

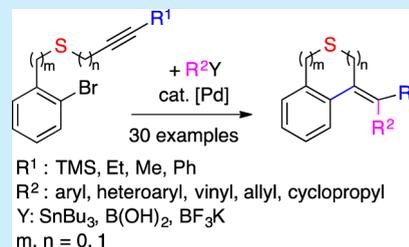
Cyclocarbopalladation/Cross-Coupling Cascade Reactions in Sulfide Series: Access to Sulfur Heterocycles

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S 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.

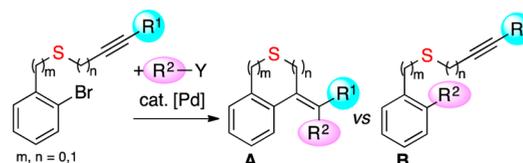


One of the main reasons for the continuous and spectacular progress in the field of palladium-catalyzed reactions is their high tolerance of various functionalized substrates. However, as far as the development of these reactions involving organosulfur substrates is concerned, the deactivation of the 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*-dibromo-vinyl 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 bond⁷ (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 R¹ substituents (Figure 1).

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

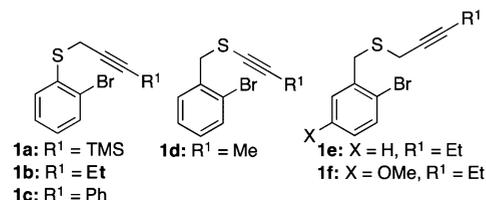
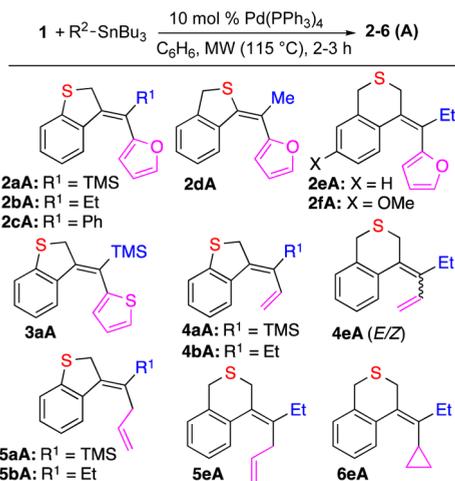


Figure 1. Starting sulfides 1.

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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

^aIsolated yield. ^bMixture of *E/Z* isomers in a 3/1 ratio. ^cThe ratio 5/6 was 2/1. ^dThe conversion was 50%. ^eNot determined.

Cascade reaction conditions that are classically used in our laboratory⁸ 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(PPh₃)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 conversion⁹ (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 ¹H 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**

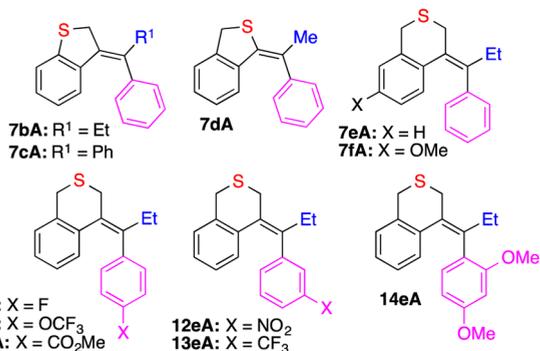
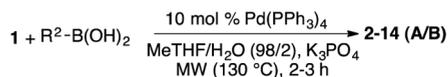
(Table 1, entry 8), which is highly acid-sensitive (fast decomposition is observed if the CDCl₃ for the NMR analysis is not neutralized prior to use). The cascade reaction was found to be effective also in the case of benzyl ynethioether **1d**, affording heterocycle **2dA** (Table 1, entry 9). The scope 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 allyltributylstannane, 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-furyltributylstannane 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(PPh₃)₄ as the catalyst and with K₃PO₄ as the base, in a mixture of 2-methyltetrahydrofuran/water 98/2 at 130 °C during 2 or 3 h under microwave irradiation¹² (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 of the expected product, we identified by ¹H 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

^aA: cascade product. B: direct coupling product. The A/B ratio was measured by NMR ¹H. ^bPdCl₂/SPHOS was used as the catalyst. ^cR²BF₃K was used as the boron reagent. ^dInstead the desired product, compound 10 was obtained; see ref 13. ^eSee 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).

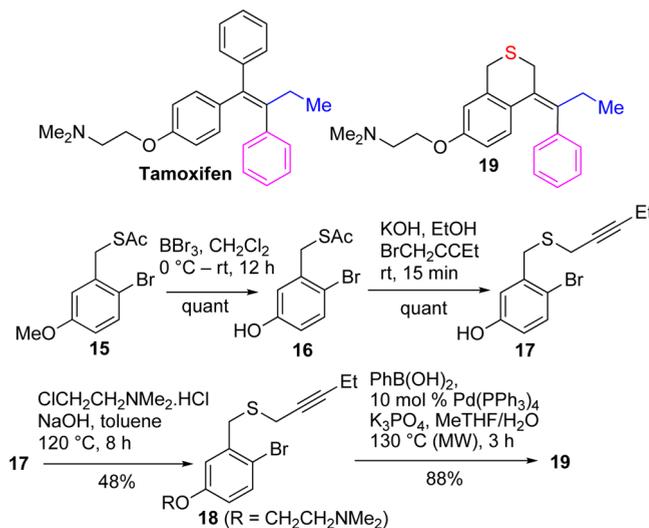
To compare the efficiency of the Stille and Suzuki reactions in this process, 2-furylboronic acid was reacted with 1e, and we found that the Suzuki conditions led only to product 2eB resulting from the direct cross-coupling. By replacing the Pd(PPh₃)₄ catalyst by PdCl₂/SPHOS, an equimolar mixture of 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 allylstannane (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

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



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.

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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- (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.