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Programmed Synthesis of Tetraarylthiophenes through Sequential C−H Arylation

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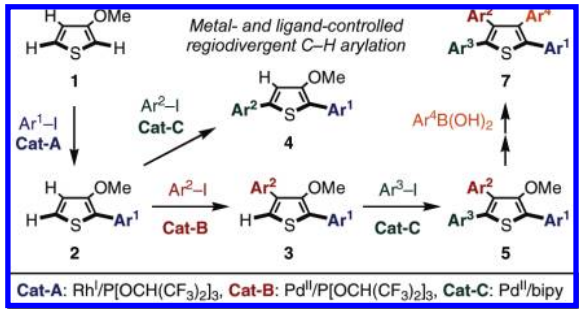
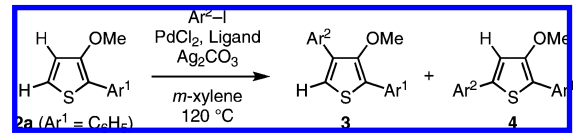
Multiply arylated thiophenes are privileged structures with many interesting functions, including optoelectronic[1] and biological[2] properties. In order to accelerate the discovery and structure−property relationship studies of new functional molecules of this class, a flexible method for accessing all possible isomers in a programmable format is much needed. We herein report a general protocol for the programmed synthesis of tetraarylthiophenes[3,4] through the sequential C−H/C−O arylation of 3-methoxythiophene (**1**). The development of regioselective C−H bond arylation catalysts has been a key to realizing our concept.



To realize a programmed synthesis of tetraarylthiophenes, a general method allowing regioselective arylations onto a thiophene core had to be developed. As a means for installing aryl groups onto the core, we selected the metal-catalyzed C−H bond arylation of thiophenes in view of synthetic expediency.[5,6] Though this approach was conceptually attractive, obstacles to overcome included insufficient reactivity and the control of regioselectivity of thienyl C−H bonds toward catalytic C−H arylation reactions.[5] For example, several groups have demonstrated that certain Pd,[5,7] Cu,[8] Rh,[9] and Ir[10] catalysts can promote the C2/C5 diarylation of thiophenes, but arylation at the C3/C4 position is very difficult. Very recently, the Miura group has demonstrated that 3-thiophenecarboxylic acid undergoes Pd-catalyzed tetraarylation with bromoarenes, accompanied by cleavage of three C−H bonds and decarboxylation.[11] However, the installation of four different aryl groups onto thiophene ring has not been realized.[3]

We selected 3-methoxythiophene (**1**) as our first-generation platform[12] for tetraarylthiophene synthesis because of its high reactivity and selectivity in catalytic C−H bond arylation with iodoarenes.[9,10] For example, **1** reacts with iodobenzene in the presence of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ catalyst (**Cat-A**) and Ag_2CO_3 to afford 3-methoxy-2-phenylthiophene (**2a**) in 80% yield with virtually complete regioselectivity. This C2-selective arylation occurs with various iodoarenes.[9] Thus, the focal point of this study was to establish a C4- and/or C5-selective catalyst for the arylation of 2-aryl-3-methoxythiophenes **2**. However, we identified that **Cat-A** is problematic for further arylations. For example, the reaction of **2a** (1.5 equiv) and iodobenzene (1 equiv) in the presence of **Cat-A** (3 mol %) and Ag_2CO_3 (1 equiv) in *m*-xylene at 150 °C furnished the C5 phenylation product (**4aa**) in only 38% yield. Even more critically, further arylation (C4 arylation) of **4aa** did not take place with **Cat-A**. Thus, the need for a new catalytic system was obvious at this point. In particular, the development of a catalyst promoting the hard-to-achieve arylation at the β-position of thiophene ring was crucial. Extensive screening led to the development of two catalysts (**Cat-B** and **Cat-C**) for the second and third arylations of **1**, respectively.

Table 1. Ligand-Controlled Regiodivergent Arylation of **2a**[a]



entry	Ar^2	ligand	major product	% yield (**3**:**4**)[b]
1	C_6H_5 (**a**)	$P[OCH(CF_3)_2]_3$	**3aa**	80 (97:3)
2	C_6H_5 (**a**)	2,2′-bipyridyl	**4aa**	89 (1:99)
3	*o*-MeC_6H_4 (**b**)	$P[OCH(CF_3)_2]_3$	**3ab**	88 (98:2)
4	*o*-MeC_6H_4 (**b**)	2,2′-bipyridyl	**4ab**	98 (2:98)
5[c]	*p*-MeC_6H_4 (**c**)	$P[OCH(CF_3)_2]_3$	**3ac**	83 (96:4)
6	*p*-MeC_6H_4 (**c**)	2,2′-bipyridyl	**4ac**	91 (1:99)
7[c]	*p*-$MeOC_6H_4$ (**d**)	$P[OCH(CF_3)_2]_3$	**3ad**	75 (98:2)
8	*p*-$MeOC_6H_4$ (**d**)	2,2′-bipyridyl	**4ad**	83 (1:>99)
9	*p*-AcC_6H_4 (**e**)	$P[OCH(CF_3)_2]_3$	**3ae**	71 (95:5)
10	*p*-AcC_6H_4 (**e**)	2,2′-bipyridyl	**4ae**	80 (1:>99)
11	*p*-$NO_2C_6H_4$ (**f**)	$P[OCH(CF_3)_2]_3$	**3af**	69 (93:7)
12	*p*-$NO_2C_6H_4$ (**f**)	2,2′-bipyridyl	**4af**	69 (2:98)
13	*p*-$CF_3C_6H_4$ (**g**)	$P[OCH(CF_3)_2]_3$	**3ag**	77 (95:5)
14	*p*-$CF_3C_6H_4$ (**g**)	2,2′-bipyridyl	**4ag**	77 (1:>99)

[a] Conditions: **2a** (1.5 equiv), Ar^2I (1 equiv), $PdCl_2$ (5 mol %), ligand (10 mol %), Ag_2CO_3 (1 equiv), *m*-xylene, 120 °C. [b] Isolated yield. Isomer ratio was determined by ^1H NMR and GC analyses. [c] $PdCl_2$ (10 mol %) and $P[OCH(CF_3)_2]_3$ (20 mol %) were employed.

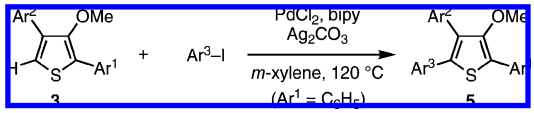
We first found that the otherwise difficult C4-selective arylation of **2a** with iodoarenes can be promoted by the catalyst $PdCl_2/P[OCH(CF_3)_2]_3$ (**Cat-B**) and Ag_2CO_3 in *m*-xylene at 120 °C, furnishing **3** with high regioselectivity (93−98% C4) (Table 1). Given the C5 selectivity of **Cat-A** for the arylation of **2a** (see above), an interesting metal-controlled regiodivergency[13] (C5 for Rh^I, C4 for Pd^{II}) has been identified in $P[OCH(CF_3)_2]_3$-bound metal catalysts. More interestingly, we found that the C4 selectivity of **Cat-B** can be switched to C5 selectivity (98 to >99%) by changing the supporting neutral ligand to 2,2′-bipyridyl[14] (**Cat-C**). This ligand-controlled regiodivergent C−H arylation[13] (C4 for $P[OCH(CF_3)_2]_3$, C5 for 2,2′-bipyridyl) turned out to be general for $PdCl_2/Ag_2CO_3$ catalysis (Table 1).[15]

With two regiodivergent C−H arylation catalysts in hand, the third C−H arylation for making 2,4,5-triaryl-3-methoxythiophenes **5** was next examined for two possible routes via either **3** or **4**. Gratifyingly, the **Cat-C** system promoted the C5 arylation of 2,4-diaryl-3-methoxythiophenes **3** with iodoarenes, giving **5** in good yields (Table 2). Under otherwise identical conditions, the **Cat-B** system was unable to promote the arylation for both **3** and **4**.

Finally, the fourth arylation to obtain the targeted tetraarylthiophenes **7** was investigated. Extensive screening of reaction conditions established a high-yield procedure involving Suzuki−Miyaura coupling[16] (Table 3). Thus, the BBr_3-promoted demethylation of **5** followed by treatment of the thus-obtained crude alcohols with $Tf_2O/i\text{-}Pr_2NEt$/

10.1021/ja906215b CCC: $40.75

Table 2. Arylation of **3** Catalyzed by Pd/bipy/Ag_2CO_3[a]

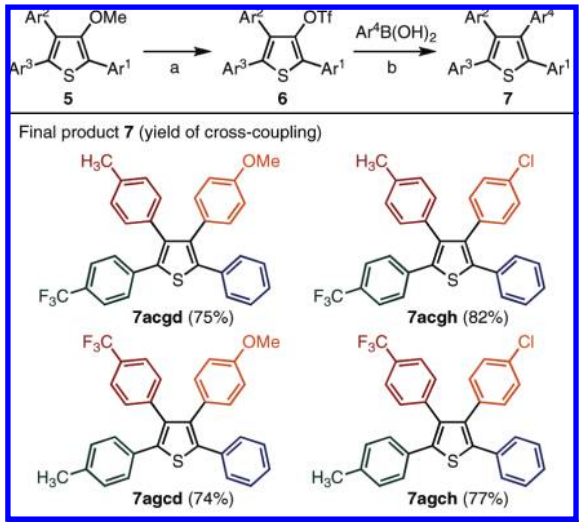


entry	Ar^2	Ar^3	**5** (% yield)
1	C_6H_5 (**a**)	C_6H_5 (**a**)	**5aaa** (87)
2	*p*-MeC_6H_4 (**c**)	*p*-$NO_2C_6H_4$ (**f**)	**5acf** (61)
3[b]	*p*-MeC_6H_4 (**c**)	*p*-$CF_3C_6H_4$ (**g**)	**5acg** (70)
4[b]	*p*-AcC_6H_4 (**e**)	*p*-MeC_6H_4 (**c**)	**5aec** (65)
5	*p*-AcC_6H_4 (**e**)	*p*-$NO_2C_6H_4$ (**f**)	**5aef** (73)
6[b]	*p*-$CF_3C_6H_4$ (**g**)	*p*-MeC_6H_4 (**c**)	**5agc** (70)

[a] Conditions: **3** (1 equiv), Ar^3I (3 equiv), $PdCl_2$ (5 mol %), 2,2′-bipyridyl (10 mol %), Ag_2CO_3 (2 equiv), *m*-xylene, 120 °C. [b] Using 1 equiv of Ag_2CO_3.

DMAP produced the corresponding triflates **6** in high yields (>70%).[17] The triflates were cross-coupled with arylboronic acids in the presence of $Pd(PPh_3)_4$ catalyst and $Ba(OH)_2$ to finally afford tetraarylthiophenes **7** in good yields with virtually complete isomeric purities (Table 3).[18]

Table 3. Synthesis of Tetraarylthiophenes **7**[a]



[a] Conditions: (a) **5**, BBr_3, CH_2Cl_2, then Tf_2O, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (see the Supporting Information for details); (b) **6** (1 equiv), $Ar^4B(OH)_2$ (3 equiv), $Pd(PPh_3)_4$ (5 mol %), $Ba(OH)_2$ (2 equiv), 1-butanol/H_2O (5:4), 65 °C.

In summary, we have established a general protocol for the programmed synthesis of tetraarylthiophenes. The utilization of three catalysts, $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, $PdCl_2/P[OCH(CF_3)_2]_3$, and $PdCl_2$/bipy, enables regioselective sequential arylations at the three C−H bonds of 3-methoxythiophene with iodoarenes. Interesting metal- and ligand-controlled regiodivergent C−H arylations have been uncovered during this study. Noteworthy features of the present method are that (i) all of the aryl groups assembled on the thiophene core stem from readily available aryl iodides or boronic acids, (ii) the installation of aryl groups at the desired positions can be achieved, and (iii) simple alteration of the application order of aryl reagents in the sequence results in the production of all possible isomers of tetraarylthiophenes. Although we focused on the synthesis of tetraarylthiophenes in this work, our strategy is also applicable to the regioselective synthesis of di- or triarylated thiophenes by skipping one or two of the C−H arylation steps prior to the final C−O bond arylation. The present strategy should find many uses for combinatorial lead-structure identification and optimization in the development of functional organic materials where the structure−property relationships are often not easily predictable. These studies as well as the mechanistic investigations of the newly developed catalysts are now the focus of our ongoing efforts.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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