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Cyclocarbopalladation/Cross-Coupling Cascade Reactions in Sulfide Series: Access to Sulfur Heterocycles

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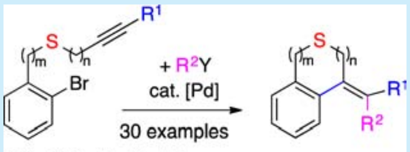
Supporting Information

ABSTRACT: Cyclocarbopalladation/cross-coupling cascade reactions were applied for the first time in a sulfur series and represent an efficient route to access sulfur heterocycles. Stille or Suzuki–Miyaura cross-coupling was successfully used as the final reaction. The products are original benzothiolane and isothiochromane scaffolds with a stereodefined tetrasubstituted exocyclic double bond. To illustrate the application of this method to the synthesis of bioactive molecules, a sulfur analogue of the anticancer agent tamoxifen was prepared as a potential selective estrogen-receptor modulator.

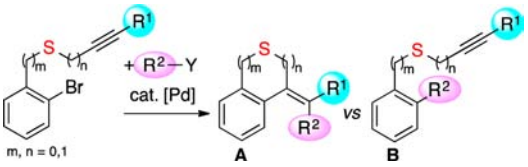


R^1 : TMS, Et, Me, Ph
R^2 : aryl, heteroaryl, vinyl, allyl, cyclopropyl
Y: $SnBu_3$, $B(OH)_2$, BF_3K
m, n = 0, 1

One of the main reasons for the continuous and spectacular progress in the field of palladium-catalyzed reactions is their high tolerance of various functionalized substrates. However, as far as the development of these reactions involving organosulfur substrates is concerned, the deactivation of the catalyst caused by the thiophilicity of palladium has been a limiting factor. This problem has been successfully overcome, and during the recent decades many palladium-catalyzed syntheses of sulfur-containing compounds have been described, in particular via C–S bond formation.[1] On the other hand, despite the interest of sulfur heterocycles as constituents of a large number of drug structures,[2] their synthesis by using palladium cross-coupling reactions remains limited.[3] Among the various palladium-catalyzed processes, the cascade cyclizations represent a powerful tool to access efficiently and with step-economy complex carbocyclic and heterocyclic molecules from simple starting materials.[4] The potential of this method has not been fully exploited in heterocycle synthesis, and as far as the synthesis of sulfur heterocycles by using this approach is concerned, only one example can be considered as a cascade process: the intermolecular C–S bond formation/thiacyclization domino reaction described by Paradies in 2011.[3h] Otherwise, an original tandem Pd-catalyzed C–S/C–C coupling on *gem*-dibromovinyl substrates was reported by Lautens in 2009.[3f] Although several cyclocarbopalladation/cross-coupling cascade reactions leading to nitrogen and oxygen heterocycles have been reported,[5,6] examples in the sulfur series are still missing. To the best of our knowledge, the reaction described herein represents the first example of this type of palladium-catalyzed cascade cyclization, leading to sulfur heterocycles.

We envisioned that reacting the appropriate starting sulfide bearing an alkyne substituent with a coupling partner in the presence of a palladium catalyst would result in a cyclocarbopalladation/cross-coupling cascade, yielding a benzene-fused five or six-membered sulfur ring (i.e., benzothiolane or isothiochromane) bearing an exocyclic, stereodefined, all-substituted double bond[7] (Scheme 1).

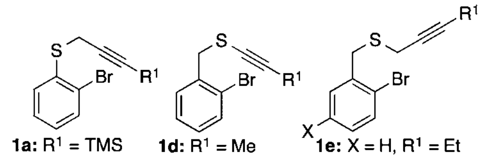
Scheme 1. Expected Pd-Catalyzed Processes



One key point of the method would be the competition between the cascade and the direct coupling reactions (formation of product **A** vs **B**), as the presence of the metal-chelating sulfur function on the substrate could influence the course of the process. The expected products of type **A** are rarely encountered scaffolds, different from benzothiophenes that are obtained by the existing metal-catalytic routes.

We first prepared a range of six starting sulfides **1a–f** bearing on sulfur a 2-bromophenyl or benzyl group and an alkyne with various R^1 substituents (Figure 1).

In our first series of experiments, we attempted a cyclocarbopalladation/Stille coupling cascade (Table 1).



1a: R^1 = TMS
1b: R^1 = Et
1c: R^1 = Ph
1d: R^1 = Me
1e: X = H, R^1 = Et
1f: X = OMe, R^1 = Et

Figure 1. Starting sulfides **1**.

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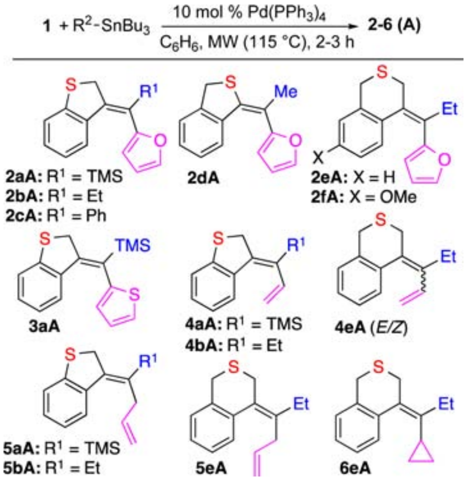
Table 1. Cyclocarbopalladation/Stille Coupling



entry	sulfide	R^2	product	yield[a] (%)
1	**1a**	2-furyl	**2aA**	65
2	**1a**	2-thienyl	**3aA**	77
3	**1a**	vinyl	**4aA**	51
4	**1a**	allyl	**5aA**	62
5	**1b**	2-furyl	**2bA**	52
6	**1b**	vinyl	**4bA**	63
7	**1b**	allyl	**5bA**	38[d]
8	**1c**	2-furyl	**2cA**	61
9	**1d**	2-furyl	**2dA**	59
10	**1e**	2-furyl	**2eA**	81
11	**1f**	2-furyl	**2fA**	70
12	**1e**	vinyl	**4eA**[b]	61
13	**1e**	allyl	**5eA** + **6eA**[c]	nd[e]

[a] Isolated yield. [b] Mixture of *E*/*Z* isomers in a 3/1 ratio. [c] The ratio **5**/**6** was 2/1. [d] The conversion was 50%. [e] Not determined.

Cascade reaction conditions that are classically used in our laboratory[8] were applied and optimized for the reaction between sulfide **1a** bearing a trimethylsilyl group on the triple bond and 2-furyltributylstannane as the coupling partner. The best results were obtained with 10 mol % of Pd(PPh$_3$)$_4$ as catalyst, with 1.3 equiv of stannane, in benzene, under microwave irradiation at 115 °C, and 3 h are necessary for a complete conversion[9] (Table 1, entry 1). Only the desired five-membered sulfur heterocyclic product **2aA** formed by a 5-*exo-dig* cyclization/Stille cascade process was obtained, without any trace of product of type **B** resulting from a direct coupling. Although the conversion was total, the isolated yield was moderate (65%) because of the difficulty in separation from the crude mixture of the nonpolar product and the stannane derivatives. Sulfide **1a** was then reacted in the same conditions with 2-thienyl, vinyl, and allylstannane, leading to the corresponding cyclic products **3aA**, **4aA**, and **5aA** (Table 1, entries 2–4). Just after purification, the vinyl derivative **4aA** was characterized as the *E* isomer, but after a few hours, isomerization occurred (due probably to the conjugated dienic structure) and a mixture of *E*/*Z* isomers was observed by ^{1}H NMR spectroscopy.

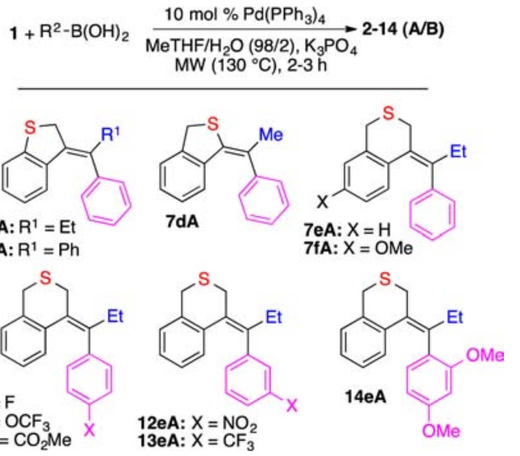
The other sulfides were then involved in the cascade process. With sulfide **1b**, the reactions with the same stannanes worked similarly to those with **1a** and led to the corresponding products **2bA**, **4bA**, and **5bA** (Table 1, entries 5–7). The reaction between sulfide **1c** and 2-furylstannane led to **2cA** (Table 1, entry 8), which is highly acid-sensitive (fast decomposition is observed if the CDCl$_3$ for the NMR analysis is not neutralized prior to use). The cascade reaction was found to be effective also in the case of benzyl ynethioether **1d**, affording heterocycle **2dA** (Table 1, entry 9). The scope of the method was then examined with benzyl propargyl sulfides **1e**,**f**, which are presumed to react via a 6-*exo-dig* cyclization to access 6-membered sulfur heterocycles, namely isothiochromanes. Thus, by reacting **1e** and **1f** with 2-furylstannane, the desired products **2eA** and **2fA** were obtained in good yields (Table 1, entries 10 and 11). The vinyl derivative **4eA** obtained from **1e** isomerized fast, and the product was isolated and characterized by NMR spectroscopy as a mixture of *E*/*Z* isomers in a 3/1 ratio, in 61% yield (Table 1, entry 12). Interestingly, by reacting **1e** with the allyltributylstanane, the expected product **5eA** was obtained together with a secondary product, in a ratio of 2/1 (Table 1, entry 13). We were not able to separate these compounds by column chromatography (same R_f in pure heptane); however, they could be characterized from the NMR spectra of the mixture. The unexpected product was found to be the cyclopropyl derivative **6eA**. Its formation occurs probably via a 4-membered palladacycle intermediate.[10]

Instead of using the benzene as the solvent, we attempted the reaction by using 2-methyltetrahydrofuran in one case. Under these conditions, the reaction between **1e** and 2-furyltributylstananne also worked well, leading to a mixture of products **2eA**/**2eB** in a 9/1 ratio. The heterocyclic product **2eA** was isolated in a 70% yield.

To extend the method to other cross-coupling reactions and also to avoid the difficulty in the product isolation using stannanes, the cyclocarbopalladation/Suzuki–Miyaura cascade reaction was investigated. A screening of various reaction conditions was done for the reaction between sulfide **1b** and phenylboronic acid to reach a complete conversion and a high selectivity in product **A**.[11] The best result was obtained with Pd(PPh$_3$)$_4$ as the catalyst and with K$_3$PO$_4$ as the base, in a mixture of 2-methyltetrahydrofuran/water 98/2 at 130 °C during 2 or 3 h under microwave irradiation[12] (Table 2, entry 1). Under these conditions, a mixture of products **7bA** and **7bB** in a 9:1 ratio was obtained. The separation of the two products having similar polarity was difficult; however, we isolated the desired heterocycle **7bA** pure, in 66% yield. We then submitted to the same reaction substrates **1c**–**f** (Table 2, entries 2–5). Ynethioether **1d** led only to the cyclic compound **7dA**, however, with a low yield of 30%, due to the difficult purification of the product (Table 2, entry 3). The 6-membered sulfur heterocycles **7eA** and **7fA** were obtained from **1e** and **1f**, respectively, with high selectivity and in good yield (Table 2, entries 4 and 5).

We next investigated the effect of varying the boronic acid. By using electron-rich or electron-poor arylboronic acids, the reaction with sulfide **1e** worked well, and the selectivity in product **A** was high to total (Table 2, entries 6–12). The coupling can also take place with a sterically congested partner such as 2,4-dimethoxyphenylboronic acid (Table 2, entry 12). In some cases, products **A** and **B** were inseparable due to their similar polarity (Table 2, entries 4, 6, and 7). One limitation was revealed in the reaction involving **1e** and 4-carboxyphenylboronic acid (Table 2, entry 8). In this case, the cyclocarbopalladation was followed by the protonation of the vinylic carbon (probably by the carboxylic acid) and not by the coupling reaction. In consequence, instead the expected product, we identified by ^{1}H NMR the protonated product

Table 2. Cyclocarbopalladation/Suzuki−Miyaura Coupling



entry	sulfide	R^2	A/B[a]	product A	yield (%)
1	**1b**	Ph	9:1	**7bA**	66
2	**1c**	Ph	1:0	**7cA**	79
3	**1d**	Ph	1:0	**7dA**	30
4	**1e**	Ph	20:3	**7eA**	91
5	**1f**	Ph	1:0	**7fA**	81
6	**1e**	4-FC$_6$H$_4$	10:1	**8eA**	83
7	**1e**	4-CF$_3$OC$_6$H$_4$	10:1	**9eA**	86
8	**1e**	4-CO$_2$HC$_6$H$_4$		*d*	nd
9	**1e**	4-CO$_2$MeC$_6$H$_4$	1:0	**11eA**	69
10	**1e**	3-NO$_2$C$_6$H$_4$	1:0	**12eA**	86
11	**1e**	3-CF$_3$C$_6$H$_4$	1:0	**13eA**	67
12	**1e**	2,4-(MeO)$_2$C$_6$H$_3$	1:0	**14eA**	60
13[b]	**1e**	2-furyl	1:1	**2eA**[e]	nd
14	**1e**	vinyl[c]	1:0	**4eA**[e]	64
15	**1e**	allyl[c]	1:0	**5eA**[e]	73
16	**1e**	cyclopropyl	1:0	**6eA**[e]	55

[a] **A**: cascade product. **B**: direct coupling product. The **A**/**B** ratio was measured by NMR ^{1}H. [b] PdCl$_2$/SPHOS was used as the catalyst. [c] R^{2}BF$_3$K was used as the boron reagent. [d] Instead the desired product, compound **10** was obtained; see ref 13. [e] See structure in Table 1.

10.[13] On the other hand, as expected, the replacement in the coupling partner of the carboxylic acid by the methyl ester group, led to product **11eA** (Table 2, entry 9).

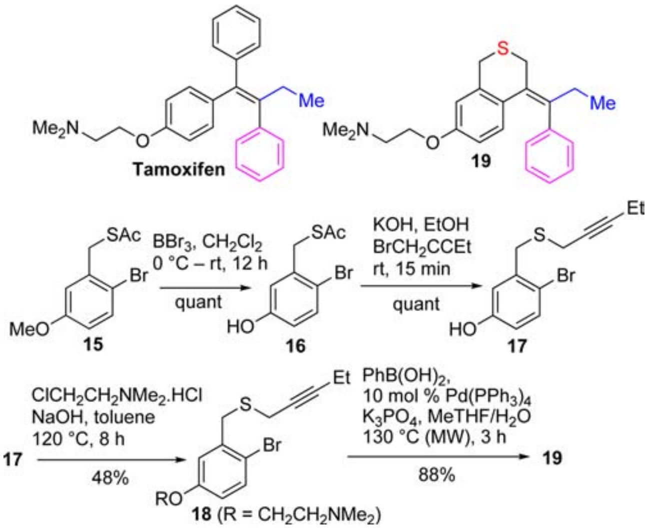
To compare the efficiency of the Stille and Suzuki reactions in this process, 2-furylboronic acid was reacted with **1e**, and we found that the Suzuki conditions led only to product **2eB** resulting from the direct cross-coupling. By replacing the Pd(PPh$_3$)$_4$ catalyst by PdCl$_2$/SPHOS, an equimolar mixture of **2eA** and **2eB** was obtained (Table 2, entry 13).[14] As a reminder, only the desired heterocycle **2eA** was formed by Stille coupling with 2-furylstannane (Table 1, entry 10).

The two possible routes, Stille vs Suzuki coupling, were also compared for the synthesis of compounds **4eA**, **5eA**, and **6eA** starting from **1e**. Trifluoroborate salts were used as coupling partners to introduce vinyl and allyl substituents (Table 2, entries 14 and 15). The vinyl derivative **4eA** was obtained as a mixture of *E*/*Z* isomers in a ratio of 3/1 and 64% yield (Table 2, entry 14), similarly to the previous results using Stille coupling (see Table 1, entry 12). The allyl derivative **5eA** was obtained as a single product (Table 2, entry 15), without the secondary cyclopropyl derivative **6eA** obtained by using the allylstananne (see Table 1, entry 13). Product **6eA** was also obtained independently, by reacting **1e** with cyclopropylboronic acid (Table 2, entry 16).

It is important to notice that the obtained products are unstable under basic conditions (aqueous 1 M NaOH solution), leading to an unidentified mixture of compounds.

Finally, to illustrate the application of this method to the synthesis of potentially bioactive molecules, we have prepared compound **19** as an analogue of the anticancer agent tamoxifen (Scheme 2). A four-step sequence was used: demethylation of *S*-(2-bromo-5-methoxybenzyl) thioacetate **15** to give the corresponding 5-hydroxy derivative **16**, S-alkylation and subsequent *O*-alkylation to obtain the appropriate cascade precursor **18**, and a palladium-catalyzed cyclization/Suzuki cascade process (Scheme 2). The desired product **19** was obtained in 42% overall yield.

Scheme 2. Tamoxifen and a Sulfur Analogue; Synthesis of Compound 19



In summary, cyclocarbopalladation/cross-coupling cascade reactions were applied for the first time in a sulfur series and enabled the access to sulfur heterocycles. The process works efficiently via either 5-*exo* or 6-*exo-dig* cyclization and is compatible with Stille and Suzuki−Miyaura cross-coupling reactions, thereby enabling the introduction of a large variety of substituents. By this method, we obtained original structures containing a benzene-fused 5- or 6-membered sulfur heterocycle and a stereodefined tetrasubstituted exocyclic double bond. Due to their structural particularities, such compounds could be interesting candidates as selective estrogen receptor modulators (SERMs). Thus, compound **19** was prepared as a sulfur analogue of tamoxifen and is presently under biological investigations. Current studies are focused on exploiting this method to access various more complex sulfur heterocycles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Max Malacria (ICSN, University of Paris 6) on the occasion of his 65th birthday

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(9) The reaction can be performed under oil bath heating but requires 9−18 h for a similar result.

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(11) The optimization of the reaction conditions for the cyclization/Suzuki−Miyaura cascade is given in the Supporting Information (Table 1).

(12) The reaction can be performed under oil bath heating but requires 5−12 h for a similar result.

(13) See the scheme of the reaction and the structure of compound **10** in the Supporting Information.

(14) See the scheme of the reaction in the Supporting Information.