CH functionalization of heteroaromatic compounds by transition metal catalysis

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Abstract. Transition metal-catalyzed CH functionalization of thiazoles and thiophenes are carried out. The reaction of thiophene with aryl halide in the presence of a palladium catalyst underwent the CC bond forming reaction at the CH bond of thiophene. By employing the reaction head-to-tail-type oligothiophene is synthesized in a stepwise manner. When several azoles are treated with secondary amines and amides in the presence of a copper catalyst, oxidative CH-NH coupling took place to form the carbon-nitrogen bond.

1. Introduction
CH functionalization by forming a carbon-carbon or carbon-heteroatom bond attracts considerable attention in organic synthesis recently. The advantage of the CH functionalization is the simplicity of the total process. Although the related reaction such as the cross coupling of main group organometallics with organic halides furnishes the similar product, the metallic species such as Grignard, boron, silicon, and tin have to be prepared with the corresponding compound bearing CX or CH moiety. We have been engaged in the development of coupling reactions at the CH bond of several heteroaromatic compounds such as thiazoles and thiophenes and shown that CH coupling of thiazole at the 2-position, which is the functionalization of acidic CH bond, takes place to afford the corresponding arylated product by Pd/Cu catalyst system. It is also shown to undergo by the catalysis of palladium the coupling at the electron enriched carbon such as the 5-position of thiazole or the carbon atom of thiophenes adjacent to the sulfur atom. In addition, oxidative homocoupling of thiophenes and thiazoles (5-position) at the CH bond is shown to occur in the presence of a palladium catalyst leading to the corresponding bithiazoles and bithiophenes. Worthy of note in the CH cross coupling and homocoupling is that the tolerance of the carbon-bromine bond on the heteroaromatic ring to remain the halogen bond after the reaction and thereby allows the obtained coupling product toward further transformation reactions. Accordingly, when the reaction of an organohalogen compound bearing both carbon-bromine and carbon-iodine bonds is designed for CH functionalization, the reaction takes place only at the carbon-iodine bond, while the carbon-bromine bond remains. If it is possible to transform the bromo group into iodide, the product can be subjected to another CH functionalization reaction.
On the other hand, introduction of heteroatoms into heteroaromatic compound also attracts considerable attention since a wide range of heteroaromatic molecules bearing a heteroatom substituents are found biologically active compounds and advanced organic materials. Transition metal catalysis is a powerful tool for the preparation of such compounds because substitution reaction at the sp$^2$ carbon-halogen bond with amines and other heteroatoms is established by Buchwald, Hartwig, and Koie. By contrast, CH functionalization of heteroaromatic compounds with heteroatom is still an unexploited area and no example of CH-NH coupling of azoles has not been shown so far to the best of our knowledge.

Herein, we describe our recent progress on the CH functionalization reactions, which involves a new strategy to constitute iterative thiophene-thiophene unit with palladium-catalyzed CH coupling reaction and oxidative amination of azoles via CH-NH coupling catalyzed by a copper(II) salt.

2. Results and discussion

2.1. Oligothiophene synthesis with iterative CH functionalization and halogen exchange

Since carbon-bromine bond is completely intact under the conditions of the palladium-catalyzed CH coupling reactions we have developed, the reaction of 2-bromothiophene at the CH bond with the carbon-iodine bond of another thiophene would induce CH-CI coupling, while carbon-bromine bond is intact. We envisaged the reaction of 2-bromo-3-hexylthiophene with a 5-substituted 3-hexyl-2-iodothiophene in the presence of AgNO$_3$/KF and palladium catalyst leading to the head-to-tail-type bithiophene. If it is possible to undergo halogen exchange of the produced bromide into the corresponding iodide, the product would be subjected to the further CH coupling reaction. Iterative CH coupling and halogen exchange sequence would lead to oligothiophenes in a stepwise manner, accordingly. The synthetic strategy is illustrated in Scheme 1.

![Scheme 1](image-url)
reaction occurred in a reasonable yield after optimization of conditions, it was found that complete conversion of bromide into iodide was not achieved. Since the difficulty of the separation of iodide from the corresponding bromide by chromatography, the reaction would not be employed for the iterative oligothiophene synthesis. After screening the reaction conditions we found that the use of excess amount of CuI at the elevated temperature shown by Yamashita allowed to show the superior conversion. A higher conversion (88%) was achieved when the reaction was carried out at 150 ºC for 8 h under heterogeneous conditions employing 10 equiv of CuI. The reaction with a mixture of CuI (5 eq) and LiI (5 eq), which allows the reaction in DMSO in a homogeneous manner, afforded the corresponding iodide in 94% conversion. Almost complete conversion was achieved by employing CuI and LiI (10 equiv each). The results are summarized in Table 1.

| entry | CuI/ eq | Mi (eq) | solvent | temp/ ºC | time/ h | %conv. |
|-------|---------|---------|---------|----------|--------|--------|
| 1     | 0.1     | NaI (3) | 1,4-dioxane | 110      | 24     | 78     |
| 2     | 5.0     | -       | DMSO    | 150      | 2      | 81     |
| 3     | 10.0    | -       | DMSO    | 150      | 8      | 88     |
| 4     | 1.0     | LiI (4) | DMSO    | 100      | 4      | 14     |
| 5     | 5.0     | LiI (5) | DMSO    | 100      | 4      | 9      |
| 6     | 5.0     | LiI (5) | DMSO    | 150      | 25     | 94     |
| 7     | 10.0    | LiI (10)| DMSO    | 150      | 25     | 97     |
| 8     | 2       | LiI (8) | DMSO    | 150      | 13     | 64     |
| 9     | 1       | LiI (9) | DMSO    | 150      | 13     | 33     |

* The reaction was carried out under a nitrogen atmosphere. Progress of the reaction was monitored by GC analysis of the reaction mixture.

With the optimum halogen exchange reaction condition in hand, stepwise reaction leading to a head-to-tail oligothiophene was performed with CH coupling/halogen exchange sequence. The reaction of 2 with ethyl 4-iodobenzoate (6) in the presence of a palladium catalyst and AgNO3/KF afforded the corresponding coupling product 7 in 86% yield. The halogen exchange reaction of 7 under the optimized condition with LiI-CuI afforded the corresponding iodide 8 in 91% yield. Repeating further iterative CH arylation and halogen exchange sequence lead to the oligothiophene tetramer iodide 11 as shown in Scheme 2.
2.2. CH-NH coupling of azoles

Benzothiazole (12) and N-methylaniline (13) was first chosen as a representative substrate and careful studies on the reaction conditions are carried out. When copper(II) acetate was employed as a catalyst species (20 mol%), the reaction was found to proceed under oxidative conditions in xylene at 140 °C in the presence of sodium acetate to afford the amination product 14 in 82% yield. Copper(II) was found to be an effective catalyst and the use of CuCl₂ also underwent the reaction with a slightly lower yield, while the reaction in the presence of 20 mol% of Cul resulted in no reaction. Other metal catalysts such as palladium(II) and iron(III) was also found to be ineffective. It is important to carry out the reaction under oxidative conditions. Indeed, the reaction under an oxygen atmosphere resulted in giving high yield, however, the yield was found to decrease (46%) under an aerobic condition and no reaction took place under a nitrogen atmosphere.

Table 2 summarizes the reaction of several azoles with amines. Benzothiazole reacted with diphenylamine and a sulfonamide, N-tosyl-n-propylamine in moderate to good yields. The reaction of 4,5-dimethylthiazole also proceeded, while 4-methylthiazole resulted in no reaction suggesting that anazole bearing the CH bond adjacent to the sulfur atom was not available. Several secondary aliphatic amines such as piperidine, and diethylamine reacted with benzoxazole in good to excellent yields. It was also found that the reaction of benzoimidazole with N-methylaniline occurred to afford the corresponding amination product in 51% yield.
Table 2. Copper-catalyzed CH-NH coupling of azoles with amines

| entry | Azole–H | amine         | product            | yield (%) b |
|-------|---------|---------------|--------------------|-------------|
| 1     | ![Azole H](image1) | H-NMePh       | ![Product 1](image2) | 81          |
| 2     | ![Azole H](image1) | H-N^Pr Ts     | ![Product 2](image3) | 65          |
| 3     | ![Azole H](image1) | H-NPh2        | ![Product 3](image4) | 47          |
| 4     | ![Azole H](image1) | H-NMePh       | ![Product 4](image5) | 73          |
| 5     | ![Azole H](image1) | H-NPh2        | ![Product 5](image6) | 71          |
| 6     | ![Azole H](image1) | H-NPh2        | ![Product 6](image7) | 66          |
| 7     | ![Azole H](image1) | H-Ncyclo      | ![Product 7](image8) | 72          |
| 8     | ![Azole H](image1) | H-NEt2        | ![Product 8](image9) | 47          |
| 9     | ![Azole H](image1) | H-NMePh       | ![Product 9](image10) | 51          |

a The reaction was carried out with azole (1 eq), amine (4 eq), Cu(OAc)$_2$ (20 mol%), PPh$_3$ (40 mol%), and NaOAc (4 eq) in xylene at 140 ºC for 20 h under O$_2$. b Isolated yield.
3. Conclusion
In summary, CH functionalization of five-membered heteroaromatic compounds such as thiophene and azoles was described. CC bond-formation of thiophene and thiazole was shown to take place at the electron-enriched carbon atom of heteroaromatic ring in the presence of a palladium catalyst. On the other hand, CH-NH coupling of azoles proceeded at the 2-position, which is the electron-deficient CH bond, with secondary amines and amides. These reactions involve potential utilities for the preparation of advanced electronic materials and biologically important organic compounds.

4. Experimental section

General procedure for the palladium-catalyzed CH arylation.
To a mixture of PdCl₂(PPh₃)₂ (8.8 mg, 0.01 mmol), potassium fluoride (18.2 mg, 0.31 mmol), and 4-iodobenzoic acid ethyl ester 6 (69 mg, 0.25 mmol) in 3 mL of DMSO was added 2-bromo-3-hexylthiophene 2 (0.07 mL, 0.3 mmol) and stirred at 100 °C for 5 h. AgNO₃ (10.6 mg, 0.31 mmol) was then added in five portions with an hour interval. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed with chloroform repeatedly. The organic layer was concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 85 mg of 7 as a yellow solid (86%).

General procedure for the halogen exchange reaction.
In a 100 mL of schlenk tube 7 (0.874 g, 2.21 mmol) was dissolved 25 mL of DMSO. To the solution were added copper iodide (I) (4.2 g, 22.1 mmol) and lithium iodide (2.96 g, 22.1 mmol) and stirred at 150 °C for 25 h. After cooling to room temperature, the mixture was quenched with water and it was passed through a Celite pad, which was washed with chloroform repeatedly. The organic layer was washed with Na₂S₂O₃ aq. and water three times, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford 0.941 g of 8 as an orange solid (96%).

Other reactions for the extension of the number of thiophene ring and CuI-LiI mediated halogen exchange were carried out in similar manners as shown above.

General procedure for the oxidative copper-catalyzed amination of heteroaromatic compounds.
A solution of Cu(OAc)₂ (7.3 mg, 0.04 mmol), PPh₃ (21 mg, 0.08 mmol), benzothiazole 12 (22 μL, 0.2 mmol), N-methylaniline 13 (88 μL, 0.8 mmol) and NaOAc (66 mg, 0.8 mmol) in 1 mL of xylene was stirred at 140 ºC for 20 h under O₂. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed with chloroform repeatedly. The filtrate was washed with water three times. The organic layer was concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel to afford 39 mg of 14 as a colorless oil (81%).

N-(4,5-Dimethyl-thiazol-2-yl)-N-methylaniline (15): ¹H NMR (500 MHz, CDCl₃) δ 2.14 (d, J = 0.6 Hz, 3H), 2.18 (d, J = 0.6 Hz, 3H), 3.48 (s, 3H), 7.16-7.23 (m, 1H), 7.33-7.43 (m, 4H) ¹³C NMR (125 MHz, CDCl₃) δ 11.1, 14.9, 40.0, 114.4, 124.7, 125.9, 129.7, 147.0, 166.4; IR (neat) 1131, 1287, 1374, 1410, 1470, 1516, 1597, 1678, 2851, 2917, 3035 cm⁻¹; HRMS found: m/z 218.0878. Calcd for 218.0878.

N-Benzoxazol-2-yl-diphenylamine (16): ¹H NMR (500 MHz, CDCl₃) δ 7.03 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 7.18-7.22 (m, 3H), 7.27-7.37 (m, 8H), 7.41 (d, J = 7.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 109.4, 117.7, 122.2, 124.4, 126.2, 126.6, 129.6, 142.2, 142.8, 148.6, 160.3; IR (neat) 1006, 1209, 1242, 1366, 1456, 1495, 1557, 1625, 2852, 2922, 3057 cm⁻¹; HRMS found: m/z 286.1106. Calcd for 286.1103.
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