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Sterics versus Electronics: Regioselective Cross-Coupling of Polybrominated Thiophenes

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Methods for the regioselective cross-coupling of 2,3,5-tribromothiophene have been developed in which selective aryl–aryl coupling occurs at the 5-position with yields up to 63 %. The difference in reactivity of the α- and β-positions then allows sequential regioselective couplings first at the 2-position, followed by the 3-position. Such regioselective cross-coupling allows unprecedented control in the generation of trifunctionalized thiophenes.

Introduction

Functionalized thiophenes have found extensive use as precursors for materials,[1] natural products,[2] and pharmaceuticals.[3] Such functionalized thiophenes are commonly generated from various halothiophenes, which can provide access to the desired product through the application of catalytic cross-coupling chemistry. However, as the desired molecular architecture becomes more complex, it is important to be able to control site-specific reactions, particularly in use of polyhalogenated precursors that contain multiple reactive centers. The most common approach to regioselective coupling in polyhalogenated thiophenes is to take advantage of the electronic differences between the α- and β-positions of the thiophene ring.[4] As the α-positions are significantly more reactive than the corresponding β-positions (ca. 95:5),[5] selective cross-coupling at the 2-position of 2,3- and 2,4-dihalothiophenes are common.[4,6] Examples of site selectivity in the cross-coupling of asymmetric 3,4- or 2,5-dihalothiophenes, however, are very rare,[7] and a general approach for achieving selectivity has not been established.

In contrast, selective debrominations of asymmetric 2,5-dibromothiophenes have been known since the 1930s,[8–13] and the lack of selective cross-couplings has led to such debrominations as the most commonly used approach in syntheses of multifunctional thiophenes. As a result, most syntheses are accomplished through combinations of bromination, debromination, and cross-coupling, resulting in a large number of synthetic steps. A recent approach to reduce the number of synthetic steps in the generation of multifunctional thiophenes can be seen in the elegant work of Mori and co-workers,[14] who demonstrate coupling at the α-hydrogen atom of brominated thiophenes with aryl iodides, thus allowing cross-coupling while retaining the bromo functionalities.

In reviewing known selective thiophene debrominations, it can be seen that these are commonly accomplished by metal/halogen exchange[13] followed by hydrolysis and that the resulting selectivity is due to a combination of electronics and sterics. Metal/halogen exchange is thought to follow an S_N2 mechanism,[15] and thus the observed selectivity is most often due to inductive effects of the functional groups. For example, in 3-alkyl-2,5-dibromothiophenes[8–13] (Table 1, Entries 1–7), the alkyl group enhances the electropositive nature of the 5-bromo group, favoring debromination at this position. Thus, selectivity is mainly due to electronics, and sterics only play a role when the alkyl group becomes very bulky (i.e. *tert*-butyl, Entries 3, 7). In such cases, the 2-position is favored as a result of *steric release*,[11,15c] where removal of strain between the *tert*-butyl group and bromine atom overcomes the electronic preference and steric shielding of the 2-position. If the size of the incoming nucleophile is also increased (Entry 4), the steric hindrance becomes too large for attack at the 2-position, and selectivity reverts to the 5-position. The use of electronegative elements activates adjacent halogen atoms,[15] and thus selectivity for both the 3-alkoxy and 3-bromo examples (Entries 8–11) favors the 2-position. As before, sterics can overcome electronics by increasing the nucleophile size, resulting in a decrease or reversal in selectivity (Entries 9, 10).

Due to the success of utilizing sterics in selective debrominations, it should be reasonable to apply the same approach to regioselective cross-couplings of polybrominated thiophenes. Sterics have a strong influence on the outcome of heterocyclic cross-coupling reactions as both oxidative addition and transmetalation steps require space around the metal center.[4] For electronically comparable sites, pref-

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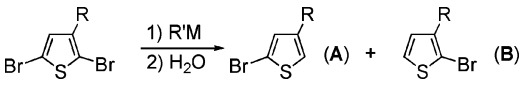
Table 1. Selective debromination of 2,5-dibromothiophenes.[a]



Entry	R	R′M	A	B	Ref.
1	ethyl	BuLi	23	77	[11]
2	isopropyl	BuLi	28	72	[11]
3	*tert*-butyl	BuLi	57	43	[11]
4	*tert*-butyl	BuLi/TMEDA	13	87	[11]
5	hexyl	EtMgCl	15	85	[12]
6	isopropyl	EtMgBr	23	77	[11]
7	*tert*-butyl	EtMgBr	64	36	[11]
8	alkoxy[b]	MeMgBr	70	30	[13]
9	alkoxy[b]	*t*BuMgBr	55	45	[13]
10	Br	MeMgBr	18	82	[8]
11	Br	BuLi	75	25	[9]
12	Br	$Pd(PPh_3)_4/NaBH_4$	6	94	[10]

[a] Values given are ratios of selectivity. [b] alkoxy = $O(C_2H_4O)_2$-CH_3.

erence is usually found for the more easily accessible position, and if steric factors are large enough it may be possible to overcome reaction at an electronically more reactive site. Hor and co-workers reported an excellent example of this with the highly selective debromination of 2,3,5-tribromothiophene (**1**) by oxidative addition of $Pd(PPh_3)_4$ followed by BH_4^- reduction (Table 1, Entry 12).[10] Extending this methodology to aryl–aryl cross-couplings, we then began investigation of the cross-coupling of **1**.

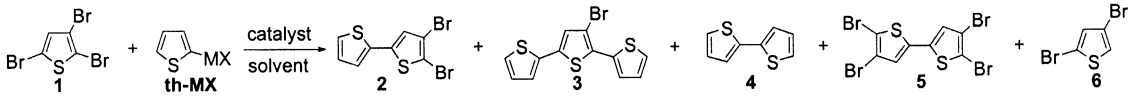
Results and Discussion

The cross-coupling of **1** with various 2-metallated thiophenes (Table 2), was investigated using $Pd(PPh_3)_4$ as the initial catalyst. While the desired 4,5-dibromo-2,2′-bithiophene (**2**) was produced exclusively over the isomeric 3,5-dibromo-2,2′-bithiophene, the yield was fairly low, and the selectivity between **2** and the corresponding terthiophene **3** was only ca. 2:1. In addition, a large amount of 2,2′-bithiophene (**4**), as well as the homocoupled **5**, were also produced. This suggested that the reductive elimination of product **2** was slow, and metathesis was able to occur between the 2-thienylzinc chloride and the (dibromothiophene)palladium complex.

In the process of the study, a deeper literature search revealed the reported cross-coupling of **1** in the presence of $Ni(PPh_3)_2Cl_2$ to give 85% of **2**,[16] although no product characterization was given. This did not seem consistent with our initial results, as reductive elimination from the more electron-rich Ni complexes are generally slower than from the Pd analogues.[17] Indeed, it was found that the claims could not be reproduced in our hands, with the Ni-catalyzed coupling giving only 3% of **2** under the reported conditions (Entry 2). As with the Pd results above, a large amount of **4** was isolated, consistent with slow reductive elimination. The isolation of an appreciable amount of **6** also indicated metathesis under these conditions, and showed the Ni-based oxidative addition favored the 2- over the 5-position of **1**.

Increasing the scope of catalysts, [bis(phosphane)]palladium complexes were then investigated. While $Pd(dppe)Cl_2$ did not provide improvements, the application of $Pd(dppf)Cl_2$ successfully resulted in both increased yields and reduced byproducts. This was presumably due to the increased rate of reductive elimination as a result of the increased bite angle of the dppf ligand.[18] Optimization of these reaction conditions (Entry 9) gave a 63% yield of the desired product **2**, with the thienylzinc reagent giving slightly higher yields than the thienyl Grignard reagent. Interestingly, the reactivity of the zinc reagent seemed to be modulated by its coordination environment, as these reagents were more reactive in weakly coordinating diethyl ether than in the more strongly coordinating THF, and the addition of TMEDA further inhibited the zinc reagent's reactivity. Negishi and co-workers[19] also noted substantial

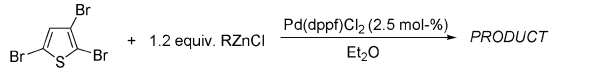
Table 2. Coupling of **1** with 2-metallated thiophenes.[a]

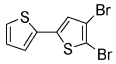
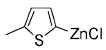
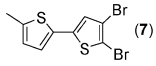
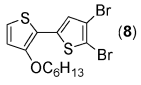
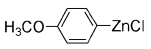
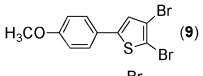
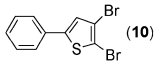
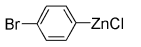
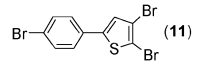
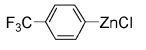
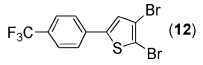


Entry	Catalyst	Equiv. of **th-MX**	MX[b]	Solvent	**1**	**2**	**3**	**4**	**5**	**6**
1	$Pd(PPh_3)_4$	1.5	ZnCl	THF	44	27	16	48	tr	
2	$Ni(PPh_3)_2Cl_2$	2.0	MgBr	THF	55	3	3	47	tr	17
3	$Pd(dppe)Cl_2$	1.5	ZnCl	THF	51	11	tr	86	tr	
4	$Pd(dppf)Cl_2$	1.5	ZnCl	THF	6	56	27	<10		
5	$Pd(dppf)Cl_2$	1.5	ZnCl	Et_2O	tr	54	31	<10		
6	$Pd(dppf)Cl_2$	1.5	ZnCl	Et_2O/THF (1:1)	7	62	21	<10		
7	$Pd(dppf)Cl_2$	1.5	ZnCl	Et_2O/THF (1:3)	11	63	21	<10		
8	$Pd(dppf)Cl_2$	1.2	ZnCl	THF	20	53	7	<10		
9	$Pd(dppf)Cl_2$	1.2	ZnCl	Et_2O	14	63	15	<10		
10	$Pd(dppf)Cl_2$	1.2	ZnCl	THF/hexane (2:1)	16	60	6	<10		
11	$Pd(dppf)Cl_2$	1.2	ZnCl(TMEDA)	THF	81	17	tr	<10		
12	$Pd(dppf)Cl_2$	1.5	MgBr	THF	18	53	15	<10		
13	$Pd(dppf)Cl_2$	1.2	MgBr	THF	34	56	10	<10		
14	$Pd(dppf)Cl_2$	1.2	MgBr	Et_2O	12	54	16	<10		

[a] Yields based on **1**, except for **4**, which is based on **th-MX**. tr = trace. [b] Arylzinc reagents formed from aryllithium precursors.

Table 3. Regioselective coupling of **1** with arylzinc chlorides.



Entry	RZnCl	Product	Isolated Yield (%)[a]
1		 (**2**)	63
2		 (**7**)	48 (59)
3		 (**8**)	55 (65)
4		 (**9**)	57
5		 (**10**)	38 (51)
6		 (**11**)	38
7		 (**12**)	11 (31)
8		*No reaction*	

[a] Yields in parentheses determined by NMR spectroscopy after initial chromatography (purity ca. 90%). Analytically pure samples required additional recrystallization in these cases, resulting in reduced isolated yields.

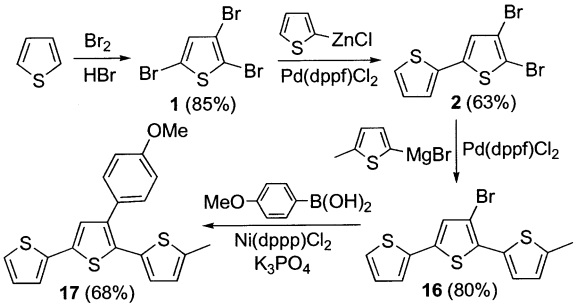
coordination effects as a result of both solvent and coordinating salts.

In order to determine the scope of the regioselective cross-coupling of **1**, a variety of arylzinc chlorides were then investigated (Table 3). As can be seen, the donating or withdrawing effects of the aryl groups have a significant effect on the yields. The lack of regioisomer 3,5-dibromo-2,2′-bithiophene (**13**) in Table 2 suggests that either oxidative addition was completely selective at the 5-position, or reaction at both the 2- or 5-position was occurring in some ratio and the relative reactivities of products **2** and **13** resulted in selective consumption of **13**. The second possibility agrees well with the prior debromination results, and selective conversion of **13** to the terthiophene **3** would explain the absence of this isomer in the recovered byproducts. This conclusion is also supported by the isolation of 3,5-dibromo-2-(4-methoxyphenyl)thiophene (**14**, ca. 6.3%) and greatly reduced triaryl production (<5%) in the preparation of **9**, which indicates the *p*-methoxy group is electron-donating enough to limit oxidative addition to **14**. From this data, it can be approximated that the selectivity between the 5- vs. 2-position of **1** is ca. 9:1. The slightly less donating 5-methylthiophene also resulted in the detection of both isomers formed from the initial coupling in a ca. 12:1 ratio. Interestingly, the minor isomer was not detected in the production of **8**, indicating that the cross-conjugated alkoxy unit had a smaller electronic effect than the fully conjugated alkyl group.

In contrast, the coupling of arylzinc reagents with electron-withdrawing groups gave less desired product and no detectable 2-coupled products due to reduced reactivity of the arylzinc reagent and enhancement of the second oxidative addition, thus resulting in higher yields of the doubly coupled triaryl byproducts. 2-Pyridylzinc chloride (Entry 8) did not react, most likely a result of aggregation, making the reagent insoluble in diethyl ether. Even the use of the more reactive 2-pyridylmagnesium chloride resulted in only a 6% yield of the desired 2,3-dibromo-5-(2-pyridyl)thiophene (**15**). The tendency for these reagents to aggregate demonstrates a potential complication in the cross-coupling of organozinc reagents containing strong coordinating groups.

Lastly, the selectivity in the presence of other aryl halides is also of significant interest. The use of (4-bromophenyl)-zinc chloride gave 38% of the desired product **11** without detectable coupling at the phenyl bromide. This further level of selectivity could allow the stepwise construction of fairly elaborate aryl systems.

To demonstrate the power of the new regioselective methods, they were applied to the synthesis of the known compound 4′-bromo-5-methyl-2,2′;5′,2"-terthiophene (**16**)[20] from thiophene (Scheme 1). By the new methods, the total number of steps was reduced from six to three, and the overall yield increased from 15 to 43%. Efficient cross coupling (68%) of a third aryl group was then achieved using $Ni(dppp)Cl_2$ to give the trifunctionalized 3′-(4-methoxyphenyl)-5-methyl-2,2′;5′,2"-terthiophene (**17**) with an overall yield of 29%.



Scheme 1. Sequential regioselective couplings.

Conclusions

Regioselective cross-coupling methods have been developed in which initial coupling occurs selectively (ca. 1:10) at the 5-position of **1** with isolated yields of up to 63%. The difference in reactivity of the α- and β-positions then allows sequential regioselective couplings first at the 2-position, followed by the 3-position. Such regioselective cross-coupling allows unprecedented control in the generation of trifunctionalized thiophenes.

Experimental Section

General Procedure for the Regioselective Cross-Coupling of 1: To a diethyl ether solution (50 mL) of arylzinc chloride (6.0 mmol) was

added 2,3,5-tribromothiophene (1.60 g, 5.0 mmol) and Pd(dppf)Cl_2 (0.10 g, 2.5 mol-%). The resulting mixture was stirred at room temperature overnight, poured into 150 mL of satd. NH_4Cl, and extracted with diethyl ether (3 × 150 mL). The combined organic phases were dried with $MgSO_4$, filtered, and purified by silica gel chromatography. Compounds **7**, **8**, **10** and **13** exhibit similar polarities to their byproducts, and thus additional recrystallization from CH_3CN was required to obtain analytically pure samples.

Supporting Information (see footnote on the first page of this article): Experimental details for all compounds and crystallographic data for **2**.

Acknowledgments

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