SYNTHESIS OF BENZO[*b*]FURAN DERIVATIVES BY TRANSITION METAL-CATALYZED HETEROCICLYZATIONS OF 2-ETHYNYLPHENOLS

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Abstract. *The benzo[b]furan skeleton may be found in numerous natural products and synthetic molecules of industrial significance. The straightforward assembly of 2-alkynylphenol derivatives has made them privileged starting materials for the preparation of this heterocyclic motif. In this chapter, several transition-metal-catalyzed processes for the preparation of benzo[b]furan derivatives from 2-alkynylphenol starting materials are covered. Most of these transformations are based on the electrophilic activation of the triple bond by the transition metal, enabling the nucleophilic addition of the vicinal oxygen. Several cascade reactions that allow for further increasing the molecular complexity are also described.*

Contents

1. Introduction

The prevalence of the benzo[*b*]furan skeleton in natural products, pharmaceuticals, agrochemicals, and other compounds of industrial relevance, makes it an interesting target for synthetic organic chemists.[1-3] Figure 1 shows several benzo[*b*]furan-containing natural products.[4-6]

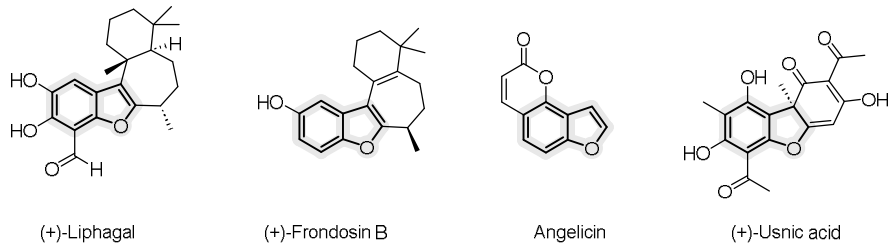


Figure 1. Benzo[*b*]furan-derived natural products.

In addition, benzo[*b*]furan derivatives have been found to exert interesting therapeutic activities, such as anticancer, antitumoral, antiproliferative, antibiotic, anti-inflammatory, or antipsychotic, amongst others.[7] Examples of benzo[*b*]furan derivatives showing different biological activities are depicted in Figure 2.

On the other hand, benzo[*b*]furan derivatives with extended conjugation have been recognized as useful materials for optical (in photochromic ophthalmic sun-lenses)[8] or electronic (as the hole-transporting material (HTM) in multilayer organic light-emitting diodes (OLEDs))[9,10] applications (Figure 3).

Several reviews have been published on the synthesis of this heterocyclic motif.[11-14] Herein we will only highlight recent methods (2013-2023), based on transition metal catalysis, and using 2-ethynylphenol derivatives as substrates.

The proximity of the phenol hydroxy group and an alkynyl moiety was early considered an ideal platform for assembling the benzo-fused furan analog. Already in 1981, Bloch described the intramolecular insertion of a pyrolytically generated vinylidene intermediate **I** into the proximal O−H bond in 2-ethynylphenol **1** (Scheme 1).[15,16] A related study with trialkylsilyl derivatives was carried out by Barton a few years later.[17]

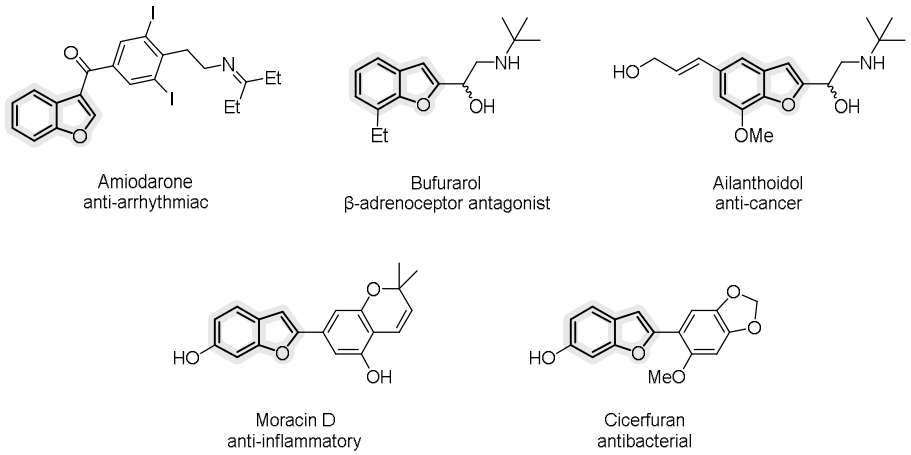


Figure 2. Benzo[*b*]furan derivatives with relevant biological activities.

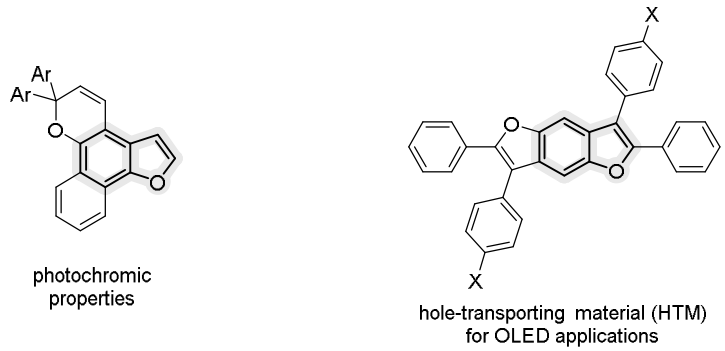
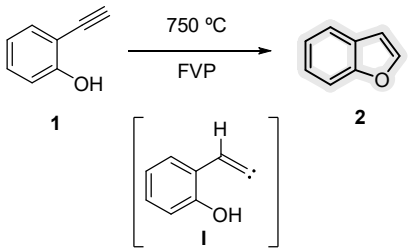


Figure 3. Benzo[*b*]furan derivatives with relevant optical or electronic properties.

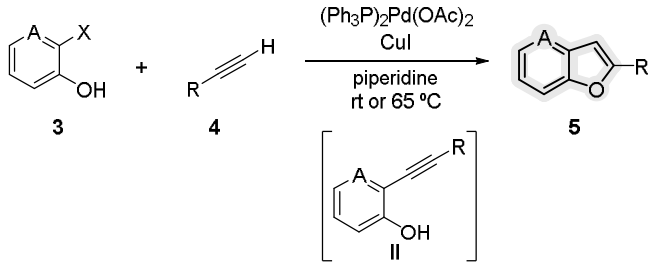


Scheme 1. Generation of a vinylidene intermediate by flash-vacum pyrolysis and subsequent O–H insertion.

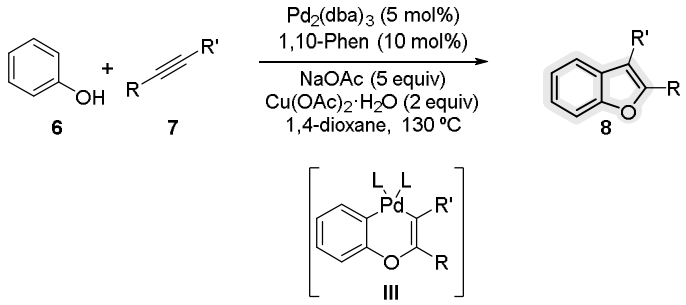
Early examples of electrophilic cyclization of 2-alkynylphenol derivatives were based on transition metal-catalyzed transformations, particularly on tandem Sonogashira cross-coupling reaction/5-*endo*-*dig* cyclization using 2-halophenol derivatives **3** and terminal alkynes **4**, with the intermediacy of the in-situ formed 2-alkynylphenol **II** (Scheme 2).[18]

A few reports have also described the direct formation of the benzo[*b*]furan ring **8** by oxidative annulation of phenols **6** with internal alkynes **7** (Scheme 3).[19-21] After an initial report using 1-bromoalkynes as substrates,[19] a more general procedure using unactivated internal alkynes was described.[20] The reaction

starts with the alkoxypalladation of the alkyne, followed by intramolecular C−H bond activation and reductive elimination on key intermediate **III**.

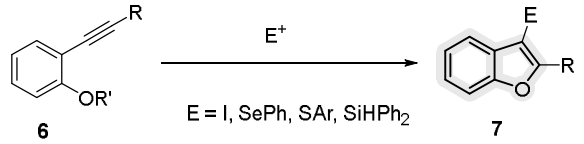


Scheme 2. Tandem Sonogashira coupling/cyclization process for the construction of benzo[*b*]furans from o-halophenols.



Scheme 3. Tandem alokypalladation/C−H activation process for the construction of benzo[*b*]furans from phenols.

A new turn in the field was brought about by the use of electrophiles other than transition metals, such as iodine or selenium or more recently silyl cations (Scheme 4).[22-25] These electrophiles are used stoichiometrically and, hence, will not be covered in detail in this chapter.

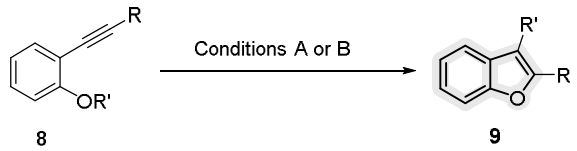


Scheme 4. Electrophile-promoted cyclization of o-alkynylphenols.

A breakthrough in this context was introduced using more carbophilic transition metal catalysts, especially those based on platinum and gold. Yamamoto and Fürstner pioneered this field using $PtCl_2$ as catalyst (Scheme 5).[26-28] However, soon gold(I)-based species took over as catalysts of choice for this transformation (see section 2). After a previous publication on the synthesis of indole derivatives using 2-alkynylacetamides as starting materials,[26] Yamamoto and Fürstner reported independently the use of the corresponding phenols or some ethers or acetals derived from them **8** for the assembly of the benzo[*b*]furan scaffold **9**.[27,28] When ethers and acetals were used as substrates, the migration of the carbon chain initially attached to the oxygen in position 3 in the final benzo[*b*]furan was observed along the carboalkoxylation process.

A few related transformations will be mentioned in this introduction, but not described in detail in the main body of the text. The first of them is the extension of this strategy to the preparation of the corresponding

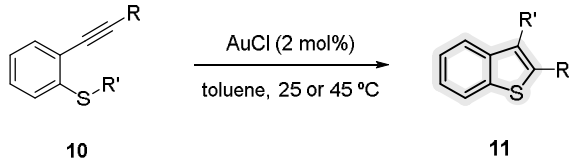
benzothiophenes **11**, described also by Yamamoto (Scheme 6).[29,30] Cross-over experiments have allowed establishing two different mechanisms depending on the nature of the group attached to the sulfur atom. On the one hand, an intramolecular migration from S to C3 is proposed in order to rationalize the lack of scrambling observed when thioacetals or allyl thioethers are used as substrates.[29] On the other hand, in the case of silylthioethers, the observation of scrambling under cross-over experimental conditions, using substrates with different substituents at the triple bond and the silicon, suggests an outer-sphere mechanism with dissociation of the silyl moiety followed by siladeauration.[30]



Conditions A (Yamamoto)
$PtCl_2$ (2 mol%)/1,5-cyclooctadiene (8 mol%)
toluene, 30 ºC
R' =CHR''(OR''')

Conditions B (Fürstner)
$PtCl_2$ (0,5-5 mol%)/CO (1 atm)
toluene, 80 ºC
R' = H, allyl, benzyl

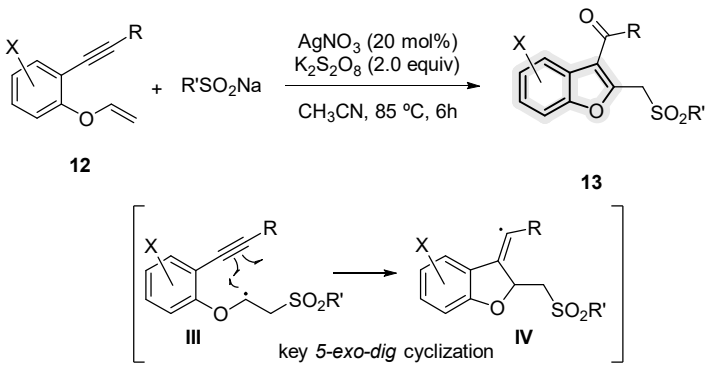
Scheme 5. Early examples of benzo[*b*]furan synthesis by means of carbophilic transition-metal catalysis.



R' = CHR''(OR'''), allyl, SiR'''_3

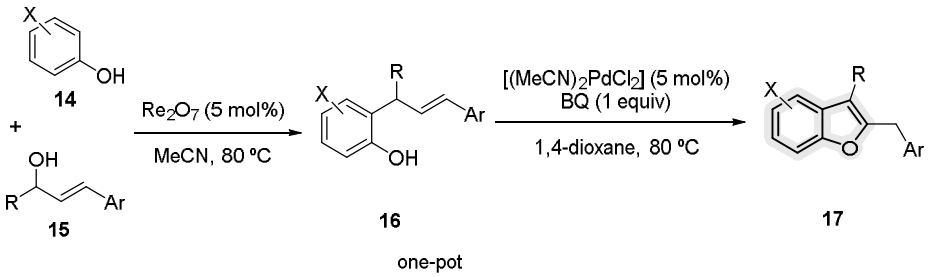
Scheme 6. Synthesis of benzo[*b*]thiophenes from o-alkynylthiols.

Second, the silver-catalyzed radical 5-*exo-dig* cyclization of *O*-vinyl-2-ethynylphenol derivatives has been reported.[31] In this case, a radical 5-*exo-dig* addition mode is responsible for the observed experimental outcome. The reaction between *O*-vinyl-2-ethynylphenol derivatives **12** and sodium sulfinates under silver catalysis, using potassium persulfate as terminal oxidant affords densely functionalized benzo[*b*]furan derivatives **13** (Scheme 7).



Scheme 7. Radical 5-*exo-dig* cyclization of *O*-vinyl-2-ethynylphenol derivatives.

2-Cinnamylphenols **16** may be used as substrates instead of 2-alkynylphenols; however, only strategies using the later will be covered in detail herein (Scheme 8).[33] The reaction consists of an intramolecular Wacker-type reaction followed by double bond isomerization driven by aromatization towards the final product **17**. In addition, the authors described a one-pot rhenium-catalyzed Friedel-Crafts/palladium-catalyzed cyclization protocol that allows to access benzo[*b*]furans **17** from phenols **14** and cinnamyl alcohols **15**.

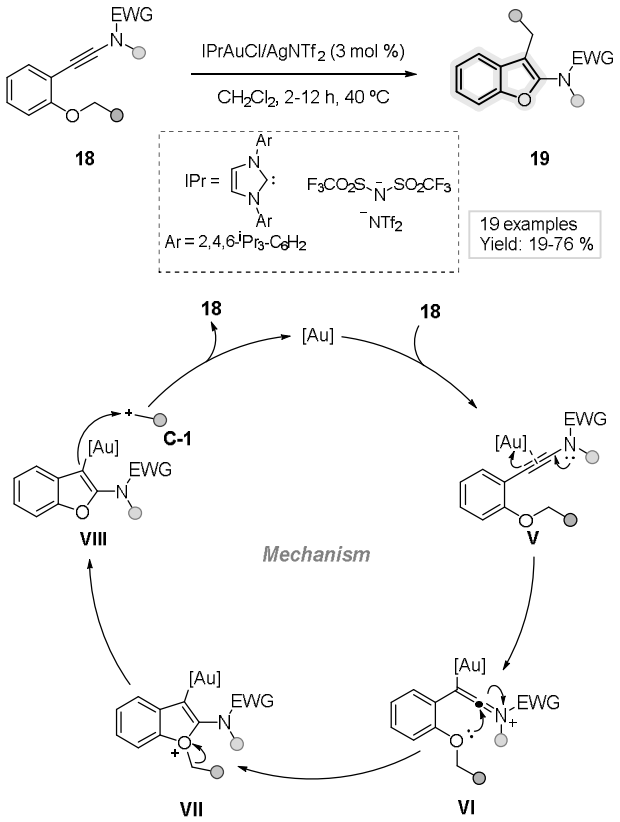


Scheme 8. Synthesis of benzo[*b*]furans from *o*-allylphenol derivatives.

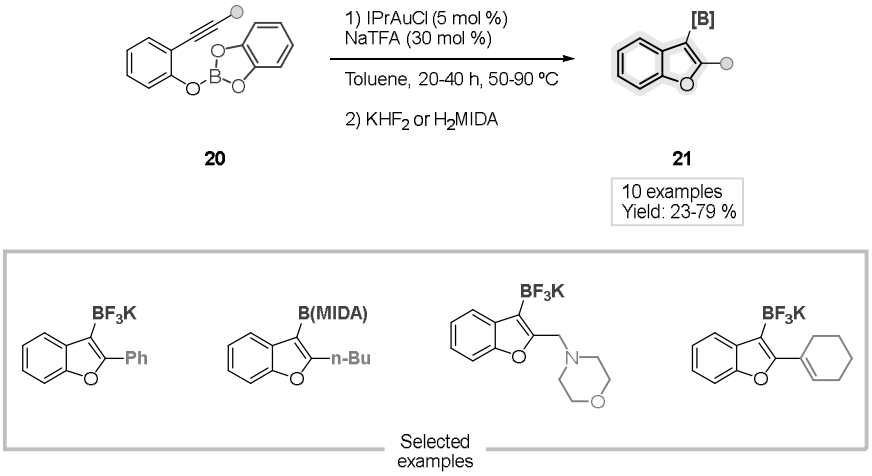
2. Heterocyclization employing gold-catalysis

In 2013, Hashmi and co-workers developed a gold-catalyzed reaction employing ynamides **1** as starting materials leading to the formation of a series of allylic, benzylic and related activated-oxonium intermediates. These compounds underwent a subsequent and facile group migration, shifting the activated alkyl moiety from the oxygen atom to the carbon atom, affording the corresponding C3-substituted 2-amino-benzo[*b*]furan derivative (Scheme 9).[34] This methodology nicely complements the previous work described by Fürstner and Davies employing phenolic allyl ethers under platinum-catalysis.[28] The structure of product **19** was corroborated by X-ray analysis of some representative samples. As mentioned above, once the cyclization reaction was optimized using a proper gold(I)-catalyst, the authors evaluated the scope of this methodology, observing that a wide range of groups successfully enter the reaction, among them simple allyl-, cinnamyl-, and common benzyl-fragments and related systems based on heteroaryl related partners being tolerated. Interestingly, this approach provides smooth access to highly substituted benzo[*b*]furans with high atom economy and low catalyst loads. They carried out an interesting experiment to study the behavior of non-stabilized carbocations such as the methyl group. However, the formation of a defined product was not observed. Thus, this methodology was limited to the use of precursors giving rise to relatively stable carbocations. In addition, the authors proposed a reasonable reaction mechanism, the first stage being the activation of ynamide **18** by the gold-catalyst, resulting in the formation of intermediate **V**. Then, **V** evolves to form intermediate **VI**, which is attacked by the oxygen atom forming the alkyl-oxonium intermediate **VII** that, subsequently, undergoes C−O bond cleavage affording the vinylgold(I)-intermediate **VIII** and the stabilized alkyl carbocation **C-1**. Next, the latter species **C-1** shifts to the most-nucleophilic position of the benzo[*b*]furan ring obtaining the corresponding benzo[*b*]furan **19**, regenerating the catalytically reactive gold-species. Other authors, like Muchalski, have employed this approach to prepare benzo[*b*]furans other than those reported by Hashmi modifying the group linked to the alkyne or the group attached to the heteroatom which participates in the cyclization.[35]

In 2014, Blum and co-workers developed an alkoxyboration reaction employing gold-catalysis.[36] The intramolecular addition of the boron-oxygen σ bond to the gold(I)-activated alkyne **20** yielded the corresponding 3-benzo[*b*]furanyl boronic acid derivates **21** with broad functional group compatibility (Scheme 10). Apart from its synthetic implication, this methodology is interesting as it conveys the activation of the very strong B−O bond (~569 kJ/mol). Due to the low stability of the catechol boronic ester products, they were isolated after their conversion into the corresponding organotrifluoroborate or *N*-methyliminodiacetic acid (MIDA) boronate derivates, both of which were air-stable indefinitely. This is a powerful methodology to synthesize organoboron reagents which are instrumental compounds for medicinal chemistry and drug discovery.[37] Moreover, these products are easily post-functionalized to form a wide range of derivatives containing useful functional groups such as ketone,[38] amine, or aryl fragments.[39]

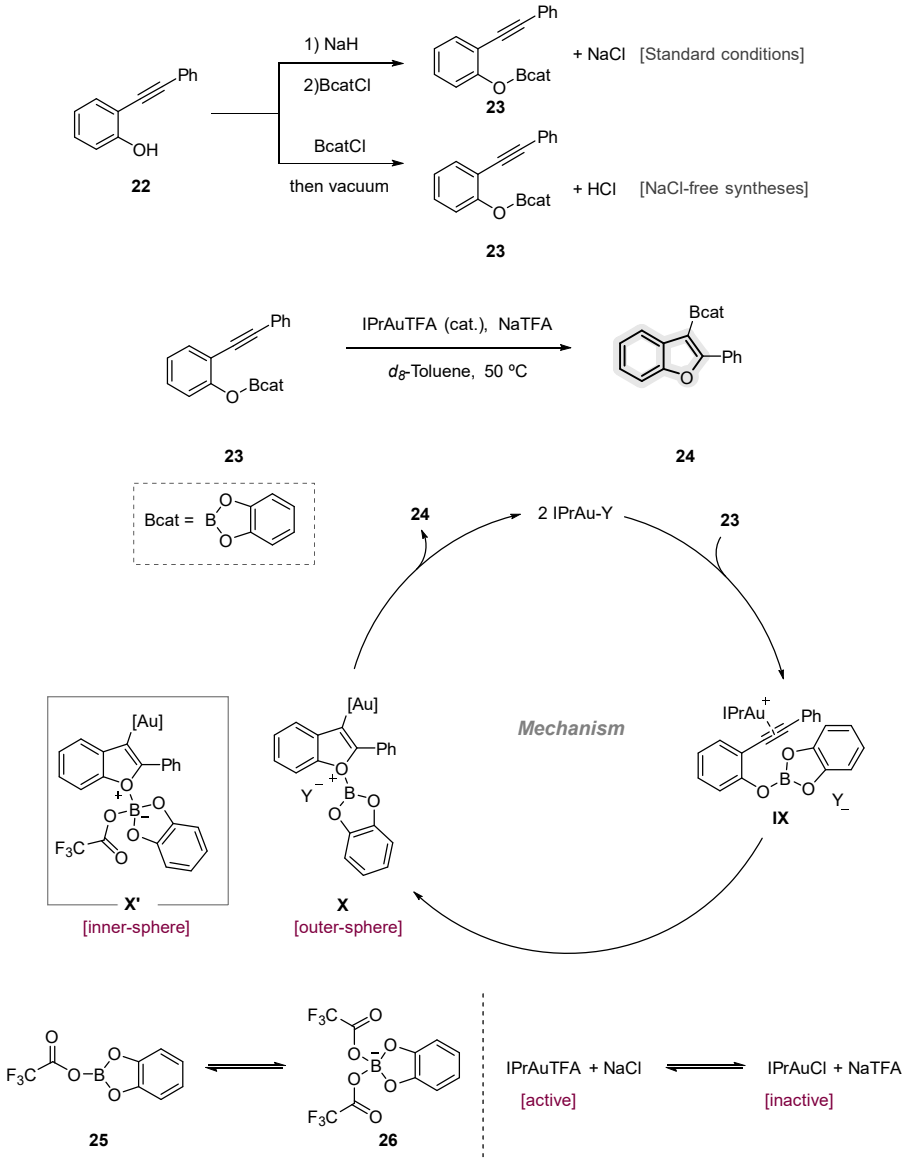


Scheme 9. Gold(I)-catalyzed 5-*endo*-*dig*-cyclization/rearrangement of oxonium intermediates.



Scheme 10. Alkoxyboration ring-closing upon addition of B−O σ bonds across alkynes.

To get a better understanding of this reaction, two years later, Blum and her co-workers carried out an in-depth kinetic study of the oxyboration reaction catalyzed by gold-species using different techniques such as mass spectrometry, ^{1}H- and ^{11}B-NMR spectroscopy. The study relies on the use of compound **23** as the starting material, which can be readily prepared from phenol **22** and B-chlorocatecholborane without the need to isolate this sensitive intermediate. They carried out different experiments modifying the synthesis of substrate **23**. Initially, the synthesis employed NaH and BCatCl, with NaCl being formed as a by-product (standard conditions) (Scheme 11).



Scheme 11. Carbophilic Lewis acid-catalyzed oxyboration and the non-innocent role of sodium chloride.

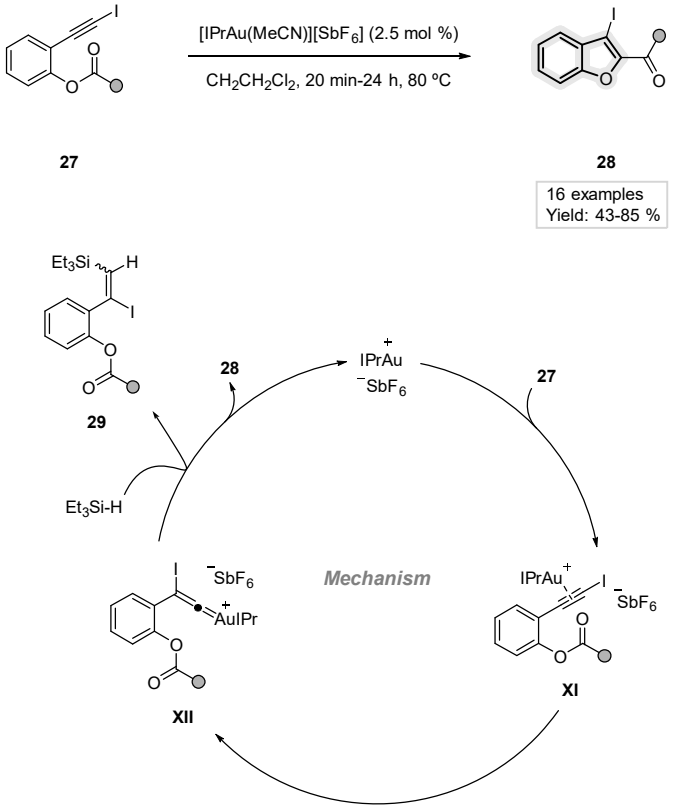
However, they hypothesized and showed that this last species could hamper the activity of the IPrAuTFA reactive catalyst generated upon addition of NaTFA as chloride scavenger and, likely, having some impact as potential transmetallation partner. Thus, they synthesized the substrate **23** through the depicted alternative chloride-free synthetic route., and the kinetic for the NaCl-free oxyboration reaction was then carefully examined. Upon adding 5 mol% of IPrAuTFA the formation of **24** was nicely observed at 50 ºC, giving higher figures for k_{obs} than the related NaCl-present procedure, speaking in favor of the hypothesis that NaCl is inhibiting the activity of the gold-catalysis. Under these reaction conditions, the reaction no longer displayed zero-order kinetics with respect to the substrate. In order to determine the kinetic dependence on substrate and catalyst the loading of the latter was varied. However, a deviation at early conversions, due to a possible catalyst induction period, did not allow determining the order in the gold catalyst. Nevertheless, the addition of 5 mol% of NaTFA led to a decrease in the reaction rate, likely due to the equilibrium between the proposed species (TFA)BCat **25** and $[(TFA)_2BCat]^-$ **26** turning shifted towards the latter. The reaction using less coordinating anions such as BF_4 and SbF_6 instead of TFA was tested, and it was observed that the reaction was successful. In the case of SbF_6 the reaction was carried out at 80 ºC due to its low solubility in toluene. This experiment ruled out the inner-sphere mechanism with assistance in the B−O bond cleavage step. Moreover, the reaction was also monitored by comparing the activity of IPrAuTFA with that of $IPrAuBF_4$. Comparable efficiencies for the reactions using either catalyst were noticed over an extended period of time, although a faster process was noticed using IPrAuTFA as the catalyst over the initial 10 h. On this basis, for the chloride-free transformation, it was proposed that the gold catalyst shows similar reactivity without the possible Lewis base assistance of the counteranion in the oxyboration reaction. But, even if the oxyboration reaction does not require an inner-sphere mechanism (*via* **X'**), its participation cannot be safely excluded when the TFA is used as the anion (Scheme 11).[40]

Likewise, other boron-heteroatom addition reactions were carried out to assemble selectively borylated different heterocycle scaffolds, such as: indoles, isoxazoles, isocumarins, 2-pyrones and benzothiofurans.[41]

In 2019, our group developed the cycloisomerization of 2-(iodoethynyl)-aryl esters **27** to give the corresponding benzo[*b*]furans **28** using gold(I)-species as catalyst (Scheme 12).[42] In this reaction, a [1,2]-iodine shift to form a gold(I)-vinylidene intermediate **XI** followed by a C−O insertion, resulting in a ring closure step that installs the ketone functionality into the benzo[*b*]furan ring.[43-45] Moreover, the Csp^2−I bond is an interesting functional group for building-block diversification by linking other molecules to the benzo[*b*]furan scaffold using catalytic cross-coupling processes. The reaction tolerates some functional groups at aromatic moiety, among them simple esters and halogens. Interestingly, the transformation is useful to accomplish a late-state selective functionalization of more sophisticated bioactive molecules such as Naproxen. The scarce number of reports on metal-catalyzed 1,1-oxyacylation reactions in the literature makes this new transformation interesting from a mechanistic point of view, in addition to its synthetic relevance. Some experiments aimed to provide mechanistic information were carried out, strongly suggesting the intramolecular nature of the process due to the absence of crossover products. Besides, an experiment to trap intermediate gold-vinylidene was carried out using Et_3SiH, and the noticed outcome was compatible with the formation of product **29**. Thus, a rational mechanism based on the structure of the products and the above-described experiments was proposed. The first step would be the coordination of gold(I) to the triple bond of the starting material **27** to form the intermediate **XI**. Then, a [1,2]-iodine shift facilitated by the donor ability of the ligand in the catalyst furnishes the key gold(I)-vinylidene intermediate **XII**. Subsequently, the insertion reaction of the O−acyl bond into the highly reactive vinylidene yields the corresponding benzo[*b*]furan **28**.

Next, in 2022, our group developed an intramolecular activation of the Si−O bond catalyzed by gold(I).[46] Based on the precedent established by our group, see Scheme 13, a challenging question was if the activation of one of the strongest bonds in organic chemistry, namely the Si−O bond whose strength bond is 798 kJ/mol, would be possible using this conceptual frame (in the previous work, the strength bond of O−acyl was 406 kJ/mol). To achieve this goal, a number of [2-(haloethynyl)aryloxy]trialkylsilanes **30** were synthesized. In this demanding transformation, the corresponding bromoalkynes afforded the best results in the formation of 3-bromo-2-silylbenzo[*b*]furan derivatives **31**. The optimized conditions to carry out this transformation consisted of the use of [IPrAu(MeCN)BArF] as the catalyst at 80 ºC in DCE. Two main characteristics were observed, bromoethynyl reagents **30** worked better than iodoethynyl reagents **30'** and the reaction was

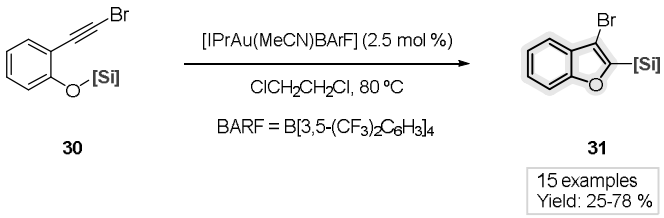
sensitive to the nature of the substituents on the silicon atom in the silyl ether group, and the results using the triisopropyl group were better than for others, such as *tert*-butyldimethyl group or triethyl group. The reaction showed a broad functional group compatibility. Moreover, the excellent and differentiated reactivity of the two new reactive points of these derivatives allowed to carry out an orthogonal derivatization of the assembled heterocyclic frame. Namely, introducing a carboxylic acid at C2 using CO_2 as a C1 synthon, by selectively activating the C−Si bond of the triisopropyl silane, leaving unaffected the C3−Br functionality. [47] In addition, carrying out a Suzuki cross-coupling reaction, the silane containing a a phenyl group attached to the C3 position of the elaborated benzo[*b*]furan was synthesized, at the expense of the sacrificial Csp^2−Br bond.

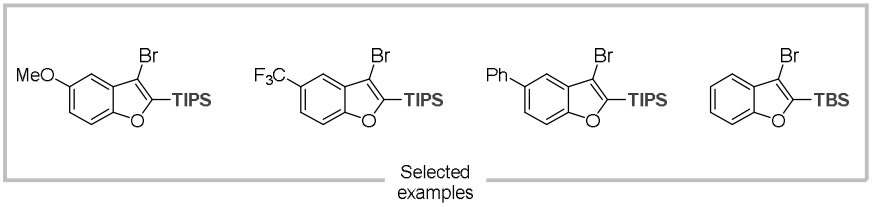


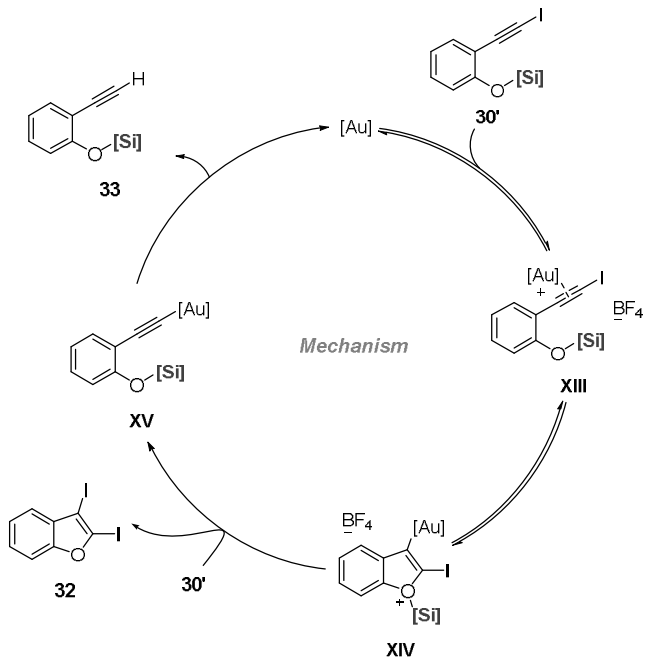
Scheme 12. Intramolecular oxyacylation reaction of iodoalkynes catalyzed by gold(I).

With regard to the mechanism of the reaction, a formally analogous reaction pathway to the one depicted in Scheme 12 was proposed. Thus, upon coordination of the alkyne to gold and 1,2 halogen shift towards the key gold-vinylidene intermediate, the O−Si bond insertion would take place and furnish benzo[*b*]furan derivatives **31**. In the case of the related iodoethynyl parent precursors, the main product formed was the related 2,3-diiodo derivative **32**, albeit in modest yield, which was formed along with variable amounts of the corresponding terminal alkyne. Taking into account the differential reactivity observed for both haloalkynyl derivatives, a mechanistic proposal accounting for the formation of **32** was tentatively formulated (Scheme 13). Thus, upon complexation of the iodo-alkyne to gold, an alternative reaction pathway, off-cycle to the previous one formulated to account for the formation of the 3-bromo-3-silyl-benzo[*b*]furan derivatives, would be operative. Now, for the iodine case, the main evolution path of the activated gold-complex results from nucleophilic addition of the ether to the intermediate **XIII**, forming the oxonium intermediate **XIV** prior to the [1,2]-halogen shift. It undergoes reaction with a second molecule of **30'** forming gold-acetylene **XV**.

Protodeauration of the latter intermediate with added water regenerates the catalyst giving the terminal alkyne **33** as a by-product.



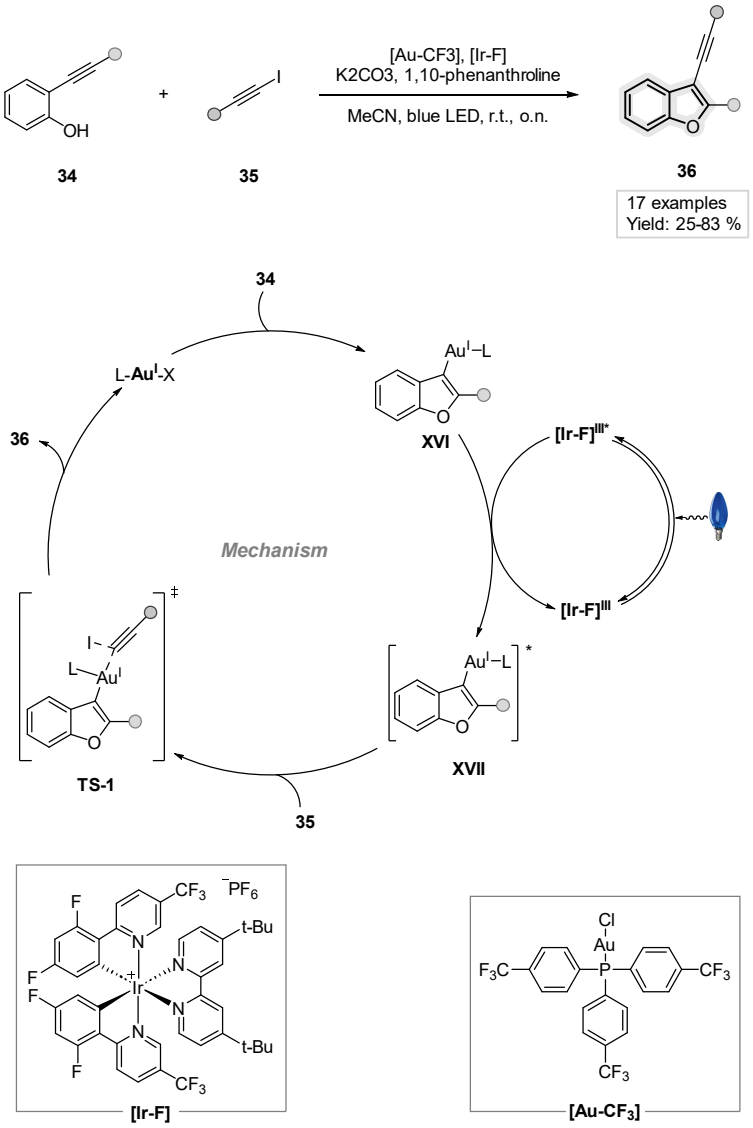




Scheme 13. Gold(I)-catalyzed synthesis of 3-bromo-2-silylbenzo[*b*]furans.

In 2019, Fensterbank and his colleagues disclosed a dual-catalysis transformation, involving the electrophilic activation of an alkyne with a gold(I)-catalyst and a Csp^2–Csp cross-coupling reaction employing an iridium photosensitizer (Scheme 14).[48] This methodology also relies on the use of 2-ethynylphenol derivatives **34** as benzo[*b*]furan ring precursors and aryl iodoethynyl derivatives **35** as cross-coupling partners. On the other hand, they used gold and iridium in catalytic amounts and K_2CO_3 and phenantroline as additives.

Blue LED irradiation afforded the best yields of the corresponding benzo[*b*]furans. This new approach allowed to take advantage of the reactivity of a vinylgold(I)-intermediate and its functionalization beyond a simple protodeauration,[49] in order to improve the atomic efficiency. The authors proposed a dual mechanism based on a luminescence study and supported by density functional theory calculations. The first step is the gold(I)-promoted 5-*endo-dig O*-cyclization to form the vinyl gold(I)-intermediate **XVI** that undergoes an energy transfer from the triplet complex of iridium, forming a triplet vinyl gold(I) **XVII**. Then, the product is formed by oxidative addition of **35** through transition state **TS-1**. Finally, a reductive elimination generated the final product **36** and the gold(I) species. Furthermore, this methodology could be applied to other vinyl and aryl gold(I).

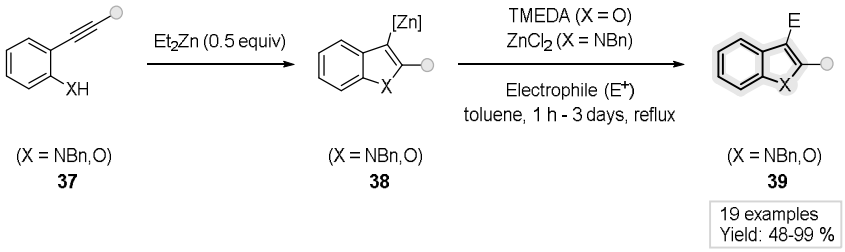


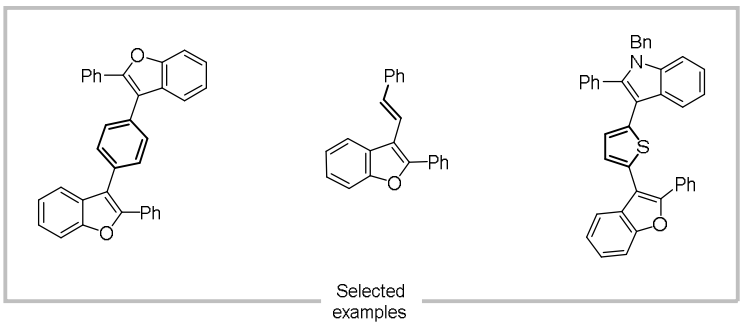
Scheme 14. Tandem gold(I)-catalyzed intramolecular hydroalkoxylation/Ir(III)-catalyzed photoredox cross-coupling.

The benzo[*b*]furans formed were valuable scaffolds for further elaboration, two main different reactions were carried out in the alkyne such as stereocomplementary *Z*/*E* hydrogenation employing palladium(0)-catalyst obtaining the corresponding alkenes,[50,51] and Huisgen type reaction employing sodium azide obtaining the corresponding triazole.[52]

3. Heterocyclization employing other transition metal-catalysis

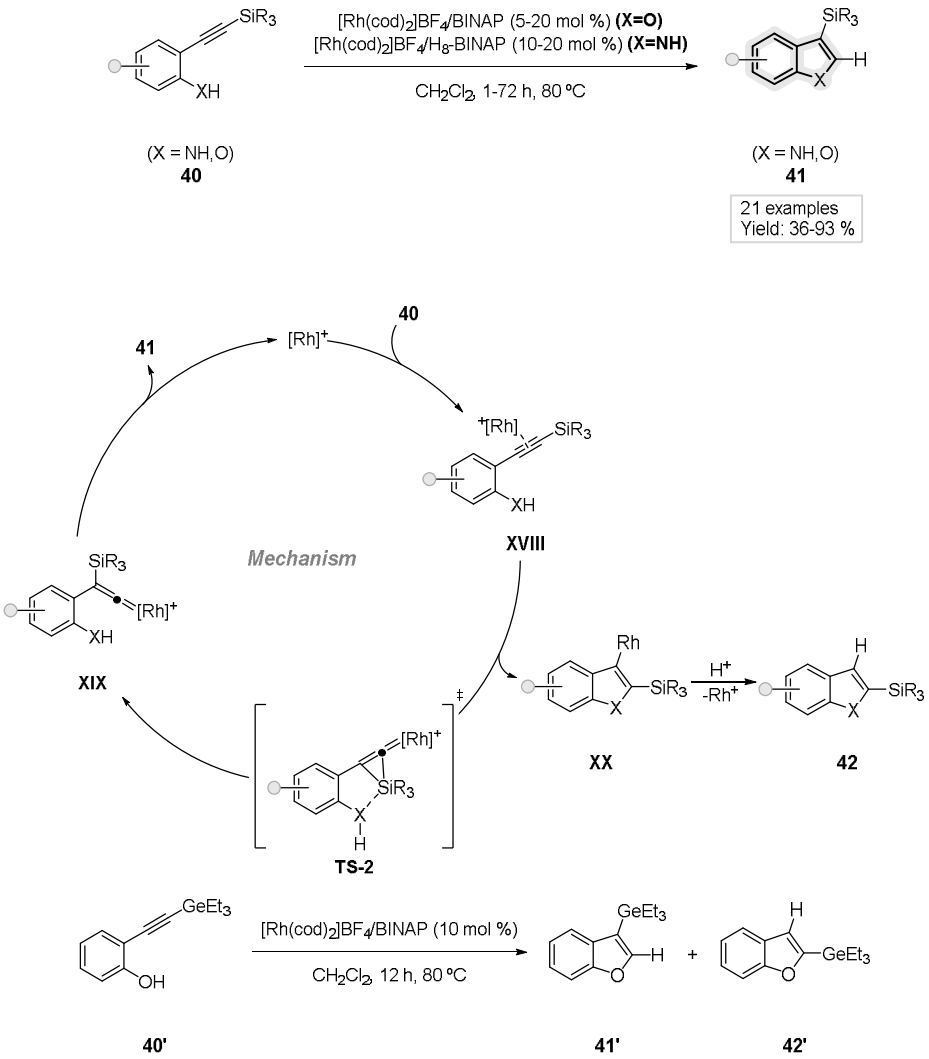
In 2006, Nakamura and co-workers reported the cyclization of a 2-alkynyl aromatic compound **37** into metallobenzo[*b*]furan **38**.[53] These substrates delivered the corresponding heteroles **39** after reaction with an electrophilic species (Scheme 15). Despite this chemistry was already known for the synthesis of several 3-metallobenzo[*b*]furan intermediates employing copper[54] or palladium,[55] the cited approach allowed access to cyclization products in high yields, affording a set of new benzo[*b*]furan and indole conjugated systems to be smoothly assembled. The process started with treatment of the corresponding 2-alkynyl phenols with 0.5 equivalents of Et_2Zn. The reaction mixture was then heated in the presence of a catalytic amount of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in refluxing toluene, allowing deprotonation of the phenols and the subsequent cyclization into 2-substituted benzo[*b*]furans **39**. The resulting compounds were isolated with excellent yields after quenching with aqueous ammonium chloride (with H playing the role of the electrophile, and TMEDA as the species to activate the aggregates originated by O-Zn interactions). The reaction was also tested on *O*-silylated phenol derivatives. However, no reaction was observed, attributed to the silicon retarding the process. Furthermore, a *N*-benzyl-protected alkynyl aniline was also used. In this case, deprotonation was carried out with butyllithium instead of TMEDA. Finally, the use of the zinc intermediate was explored by establishing the 2,3-disubstituted benzoheteroles as a key structural motif. Various palladium-catalyzed coupling reactions using several aryl and alkenyl halides and the corresponding zinc intermediates were considered, affording complex compounds inaccessible by previously known methods. The obtained products ranged from benzo[*b*]furan rings substituted with polyarene moieties (including chiral or sterically hindered ones) to an indole-thiophene-benzo[*b*]furan derivative (achieved by coupling the previously obtained 3-zincioindole intermediate with an iodothiophene reagent).





Scheme 15. Cyclization of 2-ynyl aromatic compounds by zinc(II).

In 2016, Tanaka and co-workers established that a cationic rhodium(I)/BINAP-complex could catalyze the cycloisomerization of 2-silylethynyl phenols and anilines **40**, leading to 3-silylbenzo[*b*]furans and 3-silylindoles **41**, respectively, *via* 1,2-silicon migration, allegedly through rhodium-vinylidene intermediates (Scheme 16).[56] Previously, Tanaka *et al.* also reported a rhodium(I)/BINAP-complex-catalyzed [2+2+2]-cycloaddition of biphenyl-linked diynes with alkynes.[57] However, the use 2-silylethynyl phenol as substrate for the aforementioned transformation led to an unexpected cycloisomerization product involving 1,2-silicon migration as the major product.[58] Hence, the cyloisomerization of the sylilphenol was further studied. After optimization of the reaction conditions, $[Rh(cod)_2]BF_4$ proved as an effective pre-catalyst which was activated by hydrogenation of the cod ligand. The use of BINAP as ligand and BF_4 as counteranion with a 5 mol% catalyst loading at 80ºC delivered the silyletynylphenol in high conversion. The formation of the 2-silylbenzo[*b*]furan isomer was also observed, favored when the use of $[Rh(cod)_2]BF_4$ without hydrogenation was made.



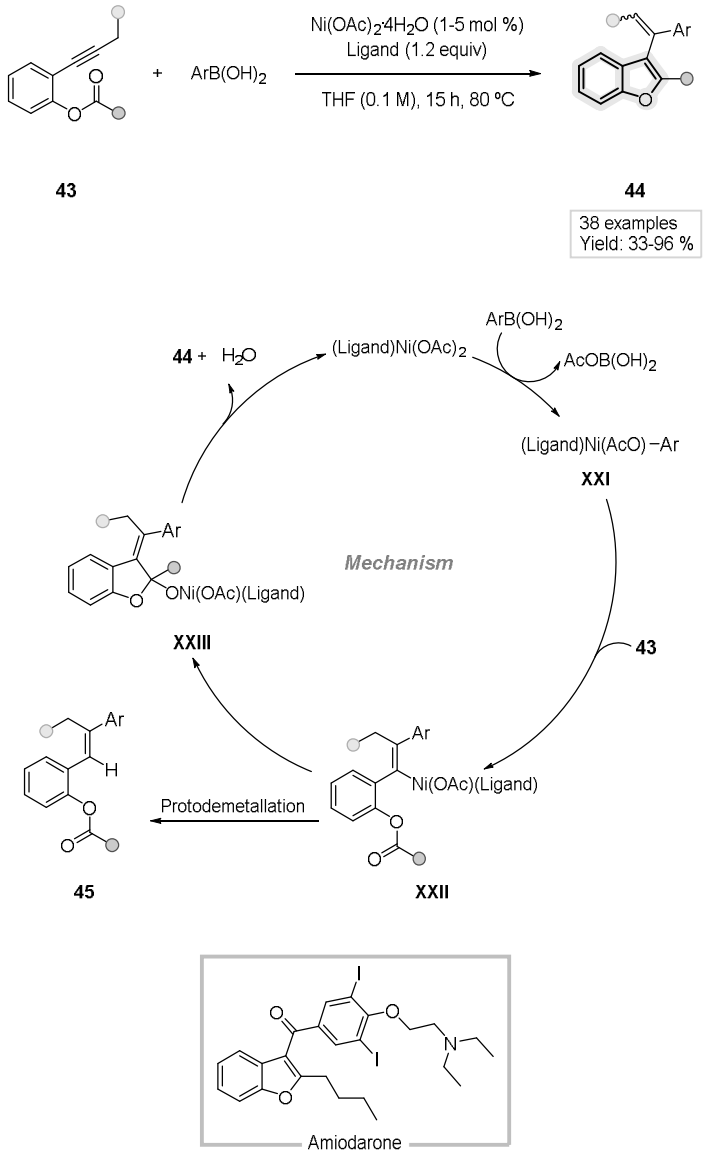
Scheme 16. Cycloisomerization of 2-silylethynyl phenols and anilines catalyzed by rhodium(I).

After the optimal conditions were established, the scope of the reaction was studied affording diverse 3-silylbenzo[*b*]furans derivatives in high conversions. In addition, a germanyl analogue **40'** was tested, providing a higher yield of standard cycloisomerization **42'** than the one resulting from 1,2-germanium migration **41'**. Finally, the ability to promote cycloisomerization in 2-silyletynylanilines was tested. Similar results as those provided by phenols were observed. However, in this case, the migration products offered moderate yields due to the formation of non-migrated byproducts. This issue was overcome by using H_8-BINAP instead of BINAP. Some mechanistic studies were performed confirming that the reaction is an intramolecular process, allowing the proposal of a plausible mechanism. The 2-silylethynyl reagent **40** reacts with cationic rhodium(I) to generate the complex **XVIII** and then evolves to the rhodium-vinylidene **XIX** through the proposed transition state **TS-2**, which is stabilized by the interaction between the oxygen or nitrogen atom and the migrating silicon atom. The subsequent cyclization step affords **42**. On the other hand, the cyclization product without heteroatom-migration **42** can be generated by means of a direct cyclization leading to the alkenyl-rhodium species **XX**, followed by protonation. Moreover, the weaker interaction between the migrating silicon atom and the aniline nitrogen, as well as the more nucleophilic nature of the amino group compared to that of the hydroxy group can explain the yield decrease in the corresponding formation of the 1,2-silicon migration product (Scheme 16).

In 2019, the Maiti group developed an unconventional method to perform the synthesis of 3-akenyl benzo[*b*]furans **44** from 2-alkynylphenols **43** by reversing the polarity of the process (Scheme 17).[59] Therefore, the nucleophilic alcohol group becomes an electrophilic ester, which undergoes nucleophilic attack by the alkenyl metal intermediate generated by aryl metalation of the alkyne moiety **XXII**, delivering an initial cyclization intermediate **XXIII**. Subsequent dehydration achieves several 3-alkenyl benzo[*b*]furan products **44**. Furthermore, the substituent on the 2-position of the benzo[*b*]furan can be effectively selected by modifying the ester moiety in the substrate in order to access specific products. The proposed mechanism is based on a catalytic cycle in which the nickel-complex undergoes transmetalation with the boronic acid affording arylnickel intermediate **XXI**. Such intermediate undergoes a regioselective *syn* addition across the alkyne towards alkenylnickel species **XXII**. Dehydrocyclization of **XXII** with phenol ester across **XXIII** leads to the desired product **44** along with regeneration of the nickel-complex. Besides, protodemetallation of **XXII** explains the formation of the non-cyclic hydroarylated side-product **45**. This methodology was also tested by studying the variation in the alkyne side chain. In this case, the formation of *E/Z* mixtures was observed when a long alkyl chain was used as substituent in the alkynyl moiety. NOE experiments showed that the *E* isomer was the major product. In addition, the process was successfully applied to the synthesis of the anti-arrhythmic drug amiodarone.[60]

In 2019, Arisawa and co-workers developed a C−O bond cleavage of 3-phenoxy acrylic acid derivatives **46**, followed by intramolecular C−O bond formation with alkynes affording 2,3-disubstituted benzo[*b*]furans **47**, present in numerous bioactive natural products and pharmaceuticals (Scheme 18).[61,62] Interestingly, all atoms contained in the starting material were maintained in the final product. Optimization of the reaction conditions showed that the use of $Ni(cod)_2$ with terpyridine as ligand in DMF allowed access to several 2,3-disubstituted benzo[*b*]furans with different substituents in the alkyne and alkene moieties as well as in the aromatic ring, with the advantageous presence of a silyl group in position 2. Derivatization of some of the obtained products was possible by means of Hiyama cross-coupling,[63] reductions, or alkylations across the different substituent positions. Moreover, DFT calculations were performed in order to propose a reaction mechanism. Initially, substrate **46** is proposed to react with the nickel-complex to form intermediate **XXIV** *via* oxidative cyclization. Subsequently, a thermodynamically favored *β*-oxygen elimination occurs to deliver intermediate **XXV**. Finally, reductive elimination of the nickel-species affords product **47** and regenerates the catalyst.

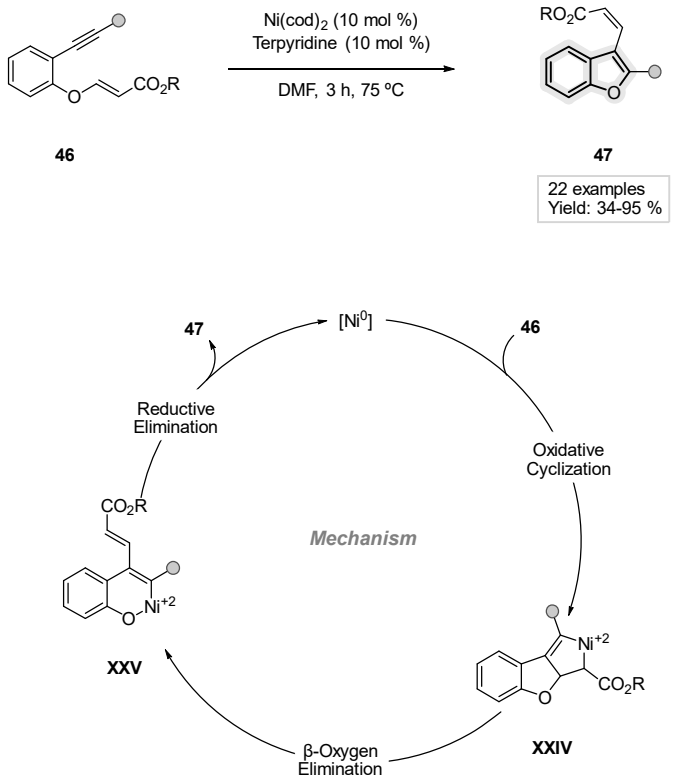
In 2011, Toste and co-workers described a gold-catalyzed cycloisomerization/Suzuki cross-coupling tandem sequence combining homogeneous gold- and palladium-catalysis using arylethynyl *N*-methyliminodiacetic acid (MIDA) boronates **48** as substrates for the preparation of substituted benzo[*b*]furan and indole skeletons **49** (Scheme 19).[64] The main objective was to achieve a high-yielding gold-catalyzed cycloisomerization clean enough to avoid further purifications and hence, be able to perform the subsequent Suzuki cross-coupling step involving the MIDA boronate moiety **XXVI** and aryl halides taking advantage of Burke's MIDA boronate chemistry.



Scheme 17. Catalytic aryl nickelation of alkynes: a versatile synthetic entry to benzo[*b*]furans.

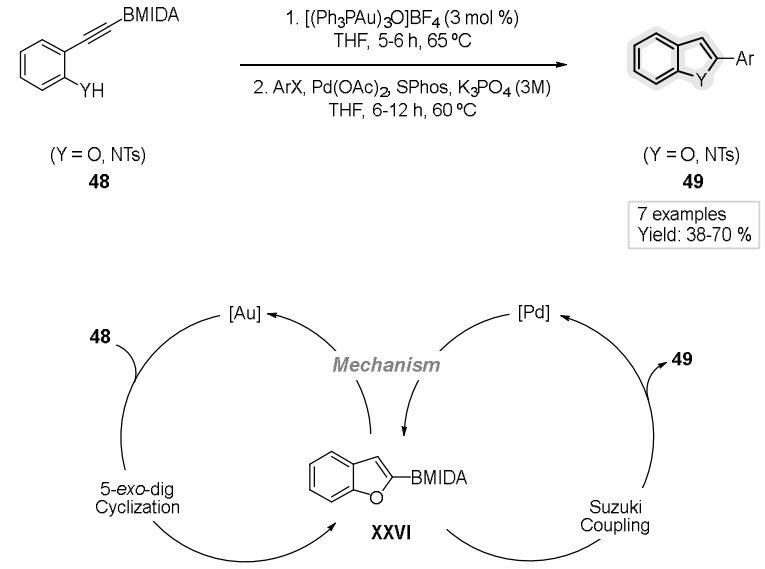
To accomplish this purpose, several optimization processes were required. On the one hand, regarding the electron-poor alkyne in the substrate due to the inductive effect of the MIDA boronate moiety, more electrophilic gold catalysts showed better performances and, after studying the effect of the solvent, the optimal conditions were established as follows, 3 mol% of $[(Ph_3PAu)_3O]BF_4$ as the catalyst in THF at 65 ºC. By assembling electron-withdrawing substituents on the phosphine ligands, the catalyst was made more electrophilic, and some yields were improved (with regard to the formation of benzo[*b*]furans and indoles); however, the formation of some other products suffered from catalyst decomposition (in the context of the preparation of phthalans from benzyl alcohols). On the other hand, a one-pot process including a subsequent

Suzuki cross-coupling was evaluated and carried out by adding the required reagents (aryl halide and base) and catalyst [$Pd(OAc)_2$ and SPhos as ligand] at the end of the first reaction, leading to yields above 50% (over two steps) in the synthesis of several benzo[*b*]furans and *N*-protected indoles. The mechanism of the overall process is schematically shown in Scheme 19.

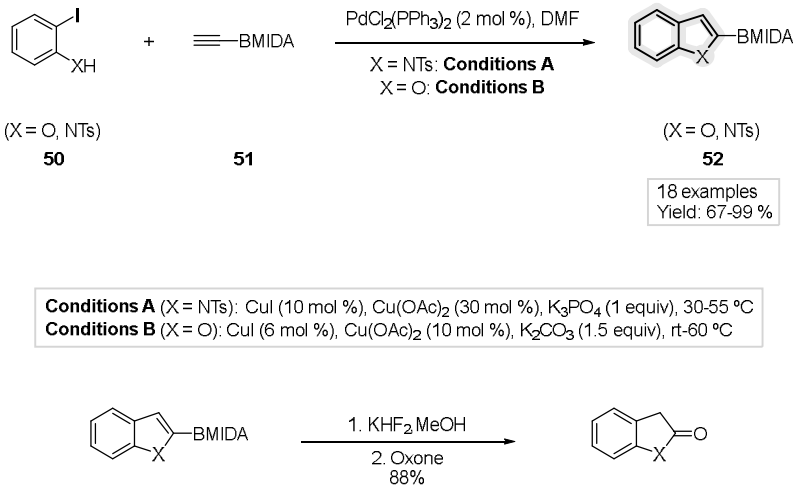


Scheme 18. Ni(0)-catalyzed cycloisomerization of phenoxy acrylic acid derivatives.

In 2016, Watson and co-workers developed a one-pot cascade for the synthesis of 2-borylated 6,5-bicyclic heterocycles using a Cu(I)/Pd(0)/Cu(II) cascade catalysis, complementary to the one described above. In Toste's report, the cycloisomerization takes place first followed by a palladium-catalyzed cross-coupling reaction (Suzuki) of the BMIDA moiety. Now, a palladium/copper-catalyzed cross-coupling reaction (Sonogashira) affords the substrate for a subsequent cycloisomerization. This method enables the synthesis of 2-boryl indoles and benzo[*b*]furans **52**, using 2-haloanilines or 2-halophenols **50** and ethynyl BMIDA **51** (Scheme 20).[65] To reach this cascade process, several reactions of *N*-tosyl-2-iodoaniline and ethynyl BMIDA were performed under different reaction conditions. Various proportions of CuI (to increase the conversion) and $Cu(OAc)_2$ (to facilitate the 5-*endo-dig* cyclization and to avoid Glaser-Hay homocoupling by-products) were analyzed. The use of Et_3N as base and the temperature balance were also tested to avoid premature hydrolysis of the generated heterocyclic BMIDA residue and subsequent protodeboronation of the resulting heterocyclic boronic acid. An analog process was also carried out for the formation of benzo[*b*]furan products from 2-iodophenol. In this case, the authors found that a proper modification of the base to K_2CO_3 avoids the Glaser-Hay coupling issue.[66] With the optimal conditions, the scope of the reaction was established affording several benzo[*b*]furans and indoles derivatives with a wide range of substituents. Moreover, the BMIDA moiety was also effectively modified by oxidation[67] with oxone® delivering oxoindoles and benzo[*b*]furanones **53** which are valuable scaffolds in kinase drug discovery.[68]



Scheme 19. Tandem cycloisomerization/Suzuki coupling of arylethynyl MIDA boronates.



Scheme 20. Cu(I)/Pd(0)/Cu(II)-cascade-catalysis of 2-iodoaniline/phenols.

4. Conclusions

The straightforward availability of 2-ethynylphenol derivatives from 2-halophenol starting materials, makes them suited substrates for the preparation of benzo[*b*]furan derivatives. The ability of gold-complexes and other carbophilic Lewis acids to activate alkynes towards nucleophilic addition has dominated this synthetic strategy since its introduction by Yamamoto and Fürstner in 2005. In addition, several tandem processes have allowed the subsequent functionalization of a specific position of the benzo[*b*]furan system, affording highly functionalized derivatives.

Acknowledgements

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