained with dpePhos (**L14**) as ligand.



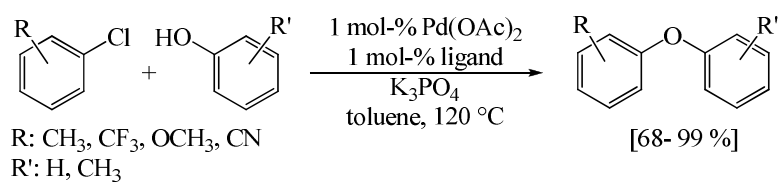
ligands



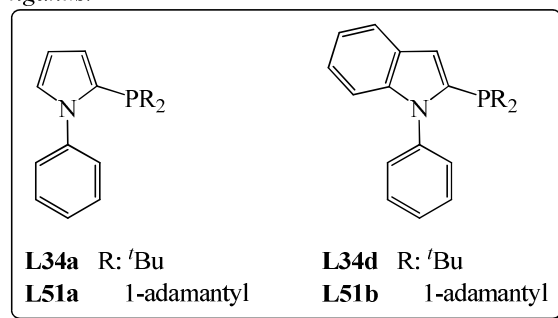
**Scheme 2.42** Etherification of porphyrins by Buchwald-Hartwig cross-coupling.<sup>74</sup>

Beller *et al.* screened several indol phosphines (Scheme 2.43) and investigated the influence of phosphorous substituent on catalytic activity, which is similar to biphenyl phosphorous ligands applied by Buchwald and co-workers.<sup>75</sup> Activated and unactivated aryl chlorides were coupled with phenols. *Tert*-butyl substituted ligands gave best results.



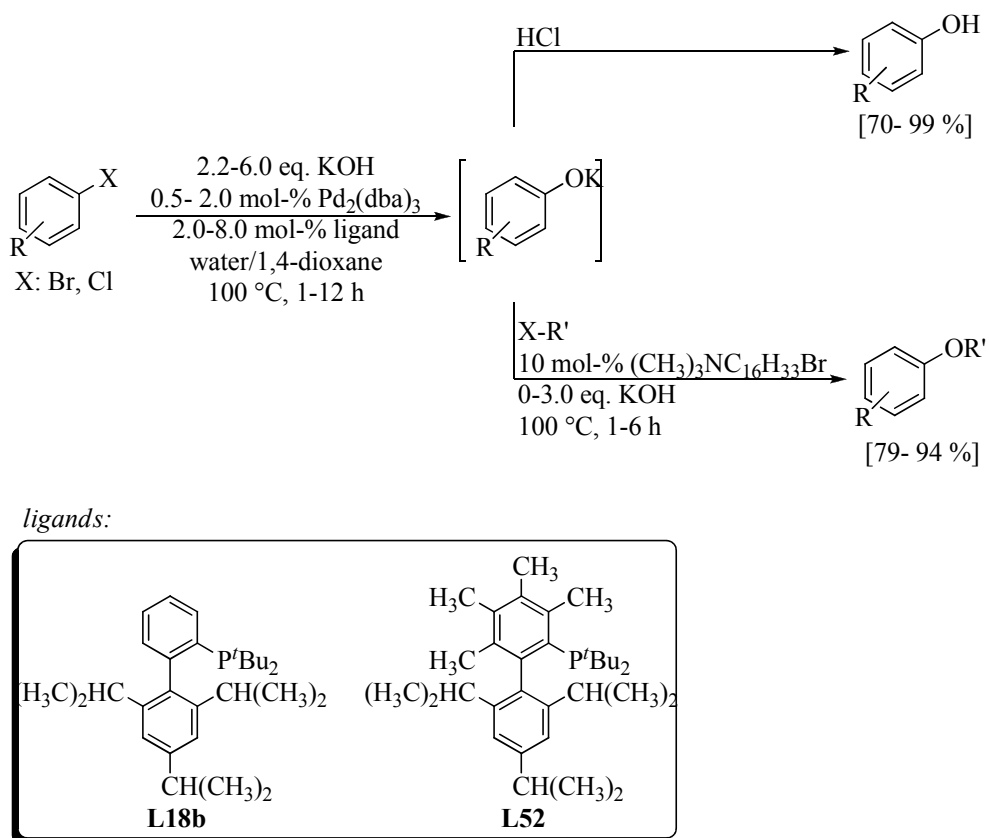


ligands:



**Scheme 2.43** Diaryl ether formation using indol phosphine derivatives as ligands.<sup>75</sup>

The palladium-catalyzed phenol formation was described by Buchwald *et al.* in 2006 (Scheme 2.44).<sup>76</sup> Electron-neutral and -rich, *ortho*-substituted and functionalized (hetero-)aryl bromides and chlorides were converted in water/ 1,4-dioxane with potassium hydroxide as base. When the reaction was performed in neat water the aryl halide was used as co-solvent. In toluene no reaction was observed. The intermediate potassium alcoholate can further be converted into alkylaryl ether with halogenated alkanes (Scheme 2.44). With potassium phosphate as base instead of potassium hydroxide the formation of diaryl ether took place. The attack of the hydroxide to  $L_n\text{Pd(II)ArBr}$  is predominant to the attack of potassium phenoxide.



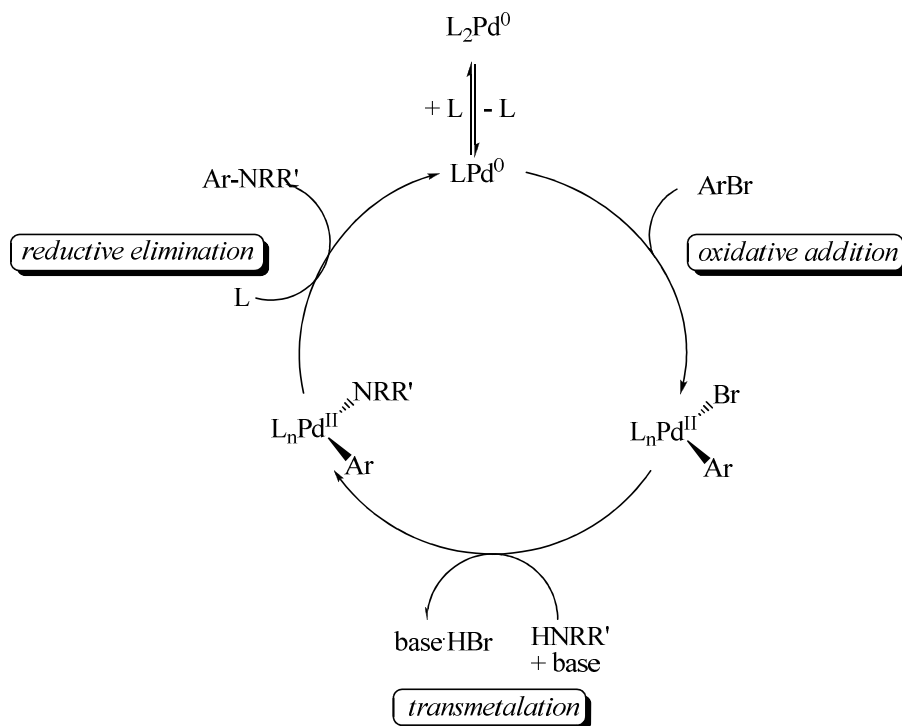
**Scheme 2.44** Formation of phenols and ethers using phosphine biphenyl ligands.<sup>76</sup>

### 2.1.3 Mechanistic Studies

Catalytic cross-couplings typically occur in three stages (Scheme 2.45): oxidative addition of an aryl halide to a palladium(0) centre, transmetalation of the nucleophile to generate an intermediate with the nucleophile bound to palladium, reductive elimination with bond formation between the aryl and the nucleophile and regeneration of the palladium(0) complex. Each of these steps is a multi-step process often including ligand dissociation.

For aryl bromides and chlorides the oxidative addition is often described as the rate limiting step. A proper choice of the ligand is necessary to accelerate the oxidative addition. The yields and scope of the reaction are generally controlled by the reductive elimination. Therefore, the reductive elimination need to be faster than the side reactions, such as  $\beta$ -H- elimination, protonolysis of the metal amide or disproportion of the aryl palladium complex to form biaryl complexes leading to the formation of biaryls after reductive elimination.

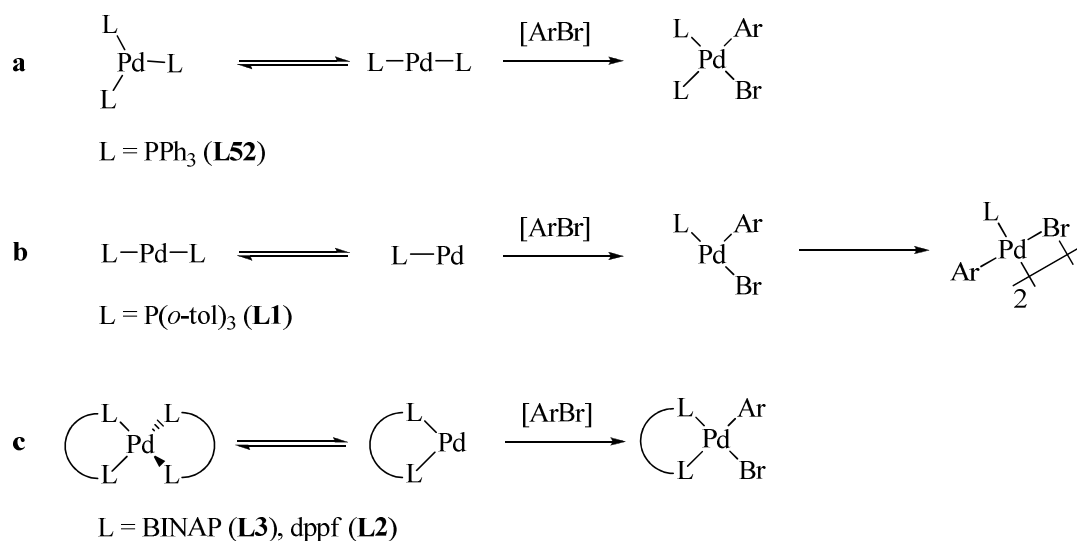
Each step was carefully investigated during the last decade by the groups of Buchwald and Hartwig.



**Scheme 2.45** General catalytic cycle for palladium-catalyzed C-N cross-coupling reaction.

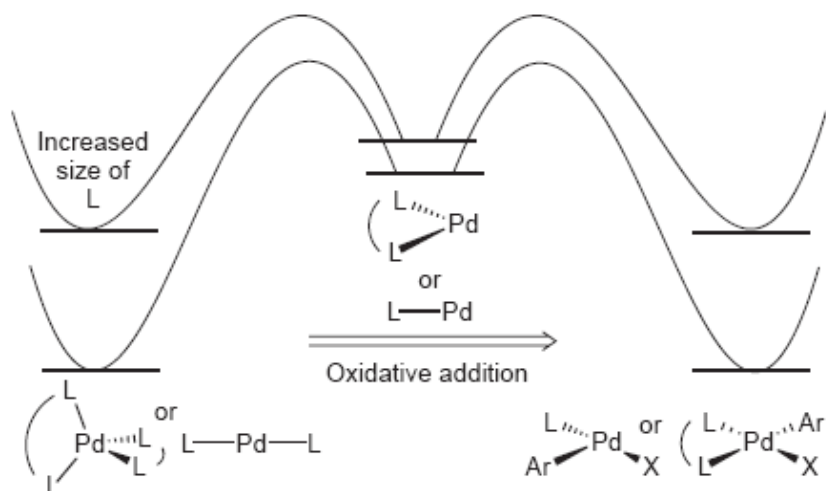
#### *Oxidative Addition:*

Depending on the phosphine ligand attached to the palladium centre several mechanisms for the oxidative addition are possible. Fauvarque and Amatore *et al.* showed that a triphenylphosphine ligand has to disappear before the  $Pd(PPh_3)_2$ -complex can insert into the aryl-halogen bond (Scheme 2.46a).<sup>77</sup> Hartwig and co-workers showed for sterical demanding ligands, such as QPhos (**L30**) or tritolylphosphine (**L1**), that one ligand needs to be cleaved off to form the reactive palladium(0) complex (Scheme 2.46b).<sup>78</sup> When the ligand is  $P(o\text{-tol})_3$  (**L1**) the tricoordinate complex forms a stable dimer. For chelating ligands a complete dissociation of one chelating ligand has to take place (Scheme 2.46c).<sup>79</sup> The resulting bent two-coordinate complex undergoes the oxidative addition of aryl bromide. A minor role plays the displacement of a bidentate ligand from a tetra-coordinate palladium complex by the reaction with aryl bromide.



**Scheme 2.46** Three proposed mechanisms for the formation of an active palladium catalyst.<sup>77-79</sup>

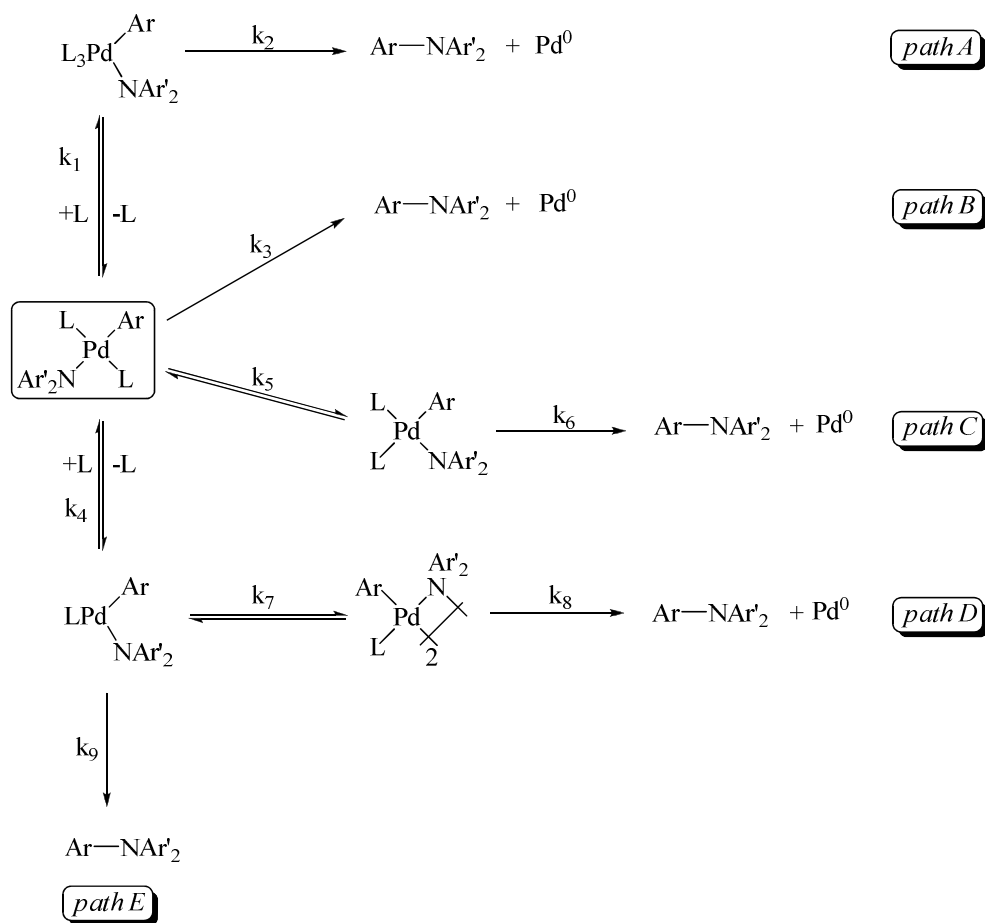
The effect of sterical hinderance on the oxidative addition of aryl halides is displayed in Chart 2.17.<sup>80</sup> Due to the ligand dissociation the catalytic active palladium(0) complex is formed, which has a higher energy level than the applied precatalyst. After the oxidative addition of the aryl halides a stable aryl-palladium halide is formed. Sterically more demanding ligands at the palladium centre increase the energy of the precatalyst in higher amount than for the low-coordinate palladium(0) intermediate. In conclusion, the energy difference between the ground state and the catalytic intermediate of the palladium(0) complex is smaller for more hindered ligands bound to the palladium.



**Chart 2.17** Energy diagram for the palladium catalyst during the oxidative addition of the aryl halide.<sup>80</sup>

#### *Reductive elimination:*

Before Hartwig and co-workers began studies on amination of aryl halides no mechanism for the reductive elimination of amines from transition metals was known. The process was studied for the formation of aromatic amines from aryl-palladium amido complexes ligated by triphenylphosphine.<sup>81</sup> In Scheme 2.47 several conceivable pathways for the reductive elimination are displayed. Kinetic studies of this reaction related to anilido and alkylamido aryl-palladium complexes showed that the reductive elimination occurs *via* two of the possible pathways. The faster elimination takes place starting from the three-coordinate palladium complex in path E. Path C is slower and includes the ligand replacement in the four-coordinate palladium complex.



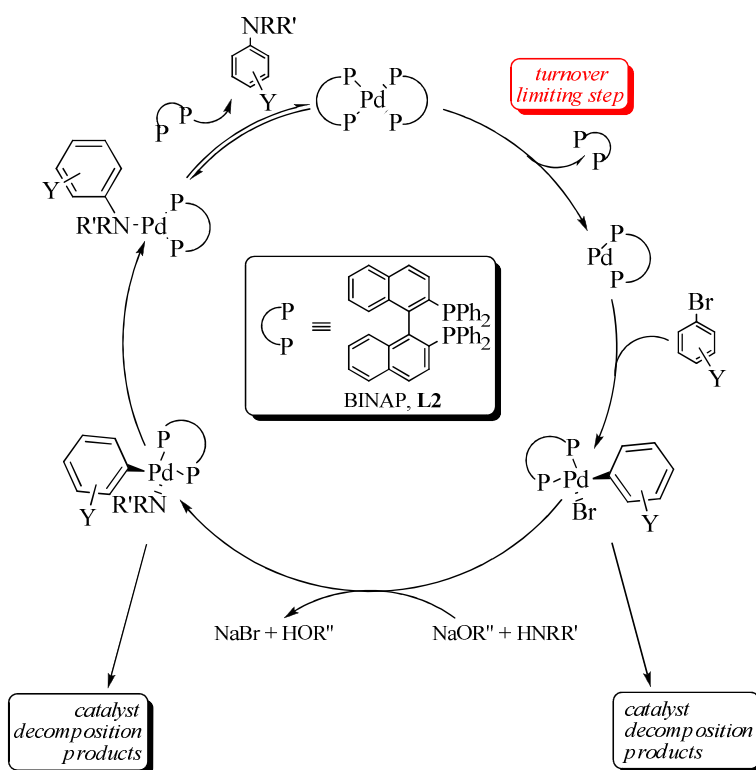
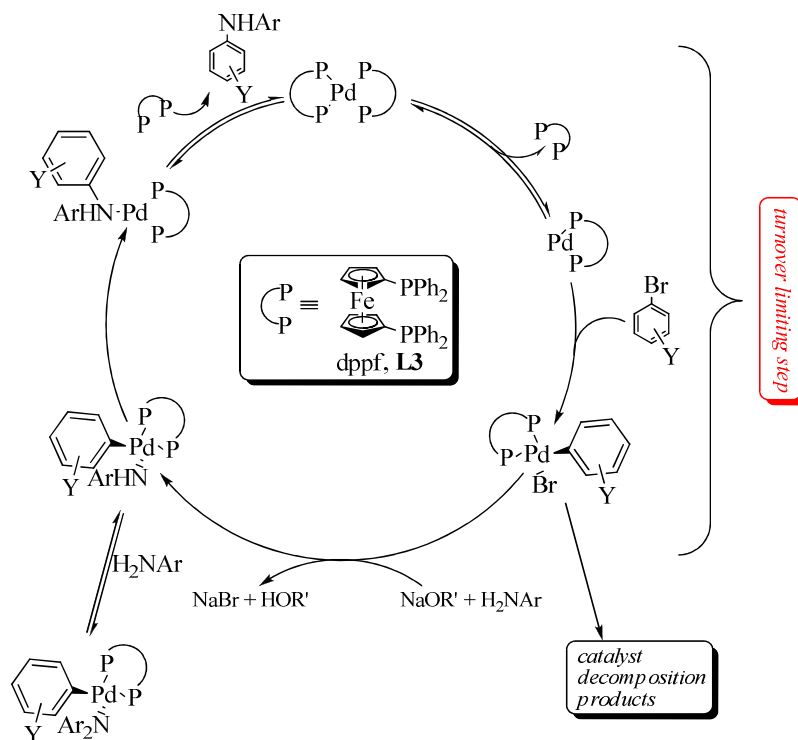
**Scheme 2.47** Conceivable reaction pathways for the formation of the C-N bond by reductive elimination.<sup>81</sup>

The palladium-catalyzed C-N cross-coupling was monitored by NMR. To confirm the kinetic data, which were implied for the reductive elimination the four-coordinate aryl-palladium amido complexes were synthesized. Observations at the reductive elimination itself showed that C-N bond formation was faster for amido complexes bearing electron-donating groups at the nitrogen. For example the formation of *N*-alkylarylamines from alkylamido complexes occurred at 0 °C, whereas the reductive elimination of triarylamines requires elevated temperatures (65 °C). On the other hand more electron-deficient aryl-groups bound to the palladium centre reacted faster. This trend could be due to the favourable coupling of the nucleophilic nitrogen to electrophilic aryl-groups.

For aryl-palladium amido complexes bearing chelating ligands the reductive elimination was preferred to  $\beta$ -hydride elimination (Scheme 2.11). The  $\beta$ -hydride elimination was shown to take place from the three-coordinate aryl-palladium amido

complex.<sup>82</sup> Therefore, chelating bidentate ligands promote the reductive elimination with formation of nitrogen-aryl bond.

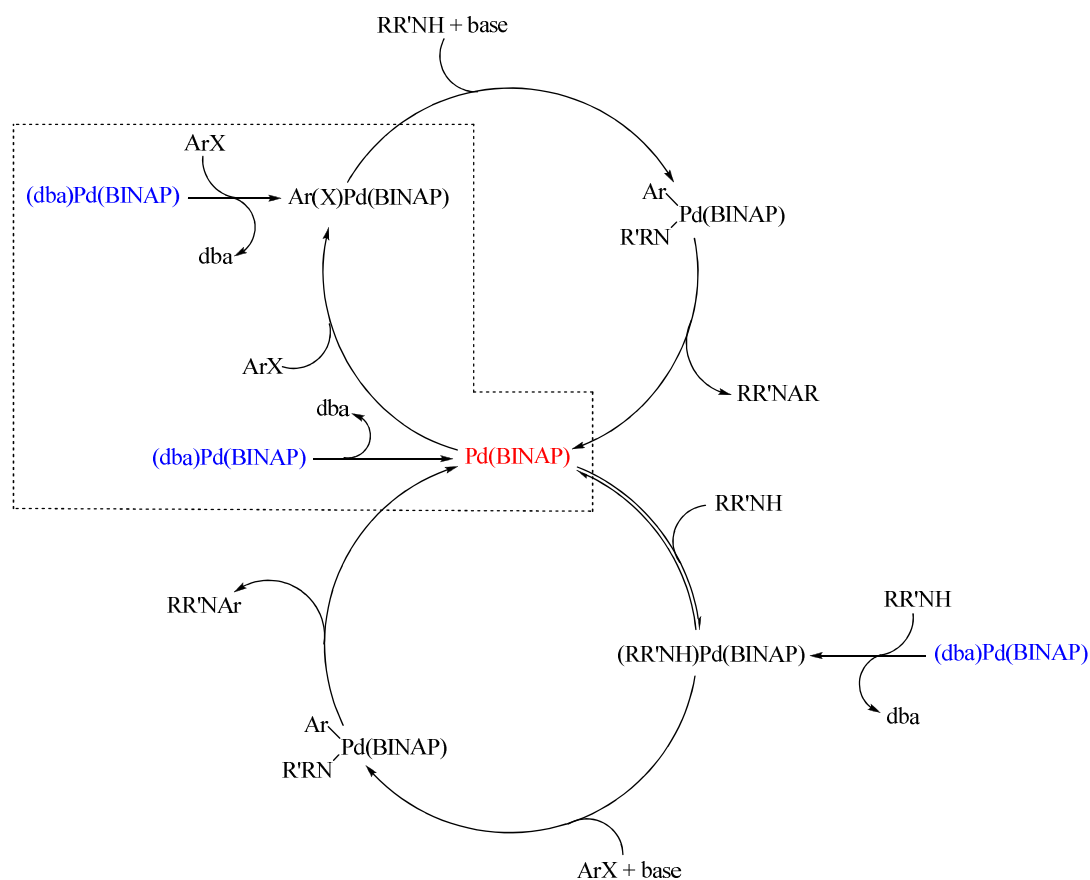
Due to the results Hartwig and co-workers found for the individual reaction steps catalytic cycles were proposed in 2000 (Scheme 2.48).<sup>79</sup> Primary alkyl- and aromatic amines and secondary cyclic alkylamines as well as secondary alkylarylamines were coupled to bromoarenes using BINAP (**L2**) as ligand (cycle A). On the other hand anilines were arylated in the presence of dppf (**L3**) as ligand at the palladium centre (cycle B). In all cases the oxidative addition turned out to be the rate limiting step. The reaction of aryl bromide with palladium-BINAP complex showed inverse first-order dependence on the added ligand for low aryl bromide concentration. For higher amounts of the reactant the reaction became solely dependent on the rate of ligand dissociation. Similar qualitatively data was found by <sup>1</sup>H NMR spectroscopy for dppf as ligand. The rate constant for the overall amination reaction was zero order in aryl bromide, amine, base and ligand for BINAP, while they were first order in catalyst loading. The reaction rate constant is exclusively dependent on the dissociation of ligand during the oxidative addition. Deviation from this data was observed when secondary amines were coupled to aryl bromide. This was due to catalyst decomposition, as detected during the kinetic studies. When dppf was applied as ligand the reaction rate constant was zero order in amine and base, inverse first order in ligand and first order in aryl bromide. At low concentrations of ligand the reaction became first order in amine. This unexpected behaviour is due to the reversible reaction between product and catalyst.

**Cycle A****Cycle B**

**Scheme 2.48** Catalytic cycles for BINAP and dppf as ligands proposed by Hartwig *et al.*<sup>79</sup>



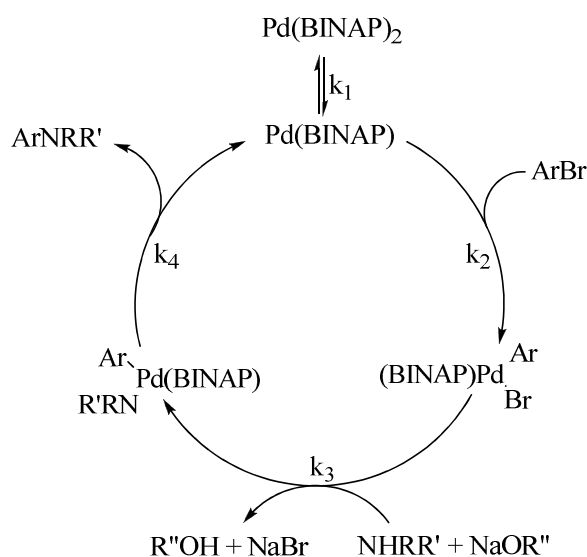
While Hartwig and co-workers did the kinetic studies mostly by NMR spectroscopy, Buchwald *et al.* undertook calorimetric kinetics.<sup>83</sup> Bromobenzene was reacted with primary and secondary amines using  $\text{Pd}_2(\text{dba})_3/\text{BINAP}$  mixture as well as several preformed catalysts with BINAP as bidentate chelating ligand. The induction period observed suggested a change of the palladium species (Scheme 2.49). Premixing of all components except bromide gave greatly increased initial rates during the sequential addition of aryl bromide. The reaction was faster for primary than for secondary amines.  $\text{Pd}(\text{BINAP})_2$  does not play a role in the catalytic cycle. Additionally to oxidative addition of aryl bromide to the palladium centre the addition of amine to  $\text{Pd}(\text{BINAP})$  was proposed and supported by kinetic modelling of sequential reaction experiments, as shown in the lower cycle in Scheme 2.49. Buchwald *et al.* found the amination to be positive order in amine and bromide and zero order in base. The part shown in dotted lines was examined by Amatore *et al.*<sup>84</sup>



**Scheme 2.49** Catalytic cycle for arylation of amines proposed by Buchwald *et al.* in 2002.<sup>83, 84</sup>

The main difference from studies made by Hartwig *et al.* lies in the reaction conditions applied for kinetic studies. While Hartwig and co-workers investigated each step individually with stoichiometric ratios of reactants and catalyst, Buchwald *et al.* investigated under concentration ratios similar to usual reaction protocols for amination of aryl bromides.

Due to complexity of the catalysis the investigation of mechanism went on. In 2006, Hartwig and Buchwald *et al.* corrected their proposals.<sup>85</sup> Several studies were combined to determine the components present in the catalytic system as well as kinetic data to calculate reaction rates. The reactions were investigated under stoichiometric and catalytic conditions. NMR spectroscopy gave insight into catalyst composition under reaction conditions. In more careful investigations the amine was found to have no effect on oxidative addition or catalyst composition, because the insertion of palladium into the aryl halide bond is much faster than the coupling of amine to the metal centre. However, the catalyst decomposes over time and the catalyst mixture is different for primary and secondary amines. The finding that primary amines react faster than secondary ones, as published by Buchwald *et al.*, was disproved. Due to sensitive incubation during the sequential addition of primary amines wrong kinetic data were determined. The bis-chelated  $\text{Pd}(\text{BINAP})_2$  complex lies off the catalytic cycle and serves as catalyst precursor. The corrected catalytic cycle is displayed in Scheme 2.50.



**Scheme 2.50** Corrected catalytic cycle for the amination of aryl bromides.<sup>85</sup>

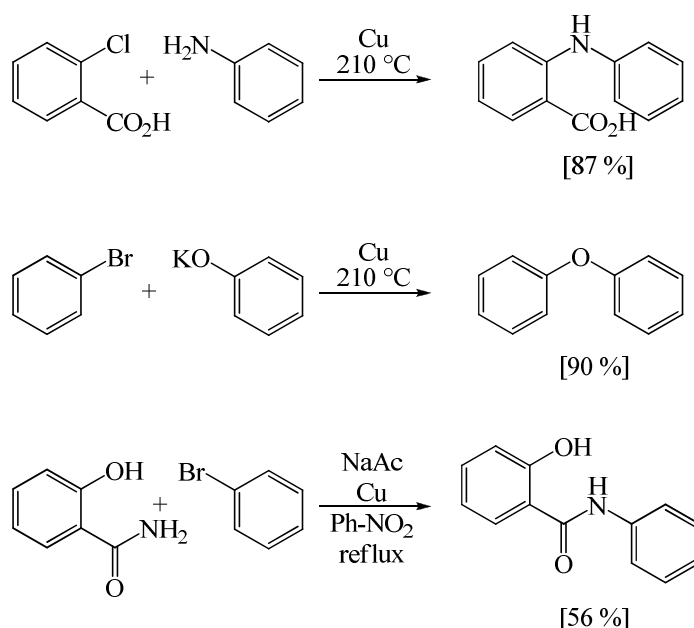
### 2.1.4 Conclusion

In contrast to copper-mediated coupling in Buchwald-Hartwig etherification bromides and chlorides gave higher yields than iodides, because a higher rate of reduction is observed for aryl iodides than for corresponding bromides and chlorides. The nature of ligand plays a key role in palladium-catalyzed amination. Electron-rich ligands increase the electron-density at the palladium centre and favour the oxidative addition. Bulky ligands shift the equilibrium between  $L_2Pd$  and  $LPd$  in favour the  $LPd$ , which is discussed to be the active species. Also the reductive elimination is facilitated by bulky ligands, but makes oxidative addition more difficult. In 1977, Tolman *et al.* published investigations about the properties of phosphine ligands in organometallic chemistry.<sup>86</sup> Several properties can be plotted against each other (e.g. electronic parameters against cone angle). For optimizing a reaction changing the ligand these plots can be used.

## 2.2 Ullmann Reaction

Ullmann cross-coupling is known since more than 100 years. In 1903, Ullmann investigated the copper-catalyzed arylation of anilines.<sup>1</sup> Two years later he described the etherification in melt using copper as catalyst.<sup>87</sup> Irma Goldberg developed an amidation of aryls using copper powder (Scheme 2.51).<sup>88</sup> For first time unactivated aryl halides were used, while the classical nucleophilic substitution required electron-deficient aryl halides and strong nucleophiles.

Two different transformations referred to Ullmann reaction. The classical one describes biaryl synthesis *via* copper catalysis. The Ullmann-type reaction, also known as Ullmann-condensation, includes copper-catalyzed nucleophilic aromatic substitution between various nucleophiles and aryl halides.



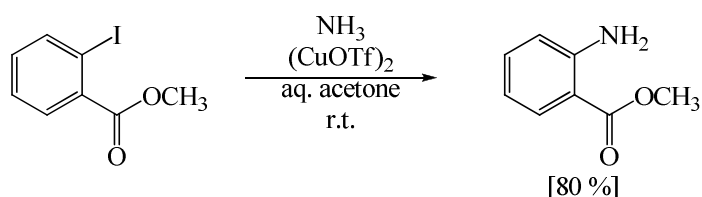
**Scheme 2.51** Copper-catalyzed arylation of *N*- and *O*-nucleophiles described by Ullmann and Goldberg.<sup>87, 88</sup>

In typical Ullmann-condensations cupric salts, which are insoluble in organic solvents, are used. The heterogeneous systems require high reaction temperatures. Also toxic solvents, such as HMPA, are used to favour the reaction. These reaction conditions don't tolerate a lot of functional groups. Additionally, inconsistent results are obtained from the use of different copper sources. Despite these drawbacks and the developments in palladium-based methodology, copper-mediated reactions remain the reaction of choice in industrial scale.<sup>89</sup> This is favoured by the use of cheap starting materials, which are insensitive to air and not affected by moisture.

Novel developments on arylation of *N*-, *O*- and *S*-nucleophiles were initiated to better understand the solubilizing and accelerating effects exhibited by substrates and ligands. The choice of ligand, solvent and base is as important as in palladium catalysis.<sup>90</sup>

### 2.2.1 Arylation of *N*-Nucleophiles

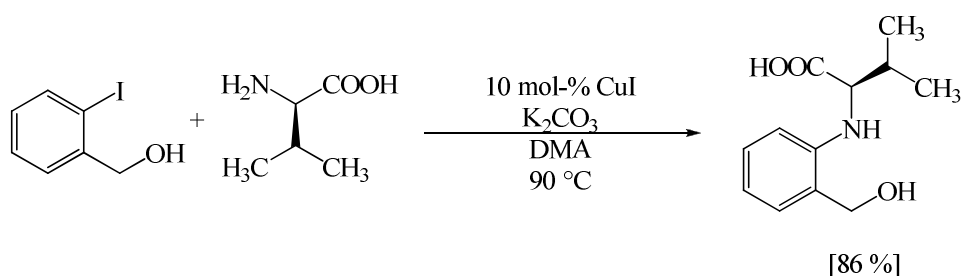
Already in 1975 Cohen and co-workers described the copper-catalyzed amination of iodobenzene derivatives using ammonia.<sup>91</sup> They observed an intramolecular assistance by neighbouring coordination groups. But the examples are rare (Scheme 2.52).



**Scheme 2.52** Formation of aniline derivatives using ammonia and a copper(I) catalyst.<sup>91</sup>

Kasai *et al.* also observed the intramolecular assistance of acid groups at aryl bromides.<sup>92</sup> For the amination of 2-bromobenzoic acid 10 mol-% copper(I) iodide was used in DMF at 100 °C. The nucleophile was deprotonated by potassium carbonate.

Not only halogenated substrates can facilitate the coupling due to coordinating functional groups. In 1998, Ma *et al.* described an effective cross-coupling of iodo- and bromobenzenes with  $\alpha$ -amino acids (Scheme 2.53).<sup>93</sup> This method was extended to  $\beta$ -amino acids to give the coupling products in good yields. The structure-catalytic activity relationship on the chelating nature of the starting amino acid was investigated.<sup>94</sup> The conditions described here were used to synthesize several pharmaceuticals.<sup>95</sup>

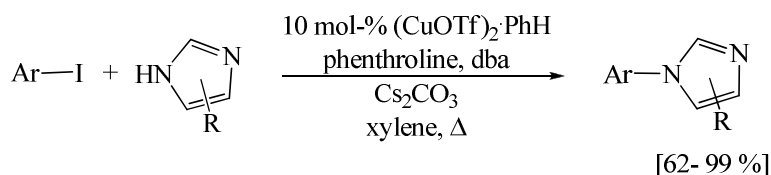


**Scheme 2.53** Copper-catalyzed C-N cross-coupling of amino acids to aryl iodides.<sup>93</sup>

The same protocol was used under microwave irradiation by Larhed and co-workers, who described the coupling of various aryl bromides with amino acids.<sup>96</sup> The reaction was carried out in water with small quantities of potassium iodide. After 40 minutes at approximately 180 to 185 °C the coupling products were obtained in good yields and purity with negligible amount of racemisation product.

Buchwald *et al.* described the arylation of imidazoles using copper(I) triflate with phenanthroline and dibenzylidene acetone (dba) as additives.<sup>97</sup> The reaction proceeds in

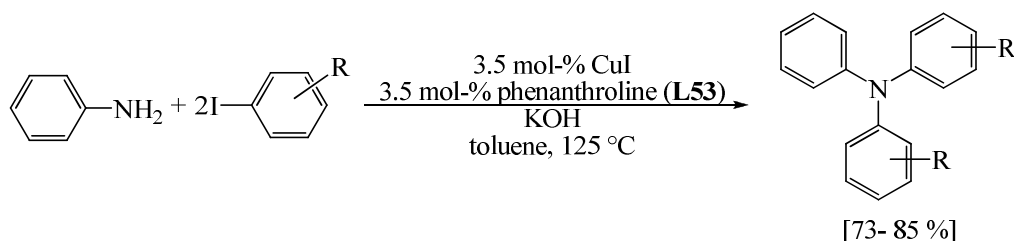
non-polar solvents using cesium carbonate as base. Both electron-rich and -deficient aryl iodides and bromides were coupled (Scheme 2.54).



**Scheme 2.54** Arylation of imidazoles using a copper(I) triflate as catalyst.<sup>97</sup>

The same catalytic system was used by Arterburn and co-workers to couple 5-iodouracil with various amines.<sup>98</sup> Best results were obtained by using equimolar amounts of phenanthroline with traces of dibenzylidene acetone. Also the use of catalytic amounts of dppf (**L3**) with copper(I) triflate gave good results. A drawback of this method is the use of an expensive cupric salt, which additionally requires special handling. Quite soon better catalytic systems were described in literature.

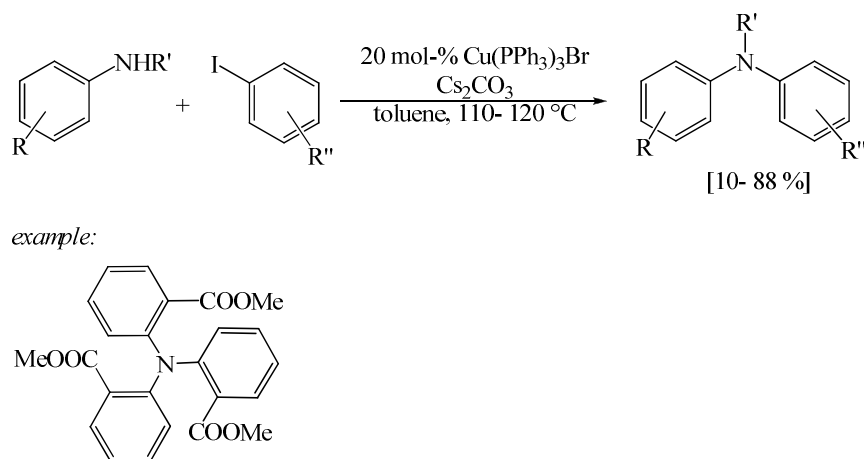
Goodbrand *et al.* described copper(I) iodide to effectively catalyze the formation of triaryl amines starting from aniline derivatives and iodo arenes.<sup>99</sup> The amines found application in photoreceptors. Both mono- and diarylation of the amine were observed. A good catalytic activity even at 50 °C was observed for both mono- and diarylation of the amine.



**Scheme 2.55** Formation of triaryl amines starting from anilines and iodobenzenes.<sup>99</sup>

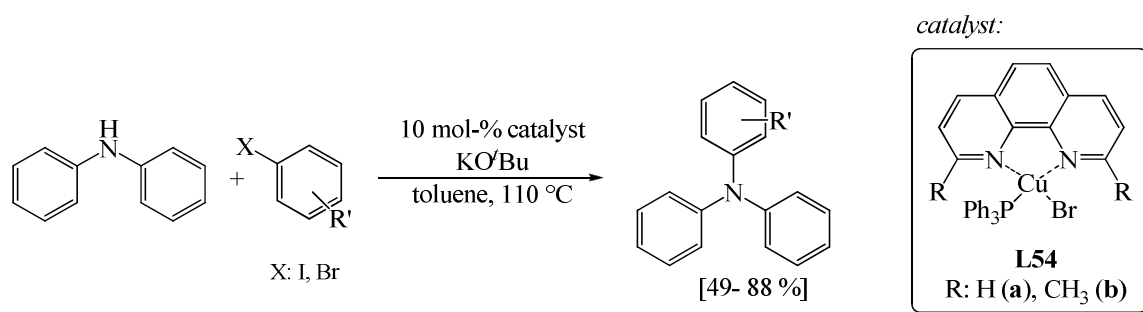
In 2001, the group of Venkataraman developed a copper(I) catalyst ( $\text{Cu}(\text{PPh}_3)_3\text{Br}$ ), which is soluble in organic solvents (e.g. THF, dichloromethane, acetonitrile, chloroform, NMP, DMF, DMSO, toluene and benzene).<sup>100</sup> It is insoluble in methanol, ethanol and

diethyl ether. The catalyst was synthesized by mixing cupric bromide with triphenylphosphine in methanol. Diarylamines were only obtained, when amine, catalyst and base were heated up to 110 °C for five minutes before the iodide was added to the mixture (Scheme 2.56). If all starting materials were mixed at room temperature and heated to 110 °C only a black precipitate was observed, without any C-N cross-coupling. Even sterical demanding triaryl amines were obtained by this method. Tri(2-methylbenzoate)-amine could not be synthesized using palladium catalyst, due to the *ortho*- ester functionality.



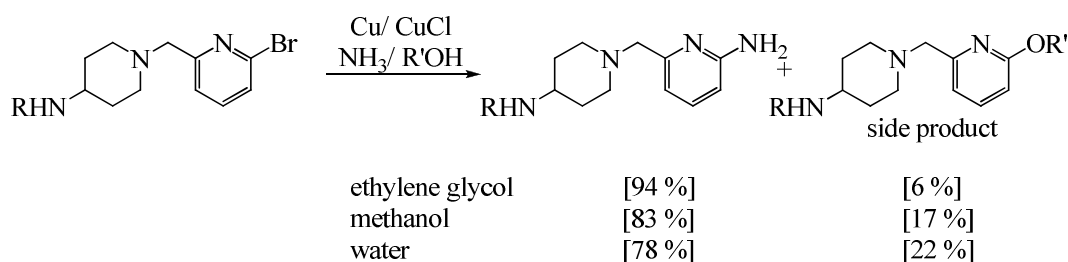
**Scheme 2.56** Copper-catalyzed amination of aryl iodides.<sup>100</sup>

The application of phenanthroline as ligand further enhanced the catalytic activity of copper(I) triphenylphosphine (Scheme 2.57).<sup>101</sup> Therefore, not only aryl iodides, but also bromides can be coupled. The complex is stable towards air and moisture and soluble in common organic solvents, as described above. Sodium *tert*-butanolate and cesium carbonate as bases are less effective, and weaker bases are ineffective to the coupling. With neocuproine as ligand instead of phenanthroline the reaction proceeds two times faster. The scope of the catalyst was further extended to the arylation of primary amines.



**Scheme 2.57** Arylation of secondary amines using a soluble copper(I) complex.<sup>101</sup>

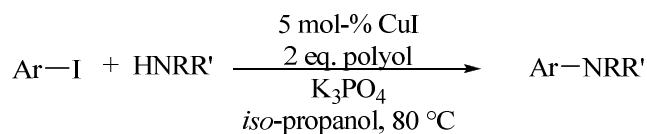
In 2001, the group of Lang investigated the amination of aryl bromides with ammonia in several protic solvents.<sup>102</sup> The coupling product of the halide with the solvent was obtained as side product. Ethylene glycol as a chelating solvent gave best results in the amination reaction (Scheme 2.58).



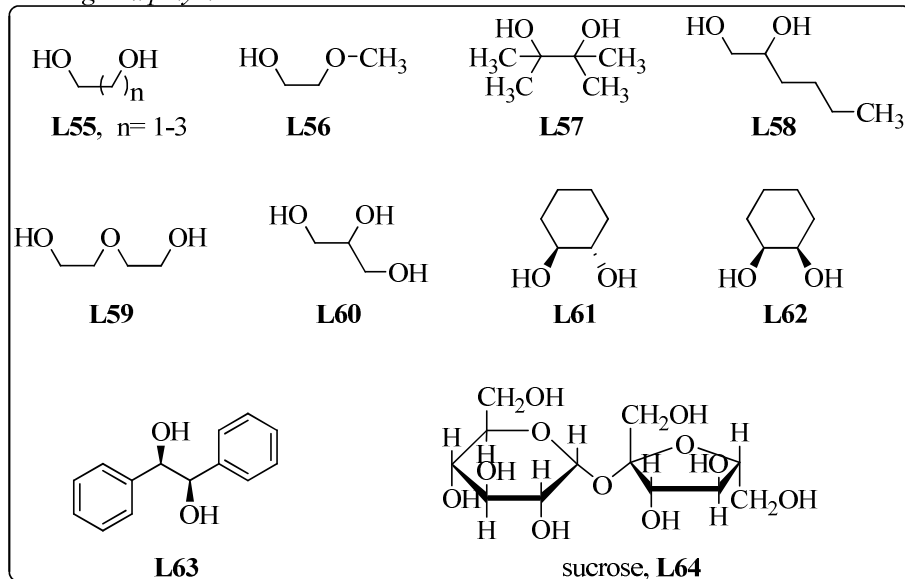
**Scheme 2.58** Amination of halogenated pyridines in protic solvents.<sup>102</sup>

Buchwald and co-workers tested several polyols for the C-N cross-coupling (Scheme 2.59).<sup>103</sup> Ethylene glycol gave the best results in this series. With a mild base and copper(I) iodide the reaction proceeded at low temperatures. Aryl iodides and bromides were coupled to anilines, and primary and secondary aliphatic amines. Copper(I) iodide turned out to be the best catalyst, but also other copper(I) and copper(II) salts were reactive precursors. The reaction is neither air nor moisture sensitive. As solvents also butanol can be used. Toluene, dioxane and DMF led to lower yields.



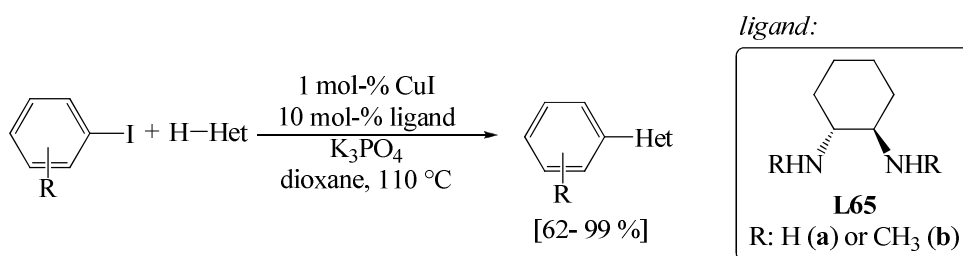


investigated polyols:



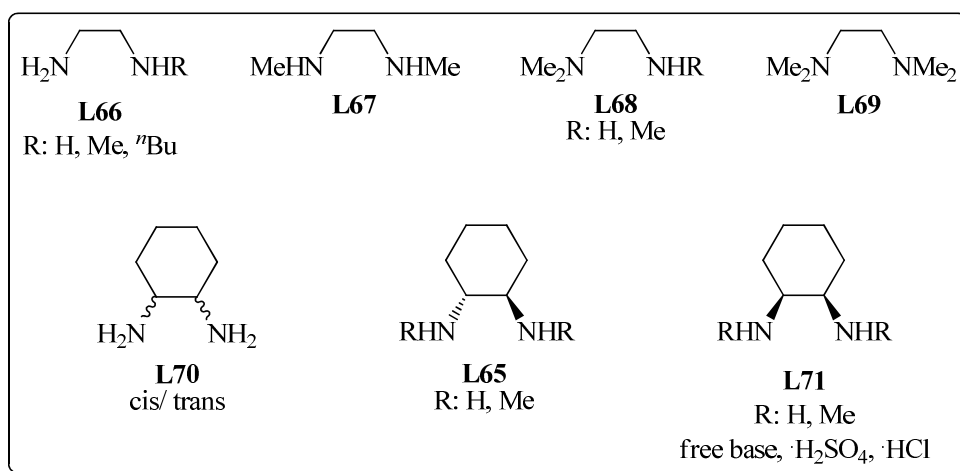
**Scheme 2.59** Optimization of C-N cross-coupling using polyols as ligands.<sup>103</sup>

Instead of diols, also diamines can be used as ligands. Buchwald *et al.* found 1,2-diaminocyclohexane to accelerate the arylation of heterocycles, such as imidazoles, indoles, carbazoles, pyrazoles and phthalazines.<sup>104</sup> With 1,2-diaminocyclohexane (**L65a**) aryl iodides and bromides can be converted. For the nucleophilic substitution of aryl chlorides the use of *N,N'*-dimethylamino cyclohexane (**L65b**) was applied (Scheme 2.60).



**Scheme 2.60** Arylation of heterocycles using 1,2-diamino cyclohexane as ligand.<sup>104</sup>

One year later a variety of diamines were screened in the arylation of indoles (Chart 2.18).<sup>105</sup> *N,N'*-Dimethylethylenediamine gave best results in combination with copper(I) iodide as precursor. Despite of this also other cupric salts and copper bronze can be applied. The choice of solvents is no critical parameter, but mostly toluene was used. For the coupling 5 mol-% of copper(I) iodide, 20 mol-% diamine were used with potassium phosphate as base in toluene. Both indole and haloarene can contain amino- and amido-groups.



**Chart 2.18** Screened diamine ligands for C-N cross-coupling of aryl bromides and indoles.<sup>105</sup>

The catalytic system developed by Buchwald *et al.* was applied to resin supported indoles by Wu and co-workers.<sup>106</sup> As arylation agent iodides and bromides can be used. The C-N cross-coupling was performed using copper(I) iodide, diaminocyclohexane (**L70**) and potassium *tert*-butanolate as base in dioxane.

Hayes *et al.* used tetrabutylammonium hydroxide as accelerating additive to copper(I) iodide in acetonitrile for the synthesis of pharmaceuticals.<sup>107</sup> Also amino acids were efficiently coupled.

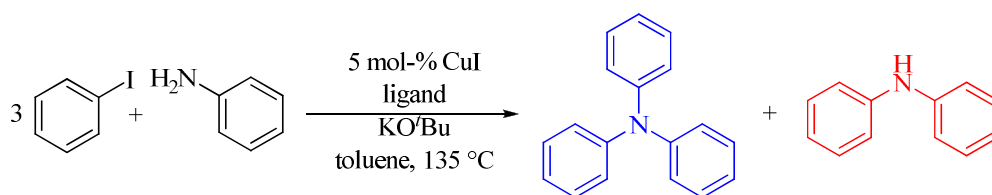
To take up the formation of triarylamines starting from anilines and aryl halides, Chaudhari and co-workers investigated a broad variety of nitrogen- and phosphine-containing ligands (Scheme 2.61).<sup>108</sup> No ligand at all gave the highest yield of desired triarylamines. Potassium *tert*-butanolate as base gave best results. Sodium *tert*-butanolate or methanolate, DBU, cesium carbonate, potassium hydroxide and sodium bicarbonate

were less effective. Highest yields were obtained, when electron-rich aromatic amines were coupled to electron-rich aryl iodides. However, no product was formed with *ortho*- or *para*-nitroaniline.

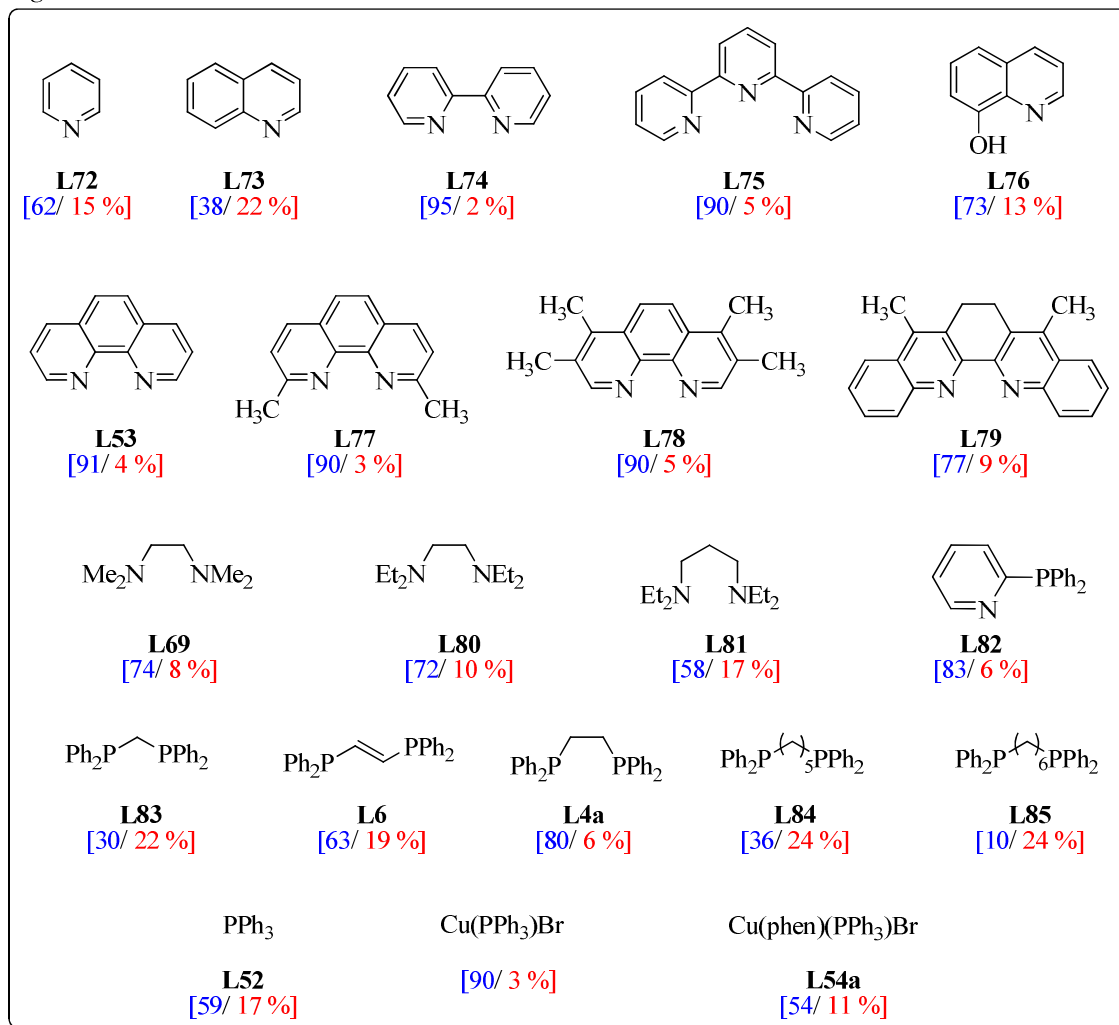
Contradictory results to Venkataraman *et al.* (Scheme 2.56) were observed. Triphenylphosphine made the reaction faster, certainly for the ratio of 1:2 for Cu/ PPh<sub>3</sub>. Pyridine and quinoline ligands were less effective. Referred to the phosphane ligands dppe (**L4a**) gave highest yields for triarylamines. Bipyridine (**L74**) was shown to be the most enhancing ligand in this study. In combination with copper(I) iodide even electron-rich aromatic amines can be coupled to electron-rich aryl iodides at 115 °C in excellent yields.

One year later other simple phosphines were developed to effectively catalyze the formation of triarylamines.<sup>109</sup> Whereas triphenylphosphine (**L52**) was not sufficient for the coupling, tributylphosphine (**L86**) enhanced the C-N cross-coupling of anilines and chlorobenzenes. For the conversion of iodo- and bromobenzene tri(*ortho*-tolyl)phosphine (**L1**) was successively applied.

Rohani and Saban *et al.* investigated similar ligands than displayed in Scheme 2.61 for the tri(tolyl)amine formation.<sup>110</sup> 2,2'-Bipyridine (**L74**) and 4,4'-bipyridine (**L87**) gave highest yields in shortest times for the conversion of *para*-toluidine and *para*-iodotoluene. Screening of the copper(I) salts showed, that the counter ion at the copper(I) centre has no effect to the reaction rate. The C-N cross-coupling of di(tolyl)amine to the tri(tolyl)amine is three times faster than the formation of the di(tolyl)amine starting from *para*-toluidine. In hydrocarbons no solvent effect was observed. But for high conversion water has to be removed.



ligands:



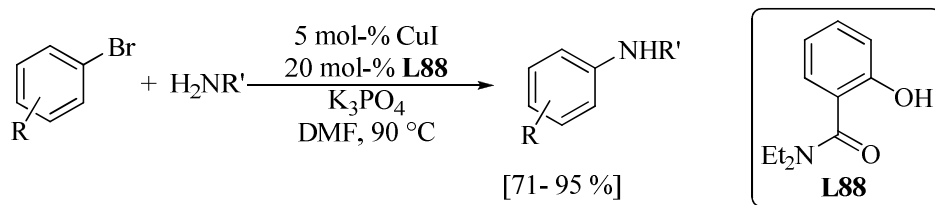
**Scheme 2.61** Formation of triarylamine starting from aniline and iodobenzene using a broad variety of ligands.<sup>108</sup>

In 2002, Fukuyama and co-workers published intramolecular amination without the need of any additive (Scheme 2.62).<sup>111</sup> The preference of cyclization is that high, that halogen atoms present in the substrate in other positions retain in the product.



**Scheme 2.62** Cyclization by Ullmann-type C-N cross-coupling.<sup>111</sup>

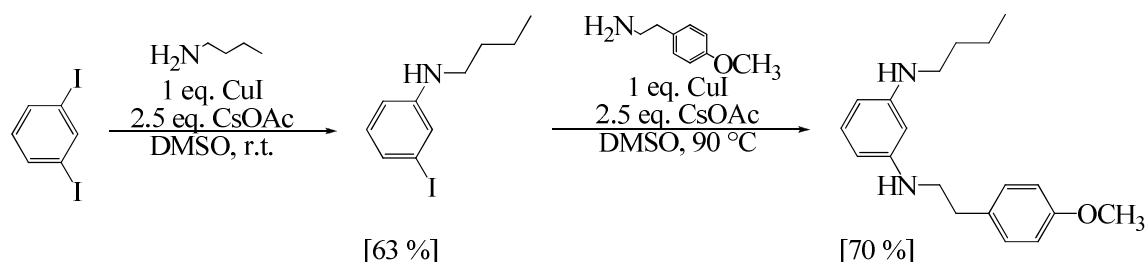
In 2003, Buchwald *et al.* investigated a series of phenols as ligand.<sup>112</sup> Diethylsalicylamide gave the highest conversion and tolerates a variety of functional groups in the bromide, such as hydroxyl-, amino-, ester- and *ortho*-functionalities (Scheme 2.63). The coupling of aryl bromides with primary amines proceeded under mild conditions. Also solvent-free conditions lead into an effective coupling. For intramolecular amination even chlorides can be applied, if higher temperatures are applied. Because the yield was remarkably low, the copper precursor was changed. With copper(I) acetate the reaction rate was enhanced. Organic bases, like DBU or DABCO, were not effective. In DMF better results were obtained than in toluene, DME, dioxane or triethylamine.



**Scheme 2.63** Arylation of primary aliphatic amines using diethylsalicylamide as additive.<sup>112</sup>

Twieg and co-workers described the selective monofunctionalization of dihalobenzenes using *N,N*-dimethylamino ethanol as solvent and chelating agent.<sup>113</sup> Bromo- and iodobenzenes were coupled to secondary and primary aliphatic amines. Copper(I) iodide (10 mol-%) served as catalyst.

The same effect was described by Fukuyama *et al.* for the synthesis of unsymmetrical *N,N'*-dialkylated phenylenediamine (Scheme 2.64).<sup>114</sup> Again copper(I) iodide was used without any additive to couple iodo- and bromobenzene to any amine (primary and secondary aliphatic and cyclic amine, as well as anilines and indoles). *Ortho*-substituted iodoarenes do not react under these conditions.

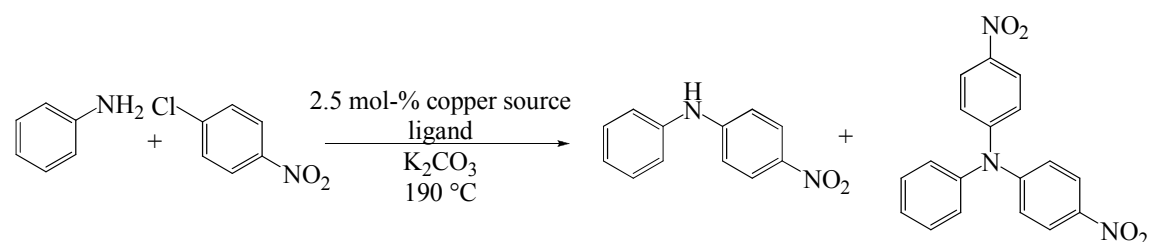


**Scheme 2.64** Synthesis of unsymmetrical *N,N'*-dialkyldiaminophenylenediamine.<sup>114</sup>

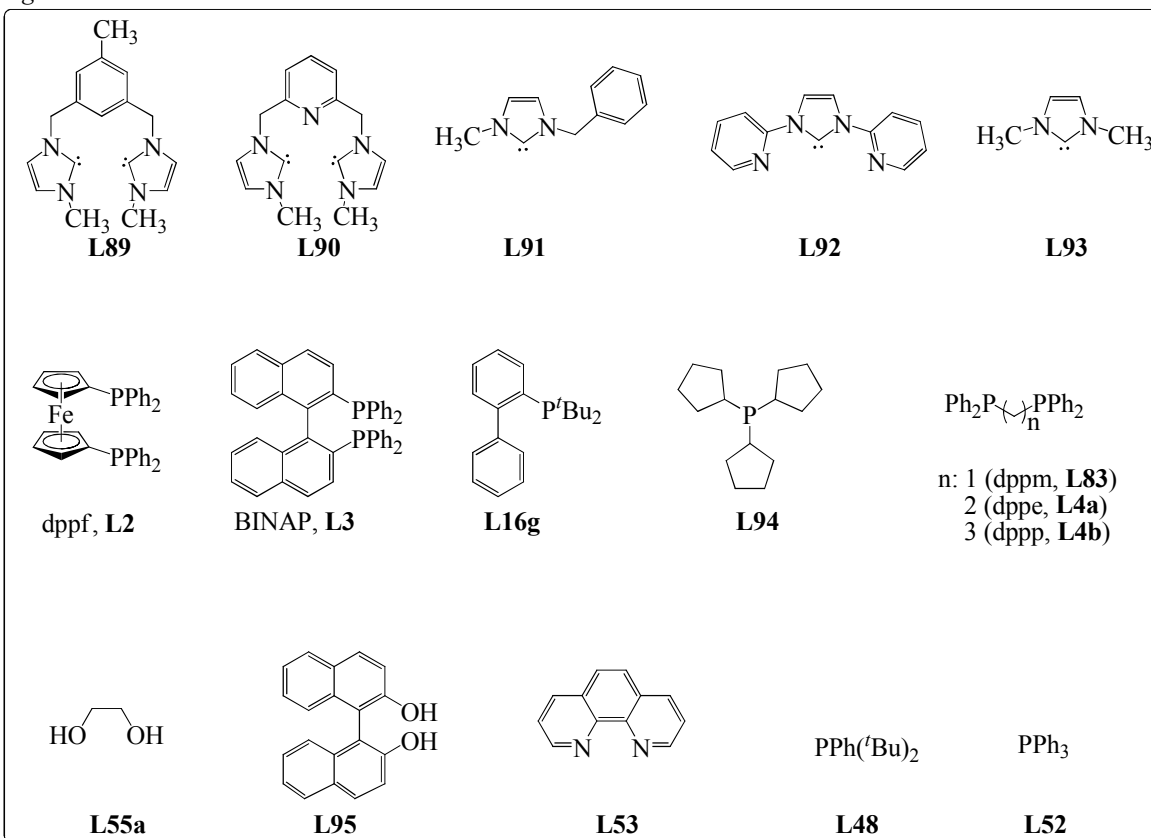
Another development in the Ullmann-type amination was the application of amino acids with secondary amino groups, like in *N*-methylglycine and proline, as ligands.<sup>56, 115</sup> With this catalytic system weaker bases (e.g. potassium carbonate) can be applied. The scope with respect to aromatic amines was not investigated in detail. *N,N*-Dimethylaminoacids were ineffective as ligands.

In the Bayer group the selective monoarylation of anilines with *para*-chloronitrobenzene was investigated.<sup>116</sup> Mono-, bi-, and tridentate ligands were applied. While bidentate ligands such as bisphosphines, phenathroline or glycol are less selective, the group of Scholz found bridged bisimidazolidenes to be most promising in this field (Scheme 2.65).

Because the formation of amines in industrial scale is of high interest for the synthesis of pharmaceuticals, in 2006, the group of Chandrasekhar tested the Ullmann-type C-N cross-coupling in a recyclable solvent.<sup>117</sup> The amination of iodo- and bromobenzene was performed using copper(I) iodide (5 mol-%), diamino ethane (**L66a**, 10 mol-%) as ligand, potassium carbonate as base in PEG-400 at 80 °C. After the extraction with cold diethylether the solvent, containing still the catalyst, was re-used. Due to loss of catalyst in each extraction step the yields decreased gradually. To overcome this problem 2 mol-% of catalyst were added after the third run.



ligands:

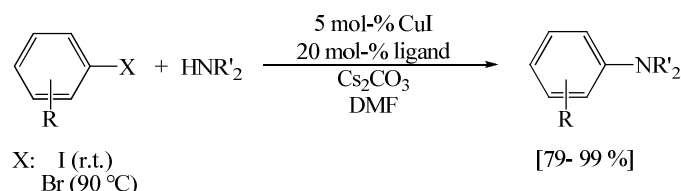


**Scheme 2.65** Ligand screening for selective monoarylation of aniline with *para*-chloronitrobenzene.<sup>116</sup>

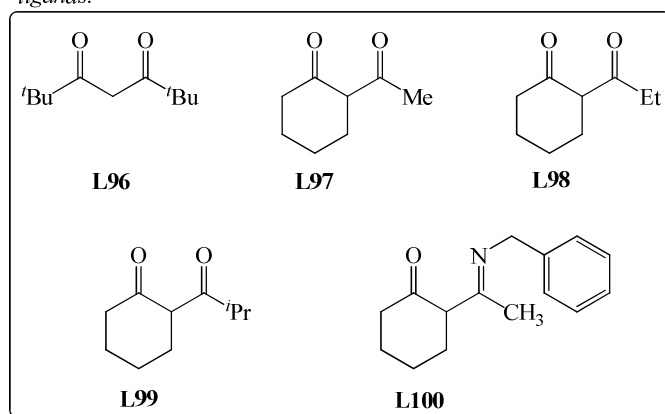
Wolf *et al.* aminated bromobenzene, with acid functionality in *ortho*-position, with primary amines.<sup>118</sup> Together with copper(I) oxide (4 mol-%) and copper (9 mol-%), 2-ethoxyethanol served as catalyst.

Further developments, with respect to the ligand, were made by the group of Buchwald.<sup>119</sup> They investigated a series of diketones, which act as bidentate ligands (Scheme 2.66). The diketones **L97** and **L99** gave conversion in highest amount, whereas with ligand **L99** the reaction rate was accelerated. By enhancing the reaction time, also *ortho*-substituted aryl halides could be aminated. Primary and secondary aliphatic amines

were arylated. These results are complementary to which observed in palladium-catalyzed methods.



ligands:



**Scheme 2.66** Amination under mild conditions using diketones as ligands.<sup>119</sup>

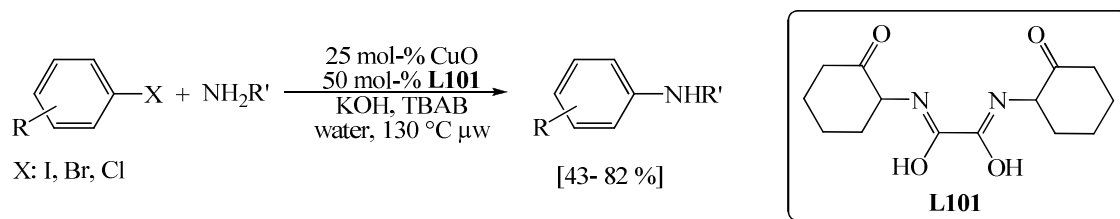
For industrial scale of amination and etherification a protocol without additives was established by van Koten *et al.*<sup>120</sup> Benzylamine and imidazoles were coupled to aryl bromides using copper(I) iodide, bromide or chloride (2.5 mol-%). Best results were obtained for bromide anion. As solvent the basic NMP was shown to be useful, together with potassium or cesium carbonate at 160 °C. For the arylation of imidazoles aryl bromides and iodides gave similar results (67- 79 %), however, chlorides were not tested. The arylation of benzylamine gave only poor results (9- 50 %).

This protocol can also be used under microwave heating conditions. Wu *et al.* described already in 2003 the conversion of aryl bromides into the corresponding amines with azoles, including pyrrole, pyrazole, imidazole and their benzo derivatives.<sup>121</sup> Even free amino groups at the aryl halide are tolerated. The reaction was performed at 195 °C for two hours and the products were obtained in moderate yields.

In 2006, Wan and co-workers described the synthesis of aromatic amines from halogenated arenes with primary amines.<sup>122</sup> The reaction was performed using cupric oxide



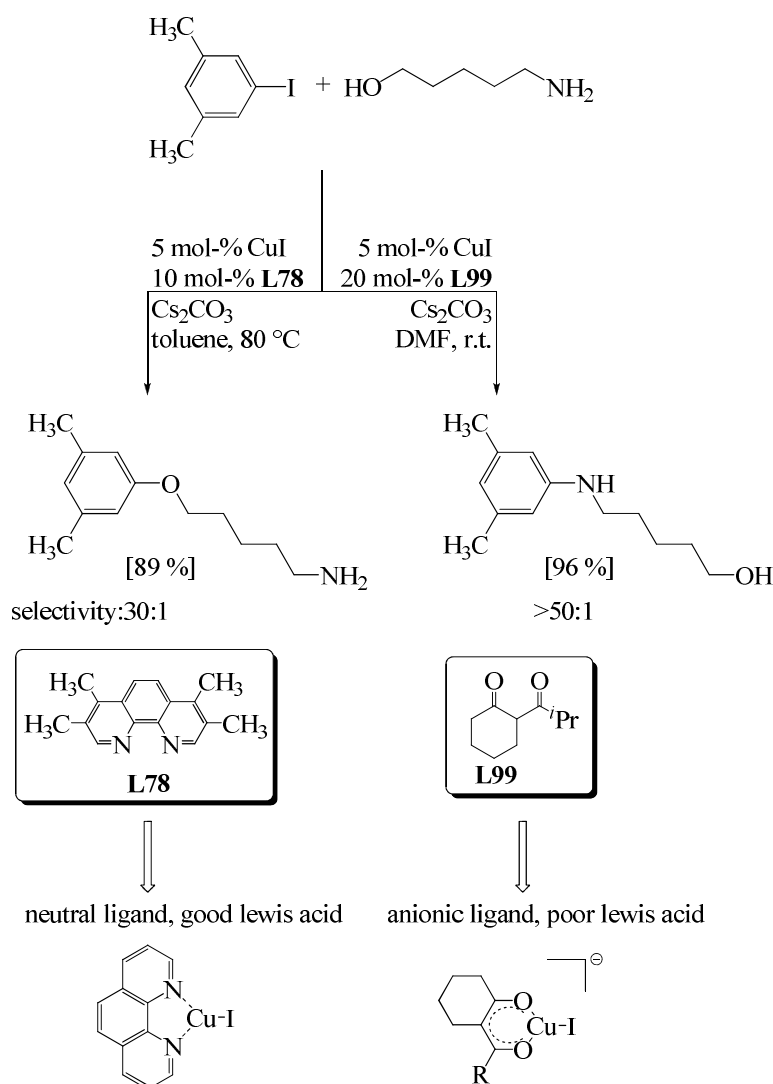
with bis(cyclohexanone)oxalyldihydrazone (BCO, **L101**) at 130 °C under microwave irradiation. Because water was used as solvent with potassium hydroxide as base, a phase-transfer catalyst was added (tetrabutylammoniumbromide, TBAB).



**Scheme 2.67** Coupling of aryl halides with primary amines.<sup>122</sup>

The coupling of aminoalcohols with iodobenzenes was described in 2002 by Buchwald *et al.*<sup>123</sup> Depending on the applied catalyst ether formation or amination was preferred. To activate the amine as nucleophile copper(I) iodide was used with ethylene glycol in *iso*-propanol. On the other hand etherification occurred with butyronitril as chelating solvent. Also the base played an important role. While the amine was deprotonated with potassium phosphate, the alcoholate was formed using cesium carbonate. Concerning the developments made for C-N and C-O cross-coupling, Buchwald proposed new reaction conditions and discussed the effect of copper complexes with respect to the respective nucleophile (Scheme 2.68).<sup>124</sup>

The copper complex with phenanthroline ligand can efficiently bind amines and alcohols. The selectivity determining step is the deprotonation of the nucleophile, which is much faster at the oxygen. However, the diketonate copper complex does not bind effectively to alcohols. Therefore, the selectivity determining step is the coordination of the nucleophile to the copper centre. Diketones as ligands form nearly exclusively arylated amines.



**Scheme 2.68** Chemoselective coupling of aminoalcohols to aryl iodides.<sup>124</sup>

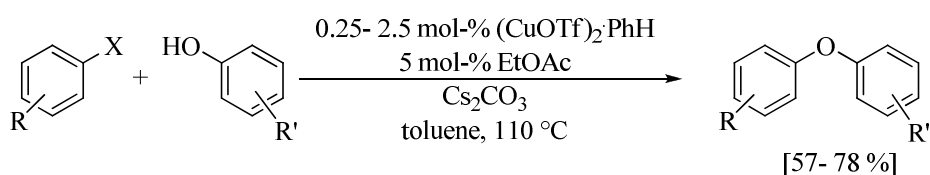
The developments of ligand-assisted couplings dramatically extended the capability of the Ullmann-type amination. The major restriction in the beginning was the low reactivity of secondary acyclic amines, which is most likely due to steric reasons. The scope usually includes primary aliphatic and saturated secondary heterocycles (piperidine, piperazine, pyrrolidine, morpholine ect.). As bases potassium carbonate, phosphate or cesium carbonate were applied. The reactions were performed in various solvents, both polar and non-polar. In classical Ullmann-condensations no difference of reactivity between aryl iodides and bromides were observed.

Palladium and copper catalysis give complementary results. While primary aromatic amines are preferably arylated by palladium catalysts, pyrrole-NH and primary aliphatic amines are effectively coupled to halogenated aryls with copper catalysts.

### 2.2.2 Arylation of *O*-Nucleophiles

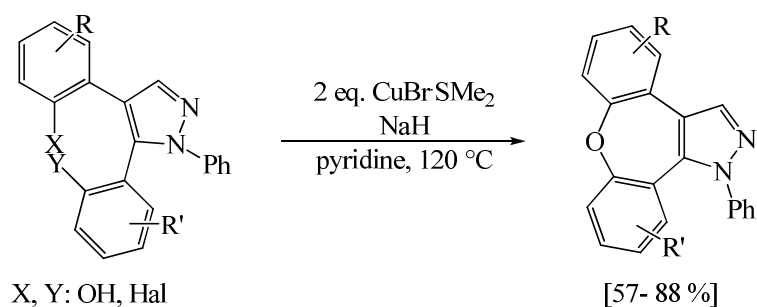
*Ortho*-chlorobenzoic acid was coupled to phenols using copper powder as catalyst in aqueous media.<sup>125</sup> To increase the yield, pyridine was applied as additive. Also ultrasound enhanced the reaction rate. But only *ortho*-activated aryl chlorides were employed.<sup>126</sup>

Buchwald and co-workers established in 1997 copper(I) triflate as soluble catalyst to couple aryl bromides with phenols (Scheme 2.69).<sup>127</sup> A wide range of activated and deactivated aryl bromides and iodides were substituted. Even *ortho*-substituents on both substrates are tolerated. However, there is a request of electron-rich or -neutral phenols. Also other cupric salts, such as copper(I) iodide, bromide, chloride, cupric bromide and sulfate were investigated. Copper(I) triflate gave highest yields due to enhanced solubility. Ethylacetate was applied as copper-ligating additive, for less soluble phenols the addition of 1-naphthoic acid led to significantly increased yields. A cesium base was essential in non-polar solvents. Additionally molecular sieves enhanced the reaction. Cuny used copper(I) triflate with pyridine as base to synthesize verbenachalcone.<sup>128</sup>



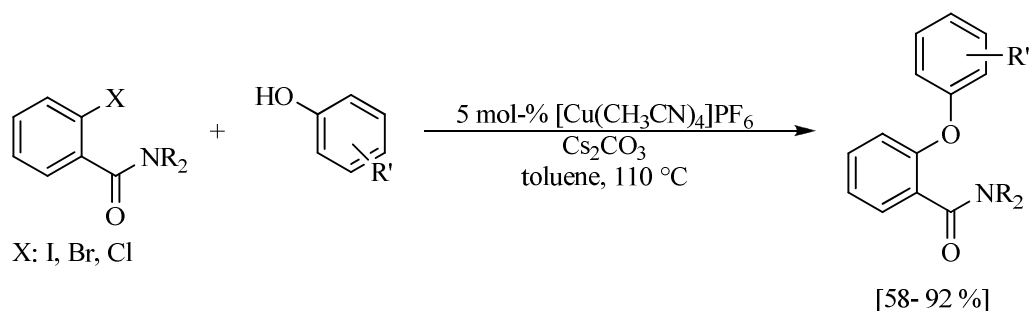
**Scheme 2.69** Synthesis of diaryl ethers using copper(I) triflate as soluble catalyst.<sup>127</sup>

In the course of the total synthesis of vancomycin aglycon the diaryl ether synthesis was performed using copper(I) bromide dimethylsulfide as catalyst.<sup>129</sup> The same complex was applied for intramolecular etherification by Dominguez *et al.* (Scheme 2.70).<sup>130</sup> Because of the higher solubility the results were remarkably better than under palladium catalysis (Pd<sub>2</sub>(dba)<sub>3</sub> with dppf or BINAP, 16- 69 % and 21- 51 %, respectively).<sup>131</sup>



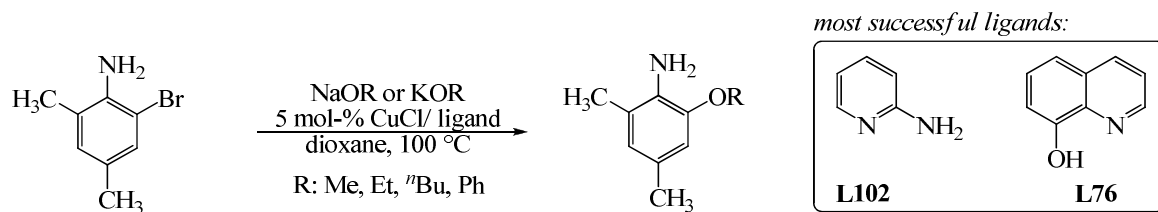
**Scheme 2.70** Intramolecular etherification using copper(I) catalyst.<sup>130</sup>

In 1999, Snieckus and co-workers applied a more air stable and soluble copper(I) catalyst for the diaryl ether formation ( $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ ).<sup>132</sup> Only activated aryl halides are suitable for the C-O cross-coupling and furthermore, *ortho*-coordinating substituents lend assistance in the synthesis (Scheme 2.71).



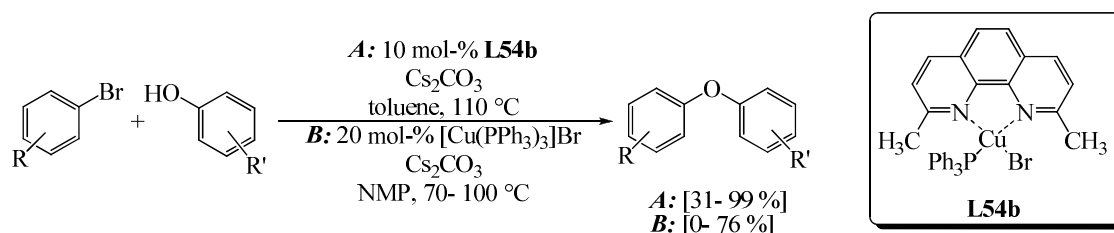
**Scheme 2.71** Formation of diaryl ethers by *ortho*-coordinating assistance.<sup>132</sup>

The group of Hauptman tested a ligand library consisting of 96 pyridine derivatives for the copper-catalyzed etherification.<sup>133</sup> The parent library included mono-, di-, and tridentate ligands. Copper(I) chloride was used as catalyst precursor for the arylation of sodium or potassium alcoholates and phenolates. Best results were obtained for primary alcohols. Secondary and tertiary alcohols gave low conversion. Bidentate chelators with small bite angles were most successful. 2-Aminopyridine (**L102**) and 8-hydroxyquinoline (**L76**) gave highest yields in shortest reaction times (Scheme 2.72). Also intramolecular etherification reactions were catalyzed effectively by this protocol. This study is illustrative for this chemistry, because the rational design of the ligands is still not possible.



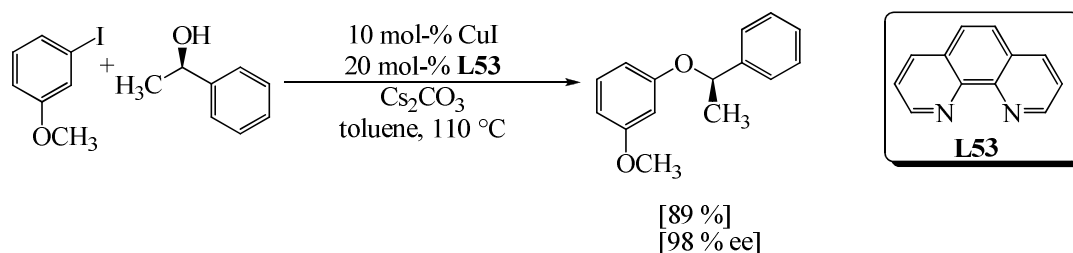
**Scheme 2.72** Investigation of 96-membered ligand library for Ullmann-type C-O cross-coupling.<sup>133</sup>

Venkataraman *et al.* showed the phenanthroline and neocuproine containing copper(I) complex (**L54**) to efficiently catalyze the diaryl ether formation.<sup>101</sup> The reaction proceeds much faster with neocuproine (**L54b**) as ligand (Scheme 2.73). The catalytic system also tolerates base-sensitive functional groups, such as ketones. The yields are substantially lower for aryl bromides bearing *ortho*-substituents. Therefore, bromotris(triphenylphosphine)-copper(I) complex was developed.<sup>134</sup> This catalyst even converts electron-rich bromoarenes. A wide range of substituents in the aryl halide and phenol is tolerated in each position, including electron-withdrawing and -donating groups. Unfortunately, no coupling of electron-rich aryl bromides with electron-deficient phenols occurred. Neither potassium carbonate, potassium *tert*-butanolate and DMAP as bases, nor toluene as solvent, were effective.



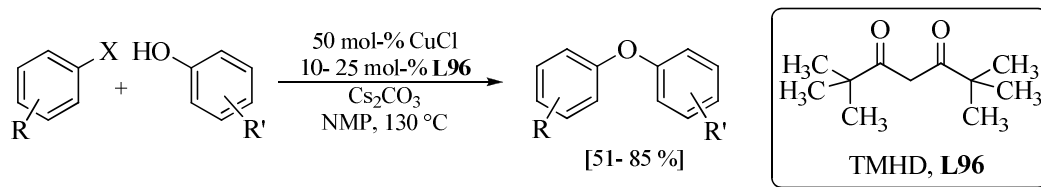
**Scheme 2.73** Diaryl ether formation using soluble and air-stable copper(I) catalysts.<sup>134</sup>

Also Buchwald *et al.* applied phenanthroline as accelerating ligand to copper-catalyzed ether formation between aryl iodides and primary and secondary aliphatic alcohols.<sup>135</sup> The reactions were performed in toluene or the appropriate alcohol as solvent. The fact that optically active alcohols react with complete retention of their configuration is remarkable (Scheme 2.74).



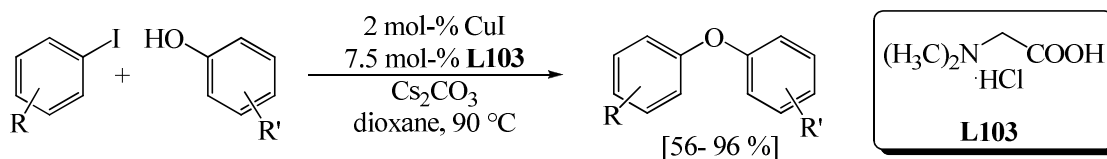
**Scheme 2.74** Arylation of optically active alcohol with retention of the configuration.<sup>135</sup>

Besides that, Song and co-workers applied a diketone (TMHD, **L96**) to accelerate the copper-catalyzed C-O cross-coupling, to form diaryl ethers, significantly (Scheme 2.75).<sup>136</sup> The catalyst gave good results for the arylation of electron-deficient phenols. However, stronger electron-withdrawing groups, such as cyanide or ketone, were not tolerated. For reaction enhancement cesium carbonate was requested, with other bases no effect was observed. Different ligands (2-aminopyridine **L102**, 8-hydroxyquinoline **L76**, phenanthroline **L53**) were tested and gave similar results. The addition of acetylacetone led to slightly increased reaction rate. Possibly **L96** forms a complex with copper(I) phenolate, which could enhance the reaction rate.



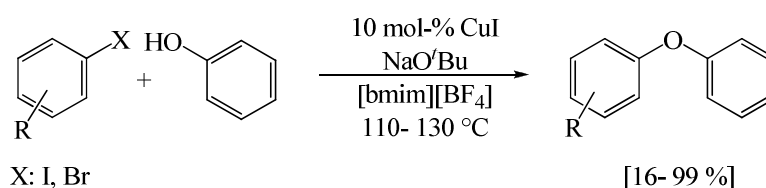
**Scheme 2.75** Diaryl ether formation using TMHD as ligand for copper(I) chloride.<sup>136</sup>

Although *N,N*-dimethylamino acids were not effective to accelerate the copper-catalyzed C-N cross-coupling<sup>56</sup>, *N,N*-dimethylglycine hydrochloride as ligand increased the coupling rate of aryl iodides and bromides with a wide range of phenols (Scheme 2.76).<sup>137</sup> Numerous substituents are tolerated in aryl halide and phenol, including electron-donating and -withdrawing groups in *ortho*-, *meta*-, and *para*-position.



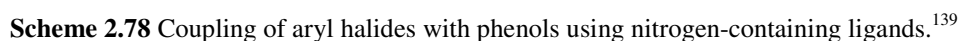
**Scheme 2.76** Diaryl ether formation using  $N,N$ -dimethylglycine hydrochloride as ligand.<sup>137</sup>

Wu and Kumar *et al.* changed the solvent to ionic liquids, like 1-*n*-butyl-3-methylimidazolium salts (Scheme 2.77).<sup>138</sup> As copper(I) precursor copper(I) iodide was applied. Also copper(I) bromide and chloride were successful at 110 to 130 °C. As bases potassium carbonate or sodium *tert*-butanolate were used. The ionic liquid phase, containing copper catalyst, can be re-used only three times after the extraction of reaction products.



**Scheme 2.77** Etherification in ionic liquids.<sup>138</sup>

Cristau and co-workers established nitrogen-containing ligands for copper(I) oxide or iodide as catalysts (Scheme 2.78).<sup>139</sup> The precursors are air stable and inexpensive. Even for hindered substrates, such as 2-iodotoluene, good results could be obtained. As best ligand served (1R,2R)- $N,N'$ -bis[(1E)-2-pyridinylmethylene]-1,2-cyclohexanediamine (**L105**). Drawbacks are low yields for the C-O cross-coupling of electron-deficient phenols.



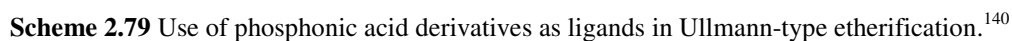
Chemical reaction scheme showing the synthesis of biaryl ethers:

Substituted phenyl halide (R-C<sub>6</sub>H<sub>4</sub>-X) + Substituted phenol (HO-C<sub>6</sub>H<sub>4</sub>-R') reacts under the following conditions:

- 20 mol-% CuI
- 30 mol-% ligand
- K<sub>2</sub>CO<sub>3</sub>
- toluene, 80-110 °C

The product is a biaryl ether (R-C<sub>6</sub>H<sub>4</sub>-O-C<sub>6</sub>H<sub>4</sub>-R').

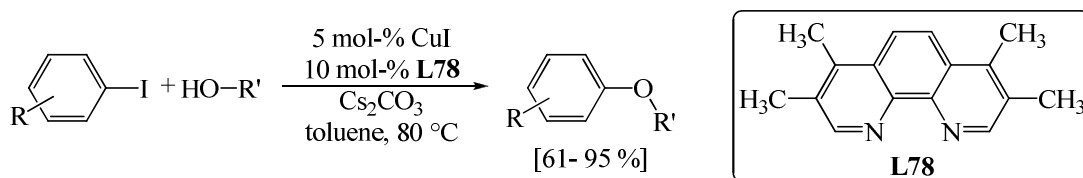
Yield: [46-95 %]



In 2008, a series of phenanthroline derivatives were tested in the coupling of 4-iodoanisole to *n*-hexanol.<sup>141</sup> Ligand **L78**, shown in Scheme 2.80, gave the best results. In



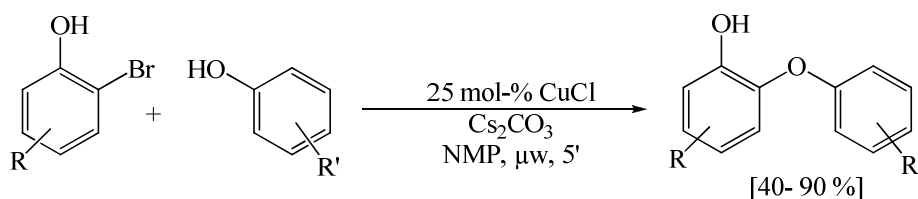
scope and limitation experiments it turned out, that it is only effective for the coupling of aryl halides to primary alcohols. For the arylation of secondary alcohols higher reaction temperatures were required. It was speculated that this is due to the low coordinating ability of secondary alcohols in comparison to primary ones.



**Scheme 2.80** Coupling of aliphatic alcohols to aryl iodides under mild conditions.<sup>141</sup>

Also Ullmann-type C-O cross-coupling can be accelerated under microwave heating, as shown by Wu *et al.* in 2003.<sup>142</sup> Even unactivated aryl iodides and bromides were coupled to phenols in absence of additives with 10 mol-% copper(I) iodide and cesium carbonate in NMP. As usual for microwave heating negative effects of overheating are compensated by shorter reaction times. However, aryl chlorides did not react.

With the improved protocol of Surolia and co-workers the reaction time was reduced from two hours to five minutes.<sup>143</sup> The coupling of 2-hydroxybromide to phenols proceeded chemoselectively without any protection of the *ortho*-hydroxy group (Scheme 2.81). Also copper(I) chloride instead of the iodide can be used as catalyst.



**Scheme 2.81** C-O cross-coupling between 2-hydroxyaryl bromides and phenols.<sup>143</sup>

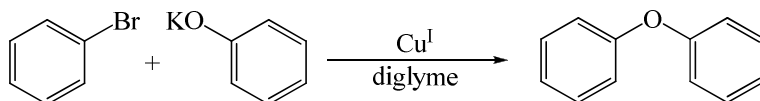
The coupling of chloro heterocycles (pyridine, quinoline and benzothiazoles) to phenols occurred with copper powder as catalyst and cesium carbonate as base.<sup>144</sup> At many substrates higher yields in significantly shorter reaction times, compared to conventional heating, were observed.

In 2007, Yi-Qian *et al.* investigated the microwave-assisted diaryl ether synthesis with copper(I) iodide.<sup>145</sup> Because water had significant impact on C-O Ullmann-condensation, anhydrous DMF or NMP were used as solvent. If the reaction mixture is not absolutely dry, higher temperatures were applied to obtain the products in high yields. Activated and unactivated aryl bromides and iodides can be coupled to phenols.

The Ullmann etherification is most useful for aliphatic alcohols, but also phenols could be coupled successfully. Electron-deficient and -neutral halogenoaryls gave best results. Even activated aryl chlorides could be converted into the corresponding ethers. With a clever optimization of the catalytic system electron-rich aryl bromides and iodides were transformed.

### 2.2.3 Mechanistic Studies

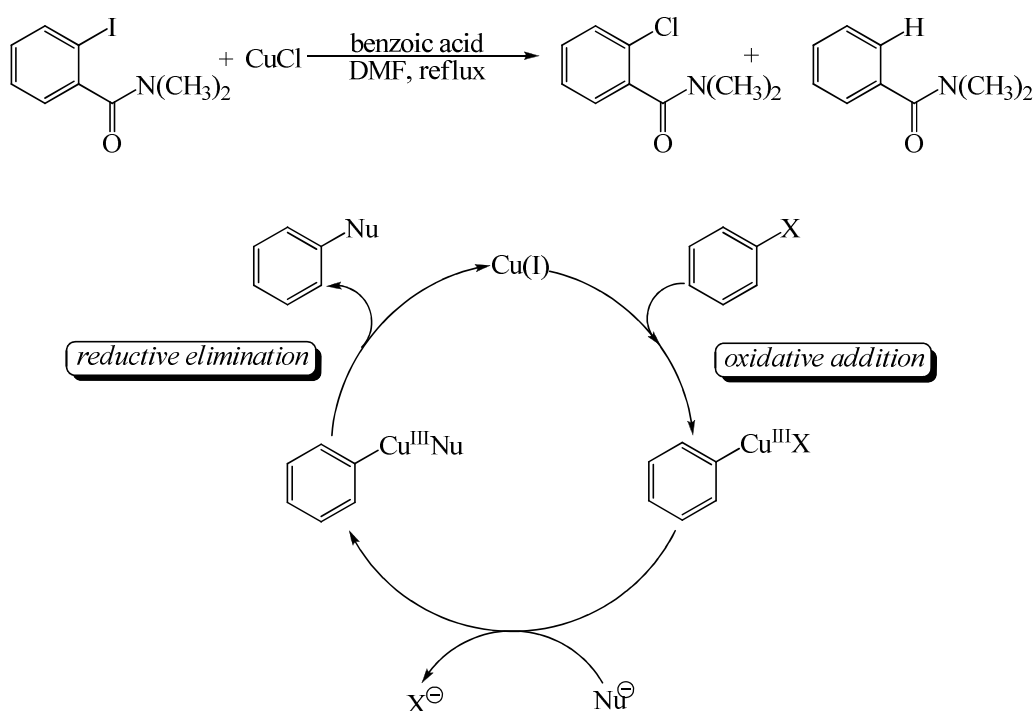
The first mechanistic studies on the Ullmann-type condensation of alcohols and aryl halogens were described by Weingarten in 1964.<sup>146</sup> For the coupling of bromobenzene to potassium phenolate an increased reaction rate was observed, when impure diglyme was used as solvent (Scheme 2.82). Careful analysis showed that diglyme contained esters, which obviously catalyze the reaction. The function of the ester seemed to be related with the higher solubility of the copper(I) salt. In ESR experiments with addition of radical traps the ESR signal changed dramatically from one reaction to the other without change of the reaction rate. This was the first conclusive evidence against a free radical mechanism. The kinetic studies *via* ESR showed that the reaction is first order in bromobenzene and copper catalyst. They assumed that copper(I) is the active catalytic species in Ullmann condensation.



**Scheme 2.82** Etherification of bromobenzene as described by Weingarten.<sup>146</sup>

Ten years later Cohen and co-workers analyzed the reaction of 2-iodobenzamide and copper(I) chloride with addition of benzoic acids in DMF at reflux.<sup>147</sup> With increasing

amounts of benzoic acid the yield of reduction product increased. When higher quantities of copper(I) chloride was used a higher iodide-chloride exchange was observed. Therefore, an organo-copper intermediate must be present. Cohen *et al.* proposed the catalytic cycle shown in Scheme 2.83. The cycle is very similar to which described for palladium and gold catalysis. Due to the similarity it became very attractive. But the existence of copper(III) has to be questioned, because to date no conclusive evidence for the formation of copper(III) intermediates in any copper-catalyzed reaction is given.

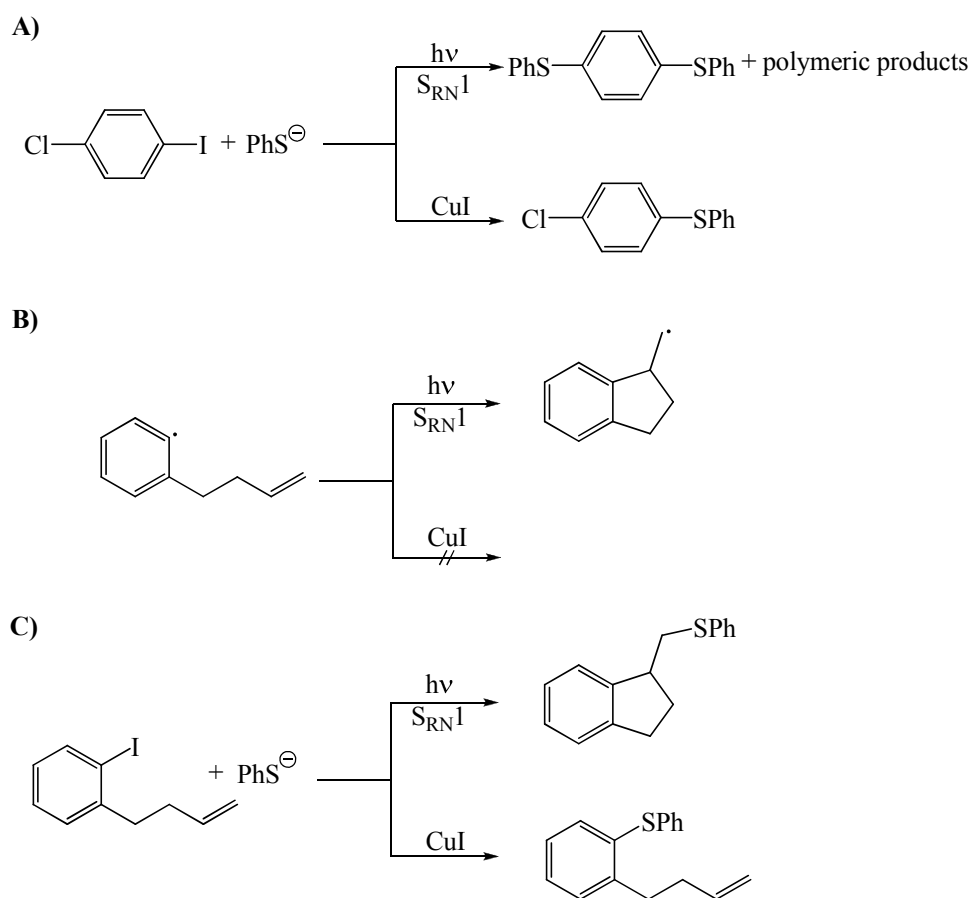


**Scheme 2.83** Proposed catalytic cycle by Cohen *et al.*<sup>147</sup>

Van Koten and co-workers disputed the conclusions of Cohen.<sup>148</sup> In former reactions arene-copper intermediates have been shown to produce aryl-aryl bonds, which Cohen *et al.* didn't observe. Therefore, the arene-copper intermediate produced under Cohen's reaction conditions should be instable. Thermolysis studies showed that an arene-copper  $\pi$ -complexing type intermediate is unlikely in copper-catalyzed reactions.

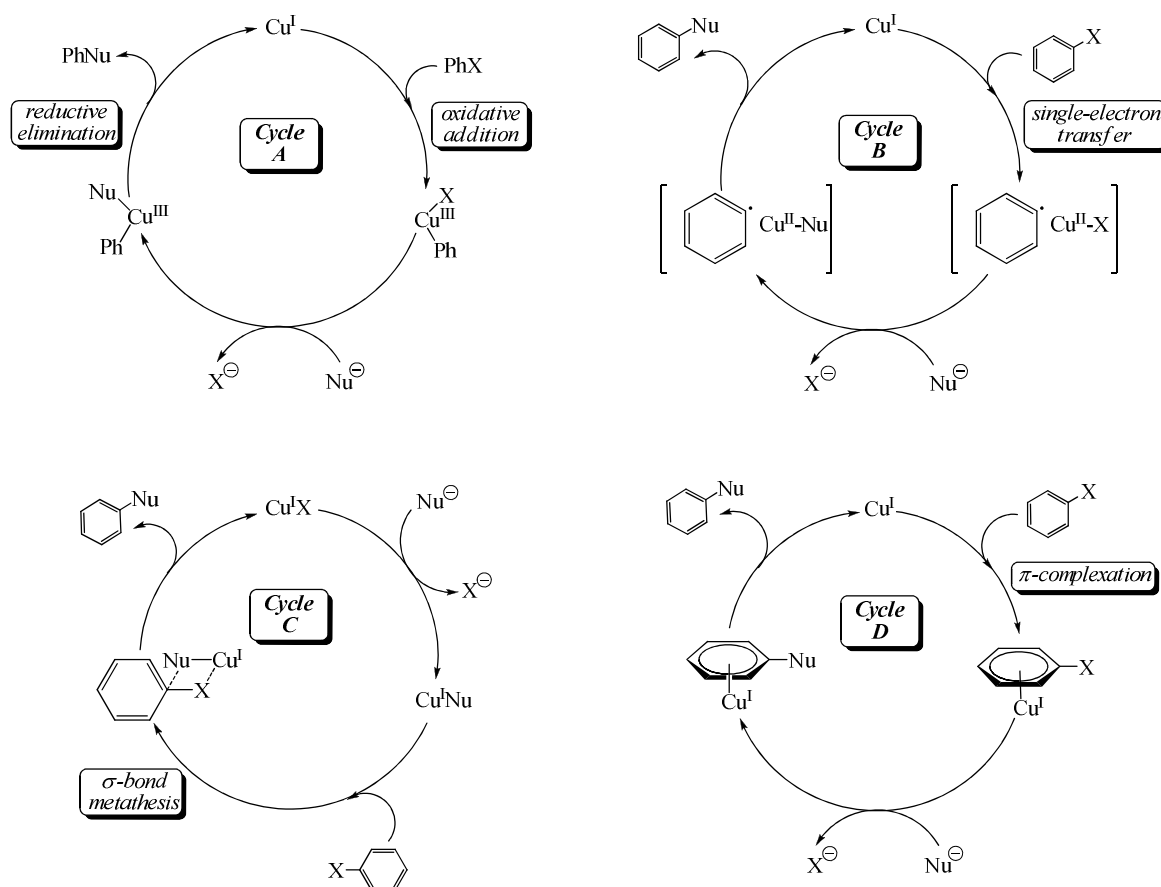
Bowman *et al.* investigated again the mechanism with respect to radical pathway (Scheme 2.84).<sup>149</sup> Therefore, 4-iodo-chlorobenzene was reacted with phenylsulfide anion (A). If the reaction is performed under radical nucleophilic substitution conditions with

light activation polymeric material was observed. With addition of copper(I) iodide 4-(chlorophenyl)-phenylsulfane was formed. In a second experiment the cyclization of the radical of but-3-enylbenzene was used as indicator (**B**). Under radicalic conditions the cyclizations product was obtained. With the addition of copper(I) no reaction occurred. The combination of this two methods (**C**) led to the assumption, that no aryl radicals are produced under copper(I)-catalyzed reaction conditions.



**Scheme 2.84** Investigation of copper-catalyzed reaction with respect to radical mechanism.<sup>149</sup>

In the group of Venkataraman van Allen investigated the mechanism of Ullmann-type nucleophilic substitution on aryl halides.<sup>150</sup> Two possible categories of catalytic cycles were postulated (Scheme 2.85). In the first class the oxidation state of copper changes throughout the cycle (cycles A and B). On the other hand two possible cycles could be postulated without any change of the oxidation state of the copper catalyst (cycles C and D).



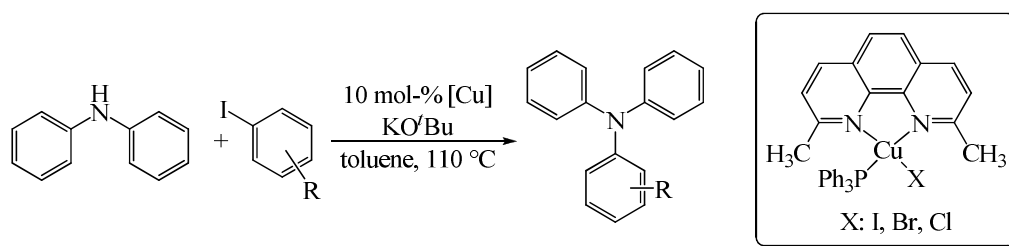
**Scheme 2.85** Four possible catalytic cycles for Ullmann-type reactions.<sup>150</sup>

In cycle A oxidative addition of the aryl halide is the first step and forms a copper(III) intermediate. This type of cycle is valid in palladium-catalyzed reactions. With the aryl-heteroatom bond formation the copper(I) catalyst is regenerated. In cycle B the oxidative addition takes place *via* a single-electron transfer within the coordination sphere to form a copper(II) radical intermediate. After halide-nucleophile exchange reductive elimination takes place with recycling of the copper catalyst. These two pathways are very similar and therefore, not easy to distinguish. Both require an equilibrium between copper and dissociated ligand to generate the active 16-electron complex.

Cycle C displays a  $\sigma$ -bond metathesis. This is a common reaction mechanism involving  $d^0$  metal complexes, which cannot undergo a change of the oxidation state. On the other hand the cycle D could be operative with a  $\pi$ -complex as copper(I) intermediate.

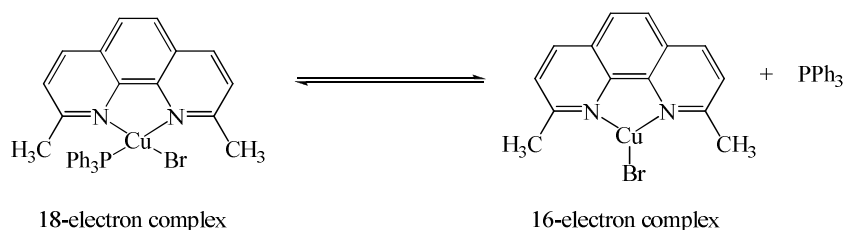
For these four mentioned catalytic cycles experimental testing conditions were constructed. To proof the elimination step well defined copper(I) complexes were

synthesized and tested in the C-N cross-coupling of diphenylamine with aryl iodides (Scheme 2.86). The reaction was monitored by GC. If the catalytic cycles A or B are valid a substantial difference in reaction rate should be observed between iodo- and chlorocomplexes. The reaction profile and reaction rate indicate that the halide has no effect on coupling. Therefore, it was assumed that cycles C or D could be applicable.



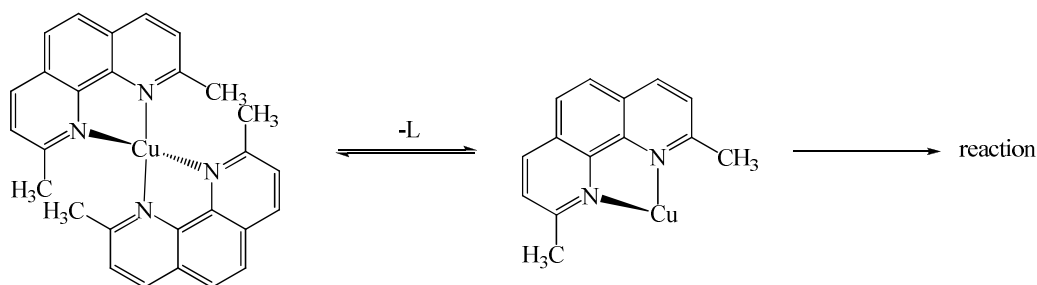
**Scheme 2.86** Testing the effect of halide on the copper catalyst during the reaction.<sup>150</sup>

Next the effect of the addition of ligand was investigated. Ligand dissociation has to take place before cross-coupling can occur. If an equilibrium, as shown in Scheme 2.87, exists the reaction rate should decrease with addition of triphenylphosphine. To distinguish between the 18-electron, and 16-electron complex as possible active catalytic species triphenylphosphine was added to the reaction mixture ranging from 0.5 to 2.0 equivalents. During the kinetic studies no change in reaction rate was observed, which lead to the assumption, that cycle C and D are valid.



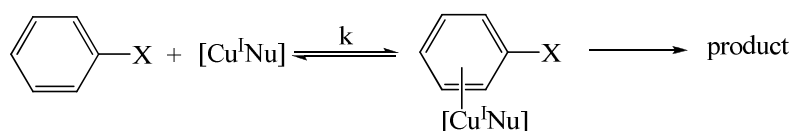
**Scheme 2.87** Investigation of active catalytic species.<sup>150</sup>

Also the addition of neocuproine, to form  $\text{Cu}(\text{neocup})_2$ , was found to be effective in Ullmann-coupling. One of the ligands need to be cleaved off before the reaction can take place (Scheme 2.88). By adding neocuproine the reaction rate was not affected, but the conversion was reduced.



**Scheme 2.88** Possible activation of  $\text{Cu}(\text{neocup})_2$  for C-O cross-coupling of phenols to aryl halides.<sup>150</sup>

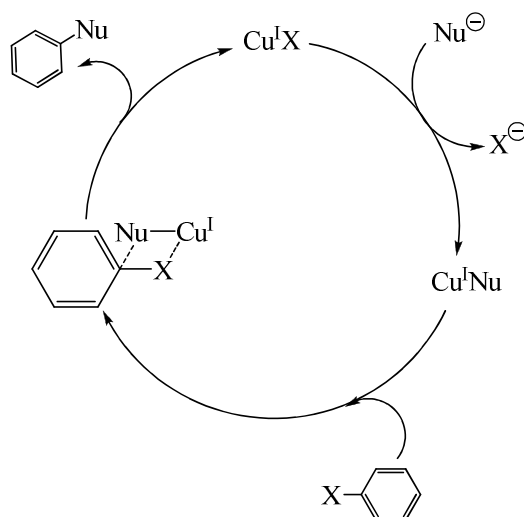
Electron withdrawing substituents on aryl halide would increase the reaction rate due to faster oxidative addition. The Meisenheimer complex in cycle C was ruled out, but possibly aryl halide and copper complex are in equilibrium (Scheme 2.89). If such an equilibrium exists the reaction rate should be dependent on the concentration of aryl-copper complex, which would depend on equilibrium constant  $k$ . Electron-deficient aryl halides will lower  $k$  and therefore, slower the reaction rate. If  $k$  is high and independent on functional groups on aryl halides, electronics should have no effect on reaction rate. For small  $k$  the reaction rate will be decreased by electron-withdrawing groups on aryl halides. This would mean, that cycle A or B are valid. In the case of  $\sigma$ -bond metathesis no change of reaction rate should be observed with changing functional groups.



**Scheme 2.89** Detection of the equilibrium constant and reaction rate.<sup>150</sup>

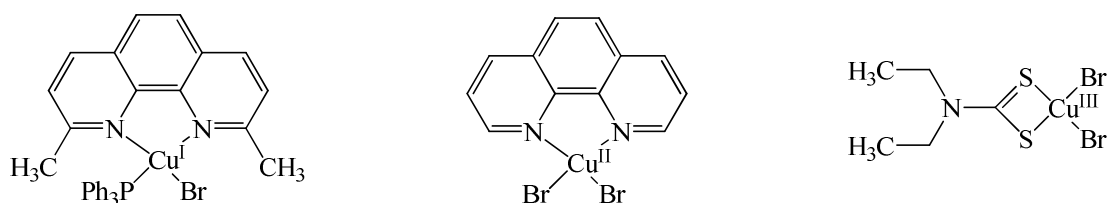
Both electron-withdrawing and -donating groups at aryl iodide were investigated and the rate constant was plotted against the Hammett operator  $\sigma$  of the respective substituent. For all substrates the consumption of aryl halide corresponds to the production of triphenylamine. If there is a substituent effect, the plot should be linear dependent. All data show little or no effect of the functional groups to the reaction rate. The only aforementioned catalytic cycle having no substituent effect on aryl halide is the  $\sigma$ -bond

metathesis. Because this mechanism was confirmed by all experiments in this series, it is believed to be the most valid (Scheme 2.90).



**Scheme 2.90** Catalytic cycle for the Ullmann-type diaryl ether synthesis *via*  $\sigma$ -bond metathesis.<sup>150</sup>

At least copper catalysts with several oxidation states were investigated in the coupling of iodobenzene to diphenylamine (Scheme 2.91). All three applied catalysts showed equal consumption of iodobenzene and identical reaction rates. For Ullmann-type coupling copper(I), copper(II) and copper(III) catalysts can be applied.



**Scheme 2.91** Three copper complexes applied to the formation of triphenylamine.<sup>150</sup>



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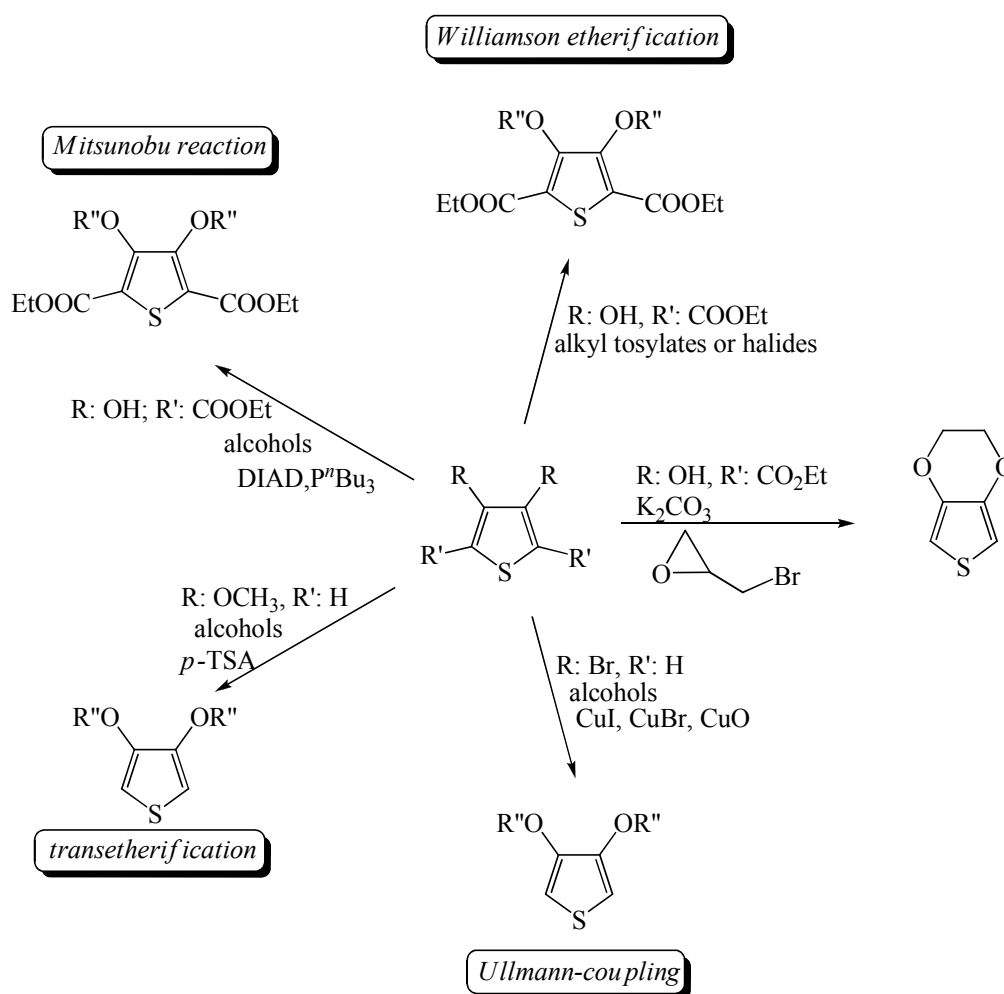
## Chapter 3

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**Thiophene Ethers *via* Transition Metal-Catalyzed  
Conversion of 3-Halogenothiophene**

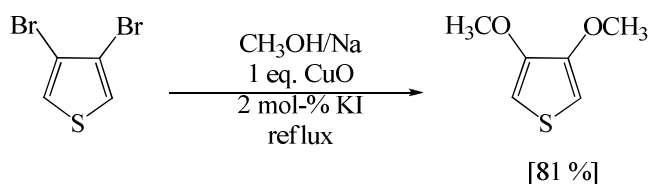
### 3.1 Synthesis of Alkoxy- and Aryloxythiophenes Described in Literature

A number of synthetic routes to obtain alkoxy- or aryloxythiophenes are known to literature. In Scheme 3.1 an overview about the reaction pathways is given.



**Scheme 3.1** Methods to synthesize alkoxythiophenes.

One of the first methods for the synthesis of thiophene ethers was the Ullmann-type coupling of alcohols to halogenothiophenes (Scheme 3.2).<sup>1</sup> Gronowitz *et al.* applied copper(II) oxide as catalyst in combination with potassium iodide. In methanol 3,4-dibromothiophene was converted to 3,4-dimethoxythiophene in good yields. The reaction required long reaction times and stoichiometric amounts of copper(II) oxide. However, this is still the method of choice for the synthesis of 3,4-dialkoxythiophenes.



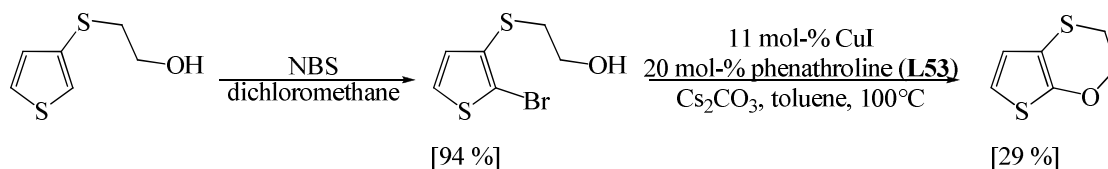
**Scheme 3.2** Copper-promoted nucleophilic substitution at 3,4-dibromothiophene.<sup>1</sup>

Brandsma *et al.* studied the influence of several parameters on the reaction rate, such as solvent, halogen atom, reaction temperature and the presence of oxygen.<sup>2</sup> Furthermore, the decomposition of the catalyst and the reduction of the thiophene halide were investigated. Copper(I) bromide with NMP as co-solvent turned out to give best results for the coupling of alcohols to bromothiophene.

Lemaire and co-workers investigated the conversion of 3-bromothiophene with polyfluorinated alcohols in detail and gave optimized conditions for the nucleophilic substitution on thiophenes.<sup>3</sup> Within the tested copper(I) catalysts copper(I) iodide gave the best results with sodium hydride as base. As solvents DMF and DME were used.

A similar protocol was established by Swager *et al.* for the synthesis of thiophene ethers.<sup>4, 5</sup> With copper(I) iodide (20 mol-%) as catalyst in basic solvents, e.g. pyridine and lutidine, with sodium *tert*-butanolate as base, the desired 3-alkoxythiophenes were obtained in good yields.

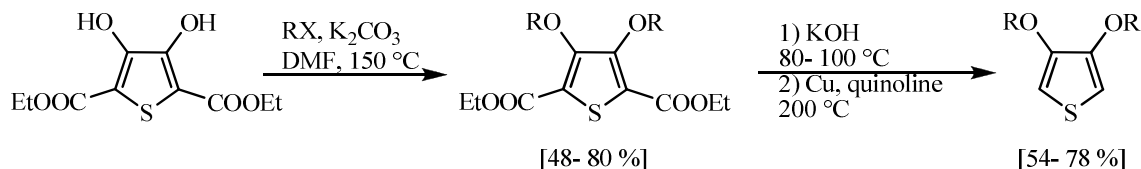
Another improvement was made by Hellberg *et al.* in 2003, who published a copper(I) iodide catalyst with phenanthroline (**L53**) as ligand (Scheme 3.3).<sup>6</sup> However, the yield for intramolecular etherification was rather low (29 %).



**Scheme 3.3** Intramolecular etherification at the thiophene ring as described by Hellberg *et al.*<sup>6</sup>

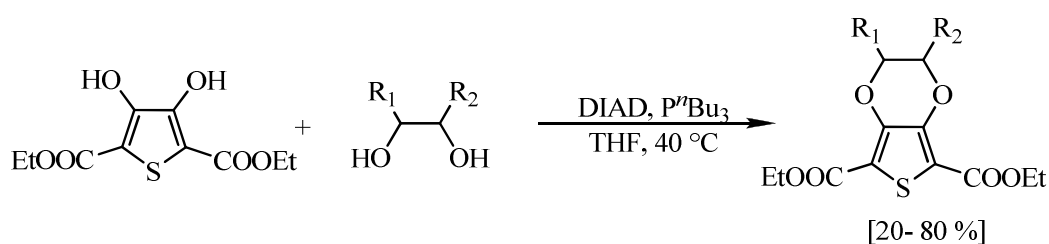
In a Williamson-etherification 3,4-dihydroxythiophene was coupled to alkyl tosylates or alkyl halides.<sup>7, 8</sup> A satisfying result was only obtained for strongly activated thiophenes. Therefore, two ester groups were inserted in 2,5-positions (Scheme 3.4). After C-O cross-

coupling under harsh reaction conditions saponification and decarboxylation is requested. The yields for twofold nucleophilic substitution starting from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and alkyl halides or alkyl tosylates are moderate.



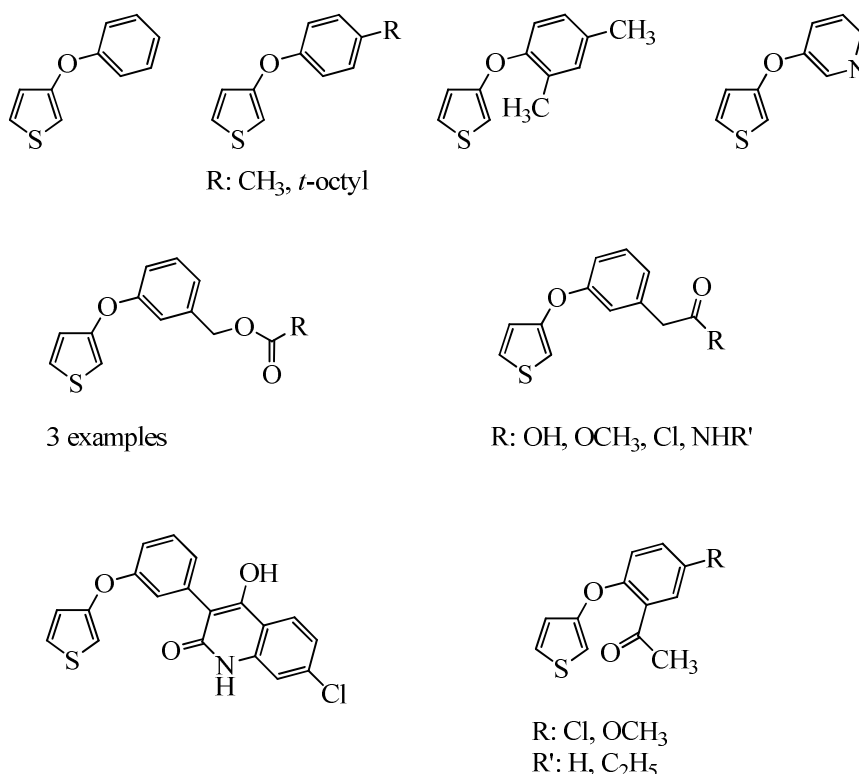
**Scheme 3.4** Formation of 3,4-dialkoxythiophenes.<sup>7</sup>

The etherification can also proceed under Mitsunobu conditions (Scheme 3.5).<sup>9, 10</sup> In a first step, tributylphosphine reacts with di-*iso*-propylazodicarboxylate (DIAD) to form a zwitterionic adduct. The anion is basic enough to deprotonate hydroxythiophene. After substitution at phosphorous by the alkoxide the resulting nitrogen-anion removes the proton from the nucleophile. Finally, the nucleophile anion attacks the phosphorous derivative of the hydroxythiophene in a normal S<sub>N</sub>2 reaction, with phosphine oxide as leaving group. With this protocol EDOT derivatives were obtained in good to excellent yields. Bäuerle *et al.* described for the first time the synthesis of chiral EDOT derivatives with high enantiomeric excess. Unfortunately, the activation of thiophene is still necessary.



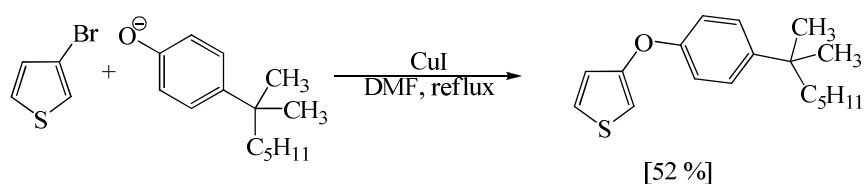
**Scheme 3.5** Synthesis of EDOT derivatives under Mitsunobu reaction conditions.<sup>9</sup>

In a transesterification protocol *para*-toluene sulfonic acid can be applied to exchange methoxy substituents by other alcohols.<sup>11</sup> For this conversion no more activation of thiophene is required. 3,4-Dimethoxythiophene was obtained as described above.



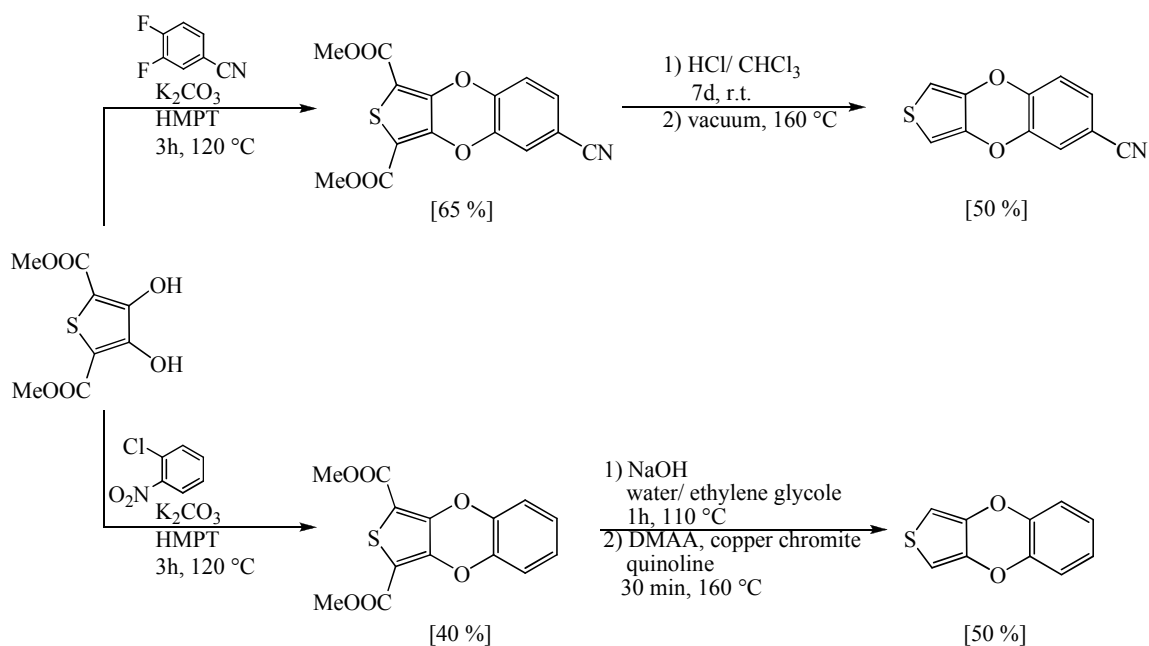
**Chart 3.1** 3-Phenoxythiophene derivatives described in literature.

In literature, only a couple of 3-aryloxythiophenes are known (Chart 3.1). Watthey *et al.* described the conversion of 3-bromothiophene and phenol using copper bronze and anhydrous potassium carbonate in the melt.<sup>12</sup> They published a yield of about 50 %. Milder reaction conditions were chosen by Leeson *et al.*<sup>13</sup> 3-Bromothiophene was coupled to methyl 2-(3-hydroxyphenyl)acetate with copper(II) oxide in pyridine. Unfortunately, no yield and catalyst loading were given. A similar protocol was applied by Raju and co-workers in 1996.<sup>14</sup> With copper(I) chloride in pyridine the nucleophilic substitution at 3-bromothiophene with phenol was effectively catalyzed. Because the etherification was part of reaction sequence no exact yield for the C-O cross-coupling was published. For the whole sequence starting from 3-bromothiophene and phenol, followed by oxidation to sulfonyl chloride a yield of 68 % was obtained. Hellberg *et al.* published a cross-coupling of 3-bromothiophene with several nucleophiles.<sup>15</sup> For the coupling of 3-bromothiophene to 4-*tert*-octylphenol a yield of 52 % was observed using copper(I) iodide in refluxing DMF (Scheme 3.6).



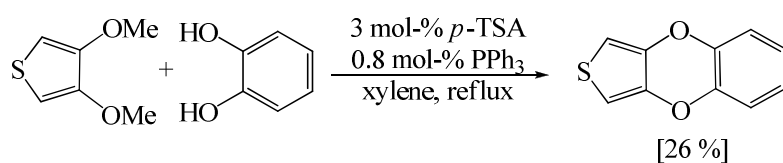
**Scheme 3.6** C-O cross-coupling of 3-bromothiophene with 4-*tert*-octylphenol.<sup>15</sup>

A completely new class of thiophene derivatives was investigated by Ritter.<sup>16</sup> Benzo[*e*]thieno[3,4-*b*][1,4]dioxine (benzoEDOT) can be obtained by the nucleophilic aromatic substitution of 3,4-dihydroxythiophenes with 3,4-difluorobenzonitrile (DFBN) or 2-chloronitrobenzene (CNB) (Scheme 3.7). The reactions were carried out in HMPT (hexamethylphosphorous triamide) as solvent in the presence of potassium carbonate as base. The coupling with DFBN led to the desired product in 65 % yield. Following saponification and decarboxylation proceeded in 50 % yield. BenzoEDOT was obtained in 20 % after C-O cross-coupling with CNB and deactivation.



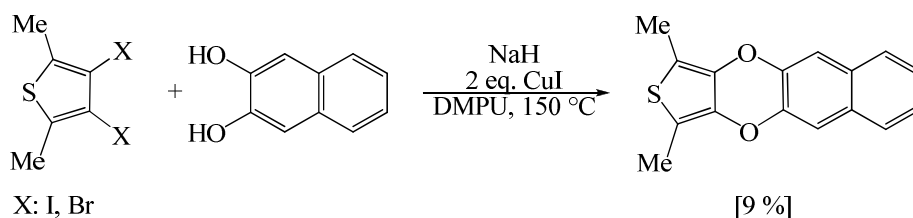
**Scheme 3.7** Formation of benzoEDOT derivatives published by Ritter *et al.*<sup>16</sup>

In the Bayer group it is synthesized by a transesterification protocol, similar to EDOT synthesis (Scheme 3.8).<sup>17</sup> BenzoEDOT was obtained in 26 % from 3,4-dimethoxythiophene and pyrocatechol with *para*-toluenesulfonic acid as catalyst.



**Scheme 3.8** Synthesis of benzoEDOT as patented by Bayer group.<sup>17</sup>

The nucleophilic substitution of 2,3-dihydroxynaphthalene with 2,5-dimethyl-3,4-dibromothiophene with copper(I) iodide as catalyst in DMPU gave only a trace amount of the product (Scheme 3.9).<sup>18</sup> Also the iodinated thiophene derivative could not be converted in higher yields.



**Scheme 3.9** Copper(I)-catalyzed synthesis of 1,3-dimethylnaphtho[2,3-*e*]thieno[3,4-*b*][1,4]dioxine.<sup>18</sup>

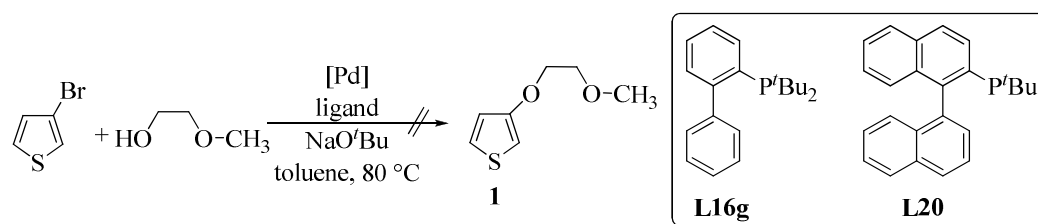
To date no palladium-catalyzed etherification at thiophenes are described.

## 3.2 Synthesis of Aliphatic Thiophene Ethers

### 3.2.1 Synthesis under “Conventional” Heating

#### 3.2.1.1 Conversion under Buchwald-Hartwig Coupling Conditions

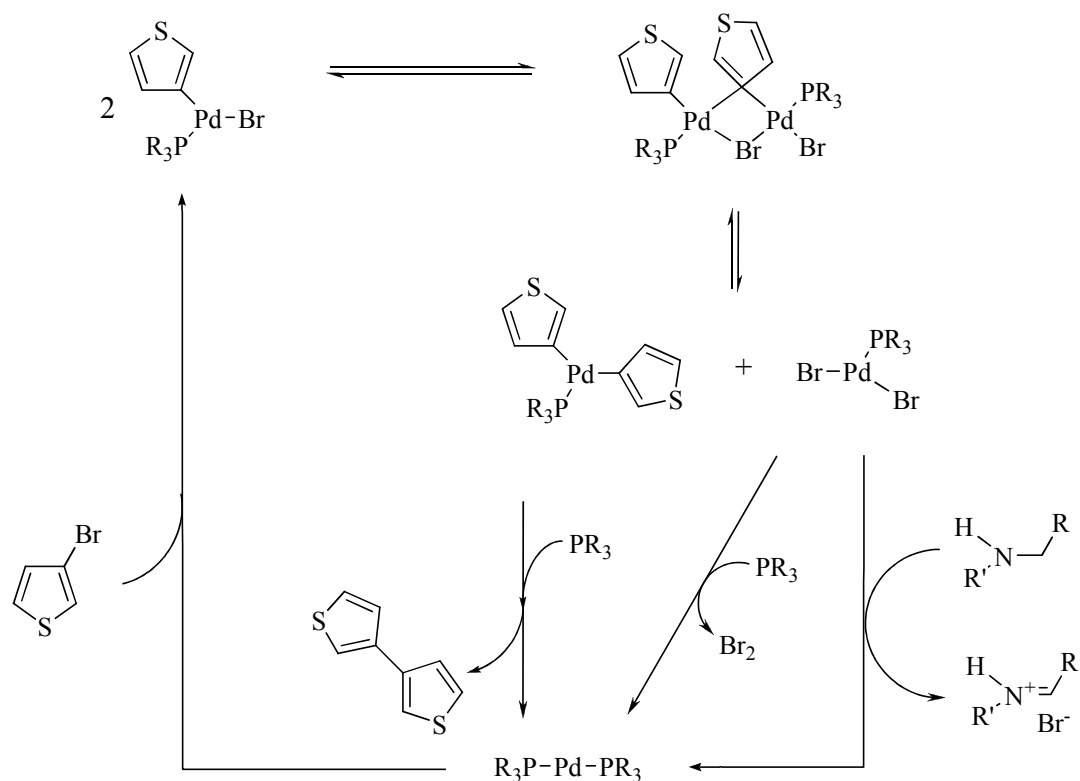
In literature, a number of palladium catalysts were described to synthesize aryl ethers. Therefore, several conditions were tested to convert 3-bromothiophene and 2-methoxyethanol into 3-(2-methoxyethoxy)-thiophene **1**. In small screw cap vials, equipped with a septum and degassed with argon, the reactants were coupled with sodium *tert*-butanolate as base in toluene at 80 °C. In Table 3.1 the results from GC-MS analysis were summarized for the catalytic systems applied to this reaction.

**Table 3.1** Coupling of 3-bromothiophene and 2-methoxyethanol via palladium catalysis in toluene at 80 °C.

	Catalyst	Ligand	Qualitative result from GC-MS analysis
1	$\text{Pd}_2(\text{dba})_3$ (2 mol-%)	<b>L16g</b> (2 mol-%)	mainly 3,3'-bithiophene
2	$\text{Pd}(\text{OAc})_2$ (1 mol-%)	<b>L16g</b> (2 mol-%)	mainly 3,3'-bithiophene
3	$\text{Pd}_2(\text{dba})_3$ (1,5 mol-%)	<b>L20</b> (3 mol-%)	mainly 3,3'-bithiophene
4	$\text{Pd}_2(\text{dba})_3$ (2 mol-%)	$\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$ (2 mol-%)	complex reaction mixture
5	$\text{Pd}(\text{OAc})_2$ (10 mol-%)	$\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$ (10 mol-%)	complex reaction mixture
6	$\text{PdCl}_2(\text{dppf})$ (1 mol-%)		mainly 3,3'-bithiophene

$\text{Pd}_2(\text{dba})_3$  served as palladium(0) precursor, while  $\text{Pd}(\text{OAc})_2$  and  $[\text{Pd}(\text{dppf})]\text{Cl}_2$  are palladium(II)-complexes. No C-O cross-coupling occurred under these conditions. In most cases, in GC-MS the formation of 3,3'-bithiophene was observed. Ogawa *et al.* got the same bithiophene in 20 % yield during the formation of aryl amines starting from 2- and 3-bromothiophenes.<sup>19</sup> They investigated this problem and proposed the cycle shown in Scheme 3.10.





**Scheme 3.10** Formation of 3,3'-bithiophene under Buchwald-Hartwig coupling conditions.<sup>19</sup>

During the catalytic cycle the palladium-thienyl complex dimerizes and homocoupling takes place. This competitive reaction can always take place in such a reaction. The etherification of 3-bromothiophene could never be observed, which led to the assumption, that either the dimerization described in Scheme 3.10 is faster or the reductive elimination, which would give the desired ether, is not possible for the electron-rich thiophene. Because every complexation is an equilibrium the reverse reaction in the catalytic cycle to the state of the palladium-thienyl complex, from which the homocoupling starts, is possible. The yield of homocoupling product was not determined.

### 3.2.1.2 Conversion under Ullmann-type Coupling Conditions

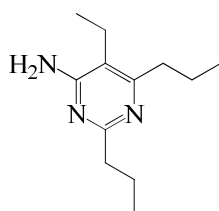
The copper catalysis for ether formation is described as much more efficient than the Buchwald-Hartwig conditions. In literature, the synthesis of 3-(2-methoxyethoxy)-thiophene **1** was already described by Marsella *et al.*<sup>5</sup> 3-Bromothiophene was converted to **1** with copper(I) iodide (10 mol-%) as catalyst in lutidine as a basic solvent. The alcohol was deprotonated by potassium *tert*-butanolate. According to this protocol the product was

obtained in 78 % as described in literature. Also other copper catalysts were investigated to increase the yield. The results are summarized in Table 3.2.

The procedure published by Gronowitz and co-workers using copper(II) oxide and potassium iodide was tested and gave the desired product in 65 % yield (Table 3.2, Entry 1).<sup>1</sup> Changing to an electron-poor heteroaromatic solvent, as quinoline or pyridine, lower conversions were observed. Adding copper(I) iodide as an additional catalyst (Table 3.2, Entry 4) led unexpectedly to much lower yield of **1**. With copper(II) oxide (Table 3.2, Entry 1) or copper(I) iodide (Table 3.2, Entry 8) independently as catalysts gave good yields. Obviously a redox reaction between copper(II) and copper(I) takes place and a non-reactive copper species is formed.

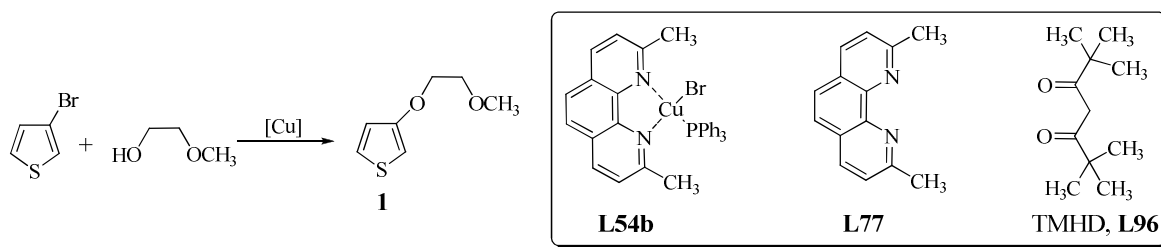
According to the procedure described in literature (CuI, KO<sup>t</sup>Bu, lutidine; Table 3.2, Entry 5) different solvents were investigated. To ensure a complete deprotonation of the alcohol and to avoid side reactions, due to the coupling of *tert*-butanolate to 3-bromothiophene, sodium hydride was applied as base.

In a polar solvent like butyronitrile with copper(I) iodide as catalyst (Table 3.2, Entry 6), no product was obtained. But the butyronitrile reacted with the strong base to form 5-ethyl-2,6-dipropylpyrimidin-4-amin (Chart 3.2), as described by Wache and Meyer.<sup>20</sup> In quinoline as basic, high boiling solvent formation of **1** occurred in only 45 % (Table 3.2, Entry 7). However, DMF instead of lutidine gave similar results (73 %, Table 3.2, Entry 8).



**Chart 3.2** 5-Ethyl-2,6-dipropylpyrimidin-4-amin built from butyronitril with a strong base.<sup>20</sup>

The catalyst described by Song *et al.* (50 mol-% CuCl with 10 mol-% **L96**; Table 3.2, Entry 9) led not to an etherification.<sup>21</sup> Only starting materials were re-isolated.

**Table 3.2** Formation of **1** from 3-bromothiophene and 2-methoxyethanol by Ullmann-protocols.

	Catalyst/ Additive	Base	Solvent	Time [d] (Temp.)	Yield [%] <sup>a</sup>
1	CuO (1 eq.)/ KI (10 mol-%)	NaH	DMF	3 (120 °C)	65
2	CuO (1 eq.)/ KI (10 mol-%)	NaH	quinoline	3 (120 °C)	13
3	CuO (1 eq.)/ KI (10 mol-%)	NaH	pyridine	6 (115 °C)	41
4	CuO (1 eq.)/ CuI (20 mol-%) KI (10 mol-%)	NaH	DMF	5 (110 °C)	17
5	CuI (20 mol-%)	KO <sup>t</sup> Bu	lutidin	1 (100 °C)	78
6	CuI (20 mol-%)	NaH	butyronitrile	19 (80 °C)	3 <sup>b</sup>
7	CuI (20 mol-%)	NaH	quinoline	6 (120 °C)	45
8	CuI (20 mol-%)	NaH	DMF	4 (110 °C)	73
9	CuCl (50 mol-%)/ <b>L96</b> (10 mol-%)	Cs <sub>2</sub> CO <sub>3</sub>	NMP	18 (80 °C)	0
10	CuI (10 mol-%)/ <b>L77</b> (20 mol-%)	Cs <sub>2</sub> CO <sub>3</sub>	toluene	19 (80 °C)	0
11	CuI (10 mol-%)/ <b>L77</b> (20 mol-%)	NaH	toluene	5 (100 °C)	12
12	CuI (10 mol-%)/ <b>L77</b> (20 mol-%)	NaH	quinoline	7 (120 °C)	4
13	<b>L54b</b> (10 mol-%)	Cs <sub>2</sub> CO <sub>3</sub>	toluene	19 (80 °C)	0
14	<b>L54b</b> (10 mol-%)	NaH	quinoline	5 (100 °C)	6

<sup>a</sup>isolated yields, <sup>b</sup>3-iodothiophene instead of 3-bromothiophene.

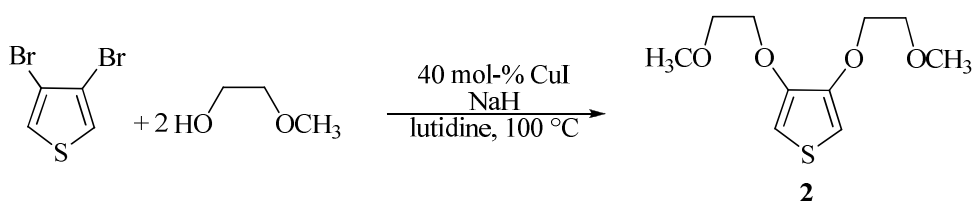
Buchwald *et al.* applied copper(I) iodide and neocuproine to synthesize aryl ethers starting from iodobenzenes.<sup>22</sup> This protocol gave no result for 3-bromothiophene (Table 3.2, Entry 10), also in quinoline as solvent (Table 3.2, Entry 12). The change to a stronger base (sodium hydride; Table 3.2, Entry 11) gave the product in unsatisfactory 12 %. The stable copper(I) neocuproine complex used by Venkataraman *et al.* in 2002, to convert halogenated aryls to their ethers, gave no conversion of 3-bromothiophene (Table 3.2, Entry 13).<sup>23</sup>

The addition of stronger bases, such as sodium hydride instead of cesium carbonate, increased the yield in very small quantity (6 %, Table 3.2, Entry 14).

The best results were obtained using copper(II) oxide with addition of potassium iodide in DMF or copper(I) iodide in lutidine or DMF. All three procedures are well known since decades. The yields could not be improved by modern methods to synthesize ethers starting from halogenated aryls.

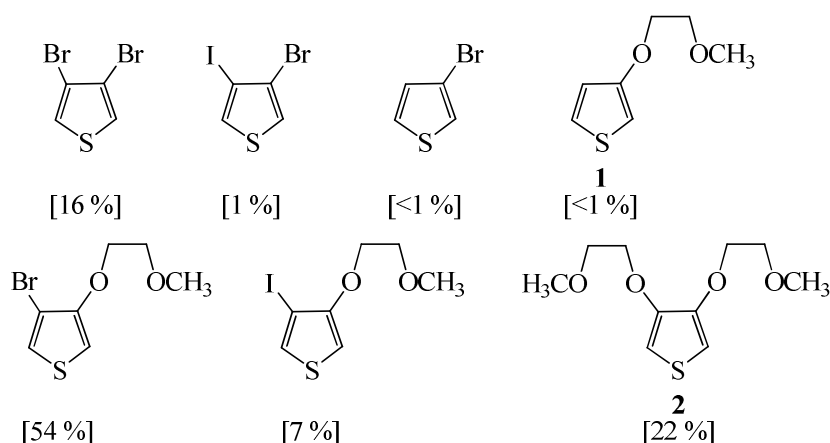
As bases sodium hydride and potassium *tert*-butanolate gave satisfactory results. Cesium carbonate is not strong enough to deprotonate 2-methoxyethanol in high amount. The solvent applied is dependent on the catalyst. Therefore, no generality can be drawn.

With the best conditions found for substitution of 3-bromothiophene also 3,4-dibromothiophene was coupled with two equivalents of 2-methoxyethanol (Scheme 3.11). To ensure complete dehydrogenation of the alcohol sodium hydride was applied as base instead of potassium *tert*-butanolate.



**Scheme 3.11** Formation of 3,4-bis(2-methoxyethoxy)-thiophene **2** from 3,4-dibromothiophene and 2-methoxyethanol.

After a reaction time of seven days a complex product mixture was obtained, which was first analyzed by GC-MS. Therefore, the substances shown in Chart 3.3 were obtained. The yields given in the scheme are GC-yields.



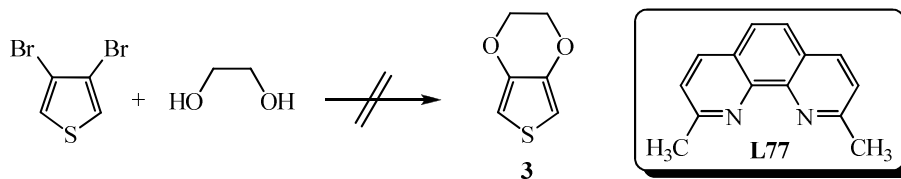
**Chart 3.3** Intermediates and products detected by GC-MS after the reaction of 3,4-dibromothiophene and 2-methoxyethanol.

No remarkable dehalogenation could be observed under these reaction conditions. All detected substances are intermediates at the reaction pathway to 3,4-bis(2-methoxyethoxy)-thiophene **2**. This reaction shows that in principle a twofold Ullmann-type substitution at 3,4-dibromothiophene is possible.

Bäuerle *et al.* described the synthesis of **2** by Williamson-ether synthesis.<sup>8</sup> Diethyl 3,4-dihydroxy-2,5-thiophene-dicarboxylate was coupled to 2-methoxyethyl-tosylate under basic conditions. After saponification and decarboxylation the product was obtained in an overall yield of 33 %. The procedure described here gave a lower yield. On the other hand the synthetic effort under milder reaction conditions was less.

The best Ullmann-type coupling conditions found for the C-O cross-coupling at 3-bromothiophene were tested for the conversion of 3,4-dibromothiophene to 2,3-dihydrothieno[3,4-*b*][1,4]dioxine (EDOT, **3**). In Table 3.3 all catalytic systems investigated are summarized.

Unfortunately, in no case a conversion could be observed. Always 3,4-dibromothiophene could be re-isolated. Ethylene glycol is known to form stable copper complexes.<sup>24</sup> This poisons the catalyst and no reaction can take place. There was no way found to overcome this problem. To date, no procedure for the formation of EDOT from 3,4-dibromothiophene was described.

**Table 3.3** Formation of EDOT (**3**) from 3,4-dibromothiophene and ethyleneglycol.

	Catalyst	Base	Solvent	Temperature
1	CuI (20 mol-%)	NaH	lutidine	100 °C
2	CuI (20 mol-%)	KO <sup>t</sup> Bu	lutidine	100 °C
3	CuI (20 mol-%)	NaO <sup>t</sup> Bu	lutidine	100 °C
4	CuI (10 mol-%)/ <b>L77</b> (20 mol-%)	Cs <sub>2</sub> CO <sub>3</sub>	toluene	100 °C
5	CuI (10 mol-%)/ <b>L77</b> (20 mol-%)	NaH	toluene	100 °C
6	CuO (1 eq.)/ KI (10 mol-%)	NaO <sup>t</sup> Bu	toluene	100 °C
7	CuO (1 eq.)/ KI (10 mol-%)	NaH	pyridine	100 °C
8 <sup>a</sup>	CuO (1 eq.)/ KI (10 mol-%)	NaH	DMF	120 °C

<sup>a</sup>4fold excess of ethyleneglycol.

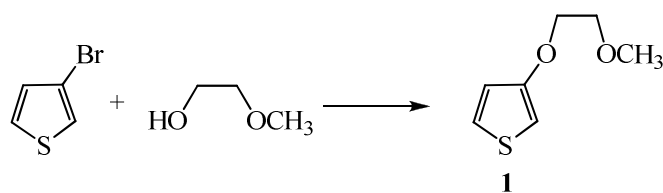
### 3.2.2 Synthesis under Microwave Irradiation

In the last decade, microwave-assisted synthesis became more and more important.<sup>25</sup> It is described as fast and effective for metal-catalyzed reactions. Due to the high dipole of the metal atom an activation as a “hot spot” is proposed. This high energy should favour the coupling reactions.

In this study, two commercial instruments were tested. On one hand a multimode microwave produced by EMLS (Start 1500S) was applied for parallel reactions in bigger batches. In the big sample compartment the microwave irradiation (2450 MHz, 1000 Watt) is distributed. Therefore, the continuous irradiation of the samples can not be guaranteed. During the reaction time the batches are rotated through the sample compartment to avoid

this disadvantage. The instrument of CEM (Discover) has a very small sample chamber. The monomodal microwave irradiation (2450 MHz) is focused by a circular single-mode cavity around the compartment. Therefore, a continuous heating of the sample can be expected. However, only small samples can be irradiated successively.

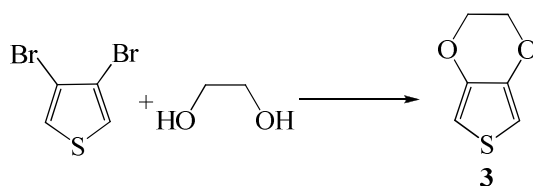
Only a few examples were tested in the CEM Discover apparatus. Therefore, the catalysts with the best results under conventional conditions were used to convert first 3-bromothiophene into 3-(2-methoxyethoxy)-thiophene **1**.



**Scheme 3.12** Formation of **1** from 3-bromothiophene and 2-methoxyethanol.

The reaction using copper(I) iodide (10 mol-%), potassium *tert*-butanolate (1 eq.) in lutidine was stirred at 150 °C for ten minutes. After work-up only 10 % of the product could be obtained. The 3-bromothiophene was re-isolated. Under conventional conditions a yield of 78 % was observed (Table 3.2, Entry 5). On the other hand, the conversion with copper(I) iodide (20 mol-%) and sodium hydride in DMF gave **1** in 64 %. The yield is rather comparable to which observed under conventional conditions (73 %, Table 3.2, Entry 8). The mixture was stirred for five minutes at 150 °C in the PowerMax mode. This means that the vial was permanently cooled by stream of air, therefore, a higher radiation was reached.

Also the formation of EDOT (**3**) was investigated with copper(I) iodide (20 mol-%) and sodium hydride in DMF. After ten minutes at 150 °C in the PowerMax mode no conversion of 3,4-dibromothiophene was observed.



**Scheme 3.13** Formation of **3** from 3,4-dibromothiophene and ethyleneglycol.

The microwave reduced the reaction time only in DMF with sodium hydride as base. An explanation would be the strength of the bases used. Because potassium *tert*-butanolate is suspended in DMF, deprotonation of the alcohol requires longer reaction time. However, sodium hydride quantitatively deprotonates alcohols. Therefore, a very high amount of nucleophiles is suitable from the beginning of the reaction. When the microwave irradiation activates the metal centre the reaction in case of sodium hydride can occur immediately. Unfortunately, also the microwave could not favour the synthesis of **3** in one step starting from 3,4-dibromothiophene.

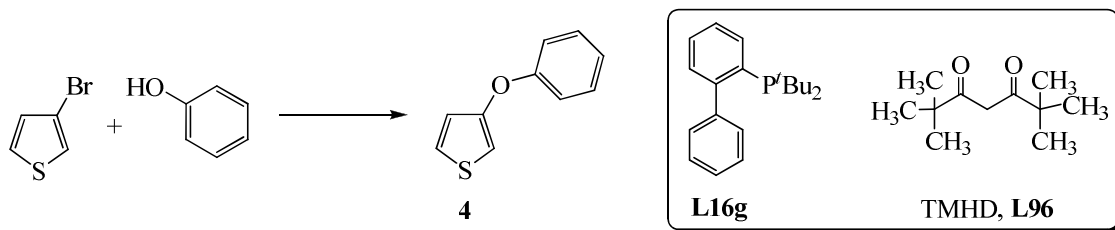
### 3.3 Synthesis of Aryloxythiophenes

#### 3.3.1 Synthesis under “Conventional” Heating

The synthesis of aromatic thiophene ethers was planned under palladium-catalyzed Buchwald-Hartwig conditions and copper-catalyzed Ullmann-type coupling methods. The coupling of 3-bromothiophene and phenol was used as model reaction. To screen a variety of catalytic systems already published reaction condition were chosen. The results are summarized in Table 3.4.

All palladium-catalyzed reactions didn't show any reaction. Just the starting materials were re-isolated. First the formation of the alcoholate seemed to be problematic, so stronger bases were used (Table 3.4, Entry 2). While this didn't lead to a reaction, a more electron-rich and spacer ligand (**L16g**, Table 3.4, Entry 3) was used, without any effect.



**Table 3.4** Synthesis of 3-phenoxythiophene **4** from 3-bromothiophene and phenol.

	Catalyst	Base	Solvent	Temp. [°C] (Time)	Yield [%] <sup>a</sup>
1 <sup>19, 26</sup>	10 mol-% Pd(OAc) <sub>2</sub> / H[P'Bu <sub>3</sub> ]BF <sub>4</sub>	KO <sup>t</sup> Bu	toluene	80 °C (4 d)	0
2	10 mol-% Pd(OAc) <sub>2</sub> / H[P'Bu <sub>3</sub> ]BF <sub>4</sub>	NaH	toluene	100 °C (4.5 d)	0
3 <sup>27</sup>	2 mol-% Pd(OAc) <sub>2</sub> / <b>L16g</b>	K <sub>3</sub> PO <sub>4</sub>	toluene	100 °C (7.5 d)	0
4 <sup>13</sup>	2.5 eq. CuO	K <sub>2</sub> CO <sub>3</sub>	pyridine	115 °C (4 d)	15
5	2.5 eq. CuO/ KI	K <sub>2</sub> CO <sub>3</sub>	pyridine	115 °C (4 d)	53
6	2.5 eq. CuO/ KI	NaO <sup>t</sup> Bu	pyridine	115 °C (3 d)	22
7	2.5 eq. CuO/ KI	(phenolate)	pyridine	115 °C (5 d)	59
8 <sup>23</sup>	10 mol-% Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	Cs <sub>2</sub> CO <sub>3</sub>	NMP	100 °C (5 d)	0
9 <sup>21</sup>	0.5 eq. CuCl/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	NMP	120 °C (3 d)	43
10	0.5 eq. CuCl/ KI/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	NMP	120 °C (3 d)	46
11	0.5 eq. CuCl/ <b>L96</b>	NaH	NMP	120 °C (3 d)	43
12	0.5 eq. CuCl/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	NMP	150 °C (3 d)	48
13	0.5 eq. CuCl/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	pyridine	115 °C (2 d)	17
14	0.5 eq. CuCl/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	lutidine	115 °C (2 d)	10
15 <sup>23</sup>	0.5 eq. CuCl/ <b>L96</b>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	115 °C (2 d)	3

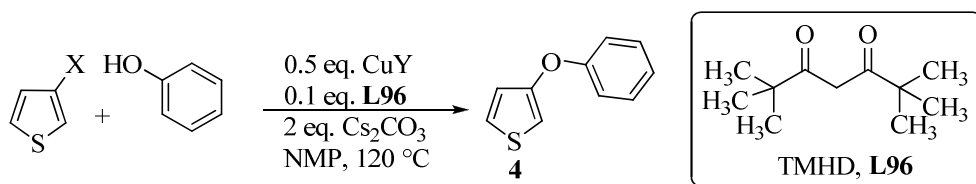
<sup>a</sup>isolated yields.

Because with palladium-catalyzed reaction conditions no product was obtained, the more favourable Ullmann-coupling was tested using cupric salts. Following the formation of 3-(methoxyethoxy)thiophene **1** with copper(II) oxide as catalyst in lutidine<sup>5</sup>, also **4** was synthesized (Table 3.4, Entry 4). The product could be obtained in 15 % yield. With the addition of potassium iodide the yield could be increased to 53 % (Table 3.4, Entry 5). This is due to an *in situ* halogen exchange according to a Finkelstein reaction. Applying an organic base (sodium *tert*-butanolate) led to lower conversion of the phenol (Table 3.4, Entry 6). Also the preformed phenolate, obtained by the reaction of phenol with sodium methanolate, enhanced the reaction rate (59 %, Table 3.4, Entry 7).

The mechanism of the nucleophilic substitution is not cleared up to date. But the need of an excess of copper(II) oxide and the high temperatures requested led us to assume, that this is an uncatalyzed nucleophilic substitution. In former investigations it was shown, that the insoluble copper(II) oxide favours the reaction, because the yields decreased with lower catalyst loadings. In the crystal lattice of copper(II) oxide the copper atoms are coordinated square planar by four oxygen and the oxygen atoms are surrounded in a tetrahedral manner by copper. Therefore, the copper atoms in the edge of the crystal lattice have formally the oxidation state +1. It is believed that copper(I) is the active catalyst. Venkataraman *et al.* described in 2001 a stable copper(I) catalyst for the formation of diaryl ethers.<sup>23</sup> But for the conversion of 3-bromothiophene to **4** it was not useful (Table 3.4, Entry 8). Only starting materials were re-isolated. A moderate yield was obtained using copper(I) chloride and 2,2,6,6-tetramethyl-3,5-heptadione (TMHD, **L96**) as catalytic system in *N*-methylpyrrolidone (NMP). This procedure was described by Song and co-workers in 2002 for the formation of diaryl ethers in high yields.<sup>21</sup> From 3-bromothiophene and phenol the desired pure product was obtained in 43 %. In other solvents like pyridine, lutidine and DMF (Table 3.4, Entries 13-15) the yield decreased. Also the addition of potassium iodide (Table 3.4, Entry 10), a stronger base like sodium hydride (Table 3.4, Entry 11) or higher temperature (Table 3.4, Entry 12) didn't affect the conversion significantly. With the addition of potassium iodide to the reaction mixture, after work-up of the reaction mixture an iodophenol species could be characterized. This is in accordance to the behaviour described by Edgar *et al.*<sup>28</sup> They described the iodination of phenols using sodium iodide as iodinating agent with sodium hypochlorite in aqueous media as oxidant. Herein potassium iodide serves as the iodinating agent with copper(I) as

oxidant. To optimize the conditions other copper(I) resources and 3-halogenothiophenes were investigated. The results are summarized in Table 3.5.

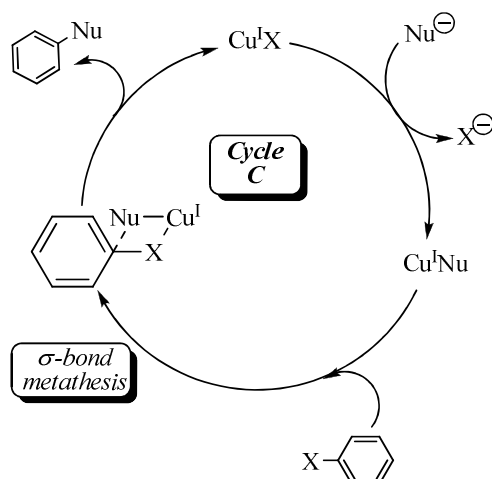
**Table 3.5** Conversion of 3-halogenothiophenes and phenol (2 eq.) using CuY (50 mol-%), **L96** (20 mol-%), Cs<sub>2</sub>CO<sub>3</sub> (2 eq.) in NMP.



	X	Y	Yield [%] <sup>a</sup>
1	Br	Cl	43
2	Br	Br	6
3	Br	I	15
4	Br	- <sup>b</sup>	27
5	I	Cl	62
6	Cl	Cl	-

<sup>a</sup>isolated yields, <sup>b</sup>copper powder was used.

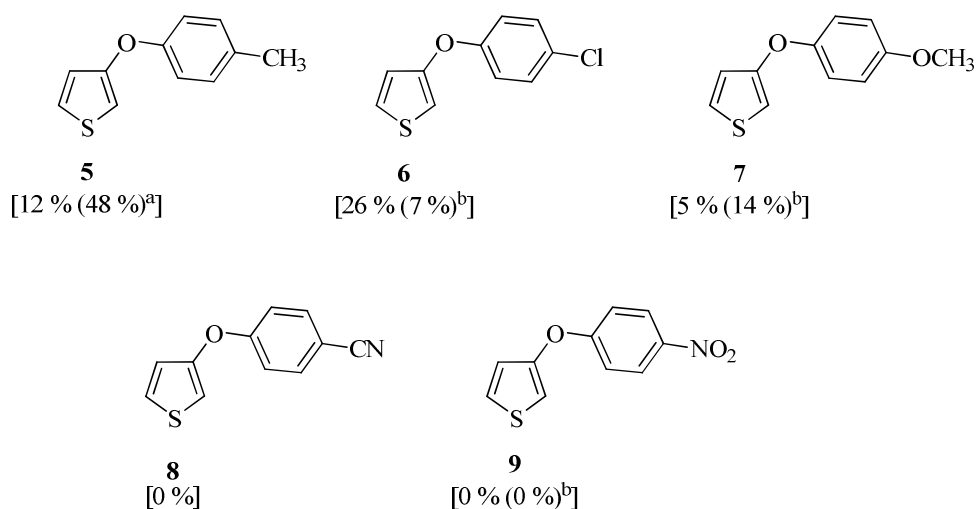
Van Allen investigated the mechanism of Ullmann-type amination of aryl halides (See also chapter 2.2.3).<sup>29</sup> On the basis of examined results the catalysis *via*  $\sigma$ -bond metathesis (Scheme 3.14) was found to be most reasonable.



**Scheme 3.14** Catalytic cycle according to  $\sigma$ -bond metathesis for Ullmann- type reactions.

In this mechanism the halide at, both, the copper centre and the aryl don't influence the reaction rate. However, for the C-O cross-coupling of 3-halogenothiophene and phenol an increased yield was obtained, when 3-iodothiophene (Table 3.5, Entry 5, 62 %) was converted. 3-Chlorothiophene could not be coupled under these reaction conditions. Starting from 3-bromothiophene the best yield was obtained for copper(I) chloride as catalyst (Table 3.5, Entry 1, 43 %). Therefore, a catalytic cycle *via*  $\sigma$ -bond metathesis is implausible. Other possible pathways include either a single-electron transfer or a copper(III) intermediate, which is comparable to palladium- or gold-catalysis. In both catalytic cycles copper undergoes a change in oxidation state from copper(I) to copper(II) or copper(III), respectively. In contrast to copper(I) chloride and bromide, copper(I) iodide is stable at this oxidation state, even in solution. The two alternatives including an oxidation state change are in accordance with the results obtained for the diaryl ether synthesis. It can be concluded that either a catalytic cycle similar to palladium- or gold-catalysis or the single-electron transfer protocol is valid. Distinction of these two pathways would request further investigations, for example ESR-experiments.

The best reaction conditions to convert 3-halogenothiophenes to 3-phenoxythiophene **4** were found to be 50 mol-% copper(I) chloride, 20 mol-% **L96**, 2 eq. cesium carbonate as base with a twofold excess of phenol in NMP at 120 °C. Although 3-bromothiophene gave lower yields, it was used for further conversions instead of 3-iodothiophene, which is quite expensive. Some new phenylsubstituted derivatives were synthesized according this protocol (Chart 3.4).



**Chart 3.4** Synthesized thiophene-3-phenoxy derivatives from 3-bromothiophene (1eq.), corresponding phenol (2 eq.), CuCl (50 mol-%), **L96** (20 mol-%), Cs<sub>2</sub>CO<sub>3</sub> (2 eq.) in NMP at 120 °C for three days. <sup>a</sup>with addition of potassium iodide (1 eq. ), <sup>b</sup>at 150 °C.

The application of substituted phenols in the Ullmann-type C-O cross-coupling with 3-halogenothiophenes led in much lower yields than observed for the synthesis of 3-phenoxythiophene **4** under identical reaction conditions. Several effects can be discussed: Phenolates are poor nucleophiles and are not well suitable for the nucleophilic substitution leading to diaryl ethers.<sup>30</sup> The nucleophilic character decreases with substituents on the benzene ring, which show a negative inductive or/ and mesomeric effect. To discuss the electronic effect of a substituent at benzene ring, Hammett defined a parameter  $\sigma$ , which sets the electron-donating and –withdrawing effect in relation to H. If  $\sigma$  is positive, the substituent is electron-withdrawing and, therefore, the corresponding phenolate is less nucleophilic than phenolate itself.

Another crucial point in the catalytic cycle is stability of the present copper complexes, because each step means an equilibrium of the reaction partners. Concerning the  $\sigma$ -bond metathesis shown in Scheme 3.14 first an equilibrium of copper(I) chloride and phenolate has to be shifted to a stable copper-phenolate complex. On the other hand, the C-O bond formation process is increased for more instable complexes. Control of these equilibria is the main task in catalysis. Méndez and Geerlings *et al.* investigated the basicity of *para*-substituted phenolates in context with the hard and soft acids and bases principle (HSAB).<sup>31</sup> The hardness of the phenolate is correlated to the basicity. Therefore, copper(I) as soft acid forms more stable complexes with phenolates of lower basicity.

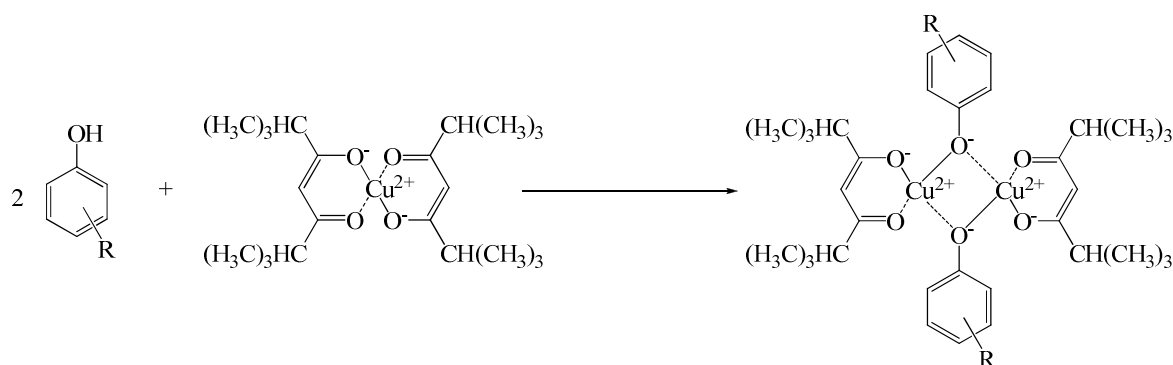
The cyanide and the nitro group have a  $\sigma_p$  (substituent is located in *para*-position) of 0.67 and 0.77, respectively.<sup>32</sup> Both *p*-cyanophenol and *p*-nitrophenol were not converted by this method to **8** and **9**. Beside the electronic effect, which led in low nucleophilicity, they form rather stable copper-phenolate complexes. The reductive elimination is expected to be interfered. Additionally, the cyano group is a ligating group for copper. It is conceivable that the catalyst is poisoned due to copper-cyanide complexation.

A moderate yield could be observed for the conversion of *p*-chlorophenol to the corresponding ether **6**. Chlorine shows also a negative inductive effect, but a weak positive mesomeric effect ( $\sigma_p$  for Cl: 0.22). The coupling of *p*-chlorophenolate to another *p*-chlorophenol to form a diaryl ether bond is expected as a side reaction. Also the coupling of *p*-chlorophenolate to 3-(4-chlorophenoxy)-thiophene **6** was observed in small amount.

In the case of *p*-hydroxyanisol only 5 % of the desired product **7** was obtained. The methoxy group has a  $\sigma_p$  of -0.29, which means that the positive mesomeric effect dominates the negative inductive effect and the nucleophilicity should be increased compared to phenol. Because the anion of *p*-hydroxyanisol is a harder base than phenolate, it should form a weaker complex with copper(I). Possibly this shift of the equilibrium to copper(I) chloride disturbs the catalytic cycle.

*p*-Cresol gave also a moderate yield. The positive inductive effect of the methyl group ( $\sigma_p$  -0.17) should help the deprotonation of the alcohol group. However, this result is in accordance to what Watthey *et al.* described in 1982.<sup>12</sup> They published a yield of 47 % for the formation of 3-phenoxythiophene **4**, and only 24 % for the *p*-cresol derivative **5** with copper bronze at elevated temperatures. As for *p*-hydroxyanisol a weak copper-phenolate interaction can be discussed.

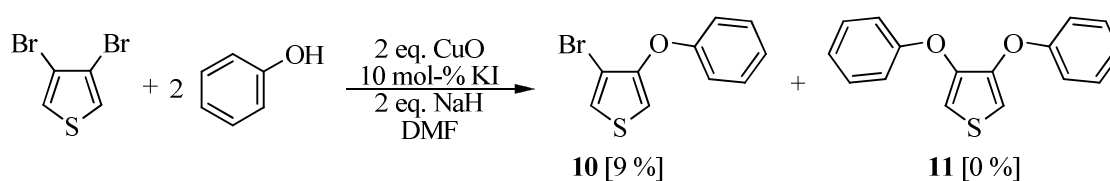
As already mentioned before, the complex stability of the copper-nucleophile intermediate has to be taken into account. In literature, only a few examples are described for copper(II) TMHD-phenolate complexes (Scheme 3.15).<sup>33</sup> The formation of such a complex is competitive to the coupling reaction wanted.



**Scheme 3.15** Phenolate-TMHD-copper(II) complexed published by Hubert-Pfalzgraf *et al.*<sup>33</sup>

When phenol was reacted with 3-bromothiophene with addition of potassium iodide the yield didn't increase. However, the C-O cross-coupling of *p*-cresol gives a four times higher yield under these conditions, when the halogen exchange can take place. Increasing temperature increased the yield for the formation of 3-(4-methoxyphenoxy)thiophene (**7**). Both observations can be attributed to a competitive nucleophilic substitution. During the conversion of *p*-chlorophenol at elevated temperatures dehalogenation of the phenol was observed. Neither the starting material, nor the product is stable under these conditions. The conversion of *p*-nitrophenol did not take place, even at 150°C.

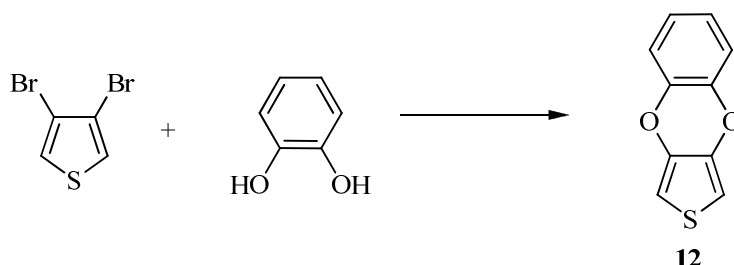
To check, if 3,4-dibromothiophene can be substituted two times it was reacted with phenolate (Scheme 3.16).



**Scheme 3.16** Reaction of 3,4-dibromothiophene and phenol.

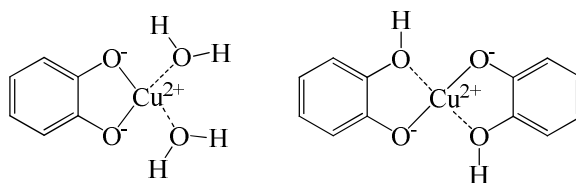
Unfortunately, no product could be detected and only 9 % of monosubstituted product **10** was obtained. Concerning the  $\sigma$ -bond metathesis, discussed as most plausible catalytic cycle, sterical hindrance might perturb the reaction. The bromine in *ortho*-position, and later on the phenoxy group, might hinder the attack of the copper-phenoxy complex at the thiophene ring.

Although no conversion of 3,4-dibromothiophene to **11** could be observed, 3,4-dibromothiophene and pyrocatechol were tested to give benzo[*e*]thieno[3,4-*b*][1,4]dioxine (benzoEDOT, **12**, Scheme 3.17).



**Scheme 3.17** Synthesis of benzo[*e*]thieno[3,4-*b*][1,4]dioxine **12** from 3,4-dibromothiophene and pyrocatechol.

As catalyst the more reactive copper(II) oxide was chosen with the addition of potassium iodide. With sodium hydride as base in pyridine no product could be isolated even after five days at 115 °C. In a second reaction the sodium salt of pyrocatechol should be prepared through the reaction with sodium methanolate at reflux. After removal of the methanol the obtained salt was used for the coupling. Unfortunately, no reaction proceeded. In another experiment copper(I) chloride was applied as catalyst with the protocol described for the formation of 3-phenoxythiophene **4**. After two days at 120 °C no product was obtained. In all reaction no conversion was observed. Also no monosubstitution of the 3,4-dibromothiophene. This reactant seems to be too inactive in the etherification protocol with aromatic alcohols. Another problem could be the formation of a stable copper-pyrocatechol complex. Tyson *et al.* investigated in 1968 the complex equilibrium constant of copper-pyrocatechol complexes in aqueous media.<sup>34</sup> The stability of the complexes depends on the ionic strength of the solution, which leads the deprotonation of the alcohols. They described a 1:1- and a 1:2-complex (Scheme 3.18).



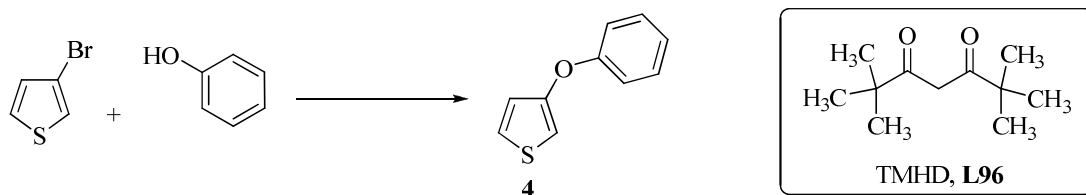
**Scheme 3.18** Stable copper(II)-complexes with pyrocatechol as ligand.



### 3.3.2 Synthesis under Microwave Irradiation

For the optimization of the method 3-bromothiophene and phenol were coupled using microwave heating. The results are summarized in Table 3.6.

**Table 3.6** Conversion of 3-bromothiophene with phenol to **4** in microwave.



	Catalyst	Base	Solvent	Time [min] (Temp.)	Yield [%] <sup>a</sup>
1	CuI (20 mol-%)	NaH	DMF	5 (150 °C) <sup>b</sup>	26
2	CuI (20 mol-%)	NaH	DMF	10 (150 C°) <sup>c</sup>	11
3	CuO (1 eq.)/ KI	NaH	pyridine	15 (150 °C) <sup>c</sup>	-
4	CuCl (50 mol-%)/ <b>L96</b> (20 mol-%)	Cs <sub>2</sub> CO <sub>3</sub>	NMP	10 (170 °C) <sup>c</sup>	19

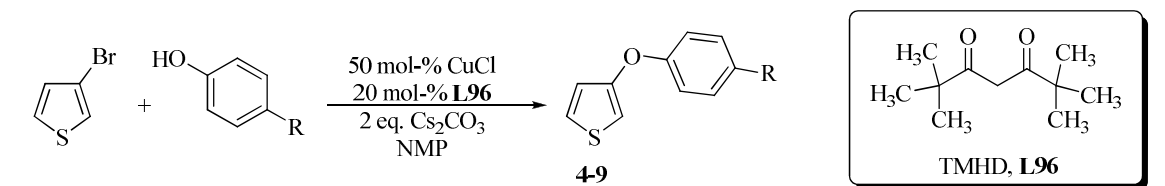
<sup>a</sup>isolated yields, <sup>b</sup>with CEM discover, <sup>c</sup>with EMLS microwave.

A higher conversion was observed when using the CEM Discover apparatus, than in EMLS Start 1500S. In the equipment discovered from CEM the microwave radiation is located in a very small reaction chamber. In the EMLS the radiation is distributed in a much larger volume. During the reaction there are places with radiation “holes”. Therefore, the reaction times were elongated in EMLS instrument. Using copper(I) iodide in DMF with sodium hydride as base to couple phenol and 3-bromothiophene a yield of 26 % and 11 % can be obtained for **4** in the CEM and EMLS apparatus respectively. When copper(II) oxide and potassium iodide were used as catalyst no conversion was observed. Under conventional heating the product was obtained in 59 % (Table 3.4, Entry 7). With the standard method used for the formation of phenoxythiophene derivatives (CuCl, **L96**, cesium carbonate in NMP) **4** was obtained in 19 % yield in the EMLS apparatus. The

reaction was not carried out in the CEM microwave oven. The yields are very low compared to the yields under conventional heating. An activation of the catalyst was not observed, which would lead to a decreased reaction time. Therefore, microwave irradiation is only another heating method for the Ullmann-type cross-coupling of 3-bromothiophene to phenols.

However, also under microwave irradiation the scope of the diaryl ether formation was investigated. In Table 3.7 the yields observed under “conventional” heating are compared to which observed in microwave instrument. 3-Bromothiophene was coupled to appropriate phenols using copper(I) chloride (50 mol-%), **L96** (20 mol-%), cesium carbonate (2 eq.) in NMP. The mixtures were stirred in the EMLS Start 1500S apparatus for 15 minutes at 150 °C (exc. phenol at 170 °C).

**Table 3.7** Conversion of 3-bromothiophene and corresponding phenol derivatives with CuCl (50 mol-%), **L96** (20 mol-%), Cs<sub>2</sub>CO<sub>3</sub> (2 eq.), NMP at 120 °C in conventional heating and 150 °C in microwave.



R	<i>Microwave Heating</i>		<i>Conventional Heating</i>	
	Time [min]	Yield [%] <sup>a</sup>	Time [days]	Yield [%] <sup>a</sup>
H ( <b>4</b> )	10	19 <sup>b</sup>	4	43 (48) <sup>c</sup>
CH <sub>3</sub> ( <b>5</b> )	10	16	3	12 (48) <sup>d</sup>
Cl ( <b>6</b> )	15	61	3	26
OCH <sub>3</sub> ( <b>7</b> )	15	8	3	5 (14) <sup>c</sup>
CN ( <b>8</b> )	15	1	3	0
NO <sub>2</sub> ( <b>9</b> )	15	0	4	0

<sup>a</sup>isolated yields, <sup>b</sup>170 °C, <sup>c</sup>150 °C, <sup>d</sup>with potassium iodide.

For the conversion of *p*-cresol to **5** and *p*-methoxyphenol to **7** no higher yields were obtained under microwave irradiation. They are rather comparable to those obtained under conventional reaction conditions. *p*-Nitrophenol (**9**) and *p*-cyanophenol (**8**) gave no conversion in microwave too. The one exceptional case is the synthesis of **6**. Under microwave heating the desired product was obtained in 61 % yield. In contrast to the reaction under conventional heating no 3-(4-(4-chlorophenoxy)-phenoxy)-thiophene could be detected. Obviously the shorter reaction time suppresses the coupling of *p*-chlorophenol to the chlorine of **6**.

Also disubstitution was investigated under microwave heating conditions. 3,4-Dibromothiophene was reacted with two equivalents of phenol using the reaction condition described for the formation of **4** (Table 3.7). After a microwave irradiation for 15 minutes no product could be detected in the crude reaction mixture. Therefore, no conversion of 3,4-dibromothiophene with pyrocatechol to benzoEDOT was done.

### 3.4 Conclusions

For the synthesis of aliphatic thiophene ethers several methods were already known. Palladium catalysts gave no conversion to the desired 3-(2-methoxyethoxy)-thiophene **1**, but homocoupling to 3,3'-bithiophene was observed. None of the investigated copper catalysts gave better results than described by Marsella (78 %, CuI in lutidine).<sup>5</sup> Using this procedure a twofold nucleophilic substitution at 3,4-dibromothiophene was observed in low yields (Chart 3.3). However, EDOT (**3**) could not be synthesized from 3,4-dibromothiophene and ethylene glycol using several promising catalysts.

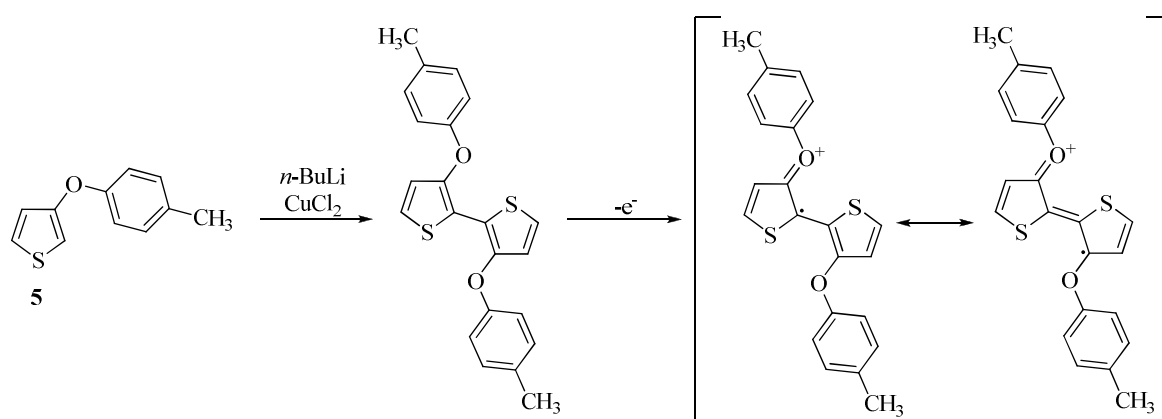
Only three examples for the etherification under microwave irradiation with aliphatic alcohols were tested. The microwave could not favour the reaction of EDOT. But the coupling of 3-bromothiophene and 2-methoxyethanol using copper(I) iodide as catalyst in DMF and sodium hydride as base a comparable yield of 64 % could be obtained in only five minutes, compared to four days under conventional heating.

The formation of phenoxythiophenes was tested with a number of catalysts described in literature, including Buchwald-Hartwig- and Ullmann-type catalysts. Unfortunately, no new general method to convert 3-halogenothiophenes into diaryl ethers was found. Watthey *et al.* synthesized 3-phenoxythiophene **4** in 50 % yield from 3-bromothiophene

with copper bronze.<sup>12</sup> Raju *et al.* used in 1996 copper(I) chloride in pyridine to catalyze this reaction, but gave no detailed yield for this reaction step.<sup>14</sup> The best result in this work was obtained using copper(II) oxide and potassium iodide in pyridine giving **4** in 59 % (Table 3.5, Entry 7). 3-Iodothiophene was most effectively coupled using copper(I) chloride and TMHD in NMP (62 %, Table 3.5, Entry 5).

A number of new 3-aryloxythiophenes could be synthesized with low to moderate yields using copper(I) chloride and TMHD in NMP as catalyst. *p*-Cresol gave lower yields (**5**, 48 %, Table 3.7) than in the catalysis described by Watthey and co-workers (86 % yield).<sup>12</sup> Due to weak nucleophilicity of phenolates not all phenol derivatives could be converted into the corresponding ethers. Also microwave irradiation didn't improved the yields, except for the formation of 3-(4-chlorophenoxy)-thiophene (**6**, Table 3.7). The twofold substitution of 3,4-dibromothiophene with phenol and pyrocatechol could not be observed, neither under conventional conditions nor microwave irradiation.

During the studies for the effective C-O cross-coupling at thiophenes Roncali *et al.* published results about the polymerization experiments of 3-(*p*-tolylloxy)-thiophene (**5**).<sup>35</sup> No polymer could be obtained electrochemically. Under chemical polymerization conditions (*n*-BuLi, CuCl<sub>2</sub>) a stable dimer was formed (Scheme 3.19). The radical cation formed at the dimer does not give a radical at the free  $\alpha$ -position of the thiophene-ring, which would lead into polymer formation.



**Scheme 3.19** Chemical dimerization of **5** and stabilization of the radical cation.

On the basis of these results, no electrochemical investigations of the phenoxythiophenes described above were carried out.

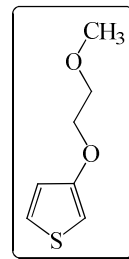
### 3.5 Experimental Part

*Thin layer chromatography* (TLC) was carried out on Silica Gel 60 F<sub>254</sub> aluminium plates (Merck). Developed plates were dried and examined under a UV lamp. *Preparative column chromatography* was carried out on glass columns of different diameters packed with silica gel Merck 60 (40-63  $\mu\text{m}$ ). *Gas chromatography* (GC) was carried out using a Varian CP-3800 gas chromatograph. Helium 5.0 was used as carrying gas, signals were examined by a flame-ionization detector (FID). *Gas chromatography-Mass spectrometry* (GC-MS) measurements were executed with a Varian 3800. Helium 5.0 was used as carrying gas, Mass spectra were recorded on a Varian Saturn 2000. Ions were generated by electron impact (EI). *Melting points* were determined in a Büchi B-545 apparatus and are uncorrected. *NMR spectra* were recorded in  $\text{CDCl}_3$  on a Bruker AMX 400 at 400 MHz ( $^1\text{H}$  nuclei) and 100 MHz ( $^{13}\text{C}$  nuclei), respectively. Chemical shifts are denoted in  $\delta$  unit (ppm), and are referenced to the solvent signal (7.26 ppm for  $\text{CDCl}_3$ ). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). *Mass spectra* were measured at Finnigan MAT, SSQ 7000 via CI. *Elemental analysis* for C, H and N were determined at Elementar Vario EL and for S at Carlo Erba 1104. *High resolution mass* was measured at a micrOTOF-Q 43 with electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI).

All reactions were carried out under an inert atmosphere of argon. 3,4-Dibromothiophene was prepared according to literature procedures.<sup>36</sup> The following reactants and solvents were purified and dried by standardized procedures: 3-Bromothiophene (VWR), DMF (*N,N*-dimethylformamide, VWR), NMP (*N*-methylpyrrolidone, VWR), 2-Methoxyethanol (VWR), ethylene glycol (VWR), phenol (Merck), *p*-chlorophenol (Merck), *p*-hydroxyanisole (Merck), *p*-cresol (Merck), lutidine (2,6-dimethylpyridine, VWR), dichloromethane (VWR), MTBE (methyl *tert*-butyl ether, Merck), sodium hydride (60 % suspension in mineral oil, Merck), potassium *tert*-butanolate (Merck), calcium carbonate (VWR), cesium carbonate (Merck), copper(I) iodide (Merck), copper(I) chloride (Merck), TMHD (2,2,6,6-tetramethyl-3,5-heptadione, Acros), hydrochloric acid (VWR), sodium hydroxide (VWR), sodium sulphate (VWR), celite (454, VWR) were used as received.

**3-(2-Methoxyethoxy)-thiophene (1)**<sup>5</sup>

2-Methoxyethanol (5.9 mL, 75 mmol) was dissolved in lutidine (1.6 mL) and potassium *tert*-butanolate (5.62 g, 50 mmol) was added in portions. After the exothermic reaction was flattened down copper(I) iodide (0.95 g, 5 mmol) and 3-bromothiophene (4.5 mL, 50 mmol) were added. After stirring for 24 hours at 100 °C the suspension was cooled to room temperature and the solid was filtered off and washed with dichloromethane (25 mL). The organic phase was treated two times with hydrochloric acid (7 %, 15 mL), dried over sodium sulphate and concentrated in vacuum. The product was distilled from calcium carbonate (58 °C,  $5 \cdot 10^{-2}$  mbar) to give 6.00 g (38 mmol, 76 %) with 99 % GC-purity (78 % lit.).



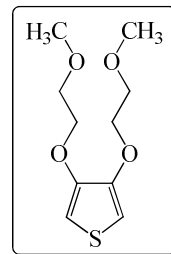
Sodium hydride (60 % suspension in mineral oil, 0.1 g, 2.5 mmol) was suspended in dry DMF (7 mL). Under argon 2-methoxyethanol (0.2 mL, 2.5 mmol) was added dropwise, followed by 3-bromothiophene (0.24 mL, 2.5 mmol) and copper(I) iodide (0.1 g, 0.5 mmol). The green suspension was stirred under microwave irradiation (PowerMax mode) in a sealed tube at 150 °C (50 W). The cool brown suspension was dissolved in dichloromethane (50 mL) and filtered through a plug of celite. After work-up as described for the conventional preparation the pure product was obtained in 0.25 g (1.6 mmol, 64 %) yield.

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 3.42 (3H, s), 3.71 (2H, m), 4.08 (2H, m), 6.23 (1H, dd, *J* 1.6 and 3.1), 6.77 (1H, dd, *J* 1.6 and 5.3), 7.14 (1H, dd, *J* 3.1 and 5.3);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 59.1, 69.3, 70.9, 97.4, 119.6, 124.6, 157.5.

**3,4-Di(2-methoxyethoxy)-thiophene (2)**<sup>8</sup>

In lutidin (10 mL) sodium hydride (60 % suspension in mineral oil, 0.4 g, 10 mmol) was suspended before 2-methoxyethanol (0.79 mL, 10 mmol) was dripped in. After gas evolution had stopped 3,4-dibromothiophene (0.55 mL, 5 mmol) and copper(I) iodide (0.95 g, 5 mmol) were added. The suspension was stirred at 100 °C for seven days. The reaction mixture was taken up in dichloromethane (40 mL) and the precipitates were filtered through celite. The organic phase was washed three times with hydrochloric acid (7 %, 70 mL) and dried over sodium sulphate. The crude product was concentrated in vacuum and analyzed by GC-MS.



**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 3.42 (6H, s), 3.72- 3.75 (4H, m), 4.09- 4.12 (4H, m), 6.23 (2H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 59.1, 69.7, 70.7, 98.0, 147.2.

### **General procedure A:**

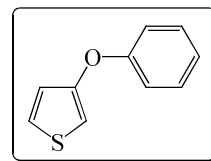
In NMP (25 mL) cesium carbonate (3.26 g, 10 mmol), corresponding phenol (10 mmol), copper(I) chloride (0.25 g, 2.5 mmol) and TMHD (0.1 g, 0.5 mmol) were suspended. After the addition of 3-bromothiophene (0.47 mL, 5 mmol) the greenish suspension was stirred at a certain temperature. The cooled mixture was treated with MTBE (15 mL), filtered and subsequently extracted with HCl (2N, 15 mL and 0.6N, 15 mL), NaOH (2N, 15 mL) and sodium chloride solution (10 %, 15 mL). The dried organic phase was concentrated in vacuum and poured onto silica gel. With hexanes as eluent the pure product was obtained.

### **General procedure B:**

Cesium carbonate (1.95 g, 6 mmol), phenol (6 mmol), 3-bromothiophene (0.28 mL, 3 mmol), TMHD (0.12 mL, 0.6 mmol) and copper(I) chloride (0.15 g, 1.5 mmol) were suspended in 10 mL NMP and stirred in the microwave oven at 150 °C (phenol at 170 °C). The cooled mixture was treated with MTBE (10 mL), filtered through a plug of celite and the residue was washed with 15 mL MTBE. The organic phase was extracted subsequently with hydrochloric acid (10 mL of 2 and 0.6 M), sodium hydroxide solution (2M, 10 mL) and brine (10 %, 10 mL). Further purification was similar to procedure A.

### **3-Phenoxythiophene (4)<sup>12, 14</sup>**

According to procedure A with phenol (0.94 g, 10 mmol) and stirring at 150°C the product was obtained as colourless liquid in 48 % yield (2.4 mmol, 422.5 mg). After applying procedure B with phenol (0.56 g) after ten minutes at 170 °C the desired product was isolated in 100.3 mg (0.6 mmol, 19 %).

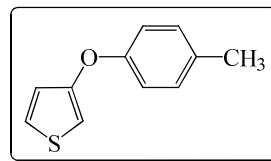


**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 6.61 (1H, dd, *J* 1.5 and 3.3), 6.87 (1H, dd, *J* 1.4 and 5.2), 7.06 (2H, d, *J* 8.7), 7.10 (1H, t, *J* 7.4), 7.26 (1H, dd, *J* 3.3 and 5.2), 7.34 (2H, dd, *J* 7.5 and 8.5);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 106.8, 117.9, 120.8, 123.2, 125.1, 129.6, 154.3, 158.0.

**3-(*p*-Tolyloxy)-thiophene (5)**<sup>12, 14</sup>

According to procedure A with *p*-cresol (1.04 mL, 10 mmol) and the addition of potassium iodide (0.38 g, 5 mmol) the pure product was obtained in 48 % (2.4 mmol, 456.6 mg) as colourless liquid.



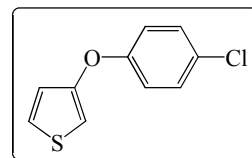
*p*-Cresol (0.63 mL) was coupled to 3-bromothiophene according to procedure B in ten minutes at 150 °C in 91.3 mg (0.5 mmol, 16 %).

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 2.37 (3H, s), 6.55 (1H, dd, *J* 1.5 and 3.3), 6.87 (1H, dd, *J* 1.5 and 5.2), 7.00 (2H, d, *J* 8.5), 7.17 (2H, d, *J* 8.6), 7.27 (1H, dd, *J* 3.3 and 5.2);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 20.7, 105.8, 118.0, 120.6, 122.7, 125.0, 126.6, 130.1, 132.8, 155.0, 155.6.

**3-(4-Chlorophenoxy)-thiophene (6)**

The conversion of 3-bromothiophene with *p*-chlorophenol (1.29 g, 10 mmol) at 120 °C according to procedure A the desired product was isolated in 273.9 mg (1.3 mmol, 26 %) as colourless liquid. Procedure B (0.77 g *p*-chlorophenol, 15 minutes, 150 °C) gave the product in 385.5 mg (1.8 mmol, 61 %).



**Elemental analysis:** C<sub>10</sub>H<sub>7</sub>ClOS requires C, 57.01, H, 3.35 %; found: C, 56.80, H, 3.49 %;

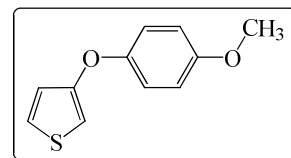
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 6.57 (1H, dd, *J* 1.5 and 3.3), 6.89 (1H, dd, *J* 1.5 and 5.2), 7.01 (2H, d, *J* 8.6), 7.17 (2H, d, *J* 8.2), 7.27 (1H, dd, *J* 3.3 and 5.3);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 105.8, 118.0, 120.6, 125.0, 130.1, 132.8, 155.0, 155.6;

**MS (CI):** *m/z* (M) = 211, (M-C<sub>6</sub>H<sub>4</sub>Cl) = 99.

**3-(4-Methoxyphenoxy)-thiophene (7)**

*p*-Hydroxyanisole (1.24 g, 10 mmol) was coupled to 3-bromothiophene according to procedure A at 150 °C. The desired product was isolated in 14 % (0.7 mmol, 144.4 mg) as colourless liquid.



Under microwave irradiation (procedure B, 0.74 g of *p*-hydroxyanisole) for 15 minutes at 150 °C the product was isolated purely in 49.5 mg (0.2 mmol, 8 %).

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 3.80 (3H, s), 6.45 (1H, dd, *J* 1.5 and 3.3), 6.85 (1H, dd, *J* 1.5 and 5.2), 6.89 (2H, d, *J* 9.1), 7.05 (2H, d, *J* 9.2), 7.24 (1H, dd, *J* 3.3 and 5.2);



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**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{CDCl}_3$ ) 55.7, 104.6, 114.7, 119.8, 120.3, 125.0, 151.3, 155.8, 156.0;

**MS (CI):**  $m/z$  (M) = 207, ( $\text{CH}_3\text{OC}_6\text{H}_4\text{O}$ ) = 123;

**MS (APCI):**  $m/z$  (M+H) 207.0467 ( $\text{C}_{11}\text{H}_{11}\text{O}_2\text{S}$  requires 207.0474).

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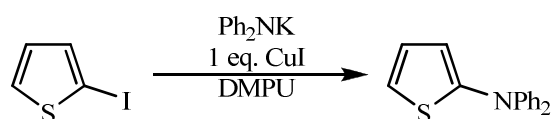
## Chapter 4

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**Thiophene Amines *via* Transition Metal-Catalyzed  
Conversion of 3-Halogenothiophenes**

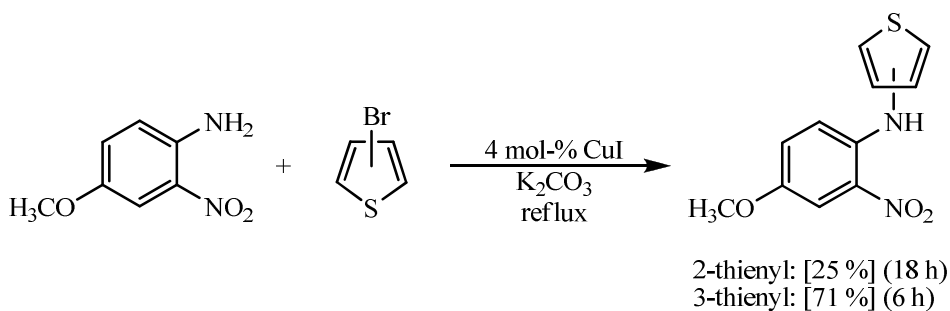
## 4.1 Metal-Catalyzed Formation of Thiophene Amines as Described in Literature

In 1996, Bedworth and Marder developed donor-acceptor systems bridged by a thiophene unit.<sup>1</sup> The piperidinyl derivative was synthesized starting from 2-mercaptothiophene. Diphenyl-2-thienylamine was obtained in moderate yield (40 %) by nucleophilic substitution of 2-iodothiophene and diphenylamine using copper(I) iodide as catalyst in dimethylpropyleneurea (DMPU) (Scheme 4.1).



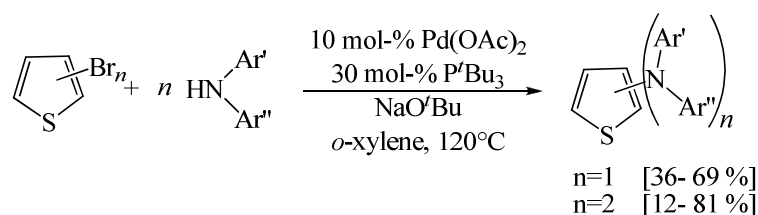
**Scheme 4.1** Formation of diphenyl-2-thienylamine by Bedworth and Marder.<sup>1</sup>

Two years later Denny *et al.* described the coupling of 2- and 3-bromothiophene to 4-methoxy-2-nitroaniline under Ullmann-type conditions.<sup>2</sup> With copper(I) iodide as co-catalyst the products were obtained after several hours in 25 and 71 % respectively (Scheme 4.2).



**Scheme 4.2** Copper-catalyzed amination of bromothiophenes.<sup>2</sup>

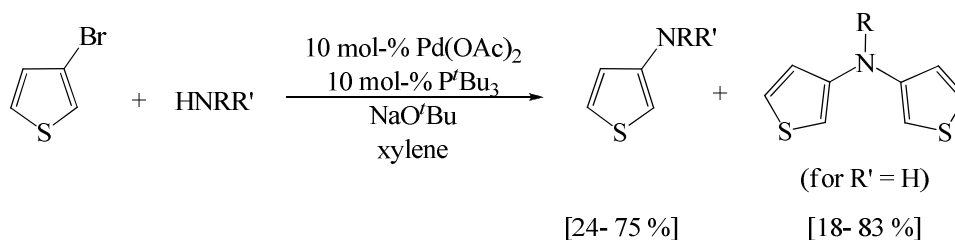
Since the rising interest in palladium-catalyzed amination also C-N cross-coupling reactions with halogenated thiophenes were published. Watanabe *et al.* described in 2000 the conversion of 2-, 3-, 2,5- and 3,4- (di)bromothiophenes to tertiary aromatic amines.<sup>3</sup> As catalyst served palladium(II)-acetate and tri-*tert*-butyl phosphine (**L22**) in *o*-xylene (Scheme 4.3).



**Scheme 4.3** Palladium-catalyzed C-N cross-coupling starting from bromothiophenes and diaryl amines.<sup>3</sup>

With this catalytic system eight examples were presented. 2-Bromothiophenes were less reactive than 3-bromothiophenes, because of the higher electron density of the  $\alpha$ -carbon in thiophenes, which hinders the nucleophilic substitution. Comparing the dibromothiophenes the trend is vice versa. For 3,4-dibromothiophene only the monosubstituted product was obtained in rather low yields. It was mentioned that the *o*-bromine prevents the complexation of the nucleophile to the palladium centre. Also *o*-dibromobenzene should be converted to the corresponding diamine, without any success. However, 2,5-dibromothiophenes gave good to excellent yields for the desired disubstituted product. The yield dropped down when BINAP (**L2**) was applied as ligand. The electron-rich and bulky  $\text{P}^t\text{Bu}_3$  (**L22**) promotes the conversion of electron-rich aryl halides.

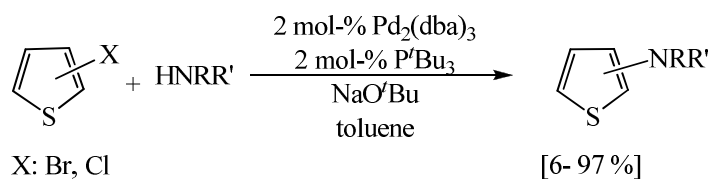
One year later the group of Rasmussen used the palladium catalyst described by Watanabe to convert 3-bromothiophene to secondary and tertiary amines (Scheme 4.4).<sup>4</sup>



**Scheme 4.4** Formation of thiophene-3-amines and *N,N*-bis(3-thienyl)-amines.<sup>4</sup>

Alkylamines gave lower yields than the aromatic ones. In all cases the primary amines gave diarylated products too. In order to reduce side reactions, like homocoupling of the bromothiophene, several conditions were tested, including different temperatures, solvents, palladium sources, catalyst loadings and ligands. In 2003 a versatile formation of *N*-functionalized dithieno[3,2-*b*:2',3'-*d*]pyrroles was published starting from *N,N*-bis(3-thienyl)-*N*-alkyl-amines.<sup>5</sup>

Hartwig *et al.* converted furane- and thiophene bromides and chlorides into tertiary and secondary amines in high yields.<sup>6</sup> As best catalyst served Pd<sub>2</sub>(dba)<sub>3</sub> with P<sup>t</sup>Bu<sub>3</sub> in toluene (Scheme 4.5). But also combinations of Pd(OAc)<sub>2</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> with BiNAP (**L2**), dppf (**L1**) and *N,N'*-bis(2,6-diisopropylphenyl)imidazolium tetrafluoroborate (IPrHBF<sub>4</sub>, **L25d**) were investigated. But only a brief summary was given for the optimization.



**Scheme 4.5** Palladium-catalyzed amination of five-membered heterocycles.<sup>6</sup>

As expected, the yields decreased when chlorothiophenes were converted instead of bromothiophenes and higher temperatures were required. 2-Bromothiophene is less reactive than 3-bromothiophene, as already described by Watanabe.<sup>3</sup> The coupling of *N*-methylaniline proceeded already at room temperature, whereas the arylation of diphenylamine was carried out at 100 °C. *N*-Phenylthiophene-3-amine synthesized from 3-bromothiophene and aniline was obtained in good yields.

## 4.2 Conversion of 3-Halogenothiophene with Primary Arylamines

#### 4.2.1 Synthesis under “Conventional” Heating

A general and efficient procedure should have been found for C-N cross-coupling at thiophenes with substituted aromatic amines. For the optimization of reaction conditions the coupling of 3-bromothiophene and aniline was selected.

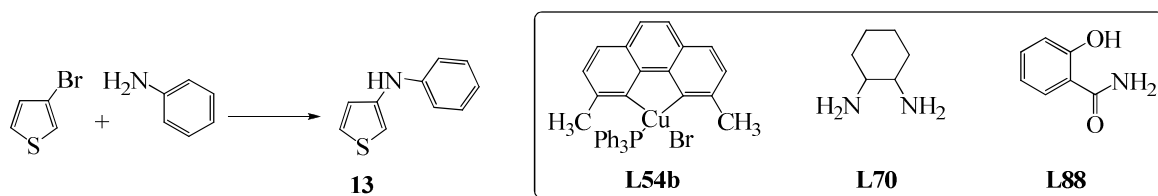
In first attempts copper catalysts were tested, which were described in literature. The results are summarized in Table 4.1.

Venkataraman and co-workers published in 2001 a stable copper(I)-catalyst to form C-O, C-N and C-C bonds.<sup>7</sup> Neocuproine and triphenylphosphine as ligands ensure solubility of copper in organic solvents and stabilize copper(I) against disproportionation. Under the described reaction conditions no amination was observed (Table 4.1, Entry 1). For etherification reactions it was recognized that the addition of potassium iodide enhanced the



reaction rate. The Finkelstein reaction produced the corresponding iodothiophene, which is more reactive than its bromo derivative. However, addition of potassium iodide (Table 4.1, Entry 2) to the reaction mixture didn't improve the conversion.

**Table 4.1** Formation of *N*-phenylthiophene-3-amine **13** from 3-bromothiophene and aniline.



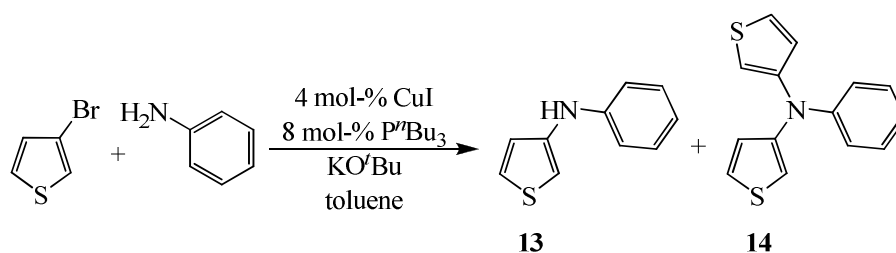
	Catalyst	Conditions	Yield [%] <sup>a</sup>
1	10 mol-% <b>L54b</b>	KO <sup>t</sup> Bu, toluene, 110 °C	-
2	10 mol-% <b>L54b</b>	KI, KO <sup>t</sup> Bu, toluene, 110 °C	1
3	5 mol-% CuI/ 2 eq. ethylene glycole	K <sub>3</sub> PO <sub>4</sub> , <i>i</i> -propanol, 80 °C	-
4	10 mol-% CuI/ 10 mol-% <b>L70</b>	K <sub>3</sub> PO <sub>4</sub> , dioxane, 110 °C	-
5	5 mol-% CuI/ 20 mol-% <b>L88</b>	K <sub>3</sub> PO <sub>4</sub> , DMF, 90 °C	-
6	4 mol-% CuI/ 8 mol-% P <sup>n</sup> Bu <sub>3</sub> ( <b>L86</b> )	KO <sup>t</sup> Bu, toluene, r.t.	9 <sup>b</sup>

<sup>a</sup>GC- yields, <sup>b</sup>*N*-phenyl-*N,N*-di(3-thienyl)-amine observed, at 100 °C no monosubstituted aniline formed.

Also several catalytic systems using copper(I) iodide as a stable inorganic copper(I) salt with different ligands are described. Using ethyleneglycole as a bidentate copper-ligand, as developed by Buchwald *et al.*,<sup>8</sup> no reaction was observed (Table 4.1, Entry 3). The chelating 1,2-diaminocyclohexane was used as ligand for the arylation of indole.<sup>9</sup> As shown in Entry 4 it could not favour the nucleophilic substitution of 3-bromothiophene. Also salicylic benzamide as ligand<sup>10</sup> was inefficient to couple aniline and 3-bromothiophene (Table 4.1, Entry 5).

A further copper catalyst investigated was copper(I) iodide with tributylphosphine as an electron-rich ligand, published by Chaudhari *et al.*<sup>11</sup> This system should favour the two-fold substitution at aniline to generate triarylamines. When 3-bromothiophene and aniline were mixed under these conditions, only a small amount of *N*-phenylthiophene-3-amine **13**

could be obtained (Table 4.1, Entry 6). First the reaction was performed at 100 °C. In GC the triarylamine (**14**) was detected (Scheme 4.6). The reaction was repeated at room temperature to favour the formation of **13**. Unfortunately, a mixture containing mainly starting materials, diarylamine and triarylamine was obtained. Also the use of less reactive 3-chlorothiophene gave only a slight conversion to di- and triarylamines. Because the process and product formation can not be controlled this catalyst was not applied to further couplings.

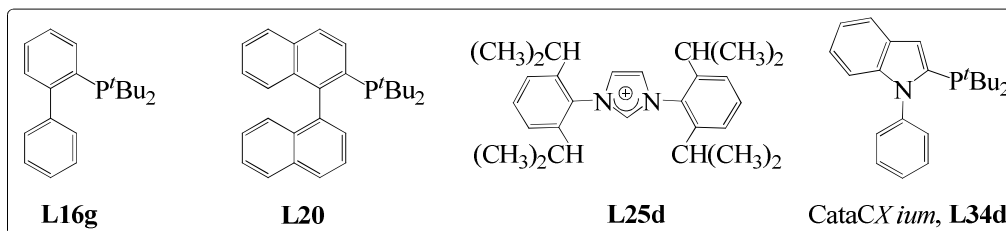
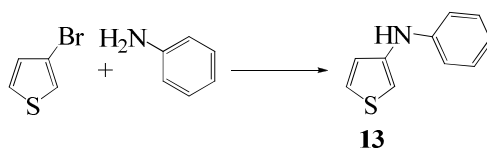


**Scheme 4.6** Reaction of 3-bromothiophene and aniline under Ullmann-type reaction conditions.

Obviously the Ullmann coupling is not suitable for the amination of electron-rich thiophenes. Therefore, palladium catalysts came into the focus of optimization. The applied catalysts and the corresponding results are displayed in the following table (Table 4.2).

Hartwig *et al.* described Pd<sub>2</sub>(dba)<sub>3</sub> with P<sup>*t*</sup>Bu<sub>3</sub> to give *N*-phenylthiophene-3-amine **13** in 88 % isolated yield.<sup>6</sup> The procedure was repeated several times under the published conditions with the more stable tetrafluoroborate salt of tri-*tert*-butylphosphine. Best care was taken to avoid moisture, water and air. Unfortunately, only a yield of 32 % after column chromatography was obtained (Table 4.2, Entry 1). **13** is sensitive to air and silica and some oxidized products were immobilized on column. By using inactivated basic alumina purification could be improved. In the reaction mixture, also *N*-phenyl-*N,N*-di(3-thienyl)-amine **14** and bithiophene were detected *via* GC-MS. Therefore, other catalytic systems were investigated, which should lead to the desired product.

Nolan *et al.* established *N*-heterocyclic carbenes as ligands for C-N cross-couplings of aryl chlorides to aromatic and aliphatic amines in good to excellent yields.<sup>12</sup> With *N,N'*-bis(2,6-diisopropylphenyl)imidazolium hydrochloride (**L25d**) as ligand no product was observed (Table 4.2, Entry 2).

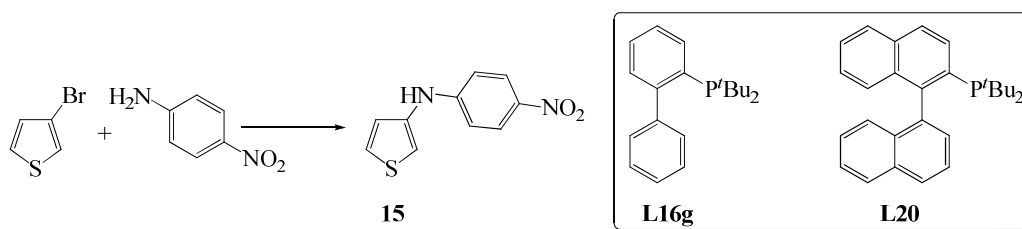
**Table 4.2** Palladium-catalyzed C-N cross-coupling of 3-bromothiophene and aniline.

	Palladium Source	Ligand	Conditions	Yield [%] <sup>a</sup>
1	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% H[P <sup><i>t</i></sup> Bu <sub>3</sub> ] <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	NaO <sup><i>t</i></sup> Bu, toluene, 100 °C	32
2	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	4 mol-% <b>L25d</b>	KO <sup><i>t</i></sup> Bu, dioxane, 100 °C	-
3	0.5 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% <b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , DME, 100 °C	29
4	0.5 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% <b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , diglyme, 150 °C	6
5	0.5 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% <b>L20</b>	K <sub>3</sub> PO <sub>4</sub> , DME, 100 °C	48
6	0.5 mol-% Pd(OAc) <sub>2</sub>	1 mol-% <b>L34d</b>	NaO <sup><i>t</i></sup> Bu, toluene, 110 °C	-

<sup>a</sup>isolated yields.

Other phosphine ligands in this series with different electronic effects were investigated. Buchwald described 1,1'-biphenyl-2-yl(di-*tert*-butyl)phosphine (**L16g**) and 1,1'-binaphthyl-2-yl(di-*tert*-butyl)phosphine (**L20**) as effective ligands in amination reactions.<sup>13</sup> 3-Bromothiophene and aniline could be coupled in 29 % and 48 %, respectively (Table 4.2, Entry 3 and 5). Higher temperatures led to more complex product mixtures (Table 4.2, Entry 4). Aniline is sensitive to oxidation, therefore, it obviously decomposes at a reaction temperature of 150 °C. The use of the less electron-rich phosphine CataCXium<sup>®</sup> (**L34d**) led to no conversion of the starting materials (Table 4.2, Entry 6).

Best results were obtained with electron-rich tri-*tert*-butylphosphine (**L22**), **L16g** and **L20**. As precursor Pd<sub>2</sub>(dba)<sub>3</sub> was used. These three catalysts were used for the cross-coupling with nitroanilines. In Table 4.3 the yields for the amination of 3-bromothiophene with *p*-nitroaniline are summarized.

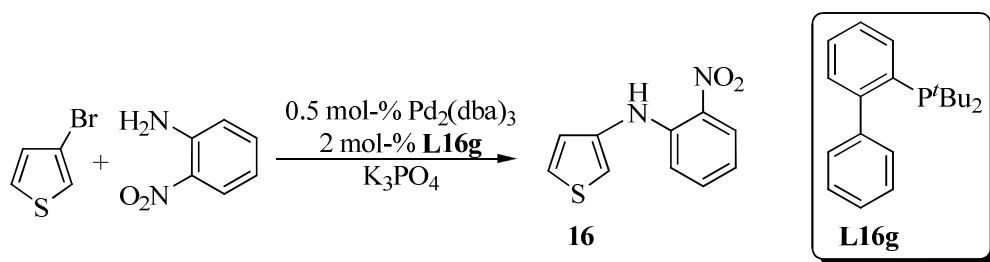
**Table 4.3** Formation of *N*-(4-nitrophenyl)thiophene-3-amine **15** from 3-bromothiophene and *p*-nitroaniline, Pd<sub>2</sub>(dba)<sub>3</sub> (0.5 mol-%) with ligand (2 mol-%) was used as catalyst.

	Ligand	Conditions	Yield [%] <sup>a</sup>
1	H[P'Bu <sub>3</sub> ]BF <sub>4</sub>	NaO <sup>t</sup> Bu, toluene, 100 °C	-
2	H[P'Bu <sub>3</sub> ]BF <sub>4</sub>	K <sub>3</sub> PO <sub>4</sub> , DME, 100 °C	-
3	<b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , DME, 100 °C	17
4	<b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , diglyme, 120 °C	60
5	<b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , diglyme, 150 °C	77
6	<b>L16g</b>	KI, K <sub>3</sub> PO <sub>4</sub> , diglyme, 150 °C	-
7	<b>L16g</b>	K <sub>3</sub> PO <sub>4</sub> , diglyme, 150 °C	- <sup>b</sup>
8	<b>L20</b>	K <sub>3</sub> PO <sub>4</sub> , diglyme, 150 °C	15

<sup>a</sup>isolated yield, <sup>b</sup>3-iodothiophene was used.

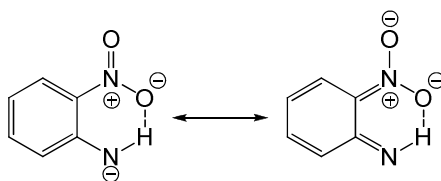
The best catalyst described for the coupling of aniline to 3-bromothiophene was Pd<sub>2</sub>(dba)<sub>3</sub> and H[P'Bu<sub>3</sub>]BF<sub>4</sub> (Table 4.3, Entry 1 and 2). A C-N cross-coupling of *p*-nitroaniline and 3-bromothiophene under these conditions could not be observed. With **L20** as ligand 15 % of the desired product was isolated (Table 4.3, Entry 8). When **L16g** was applied as less sterical demanding ligand even better results were achieved (Table 4.3, Entry 3-5). With higher temperatures the yield increased. For the use of 3-iodothiophene (Table 4.3, Entry 7) or the *in situ* generation by adding potassium iodide (Table 4.3, Entry 6) no product formation could be determined. After the reaction not the whole amount of 3-iodothiophene could be re-isolated. Obviously dehalogenation becomes much faster than amination.

3-Bromothiophene was coupled to *o*-nitroaniline with Pd<sub>2</sub>(dba)<sub>3</sub> and **L16g** as catalyst with potassium phosphate as base (Scheme 4.7).



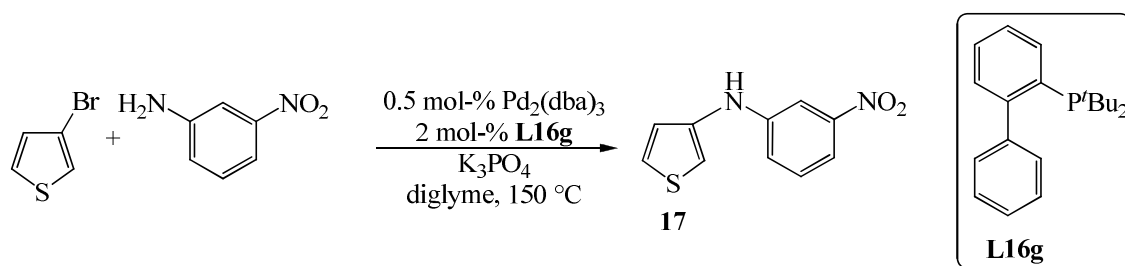
**Scheme 4.7** Formation of *N*-(2-nitrophenyl)thiophene-3-amine from 3-bromothiophene and *o*-nitroanilin.

Both in DME at 100 °C and, as well as in diglyme at 120 °C no product formation could be observed. Because the acidity of *o*-nitroaniline is the highest in the series of nitroanilines ( $pK_a$  -0.28 in water)<sup>14</sup>, the deprotonation is not problematic. The resulting amid is intramolecularly stabilized by the neighbouring nitro group (Chart 4.1). Therefore, the amid becomes less nucleophilic, which results in much less reactivity during the palladium-catalyzed amination process.



**Chart 4.1** Stabilization of the anion of *o*-nitroaniline.

However, the formation of *N*-(3-nitrophenyl)thiophene-3-amine **17** from 3-bromothiophene and *m*-nitroaniline was catalyzed by 0.5 mol-%  $\text{Pd}_2(\text{dba})_3$ , 2 mol-% **L16g**, potassium phosphate in diglyme (Scheme 4.8). After stirring at 150 °C the product was obtained in circa 30 % yield.



**Scheme 4.8** Formation of *N*-(3-nitrophenyl)thiophene-3-amine **17** from 3-bromothiophene and *m*-nitroaniline.

The product could not be obtained purely, because the diglyme could not be removed completely. Even after several washings, columns and precipitation experiments some amount of the solvent contaminated the product.

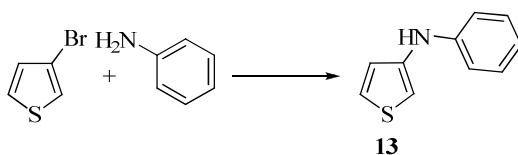
The nitro group has both, a negative inductive and a mesomeric effect. In *ortho*- and *para*-position the acidity of aniline is enhanced. If the substituent is located in *meta*-position to the amine, just the negative inductive effect needs to be taken into account, because low mesomeric stabilization can occur. Therefore, the  $pK_a$  of 3-nitroaniline is highest in the series of nitroanilines (2.45 in water).<sup>14</sup> Because the stability towards oxidation and polymerization is higher than in aniline and of cause the higher acidity ( $pK_a$  for aniline is 4.62), the yield is even higher than for the coupling of 3-bromothiophene to aniline under the same reaction conditions (Table 4.2, Entry 4, 6 %).

The low yield for the conversion of 3-bromothiophene to *N*-(3-nitrophenyl)thiophene-3-amine **17** in comparison to the formation of *N*-(4-nitrophenyl)thiophene-3-amine **15** (Table 4.3, Entry 5, 77 %) is a consequence of the lower nucleophilicity of 3-nitroaniline. The  $pK_a$  of 4-nitroaniline (0.98) is much lower than for the *meta*-substituted derivative, because herein also the negative mesomeric effect of the nitro group plays a role.

#### 4.2.2 Synthesis under Microwave Irradiation

To examine the effect of microwave irradiation to the amination of thiophenes some examples were investigated. Two different microwave systems were tested. The CEM Discover apparatus concentrates the microwave irradiation in a small chamber. The producer talks about focused, monomodular microwave irradiation, because only one wavelength of microwave (2450 MHz) is used. The instrument of EMLS has a much bigger chamber and therefore, a much bigger distribution of the energy. In the last case additives were needed to heat up less dipolar solvents like toluene. So-called Weflons were put into the reaction vessel, which contain carbon powder. This indicates a more indirect heating of the components.

For 3-bromothiophene and aniline C-N cross-coupling was investigated with the conditions described in Table 4.4.

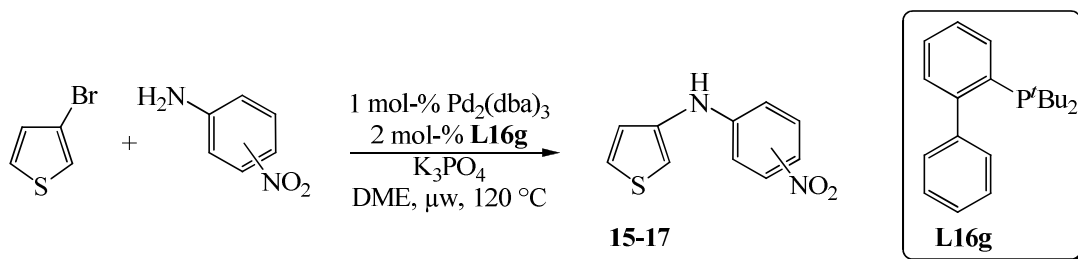
**Table 4.4** Formation of *N*-phenylthiophene-3-amine **13** from 3-bromothiophene and aniline.

	Catalyst	Ligand	Conditions	Yield [%] <sup>a</sup>
1	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% H[P <sup>t</sup> Bu <sub>3</sub> ]BF <sub>4</sub>	NaO <sup>t</sup> Bu, toluene, 10', 150 °C	35 (83) <sup>b</sup>
2	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% H[P <sup>t</sup> Bu <sub>3</sub> ]BF <sub>4</sub>	NaO <sup>t</sup> Bu, DMF, 10', 125 °C	– <sup>b,c</sup>
3	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% H[P <sup>t</sup> Bu <sub>3</sub> ]BF <sub>4</sub>	NaO <sup>t</sup> Bu, toluene, 15', 130 °C	6 <sup>d</sup>
4	1 mol-% Pd <sub>2</sub> (dba) <sub>3</sub>	2 mol-% H[P <sup>t</sup> Bu <sub>3</sub> ]BF <sub>4</sub>	NaO <sup>t</sup> Bu, toluene, 12', 150 °C	27 <sup>d</sup>
5	2 mol-% CuI	4 mol-% P <sup>n</sup> Bu <sub>3</sub>	KO <sup>t</sup> Bu, toluene, 10', 150 °C	– <sup>d</sup>

<sup>a</sup>isolated yields (GC), <sup>b</sup>CEM Discover, <sup>c</sup>PowerMax mode, <sup>d</sup>EMLS instrument.

Comparing the two apparatus no big difference can be determined (Table 4.4, Entry 1 and 4). Microwave irradiation didn't initiate the copper-catalyzed amination (Table 4.4, Entry 5). The yields obtained are comparable to those under conventional heating method. However, the reaction time was much shorter. While in the oil bath several hours were requested for the amination, only 10 to 15 minutes were necessary under microwave conditions.

Also nitro-substituted anilines (**15-17**) were converted to corresponding diarylamines. As catalyst Pd<sub>2</sub>(dba)<sub>3</sub> (1 mol-%) and **L16g** (2 mol-%) were used with potassium phosphate in DME.

**Scheme 4.9** Formation of *N*-(nitrophenyl)thiophene-3-amines **15-17** from 3-bromothiophene and nitroaniline.

After 20 minutes in the EMLS apparatus *N*-(4-nitrophenyl)thiophene-3-amine **15** could be obtained in 36 % yield. Under the same reaction conditions with conventional heating the amination proceeded with a yield of 60 %. For the *meta*-substituted nitroaniline the C-N cross-coupling resulted in low yield. Also here it was not possible to obtain a pure product. Purification by washing and chromatography was unsuccessful. The best result was observed for *o*-nitroaniline. While under conventional conditions no product was isolated, after microwave irradiation *N*-(2-nitrophenyl)thiophene-3-amine **16** was obtained in 28 %.

The acceleration of chemical reactions through microwave irradiation is based upon efficient energy transfer to the reaction mixture through “dielectric heating with microwaves”.<sup>15</sup> With increasing dipole moment of substances (solvents, reagents) the ability to convert microwave irradiation to thermal energy increases. In literature, a so-called “hot spot” is discussed. The strong microwave absorbing heterogeneous catalysts are selectively heated up, even in less polar solvents. This phenomenon can not be reproduced under conventional heating. On the other hand, the increased kinetic energy in ionic compounds, e.g., 2-(nitrophenyl)-amide, destabilizes hydrogen bonding, which was discussed before (Chart 4.1). Therefore, the nucleophilicity increases due to dielectric microwave heating and C-N cross-coupling can be observed.

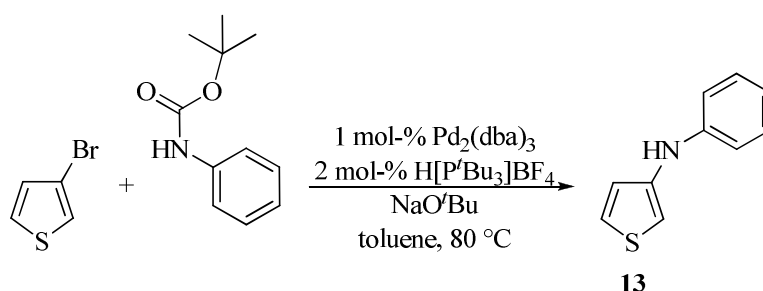
Even under microwave conditions the catalytic system needs to be optimized for each coupling. A so-called “microwave effect” can not be observed for all conversions. Therefore, not every reaction led into a decrease of reaction time or increase of yield.

## 4.3 Conversion of 3-Halogenothiophene with Secondary Amines

### 4.3.1 Synthesis under “Conventional” Heating

Due to the inherent stability problems with *N*-phenylthiophene-3-amine (**13**) *boc*-protected aniline (*tert*-butylcarbamate) was used for the coupling to 3-bromothiophene. With Pd<sub>2</sub>(dba)<sub>3</sub> (1 mol-%), H[P<sup>*t*</sup>Bu<sub>3</sub>]BF<sub>4</sub> (2 mol-%), sodium *tert*-butanolate in toluene the reactants were heated to 80 °C (Scheme 4.10).



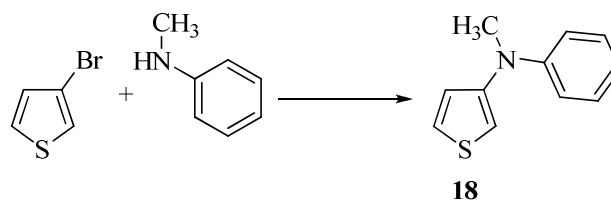


**Scheme 4.10** Formation of *N*-phenylthiophene-3-amine **13** from 3-bromothiophene and *tert*-butylphenylcarbamate.

In the reaction mixture starting materials, aniline and *N*-phenylthiophene-3-amine **13** were detected. The *boc*-protecting group does not survive the Buchwald-Hartwig conditions. The conversion was remarkably less than for the unprotected aniline. Therefore, no more investigations were undertaken.

For the synthesis of secondary amines, by amination of 3-bromothiophene, two catalytic systems were found to give good results. The C-N cross-coupling of 3-bromothiophene with aniline gave good results using Pd<sub>2</sub>(dba)<sub>3</sub> (1 mol-%), H[P<sup>*t*</sup>Bu<sub>3</sub>]<sub>3</sub>BF<sub>4</sub> (2 mol-%), sodium *tert*-butanolate in toluene at 100 °C (Table 4.2, Entry 1). On the other hand the nitro-substituted anilines could not be converted by this catalyst. Therefore, Pd<sub>2</sub>(dba)<sub>3</sub> (1 mol-%), **L16g** (2 mol-%), potassium phosphate in diglyme at 150 °C was found to be suitable (Table 4.3, Entry 5).

Hartwig described for the conversion of *N*-methylaniline with 3-bromothiophene a yield of 93 % of *N*-methyl-*N*-phenylthiophene-3-amine **18** (Scheme 4.11).<sup>6</sup>

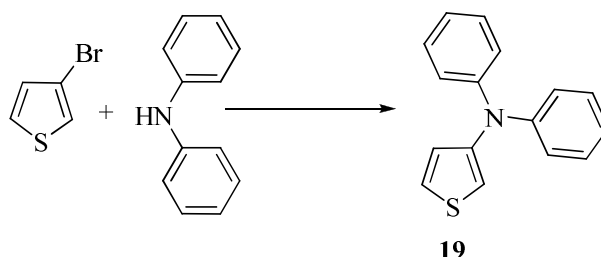


**Scheme 4.11** Formation of *N*-methyl-*N*-phenylthiophene-3-amine (**18**) from 3-bromothiophene and *N*-methylaniline.

To test the generality of the optimized catalytic system (Table 4.2, Entry 1) *N*-methylaniline and 3-bromothiophene were coupled under the same reaction conditions.

With  $\text{Pd}_2(\text{dba})_3/\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  as catalyst **18** was obtained in 77 %. When the reaction was performed in diglyme with  $\text{Pd}_2(\text{dba})_3$  (0.5 mol-%), **L16g** (2 mol-%) and potassium phosphate at 150 °C no product was obtained. Also copper catalysis (2 mol-% CuI, 4 mol-%  $\text{P}^n\text{Bu}_3$ ,  $\text{KO}^t\text{Bu}$ , toluene) didn't give the desired product, neither at room temperature nor at 70 °C.

Also the amination of 3-bromothiophene with *N,N*-diphenylamine was repeated with the two standard conditions carried out (Scheme 4.12).



**Scheme 4.12** Formation of *N,N*-diphenylthiophene-3-amine **19** from 3-bromothiophene and *N,N*-diphenylamine.

When  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  was applied as ligand at 100 °C *N,N*-diphenylthiophene-3-amine **19** was obtained in 67 % yield. Under the same conditions Hartwig published a yield of 97 %.<sup>6</sup> Using **L16g** as ligand at 150 °C a quantitative conversion was observed. However, the product was contaminated with diglyme, even after several purification methods.

### 4.3.2 Synthesis under Microwave Irradiation

Also the formation of tertiary amines was investigated using microwave irradiation. 3-Bromothiophene was coupled to *N*-methylanilin and *N,N*-diphenylamine using  $\text{Pd}_2(\text{dba})_3$  (1 mol-%) and  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  (2 mol-%) as catalyst. After 12 minutes at 150 °C in the EMLS apparatus *N*-methyl-*N*-phenylthiophene-3-amine **18** (Scheme 4.11) was obtained in 72 %, and *N,N*-diphenylthiophene-3-amine **19** (Scheme 4.12) in 62 % yield.

The synthesis of **19** was investigated using different conditions with CEM Discover microwave. The amination was performed under the same reaction conditions than in the EMLS apparatus. The product was obtained in 96 %. From 3-chlorothiophene and an extended reaction time of 30 minutes the product was obtained in 62 %. With DMF as solvent no product formation was observed. Coupling 3-bromothiophene to *N,N*-

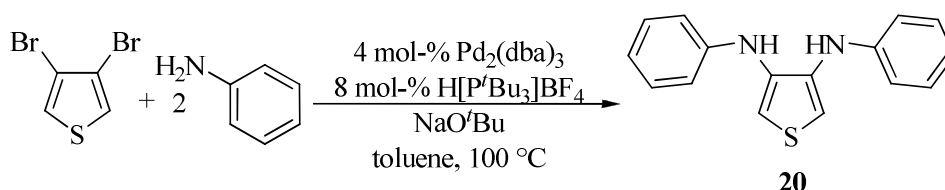
diphenylamine with sodium *tert*-butanolate in toluene without any catalyst no product could be detected after irradiation for 10 minutes at 150 °C.

The yield for **18** is comparable to which observed under “conventional” conditions (72 and 77 % respectively). **19** was obtained in 62 % in EMLS apparatus, and 67 % under conventional heating. Using microwave irradiation the temperature was significantly higher (150 °C instead of 100 °C in oil bath). The yield for **19** was remarkably higher when the reaction was performed in CEM Discover. Obviously the microwave irradiation was more effective in the smaller reaction chamber.

## 4.4 Conversion of 3,4-Dibromothiophene with Amines

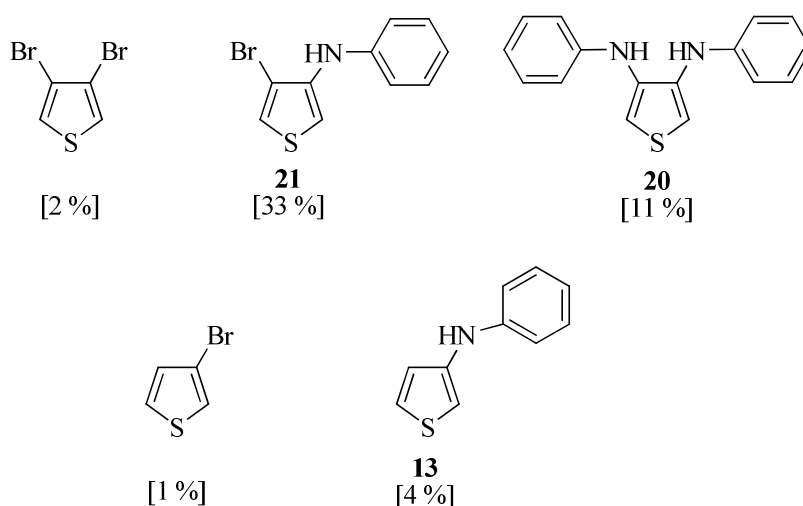
### 4.4.1 Synthesis of Secondary Amines

Analogously to the formation of *N*-phenylthiophene-3-amine 3,4-dibromothiophene should be substituted twice with aniline. The aim is the synthesis of the *N*-analogous benzoEDOT derivative. Mixing 3,4-dibromothiophene with two equivalents of aniline, 4 mol-% Pd<sub>2</sub>(dba)<sub>3</sub>, 8 mol-% H[P<sup>*t*</sup>Bu<sub>3</sub>]BF<sub>4</sub> with sodium *tert*-butanolate in toluene at 100 °C yielded a product mixture (Scheme 4.13).



**Scheme 4.13** Formation of *N*<sup>3</sup>,*N*<sup>4</sup>-diphenylthiophene-3,4-diamine **20** from 3,4-dibromothiophene and aniline.

Both disubstituted and monosubstituted products could be obtained. Unfortunately, dehalogenation occurred during the reaction as analyzed by GC-MS.



**Scheme 4.14** Product mixture analyzed by GC-MS after the reaction of 3,4-dibromothiophene and aniline.

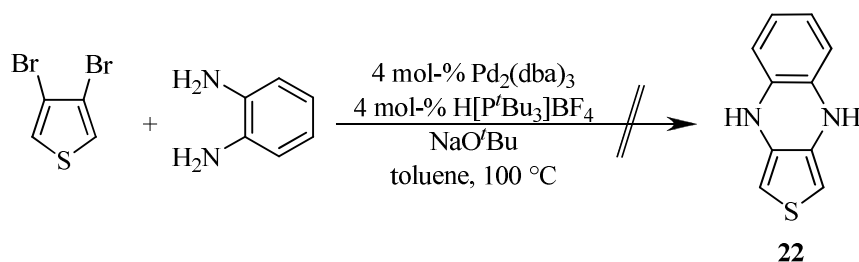
After column chromatography 4-bromo-*N*-phenylthiophene-3-amine **21** was obtained in 33 % yield. Due to very similar chemical properties in comparison to the intermediate **21** the desired product, *N*<sup>3</sup>,*N*<sup>4</sup>-diphenylthiophene-3,4-diamine **20**, could not be obtained analytically pure. The intermediate, monocoupled product **21** was converted to **20** in a second reaction under the same conditions. The product was isolated in 11 % yield.

The conversion was repeated using microwave irradiation (CEM Discovery). After 15 minutes at 150 °C the desired product was isolated in 27 %. Nearly no intermediate could be detected. Under microwave irradiation a significantly higher conversion was achieved.

Watanabe *et al.* converted 3,4-dibromothiophene with *N,N*-diphenylamine with a palladium catalyst. The monocoupled product was obtained in 12 %, no disubstitution was observed.<sup>3</sup> *o*-Dibromobenzene gave no conversion under identical conditions. The difference in the reactivity of 3,4-dibromothiophene and *o*-dibromobenzene may be ascribed to the difference of the angle of C-C-Pd bond of the resulting aryl-palladium complex after oxidative addition, in which the intramolecular coordination of a vicinal bromine to the palladium complex obtained from *o*-dibromobenzene is more likely to prevent *N,N*-diphenylamine from ligating to the palladium complex. However, aniline is less sterically demanding and therefore the higher yield for the monosubstituted intermediate **20** and the product **21** could be obtained.

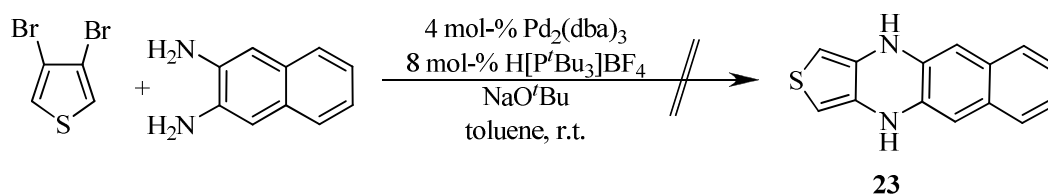
Also nitrogen analogues of benzoEDOT should be prepared starting from 3,4-dibromothiophene and 1,2-phenyldiamine (Scheme 4.15). Here also the standard proce-

dure was used (2 mol-%  $\text{Pd}_2(\text{dba})_3$ , 2 mol-%  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$ ,  $\text{NaO}^t\text{Bu}$ , toluene, 100 °C) to synthesize 4,9-dihydrothieno[3,4-*b*]quinoxaline **22**. Even after seven days no product formation was observed. The diamine is sensitive to oxidation. Because the amine could not be re-isolated it can be concluded that the decomposition of 1,2-phenylenediamine is the crucial problem in this attempted coupling.



**Scheme 4.15** Formation of 4,9-dihydrothienyl[3,4-*b*]quinoxaline **22** from 3,4-dibromothiophene and 1,2-phenylenediamine.

Also the C-N cross-coupling of 3,4-dibromothiophene with the more stable 2,3-naphthalenediamine was performed under standardized reaction conditions (Scheme 4.16). No product was obtained. The low solubility of the diamine in toluene might be a reason that the starting materials were re-isolated.

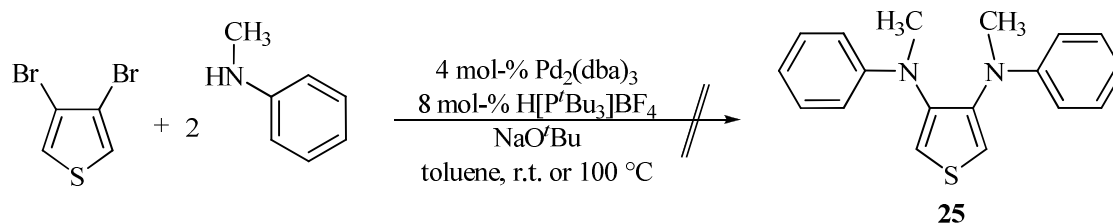


**Scheme 4.16** Formation of 4,11-dihydrobenzo[*g*]thieno[3,4-*b*]quinoxaline **23** from 3,4-dibromothiophene and 2,3-naphthalenediamine.

#### 4.4.2 Synthesis of Tertiary Amines

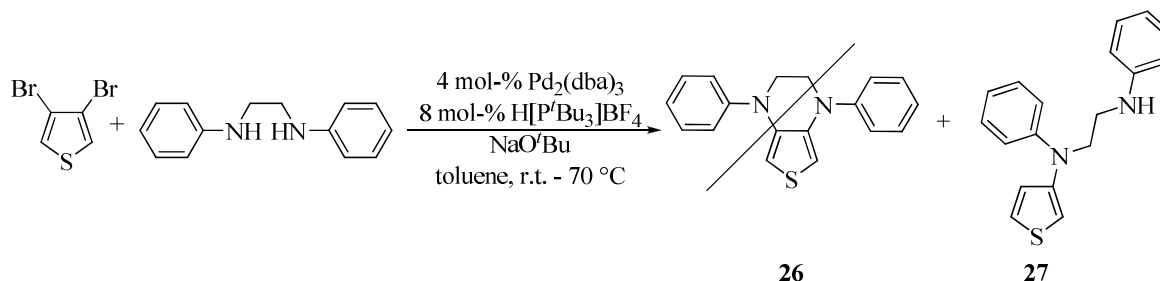
Under the standardized reaction conditions with  $\text{Pd}_2(\text{dba})_3$  as catalyst precursor and  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  as ligand, 3,4-dibromothiophene was coupled to *N*-methylaniline (Scheme 4.17). At room temperature only a slight amount of 4-bromo-*N*-methyl-*N*-phenylthiophene-3-amine **24** was formed by monocoupling reaction. No product was identified at all. After increasing the temperature to 100 °C both, intermediate and product, could

not be obtained. Dehalogenation was observed in GC-MS analyses of the crude product mixture. This side reaction is well known in Buchwald-Hartwig aminations.



**Scheme 4.17** Conversion of 3,4-dibromothiophene with *N*-methylaniline under Buchwald-Hartwig conditions.

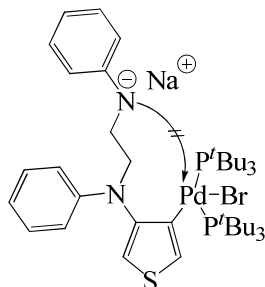
To synthesize a *N*-analogous EDOT derivative 3,4-dibromothiophene should be coupled to Wanzlick's reagent (*N*<sup>1</sup>,*N*<sup>2</sup>-diphenylethane-1,2-diamine) under standardized reaction conditions (Scheme 4.18). Instead of desired 1,4-diphenyl-1,2,3,4-tetrahydrothieno[3,4-*b*]pyrazine **26** a monosubstituted open-chain molecule **27** was obtained in 5 %, as confirmed by NMR and mass analyses.



**Scheme 4.18** Synthesis of 1,4-diphenyl-1,2,3,4-tetrahydrothieno[3,4-*b*]pyrazine **26**.

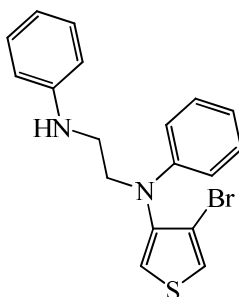
Under microwave irradiation (15 minutes at 150 °C) again no product could be determined. *N*<sup>1</sup>,*N*<sup>2</sup>-diphenyl-*N*<sup>1</sup>-(thiophen-3-yl)ethane-1,2-diamine **27** was purely obtained in 10 %. Obviously, dehalogenation during the catalytic cycle becomes much faster than the coupling reaction. After first bromine was substituted by amine no more C-N cross-coupling occurred. In the proposed intermediate palladium complex during the catalytic cycle (Chart 4.2) a definite cone angle must be reached, when nitrogen attacks the palladium centre. If the exchange of bromine with amine at palladium is too slow side reactions

become more effective. This might be a reason for the observed reduction of the thiophene ring.



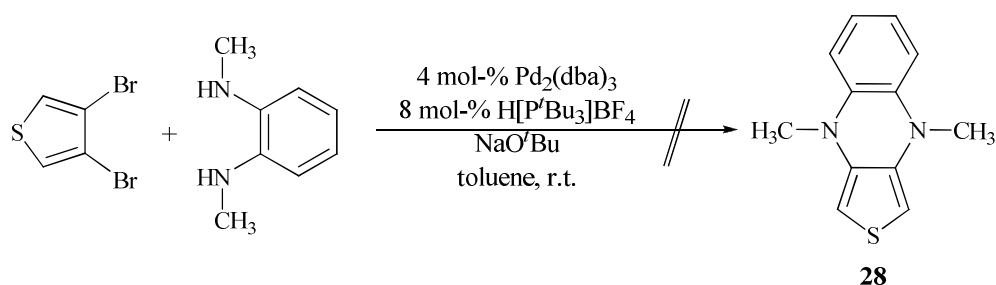
**Chart 4.2** Proposed intermediate palladium complex build during the catalytic cycle.

On the other hand, dehalogenation can take place in an earlier stage of the reaction. It is conceivable that after the reduction of 3,4-dibromothiophene to 3-bromothiophene the successful amination with Wanzlick's reagent leads to the isolated open-chain product. An indication for this reaction pathway is the absence of any brominated open-chain intermediate (Chart 4.3).



**Chart 4.3**  $N^1$ -(4-Bromothiophen-3-yl)- $N^1,N^2$ -diphenylethane-1,2-diamine.

In the reaction of *o*-diaminobenzene with 3,4-dibromothiophene a dimerization of the diamine was observed, but no C-N cross-coupling to the thiophene ring (Scheme 4.15). Coupling of 3-bromothiophene to secondary anilines, such as *N*-methylaniline, gave higher yields and more stable products towards oxidation (4.3.1) than primary anilines. Therefore,  $N^1,N^2$ -dimethylbenzene-1,2-diamine was applied to the conversion to the *N*-analogous benzoEDOT derivative **28** (Scheme 4.19). After several days some dehalogenation was observed, but no product could be determined in the reaction mixture.



**Scheme 4.19** Synthesis of 4,9-dimethyl-4,9-dihydrothieno[3,4-*b*]quinoxaline **28**.

$N^1, N^2$ -Dimethylbenzene-1,2-diamine is much more sensitive to oxidation than 1,2-phenylenediamine. Additionally, it has to be taken into account that diamines serve as efficient chelating ligands for palladium. Therefore, the catalyst might be poisoned and is no more effective for C-N cross-coupling.

## 4.5 Conclusions

Several scientists included halogenothiophenes in the scope and limitation experiments to proof their catalysts for palladium-catalyzed amination reactions.<sup>1, 3-6</sup> During this study the conversions could not be enhanced. As always mentioned for Buchwald-Hartwig reactions it is impossible to generate a general catalyst. Each coupling requires its optimized reaction conditions.

For the first time, 3-bromothiophene was coupled to an electron-deficient aniline using a palladium catalyst. Nitroanilines gave, depending on basicity and sterical hinderance, low to moderate yields when reacted with 3-bromothiophene. However, harsh reaction conditions were requested. The combination of  $\text{Pd}_2(\text{dba})_3$ , **L20** in diglyme at 150 °C gave best results.

Standardized reaction conditions, which led to good results for the conversion of 3-halogenothiophenes with anilines, were employed for the C-N cross-coupling of 3,4-dibromothiophene with both anilines and diamines. With aniline only a low yield of 11 % for **20** was observed for the disubstituted product (Scheme 4.13). When Wanzlick's reagent was used for the cyclization via a twofold amination reaction just the open-chain dehalogenated product **27** could be isolated (Scheme 4.18). Also the conversion with several primary and secondary *ortho*-diaminobenzene derivatives was unsuccessful (Scheme 4.15, Scheme 4.16, Scheme 4.19). No amination was observed at all, neither monocoupling, nor

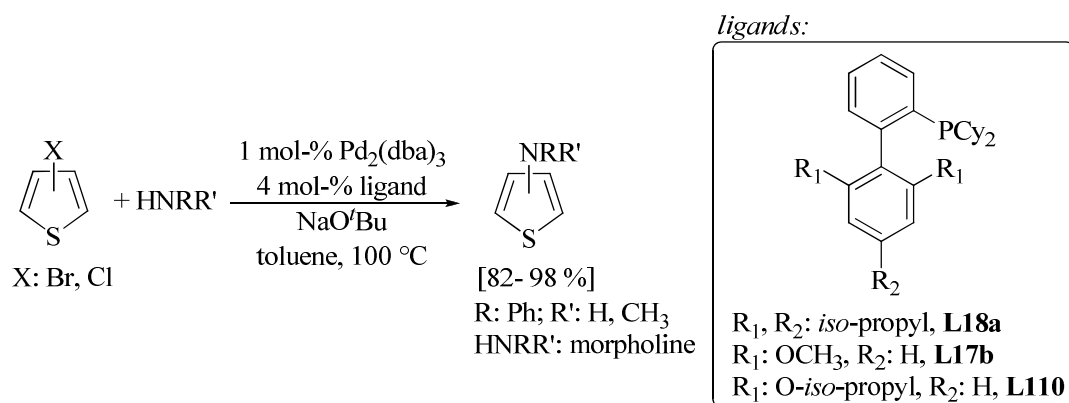


cyclization. It could be mentioned that the diamines serve as bidentate ligand to the palladium and poison the catalyst.

Unfortunately, no new method could be developed for C-N cross-coupling at halogenothiophenes. Copper-catalysis gave no conversion of the aromatic amines with 3-bromothiophene.

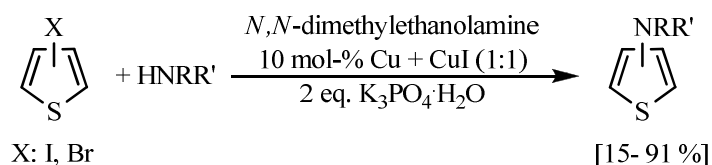
It was shown that microwave irradiation, as a rather new heating method, shortened the reaction times dramatically from hours or days to a few minutes. However, no general improvement of yields was observed compared to “conventional” heating in an oil bath. Therefore, the microwave should be seen as an alternative to obtain thiophene amines in shorter reaction times.

In parallel to this research, Buchwald established a new ligand for the conversion of chlorothiophenes with aromatic amines under mild reaction condition in good to excellent yields (Scheme 4.20).<sup>16</sup>



**Scheme 4.20** Conversion of bromo- and chlorothiophenes with amines *via* Buchwald-Hartwig protocol.

Twieg *et al.* published in 2005 the amination of iodo- and bromothiophenes with aliphatic amines using copper metal as catalyst in *N,N*-dimethylethanolamine (Scheme 4.21).<sup>17</sup> Aromatic amines gave only low yields.



**Scheme 4.21** Conversion of halogenothiophenes with aliphatic amines under Ullmann-type conditions.

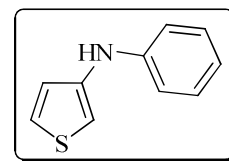
## 4.6 Experimental Part

*Thin layer chromatography* (TLC) was carried out on Silica Gel 60 F<sub>254</sub> aluminium plates (Merck). Developed plates were dried and examined under a UV lamp. *Preparative column chromatography* was carried out on glass columns of different diameters packed with silica gel Merck 60 (40-63  $\mu\text{m}$ ). *Gas chromatography* (GC) was carried out using a Varian CP-3800 gas chromatograph. Helium 5.0 was used as carrying gas, signals were examined by a flame-ionization detector (FID). *Gas chromatography-Mass spectrometry* (GC-MS) measurements were executed with a Varian 3800. Helium 5.0 was used as carrying gas, Mass spectra were recorded on a Varian Saturn 2000. Ions were generated by electron impact (EI). *Melting points* were determined in a Büchi B-545 apparatus and are uncorrected. *NMR spectra* were recorded in  $\text{CDCl}_3$  on a Bruker AMX 400 at 400 MHz ( $^1\text{H}$  nuclei) and 100 MHz ( $^{13}\text{C}$  nuclei), respectively. Chemical shifts are denoted in  $\delta$  unit (ppm), and are referenced to the solvent signal (7.26 ppm for  $\text{CDCl}_3$ ). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). *Mass spectra* were measured at Finnigan MAT, SSQ 7000 via CI. *Elemental analysis* for C, H and N were determined at Elementar Vario EL and for S at Carlo Erba 1104. *High resolution mass* was measured at a microTOF-Q 43 with electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI).

All reactions were carried out under an inert atmosphere of argon. 3,4-Dibromothiophene was prepared according to literature procedures.<sup>18</sup> The following reagents and solvents were purified and dried by standardized procedures: 3-Bromothiophene (VWR), aniline (VWR), toluene (VWR). Nitroanilines (VWR), Wanzlick's reagent ( $N^1, N^2$ -diphenylethane-1,2-diamine, ABCR), tribasic potassiumphosphate (Riedel de Hën), sodium *tert*-butanolate (VWR),  $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$  (Sigma Aldrich),  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  (Acros), 1,1'-biphenyl-2-yl(di-*tert*-butyl)phosphine (**L16g**, Acros), 1,1'-binaphthalen-2-yl(di-*tert*-butyl)phosphine (**L20**, Acros), dichloromethane (VWR), diethyl ether (VWR), diglyme (VWR), 1,2-dimethoxyethane (DME, VWR), ethyl acetate (VWR), *n*-hexane (VWR), petrol ether (VWR), sodium sulphate (VWR), celite (454, VWR) were used as received.

**N-Phenylthiophene-3-amine (13)****Procedure A**

Tribasic potassiumphosphate (1.86g, 7 mmol) was flame dried in vacuum before  $\text{Pd}_2(\text{dba})_3$  (25.9 mg, 25  $\mu\text{mol}$ ) and 1,1'-binaphthalen-2-yl(di-*tert*-butyl)phosphine (**L20**, 62.3 mg, 100  $\mu\text{mol}$ ) were added and dissolved in DME (20 mL). After the addition of 3-bromothiophene (0.46 mL, 5 mmol) and aniline (0.55 mL, 6 mmol) the violet suspension was stirred for three days at 100 °C. The cooled brownish mixture was treated with diethyl ether (50 mL) and filtered through a plug of celite. The resulting solution was concentrated in vacuum, poured on neutral and deactivated alumina and eluted with 5% diethyl ether in *n*-hexane. After column chromatography the desired product was obtained as a brownish solid in 48 % (2.4 mmol, 420 mg). The analytical data correspond to literature.

**Procedure B**

Sodium *tert*-butanolate (0.27 g, 2.8 mmol) was dissolved in toluene (5 mL) under argon. Aniline (0.23 mL, 2.5 mmol) and 3-bromothiophene (0.23 mL, 2.5 mmol) were added. The catalyst was preformed in a second flask by mixing  $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$  (25.9 mg, 25  $\mu\text{mol}$ ) and  $\text{H}[\text{P}^t\text{Bu}_3]\text{BF}_4$  (14.5 mg, 50  $\mu\text{mol}$ ) in toluene (2 mL) under argon. After the addition of the catalyst solution to the substrates via canula the red suspension was stirred for ten minutes at 150 °C (230 W). The resulting brown suspension was diluted with dichloromethane (50 mL) and filtered through a plug of celite. The crude product contained 83 % of product as examined by gas chromatography. After column chromatography as described in procedure A **13** was obtained in 35 % yield (0.9 mmol, 153 mg) with a GC-purity of 98 %.

**mp** 40.4- 41.9 °C (lit. 43- 44 °C)<sup>16</sup>;

**<sup>1</sup>H-NMR:** (400 MHz,  $\text{CDCl}_3$ ) 5.51 (1H, s, br), 6.75 (1H, dd, *J* 1.3 and 3.0), 6.87 (1H, t, *J* 7.3), 6.92 (1H, dd, *J* 1.3 and 5.1), 6.98 (2H, d, *J* 7.7), 7.23- 2.27 (3H, m);

**<sup>13</sup>C-NMR:** (100 MHz,  $\text{CDCl}_3$ ) 106.5, 115.6, 119.9, 122.9, 125.1, 129.3, 141.5, 144.6.

**N-(Nitrophenyl)thiophene-3-amine****Procedure A**

Tribasic potassiumphosphate (1.86 g, 7 mmol) was flame dried in vacuum in a Schlenk tube. Under argon  $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$  (25.9 mg, 25  $\mu\text{mol}$ ), 1,1'-biphenyl-2-yl(di-*tert*-butyl)phosphine (**L16g**, 29.8 mg, 100  $\mu\text{mol}$ ), nitroaniline (0.83 g, 6 mmol) and diglyme

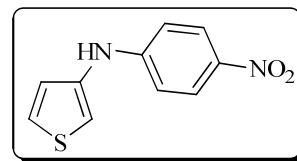
(20 mL) were added. After the addition of 3-bromothiophene (0.47 mL, 5 mmol) the red suspension was stirred for two days at 150 °C. The cooled suspension was treated with diethyl ether (50 mL) and filtered over basic alumina. The concentrated crude product was separated on neutral, deactivated alumina with petrol ether/ethyl acetate (3:2).

### Procedure B

In DME (10 mL) tribasic potassium phosphate (0.96 g, 3.6 mmol),  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (31.0 mg, 30  $\mu\text{mol}$ ), 1,1'-biphenyl-2-yl(di-*tert*-butyl)phosphine (**L16g**, 17.9 mg, 60  $\mu\text{mol}$ ) and nitroaniline (0.41 g, 3 mmol) were dissolved. After 3-bromothiophene (0.28 mL, 3 mmol) was added the red suspension was stirred at 120 °C for 20 minutes in the microwave in a sealed tube. The cooled mixture was poured into diethyl ether (20 mL) and filtered through a plug of basic alumina. After reducing the volume at rotary evaporator the crude product was purified on neutral, deactivated alumina with petrol ether/ ethyl acetate (3:2) as eluent.

### *N*-(4-Nitrophenyl)thiophene-3-amine (15)

According to procedure A with *p*-nitroaniline the pure product was obtained in 847 mg (3.9 mmol, 77 %) yield. Microwave irradiation resulted in only 385 mg (1.1 mmol, 35 %) of the orange solid.



**mp** 121.2- 122.8 °C;

**Elemental analysis:**  $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}$  requires C, 54.53, H, 3.66, N, 12.72 %; found: C, 54.39, H, 3.82, N, 12.74 %;

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 6.22 (1H, s, br), 6.86 (2H, m), 7.00 (2H, m), 7.36 (1H, dd, *J* 3.2 and 5.1), 8.12 (2H, m);

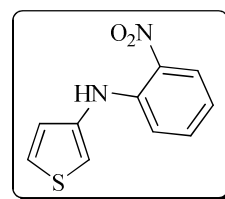
**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) 113.0, 113.5, 123.8, 126.2, 126.3, 138.0, 150.8;

**MS (CI):**  $m/z$  ( $M+H$ ) = 221.

### *N*-(2-Nitrophenyl)thiophene-3-amine (16)

Under “conventional” heating following procedure A no product could be obtained. According to procedure B **16** was obtained as a red oil in 185 mg (0.8 mmol, 28 %).

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 6.76 (1H, ddd, *J* 1.3, 7.0 and 8.4), 7.03



(1H, dd, *J* 1.4 and 5.1), 7.09 (1H, ddd, *J* 0.6, 1.3 and 3.1), 7.17 (1H, dd, *J* 1.2 and 8.7), 7.38 (2H, m), 8.19 (1H, dd, *J* 1.5 and 8.6), 9.40 (1H, s, br);

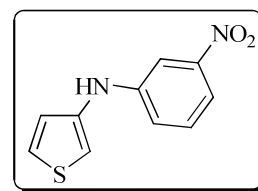
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 115.9, 116.2, 117.3, 124.9, 126.1, 126.5, 132.7, 135.9, 137.1, 143.6;

**MS (CI):** *m/z* (*M*+H) = 221;

**HRMS (ESI):** *m/z* (*M*+Na) = 243.0185 (C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>NaO<sub>2</sub>S requires 243.0199).

### ***N*-(3-Nitrophenyl)thiophene-3-amine (17)**

With both techniques no pure product was obtained. It was contaminated with solvent. The yield was estimated from NMR to be around 30 % with procedure A, and only 10 % with procedure B.



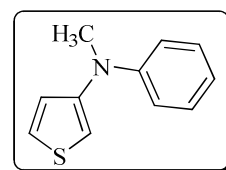
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 5.97 (1H, s, br), 6.90 (1H, dd, *J* 1.5 and 3.1), 6.95 (1H, dd, *J* 1.5 and 5.1), 7.17 (1H, ddd, *J* 0.9, 2.4 and 8.2), 7.32- 7.36 (2H, m), 7.64 (1H, ddd, *J* 0.9, 2.2 and 8.1), 7.74 (1H, t, *J* 2.3);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 108.8, 110.6, 114.0, 120.4, 123.2, 126.0, 129.9, 139.4, 146.2, 149.4.

**Elemental analysis** and **MS** could not be ascertained due to high impurity of the substance.

### ***N*-Methyl-*N*-phenylthiophene-3-amine (18)<sup>6</sup>**

The reaction was performed similar to literature. Instead of the instable tri-*tert*-butylphosphine the tetrafluoroborate was used as ligand at 100 °C. The analytical pure product was obtained as colourless oil in 364 mg (1.9 mmol, 77 %, lit. 93 %).



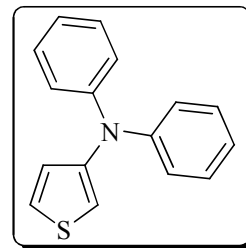
With microwave assisted heating (12 minutes, 150 °C) **18** was obtained in 340 mg (1.8 mmol, 72 %) from 3-bromothiophene, in 294 mg (1.6 mmol, 62 %) from 3-chlorothiophene.

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 3.31 (3H, s), 6.59 (1H, dd, *J* 1.5 and 3.1), 6.89 (1H, dd, *J* 1.5 and 5.2), 6.93 (1H, t, *J* 7.3), 7.02 (2H, d, *J* 7.7), 7.23 (1H, dd, *J* 3.2 and 5.2), 7.27 (2H, m);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 41.0, 107.8, 118.8, 120.7, 123.3, 124.9, 129.0, 148.4, 149.3.

***N,N*-Diphenylthiophene-3-amine (19)<sup>6</sup>**

The reaction was performed according to literature. The inflammable tri-*tert*-butylphosphine was replaced by more stable tetrafluoroborate salt. The colourless solid was obtained in 421 mg (1.7 mmol, 67 %) yield (lit. 97 %).



Under microwave irradiation the product was obtained in 389 mg (1.5 mmol, 62 %) within 12 minutes at 150 °C.

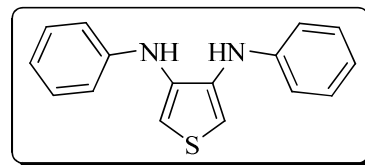
**mp** 95.2- 96.6 °C (lit. 91- 92 °C);<sup>3</sup>

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 6.59 (1H, d, *J* 1.9), 6.81 (1H, d, *J* 5.2), 6.93 (2H, t, *J* 7.3), 7.02 (4H, m), 7.19 (5H, m);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 112.8, 122.6, 123.1, 124.8, 124.9, 129.1, 146.5, 147.8.

***N*<sup>3</sup>,*N*<sup>4</sup>-Diphenylthiophene- 3,4-diamine (20)****Procedure A**

In toluene (10 mL) Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (0.21 g, 0.2 mmol) and H[P<sup>*t*</sup>Bu<sub>3</sub>]<sub>3</sub>BF<sub>4</sub> (0.12 g, 0.4 mmol) were dissolved. In another flask sodium *tert*-butanolate (1.06 g, 11 mmol), aniline (0.91 mL, 10 mmol) and 3,4-dibromothiophene (0.55 mL, 5 mmol) were dissolved in toluene (20 mL). The catalyst solution was added to the reactants. The resulting brown mixture was stirred for three days at 100 °C. The cooled suspension was poured into *n*-hexane (50 mL) and filtered through a plug of celite. The crude product was concentrated in vacuum and absorbed on neutral alumina. After elution with 5 % diethyl ether in *n*-hexane with subsequent increased amount of polarity 400 mg (1.6 mmol, 32 %) 4-Bromo-*N*-phenylthiophene-3-amine (**21**), 35 mg (0.2 mmol, 4 %) *N*-Phenylthiophene-3-amine (**13**) and 146 mg (0.5 mmol, 11 %) *N*<sup>3</sup>,*N*<sup>4</sup>-Diphenylthiophene-3,4-diamine (**20**) were obtained.

**Procedure B**

The same reaction proceeded under microwave irradiation. After 15 minutes at 150 °C (150 W) and a work-up described in procedure A **20** was obtained as red solid in 359 mg (1.3 mmol, 27 %).

**mp** >107 °C decomp.;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 5.54 (1H, s), 6.85 (2H, m), 6.92 (2H, d, *J* 7.6), 7.22 (2H, t, *J* 7.4);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 107.9, 115.6, 120.1, 129.4, 144.8;

**MS (CI):**  $m/z$  (M) = 266, ( $C_6H_5NH_3^+$ ) = 94.

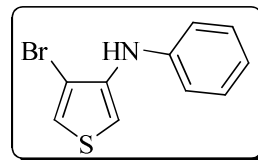
**4-Bromo-*N*-phenylthiophene-3-amine (21)**

**$^1H$ -NMR:** (400 MHz,  $CDCl_3$ ) 5.87 (1H, s), 6.76 (1H, d,  $J$  3.5), 6.95 (1H, tt,  $J$  1.0 and 7.4), 7.11 (2H, dd,  $J$  1.0 and 8.6), 7.27 (1H, d,  $J$  3.5), 7.30 (2H, dd,  $J$  7.4 and 8.5);

**$^{13}C$ -NMR:** (100 MHz,  $CDCl_3$ ) 102.2, 105.4, 116.9, 121.1, 122.1, 129.4, 138.9, 143.0;

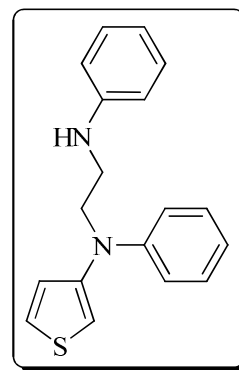
**MS (CI):**  $m/z$  (M+H) = 254, (M-Br) = 175, ( $C_6H_5NH_3^+$ ) = 94;

**MS (APCI):**  $m/z$  (M+H) 253.9644 ( $C_{10}H_9BrNS$  requires 253.9634).



***N*<sup>1</sup>,*N*<sup>2</sup>-Diphenyl-*N*<sup>1</sup>-(thiophene-3-yl)ethane-1,2-diamine (27)**

In toluene (20 mL) sodium *tert*-butanolate (1.06 g, 11 mmol), 3,4-dibromothiophene (0.55 mL, 5 mmol) and *N*<sup>1</sup>,*N*<sup>2</sup>-diphenylethane-1,2-diamine (1.06 g; 5 mmol) were dissolved.  $Pd_2(dba)_3 \cdot CHCl_3$  (207 mg; 0.2 mmol) and  $H[P^tBu_3]BF_4$  (116 mg, 0.4 mmol) were dissolved in another 15 mL toluene and added to the reactants. Because at room temperature no reaction occurred the temperature was raised to 70 °C for seven days. The cooled brown suspension was poured into *n*-hexane (50 mL) and filtered through celite. The concentrated crude product was purified on silica with dichlormethane. The open-chain, dehalogenated amine was obtained as red oil in 74 mg (0.3 mmol, 5 %).



Under microwave irradiation for 15 minutes at 150 °C (150 W) the product was obtained in 147 mg (0.5 mmol, 10 %) yield.

**$^1H$ -NMR:** (400 MHz,  $CDCl_3$ ) 3.42 (2H, t,  $J$  6.3), 3.88 (1H, s, br), 3.92 (2H, t,  $J$  6.3), 6.59 (2H, d,  $J$  7.6), 6.65 (1H, dd,  $J$  1.5 and 3.1), 6.73 (1H, tt,  $J$  1.0 and 7.4), 6.86 (1H, dd,  $J$  1.5 and 5.2), 6.94 (1H, tt,  $J$  1.0 and 7.3), 7.01 (2H, d,  $J$  7.7), 7.18 (2H, dd,  $J$  7.4 and 8.5), 7.25 (3H, m);

**$^{13}C$ -NMR:** (100 MHz,  $CDCl_3$ ) 41.5, 52.3, 109.4, 112.9, 117.6, 119.2, 121.0, 123.9, 125.2, 129.2, 129.3, 146.9, 147.8, 148.3;

**MS (CI):**  $m/z$  (M+H) = 295, (M- $C_6H_5NH$ ) = 202;

**MS (ESI):**  $m/z$  (M+H) = 295.1261 ( $C_{18}H_{19}N_2S$  requires 295.1263).

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## **Chapter 5**

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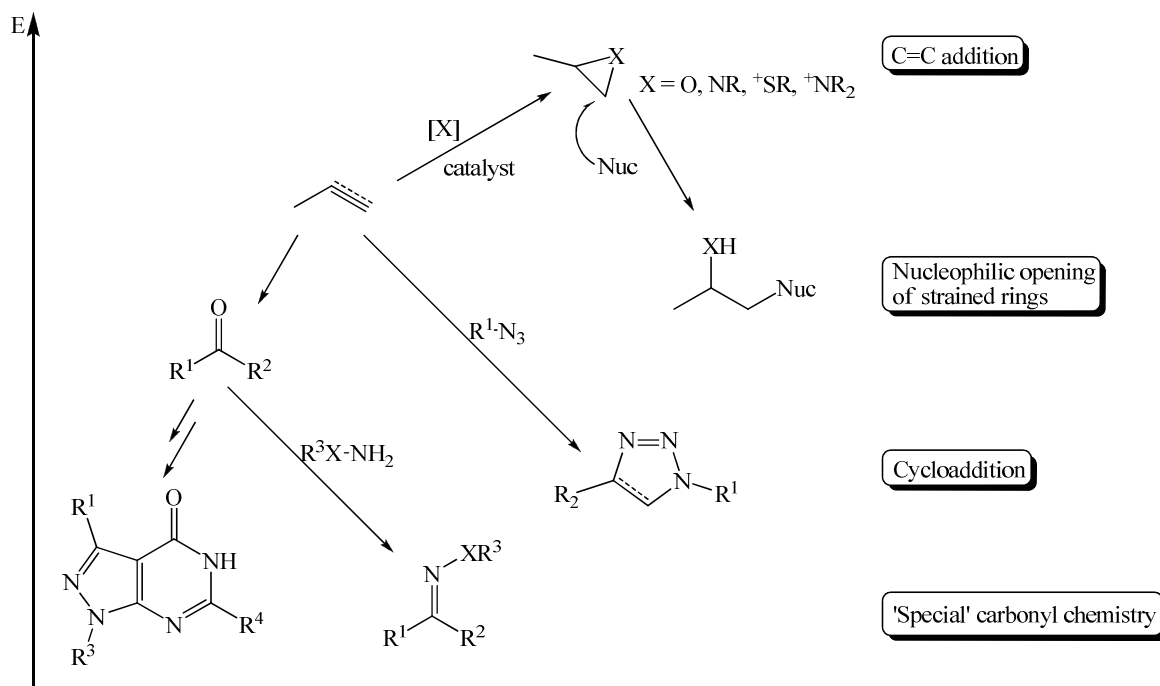
### **The Approach of “Click”-Chemistry**

## 5.1 “Click”-Chemistry

In the last few years “click”-chemistry became more and more well-known. The name of “click”-chemistry was introduced by Sharpless.<sup>1, 2</sup> It stands for a number of reactions, which are characterized by following attributes:

- wide scope,
- consistently high yields with variable and readily available starting materials,
- easy to perform, insensitive to oxygen and water,
- simple work-up and purification of the products.

In the endeavour to mimic nature’s simplicity, “click”-reactions use carbon-heteroatom bond-forming processes. Because of the lack to perfectly master reversible carbonyl chemistry in the laboratory, the outcome is controlled by using highly energetic reactants and pure kinetic control. In Scheme 5.1 the most common “click”-reactions are displayed.



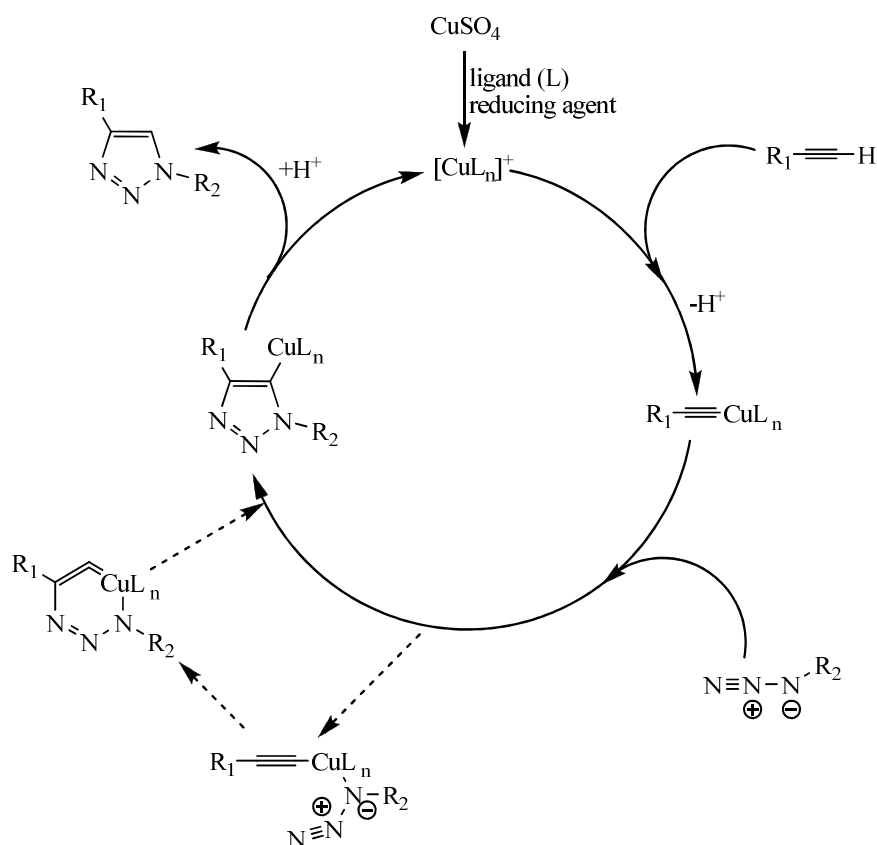
**Scheme 5.1** Survey of “click”-reactions as defined by Sharpless.<sup>1, 2</sup>

To the group of “click”-reactions belong cycloadditions, e.g., 1,3-dipolar cycloadditions and hetero-Diels-Alder reactions, nucleophilic ring opening of strained hetero-

cyclic electrophiles, carbonyl chemistry of non-aldol type and additions to C-C multiple bond.

## 5.2 1,3-Dipolar Cycloaddition

Most attention was paid to 1,3-dipolar Huisgen-cycloaddition for the coupling of azides and terminal acetylenes. 1,2,3-Triazoles are usually obtained as an isomeric mixture of 1,4- and 1,5-disubstituted derivatives. In 2002, Sharpless<sup>3</sup> and Meldal<sup>4</sup> published independently a copper(I)-catalyzed coupling of azides with terminal acetylenes to synthesize exclusively 1,4-disubstituted 1,2,3-triazoles. In the Sharpless group, copper(II) salts were reduced *in situ* to copper(I), by adding either a reducing agent (e.g., sodium ascorbate) or copper(0). However, Meldal *et al.* used copper(I) iodide and a base to couple azides to terminal acetylenes on solid phase. The assumed catalytic cycle is shown in Scheme 5.2.



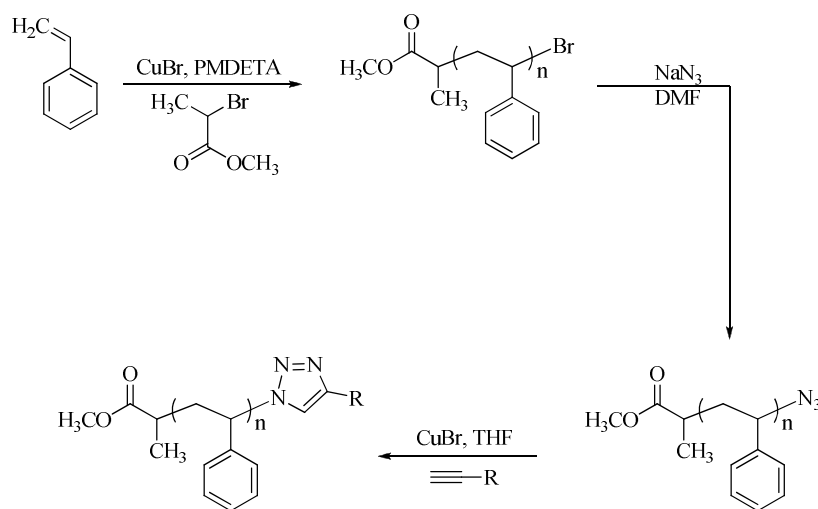
**Scheme 5.2** Assumed catalytic cycle of the copper-catalyzed 1,3-dipolar cycloaddition of azides with terminal acetylenes.<sup>3</sup>

Therefore, the copper-acetylide is formed in which the triple bond is polarized. After the coordination of the azide to the metal centre the heterocycle is formed. In the end copper is eliminated to give the desired 1,4-disubstituted 1,2,3-triazole and the recycled copper(I) catalyst. Because the catalytic cycle is just an estimation, Straub<sup>5</sup> and Fokin<sup>6</sup> *et al.* still investigate the several proposed steps. Straub and co-workers isolated a copper-triazole complex, which is a hint for the existence of the intermediate in the catalytic cycle.

Since copper-catalyzed regioselective Huisgen-cycloadditions were published, the number of publications in this field raises constantly. It is not surprising that new catalytic systems are established.<sup>7</sup> The next examples shall give just an overview about the tremendous variety of this reaction.

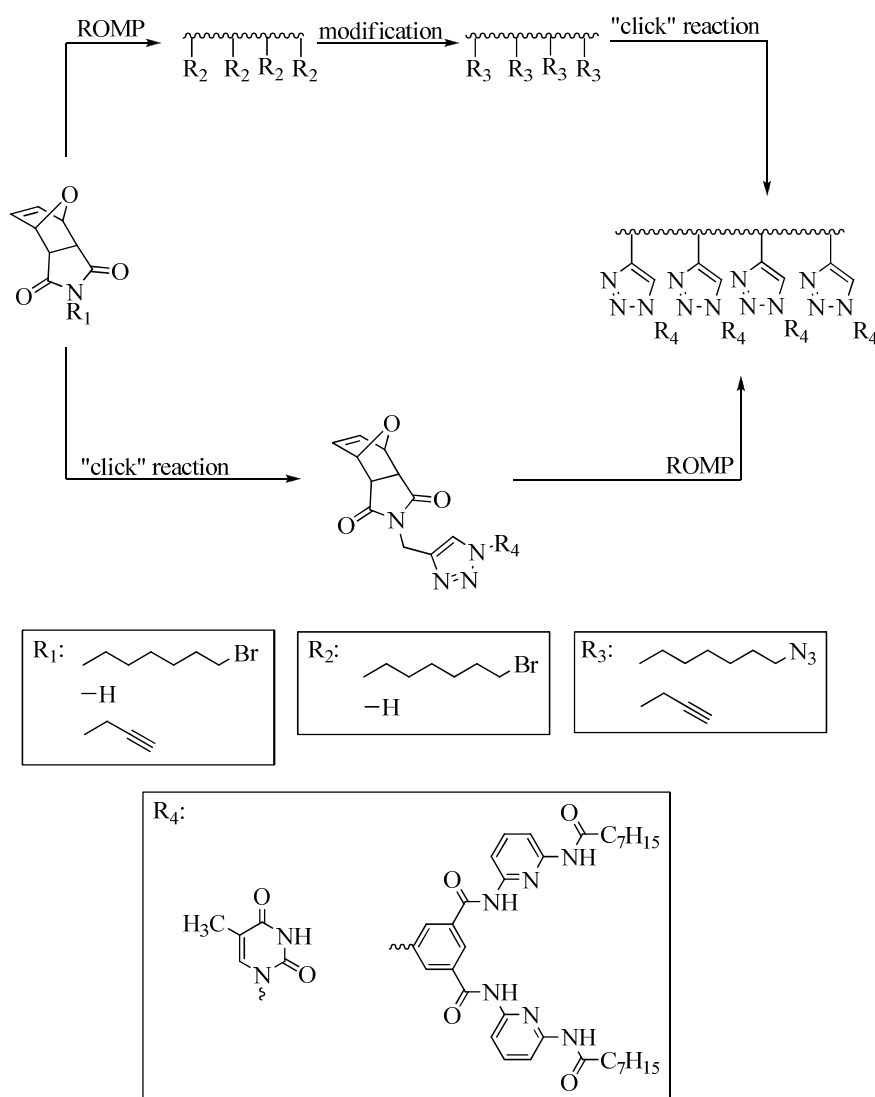
In organic synthesis and material science the azide-alkyne cycloaddition is of great interest.<sup>8, 9</sup> The “click”-reaction finds application for decorating surfaces, polymers or dendrimers with a variety of molecules.

Controlling the molecular structure is the key issue in modern polymer synthesis. The control over polymer functionalities (side chains or end groups) is essential, since functional groups can be used for further modifications. Polymers prepared by atom transfer radical polymerization (ATRP) are end-capped by a halogen atom, which easily can be transformed to an azide functionality. By copper-catalyzed cycloadditions with a terminal acetylene, the polymer can be end-capped with various functionalities in high yields, as described by Lutz *et al.* (Scheme 5.3).<sup>10</sup>



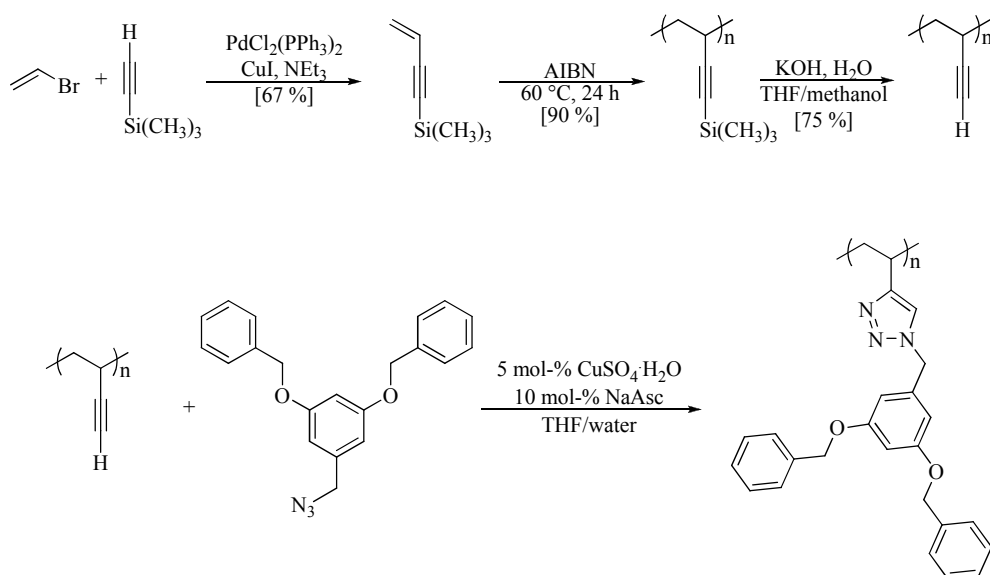
**Scheme 5.3** End chain functionalization at polymers by “click”-chemistry.<sup>10</sup>

Similar investigations were made by Bunz *et al.* for the synthesis of poly(*p*-phenyleneethynylenes) derivatized by 1,3-dipolar cycloaddition.<sup>12</sup> The desired polymers could be obtained *via* both pathways. The differences in thin-film optical and thermal properties should stem from different polymerization degrees.



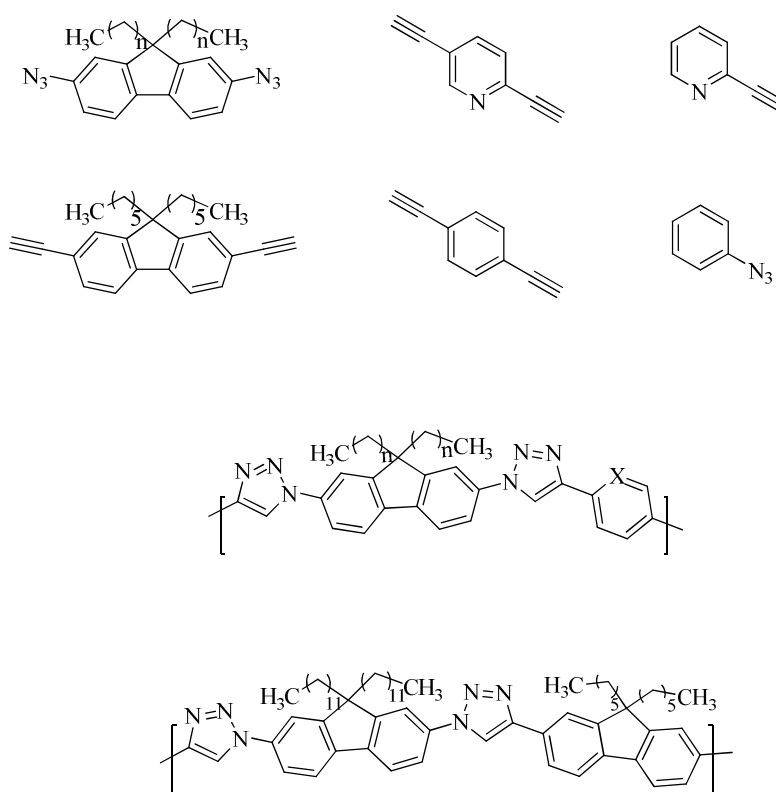
**Scheme 5.4** Combination of ROMP and “click”-chemistry for side chain modification of polymers.<sup>11</sup>

Fréchet and co-workers decorated poly(vinylacetylene) with dendrons. Therefore, three different routes are possible.<sup>13</sup> Firstly, the dendron can be coupled to a polymer, the “graft-to” approach. The convergent synthesis is very attractive, but complete coverage of the polymer is elusive. In the “graft-from” approach, the polymer is derivatized with a small generation dendron, which grows on the polymer backbone. Despite the synthetic effort is high, this route is preferred over the “graft-to” procedure, because a high degree of dendronization of the polymer is reached. If dendronized monomer units were polymerized each repeating unit has a perfect pendant group. However, with higher generations of the dendron only low polymerization degrees were reached. With the high yields of “click”-reactions the “graft-to” route was shown to be effective for the preparation of near-perfect poly(vinylacetylene)s with high generation dendrons (Scheme 5.5).



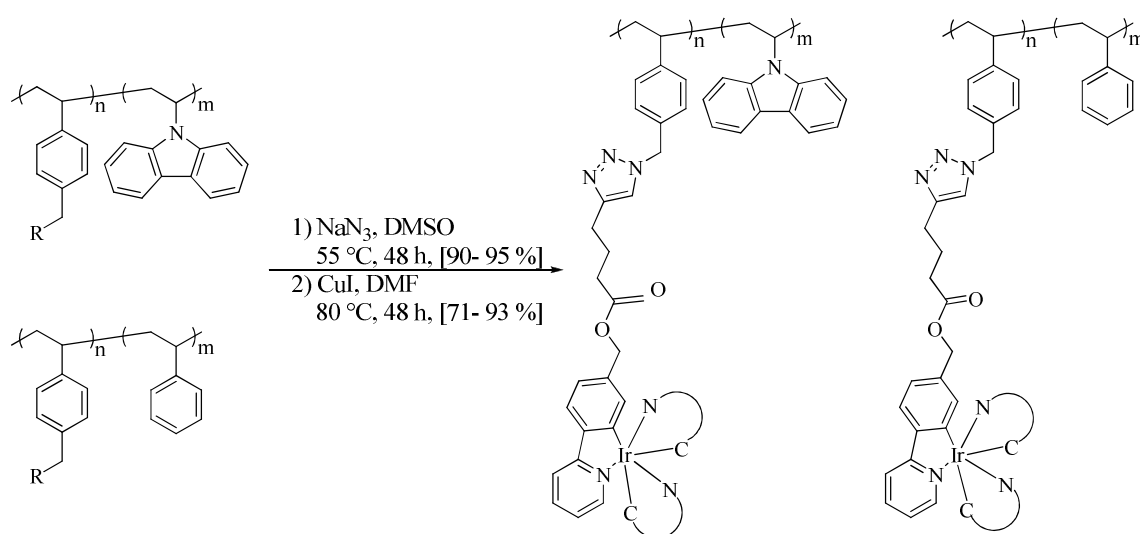
**Scheme 5.5** Dendronized poly(vinylacetylene) by “graft-to” procedure.<sup>13</sup>

Polymerization through “click”-chemistry was described by Reek and Maarseveen *et al.* who published the formation of fluorene-based conjugated polymers (Scheme 5.6).<sup>14</sup> Under typical copper-catalyzed reaction conditions fluorene-diazides were coupled to diacetylenes to yield polymers. Several solvent mixtures were investigated to obtain different polymerization degrees. Also monoacetylenes or monoazides were added after a certain reaction time to inhibit further polymerization. However, no conjugation through the triazole ring was observed.



**Scheme 5.6** Synthesis of fluorene-based conjugated polymers.<sup>14</sup>

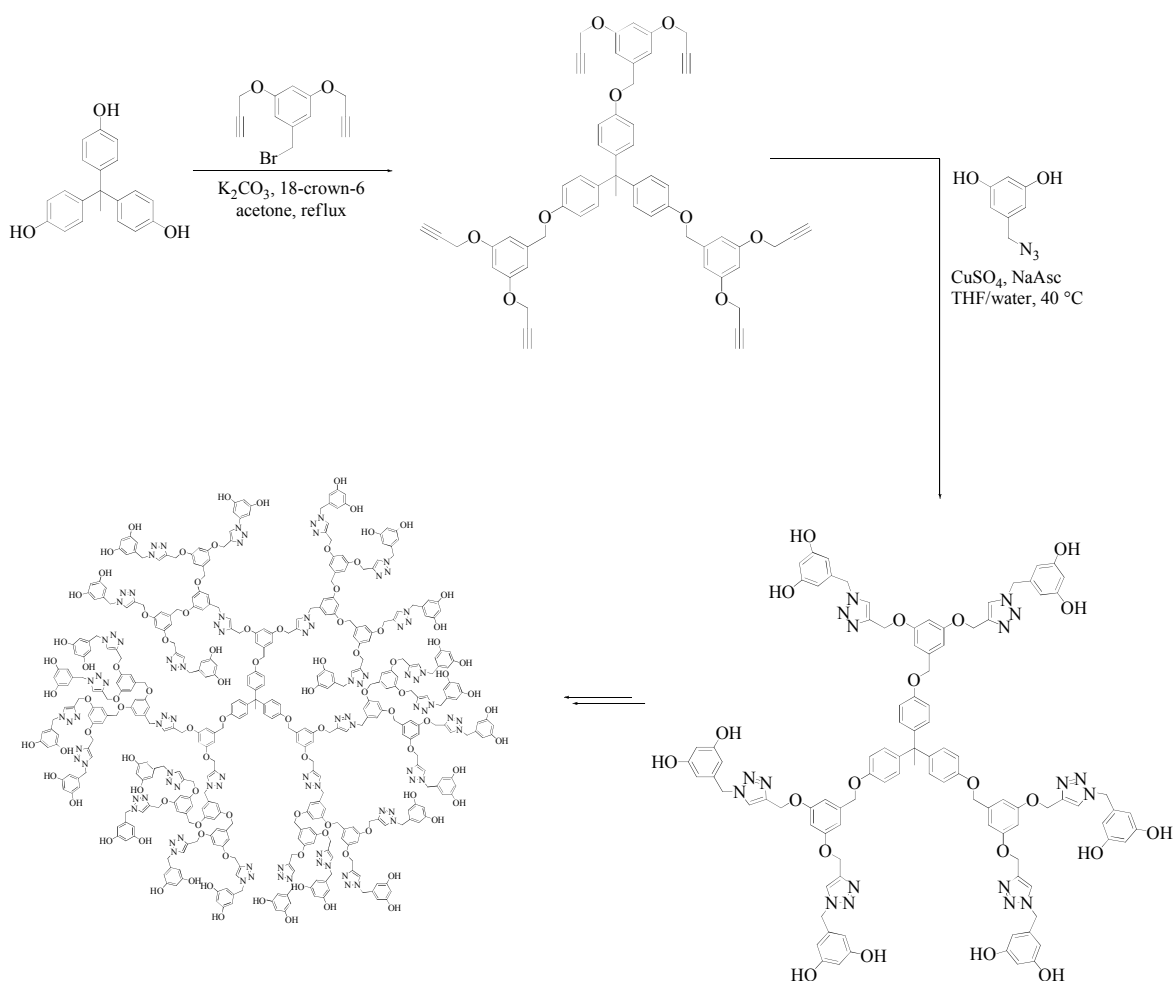
Weck *et al.* decorated polystyrene strands with highly fluorescent iridium complexes (Scheme 5.7).<sup>15</sup> The obtained material can be applied in organic light-emitting diodes.



**Scheme 5.7** Modification of polystyrenes with iridium-complexes *via* "click"-chemistry.<sup>15</sup>

Further information for the application of “click”-chemistry in material science is described in several reviews.<sup>8, 16</sup>

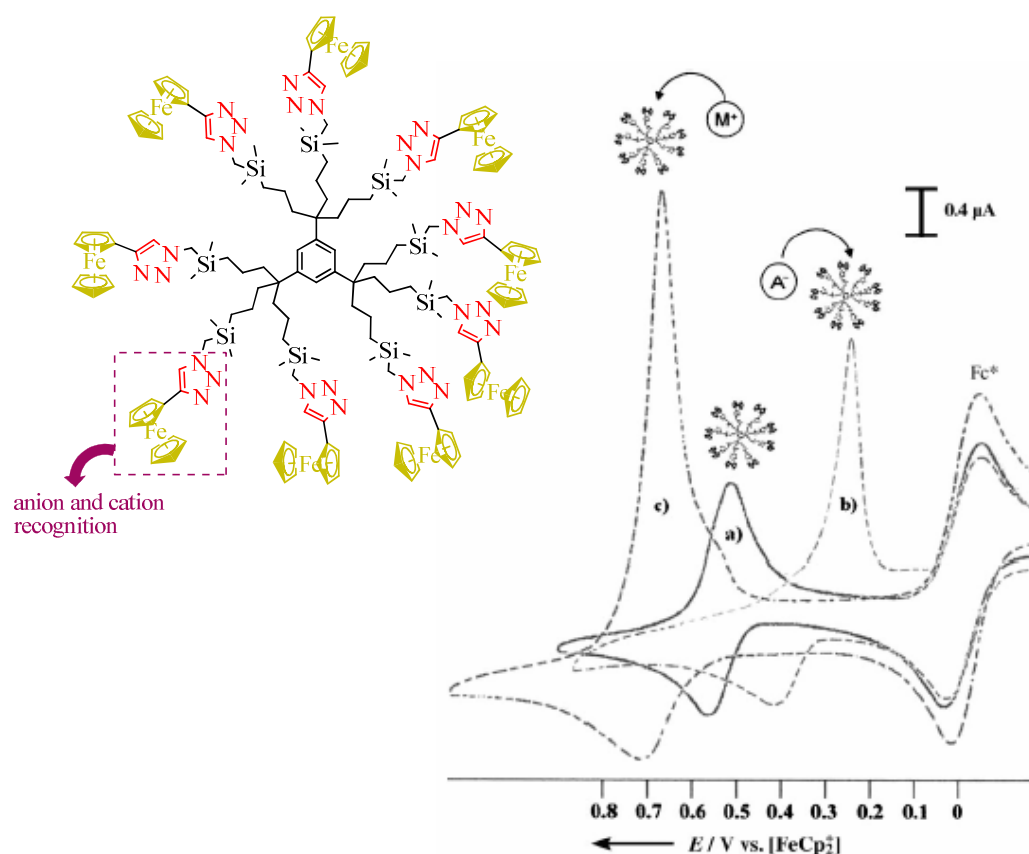
Dendrimers can be prepared by two different approaches, divergent and convergent synthesis. Both strategies give high generation dendritic structures in through repetitive growth and activation steps. To obtain perfect structures quantitative conversions are requested. “Click”-chemistry as highly efficient reaction under benign conditions should favour the formation of defect-free dendritic structures. Malkoch and Hawker *et al.* combined “click”-chemistry and esterification or etherification protocols in both divergent and convergent strategies to synthesize Fréchet-type and bis-MPA (based on 2,2-bis(hydroxymethyl)propionic acid) dendrimers.<sup>17</sup> The fourth generation dendrimer was obtained in only four steps with an overall yield of 70 %, even on multi-gram scale (Scheme 5.8).



**Scheme 5.8** Synthesis of Fréchet-type dendrimers by alternating etherification- “click”-procedures.<sup>17</sup>



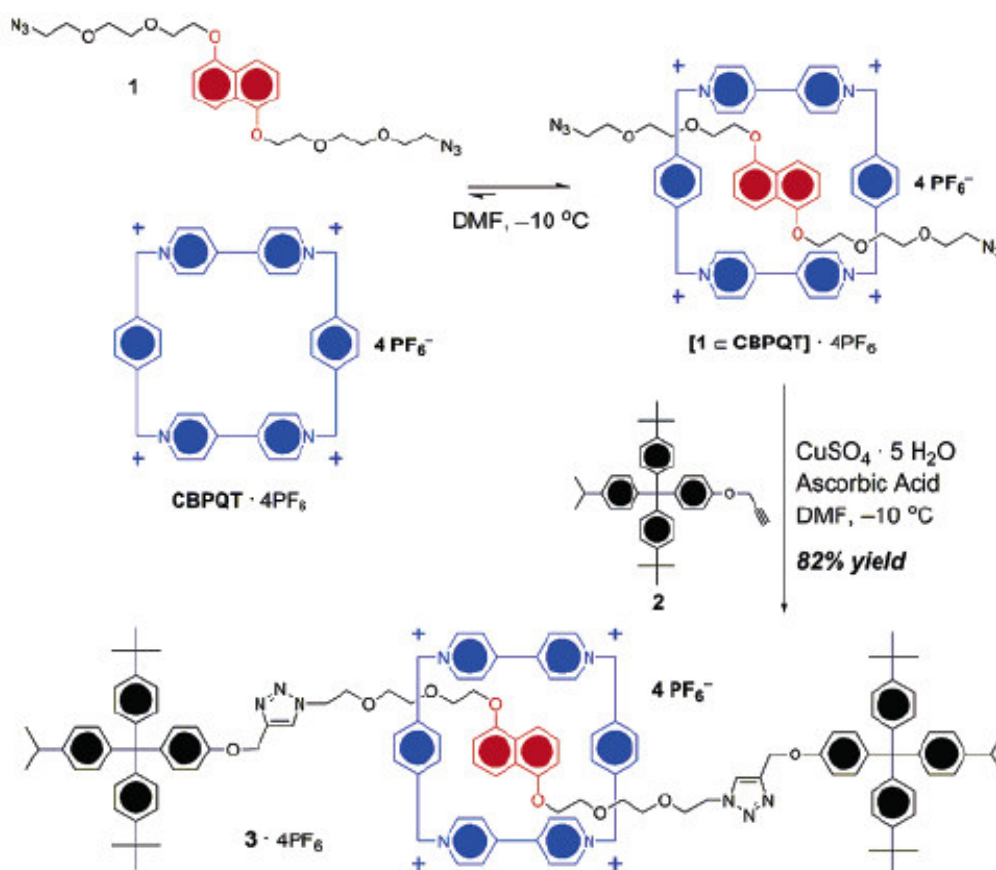
Astruc *et al.* published in 2006 first results about ferrocene-decorated dendrimers as selective electrochemical sensors for oxo anions and transition-metal cations (Scheme 5.9).<sup>18</sup> When an oxo anion ( $\text{H}_2\text{PO}_4^-$  or  $\text{ATP}^{2-}$ , but not  $\text{HSO}_4^-$ ) or a transition-metal cation ( $\text{Cu}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Pd}^{2+}$ , or  $\text{Pt}^{2+}$ ) salt is added to an electrochemical cell containing a dichloromethane solution of the “click”-dendrimer a new CV wave appears. This result is a sign of a relatively “strong redox recognition” according to the Echegoyen-Kaifer model; a modest recognition is indicated by only a shift of the initial wave. Two years later they investigated several “click”-dendrimers which coordinate palladium(II) acetate.<sup>19</sup> After reduction of palladium(II) with sodium borohydride dendrimer-encapsulated palladium nanoparticles (PdNPs) with a pre-organized number of palladium atoms were obtained. These PdNPs are highly efficient, stable and size-selective hydrogenation catalysts.



**Scheme 5.9** Dendrimers as sensor for anions and cations.<sup>18</sup>

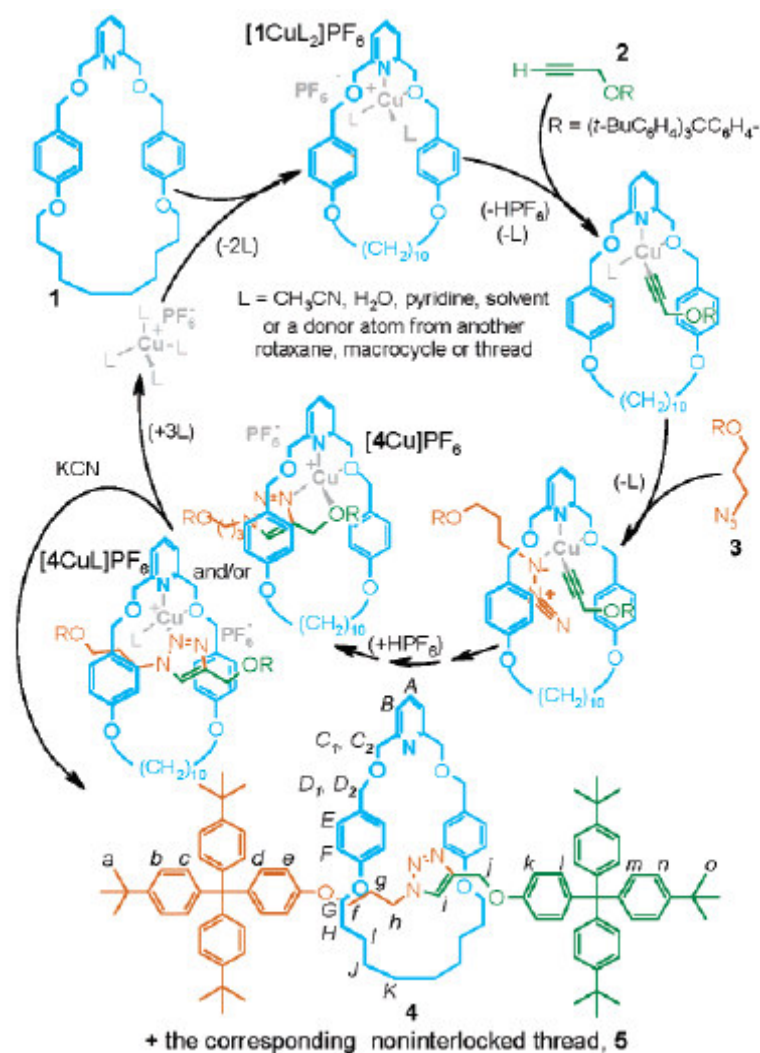
To synthesize mechanically-interlocked molecules, such as rotaxanes and catenanes, the “click”-reaction can be used for efficient covalent bond formation to stopper the

pseudo-rotaxane, as shown by Stoddart.<sup>20</sup> Compared to the clipping procedure the threading-followed-by-stoppering approach has a lot of advantages. Therefore, [2]-, [3]- and [4]-rotaxanes were synthesized in high yields by stopper the preformed pseudorotaxane *via* “click”-chemistry under mild reaction conditions (Scheme 5.10). The formation of dumbbells was not observed.



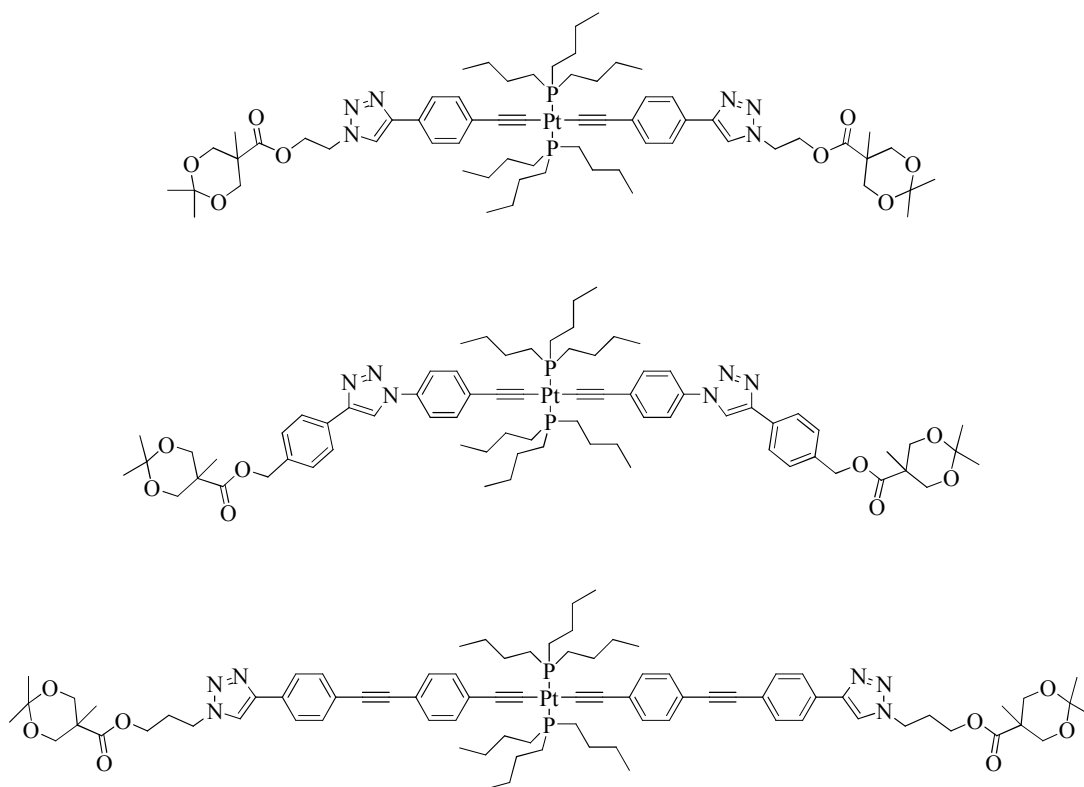
**Scheme 5.10** Formation of donor-acceptor [2]-rotaxane by threading-followed-by-stoppering approach.<sup>20</sup>

Leigh *et al.* combined the template-approach and interlocking by “click”-chemistry.<sup>21</sup> In the proposed catalytic cycle (Scheme 5.11) copper(I) was first complexed by the pyridine macrocycle. After the coordination of a terminal acetylene and an azide the [2]-rotaxane was formed. After demetallation with potassium cyanide, the metal-free [2]-rotaxane was obtained in high yield. However, also dumbbells were formed as by-products. A review about recent investigations was given by Stoddart.<sup>22</sup>



**Scheme 5.11** Substoichiometric metal-template pathway to [2]-rotaxanes.<sup>21</sup>

First examples of triazole-functionalized platinum(II) acetylides were investigated in order to obtain dendronized chromophores using “click”-chemistry.<sup>23</sup> The triazole unit was incorporated in three different positions within the chromophore, at the end or inbetween the conjugation path (Scheme 5.12). To evaluate the effect of the heterocycle on the chromophore, photophysical properties and optical power limiting abilities of these acetylide compounds were investigated. Obviously, the triazole unit breaks the conjugation path. In order to gain maximum optical limiting the triazole unit needs to be placed at the end of the conjugation pathway. However, “click”-chemistry is a useful tool to attach branched monomer units to ethynyl-phenyl arms of platinum(II) acetylides.

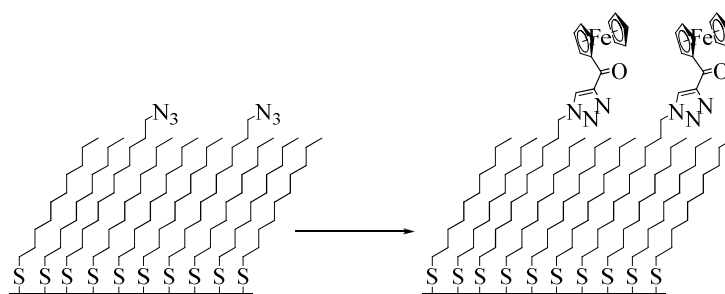


**Scheme 5.12** Investigated platinum(II) acetylides containing 1,2,3-triazole moieties.<sup>23</sup>

Modification of well-defined electrode surfaces was performed *via* “click”-chemistry by Collman and Chidsey *et al.* (Scheme 5.13).<sup>24</sup> Self-assembled monolayers (SAM) at gold surfaces containing various mixtures of  $\omega$ -azido-undecanethiol and decanethiol were freshly prepared on (111)-oriented gold substrates. The following “click”-reaction under standard conditions seemed to occur with completion as proofed with traditional surface analytical techniques.

Williams and co-workers decorated gold nanoparticles with  $\omega$ -bromoalkylthiols by standard protocols.<sup>25</sup> After bromine-azide exchange the nanoparticles were covered with terminal acetylenes *via* “click”-chemistry. The chemical functionalities of the gold nanoparticles were investigated by fluorescence spectroscopy and cyclic voltammetry.

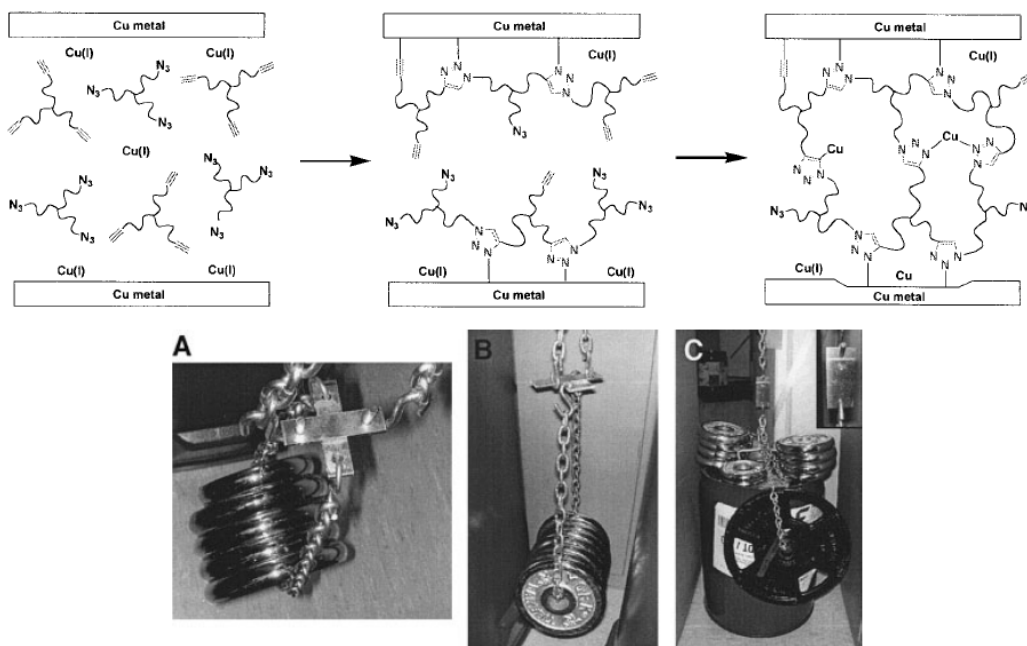
Coupling of azides to covalently immobilized, structurally well-defined acetylene-terminated organic monolayers led to functionalized Si(100) surfaces (Scheme 5.13).<sup>26</sup> Gooding *et al.* could show that “click”-chemistry is a versatile tool for the production of biosensors and molecular electronics.



**Scheme 5.13** Depiction of electrode surface before and after “click”-chemistry between azidoundecane thiol and ferrocenepropynone.<sup>24</sup>

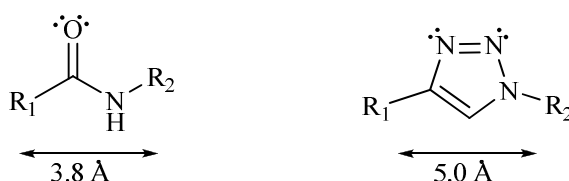
A short review about modification of solid surfaces *via* “click”-chemistry was given by Collman.<sup>27</sup>

On copper and brass surfaces azides and terminal acetylenes can be applied as strong glue (Scheme 5.14).<sup>28</sup> Copper atoms in the boundary layer act as catalyst for the 1,3-dipolar cycloaddition to produce regioselectively 1,2,3-triazoles. Alternatively, copper catalysts can be added to monomer mixtures and applied to reducing metals such as zinc to initiate polymerization. The resulting materials were found to be as effective or even superior to commercial glues.



**Scheme 5.14** Top: Copper adhesion by formation of networked triazoles. Bottom: Determination of load-bearing capacity of adhesives: A) peel test with crossed copper plates, B) peel test with crossed zinc plates, C) shear test with parallel aligned copper plates.<sup>28</sup>

Especially for biochemical applications 1,4-disubstituted 1,2,3-triazoles are of great interest. This system is able to mimic peptide bonds with a dipole moment of ~5.0 Debye (3.7 to 4.0 Debye for *N*-methyl-acetamide).<sup>2</sup> Also the C-C distance of 5 Å in 1,4-disubstituted 1,2,3-triazoles is near to the C-α distance in amides (3.8 Å). 2- And 3-nitrogen in triazole rings can act as weak hydrogen-bond acceptors, such as oxygen in amides (Chart 5.1).

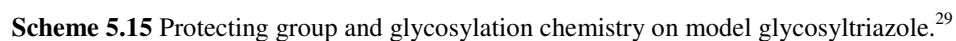


**Chart 5.1** Comparison of topological and electronic features of amides and 1,4-disubstituted 1,2,3-triazoles.<sup>2</sup>

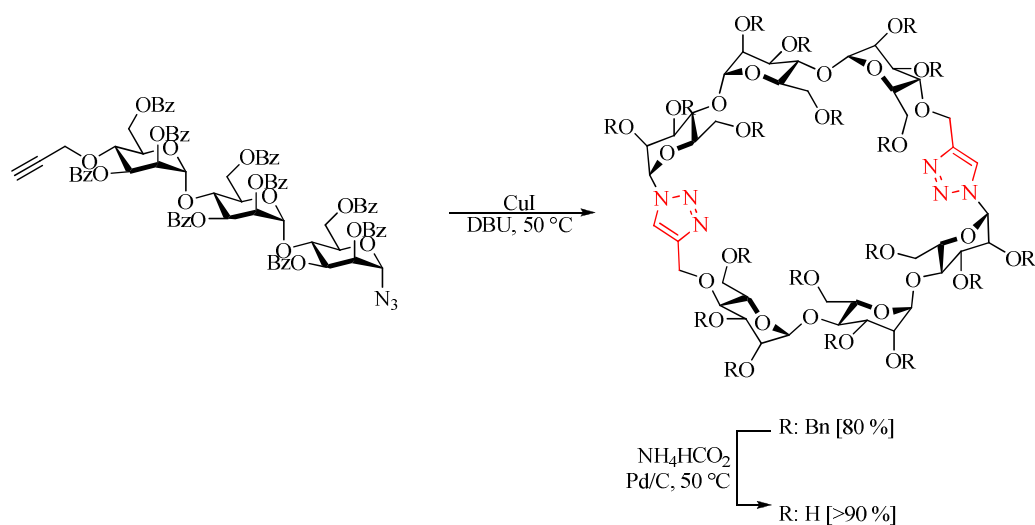
In contrast to nature's amides, triazoles cannot be cleaved and they are impossible to oxidize or reduce. Thus, it was applied to couple, e.g., sugars, peptides and viruses.

Houston *et al.* reported chemical modification of glycosyl azides with several terminal acetylenes and investigated the role of solvents and temperature.<sup>29, 30</sup> 1,3-Dipolar cycloaddition to 1,2,3-triazoles proceeded much faster at slightly elevated temperatures. Afterwards, the chemical robustness of the triazole ring was tested at typical carbohydrate chemistry reaction condition, such as alcohol protection or deprotection, *O*-glycosylation and nucleophilic displacement (Scheme 5.15). Triazole integrity was retained in all cases studied.

Also, the modification of polysaccharides (cellulose) *via* “click”-chemistry was investigated. Heinze and co-workers showed that several functionalized terminal acetylenes, i.e. carboxylic ester, thiophene and aniline moieties can be coupled to cellulose in high yield under standard reaction conditions (5 mol-% CuSO<sub>4</sub>, 10 mol-% sodium ascorbate, water).<sup>31</sup>

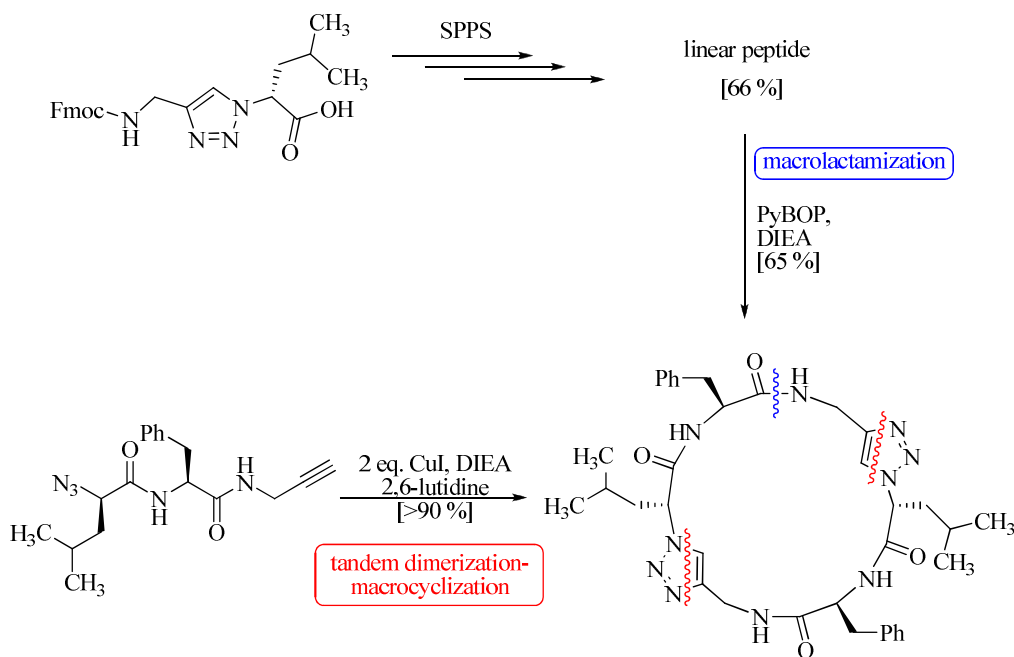


Gin *et al.* investigated macrocyclization *via* 1,3-dipolar cycloaddition of alkynyl-azido oligosaccharides.<sup>32</sup> The reaction conditions were carefully optimized at a trisaccharide to obtain mainly dimerization product (80 %) and only a small amount of cyclotrimer (15 %) (Scheme 5.16). With the best reaction conditions (CuI and DBU in toluene at 50 °C) formation of linear polymerization products could be suppressed. The subsequent deprotection of alcohol groups gave a cyclodextrine in quantitative yield.



**Scheme 5.16** Dimerization-macrocyclization of alkyne-azide trisaccharides to cyclodextrines.<sup>32</sup>

Meldal and co-workers as one of the inventors of copper-catalyzed regioselective 1,3-dipolar cycloadditions investigated coupling of resin-supported peptides bearing terminal acetylene functionalities to primary and secondary alkyl azides, aromatic azides and azido sugar. Ghadiri *et al.* used the “click”-approach to synthesize cyclic oligopeptides (Scheme 5.17).<sup>33</sup> Apart from symmetric macrocycles also the formation of unsymmetric coupling products of two different peptide backbones was described.



**Scheme 5.17** Alternative routes to cyclic peptides.<sup>33</sup>



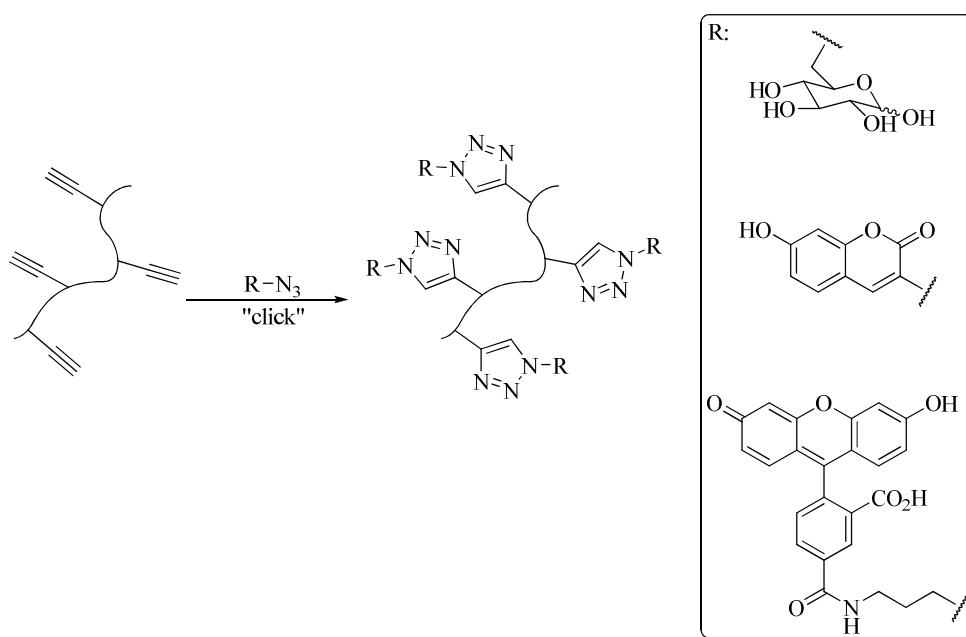
A review of Burgess *et al.* summarizes the impact of “click”-reaction to insert 1,2,3-triazoles to peptide chains or link peptides to each other and further functionalities.<sup>34</sup>

The field of proteomics requires new technologies that can functionally characterize proteins within the dynamic environment of the cell, where these biomolecules are subject to numerous posttranslational modifications and the actions of endogenous activators and inhibitors. Cravatt *et al.* reported an advanced strategy for activity-based protein profiling (ABPP) that addresses this important need (Scheme 5.18).<sup>35</sup> Several enzymes could be labeled in an activity-based manner both *in vitro* and *in vivo* by an azido-sulfonate ester probe. These labeling events could be detected in whole proteomes by copper-catalyzed ligation with a rhodamine-alkyne reagent. This “click”-chemistry based strategy for ABPP represents a unique and versatile method for functional proteome analysis.



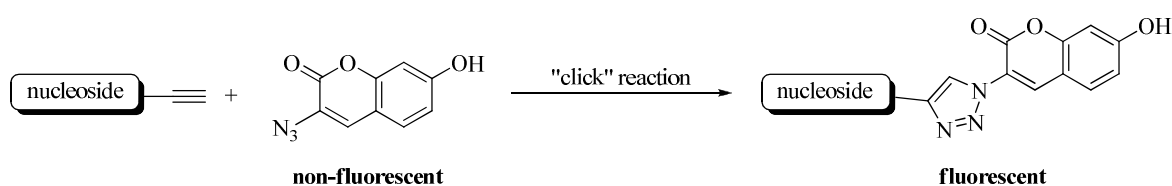
**Scheme 5.18** Activity-based protein profiling *via* copper-catalyzed 1,3-cycloaddition.<sup>35</sup>

Sequencing and detecting of DNA is important for diagnosis of pathogenic and genetic disorders.<sup>36</sup> Protocols involving the incorporation and detection of fluorescent-tagged nucleoside building blocks have been by far the most sensitive. Enzymatic replacement of each natural building block with a fluorescent-tagged analogue is a challenging task requiring highly modified protocols. The insertion of small chemical reporter units into genes by enzymatic processes (PCR) or *via* solid-phase synthesis gives the opportunity of postsynthetic functionalization. Labeling must be a highly efficient and specific process leading in quantitative conversion of the reporter units. Carell and co-workers developed a two-step process wherein the modified oligodeoxyribonucleotides (ODN's) bearing alkyne reporter units were converted by a “click”-reaction protocol with a variety of molecular labels (Scheme 5.19).



**Scheme 5.19** Postfunctionalization of DNA strands with azides of depicted labels *via* “click”-chemistry.<sup>36</sup>

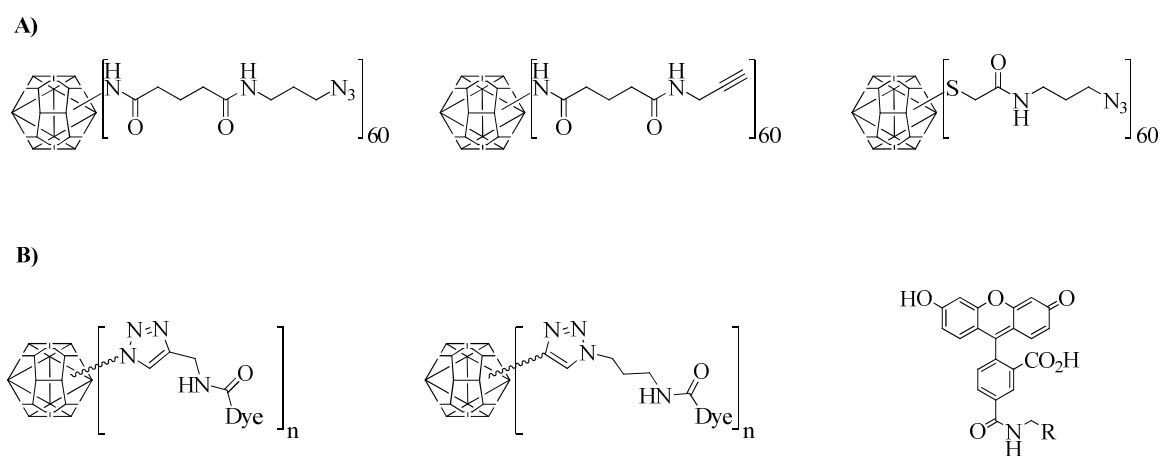
Seela *et al.* investigated decoration of nucleobases *via* 1,3-dipolar cycloaddition.<sup>37</sup> After Sonogashira reaction at the iodinated nucleosides with 1,7-octadiyne the terminal alkyne was converted to the 1,2,3-triazole by “clicking” to a non-fluorescent coumarin-dye (Scheme 5.20). The resulting modified and highly-fluorescent conjugates were investigated with respect to fluorescence properties and double-strand stability.



**Scheme 5.20** 1,3-Dipolar cycloaddition of non-fluorescent starting materials to form fluorescent coumarin dye conjugates.<sup>37</sup>

Alkynes and azides are highly energetic with weak acid-base properties. Therefore, they are inert toward biological molecules and toward chemical reaction conditions found inside living cells. The incorporation into biological molecules by organic synthesis should create unique points of addressable reactivity. Sharpless *et al.* used cowpea mosaic virus (CPMV) as a bimolecular scaffold being a structurally rigid assembly of 60 identical

copies of a two-protein asymmetric unit around a single-stranded RNA genome.<sup>38</sup> The exterior surface of the coat protein of CPMV was decorated with azides or alkynes at either reactive lysine or cysteine residues (Scheme 5.21, **A**). The desired copper-catalyzed cycloaddition was investigated with fluorescein derivatives containing complementary groups (Scheme 5.21, **B**). “Click”-reaction gave nearly quantitative yields for the modification of CPMV. Alkyne-azide ligation method should be applicable to a wide variety of biomolecules, scaffolds and cellular components, both *in vivo* and *in vitro*.



**Scheme 5.21** Labeling of cowpea mosaic virus with fluorescein *via* copper-catalyzed cycloaddition.<sup>38</sup>

For a further overview about formation of biohybrid materials and covalent labeling using “click”-chemistry also reviews of Rutjes<sup>39</sup> and Bertozzi<sup>40</sup> are available.

1,5-Disubstituted 1,2,3-triazoles can also be synthesized. Sharpless *et al.* investigated several catalysts, to obtain regioselectively this species by ruthenium(II) complexes.<sup>41</sup> In order to get 2,4-disubstituted 1,2,3-triazoles starting from alkynes and azides, a copper-catalyst was combined with palladium. This gave 2,4-disubstituted isomers in good yield.<sup>42</sup> 1,4-Disubstituted 1,2,3-triazoles can also be converted by palladium catalysis by shifting the substituent from 1-position to 2-position.

In 2004, Sharpless and co-workers described the reaction of magnesium acetylides with azides to form 1,4,5-trisubstituted 1,2,3-triazoles.<sup>43</sup> Magnesium can be converted into several substituents. Rutjes *et al.* published the synthesis of a copper(I)-mediated synthesis of trisubstituted 1,2,3-triazoles from bromoacetylenes.<sup>44</sup> 5-Iodo-1,4-disubstituted 1,2,3-

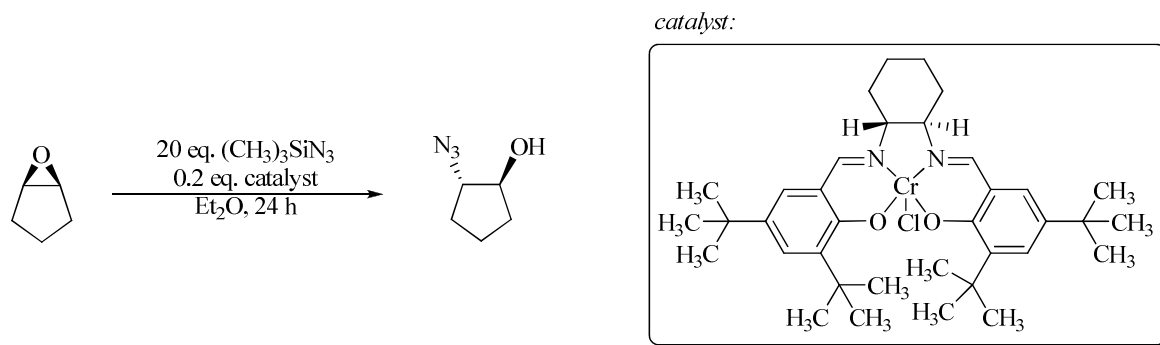
triazoles obtained by Chen *et al.*<sup>45</sup> can be converted to trisubstituted 1,2,3-triazoles by a palladium cross-coupling methods, e.g., Suzuki, Heck or Sonogashira-coupling.<sup>46</sup>

### 5.3 Formation of Azido Compounds

Because organic azides are highly energetic a lot of reactions were carried out since azides were known. They can be obtained in numerous pathways.<sup>47</sup> In principle, five pathways are possible: insertion of three nitrogen-atoms by substitution or addition of  $\text{N}_3^-$ , insertion of two nitrogen-atoms by diazo-transfer, insertion of single nitrogen by diazotization or by triazene-opening. Last but not least, azides can be synthesized by rearrangement. There is a big difference of the synthesis of aliphatic and aromatic azides.

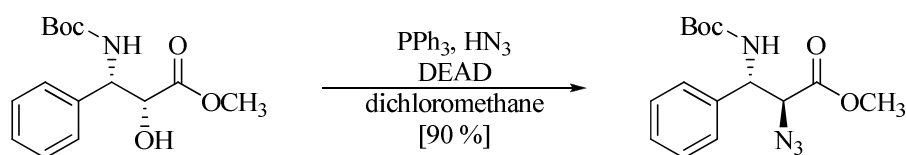
Most commonly for the preparation of alkyl azides is the displacement of halides by azide anion. With sodium azide in polar solvents, such as DMF or DMSO, the products are usually obtained in high yields. The difficulties associated with azide isolation from such solvents have stimulated investigations which led to further protocols. Several organic azide sources with good leaving groups, such as carboxyl, tosyl, mesyl or triflic azide were established to enhance reaction rate and conversion due to homogeneity of the reaction mixture. Also, the addition of phase transfer catalyst in non-polar solvents or the use of ionic liquids increased the conversion.

After ring-opening of an epoxide by azide ions a product was obtained with a hydroxyl group in  $\alpha$ -position to the azido group.<sup>48</sup> The conversion of *meso*-epoxides to anti- $\alpha,\beta$ -hydroxyazides is enantioselective (Scheme 5.22).



**Scheme 5.22** Azide formation *via* epoxide ring opening with azide anion.<sup>48</sup>

Direct conversion of alcohols to azides under Mitsunobu reaction conditions including triphenylphosphine, diethylazodicarboxylate (DEAD) and hydrogen azide as reagent is of great interest especially for reaction of secondary alcohols (Scheme 5.23).<sup>49</sup> Further studies showed that the explosive hydrogen azide can be replaced by far more stable diphenyl phosphoryl azide (DPPA).<sup>50</sup> Similar protocols, e.g., Appel-type reaction with tetrabromomethane, triphenylphosphine and sodium azide<sup>51</sup>, were also effective. Mixing secondary alcohols with DBU as base and DPPA as azide source led to alcohol-azide exchange that takes place in good to excellent yields.<sup>52</sup>

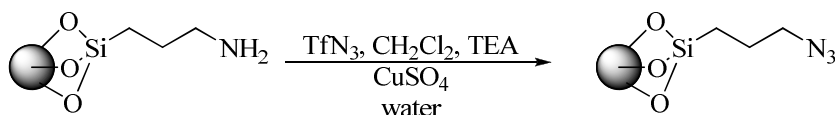


**Scheme 5.23** Mitsunobu-type hydroxyl-azide exchange with inversion of the stereo center.<sup>49</sup>

Treatment of benzylic and allylic alcohols with sodium azide in the presence of trifluoroborate etherate ( $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ) as lewis acid in dioxane gave corresponding azides in good yields.<sup>53</sup> However, unactivated alcohols such as octanol could not be converted by this protocol.

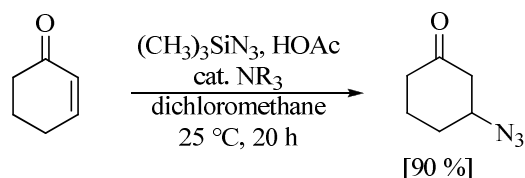
Concerning the problematic reagents requested for Mitsunobu-reactions Iranpoor and Firouzabadi developed a new synthetic procedure.<sup>54</sup> By using tetrabutylammonium azide as safe azide source, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as electron deficient reagent and triphenylphosphine, the reaction is selective for the conversion of primary alcohols over secondary, tertiary or cyclic ones. Also thiols and silyl ethers were successfully converted to azides.

Amines immobilized on solid support were effectively displaced by azides by treatment with triflic azide in dichloromethane and triethylamine in the presence of cupric sulfate and water (Scheme 5.24).<sup>55</sup> This type of reaction is also suitable for the formation of aryl azides under mild reaction conditions.<sup>56</sup>



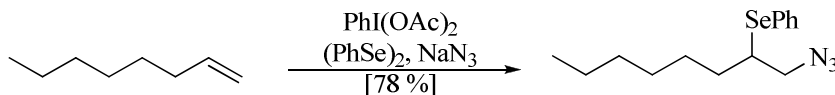
**Scheme 5.24** Amine-azide exchange on solid support with triflic azide as reagent.<sup>55</sup>

The addition of azide ions to  $\alpha,\beta$ -unsaturated carbonyls yielded after a Michael-addition reaction the alkyl azide.<sup>57</sup> Using organic azides, the formation of triazoles was observed. Miller *et al.* published results about the conversion of 2-cyclohexenon with trimethylsilyl azide and trialkylamin as Lewis-base to obtain 3-azidocyclohexanon at room temperature (Scheme 5.25).



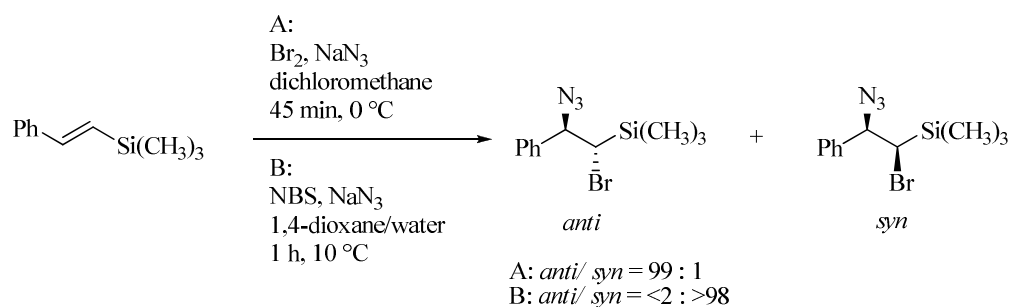
**Scheme 5.25** Michael-addition of TMS-azide to 2-cyclohexenon to give 3-azidoketone.<sup>57</sup>

Because azidyl radicals behave like a pseudohalogen radical 1,2-addition to unactivated double bonds is also possible.<sup>58</sup> The reaction of olefines with diphenyldiselenene, diacetoxyiodobenzene and sodium azide showed unusual regiochemistry (Scheme 5.26). The addition of the azide group to the less functionalized carbon is an indication for a radical reaction pathway.



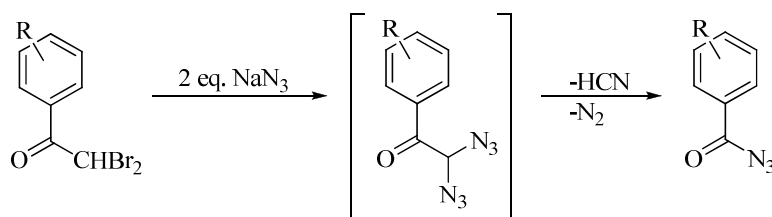
**Scheme 5.26** Radical 1,2-addition of azide to an unactivated double bond.<sup>58</sup>

The addition of bromoazide made from pre-electrophiles (bromine or *N*-bromosuccinimide, NBS) and azide ions to double bonds is a polar reaction.<sup>59</sup> With the choice of substrates and electrophiles the stereochemistry is controlled (Scheme 5.27).



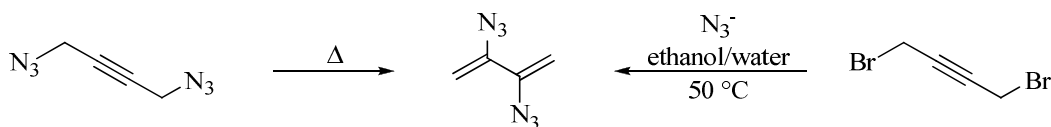
**Scheme 5.27** Control of stereochemistry by choice of the bromine source.<sup>59</sup>

Also rearrangement reactions were used for the preparation of azides.<sup>60</sup>  $\omega,\omega$ -Dibromoacetophenone derivatives gave after halogen-azide exchange corresponding aryl azide due to HCN and  $\text{N}_2$  extrusion (Scheme 5.28).



**Scheme 5.28** Formation of aryl azide after hydrocyanide and nitrogen extrusion.<sup>60</sup>

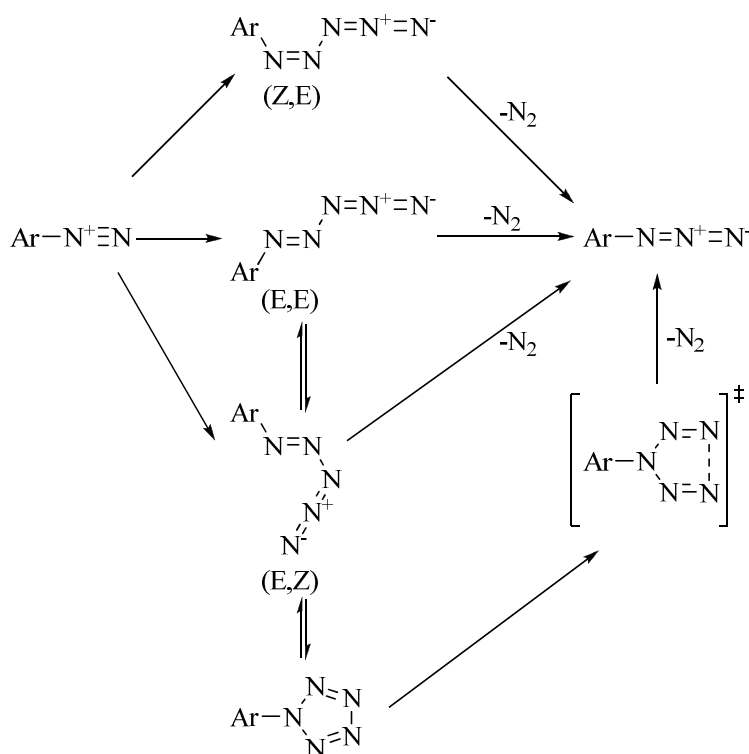
The propargylic diazide can be stored at low temperatures. At increased temperatures allyl rearrangement took place and the azido groups were shifted to vinyl position (Scheme 5.29).<sup>61</sup> However, 2,3-diazido-1,3-butadiene can also be obtained by the reaction of 1,4-dibromobut-1-yne with sodium azide at elevated temperatures in aqueous solution.



**Scheme 5.29** Allyl rearrangement of azide groups to form 2,3-diazido-1,3-butadiene.<sup>61</sup>

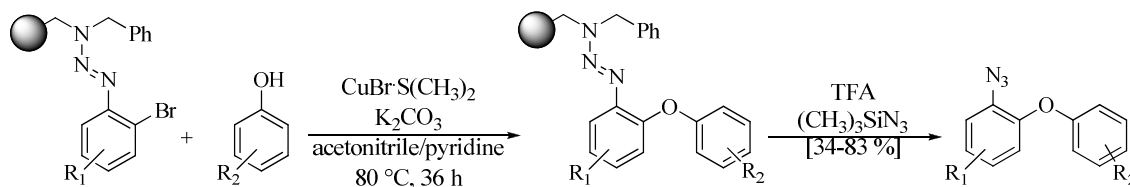
Aryl azides are mostly synthesized by conversion of diazo substrates, diazo-transfer or substitution through organo-metal exchange and nucleophilic aromatic substitution.<sup>62</sup> Aryldiazonium salts form by reaction with alkali or trimethylsilyl azide arylpentazoles

without catalysts even at low temperatures. After the follow-up cleavage of nitrogen, corresponding aryl azides can be obtained (Scheme 5.30).



**Scheme 5.30** Conversion of aromatic diazonium-salts with azide-ions.<sup>62</sup>

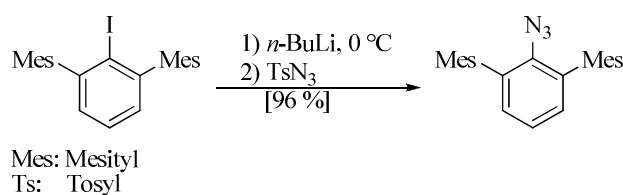
Cleavage of polymer-supported aryl triazenes by trimethylsilyl azide is another route to obtain aryl azides by diazo-transfer. A big advantage of this protocol is the possibility to modify aryl triazenes, e.g., by Ullmann coupling (Scheme 5.31), before the azide is generated.<sup>63</sup>



**Scheme 5.31** Solid-phase synthesis of aryl azides after Ullmann-Nicolaou coupling.<sup>63</sup>

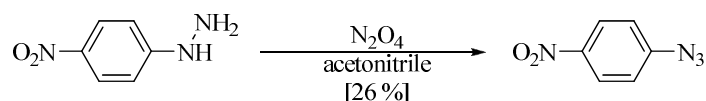
Direct nucleophilic substitution of halogens by azide ions is constrained to activated aromatics. The reaction of lithium or Grignard reagents with tosylazide results in formation of aryl azides in high yields (Scheme 5.32).<sup>64</sup>





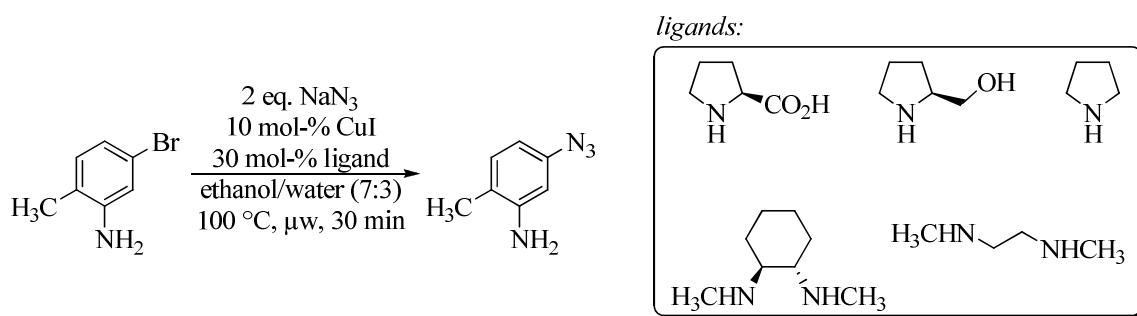
**Scheme 5.32** Metallation-azidation sequence to form aromatic azides.<sup>64</sup>

Diazotation of hydrazines is well established for the formation of alkyl, acyl or aryl azides. Reaction of hydrazines with dinitrogen tetroxide yields corresponding azides in excellent yields (Scheme 5.33).<sup>65, 66</sup>



**Scheme 5.33** Conversion of an aromatic hydrazine to the corresponding aryl azide.<sup>65</sup>

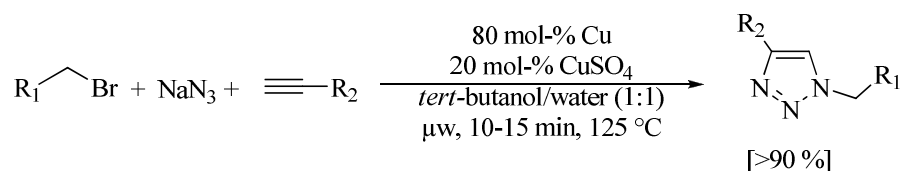
An improvement was the development of a copper-catalyzed nucleophilic substitution by Ma *et al.*<sup>67</sup> Aryl and vinyl halides were converted to azides by copper(I)-catalysis with L-proline as ligand and sodium azide as reagent. Liang and co-workers established in 2005 a more convenient ligand, which gave higher yields in shorter reaction times (Scheme 5.34).<sup>68</sup> By this protocol, also electron-rich aromatics could be converted into corresponding azides under mild reaction conditions.



**Scheme 5.34** Copper-catalyzed halogen-azide exchange as described by Liang *et al.*<sup>68</sup>

## 5.4 One-Pot Synthesis of 1,2,3-Triazoles

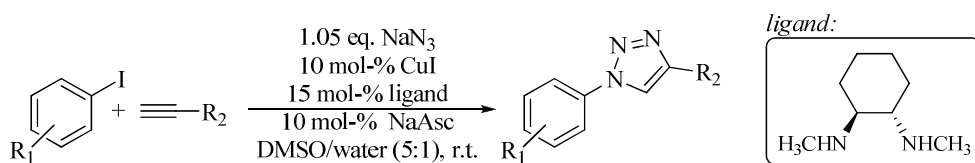
In order to avoid the purification of organic azides Fokin and Van der Eycken established a three-component one-pot procedure. Alkyl halides were converted to the corresponding azide and coupled *in situ* to a terminal acetylene to yield 1,4-disubstituted 1,2,3-triazoles (Scheme 5.35).<sup>69</sup> Under microwave irradiation halide and acetylene were heated to 125 °C with copper-turnings and cupric sulfate in a *tert*-butanol/water mixture. The desired triazoles were obtained in high yields within minutes.



**Scheme 5.35** Microwave-assisted three-component one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles.<sup>69</sup>

A similar approach was investigated for the conversion of aryl and alkenyl iodides.<sup>70</sup> Copper(I) was generated from cupric sulfate (5-10 mol-%) by the addition of sodium ascorbate (10-20 mol-%) and L-proline (20 mol-% with 20 mol-% of sodium carbonate) as stabilizing ligand. The reagents were heated to 60 °C in DMSO/water mixture (9:1) to form the 1,4-disubstituted 1,2,3-triazoles in moderate to high yields.

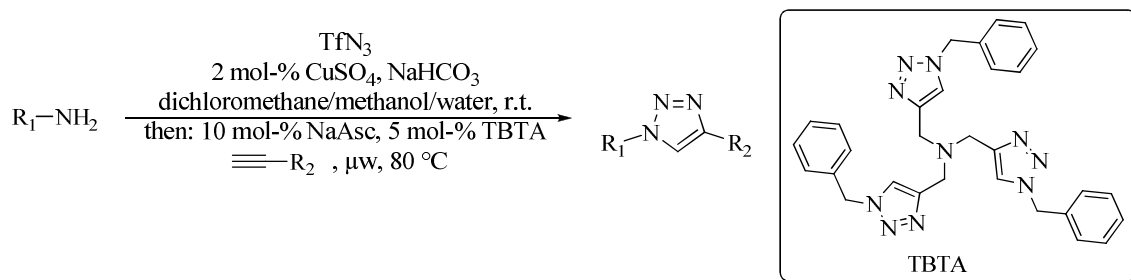
In 2005, Liang *et al.* described the *in situ* conversion of aryl halides *via* arylazide to 1,2,3-triazoles by copper catalysis (Scheme 5.36).<sup>71</sup> For this reaction sequence the same catalytic system was applied than optimized for the azide formation.<sup>68</sup>



**Scheme 5.36** *In situ* conversion of aryl iodides to synthesize 1,4-disubstituted 1,2,3-triazoles.<sup>71</sup>

Wittmann and co-workers established a procedure with azide formation *via* diazotransfer at alkyl amines and subsequent 1,3-dipolar cycloaddition with terminal acetylenes (Scheme 5.37).<sup>72</sup> After the first reaction step catalyzed by copper(II), acetylene

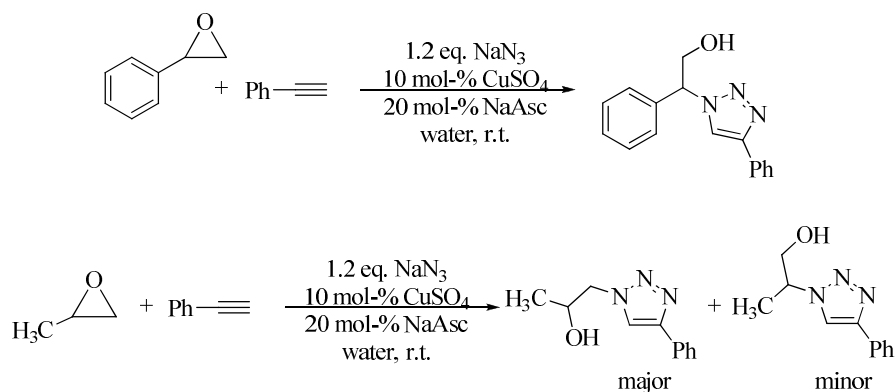
was added together with a reducing agent. The “click”-reaction with copper(I) formed the regioselectively disubstituted triazole. As ligand tris((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amine (TBTA) was applied.



**Scheme 5.37** Diazotransfer to amines followed by “click”-reaction to yield triazoles in high yields.<sup>72</sup>

In parallel, a similar procedure on aromatic amines was published by Moses *et al.* *Tert*-butyl nitrite was applied as reducing agent and trimethylsilyl azide as nitrogen source.<sup>73</sup> For the [3+2]-cycloaddition without any ligand, copper catalyst was added together with the acetylene. However, sodium ascorbate was requested to generate the active copper(I) species.

Yadav and co-workers took advantage of azide formation by epoxide ring-opening to obtain corresponding triazoles in a one-pot procedure.<sup>74</sup> Epoxides were mixed with terminal acetylenes in the presence of sodium azide, cupric sulfate and sodium ascorbate in water (Scheme 5.38). At room temperature the coupling to styrene oxide gives only one regioisomer. The azide nucleophile attacks only the  $\alpha$ -carbon. Aliphatic epoxides reacted vice versa with a minor product of the other regioisomer.



**Scheme 5.38** Three-component one-pot synthesis of 1,2,3-triazoles with epoxides as reactants.<sup>74</sup>

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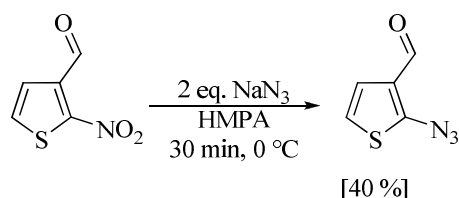
## Chapter 6

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**Conjugated Thiophene 1,2,3-Triazole Co-Oligomers**  
*via* “Click”-Chemistry

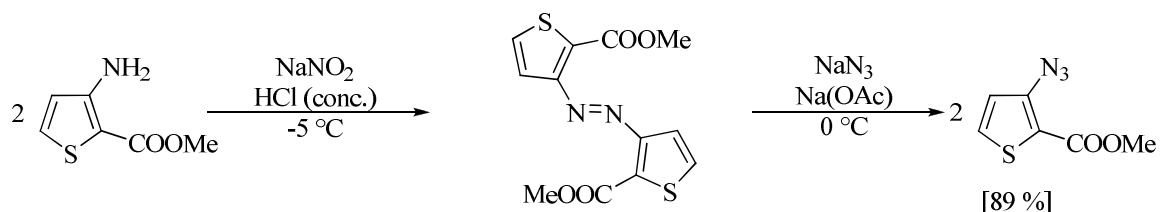
**Scheme 6.2** Azidation of 2-bromo-5-nitrothiophene by replacement of trimethylammonium bromide.<sup>2</sup>

Activated bromothiényls were also directly converted by sodium azide to corresponding azides either catalyzed by HMPA<sup>3</sup> or without catalyst.<sup>4</sup> Also the conversion of nitrothiényls into corresponding azides in HMPA (Scheme 6.3) or DMSO gave moderate yields.<sup>5</sup>



**Scheme 6.3** Azide formation by treatment of 3-formyl-2-nitrothiophene in HMPA.<sup>5</sup>

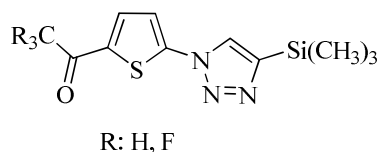
Formation of 2-azidothiophenes gave always lower yields due to the instability of the product. For the formation of 3-azidothiophenes a diazotization procedure of thiophene amines was described (Scheme 6.4).<sup>6</sup> After the diazo-derivative was synthesized, azidation was realized by reacting sodium azide in aqueous sodium acetate solution.



**Scheme 6.4** Diazotization of methyl 2-amino-3-thiophenecarboxylate.<sup>6</sup>

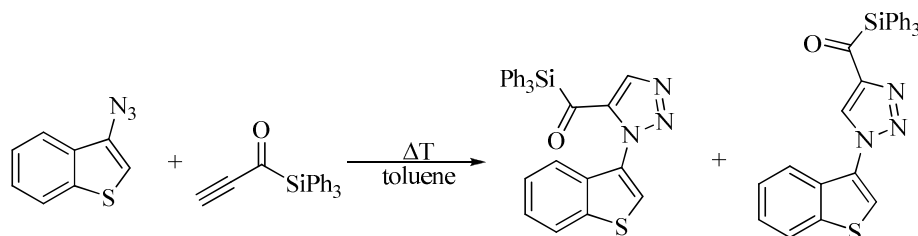
### 6.1.2 Thiophene-Containing 1,2,3-Triazoles

In literature, thiophenes linked to 1,2,3-triazoles were already known. Zanirato *et al.* described the regioselective synthesis of 1-{5-[4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]-2-thienyl}-1-ethanone and 2,2,2-trifluoro-1-{5-[4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]-2-thienyl}-1-ethanone (Chart 6.1) in excellent yields from corresponding azides and (trimethylsilyl)acetylene.<sup>7</sup> They used no catalyst to favour the 1,4-disubstituted 1,2,3-triazole. (Trimethylsilyl)acetylene yields regioselective products due to its polarity.



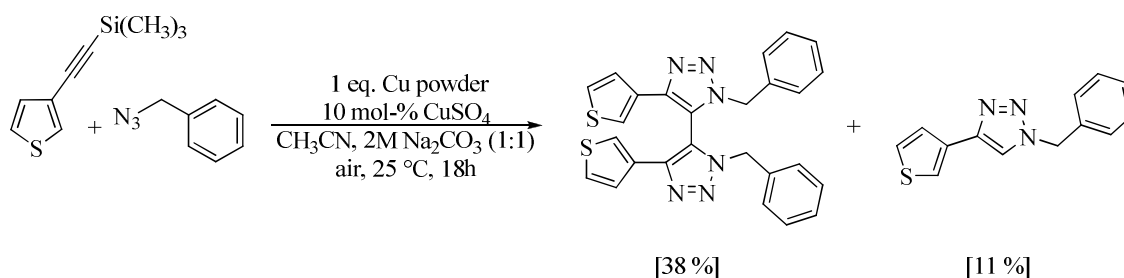
**Chart 6.1** 1-{5-[4-(Trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]-2-thienyl}-1-ethanone and 2,2,2-trifluoro-1-{5-[4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]-2-thienyl}-1-ethanone described by Zanirato *et al.*<sup>7</sup>

In 1995, Capperucci and co-workers converted 3-azido-benzo[*b*]-thiophene in a non-catalyzed 1,3-dipolar cycloaddition to 1,2,3-triazolylacylsilanes.<sup>8</sup> The authors observed a product mixture containing both, 1,4- and 1,5-disubstituted 1,2,3-triazoles in moderate yields (Scheme 6.5).



**Scheme 6.5** 1,3-Dipolar cycloaddition of 3-azido-benzo[*b*]thiophene.<sup>8</sup>

Conversion of 2-ethynylthiophene derivatives to 1,2,3-triazoles were described in a patent.<sup>9</sup> A copper catalyst was applied to synthesize the 1,4-disubstituted 1,2,3-triazoles in DMF, which were tested as Aurora kinase-inhibitors. Just recently, Sharpless and Fokin *et al.* used 3-ethynylthiophene in a “click”-chemistry protocol using copper(I) to obtain selectively 1,4-disubstituted 1,2,3-triazoles.<sup>10</sup> Burgess and co-workers synthesized bistriazoles *via* a copper(I)-catalyzed coupling procedure. The conversion of trimethyl(thien-3-ylethynyl)silane gave the bistriazole in moderate yield (Scheme 6.6).



**Scheme 6.6** Synthesis of bistriazoles *via* Huisgen-type cycloaddition.<sup>10</sup>

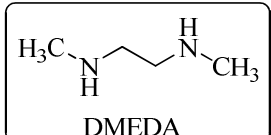
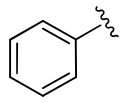
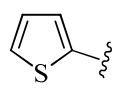
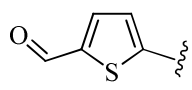
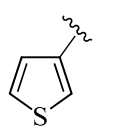
## 6.2 Synthesis of Conjugated Thiophene 1,2,3-Triazole Derivatives

### 6.2.1 Synthesis of Aryl Azides by a Mild Copper-Mediated Catalysis Starting from Arylhalides

In order to get a feeling for the synthetic route of Liang *et al.*<sup>11</sup> the phenyl azide **29** was synthesized starting from bromobenzene according to the original protocol. Therefore, two equivalents sodium azide, 10 mol-% copper(I) iodide, 5 mol-% sodium ascorbate were used in an ethanol/water (7:3) mixture. Comparable yields were obtained when *N,N'*-dimethylethylenediamine (DMEDA) was used as ligand instead of *trans-N,N'*-dimethyl-1,2-diaminocyclohexane. After two hours at reflux and purification of the crude product pure phenyl azide was obtained in nearly quantitative yield. This is in accordance to the Liang procedure.

To obtain desired thienyl azides **30-32** the same protocol was used starting from halogenated thiophenes (Table 6.1).

**Table 6.1** Copper-catalyzed formation of aryl azides starting from aryl halides with sodium azide.

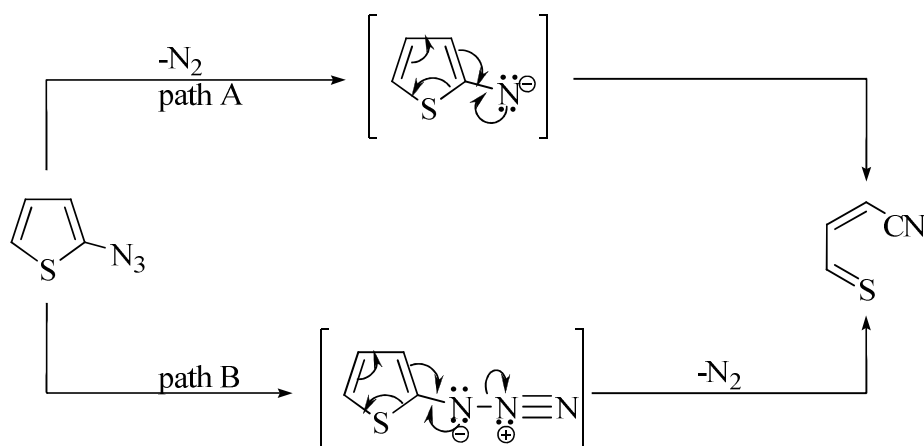
$\text{Ar-X} \xrightarrow[\substack{\text{ethanol/water (7:3)} \\ \text{reflux}}]{\substack{2 \text{ eq. NaN}_3 \\ 10 \text{ mol-\% CuI} \\ 5 \text{ mol-\% NaAsc} \\ 15 \text{ mol-\% DMEDA}}} \text{Ar-N}_3$ <div style="display: flex; justify-content: space-around; align-items: center;"> <div> <b>29-32</b> </div> <div style="border: 1px solid black; padding: 5px; text-align: center;">  <p>DMEDA</p> </div> </div>			
Compound	Ar	X	Yield [%]
<b>29</b>		Br	99
<b>30</b>		I <sup>a</sup> , Br	0
<b>31</b>		Br	0
<b>32</b>		I	99

<sup>a</sup> temperature stepwise increased from r.t. to 60 °C.

2-Bromothiophene should be converted to 2-azidothiophene **30** by this protocol. After several hours at reflux no product could be obtained, but 30 % of starting material was

re-isolated. The reaction of 2-iodothiophene under milder conditions was also investigated and was controlled by TLC. At room temperature no reaction occurred, therefore, the temperature was raised step-wise to reflux. However, no product was obtained. After work-up, 57 % of 2-iodothiophene was re-isolated.

Zanirato *et al.* described synthesis of 2- and 3-azidothiophene (**30** and **32**).<sup>12</sup> **30** was observed to be unstable at room temperature, thus, it needs to be stored at low temperatures in the dark. Stability and reactivity of azidothiophenes were investigated (Scheme 6.7). Due to mesomeric stabilization of the azide functionality, decomposition occurs by destruction of the thiophene ring. Either nitrogen is eliminated first and the highly reactive nitrene reacts under ring opening (path A) or nitrogen is released and ring opening happens in a concerted way (path B). Substituents in 5-position exerting a negative inductive effect stabilize 2-azidothiophenes. At elevated temperatures the reaction seemed to take place. Because of the instability 2-azidothiophene **30** decomposed.



**Scheme 6.7** Decomposition of **30** as proposed by Zanirato *et al.*<sup>12</sup>

Despite of this finding conversion of 3-iodothiophene to 3-azidothiophene **32** by the protocol of Liang and co-workers gave the desired product in excellent yield. The product was not stable on silica or alumina and it can not be distilled. Thus, it was used without further purification.

Because of the inductive effect of the formyl group, 2-bromo-5-formylthiophene was not reactive in this transformation. The starting material was re-isolated.

### 6.2.2 Converting Arylazides with Terminal Acetylenes to 1,4-Disubstituted 1,2,3-Triazoles

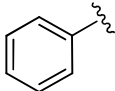
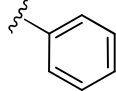
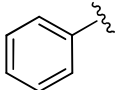
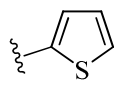
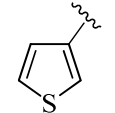
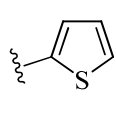
The azides formed were reacted with terminal acetylenes to obtain 1,2,3-triazoles (Table 6.2). In order to get only the 1,4-disubstituted 1,2,3-triazole regioisomer a protocol of Wang *et al.* was applied.<sup>13</sup> 1,4-Diphenyl-1*H*-1,2,3-triazole **33** was synthesized according to literature using phenylazide **29**, phenylacetylene, 1 mol-% cupric sulfate and 10 mol-% sodium ascorbate. After several hours at room temperature, the products could be obtained by filtration and washing the solid. In the original procedure, potassium ascorbate was formed by mixing ascorbic acid and potassium hydroxide. This step could be saved by applying commercial sodium ascorbate. However, the yield obtained was lower as described in literature. This led to the assumption that formation of ascorbate is an equilibrium and remaining hydroxide could enhance deprotonation of the acetylene. Therefore, copper-acetylides would be formed in higher amount.

The conversion of phenylazide and 2-ethynylthiophene to yield 1-phenyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazole **34** gave comparable yield (54 %) under identical reaction conditions.

**Table 6.2** Formation of 1,4-diaryl-1*H*-1,2,3-triazoles from aryl azides and terminal acetylenes by copper catalysis.

$$\text{Ar}'\text{N}_3 + \text{C}\equiv\text{C}-\text{Ar}'' \xrightarrow[\text{water, r.t.}]{1\text{ mol-\% CuSO}_4, 10\text{ mol-\% NaAsc}} \text{Ar}'\text{-N=N-C(=C)-Ar}''$$

**33-35**

Compound	Ar'	Ar''	Yield [%] <sup>a</sup>
<b>33</b>			59
<b>34</b>			54
<b>35</b>			52

<sup>a</sup> isolated yields

All 1,4-diaryl-1*H*-1,2,3-triazoles were obtained in good yields. 3-Azidothiophene **32** was used without purification. Despite small impurities, 1,4-dithienyl-1*H*-1,2,3-triazole **35** was formed in 52 % yield.

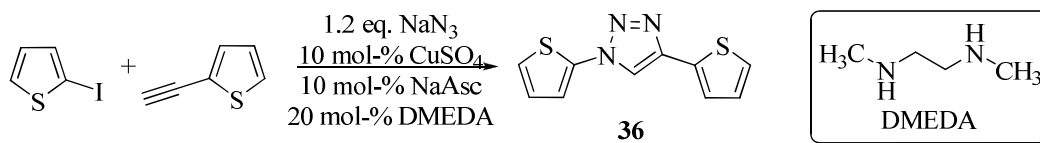
### 6.2.3 Synthesis of 1,4-Disubstituted 1,2,3-Triazoles in a Three-Component One-Pot-Procedure

Obviously, copper-catalyzed formation of 2-azidothiophenes took place, but the instable azides decomposed during reaction (see 6.2.1). Because of the inherent instability of 2-azidothiophenes, a three-component one-pot procedure was applied to obtain 1,4-diaryl-1*H*-1,2,3-triazoles. The group of Fokin and co-workers presented in 2004 a versatile method to synthesize 1,4-disubstituted 1,2,3-triazoles from *in situ* formed azides.<sup>14</sup> This protocol was overtaken for the formation of desired 1,4-dithienyl-1*H*-1,2,3-triazoles.

In the original protocol, 1.2 eq. sodium azide, 5-10 mol-% cupric sulfate, 10 or 20 mol-% sodium ascorbate and 20 mol-% L-proline were applied together with 20 mol-% sodium carbonate as base in a DMSO/water mixture (9:1) to form 1,4-disubstituted 1,2,3-triazoles from iodides and terminal acetylenes. 2-Iodothiophene and 2-ethynylthiophene gave only 10 % of pure 1,4-di(thien-2-yl)-1*H*-1,2,3-triazole **36** after several hours at 60 °C. To obtain higher yields the reaction conditions were optimized.

Firstly, another ligand was investigated. For the formation of azides Liang *et al.* found *N,N'*-dimethylethylenediamine (DMEDA) to be a more favourable ligand than L-proline.<sup>11</sup> These conditions gave 17 % of triazole **36** (Table 6.3, Entry 1). The change of solvents to ethanol/water (7:3) increased the yield to 59 % at 50 °C (Table 6.3, Entry 3). Reaction at room temperature (Table 6.3, Entry 4) gave no complete conversion of 2-iodothiophene and at 95 °C the azide was presumably decomposed (Table 6.3, Entry 5). Displacement of cupric sulfate by copper(I) iodide caused no change in yield. The application of a higher excess of sodium azide gave a slight increase of the final product yield. Formation of 1*H*-4-(2-thienyl)-1,2,3-triazole was not observed.



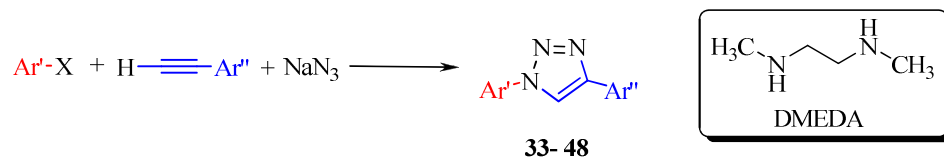
**Table 6.3** Copper-catalyzed one-pot three-component reaction of 2-iodothiophene and 2-ethynylthiophene to synthesize 1,4-di(thien-2-yl)-1*H*-1,2,3-triazole **36**.

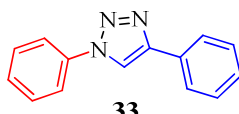
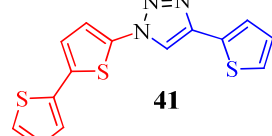
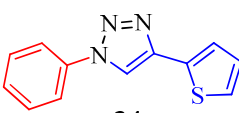
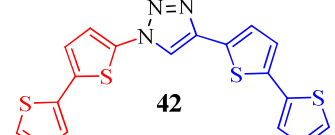
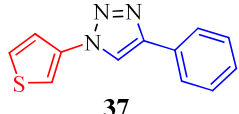
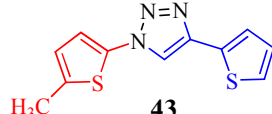
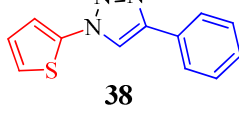
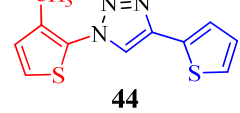
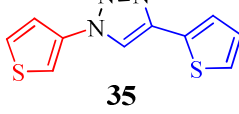
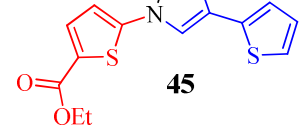
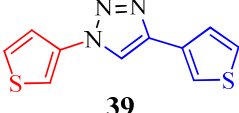
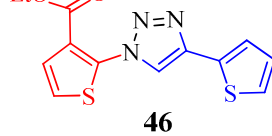
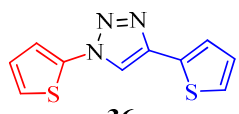
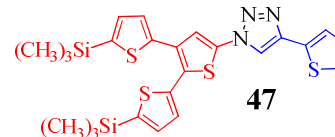
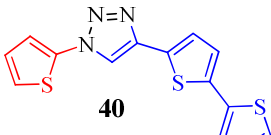
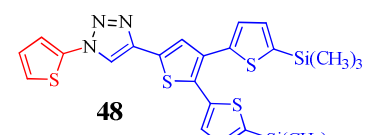
Entry	Solvent	Temperature [°C]	Yield [%] <sup>a</sup>
1	DMSO/water (9:1)	50	17
2	<i>tert</i> -butanol/water (2:1)	50	28
3	ethanol/water (7:3)	50	59
4	ethanol/water (7:3)	20	39
5	ethanol/water (7:3)	95	16

<sup>a</sup> isolated yields.

The most promising protocol to thiophene-triazole co-oligomers so far consists of sodium azide (2 eq.), copper(I) iodide (10 mol-%), sodium ascorbate (10 mol-%), DMEDA (20 mol-%) in ethanol/water (7:3) at 50 °C. A large variety of thiophene 1,2,3-triazole co-oligomers was synthesized by this protocol (Table 6.4).

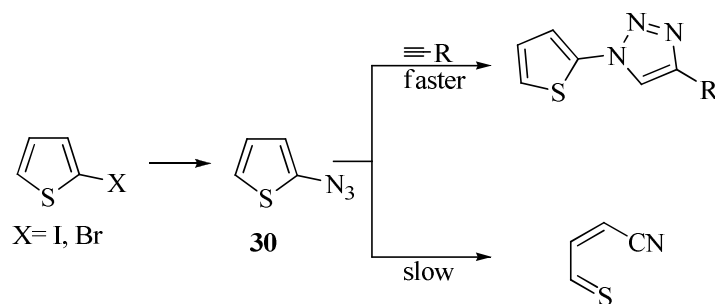
**Table 6.4** Synthesis of 1,4-disubstituted 1,2,3-triazoles from corresponding halides (1 eq.), terminal acetylenes (1 eq.) and sodium azide (2 eq.) in the presence of copper(I) iodide (10 mol-%), sodium ascorbate (10 mol-%) and *N,N'*-dimethylethylenediamine (20 mol-%) in ethanol/water (7:3) at 50 °C for 15 hours.



	Product	Yield [%] <sup>a</sup> (halide)		Product	Yield [%] <sup>a</sup> (halide)
1	 <b>33</b>	87 (I) 42 (Br) 99 (I) <sup>b</sup> 99 (Br) <sup>b, d</sup>	9	 <b>41</b>	67 (I)
2	 <b>34</b>	90 (I)	10	 <b>42</b>	33 (I)
3	 <b>37</b>	83 (I) 62 (Br)	11	 <b>43</b>	44 (I) 72 (I) <sup>c</sup>
4	 <b>38</b>	47 (I) 53 (Br)	12	 <b>44</b>	10 (I)
5	 <b>35</b>	88 (I) 45 (Br)	13	 <b>45</b>	25 (I) 62 (I) <sup>d</sup>
6	 <b>39</b>	99 (I)	14	 <b>46</b>	0 (I)
7	 <b>36</b>	67 (I) 60 (Br)	15	 <b>47</b>	44 (I)
8	 <b>40</b>	61 (I)	16	 <b>48</b>	83 (I)

<sup>a</sup> isolated yields as an average of two runs, <sup>b</sup> reaction in DMSO/water (9:1), <sup>c</sup> reaction at r.t., <sup>d</sup> reaction at 95 °C.

The following trends were observed within the several reactions: iodides are more reactive than the brominated aryls, because iodide is a better leaving group. But not in all cases higher yields were obtained. For the formation of **38** a slightly lower yield was obtained for 2-iodothiophene than for 2-bromothiophene (Table 6.4, Entry 4). This is ascribed to the instability of the *in situ* formed 2-azidothiophene **30**. Two competitive reactions are possible (Scheme 6.8). On one hand, desired 1,3-dipolar cycloadditions can take place, on the other hand, the azide intermediate can be decomposed. Because 2-bromothiophene is less reactive in substitution reactions than 2-iodothiophene azide intermediate exists in lower amounts. When 2-bromothiophene was converted 2-azidothiophene **30** can undergo the cycloaddition and the decomposition can be neglected. If the amount of **30** increases, as for the conversion of 2-iodothiophene, the ratio of decomposition over cycloaddition is increased and therefore, a lower yield of 1,2,3-triazole can be observed.



**Scheme 6.8** Competitive reaction pathways of 2-azidothiophene **30**.

As expected, 3-halogenothiophenes gave higher yields (Table 6.4, Entry 3 and 5) than 2-halogenothiophenes (Table 6.4, Entry 4 and 7), because the 3-position of the thiophene ring is less electro-negative and therefore, more reactive in nucleophilic substitution reactions. The second advantage to use 3-halogenothiophenes is the much higher thermal stability of 3-azidothiophene **32**. Highest yields were obtained for iodo- and bromobenzenes (Table 6.4, Entry 1 and 2), whereas 5-iodo-2:5'-bithiophene and branched iodothiophene gave lower yields (Table 6.4, Entry 9 and Entry 15). This could be due to solubility problems in ethanol/water mixtures.

Substituents in 5-position of 2-halogenothiophenes exerting a positive inductive effect caused slightly lower yields. 2-Iodo-5-methyl-thiophene (Table 6.4, Entry 11) is more reactive in nucleophilic substitution with azides, but the methyl group destabilizes the

azide.<sup>15</sup> Therefore, a higher degree of decomposition and competing cycloaddition was observed. The same reaction gave a higher yield at room temperature. This result confirms the first assumption. The methyl group in *ortho*-position gave a much lower yield (Table 6.4, Entry 12), which could be due to steric hindrance.

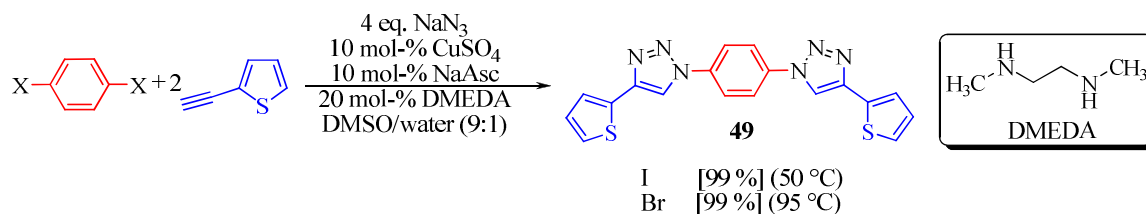
An ester group in 5-position of the thiophene gave, as expected, lower yields (Table 6.4, Entry 13). This species is less reactive in nucleophilic substitutions, but the intermediate azide should be much more stable, as Zanirato *et al.*<sup>15</sup> described. Repetition of the reaction at higher temperatures (95 °C) gave the desired product in higher yields. With an ester group at the 3-position of the thiophene (Table 6.4, Entry 14) no product formation was obtained. Steric hindrance of the ethyl ester group and a negative inductive effect hinder the formation of the azide. Therefore, the starting materials were re-isolated.

For halogenated benzenes the solvent mixture of DMSO/water (9:1) was found to be most desirable. Iodobenzene and bromobenzene gave 99 % yield of the product in the reaction with phenyl acetylene at 60 °C or 95 °C and cupric sulfate as catalyst.

For the three-component one-pot procedure with thiophenes substituent effects and the stability of the intermediate azide must be taken into consideration.

#### 6.2.4 Conversion of Dihalogenated Components with Monoacetylenes in a Three-Component One-Pot Procedure to 1,4-Disubstituted 1,2,3-Triazoles

Also two-fold reactions were investigated with the optimized protocol described in chapter 6.2.3. 1,4-Dihalogenobenzene was coupled to 2-ethynylthiophene with excellent yield (Scheme 6.9). 1,4-Diiodobenzene gave the desired bis-triazole **49** in 99 % yield at 50 °C, whereas 1,4-dibromobenzene was disubstituted at 95 °C with 98 % yield.

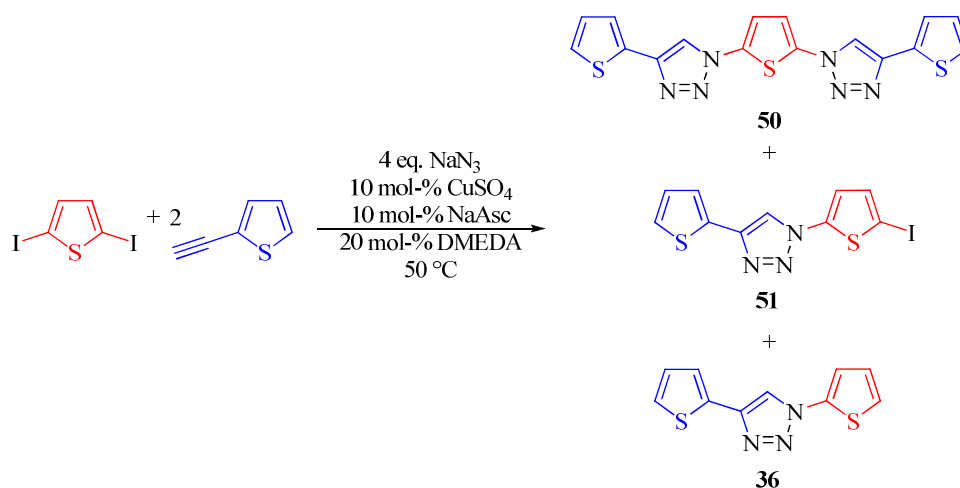


**Scheme 6.9** Formation of **49** from 1,4-dihalogenobenzene with 2 eq. 2-ethynylthiophene.

In order to get an extended thiophene 1,2,3-triazole co-oligomer, 2,5-diiodothiophene was converted with 2-ethynylthiophene under standardized reaction conditions (Table 6.5).

Only traces of product **50** were obtained in an ethanol/water mixture (Table 6.5, Entry 1). The insolubility of starting materials in protic solvents led to low conversions. In neat THF as aprotic solvent (Table 6.5, Entry 4) no conversion took place. With an oxidizing polar solvent mixture (DMSO/water, Table 6.5, Entry 3) dehalogenations to triazole **36** occurred in high yield. The best compromise between the request of a protic solvent for the catalytic reaction and solubility of the starting materials and intermediates is a mixture of THF and water (Table 6.5, Entry 2). Expected product **50** was isolated after chromatography in 43 % and traces of mono-coupled **51** were determined by NMR.

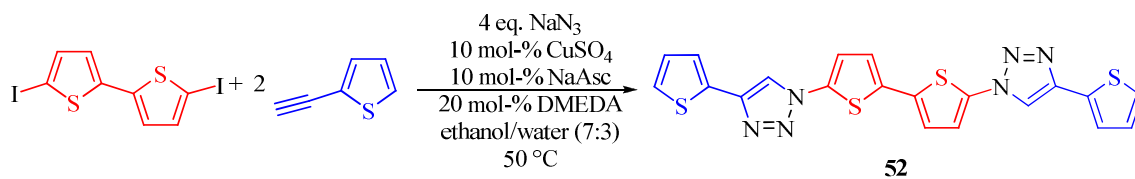
**Table 6.5** Formation of **50** from 2,5-diiodothiophene and 2-ethynylthiophen.



Entry	Solvent	Yield [%] <sup>a</sup>
1	ethanol/water (7:3)	5 ( <b>50</b> ), 3 ( <b>51</b> )
2	THF/water (5:1)	43 ( <b>50</b> ), 9 ( <b>51</b> )
3	DMSO/water (9:1)	73 ( <b>36</b> )
4	THF	0

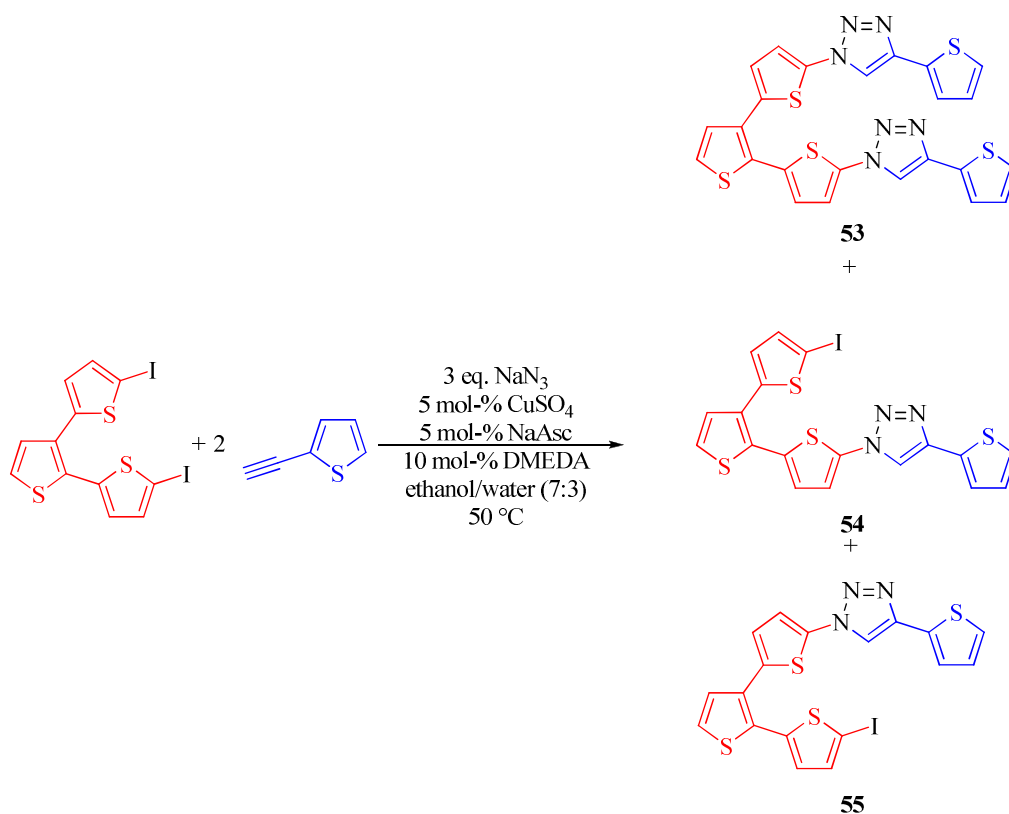
<sup>a</sup> isolated yields.

The reaction of 5,5'-diiodo-2,2'-bithiophene with 2-ethynylthiophene in ethanol/water (7:3) also gave not the desired product **52** (Scheme 6.10), because of the insolubility of the starting material.



**Scheme 6.10** Formation of **52** from 5,5'-diiodo-2,2'-bithiophene and 2-ethynylthiophene.

5,5''-Diiodo-2,2':3',2''-terthiophene was reacted with 2-ethynylthiophene (Scheme 6.11). Because of better solubility of branched molecules a higher conversion was observed in an ethanol/water (7:3) mixture. After column chromatography mono-reacted (**55** in 18 %) and the desired product (**53** in 26 %) could be obtained in pure form.

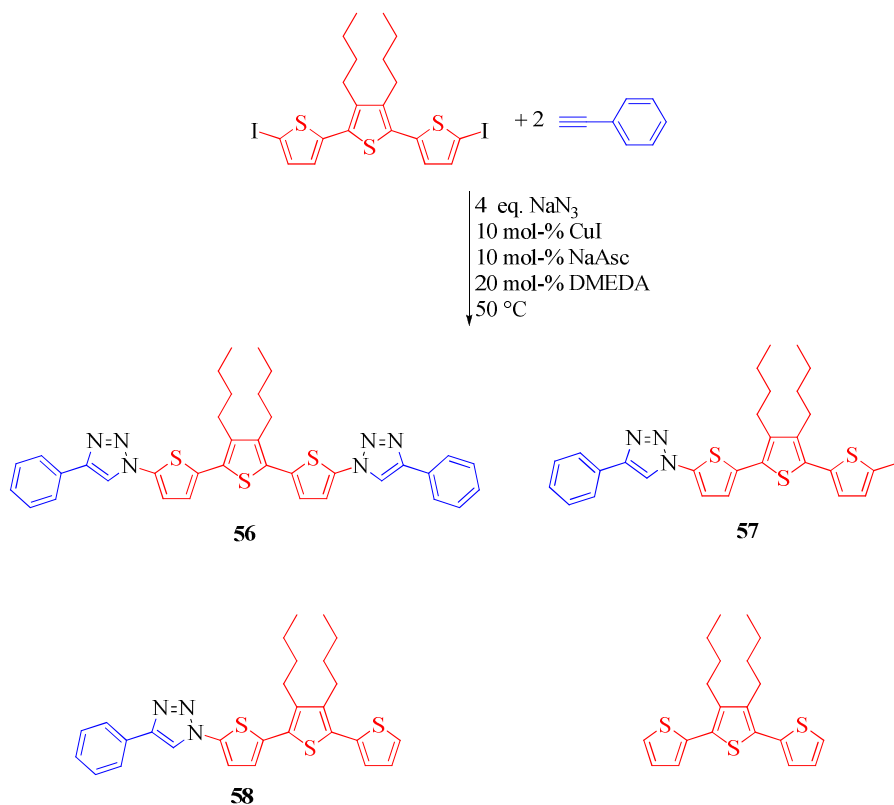


**Scheme 6.11** Formation of **53** under standardized reaction conditions from 5,5''-diiodo-2,2':3',2''-terthiophene and 2-ethynylthiophene.

Because thiophene 1,2,3-triazole co-polymers should be synthesized from dihalogenated oligothiophenes and diethynyl oligothiophenes, 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene was coupled to phenylacetylene (Table 6.6). This reaction should show the possibility to convert diiodinated oligothiophenes to azides and further to 1,2,3-

triazoles. Butyl groups increase the solubility of the halogenated component and phenylacetylene is a stable terminal acetylene. Because of very low yields under standardized reaction conditions, different solvent mixtures were investigated.

**Table 6.6** Formation of bis-triazole **56** from 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene and phenylacetylene.



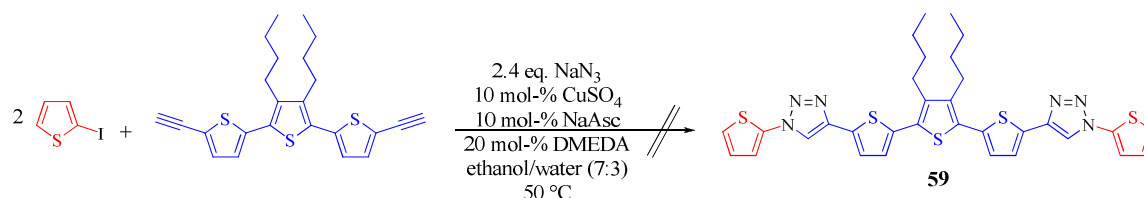
	<b>Solvent</b>	<b>56</b> [%]	<b>57</b> [%]	<b>58</b> [%]	<b>Terthiophene</b> [%]
1	ethanol/water (7:3)	22	20	25	12
2	<i>tert</i> -butanol/water (5:1)	19	15	22	29
3	THF/water (5:1)	6	0	18	0
4	DMSO/water (5:1)	12	4	12	25
5	acetonitril/water (5:1)	0	3	17	15
6	toluene	0	0	0	0
7	DMF/water (10:1)	0	0	0	0

The yields unfortunately could not be improved by change of the solvents. The best results were again obtained in protic solvent mixtures (Table 6.6, Entry 1 and 2). When a non-polar solvent was mixed with water, the yield of the bis-triazole **56** decreased. The high amount of dehalogenated products is remarkable. Triazole **58** and 3',4'-dibutyl-2,2':5',2''-terthiophene were identified by  $^1\text{H}$ -NMR studies. The starting material was analyzed carefully and showed no impurities. Obviously dehalogenation took place.

### 6.2.5 Conversion of Monohalogenated Components with Diacetylenes in a Three-Component One-Pot Procedure

In parallel, to the conversion of diiodo oligothiophenes to extended thiophene 1,2,3-triazole co-oligomers in a three-component one-pot procedure the reactivity of diethynyl oligothiophenes with thienyl azides was investigated.

3',4'-Dibutyl-5,5''-diethynyl-2,2':5',2''-terthiophene was coupled to 2-iodothiophene under standardized reaction conditions described above (Scheme 6.12). Unfortunately, no triazole formation was observed. Both 2-iodothiophene, and follow-up products of the acetylene could be identified.

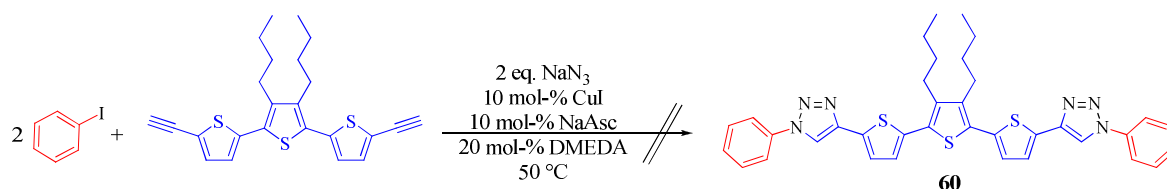


**Scheme 6.12** Formation of **59** from 3',4'-dibutyl-5,5''-diethynyl-2,2':5',2''-terthiophene and 2-iodothiophene.

Because iodobenzene can be easily converted to a stable azidobenzene in high yields, 3',4'-dibutyl-5,5''-diethynyl-2,2':5',2''-terthiophene should be converted into the co-oligomer with iodobenzene by the standard three-component one-pot procedure (Scheme 6.13). The best solvent mixtures for the conversion of 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene were investigated. However, no product was obtained, neither in ethanol/water (7:3) nor in *tert*-butanol/water (5:1).



This outcome shows that synthesis of conjugated thiophene 1,2,3-triazole copolymers is not possible by this protocol. Presumably, the diacetylene forms stable copper-acetylides and poisons the catalyst for the conversion of iodobenzene to azidobenzene.



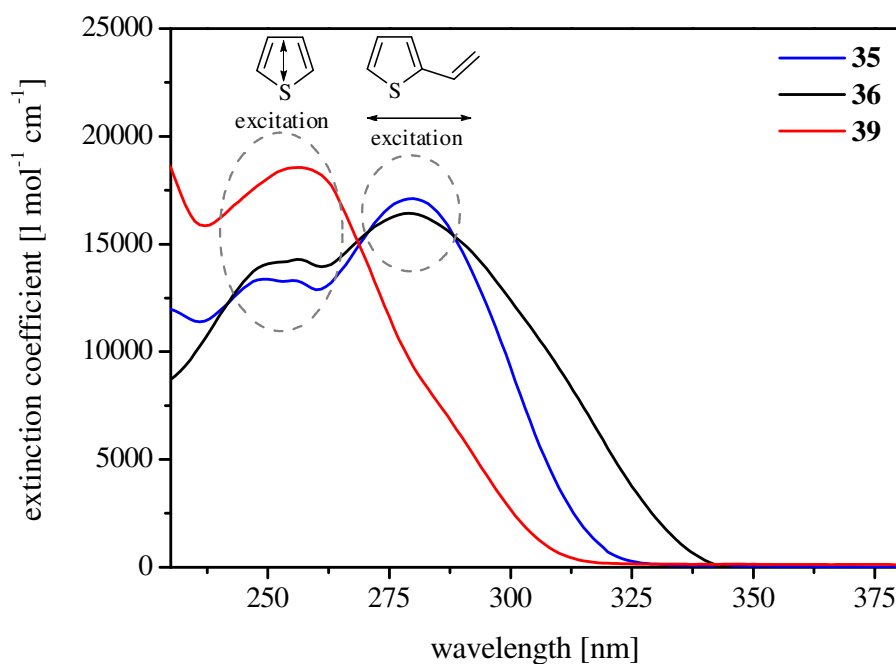
**Scheme 6.13** Formation of **60** from 3',4'-dibutyl-5,5''-diethynyl-2,2':5',2''-terthiophene and iodobenzene.

## 6.3 Spectroscopic and Electronic Properties of Selected Compounds

### 6.3.1 UV/vis Spectroscopy

Absorption spectra of compounds **33**, **35**, **36**, **39-42** were measured in dichloromethane ( $c = 5 \cdot 10^{-5} \text{ mol l}^{-1}$ ) at room temperature. The values for the absorption maxima and the logarithmic extinction coefficients are summarized in Table 6.7. UV/vis data for pure oligothiophenes **1T- 4T** were already published.<sup>16</sup> The optical band gaps were determined from the onset of the lowest energy band edge (Chart 6.2 and Chart 6.4).

For 1,4-diphenyl-1*H*-1,2,3-triazole **33** a structured absorption band with a maximum at 250 nm was observed which is comparable to the absorption of styrene ( $\lambda_{\text{max}} = 246 \text{ nm}$  in *n*-hexane)<sup>17</sup> indicating that there is now conjugation going through the triazole ring.

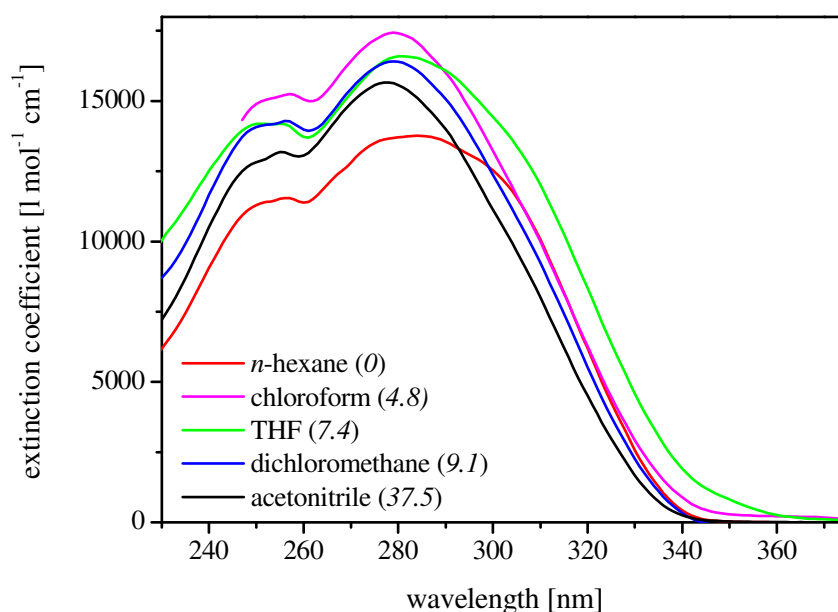


**Chart 6.2** UV/vis absorption spectra of dithienyl-triazoles **35**, **36** and **39** in dichloromethane ( $c = 5 \cdot 10^{-5} \text{ mol l}^{-1}$ ).

Thiophene 1,2,3-triazole co-oligomers **35**, **36** and **39** showed relatively unstructured absorption bands (Chart 6.2). This is due to the rather flexible aromatic system. For **35** and **36** maxima at 279 nm were observed. This corresponds to the extended conjugation of 2-ethenylthiophene ( $\lambda_{\text{max}} = 276 \text{ nm}$  in ethanol).<sup>18</sup> The second absorption maximum at 256 nm

belongs to the thiophene ring connected in 1-position of the triazole ring which is comparable to a thiophene containing an electron-withdrawing group. The absorption spectrum of **39** shows a maximum at 256 nm, and a shoulder around 280 nm. There is only a small cross-conjugation from the thiophene ring to the double bond of the triazole ring in 3-position of the thiophene, shown by the shoulder. The absorption band of **36** is broader than the bands of **35** and **39**.

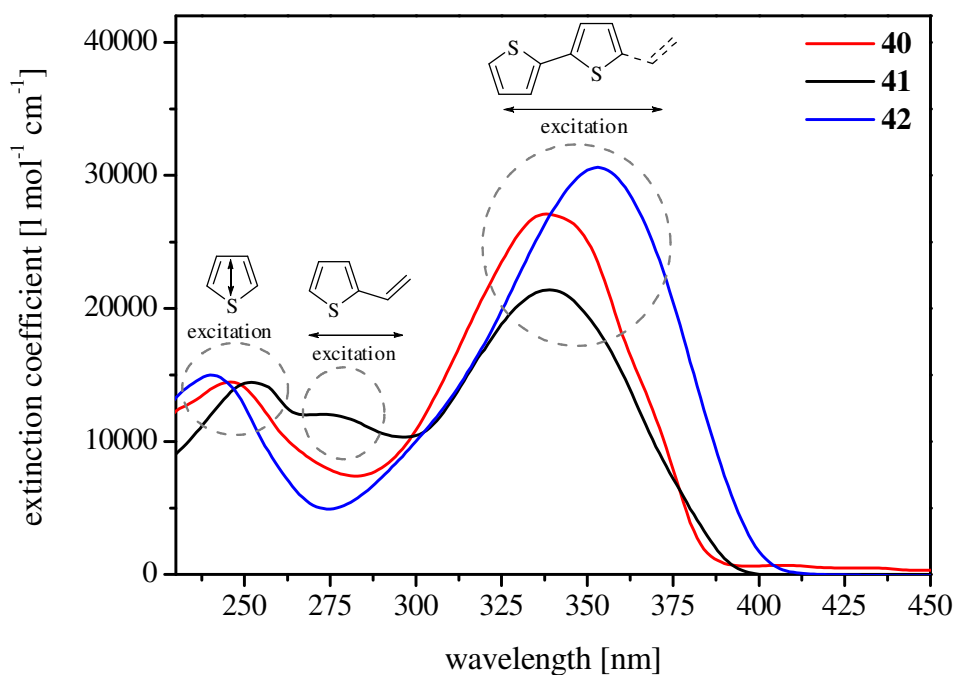
For donor-acceptor compounds an internal charge transfer character (ICT) can be expected and absorption and fluorescence behaviour changes with the polarity ( $\epsilon$ ) of the solvent. To examine, if such an effect is present in thienyl-triazoles, wherein thiophene acts as donor and triazole as acceptor, UV/vis spectra of **36** were measured in *n*-hexane ( $\epsilon$  0), chloroform (4.8), THF (7.4), dichloromethane (9.1) and acetonitrile (37.5) ( $c = 5 \cdot 10^{-5} \text{ mol l}^{-1}$ ) (Chart 6.3). As a result the absorption maximum did not change. In *n*-hexane the formation of aggregates could be observed, shown by a slightly lower extinction coefficient and a broader band. In THF the absorption spectrum is broadened without the loss of extinction intensity. It could be assumed, that in THF the molecule is more flat or partial agglomeration is present. The donor-acceptor-donor systems investigated do not show any ICT character.



**Chart 6.3** UV/vis absorption spectra of **36** in solvents with different dipole moments ( $c = 5 \cdot 10^{-5} \text{ mol l}^{-1}$ ).

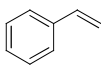
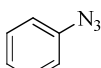

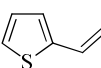
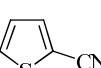

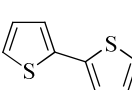
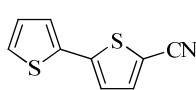
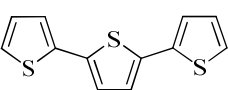
In the case of **40** and **41** one can find a maximum absorption at 337 and 339 nm, respectively, which is assigned to the bithiophene moieties. The second peak in the spectrum of **40** at 244 nm corresponds to the monothiophene connected at the 1-position of the triazole ring, whereas for **41** a slight shift to lower energies ( $\lambda_{\text{max}} = 256$  nm) and a band at 273 nm due to the ethylene-thienylene system is evident.

For bis-bithienyl-triazole **42** a maximum at 353 nm and a second peak at 240 nm were observed. The reason for the redshift of 14 nm compared to **40** or **41** is not really clear, because the same chromophores are operative, but could have to do with a beginning conjugation through the triazole unit.



**Chart 6.4** UV/vis absorption spectra of **40-42** in dichloromethane ( $c = 5 \cdot 10^{-5} \text{ mol l}^{-1}$ ).

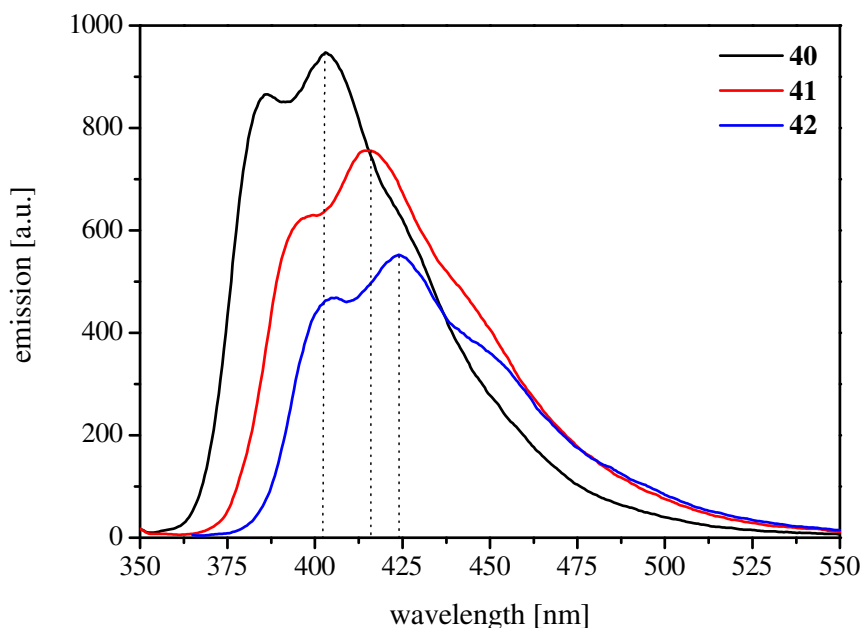
**Table 6.7** Optical properties of compounds **33**, **35**, **36**, **40-42** in comparison with oligothiophenes in dichloromethane.

Compound	$\lambda^{\text{abs}}$ [nm] <sup>(a)</sup> (lg $\epsilon$ )	$\Delta E_{\text{opt}}$ [eV] <sup>(b)</sup>
<b>33</b>	250 (4.37)	4.03
<b>35</b>	248 (4.12), 256 (4.12), 279 (4.23)	3.92
<b>36</b>	250 (4.16), 256 (4.16), 279 (4.22)	3.71
<b>39</b>	230 (4.27), 256 (4.27)	4.04
<b>40</b>	244 (4.17), 337 (4.44)	3.22
<b>41</b>	256 (4.14), 273 (4.06), 339 (4.31)	3.19
<b>42</b>	240 (4.18), 353 (4.49)	3.11
	246 <sup>c, 19</sup>	-
	250 <sup>d, 20</sup>	-
	243 <sup>16</sup>	-
	276 <sup>d, 21</sup>	-
	242 260 <sup>d, 22</sup>	-
	244 <sup>d, 21</sup>	-
	302 <sup>16</sup>	-
	331 <sup>e, 23</sup>	-
	355 <sup>16</sup>	-

<sup>a</sup>  $c = 5 \cdot 10^{-5}$  mol l<sup>-1</sup> in dichloromethane, maxima in italics, <sup>b</sup> determined from the onset of the absorption at the lower energy band edge, <sup>c</sup> in cyclohexane, <sup>d</sup> in ethanol, <sup>e</sup> in toluene.

### 6.3.2 Fluorescence Spectroscopy

Corrected spectra of triazoles **40**, **41** and **42** are displayed in Chart 6.5. They were measured in dichloromethane at room temperature ( $c = 10^{-6}$  mol l $^{-1}$  for **40** and **41**,  $5 \cdot 10^{-7}$  mol l $^{-1}$  for **42**). Emission maxima, quantum yields and Stokes shifts are summarized in Table 6.8.



**Chart 6.5** Emission spectra of **40-42** measured in dichloromethane.

Fluorescence spectra of the investigated compounds show structured bands due to vibronic splitting. This indicates a rather stiff structure of the excited state. The further redshift of the emission maximum of **42** in comparison to **40** and **41** leads to the same assumption than the observations in UV/vis for this class of compounds (see 6.3.1). There should be some communication inside the molecule going through the triazole ring.

The Stokes shifts of 4 744 to 5 344 cm $^{-1}$  were determined as the difference of the absorption maximum at the lowest energy and emission maximum with the highest energy. This points out that the molecules are less rigid in the ground state and with respect to electronic and structural properties some nuclear reorganization takes place after excitation prior to emission. This behavior is comparable to unsubstituted oligothiophenes.<sup>24</sup>

**Table 6.8** Fluorescence data of **40-42** in dichloromethane.

Compound	$\lambda_{\text{max}}^{\text{em}}$ [nm]	$\phi$ [%] <sup>c</sup>	Stokes Shift [cm <sup>-1</sup> ] <sup>d</sup>
<b>40</b> <sup>a</sup>	403	6	4 860
<b>41</b> <sup>a</sup>	414	10	5 344
<b>42</b> <sup>b</sup>	424	14	4 744

<sup>a</sup> excitation wavelength 340 nm, <sup>b</sup> excitation wavelength 353 nm, <sup>c</sup> quantum yields determined with respect to DPA<sup>25</sup>, <sup>d</sup> Stokes shift is given for the 0→0\* transition ( $\Delta\nu = \nu_{\text{max}}^{\text{abs}} - \nu_{\text{max}}^{\text{em}}$ ).

Fluorescence quantum yields of 6 to 14 % in the row **40**, **41** and **42** are rather high for bithiophenes (1.8 %) and increase with increasing molecular size (and conjugation).<sup>26</sup> Obviously, the triazole ring stabilizes the excited state decreasing the probability of non-radiative deactivation.

### 6.3.3 Cyclic Voltammetry of Selected Co-Oligomers

Cyclic voltammograms (CV) of triazoles **33**, **35**, **36**, **40-42** and unsubstituted oligothiophenes **2T**, **3T** and **4T** were determined in dichloromethane ( $c = 5 \cdot 10^{-3} \text{ mol l}^{-1}$ ) using tetrabutylammonium hexafluorophosphate (TBAHFP) as the supporting salt. Because of the low solubility of **42** in dichloromethane the concentration was decreased to  $5 \cdot 10^{-4} \text{ mol l}^{-1}$ . Oxidation potentials are given *versus* the internal standard ferrocene/ferricenium (Fc/ Fc<sup>+</sup>) in Table 6.9. All compounds showed irreversible redox processes, therefore,  $E^\circ$  was determined at  $I_0 = 0.855 \times I_p$ .<sup>27</sup> HOMO and LUMO energy levels are standardized to the ferrocene/ferricenium couple which has a calculated absolute energy of -5.10 eV.<sup>28</sup>

**Table 6.9** Electrochemical properties of triazoles **33**, **35**, **36**, **40–42** in comparison with oligothiophenes **2T–4T** in dichloromethane ( $c$   $5 \cdot 10^{-3}$  mol  $\text{l}^{-1}$  for **33–40**, and  $c$   $5 \cdot 10^{-4}$  mol  $\text{l}^{-1}$  for **41**).

Monomer			Polymer		
Compound	$E^{\circ}_{\text{ox}}$ [V] <sup>a</sup>	HOMO [eV]	$E^{\text{p}}_{\text{c}}$ [V]	$E^{\text{p}}_{\text{c}}$ [V]	$E_{\text{onset}}$ [V]
<b>33</b>	1.45	-6.21	[b]	[b]	b
<b>35</b>	1.13	-6.12	[b]	[b]	b
<b>36</b>	1.15	-6.17	0.60	0.50	0.33
<b>39</b>	1.23	-6.41	[b]	[b]	b
<b>40</b>	0.71	-5.73	0.28	0.16	-0.05
<b>41</b>	0.89	-5.91	0.68	0.27	0.34
<b>42</b>	0.69	-5.74	0.60	0.50	-0.05
<b>2T</b>	0.90	-5.87	0.55	-0.11	0.20
			0.94	0.13	
<b>3T</b>	0.72	-5.61	0.52	-0.08	0.20
			0.92		
<b>4T</b>	0.50	-5.47	n.d.	n.d.	n.d.

<sup>a</sup> irreversible redox process,  $E^{\circ}_{\text{ox}}$  determined at  $I_0 = 0.855 \times I_p^{27}$ ; <sup>b</sup> no polymerization observed.

The CV of **33** shows one irreversible oxidation wave peaking at 1.45 V indicating the formation of a radical cation in the phenylene vinylene moiety. As expected, no polymerization could be observed. No reduction wave for the triazole could be determined in the potential window of the electrolyte (-2.2 V to 1.5 V).

For thiophene-substituted triazoles **35** and **36** an irreversible oxidation wave at 1.16 V and 1.12 V, respectively, was determined which correspond to the formation of a radical cation of the thiophene subunit. In derivative **39** the oxidation potential is observed at significantly higher potentials (1.25 V). This means that in compounds **35** and **36** radical cations of the 2-ethenylthienyl subunit are formed, whereas in 3-thienyl derivative **39** only

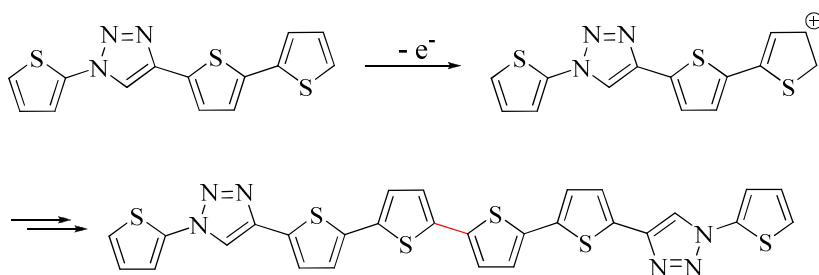


the thiophene ring is oxidized, because there is low conjugation with the double bond due to the 3-substitution.

Compounds **35** and **39** did not polymerize during the CV, even after 30 cycles. The oxidation potential is too high and only decomposition was observed. For triazole **36** a thin oligomer- or polymer film was formed on the platinum electrode. For the polymer of 2-thienyl derivative **36** an oxidation wave at 0.60 V was observed, which is considerably lower than this of the monomer unit indicating formation of oligomers/ polymers with extended conjugation.

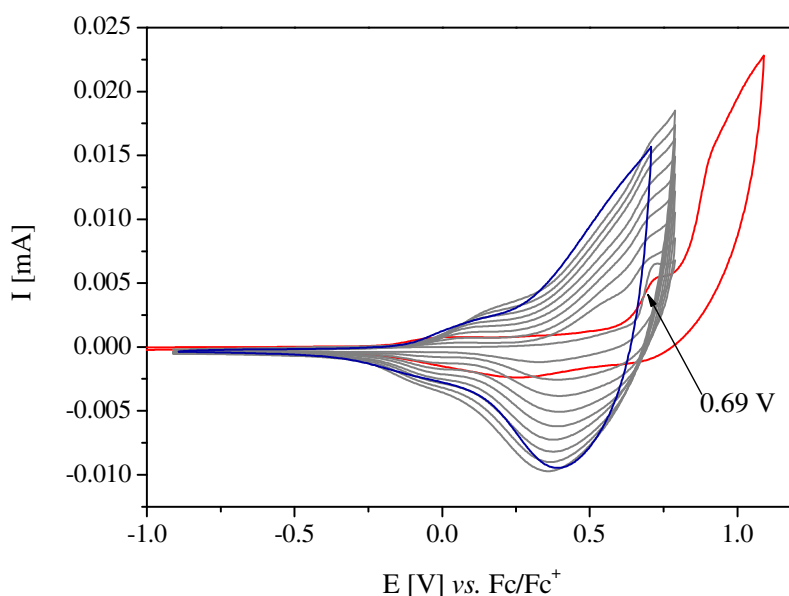
Co-oligomers containing one or two bithiophene subunits also show an interruption of the conjugated system due to the triazole ring. For triazole **40** an oxidation wave at 0.71 V was determined which is due to the formation of radical cations of the 5-ethenyl-2,2'-bithiophene subunit. This potential is comparable to the oxidation potential of terthiophene (**3T**,  $E^{\circ}_{\text{ox}} = 0.72$  V), but not for bithiophene (**2T**,  $E^{\circ}_{\text{ox}} = 0.90$  V).

An irreversible oxidation wave at 0.89 V was determined for bithiophene-triazole **41**, which is comparable to the oxidation potential of bithiophene (**2T**,  $E^{\circ}_{\text{ox}} = 0.90$  V). Therefore, the conjugated system seems to be interrupted at the connection point of the bithiophene and the triazole ring which was already indicated by optical investigations (UV/vis and fluorescence). For compounds **40** and **41** the formation of an oligomer- or polymer film on the working electrode could be observed. After washing the films, which were formed in 30 cycles the redox properties were determined by CV in dichloromethane free of monomer. CVs of the films indicated that only a dimer was formed. The polymer film of **40** showed a much lower potential ( $E^{\circ}_{\text{ox}} = 0.28$  V) than **41** ( $E^{\circ}_{\text{ox}} = 0.68$  V). This is due to the longer conjugated system, which is formed starting from **40**. During oxidation in the CV, the ethenyl bithienyl subunit is oxidized to a radical cation and reacts with another radical cation. The dimerization is taking place between two of these ethenyl bithienyl subunits of two molecules (Scheme 6.14). In **40**, a diethenyl quaterthiophene is formed and oxidized during the characterization of the film. Films of **41** contain only quaterthiophene units, which were formed during the electronical oligomerization. The oxidation potential for this film is comparable to the oxidation potential of the unsubstituted quaterthiophene (**4T**) in solution.



**Scheme 6.14** Electrochemical formation of a stable dimer of triazole **40**.

For monomer **42**, the first scan is shown in red in Chart 6.6, consecutive scans in gray and the CV of the resulting polymer film in blue which is quite typical for polythiophenes. The oxidation wave at 0.69 V is comparable to the oxidation potential of terthiophene (**3T**,  $E^\circ = 0.72$  V). Despite of the lower concentration polymerization of **42** was facile and led to a well conducting red film. Because of similar oxidation potentials for both bithienyl subunits in **42** formation of higher oligomers or polymers can be expected. The onset of the oxidation of polymer films of triazoles **40-42** start at -0.17 V. Therefore, comparable electronic structures in the polymers are responsible for redox behavior.



**Chart 6.6** Cyclic voltammetry of bithienyl-triazole **42** in dichloromethane/  $n\text{Bu}_4\text{NPF}_6$  (0.1 M) vs.  $\text{Fc}/\text{Fc}^+$  at 100 mV/s (red – monomer, gray – during polymerization, blue – polymer film).

### 6.3.4 Experimental and Theoretical Investigations into HOMO and LUMO Levels

In Chart 6.7, a HOMO- LUMO energy diagram is given for the investigated structures. Values of the HOMO were calculated from CVs, the LUMOs are determined as the difference of the HOMO energy and the optical band gap, which is determined from the absorption spectra. Band gaps could not be estimated by CV, because no reduction waves were visible in the investigated potential range.

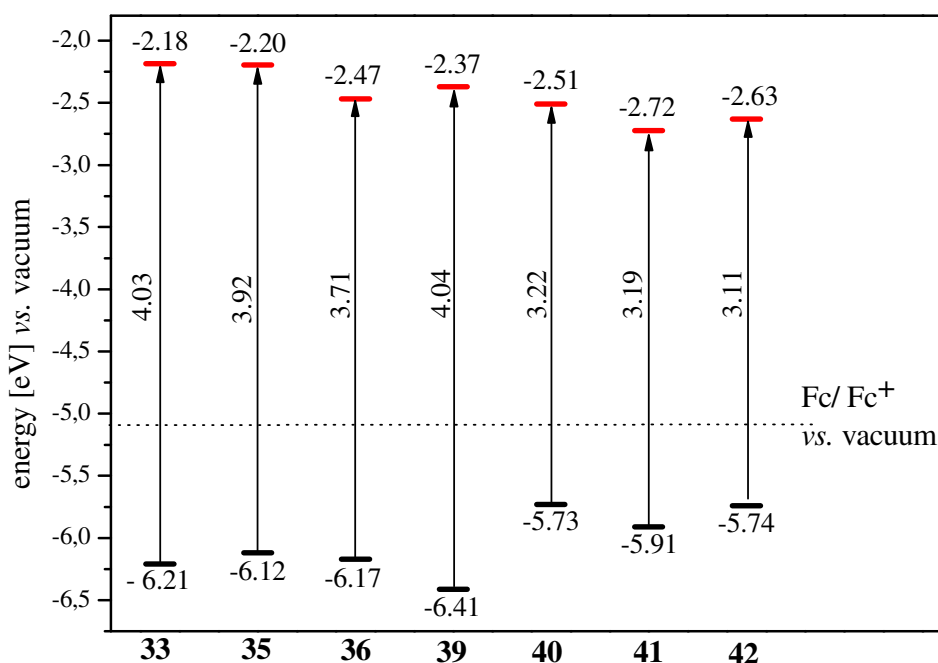
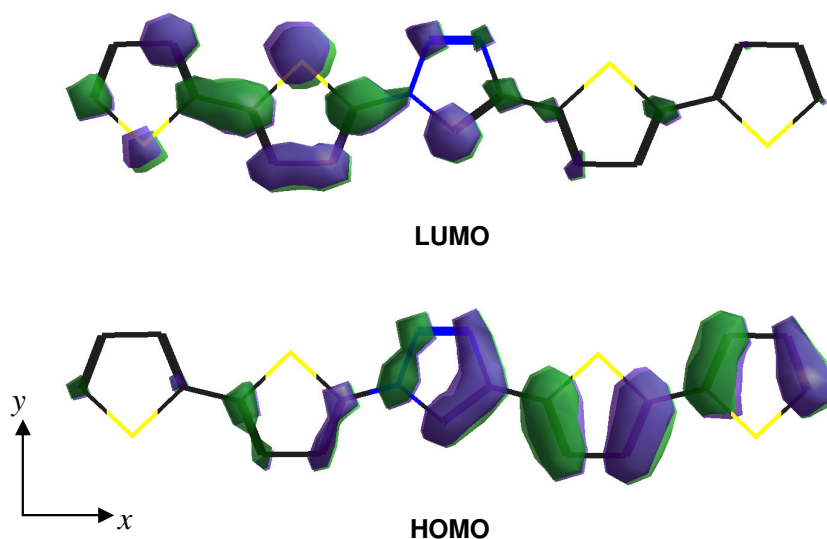


Chart 6.7 HOMO- LUMO energy diagram of triazoles **33**, **35**, **36**, **39**- **42**.

It can be seen clearly, that the HOMO-LUMO band gap decreases with increasing chain length of the oligothiophene units which is mainly due to a constant lowering of the HOMO energy levels. For compounds **36** and **41** a slight increase of the LUMO levels can be observed in comparison to **35** and **40**, respectively. This is caused by the triazole moiety which is connected *via* nitrogen as acceptor in 2-position of the thiophene subunit. Therein, the increase of the oligothiophene unit from mono- to bithienyl, in **36** and **41**, causes a further slight increase of the LUMO level.

To proof the finding, that the triazole ring rather interrupts the conjugation in the thiophene 1,2,3-triazole co-oligomers, AM1 calculations of choosen examples were

prepared. Herein, theoretical electron density distribution of the HOMO and LUMO levels for bithienyl-triazole **42** in the gas phase is shown in Chart 6.8.



**Chart 6.8** Calculated HOMO and LUMO for bithienyl-triazol **42** in gas phase.

The HOMO is located on the moiety with the longest conjugation path which is the 5-ethenyl-2,2'-bithiophene unit, whereas electron density in the LUMO is shifted to the moiety with poorer conjugation. The HOMOs are principally composed of C=C bonds, aligned predominantly along the *y*-axis. The LUMOs are principally composed of inter-ring formal C-C single bonds, the heteroatoms, and formally single intra-ring C-C bonds, all aligned predominantly along the *x*-axis. The wavefunction in the triazole ring has two nodal planes between N1 and C5, and N3 and C4, respectively. This leads to a decreased conjugation in ground state.

In co-oligomers with mixed building blocks (mono- and bithiophenes) no clear difference can be found. In triazole **41** the HOMO is not only localized in one part of the molecule, but the LUMO was localized in the bithiophene subunit.

According to the AM1 calculations of triazole **40** the HOMO was located at the 5-ethenyl-2,2'-bithiophene moiety, whereas the LUMO was distributed over the entire molecule.

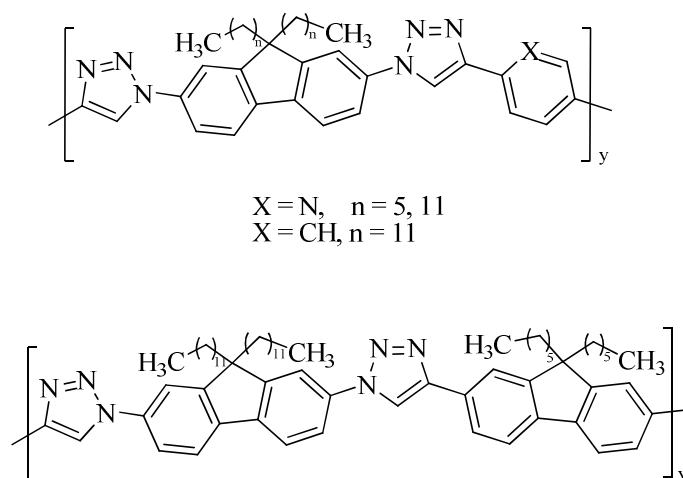
## 6.4 Conclusion

To synthesize thienyl azides a copper(I)-catalyzed procedure was applied. Unfortunately, the resulting 2-azidothiophene **30** was not stable under these reaction conditions (Scheme 6.7). To overcome this inherent instability and work-up problems a three-component one-pot procedure was developed in which halogenated thiophenes, sodium azide and terminal ethynyl thiophenes were coupled *via* copper(I) catalysis to produce novel 1,4-disubstituted 1,2,3-triazoles containing thienyl moieties in good to excellent yields (Table 6.4).

Extension of this protocol to dihalogenated and/ or bisethynyl thiophenes led in low or no conversion. Therefore, synthesis of higher oligomers and polymers, containing thiophene subunits as donors and triazole rings as acceptors, was impossible under these reaction conditions.

Spectroscopic and electronic properties of selected compounds were investigated and discussed. They led into the assumption that there is no conjugation going through the triazole ring. The substituents at the nitrogen heterocycle are electronically isolated and besides no intramolecular charge transfer could be observed for **35**. The missing of a conjugation path through 1,2,3-triazole was confirmed by theoretical calculations of HOMOs and LUMOs (Chart 6.8).

In 2005, Maarseveen *et al.* published synthesis and optical characterization of 1,2,3-triazole containing co-polymers (Scheme 6.15).<sup>29</sup> They suggested that there is no interaction between the various moieties of the polymer, thus, also in this case the triazole ring interrupts conjugation.



**Scheme 6.15** Conjugated polymers by “click”-chemistry.

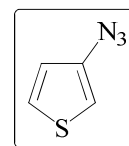
## 6.5 Experimental Part

*Thin layer chromatography* (TLC) was carried out on Silica Gel 60 F<sub>254</sub> aluminium plates (Merck). Developed plates were dried and examined under a UV lamp. *Preparative column chromatography* was carried out on glass columns of different diameters packed with silica gel Merck 60 (40-63  $\mu\text{m}$ ). *Gas chromatography* (GC) was carried out using a Varian CP-3800 gas chromatograph. Helium 5.0 was used as carrying gas, signals were examined by a flame-ionization detector (FID). *Gas chromatography-Mass spectrometry* (GC-MS) measurements were executed with a Varian 3800. Helium 5.0 was used as carrying gas, Mass spectra were recorded on a Varian Saturn 2000. Ions were generated by electron impact (EI). *Melting points* were determined in a Büchi B-545 apparatus and are uncorrected. *NMR spectra* were recorded in  $\text{CDCl}_3$ , *d*6-DMSO or *d*8-THF on a Bruker AMX 400 at 400 MHz ( $^1\text{H}$  nuclei) and 100 MHz ( $^{13}\text{C}$  nuclei), respectively. Chemical shifts are denoted in  $\delta$  unit (ppm), and are referenced to the solvent signal (7.26 ppm for  $\text{CDCl}_3$ , 2.50 ppm for *d*6-DMSO and 1.73 for *d*8-THF). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). *Mass spectra* were measured at Finnigan MAT, SSQ 7000 via CI and Bruker Daltonics REFLEX III via MALDI-TOF. *Elemental analysis* for C, H and N were determined at Elementar Vario EL and for S at Carlo Erba 1104. *High resolution mass* was measured at a micrOTOF-Q 43 with electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI). *UV/vis* spectra were taken on a Perkin-Elmer Lambda 19 in 1 cm cuvettes. *Fluorescence* spectra were measured with a Perkin-Elmer LS 55 in 1 cm cuvettes. Fluorescence quantum yields were determined with respect to 9,10-diphenylanthracene (DPA,  $\phi = 0.9$  in dichloromethane).<sup>25</sup> *Cyclic voltammetry* experiments were performed with a computer-controlled EG&G PAR 273 potentiostat in a three-electrode single-compartment cell (2 mL). The platinum working electrode consists of a platinum wire sealed in a soft glass tube with a surface of  $A = 0.785 \text{ mm}^2$ , which was polished down to 0.5  $\mu\text{m}$  with Buehler polishing paste prior to use. The counter electrode consists of a platinum wire and the reference electrode was an Ag/AgCl secondary electrode. All potential were internally referenced to the ferrocene/ferricenium couple. For the measurements the electroactive species were used in freshly distilled and deaired dichloromethane and 0.1 M tetrabutylammonium hexafluorophosphate ( $n\text{Bu}_4\text{NPF}_6$ , Fluka) which was twice recrystallized from ethanol and dried under vacuum prior to use.

All reactions were carried out under an inert atmosphere of argon. Azidobenzene<sup>11</sup>, 2-iodo-3-methylthiophene<sup>30</sup>, 2-iodo-5-methylthiophene<sup>31</sup>, 5'-iodo-5,5''-bis-trimethylsilanyl-[2,2';3',2'']terthiophene<sup>32</sup>, 5,5''-bis-trimethylsilanyl-5'-trimethylsilanylethynyl-[2,2';3',2'']terthiophene<sup>32</sup>, 5,5''-diiodo-2,2':3',2''-terthiophene<sup>33</sup>, 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene were synthesized according to Miller<sup>34</sup>, 5-formyl-2,2'-bithiophene<sup>35</sup>, 2-iodo-3-thiophene carbonyl chloride<sup>36</sup>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>37</sup> were synthesized as described in literature. The following reactants and solvents were purified and dried by standardized procedures: 3-Iodothiophene (VWR), 3-bromothiophene (VWR), 2-iodothiophene (VWR), 2-bromothiophene (VWR), iodobenzene (VWR), bromobenzene (VWR), 1,4-diiodobenzene (VWR), 1,4-bibromobenzene (VWR), 2,5-diiodothiophene (Alfa Aesar), phenylacetylene (VWR), trimethylsilanyl acetylene (Sigma Aldrich), ethyl-2-thiophene carboxylate (Alfa Aesar), sodium azide (VWR), sodium ascorbate (ABCR), sodium sulfate (anhydrous, Merck), sodium thiosulfate (VWR), sodium bicarbonate (VWR), potassium carbonate (VWR), *N*-iodosuccinimide (VWR), copper(I) iodide (VWR), iodine (doubly sublimed, VWR), *N,N'*-dimethylethylenediamine (DMEDA, Acros), diisopropylamine (VWR), tetrabromocarbon (sublimed, VWR), triphenyl phosphine (VWR), *n*-butyl lithium (15 mol-% in *n*-hexane, VWR), trifluoro acetic acid (VWR), ammonium hydroxide (25 %, VWR), hydrochloric acid (VWR), dichloromethane (VWR), chloroform (VWR), diethyl ether (VWR), ethyl acetate (VWR), *n*-hexane (VWR), petrol ether (VWR), methanol (VWR), ethanol (VWR), THF (distilled, VWR), pyridine (VWR) and DMSO (VWR) were used as received.

### 3-Azidothiophene (32)

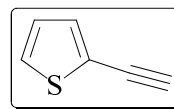
In a mixture of ethanol (2.8 mL) and water (1.2 mL) 3-iodothiophene (0.22 mL, 2 mmol), copper(I) iodide (38 mg, 0.2 mmol), sodium ascorbate (20 mg, 0.1 mmol), sodium azide (0.26 g, 4 mmol) and DMEDA (0.03 mL, 0.3 mmol) were dissolved and refluxed under argon until TLC (silica/ DCM) showed complete consumption of the starting material. After five hours the cooled brown mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (2 times, 10 mL). After washing the organic phases with brine (15 mL) they were dried over sodium sulfate and evaporated to dryness in vacuum at room temperature. Because of the instability of the product on silica it was used without further purification. The NMR data was consistent with literature<sup>38</sup>.



**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 6.79 (1H, dd, *J* 1.5 and 3.2), 6.82 (1H, dd, *J* 1.4 and 5.2), 7.30 (1H, dd, *J* 3.2 and 5.1).

### 2-Ethynylthiophene

In dry diisopropylamine (20 mL) copper(I) iodide (36 mg, 0.2 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (280 mg, 0.4 mmol) and 2-bromothiophene (1.94 mL, 20 mmol) were dissolved. Trimethylsilyl acetylene (5.8 mL, 42 mmol) was added. After two hours at 60 °C the mixture was poured into 1N hydrochloric acid at 0 °C. The aqueous solution was extracted three times with 100 mL petrol ether. The dried and concentrated organic phases were filtered through a plug of silica. Removal of the solvent gave pure 1-(trimethylsilyl)-2-(2'-thienyl)-acetylene in 3.57 g (20 mmol, 99 %) as bright yellow oil. The analytical data correspond to the literature.<sup>30</sup>



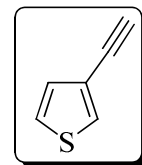
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.22- 7.24 (2H, m), 6.95 (1H, dd, *J* 3.7 and 5.1), 0.26 (9H, s).

In order to remove the TMS-group, intermediate thiophene (1 eq.) and potassium carbonate (2 eq.) were dissolved in methanol and stirred for half an hour. Water was added and the product extracted three times with diethyl ether. The dried organic phases were concentrated in vacuum at room temperature to give 2-ethynylthiophene (108 mg, 1 mmol, 99 %). The analytical data correspond to literature.<sup>30</sup>

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.27 (1H, dd, *J* 1.0 and 3.7), 7.26 (1H, dd, *J* 1.1 and 5.2), 6.97 (1H, dd, *J* 3.6 and 5.2), 3.33 (1H, s).

### 3-Ethynylthiophene

The same procedure as described for 2-ethynylthiophene was used starting from 3-bromothiophene (1.88 mL, 20 mmol). The raw material was purified by chromatography on silica (petrol ether) to give the product in 1.98 g (11 mmol, 55 %) as colorless oil. The analytical data correspond to literature.<sup>39</sup>

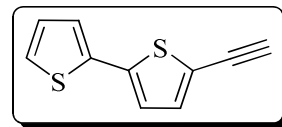


**<sup>1</sup>H-NMR** (1-(trimethylsilyl)-2-(3'-thienyl)-acetylene): (400 MHz, CDCl<sub>3</sub>) 7.48 (1H, dd, *J* 1.2 and 3.0), 7.24 (1H, dd, *J* 3.0 and 5.0), 7.13 (1H, dd, *J* 1.2 and 5.0), 0.25 (9H, s).



### 5-Ethynyl-2,2'-bithiophene

Tetrabromomethane (12.45 g, 37.5 mmol) was dissolved in dichloromethane (50 mL) at 0 °C and triphenyl phosphine (19.67 g, 75 mmol) added batchwise. The solution was stirred for 30 minutes at room temperature before 5-formyl-2,2'-bithiophene (2.91 g, 15 mmol), which was synthesized according to literature<sup>35</sup>, was added. The solution was cooled in an ice bath to keep a mild reflux. The suspension was stirred for one hour at room temperature before water (100 mL) was added. After ten minutes the aqueous phase was washed with dichloromethane. After evaporation of solvent the crude product was purified by column chromatography (dichloromethane/ petrol ether on silica) to yield the product in 3.94 g (11 mmol, 75 %).<sup>40</sup> Treatment of the 5-dibromoethenyl-2,2'-bithiophene with a threefold excess of *n*-butyl lithium in diethyl ether at -78 °C and following quenching with water the organic layer was extracted with diethyl ether. The dried organic phases were concentrated and the crude product purified by column chromatography on silica (petrol ether) to obtain acetylene in 2.12 g (11 mmol, 99 %). Analytical data correspond to literature.<sup>40</sup>

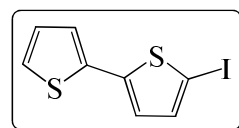


**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.24 (1H, dd, *J* 1.1 and 5.1), 7.19 (1H, dd, *J* 1.2 and 3.7), 7.18 (1H, d, *J* 3.9), 7.02 (1H, dd, *J* 3.6 and 5.1), 7.02 (1H, d, *J* 3.8), 3.39 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 133.9, 127.9, 125.2, 124.5, 123.3, 120.6, 100.0, 82.1.

### 5'-Iodo-2,2'-bithiophene

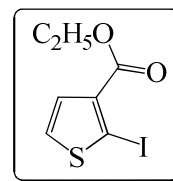
In 60 ml dry THF 2,2'-bithiophene (3.32 g, 20 mmol) was dissolved at -78 °C and *n*-butyl lithium (15 mol-% in *n*-hexane, 12.6 mL, 20 mmol) was added dropwise. The lithium component was immediately formed and quenched with an iodine solution (5.08 g, 20 mmol I<sub>2</sub> in 20 mL THF). After stirring for one hour at -78 °C, the mixture was quenched with water and extracted several times with diethyl ether. The organic phases were washed with saturated sodium thiosulfate solution and dried over sodium sulfate. After removing the solvent the product was obtained in 5.26 g (18 mmol, 90 %). The NMR showed a pure product.<sup>41</sup>



**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.22 (1H, dd, *J* 1.1 and 5.1), 7.16 (1H, d, *J* 3.8), 7.12 (1H, dd, *J* 1.1 and 3.6), 7.01 (1H, dd, *J* 3.7 and 5.0), 6.85 (1H, d, *J* 3.8).

**Ethyl-2-iodo-3-thiophenecarboxylate**

2-Iodo-3-thiophene carbonyl chloride was synthesized according to literature.<sup>36</sup> The raw material was mixed with ethanol (1.16 mL, 20 mmol) in pyridine (4 mL). The mixture was heated at reflux for six hours before it was cooled down and poured, under stirring, into 30 g ice containing 40 mL of 1N hydrochloric acid. The aqueous phase was extracted several times with diethyl ether and the organic phases were washed several times with sodium bicarbonate solution. The dried solution was concentrated and purified by chromatography (petrol ether/ ethyl acetate 9:1 on silica) to obtain the desired product.<sup>42</sup>



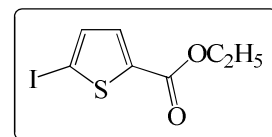
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.41 (1H, d, *J* 5.6), 7.33 (1H, d, *J* 5.6), 4.33 (2H, q, *J* 7.1), 1.36 (3H, t, *J* 7.1).

The overall yield starting from thiophene-3-carboxylic acid is ~40 %. In order to re-isolate the unreacted 2-iodo-3-thiophenecarboxylic acid the aqueous solution was acidified with 2N hydrochloric acid and extracted with diethyl ether. After drying, removing of the solvent and recrystallization pure 2-iodo-3-thiophene carboxylic acid could be obtained.

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.44 (1H, d, *J* 5.6), 7.40 (1H, d, *J* 5.6), 2.52 (vbs).

**Ethyl-2-iodo-5-thiophenecarboxylate**

In 40 mL of chloroform ethyl-2-thiophene carboxylate (1.56 g, 10 mmol) was dissolved. In the dark under an inert atmosphere, *N*-iodosuccinimide (2.48 g, 11 mmol) and trifluoroacetic acid (1 mL, 13 mmol) were added. After stirring at room temperature for seven days, the solution was concentrated and 50 mL of chloroform were added. The solution was washed with sodium thiosulfate solution and dried. The concentrated material was purified by column chromatography (petrol ether/ ethyl acetate 9:1 on silica) to obtain the product in 1.50 g (5 mmol, 53 %). The analytical data correspond to literature.<sup>42</sup>



**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.42 (1H, d, *J* 3.9), 7.25 (1H, d, *J* 3.9), 4.33 (2H, q, *J* 7.1), 1.36 (3H, t, *J* 7.1).

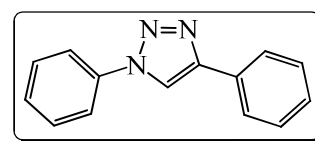
**General procedure for the formation of 1,4-disubstituted 1*H*-1,2,3-triazoles**

Halide (1 eq.) and terminal acetylene (1 eq.) were dissolved in an ethanol/water mixture (4mL, 7:3). After adding sodium azide (2 eq.), sodium ascorbate (10 mol-%), *N,N'*-dimethylethylenediamine (DMEDA, 20 mol-%) and copper(I) iodide (10 mol-%) the mix-

ture was stirred in a closed Schlenk-tube at 50 °C for about 15 hours. The cooled mixture was poured into 50 mL ice water. If the product precipitates (method A) it was filtered off and washed with NH<sub>4</sub>OH (25 %) and water. The dried product was purified by column chromatography. The non-precipitating products (method B) were treated with 10 mL NH<sub>4</sub>OH (25 %). The aqueous solution was washed three times with 50 mL ethyl acetate. After drying the organic phase over sodium sulfate the crude product was concentrated at the rotary evaporator and purified on silica.

### 1,4-Diphenyl-1*H*-1,2,3-triazole (**33**)

Iodobenzene (0.11 mL, 1 mmol) or bromobenzene (0.11 mL, 1 mmol), phenylacetylene (0.11 mL, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 µL, 0.2 mmol). Method A gave triazole **33** in 199.1 mg (900 µmol, 90 %) from iodobenzene and in 92.9 mg (420 µmol, 42 %) from bromobenzene as a white solid. Changing solvent to DMSO/water (9:1) gave **33** in 219.0 mg (990 µmol, 99 %) from iodothiophene at 60 °C and bromobenzene at 95 °C, respectively. The analytical data correspond to literature.<sup>14</sup>

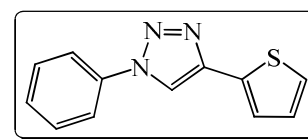


**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.37 (1H, m), 7.47 (3H, m), 7.56 (2H, m), 7.80 (2H, m), 7.92 (2H, m), 8.15 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 120.6, 125.9, 128.4, 128.8, 128.9, 129.8.

### 1-Phenyl-4-thien-2-yl-1*H*-1,2,3-triazole (**34**)

Iodobenzene (0.11 mL, 1 mmol), 2-ethynylthiophene (0.11 g, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 µL, 0.2 mmol). Method A gave the colorless product in 213.6 mg (940 µmol, 94 %). mp 136-137 °C (from EE/ *n*-hexane);



**Elemental analysis:** C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>S requires C, 63.41; H, 3.99; N, 18.49; S, 14.11 % ; found: C, 63.40; H, 4.07; N, 18.44; S, 14.43 %;

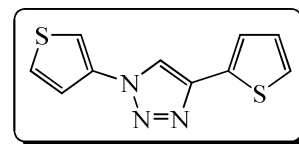
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.12 (1H, dd, *J* 3.6 and 5.1), 7.35 (1H, dd, *J* 1.1 and 5.1), 7.47 (1H, t, *J* 7.3), 7.49 (1H, dd, *J* 1.1 and 3.3), 7.56 (2H, t, *J* 7.7), 7.78 (2H, d, *J* 7.4), 8.11 (1H, s);

**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{CDCl}_3$ ) 117.06, 120.57, 124.56, 125.38, 127.71, 128.88, 129.80, 132.50, 136.93, 143.52;

**MS (CI):**  $m/z$  ( $\text{M}+\text{H}$ ) = 228, ( $\text{M}-\text{N}_2$ ) = 199.

#### 4-Thien-2-yl-1-thien-3-yl-1*H*-1,2,3-triazole (35)

3-Iodothiophene (0.13 mL, 1 mmol) or 3-bromothiophene (0.10 mL, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu\text{L}$ , 0.2 mmol). According to method A the off-white product was obtained in 230.7 mg (990  $\mu\text{mol}$ , 99 %) from 3-iodothiophene and 109.5 mg (470  $\mu\text{mol}$ , 47 %) from 3-bromothiophene.



**mp** 157-158  $^{\circ}\text{C}$  (from EE/ *n*-hexane);

**$^1\text{H}$ -NMR:** (400 MHz,  $\text{CDCl}_3$ ) 7.14 (1H, dd,  $J$  3.6 and 5.1), 7.37 (1H, dd,  $J$  1.1 and 5.1), 7.49 (1H, dd,  $J$  1.1 and 3.5), 7.51 (1H, dd,  $J$  2.5 and 5.6), 7.53 (1H, dd,  $J$  1.6 and 5.3), 7.62 (1H, dd,  $J$  1.6 and 3.1), 8.04 (1H, s);

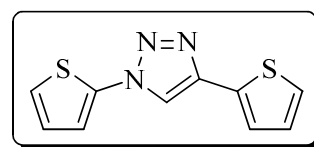
**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{CDCl}_3$ ) 100.00, 114.31, 117.41, 120.83, 124.61, 125.42, 127.35, 127.71;

**MS (CI):**  $m/z$  ( $\text{M}+\text{H}$ ) = 234, ( $\text{M}-\text{N}_2$ ) = 206, ( $\text{M}-\text{C}_4\text{H}_3\text{N}_2\text{S}$ ) = 122;

**HRMS (ESI):**  $m/z$  ( $\text{M}+\text{Na}$ ) = 255.9981 ( $\text{C}_{10}\text{H}_7\text{N}_3\text{NaS}_2$  requires 255.9974), ( $\text{M}+\text{H}$ ) = 234.0157 ( $\text{C}_{10}\text{H}_8\text{N}_3\text{S}_2$  requires 234.0154).

#### 1,4-Dithien-2-yl-1*H*-1,2,3-triazole (36)

2-Iodothiophene (0.11 mL, 1 mmol) or 2-bromothiophene (0.10 mL, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu\text{L}$ , 0.2 mmol). Method A gave the white product in 160.8 mg (690  $\mu\text{mol}$ , 69 %) from 2-iodothiophene and 186.4 mg (800  $\mu\text{mol}$ , 80 %) from 2-bromothiophene.



**mp** 125-126  $^{\circ}\text{C}$  (from toluene);

**Elemental analysis:**  $\text{C}_{10}\text{H}_7\text{N}_3\text{S}_2$  requires C, 51.48, H, 3.02, N, 18.01, S, 27.49 %; found: C, 51.54, H, 3.13, N, 17.92, S, 26.87 %;

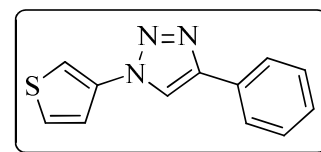
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.06 (1H, dd, *J* 3.8 and 5.5), 7.11 (1H, dd, *J* 3.6 and 5.1), 7.25 (1H, dd, *J* 1.4 and 5.5), 7.29 (1H, dd, *J* 1.4 and 3.8), 7.35 (1H, dd, *J* 1.1 and 5.1), 7.48 (1H, dd, *J* 1.1 and 3.6), 8.00 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 118.30, 118.35, 122.98, 124.80, 125.59, 126.29, 126.32, 132.04;

**MS (CI):** *m/z* (M+H) = 234, (M-N<sub>2</sub>) = 206.

#### 4-Phenyl-1-thien-3-yl-1*H*-1,2,3-triazole (37)

3-Iodothiophene (0.13 mL, 1 mmol), phenylacetylene (0.11 mL, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol),



DMEDA (20 μL, 0.2 mmol). Method A gave the pure off-white product in 186.1 mg (820 μmol, 82 %) from 3-iodothiophene and 145.3 mg (640 μmol, 64 %) from 3-bromothiophene.

**mp** 168- 169 °C (EE/ *n*-hexane);

**Elemental analysis:** C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>S requires C, 63.41, H, 3.99, N, 18.49, S, 14.11 %; found: C, 63.51, H, 4.15, N, 18.46, S, 14.35 %;

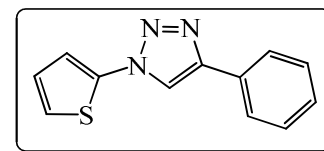
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.37 (1H, t, *J* 7.3), 7.48 (2H, t, *J* 7.7), 7.49 (1H, dd, *J* 3.3 and 5.4), 7.53 (1H, dd, *J* 1.5 and 5.3), 7.61 (1H, dd, *J* 1.4 and 3.2), 7.90 (2H, d, *J* 7.1), 8.10 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 114.14, 117.93, 120.85, 125.89, 127.29, 128.45, 128.92, 130.15, 148.01, 154.99;

**MS (CI):** *m/z* (M+H) = 228, (M-N<sub>2</sub>) = 199, (M-C<sub>4</sub>H<sub>3</sub>N<sub>2</sub>S) = 116.

#### 4-Phenyl-1-thien-2-yl-1*H*-1,2,3-triazole (38)

2-Iodothiophene (0.11 mL, 1 mmol) or 2 bromothiophene (0.10 mL, 1 mmol), phenylacetylene (0.11 mL, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol),



sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 μL, 0.2 mmol). According to method A the colorless product was obtained in 111.2 mg (490 μmol, 49 %) from 2-iodothiophene and 120.3 mg (530 μmol, 53 %) from 2-bromothiophene.

**mp** 140- 141 °C (from EE/ *n*-hexane)

**Elemental analysis:**  $C_{12}H_9N_3S$  requires C, 63.41, H, 3.99, N, 18.49, S, 14.11 %; found: C, 63.48, H, 4.03, N, 18.58, S, 13.92 %;

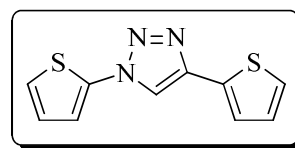
**$^1H$ -NMR:** (400 MHz,  $CDCl_3$ ) 7.07 (1H, dd,  $J$  1.4 and 5.5), 7.30 (1H, dd,  $J$  1.4 and 3.8), 7.39 (1H, t,  $J$  7.4), 7.47 (2H, t,  $J$  7.5), 7.89 (2H, d,  $J$  7.1), 8.10 (1H, s);

**$^{13}C$ -NMR:** (100 MHz,  $CDCl_3$ ) 118.18, 118.85, 122.83, 125.93, 126.28, 128.57, 128.93, 129.89, 138.43, 148.30;

**MS (CI):**  $m/z$  ( $M+H$ ) = 228, ( $M-N_2$ ) = 199.

#### 1,4-Dithien-3-yl-1H-1,2,3-triazole (39)

3-Iodothiophene (0.11 mL, 1 mmol), 3-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu$ L, 0.2 mmol). The product was obtained, according to method A, in 230.7 mg (990  $\mu$ mol, 99 %) from 3-iodothiophene.



**mp** 206- 207 °C (from EE);

**Elemental analysis:**  $C_{10}H_7N_3S_2$  requires C, 51.48, H, 3.02, N, 18.01, S, 27.49 %; found: C, 51.58, H, 3.11, N, 17.98, S, 27.73 %;

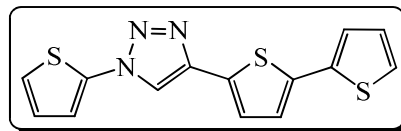
**$^1H$ -NMR:** (400 MHz,  $CDCl_3$ ) 7.42 (1H, dd,  $J$  3.0 and 5.0), 7.48 (1H, dd,  $J$  3.1 and 5.3), 7.51 (2H, m), 7.60 (1H, dd,  $J$  1.5 and 3.1), 7.76 (1H, dd,  $J$  1.2 and 3.0), 8.01 (1H, s);

**$^{13}C$ -NMR:** (100 MHz,  $CDCl_3$ ) 114.13, 117.73, 120.86, 121.63, 125.83, 126.51, 127.31;

**MS (CI):**  $m/z$  ( $M+H$ ) = 234, ( $M-N_2$ ) = 206, ( $M-C_4H_3N_2S$ ) = 122.

#### 4-(2,2'-Bithien-5-yl)-1-thien-2-yl-1H-1,2,3-triazole (40)

2-Iodothiophene (0.11 mL, 1 mmol), 5-ethynyl-2,2'-bithiophene (190 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu$ L, 0.2 mmol). The greenish-white product was obtained by method A in 195.3 mg (620  $\mu$ mol, 62 %).



**mp** 159- 160 °C decomp. (from toluene);

**Elemental analysis:**  $C_{14}H_9N_3S_3$  requires C, 53.31, H, 2.88, N, 13.32, S, 30.49 %; found: C, 53.27, H, 3.00, N, 13.24, S, 30.32 %;

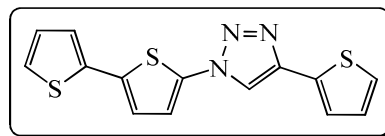
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.04 (1H, dd, *J* 3.8 and 5.2), 7.06 (1H, dd, *J* 3.7 and 5.6), 7.17 (1H, d, *J* 3.8), 7.23 (1H, dd, *J* 1.3 and 3.7), 7.24 (1H, dd, *J* 1.1 and 2.1), 7.26 (1H, m), 7.29 (1H, dd, *J* 1.4 and 3.8), 7.37 (1H, d, *J* 3.8), 8.00 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 18.16, 118.39, 123.04, 124.08, 124.23, 124.78, 125.38, 126.33, 127.95, 130.67, 136.99, 137.62, 143.11;

**MS (CI):** *m/z* (M+H) = 316, (M-N<sub>2</sub>) = 288.

#### 1-(2,2'-Bithien-5-yl)-4-thien-2-yl-1*H*-1,2,3-triazole (41)

5-Iodo-2,2'-bithiophene (317 mg, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 μL, 0.2 mmol). The pure greenish-white product was obtained by method A in 211.1 mg (670 μmol, 67 %).



**mp** 173-174 °C (from toluene);

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 7.06 (1H, dd, *J* 3.6 and 5.1), 7.09 (1H, d, *J* 4.0), 7.12 (1H, dd, *J* 3.6 and 5.1), 7.18 (1H, d, *J* 4.0), 7.23 (1H, dd, *J* 1.1 and 3.6), 7.29 (1H, dd, *J* 1.1 and 5.1), 7.36 (1H, dd, *J* 1.1 and 5.1), 7.48 (1H, dd, *J* 1.1 and 3.6), 8.02 (1H, s);

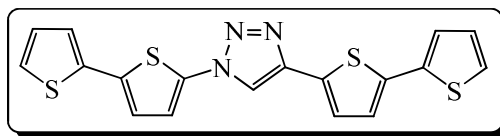
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 117.79, 118.45, 122.29, 124.64, 124.87, 125.50, 125.67, 127.76, 128.05, 131.95, 135.89;

**MS (CI):** *m/z* (M<sup>+</sup>) = 316, (M-N<sub>2</sub>) = 288;

**HRMS (ESI):** *m/z* (M+Na) = 337.9847 (C<sub>14</sub>H<sub>9</sub>N<sub>3</sub>NaS<sub>3</sub> requires 337.9851), (M+H) = 316.0026 (C<sub>14</sub>H<sub>10</sub>N<sub>3</sub>S<sub>3</sub> requires 316.0031).

#### 1,4-Di-2,2'-bithien-5-yl-1*H*-1,2,3-triazole (42)

5-Iodo-2,2'-bithiophene (0.92 g, 1 mmol), 5-ethynyl-2,2'-bithiophene (0.19 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 μL, 0.2 mmol). The pure orange product was obtained by method B in 131.3 mg (330 μmol, 33 %). The extraction with ethyl acetate failed because of the low solubility of the product. It was extracted with THF.



**mp** 235- 236 °C decomp. (from DCM/ petrol ether);

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>) 7.13 (1H, dd, *J* 3.6 and 5.0), 7.15 (1H, dd, *J* 3.6 and 5.1), 7.36 (1H, d, *J* 3.7), 7.37 (1H, d, *J* 3.2), 7.40 (1H, dd, *J* 0.9 and 3.5), 7.44 (1H, dd, *J* 1.0 and 3.6), 7.48 (1H, d, *J* 3.8), 7.54 (1H, d, *J* 4.0), 7.56 (1H, dd, *J* 0.9 and 5.1), 7.61 (1H, dd, *J* 1.0 and 5.1), 9.25 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, DMSO-*d*<sub>6</sub>) 115.79, 119.39, 119.96, 123.552, 124.97, 125.21, 125.60, 126.35, 126.97, 128.95, 129.02, 130.91, 134.14, 135.61, 135.90, 136.48, 136.86, 142.86;

**MS (CI):** *m/z* (M+H) = 399, (M-N<sub>2</sub>) = 371;

**HRMS (ESI):** *m/z* (M+Na) = 419.9716 (C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>NaS<sub>4</sub> requires 419.9728), (M+H) = 397.9907 (C<sub>18</sub>H<sub>12</sub>N<sub>3</sub>S<sub>4</sub> requires 397.9909).

### 1-(5-Methylthien-2-yl)-4-thien-2-yl-1*H*-1,2,3-triazole (43)

2-Methyl-5-iodothiophene (224 mg, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20 μL, 0.2 mmol). According to method A the pure white product was obtained in 168.0 mg (680 μmol, 68 %).

**mp** 112 °C decomp. (from methanol);

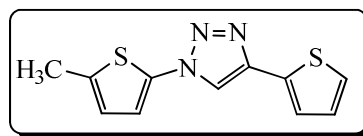
**Elemental analysis:** C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>S<sub>2</sub> requires C, 53.42, H, 3.67, N, 16.99 %, found: C, 53.17, H, 3.81, N, 16.76 %;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 2.52 (3H, d, *J* 1.0), 6.70 (1H, dd, *J* 1.1 and 3.7), 7.06 (1H, dd, *J* 3.7), 7.11 (1H, dd, *J* 3.6 and 5.1), 7.34 (1H, dd, *J* 1.1 and 5.1), 7.45 (1H, dd, *J* 1.1 and 3.6), 7.95 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 15.41, 18.08, 118.41, 124.05, 124.68, 125.48, 127.70, 132.19, 144.63, 160.35, 160.56;

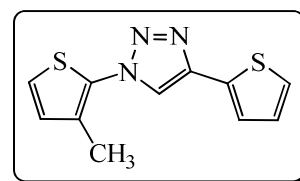
**MS (CI):** *m/z* (M+H) = 248, (M-N<sub>2</sub>) = 220;

**HRMS (ESI):** *m/z* (M+Na) = 270.0139 (C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>NaS<sub>2</sub> requires 270.0130), (M+H) = 248.0323 (C<sub>11</sub>H<sub>10</sub>N<sub>3</sub>S<sub>2</sub> requires 248.0311).



### 1-(3-Methylthien-2-yl)-4-thien-2-yl-1*H*-1,2,3-triazole (44)

2-Iodo-3-methylthiophene (224 mg, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I)





iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu$ L, 0.2 mmol). The product was obtained according to method B as an oil in 29.6 mg (120  $\mu$ mol, 12 %).

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 2.26 (3H, s), 6.91 (1H, d,  $J$  5.6), 7.12 (2H, dd,  $J$  3.6 and 5.1), 7.24 (1H, d,  $J$  5.5), 7.34 (1H, dd,  $J$  1.1 and 5.1), 7.46 (1H, dd,  $J$  1.0 and 3.6), 7.90 (1H, s);

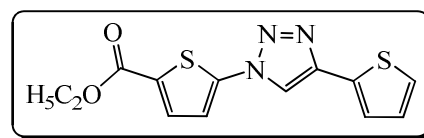
**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) 13.47, 121.12, 123.27, 124.67, 125.50, 127.74, 129.20, 132.26, 132.91, 142.89;

**MS (CI):**  $m/z$  ( $M+H$ ) = 248, ( $M-N_2$ ) = 219;

**HRMS (ESI):**  $m/z$  ( $M+Na$ ) = 270.0124 ( $\text{C}_{11}\text{H}_9\text{N}_3\text{NaS}_2$  requires 270.0130).

#### Ethyl 5-(4-thien-2-yl-1*H*-1,2,3-triazol-1-yl)thiophene-2-carboxylate (45)

Ethyl-2-iodo-5-thiophenecarboxylate (345 mg, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1



mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu$ L, 0.2 mmol). According to procedure B the product was obtained as a colorless solid in 186.1 mg (610  $\mu$ mol, 61 %).

**mp** 135  $^{\circ}\text{C}$  decomp. (from DCM/ petrol ether);

**Elemental analysis:**  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{S}_2$  requires C, 51.13, H, 3.63, N, 13.76, S, 21.00 %; found: C, 51.12, H, 3.71, N, 13.72, S, 21.07 %;

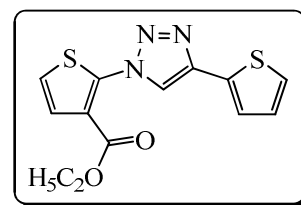
**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 1.40 (3H, t,  $J$  7.1), 4.39 (2H, q,  $J$  7.1), 7.13 (1H, dd,  $J$  3.6 and 5.1), 7.28 (1H, d,  $J$  4.1), 7.37 (1H, dd,  $J$  1.1 and 5.1), 7.49 (1H, dd,  $J$  1.1 and 3.6), 7.74 (1H, d,  $J$  4.1), 8.05 (1H, s);

**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) 14.29, 61.75, 117.45, 117.50, 125.14, 125.94, 127.82, 130.61, 131.55, 132.44, 143.87, 161.49;

**MS (CI):**  $m/z$  ( $M+H$ ) = 306, ( $M-N_2$ ) = 278, ( $M-\text{C}_2\text{H}_5\text{N}_2$ ) = 250.

#### Ethyl 2-(4-thien-2-yl-1*H*-1,2,3-triazol-1-yl)thiophene-3-carboxylate (46)

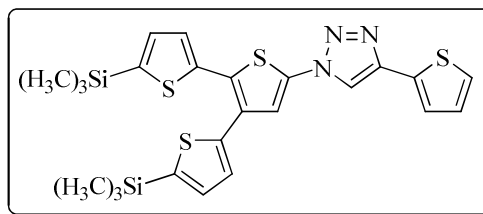
Ethyl-2-iodo-3-thiophenecarboxylate (345 mg, 1 mmol), 2-ethynylthiophene (0.11 mg, 1 mmol), sodium azide (130 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMEDA (20  $\mu$ L, 0.2 mmol). According to



procedure B no product could be isolated.

**1-[5,5''-Bis(trimethylsilyl)-2,2':3',2''-terthien-5'-yl]-4-thien-2-yl-1H-1,2,3-triazole (47)**

5-Iodo-2,3-di(5'-trimethylsilyl-2'-thienyl)-thiophene (259 mg, 0.5 mmol), 2-ethynylthiophene (54 mg, 0.5 mmol), sodium azide (65 mg, 1 mmol), copper(I) iodide (10 mg, 50  $\mu$ mol), sodium ascorbate (10 mg, 50  $\mu$ mol), DMEDA (10  $\mu$ L, 0.1 mmol). By method B the product was obtained in 111.1 mg (205  $\mu$ mol, 41 %) as yellowish needles.



**mp** 119-120 °C (from petrol ether);

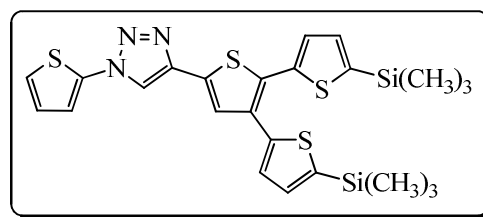
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.32 (18H, 2 x s), 7.11 (1H, dd, *J* 3.7 and 5.2), 7.13-7.16 (3H, m), 7.22 (1H, d, *J* 3.4), 7.34 (1H, s), 7.35 (1H, dd, *J* 1.0 and 5.1), 7.48 (1H, dd, *J* 1.0 and 3.5), 8.03 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) -0.15, -0.1, 117.52, 120.04, 124.89, 125.68, 127.75, 128.21, 128.67, 129.62, 130.77, 131.91, 134.21, 135.88, 138.46, 141.37, 141.55, 143.18, 143.45, 143.53, 145.41;

**HRMS (ESI):** *m/z* (*M*+Na) = 564.0513 (C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>NaS<sub>4</sub>Si<sub>2</sub> requires 564.0519).

**4-[5,5''-Bis(trimethylsilyl)-2,2':3',2''-terthien-5'-yl]-1-thien-2-yl-1H-1,2,3-triazole (48)**

2-Iodothiophene (0.03 mL, 0.25 mmol), 5-ethynyl-2,3-di(5'-trimethylsilyl-2'-thienyl)-thiophene (125 mg, 0.3 mmol), sodium azide (35 mg, 0.5 mmol), copper(I) iodide (5 mg, 25  $\mu$ mol), sodium ascorbate (5 mg, 25  $\mu$ mol), DMEDA (5  $\mu$ L, 50  $\mu$ mol). By method A the product was obtained as yellow solid in 124.6 mg (230  $\mu$ mol, 92 %).



**mp** 129-130 °C (from petrol ether);

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.32 (18H, 2 x s), 7.07 (1H, dd, *J* 3.8 and 5.4), 7.12-7.15 (3H, m), 7.21 (1H, d, *J* 3.5), 7.25 (1H, m), 7.29 (1H, dd, *J* 1.3 and 3.8), 7.52 (1H, s), 8.02 (1H, s);

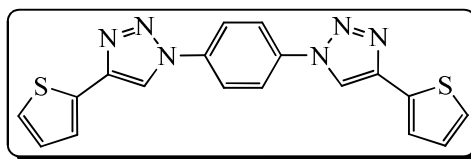
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) -0.09, -0.04, 118.29, 118.40, 123.06, 126.34, 127.47, 127.86, 128.94, 130.28, 131.73, 132.29, 134.20, 138.13, 139.79, 140.87, 142.30, 142.50, 142.76;

**MS (CI):** m/z (M+H) = 542, (M-N<sub>2</sub>) = 513, (M-Si(CH<sub>3</sub>)<sub>3</sub>) = 470, (M-N<sub>2</sub>Si(CH<sub>3</sub>)<sub>3</sub>) = 441, (M-2Si(CH<sub>3</sub>)<sub>3</sub>) = 398;

**HRMS (ESI):** m/z (M+Na) = 564.0514 (C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>NaS<sub>4</sub>Si<sub>2</sub> requires 564.0519).

#### 1,4-Phenylene-bis-(4'-thien-2''-yl-1'H-1',2',3'-triazol-1'-yl) (49)

1,4-Diiodobenzene (330 mg, 1 mmol) or 1,4-dibromobenzene (236 mg, 1 mmol), 2-ethynylthiophene (0.22 mg, 2 mmol), sodium azide (260 mg, 4 mmol), cupric sulfate pentahydrate (50



mg, 0.2 mmol), sodium ascorbate (40 mg, 0.2 mmol), DMEDA (40 μL, 0.4 mmol). The reaction was performed in DMSO/water (9:1). 1,4-Diiodobenzene yielded in 372.2 mg (990 μmol, 99 %) at 50 °C, from 1,4-dibromobenzene the disubstituted product was obtained in 368.5 mg (980 μmol, 98 %) at 95 °C.

**mp** 310 °C decomp. (from toluene);

**<sup>1</sup>H-NMR:** (400 MHz, THF-*d*8) 7.09 (2H, dd, *J* 3.6 and 5.1), 7.41 (2H, dd, *J* 1.1 and 5.1), 7.50 (2H, dd, *J* 1.1 and 3.6), 8.15 (4H, s), 8.77 (2H, s);

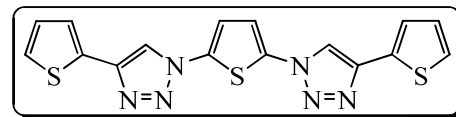
**<sup>13</sup>C-NMR:** (100 MHz, DMSO-*d*6) 100.00, 119.47, 121.89, 125.26, 126.59, 128.56, 132.63, 136.68, 143.41;

**MS (CI):** m/z (M+H) = 377, (M-N<sub>2</sub>) = 349, (M-N<sub>4</sub>) = 320;

**HRMS (ESI):** m/z (M+Na) 399.0452 (C<sub>18</sub>H<sub>12</sub>N<sub>6</sub>NaS<sub>2</sub> requires 399.0457).

#### 4-Thien-2-yl-1-[5-(4-thien-2-yl-1H-1,2,3-triazol-1-yl)thien-2-yl]-1H-1,2,3-triazole (50)

In different solvent mixtures (Table 6.5) 2,5-diiodothiophene (0.34 mg, 1 mmol), 2-ethynylthiophene (0.22 g, 2 mmol), sodium azide



(260 mg, 4 mmol), cupric sulfate pentahydrate (50 mg, 0.2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and DMEDA (0.04 mL, 0.4 mmol) were dissolved and stirred at 50 °C for 39 hours according to method A. In THF/water mixture (5:1) the dicoupled product **50** was obtained in 164.3 mg (430 μmol, 43 %).

**mp** 270 °C decomp

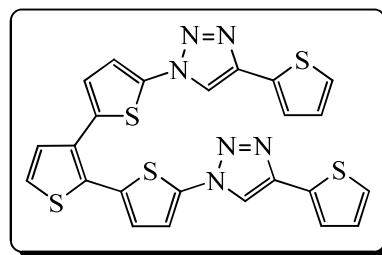
**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>) 7.20 (1H, d, *J* 3.6 and 5.0), 7.54 (1H, dd, *J* 1.1 and 3.5), 7.64 (1H, dd, *J* 1.2 and 5.0), 7.64 (1H, s), 9.27 (1H, s);

**MS (CI):** *m/z* (M) = 383, (M-N<sub>2</sub>) = 355, (M-2N<sub>2</sub>) = 327;

**HRMS (ESI):** *m/z* (M+H) = 383.0200 (C<sub>16</sub>H<sub>11</sub>N<sub>6</sub>S<sub>3</sub> requires 383.0202).

**4-Thien-2-yl-1-[5''-(4-thien-2-yl-1*H*-1,2,3-triazol-1-yl)-2,2':3',2''-terthien-5-yl]-1*H*-1,2,3-triazole (53)**

5,5''-Diiodo-2,2':3',2''-terthiophene (0.2 g, 0.4 mmol), 2-ethynylthiophene (0.1 g, 1 mmol), sodium azide (65 mg, 1 mmol), cupric sulfate pentahydrate (13 mg, 50 μmol), sodium ascorbate (10 mg, 50 μmol) and DMEDA (0.01 mL, 100 μmol) were dissolved in ethanol/water (4 mL, 7:3). For



dissolving the terthiophene 2 mL of THF were added. The work up according to method A gave a complex product mixture. After column chromatography (THF on silica) **53** was obtained in 56.8 mg (104 μmol, 26 %), and **55** in 37.7 mg (72 μmol, 18 %).

**mp** 200 °C decomp;

**<sup>1</sup>H-NMR:** (400 MHz, THF-*d*<sub>8</sub>) 7.07 (1H, dd, *J* 2.8 and 3.5), 7.08 (1H, dd, *J* 2.8 and 3.5), 7.19 (1H, d, *J* 4.0), 7.22 (1H, d, *J* 4.0), 7.33 (1H, d, *J* 5.3), 7.36 (1H, d, *J* 4.0), 7.40 (3H, m), 7.45 (1H, dd, *J* 1.1 and 3.6), 7.46 (1H, dd, *J* 1.1 and 3.6), 7.60 (1H, d, *J* 5.3), 8.65 (1H, s), 8.70 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, THF-*d*<sub>8</sub>) 117.2, 117.9, 118.0, 124.1, 124.2, 125.1, 125.2, 125.9, 126.0, 126.3, 127.2, 127.3, 127.6, 129.5, 130.7, 131.1, 132.1, 132.7, 132.8, 133.8, 139.5, 143.2, 143.3;

**MS (CI):** *m/z* (M) = 547, (M-N<sub>2</sub>) = 519, (M-2N<sub>2</sub>) = 491;

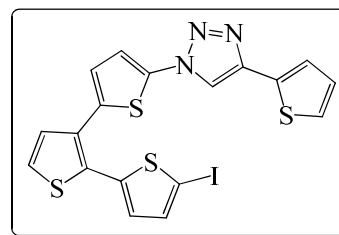
**HRMS (ESI):** *m/z* (M+H) 546.9960 (C<sub>24</sub>H<sub>15</sub>N<sub>6</sub>S<sub>5</sub> requires 546.9956).

**1-(5-Iodo-2,2':3',2''-terthien-5''-yl)-4-thien-2-yl-1*H*-1,2,3-triazole (55)**

**mp** 165 °C decomp.;

**Elemental analysis:** C<sub>18</sub>H<sub>10</sub>IN<sub>3</sub>S<sub>4</sub> requires C, 41.30, H, 1.93, N, 8.03 %; found: C, 41.65, H, 2.17, N, 7.27 %;

**<sup>1</sup>H-NMR:** (400 MHz, THF-*d*<sub>8</sub>) 6.90 (1H, d, *J* 3.8), 7.09 (1H, dd, *J* 3.6 and 5.1), 7.14 (1H, d, *J* 4.0), 7.21 (1H, d, *J* 3.8), 7.22



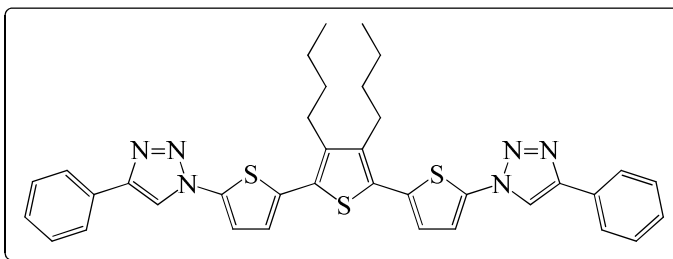
(1H, d, *J* 5.4), 7.37 (1H, d, *J* 4.0), 7.42 (1H, dd, *J* 1.2 and 5.1), 7.47 (1H, dd, *J* 1.1 and 3.6), 7.54 (1H, d, *J* 5.3), 8.66 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, THF-*d*<sub>6</sub>) 115.3, 116.1, 122.3, 123.3, 124.2, 125.4, 125.6, 126.6, 127.5, 128.3, 129.4, 130.5, 130.9, 135.3, 141.1;

**MS (CI):** *m/z* (M+H) = 524, (M-N<sub>2</sub>) = 495, (M-½I<sub>2</sub>) = 398, (M-½I<sub>2</sub>-N<sub>2</sub>) = 369.

**1-[3',4'-Dibutyl-5''-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,2':5',2''-terthien-5-yl]-4-phenyl-1*H*-1,2,3-triazole (**56**)**

In the given solvent mixtures (Table 6.6) 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene (**50** mg, 0.08 mmol), phenylacetylene (0.02 mL, 0.16 mmol), sodium



azide (21.2 mg, 0.33 mmol), sodium ascorbate (3.2 mg, 0.02 mmol), copper(I) iodide (3.1 mg, 0.02 mmol) and DMEDA (4 μL, 0.03 mmol) were suspended and treated according to method A (15 hours at 50 °C). The crude product was separated on silica using dichloromethane. The final product was obtained by washing the column with THF/ dichloromethane (1:9). From ethanol/water mixture (7:3) **56** was obtained in 11.4 mg (18 μmol, 22 %), **57** in 10.1 mg (16 μmol, 20 %), and **58** in 10.1 mg (20 μmol, 25 %).

**mp** 158.0- 161.9 °C;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.98 (3H, t, *J* 7.3), 1.48 (4H, m), 2.76 (2H, m), 7.09 (1H, d, *J* 4.0), 7.40 (1H, d, *J* 7.4), 7.48 (2H, t, *J* 7.3), 7.91 (2H, d, *J* 7.2), 8.12 (1H, s);

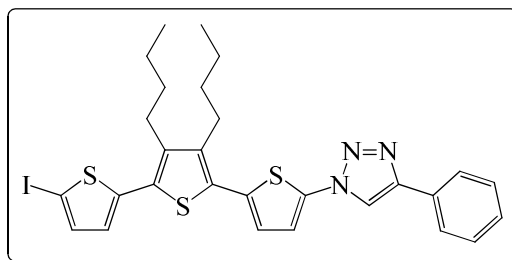
**MS (MALDI):** *m/z* (M+Dithranol) = 871.2, (M) = 647.1, (M-N<sub>2</sub>) = 591.0;

**HRMS (APCI):** *m/z* (M+H) = 647.2084 (C<sub>36</sub>H<sub>35</sub>N<sub>6</sub>S<sub>3</sub> requires 647.2080).

**1-(3',4'-Dibutyl-5''-iodo-2,2':5',2''-terthien-5-yl)-4-phenyl-1*H*-1,2,3-triazole (**57**)**

**mp** 159.6- 163.1 °C;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.96 (6H, t, *J* 7.3), 1.41- 1.59 (8H, m), 2.66- 2.75 (4H, m), 6.83 (1H, d, *J* 3.8), 7.06 (1H, d, *J* 4.0), 7.22 (1H, d, *J* 3.8), 7.24 (1H, d, *J* 4.0), 7.39 (1H, t, *J* 7.4), 7.47 (2H, t, *J* 7.5), 7.90 (2H, d, *J* 7.1), 8.11 (1H, s);



**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{CDCl}_3$ ) 13.8, 13.9, 22.9, 23.0, 27.8, 27.9, 32.9, 33.0, 118.1, 118.5, 124.7, 126.0, 127.6, 128.6, 128.8, 129.0, 129.8, 129.9, 133.7, 137.3, 137.5, 140.8, 141.2, 141.8, 148.4;

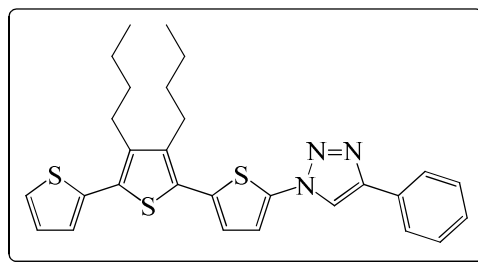
**MS (MALDI):**  $m/z$  ( $\text{M}+\text{H}$ ) = 629.9, ( $\text{M}-\text{N}_2$ ) = 602.0, ( $\text{M}-\text{N}_2-\text{I}$ ) = 504.0;

**HRMS (APCI):**  $m/z$  ( $\text{M}+\text{H}$ ) = 630.0565 ( $\text{C}_{28}\text{H}_{29}\text{IN}_3\text{S}_3$  requires 630.0563).

**1-(3',4'-Dibutyl-2,2':5',2''-terthien-5-yl)-4-phenyl-1*H*-1,2,3-triazole (58)**

The structure of this side product was only confirmed by  $^1\text{H}$ -NMR.

**$^1\text{H}$ -NMR:** (400 MHz,  $\text{DMSO}-d_6$ ) 0.93 (6H, m), 1.37- 1.58 (8H, m), 2.72 (4H), 7.17 (1H, dd,  $J$  3.6 and 5.1), 7.26 (1H, dd,  $J$  1.1 and 3.6), 7.28 (1H, d,  $J$  4.0), 7.41 (1H, t,  $J$  7.4), 7.51 (2H, t,  $J$  7.6), 7.58 (1H, d,  $J$  4.0), 7.66 (1H, dd,  $J$  1.1 and 5.1), 7.93 (2H, d,  $J$  7.2), 9.32 (1H, s).



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# Chapter 7

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**Non-conjugated Thiophene 1,2,3-Triazole Co-Oligomers  
*via* “Click”-Chemistry**

## 7.1 Introduction

### 7.1.1 Developments in Thiophene-Triazole Synthesis

In chapter 6, the synthesis of novel thiophene 1,2,3-triazole co-oligomers was described. Due to the instability of 2-azidothiophene derivatives a new protocol was developed. With a three-component one-pot procedure a series of conjugated thiophene 1,2,3-triazole co-oligomers could be synthesized from halogenated thiophenes and ethynylthiophenes. Scope and limitation experiments confirmed the instability of 2-azidothiophenes through lower yields compared to the conversion of 3-halogenothiophenes to the corresponding triazoles. Also the influence of substituents on the halogenated compound was investigated with respect to inductive and steric effects. The choice of the ethynyl thiophene moiety seems to have most importance. Elongated thienylene alkynes gave much lower yields.

The transformation of diiodothiophene derivatives with acetylenes to bistriazolyl-co-oligomers gave either low or no conversion. A monofunctionalization was often observed. The reason might be low solubility of the substances. In comparison, diacetylenic thiophenes gave no conversion at all. The alkynes could not be re-isolated. This led to the assumption that the acetylenes form stable copper acetylides and poison the catalyst.

With the protocol developed in chapter 6 no extended thiophene 1,2,3-triazole co-oligomers and –polymers could be obtained. Anyway, no conjugation through the triazole-ring was obvious. It rather separates the thiophene moieties from each other. Electropolymerization led to polymer films, which show properties of the subunits and the acceptor effect of the triazole is rather low.

### 7.1.2 Perspectives

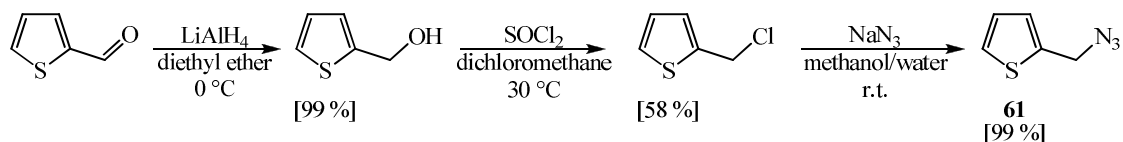
No conversion of diiodinated thiophenes was observed, because the azide formation did not take place. Therefore, a more stable azide should be used which directly in a “click”-reaction protocol can be converted to the triazole. Because linear co-polymers were of interest, no 3-azidothiophene derivatives, which were found to be stable, could be applied. In literature, several vinyl azides are described which seem to be stable. But the synthesis of vinyl azides is somewhat time-consuming. Because the conjugation is anyway rather interrupted due to the triazole ring, a methylene bridge could be inserted without a big

change of the electronic properties. On the other hand, alkyl azides are more stable than aryl azides.

The synthesis of 2-azidomethylthiophene **61** is already described in literature (Scheme 7.1).<sup>1</sup> It includes quite well known standard reactions on thiophenes. Therefore, the decision was made for this thiophene moiety.

### 7.1.3 Azide Formation

Thiophene-2-carbaldehyde was reduced with lithium aluminium hydride in diethyl ether.<sup>2</sup> This reaction quantitatively gave thien-2-yl-methanol. After substitution of the OH-group by chloride by treatment with thionylchloride in dichloromethane<sup>3</sup>, 2-chloromethylthiophene was converted to 2-azidomethylthiophene **61** in excellent yield.<sup>1</sup> The chlorinated intermediate decomposed during distillation. Column chromatography is also insufficient for purification. Presumably, 2-chloromethylthiophene decomposes to give stable benzyl-type cations. Therefore, it has to be handled with care. However, 2-azidomethylthiophene is stable at room temperature, light and air.

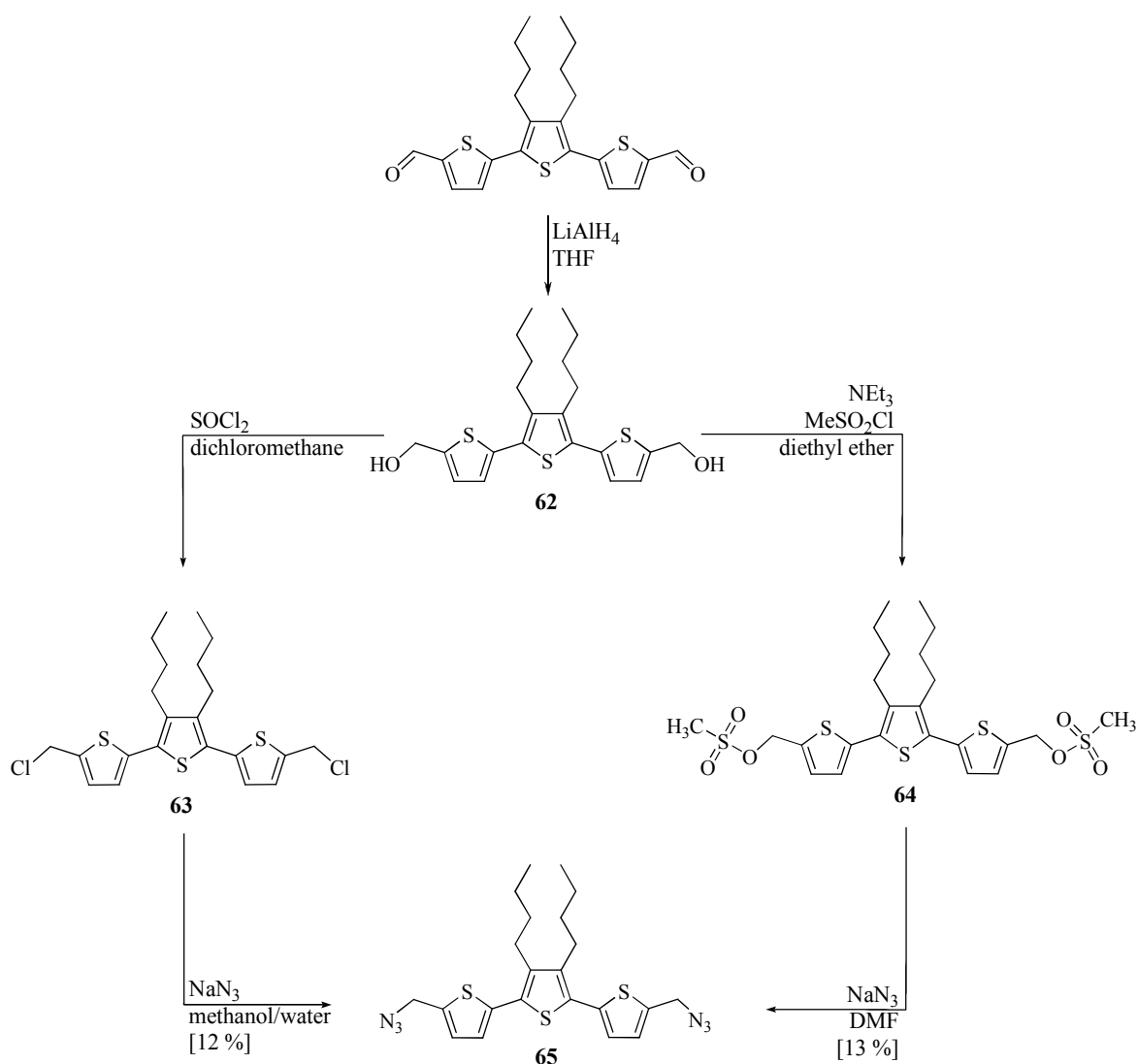


**Scheme 7.1** Synthesis of 2-azidomethylthiophene **61** from thiophene-2-carbaldehyde.

## 7.2 Synthesis of Novel Thiophene 1,2,3-Triazole Derivatives

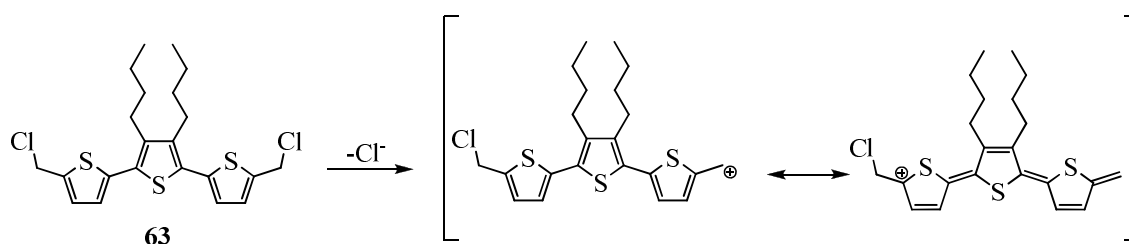
### 7.2.1 Synthesis of Azidomethylthiophene Derivatives

Since the synthesis of 2-azidomethylthiophene is already known and could be retraced, higher oligothiophenes should be converted in the same manner (Scheme 7.2). Reduction of 3',4'-dibutyl-2,2':5',2''terthiophene-5,5''-dicarbaldehyde in THF with lithium aluminium hydride gave corresponding diol **62** in quantitative yield.



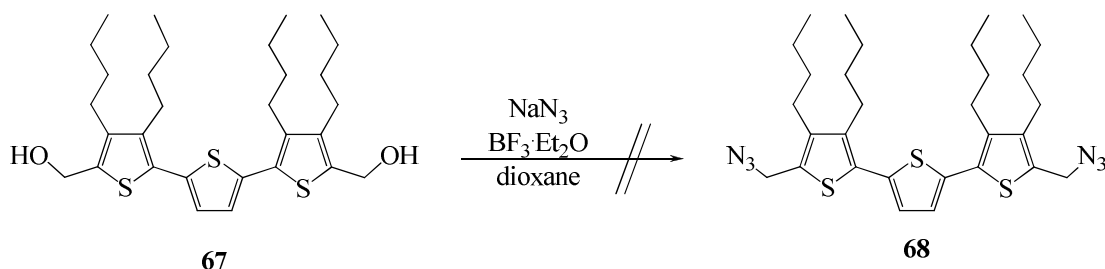
**Scheme 7.2** Synthetic route to obtain 5,5''-bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **65**.

Chlorination of terthiophene **62** with sulfonyl chloride in dichloromethane gave a brown residue indicating that decomposition took place during the reaction. Because of the instability of chloromethyl intermediate **63** it was used only with a short work-up. Nucleophilic substitution with sodium azide in a methanol/water mixture gave the desired 5,5''-bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **65** in only 12 % with respect to **62**. Conversion of the diol to the dimesylated species **64** gave finally the same low yield of azide **65**. Formation of the mesylate requires milder reaction conditions in comparison to the chlorination. But the mesylate is a better leaving group and favors formation of the mesomeric allyl stabilized benzyl-type cation (Scheme 7.3).



**Scheme 7.3** Cation formation of 5,5''-bis(chloromethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **63s**.

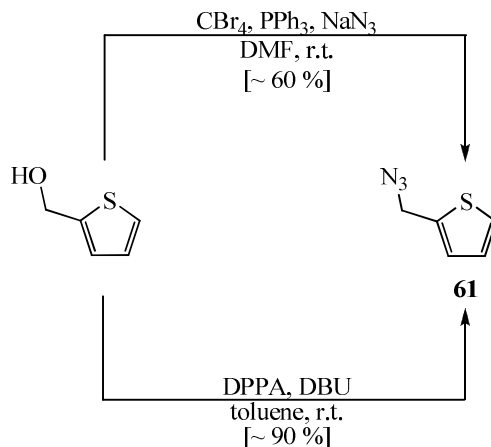
For the formation of 5,5''-bis(azidomethyl)-3,3'',4,4''-tetrabutyl-2,2':5',2''-terthiophene **68** a more direct conversion of the diol **67** into the azide was investigated (Scheme 7.4). This procedure was described in literature to obtain 2-azidomethylthiophene and other benzylazides.<sup>4</sup> However, no product could be isolated. During the addition of the trifluoroborate a darkening of solution was observed. Obviously, a benzylic cation was formed and polymerization occurred.



**Scheme 7.4** Synthesis of 5,5''-bis(azidomethyl)-3,3'',4,4''-tetrabutyl-2,2':5',2''-terthiophene **68**.

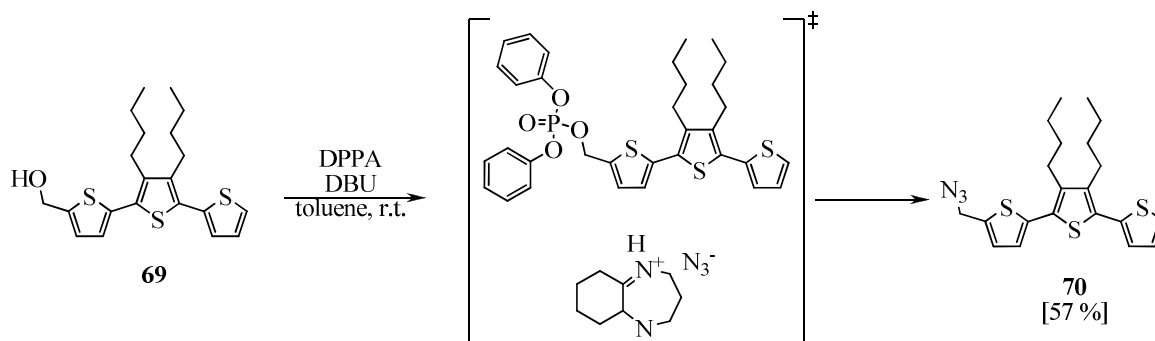
Another method had to be found to synthesize methylazides in higher yields. Along with nucleophilic substitution using several azide reagents (e.g., alkaline azides, tetraalkylammonium azides or polymer-supported azides) also other methods to convert aliphatic alcohols into azides were described. Primary and secondary alcohols can be converted in a Mitsunobu reaction with hydrogenazide, triphenylphosphine and DEAD (diethyldiazodicarboxylate). Instead of using explosive hydrogen azide DPPA (diphenylphosphoryl azide) can be applied. Another method is an Appel-type reaction starting from alcohols, tetrabromocarbon, triphenylphosphine and sodium azide. In order to develop a new procedure for the synthesis of azidomethylterthiophenes a model system was chosen. Thien-2-yl-ethanol was converted in two different ways to azide **61** (Scheme 7.5). On one hand, the Appel-type reaction conditions<sup>5</sup>, on the other hand, a variant of

Mitsunobu reaction conditions<sup>6</sup> were investigated. The conversion of the starting material was monitored by NMR after a short work-up.



**Scheme 7.5** Conversion of thien-2-ylmethanol to 2-azidomethylthiophene **61**.

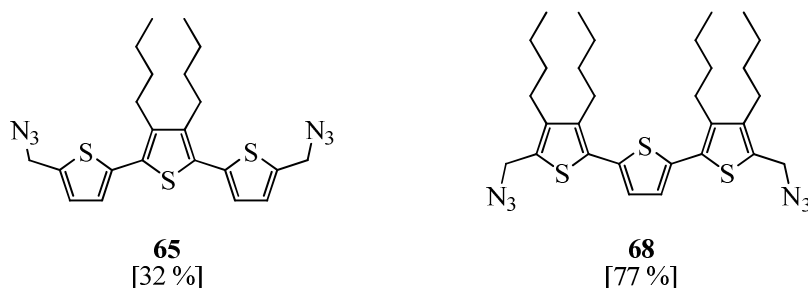
Reaction under Apple-conditions led to a conversion of around 60 %. With the Mitsunobu-type protocol 2-azidomethylthiophene was formed in 90 % yield. Because the conversion under Mitsunobu-type reaction conditions led in much higher yields, this protocol was applied to obtain methyl azides. In Scheme 7.6, the reaction mechanism is displayed for the synthesis of 5-(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **70**. The corresponding alcohol **69** is converted to a diphenylphosphorylate while the azide anion is stabilized by the protonated DBU.<sup>6</sup> By the attack of azide anions nucleophilic substitution takes place to form the stable methyl azide **70**.



**Scheme 7.6** Synthesis of 5-(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **70** from (3',4'-dibutyl-2,2':5',2''-terthien-5-yl)methanol **69**.



By this protocol, bis(azidomethyl) terthiophenes **65** and **68** were also synthesized from corresponding diols in 32 % and 77 % yield, respectively (Chart 7.1).



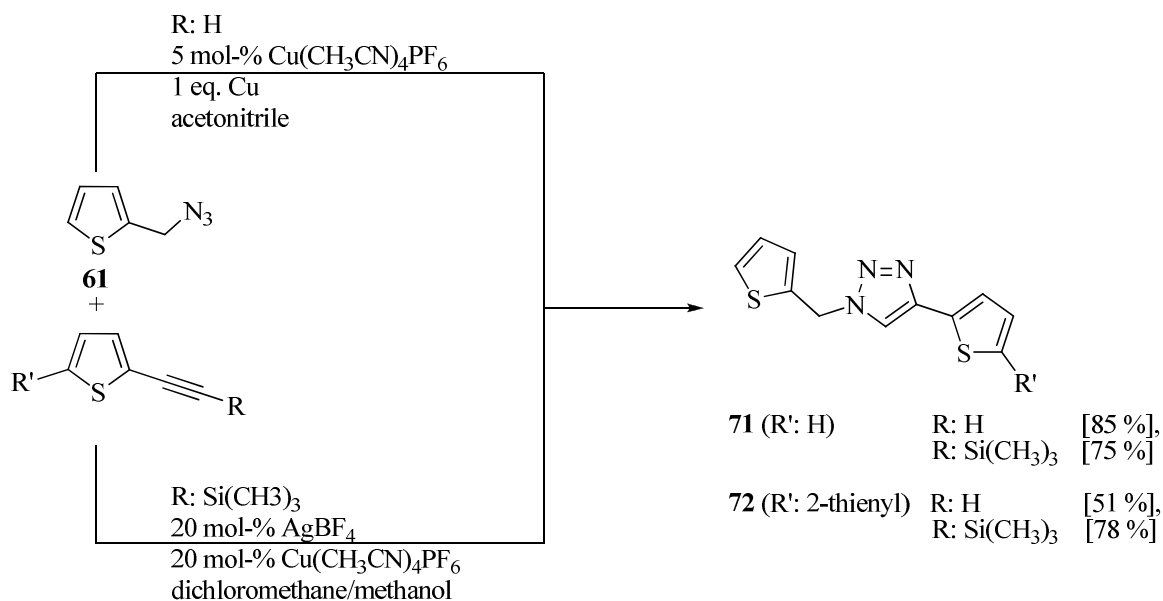
**Chart 7.1** 5,5''-Bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **65** and 5,5''-bis(azidomethyl)-3,3'',4,4''-tetrabutyl-2,2':5',2''-terthiophene **68**.

Using Mitsunobu-type conditions the yield for 5,5''-bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **65** was increased from 12 %, which were reached *via* chlorination (Scheme 7.4), to 32 %. This means 57 % per substitution reaction, which is in accordance to the conversion of **69** to **70**. **68** was obtained in much higher yield. The butyl groups in *ortho*-position to the methanol group could favor the deprotonation in the first step of the reaction due to the positive inductive effect to give the diphenylphosphorylate in higher amount. For this intermediate a bigger steric hinderance is suggested which leads to faster nucleophilic substitution with the azide anion.

### 7.2.2 “Clicking” Methyl azides to Terminal and (Trimethyl)silyl-protected Acetylenes to 1,4-Disubstituted 1,2,3-Triazoles

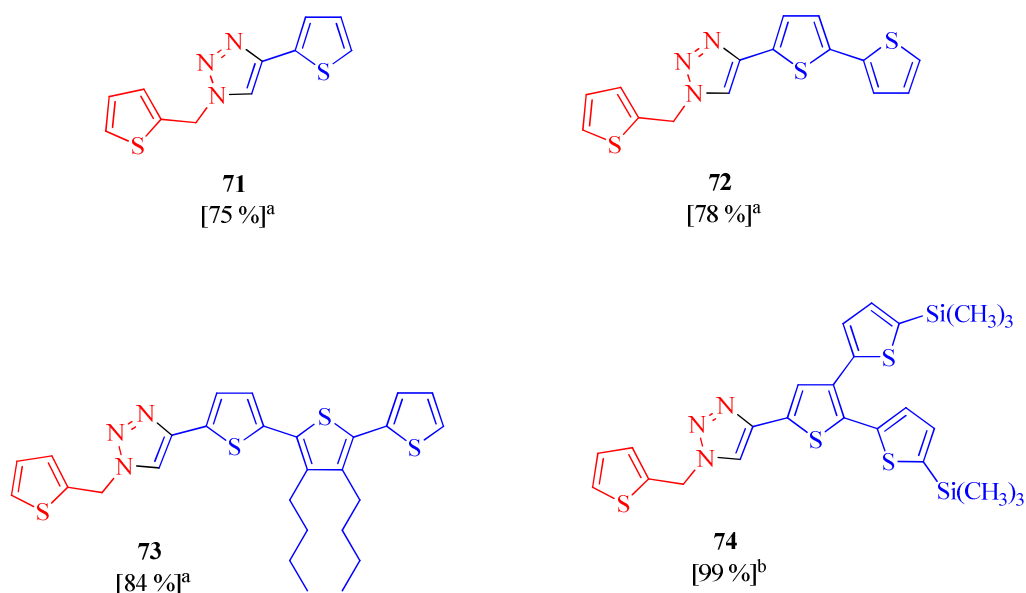
In first experiments 2-azidomethylthiophene **61** was converted with terminal ethynylthiophene and trimethyl(thien-2-yl-ethynyl)silane derivatives (Scheme 7.7). Reaction of **61** with 2-ethynylthiophene was realized under standard reaction conditions using tetrakis(acetonitrile)-copper(I) hexafluorophosphate (5 mol-%) and copper powder (1 eq.) as catalyst in acetonitrile. The pure product was obtained in 85 %. In literature an *in situ* deprotection of (trimethyl)silyl-protected alkynes by silver was described.<sup>7</sup> **61** was coupled to trimethyl(thien-2-yl-ethynyl)silane using silver(I) tetrafluoroborate (20 mol-%) and tetrakis(acetonitrile)-copper(I) hexafluorophosphate (20 mol-%) in a dichloromethane/

methanol mixture to give 4-thien-2-yl-1-(thien-2-yl-methyl)-1*H*-1,2,3-triazole (**71**) in 75 % as pure compound.



**Scheme 7.7** Synthesis of 1,4-disubstituted 1,2,3-triazoles **71** and **72**.

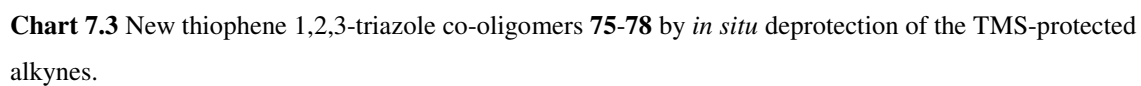
For coupling of **61** with 5-ethynyl-2,2'-bithiophene to triazole **72** a moderate yield was obtained. Branched [5'-ethynyl-5''-(trimethylsilyl)-2,2':3',2''-terthien-5-yl](trimethyl)silane was converted with **61** to 1,4-disubstituted 1,2,3-triazole **74** in 99 %. This is comparable to the observations described in Chapter 6, that higher ethynylated oligothiophenes give lower yields, while branched thiophene backbones lead to higher yields. For the *in situ* deprotection of the alkyne, product **72** could be obtained in a higher yield (78 %). Further reactions were realized by the *in situ* deprotection protocol (Chart 7.2) to obtain the desired thiophene-triazole co-oligomers in good to excellent yields. The yields slightly increased with the number of thiophene rings in the acetylenic moiety.



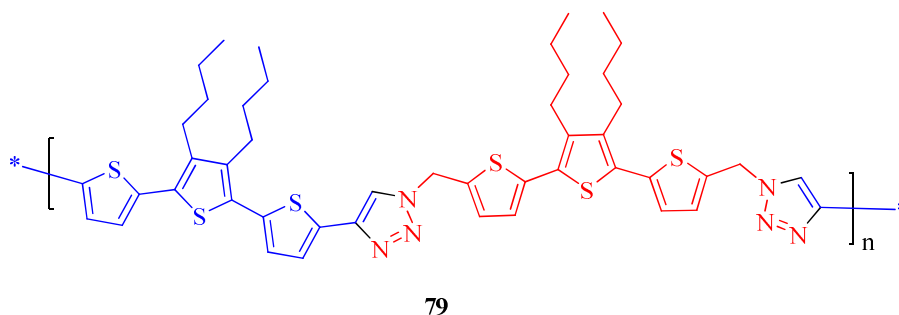
**Chart 7.2** Synthesized 1,4-disubstituted 1,2,3-triazoles **71-74** from **61**. <sup>a</sup>*In situ* deprotection of (trimethyl)silyl-protected alkynes with AgBF<sub>4</sub> (20 mol-%), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (20 mol-%) in dichloromethane/methanol; <sup>b</sup>terminal alkyne was coupled with Cu(CH<sub>3</sub>CN)<sub>4</sub> (5 mol-%) and Cu (1 eq.) in acetonitrile.

### 7.2.3 Conversion of Diazido- and Diacetylene Thiophenes to Thiophene 1,2,3-Triazole Co-Oligomers and –Polymers

To obtain higher thiophene 1,2,3-triazole co-oligomers and –polymers bis(azidomethyl)-thiophenes and bis(ethynynl)-thiophenes were coupled using the protocol of Leigh *et al.*<sup>7</sup> A series of novel substances were synthesized in good to excellent yields (Chart 7.3). Diazido terthiophene **65** was converted to ditriazoles **75** and **76** in 98 % and 97 %, respectively. On the other hand, 5,5''-bis(trimethylsilylethynyl)-3',4'-dibutyl-2,2':5',2''-terthiophene was coupled to azides **61** and **70** to obtain thiophene-triazoles **77** and **78** in 64 % and 97 %, respectively. Obviously, the choice of azide has a bigger effect to the yield than the acetylene used in this coupling reaction. The yields of **75** and **76** are rather the same, independent on the acetylene which was used. On the other hand, for **77** and **78** different yields were observed. Azide **70** with an extended  $\pi$ -conjugated backbone gave much higher yields (97 %) than 2-azidomethylthiophene **61** (64 %). However, intermediate mono-substituted products could not be detected.

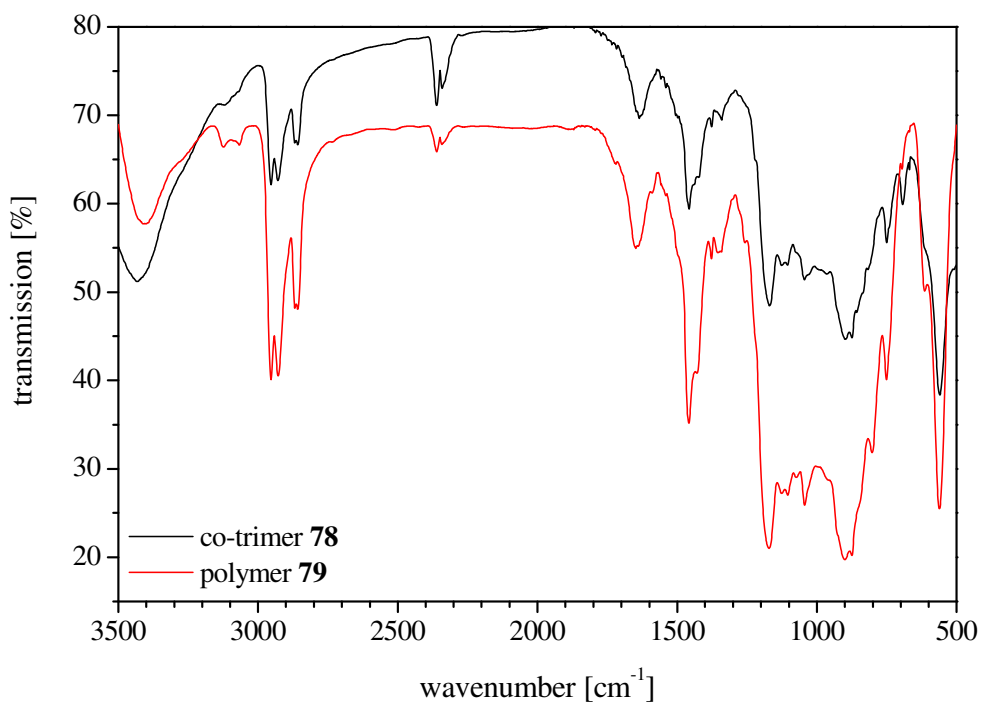


Also a co-polymer was synthesized by “click”-reaction of 5,5’-bis(azidomethyl)-3’,4’-dibutyl-2,2’:5’,2’’-terthiophene **65** and 5,5’-bis(trimethylsilylethynyl)-3’,4’-dibutyl-2,2’:5’,2’’-terthiophene (Chart 7.4).



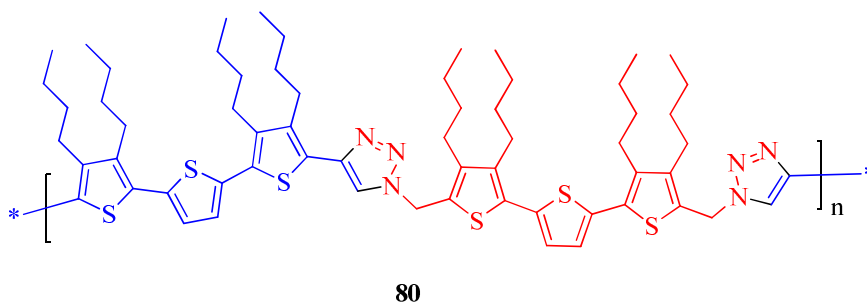
**Chart 7.4** Synthesized polymer from 5,5''-bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene **65** and 5,5''-bis(trimethylsilylethynyl)-3',4'-dibutyl-2,2':5',2''-terthiophene.

The obtained thiophene 1,2,3-triazole co-polymer **79** could not be characterized directly, because of its insolubility in common solvents. Therefore, IR spectra were determined (Chart 7.5) and compared to IR values of trimer **78**, whose structure was confirmed by NMR and mass spectra. Both compounds showed identical vibronic bands. Therefore, the same structural properties can be confirmed. Bands between 2855 and 2950  $\text{cm}^{-1}$  correspond to C-H stretching vibrations of the thiophene rings and butyl groups, additionally a strong C-H bending vibration was observed at 1453  $\text{cm}^{-1}$ . A characteristic vibration band for 1,2,3-triazoles appears at 1164  $\text{cm}^{-1}$ .<sup>8</sup> The other strong bands observed in IR spectra for **78** and **79** between 800 and 1100  $\text{cm}^{-1}$  belong to C-C and C-N stretching vibrations, C=C and C=N stretching vibration bands appear around 1625  $\text{cm}^{-1}$ . The insolubility of the polymer, except in hot DMF, led to the assumption that a high polymerization degree was reached. This claim is supported by missing characteristic strong vibronic bands for azides which should appear around 2030 to 2140  $\text{cm}^{-1}$ .



**Chart 7.5** IR spectra of **78** and polymer **79** in KBr.

Because of the insolubility, the number of butyl groups in the subunits was increased leading to a higher solubility of the co-polymer. Under standard reaction conditions 5,5''-bis(azidomethyl)-3,4,3'',4''-tetrabutyl-2,2':5',2''-terthiophene **68** and 5,5''-bis(trimethylsilyl-ethynyl)-3,4,3'',4''-tetrabutyl-2,2':5',2''-terthiophene were “clicked” to give polymer **80** (Chart 7.6).



**Chart 7.6** Polymer **80** from 5,5''-bis(azidomethyl)-3,4,3'',4''-tetrabutyl-2,2':5',2''-terthiophene **68** and 5,5''-bis(trimethylsilyl-ethynyl)-3,4,3'',4''-tetrabutyl-2,2':5',2''-terthiophene.

As expected, the solubility of the polymer was dramatically increased, e.g., in THF. The crude product was fractionated by dissolving in THF and adding petrol ether

subsequently. Due to high polydispersity ( $>1.5$ ) no signal in MALDI-TOF was observed. Therefore, the polymerization degree was determined by GPC vs. polystyrene as standard. According to the maximum of the Gaussian-shaped band the polymer should contain 18 terthiophene repeating units ( $M_w$  10.000 vs. polystyrene).

### 7.3 Spectroscopic and Electronic Properties of Selected Compounds

#### 7.3.1 UV/vis Spectroscopy

All absorption spectra were measured in dichloromethane at room temperature. The extinction coefficient was determined at several concentrations and is given as an average. Because the molecular mass of **80** could not be exactly determined, 0.6 g of substance were dissolved in 5 mL dichloromethane to take the UV/vis spectra. In Table 7.1, absorption maxima and extinction coefficients for compounds **71-78** and for polymer **80** are summarized.

**Table 7.1** UV/vis spectral values for triazoles **71-78** and **80** in dichloromethane.

	$\lambda^{abs}$ [nm] <sup>a</sup> (lg $\epsilon$ )	$\Delta E_{opt}$ [eV] <sup>b</sup>
<b>71</b>	272 (4.08), 292 (s)	4.09
<b>72</b>	334 (4.35), 363 (s)	3.26
<b>73</b>	280 (3.99), 358 (4.34)	2.94
<b>74</b>	283 (4.43), 341 (4.14)	3.09
<b>75</b>	272 (4.55), 345 (4.30)	3.04
<b>76</b>	272, 356 (4.88)	2.95
<b>77</b>	374 (4.41)	2.79
<b>78</b>	256 (4.54), 356 (4.75)	2.86
<b>80</b>	259, 367 (n.d.)	2.68

<sup>a</sup>**71-78**:  $c = 5 \cdot 10^{-5}$  mol l<sup>-1</sup> in dichloromethane, concentration of **80** undefined, maxima in italics, (s) describes shoulders, <sup>b</sup>determined from the onset of the absorption at the lower energy band edge.

As expected, the UV/vis data show the interruption of the conjugation due to the methylene bridge inbetween the thiophene 1,2,3-triazole co-oligomer subunits. As

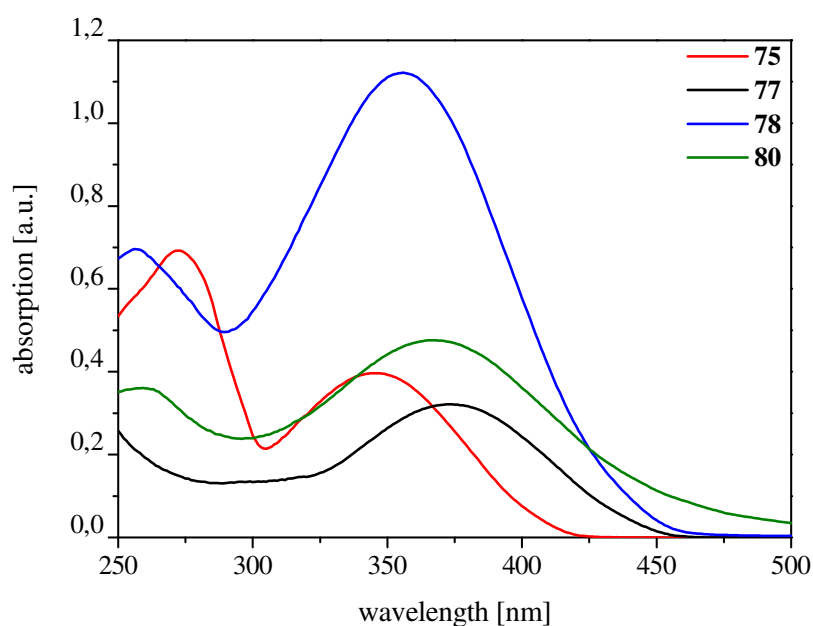
described in chapter 6 for triazole **71** maxima (272 nm) are comparable to the subunits such as 2-vinylthiophene (276 nm in ethanol<sup>9</sup>). The spectrum of **75** displays an overlay of the absorption spectra of the individual moieties. The absorption maximum at 272 nm can be assigned to the excitation of the 2-vinylthiophene backbone and at 345 nm to the terthiophene moiety. In the absorption spectrum 3',4'-dibutyl-2,2':5',2''-terthiophene showed at 335 nm.<sup>10</sup> But the positive inductive effect of the two methylene bridges in  $\alpha,\omega$ -position shift the absorption maximum to the red. Compared to 3,4,3'',4''-tetrabutyl-2,2':5',2''-terthiophene<sup>10</sup> which has an absorption maximum at 342 nm in dichloromethane, it is assumed, that there is no effect of the triazole ring as an acceptor.

Elongation of the terthiophene backbone (e.g., in **75**) by one double bond (in **73**) leads to a redshift of about 13 nm of the  $\pi$ - $\pi^*$  band. Further elongation to a bis(vinylene)-terthiophene moiety, as shown in **77**, results in a bathochromic shift of another 16 nm.

In Chart 7.7, exemplarily UV/vis spectra of **75**, **77**, **78** and polymer **80** are shown. For **78**, a superposed spectrum of **75** and **77** would be expected. The absorption maxima for the terthiophene subunits are located at 345 nm and 374 nm, respectively. Compound **78** has its highest excitation energy at 356 nm which is an average of the absorption maxima of the individual terthiophene backbones. In Chart 7.7, also the increased extinction coefficient for **78** can be determined. It is around three times higher than for **75** and **77**. All three subunits in **78** contribute equally to the absorption process.

For polymer **80** an absorption maximum at 367 nm was observed. Compared to **76** and **78**, respectively, it is redshifted. Two further butyl groups per moiety lead to a bathochromic shift of the absorption maximum. The long tailing of the absorption is caused by light scattering of non-dissolved polymer particles.





**Chart 7.7** UV/vis spectra of triazoles **75**, **77**, **78** and **80** in dichloromethane ( $c$   $2.10^{-5}$  mol  $\text{l}^{-1}$ ,  $c$ [**80**] undefined).

### 7.3.2 Fluorescence Spectroscopy

Fluorescence spectra were determined at room temperature in dichloromethane. Fluorescence quantum yields were determined with 9,10-diphenylanthracene as fluorescence standard and the Stokes shift is determined as the difference of the absorption and the emission maximum with highest energy. All data are summarized in Table 7.2.

All spectra show vibronic splitting of the emission band. For **71**, only a very weak fluorescence could be observed. In the emission spectra values for the subunits are as expected reflected because of the interruption of the conjugated system by the methylene bridge. With elongation of the conjugated chain the emission maximum is redshifted. To start from dibutyl-terthiophene **75** with an emission maximum at 423 nm, vinyl-dibutyl-terthiophene **73** and **76** have a maximum at 436 and 437 nm, respectively. The terthiophene unit in **76** has less influence in emission than the terminal vinyl-terthiophene. Comparing **77** and **78**, identical emission spectra could be obtained. Absorption maxima are not equal due to the overlay of the spectra of the subunits. Optical band gaps of **77** and **78** were determined to 2.79 and 2.86 eV, respectively. This lead to the assumption, that in these two compounds identical HOMO and LUMO values are existent. For **80** the

bathochromic shift of the emission is caused by the higher number of butyl groups in the thiophene backbone.

**Table 7.2** Fluorescence data for compounds **71-78** and polymer **80** in dichloromethane at room temperature.

	$\lambda^{\text{em}}$ [nm] <sup>a</sup>	$\Phi$ [%] <sup>b</sup>	Stokes Shift [cm <sup>-1</sup> ] <sup>c</sup>
<b>71</b>	(319)	n.d.	5 407
<b>72</b>	381, 398, 422 (s)	3	4 815
<b>73</b>	436, 461, 491 (s)	3	6 241
<b>74</b>	459	5	7 539
<b>75</b>	423, 446	4	6 564
<b>76</b>	437, 460, 491 (s)	4	6 351
<b>77</b>	458, 486, 524 (s)	9	6 204
<b>78</b>	458, 487, 523 (s)	6	7 556
<b>80</b>	464, 494, 524 (s)	2	7 005

<sup>a</sup> Fluorescence spectra are measured in dichloromethane, (s) describes shoulders, <sup>b</sup> relative to standard 9,10-diphenylanthracene,<sup>11</sup> <sup>c</sup> Stokes shift is given for the 0→0\* transition ( $\Delta\nu = \nu_{\text{max}}^{\text{abs}} - \nu_{\text{max}}^{\text{em}}$ ).

Quantum efficiencies reflect the conjugated units in the thiophene-triazole co-oligomers. With elongation of the conjugated backbone the fluorescence quantum yield increases from  $\phi = 3$  % determined for **72** and **73** (vinylbi- and terthiophene) to  $\phi = 9$  % for bis(vinyl)-terthiophene **77**. As already discussed for the observations in UV/vis, terthiophene trimers **76** and **78** showed an average value of the efficiency ( $\phi = 4$  % and 6 %, respectively). The average is formed by the excitation of the terthiophene subunits. Polymer **80** has only a low quantum efficiency of 2 %, which is lower than for tetrabutyl-terthiophene (5 %).<sup>10</sup> Fluorescence is quenched due to intramolecular deactivation of the excited state.

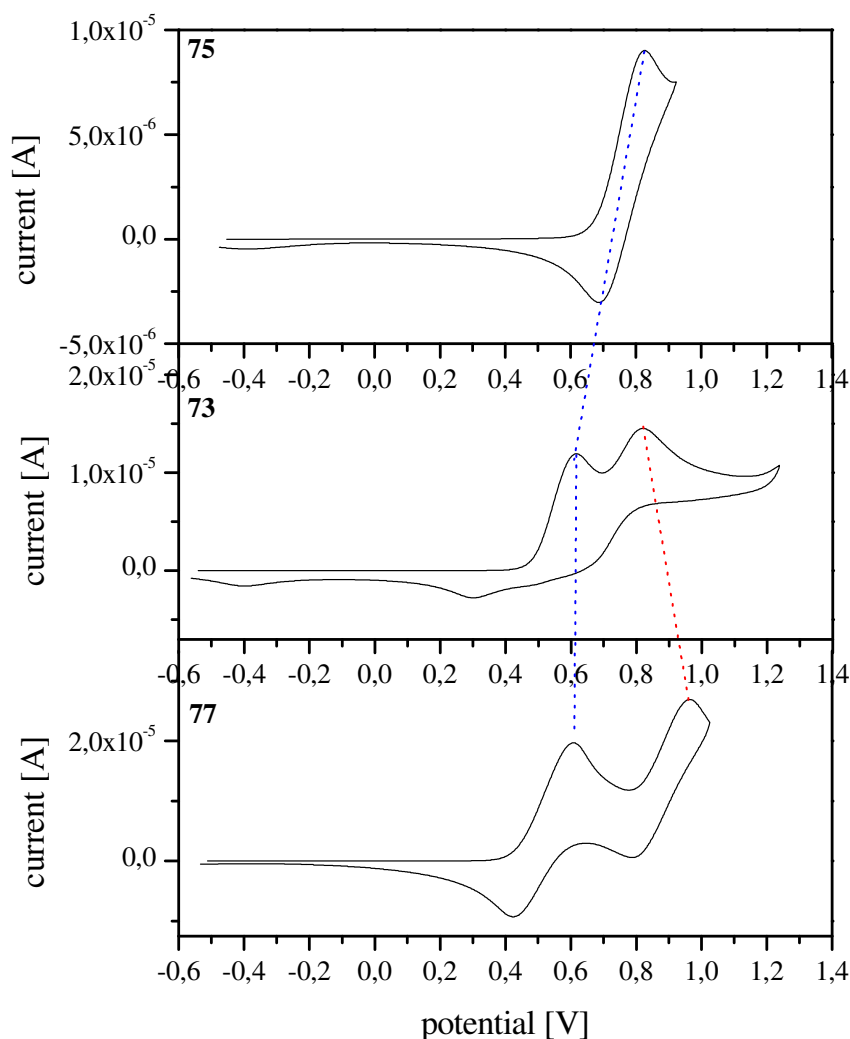
### 7.3.3 Electrochemical Investigations on Selected Compounds

Cyclic voltammograms (CV) and difference potential voltammograms (DPV) of co-oligomers **71-78** and **80** were determined in dichloromethane ( $c = 5 \cdot 10^{-2}$  to  $10^{-3}$  mol l<sup>-1</sup>) using tetrabutylammonium hexafluorophosphate (TBAHFP) as the supporting salt. Oxidation potentials are given *versus* the internal standard ferrocene/ferricenium (Fc/Fc<sup>+</sup>) in Table 7.3. For compounds with an irreversible redox processes E° was determined at  $I_0 = 0.855 \times I_p$ .<sup>12</sup> HOMO energy levels are standardized to the ferrocene/ferricenium couple which has a calculated absolute energy of -5.10 eV.<sup>13</sup>

**Table 7.3** Electrochemical properties of **71-78** and **80** in dichloromethane.

	CV			DPV	
	E° <sub>ox</sub> [V]	E <sub>onset</sub> [V]	HOMO [eV]	E <sub>p</sub> <sup>c</sup> [V]	E <sub>p</sub> <sup>a</sup> [V]
<b>71</b>	1.21	0.94	-6.04	1.22	-
<b>72</b>	0.71	0.58	-5.68	0.77	-
<b>73</b>	0.56	0.48	-5.58	0.54 0.75	0.51 0.70
<b>74</b>	0.75 1.10	0.63	-5.73	0.74 1.01 1.12	- - -
<b>75</b>	0.76	0.68	-5.78	0.78 0.94	- -
<b>76</b>	0.53	0.47	-5.57	0.56 0.80	- -
<b>77</b>	0.51 0.88	0.42	-5.52	0.53 0.88 1.14	0.50 0.86 -
<b>78</b>	0.50	0.43	-5.53	0.51 0.65 0.70 0.93 1.31	- 0.64 - - -
<b>80</b>	0.49 0.83 1.03	0.34	-5.54	0.64	0.74

The methylene bridge inhibits possible conjugation of the thiophene subunits through the triazole ring. Therefore, the oxidation waves of the thiophene moieties were detected. In these non-conjugated species also no reduction of the triazole ring could be observed. The oxidation potential for **71** was found at 1.21V which corresponds to the oxidation of 2-vinylthiophene. In **75** this value can not be determined. Its oxidation potential is close to the limiting value which can be determined in dichloromethane. The oxidation potential decreased with increased conjugation length, e.g. to 0.71V for vinylbithiophene in **72** and 0.75V in **74**. Regarding the terthiophene containing co-oligomers (see examples in Chart 7.8) for **75** a quasi-reversible oxidation wave is observed at 0.76V. This wave is assigned to the radical cation of the dimethylene-substituted terthiophene moiety.

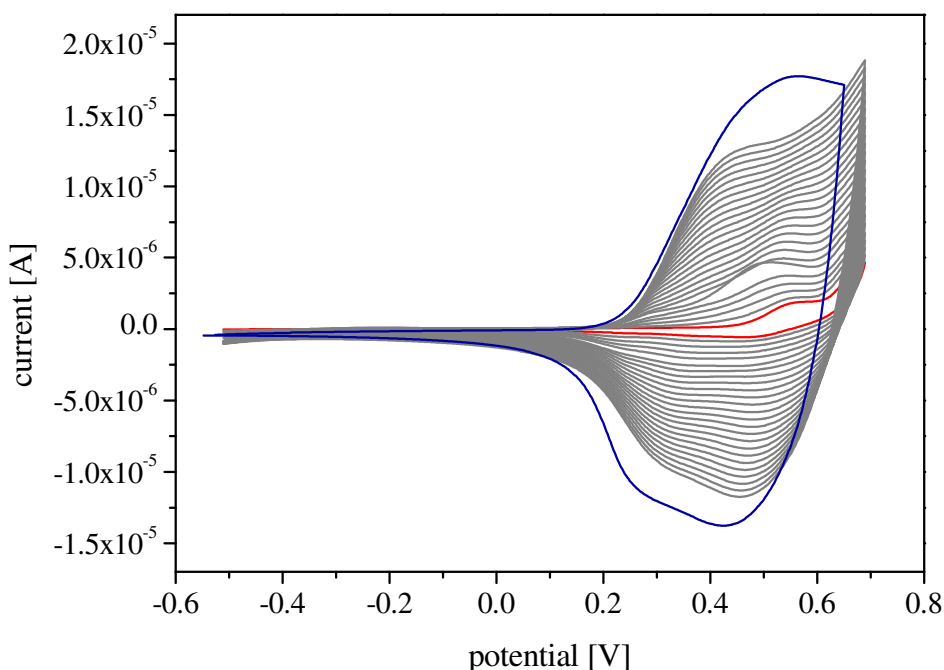


**Chart 7.8** Cyclic voltammograms of co-oligomers **73**, **75** and **77**.

Application of higher potentials gave an irreversible voltammogram with two further oxidations and decomposition of the compound. The terthiophene subunit can stabilize only a radical cation. For **76**, in DPV an oxidation potential at 0.80V could be determined, belonging to the identical subunit. Elongating the terthiophene by a double bond (e.g. in **73** and **76**) the oxidation wave shifted to lower potentials at 0.56V and 0.53V, respectively. A second ethenyl group, as in **77** and **78**, decreased the oxidation potential to 0.51V and 0.50V. The polymer **80** showed a first oxidation wave at 0.49V which is caused by the bis(vinylene)terthiophene subunits. Oxidation of the dimethylene terthiophene backbone was determined at 0.83V. The potentials of the two types of backbone are overlayed. The complex CV determined for **80** indicates that each thiophene moiety can be oxidized independently from each other.

Oxidation waves for **71-72**, **74** and **80** were irreversible. For the terthiophene and vinylterthiophene subunits in **73** and **75**, respectively, the cyclic voltammogram was quasi-reversible, which indicates a follow-up reaction during oxidation. But no polymers were deposited on the working electrode. **76** contains both terthiophene and vinylthiophene moieties. An irreversible oxidation potential was determined and a polymer was observed on the platinum electrode within 30 cycles, caused by the formation of the radical cations of vinyl-terthiophene end groups. The bis(vinyl)-terthiophene backbones in **77** and **78** showed two quasi-reversible oxidation waves. Also for **77** no polymerization was observed due to decomposition of the molecule while oxidizing the monothiophene end group. However, a polymer of **78** was formed after oxidation of the terthiophene end groups (Chart 7.9). The yellow polymer film was deposited on a platinum electrode in 30 cycles with a potential up to 0.69V. At increased potentials (1.19V) decomposition of the material leading to a black, less conducting polymer film was observed.

Polymers of **76** and **78** were characterized using a monomer-free electrolyte. The polymer films were washed carefully with dichloromethane to remove dissolved monomers. For **76**, the polymer shows an onset potential of 0.16V, for **78** this was determined at 0.21V. This slight difference, also in the shape of the cyclic voltammograms of the films, led to the assumption, that in **76** the longer conjugated system is bis(vinyl)sexithiophene, formed by homocoupling of the vinylterthiophene end groups of **76**. In **78**, the longest conjugation path is given by a sexithiophene.



**Chart 7.9** Cyclic voltammetry of co-oligomer **78** in dichloromethane/  $n\text{Bu}_4\text{NPF}_6$  (0.1M) vs.  $\text{Fc}/\text{Fc}^+$  at 100 mV/ s (red – monomer, gray – polymerization, blue – polymer film).

## 7.4 Discussion of the Results

Investigations of UV/vis and fluorescence spectra and cyclic voltammetry showed, that in the series thiophene subunits in thiophene 1,2,3-triazole co-oligomers and co-polymers are independent from each other. All data confirmed a complete interruption of the conjugation *via* triazole ring and methylene bridge. In chapter 7.3.1 it was shown that no intramolecular charge-transfer (ICT) is operative for this type of molecules. Obviously, the HOMO is located in the thiophene subunit featuring the longest conjugation path (Chart 7.10). For **77** and **78**, the energy values are the same (-5.22 eV and -5.23 eV, respectively), just as in **73** and **76** (-5.28 eV and -5.27 eV). The values for the LUMOs differ slightly. The onset in the UV/vis spectra can not be confirmed that easy, because of the broadness of the bands. The HOMO for the polymer **80** is located at the same value than for the other bis(vinyl)terthiophene containing compounds (**77** and **78**). The LUMO is formed at lower energy (-2.56 eV). The UV/vis spectrum of **80** showed a very long tailing due to the polymeric structure, therefore, the onset could not exactly be determined. Also the higher number of butyl groups in the terthiophene moiety caused a bathochromic shift of the absorption.

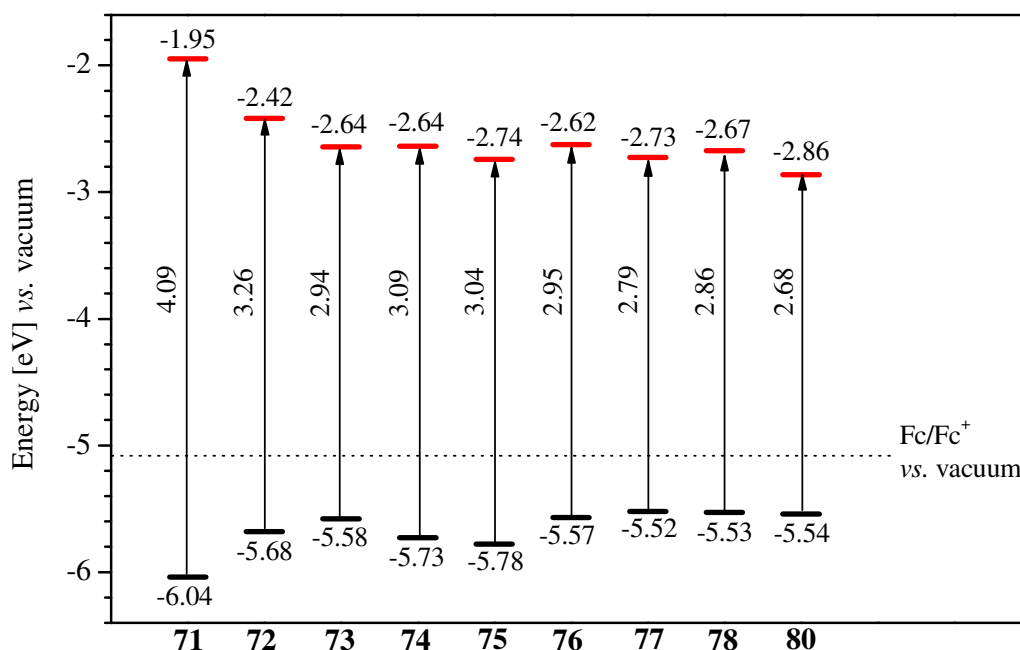
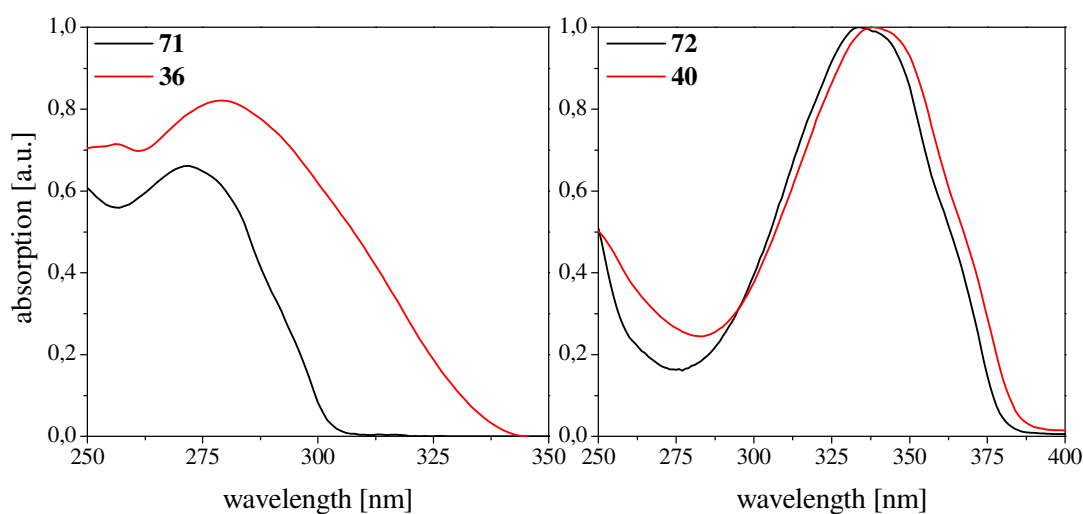


Chart 7.10 HOMO-LUMO energy diagram of triazoles **71-78** and polymer **80**.

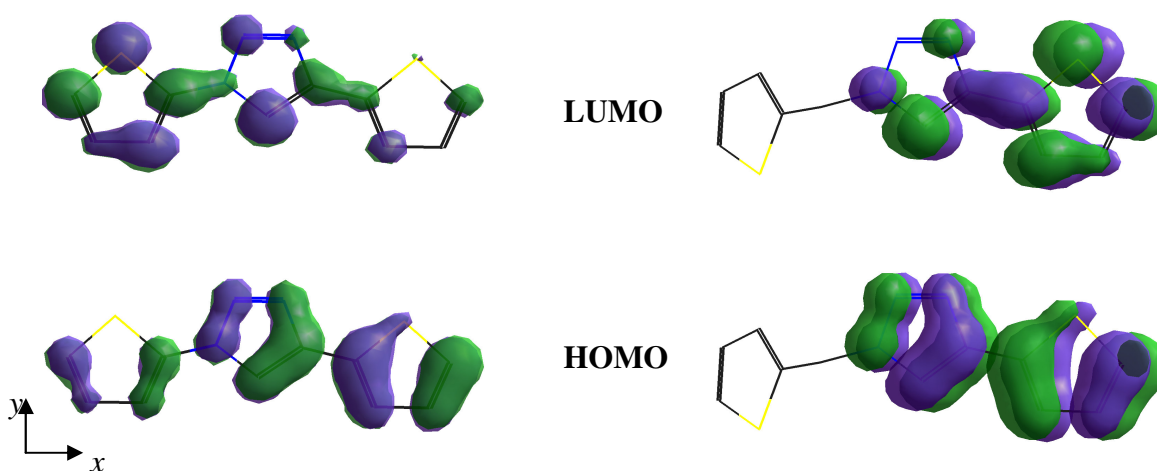
Polymer **80** showed a complete interruption of the conjugation, which appeared in a CV comparable to those of terthiophene subunits. The insertion of two more butyl groups per backbone compared to polymer **79** gave a much better solubility in common solvents. Therefore, the polymer is easily processable and could be investigated in solution.

UV/vis spectra of co-oligomers **71** and **72** were compared to corresponding conjugated species described in chapter 4.3.1. (**36** and **40**). For **36**, an interruption of conjugation through the triazole ring was discussed. Due to the methylene bridge in **71** the conjugation is definitely broken. As shown in Chart 7.11 (left) absorption bands of conjugated and non-conjugated species are different. Absorption of the thiophene subunits (thiophene and 2-vinylthiophene) in **36** is superposed by another band with lower energy. The same trend was found for triazoles **40** and **72**, for which a slight redshift of the absorption band was observed. These redshifts of the absorption bands from conjugated to non-conjugated species were assigned to a weak conjugation through the triazole ring.



**Chart 7.11** UV/vis spectra of triazoles **36** and **71** (left), **40** and **72** (right).

AM1 approximations of the electron distribution in HOMO and LUMO energy levels of compound **36** (Chart 7.12) led to the assumption that a conjugation through the triazole ring is possible, but not preferred. Both HOMO and LUMO are delocalized over the whole molecule. Concerning the AM1 calculations of the non-conjugated triazole **71** HOMO and LUMO are exclusively delocalized in the vinylthiophene subunit. Therefore, spectroscopic properties are derived from this moiety. The approximation confirms the finding in UV/vis, as discussed above.



**Chart 7.12** Electron distribution for **36** (left) and **71** (right) according to AM1 calculations in vacuum.



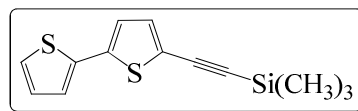
## 7.5 Experimental Part

*Thin layer chromatography* (TLC) was carried out on Silica Gel 60 F<sub>254</sub> aluminium plates (Merck). Developed plates were dried and examined under a UV lamp. *Preparative column chromatography* was carried out on glass columns of different diameters packed with silica gel Merck 60 (63-200  $\mu\text{m}$ ). *Gas chromatography* (GC) was carried out using a Varian CP-3800 gas chromatograph. Helium 5.0 was used as carrying gas, signals were examined by a flame-ionization detector (FID). *Gas chromatography-Mass spectrometry* (GC-MS) measurements were executed with a Varian 3800. Helium 5.0 was used as carrying gas, Mass spectra were recorded on a Varian Saturn 2000. Ions were generated by electron impact (EI). *Melting points* were determined in a Büchi B-545 apparatus and are uncorrected. *NMR spectra* were recorded in  $\text{CDCl}_3$ , *d*6-DMSO or *d*8-THF on a Bruker AMX 400 at 400 MHz ( $^1\text{H}$  nuclei) and 100 MHz ( $^{13}\text{C}$  nuclei), respectively. Chemical shifts are denoted in  $\delta$  unit (ppm), and are referenced to the solvent signal (7.26 ppm for  $\text{CDCl}_3$ , 2.50 ppm for *d*6-DMSO and 1.73 for *d*8-THF). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). *Mass spectra* were measured at Finnigan MAT, SSQ 7000 via CI and Bruker Daltonics REFLEX III via MALDI-TOF. *Elemental analysis* for C, H and N were determined at Elementar Vario EL and for S at Carlo Erba 1104. *High resolution mass* was measured at a microTOF-Q 43 with electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI). *UV/vis* spectra were taken on a Perkin-Elmer Lambda 19 in 1 cm cuvettes. *Fluorescence* spectra were measured with a Perkin-Elmer LS 55 in 1 cm cuvettes. Fluorescence quantum yields were determined with respect to 9,10-diphenylanthracene (DPA,  $\phi = 0.9$  in dichloromethane).<sup>11</sup> *Cyclic voltammetry* experiments were performed with a computer-controlled EG&G PAR 273 potentiostat in a three-electrode single-compartment cell (2 mL). The platinum working electrode consists of a platinum wire sealed in a soft glass tube with a surface of  $A = 0.785 \text{ mm}^2$ , which was polished down to 0.5  $\mu\text{m}$  with Buehler polishing paste prior to use. The counter electrode consists of a platinum wire and the reference electrode was an Ag/AgCl secondary electrode. All potential were internally referenced to the ferrocene/ferricenium couple. For the measurements the electroactive species were used in freshly distilled and deaired dichloromethane and 0.1 M tetrabutylammonium hexafluorophosphate ( $n\text{Bu}_4\text{NPF}_6$ , Fluka) which was twice recrystallized from ethanol and dried under vacuum prior to use.

All reactions were carried out under an inert atmosphere of argon. Thien-2-ylmethanol<sup>2</sup>, 2-chloromethylthiophene<sup>3</sup>, 2-(azidomethyl)-thiophene<sup>1</sup>, 3',4'-dibutyl-2,2':5',2''-terthiophene-5-carbaldehyde<sup>14</sup>, 3',4'-dibutyl-2,2':5',2''-terthiophene-5,5''-dicarbaldehyde<sup>14</sup>, 5-iodo-2,2'-bithiophene<sup>15</sup>, 3',4'-dibutyl-5,5''-diiodo-2,2':5',2''-terthiophene according to Miller<sup>16</sup>, 5-bromo-3',4'-dibutyl-2,2':5',2''-terthiophene<sup>17</sup>, 3,4,3'',4''-tetrabutyl-5,5''-bis-trimethylsilyl-ethynyl-[2,2':5',2'']terthiophene<sup>18</sup>, 3',4'-dibutyl-5,5''-bis-(trimethylsilyl-ethynyl)-2,2':5',2''-terthiophene was synthesized according to standard procedures in the Institute of Organic Chemistry II and Advanced Materials (University Ulm), 5,5''-bis-trimethylsilyl-5'-trimethylsilyl-ethynyl-[2,2';3',2'']terthiophene<sup>19</sup>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>20</sup> were synthesized according to literature. Thiophene-2-carbaldehyde (VWR), trimethylsilyl acetylene (Sigma Aldrich), sodium azide (VWR), diphenylphosphoryl azide (Merck), lithium aluminium hydride (VWR), thionyl chloride (VWR), mesyl chloride (Merck), phosphoryl chloride (VWR), tetrabromocarbon (sublimed, VWR), triphenyl phosphine (VWR), copper(I)-iodide (VWR), tetrakis(acetonitrile)-copper(I) hexafluorophosphate (ABCR), copper powder (VWR), silver(I) tetrafluoroborate (Merck), diisopropylamine (VWR), 1,8-diaza-bicyclo[5.4.0]undec-7-ene (VWR), triethyl amine (VWR), sodium sulfate (anhydrous, Merck), sodium bicarbonate (VWR), hydrochloric acid (VWR), acetonitrile (VWR), dichloromethane (VWR), dichloroethane (VWR), diethyl ether (VWR), ethyl acetate (VWR), petrol ether (VWR), methanol (VWR), THF (dried, VWR), *N,N*-dimethylformamide (dried, VWR), toluene (dried, VWR) were used as received.

### (2,2'-Bithien-5-ylethynyl)(trimethyl)silane<sup>21</sup>

Dichlorobis(triphenylphosphino)-palladium(II) (24 mg, 30 μmol) and copper(I)-iodide (3 mg, 20 μmol) were suspended in diisopropylamine (5 mL) before 5-iodo-2,2'-bithiophene

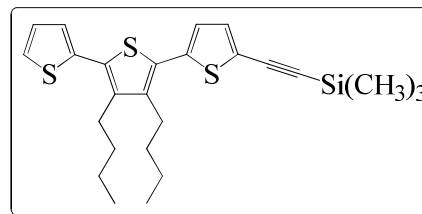


(0.5 g, 1.7 mmol) and trimethylsilylacetylene (0.5 mL, 3.6 mmol) were added. The suspension was stirred at room temperature for two hours. After the addition of hydrochloric acid (2 N, 10 mL) the aqueous phase was extracted with petrol ether (3x 15 mL). The combined organic phases were washed with sodium bicarbonate solution and dried over sodium sulfate. The concentrated crude product was separated on silica using petrol ether as eluent. The product was obtained as slightly green oil in 360.8 mg (1.4 mmol, 81 %). NMR data correspond to literature values.

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 0.25 (9H, s), 7.01 (2H, m), 7.12 (1H, d,  $J$  3.8), 7.17 (1H, dd,  $J$  1.0 and 3.6), 7.23 (1H, dd,  $J$  1.0 and 5.1).

**[(3',4'-dibutyl-2,2':5',2''-terthien-5-yl)ethynyl](trimethyl)silane**

In diisopropylamine (10 mL) 5-bromo-3',4'-dibutyl-2,2':5',2''-terthiophene (351 mg, 0.8 mmol), dichlorobis(triphenylphosphino)-palladium(II) (11 mg, 20  $\mu\text{mol}$ ) and copper(I)-iodide (2 mg, 10  $\mu\text{mol}$ ) were suspended. After addition of trimethylsilylacetylene



(0.23 mL, 1.6 mmol) the mixture was refluxed for two hours. The cooled suspension was treated with hydrochloric acid (2 N, 25 mL). The aqueous phase was extracted with petrol ether (3x 50 mL) and the combined organic phases were washed with sodium bicarbonate solution and dried over sodium sulfate. The concentrated crude product was separated on silica using petrol ether as eluent. The product was obtained as yellow oil in 280.9 mg (0.6 mmol, 77 %).

**Elemental analysis:**  $\text{C}_{25}\text{H}_{32}\text{S}_3\text{Si}$  requires C, 65.73, H, 7.06 %; found: C, 65.67, H, 7.06 %.

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 0.26 (9H, s), 0.96 (6H, m), 1.39- 1.57 (8H, m), 2.69 (4H, m), 6.97 (1H, d,  $J$  3.8), 7.06 (1H, dd,  $J$  3.6 and 5.1), 7.13 (1H, dd,  $J$  1.2 and 3.6), 7.17 (1H, d,  $J$  3.8), 7.31 (1H, dd,  $J$  1.2 and 5.1);

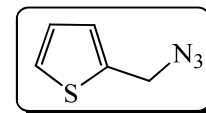
**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) -0.1, 13.8, 13.9, 22.9, 23.0, 27.8, 27.9, 32.8, 32.9, 97.5, 100.0, 122.6, 125.3, 125.5, 126.0, 127.4, 129.3, 130.5, 133.1, 136.0, 138.0, 140.2, 140.6;

**MS (CI):**  $m/z$  (M) = 456.

**2-Azidomethylthiophene (61)**

Procedure A:

Triphenylphosphin (1.1 g, 4.2 mol) and thien-2-ylmethanol (0.34 mL, 2.7 mmol) were dissolved in dry DMF. After slow addition of tetrabromocarbon (1.39 g, 4.2 mmol) at 0 °C the suspension was stirred



at 0 °C for 10 minutes before sodium azide (0.53 g, 8.2 mmol) was added. The suspension was stirred at room temperature in a sealed Schlenk- tube for 15 hours. Water (25 mL) was added and the aqueous phase was extracted with ethyl acetate (3x 50 mL). The organic phases were washed with water (2x 50 mL) and brine (50 mL), dried over sodium sulfate

and concentrated to dryness in vacuum.  $^1\text{H-NMR}$  showed 60 % product and 40 % starting material.

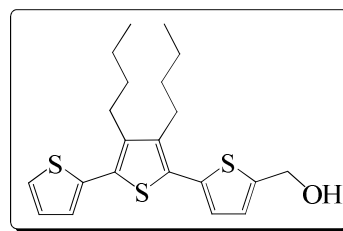
**Procedure B:**

In toluene (5 mL) DPPA (0.65 mL, 3 mmol) and thien-2-ylmethanol (0.3 mL, 2.5 mmol) were dissolved and DBU (0.49 mL, 3.3 mmol) was added slowly. The brown solution was stirred over night in a sealed Schlenk- tube. After treatment with hydrochloric acid (2N, 8 mL) the aqueous phase was extracted with diethyl ether (3x 25 mL). The organic phases were washed with water (3x 25 mL) and brine (2x 15 mL). The solvent was removed at the rotary evaporator.  $^1\text{H-NMR}$  investigations showed a conversion of about 90 %.

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 4.50 (2H, s), 7.02 (1H, dd,  $J$  3.5 and 5.1), 7.05 (1H, m), 7.53 (1H, dd,  $J$  1.2 and 5.1).

**(3',4'-Dibutyl-2,2':5',2''-terthien-5-yl)methanol (69)**

In dry THF (10 mL) lithium aluminium hydride (98 mg, 2.6 mmol) was suspended and 3',4'-dibutyl-2,2':5',2''-terthiophene-5-carbaldehyde (500 mg, 1.3 mmol), dissolved in THF (15 mL) was added dropwise with vigorous stirring. After one hour, the suspension was quenched with



hydrochloric acid (2 N, 10 mL). After extraction of the aqueous phase with diethyl ether (3x 25 mL) the organic phases were washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness to give the product quantitatively (507.0 mg) as greenish oil.

**Elemental analysis:**  $\text{C}_{21}\text{H}_{26}\text{OS}_3$  requires C, 64.57, H, 6.71, S, 24.62 %, found: C, 63.19, H, 6.59, S, 23.14 % (sample contains some amount of water);

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 0.97 (6H, t,  $J$  7.3), 1.41- 1.61 (8H, m), 2.17 (1H, sbr), 2.72 (4H, m), 4.82 (2H, s), 6.96 (1H, d,  $J$  3.6), 7.01 (1H, d,  $J$  3.6), 7.07 (1H, dd,  $J$  3.6 and 5.1), 7.15 (1H, dd,  $J$  1.2 and 3.6), 7.31 (1H, dd,  $J$  1.2 and 5.2);

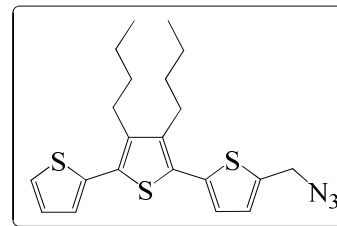
**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) 13.7, 13.8, 22.9, 27.7, 27.8, 32.8, 32.9, 60.0, 125.2, 125.5, 125.7, 125.8, 127.3, 129.8, 129.9, 136.1, 136.5, 139.9, 140.0, 143.7;

**MS (CI):**  $m/z$  (M) = 391, (M- $\text{H}_2\text{O}$ ) = 373;

**HRMS (ESI):**  $m/z$  (M) = 390.1144 ( $\text{C}_{21}\text{H}_{26}\text{OS}_3$  requires 390.1140), (M+H) = 391.1220 ( $\text{C}_{21}\text{H}_{27}\text{OS}_3$  requires 391.1219), (M+Na) = 413.1049 ( $\text{C}_{21}\text{H}_{26}\text{NaOS}_3$  requires 413.1038).

**5-(Azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene (70)**

Terthiophene **68** (452 mg, 1.16 mmol) and DPPA (0.3 mL, 1.3 mmol) were suspended in dry toluene (5 mL) and DBU (0.23 mL, 1.5 mmol) was added slowly by means of syringe. The brownish solution immediately turned deep red. After stirring over night the solution was quenched with hydrochloric acid



(2 N, 15 mL) and extracted with diethyl ether (3x 25 mL). The organic phases were washed with water and brine and dried over sodium sulfate. The concentrated crude product was purified on silica using dichloromethane as eluent to give the title compound as yellow oil in 274.5 mg (0.7 mmol, 57 %).

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.95 (6H, t, J 7.3), 1.40- 1.59 (8H, m), 2.70 (4H, m), 4.61 (2H, s), 6.95 (1H, d, J 3.6), 7.00 (1H, d, J 3.6), 7.06 (1H, dd, J 3.6 and 5.2), 7.13 (1H, dd, J 1.1 and 3.6), 7.31 (1H, dd, J 1.2 and 5.1);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.9, 23.0, 27.7, 27.8, 32.9, 49.3, 125.4, 125.6, 125.9, 127.4, 127.6, 129.3, 130.2, 136.0, 136.8, 137.4, 140.1, 140.4;

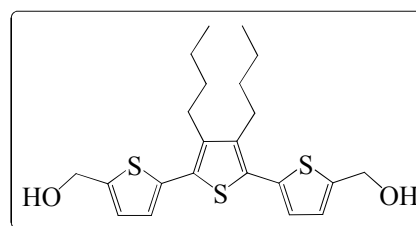
**MS (CI):** m/z (M+H) = 416, (M-N<sub>2</sub>) = 388, (M-N<sub>3</sub>) = 373;

**HRMS (ESI):** m/z (M) = 415.1216 (C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>S<sub>3</sub> requires 415.1205), (M+H) = 416.1266 (C<sub>21</sub>H<sub>26</sub>N<sub>3</sub>S<sub>3</sub> requires 416.1283);

**IR (NaCl):** 3099 (w), 3067 (w), 2952 (s), 2927 (s), 2868 (s), 2858 (s), 2093 (s, azide), 1463 (m), 1377 (m), 1340 (m), 1249 (m), 1226 (m), 855 (m), 799 (m), 692 (s).

**3',4'-Dibutyl-5,5''-bis(hydroxymethyl)-2,2':5',2''-terthiophene (62)**

In THF (20 mL) lithium aluminium hydride (0.09 g, 2.4 mmol) was suspended. 3',4'-Dibutyl-2,2':5',2''-terthiophene-5,5''-dicarbaldehyde (0.4 g, 0.95 mmol) dissolved in THF (5 mL) was added slowly. The suspension was stirred for two hours before



hydrochloric acid (2N, 25 mL) was added. Subsequently, the aqueous phase was extracted with diethyl ether (3x 25 mL) and the organic phases were washed with brine (25 mL). The dried (Na<sub>2</sub>SO<sub>4</sub>) organic phase was concentrated in vacuum to quantitatively give the desired product as beige solid (399.0 mg; purification can be done on silica using dichloromethane with 3 % methanol).

**mp** 105.1- 106.6 °C (dichloromethane);

**Elemental analysis:**  $C_{22}H_{28}O_2S_3$  requires C, 62.82, H, 6.71, S, 22.87 %; found: C, 62.57, H, 6.85, S, 21.97 %;

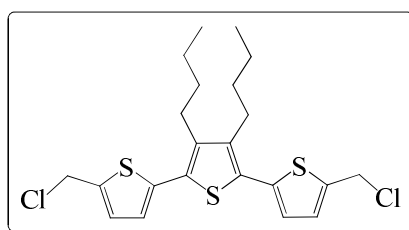
**$^1H$ -NMR:** (400 MHz,  $CDCl_3$ ) 0.95 (3H, t,  $J$  7.3), 1.39- 1.59 (4H, m), 1.84 (1H, sbr), 2.69 (2H, m), 4.83 (2H, s), 6.96 (1H, d,  $J$  3.6), 6.99 (1H, d,  $J$  3.6);  $\delta_C$  (100 MHz,  $CDCl_3$ );

**MS (CI):**  $m/z$  (M) = 420, (M- $H_2O$ ) = 403;

**HRMS (ESI):**  $m/z$  (M) = 420.1250 ( $C_{22}H_{28}O_2S_3$  requires 420.1246), (M+H) = 421.1302 ( $C_{22}H_{29}O_2S_3$  requires 421.1302), (M+Na) = 443.1151 ( $C_{22}H_{28}NaO_2S_3$  requires 443.1144).

### 3',4'-Dibutyl-5,5''-bis(chloromethyl)-2,2':5',2''-terthiophene (63)

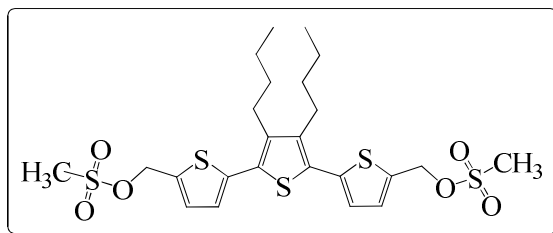
Terthiophene **62** (500 mg, 0.95 mmol) was dissolved in dichloromethane (10 mL). After the addition of thionyl chloride (2 mL, 28 mmol) at 0 °C the solution was stirred for one hour at room temperature. The solvent and excess of reagent were removed at room temperature



in vacuum. The residue was dissolved in dichloromethane (25 mL) and washed with bicarbonate solution and water, dried ( $Na_2SO_4$ ) and concentrated at the rotary evaporator. Due to instability of chloromethylene derivatives it was used without further purification.

### 3',4'-Dibutyl-5,5''-bis(methanesulfonyloxymethyl)-2,2':5',2''-terthiophen (64)

Terthiophene **62** (1.1 g, 2.6 mmol) was dissolved in diethyl ether (40 mL). Under ice cooling triethylamine (0.77 mL, 5.5 mmol) and mesylchloride (0.45 mL, 5.8 mmol) were added slowly. After stirring two hours at

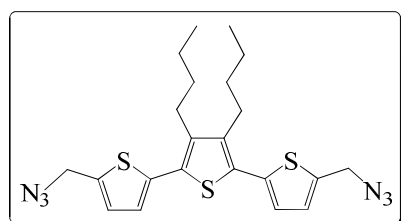


room temperature water (10 mL) was added. The organic phase was washed with brine, dried over sodium sulfate and concentrated at the rotary at room temperature. The product was as instable as the **63**. Therefore, it was used without further purification.

### 5,5''-Bis(azidomethyl)-3',4'-dibutyl-2,2':5',2''-terthiophene (65)

Procedure A:

Terthiophene **63** (1g, 2.2 mmol) and sodium azide (0.85 g, 13 mmol) were dissolved in methanol/water (7 mL,



6:1) and stirred over night. After the addition of water (10 mL) the aqueous phase was extracted with dichloromethane (3x 25 mL). The solvent was removed in vacuum and the crude product was purified on silica using dichloromethane/petrol ether as eluent. The yellow oil was obtained in 124.1 mg (0.3 mmol, 12 %). The conversion of **64** was performed in DMF to yield the azide in 158.9 mg (0.3 mmol, 13 %).

#### Procedure B:

**62** (500 mg, 1.2 mmol) and DPPA (0.62 mL, 2.9 mmol) were dissolved in dry toluene (10 mL) and DBU (0.47 mL, 3.1 mmol) was added by means of syringe. The deep-red solution was stirred over night, after which time hydrochloric acid (2 N, 15 mL) was added. The aqueous phase was extracted with THF (3x 25 mL). The organic phases were washed with brine and water and concentrated in vacuum. The crude product was purified on silica with dichloromethane/petrol ether. The yellow oil was obtained in 180.5 mg (0.4 mmol, 32 %).

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.95 (3H, t, J 7.2), 1.39- 1.57 (4H, m), 2.70 (2H, m), 4.50 (2H, s), 7.00 (1H, d, J 3.7), 7.02 (1H, d, J 3.7);

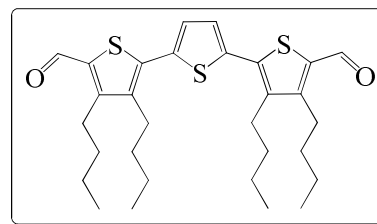
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.8, 23.0, 27.8, 32.9, 49.3, 125.7, 127.7, 129.7, 137.0, 137.2, 140.4;

**MS (CI):** m/z (M) = 470, (M-N<sub>3</sub>) = 428;

**HRMS (APCI):** m/z (M+H) = 471.1456 (C<sub>22</sub>H<sub>27</sub>N<sub>6</sub>S<sub>3</sub> requires 471.1454), (M-N<sub>2</sub>) = 443.1386 (C<sub>22</sub>H<sub>27</sub>N<sub>4</sub>S<sub>3</sub> requires 443.1392).

#### 3,3'',4,4''-Tetrabutyl-2,2':5',2''-terthiophene-5,5''-dicarbaldehyde (**66**)

DMF (1.5 mL, 19.3 mmol) was dissolved in dichloromethane (6 mL) and phosphoryl chloride (1.8 mL, 19.6 mmol) was added slowly. After stirring for one hour, the reagent was added to a solution of 3,3'',4,4''-tetrabutyl-2,2':5',2''-terthiophene (1 g, 2.1 mmol) in



dichloromethane (10 mL). The red solution was refluxed for 8 hours and cooled to room temperature. In an ice bath the solution was treated with bicarbonate solution (150 mL) and stirred for an additional hour. The aqueous phase was extracted with dichloromethane (3x 50 mL) and the dried (Na<sub>2</sub>SO<sub>4</sub>) organic phases were evaporated to dryness at the rotary evaporator. Column chromatography on silica with dichloromethane yielded a yellow solid in 1.06 g (2.0 mmol, 96 %).

**mp** 70.9- 71.9 °C (dichloromethane);

**Elemental analysis:** C<sub>30</sub>H<sub>40</sub>O<sub>2</sub>S<sub>3</sub> requires C, 68.14, H, 7.62, S, 18.19 %; found: C, 67.97, H, 7.62, S, 17.48 %;

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>) 0.92 (6H, m), 1.36- 1.58 (8H, m), 2.75 (2H, m), 2.93 (2H, m), 7.45 (1H, s), 10.04 (1H, s);

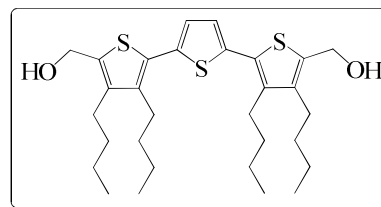
**<sup>13</sup>C-NMR:** (100 MHz, DMSO-*d*<sub>6</sub>) 13.4, 13.5, 22.0, 22.2, 26.1, 26.4, 31.9, 34.0, 128.5, 135.8, 136.1, 138.4, 140.5, 153.0;

**MS (CI):** *m/z* (M+H) = 529;

**HRMS (ESI):** *m/z* (M+H) = 529.2255 (C<sub>30</sub>H<sub>41</sub>O<sub>2</sub>S<sub>3</sub> requires 529.2263).

### 3,3'',4,4''-Tetrabutyl-5,5''-bis(hydroxymethyl)-2,2':5',2''-terthiophene (67)

The reduction was performed with lithium aluminium hydride (90 mg, 2.4 mmol) and **66** (0.5 g, 0.95 mmol) in THF (25 mL) according the procedure described for **62**. The product was separated on silica using dichloromethane containing 3 % methanol to obtain the yellow solid quantitatively (505.4 mg).



**mp** 84.3- 87.5 °C (dichloromethane);

**Elemental analysis:** C<sub>30</sub>H<sub>44</sub>O<sub>2</sub>S<sub>3</sub> requires C, 67.62, H, 8.32, S, 18.05 %; found: C, 67.46, H, 8.28, S, 17.87 %;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.92- 0.98 (6H, m), 1.37- 1.57 (8H, m), 1.63 (1H, sbr), 2.56 (2H, m), 2.70 (2H, m), 4.76 (2H, s), 7.03 (1H, s);

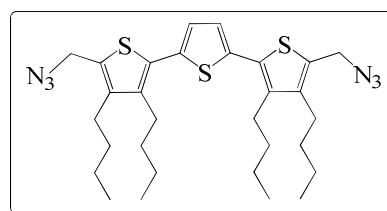
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.8, 13.9, 22.9, 23.0, 27.1, 27.8, 33.0, 33.7, 58.2, 125.9, 129.9, 136.3, 139.5, 140.7;

**MS (CI):** *m/z* (M) = 532, (M-H<sub>2</sub>O) = 515;

**HRMS (ESI):** *m/z* (M) = 532.2482 (C<sub>30</sub>H<sub>44</sub>O<sub>2</sub>S<sub>3</sub> requires 532.2498), (M+Na) = 555.2376 (C<sub>30</sub>H<sub>44</sub>NaO<sub>2</sub>S<sub>3</sub> requires 555.2396).

### 5,5''-Bis(azidomethyl)-3,3'',4,4''-tetrabutyl-2,2':5',2''-terthiophene (68)

According to procedure B described for **65**, terthiophene **67** (0.5 g, 0.94 mmol), DPPA (0.49 mL, 2.3 mmol) and DBU (0.37 mL, 2.4 mmol) were reacted in toluene (10





mL) to give the desired product was obtained as red oil in 421.3 mg (0.7 mmol, 77 %).

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.95 (3H, t, *J* 7.3), 0.97 (3H, t, *J* 7.2), 1.38- 1.56 (8H, m), 2.55 (2H, m), 2.71 (2H, m), 4.45 (2H, s), 7.06 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.8, 13.9, 23.0, 27.8, 32.9, 33.4, 47.5, 126.1, 129.7, 130.5, 136.0, 139.4, 142.2;

**MS (CI):** *m/z* (M) = 582, (M-1/2N<sub>2</sub>) = 540;

**HRMS (ESI):** *m/z* (M) = 582.2631 (C<sub>30</sub>H<sub>42</sub>N<sub>6</sub>S<sub>3</sub> requires 582.2628), (M+H) = 583.2697 (C<sub>30</sub>H<sub>43</sub>N<sub>6</sub>S<sub>3</sub> requires 583.2706), (M-1/2N<sub>2</sub>) = 540.2542 (C<sub>30</sub>H<sub>42</sub>N<sub>3</sub>S<sub>3</sub> requires 540.2535).

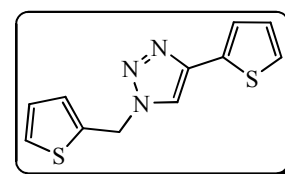
**General procedure for the formation of 1,4-disubstituted 1,2,3-1*H*-triazoles from azides and terminal alkynes (G1) or trimethylsilyl-protected acetylenes (G2)**

**G1:** The azide (1 eq.) was dissolved in acetonitrile (2 mL) and the terminal alkyne (1 eq.) was added. Copper(I)-tetrakisacetonitrile hexafluorophosphate (5 mol-%) and copper powder (1 eq.) were added and the suspension was stirred over night in a sealed Schlenk-tube. The copper was filtered off and washed with dichloromethane. The organic phase was washed with sodium bicarbonate solution and water. After the solvent was removed in vacuum the crude product was purified on silica.

**G2:** According to the Leigh protocol<sup>7</sup>, the azide (1eq.) and the trimethylsilyl-protected acetylene (1eq.) were dissolved in dichloromethane/methanol (4:1). After the addition of copper(I)-tetrakisacetonitrile hexafluorophosphate (20 mol-%) and silver(I)-tetrafluoroborate (20 mol-%) the suspension was stirred over night. Dichloromethane was added and the organic phase was washed with sodium bicarbonate solution (2x 25 mL) and water (25 mL) and dried over sodium sulfate. The solvent was removed at reduced pressure and the crude product was separated on silica.

**4-Thien-2-yl-1-(thien-2-ylmethyl)-1*H*-1,2,3-triazole (71)**

According to G1, **61** (139 mg, 1 mmol), 2-ethynylthiophene (105 mg, 1 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (19.1 mg, 50 μmol) and copper powder (63.6 mg, 1 mmol) gave the product as white solid in 210.0 mg (0.9 mmol, 85 %) yield. Procedure G2 with **61** (139 mg,



1 mmol), trimethyl(thien-2-ylethynyl)silan (180 mg, 1 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (162 mg, 0.2 mmol) and AgBF<sub>4</sub> (39 mg, 0.2 mmol) in 2.5 mL solvent mixture yielded in 185.3 mg (0.8 mmol, 75 %) (column chromatography with dichloromethane as eluent).

**mp** 115.5 °C.

**Elemental analyses:** C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>S<sub>2</sub> requires C, 53.42, H, 3.67, N, 16.99, S, 25.93 %; found: C, 53.48, H, 3.71, N, 16.95, S, 25.63 %;

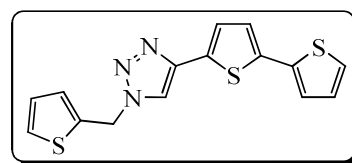
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 5.74 (2H, s), 7.03 (1H, dd, *J* 5.2 and 3.6), 7.05 (1H, dd, *J* 5.1 and 3.7), 7.15 (1H, dd, *J* 3.4 and 0.8), 7.28 (1H, dd, *J* 5.1 and 1.1), 7.36 (1H, dd, *J* 3.6 and 1.3), 7.35 (1H, dd, *J* 1.9 and 1.5), 7.68 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 48.8, 118.8, 124.4, 125.3, 127.4, 127.6, 127.7, 128.5, 136.0;

**MS (CI):** *m/z* (M+H) = 248, (M-N<sub>2</sub>H) = 218, (C<sub>5</sub>H<sub>5</sub>S) = 97.

#### 4-(2,2''-Bithien-5-yl)-1-(thien-2-ylmethyl)-1*H*-1,2,3-triazole (72)

**61** (139 mg, 1 mmol), 5-ethynyl-2,2'-bithiophene (190 mg, 1 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (19.1 mg, 50 μmol) and copper powder (63.6 mg, 1 mmol) gave the product through G1 as off-white solid in 167.8 mg (0.5 mmol, 51 %). According to



G2 **61** (70 mg, 0.5 mmol), (2,2'-bithien-5-ylethynyl)(trimethyl)silane (158 mg, 0.6 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (81 mg, 0.1 mmol) and AgBF<sub>4</sub> (19.5 mg, 0.1 mmol) in 2.5 mL solvent gave the product in 128.3 mg (0.4 mmol, 78 %) (column chromatography with dichloromethane).

**mp** 173.9 °C;

**Elemental analysis:** C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>S<sub>3</sub> requires C, 54.68, H, 3.37, N, 12.75, S, 29.20 %; found: C, 54.53, H, 3.50, N, 12.66, S, 28.15 %;

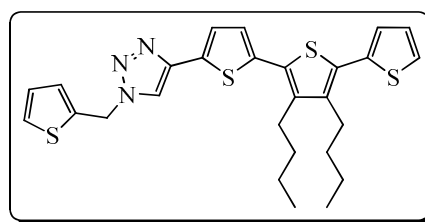
**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 5.74 (2H, s), 7.02 (1H, dd, *J* 4.6 and 3.1), 7.04 (1H, dd, *J* 4.6 and 3.0), 7.12 (1H, d, *J* 3.8), 7.16 (1, dd, *J* 3.4 and 0.7), 7.19 (1H, dd, *J* 3.6 and 1.1), 7.22 (1H, dd, *J* 5.1 and 1.1), 7.24 (1H, d, *J* 3.8), 7.37 (1H, dd, *J* 5.1 and 1.2), 7.63 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, DMSO-*d*<sub>6</sub>) 47.5, 120.6, 124.2, 124.5, 125.2, 125.6, 127.2, 127.3, 128.2, 128.4, 131.6, 135.6, 136.2, 137.3, 141.6;

**MS (CI):** *m/z* (M+H) = 330, (M-N<sub>2</sub>) = 301, (C<sub>5</sub>H<sub>5</sub>S) = 97.

#### 4-(3',4'-Dibutyl-2,2':5',2''-terthien-5-yl)-1-(thien-2-ylmethyl)-1*H*-1,2,3-triazole (73)

**61** (28 mg, 0.2 mmol) and [(3',4'-dibutyl-2,2':5',2''-terthien-5-yl)ethynyl](trimethyl)silane (92 mg, 0.2 mmol) were catalyzed by Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (32 mg, 40



$\mu\text{mol}$ ) and  $\text{AgBF}_4$  (8 mg, 40  $\mu\text{mol}$ ) in 2.5 mL dichloromethane- methanol mixture according to G2. After column chromatography with dichloromethane/THF the product was obtained as yellow solid in 88.0 mg (0.2 mmol, 84 %).

**mp** 114.4 °C;

**Elemental analysis:**  $\text{C}_{27}\text{H}_{29}\text{N}_3\text{S}_4$  requires C, 61.91, H, 5.58, N, 8.02, S, 24.49 %; found: C, 62.03, H, 5.53, N, 7.92, S, 23.68 %;

**$^1\text{H}$ -NMR:** (400 MHz,  $\text{CDCl}_3$ ) 0.94 (6H, t,  $J$  7.2), 1.44- 1.56 (8H, m), 2.67- 2.75 (4H, m), 5.57 (2H, s), 7.03 (1H, dd,  $J$  3.7 and 5.3), 7.05 (1H, dd,  $J$  3.8 and 5.3), 7.07 (1H, d,  $J$  3.7), 7.14 (1H, dd,  $J$  1.1 and 3.6), 7.16 (1H, dd,  $J$  0.5 and 3.5), 7.28 (1H, d,  $J$  3.8), 7.31 (1H, dd,  $J$  1.1 and 5.2 ), 7.36 (1H, dd,  $J$  1.1 and 5.1), 7.65 (1H, s);

**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{DMSO}-d_6$ ) 13.8, 13.9, 23.0, 27.8, 27.9, 32.8, 32.9, 48.7, 118.6, 124.5, 125.3, 125.4, 125.9, 126.2, 127.2, 127.3, 127.4, 128.4, 129.5, 132.2, 135.8, 136.0, 140.2, 140.3, 143.1

**MS (CI):**  $m/z$  (M) = 524, (M- $\text{C}_5\text{H}_5\text{S}$ ) = 427, ( $\text{C}_5\text{H}_5\text{S}$ ) = 97.

#### 4-[4,5''-Bis(trimethylsilyl)-2,2':3',2''-terthien-5'-yl]-1-(thien-2-ylmethyl)-1*H*-1,2,3-triazole (74)

According to G1, the product was formed from **61** (21 mg, 0.15 mmol), [5'-ethynyl-5''-(trimethylsilyl)-2,2':3',2''-terthien-5-yl](trimethyl)silane (125 mg, 0.3 mmol),  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (5.6 mg, 10  $\mu\text{mol}$ ) and copper powder (19.1 mg, 0.3 mmol) in 82.6 mg (0.15 mmol, 99 %) as off-white solid (column chromatography with dichloromethane).

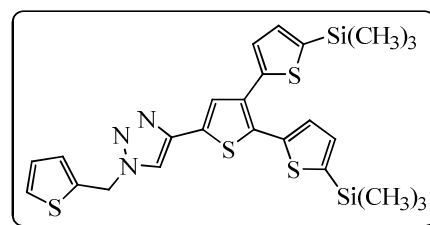
**mp** 108.5 °C;

**Elemental analysis:**  $\text{C}_{25}\text{H}_{29}\text{N}_3\text{S}_4\text{Si}_2$  requires C, 54.01, H, 5.26, N, 7.56, S, 23.07 %; found: C, 53.89, H, 5.45, N, 7.03, S, 21.65 %;

**$^1\text{H}$ -NMR:** (400 MHz,  $\text{CDCl}_3$ ) 0.29 (18H, s), 5.74 (2H, s), 7.03 (1H, dd,  $J$  5.1 and 3.5), 7.10 (3H, m), 7.15 (1H, d,  $J$  3.4), 7.17 (1H, dd,  $J$  3.4 and 0.9), 7.35 (1H, dd,  $J$  5.1 and 1.2), 7.39 (1H, s), 7.73 (1H, s);

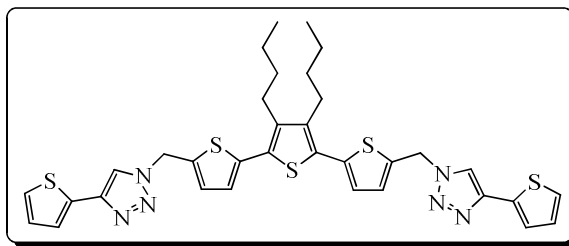
**$^{13}\text{C}$ -NMR:** (100 MHz,  $\text{CDCl}_3$ ) 0.3, 0.4, 48.4, 121.6, 127.1, 127.2, 127.9, 128.0, 128.8, 132.3, 132.5, 1342.7, 135.3, 135.6, 137.9, 139.4, 140.9, 141.7, 142.1, 142.6;

**MS (CI):**  $m/z$  (M) = 556, (M- $\text{Si}(\text{CH}_3)_3$ ) = 484.



**1-[(3',4'-Dibutyl-5''-[4-(2-thienyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2,2':5',2''-terthien-5-yl)methyl]-4-(2-thienyl)-1*H*-1,2,3-triazole (75)**

**65** (124 mg, 0.26 mmol) and 2-ethynylthiophene (54 mg, 0.5 mmol) were coupled in acetonitrile (4 mL), catalyzed by  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (40.4 mg, 50  $\mu\text{mol}$ ) and copper powder (32 mg, 0.5 mmol),



according to G1 to give the yellow solid in 174.8 mg (0.25 mmol, 98 %) after column chromatography with dichloromethane/THF as eluent.

**mp** 184.8- 185.4 °C;

**Elemental analysis:**  $\text{C}_{34}\text{H}_{34}\text{N}_6\text{S}_5$  requires C, 59.44, H, 4.99, N, 12.23, S, 23.34 %; found: C, 59.31, H, 5.12, N, 12.11, S, 23.16 %;

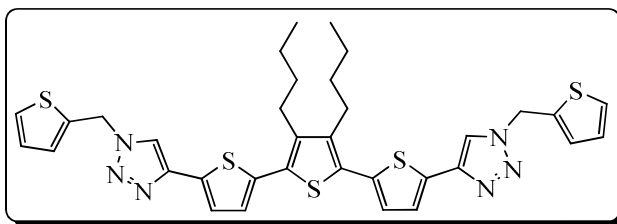
**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J$  7.2), 1.39- 1.44 (2H, m), 1.49- 1.55 (2H, m), 2.68 (2H, m), 5.75 (2H, s), 7.05 (1H, d,  $J$  3.7), 7.09 (1H, dd,  $J$  4.9 and 3.2), 7.12 (1H, d,  $J$  3.7), 7.33 (1H, d,  $J$  5.1), 7.44 (1H, s), 7.75 (1H, s);

**$^{13}\text{C-NMR}$ :** (100 MHz,  $\text{CDCl}_3$ ) 13.8, 22.9, 27.8, 32.8, 48.8, 124.3, 125.2, 125.9, 127.6, 128.7, 129.5, 135.5, 140.8;

**MS (MALDI-TOF):**  $m/z$  (M) = 686, (M-(thiophene-triazolyl)) = 536.

**4-{3',4'-Dibutyl-5''-[1-(2-thienylmethyl)-1*H*-1,2,3-triazol-4-yl]-2,2':5',2''-terthien-5-yl]-1-(2-thienylmethyl)-1*H*-1,2,3-triazole (77)**

According to G2, **61** (139 mg, 1 mmol), 3',4'-dibutyl-5,5''-bis-(trimethylsilyl-ethynyl)-2,2':5',2''-terthiophene (277 mg, 0.5 mmol),  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (162 mg, 0.2 mmol) and  $\text{AgBF}_4$  (39 mg, 0.2



mmol) were suspended in 5 mL solvent mixture. The crude product was purified on silica with dichloromethane/THF to give the pure, yellow solid in 219.5 mg (0.3 mmol, 64 %).

**mp** 205 °C;

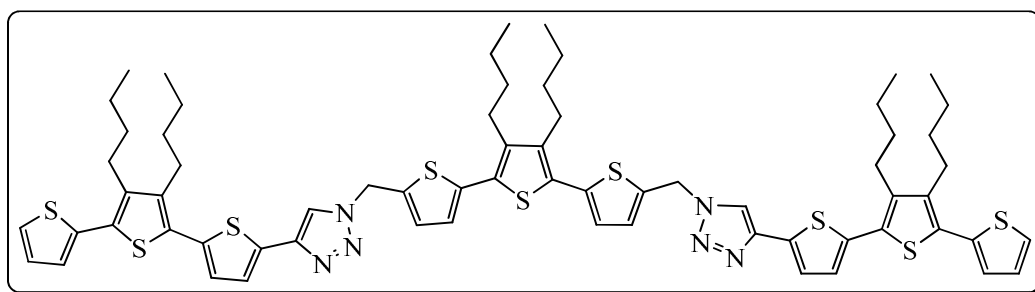
**Elemental analysis:**  $\text{C}_{34}\text{H}_{34}\text{N}_6\text{S}_5$  requires C, 59.44, H, 4.99, N, 12.23, S, 23.34 %; found: C, 59.51, H, 5.05, N, 12.12, S, 23.10 %;

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>) 0.92 (3H, t, *J* 7.2), 1.40- 1.52 (4H, m), 2.72 (2H, m), 5.87 (2H, s), 7.05 (1H, dd, *J* 5.1 and 3.5), 7.22 (1H, d, *J* 3.8), 7.25 (1H, dd, *J* 3.5 and 0.5), 7.46 (1H, d, *J* 3.8), 7.56 (1H, dd, *J* 5.1 and 1.2), 8.61 (1H, s);

**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.9, 23.0, 27.9, 32.8, 48.7, 118.6, 124.5, 126.3, 127.3, 127.4, 128.4, 129.8, 135.8, 135.9, 140.4;

**MS (MALDI-TOF):** *m/z* (M+H) = 687.

**1-[(3',4'-Dibutyl-5''-[4-(3',4'-dibutyl-2,2':5',2''-terthien-5-yl)-1*H*-1,2,3-triazol-1-yl]methyl}-2,2':5',2''-terthien-5-yl)methyl]-4-(3',4'-dibutyl-2,2':5',2''-terthien-5-yl)-1*H*-1,2,3-triazole (76)**



According to G2, **65** (96 mg, 0.2 mmol), [(3',4'-dibutyl-2,2':5',2''-terthien-5-yl)ethynyl](trimethyl)silane (185 mg, 0.4 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (131 mg, 0.16 mmol) and AgBF<sub>4</sub> (32 mg, 0.16 mmol) were reacted in 5 mL of the solvent mixture to give the desired product, after column chromatography using dichloromethane/THF, in 240.2 mg (0.2 mmol, 97 %) as yellow solid.

**mp** 156.5- 158.0 °C;

**Elemental analysis:** C<sub>66</sub>H<sub>74</sub>N<sub>6</sub>S<sub>9</sub> requires C, 63.93, H, 6.02, N, 6.78, S, 23.27 %; found: C, 63.82, H, 6.19, N, 6.71, S, 22.88 %;

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>) 0.91- 0.96 (9H, m), 1.38- 1.57 (12H, m), 2.64- 2.75 (6H, m), 5.73 (2H, s), 7.03 (1H, d, *J* 3.7), 7.06 (1H, dd, *J* 3.6 and 5.1), 7.09 (2H, m), 7.13 (1H, dd, *J* 1.1 and 3.6), 7.31 (2H, m), 7.71 (1H, s);

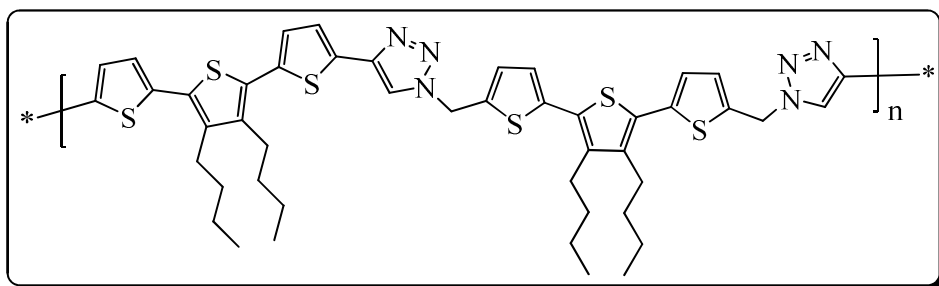
**<sup>13</sup>C-NMR:** (100 MHz, CDCl<sub>3</sub>) 13.8, 22.9, 23.0, 27.7, 27.8, 27.9, 32.7, 32.8, 32.9, 48.8, 118.6, 124.6, 125.4, 125.9, 126.0, 126.2, 127.5, 128.6, 129.6, 130.1, 132.2, 135.5, 136.1, 136.2, 138.1, 140.2, 140.3, 140.8, 143.2;

**MS (MALDI-TOF):** *m/z* (M-2N<sub>2</sub>) = 1184.3, (M-C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>S<sub>3</sub>) = 812.2;

**HRMS (ESI):** *m/z* (M+Na) = 1261.3353 (C<sub>66</sub>H<sub>74</sub>N<sub>6</sub>NaS<sub>9</sub> requires 1261.3354).

CCCCC1=C(C2=CC=CC=C2S1)C(=C3C(=C(C=C3)S2)C(=C4C(=C(C=C4)S)C(=C5C(=C(C=C5)S)C(=C6C(=C(C=C6)S)C(=C7C(=C(C=C7)S)C(=C8C(=C(C=C8)S)C(=C9C(=C(C=C9)S)C(=C10C(=C(C=C10)S)C(=C11C(=C(C=C11)S)C(=C12C(=C(C=C12)S)C(=C13C(=C(C=C13)S)C(=C14C(=C(C=C14)S)C(=C15C(=C(C=C15)S)C(=C16C(=C(C=C16)S)C(=C17C(=C(C=C17)S)C(=C18C(=C(C=C18)S)C(=C19C(=C(C=C19)S)C(=C20C(=C(C=C20)S)C(=C21C(=C(C=C21)S)C(=C22C(=C(C=C22)S)C(=C23C(=C(C=C23)S)C(=C24C(=C(C=C24)S)C(=C25C(=C(C=C25)S)C(=C26C(=C(C=C26)S)C(=C27C(=C(C=C27)S)C(=C28C(=C(C=C28)S)C(=C29C(=C(C=C29)S)C(=C30C(=C(C=C30)S)C(=C31C(=C(C=C31)S)C(=C32C(=C(C=C32)S)C(=C33C(=C(C=C33)S)C(=C34C(=C(C=C34)S)C(=C35C(=C(C=C35)S)C(=C36C(=C(C=C36)S)C(=C37C(=C(C=C37)S)C(=C38C(=C(C=C38)S)C(=C39C(=C(C=C39)S)C(=C40C(=C(C=C40)S)C(=C41C(=C(C=C41)S)C(=C42C(=C(C=C42)S)C(=C43C(=C(C=C43)S)C(=C44C(=C(C=C44)S)C(=C45C(=C(C=C45)S)C(=C46C(=C(C=C46)S)C(=C47C(=C(C=C47)S)C(=C48C(=C(C=C48)S)C(=C49C(=C(C=C49)S)C(=C50C(=C(C=C50)S)C(=C51C(=C(C=C51)S)C(=C52C(=C(C=C52)S)C(=C53C(=C(C=C53)S)C(=C54C(=C(C=C54)S)C(=C55C(=C(C=C55)S)C(=C56C(=C(C=C56)S)C(=C57C(=C(C=C57)S)C(=C58C(=C(C=C58)S)C(=C59C(=C(C=C59)S)C(=C60C(=C(C=C60)S)C(=C61C(=C(C=C61)S)C(=C62C(=C(C=C62)S)C(=C63C(=C(C=C63)S)C(=C64C(=C(C=C64)S)C(=C65C(=C(C=C65)S)C(=C66C(=C(C=C66)S)C(=C67C(=C(C=C67)S)C(=C68C(=C(C=C68)S)C(=C69C(=C(C=C69)S)C(=C70C(=C(C=C70)S)C(=C71C(=C(C=C71)S)C(=C72C(=C(C=C72)S)C(=C73C(=C(C=C73)S)C(=C74C(=C(C=C74)S)C(=C75C(=C(C=C75)S)C(=C76C(=C(C=C76)S)C(=C77C(=C(C=C77)S)C(=C78C(=C(C=C78)S)C(=C79C(=C(C=C79)S)C(=C80C(=C(C=C80)S)C(=C81C(=C(C=C81)S)C(=C82C(=C(C=C82)S)C(=C83C(=C(C=C83)S)C(=C84C(=C(C=C84)S)C(=C85C(=C(C=C85)S)C(=C86C(=C(C=C86)S)C(=C87C(=C(C=C87)S)C(=C88C(=C(C=C88)S)C(=C89C(=C(C=C89)S)C(=C90C(=C(C=C90)S)C(=C91C(=C(C=C91)S)C(=C92C(=C(C=C92)S)C(=C93C(=C(C=C93)S)C(=C94C(=C(C=C94)S)C(=C95C(=C(C=C95)S)C(=C96C(=C(C=C96)S)C(=C97C(=C(C=C97)S)C(=C98C(=C(C=C98)S)C(=C99C(=C(C=C99)S)C(=C100C(=C(C=C100)S)C(=C101C(=C(C=C101)S)C(=C102C(=C(C=C102)S)C(=C103C(=C(C=C103)S)C(=C104C(=C(C=C104)S)C(=C105C(=C(C=C105)S)C(=C106C(=C(C=C106)S)C(=C107C(=C(C=C107)S)C(=C108C(=C(C=C108)S)C(=C109C(=C(C=C109)S)C(=C110C(=C(C=C110)S)C(=C111C(=C(C=C111)S)C(=C112C(=C(C=C112)S)C(=C113C(=C(C=C113)S)C(=C114C(=C(C=C114)S)C(=C115C(=C(C=C115)S)C(=C116C(=C(C=C116)S)C(=C117C(=C(C=C117)S)C(=C118C(=C(C=C118)S)C(=C119C(=C(C=C119)S)C(=C120C(=C(C=C120)S)C(=C121C(=C(C=C121)S)C(=C122C(=C(C=C122)S)C(=C123C(=C(C=C123)S)C(=C124C(=C(C=C124)S)C(=C125C(=C(C=C125)S)C(=C126C(=C(C=C126)S)C(=C127C(=C(C=C127)S)C(=C128C(=C(C=C128)S)C(=C129C(=C(C=C129)S)C(=C130C(=C(C=C130)S)C(=C131C(=C(C=C131)S)C(=C132C(=C(C=C132)S)C(=C133C(=C(C=C133)S)C(=C134C(=C(C=C134)S)C(=C135C(=C(C=C135)S)C(=C136C(=C(C=C136)S)C(=C137C(=C(C=C137)S)C(=C138C(=C(C=C138)S)C(=C139C(=C(C=C139)S)C(=C140C(=C(C=C140)S)C(=C141C(=C(C=C141)S)C(=C142C(=C(C=C142)S)C(=C143C(=C(C=C143)S)C(=C144C(=C(C=C144)S)C(=C145C(=C(C=C145)S)C(=C146C(=C(C=C146)S)C(=C147C(=C(C=C147)S)C(=C148C(=C(C=C148)S)C(=C149C(=C(C=C149)S)C(=C150C(=C(C=C150)S)C(=C151C(=C(C=C151)S)C(=C152C(=C(C=C152)S)C(=C153C(=C(C=C153)S)C(=C154C(=C(C=C154)S)C(=C155C(=C(C=C155)S)C(=C156C(=C(C=C156)S)C(=C157C(=C(C=C157)S)C(=C158C(=C(C=C158)S)C(=C159C(=C(C=C159)S)C(=C160C(=C(C=C160)S)C(=C161C(=C(C=C161)S)C(=C162C(=C(C=C162)S)C(=C163C(=C(C=C163)S)C(=C164C(=C(C=C164)S)C(=C165C(=C(C=C165)S)C(=C166C(=C(C=C166)S)C(=C167C(=C(C=C167)S)C(=C168C(=C(C=C168)S)C(=C169C(=C(C=C169)S)C(=C170C(=C(C=C170)S)C(=C171C(=C(C=C171)S)C(=C172C(=C(C=C172)S)C(=C173C(=C(C=C173)S)C(=C174C(=C(C=C174)S)C(=C175C(=C(C=C175)S)C(=C176C(=C(C=C176)S)C(=C177C(=C(C=C177)S)C(=C178C(=C(C=C178)S)C(=C179C(=C(C=C179)S)C(=C180C(=C(C=C180)S)C(=C181C(=C(C=C181)S)C(=C182C(=C(C=C182)S)C(=C183C(=C(C=C183)S)C(=C184C(=C(C=C184)S)C(=C185C(=C(C=C185)S)C(=C186C(=C(C=C186)S)C(=C187C(=C(C=C187)S)C(=C188C(=C(C=C188)S)C(=C189C(=C(C=C189)S)C(=C190C(=C(C=C190)S)C(=C191C(=C(C=C191)S)C(=C192C(=C(C=C192)S)C(=C193C(=C(C=C193)S)C(=C194C(=C(C=C194)S)C(=C195C(=C(C=C195)S)C(=C196C(=C(C=C196)S)C(=C197C(=C(C=C197)S)C(=C198C(=C(C=C198)S)C(=C199C(=C(C=C199)S)C(=C200C(=C(C=C200)S)C(=C201C(=C(C=C201)S)C(=C202C(=C(C=C202)S)C(=C203C(=C(C=C203)S)C(=C204C(=C(C=C204)S)C(=C205C(=C(C=C205)S)C(=C206C(=C(C=C206)S)C(=C207C(=C(C=C207)S)C(=C208C(=C(C=C208)S)C(=C209C(=C(C=C209)S)C(=C210C(=C(C=C210)S)C(=C211C(=C(C=C211)S)C(=C212C(=C(C=C212)S)C(=C213C(=C(C=C213)S)C(=C214C(=C(C=C214)S)C(=C215C(=C(C=C215)S)C(=C216C(=C(C=C216)S)C(=C217C(=C(C=C217)S)C(=C218C(=C(C=C218)S)C(=C219C(=C(C=C219)S)C(=C220C(=C(C=C220)S)C(=C221C(=C(C=C221)S)C(=C222C(=C(C=C222)S)C(=C223C(=C(C=C223)S)C(=C224C(=C(C=C224)S)C(=C225C(=C(C=C225)S)C(=C226C(=C(C=C226)S)C(=C227C(=C(C=C227)S)C(=C228C(=

**IR (KBr):** 2950 (s), 2922 (s), 2857 (m), 2855 (m), 1625 (m, triazole), 1453 (s), 1418 (shoulder), 1375 (m), 1333 (m), 1164 (s, triazole), 1115 (s), 1099 (s), 1030 (s, triazole), 891 (s), 871 (s), 807 (shoulder, triazole), 747 (m), 688 (m), 556 (s).

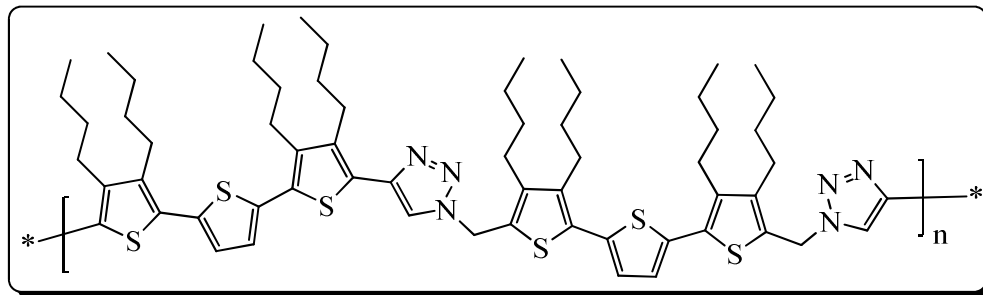
**Polymer 1 (79)**

According to G2, in 10 mL of dichloromethane/methanol **65** (178 mg, 0.38 mmol) and 3',4'-dibutyl-5,5''-bis-(trimethylsilanylethynyl)-2,2':5',2''-terthiophene (209 mg, 0.38 mmol) were polymerized using  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (122 mg, 0.15 mmol) and  $\text{AgBF}_4$  (29 mg, 0.15 mmol) as catalysts. The monomers were washed off by dichloromethane. The residual polymer was fractionated using Soxhlett-extraction with THF, toluene, dichloromethane and dichloroethane. Only in the THF fraction some yellow powder (15.5 mg) could be obtained and was characterized by high temperature NMR. The structure was confirmed by IR and compared to **78**, whose structure was proven by common analytics. After Soxhlett-extraction the residue was dissolved in boiling DMF and filtered hot. During cooling a brown, parchment-like polymer (308 mg) was obtained. The structure was only assumed due to IR, because of the insolubility of the product.

**mp** >400 °C;

**$^1\text{H-NMR}$** : (500 MHz,  $\text{DMSO-}d_6$ , 353K) 0.87 (12H, m), 1.32- 1.54 (16H, m), 2.64- 2.74 (8H, m), 5.87 (4H, s), 7.10 (2H, m), 7.21 (4H, m), 7.42 (2H, m), 8.51 (2H, s);

**IR (KBr)**: 3114 (w), 3059 (w), 2950 (s), 2923 (s), 2857 (m), 2855 (m), 1635 (m, triazole), 1453 (s), 1424 (s), 1375 (m), 1340 (m), 1246 (shoulder), 1163 (s, triazole), 1038 (s, triazole), 808 (s, triazole), 797 (s), 747 (m), 564 (s).

**Polymer 2 (80)**

In 10 mL of dichloromethane/methanol **68** (200 mg, 0.34 mmol) and 3,4,3'',4''-tetrabutyl-5,5''-bis(trimethylsilyl-ethynyl)-2,2':5',2''-terthiophene (228 mg, 0.34 mmol) were polymerized via G2, catalyzed by  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (111 mg, 0.14 mmol) and  $\text{AgBF}_4$  (27 mg, 0.14 mmol). A soluble polymer was obtained as red-brown solid (370 mg, 0.34 mmol, 98 %). Confirmation of the molecular mass by MALDI-TOF was not possible, because of the high polydispersity. The polymer was dissolved in dichloromethane and petrol ether was added subsequently, to filter off the fractions of the polymer.

**mp** >400 °C,

**$^1\text{H-NMR}$ :** (400 MHz,  $\text{CDCl}_3$ ) 0.93 (24H, m), 1.40 (32H, m), 2.70 (16H, m), 5.65 (4H, s, br), 7.03 (4H, m), 7.56 (2H, s).



## 7.6 References

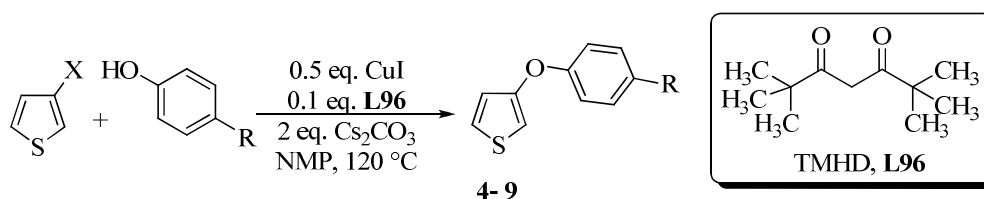
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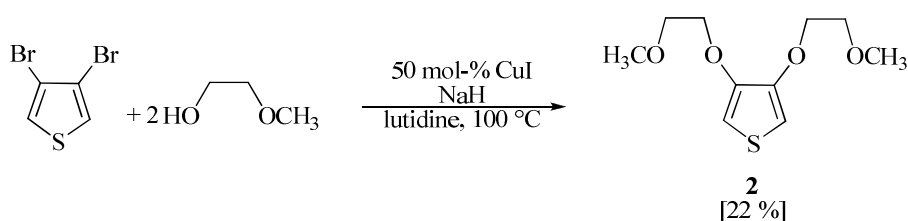
## Summary

PEDOT:PSS, known as trademark Clevios P<sup>®</sup>, is the most frequently applied polymer in organic electronics. It is used in condensers, electrochromics, OLED's or as antistatic. Task of this thesis was development of an effective method to synthesize EDOT derivatives and its *N*-analogous. Therefore, 3,4-dibromothiophene should be substituted with *O*- and *N*-nucleophiles using palladium- and copper-catalysis.

Numerous examples were already published concerning nucleophilic substitution of halogenated thiophenes with alcohols with the aid of copper salts as catalysts. It was shown that phenols could be coupled under milder reaction conditions. Therefore, modern catalyst systems were applied which were described for Ullmann-type diphenyl ether synthesis. Moderate yields for the reaction of 3-halogenothiophenes and phenols were observed with copper(I) chloride and TMHD as ligand. However, these reaction conditions were not universal.

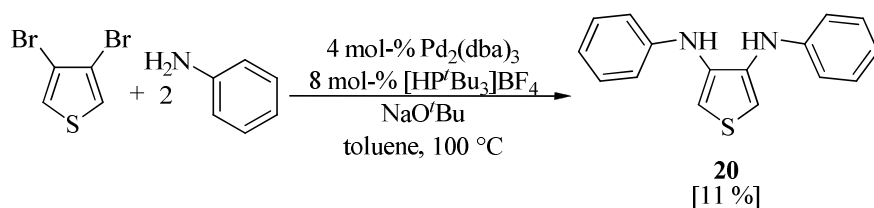


The conversion of 3,4-dibromothiophene with 2-methoxyethanol was also investigated. Only a low yield of the desired disubstituted product was obtained. Compared to the synthesis of 3,4-di(methoxyethoxy)-thiophene (**2**) described in literature, it could be shown that the synthetic effort under the new reaction conditions was much less. Therefore, the protocol was improved. Nevertheless, with none of the catalytic systems investigated during this thesis 3,4-dibromothiophene could be converted to EDOT analogs. Formation of stable copper-diol complexes was discussed. Therefore, the poisoned catalyst is ineffective. 3,4-Dibromothiophene was re-isolated in almost every case.



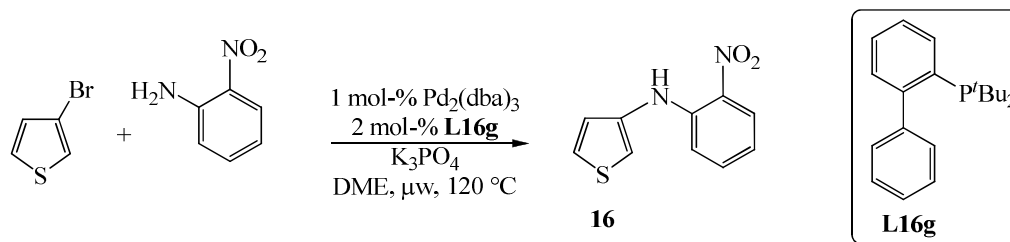
Palladium catalysts were ineffective for C-O cross-coupling for both aromatic and aliphatic alcohols. The effect of microwave irradiation was investigated for the copper-catalyzed synthesis of thiophene-phenyl ethers. Reaction times were dramatically decreased. Generally, no significant increase in product yield was observed. For the conversion of 4-chlorophenol with 3-bromothiophene C-O cross-coupling of 4-chlorophenol to 3-(4-chlorophenoxy)-thiophene **6** was suppressed due to short reaction time. Therefore, a dramatic increase in product yield was observed.

In literature, conversion of 3-bromothiophene with *N*-nucleophiles using palladium catalysts is described many times. Several ligands were investigated for C-N cross-couplings with 3-bromothiophene. However, no better ligand system could be developed, in comparison to these described by Buchwald and Hartwig. The conversion of secondary anilines gave higher yields than for primary ones. Disubstitution at 3,4-dibromothiophene with several amines gave no or only poor yields. Secondary amines, which gave good results for C-N cross-coupling at 3-bromothiophene, could not be coupled to 3,4-dibromothiophene. *N*<sup>3</sup>,*N*<sup>4</sup>-Diphenylthiophene-3,4-diamine **20** was the only disubstituted product obtained in only 11 %. Yet, it was irrelevant if 3,4-dibromothiophene was used as starting material or 4-bromo-*N*-phenylthiophene-3-amine **21**. Also for C-N cross-couplings no ring closure could be realized.



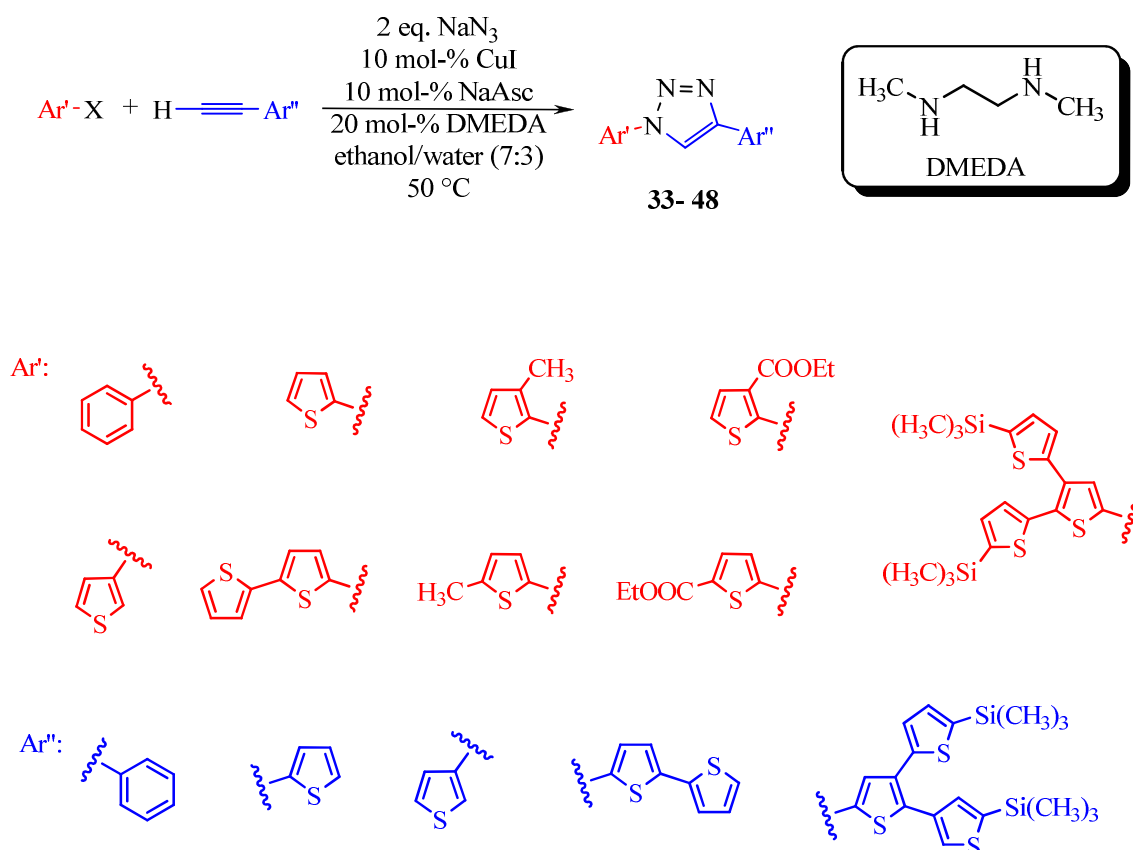
Under Ullmann-type reaction conditions, no amination of halogenothiophenes was observed. However, the effect of microwave irradiation was investigated on chosen examples for palladium catalyzed C-N cross-couplings. Reaction times could again be dramati-

cally decreased. According to GC-analysis, 3-bromothiophene was quantitatively coupled to aniline. However, due to sensitivity of the product towards oxidation only a moderate yield was obtained. Conversion of 2-nitroaniline with 3-bromothiophene was successful just under microwave irradiation. Under “conventional” reaction conditions no reaction was observed.



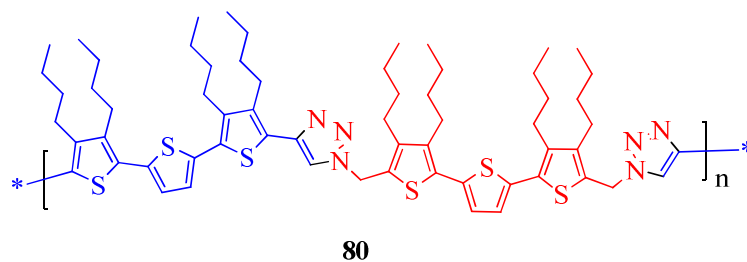
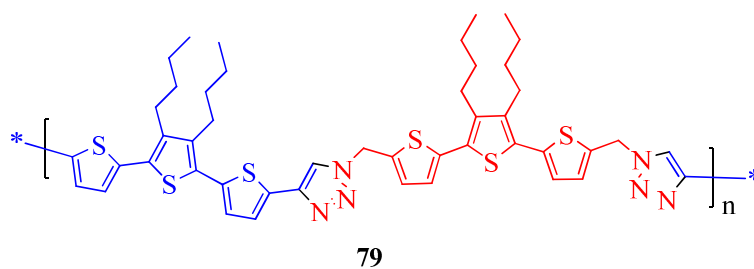
Because the investigations led not into an advanced protocol for the synthesis of EDOT derivatives and its *N*-analogous this project was stopped.

Copper-catalyzed nucleophilic substitution of azides at halogenated thiophenes was performed according to a procedure described by Liang. 3-Bromothiophene was converted into stable 3-azidothiophene **32** in excellent yield. On the other hand, 2-azidothiophene **30** was too instable under these reaction conditions. In order to solve this problem, **30** was coupled to terminal acetylenes *in situ* to yield 1,4-disubstituted 1,2,3-triazoles. Optimized catalytic conditions were applied in scope and limitation experiments. Monoiodinated thiophenes were converted in good to excellent yields, which decreased with higher oligothiophenes. However, no or only slight conversion was observed for diiodinated oligothiophenes.



Investigations of the optoelectronic properties chosen examples led to the assumption that conjugation through the triazole ring is rather small and, no intramolecular charge transfer (ICT) could be observed.

Due to these results, designed polymers with oligomeric properties should be prepared. To stabilize the azido functionality, a methylene bridge was inserted between the thiophene backbone and the azido group. Stable 2-azidomethylthiophene **61** was coupled in a “click”-reaction protocol to both, terminal and trimethylsilyl protected acetylenes, which were deprotected *in situ* with silver(I)-tetrafluoroborate. Several 1,4-disubstituted 1,2,3-triazoles were synthesized. In the series of azidomethylthiophenes yield increased with increasing number of thiophene rings. This trend is *vice versa* to azidothiophenes. Therefore, two polymers from diazides and diacetylenes could be synthesized.

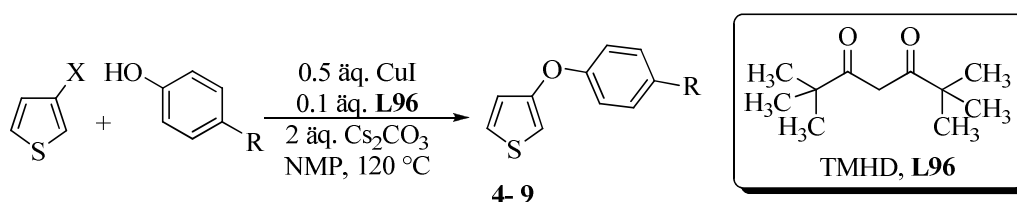


As expected, electrochemical characterization confirmed that co-oligomers and soluble co-polymer **80** showed the properties of the thiophene subunits. With this method it is possible to combine good properties of polymers (e.g., stability) with those of oligomers (e.g., optoelectronic properties). The application of such co-polymers as semiconductors in organic electronics is conceivable. Through the proper choice of monomers all properties of the resulting co-polymer can be adjusted.

## Zusammenfassung

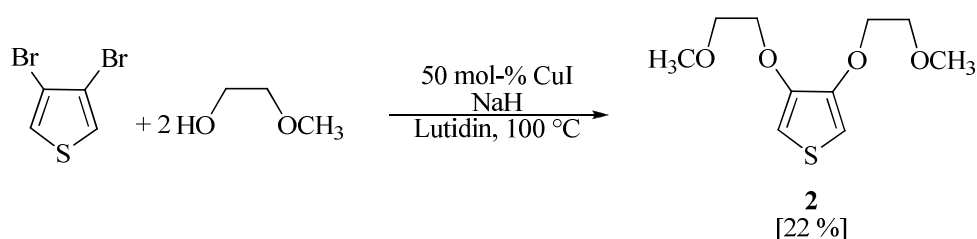
PEDOT:PSS, bekannt unter dem Markennamen Clevios P<sup>®</sup>, ist das meist verwendete Polymer in der organischen Elektrotechnik. Es findet beispielsweise Anwendung in OLED's, als Antistatikmittel, in Kondensatoren oder elektrochromen Bauteilen. Die Aufgabe im Rahmen dieser Arbeit bestand darin eine neue effektive Methode zu finden mit der EDOT Derivate und deren *N*-Analoga dargestellt werden können. Dazu sollte 3,4-Dibromthiophen mit *O*- und *N*- Nukleophilen in kupfer- bzw. palladiumkatalysierten Reaktionen umgesetzt werden.

In der Literatur sind bereits viele Beispiele zur nukleophilen Substitution von Halogenthiofenen mit Alkoholen unter der Zuhilfenahme von Kupfersalzen als Katalysatoren gegeben. Es konnte gezeigt werden, dass Phenole unter milderen Bedingungen umgesetzt werden können. Dazu wurden moderne Katalysatorsysteme verwendet die für die Ullmann-typische Diphenyletherbildung beschrieben wurden. Mit Kupfer(I)-chlorid und TMHD als Ligand konnten moderate Ausbeuten für die Umsetzung von Halogenthiofenen mit Phenolen erreicht werden. Jedoch erwiesen sich diese Reaktionsbedingungen nicht als allgemein anwendbar.



Auch die Umsetzung von 3,4-Dibromthiophen mit Monomethylethylenglykol wurde durchgeführt. Für das disubstituierte Produkt konnte nur eine niedrige Ausbeute erreicht werden. Verglichen mit der literaturbekannten Darstellung von 3,4-Di(methoxyethoxy)-thiophen **2** muss jedoch festgestellt werden, dass der synthetische Aufwand unter den hier beschriebenen Bedingungen sehr viel kleiner ist.

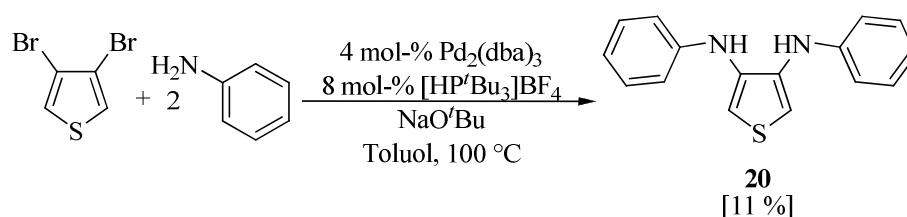




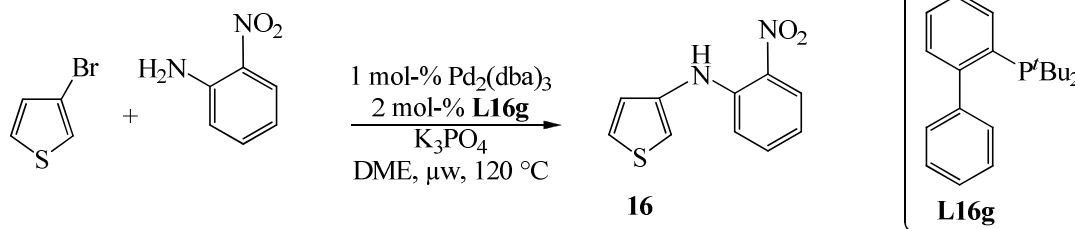
Es konnte demnach eine Verbesserung erreicht werden. Trotzdem war es mit keinem der hier angewendeten Methoden möglich 3,4-Dibromthiophen in EDOT Analoga umzusetzen. Als Ursache wird die Bildung stabiler Kupfer-Diol- Komplexe gesehen. Der so vergiftete Katalysator ist unwirksam. 3,4-Dibromthiophen konnte nach der Reaktion in allen Fällen fast vollständig zurück gewonnen werden.

Palladiumkatalysatoren waren sowohl für die Umsetzung von aliphatischen, als auch aromatischen Alkoholen unwirksam. Am Beispiel der kupferkatalysierten Darstellung von Thiophen- Phenyl- Ethern wurde der Einfluss der Mikrowellenstrahlung untersucht. Die Reaktionszeiten konnten drastisch verkürzt werden. Im Allgemeinen konnte keine signifikante Ausbeutesteigerung nachgewiesen werden. Für die Umsetzung von 4-Chlorphenol mit 3-Bromthiophen konnte beobachtet werden, dass die Reaktionszeitverkürzung die Substitution des Chlors in 3-(4-Chlorphenoxy)-thiophen **6** durch 4-Chlorphenol unterdrückt. Dies führte zu einer dramatischen Steigerung der Ausbeute.

Die Umsetzung von 3-Bromthiophen mit *N*-Nukleophilen mit Palladiumkatalysatoren ist in der Literatur vielfach beschrieben. Es wurden verschiedene Liganden für die palladiumkatalysierte C-N Kreuzkupplung an 3-Bromthiophen untersucht. Eine Verbesserung zu den bereits beschriebenen Methoden konnte nicht erreicht werden. Für die Reaktion an sekundären Aminen konnten höhere Ausbeuten beobachtet werden, als an primären Anilinen. Eine Disubstitution an 3,4-Dibromthiophen mit verschiedenen Aminen ergab keine bzw. nur sehr geringe Ausbeuten. Sekundäre Amine, welche in der C-N Kreuzkupplung an 3-Bromthiophen noch hervorragende Ergebnisse brachten, konnten nicht umgesetzt werden. *N*<sup>3</sup>,*N*<sup>4</sup>-Diphenylthiophen-3,4-diamin **20** konnte in einer Ausbeute von nur 11 % isoliert werden. Dabei war es unerheblich, ob vom 3,4-Dibromthiophen oder 4-Brom-*N*-phenylthiophen-3-amin **21** ausgegangen wurde. Auch für C-N Kreuzkupplungen konnte leider kein Ringschluss am 3,4-Dibromthiophen mit Diaminen beobachtet werden.



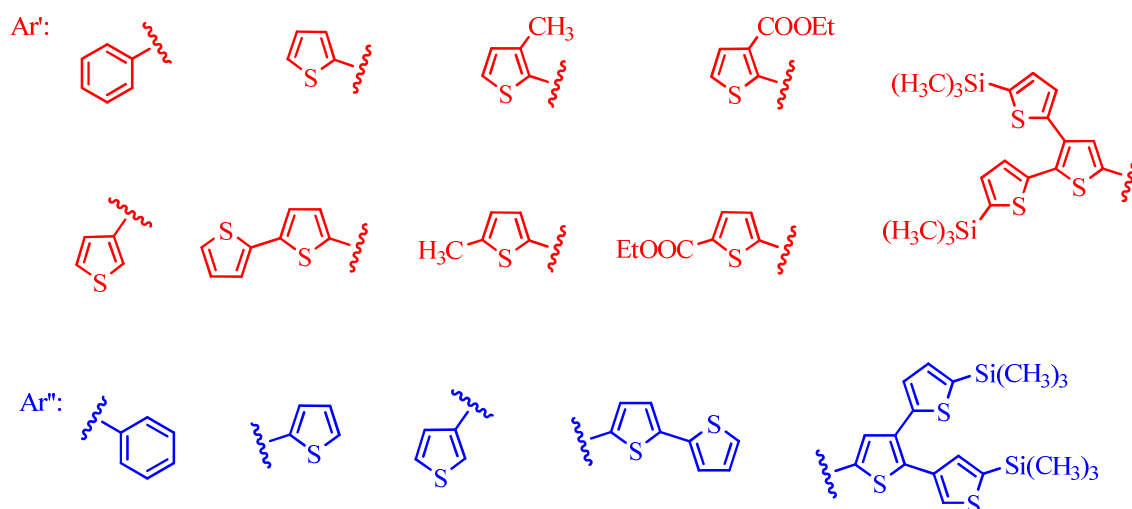
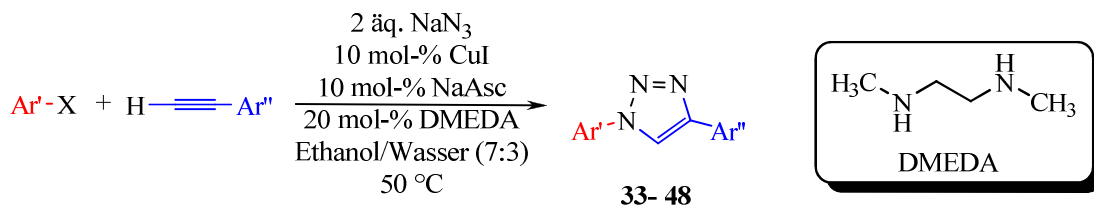
Unter Ullmann-typischen Bedingungen konnte keine Aminierung an Thiophenhalogeniden beobachtet werden. An ausgewählten palladiumkatalysierten Beispielen wurde der Einfluss von Mikrowellenstrahlung untersucht. Die Reaktionszeiten konnten auch hier erheblich gesenkt werden. Laut GC-Untersuchungen wurde 3-Bromthiophen vollständig mit Anilin zum 3-Anilinothiophen (**13**) umgesetzt. Aufgrund der Oxidationsempfindlichkeit des Produktes konnte jedoch nur eine moderate Ausbeute erzielt werden. Die Umsetzung von 2-Nitroanilin mit 3-Bromthiophen konnte lediglich in der Mikrowelle erfolgreich durchgeführt werden. Unter „konventionellen“ Reaktionsbedingungen wurde keine Reaktion beobachtet.



Da die hier durchgeführten Untersuchungen nicht zur Darstellung von EDOT Derivaten und deren *N*-Analoge führten wurde dieses Projekt beendet.

Die kupferkatalysierte nukleophile Substitution von Aziden an Halogenthiofenen wurde analog zu der von Liang beschriebenen Methode durchgeführt. Im Fall von 3-Bromthiophen konnte das stabile 3-Azidothiophen **32** in exzellenter Ausbeute isoliert werden. Dagegen ist 2-Azidothiophen **30** zu instabil, so dass es unter diesen Reaktionsbedingungen nicht isoliert werden konnte. Dieses Problem konnte behoben werden, indem **30** *in situ* mit terminalen Acetylenen zu entsprechenden 1,4-disubstituierten 1,2,3-Triazolen umgesetzt wurde. Nach der Optimierung der Reaktionsbedingungen wurde das Anwendungsspektrum der Methode getestet. Monoiodierte Thiophengerüste konnten in guten bis exzellenten Ausbeuten umgesetzt werden. Je größer das Oligothiophen gewählt wurde, desto

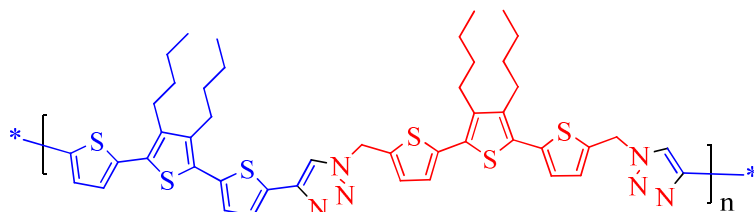
geringer wurden die Ausbeuten. Die Umsetzung von diiodierten Thiophenen lieferte nur schlechte, teilweise keine Ausbeuten.



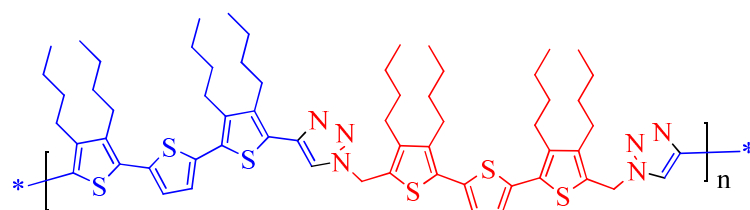
Die elektrochemische Charakterisierung ausgewählter Verbindungen zeigte, dass die Konjugation in den Donor-Akzeptor Co-Oligomeren durch den Triazolring unterbrochen bzw. drastisch gesenkt wird. Damit ist kein intramolekularer Ladungstransport (ICT) gegeben.

Aus diesem Befund heraus sollten gezielt Polymere mit Oligomer- Eigenschaften synthetisiert werden. Dazu wurde zwischen das Thiophengrundgerüst und die Azidfunktionalität eine Methylenbrücke eingeschoben. Dadurch wurde die Instabilität des 2-Azidothiophen nivelliert. Dies gab die Möglichkeit auch Trimethylsilyl- geschützte Acetylene in der sogenannten „Klick“-Reaktion umzusetzen. Die Dreifachbindung wurde *in situ* mit Silber(I)-tetrafluoroborat entschützt. Es wurden verschiedene Derivate zu 1,4-disubstituierten 1,2,3-Triazolen umgesetzt. In der Reihe der Azidomethylthiophene stieg die Ausbeute mit der Zahl der Thiopheneinheiten im Grundgerüst an. Dieser Trend ist dem

in der Reihe der Thiophenazide entgegengesetzt. So war es möglich, zwei verschiedene Polymere aus Diaziden und Diacetylenen darzustellen.



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Wie erwartet zeigten elektrochemische Untersuchungen, dass die Co-Oligomeren und das lösliche Co-Polymer die Eigenschaften der Thiophengrundgerüste aufweisen. Mit dieser Methode ist es möglich die guten Eigenschaften von Polymeren (z.B. Stabilität) mit denen der Oligomere (z.B. optoelektronische Eigenschaften) zu verbinden. Es ist vorstellbar ein derartiges Co-Polymer als Halbleiter in organischen Elektronikbauteilen einzusetzen. Durch die geeignete Wahl der Monomerbausteine können sämtliche Eigenschaften des entstehenden Co-Polymers eingestellt werden.



## Posters and Presentations

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“Tag der Chemie”, Freie Universität Berlin, **2002**

*Selective palladium(II)- recognition in fluorescence spectroscopy*

Oral presentation, 20 min

“Tag der Chemie”, Freie Universität Berlin, **2002**

*Synthesis And Complexation Studies of New Fluorescent Dithia-12-crown-4 Derivatives:*

*Selective Palladium(II) Detection by Fluorescence Spectroscopy*

Poster

ICCC35, Heidelberg, Germany, **2002**

*Synthesis And Complexation Studies of New Fluorescent Dithia-12-crown-4 Derivatives:*

*Selective Palladium(II) Detection by Fluorescence Spectroscopy*

Poster

ICSM, Dublin, Ireland, **2006**

*Conjugated Thiophene- Triazole Co- Oligomers via „ClickChemistry“*

Poster

KOPO, Blaubeuren, Germany, **2007**

*Synthesis of Thiophene- Triazole Co- Oligomers and Their Spectroscopic Properties*

Poster

## Curriculum Vitae

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 Nationality : German

### Education

- 10/2003 – 02/2008**     **Dissertation in Chemistry** (corresponds to Ph.D. degree)  
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 Institute of Organic Chemistry II and Advanced Materials  
 Supervisor: Prof. Dr. Peter Bäuerle  
 Thesis: “Transition-Metal Catalyzed Nucleophilic Substitution at Thiophene Halides”
- 10/1997 – 08/2002**     **Diplom in Chemistry** (corresponds to M.Sc.)  
*University of Potsdam, Germany*  
 Institute of Inorganic Chemistry  
 Supervisor: Prof. Dr. Hans- Jürgen Holdt  
 Thesis: “Synthesis of selective Fluoroionophores for Palladium(II)”
- 09/1999**     **Vordiplom** (corresponds to bachelor degree)  
*University of Potsdam, Germany*

### Scholastic Education

- 08/1984 – 08/1990**     POS B.-H.-Bürgel, Rathenow, Germany
- 09/1990 – 06/1997**     Grammar schools, Germany
- 06/1997**     J.-H.-A.-Duncker Gymnasium Rathenow, Germany  
 Abitur (corresponds to A-levels)





*So eine Arbeit wird eigentlich nie fertig.  
Man muss sie für fertig erklären,  
wenn man nach der Zeit und den Umständen  
das Möglichste getan hat.*

Johann Wolfgang von Goethe