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Sequential Regioselective C−H Functionalization of Thiophenes

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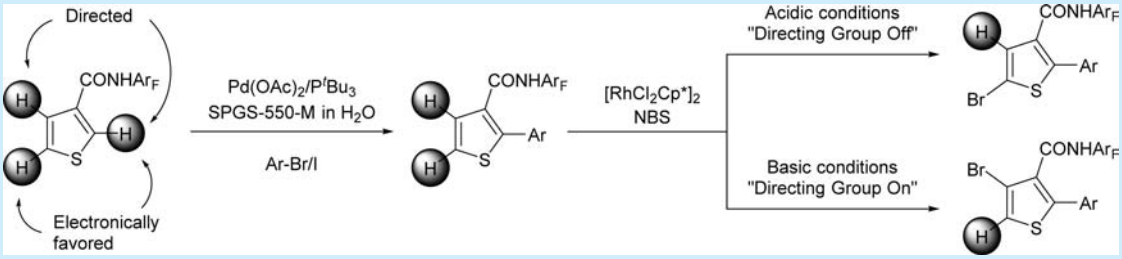
Supporting Information



ABSTRACT: Herein, the sequential functionalization of 5-membered ring heterocycles is disclosed. By employing a pH sensitive directing group both directed and nondirected C−H activation pathways are available, providing access to 2,3,4- and 2,4,5-substituted thiophenes. The C−H arylation was performed in water, and using a surfactant greatly improved the yield and mass recovery. The use of a directing group with an on/off switch offers a potentially powerful means of generating diversity around medicinally relevant cores.

Five-membered aromatic heterocycles form an important class of compounds for a wide variety of applications, including biologically active and medicinally relevant molecules[1] as well as building blocks for organic materials with optoelectronic properties.[2] Varying the substitution around these rings is important for elucidating structure−activity relationships, typically through their preparation by either *de novo* synthesis or reaction of prefunctionalized cores. While these methods can be effective in obtaining the desired compounds, they often suffer from harsh conditions or require multistep syntheses, as well as employ organic solvents, which account for about 80% of the total mass of materials used in industrial processes.[3]

An appealing alternative is sequential and selective C−H functionalization[4] that would enable access to a diverse set of heterocycle substitution patterns.[5] The unique reactivity of five-membered heterocycles, including differentiated acidity and nucleophilicity at various positions, makes these cores ideal substrates for this approach. Functionalization has been approached through undirected C−H activation, but this is best applied to unsubstituted or symmetric ring systems. Additionally, these transformations are often limited to accessing the least sterically hindered sites on (hetero)aromatic rings. Until recently, directed C−H functionalization of five-membered heterocycles has been relatively underexplored, despite their significant importance in a variety of areas of research and ability to functionalize the most sterically encumbered positions. Key examples of directed C−H activation in this substrate class include iodination,[6] lactam synthesis,[7] amination,[8] trifluoromethylation,[9] trifluorothiomethylation,[10] and alkynylation.[11] There is also an example of multiple directed arylations using both a pyrazole and a perfluorotoluimide directing group in the same molecule.[12]

Thiophenes in particular have seen limited examples of successful directed transformations, though undirected transformations have been reported.[13] Early examples using an ester directing group were postulated to involve a site-selective mechanism based on Heck-type chemistry in which an arylpalladium halide adds in a nonionic fashion to the heterocycle.[14] Miura and co-workers later demonstrated the directing power of the carboxymethyl group.[15] Doucet and Dong have also disclosed that aldehydes effectively direct arylations on thiophenes.[16] Notably, Glorius recently disclosed the ability to direct halogenation of thiophenes (and suppress nondirected halogenation) using rhodium catalysis.[17]

In this report we leverage the electronic dissymmetry of 5-membered heterocycles coupled with the application of a pH sensitive directing group to sequentially functionalize thiophenes. By utilizing both directed and undirected methods we were able to access a range of substitution patterns on the substrate (Scheme 1). Additionally, during the course of our studies we discovered a C−H arylation that proceeds under aqueous phase transfer conditions, providing a greener approach to building polyfunctionalized thiophenes. This allowed us to perform a selective and high yielding arylation at the 2-position.

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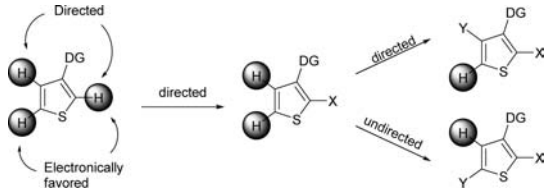
Scheme 1. Accessing Diversity via Sequential C−H Activation



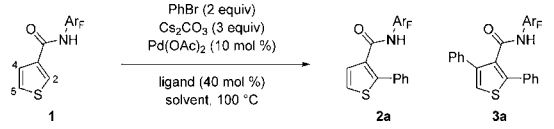
We also demonstrate a novel, mild method for selective deprotection of the directing group, enhancing its utility.

We began our investigation by optimizing the arylation of thiophene-3-carboxamide **1** (Table 1). Using the well-known perfluorotoluimide directing group[18] and reaction conditions previously reported by Miura in the C−H functionalization of thiophenes, we initially found a fairly unselective reaction, giving a mixture of products **2** and **3**. Presumably, after palladium coordination to the perfluorotoluimide directing group,[19] the more electrophilic nature of the position adjacent to the sulfur atom led to initial directed arylation at this position; no monoarylation at position 4 was detected. We found that, among the ligands tested,[20] tri-*tert*-butylphosphine was the most effective for controlling the selectivity of the reaction, but overall material recoveries were low.[21] As we explored alternative solvents, we found to our surprise that water, either on its own or in mixtures with organic solvents, was not only a viable reaction medium but also the most effective in limiting decomposition of the substrate and products. This led us to try water with designer surfactant additives developed by Lipshutz[22] to take advantage of the decrease in decomposition while also providing an organic medium in which the reaction could more effectively occur. Ultimately, we found that aqueous SPGS-550-M (Nok)[23] provided an optimal yield of the desired product **2a** with only minimal diarylation product **3a**. Although directed C−H activation reactions have been performed in water with cosolvents or surfactants,[24] this is the first perfluorotoluimide-directed C−H functionalization with water as the reaction medium to the best of our knowledge. Notably, common ionic surfactants (e.g., SDS, sodium lauroyl sarcosinate) and quaternary ammonium salts were also effective in increasing the overall recovery of the reaction, suggesting that this effect is not necessarily due to the micelles observed by Lipshutz and co-workers.[25]

After briefly screening bases, catalyst loadings, and temperatures, the optimal conditions were found to be potassium carbonate with 5 mol % $Pd(OAc)_2$ and 5 mol % $HBF_4{\cdot}P(^t\text{-Bu})_3$ at 100 °C, providing an 81% isolated yield of product **2a**, with only 7% isolated **3a** and no recovered starting material. At this point, we began to investigate the substrate scope of the reaction, detailed in Table 2.

The C−H arylation reaction was tolerant of a wide variety of aryl halides. While iodobenzene (entry 2) required a longer

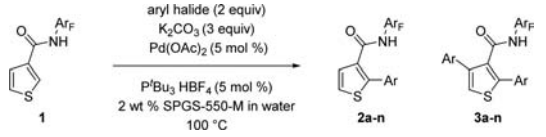
Table 1. Optimization of 2-Selective C−H Arylation

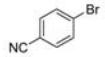
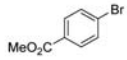
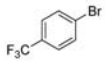
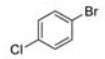
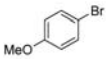
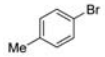
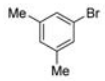
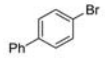
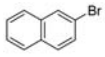
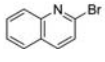


entry	ligand	solvent	yield[a] 1	2a	3a
1	PPh_3	toluene	0	50	27
2	$PtBu_3$	toluene	3	49	0
3	PCy_3	toluene	73	18	10
4	CataCXium A	toluene	44	3	0
5	Xphos	toluene	36	30	0
6	P^tBu_3	MeOH	8	47	0
7	P^tBu_3	water	4	65	4
8	P^tBu_3	toluene/H_2O	34	28	0
9	P^tBu_3	MeOH/H_2O	0	64	0
10	P^tBu_3	TPGS-750-M[b]	7	73	1
11	P^tBu_3	SPGS-550-M[b]	14	86	2

[a]Assay yield by LCMS with internal standard. See Supporting Information for more details. [b]Commercial 2 wt % solution in water.

Table 2. Aryl Halide Scope of C−H Arylation Reaction[a]



entry	aryl halide	product 2	% 2[b]	% 3[b]
1		2a	81	7
2		2a	87	0
3		2b	86	0
4		2c	85	1
5		2d	87	2
6		2e	77	6
7		2f	78	3
8		2g	62	15
9		2h	65	15
10		2i	63	10
11		2j	74	13
12		2k	84	9
13		2l	53	0
14[c]		2m	51	0
15[c]		2n	55	0

[a]Reactions were run on 100 mg or 500 mg of **1** with the appropriate aryl halide (2 equiv), K_2CO_3 (3 equiv), $Pd(OAc)_2$ (5 mol %), and tri-*tert*-butylphosphonium tetrafluoroborate (5 mol %) in a commercial solution of SPGS-550-M in water (2 wt %, 0.5 or 2.5 mL) at 100 °C for 6−140.5 h (see Supporting Information for experimental details). [b]Isolated yield. [c]Reaction run with 10 mol % $Pd(OAc)_2$ and 40 mol % PPh_3 in toluene.

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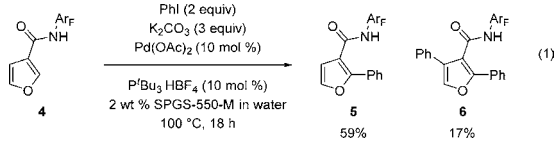
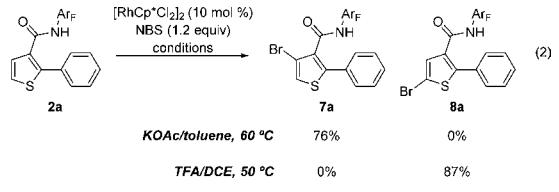
reaction time, the overall yield was excellent and produced no detectable bis-arylation product **3a**. Electron-poor substituents also provided good to excellent yields with minimal amounts of bisarylation products (entries 3−7). Electron-rich aryl halides, however, needed prolonged reaction times, likely due to their slower rates of oxidative addition (entries 8−10). This ultimately led to a significant increase in the formation of bisarylated products **3**, and reactions had to be closely monitored to ensure maximum yield. Other arenes, including heterocycles, were also competent in the reaction conditions. 2-Bromothiophene (entry 13) was slow to react, but ultimately provided bis-thiophene **2** in 53% yield. No arylation of the pendant thiophene was observed, confirming the directing group's role in guiding the C−H activation reaction. Surprisingly, while undecorated pyridine and quinoline substituents could not be effectively installed using the aqueous methods, conditions more similar to those previously used by Yu did provide the desired product in moderate yields with minimal bisarylation (entries 13 and 14).[26] We also demonstrated that this chemistry was successful with the analogous furan, although this also required slightly higher catalyst loadings (eq 1). We were able to obtain compound **5** in 59% isolated yield, along with 17% of diarylated compound **6**.



Having demonstrated the ability to use the perfluorotoluimide directing group to selectively prepare 2-aryl 5-membered heterocycles, we were interested in the functionalization of the remaining positions. While position 4 was primed for functionalization via the directing group (as evidenced by the isolation of bis-arylated products **3**), position 5 was also susceptible to functionalization due to its inherent reactivity. Thus, further elaboration of the thiophene scaffold would require reaction conditions that selectively favored either the directed or undirected pathway. Recently, Glorius demonstrated the ability to minimize nondirected chemistry and promote the involvement of an amide directing group using rhodium catalysis.[17] We reasoned that a similar strategy could provide a route for diversification of our initial arylation products. Work by Yu and co-workers has demonstrated that the perfluorotoluimide's directing ability relies on deprotonation of the amide and coordination of palladium to the sp^2 amidate nitrogen.[19] Careful control of the reaction conditions could be used to toggle the directing group "on" or "off," thereby enabling control of the selectivity in further C−H functionalizations.

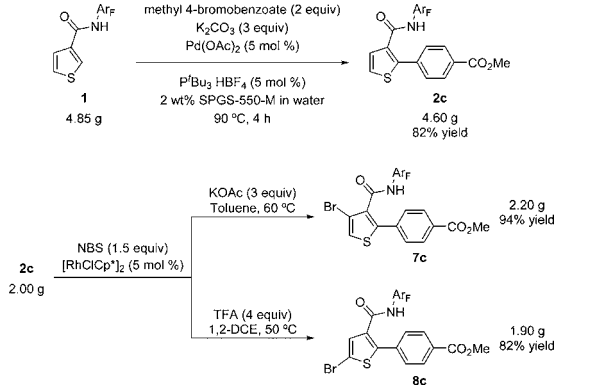
Exploration of the bromination of compound **2a** demonstrated that it was in fact possible to control the regiochemistry of C−H functionalization (eq 2). We were pleased to find that, with



potassium acetate as a mild base, rhodium-catalyzed bromination occurred exclusively at the 4-position, providing compound **7a** in 76% isolated yield. Presumably, after deprotonation of the perfluorotoluimide directing group, the Rh-catalyzed directed bromination becomes much more facile, preventing the undirected reaction from occurring first. This observation became more impressive as we discovered that, under all other acidic, neutral, or noncatalyzed conditions, we obtained primarily compound **8a**. While the high reactivity of **2a** at the 5-position meant that catalytic rhodium and a strong acid (i.e., TFA) were not necessary for the reaction to proceed, their inclusion provided the most rapid conversion and highest isolated yield (87%).[27]

To further demonstrate the synthetic utility of this chemistry, we performed a gram-scale synthesis of compounds **7c** and **8c** (Scheme 2). Compound **2c** could be prepared in excellent yield

Scheme 2. Gram Scale Syntheses of 7c and 8c



from compound **1**, consistent with our original results. A simple filtration and water rinse to collect the precipitated product provided **2c** in 91% yield, though with only 81% NMR purity. Notably, no organic solvents were employed at this stage in the synthesis. The balance of the material was primarily unchanged methyl 4-bromobenzoate with some diarylated or polymeric products present. Column chromatography could be performed to improve the purity profile of **2c** if desired, although some material was lost in this process (82% isolated yield). The purified **2c** could then successfully be brominated at either position via rhodium catalysis. Compound **7c** was obtained in 94% yield, and compound **8c** was obtained in 82% yield. Neither of these products required flash column chromatography, with only a simple filtration through silica gel required to remove impurities.

Although the perfluorotoluimide directing group is a powerful tool for guiding functionalization of C−H bonds, its use in syntheses is often limited by the harsh conditions (KOH or TFA at elevated temperatures) used to convert it to a more broadly useful functional group, such as a carboxylic acid.[28] We sought an alternative set of conditions that might tolerate the presence of sensitive functional groups such as esters. A screen of acids revealed methanesulfonic acid as being effective in the chemoselective hydrolysis of the amide over the ester. Using neat methanesulfonic acid at 50 °C affected the hydrolysis of amides **7c** and **8c** in moderate yield with minimal hydrolysis of the ester (Scheme 3). This enabled the isolation of compounds **9** and **10** in 59% and 66% yield, respectively, providing an entry to the more synthetically useful carboxylic acids. These novel conditions allow the Yu perfluorotoluimide to be considered orthogonally protected to an ester thereby increasing its utility as a diversifiable element in synthesis.

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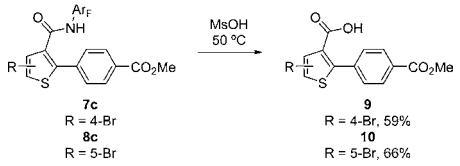
Scheme 3. Selective Hydrolysis of 7c and 8c



In summary, we have been able to successfully demonstrate a strategy for the diversification of thiophenes. A regioselective C−H arylation directed by a perfluorotoluimide directing group was discovered and optimized. Most notably, this reaction proceeded under aqueous conditions with an amphiphilic surfactant acting as a phase transfer catalyst. The arylated heterocycles formed could then be further functionalized at either of the remaining unsubstituted positions through either a directed or undirected rhodium catalyzed bromination. Finally, a mild hydrolysis of the directing group was developed, revealing a synthetically useful carboxylic acid moiety. These steps provide rapid and novel access to a diverse array of trisubstituted five-membered heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01205.

Experimental procedures, characterization data, copies of NMR spectra, solvent screening data, and control reactions for Rh catalyzed bromination (PDF)

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Notes

The authors declare no competing financial interest.

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(20) For a complete list of phosphines screened please see the Supporting Information.
(21) At this time we do not know the cause of the loss of material. Oginio and co-workers have reported the oxidative polymerization of thiophenes. Tsuchiya, K.; Ogino, K. *Polym. J.* **2013**, *45*, 281.
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