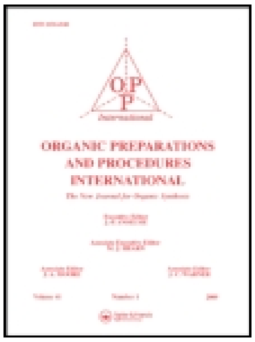

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David Gendron[1] and George Vamvounis[2]

[1]Italian Institute of Technology, Robotics, Brain and Cognitive Sciences Department, Soft Matter Design Lab, Via Morego 30, 16163, Genova, Italy
[2]James Cook University, Molecular Sciences Building 21, Polymer Research Laboratory, College of Science, Technology and Engineering, Townsville, Queensland 4811, Australia

# Synthesis and Reactions of Halo-substituted Alkylthiophenes. A Review

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[1]Italian Institute of Technology, Robotics, Brain and Cognitive Sciences Department, Soft Matter Design Lab, Via Morego 30, 16163, Genova, Italy
[2]James Cook University, Molecular Sciences Building 21, Polymer Research Laboratory, College of Science, Technology and Engineering, Townsville, Queensland 4811, Australia

## Introduction

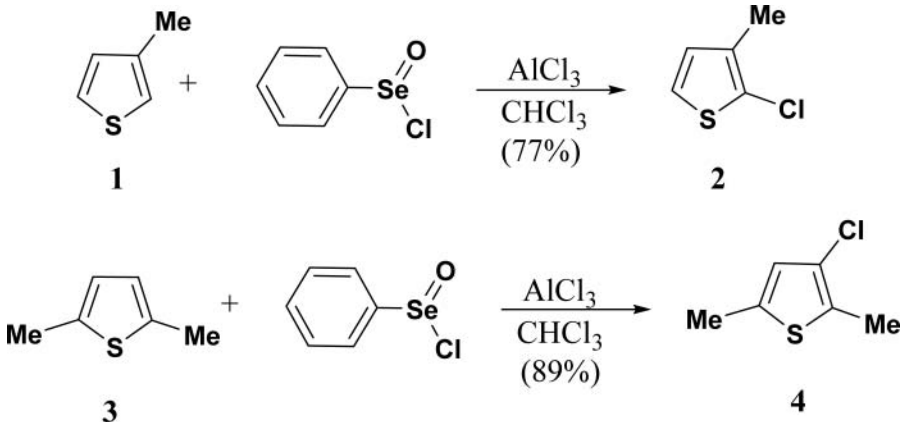
Thiophene chemistry is a flourishing area of organic semiconductors as they are useful for field effect transistors, solar cells and light-emitting diodes.[1] This interest stems from the unique optical and electronic properties of thiophene oligomers and polymers coupled with the ease of synthesis and their unique reaction selectivity. Therefore, the preparation of thiophenes is pivotal in this burgeoning area of science. Although there have been several reviews that have focused on the preparation of poly(alkylthiophene)s, this is not the case for oligomeric and monomeric materials. Halo-substituted alkylthiophenes are very useful compounds that react under various conditions to give a plethora of derivatives, which can then be used in the field of materials chemistry.

This review summarizes the advances from 1986–2013 in the synthesis and reactivity of these systems to provide a stepping-stone for the design and preparation of more complex thiophene-based molecular architectures for the next generation of materials in photonics and electronics. We will focus first on the preparation of halo-substituted alkylthiophenes by electrophilic aromatic substitution and then their reactivity using various metal-catalyzed cross-coupling methods.

## I. General Preparation of Halo-substituted Alkylthiophenes

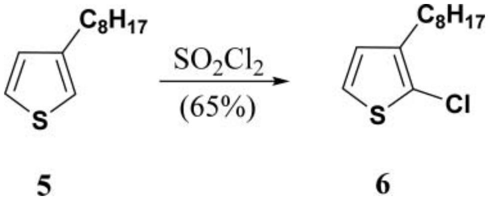
Halo-substituted alkylthiophenes can be prepared in various ways depending on the position on the thiophene ring of both the halogen atom and the alkyl chain. Different halogen atoms such as chlorine, bromine or iodine can be introduced on the ring.

Only a few studies report the preparation of chloro-substituted methyl(alkyl)thiophenes[2] *via* electrophilic aromatic substitutions.[3] The reaction of benzeneseleninyl chloride in the presence of aluminum chloride in chloroform with methylthiophenes **1** and **3** affords the corresponding target compounds **2** and **4** in high yields (77–89%) and selectivity. The authors found that the yields are greatly improved if the reaction is performed in chloroform instead of dichloromethane (*Scheme 1*).



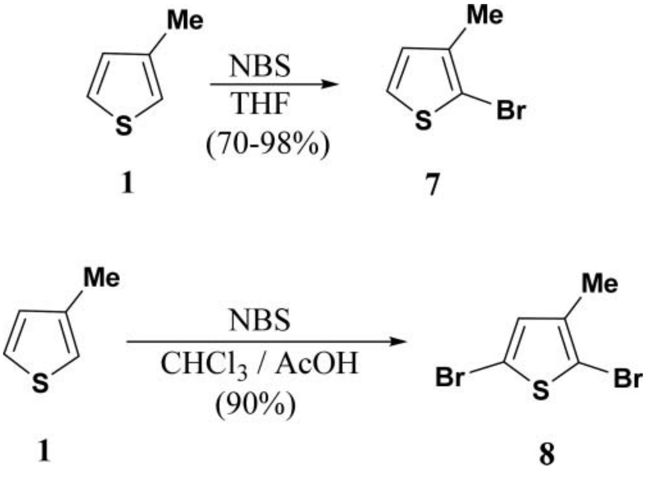
**Scheme 1**

Another method for the chlorination of alkylthiophenes reported by Bidan *et al.*[4] uses sulfuryl chloride in a polar solvent and led to the synthesis of isomerically pure compound **6** in a 65% yield (*Scheme 2*).



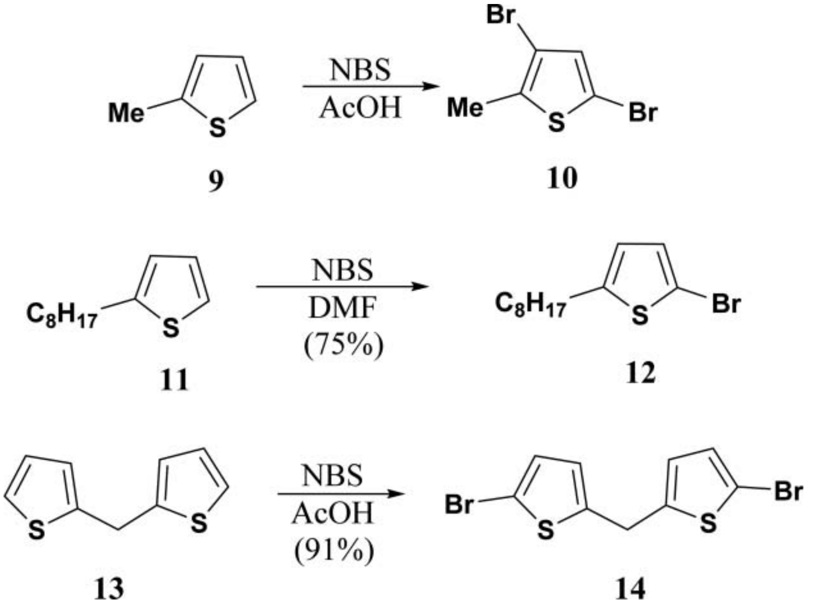
**Scheme 2**

Bromo-substituted alkylthiophenes are the most often reported halo-substituted alkylthiophenes. *N*-bromosuccinimide (NBS) in the presence of the desired alkylthiophene in an organic solvent (or solvent mixture), such as acetic acid (AcOH),[5] chloroform



**Scheme 3**

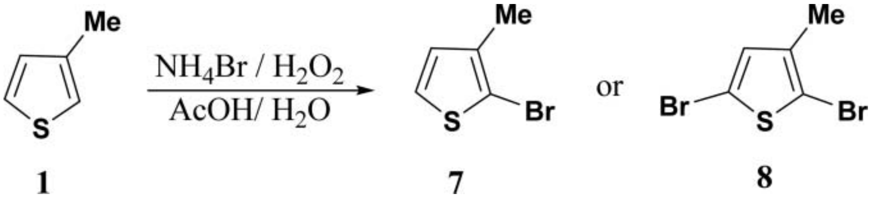
($CHCl_3$),[6] tetrahydrofuran (THF),[7] or *N,N*-dimethylformamide (DMF),[8] are the most commonly used conditions (*Scheme 3*). High yields (70–98%) are generally obtained and depending on the reaction conditions, the mono- or dibromo compounds can be obtained. With 3-alkylthiophenes, bromination occurs at the 2-position first and then at the 5-position to give the corresponding dibrominated compound. Other variations on the reaction conditions are also reported.[9–13]



**Scheme 4**

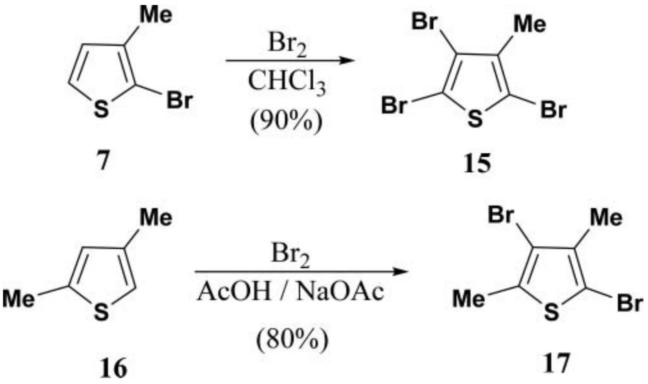
When 2-alkylthiophenes are used as the starting compounds, bromination occurs at the 5-position first (as in **12, 14**) and then at the 3-position (as in**10**) (*Scheme 4*).[5,8,14]

D'Aleo *et al.* proposed an alternate method to obtain bromo-substituted alkylthiophenes using ammonium bromide in the presence of hydrogen peroxide in aqueous acetic

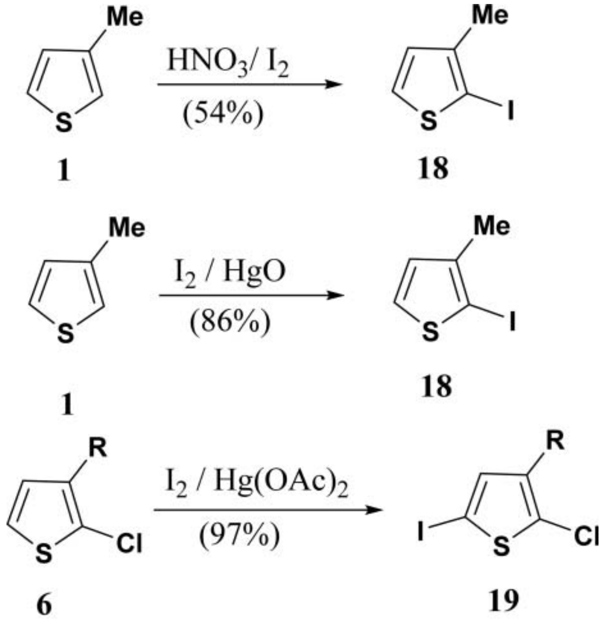


**Scheme 5**

acid to selectively access the monobromo **7** or the dibromo **8** derivative (*Scheme 5*).[15] The authors found that similar yields and selectivities were obtained when *N*-bromosuccimide was used. Moreover, this method was applied for the preparation of iodo-substituted alkylthiophenes: in this case, ammonium iodide is used instead of ammonium bromide.



**Scheme 6**



**Scheme 7**

Bromo-substituted alkylthiophene derivatives (**15**, **17**) were prepared in high yields by electrophilic substitution using bromine ($Br_2$) in solvents such as $CHCl_3$ or AcOH (*Scheme 6*).[10,16]

The preparation of iodo-substituted alkylthiophenes has also been reported, although the reaction conditions differ from those for the preparation of chloro- or bromo-substituted alkylthiophenes (*Scheme 7*). Wudl *et. al.* reported the use of iodine in the presence of dilute nitric acid to access 2-iodo-3-methylthiophene (**18**) in a 54% yield.[17] The nitric acid can be replaced with HgO or $Hg(AcO)_2$ to afford the desired iodo-substituted alkylthiophenes in 92–97% yields.[4,13,18]

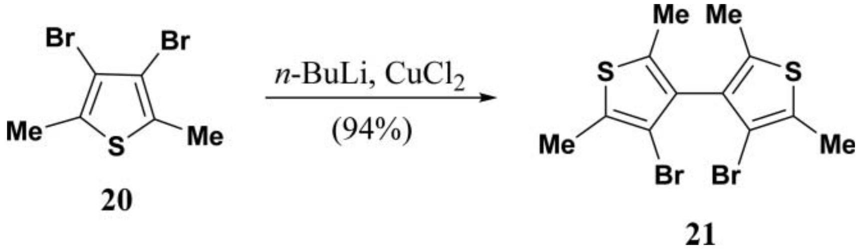
Finally, iodination of 3-alkylthiophenes using *N*-iodosuccinimide[19] in acetic acid at 0°C was reported by Jayakannan *et al.*[20] In addition to the 2-iodo compounds, the reaction also generated the isomeric 5-iodo-3-alkylthiophenes, which were difficult to remove completely. To summarize, halogenation of alkylthiophenes can be performed under various conditions depending on the derivative desired (Cl, Br or I).

## II. Reactivity of Halo-substituted Alkylthiophenes

In this section, the reactivity of the generic halo-substituted alkylthiophenes is discussed. We will first address their reactivity towards lithium reagents in lithium-halogen exchange reactions. Then, the use of alkylthiophenes in metal-catalysed cross-coupling reactions, such as the Kumada, Suzuki, Stille, and direct arylation reactions will be reviewed.

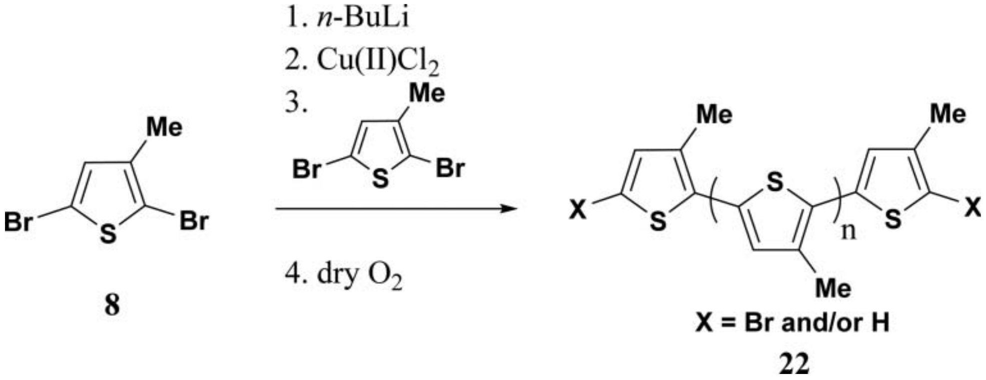
### *1. Lithiation Reactions*

A useful method to generate halo-substituted thiophenes is by a lithium-halogen exchange reaction. Hellberg *et al.* have demonstrated the preparation of the dimeric adduct **21** in 94% yield by the mono-lithiation of 3,4-dibromo-2,5-dimethylthiophene (**20**) in THF followed by an oxidative coupling with $CuCl_2$ (*Scheme 8*).[21]



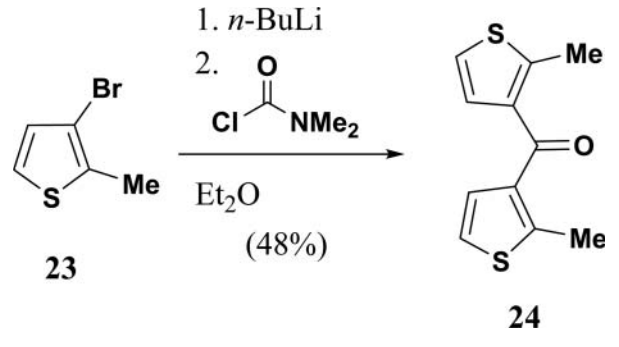
**Scheme 8**

Amer *et al.* used the *n*-BuLi/$CuCl_2$ couple as a polymerizing agent with 2,5-dibromo-3-methylthiophene (**8**) to generate the polymeric material **22** (*Scheme 9*).[18] The yield of the polymer was dependent on the reaction temperature chosen.



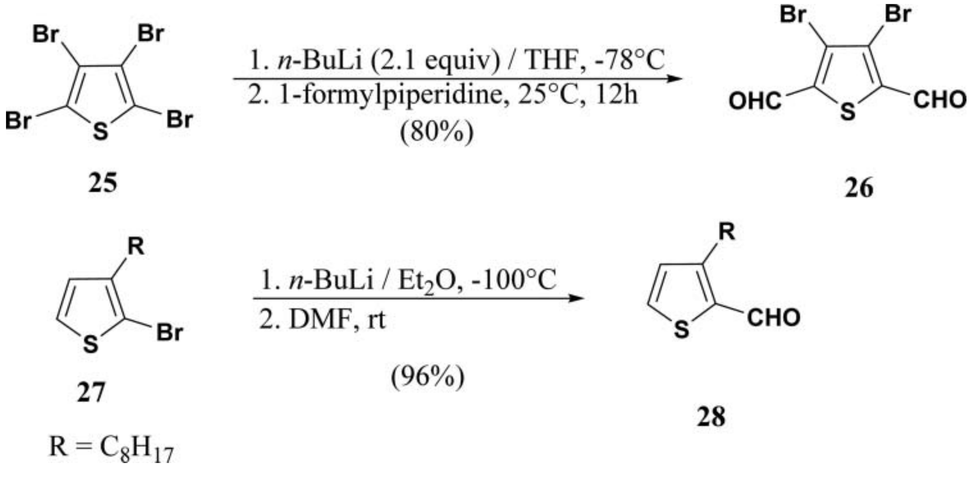
**Scheme 9**

Ikeda *et al.* reported that lithium-halogen exchange with 3-bromo-2-methylthiophene (**23**) followed by reaction with *N,N*-dimethylcarbamoyl chloride gave the *bis*(2-methyl-3-thienyl)ketone (**24**) (*Scheme 10*) in a moderate yield of 48%.[22]



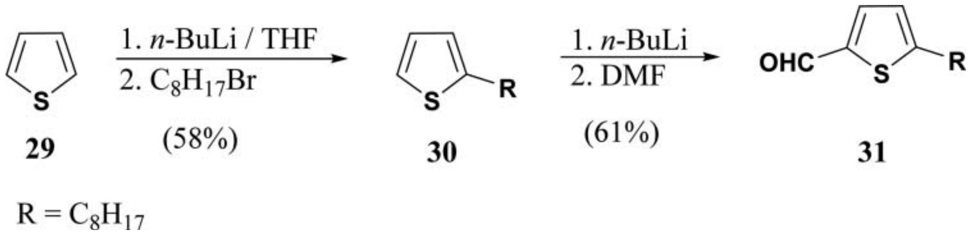
**Scheme 10**

Aldehyde-functionalized alkylthiophenes are commonly prepared from bromo-substituted alkylthiophenes (*Scheme 11*). Several groups have reported the use of the lithium-bromine exchange reaction, under slightly different reaction conditions. Thus Frey *et al.* showed that dilithiation of 2,3,4,5-tetrabromothiophene (**25**) using *n*-BuLi and quenching of the reaction with 1-formylpiperidine[23] led to an 80% yield for the dialdehyde **26**. Similarly, Elandaloussi *et al.* described the conversion of 2-bromo-3-octylthiophene (**27**) to 3-octylthiophene-2-carbaldehyde (**28**) in 96% yield using lithium-bromine exchange at −100°C followed by formylation by DMF.[24]



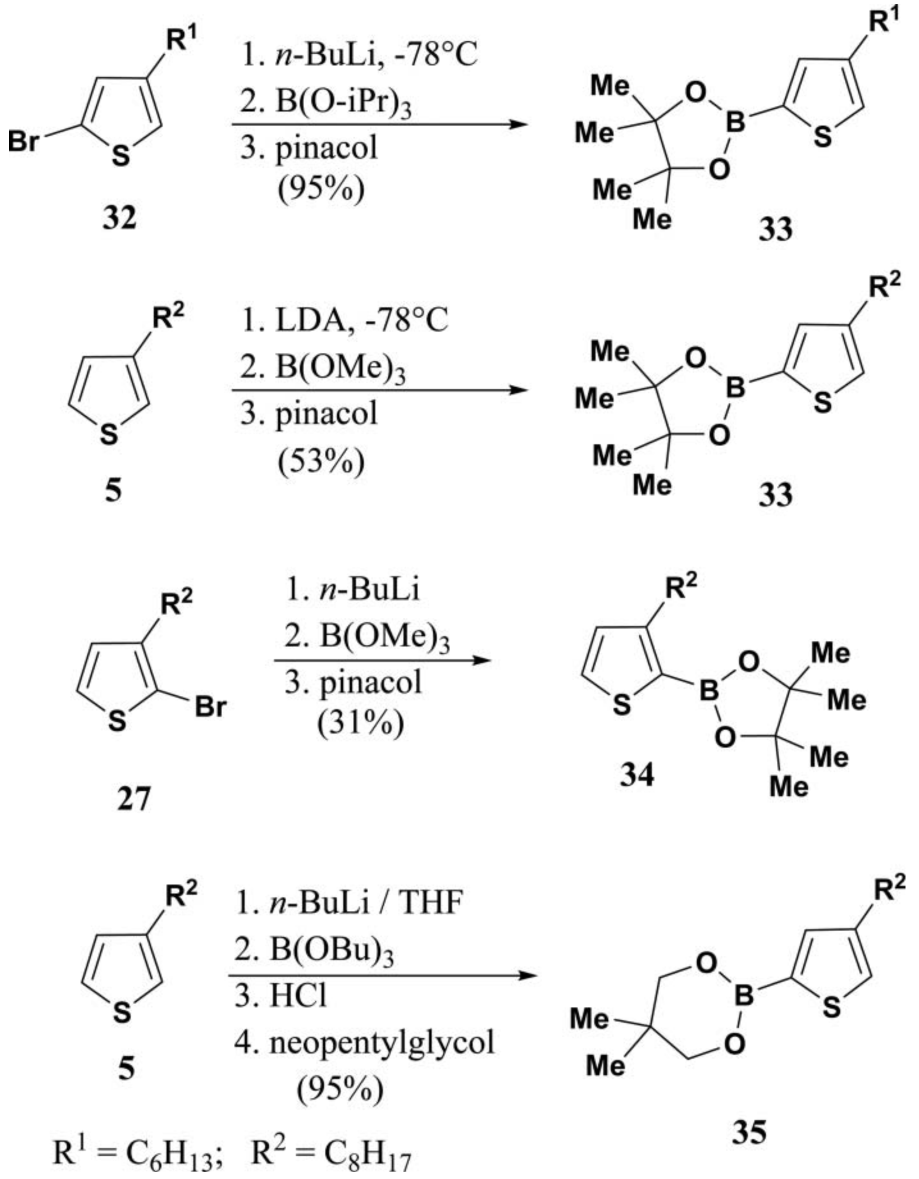
**Scheme 11**

Gong *et al.* employed a successive lithiation approach (*Scheme 12*) to first introduce an alkyl chain at the 2-position of thiophene (**29**) using *n*-BuLi in THF followed by addition of 1-bromooctane to afford 2-octylthiophene (**30**, R = *n*-octyl) in 58% yield.[6] Subsequent lithiation of **30** followed by treatment with DMF as the formylating reagent led to **31** in 61% yield.



**Scheme 12**

Lithiation reactions are very useful for the preparation of precursors for Suzuki, Stille, Hiyama and Kumada cross-coupling reagents. For instance, various boronic ester groups can be introduced on the thiophene ring using lithiation protocols (*Scheme 13*).



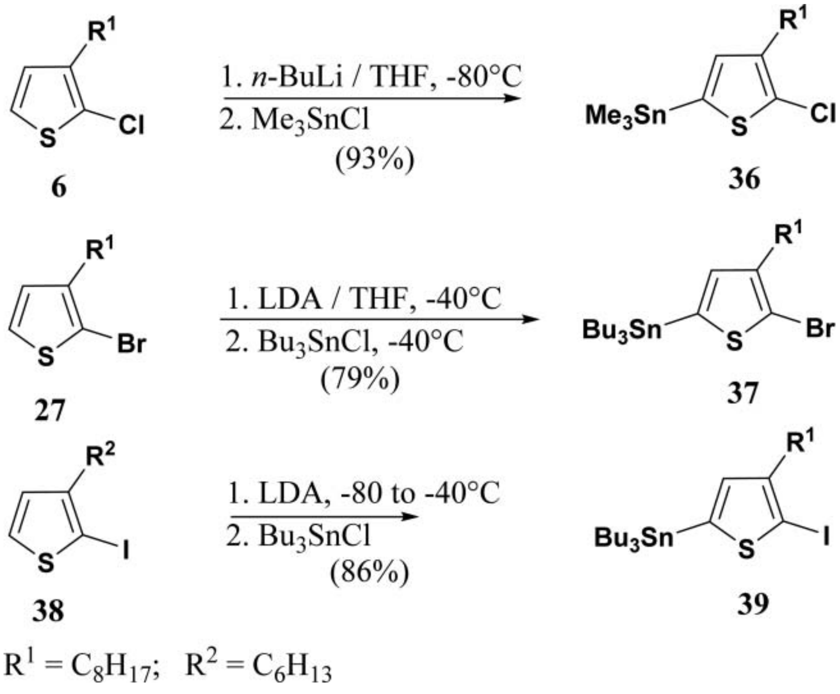
**Scheme 13**

El-Shehawy *et al.* have reported the preparation of 2-(4-*n*-hexyl-2-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**33**) from **32** in 95% yield using *n*-BuLi and *tris*-(isopropyl) borane followed by quenching with pinacol.[12] A more facile approach towards **33** was reported by Janssen *et al*. wherein **5** was selectively lithiated at the 5-position using lithium diisopropylamine (LDA), and the lithiated product was treated with trimethylborate and pinacol.[25] Alternatively, the thiophene was lithiated at the 2-position using lithium-halogen exchange with *n*-BuLi and subsequently treated with trimethylborate and pinacol to give **34** in a 31% yield.[25] Janssen *et al*. also reported that **33** and **34** were very stable towards silica, which permitted purification using silica gel column chromatography. Neopentylglycol can be used instead of pinacol for formation of the dioxaborolane as reported by Pron *et al*.[26] for the preparation of **35**.

Stannylthiophene derivatives can also be prepared using LDA or *n*-BuLi in THF (*Scheme 14*). The procedure for the preparation of 3-alkyl-2-halo-5-(tributylstannyl)thiophenes has been reported for the chloro, bromo and iodo derivatives.[27–29] When *n*-butyllithium is used as the lithiating agent, a temperature of −80°C is used to achieve good selectivity to target the kinetic product **36**[29] whereas with LDA, selective addition of the stannyl group at the 2-position can be achieved at higher temperatures (−40°C) afforded **37** or **39**.[27]

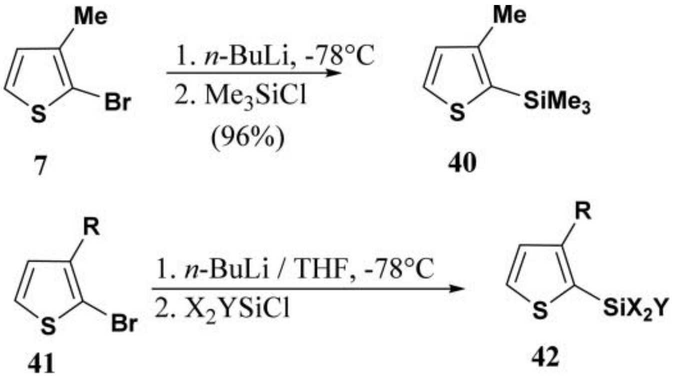
Yields ranged from 79 to 93% and it is important to point out the authors' emphasis on the excellent stability of the stannylthiophene derivatives, as they can be handled in air or water without immediate degradation.[29]

The preparation of trimethylsilylthiophene derivatives such as **40** and **42** was carried out by successive lithium-halogen exchange (*Scheme 15*). Other examples have been



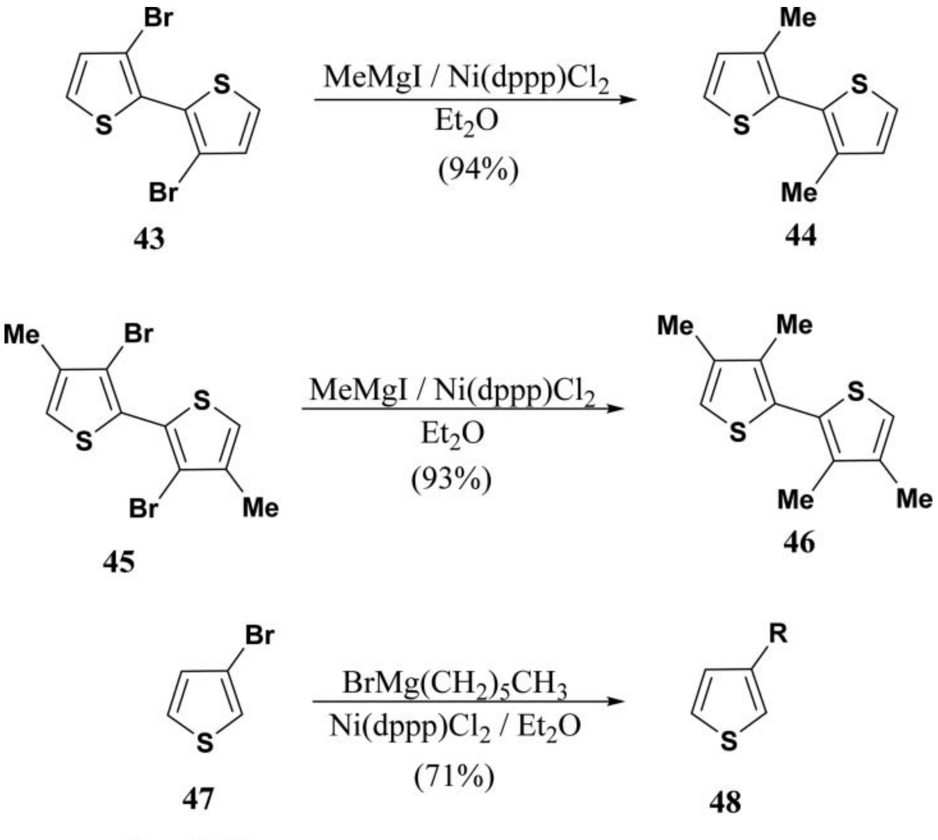
$R^1 = C_8H_{17}$; $R^2 = C_6H_{13}$

**Scheme 14**



R = $C_6H_{13}$;   X = Y = Me (TMS);   X = Y = Et (TES);
X = Y = *i*-Pr (TIPS);   X = Y = *t*-Bu (TBDMS)

**Scheme 15**



R = $C_6H_{13}$

**Scheme 16**

reported by Wu and Spivey.[30–31] A variety of silyl reagents such as trimethylsilyl chloride (TMSCl), triethylsilyl chloride (TESCl) or *tris*(isopropyl)silyl chloride (TIPSCl) can be employed, and excellent yields of up to 96% were obtained. Interestingly, the TIPS derivative **42** is readily desilylated (*ipso* attack) on contact with silica, a fact that can be attributed to the relief of steric strain caused by the adjacent hexyl group.[32–33]

## 2. *Metal-catalyzed Cross-coupling Methods*

Palladium catalyzed cross-coupling reactions provide valuable protocols for the preparation of a variety of thiophene derivatives. This section reviews the main cross-coupling methods, namely the Kumada, Suzuki, Stille and direct arylation reactions.

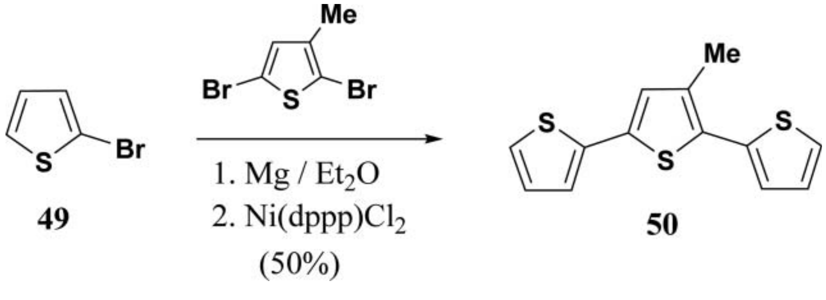
*2.1. Kumada Coupling.* Kumada coupling[34] is a nickel or palladium catalyzed cross-coupling reaction used for the preparation of carbon-carbon bonds (alkyl-aryl or aryl-aryl), and used extensively in the preparation of thiophene based materials. Several articles and reviews discussing the choice of reagents (solvents or catalyst) for Kumada cross-coupling reactions have been published.[35–39] In this section, we will focus on simple Kumada coupling between halo-substituted alkylthiophenes with another alkyl or aromatic group.

Alkylthiophenes are primarily prepared by Kumada coupling involving a halothiophene and the Grignard of a haloalkane. *Scheme 16* summarize a series of examples of various alkylations of thiophene using Kumada coupling to yield **44**, **46** or **48**).[9,21,40] Short, long or branched alkyl chains can be added to the thiophene core to afford yields often greater than 90%.

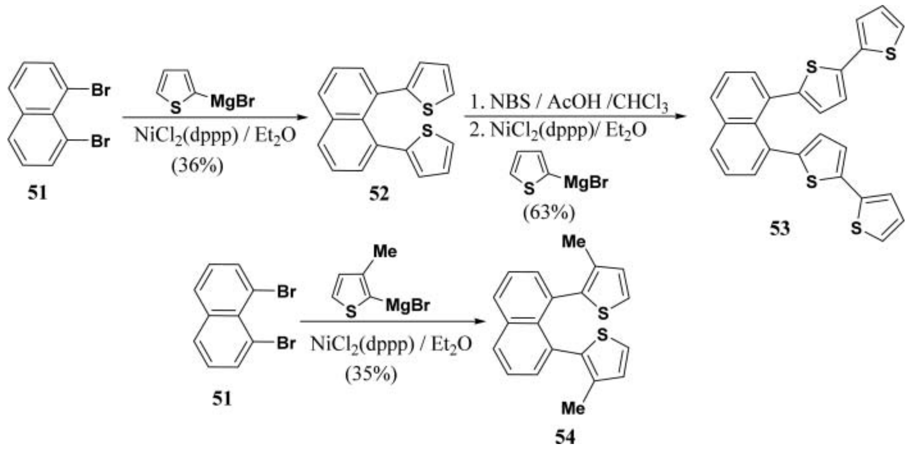
A representative Kumada coupling reaction involving an aryl-aryl coupling sequence is illustrated in *Scheme 17*.[41] First, 2-bromothiophene (**49**) reacts with magnesium in diethyl ether to generate the organomagnesium intermediate which undergoes a transmetallation with the Ni(dppp)$Cl_2$ catalyst, followed by coupling with the dibromothiophene derivative; in this particular example, a yield of 50% is reported.

Typical solvents used for this reaction are either neat diethyl ether ($Et_2O$) or tetrahydrofuran (THF), although mixed solvent systems such as $Et_2O$/benzene/THF have also been reported.[42]

Nakayama reported the use of successive Kumada cross-coupling and bromination reactions to extend the conjugation of thiophene-derivatized naphthalenes in a controlled fashion (*Scheme 18*).[43] In the first step, 1,8-diiodonaphthalene was treated with the Grignard of 2-bromothiophene to afford the desired bisthiophene (**52**) in 12% yield. Interestingly, the yield was improved 3-fold by using 1,8-dibromonaphthalene (**51**) instead of 1,8-diiodonaphthalene. The thiophene chain was extended by successive bromination and



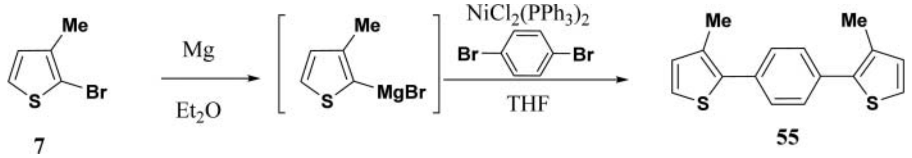
**Scheme 17**



**Scheme 18**

Kumada coupling to afford the desired tetrathiophene product **53** and up to the octathiophene derivative.[43] The Kumada coupling method was also used for the preparation of 3-methyl-2-[8-(3-methyl-2-thienyl)-1-naphthyl]thiophene (**54**) and its $^1$H NMR spectrum was investigated in depth to distinguish the presence of atropisomers.

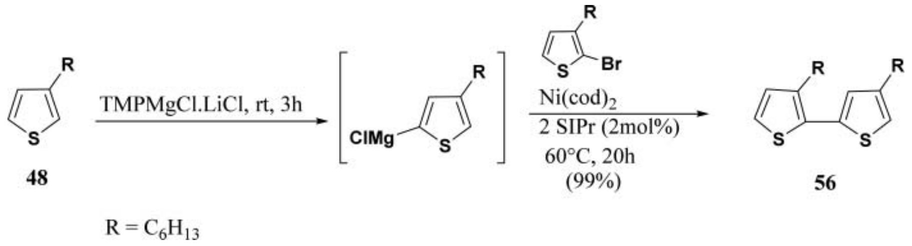
Various catalysts for such Kumada coupling reactions have been reported. For instance, Wang *et al.* reported the use of $NiCl_2(PPh_3)_2$ for the preparation of 3-methyl-2-[*p*-(3-methyl-2-thienyl)phenyl]thiophene (**55**) (*Scheme 19*).[44] In this case, reaction of 2-bromo-3-methylthiophene (**7**) with magnesium generated the Grignard reagent, which was subsequently treated with 1,4-dibromobenzene to afford **55**.



**Scheme 19**

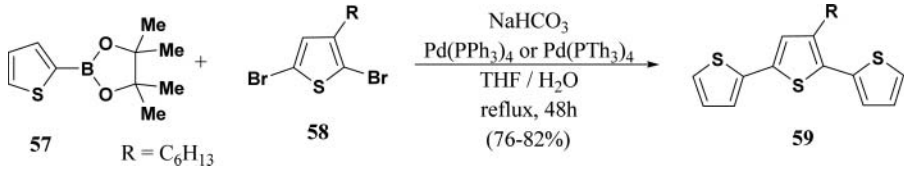
Tanaka *et al.* reported the regioselective preparation of head-to-tail (HT) oligoalkylthiophenes.[45] Their paper focused on the regioselective metallation on the 5-position of 3-*n*-hexylthiophene by hydrogen abstraction, followed by cross-coupling with 2-bromo-3-*n*-hexylthiophene to form the HT-coupled oligoalkylthiophene. In doing so, they used the Knochel-Hauser base TMPMgCl•LiCl (TMPH = 2,2,6,6-tetramethylpiperidine), as shown in *Scheme 20*, for the HT regioselective formation of **56**. Different ligand and catalyst systems were investigated and the combination of Ni$(cod)_2$ with 2 equivalents of 1,3-Bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene (SIPr) resulted in complete conversions with quantitative yields.

*2.2. Suzuki coupling.* The Suzuki-Miyaura palladium catalyzed cross-coupling reaction possesses many advantages such as wide functional group tolerance, non-toxicity, moisture insensitivity and a relative stability of some boronic derivatives.[46] The catalytic system for the Suzuki-Miyaura coupling involves three key steps: 1. oxidative addition, 2. transmetallation and 3. reductive elimination. The oxidative addition of the aryl bromide



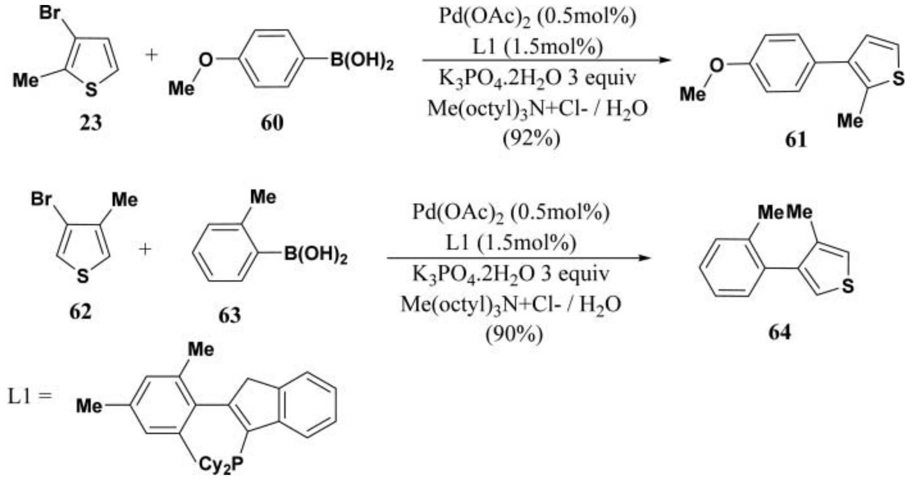
Scheme 20

represents the key step and the choice of the ligands is crucial for this step, especially for the synthesis of oligo- and polyalkylthiophene derivatives. The electron-donating ability of the ligand is therefore important as it increases the electron density of the palladium intermediate. Using electron-rich palladium ligands generally allows more efficient coupling while supressing undesired side-reactions. For instance, Li *et al.* investigated

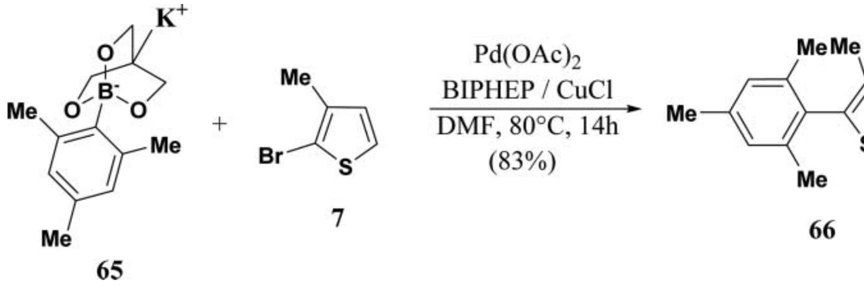


Scheme 21

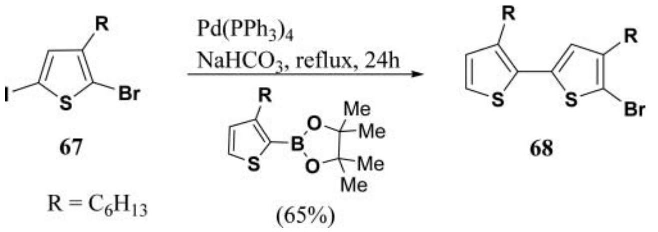
various ligands for the Suzuki coupling of thiophene-based materials (*Scheme 21*).[47] In their study, Pd($PPh_3$)$_4$ was compared with an electron-rich version *tris*[tri(2-thienyl)phosphine)palladium) or (Pd($PTh_3$)$_4$), and it was found that the latter catalytic system resulted



Scheme 22



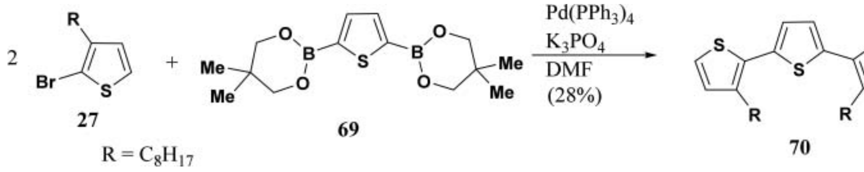
Scheme 23



Scheme 24

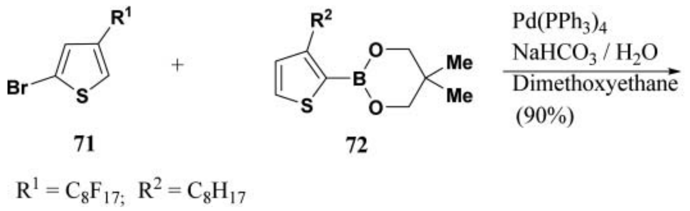
in higher yields for a wide variety of thiophene-based substrates. For example, the synthesis of **59** afforded an 82% yield when using Pd(PTh$_3$)$_4$ while the traditional Pd(PPh$_3$)$_4$ afforded a 76% yield (*Scheme 21*).

The choice of the reaction conditions is crucial in Suzuki cross-coupling reactions. For instance, Liu's group recently reported a highly active catalytic system for Suzuki-Miyaura cross-coupling reaction using water as the solvent to prepare phenyl-substituted thiophenes (**61** and **64**) (*Scheme 22*).[48] The authors reported yields over 80% when using the commercially available ligand L1. After optimizing the phase transfer agent (tetra-*n*-butylammonium bromide or Me(octyl)$_3$N$^+$Cl$^-$), the base (K$_3$PO$_4$ H$_2$O, KOAc, KOH, K$_2$CO$_3$, Na$_2$CO$_3$, NaOH, Cs$_2$CO$_3$) and time (1 or 8 h), a 98% yield was achieved on a model system. These optimal conditions were used for various substrates, including thiophene substrates, with high yields (*Scheme 22*).



Scheme 25

Miyaura *et al.* reported that the addition of copper(I) halides in Suzuki reaction conditions was highly effective for the preparation of *ortho*-substituted biaryls (*Scheme 23*).[49] For instance, they found that coupling 2-bromo-3-methylthiophene (**7**) with sterically encumbered aryltriolborates resulted in aryl-substituted thiophene (**66**) in 80–90% yields, depending on the aryltriolborate. It is proposed that the Cu(I) facilitates the transmetallation of the boronates to the aryl palladium bromide.[50] Furthermore, this



**Scheme 26**

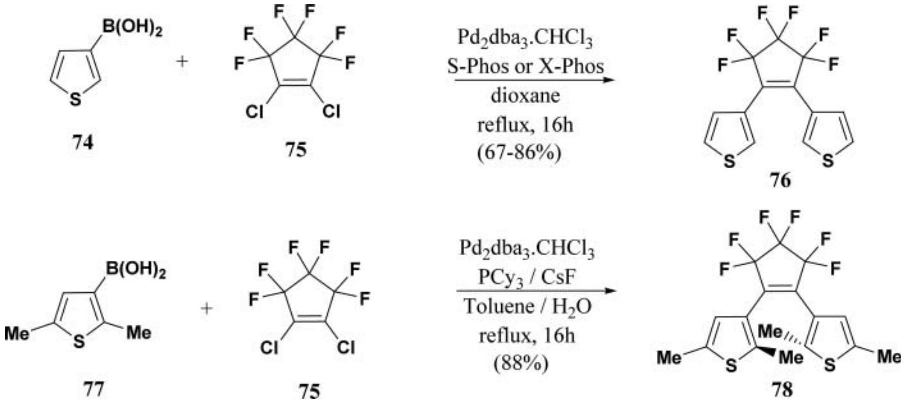
method does not use a base, which is unusual for a Suzuki-Miyaura coupling, enabling the use of starting materials containing base-sensitive functional groups.

It is also possible to perform Suzuki-Miyaura coupling selectively.[51] In the example shown in *Scheme 24*, 2-(3-*n*-hexyl-2-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane reacts selectively with the iodine on 2-bromo-3-*n*-hexyl-5-iodothiophene (**67**) to form **68** in 63% yield. The 2-bromo-3-*n*-hexyl-5-iodothiophene (**67**) was prepared by successive halogenations of 3-*n*-hexylthiophene (**48**) with *N*-bromosuccinimide then *N*-iodosuccinimide.

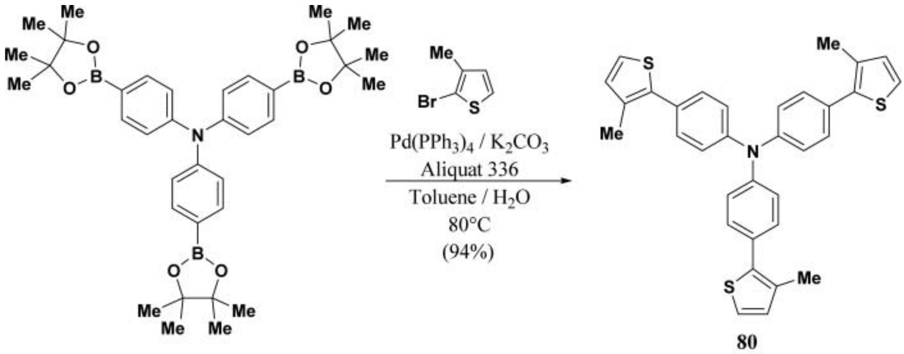
Various boronic esters have been used for the Suzuki synthesis of thiophene derivatives.[52] For example, 2-[5-(5,5-dimethyl-1,3,2-dioxaboran-2-yl)-2-thienyl]-5,5-dimethyl-1,3,2-dioxaborane (**69**) was reacted with 2-bromo-3-*n*-octylthiophene (**27**) under anhydrous conditions to generate the terthiophene **70** in 28% yield (*Scheme 25*).

Using the same boronic ester, Collard *et al.* reported the coupling of 1-(2-bromo-3-thienyl)-perfluorooctane (**71**) with **72** for the preparation of a *bis*(thiophene) derivative **73** in 90% yield (*Scheme 26*).[53] The direct attachment of a fluoroalkyl substituent on the thiophene raises the oxidation potential of the reactant compared to its alkyl analogues. This electron-withdrawing nature of the side chain renders the corresponding oligothiophene *n*-dopable, which is a useful property for electron transport materials.[53]

Hiroto *et al.* have reported an interesting route for the preparation of diarylethene photoswitchable materials.[54] Normally, synthetic methods to such species are limited to the nucleophilic addition-elimination reaction of perfluorocyclopentene with heteroaryllithium reagents at cryogenic temperatures. The perfluorocyclopentene in this reaction is difficult to handle as the boiling point is 27°C and low yields (~30%) are generally obtained. Hiroto *et al.* proposed a Suzuki-coupling approach with the use of

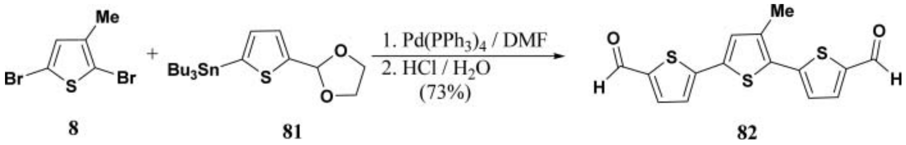


**Scheme 27**



Scheme 28

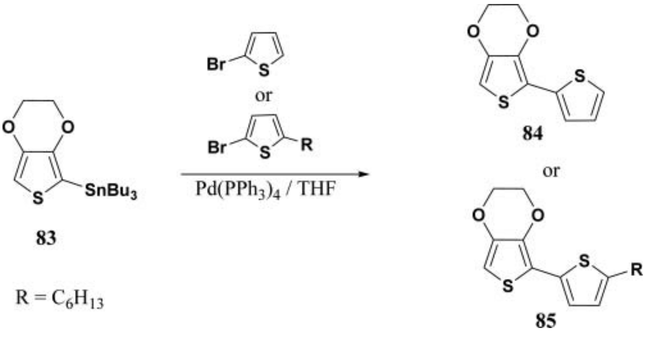
1,2-dichlorohexafluorocyclopentene (**75**), and the Suzuki-Miyaura coupling works well with ligands such as 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) or 2-dicyclohexylphosphino-2,4′,6′-triisopropylbiphenyl (XPhos) in the presence of $Pd_2dba_3.CHCl_3$ for unsubstituted thiophene boronic acid derivatives **76**. However,



Scheme 29

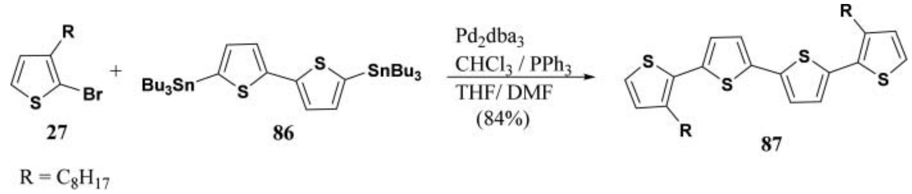
with alkylthiophene boronic acids the reaction conditions are slightly modified where tricyclohexylphosphine ($PCy_3$) is used as the ligand and CsF as the base. Yields of up to 88% were obtained (*Scheme 27*), and these reaction conditions also tolerated ester, nitrile or aldehyde functional groups.

Suzuki-Miyaura palladium catalyzed cross-coupling was also used for the preparation of a star-shaped semiconducting material for dye-sensitized solar cells, and an



Scheme 30

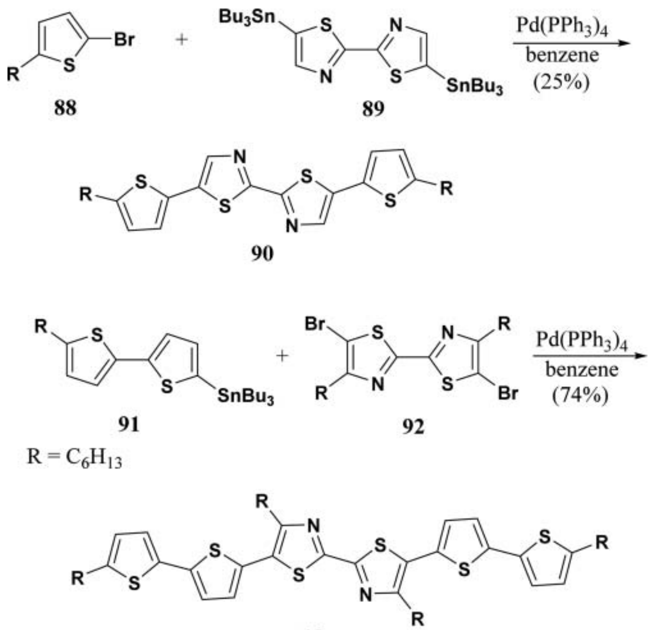
example is reported in *Scheme 28*.[55] Therein, tris(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane)phenyl)amine (**79**) was reacted with 2-bromo-3-methylthiophene under cross-coupling conditions to afford *tris*[*p*-(3-methyl-2-thienyl)phenyl]amine (**80**) in 94% yield.



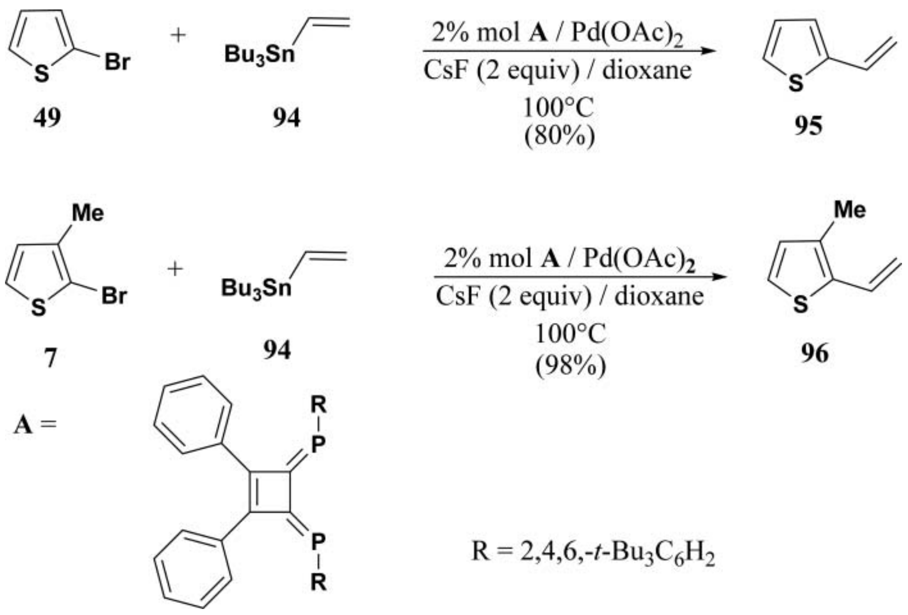
Scheme 31

*2.3. Stille Coupling.* Stille coupling is one of the most used palladium cross-coupling methods[56] for the preparation of thiophene oligomers[57] (bithiophene, terthiophene, quaterthiophene, etc.) and polymers.[58–60] For more information, mechanistic discussions are reported in a review by Espinet[61] and an excellent review on the advances in the synthesis of regioregular polythiophenes by McCullough *et al.* has also been published.[62]

*Scheme 29* depicts an example of a Stille coupling involving a halo-substituted alkylthiophene unit.[63] In this work, 2,5-dibromo-3-methylthiophene (**8**) underwent a palladium catalyzed cross-coupling reaction with the stannylthiophene protected aldehyde **81**. The reaction was performed in two steps, first the Stille coupling of **8** and **81** followed by the deprotection of the acetal to form **82** in an overall yield of 73%.

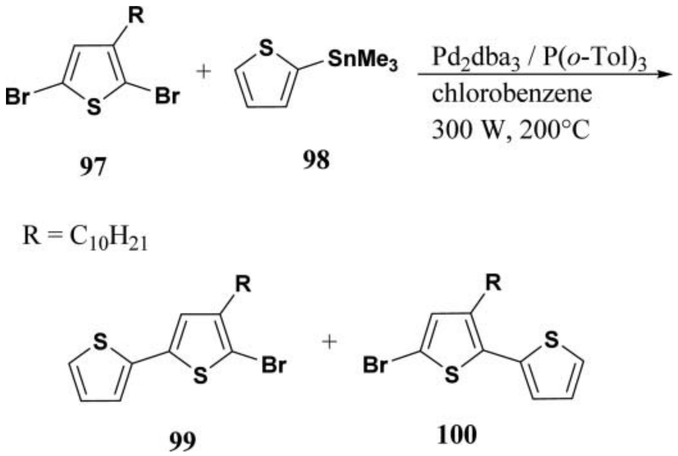


Scheme 32



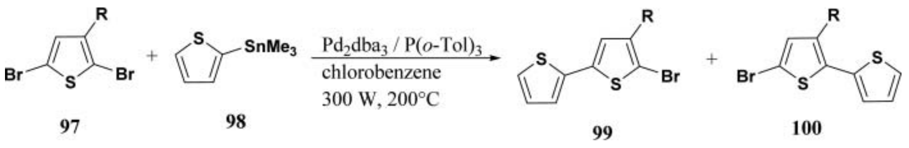
**Scheme 33**

Turbiez *et al.* reported the synthesis of various 3,4-ethylenedioxythiophene (EDOT)-thiophene oligomers[64] using Stille coupling with 2-bromothiophene and 2-bromo-5-hexylthiophene to give dimers **84** or **85** in yields ranging from 33 to 73% (*Scheme 30*).



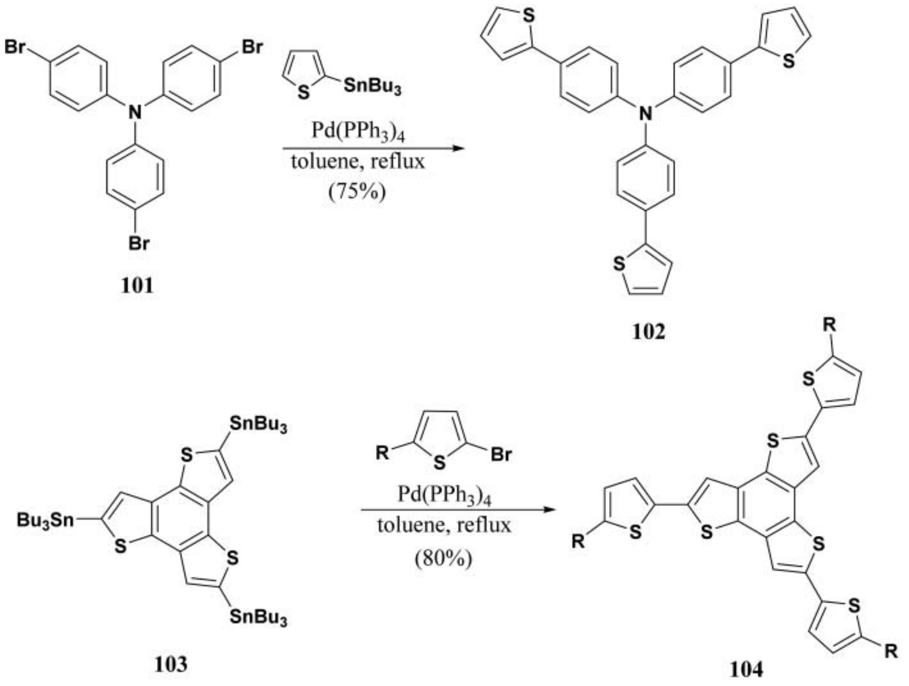
**Scheme 34**

Odobal *et al.* reported the synthesis of a quaterthiophene.[65] The quaterthiophene **87** was obtained by Stille coupling of 2-bromo-3-*n*-octylthiophene (**27**) and 5,5′-bis(tributylstannyl)-2,2′-bithiophene (**86**) in 86% yield using a two-solvent system (THF:DMF) (*Scheme 31*). The authors reported a lower yield when **86** was replaced with 5,5′-bis(trimethylstannyl)-2,2′-bithiophene. In this last case, the major compound obtained was



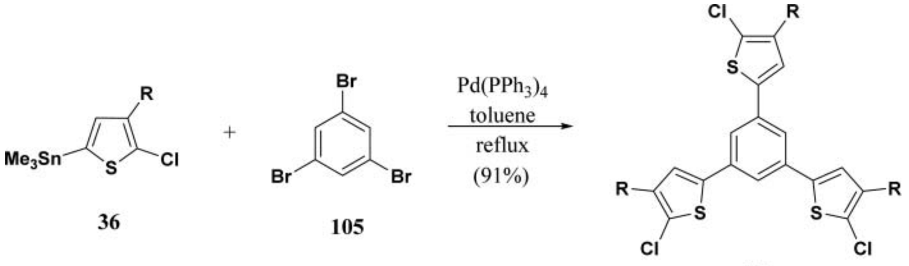
R = $C_{10}H_{21}$

Scheme 34



R = $C_6H_{13}$

Scheme 35



R = $C_8H_{17}$

Scheme 36

the 3,3′-di-*n*-octylsexithiophene which originated from the homocoupling of the bithiophene **86** before it reacted with the 2-bromo-3-*n*-octylthiophene (**27**). This side reaction has been reported by several groups.[29,66–67]

Following up the previous example, Li *et al.* have reported the synthesis of thiazole-containing hexamers (**90** and **93**) for field-effect transistors [68] The synthesis is shown in *Scheme 32* and, in general, yields for the thiazole-containing oligomers were significantly lower (around 20% for **90**) than those for the oligothiophenes. Various side-products (dimerization of *bis(*(tributylstannyl)thiazole for instance) contributed to this low yield, however, substituting the 4 and 4′ position with an alkyl chain decreased the amount of dimerized side product, thus increasing the yield of **93** up to 74%. The solubility of these alkylated thiazole-containing oligomers also increased in common organic solvents.

The cross-coupling of aryl bromides with organostannanes to form vinylthiophenes (**95** and **96**) has been reported by Gajare *et al.*[69] They reported the use of a low-coordinated diphosphinidenecyclobutene ligand for the efficient cross-coupling of electron-rich and electron-poor aryl bromides with organotin reagents. After optimizing the conditions (*Scheme 33*), the system afforded yields ranging 80–89% when halo-substituted alkylthiophenes were used. This method was compatible with nitro, aldehyde or ester functional groups.

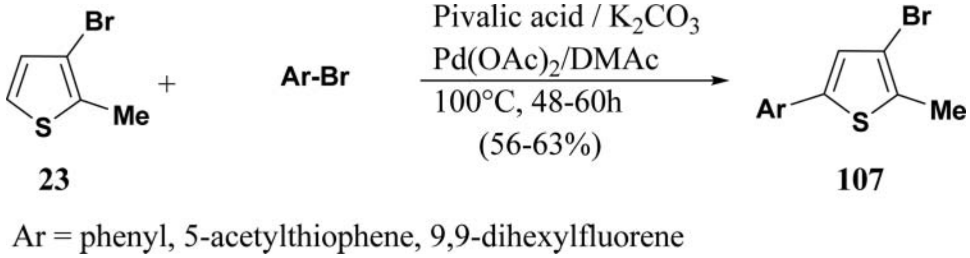
A recent article by Lundin *et al.* discusses the head-to-head (HH) and head-to-tail (HT) coupling of alkylthiophenes, the resulting regiochemistry and its impact on the polymer's properties. [70] The authors investigated the regiochemical orientation using a model system of two different alkylated bithiophenes obtained by Stille coupling (*Scheme 34*). The palladium cross-coupling reaction was performed in a microwave reactor using $Pd_2dba_3/P(o\text{-}Tol)_3$ in chlorobenzene. Two bithiophenes, 5-bromo-4-*n*-decyl-2,2′-bithiophene (**99**) and 5-bromo-3-*n*-decyl-2,2′-bithiophene (**100**), were obtained. Compound **99** is formed in preference of **100** in roughly a 2:1 ratio, a preference similar to that observed for poly(3-*n*-decylthiophene). In addition, this ratio was dependent on the number of equivalents of 2-(tributylstannyl)thiophene used, where a lower stannane equivalent resulted in a greater preference towards **99**.

Stille palladium catalyzed cross-coupling was also applied for the synthesis of star-shaped materials by several groups.[55,71] Cores such as 1,3,5-tribromobenzene, tris(4-bromophenyl)amine[55] (**101**) or 2,5,8-tris(tributylstannyl)benzo[1,2-*b*:3,4-*b*′:5,6-*b*″]trithiophene[71] (**103**) have been used under three-fold Stille coupling conditions [$(PdPPh_3)_4$/ toluene] to give the corresponding stars (*Scheme 35*). A 75% yield was obtained for the synthesis of tris[*p*-(2-thienyl)phenyl]amine (**102**) but a low yield of 10% was obtained for the benzo[1,2-b:3,4-b′:5,6-b″]-trithiophene derivative **104**. In the case of the 1,3,5-tribromobenzene (**105**) core, the Stille coupling was performed with (5-chloro-4-octylthiophen-2-yl)trimethylstannane (**36**).[29] The chlorine atoms on **36** were retained on the thiophene rings to afford **106** in 91% yield (*Scheme 36*).

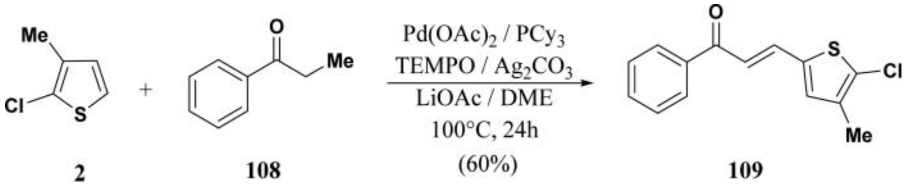
*2.4. Direct Arylation.* The conventional methods to synthesize $\pi$-conjugated systems are performed by using palladium cross-coupling reactions, such as Kumada, Suzuki-Miyaura, Stille, Sonogashira or Hiyama. Although these methodologies allow the formation of C-C bonds quite efficiently, the preparation of specific intermediates is required. For instance, Suzuki coupling requires the preparation of boronic acid (or ester) derivatives and Stille coupling requires the preparation of toxic organotin intermediates. It is also important to point out that many steps are often required to reach the desired targets and the choice of other functional groups on the molecules is limited. Direct selective arylation opens doors to greener, more efficient, syntheses of a variety of new heteroaromatic compounds, such as small molecules and macromolecules for organic, electronic materials. [72–73]

We have recently reported a selective direct arylation approach for the preparation of 2-aryl-4-bromo-5-methylthiophene derivatives.[74] Using the reaction conditions shown in *Scheme 37*, we were able to synthesize a library of 2-aryl-4-bromo-5-methylthiophenes (**107**) in one step with moderate yields (27–63%). Electron-withdrawing groups generally resulted in higher yields than electron-donating groups, and homocoupling of 3-bromo-2-methylthiophene was not observed. The observed selectivity is rationalized by the preferred oxidative addition of the aryl bromide (rather than 3-bromo-2-methylthiophene) on the Pd(OAc)$_2$ catalyst.

Shang *et al.* recently reported a versatile method for the synthesis of heterocyclic chalcone analogues using Pd-catalyzed dehydrogenative cross-coupling between heteroarenes and ethyl ketones.[75] For instance, starting with 2-chloro-3-methylthiophene (**2**) and propiophenone (**108**) it was possible to obtain the desired (*E*)-3-(5-chloro-4-methylthiophen-2-yl)-1-phenylprop-2-en-1-one (**109**) in 60% yield in one step using the conditions described in *Scheme 38*. The use of the PCy$_3$ ligand was crucial as it suppressed the homocoupling of the thiophene and improved the efficiency of the reaction by reducing the electrophilicity of the palladium. The second parameter that must be taken into account is the choice of the base. In this case, LiOAc used together with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as co-oxidant led to an increase in yield, presumably by accelerating the re-oxidation of Pd$^0$ to Pd$^{II}$.[76] Finally, a variety of functional groups were tolerated such as formyl or acetyl groups (both base sensitive) and a ketal group (acid sensitive). Likewise, both electron-withdrawing and electron-donating substituents on the benzene ring of the ethyl ketone led to excellent yields.

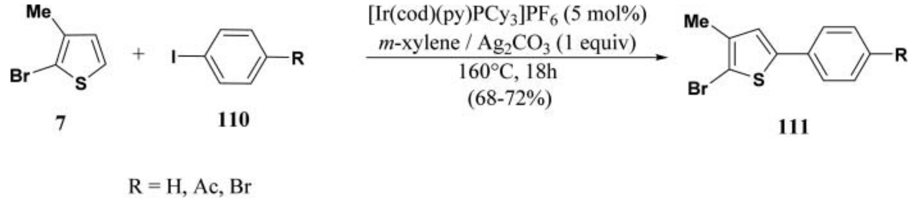


**Scheme 37**



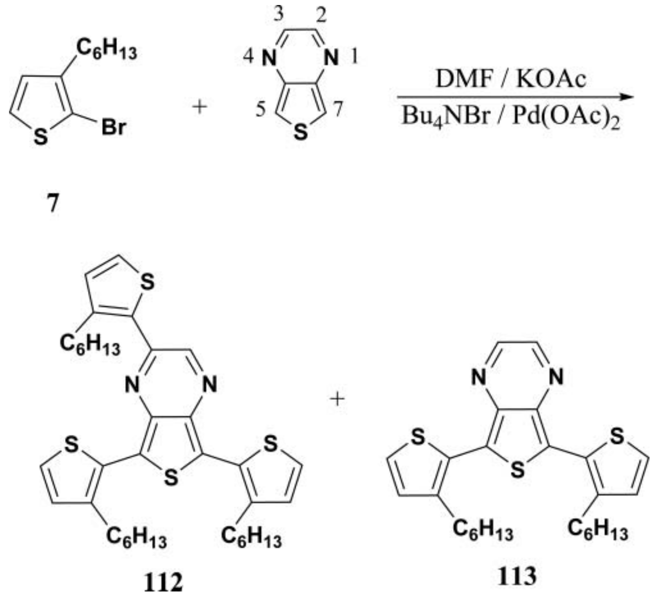
**Scheme 38**

Join *et al.* proposed the use of an Ir catalyst to achieve direct arylation of a heteroarene with iodoarene (**110**) to form phenylthiophenes (**111**) (*Scheme 39*).[77] After screening various iridium complexes and ligands with Ag$_2$CO$_3$, the authors found the PCy$_3$ ligand was the most effective ligand, affording high yields. The reaction conditions allowed the use of ketone, ester, nitro or methoxy functional groups. In addition, various heteroaryls (thiophene, furan, pyrrole, indole, benzothiophene) were applied as the coupling partner and the arylation was found to take place regioselectively; namely, the alpha position of thiophene, furan and pyrroles, the 2-position for benzothiophene and the 3-position for indoles. It is worth mentioning that Br-containing substrates underwent C-H arylation leaving the C-Br bond intact, which is very attractive for subsequent steps.



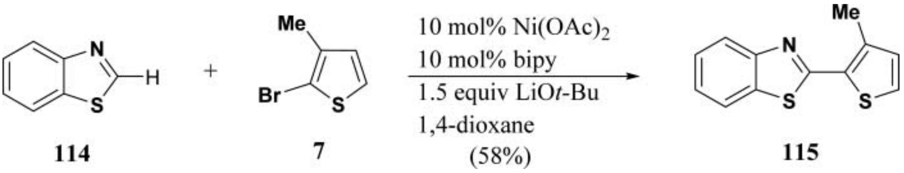
**Scheme 39**

Abdo *et al.* reported the application of a direct C-H arylation reaction between a thieno[3,4-pyrazine] (TP) and 2-bromo-3-*n*-hexylthiophene (*Scheme 40*).[78] The authors used two different approaches, a thermally activated C-H direct arylation and a microwave-assisted direct C-H arylation using Pd(OAc)$_2$/Bu$_4$NBr. With the thermal approach, a mixture of the di-substituted TP (**113**) and the tri-substituted TP (**112**) products was obtained in 50% and 22% yield, respectively. The microwave-assisted method led to a similar mixture after 5 min and increasing the time did not lead to a difference in the yield or ratio of the products.



**Scheme 40**

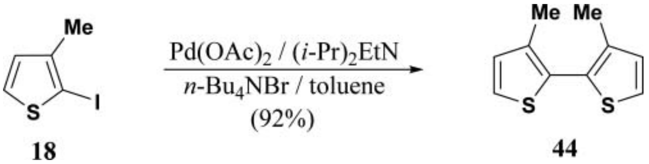
Itami *et. al.* reported the use of a Ni(OAc)$_2$/bipy catalyst system to perform C-H arylation of heteroarene rings (*Scheme 41*).[79–80] After screening a variety of Ni catalysts, ligands and bases, the authors found that the Ni catalysts and the LiO*t*-Bu base were critical in obtaining the targets.[79] In addition, bidentate ligands such as bipy, were found to be more efficient and solvents like 1,4-dioxane led to slightly higher yields compared to solvents such as 1,2-dimethoxyethane (DME), toluene, DMF or *N*-methylpyrrolidone (NMP). Using the optimum conditions, the direct arylation of 2-bromo-3-methylthiophene (**7**) with benzothiazole (**114**) afforded 2-(3-methyl-2-thienyl)-1-thia-3-azaindene (**115**) in 58% yield.



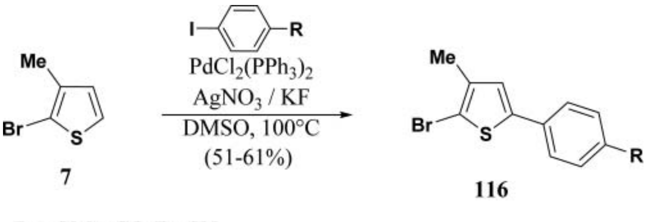
Scheme 41

Hassan *et al.* reported a convenient method to prepare symmetrical alkylbithiophenes[81] and the reaction conditions are given in *Scheme 42*. The bithiophene **44** was obtained in a 92% yield after 4h. Toluene was used to avoid carbon-hydrogen reduction and in this case, the use of the *n*-$Bu_4NBr$ did not increase or decrease the reaction yield. In general, the use of a tetraalkylammonium salt was employed to accelerate the reaction rate and increase yields.[81]

Kobayashi *et al.* reported the selective palladium catalyzed coupling reaction of halogenated methylthiophenes with iodobenzenes using a $AgNO_3$/KF system (*Scheme 43*).[82] The authors found that no reaction was observed at the C-Br bond, and the fractional addition of $AgNO_3$ improved the reaction yield. The yields of arylated alkylbromothiophenes **116** ranged from 51–61%; methoxy, ester and nitrile groups were tolerated.

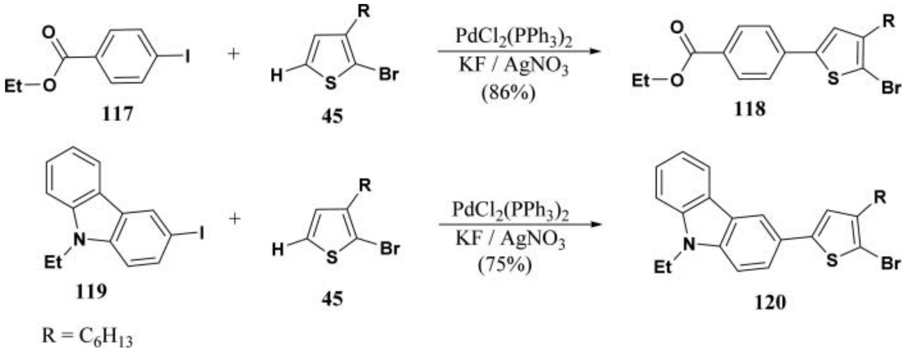


Scheme 42



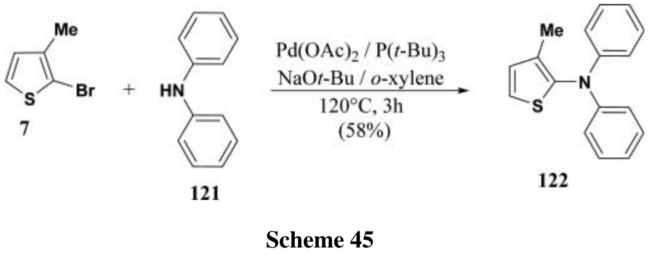
Scheme 43

The same group also reported the use of two other substrates ethyl-4-iodobenzoate (**117**) and 9-ethyl-3-iodo-9*H*-carbazole (**119**) with $PdCl_2(PPh_3)_2$ as the catalyst as illustrated in *Scheme 44*.[83,84]. Yields of 86 and 75% were obtained for ethyl *p*-(5-bromo-4-hexyl-2-thienyl)benzoate (**118**) and 2-bromo-5-(9-ethyl-9*H*-carbazol-3-yl)-3-hexylthiophene (**120**), respectively.



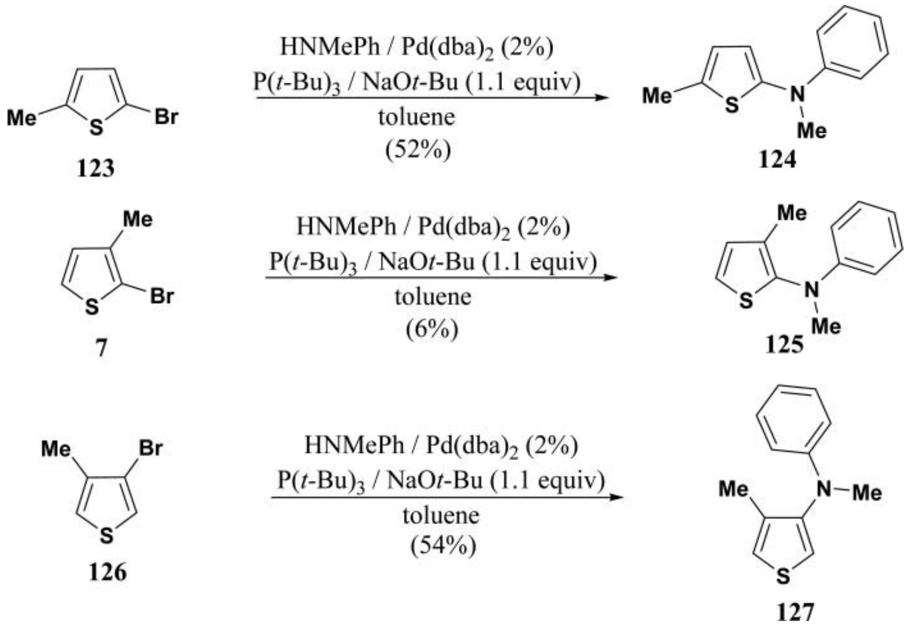
Scheme 44

*2.5. Other Palladium-catalyzed Reactions.* Although the most common reactions of halo-substituted alkylthiophenes are Kumada, Suzuki, Stille and direct arylation cross-coupling reactions, there are other important Pd-catalyzed reactions often employed. For instance, Watanabe *et al.* reported Buchwald-Hartwig palladium-catalyzed reaction using a halo-substituted alkylthiophene by treating diphenylamine (**121**) with 2-bromo-3-methylthiophene (**7**) to afford **122** in 58% yield (*Scheme 45*).[85] In addition, **121** was treated with 3-bromothiophene to afford the corresponding diphenylaminothiophene in 69% yield with only 0.25 mol % of $Pd(OAc)_2$.



Scheme 45

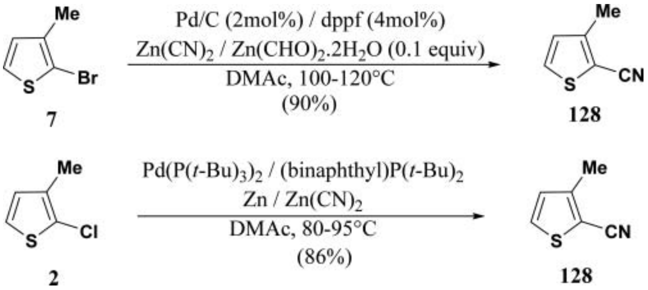
Hopper *et al.* also reported the amination of five-membered heterocyclic halides under Buchwald-Hartwig conditions using the $P(t\text{-}Bu)_3$ ligand.[86]*Scheme 46* illustrates the different locations of the methyl group on the thiophene ring led to the differences in the yields obtained from various methyl-substituted bromomethylthiophenes. Thus reaction of **123** with *N*-methyl-aniline gave a 52% yield of the aminothiophene **124** while only a 6% yield of **125** was obtained from the same reaction with 2-bromo-3-methylthiophene (**7**). In this case, the major product isolated was the amidine PhN = CHN(Me)Ph, presumably arising from a metal-mediated disproportionation of the unstable imine $CH_2$ = NHPh resulting from a *β*-hydride elimination of the palladium *N*-methylaniline



Scheme 46

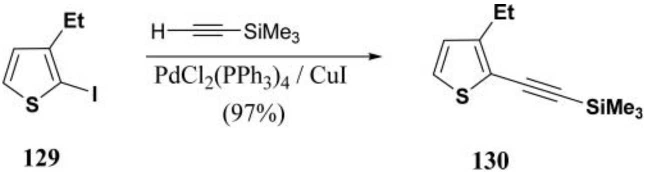
intermediate. However, the reaction of 3-bromo-4-methylthio-phene (**126**) with *N*-methylaniline afforded **127** in 54% yield, showing that the position of the bromine relative to the methyl group–namely 2-bromo-3-methylthiophene compared to 3-bromo-4-methylthiophene–has a major influence on the yield of aminothiophene derivatives.

Both Littke[87] and Yu[88] groups reported the palladium-catalyzed cyanation of heteroraryls under mild and simple conditions (*Scheme 47*) to prepare 3-methylthiophene-2-carbonitrile (**129**) in good yields (86%[87] and 90%[88] respectively). Yu *et al.* used 1,1′-*bis* (diphenylphos-phino)ferrocene (dppf) in the presence of Zn(CHO)$_2$.2H$_2$O. The zinc formate dihydrate was critical as it reactivated the palladium catalyst.[88] Littke *et al.* studied the same reaction using Pd(P($t$-Bu$_3$)$_2$ as catalyst with similar success.[87] In addition, a variety of functional groups such as aniline, phenol, ester, nitro, amide, carboxylic acid and boronic acid were tolerated.[87]



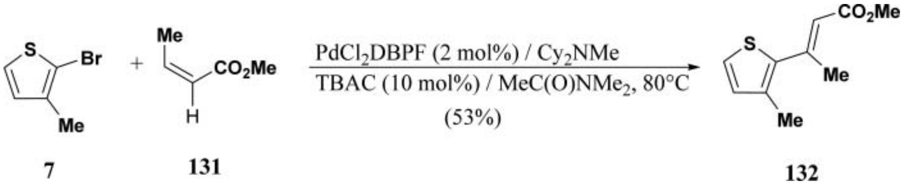
Scheme 47

Tour's group reported the reaction of 3-ethyl-2-iodothiophene (**129**) with trimethylsilylacetylene in a Sonogashira palladium cross-coupling reaction (*Scheme 48*).[89] Using standard Sonogashira conditions (CuI, $PdCl_2(PPh_3)_2$, THF), **130** was obtained from 2-iodo-3-ethylthiophene (**129**) in nearly quantitative yield (97%).



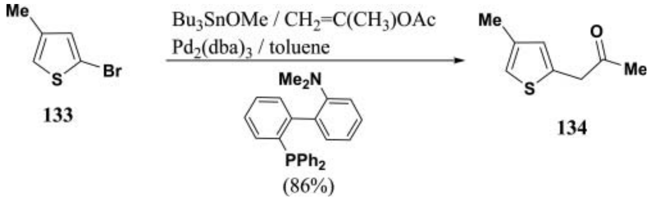
Scheme 48

Murray *et al.* reported the coupling of 2-bromo-3-methylthiophene (**7**) with methyl isocrotonate in a Heck-Mizoroki reaction (*Scheme 49*).[90] After the reaction conditions were optimized to determine the best catalyst/ligand/base/solvent system, that procol was applied to a variety of substrates to synthesize many crotonate derivatives. Interestingly, methyl (2*Z*)-butenoate (**131**) afforded a 53% yield of methyl (*E*)-3-(3-methyl-2-thienyl)-2-butenoate (**132**) without contamination from any other isomers.



Scheme 49

Liu *et al.* have reported a $Pd_2(dba)_3$/2-dimethylamino-2′-diphenylphosphino-1,1′-biphenyl catalyst system for the formal $\alpha$-heteroarylation of acetone to give **134** as shown in *Scheme 50*.[91] A variety of ligands were screened and Buchwald's *o*-biphenyl phosphines led to the best reaction yields. The reaction tolerates both electron-withdrawing groups and electron-donating groups on the aromatic group. Mechanistically, the reaction proceeds *via* a tin enolate generated *in situ*, which undergoes transmetallation, and coupling with the corresponding haloaromatic ring. In this regard, triflate, chloride and bromide moieties can be used in the aromatic substrate.



Scheme 50

## Conclusion

The chemistry of thiophenes is rich and provides several avenues for the synthesis of complex molecular architectures through the selective but reactive nature of the thiophene ring. Functionalization of these materials using various metal-catalyzed cross-coupling methods demonstrates the vast number of molecular structures available for the production of novel oligomeric and polymeric materials for the next generation of materials for organic photonics and electronics.

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