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Direct C−H Bond Arylation of Thienyl Thioamides Catalyzed by Pd−Phenanthroline Complexes

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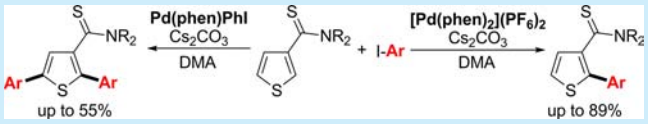
Supporting Information



ABSTRACT: A direct C−H bond arylation method for thienyl thioamides catalyzed by $[Pd(phen)_2](PF_6)_2$ was developed. This reaction selectively afforded 2-monoarylated products, while the corresponding amide thiophene derivatives furnished 2,5-diarylated products. Mechanistic studies revealed that a Pd(II)−bisthioamide complex should be the active species for the reaction of thienyl thioamides in the presence of catalytic amounts of $[Pd(phen)_2](PF_6)_2$. Similar to the reaction with amides, the reaction with thioamides selectively generated the 2,5-diarylated products when a preformed Pd(phen)PhI complex was used.

Carbonyl-containing π-conjugated moieties are a frequently encountered structural motif in modern organic functional materials. This is mostly due to the energy levels of their lowest unoccupied molecular orbitals (LUMOs), which usually render these compounds as good accepting materials.[1] Thiocarbonyl-containing π-conjugated systems also attract significant attention, especially as semiconducting materials.[2] Generally, thiocarbonyl-containing compounds are obtained from the treatment of the corresponding carbonyls with phosphorus sulfides such as Lawesson's reagent.[3] However, this method can be problematic for the preparation of functional materials, as the thus obtained products remain frequently contaminated with inseparable organophosphorous-based byproducts. Transition-metal-catalyzed C−C bond formations between preformed thiocarbonyl-containing compounds and/or other building blocks represent attractive alternatives for the construction of thiocarbonyl-containing π-conjugated systems,[4] even though transition-metal catalysts usually lose their catalytic activity after reaction with thiocarbonyl-containing substrates.[5] Because of these shortcomings, only a few examples for transition-metal-catalyzed reactions of thiocarbonyl-containing compounds have been reported, such as the asymmetric aldol-type reaction of thioamides by Kumagai and Shibasaki[6] and the thiocarbonyl-directed *ortho*-selective alkenylation of aryl thioamides with alkynes by Satoh.[7] However, these reactions do not include redox processes of the catalyst metal, which are usually involved in cross-coupling reactions. Accordingly, the development of transition-metal-catalyzed reactions including such processes still remains an important research target.

We have previously reported that palladium complexes with nitrogen-based ligands, in particular $[Pd(phen)_2](PF_6)_2$ (phen: 1,10-phenanthroline), show excellent catalytic activity in direct C−H bond arylations of heteroarenes.[8] We envisioned that these catalytic systems should also be applicable to thiocarbonyl-containing compounds, since nitrogen-based bidentate ligands are inert to thiocarbonyl groups and usually strongly coordinate to the catalyst metal and are thus inert to ligand replacement reactions induced by thiocarbonyl groups.

Herein, we report our recent results on the direct C−H bond arylation of aryl thioamides catalyzed by Pd−phenanthroline complexes. We discovered that $[Pd(phen)_2](PF_6)_2$ initiates different reaction pathways, depending on concentration of the thioamides. Owing to the strong coordination properties of the thiocarbonyl group, these reactions usually start with the formation of Pd−bisthioamide complexes.

Initially, we evaluated several catalytic systems for the reaction between *N,N*-diisopropyl-3-thiophenecarbothioamide (**1a**) and phenyl iodide (**2a**) (Table 1). When $[Pd(phen)_2](PF_6)_2$ (10 mol %) and Cs_2CO_3 (3 equiv) were used, 2-monoarylated **3aa** was obtained in high yield (82%), and the corresponding desulfurized compounds were not observed in significant quantities though the reaction with phenyl bromide did not proceed efficiently (entry 1). Notably, this result is in stark contrast to the reactions of amide **1a′** and other thiophene derivatives under identical conditions; there, the corresponding 2,5-diarylated products were obtained exclusively, even when an equimolar amount of aryl halide was used (eq 1).[8a,b] Although the addition of pivalic acid often accelerates Pd-catalyzed direct C−H bond arylations, it inhibited this reaction and **1a** was recovered almost quantitatively (entry 2). Moreover, the reaction using $Pd(OAc)_2$

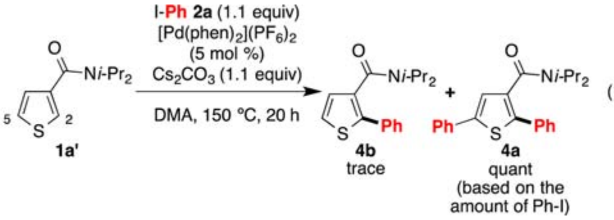


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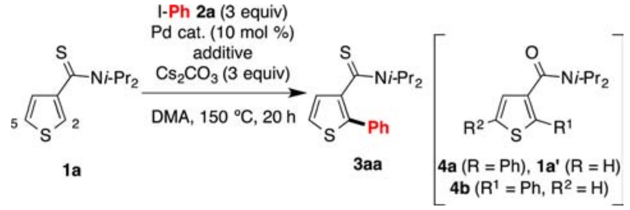
Table 1. Optimization of the Conditions for the Reaction between 1a and 2a



entry	Pd cat.	additive (mol %)	yield[a] (%)	conversion (%)
1	$[Pd(phen)_2](PF_6)_2$		82 (7)[b]	93 (39)[b]
2	$[Pd(phen)_2](PF_6)_2$	PivOH (40 mol %)	12	31
3	$Pd(OAc)_2$		trace	36
4	$Pd(OAc)_2$	dppe[c] (20 mol %)	ND[d]	100
5	$Pd(OAc)_2$	PCy_3 (20 mol %)	ND[d]	100
6	$Pd(OAc)_2$	PPh_3 (20 mol %)	ND[d]	100
7	$Pd(dba)_2$	phen (20 mol %)	ND[d]	100

[a] Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] Phenyl bromide was used instead of phenyl iodide. [c] dppe: 1,2-bis(diphenylphosphino)ethane. [d] ND: not detected.

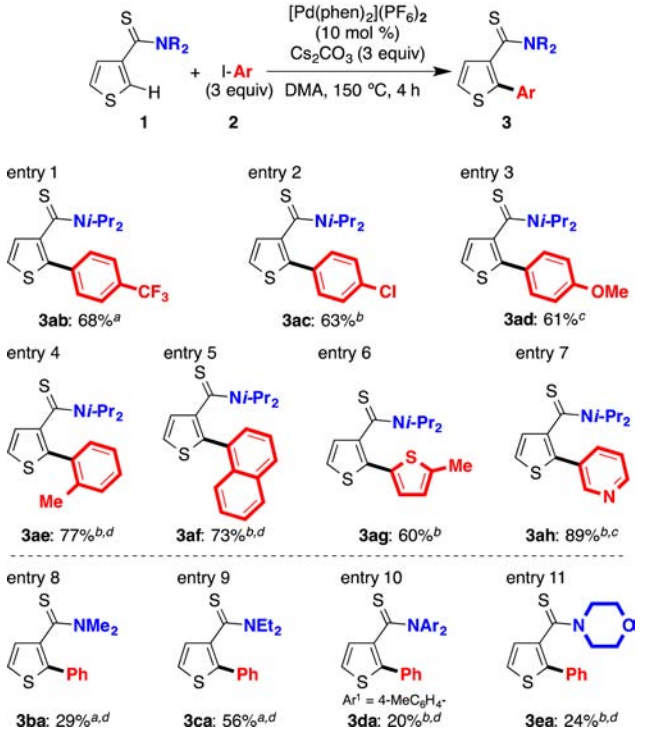


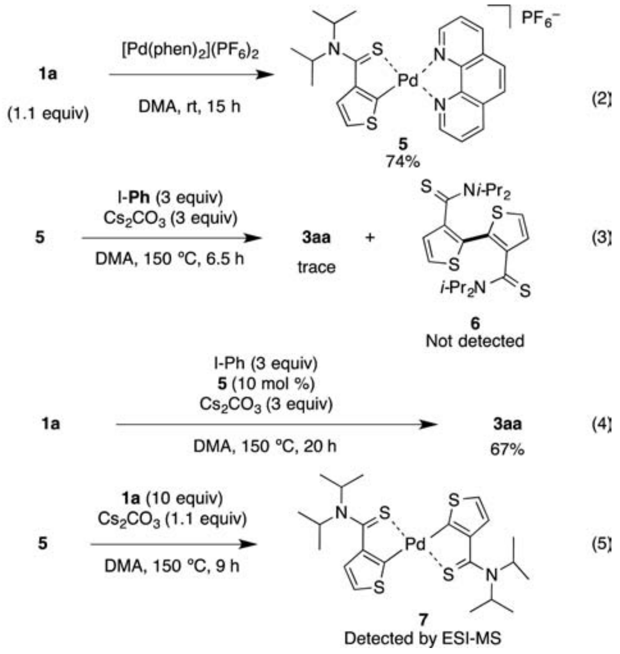
Figure 1. Substrate scope of thienyl thioamides **1** and aryl iodides **2**. Key: (a) yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard; (b) isolated yield; (c) K_2CO_3 was used instead of Cs_2CO_3; (d) reaction time 20 h.

and Cs_2CO_3 (3 equiv) in the absence of ligand did not proceed readily (entry 3). Conversely, in the presence of various phosphine ligands such as PPh_3, PCy_3, or dppe, **1a** was consumed completely but yielded complex product mixtures that did not contain **3aa** (entries 4–6). In these cases, substantial amounts of the corresponding desulfurized mono- and diarylated amides (**4a**,**b**) and the desulfurized starting material **1a′** were observed by GC–MS. Finally, we tested $Pd(dba)_2$ with 1,10-phenanthroline as a ligand and observed similar results as for the $Pd(OAc)_2$/phosphine systems (entry 7).

Encouraged by these results, we examined the substrate scope using $[Pd(phen)_2](PF_6)_2$ (Figure 1). The electronic character and steric hindrance of the aryl iodides (**2**) did not affect the reaction efficiency, and the reaction of aryl iodides **2b–f** furnished the monoarylated products **3ab–af** in good yield (entries 1–5). Heteroaryl iodides such as thienyl iodide **2g** and pyridyl iodide **2h** were also converted efficiently to afford **3ag** (60%) and **3ah** (89%).

Conversely, the steric hindrance of the substituents on the amide nitrogen atom significantly affected the reaction efficiency. Less hindered *N*,*N*-dimethyl- and diethylthioamides **1b** and **1c** furnished the corresponding arylated products in 29% and 56% yield, respectively, and the starting materials were recovered in low yield (entries 8 and 9). These results implied that the steric demand of the *N*,*N*-diisopropyl group should prevent a decomposition of the thiocarbonyl group into the S^{2-} species, which could poison the catalyst. The reaction of thioamides with diarylamino and morpholino groups (**1d** and **1e**) also afforded the corresponding products **3db** and **3eb**, albeit in low yields (entries 10 and 11).

The selective formation of monoarylated compounds made us curious about the origin of the selectivity. Consequently, we investigated the Pd species present during the induction period of the catalysis in detail. Initially, stoichiometric reactions between $[Pd(phen)_2](PF_6)_2$ and phenyl iodide **2a** or thienyl thioamide **1a**, respectively, were conducted. While the reaction with thioamide **1a** furnished palladacycle **5** in almost quantitative yield even at room temperature (eq 2),[9] the reaction did not proceed with **2a**, even at 150 °C. However, **5** is most likely not the catalytically active species for this reaction because the stoichiometric reaction of **5** and **2a** did not furnish any products (eq 3). Nevertheless, at 150 °C, **5** catalyzed the reaction with further thioamide **1a** and **2a** to give monoarylated **3aa** in good yield (eq 4). This result clearly indicated that **5** works as a catalyst in the presence of further thioamide **1a**. On the basis of this result, we speculated that excess **1a** might also participate in the reaction as a supporting ligand for the catalyst. Even though the major species detected by ESI-MS in the stoichiometric reaction mixture between **5** and **1a** at 150 °C was Pd(II)–bisthioamide **7**



(eq 5, Figure 2), it could not yet be isolated. In contrast, formation of a similar palladacycle with amide **1a**′ did not occur under identical conditions. In addition, the homocoupling product **6** was not detected in the reaction mixture of eq 4. This result suggested that the reduction of palladium via the reductive elimination of two thiophene moieties from **7** is implausible under these conditions, at least in the initial stage of the reaction, which also renders the possibility of a conventional Pd(0)/Pd(II) cycle (e.g., cycle II in Scheme 1) for the first arylation unlikely.

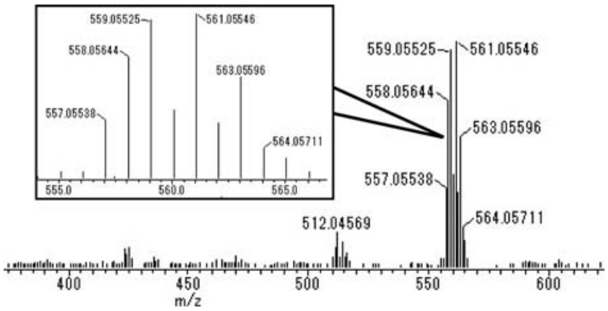
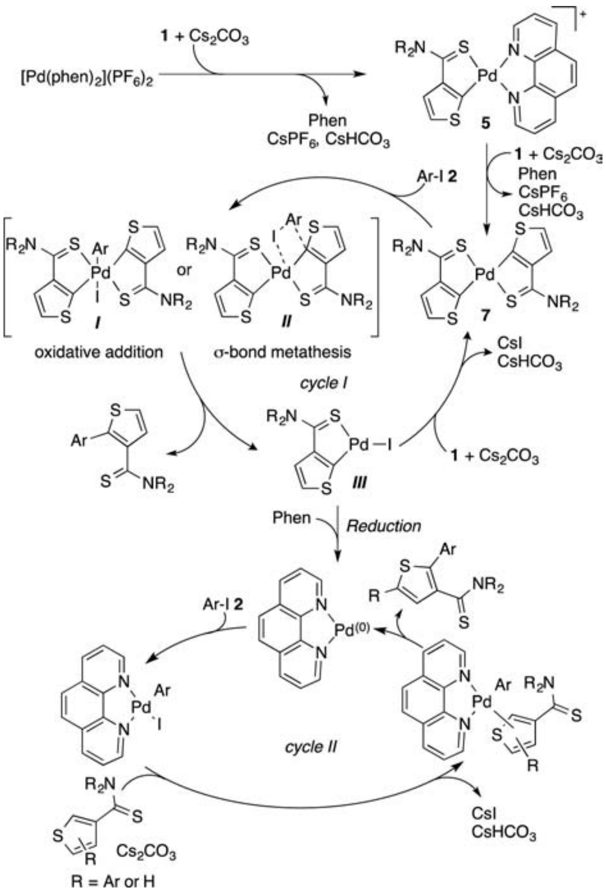
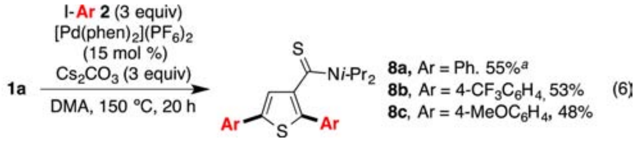


Figure 2. ESI-MS spectrum of the reaction mixture from eq 5. The observed isotope pattern around m/z = 560 is consistent with the simulated isotope pattern for **7**.

Scheme 1. Proposed Catalytic Cycles for the Direct Arylation of C−H Bonds in Thienyl Thioamides Using Pd−Phenanthroline Complexes



A slightly higher catalyst loading (15 mol %) generated 2,5-diarylated **8** (eq 6), and the solid-state structure of **8a** was determined by single-crystal X-ray diffraction (Figure 3). This result demonstrated that the second arylation is not controlled by the thiocarbonyl group. We checked the reaction profile regarding product formation and substrate consumption by GC analysis (Figure 4A) and found that the second arylation took place after the complete consumption of **1a**. We speculated that regeneration of **7** at the ultimate stage of the first arylation should not proceed efficiently due to the limited amount of **1a** available in the reaction mixture. It seems plausible that conventional catalytically active species, e.g., Pd(phen)ArX, are generated from unpoisoned Pd species and catalyze the second arylation, even though the details of the reduction of these Pd species still remains unclear. When preformed Pd(phen)PhI[10] was used instead of $[Pd(phen)_2](PF_6)_2$, **8** was obtained as the major product (eq 6). This result is consistent with previously obtained results using thiophene derivatives.[8a,b] In addition, **8** was generated in the initial stages of the reaction (Figure 4B), which is in stark contrast to the results of the reaction using $[Pd(phen)_2](PF_6)_2$.



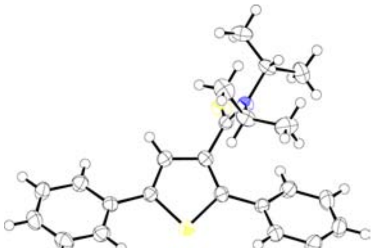


Figure 3. Molecular structure of **8a**; atomic displacement parameters set at 50% probability (yellow = S, blue = N).

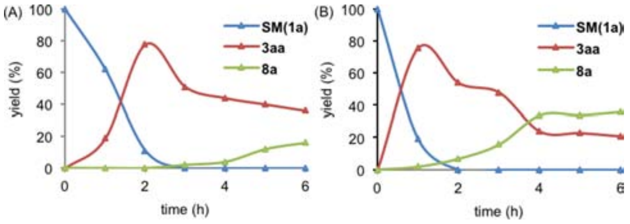


Figure 4. Reaction profiles for product formation and substrate consumption with $[Pd(phen)_2](PF_6)_2$ (15 mol %) (A), or Pd(phen)PhI (10 mol %) (B) in DMA (1 M) at 150 °C. Yields for the respective time periods were determined by GC analysis (FID) of sample mixtures using icosane as an internal standard.

On the basis of these observations, we propose plausible catalytic cycles (Scheme 1). When $[Pd(phen)_2](PF_6)_2$ is used, a 2-fold C−H palladation of **1** should generate Pd(II)-bisthioamide **7** (induction period for cycle I), which should be electron rich due to the presence of two carbanions and two electron-donating sulfur ligands. This might facilitate the generation of bisthioamide−Pd(IV)ArI (**I**) via oxidative addition of the aryl iodide.[11,12] Reductive elimination of the product to give Pd(II)−monothioamido complex **II** should then occur immediately. A σ-bond metathesis of **2** and **7** to directly afford **3** and **III** may also be possible.[13] During the last stage of the first arylation, regeneration of **7** may be hampered by low concentrations of **1**. This could lead to reductions of the palladium species, e.g., C−H palladation at C5 of the thienyl group in **3aa** prior to reductive elimination. Subsequently, the thus-generated Pd(0) species could catalyze the arylation via the conventional reaction pathway to furnish the corresponding diarylated products (cycle II).

In conclusion, we have developed a catalytic C−C cross-coupling method to afford aryl thioamides mediated by Pd−phenanthroline complexes. Depending on the concentration of thioamides, these complexes most likely catalyze different reaction pathways. Our observations imply that, due to the highly electron-rich *C,S*-ligands, one of the pathways proceeds via an unusual Pd(II)/Pd(IV) cycle. Further investigations into the reactions of other aryl thioamides,[14] mechanistic details of the catalysis, and the syntheses of thiocarbonyl-containing π-conjugated systems using the present catalytic systems are currently undertaken in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02742.

Experimental procedures, crystallographic data, and ^{1}H and ^{13}C NMR spectra (PDF)

X-ray data for **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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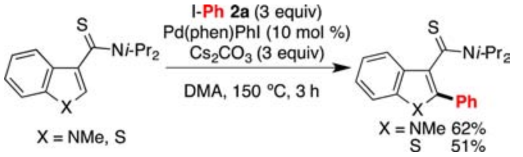
(14) Preliminary tests showed that reactions of *N,N*-diisopropyl-3-indolecarbothioamide (**9**) and *N,N*-diisopropyl-3-benzothiophenecarbothioamide (**11**) with Pd(phen)PhI afforded the corresponding arylated thioamides **10** and **12** in moderate yields.



■ NOTE ADDED AFTER ASAP PUBLICATION

The toc/abstract graphic was corrected on October 23, 2015.