Tandem Catalysis

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Efficient Synthesis of Benzothiophenes by an Unusual Palladium-Catalyzed Vinylic C–S Coupling**

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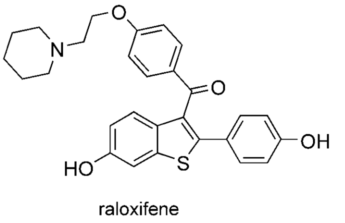
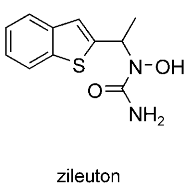
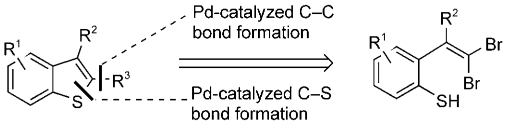
Transition-metal-catalyzed cross-coupling reactions have become indispensable tools for the synthetic chemist.[1,2] The construction of carbon–heteroatom bonds is of particular interest. Consequently, a large number of general and efficient systems for the catalytic amination and etherification of aryl and vinyl halides have been described.[3,4] In contrast, research in the field of carbon–sulfur coupling reactions has lagged behind, largely because of sulfur's long-standing reputation as a catalyst poison.[5–7] Despite this difficulty, coupling reactions of thiols with aryl halides under the catalysis of Pd,[8] Cu,[9] Ni,[10] Co,[11] Fe,[12] and In[13] have been reported. Reactions of vinyl halides are comparatively rare: only a handful of publications describe the vinylation of thiols,[14,15] and the palladium-catalyzed intramolecular coupling is unknown.[16]

We anticipated that the use of Pd could facilitate access to a number of tandem coupling reactions in which an S-vinylation reaction could be combined with orthogonal carbon–carbon bond formation in a single synthetic operation. Tandem/domino reactions are an area of intense research, as they enable streamlined synthetic sequences and a consequent reduction of waste.[17] Herein, we disclose a tandem catalytic reaction of a *gem*-dihalovinyl thiophenol system in which an intramolecular S-vinylation is paired with an intermolecular C–C bond-forming reaction (a Suzuki–Miyaura, Heck, or Sonogashira reaction) to yield 2-substituted benzothiophenes (Scheme 1). These heterocycles form the core of a number of medicinally important molecules, such as raloxifene[18] and zileuton.[19] However, catalytic routes to these targets have only recently been developed.[20] To the best of our knowledge, the reaction described herein is the first example of a tandem catalytic process that incorporates a C–S coupling, as well as the first example of the palladium-catalyzed vinylation of a thiol.







Scheme 1. Retrosynthetic strategy.

We and others have previously reported the synthesis of indoles substituted at the 2-position by tandem coupling reactions of *gem*-dihalovinyl anilines.[21–27] In these systems, an intramolecular amination or amidation was combined with an inter- or intramolecular Suzuki–Miyaura, Heck, or Sonogashira coupling, amidation, direct arylation, or carbonylation. Similar transformations involving C–S coupling would provide rapid access to benzothiophenes and expand the range of available tandem coupling reactions.

Our initial attempts were aimed at combining the carbon–sulfur bond-forming process with a Suzuki–Miyaura coupling (Table 1). We found that the conditions developed previously for the aniline system[22b] were less effective for the thiophenol substrate **1a**: the desired product was isolated in only 48% yield (Table 1, entry 1).[28] The screening of various bases (Table 1, entries 1–4, 8), precatalysts (entries 5–7), and ligand/catalyst ratios (entries 9 and 10) revealed that the best results were obtained when the reaction was carried out with $PdCl_2$, SPhos,[29] and anhydrous K_3PO_4/Et_3N in dioxane at 110°C. Under these conditions, **2a** was formed in 89% yield (Table 1, entry 10). Lowering of the catalyst loading to 1 mol% led to enhanced turnover with minimal impact on the yield (Table 1, entry 12).

With these optimized conditions in hand, we investigated the effect of varying the boronic acid on the tandem process (Table 2). The reaction was found to tolerate changes in the electronic nature of the boronic acid. Electron-poor boronic acids displayed similar reactivity to that of electron-rich 3,4-dimethoxyphenylboronic acid: the boronic acid used for optimization of the reaction (Table 2, entries 1–4). The coupling proceeded equally well when a sterically congested boronic acid was used (Table 2, entry 5). The use of heteroaromatic boronic acids gave the best results: the corresponding heterocyclic products were obtained in up to 99% yield

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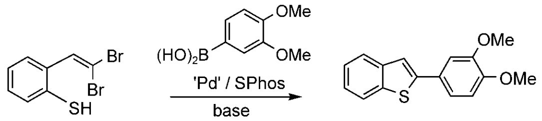
Table 1: Tandem coupling under different reaction conditions.[a]

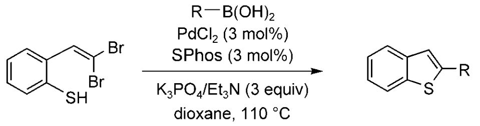


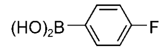
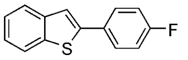
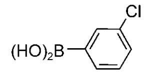
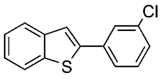
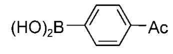
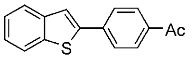
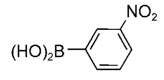
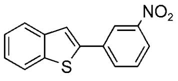
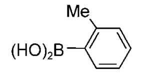
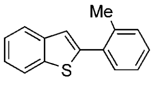
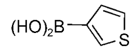
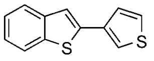
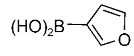
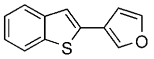
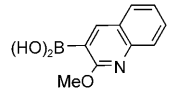
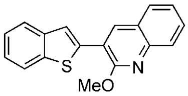
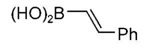
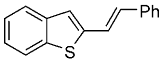
1a **2a**

Entry	Pd source	Pd loading [%]	L/Pd ratio	Base	Yield [%][b]
1	$Pd(OAc)_2$	6	2:1	$K_3PO_4 \cdot H_2O$	48
2	$Pd(OAc)_2$	6	2:1	Cs_2CO_3	n.d.
3	$Pd(OAc)_2$	6	2:1	K_3PO_4	71
4	$Pd(OAc)_2$	6	2:1	Et_3N	72
5	$PdCl_2$	6	2:1	K_3PO_4	78
6	$[Pd_2(dba)_3]$	6	2:1	K_3PO_4	65
7	Pd/C	6	2:1	K_3PO_4	39
8	$PdCl_2$	6	2:1	K_3PO_4/Et_3N	80
9	$PdCl_2$	6	4:1	K_3PO_4/Et_3N	74
10	$PdCl_2$	6	1:1	K_3PO_4/Et_3N	89
11	$PdCl_2$	3	1:1	K_3PO_4/Et_3N	87
12	$PdCl_2$	1	1:1	K_3PO_4/Et_3N	81

[a] Reactions were conducted with **1a** (0.17 mmol), the boronic acid (0.29 mmol), and the base (3 equiv) in dioxane at 110°C in a sealed tube for 16 h; see the Supporting Information for more details. [b] Yield of the isolated product. dba = dibenzylideneacetone, n.d. = not determined, SPhos = 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Table 2: Scope of the reaction with respect to the boronic acid.[a]



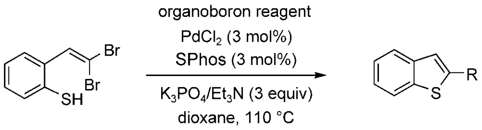
Entry	Boronic acid	Product		Yield [%][b]
1			**2b**	91
2			**2c**	83
3			**2d**	84
4			**2e**	76
5			**2f**	82
6[c]			**2g**	99
7			**2h**	96
8			**2i**	83
9			**2j**	87

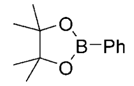
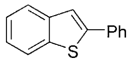
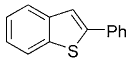
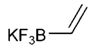
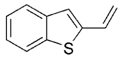
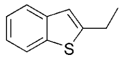
[a] Reactions were conducted with **1a** (0.17 mmol), the boronic acid (1.7 equiv), and K_3PO_4/Et_3N (3.0 equiv) in dioxane at 110°C in a sealed tube for 16 h. [b] Yield of the isolated product. [c] Reaction time: 40 h.

(Table 2, entries 6–8). Finally, a styryl boronic acid was as effective as a coupling partner as aryl boronic acids (Table 2, entry 9).

We then probed the compatibility of other boron nucleophiles with the tandem process (Table 3). When a boronic ester was used, it was necessary to add a small amount of water to obtain for full conversion (Table 3, entry 1). Both aryl and vinyl trifluoroborate salts were coupled effectively in the tandem reaction (Table 3, entries 2 and 3).[30] With these substrates, the amount of base used needed to be increased from 3 to 5 equivalents. Finally, the use of a trialkyl borane provided access to 2-ethylbenzothiophene in good yield (Table 3, entry 4).

Table 3: Alternative boron reagents.[a]



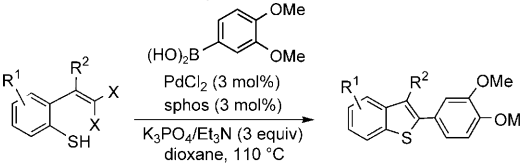
Entry	Organoboron reagent	Product		Yield [%][b]
1[c]			**2k**	80
2[d]	KF_3B—Ph		**2k**	84
3[d]			**2l**	85
4	BEt_3		**2m**	80

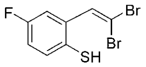
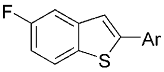
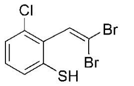
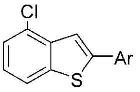
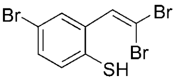
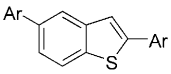
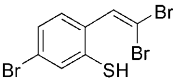
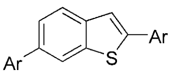
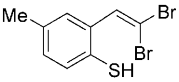
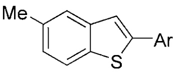
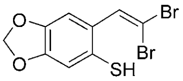
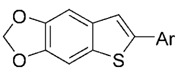
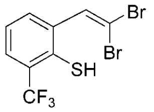
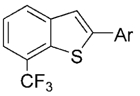
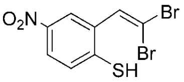
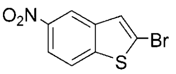
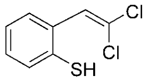
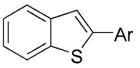
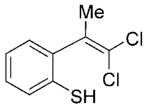
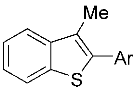
[a] Reactions were conducted with **1a** (0.17 mmol), the boron reagent (1.7 equiv), and K_3PO_4/Et_3N (3.0 equiv) in dioxane at 110°C in a sealed tube for 16 h. [b] Yield of the isolated product. [c] The reaction was carried out in the presence of water (10 μL). [d] The reaction was carried out with 5.0 equivalents of the base K_3PO_4/Et_3N.

Our next goal was to increase the utility of the methodology by examining substituent effects in the thiophenol substrate (Table 4). In contrast to the boronic acids, the electronic nature of the thiophenol fragment had a significant effect on the outcome of the reaction. Substrates with mildly electron withdrawing fluoride and chloride substituents underwent the desired coupling as expected (Table 4, entries 1 and 2). However, the presence of a more electron-deficient CF_3 substituent led to lower conversion and yield (Table 4, entry 7), and the reaction of a substrate with a powerfully electron withdrawing nitro substituent gave none of the tandem coupling product but instead produced the 2-bromobenzothiophene derivative **4h** in modest yield (entry 8).

A thiophenol derivative with a mildly electron donating methyl substituent showed similar reactivity to that of the unfunctionalized substrate (Table 4, entry 5), whereas the high efficiency of the reaction of the more electron rich substrate **3f** was masked by difficulty in isolating the product: 100% conversion was observed (Table 4, entry 6). Brominated derivatives were found to react unselectively at all

Table 4: Variation of the thiophenol derivative.[a]

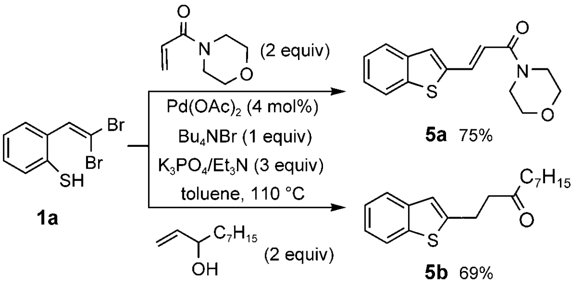


Entry	Thiophenol		Product		Yield [%][b]
1		**3a**		**4a**	78
2		**3b**		**4b**	76
3[c]		**3c**		**4c**	84
4[c]		**3d**		**4d**	75
5		**3e**		**4e**	84
6		**3f**		**4f**	64[d]
7		**3g**		**4g**	45
8		**3h**		**4h**	46
9		**3i**		**2a**	77
10		**3j**		**4j**	81

[a] Reactions were conducted with the thiophenol **3** (0.17 mmol), the boronic acid (1.7 equiv), and K_3PO_4/Et_3N (3.0 equiv) in dioxane at 110°C in a sealed tube for 16 h. [b] Yield of the isolated product. [c] The reaction was carried out with 2.4 equivalents of the boronic acid. [d] The reaction proceeded to 100% conversion.

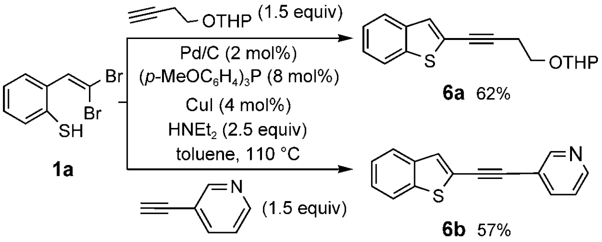
bromine-substituted positions; thus, a highly efficient process was observed in which three bonds were formed in a single operation (Table 4, entries 3 and 4). Interestingly, when fewer than two equivalents of the boronic acid were used in the reaction, no monoarylated product was isolated; instead, a mixture of the dibromide starting material and the corresponding diarylated product was obtained. We found that the reactivity of dichlorovinyl substrates was similar to that of the dibromo compounds (Table 4, entries 9 and 10). Importantly, tetrasubstituted olefins can also be used in the reaction (Table 4, entry 10). This result provides evidence of a mechanism that proceeds through reductive elimination from a thiopalladium species, rather than through addition of the thiol to an intermediate alkyne formed by elimination of HBr.[31]

Finally, the method could be extended from Suzuki–Miyaura coupling reactions to other palladium-catalyzed cross-coupling processes. The tandem C–S coupling/Heck reaction of thiophenol **1a** with *N*-acryloylmorpholine or 1-decen-3-ol proceeded under Jeffrey-type conditions to give the corresponding product in 75 and 69 % yield, respectively [Eqs. (1) and (2)].[32] The substrate is also amenable to a tandem C–S coupling/Sonogashira reaction. The treatment of thiophenol **1a** with a terminal alkyne under palladium-catalyzed conditions in the presence of CuI gave the product of the tandem reaction in moderate yield [Eqs. (3) and (4); THP = tetrahydropyranyl]. Notably, this reaction can be catalyzed by Pd/C, which is a vastly preferable precatalyst to more expensive and air-sensitive Pd^0 or Pd^{II} complexes.



(1)

(2)



(3)

(4)

In conclusion, we have developed a general, efficient method for the catalytic synthesis of diversely functionalized benzothiophenes from *gem*-dihalovinyl thiophenols. This reaction is both the first example of a tandem catalytic process that incorporates C–S coupling, and the first example of the palladium-catalyzed vinylation of a thiol. Further studies to elucidate the mechanism of this process and to apply the transformation to the synthesis of natural products are in progress in our laboratories.

Experimental Section

Representative procedure: Thiophenol **1a** (50 mg, 0.17 mmol), 4-fluorophenylboronic acid (53 mg, 0.29 mmol, 1.7 equiv), K_3PO_4 (108 mg, 0.51 mmol, 3.0 equiv), Et_3N (0.07 mL, 0.51 mmol, 3.0 equiv), and dioxane (2.5 mL) were placed in an oven-dried 2–5 mL Biotage microwave vial, and the vial was capped with a septum and degassed with argon for 5 min. The septum was removed, $PdCl_2$ (0.8 mg, 0.0051 mmol, 3 mol%) and SPhos (1.7 mg, 0.0051 mmol, 3 mol%) were added quickly, the septum was replaced, and the solution was degassed with argon for an additional 5 min. The septum was then replaced with a Teflon microwave cap, the vial was sealed, and the reaction mixture was stirred for 10 min and then heated in an oil bath for 16 h at 110 °C. The flask was then cooled to room temperature, and the solids were removed by vacuum filtration through a plug of silica gel and washed with EtOAc. The solution was concentrated, and the crude product was purified by column chromatography over silica gel (eluent: Et_2O/pentane 0–2 %).

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