

Review

Catalytic Hydrofunctionalization Reactions of 1,3-Diynes

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Abstract: Metal-catalyzed hydrofunctionalization reactions of alkynes, i.e., the addition of Y–H units (Y = heteroatom or carbon) across the carbon–carbon triple bond, have attracted enormous attention for decades since they allow the straightforward and atom-economic access to a wide variety of functionalized olefins and, in its intramolecular version, to relevant heterocyclic and carbocyclic compounds. Despite conjugated 1,3-diynes being considered key building blocks in synthetic organic chemistry, this particular class of alkynes has been much less employed in hydrofunctionalization reactions when compared to terminal or internal monoynes. The presence of two C≡C bonds in conjugated 1,3-diynes adds to the classical regio- and stereocontrol issues associated with the alkyne hydrofunctionalization processes' other problems, such as the possibility to undergo 1,2-, 3,4-, or 1,4-monoadditions as well as double addition reactions, thus increasing the number of potential products that can be formed. In this review article, metal-catalyzed hydrofunctionalization reactions of these challenging substrates are comprehensively discussed.

Keywords: 1,3-diynes; butadiynes; hydrofunctionalization; addition reactions; metal catalysis



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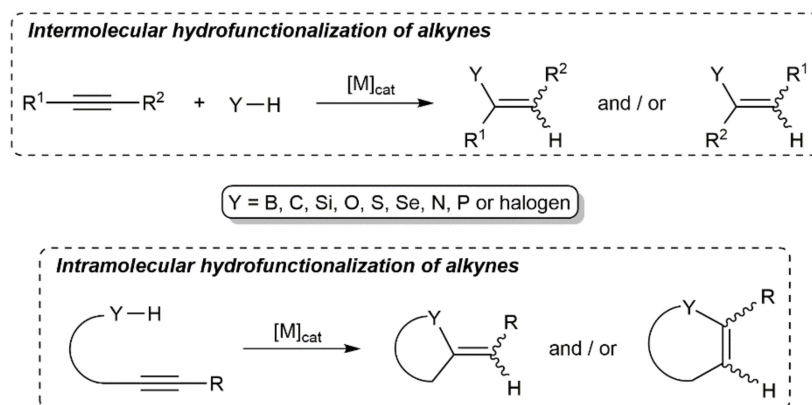
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1. Introduction

Alkynes are a pivotal class of compounds in organic chemistry and their electrophilic activation by transition metals has become a mainstay in the toolbox of synthetic chemists, biochemists, and materials scientists [1–3]. In this context, the metal-catalyzed hydrofunctionalization of alkynes, i.e., the addition of Y–H units (Y = heteroatom- or carbon-centered nucleophile) across the C≡C bond, has emerged in the last decades as one of the most powerful tools to access functionalized olefins in an atom-economical manner, its intramolecular version allowing also the rapid assembly of a wide range of heterocyclic and carbocyclic compounds (see Scheme 1) [4–9].



Scheme 1. Metal-catalyzed inter- and intramolecular hydrofunctionalization of alkynes.

A wide variety of transition metal compounds (complexes, salts, or nanoparticles) are known to promote the addition of Y–H units to alkynes by π -activation of C≡C bond,

the regio- and stereoselectivity (*syn*- or *anti*-type addition) of the process being strongly dependent on the nature of the reactants, catalyst, and reaction conditions employed, and a priori difficult to predict, particularly in the case of non-symmetrically substituted alkynes (up to four isomeric products can be potentially formed) [4–9].

On the other hand, although their unique structure, relative stability, and unsaturated nature have turned conjugated 1,3-diyne into useful and versatile building blocks in organic synthesis and materials science [10–15], this particular class of alkynes has been much less employed in hydrofunctionalization reactions when compared to terminal or internal monoynes. Obviously, the hydrofunctionalization of 1,3-diyne having two triple bonds and four active positions (see Figure 1) is much more challenging, since they can undergo 1,2-, 3,4-, or 1,4-monoadditions, as well as double Y–H addition processes, thus expanding the range of regioisomeric and stereoisomeric products that can be formed.

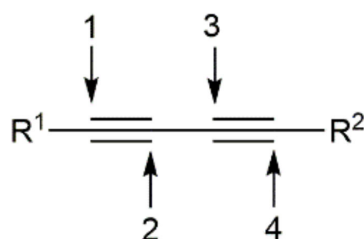
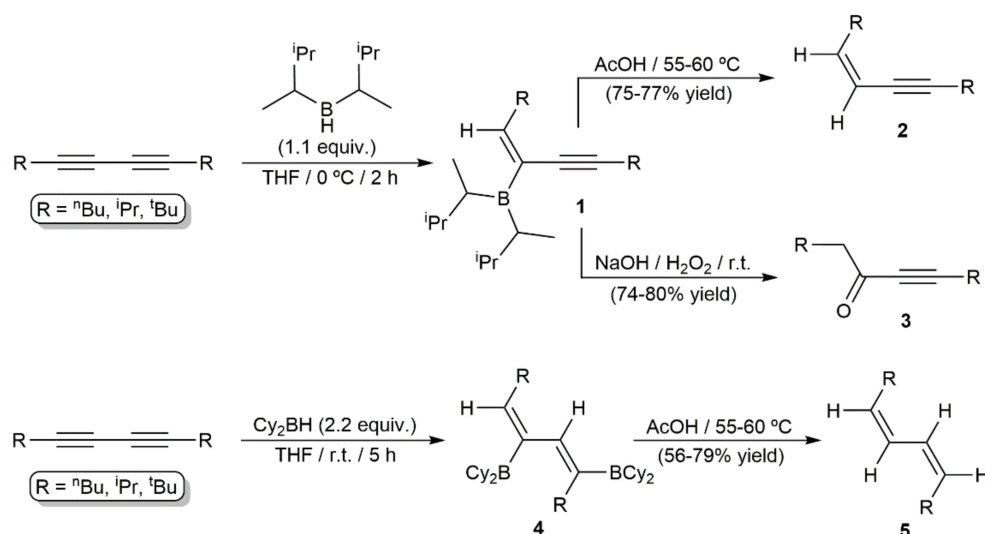


Figure 1. The four reactive positions of conjugated 1,3-diyne.

The aim of the present review article is to provide a comprehensive overview on the metal-catalyzed hydrofunctionalization of conjugated 1,3-diyne. Although reactions not involving metal-based catalysts are considered out of the scope of this review, some of them will be mentioned in order to give the reader a complete prospect of the current state of the art.

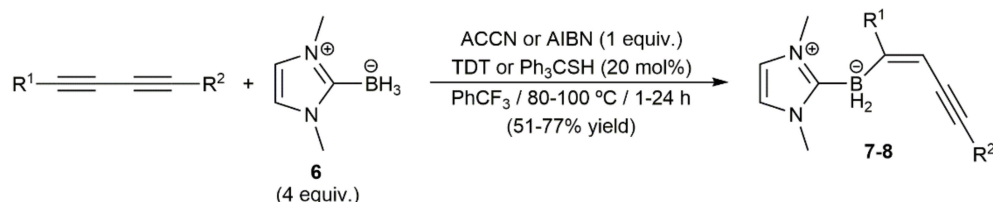
2. Hydroboration Processes

Organoboron compounds are important building blocks in organic chemistry because of their low toxicity, stability, and unique reactivity in various synthetic processes, as, for example, in the well-known Suzuki–Miyaura-type cross-couplings or the Petasis borono–Mannich reactions. In this context, the hydroboration of alkynes, including both metal-free and transition-metal-catalyzed reactions, has been widely studied in the last decades, as it provides a simple and straightforward access to valuable vinylborane synthetic intermediate compounds [16]. However, as a special class of alkynes, 1,3-diyne have been barely investigated in hydroboration processes. The first example quoted in the literature was described by Zweifel and Polston in 1970, who described the metal-free monohydroboration of symmetrically alkyl-substituted 1,3-diyne with disiamylborane [17]. The reactions led to the functionalized enynes **1** resulting from a *syn*-type addition of the B–H bond to one of the C≡C units, with the boron atom attacking the less sterically hindered internal position of the diyne system (Scheme 2). Compounds **1** were not isolated and transformed immediately into the corresponding *cis*-1,3-enynes **2** or α,β -acetylenic ketones **3** upon protonolysis with acetic acid or oxidation with alkaline hydrogen peroxide, respectively. In the same work, dihydroboration of the same alkyl-substituted diynes was successfully achieved employing a twofold excess of dicyclohexylborane, thus allowing the stereoselective access to the *cis,cis*-dienes **5** by protonolysis of the organoborane intermediates **4** (see Scheme 2). Monohydroboration of non-symmetrically alkyl-substituted 1,3-diyne was also attempted by the authors, but no discrimination between the triple bonds was observed [17]. Only when diynes of type Alk–C≡C–C≡C–SiR₃ substituted with a bulky trialkylsilyl group (SiMe₂^tBu or SiMe₂(CMe₂ⁿPr)) were employed as substrates, hydroboration of the less sterically hindered alkyl-substituted C≡C bond was preferentially observed [18].



Scheme 2. Mono- and dihydroboration reactions of symmetrically alkyl-substituted 1,3-diyne.

Following previous studies on the *anti*-hydroboration of internal alkynes with *N*-heterocyclic carbene (NHC) boranes under radical conditions [19], Curran, Taniguchi, and colleagues reported very recently the highly regio- and stereoselective access to the NHC-(*E*)-enynylboranates **7** and **8** by monohydroboration of symmetrical and unsymmetrical 1,3-diyne, respectively, with 1,3-dimethylimidazol-2-ylidene borane **6** (Scheme 3) [20]. In the reactions, an azo compound, i.e., ACCN (1,1'-azobis(cyclohexane-1-carbonitrile)) or AIBN (2,2'-azobis(2-methylpropanitrile)), was employed as the free radical initiator, and a thiol, i.e., TDT (*tert*-dodecanethiol) or Ph₃CSH, as a polarity-reversal catalyst.



Compounds 7:

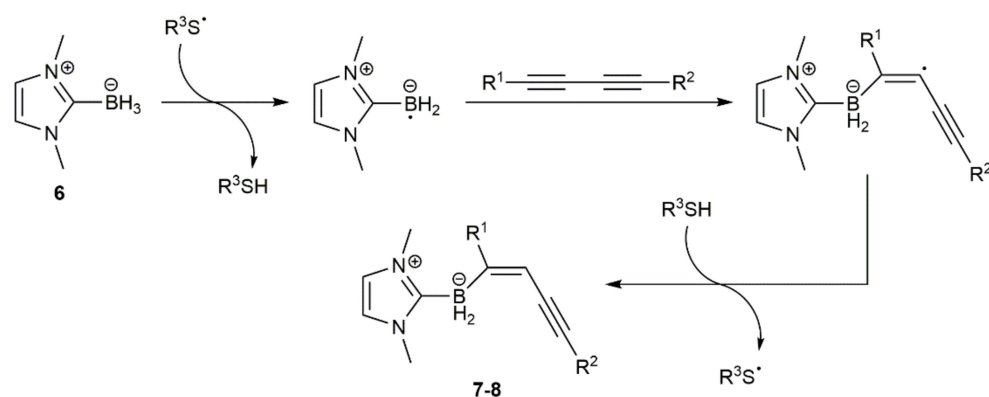
R¹ = R² = Me, ⁿPr, ^oPr, *c*-C₅H₉, Cy, CH₂Bn, CH₂NHBoc, CH₂OSi^tBuMe₂, CH₂CH₂OSi^tBuMe₂, CH₂(CH₂)₂CH₂Cl

Compounds 8:

R¹ = *n*-C₆H₁₃, CH₂OSi^tBuMe₂, CH₂CH₂OSi^tBuMe₂; R² = SiMe₃ or Si^tPr₃

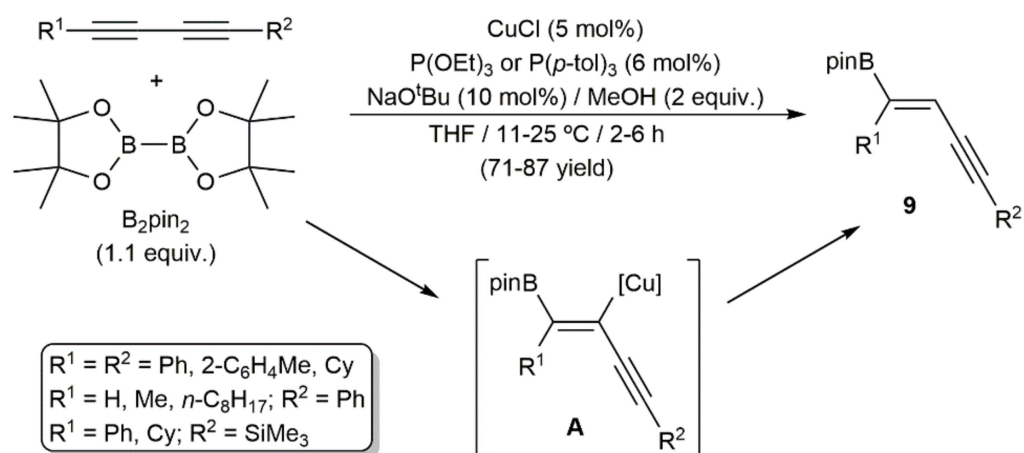
Scheme 3. Radical monohydroboration of 1,3-diyne with an *N*-heterocyclic carbene borane.

As shown in Scheme 4, a thiyl radical formed from the thiol by thermal decomposition of ACCN or AIBN initiates the reaction by abstracting a hydrogen atom from the NHC-borane **6** to generate an NHC-boryl radical, which adds to the C≡C bond of the diyne. The chemoselectivity observed in the reactions of the unsymmetrical silyl-substituted 1,3-diyne was rationalized in terms of the steric hindrance associated to the bulky SiR₃ groups. The usefulness in organic synthesis of the NHC-(*E*)-enynylboranates **7–8** was additionally demonstrated by the authors, who successfully conducted palladium-catalyzed Suzuki–Miyaura C–C coupling reactions with some representatives [20].



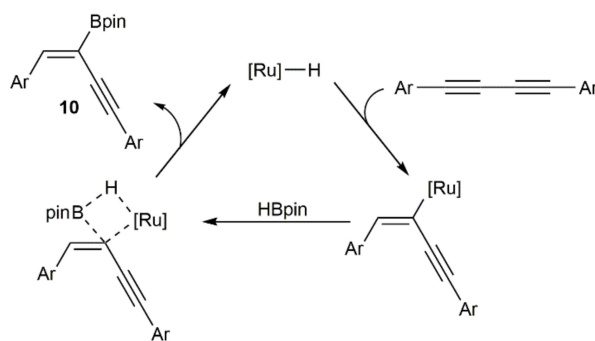
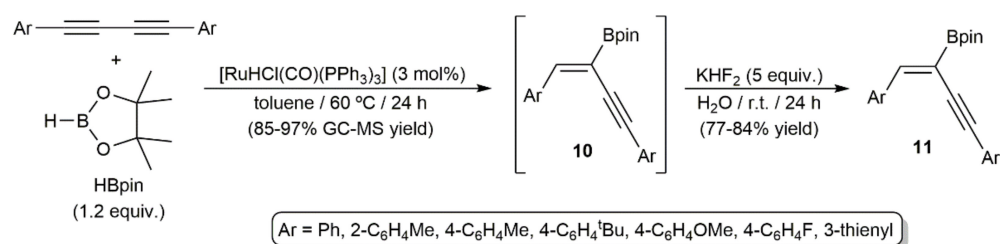
Scheme 4. Proposed mechanism for the formation of the enynylboranates 7–8.

Regarding the use of metal-based catalysts, Yun and colleagues reported in 2015 the formal copper(I)-catalyzed monohydroboration of different symmetrical and unsymmetrical 1,3-diynes with bis(pinacolato)diboron (B_2pin_2), which allowed the regio- and stereoselective access to 1-boryl-substituted 1,3-enynes **9** (Scheme 5) [21]. According to the authors, the process proceeds through the initial borylcupration of the $C\equiv C$ bond of the diynes by an in situ generated copper–boryl complex, followed by protonolysis of the metallated intermediate **A** by the methanol present in the medium.



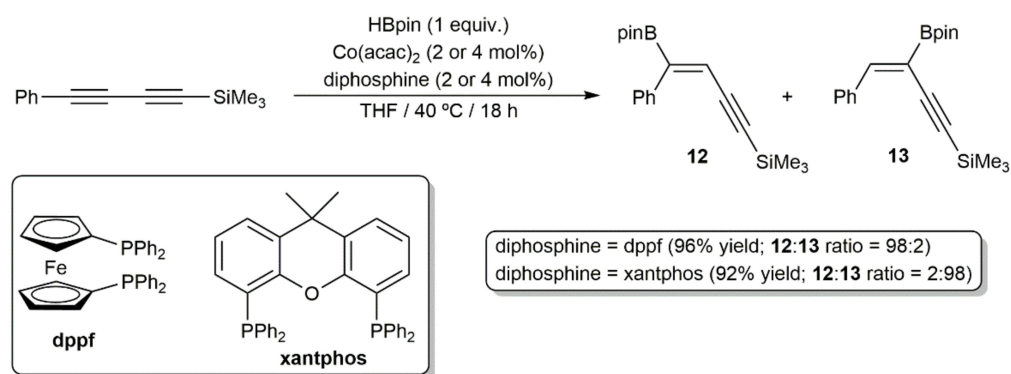
Scheme 5. Copper-catalyzed hydroboration of 1,3-diynes.

Hydroboration of a series of symmetrical 1,4-diaryl-substituted 1,3-diynes with pinacolborane (HBpin) was more recently described by Walkowiak and colleagues employing the ruthenium(II) hydride complex $[RuHCl(CO)(PPh_3)_3]$ as a catalyst (Scheme 6) [22]. The reactions, carried out in toluene at 60 °C, led to the 2-boryl-substituted 1,3-enynes **10**, which were rapidly transformed into the more stable trifluoroborate salts **11**, with complete regio- and stereocontrol (*syn*-addition). This process nicely complements the previous one, since the borane attaches now to the less hindered internal carbon atoms of the diyne. Nonetheless, it should be noted that its scope is restricted to 1,4-diaryl-substituted 1,3-diynes, with the use of alkyl- or silyl-substituted ones leading to mixtures of the corresponding mono- and dihydroborated products, along with other unidentified species. Regarding the mechanism, a reaction pathway involving the initial insertion of the diyne into the $Ru-H$ bond to generate a ruthenium(II)-enynyl intermediate, which subsequently reacts with pinacolborane through a σ -bond metathesis process, was proposed by the authors.



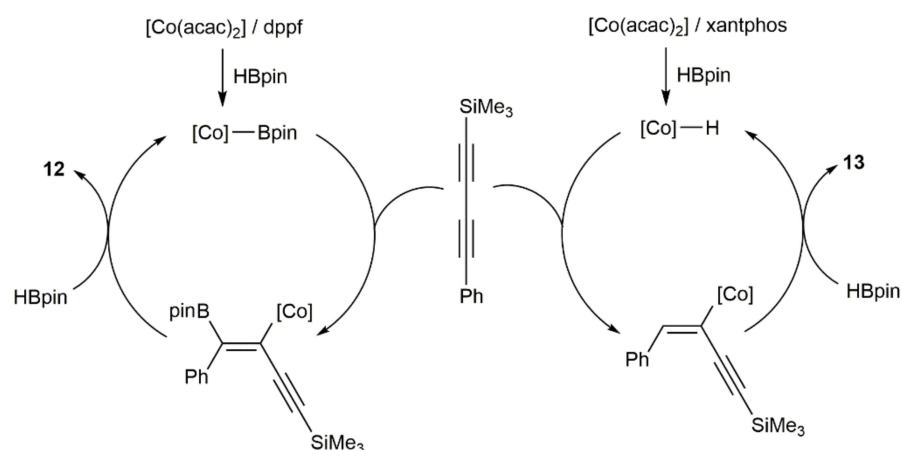
Scheme 6. Ruthenium-catalyzed hydroboration of 1,4-diaryl-substituted 1,3-diyne.

Finally, it merits to be particularly highlighted the work reported by Ge and colleagues, who were able to develop a regio-divergent stereoselective *syn*-monohydroboration protocol of symmetrical and unsymmetrical 1,3-diyne with HBpin, catalyzed by the acetylacetonate Co(II) complex Co(acac)₂ in combination with a diphosphine ligand (dppf or xantphos) [23]. Thus, as shown in the example given in Scheme 7, while the use of the ferrocenyl-diphosphine dppf led to the major formation of the enynylborane product **12** with boron addition to the external carbon of the 1,3-diyne unit, an opposite regioselectivity was observed when xantphos was employed as the auxiliary ligand (product **13**). The scope of this regio-divergent process was very high (more than 40 enynylboranes were synthesized), showed a good functional group compatibility, and could be performed in gram-scale.



Scheme 7. Cobalt-catalyzed ligand-controlled regio-divergent *syn*-hydroboration of a 1,3-diyne.

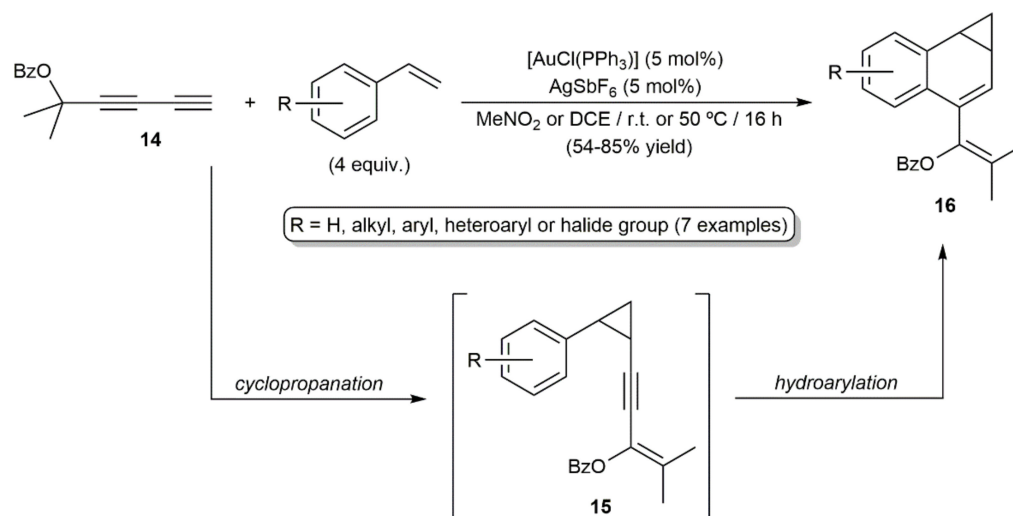
Mechanistic investigations suggested that the hydroboration reactions catalyzed by the Co(acac)₂/dppf system proceed through a cobalt-boryl intermediate, while those involving the Co(acac)₂/xantphos one through a cobalt-hydride intermediate (see Scheme 8) [23].



Scheme 8. Proposed mechanisms for the cobalt-catalyzed hydroboration of $\text{PhC}\equiv\text{CC}\equiv\text{CSiMe}_3$.

3. Hydroarylation and Hydroalkylation Processes

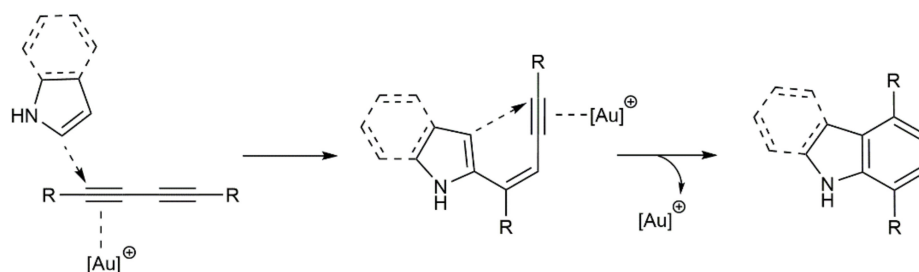
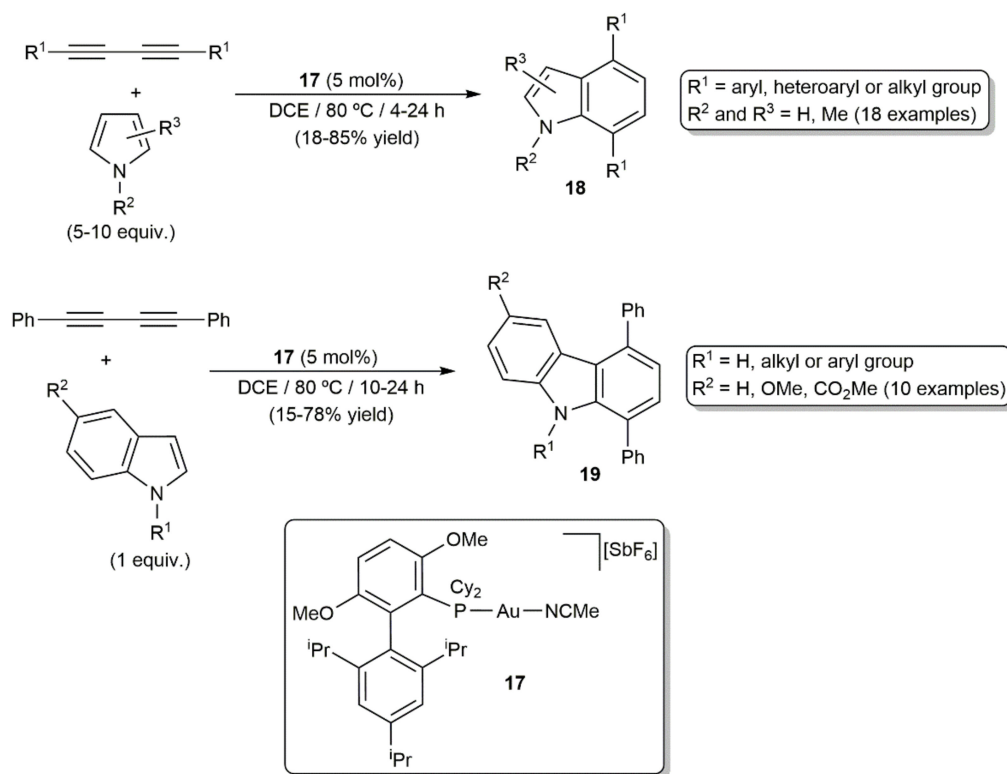
Transition-metal-catalyzed hydroarylation reactions of alkynes with substituted aromatic and heteroaromatic compounds allow the rapid construction of complex molecules from simple precursors without the need for prefunctionalization steps [24–26]. Involvement of 1,3-diynes in such processes was documented for the first time by Toste and colleagues in 2006, with the gold(I)-catalyzed [4+3] annulation reactions of the ester containing diyne **14** with styrenes depicted in Scheme 9 [27]. The benzonorcaradienes **16** were generated as the major reaction products through a cyclopropanation/hydroarylation sequence, along with minor amounts of the intermediate enynyl-cyclopropanes **15**.



Scheme 9. Gold(I)-catalyzed [4+3] annulation of the 1,3-diyne **14** with styrene derivatives.

A few years later, Ohno's group reported the coupling of pyrrole derivatives with different 1,3-diynes in the presence of catalytic amounts of the cationic gold(I) complex $[\text{Au}(\text{MeCN})(\text{BrettPhos})][\text{SbF}_6]$ (**17**) (Scheme 10) [28]. The reactions, performed in 1,2-dichloroethane (DCE) at 80 °C, provided access to substituted indoles **18** in moderate to high yields. As shown in Scheme 10, the use of indoles instead of pyrroles as the coupling partners allowed also the direct synthesis of carbazoles **19**. Although symmetrically substituted 1,3-diynes were mainly employed in this study, the reactivity of a couple of unsymmetrical 1,3-diynes towards pyrrole was also explored, the reactions leading to the isomeric mixtures of the corresponding indole products due to the difficulty associated with controlling the regioselectivity of the first hydroarylation step. Indeed, these gold-catalyzed [4+2] cycloaddition reactions involve a stepwise double hydroarylation pathway, with

participation of the pyrrole-C2 and the indole-C3 in the first intermolecular hydroarylation of the diyne, and a 6-*endo-dig* cyclization in the second one. Density functional theory (DFT) calculations have recently corroborated this mechanistic proposal [29].



Scheme 10. Gold(I)-catalyzed synthesis of indoles and carbazoles from 1,3-diyne.

The synthetic utility of the process was fully demonstrated by Ohno and colleagues with the total synthesis of the naturally occurring dictyodendrins B, C, E, and F (see Figure 2), in which the central pyrrolo[2,3-*c*]carbazole cores were generated by intermolecular annulation of a conjugated diyne with a pyrrole derivative [30]. Moreover, of note is the fact that, employing Ohno's protocol, Ungeheuer and Fürstner were able to synthesize the *para*-indolophane **21** by double hydroarylation of the macrocyclic 1,3-diyne **20** with pyrrole (Scheme 11), ratifying again the broad scope and synthetic relevance of the process [31].

Intramolecular double hydroarylation of the 2,4-diyne-1,6-diethers and diamines **22** catalyzed by the in situ generated gold(I) cation $[Au(PPh_3)]^+$ was additionally described by Lee and colleagues, the reactions providing a straightforward access to 4,4'-bi(2*H*-chromene) and bi(2*H*-quinoline) derivatives **23** (Scheme 12) [32]. Combining the gold catalyst with triflic acid allowed also the synthesis of different dioxafuoranthenes **24** from the 2,4-diyne-1,6-diethers by acid-promoted cyclization of the initially generated 4,4'-bi(2*H*-chromenes) **23** [32].

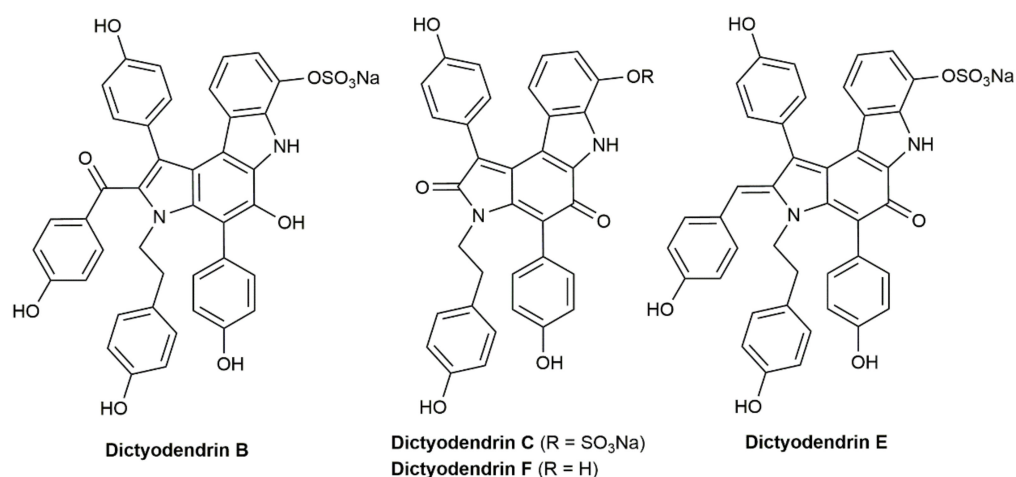
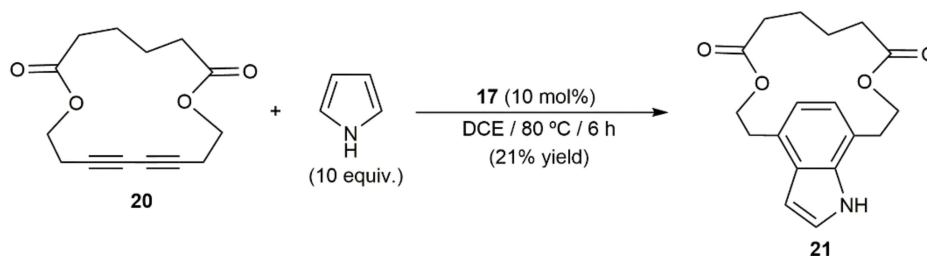
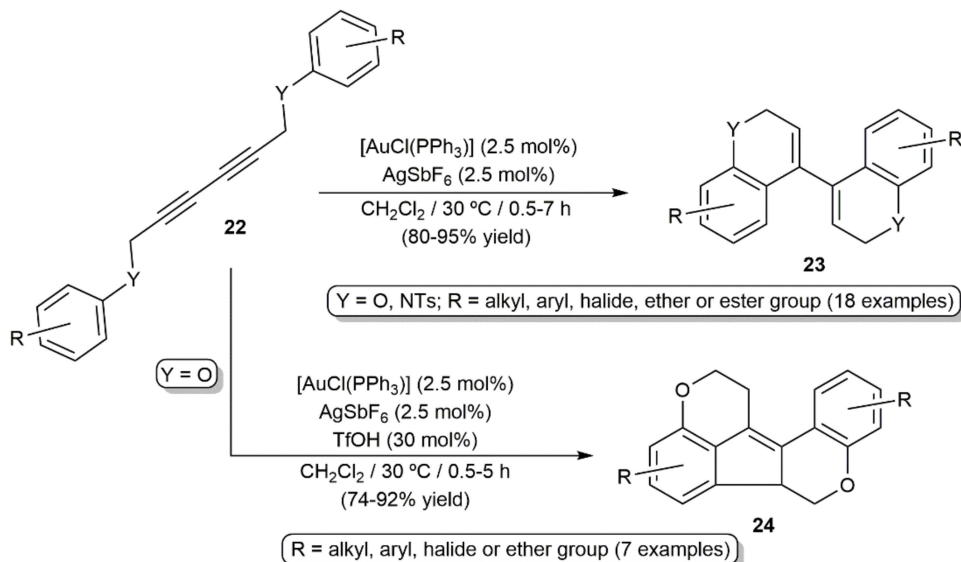


Figure 2. Structures of dictyodendrins B, C, E, and F.



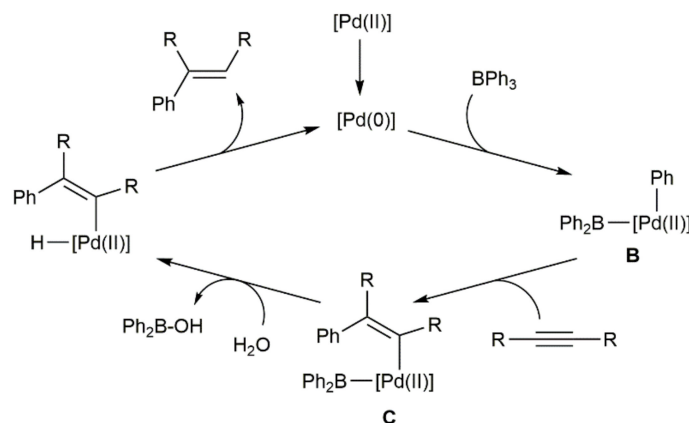
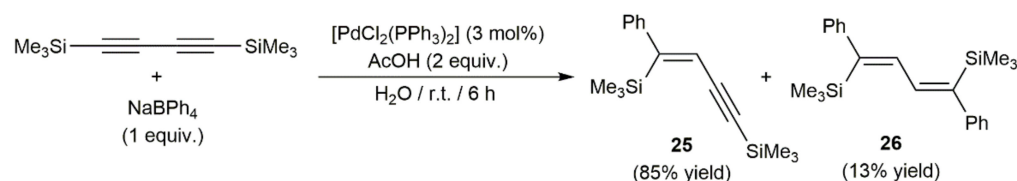
Scheme 11. Gold(I)-catalyzed synthesis of the *para*-indolophane derivative **21**.



Scheme 12. Catalytic synthesis of 4,4'-bi(2*H*-chromenes), bi(2*H*-quinolines), and dioxafuranthenes from 1,3-diynes.

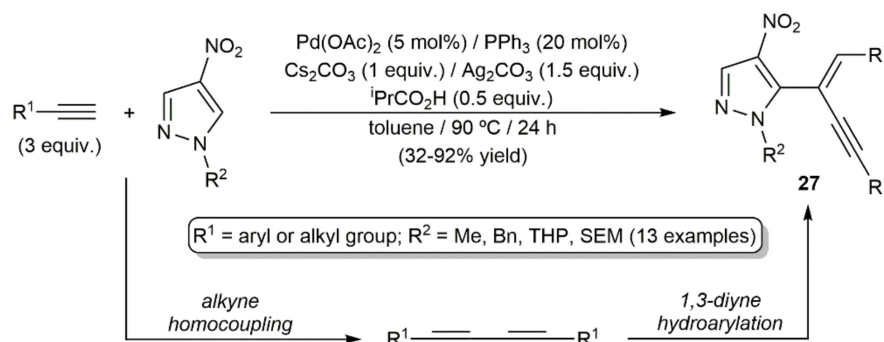
A couple of examples of palladium-catalyzed arylation of 1,3-diynes can be found in the literature. Thus, in the context of a broad study on the hydrophenylation of alkynes with sodium tetraphenylborate mediated by $[\text{PdCl}_2(\text{PPh}_3)_2]$ in water, Zeng and Hua tested the behavior of 1,4-bis(trimethylsilyl)-1,3-butadiyne [33]. As shown in Scheme 13, the conversion of the diyne was almost quantitative, the reaction affording both singly and doubly phenylated products **25** and **26** in 85 and 13% yields, respectively. As exemplified with a simple alkyne, the hydrophenylation process is believed to proceed through the oxidative addition of the B–C bond of BPh_3 , resulting from the reaction of NaBPh_4 with the

acetic acid present in the medium, to in situ generated Pd(0) species to give intermediate **B**, which evolves into **C** by *syn*-insertion of the alkyne. Hydrolysis of **C**, followed by reductive elimination, leads to the final phenylated product.



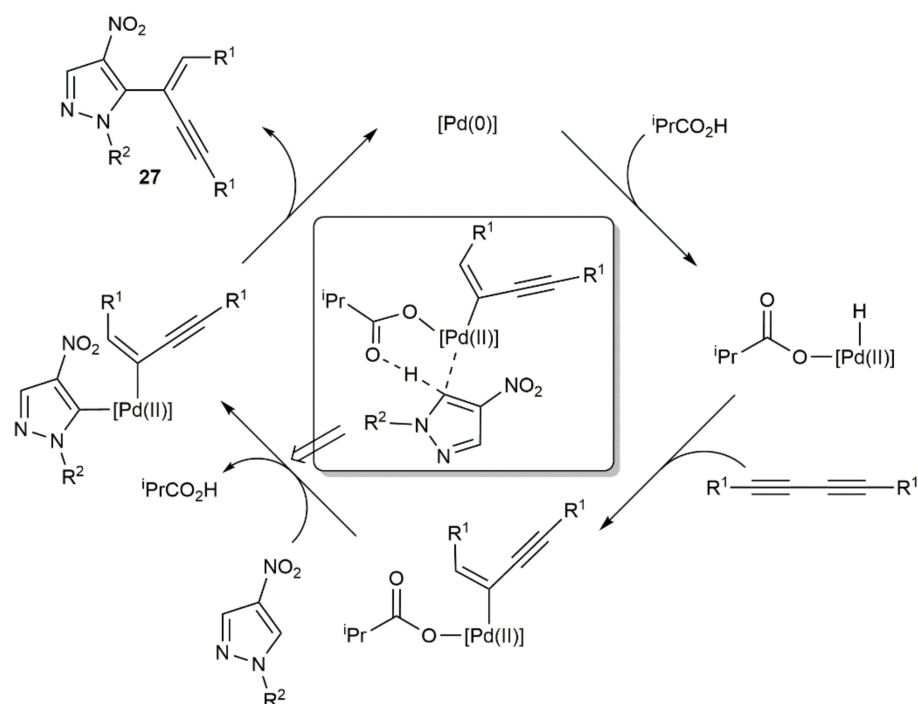
Scheme 13. Palladium-catalyzed hydrophenylation 1,4-bis(trimethylsilyl)buta-1,3-diyne.

The second example, consisting in a tandem homocoupling/hydroarylation of terminal alkynes with nitropyrazoles to afford the functionalized enynes **27**, is depicted in Scheme 14 [34].



Scheme 14. Palladium-catalyzed homocoupling/hydroarylation of terminal alkynes with pyrazoles.

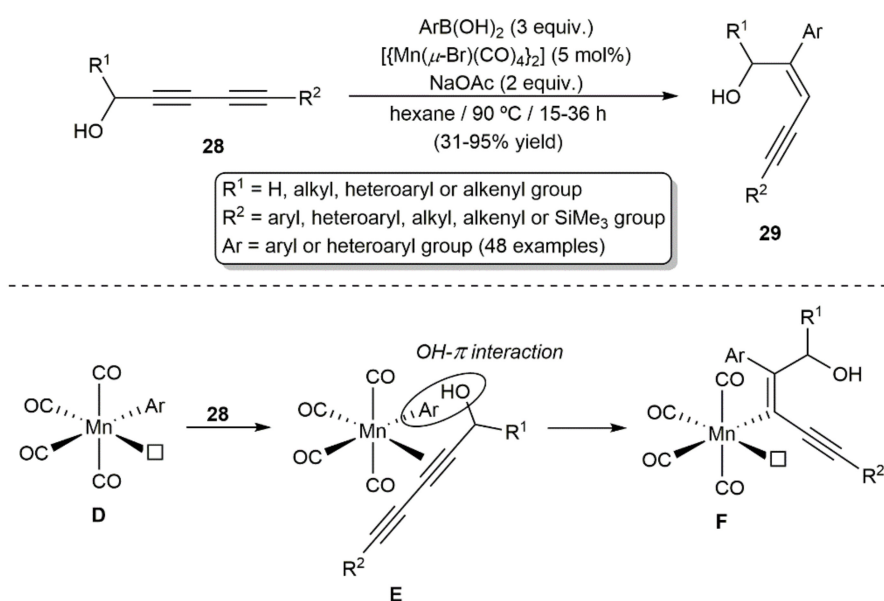
As in the precedent case, the hydroarylation of the 1,3-diyne intermediates proceeded in a *syn* manner, with the internal carbon of the diyne participating now in the formation of the new C–C bond. A reaction pathway for the hydroarylation step involving, again, in situ generated Pd(0) species was proposed by the authors, with the co-ordinated isobutyrate anion assisting the activation of the pyrazole C–H bond (see Scheme 15).



Scheme 15. Proposed mechanism for the hydroarylation step involved in the tandem process leading to enynes **27**.

Hydroarylation reactions of diynes employing less expensive earth-abundant metals can also be found in the literature. For example, Xie and colleagues developed a wide-scope procedure for the regio-, stereo-, and chemoselective synthesis of enynes **29** by hydroarylation of alcohol-substituted diynes **28** with (hetero)aryl boronic acids $\text{ArB}(\text{OH})_2$ catalyzed by the Mn(I) dimer $[\{\text{Mn}(\mu\text{Br})(\text{CO})_4\}_2]$ in conjunction with sodium acetate (Scheme 16) [35,36]. Mechanistic studies suggested the in situ generation in the reaction medium of the mononuclear 16-electron species $[\text{Mn}(\text{OAc})(\text{CO})_4]$ by cleavage of the dimer with NaOAc , which rapidly evolves into the arylated intermediate $[\text{MnAr}(\text{CO})_4]$ (**D**) by transmetalation with the boronic acid. Selective co-ordination of the diyne on the vacant co-ordination site of **D** would lead to intermediate **E**, which would evolve into **F** through a *syn*-1,2-migratory insertion process. A weak π OH–aryl interaction in intermediate **E**, found by DFT calculations, would explain the regioselectivity observed. The final enyne product is liberated from **F** by protodemetalation with water, generated by partial decomposition of the aryl boronic acid employed, with concomitant regeneration of the active species $[\text{Mn}(\text{OAc})(\text{CO})_4]$ by the acetate present in the medium. It is worth mentioning that, despite the involvement of mononuclear Mn(I) species in the reaction, dimer $[\{\text{Mn}(\mu\text{Br})(\text{CO})_4\}_2]$ proved to be a much more efficient catalyst than $[\text{MnBr}(\text{CO})_5]$.

More recently, Glorius and colleagues reported the use of $[\text{MnBr}(\text{CO})_5]$ to promote the regio- and stereoselective alkenylation of different 2-picolyl-substituted arenes and heteroarenes with 1,3-diynes [37]. The process featured a wide functional-group tolerance and single isomers of the 1,3-enyne products were, in most cases, obtained, even when unsymmetrically substituted diynes were employed as substrates (some representative examples are shown in Figure 3). Furthermore, starting from diynes bearing alcohol or protected amine substituents, furans and pyrroles **31** were accessed as single products via catalytic cyclization of the initially formed 1,3-enynes **30** (Scheme 17) [37].



Scheme 16. Mn(I)-catalyzed hydroarylation of 1,3-diyne **28** with arylboronic acids.

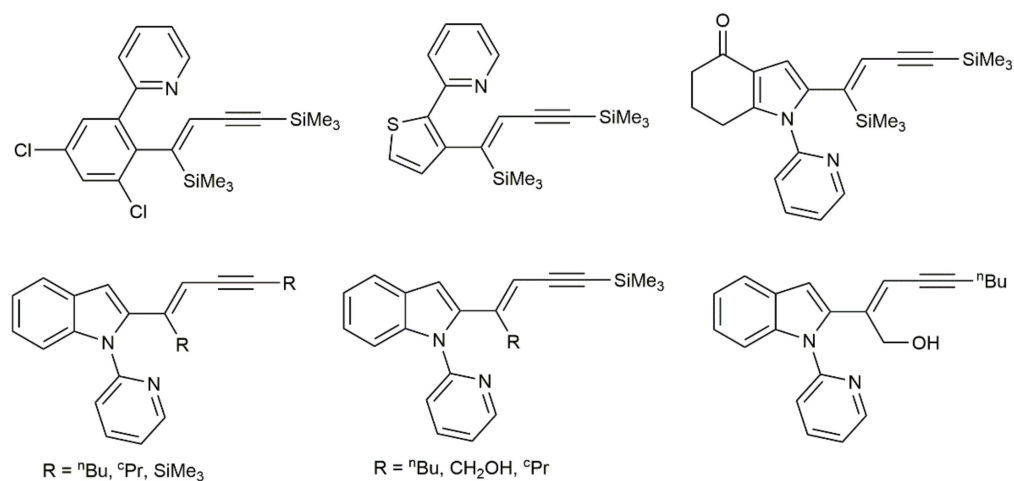
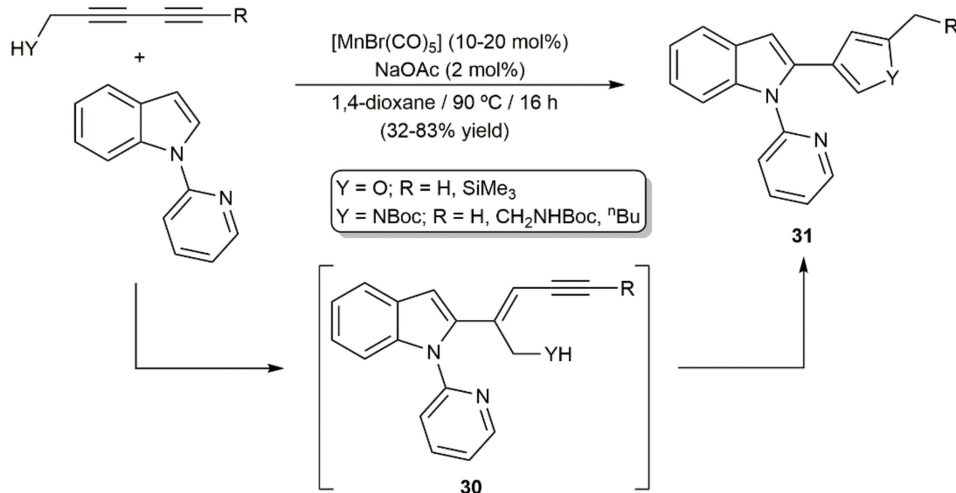
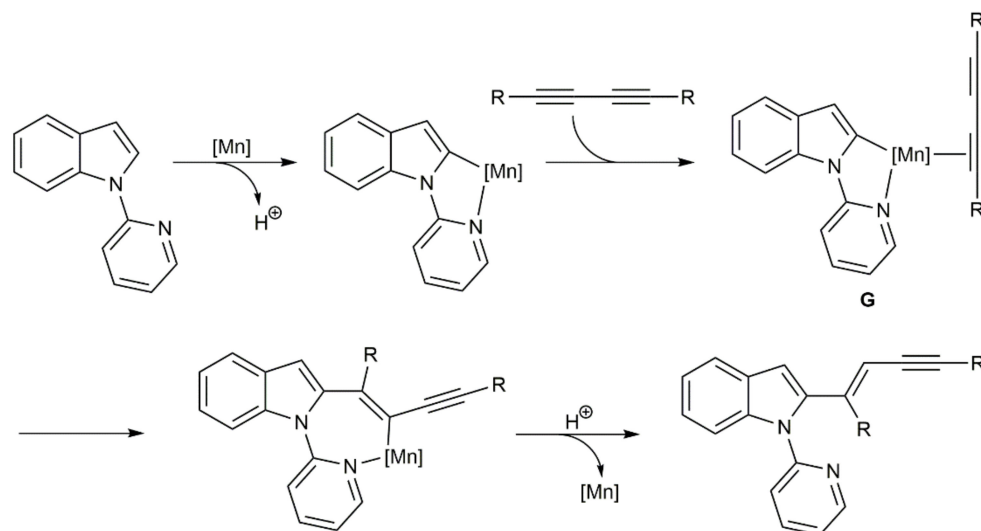


Figure 3. Selected products generated by $[\text{MnBr}(\text{CO})_5]$ -catalyzed hydroarylation of 1,3-diyne with arenes and heteroarenes.



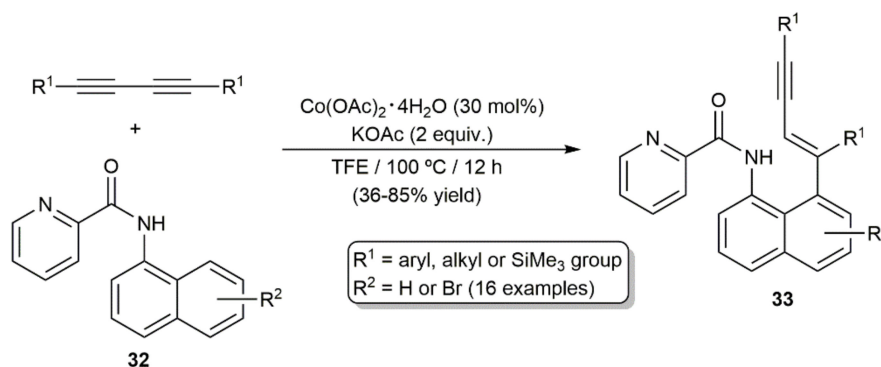
Scheme 17. Mn(I)-catalyzed synthesis of furans and pyrroles by hydroarylation of 1,3-diyne.

As illustrated in Scheme 18, a reaction pathway involving the initial directing group-assisted C–H activation of the (hetero)arene, followed by co-ordination and regioselective insertion of the diyne into the Mn–C bond of intermediate **G**, and a final protodemetalation step was proposed by Glorius and colleagues for these $[\text{MnBr}(\text{CO})_5]$ -catalyzed hydroarylation processes [37].



Scheme 18. Proposed mechanism for the hydroarylation of diynes with (hetero)arenes catalyzed by $[\text{MnBr}(\text{CO})_5]$.

On the other hand, cobalt(II) acetate, in conjunction with KOAc, was additionally employed by Feng's group to promote the hydroarylation of a variety of disubstituted diynes with picolinamides **32** (Scheme 19) [38]. The reactions, conducted in 2,2,2-trifluoroethanol (TFE) at 100 °C, afforded regioselectively the conjugated enynes **33** in moderate to good yields, and with complete *E*-selectivity (*syn* addition). As in the precedent case, a picolyl-group-directed C–H activation/diyne insertion pathway was proposed.



Scheme 19. Co-catalyzed hydroarylation of 1,3-diynes with picolinamides.

Concerning hydroalkylation processes, extending previous studies on the indium-catalyzed addition of active methylene compounds to terminal alkynes [39], Nakamura and colleagues reported the efficient synthesis (70–96% yield) of different α -ynenylated keto esters (see Figure 4) by hydroalkylation of monosubstituted 1,3-diynes $\text{HC}\equiv\text{CC}\equiv\text{CR}$ with β -keto esters [40]. The reactions, which were performed at 60 °C under solvent-free conditions with 5 mol% of $\text{In}(\text{NTf}_2)_3$ ($\text{NTf}_2 = \text{bis}(\text{trifluoromethane})\text{sulfonamide}$) as the catalyst and equimolar amounts of the reactants, were completely regioselective (only the terminal $\text{C}\equiv\text{C}$ bond of the diyne was found to participate in the addition reaction).

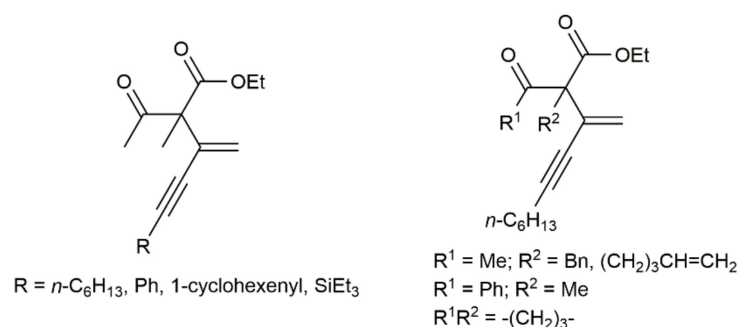
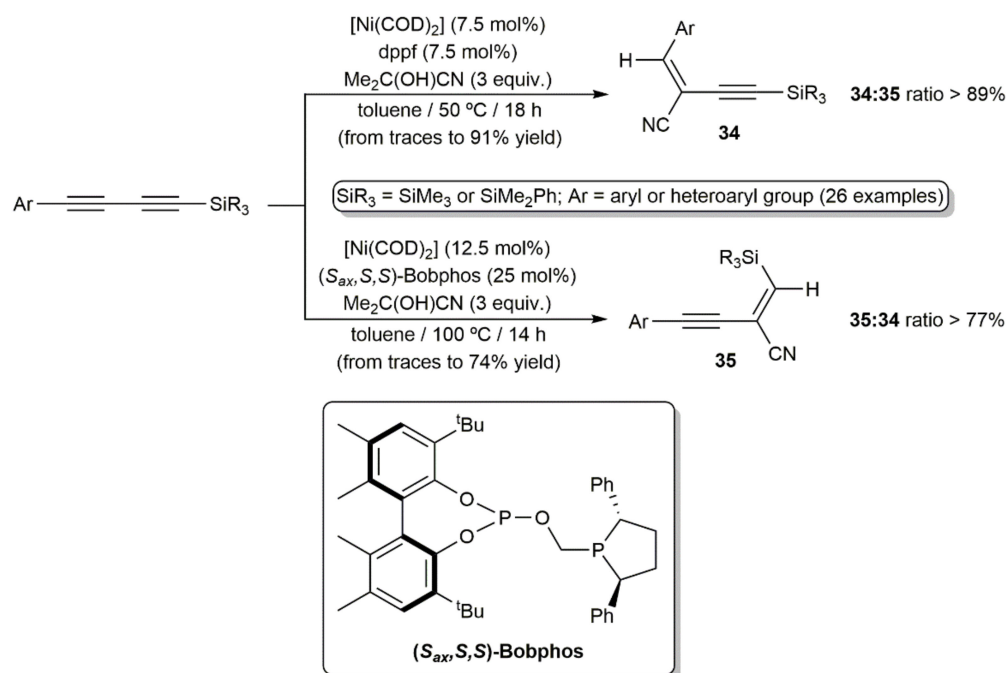


Figure 4. Products resulting from the In-catalyzed addition of β -keto esters to 1,3-diyne.

4. Hydrocyanation Processes

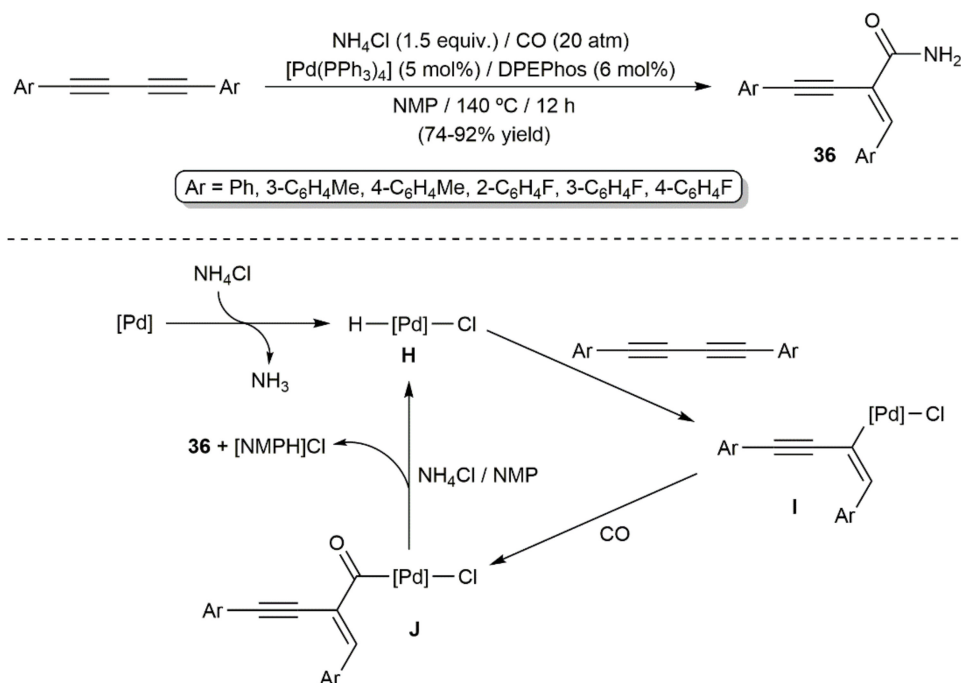
Hydrocyanation of unsaturated carbon–carbon bonds is a powerful method for the preparation of functionalized nitriles. Such reactions are commonly performed employing Ni-, Pd-, and Co-based catalysts and acetone cyanohydrin, Me_3SiCN , or $\text{Zn}(\text{CN})_2$, the latter avoiding the direct use of harmful HCN [41–43]. In sharp contrast to simple alkynes, hydrocyanation of 1,3-diyne remains a neglected area of research. Indeed, just one very recent work can be found in the literature describing the Ni-catalyzed regio-divergent hydrocyanation of unsymmetrical 1-aryl-4-silyl-1,3-butadiynes (Scheme 20) [44]. The reactions, performed in toluene with catalytic amounts of $[\text{Ni}(\text{COD})_2]$ (COD = 1,5-cyclooctadiene) and acetone cyanohydrin as the HCN surrogate, afforded with high regioselectivity and complete stereoselectivity (*syn* addition) two kinds of enynyl nitriles, i.e., compounds **34** and **35**, depending on the conditions and, capitially, the ligand employed. Thus, while the ferrocenyl-diphosphine dppf oriented the hydrocyanation process towards the formation of enynes **34**, their regioisomers **35** were preferentially generated when the chiral phosphine-phosphite (*Sax,S,S*)-Bobphos was used as the ligand. The process featured a broad scope and tolerated the presence of common functional groups on the aromatic or heteroaromatic substituent of the starting 1,3-diyne.



Scheme 20. Nickel-catalyzed regio-divergent hydrocyanation of silyl-substituted 1,3-butadiynes.

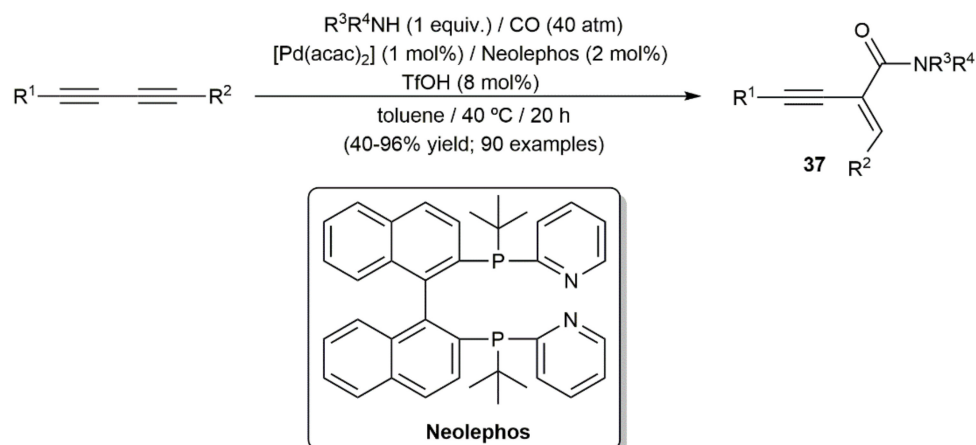
5. Other Formal C–H Bond Addition Processes

Transition-metal-catalyzed hydroaminocarbonylation reactions of alkenes and alkynes have emerged in recent years as powerful tools to access amides [45]. Within the topic covered in the present review article, only two works can be commented on. In the first one, published by Huang and colleagues in 2018, a small family of symmetrically substituted aromatic 1,3-diynes was smoothly converted into the primary amides **36** under 20 atm CO pressure, employing NH₄Cl as the amine source (Scheme 21) [46]. The reactions, catalyzed by [Pd(PPh₃)₄] in combination with the diphosphine DPEPhos (bis[(2-diphenylphosphino)phenyl]ether) and carried out in *N*-methyl-2-pyrrolidone (NMP) at 140 °C, led to amides **36** in high yields and with complete regio- and stereocontrol. A mechanism involving the initial oxidative addition of NH₄Cl to Pd(0) to furnish the catalytically active Pd(II)-hydride species **H** was proposed by the authors. Insertion of one of the C≡C bonds of the starting diyne into the Pd–H one affords the alkenyl-palladium intermediates **I**, which immediately react with CO to generate the acyl derivative **J**. The final amide products **36** result from the reaction of **J** with NH₄Cl.



Scheme 21. Pd-catalyzed hydroaminocarbonylation of 1,3-diynes with NH₄Cl.

In the second one, Beller and colleagues reported the hydroaminocarbonylation of both symmetrically and unsymmetrically substituted 1,3-diynes with primary and secondary amines and CO, employing a catalytic system composed of the palladium(II) complex [Pd(acac)₂] (acac = acetylacetonate), the diphosphine ligand Neolephos, and triflic acid (Scheme 22) [47]. The reactions proceeded in this case under milder conditions (toluene/40 °C), with mechanistic studies revealing that the pyridyl groups of Neolephos act as proton shuttles, facilitating the nucleophilic attack of the amine on the corresponding acyl-palladium intermediates. The scope of the process was very high and common functional groups on both the diyne and amine partners were tolerated. In addition, in the case of unsymmetrical diynes the regioselectivity of the process was exquisite, indicating a subtle role of the substituents in controlling the outcome of the initial diyne insertion step. In all the cases, the final amide products **37** were obtained with complete stereocontrol on the C=C bond formed.



Scheme 22. Pd-catalyzed hydroaminocarbonylation of 1,3-diynes with amines.

As illustrated in Figure 5, in which different amides containing biologically or pharmaceutically relevant skeletons are shown, the molecular complexity achieved by applying the Beller's hydroaminocarbonylation reaction was very high [47].

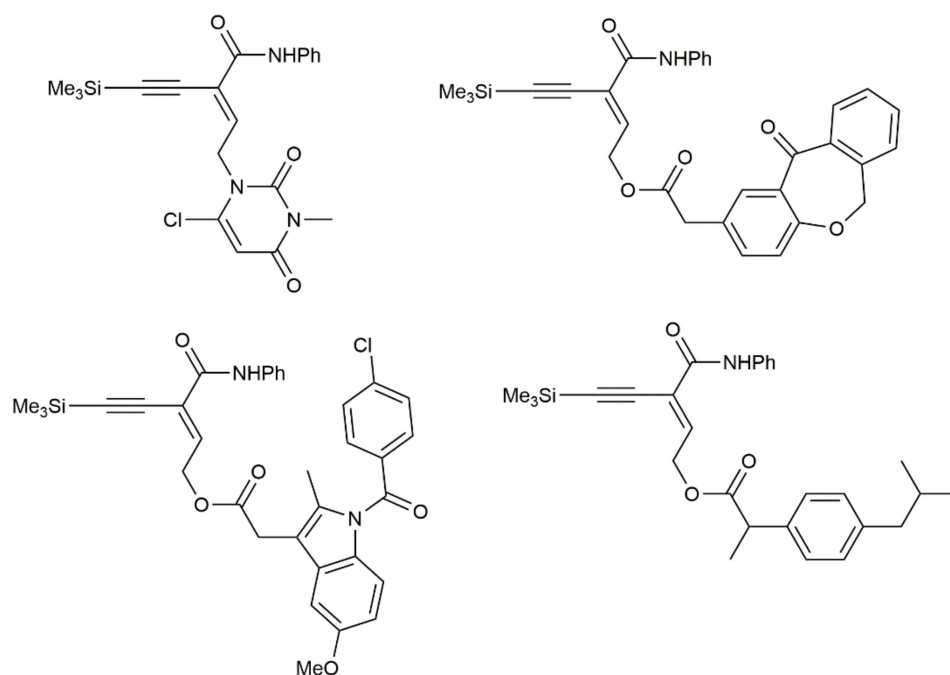
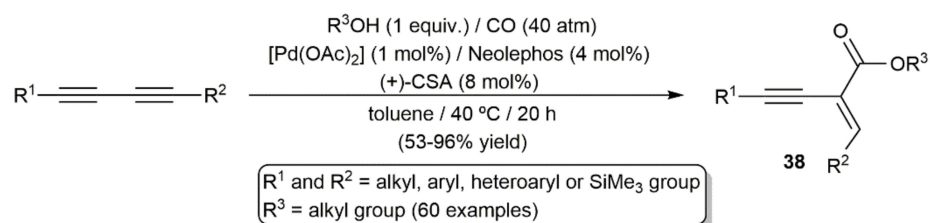


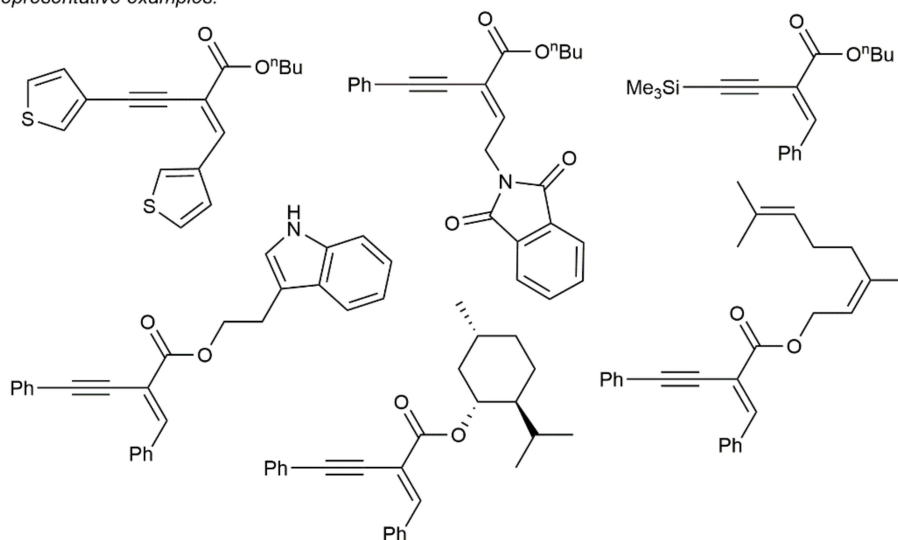
Figure 5. The structure of some elaborated amides containing bio-relevant skeletons.

It should also be noted at this point that, by combining Neolephos with Pd(OAc)₂ and (+)-10-camphorsulfonic acid (CSA), the group of Beller was also able to develop a wide-scope procedure for the monoalkoxycarbonylation of 1,3-diynes, allowing the access to functionalized 1,3-enynes of type **38** in good yields and with excellent chemoselectivity (Scheme 23) [48].

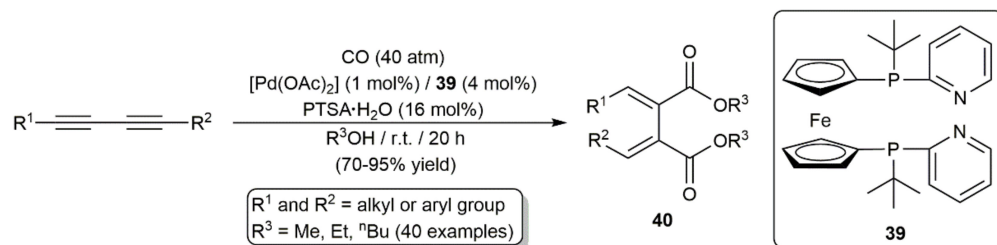
Palladium-catalyzed double alkoxycarbonylation of 1,3-diynes was additionally described by Beller and colleagues, the reactions leading to the regio- and stereoselective formation of 1,2,3,4-tetrasubstituted conjugated dienes **40** (Scheme 24) [49]. The ferrocene-based diphosphine **39**, instead of Neolephos, was, in this case, employed as the auxiliary ligand.



Representative examples:



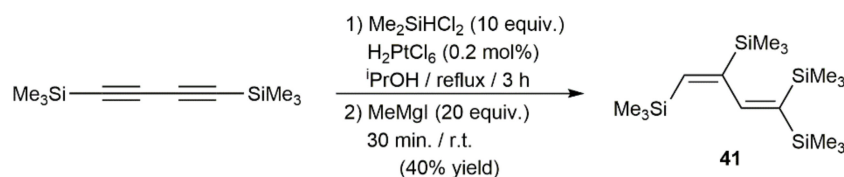
Scheme 23. Pd-catalyzed monoalkoxycarbonylation of 1,3-diyne.



Scheme 24. Pd-catalyzed access to tetrasubstituted dienes by alkoxy carbonylation of 1,3-diyne.

6. Hydrosilylation Processes

Alkyne hydrosilylation is one of the most efficient methods for preparing alkenyl-silicon derivatives and it has been for a long time a hot topic of research. The versatility of the catalytic hydrosilylation of carbon-carbon triple bonds has been exploited, not only for the preparation of useful synthetic intermediates, but also for the production of complex functional materials [50]. Noble metal catalysts based on Ru, Rh, Ir, Pd, and Pt have been extensively applied in these hydrofunctionalization reactions, and their mechanism of action perfectly established [51,52]. The first example of a 1,3-diyne hydrosilylation was described in 1968 by Bock and Seidl, who reported the preparation of 1,1,3,4-tetrakis(trimethylsilyl)butadiene **41** by reacting 1,4-bis(trimethylsilyl)-1,3-butadiyne with dichloromethylsilane in the presence of a catalytic amount of hexachloroplatinic(IV) acid (H_2PtCl_6 ; Speier's catalyst), followed by methylation with MeMgI (Scheme 25) [53].



Scheme 25. H_2PtCl_6 -catalyzed hydrosilylation of 1,4-bis(trimethylsilyl)-1,3-butadiyne with dichloromethylsilane.

Some years later, Hiyama and colleagues studied the hydrosilylation of 1,4-bis(trimethylsilyl)-1,3-butadiyne with various hydrosilanes using H_2PtCl_6 , $[\text{Pt}(\text{PPh}_3)_4]$, $[\text{Pd}(\text{PPh}_3)_4]$, $[\text{PdCl}_2(\text{PPh}_3)_2]$, or $[\text{RhCl}(\text{PPh}_3)_3]$ as catalysts [54,55]. The reactions led to three different types of products, i.e., the diene **41**, the allenes **42**, or the butenyne **43** (see Figure 6), depending on the catalyst and hydrosilane employed. In accord with the results of Bock and Seidl, the diene **41** was selectively generated using H_2PtCl_6 and Me_2SiHCl after treatment of the reaction mixture with MeMgBr . In the rest of the cases, compounds **42** or **43** were formed in different ratios, with allenes **43** resulting from the hydrosilylation of the primary products **42** via a metallacyclopropene intermediate **K**, whose generation is favored with the low-valent metal catalysts $[\text{Pt}(\text{PPh}_3)_4]$, $[\text{Pd}(\text{PPh}_3)_4]$, and $[\text{RhCl}(\text{PPh}_3)_3]$. Related mixtures of allene and butenyne products were obtained by Tillack and colleagues when studying the hydrosilylation of $\text{RC}\equiv\text{CC}\equiv\text{CR}$ ($\text{R} = \text{SiMe}_3, \text{Ph}, ^t\text{Bu}$) with Ph_2SiH_2 , PhMe_2SiH , and Et_3SiH in the presence of different low-valent $\text{Ni}(0)$ -butadiyne catalysts [56]. In this point, the attempts made by Tillack's group to generate the allenes in an enantioselective manner must also be noted, employing the dimeric rhodium(I) catalyst $[\{\text{Rh}(\mu\text{-Cl})(\text{COD})\}_2]$ in combination with chiral mono- and diphosphine ligands [57,58]. Unfortunately, an enantiomeric excess up to 27% was achieved at best.

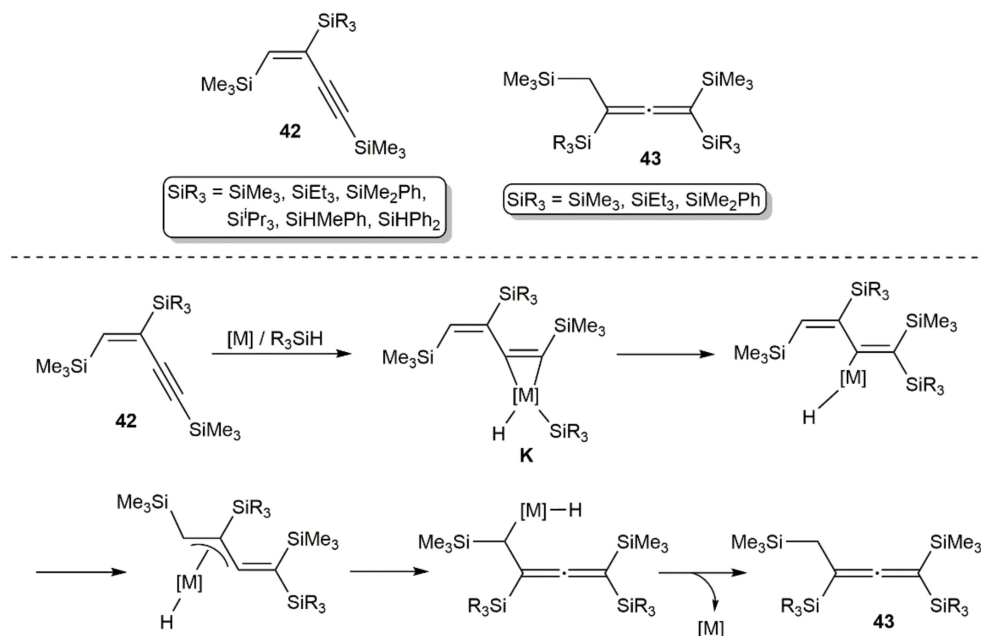


Figure 6. Structure of compounds **42** and **43**, and how **43** are formed from **42**.

Employing the well-known hydrosilylation catalyst **44** (Karstedt's catalyst; Figure 7), Perry and colleagues studied the hydrosilylation of diynes $\text{RC}\equiv\text{CC}\equiv\text{CR}$ ($\text{R} = \text{Ph}, ^n\text{Bu}, ^t\text{Bu}$) with PhMe_2SiH , $(\text{Me}_3\text{SiO})\text{Me}_2\text{SiH}$, $(\text{EtO})\text{Me}_2\text{SiH}$, Ph_2MeSiH , Ph_3SiH , and $(\text{Me}_3\text{SiO})_3\text{SiH}$ [59]. Performing the reactions in toluene or xylene in the temperature range 80–140 °C with a diyne/silane ratio of 1:2, they obtained selectively the mono- and bis-silylated products **45** and **46** (see Figure 7), the formation of the latter being, in general, favored at high temperature. Nonetheless, the most important factor in guiding the reaction towards the formation

of the mono- or dihydrosilylated products was found to be the steric hindrance between the diyne and silane substituents. Thus, the results obtained indicated that compounds **46** are only accessible when the steric constraints are not too high [59]. Regardless of the product obtained, addition of the Si–H bonds to the C≡C units proceeded in all the cases in a *syn* manner.

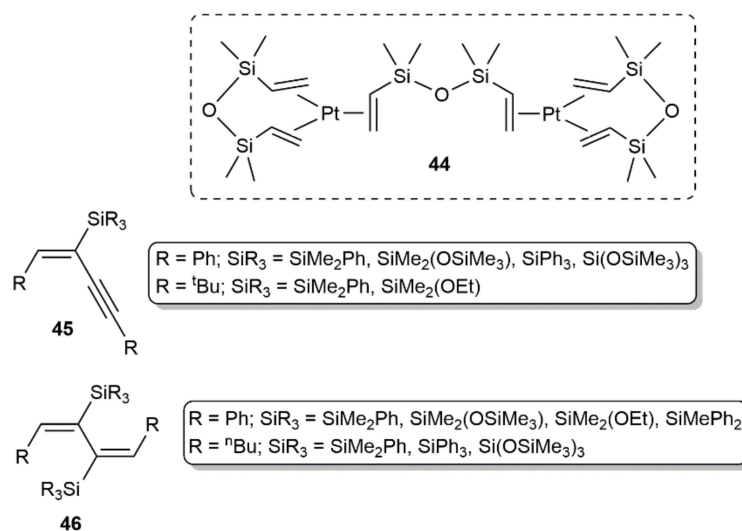
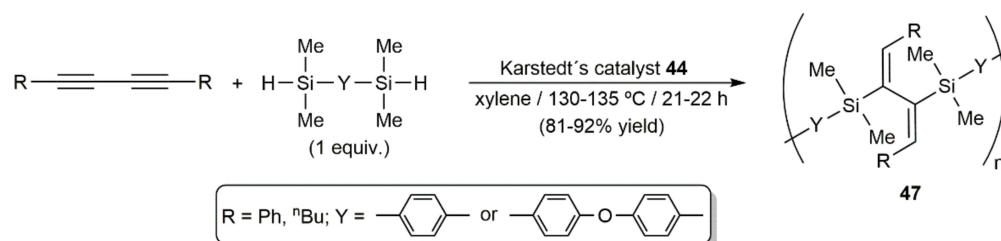


Figure 7. Structure of the Karstedt's catalyst **44** and the silylated compounds **45** and **46**.

In the same work, the silicon-containing polymers **47** were also synthesized in high yield by bis-hydrosilylation of diynes RC≡CC≡CR (R = Ph, ⁿBu) with 1,4-bis(dimethylsilyl)benzene and 4,4'-bis(dimethylsilyl)diphenyl ether (Scheme 26) [59].

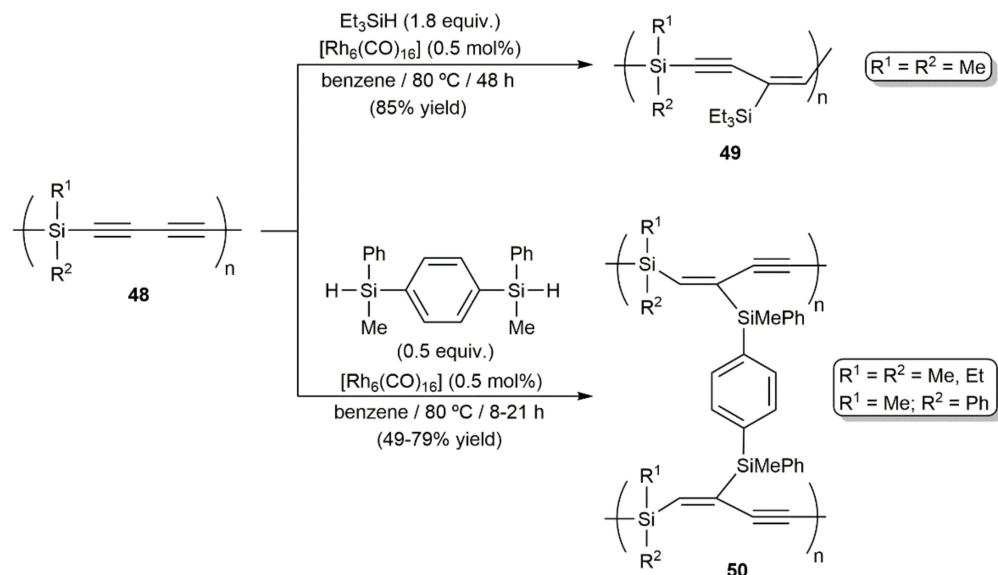


Scheme 26. Synthesis of silicon-containing polymers by Pt-catalyzed bis-hydrosilylation of 1,3-diynes.

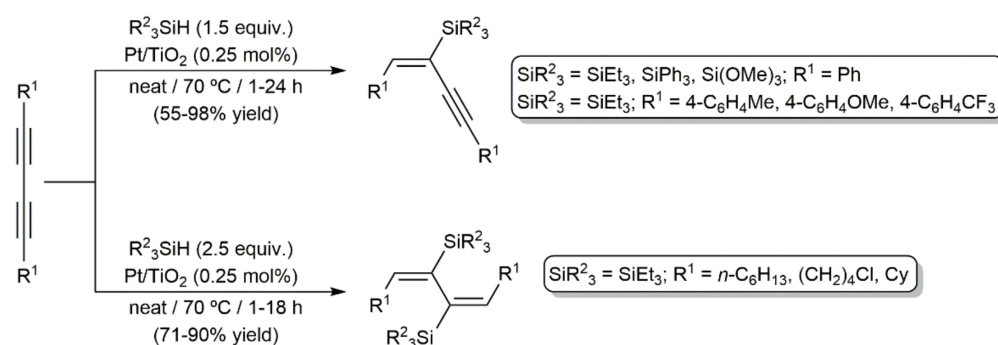
At this point, it must also be mentioned that access to other organosilicon polymers, i.e., compounds **49** and **50**, through the stereoselective and regioselective hydrosilylation of the poly[(silylene)but-1,3-diynes] derivatives **48** with triethylsilane and 1,4-bis(methylphenylsilyl)benzene, respectively, was described by Ishikawa and colleagues, employing, in this case, [Rh₆(CO)₁₆] as the catalyst (Scheme 27) [60,61].

In an independent study, Walkowiak and colleagues explored the addition of triethyl- and triphenylsilane to diynes RC≡CC≡CR (R = Me, Ph, ^tBu, (CH₂)₈CO₂Me, CMe₂OSiMe₃) catalyzed by the Karstedt's catalyst **44**, as well as [Pt(PPh₃)₄] and PtO₂ [62]. By selecting appropriate reaction conditions (temperature, stoichiometry, and catalyst), and depending on the steric constraints of the reagents, they were able to synthesize mono- and bis-silylated products related to those obtained by Perry and colleagues (**45** and **46** in Figure 7) with high yields and selectivities. In a later work, the same group also demonstrated the possibility of using a silsesquioxane-functionalized silane, i.e., (HSiMe₂O)(^tBu)₇Si₈O₁₂, as a substrate in these Pt-catalyzed hydrosilylation processes [63]. On the other hand, as shown in Scheme 28, mono- and bis-addition products were also selectively obtained by using titania-supported platinum as the catalyst [64]. In addition to the stoichiometry employed, the aromatic or aliphatic nature of the starting 1,3-diyne was, in this case, key to obtaining

one product or the other. As in the previous examples, the reactions were, again, highly stereo- and regioselective, leading to the monosilylated enynes and disilylated dienes with exclusive *E*-stereochemistry (*syn* addition) and with the silicon atoms bonded to the internal carbons of the diyne units.



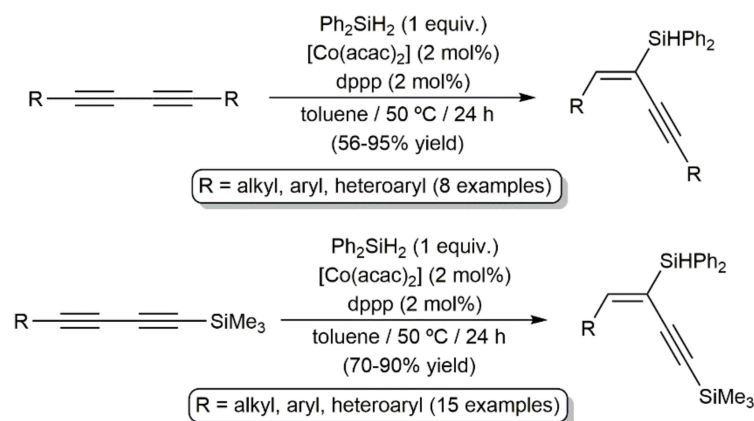
Scheme 27. Rhodium-catalyzed hydrosilylation reactions of poly[(silylene)but-1,3-diyne] **48**.



Scheme 28. Hydrosilylation of 1,3-diyne catalyzed by the heterogeneous system Pt/TiO₂.

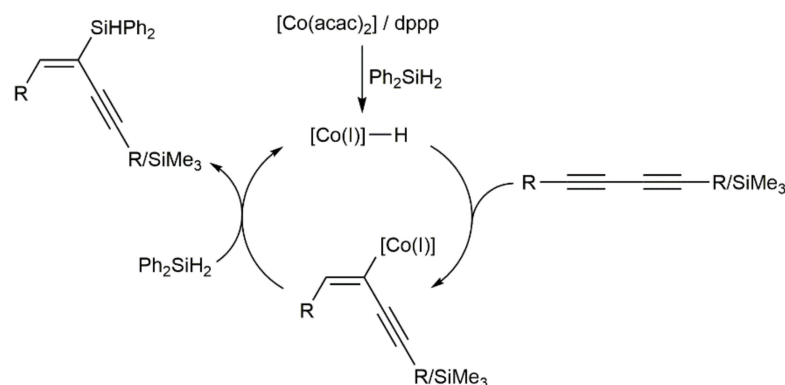
In addition to PtO₂ and Pt/TiO₂, other heterogeneous catalysts capable of promoting the hydrosilylation of 1,3-diyne quoted in the literature are: impregnated platinum on magnetite, i.e., PtO/PtO₂-Fe₃O₄ [65], Pd(0) nanoparticles supported on polymeric resins [66] or stabilized by imidazolium salts [67], Rh(0) nanoparticles stabilized by a nitrogen-rich polyethylene glycol (PEG) derivative [68] and a nickel(II)-containing porous organic polymer [69]. All of them showed an exquisite *syn* selectivity and, depending on the reaction conditions employed, led to the corresponding mono- or bis-addition products.

In another vein, the current demand for economical and environmentally benign catalysts has spurred the search for efficient cobalt-based systems able to promote the hydrosilylation of both terminal and internal alkynes [70,71]. In this context, Ge and colleagues reported in 2019 the regio- and stereoselective access to a broad range of silyl-functionalized 1,3-enynes by hydrosilylation of 1,3-diyne (*syn* addition), employing a catalyst generated from bench-stable Co(acac)₂ and 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 29) [72].



Scheme 29. Cobalt-catalyzed hydrosilylation of 1,3-diyne.

A classical hydrometallation pathway via a cobalt(I)-hydride intermediate was proposed by the authors for this co-catalyzed hydrosilylation of 1,3-diyne (see Scheme 30) [72].



Scheme 30. Proposed mechanism for the cobalt-catalyzed hydrosilylation of 1,3-diyne.

Related hydrosilylation reactions, featuring the same regio- and stereocontrol, were subsequently described with other cobalt-based catalytic systems, such as complexes **51** [73] and **52** [74] (see Figure 8) or the $\text{CoCl}_2/\text{dppp}$ combination [75]. In these cases, the reducing agent NaHBEt_3 was systematically employed as a co-catalyst, allowing the reactions to proceed under milder conditions (r.t. or 30°C) and shorter times (from 5 min to 1 h).

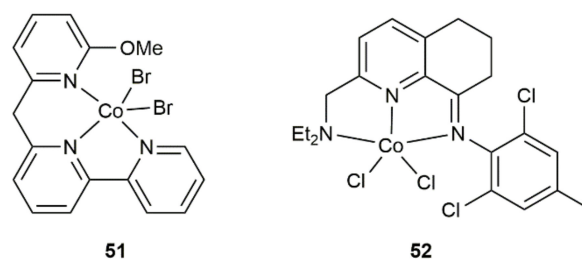
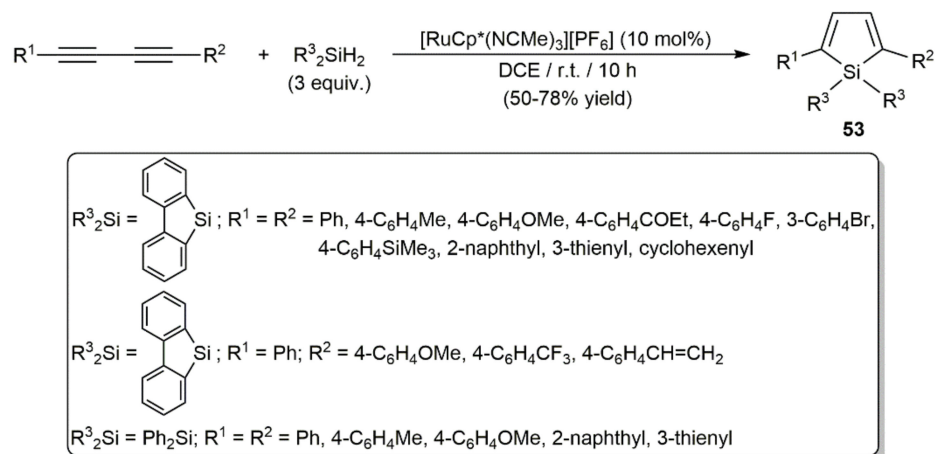


Figure 8. Structure of the cobalt(II) complexes **51** and **52**.

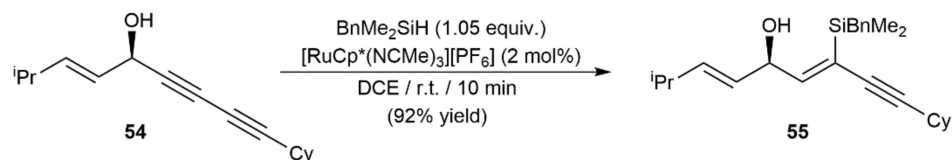
Access to 2,5-disubstituted heteroles (heteroatom-substituted cyclopentadienes) by [4+1]-type annulation reactions of 1,3-diyne with appropriate group 14–16 element compounds is well documented in the literature [76]. In line with this, Murakami and colleagues reported the preparation of several 2,5-disubstituted siloles **53** facing different symmetrically and unsymmetrically substituted 1,3-diyne to diphenylsilane or 9-silafluorene in the presence of catalytic amounts of the cationic ruthenium(II) complex $[\text{RuCp}^*(\text{NCMe})_3][\text{PF}_6]$ (Cp^* = pentamethylcyclopentadienyl) (Scheme 31) [77]. The reactions, which were conducted in 1,2-dichloroethane at room temperature, proceed through the sequential double

anti-hydrosilylation of the diynes. By employing diphenylgermane Ph₂GeH₂ instead of Ph₂SiH₂ or 9-silafluorene and applying identical reaction conditions, 2,5-substituted germoles could be equally generated in moderate to high yields [78].



Scheme 31. Ru-catalyzed synthesis of 2,5-disubstituted siloles by hydrosilylation of 1,3-diynes.

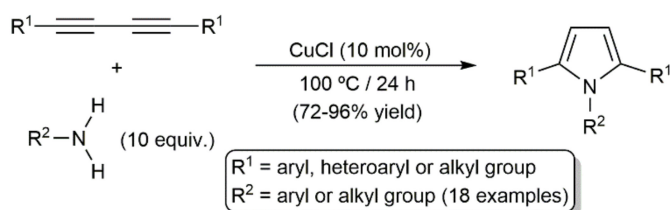
As shown in Scheme 32, the Ru(II) complex [RuCp*(MeCN)₃][PF₆] was also capable of promoting the *anti*-addition of the tertiary silane BnMe₂SiH to the chiral diyneol **54** [79]. The resulting enynyl-silane product **55** was isolated in excellent yield, with other possible isomers not being observed in the reaction crude.



Scheme 32. Ru-catalyzed hydrosilylation of the chiral diyneol **14** with BnMe₂SiH.

7. Hydroamination and Hydroamidation Processes

In line with the silole-ring formation reactions discussed above (see Scheme 31), access to 1,2,5-trisubstituted pyrroles by double addition of the N–H bonds of primary amines across 1,3-diynes is well documented. Such transformations were first reported in 1961, employing 0.1 mol% of CuCl as a catalyst at 150–180 °C [80,81], but, as shown in Scheme 33, they also proceed in high yields at a lower temperature (100 °C), increasing the amount of CuCl to 10 mol% [82].



Scheme 33. CuCl-catalyzed annulation reactions of 1,3-diynes with primary amines.

Although these pyrrole-ring formation reactions are also known to proceed in the presence of KOH [83], the synthetic utility of the process, exemplified with the preparation of compounds **56–61** featuring interesting photophysical properties (see Figure 9), has only been demonstrated using catalytic CuCl [84–89]. In all the cases, the central pyrrolic unit was generated through the initial copper-catalyzed annulation of a primary amine with a 1,3-diyne system.

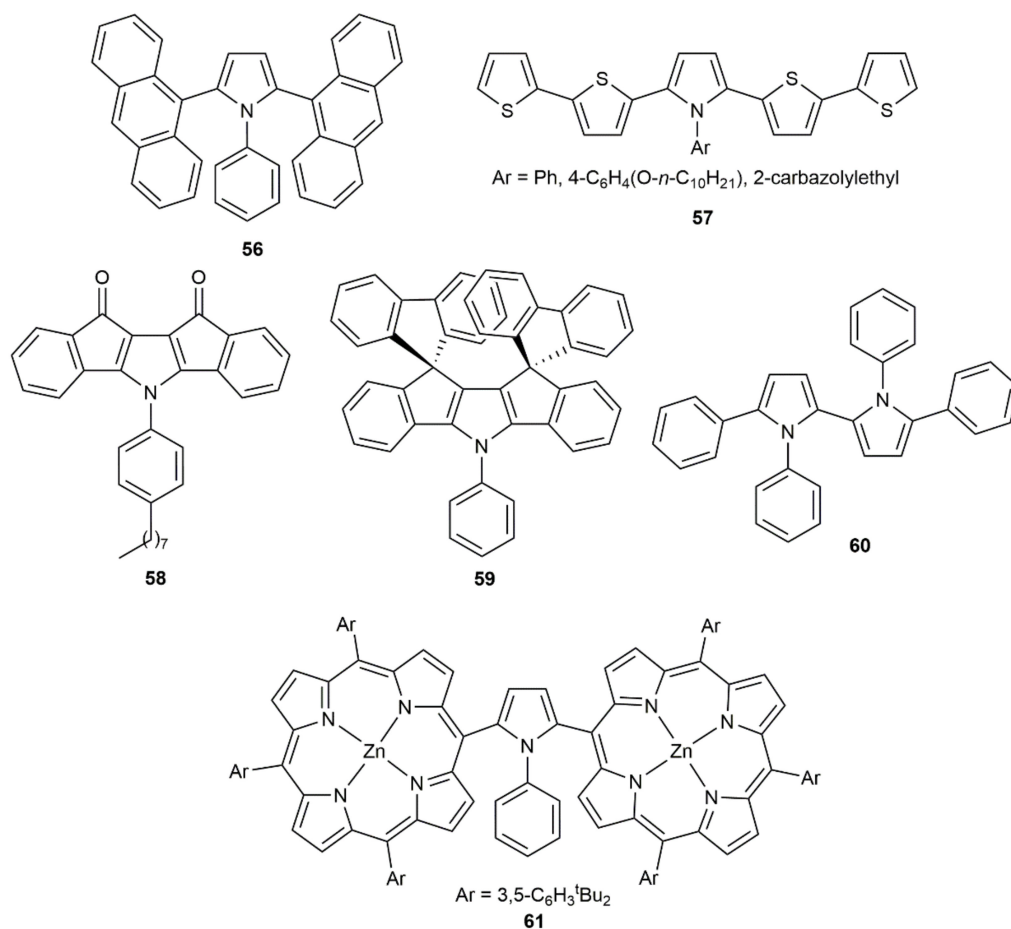
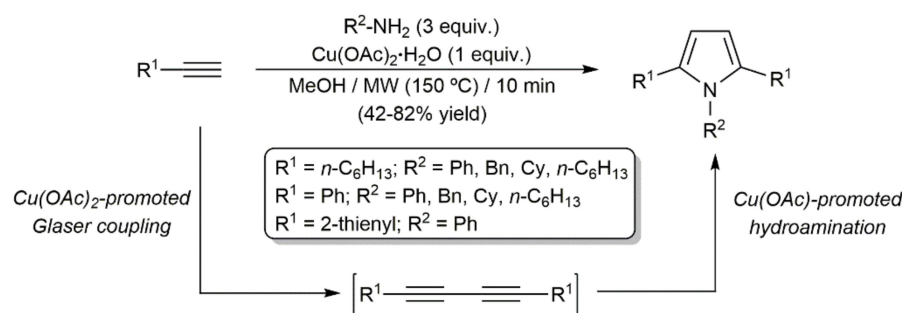


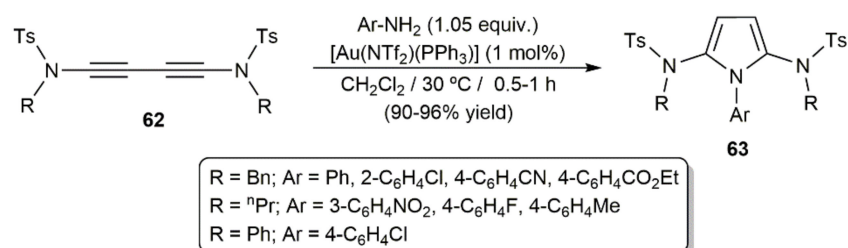
Figure 9. Structure of the elaborated pyrrole derivatives **56–61**.

In this context, we must note that several 1,2,5-trisubstituted pyrroles were synthesized by Jun and colleagues by reacting terminal alkynes with primary amines in the presence of Cu(OAc)₂·H₂O (Scheme 34) [90]. The process was performed under microwave (MW) irradiation and involved the initial Cu(OAc)₂-promoted Glaser homocoupling of the alkynes, followed by the double hydroamination of the resulting diynes. In the cyclization step, the Cu(I) salt Cu(OAc) generated during the homocoupling reaction was proposed by the authors to serve as the catalytically active species.

On the other hand, taking advantage of the well-known ability of gold complexes to promote the addition of N–H bonds across C–C multiple bonds [91], the access to pyrrole derivatives from diynes and primary amines has also been achieved under gold catalysis. Thus, Skrydstrup and colleagues synthesized the 2,5-diamidopyrroles **63** in excellent yields, short times, and under mild conditions when 1,3-diyndiamides R(Ts)NC≡CC≡CN(Ts)R (**62**; Ts = *p*-toluenesulfonyl) and different anilines were subjected to the catalytic action of the Au(I)-phosphine complex [Au(NTf₂)(PPh₃)] (Scheme 35) [92].

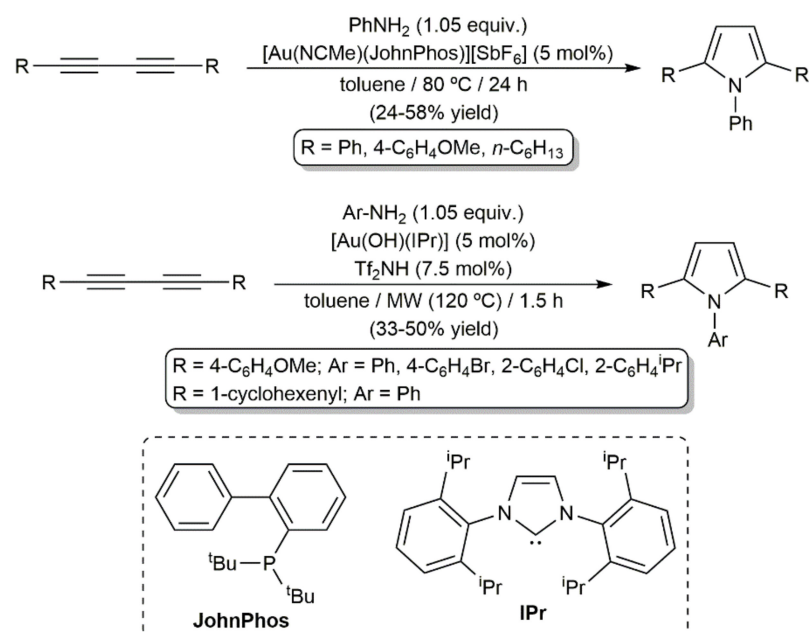


Scheme 34. Direct access to pyrroles from terminal alkynes and primary amines.

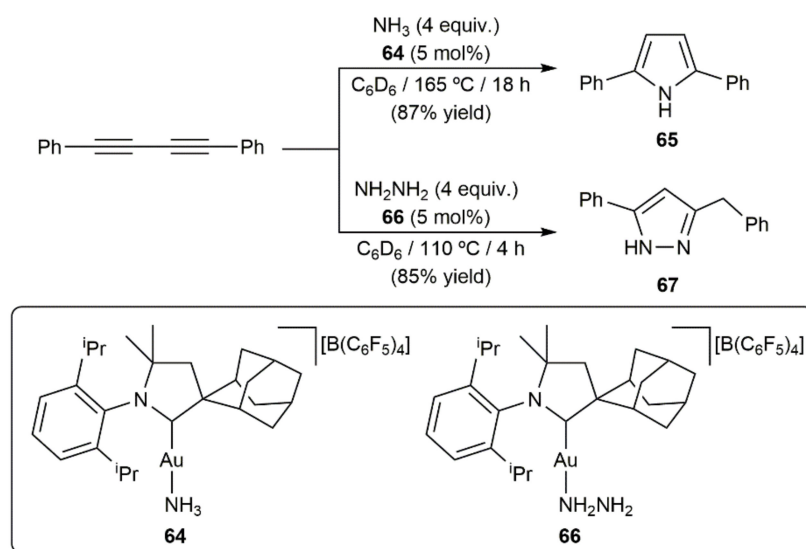


Scheme 35. Gold-catalyzed synthesis of 2,5-amidopyrroles.

In the same work, the hydroamination of more classical alkyl- and aryl-substituted diynes with aniline was additionally explored, a process that proved to be more difficult due to the lower electronic activation of the $\text{C}\equiv\text{C}$ bonds in comparison to those of compounds **62**. In fact, only when the reactions were performed in toluene at $80\text{ }^\circ\text{C}$ with 5 mol% of the cationic complex $[\text{Au}(\text{NCMe})(\text{JohnPhos})][\text{SbF}_6]$ could the desired pyrroles be accessed, albeit in modest yield and after remarkably longer times (Scheme 36) [92]. Comparable yields were reached by Nolan and colleagues when studying related hydroamination processes with complex $[\text{Au}(\text{OH})(\text{IPr})]$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) under MW irradiation (see Scheme 37) [93].



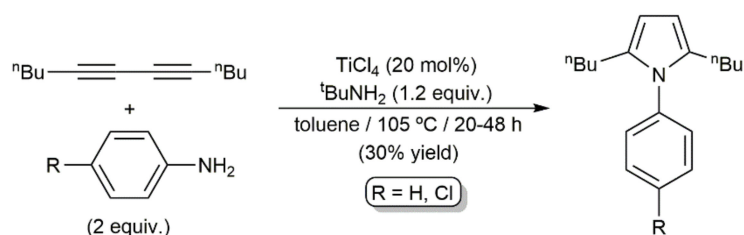
Scheme 36. Gold-catalyzed synthesis of pyrroles from alkyl- and aryl-substituted 1,3-diynes.



Scheme 37. Gold-catalyzed hydroamination reactions of 1,4-diphenylbuta-1,3-diyne with ammonia and hydrazine.

In addition to the examples just commented upon, Bertrand and colleagues successfully achieved the catalytic hydroamination of 1,4-diphenylbuta-1,3-diyne with parent ammonia and hydrazine to afford the *N*-unsubstituted pyrrole **65** [94] and the pyrazole derivative **67** [95], respectively, employing the cationic gold(I) complexes **64** and **66** having a bulky cyclic (alkyl)(amino)carbene ligand (Scheme 37). Within this context, we must mention that access to substituted pyrazoles through metal-free Cope-type hydroamination of 1,3-diyne with hydrazine derivative H_2NNHR ($R = H$, alkyl or aryl group) under thermal or base-promoted conditions has been amply reported [96–102]. Similarly, catalyst-free protocols for the construction of isoxazole [96,100,101,103,104] and pyrimidine [105–107] scaffolds by Cope-type hydroamination of 1,3-diyne with hydroxylamine and guanidines, respectively, can also be found in the literature.

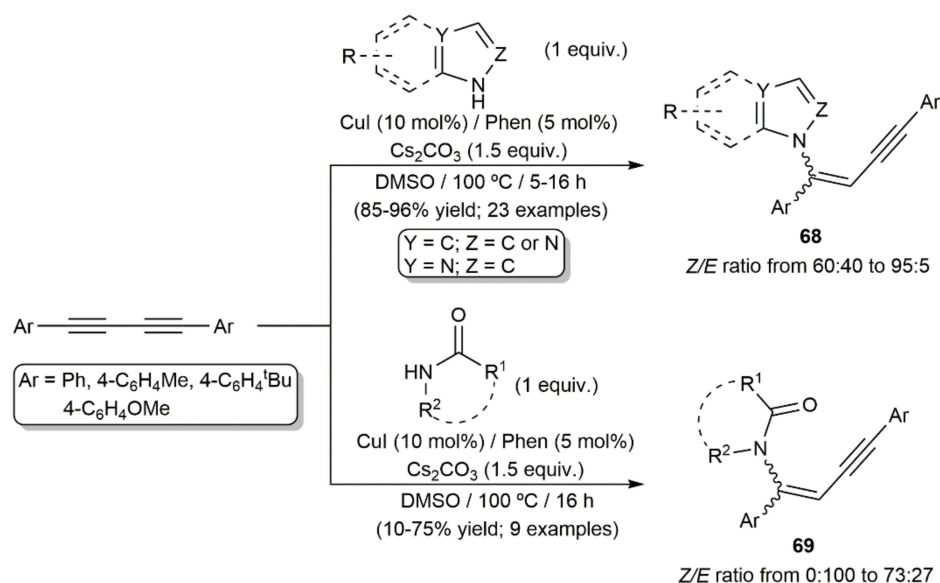
As shown in Scheme 38, a catalytic system composed of $TiCl_4$ and *tert*-butylamine was also able to promote the coupling of an aliphatic 1,3-diyne with aromatic primary amines to afford pyrroles, albeit featuring a low efficiency [108].



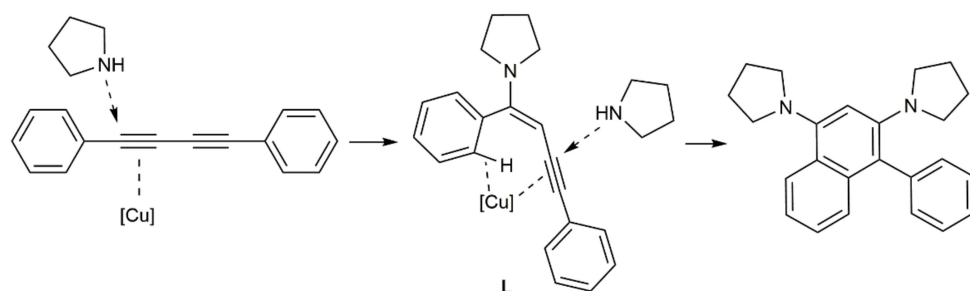
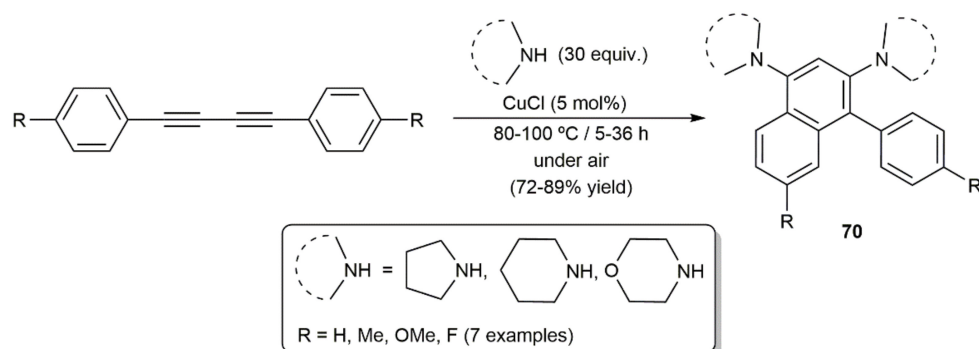
Scheme 38. $TiCl_4/tBuNH_2$ -catalyzed pyrrole synthesis from dodeca-5,7-diyne and aromatic primary amines.

On the other hand, intermolecular copper-catalyzed hydroamination reactions of aromatic 1,3-diyne with indole, imidazole, and pyrazole derivatives were described by Kundu and colleagues (Scheme 39) [109]. The reactions, conducted in DMSO at 100 °C with a $CuI/Phen/Cs_2CO_3$ ($Phen = 1,10$ -phenanthroline) combination, afforded the linear *N*-alkenyne **68** in high yields as mixtures of the corresponding *E* and *Z* isomers, with the latter being predominant in all the cases. Employing the same reaction conditions, addition of the *N*-H bond of both cyclic and acyclic amides to the diynes also took place, leading to the corresponding *N*-alkenyne products **69** with generally lower yields (Scheme 40). Interestingly, while a similar *Z*-stereoselectivity was observed when employing cyclic

amides, the hydroamidation reactions with the acyclic ones afforded compounds **69** as the *E*-stereoisomers exclusively.



Scheme 39. Cu-catalyzed hydroamidation and hydroamidation reactions of 1,3-diyne with indoles, azoles, and amides.

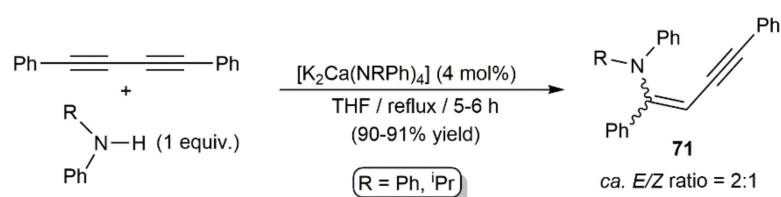


Scheme 40. Access to diamino-substituted naphthalenes from 1,3-diyne and cyclic amines.

In 2011, Hua and colleagues developed an efficient and atom-economic approach to diamino-substituted naphthalene derivatives **70** through a CuCl-catalyzed coupling reaction of aromatic diynes and cyclic primary amines (Scheme 40) [110]. The process involves the initial hydroamination of one of the C≡C bonds of the diyne to generate an *N*-alkenyne intermediate **L**, in which the remaining alkyne group and the *ortho*-C–H of the aryl substituent are activated by the copper catalyst, evolving into naphthalenes **70** through the intramolecular hydroarylation of the C≡C bond and subsequent reaction with a second equivalent of the amine.

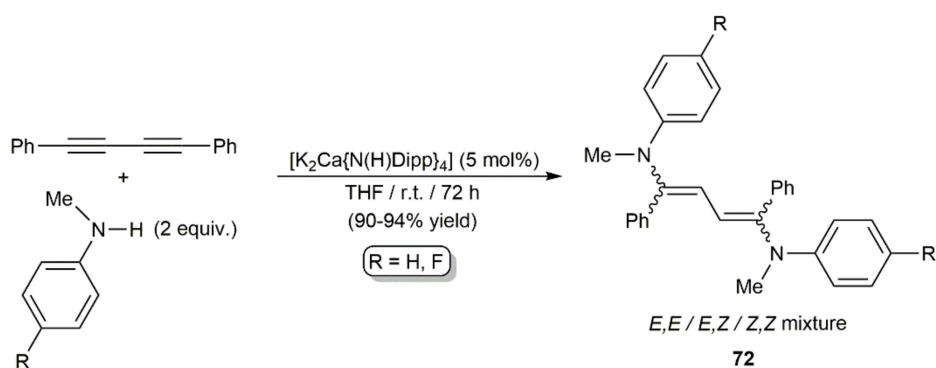
Access to related diamino-substituted naphthalenes was later described by Lee and Jung starting from both cyclic and acyclic amines and aryl alkynyl carboxylic acids $\text{ArC}\equiv\text{CCO}_2\text{H}$, which, under the action of $\text{CuCl}/\text{Cu}(\text{OTf})_2$, are transformed in situ into the corresponding 1,3-diynes $\text{ArC}\equiv\text{CC}\equiv\text{CAr}$ [111]. 1,4-Bis(trimethylsilyl)-1,3-butadiyne was additionally employed as a precursor of compound $\text{ArC}\equiv\text{CC}\equiv\text{CAr}$ in this type of transformation. A co-operative Pd/Cu catalytic system, enabling the initial double Sonogashira coupling of $\text{Me}_3\text{SiC}\equiv\text{CC}\equiv\text{CSiMe}_3$ with aryl halides, was, in this case, used to generate the naphthalene products in a *one-pot* manner [112].

Hydroamination reactions of 1,4-diphenyl-1,3-butadiyne with s-block metal catalysts were studied by the group of Westerhausen. Thus, in an initial report, they found that monoaddition of the secondary amine HNRPh ($\text{R} = \text{Ph}, ^i\text{Pr}$) to the diyne can be promoted by the respective heterobimetallic amides $[\text{K}_2\text{Ca}(\text{NRPh})_4]$ in refluxing THF, the reactions affording *E/Z* mixtures of the 1-anilino-1,4-diphenylbut-1-ene-3-yne **71** in excellent yields (Scheme 41) [113].



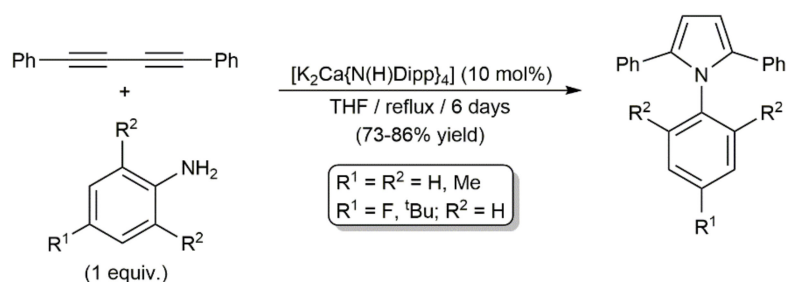
Scheme 41. Hydroamination 1,4-diphenyl-1,3-butadiyne with secondary amines catalyzed by heterobimetallic amides.

Later, they described related hydroamination reactions of $\text{PhC}\equiv\text{CC}\equiv\text{CPh}$ with *N*-methylanilines HNMeAr ($\text{Ar} = \text{Ph}, 4\text{-C}_6\text{H}_4\text{F}$) under milder conditions (r.t.) using catalytic amounts of $[\text{K}_2\text{Ca}\{\text{N}(\text{H})\text{Dipp}\}_4]$ ($\text{Dipp} = 2,6\text{-diisopropylphenyl}$) [114]. This calcium complex allowed not only access to the monoaddition products (*E/Z*)- $\text{PhC}\equiv\text{CCH} = \text{CPh}(\text{NMeAr})$, but also to the diaddition ones **72** when the reactions were carried out with a twofold excess of the amines (Scheme 42). Dienes **72** were, in all the cases, generated as mixtures of the three possible stereoisomers.



Scheme 42. Double hydroamination of 1,4-diphenyl-1,3-butadiyne with *N*-methylanilines.

Complex $[\text{K}_2\text{Ca}\{\text{N}(\text{H})\text{Dipp}\}_4]$ also catalyzed the addition of *N*-unsubstituted anilines to $\text{PhC}\equiv\text{CC}\equiv\text{CPh}$. As shown in Scheme 43, the reactions conducted in refluxing THF for six days afforded the corresponding pyrrole derivatives in 73–86%, regardless of the substitution pattern of the aromatic ring [115]. Harsh conditions were needed for the intramolecular hydroamination of the second alkyne unit in the intermediate species (*E/Z*)- $\text{PhC}\equiv\text{CCH} = \text{CPh}(\text{NHAr})$ to proceed. Conversely, when these hydroamination processes were performed at room temperature, other reaction pathways took place, leading to, depending on the stoichiometry employed and the substituents in *ortho*-position of the anilines, different compounds, such as those depicted in Figure 10, whose formation was explained through radical mechanisms [115,116].



Scheme 43. Access to pyrrole derivatives using the calciate catalyst $[K_2Ca\{N(H)Dipp\}_4]$.

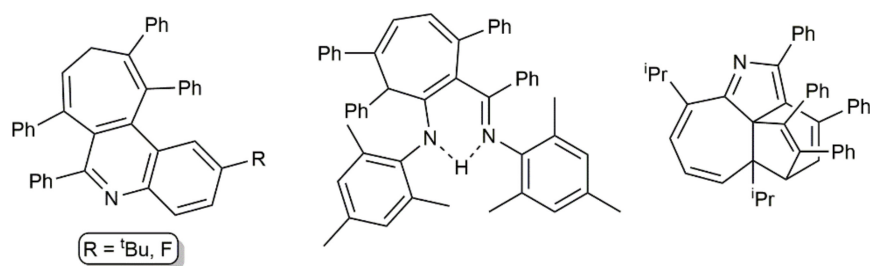


Figure 10. Other products generated from 1,4-diphenyl-1,3-butadiyne and anilines using the calciate catalyst $[K_2Ca\{N(H)Dipp\}_4]$.

In an additional work, Westerhausen and colleagues attempted the generation of cyclic butadiene derivatives by double hydroamination of $PhC\equiv CC\equiv CPh$ with a linear diamine, i.e., N,N' -diphenylethylenediamine. The expected cyclic product was not formed, the reaction yielding compound **73**, resulting from the addition of the diamine to two molecules of the diyne (Figure 11) [117]. For this particular transformation, the resulting complex $[K_2Ca\{N(H)Dipp\}_4]$ was completely inoperative, and a mixture of the potassium and calcium complexes $[(THF)_3K_2\{1,2-(PhN)_2C_2H_4\}]$ and $[(THF)_5Ca_2\{1,2-(PhN)_2C_2H_4\}_2]$ in 2:1 ratio were, in this case, employed to promote the process.

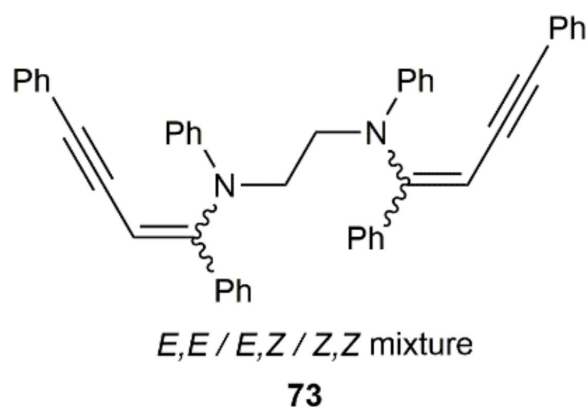
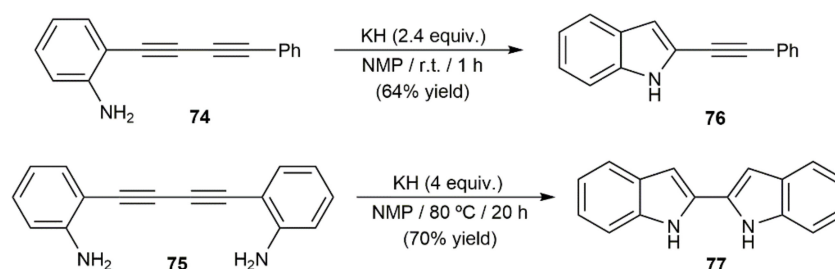


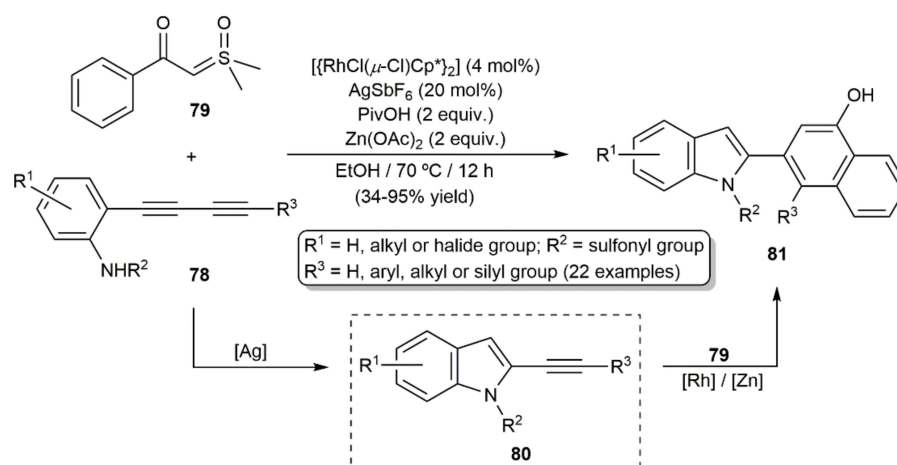
Figure 11. Structure of compound **73** generated from N,N' -diphenylethylenediamine and 1,4-diphenyl-1,3-butadiyne.

Intramolecular hydroamination reactions of 1,3-diyne functionalized with pendant amino groups have also been described. As exemplified in Scheme 44 with the 5-*endo*-dig-cyclization of the *o*-aniline-substituted diynes **74** and **75** into the indole derivatives **76** and **77**, respectively, such reactions do not require metal catalysts to proceed, being conveniently promoted by a base [118,119]. However, we must note that conversion of **74** into **76** was successfully achieved under neutral conditions employing catalytic amounts of $PdCl_2$ (5 mol%). Thus, after 12 h of heating at 80 °C in 1,2-dichloroethane, the 2-alkynylindole **76** could be isolated in 54% yield [120].



Scheme 44. Base-mediated intramolecular hydroamination of 1,3-diyne.

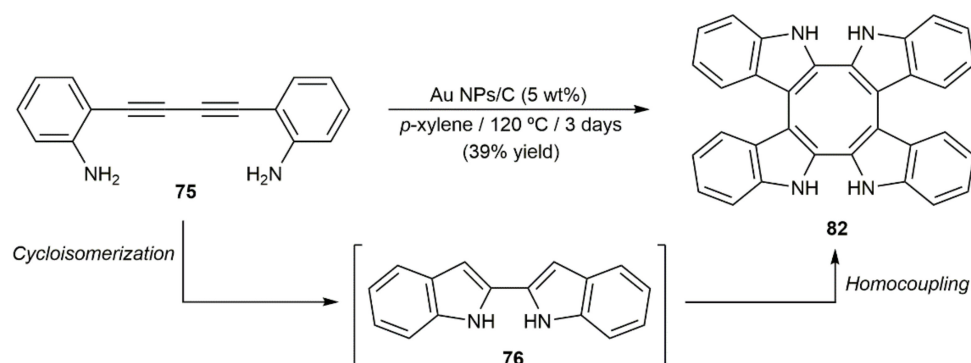
Shi and colleagues described the synthesis of a broad family of naphthol-indole derivatives **81** by coupling the related 1,3-diyne **78** with the sulfoxonium ylide **79**, employing a catalytic system composed of the Rh(III) dimer $[\{\text{RhCl}(\mu\text{-Cl})\text{Cp}^*\}_2]$ and the silver(I) salt AgSbF_6 in combination with pivalic acid (PivOH) and zinc acetate (Scheme 45) [121]. Control experiments indicated that the process involves the initial AgSbF_6 -catalyzed cyclization of the diynes to generate the 2-alkynylindole intermediates **80**. Subsequent reaction of ylide **79** with compounds **80** leads to the final naphthol-indole products **81** through a Rh-catalyzed Zn-assisted *ortho* C–H activation/annulation cascade.



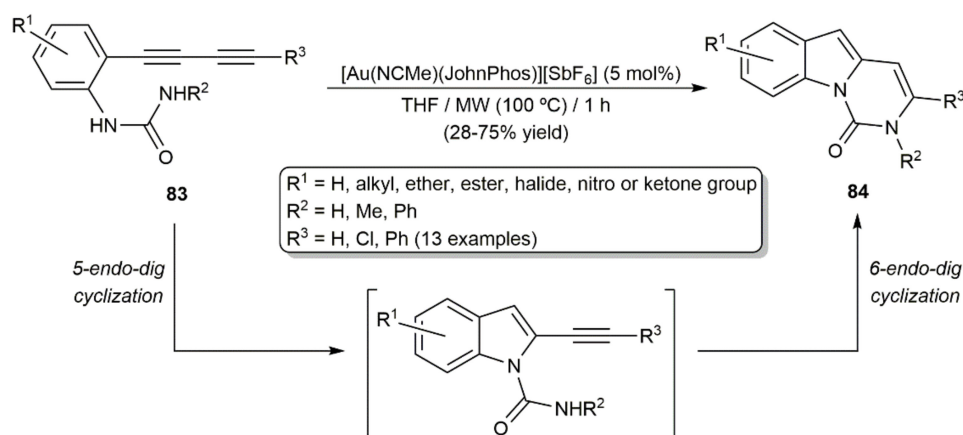
Scheme 45. Access to naphthol-indoles **81** from 1,3-diyne **78** and the sulfoxonium ylide **79**.

In the context of a broad study on the cycloisomerization of 2-alkynylanilines catalyzed by carbon-supported gold nanoparticles (NPs), the groups of Lopez-Sanchez and Helaja developed an effective cascade process to obtain 3,3'-biindoles by combining the cycloisomerization of the substrates with a subsequent indole homocoupling reaction [122]. As shown in Scheme 46, when the diyne **75** was subjected to the catalytic action of the supported Au NPs in *p*-xylene at 120 °C the 3,3',3'-tetraindole **82** containing a cyclooctatetraene core was selectively formed, albeit in only 39% yield.

On the other hand, Banwell's group elegantly combined two consecutive intramolecular hydroamidation processes with the *o*-(1,3-diyne)-substituted *N*-aryl ureas **83** to produce the polycyclic pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives **84** (Scheme 47) [123]. In these reactions, the initial 5-*endo-dig* cyclization of the substrates is followed by a 6-*endo-dig* one, both ring-closure processes being catalyzed by the cationic complex $[\text{Au}(\text{NCMe})(\text{JohnPhos})][\text{SbF}_6]$ under MW irradiation.

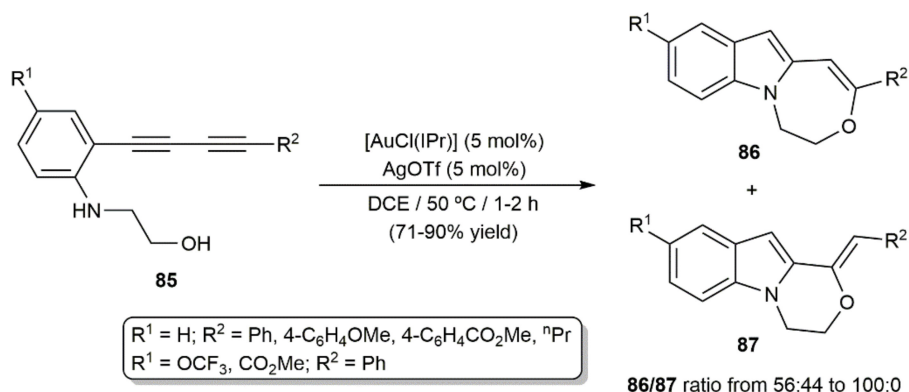


Scheme 46. Au-catalyzed conversion of diyne 75 into tetraindole 82.



Scheme 47. Gold-catalyzed synthesis of pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives.

Uchiyama, Ohno, and colleagues developed a related cascade process with 1,3-diyne **85**, in which the initial gold(I)-catalyzed 5-*endo-dig* indole formation reaction was followed by the hydroalkoxylation of the remaining C≡C bond (Scheme 48) [124]. Although in the last step a marked preference for the 7-*endo-dig* cyclization was observed, the oxepino[1,7-*a*]indole products **86** were not selectively formed and minor amounts of the isomeric species **87**, resulting from a 6-*exo-dig* cyclization, were also generated in most of the cases.

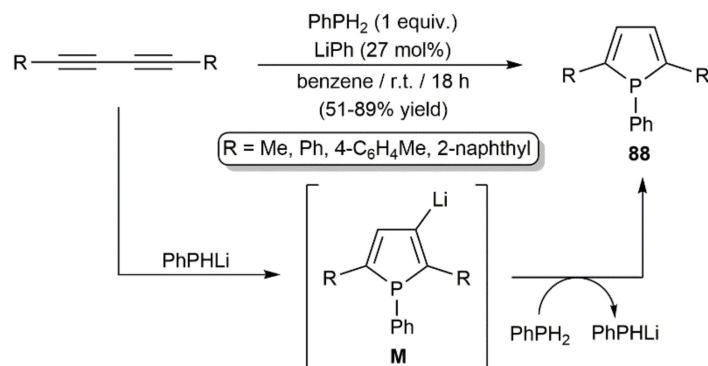


Scheme 48. Gold-catalyzed hydroamination/hydroalkoxylation cyclization cascade of diynes **85**.

8. Hydrophosphination and Hydrophosphorylation Processes

An early work by Märkl and Potthast in 1967 showed that 2,5-disubstituted phospholes can be easily obtained by double hydrophosphination of symmetrically substituted 1,3-diyne with phenylphosphine in the presence of catalytic amounts of phenyllithium (Scheme 49) [125]. In the process, in situ generated lithium phosphide PhPLi adds to

the diyne generating the lithiated phosphole intermediates **M**, which rapidly react with a second equivalent of the phosphine. In this way, the final reaction products **88** are formed and the nucleophile PhPHLi regenerated.



Scheme 49. LiPh-catalyzed synthesis of 2,5-disubstituted phospholes from 1,3-diynes and PhPH₂.

Applying the same protocol, but using LiⁿBu instead of LiPh, the synthesis of 2,5-di(1-naphthyl)phosphole **89** [126], the chiral derivatives **90** [127] and **91** [128], and the ferrocenyl-substituted phospholes **92** [129–131] was later described by reacting the respective 1,3-diyne with a primary aryl phosphine (see Figure 12). Noncatalytic transformations allowing the access to phosphole derivatives from 1,3-diynes have additionally been described employing stoichiometric amounts of lithium-phosphide reagents [132–134]. Moreover, of note is the fact that, by using phenylarsane PhAsH₂ instead a primary aryl phosphine, several arsoles were synthesized by Hauptmann and colleagues by LiⁿBu-catalyzed addition to 1,3-diynes [135,136].

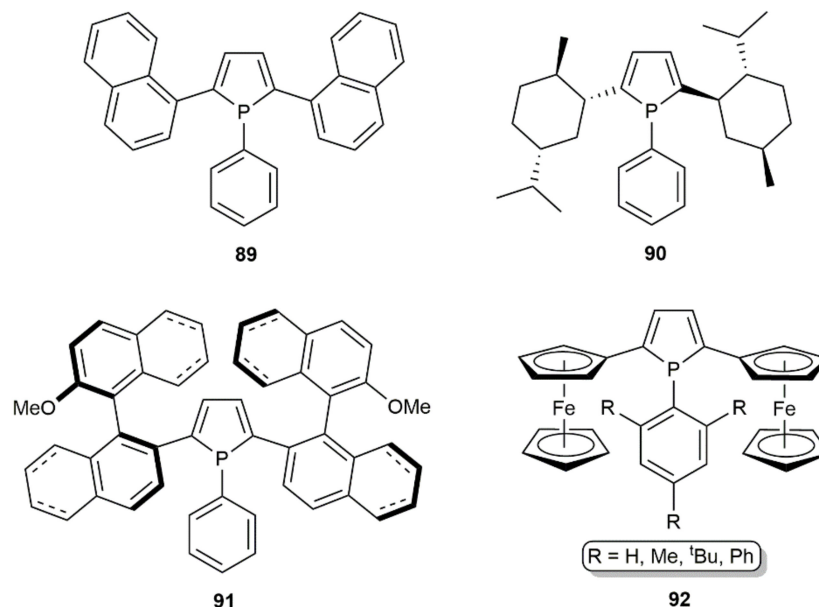
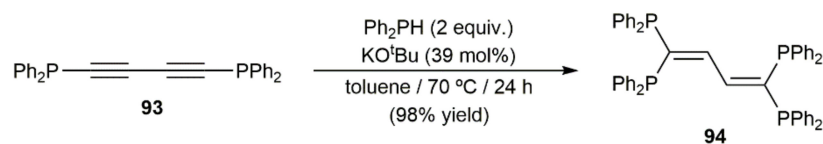


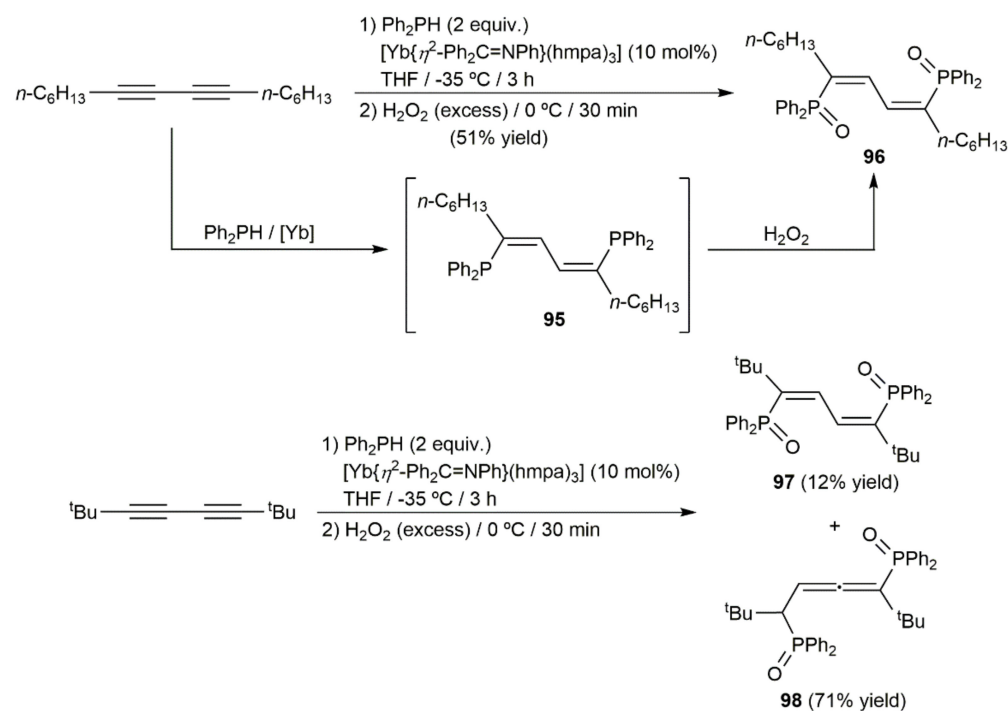
Figure 12. Structure of the 2,5-disubstituted phospholes **89–92**.

Base-catalyzed additions of secondary phosphines to 1,3-diynes can also be found in the literature. For example, Schmidbauer and colleagues reported in 1995 the high-yield preparation of 1,1,4,4-tetrakis(diphenylphosphino)-1,3-butadiene **94** by double hydrophosphination of 1,4-bis(diphenylphosphino)-1,3-butadiyne **93** with Ph₂PH, using KO^tBu as a promoter (Scheme 50) [137].



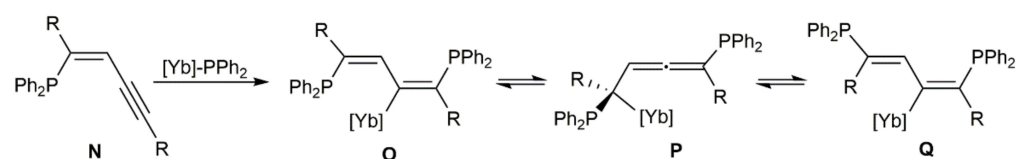
Scheme 50. Base-catalyzed double hydrophosphination of diyne **93** with Ph_2PH .

On the other hand, taking advantage of the ability of organolanthanides to promote intermolecular hydrophosphination reactions of multiple C–C bonds [138], Takaki and colleagues described the stereoselective synthesis of the (*Z,Z*)-bis(diphenylphosphiny)diene **96** under mild conditions by double hydrophosphination of 7,9-hexadecadiyne with Ph_2PH , catalyzed by the ytterbium–imine complex $[\text{Yb}\{\eta^2\text{-Ph}_2\text{C}=\text{NPh}\}(\text{hmpa})_3]$ (hmpa = hexamethylphosphoramide), and subsequent oxidation with H_2O_2 of the initially formed bis(diphenylphosphino)diene **95** (Scheme 51) [139,140]. Starting from 2,2,7,7-tetramethyl-3,5-octadiyne and applying the same protocol, a mixture of the corresponding diene **97** and the allene **98** was formed, with the latter being largely major.



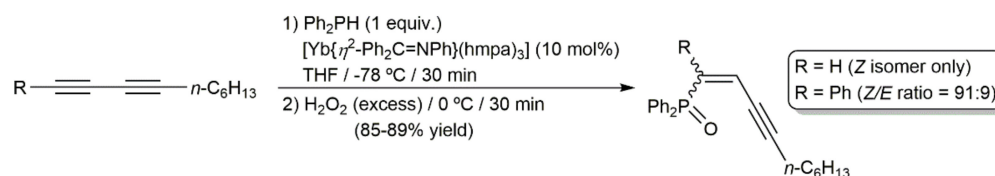
Scheme 51. Ytterbium-catalyzed double hydrophosphination reactions of diynes with Ph_2PH .

The hydrophosphination reactions depicted in Scheme 51 are believed to proceed through the sequential *anti* addition of in situ generated ytterbium-phosphide species $[\text{Yb}]\text{-PPh}_2$ to the $\text{C}\equiv\text{C}$ bonds of the diyne substrate [141]. In this way, enynes **N** are initially generated and rapidly transformed into the metallated dienes **O**, which evolve into compounds **96** and **97** by protodemetalation and oxidation (Scheme 52). Formation of allene **98** most probably results from the metallated species **P**, generated by isomerization of the corresponding **O** one.



Scheme 52. Intermediate species involved in the Yb-catalyzed double hydrophosphination reactions of diynes.

These initial studies were subsequently extended to other 1,3-diynes using $[\text{Yb}\{\eta^2\text{-Ph}_2\text{C}=\text{NPh}\}(\text{hmpa})_3]$ or $[\text{Yb}\{\text{N}(\text{SiMe}_3)_2\}(\text{hmpa})_2]$ as the catalyst [141]. As a general trend, the bis(diphenylphosphinyl)diene products were mostly generated as the corresponding (*Z,Z*)-isomers when disubstituted diynes were employed as substrates, while (*E,Z*)-butadienes were the major products starting from terminal 1,3-diynes $\text{HC}\equiv\text{CC}\equiv\text{CR}$ ($\text{R} = \text{aryl}$ or alkyl group). The different stereochemistry found for the latter seems to indicate that conversion of the dienylytterbium intermediates **O** into the isomeric **Q** ones via the metallated allenes **P** rapidly occurs in solution for these particular substrates (see Scheme 52). Moreover, of note is the fact that, as illustrated in Scheme 53, single hydrophosphination of unsymmetrical diynes was successfully achieved, with high regio- and stereocontrol, by performing the reactions at -78°C with an equimolar amount of diphenylphosphine.



Scheme 53. Ytterbium-catalyzed single hydrophosphination reactions of diynes with Ph_2PH .

Double hydrophosphination reactions of 1,3-diynes $\text{RC}\equiv\text{CC}\equiv\text{CR}$ ($\text{R} = \text{Me}$, ^tBu , SiMe_3 , Ph , $2,4,6\text{-C}_6\text{H}_2\text{Me}_3$) with diphenylphosphine catalyzed by the phosphido–calcium complex $[\text{Ca}(\text{THF})_4(\text{PPh}_2)_2]$ were additionally described by Westerhausen and colleagues [142,143]. A low selectivity was, in general, observed, the reactions leading to complex mixtures containing the corresponding 1,4-bis(diphenylphosphino)-1,3-dienes **99** (major products), along with the 1,2-bis(diphenylphosphino)-1,3-dienes **100** (the four possible stereoisomers) and, in some cases, the allenic derivative **101** (see Figure 13).

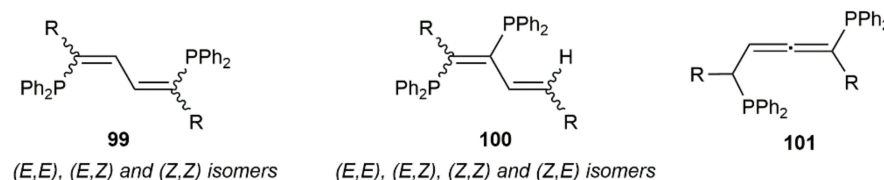
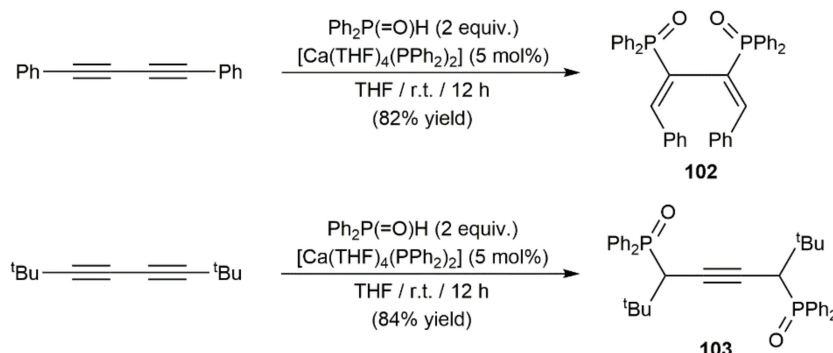


Figure 13. Products formed in the $[\text{Ca}(\text{THF})_4(\text{PPh}_2)_2]$ -catalyzed hydrophosphination of 1,3-diynes.

As shown in Scheme 54, complete regio- and stereoselective transformations were reached when $[\text{Ca}(\text{THF})_4(\text{PPh}_2)_2]$ was employed to promote the hydrophosphorylation of $\text{RC}\equiv\text{CC}\equiv\text{CR}$ ($\text{R} = \text{Ph}$, ^tBu) with diphenylphosphine oxide, reactions from which the diene **102** and the alkyne **103** were isolated in high yields [144]. The structures of compounds **102** and **103** differ markedly from those generated in the hydrophosphination processes (see Figure 13), and the differences observed were suspected to be related with the higher stability of the intermediate species $[\text{Ca}]\text{-P}(=\text{O})\text{Ph}_2$ vs. the $[\text{Ca}]\text{-PPh}_2$ ones involved in these P–H bond addition reactions. Thus, intermediates of type $[\text{Ca}]\text{-PPh}_2$ can undergo dissociation and reorganization processes in solution, which would explain the low regio- and stereocontrol in the hydrophosphination processes. Moreover, the use of a phosphine oxide offers the possibility to maintain close contact between the calcium center and the corresponding phosphorylated intermediates, via Ca–O Lewis acid–base interactions, a key factor for the effective regiocontrol in the reactions depicted in Scheme 54.

Within this section, we must finally mention the synthesis of the 1,3-butadiene derivatives **104** (see Figure 14) by Westerhausen's group through the sequential hydroamination and hydrophosphination of 1,4-diphenyl-1,3-butadiyne catalyzed by $[\text{K}_2\text{Ca}\{\text{N}(\text{H})\text{Dipp}\}_4]$ [145]. Whereas the initial hydroamination step is regio- (amino group in 1-position) but not stereoselective (formation of *E* and *Z* isomers), the subsequent hydrophosphination one proceeded with complete regio- and stereocontrol.



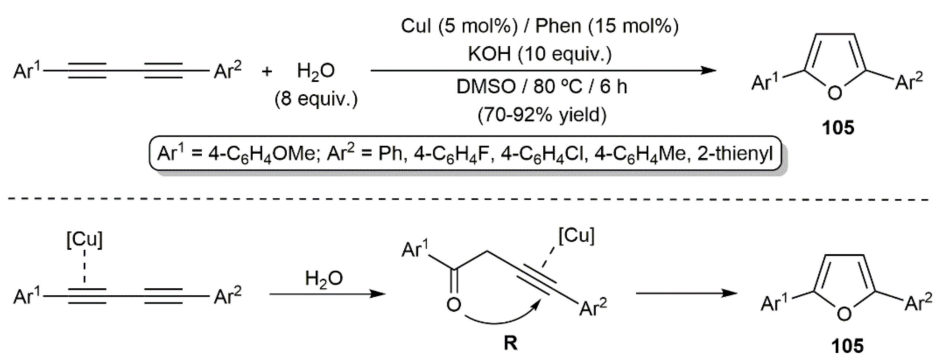
Scheme 54. $[\text{Ca}(\text{THF})_4(\text{PPh}_2)_2]$ -catalyzed hydrophosphorylation of 1,3-diyne with $\text{Ph}_2\text{P}(=\text{O})\text{H}$.



Figure 14. Structure of the 1,3-butadiene derivatives **104**.

9. Hydration Processes

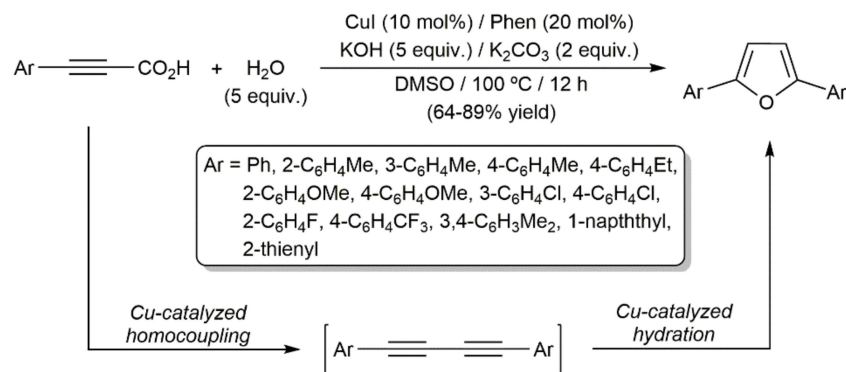
As in the case of simple alkynes [146], the Bronsted-acid-promoted hydration of 1,3-diyne leading to carbonyl compounds is well documented, particularly under photochemical conditions [147–153]. Although similar reaction products would also be expected when using metal-based catalysts [146], the works carried out by different authors have shown the preferential formation of furan derivatives as the result of the formal double addition of the water O–H bonds to the diyne. This was evidenced for the first time by Jiang and colleagues in 2012, with the synthesis of the 2,5-diaryl-substituted furans **105** (Scheme 55) [154]. The hydration process is catalyzed by a CuI, in conjunction with 1,10-phenanthroline and KOH, in dimethyl sulfoxide (DMSO) at 70 °C. A reaction pathway involving the initial formation of the ketone intermediate **R** by single hydration of the diyne, followed by a Cu(I)-catalyzed cyclization, was proposed by the authors (see Scheme 55). Moreover, of note is the fact that related symmetrically substituted 2,5-diaryl furans were accessed, under the same reaction conditions, starting from haloalkynes $\text{ArC}\equiv\text{CX}$, which, by means of the Cu(I) catalyst, are in situ converted into the respective 1,3-diyne $\text{ArC}\equiv\text{CC}\equiv\text{CAr}$ by homocoupling.



Scheme 55. Copper-catalyzed hydration of 1,3-diyne.

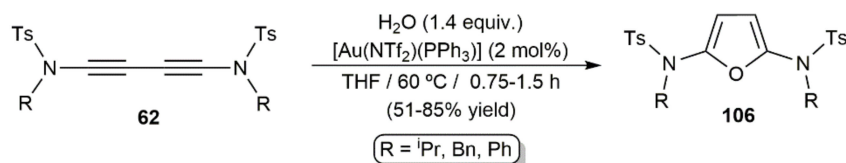
A slight modification of this catalytic system was later shown to be capable of promoting the one-pot generation of 2,5-diaryl-substituted furans from aryl-substituted propiolic acids through the initial copper-catalyzed decarboxylative coupling of the substrates to generate the corresponding diynes and subsequent reaction with water (Scheme 56) [155]. Conversion of preformed 1,4-diaryl-1,3-diyne into the corresponding 2,5-disubstituted furans catalyzed by $[\text{Pd}(\text{PPh}_3)_4]$ was also described by Hua and colleagues, the reactions

requiring, again, the assistance of a base (KOH) [156]. It should be mentioned at this point that some studies showing the ability of KOH to promote, by itself, the hydration of 1,3-diynes into furans can be found in the literature [83,157,158].



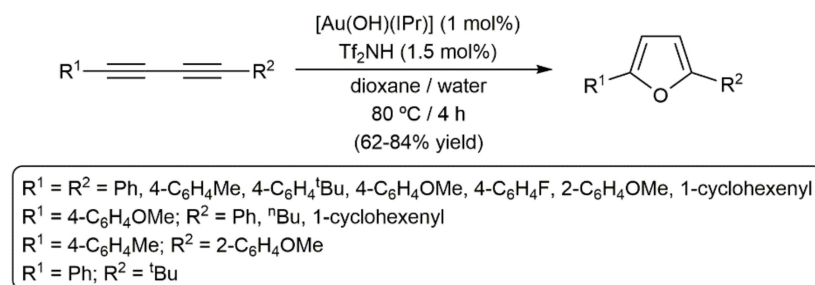
Scheme 56. Copper-catalyzed synthesis of 2,5-disubstituted furans from propiolic acids.

On the other hand, hydration of 1,3-diynes under base-free conditions has been reported to occur in the presence of gold(I) complexes. This was evidenced for the first time by Skrydstrup and colleagues in 2010 with the synthesis of the 2,5-diamidofurans **106** from the corresponding 1,3-diyne **62** upon the catalytic action of the Au(I)-phosphine complex [Au(NTf₂)(PPh₃)] (Scheme 57) [92].



Scheme 57. Gold-catalyzed synthesis of the 2,5-diamidofurans **106**.

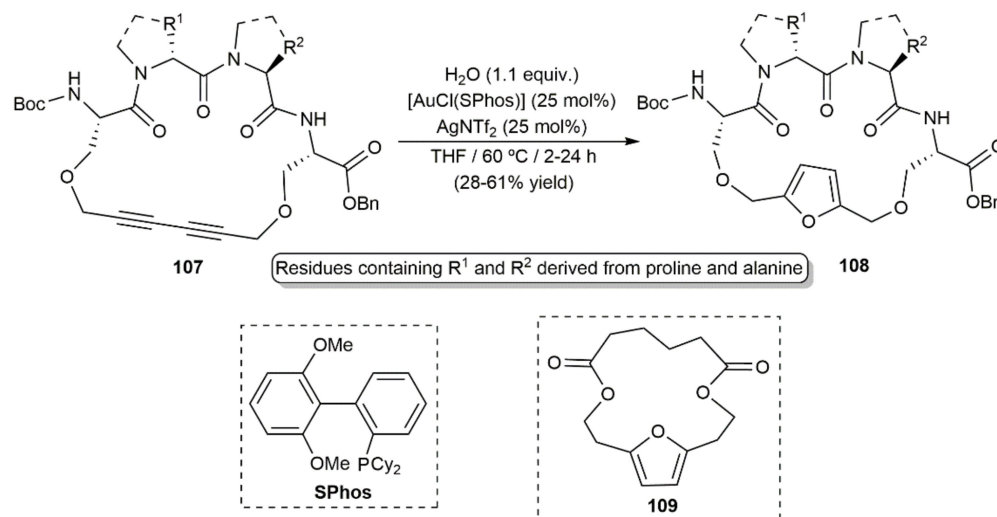
In a broader substrate-scope study, Nolan and colleagues successfully employed the NHC-gold(I) complex [Au(NTf₂)(IPr)], generated in situ from the hydroxo-derivative [Au(OH)(IPr)] and trifluoromethanesulfonimide (Tf₂NH), to promote the process [93]. As shown in Scheme 58, the reactions were conveniently conducted in a dioxane/water mixture and both symmetric and unsymmetric diynes, substituted with aromatic, aliphatic, or alkenyl groups, were tolerated. Moreover, of note is the fact that DFT calculations confirmed that a reaction pathway analogous to that commented on above for copper (see Scheme 56) also operates in the present case.



Scheme 58. Hydration of 1,3-diynes catalyzed by an NHC-gold(I) complex.

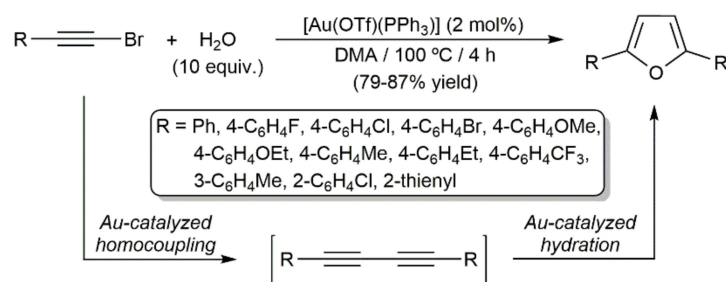
The utility of these gold(I)-catalyzed furan-ring formation reactions was fully demonstrated by Verniest and colleagues with the synthesis of the furan-bridged peptidic macrocycles **108** by hydration of diynes **107**, reactions in which [Au(NTf₂)(SPhos)], generated in situ from [AuCl(SPhos)] and AgNTf₂, was used as the catalyst (Scheme 59) [101].

[Au(NTf₂)(SPhos)] was additionally applied by Furstner's group, in the context of the total synthesis of Ivorenolide B, to synthesize the 15-membered macrocyclic dilactone **109** (see Scheme 59) from the corresponding 1,3-diyne (**20** in Scheme 11) [31].



Scheme 59. Gold-catalyzed synthesis of the 2,5-diamidofurans **106**.

In addition, Guo demonstrated the possibility of preparing 2,5-substituted furans directly from bromoalkynes, employing the triflate-gold(I)-phosphine complex [Au(OTf)(PPh₃)] as a catalyst in dimethylacetamide (DMA) at 100 °C (Scheme 60) [159]. The domino process was operative with aromatic and heteroaromatic bromoalkynes, but completely ineffective with aliphatic ones. As demonstrated for PhC≡Cl, which led to the corresponding furan in 87% yield under identical experimental conditions, this gold-catalyzed transformation can be extended to iodoalkynes.

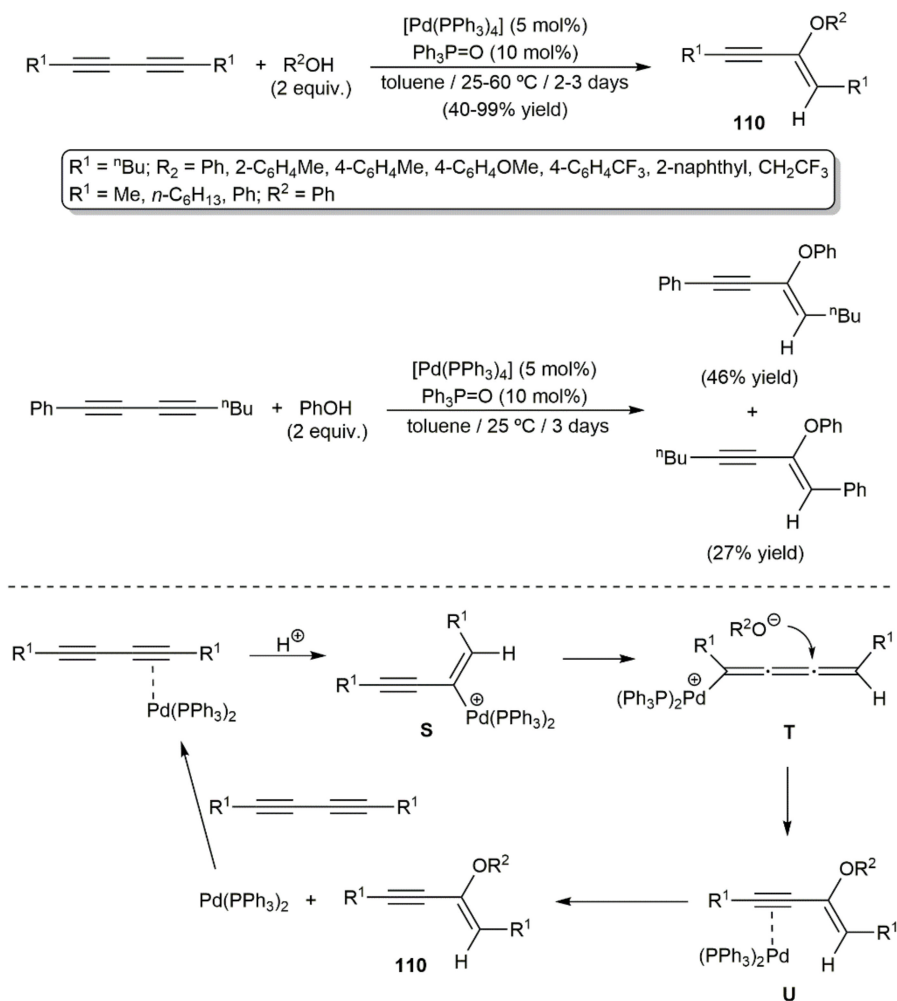


Scheme 60. Gold-catalyzed synthesis of 2,5-disubstituted furans from bromoalkynes.

10. Hydroalkoxylation Processes

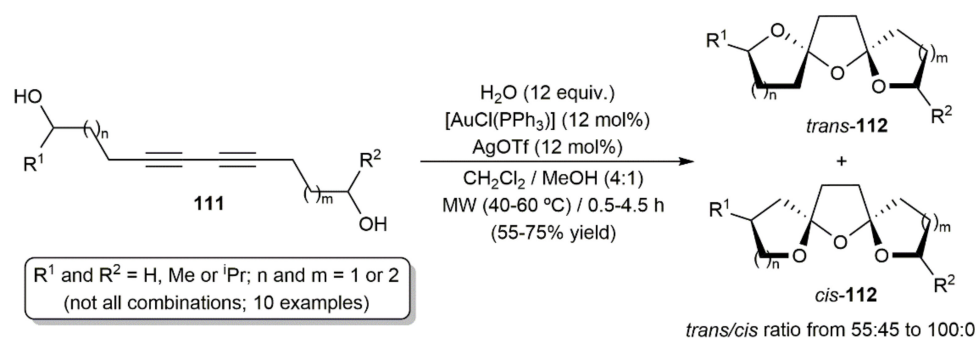
Only one example describing the intermolecular addition of alcohols to 1,3-diynes promoted by a transition metal can be currently found in the literature. It was reported by Yamamoto and colleagues in 2002, who found that the palladium(0) complex [Pd(PPh₃)₄] was able to catalyze the regio- and stereoselective *trans* addition of acidic alcohols (phenols or CF₃CH₂OH) to different symmetrically substituted diynes to afford the alkoxyated enynes **110** (Scheme 61) [160]. Only the monoaddition products were formed even over longer reaction periods or at higher temperatures. In the study, the addition of phenol to the nonsymmetrical substituted substrate octa-1,3-dinyl-1-ylbenzene was also explored, the reaction leading to mixtures of regioisomers, since the catalyst was not capable of discriminating between the two C≡C bonds (Scheme 61). A reaction pathway involving the initial activation of one of the C≡C bonds by co-ordination to the Pd(0) center, followed by protonation to generate the metallated intermediate **S**, was proposed by the authors. Rearrangement of **S** into the σ -cumulenyl palladium complex **T** then allows the nucleophilic

attack of the alkoxyde. This attack occurs on the opposite side of the bulky PPh₃ ligands, thus explaining the *trans* selectivity of the process. Intermediate **U** is formed in this way, from which the product is liberated after de-coordination of the catalytically active Pd(0) fragment. In favor of this mechanistic proposal is the fact that no reaction was observed when simple alkynes were employed as substrates. Moreover, of note is the fact that the exquisite *trans* selectivity observed in this Pd(0)-catalyzed hydroalkoxylation process contrasts with that of related metal-free addition reactions, where mixtures of *Z/E* isomers are usually obtained [161,162].



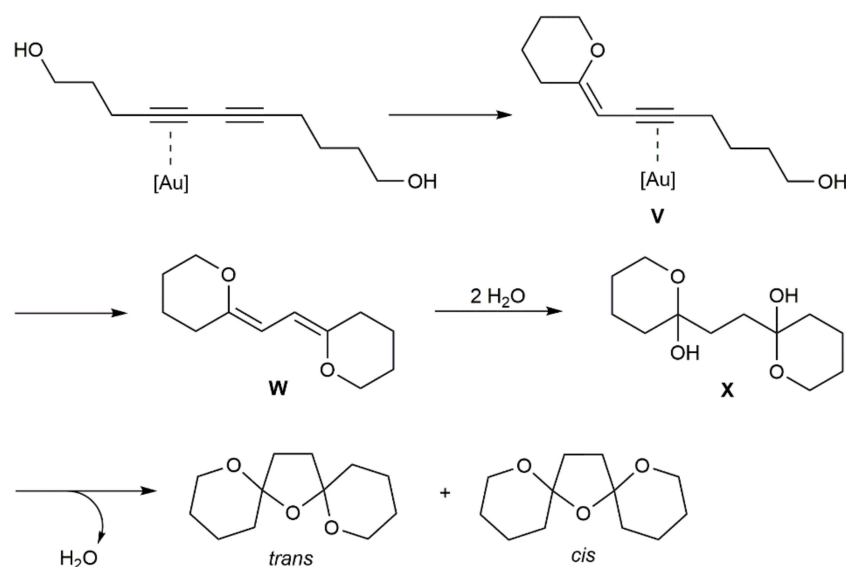
Scheme 61. Pd(0)-catalyzed intermolecular hydroalkoxylation of 1,3-diyne.

Regarding intramolecular processes, Lee and colleagues described the synthesis of a variety of bis-spiroketal derivatives **112** from the diynediols **111** through a gold(I)-catalyzed tandem addition of the tethered hydroxyl groups and one equivalent of water (Scheme 62) [163]. The hydroalkoxylation/hydration reactions, conducted under MW irradiation with the in situ generated complex [Au(OTf)(PPh₃)], led, in most of the cases, to the bis-spiroketals **112** as separable mixtures of the corresponding *trans* (major) and *cis* (minor) isomers, which, once isolated, were found to interconvert in solution to reach an equilibrium. Preference for the C₂ symmetrical *trans* isomers *vs.* the unsymmetrical *cis* ones was reasoned in terms of the most favorable anomeric effect in the former.



Scheme 62. Gold-catalyzed synthesis of bis-spiroketal from diynediol derivatives.

The reaction pathway leading to compounds **112** was elucidated by DFT calculations using 5,7-diyne-1,12-diol as a model [164]. As shown in Scheme 63, the pyranyl enol ether intermediate **V** is initially generated by a gold-mediated 6-*exo-dig* cyclization, evolving into the bis-enol ether **W** by a second 6-*exo-dig* addition. A subsequent dihydration of **W** leads to **X**, which converts into the final bis-spiroketal products by dehydrative ring closure. In complete agreement with the *trans/cis* ratio experimentally observed (69:31), the computations indicated a slightly lower energy for the *trans* isomer (1.08 Kcal/mol).



Scheme 63. Mechanism for the conversion of 5,7-diyne-1,12-diol into the bis-spiroketal isomers.

Employing the cationic gold(I) complex $[\text{Au}(\text{NCMe})(\text{JohnPhos})][\text{SbF}_6]$ as a catalyst, the related bis-spiroketal **113–115** were synthesized by Iglesias-Arteaga and colleagues through the hydroalkoxylation/hydration of the respective steroid-derived diynediols (Figure 15) [165]. The double spiroacetalization process proceeded in high yields ($\geq 68\%$) and produced almost exclusively the C_2 symmetrical *trans* diastereoisomers (only in the case of **115** was a small amount of the unsymmetrical *cis* isomer formed). DFT calculations indicated a higher stability of the *trans* vs. *cis* diastereoisomers for these particular compounds (*ca.* 4 Kcal/mol), with the fusion of the side tetrahydropyran rings to rigid scaffolds suppressing the conformational equilibrium between both isomers.

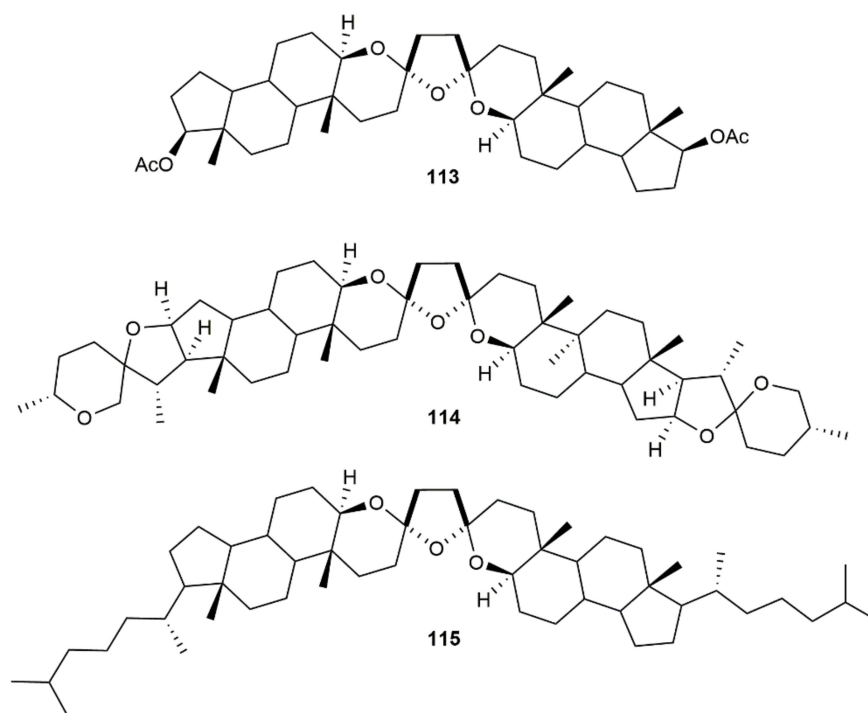
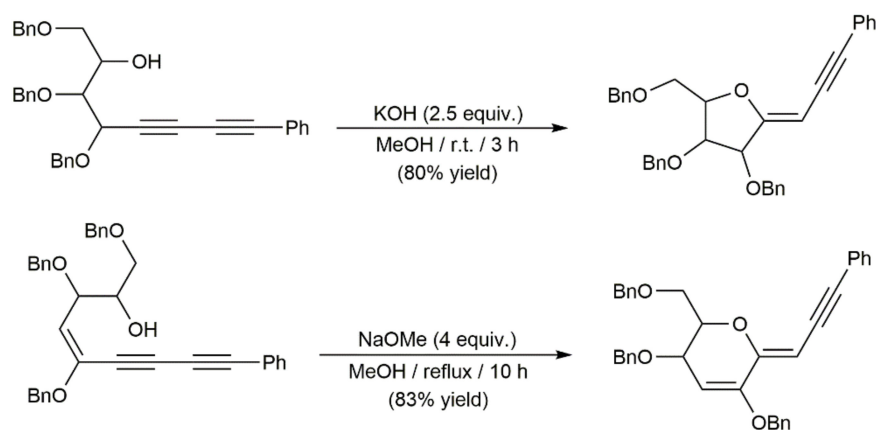


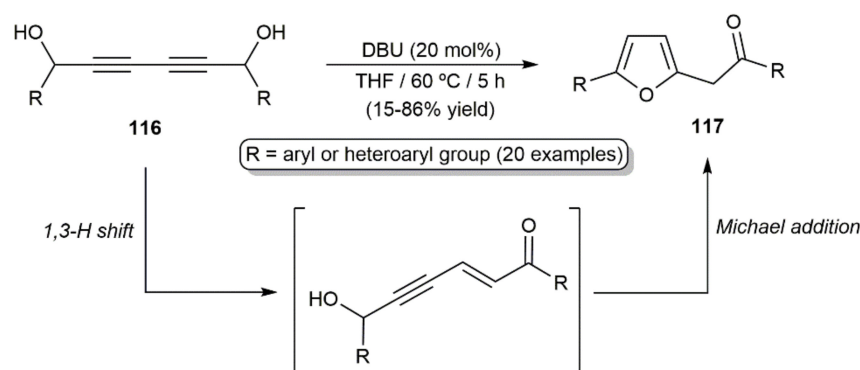
Figure 15. Structure of the steroid-derived bis-spiroketal **113–115**.

In addition to the gold-catalyzed reactions just commented on, several works describing the base-promoted cyclization of 1,3-diyne substrates bearing tethered hydroxyl groups can be found in the literature [166–172]. A couple of illustrative examples are given in Scheme 64 [172].



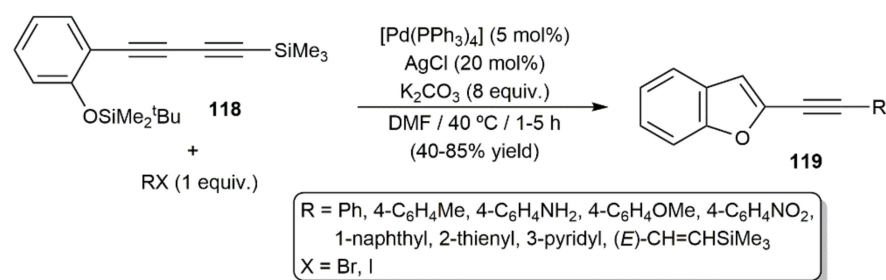
Scheme 64. Base-promoted cyclization of hydroxyl-containing 1,3-diyne.

These cyclization processes have been studied with substrates in which one of the diyne $C\equiv C$ bonds and the hydroxyl group are connected through three to five carbon chain linkers, thus giving access to five- to seven-membered ring cyclic enol ethers. A particular case is that of the diynyl-1,6-diols **116**, which, in the presence of the DBU base (1,8-diazabicycloundec-7-ene), evolved into furans **117** through a cascade 1,3-H shift/intramolecular Michael addition reaction (Scheme 65) [173].



Scheme 65. Synthesis of 2,5-disubstituted furan derivatives from diynyl-1,6-diols.

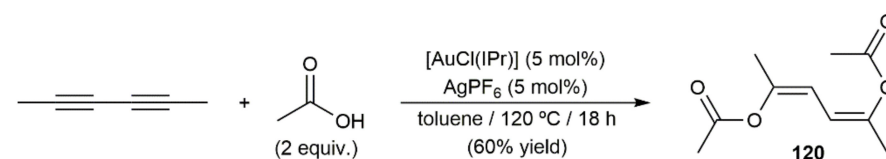
On the other hand, Fiandanese and colleagues developed a protocol for the expeditious synthesis of 2-alkynylbenzofurans **119** by reacting 2-(4-trimethylsilyl)-1,3-butadiyn-1-yl)-*tert*-butyldimethylsilylphenol **118** with organic halides through a tandem Sonogashira coupling/cyclization reaction (Scheme 66) [119]. Given that, in the presence of disilylating agents, the cyclization of compound **118** into the parent 2-ethynyl-1-benzofuran was previously found to occur without the assistance of a metal [174], participation of the palladium catalyst in the cyclization step can probably be discarded.



Scheme 66. Synthesis of 2-alkynylbenzofuran derivatives from 1,3-diyne **118**.

11. Hydro-Oxycarbonylation Processes

Addition of carboxylic acids to alkynes catalyzed by transition metals represents one of the most efficient ways to prepare synthetically useful enol esters [175–178]. Among the different catalytic systems reported to date, gold complexes have emerged in recent years as the most effective, as they can be successfully applied in the hydro-oxycarbonylation, not only of terminal alkynes, but also of the more challenging internal ones [179]. Indeed, the only example involving a 1,3-diyne as substrate that can be found in the literature made use of the in situ generated cationic NHC-gold(I) catalyst $[\text{Au}(\text{IPr})][\text{SbF}_6]$ [180]. As shown in Scheme 67, it was able to promote the double addition of acetic acid to 2,4-hexadiyne to generate in a regio- and stereospecific manner the diene-diester **120**. The *Z* configuration found for the C=C bonds of **120** is in complete accord with the marked preference of gold complexes to promote *anti*-type addition processes [179].

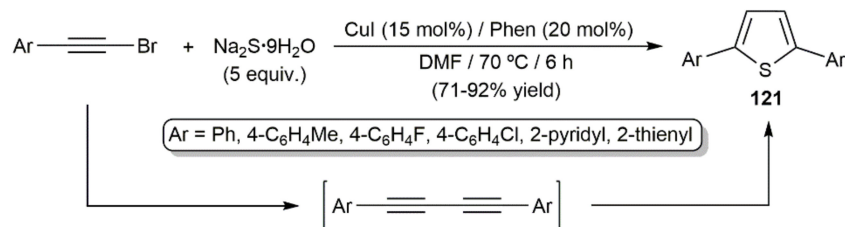


Scheme 67. Gold-catalyzed addition of acetic acid to 2,4-hexadiyne.

12. Hydrothiolation, Hydroselenation, and Hydrotelluration Processes

In 2012, Jiang and colleagues described the synthesis of different 2,5-diaryl-substituted thiophenes **121** by reacting aromatic bromoalkynes with sodium sulfide hydrate, i.e.,

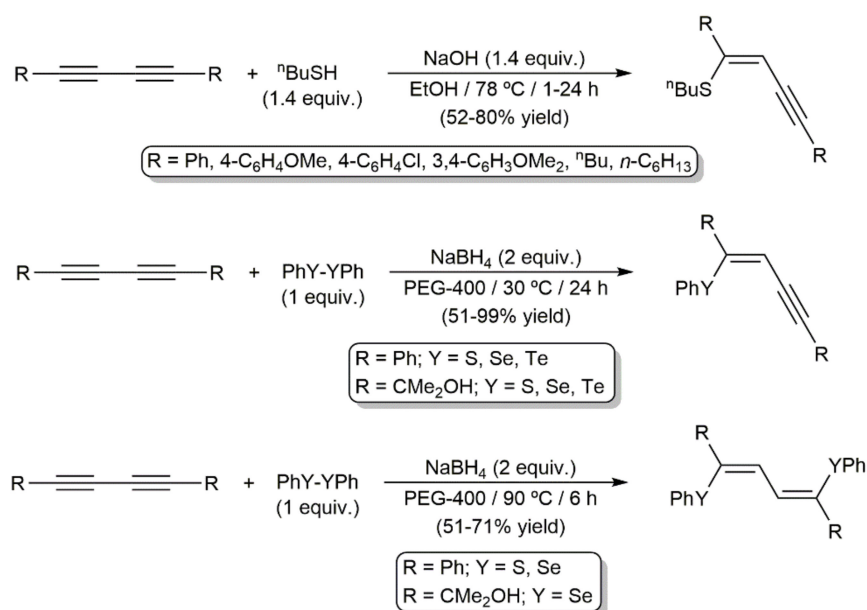
$\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$, in the presence of CuI and the 1,10-phenanthroline ligand (Scheme 68) [154]. Compounds **121** are the result of the formal double hydrothiolation of the corresponding 1,3-diynes, generated in situ by copper-catalyzed homocoupling of the starting bromoalkynes.



Scheme 68. Copper-catalyzed synthesis of 2,5-disubstituted thiophenes from bromoalkynes.

Related thiophene-ring formation reactions using 1,3-diynes as starting materials have been described in the absence of any metal catalyst, the cyclization process taking place properly in the presence of a simple base (KOH , KO^tBu or NH_4OAc) and employing not only $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$, but also NaHS or S_8 as the sulfur source [83,87,101,155,181–186]. Similarly, metal-free protocols to access selenophenes [187,188] and tellurophenes [189–191] from 1,3-diynes are known.

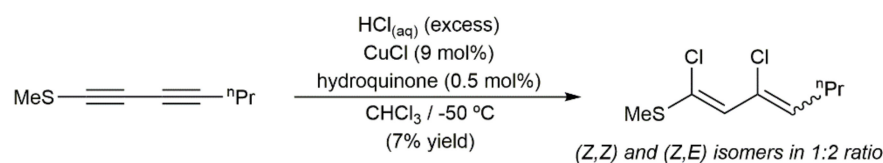
On the other hand, base-promoted mono- and dihydrochalcogenation reactions of 1,3-diynes with organic thiols RSH [192–194] and dichalcogenides (RSSR , RSeSeR , or RTeTeR) [195–201] to afford functionalized enynes or butadienes, respectively, can also be found in the literature. In general, the reaction products were obtained with high or complete *Z*-selectivity (*anti*-type addition). Illustrative examples are shown in Scheme 69.



Scheme 69. Base-promoted hydrochalcogenation reactions of 1,3-diynes.

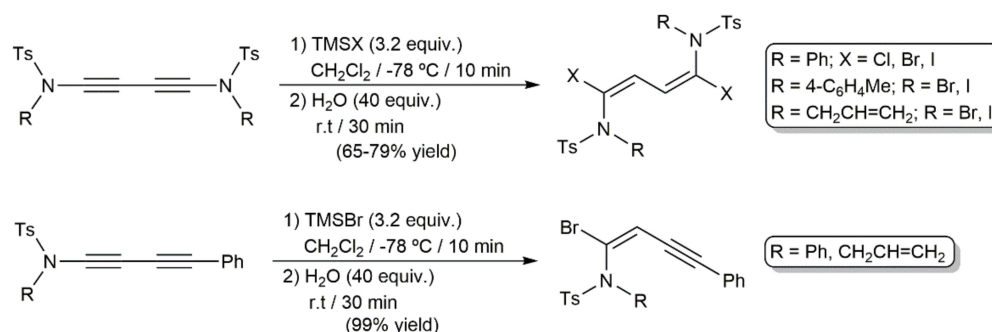
13. Hydrohalogenation Processes

Very few works dealing with the addition of halogen–hydrogen bonds to 1,3-diynes can be currently found in the literature. Hydrohalogenations using aqueous or gaseous HX under CuCl catalysis were described in early reports, but the yields reached were, in general, very low and the reactions led, in most cases, to isomeric mixtures of products (a representative example is given in Scheme 70) [202–204].



Scheme 70. CuCl-catalyzed hydrochlorination of $\text{MeSC}\equiv\text{CC}\equiv\text{C}^n\text{Pr}$.

In a more recent study, regio- and stereoselective hydrohalogenation reactions of 1,3-diynes containing ynamide moieties were described by Iwasawa and colleagues under catalyst-free conditions (Scheme 71) [205]. The corresponding HX reagent was generated in situ by hydrolysis of the respective halotrimethylsilane Me_3SiX (TMSX; X = Cl, Br, I). In complete accord with the lack of reactivity observed when the diyne $\text{PhC}\equiv\text{CC}\equiv\text{CPh}$ was employed as a substrate, in the case of compound $\text{R}(\text{Ts})\text{NC}\equiv\text{CC}\equiv\text{CPh}$, only the ynamide $\text{C}\equiv\text{C}$ bond participated in the process. In all the cases, the addition proceeded in *syn*-mode, with the halogen attacking the electrophilic ynamide α carbon.



Scheme 71. Hydrohalogenation of ynamide-containing 1,3-diynes with in situ generated HX.

14. Summary

In this contribution, metal-catalyzed hydrofunctionalization reactions of conjugated 1,3-diynes have been comprehensively reviewed for this first time, thus complementing previous review articles and accounts covering the synthesis and applications of this particular class of alkynes [10–15,76]. The challenges associated with the presence of two reactive $\text{C}\equiv\text{C}$ units, as the number of potential regio- and stereoisomeric products that can be formed increases, have made these substrates much less employed in hydrofunctionalization processes compared to classical monoynes. However, many examples collected in this review highlight the possibility of obtaining unique products through the selection of suitable catalytic systems, making 1,3-diynes interesting building blocks for obtaining functionalized enynes, dienes, as well as a wide variety of heterocyclic and carbocyclic compounds, in a selective manner. The enormous potential offered by 1,3-diynes in hydrofunctionalization processes will deserve undoubtedly more attention in the coming years and will continue to greatly contribute to modern synthetic chemistry.

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