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Sterics vs Electronics: Revisiting the Catalytic Regioselective Hydrodebromination of 2,3,5-Tribromothiophene

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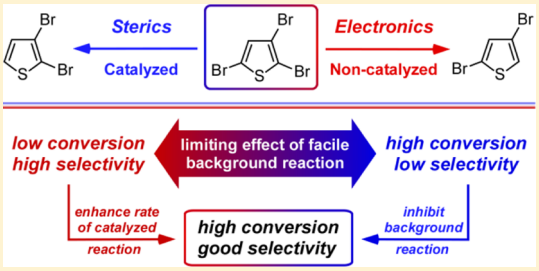
Supporting Information

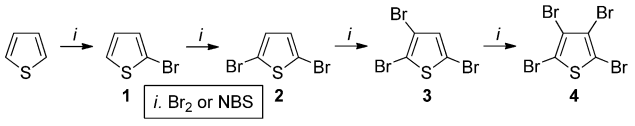
ABSTRACT: The application of sterically hindered palladium catalysts to the regioselective hydrodebromination of 2,3,5-tribromothiophene has been studied in detail, including the effects of catalyst choice, solvent, reaction time, and temperature, as well as the method of $NaBH_4$ addition and the role of chelating additives to effect $NaBH_4$ solubility. Ultimately it was determined that the background reaction between $NaBH_4$ and bromothiophenes is too facile to allow both total conversion and high selectivity. Optimized conditions finally allowed a selectivity of ca. 16:1 with overall conversion of 100%. However, complications of over-debromination under these conditions still limit the yield of the desired 2,3-dibromothiophene to 65%.



INTRODUCTION

Halothiophenes, especially bromothiophenes, are the most common synthetic precursors for the production of functionalized thiophenes,[1] which in turn have found extensive use as building blocks for the synthesis of materials,[2] natural products,[3] and pharmaceuticals.[4] Such bromothiophenes are typically prepared from direct bromination of thiophene with Br_2 or *N*-bromosuccinimide (NBS). As illustrated in Scheme 1,

Scheme 1. Sequential Bromination of Thiophene



the electronic differences between the α- and β-positions[5,6] of the thiophene ring favor the successive formation of 2-bromothiophene (**1**),[7,8] 2,5-dibromothiophene (**2**),[8,9] 2,3,5-tribromothiophene (**3**),[10,11] and 2,3,4,5-tetrabromothiophene (**4**).[12] While these synthetic steps are relatively straightforward, the production of bromothiophenes can become complex when attempting to selectively brominate the less readily accessible β-positions, which then requires either blocking of the more reactive α-positions or removing unwanted α-bromides following polybromination.

This can become even more intricate for the production of asymmetric dibromothiophenes containing both α- and β-bromides.[13−19] The most simple transformation is the selective debromination of **3** to give 2,4-dibromothiophene (**5**) (Scheme 2).[13,14,17] This can be accomplished with either butyllithium or $NaBH_4$ (Table 1, entries 1 and 2) and takes advantage of the fact that the most reactive bromide is being removed in the

Scheme 2. Synthesis of Asymmetric Dibromothiophenes

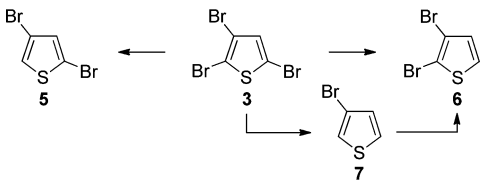


Table 1. Debromination of 2,3,5-Tribromothiophene

entry	reagent	5[a]	6[a]	ref
1	BuLi	75	25	13, 14
2	$NaBH_4$	95	3	17
3	MeMgBr	18	82	15
4	$Pd(PPh_3)_4/NaBH_4$	6	92	17, 18

[a]Values given are ratios of products **5** and **6**.

process and thus the electronics drive selectivity.[19] Such electron preference can be overcome via the use of larger reagents, as has been demonstrated through the use of Grignard reagents (Table 1, entry 3) to selectively produce 2,3-dibromothiophene (**6**).[15] In this case, steric hindrance between the 3-bromo group and the incoming reagent inhibits reaction at the 2-position and thus debromination at the 5-position is observed. Due to either cost or difficulties in preparing the Grignard reagents, however, it is still far more common to use inexpensive reagents to just remove both α-bromides to give 3-bromothiophene (**7**), followed by a single bromination to give **6**.[16]

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A significant advance was then reported by Hor and co-workers beginning in 1996.[17,18] In two reports, the authors presented an approach that combined the use of stoichiometric $NaBH_4$ with a sterically bulky Pd catalyst, citing both 100% conversion and high selectivity for **6** over the electronically favored **5** (ca. 15:1, Table 1, entry 4). As such, these methods allowed the simple production of **6** without the previously necessary Grignard reagents, with even higher selectivity.

This approach of utilizing sterically bulky Pd catalysts to overcome the thiophene electronics was then successfully applied to regioselective cross-coupling by the Rasmussen group in 2008.[19] Extending the methods of Hor and co-workers to cross-coupling reactions of **3**, the application of the bulky catalyst $Pd(dppf)Cl_2$ (where dppf = 1,1′-bis(diphenylphosphino)ferrocene) disfavored oxidative addition at the electronically favored 2-position to allow selective coupling of a variety of arylzinc chlorides at the 5-position. The observed selectivity in all cases was ca. 10:1.[19]

Recent attempts to apply the previous Pd-catalyzed hydrodebromination methods, however, revealed significant variability in selectivity. As these observations seemed inconsistent with the reports of either Hor[17,18] or Rasmussen,[19] it was decided that it was worthwhile to revisit methods to utilize catalyst sterics to overcome electronic selectivity, with the goal to provide greater understanding concerning the generality of this approach to controlling selectivity in halothiophenes. As such, a detailed investigation of the catalytic hydrodebromination of **3** is presented here, in which the interplay of sterics and electronics will be discussed in relation to effects on the observed selectivity. Other experimental conditions that dictate both selectivity and reactivity will also be presented.

RESULTS AND DISCUSSION

As a starting point, efforts were made to replicate the previously reported reaction conditions as closely as possible. A complication is that different reaction conditions are reported between the initial report in 1996[17] and the more detailed paper in 1998.[18] It is worth noting that although the reaction conditions changed between these two reports ($NaBH_4$ amount, catalyst amount, reaction time), the stated results remain essentially identical (Table 2, entries 1 and 2). Assuming the later conditions to be the more optimized, it was these conditions that were first investigated. Still, questions remained concerning the method of the addition of the $NaBH_4$, with the published procedure stating that it was "added in small portions" over 1.5 h.[18] As such, two methods were investigated, one in which small powder portions were added to the reaction five times over the specified 1.5 h (entry 3) and a second case which utilized a powder addition funnel (entry 4). In both cases, however, neither the percent conversion nor selectivity previously reported could be obtained in our hands.

Table 2. Comparative Results from Literature Procedures[a]

					products[b]		
entry	$NaBH_4$ (mmol)	catalyst (mol %)	time (h)	conversn (%)	**5**	**6**	**7**
1[c]	20	5	24	100	6.1	92.5	1.4
2[d]	30	1	6	100	6	92	1
3	30[e]	1	6	79	48	43	9
4	30[f]	1	6	85	40	52	8
5	30[f]	1[g]	6	88	40	50	10
6	30[f]	5	6	100	14	66	20

[a]Constant conditions: **3** (20 mmol), $NaBH_4$, and $Pd(PPh_3)_4$ in 100 mL of CH_3CN and heated at 70 °C. [b]Values given are ratios of products **5**–**7**. [c]Reference 17. [d]Reference 18. [e]Added in small solid aliquots. [f]Added via powder addition funnel. [g]Catalyst synthesized from ref 20.

As the previous reports had not used a commercial catalyst but had synthesized and purified $Pd(PPh_3)_4$ in house, the potential effects of catalyst purity were then investigated. Fresh $Pd(PPh_3)_4$ was synthesized[20] and purified via the same methods reported by Hor and co-workers, after which the conditions given in entry 4 were repeated with the fresh catalyst. As can be seen in entry 5, this gave nearly identical results and thus it was concluded that the catalyst source was not a significant factor. Finally, the amount of catalyst was increased to 5 mol %, which did result in the complete conversion and an increase in selectivity for the production of **6**. However, this selectivity is still well below that previously reported.[17,18]

The lack of reproducibility here was assumed to be due to an unintentional lack of detail in the published procedure. The most likely factor was thought to be the nature and method of the $NaBH_4$ addition, which had already been shown to affect both conversion and selectivity in the initial trials (Table 2). As such, various conditions were investigated concerning the $NaBH_4$ addition (see Table S1 in the Supporting Information). While adding the $NaBH_4$ as slow as possible resulted in slight improvements in selectivity, this was not very practical and any improvement in selectivity was offset by lower conversion.

Attempting to better understand the effect of $NaBH_4$ addition, we then studied noncatalyzed conditions in order to determine the extent of any background reaction. As shown in Table 3, the noncatalyzed debromination of **3** was previously reported by Hor and co-workers in DMSO.[17] In this solvent, the direct reaction at room temperature is highly facile, with 100% conversion within 4 h when 2 equiv of $NaBH_4$ was utilized (entry 3). Conversion becomes less efficient with lower amounts of $NaBH_4$, along with a slight decrease in selectivity. However, as the previously reported catalytic methods utilized CH_3CN,[17,18] it was unclear to what extent the change in solvent may inhibit this background reaction.

To quantify this effect of solvent choice, noncatalyzed debromination of **3** in CH_3CN was first carried out at room temperature (Table 3, entry 4). The change to CH_3CN gave almost no reaction at room temperature, with only 3% conversion after 7 h. Selectivity for the electronically favored 2-position, however, was complete and no reaction was observed at the 5-position. However, when the reaction was carried out at the temperature given under the reported catalytic conditions (i.e., 70 °C), it is essentially complete within 6 h and shows the expected selectivity for the electronically favored 2-position (entry 5).

The reactivity of $NaBH_4$ with **3** in hot CH_3CN is quite problematic and explains the difficulty in achieving the high selectivity previously reported by Hor and co-workers. As selective debromination at the 5-position only occurs when it is mediated by the bulky catalyst, conditions would need to inhibit any background reaction. However, as the background reaction readily occurs under the conditions utilized, the only way selectivity could possibly be achieved is if the $NaBH_4$ were added at a rate in which it was immediately consumed in the catalytic cycle (Scheme 3) and not allowed to participate in direct reaction with **3**, something which would be highly

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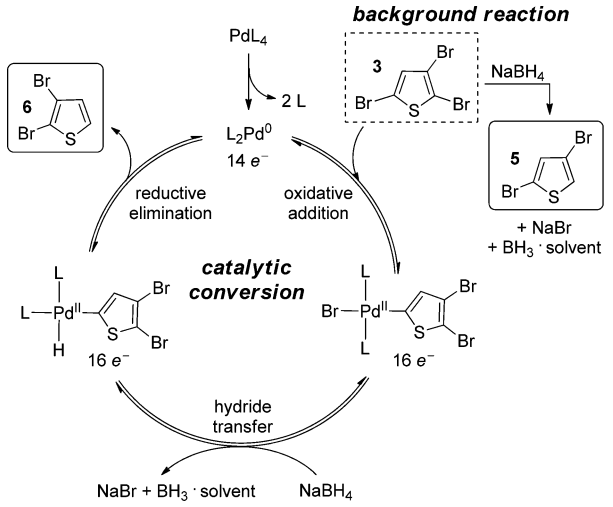
Table 3. Noncatalyzed $NaBH_4$ Debromination of 3[a]

entry	solvent	3:$NaBH_4$	temp (°C)	time (h)	conversn (%)	products[b] 5	6	7
1[c]	DMSO	1:1	room temp	24	50	90	1	8
2	DMSO	1:1.5	room temp	6	73	93	7	0
3[c]	DMSO	1:2	room temp	4	100	95	2.6	2.9
4	CH_3CN	1:1.5	room temp	7	3	100	0	0
5	CH_3CN	1:1.5	70	6	99	95	5	0
6	THF	1:1.5	room temp	6	0	0	0	0
7	THF	1:1.5	66	6	2	100	0	0

[a]Constant conditions: 3 (5 mmol) and $NaBH_4$ in 100 mL of solvent. [b]Values given are ratios of products 5–7. [c]Reference 17.

Scheme 3. Catalytic Cycle and Competing Background Reaction for Hydrodebromination of 3



difficult to control. In addition, the general trend found above is that slower addition also contributes to lower conversion. For the majority of the catalytic debrominations reported by Hor and co-workers,[18] this would not be an issue, as the bromide being removed is in the electronically favored position and thus the catalyzed and background reactions would give the same product. In fact, it is only the example of 3 in which this background reaction would play a role in affecting selectivity. Unfortunately, the selective debromination of the 5-position of 3 under these conditions does not seem to be practical.

Coming to this disappointing conclusion, alternate conditions where then investigated in an attempt to find practical methods that would inhibit the background reaction while still allowing efficient and selective conversion of 3 to 6. As solvent choice plays a large role in the background reaction, this was the initial variable considered. The extent of the background reaction is essentially controlled by the solubility of $NaBH_4$ under the selected conditions. As shown in Table 3, CH_3CN provides low solubility and thus low reactivity at room temperature but better solubility and high reactivity at higher temperatures. However, it should be pointed out that $NaBH_4$ is still not completely soluble in hot CH_3CN, which accounts for its slower reactivity in comparison to DMSO. More polar solvents such as DMF provide good solubility and fall in between CH_3CN and DMSO in terms of facilitating the background reaction. At the other end of the scale is diethyl ether, which showed no solubility or reactivity at either room temperature or reflux temperatures. The closely related THF, however, provided an intermediate solubility between that of CH_3CN and diethyl ether and was thus selected as the primary solvent.

In addition to the change in solvent, it was decided to move from $Pd(PPh_3)_4$ to $Pd(dppf)Cl_2$. This change was motivated by the fact that the bulkier dppf ligand was found to give slightly better steric-mediated selectivity in the Pd-catalyzed cross-coupling of 3[19] and thus should provide increased selectivity here as well. In order to keep the methods as simple as possible, initial trials utilized a one-pot method in which all reagents were added collectively at the start (Table 4). These initial conditions exhibited reasonable selectivity but poor product conversion, as shown in entry 1.

Table 4. Comparative Results from One-Pot Methods[a]

entry	catalyst (mol %)	$NaBH_4$: TMEDA	time (h)	conversn (%)	products[b] 5	6	7
1	1	1:0	7	9	19	81	0
2	1	1:1	7	11	17	83	0
3	1	1:1	24	34	29	72	0
4	2.5	1:1	48	33	22	78	0
5	2.5	1:2	24	30	17	83	0

[a]Constant conditions: 3 (5 mmol), $NaBH_4$ (1.5 equiv), and $Pd(dppf)Cl_2$ in 100 mL THF at reflux. [b]Values given are ratios of products 5–7.

Assuming that the low conversion was due to limited $NaBH_4$ solubility, it was thought that this could be tuned via the addition of agents to chelate the sodium cation. This might thus allow optimization of the $NaBH_4$ solubility such that conversion is enhanced while still minimizing the background reaction. The addition of various crown ethers to $NaBH_4$ solutions seemed too successful at solubilizing the sodium salt, and thus our attention shifted to tetramethylethylenediamine (TMEDA) as a potential additive. The use of TMEDA as an additive in metal-catalyzed $NaBH_4$ reductions has been previously reported,[21] and its addition to $NaBH_4$ solutions qualitatively appeared to give a good level of solubility adjustment.

Reactions in THF with TMEDA did show slightly better conversion, along with a slight enhancement in selectivity (Table 4, entry 2). Extending the reaction time (entry 3) resulted in a substantial increase in conversion, although it was still lower than desired and was coupled with a reduction in selectivity. Further increasing the reaction time did not result in further increases in conversion, but increasing the catalyst loading to 2.5 mol % did help counteract the lower selectivity (entry 4).

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Previous reports have attributed the effect of the TMEDA as either stabilizing the resting state of the catalyst via coordination of Pd or assisting in the hydride transfer step by coordinating the resulting BH_3.[21] While coordinating the resting state of the catalyst is possible, the addition of the bidentate TMEDA ligand would result in an 18-electron Pd species,[22] which would significantly inhibit oxidative addition, either quenching catalytic activity or negatively affecting the corresponding kinetics. As such, TMEDA chelation would most likely necessitate the dissociation of a third PPh_3 ligand in order to maintain catalytic activity. Coordination to boron is also a possibility, but the fact that these reactions are carried out in a coordinating solvent makes it much more likely that solvent coordination satisfies the electron-deficient BH_3, particularly as the solvent is present in molar quantities much higher than that of the added TMEDA (ca. 80:1). As such, the most likely effect of the TMEDA is simple coordination to the sodium cation of $NaBH_4$, thus enhancing the solubility of the salt in THF. This is supported by both the enhanced THF solubility of TMEDA/$NaBH_4$ mixtures by visible inspection and the reports of multiple crystal structures exhibiting the chelation of sodium by TMEDA.[23]

With the conditions starting to look promising for the one-pot methods, efforts moved to investigation of slow addition methods in order to further optimize the reaction. During the initial investigations outlined in Table 1, the catalyst and **3** were combined in solvent and the reducing agent was added in small portions as a solid while the reaction mixture was stirred under N_2 at an elevated temperature. In this case, however, the addition of $NaBH_4$ required the removal of a septum, which both exposed the reaction to O_2 and introduced loss of solvent via escaping vapor at reflux. These issues could be bypassed via the use of a powder addition funnel, but this was impractical due to the small quantities of reducing agent involved, unless the reaction was carried out on a suitably large scale. Likewise, attempts to add the reducing agent via solution addition funnel were unsuccessful because of the low solubility of $NaBH_4$ in almost all solvents, and when $NaBH_4$ was soluble, the background reaction was predominant (Table 3). Thus, a reverse approach was taken by limiting the amount of **3** in solution, rather than trying to control $NaBH_4$. By controlling the availability of **3** via its slow addition to the reaction mixture, it should be possible to maintain a concentration near the catalyst concentration, thus limiting transformation via the background reaction. Therefore, reactant **3** in 50 mL of THF was added dropwise to the hot reaction mixture consisting of the remaining components dissolved in another 50 mL (total solvent thus still 100 mL).

As can be seen in Table 5, the slow addition of reactant **3** to $NaBH_4$ resulted in significantly large increases in conversion such that complete consumption of **3** had occurred within 19–20 h (entries 1 and 2). Unfortunately, this quite positive advance in conversion was coupled with significant amounts of overdebromination, such that ca. 60% of the recovered product was the doubly debrominated product 3-bromothiophene (**7**).

At this point, the previous decision to move from $Pd(PPh_3)_4$ to the bulkier $Pd(dppf)Cl_2$ was then called into question. Although this original decision was due to the enhanced steric-mediated selectivity previously observed for $Pd(dppf)Cl_2$,[19] it was realized that the enhanced sterics most likely contributed to a reduction in reaction rate. For example, it is known that increasing ligand sterics negatively affects the rate of oxidation addition.[24−26] Thus, any benefits in reaction selectivity may not be worth the associated cost in terms of reduced reaction rate. To test this possibility, these high conversion conditions were repeated with $Pd(PPh_3)_4$. As shown in entry 3 of Table 5, a substantial increase in reaction rate was observed, with the total reaction time reduced by half. In addition, the problem of overdebromination was also significantly reduced and selective debromination of the 5-position over the more reactive 2-position was quite high (16:1).

Table 5. Effect of Slow Addition of Tribromothiophene[a]

					products[b]		
entry	precatalyst	add time (h)	total time (h)	conversn (%)	**5**	**6**	**7**
1	$Pd(dppf)Cl_2$	2	20	100	5	31	64
2	$Pd(dppf)Cl_2$	3	19	100	10	34	56
3	**$Pd(PPh_3)_4$**	**1.5**	**6**	**100**	**4**	**65**	**31**
4	$Pd(PPh_3)_4$	1.5	4	69	10	63	27
5[c]	$Pd(PPh_3)_4$	1.5	6	71	9	76	15

[a]Constant conditions: **3** (5 mmol), $NaBH_4$ (1.5 equiv), TMEDA (3 equiv), and catalyst (2.5 mol %) in 100 mL THF at reflux. Optimized conditions are given in boldface. [b]Values given are ratios of products **5**–**7**. [c]Only 1 equiv of $NaBH_4$ used.

In final hopes to further limit overdebromination and increase the isolated yield of 2,3-dibromothiophene **6**, the reaction time was limited to only 4 h (entry 4). Unfortunately, this negatively affected conversion to a greater extent than reducing overdebromination, thus confirming that these conditions required the full 6 h to run to completion. Attempts to reduce the $NaBH_4$ to 1 equiv (entry 5) had a greater effect in limiting overdebromination but also negatively affected total conversion. This final result was consistent with the initial studies of the background reaction under optimal conditions (Table 3), which revealed that an excess of $NaBH_4$ was necessary to reach complete conversion.

As neither of the final two modifications successfully increased the isolation of **6**, the maximum yield observed under the final optimized conditions provided here was limited to only 65% (Table 5, entry 3). This is not to say that additional gains are impossible via further tuning of the reaction conditions. For example, the moderate investigation of solvent choice described above could be expanded to include mixed solvent systems, which could allow more fine-tuning of the $NaBH_4$ solubility and contributions from the background reaction under the reaction conditions applied. However, at this point, such gains would be expected to be relatively minor.

Although the yield provided by the optimized conditions here is not as high as was hoped and is substantially lower than that originally reported by Hor and co-workers,[17,18] the conditions still provide better selectivity than is possible via noncatalytic sterically controlled methods such as the use of Grignard reagents (Table 1). In addition, the methods reported here result in the production of very low amounts of dibromothiophene **5**, which allows the ultimate purification of the desired isomer **6**. These two isomers are difficult to separate from one another, as they elute similarly on silica gel and exhibit very similar boiling points (210–212 °C for **5**;[27] 218.6–219.6 °C for **6**[28]). Under the optimized conditions given here, the primary byproduct is the monobromo product **7**, which is considerably easier to remove from the desired product.

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CONCLUSION

The results reported here reconfirm previous reports[17−19,29] that reactivity at the more electronically favored 2-postion of 2,3,5-tribromothiophene can be overcome through the use of sterically bulky catalysts to give selective reaction at the less hindered 5-postion. However, *this can only really be successful in the absence of any significant background reaction*. As such, attempts to apply this methodology to the hydrodebromination of haloheterocycles are limited by the very facile noncatalyzed background reaction when $NaBH_4$ is used as the hydrogen source. As shown in the results here, attempts to restrict the background reaction generally results in low conversion, while conditions that enhance conversion tend to make the background reaction more favorable. The final optimized conditions reported here do the best to balance these factors yet still suffer from significant overdebromination that lowers the yield of the desired product. As such, the extremely high levels of selectivity previously reported by Hor and co-workers[17,18] are just not practical via the use of $NaBH_4$. It is possible that this was also suspected by Hor and co-workers, as later efforts shifted to the use of alcohols as the hydrogen source for such hydrodebrominations.[30] It should be pointed out that, of the 30 different examples of "selective" catalytic hydrodehalogenation of bromothiophenes and related analogues reported by the groups of Hor and Chelucci,[17,18,21] the example studied in this current report is the only case in which the catalyzed process and the background reaction would be expected to give different products. As a result, it is perhaps not surprising that this complicating issue with the facile background reaction has been previously overlooked.

EXPERIMENTAL SECTION

Unless otherwise specified, all reactions were carried out under an N_2 atmosphere with reagent grade materials. Diethyl ether and THF were distilled from sodium/benzophenone prior to use. Acetonitrile was dried over calcium hydride and distilled prior to use. Sodium borohydride was stored in a desiccator and used within 1 year of purchase. Palladium catalysts were purchased from Sigma-Aldrich, and $Pd(PPh_3)_4$ was stored at −5 °C in the absence of light. 2,3,5-Tribromothiophene (**3**)[11] was synthesized using literature procedures and purified by distillation. ^{1}H NMR spectra were measured on a 400 MHz Varian spectrometer in $CDCl_3$ unless otherwise stated. Percent conversions and product distributions were determined through integration of NMR peaks. All NMR data were referenced to residual solvent peaks, and peak multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets.

General One-Pot Reaction Conditions. Tribromothiophene **3** (5.0 mmol), $NaBH_4$ (7.5 mmol), TMEDA, and $Pd(dppf)Cl_2$ were placed in a flask equipped with a condenser. The flask was then evacuated and back-filled three times with N_2, followed by the addition of THF (100 mL). The reaction mixture was heated to reflux with stirring, and heating was continued for the allotted time. The reaction mixture was then cooled to room temperature and the solvent removed via rotary evaporation. An aliquot of the crude product was then dissolved in $CDCl_3$ and analyzed by ^{1}H NMR to determine product distribution.

*2,3,5-Tribromothiophene (**3**).* ^{1}H NMR: δ 6.89 (s, 1H). ^{13}C NMR: δ 132.3, 113.7, 112.3, 110.8. NMR spectral data agree well with previously reported values.[10]

*2,4-Dibromothiophene (**5**).* ^{1}H NMR: δ 7.14 (d, J = 1.7 Hz, 1H), 6.96 (d, J = 1.7 Hz, 1H). ^{13}C NMR: δ 132.3, 124.8, 113.5, 110.0. NMR spectral data agrees well with previously reported values.[17,19]

*2,3-Dibromothiophene (**6**).* ^{1}H NMR: δ 7.23 (d, J = 6.0 Hz, 1H), 6.91 (d, J = 6.0 Hz, 1H). ^{13}C NMR: δ 130.4, 127.2, 114.3, 111.5. NMR spectral data agree well with previously reported values.[17,18,31]

*3-Bromothiophene (**7**).* ^{1}H NMR: δ 7.28 (dd, J = 3.1, 5.1 Hz, 1H), 7.22 (dd, J = 1.4, 3.1 Hz, 1H), 7.01 (dd, J = 1.4, 5.1 Hz, 1H). ^{13}C NMR: δ 130.0, 126.7, 122.8, 110.2. NMR spectral data agree well with previously reported values.[10,18]

General Reaction Conditions for Slow Addition of Tribromothiophene. $NaBH_4$ (7.5 mmol), TMEDA (15 mmol), and catalyst (2.5 mol %) were placed in a flask equipped with a condenser and an addition funnel that was then evacuated and back-filled three times with N_2, followed by the addition of THF (50 mL). The addition funnel was then charged with **3** (5.0 mmol) in 50 mL of THF. The reaction mixture was heated to reflux with stirring and the solution of **3** added dropwise over the specified time period. Heating was continued for the allotted time, after which the reaction mixture was cooled to room temperature and the solvent removed via rotary evaporation. An aliquot of the crude product was then dissolved in $CDCl_3$ and analyzed by ^{1}H NMR to determine product distribution.

Optimized Reaction Conditions. $NaBH_4$ (7.5 mmol), TMEDA (15 mmol), and catalyst (2.5 mol %) were placed in a flask equipped with a condenser and an addition funnel. The flask was then evacuated and back-filled three times with N_2, followed by the addition of THF (50 mL). The addition funnel was then charged with **3** (5.0 mmol) in 50 mL of THF. The reaction mixture was heated to reflux with stirring and the solution of **3** added dropwise over 1.5 h. Heating was continued for 4.5 h, after which the reaction mixture was cooled to room temperature and poured into H_2O. This mixture was then extracted with diethyl ether, washed with H_2O, and dried over $MgSO_4$, and the solvent was removed via rotary evaporation. The crude material was then purified by silica gel chromatography (hexanes) to give product **6** as a pale oil (60−65% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00587.

Details of attempts to reproduce literature data, details of studies on background reactions, and sample NMR spectra used in analysis of product distribution (PDF)

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Notes

The authors declare no competing financial interest.

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