Pd AND Cu-MEDIATED DOMINO REACTIONS FOR THE SYNTHESIS OF SULFUR HETEROCYCLES

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Abstract. *Pd and Cu-mediated domino reactions are powerful tools for the synthesis of heterocycles. In this chapter we have compiled the most relevant examples of such transformations for the synthesis of sulfur-containing heterocycles. These sequences have been organized by type of heterocycle formed and the nature of the substrates (with or without a sulfur atom).*

Contents

1. Introduction

The impact of organosulfur compounds in pharmaceutical industry is significant, several sulfur-containing drugs being among the most prescribed and sold at present in the world.[1] Some of them contain in their structure a sulfur heterocycle (Figure 1). Considering the continual need for the development of medicinal therapies, new *S*-heterocyclic compounds could lead to forthcoming pharmaceuticals.

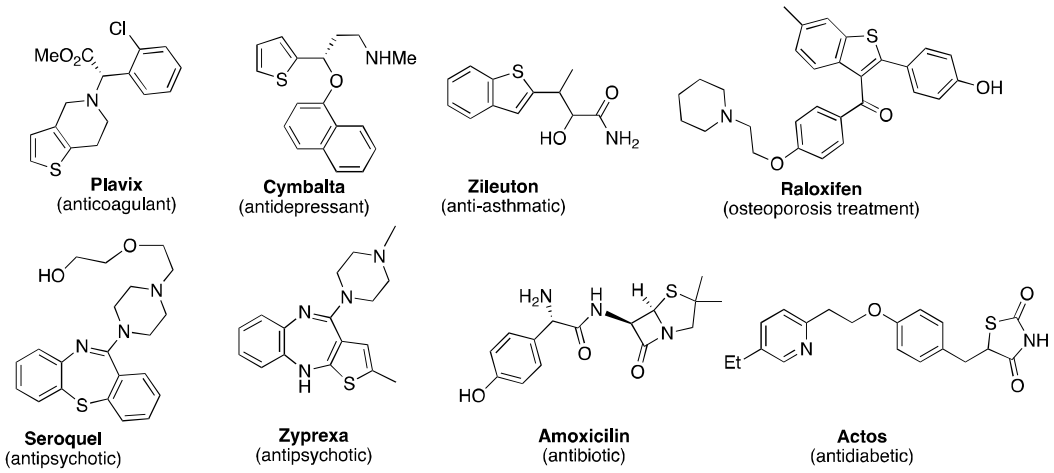


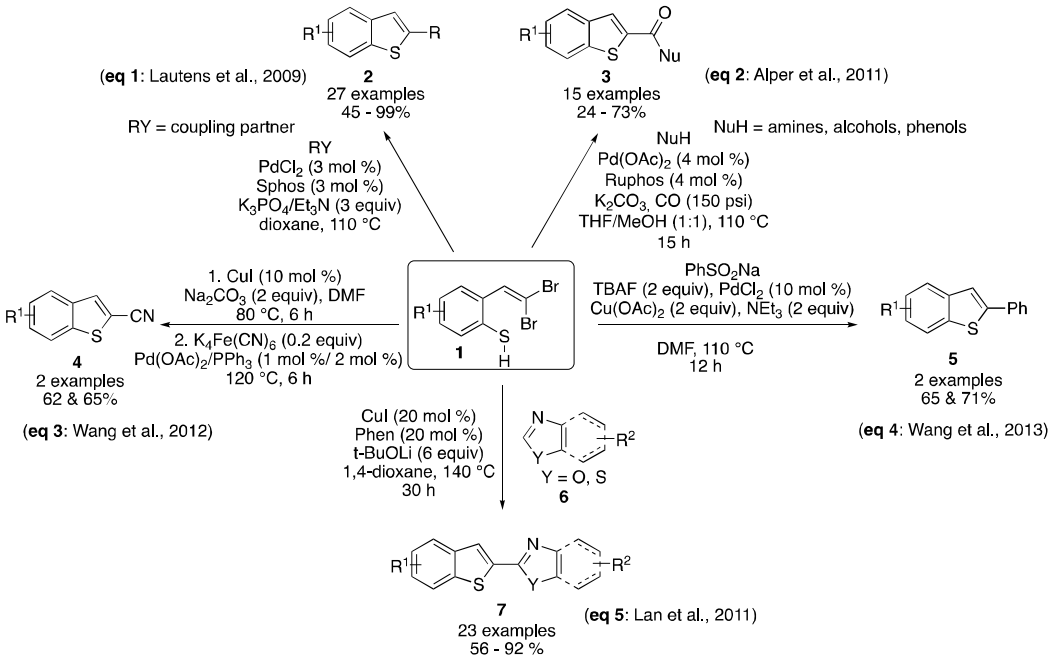
Figure 1. Structures of drugs containing a sulfur-heterocycle.

As a consequence, the search for new syntheses to provide original compounds of these types represents a topical subject. Among the various metal-catalyzed processes, domino reactions represent a powerful tool to access, efficiently and with step economy, complex heterocyclic molecules from simple starting materials.[2] In the present contribution, will be highlighted the methodologies based on Pd and Cu-catalyzed sequences. We will cover the literature of the last 20 years.

2. Synthesis of heterocycles incorporating only sulfur as heteroatom

2.1. From sulfur-containing starting material

Benzothiophene derivatives represent an important class of sulfur-containing heterocycles in pharmaceutical sciences.[3] This scaffold is present in many top-sold drugs such as Raloxifene,[4] a selective estrogen receptor modulator used in hormonal treatments, and Zileuton, a 5-lipoxygenase inhibitor used in the treatment of asthma[5] (Figure 1). The development of straightforward and effective methodologies to synthesize these compounds, especially poly-substituted derivatives, has been of great interest in organic chemistry over the last decades. Therefore, different synthetic methods involving tandem or domino reactions and the use of palladium or copper have been successfully investigated. Notably, 2-(2,2-dibromovinyl) thiophenol **1** appeared to be a practical substrate that has been intensively studied to synthesize 2-subtituted benzothiophenes (Scheme 1).

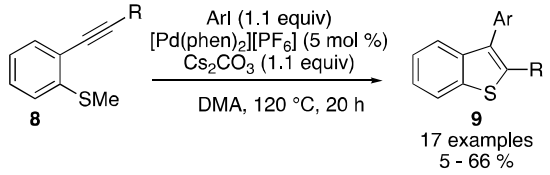


Scheme 1. Diverse approaches to benzothiophene derivatives starting from 2-(2,2-dibromovinyl) thiophenol.

The Lautens group reported a first relevant example in 2009 by setting up a domino process involving two transformations. The first allows the formation of a C-S bond by cyclizing *S*-vinylation *via* an intramolecular coupling between thiophenol and the dibromo vinyl system. The second transformation involves intermolecular cross-coupling to form a C-C bond and functionalizing the 2-position of benzothiophene (Scheme 1, equation 1).[6] Suzuki coupling was mainly used and the authors showed that different borated species can be used as coupling partner (boronic acids, pinacol boronates, potassium organotrifluoroborates). The methodology was then extended to Heck and Sonogashira couplings allowing different functionalizations at the C2-position (*i.e.* alkenes, alkynes).

Subsequently, Zheng and Alper elaborated the synthesis of 2-carbonylbenzothiophene **3** *via* the same *S*-vinylation followed this time by insertion of CO and addition of a nucleophile[7] (Scheme 1, equation 2). Notably, the use of hindered and electron-rich ligands is crucial to the success of this transformation. Different oxygenated or aminated nucleophiles have been used to complete the synthesis, nevertheless, a good nucleophilicity is necessary to obtain a good yield of **3**. When substrates **1** are functionalized on the aryl moiety with strong electron-withdrawing groups such as CF_3, the reaction cannot take place. Later, Wang's team developed two methods to form 2-cyanobenzothiophenes **4** (Scheme 1, equation 3)[8] and 2-phenylbenzothiophenes **5**.[9] The first go through a tandem process involving two metal-catalyzed transformations. A copper-catalyzed cyclization *via* an Ullmann-type coupling between the sulfur and the dibromo-olefin leads to the thiophene moiety. Then, a palladium-catalyzed cyanation reaction take place to functionalize the 2-position of the heterocycle.[10] The second method is a palladium-catalyzed domino process involving a cyclization through an *S*-vinylation followed by an arylation reaction at the 2-position of the thiophene. A stoechiometric quantity of copper is used as oxidizing agent to regenerate the Pd(II) species at the end of the catalytic cycle. A similar approach has been then reported by the Lan's group to synthesize 2-benzoxazoles-benzothiophenes **7**. However, in that case, the Ullmann-type cyclization is followed by a coupling at the 2-position involving the C-H activation of benzazole derivatives **6** (Scheme 1, equation 5).[11]

Recently, the Murai group reported for the first time the synthesis of 3-arylbenzothiophenes **9** by a palladium-catalyzed domino reaction. From an alkynylthioanisole **8**, the process starts with the oxidative addition of the aryl iodide to $[Pd(phen)_2][PF_6]$ to form a palladium(II) complex. The latter activates the triple bond to allow an intramolecular nucleophilic attack of the sulfur on the alkyne. A cleavage step of the S-Me linkage ends the domino reaction sequence (Scheme 2).[12] Additional investigations have demonstrated that S-Me cleavage involves an ionic process. In addition, the use of a radical inhibitor did not inhibit the reaction demonstrating heterolytic bond cleavage. These conditions allowed the synthesis of various 3-arylbenzothiophenes **9** with moderate yields.



Scheme 2. Murai's synthesis of 3-arylbenzothiophene derivatives.

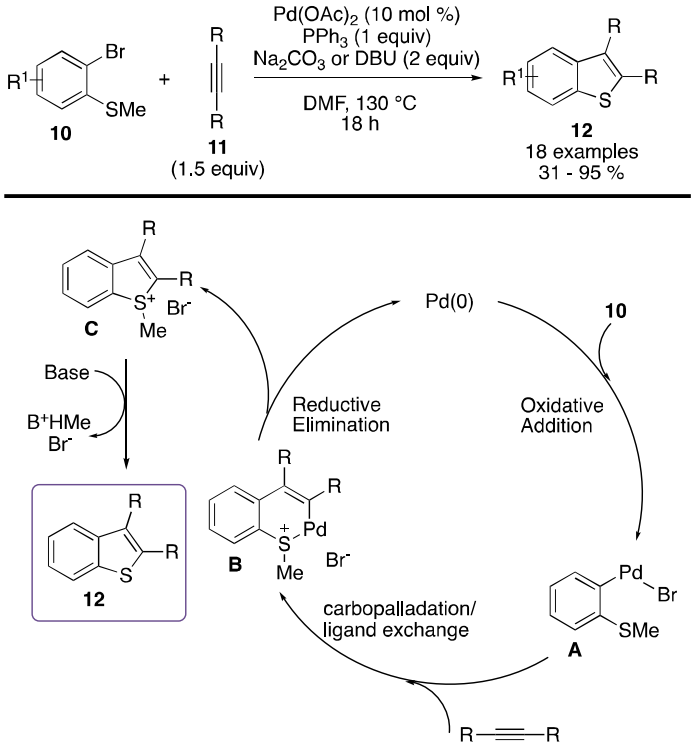
Concomitantly, the team of Chatani and Tobisu developed an intermolecular version of this transformation between 2-bromothioanisoles **10** and diverse disubstituted alkynes **11** (Scheme 3).[13] This approach gave access in good yields to polysubstituted benzothiophenes **12**. The reaction involves the successive construction of a C-C bond, by carbopalladation followed by a C-S bond by *S*-vinylation. Alkyl and aryl alkynes were used in this reaction. Remarkably the use of DBU gave the best results with aryl alkynes when sodium carbonate appeared as the base of choice with alkyl alkynes. For this transformation a four-step mechanism has been proposed:

1. oxidative addition of Pd(0) into the C-C bond;
2. carbopalladation of the alkyne followed by a nucleophilic attack of the thioether on the palladium center to obtain a 6-membered palladacycle;
3. reductive elimination to form the C-S bond;
4. ionic cleavage of the S-Me bond under basic conditions.

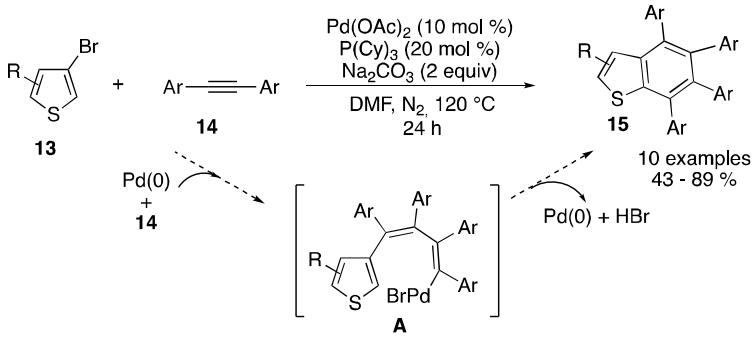
In addition, the reaction showed great regioselectivity. Indeed, when a dissymmetric alkyne is used, the authors have systematically observed that palladium added to the most congested carbon.

In 2011, Duan reported a palladium catalyzed multi-component synthesis of poly-functionalized benzothiophenes **15** starting from a thiophene derivative and twice an alkyne. The process starts with an oxidative addition of the C-Br bond to the catalyst which undergoes two successive carbopalladation on the two molecules of alkyne **14**, forming the intermediate **A**. The latter undergoes cyclization, by C-H

activation, giving rise to the desired heterocycles **15** (Scheme 4).[14] Notably, this method can also be applied to access indoles when a bromopyrrole is used instead of the starting thiophene.



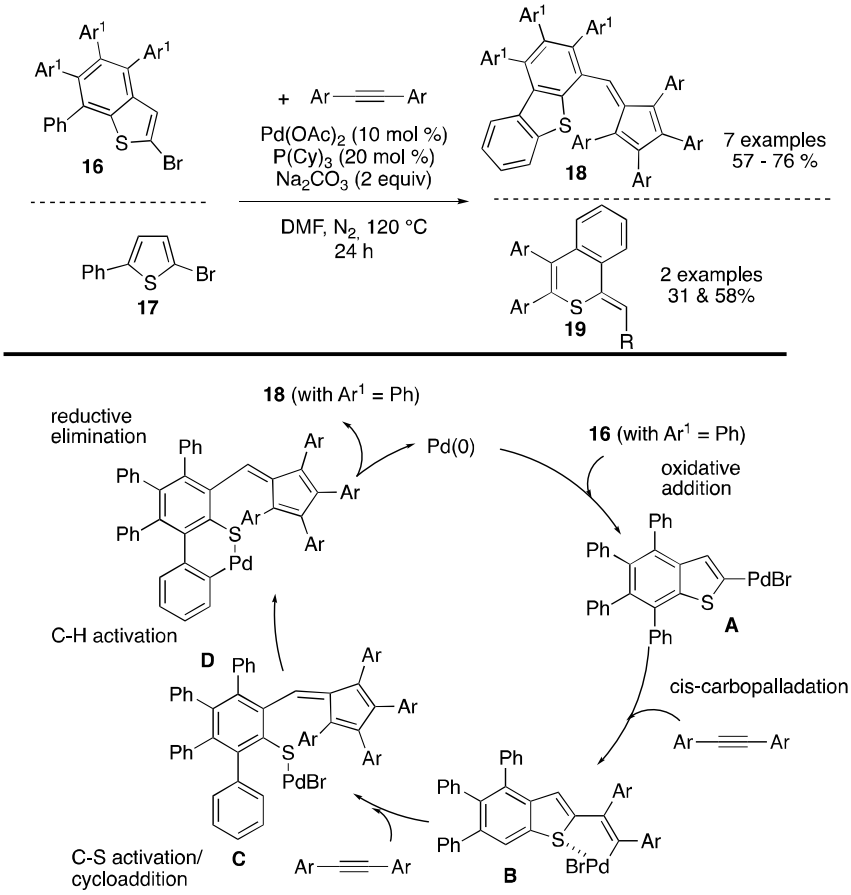
Scheme 3. Annulation access to benzothiophene derivatives starting from 2-bromothioanisoles and alkynes.



Scheme 4. Synthesis of poly-functionalized benzothiophenes starting from bromo-thiophenes and diaryl alkynes.

While studying this reaction, the authors noticed that the use of arylated 2-bromothiophenes, such as **16** or **17**, did not lead to the same heterocycles (Scheme 5).[15] They observed the opening of the thiophene cycle through a selective cleavage of the bond between the brominated carbon and sulfur. Additional investigations to explain the formation of **18** from **16** allowed the authors to postulate a reaction pathway going through five steps:

1. oxidative addition of Pd(0) to the C-Br bond;
2. a first carbopalladation forms the Pd(II) vinylic intermediate **B**;
3. activation of the C-S bond by the chelation of the metal by the sulfur atom followed by the insertion of palladium. Then the insertion of a second alkyne gives the intermediate **C**. This step is not yet fully understood;
4. activation of the C-H bond near the Pd gives the palladacycle **D**;
5. reductive elimination forms product **18** and regenerate the catalyst.

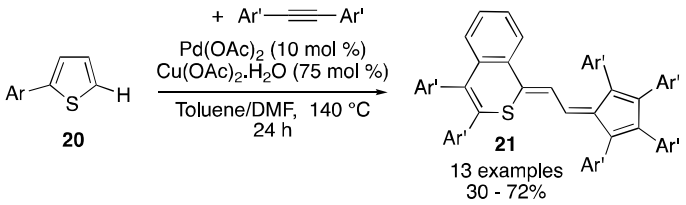


Scheme 5. Palladium-catalyzed coupling/opening of bromo-benzothiophenes with alkynes.

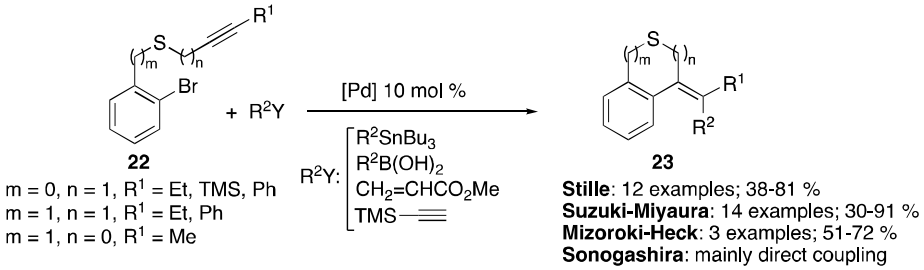
This method was extended to non-brominated thiophenes **20** (Scheme 6). In this case, the reaction begins with a C-H activation introducing the palladium at the α-position to the sulfur. Then, the reaction follows the same steps as the previous method. The problem of regioselectivity of this activation is solved by substituting one of the two carbons in α-position to the sulfur. The desired products **21** are obtained in moderate to good yields.[16]

In 2014, Gulea and coworkers reported the synthesis of unprecedented 5- or 6-membered *S*-heterocycles **23** bearing an exocyclic stereodefined tetrasubstituted C=C double bond.[17] The strategy is based on a cyclocarbopalladation/cross-coupling (Stille, Suzuki-Miyaura, Mizoroki-Heck and Sonogashira) domino reaction starting from appropriately designed sulfides **22** (Scheme 7). In the case of Stille coupling as final cross coupling step, the yields were moderate mainly due to the difficulty to purify the relatively

non-polar products in presence of stannanes. To overcome this issue, the cyclocarbopalladation/Suzuki-Miyaura sequence was then investigated. By using electron-rich or electron-poor arylboronic acids, as well as vinyl, allyl, and cyclopropyl derivatives as coupling partners, the reaction worked well, and corresponding sulfur heterocycles **23** have been obtained in good yields (Scheme 7).[18] To extend the structural diversity of these new thiacycles, the Mizoroki-Heck coupling was then evaluated as ending coupling step and furnished the targeted compounds in good yields. Finally, the Sonogashira coupling was tested as final reaction in this domino sequence. It appeared that the kinetic of this coupling is so fast that the cyclocarbopalladation does not have the possibility to take place and so the direct insertion of the alkyne at the formerly brominated position of the substrate was the main product of this reaction. Interestingly this issue can be partly overwhelmed by performing a Stille coupling using an alkynylstannane as partner.[19]



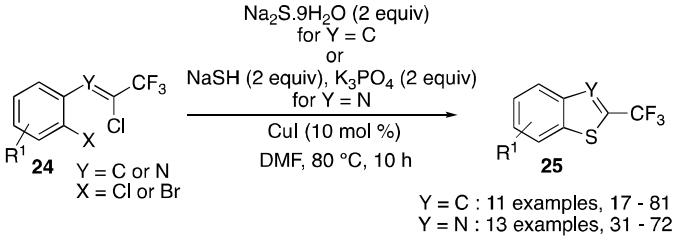
Scheme 6. Synthesis of thiochromene derivatives involving the C-H activation of thiophenes.



Scheme 7. Cyclocarbopalladation/coupling domino access to *S*-heterocycles.

2.2. Synthesis involving the introduction of sulfur on sulfur-free starting material

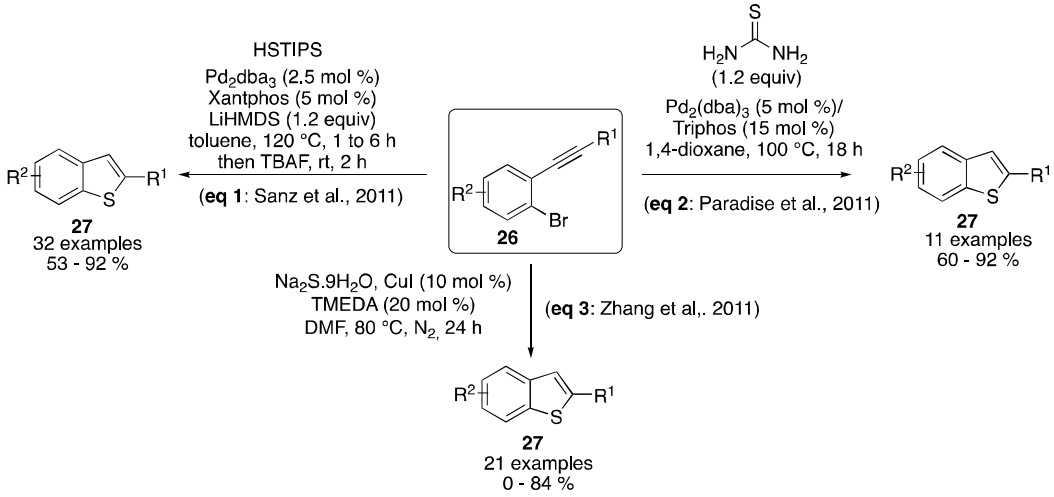
Domino processes involving the use of a sulfurizing agent allowed the synthesis of thiacycles starting from non-sulfured substrates. For instance, the Li group set up a copper-catalyzed cascade process starting from *o*-halo-styrene derivatives and involving the successive formation of two C-S bonds.[20] A first intermolecular coupling, using Na_2S as sulfurizing agent, introduces the sulfur on the molecule. Then the cyclization occurs *via* a coupling between the newly installed sulfur atom and the alkene moiety to form various 2-trifluoromethyl benzothiophenes **24** (Scheme 8, Y=C). The reaction is tolerant to a wide range of functional groups on the aromatic moiety of substrate. Notably, the presence of the trifluoromethyl group on the double bond appeared to be crucial to the success of the overall process as the product **25** is never obtained when it lacks on the starting material.



Scheme 8. Cu-catalyzed cascades starting from *o*-halo-styrene derivatives.

This method was then extended to the synthesis of benzothiazoles (Scheme 8, Y=N). However, in order to obtain these molecules the sulfurizing agent has to be changed to NaSH and a base such as potassium phosphate is required.

Several domino syntheses of benzothiophenes have been developed starting 1-bromo-2-alkynylbenzene **26** and a sulfur source (Scheme 9). These domino processes all involve an intermolecular carbon-sulfur Ullmann or Buchwald type coupling, between the aryl halide **26** and a nucleophilic sulfurizing agent, followed by a cyclization between the newly formed thiolate and the triple bond. For instance, Sanz team developed this approach using a Pd-based catalyst and triisopropylsilanethiol (HSTIPS) as the sulfur source (Scheme 9, equation 1).[21] After the coupling between HSTIPS and the aryl moiety, TBAF is added to attack the silyl group and release the corresponding thiolate. Subsequently, this *S*-nucleophile cyclizes on the alkyne. Alternatively, as reported by the Paradies group, thiourea can be used as the sulfur source in these domino reactions (Scheme 9, equation 2).[22] A study of the influence of the electronic nature of the substituent present on the triple bond has shown that an electron-withdrawing group makes the reaction more efficient by increasing the electrophilicity of the alkyne. The benzene ring of the starting substrate **26** was then replaced with a thienyl unit which allowed to obtain thienothiophenes. Finally, the Zhang team used hydrated sodium sulfide to set up their reaction. However, in that case copper was used instead of palladium as catalyst. Notably the same steps are involved to reach the desired heterocycles **27** (Scheme 9, equation 3).[23] These methods have thus made possible the synthesis of a wide range of benzothiophenes, bearing both electron-donating and electron-withdrawing substituents on the aryl as well as on the triple bond.

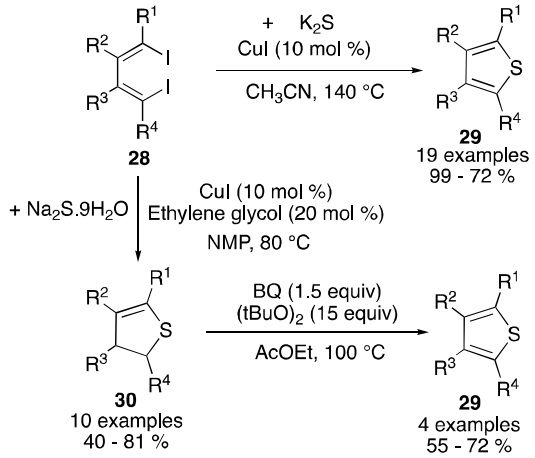


Scheme 9. Benzothiophene syntheses starting from 1-bromo-2-alkynylbenzenes and diverse sulfur sources.

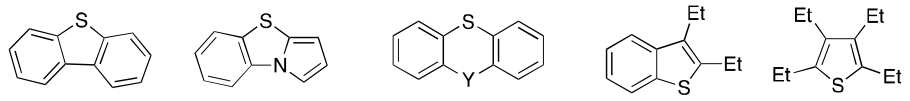
To access poly-substituted thiophenes,[24] the Xi group investigated the development of a synthesis involving the formation of two successive C-S bonds by a copper-catalyzed bis alkenylation of diiodobutadiene derivatives **28** (Scheme 10).[25] From 1,4-diiodo-buta-1,3-diene, potassium sulfide and a catalytic amount of copper iodide, without ligand, various di-, tri- and tetra-substituted thiophenes **29** were obtained. The same group developed the efficient synthesis of dihydrothiophenes **30** *via* a copper-catalyzed domino process involving an *S*-alkylation and an *S*-alkenylation. Sodium sulfide hydrate was used as a source of sulfur.[26] Notably when carried out with potassium sulfide under the same conditions, the reaction drove to a complex mixture of several products. Dihydrothiophenes **30** were subsequently aromatized with benzoquinone to give poly-substituted thiophenes **29**.

After having established a catalytic system allowing intermolecular double *S*-arylation on aryl iodides with carbon disulfide to obtain diaryl thioethers, an intramolecular strategy was developed by the Xi team. They developed a synthesis of various sulfur-containing heterocycles: dibenzothiophene **31**, benzo-pyrrolo-

thiazole **32**, phenoxathiine **33**, benzothiophene **34** and thiophene **35**, *via* a double coupling reaction Csp^2-S with good yields (Figure 2).[27]



Scheme 10. Cu-catalyzed of thiophenes starting from diiodobutadiene derivatives.

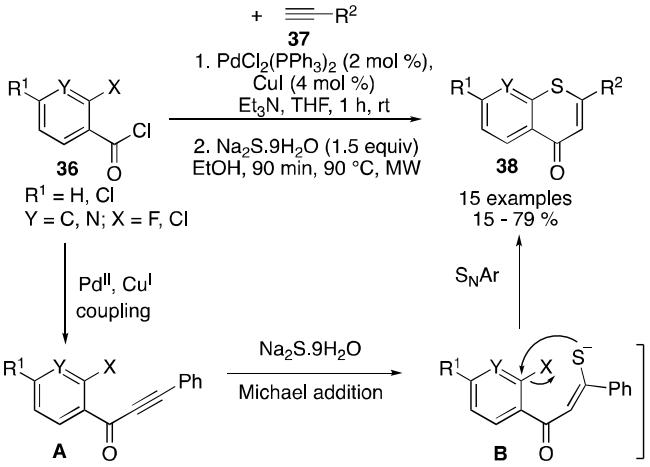


31 (75 %) **32** (62 %) **33** Y = S (65 %); Y = O (72 %) **34** (74 %) **35** (78 %)

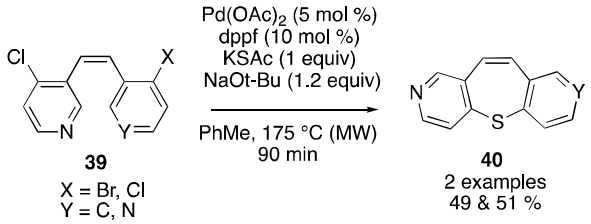
Figure 2. Heterocycles synthesized by the Xi group using diverse diiodo-substrates and a sulfur source.

Several thiochromenones are interesting molecules as they are known to have antimicrobial, antifungal, anti-bacterial, anti-carcinogenic activities or antimalaria properties.[28] Multi-step syntheses are generally used to form these molecules, employing harsh conditions and generally giving the targeted compound in poor yield. Thus, in order to obtain a quick and efficient access to different thiochromenones, the group of Thomas Müller has set up a tri-component tandem reaction from benzoyl chloride **36** (bearing an halogen in *ortho* position), a terminal alkyne **37** and sodium sulfide (Scheme 11).[29,30] This tandem process involves a Sonogashira coupling giving **A**, followed by Michael addition of the nucleophilic sulfur added in the reaction. Then the newly formed thiolate **B** perform an intramolecular cyclization *via* an aromatic nucleophilic substitution. This allowed the formation of thiochromenones **38** in good yields. The multi-stage syntheses generally used to form these molecules do not allow the synthesis of thiocromenones substituted by methoxy groups. Thus, the authors used phenylacetylenes containing methoxy substituents to overcome this problem.

After the development of a synthesis of azepines *via* a domino process involving two successive palladium-catalyzed inter- and intramolecular C-N couplings, the Solaja team applied this approach to the synthesis of dibenzothiepines **40** (seven-membered sulfur-containing heterocycles) by a double C-S coupling (Scheme 12).[31] The domino reaction was carried out under microwave irradiation and using potassium thioacetate as sulfur source. After the first intermolecular coupling between potassium thioacetate and substrate **39**, the newly formed thioacetate derivative is deprotected under basic conditions to form a thiolate that is subsequently engaged in an intramolecular coupling to close the medium-sized ring. Two dibenzothiepines were synthesized in 49% and 51% yields respectively.



Scheme 11. Synthesis of thiocromenones starting from acyl chlorides and alkynes.



Scheme 12. Synthesis of azepines *via* a Pd-catalyzed domino process starting from stilbene derivatives.

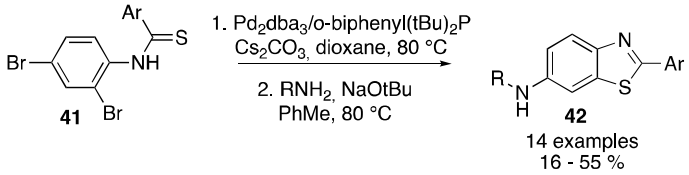
3. Synthesis of heterocycles incorporating a sulfur and, at least, another heteratom

3.1. *N,S*-Heterocycles

3.1.1. From sulfur-containing starting material

Due to their numerous pharmaceutical applications, benzothiazoles represent one of the most important class of mixed sulfur-nitrogen heterocycles.[32] Several metallo-induced domino or tandem syntheses have been developed from different substrates.

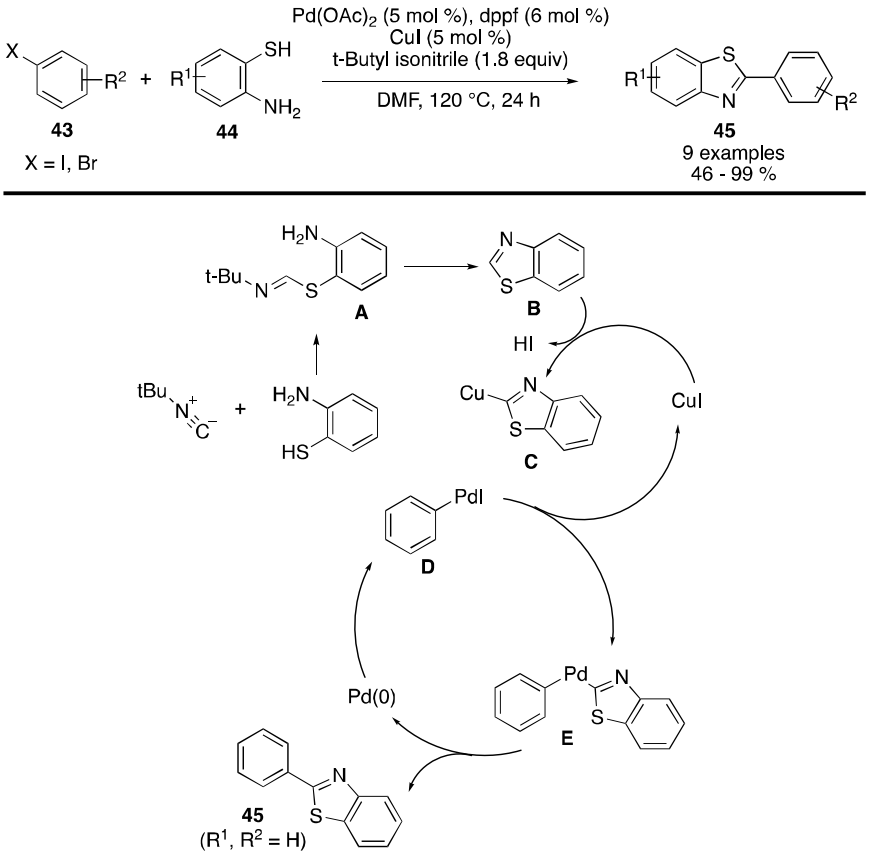
The Pelletier group synthesized a library of 2-arylbenzothiazoles **42** substituted with an amine on the aryl ring by carrying out two Pd-catalyzed reactions in one pot. The first step is the cyclization *via* the formation of a C-S bond between thioamide and the *ortho* brominated carbon. Subsequently a Buchwald-type amination on the carbon in *para* position of the thioamide introduces an amino group (Scheme 13).[33]



Scheme 13. Synthesis of benzothiazoles starting from aryl-thioamides**.**

The Lang group reported the synthesis of benzothiazoles **45** starting from 2-aminothiophenol derivatives **44** *via* a palladium-catalyzed tandem reaction. The sequence involves a nucleophilic attack of the SH function on the isonitrile followed by the condensation of the NH_2 function on the resulting imine to

form the benzothiazole **B**. Then a copper and palladium catalyzed coupling can take place to form the 2-aryl benzothiazole **45** (Scheme 14).[34]

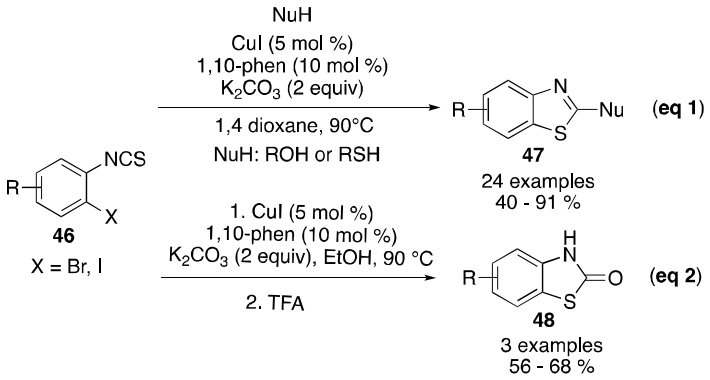


Scheme 14. Pd-catalyzed synthesis of benzothiazoles starting from 2-aminothiophenol.

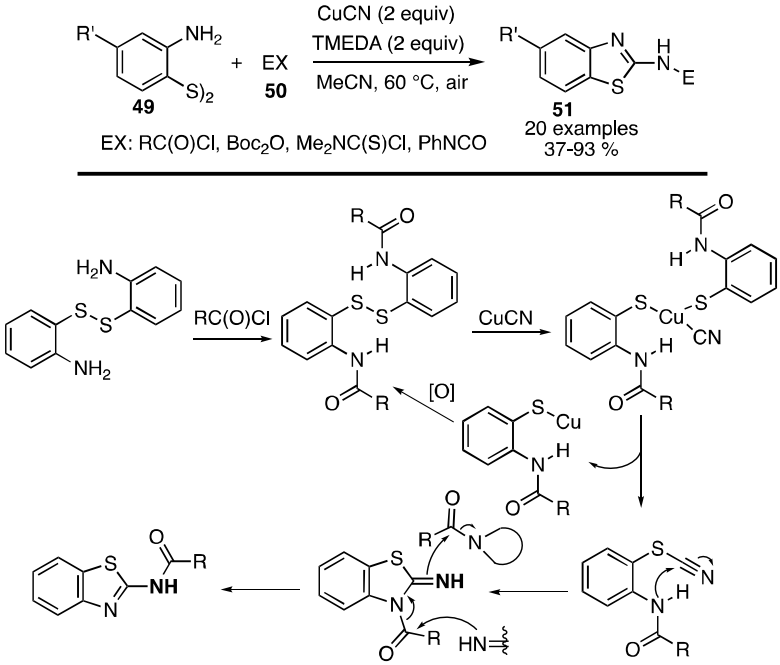
In addition to the work performed on palladium catalysis, copper-catalyzed reactions have also been investigated to obtain 2-substituted benzothiazoles. In 2009, Patel developed a domino reaction involving the nucleophilic addition to an isothiocyanate **46** resulting in a thiolate that reacts subsequently intramolecularly *via* an Ullmann-type coupling. This process allows the synthesis of poly-functionalized benzothiazoles **47** in good yields (Scheme 15, equation 1).[35] In addition, various sulfur or oxygen nucleophiles have been used to functionalize the 2-position. This method has been extended to the synthesis of benzothiazolone **48**. Ethanol used both as a nucleophile and solvent allowed, after acidic treatment, a dealkylation of oxygen to form the carbonyl group at the position 2 (Scheme 15, equation 2).

2-Aminobenzothiazoles have shown a wide variety of biological activities, making it an important class of benzothiazole derivatives.[36] One of the most significant examples is Riluzole, used to treat amyotrophic lateral sclerosis. Thus, many efforts are made to synthesize this type of compounds. In 2016, Donnard, Gulea and collaborators reported the synthesis of diversely *N*-substituted 2-amino-benzothiazole derivatives **51** *via* a domino sequence involving an oxidative copper-mediated *S*-cyanation of 2-amino-benzene disulfides **49** as the key-step.[37] First this group investigated the practical and safe access to aromatic thiocyanates by using CuCN as the cyanating agent of thiols/disulfides.[38] This reaction appeared to be remarkably mild and tolerant to a wide range of functional groups and so it was then integrated in a domino three-component process involving aromatic disulfides bearing a nucleophilic amino group at the *ortho*

position. These aerobic reactions have been performed between diverse 2,2′-diaminodiphenyl disulfides **49**, CuCN, and a selection of different electrophiles **50**. Aromatic and aliphatic acyl chlorides, Boc anhydride, menthyl chloroformate, and phenyl isocyanate have been successfully used as electrophiles to lead to variously *N*-substituted 2-amino-benzothiazoles **51**. Interestingly, control experiments demonstrated that the mechanism is not as straightforward as it looks at the first glance. After the rapid acylation of the amino group of the substrate, the cyanation step takes place to give the corresponding thiocyanate. Finally, an intermolecular transfer of the acyl moiety leads to the formation of the targeted benzothiazoles **51** (Scheme 16).



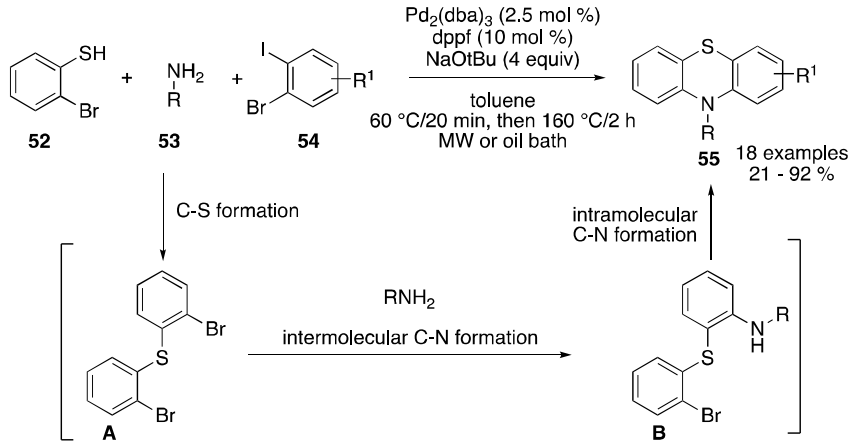
Scheme 15. Synthesis of 2-substituted benzothiazoles starting from isothiocyanates.



Scheme 16. Synthesis of 2-aminobenzothiazoles involving a copper-mediated cyanation step.

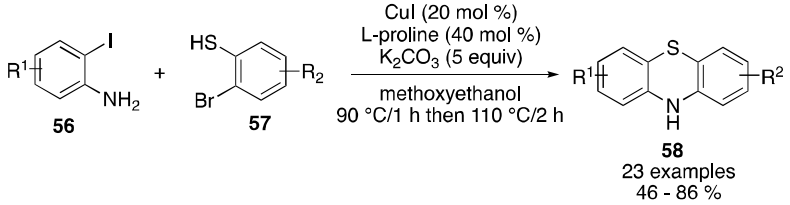
The phenothiazine skeleton has often been used to design many molecules with pharmaceutical activity, especially in promazines having antipsychotic activity, antitumor and anti-inflammatory agent.[39]

After studying C-S and C-N bond formations from thiophenol and aniline respectively, Jørgensen developed a multi-component tandem reaction to access the phenothiazine skeleton and obtain poly-substituted promazines quickly and efficiently (Scheme 17).[40] 2-Bromothiophenol **52**, primary amine **53**, and 1-bromo-2-iodobenzene **54** were used as starting materials. This reaction allowed the formation of three carbon-heteroatom bonds. A first C-S bond is resulting from the coupling between **52** and iodobenzene **54** to give the intermediate **A**. Then, two C-N bonds are built successively. The first is formed by an intermolecular coupling, creating the aniline **B**, and the second by intramolecular coupling, giving rise to cyclization to reach the phenothiazine skeleton of **55**. These three transformations result in the synthesis of various highly functionalized promazines **55** in moderate to good yields. Several primary amines have been investigated but the use of an allyl amine represents a limitation of this method as the reaction only furnish a complex mixture in this case.



Scheme 17. Pd-catalyzed three-component synthesis of phenothiazine.

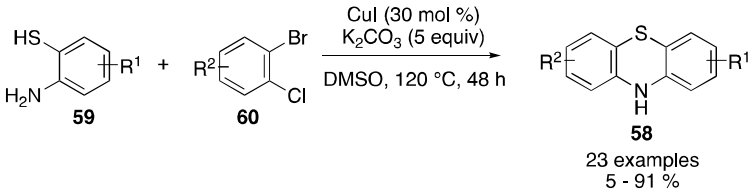
2-Iodoanilines being more available than 1-iodo-2-bromobenzenes, Ma has developed a synthetic method using iodoanilines **56** and 2-bromothiophenols **57** as the starting material.[41] This tandem reaction involves two successive Ullmann couplings catalyzed by the CuI/*L*-proline system (Scheme 18). These two couplings induce the successive formation of a C-S bond and a C-N bond. However, since thiophenol **57** is more reactive than aniline **56**, homo-coupling of **57** is possible. A strict control of the temperature have helped prevent this phenomenon and the desired phenothiazine derivatives **58** were obtained in good yields. The *S*-arylation was carried out at 90° C and subsequently the temperature was increased to 110° C to allow the *N*-arylation to take place.



Scheme 18. Synthesis of phenothiazine starting from 2-bromothiophenol and iodoanilines.

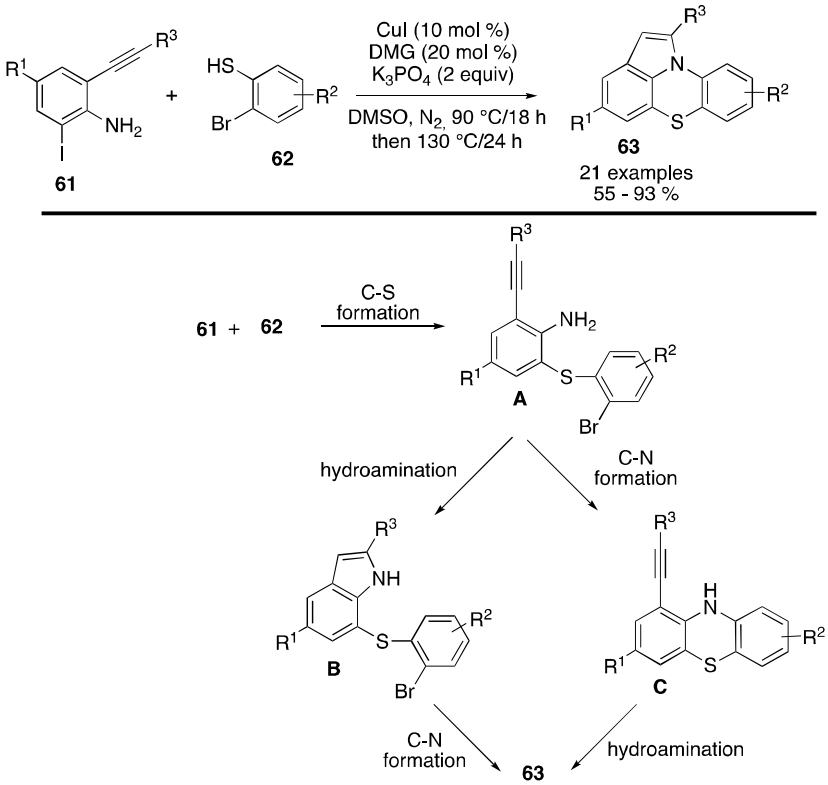
To avoid the formation of by-products (mainly coming from homo-coupling), and to address the regio-selectivity problem, Zeng *et al.* have synthesized phenothiazines from 2-aminothiophenols **59** and bromo-2-chlorobenzenes **60** (Scheme 19).[42] Since oxidative addition is faster in a C-Br bond than in a C-Cl and considering that thiophenol is a better nucleophile than aniline, the coupling between the Csp^2-Br of **60**, and

Csp^2-S of **59**, is the first step. This transformation is followed by a C-N coupling, forming the heterocycle **58** without condition control. In a catalytic system, the ligand is generally the most expensive compound. Therefore, the authors decided to perform the ligand-free reaction. They postulated that aminothiophenol **59** could play this role in order to allow copper to react. Several poly-functionalized phenothiazines have been synthesized in yields up to 91% and a great control of the regiochemistry.



Scheme 19. Synthesis of phenothiazine starting from aminothiophenols and 2-bromo-chlorobenzene.

This motif can also be found in more complex structures such as pyrrolophenothiazines **63** (tetracyclic compounds). The Lv group developed a synthesis of these molecules from poly-functionalized substrates **61** and **62** *via* a copper-catalyzed tandem reaction involving a C-S coupling followed by two successive cyclizations involving a 5-*endo*-dig hydroamination and a C-N intramolecular coupling (Scheme 20).[43]

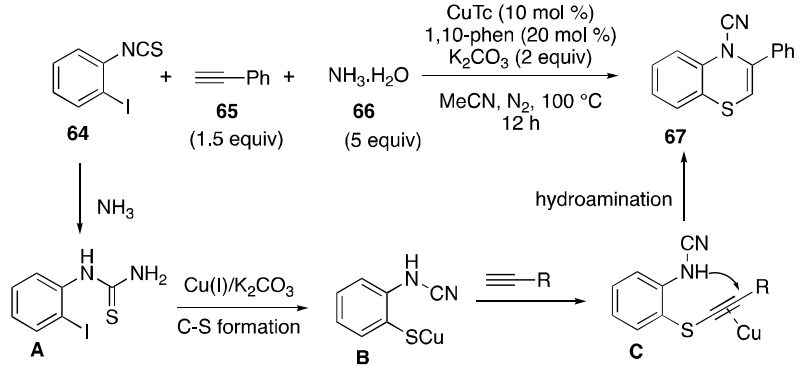


Scheme 20. Copper-catalyzed synthesis of pyrrolophenothiazines from alkynylanilines.

In order to elucidate the mechanism of this domino reaction, control experiments were carried out. As a result, two credible pathways were postulated by the authors. Both begin with the C-S coupling between

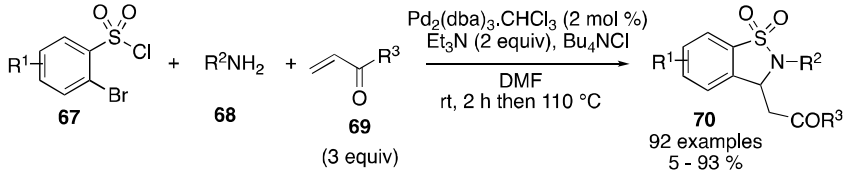
the iodobenzene function of **61** and the thiophenol **62** to form intermediate **A**. Then, two rapid cyclizations take place without the possibility to isolate intermediates **B** or **C**. Thus, two routes, equivalently possible, have been proposed: 1) 5-*endo*-dig cyclization/intramolecular C-N coupling; 2) intramolecular C-N coupling/cyclization 5-endo-dig.

1,4-Benzothiazine derivatives possess a broad spectrum of biological activities such as antibacterial, antidiabetic or antitumor activities.[44] Recently, Zhang's group developed a tri-component domino reaction to obtain 1,4-benzothiazine derivatives **67** in good yields from 2-iodophenyl isothiocyanate **64**, a terminal alkyne **65** and ammonia (Scheme 21).[45] This copper-catalyzed process involves the addition of ammonia to the isothiocyanate to give the intermediate **A**. Then, the copper-catalyzed successive formation of two C-S bonds allows to obtain the intermediate **B**. Finally, an intramolecular hydroamination leads to the desired compound **67**. Starting from 2-bromophenyl isothiocyanate systematically gave lower yields than when 2-iodophenyl isothiocyanate **64**, while the chlorinated derivative was totally unreactive.



Scheme 21. Cu-catalyzed of 1,4-benzothiazine derivatives from isothiocyanates.

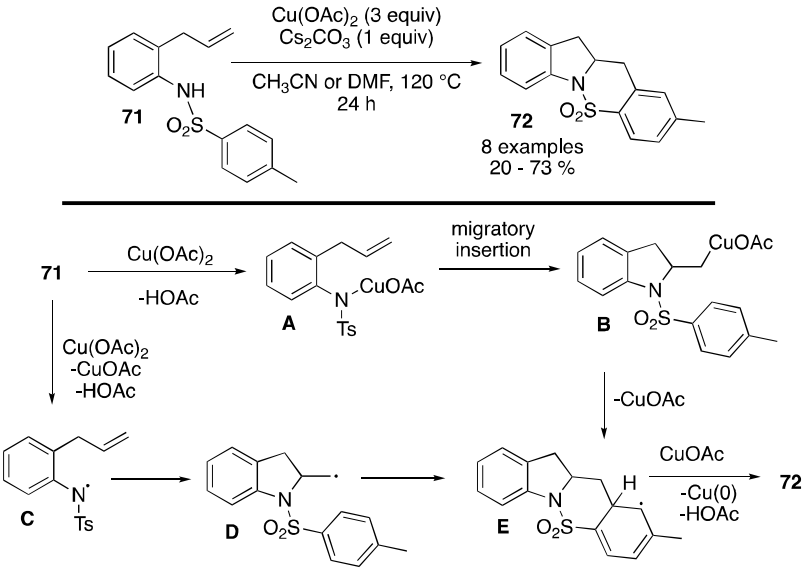
Many polyfunctionalized sultams have recently emerged in the literature as promising bioactive compounds. For instance they have been identified as inhibitors of several enzymes (COX-2, HIV integrase, lipoxygenases, cysteine protease).[46] In order to develop a library of biologically active molecules, Hanson implemented a palladium-catalyzed tandem process involving a Heck reaction, followed by the formation of a sulfonamide and an intramolecular hydroamination, to obtain different cyclic sultams **70** (Scheme 22).[47] Many polyfunctionalized starting substrates were used, allowing the synthesis of 92 molecules in yields up to 93%.



Scheme 22. Sultam synthesis starting from sulfonyl chloride and amines.

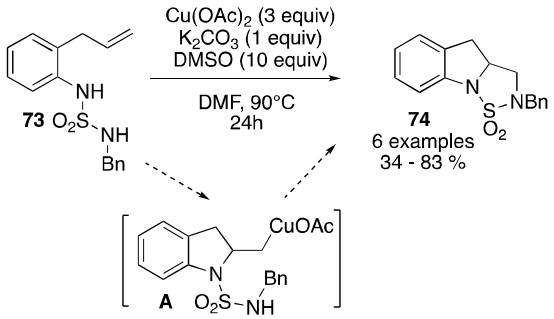
In 2004, the Chemler team used an *N*-tosylated *o*-allyl-aniline substrate **71** leading to a domino reaction involving two intramolecular transformations, namely an aminocupration and a radical cyclization. This process, using an excess of copper acetate, leads to the synthesis of tetracyclic sultams **72** with good yields (Scheme 23).[48] Notably, the use of the nosyl group in place of the tosyl considerably reduces the yield. Two mechanisms have been postulated for this reaction. First, a radical path was considered. A monoelectronic oxidation of the nitrogen of aniline **71** followed by the 5-*exo*-trig addition of the newly formed radical on the olefin could lead to the intermediate **D**. The addition of the resulting carbon radical on the aryl of the tosyl moiety would then form the intermediate **E**. The latter would then undergo a re-

aromatization to give the desired product **72**. The second possible mechanism would involve a first step of C-N coupling *via* an amino-cupration of the nitrogen-copper(II) complex **A** on the olefin to give the intermediate **B**. The latter would then follow the same radical mechanism as in the first way to obtain the tetracycle sultam **72**. An asymmetric version of this reaction was set up by the same team using a chiral ligand.[49] Thus, the use of 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]propane allows the stereocontrolled amino-cupration to access targeted cyclic sulfonamide derivatives in good yields and with enantiomeric excesses ranging from 46 to 94%.



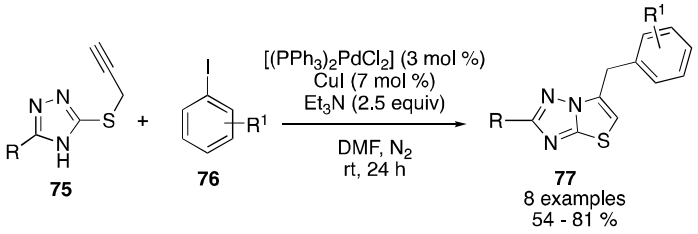
Scheme 23. Synthesis of sultams starting from tosylamines.

The same team extended this method to give rise to the diamination of a non-activated olefin (Scheme 24).[50] The olefin of compound such as **73** can be activated by copper acetate to allow the nitrogen at the *ortho* position to undergo a nucleophilic addition to reach the Cu(II) complex **A**. Then, a second nucleophilic addition performed by the benzyl amine moiety allow to obtain the targeted heterocycle **74**. This intramolecular diamination is highly regio-selective. Notably, the olefin can be substituted. However, this reaction appeared to be highly sensitive to the hindrance.



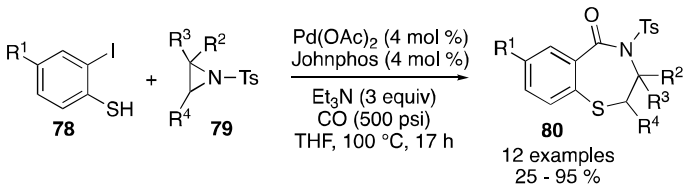
Scheme 24. Copper-catalyzed synthesis of bicyclic sulfamides.

The several syntheses of substituted thiazolo-1,2,4-triazoles have been developed, however, a classical challenge sits in the lack of regioselectivity. In this context, Heravi *et al.* have decided to focus on the development of a regioselective synthesis *via* a domino process involving a Sonogashira reaction followed by a nucleophilic addition of nitrogen on the triple bond of **75** and ending with a base-induced aromatization to give **77** (Scheme 25).[51] During the synthesis, the selective cyclization of nitrogen-3 allow specifically to form the five membered-ring. In addition, the authors observed experimentally that an electron-withdrawing group (-NO_2, -CF_3, -Cl) on iodobenzene **76** was crucial to the success of the overall process. The use of unsubstituted iodobenzene led only to a complex mixture of products.



Scheme 25. Pd-catalyzed domino synthesis of thiazolo-1,2,4-triazoles.

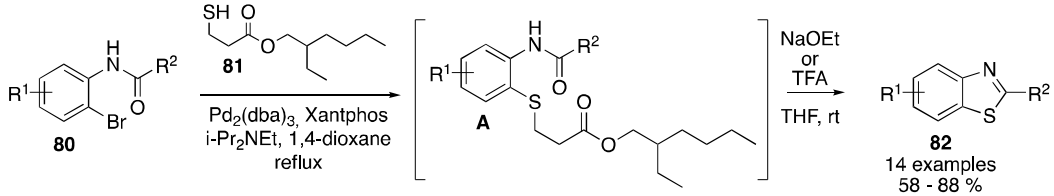
1,4-Thiazepinones **80**, are an important class of medium-sized mixed sulfur/nitrogen heterocycles. They possess remarkable biological activities and various compounds bearing this motif have been identified as antitumor, antiplatelet, antidepressant and inhibitors of the enzyme HIV-1 integrase and reverse transcriptase.[52] However, the traditional approaches to this scaffold generally use harsh conditions, are poorly regioselective and yields are classically low. Alper and Zheng were interested in setting up a domino strategy to synthesize efficiently and regioselectively these scaffolds. From *N*-tosylaziridines **79** and an *ortho*-iodothiophenol **78**, they developed a domino sequence involving the opening of an aziridine by the nucleophilic addition of thiophenol **78**, followed by a Pd-catalyzed intramolecular carboxyamidation to form the seven-membered ring (Scheme 26).[53] Sulfur adds selectively to the least substituted carbon of aziridine. This method tolerates both the presence of electron-withdrawing or electron-donating groups on **78**.



Scheme 26. Synthesis of 1,4-thiazepinones starting from aziridines and thiophenols.

3.1.1. From sulfur-free starting material

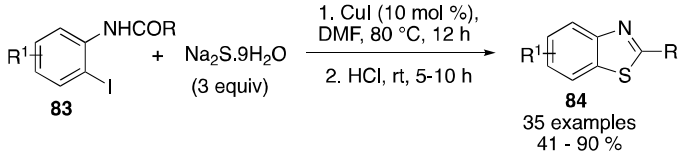
In 2007, Itoh's team developed a synthesis of substituted benzothiazoles from 2-bromoanilides **80** and a β-sulfanyl ester **81** *via* a tandem C-S coupling reaction followed by an intramolecular nucleophilic cyclization (Scheme 27).[54]



Scheme 27. Domino synthesis of substituted benzothiazoles from 2-bromoanilides and thiols.

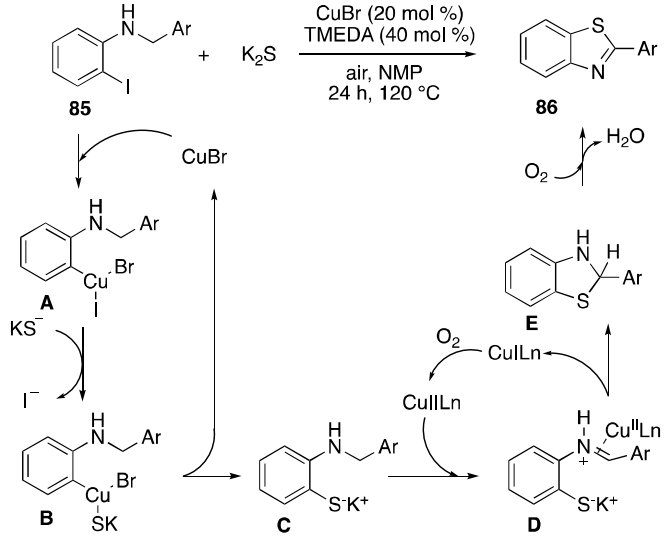
After a palladium catalyzed *S*-arylation, a basic treatment is carried out to form a thiolate that undergoes an intramolecular condensation on the carbonyl of the amide at the *ortho* position to reach the targeted benzothiazoles **82** in good yields. The conditions of the formation of the thiolate and therefore of the intramolecular condensation will depend on the substrates employed. Those possessing on the carbonyl of the amide an electron-poor or a neutral substituent cyclize rapidly under basic conditions (use of NaOEt to form the thiolate). Oppositely, those having an electron-rich amide or an electron-withdrawing group on the benzene of the anilide, cyclize under acid catalysis by activating the carbonyl function.

Using the same strategy, the Ma group developed a tandem reaction for the synthesis of 2-substituted benzothiazoles using sodium sulfide as a sulfur source. First, a copper-catalyzed C-S bond formation occurs. Then an acidic catalysis allows the cyclization by condensation of the thiol on the carbonyl of the amide. These simpler conditions give rise to the synthesis of benzothiazoles **84** in good yields (Scheme 28).[55]



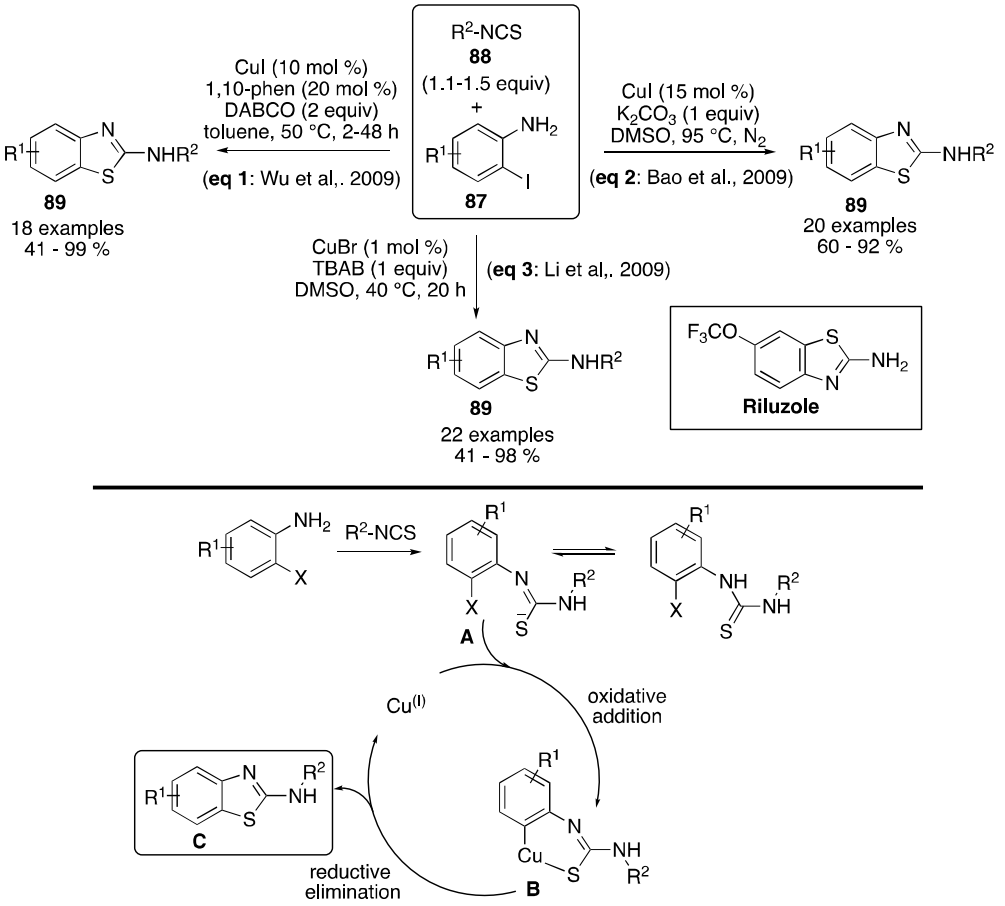
Scheme 28. Domino synthesis of substituted benzothiazoles from 2-iodoanilides and sodium sulfide.

In 2014, Liang's team used a CuBr/air/K_2S system in a domino reaction leading efficiently to 2-arylbenzothiazoles **86** starting from *N*-benzyl-2-iodoanilines **85**. The process involves successive formation of two C-S bonds, under copper-catalysis (Scheme 29).[56] When applied to *N*-acyl-2-iodoanilines, the same catalytic system can also promote the synthesis of 2-acylbenzothiazole derivatives in yields between 71% and 82%. A control study demonstrated the reaction pathway. First an Ullmann-type coupling is taking place to form the intermediate **C**, that can then be oxidized by the copper salt and the oxygen from air to form the intermediate **D**. Finally, compound **D** cyclizes by attack of the thiolate on the imine moiety to give heterocycle **E** that spontaneously aromatizes under these aerobic conditions to give the targeted benzothiazole **86**.



Scheme 29. Synthesis of 2-arylbenzothiazoles starting from *N*-benzyl-2-iodoanilines and K_2S.

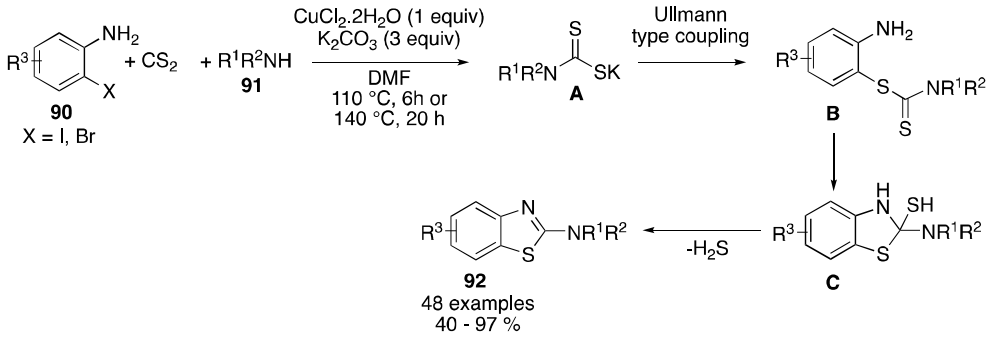
In 2009, three distinct domino reactions using the same transformations but under different conditions have been concomitantly developed to synthesize 2-aminobenzothiazoles starting from iodobenzamides **87** and isothiocyanates **88** (Scheme 30). All these reactions follow a similar mechanism. First, the nucleophilic addition of the aniline to the isothiocyanate generates thiolate **A**. Then, Ullmann-type coupling forms the C-S bond to obtain the targeted heterocycles. J. Wu's team developed conditions using copper, a ligand, and a base, which induces the formation of the thiolate intermediate (Scheme 30, equation 1).[57] The reaction time depends on the electrophilic character of the isothiocyanate. The more electrophilic it is, the faster the reaction. Subsequently, Bao et al. used basic, ligand-free conditions (Scheme 30, equation 2).[58] The authors postulated that thiolate **A** could act as a ligand by chelation of copper by the sulfur and the nitrogen atoms. To finish, Li's team developed conditions without a ligand and in the presence of tetrabutylammonium bromide, in DMSO (Scheme 30, equation 3).[59] All these syntheses allowed to obtain 2-aminobenzothiazoles **89** substituted by electron-withdrawing or donor groups in good yields.



Scheme 30. Syntheses and mechanism of 2-aminobenszothiazoles starting from iodoanilines and isothiocycnates.

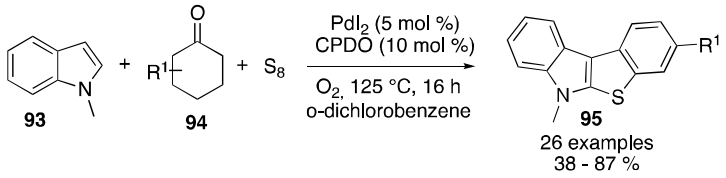
To increase the scope of accessible 2-aminobenzothiazoles, Ma developed an approach using CS_2, a secondary amine **91** and a poly-functionalized *ortho*-halo-aniline **90** (Scheme 31).[60] These aniline-based substrates are easier to access and have allowed the design of an efficient three-component reaction. The latter involves the nucleophilic addition of the amine on carbon disulfide to give the corresponding

dithiocarbamate salt **A** which undergoes a copper-catalyzed coupling with the aryl halide to give the corresponding aryl dithiocarbamate **B**. Finally, heterocycles **92** are obtained after the cyclization by attack of the aniline on the thiocarbonyl and elimination of hydrogen sulfide. A large number of functional groups and amines with good nucleophilicity are tolerated in this reaction. A large number of aminobenzothiazoles **92** have been synthesized in good yields. Notably, if 2-iodoanilines **90** are mainly used, the corresponding 2-bromoanilines can also be used but require a higher temperature and a longer reaction time.



Scheme 31. Approach to 2-aminobenzothiazoles using CS_2, a secondary amine and a poly-functionalized *ortho*-halo-aniline.

In order to develop a fast and efficient synthesis of benzothienoindoles **95**, C. J. Li developed a domino reaction involving a condensation step followed by the formation of two C-S bonds by palladium-catalyzed C-H activation and starting from indole **93**, cyclohexanone **94** and elemental sulfur (Scheme 32).[61]



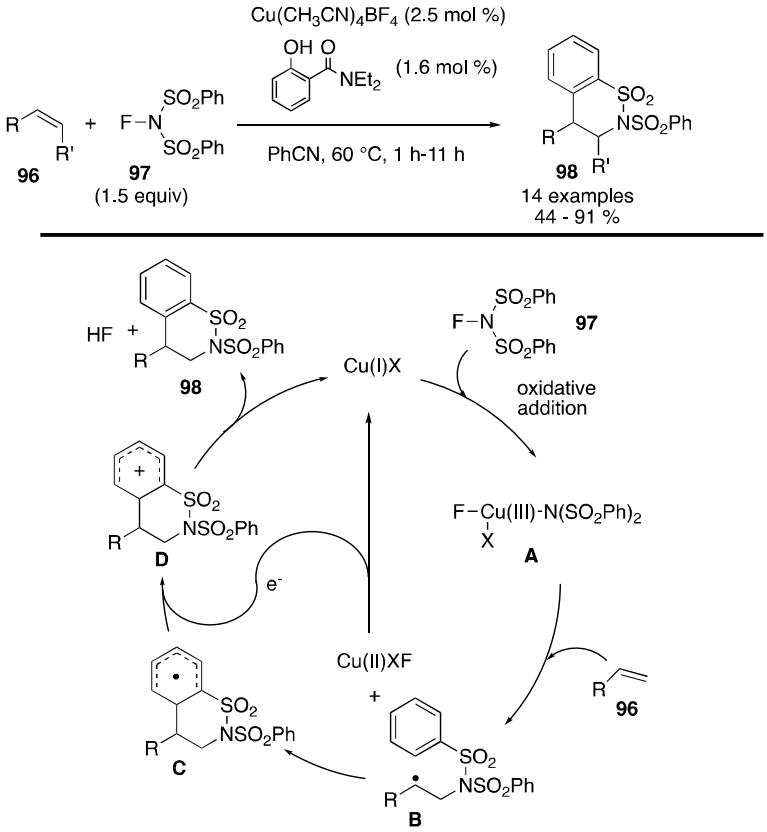
Scheme 32. Pd-catalyzed synthesis of benzothienoindoles.

The synthesis of sultams by carbo-amination of alkenes has also been developed intermolecularly by Matsunaga and Kanai starting from a non-activated alkene **96** and N-fluorobenzenesulfonimide **97** (Scheme 33).[62] Notably, in this case, the use of a base is not necessary. However, it appeared that the presence of a nitrile function on the solvent is essential to obtain the desired product. This study showed that it was possible to use both terminal and internal alkenes to obtain only the *cis*-addition product. However, the use of styrene did not lead to the desired product, but to the diamine product on the alkene. The authors propose a mechanism starting with the oxidative addition of copper to give the Cu(III) complex **A** and postulate that this complex would then undergo an amino-cupration on the olefin. Subsequently, the homolytic cleavage of the C-Cu bond would form radical **B**. The latter attacks the aromatic and, after an oxidation / re-aromatization step, the desired sultam derivatives **98** are obtained in good to high yields.

3.2. *O,S*-Heterocycles

3.2.1. From sulfur-containing starting material

To the best of our knowledge, there is no report of synthesis of *O,S*-heterocycles using Pd or Cu catalysis and starting from a substrate bearing a sulfur atom.

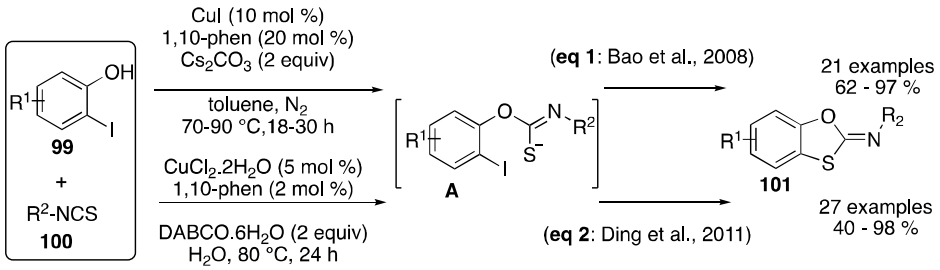


Scheme 33. Synthesis of sultams using *N*-fluorobenzenesulfonimide and alkenes.

3.2.2. From sulfur-free starting material

Iminobenzo-oxathioles have shown a wide scope of biological activities[63] stimulating the development of similar syntheses to those reported to obtain 2-aminobenzothiazoles (*vide supra*). Two copper-catalyzed domino reactions, involving the same transformations, have been reported.

The nucleophilic addition of an *ortho*-iodophenol **99** on an isothiocyanate **100** induces the formation of intermediate **A** which is then engaged in a Ullmann-type C-S coupling to give the desired heterocyclic compounds in good yields (Scheme 34). In 2008, Bao and collaborators were the first to report this synthesis of iminobenzo-oxathioles **101** using CuI as metal source, cesium carbonate as the base, and 1,10-phenanthroline as the ligand (Scheme 34, equation 1).[64] After the nucleophilic addition of phenol **99** to isothiocyanate **100**, two distinct couplings are possible (C-S coupling or C-N coupling) but this optimized catalytic system allowed to perform the C-S coupling with a very good selectivity. The temperature and the reaction time are dependent on the substrates employed. By increasing the electrophilic character of the isothiocyanate, the temperature and the reaction time can be decreased. Subsequently, with the aim of developing more environmentally friendly reactions, Ding developed an aqueous version of this transformation (Scheme 34, equation 2).[65] Copper chloride dihydrate and DABCO.$6H_2O$ were used. The iminobenzo-oxathiole derivatives **101** are not soluble in water, and so, for the majority of them, they can be isolated by simple filtration. This reaction can be easily scaled up (15 mmol) to obtain the corresponding benzo-oxathiol in 93% yield after simple filtration.



Scheme 34 Strategies to access iminobenzo-oxathioles

Conclusion

Over the last decades, it appeared that Pd and Cu-mediated domino reactions are powerful and versatile tools for the synthesis of valuable sulfur-heterocycles. These reactions are involving a wide scope of sequences and the ever increasing interest of the scientific community into these reactions will undoubtedly result in a big number of new and innovative approaches to these compounds. Interestingly, in many cases, the mechanism of these domino reactions is only postulated and a significant work is still needed in order to uncover the exact chronology as well as the individual steps of these sequences.

Acknowledgments

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References

1. (a) Balaban, A. T.; Oniciu, D. C.; Katrizky, A. R. *Chem. Rev.* **2004**, *104*, 2777; (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem*., **2014**, *57*, 2832.
2. For selected reviews see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341; (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095; (d) Ball, C. J.; Willis, M. C. *Eur. J. Org. Chem.* **2013**, 425; (e) Broja, T.; Fuchs, P. J. W.; Zeitler, K. *Nat. Chem.* **2015**, *7*, 950; (f) Blouin, S.; Blond, G.; Donnard, M.; Gulea, M.; Suffert, J. *Synthesis* **2017**, *49*, 1767; for selected recent examples see: (g) Wagner, P.; Gulea, M.; Suffert, J.; Donnard, M. *Chem. Eur. J.* **2017**, *23*, 7458; (h) Salacz, L.; Charpentier, C.; Suffert, J.; Girard N. *J. Org. Chem.* **2017**, *82*, 2257; (i) Yao, T.; He, D. *Org. Lett.* **2017**, *19*, 842; (j) Chen, J.; Huang, Y. *Org. Lett.* **2017**, *19*, 5609; (k) Schempp, T. T.; Daniels, B. E.; Staben, S. T.; Stivala, E. C. *Org. Lett.* **2017**, *19*, 3616.
3. (a) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Lopez Cara, C.; Preti, D.; Fruttarolo, F.; Pavani, M.G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Di Antonella, C.; Balzarini, J.; Hadfield, J. A.; Brancale, A.; Hamel, E. *J. Med. Chem.* **2007**, *50*, 2273; (b) Tao, Z.-F.; Hasvold, L.A.; Leverson, J. D.; Han, E.K.; Guan, R.; Johnson, E. F.; Stoll, V. S.; Stewart, K. D.; Stamper, G.; Soni, N.; Bouska, J. J.; Luo, Y.; Sowin, T. J.; Lin, N. H.; Giranda, V. S.; Rosenberg, S. H.; Penning, T. D. *J. Med. Chem.* **2009**, *52*, 6621; (c) Guo, H. F.; Shao, H. Y.; Yang, Z. Y.; Xue, S. T.; Li, X.; Liu, Z. Y.; He, X. B.; Jiang, J. D.; Zhang, Y. Q.; Si, S. Y.; Li, Z. R. *J. Med. Chem.* **2010**, *53*, 1819.
4. Qin, Z.; Kasrati, I.; Chandrasena, E. P.; Liu, H.; Yao, P.; Petukhov, P.A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682.
5. Hsiao, C. N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629.
6. Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *121*, 7198.
7. Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868.
8. Zhou, W.; Chen, W.; Wang, L. *Org. Biomol. Chem.*, **2012**, *10*, 4172.
9. Chen, W.; Li, P.; Miao, T.; Meng, L. G.; Wang, L. *Org. Biomol. Chem.*, **2013**, *11*, 420.
10. (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.*, **2004**, 1388; (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.*, **2005**, *70*, 1508; (c) Grossmann, O.; Gelman, D. *Org. Lett.*, **2006**, *8*, 1189.
11. Qin, X.; Cong, X.; Zhao, D.; You, J.; Lan, J. *Chem. Commun.*, **2011**, 47, 5611.

12. Yamauchi, T.; Shibahara, F.; Murai, T. *Tetrahedron Lett.* **2016**, *57*, 2945.
13. Masuya, Y.; Tobisu, M.; Chatani, N. *Org. Lett.*, **2016**, *18*, 4312.
14. Huang, H. N.; Li, J.; Zhao, W. N.; Mei, Y. B.; Duan, Z. *Org. Biomol. Chem.* **2011**, *9*, 5036.
15. Huang, H. N.; Li, J.; Lescop, C.; Duan, Z. *Org. Lett.* **2011**, *13*, 5252.
16. Li, J.; Huang, H.; Liang, W.; Gao, Q.; Duan Z. *Org. Lett.* **2013,** *15*, 282.
17. Castanheiro, T.; Donnard, M.; Gulea, M.; Suffert, J. *Org. Lett.* **2014**, *16*, 3060.
18. Castanheiro, T.; Suffert, J.; Donnard, M.; Gulea, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 162.
19. Castanheiro, T.; Schoenfelder, A.; Suffert, J.; Donnard, M.; Gulea, M. *C. R. Chimie* **2017**, *20*, 624.
20. Li, C. L.; Zhang, X. G.; Tang, R. Y.; Zhong, P.; Li, J. H. *J. Org. Chem.* **2010**, *75*, 7037.
21. Guilarte, V.; Fernandez-Rodrigues, M. A.; Garcia-Garcia, P.; Hernando, E.; Sanz, R. *Org. Lett.* **2011**, *13*, 5100.
22. Kuhn, M.; Falk, F. C.; Paradies, J. *Org. Lett.*, **2011,** *13*, 4100.
23. Sun, L. L.; Deng, C. L.; Tang, R.Y.; Zhang, X. G. *J. Org. Chem.* **2011**, *76*, 7546.
24. (a) Modica, M.; Santagati, M.; Guccione, S.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. *Eur. J. Med. Chem.* **2000**, *35*, 1065; (b) Wu, C.; Decker, E. R.; Blok, N.; Bui, H.; You, T. J.; Wang, J.; Bourgoyne, A. R.; Knowles, V.; Berens, K. L.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *J. Med. Chem.* **2004**, *47*, 1969; (c) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197; (d) Ramos, A. C.; Pelaez, R.; Lopez, J. L.; Caballero, E.; Medarde, M.; Feliciano, A. S. *Tetrahedron* **2001**, *57*, 3963.
25. You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930.
26. Liao, Q.; You, W; Lou, Z. B. Wen, L. R.; Xi, C. *Tetrahedron Lett.* **2013**, *54*, 1475.
27. Zhao, P.; Yin, H.; Gao, H.; Xi, C. *J. Org. Chem.* **2013**, *78*, 5001.
28. (a) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1985**, *22*, 1593; (b) Nakazumi, H. ; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1984**, *21*, 193; (c) Holshouser, M. H.; Loeffler, L. J.; Hall, I. H. *J. Med. Chem.* **1981**, *24*, 853; (d) Razdan, R. K.; Bruni, R. J.; Mehta, A. C.; Weinhardt, K. K.; Papanastassiou, Z. B. *J. Med. Chem.* **1978**, *21*, 643.
29. Willy, B.; Müller, T. J. J. *Synlett* **2009**, 1255.
30. Willy, B.; Frank, W.; Müller, T. J. J. *Org. Biomol. Chem.*, **2010**, *8*, 90.
31. Bozinovic, N.; Opsenica, I.; Solaja, B. A. *Synlett* **2013**, *24*, 49.
32. (a) Kashiyama, E.; Hutchinson, I.; Chua, M. S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172; (b) Hutchinson, I.; Chua, M. S.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446; (c) Palmer, P. J.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 248; (d) Rakowitz, D.; Hennig, B.; Nagano, M.; Steger, S.; Costantino, L.; Matuszczak, B.; *Arch. Pharm.* (Weinheim, Ger.) **2005**, *338*, 411; (e) Dumas, J.; Brittelli, D.; Chen, J.; Dixon, B.; Hatoum-Mokdad, H.; Konig, G.; Sibley, R.; Witowsky, J.; Wong, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531.
33. Vera, M. D.; Pelletier, J.C. *J. Comb. Chem.* **2007,** *9*, 569.
34. Bochataya, V. N.; Boissarie, P. J.; Murphy, J. A.; Suckling, C. J.; Lang, S. *J. Org. Chem.* **2013**, *78*, 1471.
35. Murru, S.; Mondal, P; Yella, R.; Patel, B. K. *Eur. J. Org. Chem.* **2009**, 5406.
36. (a) Namani, V.; Goud, B. B. K.; Kumari, Y. B.; Kumbham, R.; Balakrishna, K.; Bhima, B. *Asian J. Chem.* **2015**, *27*, 4575; (b) Nooka Raju, D.; Subhadra Devi, D. V. R.; Grace Aghastina, D.; Govinda Rao, K.; Sathish Kumar, K. *World J. Pharm. Pharm. Sci.* **2015**, *4*, 1815; (c) Cho, H. Y.; Ul Mushtaq, A.; Lee, J. Y.; Kim, D. G.; Seok, M. S.; Jang, M.; Han, B. W.; Kim, S.; Jeon, Y. H. *FEBS Lett*. **2014**, *588*, 2851; (d) Chikhale, R.; Menghani, S.; Babu, R.; Bansode, R.; Bhargavi, G.; Karodia, N.; Rajasekharan, M. V.; Paradkar, A.; Khedekar, P. *Eur. J. Med. Chem.* **2015**, *96*, 30.
37. Castanheiro, T.; Suffert, J.; Gulea, M.; Donnard, M. *Org. Lett.* **2016,** *18*, 2588.
38. Castanheiro, T.; Gulea, M.; Donnard, M.; Suffert, J. *Eur. J. Org. Chem.* **2014**, *2014*, 7814.
39. (a) Basta-Kaim, A.; Budziszewska, B.; Jaworska-Feil, L.; Tetich, M.; Kubera, M.; Leskiewicz, M.; Otczyk, M.; Lason, W. *Neuropsycho-pharmacology* **2006**, *31*, 853; (b) Bisi, A.; Meli, M.; Gobbi, S.;

Rampa, A.; Tolomeo, M.; Dusonchet, L. *Bioorg. Med. Chem.* **2008**, *16*, 6474; (c) Mylari, B. L.; Carty, T. J.; Moore, P. F.; Zembrowski, W. J. *J. Med. Chem.* **1990**, *33*, 2019.
40. Dahl, T.; Tornøe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jørgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1726.
41. Ma, D.; Geng, Q.; Zhang, H; Jiang, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 1291.
42. Dai, C.; Sun, X.: Tu, X.; Wu, L.; Zhan, D.; Zeng, Q. *Chem. Commun.*, **2012**, *48*, 5367.
43. Tang, J.; Xu, B.; Mao, X.; Yang, H.; Wang, X.; Lv, X. *J. Org. Chem.* **2015**, *80*, 11108.
44. (a) Schiaffella, F.; Macchiarulo, A.; Milanese, L.; Vecchiarelli, A.; Costantino, G.; Pietrella, D.; Fringuelli, R. *J. Med. Chem.* **2005**, *48*, 7658; (b) Tawada, H.; Sugiyama, Y.; Ikeda, H. ; Yamamoto, Y.; Meguro, K. *Chem. Pharm. Bull.* **1990**, *38*, 1238; (c) Coughlin, S. A.; Danz, D. W.; Robinson, R. G.; Klingbeil, K. M.; Wentland, M. P.; Corbett, T. H.; Waud, W. R.; Zwelling, L.A.; Altschuler, E.; Bales, E.; Rake, J. B. *Biochem. Pharmacol.* **1995**, *50*, 111; (d) Hasegawa, K.; Ito, S.; Inoue, S.; Wakamatsu, K.; Ozeki, H.; Ishiguro, I. *Biochem. Pharmacol.* **1997**, *53*, 1435.
45. Chu, J. J.; Hu, B. L.; Liao, Z.Y.; Zhang, X. G. *J. Org. Chem. **2016**, 81, 8647*.
46. (a) Levy, L. *Drugs Future* **1992**, *17*, 451; (b) Rabasseda, X.; Hopkins, S. L. *Drugs Today* **1994**, *30*, 557; (b) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P., Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J., Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453; (c) Valente, C.; Guedes, R. C.; Moreira, R.; Iley, J.; Gut, J.; Rosental, P. J. *Biorg. Med. Chem. Lett.* **2006**, *16*, 4115; (e) Misu, Y.; Togo, H. *Org. Biomol. Chem.* **2003**, *1*, 1342.
47. Rolfe, A.; Young, K.; Volp, K.; Schoenen, F.; Neuenswander, B.; Lushington, G. H.; Hanson P.R. *J. Comb. Chem.* **2009,** *11*, 732.
48. Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573.
49. Zeng, W; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, 129, 12948.
50. Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250.
51. Heravi, M. M.; Kivanloo, A.; Rahimzadeh, M.; Bakavoli, M.; Ghassemzadeh, M.; Neumüller, B. *Tetrahedron Lett.* **2005**, *46*, 1607.
52. (a) Garofalo, A.; Campiani, G.; Fiorini, I.; Nacci, V. *Farmaco* **1993**, *48*, 275; (b) Li, R.; Farmer, S. P.; Xie, M.; Quilliam, M. A.; Pleasance, S.; Howlett, S. E.; Yeung, P. K. F. *J. Med. Chem.* **1992**, *35*, 3246; (c) Krapcho, J.; Turk, C. F. *J. Med. Chem.* **1966**, *9*, 191; (d) Neamati, N.; Turpin, J. A.; Winslow, H. E.; Christensen, J. L.; Williamson, K.; Orr, A.; Rice, W. G.; Pommier, Y.; Garofalo, A.; Brizzi, A.; Campiani, G. *J. Med. Chem.* **1999**, *42*, 3334; (e) Maruenda, H.; Johnson, F. *J. Med. Chem.* **1995**, *38*, 2145.
53. Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 5567.
54. Itoh, T; Mase, T. *Org. Lett.* **2007**, *9*, 3687.
55. Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem. Int. Ed.* **2009**, *121*, 4286.
56. Zhang, X.; Zeng, W.; Yang, Y.; Huang, H.; Liang, Y. *Org. Lett.* **2014**, *16*, 876.
57. Ding, Q.; He, X.; Wu., J. *J. Comb. Chem.* **2009,** *11*, 587.
58. Shen, G.; Lv, X; Bao W. *Eur. J. Org. Chem.* **2009**, 5897.
59. (a) Guo, Y. J.; Tang, R. Y.; Zhong, P.; Li, J. H. *Tetrahedron Lett.* **2010**, *51*, 649; (b) Li, J. H.; Li, J. L.; Xie, Y. X. *Synthesis* **2007**, 984; (c) Liu, W. J.; Xie, Y. X.; Liang, Y.; Li, J. H. *Synthesis* **2006**, 860; (d) Bedford, R. B. ; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466.
60. Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu X. *Angew. Chem. Int. Ed.* **2011**, *50*, 1118.
61. Liao, Y.; Peng, Y.; Qi, H.; Deng, G. J.; Gong, H.; Li, C. J. *Chem. Commun.*, **2015**, *51*, 1031.
62. Kaneko, K.; Yoshino, T.; Mastsunaga, S.; Kanai, M. *Org. Lett.* **2013**, *15*, 2502.
63. (a) Kiku-chi, T.; Mizukoshi, T.; Niki, T. T. Japanese Patent 2002,226,463, 2002; Chem. Abstr. 2002, 137, 154930; (b) Konieczny, M.T.; Konieczny, W.; Sabisz, M.; Skladanowski, A.; Wakiec, R.; Augustynowicz–Kopec, E.; Zwolska, Z. *Eur. J. Med. Chem.* **2007**, *42*, 729; (c) Konieczny, M. T. ; Konieczny, W.; Sabisz, M.; Skladanowski, A.; Wakiec, R.; Augustynowicz–Kopec, E.; Zwolska, Z. *Chem. Pharm. Bull.* **2007**, *55*, 817.
64. Lv, X.; Liu, Y.; Qian, W.; Bao, W. *Adv. Synth. Catal.* **2008**, *350*, 2507.
65. Ding, Q.; Liu, X.; Cao, B.; Zong, Z.; Peng, Y. *Tetrahedron Lett.* **2011**, *52*, 1964.