C–H Functionalization

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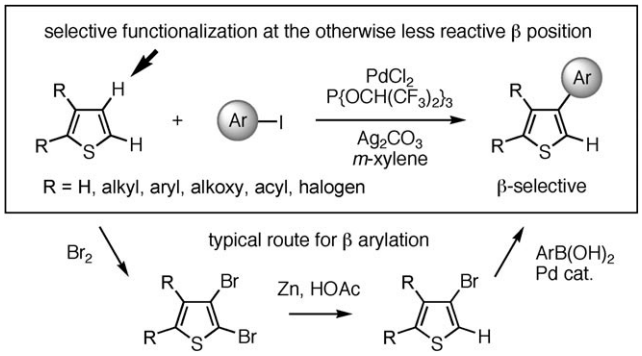
A General Catalyst for the β-Selective C–H Bond Arylation of Thiophenes with Iodoarenes**

*Kirika Ueda, Shuichi Yanagisawa, Junichiro Yamaguchi, and Kenichiro Itami**

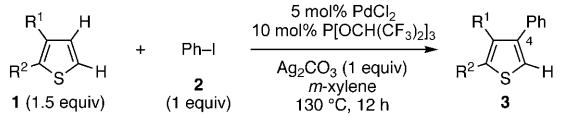
The functionalization of thiophenes is an important and fundamental transformation in organic chemistry.[1] Representative examples include electrophilic substitution and base-mediated metalation followed by reaction with an electrophile. The direct functionalization of C–H bonds[2,3] of thiophenes under the catalysis of transition metals is a rapidly growing area of extensive research. However, most of these reactions are known to occur preferentially at the α position of thiophene rings when both α and β positions are available, and a general method for selective functionalization of the β position has not been forthcoming.[4] Herein we report the first general catalytic system for the β-selective arylation of thiophene C–H bonds.[3] This new methodology for direct functionalization will significantly streamline the synthesis of β-aryl thiophenes: in the current multistep approach, a sequence of α,β dibromination, α debromination, and organometallic cross-coupling is typically required (Scheme 1).

As an application of catalytic C–H-bond arylation technology[5] to the synthesis of useful classes of compounds, we recently established a general protocol for the programmed synthesis of tetraarylthiophenes.[5d] During that study, the β selectivity observed in the arylation of the methoxy-substituted thiophene **1a** with iodobenzene (**2**) under the catalysis of $PdCl_2/P\{OCH(CF_3)_2\}_3/Ag_2CO_3$ (Table 1, entry 1)



Scheme 1. Comparison of synthetic approaches to β-aryl thiophenes: the method presented herein for direct functionalization, and the multistep route typically used for the β arylation of thiophenes.

Table 1: Generality of the reaction in terms of the thiophene coupling partner.



Entry	1	Major product	Yield [%] (regioselectivity)
1	 **1a**	 **3a**	81 (96:4)[a]
2	 **1b**	 **3b**	69 (>99:1)
3	 **1c**	 **3c**	66 (>99:1)
4	 **1d**	 **3d**	48 (97:3)[a,b]
5	 **1e**	 **3e**	76 (84:16)[a,b]
6	 **1f**	 **3f**	56 (>99:1)
7	 **1g**	 **3g**	46 (95:5)[b,c]
8	 **1h**	 **3h**	56 (>99:1)[b]
9	 **1i**	 **3i**	40 (83:17)[c]
10	 **1j**	 **3j**	60 (95:5)[c]
11	 **1k**	 **3k**	53 (95:5)[b,c]
12	 **1l**	 **3l**	61 (88:12)[b,c,d]
13			86 (88:12)[b,c,e]
14			30 (88:12)[c,f]

[a] The minor isomer is the C5-phenylation product. [b] The reaction was carried out with 10 mol% $PdCl_2$ and 20 mol% $P\{OCH(CF_3)_2\}_3$. [c] The minor isomer is the C2-phenylation product. [d] The reaction was carried out with 10 equivalents of **1l**. [e] The reaction was carried out with 25 equivalents of **1l**. [f] The reaction was carried out with 1 mol% $PdCl_2$, 2 mol% $P\{OCH(CF_3)_2\}_3$, and 6 equivalents of **1l**. The reaction time was 20 h.

[*] K. Ueda, S. Yanagisawa, Dr. J. Yamaguchi, Prof. Dr. K. Itami
Department of Chemistry, Graduate School of Science
Nagoya University, Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-788-6098
E-mail: itami@chem.nagoya-u.ac.jp
Homepage: http://synth.chem.nagoya-u.ac.jp

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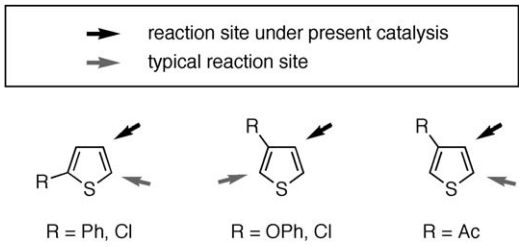
was an intriguing phenomenon, since the transition-metal-catalyzed arylation of thiophene C–H bonds generally proceeds at α positions (C2 and/or C5) according to the typical reactivity profile of the thiophene ring.[3–5]

Following this discovery, we considered the critical question as to whether the observed β selectivity was due to substrate control (directing effect of the methoxy group)[6] or catalyst control. To answer this question and determine the generality of the protocol, we subjected a range of thiophene derivatives to arylation in the presence of the $PdCl_2$/P{OCH-$(CF_3)_2$}$_3$/Ag_2CO_3 catalytic system (Table 1).

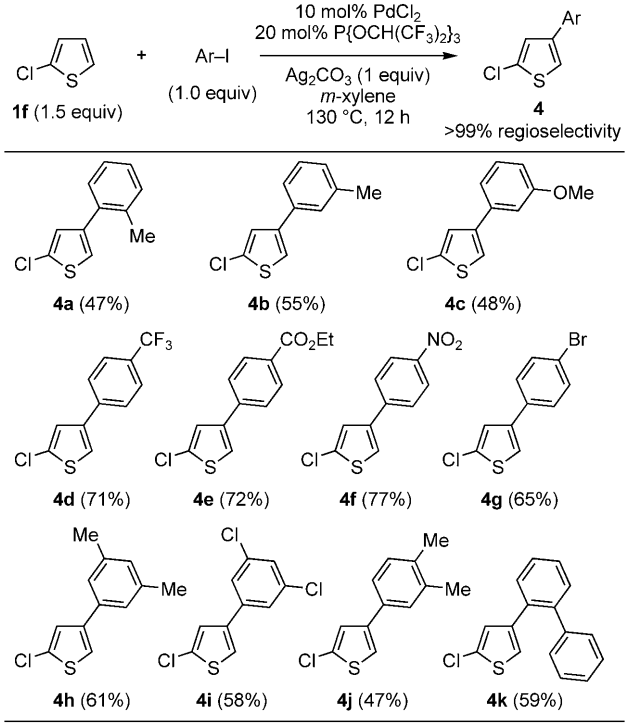
Reactions of 2,3-disubstituted thiophenes, **1b**–**1d**, did indeed afford C4-arylated products with very high regioselectivity (Table 1, entries 2–4). The fact that β selectivity was observed without the methoxy group on the thiophene ring clearly indicates that the observed regioselectivities are a result of catalyst control. Arylation of the 2-substituted thiophenes **1e** and **1f** proceeded at the 4-position (Table 1, entries 5 and 6). In fact, the 4-position is generally the least reactive site in thiophenes when the 2-position is occupied by *ortho*/*para*-directing groups, such as Ph or Cl (Scheme 2). The



Scheme 2. Unique regioselectivity of Pd/P{OCH$(CF_3)_2$}$_3$ catalysis.

arylation of 3-substituted thiophenes, **1g**–**1i**, one of the most problematic substrate classes,[7] also occurred selectively at the 4-position (Table 1, entries 7–9). Interestingly, the observed selectivities override the inherent influence of *ortho*/*para*- (OPh, Cl) and *meta*-directing groups (Ac), as well as that of the thiophene ring itself (Scheme 2). Thiophene-containing fused aromatic compounds, such as benzo[*b*]thiophene (**1j**) and thieno[3,2-*b*]thiophene (**1k**), as well as thiophene itself (**1l**), were also arylated with high β selectivity (Table 1, entries 10–14). Although we typically used relatively high catalyst loadings (5–10 mol% of Pd), the arylation also took place with 1 mol% of Pd (Table 1, entry 14). In this particular reaction, the turnover number reached 30.

We next examined the scope of the reaction with respect to the iodoarene coupling partner. Representative results are summarized in Scheme 3. Various iodoarenes reacted with 2-chlorothiophene (**1f**) to give the corresponding arylated thiophenes **4** in good yields. Both electron-rich (in products **4a**–**4c**, **4h**, and **4j**) and electron-deficient aryl groups (in products **4d**–**4g** and **4i**) could be installed on the thiophene ring. Aryl iodides with electron-withdrawing groups showed higher reactivity. Severe steric hindrance imposed by *ortho* substitution (in **4a** and **4k**) was tolerated, as were functional groups such as ester and nitro groups (in **4e** and **4f**). Notably,



Scheme 3. Generality of the reaction with respect to the iodoarene coupling partner. Product yield given in parentheses.

the cross-coupling of Cl- and Br-containing iodoarenes with 2-cholorothiophene (**1f**) left the C–Cl and C–Br bonds intact (in products **4g** and **4i**), which is attractive for further synthetic elaboration. In all cases examined, the reaction took place exclusively at the 4-position.

This investigation of substrate scope clearly showed that the β selectivity observed with $PdCl_2$/P{OCH$(CF_3)_2$}$_3$/Ag_2CO_3 is a remarkably general phenomenon, and that the β selectivity is catalyst-based. Thus, we next examined the effect of the reaction parameters, including the Pd source, the ligand, additives, the solvent, and the temperature, in the phenylation of thiophene (Table 2; see also Tables S1–S5 in the Supporting Information).

$PdCl_2$, $PdBr_2$, PdI_2, and 2 NaCl·$PdCl_2$ performed equally well as the Pd source. The complex [Pd_2(dba)$_3$] (dba = dibenzylideneacetone) also promoted the β-selective arylation, albeit in lower yield. On the other hand, $Pd(OAc)_2$, Pd-$(OCOCF_3)_2$, and [$Pd(CH_3CN)_4$](BF_4)$_2$ preferentially catalyzed the formation of 2-phenylthiophene. The effect of the supporting ligand was most striking. The extremely electron-withdrawing ligand P{OCH$(CF_3)_2$}$_3$ was found to be the best ligand for the β-selective arylation of thiophenes (Table 2, entry 1). Albeit less efficiently, PhP{OCH$(CF_3)_2$}$_2$ also promoted the reaction with good β selectivity (Table 2, entry 2). These results clearly implicate the importance of the 1,1,1,3,3,3-hexafluoro-2-propoxy group on phosphorus for the β-selective arylation of thiophenes. Among various silver-based additives examined, Ag_2CO_3 and AgO promoted the β-selective arylation with reasonable efficiency. Quite interestingly, the β-selective arylation occurred in a wide variety of solvents (*m*-xylene, toluene, hexafluorobenzene, chloroben-

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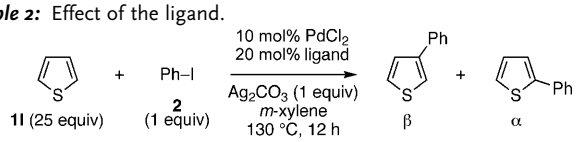
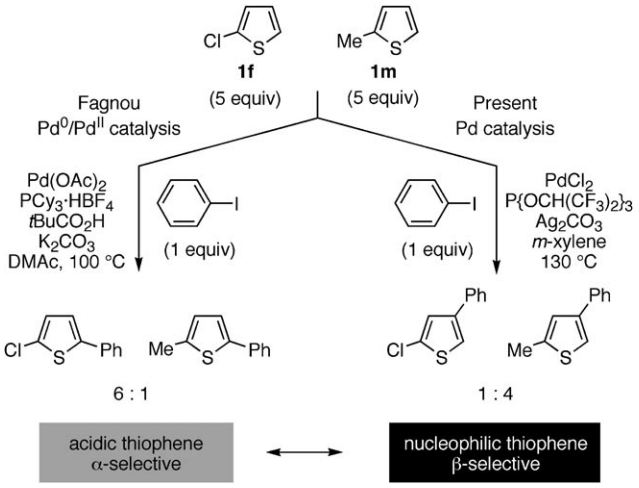
Table 2: Effect of the ligand.



Entry	Ligand	β/α	Yield [%]
1	**$P\{OCH(CF_3)_2\}_3$**	**86:14**	**86**
2	**$PhP\{OCH(CF_3)_2\}_2$**	**63:37**	**61**
3	$P\{OCH(CH_3)_2\}_3$	30:70	18
4	$P(OCH_2CF_3)_3$	34:66	18
5	$P(OCH_3)_3$	18:82	15
6	$P(OPh)_3$	38:62	14
7	$P(OC_6H_4(o\text{-}CH_3))_3$	45:55	37
8	PPh_3	4:96	75
9	$P(C_6H_4(p\text{-}CF_3))_3$	31:69	58
10	$P(C_6F_5)_3$	31:69	66
11	PCy_3	<1:99	>99
12	$Ph_2P(CH_2)_2PPh_2$	<1:99	73
13	none	–	2

zene, 1,2,4-trichlorobenzene, cyclooctane, cyclopentyl methyl ether, and 1,4-dioxane) in the presence of $PdCl_2/P\{OCH(CF_3)_2\}_3/Ag_2CO_3$.

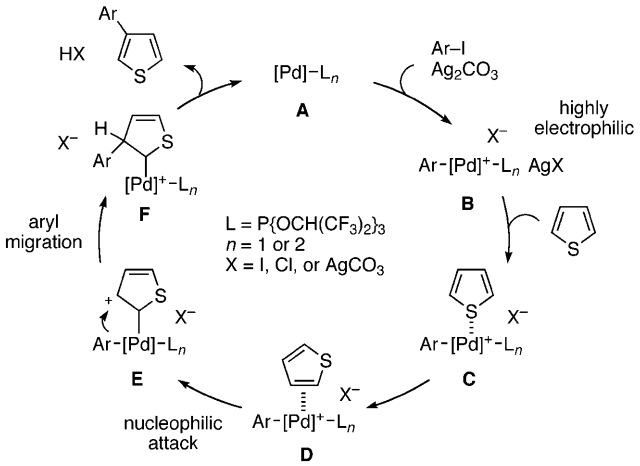
To better understand the characteristics of the present reaction, we compared it with the Pd^0/Pd^{II} catalytic system described by Fagnou and co-workers[7] (one of the most reliable systems to date) through intermolecular competition experiments (Scheme 4). Fagnou and co-workers demonstrated that their $Pd/PCy_3/tBuCO_2H/K_2CO_3$ catalytic system not only favors arylation at the α position but also reacts preferentially with acidic 2-chlorothiophene (**1f**) over nucleophilic 2-methylthiophene (**1m**).[7b] These observations are in line with their proposal of a Pd^0/Pd^{II} redox cycle involving not an electrophilic aromatic substitution mechanism but a concerted metalation–deprotonation pathway.[7] When the competition reaction was conducted with the present catalytic system, arylation occurred preferentially with nucleophilic 2-methylthiophene (**1m**). These contrasting results with respect



Scheme 4. Comparison with the Pd^0/Pd^{II} catalytic system developed by Fagnou and co-workers. Cy = cyclohexyl, DMAc = *N*,*N*-dimethylacetamide.

to the preferred substrate (acidic versus nucleophilic) and the regioselectivity (α versus β) indicate that the present catalytic system may react by a mechanism distinct from that proposed by Fagnou and co-workers.

A potential mechanism that takes into account the importance of the π-accepting $P\{OCH(CF_3)_2\}_3$ ligand, the preferential reaction of nucleophilic thiophenes, and the unprecedented β selectivity is shown in Scheme 5. The



Scheme 5. Possible mechanism.

proposed mechanism involves 1) oxidative addition of ArI to the Pd complex **A**, 2) silver-mediated generation of the cationic and electrophilic aryl palladium species **B**, 3) coordination of the thiophene to Pd to give **C**[8] and/or **D**,[9] 4) C_α–Pd bond formation to give **E**, 5) migration of the aryl group from Pd to the β carbon atom to form a formal Ar–Pd-insertion intermediate **F**,[10] and 6) proton abstraction to produce a β-aryl thiophene with the regeneration of **A**. The observed electronic preferences of the present system, such as 1) the requirement for the extremely electron-withdrawing $P\{OCH(CF_3)_2\}_3$ ligand, 2) the preferential reactivity with nucleophilic thiophenes, and 3) the positive influence of electron-withdrawing substituents on the iodoarene coupling partner, are all likely to promote the otherwise weak thiophene–palladium interaction, for example, in **C** or **D**.[11]

In summary, we have established a general catalytic system that promotes the β-selective arylation of thiophene derivatives with iodoarenes. This previously inaccessible selective β functionalization of thiophenes should have significant synthetic utility in materials science as well as pharmaceuticals and natural products synthesis.

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[10] Although unlikely, a concerted insertion mechanism (*syn* carbopalladation) cannot be excluded for the formation of **F** from **B.**

[11] The differing strengths of thiophene–palladium and pyrrole–palladium interactions might explain the α selectivity and low reactivity observed when pyrroles were used as substrates.

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