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A mild and practical copper catalyzed amination of halothiophenes☆

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Abstract—We have found that *N*,*N*-dimethylethanolamine (deanol) is a useful solvent and ligand for copper catalyzed amination of a variety of unactivated and activated 2- or 3-halothiophenes. Primary amines, acyclic secondary amines, cyclic secondary amines and acyclic secondary amines with 2-hydroxyethyl functionality react with halothiophenes in moderate to excellent yields. The mildly basic conditions utilized are compatible with many functional groups. The amination of halobithiophenes has also been examined. The aminothiophenes produced by this method are important intermediates in a variety of electronic and optoelectronic materials.

1. Introduction

The thiophene ring is often substituted for benzene in many materials and systems so as to deliver some enhanced function, as in the case of pharmaceuticals[1–3] and optoelectronic materials.[4,5] More specifically, and in spite of an often relatively difficult synthesis, aminothiophenes have been widely compared to anilines due to their exceptional electronic properties.[6] However, little in the way of general or straightforward synthetic methodology exists for amine-substituted thiophenes, especially those that are electron-neutral or electron-rich. The methods available for the synthesis of aminothiophenes include these categories: (1) creation of the thiophene ring by conversion of acyclic starting materials;[7–10] (2) reactions of halothiophenes with metal amide, reduction of nitrothiophenes and rearrangement reactions that are limited to the parent aminothiophenes without alkyl substitution;[11,12] (3) alkylation of one aminothiophene to create another;[13] (4) nucleophilic aromatic substitution of halogenated substrates bearing one or more electron withdrawing and activating substituents;[14] (5) substitution reactions of mercaptothiophenes;[15] (6) electrophilic substitution of thienyl cuprates with *N*-alkylhydroxylamines;[16] (7) oxidative intramolecular coupling of amidocuprates[17] and, finally, (8) transition metal mediated amination reactions of halothiophenes.[18–20]

Some of these preparative methods are generally limited by either the availability of starting materials or by the compatibility of sensitive functional groups in the substrates. Multi-step synthesis may often be required to obtain even the starting materials required for thiophene ring building. Since the parent aminothiophenes are themselves generally unavailable and unstable, an alkylation approach to make *N*-substituted aminothiophenes is impractical.[11,21] 2-Methylaminothiophene and 2-isopropylaminothiophene were made by electrophilic amination of cuprates with *N*-alkyl-*O*-(trimethylsilyl) hydroxylamines but this method is not compatible with other base sensitive functionality.[16] Nucleophilic aromatic substitution (S_NAr) is an established and straightforward method, but it is limited to the thiophenes with the appropriate type, number and location of electron deficient-substituents. For example, Prim demonstrated that some weakly activated bromothiophenes such as 5-bromothiophene-2-carboxaldehyde react efficiently with a variety of secondary aliphatic amines in aqueous media by S_NAr reaction and no transition metal catalyst was required.[14] However, 4-bromothiophene-2-carboxaldehyde did not give any amination product with cycloaliphatic amines under the same conditions. Aminothiophenes bearing a secondary amine group have been prepared from 2-mercaptothiophene and the corresponding aliphatic secondary amines.[15] This method is still used to prepare this family of compounds although it 'requires several unattractive steps with respect to yields and substituent variations'.[22] The oxidative intramolecular coupling may be described as a special case of copper mediated amination process, but it often requires sensitive organometallic reagents that are not compatible with some

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functional groups, although in certain cases it has clear-cut advantages for the application to bulky alkylamines and arylamines.[23,24]

Transition metal mediated substitution reactions have been extensively explored in recent years and have been successfully applied to the amination of a range of halothiophenes.[25,26] Watanabe reported the amination of unactivated bromothiophenes with diarylamines under strongly basic conditions with *t*-BuONa and a $Pd(OAc)_2$/P-*t*-Bu_3 catalyst. No aliphatic amines were examined in this report.[18] Rasmussen expanded the use of the same catalyst system to reactions of 3-bromothiophene with primary and secondary aliphatic amines.[27] When primary amines were used under these reaction conditions a mixture of 3-(*N*,*N*-dialkyl) and 3-(*N*-alkyl)-aminothiophenes was obtained in moderate yield. Luker described an amination reaction with a palladium/BINAP catalyst and Cs_2CO_3 base for halothiophenes with a halogen activated by an electron-deficient group. This method failed when applied to non-conjugated activated halothiophenes such as the 2,4 isomer and electron neutral or rich substrates.[28] In a recent systematic report Hartwig showed that unfunctionalized bromothiophenes and other five membered haloheterocycles reacted smoothly with *N*-methylaniline in the presence of $Pd(dba)_2$/P^{t}Bu$_3$.[20] However, the reactions of hexylamine, dibutylamine, piperidine, or morpholine with most 2-halothiophenes afforded 'little or no amination products'. Secondary amines such as morpholine and 4-phenylpiperazine reacted with 3-bromothiophene in moderate to good yields but the reactions of primary amines with 3-bromothiophene under these conditions were less successful. For example, *n*-hexylamine reacted with 3-bromothiophene in only 20–30% yield.

The copper-catalyzed Ullmann condensation is a very attractive approach because of economic considerations for large-scale industrial applications.[29] In some cases, stoichiometric amounts of copper and a polar aprotic solvent such as HMPT were required for this method.[30,31] Padwa recently reported copper-catalyzed amidations of bromine substituted furans and thiophenes in the presence of *N*,*N*′-dimethylethylenediamine as ligand.[19,32] Buchwald disclosed an example of copper catalyzed amination of 3-bromobenzothiophene with primary amines.[33] In contrast, copper catalyzed amination of the readily available electron neutral 2-halo or 3-halo thiophenes still remains unexplored. We have recently described a mild copper catalyzed amination reaction with *N*,*N*-dimethylethanolamine (deanol) as solvent and found that 2-iodo and 2-bromothiophene could be successfully coupled with a variety of primary amines and cyclic secondary amines.[34] Subsequently, deanol was examined as a ligand for copper-catalyzed amidation of vinyl halides, but no accelerating effect was observed in this case.[35] The palladium catalyzed amination of electron rich thiophenes with aliphatic amine are not successful. It has been observed that copper and palladium catalyzed amination processes often provide complementary results.[36] We now disclose the details of the copper-catalyzed amination reactions of 2-halothiophenes in deanol and extend the scope of this method to the amination of 3-bromothiophene and halobithiophenes with a more diverse selection of amines. The method described here provides an alternative and sometimes complementary or superior approach to palladium-mediated aminations.

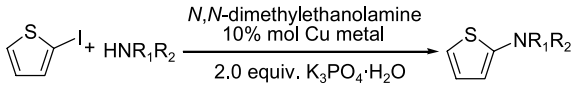
2. Results and discussion

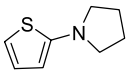
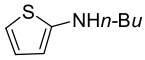
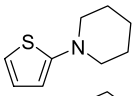
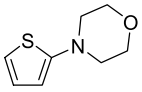
In our initial communication, we reported a mild copper-catalyzed amination reaction of aromatic iodides with unhindered primary amines and cyclic secondary amines by using *N*,*N*-dimethylethanolamine (deanol) as ligand and solvent. While aryl bromides were generally not good amination substrates we found that 2-bromothiophenes to be exceptionally reactive. This observation prompted us to explore further additional copper-mediated reactions of bromothiophenes and amines. We have since investigated the coupling of a larger variety of amines with 2-bromothiophene and we have also found that 3-bromothiophene is a good substrate for this reaction, even with primary amines. This latter finding is in contrast to the case of some palladium-catalyzed reactions of primary amines that have been reported to poison reactions with 2-bromothiophenes and are also not very successful for 3-bromothiophenes.[20] We have also found that reaction of acyclic secondary amines with bromothiophenes are only moderately successful but acyclic secondary amines with β-hydroxyl functionality are exceptionally reactive towards bromothiophenes and give very good amination yields.

The amination reaction conditions described here were modified somewhat since our initial report.[34] Copper metal was originally used as the catalyst for 2-iodothiophenes and copper metal alone has proven very successful for iodide substrates. However, in the case of bromothiophenes a mixture of copper metal and CuI (1:1 to 3:1) is employed as an induction period is observed when copper metal alone is used. The reaction temperatures and reaction times have been chosen depending on the reaction progress monitored by GC and TLC.

The amination reactions of 2-iodothiophene with a range of amines are found in Table 1. The reactions of 2-iodothiophene with both primary amines and cyclic secondary amines proceed smoothly. Compared to iodobenzene, 2-iodothiophene is more reactive and shorter reaction times and lower temperatures are required. The coupling products between primary amine 2-iodothiophene are somewhat unstable. Since *N*-monoalkylaminothiophenes are fairly unstable to oxidation and acidic conditions due to tautomerization,[11,37,38] we have employed Kugelrohr distillation to purify these products. Nevertheless, once purified they rapidly turn red upon exposure to air and/or light. The reason for some of the relatively low yields here is probably due at least in part to this poor stability and the related mechanical losses during workup and purification. We have found that 2-pyrrolidinothiophene is unstable on silica gel unless the column is pretreated with 5% triethylamine in hexane to neutralize the most active acidic sites. However, 2-pyrrolidinothiophene is easily purified by vacuum distillation. Thiophene derivatives with six-membered ring amines are generally more stable than analogues containing five-membered ring amines and primary amines.

Table 1. Copper metal catalyzed amination of 2-iodothiophene



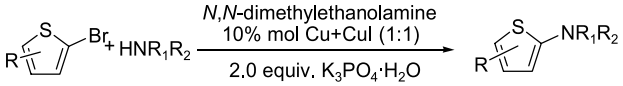
Entry	Amine	Product	Temperature/time (°C/h)	Yield (%)[a]
1			60/10	91
2	$H_2Nn\text{-}Bu$		60/11	62
3			70/10	87
4			75/24	62

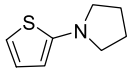
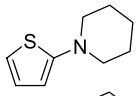
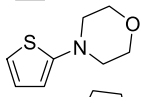
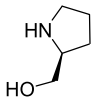
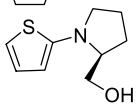
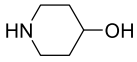
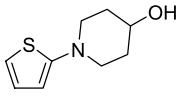
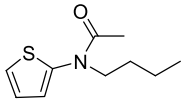
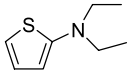
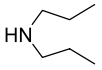
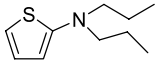
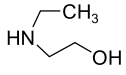
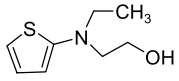
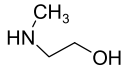
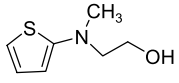
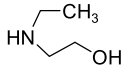
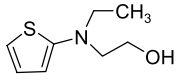
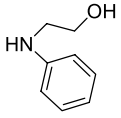
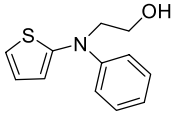
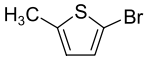
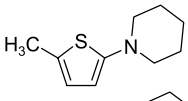
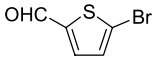
[a] Isolated yield, with 10 mmol 2-iodothiophene and 1.5 equiv of amine.

Since 2-bromothiophene is more accessible than 2-iodothiophene, and encouraged by our early results reacting this bromide with pyrrolidine, we have extended this amination reaction to other amines (Table 2). Cyclic six-member ring amines also afforded very good yields of amination products (Table 2, entries 2 and 3). Cyclic amines with hydroxyl functionality were also examined. The reactivity of (*S*)-(+)-pyrrolidinemethanol and 4-hydroxypiperidine are quite similar to the amines without additional hydroxyl functionality (Table 2, entries 4 and 5). However, the reaction between 2-bromothiophene and primary amines is not very satisfactory. For example, when *n*-butylamine is coupled with 2-bromothiophene, the reaction mixture turned black quickly and the reaction did not proceed to completion. Longer reaction times, higher catalyst loading and higher reaction temperatures also resulted in incomplete conversion of 2-bromothiophene. The reasons for the difficulty in conversion of 2-bromothiophene are not straightforward to elucidate. Hartwig observed an immediate poisoning effect of hexylamine in the palladium-catalyzed coupling of 2-bromothiophene with *N*-methylaniline while the poisoning effect was not observed for the reaction of bromobenzene with *N*-methylaniline.[20] It appears unlikely here that the primary amine alone would poison the catalyst because primary amines are coupled to 3-bromothiophenes very successfully (Table 3, entries 1–3). In another experiment, the reaction started with 10 mmol of 2-bromothiophene and a 1:1 ratio of pyrrolidine (1.2 equiv) and *n*-butylamine (1.2 equiv) under the typical reaction conditions. Incomplete conversion of 2-bromothiophene was observed (~15% remained) and additional reaction time and catalyst did not help. Interestingly, the ratio of the two amination products was 1:1, the same mole ratio as the starting amines, indicating similar reactivity for the two amines. We assumed that the unstable 2-(*n*-butylamino)thiophene product might interact with the active catalytic species and inhibit the catalytic process. In order to test this hypotheses, 30% mol of 2-(*n*-butylamino)thiophene was added to the reaction of 2-bromothiophene and pyrrolidine before the reaction started. The 2-(*n*-butylamino)thiophene additive almost completely stopped this reaction as less than 5% conversion of 2-pyrrolidinothiophene was observed after 48 h at 80 °C. Here again, additional catalyst and reaction time did not further improve the conversion. These experiments suggest that it is the amination product of 2-bromothiophene or possibly some degradation product of that amine product, rather than the primary amine itself, that inhibits this copper-catalyzed amination reaction. Due to the instability of 2-(*n*-butylamino)thiophene, for characterization purposes we chose to convert it to a more stable amide by reacting with acetic anhydride in pyridine. The stable *N*-butyl-*N*-2-thienylacetamide can be separated easily by flash chromatography on silica gel (Table 2, entry 6).

In the case of halobenzenes, a limitation of this copper-catalyzed deanol method was already observed in its inapplicability to coupling with ordinary acyclic secondary amines.[34] For example, only 2% of *N*,*N*-diethylaniline was isolated from the reaction of iodobenzene with diethylamine with deanol/copper catalyst. It has been reported that the palladium-catalyzed amination of 2-bromothiophene with most secondary aliphatic amines is very challenging. For example, no amination product was obtained from the reaction of dibutylamine with 2-bromothiophene.[20] However, we have found moderate success for the reaction between an acyclic secondary amine with 2-bromothiophene (Table 2, entries 7 and 8). 2-*N*,*N*-Diethylaminothiophene was isolated in 39% yield and 2-*N*,*N*-dipropylaminothiophene was isolated in 35% yield from the respective amines and 2-bromothiophene with a high loading of both catalyst (30–40%) and amine (4 equiv). No advantage was observed for the use of 2-iodothiophene instead of 2-bromothiophene in these reactions as a higher amount of deanol ether byproduct was obtained (~20% yield) using iodothiophene. The main reason for the low yields here was that a slow poisoning effect quite similar to the reaction of primary amine with 2-bromothiophene was also observed in the reaction of diethylamine and dipropylamine with 2-bromothiophene. However, the stability of 2-*N*,*N*-dialkylaminothiophenes appear to be higher than 2-*N*-monoalkylaminothiophenes and so a high catalyst and amine loading could push the reaction to high conversion. As yet another complication, the stability of 2-*N*,*N*-dialkylaminothiophenes on silica gel is far less than

Table 2. Copper metal–cuprous iodide catalyzed amination of 2-bromothiophenes



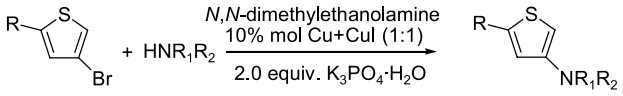
Entry	Thiophene	Amine	Product	Temperature/time (°C/h)	Yield (%)
1				80/50	81[a]
2				80/50	73[a]
3				80/72	65[a]
4				80/50	71[a,b]
5				80/50	64[a]
6		H_2Nn-Bu		Two steps	23[c]
7				80/48	39[d]
8				80/48	35[d]
9				80/72	31[a]
10				80/24	81[e]
11				80/24	81[e]
12				80/48	15[e]
13				80/24	71[a]
14				65/48	77[a]

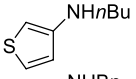
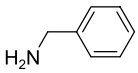
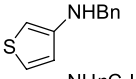
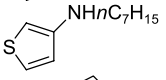
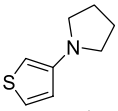
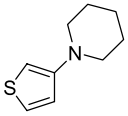
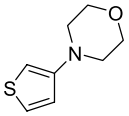
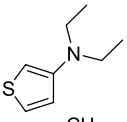
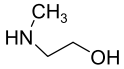
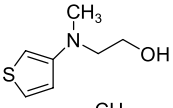
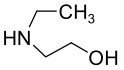
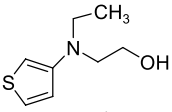
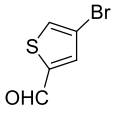
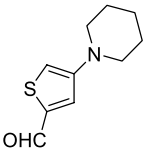
[a] Deanol was used as solvent, 10 or 20 mmol of bromothiophene and 1.5 equiv of amine.
[b] 10 mmol of amine and 15 mmol of 2-bromothiophene.
[c] Copper-catalyzed amination followed by acylation using acetic anhydride and pyridine.
[d] 40% mol of Cu and 4.0 equiv of amine.
[e] 2-Alkylaminoethanol was used as solvent.

2-pyrrolidinothiophene and so they were purified using a neutral alumina column.

In contrast to the ordinary acyclic secondary amines, acyclic secondary amines with 2-hydroxyethyl functionality possess extraordinary reactivity (Table 2, entries 9–12). Such amines are frequently introduced into opto-electronic materials and polymers by nucleophilic aromatic substitution reaction.[39] With our standard method, in which deanol was used as solvent and 2-(*N*-ethylamino)ethanol was used as reactant, a low yield (31%, Table 2, entry 9) was obtained in coupling with 2-bromothiophene. However, when deanol was omitted and the amino alcohol was used as the solvent, the reactions of 2-(*N*-methylamino)ethanol and

Table 3. Copper-catalyzed amination of 3-bromothiophenes

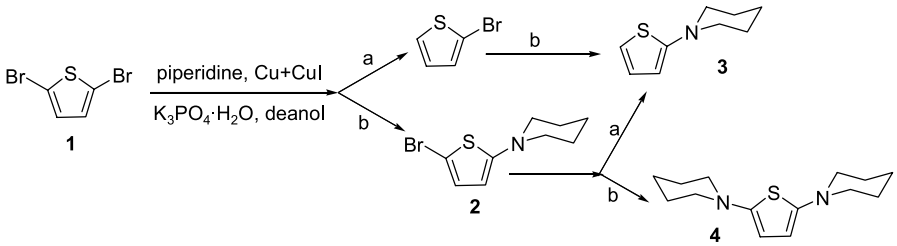


Entry	Thiophene	Amine	Product	Temperature/time (°C/h)	Yield (%)
1		H_2Nn-B*u*		80/36	85[a]
2				80/40	86[a]
3		$H_2NnC_7H_{15}$		80/45	83[a]
4				80/45	83[a]
5				80/40	73[a]
6				80/70	23[a]
7				85/60	15[b]
8				80/24	90[c]
9				80/45	45[c]
10				65–75/70	53[a]

[a] Deanol as solvent, 10 or 20 mmol of bromothiophene and 1.5 equiv of amine.
[b] 35% of Cu and CuI (4:1) and 4 equiv of diethylamine.
[c] Alkylaminoalcohol as solvent.

2-(*N*-ethylamino)ethanol with 2-bromothiophene both afforded an 81% yield of the respective amination product. No reaction was observed between 2-bromothiophene and the aromatic amines aniline, diphenylamine and carbazole under the typical reaction conditions. In contrast, the reaction between 2-anilinoethanol and 2-bromothiophene afforded the amination product in 15% yield when 2-anilinoethanol was used a solvent at 90 °C for 48 h. Attempts to enhance this yield with higher temperature (up to 120 °C), longer reaction time and higher catalyst loading were all unsuccessful. In spite of the low yield, this additional case substantiates the enhanced reactivity of β-aminoethanols in copper-catalyzed aminations.

We have also examined the amination of some other functionalized bromothiophenes. Coupling of 2-bromo-5-methylthiophene with piperidine afforded almost the same amination yield as the reaction of 2-bromothiophene, but the product with methyl substitution is more stable (Table 2, entry 13).[40] The 5-proton may play a role in the instability of 2-piperidinothiophene and the methyl group may inhibit reaction at this site in the tautomer of 2-piperidino-5-methylthiophene. This copper-mediated method in deanol also works well with thiophenes bearing conjugated electron-withdrawing groups. 5-Bromo-2-thiophenecarboxaldehyde was successfully reacted with piperidine at 65 °C and the corresponding 2-piperidinothiophene-5-carboxaldehyde was isolated in 77% yield (Table 2, entry 14). The lower yield here compared to that obtained from the corresponding aromatic nucleophilic substitution reaction may be due to competitive C–Br reduction.[14] The reaction temperature employed here is lower compared to conditions reported for the uncatalyzed aromatic nucleophilic substitution reaction (110 °C).[41] A similar reaction under the same



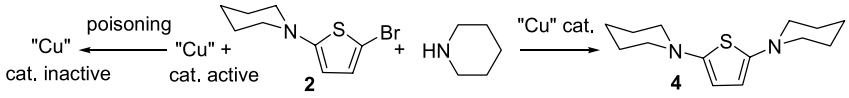
Scheme 1. Amination of 2,5-dibromothiophene (**1**) with piperidine.

conditions but without copper catalyst was also examined. Only 19% yield of amination product was separated and the major byproduct was 2-thiophenecarboxaldehyde accompanied by some decarbonylation product 2-bromothiophene. This dehalogenation is often observed during transition metal-catalyzed coupling or reduction.[42,43] We are still uncertain how the decarbonylation reaction happened here, nevertheless the experiments prove that copper played a catalytic role.

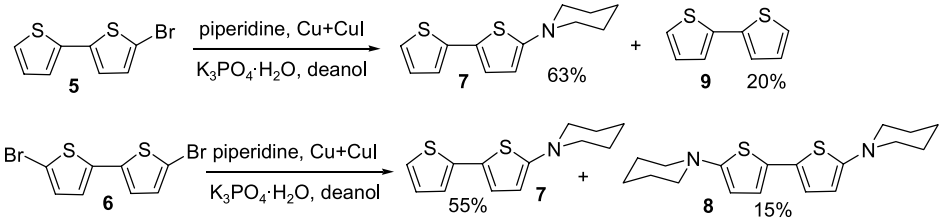
We have also explored the amination of 2,5-dibromothiophene with the intended goal to prepare 2-bromo-5-dialkylaminothiophenes (Scheme 1). However, we found that the reaction of **1** with 1.2–3.0 equiv piperidine stopped within 24 h and most of **1** was recovered. Analysis of the reaction mixture by GC–MS indicates that the concentration of the component assigned as 2-bromo-5-piperidinothiophene was low at all times during the whole reaction process. Significant dehalogenation was also evident in this reaction. For instance, after 48 h reaction between 2,5-dibromothiophene and piperidine (3.0 equiv) at 80 °C, the major products were isolated 2-piperidinothiophene (31%) and 2,5-dipiperidinothiophene (20%) along with a smaller amount of 2-bromothiophene. Although the 2-bromo-5-piperidinothiophene was detected by GC–MS all attempts to isolate a pure sample by silica gel chromatography failed. This result is similar to the reaction of 2-bromothiophene with primary amines wherein the reaction gradually came to a halt prior to completion. The use of less amine (1.2 or 1.5 equiv) resulted in earlier termination of the reaction and more (>50%) of 2,5-dibromothiophene remaining. After aqueous work-up and extraction with diethyl ether, a significant amount of black precipitate was observed in the aqueous layer. This result may be due to the formation of a labile 2-bromo-5-piperidinothiophene (**2**) that would react with the catalytic copper species and precipitate out from the solution. However, and to our surprise, when more piperidine (6 equiv) and copper catalyst (20% mol, Cu/CuI is 3:1) were used, all the 2,5-bromothiophene (**1**) was consumed, the half reduced product 2-piperidinothiophene (**3**) was isolated in 26% yield and 2,5-dipiperidinothiophene (**4**) was now isolated in 46% yield.

Since intermediate **2** is present as a low concentration species in all cases (with 1.2–6.0 equiv of piperidine and at low or high catalyst loading), we assume that the intermediate **2** is more reactive than other bromothiophenes towards this copper-catalyzed amination reaction to form products of reduction or amination. Scheme 2 describes a competition between the desired catalytic reaction and the 'Cu' poisoning reaction. If the concentration of piperidine and catalyst loading were both low, the amination reaction of intermediate **2** would be slow. In this case, the reaction of intermediate **2** with the active copper catalyst species becomes a significant one and therefore the copper catalytic species would precipitate out from the solution. This process would slow down and eventually stop the catalytic amination reaction; if the piperidine concentration and the catalyst load are increased, intermediate **2** would react with piperidine faster than reacting with copper species towards the poisoning direction, and therefore the whole catalytic reaction moves to the amination product and all the starting material could be converted. However, the poisoning reaction could not be excluded even in the later case because a small amount of brown precipitate was also observed.

The amination of bromobithiophenes was also briefly



Scheme 2. Competition between the catalytic reaction and the 'Cu' poisoning reaction.



Scheme 3. Amination of 5-bromo-2,2-bithiophene (**5**) and 5,5-dibromo-2,2-bithiophene (**6**).

explored as is illustrated in Scheme 3. Reaction of 5-bromo-2,2′-bithiophene (**5**) with piperidine appeared slightly more facile than the reaction of 2-bromothiophene with piperidine, although the yield of 5-piperidino-2,2′-bithiophene (**7**) (63%) was less than the reaction giving 2-piperidinothiophene (**3**, Table 2, entry 2, 73%). It appears that 5-bromo-2,2′-bithiophene (**5**) has a higher tendency to be reduced than 2-bromothiophene as about 20% of 2,2′-bithiophene (**9**) was isolated from this reaction. Although poisoning effects were noticeable for the amination of 2,5-dibromothiophene, no obvious poisoning was observed in the case of 5,5′-dibromo-2,2′-bithiophene (**6**). To our surprise, the major product (54%) from the reaction of 5,5′-dibromo-2,2′-bithiophene (**6**) with piperidine was the half reduced amination product 5-piperidino-2,2′-bithiophene (**7**). The 5,5′-dipiperidino-2,2′-bithiophene (**8**) was isolated in a substantially lower yield (14%) and the doubly reduced product, 2,2′-bithiophene (**9**) was also isolated in 9% yield.

Based on these very preliminary results the copper-deanol method appears to be quite useful for the amination of dihalothiophenes and halooligothiophenes. However, studies with these substrates do point out the role that reduction plays in the diminution of yield of the desired amination products. The use of more amine in these reactions may be beneficial in minimizing the amount of reduction.

In order to expand and elucidate the scope of this mild amination reaction for other electron-neutral and electron-rich thiophenes, we have also performed reactions of 3-bromothiophene with a range of aliphatic amines. In contrast to the unsuccessful or complicated product distributions reported for palladium-catalyzed amination reactions of primary amines with 3-bromothiophene,[20,27] we found that the copper-mediated deanol method is a mild and effective process even for primary amines.

Table 3 shows the copper-catalyzed amination results of 3-bromothiophenes. All the primary amines examined afforded very good yields of monoarylation products in contrast to palladium-catalyzed aminations that also gave diarylation byproducts as well as monoarylation product.[27] The successful amination of 3-bromothiophene with primary amines may be related to the better stability of 3-(*N*-alkylamino)thiophenes compared with 2-(*N*-alkylamino)thiophenes. Unlike 2-(*N*-alkylamino)thiophene, a longer reaction time is less prone to decompose 3-(*N*-alkylamino)thiophenes in the reaction system and no poisoning effect was observed for 3-(*N*-alkylamino)thiophenes. Amines with longer alkyl chains required a longer reaction time (entry 3, Table 3). In addition, the 3-aminothiophenes are fairly stable to air for short periods and the products can be easily purified by flash chromatography on silica gel, however, they are not stable for long term storage even at low temperature. The 3-bromothiophene is less reactive to acyclic secondary amines than 2-bromothiophene but the product is more stable and can be isolated by silica gel chromatography. For instance, after 60 h reaction at high catalyst and amine loading, only 15% of 3-*N*,*N*-diethylaminothiophene was isolated. Similar to 2-bromothiophene, most cyclic secondary amines also afforded good yields (Table 3, entries 4–6) and the lack of reactivity of 3-bromothiophenes towards acyclic secondary amines is quite similar to that of 2-bromothiophene. The ordinary acyclic secondary amines are again not reactive under these conditions, but amines with 2-hydroxyethyl functionality also possess significantly enhanced reactivity for 3-bromothiophene. For instance, when the 2-(*N*-methylamino)ethanol and 2-(*N*-ethylamino)ethanol were used as solvent, both successfully coupled with 3-bromothiophene and afforded 90 and 45% yields of the respective amination products (Table 3, entries 8 and 9).

It is particularly interesting to apply this process to the amination of 4-bromo-2-thiophenecarboxaldehyde since this substrate failed to give any amination product by the nucleophilic aromatic substitution method.[14] We have found that the present method does provide a moderate yield of amination product when 4-bromo-2-thiophenecarboxaldehyde reacts with piperidine at 65–75 °C (Table 3, entry 10). The product of reductive debromination (2-thiophenecarboxaldehyde) was isolated as the major byproduct and the decarbonylation product (2-piperidinothiophene) was also observed as another byproduct. It is worth noting that if the reaction was run at higher reaction temperature (>85 °C), the amination product yield was not improved, probably due to the instability of the aminothiophenecarboxaldehyde or the starting aldehyde.

A usually minor but ubiquitous competing side reaction of the copper-catalyzed amination reaction of aryl halides in deanol is aryl ether formation involving the alcohol group of deanol. In our earlier study with aryl halide substrates the aryl ether byproducts were isolated.[34] In the case of the thiophenes studied here no systematic effort was made to isolate and characterize these deanol ether byproducts except those from 2-bromothiophene and 3-bromothiophene (see supporting information). The thiophene ethers from deanol are significantly more polar than the desired amine derivatives and were not isolated by chromatography. The yield of these ether byproducts is estimated at 2–10% depending on the reactivity of the specific halothiophenes and amines. Larger amounts of aryl ethers were isolated when acyclic secondary amines were used as reactants. The more reactive iodothiophene gave less ether byproduct. Another side reaction is the reduction of the halo group in halothiophene. Bithiophenes and thiophenes with electron-withdrawing substitution seem to afford more reduced product. We found that this method could not be extended to a useful synthesis of ether-substituted thiophenes. For example, treatment of 2-iodothiophene with 3 equiv of 1-propanol and 15% mol Cu and CuI (2:1) catalyst for 24 h at 80 °C (standard amination conditions), produced mainly the deanol ether of 2-iodothiophene ($\sim$40% isolated) and only a trace of 2-propoxythiophene was detected.

All the workups and purifications described here were carried out in the air and noticeable color changes of many of these aminothiophenes were observed. Even refrigeration will not prevent the degradation of neat samples of these aminothiophenes, particularly the mono-alkylated aminothiophenes, and so immediate subsequent follow-up reaction or use is suggested.

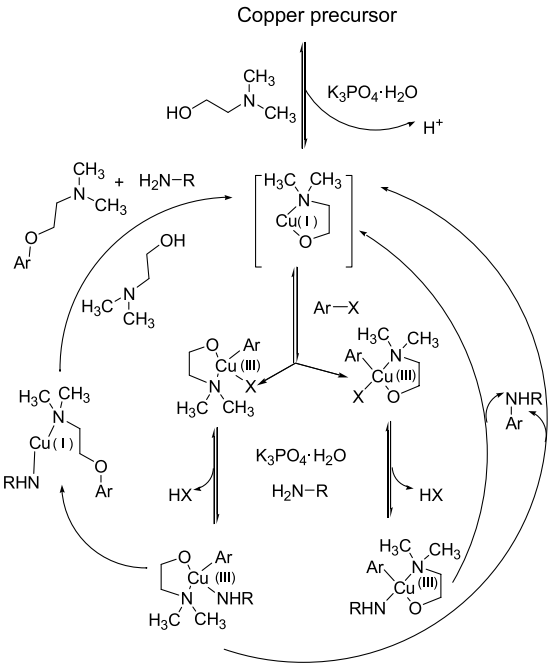


Figure 1. Proposed mechanism for copper-catalyzed amination in deanol.

The proposed mechanism is shown in Figure 1 and uses aromatic halides and a primary amine as an example. The reaction proceeds via a pathway involving copper (III) intermediate(s) similar to the recently developed copper catalyzed coupling reactions of pentavalent bismuth, trimethylsiloxanes, aryboronic acids and arylstannanes.[44–47] In the past, copper (III) intermediates were sometimes described as elusive high-energy species that were unlikely intermediates even though Cu(III) intermediate has often been proposed for copper mediated coupling reactions.[48,49] However, recently more and more copper (III) compounds have been prepared and characterized with X-ray crystallography and spectroscopic methods.[50,51] Reductive elimination of a copper (III) peralkyl intermediate has been proposed for the 1,4-addition in organocuprate reactions.[52] In some cases, oxygen was used to convert a copper (II) intermediate to a copper (III) intermediate to facilitate reductive elimination.[45] The catalytic cycle starts with a Cu(I) deanol complex. The mechanism includes mainly three steps: (a) oxidative addition of ArX occurs first to generate two aromatic and deanol coordinated Cu(III) species; (b) ligand exchange between X and amine; and (c) reductive elimination which lead to the final amination product. Reductive elimination of coordinated deanol and aryl group leads to aryl deanol byproduct.

In conclusion, we have demonstrated that copper-catalyzed amination in *N*,*N*-dimethylethanolamine is a mild and practical method to prepare amine derivatives from a variety of 2 and 3-halothiophenes, 2,5-dihalothiophenes and halobithiophenes. To our knowledge, this is the first report of copper catalyzed reaction of unactivated halothiophenes with aliphatic amines under such mild conditions. Primary, secondary acyclic, and cyclic amines, and acyclic secondary amines with hydroxyethyl functionality, provided moderate to excellent yields of the corresponding aminated thiophenes. The application of this new copper mediated amination in deanol, in combination with other existing methods, provides a means from wide range of aromatic halide to aromatic amine transformation.

3. Experimental

3.1. General methods

Unless otherwise noted, all chemicals were used as received from commercial suppliers. Copper metal (~45 μm powder) and CuI were purchased from ACROS. 5-Bromo-2,2′-bithiophene and 5,5′-dibromo-2,2′-bithiophene were prepared according to literature procedures.[53] ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm) downfield from internal standard Me_4Si (TMS) for ^{1}H and ^{13}C coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and br, broad. The infrared spectra were recorded neat on Bruker Vector 33 and are reported in wave numbers (cm^{-1}). Melting points were measured on Olympus BH-2 polarized light microscope equipped with a Mettler FP5 temperature controller and FP52 hot stage. Low-resolution mass spectra were obtained on a Thermo Finnigan Polaris Q Ion Trap GC(Trace GC ultra)/MS with Electron Ionization or Chemical Ionization. High-resolution mass spectra were obtained for selected compounds on a Micromass Q-TOF II Mass Spectrometer at the Mass Spectrometry and Proteomics Facility, Ohio State University. Candidate samples for HRMS were chosen on the basis of stability and as representative of the type of amines prepared. The purity of all the isolated compounds was higher than 95% which was examined by TLC, GC and ^{1}H NMR. Copies of ^{1}H and ^{13}C NMR of all new compounds and some of the known compounds are available in supporting materials.

In most cases, aminothiophenes are sensitive to air, light and acid but they are sufficiently stable for manipulation neat or in solution. However, immediate use rather than protracted storage (even at low temperature) is advised. For example, severe decomposition was observed for 3-(*N*-benzylamino)thiophene (Table 3, entry 2) and 3-*N*-(heptylamino)thiophene (Table 3, entry 1) after two months of storage in the freezer (−16 °C). Chromatography columns employed for purification of sensitive compounds by gravity or flash methods were prepared from a slurry of silica gel in hexane/triethylamine (97:3).

3.1.1. 2-Pyrrolidinothiophene.[54] (Table 1, entry 1) 2-Iodothiophene (2.1 g, 10 mmol), pyrrolidine (1.1 g, 15 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 60 °C for 11 h under nitrogen positive pressure. After the reaction cooled to room temperature, 10 ml of water was added and the mixture was extracted with diethyl ether (3× 100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed by rotary evaporation and the residue was purified

by Kugelrohr distillation (75 °C, 0.05 mmHg). The product was obtained as a yellow liquid that turns blue on exposure to air and is unstable on silica gel. (1.40 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, J=5.4, 3.9 Hz, 1H), 6.42 (dd, J=5.4, 1.2 Hz, 1H), 5.79 (dd, J=5.4, 1.2 Hz, 1H), 3.32–3.28 (m, 4H), 2.07–2.02 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.97, 126.94, 108.35, 100.08, 51.25, 25.90. GC–MS (CI) 154.1 (M+H, 47), 52.9 (100), 153.1 (62), 152.1 (56), 55 (37), 91 (34), 120.1 (30).

3.1.2. *N*-Butylthiophen-2-amine (Table 1, entry 2). 2-Iodothiophene (2.1 g, 10 mmol), *n*-butylamine (1.1 g, 15 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 60 °C for 11 h under nitrogen positive pressure. After the reaction cooled to room temperature, 10 ml of water was added and the black mixture was quickly extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$ for 3 min. Solvent was removed in vacuo, and the residue was purified by Kugelrohr distillation (75 °C, 0.05 mmHg). The product was obtained as a light yellow liquid, but quickly turned red on exposure to air (0.96 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, J=3.57, 5.50 Hz, 1H), 6.46 (dd, J=1.38, 5.50 Hz, 1H), 6.02 (dd, J=1.38, 3.57 Hz, 1H), 3.78 (s, br, 1H), 3.13 (t, J=7.0 Hz, 2H), 1.67–1.60 (m, 2H), 1.47–1.42 (m, 2H), 0.97 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.70, 126.39, 110.19, 103.80, 48.14, 31.85, 20.39, 14.04. GC–MS (CI) 156.1 (M+H, 100), 112.1 (65), 155.1 (58), 100.1 (54), 67.1 (15), 157.1 (13).

3.1.3. 2-Piperidinothiophene.[15] (Table 1, entry 3) *From 2-iodothiophene (10 mmol).* 2-Iodothiophene (2.1 g, 10 mmol), piperidine (1.3 g, 15 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 70 °C for 10 h under nitrogen positive pressure. After the reaction cooled to room temperature, 10 ml of water was added and the mixture was extracted with diethyl ether (100 ml, 3×). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane and then hexane/EtOAc (10:1). The product was obtained as a liquid (1.45 g, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, J=3.85, 5.50 Hz, 1H), 6.58 (dd, J=1.38, 5.50 Hz, 1H), 6.11 (dd, J=1.38, 3.85 Hz, 1H), 3.13 (t, J=5.6 Hz, 4H), 1.77–1.69 (m, 4H), 1.61–1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.51, 126.24, 111.86, 105.02, 53.10, 25.59, 23.99. GC–MS (CI) 167.1 (M+H, 87), 168.1 (100), 166.1 (46), 134.1 (24), 169.1 (13), 84.1 (11).

3.1.4. 2-(Morpholino)thiophene.[15] (Table 1, entry 4) *From 2-iodothiophene (10 mmol).* 2-Iodothiophene (2.1 g, 10 mmol), morpholine (1.75 g, 20 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 75 °C for 24 h under nitrogen positive pressure. After the reaction cooled to room temperature, 10 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane and then hexane/EtOAc (4:1). The product was obtained as a liquid, 1.04 g, 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J=5.5, 3.9 Hz, 1H), 6.64 (dd, J=5.5, 1.4 Hz, 1H), 6.16 (dd, J=3.9, 1.4 Hz, 1H), 3.86–3.83 (m, 4H), 3.14–3.11 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 126.24, 112.87, 105.76, 66.56, 52.08. GC–MS (CI) 170.01 (M+H, 100), 169.1 (67), 171.7 (15), 168.1 (13).

3.1.5. 2-Pyrrolidinothiophene.[54] (Table 2, entry 1) *From 2-bromothiophene (160 mmol).* 2-Bromothiophene (26.2 g, 160 mmol), pyrrolidine (17.2 g, 240 mmol), Cu metal (~45 μm powder, 1.0 g, 16 mmol), $K_3PO_4\cdot H_2O$ (73 g, 320 mmol) and deanol (160 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 50 h under nitrogen positive pressure. After the reaction cooled to room temperature, 100 ml of water was added and the mixture was extracted with diethyl ether (3×300 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed by rotary evaporation and the residue was purified by distillation under vacuum (67–69 °C, 0.05 mmHg). The product was obtained as a colorless liquid, 20.1 g, 81% yield.

3.1.6. 2-Piperidinothiophene.[15] (Table 2, entry 2) *From 2-bromothiophene (20 mmol).* 2-Bromothiophene (3.3 g, 20 mmol), piperidine (2.6 g, 30 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (9.2 g, 40 mmol) and deanol (20 ml) were added to a flask with a magnetic stirbar, fitted with a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 48 h under nitrogen positive pressure. After the reaction cooled to room temperature 20 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane and then hexane/EtOAc (10:1). The product was obtained as a liquid (2.43 g, 73% yield).

A larger scale reaction with 100 mmol of 2-bromothiophene was also run. After 50 h the reaction was worked up by extraction with diethylether and this ether solution was dried over anhydrous $MgSO_4$. Solvent was removed and the product was further purified by vacuum fractional distillation with a Vigreux column. Bp 71–73 °C, 0.15 mmHg. 12.7 g, 76% yield.

3.1.7. 2-(Morpholino)thiophene.[15] (Table 2, entry 3) *From 2-bromothiophene (10 mmol).* 2-Bromothiophene (3.3 g, 20 mmol), morpholine (3.5 g, 40 mmol), Cu metal (~45 μm powder) (64 mg, 1 mmol), CuI (190 mg,

1 mmol), $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) and deanol (20 ml) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 72 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3× 100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane and then hexane/EtOAc (4:1). The product was obtained as a liquid (2.18 g, 65% yield).

3.1.8. (*S*)-2-(2-Hydroxymethylpyrrolidino)thiophene (Table 2, entry 4). 2-Bromothiophene (2.45 g, 15 mmol), (*S*)-(+)-pyrrolidinemethanol (1.01 g, 10 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) and deanol (10 ml) were added to a flask with a magnetic stirbar, fitted with a condenser and sealed with a septum. The flask was cooled to −78 °C, air was evacuated and nitrogen was backfilled. The reaction mixture was stirred at 80 °C for 48 h under nitrogen positive pressure. After the reaction cooled to room temperature 20 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel pretreated with 4% of triethylamine. The product was eluted with hexane/EtOAc (4:1) and was obtained as an oil (1.3 g, 71% % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J=3.8, 5.5 Hz, 1H), 6.45 (dd, J=1.38, 5.50 Hz, 1H), 5.94 (dd, J=1.38, 3.85 Hz, 1H), 3.79–3.72 (m, 1H), 3.65–3.58 (m, 2H), 3.53–3.47 (m, 1H), 3.20–3.11 (m, 1H), 2.21 (t, br. J=5.6 Hz, 1H), 2.08–1.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.30, 126.74, 109.50, 102.08, 64.93, 63.80, 53.75, 29.20, 24.86. MS (EI) 183.1 (M^+, 32), 152.1 (100), 110.2 (33), 153.1 (18). HRMS (EI) calcd for $C_9H_{14}NOS$: 184.0796 ($M+H^+$), found: 184.0795. IR (neat, cm^{-1}) 3356, 3107, 3067, 2948, 2874, 2833, 1531, 1468, 1367, 1351, 1311, 1280, 1250, 1230, 1180, 1148, 1078, 1033, 1002, 982, 836, 754, 651.

3.1.9. 2-(4-Hydroxypiperidino)thiophene (Table 2, entry 5). 2-Bromothiophene (1.65 g, 10 mmol), 4-hydroxypiperidine (1.35 g, 13 mmol) Cu (32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), and deanol (10 ml) were added to a flask with a magnetic stirbar, fitted with a condenser and sealed with a septum. The flask was cooled to −78 °C, air was evacuated and nitrogen was introduced. The reaction mixture was stirred at 80 °C for 72 h under nitrogen positive pressure. After the reaction cooled to room temperature 20 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel pretreated with 3% of triethylamine and eluted with hexane/EtOAc (3:1). The product was obtained as an oil (1.18 g, 64.5% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J=3.85, 5.50 Hz, 1H), 6.59 (dd, J=1.38, 5.50 Hz, 1H), 6.12 (dd, J=1.38, 3.85 Hz, 1H), 3.88–3.79 (m, 1H), 3.49–3.42 (m, 2H), 2.98–2.90 (m, 2H), 2.04–1.95 (m, 2H), 1.78–1.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.38, 126.35, 112.50, 105.98, 67.40, 49.94, 33.82. GC–MS (EI) 183.1 (M^+, 100), 164.0 (43), 110.0 (37), 182.1 (19), 138.1 (19), 111.0 (15), 184.2 (14), 112.1 (14), 165.1 (10). IR (neat, cm^{-1}) 3344, 3106, 3069, 2943, 2819, 1528, 1450, 1380, 1336, 1258, 1222, 1197, 1142, 1112, 1069, 1055, 1011, 978, 878, 838, 774, 662.

3.1.10. *n*-Butyl-*N*-2-thienylacetamide (Table 2, entry 6). 2-Bromothiophene (3.3 g, 20 mmol), *n*-butylamine (3.0 g, 40 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) and deanol (20 ml) were added to a flask with a magnetic stirbar, fitted with a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 75 °C under nitrogen positive pressure until almost all the 2-bromothiophene was consumed (usually about 24 h). After the reaction cooled to room temperature, 20 ml of water was added and the black mixture was quickly extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed by rotary evaporation and the residue was Kugelrohr distilled (75 °C, 0.05 mmHg). The distillate was quickly added to a premixed mixture of pyridine (31 mmol) and acetic anhydride (30 mmol) and stirred at room temperature for 3 h. EtOAc (200 ml) was added and washed with water (40 ml, 3×). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed. The residue was further purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate (3:1). The product was obtained as liquid (0.90 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J=1.38, 5.50 Hz, 1H), 6.91 (dd, J=3.57, 5.50 Hz, 1H), 6.77 (dd, J=1.38, 3.57 Hz, 1H), 3.63 (t, J=7.56 Hz, 2H), 1.94 (s, 3H), 1.57–1.47 (m, 2H), 1.36–1.23 (m, 2H), 0.88 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.33, 146.01, 125.90, 125.36, 124.68, 49.86, 29.97, 22.57, 20.02, 13.92. GC–MS (CI) 198.1 (M+H, 100), 156.1 (96), 197.0 (15), 100.1 (14), 155.1 (12), 157.1 (12), 112.1 (12), 199.1 (10), 196.1 (9). HRMS (EI) calcd for $C_{10}H_{15}NOSNa$: 220.0772 (M+Na), found: 220.0768.

3.1.11. 2-*N*,*N*-Diethylaminothiophene.[15] (Table 2, entry 7) 2-Bromothiophene (1.63 g, 10 mmol), diethyamine (2.95 g, 40 mmol), Cu (190 mg, 3 mmol), CuI (100 mg, 0.5 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 80 °C under nitrogen positive pressure for 48 h. After the reaction cooled to room temperature, 150 ml of water was added and the mixture was extracted with diethyl ether (3× 150 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuum, and the residue was added to a short silica gel (pretreated with triethylamine) column and eluted with hexane. A crude product containing about 6% of 2-bromothiophene was obtained by removing the solvent. The crude product was further purified by column chromatography on neutral alumina and the product was obtained as a liquid, 0.60 g, 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J=3.8, 5.5 Hz, 1H), 6.46 (dd, J=1.4, 5.5 Hz, 1H), 5.91 (dd, J=1.4, 3.8 Hz,

1H), 3.28 (q, J=7.1 Hz, 4H), 1.18 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.58, 126.65, 109.48, 102.70, 47.53, 12.33. GC–MS (EI) 155.1 (M^+, 57), 140.0 (100), 112.0 (85), 85.0 (34), 98.0 (29), 54.0 (27), 110.1 (21), 78.0 (19), 97.0 (17). IR (neat, cm^{-1}) 3108, 3070, 2971, 2932, 2870, 1534, 1483, 1462, 1444, 1375, 1359, 1302, 1243, 1198, 1180, 1127, 1077, 1053, 834, 785, 753, 650, 564.

3.1.12. 2-*N*,*N*-Dipropylaminothiophene (Table 2, entry 8). 2-Bromothiophene (1.63 g, 10 mmol), dipropylamine (4.0 g, 40 mmol), Cu (190 mg, 3 mmol), CuI (100 mg, 0.5 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 80 °C under nitrogen positive pressure for 48 h. After the reaction cooled to room temperature, 100 ml of water was added and the mixture was extracted with diethyl ether (3× 150 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuum, and the residue was added to a short silica gel (pretreated with triethylamine) column and eluted with hexane. A crude product containing about 8% of 2-bromothiophene was obtained by removing the solvent. The crude product was further purified by column chromatography on neutral alumina and the product was obtained as a liquid, 0.65 g, 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (dd, J=3.8, 5.5 Hz, 1H), 6.41 (dd, J=1.4, 5.5 Hz, 1H), 5.85 (dd, J=1.4, 3.8 Hz, 1H), 3.20–3.15 (m, 4H), 1.71–1.58 (m, 4H), 0.94 (t, J= 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.26, 126.67, 108.67, 101.66, 56.06, 20.47, 11.67. GC–MS (EI) 183.1 (M^+, 85), 126.2 (100), 154.1 (87), 112.2 (57), 184.1 (32), 85.3 (16), 78.2 (15), 127.1 (10). HRMS (EI) calcd for $C_{10}H_{18}NS$: 184.1160 ($M+H^+$), found: 184.1163. IR (neat, cm^{-1}) 3109, 3070, 2960, 2933, 2872, 1535, 1482, 1466, 1452, 1379, 1368, 1346, 1304, 1271, 1221, 1179, 1133, 1102, 1077, 1053, 960, 946, 882, 837, 749, 688, 649, 580, 571, 562.

3.1.13. 2-[Ethyl(2-thienyl)amino]ethanol (deanol was used as a solvent) (Table 2, entry 9). 2-Bromothiophene (3.3 g, 20 mmol), 2-(ethylamino)ethanol (3.6 g, 40 mmol), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) and deanol (20 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 72 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluted with hexane/EtOAc (4:1). The product was obtained as a liquid, 1.06 g, 31% yield.

3.1.14. 2-(*N*-Methyl-*N*−2-hydroxyethylamino)thiophene (Table 2, entry 10). 2-Bromothiophene (3.3 g, 20 mmol), 2-(methylamino)ethanol 15 ml (also solvent), Cu metal (−45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), and $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 24 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×150 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane/EtOAc (1:1). The product was obtained as a liquid that easily changed to blue color, 2.54 g, 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J=5.5, 3.8 Hz, 1H), 6.50 (dd, J=5.5, 1.4 Hz, 1H), 5.98 (dd, J=3.8, 1.4 Hz, 1H), 3.78 (t, J=5.6 Hz, 2H), 3.35 (t, J= 5.6 Hz, 2H), 2.95 (s, 3H), 2.42 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 126.75, 110.74, 103.65, 59.85, 58.75, 41.64. MS (EI) 157.0 (25), 126.0 (100), 85.0 (14), 110 (11), 898.1 (9). IR (neat, cm^{-1}) 3355, 3109, 3068, 2944, 2875, 2805, 1536, 1483, 1437, 1418, 1356, 1265, 1112, 1073, 1045, 836, 756, 655.

3.1.15. 2-[Ethyl(2-thienyl)amino]ethanol (Table 2, entry 9 and 11). 2-Bromothiophene (3.3 g, 20 mmol), 2-(ethylamino) ethanol 20 ml (also solvent), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), and $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 24 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×150 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel eluted with hexane/EtOAc (1:1). The product was obtained as a liquid, very easily changed to blue color, 2.77 g, 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (dd, J=5.5, 3.6 Hz, 1H), 6.52 (dd, J=5.5, 1.4 Hz, 1H), 6.02 (dd, J=3.6, 1.4 Hz, 1H), 3.74 (t, J=5.6 Hz, 2H), 3.34–3.28 (m, 4H), 1.16 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.40, 126.56, 111.24, 105.18, 59.83, 55.98, 49.82, 12.01. GC–MS (EI) 171.1 (24), 140.0 (100), 112.1 (52), 98 (16), 85 (21), 78 (16). IR (neat, cm^{-1}) 3362, 3108, 3068, 2969, 2931, 2871, 1532, 1482, 1460, 1443, 1373, 1361, 1298, 1244, 1073, 1047, 835, 755, 652.

3.1.16. 2-[Phenyl(2-thienyl)amino]ethanol (Table 2, entry 12). 2-Bromothiophene (3.3 g, 20 mmol), 2-anilinoethanol as solvent 20 ml (also solvent), Cu metal (~45 μm powder, 64 mg, 1 mmol), CuI (190 mg, 1 mmol), and $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 85 °C for 48 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with water and brine. Diethylether was removed in vacuo, and the anilinoethanol was removed by Kugelrohr distillation. The residue was purified by column chromatography on silica gel eluted with hexane and ethyl acetate (9:1 to 3:1). The product was obtained as a liquid, 0.65 g, 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H), 7.03–6.89 (m, 5H), 6.72–6.70 (dd, J=3.0, 1.2 Hz, 1H), 3.86 (s, 4H), 2.19 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.15, 149.11, 129.32, 126.13, 120.84, 120.69, 120.48, 117.04, 60.05, 56.30. GC–MS (EI)

219.0 (M+, 65), 188.1 (100), 91.1 (97), 77.0 (37), 175.0 (21), 189.1 (14), 104.1 (13), 220.1 (11), 65.1 (11), 173.1 (10). IR (neat, cm^{-1}) 3364, 3066, 3037, 2929, 2880, 1596, 1537, 1496, 1460, 1436, 1365, 1339, 1281, 1241, 1208, 1178, 1089, 1034, 843, 748, 690.

3.1.17. 2-Piperidino-5-methylthiophene (Table 2, entry 13). 2-Bromo-5-methylthiophene (0.95 g, 5.4 mmol), piperidine (1.0 g, 12 mmol), Cu (32 mg, 0.5 mmol), CuI (50 mg, 0.25 mmol), $K_3PO_4 \cdot H_2O$ (3.9 g, 15 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 24 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×80 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane. The product was obtained as a white solid, 0.67 g, 71% yield. Mp 31.2–32.0 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41–6.39 (m, 1H), 5.90 (d, J=3.6 Hz, 1H), 3.05 (t, J=5.5 Hz, 4H), 2.36 (d, J=0.8 Hz, 3H), 1.75–1.66 (m, 4H), 1.58–1.50 (m, 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.35, 126.72, 123.46, 105.29, 53.39, 25.64, 24.01, 15.47. GC–MS (EI) 181.1 (M+, 100), 180.1 (75), 97.0 (20), 124.1 (17), 112.1 (15), 182.1 (15), 111.1 (15), 166.1 (14). HRMS (EI) calcd for $C_{10}H_{16}NS$: 182.1003 ($M+H^+$), found: 182.1001. IR (neat, cm^{-1}) 3089, 3033, 2933, 2854, 2823, 1559, 1506, 1444, 1381, 1233, 1195, 1158, 1126, 1015, 886, 862, 840, 832, 758.

3.1.18. 5-(Piperidino)thiophene-2-carboxaldehyde (Table 2, entry 14). 5-Bromo-2-thiophenecarboxaldehyde (0.96 g, 5 mmol), piperidine (1.7 g, 20 mmol), Cu (32 mg, 0.5 mmol), CuI (50 mg, 0.25 mmol), and $K_3PO_4 \cdot H_2O$ (2.3 g, 10 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 65 °C under nitrogen positive pressure until the 5-bromo-2-thiophenecarboxaldehyde was consumed (up to 48 h). After the reaction cooled to room temperature, 100 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (3:1). The product was obtained as orange crystals, 0.75 g, 77% yield. Mp 92.8–93.5 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.47 (d, J=4.4 Hz, 1H), 6.06 (d, J=4.4 Hz, 1H), 3.34 (t, J=5.5 Hz, 4H), 1.72–1.63 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.53, 168.63, 140.45, 126.75, 104.06, 51.07, 25.08, 23.68. GC–MS (EI) 195.1 (M+, 100), 194.1 (85), 138.0 (22), 196.1 (16), 166.2 (12), 154.1 (10), 111.1 (15), 180.1 (10). IR (neat, cm^{-1}) 3050, 3032, 2937, 2855, 2728, 1619, 1536, 1474, 1442, 1380, 1264, 1129, 1121, 1063, 1039, 1011, 890, 857, 763, 752, 742.

3.1.19. 2,5-Dipiperidinothiophene (compound 4). 2,5-Dibromothiophene (2.90 g, 12 mmol), piperidine (6.0 g, 70 mmol), Cu (100 mg, 1.56 mmol), CuI (100 mg, 0.50 mmol), and $K_3PO_4 \cdot H_2O$ (11.0 g, 48 mmol) and deanol (16 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 75–80 °C under nitrogen positive pressure until the 2,5-dibromothiophene was consumed (usually 48 h, additional 50 mg Cu metal may be added if the conversion is not completed). After the reaction cooled to room temperature, 50 ml of water was added and the mixture was extracted with diethyl ether (3×120 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel pretreated with 3% triethylamine in hexane. The column was first eluted with hexane and then hexane/ethyl acetate (97:3). 2-Piperidinothiophene was eluented first (0.53 g, 26%). The 2,5-dipiperidinothiophene was obtained as yellow crystals, 1.38 g, 46% yield. Mp 47.8–48.8 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 2H), 2.98 (t, J=5.6 Hz, 8H), 1.72–1.64 (m, 8H), 1.55–1.49 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.52, 105.90, 54.27, 25.83, 24.02. GC–MS (EI) 250.1 (M^+, 100), 180.3 (64), 207.2 (53), 208.2 (47), 181.2 (35), 84.2 (25), 251.2 (16), 194.3 (11). Anal. Calcd $C_{14}H_{22}N_2S_2$: C, 67.15; H, 8.86; N, 11.19; S, 12.81. Found: C, 66.87; H, 9.02; N, 11.27; S, 12.63. HRMS (EI) calcd for $C_{14}H_{22}N_2SNa$: 273.1401 (M+Na), found: 273.1400. IR (neat, cm^{-1}) 2927, 2850, 2818, 1556, 1528, 1463, 1446, 1381, 1324, 1230, 1189, 1126, 1120, 1019, 891, 858, 740, 717, 606.

3.1.20. 5-Piperidino-2,2′-bithiophene (compound 7).[10] 5-Bromo-2,2′-bithiophene (1.25 g, 5 mmol), piperidine (0.65 g, 8 mmol), Cu (32 mg, 0.5 mmol), CuI (50 mg, 0.25 mmol), and $K_3PO_4 \cdot H_2O$ (2.3 g, 10 mmol) and deanol (7 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 80 °C under nitrogen positive pressure until the 5-bromo-2,2′-bithiophene was consumed (36 h). After the reaction cooled to room temperature, 50 ml of water was added and the mixture was extracted with diethyl ether (3×60 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel first eluted with hexane and then hexane/ethyl acetate (97:3). The product was obtained as yellow crystals, 0.78 g, 63% yield. Mp 59.8–60.0 °C (hexane). Lit 59–60 °C.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.07 (m, 1H), 6.97–6.95 (m, 1H), 6.87 (d, J=3.9 Hz, 1H), 5.98 (d, J=3.9 Hz, 1H), 3.15 (t, J=5.6 Hz, 4H), 1.76–1.68 (m, 4H), 1.61–1.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.21, 138.80, 127.74, 123.31, 122.55, 121.51, 105.16, 52.58, 25.38, 23.88. GC–MS (EI) 249.1 (M^+, 100), 179.0 (25), 248.2 (24), 96.0 (24), 207.0 (20), 194.1 (20), 180.0 (19), 250.1 (18), 193.1 (18), 121.0 (16), 69.0 (14). HRMS (EI) calcd for $C_{13}H_{16}NS_2$: 250.0724 ($M+H^+$), found: 250.0708. IR (neat, cm^{-1}) 3104, 3068, 2939, 2853, 2830, 1510, 1485, 1459, 1444, 1380, 1256, 1242, 1219, 1192, 1127, 1067, 1012, 860, 824, 809, 758, 692, 679.

3.1.21. 5,5′-Diperidino-2,2′-bithiophene (compound 8). 5,5′-Dibromo-2,2′-bithiophene (1.62 g, 5 mmol), piperidine (1.62 g, 20 mmol), Cu (32 mg, 0.5 mmol), CuI (50 mg, 0.25 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (8 ml) were added to a flask fitted with a magnetic stirbar, a

condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 80 °C under nitrogen positive pressure until all the 5,5′-dibromo-2,2′-bithiophene (48 h) was consumed. After the reaction cooled to room temperature, 50 ml of water was added and the mixture was extracted with diethyl ether (3× 150 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel first eluted with hexane and then hexane/ethyl acetate (50:1 to 10:1). 5-Piperidino-2,2′-bithiophene was isolated as a major product. It was obtained as yellow crystals, 0.68 g, 54.5% yield. The targeted 5,5′-dipiperidino-2,2′-bithiophene was also isolated as orange crystals. Mp 189.6–190.0 °C (ethyl acetate). 0.24 g, 14.5% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, br, 2H), 5.95 (s, br, 2H), 3.11 (s, br, 8H), 1.74–1.67 (m, 8H), 1.59–1.53 (m, 4H). (Note: The ^{1}H NMR resonances of the aromatic protons and the protons on the carbons connected to nitrogen of the piperidine ring were either very broad or sometimes disappeared entirely. The $CDCl_3$ solution turns red and eventually purple. The ^{13}C NMR spectrum was normal). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.06, 124.90, 120.91, 105.24, 52.76, 25.47, 23.93. MS (ASCI) 333.2 (M+1). Anal. Calcd $C_{18}H_{24}N_2S_2$: C, 65.02; H, 7.27; N, 8.42; S, 19.29. Found: C, 64.66; H, 7.40; N, 8.47; S, 19.33. HRMS (EI) calcd for $C_{18}H_{24}N_2S_2Na$: 355.1279 (M+Na), found: 355.1284. IR (neat, cm^{-1}) 3084, 3023, 2933, 2853, 2819, 1527, 1477, 1459, 1442, 1377, 1297, 1232, 1188, 1120, 1065, 1041, 1013, 892, 858, 822, 753.

3.1.22. 3-*N*-(Butylamino)thiophene (Table 3, entry 1). 2-Bromothiophene (3.3 g, 20 mmol), *n*-butylamine (2.2 g, 30 mmol), Cu (64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (9.2 g, 40 mmol) and deanol (30 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 80 °C for 36 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/triethylamine (98:2). The product was obtained as a yellow liquid (2.54 g, 84.5% yield) that turns red quickly on exposure to air. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, J=5.2, 3.0 Hz, 1H), 6.62 (dd, J=5.2, 1.7 Hz, 1H), 5.95 (dd, J=3.0, 1.7 Hz, 1H), 3.56 (s, br, 1H), 3.08 (t, J=7.0 Hz, 2H), 1.67–1.57 (m, 2H), 1.50–1.38 (m, 2H), 0.97 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.07, 125.18, 120.07, 95.39, 46.24, 31.90, 20.50, 14.08. MS (EI) (%) 155.1 (M^+, 26), 112.0 (100), 85.0 (27), 50.8 (14), 113.1 (11). IR (neat) 3390, 3101, 2957, 2928, 2861, 1560, 1478, 1425, 1366, 1229, 1191, 1077, 868, 834, 743, 623.

3.1.23. 3-(*N*-Benzylamino)thiophene (Table 3, entry 2). 2-Bromothiophene (3.3 g, 20 mmol), benzylamine (3.2 g, 30 mmol), Cu (64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4\cdot H_2O$ (9.2 g, 40 mmol) and deanol (30 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and filled with nitrogen. The reaction mixture was stirred at 80 °C for 40 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/triethylamine/EtOAc (94:2:4). The product was obtained as a red-brown liquid (3.16 g, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.37 (m, 5H), 7.20 (dd, J=5.2, 3.0 Hz, 1H), 6.68 (dd, J=5.2, 1.7 Hz, 1H), 6.02 (dd, J=3.0, 1.7 Hz, 1H), 4.31 (s, 2H), 4.03 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.70, 139.50, 128.82, 127.94, 127.53, 125.41, 120.14, 96.26, 50.83. MS (EI) (%) 189.1 (M^+, 57), 91 (100), 188.1 (25), 65.0 (25), 50.7 (17). IR (neat, cm^{-1}) 3384, 3101, 3061, 3028, 2923, 2836, 1558, 1493, 1452, 1424, 1232, 1186, 1076, 1028, 864, 840, 800, 745, 697.

3.1.24. 3-*N*-(Heptylamino)thiophene (Table 3, entry 3). 2-Bromothiophene (1.65 g, 10 mmol), *n*-heptylamine (1.73 g, 15 mmol), Cu (32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), $K_3PO_4\cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 80 °C for 45 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/triethylamine (98:2). The product was obtained as a yellow liquid (1.6 g, 83% yield) that turns red quickly on exposure to air. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, J=5.2, 3.0 Hz, 1H), 6.62 (dd, J=5.2, 1.7 Hz, 1H), 5.96 (dd, J=3.0, 1.7 Hz, 1H), 3.59 (s, br, 1H), 3.08 (t, J=7.0 Hz, 2H), 1.66–1.59 (m, 2H), 1.44–1.29 (m, 8H), 0.92 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.07, 125.18, 120.11, 95.36, 46.58, 32.03, 29.81, 29.36, 27.40, 22.82, 14.30. MS (EI) (%) 197.1 (M^+, 27), 112.0 (100), 85.0 (23), 133.0 (13), 154.1 (8).

3.1.25. 3-(Pyrrolidino)thiophene (Table 3, entry 4).[15] 3-Bromothiophene (1.65 g, 10 mmol), pyrrolidine (1.1 g, 150 mmol), Cu (32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), $K_3PO_4\cdot H_2O$ (4.6 g, 20 mmol) and deanol (15 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 80 °C for 48 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/ethylacetate (99:1). The product was obtained as a yellow liquid (1.3 g, 85% yield) that turns red on exposure to air. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J=5.2, 3.0 Hz, 1H), 6.72 (dd, J=3.0, 1.7 Hz, 1H), 5.81 (dd, J=5.2, 1.7 Hz, 1H), 3.28–3.24 (m, 4H), 2.01–1.97 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.99, 125.20, 118.66, 93.88, 49.99, 25.47. MS (EI) 153.1 (M^+, 63), 152.1 (100), 97.0 (31), 110.1 (27), 154.0 (11). IR (neat, cm^{-1}) 3106, 2967, 2884, 2823, 1552, 1487, 1460, 1426, 1398, 1356, 1286, 1217, 1171, 1150, 1085, 997, 846, 737, 616.

3.1.26. 3-(Piperidino)thiophene (Table 3, entry 5).[55] 2-Bromothiophene (3.3 g, 20 mmol), piperidine (2.6 g, 30 mmol), Cu (64 mg, 1 mmol), CuI (190 mg, 1 mmol), $K_3PO_4 \cdot H_2O$ (9.2 g, 40 mmol) and deanol (30 ml) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 80 °C for 40 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/triethylamine/EtOAc (92:2:6). The product was obtained as a yellow liquid (2.38 g, 73.3% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J=5.2, 3.0 Hz, 1H), 6.89 (dd, J=5.2, 1.7 Hz, 1H), 6.18 (dd, J=3.0, 1.7 Hz, 1H), 3.07 (t, J=7.0 Hz, 4H), 1.76–1.68 (m, 4H), 1.60–1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.53, 125.13, 120.70, 100.14, 51.93, 25.82, 24.27. MS (EI) (%) 167.1 (M^+, 65), 166.1 (100), 110.0 (36), 138.1 (18), 152.1 (14), 111.1 (13), 168.1 (12). IR (neat) 3112, 2933, 2853, 2802, 1538, 1450, 1421, 1385, 1255, 1216, 1190, 1132, 1088, 959, 882, 866, 837, 799, 749, 677.

3.1.27. 3-(Morpholino)thiophene (Table 3, entry 6).[20] 3-Bromothiophene (1.65 g, 10 mmol), morpholine (1.5 g, 30 mmol), Cu (32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (15 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed from the reaction system and replaced with nitrogen. The reaction mixture was stirred at 80 °C for 40 h under nitrogen positive pressure. After the reaction cooled to room temperature, 60 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluted with hexane/triethylamine/EtOAc (92:2:6). The product was obtained as a yellow liquid (0.4 g, 23% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J=5.2, 3.0 Hz, 1H), 6.86 (dd, J=5.2, 1.7 Hz, 1H), 6.20 (dd, J=3.0, 1.7 Hz, 1H), 3.84 (t, J=5.0 Hz, 4H), 3.09 (t, J=5.0 Hz 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.59, 125.74, 119.77, 100.58, 66.82, 50.90. MS (EI) (%) 169.1 (M^+, 90), 100.0 (100), 111.0 (94), 154.0 (63), 84 (20), 112.1 (17), 170.1 (10). HRMS (EI) calcd for $C_8H_{12}NOS$: 170.0639 ($M+H^+$), found: 170.0639. IR (neat, cm^{-1}) 3112, 2933, 2853, 2802, 1538, 1450, 1421, 1385, 1255, 1216, 1190, 1132, 1088, 959, 882, 866, 837, 799, 749, 677.

3.1.28. 3-Diethylaminothiophene (Table 3, entry 7).[13] 3-Bromothiophene (1.63 g, 10 mmol), diethylamine (2.95 g, 40 mmol), Cu (190 mg, 3 mmol), CuI (100 mg, 0.5 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 85 °C under nitrogen positive pressure for 60 h. After the reaction cooled to room temperature, 150 ml of water was added and the mixture was extracted with diethyl ether (3× 150 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuum, and the residue was purified by silica gel column and eluted with hexane and hexane: ethyl acetate (50:1). The product was obtained as a liquid, 0.24 g, 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ. ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.20 (dd, J=3.0, 5.2 Hz, 1H), 6.77 (dd, J=1.7, 5.2 Hz, 1H), 5.90 (dd, J=1.7, 3.0 Hz, 1H), 3.25 (q, J=7.0 Hz, 4H), 1.13 (t, J=1.13 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.12, 124.00, 119.33, 95.95, 45.73, 12.48. GC–MS (EI) 155.1 (M+, 50), 140.1 (100), 112.0 (68), 85.0 (25), 110.0 (25), 97.1 (9). IR (neat, cm^{-1}). 3112, 2969, 2930, 2897, 2870, 1547, 1460, 1447, 1427, 1375, 1362, 1347, 1290, 1255, 1228, 1177, 1137, 1115, 1090, 1076, 1017, 950, 849, 781, 738, 640.

3.1.29. 3-[*N*-Methyl-(*N*-2-hydroxy)amino]thiophene (Table 3, entry 8). 3-Bromothiophene (1.65 g, 10 mmol), 2-(methylamino)ethanol 15 ml (also solvent), Cu metal (−45 μm powder, 32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 24 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×150 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane/EtOAc (1:1). The product was obtained as a liquid, 1.40 g, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, J=5.2, 3.0 Hz, 1H), 6.81 (dd, J=5.2, 1.7 Hz, 1H), 6.02 (dd, J=3.0, 1.7 Hz, 1H), 3.74 (t, J=5.5 Hz, 2H), 3.31 (t, J=5.5 Hz, 2H), 2.87 (s, 3H), 2.36 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.26, 125.54, 119.62, 97.67, 59.97, 57.24, 40.06. MS (EI) 157.0 (22), 126.1 (100), 97.2 (14), 93.2 (13), 93.1 (12), 110.1 (12), 65.2 (11). IR (neat, cm^{-1}) 3355, 3110, 2946, 2873, 2797, 1548, 1448, 1431, 1413, 1393, 1261, 1169, 1121, 1086, 1066, 1042, 986, 939, 864, 845, 830, 805, 742, 629.

3.1.30. 3-[*N*-Ethyl-(*N*−2-hydroxy)amino]thiophene (Table 3, entry 9). 3-Bromothiophene (1.65 g, 10 mmol), 2-(ethylamino)ethanol 15 ml (also solvent), Cu metal (−45 μm powder, 32 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol), and $K_3PO_4 \cdot H_2O$ (4.6 g, 20 mmol) were added to a flask with a magnetic stirbar, a condenser and sealed with a septum. The reaction mixture was stirred at 80 °C for 45 h under nitrogen positive pressure. After the reaction cooled to room temperature, 20 ml of water was added and the mixture was extracted with diethyl ether (3×150 ml). The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane/EtOAc (1:1). The product was obtained as a yellow liquid (0.75 g, 45% yield) that turns brown quickly on exposure to air. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J=5.2, 3.0 Hz, 1H), 6.79 (dd, J=5.2,

1.7 Hz, 1H), 5.99 (dd, $J=3.0$, 1.7 Hz, 1H), 3.73 (t, $J=5.5$ Hz, 2H), 3.33–3.27 (m, 4H), 2.33 (s, br, 1H), 1.12 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.14, 125.34, 119.71, 97.54, 60.08, 54.23, 47.55, 11.97. IR (neat, cm^{-1}) 3357, 3115, 2968, 2931, 2872, 1547, 1425, 1374, 1257, 1166, 1129, 1072, 1045, 1009, 845, 784, 739, 634. MS (EI) (%) 171.1 (M^+, 19.5), 140.0 (100), 112.0 (53), 50.8 (39.0), 85.1 (23.1) 110.0 (17.5).

3.1.31. 4-(Piperidino)thiophene-2-carboxaldehyde (Table 3, entry 10). 4-Bromo-2-thiophenecarboxaldehyde (0.96 g, 5 mmol), piperidine (1.7 g, 20 mmol), Cu metal (32 mg, 0.5 mmol), CuI (50 mg, 0.25 mmol), and $K_3PO_4 \cdot H_2O$ (2.3 g, 10 mmol) and deanol (10 ml) were added to a flask fitted with a magnetic stirbar, a condenser and sealed with a septum. Air was removed and replaced with nitrogen. The reaction mixture was stirred at 65–75 °C under nitrogen positive pressure until 4-bromo-2-thiophenecarboxaldehyde was consumed (up to 72 h). After the reaction cooled to room temperature, 100 ml of water was added and the mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were then washed with brine. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (3:1). The product was obtained as a liquid, 0.50 g, 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (d, $J=1$, 2 Hz, 1H), 7.51 (d, $J=1.9$ Hz, 1H), 6.62–6.61 (m, 1H), 3.09 (t, $J=5.5$ Hz, 4H), 1.75–1.66 (m, 4H), 1.60–1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.17, 154.03, 142.33, 127.79, 110.40, 51.41, 25.56, 23.98. GC–MS (EI) 195.1 (M+, 86), 194.1 (100), 138.1 (30), 139.0 (16), 166.1 (16), 196.1 (12). IR (neat, cm^{-1}) 3320, 3103, 2935, 2852, 2809, 1663, 1547, 1439, 1386, 1365, 1248, 1227, 1177, 1120, 1045, 1028, 976, 885, 861, 831, 803, 728, 667.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all new and some known compounds are provided.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.11.017

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