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Tandem Double-Cross-Coupling/Hydrothiolation Reaction of 2-Sulfenyl Benzimidazoles with Boronic Acids

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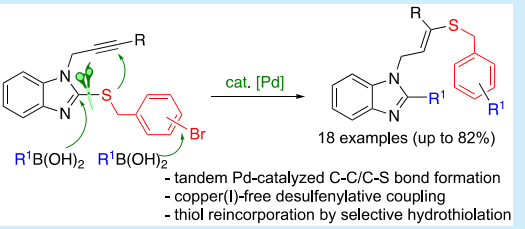
Supporting Information

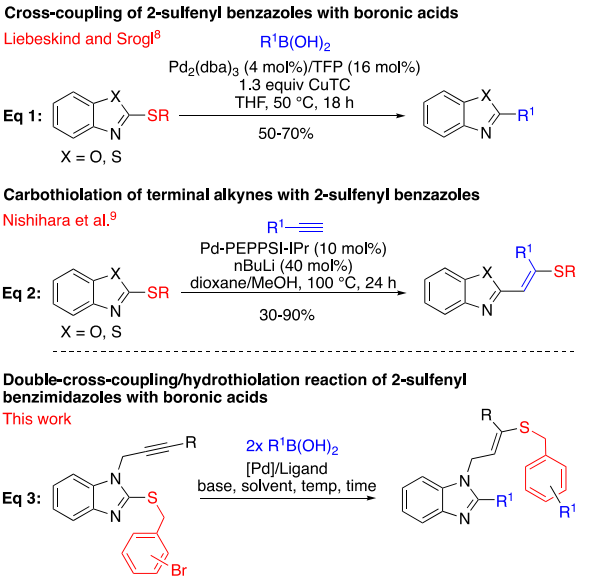
ABSTRACT: A new tandem palladium-catalyzed reaction involving a Suzuki−Miyaura coupling, a desulfenylative coupling, and a hydrothiolation of a triple bond is reported. Notably, the desulfenylative coupling occurs without copper(I) assistance and the hydrothiolation is totally regioselective and stereoselective. The overall process results in the double incorporation of the boronic acid and the reincorporation of the sulfenyl moiety into the product structure. Starting from 2-(bromobenzylsulfenyl)-1-propargyl benzimidazoles, the transformation led to variously substituted benzimidazoles bearing a stereodefined alkenyl sulfide.



Because of the important role of organosulfur compounds in synthetic chemistry and in applied fields such as materials science and the pharmaceuticals industry, the research of efficient methods for the C−S bond formation is constantly advancing. Among these methods, transition-metal-catalyzed cross-coupling of S-nucleophiles with aromatic or alkenyl halides and hydrothiolation of double or triple bonds were widely studied and developed in recent years.[1,2] In parallel to this, metal-catalyzed reactions involving a C−S bond cleavage with release of the sulfur function of the S-electrophilic partner emerged as a complementary and practical alternative to more classical C−C cross-couplings using organohalides.[3] One well-known method based on C−S cleavage was developed starting with the 2000 publication by Liebeskind and Srogl[4] of a new reaction consisting of the Pd-catalyzed coupling of thioesters with boronic acids, in the presence of a stoichiometric amount of thiophene-2-carboxylate (CuTC) as an activator. This method found a huge amount of synthetic applications and was extended to other nucleophilic coupling partners and particularly to heteroaromatic sulfides substrates.[5] In 2012, the Weller and Willis group reported the Rh(I)-catalyzed carbothiolation of alkynes by aryl methyl sulfides, involving an Ar−S bond cleavage.[6] This represents a very interesting atom economical process, as the methylsulfenyl leaving-group released in the course of the reaction is integrated in the final product as an alkenyl methyl sulfide.

Because of their widespread occurrence in biologically active compounds and drugs of benzazole moiety,[7] it was not surprisingly that 2-sulfenyl derivatives of these heteroaromatics have been used as substrates in the above-mentioned metal-catalyzed cross-coupling reactions. Thus, 2-sulfenyl benzoxazoles and benzothiazoles have been successfully coupled with aryl or heteroaryl boronic acids under the Liebeskind−Srogl reaction conditions (Scheme 1, eq 1).[8] Furthermore, the alkynes carbothiolation was applied to 2-sufenyl benzoxazoles and benzothiazoles by Nishihara and co-workers using Pd catalysis (Scheme 1, eq 2).[9] Surprisingly, we did not find examples involving benzimidazole substrates.

Scheme 1. Pd-Catalyzed Processes Involving Desulfenylative Cross-Coupling of 2-Sulfenyl Benzazoles



In an approach inspired by these two methodologies and by an unexpected finding obtained in a previous study (see below for details), we report here a Pd-catalyzed tandem one-pot transformation that consists of a classical Suzuki−Miyaura coupling and a desulfenylative cross-coupling of 2-benzylsulfenyl benzimidazole with aryl boronic acids, followed by an

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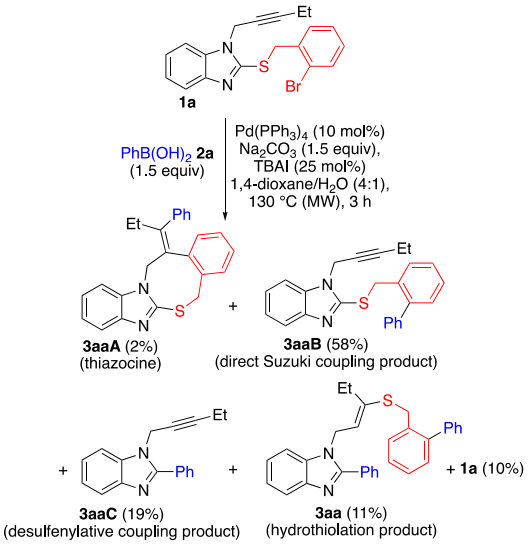
intermolecular regioselective and stereoselective hydrothiolation of the triple bond of the *N*-propargyl benzimidazole (Scheme 1, eq 3). As the result of the overall transformation, the sulfenyl moiety is reincorporated into the product structure as an alkenyl benzyl sulfide, and the aryl substituent provided by the boronic acid partner is introduced twice: once in the 2-position of the benzimidazole and again on the benzene ring of the benzylsulfenyl group. It was possible to achieve the two types of coupling with the boronic acid under the same reaction conditions, because, in our case, the desulfenylative coupling occurred efficiently without the use of copper(I) carboxylate. Thus, substrates bearing an aryl bromide (present in the form of a bromobenzyl substituent on the S atom) were used. This choice could be considered as complementary to the strategies using orthogonal reactivity,[10] increasing the molecular complexity and diversity of the final products.

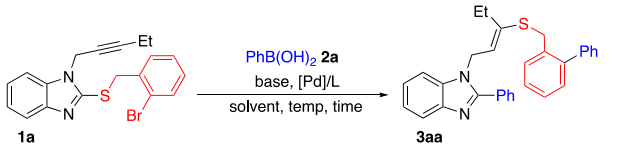
Initially, substrate **1a** was designed to produce thiazocine **3aaA** via a Pd-catalyzed 8-*exo*-dig cyclization/Suzuki coupling domino reaction (Scheme 2), based on a methodology that

Scheme 2. Initial Pd-Catalyzed Reaction of Benzimidazole 1a with Boronic Acid 2a



was developed previously in our group to access five- and six-membered sulfur heterocycles.[11] In a preliminary experiment, by reacting **1a** with phenyl boronic acid **2a**, a very small amount of the desired product **3aaA** was detected (2%),[12] together with a majority of product **3aaB** resulting from the competing direct coupling (58%), but also with two other products, which were identified as the desulfenylative coupling product **3aaC** (19%), and the unexpected alkenyl sulfide **3aa** (11%). Each product was isolated from the crude mixture and characterized by NMR and mass spectroscopy. We noted that the hydrothiolation of the triple bond occurred with a remarkable regioselectivity and stereoselectivity, since alkenyl sulfide **3aa** was present as a single stereoisomer, resulting from the *syn*-addition of the thiol[2,13] on the carbon bearing the ethyl substituent. The structure of **3aa** and the stereochemistry of its double bond have been unambiguously assigned by a two-dimensional nuclear Overhauser spectroscopy (2D-NOESY) experiment (see spectra in the Supporting Information). In this context, note that hydrothiolations of internal dissymmetric alkynes are rather rare. Intrigued by this result and considering the originality of the tandem transformation, we decided to optimize the reaction conditions to obtain **3aa** as the main product. Many experiments have been performed, varying all parameters (Pd-source, ligand, base, solvent, temperature, reaction time), and selected results are summarized in Table 1

Table 1. Optimization of the Reaction of 1a with 2a To Access 3aa[a]



entry	Pd catalyst	ligand L	base	yield[b] (%)
1	$Pd(PPh_3)_4$	–	K_2CO_3	43
2[c]	$Pd(PPh_3)_4$	–	K_2CO_3	13
3	$Pd(PPh_3)_4$	–	K_3PO_4	44
4	$Pd(PPh_3)_4$	–	LiOH	32
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	19
6	$Pd_2(dba)_3$	TFP	K_2CO_3	15
7	$Pd_2(dba)_3$	PCy_3	K_2CO_3	53
8	$Pd_2(dba)_3$	cataCXium	K_2CO_3	33
9[d]	$Pd_2(dba)_3$	PCy_3	K_2CO_3	66

[a]Reaction conditions: **1a** (1 equiv), **2a** (3 equiv), catalyst loading (15 mol % Pd), ligand (30 mol %), base (3 equiv), dioxane/H_2O 8/2 or 7/3 (0.1 M), 130 °C, 19 h. [b]Isolated yield. [c]Performed at 140 °C, for 8 h. [d]$Pd_2(dba)_3$ (5 mol %), ligand (20 mol %).

(more details are given in the Supporting Information). Compared with the initial reaction conditions (Scheme 2), we increased the amount of boronic acid (since 2 equiv are required anyway necessary to obtain **3aa**), of the base, and the catalyst loading (from 10 mol % to 15 mol% Pd), and a significant improvement (43% yield; see Table 1, entry 1) was obtained by removing TBAI, using K_2CO_3 as the base, changing the reaction concentration from 0.05 M to 0.1 M, and prolonging the reaction time from 3 h (at 130 °C, MW) to 19 h (at 130 °C, in oil bath). Keeping the same catalyst and base but heating only for 8 h, at 140 °C, in an oil bath, the yield turned low again (13%; see Table 1, entry 2). Changing the base to K_3PO_4 did not modify the result, while the use of LiOH decreased the yield slightly (Table 1, entries 3 and 4). The conventional $Pd(OAc)_2/PPh_3$ catalytic systems was found to be less effective (Table 1, entry 5). Then, $Pd_2(dba)_3$ was used in combination with different phosphine ligands, such as tri(2-furyl)phosphine (TFP), tricyclohexyl phosphine (PCy_3), or di(1-adamantyl)-*n*-butylphosphine (catCXiumA) (Table 1, entries 6–8). The best result was obtained with the $Pd_2(dba)_3/PCy_3$ combination (Table 1, entry 7) and the yield was even improved with less catalyst loading (Table 1, entry 9). The amount of catalyst used in this reaction remains high, compared, in particular, to domino reactions involving carbopalladation; however, the presence of a sulfur species represents a difficult case, because of the catalyst deactivation caused by the thiophilicity of palladium. Thus, the use of 5 mol % of $Pd_2(dba)_3$, enabling a satisfactory yield of 66%, with respect to three one-pot Pd-catalyzed processes, can reasonably be accepted. Thus, these last reaction conditions were kept for the further stages of the study.

The sequence of this Pd-catalyzed tandem reaction would reasonably consist of three steps: (i) direct Suzuki coupling on the phenyl bromide moiety of **1a** with boronic acid **2a** leading to **3aaB**, (ii) desulfenylative coupling of the latter with **2a** to

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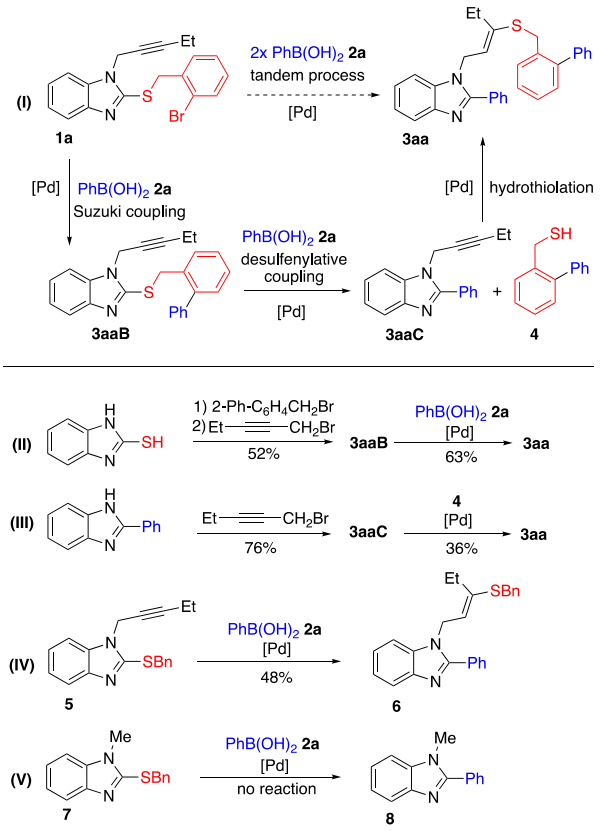
give **3aaC** and thiol **4**, and (iii) hydrothiolation by **4** of the triple bond of **3aaC** to afford the alkenyl sulfide **3aa** as the final product (Scheme 3, **I**). To confirm this, we decided to perform

Scheme 3. Proposed Mechanism and Control Experiments



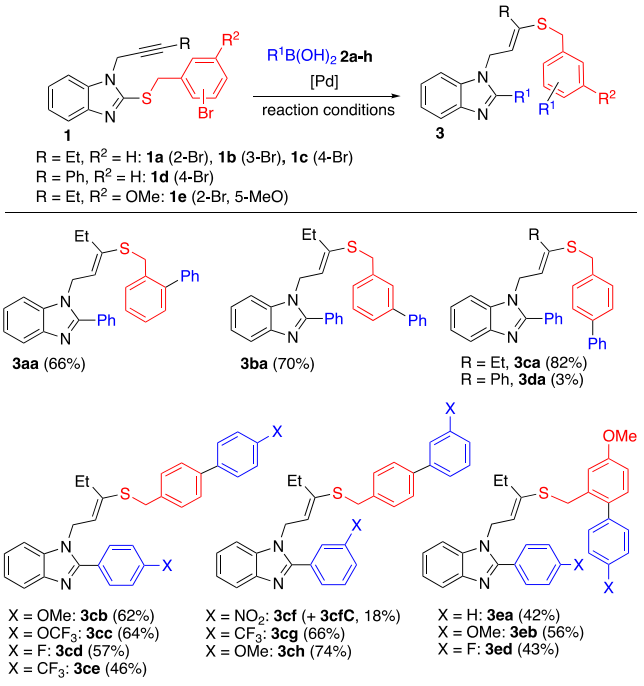
these different steps independently under the same Pd-catalyzed reaction conditions (Scheme 3, **II**, **III**). First, compound **3aaB** was prepared separately from commercial reagents, by S-benzylation with 2-(bromomethyl)-1,1′-biphenyl and subsequent N-propargylation with 1-bromopent-2-yne of 2-mercaptobenzimidazole. Its reaction with boronic acid **2a** under the established reaction conditions led to the expected product **3aa** in 63% yield, via a tandem desulfenylative cross-coupling/hydrothiolation (Scheme 3, **II**). To examine the triple-bond hydrothiolation, we prepared substrate **3aaC** by N-propargylation of 2-phenyl-benzimidazole, as well as the appropriated thiol **4** in two steps from 2-(bromomethyl)-1,1′-biphenyl and potassium thioacetate. Under the same reaction conditions, the hydrothiolation led to the expected product **3aa** (36% yield), which was separated from the recovered starting materials, **3aaC** and the disulfide formed from thiol **4** (Scheme 3, **III**). Although the same Pd-catalyst and reaction conditions were used, the absence of the boronic acid and the different nature of the precursor of the active Pd–S species could explain the lower yield in product **3aa** obtained in this way.

We also examined the importance of the presence of the aryl bromide and of the triple bond on the reaction (Scheme 3, **IV**, **V**). Suppressing the bromine on the benzene ring of the substrate, the desulfenylative coupling/hydrothiolation process worked in a satisfactory manner, leading to the expected alkenyl sulfide **6** in 48% isolated yield (Scheme 3, **IV**). Remarkably, all these hydrothiolations have occurred with total regioselectivity and stereoselectivity, as only one stereoisomer of the alkenyl sulfide is formed. For comparison, we also reacted substrate **5** with **2a** under classical Liebeskind–Srogl conditions (1.3 equiv CuTC, 4 mol % $Pd_2(dba)_3$, 16 mol % TFP, in THF, 50 °C, 18 h).[8] The result obtained in this case showed the particularity of our substrate, as the crude mixture contained the starting product **5**, the desulfenylative coupling product **3aaC**, and the hydrothiolation product **6** in a ratio of 67:20:13. Finally, we checked if the presence of the triple bond is beneficial to the desulfenylative coupling process, which has no need of Cu(I)-carboxylate in our case. We prepared for this purpose 2-(benzylthio)-1-methyl-benzimidazole **7** in which the propargyl chain was replaced by a methyl substituent. Its reaction with $PhB(OH)_2$, under the same catalytic conditions, did not afford the coupling product **8**; only the starting material was recovered (Scheme 3, **V**). The latter result, together with the low yield obtained in the hydrothiolation of **3aaC** with thiol **4**, may suggest that the triple bond is ideally placed to coordinate the palladium–thiolate species, thereby facilitating the hydrothiolation step in the tandem process. The regioselectivity could be explained by the fact that the sp-hybridized carbon bearing the 1-methylene-2-phenyl benzimidazole is more sterically hindered than the ethyl-substituted one. However, the validation of such hypotheses requires additional experimental and theoretical studies.

We next investigated the scope and limitations of the reaction by varying the substituents on the substrate and the boronic acid partners (Table 2).

Thus, we prepared two other 2-(bromobenzylsulfenyl)-1-propargyl benzimidazole derivatives **1b** and **1c**, bearing the bromide in *meta* and *para* position, respectively. Their reaction with $PhB(OH)_2$ **2a**, under the optimized reaction conditions,

Table 2. Tandem Reaction of Various Substrates 1 and Aryl Boronic Acids 2[a]



[a]Reaction conditions: **1** (1 equiv), **2** (3 equiv), $Pd_2(dba)_3$ (5 mol %), PCy_3 (20 mol %), K_2CO_3 (3 equiv), dioxane/H_2O 4/1 (0.1 M), 130 °C, 19 h; isolated yields are given.

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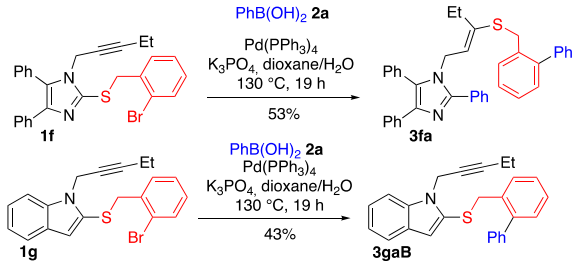
led to the expected products **3ba** and **3ca**, in higher yields (70% and 82%, respectively) than that obtained with the *ortho* derivative **1a**. In the case of substrate **1d**, we changed the substituent on the triple bond, from ethyl to phenyl. The reaction of **1d** with **2a** afforded a complex mixture, in which only a very small amount of the expected alkenyl sulfide **3da** was isolated and characterized by ^{1}H NMR and mass analyses. We then decided to pursue the study by reacting the substrate **1c** with various boronic acids. By using electron-rich or electron-poor arylboronic acids substituted either in the *para* or in *meta* position, the reaction worked well, leading to the desired alkenyl sulfides **3** with yields ranging from 46% to 74%. In the case of product **3cc**, the procedure was scaled up on 1 mmol (50% isolated yield). Only in the case of the use of 3-(nitrophenyl)boronic acid **2f**, the crude reaction mixture contained unreacted substrate **1c**, both of coupling products **3cfB** and **3cfC**, and the desired compound **3cf** (**2c**/**3cfB**/**3cfC**/**3cf** ratio = 2:1:1:2). After column chromatography, an inseparable mixture of **3cf** and **3cfC** in a 3:1 ratio was obtained. Finally, we also prepared substrate **1e** having bromine in the *ortho*-position and a methoxy group in the *meta*-position and involved it in reactions with three boronic acids: **2a**, **2b**, and **2d**. The corresponding desired products were obtained in satisfactory yields, up to 56%.

Other modifications of the substrate were made to determine their influence on the efficiency of the reaction and to identify its limitations. Thus, the heterocyclic part of the substrate was modified by replacing the benzimidazole by an imidazole and by an indole (Scheme 4). Starting from the 4,5-

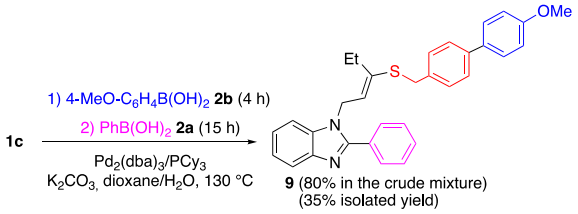
Scheme 4. Scope and Limitations: Replacement of Benzimidazole by Another Heterocycle



diphenyl-imidazole derivative **1f** and phenyl boronic acid **2a**, the tandem process still worked well, leading to the expected alkenyl sulfide **3fa**; in this case, the use of $Pd(PPh_3)_4$ furnished a better yield than the use of a $Pd_2(dba)_3/PCy_3$ catalyst (53% vs 39%). In contrast, the use of indole-based substrate **1g**, which contained the sulfenyl group, under the same conditions, led only to the direct coupling product **3gaB**, isolated in 43% yield.

Finally, we investigated the challenging possibility to perform this reaction in one-pot fashion, keeping the same reaction conditions, by using two different boronic acids: one for the debrominative coupling and another for the desulfenylative coupling (see Scheme 5). Therefore, substrate **1c** was placed in the reaction conditions with 1 equiv of boronic acid **2b**. After 4 h, the starting material was consumed, and the main product detected by HPLC was the Suzuki coupling product (**3cbB**). At this stage, 1.5 equiv of boronic acid **2a** was added and the reaction continued for 15 h. The desired product **9** was identified in the crude mixture as the major component (80% by ^{1}H NMR), together with other

Scheme 5. One-Pot Suzuki−Miyaura Cross-Coupling and Desulfenylative Cross-Coupling/Hydrothiolation



products, which were difficult to assign. Separation via column chromatography was difficult, and, although pure **9** was isolated with only 35% yield, we succeeded to validate the proof of concept.

In summary, we have developed a Pd-catalyzed tandem process involving 2-(bromobenzylsulfenyl)-1-propargyl benzimidazoles and boronic acids. It consists of three reactions: first, a classical Suzuki debrominative cross-coupling; then, a desulfenylative coupling in the 2-position of the benzimidazole that does not require copper(I) assistance; and, finally, an intermolecular regioselective and stereoselective hydrothiolation of the triple bond of the *N*-propargyl benzimidazole. The overall process results in the double incorporation of the boronic acid partner and the reincorporation of the sulfenyl moiety into the product structure, as an alkenyl benzyl sulfide. Further studies will be conducted to extend the scope of the Pd-catalyzed desulfenylative coupling/hydrothiolation tandem reaction to other related heterocycles. Moreover, the alkenyl sulfenyl pendent resulting from hydrothiolation can be converted to other functionalities by known methods.[6]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02067.

Detailed experimental procedures and spectra data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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