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Communication

The Unprecedented Side Reactions of Stille Coupling: Desired Ones for Stille Polycondensation

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Two kinds of unprecedented side reactions were identified in the Stille coupling reactions, including the direct C-H stannylation on α -hydrogen of thiophene units and the 10 stannylation of arylbromides with trialkylstanne bromide. These results reveal the major source which enhances the Stille polycondensation efficiency.

The Stille coupling has become an appealing synthetic methodology and has been widely applied to the syntheses of 15 numerous organic compounds.^{1,2} The impact of this methodology has been spread to organic semiconducting material areas,³ which are important for the development of next-generation optoelectronic devices.^{4,5} A survey of the literatures on conjugated materials will advance the idea that Stille coupling 20 reaction has emerged as the most significant synthetic method towards the thiophene-bearing materials, especially thiophenebearing polymers used in OFETs and OPVs.⁶ Taking advantage of the pairing of highly electron-rich thiophene monomers with electron-deficient halide and triflate monomers, the Stille 25 polycondensation method typically gives excellent yields, provides a facile route to high molecular weight, narrowly dispersed polymers under mild conditions, while tolerating a wide variety of functional groups.⁶

Mechanistically, the Stille cross-coupling reaction involves a ³⁰ repeating oxidative addition, transmetalation and reductive elimination sequence, which yields the products and regenerates the catalyst.⁷ (see ESI[†], Fig. S1.) Including the organostannyls and organohalides, all parameters of ligands, solvents, and additives have played major roles in the outcome of Stille

- ³⁵ coupling. Elucidation of the mechanism through the interplay of these variables has been investigated by many researchers. Except the homocoupling of organotin compounds and the decomposition of organotin under palladium catalyst,⁸ few systematic investigations on the side reactions of Stille coupling
- ⁴⁰ have been rarely conducted. Especially, to the best of our knowledge, there are no published works on the study of Bu₃SnX, which is generated during the Stille coupling reaction by stoichiometric quantity.

Our current research focuses on synthesis of novel thiophene-45 based molecules for organic photovoltaics and organic fieldeffect transistors.⁹ We found the Stille coupling methodology was by no means problem-free. For example, numerous conjugated polymers based on benzo[1,2-b:4,5-b']dithiophene (BDT) have been synthesized with molecular weights as high as 100 kd in ⁵⁰ good yields using BDT-tin monomers.^{6a,10} Yet, even the reported reactions were run under the similar conditions as their polymeric counterparts, when considering the synthesis of BDT-bearing small molecules, the yields are always low.¹¹ It is very important to identify this paradoxical fact that the low yield Stille coupling ⁵⁵ for small molecules is very efficient as polycondensation method

for high molecular weight polymers. Since the reaction yields of the Stille cross-coupling reactions can vary in very large ranges, we assume there must be other side reactions which affect the yields but have not been noted.



Scheme 1 Organotin and organo-halides tested in this work

With the motivation to explicitly confirm the possible side reactions which happened in the Stille reaction, a series of model experiments were systematically designed by combining the ⁶⁵ reactants and the reaction conditions. As starting materials, we synthesized 4,7-dibromoquinoxaline (**BrQBr**)¹² as ideal dibromo compound in that the proton NMR chemical shifts of **BrQBr** were clearly separated from each other and the two long alkyl chains on **BrQBr** could improve the solubility of the target ⁷⁰ products(see Scheme 1). In order to obtain a universal conclusion on the side-reaction issue, two catalyst systems, both Pd(PPh₃)₄ and Pd₂(dba)₃/P(*o*-tol)₃ in toluene were tested.

The reactions of Equation 1 and 2 were conducted to confirm the Stille coupling conditions in our hands (see Scheme 2). The ⁷⁵ typical conditions with Pd(PPh₃)₄/toluene or Pd₂(dba)₃/P(*o*tol)₃/toluene under argon atmosphere were tested. For Equation 1, after being heated at 110 °C for 16 hr, it could give the target product 7 with an excellent yield of around 95%. When Equation 1 was scaled up to 3.0 grams level, the yield was slightly reduced ⁸⁰ by 2.5%. These results indicated that the two reaction conditions were very efficient in the present work. All of the following designed reactions will be tested with both of these two conditions. But for Equation 2, even the mole ratio of 1 to **DSnTT** was 2.4/1.0, the yield of **8** was around 84%. Due to the decomposition of **DSnTT** under Pd-catalyst, mono-coupling product of 2-(5-hexylthiophenyl)- thieno[3,2-b]thiophene was observed by GC-MS measurement. The proton NMR ⁵ measurements of all products generated with **Equation 1** and **2** indicated that our starting materials designation was reasonable since all proton signals could be conclusively assigned.



Scheme 2 Confirmation of the Stille reaction conditions

- As shown in Scheme 3, another two Stille reactions of 3.a and
 3.b were tested by replacing both 2 and 1 with 4 and 3, respectively. Interestingly, the yields of major products for these two reactions decreased dramatically with low yields of 62% (for 1Q2T, 4 entries average) and 54% (for 9, 3 entries average).
 ¹⁵ When we moved to the catalyst of Pd(PPh₃)₄, the yields were still very low. By carefully checking the reaction mixture by thin layer chromatography, there were still more polar side products observed for both Equation 3 and Equation 4.
- Firstly, the reaction residue of Equation 3 was carefully 20 separated with silica column chromatography. At least, three cross-coupling side products of 2Q3T, 3Q4T and 4Q5T were collected with the preparation yields of 21%, 8% and 3%, respectively. All of these products were conclusively confirmed with ¹H NMR and matrix-assisted laser desorption ionization 25 time-of-flight (MALDI-TOF) mass spectrometry. As shown in Figure 1, the end group of thiophene units for all three products exhibits clear and feature multiple peaks with chemical shifts at 7.18, 7.50 and 7.82 ppm. The thiophene units in the centre part of the two side products show peaks with chemical shifts at 7.77 ³⁰ ppm (for **3Q4T**) and and 7.75 ppm (for **4Q5T**). Due to the structural symmetry, there are two kinds of guinoxaline units in 3Q4T, which exhibit two adjacent peaks at 8.11 and 8.16 ppm. The integration of all peaks for each compound and the mass spectra are also clearly coincident with their structures. (see ESI[†])
- ³⁵ Although the side-products generated from Equation 4 were not fully isolated with silica gel chromatography after many attempts due to their poor solubility and low polar properties, their structures were unambiguously identified by MALDI-TOF mass spectrometry. Alternating oligomers composed of 3-40 hexylthiophene units and thieno-thiophene units were clearly observed according to their mass spectra (see ESI[†]). After
- collecting all of these side products with chloroform as eluent, they account for 33% of total yields by calculating their weights. Obviously, the first side reaction we observed in Equation 3
- ⁴⁵ and 4 happened when there were α -hydrogens on the thiophene units, by comparing the reactions shown in Scheme 2 and 3. The driving force to selectively generate this side reaction is still unclear. Interestingly, after Equation 3 was run for 25 min,

1Q2T, 2Q3T and 3Q4T had been generated and for 75 min, 50 405T was also appeared whenc checking the reaction mixture with MALDI-TOF-MS. In addition, 1Q2TSn and 2Q3TSn were both clearly observed with relatively strong peaks on their MALDI-TOF-MS spectra after Equation 3 was run for more than 75 min. (see ESI Fig. S26 and S27) With these results, it 55 could be assumed there may be a C-H direct stannylation intermediate generated after 1Q2T was generated in the reaction mixture, i.e. 1Q2TSn (see Equation 5). Thus, this C-H stannylated intermediate reacted with BrQT to give 2Q3T, then further to generate 3O4T with the intermediate of 2O3TSn. And 60 the tributylstannyl bromide worked as the organotin source. Via the similar procedure, the side-products of 9 would be generated in **3.b**. When **3.a** was run at a higher temperature of 145 °C with microwave irradiation for 1 hour,¹³ the direct stannylation side reaction on the α -hydrogen was improved. When all reaction 65 conditions were fixed for reactions of 3.a and 3.b, it was found that the yields of **1Q2T** and **9** with $Pd(PPh_3)_4$ as catalyst were slightly higher than those with $Pd_2(dba)_3/P(o-tol)_3$ as catalyst. These results indicate that the catalyst of Pd2(dba)3/P(o-tol)3 is more efficient than Pd(PPh₃)₄ for the C-H direct stannylation and 70 the direct stannylation reaction will be improved by increasing



Scheme 3 C-H transformation based side reactions: a) Pd₂(dba)₃, P(*o*-tol)₃, toluene, 110 °C, 16 hr; 3.c) Possible mechanism towards **2Q3T** and 75 **3Q4T**.

We tried two model reactions to further interrogate the assumption that Bu₃SnBr could play a crucial role in Stille coupling reaction with aromatic halides (see in Scheme 4). With

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Pd₂(dba)₃/P(*o*-tol)₃ as the catalyst, **BrQQH** was synthesized with a yield of about 83% (3 entries average) by mixing **BrQBr** with 1.1 equivalent of Bu₃SnCl in toluene. And with Bu₃SnBr as reagent for **Equation 6**, the yield was almost the same. With **5** as s starting materials, **10** was also obtained with a yield of 91%.

- When we tested Equation 6 and 7, by using 0.6 equivalent of Bu₃SnCl, we obtained both **BrQQH** and **10** with relatively lower yields. Meanwhile, in both cases, the starting materials conversion ratio reached 97%. But, if no Bu₃SnBr or Bu₃SnCl ¹⁰ was added to the reaction mixture, there was no BrQQH and **10**
- generated. These results show that under Stille coupling conditions, the aryl bromides undergo an unusual coupling reaction with the mediation of Bu₃SnCl (or Bu₃SnBr). Usually, this kind of reaction is conducted by combining aryl bromides ¹⁵ with hexabutyldistannane.¹⁴ By monitoring **Equation 6** and **7** with MALDI-TOF-MS and GC-MS after they were run for 2 hr, there were at least two kinds of stannylated intermediates observed. (see ESI Fig. **S28** & **S29**) And these intermediates show similarly structural characters. Therefore, we propose the ²⁰ mechanism as follows. Firstly, when Bu₃SnBr was heated in toluene, it gave rise to Bu₂HSnSnHBu₂ and other organo-stannes. (see ESI Fig. S30) Then, **BrQBr** was stannylated with these distannyl compounds. After this, Stille coupling took place to give **BrQOBr**. Later, **BrQOBr** was further stannylated as

25 BrQQSn. When running the purification by silica column

chromatography, **BrQQSn** was decomposed as **BrQQH**, due to the organotin decomposition induced by silica gel. Accordingly, the second possible side reaction of Bu₃SnX mediated aryl-aryl coupling was identified.









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³⁵ Since no quinoxaline-quinoxaline directly linked side products in reaction **Equation 3** are isolated, it seems that two kinds of side reactions do not equally take place. The direct stannylation side reaction on α -hydrogen of thiophene is more competitive than arylbromide stannylation side reaction in the same reaction ⁴⁰ system. In case of Stille polycondensations, a quantitative of Bu₃SnBr (or Me₃SnBr) is always generated during the polymerization. And the decomposition of thiophene-based organotin monomers is inevitable, which will generate building blocks with α -hydrogen and make the dibromo monomer ⁴⁵ excessive. It can be expected that these side reactions involved with trialkyl bromides can improve the polymerization degree and increase the polymer molecular weight by direct stannylation of the α -hydrogen containing building blocks and Bu₃SnBr mediated C-C bond formation. So, both side reactions are desired for Stille polycondensation if higher molecular weight polymers ⁵ are wanted. In addition, the existence of these two side reactions gives a reasonable explanation that the Stille polymerization can be improved by extending the reaction time and using a little excessive of organotin monomer. ^{9a-c,12}

In conclusion, we have identified two unprecedented side ¹⁰ reactions in the standard Stille coupling reaction by carefully designing the starting materials. One is the direct stannylation on thiophene units when there is α-hydrogen on them; the other is the stannylation of aryl bromides. Both of these two side reactions are based on the trialkylstanne bromide generated ¹⁵ during the Stille coupling reaction. These two side reactions will be promoted by increasing the reaction temperature. Both of these two side reactions will improve the efficiency of the Stille polycondensation for high molecular weight polymers, but are detrimental to the synthesis of small molecules. The results ²⁰ presented here represent an interesting and important recognition on the mechanism of Stille coupling. Further investigation of the mechanism is still under way.

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Notes and references

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