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Salima Bouarfa,[a,b] Simon Graβl,[c] Maria Ivanova,[c] Timothy Langlais,[a,c] Ghenia Bentabed-Ababsa,*[b] Frédéric Lassagne,[a] William Erb,[a] Thierry Roisnel,[a] Vincent Dorcet,[a] Paul Knochel*[c] and Florence Mongin*[a]

Abstract: Thienylzinc halides and related compounds prepared by deprotonation followed by transmetalation were used in copper-catalyzed amination using *N*-benzoyloxy secondary amines. By extending the reaction to 1,5-naphthyridine, it was showed that the competitive dimer formation observed in the case of thiophenes was linked with the low stability of some thienylamines rather than homocoupling. Interestingly, thienylzinc halides and related compounds prepared by transmetalation of thienylmagnesium halides, either prepared from their bromo-precursors or generated by deprotometalation, were satisfactorily employed in cobalt-catalyzed aminations. Finally, aminothiophenes were involved in copper-catalyzed mono- and di-*N*-arylations, affording differently substituted di- and triphenylamines.

Introduction

Electron-rich thiophenes and related compounds are an important class of five-membered aromatic heterocycles, notably for various applications in the fields of medicinal chemistry and materials.[1] Thiophene for example is found in the skeleton of important pharmaceuticals such as duloxetine and olanzapine, which respectively target major depressive disorder and schizophrenia, and dorzolamide, an anti-glaucoma agent. The thiophene scaffold is also present in many organic materials among which we can cite light-emitting diodes, field effect transistors and solar cells.[1] To access these aforementioned scaffolds, the functionalization of thiophenes is in general preferred over cyclizations of suitable substrates. As a consequence, efficient methods to regio- and chemoselectively introduce substituents onto thiophenes and related compounds are required.

From the perspective of the pharmaceutical industry, one current challenge of organic synthesis remains the introduction of amines into drug molecules, if possible through C-H bond activation, and more generally by formation of C-N bonds.[2] Heteroaromatic C(sp^2)-N bonds can be formed by transition metal-catalyzed couplings from the corresponding halides,[3] either using palladium-[4] or copper-catalysts.[5] Two complementary approaches have since been developed for the direct functionalization of heteroarenes,[6] oxidative reactions in the presence of a suitable metal catalyst-oxidant combination,[7] and transition metal-catalyzed electrophilic amination reactions.[8]

Among the methods used to introduce aliphatic amines onto thiophenes, the oxidative nucleophilic substitution of hydrogen has been described but remains limited to specific nitro compounds;[9] therefore, most of the studies follow one of the above-mentioned strategies. Zinc amidocuprates formed from thienylzincs and lithium amides were involved in copper(I)-mediated oxidative aminations.[10] Owing to a picolinamide directing group, morpholine can be introduced onto thiophene in the presence of a copper(II)-catalyst and $PhI(OAc)_2$ as oxidant.[11] The *in situ* formation of diaryl-λ3-iodanes followed by copper(I)-catalyzed reaction with morpholine can be similarly applied to thiophene in average yields.[12] Provided that a carboxamide group is present, ruthenium(II)-catalyzed C-H amination of thiophenes can be performed with *N*-(benzoyloxy)morpholine in moderate yields.[13] The use of *O*-benzoyl hydroxylamines ($BzO-NR_2$) to intercept thienylmetals under copper(I)-catalysis displays a broader substrate scope, and has been developed from arylmetals prepared by C-H lithiation-transalumination[14] and, above all, by deprotozincation.[15]

If copper was employed as catalyst in the Johnson pioneered electrophilic amination of diarylzincs by $BzO-NR_2$ in 2004,[16] cobalt can also be used to catalyze amination of arylzincs.[8b] Indeed, we recently showed that both arylzinc pivalates[17] and chlorides[18] can be involved in such an amination in the presence of cobalt salts. In the present paper, we report our studies on copper- and cobalt-catalyzed reactions involving thienylzincs and *O*-benzoyl secondary hydroxylamines. Our investigations on the copper-catalyzed mono and double *N*-arylation of thienylamines by aromatic iodides to access thiophene-based triarylamines are also presented.

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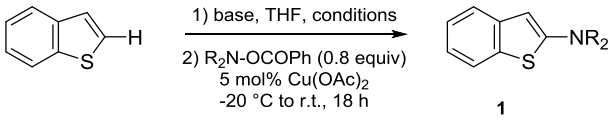
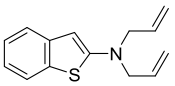
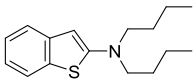
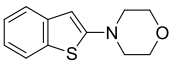
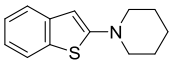
Results and Discussion

We first studied a 'deprotolithiation-transmetalation to zinc-copper catalyzed amination' sequence in THF (THF = tetrahydrofuran) by starting from benzothiophene (Table 1). In order to generate the corresponding arylzinc halide, we compared two methods, (i) butyllithium-mediated deprotolithiation followed by transmetalation using $ZnCl_2$·TMEDA[19] (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine; entry 1) and (ii) deprotolithiation using LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) in the presence of $ZnCl_2$·TMEDA as *in situ* trap (entry 2).[20] Amination was next performed by using *N*-(benzoyloxy)diallylamine and a catalytic amount of copper(II) acetate. Under these conditions, the expected product **1a** was isolated in 51-52% yield in spite of its propensity to turn into 2,2'-bi(benzothiophene) (**1'**; entries 1 and 2). These results suggest that lithium chloride and TMEDA, that are both present, do not hamper the reaction. In contrast, attempts to directly use benzothienyllithium (formed by reaction with LiTMP) instead of the corresponding zinc compound did not furnish **1a** (entry 3). The presence of the electrophile and catalyst during the addition of the base to the substrate similarly failed (entry 4). *N*-(benzoyloxy)dibutylamine, *N*-(benzoyloxy)morpholine and *N*-(benzoyloxy)piperidine were used under the best reaction conditions to afford the expected benzothienylamines **1b**-**d** (entries 5-7; Figure 1, top).

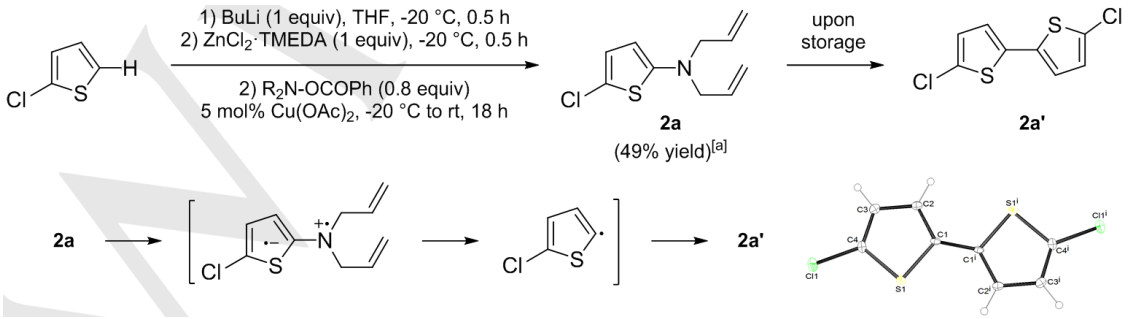
Table 1. Optimization of the conversion of benzothiophene into 2-benzothienylamines **1**.



1

Entry	Base (equiv), conditions	Product **1**, Yield [%][a]
1	1) BuLi (1), –20 °C, 0.5 h 2) $ZnCl_2$·TMEDA (1), –20 °C, 0.5 h	 **1a**, 51[b]
2	1) $ZnCl_2$·TMEDA (1) 2) LiTMP (1), –20 °C, 0.5 h	**1a**, 52[b]
3	LiTMP (1), –20 °C, 0.5 h	**1a**, 0[c]
4	LiTMP (1) added to the solution of benzothiophene, $(allyl)_2$N-OCOPh and $Cu(OAc)_2$ in THF, –20 °C, 0.5 h	**1a**, 0[d]
5	1) BuLi (1), –20 °C, 0.5 h 2) $ZnCl_2$·TMEDA (1), –20 °C, 0.5 h	 **1b**, 63[b]
6	1) BuLi (1), –20 °C, 0.5 h 2) $ZnCl_2$·TMEDA (1), –20 °C, 0.5 h	 **1c**, 29[b]
7	1) BuLi (1), –20 °C, 0.5 h 2) $ZnCl_2$·TMEDA (1), –20 °C, 0.5 h	 **1d**, 68[b]

[a] After purification (see experimental part). [b] 2,2'-Bi(benzothiophene) (**1'**) was detected in the crude and proved to be more or less difficult to separate, depending on both the polarity and the stability of the product **1**. [c] Benzothiophene was present in the crude (<20% yield) together with an unidentified product, but **1'** was not detected. [d] Benzothiophene was present in the crude together with the same unidentified product.



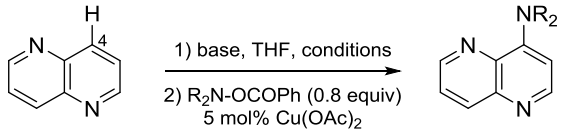
Scheme 1. Extension of the sequence to 2-chlorothiophene and proposed mechanism to rationalize the degradation of **2a**. [a] 5,5'-Dichloro-2,2'-bithiophene (**2a'**) was also isolated in 32% yield.

When the reaction was extended to 2-chlorothiophene, we isolated both the expected diallylamine **2a** in 49% yield and the dimer **2a'** in 32% yield (Scheme 1). Interestingly we observed that, upon storage in a fridge, isolated **2a** turns dark blue in a few days (or in a few minutes if dissolved in chloroform) while it is converted into the dimer **2a'**. This result tends to show that dimerization is not related to a side homocoupling taking place in the course of the reaction, but rather associated with the thienylamine instability.[21] We thus decided to move to a substrate for which the corresponding amines are stable.

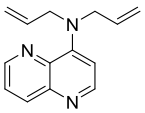
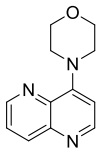
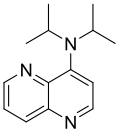
The 1,5-naphthyridine heterocycle is present in numerous compounds endowed with biological properties as well as in OLED materials.[22] Besides direct introduction of an amino group by a Chichibabin reaction,[23] its functionalization at C4 can be achieved by deprotometalation. The latter was performed by using a lithium amide provided that a directing group is present at C3.[24] However, from bare 1,5-naphthyridine, a regioselective reaction at C4 was found possible after precomplexation of the substrate with $(TMP)_2Mg{\cdot}2LiCl$, and takes place in THF within 5 min at –78 °C.[22] In order to prepare amines (Table 2), we first evaluated the 'deprotolithiation-transmetalation to zinc-copper catalyzed amination' sequence, successful from benzothiophene, by using *N*-(benzoyloxy)diallylamine as electrophile. However, under these conditions, the expected amine **3a** was isolated in a maximum 10% yield (entries 1 and 2). In order to understand the reason of this failure, we tested iodine as electrophile, and obtained the 4-iodo **3-I** and 4,8-diiodo **3'-I** in respective yields of 34 and 6% alongside with remaining starting material (Scheme 2, left). Concerned by the potential low stability of the intermediate 4-lithio compound, we next moved to more stable zinc amides. After deprotozincation using TMPZnCl·LiCl[25] (1.1 equiv) at room temperature for 2 h, interception with *N*-(benzoyloxy)diallylamine as before led to **3a** in 64% yield (entry 3), a rather good result since trapping with iodine afforded **3-I** in 72% yield (Scheme 2, left). $(TMP)_2Zn{\cdot}2LiCl$, prepared from LiTMP and $ZnCl_2$ in a 2:1 ratio, was similarly employed and furnished the amine **3c** after copper-catalyzed reaction with *N*-(benzoyloxy)morpholine (entry 4). Interestingly, a magnesium intermediate generated by TMPMgCl·LiCl[26] is tolerated,[27] as evidenced by quenching with *N*-(benzoyloxy)diisopropylamine to afford the amine **3b** in 52% yield (entry 5).

Alternatively, the synthesis of the amines **3a**-**c** can be considered by nucleophilic substitution of the iodo **3-I**. If such a possibility efficiently worked by using morpholine as nucleophile, the yield dropped to 17% with diallylamine, and the reaction failed with diisopropylamine, a result probably due to important steric hindrance in this case (Scheme 2, right). Thus, deprotometalation-amination and deprotometalation-iodolysis-substitution appear as being complementary to access 1,5-naphthyridines 4-substituted by various amino groups.

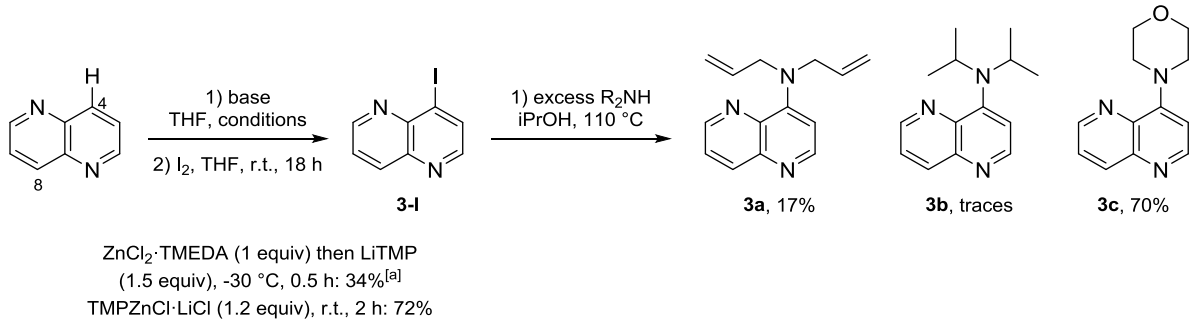
Table 2. Extension to 1,5-naphthyridine.



3

Entry	Base (equiv), conditions	Product **3**, Yield [%][a]
1	1) $ZnCl_2{\cdot}TMEDA$ (1) 2) LiTMP (1.2), –30 °C, 0.5 h	 **3a**, 0[b]
2[c]	1) $ZnCl_2{\cdot}TMEDA$ (1) 2) LiTMP (2.2), –30 °C, 0.5 h	**3a**, 10[b]
3	TMPZnCl·LiCl (1.1), r.t., 2 h	**3a**, 64
4	$(TMP)_2Zn{\cdot}2LiCl$ (1.1), r.t., 2 h	 **3c**, 52
5	TMPMgCl·LiCl (1.1), –40 °C, 1 h	 **3b**, 52

[a] After purification (see experimental part). [b] The rest is starting material. [c] By using 2.2 equivalents of $(allyl)_2N$-OCOPh.

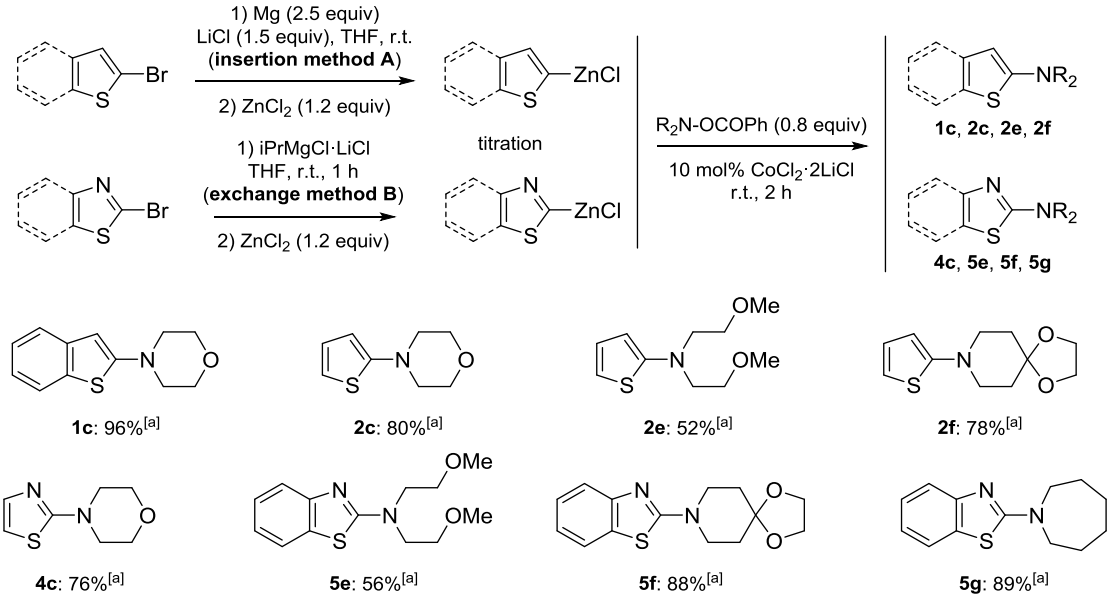


Scheme 2. Alternative way to access 1,5-naphthyridines 4-substituted by amino groups. [a] 4,8-Diiodo-1,5-naphthyridine (**3'-I**) was also isolated in 6% yield.

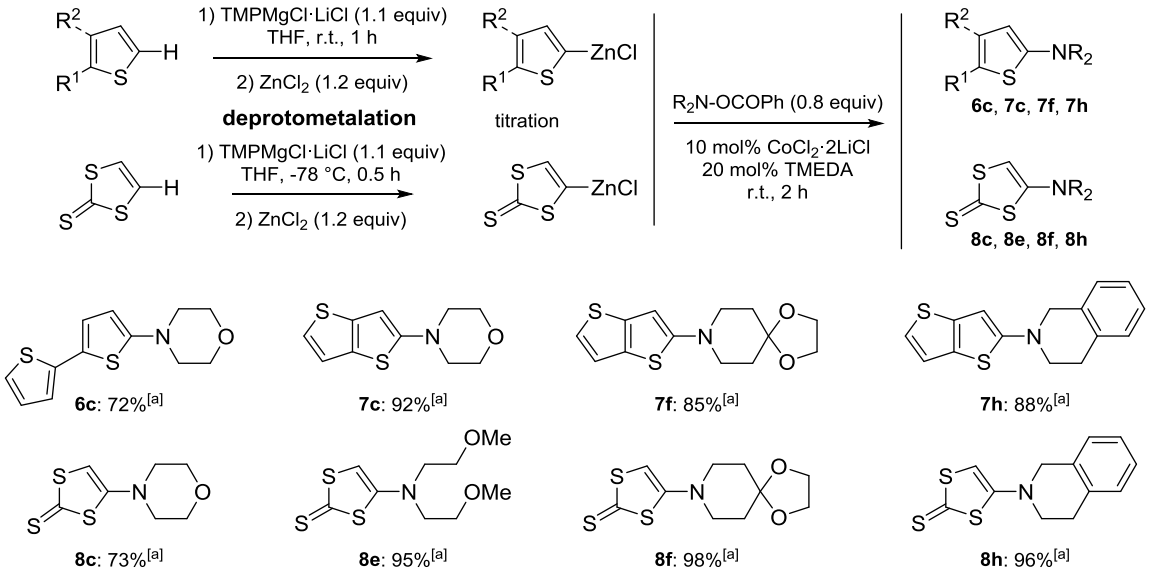
We next involved thiophene-based and related organozinc chlorides in cobalt-catalyzed amination reactions. First, arylzinc compounds were prepared by transmetalation of the corresponding arylmagnesium reagents obtained by LiCl-favored reactions: 2-thienyl- and 2-benzothienylmagnesium bromides by Grignard reaction (**insertion method A**;[28] Scheme 3, top), and 2-thiazolyl- and 2-benzothiazolylmagnesium bromides by bromine/metal exchange (**exchange method B**,[29] bottom). The amination step was successfully performed to respectively afford **1c**, **2c**, **2e**, **2f** and **4c**, **5e**, **5f**, **5g** by using *N*-(benzoyloxy) secondary amines in the presence of $CoCl_2$·2LiCl,[17] a combination that recently proved efficient to functionalize organozincs prepared from other aryl halides.[17-18]

For atom economy reason and to avoid the use of costly aryl bromides, we finally employed organozinc compounds prepared by deprotometalation-transmetalation in this cobalt-catalyzed amination (Scheme 4). This represents an additional challenge as very few cobalt-catalyzed electrophilic trappings have been achieved from arylzincs prepared by deprotometalation.[30]

To this purpose, we involved in the amination 2-thienylzinc chlorides prepared from 2,2'-bithiophene and thieno[3,2-*b*]thiophene by deprotomagnesiation using TMPMgCl·LiCl[26,31] followed by transmetalation (top). Similarly, we performed the amination of the organozinc chloride coming from 1,3-dithiole-2-thione, generated by using the same base at low temperature[32] followed by transmetalation (bottom). The reactions gave the expected amines **6c**, **7c**, **7f**, **7h** and **8c**, **8e**, **8f**, **8h** in high yields in the presence of TMEDA (0.2 equiv),[17] making this cobalt-catalyzed 'deprotonation-transmetalation-amination' a general way to obtain amino-substituted thiophenes and related compounds.



Scheme 3. Cobalt-catalyzed amination of (benzo)thienylzinc and (benzo)thiazolylzinc chlorides prepared from the corresponding halides. [a] Yields are given after purification (see experimental part).



Scheme 4. Cobalt-catalyzed amination of organozinc chlorides prepared by deprotonation-transmetalation. [a] Yields are given after purification (see experimental part).

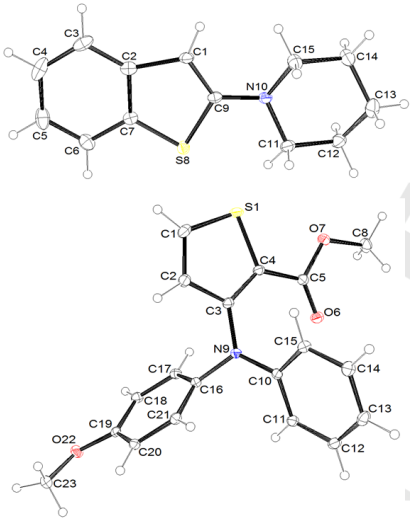


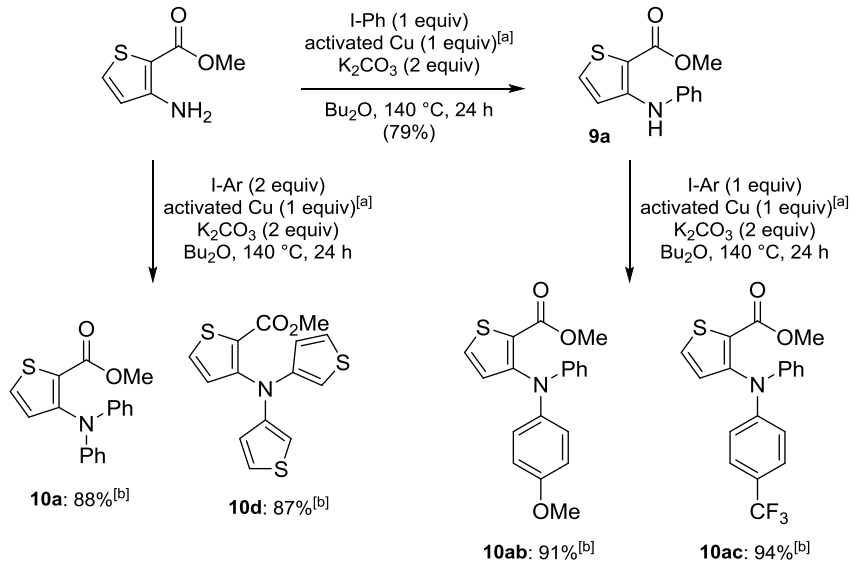
Figure 1. ORTEP diagrams (50% probability) of the compounds **1d** and **10ab**.

Apart from nucleophilic substitution reactions that require activated aryl halides and strong reaction conditions,[33] access to thiophene-based triarylamines is more readily possible by applying the Buchwald-Hartwig approach. Thus, palladium-catalyzed reactions have been used to *N*-arylate 2-amino-[33a,34] and 3-amino-[35] thiophenes or benzothiophenes. To avoid the use of expensive transition metal, and following our interest in *N*-arylation reactions,[36] we next investigated the copper-catalyzed *N*-arylation of thiophene-based anilines. Indeed, if copper has been employed to catalyze *N*-arylation of an aminothiophene with organoboron reagents,[37] aryl halides have to our knowledge never been used in such reactions.

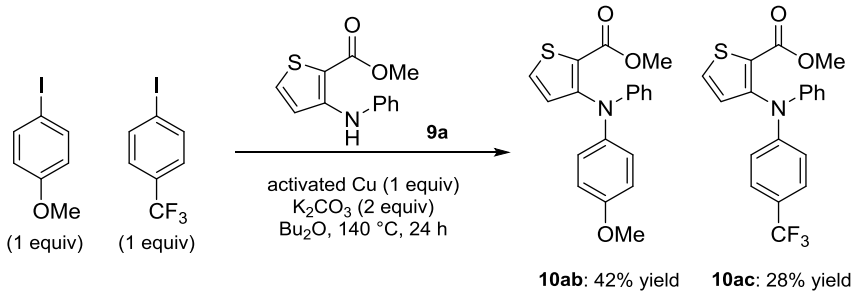
We recently reported the use of 2-aminophenones as substrates in copper-catalyzed *N*-arylation with aryl and heteroaryl iodides.[36d] To achieve the reactions, we employed a catalytic amount of activated copper and potassium carbonate as a base at the reflux temperature of dibutylether. We chose these conditions as starting point to investigate the reaction from methyl 3-amino-2-thiophenecarboxylate and methyl 2-amino-3-thiophenecarboxylate. Preliminary results led us to rapidly realize that reproducibility of the reactions could be ensured by using stoichiometric copper (5 x 0.2 equiv added every 2 h), conditions that were kept to perform the whole study.

When methyl 3-amino-2-thiophenecarboxylate (Scheme 5) was treated by 1.5 equivalents of iodobenzene, a mixture of the mono- and diphenylated products **9a** and **10a** was formed in a ~1:1 ratio under these conditions. By reducing the amount of aryl iodide to one equivalent, monoarylation was favored, affording **9a** in 79% yield; only traces of **10a** were observed in the crude, and could be easily removed by purification over silica gel (top). Conversely, increasing the amount of iodide to 2 equivalents allowed **10a** to be obtained in a high 88% yield; using 3-iodothiophene instead of iodobenzene similarly furnished **10d** (bottom left).

The formation of the monophenylated **9a** in high yield using 1 equivalent of iodide shows that **9a** is less reactive than starting 3-amino-2-thiophenecarboxylate in the *N*-arylation reaction. It is nevertheless possible, by using an excess of the iodide, to prepare triarylamines, as shown with the products **10a** and **10d**. Furthermore, a different aryl iodide could be used in the second *N*-arylation reaction and, when **9a** was treated by 4-iodoanisole and 1-iodo-4-(trifluoromethyl)benzene under the same reaction conditions, the differently substituted triarylamines **10ab** (Figure 1, bottom) and **10ac** were isolated in high yields (bottom right).



Scheme 5. *N*-arylation of methyl 3-amino-2-thiophenecarboxylate to afford either **9** or **10**. [a] Added by portions of 0.2 equivalent every 2 h. [b] After purification (see experimental part).

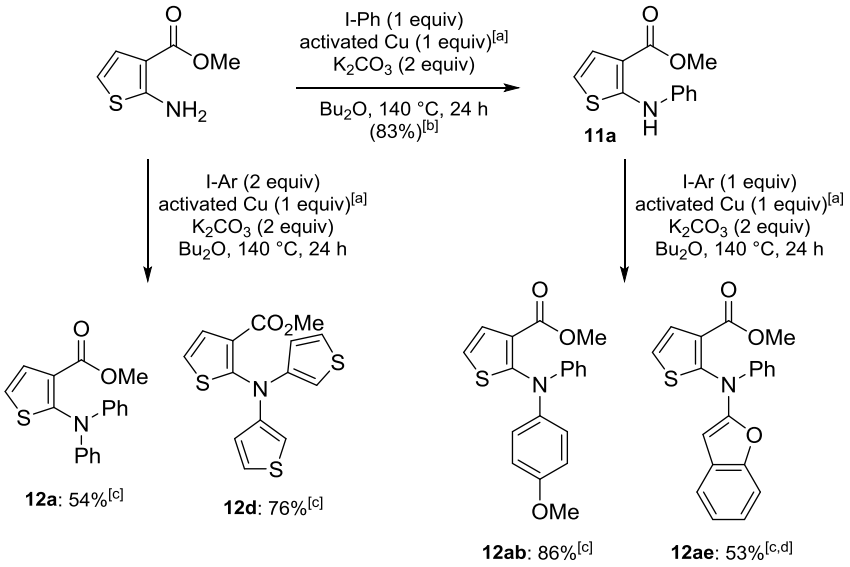


Scheme 6. Compared reactivities of 4-iodoanisole and 1-iodo-4-(trifluoromethyl)benzene in the *N*-arylation of **9a**.

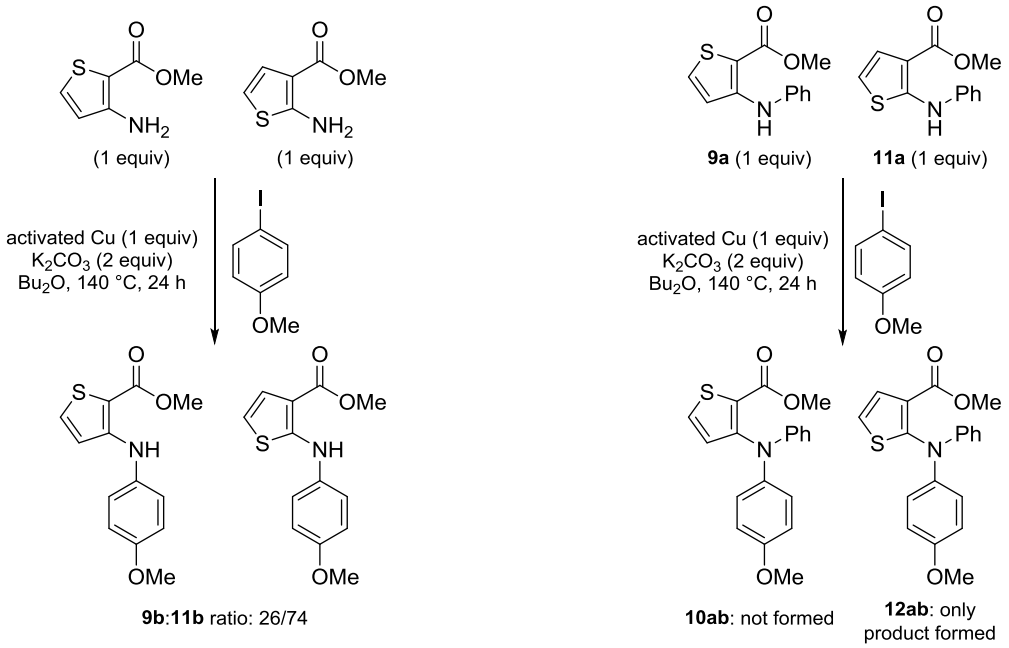
A competitive reaction performed on **9a** in the presence of two halides, 4-iodoanisole and 1-iodo-4-(trifluoromethyl)benzene, showed close reactivities, but in favor of more electron-rich 4-iodoanisole (Scheme 6). When compared with works on both the Goldberg reaction[38] and the copper-catalyzed *N*-arylation of aniline with aryl bromides,[39] in which electron-withdrawing substituents at the *para* position of the aryl halide facilitate the reaction rates, our competition study revealed a different behavior for the 4-trifluoromethylated iodide.

We next turned to the isomeric methyl 2-amino-3-thiophenecarboxylate (Scheme 7). As observed for methyl 3-amino-2-thiophenecarboxylate, reaction with 1.5 equivalents of iodobenzene under the same reaction conditions led to a mixture of the mono- and diphenylated products **11a** and **12a** in respective yields of 59% and 30%. It proved easy to achieve monophenylation by using 1 equivalent of iodobenzene (83% yield; top). Though somewhat less efficient, diphenylation was also possible (54% and 76% yield, respectively using iodobenzene and 3-iodothiophene; bottom left). The *N*-arylation of **11a** with 4-iodoanisole and 2-iodobenzofuran satisfactorily led to two new thiophene-based triarylamines (bottom right).

We finally compared the reactivity of 2-aminothiophenes and 3-aminothiophenes in this *N*-arylation reaction (Scheme 8). To this purpose, we chose 4-iodoanisole to first attempt a competitive reaction between methyl 3-amino-2-thiophenecarboxylate and methyl 2-amino-3-thiophenecarboxylate (left). Even if the former also reacted, we noticed a higher reactivity of the latter (a ~1:3 ratio was recorded). As monophenylated **9a** and **11a** are less reactive than their precursors (at the origin of the possible monoarylation reactions), this reactivity difference towards 4-iodoanisole is logically more pronounced between less reactive **9a** and **11a** (right). It is difficult to rationalize such a reactivity difference, but more studies will be performed in order to get general trends and connect them with possible reaction mechanisms.



Scheme 7. *N*-arylation of methyl 2-amino-3-thiophenecarboxylate to afford either **11** or **12**. [a] Added by portions of 0.2 equivalent every 2 h. [b] The diphenylated product **12a** was also isolated in 6% yield. [c] After purification (see experimental part). [d] Starting iodide and benzofuran were present in the crude, but no more aminothiophene.



Scheme 8. Left: Compared reactivities of methyl 3-amino-2-thiophenecarboxylate and methyl 2-amino-3-thiophenecarboxylate in the *N*-arylation using 4-iodoanisole. Right: Compared reactivities of methyl 3-(phenylamino)-2-thiophenecarboxylate (**9a**) and methyl 2-(phenylamino)-3-thiophenecarboxylate (**11a**) in the *N*-arylation using 4-iodoanisole.

Conclusions

In the course of this study dedicated to the synthesis of thiophene-based tertiary amines, we have developed three approaches that are copper-catalyzed and cobalt-catalyzed amination of thienylzinc halides or related compounds, and copper-catalyzed arylation of aminothiophenes. The amination allowed thienylzinc halides, obtained by bromine/metal exchange but also by deprotometalation, to be functionalized; the only limit seems to be the low stability of some of the generated thienylamines. Concerning copper-catalyzed *N*-arylation of aminothiophenes, a single reaction can be selectively achieved, but also diarylation using two different aryl iodides. Such reactions will undoubtly find applications given the interest for thiophenes and related compounds in the fields of medicinal chemistry and materials.

Experimental Section

General

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium-benzophenone under nitrogen or argon and stored over molecular sieves. Column chromatography separations were achieved on silica gel (40-63 µm) from Merck. Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded either on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively, or on a Bruker ARX-400 spectrometer at 400 MHz and 101 MHz respectively. ^{1}H chemical shifts (δ) are given in parts per million (ppm) relative to the solvent residual peak and ^{13}C chemical shifts are relative to the central peak of the solvent signal.[40] Mass spectra and high resolution mass spectra (HRMS) were recorded using electron ionization (EI) except otherwise noted. Gas-chromatographical analyses were performed on machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 µm).

Starting materials

iPrMgCl·LiCl was purchased as a solution in THF from Albemarle and titrated against iodine prior to use.[41]

$ZnCl_2$ solution (1.0 M in THF) was prepared by drying $ZnCl_2$ (136 g, 0.10 mol) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, dry THF (100 mL) was added and stirring was continued until all salts were dissolved (12 h). $ZnCl_2$·TMEDA was prepared as reported previously.[19a]

After opening a new bottle of 2,2,6,6-tetramethylpiperidine, KOH pellets were added and storage in a desiccator was necessary. LiTMP was prepared by adding BuLi (about 1.6 M hexanes solution, 1.5 mmol) to a stirred, cooled (–10 °C) solution of 2,2,6,6-tetramethylpiperidine (0.28 mL, 1.7 mmol) in THF (3 mL) and stirring for 5 min. If necessary, the solution was titrated as reported previously.[26]

TMPZnCl·LiCl was prepared as follows.[25] A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 2,2,6,6-tetramethylpiperidine (10.2 mL, 60 mmol) and THF (60 mL). The solution was cooled to –40 °C before dropwise addition of BuLi (2.4 M in hexane, 25 mL, 60 mmol). Then, the reaction mixture was allowed to warm up slowly to –10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was added dropwise and the resulting solution was stirred for 0.5 h at –10 °C and then for 0.5 h at 25 °C. The solvents were then removed under vacuum to afford a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine1 as indicator.[42]

$(TMP)_2Zn$·2LiCl was prepared as follows in a nearly quantitative yield. A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 2,2,6,6-tetramethylpiperidine (10.2 mL, 60 mmol) and THF (60 mL). The solution was cooled to –40 °C before dropwise addition of BuLi (2.4 M in hexane, 25 mL, 60 mmol). Then, the reaction mixture was allowed to warm up slowly to –10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 30 mL, 30 mmol) was added dropwise and the resulting solution was stirred for 0.5 h at –10 °C and then for 0.5 h at 25 °C. The solvents were then removed under vacuum. Freshly distilled THF was then slowly added to the residue under vigorous stirring until the salts were completely dissolved and an orange solution obtained.

TMPMgCl·LiCl was prepared as follows.[26] In a dry and argon flushed Schlenk-flask, 2,2,6,6-tetramethylpiperidine (14.8 g, 105 mmol) was added to iPrMgCl·LiCl (71.4 mL, 0.10 mol, 1.4 M in THF) at 25 °C and the mixture was stirred for 3 days at 25 °C. The freshly prepared TMPMgCl·LiCl was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.[42]

$CoCl_2$·2LiCl was prepared as follows.[17] A dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with anhydrous LiCl (5.9 g, 0.14 mol) and heated to 150 °C under high vacuum for 5 h. After cooling to room temperature under vacuum, anhydrous $CoCl_2$ (9.1 g, 70 mmol) was added under argon. The Schlenk-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with dry THF (70 mL). The mixture was vigorously stirred until all solids were dissolved (ca. 8 h). The reagent $CoCl_2$·2LiCl (1 M in THF) is obtained as a dark blue solution.

1,5-Naphthyridine,[22] activated Cu,[43] methyl (2-aminothiophene-3-carboxylate[44] and 2-iodobenzofuran[45] were prepared as reported previously.

All reagents not listed in the publication (main paper or supporting information) were obtained from commercial sources.

Crystallographic data

CCDC 1896366 (**1d**), 1896367 (**2a'**) and 1896368 (**10ab**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å, multilayer monochromator). The X-ray diffraction data of the compounds **1d**, **2a'** and **10ab** were collected at 150(2) K by using a D8 VENTURE Bruker AXS diffractometer equipped with a (CMOS) PHOTON

100 detector. The structure was solved by dual-space algorithm using the *SHELXT* program,[46] and then refined with full-matrix least-square methods based on F^2 (*SHELXL-2014*).[47] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02).[48]

General procedure 1 for the *N*-benzoyloxylation of secondary amines.

To dibasic potassium phosphate (K_2HPO_4; 1.3 g, 7.5 mmol) and freshly dried benzoyl peroxide (1.2 g, 5.0 mmol) in DMF (20 mL) under argon was slowly added the secondary amine (6.0 mmol). The reaction mixture was stirred at room temperature until disappearance of benzoyl peroxide (about 12 h, as shown by TLC monitoring). After addition of saturated aqueous ammonium chloride (30 mL), extraction was performed using AcOEt (3x20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), and then dried over Na_2SO_4. Removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

***N*-(Benzoyloxy)diallylamine.**

The general procedure 1 using diallylamine (0.74 mL) gave *N*-(benzoyloxy)diallylamine (eluent: hexanes-AcOEt 80:20; R_f = 0.67) in 76% yield (0.83 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (d, 2H, *J* = 6.5 Hz), 4.90 (dd, 2H, *J* = 10.2 and 1.6 Hz), 5.00 (dd, 2H, *J* = 17.2 and 1.6 Hz), 5.76 (ddt, 2H, *J* = 16.8, 10.1 and 6.5 Hz), 7.12 (dd, 2H, *J* = 8.3 and 6.9 Hz), 7.24 (tt, 1H, *J* = 7.4 and 1.9 Hz), 7.72 (dd, 2H, *J* = 8.3, 1.4 Hz). The analyses are as described previously.[17] ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.7 ($2CH_2$), 119.5 ($2CH_2$), 128.3 (2CH), 129.2 (C), 129.4 (2CH), 132.5 (2CH), 133.0 (CH), 165.3 (C, C=O).

***N*-(Benzoyloxy)dibutylamine.**

The general procedure 1 using dibutylamine (1.01 mL) gave *N*-(benzoyloxy)dibutylamine (eluent: hexanes-AcOEt 95:5; R_f = 0.62) in 59% yield (0.74 g) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.3 Hz), 1.34 (sext, 2H, *J* = 7.3 Hz), 1.54 (ddd, 2H, *J* = 15.1, 8.7 and 6.1 Hz), 2.92 (d, 1H, *J* = 7.4 Hz), 2.94 (d, 1H, *J* = 7.4 Hz), 7.39 (t, 2H, *J* = 7.4 Hz), 7.51 (tt, 1H, *J* = 7.4 and 1.9 Hz), 7.99 (d, *J* = 7.1 Hz, 1H). The ^{1}H NMR data are as described previously.[49] ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 ($2CH_3$), 20.5 ($2CH_2$), 29.0 ($2CH_2$), 59.5 ($2CH_2$), 128.4 (2CH), 129.4 (C), 129.5 (2CH), 132.9 (CH), 165.6 (C, C=O).

***N*-(Benzoyloxy)morpholine.**

The general procedure 1 using morpholine (0.52 mL) gave *N*-(benzoyloxy)morpholine (eluent: hexanes-AcOEt 50:50; R_f = 0.62) in 37% yield (0.39 g) as a white powder: mp 82 °C (lit.[50] 81-82 °C); IR (ATR): 677, 708, 793, 857, 1008, 1023, 1049, 1066, 1083, 1100, 1247, 1316, 1386, 1453, 1600, 1728, 2849, 2966 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99-3.01 (m, 2H), 3.39-3.41 (m, 2H), 3.78-3.91 (m, 4H), 7.40 (t, 2H, *J* = 7.6 Hz), 7.52 (t, 1H, *J* = 7.3 Hz), 7.97 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.9 ($2CH_2$), 65.8 ($2CH_2$), 128.4 (2CH), 129.0 (C), 129.4 (2CH), 133.2 (CH), 164.5 (C, C=O).

***N*-(Benzoyloxy)piperidine.**

The general procedure 1 using piperidine (0.59 mL) gave *N*-(benzoyloxy)piperidine (eluent: hexanes-AcOEt 70:30; R_f = 0.75) in 64% yield (0.66 g) as a beige powder: mp 65 °C (lit.[50] 62.5-63 °C); IR (ATR): 428, 675, 713, 782, 850, 917, 1019, 1037, 1070, 1092, 1184, 1235, 1249, 1270, 1280, 1319, 1453, 1601, 1728, 2847, 2940 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.59 (m, 6H), 2.55 (br s, 2H), 3.28 (br s, 2H), 7.18 (t, 2H, *J* = 7.7 Hz), 7.30 (t, 1H, *J* = 7.3 Hz), 7.79 (d, 2H, *J* = 7.8 Hz).

***N*-(Benzoyloxy)diisopropylamine.**

The general procedure 1 using diisopropylamine (0.84 mL) gave *N*-(benzoyloxy)diisopropylamine (eluent: hexanes-AcOEt 90:10; R_f = 0.30) in 45% yield (0.50 g) as a yellow oil: IR (ATR): 644, 663, 708, 729, 874, 913, 1025, 1061, 1081, 1177, 1243, 1314, 1383, 1451, 1601, 1740, 2226, 2877, 2938, 2978 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 12H, *J* = 6.3 Hz), 3.28 (hept, 2H, *J* = 6.2 Hz), 7.31 (t, 2H, *J* = 7.3 Hz), 7.43 (t, 1H, *J* = 7.3 Hz), 7.91 (d, 2H, *J* = 7.7 Hz). The NMR data are as described previously.[51] ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2 (br s, $2CH_3$), 20.1 (br s, $2CH_3$), 53.3 (2CH), 128.3 (2CH), 129.1 (C), 129.3 (2CH), 132.8 (CH), 166.1 (C, C=O).

***N*-(Benzoyloxy)di(2-methoxyethyl)amine.**

The general procedure 1 using di(2-methoxyethyl)amine (0.89 mL) gave *N*-(benzoyloxy)di(2-methoxyethyl)amine (eluent: hexanes-AcOEt 50:50) in 76% yield (0.96 g) as a colorless oil: IR (ATR): 1022, 1056, 1116, 1198, 1241, 1450, 1740, 2888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (t, 4H, *J* = 5.6 Hz), 3.29 (s, 6H), 3.61 (t, 4H, *J* = 5.8 Hz), 7.43-7.45 (m, 2H), 7.57 (t, 1H, *J* = 7.4 Hz), 8.02 (dd, 2H, *J* = 8.3 and 1.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.0 ($2CH_3$), 59.4 ($2CH_2$), 69.9 ($2CH_2$), 128.5 (2CH), 129.6 (C), 129.7 (2CH), 133.2 (CH), 165.6 (C, C=O); MS (EI, 70 eV) *m/z* (%) 42 (87), 44 (36), 51 (10), 56 (10), 59 (13), 76 (37), 88 (16), 104 (100), 105 (11), 121 (19), 208 (29); HRMS (EI) *m/z* calcd for $C_{13}H_{19}NO_4$: 253.1314; found: 253.1307.

***N*-(Benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane.**

The general procedure 1 using 1,4-dioxa-8-azaspiro[4.5]decane (0.77 mL) gave *N*-(benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane (eluent: hexanes-AcOEt 50:50) in 71% yield (0.93 g) as a white solid: IR (ATR): 1060, 1081, 1122, 1245, 1447, 1733, 2959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, 4H, *J* = 5.7 Hz), 3.27 (br s, 2H), 3.45 (br s, 2H), 4.00 (s, 4H, OCH_2CH_2O), 7.44 (t, 2H, *J* = 7.5 Hz), 7.57 (t, 1H, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 32.8 ($2CH_2$), 54.1 ($2CH_2$), 64.6 ($2CH_2$), 106.3 (C), 128.5 (2CH), 129.6 (2CH), 129.6 (C), 133.1 (CH), 164.9 (C, C=O). The NMR data are as described previously.[52] MS (EI, 70 eV) *m/z* (%) 42 (11), 43 (100), 45 (14), 50 (14), 61 (12), 77 (49), 88 (11), 87 (13), 122 (55); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NO_4$: 263.1158; found: 263.1156.

***N*-(Benzoyloxy)azepane.**

The general procedure 1 using azepane (0.68 mL) gave *N*-(benzoyloxy)azepane as reported previously.[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (dt, 4H, *J* = 6.1 and 3.0 Hz), 1.82 (ddd, 4H, *J* = 6.8, 4.4 and 1.8 Hz), 3.33 (t, 4H, *J* = 5.5 Hz), 7.43 (t, 2H, *J* = 7.7 Hz), 7.55 (t, 1H, *J* = 7.4 Hz), 8.00 (dd, 2H, *J* = 8.3 and 1.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.2 ($2CH_2$), 26.5 ($2CH_2$), 59.6 ($2CH_2$), 128.5 (2CH), 129.5 (2CH), 129.8 (C), 133.0 (CH), 164.9 (C, C=O).

***N*-(Benzoyloxy)-1,2,3,4-tetrahydroisoquinoline.**

The general procedure 1 using 1,2,3,4-tetrahydroisoquinoline (0.76 mL) gave *N*-(benzoyloxy)-1,2,3,4-tetrahydroisoquinoline as reported previously.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (t, 2H, *J* = 6.0 Hz), 3.55 (br s, 2H), 4.43 (br s, 2H, H1'), 7.06 (d, 1H, *J* = 6.4 Hz), 7.12-7.23 (m, 3H),

7.42 (t, 2H, *J* = 7.7 Hz), 7.55 (t, 1H, *J* = 7.4 Hz), 8.00 (d, 2H, *J* = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.7 (CH_2), 53.4 (CH_2), 58.1 (CH_2), 126.3 (CH), 126.8 (CH), 126.9 (CH), 128.4 (CH), 128.4 (2CH), 129.3 (C), 129.5 (2CH), 132.3 (C), 132.9 (C), 133.1 (CH), 164.9 (C, C=O).

General procedure 2 for the deprotolithiation-zincation-amination of benzothiophene.

To a stirred mixture of benzothiophene (0.20 g, 1.5 mmol) and $ZnCl_2$·TMEDA (0.39 g, 1.5 mmol) in THF (3 mL) at –20 °C was added dropwise a THF-hexane solution of LiTMP (1.5 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.28 mL, 1.7 mmol) in THF (3 mL) and stirring for 5 min) cooled at –20 °C. After 0.5 h at –20 °C, the solution was added dropwise to the *N*-benzoyloxy secondary amine (1.2 mmol) and anhydrous copper(II) acetate (14 mg, 75 µmol) in THF (3 mL) at –20 °C. The mixture was stirred overnight before addition of an aqueous saturated solution of Na_2CO_3 (5 mL) and extraction with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

2-(Diallylamino)benzothiophene (1a).

The general procedure 2 using *N*-(benzoyloxy)diallylamine (0.26 g) gave **1a** (eluent: hexanes-CH_2Cl_2 95:5; R_f = 0.42) in 52% yield (0.14 g) as a yellow oil: IR (ATR): 566, 704, 736, 794, 863, 923, 1016, 1065, 1184, 1258, 1355, 1416, 1439, 1540, 1563, 1640, 2962 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (dt, 4H, *J* = 5.6 and 1.5 Hz), 5.26 (dd, 2H, *J* = 8.9 and 1.5 Hz), 5.33 (dd, 2H, *J* = 17.3 and 1.6 Hz), 5.92 (ddt, 2H, *J* = 17.0, 10.1 and 5.6 Hz), 6.06 (s, 1H, H3), 7.06 (t, 1H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.43 (dd, 1H, *J* = 8.0 and 1.1 Hz), 7.59 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9 ($2CH_2$), 96.5 (CH), 117.4 ($2CH_2$), 120.0 (CH), 120.3 (CH), 121.2 (CH), 124.4 (CH), 131.8 (C), 133.0 (2CH), 141.4 (C), 155.7 (C). HRMS (EI) *m/z* calcd for $C_{14}H_{15}NS$: 229.0925; found: 229.0921. 2,2'-Bi(benzothiophene) (**1'**) was also isolated. This compound could be obtained in 25% yield by performing the same procedure without *O*-benzoyl hydroxylamine: white powder; mp 262 °C (lit.[54] 260-261 °C); IR (ATR): 476, 557, 722, 736, 814, 937, 1013, 1067, 1177, 1250, 1420, 1451, 1711, 1944, 2851, 2923, 3053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.39 (m, 4H), 7.52 (s, 2H), 7.74-7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.6 (CH), 122.3 (CH), 123.9 (CH), 124.9 (CH), 125.1 (CH), 137.4 (C), 139.6 (C), 140.3 (C).

2-(Dibutylamino)benzothiophene (1b).

The general procedure 2 using *N*-(benzoyloxy)dibutylamine (0.30 g) gave **1b** (eluent: hexanes-Et_3N 95:5; R_f = 0.67) in 63% yield (0.25 g) as a yellow oil: IR (ATR): 726, 756, 919, 1018, 1065, 1111, 1133, 1194, 1243, 1279, 1311, 1369, 1440, 1539, 1562, 2861, 2928, 2955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 6H, *J* = 7.3 Hz, CH_3), 1.38 (dq, 4H, *J* = 14.6 and 7.0 Hz, CH_2), 1.65 (quintuplet, 4H, *J* = 7.5 Hz, CH_2), 3.28 (t, 4H, *J* = 7.5 Hz, CH_2), 5.88 (s, 1H, H3), 6.97 (t, 1H, *J* = 7.5 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 7.9 Hz), 7.53 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 ($2CH_3$), 20.4 ($2CH_2$), 29.5 ($2CH_2$), 53.2 ($2CH_2$), 94.9 (CH), 119.6 (CH), 119.8 (CH), 121.3 (CH), 124.5 (CH), 131.6 (C), 141.9 (C), 156.3 (C). HRMS (EI) *m/z* calcd for $C_{16}H_{23}NS$: 261.1551; found: 261.1549.

2-(Morpholino)benzothiophene (1c).

The general procedure 2 using *N*-(benzoyloxy)morpholine (0.25 g) gave **1c** (eluent: hexanes-Et_3N 98:2; R_f = 0.30) in 29% yield (76 mg) as a beige powder: mp 180 °C (lit.[10a] 180-181.5 °C); IR (ATR): 569, 592, 653, 723, 744, 780, 868, 901, 1013, 1065, 1116, 1186, 1212, 1250, 1264, 1303, 1375, 1437, 1455, 1527, 1557, 2850, 2958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24 (t, 4H, *J* = 4.9 Hz), 3.86 (t, 4H, *J* = 4.8 Hz), 6.23 (s, 1H, H3), 7.10 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.48 (d, 1H, *J* = 7.9 Hz), 7.61 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1 ($2CH_2$), 66.4 ($2CH_2$), 99.6 (CH), 121.2 (CH), 121.7 (CH), 121.8 (CH), 124.7 (CH), 132.8 (C), 140.4 (C), 157.9 (C). These data are as reported previously.[10a]

2-(Piperidino)benzothiophene (1d).

The general procedure 2 using *N*-(benzoyloxy)piperidine (0.25 g) gave **1d** (eluent: hexanes-Et_3N 98:2; R_f = 0.40) in 68% yield (0.18 g) as a white powder: mp 102 °C (lit.[55] 99-100 °C); IR (ATR): 479, 558, 581, 641, 721, 734, 772, 812, 855, 1009, 1069, 1117, 1203, 1236, 1255, 1316, 1384, 1439, 1532, 1559, 1717, 2935, 3055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61-1.67 (m, 2H), 1.73-1.80 (m, 4H), 3.28 (t, 4H, *J* = 5.5 Hz), 6.18 (s, 1H, H3), 7.08 (t, 1H, *J* = 7.5 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.61 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0 (CH_2), 25.3 ($2CH_2$), 52.1 ($2CH_2$), 98.5 (CH), 120.7 (CH), 121.0 (CH), 121.6 (CH), 124.5 (CH), 132.7 (C), 141.0 (C), 158.6 (C). **Crystal data for 1d.** $C_{13}H_{15}NS$, M = 217.32, triclinic, *P* -1, *a* = 6.0747(7), *b* = 12.9937(15), *c* = 14.7777(18) Å, *α* = 74.742(4), *β* = 82.826(4), *γ* = 86.354(4) °, *V* = 1115.9(2) Å^3, *Z* = 4, *d* = 1.293 g cm^{-3}, *µ* = 0.255 mm^{-1}. A final refinement on F^2 with 5071 unique intensities and 297 parameters converged at ω*R*(F^2) = 0.0949 (*R*(*F*) = 0.0411) for 4457 observed reflections with *I* > 2σ(*I*). CCDC 1896366.

2-Chloro-5-(diallylamino)thiophene (2a).

The general procedure 2, from 2-chlorothiophene (0.18 g) instead of thiophene, using *N*-(benzoyloxy)diallylamine (0.26 g) gave **2a** (eluent: hexanes-Et_3N 95:5; R_f = 0.50) in 49% yield (0.13 g) as a colorless oil of low stability (e.g. a solution in $CDCl_3$ becomes dark after a few minutes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, 1H, *J* = 5.8 Hz), 5.20 (dd, 2H, *J* = 10.0 and 1.3 Hz), 5.22 (dd, 2H, *J* = 17.2 and 1.5 Hz), 5.71 (d, 1H, *J* = 4.0 Hz), 5.83 (ddt, 2H, *J* = 16.0, 10.4 and 5.8 Hz), 6.53 (d, 1H, *J* = 4.0 Hz). Before the IR spectra and ^{13}C NMR could be recorded, degradation to give allylated products was noticed and formation of **5,5'-dichloro-2,2'-bithiophene (2a')** was identified by NMR: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, 2H, *J* = 3.9 Hz), 6.85 (d, 2H, *J* = 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.2 (2CH), 127.0 (2CH), 129.3 (2C), 135.2 (2C). These NMR data are similar to those reported previously.[56] **Crystal data for 2a'.** $C_8H_4Cl_2S_2$, M = 235.13, orthorhombic, *P c c n*, *a* = 7.3894(12), *b* = 21.610(3), *c* = 5.7035(9) Å, *V* = 910.8(2) Å^3, *Z* = 4, *d* = 1.715 g cm^{-3}, *µ* = 1.104 mm^{-1}. A final refinement on F^2 with 1041 unique intensities and 55 parameters converged at ω*R*(F^2) = 0.1336 (*R*(*F*) = 0.0682) for 904 observed reflections with *I* > 2σ(*I*). CCDC 1896367.

4-(Diallylamino)-1,5-naphthyridine (3a) by deprotometalation-amination of 1,5-naphthyridine.

To a stirred mixture of 1,5-naphthyridine (0.13 g, 1.0 mmol) in THF (3 mL) at room temperature was added dropwise a solution of TMPZnCl·LiCl (1.04 M THF solution; 1.1 mmol). After 2 h at this temperature, the mixture was treated dropwise by a solution of *N*-(benzoyloxy)diallylamine (0.18 g, 0.8 mmol) and anhydrous copper(II) acetate (9 mg, 50 µmol) in THF (3 mL). It was stirred overnight before addition of an aqueous saturated solution of NH_4Cl (4 mL) and extraction with AcOEt (3 x 10 mL). The combined organic layers were washed by aqueous saturated solutions of $NaHCO_3$ (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford,

after chromatography over silica gel (eluent: AcOEt; R_f = 0.50), **3a** in 64% yield (0.11 g) as a yellow oil: IR (ATR): 555, 610, 657, 712, 790, 823, 919, 993, 1111, 1171, 1232, 1249, 1288, 1347, 1411, 1480, 1504, 1563, 1639, 2910, 2980, 3075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (dd, 4H, *J* = 4.3 and 2.8 Hz, H1'), 5.19-5.25 (m, 4H, H3'), 6.04 (ddt, 2H, *J* = 17.8, 9.9 and 5.5 Hz, H2'), 6.69 (d, 1H, *J* = 5.5 Hz, H3), 7.50 (dd, 1H, *J* = 8.5 and 4.0 Hz, H7), 8.23 (dd, 1H, *J* = 8.5 and 1.8 Hz, H8), 8.50 (d, 1H, *J* = 5.5 Hz, H2), 8.73 (dd, 1H, *J* = 4.1 and 1.7 Hz, H6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.7 ($2CH_2$), 107.1 (CH), 117.4 ($2CH_2$), 123.8 (CH), 134.0 (2CH), 137.4 (CH), 137.9 (C), 145.3 (C), 146.0 (CH), 150.8 (CH), 152.5 (C). HRMS (EI) *m/z* calcd for $C_{14}H_{15}N_3$: 225.1266; found: 225.1268.

4-(Diisopropylamino)-1,5-naphthyridine (3b) by deprotometalation-amination of 1,5-naphthyridine.

To a stirred mixture of 1,5-naphthyridine (0.13 g, 1.0 mmol) in THF (3 mL) at –40 °C was added dropwise a solution of TMPMgCl·LiCl (1.07 M THF solution; 1.1 mmol). After 1 h at this temperature, the mixture was treated dropwise by a solution of *N*-(benzoyloxy)diisopropylamine (0.18 g, 0.8 mmol) and anhydrous copper(II) acetate (9 mg, 50 µmol) in THF (3 mL). It was slowly warmed to room temperature and stirred overnight before addition of an aqueous saturated solution of NH_4Cl (4 mL) and extraction with AcOEt (3 x 10 mL). The combined organic layers were washed by aqueous saturated solutions of $NaHCO_3$ (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford, after chromatography over silica gel (eluent: AcOEt; R_f = 0.27), **3b** in 52% yield (95 mg) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 12H, *J* = 6.8 Hz, CH_3), 4.57 (septuplet, 2H, *J* = 6.8 Hz), 6.95 (d, 1H, *J* = 5.6 Hz, H3), 7.46 (dd, 1H, *J* = 8.5 and 4.0 Hz, H7), 8.20 (dd, 1H, *J* = 8.5 and 1.7 Hz, H8), 8.46 (d, 1H, *J* = 5.6 Hz, H2), 8.71 (dd, 1H, *J* = 4.0 and 1.7 Hz, H6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.9 ($4CH_3$), 50.5 (2CH), 110.2 (CH), 123.6 (CH), 137.2 (CH), 139.7 (C), 145.6 (CH), 145.8 (C), 149.8 (CH), 152.9 (C). Note that **3b** is contaminated with impurities.

4-Iodo-1,5-naphthyridine (3-I).

To a stirred mixture of 1,5-naphthyridine (0.26 g, 2.0 mmol) in THF (4 mL) at room temperature was added dropwise a solution of TMPZnCl·LiCl[22] (1.04 M THF solution; 2.4 mmol). After 2 h at room temperature, a solution of iodine (0.76 g, 3.0 mmol) in THF (3 mL) was added. The resulting mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) and extraction with AcOEt (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluent: hexanes-AcOEt 60:40) to afford **3-I** in 72% yield (0.37 g) as a whitish powder: mp 91-93 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, 1H, *J* = 8.5 and 4.2 Hz, H7), 8.28 (d, 1H, *J* = 4.5 Hz), 8.37 (dd, 1H, *J* = 8.4 and 1.6 Hz, H8), 8.53 (d, 1H, *J* = 4.5 Hz), 9.06 (dd, 1H, *J* = 4.2 and 1.6 Hz, H6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.4 (C, C-I), 125.5 (CH), 135.4 (CH), 138.4 (CH), 143.9 (C), 144.0 (C), 150.8 (CH), 152.2 (CH). These data are similar to those described previously.[22] Using procedure 3 led to both **3-I** (34% yield) and **4,8-diiodo-1,5-naphthyridine 3'-I**. The latter was isolated in 6% yield as a white powder: mp > 260 °C; IR (ATR): 491, 590, 630, 683, 851, 1031, 1079, 1167, 1210, 1257, 1325, 1358, 1376, 1398, 1459, 1578, 1695, 1957, 2851, 2921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, 2H, *J* = 4.5 Hz), 8.58 (d, 2H, *J* = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.6 (2C, C4 and C8), 136.4 (2CH, C3 and C7), 143.6 (2C), 151.5 (2CH, C2 and C6).

4-Morpholino-1,5-naphthyridine (3c).

A degassed sealed tube containing 4-iodo-1,5-naphthyridine (**3-I**; 96 mg, 0.375 mmol) and morpholine (0.195 mL, 2.25 mmol) in isopropanol (1 mL) was heated at 110 °C for 72 h. The cooled residue was poured onto brine and extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluent: AcOEt; R_f = 0.30) to afford **3c** in 70% yield (57 mg) as a white powder: mp 116-118 °C; IR (ATR): 1026, 1111, 1249, 1265, 1305, 1372, 1414, 1477, 1503, 1566, 1604, 2864, 2966, 3205, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68-3.71 (m, 4H, $2CH_2$), 3.97-4.01 (m, 4H, $2CH_2$), 6.84 (d, 1H, *J* = 5.1 Hz, H3), 7.55 (dd, 1H, *J* = 8.5 and 4.1 Hz, H7), 8.30 (dd, 1H, *J* = 8.5 and 1.8 Hz, H8), 8.68 (d, 1H, *J* = 5.1 Hz, H2), 8.81 (dd, 1H, *J* = 4.1 and 1.7 Hz, H6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1 ($2CH_2$), 66.9 ($2CH_2$), 109.0 (CH), 124.0 (CH), 138.0 (CH), 138.6 (C), 145.1 (C), 147.4 (CH), 151.5 (CH), 154.9 (C). HRMS (EI) *m/z* calcd for $C_{12}H_{13}N_3O$: 215.1059; found: 215.1055.

General procedure 3 for the preparation of 2-thienylzinc chloride or 2-benzothienylzinc chloride (insertion method A),[28] and subsequent amination.[17]

A dry and argon flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (0.30 g, 12.5 mmol), LiCl (0.32 g, 7.5 mmol) and THF (15 mL). The aromatic bromide (5.0 mmol) was added dropwise. If necessary, the Schlenk flask was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with an aqueous saturated NH_4Cl solution and/or iodine. Upon completion of the insertion, $ZnCl_2$ (1.0 M) solution (6.0 mL, 6.0 mmol) was added dropwise. The organozinc reagent was titrated using iodine solution (1.0 M in THF) before use in the amination reaction. A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with the *N*-benzoyloxy secondary amine (0.50 mmol) and THF (2 mL). To the mixture $CoCl_2$·2LiCl (50 µmol) was added as a 1.0 M solution in THF. Then, the prepared organozinc chloride (0.55 mmol) in THF was added dropwise. The solution was stirred for 2 h at room temperature and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h), the reaction was quenched with saturated aqueous NH_4Cl solution (1 mL) and the product was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

2-(Morpholino)benzothiophene (1c).

The general procedure 3 using 2-bromobenzothiophene (1.1 g) and *N*-(benzoyloxy)morpholine (0.10 g) gave **1c** (eluent: hexanes-AcOEt 90:10) in 96% yield (0.10 g) as a white powder: IR (ATR): 900, 1012, 1090, 1263, 1298, 1374, 1435, 1526, 1666, 2838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.24 (t, 4H, *J* = 4.9 Hz), 3.86 (t, 4H, *J* = 4.8 Hz), 6.23 (s, 1H, H3), 7.10 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.48 (d, 1H, *J* = 7.9 Hz), 7.61 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.1 ($2CH_2$), 66.4 ($2CH_2$), 99.6 (CH), 121.2 (CH), 121.7 (CH), 121.8 (CH), 124.7 (CH), 132.8 (C), 140.4 (C), 157.9 (C). These data are as reported previously.[10a] MS (EI, 70 eV) *m/z* (%) 69 (12), 89 (44), 121 (17), 133 (14), 134 (72), 147 (50), 160 (100), 161 (99), 219 (19); HRMS (EI) *m/z* calcd for $C_{12}H_{13}NOS$: 219.0718; found: 219.0711.

2-Morpholinothiophene (2c).

The general procedure 3 using 2-bromothiophene (0.82 g) and *N*-(benzoyloxy)morpholine (0.10 g) gave **2c** (eluent: hexanes-AcOEt 90:10) in 80% yield (68 mg) as a brown oil: IR (ATR): 928, 1028, 1090, 1208, 1269, 1293, 1374, 1443, 1466, 1528, 2853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.12-3.14 (m, 4H), 3.83-3.85 (m, 4H), 6.16 (dd, 1H, *J* = 3.7 and 1.4 Hz, H3), 6.64 (dd, 1H, *J* = 5.2 and 1.1 Hz, H5), 6.80 (dd, 1H, *J* = 5.4 and 3.8 Hz, H4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.2 ($2CH_2$), 66.7 ($2CH_2$), 105.9 (CH), 113.1 (CH), 126.4 (CH), 159.5 (C). These data are as reported previously.[57] MS (EI, 70 eV) *m/z* (%) 110 (33), 111 (61), 154 (11), 169 (100); HRMS (EI) *m/z* calcd for $C_8H_{11}NOS$: 169.0561; found: 169.0554.

2-[Di(2-methoxyethyl)amino]thiophene (2e).

The general procedure 3 using 2-bromothiophene (0.82 g) and *N*-(benzoyloxy)di(2-methoxyethyl)amine (0.13 g) gave **2e** (eluent: hexanes-AcOEt 90:10) in 52% yield (56 mg) as a brown oil: IR (ATR): 1012, 1100, 1185, 1360, 1446, 1533, 1639, 2922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 6H, OMe), 3.49 (td, 4H, *J* = 5.8 and 0.7 Hz, CH_2), 3.57 (td, 4H, *J* = 5.8 and 0.85 Hz, CH_2), 5.90 (dd, 1H, *J* = 3.7 and 1.3 Hz, H3), 6.42 (dd, 1H, *J* = 5.4 and 1.4 Hz, H5), 6.75 (dd, 1H, *J* = 5.5 and 3.7 Hz, H4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 54.3 ($2CH_2$), 59.1 ($2CH_3$), 70.2 ($2CH_2$), 102.3 (CH), 109.3 (CH), 126.7 (CH), 157.3 (C); MS (EI, 70 eV) *m/z* (%) 112 (10), 138 (12), 170 (100), 215 (31); HRMS (EI) *m/z* calcd for $C_{10}H_{17}NO_2S$: 215.0980; found: 215.0974.

2-[8-(1,4-Dioxa-8-azaspiro[4.5]decyl)]thiophene (2f).

The general procedure 3 using 2-bromothiophene (0.82 g) and *N*-(benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane (0.13 g) gave **2f** (eluent: hexanes-AcOEt 90:10) in 78% yield (88 mg) as a brown oil: IR (ATR): 1035, 1100, 1141, 1226, 1363, 1454, 1527, 2955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (t, 4H, *J* = 5.9 Hz), 3.28 (t, 4H, *J* = 5.8 Hz), 3.98 (s, 4H, OCH_2CH_2O), 6.12 (dd, 1H, *J* = 3.8 and 1.4 Hz, H3), 6.59 (dd, 1H, *J* = 5.5 and 1.4 Hz, H5), 6.76 (dd, 1H, *J* = 5.5 and 3.8 Hz, H4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.2 ($2CH_2$), 50.5 ($2CH_2$), 64.5 ($2CH_2$), 106.1 (CH), 106.8 (C, C5'), 112.5 (CH), 126.2 (CH), 159.1 (C); MS (EI, 70 eV) *m/z* (%) 110 (25), 111 (67), 138 (21), 164 (13), 180 (12), 225 (100), 226 (11); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO_2S$: 225.0823; found: 225.0816.

General procedure 4 for the preparation of 2-thiazolylzinc chloride or 2-benzothiazolylzinc chloride (exchange method B),[29] and subsequent amination.[17]

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with iPrMgCl·LiCl (1.0 mL, 1.05 mmol, 1.05 M in THF). The neat aryl bromide (1.0 mmol) was added at room temperature. The reaction mixture was stirred for 0.5 h, and the completion of the Br/Mg exchange was checked by GC-analysis using tetradecane as internal standard. Upon completion of the exchange, $ZnCl_2$ (1.0 M) solution (1.2 mL, 1.2 mmol) was added dropwise. The organozinc reagent was titrated using iodine solution (1.0 M in THF) before use in the amination reaction. A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with the *N*-benzoyloxy secondary amine (0.50 mmol) and THF (2 mL). To the mixture $CoCl_2$·2LiCl (50 µmol) was added as a 1.0 M solution in THF. Then, the prepared organozinc chloride (0.55 mmol) in THF was added dropwise. The solution was stirred for 2 h at room temperature and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h), the reaction was quenched with saturated aqueous NH_4Cl solution (1 mL) and the product was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

2-Morpholinothiazole (4c).

The general procedure 4 using 2-bromothiazole (0.16 g) and *N*-(benzoyloxy)morpholine (0.10 g) gave **4c** (eluent: hexanes-AcOEt 90:10) in 76% yield (65 mg) as a brown oil: IR (ATR): 905, 1034, 1140, 1229, 1270, 1373, 1447, 1511, 2852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.46-3.48 (m, 4H), 3.81-3.83 (m, 4H), 6.60 (d, 1H, *J* = 3.6 Hz), 7.22 (d, 1H, *J* = 3.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 48.9 ($2CH_2$), 66.1 ($2CH_2$), 108.1 (CH), 139.8 (CH), 172.6 (C). These data are as reported previously.[58] MS (EI, 70 eV) *m/z* (%) 58 (18), 85 (49), 86 (15), 99 (14), 100 (33), 101 (11), 111 (19), 112 (34), 113 (88), 125 (32), 126 (13), 139 (42), 151 (12), 155 (20), 168 (22), 169 (23), 170 (100); HRMS (EI) *m/z* calcd for $C_7H_{10}N_2OS$: 170.0514; found: 170.0506.

2-[Di(2-methoxyethyl)amino]benzothiazole (5e).

The general procedure 4 using 2-bromobenzothiazole (0.21 g) and *N*-(benzoyloxy)di(2-methoxyethyl)amine (0.13 g) gave **5e** (eluent: hexanes-AcOEt 90:10) in 56% yield (74 mg) as a yellow oil: IR (ATR): 749, 1111, 1309, 1442, 1549, 1560, 1702, 2875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 6H, OMe), 3.70 (t, 4H, *J* = 5.5 Hz), 3.82 (t, 4H, *J* = 5.5 Hz), 7.04 (ddd, 1H, *J* = 7.8, 7.3 and 1.2 Hz), 7.27 (ddd, 1H, *J* = 8.6, 7.4 and 1.3 Hz), 7.53 (ddd, 1H, *J* = 8.1, 1.0 and 0.4 Hz), 7.59-7.61 (ddd, 1H, *J* = 7.8, 1.2 and 0.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.3 ($2CH_2$), 59.3 ($2CH_3$), 70.8 ($2CH_2$), 119.1 (CH), 120.9 (CH), 121.3 (CH), 126.2 (CH), 131.1 (C), 153.4 (C), 168.2 (C). These data are as reported previously.[59] MS (EI, 70 eV) *m/z* (%) 136 (16), 150 (21), 163 (100), 178 (25), 191 (43), 208 (36), 221 (20); HRMS (EI) *m/z* calcd for $C_{13}H_{18}N_2O_2S$: 266.1089; found: 266.1079.

2-[8-(1,4-Dioxa-8-azaspiro[4.5]decyl)]benzothiazole (5f).

The general procedure 4 using 2-bromobenzothiazole (0.21 g) and *N*-(benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane (0.13 g) gave **5f** (eluent: hexanes-AcOEt 90:10) in 88% yield (0.12 g) as a yellow oil: IR (ATR): 922, 1099, 1291, 1446, 1543, 1595, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (t, 4H, *J* = 5.9 Hz), 3.75 (dd, 4H, *J* = 6.6 and 5.1 Hz), 4.02 (s, 4H, OCH_2CH_2O), 7.06 (td, 1H, *J* = 7.6 and 1.1 Hz), 7.28 (ddd, 1H, *J* = 8.5, 7.4 and 1.3 Hz), 7.54 (dd, 1H, *J* = 8.1 and 0.6 Hz), 7.58-7.60 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.7 ($2CH_2$), 47.1 ($2CH_2$), 64.8 ($2CH_2$), 107.2 (C, C5'), 119.3 (CH), 121.0 (CH), 121.7 (CH), 126.3 (CH), 131.3 (C), 153.2 (C), 168.6 (C). These data are as reported previously.[60] MS (EI, 70 eV) *m/z* (%) 99 (20), 108 (14), 134 (12), 135 (46), 136 (12), 149 (59), 161 (13), 162 (13), 163 (77), 175 (89), 176 (39), 177 (25), 189 (12), 203 (12), 207 (16), 276 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{16}N_2O_2S$: 276.0932; found: 276.0922.

2-(1-Azepanyl)benzothiazole (5g).

The general procedure 4 using 2-bromobenzothiazole (0.21 g) and *N*-(benzoyloxy)azepane (0.11 g) gave **5g** (eluent: hexanes-AcOEt 90:10) in 89% yield (0.10 g) as a yellow oil: IR (ATR): 748, 1249, 1299, 1359, 1441, 1560, 2923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61-1.64 (m, 4H), 1.85-1.91 (m, 4H), 3.69 (t, 4H, *J* = 6.0 Hz), 7.03 (td, 1H, *J* = 7.6 and 1.1 Hz), 7.28 (ddd, 1H, *J* = 8.2, 7.4 and 1.3 Hz), 7.55 (ddd, 1H, *J* = 8.0, 1.0 and 0.4 Hz), 7.59 (ddd, 1H, *J* = 7.8, 1.2 and 0.4 Hz)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.9 ($2CH_2$), 28.2 ($2CH_2$), 51.1 ($2CH_2$), 118.7 (CH), 120.7 (CH), 120.9 (CH), 126.2 (CH), 130.9 (C), 153.7 (C), 168.5 (C). These data are as reported previously.[61] MS (EI, 70 eV) *m/z* (%) 98 (11), 135 (17), 136

(31), 149 (38), 150 (49), 162 (23), 163 (46), 175 (37), 177 (14), 189 (65), 199 (23), 203 (18), 217 (27), 232 (100), 233 (14); HRMS (EI) *m/z* calcd for $C_{13}H_{16}N_2S$: 232.1034; found: 232.1030.

General procedure 5 for the preparation of 5-(2-thienyl)-2-thienylzinc chloride or 2-(thieno[3,2-*b*]thienyl)zinc chloride (deprotometalation)[31] and subsequent amination.[17]

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirrer and a septum, was charged with the starting bithiophene or thienothiophene (0.50 mmol) in THF (approximately 1.0 M solution) at room temperature. A solution of TMPMgCl·LiCl (0.55 mmol) in THF was added dropwise and the reaction mixture stirred for 1 h (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF). Upon completion of the deprotonation, $ZnCl_2$ (1.0 M) solution (0.60 ml, 0.60 mmol) was added dropwise. The organozinc reagent was titrated using iodine solution (1.0 M in THF) before use in the amination reaction. A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with the *N*-benzoyloxy secondary amine (0.50 mmol) and THF (about 2 mL). $CoCl_2$·2LiCl (50 µmol; 1.0 M solution in THF) and TMEDA (15 µL, 0.10 mmol) were added to the mixture. Then, the prepared organozinc chloride (0.55 mmol) in THF was added dropwise. The solution was stirred for 2 h at room temperature and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h), the reaction was quenched with saturated aqueous NH_4Cl solution (1 mL) and the product was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

5-Morpholino-2,2'-bithiophene (6c).

The general procedure 5, but without TMEDA, using 2,2'-bithiophene (83 mg) and *N*-(benzoyloxy)morpholine (0.10 g) gave **6c** (eluent: hexanes-AcOEt 90:10) in 72% yield (90 mg) as a yellow powder: IR (ATR): 899, 1115, 1296, 1450, 1535, 1594, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.15-3.16 (m, 4H), 3.85-3.87 (m, 4H), 6.08 (d, 1H, *J* = 3.9 Hz), 6.88 (d, 1H, *J* = 3.7 Hz), 6.96 (dd, 1H, *J* = 5.1 and 3.6 Hz, H4'), 6.99 (dd, 1H, *J* = 3.6 and 1.2 Hz, H3'), 7.11 (dd, 1H, *J* = 5.0 and 1.3 Hz, H5'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.6 ($2CH_2$), 66.6 ($2CH_2$), 106.0 (CH), 122.1 (CH), 123.1 (CH), 123.2 (CH), 124.6 (C), 127.9 (CH), 138.5 (C), 158.5 (C). These data are as reported previously.[62] MS (EI, 70 eV) *m/z* (%) 121 (16), 179 (12), 191 (38), 193 (77), 251 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{13}NOS_2$: 251.0439; found: 251.0435.

2-(Morpholino)thieno[3,2-*b*]thiophene (7c).

The general procedure 5 using thieno[3,2-*b*]thiophene (70 mg) and *N*-(benzoyloxy)morpholine (0.10 g) gave **7c** (eluent: hexanes-CH_2Cl_2 80:20) in 92% yield (0.10 g) as a white powder: IR (ATR): 925, 1100, 1217, 1261, 1374, 1442, 1509, 2831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.16-3.18 (m, 4H), 3.85-3.88 (m, 4H), 6.37 (s, 1H), 7.10 (d, 1H, *J* = 5.2 Hz), 7.12 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.1 ($2CH_2$), 66.4 ($2CH_2$), 99.5 (CH), 119.6 (CH), 122.8 (CH), 128.6 (C), 138.1 (C), 160.1 (C). MS (EI, 70 eV) *m/z* (%) 69 (10), 122 (12), 139 (10), 140 (46), 153 (23), 166 (47), 167 (99), 207 (13), 223 (16), 225 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{11}NOS_2$: 225.0282; found: 225.0276.

2-[8-(1,4-Dioxa-8-azaspiro[4.5]decyl)]thieno[3,2-*b*]thiophene (7f).

The general procedure 5 using thieno[3,2-*b*]thiophene (70 mg) and *N*-(benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane (0.13 g) gave **7f** (eluent: hexanes-CH_2Cl_2 80:20) in 85% yield (0.12 g) as a green powder: IR (ATR): 1066, 1115, 1297, 1442, 1520, 2926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (t, 4H, *J* = 5.9 Hz), 3.32 (t, 4H, *J* = 5.8 Hz), 4.00 (s, 4H, OCH_2CH_2O), 6.32 (s, 1H), 7.08 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.2 ($2CH_2$), 50.4 ($2CH_2$), 64.6 ($2CH_2$), 98.9 (CH), 106.8 (C, C5'), 119.6 (CH), 121.9 (CH), 128.2 (C), 138.4 (C), 160.7 (C); MS (EI, 70 eV) *m/z* (%) 140 (22), 166 (20), 167 (100), 207 (38), 209 (21), 225 (48), 281 (34); HRMS (EI) *m/z* calcd for $C_{13}H_{15}NO_2S_2$: 281.0544; found: 281.0537.

2-[2-(1,2,3,4-tetrahydroisoquinolyl)]thieno[3,2-*b*]thiophene (7h).

The general procedure 5 using thieno[3,2-*b*]thiophene (70 mg) and *N*-(benzoyloxy)-1,2,3,4-tetrahydroisoquinoline (0.13 g) gave **7h** (eluent: hexanes-CH_2Cl_2 80:20) in 88% yield (0.12 g) as a green powder: IR (ATR): 928, 1196, 1380, 1454, 1519, 2831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04 (t, 2H, *J* = 6.0 Hz), 3.54 (t, 2H, *J* = 6.0 Hz), 4.41 (s, 2H, H1'), 6.40 (s, 1H), 7.08 (d, 1H, *J* = 5.2 Hz), 7.11 (d, 1H, *J* = 5.2 Hz), 7.14-7.23 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.8 (CH_2), 49.6 (CH_2), 53.1 (CH_2), 97.9 (CH), 119.6 (CH), 121.8 (CH), 126.3 (CH), 126.5 (CH), 126.7 (CH), 127.6 (C), 128.9 (CH), 133.1 (C), 134.0 (C), 138.6 (C), 160.1 (C); MS (EI, 70 eV) *m/z* (%) 73 (13), 77 (12), 78 (15), 88 (11), 91 (16), 103 (16), 104 (58), 115 (24), 117 (49), 139 (17), 166 (68), 270 (30), 271 (100), 272 (21), 273 (13), 277 (22); HRMS (EI) *m/z* calcd for $C_{15}H_{13}NS_2$: 271.0489; found: 271.0498. This compound is quite instable in $CDCl_3$.

General procedure 6 for the preparation of 2-thiooxo-4-(1,3-dithiolyl)zinc chloride (deprotometalation),[32] and subsequent amination.[17]

A dry and argon flushed Schlenk flask was charged with a solution of 1,3-dithiole-2-thione (0.50 mmol) in anhydrous THF (approximately 0.5 M solution). A solution of TMPMgCl·LiCl (0.55 mmol) in THF was added dropwise at –78 °C and the mixture was stirred at this temperature for 0.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with I_2. Upon completion of the deprotonation, a $ZnCl_2$ (0.60 mL, 0.60 mmol) solution (1.0 M in THF) was added dropwise. The organozinc reagent was titrated using iodine solution (1.0 M in THF) before use in the amination reaction. A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with the *N*-benzoyloxy secondary amine (0.50 mmol) and THF (about 2 mL). $CoCl_2$·2LiCl (50 µmol; 1.0 M solution in THF) and TMEDA (15 µL, 0.10 mmol) were added to the mixture. Then, the prepared organozinc chloride (0.55 mmol) in THF was added dropwise. The solution was stirred for 2 h at room temperature and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h), the reaction was quenched with saturated aqueous NH_4Cl solution (1 mL) and the product was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

4-Morpholino-1,3-dithiole-2-thione (8c).

The general procedure 6 using *N*-(benzoyloxy)morpholine (0.10 g) gave **8c** (eluent: hexanes-AcOEt 90:10) in 73% yield (80 mg) as a yellow powder: IR (ATR): 867, 1000, 1111, 1214, 1273, 1375, 1442, 1531, 2834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.07-3.10 (m, 4H), 3.79-3.81 (m, 4H), 5.63 (s, 1H, H5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.0 ($2CH_2$), 66.1 ($2CH_2$), 98.8 (CH, C5), 155.2 (C, C4), 207.9 (C, C=S); MS (EI, 70 eV) *m/z* (%) 48

(27), 49 (100), 50 (12), 52 (25), 60 (15), 73 (11), 75 (14), 84 (30), 115 (11), 143 (31); HRMS (EI) *m/z* calcd for $C_7H_9NOS_3$: 219.9846; found: 219.9902.

4-[Di(2-methoxyethyl)amino]-1,3-dithiole-2-thione (8e).

The general procedure 6 using *N*-(benzoyloxy)di(2-methoxyethyl)amine (0.13 g) gave **8e** (eluent: hexanes-AcOEt 90:10) in 95% yield (0.13 g) as a red oil: IR (ATR): 942, 1054, 1099, 1363, 1455, 1534, 2978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 6H, OMe), 3.43 (t, 4H, *J* = 6.0 Hz), 3.54 (t, 4H, *J* = 6.0 Hz), 5.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.9 ($2CH_2$), 59.2 ($2CH_3$), 70.1 ($2CH_2$), 93.1 (CH, C5), 153.6 (C, C4), 206.7 (C, C=S); MS (EI, 70 eV) *m/z* (%) 76 (100), 78 (10), 207 (13), 225 (11); HRMS (EI) *m/z* calcd for $C_9H_{15}NO_2S_3$: 265.0265; found: 265.0264.

4-[8-(1,4-Dioxa-8-azaspiro[4.5]decyl)]-1,3-dithiole-2-thione (8f).

The general procedure 6 using *N*-(benzoyloxy)-1,4-dioxa-8-azaspiro[4.5]decane (0.13 g) gave **8f** (eluent: hexanes-AcOEt 90:10) in 98% yield (0.13 g) as a yellow powder: IR (ATR): 920, 1022, 1099, 1145, 1365, 1455, 1532, 2950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (t, 4H, *J* = 5.9 Hz, $2CH_2$), 3.20 (t, 4H, *J* = 5.9 Hz, $2CH_2$), 3.94 (s, 4H, OCH_2CH_2O), 5.55 (s, 1H, H5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 33.9 ($2CH_2$), 49.5 ($2CH_2$), 64.6 ($2CH_2$), 98.5 (CH, C5), 106.0 (C, C5'), 155.1 (C, C4), 208.2 (C, C=S); MS (EI, 70 eV) *m/z* (%) 43 (100), 45 (14), 61 (19), 70 (14), 98 (13), 275 (50); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO_2S_3$: 275.0108; found: 275.0100.

4-[2-(1,2,3,4-tetrahydroisoquinolyl)]-1,3-dithiole-2-thione (8h).

The general procedure 6 using *N*-(benzoyloxy)-1,2,3,4-tetrahydroisoquinoline (0.13 g) gave **8h** (eluent: hexanes-AcOEt 90:10) in 96% yield (0.13 g) as a yellow powder: IR (ATR): 842, 1038, 1179, 1381, 1448, 1532, 2921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98 (t, 2H, *J* = 5.5 Hz), 3.46 (t, 2H, *J* = 6.0 Hz), 4.33 (s, 2H, H1'), 5.57 (s, 1H, H5), 7.11 (dd, 1H, *J* = 5.2 and 3.6 Hz), 7.16 (dd, 1H, *J* = 5.3 and 3.8 Hz), 7.20-7.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.6 (CH_2), 49.1 (CH_2), 52.0 (CH_2), 96.3 (CH, C5), 126.4 (CH), 126.7 (CH), 127.2 (CH), 128.9 (CH), 131.9 (C), 133.5 (C), 154.3 (C, C4), 207.5 (C, C=S); MS (EI, 70 eV) *m/z* (%) 42 (42), 75 (11), 91 (16), 103 (12), 104 (15), 115 (24), 117 (81), 118 (18), 132 (14), 156 (21), 188 (57), 189 (15), 265 (100), 267 (14); HRMS (EI) *m/z* calcd for $C_{12}H_{11}NS_3$: 265.0054; found: 265.0048.

Methyl 3-(phenylamino)-2-thiophenecarboxylate (9a).

To iodobenzene (0.11 mL, 1.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 3-amino-2-thiophenecarboxylate (0.16 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (eluent: hexanes-AcOEt 95:5; R_f = 0.525) afforded **5a** in 79% yield (0.18 g) as a yellow powder: mp 68 °C (lit.[35a] 66-67 °C); IR (ATR): 692, 754, 772, 1090, 1226, 1254, 1394, 1418, 1435, 1566, 1593, 1667, 2948, 3309 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H, OMe), 7.06 (t, 1H, *J* = 7.4 Hz, H4'), 7.10 (d, 1H, *J* = 5.5 Hz, H4), 7.18 (d, 2H, *J* = 7.7 Hz, H2' and H6'), 7.33 (t, 2H, *J* = 7.7 Hz, H3' and H5'), 7.35 (d, 1H, *J* = 5.3 Hz, H5), 8.80 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5 (CH_3), 103.0 (C, C2), 118.0 (CH), 120.3 (2CH, C2' and C6'), 123.1 (CH), 129.4 (2CH, C3' and C5'), 131.8 (CH, C4), 141.5 (C, C1'), 151.5 (C, C3), 165.2 (C, C=O). These data are similar to those described previously.[35a]

General procedure 7 for the bis-*N*-arylation of methyl 3-amino-2-thiophenecarboxylate using the same iodide.

To the required iodide (2.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 3-amino-2-thiophenecarboxylate (0.16 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3 x 10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

Methyl 3-(diphenylamino)-2-thiophenecarboxylate (10a).

The general procedure 7 using iodobenzene (0.22 mL) gave **10a** (eluent: hexanes-AcOEt 95:5; R_f = 0.35) in 88% yield (0.27 g) as a yellow oil; IR (ATR): 503, 583, 637, 674, 694, 754, 776, 853, 951, 1041, 1074, 1094, 1175, 1226, 1253, 1394, 1418, 1438, 1481, 1524, 1567, 1592, 1667, 1714, 2950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H, OMe), 6.81 (d, 1H, *J* = 5.3 Hz, H4), 7.00 (t, 2H, *J* = 7.2 Hz, H4'), 7.04 (d, 4H, *J* = 8.1 Hz, H2' and H6'), 7.23 (t, 4H, *J* = 7.8 Hz, H3' and H5'), 7.42 (d, 1H, *J* = 5.3 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7 (CH_3), 121.1 (C, C2), 122.7 (4CH, C2' and C6'), 122.9 (2CH, C4'), 128.6 (CH), 129.1 (4CH, C3' and C5'), 130.3 (CH), 147.7 (2C, C1'), 149.8 (C, C3), 161.3 (C, C=O). HRMS (EI) *m/z* calcd for $C_{18}H_{15}NO_2S$: 309.0823; found: 309.0820.

Methyl 3-(di(3-thienyl)amino)-2-thiophenecarboxylate (10d).

The general procedure 7 using 3-iodothiophene (0.20 mL) gave **10d** (eluent: hexanes-AcOEt 90:10; R_f = 0.52) in 87% yield (0.28 g) as a yellow oil; IR (ATR): 605, 626, 649, 726, 749, 761, 841, 914, 986, 1042, 1073, 1099, 1151, 1188, 1214, 1297, 1375, 1401, 1423, 1437, 1520, 1692, 1713, 2947, 3105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H, OMe), 6.58 (dd, 2H, *J* = 3.1 and 1.2 Hz, H2'), 6.86 (dd, 2H, *J* = 5.2 and 1.2 Hz, H4'), 6.88 (d, 1H, *J* = 5.6 Hz, H4), 7.18 (dd, 2H, *J* = 5.2, 3.2 Hz, H5'), 7.40 (d, 1H, *J* = 5.3 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8 (CH_3), 109.7 (2CH), 120.0 (C), 123.3 (2CH), 124.8 (2CH), 127.3 (CH), 130.2 (CH), 146.8 (2C, C3'), 149.9 (C), 161.4 (C, C=O). HRMS (EI) *m/z* calcd for $C_{14}H_{11}NO_2S_3$: 320.9952; found: 320.9957. **Methyl 3-(3-thienylamino)-2-thiophenecarboxylate (9d)** was similarly isolated (eluent: hexanes-AcOEt 90:10; R_f = 0.575) in <10% yield as a yellow oil: IR (ATR): 455, 584, 610, 722, 770, 840, 958, 1035, 1083, 1238, 1350, 1402, 1424, 1444, 1556, 1571, 1661, 2949, 3103, 3330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H, OMe), 6.82 (dd, 1H, *J* = 3.2, 1.4 Hz, H2'), 6.95 (dd, 1H, *J* = 5.2, 1.4 Hz, H4'), 7.03 (d, 1H, *J* = 5.5 Hz, H4), 7.27 (dd, 1H, *J* = 5.1, 3.1 Hz, H5'), 7.36 (d, 1H, *J* = 5.5 Hz, H5), 8.75 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5 (CH_3), 102.0 (C), 109.1 (CH), 118.0 (CH), 123.4 (CH), 125.5 (CH), 132.1 (CH), 140.4 (C), 152.4 (C), 165.3 (C).

General procedure 8 for the *N*-arylation of methyl 3-(phenylamino)-2-thiophenecarboxylate (9a).

To the required iodide (1.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 3-(phenylamino)-2-thiophenecarboxylate (**9a**, 0.23 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was

added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3 x 10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

Methyl *N*-(4-methoxyphenyl)-*N*-phenyl-3-amino-2-thiophenecarboxylate (10ab). The general procedure 8 using 4-iodoanisole (0.23 g) gave **10ab** (eluent: hexanes-AcOEt 95:5; R_f = 0.27) in 91% yield (0.31 g) as a yellow powder: mp 122 °C; IR (ATR): 665, 693, 720, 747, 769, 779, 789, 805, 836, 1026, 1041, 1073, 1098, 1225, 1247, 1258, 1442, 1489, 1505, 1594, 1709, 2922, 2957 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.77 (d, 1H, *J* = 5.4 Hz, H4), 6.81 (d, 2H, *J* = 9.0 Hz), 6.90-6.95 (m, 3H, H2', H4' and H6'), 7.03 (d, 2H, *J* = 8.9 Hz), 7.19 (t, 2H, *J* = 7.9 Hz, H3' and H5'), 7.39 (d, 1H, *J* = 5.4 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7 (CH_3), 55.6 (CH_3), 114.6 (2CH), 119.9 (C), 121.1 (2CH), 122.0 (CH), 125.8 (2CH), 128.3 (CH), 129.0 (2CH), 130.2 (CH), 140.8 (C), 148.6 (C), 150.2 (C), 156.3 (C), 161.3 (C); HRMS (EI) *m/z* calcd for $C_{19}H_{17}NO_3S$: 339.0929; found: 339.0926. **Crystal data for 10ab.** $C_{19}H_{17}NO_3S$, M = 339.39, triclinic, *P* -1, *a* = 9.2351(10), *b* = 9.7922(11), *c* = 9.9542(11) Å, *α* = 102.222(4), *β* = 96.641(4), *γ* = 108.875(4) °, *V* = 815.80(16) $Å^3$, *Z* = 2, *d* = 1.382 g cm^{-3}, *μ* = 0.215 mm^{-1}. A final refinement on F^2 with 3725 unique intensities and 219 parameters converged at $\omega R(F^2)$ = 0.0824 ($R(F)$ = 0.0333) for 3289 observed reflections with $I > 2\sigma(I)$. CCDC 1896368.

Methyl *N*-phenyl-*N*-(4-(trifluoromethyl)phenyl)-3-amino-2-thiophenecarboxylate (10ac). The general procedure 8 using 1-iodo-4-(trifluoromethyl)benzene (0.15 mL) gave **10ac** (eluent: hexanes-AcOEt 95:5; R_f = 0.40) in 94% yield (0.35 g) as a yellow oil: IR (ATR): 508, 522, 611, 646, 684, 698, 732, 749, 769, 838, 951, 1011, 1040, 1066, 1110, 1161, 1183, 1226, 1279, 1297, 1316, 1396, 1438, 1490, 1515, 1528, 1591, 1614, 1715, 2951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H, OMe), 6.87 (d, 1H, *J* = 5.3 Hz, H4), 7.03 (d, 2H, *J* = 8.5 Hz), 7.09-7.15 (m, 3H), 7.31 (t, 2H, *J* = 7.8 Hz, H3' and H5'), 7.45 (d, 2H, *J* = 8.6 Hz), 7.50 (d, 1H, *J* = 5.3 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8 (CH_3), 119.9 (2CH), 123.1 (C), 123.2 (q, C, *J* = 32.4 Hz, C4"), 124.2 (2CH), 124.5 (CH), 124.6 (q, C, *J* = 269 Hz, CF_3), 126.2 (q, 2CH, *J* = 3.7 Hz, C3" and C5"), 128.7 (CH), 129.4 (2CH), 130.9 (CH), 146.2 (C), 148.5 (C), 150.8 (d, C, *J* = 1.3 Hz), 160.9 (C). HRMS (EI) *m/z* calcd for $C_{19}H_{14}F_3NO_2S$: 377.0697; found: 377.0698.

Methyl 2-(phenylamino)-3-thiophenecarboxylate (11a). To iodobenzene (0.11 mL, 1.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 2-amino-3-thiophenecarboxylate (0.16 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3 x 10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (eluent: hexanes-AcOEt 95:5; R_f = 0.50) afforded **11a** in 83% yield (0.19 g) as a white powder: mp 64 °C (lit.[37] 59-60 °C); IR (ATR): 490, 503, 661, 684, 751, 782, 1012, 1084, 1154, 1193, 1241, 1337, 1382, 1407, 1440, 1498, 1509, 1553, 1592, 1670, 2948, 3213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H, OMe), 6.31 (d, 1H, *J* = 5.7 Hz), 7.07 (t, 1H, *J* = 7.1 Hz, H4'), 7.15 (d, 1H, *J* = 5.8 Hz), 7.31 (d, 2H, *J* = 7.6 Hz, H2' and H6'), 7.37 (t, 2H, *J* = 7.8 Hz, H3' and H5'), 9.91 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.3 (CH_3), 107.1 (CH), 107.5 (C), 118.2 (2CH), 122.9 (CH), 125.4 (CH), 129.5 (2CH), 140.9 (C), 158.5 (C), 166.4 (C). These data are similar to those described previously.[37]

General procedure 9 for the bis-*N*-arylation of methyl 2-amino-3-thiophenecarboxylate using the same iodide.

To the required iodide (2.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 2-amino-3-thiophenecarboxylate (0.16 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3 x 10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

Methyl 2-(diphenylamino)-3-thiophenecarboxylate (12a).

The general procedure 9 using iodobenzene (0.22 mL) gave **12a** (eluent: hexanes-AcOEt 95:5; R_f = 0.27) in 54% yield (0.17 g) as a yellow powder: mp 110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H, OMe), 6.98 (d, 1H, *J* = 5.9 Hz), 7.03 (t, 2H, *J* = 7.5 Hz, H4'), 7.08 (d, 4H, *J* = 7.9 Hz, H2' and H6'), 7.25 (t, 4H, *J* = 7.8 Hz, H3' and H5'), 7.33 (d, 1H, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.4 (CH_3), 120.1 (CH), 122.5 (4CH), 123.2 (2CH), 124.7 (C), 128.2 (CH), 129.1 (4CH), 147.9 (2C), 156.8 (C), 162.5 (C). HRMS (EI) *m/z* calcd for $C_{18}H_{15}NO_2S$: 309.0823; found: 309.0819.

Methyl 2-(di(3-thienyl)amino)-3-thiophenecarboxylate (12d).

The general procedure 9 using 3-iodothiophene (0.20 mL) gave **12d** (eluent: hexanes-AcOEt 90:10; R_f = 0.52) in 76% yield (0.24 g) as a yellow oil: IR (ATR): 472, 601, 630, 637, 668, 694, 734, 761, 782, 829, 836, 846, 871, 970, 997, 1072, 1083, 1129, 1148, 1185, 1237, 1256, 1285, 1383, 1395, 1453, 1522, 1537, 1695, 2949, 3104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H, OMe), 6.64 (d, 2H, *J* = 2.4 Hz, H2'), 6.89 (d, 2H, *J* = 5.2 Hz, H4'), 6.93 (d, 1H, *J* = 5.9 Hz), 7.18 (dd, 2H, *J* = 5.1 and 3.2 Hz, H5'), 7.32 (d, 1H, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.3 (CH_3), 109.9 (2CH), 119.4 (CH), 122.7 (2CH), 123.6 (C), 124.8 (2CH), 127.9 (CH), 146.7 (C), 156.5 (C), 162.2 (C). HRMS (EI) *m/z* calcd for $C_{14}H_{11}NO_2S_3$: 320.9952; found: 320.9948.

General procedure 10 for the *N*-arylation of methyl 2-(phenylamino)-3-thiophenecarboxylate (11a)

To the required iodide (1.0 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.20 mmol), methyl 2-(phenylamino)-3-thiophenecarboxylate (**11a**, 0.23 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The mixture was degassed and heated at 140 °C under argon for 24 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3 x 10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

Methyl *N*-(4-methoxyphenyl)-*N*-phenyl-2-amino-3-thiophenecarboxylate (12ab).

The general procedure 10 using 4-iodoanisole (0.23 g) gave **12ab** (eluent: hexanes-AcOEt 90:10; R_f = 0.25) in 86% yield (0.29 g) as a red oil: IR (ATR): 533, 570, 614, 632, 645, 694, 750, 823, 910, 1003, 1033, 1084, 1108, 1144, 1191, 1238, 1284, 1387, 1438, 1463, 1490, 1506, 1531, 1594, 1704, 2835, 2949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.55 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.86 (d, 2H, *J* = 8.9 Hz, H2" and H6"), 6.91

(d, 1H, *J* = 5.9 Hz), 6.95-6.99 (m, 3H), 7.15 (d, 2H, *J* = 8.9 Hz, H3" and H5"), 7.18-7.24 (m, 2H), 7.32 (d, 1H, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.2 (CH_3), 55.4 (CH_3), 114.5 (2CH), 119.3 (CH), 120.3 (2CH), 121.9 (CH), 123.4 (C), 125.8 (2CH), 128.0 (CH), 128.9 (2CH), 140.7 (C), 148.6 (C), 156.6 (C), 157.5 (C), 162.3 (C) ; HRMS (EI) *m/z* calcd for $C_{19}H_{17}NO_3S$: 339.0929; found: 339.0932.

Methyl *N*-(2-benzofuryl)-*N*-phenyl-2-amino-3-thiophenecarboxylate (12ae).

The general procedure 10 using 2-iodobenzofuran (0.24 g) gave **12ae** (eluent: hexanes-AcOEt 90:10; R_f = 0.425) in 53% yield (0.18 g) as an orange oil: IR (ATR): 486, 501, 692, 708, 744, 764, 828, 908, 971, 1006, 1084, 1105, 1153, 1152, 1211, 1248, 1281, 1342, 1389, 1437, 1452, 1492, 1536, 1582, 1709, 2949, 3062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H, OMe), 6.11 (s, 1H, H3"), 7.09 (d, 1H, *J* = 5.9 Hz), 7.11-7.22 (m, 5H), 7.31-7.39 (m, 3H), 7.42-7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6 (CH_3), 91.8 (CH), 110.7 (CH), 119.8 (CH), 121.1 (2CH), 121.2 (CH), 122.8 (CH), 123.1 (CH), 124.0 (CH), 125.9 (C), 128.2 (CH), 129.2 (2CH), 129.3 (C), 145.6 (C), 151.3 (C), 152.5 (C), 155.2 (C), 162.2 (C). HRMS (EI) *m/z* calcd for $C_{20}H_{15}NO_3S$: 349.0773; found: 349.0770.

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Key topic: Thiophene aminations

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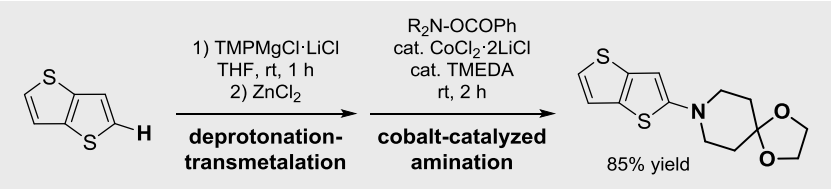

Both copper- and cobalt-catalyzed aminations of arylzincs using *N*-benzoyloxy amines are possible. Thus, thienylzincs prepared by transmetalation from thienylmagnesium halides obtained by various methods including deprotometalation were aminated with success. In addition, triarylamines were prepared from aminothiophenes by consecutive copper-catalyzed *N*-arylations using iodoarenes.

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Copper- and Cobalt-Catalyzed Syntheses of Thiophene-Based Tertiary Amines