EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis of benzimidazole-fused medium-sized N,S-heterocycles via palladium-catalyzed cyclizations

Authors: Alexandra Basilio Lopes, Patrick Wagner, and Mihaela Gulea

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801686

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801686

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201801686

WILEY-VCH

FULL PAPER

Synthesis of Benzimidazole-Fused Medium-Sized *N,S*-Heterocycles *via* Palladium-Catalyzed Cyclizations

Alexandra Basilio Lopes,[a] Patrick Wagner,[a] and Mihaela Gulea*[a]

Abstract: The synthesis of unprecedented benzimidazole-fused thiazocines, thiazonines, and thiazecines having an exocyclic double bond is reported. The process consists in an 8-, 9-, or 10-*exo*-dig cyclocarbopalladation followed by reduction. The scope and limitations were established and showed the importance of the precursor structure for the success of the reaction. A competition between the *exo*-dig and the *endo*-dig cyclization was observed for two substrates bearing an *N*-homopropargyl chain, the *endo*-cyclization leading to rarely encountered 10- and 11-membered *N,S*-heterocycles with a *trans*-endocyclic double bond. X-ray structures of three products were obtained by co-crystallization with fumaric acid and show the twisted structures of these molecules.

Introduction

The significant impact of organosulfur compounds in pharmaceutical industry is demonstrated by the large numbers of sulfur-containing drugs (362 approved by the FDA) and the presence of some of them among the drugs the most prescribed and sold at present in the world.[1] Some of these drugs contain in their structures 5-, 6-, or 7-membered *N,S*-heterocycles,[2] as for example Actos® (thiazolidinedione), Claforan® (thiazole and thiazine), and Seroquel® (thiazepine) (Figure 1). Moreover, the role of noncovalent sulfur interactions in drug design and molecular recognition has been recently highlighted.[3] Considering the continual need for the development of medicinal therapies, rarely encountered or still unknown medium-sized *N,S*-heterocyclic compounds could lead to forthcoming pharmaceuticals. Medium-sized heterocycles are interesting non-planar scaffolds[4] for exploring new area of chemical space in order to identify molecules with original, patentable structures capable to modulate challenging therapeutic targets.[5,6] Indeed, recent exploration of drug candidates containing medium-ring *N*-heterocycles (8 to 12 atoms) has shown the importance of conformational constraints in these structures.[7]

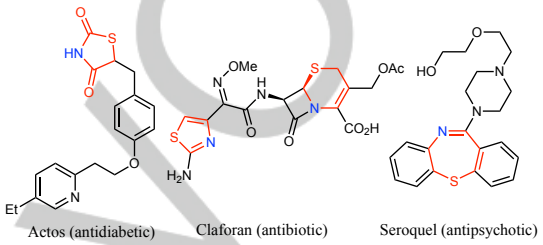


Figure 1. Examples of drugs containing *N,S*-heterocycles.

From an organic synthesis point of view, the access to medium-sized rings is particularly difficult because of the high degree of transannular strain and unfavorable entropic factors involved.[8] Several methods to access 8- and 9-membered *N,S*-heterocycles have been published, including inter or intramolecular cyclizations of N/S-nucleophiles,[9] ring-closing metathesis,[10] intramolecular Friedel-Crafts,[11] and carbonylation reactions.[12] However, compared to the numerous syntheses of 5 to 7-membered *N,S*-heterocyclic counterparts, they remain rather limited. Published medium-ring *N,S*-heterocyclic structures are mainly benzene-fused thiazocines or thiazonines, based on 2-aminobenzenethiol moiety (Figure 2, structures **I-IV**). Moreover, some of these compounds have been reported to possess promising biological activity, as antagonists of the mitochondrial sodium-calcium exchanger (mNCE),[13] or as 17β-hydroxysteroid dehydrogenase type 3 (17 β-HSD3) inhibitors.[14] As part of our research dealing with the synthesis of *N,S*-heterocycles (i.e. thiazolines, thiazines, benzothiazoles),[15] we decided to focus on a unique class of benzimidazole-fused thiazocines and thiazonines **V**, bearing an exocyclic double bond, as new scaffolds for medicinal chemistry (Figure 2). No hit of such structures has been found by SciFinder search. The benzimidazole moiety provides the advantage of its widespread occurrence in biologically active compounds and drugs.[16] For a well-known example, Nexium®, a proton-pump inhibitor used in the treatment of ulcer disease, bears a benzimidazole moiety with a sulfinyl substituent in 2-position.

[a] Dr. A. Basilio Lopes, P. Wagner, Dr. M. Gulea
Laboratoire d'Innovation Thérapeutique (LIT) UMR 7200, Faculté de Pharmacie
Université de Strasbourg, CNRS
74, route du Rhin, 67401 Illkirch, France
E-mail: gulea@unistra.fr
http://medchem.unistra.fr/synthese-organique-metallo-induite-et-heterochimie-somhet/

Supporting information for this article is given via a link at the end of the document.

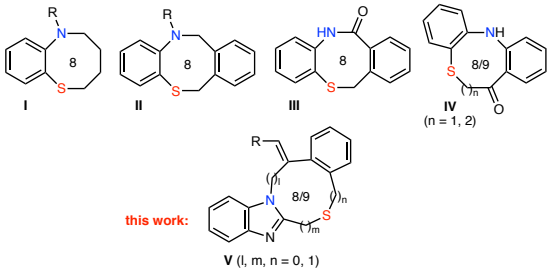
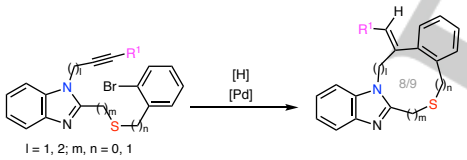


Figure 2. Known thiazocines and thiazonines scaffolds **I-IV** and our proposed benzimidazole-fused structures **V**.

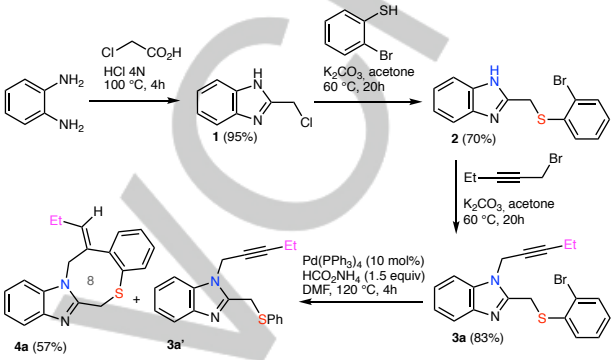
Palladium-catalyzed cyclizations represent a modern powerful tool to access efficiently, with step economy and high selectivity, complex heterocyclic molecules from simple starting materials.[17] However, these reactions remain rare in medium-sized ring heterocyclic series.[18] Because of the risk of catalyst deactivation caused by the thiophilicity of palladium, Pd-catalyzed domino cyclizations have been rarely performed on sulfur-containing substrates. Our group recently showed the feasibility of Pd-catalyzed domino reactions in sulfide series for the synthesis of 5- and 6-membered *S*-heterocycles.[19] The extension of such methods to larger ring-sizes represents a challenging task as competitive reactions such as direct reduction or direct cross-coupling could become predominant, as well as *endo vs exo* cyclization may occur. We report herein the synthesis of benzimidazole-fused thiazocines and thiazonines, by involving judiciously designed precursors in domino processes consisting in the 8- or 9-*exo*-dig reductive cyclocarbopalladation (Scheme 1).



Scheme 1. Pd-catalyzed reductive cyclization approach to benzimidazole-fused thiazocines and thiazonines.

Results and Discussion

We first prepared 2-(chloromethyl)benzimidazole **1** from commercially available benzene-1,2-diamine and 2-chloroacetic acid, then used it to alkylate 2-bromothiophenol to access 2-sulfanylated benzimidazole **2** (Scheme 2). *N*-alkylation of this later by 1-bromopent-2-yne led to the desired precursor **3a** in 83% yield. Then we placed substrate **3a** under Pd-catalyzed reductive cyclization reaction conditions, in the presence of ammonium formate as the hydrogen donor,[20] and succeeded in obtaining the desired 8-membered *N,S*-heterocycle **4a**. The *Z*-geometry of the generated double bond was controlled *via* the well-established *syn*-carbopalladation process. Although the conversion was almost total (95%), the isolated yield in **4a** was moderate. We found that $Pd(PPh_3)_4$ catalyst gave better results than $Pd(OAc)_2/PPh_3$ (57% *vs* 36% isolated yield). The use of ethanol as the hydride source[18b] did not work in our case. The direct reduction of **3a** is a competitive reaction resulting in the side-product **3a'**, which was separated from **4a** by column chromatography. The ratio **4a/3a'/3a** measured by ^1H NMR in the crude mixture was 89:6:5.



Scheme 2. Synthetic sequence to access benzimidazole-fused thiazocine **4a**.

We then have succeeded a single crystal by co-crystallization of thiazocine **4a** with fumaric acid and the analysis by X-ray diffraction showed two molecules of **4a** interacting with one molecule of diacid *via* O-H···N hydrogen bonds (Figure 3, [a]). Two views (**A** and **B**) of the crystal structure are shown after suppression of the diacid molecule (Figure 3, [b]), highlighting the 8-membered ring and its conformation.

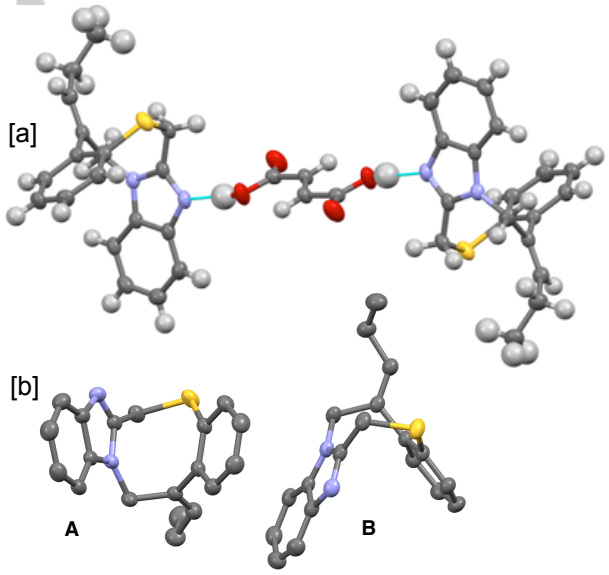
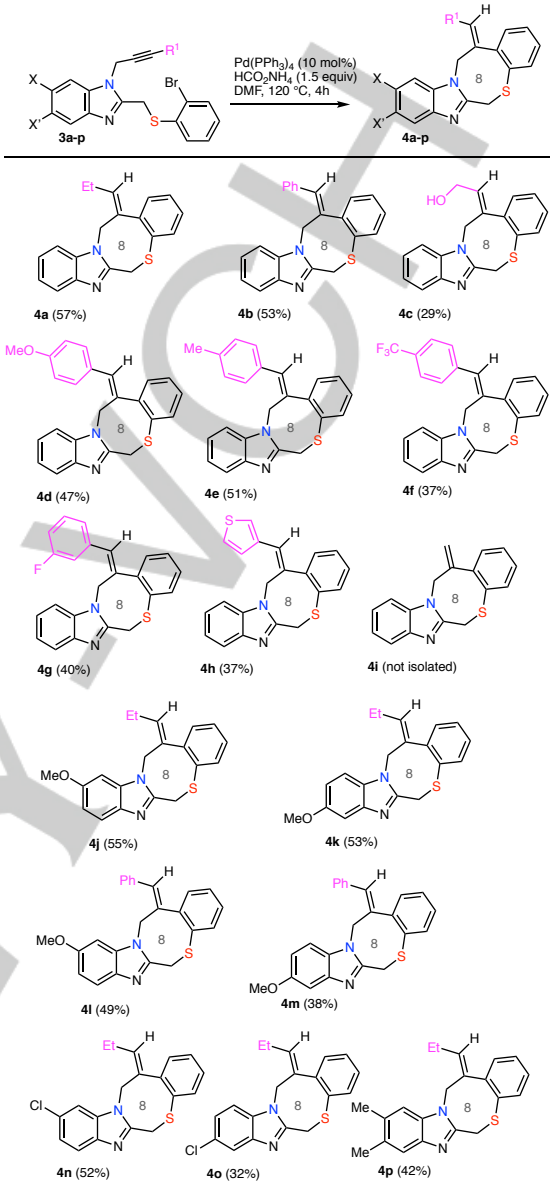


Figure 3. (a) X-ray structure of co-crystal **4a.fumaric acid.** (b) Two views (**A** & **B** with diacid and H-atoms suppressed).

Structural modifications of the substrate were then investigated in order to study the scope and limitations of the reaction and

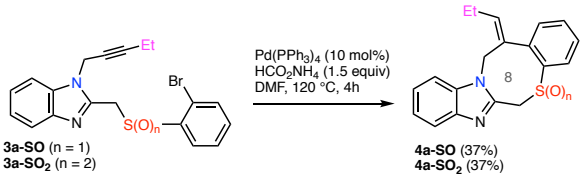
expand the structural diversity around the benzimidazole-fused medium-sized *N,S*-heterocyclic new scaffolds. We started by changing the substituent on the triple bond (Scheme 3). Precursors **3b** and **3c** were synthesized similarly to **3a**, by N-alkylation of **2** with (3-chloroprop-1-yn-1-yl)benzene or with 4-chlorobut-2-yn-1-ol, respectively. The other derivatives **3d-h** were prepared *via* Sonogashira cross-coupling with the corresponding aryl or heteroaryl iodides starting from the *N*-propargyl substrate **3i** that resulted from *N*-propargylation of **2** (see in Supporting Information). The reaction worked in all cases, with electron donating or withdrawing substituents on the aromatic ring, and the expected benzimidazole-fused thiazocines **4b,d-g** were isolated in moderate yields (37 to 57%). A lower yield of 29% was obtained for the product **4c** bearing a CH_2OH group on the exocyclic double bond. 3-Thienyl derivative **4h** was also obtained and isolated in 37% yield. Substrate **3i** with R^1 = H was also tested, however the desired cyclization product **4i** was accompanied by two side-products derived from the reduction of the triple bond into double bond and from *N*-depropargylation that occurs more easily on the terminal alkynyl substrate in the presence of the palladium catalyst.[21] We next performed the reaction on substrates **3j-p** bearing various substituents (X, X') on different positions of the benzimidazole benzene ring. The preparation and the characterization of these substrates are given in the Supporting information. The position of the methoxy group on **3j** and **3k** did not influence the efficiency of the reaction (55% for **4j** *vs* 53% yield for **4k**). The obtained yields were however slightly higher with an ethyl than with a phenyl substituent on the triple bond (55% for **4j** *vs* 49% yield for **4l**). In the case of chlorinated substrates, a better yield was obtained for derivative **4n** than for **4o** (52% for **4n** *vs* 32% yield for **4o**). The 9,10-dimethyl benzimidazole derivative **4p** was obtained in 42% yield. Note that in almost all cases, a small amount of starting material **3** was recovered and the product mixture contained also the reduced compound of type **3'** (the ratios **3/4/3'** measured in the crude mixture by ^{1}H NMR are given in Table 1 in the Supporting information). This was the main reason of the moderate isolated yields obtained for the desired thiazocines **4**.



Scheme 3. Scope of the reductive cyclization to access benzimidazole-fused thiazocines **4**: variation of the substituents on the triple bond and on benzimidazole.

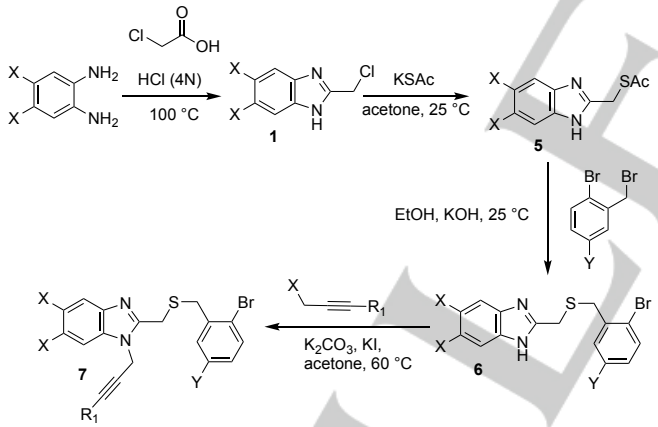
The oxidation of a sulfide into the corresponding sulfoxide or sulfone changes its reactivity and its physicochemical properties. For therapeutic applications this transformation may affect the biological properties of the initial molecule via the modification of its polarity, conformation, solubility, lipophilicity, etc. This allows also identifying the sulfur-species formed in biological media from a sulfured biomolecule. Moreover, sulfoxides and sulfones are valuable sulfur functions present in known bioactive molecules. In this context we decided to prepare the S-oxidized derivatives of thiazocine **4a**, sulfoxide **4a-SO** and sulfone **4a-SO$_2$**. Rather than accomplishing this transformation by direct oxidation of **4a**, we have chosen to test the efficiency of the reductive cyclization on

the S-oxidized substrates derived from **3a** (Scheme 4). A possible difference in the reactivity could be caused by a different interaction of the palladium with the three sulfur functions (i.e. sulfide, sulfoxide, sulfone). Substrates **3a-SO** and **3a-SO$_2$** were prepared respectively by mono- or dioxidation of the sulfur atom of **3a**. Placed under the same reaction conditions, they led to the expected S-oxide and S-dioxide thiazonines **4a-SO** and **4a-SO$_2$**, both of them in 37% yield, bellow the yield obtained previously in the case of thiazocine **4a** (57%).

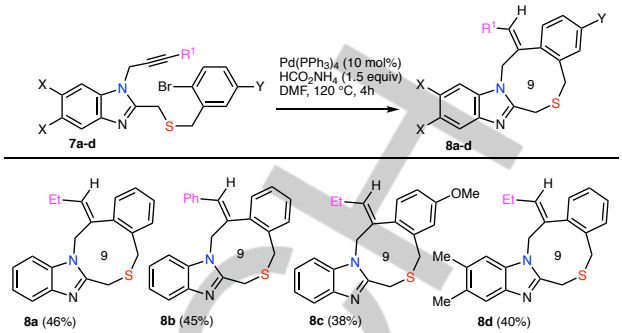


Scheme 4. Reductive cyclization using S-oxidized substrates.

Then we investigated the reaction scope by modifying the substrate tether length in order to obtain 9-membered thiazonine ring. Substrates **7** bearing a benzylsulfenyl group were synthesized via thioacetate intermediate of type **5** by consecutive *S*-benzylation, then *N*-propargylation (Scheme 5). Although the isolated yields remained moderate (38 to 46%), the reductive cyclization still worked on these extended substrates affording the expected corresponding thiazonines **8a-d** (Scheme 6).



Scheme 5. Synthetic route to substrates **7**.



Scheme 6. Reductive cyclization to access benzimidazole-fused thiazonines **8**.

A single crystal of **8c** co-crystallized with fumaric acid was isolated and its structure confirmed by X-ray diffraction analysis (Figure 4).

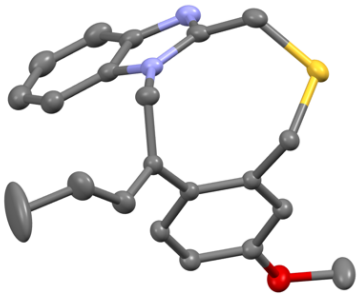
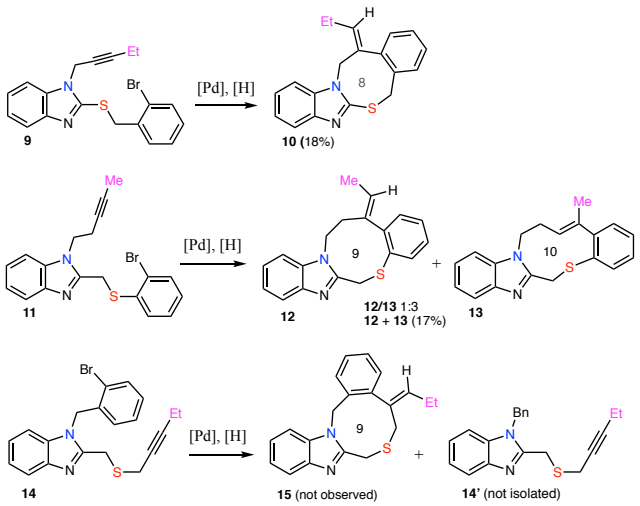


Figure 4. X-ray structure of co-crystal **8c.fumaric acid** (diacid and H-atoms suppressed).

Other modifications of the substrate were made to determine their influence on the efficiency of the reaction under the same conditions and several limitations were pointed out (Scheme 7). In the case of substrate **9** in which the sulfur atom was placed in 2-position of the benzimidazole ring, the corresponding thiazocine **10** was obtained in low yield (18%). This was probably due to the competitive desulfanylation occurring on heteroaromatic thioether such substrate **9** in the presence of the palladium catalyst.[22]
When substrate **11** bearing a homopropargyl chain on the nitrogen atom was placed under the same reaction conditions, a competition between the 9-*exo*-dig and the 10-*endo*-dig cyclization took place leading to a difficult to separate mixture of thiazonine **12** and thiazecine **13** in a 1:3 ratio and a combined yield of 17%, after purification by column chromatography. The low yield could be explained by the incomplete conversion (89%) and the presence of the reduced product **11'** (11% isolated yield). It is to notice that the 10-*endo*-dig cyclization was not observed in the case of *N*-propargyl substrates **7**, as probably the conformational constraint in this cyclization is higher than in the case of substrate **11**. In the case of substrate **14** the substituents on the heteroatoms were inverted, the sulfur was propargylated and the nitrogen was benzylated. Surprisingly, the expected thiazonine **15** was not obtained in this case, but a complex crude

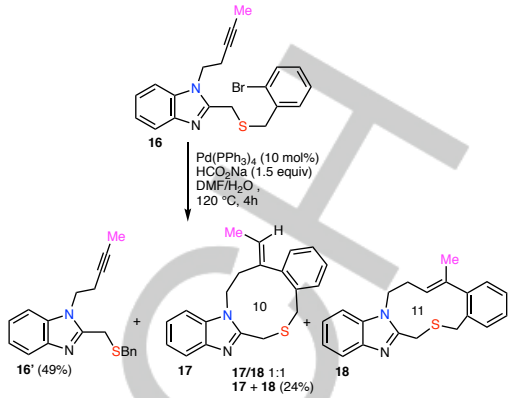
mixture containing the starting material and the reduced product **14'** that were detected in ^{1}H NMR.



Scheme 7. Limitations of the reductive cyclization to access benzimidazole-fused medium-sized *N,S*-heterocycles.

We then attempted to extend the method to access larger rings. Substrate **16** was prepared and tested for this purpose, but a substantial amount of the reduced product **16'** was present in the crude mixture together with two other products. After purification by column chromatography the two products were isolated in 9% combined yield. The analysis of the NMR spectra of the mixture allowed us to assign to these products the structures of thiazecine **17** and of thiazaundecine **18** (Scheme 8). This result represents a rare example of competing processes between 10-*exo* and 11-*endo* cyclocarbopalladation of alkynes. Similar results have been reported for the cyclocarbopalladation of alkenes, in carbocyclic series.[23] To improve the yield in cyclic products, we tested other reaction conditions. Thus, we changed the hydrogen donor from ammonium formate to sodium formate and used a mixture of DMF/H_2O as the solvent to increase the solubility of the sodium salt.[24] The major product was again **16'** (49% isolated yield) accompanied by **17** and **18** in a 1:1 ratio. However, we noted an improvement of the cyclization reaction, achieving a combined isolated yield of 24% of **17** and **18**. The good results obtained with HCO_2Na in DMF/H_2O prompted us to test these conditions on two other substrates, **3a** and **7b**. Indeed, the isolated yields of the desired products were improved compared to those obtained with HCO_2NH_4 in DMF, with 69% (*vs* 57%) for **4a** and 58% (*vs* 45%) for **8b**.

To our delight a single crystal of **18** co-crystallized with fumaric acid was isolated and its original structure having a *trans*-endocyclic double bond was confirmed by X-ray diffraction analysis (Figure 5).



Scheme 8. Reductive cyclization to access benzimidazole-fused 10- and 11-membered *N,S*-heterocycles.

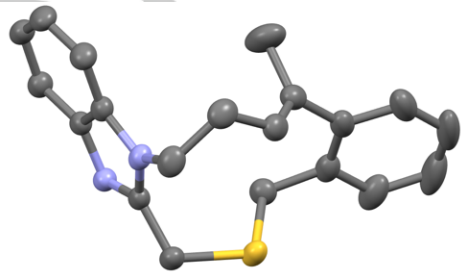
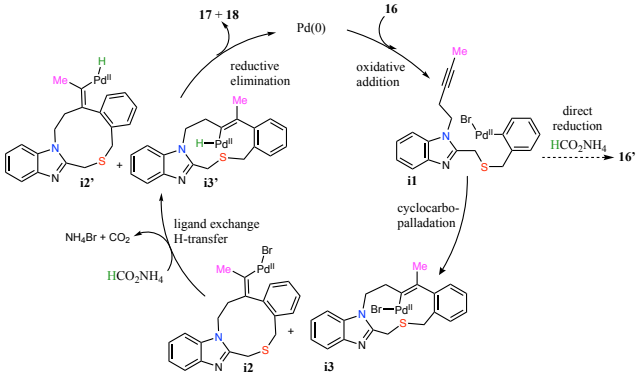


Figure 5. X-ray structure of co-crystal **18.fumaric acid** (diacid and H-atoms suppressed).

The mechanism of the reductive Pd-catalyzed processes involving substrate **16** is given in Scheme 9. Arylpalladium(II) species **i1** led either to the reduced compound **16'** *via* bromide to formate ligand exchange, followed by common hydride transfer and reductive elimination steps, or to the cyclic alkenylpalladium(II) species **i2** and **i3**, *via* 10-*exo*-dig and 11-*endo*-dig cyclizations, respectively. These species led after the reductive process to the corresponding thiazecine **17** and thiazaundecine **18**.



Scheme 9. Mechanism of the reductive Pd-catalyzed processes involving substrate **16**.

Conclusions

In summary, we have described the synthesis of unprecedented benzimidazole-fused medium-sized *N,S*-heterocycles (nineteen thiazocines, five thiazonines, and one thiazecine) bearing an exocyclic double bond, through a Pd-catalyzed reductive cyclization involving 8-*exo,* 9-*exo,* or 10-*exo*-dig cyclocarbopalladation. The yields were low to moderate, but we finally found that they can be improved by using sodium formate instead of ammonium formate as the hydride donor, making the method synthetically more effective. A competition between *exo*-dig and *endo*-dig cyclizations was observed for two substrates bearing an *N*-homopropargyl chain, the latter leading to rarely encountered 10- and 11-membered *N,S*-heterocycles, one thiazecine and one thiazaundecine, having a *trans*-endocyclic double bond. Further experimental and theoretical studies will be done to rationalize this competing cyclizations. X-ray structures were obtained by co-crystallization with fumaric acid for one thiazocine, one thiazonine, and the thiazaundecine, showing their twisted structures. These compounds represent interesting new scaffolds for drug discovery.

Experimental Section

General Information: Reagents and dry solvents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates and was visualized under UV light and revealed with $KMnO_4$ stain. Crude products were purified by flash column chromatography on silica gel Si 60 (40-63 µm). NMR spectra were recorded at 400 or 500 MHz for ^{1}H, at 100 or 125 MHz for ^{13}C, and at 376 MHz for ^{19}F. Chemical shifts (δ) were reported in ppm relative to residual solvent. Coupling constants (*J*) were reported in hertz (Hz). Assignments of ^{1}H and ^{13}C signal were made by DEPT, COSY, HSQC, HMBC and NOESY-2D experiments. The following abbreviations were adopted in reporting NMR data: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), broad signal (br), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq), triplet of doublets (td), triplet of triplets (tt), quartet of triplets (qt) or multiplet (m). HRMS were performed with a Q-TOF analyzer sing electrospray ionization (ESI). Melting points were determined in open capillary tubes and were uncorrected.

General Procedure for reductive cyclization (GP):
Method A. Under an argon atmosphere, a mixture of benzimidazole derivative (1 equiv), ammonium formate (1.5 equiv), and $Pd(PPh_3)_4$ (10 mol%), in DMF (10 mL/mmol substrate) was stirred at 120 °C for 4 h. The mixture was concentrated to dryness under reduced pressure and the crude residue was purified by flash column chromatography on silica gel to give the heterocyclic product.
Method B. Ammonium formate was replaced by sodium formate and DMF by DMF/H_2O (3.5:1).

***(Z)*-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazocine (4a):** Following the GP, starting from **3a** (100 mg, 0.26 mmol), **4a** was obtained after purification by flash chromatography (5-40% AcOEt in pentane) as a brownish oil (Method A: 45 mg, 57%, Method B: 55 mg, 69%). TLC (heptane/AcOEt 1:1, R_f = 0.39). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3H), 2.09 (quint, *J* = 7.5 Hz, 2H), 4.55 (s, 2H), 5.31 (s, 2H), 6.04 (t, *J* = 7.5 Hz, 1H), 7.23-7.40 (m, 6H), 7.47-7.49 (m, 1H), 7.50-7.52 (m, 1H), 7.76 (m, 7.75-7.78 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 21.9, 31.4, 42.7, 108.6, 119.7, 122.1, 122.7, 127.9, 130.9, 132.4, 132.5, 134.4, 135.6, 139.2, 141.7, 142.1, 151.1. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{18}N_2S$ $[M+H]^+$: 307.1269, found: 307.1259.

(*Z*)-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazocine 5-oxide (4a-SO): Following the GP Method A, starting from **3a-SO** (57 mg, 0.14 mmol), **4a-SO** was obtained after purification by flash chromatography (50-100% AcOEt in DCM) as a yellowish amorphous solid (17 mg, 37%). TLC (DCM/AcOEt 3:2, R_f = 0.16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, 3H), 2.44 (quint, *J* = 7.6 Hz, 2H), 4.34 (d, *J* = 14.4 Hz, 1H), 5.09 (d, *J* = 17.5 Hz, 1H), 5.17 (d, *J* = 14.4 Hz, 1H), 5.37 (d, *J* = 17.5 Hz, 1H), 5.82 (tt, *J* = 2.0, 7.4 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 7.08-7.21 (m, 4H), 7.26-7.29 (m, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.0, 45.0, 57.4, 108.8, 119.9, 122.5, 123.1, 124.6, 128.7, 129.5, 131.5, 133.6, 135.0, 136.6, 137.1, 139.3, 142.7, 147.7. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{18}N_2OS$ $[M+H]^+$: 323.1218, found: 323.1213.

(*Z*)-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazocine 5,5-dioxide (4a-SO$_2$): Following the GP Method A, starting from **3a-SO$_2$** (56 mg, 0.14 mmol), **4a-SO$_2$** was obtained after purification by flash chromatography (0-20% AcOEt in DCM) as a white amorphous solid (17 mg, 37%). TLC (heptane/AcOEt 1:1, R_f = 0.29). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.5 Hz, 3H), 2.45 (quint, *J* = 7.5 Hz, 2H), 5.10 (d, *J* = 3.7 Hz, 2H), 5.19 (d, *J* = 16.6 Hz, 1H), 5.49 (d, *J* = 16.7 Hz, 1H), 5.92 (tt, *J* = 1.9, 7.4 Hz, 1H), 7.08 (dd, *J* = 1.6, 7.3 Hz, 1H), 7.14-7.31 (m, 6H), 7.57 (dt, *J* = 1.1, 7.8 Hz, 1H), 7.92 (dd, *J* = 1.6, 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 22.0, 44.2, 59.3, 109.0, 120.3, 122.81, 123.6, 128.5, 128.5, 130.8, 132.9, 134.0, 135.4, 137.3, 138.1, 138.6, 142.7, 143.5. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{18}N_2O_2S$ $[M+H]^+$: 339.1167, found: 339.1157.

(*Z*)-14-benzylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazocine (4b): Following the GP Method A, starting from **3b** (100 mg, 0.23 mmol), **4b** was obtained after purification by flash chromatography (0-25% AcOEt in heptane) as a white amorphous solid (43 mg, 53%). TLC (heptane/AcOEt 1:1, R_f = 0.32). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.53 (s, 2H), 5.63 (s, 2H), 6.89 (s, 1H), 6.96-6.99 (m, 1H), 7.07-7.12 (m, 4H), 7.17-7.19 (m, 1H), 7.28-7.33 (m, 1H), 7.35-7.42 (m, 4H), 7.48-7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 45.6, 108.7, 119.4, 122.1, 122.6, 127.9, 128.7, 128.8, 128.8, 129.33, 130.2, 130.2, 133.3, 135.3, 136.0, 138.8, 142.0, 144.6, 150.3. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{23}H_{18}N_2S$ $[M+H]^+$: 355.1269, found: 355.1256.

(*Z*)-2-(6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazocin-14(13*H*)-ylidene)ethan-1-ol (4c): Following the GP Method A, starting from **3c** (43 mg, 0.11 mmol), **4c** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane) as a yellowish amorphous solid (10 mg, 29%). TLC (DCM/AcOEt 3:2, R_f = 0.30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (d, *J* = 6.2 Hz, 2H), 4.38 (s, 2H), 5.30 (s, 2H), 6.14 (t, *J* = 6.1 Hz, 1H), 7.15-7.30 (m, 6H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.41-7.46 (m, 1H), 7.58 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 43.1, 58.9, 108.7, 119.5, 122.6, 123.1, 128.4, 128.5, 130.8, 132.2, 133.2, 135.3, 135.4, 137.0, 141.3, 141.5, 150.9. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{18}H_{16}N_2OS$ $[M+H]^+$: 309.1061, found: 309.1049.

(*Z*)-14-(4-methoxybenzylidene)-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4d): Following the GP Method A, starting from **3d** (85 mg, 0.18 mmol), **4d** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane) as a yellowish oil (33 mg, 47%). TLC (heptane/AcOEt 1:1, R_f = 0.24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.52 (s, 2H), 5.61 (s, 2H), 6.82 (s, 1H), 6.88-6.92 (m, 2H), 6.98 – 7.02 (m, 1H), 7.08-7.12 (m, 4H), 7.16-7.18 (m, 1H), 7.27-7.30 (m, 2H), 7.45-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 45.6, 55.4, 108.8, 114.2, 119.3, 122.1, 122.6, 128.4, 128.5, 129.2, 130.2, 130.3, 133.1, 135.3, 135.8, 136.9, 141.8, 144.8, 150.4, 159.3. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{20}N_2OS$ $[M+H]^+$: 385.1374, found: 385.1349.

(*Z*)-14-(4-methylbenzylidene)-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4e): Following the GP Method A, starting from **3e** (86 mg, 0.19 mmol), **4e** was obtained after purification by flash chromatography (5-30% AcOEt in cyclohexane) as a beige amorphous solid (36 mg, 51%). TLC (heptane/AcOEt 1:1, R_f = 0.39). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.53 (s, 2H), 5.63 (s, 2H), 6.85 (s, 1H), 6.97-7.00 (m, 1H), 7.06-7.13 (m, 4H), 7.16-7.21 (m, 3H), 7.25-7.27 (m, 3H), 7.47-7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 32.1, 45.6, 108.8, 119.3, 122.2, 122.6, 128.6, 128.8, 129.3, 129.5, 130.2, 130.2, 133.1, 133.5, 135.2, 136.0, 137.9, 144.7, 150.4. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{20}N_2S$ $[M+H]^+$: 369.1425, found: 369.1410.

(*Z*)-14-(4-(trifluoromethyl)benzylidene)-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo [2,1-*c*][1,4]thiazocine (4f): Following the GP Method A, starting from **3f** (90 mg, 0.18 mmol), **4f** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane) as a yellowish amorphous solid (28 mg, 37%). TLC (heptane/AcOEt 1:1, R_f = 0.36). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 2H), 5.57 (s, 2H), 6.86-6.93 (m, 2H), 7.05-7.21 (m, 5H), 7.38-7.45 (m, 2H), 7.46-7.55 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 45.0, 108.3, 119.36, 122.2, 122.6, 125.2, 125.5, 125.6, 125.6, 125.6, 128.8, 128.9, 129.2, 129.6, 130.4, 131.9, 135.1, 135.8, 139.4, 141.0, 141.7, 143.8, 150.1. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{17}F_3N_2S$ $[M+H]^+$: 423.1143, found: 423.1124.

(*Z*)-14-(3-fluorobenzylidene)-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4g): Following the GP Method A, starting from **3g** (79 mg, 0.18 mmol), **4g** was obtained after purification by flash chromatography (5-30% AcOEt in cyclohexane) as a yellowish amorphous solid (26 mg, 40%). TLC (heptane/AcOEt 1:1, R_f = 0.49). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 5.62 (s, 2H), 6.83 (s, 1H), 6.96-7.03 (m, 2H), 7.06-7.17 (m, 7H), 7.34 (td, J = 6.0, 8.0 Hz, 1H), 7.48-7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 45.4, 108.6, 114.8, 115.0, 115.6, 115.8, 119.4, 122.3, 122.7, 124.5, 124.6, 128.9, 129.4, 130.1, 130.2, 130.3, 130.4, 132.0, 132.0, 135.2, 136.2, 138.1, 138.2, 140.2, 144.3, 150.2, 161.7, 164.2. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{23}H_{17}FN_2S$ $[M+H]^+$: 373.1174, found: 373.1150.

(*Z*)-14-(thiophen-3-ylmethylene)-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4h): Following the GP Method A, starting from **3h** (79 mg, 0.18 mmol), **4h** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane) as a yellowish amorphous solid (24 mg, 37%). TLC (heptane/AcOEt 1:1, R_f = 0.33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (s, 2H), 5.63 (s, 2H), 6.82 (s, 1H), 7.09-7.17 (m, 5H), 7.25-7.26 (m, 2H), 7.36 (dd, J = 2.9, 5.0 Hz, 1H), 7.47-7.49 (m, 1H), 7.52-7.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 45.9, 108.8, 119.4, 122.4, 122.8, 124.6, 126.2, 127.4, 128.6, 128.6, 129.2, 130.2, 130.5, 135.3, 135.7, 137.0, 137.4, 141.7, 144.7, 150.5. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{21}H_{16}N_2S_2$ $[M+H]^+$: 361.0833, found: 361.0820.

14-methylene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazocine (4i): Following the GP Method A, starting from **3i** (100 mg, 0.28 mmol), an inseparable mixture of **4i** and **2a** in a ratio 2:1 was obtained (23 mg) after purification by flash chromatography (5-40% AcOEt in pentane). **4i** was characterized from the mixture. TLC (heptane/AcOEt 2:3, R_f = 0.49). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 2H), 5.47 (s, 2H), 5.51 (s, 1H), 5.54 (s, 1H), 7.13-7.28 (m, 5H), 7.34 (d, J = 8.0 Hz, 1H), 7.47-7.51 (m, 1H), 7.59-7.62 (m, 1H). HRMS (ESI-Q-TOF) *m/z* calcd for $C_{17}H_{14}N_2S$ $[M+H]^+$: 279.0956, found: 279.0945.

(*Z*)-10-methoxy-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4j): Following the GP Method A, starting from **3j** (100 mg, 0.24 mmol), **4j** was obtained after purification by flash chromatography (5-30% AcOEt in cyclohexane as an orange oil (45 mg, 55%). TLC (heptane/AcOEt 1:1, R_f = 0.34). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 2.00 (quint, J = 7.5 Hz, 2H), 3.89 (s, 3H), 4.43 (s, 2H), 5.17 (s, 2H), 5.96 (t, J = 7.4 Hz, 1H), 6.85-6.89 (m, 2H), 7.16-7.25 (m, 3H), 7.41-7.43 (m, 1H), 7.55 (d, J = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 22.0, 31.4, 42.8, 56.0, 93.0, 110.9, 120.1, 128.0, 131.0, 132.5, 132.6, 134.4, 135.9, 136.2, 139.3, 142.1, 150.3, 156.8. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{20}H_{20}N_2OS$ $[M+H]^+$: 337.1374, found: 337.1360.

(*Z*)-9-methoxy-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4k): Following the GP Method A, starting from **3k** (87 mg, 0.21 mmol), **4k** was obtained after purification by flash chromatography (5-30% AcOEt in cyclohexane) as an orange oil (37 mg, 53%). TLC (heptane/AcOEt 1:1, R_f = 0.29). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 2.01 (quint, J = 7.5 Hz, 2H), 3.84 (s, 3H), 4.44 (s, 2H), 5.20 (s, 2H), 5.94 (t, J = 7.4 Hz, 1H), 6.94 (dd, J = 2.4, 8.8 Hz, 1H), 7.14-7.23 (m, 4H), 7.26 (d, J = 8.8 Hz, 1H), 7.41-7.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 21.9, 31.3, 43.0, 55.9, 101.9, 109.0, 112.8, 128.0, 128.1, 130.2, 130.9, 132.3, 132.7, 134.5, 139.1, 142.1, 142.2, 151.1, 156.2. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{20}H_{20}N_2OS$ $[M+H]^+$: 337.1374, found: 337.1360.

(*Z*)-14-benzylidene-10-methoxy-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazocine (4l): Following the GP Method A, starting from **3l** (84 mg, 0.18 mmol), **4l** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane) as a beige solid (34 mg, 49%). TLC (heptane/AcOEt 1:1, R_f = 0.24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.49 (s, 2H), 5.54 (s, 2H), 6.41 (d, J = 2.3 Hz, 1H), 6.73 (dd, J = 2.4, 8.8 Hz, 1H), 6.90 (s, 1H), 7.11-7.13 (m, 2H), 7.20-7.22 (m, 1H), 7.28-7.40 (m, 7H), 7.48-7.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 45.4, 55.9, 93.0, 110.8, 119.7, 127.9, 128.6, 128.7, 128.8, 129.2, 130.2, 130.5, 133.5, 135.9, 136.0, 136.1, 136.3, 138.8, 144.4, 149.5, 156.5. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{20}N_2OS$ $[M+H]^+$: 385.1374, found: 385.1353.

(*Z*)-14-benzylidene-9-methoxy-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazocine (4m): Following the GP Method A, starting from **3m** (85 mg, 0.18 mmol), **4m** was obtained after purification by flash chromatography (5-40% AcOEt in cyclohexane as a yellowish amorphous solid (27 mg, 38%). TLC (heptane/AcOEt 1:1, R_f = 0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.49 (s, 2H), 5.58 (s, 2H), 6.73 (dd, J = 2.4, 8.8 Hz, 1H), 6.83-6.86 (m, 2H), 6.97 (d, J = 2.4 Hz, 1H), 7.09-7.13 (m, 2H), 7.16-7.18 (m, 1H), 7.29-7.42 (m, 5H), 7.47-7.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 45.7, 55.7, 101.6, 109.0, 112.5, 127.9, 128.6, 128.7, 128.9, 129.3, 129.9, 130.1, 130.2, 133.2, 136.0, 136.1, 138.9, 142.6, 144.6, 150.4, 156.1. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{20}N_2OS$ $[M+H]^+$: 385.1374, found: 385.1362.

(*Z*)-10-chloro-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*] [1,4]thiazocine (4n): Following the GP Method A, starting from **3n** (100 mg, 0.24 mmol), **4n** was obtained after purification by flash chromatography (0-3% Et_2O in DCM) as a yellowish amorphous solid (42 mg, 52%). TLC (heptane/AcOEt 4:1, R_f = 0.17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 2.01 (quint, J = 7.5 Hz, 2H), 4.43 (s, 2H), 5.19 (s, 2H), 5.96 (t, J = 7.4 Hz, 1H), 7.15-7.25 (m, 4H), 7.37 (d, J = 1.9 Hz, 1H), 7.42-7.44 (m, 1H), 7.56 (d, J = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 22.0, 31.4, 43.1, 108.9, 120.6, 122.9, 128.1, 128.2, 128.7, 131.0, 132.1, 132.8, 134.2, 136.2, 139.4, 140.4, 142.1, 152.1. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{17}ClN_2S$ $[M+H]^+$: 341.0889, found: 341.0865.

(*Z*)-9-chloro-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazocine (4o): Following the GP Method A, starting from **3o** (100 mg, 0.24 mmol), **4o** was obtained after purification by flash chromatography (0-3% Et_2O in DCM) as a yellowish amorphous solid (26 mg, 32%). TLC (heptane/AcOEt 4:1, R_f = 0.22). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H), 1.97 (p, J = 7.5 Hz, 2H), 4.41 (s, 2H), 5.20 (s, 2H), 5.93 (t, J = 7.5 Hz, 1H), 7.13-7.22 (m, 3H), 7.23-7.24 (m, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.40-7.42 (m, 1H), 7.61 (d, J = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.1, 21.9, 31.4, 43.1, 109.3, 119.6, 123.2, 127.7, 128.1, 128.2, 130.9, 132.1, 132.8, 134.32, 134.3, 139.2, 142.2, 142.6, 152.5. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{17}ClN_2S$ $[M+H]^+$: 341.0879, found: 341.0872.

(*Z*)-9,10-dimethyl-14-propylidene-13,14-dihydro-6*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazocine (4p): Following the GP Method A, starting from **3p** (100 mg, 0.24 mmol), **4p** was obtained after purification by flash chromatography (0-7% Et_2O in DCM) as a yellowish oil (34 mg, 42%). TLC (heptane/AcOEt 1:1, R_f = 0.43). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 2.00 (quint, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.41 (s, 3H), 4.43 (s, 2H), 5.16 (s, 2H), 5.94 (t, J = 7.4 Hz, 1H), 7.14-7.26 (m, 4H), 7.40-7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 20.3, 20.8, 21.9, 31.3, 42.8, 108.9, 119.7, 127.9, 127.9, 131.0, 131.1, 131.9, 132.4, 132.6, 134.2, 134.6, 139.2, 140.1, 142.1, 150.2. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{21}H_{22}N_2S$ $[M+H]^+$: 335.1582, found: 335.1576.

(*Z*)-13-propylidene-13,14-dihydro-6*H*,8*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazonine (8a): Following the GP Method A, starting from **7a** (100 mg, 0.25 mmol), **8a** was obtained after purification by flash chromatography (5-30% AcOEt in heptane) as a yellowish amorphous solid (37 mg, 46%). TLC (heptane/AcOEt 1:1, R_f = 0.24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.5 Hz, 3H), 2.40 (p, J = 7.5 Hz, 2H), 3.81 (s, 2H), 4.00 (s, 2H), 5.16 (s, 2H), 5.65 (tt, J = 1.9, 7.3 Hz, 1H), 6.72-6.79 (m, 2H), 6.98 (td, J = 1.8, 7.3 Hz, 1H), 7.11-7.20 (m, 3H), 7.23 (d, J = 7.7 Hz, 1H), 7.50 (dt, J = 1.0, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.8, 27.6, 34.1, 44.5, 109.6, 119.5, 122.2, 122.4, 126.1, 128.3, 129.3, 129.8, 134.8, 135.6, 137.6, 138.1, 142.6, 152.6. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{20}H_{20}N_2S$ $[M+H]^+$: 321.1425, found: 321.1435.

(*Z*)-13-benzylidene-13,14-dihydro-6*H*,8*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazonine (8b): Following the GP, starting from **7b** (100 mg, 0.22 mmol), **8b** was obtained after purification by flash chromatography (5-40% AcOEt in pentane) as a yellowish amorphous solid (Method A: 37 mg, 45%, Method B: 48 mg, 58%,). TLC (heptane/AcOEt 1:1, R_f = 0.16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 2H), 4.10 (s, 2H), 5.44 (d, J = 1.7 Hz, 3H), 6.73 (td, J = 1.3, 7.5 Hz, 1H), 6.78 (t, J = 2.4 Hz, 1H), 6.88 (dd, J = 1.4, 7.7 Hz, 1H), 6.98 (td, J = 1.5, 7.6 Hz, 1H), 7.04-7.14 (m, 3H), 7.17 (dd, J = 1.3, 7.8 Hz, 1H), 7.38-7.53 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 34.4, 45.7, 109.7, 119.4, 122.3, 122.4, 126.1, 128.1, 128.6, 128.9, 129.1, 129.3, 130.0, 132.7, 134.6, 135.9, 137.1, 137.9, 138.6, 142.3, 152.2. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{24}H_{20}N_2S$ $[M+H]^+$: 369.1425, found: 369.1411.

(*Z*)-10-methoxy-13-propylidene-13,14-dihydro-6*H*,8*H*-benzo[*g*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazonine (8c): Following the GP Method A, starting from **7c** (90 mg, 0.21 mmol), **8c** was obtained after purification by flash chromatography (5-70% AcOEt in pentane) as an orange crystalline solid (28 mg, 38%); mp 91-93 °C. TLC (heptane/AcOEt 2:3, R_f = 0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 3H), 2.38 (p, J = 7.5 Hz, 3H), 3.61 (s, 3H), 3.77 (s, 2H), 4.01 (s, 2H), 5.12 (s, 2H), 5.61 (tt, J = 1.9, 7.3 Hz, 1H), 6.30 (dd, J = 2.7, 8.5 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 7.12-7.24 (m, 3H), 7.51-7.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.8, 27.7, 34.5, 44.7, 55.1, 109.6, 112.8, 114.0, 119.5, 122.3, 122.5, 130.5, 130.7, 134.8, 135.2, 135.5, 138.9, 142.3, 152.6, 159.2. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{21}H_{22}N_2OS$ $[M+H]^+$: 351.1531, found: 351.1515.

(*Z*)-2,3-dimethyl-13-propylidene-13,14-dihydro-6*H*,8*H*-benzo[*g*]benzo[4,5]imidazo [2,1-*c*][1,4]thiazonine (8d): Following the GP Method A, starting from **7d** (80 mg, 0.19 mmol), **8d** was obtained after purification by flash chromatography (5-70% AcOEt in heptane) as a yellowish amorphous solid (26 mg, 40%). TLC (heptane/AcOEt 1:1, R_f = 0.17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 3H), 2.28 (s, 3H), 2.38 - 2.43 (m, 5H), 3.80 (s, 2H), 3.95 (s, 2H), 5.08 (s, 2H), 5.62 (tt, J = 1.9, 7.3 Hz, 1H), 6.76-6.81 (m, 2H), 6.98-7.02 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.3, 20.7, 21.7, 27.7, 34.1, 44.5, 76.8, 77.1, 77.4, 109.7, 119.6, 126.2, 128.2, 129.2, 129.8, 130.9, 131.4, 133.5, 135.4, 135.8, 137.6, 138.5, 141.2, 151.6. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{22}H_{24}N_2S$ $[M+H]^+$: 349.1738, found: 349.1731.

(*Z*)-12-propylidene-12,13-dihydro-7*H*-benzo[*f*]benzo[4,5]imidazo[2,1-*b*][1,3]thiazocine (10): Following the GP Method A, starting from **9** (100 mg, 0.26 mmol), **10** was obtained after purification by flash chromatography (0-40% AcOEt in heptane) as a brownish amorphous solid (15 mg, 18%). TLC (heptane/AcOEt 2:3, R_f = 0.54). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.5 Hz, 3H), 2.44 (quint, J = 7.5 Hz, 2H), 4.27 (s, 2H), 5.35 (s, 2H), 5.81 (tt, J = 2.0, 7.3 Hz, 1H), 6.87 (dd, J = 1.6, 7.6 Hz, 1H), 6.93 (td, J = 1.3, 7.4 Hz, 1H), 7.06-7.19 (m, 4H), 7.23 (dd, J = 1.3, 7.6 Hz, 1H), 7.49-7.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.8, 35.9, 44.8, 108.1, 119.3, 122.2, 122.6, 128.3, 128.6, 129.3, 129.9, 133.2, 135.1, 135.6, 136.1, 139.9, 143.0, 149.0. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{18}N_2S$ $[M+H]^+$: 307.1269, found: 307.1258.

(*E*)-15-ethylidene-14,15-dihydro-6*H*,13*H*-benzo[*h*]benzo[4,5]imidazo[2,1-*c*][1,4] thiazonine (12) and (*E*)-5-methyl-7,8-dihydro-15*H*-benzo[*i*]benzo[4,5]imidazo[2,1-*c*][1,4]thiazecine (13): Following the GP Method A, starting from **11** (57 mg, 0.15 mmol), a mixture of **12** and **13** in a ratio 1:3 was obtained (8 mg, 17%) after purification by flash chromatography (5-40% AcOEt in pentane. A small amount of **13** was isolated pure and fully characterized.
12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 7.2 Hz, 3H), 2.99 (br, 2H), 4.08 (br, 2H), 4.14 (br, 2H), 5.48-5.51 (m, 1H), 7.20-7.23 (m, 1H), 7.43-7.46 (m, 2H), 7.52-7.57 (m, 1H), 7.64-7.71 (m, 2H), 7.76-7.78 (m, 1H), 7.91-7.96 (m, 1H). **13:** TLC (heptane/AcOEt 2:3, R_f = 0.54). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 2.57 (br, 2H), 4.26 (br, 4H), 5.53 (t, J = 8.8 Hz, 1H), 7.07 (dd, J = 1.6, 7.2 Hz, 1H), 7.15-7.25 (m, 2H), 7.28-7.34 (m, 2H), 7.39-7.42 (m, 1H), 7.49-7.51 (m, 1H), 7.79-7.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 27.8, 31.7, 44.1, 109.1, 119.7, 122.7, 122.8, 127.1, 127.2, 128.0, 128.6, 132.2, 132.4, 134.2, 142.7, 153.7. HRMS (ESI-Q-TOF) *m/z* calcd for $C_{19}H_{18}N_2S$ $[M+H]^+$: 307.1269, found: 307.1258.

(*E*)-13-ethylidene-8,13,14,15-tetrahydro-6H-benzo[h]benzo[4,5]imidazo[2,1-c][1,4]thiazecine (17) and (*E*)-13-methyl-15,16-dihydro-6H,8H-benzo[i]benzo[4,5]imidazo[2,1-c][1]thia[4]azacycloundecine (18): Following the GP Method B, starting from **16** (60 mg, 0.15 mmol), **17** and **18** as a mixture in a ratio 1:1 (12 mg, 24%), and the side product **16'** (24 mg, 49%) were obtained after purification by flash chromatography (0-35% AcOEt in heptane). TLC (heptane/AcOEt 2:3, R_f = 0.43 (**17**), 0.51 (**18**)). A small amount of **18** was isolated pure and co-crystallized with fumaric acid.
17: ^{1}H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.17 (d, J = 7.0 Hz, 3H), 3.47 (br, 4H), 4.07 (s, 4H), 5.15 (q, J = 7.0 Hz, 1H), 7.11-7.32 (m, 5H), 7.46-7.49 (m, 1H), 7.72 (dd, J = 1.0, 7.5 Hz, 1H), 7.75-7.77 (m, 1H).
18: ^{1}H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.14 (s, 3H), 2.83 (br, 2H), 3.48 (br, 2H), 4.15 (br, 2H), 4.42 (s, 2H), 5.65 (td, J = 1.7, 8.4 Hz, 1H), 6.95 (dd, J = 2.2, 6.6 Hz, 1H), 7.12-7.18 (m, 2H), 7.21 (dd, J = 1.9, 7.1 Hz, 1H), 7.34 (dt, J = 7.4, 21.6 Hz, 3H), 7.51 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H). HRMS (ESI-Q-TOF) *m/z* calcd for $C_{20}H_{20}N_2S$ $[M+H]^+$: 321.1425, found: 321.1412.
16': ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (t, J = 2.5 Hz, 3H), 2.61 (tq, J = 2.5, 7.2 Hz, 2H), 3.74 (s, 2H), 3.96 (s, 2H), 4.25 (t, J = 7.1 Hz, 2H), 7.18-7.34 (m, 8H), 7.72-7.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 20.0, 27.5, 35.9, 43.1, 75.1, 78.9, 109.4, 119.8, 122.2, 122.8, 127.2, 128.6, 129.2, 135.3, 137.7, 142.5, 150.9.

Acknowledgments

This work has been published under the framework of the IdEx Unistra and benefits from a funding from the state managed by the French National Research Agency as part of the Investments for the future program (postdoctoral grant for A.B.L.). The ''Centre National de la Recherche Scientifique (CNRS)'' and the University of Strasbourg are acknowledged for financial support. We thank Dr. D. Garnier and E. Oliva (PACSI, GDS 3670) for NMR and mass analyses, and Dr. L. Karmazin and C. Bailly (GDS 3648) for X-ray analyses.

Keywords: *N,S*-heterocycles • medium-sized heterocycles • benzimidazole • carbopalladation • cyclization

[1] a) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832-2842; b) K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, *376:5*, https://doi.org/10.1007/s41061-018-0184-5.

[2] A. Martinez, C. Gil *in Privileged Scaffolds in Medicinal Chemistry*, chap. 9 (RSC Drug Discovery Series **2016**, 50, pp231-261).

[3] a) B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 4383-4438; b) W. B. Motherwell, R. B. Moreno, I. Pavlakos, J. R. T. Arendorf, T. Arif, G. J. Tizzard, Simon J. Coles, A. E. Aliev, *Angew. Chem.* **2018**, *130*, 1207-1212; *Angew. Chem. Int. Ed.* **2018**, *57*, 1193-1198.

[4] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[5] a) S. L. Schreiber, *Science*, **2000**, *287*, 1964-1969; b) J-S. Reymond, M. Awale, *ACS Chem. Neurosci.* **2012**, *3*, 649-657; c) C. M. Dobson, *Nature* **2004**, *432*, 824-828; d) S. Dandapani, L. A. Marcaurelle, *Nature Chem. Biol.* **2010**, *6*, 861-863.

[6] F. Ortuso, D. Bagetta, A. Maruca, C. Talarico, M. L. Bolognesi, N. Haider, F. Borges, S. Bryant, T. Langer, H. Senderowitz, S. Alcaro, *Front. Chem.* **2018**, **6**:130. DOI: 10.3389/fchem.2018.00130.

[7] See for examples: a) J. E. Hall, J. V. Matlock, J. W. Ward, K. V. Gray, J. Clayden, *Angew. Chem.* **2016**, *128*, 11319-11323; *Angew. Chem. Int. Ed.* **2016**, *55*, 11153-11157; b) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. (Mimi) Hii, P. N. Horton, M. B Hursthouse, *J. Org. Chem.* **2005**, *70*, 1545-1551; c) V. Srinivasulu, K. D. Janda, I. A. Abu-Yousef, M. J. O'Connor, T. H. Al-Tel, *Tetrahedron* **2017**, *73*, 2139-2150; d) S. S. Scully, S.-L. Zheng, B. K. Wagner, S. L. Schreiber, *Org. Lett.* **2015**, *17*, 418-421; e) H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka,

T. Tanaka, *J. Am. Chem. Soc.* **2004**, *126*, 8744-8754; f) J. Cheng, X. Jiang, S. Ma, *Org. Lett.* **2011**, *13*, 5200−5203; g) Z.-Q. Rong, L.-C. Yang, S. Liu, Z. Yu, Y.-N. Wang, Z. Y. Tan, R.-Z. Huang, Y. Lan, Y. Zhao, *J. Am. Chem. Soc.* **2017**, *139*, 15304-15307; h) A. Osipyan, A. Sapegin, A. S. Novikov, M. Krasavin, *J. Org. Chem.* **2018**, *83*, 9707–9717; i) N. Zou, J.-W. Jiao, Y. Feng, C.-H. Chen, C. Liang, G.-F. Su, D.-L. Mo, *Adv. Synth. Catal.* **2017**, *359*, 3545-3550; j) X.-P. Ma, L.-G. Li, H.-P. Zhao, M. Du, C. Liang, D.-L. Mo, *Org. Lett.* **2018**, *20*, 4571–4574.

[8] a) J. R. Donald, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 8780-8799; b) A. Hussain, S. K. Yousuf, D. Mukherjeem, *RSC Adv.* **2014**, *4*, 43241-43257; c) L. Huang, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138*, 5793-5796. d) M. A. Casadei, C. Galli, L. Mandolini, *J. Am. Chem. Soc.* **1984**, *106*, 1051-1056.

[9] a) H. Yale, F. Sowinski, E. Spitzmiller, *J. Het. Chem.* **1972**, *9*, 899-909; b) C. Mukherjee, E. Biehl, *Heterocycles* **2004**, *63*, 2309-2318; c) H. Sashida, T. Tsuchiya, *Heterocycles* **1984**, *22*, 1303-1306; d) M. S. Manhas, S. G. Amin, A. K. Bose, *Heterocycles* **1976**, *5*, 669–699; e) H. J. Federsel, G. Glassare, K. Hogstrom, J. Wiestal, B. Zinko, C. Odman, *J. Org. Chem.* **1995**, *60,* 2597-2606.

[10] a) D. K. Bates, X. Li, P. V. Jog, *J. Org. Chem.* **2004**, *69*, 2750-2754; b) W. A. L. van Otterlo, G. L. Morgans, S. D. Khanye, B. A. A. Aderibigbe, J. P. Michael, D. G. Billing, *Tetrahedron Lett.* **2004**, *45*, 9171-9175.

[11] H. A. K. El-Aal, *Arkivoc* **2018**, part iii, 45-61.

[12] S. M. Lu, H. Alper, *J. Am. Chem. Soc.* **2005**, *127*, 14776-14784.

[13] Y. Pei, M. J. Lilly, D. J. Owen, L. J. D'Souza, X.-Q. Tang, J. Yu, R. Nazarbaghi, A. Hunter, C. M. Anderson, S. Glasco, N. J. Ede, I. W. James, U. Maitra, S. Chandrasekaran, W. H. Moos, S. S. Ghosh, *J. Org. Chem.* **2003**, *68*, 92-98.

[14] B. E. Fink, A. V. Gavai, J. S. Tokarski, B. Goyal, R. Misra, H-Y. Xiao, S. D. Kimball, W-C. Han, D. Norris, T. E. Spires, D. You, M. M. Gottardis, M. V. Lorenzi, G. D. Vite, *Bioorg. Med. Chem. Lett.* **2016**, *16*, 1532–1536.

[15] See in this topic: a) I. Abrunhosa, M. Gulea, J. Levillain, S. Masson, *Tetrahedron: Asymmetry* **2001**, *12*, 2851-2859; b) G. Mercey, J-F. Lohier, A-C. Gaumont, J. Levillain, M. Gulea, *Eur. J. Org. Chem.* **2009**, 4357-4364; c) F. Peudru, F. Le Cavelier, J-F. Lohier, V. Reboul, M. Gulea, *Tetrahedron,* **2012**, *68,* 9016-9022; d) F. Peudru, F. Le Cavelier, J-F. Lohier, M. Gulea, V. Reboul, *Org Lett.* **2013**, *15*, 5710-5713; e) T. Castanheiro, J. Suffert, M. Gulea, M. Donnard, *Org. Lett.* **2016**, *18*, 2588-2591.

[16] See reviews: a) S. Salahuddin, M. Shaharyar, A. Mazumder *Arabian J. Chem.*, **2017**, *10*, S157-S173; b) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow, D. A. Pippin, *Comb. Chem. High Throughput Screen.* **2004**, *7*, 473-494; c) M. Gaba, C. Mohan, *Med. Chem. Res.,* **2016**, *25*, 173-210; d) S. Yadav, B. Narasimha, H. Kaur, *Anticancer Agents Med. Chem.* **2016**, *16*, 1403-1425.

[17] Reviews: a) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809-841; b) C. J. Ball, M. C. Willis, *Eur. J. Org. Chem.* **2013**, 425-441; c) A. Düfert, D. B. Werz, *Chem. Eur. J.* **2016**, 16718-16732; d) S. Blouin, G. Blond, M. Donnard, M. Gulea, J. Suffert, *Synthesis* **2017**, *49*, 1767-1784; e) M. Donnard, T. Castanheiro, M. Gulea in *Targets in Heterocyclic Systems*, *Vol. 21* (Eds. Attanasi, O. A.; Spinelli, D., Ed. Italian Society of Chemistry, **2017**, pp 254-276); f) J. Biemolt, E. Ruijter *Adv. Synth. Catal.* **2018**, *360*, 3821-3871.

[18] a) L. F. Tietze, S.-C. Duefert, J. Clerc, M. Bischoff, C. Maaβ, D. Stalke, *Angew. Chem.* **2013**, *125*, 3273-3276; *Angew. Chem. Int. Ed.* **2013**, *52*, 3191-3194; b) C. D. Campbell, R. L. Greenaway, O; T. Holton, P. R; Walker, H. A. Chapman, C. A. Russell, G. Carr, A. L. Thomson, E. A. Anderson, *Chem. Eur. J.* **2015**, *21*, 12627-12639; c) R. Grigg, I. Koppen, M. Rasparini, V. Sridharan, *Chem. Commun.* **2001**, 964-965; d) K. C. Majumdar, *RSC Advances*, **2011**, *1*, 1152-1170; e) P. A. Donets, E. V. Van der Eycken, *Org. Lett.* **2007**, *9*, 3017-3020.

[19] a) T. Castanheiro, M. Donnard, M. Gulea, J. Suffert, *Org. Lett.* **2014**, *16*, 3060-3063; b) T. Castanheiro, J. Suffert, M. Donnard, M. Gulea, *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 162-165; c) T. Castanheiro, A. Schoenfelder, J. Suffert, M. Donnard, M. Gulea, *C. R. Chim.* **2017**, *20*, 624-633; d) T. Castanheiro, A. Schoenfelder, M. Donnard, I. Chataigner, M. Gulea, *J. Org. Chem.* **2018**, *83*, 4505-4515.

[20] S. Couty, B. Liégault, C. Meyer, J. Cossy, *Org. Lett.* **2004**, *6*, 2511-2514.

[21] M. Pal, K. Parasuraman, K. R. Yeleswarapu, *Org. Lett.* **2003**, *5*, 349-352.

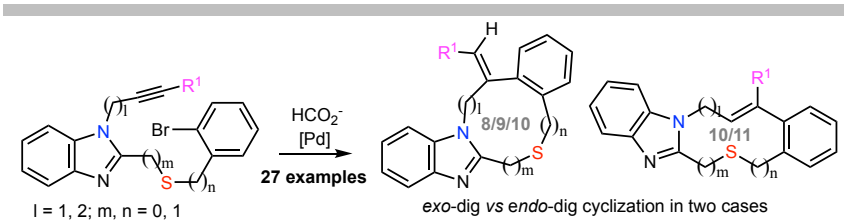
[22] Srogl-Liebeskind type reaction: L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979-981.

[23] S. Ma, E. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 6345-6357.

[24] a) T. Ghosh, *New J. Chem.*, **2017**,*41*, 2927-2933; b) J. A. Gurak, K. M. Engle, *ACS Catal.* **2018**, *8*, 8987-8992.

Layout 2:

FULL PAPER



Benzimidazole-fused medium-sized *N,S*-heterocycles (8 to 10 ring atoms) having an exocyclic double bond were synthesized by using *exo*-dig Pd-catalyzed reductive cyclizations. In the case of two substrates bearing an *N*-homopropargyl chain, a competing *endo*-dig cyclocarbopalladation occurred, leading to rarely encountered 10- and 11-membered *N,S*-heterocyles with an endocyclic double bond.

Medium-sized heterocycles

*Alexandra Basilio Lopes,[a] Patrick Wagner,[a] and Mihaela Gulea**

Page No. – Page No.

Synthesis of Benzimidazole-Fused Medium-Sized *N,S*-Heterocycles via Palladium-Catalyzed Cyclizations